I was thinking of having opened a door
with a key to many doors , perhaps all of them .
I was thinking of having thought of something
that nobody else had thought .....

Primo Levi
The Periodic Table

ACKNOWLEDGEMENTS

Firstly , I must express my gratitude to Dr. John Bloodworth for his encouragement and patience , the latter must have been sorely tried during the prolonged writing-up period.

Secondly , I wish to thank all the many people who came to and went from the fourth floor labs during my time there. Special thanks must go to Drs. Kevin Bowyer , Tracey Melvin , and Neville Hargreaves for their guidance. Thanks are also due to Mike Spencer for running most of the 400 MHz spectra and to Yasmin , Steve , John , Tim , Duncan , Linda , Jack and Navin , for just being there.

Thirdly , I must thank all the support staff of the Christopher Ingold Laboratories , special thanks going to Steve Corker *et al* in analysis , and Margaret of Mass Spectrometry.

Finally , I would like to thank SERC for the award of a CASE studentship and Dr. Alan Comyns and Mr. Bill Sanderson of Interox Chemicals for their invaluable support and Mrs. Layla Buzinin for typing this thesis.

THE SYNTHESIS AND REACTIONS OF SOME CYCLIC PEROXIDES

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

by

Richard John Curtis

The Christopher Ingold Laboratories

University College London

University of London

September 1990

ABSTRACT

A series of 1,2-dioxanes was prepared with the intention of studying the effect of substituents upon their rearrangement/decomposition.

The synthesis of the 1,2-dioxanes involves mercury (II) salt mediated cyclizations of appropriate δ,ϵ-unsaturated hydroperoxides followed by reductive demercuration. In this way, the 3-methyl-1,2-dioxanes:3-methyl-5-phenyl-1,2-dioxane, 3,6-dimethyl-5-phenyl-1,2-dioxane, 3,6-dimethyl-3-phenyl-1,2-dioxane, 3,3,6-trimethyl-1,2-dioxane, 3,3,6,6-tetramethyl-1,2-dioxane, 5-ethenyl-3-methyl-1,2-dioxane, and 3-methyl-1,2-dioxane itself were prepared; of which, five are novel.

The 1,2-dioxanes were subjected to flash vacuum pyrolysis (fvp), to treatment with iron(II) sulphate, and in a limited number of cases, to photolysis. In all reactions a preference for rearrangement via 1,5-transfer of a hydrogen from C-3 or C-6 to an oxygen centred radical was observed. In the case of 5-ethenyl-3-methyl-1,2-dioxane, the 1,5-hydrogen transfer product was not isolated because of a novel tandem decarbonylation.

Two other areas of cyclic peroxide chemistry were investigated. These were the cycloperoxyhalogenation of γ,δ-unsaturated hydroperoxides and the synthesis and reactions of diene hydroperoxides.

The reaction of γ,δ-unsaturated hydroperoxides with N-iodosuccinimide (NIS), N-bromosuccinimide (NBS), bromine

and iodine each gave the corresponding 3-halogenomethyl-1,2-dioxolane. The cyclization with NIS was found to have a wholly radical mechanism and that with halogen a wholly polar mechanism, whereas the NBS reaction was found to have both radical and polar components.

A novel diene hydroperoxide capable of both 5-exo and 6-exo cyclizations was prepared and its reactions with a variety of reagents studied. Radical cyclization afforded the 1,2-dioxolanes in a regio- and stereo-specific manner, whereas polar cyclizations gave both 1,2-dioxanes and 1,2-dioxolanes.

CONTENTS

CHAPTER 1

INTRODUCTION

Organic peroxides play important roles in industry, in biology, in synthesis as reagents or intermediates and as precursors to reactive intermediates of theoretical value such as peroxonium ions, biradicals and radical anions.

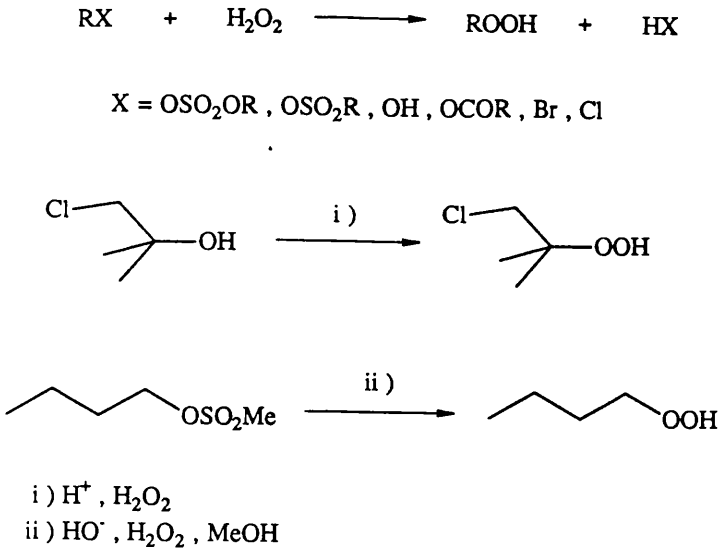
Organic peroxides[1,2] cover a large range of compound types such as alkyl hydroperoxides, dialkyl peroxides (including cyclic peroxides), α-oxy and α-peroxy peroxides, diacyl peroxides and peroxyesters. Of these, the two simplest and most commonly occurring are the alkyl hydroperoxides (1) and dialkyl peroxides (2).[3] These compounds may be simply regarded as alkylated derivatives of hydrogen peroxide, and it is with these peroxides that much of the work described in this thesis is primarily concerned.

ROOH (1) ROOR' (2)

1. Alkyl Hydroperoxides

Hydrogen peroxide and its anion are powerful nucleophiles and as such, reaction with an alkylating agent RX (where X is a good leaving group) has been employed to prepare alkyl hydroperoxides (Scheme 1).

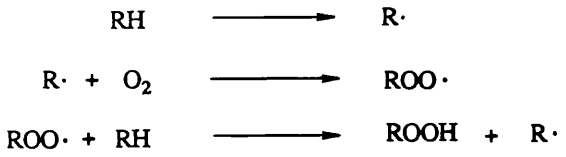
As well as hydrogen peroxide, molecular oxygen can also be used as a source of the dioxygen group in peroxides. The reactions of triplet oxygen ($^3O_2$) and



(Scheme 1)

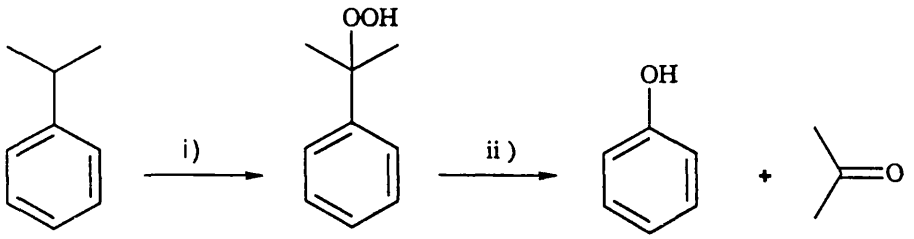
singlet oxygen ($^1O_2$) with appropriate hydrocarbons have been used to prepare hydroperoxides.

The autoxidation (oxidation at less than 120°C without a flame) of hydrocarbons has been used to prepare alkyl and aralkyl hydroperoxides. This is a free-radical chain reaction (Scheme 2), the site of reaction being that which provides the most stable radical. Consequently the most easily oxidized hydrocarbons are tertiary aralkanes and alkenes, especially dienes and other polyunsaturated hydrocarbons containing $-CH=CH-CH_2-CH=CH-$ units.



(Scheme 2)

Industrial applications of autoxidation include the preparation of t-butyl hydroperoxide from t-butane and the preparation of acetone and phenol from cumene by the acid catalysed decomposition of cumene hydroperoxide (Scheme 3).



$$(CH_3)_3CH + O_2 \xrightarrow{i)} (CH_3)_3COOH$$

i) O_2 , Δ
ii) H^+

(Scheme 3)

Another example of autoxidation is that of alkyl metal compounds. Treatment of alkyl derivatives of magnesium, lithium, boron, zinc and cadmium with oxygen affords alkylperoxymetal compounds which can be hydrolysed to the alkyl hydroperoxides (Scheme 4).

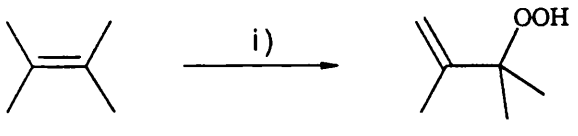
$$RMgX + O_2 \longrightarrow ROOMgX \xrightarrow{i)} ROOH + MgX_2$$

$$CdR_2 + O_2 \longrightarrow Cd(OOR)_2 \xrightarrow{ii)} 2\,ROOH + CdO$$

i) H^+ , H_2O
ii) H_2O

(Scheme 4)

Singlet oxygen has been used to prepare hydroperoxides through the sensitized photooxygenation of alkenes[4,5] containing allylic hydrogens which affords allylic hydroperoxides. Thus, tetramethylethylene (3) provides the allylic hydroperoxide (4).

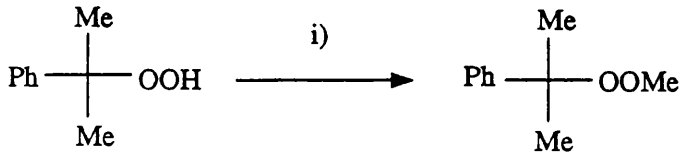


(3) (4)

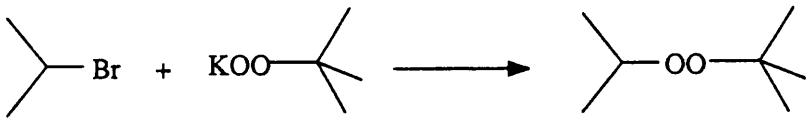
i) $^1O_2$

2. Dialkyl Peroxides

Dialkyl peroxides[1,2,3] have been prepared in a similar manner to alkyl hydroperoxides. Thus, reaction of hydrogen peroxide (or its anion) with two equivalents of an alkylating agent RX affords symmetrical dialkyl peroxides and the reaction of a hydroperoxide R'OOH with an alkylating agent RX gives the unsymmetrical peroxides (Scheme 5).

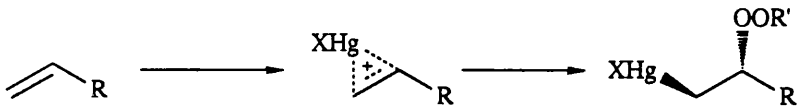


i) Me_2SO_4 , Base

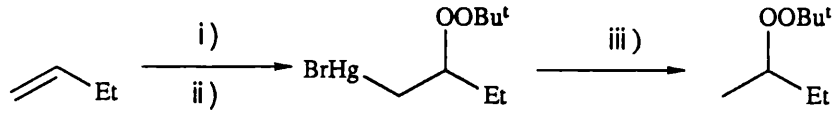


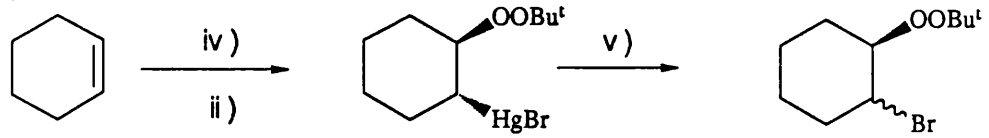
(Scheme 5)

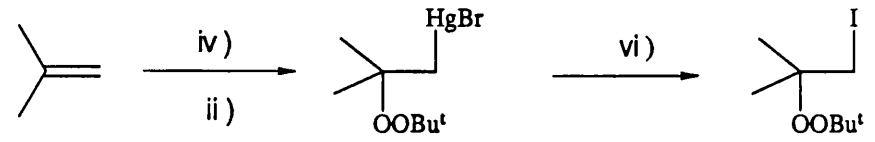
A more recent method[6] of dialkyl peroxide preparation is by the peroxymercuration/demercuration of alkenes (Scheme 6). It is supposed that the mercuration reaction proceeds by a mechanism involving an initial electrophilic attack by a mercury(II) salt on the double bound to form a mercurinium ion (5) which undergoes nucleophilic attack by the hydroperoxide (Scheme 6).



(5)



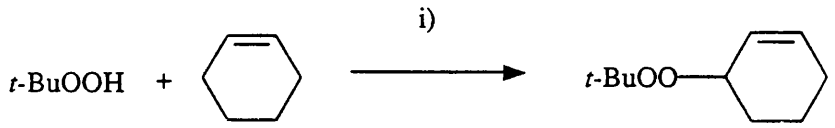


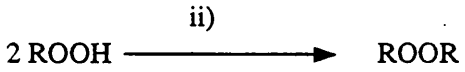


i) $Hg(OAc)_2$, t-BuOOH, CH_2Cl_2
ii) KBr , H_2O
iii) $NaBH_4$, 3M NaOH , Et_2O
iv) $Hg(O_2CCF_3)_2$, t-BuOOH , CH_2Cl_2
v) Br_2 , CH_2Cl_2
vi) I_2

(Scheme 6)

Two other techniques of dialkyl peroxide preparation[2] involve the use of metal salts. For example, the treatment of an alkyl hydroperoxide and substrate R'H (where H is readily abstracted) with cobalt or copper salts affords dialkyl peroxides. Also lead(IV) acetate has been used to prepare symmetrical dialkyl peroxides (Scheme 7).



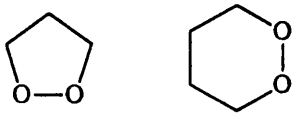


i) Co or Cu salt

ii) $Pb(OAc)_4$

(Scheme 7)

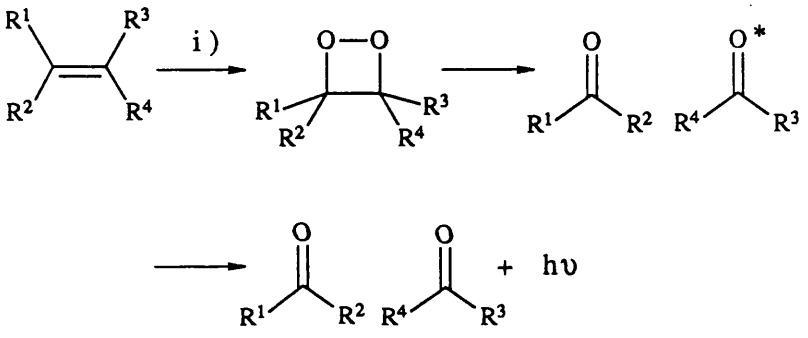
Structurally related to dialkyl peroxides are the cyclic peroxides.[7] Although cyclic peroxides with a ring size of three[8] to nine atoms[9] are known, the most commonly encountered are derivatives of the five-membered 1,2-dioxacyclopentane (6) and six-membered 1,2-dioxacyclohexane (7), usually referred to as 1,2-dioxolanes and 1,2-dioxanes respectively. The main



(6) (7)

methods of preparing cyclic peroxides involve extensions of the methods used to prepare acyclic dialkyl peroxides and will be discussed in detail in chapters 2 and 4.

Although there is no preparation of an acyclic dialkyl peroxide from singlet oxygen, the cyclo additions of singlet oxygen to certain alkenes and dienes afford cyclic peroxides. The [2 + 2] cycloaddition of singlet oxygen to an alkene[5,10] bearing no allylic hydrogens produces a four-membered ring peroxide, a 1,2-dioxetane, (Scheme 8). In some cases these can be isolated but they



i) $^1O_2$

(Scheme 8)

tend to decompose at ambient temperatures to give two carbonyl products, one of which is electronically excited and luminesces. The [4 + 2] cycloaddition of singlet oxygen[5,7] to a cisoid conjugated diene gives unsaturated six-membered ring peroxides, the 1,2-dioxenes. Most of the dienes used have been cyclic and hence have afforded bicyclic peroxide adducts. These may be reduced by the mild reducing agent diimide to the saturated bicyclic peroxides (Scheme 9).

(Scheme 9)

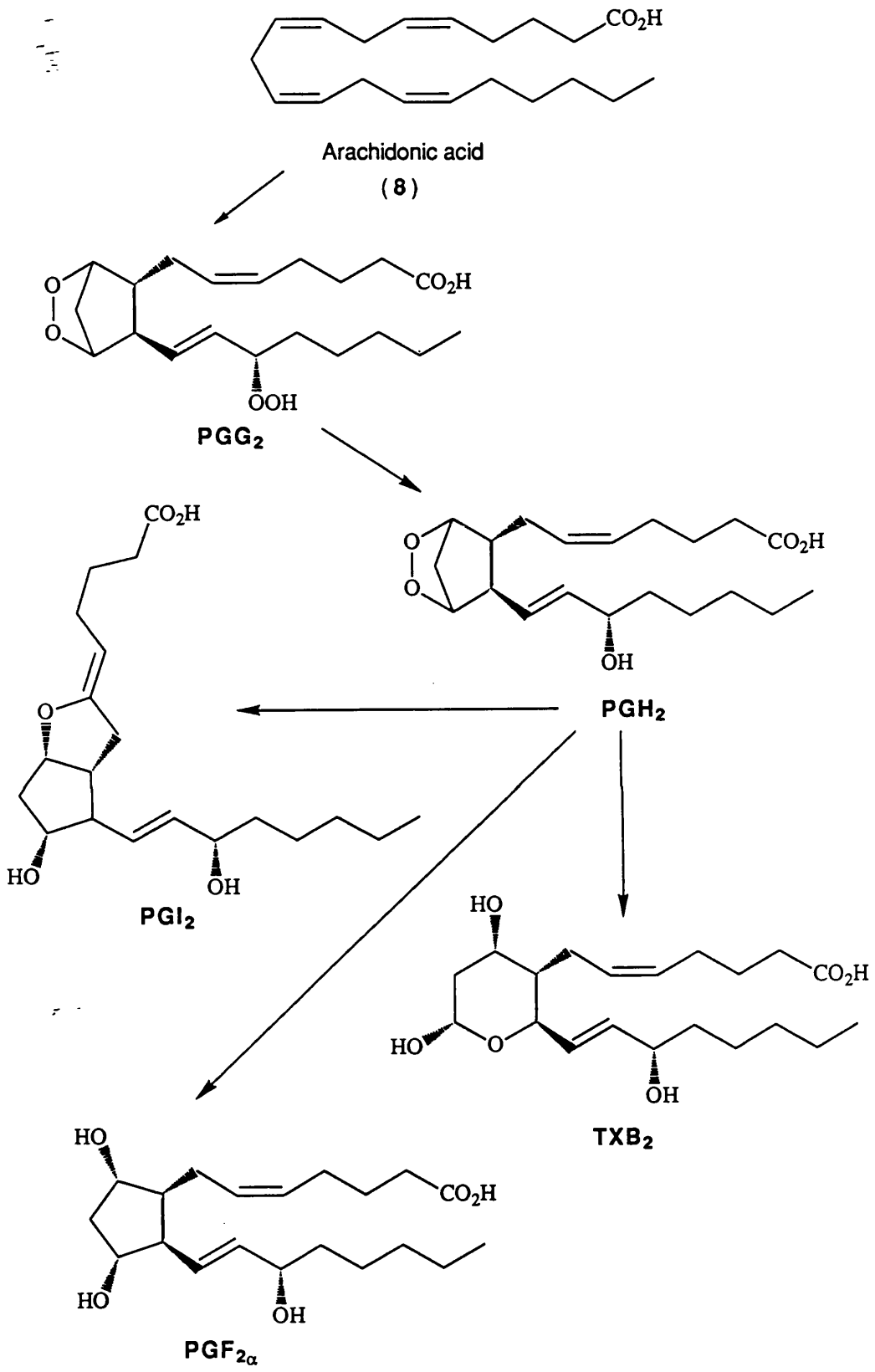
i) $^1O_2$
ii) HN=NH

3. Naturally Occurring Peroxides

The peroxidation of lipids[11] is a wide ranging topic, being implicated, for example, in the degradation of rubbers and in an important biosynthetic pathway. The intermediacy of a bicyclic peroxide had long been suspected in the biosynthesis of eicosanoids (the prostaglandin series, prostacyclins and thromboxanes) from arachidonic acid. This intermediate, PGH_2, was isolated in 1973[12] and since then the extent of the 'arachidonic acid cascade' has become apparent.[13,14]

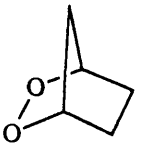
The intermediate PGH_2 arises from the peroxidation of arachidonic acid (8) at C-11 followed by two cyclizations and trapping of oxygen to give the C-15 hydroperoxy compound (PGG_2), and finally reduction to the C-15 hydroxy compound (PGH_2) (Scheme 10). These reactions are enzyme-controlled and attempts to model the process by free radical cyclizations[15,16,17] result in products epimeric (at C-8 and C-12) to PGH_2.

PGH_2 is converted into three main compound types, namely the prostaglandins, thromboxanes and prostacyclins exemplified by $PGF_{2\alpha}$, TXB_2 and PGI_2 in Scheme 10.

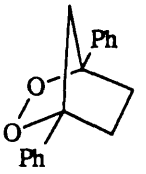

CO2H
Arachidonic acid
(8)
O
O
CO2H
OOH
PGG2
CO2H
O
O
OH
PGH2
CO2H
O
HO
OH
PGI2
HO
CO2H
HO
O
OH
TXB2
HO
CO2H
HO
OH
PGF2α

(Scheme 10)

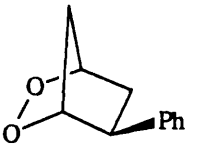
This discovery prompted a large amount of work in synthesizing[18] and modelling the PGH_2 molecule. Techniques were developed for the preparation of bicyclic[19] and cyclic peroxides such as 2,3-dioxa bicyclo[2.2.1]heptane (9)[20], its derivatives (10)[21] and (11)[22] for example, homologues (12)[23] and related 1,2-dioxanes and 1,2-dioxolanes.



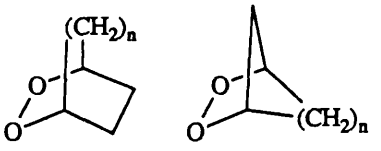
(9)



(10)

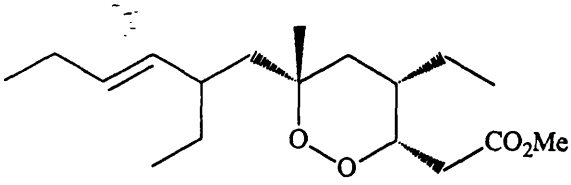


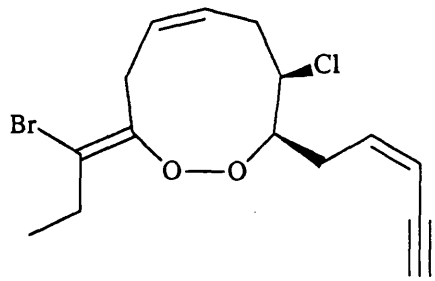
(11)

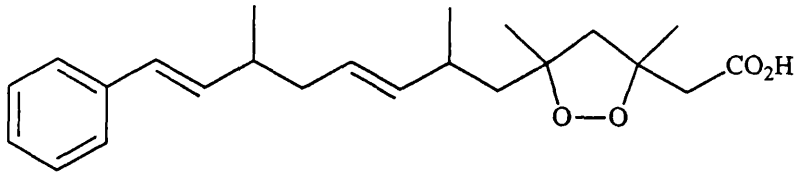


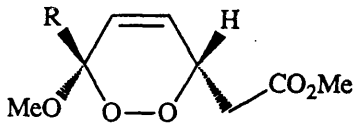
(12)

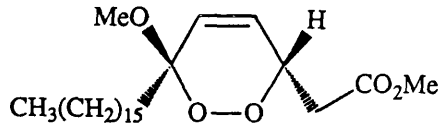
Interest has also been shown in other naturally occurring compounds which contain a cyclic peroxide moiety which appear to have important medical applications. A multitude of organic peroxides with a variety of structures have been isolated from marine organisms such as sponges[24], soft coral[25] and seaweed[9] (Scheme 11). The cyclic peroxides (13 a-d)[24d] isolated from the sponge Plakortis lita exhibit "significant anti-tumour activity". Other examples of naturally occurring peroxides are those isolated from plants, one of which, artemisinin (14) from artermisia annua, displays anti-malarial properties.[26]











(13)

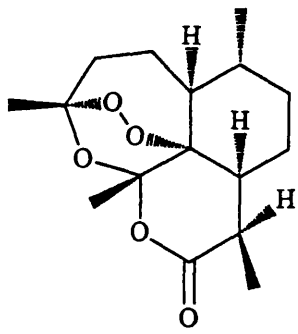
a) R = $-(CH_2)_{11}CH_3$

b) R = $-(CH_2)_9-CH=CH-CH_3$

c) R = $-(CH_2)_7-CH=CH-CH=CH-CH_3$

d) R = $-(CH_2)_9-CH=CH-CH=CH-CH_3$

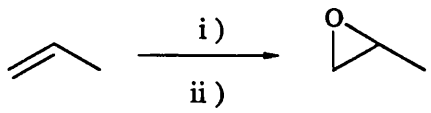
(Scheme 11)



(14)

4. Uses of Peroxides

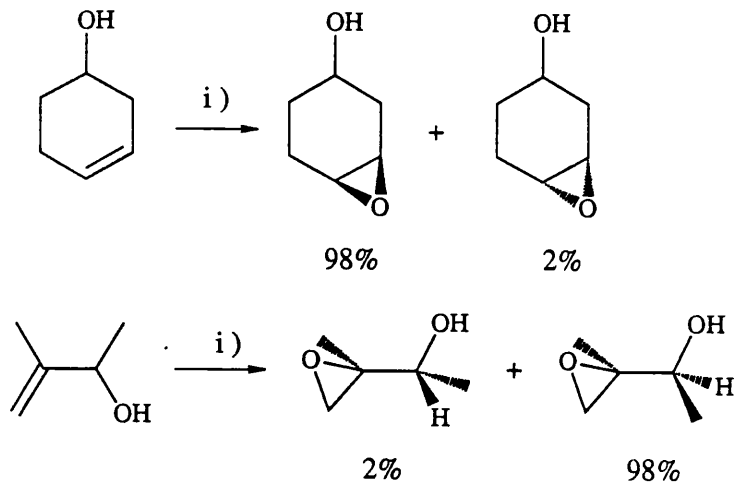
The industrial exploitation of peroxides includes the use of diacyl and peracetic acid as bleaching agents[2]. Peracetic acid has also been employed as an epoxidizing agent and as a fungicide/germicide in food processing plants[2]. Another industrial process, the preparation of phenol and acetone from cumene hydroperoxide was mentioned earlier. However, the main use of peroxides is as a radical source, especially as initiators in the polymer industry. The radicals are usually generated thermally or by the use of a reducing agent such as iron(II) sulphate. Finally, propylene oxide is now manufactured by the epoxidation of propylene by either t-butyl hydroperoxide/ molybdenum(VI) or 1-phenylethyl hydroperoxide/titanium (IV) systems (Scheme 12)[3].



i) Mo(VI), *t*-BuOOH or PhCH(Me)OOH
ii) Ti(IV), PhCH(Me)OOH

(Scheme 12)

This reaction, known as the Sharpless oxidation[3], has found great application in synthetic organic chemistry. t-Butyl hydroperoxide in conjunction with $Mo(CO)_6$ or $VO(acac)_2$ shows high stereoselectivity in the epoxidation of cyclic and acyclic allylic and homoallylic alcohols (Scheme 13). In a similar manner the asymmetric

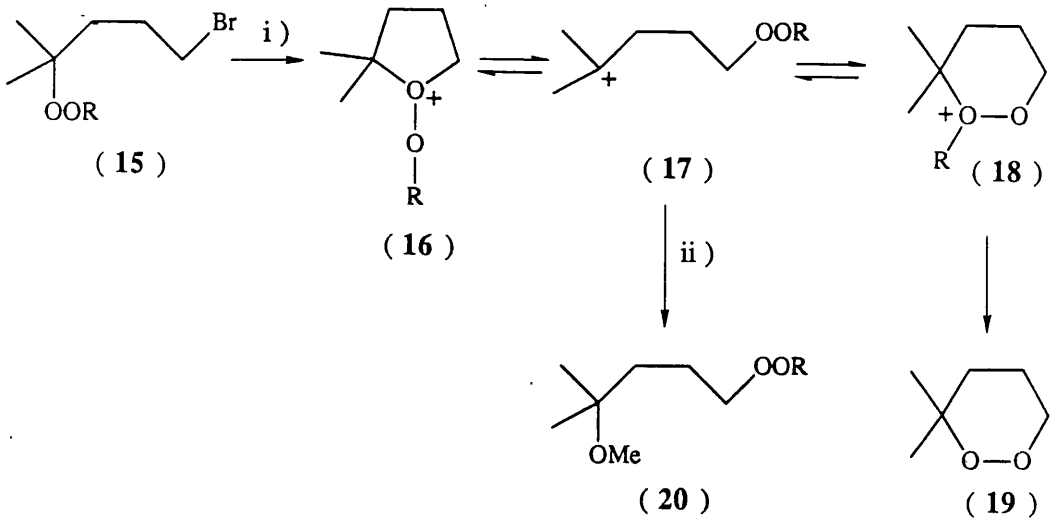


i) *t*-BuOOH , $VO(acac)_2$

(Scheme 13)

epoxidation of allylic alcohols has been effected by the use of t-butyl hydroperoxide with stoichiometric amounts of titanium(IV) isopropoxide and a chiral ligand ((+)- or (-)-diethyl tartrate). By this method, enantiomeric excesses of greater than 90% have been achieved.

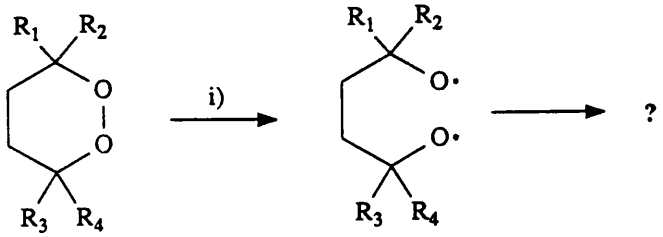
Peroxides can also be the precursors to reactive intermediates of theoretical interest such as peroxonium ions. Porter and Mitchell[23] have proposed the intermediacy of such species in the reaction of the bromo-peroxides (15) with a silver salt. In a non-nucleophilic solvent such as dichloromethane the dioxane (19) is obtained. However, in methanol the peroxy-transfer products (20) are produced. The mechanism offered involves the peroxonium ions (16) and (18) and the acyclic cations (17) which are trapped by methanol to give (20).



a) R = *t* -Bu
b) R = H

i) Ag^+
ii) MeOH

Other interesting species such as dioxyl biradicals are generated by the homolysis of the oxygen-oxygen bond in cyclic peroxides. This is usually brought about by pyrolysis (solution or flash vacuum) or photolysis (Scheme 14). The decompositions/rearrangements of several such species have been reported[28,29].



i) hυ or Δ

(Scheme 14)

The treatment of cyclic peroxides with electron transfer reagents such as iron(II) sulphate gives radical anions. The formation of such a species is suggested by

Kishi[22] as the first step in the rearrangement of the PGH_2 model (11). This reaction was intended to mimic the bioconversion of PGH_2 to TXB_2 and indeed some TXB_2- like products were formed.

The work described in this thesis includes the development of a new preparative method for 1,2-dioxolanes, the preparation of several novel 1,2-dioxanes, and an investigation into the effect of substitution patterns in the fate of biradicals and radical anions.

CHAPTER 2

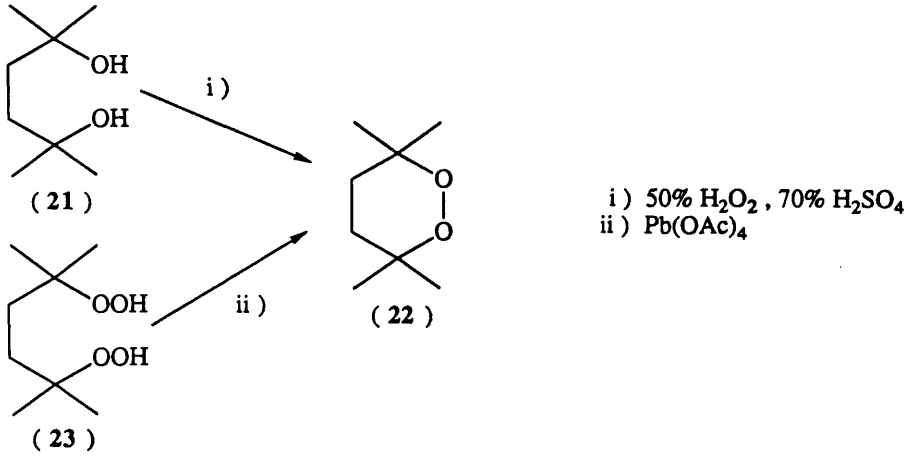
SYNTHESIS OF SOME NOVEL 1,2-DIOXANES

1. INTRODUCTION

The preparation of 1,2-dioxanes can be divided into four main areas according to the nature of the starting materials. 1,2-Dioxanes have been prepared from (i) 1,4-diols and their derivatives, (ii) by the peroxymercuration of dienes, (iii) by the cyclization of acyclic peroxides and, (iv) by the photooxygenation of cyclobutanes and alkenes.

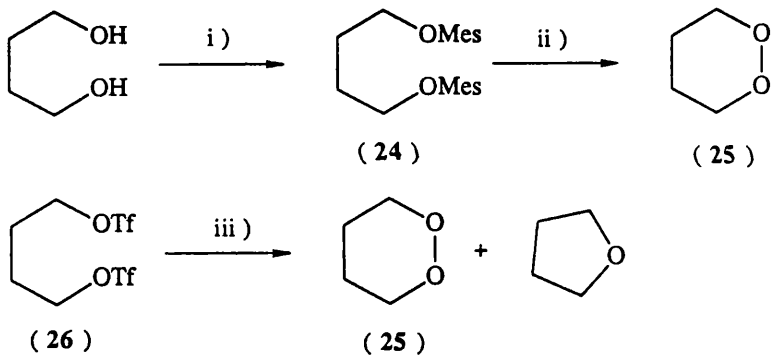
1.1 1,2-Dioxanes from 1,4-Diols and Derivatives

The first preparation of a 1,2-dioxane was reported in 1955 by Criegee.[30] It involved treating 2,5-dimethyl hexane-2,5-diol (21) with acidified hydrogen peroxide whereby 3,3,6,6-tetramethyl-1,2-dioxane (22) was isolated in a yield of 28%. A means whereby the bis hydroperoxide (23) could be converted to the dioxane (22) upon treatment with lead(IV) acetate was also given. A year later,



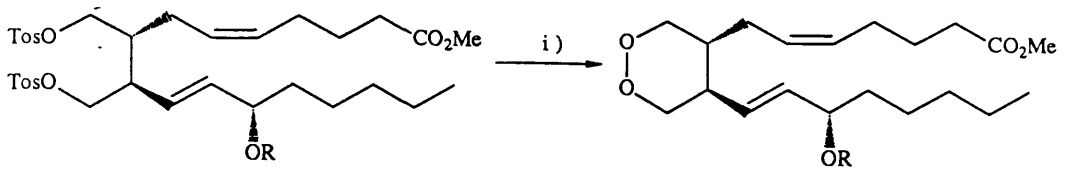
Criegee[31] reported the preparation of unsubstituted 1,2-dioxane (25) in a yield of 30% by treating the methanesulphonate ester (24) of butane-1,4-diol with basic hydrogen peroxide. The mechanism of this reaction is presumably S_N2.

This reaction has been improved by Salomon and Salomon[32] by the use of a novel peroxide transfer reagent. Thus, the reaction of bis(tri-n-butyltin) peroxide with the bistrifluoromethanesulphonate (26) gave 1,2-dioxane (25) in a yield of 65%, together with a yield of 24% of tetrahydrofuran.



i) MesCl , pyridine
ii) KOH , 30% H_2O_2 , MeOH
iii) (n -$Bu_3SnO)_2$, CH_2Cl_2 , 15 mins.

The p-toluenesulphonate esters (27) of the 1,4-diols derived from prostaglandin A_2 (PGA_2) were used to prepare the monocylic PGH_2 analogues 10-nor-9,11-secoprostaglandins (28)[33]. Reaction of (27) with potassium superoxide in DMF afforded the dioxanes (28) in yields of 56% and 69% respectively.



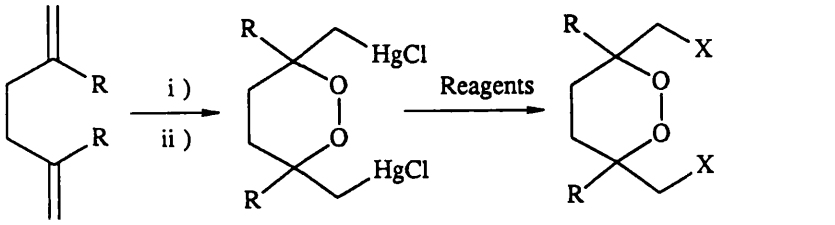
(27) (28)

a) R = COMe
b) R = H

i) KO_2 , DMF

1.2 1,2-Dioxanes from Dienes

Bloodworth, Loveitt and Khan[34] prepared 1,2-dioxanes by the peroxymercuration of dienes. The reaction of the 1,5-dienes (29) with mercury(II) nitrate and 85% hydrogen peroxide in dichloromethane followed by anion exchange with potassium chloride gave the bismercurials (30). Treatment of these mercurials with either bromine in dichloromethane or basic sodium borohydride afforded either the dibromides (31) or the dioxanes (32) and (22) respectively. In addition to these examples, hexa-1,4-diene (33) underwent peroxymercuration followed by bromodemercuration to give 4-bromo-6-bromomethyl-3-methyl-1,2-dioxane (34).



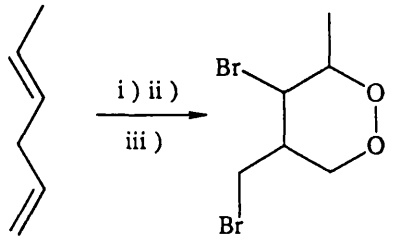
(29) (30)

(31) X = Br
(32) X = H , R = H
(22) X = H , R = Me

a) R = H
b) R = Me

i) $Hg(NO_3)_2$. H_2O , 85% H_2O_2 , CH_2Cl_2
ii) KCl_{aq}

Reagents X = Br Br_2 , CH_2Cl_2
X = H $NaBH_4$, 3MNaOH , CH_2Cl_2



(33) (34)

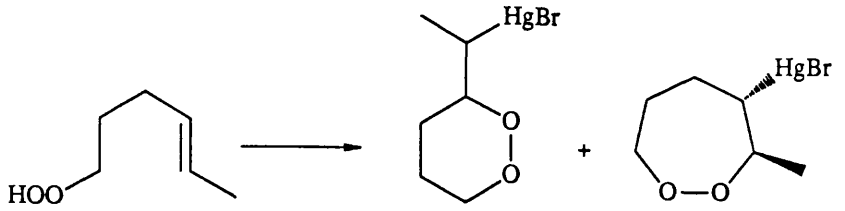
i) $Hg(NO_3)_2$. H_2O , 85% H_2O_2 , CH_2Cl_2
ii) KCl_{aq}
iii) Br_2 , CH_2Cl_2

1.3 1,2-Dioxanes from Acyclic Peroxides

The cyclization of acyclic peroxides has provided several routes to 1,2-dioxanes. Methods used include (i) cycloperoxymercuration of unsaturated hydroperoxides, (ii) cyclization of 4-penten-1-peroxyl radicals, (iii) the treatment of bromoalkyl peroxides with silver salts, and (iv) the treatment of δ-aryl hydroperoxides with lead (IV) acetate.

1.3.1 Cycloperoxymercuration

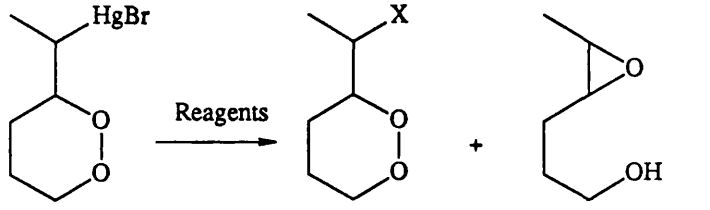
The cycloperoxymercuration of unsaturated hydroperoxides has been used to prepare mercurio-1,2-dioxanes. Porter et al.[35] effected the cyclizations of several unsaturated hydroperoxides upon treatment with mercury(II) nitrate. Most of the examples of this reaction given by Porter involved the cyclization of γ,δ-unsaturated hydroperoxides to 1,2-dioxolanes, only one gave a 1,2-dioxane. However, the hydroperoxide (35) used did not have a terminal alkene function and the competition between 6-exo and 7-endo[38] cyclizations



(35) (36) (37)

i) $Hg(NO_3)_2.H_2O$, CH_2Cl_2
ii) H_2O , KBr

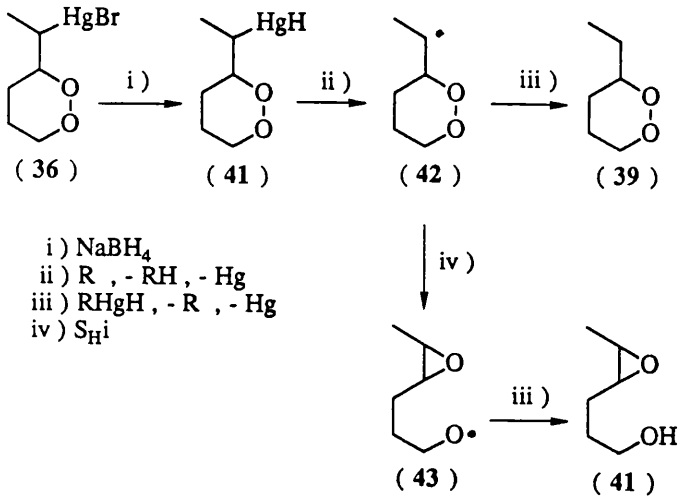
resulted in a 3:1 mixture of dioxane (36) and dioxepane (37). The mixture was separated and the 3-(1-bromomercurioethyl)-1,2-dioxane (36) was treated with bromine in dichloromethane to afford 3-(1-bromoethyl)-1,2-dioxane (38) in a yield of 38%. Treatment of (36) with basic borohydride afforded 3-ethyl-1,2-dioxane (39) in a yield of less than 10% and the epoxyalcohol (40) in a



(36) (38) X = H (39) X = Br (40) X = H

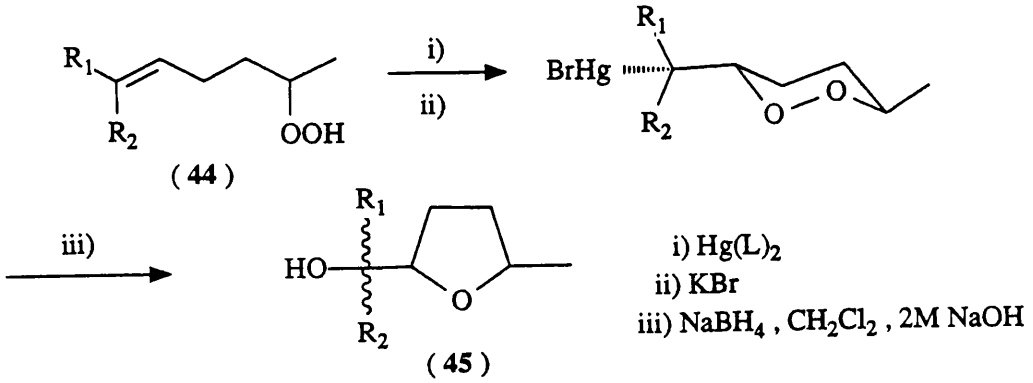
Reagents X = H $NaBH_4$, 3M NaOH , CH_2Cl_2
X = Br Br_2 , CH_2Cl_2

yield of 90%. This product distribution was explained by considering the mechanism of hydridodemercuration. The organomercury bromide (36) is converted into the organomercury hydride (41) followed by hydrogen abstraction and loss of mercury to generate the radical (42). This radical can either abstract a hydrogen from

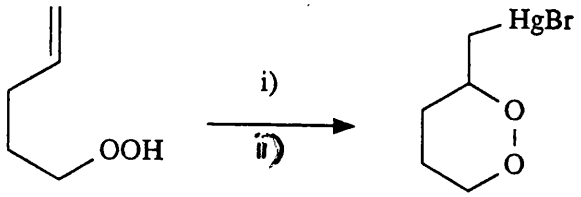


the organomercury hydride (41) to give dioxane (39) or undergo an S_Hi reaction to give the epoxyalcohol (40) via the alkyl radical (43).

Three other examples of cycloperoxymercuration are reported by Porter and Zuraw[36]. The hydroperoxides (44) when treated with mercury(II) pivalate afforded mercurio dioxanes. Reaction of these with sodium borohydride followed by treatment of the crude products with trichloroacetic acid (TCA) is reported to yield tetrahydrofuranols (45). No mention is made of 1,2-dioxane products being recovered, though one would expect their formation in such a reaction.



The cyclization of 4-penten-1-hydroperoxide (46) upon treatment with mercury (II) nitrate was also mentioned by Bloodworth and Khan[34b], but no further reactions were performed upon the mercurial (47).

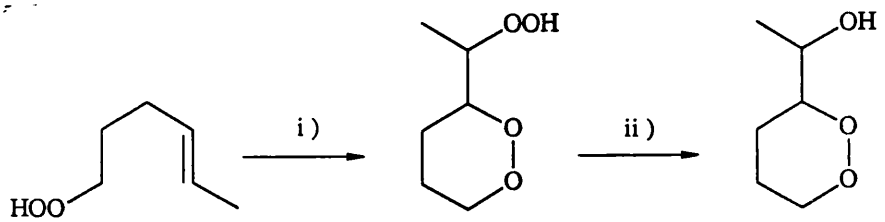


(46) (47)

i) $Hg(NO_3)_2$
ii) KBr

1.3.2 Cyclization of peroxyl radicals

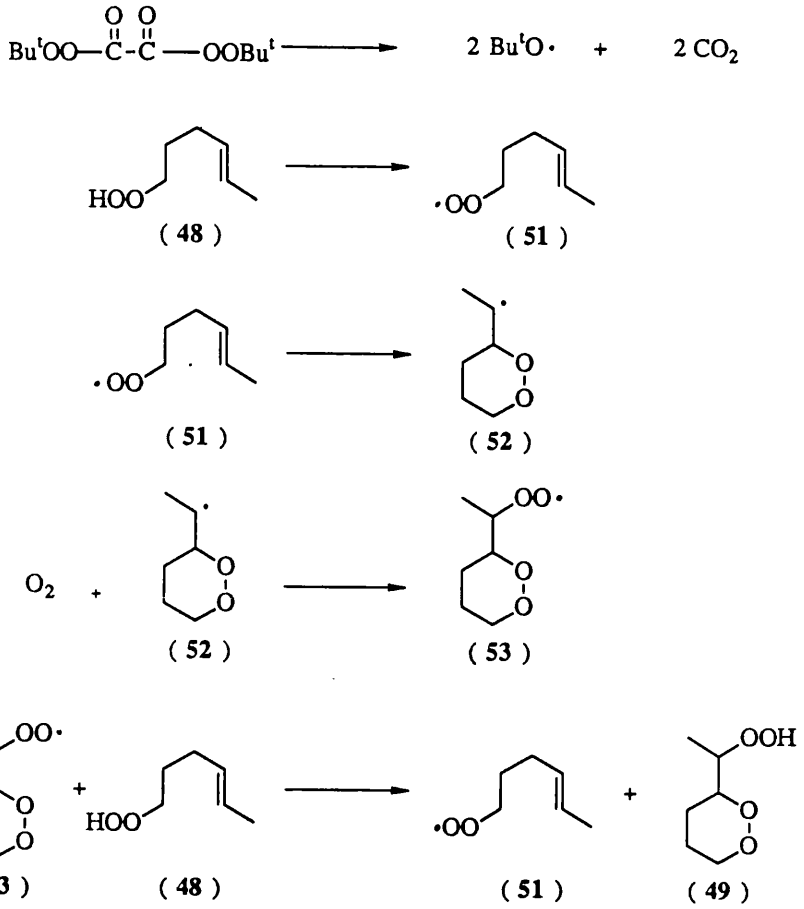
Porter et. al.[37] have reported the cyclizations of unsaturated hydroperoxides upon treatment with di-t-butylperoxalate (DBPO) in oxygenated benzene for 48 hr. Thus, the hydroperoxide (48) afforded 3-(1-hydroperoxyethyl)-1,2-dioxane (49), which was reduced to the alcohol (50) upon treatment with triphenylphosphine.



(35) (49) (50)

i) DBPO, C_6H_6, O_2, 48 hr.
ii) Ph_3P

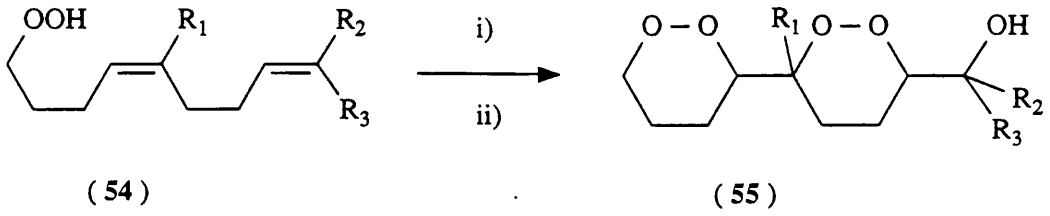
The mechanism is that of a free radical chain initiated by thermolysis of DBPO to afford t-butoxyl radicals. Abstraction of a hydrogen by a t-butoxyl



radical generates the peroxyl radical (51) which cyclizes by the 6-exo-Trig[38] mode to the alkyl radical (52). This alkyl radical is trapped by oxygen to give a second peroxyl radical (53) which abstracts a hydrogen from the hydroperoxide (48) to give the product (49) and a peroxyl radical (51), thus propagating the chain.

This technique has also been used by Porter et. al.[39] to study the serial cyclizations of diene hydroperoxides as a model for the degradation of rubbers and polybutadienes by autoxidation. Treatment of the diene hydroperoxides (54) with DBPO in oxygenated benzene

followed by treatment with triphenyl phosphine afforded the two diperoxides (55).



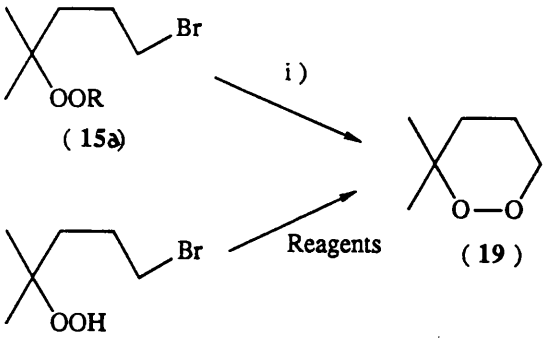
(54) (55)

i) C_6H_6 , air , DTBO or DTBH , 30°C
ii) Ph_3P

a) $R_1=R_2=H$, $R_3=Et$
b) $R_1=R_2=R_3=Me$

1.3.3 Cyclization of bromoalkyl peroxides

Another method of 1,2-dioxane preparation is that described by Porter and Mitchell[27], whereby the reaction of the bromoalkyl peroxides (15) with silver tetrafluoroborate affords 3,3-dimethyl-1,2-dioxane (19). The reaction of the bromoalkyl hydroperoxide (15b) with bases also gave the dioxane (19) in good yields.



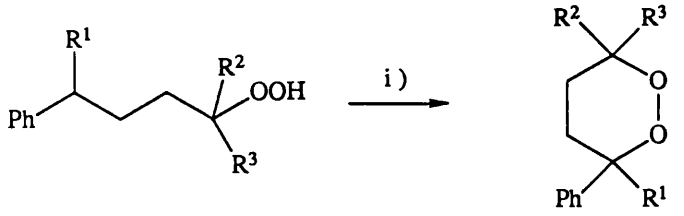
a) R = *t*-Bu
b) R = H

i) $AgBF_4$, CH_2Cl_2

Reagents NaH , Pentane
or NaOMe , MeOH

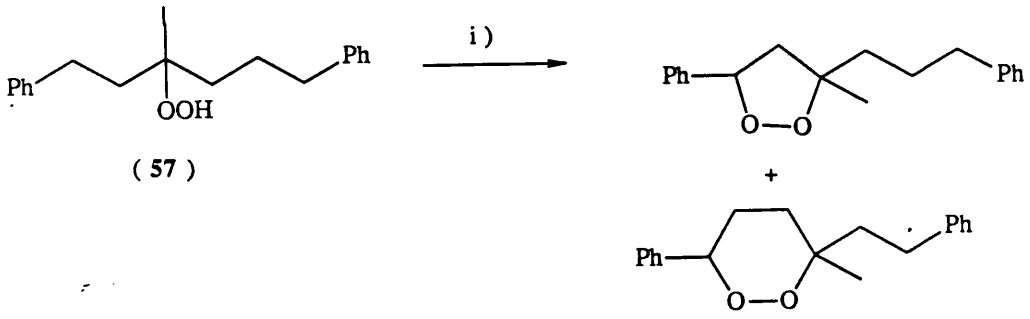
1.3.4 Cyclization of δ-aryl hydroperoxides

The cyclization of hydroperoxides (56) (57) (58) with a δ-benzylic hydrogen upon treatment with lead(IV) acetate (Barton-Type Reaction) has been employed by Kropf and coworkers[40,41] to prepare several dioxanes (59) (60) (61). The mechanism suggested for these cyclizations

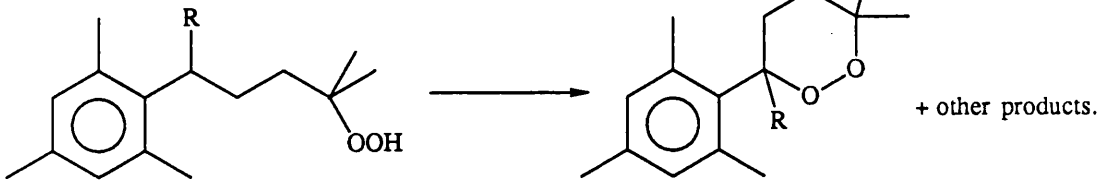


(56) (59)

a) R_1= H R_2= Me R_3= Me
b) R_1= Me R_2= Me R_3= Me
c) R_1= Me R_2= Me R_3= Ph
d) R_1= Ph R_2= Me R_3= Me



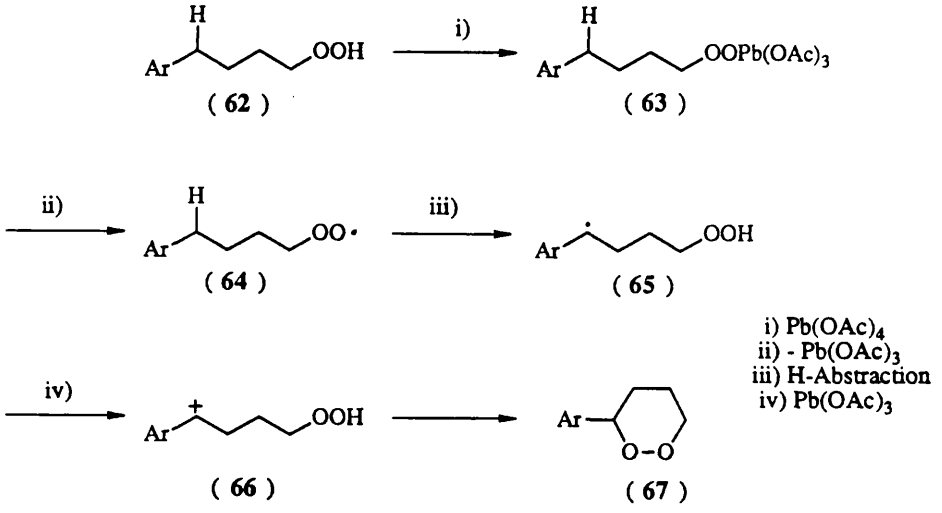
(57) (60)



(58) (61)

i)$Pb(OAc)_4$, pentane

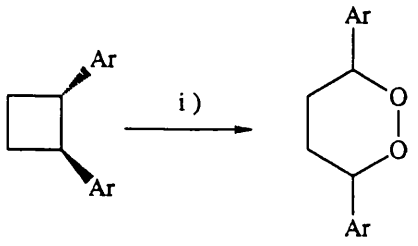
starts with the reaction of lead(IV) acetate with the hydroperoxide (62) to give the salt (63) which dissociates to the peroxyl radical (64) and lead(III) acetate. The peroxyl radical abstracts the benzylic hydrogen either inter- or intra-molecularly to give the benzylic radical (65). This radical undergoes an electron transfer to the lead(III) acetate and the resultant benzylic carbocation (66) undergoes cyclization to the dioxane (67).



1.4 1,2-Dioxanes by Photooxygenation

1,2-Dioxanes have also been prepared by the photooxygenation of a cyclobutane and alkenes. However, this technique seems to be restricted to heavily aromatically substituted starting materials.

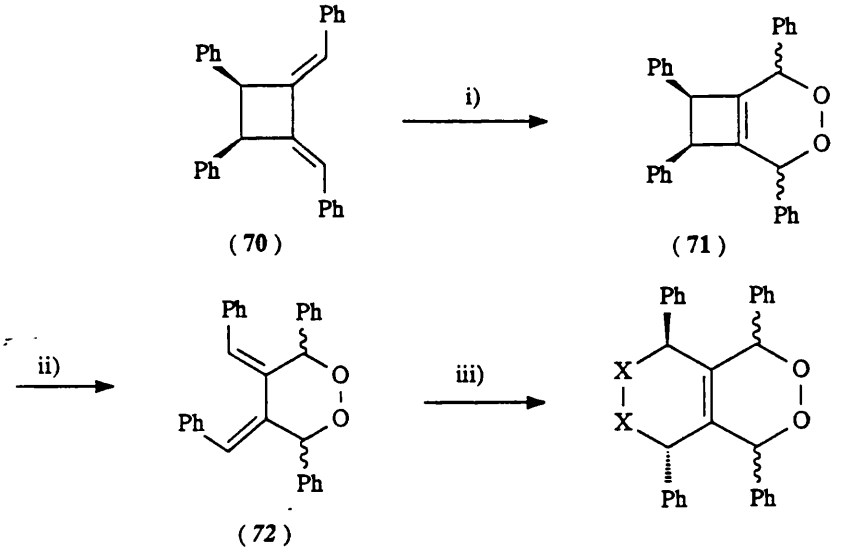
Mizuno et. al.[42] have prepared the dioxane (69) by the 9,10-dicyanoanthracene (DCA) sensitized photooxygenation of trans-1,2-di(carbazol-9-yl) cyclobutane (68).



(68) (69)

i) hυ , DCA , O_2 , MeCN

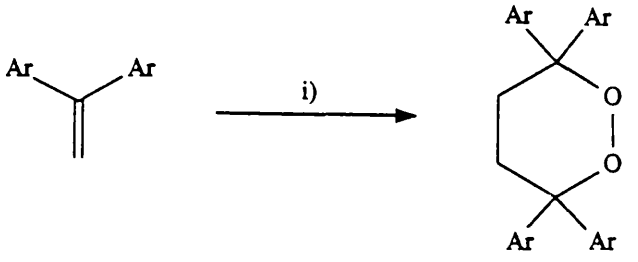
Rigaudy et. al.[43] have treated a cyclobutane (70) with singlet oxygen. However the singlet oxygen added in a [4 + 2] cycloaddition to the diene function to give the dihydro-dioxin (71) which underwent thermal rearrangement to the dioxane (72) which was treated with dienophiles to afford further dihydro-dioxins.



(70) (71) (72)

i) $^1O_2$
ii) Δ
iii) X = O, X = O, N-Me, O

The preparation of 1,2-dioxanes from alkenes has also been reported. Haynes et. al.[44] found that when 1,1-diarylethenes (73 a-d) were irradiated in dichloromethane in the presence of oxygen and catalytic amounts of antimony(V) chloride, the 3,3,6,6-tetraaryl-1,2-dioxanes (74 a-d) were formed in high yields (80% - 90%).

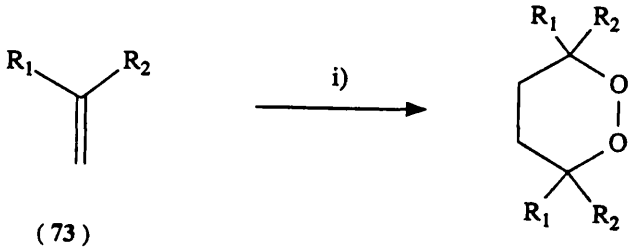


(73) (74)

a) Ar = C_6H_5
b) Ar = p-C_6H_4Me
c) Ar = p-$C_6H_4CMe_3$
d) Ar = p-C_6H_4OMe

i) O_2, $SbCl_5$, CH_2Cl_2, hυ

Similarly Gollnick and Schnatterer[45] report that electron-rich 1,1-diarylethenes (73 d-i) undergo electron transfer photooxygenation in the presence of DCA to give the 3,3,6,6-tetraaryl-1,2-dioxanes (74 d-i) in isolated yields of 80% - 90%.

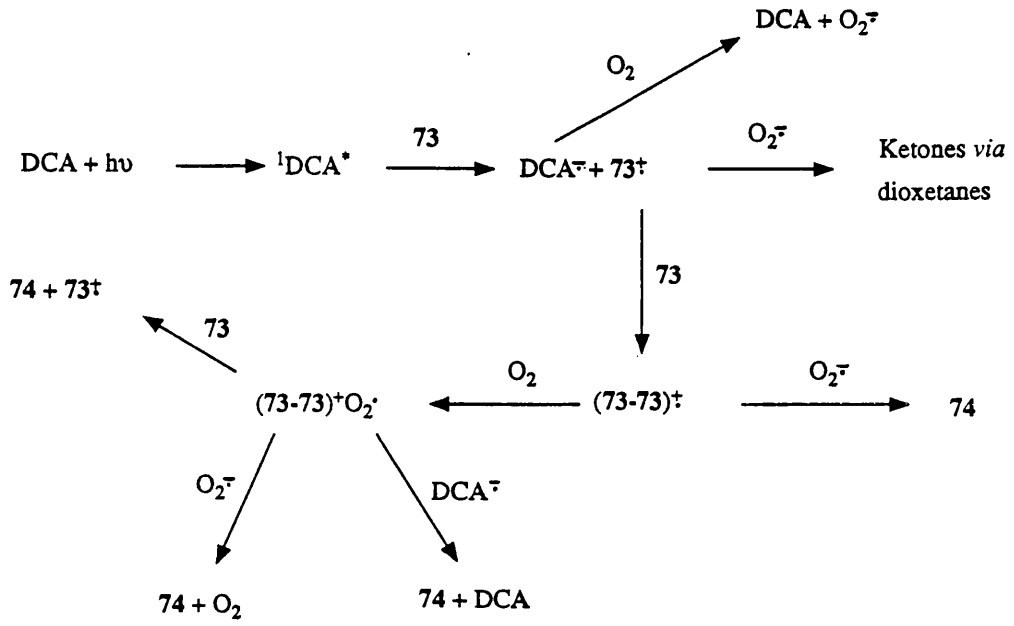


(73) (74)

i) DCA, O_2, CH_3CN, hυ

d) R_1 = p-$MeOC_6H_4$ R_2 = p-$MeOC_6H_4$
e) R_1 = p-$MeOC_6H_4$ R_2 = C_6H_5
f) R_1 = o-$MeOC_6H_4$ R_2 = o-$MeOC_6H_4$
g) R_1 = p-$MeOC_6H_4$ R_2 = p-ClC_6H_4
h) R_1 = p-$Me_2NC_6H_4$ R_2 = p-$Me_2NC_6H_4$
i) R_1 = Carbazoyl-9-yl R_2 = H

The mechanism of 1,2-dioxane formation in this reaction is outlined in scheme 15. The photo-oxygenation of a cyclobutane by Mizuno mentioned above is reported to proceed by a similar mechanism.



2 RESULTS AND DISCUSSION

Although the peroxymercuration/demercuration[35] of δ,ϵ-unsaturated hydroperoxides has been reported, it has not been fully exploited in the synthesis of 1,2-dioxanes. In this work it was employed to prepare a series of 1,2-dioxanes with various substituents at the 3,5, and 6 positions. In order to achieve the desired range of 1,2-dioxanes, it was necessary to employ three different methods to prepare the appropriate δ,ϵ-unsaturated hydroperoxides. Firstly, the silver salt assisted nucleophilic substitution reaction of an appropriate tertiary bromide with hydrogen peroxide was used to prepare tertiary hydroperoxides. Secondly, the oxidation of N-alkenyl-N'-tosylhydrazines was used to prepare some primary and secondary hydroperoxides and finally, two examples of primary hydroperoxides were prepared by nucelophilic displacement from the corresponding methanesulphonate esters.

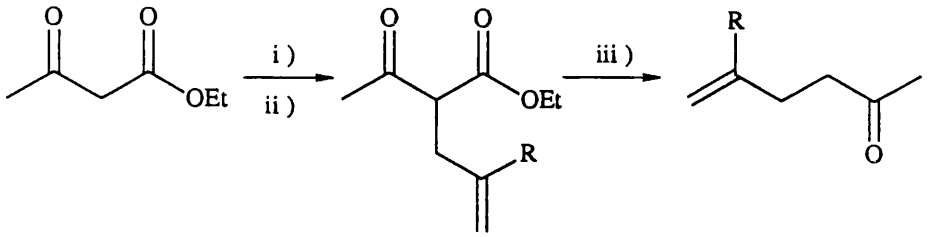
The syntheses of the 1,2-dioxanes are grouped according to the method of hydroperoxide preparation.

2.1 1,2-Dioxanes via hydroperoxides prepared from tertiary bromides

Following the successful synthesis by Hay-Motherwell[46] of 2-methyl-5-hexen-2-hydroperoxide (75) from the corresponding bromide, it was decided to use this method as a basis for preparing examples of 3,3,6-trialkyl

and 3,3,6,6-tetraalkyl-1,2-dioxanes.

The starting point of the synthetic route was a 5-hexen-2-one, two examples of which were used, 5-hexen-2-one (76) itself and 5-methyl-5-hexen-2-one (77). These two ketones were easily prepared in yields of approximately 40% by the alkylation, hydrolysis and subsequent decarboxylation of ethyl acetoacetate.



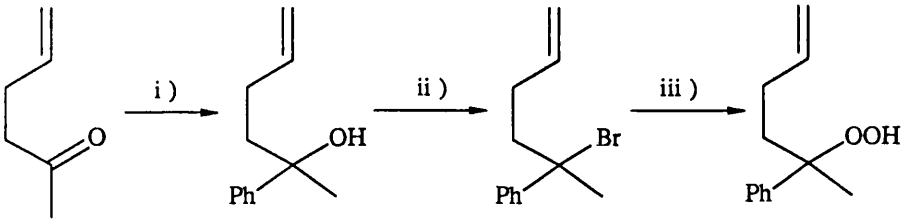
i) NaOEt , EtOH
ii) CH_2=CR-CH_2X
iii) NaOH $_{aq}$, Δ

(76) R = H
(77) R = Me

2.1.1 <u>3,6-Dimethyl-3-phenyl-1,2-dioxane (82)</u>

The reaction of 5-hexen-2-one (76) with phenylmagnesium bromide afforded 2-phenyl-5-hexen-2-ol (78) in a yield of 79% after distillation. Treatment of this alcohol with phosphorus tribromide gave crude 2-bromo-2-phenyl-5-hexene (79) in a yield of 93%. An attempt to distil the bromide at an oil bath temperature of ~80°C and at 0.09 mm Hg resulted in extensive elimination of hydrogen bromide. However, the crude bromide, when treated with a slight excess of silver tetrafluoroborate and an approximately ten-fold excess of

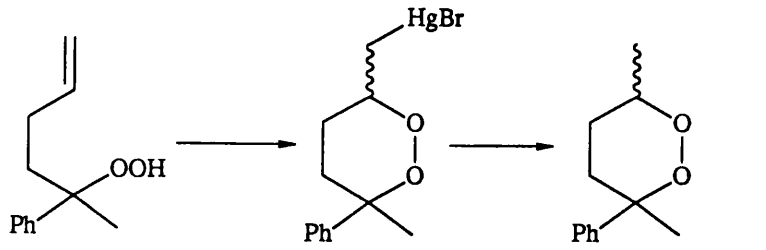
hydrogen peroxide in ether, afforded crude 2-phenyl-5-hexen-2-hydroperoxide (80) in yields of 88% and 91%. The ^{13}C-n.m.r. spectrum of the crude hydroperoxide showed that little, if any, of the corresponding dialkylperoxide was



(76) (78) (79) (80)

i) PhMgBr , Et_2O
ii) PBr_3 , pyridine , < 0°C
iii) $AgBF_4$, H_2O_2 , Et_2O , -78°C

present. The hydroperoxide (80) was treated with mercury(II) nitrate in dichloromethane followed by aqueous potassium bromide. The resulting crude mixture of diastereoisomeric 6-bromomercuriomethyl-3-methyl-3-phenyl-1,2-dioxanes (81) was treated with basic sodium borohydride solution at < 0°C to afford <u>cis</u> and <u>trans</u>-3,6-dimethyl-3-phenyl-1,2-dioxane (82) in a yield of only 15% (based on the hydroperoxide).



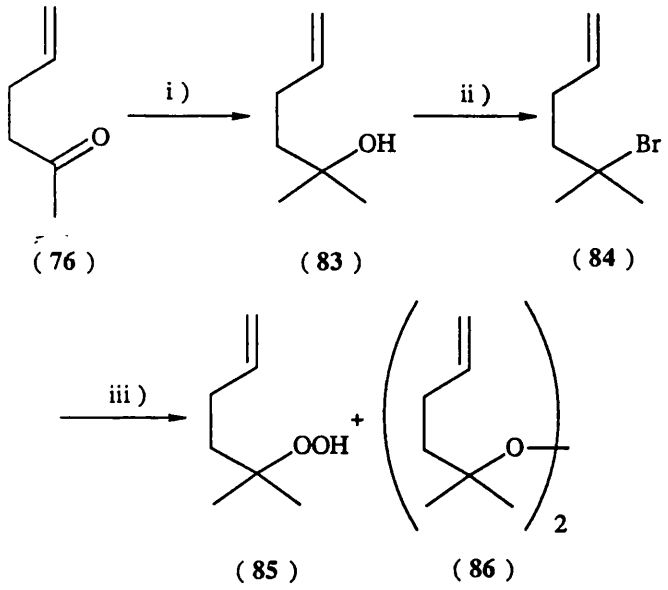
(80) (81) (82)

i) $Hg(NO_3)_2$. H_2O , CH_2Cl_2
ii) H_2O , KBr
iii) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C

2.1.2 3,3,6-Trimethyl-1,2-dioxane (88)

5-Hexen-2-one (76) was treated with methylmagnesium iodide to afford 2-methyl-5-hexen-2-ol (83) in a yield of 75% after distillation. The reaction of this alcohol with phosphorus tribromide gave crude 2-bromo-2-methyl-5-hexene (84) in a yield of 82%, but this was reduced to 39% upon vacuum distillation. Treatment of this bromide with silver tetrafluoroborate and hydrogen peroxide in ether gave a mixture of the hydroperoxide (85) and the corresponding dialkyl peroxide (86). Separation by HPLC afforded 2-methyl-5-hexen-2-hydroperoxide (85) in a yield of 23% based on the bromide.

Reaction of the hydroperoxide with mercury(II) nitrate in dichloromethane followed by anion exchange with

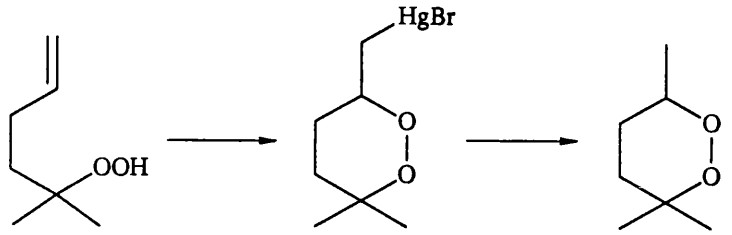


(76) (83) (84)

(85) (86)

i) MeMgI , Et_2O
ii) PBr_3 , pyridine , < O°C
iii) $AgBF_4$, H_2O_2 , Et_2O , -78°C

potassium bromide afforded 6-bromomercuriomethyl-3,3-dimethyl-1,2-dioxane (87) in a yield of 67% after purification by column chromatography. Hydridodemercuration of this mercurial with basic sodium borohydride gave 3,3,6-trimethyl-1,2-dioxane (88), isolated in a yield of 68% by column chromatography.



(85) (87) (88)

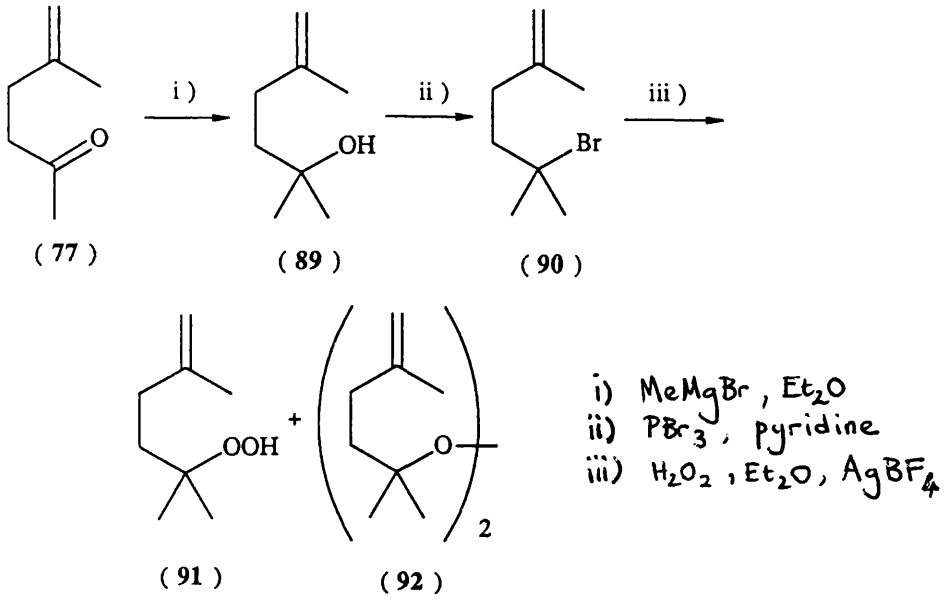
i) $Hg(NO_3)_2$, H_2O , CH_2Cl_2
ii) H_2O , KBr
iii) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C

2.1.3 3,3,6,6-Tetramethyl-1,2-dioxane (22)

The title compound is a known dioxane, which has been prepared from 2,5-dimethylhexane-2,5-diol (21)[30], 2,5-dimethylhexane-2,5-bishydroperoxide (23), and 2,5-dimethyl-1,5-hexadiene (29a)[34].

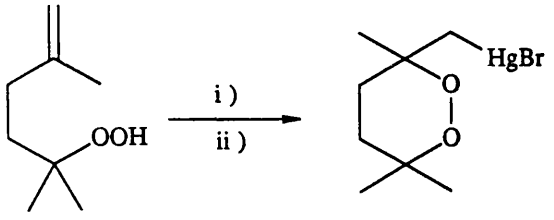
5-Methyl-5-hexen-2-one (77) was treated with methylmagnesium iodide to afford 2,5-dimethyl-5-hexen-2-ol (89). Reaction of this alcohol with phosphorus tribromide gave 2-bromo-2,5-dimethyl-5-hexene (90) in a yield of 26% after distillation. Treatment of the bromide with silver tetrafluoroborate and hydrogen peroxide in ether gave a mixture of 2,5-dimethyl-5-hexen-2-hydroperoxide (91) and

the dialkyl peroxide (92). Separation by HPLC afforded the hydroperoxide (91) in a yield of 41% based on the bromide.



(77) (89) (90) (91) (92)

Reaction of the hydroperoxide with mercury(II) nitrate in dichloromethane followed by anion exchange with potassium bromide gave 3-bromomercuriomethyl-3,6,6-trimethyl-1,2-dioxane (93), isolated in a yield of 46% by column chromatography.

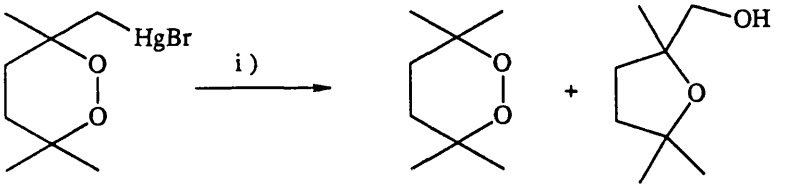


(91) (93)

i) $Hg(NO_3)_2$, H_2O, CH_2Cl_2
ii) H_2O, KBr

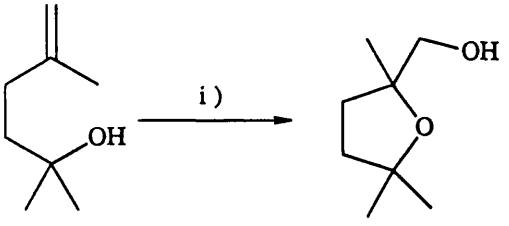
The 20 MHz ^{13}C-nmr spectrum of the mercurial (**93**) at 30°C showed a mixture of broad and sharp peaks, whereas the 50 MHz ^{13}C-nmr spectrum at -50°C showed sixteen peaks (Figure 1). This was taken to indicate that at 30°C (and 20 MHz) the rate of ring inversion was such as to cause coalescence of the peaks of individual conformers. At -50°C (and 50 MHz) the rate of ring inversion was slow enough for the conformers to be 'frozen out'.

The hydridodemercuration of the mercurial (**93**) upon treatment with basic sodium borohydride afforded 3,3,6,6-tetramethyl-1,2-dioxane (**94**) in a yield of 46% after column chromatography. A slow-running, non-peroxidic fraction was also collected and on the basis of spectroscopic evidence was identified as 2-hydroxymethyl-2,5,5-trimethyltetrahydrofuran (**95**). This was confirmed



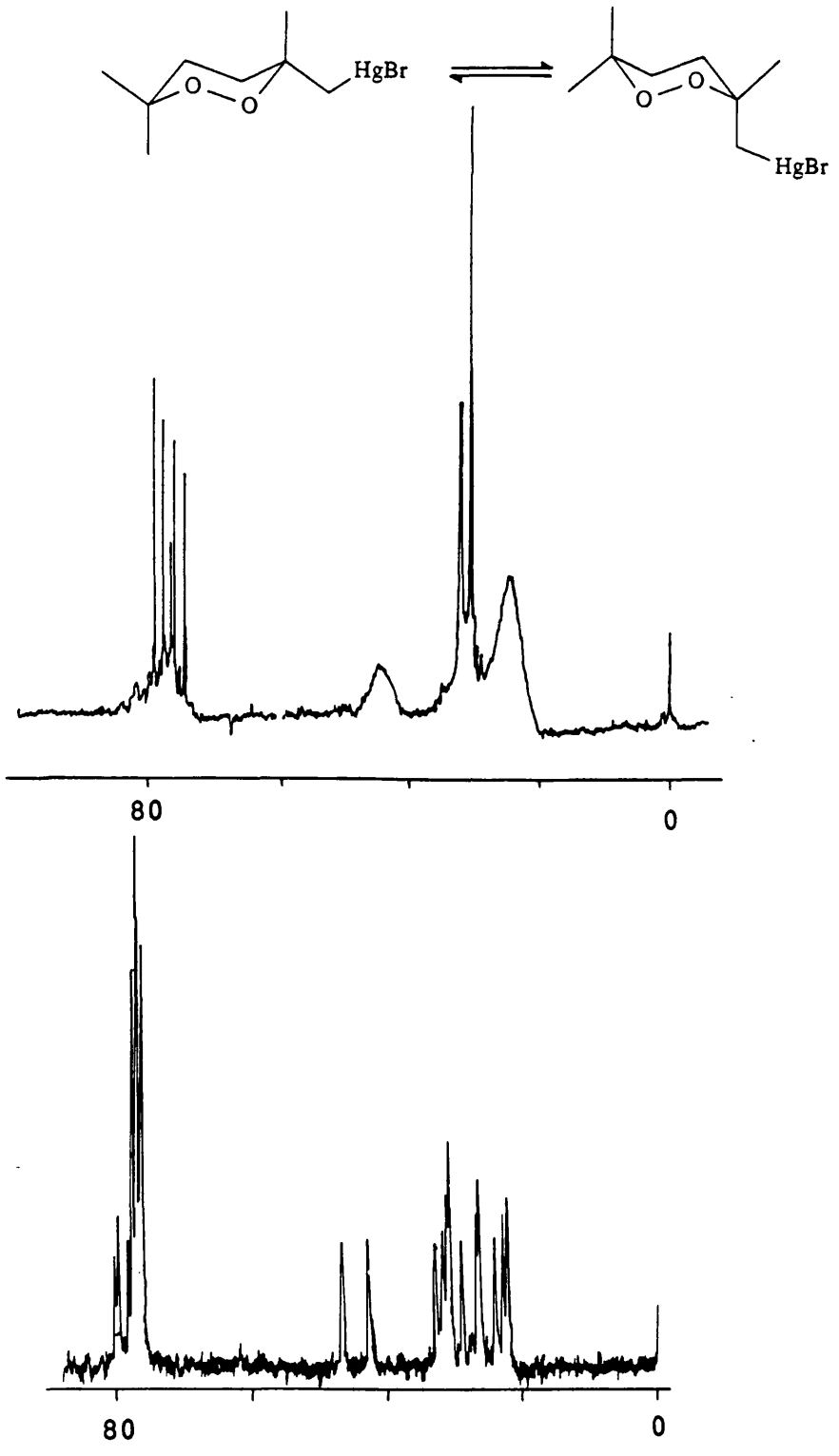
(93) (94) (95)

i) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C



(89) (95)

i) MCPBA , CH_2Cl_2

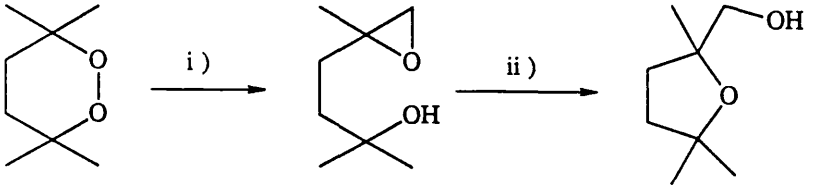


(Figure 1)

^{13}C-nmr Spectrum of 3-bromomercuriomethyl-3,3,6-trimethyl-1,2-dioxane (93) at 30°C (20MHz) and -50°C (50MHz).

by the preparation of an authentic sample of (95) by the epoxidation/acid catalysed cyclization of 2,5-dimethyl-5-hexen-2-ol (89).

The furanol (95) is taken to be the rearranged product of the epoxyalcohol (96) which one would expect to be formed by an S_Hi reaction of the intermediate radical (97)[36,47].

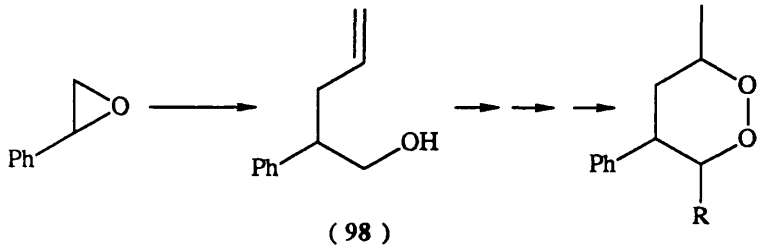


(97) (96) (95)

i) S_Hi , +H
ii) H^+

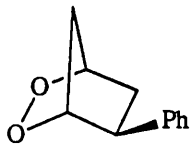
2.2 1,2-Dioxanes via hydroperoxides prepared from N-alkenyl-N'-tosylhydrazines

The regiospecific ring opening of styrene oxide with allylmagnesium bromide affords 2-phenyl-4-penten-1-ol (98). The availability of this alcohol held out the possibility of the synthesis of 4-phenyl-1,2-dioxanes. These were thought to be interesting compounds for the rearrangement/decomposition studies since they would bear



(98)

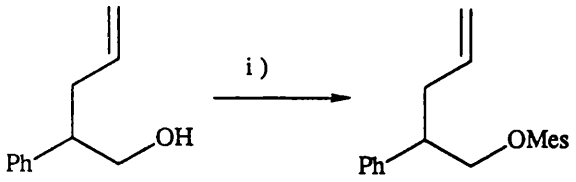
a structural similarity to the dioxane fragment of the PGH_2 nucleus and the PGH_2 model (11) of Kishi[22].



(11)

2.2.1 3-Methyl-5-phenyl-1,2-dioxane (105)

The preparation of a primary hydroperoxide from the alcohol is normally effected by perhydrolysis of the methanesulphonate ester[48]. 2-Phenyl-4-penten-1-methanesulphonate (**99**) was easily prepared in a yield of 96% upon treatment of the alcohol (**98**) with methanesulphonyl chloride. However, the methanesulphonate (**99**) proved to be unreactive to the usual perhydrolysis conditions of 30% hydrogen peroxide and 50% potassium hydroxide in methanol, and 90% - 100% of it was recovered.



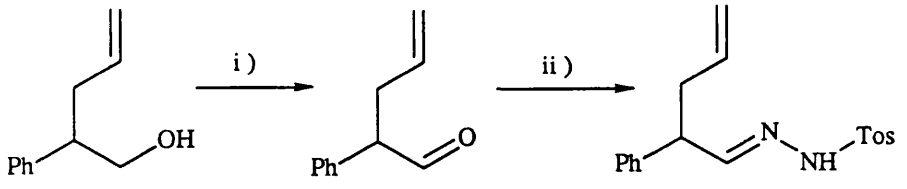
(98) (99)

i) MesCl , pyridine , < O °C

This failure prompted the search for an alternative route, and that reported by Caglioti[49] seemed promising. Caglioti claims high yields (87% - 95%) of hydroperoxides, even sterically hindered ones such as neo-pentyl

hydroperoxide, from the oxidation of N-alkyl-N'-tosylhydrazines with basic hydrogen peroxide in THF. The tosylhydrazines had been prepared from the corresponding N-acyl-N'-tosylhydrazines and tosylhydrazones by borane/THF reduction[50].

2-Phenyl-4-penten-1-ol (98) was selectively oxidized to 2-phenyl-4-pentenal (100) by the use of the mild oxidizing agent pyridinium chlorochromate (PCC)[51]. The tosylhydrazone (101) was easily prepared from either crude or distilled 2-phenyl-4-pentenal (100) by reaction with p-toluenesulphonhydrazide in warm ethanol.

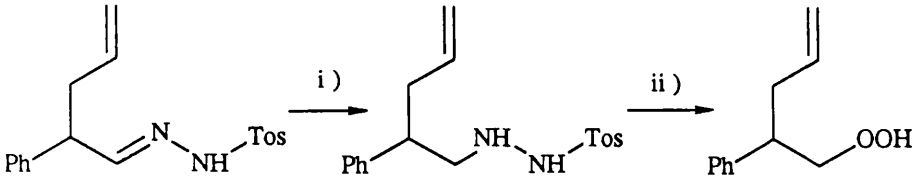


(98) (100) (101)

i) PCC , CH_2Cl_2
ii) $TosNHNH_2$, EtOH , 40 - 50 °C

The reduction of the tosylhydrazone (101) to the tosylhydrazine was not attempted with diborane because of the carbon-carbon double bond present, and the use of sodium borohydride in ethanol/water as reported by Courtneidge[52] proved ineffective in this case. However, treatment of the tosylhydrazone (101) with sodium cyanoborohydride in acidifed THF as described by Rossini et. al.[53] quantitatively afforded crude N-(2-phenyl-4-penten-1-yl)-N'-tosylhydrazine (103) as an oil. No

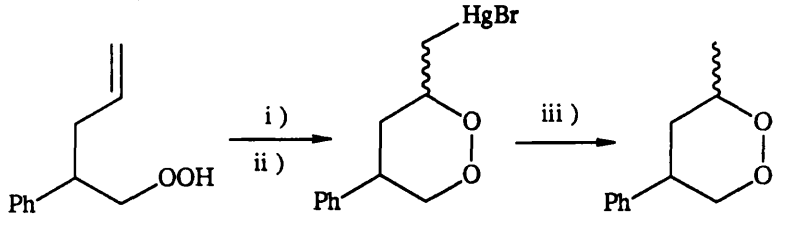
attempt was made to purify this or subsequent tosylhydrazines, the crude material being treated with 30% hydrogen peroxide and sodium peroxide in THF for 24 hr. This afforded 2-phenyl-4-penten-1-hydroperoxide (102) in a yield of 50% after base extraction. Treatment of this



(101) (102) (103)

i) $NaBH_3CN$, TosOH . H_2O , THF , pH 3.5 , 3 hr .
ii) Na_2O_2 , H_2O_2 , THF , 24 hr.

hydroperoxide with mercury(II) nitrate in dichloromethane followed by anion exchange with potassium bromide afforded 3-bromomercuriomethyl-5-phenyl-1,2-dioxane (104), as a mixture of the <u>cis</u> and <u>trans</u> isomers, in a yield of 75% after column chromatography. The hydridodemercuration of the mercurials (104) upon treatment with basic sodium borohydride afforded a 3:1 mixture of <u>cis</u>- and <u>trans</u>-3-methyl-5-phenyl-1,2-dioxanes (105) isolated in a yield of 62% by column chromatography.



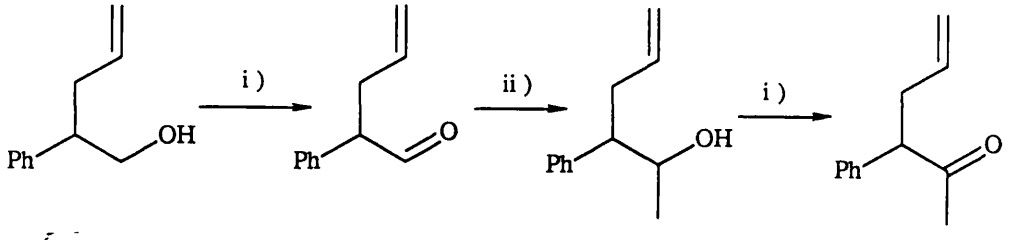
(103) (104) (105)

i) $Hg(NO_3)_2$, H_2O , CH_2Cl_2
ii) H_2O , KBr
iii) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < O°C

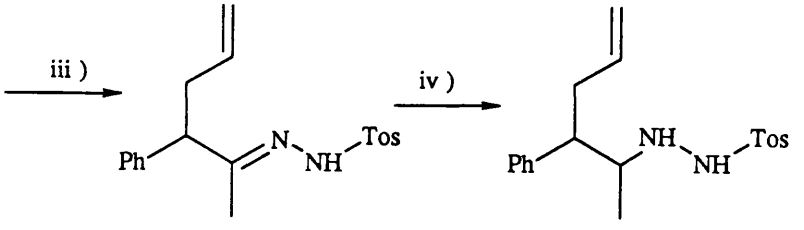
The configuration of the major isomer of (105) was determined by ^{1}H-nmr analysis (Figure 2). From the doublet of triplets due to H_c, it was found that $^3J_{c-d}$ = 12.5 Hz and upon decoupling of the methyl group, the multiplet due to H_a collapsed to a doublet of doublets with coupling constants $^3J_{a-b}$ = 2.0 Hz and $^3J_{a-c}$ = 10.7 Hz. These three coupling constants are consistent with the cis (diequatorial) configuration.

2.2.2 3,6-Dimethyl-4-phenyl-1,2-dioxane (113)

The starting material for the preparation of this 1,2-dioxane was again 2-phenyl-4-penten-1-ol (98). This alcohol was oxidized with PCC to the aldehyde (100) which, when treated with methylmagnesium iodide, afforded crude 3-phenyl-5-hexen-2-ol (106) in a yield of 89%. This

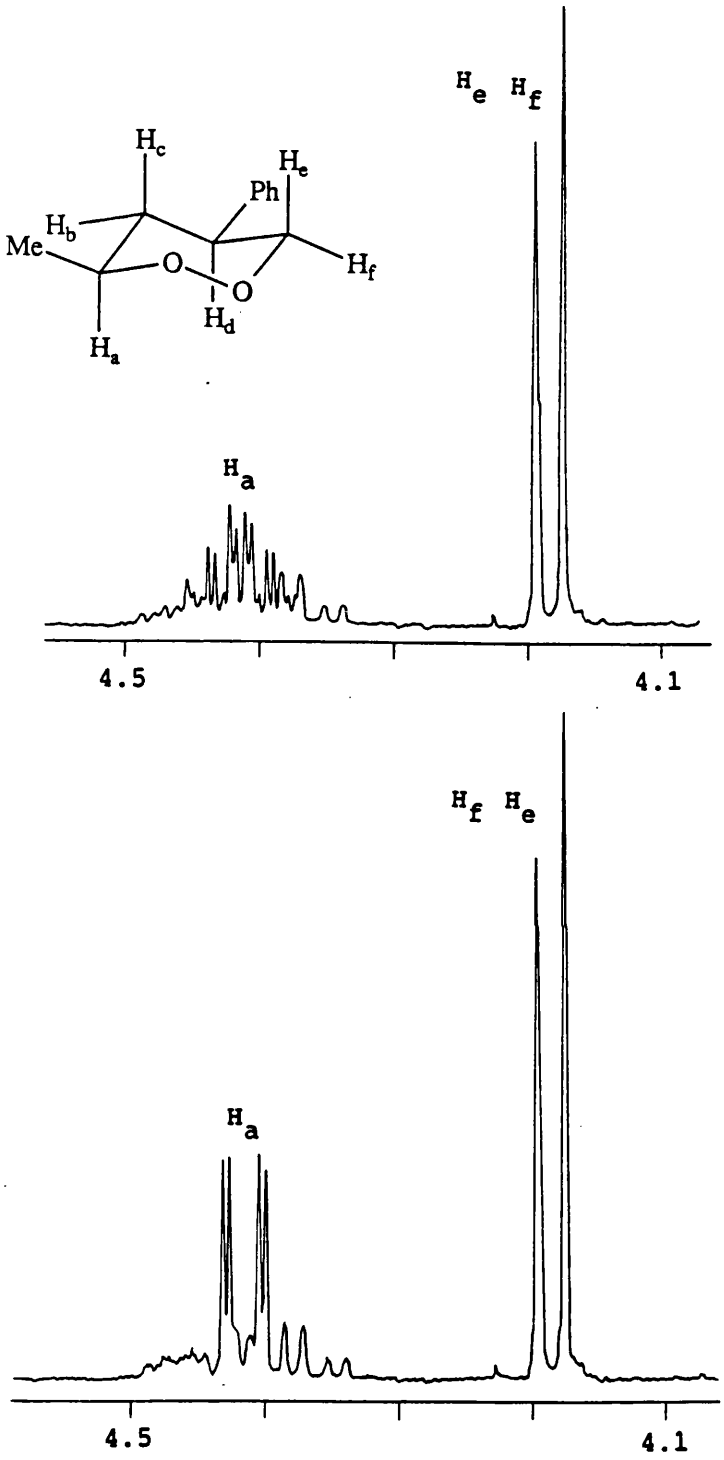


(98) (100) (106) (107)



(108) (109)

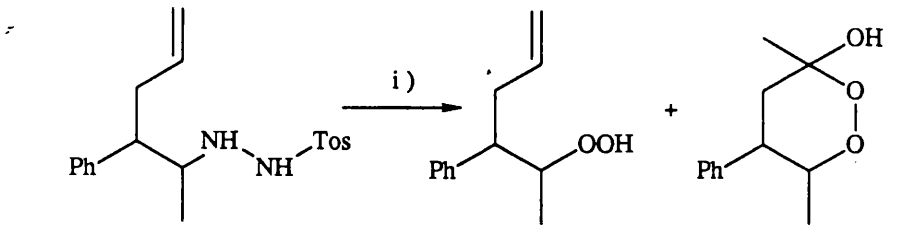
i) PCC , CH_2Cl_2
ii) MeMgI , Et_2O
iii) $TosNHNH_2$, EtOH , 40 - 50 °C
iv)$NaBH_3CN$, $TosOH . H_2O$, THF , pH 3.5



(Figure 2)

The signals due to protons H_a , H_e , and H_f in the ^{1}H-nmr spectrum of 3-methyl-5-phenyl-1,2-dioxane (105). Decoupling of the methyl protons results in the multiplet due to H_a collapsing to doublet of doublets.

alcohol was oxidized with PCC to 3-phenyl-5-hexen-2-one (107) which was isolated in a yield of 59% by vacuum distillation. The reaction of this ketone with p-toluenesulphonhydrazide in warm ethanol gave 3-phenyl-5-hexen-2-tosylhdrazone (108) as a white crystalline solid in a yield of 55%. The reduction of the tosylhydrazone with sodium cyanoborohydride in acidified THF afforded N-(3-phenyl-5-hexen-2-yl)-N'-tosylhydrazine (109) as a yellow oil. Treatment of the crude hydrazine (109) with 30% hydrogen peroxide and sodium peroxide in THF gave a mixture of peroxidic products upon base extraction. The mixture was separated by column chromatography, giving a mixture of the two diastereoisomers of 3-phenyl-5-hexen-2-hydroperoxide (110) in a yield of only 8%. Also isolated were what appeared to be four diastereoisomers of a peroxyhemiacetal (111) tentatively assigned the structure shown, on the basis of ^{13}C and ^{1}H-nmr spectroscopic evidence.

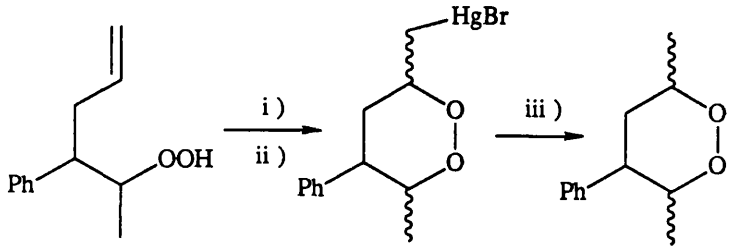


(109) (110) (111)

i) Na_2O_2, H_2O_2, THF, 24 hr.

The hydroperoxide (110), when treated with mercury (II) nitrate followed by anion exchange with potassium

bromide afforded a mixture of the four diastereoisomers of 6-bromomercuriomethyl-3-methyl-4-phenyl-1,2-dioxane (112) in a yield of 70% after column chromatography. The hydridodemercuration of the mercurials (112) upon treatment basic sodium borohydride solution afforded a mixture of the four diastereoisomers of 3,6-dimethyl-4-phenyl-1,2-dioxane (113) in a yield of 65% after column chromatography.



(110) (112) (113)

i) $Hg(NO_3)_2$, H_2O, CH_2Cl_2
ii) H_2O, KBr
iii) $NaBH_4$, 3M NaOH, CH_2Cl_2, < 0°C

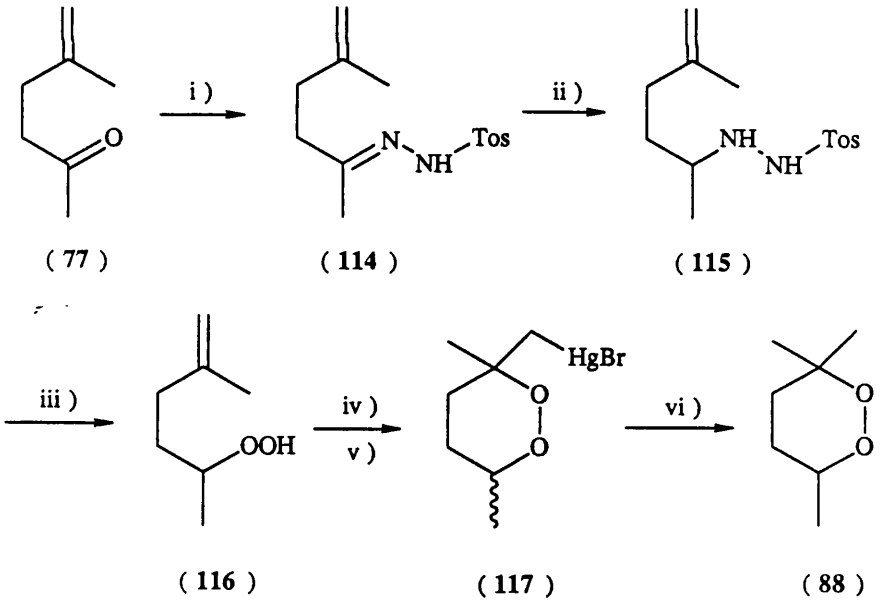
Owing to the low yield at the hydroperoxide stage and the complex mixture of diastereoisomers obtained, this dioxane was not investigated in the subsequent rearrangement/decomposition studies.

2.2.3 3,3,6-Trimethyl-1,2-dioxane (88)

Although successfully prepared from the tertiary hydroperoxide (85) as described earlier, this alternative preparation was attempted because of the availability of 5-methyl-5-hexen-2-one (77).

5-Methyl-5-hexen-2-tosylhydrazone (114) was prepared

in a yield of 67% by treating 5-methyl-5-hexen-2-one (77) with p-toluenesulphonhydrazide in warm ethanol. Reduction of the tosylhydrazone with sodium cyanoborohydride in acidified THF afforded N-(5-methyl-5-hexen-2-yl)-N'-tosylhydrazine (115). Treatment of this hydrazine with sodium peroxide and 30% hydrogen peroxide in THF gave 5-methyl-5-hexen-2-hydroperoxide (116) in a yield of 59%. Reaction of this hydroperoxide with mercury (II) nitrate followed by anion exchange with potassium bromide gave 3-bromomercuriomethyl-3,6-dimethyl-1,2-dioxane (117) in an isolated yield of 45%. The hydridodemercuration of the mercurial with basic sodium borohydride afforded 3,3,6-trimethyl-1,2-dioxane (88) in a yield of 46% after chromatography. The product by this route had identical



(77) (114) (115)

(116) (117) (88)

i) $TosNHNH_2$, EtOH , 40 - 50 °C
ii) $NaBH_3CN$, TosOH . H_2O , pH 3.5
iii) Na_2O_2 , H_2O_2 , THF
iv) $Hg(NO_3)_2$. H_2O , CH_2Cl_2
v) H_2O , KBr
vi) $NaBH_4$, 3M NaOH , < 0°C

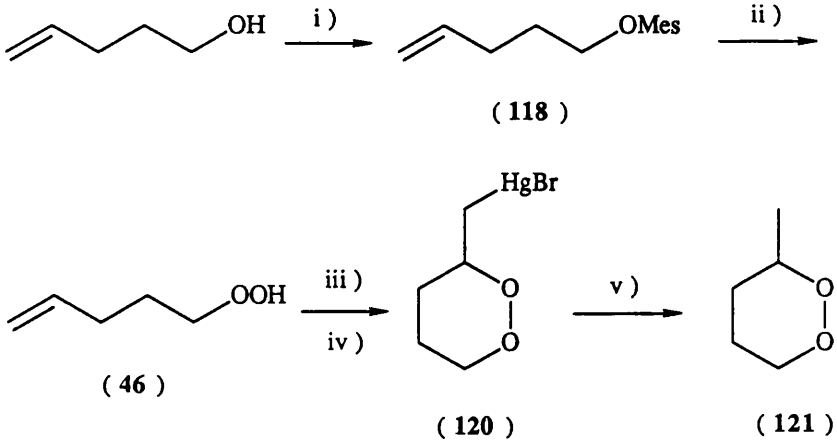
^{1}H and ^{13}C-nmr spectra to the product prepared by the tertiary bromide route (Section 2.1.2).

2.3 1,2-Dioxanes via hydroperoxides prepared from methanesulphonate esters

The preparation of primary and secondary alkyl hydroperoxides from the corresponding alcohols via the methanesulphonates is a long established technique[48]. Here it was used to prepare two primary hydroperoxides.

2.3.1 3-Methyl-1,2-dioxane (121)

4-Penten-1-methanesulphonate (118) was prepared from 4-penten-1-ol (98) in a yield of 88%. Reaction of this with basic hydrogen peroxide gave 4-penten-1-hydroperoxide (119) in a yield of 36%. The hydroperoxide was treated with mercury(II) nitrate followed by anion exchange with potassium bromide to afford 3-bromomercuriomethyl-1,2-

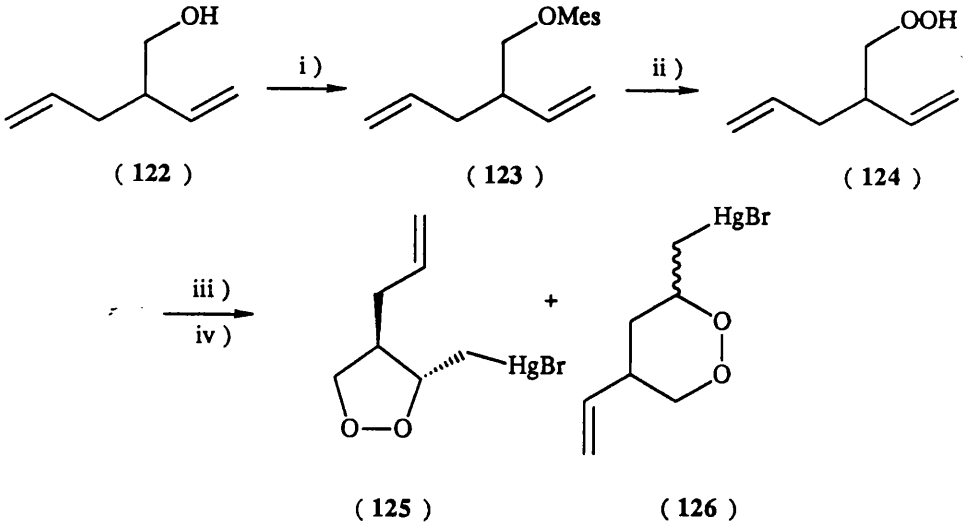


i) MesCl , pyridine , O°C
ii) 50% KOH , 30% H_2O_2 , MeOH
iii) $Hg(NO_3)_2$. H_2O , CH_2Cl_2
iv) H_2O , KBr
v) $NaBH_4$, 3M NaOH , CH_2Cl_2 , <O°C

dioxane (120). The hydridodemercuration of this mercurial when treated with basic sodium borohydride gave 3-methyl-1,2-dioxane (121) in an isolated yield of 45%.

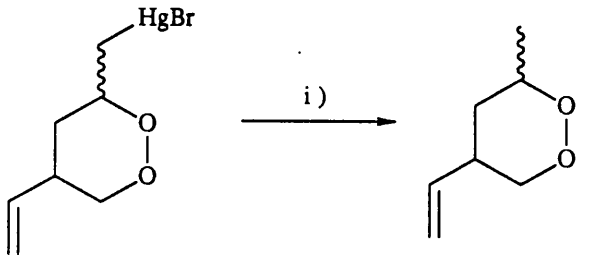
2.3.2 5-Ethenyl-3-methyl-1,2-dioxane (127)

Reaction of the alcohol (122) with methanesulphonyl chloride gave the methanesulphonate (123) which afforded 2-ethenyl-4-penten-1-hydroperoxide (124) when treated with basic hydrogen peroxide in methanol. Treatment of the hydroperoxide with mercury(II) nitrate followed by anion exchange with potassium bromide afforded a mixture of the regioisomers (125) and (126) which were separated by HPLC. The full details of this synthesis are given in chapter 5.



i) MesCl , pyridine , < 0°C
ii) 30% H_2O_2 , 50% KOH , MeOH
iii) $Hg(NO_3)_2.H_2O$, CH_2Cl_2
iv) KBr , H_2O

The hydridodemercuration of 3-bromomercuriomethyl-5-ethenyl-1,2-dioxane (126) upon treatment with basic sodium borohydride afforded a 3:1 mixture of cis- and trans-5-ethenyl-3-methyl-1,2-dioxane (127) in an isolated yield of 39%.



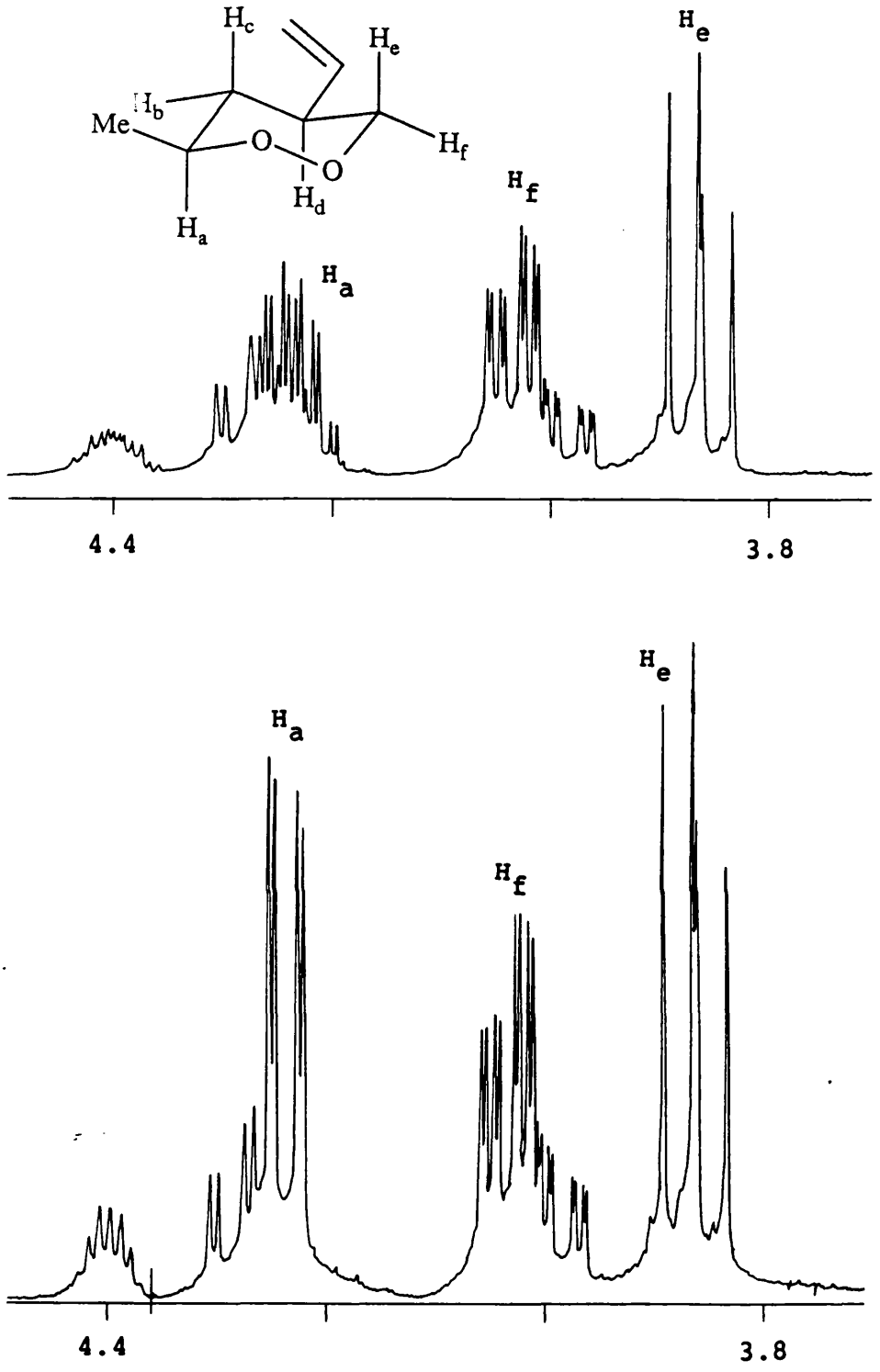
(126) (127)

i) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C

The configuration of the major isomer of (127) was determined in the same manner as that of 3-methyl-5-phenyl-1,2-dioxane (105), mentioned earlier. The coupling constant $^3J_{d-e}$ was found to be 12.2 Hz and upon decoupling of the methyl group (Figure 3), $^3J_{a-b}$ and $^3J_{a-c}$ were found to be 2.0 Hz and 10.4 Hz respectively. These coupling constants are consistent with the cis (diequatorial) configuration.

2.4 Other routes to 1,2-dioxanes

3,6-Dimethyl-1,2-dioxane (32) was prepared by an established route and several attempts were made to prepare 3,6-diphenyl-1,2-dioxane (128).

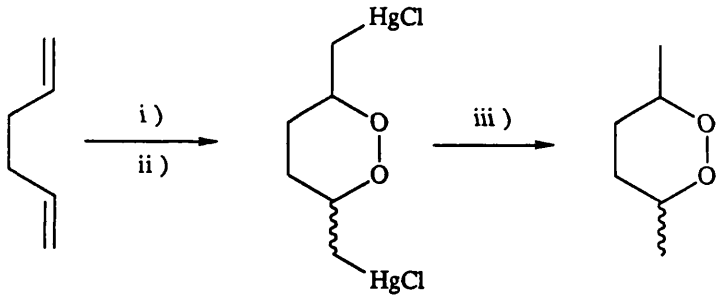


(Figure 3)

The signals due to protons H_a , H_e , and H_f in the ^{1}H-nmr spectrum of 5-ethenyl-3-methyl-1,2-dioxane (127). Decoupling of the methyl protons results in the multiplet due to H_a collapsing to a doublet of doublets.

2.4.1 3,6-Dimethyl-1,2-dioxane (32)

The method of Bloodworth, Loveitt and Khan[34] was used to prepare 3,6-dimethyl-1,2-dioxane (**32**). 1,5-Hexadiene was treated with mercury(II) nitrate and 85% hydrogen peroxide in dichloromethane followed by anion exchange with potassium chloride to give 3,6-bis(chloromercuriomethyl)-1,2-dioxane (30a). This mercurial underwent hydridodemercuration when treated with a basic solution of sodium borohydride, the resulting 3,6-dimethyl-1,2-dioxane (**32**) being purified by either column chromatography or GLC. The cis- and trans-isomers could also be separated by the latter technique.



(30a) (32)

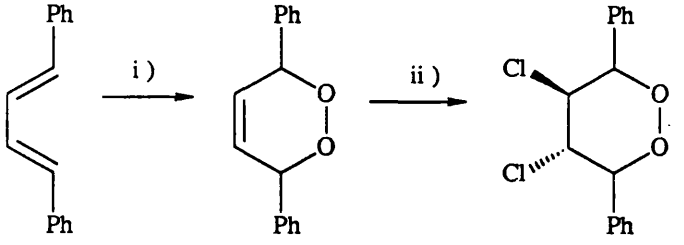
i) 85% H_2O_2 , $Hg(NO_3)_2$. H_2O , CH_2Cl_2
ii) KCl_{aq}
iii) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C

2.4.2 3,6-Diphenyl-1,2-dioxane (128)

3,6-Diphenyl-1,2-dioxane was considered to be a desirable target molecule and a synthetic route from the easily accessible cis-3,6-diphenyl-3,6-dihydro-1,2-dioxin (129) was envisaged.

This cyclic peroxide (129) was prepared by the

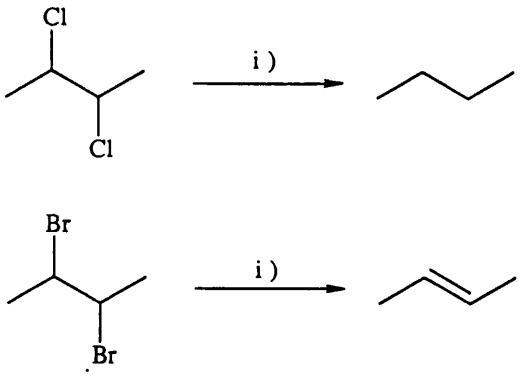
sensitized photooxygenation of 1,4-diphenyl-1,3-butadiene[54]. Previous attempts by Fearn[55] to reduce (129) with diimide or prepare the dibromide had failed, but trans-4,5-dichloro-cis-3,6-diphenyl-1,2-dioxane (130) had been prepared in high yield upon treatment of (129) with chlorine in chloroform. Reduction of (130) would have presented a simple route to cis-3,6-diphenyl-1,2-dioxane (128) and, possibly, other dioxanes.



(129) (130)

i) O_2 , TPP , hυ , $CHCl_3$
ii) Cl_2 , $CHCl_3$

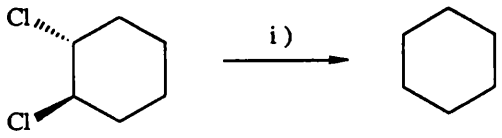
The reactions of vicinal dibromides and dichlorides with organotin hydrides have been reported by Strunk et. al.[56], and the results given were promising. The uv-initiated reaction of tri-n-butyltin hydride with 2,3-dibromobutane gave 2-butene whereas 2,3-dichlorobutane gave butane (Scheme 16). To determine if this reaction (modified by the use of a chemical initiator) could be used to prepare the dioxane (128), several model reactions were carried out. Firstly, the ease of reduction of a cyclic 1,2-dichloride was investigated. trans-1,2-



i) *n* - Bu_3SnH , hυ

(Scheme 16)

Dichlorocyclohexane (**131**) was treated with tri-n-butyltin hydride and AIBN in toluene at 90°C to give cyclohexane in a yield of 53%. Secondly, the stability of a 1,2-dioxane



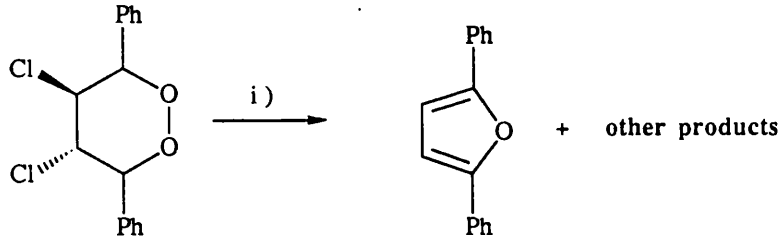
(**131**)

i) *n* - Bu_3SnH , toluene , AIBN , 90 °C

(3,6-dimethyl-1,2-dioxane (**32**)) to reagents and products was examined. In the presence of tri-n-butyltin hydride and tri-n-butyltin chloride the dioxane (**32**) showed no signs of decomposition after 41 hours at room temperature, 5 hours at 40°C, or 3 hours at 65°C with AIBN, as judged by ^{1}H-nmr.

In contrast to the encouraging results from the model reactions, the AIBN- and di-t-butylhyponitrite (DTBH)-initiated reactions of 4,5-dichloro-3,6-diphenyl-1,2-

dioxane (130) with tri-n-butyltin hydride in toluene and benzene respectively each gave a complicated mixture of products. A small amount of 2,5-diphenylfuran (3%) was isolated from the reaction, but no other products were identified.



(130)

CHAPTER 3

REARRANGEMENTS AND FRAGMENTATIONS OF SOME 1,2-DIOXANES

1. INTRODUCTION

Cyclic peroxides are useful precursors to reactive intermediates of theoretical interest such as dioxyl diradicals and radical anions.

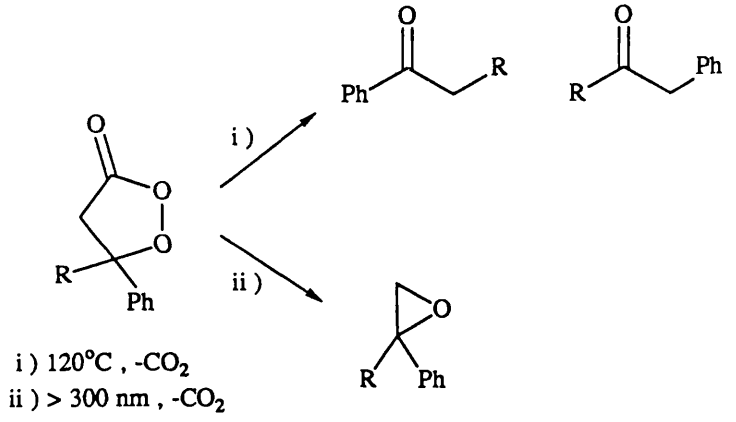
The diradicals of a number of types of cyclic peroxide have been generated by such techniques as flash vacuum pyrolysis, solution thermolysis, and photolysis. Flash vacuum pyrolysis is the passage of a vaporized sample through a heated glass tube at very low pressures. Rearrangements under these conditions are taken to be unimolecular.

Radical anions have been implicated in the rearrangements of a number of cyclic peroxides, mainly bicyclic, upon treatment with electron transfer reagents such as iron(II).

The literature shows that the nature of the rearrangement/ decomposition products of a cyclic peroxide are dependent not only on the structure of that cyclic peroxide, but also on the manner in which the reaction was initiated. The most studied cylic peroxides are the β-peroxylactones, bicyclic peroxides, 1,2-dioxolanes and 1,2-dioxanes.

1.1 Peroxylactones

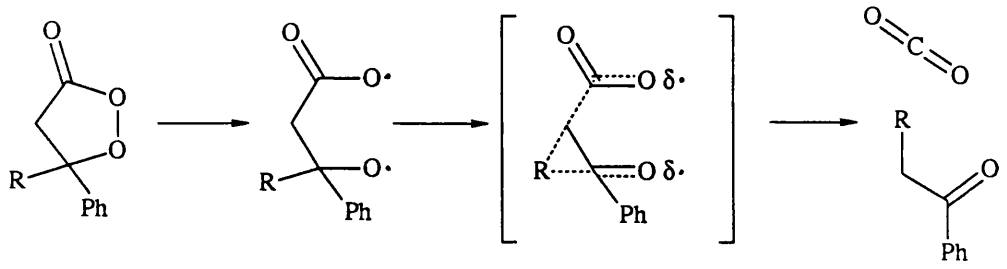
These compounds, which are easily prepared from the acid-catalysed cyclization of β-hydroxy acids with 98% hydrogen peroxide or by the perhydrolysis of β-lactones, have been used by Adam and co-workers[57] as sources of diradicals. The solution thermolyses of a series of these β-peroxylactones afforded different main products from those obtained from the corresponding photolyses. The thermolyses gave mainly alkyl and phenyl migrated ketones while the photolyses yielded the epoxides (Scheme 17).



(Scheme 17)

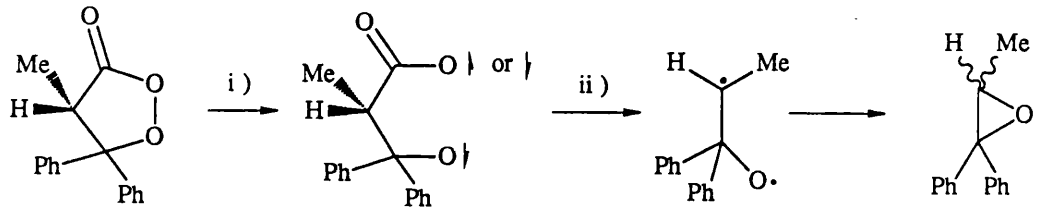
The investigation of the thermolysis using studies of deuterium isotope effects, solvent effects, and stereolabelling established that the reaction proceeds by the extrusion of carbon dioxide from the 1,5-diradical with a synchronous alkyl shift (Scheme 18).

The photodecarboxylation of an optically active β-peroxylactone in acetone as solvent and sensitizer afforded a racemized epoxide, presumably via the free 1,3-



(Scheme 18)

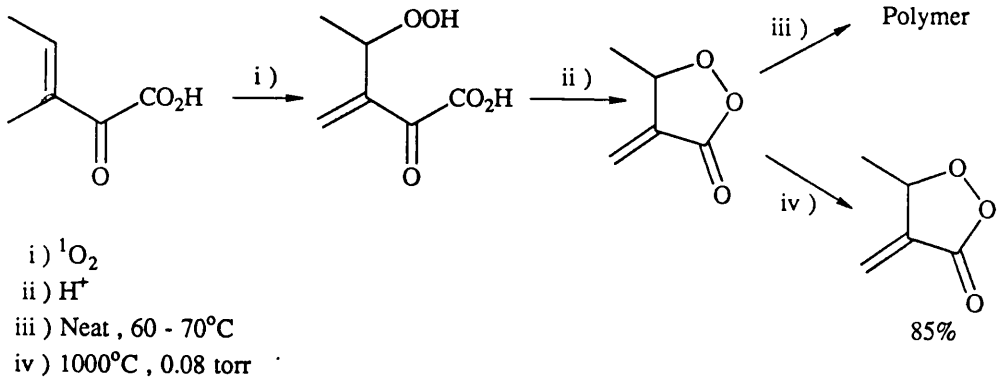
diradical. It was suggested that this radical arises by the decarboxylation of the triplet or singlet, 1,2-diradicals with the σ-configuration at the acyloxyl site (Scheme 19).



i) hυ , Me_2CO
ii) $-CO_2$

(Scheme 19)

A recent interesting example of a β-peroxylactone is that reported by Adam and Griesbeck[58]. The photo-oxygenation of tiglic acid followed by acid catalysed cyclization afforded an α-methylene-β-peroxylacetone (Scheme 20). This compound, although easily polymerized at 70-80°C is remarkably stable to flash vacuum pyrolysis, being recovered in a yield of 85% after passing through a 60cm tube heated to 1000°C at 0.08 torr. This stability is attributed to the fact that decarboxylation of both the σ- and π-radicals (at the acyloxyl site) is disfavoured.



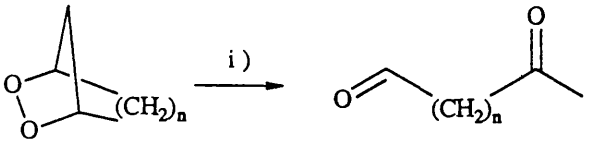
(Scheme 20)

1.2 Bicyclic peroxides

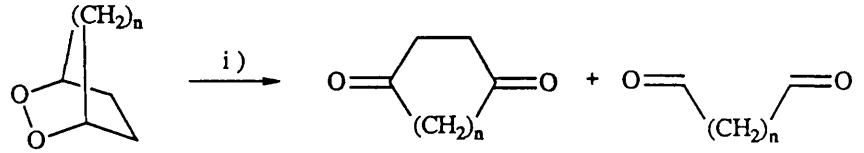
The reactions of this class of compound have received much attention and much of this effort has been made to gain an understanding of the processes leading to the diverse range of compounds produced from PGH_2. Techniques by which the diradicals have been generated are flash vacuum pyrolysis, photolysis, and solution thermolysis, while treatment with electron transfer reagents and Lewis acids have been used to produce charged species.

The flash vacuum pyrolysis of a series of bicyclic peroxides has been reported by Bloodworth and co-workers.[59] A marked difference in the behaviour of [n.2.1] (12a) and [n.2.2] compounds (12b) under fvp conditions was observed; the former rearranged to ketoaldehydes, while the latter fragmented to dialdehydes plus ethylene and cycloalkane-1,4-diones plus hydrogen.

The direct photolysis of the same compounds was reported by Bloodworth and Eggelte[60]. While the photolysis of [n.2.2] peroxides (12b) afforded mainly

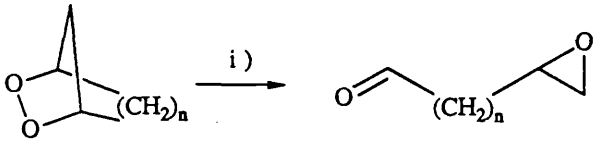


(12 a)

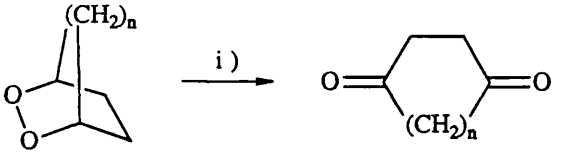


(12 b)

i) Flash Vacuum Pyrolysis



(12 a)



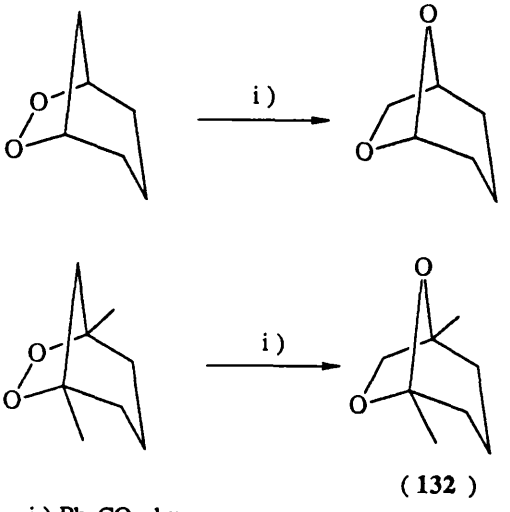
(12 b)

i) hυ

cycloalkane-1,4-diones as found under fvp conditions, the [n.2.1] peroxides (12a) gave epoxyaldehydes as major products.

The benzophenone-sensitized photolysis of 6,7-dioxabicyclo[3.2.1]octane afforded 6,8-dioxabicyclo [3.2.1]octane. This parallels the earlier work of Wilson and Rekers[61], who prepared the pine beetle pheromone frontalin (132) by benzophenone-sensitized photolysis of 1,5-dimethyl-6,7-dioxabicyclo[3.2.1]octane. In these sensitized photolyses, oxygen-oxygen bond homolysis and cleavage of the one-carbon bridge which results in a

triplet 1,3-diradical which can add intramolecularly to the carbonyl before spin inversion (Scheme 21). Direct photolysis gives the singlet 1,3-diradical which collapses to the epoxyaldehyde.



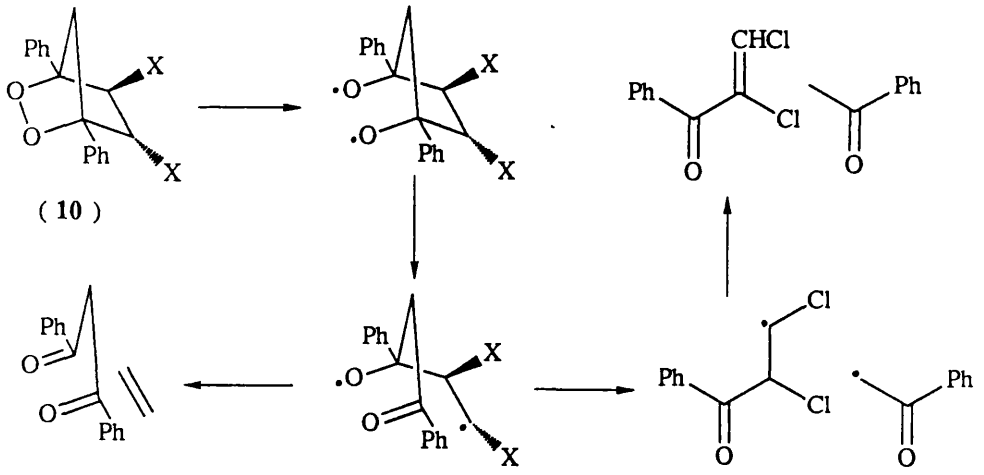
(132)

i) Ph_2CO , hυ

(Scheme 21)

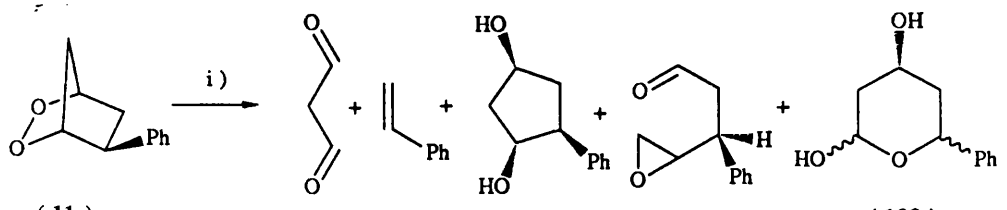
An example of solution thermolysis of a bicyclic peroxide is that reported by Coughlin and Salomon[62]. The peroxides (10a,b) prepared by either diimide reduction or chlorination of the unsaturated bicyclic peroxide, were heated at 110°C-140°C in benzene in sealed tubes. The peroxide (10a) afforded the diketone and ethylene while the chlorinated peroxide (10b) afforded acetophenone and a dichlorinated α,β-unsaturated ketone.

The rearrangements of PGH_2 are unlikely to proceed <u>via</u> diradicals; enzyme-initiated rearrangements by a single electron transfer or electrophilic attack have been suggested[63]. As a result, the reactions of bicyclic peroxides with electron transfer reagents and Lewis acids



have recently attracted attention. The most studied electron transfer reagent is iron(II)[22,64] but the reactions of Pd(0)[65], Co(II)TPP[66], and Ru(II)[67] with bicyclic peroxides have also been explored.

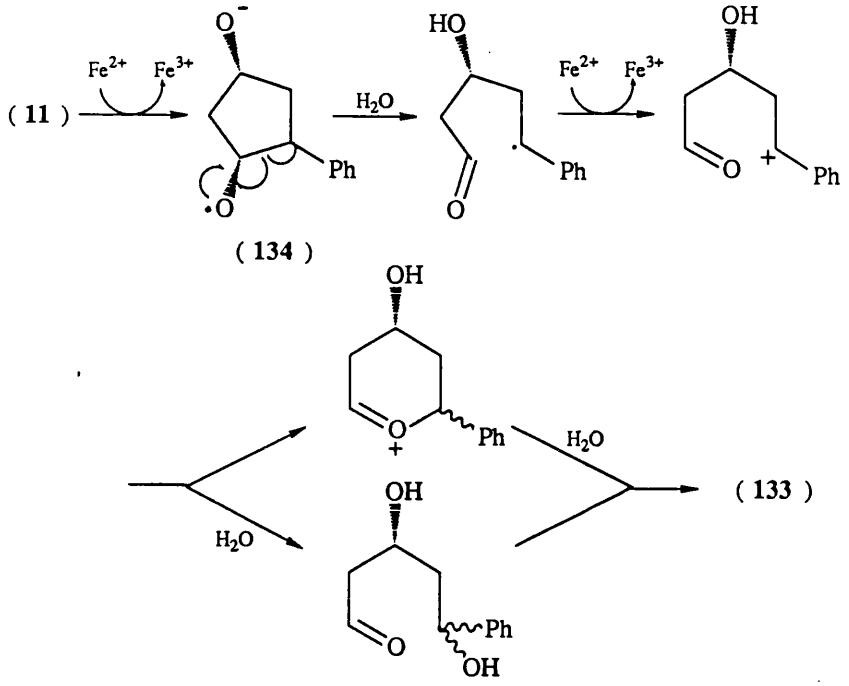
The most recent of these studies is the modelling of prostaglandin and thromboxane production by treatment of the PGH_2 model (11) with iron(II) sulphate as reported by Kishi and Takahashi[22]. The mechanism suggested for the



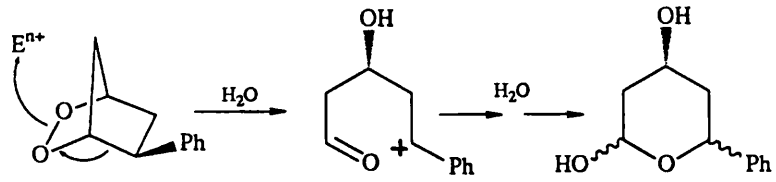
(11) (133)

i) $FeSO_4$, H_2O , MeCN , N_2

production of the TXB_2-like compound (133) involves the prior formation of the radical anion (134). Kishi and Takahashi[68] also reported that the treatment of (11) with iron(III) and copper(I) salts affords the TXB_2- and PG-



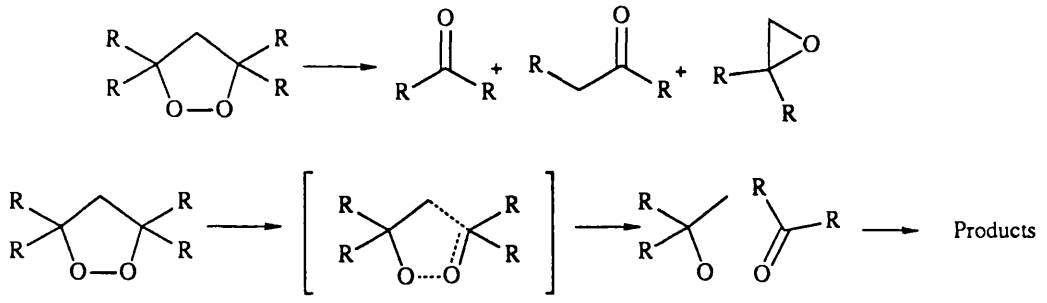
like products in much higher yields than those in the reaction with iron(II). The mechanism suggested for this reaction is given in scheme 22.



(Scheme 22)

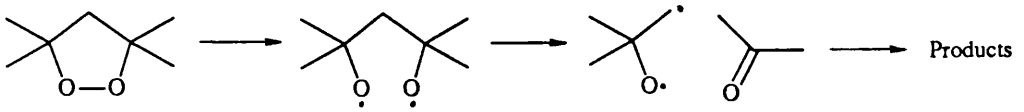
1.3 1,2-Dioxolanes

The solution thermolysis of a series of 3,3,5,5-tetrasubstituted 1,2-dioxolanes, as reported by Adam and Duran[69], afforded a mixture of ketones and epoxides. The mechanism proposed did not involve the 1,5-diradical, but rather a concerted two-bond fragmentation to a ketone and a 1,3-diradical which either collapsed to an epoxide or



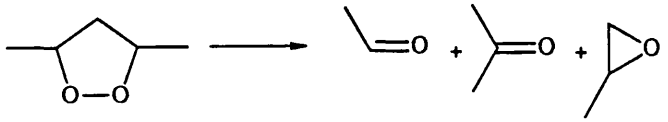
(Scheme 23)

underwent a phenyl or methyl migration give a ketone (Scheme 23). Subsequently Richardson et. al.[70] carried out a kinetic study of the thermolysis of 3,3,5,5-tetramethyl-1,2-dioxolane (135) in benzene with a radical inhibitor and in the gas phase. This showed the fragmentation of (136) followed a stepwise diradical mechanism with an initial 1,5-dioxyl diradical.



(135) (136)

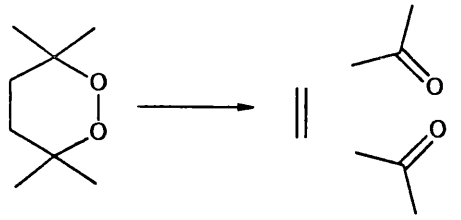
Another example of the rearrangement of a 1,2-dioxolane is the fvp of 3,5-dimethyl 1,2-dioxolane (137) reported by Bloodworth and Baker[28]. This afforded mainly the expected acetaldehyde, propene oxide and acetone.



(137)

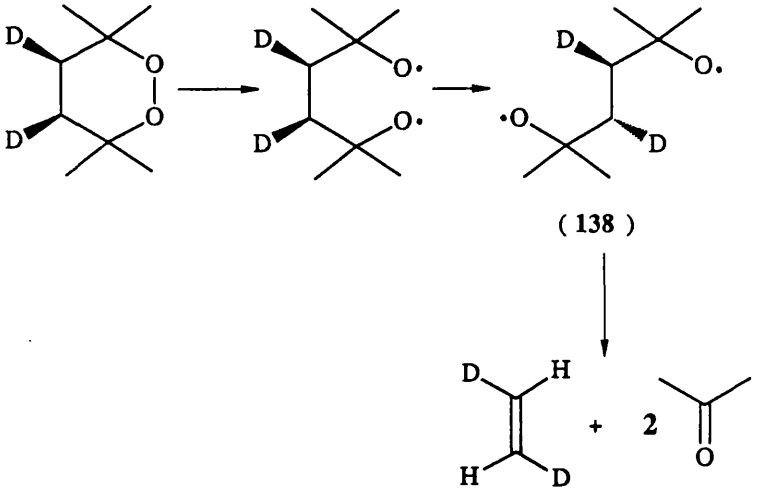
1.4 1,2-Dioxanes

The most intensive study of the decomposition of a 1,3-dioxane is that, by Adam and Sanabia[29], of 3,3,6,6-tetramethyl-1,2-dioxane (22). Under both photolysis and solution thermolysis conditions (22) affords acetone and ethylene in high yield. The deuterium labelled 1,2-



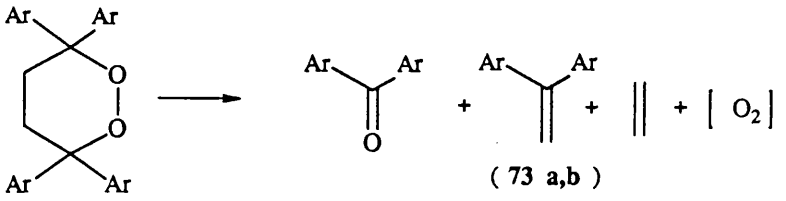
(22)

dioxanes meso- and dl-3,3,6,6-tetramethyl-1,2-dioxane-4,5-d_2 were prepared and thermolysis of these gave 70% inversion of stereochemistry. From this evidence it was concluded that the preferred configuration of the 1,6-dioxyl (138) was transoid.



(138)

Other isolated cases of 1,2-dioxane thermolysis have been reported, usually as a proof of structure[42,44]. The flash vacuum pyrolyses of two 3,3,6,6-tetraaryl-1,2-dioxanes (**74a,b**) reported by Haynes[44] are interesting in that as well as the expected ketones and ethene, 4-7% of the 1,1-diaryl alkenes (**73a,b**) was obtained.

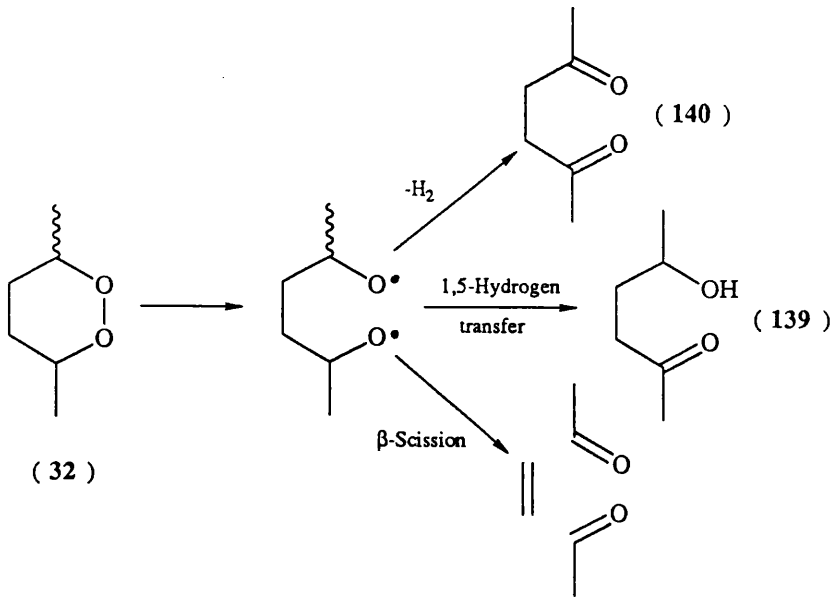


(74 a,b)

(73 a,b)

Secondary cyclic peroxides offer new pathways of rearrangement or fragmentation not available to the tertiary examples given above, an example being the flash vacuum pyrolysis of 3,6-dimethyl-1,2-dioxane (**32**) reported by Bloodworth and Baker[28,71]. Rearrangement by 1,5-hydrogen transfer is the dominant process, affording 5-hydroxyhexan-2-one (**139**) while dehydrogenation to the diketone (**140**) and β-scission play minor roles.

Diagram overleaf


(140)
-H2
1,5-Hydrogen
transfer
OH
(139)
β-Scission
(32)

2 RESULTS AND DISCUSSION

The fragmentations and/or rearrangements of several 1,2-dioxanes were carried out using mainly flash vacuum pyrolysis (fvp), treatment with iron(II) salt, and in a limited number of cases, photolysis.

Flash vacuum pyrolysis was carried out by passing a vaporized sample of the 1,2-dioxane through a 1.5x30cm pyrex tube heated to 450°C at a pressure of 10^{-3} mm Hg. The products were collected in a trap cooled to liquid nitrogen temperature, but if the dioxane contained a phenyl group some of the products tended to condense immediately after the hot zone. In this case the products were simply washed into the trap with $CDCl_3$.

Treatment of cyclic peroxides with iron(II) is known to generate radical anions, and the behaviour of these species was to be compared with that of the corresponding diradicals produced by fvp or photoysis. Following the procedure described by Kishi and Takahaski[22], a small sample of the 1,2-dioxane was treated with a two fold excess of iron(II) sulphate in aqueous acetonitrile, the products being recovered by dichloromethane extraction.

Solutions of 1,2-dioxanes for photolysis were made up in C_6D_6 in nmr tubes and exposed to uv radiation from a medium pressure mercury vapour lamp. The progress of the photolysis was followed by ^1H-nmr.

The decompositions/rearrangements described here are

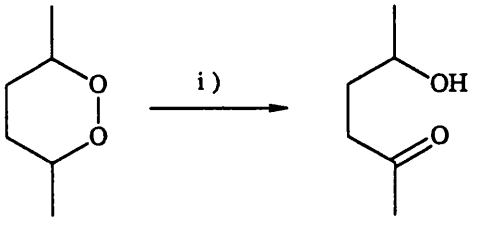
separated into three sections according to the substitution patterns of the 1,2-dioxanes. In many of the reactions, the products were new compounds and their identities were verified by comparison with independently prepared samples. These independent syntheses are described in Section 2.4.

2.1 3,6-Disubstituted-1,2-dioxanes

2.1.1 3,6-Dimethyl-1,2-dioxane (32)

This cyclic peroxide had previously been studied by Baker[28] and Hagelberg[71], and this work was repeated in order to check the previously obtained results and to gain experience of the techniques involved.

When 3,6-dimethyl-1,2-dioxane (32) was subjected to flash vacuum pyrolysis, the ^{1}H-nmr spectrum of the pyrolysate showed there to be mainly the 1,5-hydrogen transfer product 5-hydroxyhexan-2-one (139). There



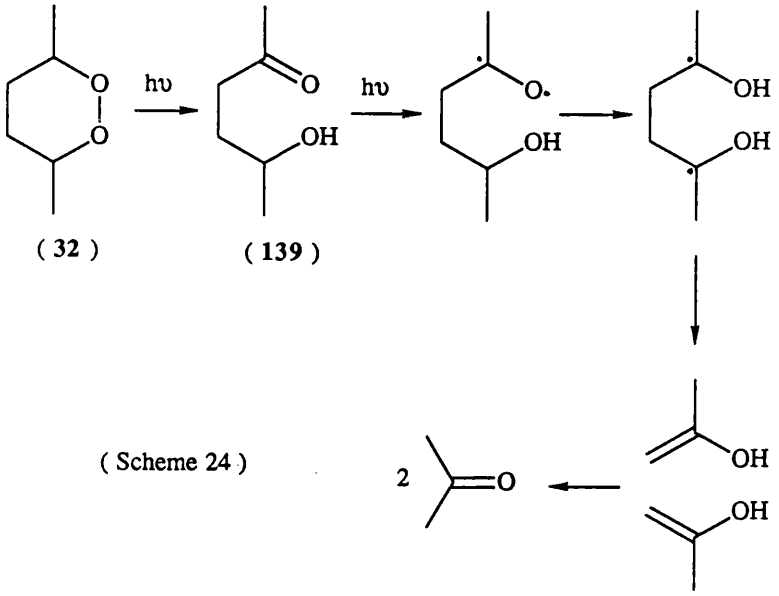
(32) (139)

i) 450 °C, 10^{-3}mmHg

appeared to be little if any of the dehydrogenation product hexane-2,5-dione (140) or the β-scission product

acetaldehyde. This result is at odds with that reported by Baker[28], but is in agreement with the later findings of Hagelberg[71].

The direct photolysis of 3,6-dimethyl-1,2-dioxane (32) in benzene-d_6 was followed by ^{1}H-nmr. Over the course of 24 hours, the signals due to the dioxane (32) slowly diminished while a singlet gradually grew at δ 1.65. The likely explanation is that 5-hydroxyhexan-2-one (139) is the primary photolysis product but is further photolysed and undergoes a Norrish type II process to give two molecules of acetone (Scheme 24). This mechanism was supported by the fact that the photolysis of an authentic sample of 5-hydroxyhexan-2-one (139) (see section 4.2.1) under similar conditions also yielded acetone.

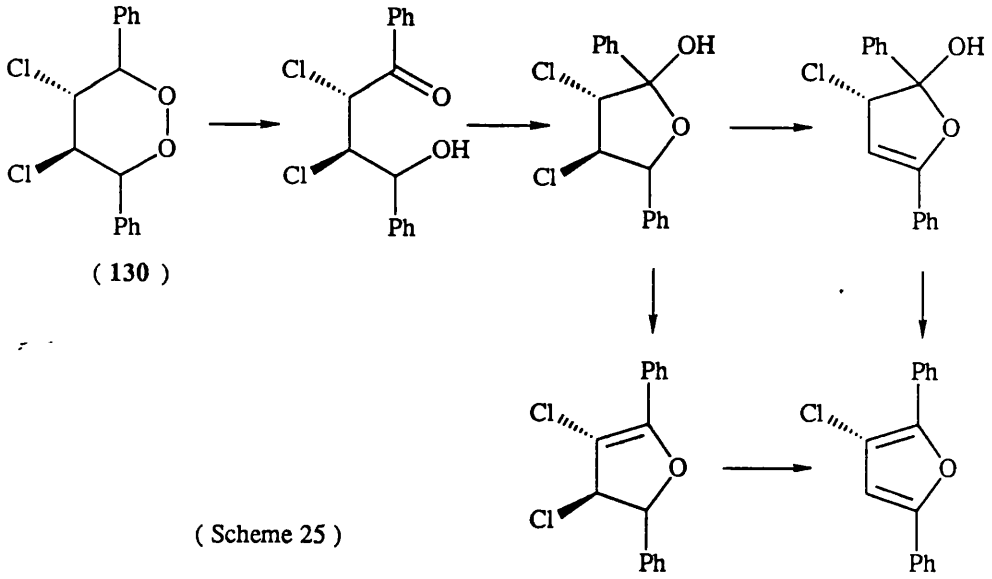


(32) (139)

(Scheme 24)

2.1.2 4,5-Dichloro-3,6-diphenyl-1,2-dioxane (130)

The direct photolysis of (130) in benzene-d_6 was followed by ^{1}H-nmr. After 2 hours, much of the dioxane appeared to have been consumed. However, separation of the product mixture by column chromatography gave 3-chloro-2,5-diphenylfuran (141) and unreacted 1,2-dioxane (130) in a 1:1 ratio. The production of 3-chloro-2,5-diphenylfuran (141) can be accounted for by the mechanism outlined in Scheme 25. 1,5-Hydrogen transfer in the initial dioxyl diradical affords the hydroxyketone which undergoes hemiacetal formation followed by dehydration and dehydrochlorination.



(130)

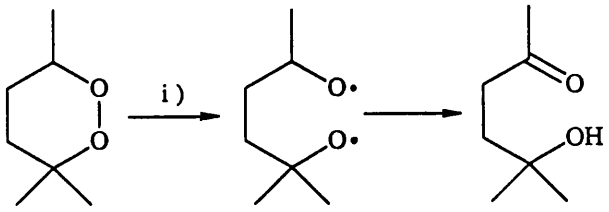
(Scheme 25)

(141)

2.2 3,3,6-Trisubstituted-1,2-dioxanes

2.2.1 3,3,6-Trimethyl-1,2-dioxane (88)

The flash vacuum pyrolysis products of this dioxane were taken up in $CDCl_3$ while still cold in order to ensure that none of the more volatile products were lost. However, the ^{13}C-nmr spectrum revealed that fvp had principally given the 1,5-hydrogen abstraction product 5-hydroxy-5-methylhexan-2-one (142) with little or no acetone formation. The identification of the major product was made by comparison of the ^{13}C-nmr spectrum with that of 5-hydroxy-5-methylhexan-2-one (142) prepared by an independent route (see section 4.2.3). The introduction of a methyl group in place of one of the hydrogens capable of undergoing abstraction does not appear to alter the nature of the reaction. As was the case with 3,6-dimethyl-1,2-dioxane (32), 3,3,6-trimethyl-1,2-dioxane gives almost exclusively a 1,5-hydrogen transfer product.

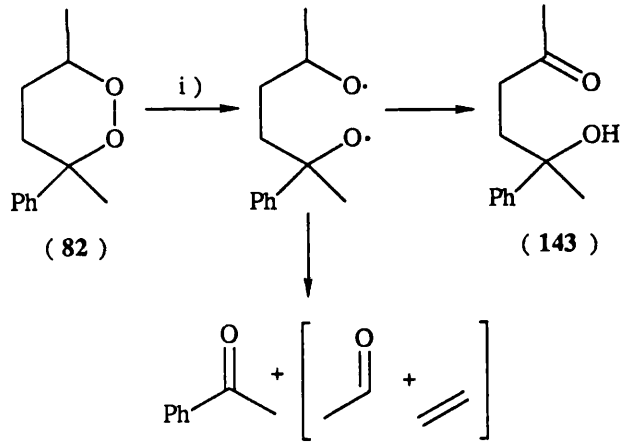


(88) (142)

i) 450 °C , 10^{-3}mmHg

2.2.2 3,6-Dimethyl-3-phenyl-1,2-dioxane (82)

It was anticipated that the inclusion of a 3-phenyl substituent might increase the amount of β-scission by virtue of conjugation between the carbonyl and phenyl groups. This proved to be the case. Thus, the flash vacuum pyrolysis of (82) yielded two main products, acetophenone and 5-hydroxy-5-phenylhexan-2-one (143). These compounds were identified by comparison of the ^{1}H and ^{13}C-nmr spectra and GLC retention times of the product mixture with those of authentic samples (see Section 2.4.2). The ratio of acetophenone to 5-hydroxy-5-phenylhexan-2-one (143) was found to be 2:3 by GLC analysis.



i) 450 °C, 10^{-3}mmHg

2.3 3,5-Disubstituted-1,2-dioxanes

We wished to investigate the effect that an unsaturated substituent in the five position might have on

the reactions of 1,2-dioxanes. A vinylic substituent in the corresponding position in PGH_2 is believed to influence the nature of the rearrangements through resonance stabilization of intermediates. However, it must be borne in mind that the dioxyl diradicals derived from bicylic peroxides are sterically prevented, by the pressure of the cycloalkane ring, from rearrangement by hydrogen transfer of the type undergone by acylic 1,6-diradicals.

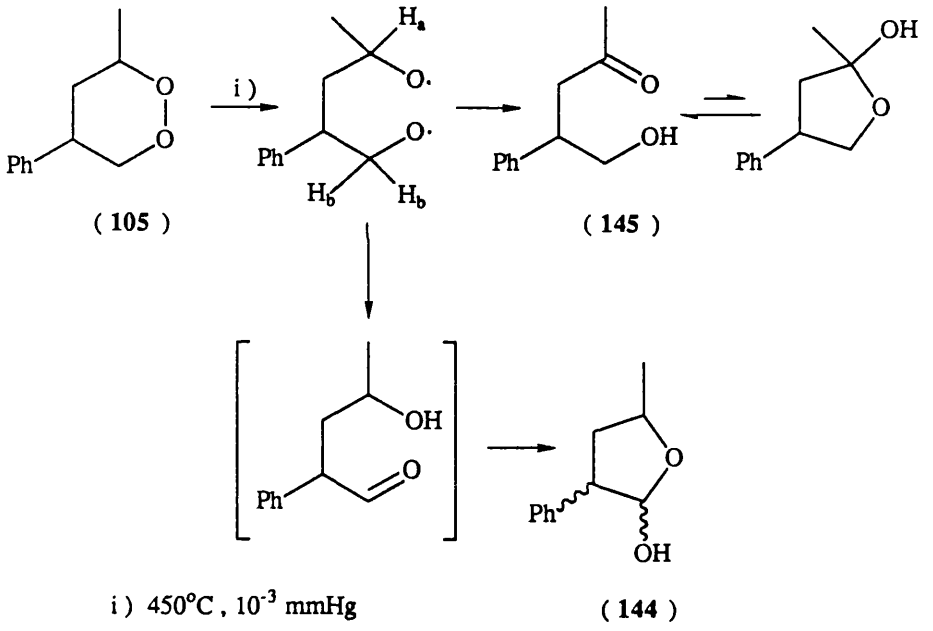
The reactions of 3-methyl-5-phenyl-1,2-dioxane (105) under fvp conditions and upon treatment with iron(II) sulphate, were compared with those of the unsubstituted 3-methyl-1,2-dioxane (121) under identical conditions.

2.3.1 3-Methyl-5-phenyl-1,2-dioxane (105)

The flash vacuum pyrolysis of this dioxane afforded two main products. The conclusion that these were the alternative 1,5-hydrogen transfer products of the intermediate 1,6-dioxyl diradical was confirmed by preparing authentic samples (see Section 2.4.4 and 2.4.5) and comparing their nmr spectra and HPLC retention times with those of the pyrolysate. Only a very small amount of the β-scission product, styrene, was detected. The formation of this conjugated alkene does not offer a sufficient advantage to divert the dioxyl diradical from the favoured 1,5-hydrogen transfer. This contrasts the

behaviour of (82) described above (Section 2.2.2). This dioxane has a 3-phenyl substituent which gives ca. 40% β-scission products upon fvp.

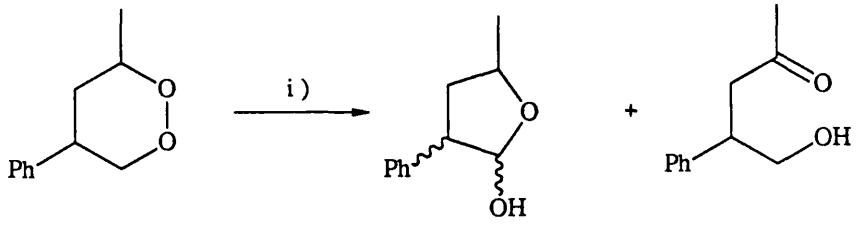
1,5-Hydrogen abstraction from the primary site (H_b) gives the four diastereoisomeric 5-methyl-3-phenyltetrahydro-2-furanols (144), presumably via the hydroxyaldehyde. 1,5-Hydrogen abstraction from the secondary site (H_a) affords 5-hydroxy-4-phenyl-2-pentanone (145) which is in equilibrium with the intramolecular hemiacetal.



The iron(II) induced rearrangement of 3-methyl-5-phenyl-1,2-dioxane (105) also afforded a mixture of the two hydrogen transfer products (144) and (145).

The ratio of furanol (144) to hydroxyketone (145) was determined by analytical HPLC. For duplicate flash vacuum pyrolyses, ratios of 10:1 and 6:1 were found, whereas for

duplicate iron(II)-induced rearrangements the ratio was found to be 1.3:1 in each case. Thus the products remain the same but the distribution is dramatically changed upon going from fvp to iron(II) induced decomposition.

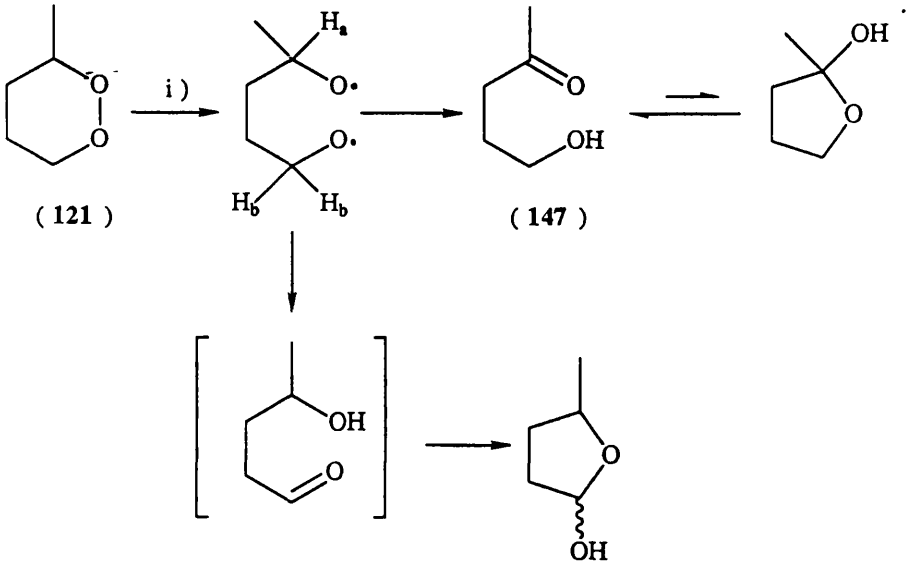


(105) (144) (145)

i) $FeSO_4$, H_2O , CH_3CN , N_2

2.3.2 3-Methyl-1,2-dioxane (121)

The flash vacuum pyrolysis of 3-methyl-1,2-dioxane (121) afforded a mixture of the two expected 1,5-hydrogen transfer products. These were identified as the primary hydrogen (H_b) abstraction products, cis- and trans-5-

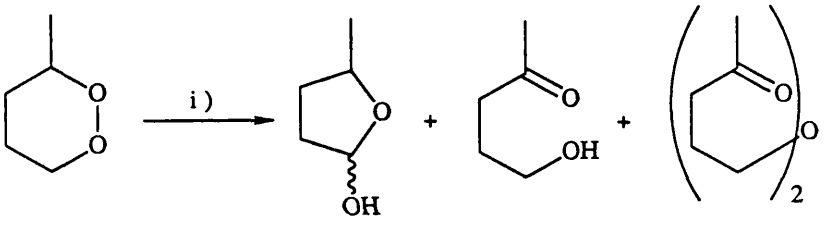


(121) (147) (146)

i) 450 °C , 10^{-3}mmHg

methyltetrahydro-2-furanol (146) and the secondary hydrogen (H_a) abstraction product, 5-hydroxypentan-2-one (147) by comparison of spectra with those of authentic samples (see section 2.4.6 and 2.4.7).

The treatment of (121) with iron(II) sulphate in aqueous acetonitrile afforded three main products, the expected furanol (146) and hydroxyketone (147) but also the ether (148). The ether was thought to arise by iron (II) catalyzed dehydration of the hydroxyketone and this was confirmed in an independent experiment.



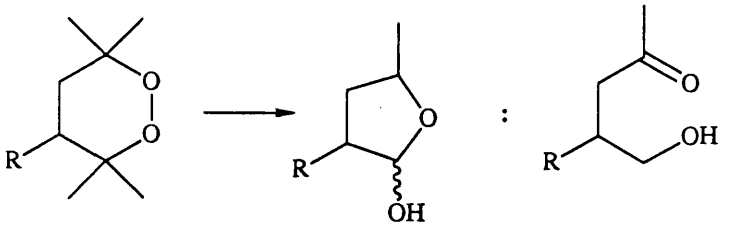
(105) (146) (147) (148)

i) $FeSO_4$, H_2O, MeCN, N_2

The ratio of furanol (146) to hydroxyketone-type products (147) and (148) was determined by ^{1}H-nmr. For the flash pyrolysis, a ratio of 2:1 was found whereas for the iron(II)-induced rearrangements the ratio was found to be 1:1.

Thus, our results show that the introduction of a phenyl group at the five position of a 3-methyl-1,2-dioxane ring greatly increases the amount of primary hydrogen (H_b) abstraction under fvp conditions, but has a

negligible effect in the iron(II) induced rearrangement (Scheme 26).

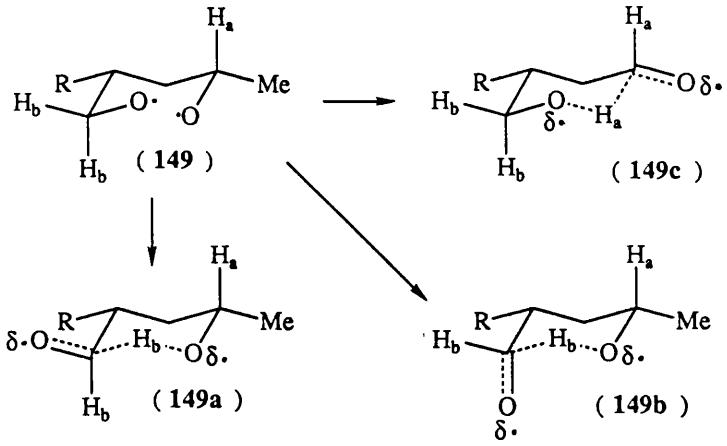


fvp	R = H	2	:	1
	R = Ph	8	:	1
Fe^{2+}	R = H	1	:	1
	R = Ph	1.3	:	1

(Scheme 26)

Considering first the flash vacuum pyrolyses, several factors will influence hydrogen abstraction in the diradical. These include the statistical effect of the numbers of abstractable hydrogens, differences in the bond dissociation energies of $C\text{-}H_a$ and $C\text{-}H_b$, electronic effects of the phenyl substituent, and steric effects.

Setting aside for the moment any steric or electronic effects, a purely statistical distribution of products is unlikely as the bond dissociation energy of the $C\text{-}H_a$ bond will be less than that of the $C\text{-}H_b$ and so a product ratio of less than 2:1 would be expected. Thus, the observed values of > 2:1 clearly indicate preferential primary (H_b) abstraction for steric and/or electronic reasons. A steric effect can be invoked if hydrogen abstraction in the 1,6-dioxyl diradical proceeds through one of the three chair-like transition states pictured in scheme 27. These

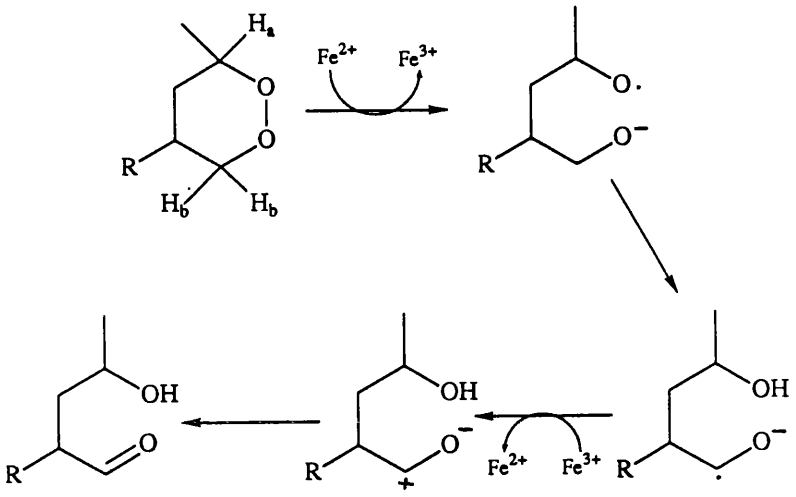


(Scheme 27)

transition states arise from the initially formed dioxyl diradical by rotation about the carbon-carbon bonds β to the radical site. Only in (149a) are all three substituents (O·, phenyl and methyl) equatorial, therefore one might expect this transition state to be favoured and primary hydrogen abstraction to be preferred. However, it is not easy to see on steric grounds how the introduction of a phenyl at the 5-position (R = Ph) renders the difference in stability between (**149a**) and (**149b**) versus (**149c**) greater than when R=H.

The iron(II)-induced decompositions probably proceed <u>via</u> radical anions (Scheme 28). These would appear to be less discriminating radicals, giving furanol to hydroxyketone ratios of approaching 1:1. However, this issue is complicated by the question of the role played by the iron. A completely free radical anion is unlikely and it is more likely to be coordinated to the iron. The nature of this co-ordination could be crucial in

influencing the selectivity, but unfortunately nothing appears to be known about the topic.



(Scheme 28)

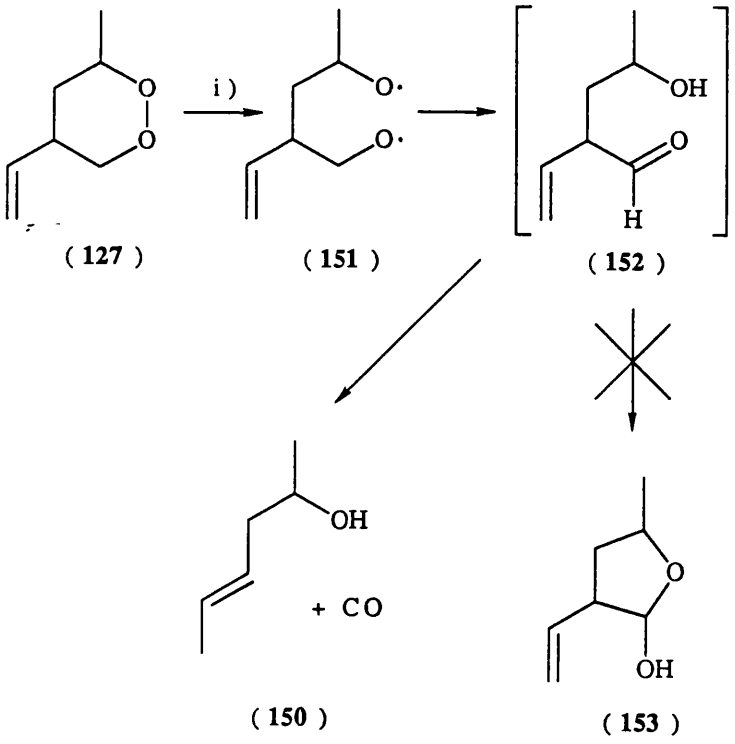
2.3.4 5-Ethenyl-3-methyl-1,2-dioxane (127)

Only one flash vacuum pyrolysis was carried out on this dioxane because of the small amounts available. The ^{13}C-nmr spectrum showed a major product with six carbon atoms. APT ^{13}C-nmr and ^{1}H-nmr spectra suggested that the product was an isomer of 4-hexen-2-ol (150). This identification was confirmed by comparison of the nmr data with those reported in the literature for cis- and trans-4-hexen-2-ol (150) [72]. The ^{13}C-nmr chemical shifts for the non-vinylic carbons are in agreement with those reported for the trans-isomer but the data for the vinylic carbons correspond more closely to reported values for the cis-isomer (Table 1). This may be due to an error in the paper.

4-hexen-2-ol (150) cis	trans	Flash vacuum pyrolysis product of (127)
13.1	18.1	18.09
22.8	22.6	22.62
36.8	42.5	42.52
67.7	67.7	67.19
126.8	125.9	127.07
128.5	126.2	126.06

(Table 1)

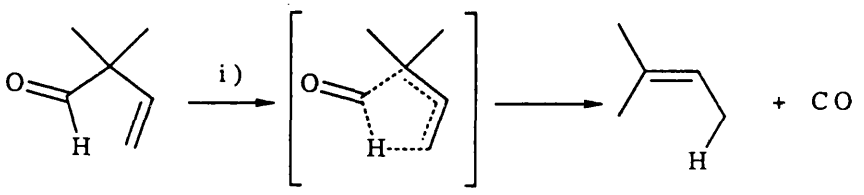
Therefore it would appear that the fvp of 5-ethenyl-3-methyl-1,2-dioxane (127) brings about a decarbonylation. The most likely mechanism for this reaction is given in scheme 29. The peroxide bond undergoes homolysis to give the 1,6-diradical (151). Drawing a parallel with the 5-phenyl analogue (105), one would expect 1,5-hydrogen



(127) (151) (152)

(150) (153)

transfer from the primary site to be favoured. This produces the hydroxyaldehyde (152) which instead of rearranging to the lactol (153), undergoes decarbonylation with hydrogen migration and a double bond shift. There appears to be only one previous example of a thermal decarbonylation of this type, namely that reported by Crawford et. al.[73] for 2,2-dimethyl-3-butenal (154). From their kinetic studies and deuterium labelling studies it was concluded that the mechanism is concerted.

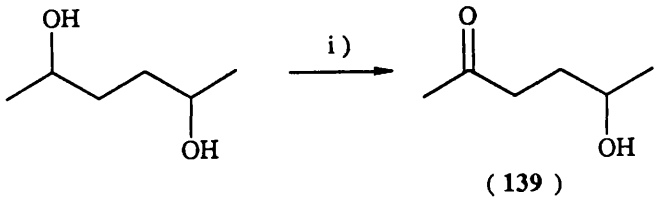


(154)

2.4 Preparation of authentic samples

2.4.1 5-Hydroxyhexan-2-one (139)

5-Hydroxyhexan-2-one (139) was prepared by the partial oxidation of hexan-2,5-diol with silver carbonate on Celite, and purified by column chromatography[74]. The yield was 20%.

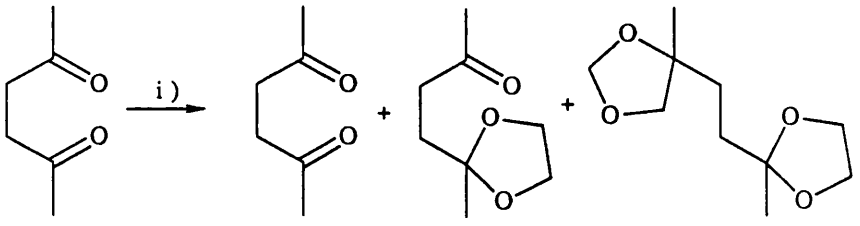


(139)

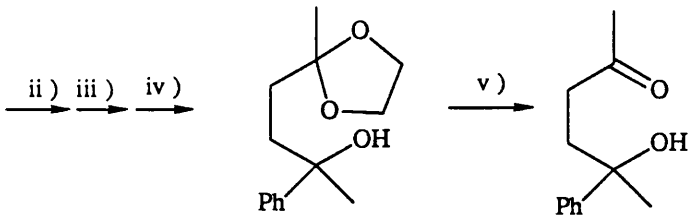
i) Ag_2CO_3, C_6H_6, Δ, $-H_2O$

2.4.2 5-Hydroxy-5-phenylhexan-2-one (143)

Treatment of hexan-2,5-dione (140) with half an equivalent of phenylmagnesium bromide did not yield appreciable quantities of the hydroxyketone (143). As a result, an attempt was made to prepare the monoacetal of hexan-2,5-dione (140) by reaction of (140) with one equivalent of ethane-1,2-diol. This afforded a 1:2:1 mixture of dione (140), monoacetal (155), and diacetal (156) which proved difficult to separate by column chromatography. However, upon cooling in a freezer the diacetal (156) crystallized out and could be filtered off. The resulting mixture of dione (140) and monoacetal (155) was treated with phenylmagnesium bromide and gave a mixture of products. The unwanted product crystallized



(140) (140) (155) (156)



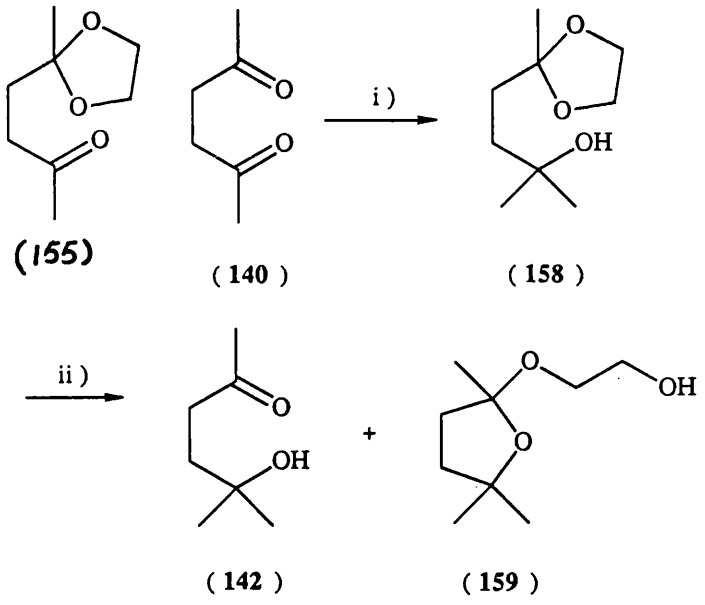
(157) (143)

i) $HOCH_2CH_2OH$, H^+ , C_6H_6 , Δ , $-H_2O$
ii) < O°C , Crystallise diacetal
iii) PhMgBr , Et_2O
iv) Filter
v) H^+ , H_2O , SiO_2 , CH_2Cl_2

out upon cooling and the resulting crude 2-methyl-2-(3-hydroxy-3-phenylbutan-1-yl)-1,3-dioxolane (157) was treated with 15% H_2SO_4 adsorbed on silica[75] to give the hydroxyketone (143) in only 7% yield after column chromatography.

2.4.3 5-Hydroxy-5-methylhexan-2-one (142)

The dione (140) monoacetal (155) mixture (Section 2.4.2) was treated with methylmagnesium bromide and gave a mixture of products from which 2-methyl-2-(3-hydroxy-3-methylbutan-1-yl)-1,3-dioxolane (158) was isolated by column chromatography. The deacetalization of (158) upon treatment with dilute acid/silica did not cleanly give the hydroxyketone (142). Of the several products formed, only one was identified. This proved to be the intramolecular

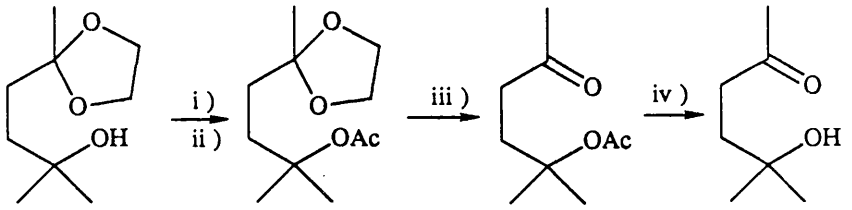


(155) (140) (158)

(142) (159)

i) MeMgBr , Et_2O
ii) H^+ , H_2O , SiO_2 , CH_2Cl_2

acetal (**159**) resulting from trapping by the tertiary alcohol group of the carbocation produced upon semi-deprotection. However, the acetate (**160**), prepared in a yield of 30%, was cleanly deacetalized to (**161**) in a yield of 61%. This acetate (**161**) was easily hydrolysed with methanolic base to afford 5-hydroxy-5-methylhexan-2-one (**142**) in a yield of 92%.



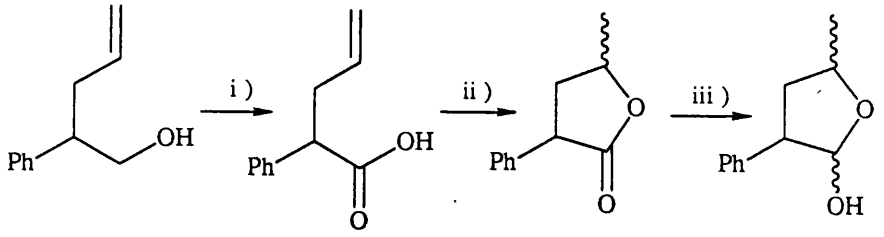
(158) (160) (161) (142)

i) Na , Et_2O , N_2 , 48 hr
ii) AcCl
iii) H^+ , H_2O , SiO_2 , CH_2Cl_2
iv) NaOH , H_2O , MeOH

2.4.4 5-Methyl-3-phenyltetrahydro-2-furanol (144)

2-Phenyl-4-pentenoic acid (**162**) was prepared in a yield of 73% by oxidation of 2-phenyl-4-penten-1-ol (**98**) with Jones Reagent. Refluxing the acid (**162**) with 50% sulphuric acid effected cyclization to 5-methyl-3-phenyldihydro-2-furanone (**163**) in a yield of 69%. This lactone was reduced to 5-methyl-3-phenyltetrahydro-2-furanol (**144**) upon treatment with diisobutylaluminium hydride (DIBAL-H). Purification of the lactol by column chromatography followed by short-path distillation using a Kugelrohr apparatus gave a clear colourless oil which

slowly crystallized.



(98) (162) (163) (144)

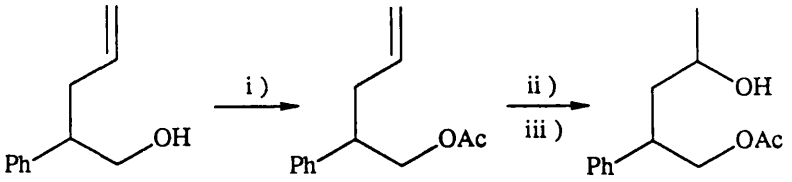
i) $HCrO_3$, Me_2CO
ii) 50% H_2SO_4 , Δ
iii) DIBAL-H , Et_2O , -76°C , N_2

2.4.5 5-Hydroxy-4-phenlpentan-2-one (145)

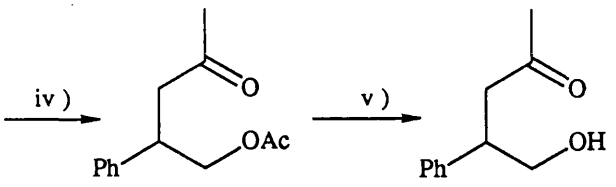
2-Phenyl-4-penten-1-ol (98) was refluxed with glacial acetic acid and a catalytic amount of concentrated sulphuric acid to give 2-phenyl-4-penten-1-yl acetate (164). The hydroxymercuration/demercuration of (164) afforded 4-hydroxy-2-phenylpentan-1-yl acetate (165) in an isolated yield of 48%. Care has to be taken with the concentration of the base used during the hydridodemercuration. Using 0.5M sodium hydroxide caused deoxymercuration, the acetate (164) being recovered, whilst 3M sodium hydroxide hydrolysed the acetate function. However 1.5M sodium hydroxide solution prevented deoxymercuration without extensive hydrolysis of the acetate group during hydridodemercuration.

The hydroxyacetate (165) was oxidized to 5-acetoxy-4-phenylpentan-2-one (166) upon treatment with PCC in a

yield of 62%. Finally, the ketoacetate (**166**) was hydrolysed with methanolic sodium hydroxide to give 5-hydroxy-4-phenylpentan-2-one (145) in an isolated yield of 83%.



(98) (164) (165)

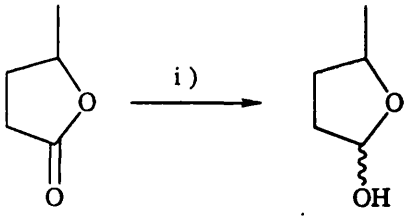


(166) (145)

i) AcOH , H^+ , Δ
ii) $Hg(OAc)_2$, H_2O , THF
iii) $NaBH_4$, 1.5M NaOH
iv) PCC , CH_2Cl_2
v) NaOH , H_2O , MeOH

2.4.6 5-Methyltetrahydro-2-furanol (146)

γ-Valerolactone was reduced with DIBAL-H to give the furanol (**146**) in a yield of 31%.

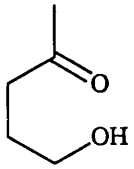


(146)

i) DIBAL-H , Et_2O , -76°C , N_2

2.4.7 5-Hydroxypentan-2-one (147)

5-Hydroxypentanone (**147**) is commercially available and was obtained from the Aldrich Chemical Co. Ltd.



(**147**)

CHAPTER 4

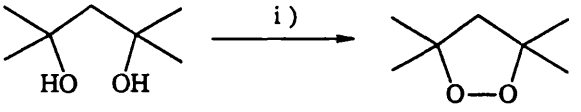
PREPARATION OF 1,2 - DIOXOLANES BY CYCLOPEROXYHALOGENATION

1. INTRODUCTION

There are many diverse preparations of 1,2-dioxolanes reported in the literature. These are most easily classified according to the nature of the starting materials. For the purpose of this short review, 1,2-dioxolanes will be considered as originating from (i) 1,3-diols and 1,3-dihalides, (ii) acyclic peroxides, (iii) dienes, (iv) cyclopropanes, and (v) carbonyl oxides.

1.1 Dioxolanes from 1,3-diols, -dihalides, and -diesters

The synthesis of a 1,2-dioxolane was first reported by Criegee[30] in 1955 and since then 1,3- diols and their derivatives have afforded several 1,2-dioxolanes. Criegee prepared 3,3,5,5-tetramethyl-1,2-dioxolane (135) in a yield of 31% by treating the diol (167) with acidified hydrogen peroxide.

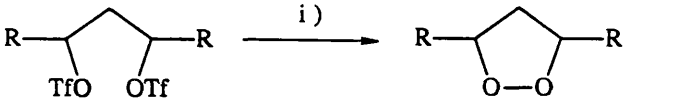


(167) (135)

i) 50% H_2O_2, 70% H_2SO_4

The use of sulphonate esters of 1,3-diols has facilitated the preparation of primary and secondary 1,2

dioxolanes. Salomon and Salomon[32] have used bis(tri-n-butyltin) peroxide to prepare dioxolanes from the corresponding bistrifluoromethanesulphonates. Thus, (168a) and (168b) when treated with bis(tri-n-butyltin) peroxide afforded 1,2-dioxolane (169) and 3,5-dimethyl-1,2-dioxolane (137) in yields of 68% and 52% respectively.

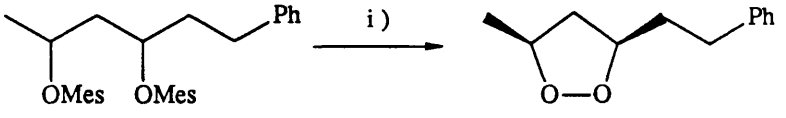


(168)

i) $(n\text{-}Bu_3SnO)_2$

(137) R = Me
(169) R = H

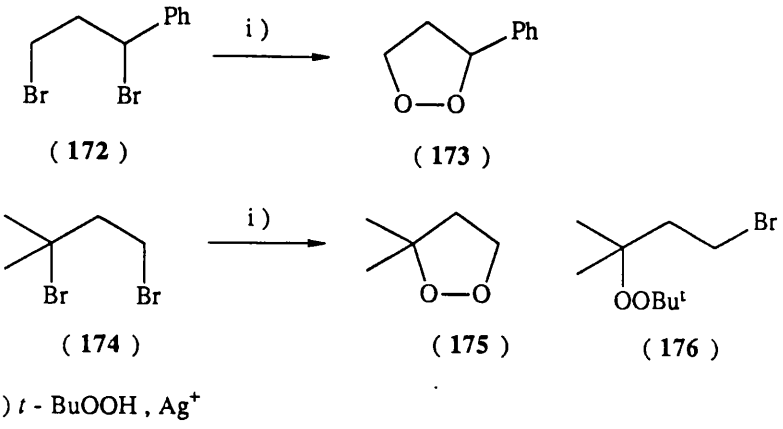
Corey[76] used potassium superoxide and a phase transfer catalyst (18-crown-6) in DMSO to prepare the dioxolane (170) from the bismethanesulphonate (171) in a yield of 35%.



(170) (171)

i) 4 KO_2, 5 18-Crown-6, DMSO, 25°C, 3 min.

Porter and Mitchell[27] reported that the reaction of 1,3-dibromides with a silver salt and 90% t-butyl hydroperoxide gave the corresponding 1,2-dioxolanes. Thus, dibromide (172) gave 3-phenyl-1,2-dioxolane (173) in a yield of 50%, while (174) gave 3,3-dimethyl-1,2-dioxolane (175) in a yield of 30% together with 11-18% of the bromoperoxide (176).

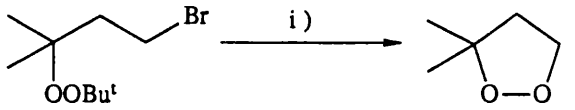


(172) (173)

(174) (175) (176)

i) t - BuOOH , Ag^+

This bromoperoxide (176) is an intermediate in the conversion of (174) to (175) and gives the dioxolane (175) in high yield when treated with a silver salt.



(176) (175)

i) t - BuOOH , Ag^+

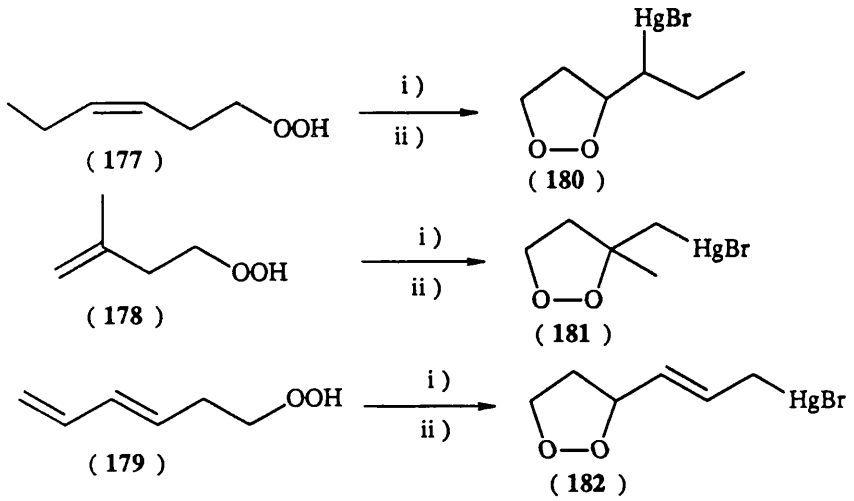
This reaction has been utilized by Bloodworth, Cooksey and Chan[77,78] to prepare 1,2-dioxolanes from bromoperoxides prepared by the peroxymercuration/bromodemercuration of cyclopropanes and is described in detail later. (Section 1.4).

1.2 Dioxolanes from acyclic peroxides

The cyclization of an acyclic peroxide is quite a common technique in 1,2-dioxolane preparation. In particular, hydroperoxides with a suitable functional

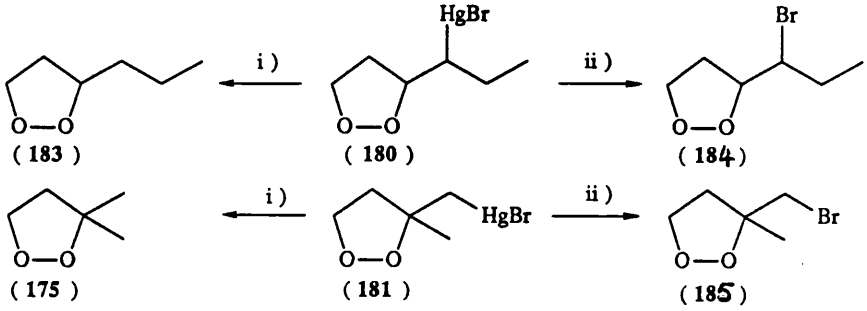
group at the γ-carbon may be converted into 1,2-dioxolanes.

Porter[35] has reported the cyclization of unsaturated hydroperoxides upon treatment with mercury(II) nitrate, followed by anion exchange with potassium bromide. The hydroperoxides (177) (178) (179) gave the bromomercurio-dioxolanes (180) (181) (182) in yields of 60% to 70%. The



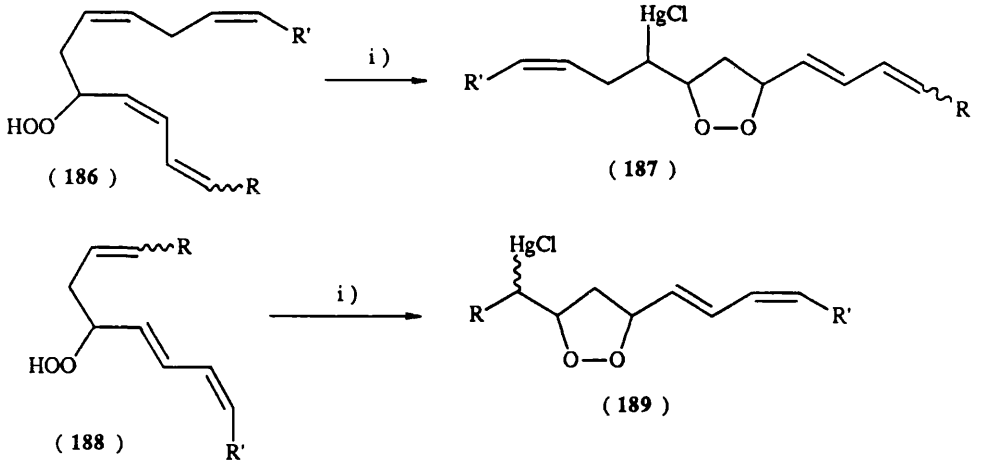
i) $Hg(NO_3)_2 \cdot \frac{1}{2} H_2O$, CH_2Cl_2
ii) H_2O , KBr

dioxolanes (183) and (175) or β-bromodioxolanes (184) (185) were prepared by treating the mercurials (180) or (181) with either a basic sodium borohydride solution or with bromine in dichloromethane.



i) $NaBH_4$, 3M NaOH , CH_2Cl_2 , < 0°C
ii) Br_2 , CH_2Cl_2

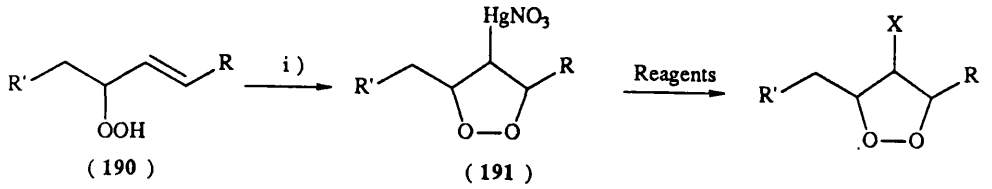
Cycloperoxymercuration has been utilized by Corey et al.[16,17] in the preparation of 1,2-dioxolane intermediates in the 'biomimetic' synthesis of prostaglandins. The four hydroperoxides (186) and (188) were each treated with mercury(II) chloroacetate to afford one diastereoisomer of the dioxolanes (187) and (189).



(186) (187) (188) (189)

i) XS $Hg(O_2CCH_2Cl)_2$, THF

Gunstone and Bascetta[79] have cyclized the hydroperoxides derived from methyl oleate (190). These are allylic hydroperoxides, but upon treatment with mercury(II) nitrate they cyclize by the 5-endo mode to give the 1,2-dioxolanes (191). Treatment of these nitratomercuriodioxolanes (191) with a potassium halide gave the chloro- and bromo-mercuriodioxolanes (192) and treatment with sodium borohydride gave the dioxolanes (193). Porter[37] also reported that γ,δ-unsaturated hydroperoxides (177) when treated with di-t-butyl peroxalate (DBPO) in oxygenated benzene followed by

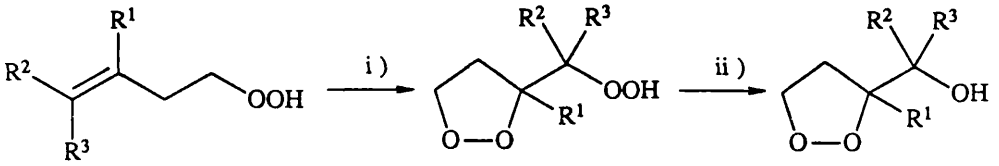


(190) (191)

a) R' = $(CH_2)_6Me$, R = $(CH_2)_6CO_2Me$
b) R' = $(CH_2)_6CO_2Me$, R = $(CH_2)_6Me$

		Reagents
(192a)	X = HgCl	KCl
(192b)	X = HgBr	KBr
(193)	X = H	$NaBH_4$

triphenyl phosphine, gave β-hydroxy dioxolanes (197)

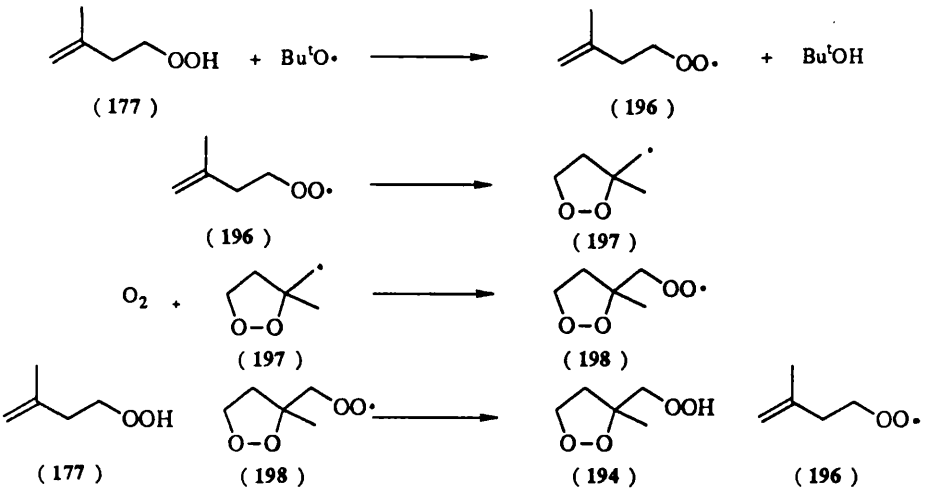


(177) (194) (195)

a) R^1 = Me , R^2 = R^3 = H
b) R^1 = R^2 = H , R^3 = Et
c) R^1 = H , R^2 = R^3 = Me

i) DBPO , C_6H_6 , 48 hr , O_2
ii) Ph_3P

The reaction proceeds by a free-radical chain mechanism. Thermolysis of DBPO affords t-butoxyl radicals which abstract hydrogens from for example, the hydroperoxide (177) to give the peroxyl radical (196).



(177) (196)

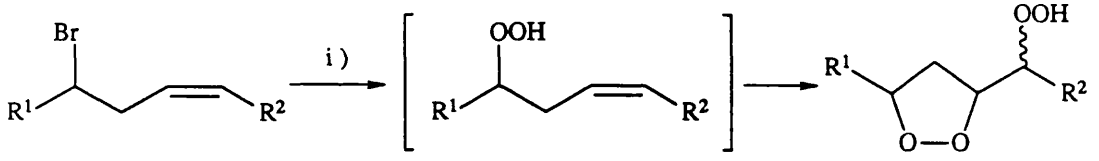
(196) (197)

(197) (198)

(177) (198) (194) (196)

This radical then cyclizes by the 5-exo-Trig mode to the alkyl radical (197) which is trapped by oxygen giving a second peroxyl radical (198). This abstracts a hydrogen from the hydroperoxide (177) to give the product (194).

Another, apparently accidental, example of radical cyclization of an unsaturated hydroperoxide has been reported by Gunstone[80]. In an attempt to prepare the hydroperoxide (200) from the bromide (199), the hydroperoxide appears to have undergone radical cyclization followed by trapping with oxygen to give the hydroperoxy dioxolane (201). It has also been reported that the photooxygenation of linoleate and linolenate esters affords 1,2-dioxolanes alongside the expected hydroperoxides.[100,101]

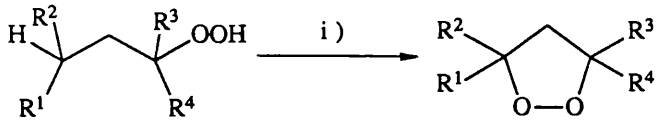


(199) (200) (201)

i) Ag^{+}, H_2O_2

Kropf and von Wallis[40,47,81] reported the cyclization of γ-aryl substituted hydroperoxides to 1,2-dioxolanes by a Barton-type-reaction. In the absence of a γ-aryl substituent no cyclization products were observed.

The treatment of such hydroperoxides (202) with lead (IV) acetate afforded 1,2-dioxolanes (203).

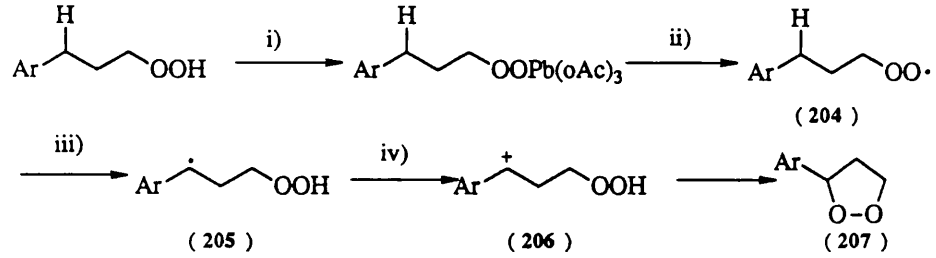


(202) (203)

i) $Pb(OAc)_4$, Petroleum ether

	R^1	R^2	R^3	R^4
a)	C_6H_5	H	CH_3	CH_3
b)	C_6H_5	H	CH_3	C_6H_5
c)	C_6H_5	CH_3	CH_3	CH_3
d)	*p*-$NO_2C_6H_4$	H	CH_3	CH_3
e)	*p*-$CH_3OC_6H_4$	H	CH_3	CH_3
f)	*o*-$CH_3C_6H_4$	H	CH_3	CH_3

The mechanism suggested involves a reaction of a hydroperoxide (202) with lead(IV) acetate, followed by dissociation to the peroxyl radical (204) and lead(III) acetate. The peroxyl radical abstracts the benzylic hydrogen either inter- or intra-molecularly to give the benzylic radical (205). This radical undergoes an electron transfer reaction to the lead(III) acetate and the resultant benzylic carbocation (206) undergoes cyclization to the dioxolane (207).

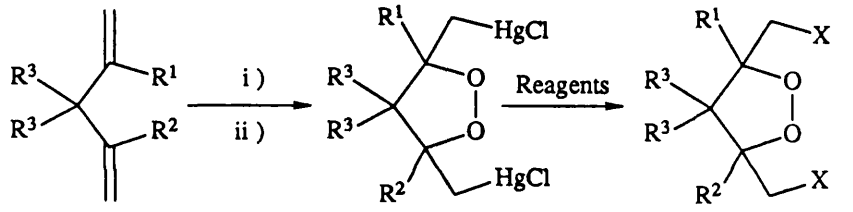


(204) (205) (206) (207)

i) $Pb(OAc)_4$
ii) - $Pb(OAc)_3$
iii) H-Abstraction
iv) $Pb(OAc)_3$

1.3 Dioxolanes from 1,4-dienes

Bloodworth, Khan and Loveitt[34] have prepared 1,2-dioxolanes and dibromodioxolanes by the peroxymercuration of dienes followed by either hydrido- or bromo-demercuration. The reaction of 1,4-dienes (208) with mercury(II) nitrate and 85% hydrogen peroxide in dichloromethane followed by anion exchange with potassium chloride afforded the mercurials (209) which gave the dioxolanes (135), (137), (210) and (211) upon treatment with basic sodium borohydride and the dibromodioxolanes (212)-(215) when treated with bromine in dichloromethane.



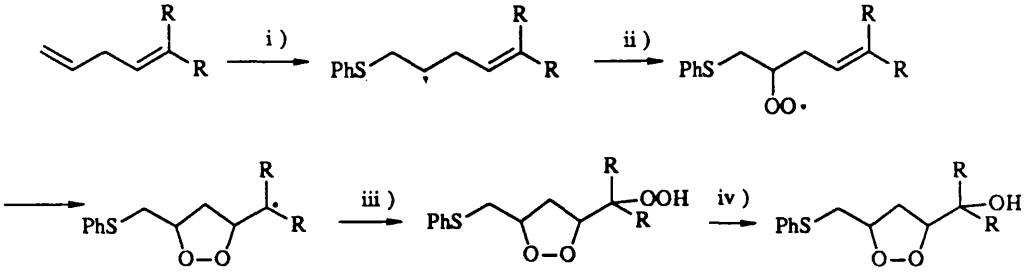
(208) (209)

	X=H	X=Br
$R^1=R^2=R^3=H$	(135)	(212)
$R^1=Me, R^2=R^3=H$	(137)	(213)
$R^1=R^2=Me, R^3=H$	(210)	(214)
$R^1=R^2=H, R^3=Me$	(211)	(215)

i) $Hg(NO_3).H_2O$, 85% H_2O_2, CH_2Cl_2
ii) KCl_{aq}
Reagents: X=H $NaBH_4$, 3M NaOH, CH_2Cl_2, < 0°C
X=Br Br_2, CH_2Cl_2

1,2-Dioxolanes have also been prepared from 1,4-dienes by thiol-oxygen cooxidation (TOCO). Several examples of this reaction have been reported by Beckwith and Wagner[82]. The mechanism is straightforward. The thiophenoxyl radical formed in the initiation step adds to the vinyl group to generate the alkyl radical. This is

trapped by oxygen to give the peroxyl radical which undergoes a 5-exo-Trig cyclization to the alkyl radical. This radical is trapped by oxygen and the peroxyl radical thus generated abstracts a hydrogen from thiophenol to give hydroperoxide and regenerate the thiophenoxyl radical to carry the chain. The hydroperoxide is reduced to the alcohol upon treatment with triphenylphosphine (Scheme 29).



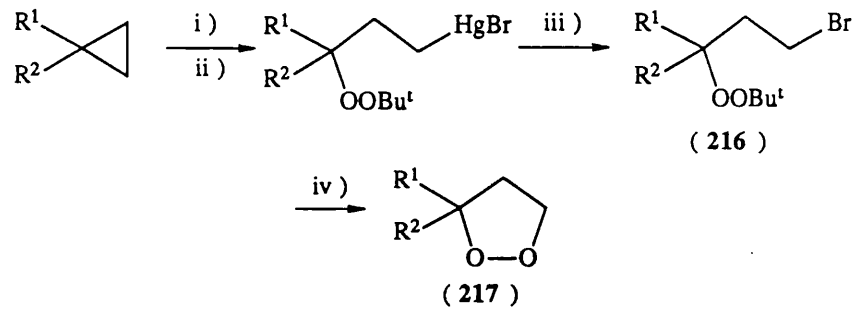
i) PhS·
ii) O_2
iii) O_2, PhSH
iv) Ph_3P

(Scheme 29)

1.4 Dioxolanes from cyclopropanes

1,2-Dioxolanes have been prepared from cyclopropanes by several very different techniques. The electrophilic ring opening of cyclopropanes has been employed to prepare γ-bromo peroxides which can be cyclized to the dioxolanes by treatment with a silver salt. The method described by Adam[83] was the reaction of cyclopropanes with N-bromosuccinimide (NBS) and hydrogen peroxide, but this proved problematical. Bloodworth, Cooksey and Chan[77,78]

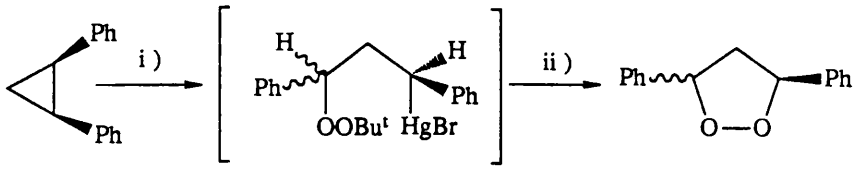
have used t-butylperoxymercuration of cyclopropanes followed by bromodemercuration to prepare a series of γ-bromo-t-butyl peroxides (216), which when treated with a silver salt afforded the 1,2-dioxolanes (217) in yields of 80-100% of crude material.



a) R^1=H , R^2=H
b) R^1=Et , R^2=H
c) R^1=Ph , R^2=H
d) R^1=Me , R^2=Me
e) R^1=Me , R^2=Ph
f) R^1=Ph , R^2=Ph

i) *t* -BuOOH , $Hg(OAc)_2$, 20 mol% $HClO_4$, CH_2Cl_2
ii) KBr_{aq}
iii) Br_2 , CH_2Cl_2
iv) Ag^+

A special case of 1,2-dioxolane formation from a cyclopropane has been reported by Bloodworth and Lampman[84]. From the reaction of cis-1,2-diphenylcyclopropane (218) with mercury(II) acetate in t-butyl hydroperoxide, no peroxy mercurials (219) were recovered, but cis-3,5-diphenyl-1,2 dioxolane (220) was isolated in a yield of 10%. This dioxolane formation is explained by the oxidative demercuration of the mercurial (219). When the reaction was repeated with 2-equivalents of mercury (II) acetate and t-butyl hydroperoxide in dichloromethane, both cis and trans-dioxolanes were formed

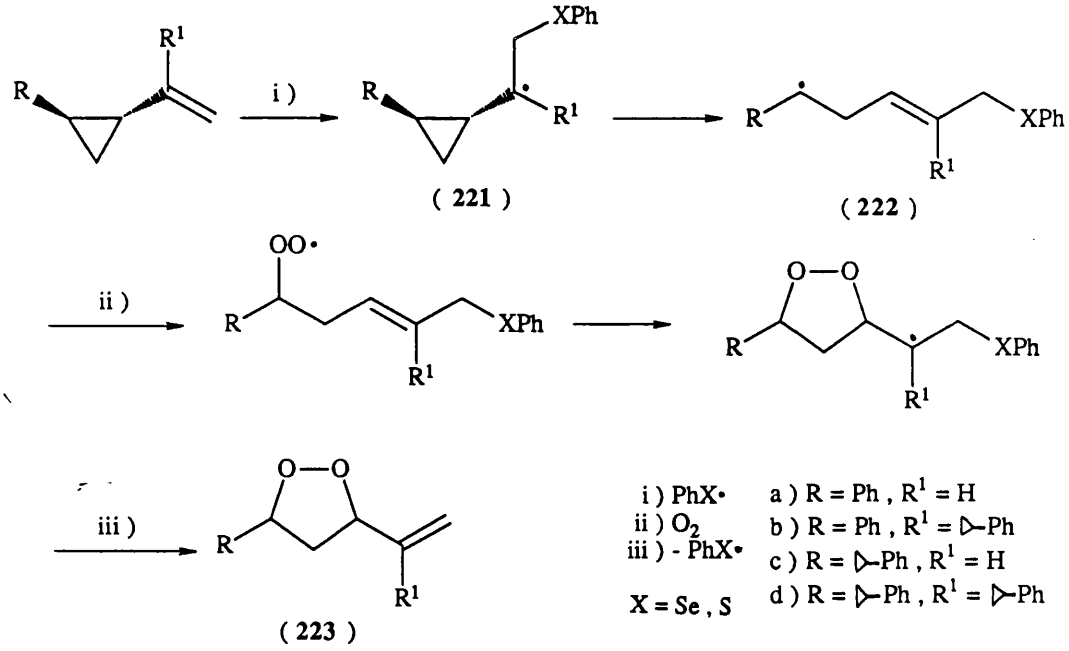


(218) (219) (220)

i) $Hg(OAc)_2$, t -BuOOH , 20 mol% $HClO_4$
ii) $Hg(OAc)_2$

and isolated in a combined yield of 39%. The trans-1,2-diphenylcyclopropane gave no such dioxolane formation.

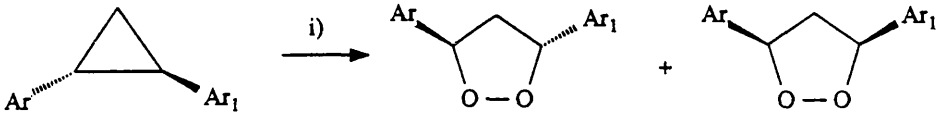
The opening of a cyclopropylcarbinyl radical (221) to homoallylic radical (222) has been employed by Feldman et al.[85] to prepare 1,2-dioxolanes (223).



By making R and/or R_1 a 2-phenyl substituted cyclopropane, a chain of two or three dioxolane rings could be formed.

1,2-Dioxolanes have also been prepared by the sensitized photooxygenation of cyclopropanes, though this is mainly restricted to cyclopropanes bearing aromatic substituents.

Using cyclopropanes (224) with electron-rich aryl substituents and 9,10-dicyanoanthracene (DCA) as a sensitizer, Mizuno and coworkers[86] have obtained 1,2-dioxolanes (225) in yields generally in excess of 90%.

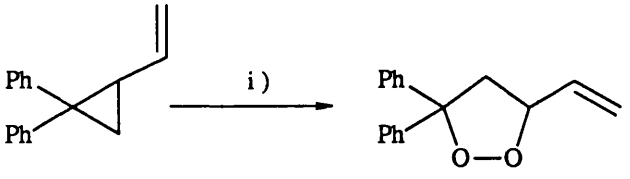


(224) (225)

i) hυ , O_2 , DCA , CH_3CN

a)	Ar=p-$Me_2NC_6H_4$, Ar_1=p-$MeOC_6H_4$	90%
b)	Ar=p-$Me_2NC_6H_4$, Ar_1=C_6H_5	95%
c)	Ar=Ar_1=$MeOC_6H_4$	95%
d)	Ar=Ar_1=m,p-$(MeO)_2C_6H_3$	80%
e)	Ar=p-$MeOC_6H_4$, Ar_1=p-MeC_6H_4	95%
f)	Ar=p-$MeOC_6H_4$, Ar_1=p-ClC_6H_4	95%
g)	Ar=p-$MeOC_6H_4$, Ar_1=C_6H_5	95%

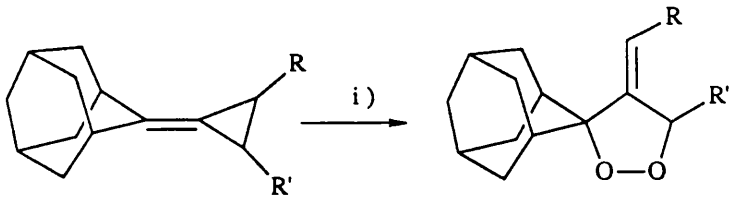
Using similar conditions, but with a biphenyl co-sensitizer Shim and Song[87] have prepared 3,3-diphenyl-5-ethenyl-1,2-dioxolane (227) from 1,1-diphenyl-2-ethenylcyclopropane (226) in a yield of 90%.



(226) (227)

i) hυ , DCA , Biphenyl , CH_3CN

Akasaka and Ando[88] have also prepared 1,2-dioxolanes (229) by the singlet oxygenation of two methylenecyclopropanes (228).

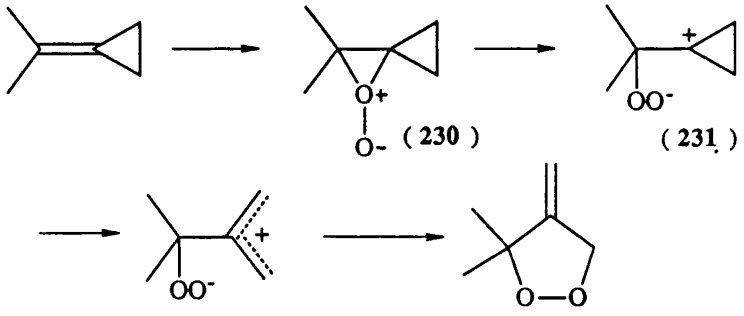


(228) (229)

a) R, R' = 

b) R, R' = 

The proposed mechanism involves the formation of a perepoxide (230) which rearranges to a cylopropylcation (231) which is turn rearranges to an allylic cation (232).

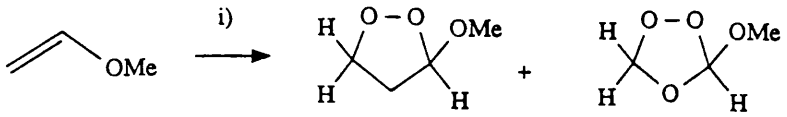


(230) (231)

(232)

1.5 1,2-Dioxolanes from Carbonyl Oxides

Kuczkowski[89] reported the formation of 1,2-dioxolanes from the ozonolysis of alkyl vinyl ethers. The intermediate carbonyl oxide undergoes a [3+2] cycloaddition with alkyl vinyl ether to give 3-alkoxy-1,2-dioxolanes (233).



(233)

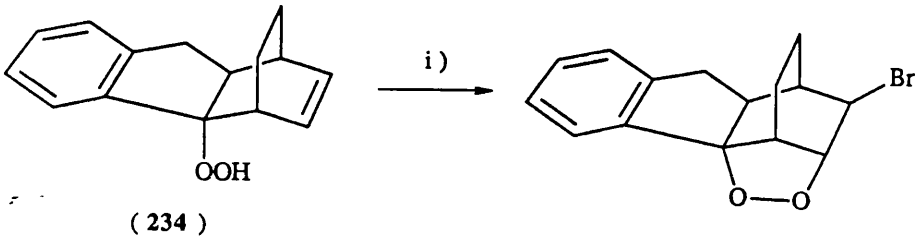
68%

9%

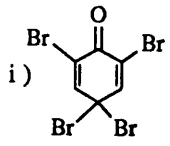
i) O_3 , Pentane

1.6 Cycloperoxyhalogenation

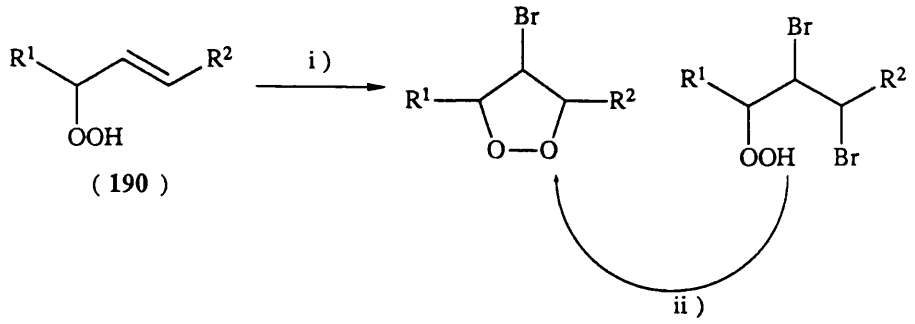
Iodocyclization is an important synthetic route to oxygen[90] and nitrogen[91] heterocycles. However, it appears that this technique has not been applied to the preparation of cyclic peroxides. Indeed, only two isolated examples of bromocyclization could be found. Firstly, Paquette et. al.[92] used 2,4,4,6-tetrabromocyclo-2,5-hexadienone to cyclize the unsaturated hydroperoxide (234) in order to prove the configuration at the carbon bearing the peroxide function. Secondly, Gunstone and



(234)



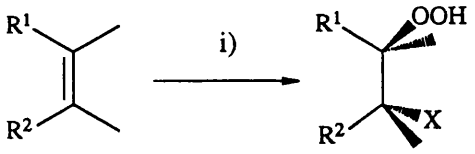
Bascetta[79] used bromine to cyclize the allylic hydroperoxides (190) by the 5-endo mode. Also produced were the vicinal dibromohydroperoxides, which were converted into the same dioxolanes by treatment with silver salts.



(190)

i) Br_2 a) $R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_6CO_2Me$
ii) Ag^+ b) $R^1 = MeO_2C(CH_2)_7$, $R^2 = (CH_2)_6Me$

There are, however, several reported cases of the intermolecular peroxyhalogenation of alkenes to give β-halohydroperoxides. For example, Kopecky et. al.[93] used 1,3-dibromo-5,5-dimethylhydantoin and N-chloroacetamide to prepare β-bromo- and β-chloro-alkylhydroperoxides (235) from the alkenes (236).



(236) (235)

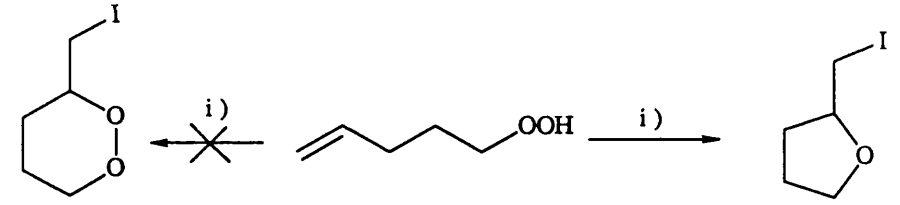
i) 1,3-Dibromo-5,5-dimethylhydantoin
ii) N-Chlorosuccinimide

The general lack of examples of cycloperoxy-halogenation led us to investigate this reaction as a method of preparing 1,2-dioxanes and 1,2-dioxolanes.

2. RESULTS AND DISCUSSION

2.1. 4-Penten-1-hydroperoxide (46)

4-Penten-1-hydroperoxide (46) was prepared in a yield of 36% from the alcohol via the methanesulphonate using the procedure described by Williams and Mosher[48]. Using the iodolactonization of unsaturated acids[94] as a model for conditions, 4-penten-1-hydroperoxide (46) was treated with excess iodine in dichloromethane. After the removal of excess iodine with sodium thiosulphate and the removal of the solvent, the sole product proved to be 2-iodomethyl-tetrahydrofuran (237) and not the desired 3-iodomethyl-1,2-dioxane (238).

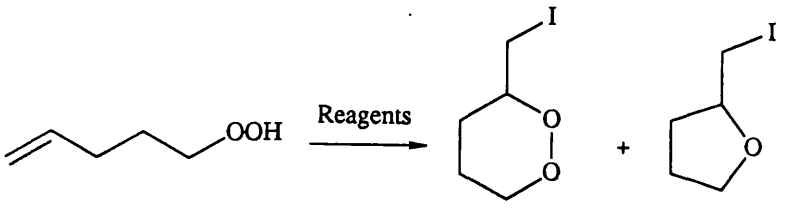


(238) (46) (237)

i) I_2^-, CH_2Cl_2

The reactions of 4-penten-1-hydroperoxide (46) with iodine in aqueous sodium hydrogen carbonate with or without potassium iodide and with iodine and pyridine in dichloromethane each gave a mixture of 2-iodomethyltetrahydrofuran (237) and a product that was taken to be 3-iodomethyl-1,2-dioxane (238) on the basis of

a consistent ^{13}C-nmr spectrum and a positive peroxide test using acidified ferrous thiocyanate. However, the tetrahydrofuran (237) was the major product in each reaction, exceeding the dioxane (238) by a factor of at least 2.5.

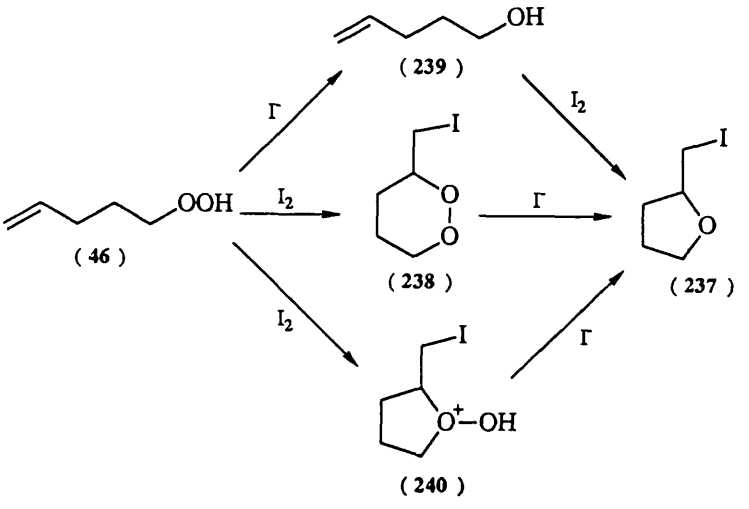


(46) (238) (237)

1 : > 2.5

Reagents = KI , $NaHCO_3$, H_2O , I_2
or = $NaHCO_3$, H_2O , I_2
or = I_2 ,pyridine , CH_2Cl_2

Three explanations can be offered for the production of 2-iodomethyltetrahydrofuran (237). Firstly, the inorganic iodide co-produced in the cycloperoxyiodination might be oxidized to iodine by unreacted hydroperoxide (46) to give unsaturated alcohol (239) which can then undergo iodoetherification to the tetrahydrofuran (237). Secondly, 3-iodomethyl-1,2-dioxane (238) might itself be reduced. However, this would seem unlikely since other cyclic peroxides have been exposed to iodine/iodide systems with no apparent reduction (see later). Finally, one can invoke the intermediacy of a gem-dialkyl peroxonium ion (240), a species known to undergo oxygen transfer in the presence of a suitable substrate[95].

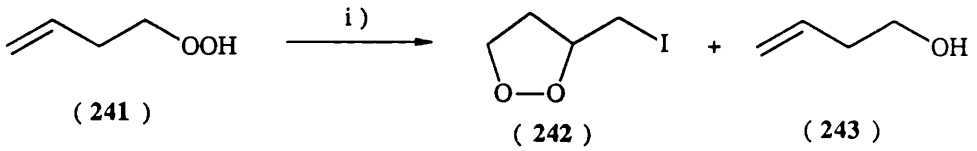


A reduction in the carbon chain length of the unsaturated hydroperoxide should exclude such gem-dialkyl peroxonium ion formation and any alcohols formed would be unlikely to cyclize[38]. It was therefore decided to extend the reaction to 3-buten-1-hydroperoxides.

2.2. 3-Buten-1-hydroperoxide (241) and 3-Methyl-3-buten-1-hydroperoxide (178)

3-Buten-1-hydroperoxide (241) and 3-methyl-3-buten-1-hydroperoxide (178) were prepared by the method of Williams and Mosher[48] in yields of 13% and 34% respectively. 3-Buten-1-hydroperoxide (178) was treated with a twofold excess of iodine and one equivalent of pyridine in dichloromethane. Removal of the solvent and purification by column chromatography gave only a 6% yield of 3-iodomethyl-1,2-dioxolane (242). A repeat of the reaction in CD_2Cl_2 and observation of the reaction mixture

by ^{13}C-nmr revealed that the major product was the dioxolane (**242**). The spectrum also showed about 20% of 3-buten-1-ol (**243**). There would therefore seem to be some reduction of the hydroperoxide to alcohol by iodide, but not enough to account, alone, for the extensive furan (**237**) formation from 4-penten-1-hydroperoxide (**46**)

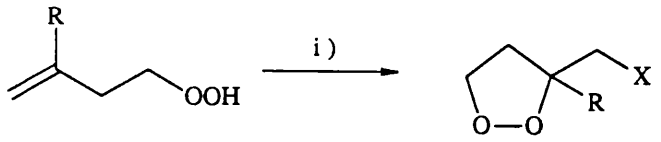


(241) (242) (243)

i) I_2 , pyridine , CD_2Cl_2

Partly in order to overcome the problems of reduction of the hydroperoxides and partly to extend the scope of the reaction, the use of alternative sources of electrophilic halogens was investigated. The readily available N-halosuccinimides were an obvious first choice.

3-Buten-1-hydroperoxide (**241**) and 3-methyl-3-buten-1-hydroperoxide (**178**) were each treated with N-iodosuccinimide (NIS) in dichloromethane to give 3-iodomethyl-1,2-dioxolane (**242**) and 3-iodomethyl-3-methyl-1,2-dioxolane (**244**) in isolated yields of 49% and 59% respectively. Similar reactions with N-bromosuccinimide (NBS) gave the analogous bromodioxolanes, 3-bromomethyl-1,2-dioxolane (**245**) and 3-bromomethyl-3-methyl-1,2-dioxolane (**184**) in isolated yields of 42% and 35% respectively.



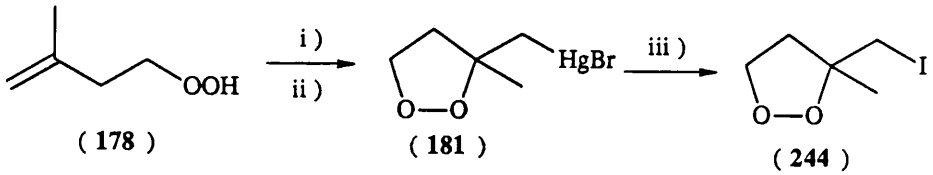
a) R = H (241)
b) R = Me (178)

	X =	I	Br
a) R = H		(242)	(245)
b) R = Me		(244)	(184)

i) NXS , CH_2Cl_2

All the halodioxolanes were new except for (184) which has been prepared by Porter et. al.[35] by peroxymercuration/bromodemercuration of the hydroperoxide (178). The spectroscopic data for (184) were in agreement with those previously reported.

In an independent synthesis of 3-iodomethyl-3-methyl-1,2-dioxolane (244), 3-bromomercuriomethyl-3-methyl-1,2-dioxolane was prepared in the prescribed manner[35] and subjected to iododemercuration as described by Bloodworth, Bowyer and Mitchell[6c]. This gave a sample of 3-iodomethyl-3-methyl-1,2-dixolane (244) identical to that prepared in the NIS reaction.

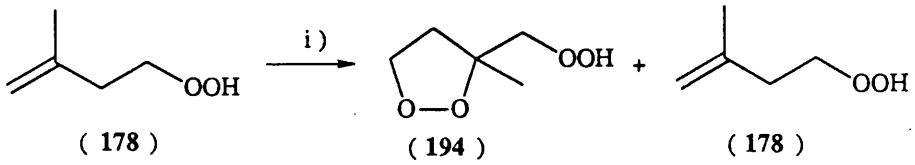


(178) (181) (244)

i) $Hg(NO_3)_2$. H_2O , CH_2Cl_2
ii) H_2O , KBr
iii) I_2 , CH_2Cl_2 , Δ

The reaction of N-chlorosuccinimide (NCS) with 3-methyl-3-buten-1-hydroperoxide (178) in dichloromethane at

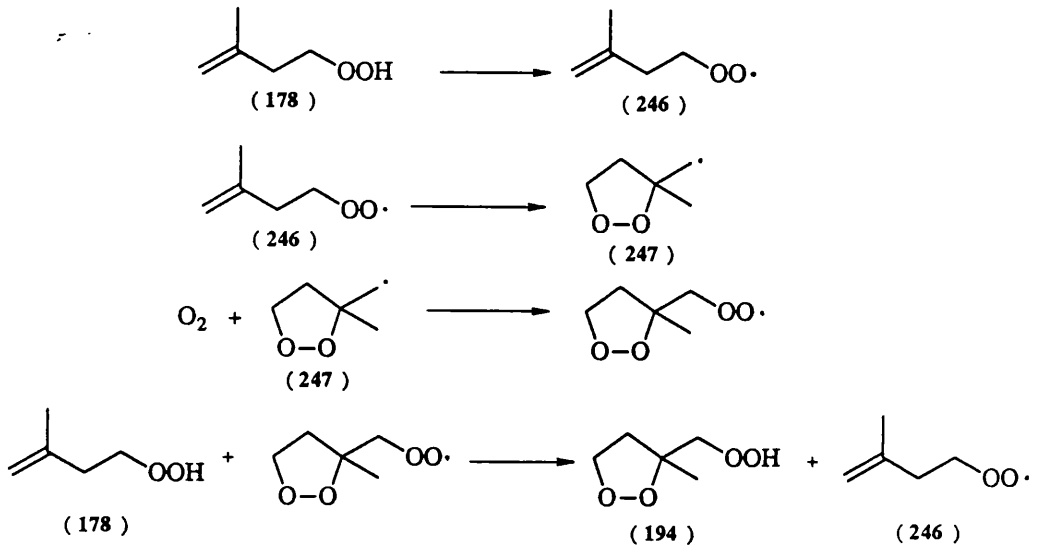
room temperature did not give the chlorodioxolane. With no apparent change in the reactants after 2 days as judged by TLC analysis, the solvent was removed at reduced pressure to afford a clear oil. The ^{13}C-nmr spectrum of this oil revealed the presence not only of starting hydroperoxide (178), but also of a single product.
The ^{13}C-nmr spectrum was consistent with the product being 3-hydroperoxymethyl-3-methyl-1,2-dioxane (194).



(178) (194) (178)

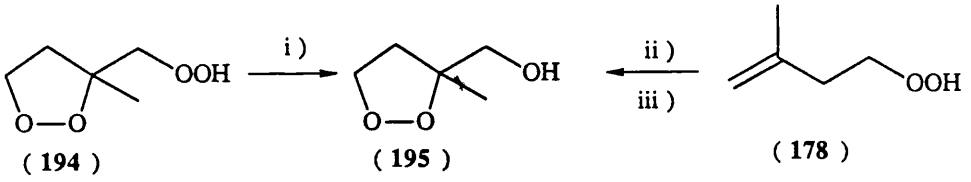
i) NCS , CH_2Cl_2 , Room teperature , 48 hr.

It seems likely that this was formed by the generation and subsequent cyclization of the peroxyl radical (246) followed by trapping of the resultant alkyl radical (247) by oxygen. Such a process, initiated by t-



butoxyl radicals, has been previously reported by Porter et. al.[37]

The identity of 3-hydroperoxymethyl-3-methyl-1,2-dioxolane (**194**) was confirmed in the manner described by Porter.[37] Thus, the crude mixture of (**194**) and (**178**) was reduced with triphenylphosphine to give 3-hydroxymethyl-3-methyl-1,2-dioxolane (**195**) which was compared with an authentic sample prepared by the epoxidation/acid-catalysed cyclization of 3-methyl-3-buten-1-hydroperoxide (**178**). The two different samples had identical ^{13}C-nmr spectra.

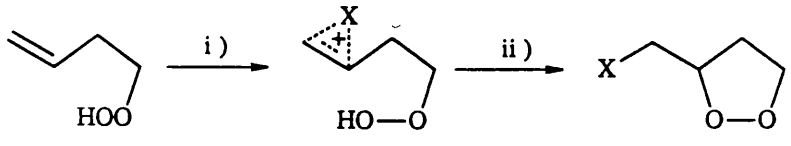


(194) (195) (178)

i)Ph_3P
ii)MCPBA
iii)Cl_3CCO_2H

2.3 cis and trans-3-Hexen-1-hydroperoxides (177a,b)

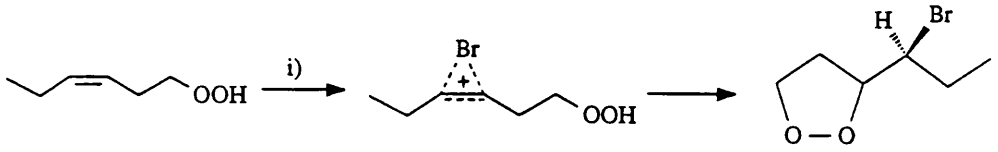
The mechanism we had envisaged for the reaction of NIS or NBS with γ,δ-unsaturated hydroperoxides involved an intermediate iodonium or bromonium ion (**248**) which underwent intramolecular nucleophilic attack to give the halodioxolane (Scheme 30).



(248)

i) NXS , CH_2Cl_2
ii) $-H^+$

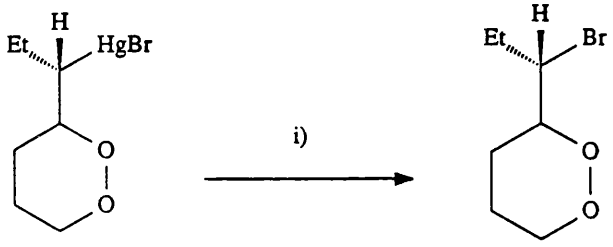
Such a mechanism would offer a stereospecific halodioxolane synthesis. For example, cis-3-hexen-1-hydroperoxide (177a) would give a bromonium ion which would close to give the threo-bromodioxolane (185a).



(177a) (185a)

i) Br^+

There are few examples of this reaction in the literature. Porter et al,[35] report the stereospecific preparation of erythro-3-(1-bromoethyl)-1,2-dioxane by the bromodemercuration of erythro-3-(1-bromomercurioethyl)-1,2-dioxane with bromine in pyridine, a reaction known to proceed with retention of configuration. In our hands the



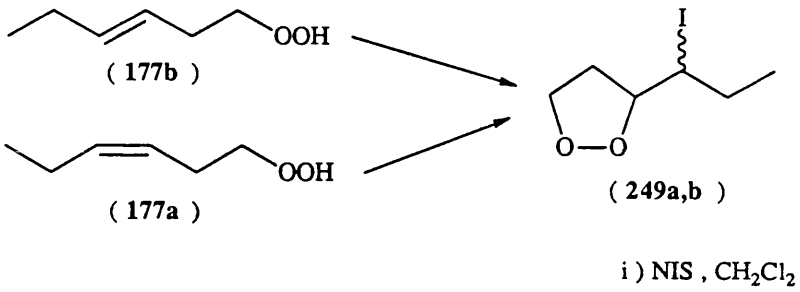
i) Br_2, Pyridine

stereospecific bromodemercuration of a mercuriodioxolane proved problematical. Therefore the reactions of NIS and NBS with cis and trans-3-hexen-1-hydroperoxides (177a,b) were investigated.

cis and trans-3-Hexen-1-hydroperoxides (177a,b) were

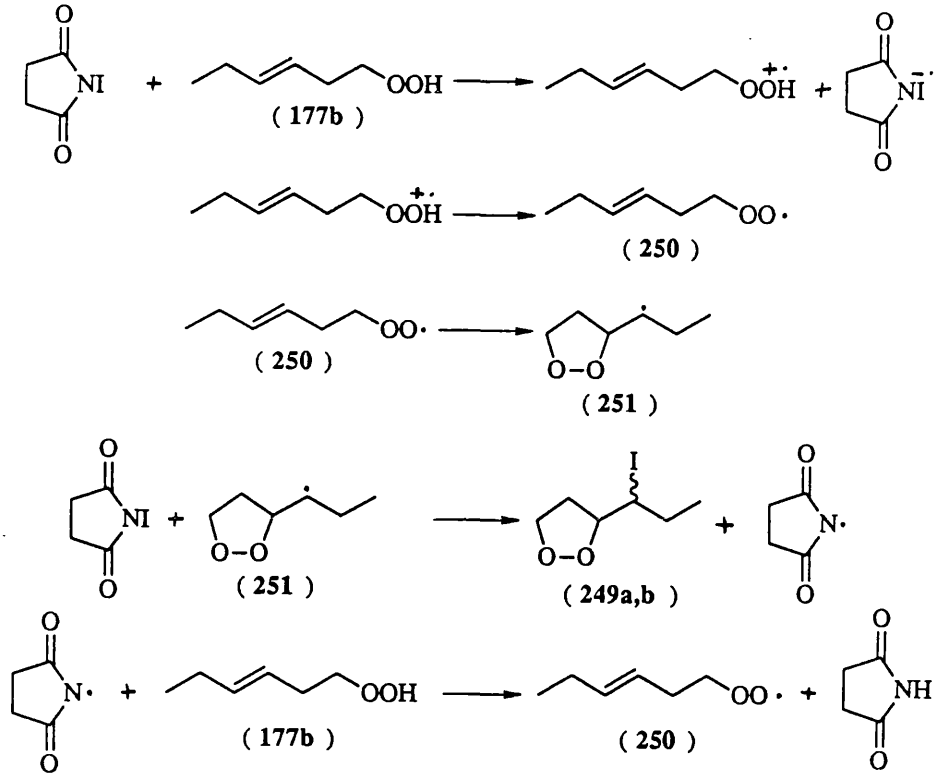
prepared in the manner of Williams and Mosher[48] in yields of 49% and 42% respectively.

Contrary to expectations, reaction of either (177a) or (177b) with NIS in dichloromethane gave the same, approximately 1:1, mixture of erythro and threo-3-(1-iodopropyl)-1,2-dioxolanes (249a,b)



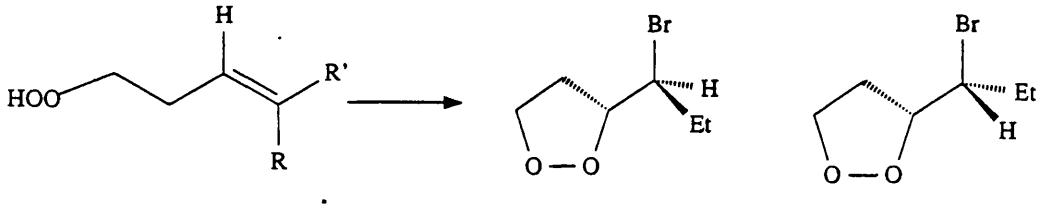
The possibility that either the starting hydroperoxides (177a,b) or the product iododioxolanes (249a,b) underwent isomerization was discounted by the following experiments. Firstly, reaction of cis-3-hexen-1-hydroperoxide (177a) with 10 mol% of NIS in dichloromethane revealed no production of the isomeric trans-3-hexen-1-hydroperoxide, yet the 1:1 product (249a,b) mixture was already established. Secondly, a sample of one product isomer, threo-3-(1-iodopropyl)-1,2-dioxolane (249) (preparation described below), was exposed to NIS and succinimide in dichloromethane and no isomerization ensued. With the stability of reactants and products proved, it would appear that a common intermediate is involved. It is proposed that the reaction proceeds by a free radical chain mechanism.

Initiation is likely to be by an electron transfer reaction to produce the peroxyl radical (250) which is known to undergo a 5-exo-Trig cyclization to the alkyl radical (251). This radical is the common intermediate, being produced by both cis and trans-hydroperoxides (177a,b). It abstracts an iodine from NIS giving the iododioxolanes (249a,b) and the succinimidyl radical which abstracts a hydrogen from the hydroperoxide (177b) thus propagating the chain.



When cis and trans-3-hexen-1-hydroperoxides (177a,b) were treated with NBS in dichloromethane each gave mixtures of the diasteroisomeric 3-(1-bromopropyl)-1,2-dioxolanes (185a,b) but with different isomer ratios. The

cis-hydroperoxide (177a) gave an approximately 75:25 mixture of threo and erythro-bromodioxolanes (185a,b) whereas the trans hydroperoxide (177b) gave an approximately 20:80 mixture of threo and erythro-bromodioxolanes (185a,b).

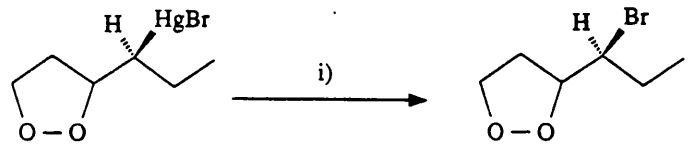


threo (185a) *erythro* (185b)

(177a) R=H, R'=Et	75	:	25
(177b) R=Et, R'=H	20	:	80

Initially there had been confusion as to the identities of the products. Using the ^{13}C-nmr data reported by Porter et. al.[35] it had appeared that the NBS reaction with the cis-hydroperoxide (177a) gave predominantly erythro-bromodioxolane (185b) while trans-hydroperoxide (177b) gave predominantly threo-bromodioxolane (185a). This would imply a cis addition to the double bond, an unlikely mechanism. It seemed more likely that the reported ^{13}C-nmr data for the two bromodioxolanes had been transposed. In order to prove this and correctly assign the stereochemistries of the products, a sample of threo-3-(1-bromopropyl)-1,2-dioxolane (185a) was prepared in the manner described by Porter in the same paper. threo-3-(1-Bromomercurio-

propyl)-1,2-dioxolane (180) was treated with bromine in pyridine to give threo-3-(1-bromopropyl)-1,2-dioxolane (185a) in poor (<10%) yield. The ^{13}C-nmr shifts of this authentic threo-bromodioxolane (185a) corresponded exactly to those assigned by Porter to erythro (185b).



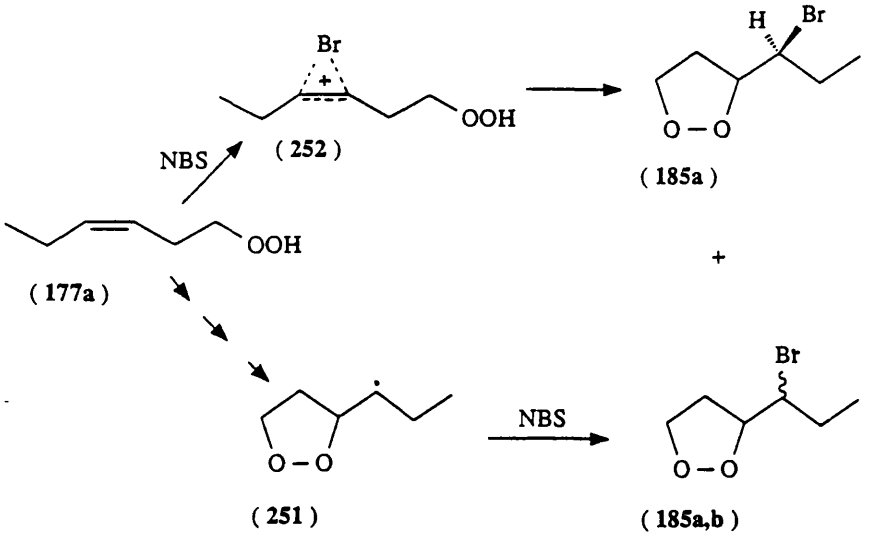
(180) (185a)

i) Br_2, Pyridine

As with the analogous NIS, the stabilities of stating materials and products to reaction conditions were examined. Firstly, a sample of erythro-3-(1-bromopropyl)1,2-dioxolane (185b) (preparation described below) was treated with NBS and succinimide in dichloromethane with no isomerization detected. Secondly, when cis and trans-3-hexen-1-hydroperoxides (177a,b) were each treated with 50 mol% NBS in dichloromethane, there was no isomerization of the trans-hydroperoxide (177b), but there was about 30% isomerization of cis hydroperoxide (177a) to trans hydroperoxide (177b). However, in each case the bromodioxolanes (185a,b) had been produced in the ratios reported above. As the isomerization of cis-hydroperoxide to trans-hydroperoxide did not affect the bromodioxolane distribution, then the cis to trans-isomerization must be a slow process compared with cycloperoxybromination.

Knowing that the bromodioxolanes (185a,b) and trans-hydroperoxide (177b) were stereochemically stable to reaction conditions and that the isomerization of cis-hydroperoxide (177a) to trans-hydroperoxide (177b) had no effect on bromodioxolane (185ab) distribution, it was concluded that the production of 20-25% of the epimeric bromodioxolanes was a mechanistic effect.

The higher degree of stereoselectivity for trans-addition in the NBS reaction, compared with the NIS reaction, suggests that a polar mechanism involving a bromonium ion (252) is now competing with the free radical cyclization.



This proposal was supported by the results of experiments designed to suppress the free radical component by including the effective free radical trap, Galvinoxyl, in the reaction mixture. The reactions of cis-3-hexen-1-hydroperoxide (177a) with NBS in dichloromethane with

5,20, and 100 mol% of Galvinoxyl present, were monitored by TLC. Galvinoxyl has a dark brown colour in dichloromethane solution and this colour persisted for about 1 to 5 minutes when 5 and 20 mol% of Galvinoxyl were present, but the solutions then suddenly changed to a light yellow colour. TLC revealed that before the colour change only one bromodioxolane was being formed, but that after the colour change both isomers could be detected. When 100 mol% of Galvinoxyl was included there was no decolourization and only one bromodioxolane product was detected by TLC*. We conclude that whereas the reaction of NIS with γ,δ-unsaturated hydroperoxide proceeds wholly by a free radical chain process, the reaction of NBS with a γ,δ-unsaturated hydroperoxide proceeds with roughly equal contributions from both radical and polar mechanisms. The polar reaction is stereospecific whereas the radical reaction should produce equal quantities of the epimers, thus giving the 3:1 ratios observed.

The cyclization of alkenyl hydroperoxides upon treatment with NIS appears to proceed by a wholly free radical mechanism. However, in the corresponding NBS reaction this radical cyclization is in competition with cyclization *via* the bromonium ion. A possible explanation would be the slower rate of bromine abstraction by the dioxolanylalkyl radical from NBS compared to that for

---

* *threo* and *erythro*-3-(1-bromopropyl)-1,2-dioxolanes (185a,b) are well separated (R_f difference of 0.08) using CH_2Cl_2/Pet (3:1) on silicon.

iodine from NIS. The relative rate constants for the abstraction of halogen from NCS, NBS, and NIS as reported by Davies et. al.[96] support this view (Table 2)

R·	NCS	NBS	NIS
Pr·	1	7	22
$PhCH_2$·	1	7.3	22

(Table 2)

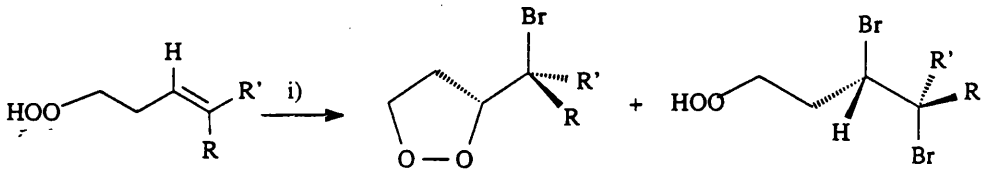
These figures also explain the slow formation of 3-hydroperoxymethyl-3-methyl-1,2-dioxolane (**194**) during the reaction of 3-methyl-3-buten-1-hydroperoxide (**178**) with NCS (Section 2.2). The abstraction of chlorine by the dioxolanylalkyl radical is so slow that oxygen trapping occurs at its exclusion.

However, there is another factor to consider, which is the extent to which the N-halosuccinimides initiate the radical reactions by generation of peroxyl radicals from hydroperoxides. Of this, little appears to be known.

The reactions of alkenes with halogens are known to proceed through the halonium ions, therefore treatment of the 3-hexen-1-hydroperoxides (**177a,b**) with halogens might be expected to give the halodioxolanes stereospecifically.

The reactions of cis and trans-3-hexen-1-hydroperoxides (**177a,b**) with bromine and one equivalent of

pyridine in dichloromethane each gave two products, both peroxidic, which were easily separated by column chlromatography. For the reaction of trans-3-hexen-1-hydroperoxide (177b), the faster running product proved to be the expected erythro-3-(1-bromopropyl)-1,2-dioxolane (185b). It was isolated in a yield of 15%. The slower running product appeared to be a saturated hydroperoxide by ^{13}C, ^{1}H-nmr, and IR spectroscopy. Mass spectrometry and elemental analysis showed two bromines to be present, and it would therefore appear to be erythro-3,4-dibromohexan-1-hydroperoxide (253b). It was isolated in a yield of 19%. Similarly, cis-3-hexen-1-hydroperoxide (177a) gave the corresponding threo-3-(1-bromopropyl)-1,2-dioxolane (185a) and threo-3,4-dibromohexan-1-hydroperaxide (253a) in yields of 17% and 31% respectively. This is not without precedent. Gunstone

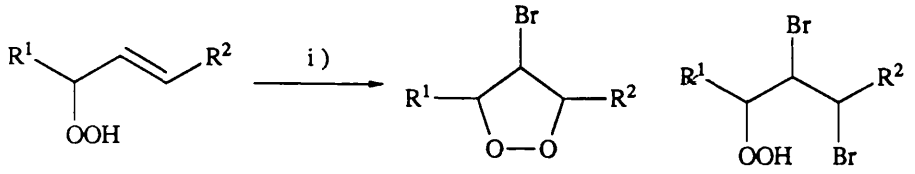


(177) (185) (253)

a, R=Et, R'=H
b, R=H, R'=Et

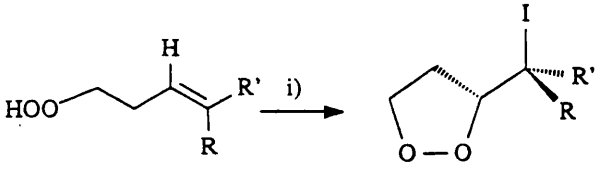
i) Br_2, CH_2Cl_2

and Bascetta[79] reported the formation of a dibromohydroperoxide (254). However, this was in competition with a less favourable 5-endo cyclization.



i) Br_2 a) $R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_6CO_2Me$
b) $R^1 = MeO_2C(CH_2)_7$, $R^2 = (CH_2)_6Me$

The corresponding reactions of cis and trans-3-hexen-1-hydroperoxide (177a,b) with iodine in pyridine each yielded only one peroxidic product. These proved to be single isomers of 3-(1-iodopropyl)-1,2-dioxolane (249a,b), cis (177a) presumably giving threo-iododioxolane (249a), which was isolated in a yield of 35%, and trans (177b) presumably giving erythro-iododiaxolane (249b) which was isolated in a yield of 42%. One other product was formed in each reaction, accounting for ~20 mol% of total products, but it could not be isolated. The unidentified



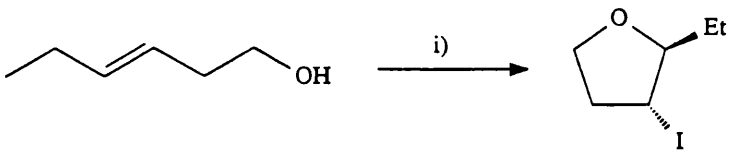
(177) (249)

a, R=Et, R'=H
b, R=H, R'=Et

i) I_2, CH_2Cl_2

products were not cis or trans-3-hexen-1-ols, nor were they derived from these, as reaction of trans-3-hexen-1-ol (255) with iodine and pyridine in dicloromethane gave a 2-ethyl-3-iodotetrahydrofuran (256) by the 5-endo

cyclization mode, and the ^{13}C-nmr spectrum of this did not correspond to that of the unknown products.



(255) (256)

i) I_2 , Pyridine , CH_2Cl_2

We believe that cycloperoxyhalogenation of γ,δ-unsaturated hydroperoxides by NBS and NIS offers a quick and simple method of preparing bromo and iodo-1,2-dioxolanes. In addition, the corresponding reaction with halogen in pyridine/dichloromethane offers a stereospecific synthesis superior to the conventional mercuration/halodemercuration reaction.

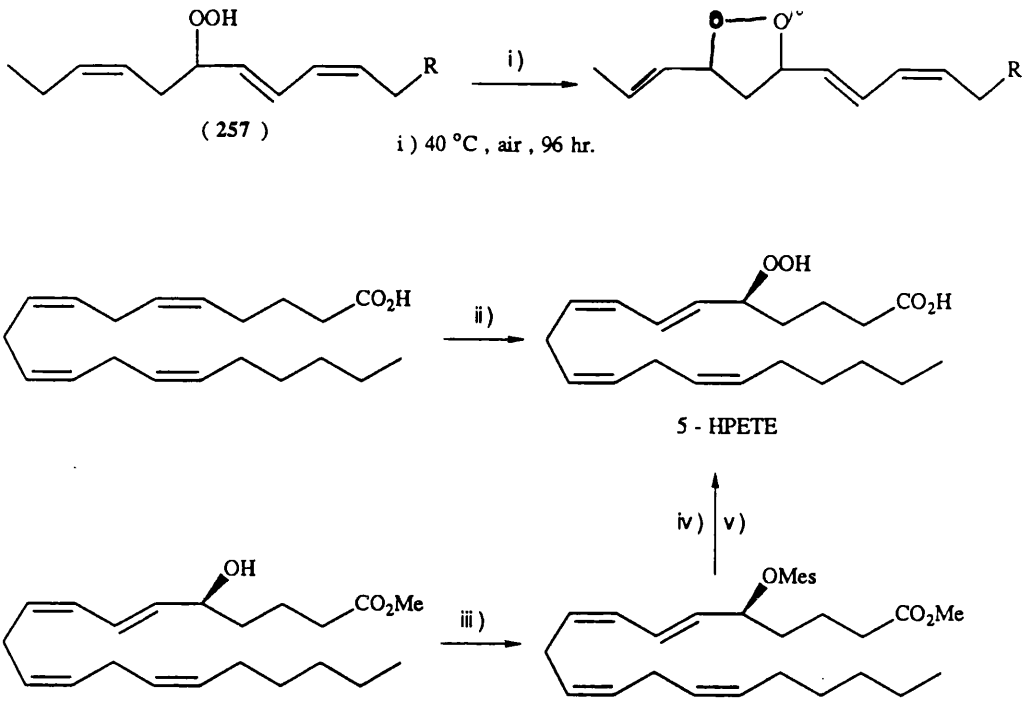
CHAPTER 5

SYNTHESIS AND REACTIONS OF SOME DIENE HYDROPEROXIDES

1. INTRODUCTION

Most of the reported research in the field of diene and polyunsaturated hydroperoxides has been concerned with the process of lipid peroxidation. Several methods of lipid hydroperoxide preparation have been described such as the action of lipoxygenase enzymes, nucleophilic displacement from a methanesulphonate, the ring opening of a vinylcyclopropyl bromide and singlet oxygenation. In addition to the direct study of lipid hydroperoxides, the thiol-oxygen co-oxidation of trienes has been used to model lipid peroxidation.

The linolenate hydroperoxide (257) was prepared by Chan *et. al.*[97] by the lipoxygenase catalysed oxygenation of linolenic acid followed by methylation with diazomethane. This hydroperoxide underwent a free radical cyclization when left in air at 40°C for 96h. Corey[98] has also used a lipoxygenase (from potato) to prepare (S)-5-hydroperoxy-6,8,11,14-eicosateraenoic acid (5-HPETE) from arachidonic acid and a racemic mixture of 5-HPETE was obtained from the methyl ester of 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) via the methanesulphonate (Scheme 31). The methanesulphonate method was again used by Corey *et. al.*[16,17] to prepare the hydroperoxides (186) and (188) to be used in the



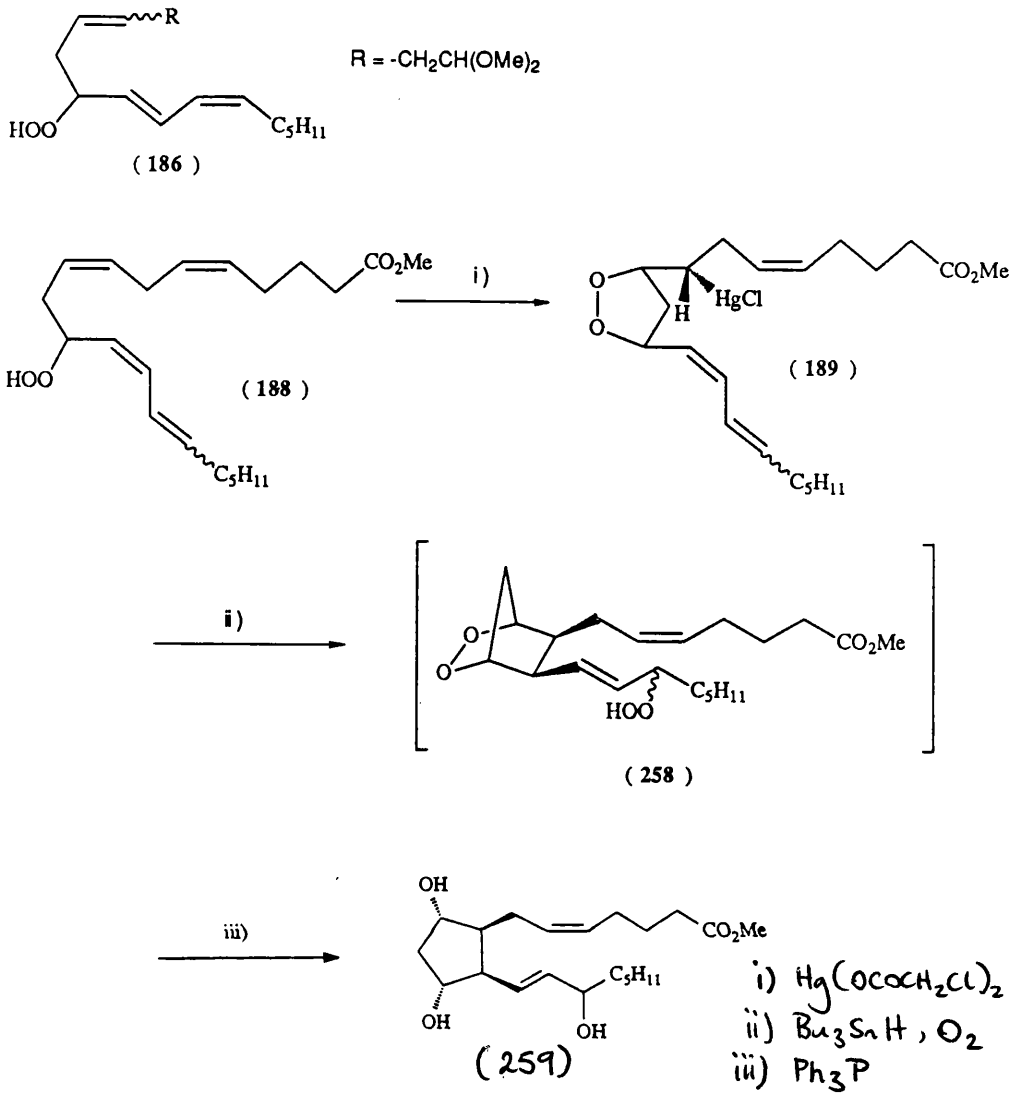
(257)

i) 40 °C , air , 96 hr.

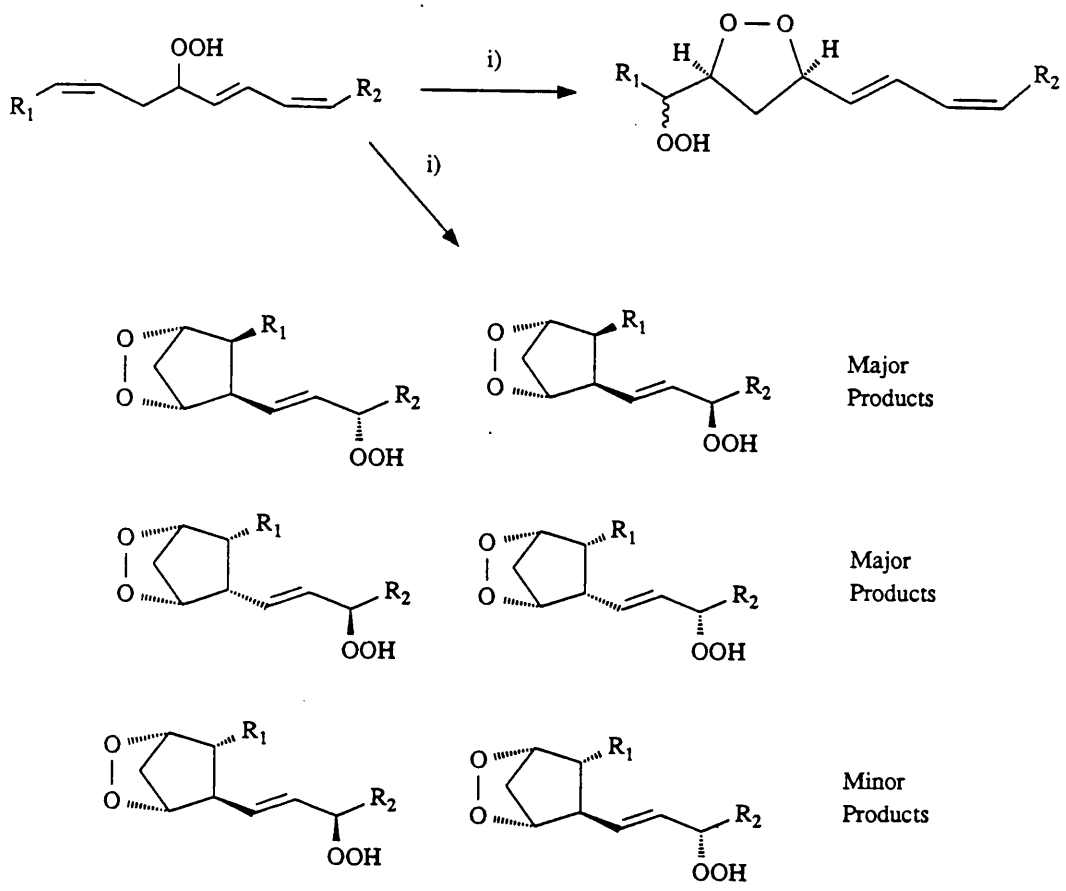
ii) pH 6.4 , Lipoxygenase , O_2 , 12 min
iii) $MeSO_2Cl$, CH_2Cl_2 , NEt_3 , 30 min
iv) XS 3M H_2O_2 in Et_2O , -110°C , 15 min
v) LiOH , H_2O_2 , $MeOCH_2CH_2OMe$ / H_2O , 23°C , 15 min

(Scheme 31)

biomimetic syntheses of PGH_2 analogues. For example the hydroperoxides (188) were prepared in a yield of ~60% by this method and were cyclized, by treatment with mercury(II) chloroacetate, to the mercuriodioxolanes (189). Reduction of the mercurials (189) with tri-n-butyltin hydride in the presence of oxygen followed by reaction with triphenylphosphine gave $PGF_{2\alpha}$-like products (259), presumably from the PGH_2 analogue (258). The $PGF_{2\alpha}$-like products differ from natural prostaglandins in the stereochemistry of the two side chains. The explanation offered by Corey is that non-enzymatic, free-



radical ring closure preferentially forms a product with cis (endo, endo or exo, exo) orientation of the side chains. This divergence from natural prostaglandin stereochemistry was also observed by O'Conner, Mihelich, and Coleman[15] upon the autoxidation of two polyunsaturated hydroperoxides (Scheme 32). Again, the majority of the bicyclic peroxide products had a cis-arrangement of the side chains, the trans-isomer being only a minor product.

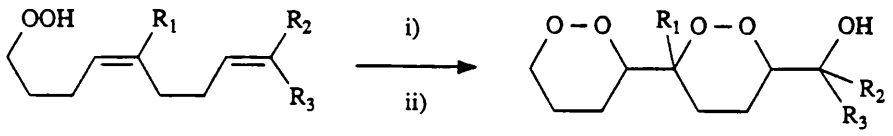


$R_1 = CH_2CH_3$, $R_2 = (CH_2)_7CO_2CH_3$
$R_1 = (CH_2)_4CO_2CH_3$, $R_2 = (CH_2)_4CH_3$

i) O_2 , CCl_4

(Scheme 32)

The serial cyclizations of the two hydroperoxides (54a) and (54b) were studied by Porter[39] as models for the peroxidation of polyunsaturated isoprenoids such as polyprenols and polybutadiene. The hydroperoxides (54a) and (54b), prepared from the corresponding methane-sulphonates, were treated with t-butoxyl radical sources (DTBN, DBPO) in oxygenated benzene and the products reduced with triphenylphosphine to give the diperoxides (55a) and (55b) each as a mixture of diastereoisomers.

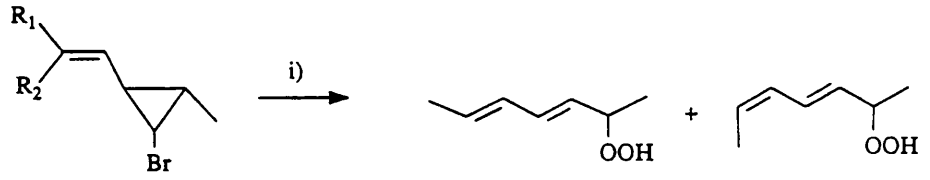


(54) (55)

i) C_6H_6 , air , DTBO or DTBH , 30°C

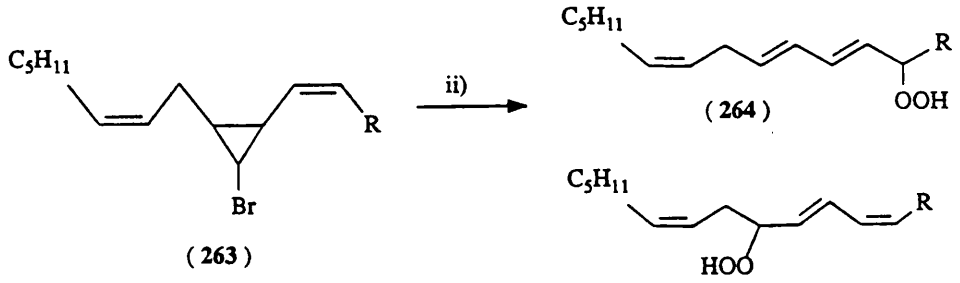
a) R_1=R_2=H , R_3=Et
b) R_1=R_2=R_3=Me

Porter has also devised a rather elegant route to diene and triene hydroperoxides by ring opening of vinylcyclopropyl bromides upon treatment with silver salts and hydrogen peroxide. The model compounds (260a) and (260b) gave mixtures of the geometric isomers (261) and (262), and the bromides (263a,b) gave mixtures of the isomers (264) and (265).



(260) (261) (262)

a) R_1=Me , R_2=H
b) R_1=H , R_2=Me

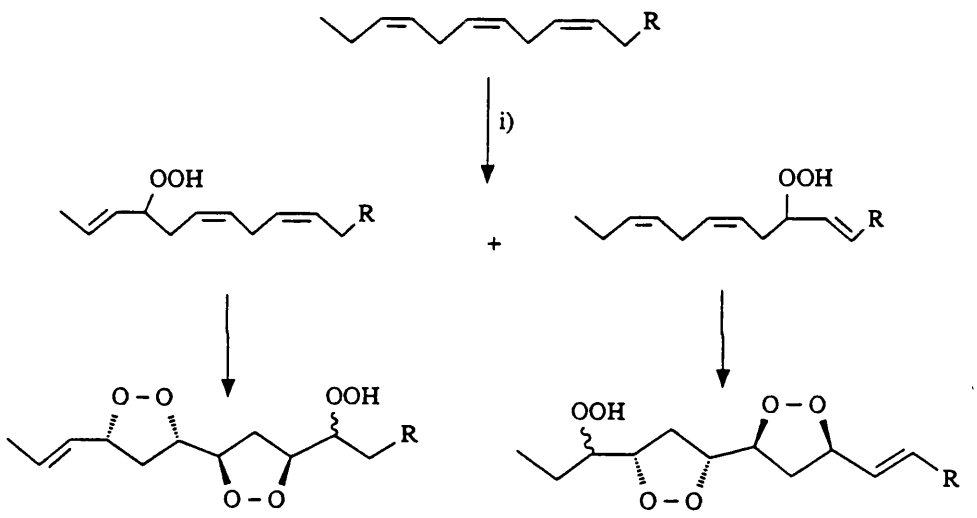


(263) (264) (265)

a) R = -$(CH_2)_6CO_2Me$
b) R = -CH_2CH=CH-$(CH_2)_3CO_2Me$

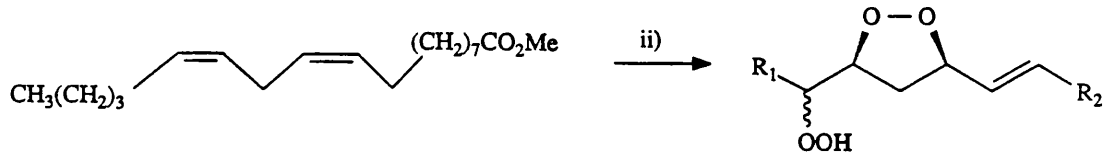
i) XS $AgBF_4$ / H_2O_2 , Et_2O , 25°C
ii) $Ag(O_2CCF_3)_2$ / H_2O_2 , Et_2O ,0°C ,5 min

The singlet oxygenation of lipids has been used to prepare hydroperoxides, but this is an unsatisfactory method, the large number of possible reaction sites leads to formation of a number of isomeric hydroperoxides. In addition to this, cyclization reactions can occur. For example, Frankel[100] and Mihelich[101] have obtained 1,2-dioxolanes as well as hydroperoxides from the photooxygenation of methyl linolenate and methyl linoleate (Scheme 33).



+ other hydroperoxides and cyclic peroxides

R = $(CH_2)_6CO_2Me$
i) hυ , O_2 , 0°C , CH_2Cl_2 , Methylene Blue



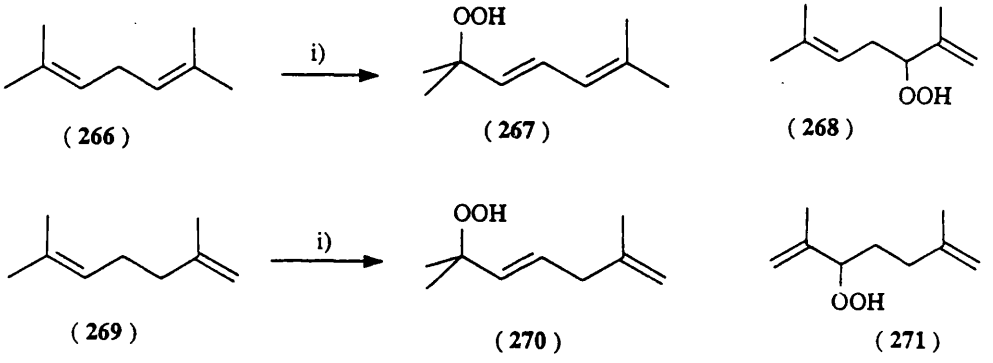
ii) hυ , O_2 , Neat , Rose Bengal

$R_1 = (CH_2)_7CO_2Me$, $R_2 = (CH_2)_3Me$

$R_1 = (CH_2)_3Me$, $(CH_2)_7CO_2Me$

(Scheme 33)

The photooxygenation of arachidonic acid, described by Porter[102], yields a mixture of the eight isomeric hydroperoxides (HPETEs) separation being effected by HPLC. The singlet oxygenation of simple dienes has also been reported[103] to give mixtures of hydroperoxides and cyclic peroxides. Carless[104] reported that upon singlet oxygenation, the dienes (266) and (269) each afforded a mixture of two hydroperoxides, (267), (268) and (270), (271) respectively.



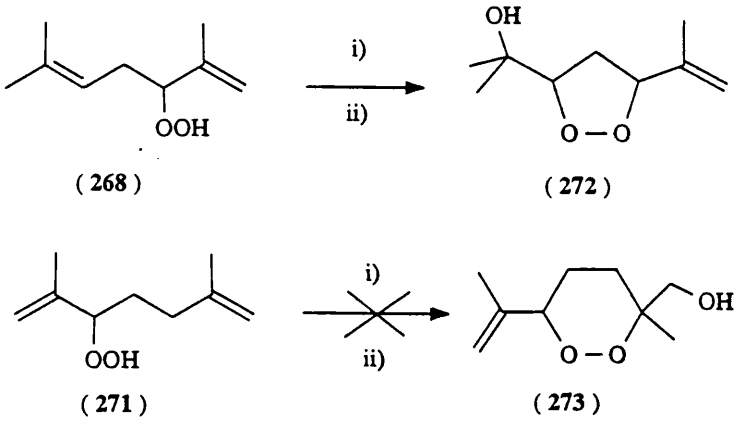
(266) (267) (268)

(269) (270) (271)

i) hυ , O_2 , TPP , CH_2Cl_2 , -50°C , 2h

These hydroperoxides were isolated and each treated with DBPO in oxygenated benzene and the products reduced with triphenylphosphine. Only one hydroperoxide (268), produced a cyclic product (272). This had the cis-configuration consistent with the guidelines given by Beckwith[105]. It might appear unusual that (271) did not cyclize to the 1,2-dioxane (273) considering the examples of 6-exo-Trig cyclizations reported by Porter. However, in his guidelines for radical cyclizations, Beckwith[105]

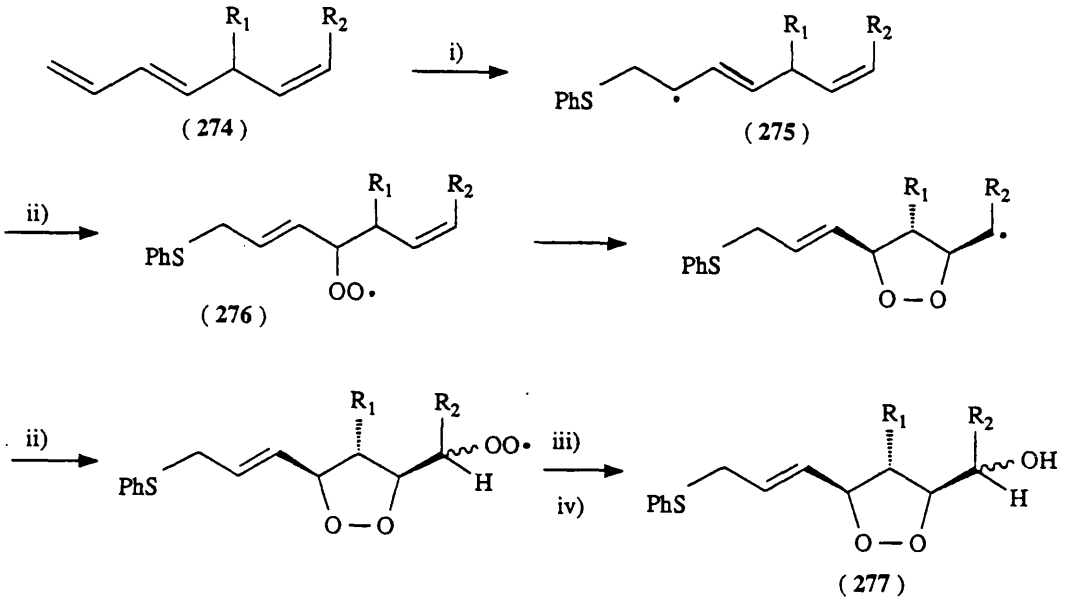
states that substituents on an olefinic bond disfavour homolytic addition at the substituted position, and this may explain the lack of cyclization within (271).



i) DBPO , C_6H_6 , O_2
ii) Ph_3P

The cyclization of diene peroxyl radicals has also been studied by Beckwith[106]. The peroxyl radicals were not generated from the hydroperoxide, as in most other cases, but by thiol-oxygen co-oxidation (TOCO) of trienes. Treatment of the trienes (274) with thiophenol and DBPO in the presence of oxygen afforded the dioxolane (277a) as a mixture of epimers and (277b) as a single isomer in yields of 59% and 49% respectively (Scheme 34).

Diagram overleaf

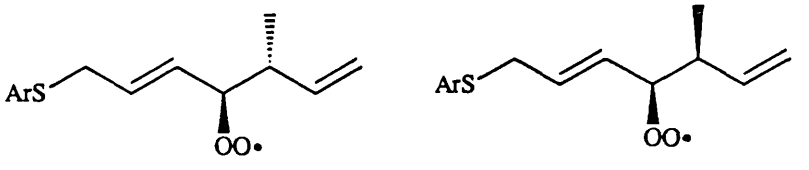


i) PhS•
ii) O_2
iii) PhSH , -PhS
iv) Ph_3P

a) $R_1 = H$, $R_2 = Me$
b) $R_1 = Me$, $R_2 = H$

(Scheme 34)

In a later publication, Beckwith[107] reported the reaction involving (274b) in more detail. The stereospecificity of the reaction is explained as follows. Both the <u>erythro</u> and <u>threo</u>-peroxyl radicals (276b) are



erythro - (276b)

threo - (276b)

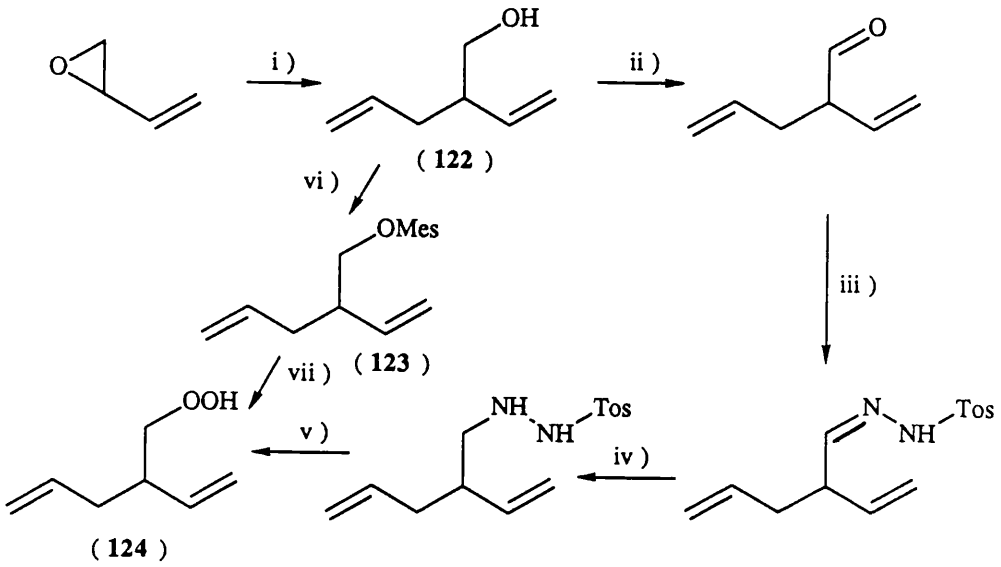
formed in a reversible reaction of (275b) with oxygen. However, only the <u>erythro</u> undergoes cyclization, both thiophenylalkenyl and methyl substituents being able to take equatorial positions in a chair-like transition

state, which is not so for the threo-radical. This explanation is in agreement with the guidelines given by Beckwith[106] for the cyclization of substituted hexenyl radicals.

The regioselectivity in these TOCO reactions is not unexpected, the favoured 5-exo-Trig[38] process being in competition with either a 5- or 6-endo-Trig cyclization.

That there was no reported example of a hydroperoxide capable of undergoing cyclization by two favourable modes prompted us to design a system whereby the competition between 5- and 6-exo cyclizations could be studied. 2-Ethenyl-4-penten-1-hydroperoxide (124) would provide such a competition and it was envisaged that a synthetic route parallel to that used to prepare 2-phenyl-4-penten-1-hydroperoxide (102) (Chapter 2, Section 2.2.1) could be employed to prepare the diene hydroperoxide (124).

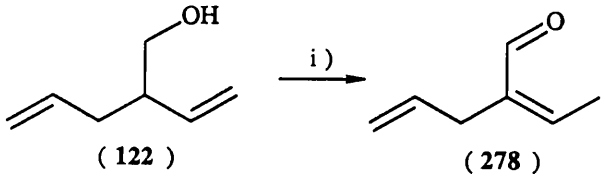
The synthesis of the hydroperoxide (124) was initially investigated by Navin Mistry as an undergraduate research project. Butadienemonoxide, when treated with allylmagnesium bromide, was ring-opened regiospecifically to give 2-ethenyl-4-penten-1-ol (122). This is somewhat unexpected and may be the first such example of regiospecific opening of butadiene monoxide by a Grignard reagent.[108]



i) CH_2=$CHCH_2MgBr$, Et_2O
ii) PCC , CH_2Cl_2
iii) $TosNHNH_2$, EtOH
iv) $NaBH_3CN$, THF , pH 3.5
v) Na_2O_2 , 30% H_2O_2 , THF
vi) MesCl , Pyridine
vii) 50% KOH , 30% H_2O_2 , MeOH

(Scheme 35)

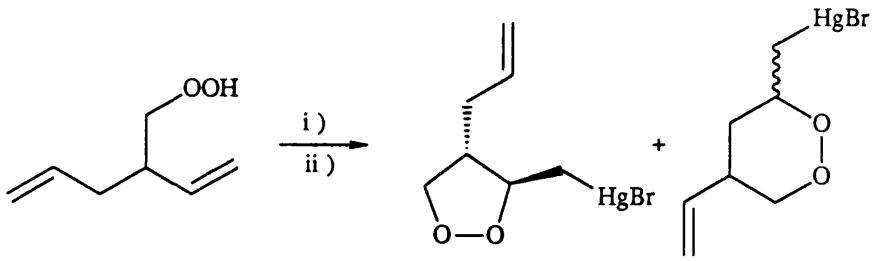
The anticipated route through aldehyde, tosylhydrazone, and tosylhydazine (Scheme 35, Steps ii → v) was unsuccessful as the PCC oxidation of alcohol (122) occurred with rearrangement to the aldehyde (278).



i) PCC , CH_2Cl_2

However, the methanesulphonate (123) was prepared and this gave the hydroperoxide (124) on treatment with basic

hydrogen peroxide, albeit in a yield that never exceeded 6%. Using the small amount of 2-ethenyl-4-penten-1-hydroperoxide (124) he had obtained, Navin Mistry carried out a cycloperoxymercuration and obtained a mixture of dioxolane (125) and dioxane (126) which were separated by HPLC.



(124) (125) (126)

i) $Hg(NO_3)_2.H_2O$, CH_2Cl_2
ii) H_2O , KBr

The aims of my work were to try to improve the yield of the hydroperoxide and to study the 5-exo versus the 6-exo product distribution for several cyclization reactions. It was planned to treat (124) with reagents known to generate peroxyl radicals from hydroperoxide and with electrophiles expected to give bridged carbocations with alkenes. In this way the competition between 5-exo and 6-exo cyclization could be investigated for the first time with both radical and polar mechanisms and the characteristic stereochemistries of the processes could be determined.

2 RESULTS AND DISCUSSION

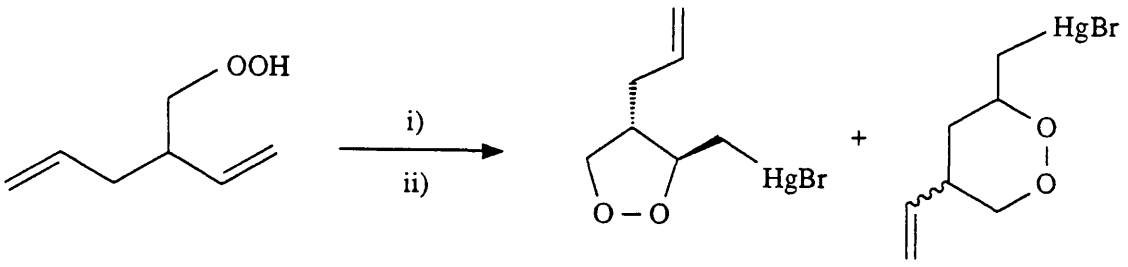
2.1 Synthesis and cyclization reactions of 2-ethenyl-4-penten-1-hydroperoxide 124

2-Ethenyl-4-penten-1-hydroperoxide (124) was prepared from the alcohol (122) via the methanesulphonate (123) using the conditions described by Williams and Mosher[48]. The yields initially obtained were disappointingly low at 3%-6%, but were improved to 15% by reducing the amount of methanol used.

2-Ethenyl-4-penten-1-hydroperoxide (124) was treated with reagents known to bring about cyclization by either a polar or radical mechanism.

2.1.1 Reaction with Mercury(II) Nitrate

The cycloperoxymercuration of unsaturated hydroperoxides is known to proceed by a polar mechanism[35]. The reaction of 2-ethenyl-4-penten-1-hydroperoxide (124) with mercury(II) nitrate in dry dichloromethane followed by anion exchange gave a mixture of the regioisomers 3-bromomercuriomethyl-5-ethenyl-1,2-dioxane (126) and 3-bromomercuriomethyl-4-(2-propen-1-yl)-1,2-dioxolone (125). These regioisomers were separated by semi-preparative HPLC and found to be in a 1:2 ratio in favour of the dioxolane (125).



(124) (125) (126)

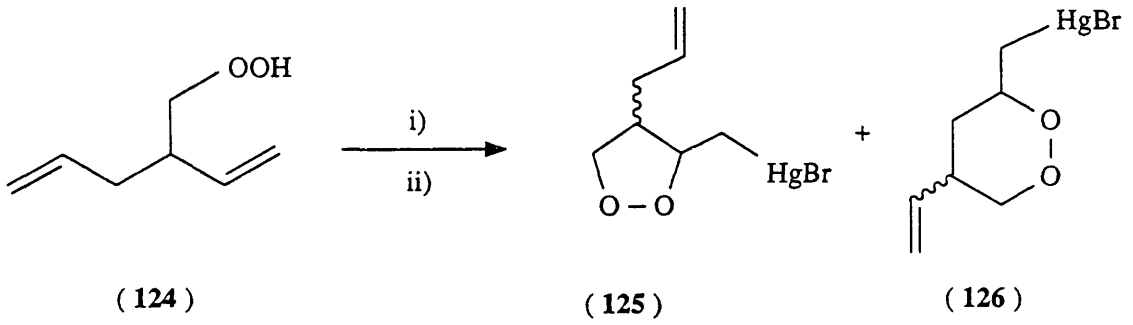
i) $Hg(NO_3)_2 .H_2O$, CH_2Cl_2
ii) KBr , H_2O

Analysis of the ^1H and ^{13}C-nmr spectra of 3-bromomercuriomethyl-5-ethenyl-1,2-dioxane (126) showed it to be a mixture of the cis and trans isomers, the cis predominating. However, the ^{13}C and ^1H-nmr spectra of 3-bromomercuriomethyl-4-(2-propen-1-yl)-1,2-dioxolane (125) showed there to be only one isomer. This isomer was shown to have the trans-configuration in work described later in this chapter (Section 2.1.6).

2.1.2 Reaction with Mercury(II) acetate with sonication

An interesting development in the mercuration of 2-ethenyl-4-penten-1-hydroperoxide (124) was the combined effect of using mercury(II) acetate and sonication on the product isomer ratios. Under these reaction conditions a marked difference in both regioisomer and diastereoisomer distribution was noticed. Whereas treatment with mercury(II) nitrate and magnetic stirring reproducibly gave a 2:1 mixture of trans-dioxolane (125a) and a mixture

of cis-and trans-dioxane (126a,b) treatment with mercury(II) acetate and sonication afforded a 7:1 mixture of cis-and trans-dioxolane (125a,b) and cis- and trans-dioxane (126a,b). The production of cis-3-bromomercuriomethyl-4-(2-propen-1-yl)-1,2-dioxolane (125b) is especially interesting as most cyclizations of (124) afford the dioxolanes exclusively as trans (work described later in this chapter).



(124) (125) (126)

i) $Hg(OAc)_2$, CH_2Cl_2, Sonication
ii) KBr, H_2O

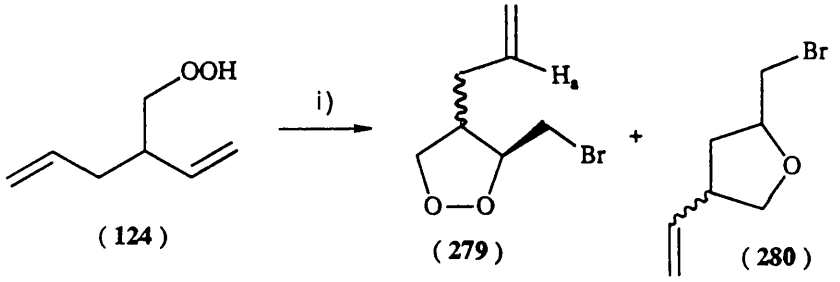
Unfortunately, lack of time prevented a further investigation of this intriguing cyclization. A series of experiments need to be carried out to determine whether the use of mercury(II) acetate, sonication, or both are responsible for the divergence from the mercury(II) nitrate reaction.

2.1.3 Reaction with N-bromosuccinimide

Another reagent shown to bring about the cyclization of γ,δ-unsaturated hydroperoxides is N-bromosuccinimide (NBS)[109] (Chapter 4). When 2-ethenyl-4-penten-1-

hydroperoxide (124) was treated with NBS in dichloroethane, a mixture of products was obtained. Separation by semi-preparative HPLC afforded four main products numbered 1 to 4 in order of elution. Fractions 1 and 2 were identified as the cis and trans isomers of 3-bromomethyl-4-(2-propen-1-yl)-1,2-dioxolane (279) and fractions 3 and 4 were identified as the cis and trans isomers of 2-bromomethyl-4-ethenyltetrahydrofuran (280).

The ratio of dioxolanes (279) to tetrahydrofurans (280) was found to be 2.1:1.



(124) (279) (280)

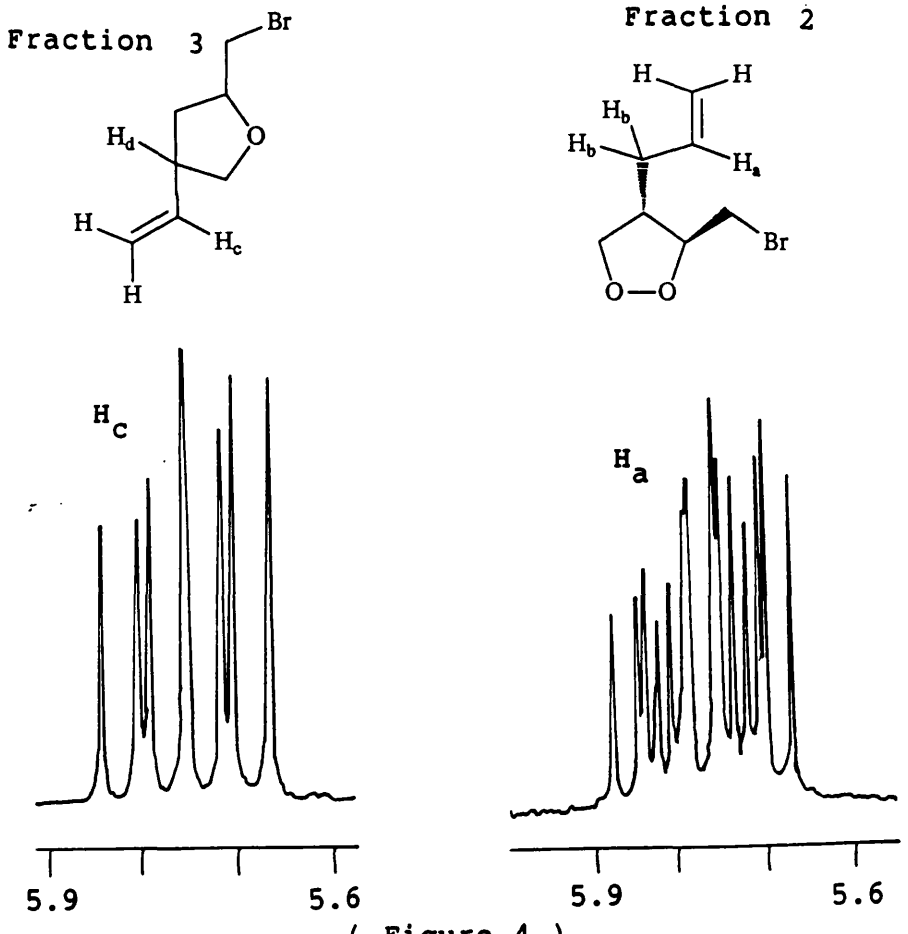
i) NBS , CH_2Cl_2

The assignments were made on the basis of ^{13}C and ^{1}H-nmr spectroscopic data and were supported by the results of testing for oxidant character (peroxide) with acidified ferrous thiocyanate.

Fractions 1 and 2 gave a positive result to the ferrous thiocyanate test and are therefore likely to be peroxides. The ^{13}C-nmr spectra were consistent with the structures proposed; in particular the substituted apex carbons (C-4) of 1,2-dioxolanes have a characteristically high chemical shift and values of 53.11 and 50.45 ppm were

found. In the vinylic regions of the ^{1}H-nmr spectra the signals due to proton H^{a} showed a multiplicity consistent with an adjacent methylene group ($CH_2{}^{b}$) (Figure 36).

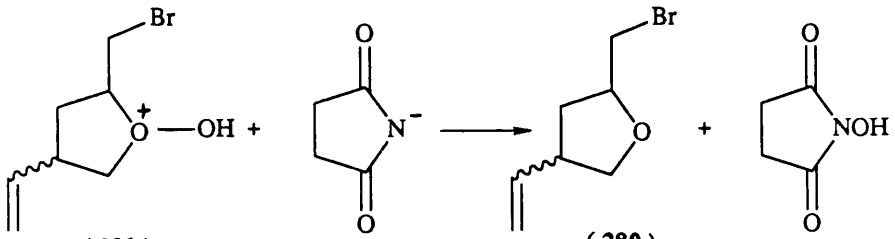
Fractions 3 and 4 did not give a positive result to the ferrous thiocyanate test and are therefore unlikely to be peroxides. The ^{13}C-nmr spectra were consistent with the structures (279) proposed, and the signals due to H^{c} in the ^{1}H-nmr spectra showed a multiplicity (ddd) expected with an adjacent methine group (CH^{d}) (Figure 36).



(Figure 4)

Portions of the vinylic regions of ^{1}H-nmr spectra showing the multiplicities due to -C<u>H</u>=CH$_2$ in the two different fractions types.

The formation of 2-bromomethyl-4-ethenyltetrahydrofurans (**7a,b**) can be explained by oxygen transfer from an intermediate gem-dialkylperoxonium ion (**281**)[95] and is thus consistent with NBS/unsaturated hydroperoxide reactor having a polar component. It is worth noting that no six membered ring products were detected.



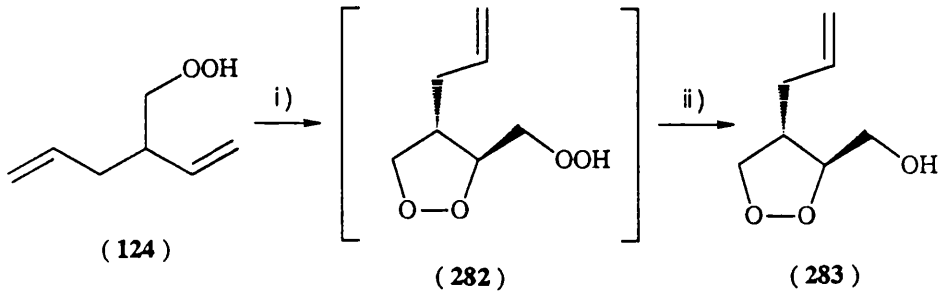
(**281**) (**280**)

Following the cyclizations with polar reagents, the cyclizations of the peroxyl radical (**284**) generated from the hydroperoxide (**124**) were explored.

2.1.4 Reaction with Di-t-Butyl Peroxalate (DBPO) in Oxygenated Benzene

For the t-butoxyl radical intiated cyclization[37], 2-ethenyl-4-penten-1-hydroperoxide (**124**) and 39 mol% of di-t-butylperoxalate (DBPO) were stirred in benzene for two days under air at room temperature. After the addition of triphenylphosphine and removal of the benzene, the ^{13}C-nmr spectrum of the crude product indicated only one major product.

This was isolated by column chromatography in a yield of 10% and identified as a single isomer of 3-hydroxymethyl-4-propenyl-1,2-dioxolane (**283**). This was

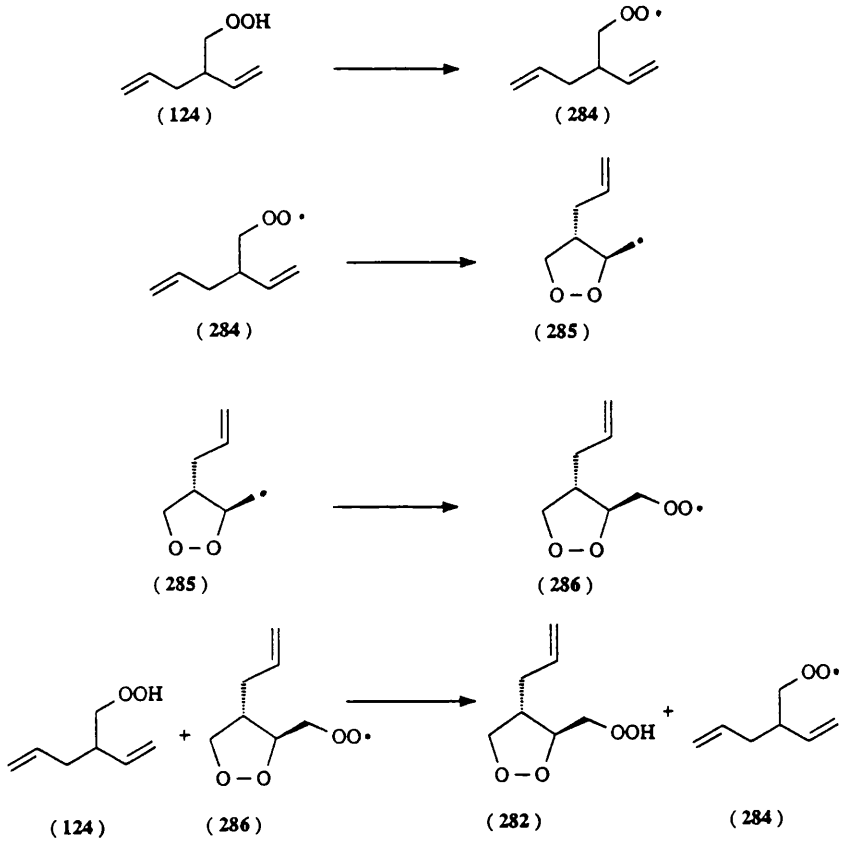


(124) (282) (283)

i) C_6H_6 , DBPO , 2 days , RT , air
ii) Ph_3P

tentatively identified as the trans-isomer by analogy to the products of other cyclizations (Sections 2.1.1, 2.1.5).

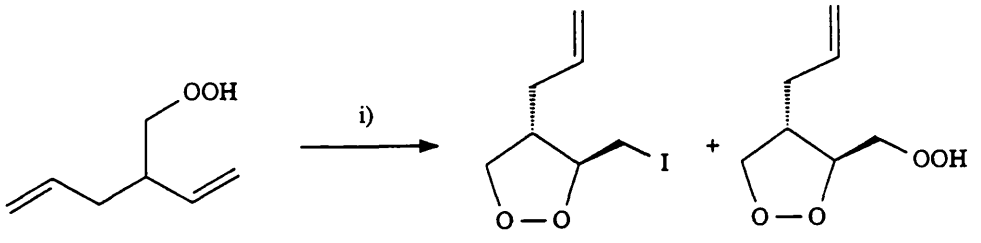
The mechanism by which the intermediate hydroperoxide (282) is formed is assumed to be parallel to that reported by Porter[37]. Initiation is by the abstraction of



a hydrogen from the hydroperoxide (124) by t-butoxyl radical to give the peroxyl radical (284)which undergoes a 5-exo-Trig cyclization[38] to the alkyl radical (285). This radical is trapped by atmospheric oxygen to give the peroxyl radical (286) which abstracts a hydrogen from the hydroperoxide (282) thus propagating the chain.

2.1.5 Reaction with N-Iodosuccinimide (NIS)

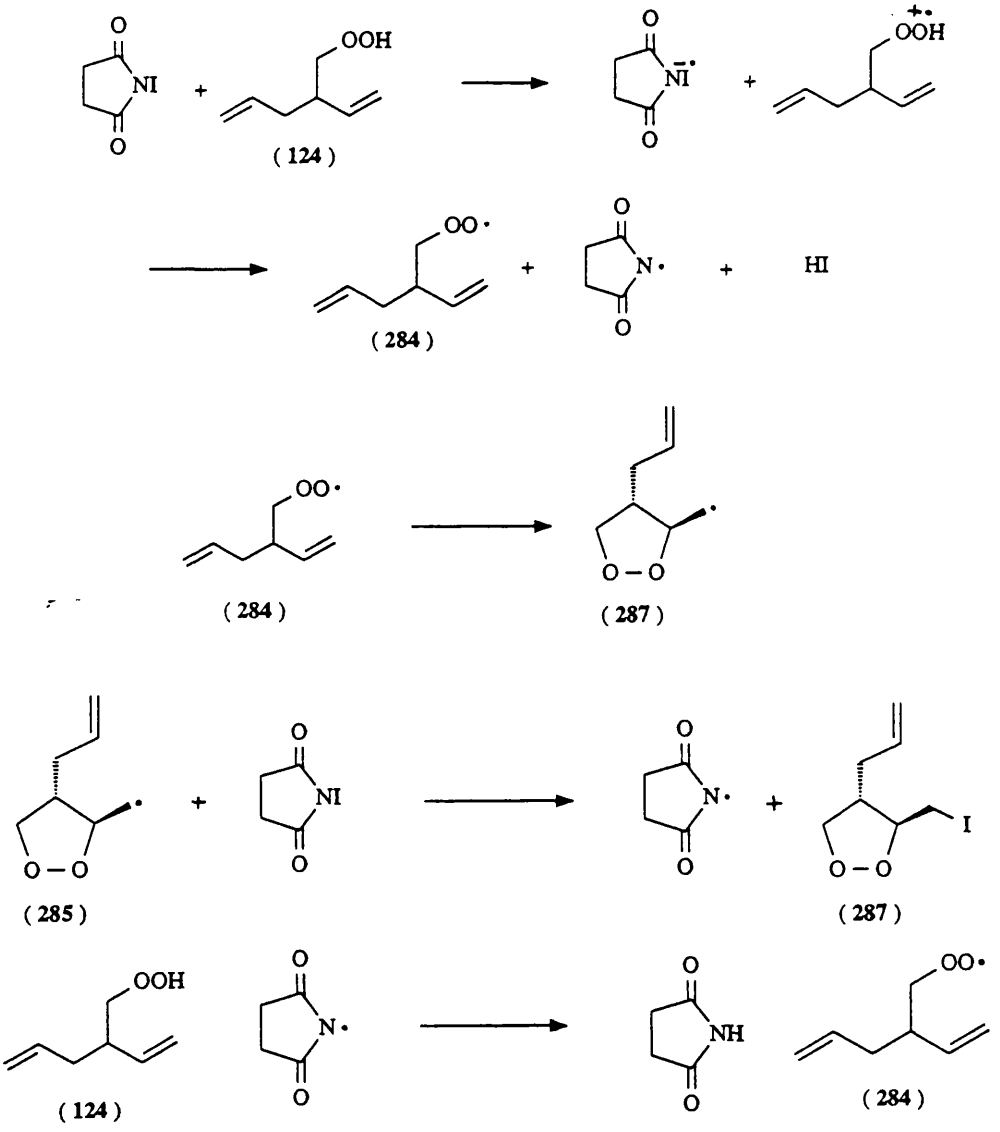
We have obtained evidence that N-Iodosuccinimide (NIS) also brings about the radical cyclization of γ,δ-unsaturated hydroperoxides[109] (Chapter 4). The reaction of 2-ethenyl-4-penten-1-hydroperoxide (124) with NIS was faster than that with DBPO, being over in 2 hours. The crude product mixture showed just one major product, by ^{13}C-nmr spectroscopy, which was isolated in a yield of 54% and identified as a single isomer of 3-iodomethyl-4-(2-propen-1-yl)-1,2-dioxolane (287). This isomer was shown to have the trans-configuration in work described later in this Chapter (Section 2.1.6). In addition to the



(124) (287) (282)

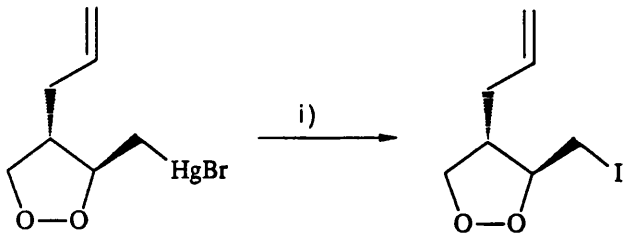
i) NIS , CH_2Cl_2

iododioxolane (287), a small amount (4 mol%) of 3-hydroperoxymethyl-4-(2-propen-yl)-1,2-dioxolane (282) was recovered. This may have been produced during the reaction by oxygen trapping of the radical (285) or it may have resulted from the self initiated cyclization of the hydroperoxide (124) on standing. The latter phenomenon has recently been observed by Bloodworth and Rimmer[110] in 4-penten-2-hydroperoxide.



The same mechanism as that proposed for reactions of NIS with other γ,δ-unsaturated hydroperoxides (Chapter 4) can be envisaged. Initiation is by an electron transfer process. The peroxyl radical (284) thus generated undergoes a 5-exo-Trig cyclization to the alkyl radical (285) which abstracts an iodine from NIS giving the iododioxolane (287) and a succinimidyl radical. This radical abstracts a hydrogen from the hydroperoxide (124) giving succinimide and the peroxyl radical (286) thus propagating the chain.

Additional proof of the structure of iododioxolane (287) was obtained by an independent synthesis. Thus, iododemercuration of 3-bromomercuriomethyl-4-(2-propen-1-yl)-1,2-dioxolane (125) was carried out with iodine in dichloromethane at reflux. The ^{13}C-nmr spectrum of this iododioxolane (288) was identical to that of the product prepared in the NIS reaction. This also established that the mercuriodioxolane (125) and iododioxolane (287) have the same configuration.

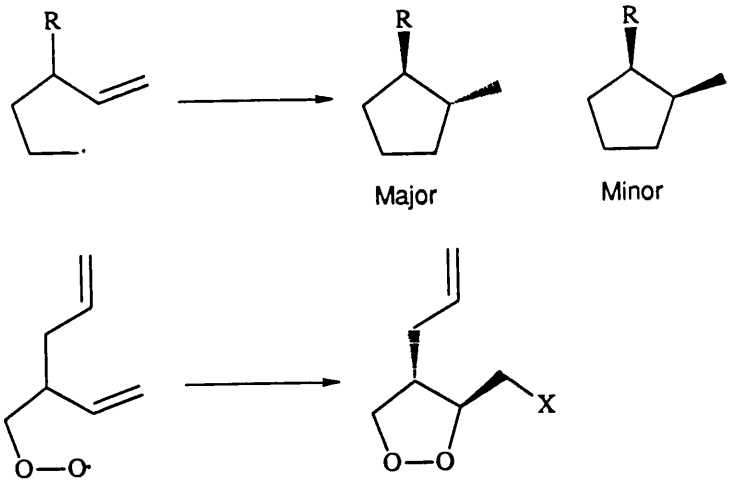


(125) (287)

i) I_2, CH_2Cl_2, Δ

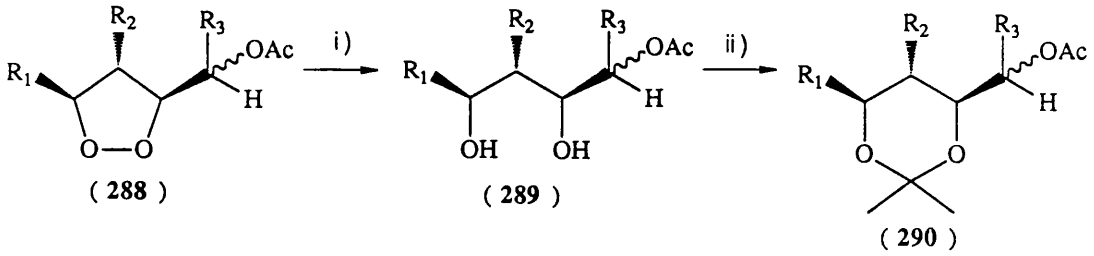
2.1.6 Determination of Dioxolane Configuration

As the radical cyclization of 2-ethenyl-4-penten-1-hydroperoxide (124) was regio- and stereo-specific it was desirable to determine the configuration of the products. Work reported by Beckwith helped in this determination[105,106]. If the guidelines for cyclization of variously substituted alkenyl radicals, reported by Beckwith et. al.[105], can be applied to the analogous peroxyl radicals, then the trans configuration would be favoured (Scheme 37).



(Scheme 36)

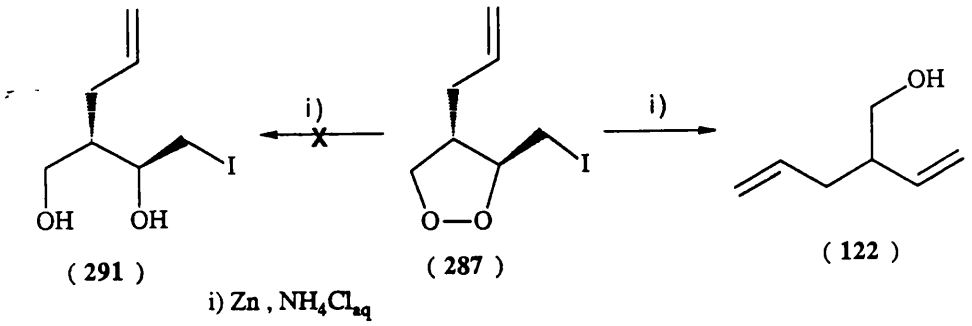
Beckwith and Wagner[106] also reported a method for the determination of configuration of the 1,2-dioxolanes (288), by reduction to the diols (289) and formation of the 1,3-dioxanes (290). The assignment of configuration then followed from the analysis of the ^{1}H-^{1}H coupling constants of ring protons.



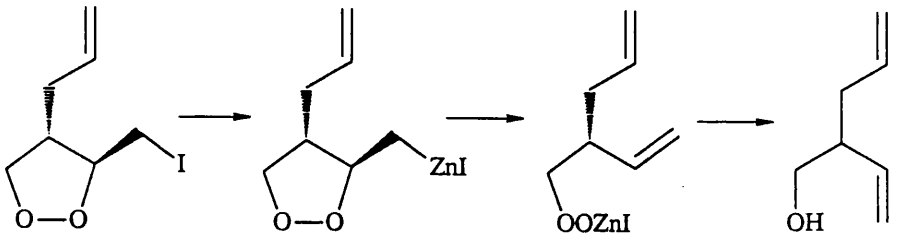
a) R_1= PhS⌒⌒ , R_2=H , R_3=Me
b) R_1= PhS⌒⌒ , R_2=Me , R_3=H

i) Zn , $NH_4Cl_{(aq)}$
ii) $Me_2C(OMe)_2$, Me_2CO , H^+

An attempt was made by this method to determine the configuration of the 3-iodomethyl-4-(2-propen-1-yl)-1,2-dioxolane (287). However, treatment of the iododioxolane (287) with powdered zinc in saturated ammonium chloride solution gave not the desired diol (291), but 2-ethenyl-4-penten-1-ol (122) in quantitative yield.



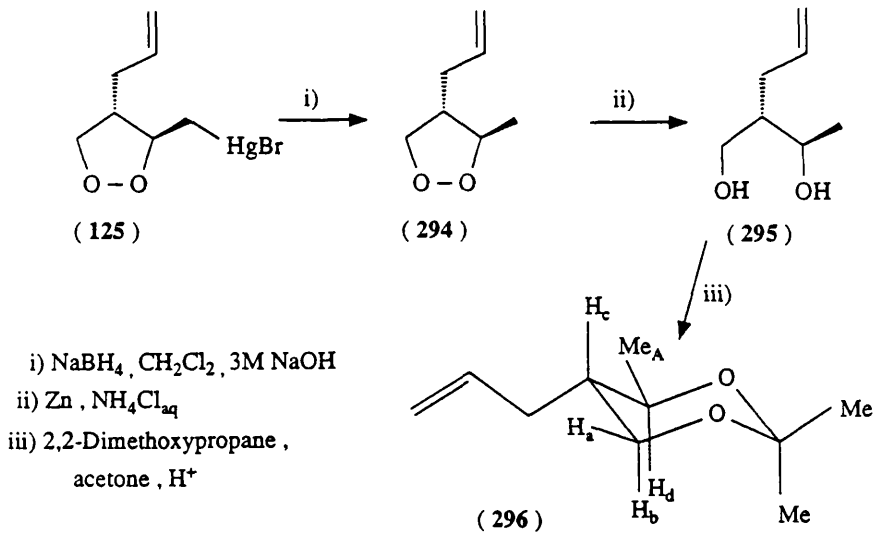
A speculative mechanism can be proposed in which the formation of an organozinc iodide (292) followed by elimination to (293) and subsequent reduction gives the alcohol (122).



(287) (292) (293) (122)

Further attempts to reduce the dioxolane (287) to the diol (291), by reaction with lithium aluminium hydride and with hydrogen/Adam's catalyst, also failed, starting material being recovered in both cases.

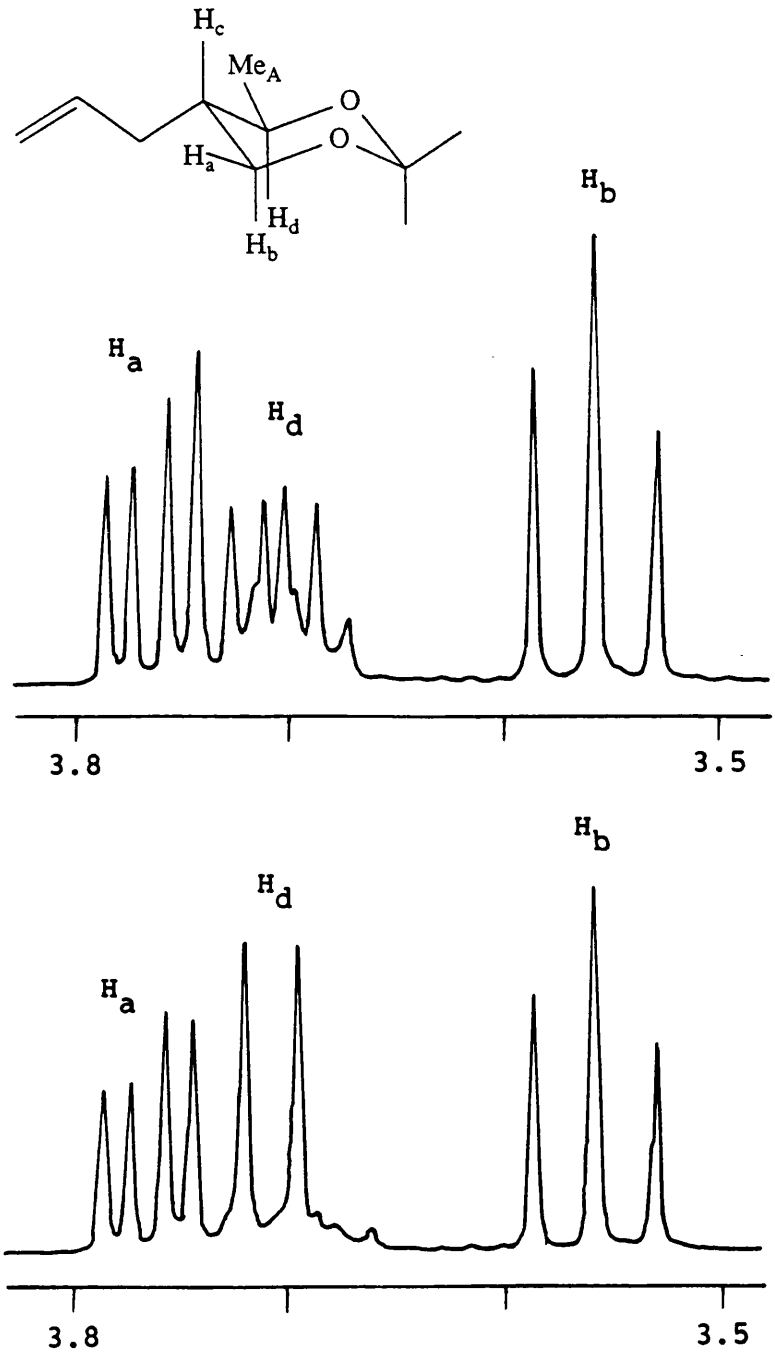
Since the mercuriodioxolane (125) had the same stereochemistry as the iododioxolane (287), hydridodemercuration of the mercuriodioxolane (125) would provide a methyldioxolane (294) also of the same configuration, but expected to be more amenable to the zinc/ammonium chloride reduction. 3-Bromomercuriomethyl-4-(2-propen-1-yl)-1,2-dioxolane (125) was reduced to 3-methyl-4-(2-propen-1-yl)-1,2-dioxolane (294) by sodium borohydride in 3M sodium hydroxide in a yield of 64%. This dioxolane (294) was easily reduced by powdered zinc in saturated ammonium chloride to 2-(2-propen-1-yl)butane-1,3-diol (295) in high yield. This diol (295), when treated with 2,2-dimethoxypropane in acetone with a p-toluenesulphonic acid catalyst gave 2,2,4-trimethyl-5-(2-propen-1-yl)-1,3-dioxane (296) in high yield.



(125) (294) (295) (296)

i) $NaBH_4$, CH_2Cl_2 , 3M NaOH
ii) Zn , NH_4Cl_{aq}
iii) 2,2-Dimethoxypropane , acetone , H^+

The crude 1,3-dioxane (296) was of sufficient purity for use in the nmr experiment. In the 400 MHz ^{1}H-nmr spectrum of (296) (Figure 38) a doublet of quartets lay between a doublet of doublets and a triplet (H_a,H_b). When the methyl doublet of Me_A (δ 1) was irradiated, the doublet of quartets collapsed to a doublet (H_d coupling to H_C) with a coupling constant of 10.0Hz. This coupling constant is consistent with a <u>trans</u> (diequatorial) arrangement of the methyl and propenyl substituents in the dioxane (296) and hence in the dioxolanes (287), (125), (194). Although we have no direct proof of the configuration of 3-hydroperoxymethyl-4-(2-propen-1-yl)-1, 2-dioxolane (282), the preponderance of <u>trans</u>-configuration in similar 1,2-dioxolanes suggests that (282) is also <u>trans</u>.



(Figure 5)

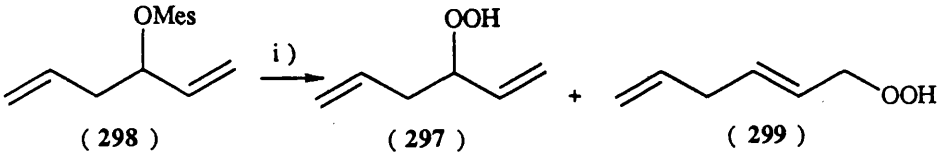
The effect of decoupling the methyl protons on the ^{1}H-nmr spectrum of 2,2,4-trimethyl-5-(2-propen-1-yl)-1,3-dioxane (**296**). The multiplet due to H_d is seen to collapse to a doublet.

2.1.7 Summary

There are two main points which arise from the investigation of the cyclization reactions of 2-ethenyl-4-penten-1-hydroperoxide (**124**). Firstly, the preference for 5-membered ring formation under both polar and radical mechanisms. In the NBS reaction with (**124**), five membered 1,2-dioxolanes and tetrahydrofurans are the only products, the latter formed by oxygen transfer the peroxonium intermediate. Secondly, the preference for the trans-configuration of 1,2-dioxolanes, as witnessed in mercury(II) nitrate, NIS and DBPO reactions.

2.2 Synthesis and cyclization reactions of 1,5-hexadiene-3-hydroperoxide 297

An attempted synthesis of 1,5-hexadiene-3-hydroperoxide (**297**) starting from the commercially available 1,5-hexadiene-3-ol was not without problems. Firstly, preparation of the methanesulphonate (**298**) upon treatment of the alchohol with methanesulphonyl chloride did not go to completion. Secondly, this crude



(298) (297) (299)

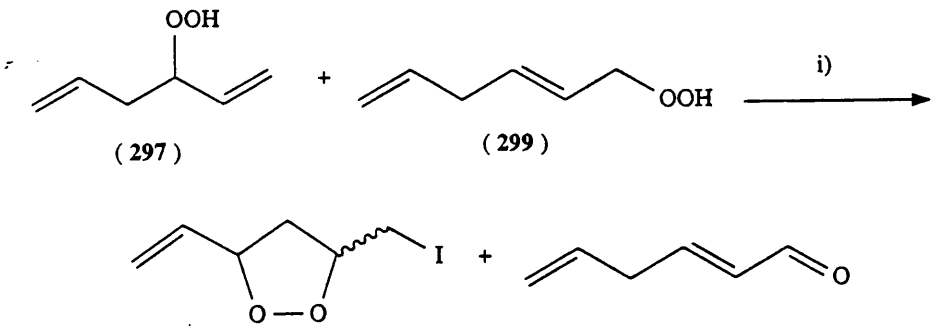
i) 30% H_2O_2, 50% KOH, MeOH

methanesulphonate (**298**) gave a mixture of two isomeric hydroperoxides upon treatment with basic hydrogen

peroxide. This was identified as a 2:3 mixture of 1,5-hexadiene-3-hydroperoxide (297) and 2,5-hexadiene-1-hydroperoxide (299) from the ^{13}C-nmr spectrum. The mixture of isomeric hydroperoxides would seemingly arise from either the competition between S_N2 and S_N2' or by an allylic rearrangment of one or other hydroperoxide.

2.2.1 Reaction with N-iodosuccinimide (NIS)

Owing to the small quantity of this mixture obtained, it was decided not to attempt a separation, but to treat the mixture with N-iodosuccinimide (NIS). Analysis of the ^{13}C-nmr spectrum of the crude product mixture suggested the presence of one cyclic peroxide and one other product. These were easily separated by column chromatography and identified as a 3:1 mixture of cis and trans-3-ethenyl-5-iodomethyl-1,2-dioxolane (300) together with trans-2,5-hexadienal (301). Therefore, it would appear that 1,5-



(297) (299) (300) (301)

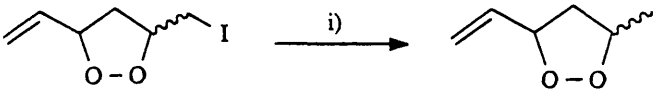
i) NIS , CH_2Cl_2

hexadiene-3-hydroperoxide (297) undergoes a 5-exo cyclization, presumably by a radical mechanism as

postulated for several cyclizations mentioned earlier (Chapter 4). The observed preference for a cis-orientation of the 3,5-substituents is in agreement with Beckwith's guidelines[105]. However, 2,5-hexadiene-1-hydroperoxide (299) can undergo no favourable cyclization by the Baldwin rules[38] and dehydration to trans-2,5-hexadienal (301) takes place.

Since this work was done, Tallant[111] has isolated 2,5-hexadien-1-hydroperoxide (299) by preferentially mercurating 1,5-hexadien-3-hydroperoxide (297) and has subsequently shown that NIS brings about the dehydration of (299) to trans-2,5-hexadienal (301).

The reduction of the iododioxolane (300) with tri-n-butyltin hydride yielded only 3-ethenyl-5-methyl-1,2-dioxolane (302) which was difficult to isolate from the tri-n-butyltin residues. However, it was possible by ^{1}H-nmr to determine the ratio of cis to trans to be approximately 3:1.



(300) (302)

i) n-Bu_3SnH, Petroleum Spirit, N_2

CHAPTER 6

EXPERIMENTAL

1 Introduction

1.1 Solvents

Solvents were dried in the following ways: benzene and diethyl ether were dried over freshly formed sodium wire, pyridine was dried over potassium hydroxide pellets, and dichloromethane was dried by distillation from calcium hydride.

Ethyl acetate and petroleum spirit were distilled in order to free them of high boiling impurities. All other solvents were used as received.

1.2 Reagents

Phosphorus tribromide and acetyl chloride were always distilled immediately prior to use.

Owing to the extremely hygroscopic nature of silver tetrafluoroborate, this compound was handled in a glove-box under a dry nitrogen atmosphere. In this fashion, quantities of silver tetrafluoroborate were weighed into air-tight containers which were removed from the glove-box and the contents added to the reaction mixture.

Commercial mercury(II) nitrate hemihydrate was found to be too wet to use. Consequently, it was dried *in vacuo* over phosphorus pentoxide.

Both N-iodosuccinimide (NIS) and N-bromosuccinimide (NBS) were recrystallized prior to use. NIS was recrystallized from carbon tetrachloride/dioxan and NBS from water.

Only two reagents needed to be prepared. Firstly, tri-n-butyltin hydride was prepared from bis(tri-n-butyltin) oxide and polymethylhydrosiloxane (PMHS) according to the method of Hayashi et. al.[112] Secondly, di-t-butylperoxalate (DBPO) was prepared from t-butyl hydroperoxide and oxalyl chloride according to the method of Bartlett et. al.[113]

1.3 Equipment

Four nmr spectrometers were used during the course of the work. 20 MHz ^{13}C-Spectra were recorded on a Varian CFT-20 and 60 MHz ^{1}H-spectra on a Jeol PMX-60. High-field spectra were recorded using a Varian XL-200 (^{1}H, 200MHz; ^{13}C, 50MHz) and a Varian VXR-400 (^{1}H, 400MHz; ^{13}C, 100MHz). The nmr data given, were obtained on the XL-200 unless otherwise stated.

Infra red spectra were recorded on a Perkin-Elmer 983 with separate data station.

Mass spectra were recorded using a VG 7070 F/H machine with Finigan INCOS data system.

Micro-analyses were performed by the Analytical Chemistry Unit of University College London.

1.4 Chromatography

Two GLC machines were used. A Pye-Unicam 204 was used for preparative GLC and Pye-Unicam 304 with a Texas Instruments reporting integrator was used for analytical GLC.

Analytical and semi-preparative HPLC was carried out by Mr. Steve Corker using a Waters M6000 pump and R401 refractometer with a Rheodyne 7125 injection valve. Preparative HPLC was performed on a Waters Prep LC system 500 with a refractometer.

Column chromatography made use of Merck Kieselgel 60 (70-230 Mesh) and TLC was performed using precoated aluminium-backed plates (Kieselgel 60) with and without fluorescent indicator.

Two main methods of development were used for the TLC plates. The general method employed a 5% w/v solution of phosphomolybdic acid (PMA) in ethanol as a dip. For testing oxidizing character, the TLC plates were sprayed with an acidified solution of ferrous thiocyanate made up thus:

Ferrous ammonium sulphate	0.87g
Ammonium thiocyanate	0.67g
Water	12.5cm^3
98% Sulphuric acid	0.125cm^3

Alkyl hydroperoxides, 1,2-dioxanes, and 1,2-dioxolanes will all produce bright red spots.

2 Experimental details relating to Chapter 2

2.1 5-Hexen-2-one(76) and 5-methyl-5-hexen-2-one(77)

Sodium (23.0g, 1.0mol) was dissolved in warm ethanol ($600cm^3$). Ethyl acetoacetate (130.14g, 1.0mol) was added and the mixture brought to reflux. Allyl bromide or methallyl chloride (1.0mol) were added over ½ hr. The reaction mixture was refluxed for 4 hr, cooled, the solids removed by filtration, and the ethanol removed at reduced pressure. The crude allylated ethyl acetoacetate was heated with sodium hydroxide solution (120g in $800cm^3$ of water) in a large flask fitted with a tall Vigreux column. The crude ketone distilled at 82-100°C with water and ethanol. The crude ketone was washed with water, dried, and distilled at reduced pressure.

5-methyl-5-hexen-2-one(77)	60°C/18mmHg	40%
5-hexen-2-one(76)	69-71°C/10mmHg	41%

2.2 5-Hexen-2-ols (78)(83)(89)

All apparatus (including magnesium turnings) was dried in a hot oven for at least 1 hour prior to use.

To stirred magnesium turnings (2.90g, 0.12 mol) and dry diethyl ether ($5cm^3$) were added a few drops of a solution of methyl iodide or phenyl bromide (0.12mol) in dry diethyl ether ($50cm^3$). When the reaction started the bulk of the halide solution was added at such a rate as to

maintain gentle reflux. When the addition was complete the mixture was refluxed for ½ hr, cooled in an ice/salt bath and a solution of the ketone (76)(77) (0.10mol) in dry ether (20cm^3) was added dropwise. The reaction mixture was left to stand at room temperature overnight, cooled in an ice/salt bath, and saturated ammonium chloride (25cm^3) was added. After 2 hrs the solids were filtered off and washed with dry diethyl ether. The diethyl ether was removed at reduced pressure to give the crude 5-hexen-2-ols (78)(83)(89) in yields of 96-100%. The alcohols were distilled at reduced pressure.

2-phenyl-5-hexen-2-ol(78)

Yield = 79%

b.p. = 74-76°C/18-20mmHg.

δ_H ($CDCl_3$,60MHz) 1.6(s,3H), 1.9(m, 5H), 5.0(m,2H), 5.8 (br m,1H), 7.4 (m,5H).

δ_C ($CDCl_3$) δ 28.15, 29.71, 42.83, 74.19, 114.07 138.42, 147.48, 127.75, 126.14, 124.56.

2-methyl-5-hexen-2-ol(83)

Yield = 75%

b.p. = 50°C/8mm Hg

δ_H ($CDCl_3$, 60MHz) 1.2(s,6H), 1.5(m,3H), 2.0(m,2H), 5.0(m,2H), 5.8(br m,1H),

δ_C ($CDCl_3$) 28.37, 28.87(2C), 42.68, 70.21, 113.72,

138.76.

2,5-Dimethyl-5-hexen-2-ol(89)

b.p. = 68°C/25mmHg.

δ_H ($CDCl_3$) 1.24(s,6H), 1.50(br m,3H), 1.76 (br s,3H), 2.10(m,2H), 5.08(br s,2H).

δ_C ($CDCl_3$) 22.72, 29.19(2C), 36.64, 41.85, 70.69, 109.62, 146.12.

6.2.3 2-Bromo-5-hexenes (79)(84)(90)

To a mixture of freshly distilled phosphorus tribromide (3.90g, 14.4 mmol), dry benzene (1.80cm^3), and dry pyridine (0.55cm^3) at -5°C was added a mixture of the alcohol (78), (83) or (89) (35.9 mol) and dry pyridine (0.18cm^3), keeping the temperature below -3°C. After addition, the reaction mixture was allowed to come to room temperature. The supernatant liquid was decanted from the solids which were washed several times with dry benzene. The combined benzene washings were concentrated at reduced pressure. The 2-methyl-substituted bromides (84) and (90) were distilled, 2-bromo-2-phenyl-5-hexene (79) eliminated HBr and was therefore used as the crude product.

2.4 5-Hexen-1-hydroperoxides (80)(85)(91)

An anhydrous solution of hydrogen peroxide in diethyl

ether was prepared by adding 85% hydrogen peroxide (3.10g, 78mmol) to diethyl ether ($50cm^3$) which was dried over $MgSO_4$ and filtered. A 2-bromo-5-hexene (79)(84) or (90) (13 mmol) was added to this solution and the mixture cooled to -78°C. Silver tetrafluoroborate (≈15mmol) was added with stirring, in one portion. After 20 minutes the reaction mixture was allowed to come to room temperature. Water ($20cm^3$) was added followed by saturated sodium hydrogen carbonate solution (50 cm^3). The ether layer was separated and the aqueous layer washed with diethyl ether (4 x 20 cm^3). The combined ether layer was dried ($MgSO_4$) and the ether removed at reduced pressure to give a mixture of the diakylperoxides (86)(92) and hydroperoxides (85)(91) which were separated by preparative HPLC using 10% ethyl acetate in petroleum spirit (60-80°C). The hydroperoxide (80) had no corresponding dialkyl peroxide and was used as the crude product.

2-Phenyl-5-hexen-2-hydroperoxide (80)

Crude Yield = 88%

δ_C ($CDCl_3$) 22.77, 28.13, 38.66, 85.97, 114.82, 125.63, 127.24, 128.36, 138.30, 143.77.

2-Methyl-5-hexen-2-hydroperoxide (85)

Yield = 23%

δ_H ($CDCl_3$, 60MHz) 1.1(s,3H), 1.7(m,2H), 2.1(m,2H), 5.0(m,2H), 5.7(m,1H), 7.2(br s,1H).

2,5-Dimethyl-5-hexen-2-hydroperoxide (91)

Yield = 41%

δ_H ($CDCl_3$, 400MHz) 1.23(s,6H), 1.72(m,2H), 1.74(s,3H), 2.02(m,2H), 4.70(m,2H), 7.43(s,1H)

δ_C ($CDCl_3$, 100MHz) 22.63, 23.83(2C), 31.89, 36.41, 82.49, 109.46, 146.09.

2.5 2-Phenyl-4-penten-1-ol(98)

All apparatus was dried in a hot oven for at least 1 hour prior to use.

To stirred magnesium turnings (29.17g, 1.20mol) in dry diethyl ether (100cm^3) was added a small amount of a solution of allyl bromide (133.08g, 1.1mol) in dry diethyl ether (350cm^3). When the reaction had started the bulk of the allyl bromide solution was added at such a rate as to maintain gentle reflux. After the addition of the allyl bromide solution the mixture was refluxed for ½ hr and cooled in an ice/salt bath. Styrene oxide (120.15g, 1.0mol) in dry diethyl ether (200cm^3) was added and the mixture left to stand overnight.

Saturated ammonium chloride solution (250cm^3) was added to the cooled reaction mixture. After 2hr the solids were filtered off, washed with dry ether, and the solvent removed from the filtrate at reduced pressure to give crude 2-phenyl-4-penten-1-ol (98) (163.8g).

Distillation at reduced pressure gave 2-phenyl-4-penten-1-ol (98) (84.24g, 52%, 87-90°C/0.001 mmHg).

δ_H ($CDCl_3$) 1.75(s,1H), 2.43(m,2H), 2.84(m,1H), 3.68(dd,1H, ^3J = 7.1Hz, ^2J = 10.7Hz), 3.73(dd,1H, ^3J = 6.1Hz, ^2J = 10.7Hz), 4.97(m,2H), 5.68(m,1H), 7.20(m,5H).

δ_C ($CDCl_3$), 20MHz) 36.53, 48.08, 66.48, 116.17, 126.50, 128.01, 128.37, 136.35, 142.35.

ν_{max}(neat) 3372, 3019, 2919, 1638, 1598, 1491, 1448, 1054, 1027, 914, 757, 699 cm^{-1}.

2.6 2-Phenyl-4-pentenal (100)

To a rapidly stirred suspension of pyridinium chlorochromate (39.87g, 185mmol) in dry dichloromethane (200cm^3) was added 2-phenyl-4-penten-1-ol (98) (20.00g, 123mmol) in dichloromethane (20cm^3). After 18hr the supernatant liquid was decanted and the solids washed with dry diethyl ether (3 x 100 cm^3). The combined solution was filtered through a thick pad of Celite and silica and the solvent removed at reduced pressure to give crude product. Distillation gave 2-phenyl-4-pentenal (100) (12.99g, 65%, 77-78°C/0.3-0.4mmHg.)

δ_H ($CDCl_3$) 2.50(m,1H), 2.82(m,1HO, 3.62(dt,1H, ^3J = 1.7, 7.3Hz), 5.04(m,2H), 5.71(m,1H), 7.36(m,5H), 9.70(d,1H, ^3J = 1.7Hz).

δ_C ($CDCl_3$) 33.94, 58.71, 117.15, 127.65, 128.86, 129.04,

134.87, 135.69, 200.06.

2.7 3-Phenyl-5-hexen-2-ol (106)

All the apparatus was dried in a hot oven for at least 1 hr prior to use.

To stirred magnesium turnings in dry diethyl ether ($10cm^3$) were added a few drops of a solution of methyl iodide (9.82g, 69.2 mmol) in diethyl ether ($20cm^3$); when reaction had started the remainder was added at such a rate as to maintain gentle reflux. After the addition of the methyl iodide solution the mixture was refluxed for ½ hr then cooled in an ice bath. 2-Phenyl-4-pentenal (100) (10.55g, 65.9mmol) in diethyl ether ($20cm^3$) was added slowly and the mixture left to stand overnight.

Saturated ammonium chloride solution ($15cm^3$) was added to the cooled reaction mixture. After 2 hr, the solids were filtered off and washed with large amounts of dry diethyl ether. The solvent was removed at reduced pressure to give crude 3-phenyl-5-hexen-2-ol (106) in a yield of 96%

δ_H ($CDCl_3$) 1.03, 1.18(d,3H, ^3J = 6.3, 6.3Hz), 2.3-2.7(br m,3H), 3.88(m,1H), 4.94(m,2H), 5.65(m,1H), 7.25(m,5H).

2.8 3-Phenyl-5-hexen-2-one (107)

To a rapidly stirred suspension of pyridinium chlorochromate (21.14g, 98mmol) in dry dichloromethane ($200cm^3$) was added 3-phenyl-5-hexen-2-ol (**106**) (11.51g, 65.3mmol) in dichloromethane ($20cm^3$). After 18 hrs the supernatant liquid was decanted and the solids washed with dry diethyl ether ($3 \times 100cm^3$). The combined solution was filtered through silica, twice, and the solvent removed at reduced pressure to give crude 3-phenyl-5-hexen-2-one (**107**) which was distilled at reduced pressure (6.50g, 57%, 64-66°C/0.3mmHg).

δ_H ($CDCl_3$) 2.06(s,3H), 2.46(m,1H), 2.75(m,1H), 3.70(t,1H, ^3J = 7.5Hz), 4.98(m,2H), 5.62(m,1H), 7.31(m,5H).

δ_C ($CDCl_3$) δ 28.99, 36.14, 59.29, 116.55, 127.31, 128.22, 128.89, 135.72, 138.36, 207.39.

2.9 Tosylhydrazones (101)(108)(114)

To a stirred slurry of p-toluenesulphonhydrazide and ethanol at 40-50°C was added one equivalent of the ketone. After about 15 mins all the solids had dissolved and the solution was allowed to cool to room temperature (or placed in a fridge if necessary) and the p-toluenesolphonhydrazones crystallized out. The crystals were filtered off and recrystallized from ethanol or ethanol/water.

2-Phenyl-4-penten-1-tosylhydrazone (101)

Yield = 42%

mp = 109-111°C

δ_H ($CDCl_3$) 2.43(s,3H), 2.40-2.68(m,2H), 3.52(m,1H), 4.89(m,2H), 5.53(m,1H), 7.00-7.32(m,8H), 7.50(s,1H), 7.78(d,2H, ^3J = 8.3Hz).

δ_C ($CDCl_3$) 21.62, 37.03, 48.27, 116.87, 127.07, 127.99, 128.01, 128.66, 129.58, 135.06, 135.26, 139.52, 144.12, 153.31.

m/z 329($M+1^+$, 3.23%), 173(20.01), 155(11.30), 133(29.39), 131(75.67), 128(22.24), 115(20.63), 103(60.77), 91(100.00), 77(39.23), 51(27.56), 41(57.70).

Found: C, 65.70; H, 6.15; N, 8.72. $C_{18}H_{20}N_2O_2S$ requires C, 65.83; H, 6.14; N, 8.53%

3-Phenyl-5-hexen-2-tosylhydrazone (108)

Yield = 55%

m.p. = 123-124°C

δ_H ($CDCl_3$) 1.57(s,3H), 2.40(m,1H), 2.48(s,3H), 2.64(m,1H), 3.43(m,1H), 4.84(m,2H) 5.51(m,1H), 6.98(m,2H), 7.19-7.38(m,6H), 7.89(d,2H, ^3J = 8.4Hz).

δ_C ($CDCl_3$) 15.15, 21.58, 36.62, 53.84, 116.12, 126.89, 127.95, 128.14, 128.43, 129.48, 135.40, 136.23, 140.09, 143.89, 157.95.

m/z 343($M+1^+$,33.80%), 187(29.64), 173(15.19), 155(6.15), 147(76.15), 145(90.49), 131(34.23), 129(24.88),

128(28.53), 115(74.09), 91(100.00), 89(23.10), 77(21.24), 65(19.22), 63(15.59), 57(13.39), 51(20.60).

Found: C, 66.39; H, 6.51; N, 8.14. $C_{19}H_{22}N_2O_2S$ requires C, 66.64; H, 6.47; N, 8.18%.

5-methyl-5-hexen-2-tosylhydrazone (114)

Yield = 67%

mp = 110-111°C

δ_H ($CDCl_3$) 1.61(s,3H), 1.76(s,3H), 2.14(m,2H), 2.35(m,2H), 2.43(s,3H), 4.60(m,2H), 7.31(d,2H, ^3J = 8.5Hz), 7.85(d,2H), ^3J = 8.5Hz), 8.12(br s,1H).

δ_C ($CDCl_3$). 15.68, 21.59, 22.23, 33.84, 36.86, 110.42, 128.05, 129.44, 135.46, 143.85, 144.47, 157.81,

m/z 281($M+1^+$,1.37%), 155(13.10), 126(22.85), 125(37.71), 111(19.91), 95(44.93), 91(73.79), 89(25.66), 81(15.93), 67(31.12), 55(47.89), 41(100.00).

Found: C, 60.05; H, 7.25; N, 10.11. $C_{14}H_{20}N_2O_2S$ requires C, 59.97; H, 7.18; N, 9.99%.

2.10 Tosylhydrazines (102)(109)(115)

To a stirred solution of the tosylhydrazone (10mmol), sodium cyanoborohydride (40mmol), and bromocresol green (few mg) in THF (200cm^3) under nitrogen was added a solution of p-toluenesulphonic acid monohydrate (20mmol) in THF(50cm^3) at such a rate as to keep the indicator just yellow.

After 3-4 hrs the reaction mixture was filtered

through a pad of Celite moistened with THF (it may be necessary to scrape the surface of the Celite with a spatula to prevent clogging). The filtrate was concentrated to 1/4-1/5 of the original volume at reduced pressure and water ($30cm^3$) was added. After about 15 mins the mixture was extracted with dichloromethane (2 x $50cm^3$), these extracts were washed with water (2 x $50cm^3$) and dried over $MgSO_4$. The solvent was removed at reduced pressure to give the crude tosylhydrazines (102)(109)(115) usually as cloudy yellow oils.

N-(2-phenyl-4-penten-1-yl)-N'-tosylhydrazine(102)

δ_C ($CDCl_3$, 20MHz) 21.25, 38.09, 43.36, 56.21, 116.17, 127.44, 127.75, 128.33, 129.41, 134.38, 135.60, 144.81, 143.96.

N-(5-methyl-5-hexen-2-yl)-N'-tosylhydrazine (115)

δ_C ($CDCl_3$) 18.23, 21.37, 22.26, 37.17, 33.65, 54.91, 109.64, 128.00, 129.28, 135.18, 143.58, 145.28.

2.11 Hydroperoxides (103),(110),(116)

To an ice-cold, stirred solution of the tosylhydrazine (15mmol) and 30% hydrogen peroxide ($\approx 160cm^3$, $\approx$1500mmol) in THF ($200cm^3$) was added sodium peroxide (1.75g, 22.5mmol). The mixture was allowed to come to room temperature. After 24 hr water ($600cm^3$) was added, the reaction mixture neutralized with 2M HCl and

extracted with dichloromethane (3 x 150cm^3). The dichloromethane extracts were dried over $MgSO_4$ and the solvent removed at reduced pressure to give the crude hydroperoxide. The crude hydroperoxide was taken up in n-hexane (40cm^3) and extracted with cold 25% potassium hydroxide (2 x 10g). The base extract was neutralized at ice bath temperature with cold 2M HCl and extracted with diethyl ether. The other extracts were dried (Na_2SO_4) and the solvent removed to give the hydroperoxides (103), (116).

3-Phenyl-5-hexen-2-hydroperoxide (110) was not pure enough for further work and purification was effected by column chromatography on silica with 30% diethyl ether in petroleum spirit (60-80°C).

2-Phenyl-4-penten-1-hydroperoxide (103)

Yield = 39%

δ_H ($CDCl_3$) 2.45(m,2H), 3.13(m,1H), 4.15(d(d),1H, ^3J = 6.9Hz), 4.19(d(d),1H, ^3J = 7.0Hz), 5.06(m,2H), 5.69(m,1H), 7.30(m,5H), 8.05(s,1H).

δ_C ($CDCl_3$) 36.92, 43.71, 80.42, 116.48, 126.59, 127.88, 128.40, 136.00, 141.66.

3-Phenyl-5-hexen-2-hydroperoxide (110)

Yield = 8%

δ_H ($CDCl_3$) 1.06, 1.18 (d,3H, ^3J = 6.3, 6.4Hz),

2.55(m,2H), 2.99(m,1H), 4.22(m,1H), 5.06(m,2H) 5.60(m,1H), 7.28(m,5H), 7.74(br s,1H)

δ_C ($CDCl_3$) 15.26, 15.94, 34.41, 36.25, 48.84, 48.92, 84.37, 84.53, 116.17, 116.32, 126.54, 126.60, 128.26, 128.26, 128.51, 128.69, 136.59, 136.66, 140.65, 140.88.

5-Methyl-5-hexen-2-hydroperoxide (116)

Yield = 59%

δ_H ($CDCl_3$) 1.25 (d,3H, ^3J = 6.1Hz), 2.5-2.9(m,2H), 1.74(s,3H), 2.09(m,2H), 4.08(m,1H), 4.73(m,2H), ≈8.1(br, 1H).

δ_C ($CDCl_3$, 100MHz) 18.11, 22.45, 31.91, 33.41, 81.19, 110.00, 145.44.

2.12 3-Bromomercuriomethyl-1,2-dioxanes(81),(87),(93),(104),(112),(117),(120),(126)

To a stirred suspension of mercury(II) nitrate hemihydrate (0.98g, 2.95mmol) in dichloromethane (70cm^3) under N_2 was added, dropwise over 15 mins., a solution of the hydroperoxide (2.81mmol) in dry dichloromethane (30cm^3).

After stirring for a further 15 minutes the supernatant liquid was decanted and water (20cm^3) was added, closely followed by potassium bromide (0.37g, 3.09mmol). Stirring was continued for approximately 10

minutes until the white precipitate had disappeared from the aqueous phase. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane ($20cm^3$). The combined dichloromethane layer was dried over Na_2SO_4 and the solvent removed at reduced pressure to give the crude mercurial as an oil. The mercurials (81)-->(126) were purified by column chromatography, eluting on silica with the solvent indicated.

6-Bromercuriomethyl-3-methyl-3-phenyl-1,2-dioxane (81)

Dichloromethane

Yield = 15%

δ_H ($CDCl_3$, 400MHz) 1.35, 1.64(s,3H), 1.5-2.6(m,6H), 4.50-4.65(m,1H), 7.40(m,5H).

δ_C ($CDCl_3$, 100MHz) 24.34, 29.83, 29.95, 30.39, 33.01, 37.24, 37.44, 79.23, 79.37, 81.06. 82.17, 124.66, 125.62, 126.87, 127.46, 128.32, 128.49, 143.17, 144.59.

6-Bromomercuriomethyl-3,3-dimethyl-1,2-dioxane (87)

Dichloromethane

Yield = 67% mp= 71-72°C

δ_H ($CDCl_3$) 1.17(s,3H), 1.36(s,3H), 1.68(m,4H), 2.02(dd,1H, ^2J = 11.7Hz, ^3J = 6.4Hz), 2.22(dd,1H, ^2J = 11.7Hz, ^3J = 6.0Hz), 4.48 (m,1H).

δ_C ($CDCl_3$, 100MHz) 22.92, 27.18, 30.53, 34,28, 37.61, 77.86, 79.30.

Found: C, 20.52; H, 3.09. $C_7H_{13}BrHgO_2$ requires C, 20.52; H, 3.20%.

3-Bromomercuriomethyl-3,6,6-trimethyl-1,2-dioxane (93)

Dichloromethane

Yield = 46%

δ_H ($CDCl_3$, 60MHz) 1.3(s,6H) 1.4(s,3H) 1.7(m,4H), 2.2(m,2H).

δ_C ($CDCl_3$) 22.40, 23.03, 24.29, 26.64, 27.00, 29.12, 30.95, 31.30, 31.99, 33.10, 43.10, 47.07, 76.43, 78.31, 79.87, 80.38.

3-Bromomercuriomethyl-5-phenyl-1,2-dioxane (104)

Dichloromethane

Yield = 75%

δ_H ($CDCl_3$) 1.6-2.3(m,4H), 3.23(m,1H), 4.21, 4.46(d,m,2H, J(d) = 8.3Hz), 4.74(m,1H) 7.36(m,5H).

δ_C (CD_2Cl_2) Major isomer: 37.51 (^{13}C-^{199}Hg J = 1522Hz), 40.34, 41.63(^{13}C-^{199}Hg J = 29Hz), 77.15, 80.47(^{13}C-^{199}Hg J = 108Hz), 127.36, 127.62, 128.98, 140.66. Minor isomer: 76.22, 77.45, 126.89, 128.16, 128.80.

Found: C, 28.58; H, 2.66. $C_{11}H_{13}BrHgO_2$ requires C, 28.87; H, 2.86%.

3-Bromomercuriomethyl-6-methyl-5-phenyl-1,2-dioxane (112)

Dichloromethane

Yield = 70%

δ_H ($CDCl_3$) 0.96, 1.03, 1.08, 1.14 (d,3H, J = 6.3, 6.8, 6.4, 6.6Hz), 1.6-3.0(m,5H), 3.5-5.0(m,2H), 7.31(m,5H)

δ_C ($CDCl_3$) 12.58, 16.09, 16.41, 16.93, 32.62, 36.75, 37.13, 37.29, 37.43, 37.59, 40.38, 41.83, 42.93, 43.03, 43.29, 48.83, 75.22, 78.39, 79.53, 79.59, 80.00, 80.18, 81.38, 81.88, 126.57, 126.86, 127.02, 127.40, 127.67, 127.78, 128.37, 128.59, 128.74, 129.39, 149.19, 140.98, 141.19.

Found: C, 30.11; H, 3.10. $C_{12}H_{15}BrHgO_2$ requires C, 30.55; H, 3.20%.

3-Bromomercuriomethyl-3,6-dimethyl-1,2-dioxane (117)

Dichloromethane

Yield = 45%

δ_H ($CDCl_3$) 1.15,1.20(d,3H) 1.31, 1.46(s,3H), 1.72(m,4H), 2.17,2.32(AB_q,2H, ^2J=12.1Hz & $^2J(^1H-^{199}Hg)$=206Hz, ^2J=11.7Hz & $^2J(^1H-^{199}Hg)$=194Hz) 4.22(m,1H).

δ_C ($CDCl_3$) 18.55, 18.72, 24.59, 28.09, 28.52, 29.67, 34.67, 36.38, 43.11($^1J(^{13}C-^{199}Hg)$ = 1500Hz), 47.05($^1J(^{13}C-^{199}Hg)$ = 1489Hz), 76.94(2C), 80.34, ($^2J(^{13}C-^{199}Hg)$ = 95Hz), 80.50($^2J(^{13}C-^{199}Hg)$ = 105Hz).

δ_C ($CDCl_4$) 18.51, 18.68, 24.63, 28.20, 28.61, 29.65, 34.72, 36.47, 42.72, 47.04, 76.14, 76.32, 79.73, 79.93. Found: C, 20.42; H, 3.19. $C_7H_{13}BrHgO_2$ requires C, 20.52; H, 3.20%.

3-Bromomercuriomethyl-1,2-dioxane (120)

Dichloromethane

Crude Yield = 93%

δ_H ($CDCl_3$) 1.5-2.0(m, 4H), 1.99(dd, 1H, ^2J = 11.9Hz, ^3J = 6.3Hz, $^2J(^1H-^{199}Hg)$ = 207Hz), 2.21(dd, 1H, ^2J = 11.9Hz, ^3J = 6.1Hz, $^2J(^1H-^{199}Hg)$ = 211Hz), 4.16(m, 2H), 4.59(m, 1H).

δ_C ($CDCl_3$) 23.92, 32.45($^3J(^{13}C-^{199}Hg)$ = 143Hz), 37.12($^1J(^{13}C-^{199}Hg)$ = 1569Hz), 72.31, 80.51($^2J(^{13}C-^{199}Hg)$ = 104Hz).
Found: C, 16.02; H, 2.35. $C_5H_9BrHgO_2$ requires C, 15.74; H, 2.38%.

3-Bromomercuriomethyl-5-ethenyl-1,2-dioxane (126)

For preparation see experimental Ch. 5.

Yield = 32%

δ_H ($CDCl_3$, 400MHz) 1.32, 1.74, 2.02(m,2H); 1.97(dd,1H, ^3J = 6.2Hz), ^2J = 11.9Hz); 2.23(dd,1H, ^3J = 5.7Hz, ^2J = 11.9Hz); 2.66(m,1H); 3.93, 4.07, 4.36(m,2H); 4.61, 4.76(m,1H); 5.14(m,2H); 5.63, 6.00(ddd + m,1H, J = 7.7,

11.0, 17.6Hz).

δ_C ($CDCl_3$) Major: 37.45($^1J(^{13}C-^{199}Hg)$ = 1513Hz), 38.84, 39.02, 75.65, 79.61($^2J(^{13}C-^{199}Hg)$ = 102Hz), 116.39, 136.75.

Found: C, 20.01; H, 2.47. $C_7H_{11}BrHgO_2$ requires C, 20.62; H, 2.72%.

2.13 3-Methyl-1,2-dioxanes (121),(82),(88),(105),(113),(22),(137)

To a rapidly stirred solution of the mercurial (2.5mmol) in dichloromethane (15cm^3) at -10°C under N_2 was added a chilled solution of sodium borohydride (0.19g, 5.0mmol) in 3M sodium hydroxide (15cm^3), the reaction temperature was not allowed to rise above 0°C. The reaction mixture was kept at <0°C for ½ hr. and then allowed to come to room temperature. The dichloromethane layer was separated and the aqueous layer washed with dichloromethane (3 x 10cm^3). The combined dichloromethane layer was dried over $MgSO_4$ and the solvent was removed at reduced pressure to give the crude 1,2-dioxane which was purified by column chromatography, eluting on silica with the solvent system indicated.

3-Methyl-1-2-dioxane (121)

75% dichloromethane/25% Petroleum spirit (30-40°C)

Yield = 45%

δ_C ($CDCl_3$) 19.03, 23.79, 30.33, 72.30, 77.86.

3,6-Dimethyl-3-phenyl-1,2-dioxane (82)

50% dichloromethane/50% petroleum spirit.

Yield = 15% (from the crude mercurial)

δ_C ($CDCl_3$) 0.99, 1.25(d,3H, J = 6.4, 6.3Hz), 1.33, 1.65(s,3H), 1.7-2.5(m,4H), 4.25(m,1H) 7.40(m,5H).

δ_C ($CDCl_3$) 18.45, 18.63, 24.35, 28.10, 28.52, 30.32, 33.19, 33.42, 76.82, 77.10, 80.74, 81.91, 124.74, 125.87, 126.59, 127.53, 128.25, 144.32, 145.57.

m/z 192(M^+, 0.36%), 131(62.50), 121(32.45), 120(22.33), 118(38.41), 105(100.00), 91(15.64), 77(48.83), 51(20.96), 43(63.67).

Accurate Mass Spectrum. Found 192.1155.$C_{12}H_{16}O_2$ requires 192.1149.

3,3,6-Trimethyl-1,2-dioxane (88) (from (87))

Dichloromethane (flash chromatography)

Yield = 68%

δ_H ($CDCl_3$) 1.14(d,3H), 1.15(s,3H), 1.36(s,3H), 1.65(m,4H), 4.11(m,1H).

δ_C ($CDCl_3$, 100MHz) 18.93, 22.74, 27.47, 28.39, 34.33, 76.80, 77.53.

m/z 115(1.45%), 97(2.84), 69(42.87), 59(27.20), 55(16.69), 43(100.00), 41(24.96).

Accurate Mass Spectrum of $(M-Me)^+$

Found 115.0765. $C_6H_{11}O_2$ requires 115.0758.

3,3,6-Trimethyl-1,2-dioxane (88) (from (117))

75% dichloromethane/25% petroleum spirit

Yield = 45%

δ_H ($CDCl_3$) 1.14(d, 3H, ^3J = 6.3Hz), 1.15(s,3H), 1.36(s,3H), 1.64(m,4H), 4.14(m,1H).

m/z 129($M-1^+$, 3.84%), 111(6.46), 97(15.05), 69(35.92), 55(22.51), 43(100.00), 41(37.03).

Accurate Mass Spectrum of $(M-H)^+$

Found 129.0930. $C_7H_{13}O_2$ requires 129.0915

3-Methyl-5-phenyl-1,2-dioxane (105)

60% dichloromethane/40% petroleum spirit.

Yield = 62%

δ_H ($CDCl_3$) 1.20, 1.30(d,3H, ^3J = 6.4, 6.5Hz), 1.5-2.1(m,2H), 3.20(m,1H), 4.19,4.41(d^+m,3H, ^3J(d) = 8.43Hz), 7.26(m,5H).

δ_C ($CDCl_3$, 100MHz) (Major) 19.06, 38.19, 41.34, 77.05, 77.63, 127.09, 127.33, 128.75, 140.67. (Minor) 18.37, 36.15, 36.35, 74.61, 76.15 126.65, 127.82, 128.55.

δ_C (CCl_4) (Major) 18.88, 38.33, 41.34, 76.12, 76.48, 126.63, 128.32, 140.51. (Minor) 18.25, 36.37(2C?), 73.33, 75.15, 126.21, 127.45, 128.14.

m/z 178(M^+, 2.09%), 160(28.57), 132(39.34), 117(75.50), 105(44.02), 104(84.58), 103(53.67), 91(39.84), 77(36.46), 51(30.37), 43(100.00).

Accurate Mass Spectrum. Found 178.1002.$C_{11}H_{14}O_2$ requires 178.0993.

Found: C, 73.95; H, 8.00.$C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%.

3,6-Dimethyl-4-phenyl-1,2-dioxane (113)

50% diethyl ether/50% petroleum spirit.

Yield = 65%

δ_H ($CDCl_3$) 0.96,1.02,1.11,1.15,1.17,1.24,1.52(d,6H,^3J = 6.3,6.8,6.4,6.6,6.4,6.4,6.5 Hz), 1.6-2.3(m,2H), 2.6-3.5(m,1H), 4.2-4.8(m,2H), 7.30(m,5H).

δ_C ($CDCl_3$) 12.45, 16.25, 16.54, 16.84, 17.60, 18.74, 19.13, 30.66, 36.08, 38.30, 39.97, 42.86, 43.24, 43.46, 48.91, 72.66, 75.66, 77.52, 79.40, 79.76, 81.33, 81.69, 126.45, 126.75, 126.91, 127.44, 127.72, 127.81, 128.29,

128.57, 128.71, 129.46, 140.85, 141.61, 141.76, 141.89.

m/z 192(M^+, 0.24%), 174(3.56), 148(5.84), 132(7.18), 117(10.67), 105(64.53), 104(100.00), 91(8.11), 78(6.64), 43(13.00).

Accurate Mass Spectrum. Found 192.1135.$C_{12}H_{16}O_2$ requires 192.1149.

3,3,6,6-Tetramethyl-1,2-dioxane (22)

50% diethyl ether/50% petroleum spirit.

Yield = 36%

^1H ($CDCl_3$, 60MHz) 1.3(s,12H), 1.6(s,4H)

5-Ethenyl-3-methyl-1,2-dioxane (137)

50% dichloromethane/50% petroleum spirit (60-80°C).

Yield = 39%

δ_H ($CDCl_3$) 1.10,1.15(d,3H, ^3J = 6.4,6.5Hz), 2.2-2.9(m,2H), 2.57(m,1H), 3.87(dd,1H, ^3J = 10.9Hz, ^2J = 12.3Hz), 4.03(ddd,1H, $^3J_{Trans}$ = 17.3Hz, $^3J_{cis}$ = 10.4Hz, ^3J = 6.9Hz)

δ_C ($CDCl_3$, 100MHz) Major: 19.19, 37.35, 39.47, 76.18, 77.46, 116.00, 138.01. Minor: 18.95, 35.44, 35.84, 74.71, 115.74, 139.51.

2.14 2-Phenyl-4-penten-1-methanesulphonate (99)

To a stirred, cooled mixture of 2-phenyl-4-penten-1-ol(98) (5.00g, 30.8mmol) and methanesulphonyl chloride (3.53g, 30.8mmol) at 0°C was added pyridine (4.87g, 61.6mmol) over 1½ hr. so that the temperature did not rise above 5°C. After a further 2 hr. at 0°C, the reaction mixture was poured into ice-cold 10% hydrochloric acid ($25cm^3$) and extracted with ether (2 x $20cm^3$). The ether extracts were washed with saturated sodium hydrogen carbonate solution ($20cm^3$) and dried over potassium carbonate. The solvent was removed at reduced pressure to give the methanesulphonate (7.10g, 96%) of sufficient purity for further reactions.

δ_H ($CDCl_3$) 2.50(m,2H), 2.76(s,3H), 3.10(m,1H), 4.35(m,2H), 5.10(m,2H), 5.66(m,1H), 7.28(m,5H).

δ_C ($CDCl_3$, 100MHz) 35.92, 36.91, 44.66, 72.77, 117.28, 127.11, 127.72, 128.50, 134.71, 139.84.

2.15 2-Hydroxymethyl-2,5,5,-trimethyltetrahydrofuran (95)

To a chilled solution of 2,5-dimethyl-5-hexen-2-ol (89) (1.00g, 7.8mmol) in dichloromethane ($15cm^3$) was added a solution of MCPBA (1.68g, 7.8mmol of 80%) in CH_2Cl_2($25cm^3$). The reaction mixture was removed from the ice bath and stirred at room temperature. After 24 hr.

water ($50cm^3$) and a single crystal of sodium thiosulphate were added. The pH of the mixture was adjusted to 8 by the addition of potassium carbonate. The dichloromethane layer was separated and the aqueous layer extracted with more dichloromethane ($25cm^3$). The combined dichloromethane layer was dried over potassium carbonate and the solvent removed at reduced pressure to give 1.32g clear liquid. Purification was effected by trap-to-trap distillation.

δ_H ($CDCl_3$) 1.21(s,3H), 1.25(s,3H), 1.30(s,3H), 1.7-2.1(m,5H), 3.40(m,2H).

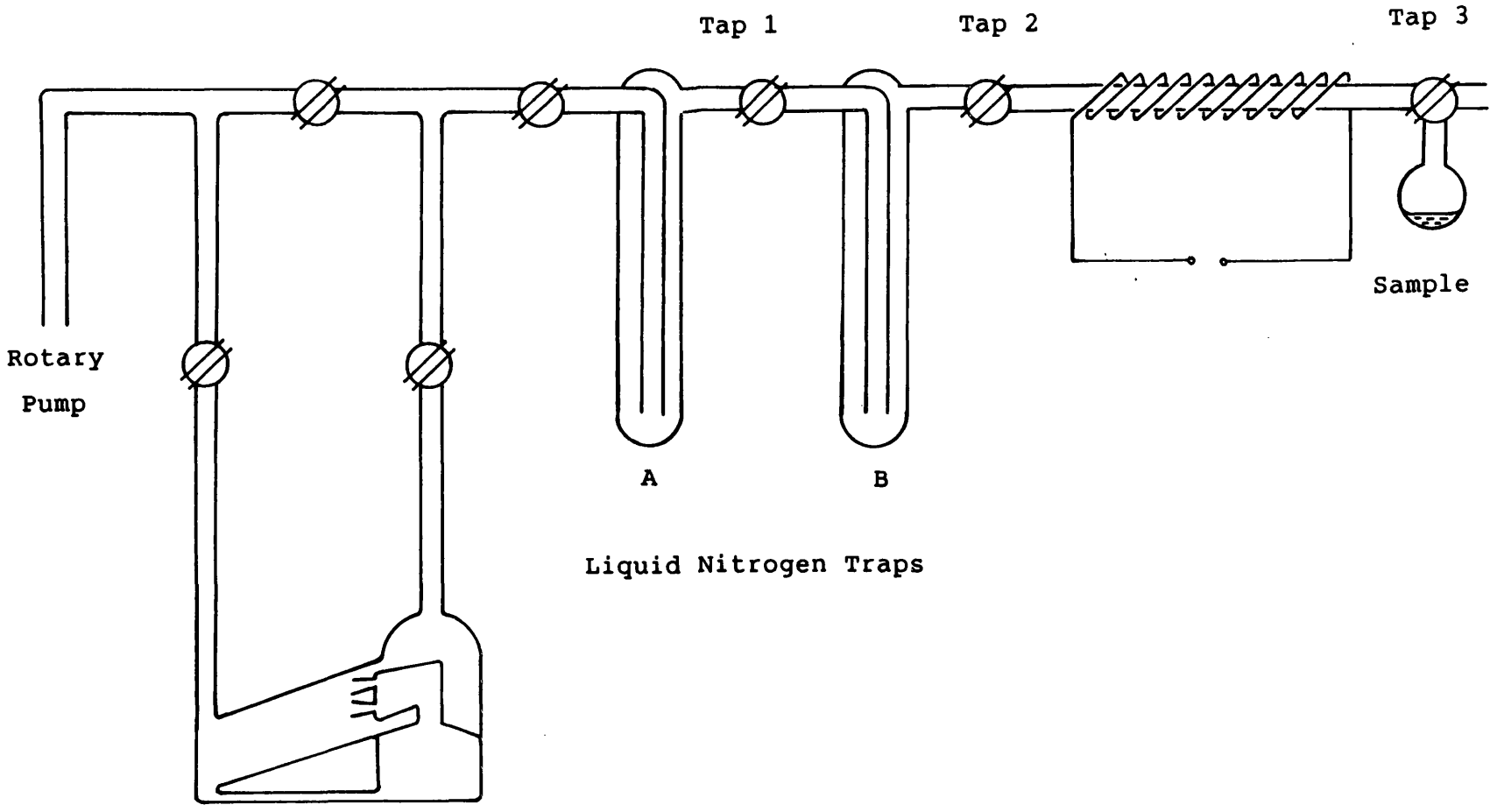
cf by product of reduction of (93)

δ_H ($CDCl_3$) 1.21(s,3H), 1.25(s,3H), 1.30(s,3H), 1.7-2.2(m,5H), 3.39(m,2H).

3 Experimental details relating to Chapter 3

3.1 Flash vacuum pyrolysis

The apparatus used for the flash vacuum pyrolysis is depicted in Figure 6 . The apparatus was evacuated to Tap 2 and the sample of 50-100mg of 1,2-dioxane was immersed in liquid nitrogen. The whole apparatus was then evacuated to 10^{-3}mmHg. The pyrolysis tube was heated to 450°C and the liquid nitrogen removed from the sample. On warming to room temperature the sample evaporated and passed through the pyrolysis tube, the pyrolysate



(Figure 6) Flash Vacuum Pyrolysis Apparatus

condensed in the liquid nitrogen tap (Trap B).

Taps 1 and 2 were closed isolating Trap B, from which the liquid nitrogen was removed. When Trap B was warmed to about 0°C dry air was introduced through Tap 3 followed by Tap 2. The pyrolysate was quickly taken up in approximately $3cm^3$ of $CDCl_3$ with TMS and the ^1H-and ^{13}C-nmr spectra were taken.

In the case of a phenyl substituted 1,2-dioxane (82) or (105), evaporation was slow at room temperature and the sample was evaporated upon gentle heating with a hot air gun. Some of the resultant pyrolysate condensed immediately after the 'hot zone' and was washed into the trap with $CDCl_3$.

3,6-Dimethyl-1,2-dioxane (32)

Major product of pyrolysis was 5-hydroxyhexan-2-one (139)

δ_H ($CDCl_3$) 1.21(d,3H, J = 6.1Hz), 1.76(m,2H), 2.18(s,3H), 2.60(t,2H, J = 7.0Hz), 3.79(m,1H)

δ_C ($CDCl_3$) 23.75, 30.04, 32.57, 40.05, 67.48, 209.65.

3,6-Dimethyl-3-phenyl-1,2-dioxane (82)

3,6-Dimethyl-3-phenyl-1,2-dioxane(82)(0.0690g) was subjected to fvp as described above and the pyrolysate (0.0452g, 66%) analysed by nmr and GLC. The two major products were identified as 5-hydroxy-5-phenylhexan-2-one

(**143**) and acetophenone in a 3:2 ratio.

δ_H ($CDCl_3$) 5-Hydroxy-5-phenylhexan-2-one (**143**): 1.48, 1.56,1.63,1.66,2.07(s); 2.10,2.36(m); 7.47(m). Acetophenone: 2.61(s); 7.47,7.95(m).

δ_C ($CDCl_3$) 5-Hydroxy-5-phenylhexan-2-one (**143**): 30.05, 31.24, 37.25, 38.81, 73.95, 124.78, 126.61, 128.13, 137.12, 210.08. Acetophenone: 26.63, 128.24, 128.57, 133.11, 137.12, 198.20.

3,3,6-Trimethyl-1,2-dioxane (88)

Major product of fvp was 5-hydroxy-5-methylhexan-2-one (**142**), also visible were peaks due to the hemiacetal, 2,5,5-trimethyl-2-furanol.

δ_C ($CDCl_3$) 5-Hydroxy-5-methylhexan-2-one (**142**): 29.37, 30.08, 36.60, 38.71, 70.12, 209.87. 2,5,5,-Trimethyl-2-furanol: 28.31, 28.62, 30.36, 37.55, 38.19, 108.09.

3-Methyl-5-phenyl-1,2-dioxane (105)

3-Methyl-5-phenyl-1,2-dioxane (**105**) (0.0900g) was subjected to fvp as described above. The recovered pyrolysate (0.0621g, 69%) was analysed by nmr and analytical HPLC to reveal two major products, 5-methyl-3-phenyltetrahydro-2-furanol (**144**) and 5-hydroxy-4-phenylpentan-2-one (**145**) in 10:1 and 6:1 ratio. The signals due to (**144**) are visible by nmr.

δ_H ($CDCl_3$) 1.37,1.41, 1.45(d,3H, J = 6.1Hz, 6.3Hz, 6.4Hz); 2.15(m,1H); 2.50(m,1H); 3.00(d,1H, J = 3.2Hz); 3.35(m,1H); 4.50(m,1H); 5.45(t,1H, J = 3.5Hz); 7.31(m,5H).

δ_C ($CDCl_3$) 20.35, 42.17, 53.79, 75.02, 104.56, 126.66, 127.32, 128.59, 141.80.

3-Methyl-1,2-dioxane (121)

3-Methyl-1,2-dioxane (**121**) (0.1085g) was subjected to fvp as described above. The recovered pyrolysate (0.0825g, 76%) was analysed by nmr to reveal two major products 5-methyltetrahydro-2-furanol (**146**) and 5-hydroxypentan-2-one (**147**) in a 2:1 ratio.

δ_H ($CDCl_3$, 400MHz) 5-Methyltetrahydro-2-furanol: 1.22, 1.35(d,J = 6.0Hz, 6.0Hz); 4.0-4.3(m); 5.46,5.56(m). 5-Hydroxypentan-2-one: 2.18(s); 2.58,3.63(t, J = 7.0Hz).

δ_C ($CDCl_3$, 100MHz) 5-Methyltetrahydro-2-furanol: 20.93, 31.28, 33.24, 74.25, 98.41 & 22.79, 31.00, 34.26, 77.11, 98.35. 5-Hydroxypentan-2-one: 26.45, 30.03, 40.37, 61.91, 209.74.

5-Ethenyl-3-methyl-1,2-dioxane (127)

The main product of the fvp of 5-ethenyl-3-methyl-1,2-dioxane (**127**) was identified as trans-4-hexen-2-ol. (**150**).

δ_H ($CDCl_3$) 1.46(d,3H, J = 6.3Hz), 1.70(d + m,4H, J = 5.6Hz), 2.15(m,2H), 3.80(m,1H), 5.50(m,2H)

δ_C ($CDCl_3$) 18.09, 22.62, 42.52, 67.19, 127.36, 129.06.

3.2 Iron(II) Sulphate induced rearrangements

To a chilled (ice bath) solution of 1,2-dioxane (35-40mmol) in 1:1 water/acetonitrile ($2cm^3$), under N_2 was added 1M iron(II) sulphate solution ($0.7cm^3$, 70mmol, 2 equiv.). After stirring at ice bath temperature for 2 hours the reaction mixture was extracted with dichloromethane ($2x5cm^3$). The extract was dried over magnesium sulphate and the solvent removed at reduced pressure to yield the rearrangement products.

3-Methyl-5-phenyl-1,2-dioxane (105)

3-Methyl-5-phenyl-1,2-dioxane (**105**)(0.0625g) was treated with $FeSO_4$ as described above. The product mixture (0.0601g, 96%) was identified as a mixture of 5-hydroxy-4-phenylpentan-2-one (**145**) and 5-methyl-3-phenyltetrahydro-2-furanol (**144**), by nmr and analytical HPLC, in a ratio of 1:1.3.

δ_H ($CDCl_3$) 5-Methyl-3-phenyltetrahydro-2-furanol: 1.29, 1.35,1.40,1.44(d,J = 6.3,6.0,6.3,5.9Hz); 4.5(m); 5.43(m); 7.3(m). 5-Hydroxy-4-phenylpentan-2-one: 2.11(s), 2.80(dd,J = 6.7,17.1Hz), 2.92(dd,J = 7.1,17.0Hz), 3.39(m), 7.3(m).

δ_C ($CDCl_3$, 100MHz). 5-Hydroxy-4-phenylpentan-2-one: 30.54, 43.29, 46.42, 67.06, 208.22. 5-Methyl-3-phenyltetrahydro-2-furanol: 20.36, 42.15, 53.72, 74.95, 104.50; 23.36, 39.00, 52.30, 76.09, 103.64.

3-Methyl-1,2-dioxane (121)

3-Methyl-1,2-dioxane (**121**)(0.0417g) was treated with $FeSO_4$ as described above. The product mixture (0.0276g, 66%) was identified as a mixture of 5-methyltetrahydro-2-furanol (**146**), 5-hydroxypentan-2-one (**147**), and bis-(4-oxopentyl) ether (**148**) in ratio of 1:1.

δ_H ($CDCl_3$) 5-Methyltetrahydro-2-furanol: 1.22,1.35(d, J = 6.2,6.2Hz); 1.9(m); 4.1-4.5(m) 5.46,5.57(m). 5-Hydroxypentan-2-one: 2.18(s), 2.60(t, J = 7.0Hz), 3.43(m), 3.65(t, J = 6.1Hz), 3.88(m). bis-(4-Oxopentyl)ether 2.15(s), 2.50(t, J = 7.4Hz).

δ_C ($CDCl_3$, 100MHz) 5-Methyltetrahydro-2-furanol: 20.94, 31.24, 33.28, 74.29, 98.51; 22.86, 30.96, 34.33, 76.94, 98.45. 5-Hydroxypentan-2-one: 26.44, 30.03, 40.43, 62.11, 209.05. 2-Methyltetrahydro-2-furanol & bis-(4-oxopentyl) ether: 22.00, 24.45, 24.55, 29.89, 37.92, 40.70, 59.88, 67.52, 107.37.

3.3 5-Hydroxyhexan-2-one (139)

5-Hydroxyhexan-2-one was prepared by the partial

oxidation of hexane-2,5-diol with silver carbonate on Celite as described by Davis et. al.[74]

The Celite was washed with 10% hydrochloric acid in methanol and water until neutral. It was dried under vacuum and 30g were added to a solution of silver nitrate (34.0g, 0.2mol) in water ($200cm^3$). To this suspension was added sodium carbonate decahydrate (30g, 0.11mol) in water ($300cm^3$). After stirring for 10 mins. the solid was filtered off, washed with water until neutral and dried in vacuo.

Silver carbonate on Celite (40.06g) was added to a solution of hexan-2,5-diol(2.50g, 16.9mmol) in dry benzene ($150cm^3$) which was refluxed in a Dean and Stark apparatus. After $1.3cm^3$ of water had been collected the reaction mixture was cooled and the solid removed by filtration. The benzene was removed at reduced pressure to give crude product (1.61g, 82%). Chromatography on silica gel eluting with ethyl acetate yielded 5-hydroxyhexan-2-one (139) (0.39g, 20%).

δ_H ($CDCl_3$) 1.15(d, 3H, J = 6.2Hz), 1.70(m,2H), 2.12(s,3H), 2.24(brs,1H), 2.54(t,2H, J = 7.1Hz), 3.77(m,1H).

3.4 Reaction of 2,5-hexanedione with ethane-1,2-diol

A mixture of 2,5-hexanedione (15.00g, 130mmol), ethane-1,2-diol (8.16g, 130mmol), and p-toluenesulphonic

acid (0.06g) in dry benzene ($60cm^3$) was refluxed in a Dean and Stark apparatus until $2.3cm^3$ of water had been collected. The cooled reaction mixture was washed with 10% sodium hydroxide solution ($20cm^3$) and water ($5x10cm^3$) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give a mixture of dione, monoacetal and diacetal. Most of the diacetal crystallizes out at -10°C and can be removed by filtration.

3.5 5-Hydroxy-5-phenylhexan-2-one (143)

To stirred magnesium turnings (0.78g, 32mmol) in dry ether ($5cm^3$) under N_2 was added a little of a solution of bromobenzene (4.84g, 30mmol) in ether ($10cm^3$). Once reaction had started the remainder of the bromobenzene solution was added at such a rate as to maintain gentle reflux. The reaction mixture was refluxed for a further 20 minutes then cooled in an ice bath. A solution of an approximately 2:1 mixture of hexane-2,5-dione monoacetal and hexane-2,5-dione(2.84g) in ether ($10cm^3$) was added. The reaction mixture was left at room temperature overnight and then poured onto a slurry of ice and sulphuric acid. The ether layer was separated and the aqueous phase extracted with ether (3 x $20cm^3$). The combined ether extracts were washed with saturated sodium hydrogen carbonate and dried over magnesium sulphate. The solvent was removed at reduced pressure to give a mixture

of products. On standing, this liquid produced crystalline solid which was removed by filtration to afford 2-methyl-2-(3-hydroxy-3-phenylbutanyl)-1,3-dioxolane (157) (2.92g).

15% Sulphuric acid (19 drops) was added to a stirred suspension of silica (Merck 60, 70-230 mesh) (5.70g) in dichloromethane ($10cm^3$). After 5 mins. the dilute acid had been adsorbed and crude 2-methyl-2-(3-hydroxy-3-phenylbutanyl)-1,3-dioxolane (157) (1.69g, 7.15mmol) was added. After 2 hours the silica was filtered off and washed with dichloromethane. The filtrate and washings were combined and the solvent removed at reduced pressure to give a mixture of products (0.75g). Chromatography on silica with dichloromethane-diethyl ether (9:1) as eluant yielded 5-hydroxy-5-phenylhexan-2-one (143) (0.06g, 7%).

δ_H ($CDCl_3$) 1.56(s,3H), 2.07(s,3H), 2.10(m,2H), 2.37(m,2H), 7.40(m,5H).
Additional peaks due to the two isomeric hemiacetals were also seen including four methyl singlets at δ 1.48, 1.62, 1.63, 1.66.

δ_C ($CDCl_3$) 30.03, 31.18, 37.26, 38.79, 73.93, 127.77, 126.59, 128.22, 147.12, 210.11.
Additional peaks due to the two isomeric hemiacetals were also seen:

δ_C ($CDCl_3$) 27.64, 28.10, 30.34, 31.80, 37.63, 38.21, 38.47, 39.44, 85.67, 85.95, 105.55, 105.60, 124.56,

124.65, 126.38, 126.42, 128.02, 128.10, 148.12, 149.12.

Found: C, 74.89; H, 8.41. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%.

3.6 2-Methyl-2-(3-hydroxy-3-methylbutanyl)-1,3-dioxolane (158)

To stirred magnesium turnings (3.12g, 128mmol) in diethyl ether (20cm^3) was added a little of a solution of iodomethane (16.33g, 115mmol) in diethyl ether (90cm^3). Once reaction had started, the remainder of the iodomethane solution was added at such a rate as to maintain gentle reflux. After the addition, the reaction mixture was stirred for ½ hr. and cooled in an ice/salt bath. A solution of approximately 2:1 hexane-2,5-dione monoacetal (155) and hexane-2,5-dione (140) (4.60g) in ether (20cm^3) was added. After 1 hour saturated ammonium chloride solution (20cm^3) was added and the mixture was left for 2 hours. The solid residues were filtered off and washed with dry ether. The ether was removed from the combined filtrate and washings to afford a mixture of products (4.15g). Chromatography on silica gel eluting with diethyl ether as eluant yielded 2-methyl-2-(3-hydroxy-3-methylbutanyl)-1,3-dioxolane (158) (2.29g, 68%).

δ_H ($CDCl_3$). 1.22(6H,s), 1.34(3H,s), 1.59(1H,m), 1.76(1H,m), 1.85(1H,br s), 3.96(2H,s).

δ_C ($CDCl_3$) 23.85, 29.31(2C), 33.68, 37.54, 64.61(2C), 70.21, 110.14.

3.7 2-Methyl-2-(3-acetoxy-3-methylbutanyl)-1,3-dioxolane (160)

To a stirred solution of 2-methyl-2-(3-hydroxy-3-methylbutanyl)-1,3-dioxolane (158) (2.18g, 12.5mmol) in dry ether (15cm^3) under nitrogen was added sodium (0.51g, 22.2mmol) as freshly cut, small lumps. After stirring for 48 hours, the unused sodium was removed and the solution cooled in an ice bath. Freshly distilled acetyl chloride (1.18g, 15mmol) was added. After stirring for 40 mins, water (30cm^3) was added, the ether layer removed, and the aqueous layer extracted with ether (2 x 20cm^3). The combined extracts were washed with saturated sodium hydrogen carbonate solution (20cm^3) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give crude product (2.21g). Chromatography on silica with diethyl ether as eluant yielded 2-methyl-3(3-acetoxy-3-methylbutan)-1,3-dioxolane (160) (0.80g, 30%).

δ_H ($CDCl_3$) 1.33(3H,s), 1.44(3H,s), 1.75(4H,m), 1.97(3H,s), 3.95(4H,m).

δ_C ($CDCl_3$) 22.41, 23.82, 25.95, 33.33, 35.22, 64.65, 81.72, 109.85, 170.37.

3.8 5-Acetoxy-5-methylhexan-2-one (161)

To 15% sulphuric acid (9 drops) adsorbed onto silica (2.40g) in dichloromethane (6cm^3) was added 2-methyl-2-(3-acetoxy-3-methylbutanyl)-1,3-dioxolane (**160**) (0.80g, 3.69mmol). After stirring for 3½ hours sodium hydrogen carbonate (0.1g) was added and after 5 mins. the solids were filtered off and washed with dichloromethane (10cm^3). The filtrate and washings were combined and the solvent removed at reduced pressure to yield 5-acetoxy-5-methylhexan-2-one (**161**) (0.39g, 61%).

δ_H ($CDCl_3$) 1.45 (6H,s), 1.97(3H,s), 2.00(2H,m), 2.18(3H,s), 2.50(2H,m).

δ_C ($CDCl_3$) 22.35, 25.81(2C), 29.92, 34.88, 38.41, 81.28, 170.32, 208.20.

3.9 5-Hydroxy-5-methylhexan-2-one (142)

To a stirred solution of 5-acetoxy-5-methylhexan-2-one (**161**) (0.39g, 2.26mmol) in methanol (10cm^3) was added 3M sodium hydroxide solution (10cm^3). After 45 minutes water (30cm^3) was added and the reaction mixture was extracted with dichloromethane (3 x 20cm^3). The extracts were dried over magnesium sulphate and the solvent removed at reduced pressure to yield crude 5-hydroxy-5-methylhexan-2-one (**142**) (0.27g, 92%).

δ_C ($CDCl_3$, 100MHz) 29.31, 30.70, 36.67, 38.74, 70.05, 210.07.

3.10 2-Phenyl-4-pentenoic acid (162)

Jones reagent was prepared by dissolving chromium trioxide (16.0g, 160mmol) in water (46cm^3), cooling this solution, and adding 98% sulphuric acid (14cm^3) with stirring. The Jones reagent was added with stirring to a cooled solution of 2-phenyl-4-penten-1-ol (**98**) (16.22g, 100mmol) in acetone (250cm^3) over 15 minutes. The reaction mixture was left at room temperature for 1 hr. Isopropanol (5cm^3), to remove excess oxidizing agent, and water (300cm^3) to dissolve solid residues, were added. The acetone was removed at reduced pressure and the remaining aqueous solution was extracted with ether (4 x 150cm^3). The ether extract was dried over magnesium sulphate and the solvent removed at reduced pressure to give crude 2-phenyl-4-pentenoic acid (**162**) (18.89g) as a pale green liquid. Purification by base extraction with potassium hydroxide gave 2-phenyl-4-pentenoic acid (**162**) (12.94g, 69%).

δ_H ($CDCl_3$) 2.51(1H,m), 2.78(1H,m), 3.64(1H,m), 5.03(2H,m), 5.69(1H,m), 7.31(5H,m), 11,59(1H,br s).

δ_C ($CDCl_3$) 37.12, 51.38, 117.13, 127.47, 128.03, 128.65, 134.98, 138.06, 178.74.

3.11 5-Methyl-3-phenyldihydro-2-furanone (163)

2-Phenyl-4-pentenoic acid (162) (4.77g, 27.1mmol) was refluxed with 50% sulphuric acid ($30cm^3$) for 1 hour. Water ($50cm^3$) was added and the mixture was extracted with ether (3 x $30cm^3$). These extracts were washed with saturated sodium hydrogen carbonate ($30cm^3$) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give crude 5-methyl-3-phenyldihydro-2-furanone (163) (3.87,g, 81%). Small quantities were distilled using a Kugelrohr apparatus.

δ_H ($CDCl_3$) 1.47,1.50(3H,d, J = 7.4,6.3Hz), 1.9-2.8(4H,m), 3.91(1H,m), 4.5-4.8(1H,m), 7.31(5H,m).

δ_C ($CDCl_3$) 20.69, 20.89, 37.73, 39.66, 45.56, 47.59, 74.96, 75.18, 127.43, 127.62, 128.08, 128.70, 128.86, 136.66, 137.12, 176.98, 177.24.

3.12 5-Methyl-3-phenyltetrahydro-2-furanol (144)

To a solution of 5-methyl-3-phenyldihydro-2-furanone (163) (0.50g, 2.84mmol) in dry ether ($10cm^3$) at -76°C and under nitrogen was added a 1M solution of diisobutylaluminium hydride (DIBAL-H) in benzene ($4.3cm^3$, 4.3mmol) over 20 minutes. The reaction mixture was kept at -76°C for 1 hour and then methanol ($0.2cm^3$) was added. The reaction mixture was allowed to come to room temperature. Ether ($50cm^3$) was added to the reaction

mixture which was washed with saturated potassium sodium tartrate solution (1 x 40cm^3 and 2 x 20cm^3), saturated sodium chloride solution (20cm^3) and dried over magnesium sulphate. The solvent was removed at reduced pressure to yield crude 5-methyl-3-phenyltetrahydro-2-furanol (144) (0.46g, 90%). A little was purified by Kugelrohr distillation, the colourless liquid slowly crystallizing on standing.

δ_H ($CDCl_3$) 1.31,1.36,1.41,1.45(3H,d,J = 6.4,6.1,6.2, 6.2.Hz), 1.62-2.52(3H,m), 4.47(1H,m), 5.45(1H,m), 7.30(5H,m).

δ_C ($CDCl_3$) (two major isomers) 20.29, 42.09, 53.51, 74.88, 104.31, 127.18, 127.33, 128.53, 141.77; 23.20, 39.02, 52.07, 75.98, 103.51, 126.58, 128.19, 128.55, 141.59.

m/z 178(M^+, 0.07%), 160(14.13), 148(14.67), 132(90.16), 117(100.00), 105(84.14), 91(75.48), 77(56.02), 65(23.46), 51(38.25), 45(75.33).

Accurate Mass Spectrum. Found 178.0980. $C_{11}H_{14}O_2$ requires 178.0993.

Found: C, 73.90; H, 7.89. $C_{11}H_{14}O_2$ requires C, 73.72; H, 7.87%.

3.13 2-Phenyl-4-penten-1-yl acetate (164)

A mixture of 2-phenyl-4-penten-1-ol (**98**) (10.00g, 62mmol), glacial acetic acid (7.45g, 124mmol) and concentrated sulphuric acid (15 drops) was refluxed for 2 3/4 hr. and allowed to cool. Dichloromethane ($25cm^3$) was added to the reaction mixture which was then washed with water ($25cm^3$), saturated sodium hydrogen carbonate solution ($25cm^3$), and dried over magnesium sulphate. The solvent was removed at reduced pressure to yield crude 2-phenyl-4-penten-1-yl acetate (**164**) (11.83g, 94%). Distillation using Kugelrohr gave pure samples.

δ_H ($CDCl_3$) 1.98(3H,s), 2.50(2H,m), 3.00(1H,m), 4.22(2H,m), 5.00(2H,m), 5.72(1H,m), 7.22(5H,m).

δ_C ($CDCl_3$) 20.75, 36.91, 44.54, 67.63, 116.69, 126.75, 127.81, 128.41, 135.66, 141.35, 170.74.

3.14 1-Acetoxy-2-phenylpentan-4-ol (165)

To a stirred solution of mercury(II) acetate (3.12g, 9.8mmol) in water ($10cm^3$) was added THF ($10cm^3$) and 2-phenyl-4-penten-1-yl acetate (**164**) (2.00g, 9.8mmol). After 15 mins. 1.5M sodium hydroxide solution ($10cm^3$) was added, followed by a solution of sodium borohydride (0.18g, 4.8mmol) in 1.5M sodium hydroxide ($10cm^3$). Salt was added to separate the THF layer, the aqueous layer was washed with dichloromethane (2 x $10cm^3$) and the combined

organic phase dried over magnesium sulphate. The solvent was removed at reduced pressure to yield crude product (2.30g). Chromatography on silica, eluting with diethyl ether yielded 1-acetoxy-2-phenylpentan-4-ol (**165**) (1.03g, 48%).

δ_H ($CDCl_3$) 1.15,1.19(3H,d, J = 6.2Hz, 6.1Hz), 1.49(1H, br s), 1.80(2H,m), 2.00(3H,s), 3.0-3.3(1H,m), 3.5-3.8(1H,m) 4.20(2H,m), 7.30(5H,m).

δ_C ($CDCl_3$, 100MHz). 20.92, 23.37, 24.47, 41.64, 41.66, 41.94, 65.24, 66.07, 68.24, 68.62, 126.90, 126.98, 127.74, 128.00, 128.60, 128.69, 141.28, 141.58, 171.07.

3.15 5-Acetoxy-4-phenylpentan-2-one (166)

To a stirred suspension of pyridinium chlorochromate (1.45g, 6.75mmol) in dry dichloromethane was added 1-acetoxy-2-phenylpentan-4-ol (**165**) (1.00g, 4.50 mmol). After 2 3/4 hr. dry diethyl ether ($10cm^3$) was added and the supernatant liquid decanted. The solid residues were broken up and washed with dry ether (2 x $5cm^3$). The combined organic phase was filtered through silica/Celite. The solvent was removed from the filtrate to give crude product as a mobile green liquid (1.26g). Chromatography on silica, eluting first with dichloromethane and then ether yielded 5-acetoxy-4-phenylpentan-2-one (**166**) (0.61g, 62%).

δ_H ($CDCl_3$) 2.02(3H,s), 2.09(3H,s), 2.81(1H,dd, ^2J = 17.0Hz, ^3J = 7.5Hz), 2.87(1H,dd, ^2J = 17.0Hz, ^3J = 6.7Hz), 3.57(1H, m), 4.14(1H,dd, ^2J = 10.9Hz, ^3J = 7.2Hz), 4.24(1H,dd, ^2J = 10.9Hz, ^3J = 6.4Hz), 7.24(5H, m).

δ_C ($CDCl_3$) 20.79, 30.46, 39.90, 46.32, 67.54, 127.08, 127.68, 128.63, 140.75, 170.71, 206.44.

3.16 5-Hydroxy-4-phenyl-2-pentanone (145)

To a stirred solution of 5-acetoxy-4-phenyl-2-pentanone (166) (0.59g, 2.68mmol) in methanol (6cm^3) was added 3M sodium hydroxide solution (6cm^3). After 1 hr. water (10cm^3) was added to the reaction mixture which was extracted with dichloromethane (2 x 10cm^3). The extracts were dried over magnesium sulphate and the solvent was removed at reduce pressure to give crude product (0.47g, 98%). Chromatography on silica eluting with ether yielded 5-hydroxy-4-phenyl-2-pentanone (145) (0.40g, 83%).

δ_H ($CDCl_3$, 400MHz) 2.13(3H,s), 2.82(1H,dd, ^3J = 6.5Hz, ^2J = 17.0Hz), 2.95(1H,dd, ^3J = 7.4Hz), ^2J = 17.0Hz), 3.42(1H,m), 3.72(1H,m), 3.78(1H,m), 7.24(5H,m).

Peaks that could be assigned to the intramolecular hemiketal were seen: 1.61, 1.64(3H,s); 3.89, 3.99, 4.22, 4.42(2H, t(J = 8.0Hz), dd(^3J = 8.5Hz, ^2J = 9.9Hz), t(J = 8.1Hz), t(J = 8.0Hz)).

δ_C ($CDCl_3$) 30.52, 43.28, 46.43, 68.12, 127.03, 127.74, 127.77, 141.39, 207.98.

3.17 5-Methyltetrahydro-2-furanol (146)

To a stirred solution of γ-valerolactone (1.00g, 10mmol) in dry ether (40cm^3) under nitrogen at -76°C was added a 1M solution of diisobutylaluminium hydride (DIBAL-H) (15cm^3, 15mmol). The reaction mixture was kept at between -70 and -60°C for 1 hr. and methanol (0.81cm^3, 20mmol) was added. The reaction mixture was allowed to come to room temperature, ether (200cm^3) was added and the mixture washed with saturated potassium sodium tartrate (1 x 300cm^3 and 3 x 100cm^3). The potassium sodium tartrate washings were extracted with ether (100cm^3). The combined ether layers washed with saturated sodium chloride solution (100cm^3) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give crude product (0.49g, 48%). Chromatography on silica eluting with ethyl acetate-petroleum spirit (60-80°C) (3:1) yielded 5-methyltetrahydro-2-furanol (146) (0.32g, 31%).

δ_H ($CDCl_3$) 1.22, 1.35(3H,d, J = 6.2Hz, 6.3Hz); 2.00(4H,m); 3.91(1H,br s); 4.14, 4.34(1H,m); 5.47, 5.57(1H,m).

δ_C ($CDCl_3$). (Major isomer) 20.93, 31.28, 33.22, 74.28, 98.45; (Minor isomer) 22.81, 31.01, 34.25, 76.93, 98.40.

3.18 5-Hydroxypentan-2-one (147)

δ_C ($CDCl_3$) 26.52, 29.99, 40.32, 61.79, 209.83.

4 Experimental details relating to Chapter 4

4.1 Alkenyl methanesulphonates

All the methanesulphonates were prepared from the corresponding alcohols using the method of Williams and Mosher.[48] The crude products were of sufficient purity for further work.

4-Penten-1-methanesulphonate

Crude Yield = 88%

δ_H ($CDCl_3$, 60MHz) 2.0(m,4H), 3.0(s,3H), 4.2(t,2H, J = 6Hz), 5.0(m,2H), 5.8(m,1H).

3-Buten-1-methanesulphonate

Crude Yield = 85%

δ_C ($CDCl_3$) 33.23, 37.10, 69.12, 118.16, 132.60.

3-Methyl-3-buten-1-methanesulphonate

Crude Yield = 88%

δ_H ($CDCl_3$, 60MHz) 1.8(s,3H), 2.4(t,2H, J = 7Hz), 2.9(s,3H), 4.3(t,2H, J = 7Hz), 4.8(m,2H).

cis-3-Hexen-1-methanesulphonate

Crude Yield = 99%

δ_H ($CDCl_3$, 60MHz) 1.0(t, 3H, J = 7Hz), 1.8-2.6(m, 4H), 3.0(S, 3H), 4.2(t, 2H, J = 7Hz), 5.4(m, 2H).

trans-3-Hexen-1-methanesulphonate

Crude Yield = 91%

δ_H ($CDCl_3$, 60MHz) 1.0(t, 3H, J = 7Hz), 1.8-2.6(m, 4H), 3.0(S, 3H), 4.2(t, 2H, J = 7Hz), 5.5(m, 2H).

4.2 Alkenyl hydroperoxides

The alkenyl hydroperoxides were prepared from the methanesulphonates by an adaptation of the method of Williams and Mosher.[48]

Methanesulphonate (40mmol) and methanol (40cm^3) were mixed and cooled to <0°C. 30% Hydrogen peroxide (20g, ≈160mmol) and 50% aqueous potassium hydroxide (5.00g, 45mmol) were added and the mixture allowed to come to room temperature. After 24 hr., the mixture was cooled and 50% aqueous potassium hydroxide (15.00g, 135mmol) added. The mixture was extracted with benzene (25cm^3). The aqueous layer was cooled in an ice bath, neutralized with 2M hydrochloric acid, and extracted with benzene (4 x 25cm^3). The combined benzene extracts were extracted with cold 25% aqueous potassium hydroxide (20g). The alkaline extract

was cooled, neutralized with 2M hydrochloric acid, and extracted with diethyl ether (4 x 30cm^3). The combined ether extracts were dried over magnesium sulphate and the solvent removed at reduced pressure to give the hydroperoxides.

This procedure can be successfully carried out at double the scale.

4-Penten-1-hydroperoxide (46)

Yield = 36%

δ_H ($CDCl_3$, 60MHz) 1.5-2.5(m,4H), 4.1(t,2H, J = Hz), 5.1(m,2H), 5.8(m,1H), 8.3(br s,1H).

3-Buten-1-hydroperoxide (241)

Yield = 13%

δ_H ($CDCl_3$, 60MHz) 2.4(m,2H), 4.0(t,2H, J = 6Hz), 5.1(m,2H), 5.8(m,1H), 8.3(br s,1H).

3-Methyl-3-buten-1-hydroperoxide (178)

Yield = 34%

δ_H ($CDCl_3$, 60MHz) 1.8(s,3H), 2.4(t,2H, J = 6Hz), 4.7(s,2H), 8.8(br s,1H).

δ_C ($CDCl_3$) 22.48, 35.92, 75.11, 112.15, 142.25.

cis-3-Hexen-1-hydroperoxide (177a)

Yield = 49%

δ_H ($CDCl_3$, 60MHz) 1.0(t,3H, J = 7Hz), 1.8-2.6(m,4H), 4.0(t,2H, J = 6Hz), 5.4(m,2H), 8.5(br s,1H).

δ_C ($CDCl_3$) 14.23, 20.61, 25.91, 76.47, 123.97, 134.36.

trans-3-Hexen-1-hydroperoxide (177b)

Yield = 42%

δ_H ($CDCl_3$, 60MHz) 1.0(t,3H, J = 7Hz), 1.8-2.5(m,4H), 4.0(t,2H, J = 6Hz), 5.5(m,2H), 8.2(s,1H).

δ_C ($CDCl_3$) 13.69, 25.62, 31.09, 76.69, 124.36, 134.88.

4.3 Reaction of 4-penten-1-hydroperoxide (46) with iodine

To a stirred solution of iodine (3.10g, 12.25mmol) in dichloromethane (50cm^3) was added 4-penten-1-hydroperoxide (46) (0.50g, 4.90mmol). After 3 1/2 hr. the reaction mixture was washed with 20% sodium thiosulphate solution until colourless, dried over magnesium sulphate and the solvent was removed at reduced pressure to give 2-iodomethyltetrahydrofuran (237) (0.87g, 84%).

δ_H ($CDCl_3$) 1.66(m,1H), 2.00(m,3H), 3.21(dd,1H, ^3J = 6.5Hz, ^2J = 9.9Hz), 3.26(dd,1H, ^3J = 5.4Hz, ^2J = 9.9Hz), 3.90(m,3H).

δH ($CHCl_3$) 10.55, 26.05, 31.68, 68.83, 78.35.

m/z 212(M^+, 4.5%), 141(4.5), 127(10.6), 85(28.7), 71(44.6), 43(100.0).

Found C, 28.32; H, 4.28. C_5H_9IO requires C, 28.08; H, 4.10%.

4.4 Reaction of 4-penten-1-hydroperoxide (46) with aqueous iodine/potassium iodide

To a stirred solution of 4-penten-1-hydroperoxide (46) (0.50g, 4.89mmol) was added sodium hydrogen carbonate (0.66g, 7.82mmol). After 10 mins., potassium iodide (0.19g, 1.17mmol) and iodine (1.24g, 4.89mmol) were added in quick succession. After 1 hr. dichloromethane ($50cm^3$) and 20% sodium thiosulphate solution ($50cm^3$) was added. The dichloromethane layer was separated, dried over magnesium sulphate and the solvent removed at reduced pressure to give a brown liquid (1.19g).

δ_C ($CDCl_3$) 2-Iodomethyltetrahydrofuran (237): 10.65, 26.02, 31.82, 68.81, 78.34. 3-Iodomethyl-1,2-dioxane (238): 3.73, 23.18, 28.10, 72.46, 80.51.

4.5 Reaction of 4-penten-1-hydroperoxide (46) with iodine/pyridine

To a stirred solution of 4-penten-1-hydroperoxide (46) (0.25g, 2.45mmol) and pyridine (0.19g, 2.45mmol) was

added iodine (1.24g, 4.90mmol). After 2½ hr. the reaction mixture was washed with 10% aqueous sodium thiosulphate ($25cm^3$) until colourless, dried over magnesium sulphate and the solvent removed at reduced pressure to give a brown liquid (0.63g). ^{13}C-nmr spectroscopy also showed the furan, 1,2-dioxane mixture.

4.6 Reaction of 3-buten-1-hydroxide (241) with iodine/ pyridine

To a stirred solution of 3-buten-1-hydroperoxide (241) (0.250g, 2.84mmol) and pyridine (0.225g, 2.84mmol) in dichloromethane ($25cm^3$) was added iodine (1.442g, 5.68mmol). After stirring in the dark for 1 hr., the reaction mixture was washed with 10% aqueous sodium thiosulphate ($25cm^3$) and water ($25cm^3$), dried over magnesium sulphate and the solvent removed at reduced pressure to give a dark brown liquid (0.68g). Column chromatography on silica gel, eluting with 1:1 diethyl ether/60-80°C petroleum spirit gave 3-iodomethyl-1,2-dioxolane (**242**) (0.041g, 7%) as a slightly yellow liquid.

δ_H ($CDCl_3$) 2.50(m,1H), 2.84(m,1H), 3.16(dd,1H, ^3J = 8.2Hz, ^2J = 10.0Hz), 3.35(dd,1H, ^3J = 5.3Hz, ^2J = 10.0Hz), 4.06(m,1H), 4.23(m,1H), 4.52(m,1H).

δ_C ($CDCl_3$) 6.53, 41.05, 70.06, 79.53.

m/z 214(M^+, 2.28%), 184(8.02), 170(9.13), 141(10.07), 127(60.81), 87(15.59), 70(10.16), 55(35.94), 43(100.00).

Accurate Mass Spectrum m/z Found 213.9515. $C_4H_7IO_2$ requires 213.9493.

Found: C, 22.75; H, 3.34. $C_4H_7O_2$ requires C, 22.45; H, 3.30%.

4.7 Reaction of γ,δ-unsaturated hydroperoxides (178) (241)(177a)(177b) with N-iodosuccinimide

A solution of the hydroperoxide (0.250g) in dichloromethane (5cm^3) was added to a stirred solution of N-iodosuccinimide (1.1 equivalents) in dichloromethane (60cm^3). After stirring in the dark for ½-3hr., the reaction mixture was washed with 10% sodium thiosulphate solution, dried over magnesium sulphate and the solvent removed at reduced pressure to give the crude 3-iodomethyl-1,2-dioxolanes **(244)(242)(249a)** and **(249b)**. Column chromatography on silica gel eluting with 3:1 dichloromethane/60-80°C petroleum spirit gave the pure 3-iodomethyl-1,2-dioxolanes.

3-Iodomethyl-1,2-dioxolane (242)

Yield = 49%

δ_C ($CDCl_3$) 6.73, 41.00, 70.03, 79.44

Fully characterised in Section 6.4.6.

3-Iodomethyl-3-methyl-1,2-dioxolane (244)

Yield = 57%

δ_H ($CDCl_3$) 1.55(s,3H), 2.45(ddd,1H, ^3J = 5Hz, ^3J = 8Hz, ^2J = 12Hz), 2.76(ddd,1H, ^3J = 7Hz, ^3J = 8Hz, ^2J = 12Hz), 3.37(s,2H), 4.21(m,2H).

δ_C ($CDCl_3$) 13.83, 23.23, 44.78, 70.68, 83.09.

m/z 228(M^+, 0.98%), 184(12.57), 141(6.46), 127(32.00), 87(24.65), 55(18.85), 43(100.00).

Accurate mass spectrum. Found m/z 227.9640. $C_5H_9IO_2$ requires m/z 227.9649.
Found: C, 26.20; H, 3.92. $C_5H_9IO_2$ requires C, 26.34; H, 3.98%.

erythro and threo-3-(1-Iodopropyl)-1,2-dioxolane (249 a,b)

The data given are those for (249a,b) prepared from trans-3-hexen-1-hydroperoxide (177b). An identical product mixture was obtained from cis-3-hexen-1-hydroperoxide (177a). Column chromatography, as described above, gave a partial separation of the two isomers.

Yield = 42%

δ_C ($CDCl_3$) 13.79, 29.79, 41.66, 42.39, 70.14, 82.95; 14.46, 28.17, 38.98, 39.27, 70.52, 82.70.

m/z 242(M^+, 0.67%), 169(6.27), 127(37.62), 115(13.84),

73(69.31), 55(48.56), 43(100.00).

Accurate Mass Spectrum. Found m/z 241.9809. $C_6H_{11}IO_2$ requires 241.9806.

Found: C, 29.77; H, 4.61. $C_6H_{11}IO_2$ requires C, 29.77; H, 4.58%.

4.8 Reaction of γ,δ-unsaturated hydroperoxides (178) (241)(177a)(177b) with N-bromosuccinimide

A solution of the hydroperoxide (0.250g) in dichloromethane (5cm^3) was added to a stirred solution of N-bromosuccinimide (1.1 equivalents) in dichloromethane (45cm^3). After stirring in the dark for ½ to 3½ hr., the reaction mixture was washed with water (2 x 30cm^3), dried over magnesium sulphate and the solvent removed at reduced pressure to give the crude product. Column chromatography on silica gel, eluting with 3:1 dichloromethane/60-80°C petroleum spirit gave the pure 3-bromomethyl-1,2-dioxolanes.

3-Bromomethyl-1,2-dioxolane (245)

Yield = 42%

δ_H ($CDCl_3$) 2.52(m,1H), 2.83(m,1H), 3.33(dd,1H, ^3J = 7Hz, ^2J = 10Hz), 3.52(dd,1H, ^3J = 6Hz, ^2J = 10Hz), 4.06(m,1H), 4.23(m,1H), 4.50(m,1H).

δ_C ($CDCl_3$) 32.84, 39.81, 69.79, 78.98.

m/z 168(M^+, 7.49%), 166(M^+, 7.65%), 122(4.52), 95(12.57), 93(13.29), 82(29.19), 80(29.46), 73(100.00), 55(57.49), 43(93.19).

Accurate Mass Spectrum. Found m/z 167.9615. $C_4H_7{}^{81}BrO_2$ requires 167.9610.
Found: C, 28.86; H, 4.22. $C_4H_7BrO_2$ requires C, 28.77; H, 4.23%.

3-Bromomethyl-3-methyl-1,2-dioxolane (184)

Yield = 35%

δ_H ($CDCl_3$) 1.51(s,3H), 2.40(m,1H), 2.74(m,1H), 3.47(s,2H), 4.18(m,2H).

δ_C ($CDCl_3$) 22.08, 38.53, 44.34, 70.76, 83.79.

m/z 182(M^+, 0.02%), 180(M^+, 0.02%), 167(0.06), 165(0.05), 136(1.01), 121(1.15), 95(3.54), 93(3.79), 87(27.96), 82(2.43), 80(2.42), 55(15.87), 43(100.00).

Accurate Mass Spectrum. Found m/z 179.9792. Calculated for $C_5H_9{}^{79}BrO_2$ 179.9786.

erythro-and threo-3-(1-Bromopropyl)-1,2-dioxolane (185a,b) from cis-3-hexen-1-hydroperoxide (177a)

δ_C ($CDCl_3$) Major isomer (threo) - 12.29, 27.14, 38.17, 57.88, 70.27, 81,86. Minor isomer (erythro) - 11.58, 28.62, 40.64, 59.23, 70.01, 82.10.

erytro-and threo-3-(1-Bromopropyl)-1,2-dioxolane (185a,b) from trans-3-hexen-1-hydroperoxide (177b)

δ_C ($CDCl_3$) Minor isomer (threo) - 12.30, 27.11, 38.16, 57.86, 70.27, 81.86. Major isomer (erythro) - 11.58, 28.62, 40.65, 59.23, 70.01, 82.11.

m/z 196(M^+, 0.25%), 194(M^+, 0.28%), 151(0.50), 149(0.46), 123(7.93), 121(8.61), 82(26.35), 80(26.90), 73(46.28), 55(100.00), 41(88.78).

Accurate Mass Spectrum. Found m/z 193.9952. Calculated for $C_6H_{11}{}^{79}BrO_2$ 193.9943.
Found: C, 36.73; H, 5.67. Calculated for $C_6H_{11}BrO_2$ C, 36.95; H, 5.68%.

4.9 3-Bromomercuriomethyl-3-methyl-1,2-dioxolane (181) and threo-3-(1-bromomercuriopropyl)-1,2-dioxolane (180)

The mercurials (181) and (180) were prepared by the method of Porter et al.[35] from the corresponding hydroperoxides (178) and (177a).

3-Bromomercuriomethyl-3-methyl-1,2-dioxolane (181)

Crude Yield = 83%

δ_C ($CDCl_3$) 27.60($^3J(^{13}C-^{199}Hg)$ = 148Hz), 45.99($^1J(^{13}C-^{199}Hg)$ = 1582Hz), 48.39($^3J(^{13}C-^{199}Hg)$ = 98Hz), 70.77,

85.49($^{2}J(^{13}C-^{199}Hg)$ = 110Hz).

threo-3-(1-Bromomercuriopropyl)-1,2-dioxolane (180)

Crude Yield = 79%

δ_C ($CDCl_3$) 16.51($^{3}J(^{13}C-^{199}Hg)$ = 113Hz), 26.95($^{2}J(^{13}C-^{199}Hg)$ = 65Hz), 42.02($^{3}J(^{13}C-^{199}Hg)$ = 86Hz), 64.48($^{1}J(^{13}C-^{199}Hg)$ = 1635Hz), 69.84, 83.37($^{2}J(^{13}C-^{199}Hg)$ = 140Hz).

4.10 3-Iodomethyl-3-methyl-1,2-dioxolane (244)

An excess of iodine (2.051g, 8.08mmol) was placed in a Soxhlet extractor and thereby gradually added to a refluxing solution of 3-bromomercuriomethyl-3-methyl-1,2-dioxolane (181) (0.772g, 2.02mmol) in dichloromethane (50cm^3). After 2hr. the reaction was removed from the heat and allowed to cool. The reaction mixture was washed with saturated sodium hydrogen carbonate solution (40cm^3) and saturated sodium thiosulphate solution (40cm^3). The dichloromethane layer was separated, dried over magnesium sulphate and the solvent removed at reduced pressure to give crude 3-iodomethyl-3-methyl-1,2-dioxolane (244) (0.44g, 96%).

δ_C ($CDCl_3$) 13.90, 23.40, 44.97, 70.87, 83.31.

4.11 threo-3-(1-Bromopropyl)-1,2-dioxolane (185a)

To a stirred solution of threo-3-(1-bromodioxolane (180) (0.668g, 1.69mmol) in pyridine ($48cm^3$) was added dropwise a solution of bromine (0.405g, 2.53mmol) in pyridine ($10cm^3$) over 5 min. After 21 hr., ether ($250cm^3$) was added and the mixture extracted with 10% hydrochloric acid (2 x $250cm^3$). The acid washings were extracted with ether ($150cm^3$) and the combined ether extracts washed with 10% hydrochloric acid ($150cm^3$) followed by saturated sodium hydrogen carbonate solution ($100cm^3$). The ether layer was dried over magnesium sulphate and the solvent removed at reduced pressure to give crude threo-3-(1-bromopropyl)-1,2-dioxolane (185a)

δ_C ($CDCl_3$) 12.32, 27.05, 38.11, 57.79, 70.27, 81.83.

4.12 erythro-and threo-3-(1-Iodopropyl)-1,2-dioxolane (249a,b)

To a stirred solution of the 3-hexen-1-hydroperoxide (177a or b) (0.250g, 2.15mmol) and pyridine (0.170g, 2.15mmol) was added a solution of iodine (0.601g, 2.37mmol) in dichloromethane ($25cm^3$). After 2½ hr., the reaction mixture was washed with 10% sodium thiosulphate solution ($30cm^3$). The aqueous washings were extracted with dichloromethane ($10cm^3$). The combined dichloromethane layer was washed with water (2 x $10cm^3$) and the washings were extracted with dichloromethane

($10cm^3$). The combined dichloromethane layer was dried over sodium sulphate and the solvent was removed at reduced pressure to give the crude 3-(1-iodopropyl)-1,2-dioxolanes (**249a** or **b**). Column chromatography on silica gel, eluting with 3:1 dichloromethane/60-80°C petroleum spirit gave the pure iododioxolanes.

erythro-3-(1-Iodopropyl)-1,2-dioxolane (249b)

Yield = 35% (69% crude)

δ_H ($CDCl_3$) 1.05(t,3H, ^3J = 7Hz), 1.8(m,2H), 2.6(m,1H), 2.9(m,1H), 4.1(m,3H), 4.4(m,1H).

δ_C ($CDCl_3$) 13.78, 29.80, 41.65, 42.41, 70.14, 82.96.

ν_{max} 2959, 2925, 2865, 1451, 1431, 1378, 1334, 1281, 1201, 1151, 1124, 1094, 994, 924, 900, 794 cm^{-1}.

Found: C, 29.15; H, 4.55. $C_6H_{11}IO_2$ requires C, 29.77; H, 4.58%.

threo-3-(1-Iodopropyl)-1,2-dioxolane (249a)

Yield = 37% (81% crude)

δ_H ($CDCl_3$) 1.08(t,3H, J = 7Hz), 1.8(m,2H), 2.6(m,1H), 4.2(m,3H), 4.4(m,1H).

δ_C ($CDCl_3$) 14.46, 28.15, 38.97, 39.25, 70.53, 82.70.

ν_{max} 2965, 2925, 2872, 1455, 1381, 1338, 1278, 1201, 1164, 1124, 994, 794cm^{-1}.

Found: C, 29.48; H, 4.53. $C_6H_{11}IO_2$ requires C, 29.77, H, 4.58%.

4.13 erythro and threo-3-(1-Bromopropyl)-1,2-dioxolane (185a,b) and erythro and threo-3,4-dibromohexan -1-hydroperoxide (253a,b)

To a stirred solution of 3-hexen-1-hydroperoxide (177a or b) (0.250g, 2.15mmol) and pyridine (0.170g, 2.15mmol) in dichloromethane (10cm^3) was added dropwise a 1M solution of bromine in carbon tetrachloride (2.37cm^3, 2.37mmol). After 1 hour, the reaction mixture was washed with 10% sodium thiosulphate solution (10cm^3). The aqueous phase was extracted with dichloromethane (5cm^3) and the combined dichloromethane washings were washed with water (2 x 5 cm^3). The aqueous washings were extracted with dichloromethane (10cm^3) and the combined dichloromethane layers were dried over sodium sulphate. The solvent was removed at reduced pressure to give the crude product. Column chromatography, eluting on silica gel with 3:1 dichloromethane/60-80°C petroleum spirit gave two products. The first eluted product was identified as the 3-(1-bromopropyl)-1,2-dioxolane (185a or b) and the second as the 3,4-dibromohexan-1-hydroperoxide (253a or b).

erythro-3-(1-Bromopropyl)-1,2-dioxolane (185b)

Yield = 15% (44% of recovered product).

δ_H ($CDCl_3$) 1.07(t,3H, J = 7Hz), 1.76(m,1H), 2.11(m,1H), 2.67(m,1H), 2.81(m,1H), 3.86(m,1H), 4.04(m,1H), 4.18(m,1H), 4.37(m,1H).

δ_C ($CDCl_3$) 11.57, 28.65, 40.70, 59.25, 70.01, 82.13.

ν_{max} 2965, 2932, 2878, 1458, 1378, 1284, 1208, 1171, 1134, 1057, 997, 907, 804, 610cm^{-1}.

Found: C, 36.54; H, 5.64. Calc. for $C_6H_{11}BrO_2$: C, 36.95, H, 5.68%.

erythro-3,4-Dibromohexan-1-hydroperoxide (253b)

Yield = 19% (56% of recovered product).

δ_H ($CDCl_3$) 1.10(t,3H, J = 7Hz), 2.0-2.2(m,3H), 2.67(m,1H), 4.26(m,4H), 8.27(br s,1H).

δ_C ($CDCl_3$) 11.37, 30.30, 34.89, 54.80, 61.77, 74.32.

ν_{max} 3413(br), 2965, 2932, 2878, 2845, 1618, 1431, 1381, 1291, 1151, 1084, 1031, 800cm^{-1}.

m/z 261,259,257($M-OH^+$, 0.10%, 0.51%, 0.09%); 245, 243, 241($M-OOH^+$, 0.58%, 1.58%, 0.46%), 179(5.66), 177(5.17), 163(5.32), 161(5.81), 97(54.67), 81(53.54), 69(100.00), 55(20.66), 41(43.93).

Found: C, 25.85; H, 4.37. $C_6H_{12}Br_2O_2$ requires C, 26.11; H, 4.38%.

threo-3-(1-Bromopropyl)-1,2-dioxolane (185a)

Yield = 17% (36% of recovered product).

δ_H ($CDCl_3$) (t,3H, J = 7.2Hz), 1.77(m,1H), 1.98(m,1H), 2.57(m,1H), 2.73(m,1H), 4.00(m,1H), 4.16(m,2H), 4.51(dt,1H, J = 5.4, 8.3Hz).

δ_C ($CDCl_3$) 12.32, 27.06, 38.13, 57.80, 70.27, 81.83.

ν_{max} 2965, 2932, 2872, 1455, 1378, 1341, 1281, 1208, 1181, 1137, 994, 934, 900, 800, 607cm^{-1}.

Found: C, 36.74; H, 5.68. Calc. for $C_6H_{11}BrO_2$: C, 36.95; H, 5.68%.

threo-3,4-Dibromohexan-1-hydroperoxide (253a)

Yield = 31% (64% of recovered product).

δ_H ($CDCl_3$) 1.10(t,3H, J = 7.2Hz), 1.89(m,1H), 2.19(m,2H), 2.53(m,1H), 4.20(m,3H), 4.44(dt,1H, J = 2.9, 10.5Hz), 8.20(br s,1H).

δ_C ($CDCl_3$) 12.62, 28.79, 33.80, 54.91, 61.54, 74.20.

ν_{max} 3405(br), 2965, 2931, 2878, 2845, 1618, 1454, 1428, 1381, 1311, 1244, 1168, 1094, 1021, 903, 800cm^{-1}.

Found: C, 26.42; H, 4.39. $C_6H_{12}Br_2O_2$ requires C, 26.11; H, 4.38%.

4.14 Reaction of cis-and trans-3-hexen-1-hydroperoxide (177a,b) with 0.5 equivalents of N-bromosuccinimide (NBS)

To a stirred solution of N-bromosuccinimide (0.191g, 1.08mmol) in dichloromethane (20cm^3) was added a solution of the 3-hexen-1-hydroperoxide (**177a** or **b**) (0.250g, 2.15mmol) in dichloromethane (5cm^3). After 10 minutes, all NBS was seen to be consumed by TLC. The solvent was removed at reduced pressure, $CDCl_3$ (≈3cm^3) and TMS (≈3 drops) were added to make up a sample for ^{13}C-nmr spectroscopy.

Using cis-3-hexen-1-hydroperoxide (177a)

δ_C ($CDCl_3$) threo-3-(1-Bromopropyl)-1,2-dioxolane (**185a**) (Major Product): 12.28, 27.14, 38.17, 57.88, 70.28, 81.88. erythro-3-(1-Bromopropyl)-1,2-dioxolane (**185b**) (Minor product): 11.57, 28.61, 40.62, 59.21, 70.03, 82.10. trans-3-Hexen-1-hydroperoxide (**177b**): 13.70, 25.60, 31.07, 76.59, 124.37, 134.76.

Using trans-3-hexen-1-hydroperoxide (177b)

δ_C ($CDCl_3$) erythro-3-(1-Bromopropyl)-1,2-dioxolane (185b) (Main product): 11.57, 28.61, 40.63, 59.21, 70.02, 82.11. threo-3-(1-Bromopropyl)-1,2-dioxolane (**185a**) (Minor product): 27.13, 57.88, 70.27, 81.87.

4.15 Reaction of cis-3-hexen-1-hydroperoxide (177a) with 0.1 equivalents of N-iodosuccinimide (NIS)

To a stirred solution of N-iodosuccinimide (0.049g, 0.22mmol) in dichloromethane ($30cm^3$) was added a solution of cis-3-hexen-1-hydroperoxide (177a) (0.250g, 2.15mmol) in dichloromethane ($5cm^3$). After 10 minutes, all the NIS was seen to have been consumed by TLC. The solvent was removed at reduced pressure, $CDCl_3$ ($\approx 3cm^3$) and TMS (≈ 3 drops) were added to make up a sample for ^{13}C-nmr spectroscopy.

4.16 Attempted isomerisation of erythro-3-(1-bromopropyl)-1,2-dioxolane (185b) under simulated bromocyclisation conditions

To a stirred solution of erythro-3-(1-bromopropyl)-1,2-dioxolane (185b) (0.062g, 0.32mmol) in dichloromethane ($3cm^3$) in the dark, was added N-bromosuccinimide (0.028g, 0.16mmol). The mixture was monitored by TLC (Silica gel, 3:1 dichloromethane/60-80°C petroleum spirit). When, after 1 hr., no isomerisation had been observed, succinimide (0.016g, 0.16mmol) was added and after 40 minutes, no isomerisation had taken place.

4.17 Attempted isomerisation of threo-3-(1-iodopropyl)-1,2-dioxolane (249a) under simulated iodocyclisation conditions

To a stirred solution of threo-3-(1-iodopropyl)-1,2-dioxolane (**249a**) (0.050g, 0.21mmol) in dichloromethane ($6cm^3$) was added N-iodosuccinimide (0.025g, 0.11mmol). The mixture was monitored by TLC (Silica gel, 3:1 dichloromethane/60-80°C petroleum spirit). When, after 20 minutes, no isomerisation had been observed, succinimide (0.011g, 0.11mmol) was added and after 1hr. no isomerisation had taken place.

4.18 Reaction of cis-3-hexen-1-hydroperoxide (177a) with N-bromosuccinimide in the presence of a free radical trap (Galvinoxyl)

To a stirred solution of N-bromosuccinimide (0.077g, 0.43mmol) in dichloromethane ($4cm^3$) in the dark, were added in quick succession Galvinoxyl (0.009g, 0.036g; 5mol%; 20mol%) and a solution of cis-3-hexen-1-hydroperoxide (**177a**) (0.050g, 0.43mol) in dichloromethane ($2cm^3$). The reaction was monitored by TLC (Silica gel, 3:1 dichloromethane/60-80°C petroleum spirit).

For the reaction with 100mol% of Galvinoxyl (0.036g, 100mol%), all the amounts given above were reduced by a factor of 5.

4.19 Reaction of 3-methyl-3-buten-1-hydroperoxide (178) with N-chlorosuccinimide

To a stirred solution of N-chlorosuccinimide (0.361g, 2.70mmol) in dichloromethane (10cm^3) was added 3-methyl-3-buten-1-hydroperoxide (**178**) (0.250g, 2.45mmol) in dichloromethane (5cm^3). The mixture was stirred in the dark for 4-8hr. The solvent was removed at reduced pressure to give a mixture of clear liquid and white solid.

δ_C ($CDCl_3$). 3-Hydroperoxymethyl-3-methyl-1,2-dioxolane (**194**): 20.91, 43.11, 70.65, 80.53, 84.50.

4.20 Reduction of 3-hydroperoxymethyl-3-methyl-1,2-dioxolane (194) with triphenylphosphine

To a solution of crude 3-hydroperoxymethyl-3-methyl-1,2-dioxolane (**194**) from the above reaction in benzene (50cm^3) at 0°C was added triphenylphosphine (0.643g, 2.45mmol). After 30min., the solvent was removed at reduced pressure giving a yellow oil. Addition of cold diethyl ether to this oil caused the precipitation of a light yellow solid, which was filtered off and washed with cold ether. The solvent was removed from the filtrate to give 3-hydroxymethyl-3-methyl-1,2-dioxolane (**195**).

δ_C ($CDCl_3$) 20.65, 42.50, 66.64, 70.72, 84.97.

4.21 3-Hydroxymethyl-3-methyl-1,2-dioxolane (195)

To a stirred solution of 3-methyl-3-buten-1-hydroperoxide (**178**) (0.250g, 2.45mmol) in dichloromethane ($5cm^3$) was added, over 10 min., m-chloroperoxybenzoic acid (0.444g, 2.57mmol). After 3 hr. at room temperature, trichloroacetic acid (11mg) was added. After a further 3 hr., the reaction mixture was washed with saturated sodium hydrogen carbonate (2 x $5cm^3$) and water ($5cm^3$) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give crude 3-hydroxymethyl-3-methyl-1,2-dioxolane (**195**) (0.18g, 62%).

δ_H ($CDCl_3$, 60MHz) 1.3(s,3H), 1.8-2.7(m,3H), 3.6(s,2H), 4.1(t,2H, J = 7Hz).

δ_C ($CDCl_3$). 20.50, 42.47, 66.92, 70.85, 84.97.

5 Experimental details relating to chapter 5

5.1 2-Ethenyl-4-penten-1-ol (122)

All apparatus was dried in an oven for at least 1 hour prior to use.

To magnesium turnings (21.88g, 900mmol) in dry diethyl ether (250 cm^3) was added a little of a solution of allyl bromide (102.83g, 850mmol). Shortly reaction started and the remaining allyl bromide solution was added at such a rate as to maintain steady reflux. After complete addition, The mixture was left until reflux had ceased and was cooled in an ice/salt bath. A solution of buatadiene monoxide (20.45g, 292mmol) in dry diethyl ether (50cm^3) was added dropwise. After ½ hr. at ice bath temperatures, saturated ammonium chloride solution- (70cm^3) was carefully added and the reaction mixture left overnight.

The solids were filtered off and washed with dry diethyl ether. The solvent was removed at reduced pressure to give crude product (32.50g, 99%). Distillation gave 2-ethenyl-4-penten-1- ol (122) (25.08g, 76%) bp. 70-75°C/16mmHg.

5.2 2-Ethenyl-4-penten-1-methanesulphonate (123)

Prepared from 2-ethenyl-4-penten-1-ol (122) (24.89g, 221.9mmol) using the method of Williams and Mosher.[48]

Yield = 36.09g, 85%

δ_H ($CDCl_3$) 2.23(m,2H), 2.56(m,1H), 3.01(s,3H), 4.16(d,2H, J = 6.4Hz), 5.19(m,2H), 5.68(m,1H).

δ_C ($CDCl_3$) 34.99, 37.18, 42.50, 71.73, 117.34, 117.46, 134.89, 136.96.

ν_{max} 3079, 2979, 2939, 2912, 2845, 1641, 1465, 1441, 1418, 1354, 1174, 974, 957, 924, 844, 814, 747cm^{-1}.

m/z 149($[M-CH_2=CH-CH_2]^+$,0.61%), 121(1.88), 109(3.39), 94(21.35), 81(27.05), 79(100.00), 66(16.95), 54(42.54), 41(59.79).

Found: C, 50.61; H, 7.39. $C_8H_{14}O_3S$ requires C, 50.50; H, 7.42%.

5.3 2-Ethenyl-4-penten-1-hydroperoxide (124)

To a vigorously stirred, ice cold mixture of 2-ethenyl-4-penten-1-methanesulphonate (123) (13.50g, 71mmol), 30% hydrogen peroxide (32.19g, 284mmol) and methanol (50cm^3) was added ice cold 50% potassium hydroxide solution (8.98g, 80mmol). The reaction mixture was allowed to come to room temperature. After 48hr., the mixture was cooled in an ice/salt bath and 50% potassium hydroxide solution (26.63g) was added. The alkaline solution was extracted with benzene (70cm^3), cooled, neutralised with cold 2M hydrochloric acid and extracted with benzene (4 x 30cm^3). The benzene extracts were extracted with cold 25% potassium hydroxide solution

(34.00g). The base extract was cooled, neutralised with cold 2M hydrochloric acid, and extracted with diethyl ether (4 x 20cm^3). The ether extracts were dried over sodium sulphate and the solvent removed at reduced pressure to give 2-ethenyl-4-penten-1-hydroperoxide (**124**) (1.34g, 15%).

δ_H ($CDCl_3$) 2.18(m,2H), 2.62(m,1H), 3.96(dd,1H, ^3J = 7.0Hz), ^2J = 10.8Hz), 4.01(dd,1H, ^3J = 6.4Hz, ^2J = 10.8Hz), 5.11(m,4H), 5.75(m,2H), 8.11(s,1H).

δ_C ($CDCl_3$) 36.61, 41.86, 79.47, 116.36, 116.59, 135.82, 138.81.

ν_{max} 3413 br, 3979, 2979, 2919, 2872, 2838, 1638, 1475, 1438, 1417, 1364, 991, 917, 810, 736cm^{-1}.

5.4 Reaction of 2-ethenyl-4-penten-1-hydroperoxide (124) with mercury(II) nitrate

To a rapidly stirred suspension of mercury(II) nitrate hemihydrate (1.37g, 4.10mmol) in dichloromethane (70cm^3) was added over 10 minutes, a solution of 2-ethenyl-4-penten-1-hydroperoxide (**124**) (0.50g, 3.90mmol). After 30 minutes, the dichloromethane solution was decanted from the unused mercury salt and potassium bromide (0.51g, 4.29mmol) in water (10cm^3) was added. The mixture was stirred until the white solid had dissolved from the aqueous layer into the dichloromethane layer.

The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (2 x 10cm^3). The combined dichloromethane layer was dried over magnesium sulphate and the solvent removed at reduced pressure to give crude product (1.46g, 92.4%). This was combined with the crude product (1.59g, 100%) of an identical reaction and freed from mercury(II) bromide by column chromatography, eluting on silica gel with dichloromethane.

Separation of 2.34g of mixture by preparative HPLC gave 3-bromomercuriomethyl-5-ethenyl-1,2-dioxane (126) (0.0998g, 32%) and 3-bromomercuriomethyl-4-(2-propenyl)-1,2-dioxolane (125) (0.912g, 29%).

<u>cis & trans-3-Bromomercuriomethyl-5-ethenyl-1,2-dioxane (126)</u>

δ_H ($CDCl_3$, 400MHz) 1.32,1.74,2.02(m,2H); 1.97(dd,1H, ^3J = 6.2Hz, ^2J = 11.9Hz); 2.23(dd,1H, ^3J = 5.7Hz, ^2J = 11.9Hz); 2.66(m,1H); 3.93,4.07,4.36(m,2H); 4.61,4.76(m,1H); 5.14(m,2H); 5.63,6.00(ddd + m,1H, J = 7.4Hz, 11.0Hz, 17.6Hz).

δ_C ($CDCl_3$) Major isomer: 37.54($^1J(^{13}C-^{199}Hg)$ = 1513Hz), 38.84, 39.02, 75.65, 79.61($^2J(^{13}C-^{199}Hg)$ = 102Hz), 116.39, 136.75.

ν_{max} 3072, 2965, 2905, 2838, 1638, 1435, 1418, 1354, 1304, 1244, 1168, 1101, 991, 957, 920cm^{-1}.

Found: C, 20.01; H, 2.47. $C_7H_{11}BrHgO_2$ requires C, 20.62; H, 2.72%.

trans-3-Bromomercuriomethyl-4-(2-propenyl)-1,2-dioxolane (125)

δ_H ($CDCl_3$) 2.16(dd,1H, ^3J = 5.1Hz, ^2J = 11.9Hz), 2.26(dd,1H, ^3J = 5.9Hz, ^2J = 11.9Hz), 2.35(m,2H), 2.55(m,1H), 3.80(dd,1H, J = 6.1Hz, 8.0Hz), 4.40(m,2H), 5.15(m,2H), 5.78(m,1H).

δ_C ($CDCl_3$) 36.20, 37.82($^1J(^{13}C-^{199}Hg)$ = 1533Hz), 56.73($^3J(^{13}C-^{199}Hg)$ = 101Hz), 73.59, 84.50($^2J(^{13}C-^{199}Hg)$ = 103Hz), 117.84, 135.31.

ν_{max} 3065, 2972, 2925, 2865, 1638, 1438, 1415, 1381, 1301, 1228, 994, 920, 780, 737, 680, 660.
Found: C, 20.19; H, 2.51. $C_7H_{11}BrHgO_2$ requires C, 20.62; H, 2.72%.

5.5 Reaction of 2-ethenyl-4-penten-1-hydroperoxide (124) with mercury(II) acetate under sonication

A mixture of 2-ethenyl-4-penten-1-hydroperoxide (124) (0.250g, 1.95mmol) and mercury(II) acetate (0.622g, 1.95mmol) in dichloromethane (10cm^3) was immersed in an ultrasound bath. Most of the mercury(II) acetate was consumed in 10 mins., and all had been used after 1 hr. 10 mins. Water (10cm^3) and potassium bromide (0.256g,

2.15mmol) were added and the mixture stirred until the white precipitate had dissolved into the dichloromethane. The dichloromethane layer was separated and the aqueous layer washed with dichloromethane ($10cm^3$). The combined dichloromethane layer was dried over sodium sulphate and the solvent removed at reduced pressure to give a clear oil (0.762g, 96%).

δ_H ($CDCl_3$, 400MHz) dioxane: 5.65(ddd, 0.03H, J = 6.9, 10.4, 17.3Hz), 6.01(ddd, 0.094, J = 7.2, 10.3, 17.5Hz). Dioxolane: 5.76(m, 0.88H).

δ_C ($CDCl_3$, 400MHz) cis-dioxolane: 32.07, 32.34, 50.57, 75.04, 81.03, 117.27, 135.79. trans-dioxolane: 36.18, 37.87, 56.67, 75.60, 84.54, 117.85, 135.35. cis-dioxane: 37.50, 38.83, 39.04, 75.71, 79.68, 117.27, 136.75.

5.6 Reaction of 2-ethenyl-4-penten-1-hydroperoxide (124) with N-bromosuccinimide (NBS)

To a stirred solution of NBS (0.347g, 1.95mmol) in dichloromethane ($20cm^3$) in the dark, was added a solution of 2-ethenyl-4-penten-1-hydroperoxide (124) (0.250g, 1.95mmol) in dichloromethane ($5cm^3$). After 15 hr., the solvent was removed at reduced pressure to give crude product mixture. Elution on silica with dichloromethane removed succinimidyl residues to give 0.219 of clear colourless liquid. This was subjected to semi-preparative HPLC eluting with 1:1 dichloromethane/petroleum spirit,

four main fractions (1 -->4) being collected. Fractions 1 and 2 both gave a positive result when treated with acidic ferrous thiocyanate, whereas fractions 3 and 4 gave negative results.

Fractions 1 and 2: cis and trans-3-bromomethyl-4-(2-propenyl)-1,2-dioxolane (279)

Fraction 1

Yield = 0.0383g, 53% of recovered products.

δ_H ($CDCl_3$) 2.41(m,2H), 2.94(m,1H), 3.37(dd,1H, ^3J = 7.1Hz, ^2J = 10.4Hz), 3.50(dd,1H, ^3J = 5.9Hz, ^2J = 10.4Hz), 3.80(dd,1H, J = 6.3Hz, J = 8.1Hz), 4.18(m,1H), 4.31(t,1H, J = 7.5Hz), 5.07(m,2H), 5.72(m,1H).

δ_C ($CDCl_3$, 100MHz) 32.41, 36.75, 53.11, 75.17, 84.12, 117.58, 134.87.

Fraction 2

Yield = 0.0122g, 17% of recovered products.

δ_H ($CDCl_3$) 2.22(m,1H), 2.41(m,1H), 3.14(m,1H), 3.42(dd,1H, ^3J = 5.9Hz, ^2J = 10.7Hz), 3.48(dd,1H, ^3J = 7.4Hz, ^2J = 10.7Hz), 3.89(dd,1H, J = 7.3Hz), J = 5.6Hz), 4.28(t,1H, J = 7.4Hz), 4.55(m,1H), 5.08(m,2H), 5.71(m,1H).

δ_C ($CDCl_3$, 100MHz) 28.36, 31.56, 50.45, 74.35, 81.84, 117.35, 135.26.

Fractions 3 and 4: cis and trans-2-bromomethyl-4-ethenyl-tetrahydrofuran (280)

Fraction 3

Yield = 0.0076g, 11% of recovered products.

$\delta_H(CDCl_3)$ 2.00(m,2H), 2.96(m,1H), 3.38(dd,1H, ^3J = 6.1Hz, ^2J = 10.3Hz), 3.42(dd,1H, ^3J = 5.3Hz, ^2J = 10.3Hz), 3.55(t,1H, J = 8.1Hz), 4.08(dd,1H, J = 6.9Hz, J = 8.5Hz), 4.28(m,1H), 5.05(m,2H), 5.76(ddd,1H, J = 7.6Hz), J_{cis} = 10.0Hz, J = 17.4Hz).

δ_C ($CDCl_3$, 100MHz) 35.70, 36.62, 43.07, 73.45, 78.07, 115.68, 137.94.

Fraction 4

Yield = 0.0128g, 19% of recovered products.

δ_H ($CDCl_3$) 1.61(m,1H), 2.30(m,1H), 3.00(m,1H), 3.43(dd,1H, ^3J = 5.9Hz), ^2J = 10.2Hz), 3.47(dd,1H, ^3J = 5.4Hz, ^2J = 10.2Hz), 3.61(t,1H, J = 8.6Hz), 4.00(t,1H, J = 8.0Hz), 4.23(m,1H), 5.05(m,2H), 5.75(ddd,1H, J = 7.6Hz, J = 9.9Hz, J = 17.3Hz).

δ_C ($CDCl_3$, 100MHz) 35.69, 37.85, 44.56, 73.05, 78.80, 115.87, 137.67.

5.7 3-Hydroxymethyl-4-(2-propenyl)-1,2-dioxolane (283)

To a vigorously stirred solution of 2-ethenyl-4-penten-1-hydroperoxide (124) (0.355g, 2.77mmol) in benzene ($240cm^3$) was added a solution of di-t-butyl peroxalate (0.253g, 1.08mmol, 39mol%) in benzene ($10cm^3$). After 40 hr., triphenylphosphine (0.727g, 2.77mmol) was added. The benzene was removed at reduced pressure to give a mixture of yellow oil and solid. The addition of ice cold diethyl ether precipitated more solid which was filtered off. The solvent was removed from the filtrate to give crude product (0.771g). Chromatography on silica gel eluting with petroleum spirit (60-80°C) ($50cm^3$) followed by 1:3 ethyl acetate/petroleum spirit (60-80°C) ($100cm^3$) and finally 1:1 ethyl acetate/petroleum spirit (60-80°C) gave one main peroxidic fraction. The solvent was removed at reduced pressure to give 3-hydroxymethyl-4-(2-propenyl)-1,2-dioxolane (283) (0.040g, 10%).

δ_H ($CDCl_3$) 2.35(m,3H), 2.82(m,1H), 3.51(d,2H, J = 4.8Hz), 3.76(dd,1H, J = 6.5Hz, J = 7.9Hz), 4.06(q,1H, J = 4.6Hz), 4.27(t,1H, J = 7.7Hz), 5.07(m,2H), 5.17(m,1H).

δ_C ($CDCl_3$) 36.25, 49.60, 62.96, 75.25, 85.90, 117.38, 135.14.

ν_{max} 3419 br, 3079, 2972, 2925, 2872, 1722, 1641, 1441, 917, 784, $684cm^{-1}$.

5.8 trans-3-Iodomethyl-4-(2-propenyl)-1,2-dioxolane (287)

To a stirred solution of N-iodosuccinimide (0.288g, 1.28mmol) in dichloromethane ($30cm^3$) in the dark, was added a solution of 2-ethenyl-4-penten-1-hydroperoxide (**124**) (0.164g, 1.28mmol) in dichloromethane ($5cm^3$). After 2 hr., the reaction mixture was washed with 10% aqueous sodium thiosulphate ($20cm^3$). The aqueous layer was extracted with dichloromethane ($20cm^3$). The combined dichloromethane layer was dried over magnesium sulphate and the solvent removed at reduced pressure to give crude product (0.35g). Chromatography on silica gel eluting with 1:1 diethyl ether/petroleum spirit gave 3-iodomethyl-4-(2-propenyl)-1,2-dioxolane (**287**) (0.176g, 54%) and a product taken to be 3-hydroperoxymethyl-4-(2-propenyl)-1,2-dioxolane (**282**) (0.008g, 4%).

trans-3-Iodomethyl-4-(2-propenyl)-1,2-dioxolane (287)

δ_H ($CDCl_3$) 2.38(m,2H), 2.87(m,1H), 3.21(dd,1H, ^3J = 7.6Hz, ^2J = 10.1Hz), 3.31(dd,1H, ^3J = 5.6Hz, ^2J = 10.1z), 3.82(dd,1H, J = 6.1Hz, J = 8.1Hz), 4.10(m,1H), 4.31(t,1H, J = 7.8Hz), 5.09(m,2H), 5.74(m,1H).

δ_C ($CDCl_3$) 6.14, 36.96, 54.09, 75.29, 84.39, 117.56, 134.85.

ν_{max} 3072, 2972, 2925, 2865, 1638, 1438, 1411, 1228, 1171, 991, 920, 784, 663, $607cm^{-1}$.

m/z 254(M^+, 2.37%), 212(4.82), 170(9.80), 169(9.86), 141(12.63), 127(8.86), 97(10.48), 83(15.88), 81(17.90), 79(13.89), 69(23.20), 67(30.20), 57(19.86) 55(52.71), 53(25.23), 43(61.66), 41(100.00).

Accurate Mass Spectrum. Found m/z 253.9774. $C_7H_{11}IO_2$ requires 253.9803.

Found: C, 33.74; H, 4.52. $C_7H_{11}IO_2$ requires C, 33.09; H, 4.36%.

3-Hydroperoxymethyl-4-(2-propenyl)-1,2-dioxolane (282)

δ_C ($CDCl_3$, 100MHz) 36.29, 50.54, 75.05, 76.92, 83.18, 117.55, 135.09.

5.9 trans-3-Iodomethyl-4-(2-propenyl)-1,2-dioxolane (287)

To a stirred refluxing solution of trans-3-bromomercuriomethyl-4-(2-propenyl)-1,2-dioxolane (125) (0.258g, 0.63mmol) in dichloromethane (80cm^3) was added iodine by way of a Soxhlet extractor. After 2½ hr. reflux, the reaction mixture was allowed to cool, and washed with saturated sodium carbonate solution (40cm^3) and saturated sodium thiosulphate solution (40cm^3). The dichloromethane layer was dried over magnesium sulphate and the solvent removed at reduced pressure to give crude trans-3-iodomethyl-4-(2-propenyl)-1,2-dioxolane (287)

(0.24g).

δ_C ($CDCl_3$) 6.17, 36.94, 54.07, 75.28, 84.37, 117.55, 134.85.

5.10 Attempted reduction of trans-3-iodomethyl-4-(2-propenyl)-1,2-dioxolane (287) in an ammonium chloride solution/zinc system

To a stirred mixture of 3-iodomethyl-4-(2-propenyl)-1,2-dioxolane (287) (0.137g, 0.54mmol) and saturated ammonium chloride solution ($5cm^3$) was added powdered zinc (0.352g, 5.39mmol). After 4½ hr. the mixture was filtered through Celite and the solids washed with water ($2cm^3$). The aqueous layer was extracted with diethyl ether (5 x $5cm^3$) and the combined extracts dried over magnesium sulphate. The solvent was removed at reduced pressure to give 2-ethenyl-4-penten-1-ol (122) (0.073g).

δ_C ($CDCl_3$) 35.38, 46.22, 65.11, 116.38, 117.24, 136.13, 139.19.

5.11 trans-3-Methyl-4-(2-propenyl)-1,2-dioxolane (294)

To a stirred solution of 3-bromomercuriomethyl-4-(2-propenyl)-1,2-dioxolane (125) (0.895g, 2.20mmol) in dichloromethane ($15cm^3$) at -5°C under nitrogen was added, dropwise, a solution of sodium borohydride (0.166g,

4.40mmol) in 3M sodium hydroxide solution (15cm^3), keeping the temperature between -5°C and 0°C. The reaction mixture was left at -5°C for ½ hr. and then allowed to come to room temperature. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (2 x 10cm^3). The combined dichloromethane layer was dried over magnesium sulphate and the solvent removed at reduced pressure and low temperature (<10°C) to give crude product (0.28g). Chromatography on silica gel eluting with 3:1 dichloromethane/ petroleum spirit (60-80°C) gave, on removal of the solvent at reduced pressure/low temperature, 3-methyl-4-(2-propenyl)-1,2-dioxolane (**294**) (0.181g, 64%).

δ_H ($CDCl_3$, 400MHz) 1.27(d, 3H, J = 6.1Hz), 2.26(m, 2H), 2.53(m, 1H), 3.76(dd, 1H, J = 5.3Hz, 7.6Hz), 3.96(m, 1H), 4.21(t, 1H, J = 7.6Hz), 5.05(m, 2H), 5.73(m, 1H).

δ_C ($CDCl_3$, 100MHz) 17.80, 36.10, 54.90, 75.00 81,69, 116.88, 135,52.

Found: C, 64.89; H, 9.11. $C_7H_{12}O_2$ requires C, 65.60; H, 9.44%.

5.12 3-Hydroxymethyl-5-hexen-2-ol (295)

To a vigorously stirred mixture of 3-methyl-4-(2-propenyl)-1,2-dioxolane (**294**) (0.080g, 0.62mmol) and saturated ammonium chloride solution (6cm^3) was added

powdered zinc (0.405g, 6.20mmol). After 2½ hr., the mixture was filtered through Celite and the solids washed with water (2 x 5cm^3). The filtrate was saturated with sodium chloride and extracted with diethyl ether (5 x 10cm^3). The ether extracts were dried over magnesium sulphate and the solvent removed at reduced pressure to give 3-hydroxymethyl-5-hexen-2-ol (295) (0.077g, 95%).

δ_H ($CDCl_3$) 1.28(d,3H, ^3J = 6.3Hz), 1.56(m,1H), 2.12(m,2H), 2.93(br s,2H), 3.64(m,1H), 3.90(m,2H), 5.03(m,2H), 5.76(m,1H).

δ_C ($CDCl_3$) 21.93, 33.22, 45.81, 64.25, 71.45, 116.66, 136.38.

5.13 trans-2,2,4-Trimethyl-5-(2-propenyl)-1,3-dioxane (296)

To a stirred solution of 3-hydroxymethyl-5-hexen-2-ol (295) (0.077g, 0.59mmol) in acetone (5cm^3) were added 2,2-dimethoxypropane (0.068g, 0.65mmol) and p-toluenesulphonic acid (0.005g). After 1 hr., the solvent was removed at reduced pressure to give crude trans-2,2,4-trimethyl-5-(2-propenyl)-1,3-dioxane (296) (0.99g, 99%).

δ_H ($CDCl_3$, 400MHz) 1.21(d,3H, J = 6.1Hz), 1.39(s,3H), 1.44(s,3H), 1.60(m,1H), 1.79(m,1H), 2.11(m,1H), 3.56(t,1H, J = 11.7Hz), 3.71(dq,1H, J = 6.0Hz), J = 10.0Hz), 3.76(dd,1H, ^3J = 5.1Hz, ^2J = 11.8Hz), 5.00(m,2H),

5.66(m,1H).

δ_C ($CDCl_3$) 19.30, 19.78, 29.70, 32.34, 40.47, 64.04, 69.67, 98.00, 116.83, 135.05.

5.14 1,5-Hexadiene-3-hydroperoxide (297) and 2,5-hexadiene-1-hydroperoxide (299)

To a mixture of 1,5-hexadiene-3-ol (10.00g, 102mmol) and methanesulphonyl chloride (11.92g, 102mmol) at -5°C was added pyridine (16.14g, 204mmol) at such a rate as to keep the temperature below 0°C. After the addition of the pyridine, the reaction mixture was maintained at -5°C for 2 hr. and then poured into ice cold 10% hydrochloric acid ($80cm^3$). The resulting mixture was extracted with ether (2 x $50cm^3$). These extracts were washed with water (2 x $40cm^3$), saturated sodium hydrogen carbonate solution ($40cm^3$) and dried over potassium carbonate. The solvent was removed at reduced pressure to give crude 1,5-hexadiene-5-methanesulphonate (298) (10.39g).

To a mixture of the crude methanesulphonate (10.39g) and 30% hydrogen peroxide (15.0g) in methanol ($75cm^3$) at less than 0°C was added 50% potassium hydroxide solution (3.75g) and the mixture was allowed to come to room temperature. After 24 hr., 50% potassium hydroxide (3.75g) was added and the mixture extracted with benzene ($200cm^3$). The aqueous layer was neutralised with 2M hydrochloric acid and extracted with benzene (4 x $30cm^3$).

The combined benzene layer was extracted with 25% potassium hydroxide (20g), these extracts were neutralised with 2M hydrochloric acid and in turn extracted with diethyl ether (3 x 30cm^3). The ether layer was dried over sodium sulphate and the solvent removed at reduced pressure to give a mixture of 1,5-hexadiene-3-hydroperoxide (**297**) and 2,5-hexadiene-1-hydroperoxide (**299**) (0.31g, 3%).

δ_C ($CDCl_3$) 36.43, 36.97, 77.54, 86.12, 115.91, 117.68, 119.19, 124.90, 133.39, 135.46, 135.88, 136.34.

5.15 Reaction of 1,5-hexadiene-3-hydroperoxide (297) and 2,5-hexadiene-1-hydroperoxide (299) with N-iodosuccinimide

To a stirred solution of N-iodosuccinimide (0.547g, 2.43mmol) in dichloromethane (60cm^3) was added a solution of 1,5-hexadiene-3-hydroperoxide (**297**) and 2,5-hexadiene-1-hydroperoxide (**299**) (0.252g, 2.21mmol) in dichloromethane (5cm^3). After 2 hr., the reaction mixture was washed with 10% sodium thiosulphate solution (40cm^3) and water (40cm^3) and dried over magnesium sulphate. The solvent was removed at reduced pressure to give a mixture of two products (0.48g). Chromatography on silica gel eluting with 3:1 dichloromethane/petroleum spirit gave 3-ethenyl-5-iodomethyl-1,2-dioxolane (**300**) (0.133g, 0.55mmol) and trans-2,5-hexadienal (**301**) (0.068g,

0.71mmol). Overall recovery 57%.

cis-3-Ethenyl-5-iodomethyl-1,2-dioxolane (300)

δ_H ($CDCl_3$) 2.23(ddd,1H, J = 4.9Hz, 7.7Hz, 12.6Hz), 3.00(dt,1H, J = 12.6Hz, 7.5Hz), 3.19(dd,1H, ^3J = 8.5Hz, ^2J = 9.8Hz), 3.37(dd,1H, ^3J = 5.4Hz, ^2J = 9.8Hz), 4.70(m, 2H), 5.30(m,2H), 5.81(ddd,H, J = 7.2Hz, 10.1Hz, 17.3Hz).

δ_C ($CDCl_3$) 6.77, 46.71, 81.15, 83.06, 120.62, 133.13.

ν_{max} 3085, 2985, 2899, 1685, 1638, 1475, 1451, 1425, 1341, 1171, 987, 934, 814, 734, 684cm^{-1}.

m/z 240(M^+, 6.77%), 197(15.53), 170(9.22), 141(12.91), 127(17.38), 113(12.34), 95(10.08), 81(12.99), 69(42.46), 57(42.16), 55(100.00), 43(71.73), 41(93.31), 39(44.01).

Accurate Mass Spectrum. Found m/z 239.9653. $C_6H_9IO_2$ requires 239.9649.

trans-2,5-hexadienal (301)

δ_H ($CDCl_3$) 3.10(m,2H), 5.20(m,2H), 5.80(m,1H), 6.15(ddt,1H, J = 7.9Hz, 15.7Hz, 1.6Hz), 6.87(dt,1H, J = 15.7Hz, 6.4Hz), 9.55(d,1H, J = 7.9Hz).

δ_C ($CDCl_3$) 36.56, 117.94, 133.08 133.48, 155.72, 193.85.

ν_{max} 3079, 2979, 2919, 2818, 2738, 1688, 1631, 1425, 1131, 977, 920, 734, 680cm^{-1}.

m/z 95($M-1^+$, 27.51%), 83(17.64), 81(54.08), 79(15.75), 70(39.07), 69(57.40), 67(58.42), 57(20.32), 55(50.51), 53(25.21), 43(42.26), 41(100.00), 39(52.89).

5.16 3-Ethenyl-5-methyl-1,2-dioxolane (302)

To a stirred solution of 3-ethenyl-5-iodomethyl-1,2-dioxolane (**300**) (0.118g, 0.49mmol) in dry pentane (55cm^3), under nitrogen was added di-t-butyl peroxalate (0.006g, 0.02mol, 5mol%) and tri-n-butylin hydride (0.157g, 0.54mmol). After 6 hr. the solvent was removed at reduced pressure at 20°C to give crude product (0.32g) as a yellow liquid. Eluting on silica gel with 3:1 dichloromethane/ petroleum spirit (60-80°C) gave 3-ethenyl-5-methyl-1,2-dioxolane (**302**) (0.56g) contaminated with tin residues.

δ_H ($CDCl_3$) 1.33(d,3H, J = 6.1Hz), 2.00(dt,1H, J = 7.0Hz, 12.0Hz), 2.91(ddd,1H, J = 6.7Hz, 7.6Hz, 12.0Hz), 4.43(m,1H), 4.68(m,1H), 5.30(m,2H), 5.88(m,1H).

REFERENCES

1. A.G.Davies , "Organic Peroxides" , Butterworths , London , 1961.
2. O.L.Mageli and C.S.Sheppard , in "Organic Peroxides" , ed. D.Swern , Wiley , 1970 , p.1 .
3. R.A.Sheldon , in "The Chemistry of Peroxides" , ed. S.Patai , Wiley , 1983 , p.161 .
4. K.Gollnick and H.J.Kuhn , in "Singlet Oxygen" , ed. H.H.Wasserman , Academic Press , 1979 , p.287 .
5. A.A.Frimer , in "The Chemistry of Peroxides" , ed. S.Patai , Wiley , 1983 , p.201 .
6. a) D.H.Ballard and A.J.Bloodworth , J.Chem.Soc.(C) , 1971 , 945-949 .
   b) A.J.Bloodworth and I.M.Griffin , J.Chem.Soc.Perkin I , 1975 , 695 .
   c) A.J.Bloodworth , K.J.Bowyer , and J.C.Mitchell , J.Org.Chem. , 1986 , **51** , 1790 .
7. I. Saito and S.Sarma Nittala , in "Organic Peroxides" , ed. S.Patai , Wiley , 1983 , p.311 .
8. R. Jeyaraman and R.W.Murry , J.Am.Chem.Soc. , 1984 , **106** , 2462 .
9. W.Fenical , J.Am.Chem.Soc. , 1974 , **96** ,5580 .
10. A.P.Schaap and K.A.Zaklika , in "Singlet Oxygen", ed. H.H.Wasserman , Academic Press , 1979
11. N.A.Porter , Acc.Chem.Res. , 1986 , **19** , 262 .

12. M.Hamberg and B.Samuelsson , Proc.Nat.Acad.Sci.USA , 1973 , **70** , 899 .

13. K.C.Nicolaou , G.P.Gasic , and W.E.Barnette , Angew.Chem.Int.Ed.Engl. , 1978 , **17** , 293 .

14. N.A.Nelson , R.C.Kelly , and R.A.Johnson , Chem.Eng.News , Aug.16 , 1982 , 30 .

15. D.E.O'Conner , E.D.Mihelich , and M.C.Coleman , J.Am.Chem.Soc. , 1984 , **106** , 3577 .

16. E.J.Corey , K.Shimoji , and C.Shih , J.Am.Chem.Soc. , 1984 , **106** , 6425 .

17. E.J.Corey , C.Shih , N.-Y.Shih , and K.Shimoji , Tetrahedron Lett. , 1984 ,**25** , 5013 .

18. a) N.A.Porter , J.D.Byers , A.E.Ali , and T.E.Eling , J.Am.Chem.Soc. , 1980 , **102** , 1183 .

    b) N.A.Porter , J.D.Byers , R.C.Mebane , D.W.Gilmore , and J.R.Nixon , J.Org.Chem. ,1978 **43** , 2088 .

    c) N.A.Porter , J.D.Byers , K.M.Holden , and D.B.Menzel , J.Am.Chem.Soc. , 1979 , **101** , 4319.

19. W.Adam and A.J.Bloodworth , Top.Curr.Chem. , 1981 , **97** , 121 .

20. a) M.F.Salomon and R.G.Salomon , J.Am.Chem.Soc. , 1977 , **99** , 3501 .

    b) W.R.Marshall and F.Geiser , J.Am.Chem.Soc. , 1978 , **100** , 2225 .

    c) W.Adam and H.J.Eggelte , J.Org.Chem. , 1977 , **42** , 3987 .

21. D.J.Coughlin ,R.S.Brown , and R.G.Salomon , J.Am.Chem.Soc. , 1979 , **101** , 1533 .

22. K. Takahashi and M. Kishi , Tetrahedron , 1988 , **44** , 4737 .

23. a) A.J.Bloodworth and H.J.Eggelte , J.Chem.Soc.Perkin I , 1981 , 1375 .
b) A.J.Bloodworth and H.J.Eggelte , J.Chem.Soc.Chem.Commun. , 1982 , 865 .

24. a) M.D.Higgs and D.J.Faulkner , J.Org.Chem. , 1978 , **43** , 3454 .
b) D.W.Phillipson and K.L.Rinehart,Jr. , J.Am.Chem.Soc. , 1983 , **105** , 7735 .
c) R.J.Wells , Tetrahedron Lett. , 1976 , 2637 .
d) S.Sakemi , T.Higa , U.Anthoni , and C.Christophersen , Tetrahedron , 1987 , 43 , 263 .

25. Y.Fukazawa , S.Usui , and Y.Uchio , Tetrahedron Lett. , 1986 , 27 , 1825 .

26. D.L.Klayman , Science , 1985 , **228** , 1049 .

27. N.A.Porter and J.C.Mitchell , Tetrahedron Lett. , 1983 , **24** , 543 .

28. A.J.Bloodworth and D.S.Baker , J.Chem.Soc.Chem.Commun. , 1981 , 547 .

29. W.Adam and J.Sanabia , J.Am.Chem.Soc. , 1977 , **99** , 2735 .

30. R.Criegee and G.Pauling , Chem.Ber. , 1955 , **88** , 712 .

31. R.Criegee and G.Muller , Chem.Ber. , 1956 , **89** , 238 .

32. M.F.Salomon and R.G.Salomon , J.Am.Chem.Soc. , 1979 , **101** , 4290 .

33. Chiu Hong Lin , D.L.Alexander , and C.G.Chidster , J.Am.Chem.Soc. , 1982 , **104** , 1621 .

34. a) A.J.Bloodworth and M.E.Loveitt , J.Chem.Soc. Perkin Trans. I , 1978 , 522 .

b) A.J.Bloodworth and J.A.Khan , J.Chem.Soc.Perkin Trans. I , 1980 , 2450 .

35. J.R.Nixon , M.A.Cudd , and N.A.Porter , J.Org.Chem. , 1978 , **43** , 4048 .

36. N.A.Porter and P.J.Zuraw , J.Org.Chem. , 1984 , **49** , 1345 .

37. N.A.Porter , M.O.Funk , D.Gilmore , R.Isaac , and J.R.Nixon , J.Am.Chem.Soc. , 1976 , **98** , 6000 .

38. J.E.Baldwin , J.Chem.Soc.Chem.Commun. , 1976 , 734.

39. A.N.Roe , A.T.McPhail , and N.A.Porter , J.Am.Chem.Soc. , 1983 , **105** , 1199 .

40. H.Kropf and H.von Wallis , Synthesis , 1981 , 633 .

41. H.Kropf , H.von Wallis , and Lily Bartnick , Liebigs Ann.Chem. , 1983 , 624 .

42. K.Mizuno , K.Murakami , N.Kamiyamy , and Y.Otsuji , J.Chem.Soc.Chem.Commun. , 1983 , 462 .

43. J.Rigaudy , P.Capdevielle , S.Combrisson , and M.Maumy , Tetrahedron Lett. , 1974 , 2757 .

44. R.K.Haynes , M.K.S.Probert , and I.D.Wilmot , Aust.J.Chem. , 1978 , 31 , 1737 .

45. a) K.Gollnick and A.Schnatterer , Tetrahedron Lett. , 1984 , 25 , 185 .

b) K.Gollnick and A.Schnatterer , Tetrahedron Lett. , 1984 , 25 , 2735 .

46. A.J.Bloodworth , A.G.Davies , and R.S.Hay-Motherwell , J.Chem.Soc.Perkin Trans II , 1988 , 575 .

47. a) N.A.Porter , M.A.Cudd , R.W.Miller, and A.T.McPhail , J.Am.Chem.Soc. , 1980 , 102 , 414 .

b) A.J.Bloodworth , J.L.Courtneidge , and A.G.Davies , J.Chem.Soc.Perkin Trans. II , 1984 , 523 .

48. H.R.Williams and H.S.Mosher , J.Am.Chem.Soc. , 1954 , 76 , 2984 .

49. L.Caglioti , F.Gasparrini , D.Misiti , and G.Palmieri , Tetrahedron , 1978 , 34 , 135 .

50. L.Attansi , L.Caglioti , F.Gasarrini , and D.Misiti , Tetrahedron , 1975 , 31 , 341 .

51. G.Piancattelli , A.Scetri , M.D'Auria , Synthesis , 1982 , 245 .

52. J.L.Courtneidge , Ph.D. Thesis , University of London , 198 .

53. G.Rosini , A.Medici , and S.Massimo , Synthesis , 1979 , 789 .

54. G.Rio and J.Berthelot , Bull.Soc.Chim.Fr. , 1969 , 1664 .

55. C.J.Fearn and A.J.Bloodworth , Unpublished work .

56. R.J.Strunk , P.M.DiGiacomo , K.Aso , and H.G.Kuivila , J.Am.Chem.Soc. , 1970 , **92** , 2849 .

57. W.Adam , Acc.Chem.Res. , 1979 , **12** , 390 .

58. W.Adam and A.Griesbeck , Angew.Chem.Int.Ed.Engl. , 1985 , 1070 .

59. A.J.Bloodworth , D.S.Baker , and H.J.Eggelte , J.Chem.Soc.Chem.Commun. , 1982 , 1034 .

60. A.J.Bloodworth and H.J.Eggelte , Tetrahedron Lett. , 1984 , **25** , 1525 .

61. R.M.Wilson and J.W.Rekers , J.Am.Chem.Soc. , 1981 , **103** , 206 .

62. D.J.Coughlin and R.G.Salomon , J.Am.Chem.Soc. , 1977 , **99** , 655 .

63. V.Ullrich and M.Havrand , J.Biol.Chem. , 1985 , **260** , 15059 .

64. a) W.Herz , R.C.Ligon , J.A.Turner , and J.F.Blount , J.Org.Chem. , 1977 , **42** , 1885 .

b) W.Herz and J.A.Turner , J.Org.Chem. , 1977 , **42** , 1895 .

c) W.Herz and J.A.Turner , J.Org.Chem. , 1977 , **42** , 1900 .

65. M.Suzuki , R.Noyori , and N.Hamanaka , J.Am.Chem.Soc. , 1981 , **103** , 5606 .

66. N.Balchi and N.Akubulut , Tetrahedron , 1985 , **41** , 1315 .

67. M.Suzuki , R.Noyori , and N.Hamanaka , J.Am.Chem.Soc. , 1982 , **104** , 2024 .

68. K.Takahashi and M.Kishi , Tetrahedron Lett. , 1988 , **29** , 4595 .

69. W.Adam and N.Duran , J.Am.Chem.Soc , 1977 , **99** , 2729 .

70. W.H.Richardson , R.McGinness , and H.E.O'Neal , J.Org.Chem. , 1981 , **46** , 1887 .

71. C.Hagelberg ,M.Phil Thesis , University of London , 1985 .

72. R.W.Hoffmann and U.Weidmann , J.Organometallic Chem. , 1980 , **195** , 137 .

73. R.J.Crawford , S.Lutener , and H.Tokunaga , Can.J.Chem. , 1977 ,**55** ,3951 .

74. B.R.Davis , G.W.Rewcastle , and R.J.Stevenson , J.Chem.Soc.Perkin Trans I , 1977 , 2148 .

75. F.Huet , A.Lechavallier , M.Pellet , J.M.Conia , Synthesis , 1978 , 63 .

76. E.J.Corey , K.C.Nicolaou , M.Shibaski , Y.Machida , and C.S.Shiner , Tetrahedron Lett. , 1975 , 3183.

77. A.J.Bloodworth and C.J.Cooksey , J.Organomet.Chem. , 1985 , **295** , 131 .

78. A.J.Bloodworth , K.H.Chan , and C.J.Cooksey , J.Org.Chem. , 1985 , **51** , 2110 .

79. Emmanuele Bascetta and F.D.Gunstone , J.Chem.Soc.Perkin Trans. I , 1984 , 2207 .

80. Emmanuele Bascetta and F.D.Gunstone , J.Chem.Soc.Perkin Trans. I , 1984 , 2217 .

81. H.Kropf and H. von Wallis , Liebigs Ann.Chem. , 1983 , 610 .

82. A.L.J.Beckwith and R.Wagner , J.Am.Chem.Soc. , 1979 , **101** , 7099 .

83. W.Adam , A.Birke , C.Cadiz , S.Diaz , and A.Rodriguez , J.Org.Chem. ,1978 , **43** , 1154 .

84. A.J.Bloodworth and G.M.Lampman , J.Org.Chem. , 1988 , **53** , 2668 .

85. K.S.Feldman , R.E.Simpson , and M.Parvez , J.Am.Chem.Soc. , 1986 , **108** , 1328 .

86. K.Mizuno , N.Kamiyama , N.Ichinose , and Y.Otsuji , Tetrahedron , 1985 , **41** , 2207 .

87. S.C.Shim and J.S.Song , J.Org.Chem. , 1987 , **28** , 2817 .

88. T.Anasaka and W.Ando , Tetrahedron Lett. , 1987 , **28** , 217 .

89. a) R.L.Kuczkowski , W.H.Pearson , and B.J.Wojciehowski , 1989 , **54** , 115 .

b) H.Keul and R.L.Kuczkowski , J.Am.Chem.Soc. , 1984 , **106** , 5370.

c) R.L.Kuczkowski and H.-S.Choi , J.Org.Chem. , 1985 , **50** , 3365 .

90. M.Labelle , H.E.Morton , Y.Guindon , and J.P.Springer , J.Am.Chem.Soc. , 1988 , **110** , 4533 .

91. P.A.Hunt , C.May , and C.J.Moody , Tetrahedron Lett. , 1988 , **29** , 3001 .

92. L.A.Paquette , R.V.C.Carr , and F.Bellamy , J.Am.Chem.Soc. , 1978 , **100** , 6764 .

93. a) K.R.Kopecky , J.H.Van de Sande , and C.Mumford , Can.J.Chem. , 1968 , **46** , 25 .

b) K.R.Kopecky and J.H.van de Sande , Can.J.Chem. , 1972 , **50** , 4034 .

94. a) R.E.Ireland , R.C.Anderson , R.Badoud , B.J.Fitzsimmons , G.J.McGarvey , S.Thaisrivongs, C.S.Wilcox , J.Am.Chem.Soc. , 1983 , **105** , 1988.

b) F.M.Hauser and D.Mal , J.Am.Chem.Soc. , 1984 , **106** , 1098 .

c) M.Yoshioka , N.Nakai , and M.Ohno , J.Am.Chem.Soc. , 1984 , **106** , 1133

95. A.J.Bloodworth , Tracey Melvin , and J.C.Mitchell , J.Org.Chem. , 1988 , **53** , 1078 .

96. A.G.Davies , B.P.Roberts , and J.M.Smith , J.Chem.Soc.Perkin Trans. II , 1972 , 2221 .

97. H.W.S.Chan , J.A.Matthew , and D.T.Coxon , J.Chem.Soc.Chem.Commun. , 1980 , 235 .

98. E.J.Corey , J.O.Albright , A.E.Barton , and S.Hashimoto , J.Am.Soc. , 1980 , **102** , 1435.

99. N.A.Porter , D.H.Roberts , and C.B.Ziegler Jr. , J.Am.Chem.Soc. , 1980 , **102** , 5912 .

100. E.N.Frankel , W.E.Neff , and D.Weisleder , J.Chem.Soc.Chem.Commun. , 1982 , 599 .

101. E.D.Mihelich , J.Am.Chem.Soc. , 1980 , **102** , 7142 .

102. N.A.Porter , J.Logan , and V.Kontoyiannidou , J.Org.Chem. , 1979 , **44** , 3177 .

103. K.Gollnick and A.Griesbeck , Tetrahedron , 1984 , **40** , 3235 .

104. H.A.J.Carless and R.J.Batten , Tetrahedron Lett. , 1982 , 4735 .

105. A.L.J.Beckwith , C.J.Eaton , and A.K.Serelis , J.Chem.Soc.Chem.Commun. , 1980 , 482 .

106. A.L.J.Beckwith and R.D.Wagner , J.Chem.Soc.Chem.Commun. , 1980 , 485 .

107. P.J.Baker , A.L.J.Beckwith , and Y.Fung , Tetrahedron Lett. , 1983 , **24** , 97 .

108. a) R.J.Anderson , J.Am.Chem.Soc. , 1970 , **92** , 4978
b) R.W.Herr and C.R.Johnson , J.Am.Chem.Soc. , 1970 , **92** , 4979.

109. A.J.Bloodworth and R.J.Curtis , J.Chem.Soc.Chem. Commun. , 1989 , 173 .

110. A.J.Bloodworth and E.Rimmer , Unpublished results .

111. A.J.Bloodworth and N.A.Tallant , Unpublished results .

112. K.Hayashi , J.Organomet.Chem. , 1967 , **10** , 81 .

113. P.D.Bartlett , E.P.Benzing , and R.E.Pincock , J.Am.Chem.Soc. , 1960 , 82 , 1762 .

GLOSSARY OF ACRONYMS

ABq - AB quartet

Ac - Acyl

acac - Acetylacetone

AIBN - Azoisobutyronitrile

APT - Attached proton test

aq - Aqueous

Ar - Aryl

br - Broad

Bu - Butyl

d - Doublet

D - Deuterium

DBPO - Di-t-butyl peroxalate

DCA - 9,10-Dicyanoanthracene

DIBAL-H - Diisobutylaluminium hydride

DMF - Dimethyl formamide

DMSO - Dimethyl sulphoxide

DTBH - Di-t-butyl hyponitrite

Et - Ethyl

fvp - Flash vacuum pyrolysis

GLC - Gas liquid chromatography

HETE - Hydroxyeicosatetraenoic acid

HPLC - High performance liquid chromatography

HPETE - Hydroperoxyeicosatetraenoic acid

hr - Hour

m - Multiplet

MCPBA - meta-Chloroperoxybenzoic acid

Me - Methyl

Mes - Methanesulphonyl (Mesyl)

min - Minute

mp - Melting point

NBS - N-Bromosuccinimide

NCA - N-Chloroacetamide

NCS - N-Chlorosuccinimide

NIS - N-Iodosuccinimide

nmr - Nuclear magnetic resonance

PCC - Pyridinium chlorochromate

PG - Prostaglandin

Ph - Phenyl

PMA - Phosphomolybdic acid

PMHS - Polymethylhydrosiloxane

Pr - Propyl

q - Quartet

s - Singlet

t - Triplet

TCA - Trichloroacetic acid

Tf - Trifluoromethanesulphonate (Triflate)

THF - Tetrahydrofuran

TLC - Thin layer chromatography

TOCO - Thiol-oxygen cooxidation

Tos - p-Toluenesulphonyl (Tosyl)

TPP - Tetraphenylporphine

TX - Thromboxane

XS - Excess