THE CYCLISATION OF UNSATURATED PEROXIDES

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy of the University of London

by

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I dedicate this thesis to my parents, in gratitude for their support and encouragement during the past three years.

ACKNOWLEDGEMENTS

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Finally, special thanks are due to Pearl for her support during this work, and for her patience during the preparation of this manuscript.

ABSTRACT

The reactions of several γ,δ-unsaturated hydroperoxides with *tert*-butyl hypochlorite have been investigated, and it has been shown that this provides a general synthesis of 3-(1-chloroalkyl)-1,2-dioxolanes. It is believed that in general the reaction proceeds *via* a mixture of polar and radical pathways, but in the presence of silica the reaction appears to be entirely polar. If acetone is used as the solvent, this provides a new synthesis of substituted 1,2,4-trioxepanes which are formed as a minor product in the reaction.

The treatment of 3-cyclooctenyl hydroperoxide with *tert*-butyl hypochlorite in the presence of silica affords a chloro-substituted bicyclic peroxide, but under identical conditions 4-cyclooctenyl hydroperoxide produces very little of the expected bicyclic ether. Instead, the major product is 4-chlorocyclooctanone, which is probably formed *via* a transannular 1,5-hydride shift.

We further found that the observation of 1,2,4-trioxepane formation is not general, and that under similar conditions 1,2-dioxolanes are the exclusive products. However, it has recently been shown that under these conditions allylic hydroperoxides can form 1,2,4-trioxanes, and further investigation has found that the product formed is largely dependent on the nature of the substitution on the double bond. Thus, 3-phenylallyl (cinnamyl) hydroperoxide forms 1,2-dioxolanes, whereas 1-phenylallyl hydroperoxide forms 1,2,4-trioxanes with high stereoselectivity. One such trioxane has been found to show *in vitro* activity against malarial parasites. Good stereoselectivity was also found in the formation of 1,2,4-trioxanes from 2-methyl-2-buten-1-yl hydroperoxide. Additionally, the possibility of incorporating aldehydes derived from amino acids into the trioxanes has been demonstrated.

Investigations of the ^{13}C nmr spectra of the trioxanes synthesised showed that these compounds exhibit a reversed Perlin Effect *i.e.* $^{1}J(C\text{-}H_{ax})$ is found to be *greater* than $^{1}J(C\text{-}H_{eq})$. This was rationalised *via* a homoanomeric effect from the β-oxygen.

A general synthesis of 2-substituted 3-buten-1-yl hydroperoxides proved impossible to find. The 2-methyl compound could be synthesised by perhydrolysis of the corresponding

trifluoromethanesulphonate ester (triflate), but other analogues proved impossible to make due to the instability of the triflates. On cyclisation, 2-methyl-3-buten-1-yl hydroperoxide forms 3,4-disubstituted-1,2-dioxolanes, but generally with no stereoselectivity. However, if mercuric nitrate is used as the electrophile, then the *trans* isomer is found to be favoured.

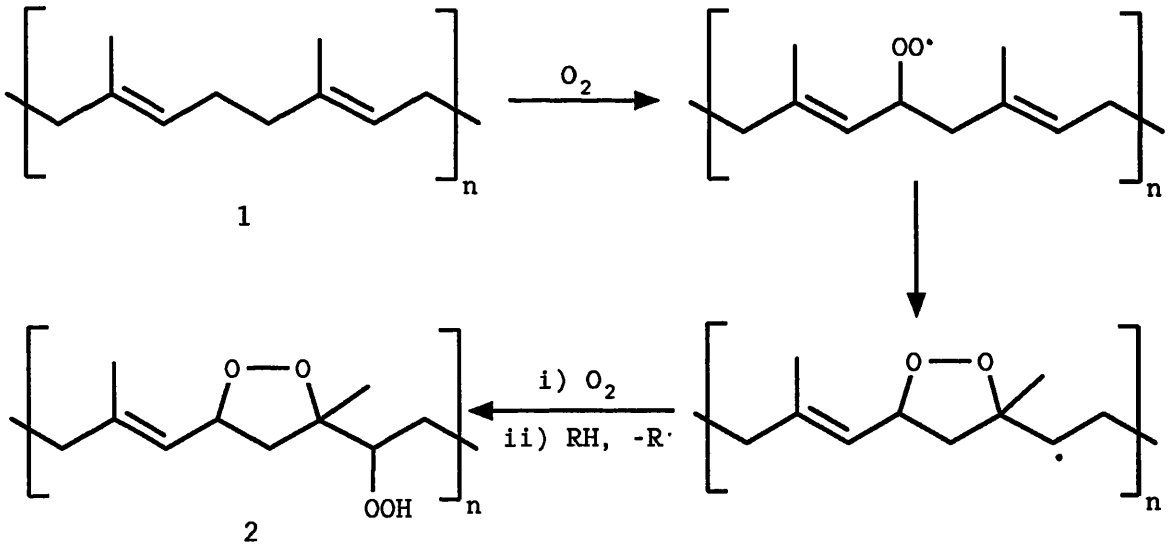
CHAPTER 1

INTRODUCTION

1.1 The Importance of Cyclic Peroxides

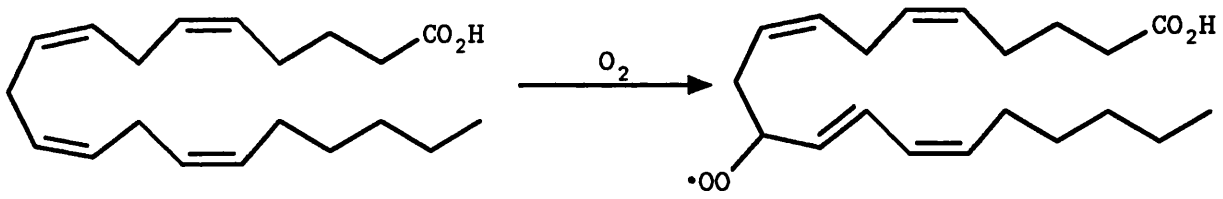
The study of unsaturated hydroperoxides and cyclic peroxides[1,2] is of biological, industrial and synthetic importance.

Industrially, these compounds are important in the study of the degradation of polyunsaturated compounds, such as rubber. The autoxidation of natural rubber (**1**) is complex, but the formation of cyclic peroxides, such as **2**, by a radical chain reaction, is a significant factor (Scheme 1). This process has received considerable attention,[3] particularly with respect to preventing the propagation steps thus prolonging the life of natural rubber.



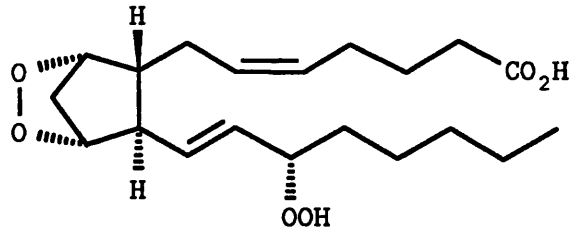
Scheme 1

Biologically, endoperoxides, of the form shown in Scheme 2, have been isolated and are known to be intermediates in the biosynthesis of prostaglandins.[4] Prostaglandins are lipids which are involved in a wide range of biological functions, such as blood clotting, blood pressure, fertility and allergic responses. The ability of these chemicals to prevent blood clots may lead to drugs which can be used to prevent heart attacks and strokes. Some prostaglandins, such as PGE_1, are powerful pyrogens, and the ability of aspirin to attack cyclo-oxygenase and prevent prostaglandin



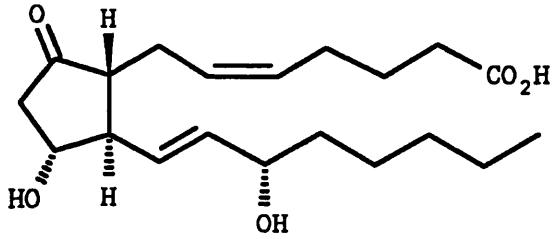
Arachidonic acid

cyclo-oxygenase



PGG_2 (a prostaglandin endoperoxide)

several steps



PGE_2 (a prostaglandin)

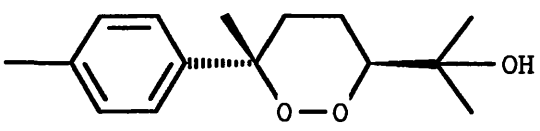
Scheme 2

synthesis may explain its anti-inflammatory action.

Indeed, several natural products include cyclic peroxide moieties.[5] These include the sesquiterpene peroxides Yingzhaosu C (**3**)[6] and Qinghaosu (**4**)[7] which show anti-malarial activity, the mycotoxin Verruculogen (**5**),[8] trunculin E (**6**)[9] and plakortin (**7**)[10] which show anti-microbial activity, and 'Inhibitor G1' (**8**)[11] which inhibits root growth in cuttings.

The use of peroxides as reagents in organic synthesis is well established,[12] and they are becoming increasingly more widespread as synthetic intermediates. Cyclic peroxides are particularly useful, as they can be transformed into a wide range of poly-oxygenated compounds such as diols, epoxy-alcohols, furans and various carbonyl compounds.[13]

The synthesis of cyclic peroxides, and precursors such as unsaturated hydroperoxides, is therefore of considerable interest.



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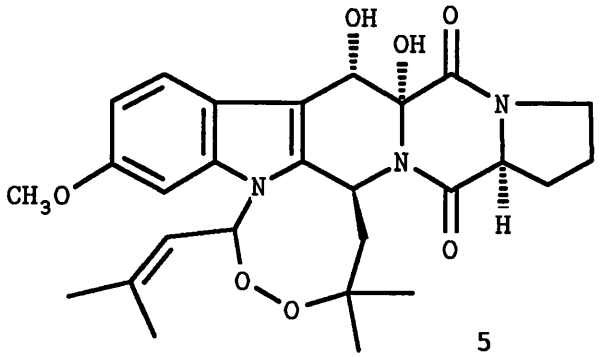

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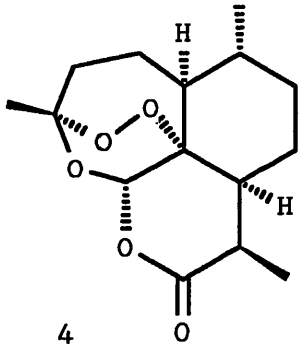

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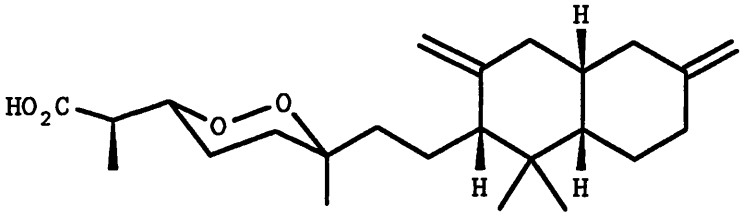

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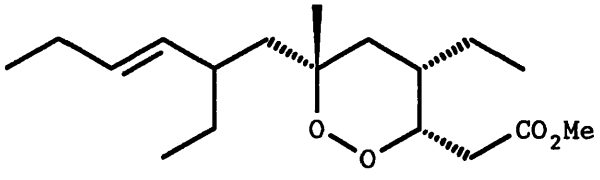

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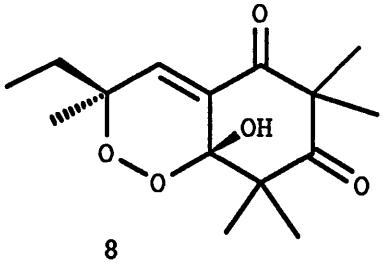

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1.2 Syntheses of Hydroperoxides

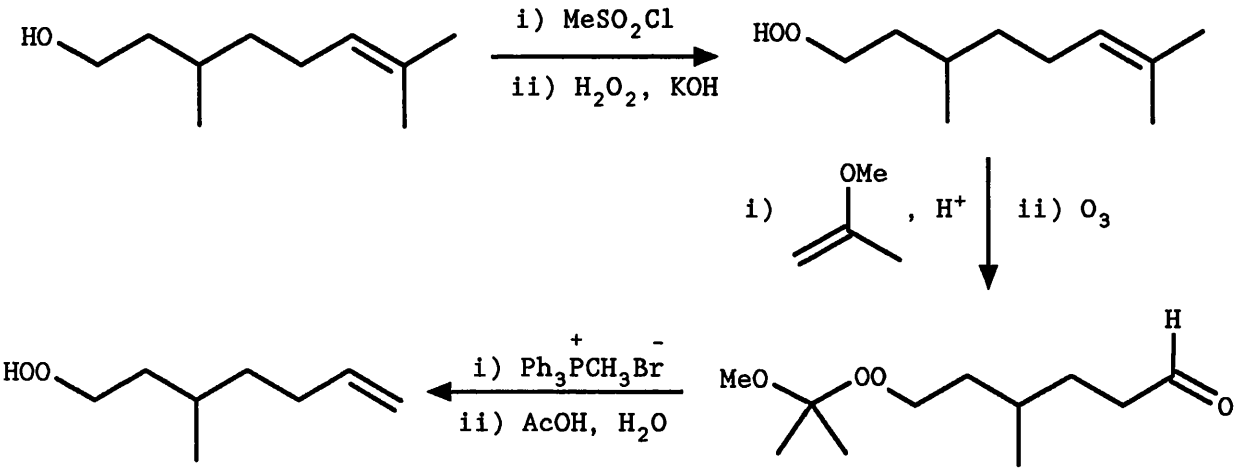
The syntheses of hydroperoxides can be split into two general categories : alkylation of hydrogen peroxide, or reaction of an organic substrate with molecular oxygen. There are numerous different methods, the most important and synthetically useful of which are discussed below.[14]

1.2.1 Alkylation of Hydrogen Peroxide

Treatment of various R-X with basic hydrogen peroxide is a simple way of producing primary and secondary hydroperoxides. The reaction follows an S_N2 mechanism in which the nucleophile is OOH^-. The most common of these reactions is when X = OSO_2Me, a reaction first described by Mosher and Williams (eq. 1).[15] This has been by

$$R-OSO_2Me \xrightarrow[MeOH\ /\ H_2O]{H_2O_2,\ KOH} R-OOH \qquad (1)$$

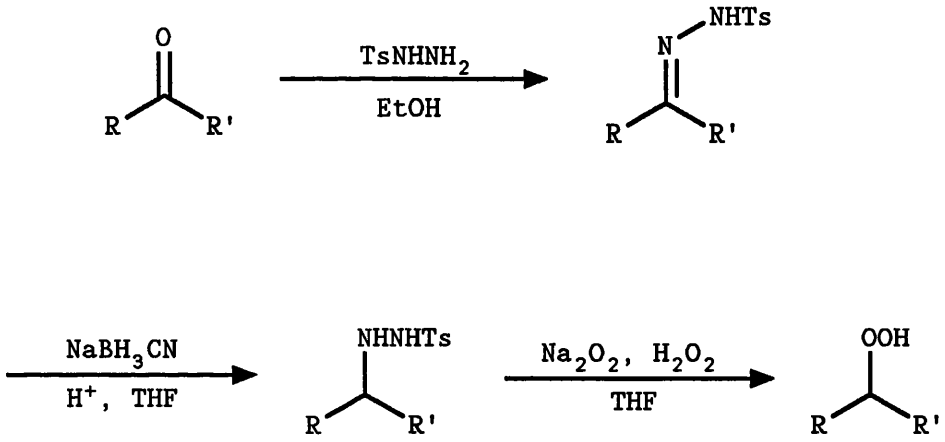
far the most important method for the synthesis of non-allylic unsaturated hydroperoxides. Its use has been reported widely,[16] and accounts for most of the published syntheses of such compounds. Generally, the perhydrolysis of the unsaturated mesylate is the final step in the synthesis, but recently Dussault[17] showed that suitable protection of the hydroperoxide group allowed the subsequent



Scheme 3

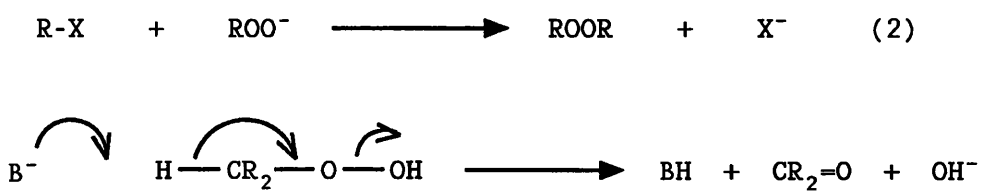
elaboration of the carbon skeleton, e.g. the introduction (or modification) of C=C double bonds *via* Wittig and related reactions (Scheme 3). The mesylate route has also found use in the synthesis of allylic hydroperoxides.[18]

Although this can work well when R is primary, the synthesis of secondary hydroperoxides by this method can be problematical. A better way of making these compounds is to use the conditions of Caglioti.[19] This involves the oxidation of an *N*-alkyl-*N*'-tosylhydrazine, which in turn can be made by reduction of an *N*'-tosylhydrazone derived from a ketone. The reduction was initially done with diborane, but Melvin[20] showed that this method could be applied to unsaturated compounds by using sodium cyanoborohydride[21] instead (Scheme 4). This work was developed further by Bloodworth *et. al.*[22]



Scheme 4

The yields in all these types of reactions are limited both by dialkyl peroxide formation due to reaction of the hydroperoxides formed with the original substrate (eq. 2), and decomposition of the hydroperoxides under the strongly basic conditions (Scheme 5).



Scheme 5

Tertiary hydroperoxides may be synthesised by nucleophilic substitution reactions proceeding by an S_N1 mechanism. These include treating tertiary alcohols with hydrogen peroxide under acid conditions[23] (eq. 3), or tertiary alkyl halides with silver salts in the presence of hydrogen peroxide[24] (eq. 4). Of these two methods,

$$R\text{-}OH + H_2O_2 \xrightarrow{H^+} R\text{-}OOH + H_2O \qquad (3)$$

$$R\text{-}X + H_2O_2 + AgBF_4 \longrightarrow R\text{-}OOH + AgX + HBF_4 \qquad (4)$$

the latter has been found to be more useful for the preparation of unsaturated hydroperoxides,[25] and has also found use in the synthesis of secondary allylic hydroperoxides.[26] However, an alkynyl hydroperoxide has been prepared by the acid catalysed perhydrolysis of the corresponding alcohol.[27]

The addition of hydrogen peroxide across double bonds under strongly acidic conditions may also be used to produce tertiary alkyl hydroperoxides[28] (eq. 5), but this is not a method which has found widespread preparative use.

$$R_2C{=}CR_2 + H_2O_2 \xrightarrow{H^+} R_2C(OOH)\text{—}CHR_2 \qquad (5)$$

A similar method using a mercury salt in place of a proton as the electrophile is more synthetically useful; the resultant hydroperoxymercurials can be converted to the parent hydroperoxides by protection of the hydroperoxy group followed by sodium borohydride induced hydridodemercuration (Scheme 6).[29]

$$RR'C{=}CHR'' \xrightarrow{i)} RR'C(OOH)CH(HgBr)R'' \xrightarrow{ii)} RR'C(OOC[OMe]Me_2)CH(HgBr)R''$$

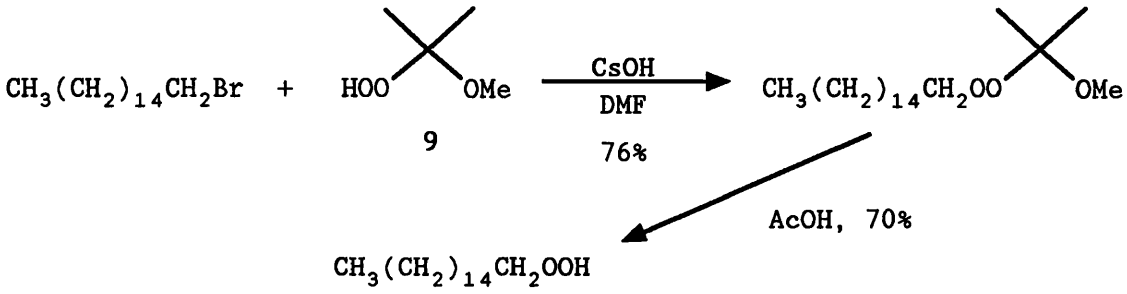
$$\xrightarrow{iii)} RR'C(OOC[OMe]Me_2)CH_2R'' \xrightarrow{iv)} RR'C(OOH)CH_2R''$$

Reagents : i) 30% H_2O_2, $Hg(OAc)_2$ then KBr ii) $MeOC(Me){=}CH_2$, pyH^+OTs^-
iii) $NaBH_4$, NaOH iv) AcOH, H_2O

Scheme 6

A new method has recently been reported, whereby 2-methoxy-

prop-2-yl hydroperoxide (**9**) has been used as a synthon for anhydrous hydrogen peroxide.[30] Treatment of an alkyl bromide with **9** and subsequent deprotection affords primary hydroperoxides in good yields (Scheme 7), but the reaction works less well for secondary compounds.

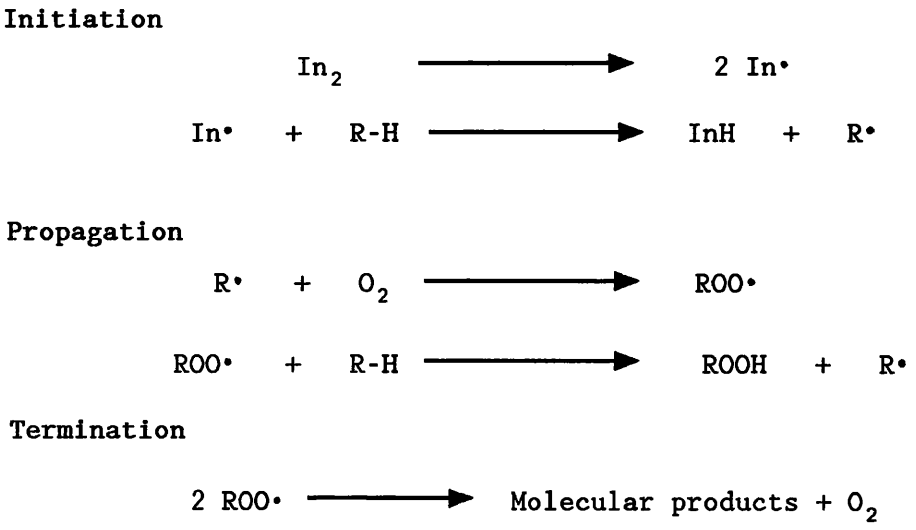


Scheme 7

Although no unsaturated hydroperoxides were made, this methodology has been used for the preparation of an unsaturated peroxyacid.

1.2.2 Oxygenation of Organic Substrates

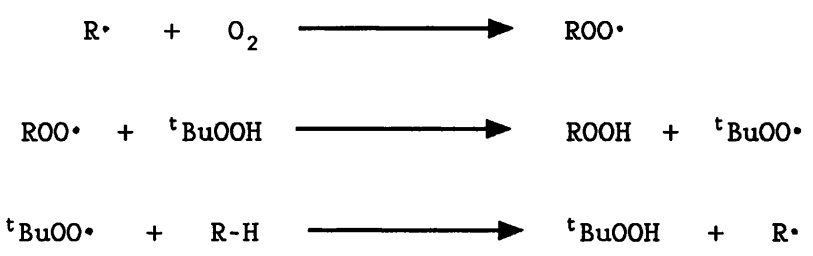
One of the most common processes by which hydroperoxides are formed in nature is by autoxidation. It is this process which is responsible for fats going rancid and it is used in the industrial synthesis of *tert*-butyl hydroperoxide and in the cumene process for the manufacture of phenol and acetone. Autoxidation is a free radical chain reaction proceeding *via* the steps shown in Scheme 8.



Scheme 8

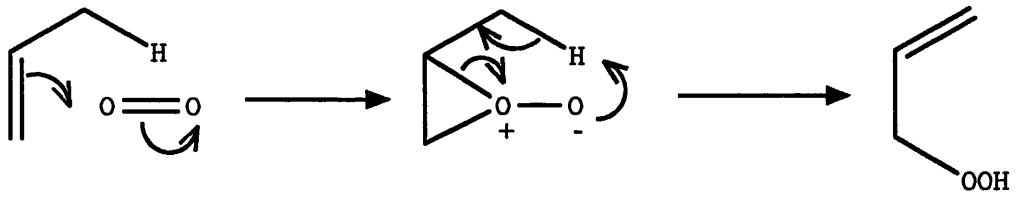
This is primarily used for the synthesis of allylic hydroperoxides, although polyunsaturated substrates will yield hydroperoxides which are also homoallylic (cf. Scheme 1). The yield of peroxidic material is often limited by the relatively rapid termination of the peroxyl radicals. However, adding *tert*-butyl hydroperoxide, a good H-donor, to the mixture prevents this, and prolongs the chains due to the slow termination of *tert*-butyl peroxyl radicals.[31] The propagation steps are now as shown in Scheme 9.

Propagation



Scheme 9

The reaction of alkenes with singlet oxygen can be used to produce allylic hydroperoxides in high yields.[32] This works better for more highly substituted alkenes. The mechanism is unclear, but it is suggested that the reaction occurs *via* a perepoxide type intermediate[33] (Scheme 10).



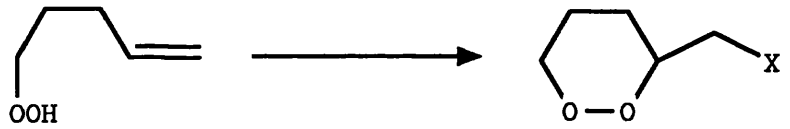
Scheme 10

1.3 Cyclisation of Unsaturated Hydroperoxides

Under appropriate conditions unsaturated hydroperoxides will cyclise to form cyclic peroxides. This reaction has been studied for a wide range of substrates, using a variety of reagents to induce the cyclisation under both polar[34] and radical[35] conditions. Most of the work has concentrated on the formation of 5-membered rings (1,2-dioxolanes : eq. 6) and 6-membered rings (1,2-dioxanes : eq.7).

(6)

10



(7)

11

1.3.1 Radical Cyclisations

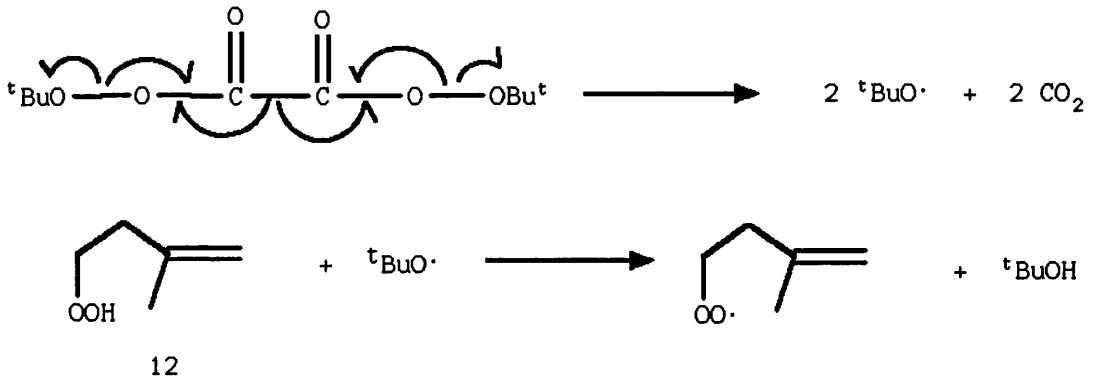
Much of the early work on the radical cyclisations was done by Porter *et. al.*[36] using di-*tert*-butylperoxyoxalate (DBPO) as the initiator. The mechanism is illustrated using 3-methyl-3-buten-1-yl hydroperoxide (**12**) (Scheme 11).

In the example given, the 1,2-dioxolan-3-ylmethyl radical (**13**) which results from cyclisation is trapped by oxygen to give the hydroperoxydioxolane. In the absence of oxygen, **13** will undergo γ-scission to produce an epoxy-alcohol (Scheme 12).

The termination reactions for peroxyl radicals depend on whether they are primary, secondary or tertiary. Primary and secondary peroxyl radicals terminate *via* the Russell mechanism[37] to produce an aldehyde or ketone and an alcohol (Scheme 13).

Tertiary peroxyl radicals have no α-hydrogen and so cannot terminate by this mechanism. Instead, the tetroxide formed breaks up to form oxygen and two alkoxyl radicals, which generally combine to give a dialkyl peroxide (Scheme 14).

Initiation



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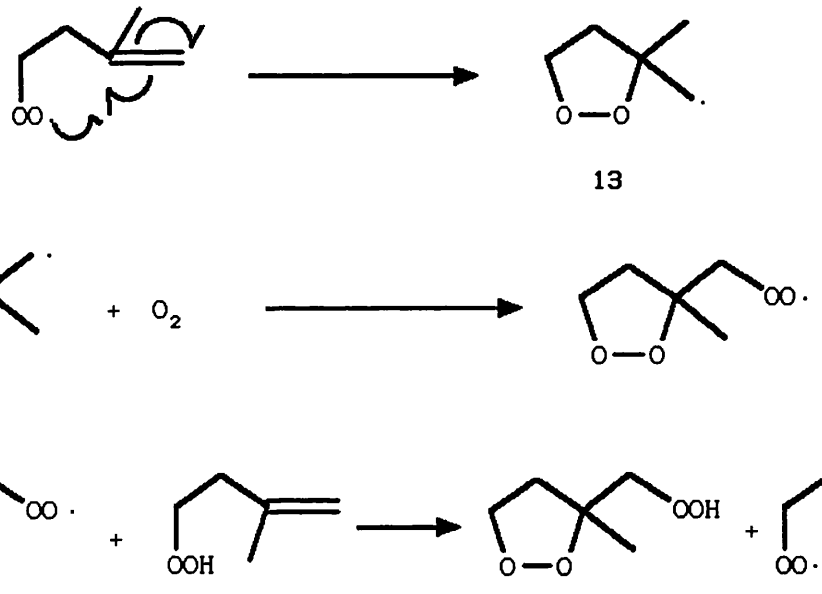
Propagation



13

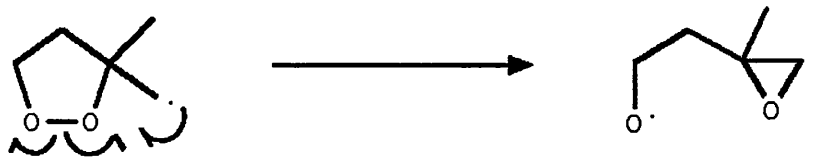
13

Termination

2 ROO· ⟶ Molecular products + O_2

Scheme 11

The regiospecificity found for the peroxyl radical cyclisations was as predicted from Baldwin's rules.[38] Hydroperoxides such as **10** could cyclise 5-*exo-trig* to form 1,2-dioxolanes or 6-*endo-trig* to form 1,2-dioxanes. Only 5-*exo* cyclisation was observed. Similarly, hydroperoxides like **11** have the option of undergoing 6-*exo-trig* or 7-*endo-trig* cyclisation, but only the 6-*exo* mode was seen.



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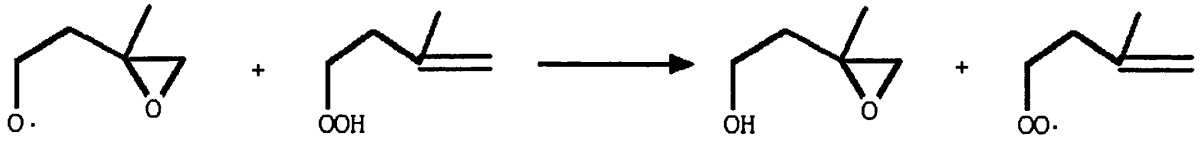

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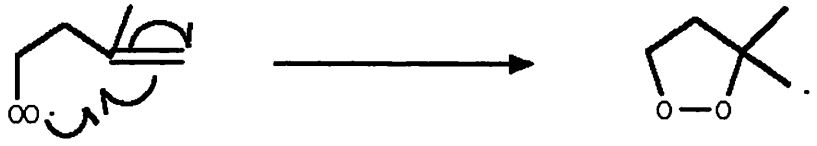

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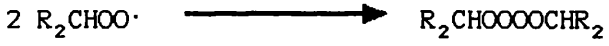
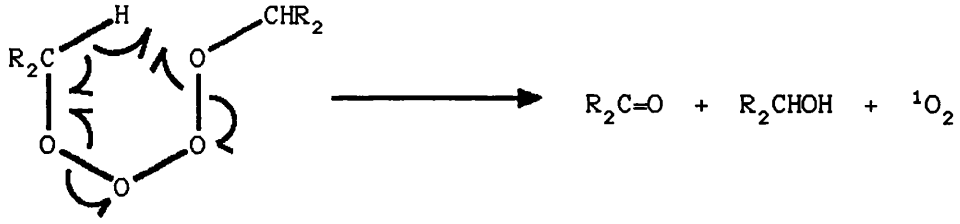
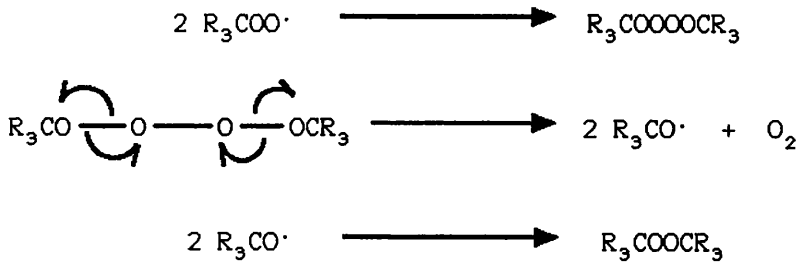
Scheme 12



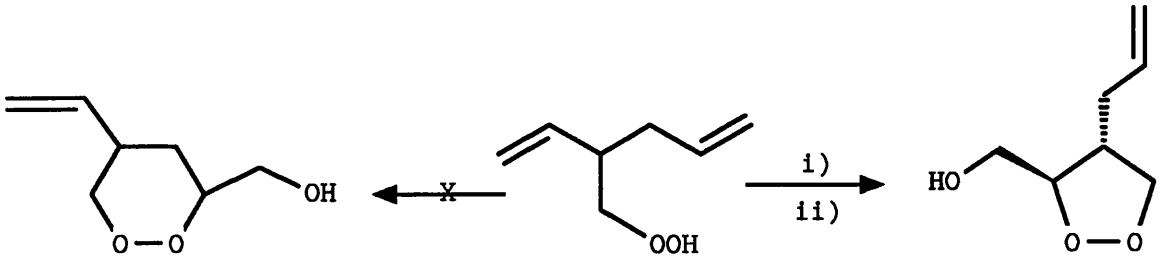


Scheme 13



Scheme 14

Further to this, work by Bloodworth, Curtis and Mistry[39] using a diene hydroperoxide (**14**) which could cyclise either 5-*exo* or 6-*exo*, showed that under radical conditions 5-*exo* cyclisation to form 1,2-dioxolanes occurred exclusively (Scheme 15). They also found



14

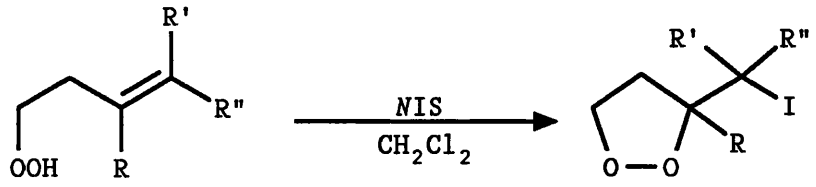
Reagents : i) DBPO, O_2 ii) PPh_3

Scheme 15

that the cyclisation occurred stereoselectively *trans*, in agreement with the findings of Beckwith for the cyclisation of similarly substituted carbon centred radicals.[40]

Apart from these simple hydroperoxides, work has also been done using peroxyl radicals derived from the autoxidation of long chain trienes, as models for the formation of prostaglandin endoperoxides from arachidonic acid.[41]

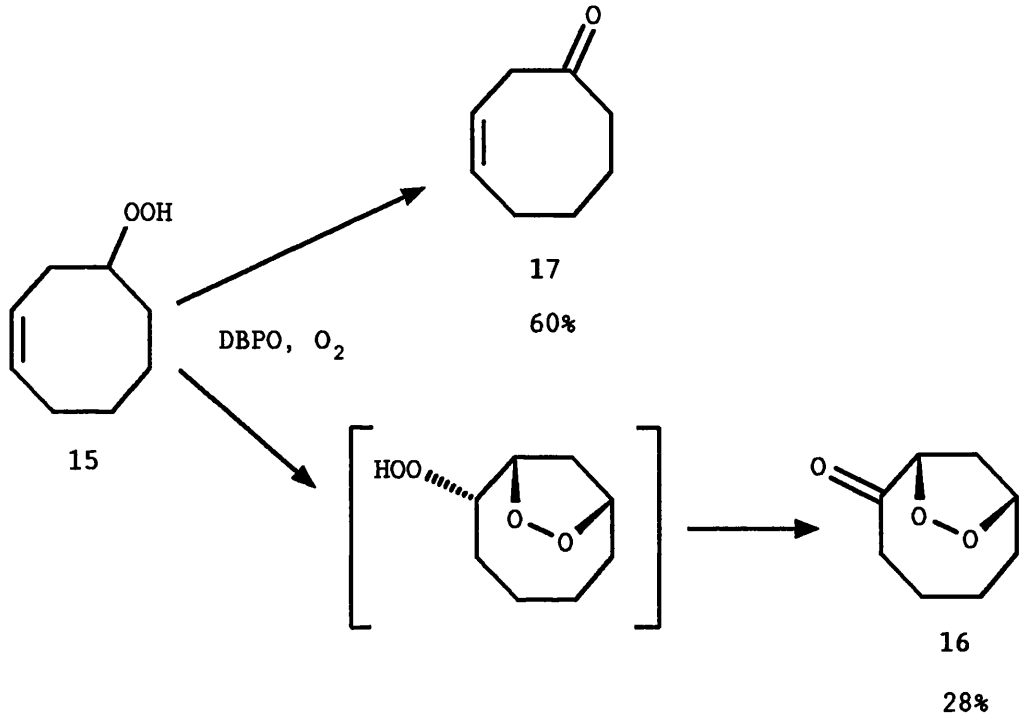
There are very few examples of the trapping of the 1,2-dioxolan-3-ylmethyl radicals (e.g. **13**) produced on cyclisation, by anything other than oxygen. Recently however, Bloodworth and Curtis showed that iodo-substituted 1,2-dioxolanes could be formed by treating unsaturated hydroperoxides with *N*-iodosuccinimide (*NIS*) (Scheme 16).[42] They believed this reaction occurred *via* a radical mechanism (see Chapter 2).



Scheme 16

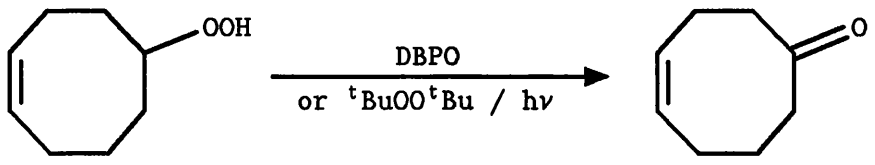
Attempts at making bicyclic peroxides by radical cyclisation of

cyclooctenyl hydroperoxides have been largely unsuccessful. In work done by Bloodworth and Spencer, treatment of 3-cyclooctenyl hydroperoxide (**15**) with DBPO produced a small amount of a bicyclic peroxide (**16**), but the major product was 3-cyclooctenone (**17**) which they proposed was formed by a radical induced elimination of water from **15** (Scheme 17).[43]



Scheme 17

The isomeric 4-cyclooctenyl hydroperoxide (**18**) produced only the monocyclic ketone on treatment with *tert*-butoxyl radicals (eq. 8).[44]

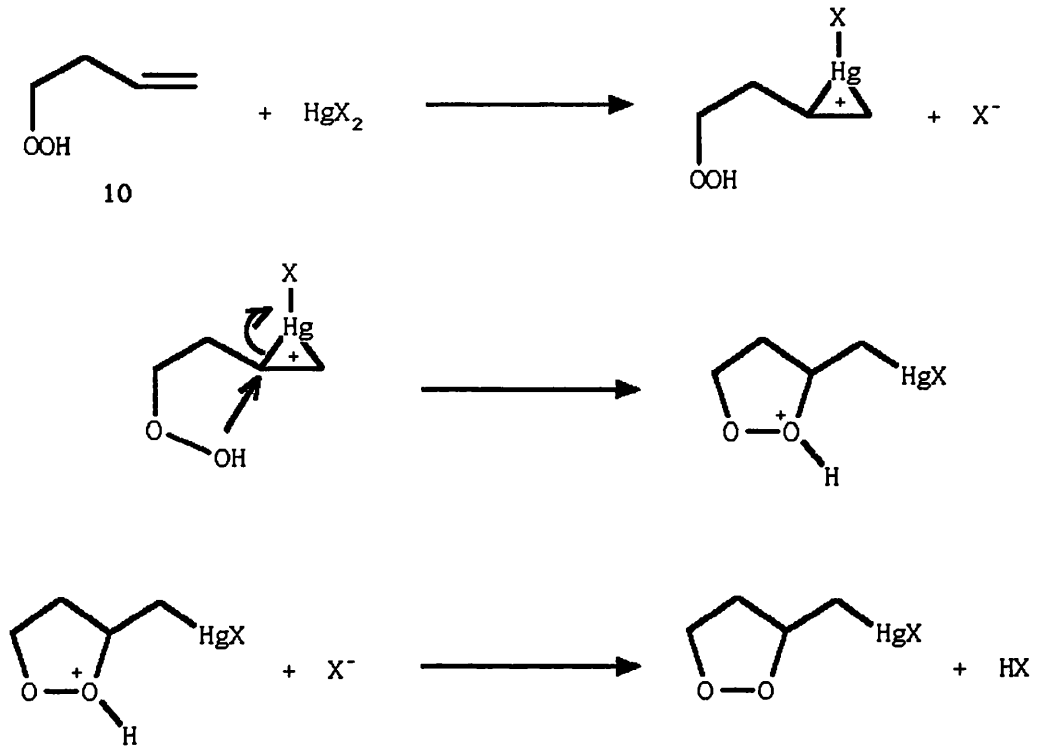


18 (8)

1.3.2 Electrophilic Cyclisations

Treatment of unsaturated hydroperoxides with electrophiles leads to cyclisation *via* a polar mechanism. In most of the work done

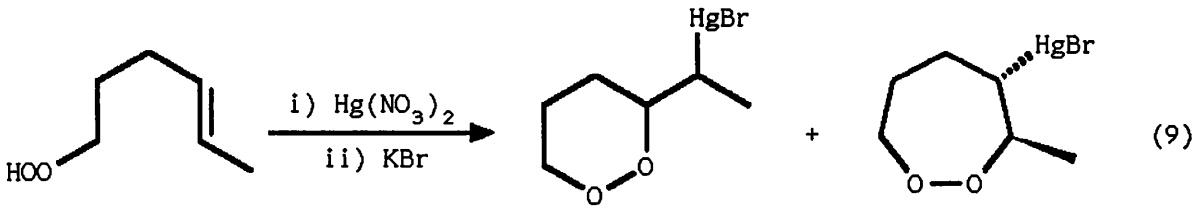
the electrophile has been a mercury(II) salt, which induces cyclisation *via* the intermediacy of a mercurinium ion (Scheme 18).



X = NO_3, OAc, O_2CCF_3...

Scheme 18

Porter *et. al.*[45] found that as with cyclisation under radical conditions, homoallylic hydroperoxides (e.g. **10**) cyclise regiospecifically to form 1,2-dioxolanes. However, *trans*-4-hexen-1-yl hydroperoxide (**19**) was found to yield a mixture of 6- and 7-membered ring peroxides (eq. 9). They also found that, as



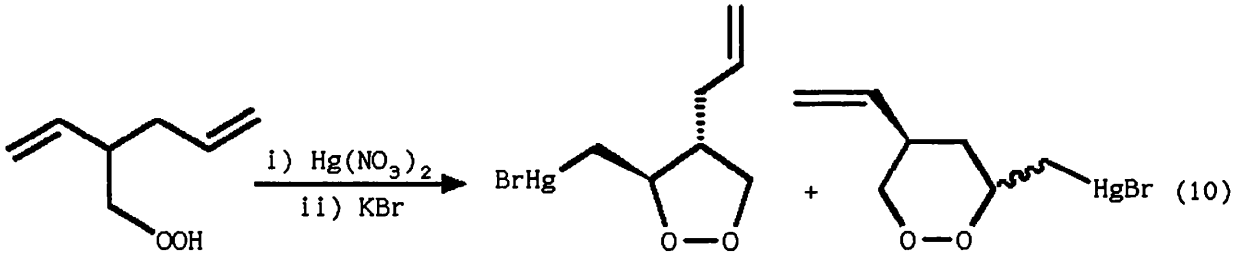
(9)

19 3 : 1

expected, the mercury and the peroxy group gave stereospecific *anti*-addition across the double bond.

In a further investigation into the regiochemistry of the cyclisation, Bloodworth *et. al.*[39] also examined the behaviour of **14** under polar conditions. Unlike the results with DBPO, the

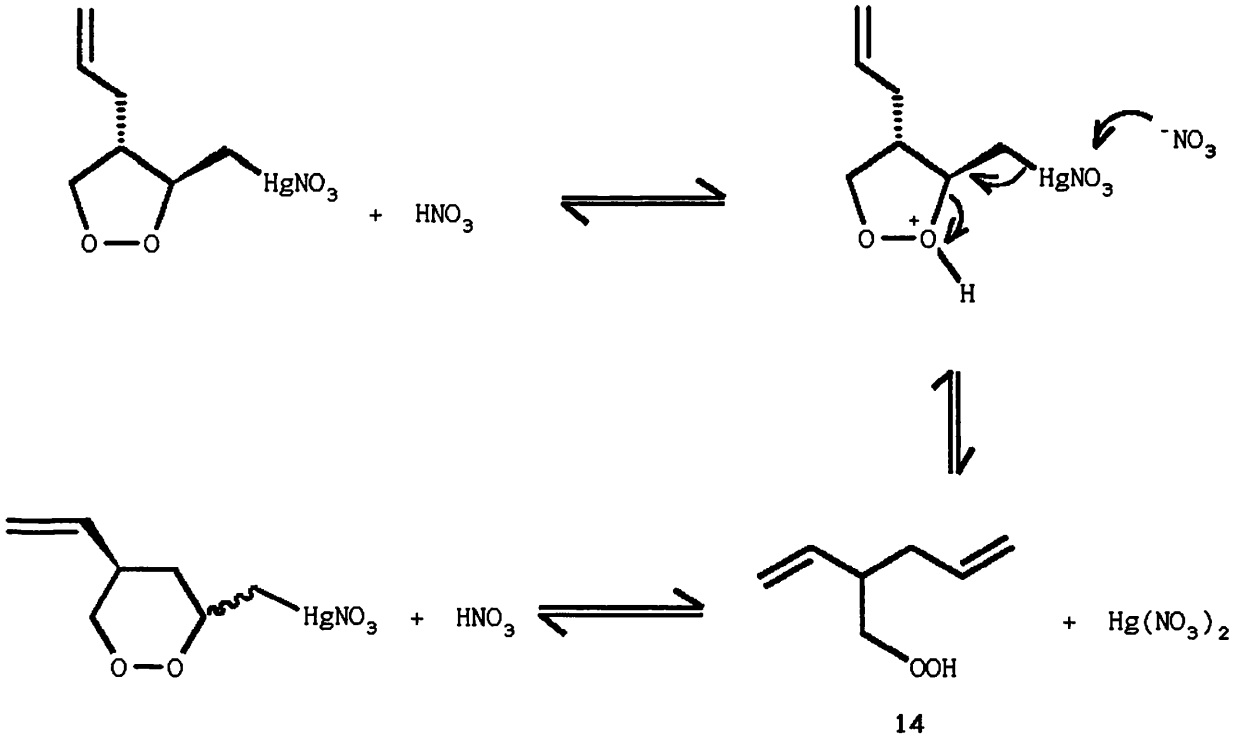
cyclisation was not regiospecific, but afforded a mixture of 5- and 6-membered ring peroxides (eq. 10). However, as



14 20 21

2 : 1

cycloperoxymercuration is reversible (Scheme 19), in contrast to the radical ring closures, it may be that this is due to the products being formed under thermodynamic, as opposed to kinetic, control.



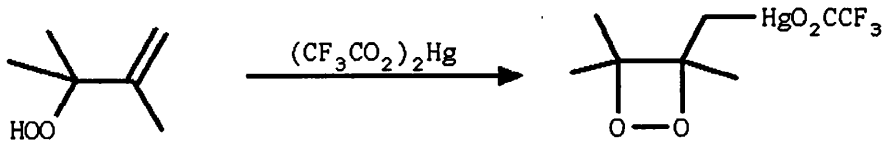
14

Scheme 19

Again the cyclisation showed high stereoselectivity with respect to the dioxolane, with only the *trans* isomer formed.

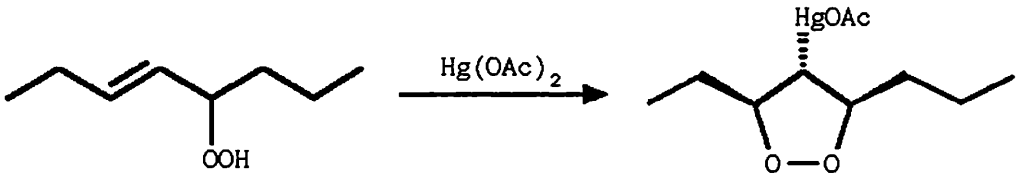
Allylic hydroperoxides cyclise less readily, as the two modes of cyclisation available to them are both unfavourable. However, dependent on the hydroperoxide used, and under suitable conditions, both 4-*exo* (eq. 11)[46] and 5-*endo* (eq. 12)[47] cyclisations have been

observed.



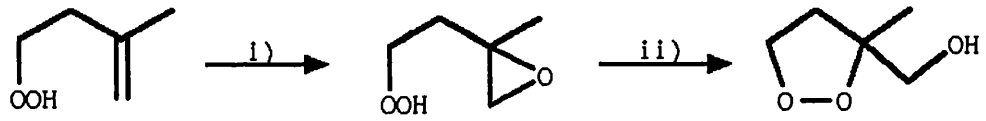
(11)

(minor product)



(12)

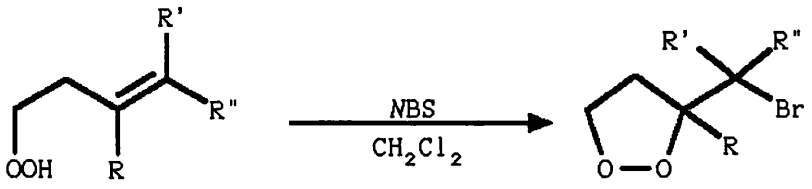
The use of other electrophiles to mediate the cyclisation of unsaturated hydroperoxides has not been extensively studied, but examples are to be found in the literature. One such example is to epoxidise the double bond with *m*-chloroperoxybenzoic acid, and induce cyclisation by treatment with a catalytic amount of trichloroacetic acid[36] (Scheme 20).



Reagents : i) *m*-CPBA ii) CCl_3CO_2H

Scheme 20

As an extension to their work with *N*IS, Bloodworth and Curtis also showed that bromo-substituted dioxolanes could be synthesised by the action of *N*-bromosuccinimide (*N*BS) on unsaturated hydroperoxides[42] (Scheme 21). Although the cyclisation was occurring



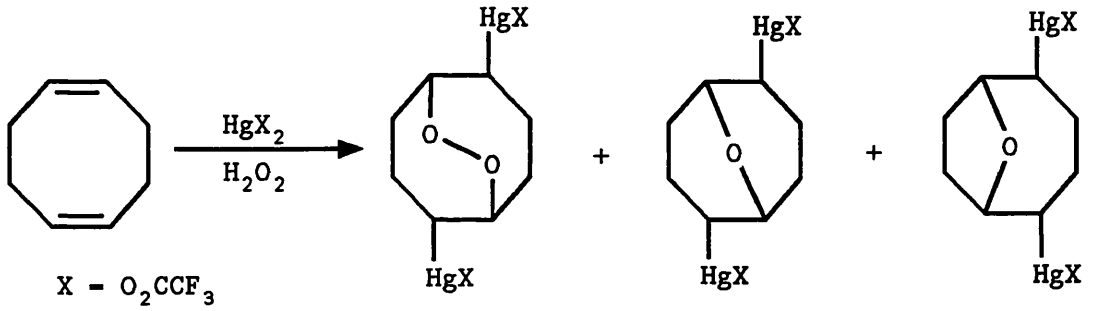
Scheme 21

partly through the peroxyl radical, there was strong evidence that bromonium ion induced cyclisation was also competing, resulting in a

predominance of products derived from *anti*-addition of bromine and the peroxy group across the double bond.

In addition to the work on acyclic hydroperoxides, extensive work has also been done on the formation of bicyclic peroxides by electrophile induced intramolecular ring closures of unsaturated cyclooctenyl hydroperoxides.

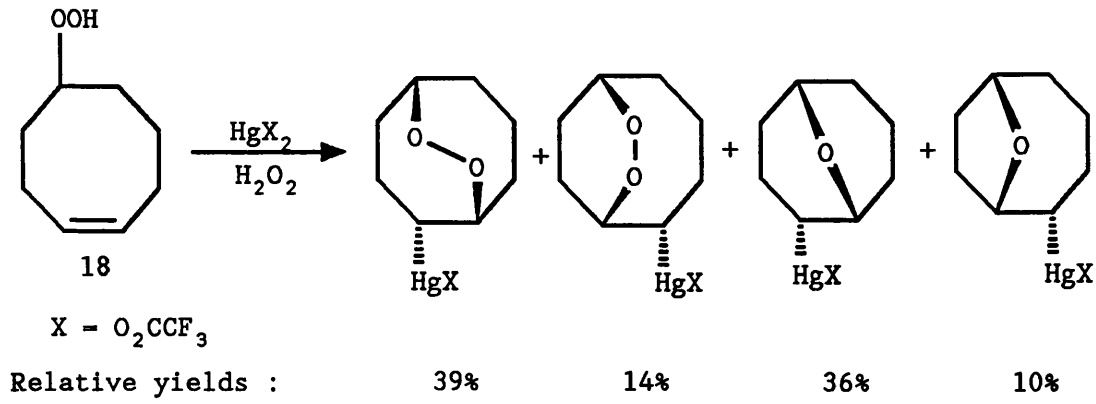
Initial work carried out by Bloodworth *et. al.*[48] looked at the reaction of *cis,cis*-1,5-cyclooctadiene with hydrogen peroxide and mercury(II) trifluoroacetate. Under these conditions a mixture of bicyclic peroxides and bicyclic ethers was formed (Scheme 22). These



Scheme 22

were assumed to arise *via* hydroperoxymercuration of one double bond, followed by mercury salt induced cyclisation.

To investigate further the cyclisation step, and gain further information about the production of ethers, Courtneidge[49] synthesised 4-cyclooctenyl hydroperoxide (**18**) and treated it with mercury(II)

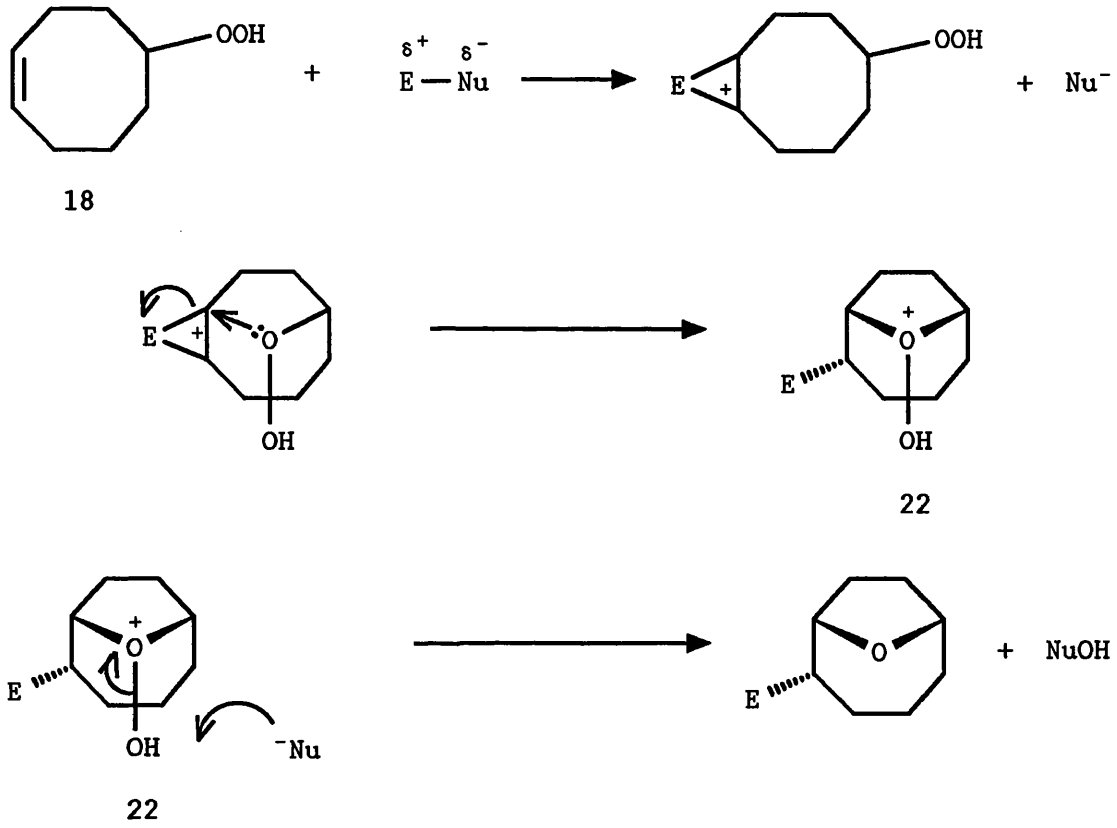


Scheme 23

trifluoroacetate. The results were similar to those obtained earlier with 1,5-cyclooctadiene, and are shown in Scheme 23.

On treating **18** with *N*BS, only bicyclic ethers were found, no peroxidic material was apparently formed.[50]

The production of ethers was rationalised by suggesting the intermediacy of a *gem*-dialkylperoxonium ion[51] (**22**; Scheme 24).



Scheme 24

Further evidence for such species was provided by Bloodworth *et. al.*,[52] who also showed that such ions were capable of transferring OH^+ to suitable substrates, such as sulphoxides.

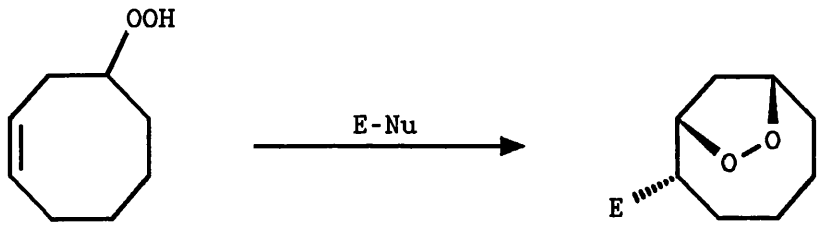
Work by Spencer[53] showed that treatment of **18** with other electrophiles (e.g. *N*IS, iodine, AcOBr, *m*-CPBA/H^+) also afforded exclusively bicyclic ethers *via* *gem*-dialkylperoxonium ions, and confirmed that mercury salt induced cyclisation was anomalous in that bicyclic peroxides were also formed.

The preference for the formation of ethers has been explained by the minimalisation of steric strain in the transition state. The anomalous behaviour with mercury salts is thought to be due to the mercurinium ion formed being larger than the bridged ions formed with

other nucleophiles, thus reducing the steric strain in the transition state which leads to bicyclic peroxides.

These findings provide further potential for unsaturated hydroperoxides, namely as precursors to oxygen-transfer species. It is hoped that such species will prove to be powerful oxidising agents.[54]

Spencer[43] also showed that 3-cyclooctenyl hydroperoxide (**15**) on treatment with electrophiles did produce the expected [5.2.1] bicyclic peroxides (Scheme 25). The formation of peroxides was again



15 E = Br, I, OH, HgOAc

Scheme 25

presumed to be due to steric considerations in the transition state.

The cyclisation of unsaturated hydroperoxides is one of the most important of several methods which are available for the synthesis of cyclic peroxides, discussions of other methods can be found elsewhere.[55]

1.4 Aims of Thesis

Although much work has been done on investigating the cyclisations of unsaturated hydroperoxides, large gaps in our knowledge still exist. The work I am presenting in this thesis aims to address three particular areas which relate to these processes :

i) Despite considerable investigation into different reagents to induce the cyclisation, as yet no method exists for the direct formation of chlorinated cyclic peroxides from unsaturated hydroperoxides. I shall show how *tert*-butyl hypochlorite achieves this aim, which complements the earlier work done on cycloperoxyhalogenation with *N*BS and *N*IS.[42]

ii) Apart from a few isolated examples in the literature, no systematic study has been done on the stereoselectivity of such cyclisations. I shall look at an area which has been particularly neglected, the synthesis of 3,4-disubstituted 1,2-dioxolanes from appropriately substituted homoallylic hydroperoxides, and show how difficulties in the syntheses of the hydroperoxides complicate the investigation.

iii) Finally, I shall investigate further recently published work, where the direct cycloperoxymercuration of allylic hydroperoxides[47] is suppressed in the presence of aldehydes and ketones in favour of the incorporation of the carbonyl compound to give 1,2,4-trioxanes instead.[56] This new synthesis of this important class of peroxides has hardly been explored. I shall look at the effect on the synthesis of changing the hydroperoxide used, and determine whether 1,2-dioxolane formation is always disfavoured in such systems.

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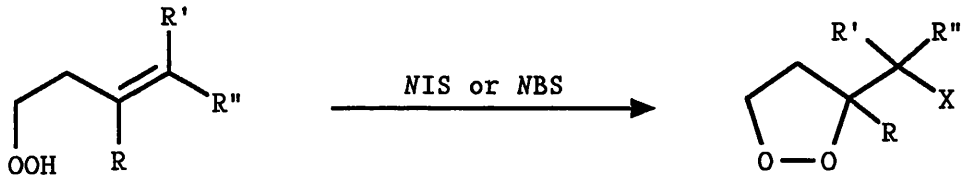
CHAPTER 2

CYCLOPEROXYCHLORINATION OF UNSATURATED HYDROPEROXIDES WITH TERT-BUTYL HYPOCHLORITE

2.1 INTRODUCTION

Previous work by Bloodworth and Curtis[1] has led to methods of producing 3-(1-halogenoalkyl)-1,2-dioxolanes, of the type shown in Scheme 1, by the cyclisation of unsaturated hydroperoxides.



1 : R = R' = R" = H

2 : R = Me. R' = R" = H

3 : R = R" = H. R' = Et

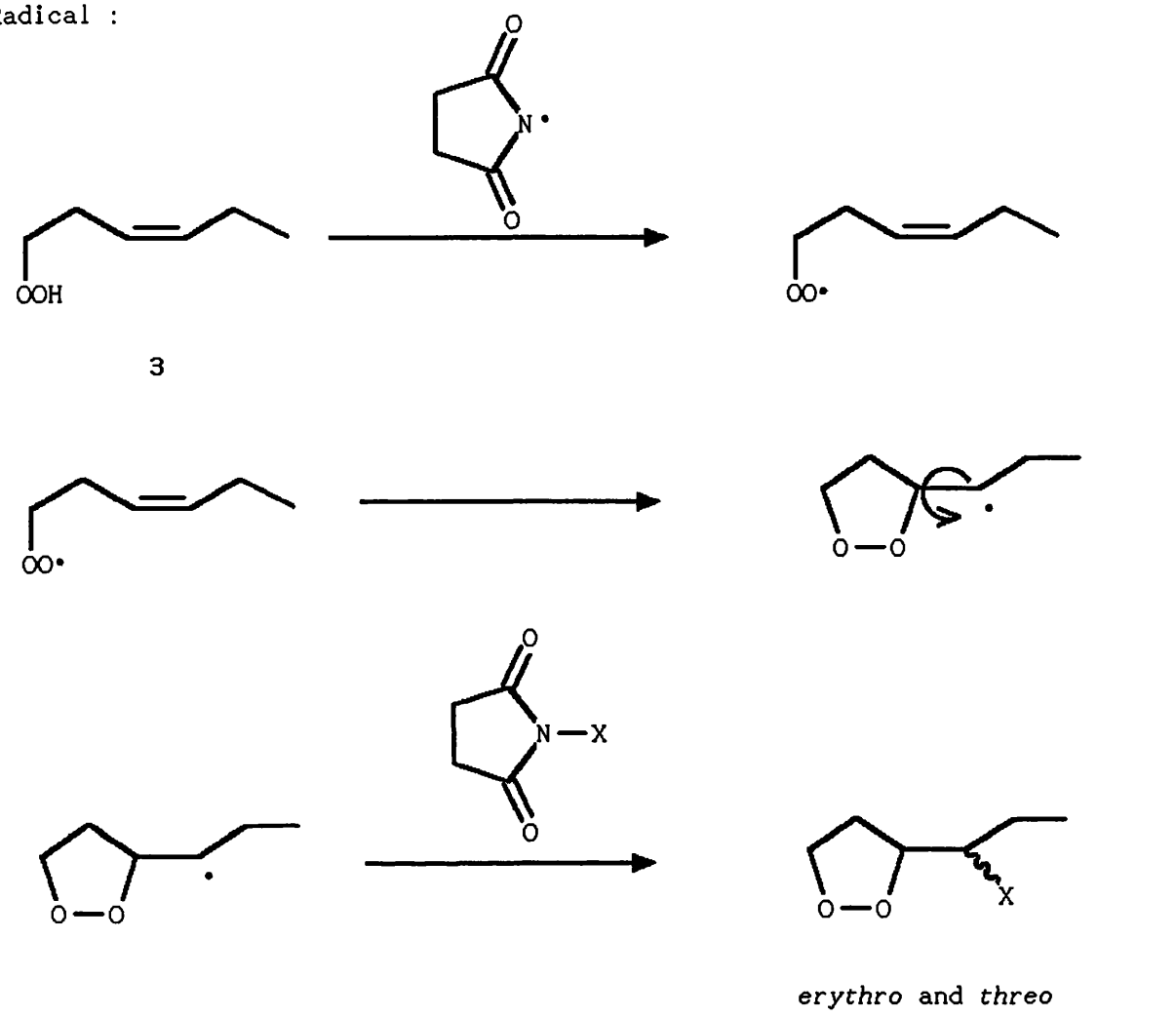
4 : R = R' = H. R" = Et

X = I, Br

Scheme 1

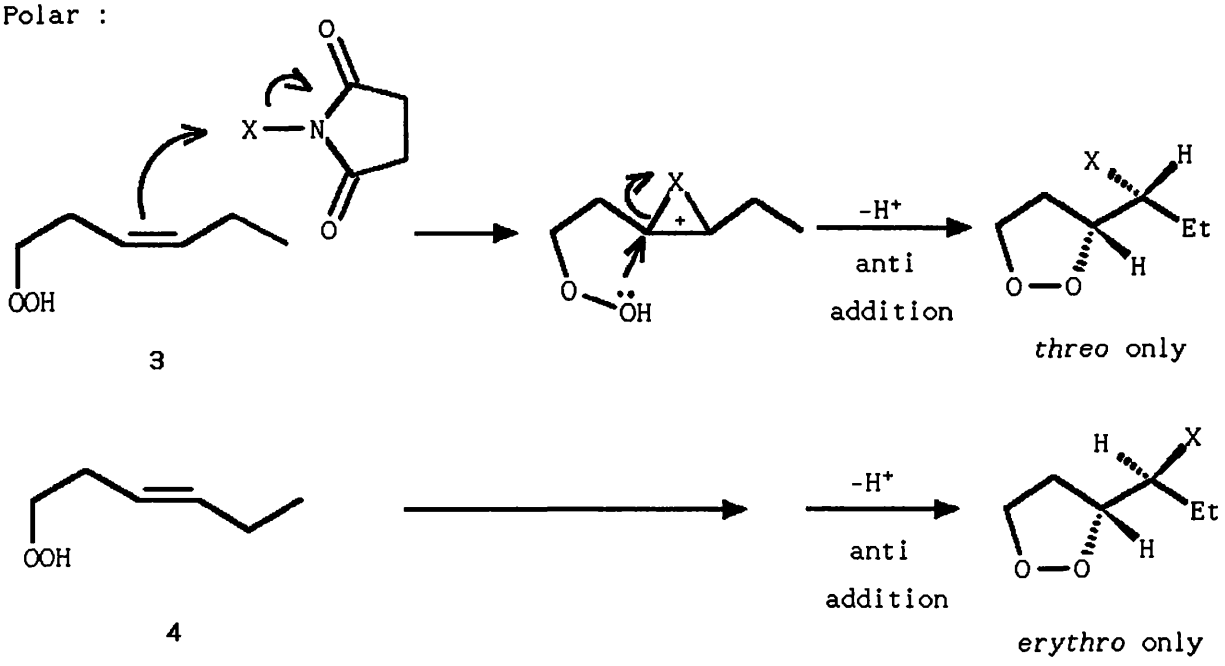
This involved treating the hydroperoxide with *N*-iodosuccinimide (*N*IS) or *N*-bromosuccinimide (*N*BS) in dichloromethane. The resulting dioxolanes were formed in around 50% yield. It was thought that these reagents would be sources of positive halogen atoms and therefore result in polar cyclisations of the hydroperoxides. The actual situation is in fact more complicated. When the two isomeric hydroperoxides *cis*-3-hexen-1-yl hydroperoxide (**3**) and *trans*-3-hexen-1-yl hydroperoxide (**4**) were treated with *N*IS, both produced an equimolar mixture of *erythro*- and *threo*-3-(1-iodopropyl)-1,2-dioxolane. This implies that both hydroperoxides are forming the products *via* a common intermediate, one in which the stereochemistry of the hydroperoxide is lost. This would be the situation if the cyclisation occurred *via* a radical mechanism. On the other hand, with *N*BS both hydroperoxides produced predominately one isomer due to the incursion of a polar mechanism in which there is stereospecific

Radical :



3

Polar :



3

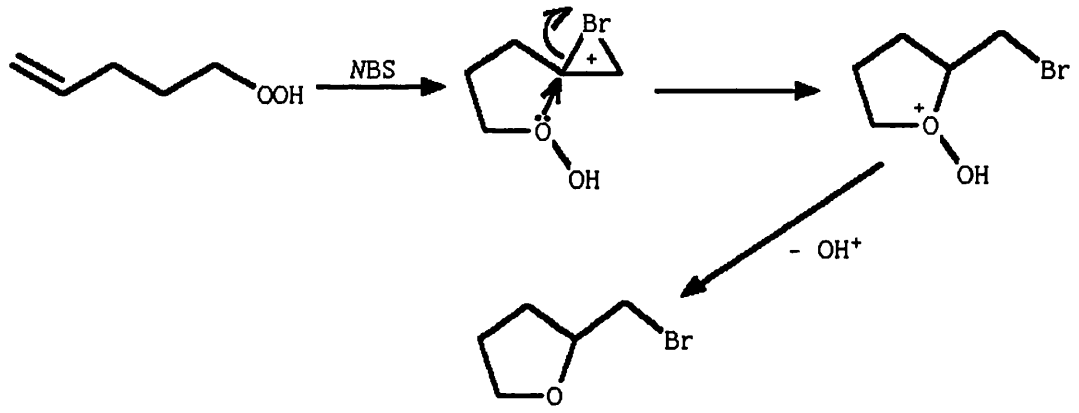
4

Scheme 2

anti-addition of bromine and the peroxy group across the double bond. This is summed up in Scheme 2.

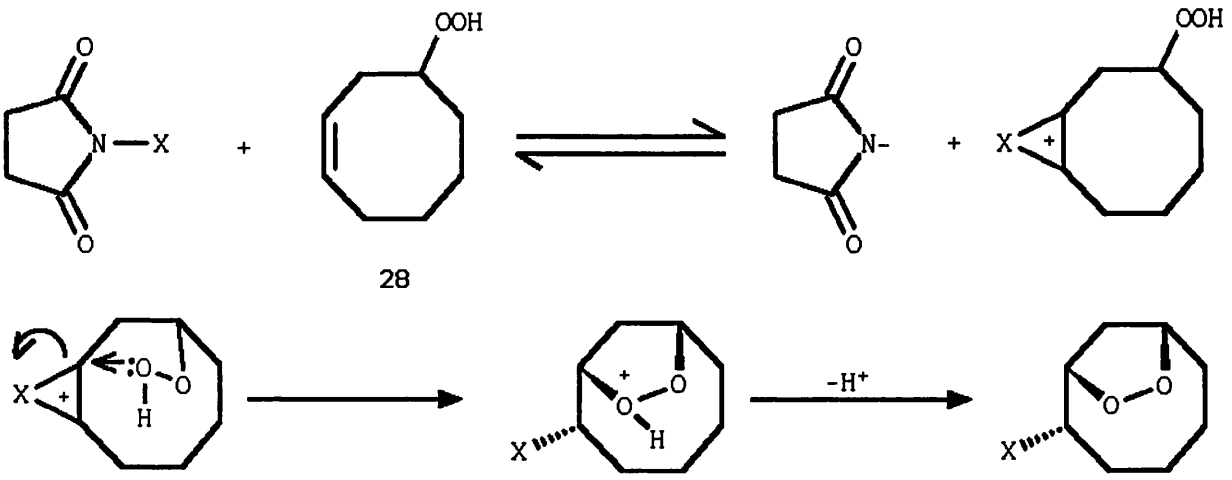
Further examples of cycloperoxyhalogenation were achieved by treating the same γ,δ-unsaturated hydroperoxides with molecular bromine and iodine in the presence of pyridine. This gave stereospecific cyclisation of **3** and **4**, although with bromine addition of the halogen across the double bond was a problem.

Attempts at forming halo-substituted 1,2-dioxanes by treating 4-penten-1-yl hydroperoxide with *N*IS and *N*BS were unsuccessful. This produced the corresponding tetrahydrofurans, probably *via* a *gem*-dialkyl peroxonium ion (Scheme 3).



Scheme 3

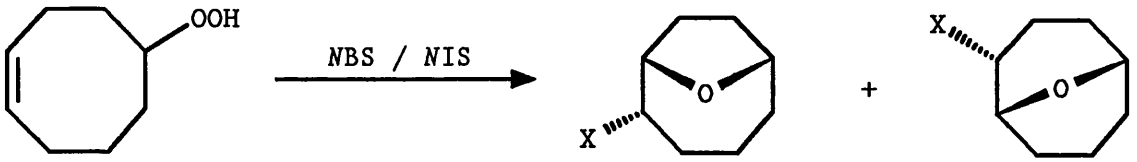
Spencer[2] extended this work to look at the reactions of cyclooctenyl hydroperoxides with these reagents. 3-Cyclooctenyl



Scheme 4

hydroperoxide (**28**) produced halo-substituted [5.2.1] bicyclic peroxides with both *N*BS and *N*IS, which he proposed were formed *via* polar cyclisation (Scheme 4).

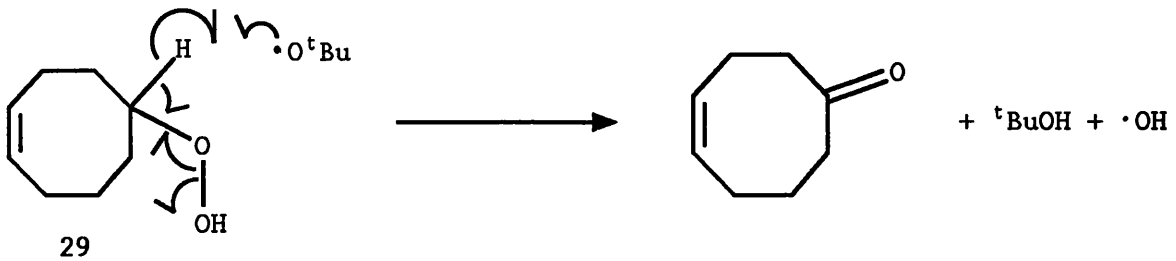
The reactions of the isomeric 4-cyclooctenyl hydroperoxide (**29**) with *N*BS and *N*IS produced the halo-substituted bicyclic ethers (Scheme 5)[3] which was rationalised *via* the intermediacy of a *gem*-dialkylperoxonium ion.[4] The [4.2.1] isomer was always favoured over the [3.3.1] isomer. This confirmed previous work done on this system by Bloodworth *et. al.*[5,6]



29 [4.2.1] [3.3.1]

Scheme 5

Both **28** and **29** also produced some cyclic ketones, particularly when the reactions were carried out in solutions of low polarity. This was attributed to competing radical reactions, as these were the major products found when these hydroperoxides were treated with *tert*-butoxyl radical sources (e.g. DBPO, di-*tert*-butyl peroxide).[2] Ketones can be formed *via* Russell disproportionation of peroxyl radicals, but this requires the formation of an equimolar amount of the corresponding alcohol. In fact much more ketone than alcohol was always found, so a mechanism involving direct attack of *tert*-butoxyl radicals on the hydroperoxide was proposed (Scheme 6).



29

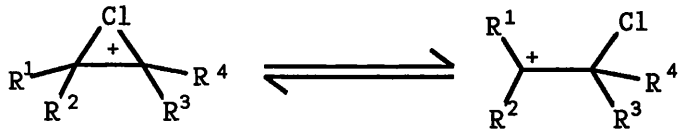
Scheme 6

However, treatment of unsaturated hydroperoxides with

N-halogenosuccinimides was found to be applicable only to the synthesis of bromo- and iodo-substituted dioxolanes. Attempts at forming chloro-substituted 1,2-dioxolanes with *N*-chlorosuccinimide were unsuccessful.

In our efforts to extend this work to include cycloperoxychlorination our attention turned instead towards *tert*-butyl hypochlorite (^{t}BuOCl) as a possible reagent. This reagent has been known to participate in both polar reactions, by providing a source of positive chlorine,[7] and in radical reactions, by providing both *tert*-butoxyl radicals and chlorine atoms.[8] If ^{t}BuOCl successfully produced the required chlorinated dioxolanes, it would then leave us with the question of which of the two possible mechanisms, shown in Scheme 7, was operating, and whether the mechanism could be changed by altering the conditions.

The polar cyclisation involves the addition of 'Cl^+' to the double bond of the hydroperoxide. This could either result in a bridged chloronium ion (as shown in Scheme 7) or a β-chloro substituted carbocation (Scheme 8). In general, it is found that the cyclic structure is the more stable form,[9,10] although ^{1}H nmr evidence indicates that for 1,1-disubstituted alkenes (e.g. **2**) the open-chain carbocation can be the preferred structure.[10] With bromine and iodine, the cyclic halonium ion is always the more stable.



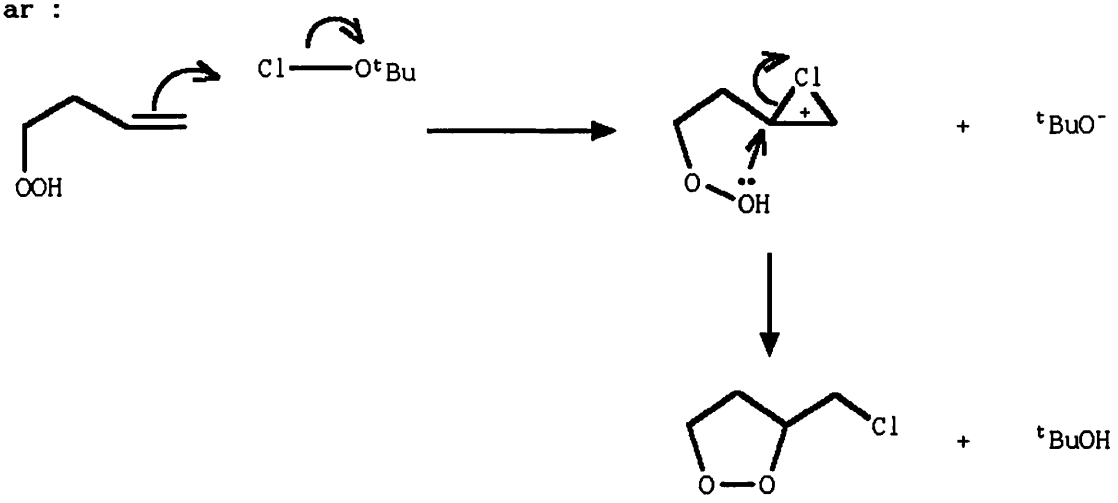
Scheme 8

Intermolecular peroxychlorination of double bonds using ^{t}BuOCl with either hydrogen peroxide or ROOH (where R is generally ^{t}Bu) has been reported to produce β-chloro alkyl hydroperoxides and dialkyl peroxides (eq. 1).[11] However, the only example of an intramolecular

$$R^1R^2C{=}CHR^3 + ROOH + {}^t\text{BuOCl} \longrightarrow R^1R^2C(OOR)CH(Cl)R^3 \qquad (1)$$

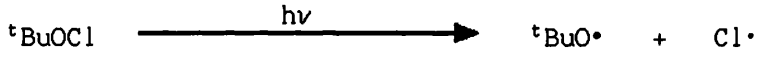
R = H, ^{t}Bu

Polar :

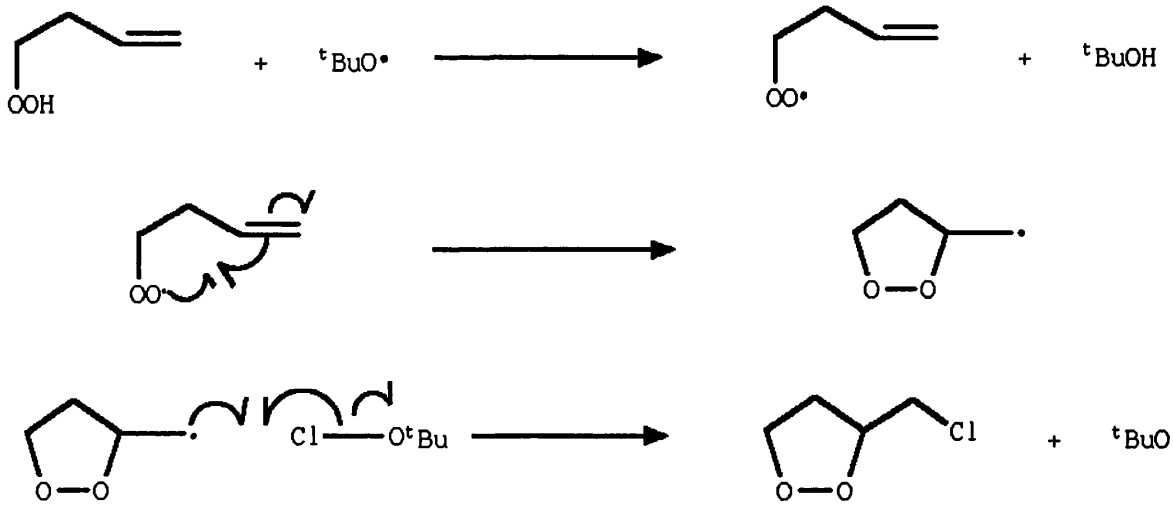


Radical :

Initiation



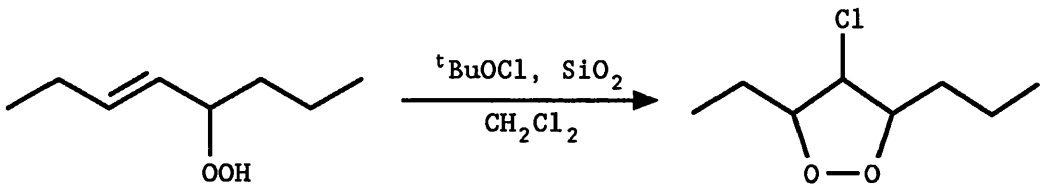
Propagation



Termination

Scheme 7

reaction of the type we are interested in is work done by Courtneidge,[12] where ^{t}BuOCl in the presence of silica was used to perform a 5-*endo-trig* cyclisation on an allylic hydroperoxide (Scheme 9). He found the reaction to be very unpredictable, and to produce



Scheme 9

the desired product in low yield as an unassignable mixture of diastereomers. There are no reports in the literature though of the syntheses of any 3-(1-chloroalkyl)-1,2-dioxolanes.

We were interested in first investigating the reaction of ^{t}BuOCl with the simple hydroperoxides **1** and **2**, then looking at the two isomeric 3-hexen-1-yl hydroperoxides (**3** and **4**) with the view of obtaining mechanistic information. We also wished to study the two cyclooctenyl hydroperoxides (**28** and **29**) to see if they would form bicyclic products.

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of Starting Materials

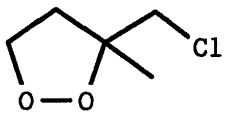
tert-Butyl hypochlorite was synthesised from *tert*-butanol, acetic acid and bleach using the method of Walling and Mintz.[13]

The acyclic hydroperoxides were synthesised from the corresponding alcohols, *via* the mesylate, according to the method of Mosher and Williams.[14] Although the mesylate could be formed from the alcohol in almost quantitative yield, the formation of the hydroperoxides from the mesylates was found to be problematical. With the longer chain hydroperoxides (**3**) and (**4**) this step went in around 30% yield, but for the shorter chain compounds (**1**) and (**2**) the yield was less than 10%. It was thought that one problem could be the solubility of the low molecular weight hydroperoxides in water, which meant that material was being lost in the long procedure of purification using base extraction. To try and counteract this we altered the work-up procedure so that the crude reaction mixture was subjected to continuous liquid-liquid extraction using diethyl ether, and the hydroperoxide was purified by column chromatography. This way, the yield of **2** was increased from 8% to 25%, but this method still only produced **1** in 11% yield. In all these reactions significant amounts of the corresponding dialkyl peroxides and unreacted mesylates were recovered.

The cyclooctenyl hydroperoxides were synthesised from the available *N'*-tosylhydrazones by sodium cyanoborohydride reduction[15] to the *N*-alkyl-*N'*-tosylhydrazines, followed by conversion to the hydroperoxides using the conditions of Caglioti *et. al.*[16,17] (*cf.* Chapter 1; Scheme 4). This method produced 3-cyclooctenyl hydroperoxide (**28**) cleanly in 46% yield over the two steps. With the other isomer (**29**) the reduction step was much less clean producing a major, unidentified, by-product, but reaction of the crude tosylhydrazine produced pure **29** in an overall yield of 30%.

2.2.2 Acyclic Systems

The initial investigations were carried out using 3-methyl-3-buten-1-yl hydroperoxide (**2**). In a preliminary experiment to investigate the feasibility of this reaction neat *tert*-butyl hypochlorite (^{t}BuOCl) (2.5 eq.) was added to a concentrated solution of **2** in $CDCl_3$. This led to a very vigorous and exothermic reaction, after which it was shown by ^{1}H nmr spectroscopy (disappearance of alkene signals), that none of the starting material remained. After removal of *tert*-butanol and unreacted ^{t}BuOCl at water pump pressure the crude material was examined by ^{13}C nmr spectroscopy. This showed there to be two major products, 3-(chloromethyl)-3-methyl-1,2-dioxolane (**5**) and 3,3-di(chloromethyl)-1,2-dioxolane (**6**) in the ratio 1.5:1 (**5:6**). These two compounds could be separated by HPLC, and identified by ^{1}H and ^{13}C nmr spectroscopy and mass spectrometry.



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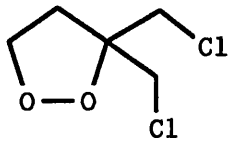


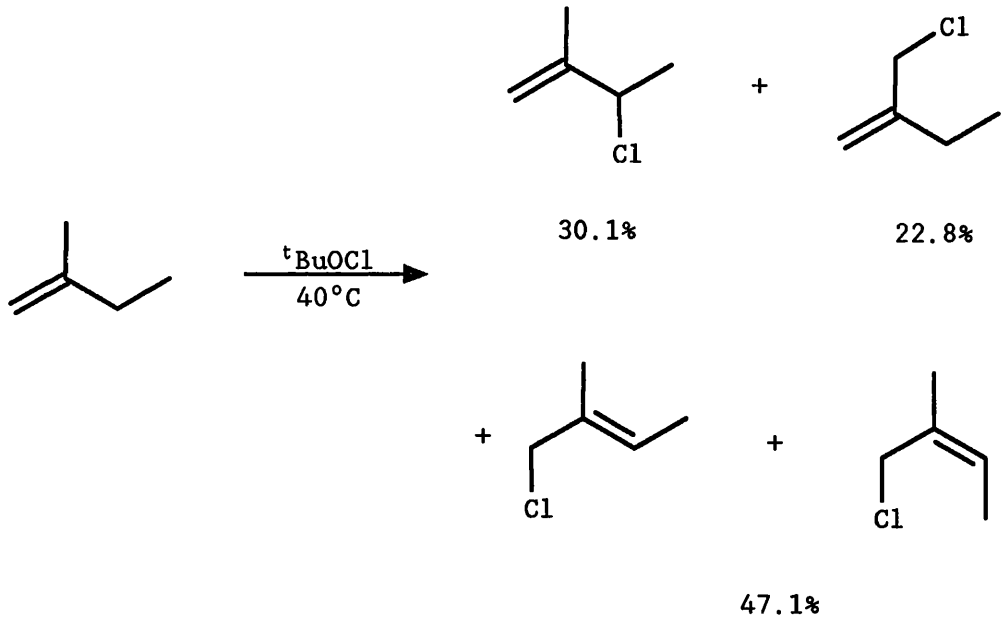
6

The above reaction was repeated, with the exception that the reagents were mixed with cooling in an ice bath. On this occasion no violent reaction occurred. After warming to room temperature, the ^{1}H nmr spectrum again showed that reaction was complete. There was no significant difference in the product distribution from the original reaction. In view of the less vigorous nature displayed it was decided that in future, mixing of hydroperoxides and ^{t}BuOCl should always be done in the cold.

The production of the mono-chlorinated dioxolane (**5**) from these reactions is easily explained by either of the mechanisms in Scheme 7. The only question mark was about the initiation step, if a radical reaction was occurring. The very rapid and vigorous reaction observed would tend to suggest that simple photolysis of the O-Cl bond is not occurring, but that there is some interaction between the hydroperoxide and the hypochlorite groups.

The formation of the dichlorinated dioxolane (**6**) was unexpected. This could be formed either by chlorination of dioxolane **5**, or by chlorination of hydroperoxide **2** at the allylic methyl group,

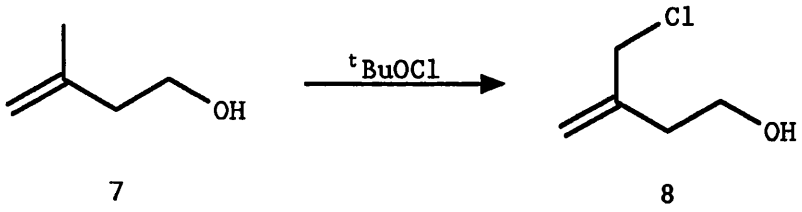
followed by cyclisation in the normal manner. The second possibility would imply a highly regioselective chlorination, as no other dichlorinated dioxolanes were found. This would be contrary to the results reported for the corresponding hydrocarbon, 2-methyl-1-butene, which gives a mixture of four isomers[18] (Scheme 10). Chlorination of the methyl group with no double bond shift is



Scheme 10

in fact the least favoured product.

As a model, the corresponding alcohol (**7**) was treated with ^{t}BuOCl in $CDCl_3$. The reaction was slow, taking about four hours to go to completion. However, the ^{13}C nmr spectrum of the crude showed five strong signals, which could be assigned to the alcohol (**8**) (Scheme 11). Why there should be such a strong tendency to form this



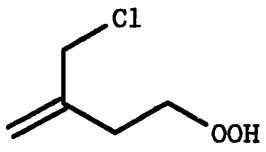
7 8

Scheme 11

isomer was unclear. Treatment of an equimolar mixture of **7** and *tert*-butyl hydroperoxide with ^{t}BuOCl produced an almost instantaneous reaction to produce predominantly a mixture of **8** and unreacted **7**. These two experiments suggest that the dichloro product (**6**) could

indeed be formed by regioselective chlorination of **2** followed by cyclisation, and confirm our suspicions about there being a very rapid reaction between ^{t}BuOCl and hydroperoxides.

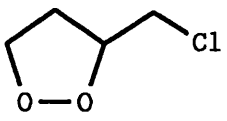
In an attempt to reduce the amount of **6** being formed, hydroperoxide **2** was treated with 1 (rather than 2.5) eq. of ^{t}BuOCl in $CDCl_3$. This did increase the ratio of **5**:**6** from 1.5:1 to about 2.2:1 (as estimated by ^{13}C nmr spectroscopy). Separation of the crude material by column chromatography led to the isolation of an impure sample of the chlorinated hydroperoxide **9**. This provides strong



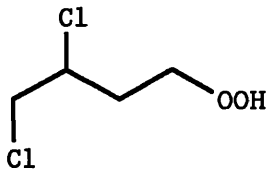
9

evidence that **6** is formed by chlorination of **2** before cyclisation.

We hoped therefore that 3-buten-1-yl hydroperoxide (**1**), which does not have an allylic methyl group, would cyclise much more cleanly. What we found, using 1 eq. of ^{t}BuOCl, was that the reaction was slightly cleaner inasmuch as the desired product 3-chloromethyl-1,2-dioxolane (**10**) was by far the major product. The yield after chromatography though was only 17%; poor recovery of the pure dioxolanes was a problem throughout. The main by-product was the dichlorohydroperoxide (**11**), which could only be isolated as a mixture containing about 10% of unreacted **1**. Again, the structure of **10** was confirmed by ^{1}H and ^{13}C nmr spectroscopy and mass spectrometry. The identity of **11** was proved by ^{13}C and ^{1}H nmr spectroscopy, backed up with spin-spin decoupling experiments.



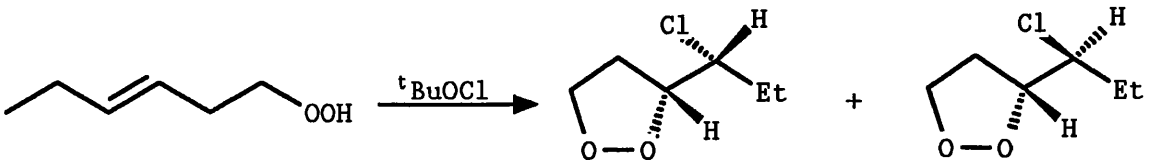
10



11

A further example of the cyclisation was provided by the reaction of *trans*-3-hexen-1-yl hydroperoxide (**4**) with ^{t}BuOCl under similar conditions. Again the reaction was not at all clean, but did produce the two isomeric dioxolanes *erythro*-3-(1-chloropropyl)-

1,2-dioxolane (**12**) and *threo*-3-(1-chloropropyl)-1,2-dioxolane (**13**) in a ratio of approximately 2:1 and combined yield of 17% (Scheme 12).



threo *erythro*

13 12

Scheme 12

The ^{13}C nmr spectrum of the major product corresponded with what was later shown to be the *erythro* isomer. The minor products were not isolated, but peaks in the ^{13}C nmr spectrum of the crude material were consistent with those expected for addition of chlorine across the double bond of the hydroperoxide. The structures of the two dioxolanes were further proved by ^{1}H nmr spectroscopy and mass spectrometry. The stereochemical scrambling observed in this system indicates that there is a significant radical contribution to the cyclisation.

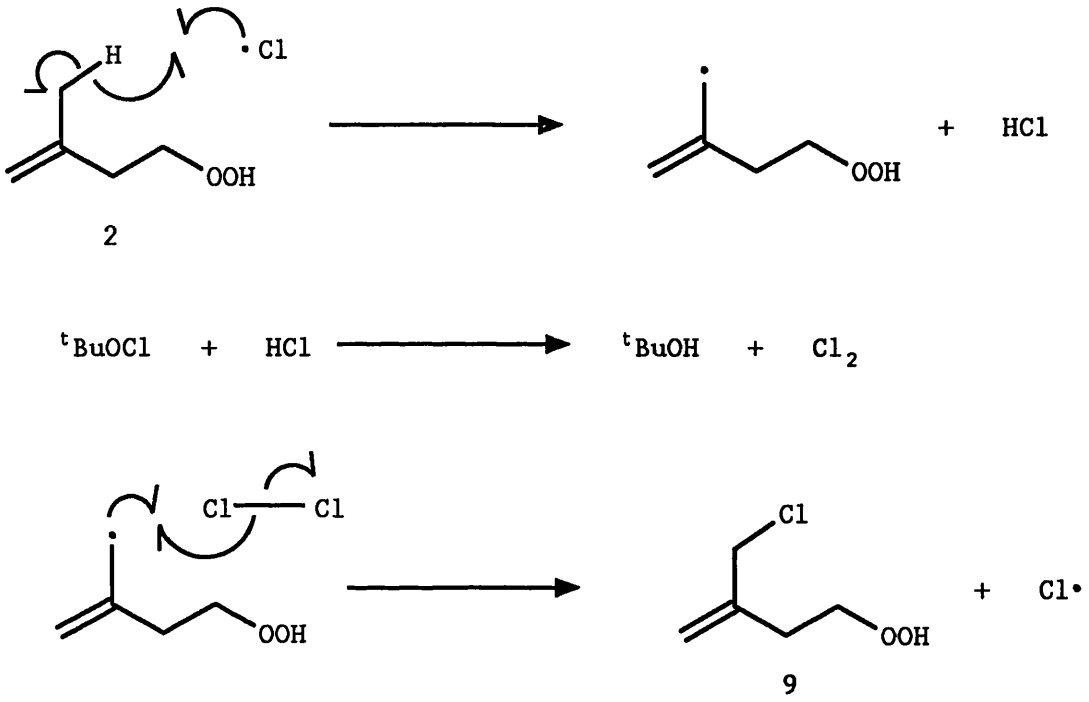
To investigate this further, the effect of a radical inhibitor on these reactions was looked at. The inhibitor chosen was 2,6-di-*tert*-butyl-4-methylphenol (BHT). When 3-methyl-3-buten-1-yl hydroperoxide (**2**) was treated with ^{t}BuOCl in dichloromethane in the presence of 0.1 eq. BHT and stirred for 2 hours, mainly unreacted starting material was recovered. In a further investigation with the same hydroperoxide, 2 eq. ^{t}BuOCl and 0.05 eq. BHT, it took some 26 hours for all the starting material to disappear (monitored by TLC). This provides strong evidence that under these conditions the reaction is almost entirely radical.

Rather than pursue these mechanistic studies immediately, it was decided first to try and optimise the conditions for the formation of 1,2-dioxolanes.

To this end, we needed to know the mechanism by which the by-products were being formed. It was decided to look specifically at hydroperoxide **2** with the aim of trying to increase the ratio of the mono-chlorinated dioxolane (**5**) to the di-chlorinated dioxolane (**6**) by inhibiting the formation of the chloro-hydroperoxide (**9**), the

precursor of **6**.

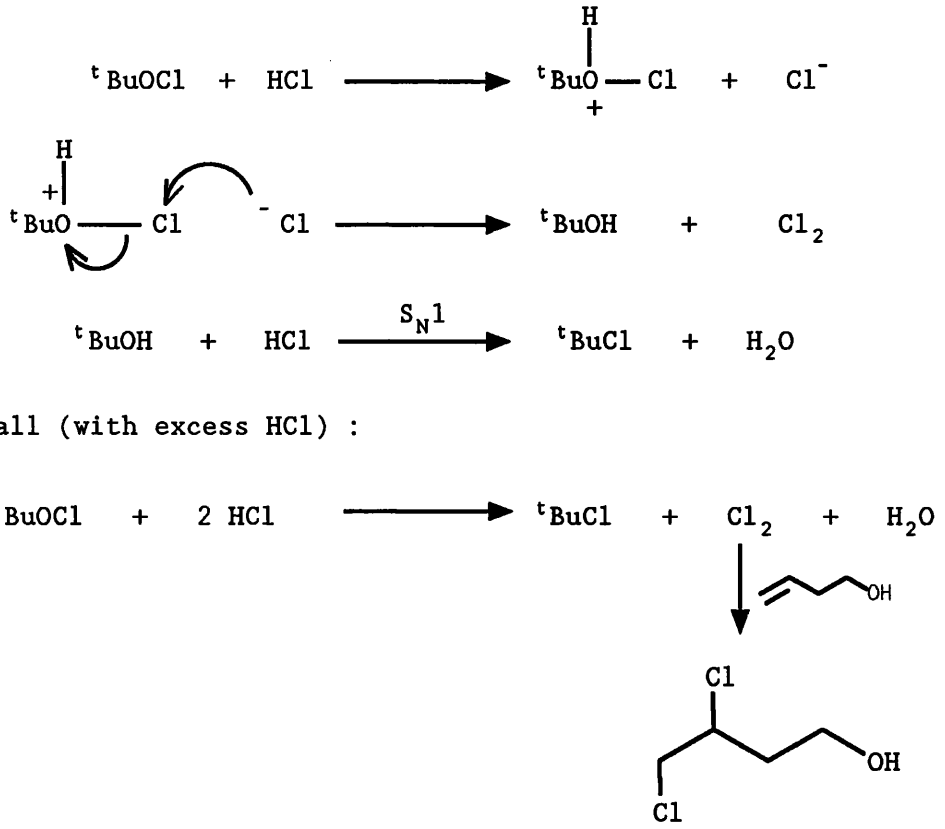
It is known from previous work that when *tert*-butoxyl radicals react with unsaturated hydroperoxides, they will almost exclusively abstract the hydroperoxy hydrogen in preference to an allylic hydrogen atom.[19] We supposed therefore that **9** was being formed by a chlorine atom carried chain with the propagation steps outlined in Scheme 13.



Scheme 13

We confirmed that the second step in the scheme occurs rapidly by bubbling hydrogen chloride gas through a solution of ^{t}BuOCl in $CDCl_3$. The resultant bright yellow solution was shown to contain chlorine by the addition of an alkene (3-buten-1-ol), which immediately decolourised the solution. The ^{13}C nmr spectrum showed that the alkene had been converted to the corresponding *vic*-dichloride (**15**) and, due to there being an excess of hydrogen chloride, the ^{t}BuOCl had been converted to *tert*-butyl chloride. The series of reactions is shown in Scheme 14.

We first looked at the effect of concentration on product distribution. This follows a report in the literature where chlorine atom carried chains were suppressed by diluting the solution.[20] The results are summarised in Table 1. The figures are product ratios estimated by averaging out ^{13}C peak heights in the nmr spectrum of the crude product. What we see is that dilution appears to retard



Scheme 14

the cyclisation of the chlorinated hydroperoxide **9**. The important figures though are those in the bottom row, which are a measure of the extent to which unwanted allylic chlorination competes with desired cycloperoxychlorination of the starting hydroperoxide (**2**). What they show, is that carrying out the reaction in a more dilute solution has little effect in reducing the extent of the side reaction.

We next investigated the possibility of using a suitable chlorine atom trap to remove the chain carrying species. It is known that the addition of chlorine atoms to chlorinated ethylenes is very rapid,[21] so 1 eq. of *cis*-1,2-dichloroethene was added to the reaction mixture. With 1.4 eq. ^{t}BuOCl the ratio of **5**:**6** was very high at 6.5:1, but as before there was a significant amount of **9** remaining, and the important ratio of **5**:(**6**+**9**) was only increased to 2.2:1. Addition of larger quantities of the alkene had no significant effect. We concluded that this was not an effective way of preventing the formation of **9**.

An alternative method of disrupting the chain was needed. The other obvious possibility was removal of the hydrogen chloride. This

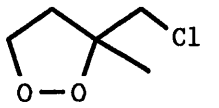
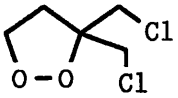
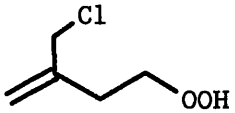
Product	2.2 eq ^{t}BuOCl 1.5 M	1.0 eq ^{t}BuOCl 1.5 M	1.0 eq ^{t}BuOCl 0.05 M
 5	1.5	2.2	6.0
 6	1.0	1.0	1.0
 9	0	0.8	3.0
Ratio 5 : (6 + 9)	1.5 : 1	1.2 : 1	1.5 : 1

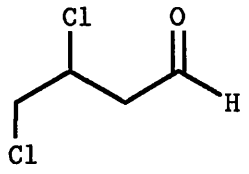
Table 1

required the use of a base which was not so strong as to decompose the hydroperoxide, and one which would not readily react with ^{t}BuOCl. A base thought to fit these requirements was pyridine.

Again using hydroperoxide **2**, the reaction was repeated with 1.4 eq. ^{t}BuOCl in dichloromethane, in the presence of 0.7 eq. pyridine. The effect now was much more marked. The ratio **5:6** was increased to 4:1 (with no **9** left unreacted) and the reaction was very clean. The yields of crude **5** and **6** were 54% and 13% respectively. The addition of larger amounts of pyridine was investigated, but was found to have no noticeable effect on the product distribution.

With this encouragement, we studied the effect of using these conditions with the other hydroperoxides. The first to be re-examined was 3-buten-1-yl hydroperoxide (**1**). The reaction was much less clean than it was for hydroperoxide **2**, but the chlorinated dioxolane (**10**) was still by far the major product. Comparing it to the corresponding reaction in the absence of pyridine, there is no real increase in yield, the main difference is in the identity of the by-products. The ^{13}C nmr spectrum of the crude product showed, apart from the signals due to **10**, four strong peaks at δ 47.46, 48.18, 53.06 and 197.65 ppm. This by-product we assigned as 3,4-dichlorobutanal (**14**). The ratio **10:14** was about 1.5:1. The aldehyde however could not be isolated, possibly due to

polymerisation on the silica column. Column chromatography did however enable the isolation of two other very minor products, 3,4-dichlorobutan-1-ol (**15**) and 4-chloro-2-butenal (**16**).



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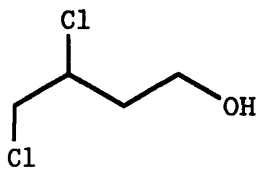

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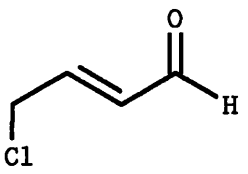
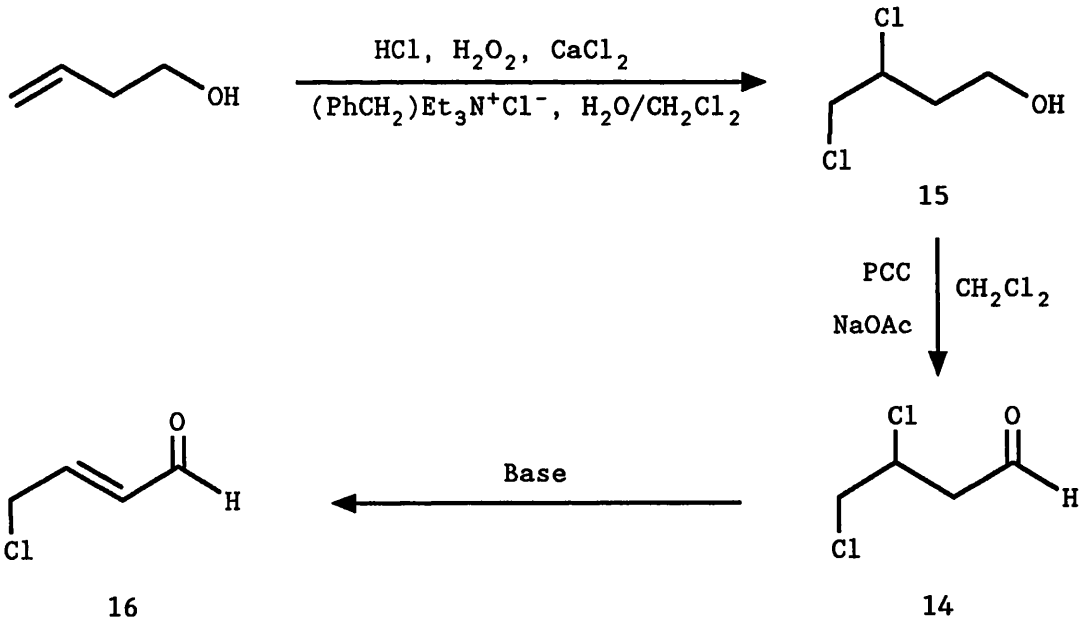


16

Although ^{1}H nmr data were available for **15**[22] and **16**,[23] we required further proof of their identity, in addition to confirming the structure of **14**. The independent syntheses of these compounds were attempted using the route shown in Scheme 15.



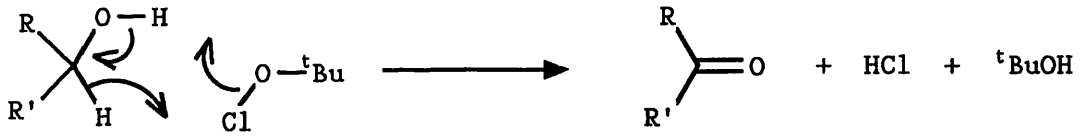
16 14

Scheme 15

The first step, using the conditions of Olah *et. al.*,[24] presented no problems, producing **15** in 45% yield after chromatography. The oxidation, using pyridinium chlorochromate (PCC)[25] was not so successful. The ^{13}C nmr spectrum of the crude product showed 16 lines of approximately equal intensity. These included signals due to **16** and also four peaks with chemical shifts identical to those of the unknown aldehyde. We were still faced with the problem of the purification of **14**. We decided to try and isolate **14** as its 2,4-dinitrophenylhydrazone, so both the crude product from the PCC reaction and that from the reaction of **1** with $^{t}BuOCl$ and

pyridine were treated with acidic 2,4-dinitrophenylhydrazine in methanol.[26] The ^{13}C nmr spectra of the two products were identical, but appeared to be just the hydrazone derived from the α,β-unsaturated aldehyde (**16**). As a final attempt to gain evidence for the structure, more of the crude product from the PCC reaction was treated with sodium acetate and pyridine in dichloromethane to try and convert **14** into **16**. This caused the four signals we had assigned to **14** to disappear as we had hoped, but did not intensify those due to **16**. However, as **16** itself could be expected to be base sensitive and be consumed by the sodium acetate, we remain confident of the identity of **14**.

How the aldehyde is formed from the hydroperoxide is not clear. Base induced dehydration would not be expected, and indeed a control reaction between 3-buten-1-yl hydroperoxide (**1**) and pyridine showed that the two did not react. A ^{t}BuOCl/pyridine system has been used to oxidise secondary alcohols to ketones.[27] The mechanism, shown in Scheme 16, involves a cyclic transition state in which the hydroxy proton is transferred to the ^{t}BuOCl to form *tert*-butanol. If the

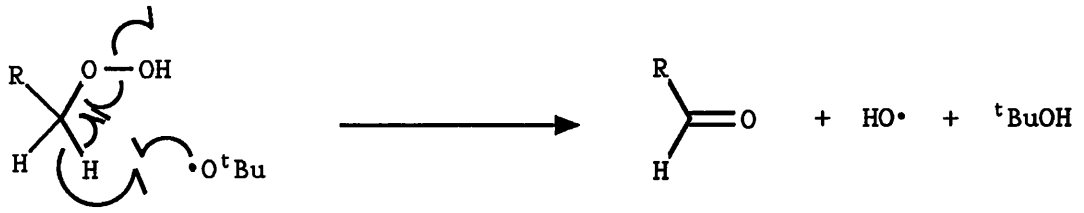


Scheme 16

alcohol was replaced with a hydroperoxide the mechanism would involve the transfer of $[OH]^{+}$ to the ^{t}BuOCl to form *tert*-butyl hydroperoxide. This seems unlikely, but the formation of hydrogen chloride does allow the production of chlorine in the reaction mixture, which is necessary to explain the chlorination of the double bond.

An alternative explanation is a radical mechanism, such as that shown in Scheme 17, with the hydroxyl radical propagating a chain (*cf.* Scheme 6). This does not, however, explain why aldehydes are not produced in the absence of pyridine.

With these conditions further investigations were made into mechanistic aspects of the reaction. The reactions of the two isomeric hydroperoxides *cis*-3-hexen-1-yl hydroperoxide (**3**) and *trans*-3-hexen-1-yl hydroperoxide (**4**) with ^{t}BuOCl and pyridine were examined.



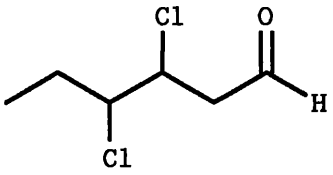
Scheme 17

The reactions of both isomers were very similar. They both produced the two dioxolanes (**12**, *erythro*) and (**13**, *threo*) as the major products and both produced one main by-product which was the same in both cases. The big difference was in the ratio of the two dioxolanes. The ratio of **12:13** was 30:70 for the *cis* hydroperoxide and 75:25 for the *trans* isomer. It should be noted that this ratio is not greatly different from that measured for the reaction in the absence of pyridine (all ratios are based on average peak heights in the ^{13}C nmr spectrum of the crude product). These cyclisations therefore occur with preferential *anti*-addition of chlorine and the peroxy group across the double bond, but still with significant stereochemical scrambling. This would imply that both polar and radical mechanisms are contributing to the cyclisation.

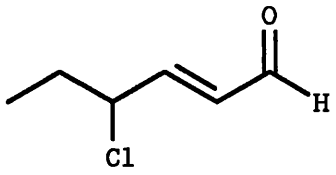
We are assuming here that the polar cyclisation occurs *via* a bridged chloronium ion, resulting in stereospecific *anti*-addition of chlorine and the peroxy group across the double bond. Literature evidence[9] suggests that for a symmetrically substituted alkene the cyclic chloronium ion is more stable than the open-chain form (Scheme 8), which would make our assumption a reasonable one.

The major by-product from these reactions, as seen in the ^{13}C nmr spectrum of the crude product, is what appears to be a single diastereomer of 3,4-dichlorohexanal (**17**), with signals at δ 10.15, 27.99, 48.43, 56.91, 66.55 and 197.84 ppm. The formation of **17** from **3** is exactly parallel to the production of **14** from **1**. Similarly, small signals at δ 131.98, 154.02 and 193.01 ppm suggest a trace amount of the corresponding α,β-unsaturated aldehyde, 4-chloro-2-hexenal (**18**). As with **14**, isolation of **17** by chromatographic means proved impossible.

Attempts at probing these systems with BHT produced ambiguous results. Even in the presence of 0.3 eq. BHT the reaction seemed to be almost instantaneous, as followed by TLC, suggesting that a polar



17



18

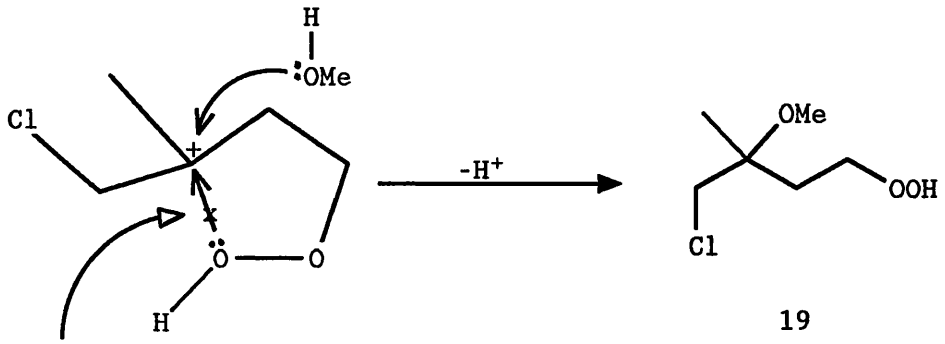
route to the dioxolanes existed. However, most of the BHT was consumed, and the expected increase in stereospecificity of the reaction was not observed. Independent experiments showed that ^{t}BuOCl reacts fairly readily with BHT on its own, so direct reaction of the two could be the cause of these confusing results.

If two mechanisms are competing it is often possible to alter the balance between the two by altering the temperature of the reaction. Hence the reaction of **3** with ^{t}BuOCl and pyridine was repeated at -35°C. This did indeed result in a change in product distribution, increasing the ratio of **12:13** from 30:70 at room temperature to 10:90. This implies a greater polar contribution to the mechanism, possibly due to a decrease in the rate of the initiation process of the radical reaction. It must be noted however, that we cannot rule out the possibility of rotation about the C-C bond in a radical intermediate being restricted at lower temperature, thus giving greater stereospecificity. Lowering the temperature does not, unfortunately, reduce the amount of the dichlorinated aldehyde (**17**) formed. This may point to a polar mechanism for the formation of **17**.

What we now wanted to look at was ways of improving the yields of the required products by working in different solvents. In particular looking at improving the ratio of the mono-chlorinated dioxolane (**5**) to the dichlorinated dioxolane (**6**) in the reaction of 3-methyl-3-buten-1-yl hydroperoxide (**2**) with ^{t}BuOCl, and increasing the stereospecificity of the cyclisations of the 3-hexen-1-yl hydroperoxides **3** and **4**. It was hoped that both these aims could be accomplished by using more polar solvents.

Initially, we looked at the reaction of **2** with 1 eq. ^{t}BuOCl in methanol. The reaction now changed dramatically. The ratio of **5:6:9** was now 4.5:1:9. So working in methanol in fact increases the degree of allylic chlorination. However, the major product was 4-chloro-3-methoxy-3-methylbut-1-yl hydroperoxide (**19**; 44%) corresponding to

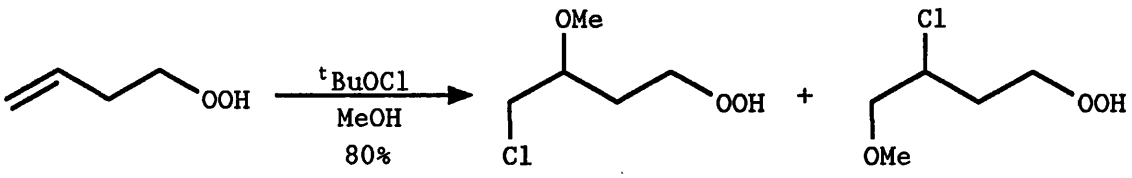
intermolecular attack by methanol on the intermediate carbocation (see dicussion below), in preference to intramolecular attack by the peroxide group, as shown in Scheme 18. Increasing the concentration



Scheme 18

of **2** in this reaction from 0.05M to 1.4M increased the amount of dioxolanes formed at the expense of **19**, but the reaction was not at all clean, and of no synthetic value.

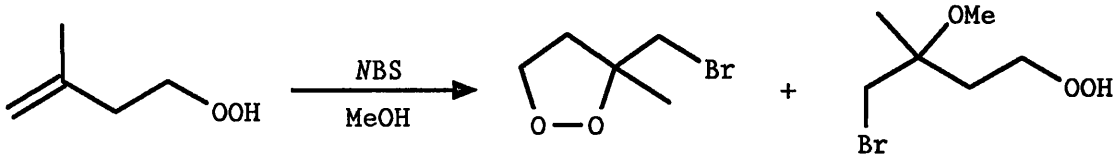
The regioselectivity of the addition can easily be explained by assuming that addition of 'Cl^{+}' to the 1,1-disubstituted alkene leads to a β-chloro substituted carbocation,[10] with the positive charge residing on the tertiary carbon atom. The high reactivity of this species relative to a chloronium ion results in there being no selectivity with regard to the nature of the attacking nucleophile. Hence, the cation is trapped by the solvent, which is present in much greater concentration than the hydroperoxide group. In contrast, under identical conditions, 3-buten-1-yl hydroperoxide (**1**) gives both regioisomers (**20** and **21**) (Scheme 19). This reflects the greater tendency of a mono-substituted alkene to form a cyclic chloronium



Scheme 19

ion, which allows attack of the solvent to occur at the less hindered primary carbon.

To investigate whether these intermolecular addition products are general for other electrophiles, a comparable reaction of **2** with *N*-bromosuccinimide in methanol was tried (Scheme 20). This time the



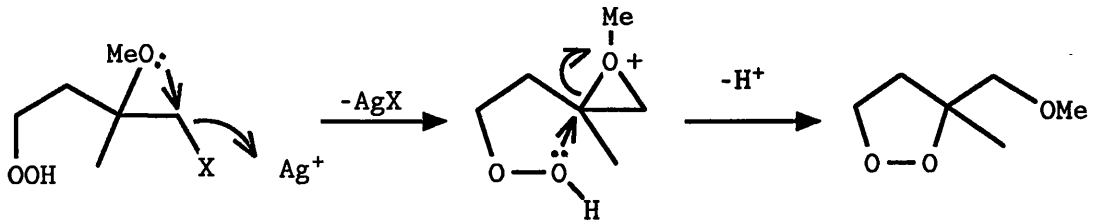
2 22 : 23

3 : 1

Scheme 20

expected dioxolane was the major product. This must be due to the fact that a bromonium ion is always found to be more stable than a β-bromo substituted carbocation,[10] due to the greater ability of bromine compared to chlorine to accommodate a positive charge. Consequently, the intermediate will be less reactive than that obtained with ^{t}BuOCl, and therefore more selective.

Attempts at cyclising hydroperoxides **19** and **23** by treatment with a suspension of silver trifluoroacetate in dichloromethane were unsuccessful. It was hoped that methoxymethyl substituted dioxolanes might be formed *via* the mechanism shown in Scheme 21, but all that was recovered was unreacted starting material.



X = Cl (19)
Br (23)

Scheme 21

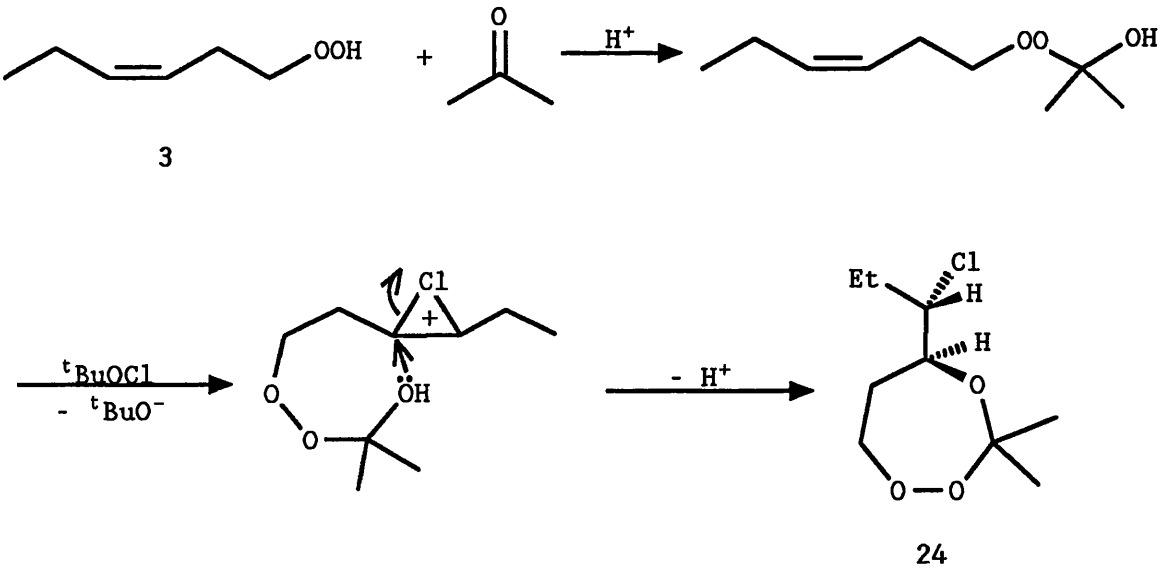
Changing the solvent from methanol to the much less nucleophilic *tert*-butanol was not successful. The reaction with **2** produced several products, the major one in fact being the chlorinated hydroperoxide (**9**), with little, if any, of either of the

two dioxolanes **5** or **6** being formed.

The next solvent we turned our attention to was acetone. When **2** was stirred with ^{t}BuOCl in acetone for two hours three major products were formed. They were the two dioxolanes which were formed in the ratio 4:1 (**5**:**6**), and an unkown by-product. The addition of 1 eq. pyridine to the reaction mixture reduced the level of impurities and further increased the ratio of **5**:**6** to 5.5:1. We took this as an indication that in acetone the chlorination reactions are suppressed, due to more favourable polar reactions occurring in this solvent.

Further evidence for the increased polar nature of the reaction in acetone was obtained by looking at the reaction with the 3-hexen-1-yl hydroperoxides (**3** and **4**) in the presence of pyridine. In both cases the cyclisation occurred with about 90% *anti*-addition, compared with only around 75% in dichloromethane. This high stereospecificity confirms that the reaction is now largely polar and provided confirmation of the assignment of *erythro* and *threo* to the two isomers **12** and **13**.

A significant by-product from the reaction with hydroperoxide **3** was isolated in reasonable purity by HPLC. This was assigned as *threo*-5-(1-chloropropyl)-3,3-dimethyl-1,2,4-trioxepane (**24**) which would be formed by the mechanism indicated in Scheme 22. Evidence



Scheme 22

for the structure was provided by ^{13}C nmr spectroscopy and high resolution mass spectrometry.

It seems surprising that the 7-*exo* cyclisation to form **24**

should occur to such a degree, when a very favourable 5-*exo* cyclisation to form the dioxolane is also available. Indeed, as will be discussed in Chapter 4, subsequent attempts at making 1,2,4-trioxepanes by this methodology were unsuccessful; only 1,2-dioxolanes were formed.

The *trans* isomer of the hydroperoxide (**4**) appeared to produce a similar product, presumably the *erythro* isomer, but to a lesser degree. The by-product from hydroperoxide **2** may well, judging by its ^{13}C chemical shifts in the crude material, be a 1,2,4-trioxepane as well. These types of compounds have been made previously, though not by this method, and with different substitution patterns.[28] The use of similar methods for the synthesis of 1,2,4-trioxanes, the corresponding 6-membered ring compounds, is discussed in Chapter 4.

In an independent experiment, it was confirmed that ^{t}BuOCl and acetone do not readily react. On the addition of some *tert*-butyl hydroperoxide a reaction does occur, but none of the signals in the ^{13}C nmr spectrum of the material produced correspond with any peaks observed in any of the alkenyl hydroperoxide reactions in acetone.

Inhibition experiments using hydroperoxide **2** with BHT confirm that the reaction can go by a polar mechanism under these conditions. The starting hydroperoxide is rapidly consumed even in the presence of 0.3 eq. BHT. This compares with the strongly inhibiting effect of BHT in dichloromethane. The ratio of **5** to **6** is not however greatly affected.

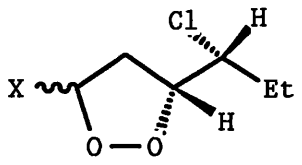
In a final look at solvent effects, the reaction was repeated in the polar aprotic solvent dimethylformamide (DMF). When the reaction of **2** with ^{t}BuOCl in DMF was examined, we found that if identical conditions and reaction times to those employed in dichloromethane were used, then most of the recovered material was unreacted hydroperoxide. The other problem was that the work-up procedure, which involved diluting the reaction mixture with water and extracting with petrol, recovered very little material. It was believed that one problem was reaction of ^{t}BuOCl with DMF, as a mixture of the two did slowly turn yellow on standing. The reaction was repeated, but neat ^{t}BuOCl was added to a solution of **3** in DMF until the yellow colour of the hypochlorite was no longer dissipated on addition. When worked up as before there was again very little material recovered (20-30%). However, the reaction was relatively

clean, and the cyclisation was completely stereospecific. The low yields though means that this system offers no real advantages over the other solvents tried.

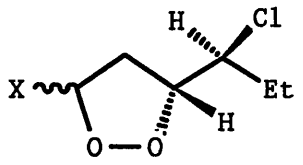
The final system we tried was to revert to dichloromethane, but to do the reaction in the presence of silica. As mentioned before, these conditions were used by Courtneidge for the cycloperoxychlorination of allylic hydroperoxides to form 4-chloro-1,2-dioxolanes.[12] The use of silica in reactions involving ^{t}BuOCl has also been reported by Yamamoto[29] for the production of allylic chlorides from alkenes.

In these reactions a pre-cooled solution of the hydroperoxide in dichloromethane was added to a solution of 1 eq. ^{t}BuOCl in dichloromethane at -10°C, in which was suspended column chromatography grade silica. The most dramatic effect was with the two hexenyl hydroperoxides (**3** and **4**). These both cyclised completely stereospecifically to produce just one of the two isomeric dioxolanes **12** and **13**. This is compared with the stereospecificity under other conditions in Table 2. The implication of this result is that the cyclisation now occurs *via* a completely polar route. The isolated yields show little improvement however, the reaction of **3** produces **13** in 18% yield after chromatography.

The by-products are also now different. The other major product from the reaction of **3** can be isolated relatively pure, and is a six-carbon species with peaks in the ^{13}C nmr spectrum at δ 10.02, 23.75, 45.38, 61.47, 81.94 and 97.15 ppm. The identity of this product is not clear, but it may have a structure similar to the substituted dioxolane **25**. The ratio **13:25** is approximately 2.5:1.



25

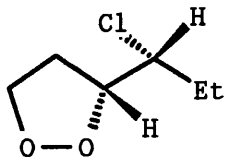


26

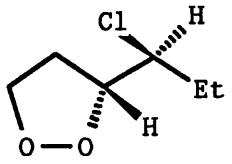
X = Cl, OH...?

A comparable by-product was also obtained from the *trans* hydroperoxide (**4**), but as a 50:50 mixture of two isomers. Again, a possible structure would be a mixture of *cis* and *trans* **26**.

The low resolution mass spectrum of **25** is somewhat



13 *threo*



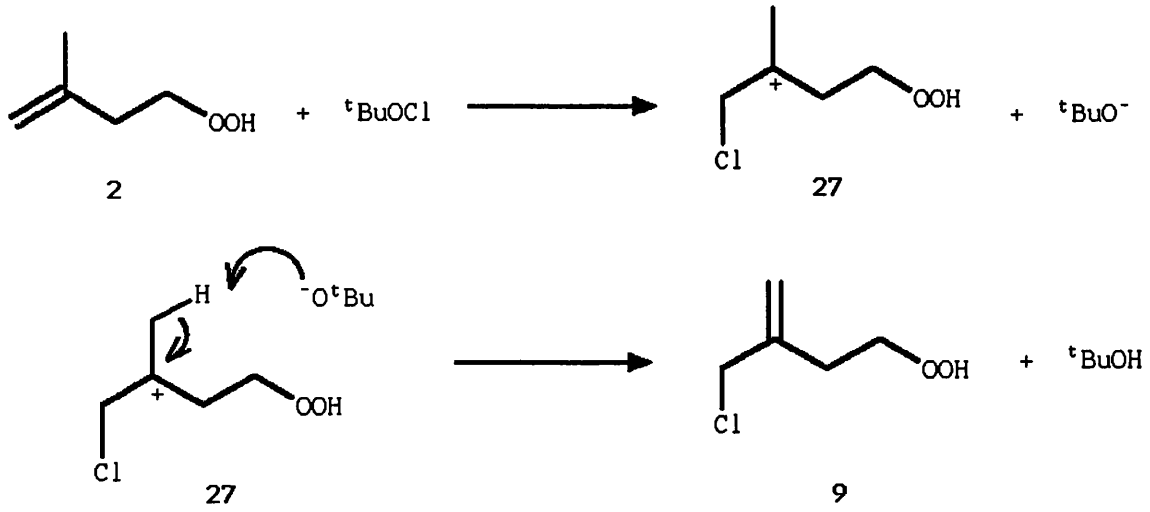
12 *erythro*

Stereochemistry of Hydroperoxide	Solvent system	13	12
cis	CH_2Cl_2 / py	70	30
cis	Acetone	95	5
cis	CH_2Cl_2 / SiO_2	100	0
trans	CH_2Cl_2 / py	25	75
trans	Acetone	15	85
trans	CH_2Cl_2 / SiO_2	0	100

Table 2 : Relative % yields of 12 and 13 from 3 (*cis*) and 4 (*trans*) under varying conditions.

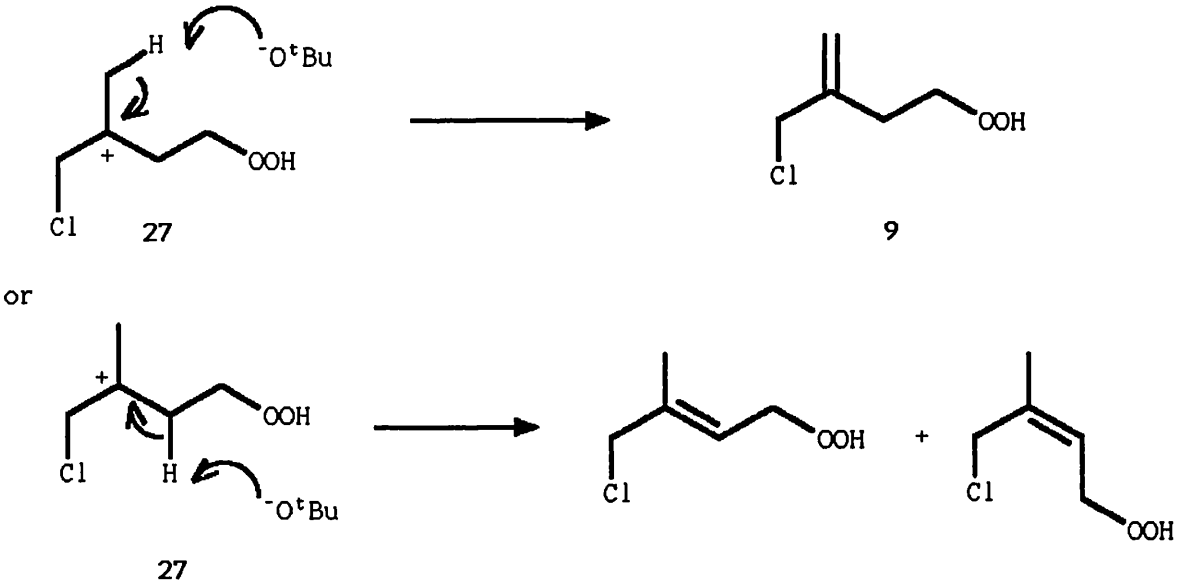
inconclusive. The major peaks in the high mass part of the spectrum are at m/z = 149 and 151, which would correspond to $[M-X]^+$. This is consistent with our proposal for the structure of **25**, but unfortunately gives no information on the nature of X.

When 3-methyl-3-buten-1-yl hydroperoxide (**2**) was treated with ^{t}BuOCl under these conditions the reaction was not very clean, but the three major products were, as before, **5**, **6** and **9** in the ratio 4.2:1:1.3. The ratio **5**:(**6**+**9**), the measure of the degree of allylic chlorination of **2**, works out at 1.8:1. This is comparable to the ratio for the reaction in dichloromethane alone, and much worse than for the reaction in the presence of pyridine. Hence the addition of silica to the reaction mixture does not inhibit the chlorination of **2** to produce **9**, despite our previous conclusion that under these conditions the reaction is completely polar. This may point to a possible polar route for the allylic chlorination reaction, outlined in Scheme 23. A similar mechanism has previously been proposed for the reaction of tetrasubstituted alkenes with ^{t}BuOCl.[30]



Scheme 23

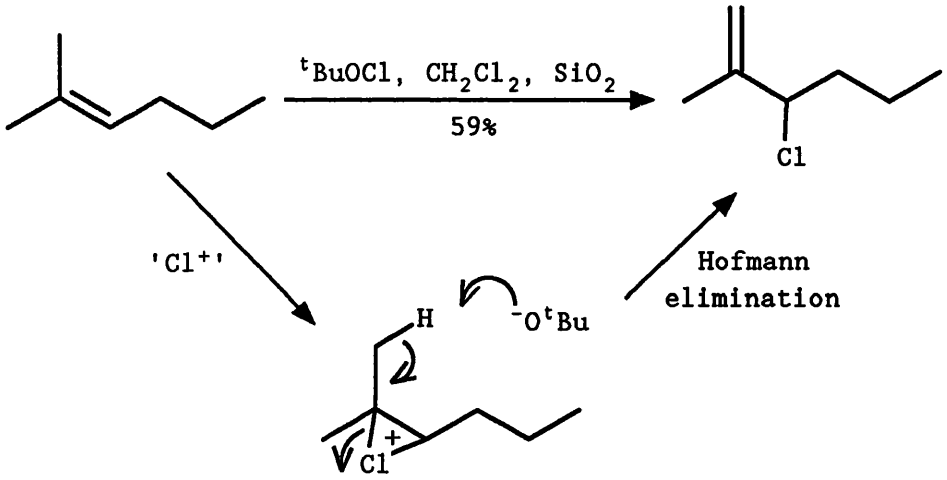
This could explain the unexpected regiospecificity of the chlorination. If **9** is formed *via* the intermediacy of the carbocation **27**, then deprotonation of **27** can lead to three possible products (Scheme 24).



Scheme 24

The loss of a proton from a carbocation (as in an E_1 elimination) generally obeys Saytzev's rule to give the more highly substituted double bond. However, according to Hammond's postulate, in the presence of a strongly basic counter-ion, such as *tert*-butoxide, the transition state for deprotonation will be more reactant-like.[31] Therefore, the more acidic methyl protons are preferentially removed to give the least substituted double bond,

i.e. Hofmann elimination. Additionally, the large steric bulk of the *tert*-butoxide ion will favour attack at the less hindered methyl group. Similarly, if the intermediate is a chloronium ion, then the deprotonation step is effectively an E_2 elimination of HCl, which, by comparison with eliminations from other positively charged substrates (e.g. $R\overset{+}{N}Me_3$, $R\overset{+}{P}Me_3$, $R\overset{+}{S}Me_2$), should also obey Hofmann's rule. It should be noted that if these suppositions are applied to the systems investigated by Yamamoto,[29] then the major product found is always identical to that which we would predict. An example is shown in Scheme 25. As with our system, a normal radical chlorination



Scheme 25

mechanism would predict a mixture of products, and you would expect chlorination of the methyl groups, giving the more highly substituted double bond, to be favoured.

Our explanation for the reduction in the amount of chlorination observed in the presence of pyridine may therefore be wrong. It is possible of course that there is a competing radical route in which pyridine scavenges hydrogen chloride, otherwise the most likely reason is that the pyridine interacts with the hydroperoxide group, possibly deprotonating it, to increase the nucleophilic nature of the peroxy group. This would result in cyclisation competing more favourably with elimination, leading to a corresponding increase in the amount of **5** being formed at the expense of the allylic chlorination product **9**. Again the reduction in allylic chlorination on going to more polar solvents such as acetone and DMF may be due to an increase in the nucleophilicity of the peroxy group under these conditions, rather than being due to the preference for polar

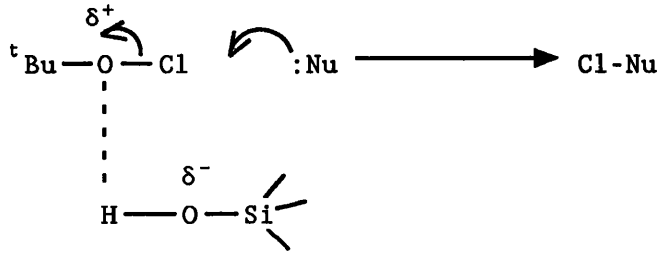
reactions over radical reactions. The failure of the chlorine atom trap to suppress chlorination could also now be explained. The reason for the chlorination of 3-methyl-3-buten-1-ol (**7**) by ^{t}BuOCl to produce **8** being much faster in the presence of *tert*-butyl hydroperoxide may be due to protonation of (or hydrogen bonding to) the hypochlorite group increasing its electrophilicity and hence increasing the rate of the polar reaction.

The ^{13}C nmr spectrum of the crude product of the reaction of **2** with ^{t}BuOCl in the presence of silica shows the possible presence of a very small amount of a by-product similar to **25** and **26**. Two weak signals are visible between δ 98 and 99 ppm, which would be due to the *cis* and *trans* isomers, in approximately equal intensity. For this hydroperoxide, the reaction in dichloromethane with pyridine is certainly better than that with silica.

In the case of 3-buten-1-yl hydroperoxide (**1**) the reaction in the presence of silica is almost identical to that in the presence of pyridine, with 3-chloromethyl-1,2-dioxolane (**10**) and 3,4-dichlorobutanal (**14**) being the major products.

The rôle of silica in all these reactions is not entirely clear, but the most probable explanation is that there is some association between the silica and the hypochlorite which increases the electrophilicity of the chlorine atom. It is known that in the presence of acid, ^{t}BuOCl shows increased electrophilic tendencies, which can be attributed to the hypochlorite existing in its protonated form.[32] This makes the chlorine atom much more susceptible to nucleophilic attack, as the leaving group under these conditions is *tert*-butanol, as opposed to the much less nucleofugic *tert*-butoxide ion. An example of this was shown earlier (Scheme 14) in the production of chlorine from ^{t}BuOCl and hydrogen chloride. It is probable that something similar is occurring with silica, possibly hydrogen bonding between OH groups in the silica and the oxygen atom of the hypochlorite (Scheme 26).

The interaction between the hydroperoxy group and the hypochlorite group is obviously of great importance in understanding these systems. With this in mind, the reaction of *tert*-butyl hydroperoxide (^{t}BuOOH) and ^{t}BuOCl was investigated. Equimolar amounts of the two compounds were mixed in $CDCl_3$ at 5°C. On mixing the solution turns a deep yellow. On warming to room temperature a



Scheme 26

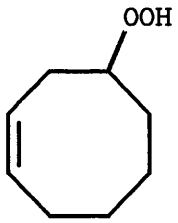
gas is evolved and the colour reduces in intensity. It was thought that possibly an unstable intermediate of the type ^{t}BuOOCl was being formed in this reaction. This species has previously been reported from the reaction of ^{t}BuOOH and chlorine(I) oxide.[33] Identification was by small shifts in the ^{1}H nmr spectra at -50 to -30°C, and we thought that low temperature ^{13}C nmr spectroscopy might show this species and provide more conclusive evidence for its existence.

Solutions of ^{t}BuOCl in $CDCl_3$ and ^{t}BuOOH in $CDCl_3$ were cooled to -20°C and their ^{13}C nmr spectra recorded. The two solutions were combined, and the ^{13}C nmr spectrum recorded. All this showed was a solution of the two components, with no sign of any reaction having occurred. The temperature of the solution was increased in 10°C intervals to +10°C. During this time there was no significant change in the spectrum. However, between 10 and 25°C a reaction did occur, the spectrum at 25°C showed the solution now contained a mixture of *tert*-butanol and ^{t}BuOCl.

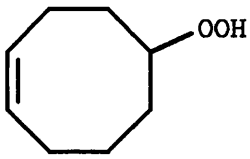
The conclusion we can draw from this is that ^{t}BuOCl and ^{t}BuOOH interact in some way to produce *tert*-butoxyl radicals. These then initiate the radical decomposition of the ^{t}BuOOH as described by Hiatt *et. al.*[34] These results confirm those of Denny and Rosen[35] when they looked at this system, but they suggested that initiation was by photolysis of the O-Cl bond of the hypochlorite. However, we found the reaction to occur in dim light at less than 25°C, and involved the production of a deep yellow intermediate. This could involve an electron transfer reaction, though we have no proof of the exact nature of this interaction.

2.2.3 Cyclooctenyl Systems

We now wished to extend the work done on acyclic systems to the two cyclic hydroperoxides 3-cyclooctenyl hydroperoxide (**28**) and 4-cyclooctenyl hydroperoxide (**29**). From the work done on these

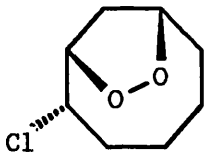


28

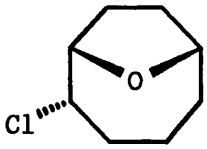


29

compounds previously, particularly by Spencer, we would predict that under radical conditions we would probably get predominantly ketones, but under polar conditions we would hope to see cyclisation occurring. By analogy with their reactions with *N*BS, we would expect to produce the bicyclic peroxide **30** from **28** and the bicyclic ethers **31** (major) and **36** (minor) from **29**.



30



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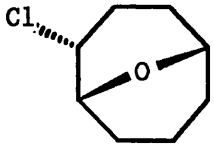
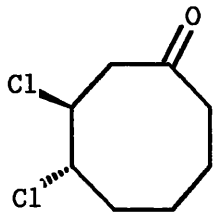
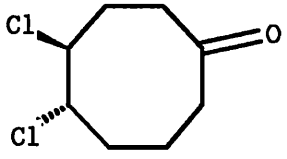


36

In the first instance both **28** and **29** were each treated with 1.5 eq. ^{t}BuOCl in dichloromethane and pyridine. The reactions were not very clean, but in each case one major compound could be identified in the ^{13}C nmr spectrum of the crude product. These were the dichloroketones, **32** from **28** and **33** from **29**. Each was formed as a



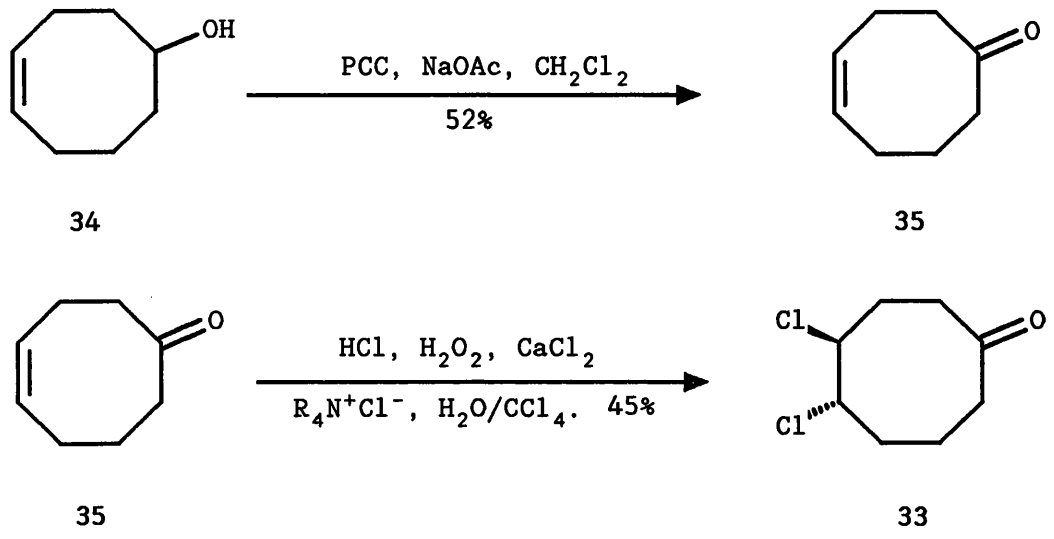
32



33

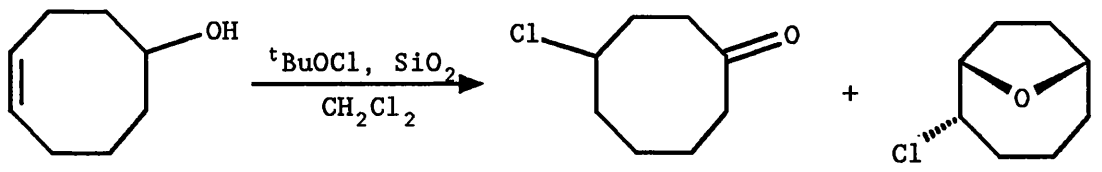
single isomer, presumed to be *trans*. The formation of these compounds closely resembles the production of **14** and **17** in the

acyclic systems. Isolation of these two compounds proved difficult, but the structure of **33** was confirmed by its independent synthesis from 4-cycloocten-1-ol (**34**) (Scheme 27).



Scheme 27

A minor product in the reaction of **29** was what appeared to be the bicyclic ether **31** : the ^{13}C nmr shifts of the two carbons next to oxygen (δ 76.14 and 81.31 ppm) are as expected for a [4.2.1] bicyclic ether rather than the [3.3.1] isomer.[3] Again an independent synthesis was required to confirm its identity. It was thought that this could be done by direct cyclisation of the alcohol (**34**) with a source of electrophilic chlorine. To this aim, **34** was treated with ^tBuOCl in dichloromethane. No reaction occurred however, only unreacted starting material could be recovered. Instead, **34** was treated with concentrated hydrochloric acid and 30% hydrogen peroxide in carbon tetrachloride with benzyltriethylammonium chloride as a phase transfer catalyst. According to the literature,[24] this system acts as a source of positive chlorine. Reaction did now occur, but it was not at all clean. The major product was 4-chlorocyclooctanone (**37**; see below), other products probably included *trans*-4,5-dichlorocyclooctan-1-ol, but not the bicyclic ether. Finally the reaction of **34** with ^tBuOCl in dichloromethane was repeated, but with silica added. This time reaction was fairly rapid, producing almost exclusively 4-chlorocyclooctanone (**37**) in around 75% yield. The required product (**31**) was also formed (8% yield after chromatography) and could be isolated and characterised (Scheme 28). A qualitatively similar result was obtained by treating



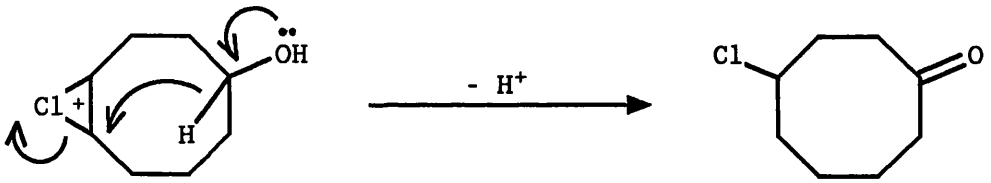
34 37 31

6 : 1

Scheme 28

34 with ^{t}BuOCl in ether in the presence of *p*-toluenesulphonic acid. This last result reinforces our earlier conclusion that the rôle of the silica in these reactions is to increase the electrophilicity of the hypochlorite group. In none of these reactions could the [3.3.1] bicyclic ether (**36**) be seen.

The mechanism of the formation of **37** probably involves the formation of a chloronium ion by attack of electrophilic ^{t}BuOCl on the double bond of **34**, followed by a 1,5-transannular hydride shift (Scheme 29). There are several literature precedents for this type



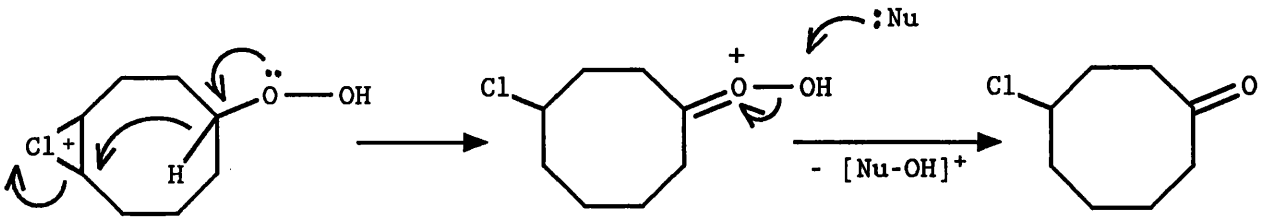
37

Scheme 29

of reaction,[36] and they all suggest that a 1,5-hydride shift to form **37** is much more likely than a 1,4-hydride shift to form 5-chlorocyclooctanone.

Following the dramatic effect of silica on the reaction of **34** with ^{t}BuOCl, it was decided to repeat the reactions with hydroperoxides **28** and **29** under these conditions.

The effect was quite striking. The reaction of 4-cyclooctenyl hydroperoxide (**29**) was now almost identical to the reaction of the alcohol (**34**), with **37** as the major product and **31** the minor product. If a comparable mechanism to that shown in Scheme 29 is proposed, then this may involve the intermediacy of a protonated carbonyl oxide (**38**) depending on whether loss of $[OH]^{+}$ and transfer of H^{-} were

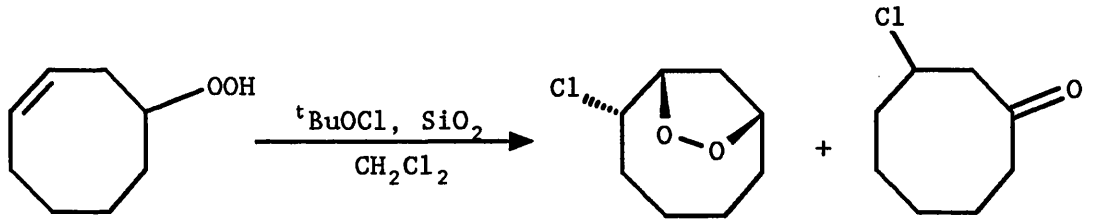


38 37

Scheme 30

concerted or not (Scheme 30). The formation of both **31** and **37** require the transfer of $[OH]^+$, but it is not clear what this is being transferred to, *i.e.* the nature of the nucleophile (Nu) shown in Scheme 27 is unknown. Other work done on a very similar system[37] however, would suggest that the nucleophile may be another molecule of the hydroperoxide.

With 3-cyclooctenyl hydroperoxide (**28**) (Scheme 31), the required crude bicyclic peroxide (**30**) was now formed in high yield (but 20% after chromatography). The other product which could be



28 30 39

Scheme 31

isolated from the reaction is what appears to be 3-chlorocyclooctanone (**39**) from its ^{13}C nmr spectrum. This must be formed by a transannular 1,4-hydride shift[38] in the intermediate chloronium ion in much the same way as **37** is formed from **29**.

As before, the different courses of these reactions must be attributable to the increased electrophilic nature of ^tBuOCl in the presence of silica.

The reactions of both **28** and **29** with ^tBuOCl in methanol were also investigated. However, both isomers produced numerous products in similar quantities (20 or 30 judging by the ^{13}C nmr spectrum of the crude material) so this line of study was not pursued further.

2.2.4 Conclusion

In conclusion, we can say that 3-(1-chloroalkyl)-1,2-dioxolanes can be synthesised by the cyclisation of homoallylic hydroperoxides with ^{t}BuOCl. However, the reactions are not generally very clean and produce the required cyclic peroxides in isolated yields of only around 20%.

Unfortunately, there does not seem to be a set of optimum conditions which can be universally applied to all hydroperoxides. With 3-methyl-3-buten-1-yl hydroperoxide (**2**) the best conditions seem to be to use ^{t}BuOCl in the presence of pyridine. Under all conditions tried the dichloro-dioxolane (**6**) is also formed in addition to the required product (**5**). This is formed *via* allylic chlorination of **2** to produce **9** (a reaction we now believe may be polar) followed by cycloperoxychlorination to give **6**. With 3-buten-1-yl hydroperoxide (**1**) the original conditions using just ^{t}BuOCl in dichloromethane seem to give as high a yield of 3-chloromethyl-1,2-dioxolane (**10**) as any. For the two isomers *cis*-3-hexen-1-yl hydroperoxide (**3**) and *trans*-3-hexen-1-yl hydroperoxide (**4**) the most favourable conditions are to use ^{t}BuOCl in dichloromethane in the presence of silica. This gives stereospecific cyclisation to produce *threo*-3-(1-chloropropyl)-1,2-dioxolane (**13**) and *erythro*-3-(1-chloropropyl)-1,2-dioxolane (**12**) respectively.

If the solvent is changed to acetone the required dioxolanes are still formed as the major products, but these conditions also provide a new and interesting route to substituted 1,2,4-trioxepanes.

The cycloperoxychlorination of 3-cyclooctenyl hydroperoxide (**28**) to form *trans*-2-chloro-8,9-dioxabicyclo[5.2.1]decane (**30**) could only be achieved by doing the reaction in the presence of silica. In its absence the major product was *trans*-3,4-dichlorocyclooctanone (**32**). 4-Cyclooctenyl hydroperoxide (**29**) also produced a dichloroketone in the ^{t}BuOCl / pyridine system, but in the presence of silica the major product was 4-chlorocyclooctanone (**37**). We can rationalise this *via* a transannular 1,5-hydride shift in the intermediate chloronium ion. The [4.2.1] bicyclic ether (**31**) was formed as a minor product in both these reactions.

Mechanistically, the system is very complicated, but there appears to be at least a large radical contribution in the absence of

silica, whereas when silica is added the reaction seems to be entirely polar.

Cycloperoxychlorination with ^{t}BuOCl does then complement the previous work done on similar systems with *N*-iodosuccinimide and *N*-bromosuccinimide, and allows us to extend the principle of cycloperoxyhalogenation to include the synthesis of chloroalkyl substituted 1,2-dioxolanes. In doing so it also provides some interesting contrasts with the previous work, such as the preference for intermolecular addition products in methanol, and the observation of transannular hydride shifts in the reaction of **29**.

2.3 EXPERIMENTAL

For details of instruments, conditions for spectroscopy and general experimental see Appendix A.

Samples of 4-cycloocten-1-ol (**34**),[17] and the *N*-tosylhydrazones of 4-cyclooctenone[17] and 3-cyclooctenone[17] were synthesised by M.D. Spencer.

2.3.1 Synthesis of Starting Materials

tert-Butyl Hypochlorite

This was prepared according to the method of Walling and Mintz.[13] Yield : 50%.

^{1}H nmr (60MHz) : δ 1.34(s) ppm.
^{13}C nmr : δ 26.81, 83.91 ppm.

Alkenyl Mesylates

These were all prepared from the commercially available alcohols (Aldrich) by the literature method.[14] All were pale yellow liquids.

3-Buten-1-yl Methanesulphonate

Yield : 81%.

^{1}H nmr (60MHz) : δ 2.48(q, J=6.5Hz, 2H); 2.96(s, 3H); 4.22(t, J=6.5Hz, 2H); 5.0-5.4(m, 2H); 5.5-6.2(m, 1H) ppm.

3-Methyl-3-buten-1-yl Methanesulphonate

Yield : 95%.

^{1}H nmr (60MHz) : δ 1.75(s, 3H); 2.43(t, J=6.8Hz, 2H); 2.95(s, 3H); 4.26(t, J=6.8Hz, 2H); 4.80(m, 2H) ppm.

cis-3-Hexen-1-yl Methanesulphonate

Yield : 98%.

^{1}H nmr (60MHz) : δ 0.98(t, J=7.2Hz, 3H); 2.06(quin, J=7.2Hz, 2H); 2.48(m, 2H); 2.98(s, 3H); 4.16(t, J=7.2Hz, 2H); 5.40 (m, 2H) ppm.

trans-3-Hexen-1-yl Methanesulphonate

Yield : 90%.

^{1}H nmr (60MHz) : δ 0.94(t, J=7.2Hz, 3H); 1.98(m, 2H); 2.38(m, 2H); 2.96(s, 3H); 4.16(t, J=6.6Hz, 2H); 5.43(m, 2H) ppm.

3-Buten-1-yl Hydroperoxide (1)

3-Buten-1-yl methanesulphonate (16.41g; 0.109mol) was dissolved in methanol (100ml) and cooled in an ice bath. To this was slowly added 30% w/v hydrogen peroxide (50ml; 0.44mol H_2O_2) and 50% potassium hydroxide (12.30g; 0.110mol KOH) in that order, and the resulting mixture was magnetically stirred for 26h. The solution was reduced to approximately half volume under reduced pressure, cooled, combined with cold 50% potassium hydroxide (30g), and washed with ether (50ml). The aqueous solution was neutralised, with cooling, with concentrated hydrochloric acid, and organic material was recovered by continuous liquid-liquid extraction with ether for 6h. This organic solution was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the crude was purified by column chromatography (ether : 60/80°C petroleum spirit; 1 : 1) to produce a colourless liquid (1.07g; 11%).

^{1}H nmr : δ 2.43(m, 2H); 4.07(t, J=6.63Hz, 2H); 5.06-5.16(m, 2H); 5.82(m, 1H); 8.70(br s, 1H) ppm.
^{13}C nmr : δ 32.13, 75.91, 116.88, 134.31 ppm.

The spectra of **1** to **4** all agree with previously reported values.[19,39]

3-Methyl-3-buten-1-yl Hydroperoxide (2)

This was prepared as above to give a colourless liquid (25%).

^{1}H nmr (60MHz) : δ 1.74(s, 3H); 2.34(t, J=6.3Hz, 2H); 4.08(t, J=6.3Hz, 2H); 4.72(m, 2H); 7.20(br s, 1H) ppm.
^{13}C nmr : δ 22.39, 35.78, 75.04, 112.01, 142.12 ppm.

***cis*-3-Hexen-1-yl Hydroperoxide (3)**

A slightly modified version of the Mosher and Williams synthesis[14] was used.

cis-3-Hexen-1-yl methanesulphonate (11.72g; 0.066mol) was dissolved in methanol (90ml) and water (8ml) and cooled in an ice bath. To this was first added 30% hydrogen peroxide (30ml; 0.27mol H_2O_2) and then 50% potassium hydroxide (7.60g; 0.068mol KOH). This was left stirring at room temperature for 22h. The solution was reduced to half volume under reduced pressure, cooled and then combined with cooled 50% potassium hydroxide (30ml). This was washed with benzene (70ml) and neutralised, with cooling, with 2M hydrochloric acid. This was then extracted with benzene (5x50ml). The benzene layers from the extraction of the neutralised solution were in turn extracted with 25% potassium hydroxide (60ml). The aqueous layer was neutralised, with cooling, with 2M hydrochloric acid and extracted with ether (3x20ml). After drying over Na_2SO_4 the solvent was removed under reduced pressure to yield a very pale yellow liquid (2.32g; 30%).

^{1}H nmr : δ 0.93(t, J=7.58Hz, 3H); 2.02(approx. quin, J_{ave}=7.41Hz, 2H); 2.36(approx. q, J_{ave}=7.30Hz, 2H); 3.97(t, J=6.60Hz, 2H); 5.28(m, 1H); 5.45(m, 1H); 8.71(br s, 1H) ppm.
^{13}C nmr : δ 14.11, 20.50, 25.80, 76.37, 123.87, 134.24 ppm.

***trans*-3-Hexen-1-yl Hydroperoxide (4)**

The synthesis was as for **3**. Yield : 28%.

^{1}H nmr (200MHz) : δ 0.92(dt, J=1.42, 7.37Hz, 3H); 1.97(m, 2H);

2.30(m, 2H); 3.98(dt, J=1.47, 6.72Hz, 2H); 5.38(m, 1H); 5.50(m, 1H); 8.51(br s, 1H) ppm.
^{13}C nmr : δ 13.66, 25.57, 31.08, 76.60, 124.38, 134.76 ppm.

N'-Tosyl-N-(3-cyclooctenyl)hydrazine[17]

3-Cyclooctenone *N'*-*p*-tosylhydrazone (2.92g; 10mmol) was dissolved in dry tetrahydrofuran (50ml) in a 250ml 3-necked round bottomed flask equipped with a reflux condenser and pressure equallising dropping funnel. The equipment was continually flushed through with nitrogen, the exit gases being passed through three Dreschel bottles, the last two filled with bleach. The flask was placed in a water bath at room temperature and the solution was magnetically stirred. A few milligrams of bromocresol green were added, followed by sodium cyanoborohydride (2.52g; 40mmol) which was added in one portion and flushed in with dry tetrahydrofuran (50ml). The dropping funnel was filled with a solution of *p*-toluenesulphonic acid (3.80g; 20mmol) in tetrahydrofuran (40ml), which was slowly added until the solution turned a lime green colour (approx. pH 3.5). Stirring was continued for 4h. After filtering through Celite, the solution was concentrated under reduced pressure and combined with water (100ml). The aqueous layer was extracted with dichloromethane (3x50ml). The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a yellow oil (2.50g; 85%).

^{13}C nmr : δ 21.45, 21.98, 25.73, 28.56, 28.76, 29.60, 60.27, 126.43, 127.99, 129.38, 131.89, 135.26, 143.69 ppm.

These agree with the quoted values.[17]

N'-Tosyl-N-(4-cyclooctenyl)hydrazine[17]

This was prepared from 4-cyclooctenone *N'*-*p*-tosylhydrazone by the method outlined above. The reaction was not clean, but the major product was the required hydrazine as identified by ^{13}C nmr spectroscopy.[17]

3-Cyclooctenyl Hydroperoxide (28)[17]

N'-Tosyl-*N*-(3-cyclooctenyl)hydrazine (2.50g; 8.49mmol) was dissolved in tetrahydrofuran (80ml) and cooled to below 0°C. 30% Hydrogen peroxide (90ml; 0.79mol H_2O_2) and sodium peroxide (1.00g; 12.8mmol) were added and the solution was magnetically stirred at room temperature for 17h. The reaction mixture was combined with water (100ml) and dichloromethane (15ml) and neutralised with 2M hydrochloric acid. The organic layer was separated off, and the aqueous layer was extracted with dichloromethane (3x20ml). The combined organic extracts were concentrated to approximately half-volume under reduced pressure. The crude oil was redissolved in toluene (15ml) and cooled in ice. The toluene was extracted with cold 4M potassium hydroxide (5x10ml). The combined extracts were then washed with toluene (2x15ml) and combined with dichloromethane (30ml). The solution was acidified with ice-cold 2M hydrochloric acid while being cooled in an ice-salt bath. The organic layer was then separated off, and the aqueous layer was extracted with dichloromethane (3x25ml). The combined organic layers were washed with water (10ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a yellow liquid (0.65g; 54%).

^{1}H nmr (60MHz) : δ 1.0-2.6(m, 10H); 3.95(m, 1H); 5.50(m, 2H); 8.20(br s, 1H) ppm.
^{13}C nmr : δ 21.43, 25.76, 28.34, 28.76, 29.09, 85.62, 125.65, 132.38 ppm.

The ^{13}C nmr spectrum of the product was in agreement with that quoted in the literature.[17]

4-Cyclooctenyl Hydroperoxide (29)[17]

The crude *N'*-tosyl-*N*-(4-cyclooctenyl)hydrazine from the cyanoborohydride reduction was oxidised as for hydroperoxide **28**. Yield of **29** from the tosylhydrazone : 30%.

^{1}H nmr (200MHz) : δ 1.35-2.40(m, 10H); 4.00(m, 1H); 5.64(m, 2H); 8.18(br s, 1H) ppm.

^{13}C nmr : δ 22.22, 25.23, 25.63, 31.54, 31.72, 86.79, 129.69, 129.80 ppm.

The ^{13}C nmr spectrum agrees with that quoted in the literature.[17]

2.3.2 Acyclic Systems

Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (2) with ^{t}BuOCl in $CDCl_3$

2.5eq. ^{t}BuOCl :

Hydroperoxide **2** (0.080g; 0.78mmol) in $CDCl_3$ (0.25ml) was placed in an nmr tube and cooled in ice. A solution of ^{t}BuOCl (0.20g; 1.84mmol) in $CDCl_3$ was cooled in ice and added to the tube. The solution was left at 0°C for 1h, by which time the ^{1}H nmr spectrum indicated that the reaction had gone to completion. The solvent was removed under reduced pressure to yield a pale yellow liquid (0.142g). This was purified by column chromatography (CH_2Cl_2) to give 54.3mg of a mixture of **5** and **6** (**5:6** = 1.5:1).

1.05eq. ^{t}BuOCl :

The reaction was as above, using 0.067g (0.66mmol) of **2**, and 0.075g (0.69mmol) ^{t}BuOCl. The solution was allowed to stand in ice for 4h. Separation by column chromatography gave a mixture of **5** and **6**, and also 17mg of an impure sample of **9**. From the crude product , **5:6:9** = 2.2:1:0.8.

3-Chloromethyl-3-buten-1-yl Hydroperoxide (9) (*New Compound; NC*)

R_f 0.24 (CH_2Cl_2)

^{1}H nmr (200MHz) : δ 2.56(t, J=6.0Hz, 2H, $=CCH_2$); 4.07(s, 2H, CH_2Cl); 4.16(t, J=6.0Hz, 2H, CH_2OOH); 5.06(s, 1H, $CH^AH^B=$); 5.22(s, 1H, $CH^AH^B=$); 8.10(br s, 1H, OOH) ppm.
^{13}C nmr : δ 31.24($=CCH_2$), 48.36(CH_2Cl), 74.97(CH_2OOH), 116.56($CH_2=$), 141.79(C=) ppm.

Reaction of Dilute Hydroperoxide 2 with ^{t}BuOCl

To a magnetically stirred solution of 3-methyl-3-buten-1-yl hydroperoxide (**2**) (0.118g; 1.16mmol) in dichloromethane at 0°C was

added ^{t}BuOCl (0.128g; 1.18mmol) in dichloromethane (10ml). This was allowed to warm to room temperature and left stirring for 4h. The solvent was removed under reduced pressure to yield 0.145g of crude material. The main products identified in the crude product by ^{13}C nmr spectroscopy were **5**, **6** and **9**. (**5**:**6**:**9** = 6:1:3).

A mixture of **5** and **6** was separated off by column chromatography (CH_2Cl_2; **5** : R_f 0.55, **6** : R_f 0.60) and combined with the samples from the above two experiments. These were separated using semi-preparative HPLC (column : 50x4.6mm + 2x250x10mm; 5μm silica gel; R.I. detection; flow rate 4.0cm^{3}min^{-1}; mobile phase : 10% ethyl acetate in hexane).

3-Chloromethyl-3-methyl-1,2-dioxolane (5) (*NC*)

Retention time : 3.54 min.

^{1}H nmr : δ 1.45(s, 3H, CH_3); 2.34(m, 1H, $C^4H^AH^B$); 2.70(m, 1H, $C^4H^AH^B$); 3.51(d, J=11.23Hz, 1H, CH^AH^BCl); 3.55(d, J=11.23Hz, 1H, CH^AH^BCl); 4.17(m, 2H, CH_2OO) ppm.
^{13}C nmr : δ 21.28(CH_3), 43.75, 49.19, 70.59(CH_2OO), 84.17(COO) ppm.
Mass spectrum : m/z(%) = 43(100), 49(27, $[CH_2{}^{35}Cl]^+$), 51(11, $[CH_2{}^{37}Cl]^+$), 87(59, $[M\text{-}CH_2Cl]^+$), 136(3, $M[{}^{35}Cl]^+$), 138(1, $M[{}^{37}Cl]^+$).
High resolution mass spectrum : $C_5H_9{}^{35}ClO_2$ requires m/z = 136.0291.
Found : m/z = 136.0300.

3,3-Di(chloromethyl)-1,2-dioxolane (6) (*NC*)

Retention time : 4.40 min.

^{1}H nmr : δ 2.64(t, J=6.85Hz, 2H, C^4H_2); 3.70(d, J=11.56Hz, 2H, CH^AH^BCl); 3.80(d, J=11.56Hz, 2H, CH^AH^BCl); 4.21(t, J=6.85Hz, 2H, CH_2OO) ppm.
^{13}C nmr : δ 41.83, 45.10(CH_2Cl), 71.12(CH_2OO), 85.87(COO) ppm.
Mass spectrum : m/z(%) = 29(100), 49(44, $[CH_2{}^{35}Cl]^+$), 51(17, $[CH_2{}^{37}Cl]^+$), 77(56), 121(28, $[M\text{-}CH_2Cl]^+$:^{35}Cl), 123(10, $[M\text{-}CH_2Cl]^+$:^{37}Cl), 170(3, $M[{}^{35}Cl\,{}^{35}Cl]^+$), 172(2, $M[{}^{35}Cl\,{}^{37}Cl]^+$), 174(0.04, $M[{}^{37}Cl\,{}^{37}Cl]^+$)

High resolution mass spectrum : $C_5H_9{}^{35}Cl_2O_2$ requires m/z = 169.9901. Found : m/z = 169.9900.

Reaction of 3-Methyl-3-buten-1-ol (7) with ^tBuOCl

3-Methyl-3-buten-1-ol (**7**) (0.052g; 0.605mmol) was weighed into an nmr tube. To this was added a solution of ^tBuOCl (0.091g; 0.837mmol) in $CDCl_3$ (0.5ml). After 4h there was very little sign of any starting material remaining by ^1H nmr spectroscopy. After removal of *tert*-butanol under reduced pressure, the crude product was examined by ^{13}C nmr spectroscopy and found to contain predominantly one compound, which was assigned as **8**.

3-Chloromethyl-3-buten-1-ol (8) (*NC*)

^{13}C nmr : δ 36.19(=CCH_2), 48.09(**C**H_2Cl), 60.44(**C**H_2OH), 116.59(CH_2=), 141.90(**C**=) ppm.

With added *tert*-butyl hydroperoxide :

3-Methyl-3-buten-1-ol (**7**) (0.105g; 1.22mmol) was weighed into an nmr tube. To this was added *tert*-butyl hydroperoxide (0.110g; 1.22mmol) in $CDCl_3$ (0.25ml) followed by ^tBuOCl (0.137g; 1.26mmol) in $CDCl_3$ (0.25ml). On addition of the hypochlorite a vigorous reaction took place producing a lot of gas and heat. A ^1H nmr spectrum recorded immediately after mixing was identical to one recorded 1h later, confirming that reaction was instantaneous. A ^{13}C nmr spectrum, after removal of *tert*-butanol under reduced pressure, showed the mixture to contain **8** and unreacted **7** (1:1) as the major components, along with unreacted *tert*-butyl hydroperoxide.

Reaction of 3-Buten-1-yl Hydroperoxide (1) with ^tBuOCl

3-Buten-1-yl hydroperoxide (**1**) (0.100g; 1.14mmol) was dissolved in dichloromethane (10ml) and cooled in an ice bath. To this magnetically stirred solution was added ^tBuOCl (0.129g; 1.19mmol). The solution was stirred at 5°C for 4h, then allowed to warm to room temperature. The solvent was removed under reduced pressure, and the crude product was separated by column chromatography (CH_2Cl_2).

3-Chloromethyl-1,2-dioxolane (10) (*NC*)

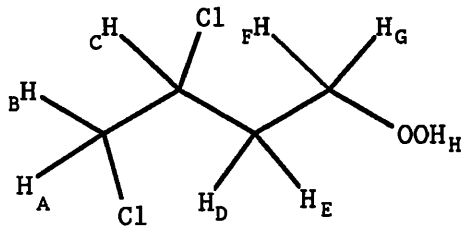
Yield : 24mg; 17%. R_f 0.53

^{1}H nmr (200MHz) : δ 2.48(m, 1H, C^{4}H^{A}H^B); 2.79(m, 1H, C^{4}H^{A}H^B); 3.44(dd, J=11.21, 6.63Hz, 1H, CH^{A}H^{B}Cl); 3.63(dd, J=11.21, 5.98Hz, 1H, CH^{A}H^{B}Cl); 4.03(approx. q, J_{ave}=7.65Hz, 1H, CH^{A}H^{B}OO); 4.20(dt, J=4.44, 7.93Hz, 1H, CH^{A}H^{B}OO); 4.50(m, 1H, CHCH$_2$Cl) ppm.
^{13}C nmr : δ 38.84, 44.61, 69.58(CH$_2$OO), 79.12(CHOO) ppm.
Mass spectrum : m/z(%) = 29(100), 49(34, [CH$_2$^{35}Cl]$^+$), 51(11, [CH$_2$^{37}Cl]$^+$), 73(59, [M-CH$_2$Cl]$^+$), 122(15, M[^{35}Cl]$^+$), 124(4, M[^{37}Cl]$^+$).
High resolution mass spectrum : $C_4H_7{}^{35}ClO_2$ requires m/z = 122.0134.
Found : m/z = 122.0140.
Found : C, 38.62; H, 5.73%. Calc. for $C_4H_7ClO_2$: C, 39.20; H, 5.76 %.

3,4-Dichlorobutan-1-yl Hydroperoxide (11) (*NC*)

Yield : 10mg; 5%. R_f 0.23

^{1}H nmr : δ 1.99(m, 1H, H_D); 2.42(m, 1H, H_E); 3.71(dd, J=11.41, 7.29Hz, 1H, H_A); 3.81(dd, J=11.41, 5.01Hz, 1H, H_B); 4.21(m, 3H); 8.00(br s, 1H, H_H) ppm.



Irradiation at δ 4.21 (H_C, H_F and H_G) causes the signals at 1.99 and 2.42 (H_D and H_E) and 3.71 and 3.81 (H_A and H_B) to all collapse to doublets, as expected.

^{13}C nmr : δ 33.25(-CH$_2$-), 48.37(CH$_2$Cl), 57.63(CHCl), 73.11(CH$_2$OOH) ppm.

The Effect of BHT on the reaction of Hydroperoxide (**2**) with ^{t}BuOCl

i) 3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.104g; 1.02mmol) and BHT (0.024g; 0.11mmol) were dissolved in dichloromethane (10ml) and cooled in an ice bath. To this magnetically stirred solution was added ^{t}BuOCl (0.111g; 1.02mmol) in dichloromethane (10ml). The mixture was left stirring for 2h. The solvent was removed under reduced pressure, and the ^{13}C nmr spectrum of the resulting material showed it to contain predominantly starting material.

ii) 3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.078g; 0.76mmol) and BHT (0.0098g; 0.04mmol) were dissolved in dichloromethane (5ml) and cooled in an ice bath. To this magnetically stirred solution was added ^{t}BuOCl (0.152g; 1.40mmol) in dichloromethane (5ml). The mixture was stirred until there was no sign of any **2** remaining by TLC (CH_2Cl_2; R_f 0.27). This took about 26h.

Cycloperoxychlorination in the Presence of a Chlorine Atom Trap

A solution of 3-methyl-3-buten-1-yl hydroperoxide (**2**) (0.126g; 1.23mmol) and *cis*-1,2-dichloroethene (0.108g; 1.11mmol) in dichloromethane (10ml) was cooled in an ice bath. To this was added ^{t}BuOCl (0.136g; 1.25mmol) in dichloromethane (10ml). The solution was magnetically stirred for 3h while warming to room temperature. After removal of the solvent the ^{13}C nmr spectrum showed there to be unreacted **2** left, hence the crude was redissolved in dichloromethane (10ml), cooled in ice, and further *cis*-1,2-dichloroethene (0.083g; 0.86mmol) followed by ^{t}BuOCl (0.083g; 0.76mmol) were added. The solution was stirred for a further hour, then the solvent was removed under reduced pressure to yield 0.121g of a mixture containing mainly **5**, **6** and **9** (**5**:**6**:**9** = 6.5:1:2).

Cycloperoxychlorination in the Presence of Pyridine

With 3-methyl-3-buten-1-yl hydroperoxide (**2**) :

Hydroperoxide **2** (0.122g; 1.19mmol) and pyridine (0.063g; 0.80mmol) were dissolved in dichloromethane (10ml) and cooled in an ice bath. To this magnetically stirred solution was added ^{t}BuOCl

(0.179g; 1.65mmol) in dichloromethane (10ml). The solution was stirred for a further hour, then washed with 2M hydrochloric acid (10ml), water (10ml) and saturated sodium bicarbonate (10ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield 0.113g of a 4.1:1 mixture (by ^{13}C nmr) of **5**:**6**. Yields from the crude material: **5** (53%), **6** (13%).

With 3-buten-1-yl hydroperoxide (**1**) :

Procedure as above. The crude product was purified by column chromatography (30% ether in 60/80°C petroleum spirit).

3-Chloromethyl-1,2-dioxolane (10)

Yield : 9%. R_f 0.37.

Two other compounds were isolated, but in a slightly impure state :

4-Chloro-2-butenal (16)

^1H nmr : δ 4.26(dd, J=5.93, 1.50Hz, 2H); 6.33(ddt, J=15.48, 7.74, 1.50 Hz, 1H); 6.83(dt, J=15.48, 5.93Hz, 1H); 9.60(d, J=7.74Hz, 1H) ppm.
^{13}C nmr : δ 42.25, 133.82, 149.58, 192.69 ppm.

The ^1H nmr data agree with the literature values.[23]

3,4-Dichlorobutan-1-ol (15)

^1H nmr : δ 1.54(br s, 1H); 1.89(m, 1H); 2.26(m, 1H); 3.71(dd, J=11.42, 7.02Hz, 1H); 3.80(dd, J=11.42, 5.08Hz, 1H); 3.86(dd, J=7.22, 4.63Hz, 2H); 4.27(m, 1H) ppm.
^{13}C nmr : δ 37.64, 48.58, 57.95, 59.18 ppm.

Again, the ^1H nmr data agree with the literature values.[22]

There were also four strong peaks visible in the ^{13}C nmr spectrum of the crude product, due to a compound which apparently

decomposed on the column. These were assigned to **14** :

3,4-Dichlorobutanal (14)

^{13}C nmr : δ 47.46, 48.18, 53.06, 197.65 ppm.

With *cis*-3-hexen-1-yl hydroperoxide (**3**) :

The crude product contained a mixture of **12** and **13** in the ratio **12:13** = 30:70 and an aldehyde assigned as **17**. An attempt to separate these by column chromatography (CH_2Cl_2 : 60/80°C petroleum spirit; 1 : 1) was unsuccessful, as **17** appeared to decompose on the column.

Peaks in the ^{13}C nmr spectrum of the crude material assigned to **3,4-dichlorohexanal** (**17**) (*NC*) : δ 10.15(**C**H_3), 27.99, 48.43, 56.91(**C**HCl), 66.55(**C**HCl), 197.84(**C**HO) ppm.

With *trans*-3-hexen-1-yl hydroperoxide (**4**) :

A mixture of **12** and **13** was obtained (**12:13** = 85:15) with **17** as the main by-product. No attempt was made at separation.

Cycloperoxychlorination in the Presence of Pyridine and BHT

cis-3-Hexen-1-yl hydroperoxide (**3**) (0.108g; 0.93mmol), BHT (0.062g; 0.28mmol) and pyridine (0.075g; 0.94mmol) were dissolved in dichloromethane (15ml). ^tBuOCl (0.148g; 1.36mmol) in dichloromethane (5ml) was then added to this magnetically stirred solution. The starting material seemed to be consumed within minutes as judged by TLC (CH_2Cl_2; R_f 0.28), although much of the BHT (R_f 0.75) also appeared to have reacted. After stirring for 1h, the solution was washed with 2M hydrochloric acid (10ml), water (10ml) and saturated sodium bicarbonate (10ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The ^{13}C nmr spectrum of the crude product showed it to contain **12** and **13** (**12:13** = 30:70), a small amount of the dichloroaldehyde (**17**) and several BHT derived products. There was no sign of any starting material.

Low Temperature Cycloperoxychlorination

cis-3-Hexen-1-yl hydroperoxide (**3**) (0.139g; 1.20mmol) and pyridine (0.104g; 1.32mmol) were dissolved in dichloromethane (10ml) and cooled to -40°C. ^{t}BuOCl (0.167g; 1.53mmol) in dichloromethane (10ml) was pre-cooled to -40°C and added dropwise to the magnetically stirred solution. The solution was stirred at -35°C for 2h, before slowly warming to room temperature over several hours. The solution was washed with 2M hydrochloric acid (10ml), water (10ml) and saturated sodium bicarbonate (10ml). After drying over $MgSO_4$ the solvent was removed under reduced pressure to yield 0.143g of crude material. The ^{13}C nmr spectrum of the crude showed it to contain mainly **12**, **13** and **17** (**12:13:17** = 1:9:9).

Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (**2**) with ^{t}BuOCl in Methanol

3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.253g; 2.48mmol) was dissolved in methanol (25ml). This was cooled in an ice bath, and to this was added a solution of ^{t}BuOCl (0.279g; 2.57mmol) in methanol (25ml). The solution was magnetically stirred, while warming to room temperature, for 4.5h. The solvent was removed under reduced pressure to yield a colourless liquid (0.331g). The ^{13}C nmr spectrum of the crude product showed the major products to be **5**, **6**, **9** and **19** (**5 : 6 : 9 : 19** = 4.5 : 1 : 9 : 23).

The material was separated by column chromatography (ether) to yield **19** (185mg; 44%). As there were still signs of a few minor impurities, the material was rechromatographed (CH_2Cl_2 : ether; 6 : 1. R_f 0.40) to produce a relatively pure sample of **19** (126mg; 30%).

4-Chloro-3-methoxy-3-methylbut-1-yl Hydroperoxide (19) (*NC*)

^{1}H nmr : δ 1.29(s, 3H, CH_3); 1.87(dt, J=14.99, 6.13Hz, 1H, $C^2H^AH^B$); 2.05(dt, J=14.99Hz, 6.51Hz, 1H, $C^2H^AH^B$); 3.25(s, 3H, OCH_3); 3.49(d, J=11.58Hz, 1H, CH^AH^BCl); 3.55(d, J=11.58Hz, 1H, CH^AH^BCl); 4.13(approx. t, J_{ave}=6.46Hz, 2H, CH_2OOH); 9.00(br s, 1H, OOH) ppm.
^{13}C nmr : δ 20.58(CH_3), 33.50(C^2), 49.04, 49.60, 72.24(CH_2OOH), 75.84(COMe) ppm.

After being left in acetone at -30°C for about 3 months, it was partly transformed into the diperoxyketal (41mg; 31%)

2,2-Bis(4-chloro-3-methoxy-3-methylbut-1-ylperoxy)propane (*NC*)

^{1}H nmr : δ 1.25(s, 3H, CH_3COMe); 1.40(s, 3H, CH_3COO); 1.89(dt, J=14.25, 6.90Hz, 1H,); 1.96(dt, J=14.25, 6.84Hz, 1H); 3.21(s, 3H, OCH_3); 3.50(s, 2H, CH_2Cl); 4.15(t, J=6.90Hz, 2H, CH_2OO) ppm.
^{13}C nmr : δ 21.12, 21,42, 33.35, 49.46, 49.54, 70.83(CH_2OO), 75.37(COMe), 108.54(OOCOO) ppm.
Found : C, 48.40; H, 8.30; Cl, 18.65%. Calc. for $C_{15}H_{30}Cl_2O_6$: C, 47.75; H, 8.01; Cl, 18.79%.

Reaction of 3-Buten-1-yl Hydroperoxide (1) with ^{t}BuOCl in Methanol

Using the same method as above, hydroperoxide **1** afforded crude **20** and **21** in 80% yield (**20:21** = 1.75:1)

The two regioisomers could not be separated on a gravity column with any solvent system tried, but the minor impurities were removed using 20% ethyl acetate in dichloromethane. Pure yield 45%.

Found : C, 38.23; H, 7.29%. Calc. for $C_5H_{11}ClO_3$: C, 38.85, H, 7.17%.
^{13}C nmr :
Assigned to **4-chloro-3-methoxybut-1-yl hydroperoxide (20)** (*NC*) :
δ 30.24(C^2), 45.10(CH_2Cl), 57.37(OCH_3), 72.78, 77.76 ppm.
Assigned to **3-chloro-4-methoxybut-1-yl hydroperoxide (21)** (*NC*) :
δ 32.50(C^2), 56.57, 58.90, 72.89, 76.27 ppm.

Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (2) with *N*-Bromosuccinimide (*N*BS) in Methanol

Hydroperoxide **2** (0.129g; 1.26mmol) was dissolved in methanol (10ml), and *N*BS (0.229g; 1.29mmol) in methanol (10ml) was added. The solution was magnetically stirred for 2h. The solvent was removed under reduced pressure, and the crude redissolved in carbon tetrachloride (10ml). The insoluble succinimide was filtered off and the solvent was removed under reduced pressure to yield a yellow

liquid (0.190g). The crude material was separated by column chromatography (10% ether in dichloromethane).

3-Bromomethyl-3-methyl-1,2-dioxolane (22)

Yield : 28%

^{13}C nmr : δ 21.92, 38.35, 44.19, 70.57, 83.58 ppm.
These values agree with those previously quoted.[39]

4-Bromo-3-methoxy-3-methylbut-1-yl Hydroperoxide (23) (*NC*)

Yield : 14%

^{1}H nmr (200MHz) : δ 1.34(s, 3H, CH_3); 2.00(m, 2H, C^2H_2); 3.26(s, 3H, OCH_3); 3.44(s, 2H, CH_2Br); 4.14(t, J=6.34Hz, 2H, CH_2OOH); 9.07(br s, 1H, OOH) ppm.
^{13}C nmr : δ 21.18(CH_3), 34.51, 38.65, 49.75(OCH_3), 72.49, 75.25 ppm.

Attempted Cyclisation of Haloalkyl Hydroperoxides

4-Chloro-3-methoxy-3-methylbut-1-yl hydroperoxide (**19**) (0.116g; 0.69mmol) and silver trifluoroacetate (0.154g; 0.70mmol) were dissolved in dry dichloromethane (10ml). The mixture was magnetically stirred for 18h in a flask wrapped in aluminium foil. After this time there was no sign of reaction by TLC [CH_2Cl_2; R_f(**19**) 0.08]. The mixture was sonicated for 15min., but there was still no sign of reaction. On passing down a silica column (20% ethyl acetate in dichloromethane) only **19** was recovered.

Similarly, treatment of **23** with silver trifluoroacetate failed to yield any cyclic peroxide.

Cycloperoxychlorination in Acetone

3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.118g; 1.16mmol) was dissolved in acetone (10ml) and cooled in an ice bath. ^{t}BuOCl (0.193g; 1.78mmol) in acetone (10ml) was added and the solution was magnetically stirred for 2h. The solvent was removed under reduced

pressure to yield a pale yellow liquid (0.161g). The ^{13}C nmr spectrum of the crude product showed it to contain mainly **5**, **6** and an unknown (**5**:**6**:unknown = 4:1:2). The unknown was tentatively assigned as **5-chloromethyl-3,3,5-trimethyl-1,2,4-trioxepane** (*NC*).

Assigned to the 1,2,4-trioxepane:
^{13}C : δ 21.24, 24.88, 36.39, 53.29(CH_2Cl), 71.34, 71.51, 108.60(OCOO) ppm +1C.

Cycloperoxychlorination in Acetone with Pyridine

With 3-methyl-3-buten-1-yl hydroperoxide (**2**) :

Hydroperoxide **2** (0.138g; 1.35mmol) and pyridine (0.101g; 1.27mmol) were dissolved in acetone (15ml) and cooled in an ice bath. ^tBuOCl (0.198g; 1.82mmol) in acetone (10ml) was added, and the solution was magnetically stirred for 4h. The acetone was removed under reduced pressure, and the crude material was redissolved in dichloromethane (20ml). This was then washed with 2M hydrochloric acid (15ml), water (10ml) and saturated sodium bicarbonate (15ml). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield 0.168g of crude product. By ^{13}C nmr spectroscopy, this contained mainly **5**, **6** and the unknown assigned as a 1,2,4-trioxepane (**5**:**6**:trioxepane = 5:1:1).

With *cis*-3-hexen-1-yl hydroperoxide (**3**) :

The crude product contained **12**, **13** and **24** in the ratio 1:9:3. This was separated using preparative HPLC (Waters LC500, 10% ethyl acetate in 60/80°C petroleum spirit, 40-60μm silica, 12in. x 1in. I.D. column, flow rate 0.5 dm^3min^{-1}):

***threo*-5-(1-Chloropropyl)-3,3-dimethyl-1,2,4-trioxepane (24) (*NC*)**

Yield : 10%. Retention time : 10-15 minutes.

^1H nmr : δ 1.05(t, J=7.32Hz, 3H, CH_3CH_2); 1.25(s, 3H, CH_3C^3); 1.44(s, 3H, CH_3C^3); 1.6-1.8(m, 2H); 1.87(m, 1H); 2.00(m, 1H); 3.79(m, 1H); 4.14(m, 2H); 4.25(m, 1H) ppm.
^{13}C nmr : δ 11.33(CH_3CH_2), 21.88, 24.82, 27.05, 33.40, 67.37(CHCl),

73.59, 73.75, 105.56(OOCO) ppm.
Mass spectrum : m/z(%) = 43(99), 59(100), 73(14), 77(10, $[CH^{35}ClEt]^+$), 79(3, $[CH^{37}ClEt]^+$), 150(4.6, $[M(^{35}Cl)\text{-MeCOMe}]^+$), 152(1.3, $[M(^{37}Cl)\text{-MeCOMe}]^+$), 208(0.3, $M[^{35}Cl]^+$).
High resolution mass spectrum : $C_9H_{17}{}^{35}ClO_3$ requires m/z = 208.0865.
Found : m/z = 208.0878.

threo-**3-(1-chloropropyl)-1,2-dioxolane (13)** (*NC*)

Yield : 14%. Retention time : 19-24 minutes.

^1H nmr : δ 1.07(t, J=7.30Hz, 3H, CH_3); 1.65(m, 1H); 1.90(m, 1H); 2.54(m, 1H, $C^4H^AH^B$); 2.70(m, 1H, $C^4H^AH^B$); 3.87(m, 1H, CHCl); 4.07(dt, J=6.83, 7.83Hz, 1H, CH^AH^BOO); 4.17(dt, J=4.77, 7.83Hz, 1H, CH^AH^BOO); 4.30(dt, J=8.20, 5.59Hz, 1H, C^3H) ppm.
^{13}C nmr : δ 11.12(CH_3), 26.89, 37.69, 64.29(CHCl), 70.10(CH_2OO), 81.79(CHOO) ppm.
Found : C, 47.66; H, 7.56%. Calc. for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36%.
Mass spectrum : m/z(%) = 29(64), 41(100), 43(42), 45(29), 55(28), 73(57, $[M\text{-}CHClEt]^+$), 77(27, $[CH^{35}ClEt]^+$), 79(8, $[CH^{37}ClEt]^+$), 150(4, $M[^{35}Cl]^+$), 152(1, $M[^{37}Cl]^+$).
High resolution mass spectrum : $C_6H_{11}{}^{35}ClO_2$ requires m/z = 150.0447.
Found : m/z = 150.0444.

With *trans*-3-hexen-1-yl hydroperoxide (**4**) :
The ^{13}C nmr spectrum of the crude material showed three products, **12**, **13** and the *erythro* isomer of **24** in the ratio 9:1:1 respectively.

The Reaction of ^tBuOCl and Acetone

Pyridine (0.117g; 1.48mmol) was dissolved in acetone (10ml). To this was added ^tBuOCl (0.260g; 2.40mmol) in acetone (10ml) and the solution was magnetically stirred for 2h. After this time there was no sign of any new, involatile products by TLC. *tert*-Butyl hydroperoxide (0.138g; 1.54mmol) in acetone (1ml) was then added, and the solution was stirred for a further 2h. After removal of the

solvent under reduced pressure, the crude product was examined by ^{13}C nmr spectroscopy. Apart from the signals due to pyridine and *tert*-butyl hydroperoxide, there were also fairly strong signals at δ 21.26, 26.18, 26.74, 30.69, 43.85, 47.32, 48.52 and 200.39 ppm.

Effect of BHT on Cycloperoxychlorination in Acetone and Pyridine

3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.110g; 1.08mmol), pyridine (0.098g; 1.24mmol) and BHT (0.075g; 0.34mmol) were dissolved in acetone (15ml). The solution was cooled in an ice bath, and then ^{t}BuOCl (0.212g; 1.95mmol) in acetone (5ml) was added. The solution was stirred for 2h at room temperature. The acetone was removed under reduced pressure, and the crude material was redissolved in dichloromethane (20ml). This was washed with 2M hydrochloric acid (15ml), water (15ml) and saturated sodium bicarbonate (15ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product (0.204g) was examined by ^{13}C nmr spectroscopy. This confirmed that the reaction had gone to completion, and that **5**, **6** and the 1,2,4-trioxepane were formed in the ratio 5:1:2.

Cycloperoxychlorination in Dimethylformamide (DMF)

Using the same conditions as for the reaction in dichloromethane :

3-Methyl-3-buten-1-yl hydroperoxide (**2**) (0.126g; 1.23mmol) was dissolved in DMF (10ml). To this was added ^{t}BuOCl (0.201g; 1.86mmol) in DMF (10ml) and the solution was magnetically stirred for 2h. It was then combined with water (40ml) and extracted with 60/80°C petroleum spirit (2x20ml). The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a yellow liquid (22mg). The ^{13}C nmr spectrum of this liquid showed it to contain **5** and unreacted **2** (**2**:**5** = 3:1) in addition to several unidentified products.

Using the modified method :

cis-3-hexen-1-yl hydroperoxide (0.119g; 1.03mmol) was dissolved in DMF (10ml) and placed in a water bath at room temperature. Neat

^{t}BuOCl was then carefully added dropwise until the yellow colour was no longer dissipated on addition. The solution was then combined with water (20ml) and extracted with 60/80°C petroleum spirit (2x10ml). The organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield *threo*-3-(1-chloropropyl)-1,2-dioxolane (**13**) (31mg; 20%). The ^{13}C nmr spectrum confirmed that the product is of quite high purity, and that none of the *erythro* isomer (**12**) was formed.

Cycloperoxychlorination in the Presence of Silica

With *cis*-3-hexen-1-yl hydroperoxide (**3**) :

Column chromatography grade silica (Merck silica gel 60, 70-230 mesh, 0.5g) was suspended in a solution of ^{t}BuOCl (0.195g; 1.80mmol) in dichloromethane (5ml). This was cooled to -20°C and a solution of *cis*-3-hexen-1-yl hydroperoxide (**3**) (0.186g; 1.60mmol) in dichloromethane (5ml), pre-cooled to -20°C, was added. The mixture was magnetically stirred for 1.5h while warming to room temperature. The silica was then filtered off and washed with dry ether. Removal of the solvent under reduced pressure yielded 0.166g of crude material which was separated by column chromatography (CH_2Cl_2 then ether).

threo-3-(1-Chloropropyl)-1,2-dioxolane (**13**) :

Yield : 44mg (18%).

Unknown assigned as **25** :

Yield : 24mg. R_f 0.59 (ether).

^{13}C nmr : δ 10.02, 23.75, 45.38, 61.47, 81.94, 97.15 ppm.
Mass spectrum : m/z(%) = 29(68), 41(60), 57(100), 59(71), 69(25), 85(22), 115(20), 149(0.4), 151(0.2).

With *trans*-3-hexen-1-yl hydroperoxide (**4**) :

As above, with the same solvent system used for the

chromatography :

erythro-**3-(1-Chloropropyl)-1,2-dioxolane (12)** (*NC*)

Yield : 8%. R_f 0.65 (CH_2Cl_2)

^1H nmr : δ 1.04(t, J=7.30Hz, 3H, CH_3); 1.64(m, 1H); 2.03(m, 1H); 2.66(m, 1H, $C^4H^AH^B$); 2.78(m, 1H, $C^4H^AH^B$); 3.75(dt, J=3.06, 8.86Hz, 1H, CHCl); 4.03(approx. q, J_{ave}=7.62Hz, 1H, CH^AH^BOO); 4.17(dt, J=4.31, 7.85Hz, 1H, CH^AH^BOO); 4.27(approx. dt, J_{ave}=4.49, 8.29Hz, 1H, C^3H) ppm.
^{13}C nmr : δ 10.36(CH_3), 28.17, 39.41, 64.85(CHCl), 69.86(CH_2OO), 82.03(CHOO) ppm.
Mass spectrum : m/z(%) = 29(85), 41(100), 55(50), 57(32), 73(51, $[M-CHClEt]^+$), 77(20, $[CH^{35}ClEt]^+$), 150(1.5, $M[^{35}Cl]^+$), 152(0.2, $M[^{37}Cl]^+$).
High resolution mass spectrum : $C_6H_{11}{}^{35}ClO_2$ requires m/z = 150.0447. Found : m/z = 150.0441.

Unknown assigned as **26**

R_f 0.58 (ether).

^{13}C nmr : δ 9.88, 10.01, 25.81, 27.44, 43.43, 43.65, 57.49, 57.89, 86.16, 88.11, 97.52 ppm.

With 3-methyl-3-buten-1-yl hydroperoxide (**2**) :

This hydroperoxide was shown, by ^{13}C nmr spectroscopy on the crude product, to yield a mixture consisting mainly of **5**, **6** and **9** in the ratio 4.2:1:1.3 respectively.

With 3-buten-1-yl hydroperoxide (**1**) :

The ^{13}C nmr spectrum of the crude product showed an approximately 2:1 mixture of **10**:**14**.

3,4-Dichlorobutan-1-ol (15)

3-Buten-1-ol (3.63g; 50mmol), calcium chloride (5.55g; 50mmol), benzyltriethylammonium chloride (100mg; 0.44mmol) and concentrated hydrochloric acid (10ml; *ca.* 125mmol HCl) in dichloromethane (10ml) were magnetically stirred while being cooled in ice. 30% w/v Hydrogen peroxide (6ml; 53mmol H_2O_2) was added dropwise to the suspension. The mixture was stirred for 2h at room temperature. It was then diluted with dichloromethane (20ml), and the aqueous layer was extracted with dichloromethane (3x20ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a colourless liquid (3.77g; 53%). This was purified on silica (ether : 60/80°C petroleum spirit; 1 : 1) to afford the pure dichloride (3.21g; 45%).

^1H nmr : δ 1.80(br s, 1H); 1.88(m, 1H); 2.24(m, 1H); 3.71(dd, J=11.42, 6.99Hz, 1H); 3.79(dd, J=11.42, 5.11Hz, 1H); 3.84(m, 2H); 4.27(m, 1H) ppm.
These agree with the literature values.[22]

^{13}C nmr : δ 37.51, 48.53, 57.86, 58.73 ppm.
Found : C, 33.48; H, 5.63; Cl, 49.39%. Calc. for $C_4H_8OCl_2$: C, 33.59; H, 5.64; Cl, 49.58%.

Oxidation of 3,4-Dichlorobutan-1-ol (15)

To a magnetically stirred suspension of pyridinium chlorochromate (4.31g; 20mmol) and sodium acetate (0.23g; 2.8mmol) in dry dichloromethane (15ml) was added 3,4-dichlorobutan-1-ol (1.43g; 10mmol) in dry dichloromethane (15ml). A condenser was attached to the flask, and the mixture was stirred for 3h. Dry ether (20ml) was then added and the liquid was decanted off. The residual black tar was washed with dry ether (3x20ml) and the combined organic layers were filtered through a sandwich of silica in Celite. Removal of the solvent under reduced pressure yielded 0.49g of crude product. Examination by ^{13}C nmr spectroscopy showed 16 strong signals :

Assigned to 3,4-dichlorobutanal (**14**) : δ 47.43, 48.15, 53.04, 197.52 ppm.
Assigned to 4-chloro-2-butenal (**16**) : δ 42.15, 133.58, 149.48, 192.53 ppm.
Others : δ 33.91, 39.99, 47.24, 47.98, 55.10, 57.17, 61.32, 169.08 ppm.

Formation of 2,4-Dinitrophenylhydrazones[26]

2,4-Dinitrophenylhydrazine (0.50g; 2.52mmol) was suspended in methanol (10ml). Concentrated sulphuric acid (1ml) was slowly added and the resultant solution filtered while still warm. The crude material from the oxidation of 3,4-dichlorobutan-1-ol (0.49g) in methanol (2ml) was then added. After being left for about 10min., an orange precipitate appeared which was filtered off (0.138g). The product was recrystallised from ethyl acetate and dried (20°C/ 0.01mmHg).

4-Chloro-2-butenal 2,4-Dinitrophenylhydrazone

^{13}C nmr (DMF; DMSO-d_6 lock tube) : δ 44.02, 116.49, 122.55, 122.69, 129.53, 130.08, 137.46, 144.49, 149.87 ppm +1C.

The spectrum was identical to that of the product formed when 3-buten-1-yl hydroperoxide (**1**) was treated with ^tBuOCl and pyridine in dichloromethane, followed by 2,4-dinitrophenylhydrazine and acid in methanol as above.

Reaction of 3,4-Dichlorobutan-1-ol Oxidation Product with Base

The above PCC oxidation of 3,4-dichlorobutan-1-ol (**15**) was repeated to give 0.43g of the same mixture as found above. This was dissolved in dichloromethane (10ml), and pyridine (0.083g; 1.05mmol) in dichloromethane (5ml) was added. This was magnetically stirred for 4h, after which there was no change in the reaction mixture as judged by TLC. Hence sodium acetate (0.083g; 1.02mmol) was added and stirring was continued for a further 3.5h. The mixture was then

washed with 2M hydrochloric acid (15ml), water (15ml) and saturated sodium bicarbonate (15ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield 0.34g of crude product. The ^{13}C nmr spectrum showed that the signals which had been assigned to 3,4-dichlorobutanal (**14**) had now disappeared.

Reaction of ^{t}BuOCl with Hydrogen Chloride

A few drops of ^{t}BuOCl were dissolved in $CDCl_3$ in an nmr tube (δ 26.78, 83.87 ppm). Hydrogen chloride (generated from the action of concentrated sulphuric acid on solid ammonium chloride) was then bubbled through the solution for 5 minutes. The solution rapidly turned deep yellow. The ^{13}C nmr spectrum was re-examined (δ 34.43, 67.42 ppm : *tert*-butyl chloride). On the addition of a couple of drops of 3-buten-1-ol the yellow colour was discharged. Apart from the signals due to *tert*-butyl chloride, there were four other signals in the spectrum (δ 37.55, 48.57, 57.87, 59.01 ppm) which were due to 3,4-dichlorobutan-1-ol (**15**). On being left to stand for a few hours, an aqueous layer separated out.

2.3.3 Cyclooctenyl Systems

Reaction of Cyclooctenyl Hydroperoxides with ^{t}BuOCl and Pyridine in Dichloromethane

With 3-cyclooctenyl hydroperoxide (**28**) :

3-Cyclooctenyl hydroperoxide (0.207g; 1.45mmol) and pyridine (0.122g; 1.54mmol) in dichloromethane (10ml) were cooled in an ice bath. ^{t}BuOCl (0.252g; 2.32mmol) in dichloromethane (10ml) was added, and the solution was magnetically stirred for 1h. The solution was then washed with 2M hydrochloric acid (10ml), water (10ml) and saturated sodium bicarbonate (10ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield 0.228g of crude material.

The ^{13}C nmr spectrum of the crude showed 8 strong peaks, assigned to **32**.

***trans*-3,4-Dichlorocyclooctanone (32)** (*NC*)

^{13}C nmr : δ 21.89, 27.07, 32.60, 40.96, 50.97, 60.65(**C**HCl), 66.84(**C**HCl), 210.08(**C**O) ppm.

With 4-Cyclooctenyl hydroperoxide (**29**) :

The ^{13}C nmr spectrum of the crude material again showed 8 strong signals, this time at δ 25.26, 28.65, 33.24, 38.60, 38.97, 64.18, 65.87, 213.86 ppm. This was shown by independent synthesis (*vide infra*) to be *trans*-4,5-dichlorocyclooctanone (**33**). The independent synthesis of *trans*-2-chloro-9-oxabicyclo[4.2.1]nonane (**31**) also enabled us to confirm the presence of this bicyclic ether in the crude product (**33:31** = 2.5:1)

Reaction of Cyclooctenyl Hydroperoxides with ^{t}BuOCl and Silica

With 3-cyclooctenyl hydroperoxide (**28**) :

Column chromatography grade silica (Merck silica gel 60, 70-230

mesh, 0.5g) was suspended in a solution of ^{t}BuOCl (0.249g; 2.29mmol) in dichloromethane (10ml) and cooled to -20°C. 3-Cyclooctenyl hydroperoxide (**28**) (0.228g; 1.60mmol) in dichloromethane (10ml), pre-cooled to -20°C, was added in one portion, and the mixture was magnetically stirred at -10°C for 1h then at room temperature for a further hour. The silica was then filtered off and washed with dry ether. Removal of the solvent under reduced pressure yielded a pale yellow liquid (0.281g) which was separated on silica (CH_2Cl_2 : 60/80°C petroleum spirit; 2 : 1).

***trans*-2-Chloro-8,9-dioxabicyclo[5.2.1]decane (30) (*NC*)**

Yield : 20%. R_f 0.53.

^{1}H nmr : δ 1.65-1.80(m, 5H); 1.99(m, 1H); 2.15(m, 1H); 2.26(m, 1H); 2.86(m, 2H); 4.33(dt, J=2.77, 4.99Hz, 1H); 4.50(m, 2H) ppm.
^{13}C nmr : δ 19.75, 25.16, 30.95, 33.96, 41.55, 60.97(**C**HCl), 76.74(**C**HOO), 80.91(**C**HOO) ppm.
Mass spectrum : m/z(%) = 35(63), 37(100), 39(85), 51(87), 53(62), 64(45), 76(25), 79(29), 94(19), 98(19), 176(2.4, M[^{35}Cl]$^+$), 178(0.6, M[^{37}Cl]$^+$).
High resolution mass spectrum : $C_8H_{13}{}^{35}ClO_2$ requires m/z = 176.0603. Found : m/z = 176.0592.

3-Chlorocyclooctanone (39) (*NC*)

Yield : 10%. R_f 0.28.

^{13}C nmr : δ 22.74, 23.58, 27.51, 37.24, 43.55, 49.83, 58.38(**C**HCl), 211.52(**C**=O) ppm.

With 4-cyclooctenyl hydroperoxide (**29**) :

The ^{13}C nmr spectrum of the crude material showed that by far the major product was 4-chlorocyclooctanone (**37**), with the bicyclic ether (**31**) as a minor product (**37:31** = 4:1). Both these compounds were identified by comparison with the ^{13}C nmr spectra of authentic samples (*vide infra*).

4-Chlorocyclooctanone (37) and *trans*-2-Chloro-9-oxabicyclo[4.2.1]-nonane (31)

4-Cycloocten-1-ol (0.272g; 2.15mmol) was dissolved in dichloromethane (5ml). Column chromatography grade silica (0.5g) was added and the mixture was magnetically stirred. The flask was cooled in ice, and a solution of ^{t}BuOCl (0.244g; 2.25mmol) in dichloromethane (5ml) was slowly added. The mixture was stirred at 0°C for 0.5h, and at room temperature for a further 2h. The silica was then filtered off and washed through with dry ether (20ml). The solvent was removed under reduced pressure to yield 0.322g of crude product, which was separated by column chromatography (25% ether in 60/80°C petroleum spirit).

***trans*-2-Chloro-9-oxabicyclo[4.2.1]nonane (31) (*NC*)**

Yield : 8%. R_f 0.44.

^{1}H nmr (200MHz) : δ 1.20-2.30(m, 10H); 4.06(m, 1H); 4.47(m, 2H) ppm.
^{13}C nmr : δ 21.30, 23.88, 34.20, 34.31, 35.43, 61.16(CHCl), 76.53(CHO), 81.72(CHO) ppm.
Mass spectrum : m/z(%) = 51(18), 54(100), 55(87), 67(74), 80(77), 95(59), 107(14), 116(9), 125(27, $[M-Cl]^{+}$), 160(30, $M[^{35}Cl]^{+}$), 162(8, $M[^{37}Cl]^{+}$).
High resolution mass spectrum : $C_8H_{13}{}^{35}ClO$ requires m/z = 160.0654. Found : m/z = 160.0651.

4-Chlorocyclooctanone (37)

Yield : 35%. R_f 0.12.

^{1}H nmr (200MHz) : δ 1.50-1.90(m, 6H); 2.20-2.70(m, 6H); 4.14(m, 1H) ppm.
^{13}C nmr : δ 22.52, 28.54, 31.22, 34.03, 39.62, 40.54, 60.94, 215.61 ppm.
I.R. : ν(C=O str.) = 1699cm^{-1} [Lit.[40] : 1706cm^{-1}]. ν(C-Cl str.) = 672cm^{-1}.

Mass spectrum : m/z(%) = 41(58), 55(100), 67(28), 83(22), 97(20, $[M-CO,Cl]^+$), 116(25), 118(9), 125(6, $[M-Cl]^+$), 132(20, $[M-CO]^+$), 134(6), 160(7, $M[^{35}Cl]^+$), 162(2, $M[^{37}Cl]^+$).
High resolution mass spectrum : $C_8H_{13}{}^{35}ClO$ requires m/z = 160.0654. Found : m/z = 160.0635.
Found : C, 59.05; H, 8.09%. Calc. for $C_8H_{13}ClO$: C, 59.81; H, 8.16%.

4-Cycloocten-1-one (35)

4-Cycloocten-1-ol (**34**) was oxidised with PCC using an identical method to that employed for 3,4-dichlorobutan-1-ol (**15**) (p. 89). The crude ketone was purified on silica (CH_2Cl_2; Yield : 52%) and had identical ^1H and ^{13}C nmr spectra to those reported in the literature.[17]

***trans*-4,5-Dichlorocyclooctanone (33)** (*NC*)

4-Cycloocten-1-one was chlorinated using the method of Olah *et. al.*[24] (see synthesis of 3,4-dichlorobutan-1-ol, p. 89). The crude product was purified on silica (ethyl acetate : 60/80°C petroleum spirit; 1 : 1) to produce a colourless liquid (45%; R_f 0.48).

^1H nmr (200MHz) : δ 1.7-2.4(m, 4H); 2.6-2.9(m, 6H); 3.98(dt, J=1.15, 8.06Hz, 1H, CHCl); 4.30(m, 1H, CHCl) ppm.
^{13}C nmr : δ 25.28, 28.93, 33.02, 38.88, 39.29, 64.20(**C**HCl), 65.84(**C**HCl), 214.08(**C**=O) ppm.
Found : C, 49.68; H, 6.55; Cl, 35.97%. Calc. for $C_8H_{12}OCl_2$: C, 49.25; H, 6.20; Cl, 36.35%.

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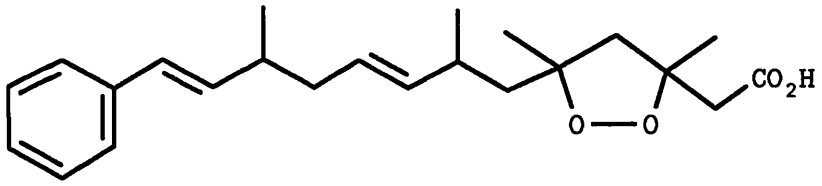
CHAPTER 3

SYNTHESIS AND CYCLISATION OF 2-SUBSTITUTED 3-BUTEN-1-YL HYDROPEROXIDES

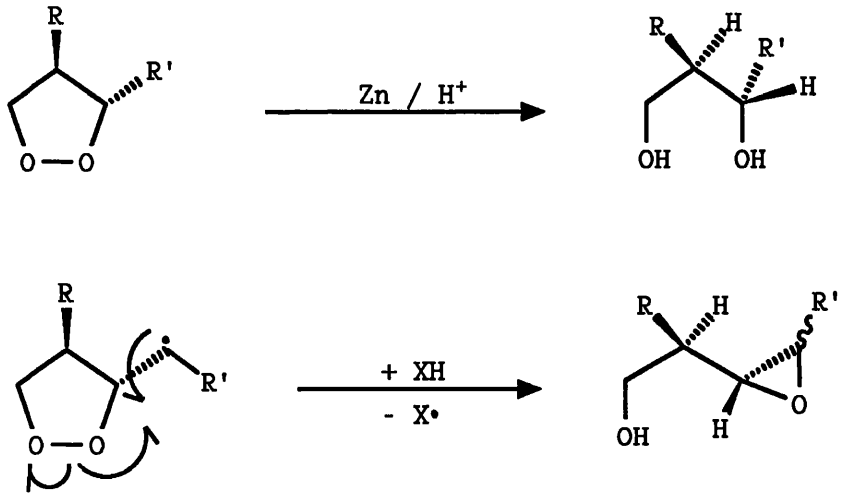
3.1 INTRODUCTION

The stereoselective synthesis of 1,2-dioxolanes is of great interest, considering the importance of such compounds both as natural products and as intermediates in organic synthesis. For example plakinic acid A (**1**),[1] the stereochemistry of which has not



1

yet been determined, is isolated from marine sponges, and has been shown to have antifungal properties. From a synthetic point of view, cyclic peroxides can be useful precursors of diols, epoxy-alcohols and other oxygenated compounds (Scheme 1).



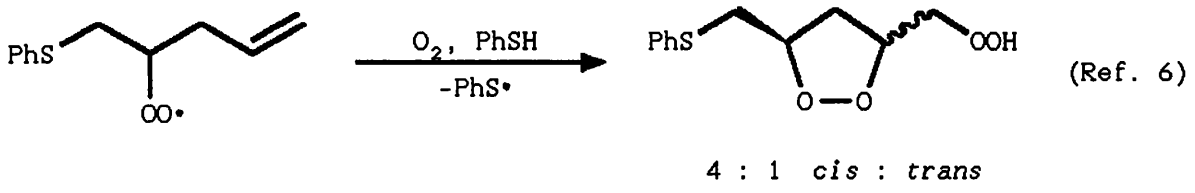
Scheme 1

A well established process for the synthesis of 1,2-dioxolanes is the cyclisation of unsaturated hydroperoxides. The stereochemistry of these reactions, particularly those leading to

3,4-disubstituted species, has not been extensively studied.

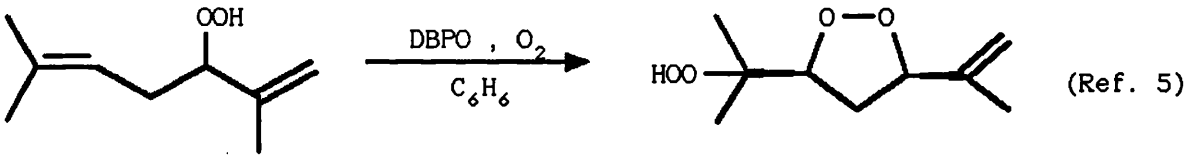
There are several examples in the literature of the cyclisation of secondary γ,δ-unsaturated hydroperoxides under both polar[2-4] and radical[5-13] conditions, a few of which are given in Scheme 2.

Radical



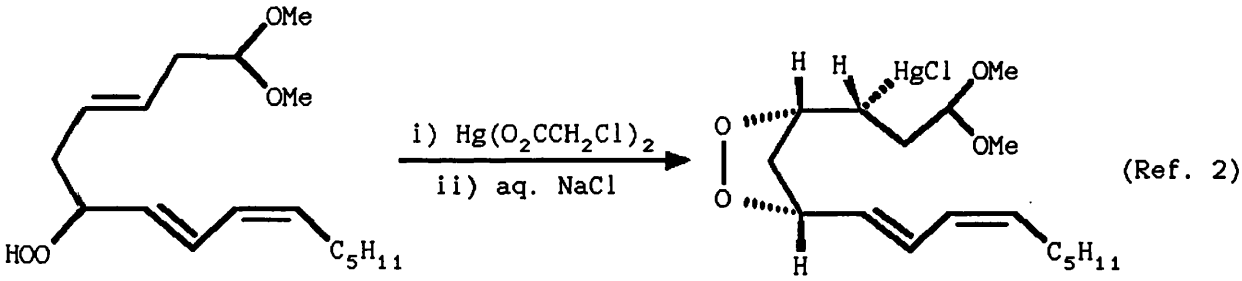
(Ref. 6)

4 : 1 *cis* : *trans*

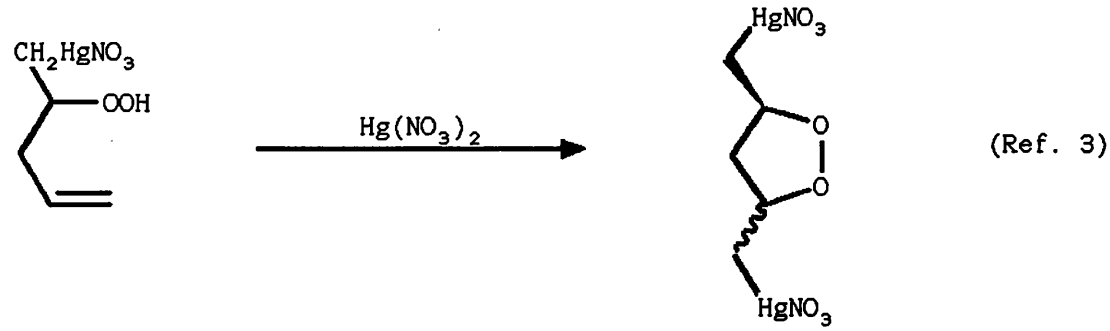


(Ref. 5)

Electrophilic



(Ref. 2)



(Ref. 3)

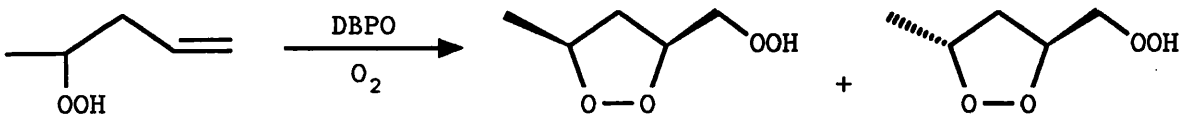
1 : 1 *cis* : *trans*

Scheme 2

A systematic study of the reactions of 4-penten-2-yl hydroperoxide (**2**) has been carried out by E. Rimmer.[14] As in the

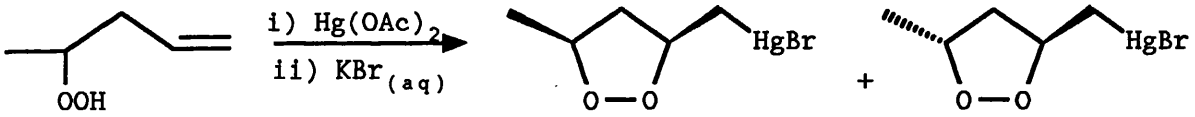
previous examples, the cyclisations produced predominantly *cis*-3,5-disubstituted-1,2-dioxolanes, with the stereoselectivity observed to be greater under radical conditions than under polar conditions (Scheme 3). The isomer ratios were dependent on whether the products were formed under kinetic (e.g. di-*tert*-butyl-peroxyoxalate : DBPO) or thermodynamic control (e.g. mercury(II) nitrate; see Chapter 1, p. 23).

Radical



2 Major Minor

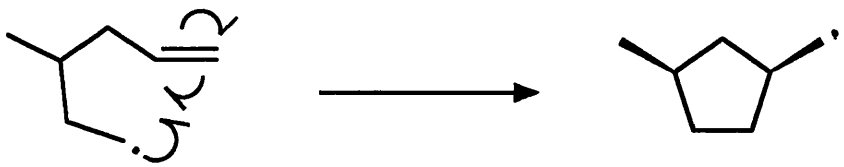
Electrophilic



2 Major Minor

Scheme 3

As indicated in Schemes 2 and 3, both radical and electrophile induced cyclisations have been studied. The radical cyclisations are generally initiated with DBPO, a mechanism for which is shown in Chapter 1 (Scheme 11). The preference for the *cis* disposition of substituents in the products derived from the cyclisation of the peroxyl radicals is in agreement with that observed for the corresponding carbon-centred radicals. Thus, the 3-methyl-5-hexen-1-yl radical (**3**) gives mainly the *cis*-(3-methylcyclopentyl)-

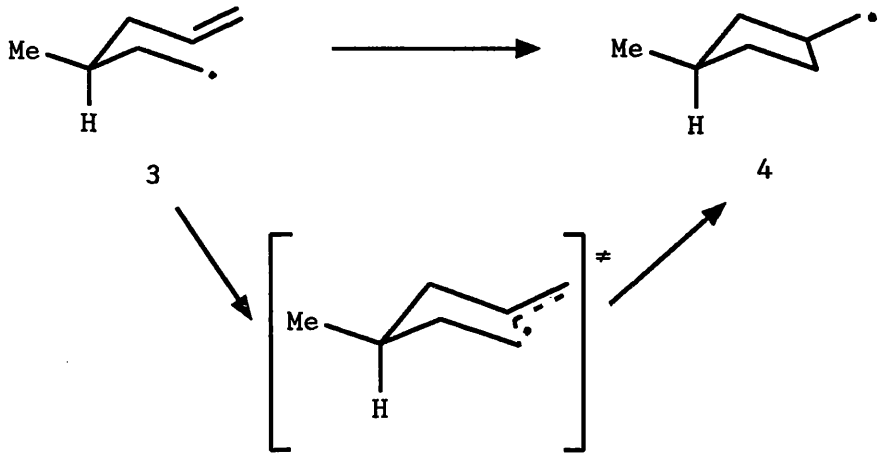


3 4

Scheme 4

methyl radical (**4**) (Scheme 4).[15]

This was rationalised by assuming that the transition state adopted a cyclohexane chair-like conformation in which the methyl group is in a pseudo-equatorial position, thus minimising steric interactions. (Scheme 5).



Scheme 5

The minor, *trans*, isomer probably arises *via* a similar transition state with a pseudo-axial substituent, though in the case of a bulky group (*e.g.* ^{t}Bu), it is found that a boat-like transition state with a pseudo-equatorial substituent is lower in energy.[16]

The stereoselectivity observed for the electrophilic cyclisations can be rationalised in a similar manner, assuming a transition state similar to that shown in Fig. 1. Most of these

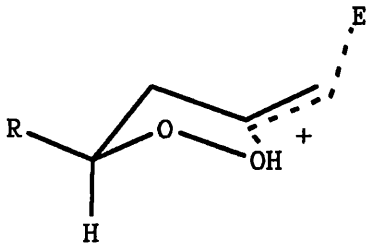
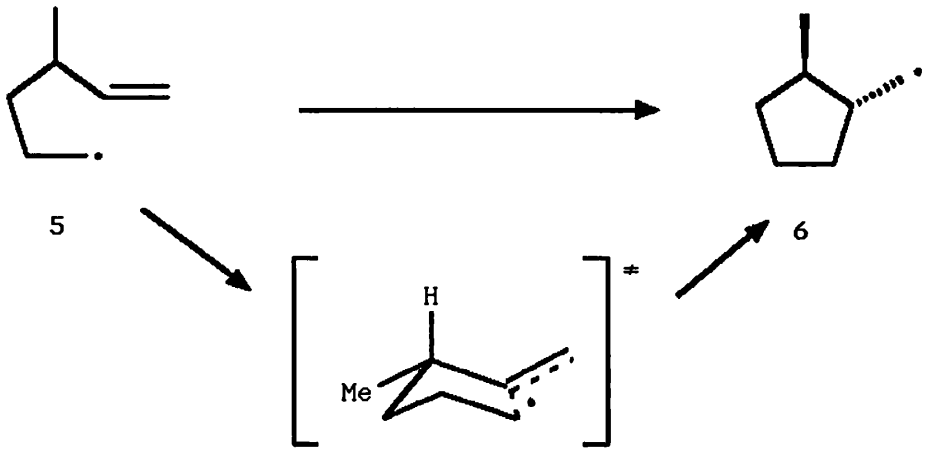


Figure 1

reactions have been carried out using a mercury(II) salt as the electrophile, the mechanism for which is also shown in Chapter 1 (Scheme 18).

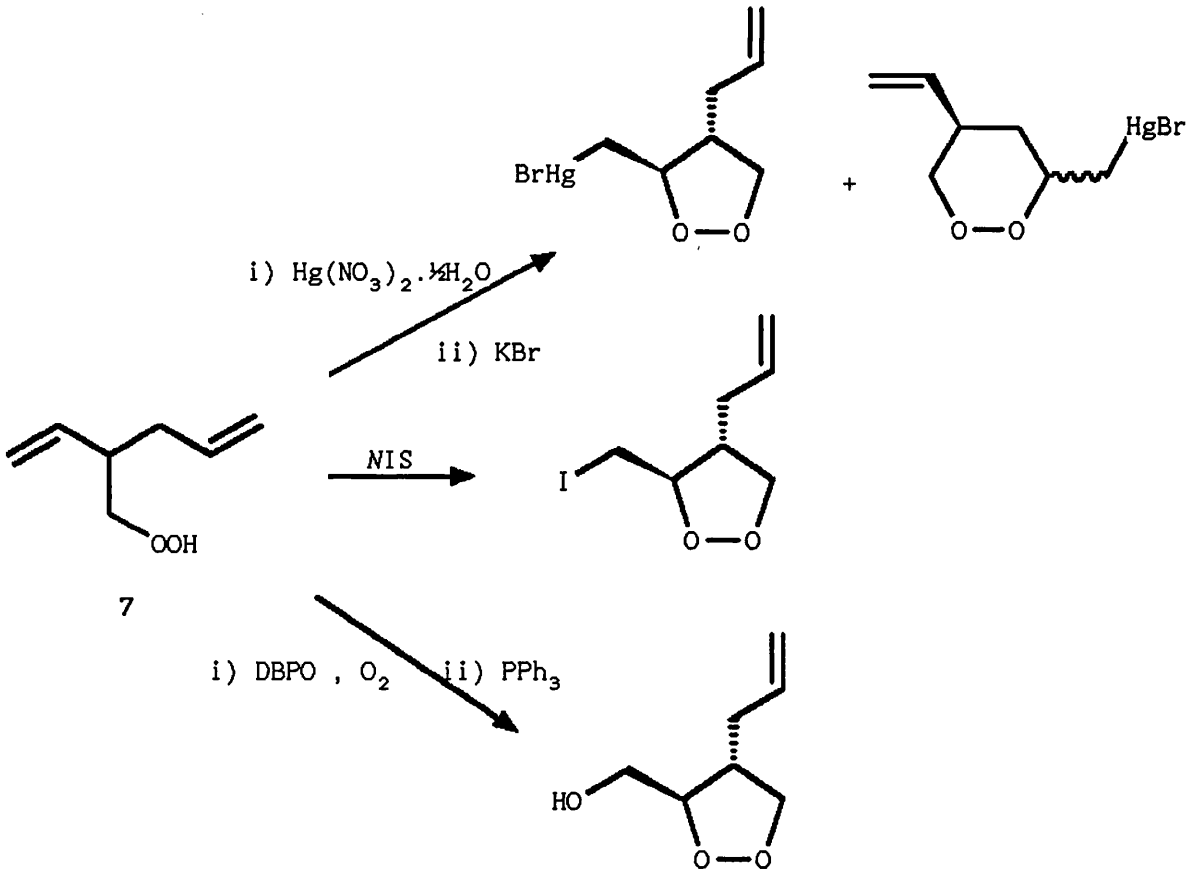
On the other hand, the work of Beckwith *et. al.*[15] showed that on cyclisation the 4-methyl-5-hexen-1-yl radical (**5**) gives mainly

trans-(2-methylcyclopentyl)methyl radical (**6**), which is rationalised in a manner similar to that for **3** (Scheme 6).



Scheme 6

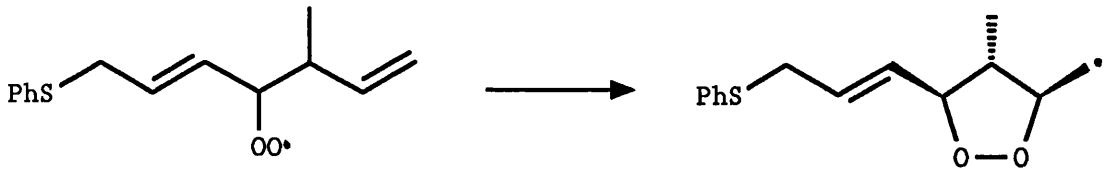
As expected, the few examples of similarly substituted hydroperoxides reported in the literature give mainly



Scheme 7

trans-3,4-disubstituted-1,2-dioxolanes. Bloodworth *et al.* looked at the cyclisation of hydroperoxide **7** with particular respect to the regioselectivity of the reactions.[17] The work does however give some information on stereoselectivity, the results are summarised in Scheme 7.

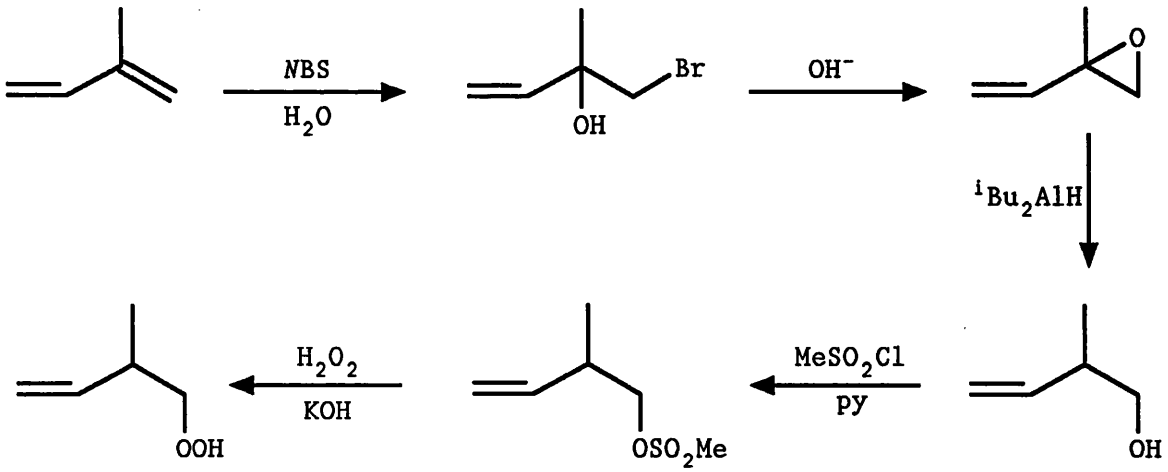
Beckwith *et al.* also showed that the peroxyl radical **8** cyclised to give a 3,4,5-trisubstituted 1,2-dioxolane with a *trans* disposition of the 3- and 4-alkyl groups (Scheme 8).[18]



8

Scheme 8

In order to carry out a more detailed study of the stereochemistry of these reactions, a general synthesis of 2-substituted-3-buten-1-yl hydroperoxides is required. 2-Methyl-3-buten-1-yl hydroperoxide (**9**) had previously been synthesised by J. Kuras using the route shown in Scheme 9.[19]



9

Scheme 9

This does however have two problems. Firstly, the overall yield of **9** is very low, a particular problem being the final step, where the methyl group in the 2-position greatly reduces the rate of S_N2 substitution at the CH_2OSO_2Me group. Secondly, it is not a route which easily lends itself to the synthesis of hydroperoxides with

different 2-substituents.

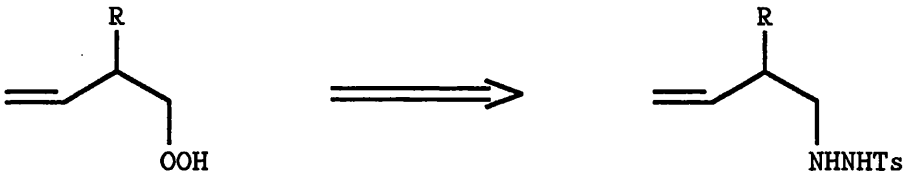
The aim therefore was to formulate an improved synthesis of these hydroperoxides, and thence investigate the stereochemistry of the cyclisation reactions using various reagents.

Of the reagents which will be used, only *N*-iodosuccinimide (*N*IS) is believed to induce an entirely radical cyclisation.[20] In contrast, the reactions with the mercury(II) salts are entirely polar. As discussed in the introduction to Chapter 2, *N*-bromosuccinimide (*N*BS) may well exhibit both polar and radical mechanisms. Similarly, *tert*-butyl hypochlorite (^{t}BuOCl) is known to cause both polar and radical cyclisations of unsaturated hydroperoxides, depending to some extent on any additives used in the reaction. In the presence of silica, polar cyclisation is observed, whilst in its absence both mechanisms operate; a full account of the reaction can be found in Chapter 2.

3.2 RESULTS AND DISCUSSION

3.2.1 Synthesis of Hydroperoxides

The problems previously encountered with synthesising hydroperoxide **9** *via* the methanesulphonate ester led us to investigate the possibility of making it, and other similarly substituted hydroperoxides, by the oxidation of the corresponding *N*'-tosylhydrazines[21] (Scheme 10).

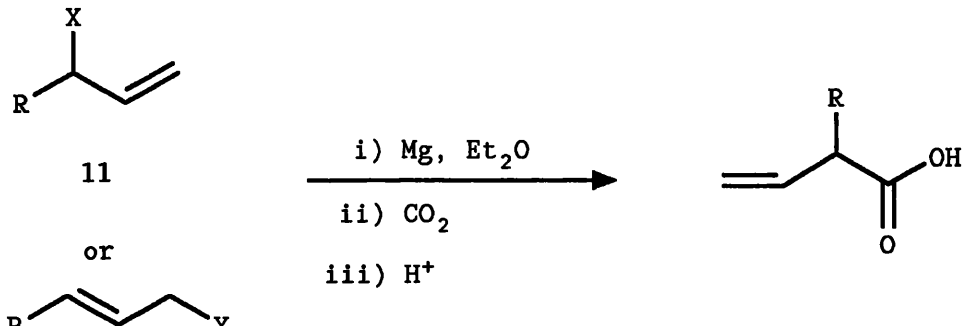


9 R = Me

10 R = Me

Scheme 10

The basic carbon skeleton can be conveniently synthesised by the carboxylation of allylic Grignard reagents[22] (Scheme 11).



13 R = Me

14 R = Ph

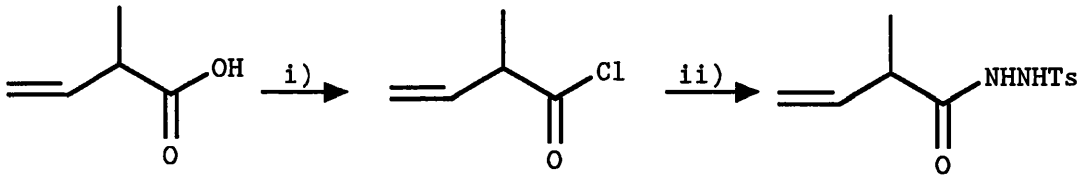
15 R = ^{t}Bu

Scheme 11

The observed rearrangement with the Grignard reagent derived from **12** is well established for the reaction of such species with all unhindered carbonyl compounds and epoxides, and is attributed to the reaction being S_E2' with respect to the Grignard reagent.[23]

The initial development work was carried out on

2-methyl-3-butenoic acid (**13**), synthesised from crotyl bromide (**12**, X=Br) in 54% yield.[24] This could be readily converted into the *N'*-tosylhydrazide (**16**) in two steps (Scheme 12).



13 41 16

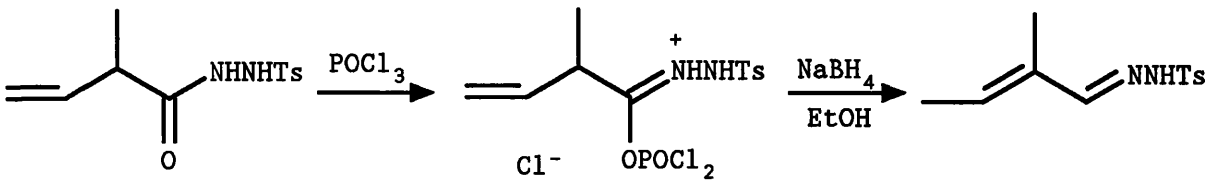
76% 64%

Reagents : i) $SOCl_2$ ii) $TsNHNH_2$, py

Scheme 12

The only literature method for the reduction of hydrazides to hydrazines involves the use of borane-tetrahydrofuran complex (BH_3.THF),[25] which was presumed to be unsuitable for an unsaturated compound. The same paper also reports that lithium aluminium hydride over-reduces to produce the corresponding hydrocarbon, while other work indicates that the hydrazide group is unaffected by sodium borohydride in the absence of additives.[26] Our first plan therefore, was to look at the behaviour of the hydrazide under conditions used to reduce amides to amines.

In three cases, when using sodium borohydride and acetic acid in dioxan,[27] with diisobutylaluminium hydride,[28] and with tetrabutylammonium borohydride,[29] mixtures of unreacted starting material and several unidentified products were formed. A mixture of sodium borohydride and nickel chloride in methanol[30] merely hydrogenated the double bond, *N'*-tosyl-2-methylbutanohydrazide being isolated in 63% yield. Finally, a two step reduction was tried,[31]



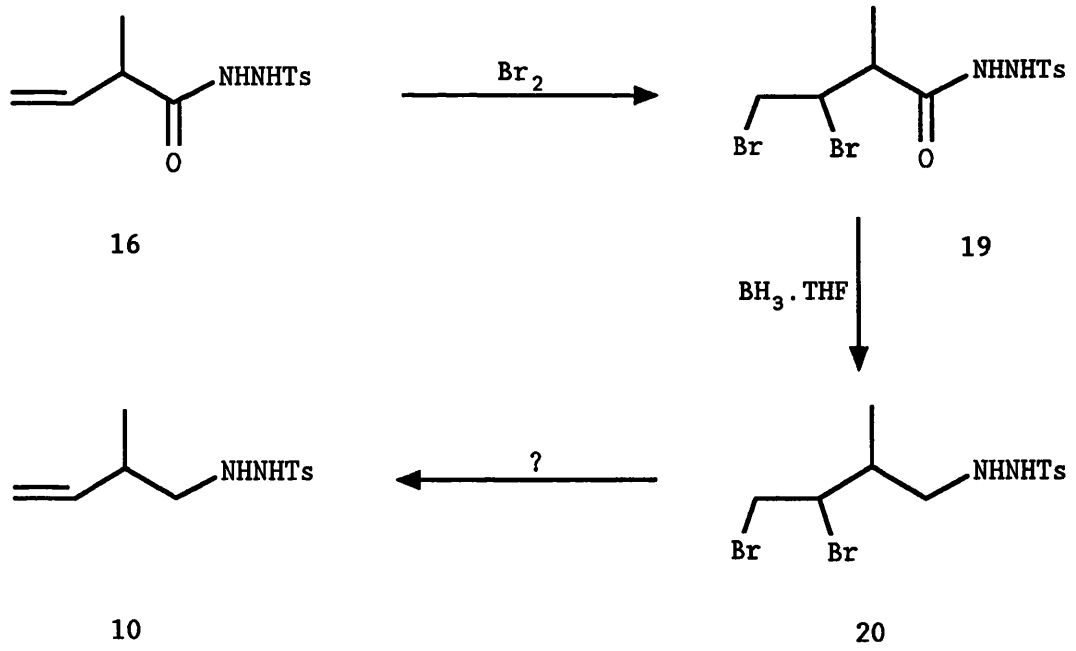
16 17 18

Scheme 13

where the hydrazide was first treated with phosphoryl chloride to form the salt (**17**), which was in turn treated with ethanolic sodium borohydride (Scheme 13). However, no hydrazine was detected, though what appeared to be the α,β-unsaturated hydrazone (**18**) was isolated in 17% yield.

Given the failure to effect direct reduction of the hydrazide, it was decided to try to protect the double bond, and reduce using diborane. Of the protecting groups available, the epoxide was disregarded due to its susceptibility to reduction by diborane, whilst complexing up the double bond to an iron compound was considered unsuitable because of the strongly acidic work-up necessary.[32] This just left the possibility of protecting the double bond as the dibromide.[33]

Hence, the unsaturated hydrazide (**16**) was treated with bromine to give the dibromide (**19**) quantitatively (Scheme 14). This was then



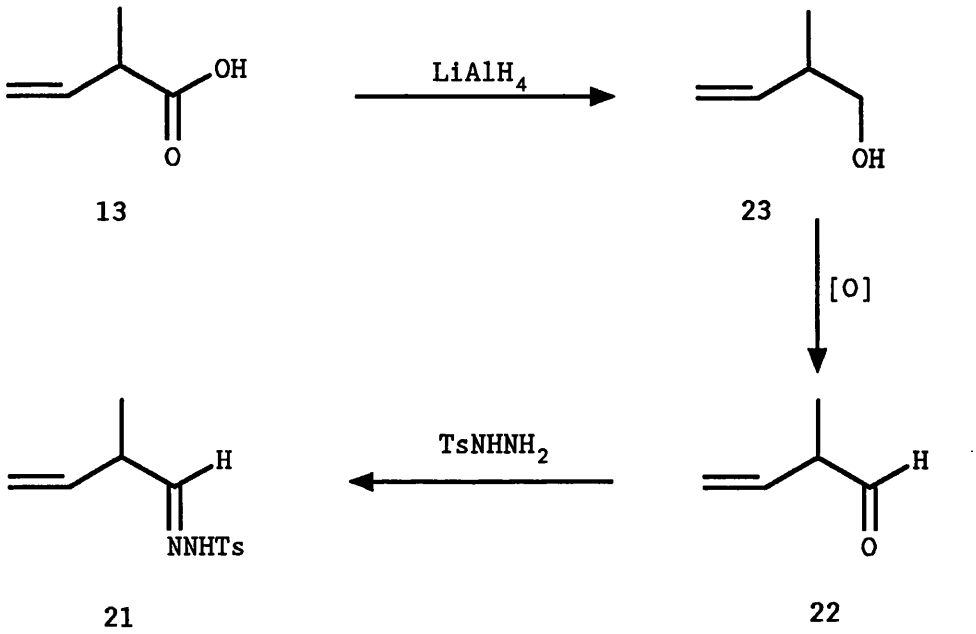
Scheme 14

treated with with borane in tetrahydrofuran, which gave a mixture in which the two diastereomeric dibromohydrazines (**20**) appeared to be the major products. No purification was attempted at this stage; the crude hydrazine was used in the debromination step.

To effect debromination we tried potassium iodide in ethanol,[34] zinc in ethanol (room temperature and reflux),[35] thiourea,[36] and iron(II) chloride with sodium acetate in ethanol and acetic acid.[37] In most cases tarring was observed and probable extrusion of

nitrogen, but there was never any sign of an unsaturated product. With zinc, it appeared as if the N-N bond was cleaved to produce an amine. This route was therefore abandoned, and an alternative synthesis of the *N'*-tosylhydrazine (**10**) was sought.

An obvious alternative was the synthesis of the *N'*-tosylhydrazone (**21**) followed by reduction with sodium cyanoborohydride.[38] This in turn required the synthesis of the unsaturated aldehyde (**22**) which can in theory be made from the corresponding acid (**13**) (Scheme 15).

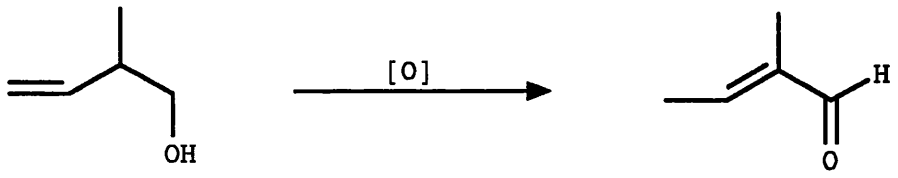


13 23 21 22

Scheme 15

The first step[39] was readily carried out to give the alcohol (**23**) in 84% yield. Production of the alcohol directly from the Grignard reagent precursor of **13** (Scheme 11) by treating it with formaldehyde instead of carbon dioxide is a possibility,[40] but we found that going *via* the acid was more convenient and gave much better yields.

Oxidation of the alcohol proved very problematical. Attempts were made using pyridinium chlorochromate (PCC),[41] dimethyl sulphoxide (DMSO) / oxalyl chloride at -60°C,[42] *N*-iodosuccinimide (*N*IS) with tetraethylammonium iodide[43] and silver carbonate on Celite,[44] but none proved successful. The major problem in all cases seemed to be the migration of the double bond into conjugation with the carbonyl group (Scheme 16). This route was therefore also abandoned.



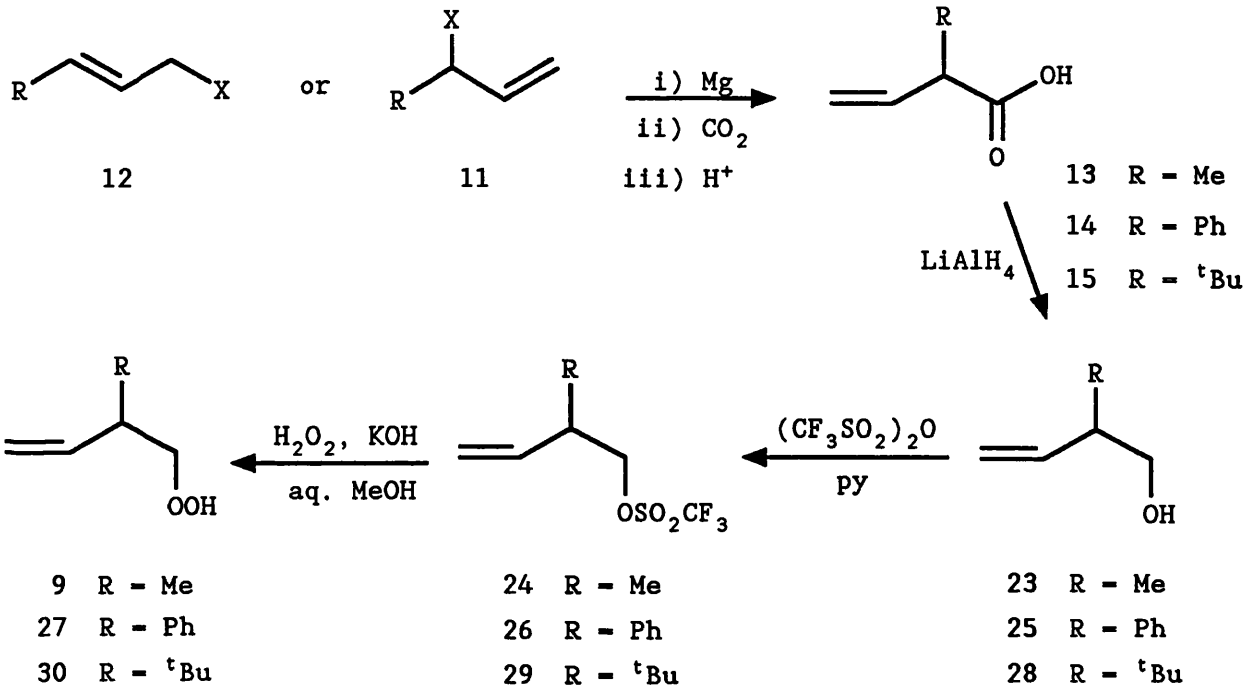
23

Scheme 16

Having failed to obtain the *N'*-tosylhydrazine (Scheme 10) our final strategy was to convert the alcohol group of **23** into a better leaving group, to facilitate a straightforward S_N2 reaction of the Mosher-Williams type.[45] The normal reaction, using the methanesulphonate ester (mesylate), had already been shown to be low yielding (4%).[19] An even better leaving group was apparently necessary, the obvious choice being to prepare the trifluoromethanesulphonate ester (triflate).[46,60]

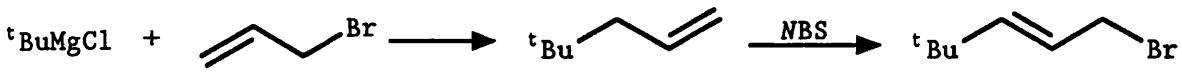
Treatment of the alcohol (**23**) with trifluoromethanesulphonic anhydride in the presence of pyridine[47] gave the crude triflate (**24**) in a yield of 85%. The ^{13}C nmr spectrum showed a small amount of impurities, but considering the instability of such compounds, purification was not attempted. The triflate was then converted to the hydroperoxide (**9**) by dissolving it in methanol and adding to an ice-cooled solution of potassium hydroxide and 30% hydrogen peroxide in water. A reaction time of only five minutes was necessary, and purification by base extraction gave up to a 35% yield of the hydroperoxide. The main by-product was presumably isoprene, formed by elimination of trifluoromethanesulphonic acid, but due to its volatility it was never detected. We therefore had a potentially general route to 2-substituted 3-buten-1-yl hydroperoxides (Scheme 17).

We next tried to extend this route to the phenyl substituted compounds. Starting from cinnamyl chloride (**12**, R = Ph, X = Cl), 2-phenyl-3-butenoic acid[48] (**14**) was prepared in 25% yield. This was reduced quantitatively to the alcohol (**25**). However, great problems were encountered when this was converted to the triflate (**26**). Isolation of this compound was impossible due to its instability, and attempts at perhydrolysis *in situ* were unsuccessful. After the triflate twice decomposed violently at room temperature, the synthesis of the hydroperoxide (**27**) was not pursued further.



Scheme 17

Instead we turned our attention to 2-*tert*-butyl-3-buten-1-yl hydroperoxide (**30**). For this compound it was necessary to synthesise 1-bromo-4,4-dimethylpent-2-ene[49] (**31**) by the route shown in scheme 18. Carboxylation of the Grignard reagent derived from **31** gave 2-*tert*-butyl-3-butenoic acid (**15**) in 34% yield. This was in turn reduced with lithium aluminium hydride to 2-*tert*-butyl-3-buten-1-ol (**28**) in 90% yield. However, as with the phenyl analogue, the triflate (**29**) proved very unstable at room temperature, and attempts to isolate it gave only polymeric tars.



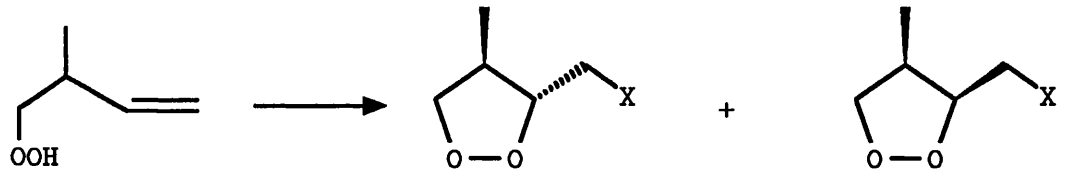
40 31

Scheme 18

Therefore, only the cyclisation of 2-methyl-3-buten-1-yl hydroperoxide (**9**) has been investigated.

3.2.2 Cyclisation of 2-Methyl-3-buten-1-yl Hydroperoxide

In order to investigate the stereochemistry of the cyclisation, 2-methyl-3-buten-1-yl hydroperoxide (**9**) was treated with a variety of reagents (Scheme 19). In each case the ratio of the *cis* and *trans* isomers was measured from the relative integrals of the two methyl doublets in the ^{1}H nmr spectrum of the crude product (Table 1).



9

Reagent		X	
HgY_2/KBr	**32t**	HgBr	**32c**
HgY_2/KCl	**33t**	HgCl	**33c**
*N*IS	**34t**	I	**34c**
*N*BS	**35t**	Br	**35c**
^{t}BuOCl	**36t**	Cl	**36c**

Scheme 19

As can be seen, only the cyclisation with mercury(II) nitrate produces a significant amount of stereoselectivity (compare the ^{1}H nmr spectra of **32** derived from mercury(II) acetate and mercury(II) nitrate cyclisations shown in Fig. 2). This is presumed to be due to the nitric acid which is formed as a by-product and is capable of bringing about the deoxymercuration of the product. This enables an equilibrium to be established between the *cis* and *trans* isomers, giving thermodynamic as opposed to kinetic control of the product distribution (cf. Chapter 1, Scheme 19). With mercury(II) acetate, acetic acid is the by-product, which is too weak an acid to bring about deoxymercuration.

In order to determine the stereochemistry of the major isomer in the mercury(II) nitrate reaction, the resultant organomercurial (predominantly **32t**) was treated with tributyltin hydride[52] to give 3,4-dimethyl-1,2-dioxolane (**37**). The usual conditions for hydridodemercuration,[53] using basic sodium borohydride, gave a complex mixture of several compounds which proved impossible to

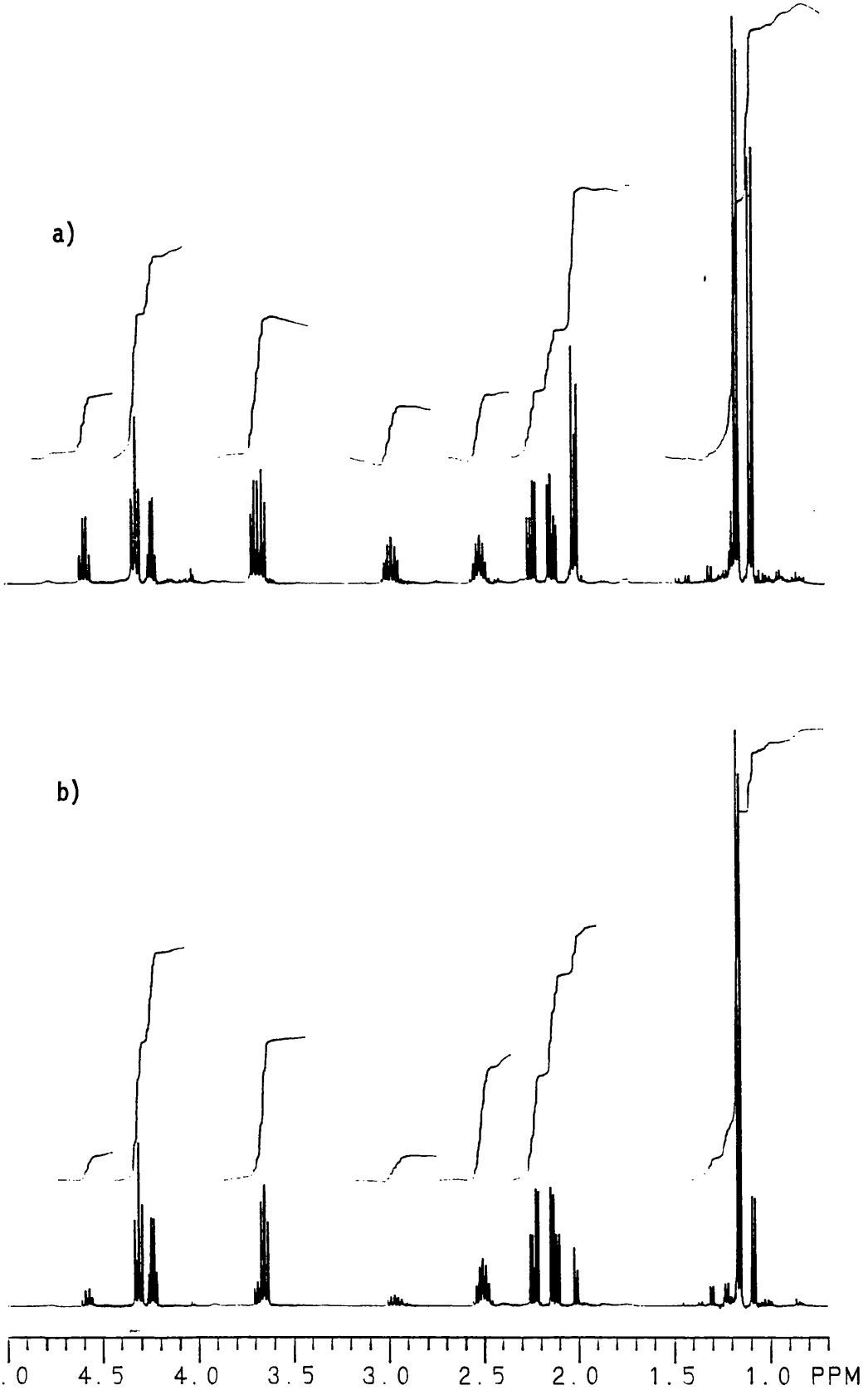


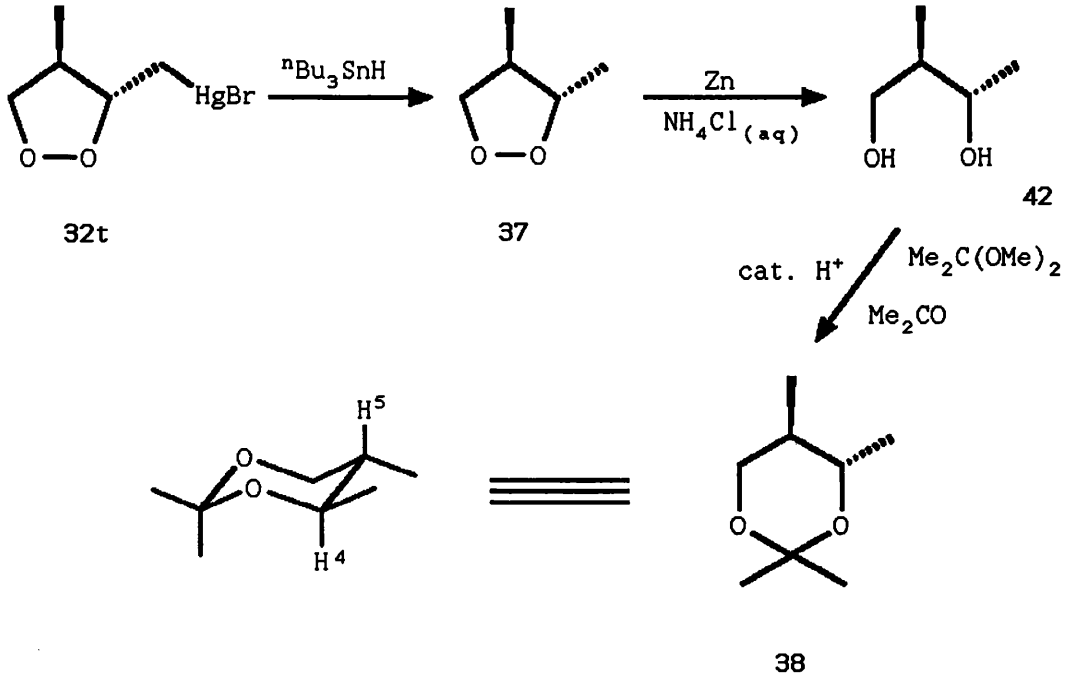
Figure 2 : The ^1H nmr spectra of the crude mixtures of **32c** and **32t** derived from cycloperoxymercuration of **9** with a) mercuric acetate and b) mercuric nitrate.

Product	Reagent	Ref.	*cis* : *trans*	Yield[a]
32	i) $Hg(OAc)_2$ ii) KBr	50	1 : 1	80%
32	i) $Hg(NO_3)_2.1/2H_2O$ ii) KBr	50	1 : 5	80%
33	i) $Hg(NO_3)_2.1/2H_2O$ ii) KCl	50	1 : 5	88%
34	*N*-Iodosuccinimide	20	1 : 1.3	45%
35	*N*-Bromosuccinimide	20	1 : 1	52%
36	^tBuOCl / SiO_2	51	1 : 2	29%

[a] After chromatography on SiO_2 except for the mercurials, which are yields for the crude material.

Table 1

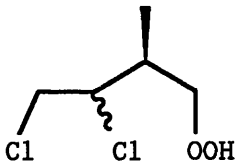
analyse. The dioxolane was then converted in two steps[17] to the 1,3-dioxane (**38**) (Scheme 20).



Scheme 20

Spin-spin decoupling experiments showed that the H^4-H^5 coupling constant was 8.2 Hz, consistent with an axial-axial disposition of these two protons,[6] as is found in the *trans* isomer.

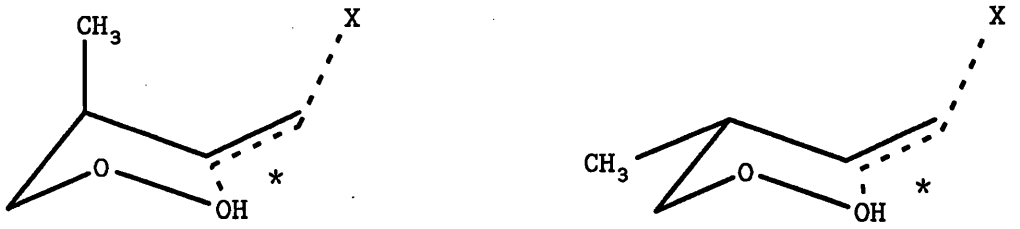
Having established the stereochemistry of **32t**, the stereochemistries of the halogenomethyl products could be determined by halogenodemercuration. Thus, treatment of **32t** with bromine or iodine[55] gave **35t** and **34t** respectively, confirming that the slightly favoured isomer in the *N*IS cyclisation is also *trans*. However, chlorodemercuration[56] of **33t** did not proceed smoothly, but gave **36c**, **36t**, **39e** and **39t** in equal quantities. Adding pyridine to the mixture



39e : *erythro*
39t : *threo*

largely suppressed the formation of the dichlorohydroperoxides, but both isomers of **36** were still formed in the ratio 2 : 1. The major isomer was identical to the major product from the *tert*-butyl hypochlorite cyclisation, and was assumed to be *trans* by analogy with the *N*IS and mercury(II) nitrate reactions. The reason for the side reactions is probably the presence of some hydrogen chloride in the solution of chlorine in chloroform. This would promote deoxymercuration to give the hydroperoxide (**9**) which would then react with chlorine to give the mixture of dioxolanes and chlorinated hydroperoxides observed. Indeed, treatment of **9** with chlorine in chloroform gave an almost identical product mixture to that obtained from the chlorodemercuration reaction in the absence of pyridine.

To account for the lack of stereoselectivity it must be assumed that the methyl group is not sufficiently bulky to produce any significant steric effects when placed in a pseudo-axial position in the transition state of the cyclisation reaction (Fig. 3). It should be noted that one of the 1,3-diaxial interactions of the methyl group is with an oxygen lone-pair, and it is known from work with 1,3-dioxanes[54] that alkyl - oxygen lone-pair interactions are weaker than alkyl - C-H interactions. Once the dioxolane is formed, then interactions between the adjacent methyl and CH_2X groups will result in the *trans*-3,4-disubstituted-1,2-dioxolane being slightly more stable than the *cis* isomer.



a) Transition state leading to *cis* isomer (32c)

b) Transition state leading to *trans* isomer (32t)

X = HgOAc, $HgNO_3$, Cl, Br, I. * = + or •

Figure 3

The poor selectivity observed is in contrast to that seen by Bloodworth *et. al.* for the corresponding 4-allyl compounds.[17] With *N*IS they found a high selectivity in favour of the *trans* isomer (Scheme 7), though this was reduced somewhat when *N*BS was used. As in our case, mercury(II) nitrate also gave predominantly the *trans* disubstituted 1,2-dioxolane. It must be assumed that the higher selectivity is due to the greater steric bulk of the allyl group in comparison with the methyl group.

If in both the allyl and methyl cases the minor isomer arises *via* a boat-like transition state with a pseudo-equatorial substituent,[16] then the nature of the alkyl group should have little effect on the stereoselectivity observed. Therefore, it seems likely that in at least one case (though not necessarily both) the minor isomer arises *via* a chair-like transition state with a pseudo-axial substituent. This is obviously more likely to occur with the less bulky methyl group, hence the representation of the transition state in Fig. 3a).

3.2.3 Conclusion

The synthesis of 2-substituted 3-buten-1-yl hydroperoxides by the carboxylation of appropriate allylic Grignard reagents followed by reduction to the alcohol, conversion to the triflate and subsequent treatment with basic hydrogen peroxide appears to be less general than hoped, due to the instability of the triflates. This route does however allow the preparation of 2-methyl-3-buten-1-yl hydroperoxide, cyclisation of which under kinetically controlled conditions gives an almost equimolar mixture of *cis*- and *trans*-3,4-disubstituted-1,2-dioxolanes. Only under thermodynamically controlled conditions, such as cyclisation with mercuric nitrate, is significant stereoselectivity observed, with the *trans* isomer being preferred.

Attempts at synthesising the hydroperoxides *via* an intermediate hydrazide failed, as no conditions could be found in which the hydrazide could be converted to the corresponding hydrazine. Similarly, the β,γ-unsaturated hydrazone proved impossible to make, due to the tendency of the double bond to migrate into conjugation during the synthesis of the aldehyde precursor.

3.3 EXPERIMENTAL

For information on the instruments used, the conditions employed for spectroscopy, and general experimental details see Appendix A.

2-Methyl-3-butenoic acid (13)[24]

This was synthesised using a method very similar to that used by Roberts *et al.*[24]

Dry magnesium turnings (14.64g; 0.60mol) were suspended in dry ether (130ml) under nitrogen in a 500ml round bottomed flask equipped with mechanical stirrer, reflux condenser and dropping funnel. 3-Chloro-1-butene (18.11g; 0.20mol) in dry ether (70ml) was added over 1h at such a rate as to maintain a gentle reflux. The mixture was stirred for a further hour while being gently heated on a water bath. The mixture was then cooled in a dry ice/acetone bath, and poured onto solid carbon dioxide (*ca.* 230g; 5.2mol). After the excess carbon dioxide had evaporated, a mixture of ice and conc. hydrochloric acid (50ml) was added. The mixture was shaken vigorously and the ether layer was separated off. The aqueous layer was extracted with further ether (3x75ml), and the combined organic layers were extracted with 10% sodium carbonate (3x100ml). The basic extracts were washed with ether (50ml) and acidified with conc. hydrochloric acid. After saturating with sodium chloride, they were then extracted with ether (4x50ml). The ether extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a very pale yellow liquid (10.79g; 54%).

^1H nmr (200MHz): δ 1.29(d, J=7.16Hz, 3H); 3.19(m, 1H); 5.16(m, 2H); 5.93(m, 1H); 9.80(br s, 1H) ppm.
^{13}C nmr (50MHz): δ 16.20, 43.36, 116.07, 136.41, 180.51 ppm.

2-Phenyl-3-butenoic acid (14)[48]

This was prepared as for **13**, starting from freshly distilled cinnamyl chloride.

Pale yellow solid which melts at room temperature. (Lit.[48] m.p.

31-32°C)

Yield : 25%

^{1}H nmr (200MHz) : δ 4.38(d, J=8.04Hz, 1H); 5.26(m, 2H); 6.28(m, 1H); 7.38(s, 5H); 11.56(br s, 1H) ppm.

^{13}C nmr : δ 55.50, 118.07, 127.58, 128.03, 128.75, 134.86, 137.24, 179.00 ppm.

2-*tert*-Butyl-3-butenoic acid (15) (*New Compound; NC*)

This was prepared as for **13**, starting from 1-bromo-4,4,-dimethyl-2-pentene (**31**)

White crystalline solid (m.p. 73-75°C).

Yield : 18%

^{1}H nmr : δ 0.98 (s, 9H, $[CH_3]_3C$); 2.77(d, J=9.83Hz, 1H, ^{t}BuCH); 5.14(m, 2H, CH_2=); 5.90(ddd, J=17.06, 10.21, 9.83Hz, 1H, -CH=); 8.90(br s, 1H, CO_2H) ppm.

^{13}C nmr : δ 27.59($[CH_3]_3C$), 33.49($[CH_3]_3$**C**), 60.95, 118.98, 133.55, 179.44(CO_2H) ppm.

Found : C, 67.54; H, 10.30%. Calc. for $C_8H_{14}O_2$: C, 67.57; H, 9.92%.

4,4,-Dimethyl-1-pentene (40)[57]

Dry magnesium turnings (46.61g; 2.0mol), dry ether (250ml), a crystal of iodine, and *tert*-butyl chloride (10ml) were placed in a 1-litre 3-necked round bottomed flask equipped with mechanical stirrer, reflux condenser, pressure equalising dropping funnel and nitrogen inlet. The mixture was stirred and gently heated on a warm water bath to initiate the reaction. The bath was removed, and a further 100ml of *tert*-butyl chloride (total: 110ml; 1.0mol) in dry ether (150ml) was added at such a rate as to maintain a gentle reflux. On completion of the addition the mixture was refluxed for a further 30min. on a warm water bath. The solution of the Grignard reagent was then quickly decanted into a 1-litre pressure equalising dropping funnel, and slowly added to an ice-cooled solution of allyl bromide (70ml; 0.80mol) in dry ether (80ml) in a 3-necked flask equipped with mechanical stirrer, reflux condenser and nitrogen inlet. On completion of the addition, the mixture was allowed to stir at room temperature for 2h. The flask was then cooled in ice

again, and ice-cold 5M hydrochloric acid (350ml) was slowly added. The top, ethereal, layer was separated off, and the remainder was extracted with ether (2x100ml). The combined ethereal extracts were washed with 2M hydrochloric acid (50ml), brine (50ml) and dried over $MgSO_4$. After filtering, the ether was removed by distillation through a 10cm Vigreux column, and the residue was fractionally distilled to give the alkene as a colourless liquid (40.78g; 52%). b.p. 70-72°C (Lit.[57] : 70.7-71.2°C/ 724mmHg).

^1H nmr (60MHz) : δ 1.04(s, 9H); 2.06(d, J=7.2Hz, 2H); 4.90-5.26(m, 2H); 5.50-6.10(m, 1H) ppm.
^{13}C nmr : δ 25.67, 29.19, 48.49, 116.38, 136.08 ppm.

1-Bromo-4,4-dimethyl-2-pentene (31)[49]

4,4-Dimethyl-1-pentene (**40**) (14.73g; 0.15mol), *N*-Bromosuccinimide (26.70g; 0.15mol) and a few grains of benzoyl peroxide were refluxed in carbon tetrachloride (150ml) for 4h. The solution was allowed to cool, and the succinimide was filtered off. After removal of the solvent under reduced pressure, the residue was fractionally distilled to yield the colourless bromoalkene (13.55g; 51%). b.p. 58°C/ 20mmHg (Lit.[49a] : 61.5-62°C/ 28mmHg).

^1H nmr : δ 1.00(s, 9H); 3.93(d, J=7.55Hz, 2H); 5.57(dt, J=15.10, 7.55Hz, 1H); 5.75(d, J=15.10Hz, 1H) ppm.
^{13}C nmr : δ 29.20, 33.03, 34.07, 121.46, 147.03 ppm.

2-Methyl-3-butenoyl chloride (41)[24]

2-Methyl-3-butenoic acid (10.60g; 0.11mol) was added dropwise to thionyl chloride (15.00g; 0.13mol) in a 100ml round bottomed flask equipped with reflux condenser, dropping funnel and nitrogen inlet. The solution was then magnetically stirred at 40°C for 5h. Dissolved gases were removed by briefly subjecting the product to reduced pressure (20mmHg for 15min.), and the residue was fractionally distilled to afford the acid chloride as a colourless liquid (9.96g; 76%). b.p. 55-62°C/ 150mmHg (Lit.[24] : 55-58°C/ 110mmHg)

^{1}H nmr (200MHz) : δ 1.36(d, J=6.99Hz, 3H); 3.49(m, 1H); 5.25(m, 2H); 5.83(m, 1H) ppm.
^{13}C nmr : δ 16.86, 55.02, 118.79, 134.24, 175.34 ppm.

N'-p-Tosyl-2-methyl-3-butenohydrazide (16) (*NC*)

Pyridine (13.84g; 0.175mol) was added dropwise over 30min. to a suspension of 2-methyl-3-butenoyl chloride (**41**) (4.67g; 0.039mol) and *p*-toluenesulphonhydrazide (10.45g; 0.056mol) in dry ether (20ml) under nitrogen. The mixture was mechanically stirred for a further 3h. Further ether (150ml) was added plus sufficient dichloromethane to dissolve all the solid, and the solution was washed with 2M hydrochloric acid (3x75ml). The aqueous layers were extracted with dichloromethane (2x50ml), and the combined organic extracts were washed with water (50ml) and saturated sodium bicarbonate solution (2x50ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to give a pale yellow solid. Recrystallisation from chloroform afforded the hydrazide as white crystals (6.78g; 64%). m.p. 133-134°C.

^{1}H nmr (200MHz) : δ 1.03(d, J=7.02Hz, 3H, CH_3CH); 1.68(br s, 1H, NH); 2.41(s, 3H, CH_3Ar); 2.87(m, 1H, CH_3CH); 5.11(m, 2H, CH_2=); 5.56(m, 1H, -CH=); 7.27(m, 3H); 7.85(m, 2H) ppm.
^{13}C nmr (50MHz) : δ 16.65(CH_3CH), 21.69(CH_3Ar), 43.02(CH_3CH), 117.34, 128.73, 129.52, 132.88, 136.40, 144.92, 172.66(CONH) ppm.
Found : C, 53.96; H, 6.04; N, 10.13%. Calc. for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44%.

Attempted Reductions of *N*'-Tosyl-2-methyl-3-butenohydrazide (TMBH) (16)

a) Sodium Borohydride / Acetic Acid[27]

Acetic acid (0.60g; 10mmol) in dioxan (2ml) was added dropwise to a suspension of sodium borohydride (0.38g; 10mmol) and **16** (0.54g; 2.0mmol) in dioxan (8ml) at 15°C. A strong evolution of gas and a thick white precipitate were observed. The suspension was magnetically stirred under reflux for 2.5h. The solvent was then

removed under reduced pressure, the residual reagent was destroyed by the addition of water (20ml), and the aqueous layers were extracted with dichloromethane (3x15ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a viscous liquid (0.23g).

Examination of the ^{13}C nmr spectrum of the product shows a profusion of signals, including strong ones which correspond to the spectrum of the starting hydrazide.

b) Diisobutylaluminium Hydride[28]

TMBH (**16**) (100mg; 0.373mmol) was dissolved in dimethoxyethane (10ml) in a 50 ml round bottomed flask equipped with a septum. The flask was filled with argon, and a steady stream of the gas was maintained throughout the reaction. The flask was cooled to 0°C, and a 1.5M solution of diisobutylaluminium hydride in toluene (2.5ml; 3.75mmol) was slowly added *via* a syringe. The suspension was stirred at room temperature for 2h. Methanol (10ml) and water (1ml) were added, and the precipitate was removed by filtration through Celite. The solvent was removed under reduced pressure to yield a pale yellow solid (110mg).

The ^{13}C nmr spectrum of the product shows almost entirely unreacted starting material, with only a few small additional peaks.

c) Tetrabutylammonium Borohydride[29]

TMBH (**16**) (0.27g; 1.0mmol) and tetrabutylammonium borohydride (0.28g; 1.1mmol) were refluxed in dichloromethane (10ml) for 42h. 3% Hydrogen peroxide (10ml) was then added, followed by 10% potassium hydroxide (5ml), and the mixture was stirred for a further 2h. The organic layer was separated off, and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic layers were washed with saturated sodium sulphite solution (10ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow oil (0.58g).

The ^{13}C nmr spectrum indicates the product to be largely tetrabutylammonium salts.

d) Sodium Borohydride / Nickel Chloride[30] : **N'-Tosyl-2-methyl-butanohydrazide** (*NC*)

TMBH (**16**) (0.54g; 2.0mmol) and nickel(II) chloride hexahydrate (0.95g; 4.0mmol) were dissolved in methanol (15ml) and magnetically stirred. The flask was placed in a water bath, and sodium borohydride (0.76g; 20mmol) was slowly added in portions. A thick black precipitate appeared, and evolution of gas was observed. The suspension was allowed to stir at room temperature for 24h. 2M Hydrochloric acid (10ml) was then added, and the mixture was filtered through Celite. Most of the methanol was removed under reduced pressure, and the remaining solution was extracted with ether (3x30ml). The organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a white solid. The solid was taken up in chloroform (25ml), and the insoluble matter was filtered off. Removal of the solvent *in vacuo* afforded the saturated hydrazide as a pale yellow solid (0.34g; 63%).

^1H nmr : δ 0.66 (t, J=7.43Hz, 3H, CH_3CH_2); 0.91(d, J=6.92Hz, 3H, CH_3CH); 1.24(m, 1H); 1.40(m, 1H); 2.04(m, 1H); 2.39(s, 3H, CH_3Ar); 7.27(m, 2H); 7.77(m, 2H); 8.09(br s, 1H, NH) ppm. (2nd. N-H signal not observed).
^{13}C nmr : δ 11.38, 16.96, 21.62, 26.60, 40.33, 128.76, 129.46, 132.95, 144.88, 175.07(CONH) ppm.

e) Phosphoryl Chloride / Sodium Borohydride[31] : **2-Methyl-2-butenal N'-Tosyl Hydrazone (18)** (*NC*)

TMBH (**16**) (0.27g; 1.0mmol) was refluxed in freshly distilled phosphoryl chloride (10ml) for 30min. The phosphoryl chloride was then removed under reduced pressure (20mmHg then 0.01mmHg) to yield a pale purple solid. The solid was dissolved in dimethoxyethane (3ml), cooled in ice, and a 0.7M solution of sodium borohydride in ethanol (5ml) was slowly added. Stirring was continued at room temperature for 2h. 2% Hydrochloric acid (5ml) was added, and the organic solvent was removed under reduced pressure. The resultant aqueous suspension was extracted with ether (3x10ml). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow

oily solid. Purification by chromatography on silica (ether : petroleum spirit 60/80 1 : 1; R_f 0.23) afforded a liquid which was assigned as the unsaturated hydrazone (**18**) (41mg; 17%).

^{1}H nmr : δ 1.72(s, 3H, CH_3C=); 1.73(d, J=9.66Hz, 3H, CH_3CH=); 2.38(s, 3H, CH_3Ar); 5.75(m, 1H, CH=C); 7.26(m, 2H); 7.35(s, 1H, CH=N); 7.80(m, 2H); 7.96(br s, 1H, NH) ppm.
^{13}C nmr : δ 10.88, 14.08, 21.55, 127.92, 129.46, 133.64, 135.19, 135.38, 143.96, 153.44(**C**=N) ppm.

N'-Tosyl-3,4-dibromo-2-methylbutanohydrazide (19) (*NC*)

TMBH (**16**) (1.08g; 4.0mmol) was dissolved in dichloromethane (20ml) and cooled in ice. Bromine (0.80g; 5.0mmol) was added dropwise over 10min., during which time a thick precipitate formed. Stirring was continued at room temperature for 1h. The precipitate was filtered off and dried under vacuum to afford the dibromide as a 1:1 mixture of diastereomers (1.27g; 75%). m.p. 145-146°C (dec.).

^{1}H nmr : δ 0.90(d, J=6.99Hz, 3H, CH_3CH); 1.05(d, J=6.92Hz, 3H, CH_3CH); 2.29(s, 3H, CH_3Ar); 2.30(s, 3H, CH_3Ar); 2.66(m, 1H); 2.74(m, 1H); 3.41(dd, J=11.46, 5.51Hz, 1H, CH^AH^BBr); 3.46(dd, J=11.46, 4.88Hz, 1H, CH^AH^BBr); 3.64(dd, J=11.91, 3.54Hz, 1H, [CH^AH^BBr]'); 3.71(dd, J=11.91, 4.70Hz, 1H, [CH^AH^BBr]'); 4.12(m, 2H, CHBr); 7.23(m, 4H); 7.69(m, 4H) ppm.

Borane-tetrahydrofuran Complex

A solution of diborane in tetrahydrofuran was prepared according to the method of Brown and Zweifel.[58] The solution was stored under argon at -30°C.

Determination of concentration

1cm^3 of the borane.tetrahydrofuran solution was added *via* syringe to a 1 : 1 : 1 water : tetrahydrofuran : glycerol mixture (30ml), and the hydrogen evolved was collected under water.

Total volume of hydrogen evolved = 80cm^3.

Taking V_m = 22.414 x 10^{-3} m^3mol^{-1} at stp. :
80cm^3 is the volume occupied by (80 x 10^{-6} m^3)/(22.414 x 10^{-3} m^3mol^{-1}) = 3.57 x 10^{-3} mol.
1 mol BH_3 produces 3 mol H_2.
∴ 1cm^3 BH_3.THF solution contains approximately 1.2 x 10^{-3} mol BH_3.
∴ Concentration of the solution is *ca.* 1.2M.

N'-Tosyl-N-(3,4-dibromo-2-methylbutyl)hydrazine (20) (*NC*)

N'-Tosyl-3,4-dibromo-2-methylbutanohydrazide (**19**) (0.43g; 1.0mmol) was dissolved in tetrahydrofuran (5ml) under an argon atmosphere. Borane-tetrahydrofuran complex (3.00ml; 3.6mmol BH_3) was slowly added *via* syringe, and the solution was magnetically stirred for 23h. Methanol (15ml) was then added, and stirring was continued for a further hour. The solvent was removed under reduced pressure to give a pale yellow solid. The solid was extracted with chloroform, and the solvent removed *in vacuo* to afford the crude hydrazine (0.34g; 83%).

As the hydrazine is formed as a mixture of isomers, it was decided to delay purification until after debromination, when the isomerism is lost. However, the ^{13}C nmr spectrum of the crude product shows no signals in the region of δ 170ppm (**C**ONHNH), but does show several signals in the region δ 55 - 65ppm (CH_2NHNH as well as **C**-Br).

Attempted Debromination of **20**

a) Potassium Iodide[34]

Dibromide **20** (0.34g; 0.82mmol) and potassium iodide (0.83g; 5mmol) were refluxed in absolute ethanol (15ml) for 45min. The solvent was removed *in vacuo*, and the residue was partitioned between dichloromethane (20ml) and 0.1M sodium thiosulphate (20ml). The organic layer was washed with two further portions of 0.1M sodium thiosulphate, dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a dark brown liquid (0.14g). Examination of the ^{13}C nmr spectrum appears to indicate the presence of only a

p-tolyl group with signals at δ 20.93, 128.36, 129.64, 133.69 and 137.27 ppm.

b) Zinc[35]

Dibromide **20** (0.41g; 1.0mmol) in absolute ethanol (5ml) was slowly added to a vigorously stirred suspension of zinc dust (0.080g; 1.2mmol) in absolute ethanol (2ml). The suspension was stirred at room temperature for 20h. Water (50ml) was added, and the resultant suspension was extracted with dichloromethane (2x20ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to produce a pale yellow oil (0.16g).

Examination of the ^1H nmr spectrum indicates the absence of any alkene (no signals in the region δ 5.0-6.0 ppm).

Refluxing the dibromide with zinc for 4 hours produces more extensive decomposition, affording a foul smelling (amine-like) oil.

c) Thiourea[36]

The dibromide **20** (0.30g; 0.72mmol) and thiourea (0.060g; 0.79mmol) were dissolved in ethanol (6ml) and refluxed for 3h. Water (30ml) was added to the solution, and the resultant suspension was extracted with dichloromethane (2x20ml). After drying over $MgSO_4$, the organic layers were concentrated *in vacuo* to produce a brown oil (0.01g).

Examination of the ^1H nmr spectrum shows no signals in the region δ 5-6 ppm, where alkene signals ought to appear.

d) Iron(II) chloride / sodium acetate[37]

Dibromide **20** (0.26g; 0.63mmol) and sodium acetate (0.33g; 4.0mmol) were dissolved in absolute ethanol (5ml) and acetic acid (0.5ml) and warmed on a water bath. Iron(II) chloride tetrahydrate (0.50g; 2.5mmol) was added in one portion, and the mixture was refluxed for 1h. The mixture was then combined with water (40ml) and extracted with dichloromethane (2x20ml). The organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure

to yield a brown oil (0.14g).

The ^1H nmr spectrum showed a multitude of signals, but again none that could obviously be assigned to a terminal alkene.

2-Methyl-3-buten-1-ol (23)

A suspension of lithium aluminium hydride (2.40g; 63mmol) in dry ether (100ml) was placed in a 500ml 3-necked round bottomed flask equipped with reflux condenser, mechanical stirrer and dropping funnel. All outlets were protected with calcium chloride guard tubes. A solution of 2-methyl-3-butenoic acid (**13**) (4.80g; 48mmol) in dry ether (75ml) was then added at such a rate as to maintain a gentle reflux. On completion of the addition the mixture was stirred for a further hour, and the flask was then cooled in ice and water was added slowly (CAUTION!) until all the excess hydride had been decomposed. When the precipitate was completely white, 10% sulphuric acid (80ml) was added, and stirring was continued until all the solid had dissolved. The ether layer was separated off, and the aqueous layer was saturated with sodium chloride and extracted with further ether (2x50ml). The organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude alcohol as a very pale yellow liquid. The alcohol was purified by trap-to-trap distillation (70°C/20mmHg) to give **23** as a colourless liquid (3.45g; 84%). Lit.[59] b.p. : 120-121°C/756mmHg.

^1H nmr (60MHz) : δ 1.06(d, J=7.2Hz, 3H); 2.24(s, 1H); 2.35(m, 1H); 3.52(d, J=6.0Hz, 2H); 4.8-5.1(m, 2H); 5.4-6.0(m, 1H) ppm.
^{13}C nmr : δ 15.78, 40.18, 66.68, 114.76, 140.82 ppm.

2-Phenyl-3-buten-1-ol (25) (*NC*)

This was prepared as for **23** from 2-phenyl-3-butenoic acid (**14**).

Pale yellow liquid. Yield of crude material : 98%.

Purified further by reduced pressure distillation, but this only intensified the yellow colouration.

^1H nmr (60MHz) : δ 1.84(br s, 1H, OH); 3.0-3.7(m, 3H); 4.90(m, 2H, CH_2=); 5.72(m, 1H, CH=); 7.0(s, 5H, C_6H_5) ppm.

^{13}C nmr : δ 52.24(**C**-2), 65.81(**C**H_2OH), 116.66, 126.67, 127.83, 128.51, 138.20, 140.65 ppm.

2-*tert*-Butyl-3-buten-1-ol (28) (*NC*)

This was prepared as for **23** from 2-*tert*-butyl-3-butenoic acid (**15**).

Colourless liquid. Yield : 90%.

^{1}H nmr : δ 0.86(s, 9H,[CH_3]C); 1.48(br s, 1H, OH); 1.92(dt, J=3.91, 9.97Hz, 1H, CH); 3.35(approx. t, J_{ave}=10.39Hz, 1H, CH^AH^BOH); 3.73(m, 1H, CH^AH^BOH); 5.10(d, J=17.00Hz, 1H, CH^AH^B=); 5.20(d, J=10.27Hz, 1H, CH^AH^B=); 5.66(approx. dt, J_{ave}=17.00, 10.01Hz, 1H, CH=) ppm.
^{13}C nmr : δ 27.93([CH_3]$_3$C), 31.68([CH_3]$_3$**C**), 57.79, 61.47, 119.03, 137.66 ppm.

Attempted Oxidation of 2-Methyl-3-buten-1-ol (**23**) to 2-Methyl-3-butenal (**22**)

a) Pyridinium Chlorochromate (PCC)[41]

PCC (16.10g; 75mmol) and sodium acetate (1.22g; 15mmol) were suspended in dry dichloromethane (100ml) in a flask equipped with a reflux condenser. Alcohol **23** (4.16g; 48mmol) in dry dichloromethane (15ml) was added in one portion and the mixture was stirred for 2h. Dry ether (100ml) was then added, and the liquid was decanted off. The black tar was extracted with ether (3x25ml), and the combined organic solutions were filtered through a sandwich of silica in Celite. The solvent was removed under reduced pressure to yield a dark green viscous liquid. This was eluted with ether through a short silica column to afford a pale green liquid (1.33g).

Examination of the ^{1}H nmr spectrum showed the crude product to consist essentially of two components, one of which was unreacted alcohol. The other compound was an aldehyde [δ 9.0 ppm (s)], but a signal at δ 6.5 ppm (q) strongly suggests the aldehyde to be α,β-unsaturated and not β,γ-unsaturated as required.

b) Dimethyl sulphoxide (DMSO) / Oxalyl Chloride[42]

To a 50ml round bottomed flask equipped with low temperature thermometer, magnetic stirrer and dropping funnel was added a solution of oxalyl chloride (0.76g; 6mmol) in dry dichloromethane (12ml). The solution was cooled to -60°C, and a solution of DMSO (0.94g; 12mmol) in dichloromethane (4ml) was added over 5min. Stirring was continued for 10min., and **23** (0.43g; 5mmol) in dry dichloromethane (5ml) was added over 5min. The mixture was stirred for a further 15min. at -65°C, and then triethylamine (2.53g; 25mmol) was added over 5min. The cooling bath was removed, and the mixture was allowed to warm to room temperature. Water (15ml) was added and the mixture was stirred for 10min. The organic layer was separated off, and the aqueous layer was extracted with dichloromethane (10ml). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a yellow oil.

The ^1H nmr spectrum again displayed a quartet at δ 6.5 ppm, although there were now two aldehydes present (^{13}C nmr : δ 194.76, 200.94 ppm). However, the signals due to unreacted alcohol are much stronger, so if there is any of the required aldehyde (**22**) it must be a very minor product.

c) *N*-Iodosuccinimide (*N*IS) / Tetraethylammonium iodide[43]

A solution of **23** (0.22g; 2.5mmol) in dichloromethane (8ml) was added to a magnetically stirred suspension of *N*IS (2.83g; 12.5mmol) and tetraethylammonium iodide (0.93g; 3.6mmol) in dichloromethane (25ml). The mixture was stirred for 5h. Saturated sodium thiosulphate solution (50ml) was then added, and the organic layer was separated off. The organic layer was washed with water (3x50ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to produce a yellow liquid containing some white solid (0.43g).

The ^1H nmr spectrum showed very little sign of any signals due to an aldehydic proton. It is probably largely a mixture of unreacted alcohol and tetraethylammonium salts.

d) Silver Carbonate on Celite[44]

Preparation of reagent

Celite was purified by washing with a 10% solution of conc. hydrochloric acid in methanol, followed by deionised water, and leaving to dry at 125°C.

Celite (10g) was placed in a 500ml round bottomed flask equipped with mechanical stirrer. A solution of silver nitrate (11.30g; 66mmol) in water (70ml) was added, followed by sodium carbonate (3.71g; 35mmol) in water (110ml). Stirring was continued for 10min., then the lime green reagent was filtered off. After washing with deionised water it was dried on a rotary evaporator at 40°C for several hours.

This method produces 33mmol silver carbonate (9.10g) on 10g Celite. Hence (19.10÷33) = 0.58g of reagent contains *ca.* 1mmol silver carbonate.

Oxidation of alcohol

2-Methyl-3-buten-1-ol (**23**) (0.259g; 3mmol) and silver carbonate on Celite (7.0g; *ca.* 12.3mmol Ag_2CO_3) were refluxed in n-hexane (60ml) for 4h. After cooling to room temperature, the spent reagent was filtered off, and washed through with dry ether. After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a pale yellow oil (0.08g).

By nmr spectroscopy the reaction appeared somewhat cleaner than the previous attempts. However, a large amount of unreacted alcohol was still present, and the other major product [^{1}H nmr : δ 9.34(s, 1H); 6.42(m, 1H); 1.69(s, 3H) ppm + others. ^{13}C nmr : δ 140.24, 151.62, 194.74 ppm + others] is much more likely to be an α,β-unsaturated aldehyde than a β,γ-unsaturated aldehyde.

Trifluoromethanesulphonic (Triflic) Anhydride[46]

Phosphorous pentoxide (25.0g; 0.176mol) and an approximately equal volume of Celite were thoroughly mixed in a flask under a dry argon atmosphere, and triflic acid (25.0g; 0.167mol) was added to the

mixture. After standing at room temperature for 1h, the mixture was distilled to afford the anhydride as a colourless liquid (15.54g; 66%). b.p. 82°C (Lit.[46] : 81°C).

2-Methyl-3-buten-1-yl Trifluoromethanesulphonate (24) (*NC*)

A solution of 2-methyl-3-buten-1-ol (1.29g; 15mmol) and pyridine (1.26g; 16mmol) in dry dichloromethane (5ml) was very slowly added to a solution of triflic anhydride (2.85cm^3; 17mmol) in dry dichloromethane at ice bath temperature. The solution was allowed to warm to room temperature and stirred for a further 15min. The mixture was washed with water (2x10ml), dried over $MgSO_4$, and the solvent removed under reduced pressure to afford the crude triflate as a dark purple liquid (2.82g; 86%). Considering the inherent instability of homoallylic triflates, no purification was attempted.

^{1}H nmr (200MHz) : δ 1.12(d, J=6.81Hz, 3H, CH_3); 2.67(m, 1H, CH); 4.34(dd, J=9.95, 5.15Hz, 1H, CH^AH^BOTf); 4.37(dd, J=9.95, 5.08Hz, 1H, CH^AH^BOTf); 5.12-5.22(m, 2H, CH_2=); 5.69(m, 1H, CH=) ppm.
^{13}C nmr : δ 15.66(CH_3), 37.46(CH), 80.26(CH_2OTf), 117.26, 118.65[q, J(^{13}C-^{19}F)=319Hz, CF_3], 136.98 ppm.

2-Methyl-3-buten-1-yl Hydroperoxide (9) (*NC*)

A solution of potassium hydroxide (1.19g; 21mmol) in water (5ml) was added to 30% w/v hydrogen peroxide (10.7cm^3; 95mmol H_2O_2) in a 250ml round bottomed flask cooled in ice. 2-Methyl-3-buten-1-yl triflate (**24**) (4.35g; 20mmol) was dissolved in methanol (60ml) and immediately added in one portion to the basic hydrogen peroxide solution. After stirring for 5min., water (20ml) was added. The solution was saturated with sodium chloride, and extracted with dichloromethane (5x30ml). The combined organic layers were washed with brine (2x30ml) and extracted with 20% potassium hydroxide (25ml). The base extract was acidified, with cooling, with 10% hydrochloric acid, saturated with sodium chloride, then extracted with ether (3x30ml). The organic layers were washed with brine (20ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the hydroperoxide as a colourless liquid (0.53g;

26%). In subsequent repeats, yields up to 35% were obtained.

^{1}H nmr (200MHz) : δ 1.00(d, J=6.84Hz, 3H, CH_3); 2.61(m, 1H, CH); 3.88(m, 2H, CH_2OOH); 5.05(m, 2H, CH_2=); 5.74(m, 1H, CH=); 8.49(br s, 1H, OOH) ppm.
^{13}C nmr : δ 16.23(CH_3), 36.11(CH), 81.15(CH_2OOH), 114.65(CH_2=), 140.48(-CH=) ppm.

3-Bromomercuriomethyl-4-methyl-1,2-dioxolane (32) (*NC*)

2-Methyl-3-buten-1-yl hydroperoxide (**9**) (0.20g; 2.0mmol) in dry dichloromethane (15ml) was added to a vigorously stirred suspension of mercury(II) acetate (0.65g; 2.0mmol) in dry dichloromethane (35ml). The mixture was stirred for 2h. Water (10ml) was then added, followed by potassium bromide (0.27g; 2.3mmol), and stirring was continued for a further 30min. The aqueous layer was separated off and extracted with dichloromethane (10ml), and the combined organic layers were washed with water (20ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a pale yellow, very viscous oil (0.61g; 80%) which is essentially pure by nmr spectroscopy.

An analytically pure sample of **32** could be obtained by chromatography on silica [CH_2Cl_2; R_f 0.38 (**32t**) and 0.33 (**32c**)]. Overall yield 64%.

Found : C, 16.20; H, 2.33%. Calc. for $C_5H_9BrHgO_2$: C, 15.74; H, 2.38%.

The ^{1}H nmr spectrum of the crude product shows two methyl doublets at δ 1.09 and 1.16 ppm in the ratio 1 : 1.

If the procedure is repeated exactly as above, but using mercury(II) nitrate hemihydrate instead of mercury(II) acetate, the two methyl doublets are now present in the ratio 5 : 1 in the crude product. Yield of crude material : 80%. The major spot by TLC (CH_2Cl_2) is at R_f 0.38.

Major isomer : **32t**

^{1}H nmr : δ 1.16(d, J=6.77Hz, 3H, CH_3); 2.12(dd, J=11.87, 5.23Hz, 1H, CH^AH^BHgBr); 2.24(dd, J=11.87, 5.62Hz, 1H, CH^AH^BHgBr); 2.51(m, 1H, C^4H); 3.66(approx. t, J_{ave}=7.04Hz, 1H, CH^AH^BOO); 4.24(approx. q, J_{ave}=5.52Hz, 1H, $CHCH_2HgBr$); 4.32(approx. t, J_{ave}=7.59Hz, 1H, CH^AH^BOO) ppm.
^{13}C nmr : δ 16.02(CH_3), 36.70[J(^{13}C-^{199}Hg)=1544Hz, CH_2HgBr], 51.95(C-4), 77.08(CH_2OO), 86.09(CHOO) ppm.

Minor isomer : **32c**

^{1}H nmr : δ 1.09(d, J=7.14Hz, 3H, CH_3); 2.01(m, 2H, CH_2HgBr); 2.97(m, 1H, C^4H); 3.69(approx. t, J_{ave}=6.99Hz, 1H, CH^AH^BOO); 4.31(approx. t, J_{ave}=6.65Hz, 1H, CH^AH^BOO); 4.58(approx. q, J_{ave}=7.04Hz, 1H, $CHCH_2HgBr$) ppm.
^{13}C nmr : δ 12.98(CH_3), 30.88(CH_2HgBr), 45.59(C-4), 76.93(CH_2OO), 81.30(CHOO) ppm.

3-Chloromercuriomethyl-4-methyl-1,2-dioxolane (33) (*NC*)

The procedure was as for **32**, using mercury(II) nitrate as the electrophile, but replacing potassium bromide with potassium chloride. Yield of crude material : 88%.

The ^{1}H nmr spectrum of the crude product showed two methyl doublets at δ 1.18 and 1.11 ppm in the ratio 5 : 1 respectively.

Major isomer : **33t**

^{1}H nmr (200MHz) : δ 1.18(d, J=6.77Hz, 3H, CH_3); 2.09(dd, J=12.03, 5.17Hz, 1H, CH^AH^BHgCl); 2.22(dd, J=12.03, 5.49Hz, 1H, CH^AH^BHgCl), 2.51(m, 1H, C^4H); 3.68(approx. t, J_{ave}=7.07Hz, 1H, CH^AH^BOO); 4.22(approx. q, J_{ave}=5.42Hz, 1H, $CHCH_2HgCl$); 4.34(approx. t, J_{ave}=7.62Hz, 1H, CH^AH^BOO) ppm.
^{13}C nmr : δ 16.02(CH_3), 33.29[J(^{13}C-^{199}Hg)=1581Hz, CH_2HgCl], 52.03(C-4), 77.09(CH_2OO), 85.87(CHOO) ppm.

Minor isomer : **33c**

^{1}H nmr (200MHz) : δ 1.11(d, J=7.06Hz, 3H, CH_3); 1.99(d, J=7.09Hz, 2H, CH_2HgCl) ppm. All other signals are impossible to separate from the major isomer.
^{13}C nmr : δ 12.96(**C**H_3), 27.93(**C**H_2HgCl), 45.56(**C**-4), 76.95(**C**H_2OO), 81.09(**C**HOO) ppm.

3-Iodomethyl-4-methyl-1,2-dioxolane (34) (*NC*)

a) From *N*-Iodosuccinimide (*N*IS) and 2-Methyl-3-buten-1-yl Hydroperoxide (**9**)

*N*IS (0.39g; 1.73mmol) was dissolved in dichloromethane (25ml) in a flask wrapped in aluminium foil to exclude light. Hydroperoxide **9** (0.17g; 1.66mmol) in dichloromethane (10ml) was added, and the solution was stirred for 1h. The solution was then washed with 10% sodium thiosulphate (30ml), which was in turn extracted with dichloromethane (2x15ml). The combined organic layers were washed with water (10ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude dioxolane, which was examined by nmr spectroscopy.

The ^{1}H nmr spectrum showed two methyl doublets at δ 1.24 and 1.12 ppm in the ratio 1.3 : 1 respectively.

The product was purified by column chromatography (CH_2Cl_2; R_f 0.57) to afford **34** as a colourless liquid (0.172g; 45%).

Found : C, 26.80; H, 4.29%. Calc. for $C_5H_9IO_2$: C, 26.34; H, 3.98%.
Mass spectrum : m/z(%) : 29(100), 43(88), 57(53), 71(26), 87(26, $[M-CH_2I]^+$), 101(16, $[M-I]^+$), 127(58, I^+), 128(52, $[HI]^+$), 142(30), 170(65), 228(3, M^+).
Required for $C_5H_9IO_2$: m/z = 227.9649. Found : m/z = 227.9664.

b) By Iododemercuration of *trans*-3-Bromomercuriomethyl-4-methyl-1,2-dioxolane (**32t**)

Iodine (1.051g; 4.14mmol) was added *via* a Soxhlet extractor to a solution of **32** (**32t** : **32c** = 5 : 1) (0.35g; 0.92mmol) in dichloromethane (80ml). After refluxing for 2h., the solution was

allowed to cool, and was then washed with saturated sodium thiosulphate solution (20ml) and water (10ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to afford the crude dioxolane (**34**) (0.22g; *ca.* 100%).

As with the *N*IS reaction, the ^1H and ^{13}C nmr spectra showed the presence of two isomers, but this time in the ratio of 5 : 1. The major isomer (**34t**) was the isomer slightly favoured by direct cyclisation of **9** with *N*IS.

Major isomer : **34t**

^1H nmr : δ 1.24(d, J=6.90Hz, 3H, CH_3); 2.83(m, 1H, C^4H); 3.16(dd, J=9.99, 8.17Hz, 1H, CH^AH^BI); 3.27(dd, J=9.99, 5.34Hz, 1H, CH^AH^BI); 3.67(dd, J=7.87, 6.73Hz, 1H, CH^AH^BOO); 3.98(m, 1H, $CHCH_2I$); 4.30(dd, J=7.87, 7.33Hz, 1H, CH^AH^BOO) ppm.
^{13}C nmr : δ 5.92(CH_2I), 17.62(CH_3), 49.48(C-4), 77.13(CH_2OO), 86.31(CHOO) ppm.

Minor isomer : **34c**

^1H nmr : δ 1.12 (d, J=7.18Hz, 3H, CH_3); 3.07(dd, J=10.31, 6.61Hz, 1H, CH^AH^BI); 3.10(m, 1H, C^4H); 3.18(dd, J=10.31, 7.39Hz, 1H, CH^AH^BI); 3.76(dd, J=7.09, 5.28Hz, 1H, CH^AH^BOO); 4.29(approx. t, J_{ave}=7.14Hz, 1H, CH^AH^BOO); 4.47(approx. q, J_{ave}=6.94Hz, 1H, $CHCH_2I$) ppm.
^{13}C nmr : δ -0.63(CH_2I), 12.31(CH_3), 45.29(C-4), 76.62(CH_2OO), 82.67(CHOO) ppm.

3-Bromomethyl-4-methyl-1,2-dioxolane (35) (*NC*)

a) From *N*-Bromosuccinimide (*N*BS) and 2-Methyl-3-buten-1-yl Hydroperoxide (**9**)

2-Methyl-3-buten-1-yl hydroperoxide (**9**) (0.242g; 2.37mmol) in dichloromethane (5ml) was slowly added to a stirred solution of *N*BS (0.561g; 3.15mmol) in dichloromethane (20ml) in the dark. The solution was left to stir for 3h. The solution was then washed with water (2x25ml), dried over $MgSO_4$, and the solvent removed under reduced pressure to give crude **35**.

The ^1H nmr spectrum of the crude product showed two signals for the methyl group in the ratio 1 : 1.

Column chromatography (silica, CH_2Cl_2) afforded the pure dioxolane (0.223g; 52%).

Mass spectrum : m/z(%) : 43(100), 55(33), 57(42), 69(26), 80(29, $[H^{79}Br]^+$), 82(29, $[H^{81}Br]^+$), 87(22, $[M-CH_2Br]^+$), 122(7), 124(7), 150(2), 152(2), 180(0.6, $M[^{79}Br]^+$), 182(0.6, $M[^{81}Br]^+$).
Required for $C_5H_9{}^{79}BrO_2$: m/z = 179.9785. Found : m/z = 179.9779.

b) By Bromodemercuration of *trans*-3-Bromomercuriomethyl-4-methyl-1,2-dioxolane (**32t**)

32 (**32t** : **32c** = 5 : 1) (0.40g; 1.05mmol) in dichloromethane (15ml) was added dropwise to a magnetically stirred solution of bromine (0.50g; 3.13mmol) in dichloromethane (15ml) under argon in subdued lighting. The solution was stirred for 1.5h. The solvent was removed under reduced pressure, and carbon tetrachloride (15ml) was added to the residue. The mixture was dried over $MgSO_4$, all insoluble matter was filtered off, and the solvent was removed under reduced pressure to afford **35** as a pale yellow liquid (0.178g; 94%).

Major isomer : **35t**

^1H nmr : δ 1.24(d, J=6.88Hz, 3H, CH_3), 2.88(m, 1H, C^4H); 3.33(dd, J=10.25, 7.53Hz, 1H, CH^AH^BBr); 3.47(dd, J=10.25, 5.68Hz, 1H, CH^AH^BBr); 3.67(dd, J=7.88, 6.89Hz, 1H, CH^AH^BOO); 4.04(m, 1H, $CHCH_2Br$); 4.31(approx. t, J_{ave}=7.62Hz, 1H, CH^AH^BOO) ppm.
^{13}C nmr : δ 17.33(CH_3), 32.31(CH_2Br), 48.49(C-4), 77.05(CH_2OO), 86.00(CHOO) ppm.

Minor isomer : **35c**

^1H nmr : δ 1.14(d, J=7.20Hz, 3H, CH_3); 3.14(m, 1H, C^4H); 3.34(dd, J=10.51, 5.78Hz, 1H, CH^AH^BBr); 3.41(dd, J=10.51, 7.21Hz, 1H, CH^AH^BBr); 3.74(dd, J=7.10, 5.42Hz, 1H, CH^AH^BOO); 4.30(approx. t, J_{ave}=7.18Hz, 1H, CH^AH^BOO); 4.47(approx. q, J_{ave}=6.84Hz, 1H, $CHCH_2Br$) ppm.

^{13}C nmr : δ 12.22(CH_3), 28.09(CH_2Br), 45.29(C-4), 76.44(CH_2OO), 82.03(CHOO) ppm.

3-Chloromethyl-4-methyl-1,2-dioxolane (36) (*NC*)

a) By *tert*-Butyl Hypochlorite Induced Cyclisation of 2-Methyl-3-buten-1-yl Hydroperoxide (9)

Column chromatography grade silica (*ca.* 1g) was suspended in a solution of *tert*-butyl hypochlorite (0.192g; 1.77mmol) in dichloromethane (10ml) cooled to -20°C. A solution of **9** (0.162g; 1.59mmol) in dichloromethane (10ml) was added, and the mixture was magnetically stirred for 3h while warming to room temperature. The silica was filtered off, and washed with further solvent. Removal of the solvent under reduced pressure gave a mobile colourless liquid.

The ^1H nmr spectrum showed two methyl signals at δ 1.23 and 1.14 ppm in the ratio 2 : 1 respectively.

Column chromatography (silica, CH_2Cl_2) afforded the pure chlorinated dioxolane (0.062g; 29%).

Major isomer : **36t**

^1H nmr : δ 1.23(d, J=6.86Hz, 3H, CH_3); 2.88(m, 1H, C^4H); 3.47(dd, J=11.20, 6.80Hz, 1H, CH^AH^BCl); 3.61(dd, J=11.20, 5.88Hz, 1H, CH^AH^BCl); 3.65(dd, J=6.91, 7.88Hz, 1H, CH^AH^BOO); 3.99(m, 1H, $CHCH_2Cl$); 4.29(approx. t, J_{ave}=7.58Hz, 1H, CHHOO) ppm.
^{13}C nmr : δ 17.09(CH_3), 44.10, 47.59, 76.87(CH_2OO), 86.23(CHOO) ppm.

Minor isomer : **36c**

^1H nmr : δ 1.14(d, J=7.21Hz, 3H, CH_3); 3.15(m, 1H, C^4H); 3.52(dd, J=11.52, 5.95Hz, 1H, CH^AH^BCl); 3.57(dd, J=11.52, 7.05Hz, 1H, CH^AH^BCl); 3.71(dd, J=6,98, 5.64Hz, 1H, CH^AH^BOO); 4.28(approx. t, J_{ave}=7.24Hz, 1H, CH^AH^BOO); 4.39(approx. q, J_{ave}=6.06Hz, 1H, $CHCH_2Cl$) ppm.

^{13}C nmr : δ 12.19(CH_3), 40.96, 45.12, 76.82(CH_2OO), 82.10(CHOO) ppm.

Mixture of isomers : Found : C, 43.61; H, 6.28%. Calc. for $C_5H_9ClO_2$: C, 43.97; H, 6.64%.

b) By Chlorodemercuration of *trans*-3-Chloromercuriomethyl-4-methyl-1,2-dioxolane (**33t**)

A solution of chlorine in chloroform (10ml) and pyridine (1ml) was prepared by bubbling chlorine through the solvent until there was no further colour change. This solution was then added dropwise to a solution of **33** (**33t** : **33c** = 5 : 1) (0.55g; 1.63mmol) in chloroform (25ml) until the yellow colouration persisted. The mixture was stirred for a further 30min., then the supernatant liquid was decanted off, and washed successively with 2M hydrochloric acid (2x15ml) and water (2x15ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a pale yellow liquid (0.301g; >100%).

The ^1H and ^{13}C nmr spectra showed an approximately 2 : 1 mixture of **36t** and **36c**.

Chlorodemercuration in the Absence of Pyridine

A saturated solution of chlorine in chloroform was prepared by bubbling the gas through the solvent until no further colour change occurred.

trans-3-Chloromercuriomethyl-4-methyl-1,2-dioxolane (**33** [**33t** : **33c** = 5 : 1]) (0.358g; 1.06mmol) was dissolved in chloroform (5ml) under a nitrogen atmosphere. The solution of chlorine in chloroform was added dropwise until no more precipitate appeared and the yellow colour of the solution was no longer discharged (*ca.* 2ml). Stirring was continued for a further 15min. The supernatant liquid was decanted off, and the solvent was removed under reduced pressure. The residue was extracted with petroleum ether (b.p. 30-40°C), and the solvent was removed under reduced pressure to afford a colourless liquid (0.161g).

The ^1H nmr spectrum is impossible to assign, particularly in the region δ 3.4-4.4 ppm. There are, however, four high field doublets

at δ 1.22(**36t**), 1.13(**36c**), 1.04 and 0.91 ppm. The latter two signals we would assign to the dichlorohydroperoxides (**39e** and **39t**).

The ^{13}C nmr spectrum also shows an abundance of peaks, but there are essentially 20 strong signals.

Assigned to **36c** : δ 12.16, 40.97, 45.09, 76.32, 82.09 ppm.

36t : δ 17.03, 44.06, 47.53, 76.82, 86.21 ppm.

39e and **39t** : δ 9.26, 15.06, 32.96, 34.30, 45.42, 47.00, 61.91, 65.00, 77.57, 78.57 ppm.

Reaction of 2-Methyl-3-buten-1-yl Hydroperoxide (9) with Chlorine

A saturated solution of chlorine in chloroform (see above) was added dropwise to a stirred solution of **9** (0.101g; 1.00mmol) in chloroform (5ml) until the yellow colour was no longer discharged. The solution was allowed to stir for a further hour, and the solvent was then removed under reduced pressure to yield a yellow oil (0.138g).

The ^{13}C nmr spectrum of this crude product is essentially identical to that obtained in the experiment above.

trans-3,4-Dimethyl-1,2-dioxolane (37)

A mixture of *trans*-3-bromomercuriomethyl-4-methyl-1,2-dioxolane (**32t**) (0.47g; 1.23mmol) and polymethylhydrosiloxane (PMHS) (1ml) was slowly added to a stirred mixture of bis(tributyltin) oxide (4.00g; 6.71mmol) and PMHS (1.0g) cooled in an ice bath. The mixture was allowed to stir for 1h, then purified by trap-to-trap distillation (10mmHg/20°C). 11.4mg of distillate was collected, and immediately reduced.

2-Methyl-1,3-butanediol (42)

trans-3,4-Dimethyl-1,2-dioxolane (**37**) (max. 11.4mg; 0.112mmol) was vigorously stirred with a saturated solution of ammonium chloride (5ml). Zinc dust (73mg; 1.12mmol) was added in one portion, and stirring was continued for 2h. The mixture was filtered through Celite, saturated with sodium chloride, and extracted with ether (3x5ml). After drying over $MgSO_4$, the solvent was removed under

reduced pressure to yield a colourless liquid (2.3mg).

^{1}H nmr : δ 0.84(d, J=7.02Hz, 3H); 1.23(d, J=6.21Hz, 3H); 1.60(br s, 3H); 3.62(dd, J=10.83, 7.80Hz, 1H); 3.74 (m, 2H) ppm.

trans-2,2,4,5-Tetramethyl-1,3-dioxane (38)

2-Methyl-1,3-butanediol (**42**) (2.7mg; 2.59×10^{-5}mol) was stirred in acetone (1ml) with one drop of 2,2-dimethoxypropane and a small crystal of *p*-toluenesulphonic acid for 1h. The solvent was removed under reduced pressure to afford the dioxane as a colourless liquid (2.1mg; 66%).

Unfortunately, due to the presence of some impurities, the ^{1}H nmr spectrum is difficult to assign. However, there are clearly two methyl doublets at δ 0.82 and 1.23 ppm, and a series of multiplets in the region δ 3.60-3.85 ppm (CH-O). Irradiation of the doublet at δ 1.23 ppm causes a signal at δ 3.78 ppm to collapse to a doublet with J=8.2Hz. Irradiation at δ 0.82 ppm has no effect on the multiplets in the CH-O region.

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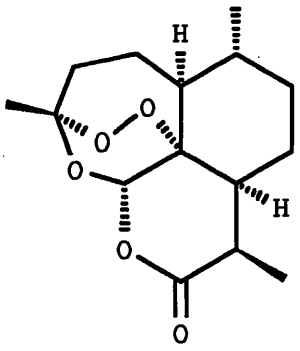
CHAPTER 4

1,2,4-TRIOXANES AND 1,2,4-TRIOXEPANES

4.1 INTRODUCTION

Much interest has recently been generated in 1,2,4-trioxanes following the discovery that artemisinin (qinghaosu) (**1**), found in the leaves of the plant *Artemisia annua L.*, is a powerful anti-malarial agent.[1] Malaria, a disease caused by parasites, is causing great concern in many tropical countries due to its ever increasing incidence.[2] Currently, around 300 million cases a year are reported, of which around two million are fatal. New drugs against malaria are desperately needed due to the growing resistance of the major malarial parasite, *Plasmodium falciparum*, against chloroquine, the most common anti-malarial drug in present use.



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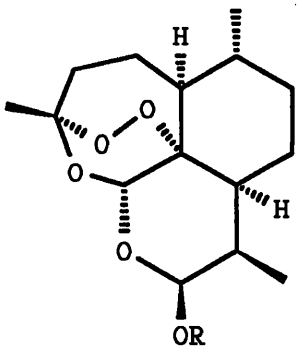


2 R = H

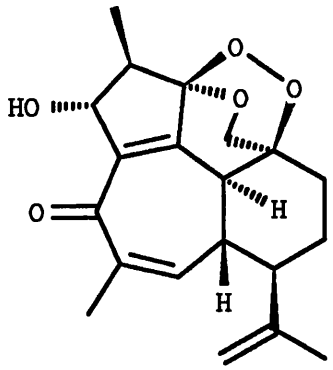
3 R = Me

4 R = $COCH_2CH_2CO_2^-Na^+$

Testing of similar compounds showed that the 1,2,4-trioxane moiety is essential for the biological action of **1**, and that derivatives of the compound such as dihydroartemisinin (**2**), artemether (**3**) and sodium artesunate (**4**) are more potent than **1** itself.

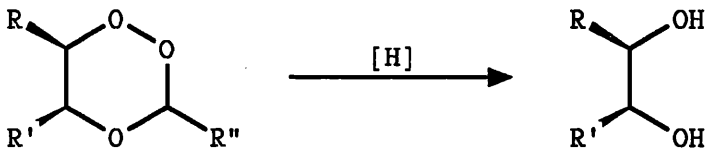
Another naturally occurring 1,2,4-trioxane is caniojane (**5**) which has been isolated from the root of *Jatropha grossidentata*.[3] Although this plant has been used in folk medicine, there is no indication of whether or not **5** has any biological activity.

Additionally, it is becoming clear that 1,2,4-trioxanes are also potentially useful synthetic intermediates. A particularly



5

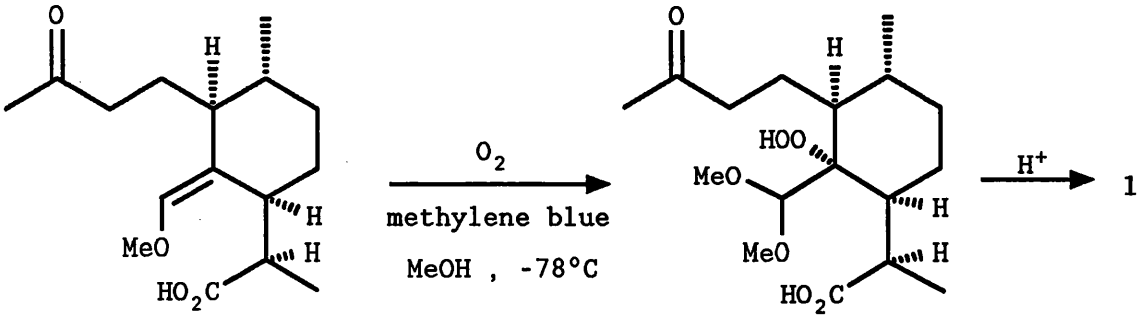
important reaction of such compounds is their reduction,[4] which occurs stereospecifically to afford 1,2-diols (Scheme 1).



Scheme 1

3-Monosubstituted 1,2,4-trioxanes on treatment with base afford 1,2-diol monoesters,[5] whilst certain trioxanes can be converted into benzofurans[6] and medium ring lactones.[7] There is also work which suggests that 1,2,4-trioxanes could be used as acid insensitive carbonyl protecting groups.[4]

A few total syntheses of **1**, and closely related compounds, are to be found in the literature. These provide some examples of the methods used for the synthesis of 1,2,4-trioxanes.



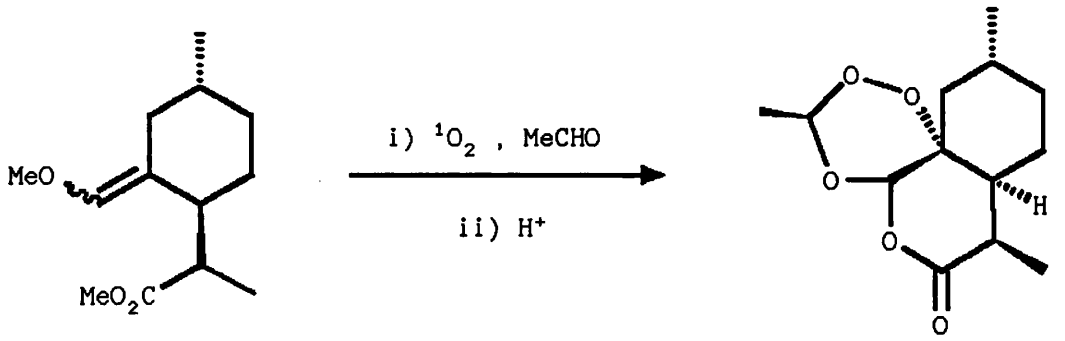
6 7

Scheme 2

Schmid and Hofheinz,[8] starting from (-)-isopulegol, synthesised the enol ether (**6**; Scheme 2), which was then photooxygenated in

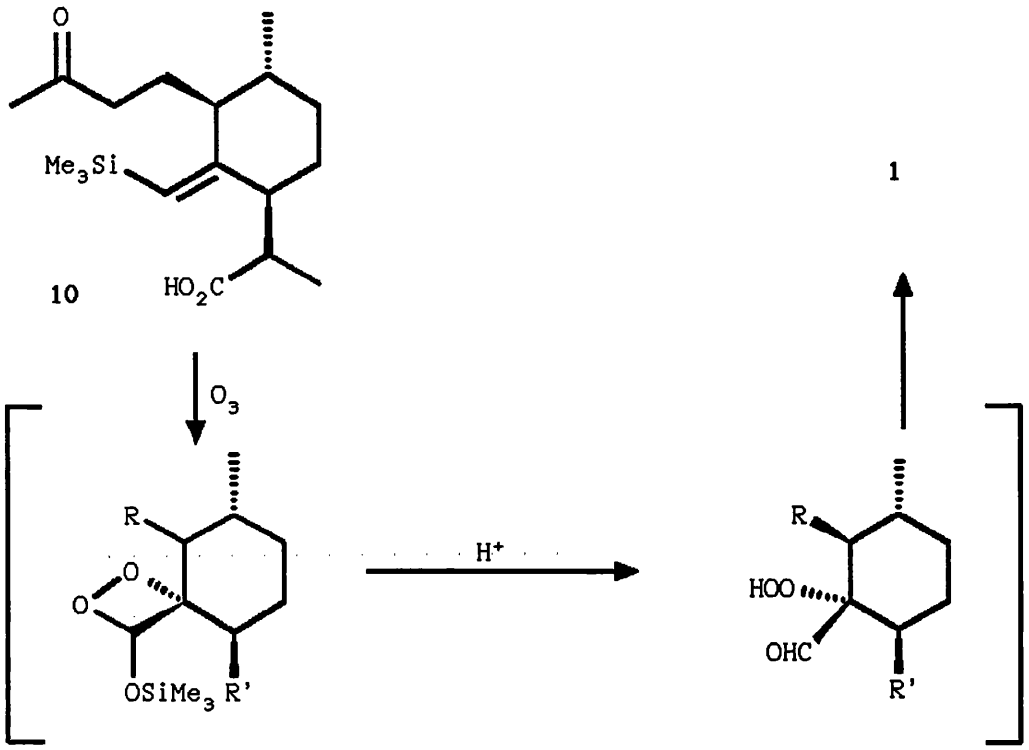
methanol to give hydroperoxide (**7**). Treatment of **7** with acid affords **1** in 30% yield.

In the total synthesis published by Zhou[9] an identical method was used to introduce the 1,2,4-trioxane moiety. McPhail *et al.*[10] also used singlet oxygenation of a methyl enol ether (**8**), in the presence of acetaldehyde, in their synthesis of desethanoqinghaosu (**9**) (Scheme 3).



8 9

Scheme 3

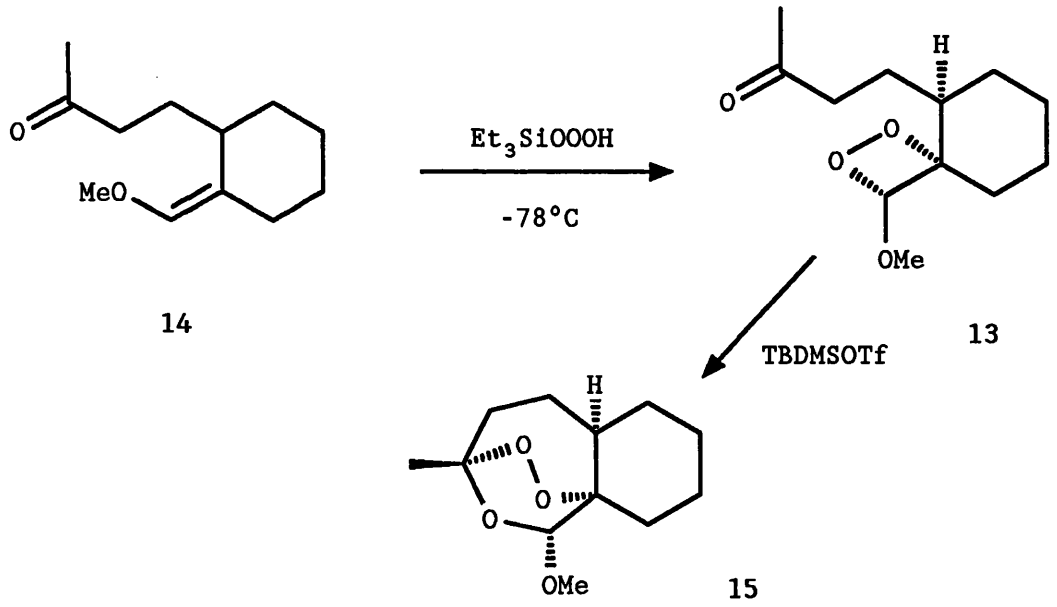


11 12

Scheme 4

Avery *et al.*[11] used a different approach for the introduction of the peroxy group. They took a vinyl silane (**10**) and treated it with ozone to give a transient silyloxydioxetane (**11**). On treatment with acid this ring opens to a labile α-hydroperoxy aldehyde (**12**) (cf. **7**, an α-hydroperoxy dimethyl acetal) which cyclises to give the desired product (Scheme 4). They also used this approach to synthesise various derivatives of artemisinin.[12-14]

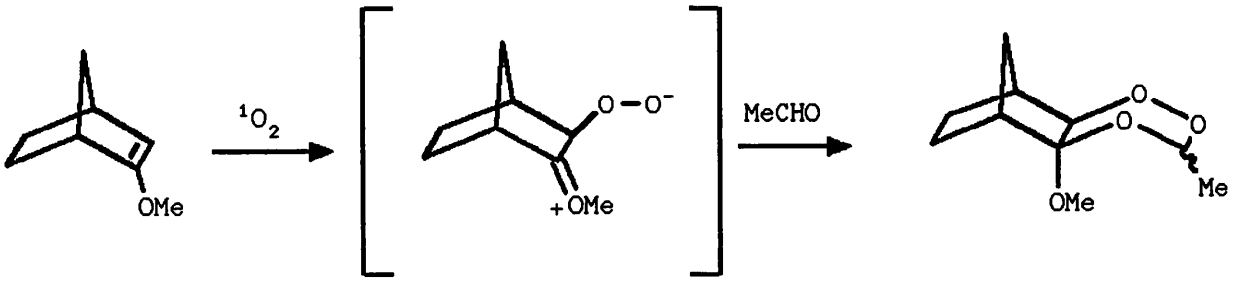
In recent work by Posner *et al.*,[15] methoxy dioxetanes (**13**) were synthesised by treating methyl enol ethers (e.g. **14**) with triethylsilyl hydrotrioxide. 1,2,4-Trioxanes (**15**) could then be produced in yields of between 40 and 60% by cyclisation of the dioxetanes with *tert*-butyldimethylsilyl trifluoromethanesulphonate (Scheme 5).



Scheme 5

A variation of the method used by McPhail has been employed by Jefford *et. al.* for the synthesis of simple 1,2,4-trioxanes.[16] Again, photooxygenation of an enol ether (e.g. **16**) in the presence of an aldehyde gives a 1,2,4-trioxane (**17**), though they rationalise the result by proposing the intermediacy of a zwitterionic peroxide (**18**) (Scheme 6).

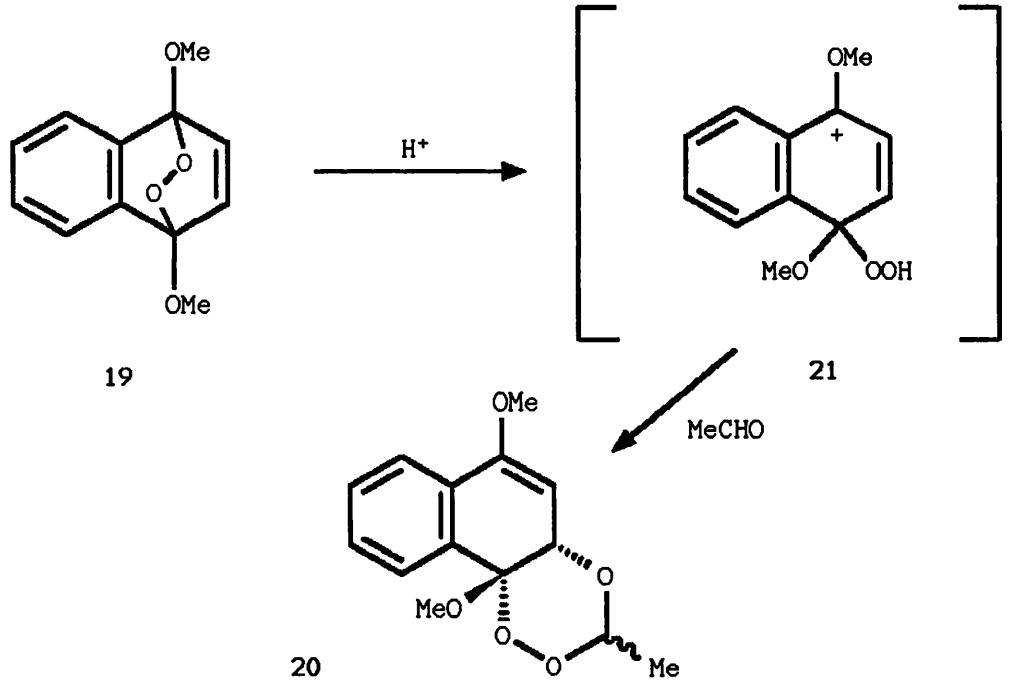
They have also proposed β-hydroperoxy carbocations as intermediates in 1,2,4-trioxane syntheses. Thus, treatment of endoperoxide **19** with acetaldehyde and an acid catalyst gives the



16 18 17

Scheme 6

product (**20**) *via* the carbocation (**21**) (Scheme 7).[17] Trimethylsilyl trifluoromethanesulphonate is also an efficient catalyst for this reaction.

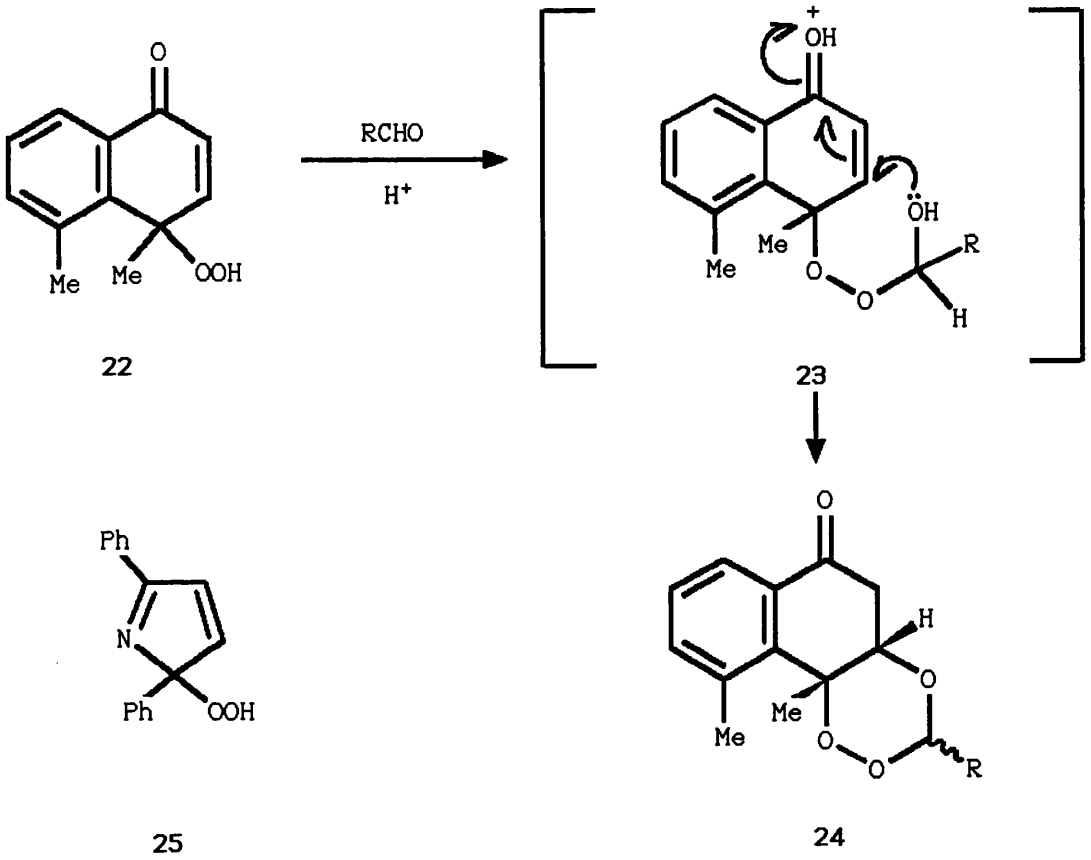


19 21 20

Scheme 7

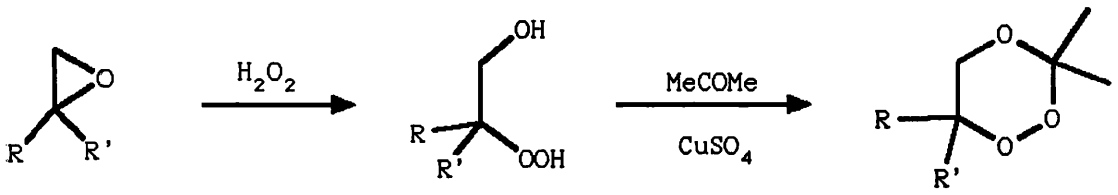
In a method very closely related to that shown in Scheme 7, cyclic allylic hydroperoxides (e.g. **22**) were treated with an aldehyde to give hemiperacetals (**23**), which underwent acid catalysed cyclisations to give 1,2,4-trioxanes (**24**) in high yields (Scheme 8).[18] However, when hydroperoxide **25** was used yields were typically only 20%.

Another method which has been widely used for the synthesis of 1,2,4-trioxanes is the condensation of β-hydroperoxy alcohols with



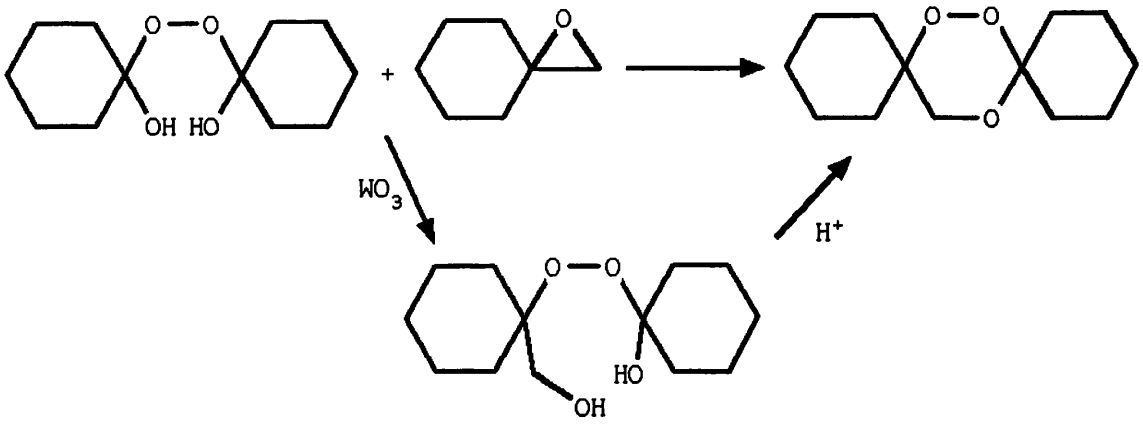
Scheme 8

aldehydes and ketones. Such compounds are commonly made by the action of hydrogen peroxide on an epoxide in the presence or absence of tungstic acid catalyst (Scheme 9).[19]



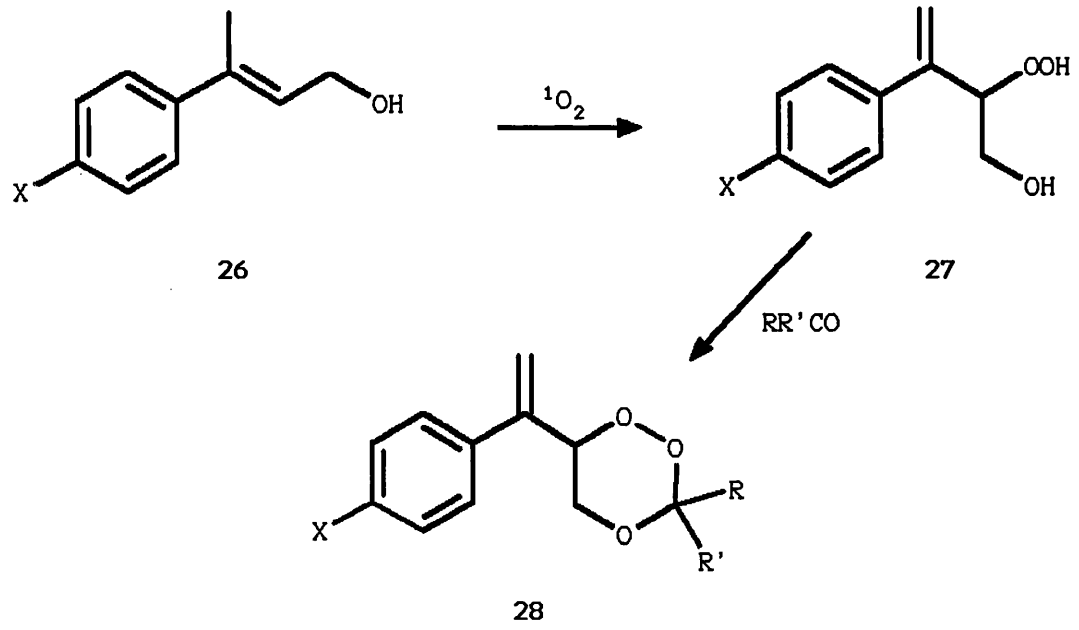
Scheme 9

A related reaction was used by Nojima,[20] in which an α-hydroxy peroxide is treated with an epoxide, tungstic anhydride and a catalytic amount of chlorosulphonic acid to give a 1,2,4-trioxane. The reaction involves the initial tungstic anhydride catalysed attack of the peroxide on the epoxide to form an α,β'-dihydroxy peroxide and a ketone. Acid catalysed dehydration of the diol then leads to the observed trioxanes, which are formed as single diastereomers. An example is shown in Scheme 10.



Scheme 10

An alternative synthesis of β-hydroperoxy alcohols was used by Singh.[21] Here, singlet oxygenation of allylic alcohols (**26**) afforded the allylic hydroperoxides (**27**), which on treatment with acetone, cyclohexanone or *p*-anisaldehyde gave the desired 1,2,4-trioxanes (**28**) in yields of 34-74% (Scheme 11). The products showed *in vitro* activity against *P. falciparum*.

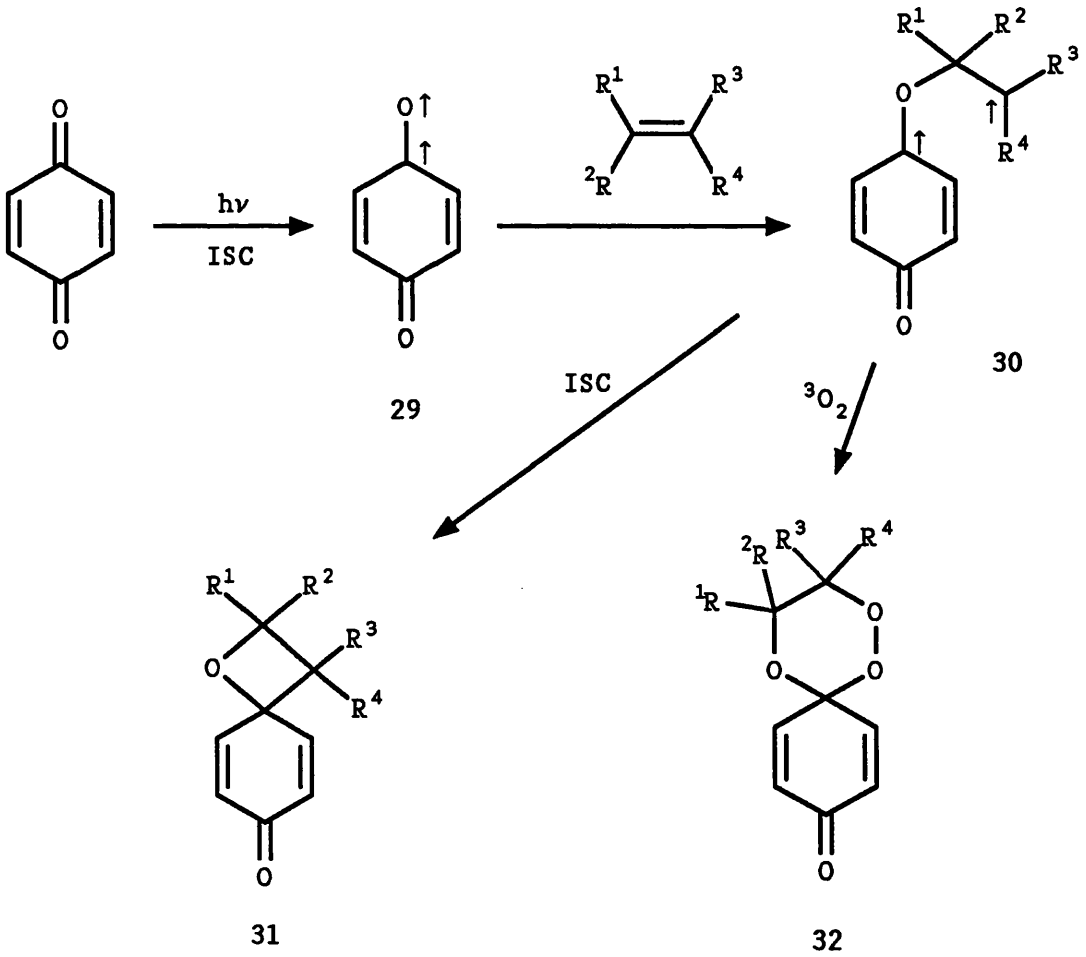


28

X = H, Me, OMe, F, Cl

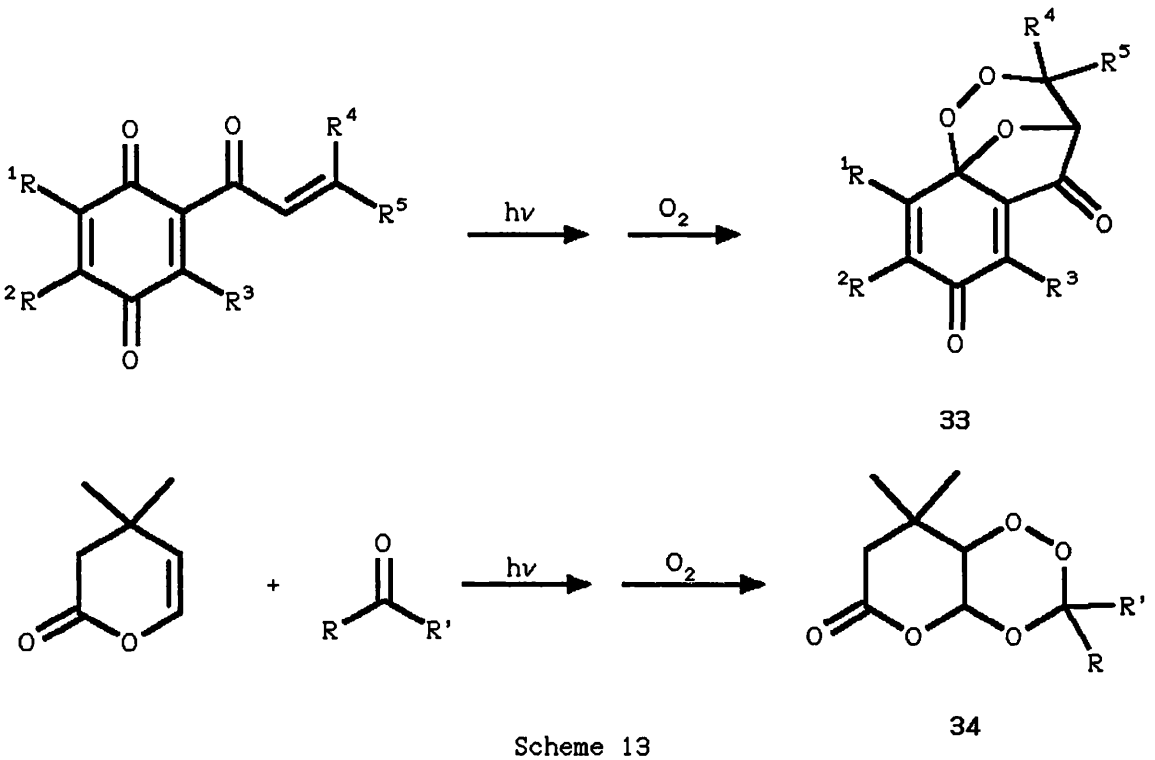
Scheme 11

Trapping of Paterno-Büchi diradicals by molecular oxygen is also a well studied method for the synthesis of 1,2,4-trioxanes.[22] Photolysis of quinones by an argon ion laser gives a singlet biradical, which after undergoing an inter-system crossing (ISC) to the triplet state (**29**), can then add to an alkene to form the preoxetane biradical (**30**). The two radical centres could then undergo a further inter-system crossing and combine to form an oxetane (**31**), or alternatively **30** can be trapped by triplet molecular oxygen leading to the 1,2,4-trioxane (**32**) in an overall yield of typically 50% (Scheme 12).



Scheme 12

Apart from simple 1,2,4-trioxanes, this method has also been used for the synthesis of bicyclic trioxanes (**33**),[23] and artemisinin-like trioxane lactones (**34**)[24] (Scheme 13).

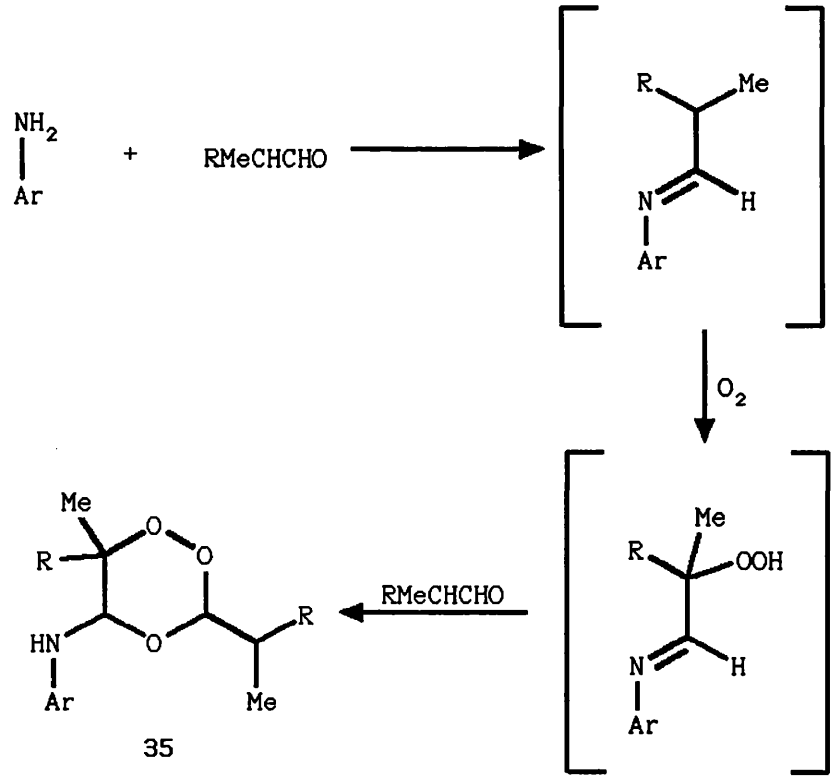


33

34

Scheme 13

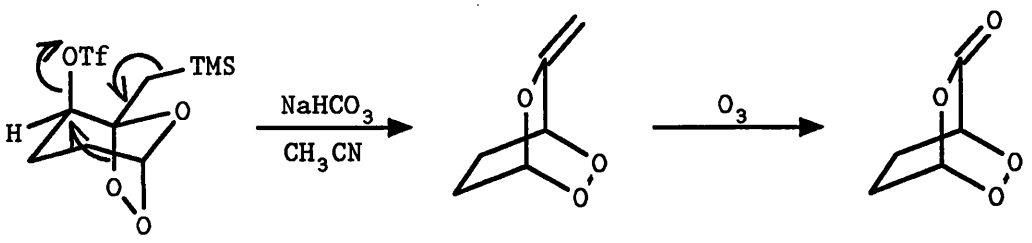
Yamamoto *et al.*[25] showed that treatment of an aryl amine with oxygen and an aldehyde in hexane leads to the formation of 5-arylamino-1,2,4-trioxanes (**35**) via the intermediate α-hydroperoxy imine (Scheme 14).



35

Scheme 14

The most recent approach[26] to the 1,2,4-trioxane moiety involves the ring expansion of a 1,2,4-trioxolane (an ozonide) (Scheme 15). Treatment of ozonide **36** with a mild base causes a

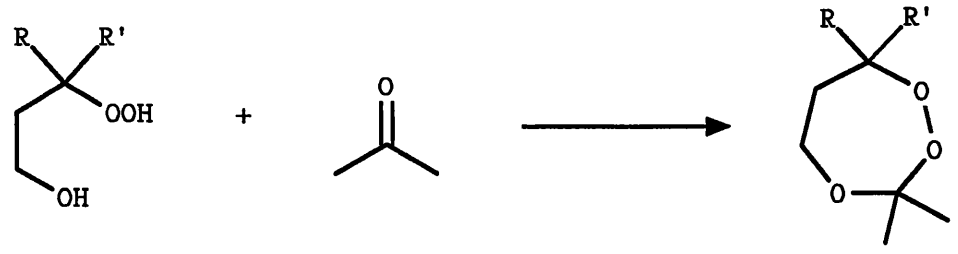


36 37 38

Scheme 15

rearrangement to occur, affording the bicyclic 1,2,4-trioxane (**37**). The rearrangement is sensitive to substrate structure, requiring the triflate and peroxy groups to be anti-periplanar; the isomer of **36** with an equatorial triflate group does not rearrange. Ozonolysis of **37** yields a 1,2,4-trioxan-5-one (**38**). Other approaches to this particular ring structure exist in the literature,[27] but they shall not be discussed here.

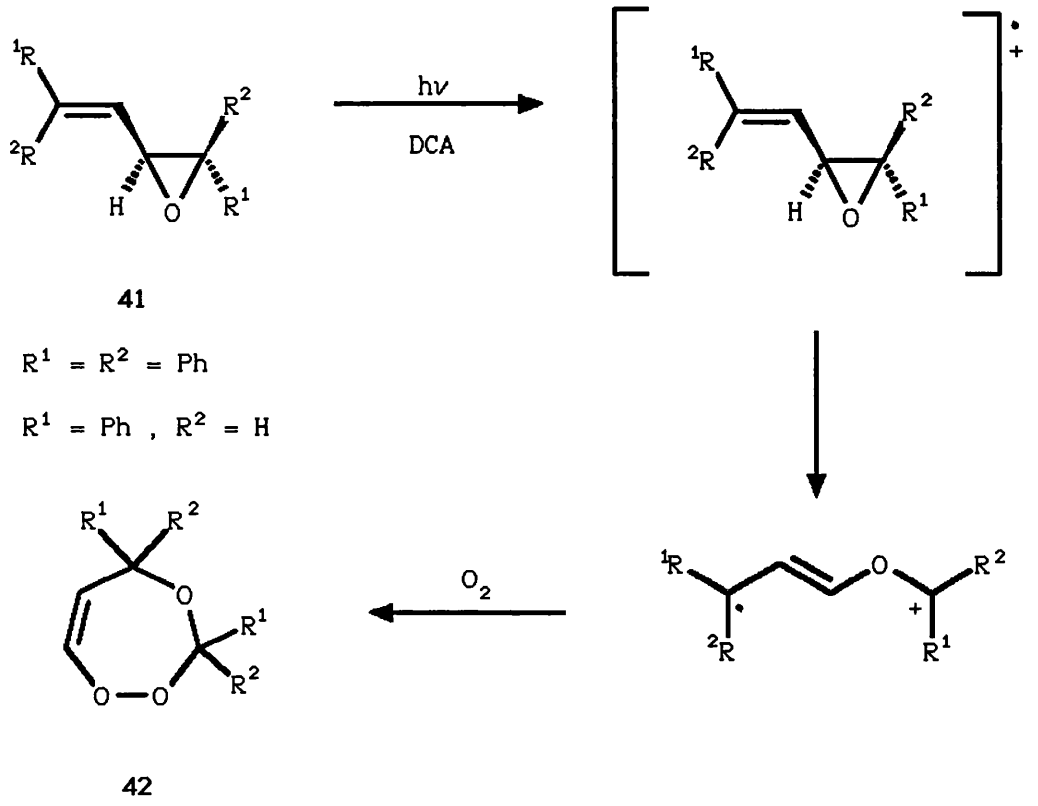
Despite the profusion of approaches to 1,2,4-trioxanes, only one synthesis of the corresponding 7-membered rings (1,2,4-trioxepanes) has been published. Adam[28] synthesised the γ-hydroxy hydroperoxides (**39**) by treating the corresponding diols with acidic hydrogen peroxide. Condensation of these compounds with acetone gave the 1,2,4-trioxepanes (**40**) (Scheme 16).



39 40

Scheme 16

However, 9,10-dicyanoanthracene sensitised photo-oxidation of arylvinyloxiranes (**41**) affords the closely related 1,2,4-trioxepines (**42**), probably via an electron transfer mechanism (Scheme 17).[29]



41

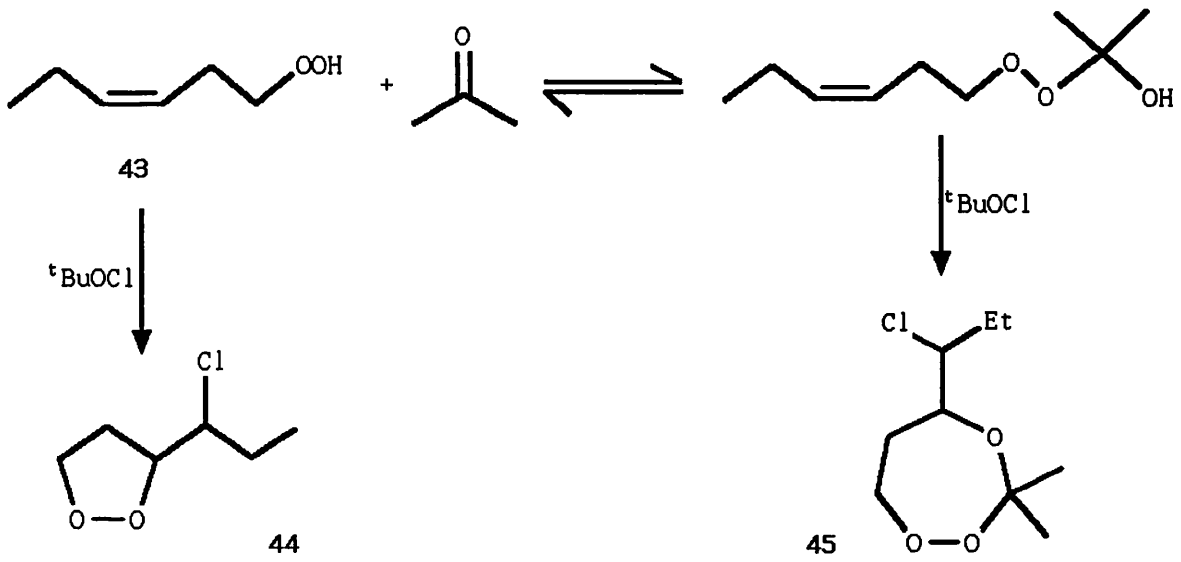
$R^1 = R^2 = Ph$

$R^1 = Ph$, $R^2 = H$

42

Scheme 17

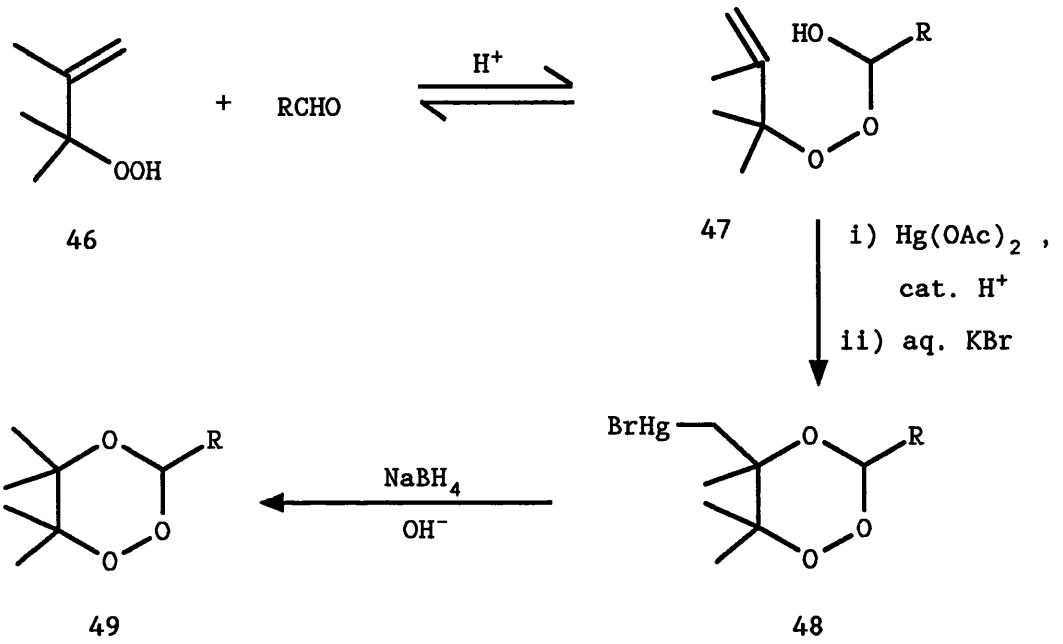
During attempts to cyclise homoallylic hydroperoxides with *tert*-butyl hypochlorite,[30] we investigated the effect of changing the solvent. When the reaction was carried out with *cis*-3-hexen-1-yl hydroperoxide (**43**) in acetone, apart from the expected 1,2-dioxolane (**44**), another product was isolated, which was assigned as a 1,2,4-trioxepane (**45**) (Scheme 18).



43 44 45

Scheme 18

This methodology was further investigated by Bloodworth and Shah with a view to developing a new synthesis of 1,2,4-trioxanes [31] (Scheme 19). Starting from an allylic hydroperoxide (**46**) and an



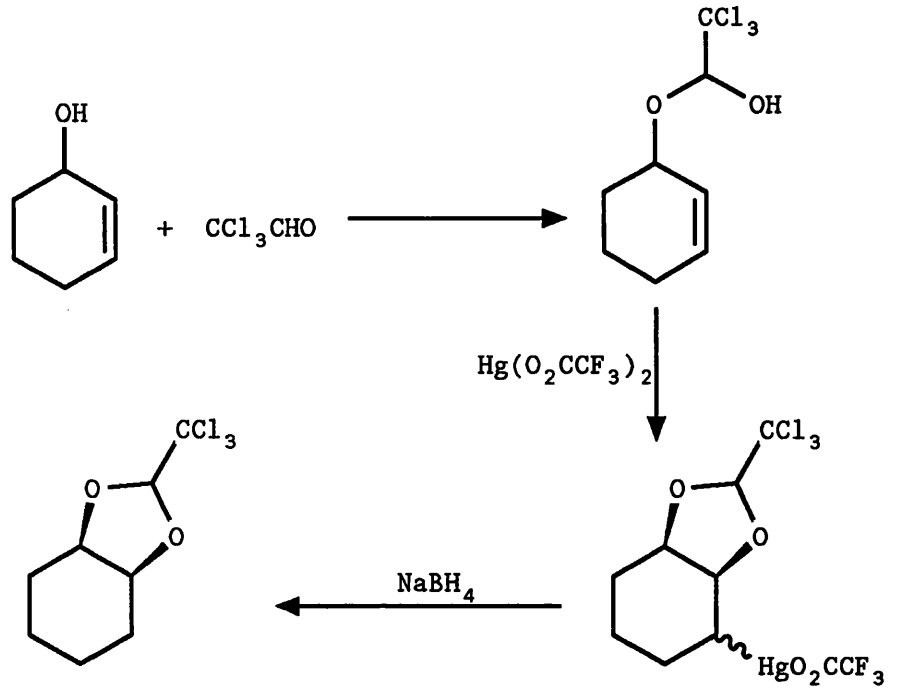
46 47 48 49

Scheme 19

aldehyde, it was found that cyclisation of the intermediate hemiperoxyacetal (**47**) could be induced by treating the mixture with mercury(II) acetate. The resultant 1,2,4-trioxanes (**48**) were formed in good yield (35-62% after anion exchange to the organomercury bromides) and were readily transformed to the mercury-free compounds (**49**). Moreover, in contrast to Scheme 18, reaction of the hydroperoxide with the electrophile did not compete effectively with the cyclisation of the hemiperoxyacetal. It was also found that the parent trioxanes (**49**) were readily synthesised by *in situ* reduction of the organomercury acetates, without the need to isolate any of the intermediates.

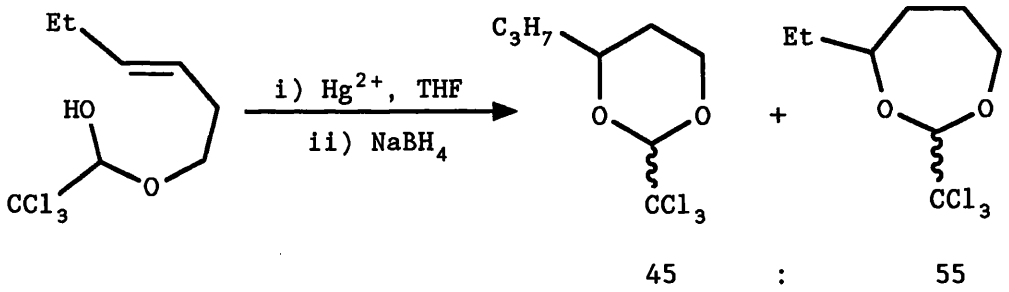
A comparable reaction with hemiacetals has been reported,[32] whereby condensation of an allylic alcohol with chloral, followed by treatment with mercury(II) trifluoroacetate and *in situ* hydridodemercuration with sodium borohydride afforded 1,3-dioxolanes (Scheme 20). Reductive cleavage of the dioxolanes with sodium in ether led to the formation of 1,2-diols.

It was found that acyclic alcohols afforded a mixture of 1,3-dioxolanes and 1,3-dioxanes (by 6-*endo* cyclisation); with



Scheme 20

cinnamyl alcohol only the 6-membered ring was found. Similarly, homoallylic alcohols afforded mixtures of 1,3-dioxanes and 1,3-dioxepanes (Scheme 21).



Scheme 21

Of the syntheses of 1,2,4-trioxanes that have been discussed in this section, none can claim to be a general route to such compounds. The methods involving the singlet oxygenation of methyl enol ethers[8-10] or ozonolysis of vinyl silanes[11-14] have only been applied to the syntheses of complex polycyclic qinghaosu-like trioxanes, and are likely to be of little use in the synthesis of simple monocyclic trioxanes. The same is probably true of Posner's approach using triethylsilyl hydrotrioxide and enol ethers.[15] The condensation of β-hydroperoxy alcohols with ketones[19] however, has been used to

synthesise simple 1,2,4-trioxanes. The problem with this method though, is that the syntheses of the hydroperoxides require quite forcing conditions, e.g. stirring an epoxide with 98% hydrogen peroxide for several days.

Some of the other methods discussed are also limited in the range of compounds that can be made. For instance, Singh's photooxygenation method[21] necessarily produces 6-(1-methylenealkyl)-1,2,4-trioxanes, and Yamamoto's route[25] is only applicable to the synthesis of 5-arylamino-1,2,4-trioxanes. The ring expansion of an ozonide[26] is even more restricted as only ozonides with very specific substitution patterns will undergo such a rearrangement; in fact only one trioxane has been made by this route. Another very restrictive method is that involving Paterno-Büchi diradicals,[22-24] as expensive and complex equipment is required for the reaction.

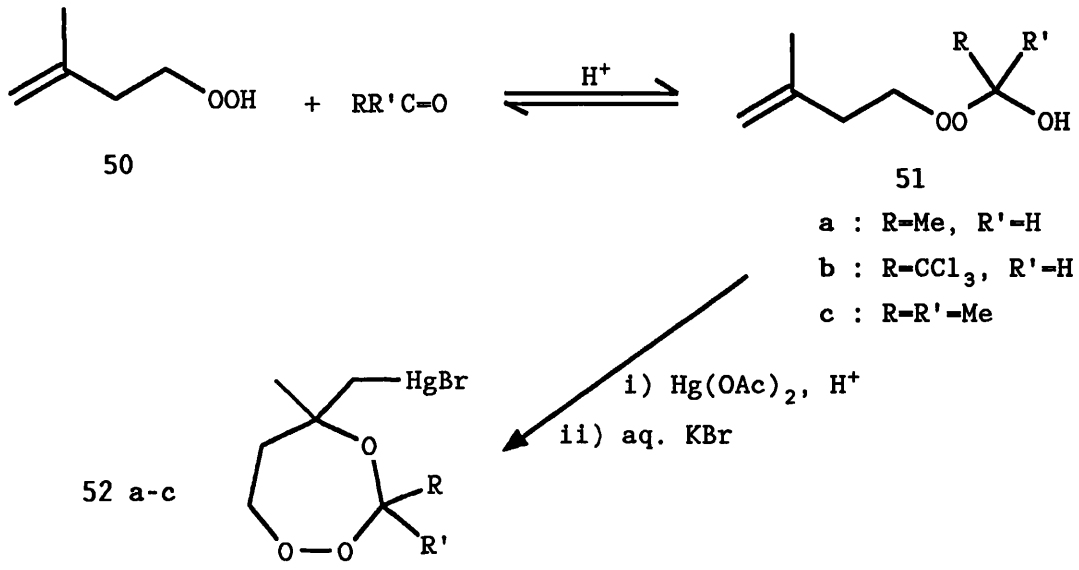
Of the routes that have been discussed here, the most useful and most thoroughly investigated are those devised by Jefford.[16-18] Although many examples have been published, and the trioxanes are often formed in high yield, even these syntheses suffer from the problem that bicyclic endoperoxides (or their equivalents) are used as the starting materials, and therefore the trioxanes formed all have fused ring systems.

The new synthesis developed by Bloodworth and Shah[31] should prove to be a very useful addition to these methods, as it lacks many of the limitations mentioned above. Therefore, it was decided to look further at the series of reactions outlined in Schemes 18 and 19, to see if 1,2,4-trioxepanes in general could be synthesised by cyclisation of unsaturated hemiperoxyacetals, and also to ascertain the generality of this method for the preparation of 1,2,4-trioxanes.

4.2 RESULTS AND DISCUSSION

4.2.1 Attempted Synthesis of 1,2,4-Trioxepanes

We started by investigating the application of intramolecular oxymercuration of a hemiperoxyacetal to the synthesis of 1,2,4-trioxepanes. This would involve the series of reactions outlined in Scheme 22.



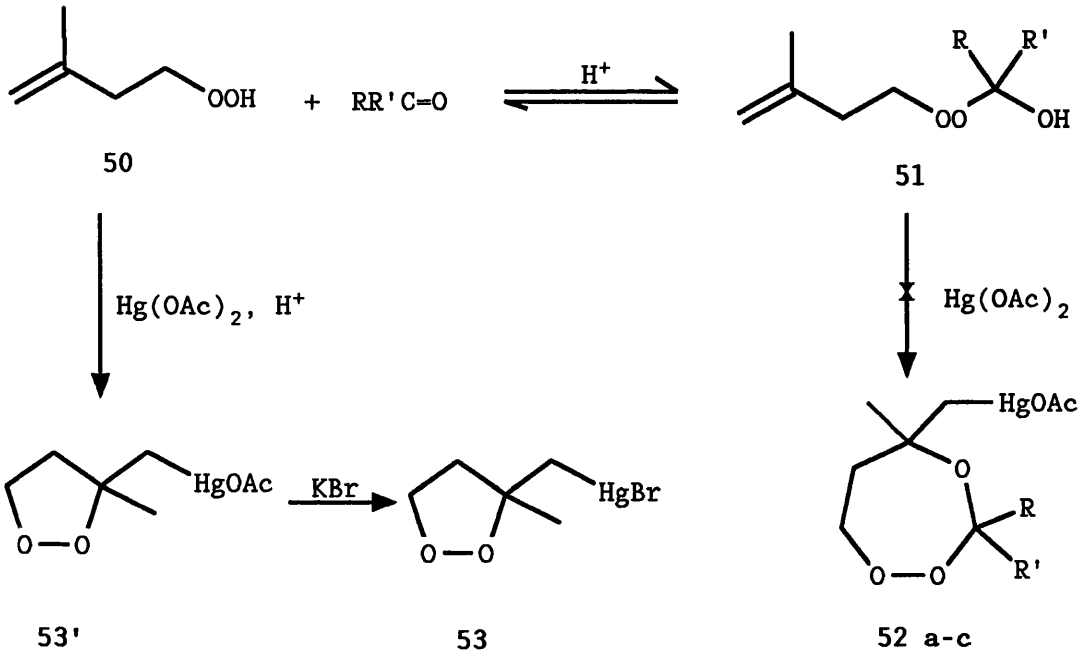
Scheme 22

Hydroperoxide **50** was synthesised by the standard method of Mosher and Williams,[33] and was formed in 40% overall yield from the alcohol (see Chapter 2).

Hemiperoxyacetal **51a** was formed by stirring **50** with acetaldehyde and trifluoroacetic acid catalyst in dichloromethane. Examination of the product by ^{1}H nmr spectroscopy showed approximately equal amounts of **50** and **51a**. In general, the intermediate hemiperoxyacetal was not isolated, but was treated *in situ* with an electrophile.

However, attempts at cyclising **51a** were unsuccessful. Instead, treatment of **51a** with mercury(II) acetate and perchloric acid catalyst produced only the 1,2-dioxolane (**53**) from cyclisation of **50**. The greater nucleophilicity of the OOH group compared with the OH group, coupled with the very favourable 5-*exo* mode of cyclisation available to **50**, means that cyclisation of **50** is much faster than cyclisation of **51a**, and the equilibrium reacts exclusively on the

left hand side (Scheme 23).

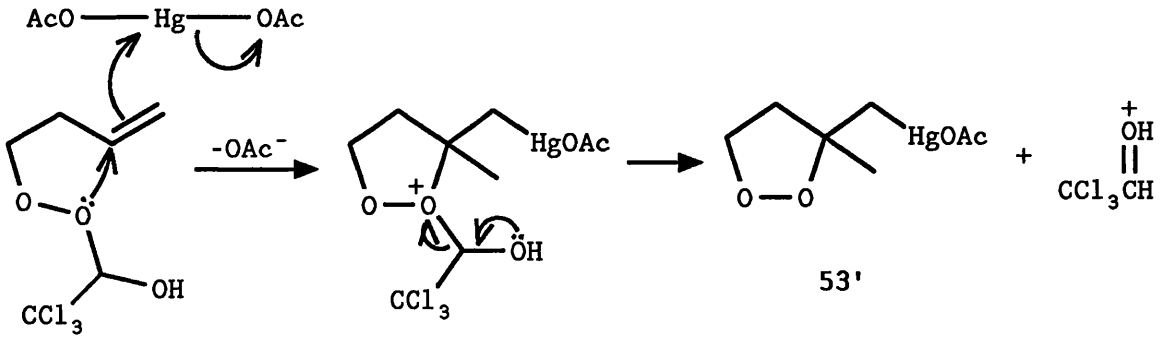


Scheme 23

To try and overcome this problem we tried replacing acetaldehyde with trichloroacetaldehyde (chloral). As expected, the strongly electron withdrawing nature of the trichloromethyl group resulted in quantitative formation of the hemiperoxyacetal **51b**. Unfortunately, subsequent treatment of **51b** with mercury(II) acetate again afforded only the dioxolane (**53**).

Considering the relative concentrations of **50** and **51b** in this system, it seemed unlikely that **50** could cyclise exclusively at the expense of the much more abundant hemiperoxyacetal (**51b**). An alternative proposition would be that the 1,2-dioxolane (**53**) derives from cyclisation of the hemiperoxyacetal, and not the hydroperoxide. This would necessitate the intermediacy of a peroxonium ion[34] (**54**), which upon losing protonated chloral would form the observed product (**53**) (Scheme 24).

Another approach tried was to carry out the cyclisation at lower temperature. This was to check whether the trioxepane was in fact the kinetic product of the reaction, but at higher temperature was reverting to the thermodynamically more stable dioxolane. Problems with the solubility of mercury(II) acetate at low temperature meant that mercury(II) trifluoroacetate had to be used as the electrophile. However, repeating the synthesis at -20°C made no

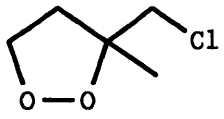


51b 54 53'

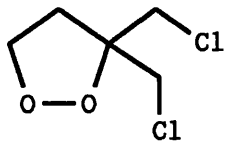
Scheme 24

difference, giving the same result as before.

Changing the electrophile was the obvious next step. As 1,2,4-trioxepane formation was previously observed in reactions involving *tert*-butyl hypochlorite (see Chapter 2), this seemed a logical reagent to use. The cyclisation was attempted with all three hemiperoxyacetals (**51a**, **b** and **c**), at temperatures ranging from -60°C to room temperature, and with or without the addition of silica. In all but one instance, only the chlorinated dioxolanes **55** and **56** were observed. The one exception was the attempted cyclisation of **51c**

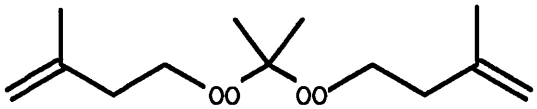


55



56

with *tert*-butyl hypochlorite, in the absence of silica, at -60°C. Under these conditions four new products were formed, which were identified as the acetone perketals **57**, **58** and **59** and the hydroperoxide **60**. The structures of these were elucidated through ^{1}H and ^{13}C nmr spectroscopy, and the relative molecular masses were confirmed by fast atom bombardment (FAB) mass spectrometry. The formation of perketals by the condensation of hydroperoxides with ketones is well established,[35] **58**, **59** and **60** presumably being formed by the trapping of an intermediate β-chloro carbocation with the water present as a by-product. The observed regioselectivity is in agreement with that observed for the trapping of such ions by methanol.[36]



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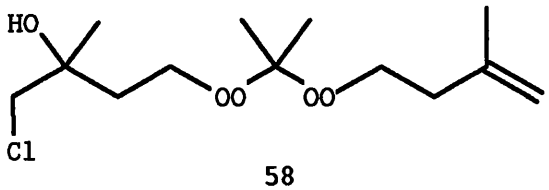

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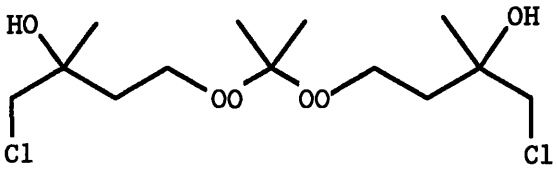

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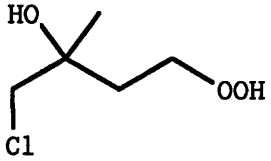

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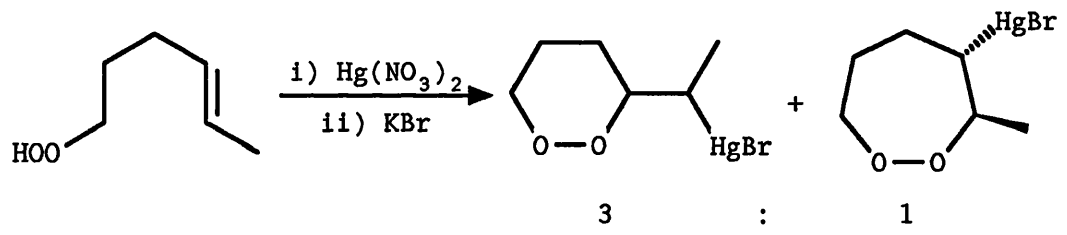
4.2.2 The Synthesis of 1,2,4-Trioxanes and 1,2-Dioxolanes

4.2.2.1 1-Phenylallyl Hydroperoxide and Cinnamyl Hydroperoxide

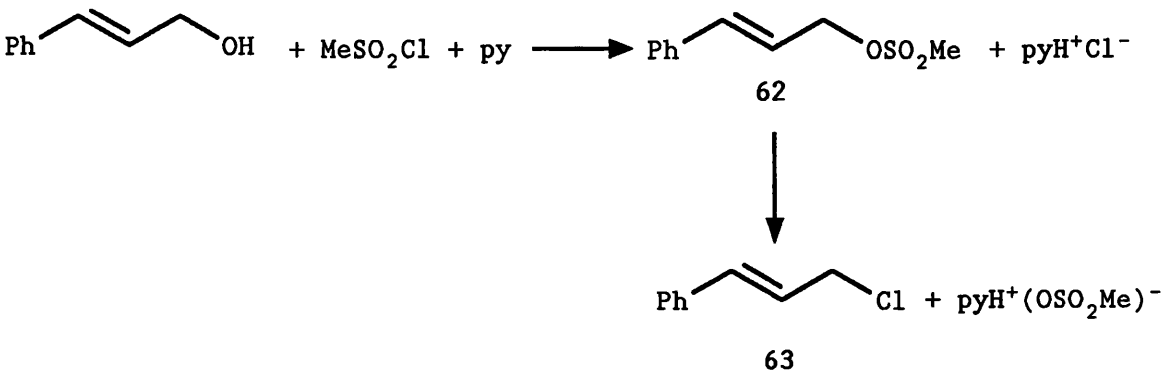
The failure of the previous systems to form 1,2,4-trioxepanes led us to look instead at the formation of 1,2,4-trioxanes from allylic hydroperoxides. The target hydroperoxide chosen was cinnamyl hydroperoxide (**61**), as this offered the possibility of 1,2,4-trioxepane formation *via* a 7-*endo* cyclisation of the hemiperoxyacetal competing with 1,2,4-trioxane formation *via* the previously observed 6-*exo* cyclisation. This is in parallel with the regiochemistry seen in the cyclisation of hemiacetals derived from homoallylic alcohols (Scheme 21) and in the cyclisation of δ,ϵ-unsaturated hydroperoxides (Scheme 25).[37]



Scheme 25

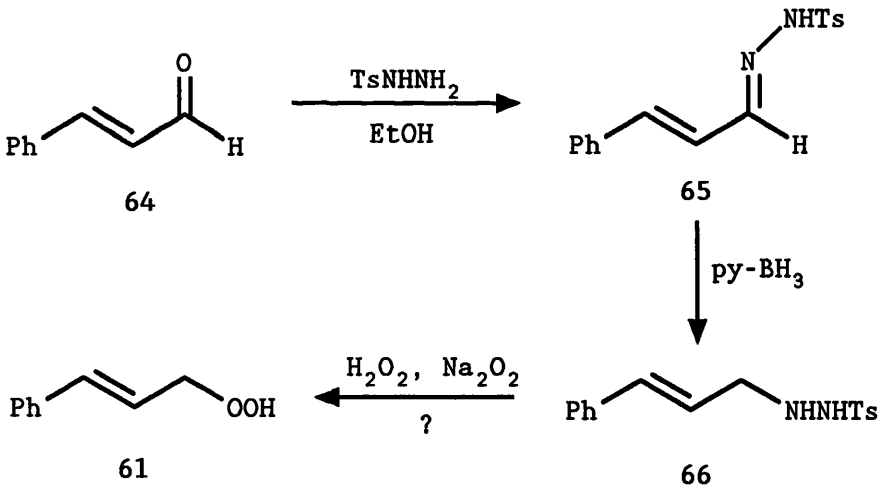
The synthesis of cinnamyl hydroperoxide proved to be less simple than it first appeared. The usual Mosher-Williams perhydrolysis of the methanesulphonate ester (mesylate) of the corresponding alcohol was tried first. This proved unsuccessful due to the lability of the mesylate (**62**). The usual conditions for the synthesis of the mesylate (alcohol, methanesulphonyl chloride, pyridine) yielded only cinnamyl chloride (**63**), which was rationalised by assuming reaction of the mesylate with the chloride ions formed as a by-product (Scheme 26). Therefore the alcohol was treated with pyridine and methanesulphonic anhydride, a system which does not possess the problem of having a nucleophilic counter-ion present. However, attempted isolation of the mesylate produced only a polymeric tar.

Instead, the synthesis of cinnamyl hydroperoxide by the oxidation of the corresponding *N'*-tosylhydrazine was investigated (Scheme 27). *trans*-Cinnamaldehyde (**64**) was converted to the



Scheme 26

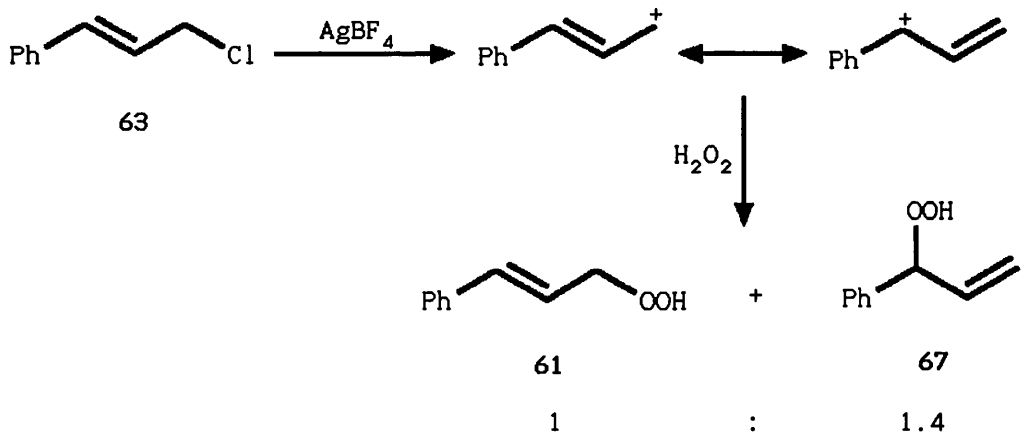
N'-tosylhydrazone (**65**) by the method of Bartlett and Stevens,[38] and then reduced with pyridine-borane to the *N'*-tosylhydrazine[39] (**66**). However, treatment of **66** with hydrogen peroxide and sodium peroxide in tetrahydrofuran[40,41] led to a complex mixture containing only trace amounts of hydroperoxide, as judged by ^{13}C nmr spectroscopy.



Scheme 27

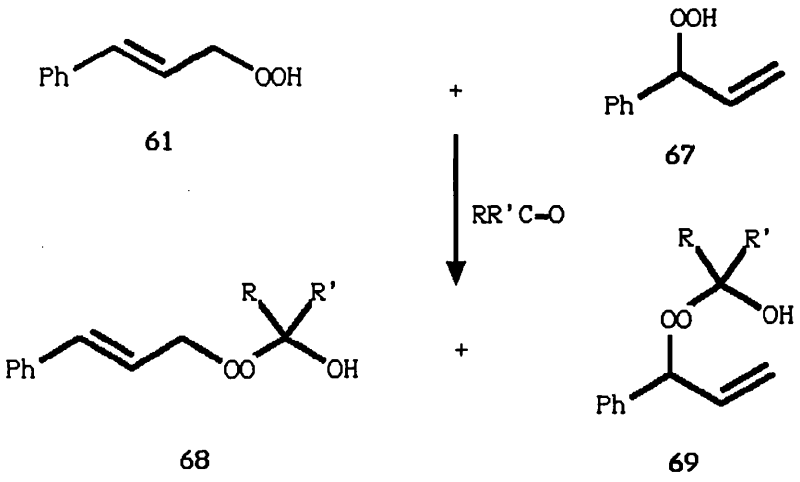
A third approach was to treat cinnamyl chloride (**63**) with a silver salt and hydrogen peroxide. This time hydroperoxide formation was observed, but in addition to cinnamyl hydroperoxide (**61**), 1-phenylallyl hydroperoxide (**67**) was also formed in the ratio of *ca.* 1.4:1 in favour of **67** (Scheme 28). Ordinary column chromatography failed to separate the two isomers, but allowed the isolation of the mixture in 64% yield. Initial experiments were then carried out on this isomeric mixture.

The hydroperoxides (**61**) and (**67**) were treated with acetaldehyde or isobutyraldehyde in dichloromethane in the presence of

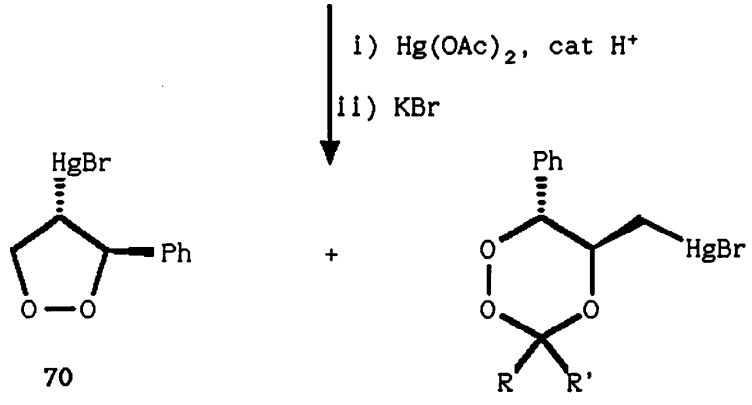


Scheme 28

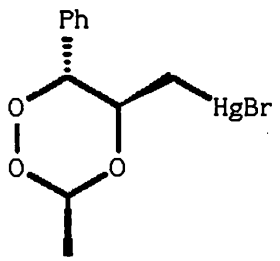
trifluoroacetic acid catalyst to form a mixture of hemiperoxyacetals (**68** and **69**). These were then cyclised with mercury(II) acetate and a drop of perchloric acid catalyst to form a mixture of a 1,2-dioxolane



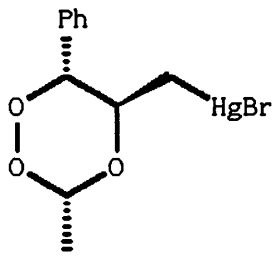
a : R=Me, R'=H **d** : R=*p*-ClC_6H_4, R'=H **g** : R=CCl_3, R'=H
b : R=^{i}Pr, R'=H **e** : R=*p*-$MeOC_6H_4$, R'=H **h** : R=R'=Me
c : R=^{s}Bu, R'=H **f** : R=C_6F_5, R'=H



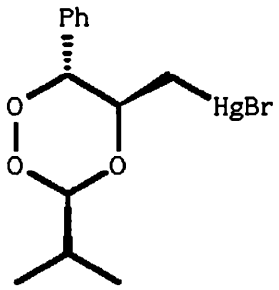
Scheme 29



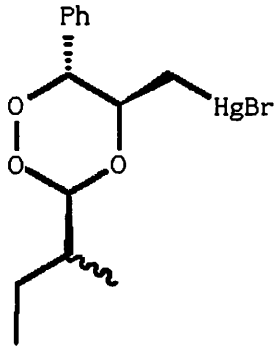
71e



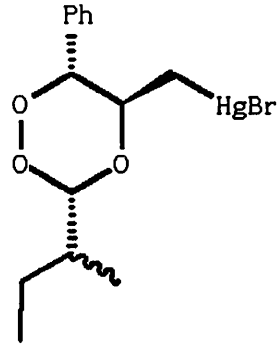
71a



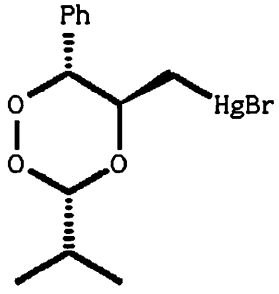
72e



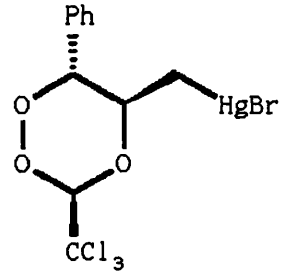
73e



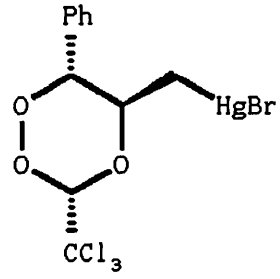
73a



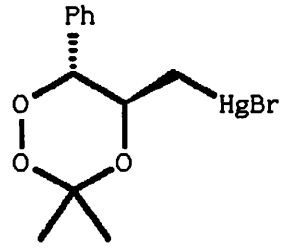
72a



74e



74a



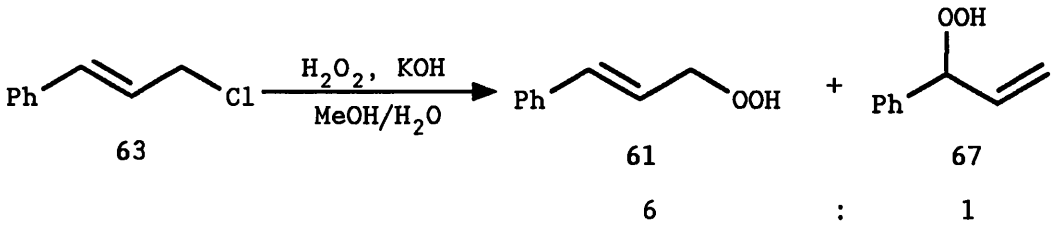
75

(**70**) and 1,2,4-trioxanes (**71** or **72**; the 'a' and 'e' designations refer to the disposition of the alkyl group at C-3 being axial or equatorial respectively in the most stable chair conformation of the 1,2,4-trioxane) (Scheme 29). Note that all mercurials are isolated as the corresponding organomercury bromides, which are chromatographically easier to handle than the highly polar acetates.

From the structures of the trioxanes it was obvious that these were derived from 1-phenylallyl hydroperoxide (**67**), and that cinnamyl hydroperoxide (**61**) must be reacting to give the 1,2-dioxolane (**70**).

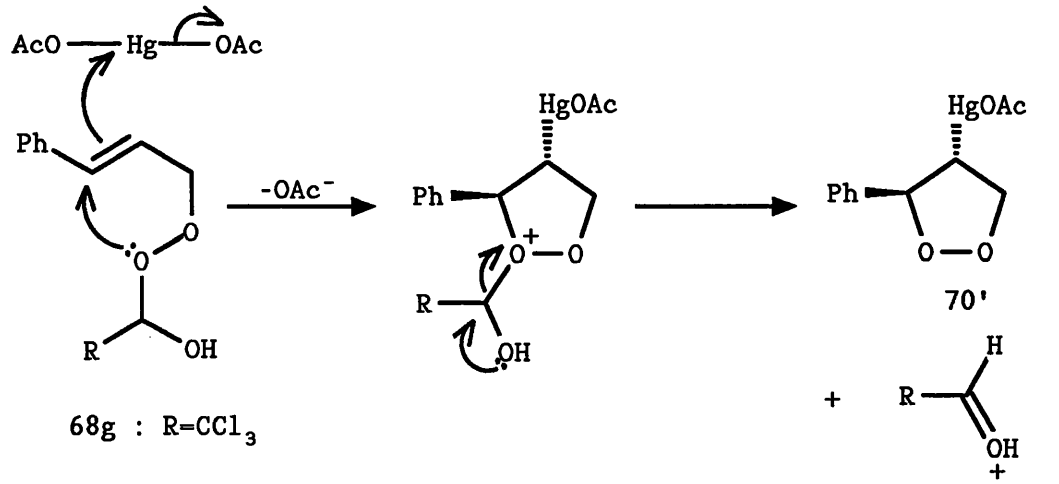
The formation of **70** was very unexpected. To investigate this reaction further we required a sample of pure **61**. We found that treatment of cinnamyl chloride (**63**) with basic hydrogen peroxide gave

a mixture of hydroperoxides greatly enriched in the primary isomer (**61** : **67** = 6 : 1) in 12% yield (Scheme 30).



Scheme 30

When **61** was treated with chloral, the hemiperoxyacetal **68g** was formed quantitatively. However, cyclisation with either mercury(II) acetate at room temperature, or mercury(II) trifluoroacetate at -20°C, produced only **70**. Only one isomer of the 1,2-dioxolane was formed, which was assumed to be *trans* due to *anti* addition of mercury and the peroxy group across the double bond. When acetaldehyde or isobutyraldehyde is used as the carbonyl component, **70** may well arise *via* direct 5-*endo* cyclisation of the hydroperoxide. However, when chloral is used there is essentially no free hydroperoxide available, therefore the dioxolane probably arises *via* cyclisation of **68g** (Scheme 31), in much the same way as suggested earlier for hemiperoxyacetal **51b** (Scheme 24). Although 5-*endo* cyclisations are

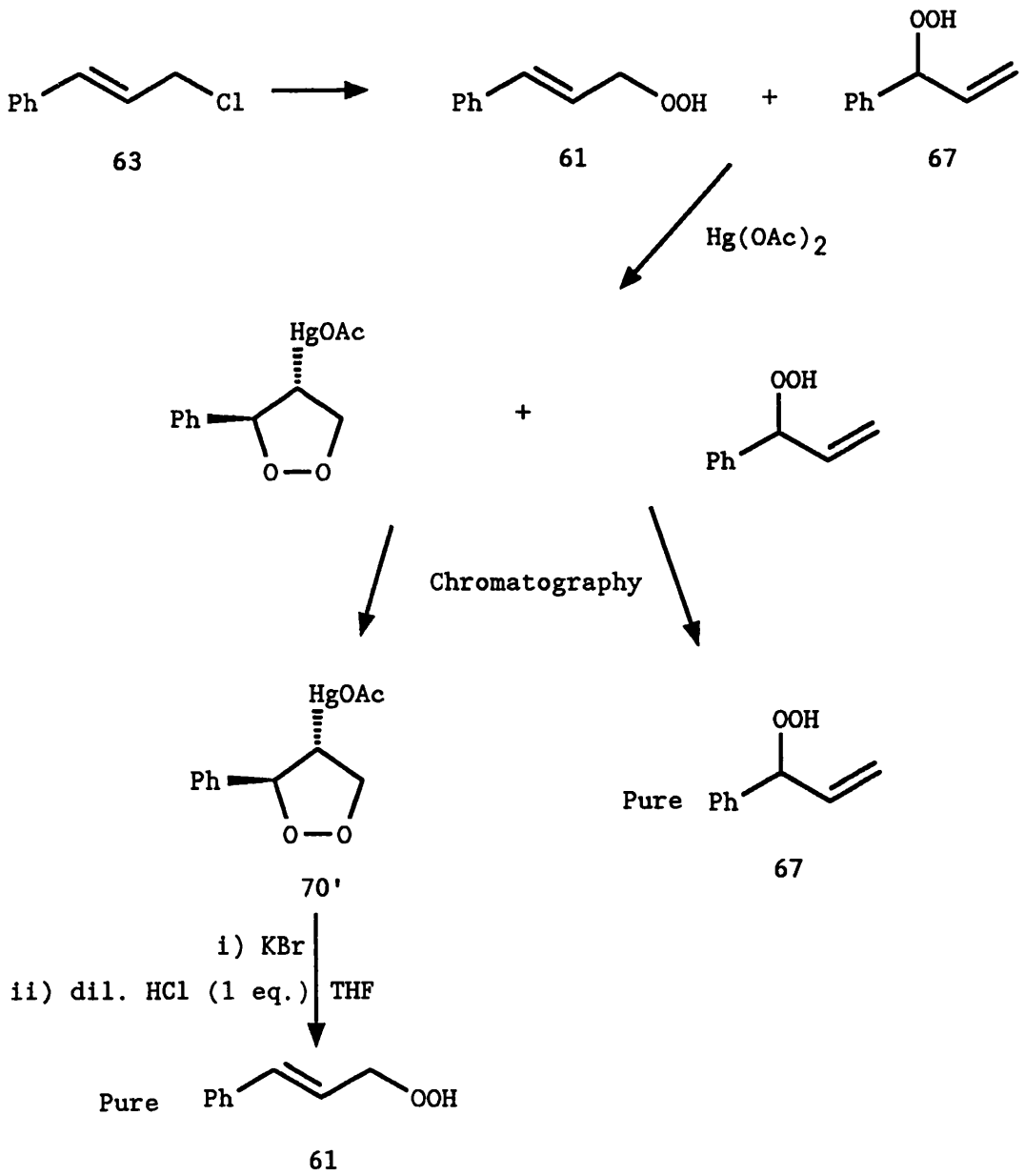


Scheme 31

generally considered unfavourable, there are precedents in the literature involving cycloperoxymercurations.[42]

The divergent behaviour observed for the two isomeric hydroperoxides **61** and **67**, gave us a convenient method for isolating

pure samples of both isomers. Treatment of the mixture with *ca.* 0.5 eq. of mercury(II) acetate in dichloromethane causes the selective cyclisation of cinnamyl hydroperoxide (**61**) to the mercurated dioxolane (**70'**). If only hydroperoxide **67** is required, then immediate chromatography readily separates off the highly polar organomercury acetate (**70'**), leaving a pure sample of 1-phenylallyl hydroperoxide.[43] If hydroperoxide **61** is required, then conversion of the organomercury acetate to the organomercury bromide (**70**) is necessary before chromatography. Treatment of isolated **70** with *ca.* 1 eq. of dilute hydrochloric acid in tetrahydrofuran, followed by



Scheme 32

chromatography, then affords a pure sample of cinnamyl hydroperoxide (**61**) (Scheme 32).

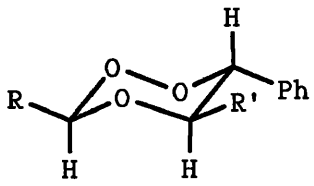
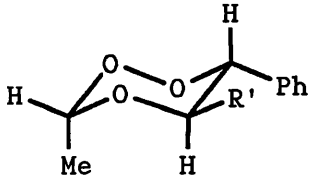
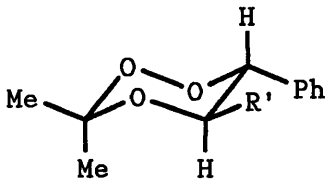
Having obtained pure 1-phenylallyl hydroperoxide, we were now free to investigate further the formation of 1,2,4-trioxanes. Using 2-methylbutyraldehyde as the carbonyl component, we were able to form the 3-*sec*-butyl compounds (**73**). Similarly, chloral gave the 3-trichloromethyl-1,2,4-trioxanes (**74**), though these proved difficult to purify. In contrast, all the aromatic aldehydes tried (*p*-chlorobenzaldehyde, pentafluorobenzaldehyde and *p*-anisaldehyde) failed to give any 1,2,4-trioxanes. The only product observed was the 1,2-dioxolane (**70**). This must have arisen *via* acid-catalysed equilibration of **67** to **61**, with subsequent cyclisation. Note that in the absence of acid, no equilibration was observed over such a relatively short time (*ca.* 2 hours).

The only ketone tried was acetone, and under the standard conditions this gave only a poor yield (8%) of the 1,2,4-trioxane (**75**). However, on using a large excess of acetone (by using acetone as the solvent) the yield could be improved to 40%. Similarly, it was found that by using 17eq. of acetaldehyde, the yield of **71** was increased from 43% to 70%.

The most notable aspect of the formation of the 1,2,4-trioxanes was the high stereoselectivity observed in their formation. The 3-methyl compound (**71**) was formed as essentially two isomers, in the ratio 85 : 15 (**71e** : **71a**), and when a bulky group such as isopropyl, *sec*-butyl or trichloromethyl was placed in the 3-position there was almost complete ($\geq$ 95%) stereoselectivity around the ring (**73e** was in fact formed as a 1 : 1 mixture of isomers, which could not be separated by HPLC, due to the exocyclic chiral centre). The isomers formed were **72e**, **73e** and **74e** respectively. Similarly, **75**, lacking any stereochemistry at the 3-position, was formed as a single (*trans*) isomer.

The isomers formed are those with all three substituents in equatorial positions, assuming a chair conformation of the trioxane ring. The minor isomer found in the reaction with acetaldehyde (**71a**) differs in having an axial substituent at C-3 (Fig. 1). The evidence for the stereochemistries are discussed in section 4.2.4.

The parent trioxanes (**76** - **80**) could be obtained in yields of around 50-70% by treating the isolated mercurials with basic sodium

71e R = Me
72e R = ^{i}Pr
73e R = ^{s}Bu
74e R = CCl_3

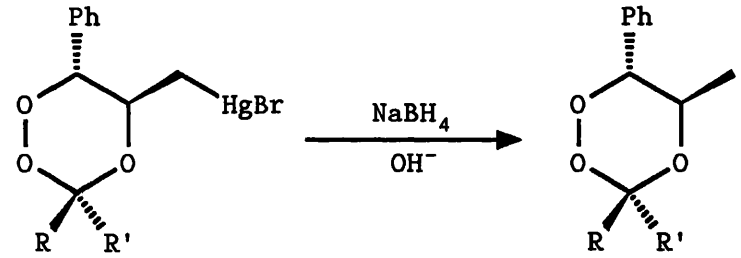
71a

75

In all compounds, R' = CH_2HgBr

Figure 1

borohydride[44] (Scheme 33). Obviously, the reduction does not affect the stereochemistry around the ring, so the isomer ratios of the reduced trioxanes reflect those of the precursor materials.



71 - 75

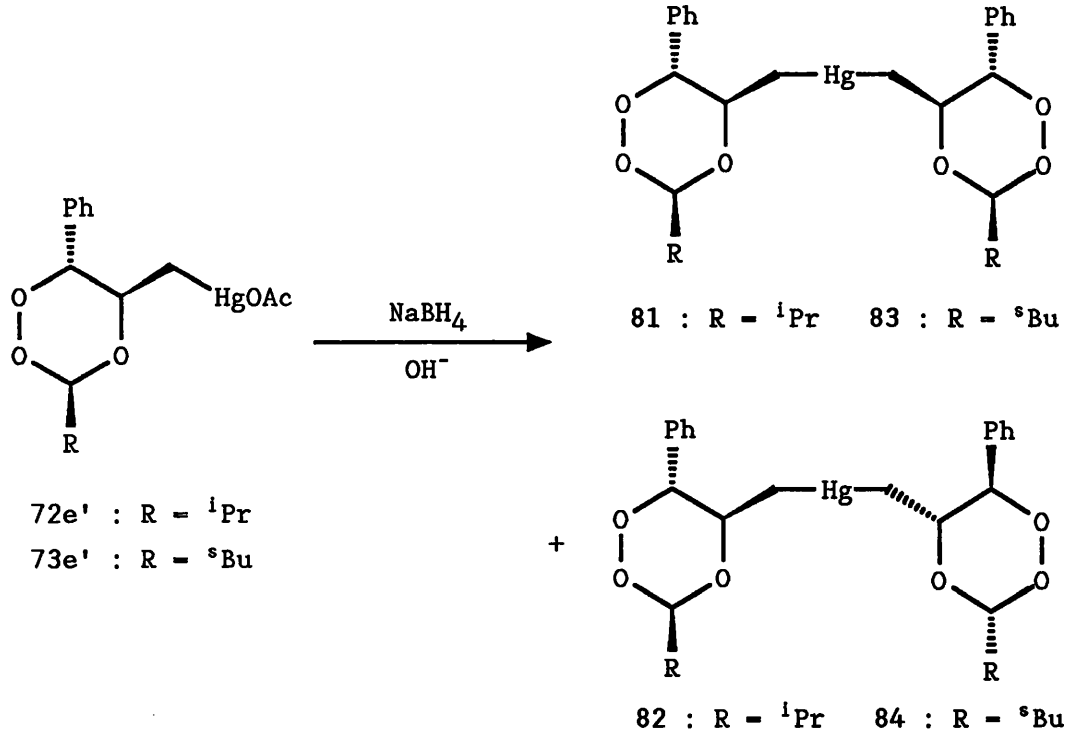
76e : R=Me, R'=H
76a : R=H, R'=Me
77e : R=^{i}Pr, R'=H
78e : R=^{s}Bu, R'=H
79e : R=CCl_3, R'=H
80 : R=R'=Me

Scheme 33

The 3,3-dimethyl compound (**80**) thus obtained was tested for *in vitro* activity against a chloroquine-resistant strain of *P. falciparum*.[45] The activity found was remarkably high, comparable with that of qinghaosu, but the result of just one test should be treated with caution, especially as contamination with traces of mercury cannot be ruled out.

In the original work by Bloodworth and Shah,[31] the organomercury acetates derived from cyclooxymercuration of the hemiperoxyacetals could be reduced *in situ* to give the mercury-free 1,2,4-trioxanes. However, when attempts were made to synthesise **77e** and **78e** by this method, the major products were not as expected.

Examination of the ^{1}H and ^{13}C nmr spectra appeared to indicate the presence of two very similar isomers (four in the case of the ^{s}Bu compound with its exocyclic chiral centre) and it was proposed that these were the dialkylmercury compounds **81** - **84** (Scheme 34). The



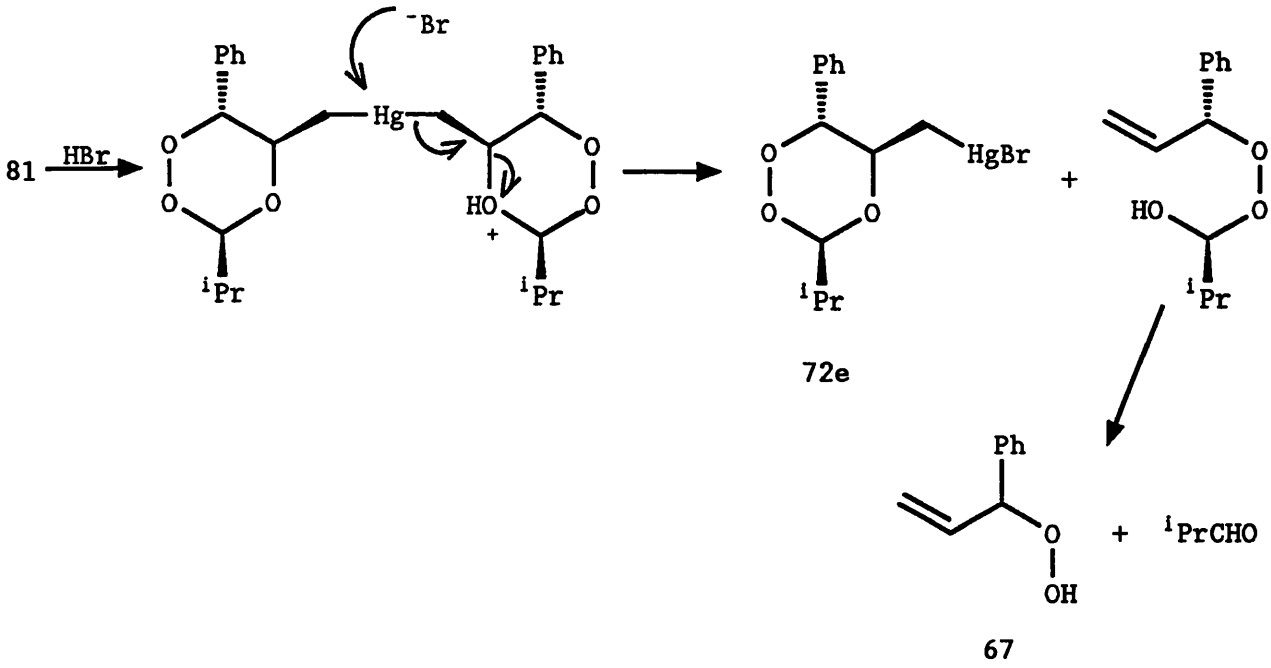
Scheme 34

molecular formulae were confirmed by elemental analysis, and the mixture of **81** and **82** gave a single broad line in the ^{199}Hg nmr spectrum at δ -364 ppm, which is typical for a dialkylmercury compound[46] (cf. **72e** which gives a signal at δ -1080 ppm). As further proof, treatment of **81** and **82** with hydrobromic acid produced the expected organomercury bromide (**72e**) and 1-phenylallyl hydroperoxide (**67**) by the mechanism outlined in Scheme 35.

The synthesis of dialkylmercury compounds from organomercury(II) salts, with concomitant formation of inorganic mercury(II) salts, is known as symmetrisation (eq. 1), and has been

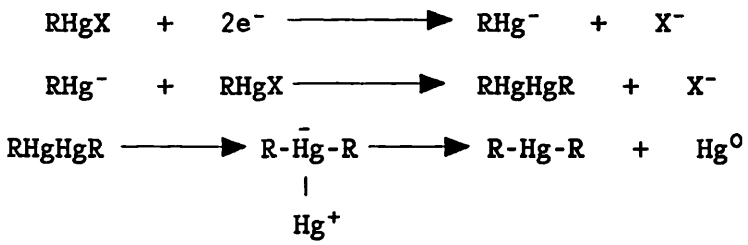
$$2\ RHgX \longrightarrow R_2Hg + HgX_2 \qquad (1)$$

achieved by the use of such reagents as hydrazine,[47] sodium



Scheme 35

dithionite[48] and sodium stannite.[49] The reaction is proposed to proceed *via* a two electron reduction[50] (Scheme 36).



Scheme 36

There have been reports of symmetrisation occurring with sodium borohydride, but these have been few and far between.[51-53] As hydridodemercuration of organomercury(II) salts with sodium borohydride occurs *via* a radical mechanism (Scheme 37), it has been

Scheme 37

proposed[51] that in such systems dialkylmercury formation may arise by combination of RHg· and R·, or by dimerisation of RHg· to form RHgHgR

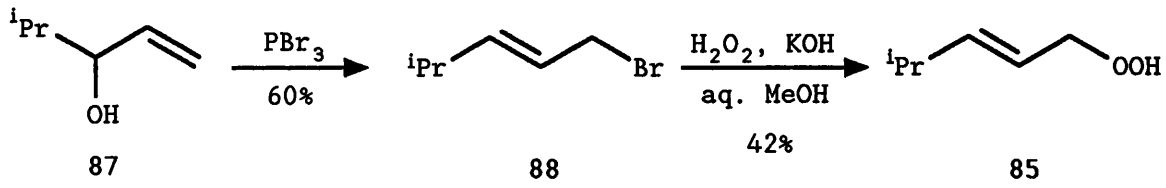
which can then extrude mercury in the manner shown in Scheme 36.

There is no obvious explanation however why we should observe symmetrisation with our trioxanes, whilst the 5,5,6,6-tetramethyl-1,2,4-trioxanes behave normally. Neither is it clear why reduction of the organomercury acetates gives different products to those obtained by reduction of the organomercury bromides, though the greater water solubility of the acetates may be significant. It may be that the exact experimental conditions are crucial in determining the course of the reaction. Whereas we pre-treated the organomercury(II) acetate with 2M sodium hydroxide, before adding 10 eq. of sodium borohydride in 2M sodium hydroxide, Bloodworth and Shah[31] washed the crude acetate with sodium bicarbonate, then treated the organic layer with the basic sodium borohydride (1 eq.). Having said that, it should also be pointed out that the conditions we used were identical to those employed by Overman and Campbell[32] for the *in situ* reduction of the organomercurials derived from cyclisation of the chloral hemiacetals. They did not find dialkylmercury formation to be a problem; the fully reduced compounds were formed in yields of up to 94%, as measured by gc analysis.

4.2.2.2 Other Hydroperoxides

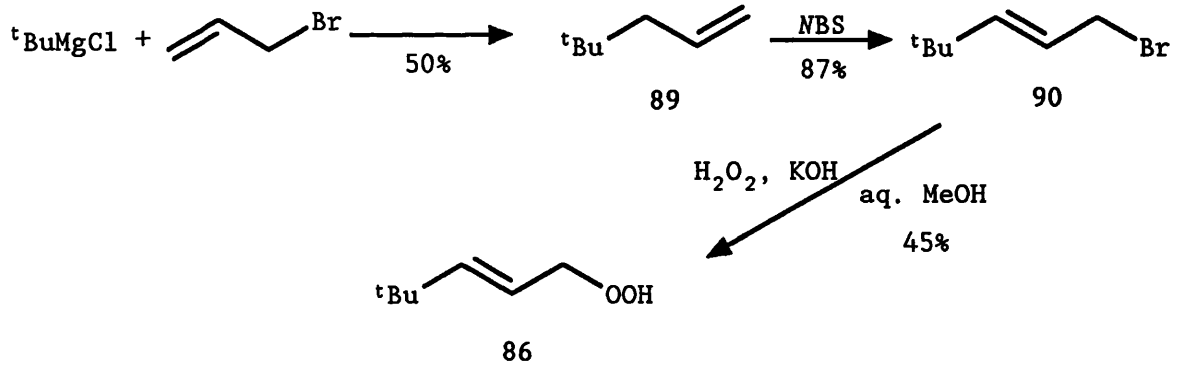
Having shown that cinnamyl hydroperoxide (**61**) fails to yield any 1,2,4-trioxanes on treatment with aldehydes and mercury(II) acetate, we needed to know whether other similarly substituted hydroperoxides would behave in the same way, or whether the electronic effects of the phenyl group were responsible for the behaviour of **61**.

To this end, both 3-isopropylallyl hydroperoxide (**85**) (Scheme 38) and 3-*tert*-butylallyl hydroperoxide (**86**) (Scheme 39) were synthesised. The hydroperoxides were made from the corresponding



87 88 85

Scheme 38

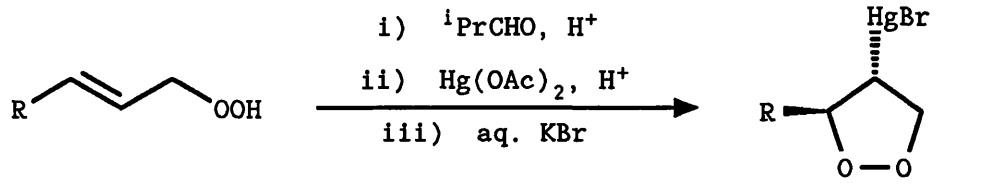


89 90 86

Scheme 39

bromides using the method described by Hoffman.[54] In both cases the hydroperoxides were formed as essentially single isomers; S_N2' attack of the hydroperoxide ion on the allylic bromide to form the secondary hydroperoxide is inhibited by the adjacent bulky alkyl group. Measurement of the coupling constants between the vinylic protons (**85** : J=15.49Hz; **86** : J=15.65Hz) confirmed that the double bond was *trans* in both compounds.

Treatment of **85** and **86** with isobutyraldehyde, then mercury(II) acetate, produced only a 1,2-dioxolane in both cases (Scheme 40). As



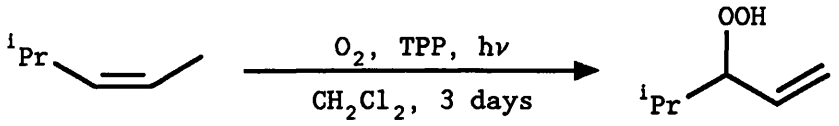
85 : R = ^{i}Pr
86 : R = ^{t}Bu

91 : R = ^{i}Pr (63%)
92 : R = ^{t}Bu (83%)

Scheme 40

with cinnamyl hydroperoxide, the yields were good (**91** : 63%; **92** : 83%), and only one isomer of each dioxolane was formed due to the presumed stereospecific *anti*-addition of mercury and the peroxide group across the *trans* double bond of the hydroperoxide.

To verify that the position of the substituent in the hydroperoxides is important, 1-isopropylallyl hydroperoxide (**93**), which by analogy with 1-phenylallyl hydroperoxide (**67**) ought to produce 1,2,4-trioxanes, was synthesised. Singlet oxygenation of *cis*-4-methyl-2-pentene (**94**) afforded the required hydroperoxide.[55] However, as a disubstituted alkene, **94** reacts only slowly with singlet oxygen, hence the long reaction time and poor yield (Scheme 41).

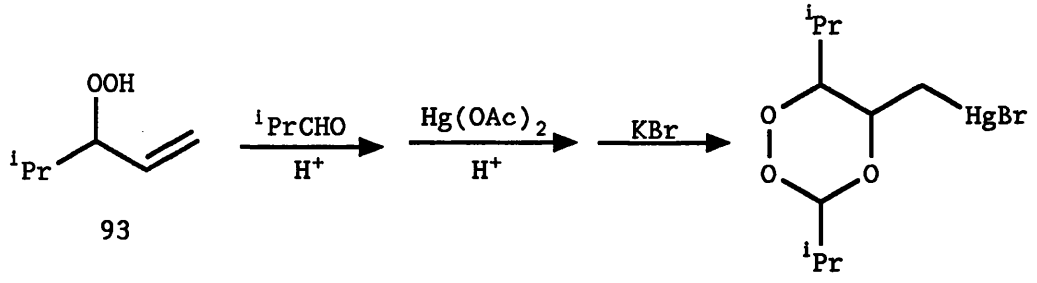


94

93 (10%)

Scheme 41

As expected, treatment of **93** with isobutyraldehyde and mercury(II) acetate afforded 1,2,4-trioxanes (**95**) (Scheme 42). In

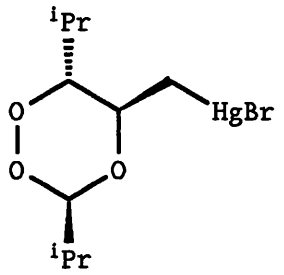


93

95

Scheme 42

contrast to the comparable reaction with 1-phenylallyl hydroperoxide (**67**), where essentially only one isomer of the 1,2,4-trioxane (**72e**) was formed, a mixture of apparently all four possible isomers was produced in an approximate ratio of 13:3:3:1. Column chromatography afforded two fractions (overall yield 44%). The first contained only the major isomer (**95e**; 16%) which was shown (see section 4.2.4) to have the same stereochemistry as the corresponding 6-phenyl compound (**72e**) *i.e.* with all three ring substituents equatorial. The second

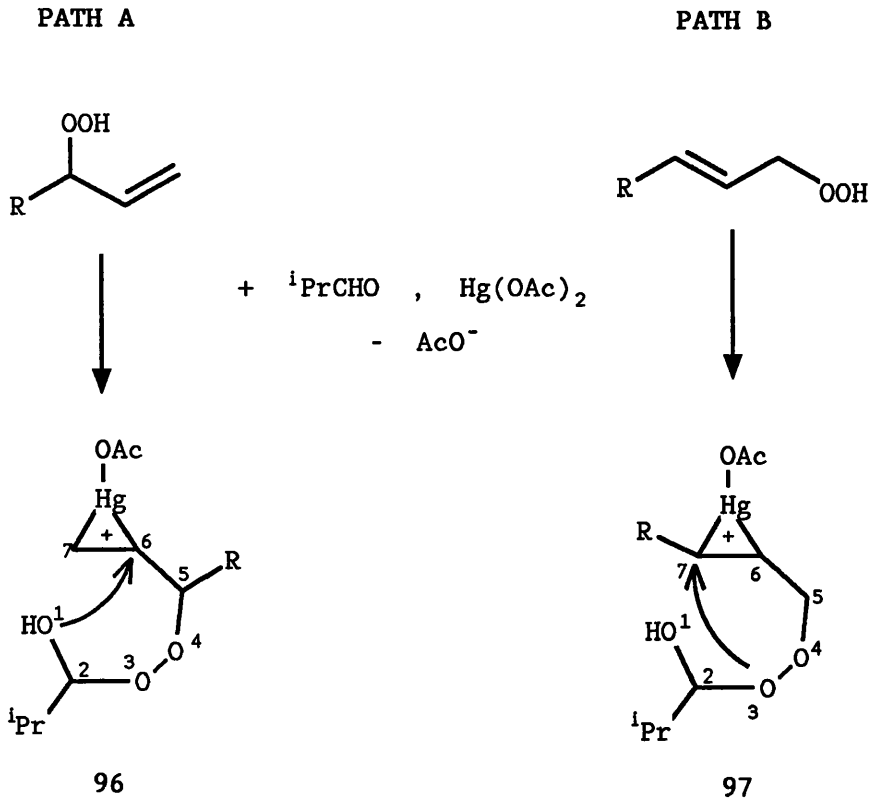


95e

fraction was a mixture of all four isomers, with **95e** as the major component. Elemental analysis confirmed that this mixture had the same elemental composition as that found for pure **95e**, and was consistent with the proposed structure. The stereochemistries of the minor isomers were not determined.

The question now arose as to why the two sets of hydroperoxides, the primary hydroperoxides (**61**, **85** and **86**) on one hand, and the secondary hydroperoxides (**67** and **93**) on the other, behaved differently. NMR studies confirmed that the degree of hemiperoxyacetal formation is comparable for **61** and **67** (both exist as *ca.* 75% hemiperoxyacetal and 25% hydroperoxide in a $CDCl_3$ solution with 1 eq. of isobutyraldehyde), so this cannot be the cause. Instead as a hypothesis, it was proposed that the nature of the substitution on the double bond affects the delocalisation of positive charge in the intermediate mercurinium ion, which then determines whether cyclisation to produce 1,2,4-trioxanes or 1,2-dioxolanes is favoured (Scheme 43).

In path A, the positive charge in the mercurinium ion (**96**) will be delocalised largely onto the secondary carbon atom (C-6) (ignoring delocalisation onto mercury). Of the three oxygen atoms present, O-4 is not in a position to compete effectively with O-1 and O-3 as an intramolecular nucleophile. Attack of O-3 on C-6 would result in a highly disfavoured 4-*exo* ring closure, whereas attack of O-1 results



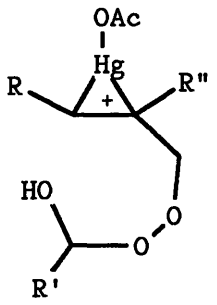
Scheme 43

in a favourable 6-*exo* cyclisation. Hence in path A, intramolecular attack of O-1 on the mercurinium ion is favoured to afford 1,2,4-trioxanes. The situation is different in path B. The greater symmetry of the mercurinium ion (**97**) will result in a more equal distribution of the positive charge between C-6 and C-7. In contrast to **96**, attack of O-3 on C-7 can now compete with attack of O-1 on C-6 (or C-7). Although this will result in a normally unfavourable 5-*endo* ring closure, the greater nucleophilicity of O-3 compared to O-1 (the "α-effect")[56] outweighs this factor, and 1,2-dioxolane formation is preferred.

It should be noted here that the observed competition between *exo* and *endo* ring closures of chloral hemiacetals (Scheme 21) reported by Overman and Campbell[32] is very different from that seen in our system. With the chloral hemiacetals it was a straightforward competition between attack of O-1 on either end of the mercurinium ion, whereas in our case the two products derive from attack of different oxygen atoms on the ion. The argument they put forward to explain the unusual preference for an *endo* cyclisation (proposing that the hemiacetal hydroxyl group is co-ordinated to mercury) is

therefore not relevant.

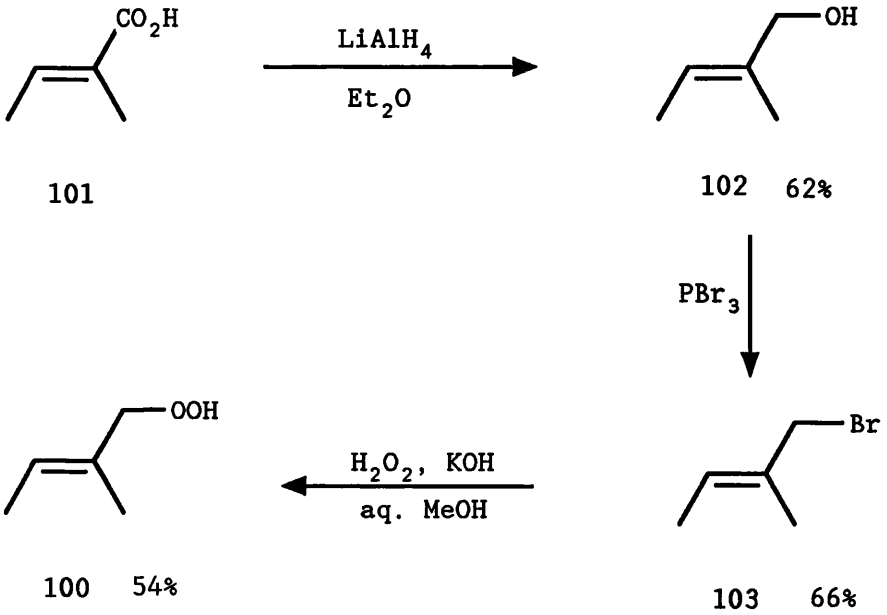
If our theory is correct, it would imply that in general 1,2,4-trioxane formation is preferred if the positive charge in the intermediate mercurinium ion is delocalised mainly onto C-6. If we just consider simple alkyl groups as the substituents, this would mean that 1,2,4-trioxane formation would be preferred if there was greater substitution on C-6 than on C-7. Thus, taking **97** and adding an extra group to C-6, giving the mercurinium ion **98**, ought to once again result in 1,2,4-trioxane formation.



98

99 : R = R" = Me R' = ^{i}Pr

To test this, (*E*)-2-methyl-2-buten-1-yl hydroperoxide (**100**) was synthesised from tiglic acid (**101**) using the route shown in Scheme 44. Judging from the ^{1}H and ^{13}C nmr spectra of **100**, the product

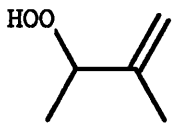


101 **102** 62%

100 54% **103** 66%

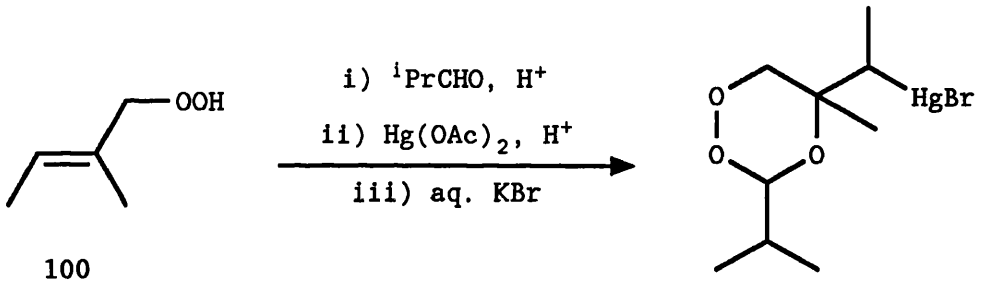
Scheme 44

appeared to be contaminated with a small amount of the isomeric 2-methyl-1-buten-3-yl hydroperoxide (**104**), which could be formed by S_N2' attack of hydroperoxide ion on **103**, *via* a rearrangement in the bromination step, or by the allylic rearrangement of **100** itself.



104

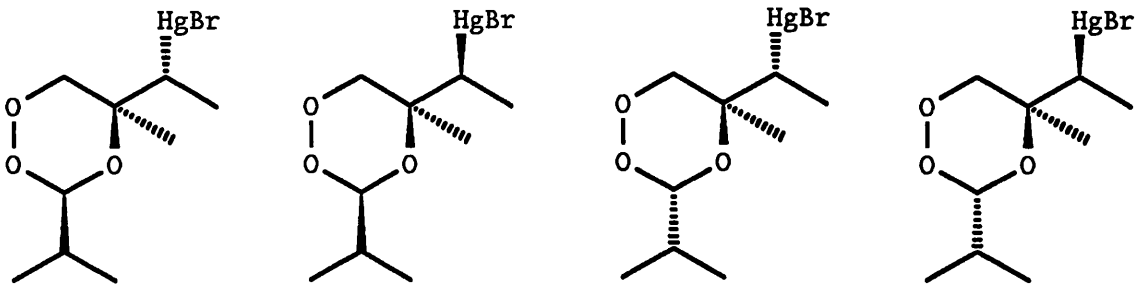
Hydroperoxide **100** could now be treated with isobutyraldehyde followed by mercury(II) acetate using the standard procedure. As was predicted, a good yield of 1,2,4-trioxanes (**105**) was recovered (Scheme 45).



100 105 59%

Scheme 45

As **105** contains three chiral centres, four diastereomers are possible : **105c**, **105c***, **105t** and **105t***. However, as the

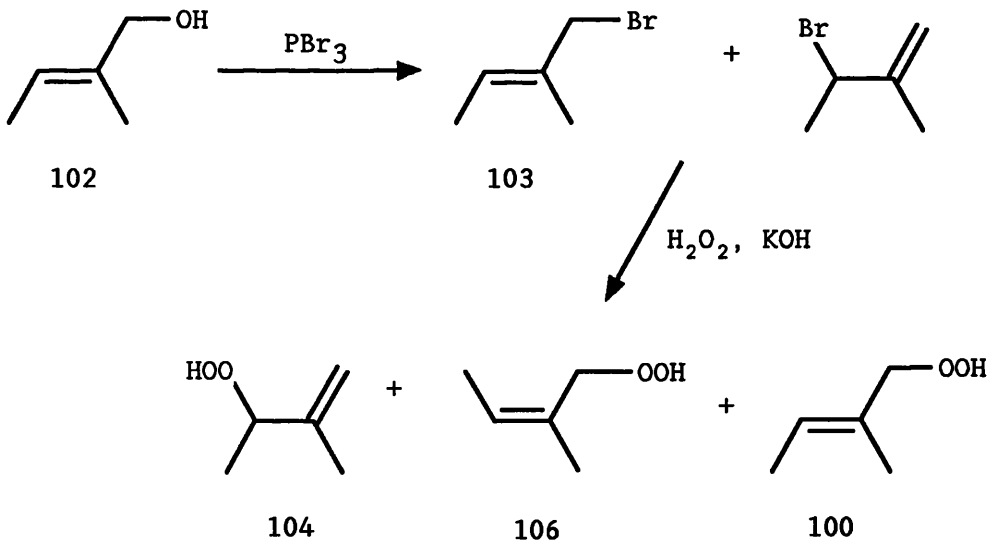


105c 105c* 105t 105t*

oxymercuration step is a stereospecific *anti*-addition to the double bond, then the stereochemistry at the carbon attached to mercury should be fixed relative to the stereochemistry at C-5, *i.e.* **105c***

and **105t*** should not be formed. Nevertheless the ^{1}H and ^{13}C nmr spectra confirm the presence of all four isomers, albeit the signals due to **105t*** are very weak and difficult to pick out. From the ^{1}H nmr spectrum of the crude material, the ratio **105c : 105t : 105c*** = 9 : 2 : 1 (the assignment of stereochemistries is discussed in section 4.2.4). Column chromatography allowed the isolation of pure **105t** and a mixture containing only **105c** and **105c***.

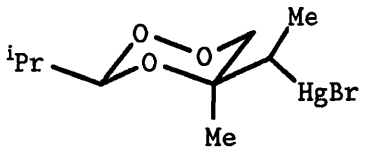
The formation of **105c*** and **105t*** from **100** would require a non-stereospecific oxymercuration step. Although examples of *cis* methoxymercuration and acetoxymercuration appear in the literature,[57] for which an explanation involving the collapse of a solvated mercurinium ion has been put forward,[58] such observations have only been made with strained alkenes (*e.g.* norbornene) and there is no evidence that *syn*-addition occurs in the cyclooxymercuration of simple acyclic species. A more likely explanation is the contamination of **100** with its double bond isomer (**106**). This could arise by S_N2' reactions occurring in both the bromination and perhydrolysis steps of Scheme 44, as outlined in Scheme 46, or by the



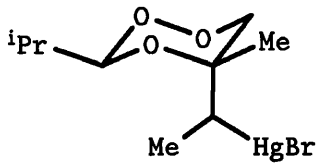
Scheme 46

rearrangement of **104**, which could be expected to afford both **100** and **106**. Although the presence of **106** is not obvious in the ^{1}H and ^{13}C nmr spectra of **100**, the very close similarity of the two compounds will result in them having very similar spectra, hence the presence of **106** cannot be ruled out.

As would be expected, the major isomer (**105c**) is that in which the two bulky groups (^{i}Pr and CH[Me]HgBr) are *cis* diequatorial (Fig. 2). The next most abundant isomer (**105t**) is that in which the two



105c



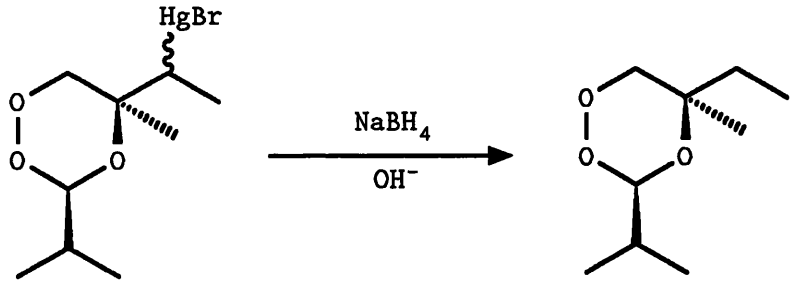
105t

Figure 2

groups on C-5 are transposed. The structures of **105c*** and **105t*** are similar to **105c** and **105t** respectively, but with the alternative stereochemistry at the exocyclic chiral centre.

The lower stereoselectivity observed at C-5 in this system compared with that seen for the formation of **72** can be attributed to the greater difference in steric bulk between a proton and a CH_2HgBr group than between a methyl and a CH(Me)HgBr group.

Hydridodemercuration of a sample of **105c** containing a small amount (*ca.* 10mol%) of **105c***, gives a single diastereomer of the mercury-free 1,2,4-trioxane (**107**) (Scheme 47). This confirms the relationship of **105c*** to **105c**.

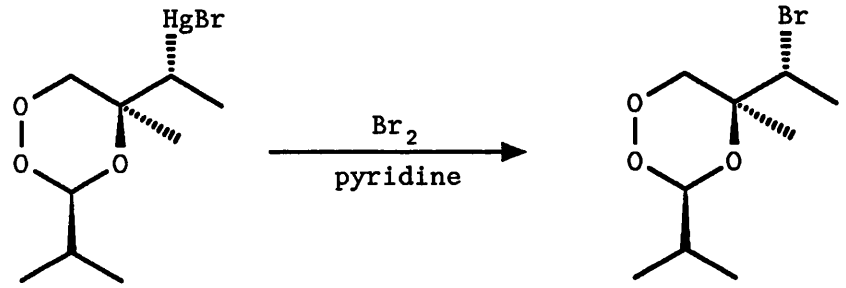


105c : 105c*
9 : 1

107

Scheme 47

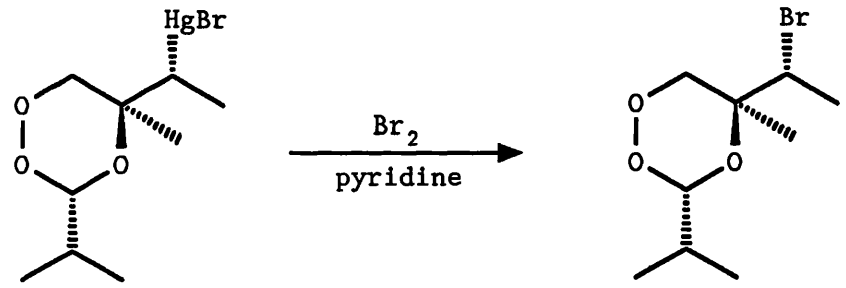
Unfortunately, on reduction one of the stereocentres is lost. However, treatment of **105c** with bromine in pyridine[37] results in bromodemercuration occurring with (by ^{1}H nmr of the crude material) almost complete retention of stereochemistry at the exocyclic chiral centre to give the corresponding bromo compound (**108**) (Scheme 48). Contamination of **105c** with **105c*** does make any evaluation of the



105c 108

Scheme 48

degree of stereospecificity somewhat unreliable, so as verification a sample of pure **105t** was treated under identical conditions to give **109** (Scheme 49). Column chromatography afforded only one fraction containing a bromo trioxane, which was around 95% isomerically pure by ^{1}H nmr.



105t 109

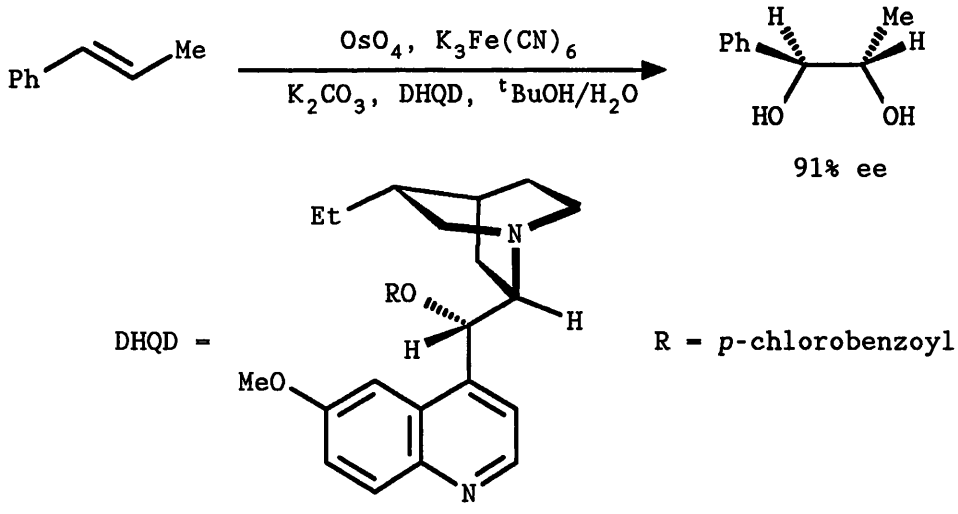
Scheme 49

Introduction of the bromo group into the trioxane skeleton theoretically allows further elaboration of these compounds. It must be borne in mind however, that many of the reactions of alkyl bromides are incompatible with the presence of the 1,2,4-trioxane ring. Thus, conversion into a Grignard reagent would result in the reduction of the peroxide linkage,[20] and treatment with base causes abstraction of H-3 in 3-monosubstituted 1,2,4-trioxanes.[5]

4.2.3 1,2,4-Trioxane Synthesis Using α-Amino Aldehydes

Having observed high diastereoselectivity for the formation of trioxane **72**, we wondered whether this selectivity could also be useful in the synthesis of other, non-trioxane, compounds. In particular, reduction with zinc in acetic acid[4] would provide a diastereoselective synthesis of 1,2-diols. Bearing in mind the ready availability of diastereomerically pure 1,2-diols by the treatment of an alkene with *m*-chloroperoxybenzoic acid / aqueous acid or potassium permanganate, this does not at first appear to be a particularly attractive proposition. However, if the 1,2,4-trioxanes could also be made optically pure, we would then have a route to optically pure 1,2-diols. Additionally of course, the asymmetric synthesis of 1,2,4-trioxanes would be of great interest from the point of view of their biological activity.

Several examples appear in the literature of the formation of enantiomerically pure 1,2-diols either by asymmetric synthesis[59-69] or by the resolution of the racemic diol.[70-73] The most useful of these is the asymmetric dihydroxylation (ADH) of an alkene using osmium tetroxide and a chiral ligand, often a quinine or quinidine derivative. An example is shown in Scheme 50.[59] The two main



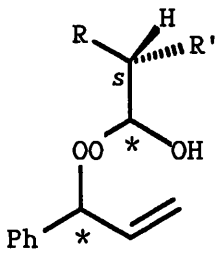
Scheme 50

problems with this are the use of the highly toxic osmium tetroxide (although only catalytic quantities are necessary), and the poor selectivity observed with some alkenes.[74]

The synthesis of 1,2,4-trioxanes from hemiperoxyacetals (Scheme 29) has three points at which chirality can be introduced. Firstly, the use of an optically pure hydroperoxide would give a single trioxane, and on reduction a diol, of high optical purity. The problem with this is the difficulty in the synthesis of optically pure allylic hydroperoxides. Even at low temperature, the reaction of optically pure allylic mesylates[75] or phosphites[76] with hydrogen peroxide proceeds with very poor stereospecificity. The only truly asymmetric synthesis involves the enzyme catalysed oxygenation of unsaturated fatty acids.[77] This is very limited in the range of substrates available, although protection of the hydroperoxy group as a perketal allows further elaboration of the carbon skeleton.[78] The resolution of racemic hydroperoxides by their conversion to diastereomeric perketals has been demonstrated,[79] but the need to separate isomers by HPLC severely limits the scale on which the hydroperoxides can be prepared.

The other two possibilities both involve using an exocyclic chiral centre to induce asymmetry in the ring. This could be done either by using a chiral aldehyde[80] (induction at C-3) or a chiral mercury salt (induction at C-5). The problem here is that unless you obtain complete induction, the trioxanes will be formed as a mixture of diastereomers. The individual, optically pure, isomers would then have to be separated, which may prove difficult. However, it was decided to try this approach using chiral aldehydes; the possibility of obtaining asymmetric induction on cyclisation by using an optically active mercury salt seemed the less likely of the two possibilities. This follows earlier reports on the use of chiral mercury salts to promote asymmetric oxymercuration of alkenes.[81] Although mercury(II) tartrate afforded alcohols in up to 32% enantiomeric excess (ee), the ee's obtained with other salts was generally less than 10%.

As the starting hydroperoxide (**67**) is racemic, treatment with say an (*S*)-aldehyde would give a mixture of four diastereomeric hemiperoxyacetals (**110**; Fig. 3). If we assume that upon cyclisation all three ring substituents will adopt equatorial positions (*i.e.* the stereochemistry around the ring is either 3*R*,5*S*,6*R* or 3*S*,5*R*,6*S*), then only the *SRS* and *RSS* isomers of the hemiperoxyacetal will cyclise (**N.B.** on cyclisation the assignment of the stereocentre



110

Four diastereomers : *RRS*

RSS

SRS

SSS

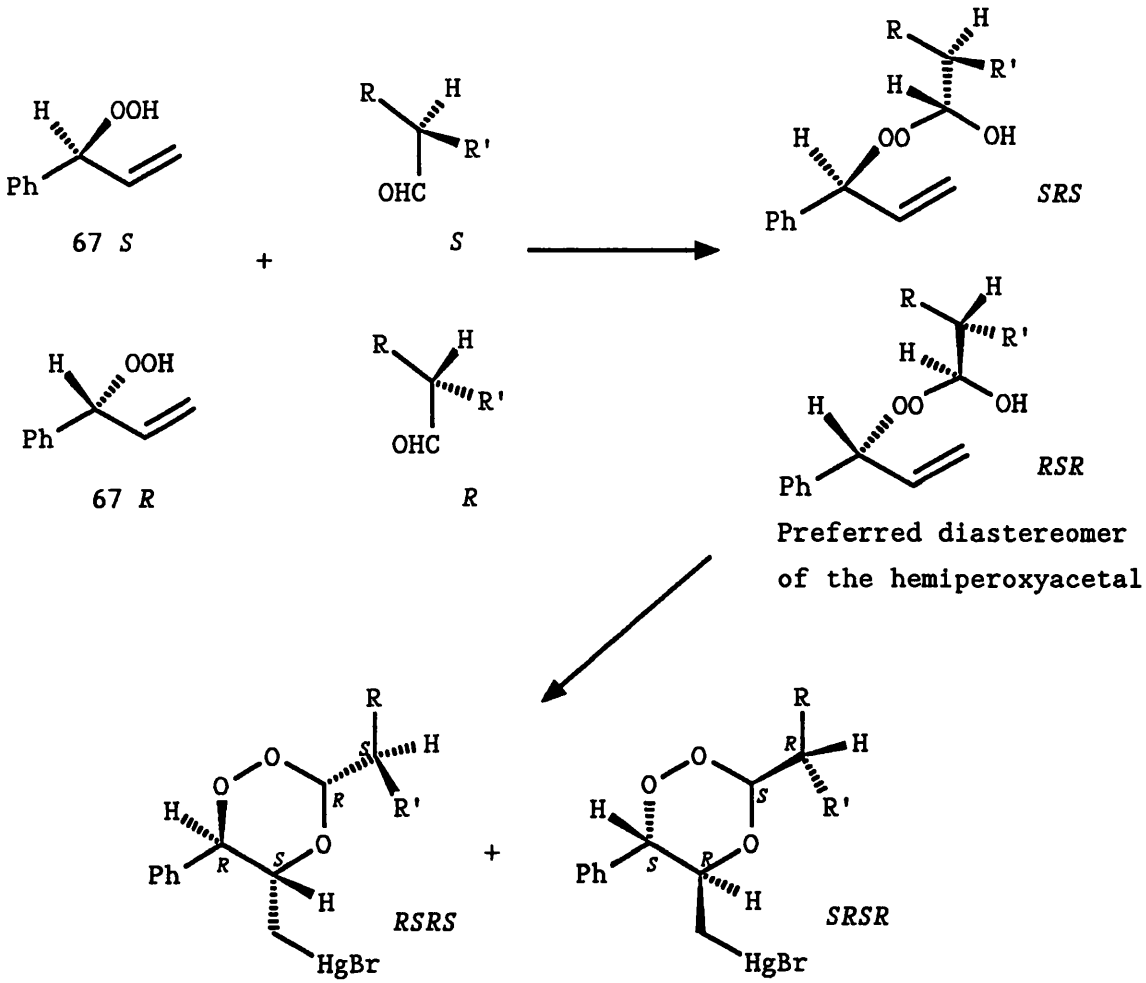
Labelling order : peroxide, hemiperoxyacetal, aldehyde.

N.B. Peroxide and hemiperoxyacetal centres become 6 and 3 respectively upon cyclisation to 1,2,4-trioxanes

Figure 3

derived from the hydroperoxide changes because the vinyl group is transformed into a substituent of higher priority than phenyl *i.e.* the (6*R*)-trioxane is derived from the (*S*)-hydroperoxide, and the (6*S*)-trioxane comes from the (*R*)-hydroperoxide). If, due to the influence of the chiral centre in the aldehyde, there is a preference for the formation of one of these isomers, then by limiting the extent to which the reaction takes place (*e.g.* by using only 0.5 eq. of the aldehyde) we should observe upon cyclisation a predominance of the trioxane derived from this isomer, *i.e.* we would achieve a kinetic resolution of the hemiperoxyacetal of the starting hydroperoxide. Upon hydridodemercuration and zinc/acetic acid reduction, the mixture of diastereomeric trioxanes would give a mixture of both enantiomers of a single diastereomer of the 1,2-diol. Therefore, the greater the diastereomeric purity of the 1,2,4-trioxane, the greater will be the enantiomeric purity of the resultant diol. To test for any preference in the formation of the hemiperoxyacetals, the easiest way is to treat the racemic hydroperoxide with racemic aldehyde thus forming both enantiomers of the preferred diastereomer (Scheme 51).

As has already been discussed, 2-methylbutyraldehyde, which possesses a chiral centre, has been treated with 1-phenylallyl hydroperoxide (**67**) and mercury(II) acetate to give the 1,2,4-trioxanes **73e** and **73a**. Although there was a very strong preference for the stereochemistry around the ring (**73a** was virtually



Preferred diastereomer of the 1,2,4-trioxane, assuming a strong preference for equatorial substituents at C-3, C-5 and C-6. The indicated preference for the stereochemistry at the exocyclic chiral centre is purely arbitrary.

Scheme 51

absent), no stereoselectivity was observed for the exocyclic chiral centre. Additionally, the two epimers proved impossible to separate by HPLC. Therefore, we would not expect to see any asymmetric induction into the ring using pure (*S*)-2-methylbutyraldehyde, and we would not be able to separate the two resulting diastereomers. An alternative chiral aldehyde was therefore sought.

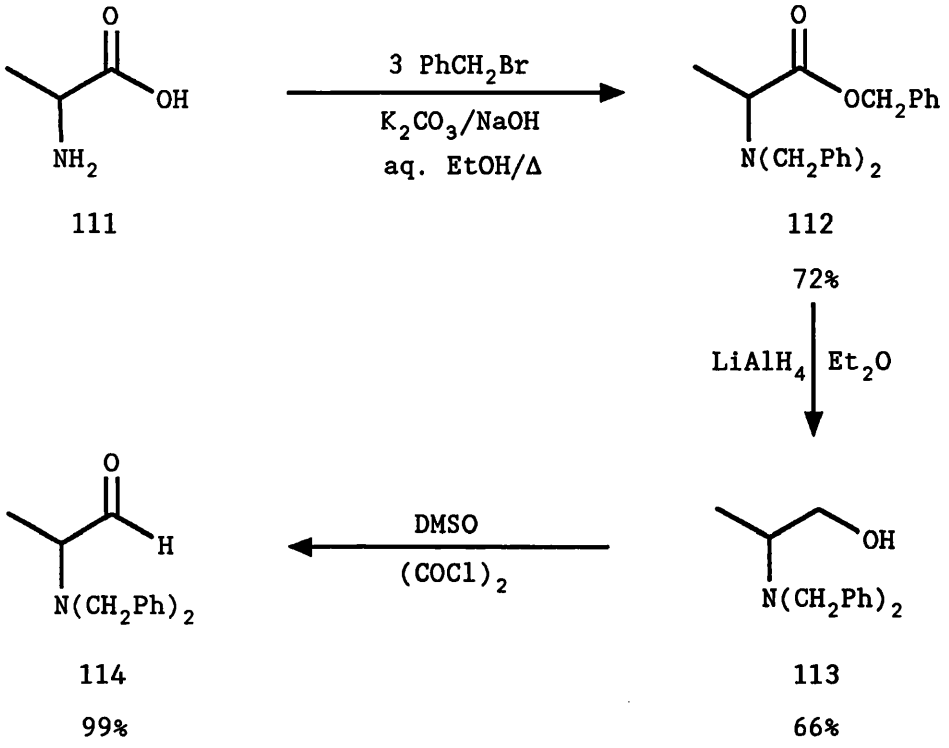
We required an aldehyde which would be readily available in an optically pure form, and possessed some structural feature which would aid asymmetric induction, *i.e.* a feature which would result in

there being a strong preference for the stereochemistry at the hemiperoxyacetal carbon relative to the chiral centre in the aldehyde. As the hemiperoxyacetal carbon has an O-H group attached, it was thought that selectivity could be increased by using an aldehyde containing a heteroatom to enable intramolecular hydrogen bonding to occur. If the heteroatom was nitrogen, then we would require α-amino aldehydes,[82] which are readily available in both racemic and optically pure forms from α-amino acids. This would have three additional advantages : i) the wide range of available α-amino acids would allow us to vary the substituents in the aldehyde, ii) both (*R*) and (*S*) forms are readily available and iii) the trioxanes themselves would be of great interest in terms of their biological activity, irrespective of whether the reaction proved to be a successful route to 1,2-diols.

We decided to start with the simplest chiral amino acid, namely α-alanine. A protecting group was required for the amine function, to prevent the formation of imines on the introduction of the aldehyde group. It has been reported in the literature that *N,N*-dibenzyl α-amino aldehydes are readily synthesised, and are optically stable[83] (remembering however, that to begin with we require only the racemic aldehyde). This, then, was our starting point.

The treatment of DL-α-alanine (**111**) with benzyl bromide and base[83,84] gave the *N,N*-dibenzyl benzyl ester (**112**). Reduction with lithium aluminium hydride[85] produced the alcohol (**113**), which was oxidised to the required aldehyde (**114**) using activated DMSO[86] (Scheme 52).

On substituting aldehyde **114** into our standard procedure with 1-phenylallyl hydroperoxide (**67**), no 1,2,4-trioxanes were formed. In fact it appeared as if a reaction other than the required hemiperoxyacetal formation occurred on mixing the aldehyde and hydroperoxide. This was confirmed by stirring the two components with a drop of trifluoroacetic acid in dichloromethane. Complete reaction occurred in *ca.* 2 hours. Two products could be isolated from the mixture, one of which was 1-phenylallyl alcohol (**115**; 80%). Obviously a redox reaction was occurring, but the identity of the second component was unclear. The ^{1}H and ^{13}C nmr spectra showed the presence of two benzyl groups, plus peaks at δ 8.40(s, 1H) ppm in the

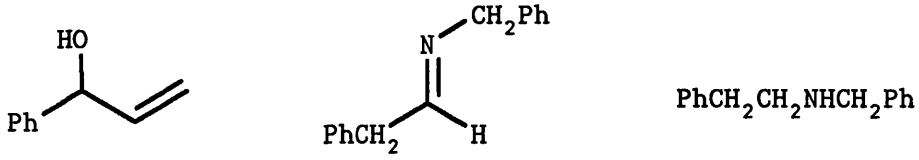


111 112 113 114

99% 66%

Scheme 52

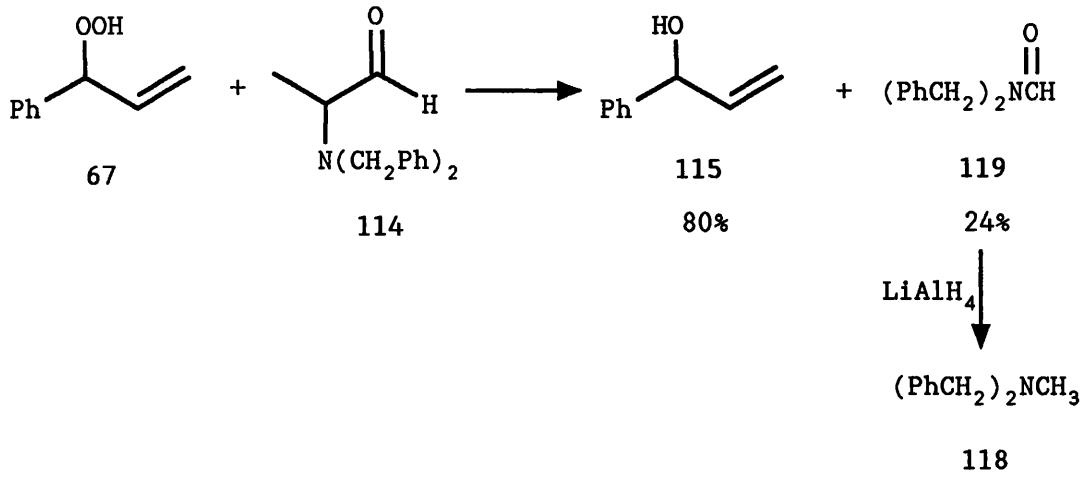
^{1}H nmr spectrum and δ 162.79 ppm in the ^{13}C nmr spectrum. It was thought that *N*-(2-phenylethylidene)benzylamine (**116**) would fit the spectral data. To check, the compound was reduced with lithium



115 116 117

aluminium hydride.[87] However, comparison with literature spectra showed that the product was not *N*-benzyl-2-phenethylamine[88] (**117**) as expected, but was in fact (*N*-methyl)dibenzylamine[89] (**118**). This amine could be formed by reduction of *N*,*N*-dibenzylformamide (**119**), and comparison with literature spectra[90] confirmed that **119** was in fact our unknown (Scheme 53).

To account for these products, we ruled out the possibility of the known reaction between amines and hydroperoxides to form *N*-oxides occurring,[91] as there seemed no reasonable way in which **119** could be formed from the intermediate *N*-oxide. However, peroxides are known to undergo electron transfer reactions with electron rich

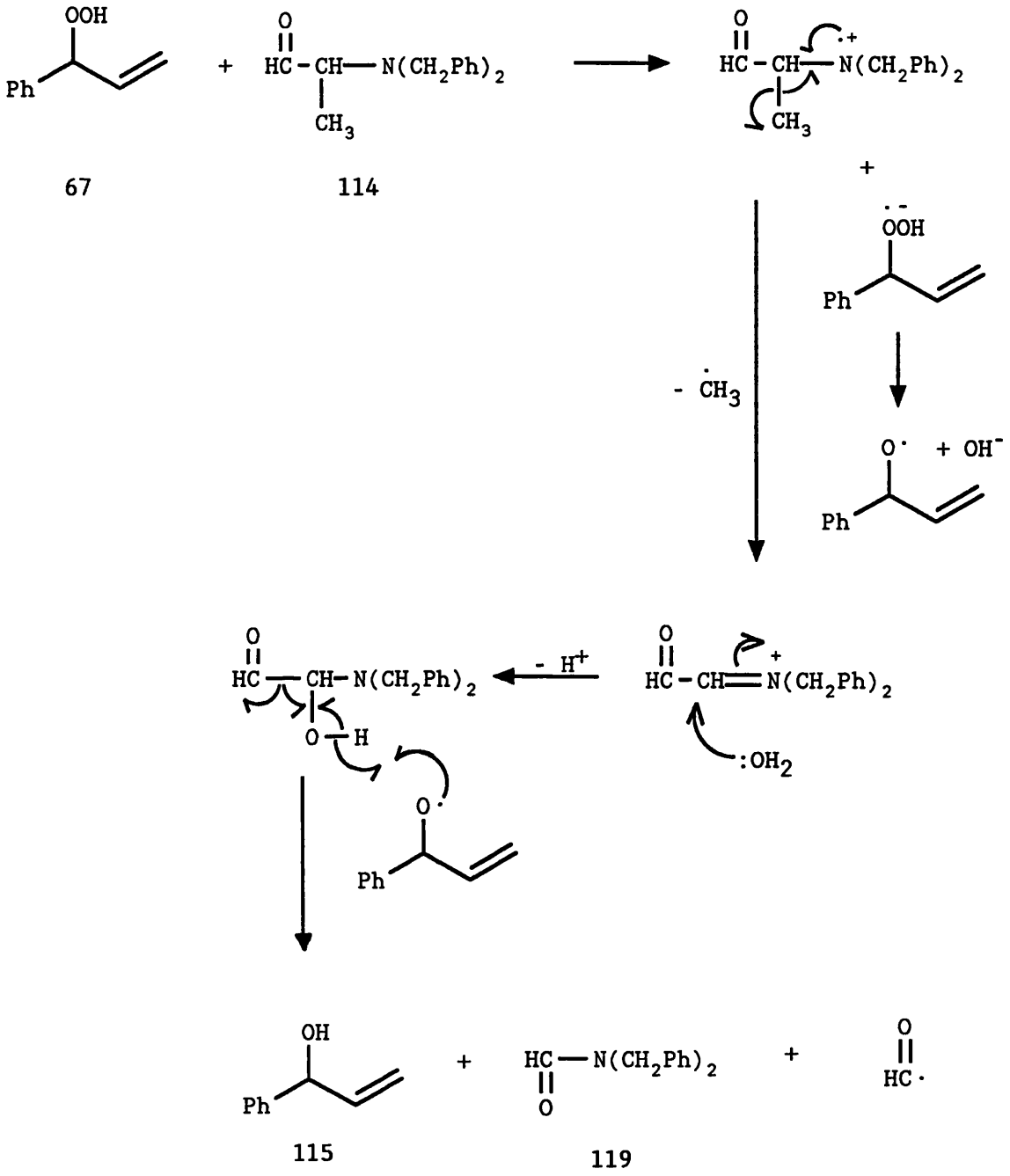


Scheme 53

species[20,92] (which the tertiary amine will be), and a possible mechanism could be formulated to account for the formation of **115** and **119** in which an electron transfer from the amine to the hydroperoxide is the first step (Scheme 54). The formamide was also the main product from the reaction of **114** with *tert*-butyl hydroperoxide. As the *N,N*-dibenzyl aldehyde was obviously not going to give any trioxanes, this system was not investigated further.

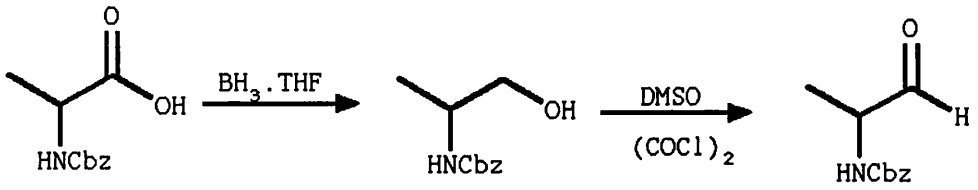
What we required was a more electron withdrawing protecting group on the nitrogen, the one chosen being carbobenzyloxy (Cbz; $PhCH_2OC[O]$). Commercially available *N*-Cbz-DL-α-alanine (**120**) was reduced to the corresponding alcohol (**121**) in high yield with borane-tetrahydrofuran complex.[93] Oxidation of **121** was a little problematical, but treatment with activated DMSO[86] gave *N*-Cbz-DL-α-alaninal (**122**) in moderate yield (Scheme 55).

This time, on treatment of a mixture of **122** and 1-phenylallyl hydroperoxide (**67**) with mercury(II) acetate, 1,2,4-trioxane formation was observed. The nmr spectra of the crude material showed essentially three isomers (**123**), which were isolated as a mixture in 24% yield by column chromatography (Scheme 56). The formation of three isomers in the mixture was a little disappointing, as this implies that we are no longer getting the high stereoselectivity we had hoped for around the ring. Some form of complexation between the mercury salt and the carbamate group may account for this. However, in contrast to the result with 2-methylbutyraldehyde, a preferred stereochemistry (**123e**) was observed (**123e** : **123e*** : **123a** = 6 : 3 : 2), and the three isomers were separable by HPLC. Nmr studies (see



Scheme 54

section 4.2.4) showed that **123e** and **123e*** both had all three ring substituents in equatorial positions, and differed only in the stereochemistry at the exocyclic chiral centre. On the other hand, **123a** had the aminoalkyl group on C-3 in an axial position. The stereochemistries at the exocyclic chiral centre could not be determined. Presumably a fourth isomer was formed (**123a***) which is related to **123a** in the same way that **123e*** is related to **123e**, but in too small an amount to be detected.

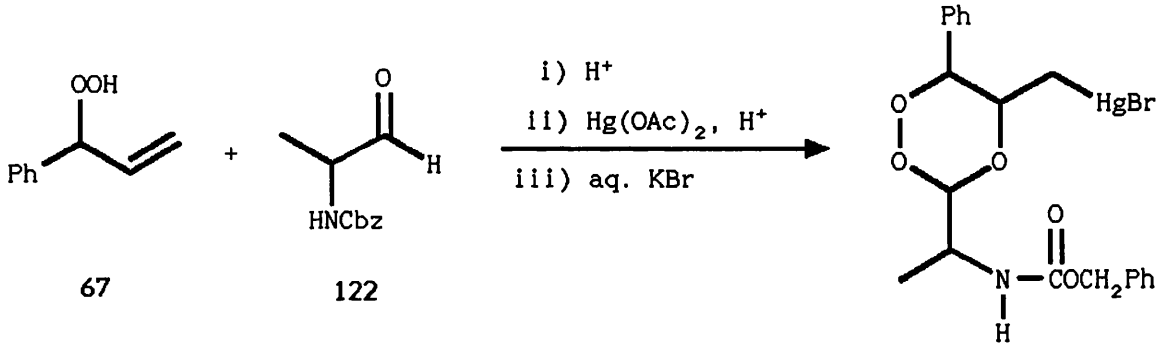


120 121 122

85% 53%

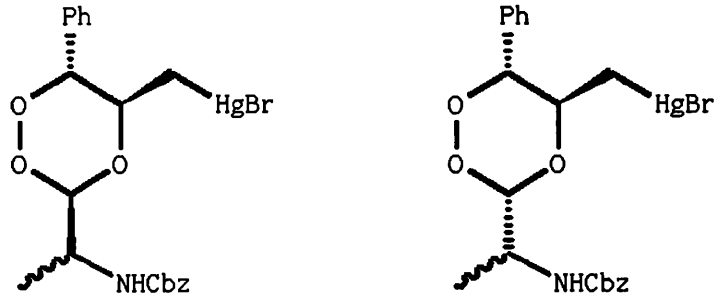
Cbz = $COCH_2Ph$

Scheme 55



67 122 123

24%



123e (major) 123a

123e* (minor)

Scheme 56

Unfortunately, the quantities of the 1,2,4-trioxanes formed were too small to allow any further chemistry to be carried out on them.

From these results we can see that by using optically active

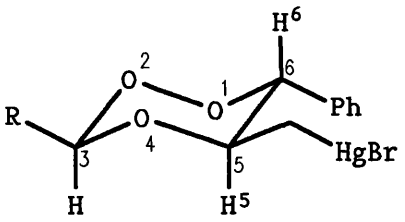
N-Cbz-alaninal we ought to be able to achieve a kinetic resolution of the two enantiomers of **67** to give a mixture of optically active 1,2,4-trioxanes enriched in one diastereomer. However, the asymmetric induction into the ring is likely to be low, so reduction without separation of the isomers would give optically active 1,2-diols with poor ee. Considering the routes already available to optically pure 1,2-diols, it would appear that the usefulness of this system is very limited, although the trioxanes themselves still remain very interesting from a biological point of view. Further investigation, with different amino acids and different protecting groups, could still prove very productive.

4.2.4 NMR Studies and the Determination of the Stereochemistries of the 1,2,4-Trioxanes

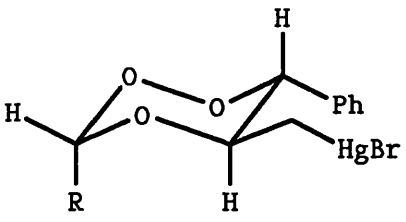
One of the most important aspects of the preceding work was the assignment of the stereochemistries of the 1,2,4-trioxanes. This was done largely through ^{1}H and ^{13}C nmr studies.

4.2.4.1 Stereochemistry at C-5 and C-6 ($^{3}J_{HH}$ Values)

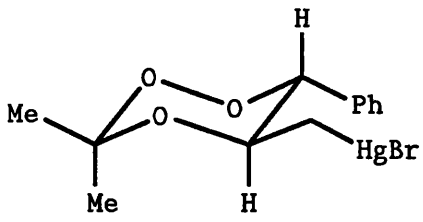
Let us look first at the stereochemistry at C-5 and C-6 of trioxanes **71-75, 95e** and **123** (Fig. 4). The main piece of evidence



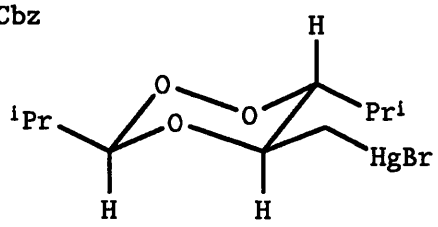
71e : R = Me
72e : R = ^{i}Pr
73e : R = ^{s}Bu
74e : R = CCl_3
123e : R = $CH(CH_3)NHCbz$



71a : R = Me
123a : R = $CH(CH_3)NHCbz$



75



95e

Figure 4

here was the coupling constant between H^5 and H^6. The signals due to these two protons are easy to identify, as H^5 appears as a multiplet in the region δ 4.2-4.6 (δ 4.07 in **95e**) and H^6 appears as a doublet in the region δ 4.75-5.00 (δ 3.76[dd] in **95e**). The coupling constant was readily measured from the peak due to H^6 and was found to be consistently in the range 8.7 - 9.5 Hz (Table 1). Such a large value is typical for the coupling between two axial protons in a 6-membered ring with a chair conformation. This is in agreement with the Karplus equation,[94] which states that the coupling constant between vicinal protons is at a maximum when the dihedral angle between the two protons is around 180°. That the values observed for **76a** (derived from **71a** - see below) and **123a** are lower than the others is

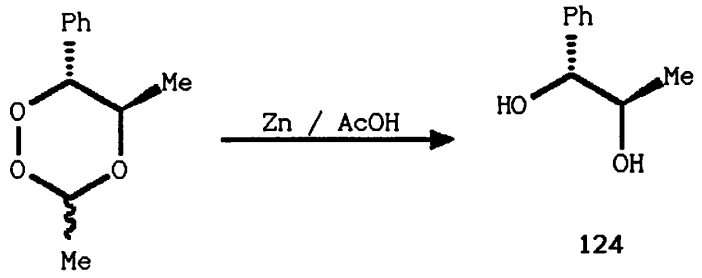
COMPOUND	$^3J(H^5\text{-}H^6)$ / Hz
71e (76e)	8.92 (9.05)
71a (76a)	n.d. (7.36)
72e (77e)	8.98 (8.98)
73e (78e)	8.98 (9.05)
74e (79e)	9.20 (9.30)
75 (80)	9.49 (9.55)
95e	8.88
123e	9.08
123e*	8.99
123a	8.71

Table 1. Values of $J(H^5\text{-}H^6)$ for some mercurated 1,2,4-trioxanes. The values in brackets are the corresponding coupling constants in the mercury-free compounds. n.d. = not determinable.

probably due to steric interactions from the axial C-3 group distorting the ring, thus altering the dihedral angle between H^5 and H^6.

The synthesis of trioxanes **76-80** by hydridodemercuration of **71-75** should not affect the stereochemistry at C-5 and C-6, and this is confirmed by the similarly large values of $^3J(H^5\text{-}H^6)$, which are also shown in Table 1.

Further confirmation for the stereochemistries of **76e** and **76a** were obtained by the reduction of a 5:1 (**76e:76a**) mixture of the two compounds with zinc and acetic acid[4] (Scheme 57). Only one isomer of the diol (**124**) was obtained, proving that **76e** and **76a** (and hence **71e** and **71a**) differed only in the stereochemistry at C-3. Comparison of the physical data of the product with literature values for *erythro*- and *threo*-1-phenylpropan-1,2-diol[95] (Table 2) showed unequivocally that **124** was the *threo* isomer. As the reduction is known to occur stereospecifically, then the phenyl and C-5 methyl groups in **76e** and **76a** must be *trans*.



76 124

Scheme 57

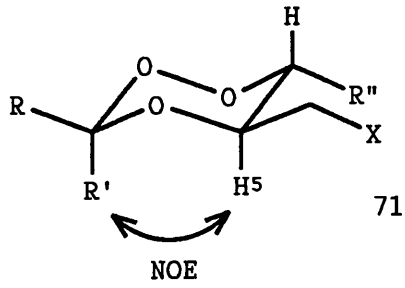
COMPOUND	m.p. / °C	δ H^1 / ppm	$^3J(H^1-H^2)$/Hz
124	47 - 51	4.34	7.45
erythro-1-phenylpropan-1,2-diol	89 - 91	4.62	4
threo-1-phenylpropan-1,2-diol	51 - 53	4.29	7.5

Table 2. Values for 1-phenylpropan-1,2-diol are obtained from ref. 95.

4.2.4.2 Stereochemistry at C-3 (NOE)

To determine the stereochemistry at C-3, nuclear Overhauser effect (NOE) measurements were made.[96] The principle of NOE is that two protons which are close in space will interact, such that saturation of the signal due to one proton will cause a more rapid relaxation of the other proton resulting in an increased signal strength for the second proton. For the compounds we are interested in, we know that H^5 is axial, and therefore any proton on C-3 exhibiting an NOE to H^5 must also be axial, or part of an axial group (Fig. 5). The results of the NOE experiments are summarised in Table 3.

The results show that in all cases, the major isomer formed in the reaction (**71e, 72e, 95e, 123e**) must have an axial proton at H^3, *i.e.* the alkyl group on C-3 is in an equatorial position. The result for **71a** confirms that **71a** differs from **71e** in having an axial methyl group on C-3. Although no NOE measurements were made on **72e** and **73e**, it can be safely presumed that the bulky groups on C-3 (*sec*-butyl and trichloromethyl respectively) lie in an equatorial position by



71a : R=H^3, R'=Me

71e, 72e, 76e, 95e, 123e, 123e* : R'=H^3

Figure 5

COMPOUND	H^i	H°	% Enhancement of H°
71e	H^3	H^5	7.5
71a	Me	H^5	4
72e	H^3	H^5	4
76e	H^5	H^3	4[a]
95e	H^3	H^5	5 (Fig. 6)
123e	H^5	H^3	7 (Fig. 7)
123e*	H^5	H^3	6

H^i = Proton irradiated

H° = Proton observed

[a]No NOE was observed at the C-3 methyl group.

Table 3. NOE measurements for some 1,2,4-trioxanes. For structures see Figs. 4 & 5.

analogy with **72e**. The absence of an NOE between the equatorial C-3 methyl group and H^5 in **76e** confirms that such an effect is only observable between 1,3-diaxial groups.

The NOE results also show that the two major isomers of **123** both have equatorial alkyl groups, and must therefore differ in the stereochemistry of the exocyclic chiral centre. The minor isomer (**123a**) must have an axial substituent at C-3, but unfortunately all the signals of interest in the ^1H nmr spectrum lie almost on top of each other, precluding any NOE measurements.

The 1,2,4-trioxanes derived from the reaction of

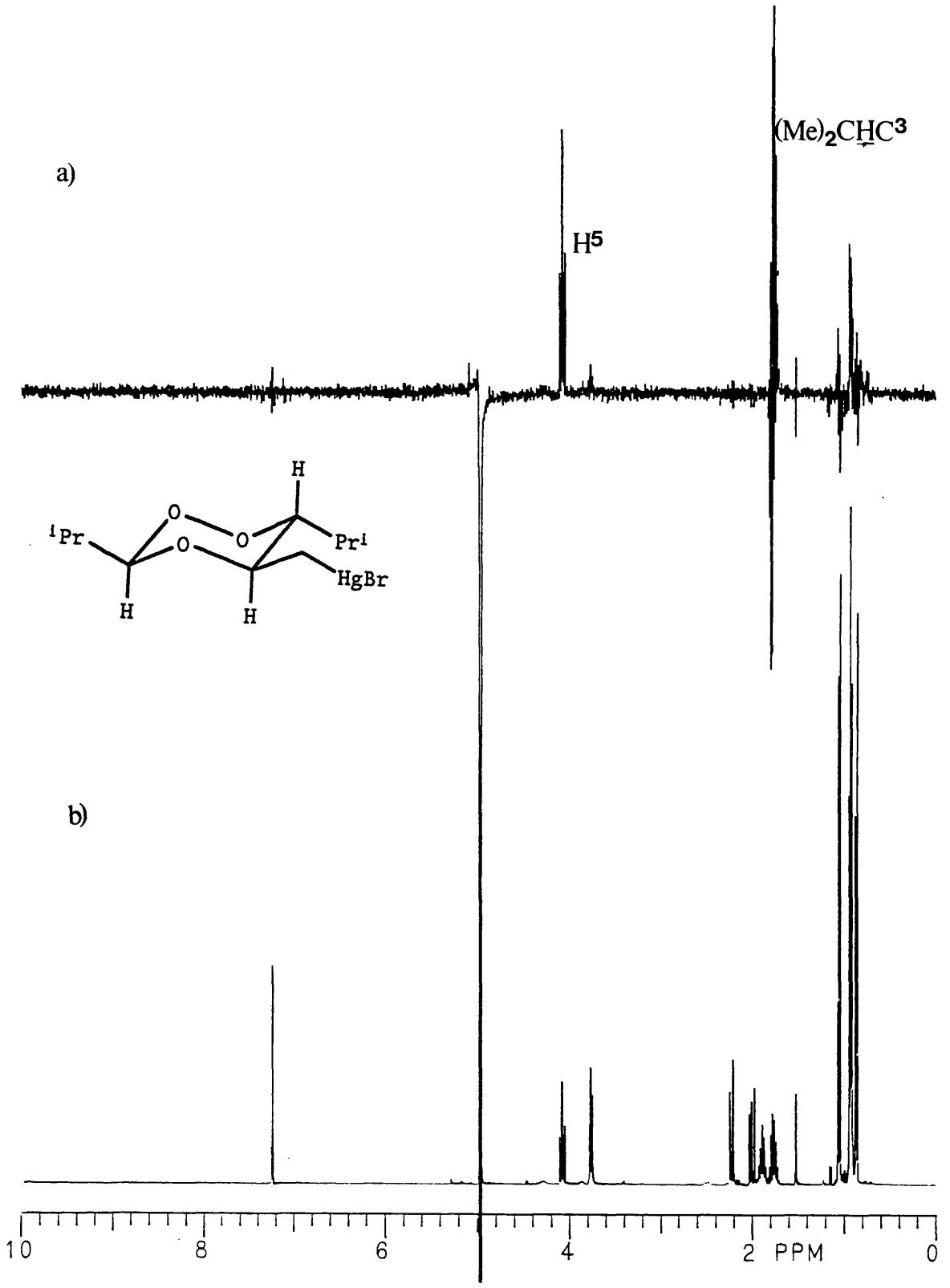


Figure 6. NOE measurements on **95e**. Spectrum a) is derived by subtracting the normal spectrum from the spectrum obtained on saturation of C(3)-H. Any protons close in space to C(3)-H appear as positive signals. The large negative signal is the irradiated proton. Spectrum b) is the normal ^1H nmr spectrum.

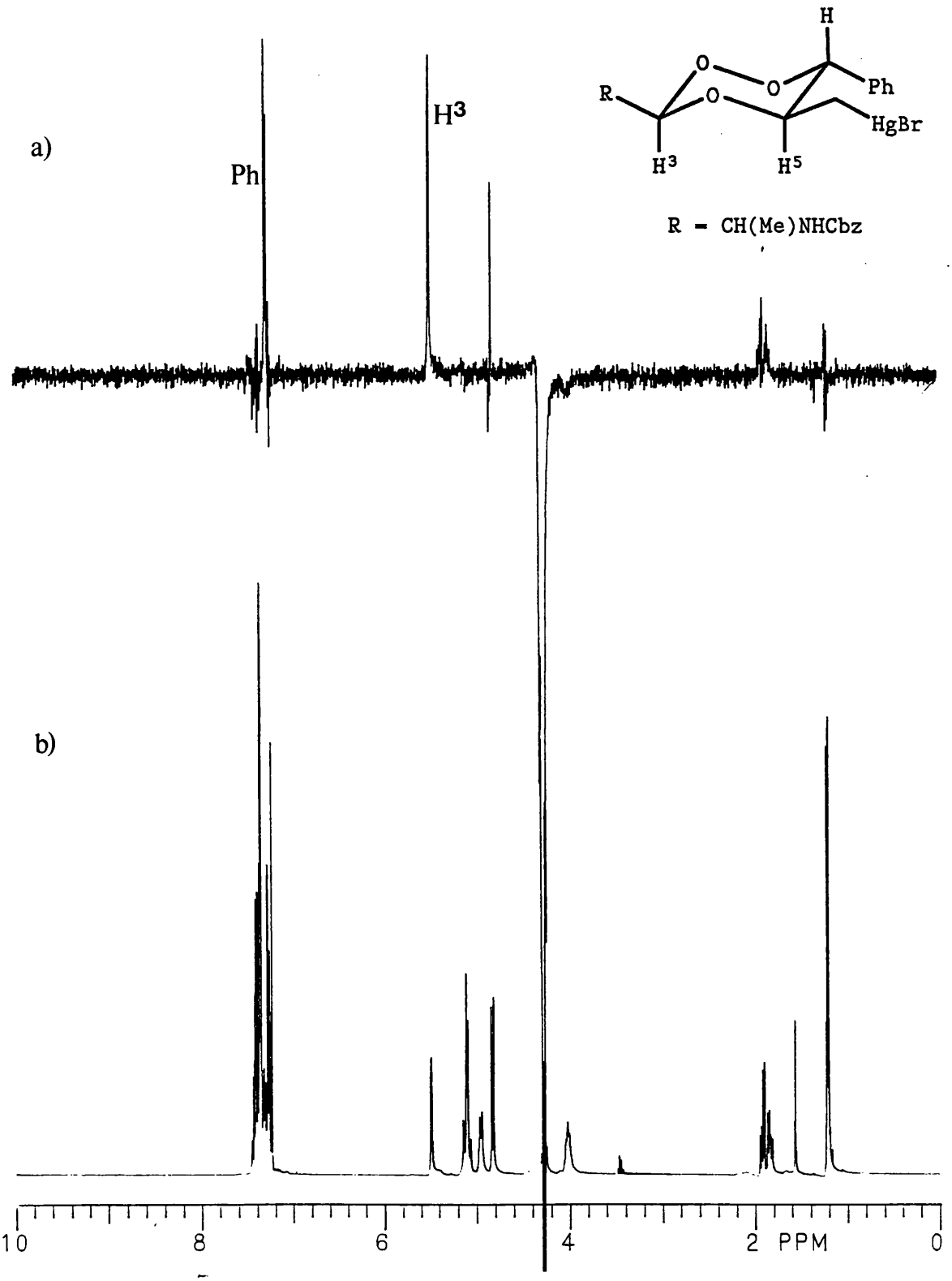
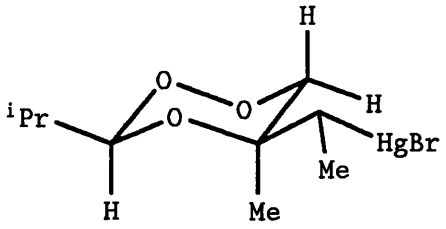
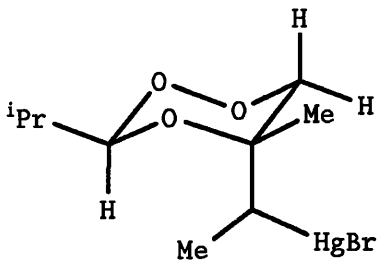


Figure 7. NOE measurements on **123e.** Spectrum a) is derived by subtracting the normal spectrum from the spectrum obtained on saturation of C(5)-H. Any protons close in space to C(5)-H appear as positive signals. The large negative signal is the irradiated proton. Spectrum b) is the normal ^{1}H nmr spectrum.

2-methyl-2-buten-1-yl hydroperoxide (**100**) with isobutyraldehyde and mercury(II) acetate also had their structures determined by ^1H nmr spectroscopy. As already discussed earlier, hydridodemercuration of **105c** and **105c*** showed that these two compounds differed only in the stereochemistry at the exocyclic chiral centre. The two major isomers (**105c** and **105t**) must therefore differ in their stereochemistry at C-5 (Fig. 8).



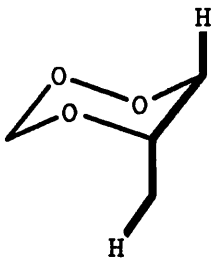
105c



105t

Figure 8

The disposition of the two groups on C-5 could be determined by looking for long range coupling between the methyl group on C-5 and the axial proton on C-6. These two groups are ideally aligned to exhibit W-plan coupling[97] (Fig. 9). What is observed is that the



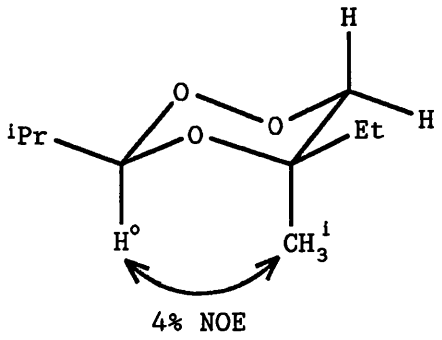
105c

Figure 9. The 'W' configuration of H^6(axial) and the axial methyl group on C-5 in 105c.

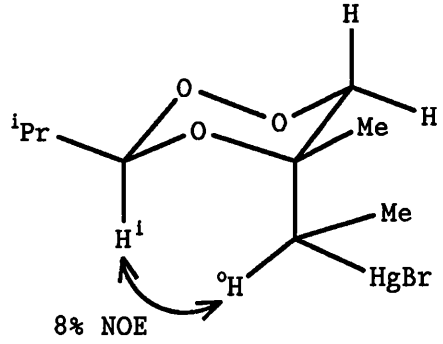
apparent methyl singlet in the major isomer actually appears as a narrow doublet (J=0.96Hz). Similarly, of the two protons attached to C-6 (δ 3.81 and 4.25 ppm), the high field proton appears as a simple doublet, whilst the signal at δ 4.25 ppm shows an additional coupling of 0.96Hz. This not only shows that the major isomer (**105c**) has an axial methyl group at C-5, as shown in Fig. 8, but also enables us to distinguish between the axial and equatorial protons on C-6.

As with the previous trioxanes discussed, the equatorial disposition of the isopropyl group was confirmed by NOE measurements.

For **105c**, the measurement was actually done on the mercury free compound (**107**), as the irradiated protons were further removed from other signals. The details are summarised in Figure 10, and the result for **105t** is shown in Figure 11.



107



105t

H° = observed proton H^{i} = irradiated proton

Figure 10

4.2.4.3 One-Bond ^{13}C-^{1}H Coupling Constants (The Perlin Effect)

During the course of our studies we were made aware of work done by another group on 1,2,4-trioxanes.[98] They also wanted to determine stereochemistries at C-3, but NOE measurements proved inconclusive. Instead, they looked to measure the one-bond coupling constant between C^3 and H^3.

The use of such measurements in the determination of stereochemistry was first described by Perlin[99] in 1969, and has subsequently been termed the Perlin Effect.[100] He showed that the value of $^{1}J(^{13}C\text{-}^{1}H)$ is greater for the equatorial anomeric proton in α-D-glucopyranose (**125**) than it is for the axial anomeric proton in β-D-glucopyranose (**126**) (^{13}C labelled) (Fig. 12) This has since been shown to be general for all heterocycles in which the carbon in question is flanked by one or two first-row heteroatoms, though the situation is reversed if both heteroatoms are from the second-row or below.[101]

In the oxygen heterocycles the Perlin effect can be considered to be a manifestation of the anomeric effect[102] (the observation that the anomeric OH group in D-glucopyranose has a much greater

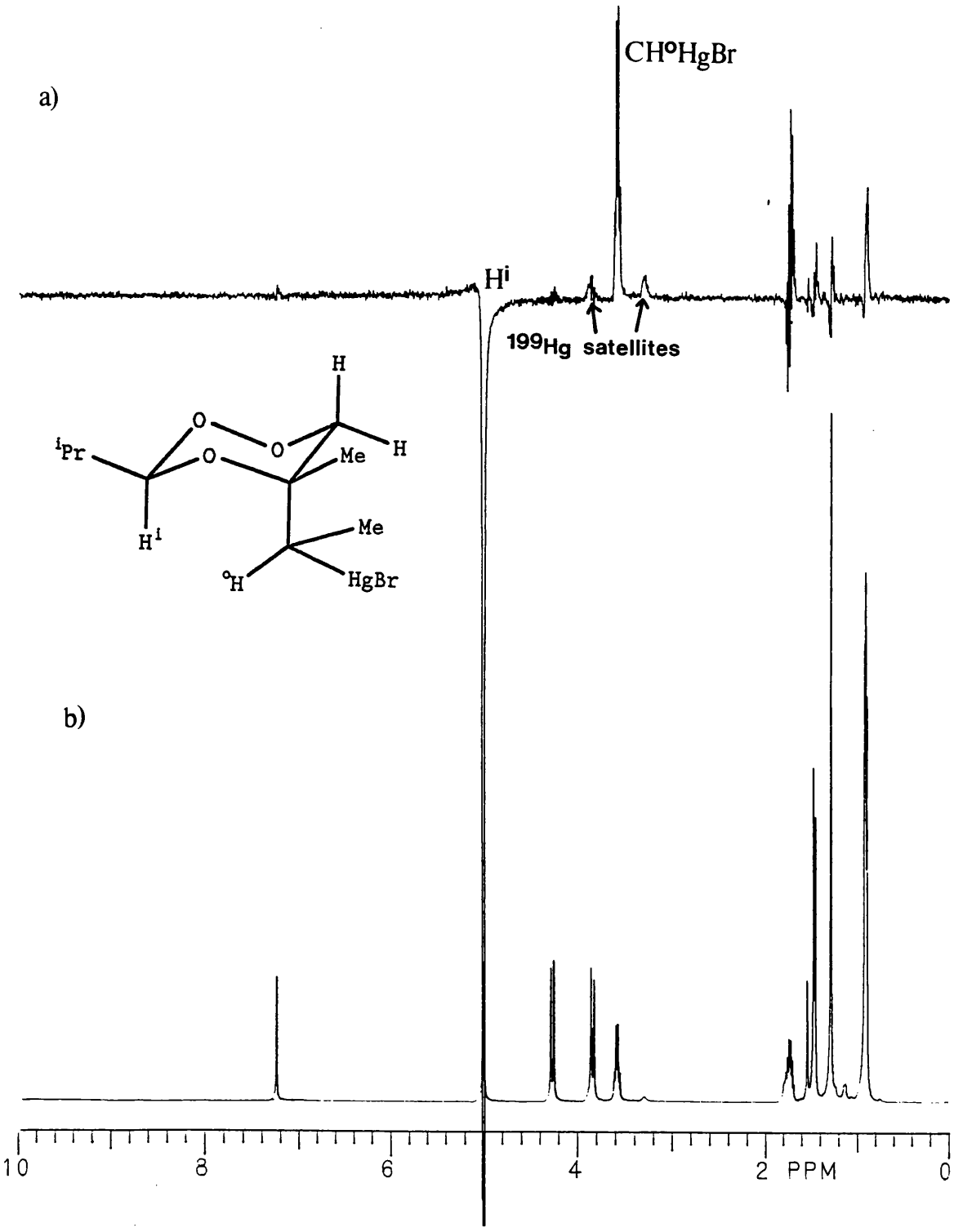
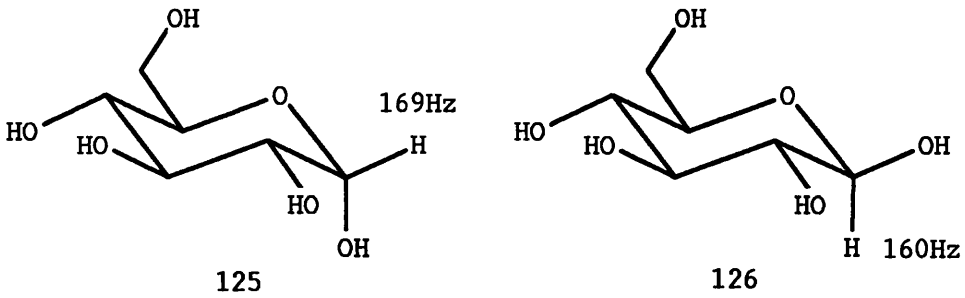


Figure 11. NOE measurements on **105t**. Spectrum a) is derived by subtracting the normal spectrum from the spectrum obtained on saturation of C(3)-H. Any protons close in space to C(3)-H appear as positive signals. The large negative signal is the irradiated proton. Spectrum b) is the normal ^{1}H nmr spectrum.

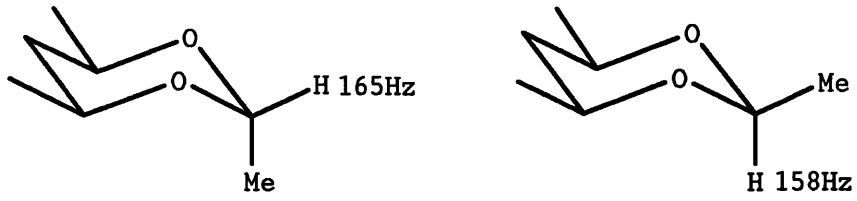


One-bond ^{13}C-^{1}H coupling constants in D-glucopyranose

Figure 12

preference to be axial than would be predicted on steric grounds alone) which is sometimes explained in terms of the population of the σ^* orbital of the *anti*-oriented (axial) C-H bond by the non-bonding electron pair on oxygen.[103] This will weaken, and lengthen, the axial C-H bond. As the Fermi contact term is the most important factor in determining the coupling constant between directly bonded nuclei,[104] such coupling constants would be expected to be inversely proportional to bond length. Indeed, Wolfe has established an inverse correlation between calculated bond lengths and observed one-bond coupling constants.[100]

What we wanted to know was whether the Perlin Effect was applicable to 1,2,4-trioxanes. Bock and Wiebe[105] had already shown that $^{1}J(^{13}C$-$^{1}H2)$ in the closely related 1,3-dioxanes was significantly greater for equatorial hydrogens than for axial hydrogens (an example is shown in Fig. 13). In contrast to the work of Davies and Cai,[98] we know, from NOE measurements, the



One-bond ^{13}C-^{1}H coupling constants in axially and equatorially 2-substituted 1,3-dioxanes.

Figure 13

configurations of our trioxanes at C-3. Therefore, the $^{13}C(3)$-^{1}H one-bond coupling constants were measured for several of our compounds, and are displayed in Table 4. We find that the average

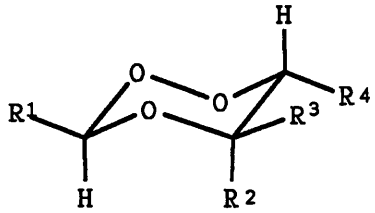
COMPOUND	$^{1}J[^{13}C(3)-^{1}H_{ax}]$/Hz	$^{1}J[^{13}C(3)-^{1}H_{eq}]$/Hz
71e	169.4	
71a		163.5
72e	169.0	
76e	168.9	
76a		164.6
95e	167.8	
105c	169.3	
105t	166.8	
123e	172.6	
123e*	171.7	
123a		164.1

Table 4 One-bond ^{13}C-^{1}H coupling constants at C-3 for some 1,2,4-trioxanes as measured from their ^{1}H coupled 100MHz ^{13}C nmr spectra.

For structures see Figs. 4 and 8.

value for an axial proton is 169.4(±1.9) Hz, and for an equatorial proton it is 164.1(±0.6) Hz. So a difference is found, but in fact ^{1}J(C-H) is *greater* for an axial proton than for an equatorial proton *i.e.* a reversed Perlin Effect. The values obtained by Davies and Cai are quantitatively similar (Table 5), and confirm that in their compounds the methyl group at C-3 is equatorial, as would be expected.

It should be noted that the value we obtain for **123a** is some 7Hz less than for **123e** and **123e***, which by analogy with **71e** and **71a** would suggest that our prediction (p. 194) of an axial substituent at C-3 of **123a** was correct.



Entry	R^1	R^2	R^3	R^4	$^1J(C\text{-}H_{ax})$/Hz	$^1J(C\text{-}H_{eq})$/Hz
1	H	H	CH_2HgBr	H	168.6	164.8
2	Me	H	Me	H	169.0	
3	Me	H	CH_2HgBr	H	169.6	
4	Me	Me	H	Me	168.4	
5	Me	CH_2HgBr	H	H	167.8	
6	Me	H	Me	Me	168.6	
7	Me	Me	Me	H	169.8	

Table 5 One-bond $^{13}C(3)$-^1H coupling constants for a series of 1,2,4-trioxanes, determined by Davies and Cai.

We can rationalise this reversed effect by assuming an interaction exists between C-3 and O-1 (a 'homoanomeric effect'). An equatorially placed sp^3 type orbital on O-1 (containing a non-bonding electron pair) would adopt a W conformation with respect to the σ^* antibonding orbital of $C(3)\text{-}H_{eq}$ (Fig. 14). Donation of electron

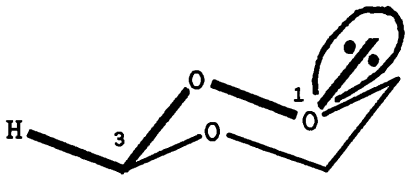


Figure 14 The homoanomeric interaction between O-1 and the equatorial C(3)-H bond.

density into the anti-bonding orbital would weaken the equatorial C-H bond, lowering the coupling constant. It must be assumed that this homoanomeric effect is much stronger than the anomeric effect to

allow for the complete reversal of the relative magnitudes of $^1J(C\text{-}H_{eq})$ and $^1J(C\text{-}H_{ax})$. In summary, anomeric effects from O-2 and O-4 reduce $^1J(C\text{-}H_{ax})$ but the homoanomeric effect from O-1 reduces $^1J(C\text{-}H_{eq})$ by a larger amount.

If this is so, then such an effect should also be observable at C-6, where two homoanomeric interactions exist for the equatorial hydrogen (Fig. 15). Therefore, the one-bond coupling constants at

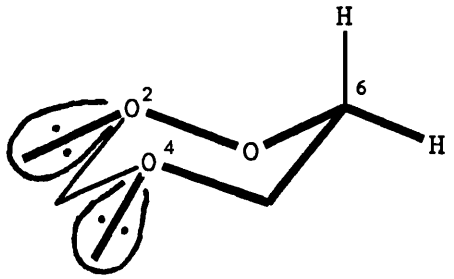
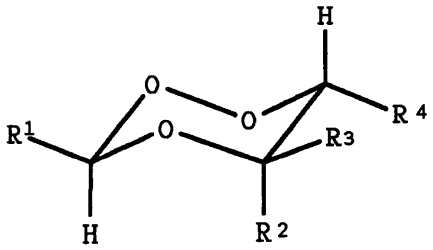


Figure 15 The homoanomeric interactions of O-2 and O-4 with the equatorial C(6)-H bond.

C-6 were also measured for our compounds. The values obtained are shown in Table 6. The two values measured for **105c** could be assigned by observation of the ^{13}C satellites of the peak at δ 3.81 ppm in the ^1H nmr spectrum. As already discussed (p. 197), we know that this signal is due to the equatorial proton on C-6 (by observation of long range coupling between the axial proton and the methyl group on C-5), and the coupling constant measured from the satellites is 140.6Hz. The assignments for **105t** are based purely on comparison with the values for the other trioxanes. As predicted, we do indeed find that $^1J(C\text{-}H_{ax})$ is again greater than $^1J(C\text{-}H_{eq})$. For **105t** the difference is almost 14Hz, this large value attributable to the fact that at C-6 we have two homoanomeric effects and only one anomeric effect.

From these results we would also predict that an axial proton on C-5 would again exhibit a larger one-bond coupling constant than would an equatorial proton, due to the presence of a homoanomeric effect from O-1 which should outweigh the anomeric effect from O-4. Unfortunately none of the trioxanes we made possess an equatorial C(5)-H group, but hopefully measurements by Davies and Cai on their compounds (*e.g.* entries 4 *v* 6 and 5 *v* 3 in Table 5) will confirm our prediction.



COMPOUND	R^1	R^2	R^3	R^4	$^1J(C6\text{-}H_{ax})$/Hz	$^1J(C6\text{-}H_{eq})$/Hz
71e	Me	H	CH_2HgBr	Ph	150.7	
72e	^{i}Pr	H	CH_2HgBr	Ph	153.6	
76e	Me	H	Me	Ph	155.2	
95e	^{i}Pr	H	CH_2HgBr	^{i}Pr	149.9	
105c	^{i}Pr	Me	CH(Me)HgBr	H	147.9	140.7
105t	^{i}Pr	CH(Me)HgBr	Me	H	151.6	137.9
123e	CH(Me)NHCbz	H	CH_2HgBr	Ph	150.0	
123e*	CH(Me)NHCbz	H	CH_2HgBr	Ph	148.2	

Table 6 One-bond C(6)-H coupling constants for some 1,2,4-trioxanes as measured from their ^1H coupled 100MHz ^{13}C nmr spectra.

4.2.5 Conclusion

Cinnamyl hydroperoxide (**61**) can be synthesised by the reaction of cinnamyl chloride with basic hydrogen peroxide, but only in low yield. The yield is much improved by the use of anhydrous hydrogen peroxide and a silver salt, but the isomeric 1-phenylallyl hydroperoxide (**67**) is the major product under these conditions. Pure **67** can be obtained by treating the mixture with mercury(II) acetate to selectively cyclise **61**. Treatment of the resultant mercurated peroxide with hydrochloric acid allows the isolation of a sample of **61** free from **67**.

On treating the mixture of **61** and **67** with an aldehyde and mercury(II) acetate, only 1,2,4-trioxanes derived from **67** can be isolated. Cinnamyl hydroperoxide (**61**) cyclises directly (or *via* a *gem*-dialkylperoxonium ion) to give *trans*-4-bromomercurio-3-phenyl-1,2-dioxolane (**70**). 1-Phenylallyl hydroperoxide (**67**) gives no trioxanes with aromatic aldehydes, and with ketones a large excess of the carbonyl component has to be used to obtain a reasonable yield. When a bulky aldehyde is used, the 1,2,4-trioxanes are formed with high stereoselectivity, the isomer with all equatorial groups being preferred. Hydridodemercuration of the isolated organomercury bromides allows the isolation of the mercury-free 1,2,4-trioxanes in fair yields, but *in situ* reduction leads only to dialkyl mercury compounds.

Other hydroperoxides with a similar substitution pattern on the double bond to cinnamyl hydroperoxide also give only 1,2-dioxolanes on treatment with isobutyraldehyde and mercury(II) acetate, whereas 1-isopropylallyl hydroperoxide, which is structurally related to **67**, gives 1,2,4-trioxanes. We rationalise this by considering the delocalisation of the positive charge in the intermediate mercurinium ion. If the structure of the ion is such that the positive charge is stabilised to a greater extent on the carbon nearer to the peroxide group, then 1,2,4-trioxanes result, otherwise 1,2-dioxolanes are formed.

To test this theory, 2-methyl-2-buten-1-yl hydroperoxide (**100**) was synthesised and found, as predicted, to give 1,2,4-trioxanes.

Aldehydes derived from amino acids can be incorporated into the 1,2,4-trioxane synthesis by protection of the nitrogen with the

carbobenzyloxy group. Stereoselectivity is not particularly high however, and yields are fairly low. Thoughts that this may provide a viable route to optically active 1,2-diols seems over-optimistic, particularly in view of recent developments in the field of asymmetric dihydroxylation.

Finally, we have shown that one-bond ^{13}C-^{1}H coupling constants in these 1,2,4-trioxanes exhibit a reversed Perlin Effect *i.e.* $^{1}J(C3\text{-}H_{ax})$ is *greater* than $^{1}J(C3\text{-}H_{eq})$. We rationalise this *via* a 'homoanomeric effect' involving electron donation from a lone pair of electrons on O-1 into the σ^* antibonding orbital of $C3\text{-}H_{eq}$. A similar effect was found at C-6.

4.3 EXPERIMENTAL

For information on the instruments used, the conditions employed for spectroscopy, and general experimental details see Appendix A.

The preparation of 3-methyl-3-buten-1-yl hydroperoxide (**50**) is described in Chapter 2. The preparations of 4,4-dimethyl-1-pentene (**89**), 1-bromo-4,4-dimethyl-2-pentene (**90**) and borane-tetrahydrofuran complex are described in Chapter 3.

4.3.1 Attempted Synthesis of 1,2,4-Trioxepanes

1-Hydroxyethyl 3-Methyl-3-buten-1-yl Peroxide (51a) (*New Compound; NC*)

3-Methyl-3-buten-1-yl hydroperoxide (**50**) (0.41g; 4mmol) was dissolved in dichloromethane (15ml) and cooled in an ice bath. Acetaldehyde (0.18g; 4mmol) in dichloromethane (5ml) was then added, followed by two drops of trifluoroacetic acid. The solution was allowed to warm to room temperature, and was stirred for 30min. The solvent was then removed under reduced pressure to give a mixture of the hemiperoxyacetal (**51a**), unreacted **50** and acetaldehyde (0.52g). Ratio **51a**:**50**:MeCHO = 8:7:1.

^{1}H nmr : δ 1.26(d, J=5.46Hz, 3H, CH_3CH); 1.73(s, 3H, CH_3C=); 5.35(q, J=5.46Hz, 1H, OOCHO) ppm. All the other signals are indistinguishable from those due to **50**.
^{13}C nmr : δ 18.80, 22.58, 35.83, 73.19(CH_2OO); 96.93(OOCHO); 111.94, 142.09 ppm.

1-Hydroxy-2,2,2-trichloroethyl 3-Methyl-3-buten-1-yl Peroxide (51b) (*NC*)

This was prepared from 3-methyl-3-buten-1-yl hydroperoxide (**50**) and chloral as described for **51a**.

Yield : 80%. No unreacted hydroperoxide was visible in the nmr spectrum.

^{1}H nmr (60MHz) : δ 1.88(s, 3H, CH_3C=), 2.49(t, J=7.2Hz, 2H); 4.36(t, J=7.2Hz, 2H, CH_2OO); 4.84(m, 2H, CH_2=); 5.49(s, 1H, OOCHO) ppm.

Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (**50**) with an Aldehyde and Mercury(II) Acetate

3-Methyl-3-buten-1-yl hydroperoxide (**50**) (0.41g; 4mmol) was dissolved in dichloromethane (20ml) and cooled in ice. Acetaldehyde (0.18g; 4mmol) in dichloromethane (1ml) was added, followed by two drops of trifluoroacetic acid. The ice bath was removed, and the mixture was stirred for 15min. Mercury(II) acetate (1.27g; 4mmol) was then added, along with two drops of 60% perchloric acid. After a further 15min., potassium bromide (0.48g; 4mmol) and water (5ml) were added, and the mixture was vigorously stirred for 10min. The organic layer was then separated off, washed with water (20ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a viscous oil, identified by comparison with literature spectra[37] as 3-bromomercuriomethyl-3-methyl-1,2-dioxolane (**53**) (1.11g; 73%).

^{1}H nmr : δ 1.45(s, 3H); 2.20(d, J=11.94Hz, 1H); 2.29(d, J=11.94Hz, 1H); 2.41(m, 2H); 4.11(approx. q, J_{ave}=7.77Hz, 1H); 4.21(dt, J=4.98, 8.08Hz, 1H) ppm.
^{13}C nmr : δ 27.59, 46.43, 48.39, 70.67, 85.44 ppm.

Replacing acetaldehyde with chloral had no effect on the product formed.

Low Temperature Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (**50**) with Chloral and Mercury(II) Trifluoroacetate

Hydroperoxide **50** (0.20g; 2mmol) and chloral (0.30g; 2mmol) were mixed in dry dichloromethane (15ml) with two drops of trifluoroacetic acid, and stirred for 1h. The solution was cooled to -20°C, and mercury(II) trifluoroacetate (0.85g; 2mmol) was added in one portion. After stirring for 1h, the solution was allowed to warm to room temperature, and water (5ml) and potassium bromide (0.25g; 2.1mmol) were added. The organic layer was separated off and the aqueous

layer was washed with dichloromethane (5ml). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield an orange coloured solid (0.60g). As previously, this could be identified from its ^1H and ^{13}C nmr spectra as the mercurated 1,2-dioxolane **53**.

A Typical Procedure for the Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (**50**) with a Carbonyl Compound and *tert*-Butyl Hypochlorite

Column chromatography grade silica (0.75g) was suspended in a solution of *tert*-butyl hypochlorite (0.313g; 2.88mmol) in dichloromethane (5ml) which was cooled to -20°C. A solution of the hemiperoxyacetal (1.35mmol) (prepared as described earlier) in dichloromethane (5ml), pre-cooled to -30°C, was added in one portion, and the mixture was magnetically stirred for 1h while gradually warming to room temperature. The silica was filtered off, washed with dichloromethane, and the solvent was removed under reduced pressure to yield a colourless liquid.

With the one exception (indicated below), examination of the ^{13}C nmr spectrum of the crude material shows almost exclusively the chlorinated dioxolanes **55** and **56**, identified by comparison with the spectra of the authentic compounds (see Chapter 2).

The carbonyl compound used was acetaldehyde, chloral or acetone, and the reaction temperature was varied between -60°C and 20°C. In no case was there a signal observed in the region of δ 95-110 ppm as would be predicted for the chemical shift of C-3 in a 1,2,4-trioxepane.

Reaction of 3-Methyl-3-buten-1-yl Hydroperoxide (**50**) with Acetone and *tert*-Butyl Hypochlorite at -60°C

Hydroperoxide **50** (0.20g; 2mmol) was dissolved in acetone (20ml) and stirred at room temperature for 1.5h. The solution was cooled to -60°C, and the *tert*-butyl hypochlorite (0.280g; 2.6mmol) was added dropwise. After stirring at this temperature for 15min. the solution was allowed to warm to room temperature. Removal of the solvent under reduced pressure gave a colourless liquid which was separated

by column chromatography (CH_2Cl_2 then ether).

2,2-Bis(3-methyl-3-buten-1-ylperoxy)propane (57) (*NC*)

Yield : 52mg (21%). R_f 0.66 (CH_2Cl_2).

^1H nmr : δ 1.41(s, 6H, $[CH_3]_2C$); 1.73(s, 6H, 2x $CH_3C=$); 2.33(t, J=6.86Hz, 4H); 4.16(t, J=6.86Hz, 4H, 2x CH_2OO); 4.72-4.75(m, 4H, 2x $CH_2=$) ppm.
^{13}C nmr : δ 21.43, 22.73, 35.84, 73.74(CH_2OO), 108.64(OOCOO), 111.66($CH_2=$), 142.17($CH_3C=$) ppm.
Mass spectrum (FAB, NaI matrix) : m/z(%) = 42(29), 54(100), 135(4), 176(3), 267(2, $[M+Na]^+$).

2-(3-Methyl-3-buten-1-ylperoxy)-2-(4-chloro-3-hydroxy-3-methylbut-1-ylperoxy)propane (58) (*NC*)

Yield : 35mg (12%). R_f 0.20 (CH_2Cl_2).

^1H nmr : δ 1.29 (s, 3H, CH_3COH); 1.40(s, 6H, $[CH_3]_2C$); 1.73(s, 3H, $CH_3C=$); 1.90(dt, J=15.02, 6.35Hz, 1H); 1.97(dt, J=15.02, 5.87Hz, 1H); 2.32(t, J=6.93Hz, 2H); 2.60(br s, 1H, OH); 3.53(s, 2H, CH_2Cl); 4.14(t, J=6.93Hz, 2H, CH_2OO); 4.26(approx. t, J_{ave}=6.08Hz, 2H, CH_2OO); 4.72-4.76(m, 2H, $CH_2=$) ppm.
^{13}C nmr : δ 21.37, 22.71, 25.00, 35.77, 36.56, 53.31(CH_2Cl), 71.60, 73.71, 108.68(OOCOO), 111.79, 141.98 ppm.
Mass spectrum (FAB, NaI matrix) : m/z(%) = 42(35), 54(100), 58(35), 92(4.3), 219(5), 319(10, $[M<^{35}Cl>+Na]^+$), 321(3, $[M<^{37}Cl>+Na]^+$).

2,2-Bis(4-chloro-3-hydroxy-3-methylbut-1-ylperoxy)propane (59) (*NC*) and **4-Chloro-3-hydroxy-3-methylbut-1-yl Hydroperoxide (60)** (*NC*)

These were isolated as a 2:1 mixture of **60:59**.
Yield : 28mg (*ca.* 8%). R_f 0.60 (ether).

^1H nmr : δ 1.29(s, 3H); 1.32(s, 3H); 1.40(s, 3H); 1.89(m, 2H); 1.98(m, 2H): 2.4-2.9(br s, 2H); 3.52(m, 4H); 4.19(t, J=6.01Hz, 2H); 4.23(t, J=6.17Hz, 2H); 9.50(br s, 1H, **60** : OOH) ppm.

^{13}C nmr : δ 21.34, 24.68, 24.96, 36.42, 36.46, 53.34, 53.56, 71.46, 71.71, 71.90, 72.78, 108.76(**59** : OOCOO) ppm.
Mass spectrum (FAB, NaI matrix) : m/z(%) = 54(100), 58(73), 68(15), 84(12), 88(13), 92(15), 135(10), 153(15), 175(11), 219(24), 221(6.6), 371(18, [M<**59** : $^{35}Cl^{35}Cl$>+Na]$^+$), 373(13, [M<**59** : $^{35}Cl^{37}Cl$>+Na]$^+$), 375(1, [M<**59** : $^{37}Cl^{37}Cl$>+Na]$^+$).

4.3.2 Hydroperoxide Syntheses

Attempted Syntheses of Cinnamyl Methanesulphonate (62)

a) Methanesulphonyl Chloride

Methanesulphonyl chloride (11.46g; 0.10mol) and cinnamyl alcohol (13.42g; 0.10mol) were mixed together in a 100ml round bottomed flask equipped with mechanical stirrer, pressure equalising dropping funnel and nitrogen inlet. The flask was cooled in ice, and pyridine (15.82g; 0.20mol) was added dropwise. Stirring was continued for 30min. at 0°C, and a further 30min. at room temperature. The mixture was then combined with 10% hydrochloric acid (60ml) and extracted with ether (2x50ml). The ethereal layers were washed with water (2x40ml) and saturated sodium bicarbonate solution (50ml), dried over K_2CO_3, and the solvent was removed under reduced pressure to yield a pale yellow liquid (10.27g).

By comparison of the ^1H nmr spectrum with an authentic sample, the product was shown to be cinnamyl chloride (yield : 67%).

b) Methanesulphonic Anhydride

Methanesulphonic anhydride (1.74g; 10mmol) was dissolved in dry dichloromethane (20ml) in a 3-necked round bottomed flask equipped with dropping funnel and inlet for sulphuric acid-dried argon. The flask was cooled in ice, and a solution of cinnamyl alcohol (1.34g; 10mmol) and pyridine (0.79g; 10mmol) in dry dichloromethane (5ml) was slowly added. On completion of the addition, the mixture was stirred for 15min. at 0°C and a further 30min. at room temperature. The mixture was then washed with water (2x20ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a black tarry product.

Cinnamaldehyde p-Toluenesulphonhydrazone (65)[38]

p-Toluenesulphonhydrazide (3.72g; 20mmol) was suspended in absolute ethanol (40ml) at 50°C. Freshly distilled cinnamaldehyde (2.64g; 20mmol. b.p. 138°C/20mmHg) was added in one portion, and as

soon as all the starting hydrazide had gone into solution, a large amount of solid material crystallised out. The mixture was cooled in ice and filtered. The product was washed with pentane and dried under high vacuum to afford the hydrazone as a pale yellow fluffy solid (5.45g; 91%). m.p. 165°C (dec.). Lit.[38] : 166°C (dec.).

^{1}H nmr : δ 2.42(s, 3H); 6.75-6.87(m, 2H); 7.26-7.41(m, 7H); 7.60(d, J=8.08Hz, 1H); 7.87(d, J=8.36Hz, 2H); 8.25(br s, 1H) ppm.
^{13}C nmr : δ 21.61, 124.32, 127.04, 127.88, 128.80, 129.13, 129.75, 135.24, 135.54, 139.99, 144.30, 149.82 ppm.

Cinnamyl N'-p-Toluenesulphonylhydrazine (66)[39]

Cinnamaldehyde *p*-tosylhydrazone (**65**) (0.60g; 2mmol) was dissolved in dioxan (8ml) and ethanol (2ml) under a nitrogen atmosphere. Pyridine-borane complex (0.60ml; 6mmol) was added and the solution was cooled in ice. A 20% solution of concentrated hydrochloric acid in ethanol (10ml) was slowly added, and the solution was stirred for 10min. The solution was then concentrated to *ca.* one-quarter volume, and sufficient 10% sodium carbonate solution was added to neutralise the acid. The solid formed was filtered off, washed with water, and dried under high vacuum to afford the hydrazine as a very pale yellow solid (0.55g; 92%). m.p. 74°C (Lit.[39] : 79°C).

^{1}H nmr : δ 2.41(s, 3H); 3.42(d, J=6.76Hz, 2H); 3.67(br s, 1H); 5.97(dt, J=15.88, 6.76Hz, 1H); 6.37(d, J=15.88Hz, 1H); 6.35(br s, 1H); 7.28(m, 7H); 7.84(d, J=8.30Hz, 2H) ppm.
^{13}C nmr : δ 21.58, 53.74, 124.51, 126.43, 127.79, 128.14, 128.52, 129.60, 134.09, 135.51, 136.36, 143.96 ppm.

Oxidation of Cinnamyl *N*'-Tosylhydrazine (66) with Hydrogen Peroxide

30% Hydrogen peroxide (17ml; 150mmol H_2O_2) and sodium peroxide (0.36g; 4.5mmol) were added, with stirring, to a solution of cinnamyl *N*'-tosylhydrazine (**66**) (0.45g; 1.5mmol) in tetrahydrofuran (40ml). The mixture was stirred for 20h. The solution was then diluted with water (100ml), and neutralised with 2M hydrochloric acid. This was

extracted with dichloromethane (4x25ml), and the combined organic extracts were washed with water (3x25ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure to yield a yellow liquid (0.14g).

The ^1H nmr spectrum of the crude material showed a profusion of signals. TLC also indicated several compounds, one of which gave a positive test for peroxide (acidic iron(II) thiocyanate). Isolation of this fraction by column chromatography (CH_2Cl_2 : petrol 60/80°C; 2 : 1) yielded only 16mg (4%), and even then the ^1H nmr showed a lot of signals which could not possibly arise from cinnamyl hydroperoxide (**61**).

Cinnamyl Hydroperoxide (61) and 1-Phenylallyl Hydroperoxide (67)

85% w/w Hydrogen peroxide (2.00ml; 66mmol H_2O_2) was dissolved in ether (50ml), and the solution was dried over $MgSO_4$. After filtration, this was combined with cinnamyl chloride (1.53g; 10mmol) and cooled to -78°C. Silver tetrafluoroborate (2.13g; 11mmol) was quickly added in one portion in subdued light, and the mixture was stirred for 30min. before being allowed to warm to room temperature. Saturated sodium bicarbonate solution (40ml) was added, and the mixture was stirred for a further hour. The aqueous slurry was separated off and extracted with ether (2x20ml). The combined ether layers were washed with water (5x10ml) and brine (20ml), dried over $MgSO_4$, and the solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2, R_f 0.28 & 0.25) afforded a mixture of **61** and **67** as a colourless liquid (0.96g; 64%).

Found : C, 71.82; H, 6.64%. Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%.

Cinnamyl Hydroperoxide (61) (*NC*)

a) From Cinnamyl Chloride and Hydrogen Peroxide

Cinnamyl chloride (7.63g; 50mmol) was dissolved in methanol (130ml) and water (20ml) and cooled in ice. 30% w/v Hydrogen peroxide (22.5ml; 200mmol H_2O_2) followed by potassium hydroxide (3.05g; 50mmol) in water (3ml) were added, and the mixture was

magnetically stirred for 5h. Water (100ml) was added, and the mixture was extracted into ether (5x20ml). The combined ether layers were extracted with ice-cold 20% potassium hydroxide (2x15ml), and the aqueous layers were immediately acidified and extracted back into dichloromethane (4x40ml). The organic layers were washed with water (40ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the hydroperoxide as a colourless liquid (0.92g; 12%).

The ^1H nmr spectrum shows the product to be about 85% cinnamyl hydroperoxide, the rest being 1-phenylallyl hydroperoxide.

b) From *trans*-4-Bromomercurio-3-phenyl-1,2-dioxolane (**70**)

2% Hydrochloric acid (0.60ml; *ca.* 0.39mmol HCl) was added to a solution of **70** (0.109g; 0.25mmol) in tetrahydrofuran (5ml), and the solution was stirred for 2h. Water (10ml) and dichloromethane (10ml) were added, the organic layer was separated off, and the aqueous layer was extracted with further dichloromethane (5ml). The combined organic extracts were washed with water (5ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was extracted into carbon tetrachoride, insoluble mercury salts were filtered off, and the solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2, R_f 0.24) afforded pure **61** as a colourless liquid (0.013g; 34%).

^1H nmr (200MHz) : δ 4.65(d, J=6.56Hz, 2H, CH_2OOH); 6.33(dt, J=15.87, 6.56Hz, 1H, $=CHCH_2$); 6.69(d, J=15.87Hz, 1H, PhCH=); 7.38-7.45(m, 5H, C_6H_5); 8.74(br s, 1H, OOH) ppm.
^{13}C nmr : δ 77.67(CH_2OOH), 123.01, 126.68, 128.20, 128.63, 135.89, 136.13 ppm.

1-Phenylallyl Hydroperoxide (67)

A mixture of 1-phenylallyl hydroperoxide (**67**) and cinnamyl hydroperoxide (**61**) was prepared as above from cinnamyl chloride (4.58g; 30mmol), silver tetrafluoroborate (6.23g; 32mmol) and 85% hydrogen peroxide (5.0ml; 166mmol H_2O_2). The crude product was redissolved in dichloromethane (50ml), mercury(II) acetate (4.78g;

15mmol) was added, and the mixture was stirred for 20h. After filtering, the solution was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2; R_f 0.28) to afford the pure hydroperoxide (1.03g; 23%).

^1H nmr : δ 5.34(m, 2H); 5.40(d, J=6.85Hz, 1H); 6.05(ddd, J=17.78, 9.92, 6.85Hz, 1H); 7.33-7.41(m, 5H); 8.25(br s, 1H) ppm.
^{13}C nmr : δ 88.64, 119.44, 127.44, 128.44, 128.55, 135.37, 138.21 ppm.
Found : C, 71.08; H, 6.92%. Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%.

1-Bromo-4-methyl-2-pentene (88)[106]

Phosphorous tribromide (1.60ml; 17mmol) was dissolved in dry benzene (3ml) in a flask equipped with magnetic stirrer, dropping funnel and low temperature thermometer. Pyridine (0.75ml) was slowly added to the solution, which was then cooled in an ice-salt bath to -10°C. Pyridine (0.25ml. Total : 1.00ml; 12mmol) and 4-methyl-1-penten-3-ol (ex. Aldrich) (5.00g; 50mmol) were combined and slowly added to the solution, so as to maintain the temperature of the mixture below -5°C. On completion of the addition the solution was warmed to room temperature and allowed to stand overnight. Dichloromethane (15ml) and water (15ml) were added, and the mixture was vigorously stirred for 5min. The organic layer was separated off, and the aqueous layer was extracted with dichloromethane (10ml). The combined organic layers were washed with water (5ml), dried over $MgSO_4$, and the sovent was removed under reduced pressure to give a very pale yellow liquid (4.93g; 60%) containing predominantly **88** with a small amount of the isomeric 3-bromo-4-methyl-1-pentene.

^1H nmr : δ 0.97(d, J=6.77Hz, 6H); 2.30(m, 1H); 3.92(d, J=7.51Hz, 2H); 5.63(m, 1H); 5.72(dd, J=15.68, 6.22Hz, 1H) ppm.
^{13}C nmr : δ 21.91, 30.64, 33.76, 123.52, 143.25 ppm.

(E)-2-Methyl-2-buten-1-ol (102)[107]

Lithium aluminium hydride (4.75g; 0.125mol) was suspended in dry ether (180ml) in a 1 litre 3-necked round bottomed flask equipped

with mechanical stirrer, pressure equalising dropping funnel, reflux condenser and calcium chloride guard tube. Tiglic acid (10.01g; 0.10mol) in dry ether (150ml) was added at such a rate as to maintain a gentle reflux. On completion of the addition, the mixture was stirred for a further 15min. The flask was then cooled in ice, and excess hydride was destroyed by the careful addition of water (50ml) (CAUTION!). The ice bath was removed, and the mixture was stirred until the precipitate had turned completely white. 10% Sulphuric acid (150ml) was then added slowly and stirring was continued until all the precipitate had dissolved. The ethereal layer was separated off, and the aqueous layer was extracted with ether (2x50ml). The combined organic layers were washed with saturated sodium bicarbonate solution (50ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Distillation of the crude product afforded the alcohol as a colourless liquid (5.38g; 62%). b.p. 137-138°C (Lit.[107] : 137-138°C).

^1H nmr : δ 1.58(d, J=6.71Hz, 3H); 1.62(d, J=1.13Hz, 3H); 1.74(br s, 1H); 3.95(s, 2H); 5.44(m, 1H) ppm.
^{13}C nmr : δ 13.01, 13.27, 68.87, 120.48, 135.44 ppm.

(E)-1-Bromo-2-methyl-2-butene (103)

This was prepared from **102** according to the method of Edelson *et al.*[108]

Yield : 66%.

^1H nmr : δ 1.61(d, J=7.18Hz, 3H); 1.73(s, 3H); 3.96(s, 2H); 5.67(m, 1H) ppm.
^{13}C nmr : δ 13.88, 14.31, 41.80, 125.78, 132.69 ppm.

Preparation of Primary Allylic Hydroperoxides from Primary Allylic Bromides[54]

A typical procedure was as follows :

The allylic bromide (20mmol) was dissolved in methanol (70ml) and cooled in ice. 30% w/v Hydrogen peroxide (15ml; 130mmol H_2O_2) was slowly added, followed by a solution of potassium hydroxide

(1.36g; 24mmol) in water (5ml). The solution was allowed to stir at room temperature for 48h. Water (150ml) was added, and the solution was saturated with ammonium sulphate and extracted with dichloromethane (4x50ml). The combined organic layers were washed with water (2x50ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude hydroperoxide. The crude material was then dissolved in ether (20ml) and cooled to -30°C. This solution was shaken vigorously with a solution of potassium hydroxide (2.50g; 45mmol) in water (4ml) also pre-cooled to -30°C. The ethereal layer was decanted off, and the thick white precipitate was dissolved in water and cooled in ice. This was immediately acidified by the dropwise addition of an ice-cold solution of acetic acid (3.00ml; 52mmol) in ether (20ml). After vigorously stirring for 5min., the organic layer was separated off, washed with saturated sodium bicarbonate solution (10ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the pure hydroperoxide.

4,4-Dimethyl-2-penten-1-yl Hydroperoxide (3-*tert*-Butylallyl Hydroperoxide) (86) (*NC*)

This was synthesised from 1-bromo-4,4-dimethyl-2-pentene (**90**).
Yield : 45%.

^{1}H nmr : δ 1.00(s, 9H, CH_3); 4.30(d, J=6.68Hz, 2H, CH_2OOH); 5.46(dt, J=15.65, 6.68Hz, 1H, $=CHCH_2$); 5.80(d, J=15.65Hz, 1H, $=CH^tBu$); 8.24(br s, 1H, OOH) ppm.
^{13}C nmr : δ 29.24(CH_3), 33.15($[CH_3]_3C$), 78.11(CH_2OOH), 118.17, 149.24 ppm.
Found : C, 64.71; H, 10.94%. Calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.84%.

4-Methyl-2-penten-1-yl Hydroperoxide (3-isopropylallyl Hydroperoxide) (85) (*NC*)

This was synthesised from 1-bromo-4-methyl-2-pentene (**88**).
Yield : 42%.

^{1}H nmr : δ 0.98(d, J=6.80Hz, 6H, CH_3); 2.30(m, 1H, $[CH_3]_2CH$); 4.41(d, J=6.66Hz, 2H, CH_2OOH); 5.50(dt, J=15.49, 6.66Hz, 1H, $=CHCH_2$);

5.76(dd, J=15.49, 6.48Hz, 1H, =CH^{i}Pr); 8.33(br s, 1H, OOH) ppm.
^{13}C nmr : δ 21.97(CH_3), 30.85($[CH_3]_2CH$), 77.89(CH_2OOH), 120.46, 145.33 ppm.
Found : C, 62.16; H, 10.72%. Calc. for $C_6H_{12}O_2$: C, 62.04; H, 10.41%.

(E)-2-Methyl-2-buten-1-yl Hydroperoxide (94) (*NC*)

This was synthesised from (*E*)-1-bromo-2-methyl-2-butene (**103**).
Yield : 54%.

^{1}H nmr : δ 1.63(d, J=5.74Hz, 3H, CH_3CH=); 1.67(s, 3H, CH_3C=); 4.34(s, 2H, CH_2OO); 5.55(m, 1H, CH=); 8.10(br s, 1H, OOH) ppm.
^{13}C nmr : δ 13.33, 13.66, 83.36(CH_2OOH), 126.01, 130.96 ppm.

4-Methyl-1-penten-3-yl Hydroperoxide (1-Isopropylallyl Hydroperoxide) (93)[55]

cis-4-Methyl-2-pentene (**94**) (1.68g; 20mmol) was dissolved in dichloromethane (25ml), and a few milligrams of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) were added. The solution was saturated with oxygen, and stirred under an oxygen atmosphere while being irradiated with a 400W sodium discharge lamp for 3 days (an extra portion of TPP was added after 1 day). The solvent was then removed under reduced pressure to give a yellow oil. Column chromatography (CH_2Cl_2; R_f 0.28) afforded the pure hydroperoxide as a very pale yellow liquid (0.15g; 6%).

^{1}H nmr : δ 0.86(d, J=6.89Hz, 3H); 0.93(d, J=6.80Hz, 3H); 1.83(m, 1H); 4.03(dd, J=7.80, 7.02Hz, 1H); 5.27-5.34(m, 2H); 5.72-5.81(m, 1H); 7.94(br s, 1H) ppm.
^{13}C nmr : δ 18.04, 18.66, 30.36, 92.28, 120.02, 135.34 ppm.

4.3.3 Syntheses and Reactions of 1,2,4-Trioxanes and 1,2-Dioxolanes

Synthesis of Mercurated 1,2,4-Trioxanes and 1,2-Dioxolanes

In a typical procedure, the hydroperoxide (1mmol) and aldehyde (1-20mmol) were stirred in dichloromethane (10ml) with a drop of trifluoroacetic acid for 30min. Mercury(II) acetate (0.319g; 1mmol) was then added, along with two drops of 60% perchloric acid, and stirring was continued for 2h. Water (5ml) and potassium bromide (0.179g; 1.5mmol) were then added, and the mixture was vigorously stirred for 15min. The organic layer was separated off, and the aqueous layer was extracted with dichloromethane (5ml). The combined organic layers were washed with water (5ml), dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield the crude product. Purification was achieved by column chromatography (CH_2Cl_2 unless otherwise stated) to afford the 1,2,4-trioxanes and 1,2-dioxolanes as oils. Analytically pure samples could be obtained by crystallisation from a suitable solvent.

*Cinnamyl Hydroperoxide (**61**) / 1-Phenylallyl Hydroperoxide (**67**) Mixture and Acetaldehyde*

The reaction was carried out using a 1.4 : 1 mixture of **67** : **61** with 2 eq. of acetaldehyde.

Chromatography was carried out with $CHCl_3$ as the eluant.

trans-4-Bromomercurio-3-phenyl-1,2-dioxolane (**70**)

Yield : 82% (from **61**). R_f 0.19 ($CHCl_3$).

The product has a low solubility in chloroform.

For characterisation, see below.

5-Bromomercuriomethyl-3-methyl-6-phenyl-1,2,4-trioxane (71) (*NC*)

Yield : 43% (from **67**). The product was formed as a 5:1 mixture of **71e:71a**. R_f 0.48 ($CHCl_3$).

Major isomer (**71e**) :

^{1}H nmr : δ 1.38(d, J=5.36Hz, 3H, CH_3); 1.87(dd, J=12.11, 7.15Hz, 1H, CH^AH^BHgBr); 1.94(dd, J=12.11, 6.74Hz, 1H, CH^AH^BHgBr); 4.26(approx. dt, J_{ave}=8.92, 6.97Hz, 1H, CHO); 4.84(d, J=8.92Hz, 1H, CHOO); 5.62(q, J=5.36Hz, 1H, OCHOO); 7.30-7.44(m, 5H, C_6H_5) ppm.
NOE : Saturation of the signal at δ 5.62 ppm causes a 7.5% enhancement of the signal at δ 4.26 ppm.
^{13}C nmr : δ 17.99(CH_3), 34.69(CH_2HgBr), 77.77(CO), 88.70($^1J[^{13}C-^1H]$ = 150.7Hz, COO), 101.88($^1J[^{13}C-^1H]$ = 169.4Hz, OCOO), 128.25, 129.35, 130.21, 134.05 ppm.

Minor isomer (**71a**) :

^{1}H nmr : δ 1.77(d, J=5.83Hz, 3H, CH_3); 4.59(m, 1H, CHO); 5.56(q, J=5.83Hz, 1H, OCHOO) ppm. All other signals are hidden by the major isomer.
NOE : Saturation of the methyl doublet at δ 1.77 ppm causes a 4% enhancement of the multiplet at δ 4.59 ppm.
^{13}C nmr : δ 16.98(CH_3), 35.39(CH_2HgBr), 69.96(CO), 82.30(COO), 99.12($^1J[^{13}C-^1H]$ = 163.5Hz, OCOO) ppm. The signals for the aromatic carbons are obscured by those from the major isomer.

Mixture :

Crystallised at -30°C from dichloromethane / pentane.
White crystals, m.p. 102-104°C.

Found : C, 28.07, H, 2.68%. Calc. for $C_{11}H_{13}BrHgO_3$: C, 27.89; H, 2.55%.

*1-Phenylallyl Hydroperoxide (**67**) and Acetaldehyde*

With 17 eq. of acetaldehyde, the yield of **71** was increased to 70%.

*Cinnamyl Hydroperoxide (**61**) / 1-Phenylallyl Hydroperoxide (**67**) Mixture and Isobutyraldehyde*

The reaction was carried out using a 1.4 : 1 mixture of **67** : **61** and 1.2 eq. of isobutyraldehyde.

***trans*-4-Bromomercurio-3-phenyl-1,2-dioxolane (70) (*NC*)**

R_f 0.40 (CH_2Cl_2). Yield : 70% (from **61**).

^1H nmr : δ 3.20(approx. dt, J_{ave}=7.55, 9.55Hz, 1H, CHHgBr); 4.38(dd, J=7.77, 9.80 Hz, 1H, CH^AH^BOO); 4.61(approx. t, J_{ave}=7.66Hz, 1H, CH^AH^BOO); 5.34(d, J=9.27Hz, 1H, CHPh); 7.39(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 64.79(CHHgBr), 73.53(CH_2OO), 84.52(CHPh), 126.80, 129.05, 129.12, 136.64 ppm.

Crystallised from CH_2Cl_2 / pentane at -30°C.
White fluffy needles. m.p. 75°C.
Found : C, 24.81; H, 1.82% Calc. for $C_9H_9BrHgO_2$: C, 25.16; H, 2.11%

5-Bromomercuriomethyl-3-isopropyl-6-phenyl-1,2,4-trioxane (72e) (*NC*)

Essentially one isomer. Ratio major : minor isomers ≅ 30 : 1.

^1H nmr : δ 0.99(d, J=6.99Hz, 3H, CH_3); 1.00(d, J=6.96Hz, 3H, CH_3); 1.87(dd, J=12.04, 6.93Hz, 1H, CH^AH^BHgBr); 1.88(m, 1H, $[CH_3]_2CH$); 1.93(dd, J=12.04, 6.85Hz, 1H, CH^AH^BHgBr); 4.22(dt, J=8.98, 6.89Hz, 1H, CHO); 4.79(d, J=8.98Hz, 1H, CHOO); 5.20(d, J=5.40Hz, 1H, OCHOO); 7.26-7.40(m, 5H, C_6H_5) ppm.
NOE : Saturation of the signal at δ 5.20 ppm causes a slight enhancement of the signals for the neighbouring isopropyl group, and additionally causes a 4% enhancement of the multiplet at δ 4.22 ppm.
^{13}C nmr : δ 17.08(CH_3), 31.00($[CH_3]_2CH$), 35.06($^1J[^{13}C-^{199}Hg]$ = 1538Hz), 77.65(CHO), 88.88(CHOO), 108.00($^1J[^{13}C-^1H]$ = 169.0Hz, OCHOO), 128.22, 129.23, 130.06, 134.13 ppm.
^{199}Hg nmr ($CDCl_3$, 71.5MHz, δ [Ph_2Hg] = -745 ppm) : δ -1080(q, J=184Hz) ppm

An analytical sample was crystallised from CH_2Cl_2 / pentane at -30°C.

White solid. m.p. 93-94°C.

Found : C, 31.36; H, 3.46%. Calc. for $C_{13}H_{17}BrHgO_3$: C, 31.12; H, 3.42%.

*1-Phenylallyl Hydroperoxide (**67**) and 2-Methylbutyraldehyde*

The reaction was carried out using 1.5 eq. of the aldehyde.

5-Bromomercuriomethyl-3-*sec*-butyl-6-phenyl-1,2,4-trioxane (73e) (*NC*)

Yield : 48%. R_f 0.61 (CH_2Cl_2).

The trioxane was formed as a 1:1 mixture of isomers due to the exocyclic chiral centre.

^1H nmr : δ [0.92(t, J=7.44Hz) & 0.93(t, J=7.41Hz), 3H, CH_3CH_2]; [0.97(d, J=6.96Hz) & 0.98(d, J=6.87Hz), 3H, CH_3CH]; 1.25(m, 1H); 1.56-1.71(m, 2H); [1.87(m) & 1.93(dd, J=12.05, 6.83Hz), 2H, CH_2HgBr]; 4.22(dt, J=8.98, 6.94Hz, 1H, CHO); 4.79(d, J=8.98Hz, 1H, CHOO); [5.28(d, J=5.31Hz) & 5.29(d, J=5.05Hz), 1H, OCHOO]; 7.27-7.42(m, 5H, C_6H_5) ppm.

^{13}C nmr : δ 11.36, 11.45, 13.62, 13.64, 24.13, 24.32, 35.07, 35.11, 37.40, 37.59, 77.64 & 77.70(CO), 88.93(COO), 107.20 & 107.37(OCOO), 128.23, 129.24, 130.06, 134.15 ppm.

Crystallised from CH_2Cl_2 / petrol at -30°C. Very slight fractional crystallisation appears to occur.

White crystalline solid of indefinite melting point.

Found : C, 32.30; H, 3.64%. Calc. for $C_{14}H_{19}BrHgO_3$: C, 32.60; H, 3.71%.

*1-Phenylallyl Hydroperoxide (**67**) and Chloral*

The reaction was carried out using 2 eq. chloral.

Chromatography was performed with $CHCl_3$ as the eluant.

5-Bromomercuriomethyl-6-phenyl-3-trichloromethyl-1,2,4-trioxane (74e) *(NC)*

Yield : 28% (not entirely pure). R_f 0.55 ($CHCl_3$).

^1H nmr : δ 1.93(dd, J=12.15, 7.44Hz, 1H, CH^AH^BHgBr); 2.01(dd, J=12.15, 6.38Hz, 1H, CH^AH^BHgBr); 4.54(m, 1H, CHO); 4.98(d, J=9.20Hz, 1H, CHOO); 5.78(s, 1H, OCHOO); 7.27-7.50(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 34.03(CH_2HgBr), 79.55(CO), 88.66(COO), 104.56(OCOO), 128.36, 129.58, 130.76, 132.55 ppm +1C.

Crystallised from CCl_4 / petrol at -30°C.
White solid melting over a wide range of temperatures.

Found : C, 24.78; H, 1.99%. Calc. for $C_{11}H_{10}BrCl_3HgO_3$: C, 22.90; H, 1.75%.

1-Phenylallyl Hydroperoxide (67) and N-Carbobenzyloxy-DL-alaninal (122)

The reaction was carried out with 1.3 eq. of **122**
The mixture of isomeric 1,2,4-trioxanes was obtained by column chromatography with CH_2Cl_2 as eluant (R_f 0.14) and rechromatographed with 10% ethyl acetate in chloroform as eluant (R_f 0.49; Yield : 24%). HPLC (Kromasil silica gel, 5μm. 40% ether, 60% hexane) afforded the separate isomers in the ratio of approximately 6 : 3 : 2 **(123e : 123e* : 123a)**

5-Bromomercuriomethyl-3-(1-carbobenzyloxyaminoethyl)-6-phenyl-1,2,4-trioxane (123) *(NC)*

Major isomer **(123e)** :

Yield 6%.

^{1}H nmr : δ 1.21(d, J=7.02Hz, 3H, CH_3); 1.85(dd, J=12.10, 7.45Hz, 1H, CH^AH^BHgBr); 1.93(dd, J=12.10, 6.57Hz, CH^AH^BHgBr); 4.02(m, 1H, CHN); 4.29(m, 1H, CHO); 4.83(d, J=9.08Hz, 1H, CHOO); 4.95(d, J=8.76Hz, 1H, NH : exchanges with D_2O); 5.09(d, J=12.15Hz, 1H, $PhCH^AH^BO$); 5.13(d, J=12.15Hz, 1H, $PhCH^AH^BO$); 5.48(br s, 1H, OCHOO); 7.26-7.46(m, 10H) ppm.

NOE : Saturation of the signal at δ 4.29 ppm causes a 7% enhancement of the peak at δ 5.48 ppm (plus a 5% enhancement of a doublet at δ 7.27 ppm).

^{13}C nmr : δ 15.05(CH_3), 34.51[$^1J(^{13}C-^{199}Hg)$ = 1532Hz], 48.19(CHN), 66.99($PhCH_2O$), 78.16(CO), 89.11[$^1J(^{13}C-^1H)$ = 150.0Hz, COO], 104.12[$^1J(^{13}C-^1H)$ = 172.6Hz, OCOO], 128.20, 128.24, 128.56, 129.55, 130.51, 133.71, 155.59(C=O) ppm.

Crystallised from ether.
White needles, m.p. 136-138°C.

Found : C, 37.67; H, 3.34; N, 2.12%. Calc. for $C_{20}H_{22}BrHgNO_5$: C, 37.72; H, 3.48; N, 2.20%.

Middle isomer (**123e***) :

Yield : 3%.

^{1}H nmr : δ 1.20(d, J=7.02Hz, 3H, CH_3); 1.89(d, J=6.45Hz, 2H, CH_2HgBr); 4.03(m, 1H, CHN); 4.31(m, 1H, CHO); 4.82(d, J=8.99Hz, 1H, CHOO); 4.87(m, 1H, NH); 5.12(s, 2H, $PhCH_2O$); 5.49(br s, 1H, OCHOO); 7.26-7.46(m, 10H) ppm.

NOE : Saturation of the signal at δ 4.31 ppm causes a 6% enhancement of the peak at δ 5.49 ppm (plus a 5% enhancement of a doublet at δ 7.27 ppm).

^{13}C nmr : δ 15.09(CH_3), 34.44(CH_2HgBr), 47.76(CHN), 66.95($PhCH_2O$), 77.93(CO), 89.12[$^1J(^{13}C-^1H)$ = 148.2Hz, COO], 103.81[$^1J(^{13}C-^1H)$ = 171.7Hz, OCOO], 128.19, 128.25, 128.57, 129.56, 130.52, 133.67, 155.64(C=O) ppm.

Crystallised from ether.
White needles. m.p. 134-140°C.

Found : C, 37.67; H, 3.13; N, 2.12%. Calc. for $C_{20}H_{22}BrHgNO_5$: C, 37.72; H, 3.48; N, 2.20%.

Minor isomer (**123a**) :

Yield : 2%.

^1H nmr : δ 1.28(d, J=6.52Hz, 3H, CH_3); 1.70(dd, J=11.83, 4.75Hz, 1H, CH^AH^BHgBr); 1.83(m, 1H, CH^AH^BHgBr); 4.70(m, 1H); 4.78(d, J=8.71Hz, 1H, CHOO); 4.81-4.91(m, 2H); 4.98(m, 1H); 5.17(d, J=12.29Hz, 1H, $PhCH^AH^BO$); 5.24(d, J=12.29Hz, 1H, $PhCH^AH^BO$); 7.28-7.40(m, 10H) ppm.
^{13}C nmr : δ 16.89(CH_3), 34.80(CH_2HgBr), 44.63(CHN), 67.52($PhCH_2O$), 71.37(CO), 89.78[$^1J(^{13}C-^1H)$ = 151.2Hz, COO], 104.61[$^1J(^{13}C-^1H)$ = 164.1Hz, OCOO], 128.21, 128.31, 128.55, 129.09, 130.04, 134.32, 136.31, 156.33(C=O) ppm.

Crystallised from ether / petrol.
White solid. m.p. 59-62°C.
Found : C, 38.40; H, 3.67; N, 1.98%. Calc. for $C_{20}H_{22}BrHgNO_5$: C, 37.72; H, 3.48; N, 2.20%.

*1-Isopropylallyl Hydroperoxide (**93**) and Isobutyraldehyde*

The reaction was carried out using 5 eq. of isobutyraldehyde.

5-Bromomercuriomethyl-3,6-diisopropyl-1,2,4-trioxane (95) (*NC*)

Yield : 44%.
Chromatography afforded two fractions. The first fraction contained only the major isomer of the product, while about 50% of the second fraction was the major isomer, the other 50% being a mixture of the other isomers.

First fraction (**95e**) :

Yield : 16% (oil). R_f 0.63 (CH_2Cl_2).

^{1}H nmr : δ 0.86(d, J=7.14Hz, 3H); 0.92(d, J=6.83Hz, 3H); 0.93(d, J=6.89Hz, 3H); 1.04(d, J=7.05Hz, 3H); 1.77(m, 1H); 1.89(m, 1H); 2.00(dd, J=11.94, 8.73Hz, 1H, CH^AH^BHgBr); 2.22(dd, J=11.94, 4.75Hz, 1H, CH^AH^BHgBr); 3.76(dd, J=8.88, 2.64Hz, 1H, CHOO); 4.07(dt, J=4.75, 8.78Hz, CHO); 4.96(d, J=5.65Hz, 1H, OCHOO) ppm.
NOE : Saturation of the signal at δ 4.96 ppm causes a 5% enhancement of the peak at δ 4.07 ppm.
^{13}C nmr : δ 15.37, 17.06, 17.08, 20.02, 28.33, 30.88, 36.29[$^1J(^{13}C-^{199}Hg)$ = 1540Hz]; 75.07(CO); 90.00[$^1J(^{13}C-^1H)$ = 149.9Hz, COO]; 107.73[$^1J(^{13}C-^1H)$ = 167.8Hz, OCOO] ppm.

Found : C, 25.24; H, 4.21%. Calc. for $C_{10}H_{19}BrHgO_3$: C, 25.68; H, 4.09%.

Second fraction :

Yield : 28%.

The nmr spectra are complex, but the signals due to H-3 and C-3 can be picked out :

^{1}H nmr : δ 4.95(d, J=4.31Hz); 4.96(d, J=5.62Hz); 5.08(d, J=6.21Hz); 5.17(d, J=5.61Hz) ppm.
^{13}C nmr : δ 100.82, 102.12, 107.70, 111.26 ppm.

Found : C, 25.83; H, 4.29%. Calc. for $C_{10}H_{19}BrHgO_3$: C, 25.68; H, 4.09%.

*3-tert-Butylallyl Hydroperoxide (**86**) and Isobutyraldehyde*

The reaction was carried out using 5 eq. of isobutyraldehyde.

Chromatography was unnecessary, the crude product was essentially pure.

***trans*-4-Bromomercurio-3-*tert*-butyl-1,2-dioxolane (92) (*NC*)**

White solid. Yield : 83%.

^{1}H nmr : δ 0.99(s, 9H, CH_3); 2.91(m, 1H, CHHgBr); 4.21 (m, 1H, CH^AH^BOO); 4.24(d, J=8.43Hz, 1H, CH^tBu); 4.43(m, 1H, CH^AH^BOO) ppm.
^{13}C nmr : δ 26.46(CH_3), 34.15($[CH_3]_3C$), 55.81(CHHgBr), 73.41(CH_2OO), 90.24(CH^tBu) ppm.

An analytically pure sample was obtained by crystallisation from CH_2Cl_2 / petrol at -30°C. m.p. : d. 124°C.
Found : C, 20.34; H, 3.06% Calc. for $C_7H_{13}BrHgO_2$: C, 20.52; H, 3.20%

*3-Isopropylallyl Hydroperoxide (**85**) and Isobutyraldehyde*

The reaction was carried out using 5 eq. of isobutyraldehyde.

***trans*-4-Bromomercurio-3-isopropyl-1,2-dioxolane (91) (*NC*)**

R_f 0.25 (CH_2Cl_2). Yield : 63%.

^{1}H nmr : δ 1.01(d, J=7.24Hz, 6H, CH_3); 1.86(m, 1H, $[CH_3]_2CH$); 2.86(approx. q, J_{ave}=8.20Hz, 1H, CHHgBr); 4.24(m, 2H); 4.43(t, J=8.00Hz, 1H) ppm.
^{13}C nmr : δ 19.23(CH_3), 19.73(CH_3), 31.95($[CH_3]_2CH$), 57.79(CHHgBr), 73.32(CH_2OO), 88.11(CH^iPr) ppm.

Analytical sample was crystallised from CH_2Cl_2 / pentane at -30°C.
White solid. m.p. 75-77°C.
Found : C, 17.53; H, 2.72% Calc. for $C_6H_{11}BrHgO_2$: C, 18.21; H, 2.80%

*(E)-2-Methyl-2-buten-1-yl Hydroperoxide (**100**) and Isobutyraldehyde*

The reaction was carried out using 5 eq. of isobutyraldehyde.
The crude product shows three doublets in the ^{1}H nmr at δ 5.24, 5.00 and 5.20 ppm in the ratio 9:2:1 respectively. Column chromatography affords two fractions :

5-(1-Bromomercurioethyl)-3-isopropyl-5-methyl-1,2,4-trioxane (105) *(NC)*

Fraction 1 :

R_f 0.60 (CH_2Cl_2).

This contains a mixture of the major (**105c**) and minor (**105c***) isomers. Yield : 48%.

Crystallisation from CH_2Cl_2 / petrol at -30°C affords a sample of almost pure **105c**.

Major isomer (**105c**) :

^1H nmr : δ 0.91(d, J=7.02Hz, 3H); 0.92(d, J=6.96Hz, 3H); 1.37(d, J=7.79Hz, 3H, $CH_3CHHgBr$); 1.43(d, J=0.96Hz, 3H, CH_3CO); 1.77(m, 1H); 2.81(q, J=7.79Hz, 1H, CHHgBr); 3.81(d, J=12.27Hz, 1H, $CH_{eq}OO$); 4.25(dd, J=12.27, 0.96Hz, 1H, $CH_{ax}OO$); 5.24(d, J=4.49Hz, 1H, OCHOO) ppm.
^{13}C nmr : δ 14.42, 16.73(2C), 20.77, 31.25, 61.06[$^1J(^{13}C-^{199}Hg)$ = 1631Hz]; 74.68(CO); 79.13[$^1J(^{13}C-^1H)$ = 140.7, 149.7Hz, COO]; 102.00[$^1J(^{13}C-^1H)$ = 169.3Hz, OCOO] ppm.

White solid. m.p. 45-52°C.
Found : C, 23.65; H, 3.33%. Calc. for $C_9H_{17}BrHgO_3$: C, 23.82; H, 3.78%.

Fraction 2 :

R_f 0.55 (CH_2Cl_2). Yield : 11%. Essentially pure **105t**.

Middle isomer (**105t**) :

^1H nmr : δ 0.89(d, J=6.73Hz, 3H); 0.90(d, J=6.40Hz, 3H); 1.28(s, 3H, CH_3CO); 1.47(d, J=7.60Hz, 3H, $CH_3CHHgBr$); 1.75(m, 1H); 3.58(q, J=7.60Hz, 1H, CHHgBr); 3.86(d, J=12.84Hz, 1H, CH^AH^BOO); 4.25(d, J=12.84Hz, 1H, CH^AH^BOO); 5.00(d, J=5.62Hz, 1H, OCHOO) ppm.
NOE : Saturation of the signal at δ 5.00 ppm causes an 8% enhancement of the signal at δ 3.58 ppm.
^{13}C nmr : δ 13.94, 16.64, 16.95, 25.75, 31.35, 53.62[$^1J(^{13}C-^{199}Hg)$ = 1543Hz], 73.86(CO), 80.20[$^1J(^{13}C-^1H)$ = 137.9, 151.6Hz, COO],

102.02[$^{1}J(^{13}C-^{1}H)$ = 169.0Hz, OCOO] ppm.

Crystallised from CH_2Cl_2 / petrol at -30°C.
White solid. m.p. 135-138°C.
Found : C, 23.49; H, 3.74%. Calc. for $C_9H_{17}BrHgO_3$: C, 23.82; H, 3.78%.

Modified Procedure for the Synthesis of **5-Bromomercuriomethyl-3,3-dimethyl-6-phenyl-1,2,4-trioxane (75)** (*NC*)

1-Phenylallyl hydroperoxide (**67**) (0.164g; 1.09mmol) was dissolved in acetone (5ml) and cooled in an ice bath. A drop of trifluoroacetic acid was added, and the solution was stirred for 15min. Mercury(II) acetate (0.372g; 1.17mmol) and two drops of 60% perchloric acid were added, and stirring was continued for 30min. Dichloromethane (5ml), water (5ml) and potassium bromide (0.160g; 1.34mmol) were added, and after stirring vigorously for 30min. the organic layer was separated off. The aqueous layer was extracted with dichloromethane (5ml), and the combined organic layers were washed with water (4ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure. Column chromatography (CH_2Cl_2; R_f 0.50) afforded pure **75** as an oil (0.205g; 39%).

^{1}H nmr : δ 1.42(s, 3H); 1.78(s, 3H); 1.84(dd, J=12.01, 6.92Hz, 1H, CH^AH^BHgBr); 1.88(dd, J=12.01, 6.34Hz, 1H, CH^AH^BHgBr); 4.50(m, 1H, CHO); 4.72(d, J=9.49Hz, 1H, CHOO); 7.27-7.42(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 20.96, 26.05, 35.38[$^{1}J(^{13}C-^{199}Hg)$ = 1544Hz], 71.73(CO), 88.85(COO), 103.60(OCOO), 128.20, 129.36, 130.13, 134.56 ppm.

Crystallised from CH_2Cl_2 / petrol at -30°C.
White solid. m.p. 123-125°C.
Found : C, 29.65; H, 3.13%. Calc. for $C_{12}H_{15}BrHgO_3$: C, 29.55; H, 3.10%.

Hydridodemercuration of Organomercury Bromides[44]

A typical procedure was as follows :

The organomercury bromide (0.50mmol) in dichloromethane (8ml) was rapidly added to an ice-cooled, vigorously stirred mixture of sodium borohydride (0.190g; 5.03mmol), 2M sodium hydroxide (2ml) and dichloromethane (4ml) under an argon atmosphere. After stirring for 30min., the mixture was filtered through phase separation paper, and the aqueous layer was washed with further dichloromethane (5ml). The filtrate was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product. Column chromatography (CH_2Cl_2) afforded the pure mercury-free 1,2,4-trioxane.

3,5-Dimethyl-6-phenyl-1,2,4-trioxane (76) (*NC*)

Yield : 54%. Approximately 5:1 mixture of **76e:76a**.

76e :

^1H nmr : δ 1.05(d, J=6.34Hz, 3H, CH_3C^5); 1.35(d, J=5.35Hz, 3H, CH_3C^3); 3.98(dq, J=9.05, 6.34Hz, 1H, CHO); 4.85(d, J=9.05Hz, 1H, CHOO); 5.57(q, J=5.35Hz, 1H, OCHOO); 7.28-7.38(m, 5H, C_6H_5) ppm.
NOE : Saturation of the signal at δ 3.98 ppm causes a 4% enhancement of the peak at δ 5.57 ppm. No effect is observed on the doublet at δ 1.35 ppm.
^{13}C nmr : δ 16.33, 17.96, 74.92(CO), 87.80[$^1J(^{13}C-^1H)$ = 155.2Hz, COO], 101.69[$^1J(^{13}C-^1H)$ = 168.9Hz, OCOO], 128.22, 128.68, 129.39, 134.34 ppm.

76a :

^1H nmr : δ 1.15(d, J=6.34Hz, 3H, CH_3C^5); 1.66(d, J=5.67Hz, 3H, CH_3C^3); 4.34(m, 1H, CHO); 4.81(d, J=7.36Hz, 1H, CHOO) ppm. All other signals are obscured by those from **76e**.
^{13}C nmr : δ 16.69, 17.00, 67.04(CO), 87.32(COO), 98.20[$^1J(^{13}C-^1H)$ = 164.6Hz, OCOO] ppm. Aromatic signals are obscured by **76e**.

Mixture :
Found : C, 67.94; H, 7.59%. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%.

3-Isopropyl-5-methyl-6-phenyl-1,2,4-trioxane (77e) (*NC*)

Yield : 76%. R_f 0.65 (CH_2Cl_2).

^1H nmr : δ 0.99(d, J=7.28Hz, 3H); 1.01(d, J=6.85Hz, 3H); 1.05(d, J=6.40Hz, 3H, CH_3C^5); 1.88(m, 1H); 3.95(m, 1H, CHO); 4.83(d, J=8.98Hz, 1H, CHOO); 5.16(d, J=5.45Hz, 1H, OCHOO); 7.27-7.35(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 16.35, 17.08, 17.14, 31.16, 74.97(CO), 88.03(COO), 108.03(OCOO), 128.20, 128.64, 129.31, 134.54 ppm.

Found : C, 70.45; H, 8.37%. Calc. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%.

3-*sec*-Butyl-5-methyl-6-phenyl-1,2,4-trioxane (78e) (*NC*)

Yield : 67%. R_f 0.68 (CH_2Cl_2).
The product was formed as an approximately 1:1 mixture of isomers due to the exocyclic chiral centre.

^1H nmr : δ [0.92(t, J=7.41Hz) & 0.93(t, J=7.38Hz), 3H, CH_3CH_2); [0.97(d, J=6.86Hz) & 0.98(d, J=6.83Hz), 3H, CH_3CHC^3]; [1.04(d, J=6.33Hz) & 1.05(d, J=6.33Hz), 3H, CH_3C^5]; 1.26(m, 1H); 1.59-1.69(m, 2H); 3.95(m, 1H, CHO); 4.83(d, J=9.05Hz, 1H, CHOO); [5.23(d, J=4.99Hz) & 5.25(d, J=4.84Hz), 1H, OCHOO]; 7.27-7.35(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 11.33, 11.47, 13.56. 13.66, 16.37, 24.25, 37.61, 37.76, 74.96 & 74.99(CO), 88.07(COO), 107.21 & 107.33(OCOO), 128.21, 128.63, 129.30, 134.55 ppm.

Found : C, 71.50; H, 8.76%. Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.

5-Methyl-6-phenyl-3-trichloromethyl-1,2,4-trioxane (79e) (*NC*)

Yield : 27%. R_f 0.71 (CH_2Cl_2).

^1H nmr : δ 1.19(d, J=6.35Hz, 3H, CH_3); 4.25(dq, J=9.30, 6.35Hz, 1H, CHO); 5.00(d, J=9.30Hz, 1H, CHOO); 5.73(s, 1H, OCHOO); 7.29-7.40(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 16.15(CH_3), 76.82(CO), 87.91(COO), 104.99(OCOO), 128.30, 128.94, 129.98, 132.89 ppm +1C.

3,3,5-Trimethyl-6-phenyl-1,2,4-trioxane (80) (*NC*)

Yield : 54%. R_f 0.50 (CH_2Cl_2).

^1H nmr : δ 1.00(d, J=6.26Hz, 3H, CH_3C^5); 1.42(s, 3H, CH_3C^3); 1.78(s, 3H, CH_3C^3); 4.21(dq, J=9.55, 6.26Hz, 1H, CHO); 4.75(d, J=9.55Hz, 1H, CHOO); 7.30-7.37(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 16.78, 20.72, 26.01, 68.64(CO), 87.83(COO), 102.93(OCOO), 128.13, 128.65, 129.27, 134.93 ppm.

Found : C, 69.11; H, 7.59%. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

cis-**5-Ethyl-3-isopropyl-5-methyl-1,2,4-trioxane (107)** (*NC*)

A mixture of the major and minor isomers of the organomercury bromide (**105c** and **105c***) was used (see synthesis above, fraction 1), but only one isomer was observed in the product.

Yield : 47%. R_f 0.65 (CH_2Cl_2).

^1H nmr : δ 0.89-0.93(m, 9H, 3x CH_3); 1.30(s, 3H, CH_3C^5); 1.47(m, 2H); 1.72(m, 1H); 3.60(d, J=12.23Hz, 1H, $CH_{eq}OO$); 4.15(dd, J=12.23, 0.93Hz, 1H, $CH_{ax}OO$); 5.15(d, J=5.33Hz, 1H, OCHOO) ppm.
NOE : Saturation of the signal at δ 1.30 ppm causes enhancement of the signals at δ 5.15(4%) and 3.60(2%) ppm.
^{13}C nmr : δ 6.73, 16.82, 16.87, 18.38, 31.34, 31.99, 71.30(CO),

78.32(COO), 102.11(OCOO) ppm.

Found : C, 61.69; H, 10.45%. Calc. for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.

Bis[(3-*sec*-butyl-6-phenyl-1,2,4-trioxan-5-yl)methyl]mercury (83 and 84) (*NC*)

1-Phenylallyl hydroperoxide (**67**) (0.148g; 0.99mmol) and 2-methylbutyraldehyde (0.176g; 2.04mmol) were stirred in dichloromethane (10ml) with a drop of trifluoroacetic acid for 30min. Mercury(II) acetate (0.338g; 1.06mmol) and two drops of 60% perchloric acid were added, and stirring was continued for 2h. The solution was cooled in ice, and 2M sodium hydroxide (1ml) was slowly added under nitrogen, followed by a solution of sodium borohydride (0.362g; 9.5mmol) in 2M sodium hydroxide (5ml). After stirring for a further hour, the mixture was filtered through phase separation paper, and the aqueous layer was washed with further dichloromethane. After drying the filtrate over $MgSO_4$, the solvent was removed under reduced pressure. Column chromatography (CH_2Cl_2; R_f 0.48) afforded the dialkylmercury compounds as a colourless oil (0.093g; 28%).

^{1}H nmr : δ 0.52-0.58(m, 1H, CH^AH^BHg); 0.68-0.72(m, 1H, CH^AH^BHg); [0.92(t, J=7.41Hz) & 0.92(t, J=7.28Hz) & 0.96(d, J=6.89Hz) & 0.97(d, J=6.45Hz), 6H, 2x CH_3]; 1.25(m, 1H); 1.57-1.66(m, 2H); 3.98(m, 1H, CHO); 4.64(d, J=8.93Hz, 1H, CHOO), [5.19(d, J=5.40Hz) & 5.20(d, J=5.05Hz), 1H, OCHOO]; 7.21-7.34(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 11.31, 11.47, 13.64, 13.78, 24.31, 24.35, 37.57, 37.69, [39.76, 39.80, 39.85(CH_2Hg)], [80.60, 80.67(CO)], 89.64(COO), [107.23, 107.37(OCOO)], 128.48, 129.00, 129.48, 135.32 ppm.

Crystallised from CH_2Cl_2 / petrol at -30°C.
White solid, most of which melts in the range 84-94°C.
Found : C, 50.20; H, 5.54%. Calc. for $C_{28}H_{38}HgO_6$: C, 50.11; H, 5.71%.

Bis[(3-isopropyl-6-phenyl-1,2,4-trioxan-5-yl)methyl]mercury (81 and 82) (*NC*)

These were prepared as for **83** and **84**, but using isobutyraldehyde (2.5 eq.) as the carbonyl component.

Yield : 30%. R_f 0.48 (CH_2Cl_2).
Crystallised from petrol.
White solid. m.p. 138°C.

^1H nmr : δ 0.54(dd, J=12.64, 9.39Hz, 1H, CH^AH^BHg); [0.70(dd, J=12.64, 5.34Hz) & 0.71(dd, J=12.64, 5.31Hz), 1H, CH^AH^BHg]; 0.97(d, J=6.59Hz, 3H); 0.99(d, J=6.39Hz, 3H); 1.85(m, 1H); 3.98(m, 1H, CHO); 4.63(d, J=8.42Hz, 1H, CHOO); 5.10(d, J=5.62Hz, 1H, OCHOO); 7.21-7.33(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 17.16, 17.29, 31.15, [39.79, 39.83(CH_2Hg)], 80.65(CO), 89.63(COO), 108.09(OCOO), 128.50, 129.02, 129.51, 135.32 ppm.
^{199}Hg nmr : (71.5MHz, $CDCl_3$, δ [Ph_2Hg] = -745 ppm) : δ -364 ppm.

Found : C, 48.40; H, 5.56%. Calc. for $C_{26}H_{34}HgO_6$: C, 47.81; H, 5.25%.

Reaction of **81** and **82** with Hydrobromic Acid

A 1% w/v solution of hydrobromic acid was prepared by diluting a 45% w/v solution of hydrogen bromide in acetic acid with 44 times its volume of water.

The mixture of dialkylmercury compounds **81** and **82** (92mg; 0.143mmol) was dissolved in tetrahydrofuran (5ml) and 1% hydrobromic acid (1.15ml; 0.143mmol HBr) was added. After stirring for 24h, saturated sodium bicarbonate solution (10ml) was added, and the mixture was extracted with dichloromethane (2x10ml). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a viscous oil (63mg).

^{13}C nmr :

Essentially three compounds are visible; unreacted **81/82**, the

corresponding organomercury bromide (**72e**) and 1-phenylallyl hydroperoxide (**67**), in the ratio 1:1:0.5 respectively.

Assigned to **81** and **82** : δ 17.01, 17.25, 31.10, 39.71, 39.74, 80.61, 89.57, 108.04, 135.26 ppm.
Assigned to **72e** : δ 17.09, 31.01, 34.95, 77.71, 88.95, 108.04, 130.08, 134.14 ppm.
Assigned to **67** : δ 88.61, 119.33, 127.45, 135.55, 138.41 ppm.
The aromatic signals in the region δ 128-130 ppm are too complex to assign.

cis-5-(1-Bromoethyl)-3-isopropyl-5-methyl-1,2,4-trioxane (108) (*NC*)

Organomercurial **105c** (containing *ca.* 10mol% **105c***) (0.237g; 0.52mmol) was dissolved in pyridine (13ml) and magnetically stirred. A solution of bromine (0.125g; 0.78mmol) in pyridine (3ml) was added dropwise, and stirring was continued, in subdued light, for 20h. Ether (150ml) was then added, and the mixture was washed with 10% hydrochloric acid (2x50ml). The aqueous layers were extracted with further ether (50ml), and the combined organic layers were then washed with 10% hydrochloric acid (25ml) and saturated sodium bicarbonate solution (25ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure. Column chromatography (CH_2Cl_2 : petrol 40/60°C, 1 : 1) afforded two fractions, the first containing pure **108** (37%) and the second containing a 2.5:1 mixture of **108** and the bromide derived from **105c*** respectively (28%).

Total yield : 65%.

108 :

R_f 0.54 (CH_2Cl_2 : petrol, 1 : 1); 0.71 (CH_2Cl_2).

^1H nmr : δ 0.89(d, J=6.90Hz, 3H); 0.90(d, J=6.93Hz, 3H); 1.43(d, J=0.97Hz, 3H, CH_3C^5); 1.69(d, J=6.80Hz, 3H, CH_3CHBr); 1.73(m, 1H); 3.95(q, J=6.80Hz, 1H, CHBr); 3.99(d, J=12.47Hz, 1H, $CH_{eq}OO$); 4.07(dd, J=12.47, 0.97Hz, 1H, $CH_{ax}OO$); 5.08(d, J=5.46Hz, 1H, OCHOO) ppm.

^{13}C nmr : δ 13.30, 16.67, 16.98, 19.23, 31.12, 52.93(CHBr), 72.73(CO), 78.83(COO), 102.31(OCOO) ppm.

Found : C, 43.12; H, 7.04%. Calc. for $C_9H_{17}BrO_3$: C, 42.70; H, 6.77%.

trans-5-(1-Bromoethyl)-3-isopropyl-5-methyl-1,2,4-trioxane (109) (*NC*)

This was prepared by the same method used to synthesise **108**, but starting from **105t**.

Yield : 25%. R_f 0.52 (CH_2Cl_2 : petrol, 1 : 1).

^1H nmr : δ 0.90(d, J=6.89Hz, 3H); 0.91(d, J=6.90Hz, 3H); 1.27(s, 3H, CH_3C^5); 1.69(d, J=6.92Hz, 3H, CH_3CHBr); 1.73(m, 1H); 4.13(d, J=12.99Hz, 1H, CH^AH^BOO); 4.45(d, J=12.99Hz, 1H, CH^AH^BOO); 4.88(q, J=6.92Hz, 1H, CHBr); 5.03(d, J=5.46Hz, 1H, OCHOO) ppm.
^{13}C nmr : δ 16.57, 16.89, 18.47, 18.81, 31.31, 47.26(CHBr), 73.44(CO), 76.45(COO), 101.87(OCOO) ppm.

Found : C, 42.56; H, 6.82%. Calc. for $C_9H_{17}BrO_3$: C, 42.70; H, 6.77%.

Reduction of 3,5-Dimethyl-6-phenyl-1,2,4-trioxane (76)

Zinc powder (0.338g; 5.2mmol) was added in one portion to a solution of 3,5-dimethyl-6-phenyl-1,2,4-trioxane (**76e:76a** = 5:1) (45.4mg; 0.234mmol) in acetic acid (0.50ml; 8.7mmol) and ether (3ml). The mixture was magnetically stirred until the reaction was complete, as judged by TLC (1.5h). The zinc was removed by filtration through Celite, and washed with further ether (10ml). The filtrate was washed with saturated sodium bicarbonate solution (2x5ml), dried over K_2CO_3, and the solvent was removed under reduced pressure to yield a colourless oil. On exposure to high vacuum, the oil slowly crystallised to afford a single isomer of 1-phenylpropan-1,2-diol as a white crystalline solid (23.2mg; 65%).

***threo*-1-Phenylpropan-1,2-diol (124)**

m.p. 47-51°C (Lit.[95] : 51-53°C). [cf. erythro[95] : m.p. 89-91°C].

^{1}H nmr : δ 1.03(d, J=6.35Hz, 3H); 2.6-2.9(br s, 2H); 3.83(dq, J=7.45, 6.35Hz, 1H); 4.34(d, J=7.45Hz, 1H); 7.32(m, 5H) ppm.
Lit.[95] values for the CHPh signal :
threo : δ 4.29(d, J=7.5Hz) ppm.
erythro : δ 4.62(d, J=4Hz) ppm.

^{13}C nmr : δ 18.74, 72.21, 79.48, 126.83, 128.12, 128.49, 141.03 ppm.

4.3.4 Syntheses of α-Amino Aldehydes and Miscellaneous Experimental

N,N-Dibenzyl-DL-α-alanine Benzyl Ester (112)

DL-α-Alanine (0.89g; 10mmol), potassium carbonate (2.07g; 15mmol) and sodium hydroxide (0.44g; 11mmol) were dissolved in ethanol (10ml) and water (10ml). The solution was heated to reflux, and benzyl bromide (5.47g; 32mmol) was added dropwise. After refluxing for a further hour, the solution was allowed to cool, water (30ml) was added, and the mixture was extracted with dichloromethane (3x25ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure. Column chromatography (CH_2Cl_2; R_f 0.63) afforded the pure ester as a viscous liquid (2.59g; 72%).

^1H nmr : δ 1.37(d, J=7.13Hz, 3H); 3.58(q, J=7.13Hz, 1H); 3.65(d, J=13.96Hz, 2H); 3.85(d, J=13.96Hz, 2H); 5.17(d, J=12.36Hz, 1H); 5.25(d, J=12.36Hz, 1H); 7.22-7.43(m, 15H) ppm.
^{13}C nmr : δ 14.92, 54.38, 56.18, 56.98, 126.88, 128.18, 128.21, 128.26, 128.53, 128.60, 136.10, 139.77, 173.49 ppm.

N,N,-Dibenzyl-DL-α-alaninol (113)

Lithium aluminium hydride (0.091g; 2.4mmol) was suspended in dry ether (10ml) in a round bottomed flask equipped with dropping funnel, mechanical stirrer and reflux condenser. All outlets were protected with calcium chloride guard tubes. *N,N*-Dibenzyl- DL-α-alanine benzyl ester (**112**) (1.08g; 3mmol) in dry ether (10ml) was added at such a rate as to maintain a gentle reflux. The mixture was stirred for 10min. after the completion of the addition, and the flask was cooled in ice while the excess hydride was decomposed by the careful addition of water (CAUTION!). When all the precipitate had turned white, 10% sodium hydroxide solution (10ml) was added slowly, and the mixture was stirred for a further hour. The ether layer was then separated off, and the aqueous layer was extracted with further ether (4x15ml). The combined organic extracts were washed with water and concentrated to *ca.* 10ml. This solution was then extracted with 10%

hydrochloric acid (10ml), and the extracts were made basic by the addition of solid potassium carbonate. The resultant cloudy solution was extracted with ether (2x10ml). The organic extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield a white crystalline solid (0.51g; 66%). m.p. 53-57°C.

^1H nmr : δ 0.97(d, J=6.70Hz, 3H); 2.98(m, 1H); 3.10(br s, 1H); 3.32(dd, J=10.45, 5.12Hz, 1H); 3.35(d, J=13.44Hz, 2H); 3.45(t, J=10.45Hz, 1H); 3.81(d, J=13.44Hz, 2H); 7.21-7.36(m, 10H) ppm.
^{13}C nmr : δ 8.62, 52.87, 54.14, 62.27, 127.15, 128.42, 128.92, 139.22 ppm.

The ^1H and ^{13}C nmr spectra agree with literature values.[109]

N-Carbobenzyloxy-DL-α-alaninol (121) (*NC*)

1.2M Borane-tetrahydrofuran complex (20ml; 24mmol BH_3) was placed in a round bottomed flask equipped with dropping funnel, nitrogen inlet and magnetic stirrer. The flask was cooled in ice, and *N*-carbobenzyloxy-DL-α-alanine (2.23g; 10mmol) in tetrahydrofuran (20ml) was added over a period of 30min. The solution was stirred for a further 2h at 0°C, and then quenched by the addition of a 10% solution of acetic acid in tetrahydrofuran (10ml). The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (15ml). The solution was washed successively with 1M hydrochloric acid (10ml), water (5ml), 1M potassium carbonate solution (10ml) and brine (5ml), then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the alcohol as a white crystalline solid (1.74g; 83%). m.p. 45-52°C.

^1H nmr : δ 1.10(d, J=6.89Hz, 3H, CH_3); 3.16(br s, 1H, OH); 3.44(dd, J=10.99, 5.87Hz, 1H, CH^AH^BOH); 3.57(dd, J=10.99, 3.90Hz, 1H, CH^AH^BOH); 3.77(m, 1H, CHN); 5.05(s, 2H, $PhCH_2O$); 5.20(br s, 1H, NH); 7.31(m, 5H, C_6H_5) ppm.
^{13}C nmr : δ 17.11(CH_3), 48.81(CHN), 66.36, 66.68, 127.97, 128.03, 128.38, 128.41, 136.28, 156.52(C=O) ppm.

Found : C, 62.74; H, 7.36; N, 6.84%. Calc. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%.

N,N,-Dibenzyl-DL-α-alaninal (114)[83]

Oxalyl chloride (1.00ml; 11mmol) was dissolved in dry dichloromethane (25ml) in a 100ml 3-necked round bottomed flask equipped with dropping funnel, magnetic stirrer and low temperature thermometer. The flask was cooled to -50°C, and dimethyl sulphoxide (1.50ml; 22mmol) was added over 5min. After a further 10min., *N,N*-dibenzyl-DL-α-alaninol **(113)** (2.55g; 10mmol) in dichloromethane (10ml) was added over 5min. The solution was then stirred for 15min., maintaining the temperature at -50°C. Triethylamine (7.00ml; 50mmol) was then added over 5min., again keeping the temperature at around -50°C. The mixture was allowed to warm to room temperature, then water (30ml) was added. The mixture was stirred for a further 10min. and the organic layer was separated off. The aqueous layer was extracted with dichloromethane (10ml), and the combined extracts were dried over $MgSO_4$. Finally, the solvent was removed under reduced pressure (10mmHg then 0.01mmHg) to give the crude aldehyde as a yellow oil (2.50g; 99%). The aldehyde was used without further purification.

^1H nmr (200MHz) : δ 1.19(d, J=6.84Hz, 3H); 3.34(q, J=6.84Hz, 1H); 3.57(d, J=13.53Hz, 2H); 3.75(d, J=13.53Hz, 2H); 7.25-7.45(m, 10H); 9.75(s, 1H) ppm.
^{13}C nmr : δ 6.76, 54.89, 62.82, 127.28, 128.37, 128.72, 138.96, 204.33 ppm.

N-Carbobenzyloxy-DL-α-alaninal (122)[110]

This was synthesised by the oxidation of *N*-Cbz-DL-α-alaninol **(121)** as per the above method for **114**, except that the temperature of the solution was raised to -10°C for the addition of the alcohol and the triethylamine.

Yield : 53%.

^{1}H nmr : δ 1.32(d, J=7.52Hz, 3H); 4.26(m, 1H); 5.09(s, 2H); 5.51(br s, 1H); 7.33(m, 5H); 9.51(s, 1H) ppm.
^{13}C nmr : δ 14.65, 55.79, 66.95, 128.04, 128.16, 128.47, 136.05, 155.79, 199.10 ppm.

The Reaction of 1-Phenylallyl Hydroperoxide (**67**) with *N,N*-Dibenzyl-DL-α-alaninal (**114**)

Aldehyde **114** (0.208g; 0.82mmol) in dichloromethane (3ml) was added dropwise to a magnetically stirred solution of 1-phenylallyl hydroperoxide (**67**) (0.123g; 0.82mmol) in dichloromethane (5ml) which was cooled in ice. A drop of trifluoroacetic acid was added, and the solution was stirred at room temperature for 3h. The solvent was then removed under reduced pressure to yield a yellow oil, which was separated by column chromatography (5% ethyl acetate in CH_2Cl_2).

Two identifiable fractions were isolated :

1-Phenylallyl Alcohol (115)

Yield : 0.087g (80%). R_f 0.38.

^{1}H nmr : δ 2.52(br s, 1H); 5.17(m, 2H); 5.33(dt, J=17.13, 1.43Hz, 1H); 6.04(ddd, J=17.13, 10.20, 5.99Hz, 1H); 7.37(m, 5H) ppm.
^{13}C nmr : δ 75.13, 114.92, 126.24, 127.56, 128.40, 128.82, 140.16, 142.53 ppm.

N,N-Dibenzylformamide (119)[90]

Yield : 0.045g (24%). R_f 0.24

^{1}H nmr : δ 4.24(s, 2H); 4.40(s, 2H); 7.14-7.38(m, 10H); 8.40(s, 1H) ppm.
^{13}C nmr : δ 44.58, 50.18, 127.59, 127.63, 128.07, 128.44, 128.62, 128.84, 135.53, 135.91, 162.79 ppm.

Reduction of *N,N*-Dibenzylformamide (**119**)

N,N-Dibenzyl formamide (**119**) (0.045g; 0.22mmol) in dry ether (2ml) was added dropwise *via* a syringe to a magnetically stirred suspension of lithium aluminium hydride (0.017g; 0.45mmol) in dry ether (2ml) in a flask equipped with a reflux condenser and a septum. On completion of the addition the solution was refluxed for a further 20min. It was then cooled in ice, and excess hydride was destroyed by the careful addition of water (CAUTION!). After stirring at room temperature for 15min., 20% potassium sodium tartrate solution (2ml) was added, followed by 10% sodium hydroxide solution (1ml). The ether layer was separated off, dried over K_2CO_3, and the solvent was removed under reduced pressure to give a colourless liquid (0.024g). Comparison of the ^1H and ^{13}C nmr spectra with literature values,[89] confirmed the identity of the product as :

N-Methyl Dibenzylamine (118)

^1H nmr : δ 2.18(s, 3H); 3.52(s, 4H); 7.26-7.37(m, 10H) ppm.
^{13}C nmr : δ 42.22, 61.84, 126.90, 128.19, 128.92, 139.26 ppm.

The Reaction of *tert*-Butyl Hydroperoxide with *N,N*-Dibenzyl-DL-alaninal (**114**)

Aldehyde **114** (0.269g; 1.06mmol) in dichloromethane (5ml) was added to an ice-cooled solution of a 3.1M solution of *tert*-butyl hydroperoxide in toluene (0.35ml; 1.09mmol ^tBuOOH) in dichloromethane (5ml). After warming to room temperature and stirring the mixture for 1h, the solvent was removed under reduced pressure to yield 0.408g of crude material.

The ^{13}C nmr spectrum of this material confirmed that *N,N*-dibenzylformamide (**119**) was a major product, with signals at δ 44.65 and 50.32 ppm.

NMR Investigation of the Equilibrium Between an Allylic Hydroperoxide, an Aldehyde and a Hemiperoxyacetal

a) Cinnamyl Hydroperoxide and Isobutyraldehyde

A solution was prepared containing cinnamyl hydroperoxide (**61**) (0.0215g; 0.143mmol) and isobutyraldehyde (0.0101g; 0.140mmol) in CD_2Cl_2 (0.7ml). The ^1H nmr spectrum was recorded after 4h at room temperature. Selected integrals were as follows :

δ 1.79 ppm [$(CH_3)_2CHCH(OH)OOR$: **68b**] : 19mm.
δ 2.41 ppm [$(CH_3)_2CHCH=O$] : 9mm.
δ 8.50 ppm [ROOH : **61**] : 6mm.

R = $PhCH=CH_2$

∴ The hydroperoxide exists in the form of its hemiperoxyacetal to the extent of 19/(19+6) = 75%.

b) 1-Phenylallyl Hydroperoxide and Isobutyraldehyde

A solution was prepared containing 1-phenylallyl hydroperoxide (**67**) (0.0219g; 0.146mmol) and isobutyraldehyde (0.0098g; 0.136mmol) in CD_2Cl_2 (0.7ml). After 4h at room temperature, the ^1H nmr spectrum was recorded, and selected integrals were as follows :

δ 1.72 ppm [$(CH_3)_2CHCH(OH)OOR$: **69b**] : 26mm.
δ 2.41 ppm [$(CH_3)_2CHCH=O$] : 9mm.
δ 8.27 ppm [ROOH : **67**] : 9mm.

R = $PhCH(CH=CH_2)$

∴ The hydroperoxide exists in the form of its hemiperoxyacetal to the extent of 26/(26+9) = 75%.

After a further 4 days at room temperature the ^1H nmr spectrum was re-recorded. There were no significant changes from the original spectrum.

Biological Testing

trans-3,3,5-Trimethyl-6-phenyl-1,2,4-trioxane (**80**) was tested for *in vitro* anti-malarial activity. The parasite used was *P. falciparum*, a chloroquine resistant K1 strain (IC_{50} for chloroquine : 1.645×10^{-7} moldm^{-3}). The top concentration employed was 50μg/ml.

IC_{50} : 0.001279 μg/ml ≡ 6.14×10^{-9} moldm^{-3}.

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APPENDIX A

GENERAL EXPERIMENTAL

NMR Spectroscopy

Unless otherwise indicated, all nmr spectra were recorded at 400 MHz (^{1}H) or 100 MHz (^{13}C) as solutions in $CDCl_3$ and referenced to $CHCl_3$ (δ 7.24 ppm for ^{1}H, δ 77 ppm for ^{13}C) using a Varian VXR400 spectrometer. 200 MHz ^{1}H (50 MHz ^{13}C) nmr spectra were similarly recorded on a Varian XL200 spectrometer, and 60 MHz spectra on a Jeol PMX60 spectrometer

IR Spectroscopy

Infra-red spectra were recorded as thin films between sodium chloride plates using a Perkin Elmer 983 spectrometer.

Mass Spectrometry

Mass spectra were recorded on a VG ZAB-2F mass spectrometer. Unless otherwise indicated, all spectra were recorded using a 70eV electron impact (EI) ionisation current.

Reagents

Diethyl ether and benzene were dried over sodium wire. Dichloromethane and tetrahydrofuran were dried by distillation from calcium hydride. Carbon tetrachloride was dried over 4Å molecular sieves.

All reagents for which syntheses are not given were available from commercial sources. 85% Hydrogen peroxide was a gift from Interox Chemicals Ltd.

Chromatography

Column chromatography was performed on silica gel 60 (70-230 mesh, 'Merck 7734'). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminium backed plates ('Merck 5554'). For general work, the plates were visualised using an acidic solution of *p*-anisaldehyde in ethanol. To test for peroxides, an acidic solution of iron(II) thiocyanate was used[1] - peroxides gave a blood red spot. Organomercurials were visualised using a 0.2% solution of dithizone in chloroform, a yellow spot indicated a positive test.

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APPENDIX B

LIST OF ABBREVIATIONS

ADH	Asymmetric dihydroxylation
BHT	Butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol)
Cbz	Carbobenzyloxy ($PhCH_2OC[=O]$)
m-CPBA	*meta*-Chloroperoxybenzoic acid
DBPO	Di-*tert*-butylperoxyoxalate
DCA	9,10-Dicyanoanthracene
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
FAB	Fast atom bombardment
ISC	Inter-system crossing
*N*BS	*N*-Bromosuccinimide
NC	New compound
*N*IS	*N*-Iodosuccinimide
NOE	Nuclear Overhauser effect
PCC	Pyridinium chlorochromate
PMHS	Polymethylhydrosiloxane
py	Pyridine
TBDMS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TMBH	*N*'-Tosyl-2-methyl-3-butenohydrazide
TPP	5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine