THE SYNTHESIS AND REACTIONS OF SOME POTENTIALLY ANTIMALARIAL 1,2,4-TRIOXANES

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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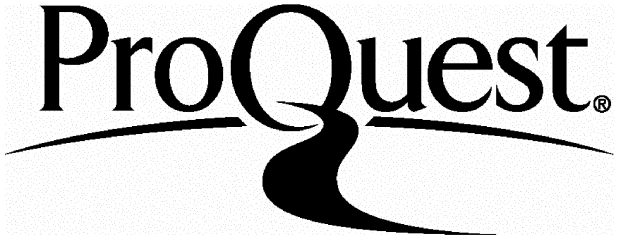

For my mother and sisters Hina, Subi and Asma
with love.

The thing has already taken
form in my mind before I start it.

The first attempts are
absolutely unbearable.

I say this because I want you
to know that if you see something
worthwhile in what I am doing,
it is not by accident but because
of real direction and purpose.

Vincent Van Gogh

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr A.J. Bloodworth for all his help and advice during my studies and the SERC for providing financial assistance.

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CONTENTS

Chapter 1: Introduction

Chapter 2: Aldehyde-derived 1,2,4-trioxanes synthesised *via* an Intramolecular Oxymercuriation route

Chapter 3: The synthesis of some tetra- and hexa-alkyl-1,2,4-trioxanes and dynamic NMR studies of their conformational mobility

Chapter 4: A Halogenocyclisation route to 1,2,4-trioxanes

Chapter 5: A silver-salt-assisted cyclisation to 1,2,4-trioxanes

Chapter 6: Some reactions of 1,2,4-trioxanes: Photolysis and Reaction with iron(II) sulfate

Published papers

ABSTRACT

A series of potentially antimalarial 1,2,4-trioxanes were prepared by the electrophile-mediated cyclisation of allylic hemiperoxyacetals. The starting allylic hemiperoxyacetals were obtained by the addition of allylic hydroperoxides to aldehydes and ketones. Studies were carried out on the effects upon 1,2,4-trioxane yields of varying the starting aldehydes, ketones, hydroperoxides and electrophiles.

Generally 1,2,4-trioxanes derived from aldehydes (CHO) were isolated in higher yields than those derived from ketones (R_1COR_2). In addition aliphatic aldehydes gave higher yields than aromatic aldehydes. Ketone-derived 1,2,4-trioxanes in which $R_1=R_2$ were not conformationally locked. The ring inversion barriers for these compounds were determined from dynamic nmr studies of their conformational mobility.

Different electrophiles were used to effect the cyclisation step. Mercury(II) acetate, mercury(II) trifluoroacetate, N-iodosuccinimide and N-bromosuccinimide were all used. In general the intramolecular oxymercuriations proved to be much more versatile and gave higher yields than the halogenocyclisations.

The starting allylic hydroperoxides were obtained by singlet oxygenation of the appropriate alkene. The two allylic hydroperoxide systems studied were 2,3-dimethylbutyl-1-en-3-yl hydroperoxide and cyclohex-2-enyl hydroperoxide. The 2,3-dimethylbutyl-1-en-3-yl hydroperoxide system was the more versatile of the two and gave the highest 1,2,4-trioxane yields *via* both the intramolecular oxymercuriation and halogenocyclisation routes. The cyclohex-2-enyl hydroperoxide-derived hemiperoxyacetal only yielded bicyclic 1,2,4-trioxanes *via* mercury(II) trifluoroacetate-mediated ring closure.

A silver-salt-assisted substitution method for the synthesis of 1,2,4-trioxanes was also attempted. Halogen-containing hemiperoxyacetals derived from the reaction of β-halohydroperoxides and aldehydes, were treated with silver(I) salts with limited success.

The 1,2,4-trioxanes were subjected to photolysis and to treatment with iron(II) sulfate. In both cases preference for rearrangement *via* 1,5-transfer of a hydrogen from C-3 to an oxygen centred radical was observed.

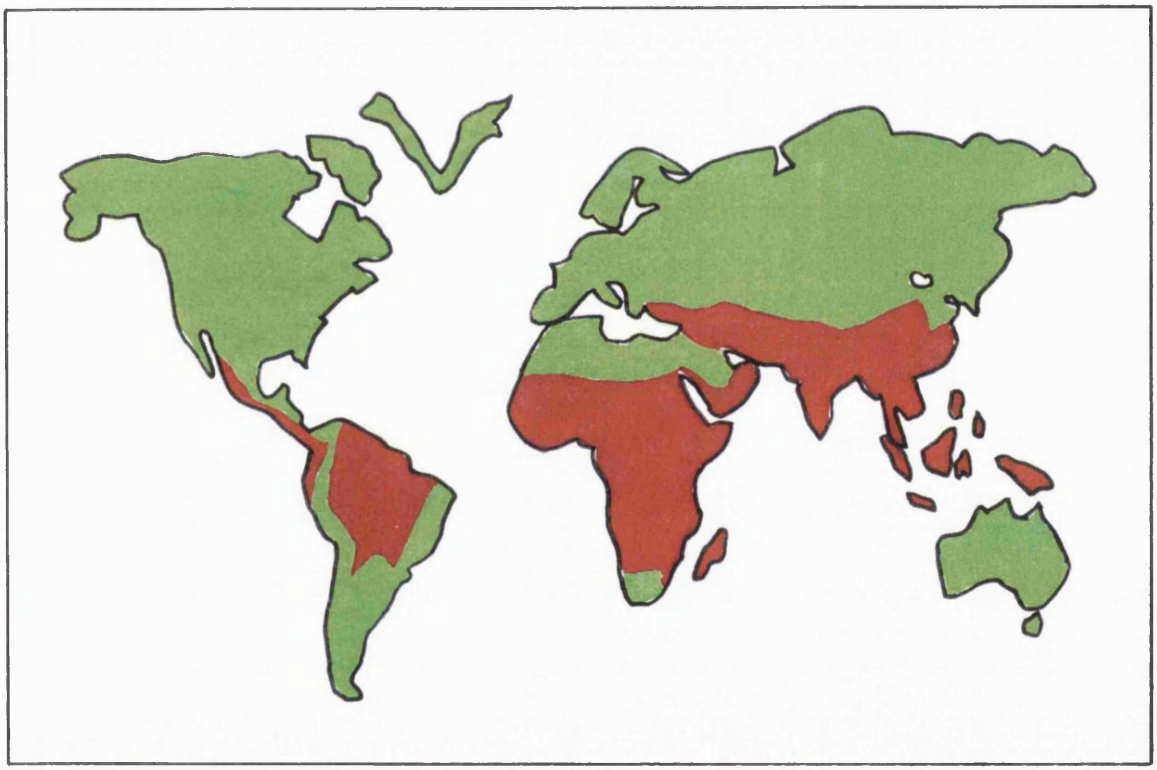
Some 1,2,4-trioxane compounds were tested for antimalarial activity *in vitro* and were found to be significantly active.

INTRODUCTION

1.1 Malaria

Malaria affects the lives of nearly one half of the world's population. The disease is endemic in nearly 100 countries, where there are between 250-500 million cases reported every year, with an estimated mortality of 1-2.5 million mainly among children[1].

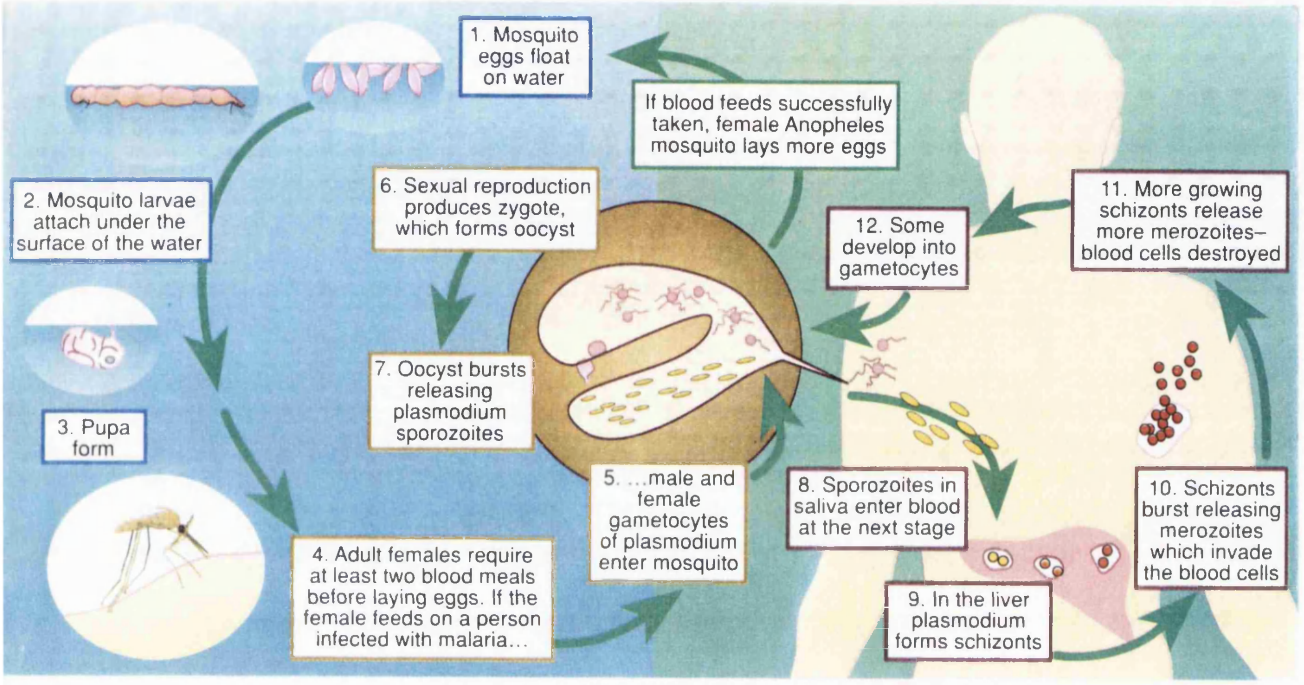
Malaria on the map



regions where people are at risk from malaria

The malarial infection is caused by four species of protozoan parasites which live in mosquitoes. The most common form is the *Plasmodium vivax* species, but the most dangerous infection results from *Plasmodium falciparum* . This species causes parasitized red blood cells to block capillaries in various deep organs such as the brain, frequently resulting in death.

The life cycle of the malaria parasite



The life cycle of the parasite is very complicated as it involves both humans and mosquitoes. However, there are several stages where the parasite may be attacked. The most obvious way to kill the parasite is by attacking its host, the mosquito. Traditionally malaria was controlled by the use of insecticides which destroyed the adult mosquitoes or their larvae. Unfortunately, mosquitoes in all parts of the world have now acquired resistance to most major pesticides as a result of their widespread usage. The parasite enters a persons body from the bite of an infected female mosquito which needs a blood meal before laying her eggs. At this stage in the cycle it is in the sporozoite form. Once in the body the sporozoites travel to the liver, where they mature into schizonts which contain up to 30,000 'daughter' organisms called merozoites. After a few days in the liver the schizonts burst releasing the merozoites which go on to invade the bloodstream, destroying the red blood cells and causing the characteristic symptoms of anaemia, chills and fever in the sufferer. Some of the merozoites go on to develop into the gametocyte sexual stages so that the next time a female mosquito bites an infected human being, she takes in male and female gametocytes as part of her meal. The gametocytes can then mate in her gut to form zygotes. The zygotes mature into ookinetes, which invade the gut wall and ripen into oocytes. The oocytes then produce

thousands of new sporozoites ready for the next bite[2].

1.2 Obstacles to the development of a vaccine

Vaccines work by 'priming' the immune system, so that when our bodies meet the living infective disease organism, they already have the tools to deal with it. There are many obstacles to the development of a vaccine against malaria. A major problem is that the parasite lives through several different stages, each of which look different to the immune system. Another difficulty is that the proteins on the surface of the parasite change readily in response to selection pressure from the immune system. A vaccine that puts the parasite under severe pressure might hasten the selection of new mutants. The three main approaches to the development of a vaccine are as follows.

i. Blocking the parasite as it enters the human bloodstream in its sporozoite form.

ii. Blocking the parasite after it has emerged from its initial incubation in the liver, in the merozoite form.

iii. Development of an 'altruistic' vaccine that would block transmission by immunising against the parasite during its sexually reproductive stage in the mosquito.

An antisporozoite vaccine should theoretically prevent the development of mature parasites and also block transmission but it could not protect from merozoites, for example in donated blood. Blocking the parasite's next development stage, the merozoite would not prevent infection completely but would limit it, making disease unlikely[2]. The third line of approach to develop a vaccine against the sexual stages of the parasite has problems as these stages are not susceptible to immune attack in the red blood cells. They may however be attacked in the mosquito's gut by antibodies. A viable vaccine would realistically have to contain a 'cocktail' of antigens, each designed to achieve a particular end, including the inactivation of the sporozoites, the destruction of the liver stages, the prevention of invasion of red blood cells and the prevention of transmission.

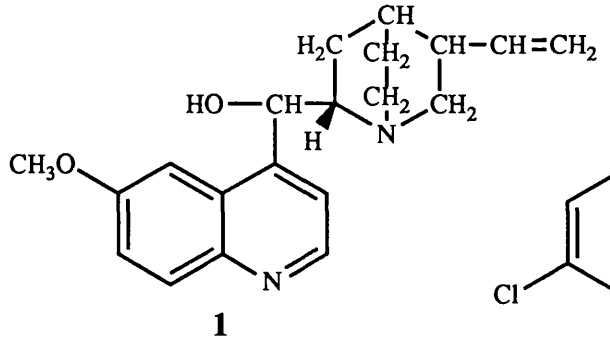
The Columbian biochemist Manuel Patarroyo, has developed a synthetic peptide vaccine based on one sporozoite protein segment and three segments from the merozoite protein. Although the vaccine appears to be safe and is claimed to be

effective, early trials lacked controls so further information is needed before it can be put to general use[2].

As well as biological obstacles, a vaccine against malaria would have to solve the more general problems of cost and distribution, so the development of new drugs against the disease is particularly important.

1.3 The quinoline and antimetabolite drugs

The prevention and cure of malaria is effected by a relatively limited number of drugs. The most important remedies are derivatives of quinoline. The first recorded antimalarial compound was extracted from the bark of the Cinchona tree in Peru. Jesuit missionaries first brought word of this treatment for malaria and fevers to Europe in the sixteenth century. The antimalarial component isolated from this bark was quinine (**1**). Many drugs based on this quinoline structure have been synthesized since. The best known is perhaps chloroquine (**2**) which was developed in 1934 and was until recently the main treatment for malaria[3]. Well known antimetabolites with antimalarial properties are the biguanidine compound proguanil (**3**) and the pyrimidine derivative pyrimethamine (**4**).



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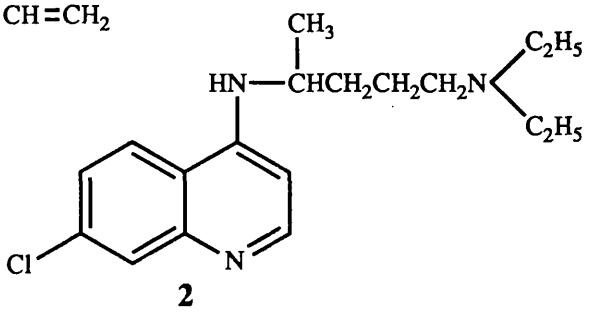

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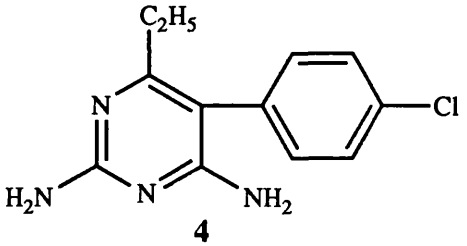

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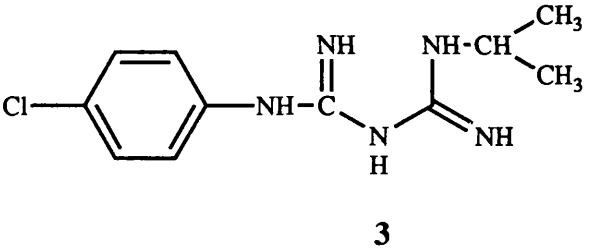


3

The complexity of the malaria life cycle means that it is necessary to attack

various stages. Each drug has its own specificity. Different drugs are required for prophylaxis or cure (Table 1). However, none of the available drugs fulfils all the criteria required.

Table 1. Some antimalarial drugs in current use

Type of drug	Common name	Treatment/ Prophylaxis	Effective against Tissue	Blood
Quinoline based drugs	quinine	T	O	OO
	chloroquine	TP	O	OO
Antimetabolites	pyrimethamine	+	*O*	+
	proquanil	P	O	*O*

+ pyrimethamine is used in combination with other drugs.
OO very active; O active; *O* inactive or weakly active.

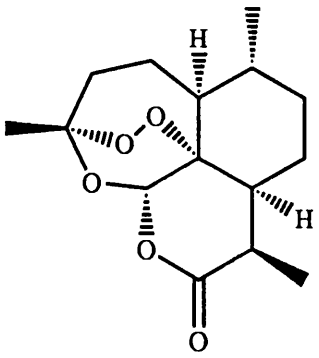
The malaria parasite digests the host cell's haemoglobin to get essential amino acids. This digestion process releases large amounts of the toxic iron porphyrin called heme. In order to avoid poisoning, the parasite polymerises the heme into an innocuous, insoluble material called hemozoin, which is sequestered inside the parasite's food vacuole. Chloroquine is believed to work against malaria by inhibiting the enzyme that polymerises and detoxifies heme[4]. Pyrimethamine inactivates the enzyme dihydrofolate reductase and so blocks the precursors necessary for making the parasite's DNA. Proguanil is also a dihydrofolate reductase inhibitor[1].

Prospects for the control of malaria have been seriously hampered by the emergence of resistance to all the quinoline-based and antimetabolite antimalarials. Resistance to chloroquine, the main drug in use is now world wide. Pyrimethamine resistance, first observed in Africa, has emerged spontaneously throughout the malarious world. It is not clear how resistance arises. In the case of chloroquine, resistant parasites accumulate reduced quantities of the drug suggesting impaired uptake or enhanced extrusion[1]. Resistance to pyrimethamine has been extensively studied at the genetic level and it appears that the malaria parasite possesses a gene that spontaneously mutates to produce dihydrofolate reductase which binds the drug less well than sensitive strains. The spread of resistant forms of malaria is also aided by the fact that during the sexual processes in the mosquito, recombination occurs. If parasites individually resistant to two antimalarial drugs co exist in a human host, some of the

sporozoites produced at the end of the life cycle will be resistant to both drugs. This has clearly been shown in the case of chloroquine and pyrimethamine[1].

1.4 Artemisinin, the new antimalarial drug

In 1967 the Chinese government began a systematic examination of indigenous plants used in traditional remedies. The herb qinghao (*artemisia annua L.*) had been used for many centuries as a treatment for fevers and malaria[3,5]. Chinese chemists were able to isolate the substance responsible for this reputed medicinal action from the aerial parts of the plant in about 1% yield[5]. The formula $C_{15}H_{22}O_5$ suggested that the compound was a sesquiterpene lactone. Reaction with triphenylphosphine gave triphenylphosphine oxide which implied the presence of a peroxide group. The compound was named Artemisinin (**5**) or Qinghaosu in chinese. The structure and absolute configuration of **5** were determined by x-ray diffraction in 1979. The lactone ring has a *trans* configuration. The most unusual feature in **5** is the 1,2,4-trioxane ring which is very rarely found in natural compounds. The only other known naturally occurring 1,2,4-trioxane is Caniojane (**6**) which was isolated from the root of Jatropha *grossidentata*[6]. There is no real evidence however that this compound has biological activity.



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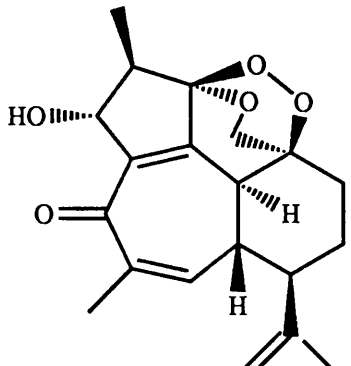
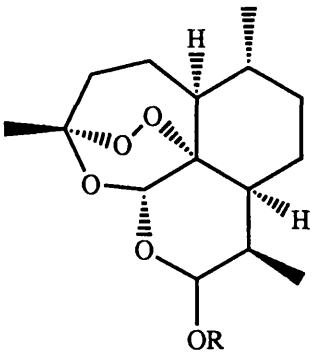


6

Artemisinin is essentially non-toxic and acts as a rapid blood schizontocide on polyresistant *P.falciparum* species. In 1979, the "*Qinghaosu Antimalaria Coordinating Research group*", reported that they had treated 2099 cases of malaria (*P.vivax* and *P.falciparum*) with different dosage forms of **5**, leading to the clinical cure of all patients. In addition, 143 cases of chloroquine-resistant *falciparum* malaria and 141 cases of cerebral malaria were treated with "good" results[5].

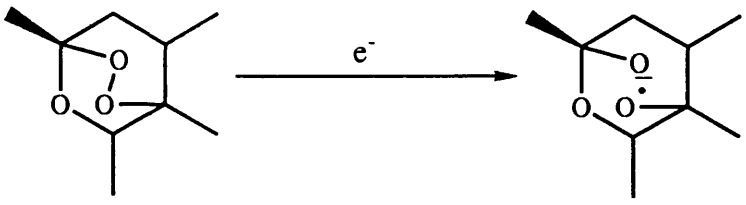
Attempts were made to modify the structure of **5** with the aim of enhancing its

antimalarial potency. Reduction with sodium borohydride gave dihydroartemisinin (**7**) which was found to be twice as active as the parent compound. Dihydroartemisinin was then converted into a series of other compounds such as artemether (**8**) and sodium artesunate (**9**) and these too were found to be much more active than **5**[5].



7, R=H
8, R=Me
9, R=$COCH_2CH_2CO_2^-Na^+$

Most research suggests that **5** acts on the malarial parasite in a completely different way to the quinoline and antifolate drugs. It has been suggested that the membrane system of the parasite is the main site of action of **5**, as changes in the ultrastructure of parasite membranes after exposure to the drug have been reported[3]. Artemisinin and its derivatives have also been found to have an inhibitory effect *in vitro* on protein synthesis in *P. falciparum*-infected human erythrocytes[5]. The parasiticidal effect of artemisinin and related compounds is believed to result from hemin-catalysed reduction of the trioxane unit which generates an oxygen-centred radical (Scheme 1)[3]. Destruction of the parasite is caused by radical attack on crucial cellular constituents. The hemin-rich internal environment of malarial parasites is thought to be responsible for the selective toxicity of 1,2,4-trioxanes like **5** towards these parasites[7].



Scheme 1

Reactive oxygen is already present in **5** in the form of its peroxide moiety. Derivatives

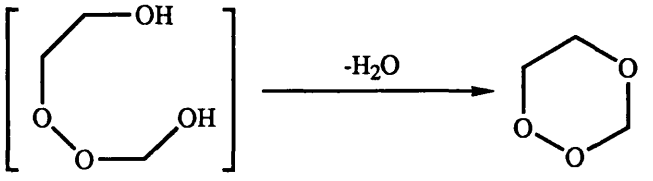
of **5** lacking the peroxide group are devoid of antimalarial activity. However even in compounds closely related to artemisinin, the possession of a peroxide bridge is not of itself sufficient condition for antimalarial activity[3]. It is almost certain that the crucial structure in **5** which endows it with antimalarial properties is the 1,2,4-trioxane ring, as other parts of the molecule have been modified without loss of activity.

The intriguing chemical structure of artemisinin combined with its outstanding biological activity has inevitably led to much interest in the synthesis of new 1,2,4-trioxanes.

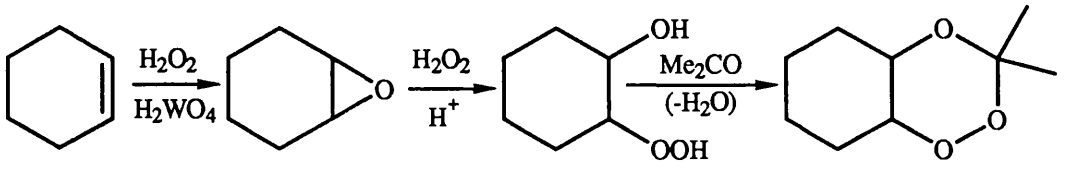
1.5 Existing routes to 1,2,4-trioxanes

Methods for the synthesis of 1,2,4-trioxanes can be divided into five main categories:

1. Dehydration of peroxy diols



Payne and co workers[8] were the first to report a route to 1,2,4-trioxanes in the literature. An epoxide was treated with 98% hydrogen peroxide and tungstic acid catalyst to give 1,2,4-trioxanes by condensation of the intermediate β-hydroperoxy alcohol **(10)** (Scheme 2).



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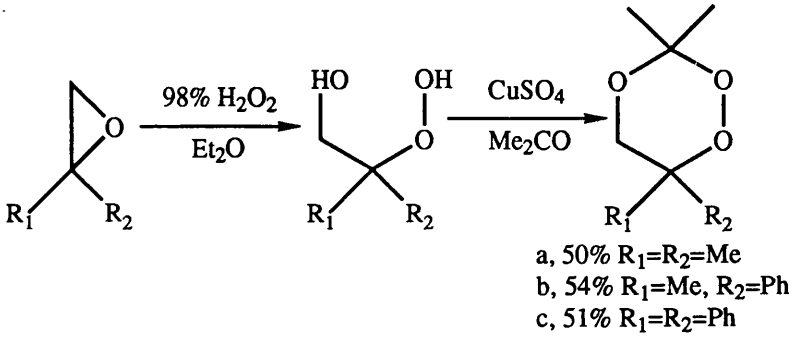
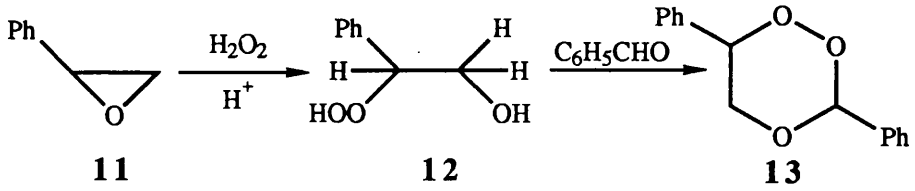
Scheme 2

A similar reaction was carried out by Adam[9], who treated epoxides with acetone in the presence of copper sulfate to give 1,2,4-trioxanes in 50% yield (Scheme 3).



Scheme 3

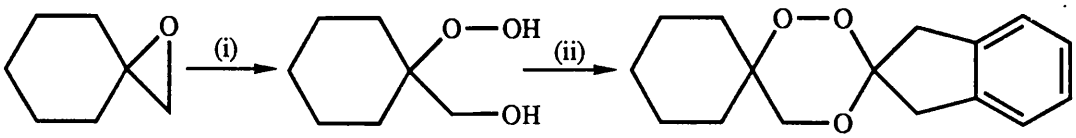
Subramanyam *et al*[10]treated epoxide (**11**) with 98% H_2O_2 to give the β-hydroperoxy alcohol (**12**), which when treated with benzaldehyde formed 1,2,4-trioxane (**13**) (Scheme 4).



11 **12** **13**

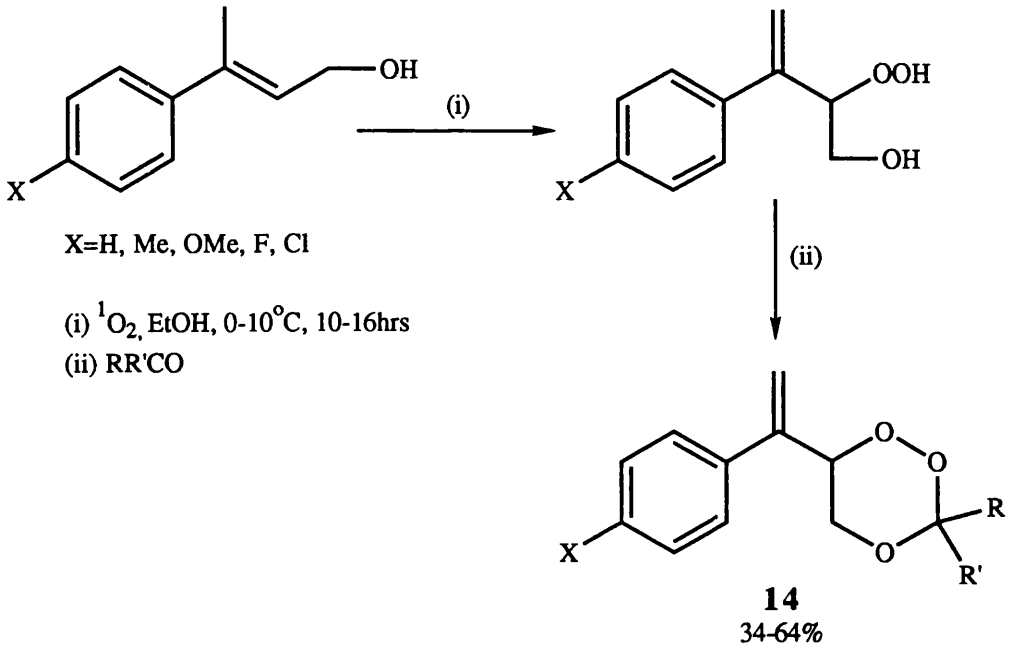
Scheme 4

McCullough *et al* [11] also synthesized 1,2,4-trioxanes in 10-15% yield from an epoxide and 98% H_2O_2 (Scheme 5).



(i) H_2O_2, Et_2O, H^+, 0°C
(ii) indan-2-one, H^+, Et_2O, 0°C

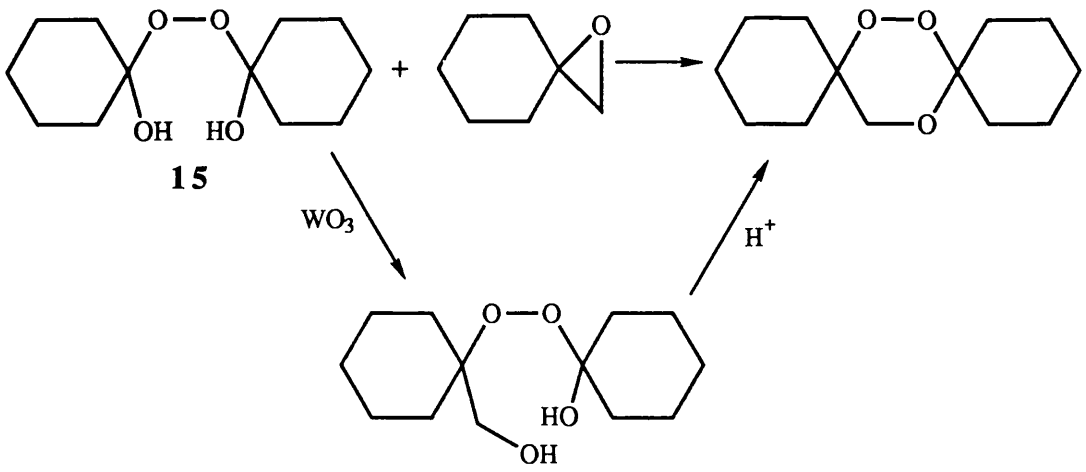
Scheme 5



Scheme 6

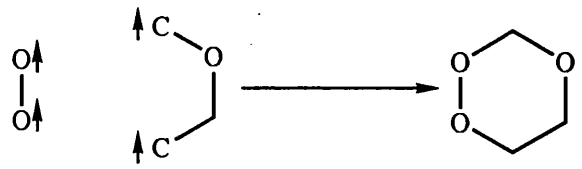
Singh[12] has recently exploited regiospecific photooxygenation of allylic alcohols as an alternative route to starting β-hydroperoxy alcohols **(14)** (Scheme 6). The trioxanes formed showed *in vitro* activity against *P. falciparum.*

Miura and co workers[13] formed 1,2,4-trioxanes by treating α-peroxy alcohols **(15)** with epoxide, tungstic anhydride and catalytic chlorosulfonic acid (Scheme 7). Starting α-peroxy alcohols were prepared by the treatment of aldehydes and ketones with 30% H_2O_2, giving this synthesis an advantage over related methods which use potentially dangerous 98% H_2O_2 to make starting β-hydroperoxy alcohols. The reaction involves the initial tungstic anhydride attack of the peroxide on the epoxide to form the α,β'-dihydroxy peroxide and a ketone. Dehydration of the diol leads to the trioxane which is seen as a single diastereoisomer.

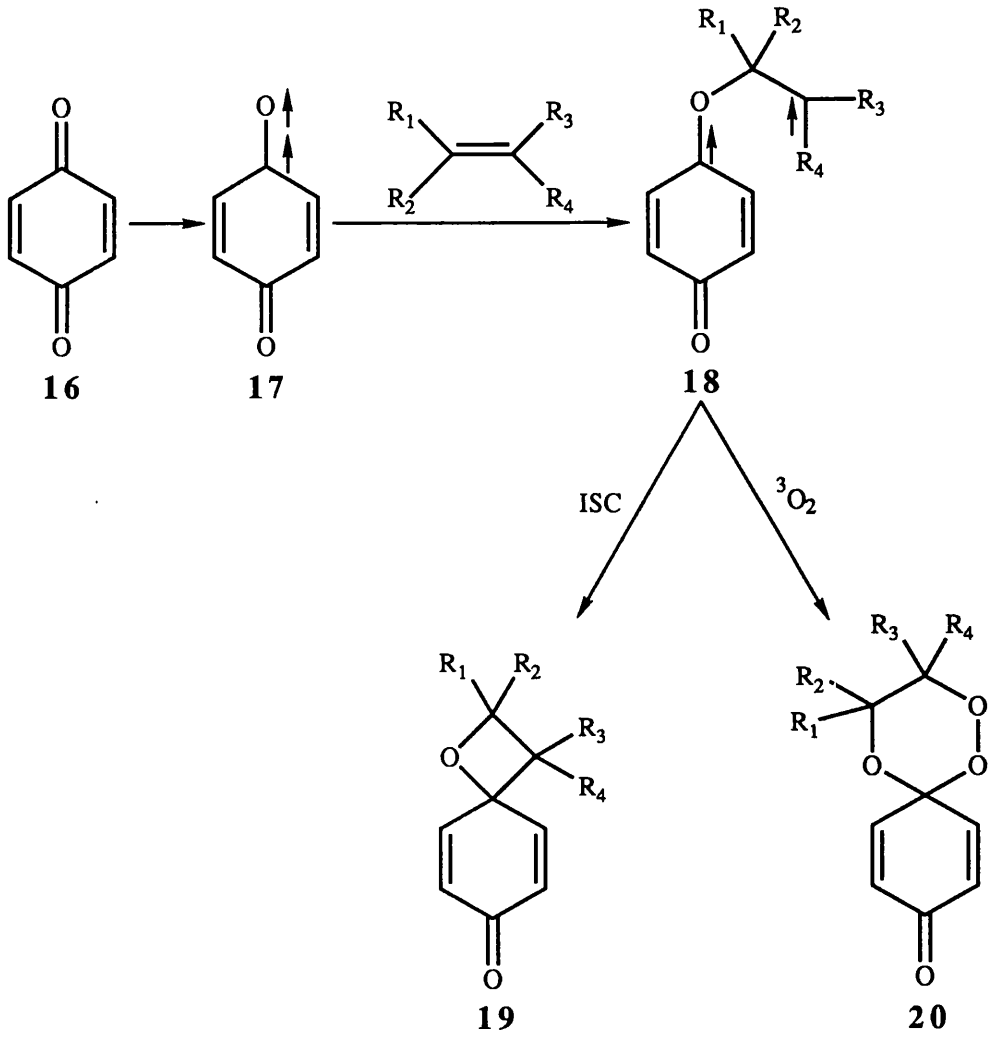


Scheme 7

2. Trapping of Paterno-Buchi triplet 1,4-diradicals by molecular oxygen

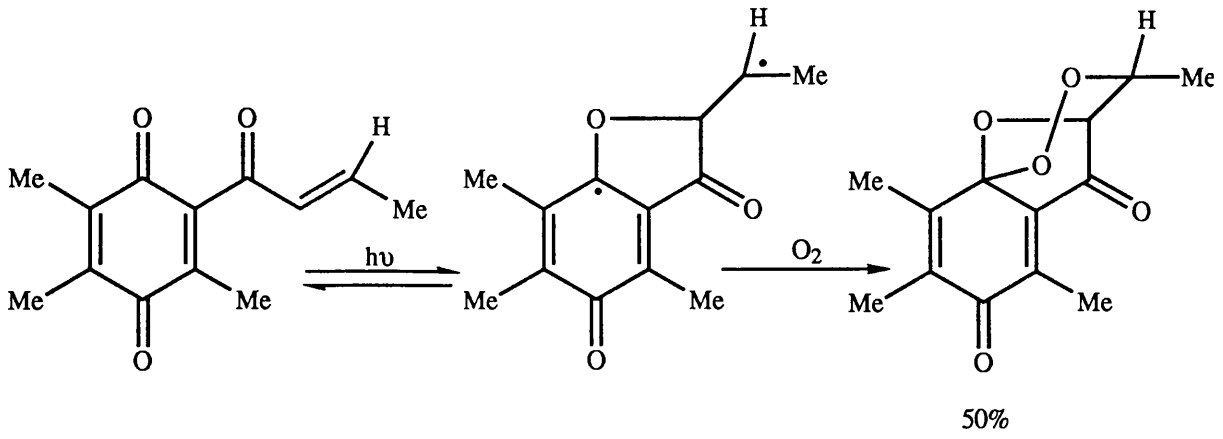


This well studied method was exploited by Wilson and co workers[14] (Scheme 8). They photolysed quinone (**16**) using an argon ion laser. This gave a singlet biradical which underwent an inter-system crossing (ISC) to the triplet state (**17**). The triplet biradical **17** could then add to an alkene to form the preoxetane biradical (**18**), which was trapped by triplet molecular oxygen to give 1,2,4-trioxane (**20**) in about 50% yield. Alternatively the two radical centres in **18** could undergo a further inter-system crossing and combine to form the oxetane (**19**).



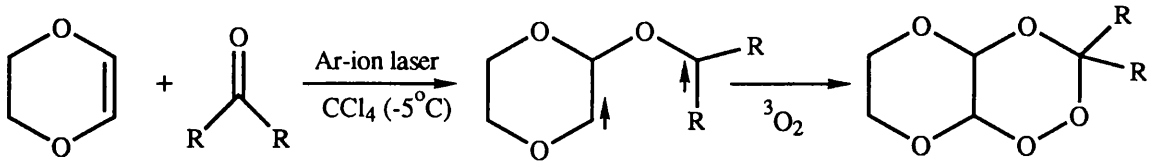
Scheme 8

Bicyclic 1,2,4-trioxanes were also made available by this method from alkenyl-1,4-quinones[15] (Scheme 9).



Scheme 9

Artemisinin-like 1,2,4-trioxanes were produced by molecular oxygen trapping of Paterno-Buchi triplet diradicals derived from 1,4-dioxene (**21**) (Scheme 10)[16]. Artemisinin-like 1,2,4-trioxane lactones were similarly formed from 3,4-dihydro-4,4-dimethyl-2H-pyran-2-one (**22**) (Scheme 11)[17].



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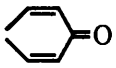
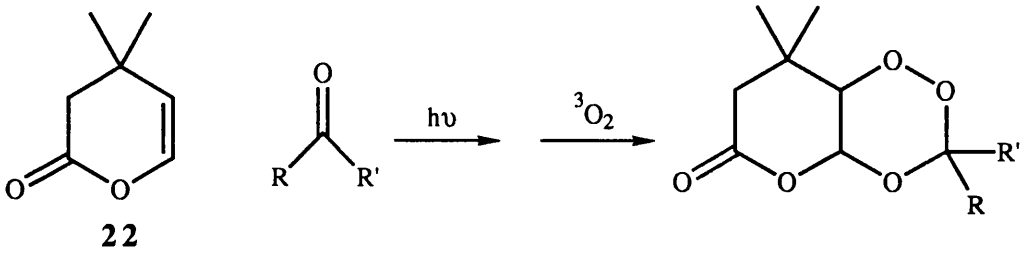
a. R=R=Ph

b. R+R= 

Scheme 10



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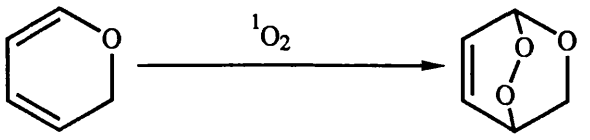
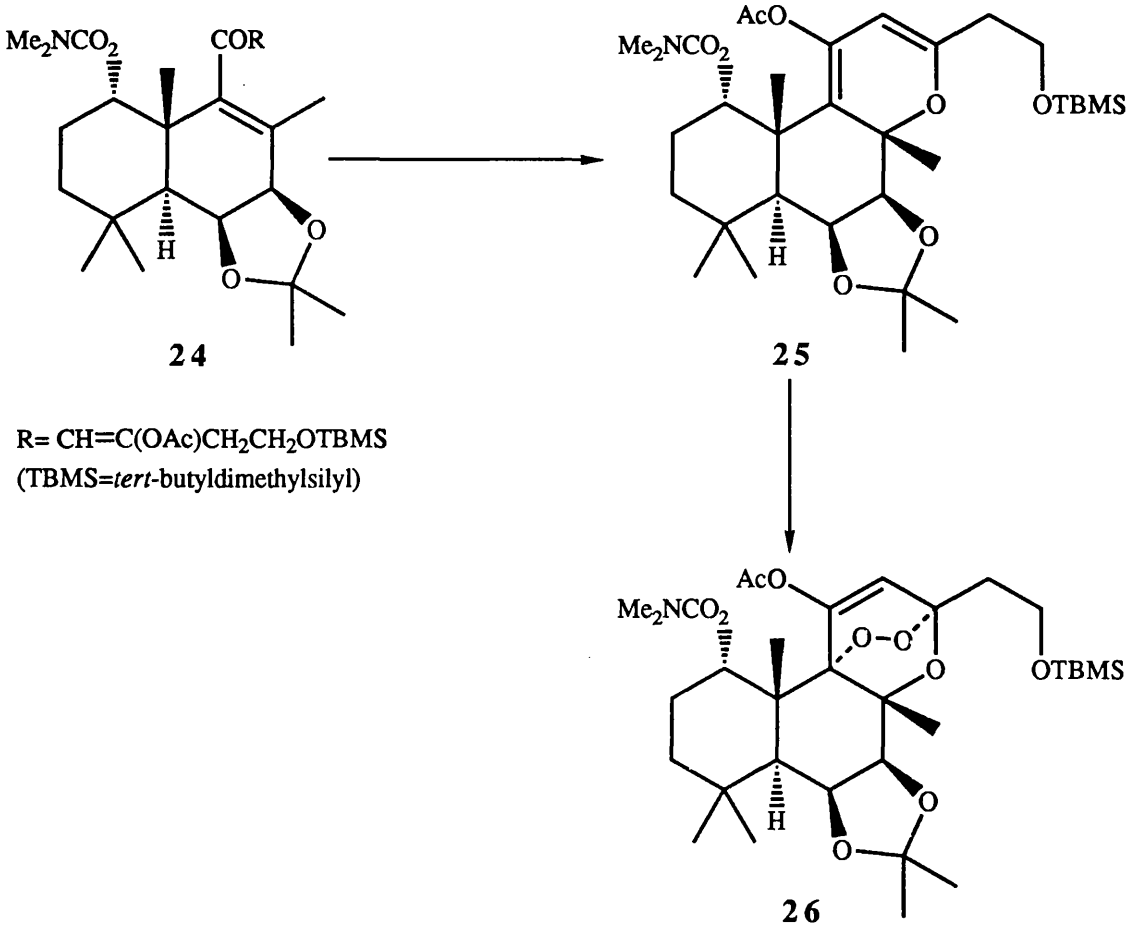
Scheme 11

3. Singlet oxygenation of α-pyrans

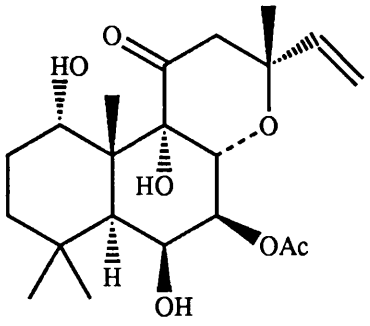


A key step in the total synthesis of Forskolin (**23**), is the synthesis of 1,2,4-trioxane (**26**) by singlet oxygenation of α-pyran (**25**) (Scheme 12)[18].



Scheme 12

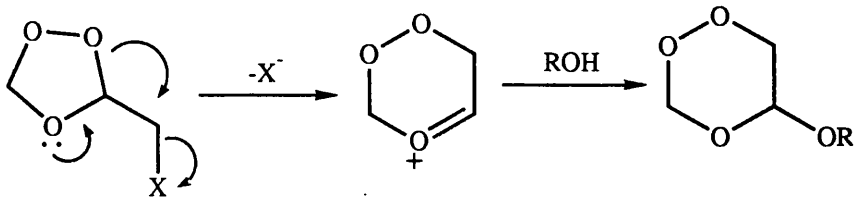
Irradiation of the enol ether (**24**) with a GE sunlamp in the presence of 2% methylene blue in O_2-saturated $CHCl_3$ at 10 °C for 4-5 hrs, resulted in photocyclisation to pyran **25** and subsequent 4+2 addition of $^1O_2$ to form 1,2,4-trioxane **26** in 55-63% yield[18].



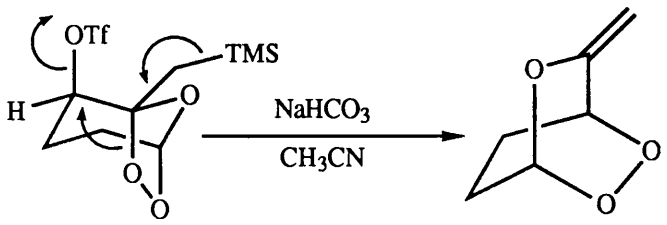
Forskolin is an activator of the enzyme, adenylate cyclase which has a number of important physiological effects.

23

4. The ring expansion of an ozonide



This method involves the cationic ring expansion of an ozonide involving 1,2-migration of the peroxide, triggered by ionization of the leaving group. Bunnelle *et al* [19] recently converted ozonide (**27**) into bicyclic 1,2,4-trioxane (**28**) by treatment with mild base. The leaving triflate group must be in the axial position and antiperiplanar to the peroxy group in order for the desired rearrangement to occur (Scheme 13).

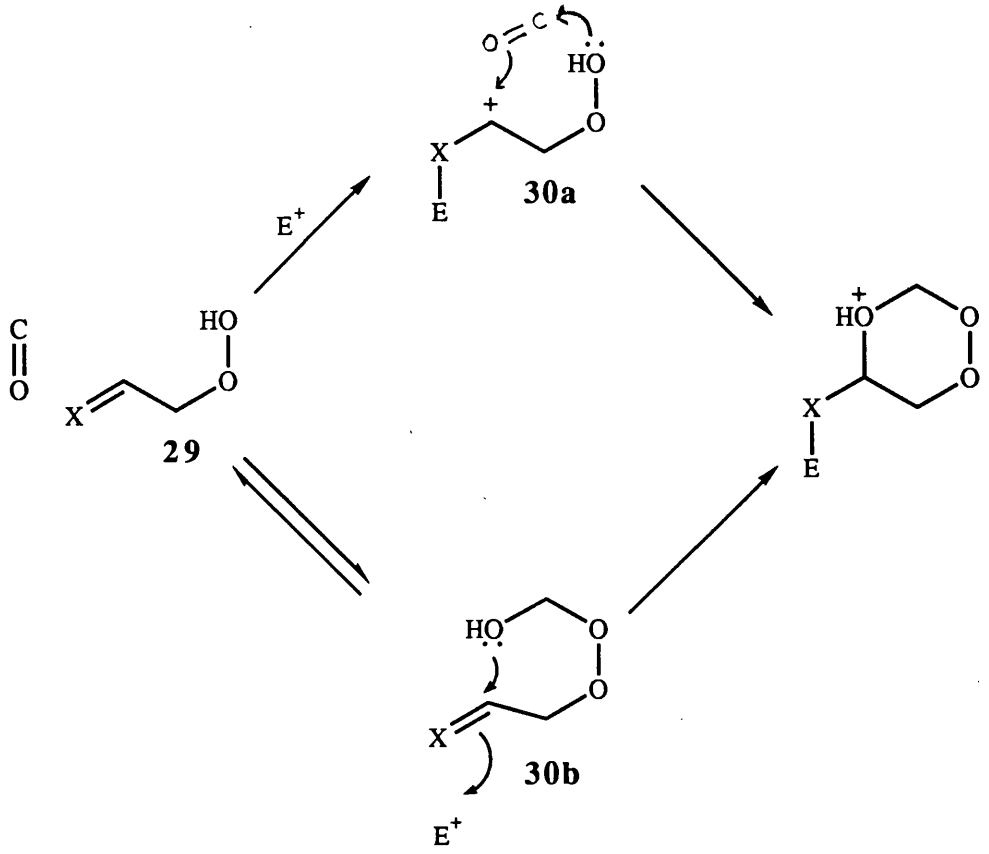


27 **28**

Scheme 13

5. Trapping of β-peroxycarbocations with aldehydes and ketones and related intramolecular electrophilic additions

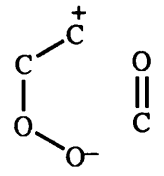
a. Trapping of β-peroxycarbocations with aldehydes and ketones



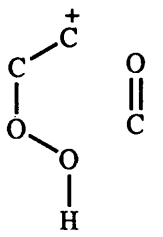
b. Intramolecular electrophilic addition

Scheme 14

Methods 5a and 5b are very closely related, in fact electrophilic addition to the X group in **29** would convert method 5b to method 5a. The main difference between the two routes is in key intermediate (**30**) (Scheme 14). If intramolecular electrophilic addition (method 5b), were to occur, the intermediate would have structure (**30b**). However in the case of method 5a, the intermediate would be a zwitterionic peroxide (**31**)[20], a hydroperoxy cation (**32**)[21] or related species.

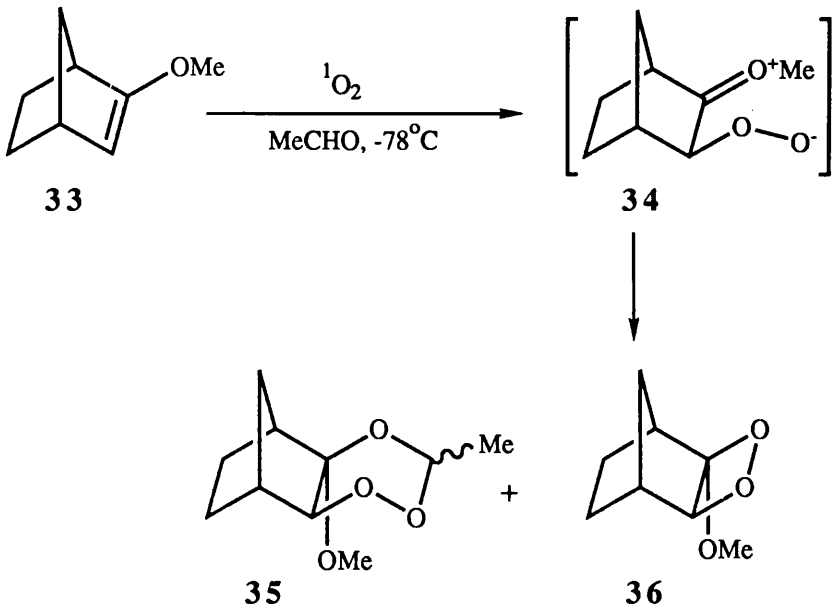


31



32

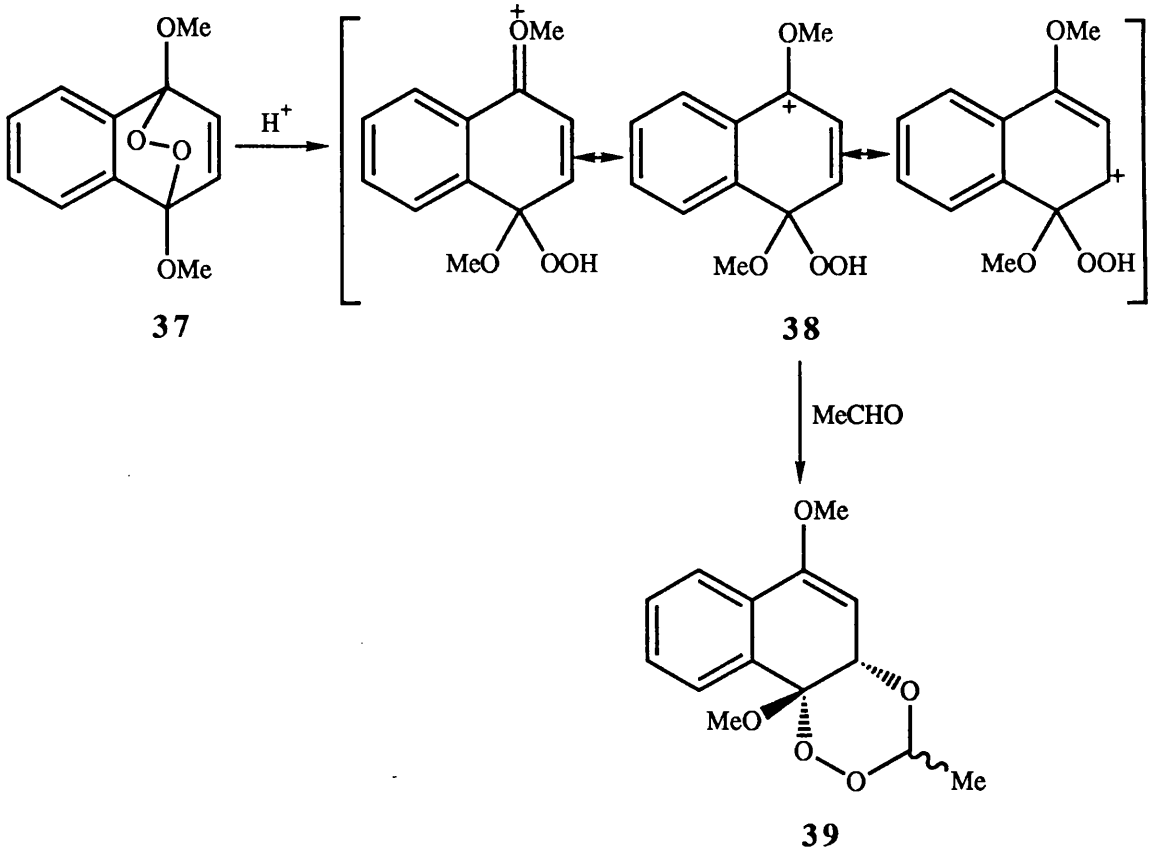
The most thoroughly investigated route to 1,2,4-trioxanes was devised by Jefford *et al.*[20-27]. It was originally discovered that the dye-sensitized photo-oxygenation of enol ether (**33**) gave 1,2-dioxetane (**36**) in aprotic solvents but was diverted to 1,2,4-trioxane (**35**) when acetaldehyde was used as solvent (Scheme 15)[20]. The diversion was rationalised by the intermediacy of zwitterionic peroxide (**34**), which was trapped by cyclisation across the carbonyl function.



33 34 35 36

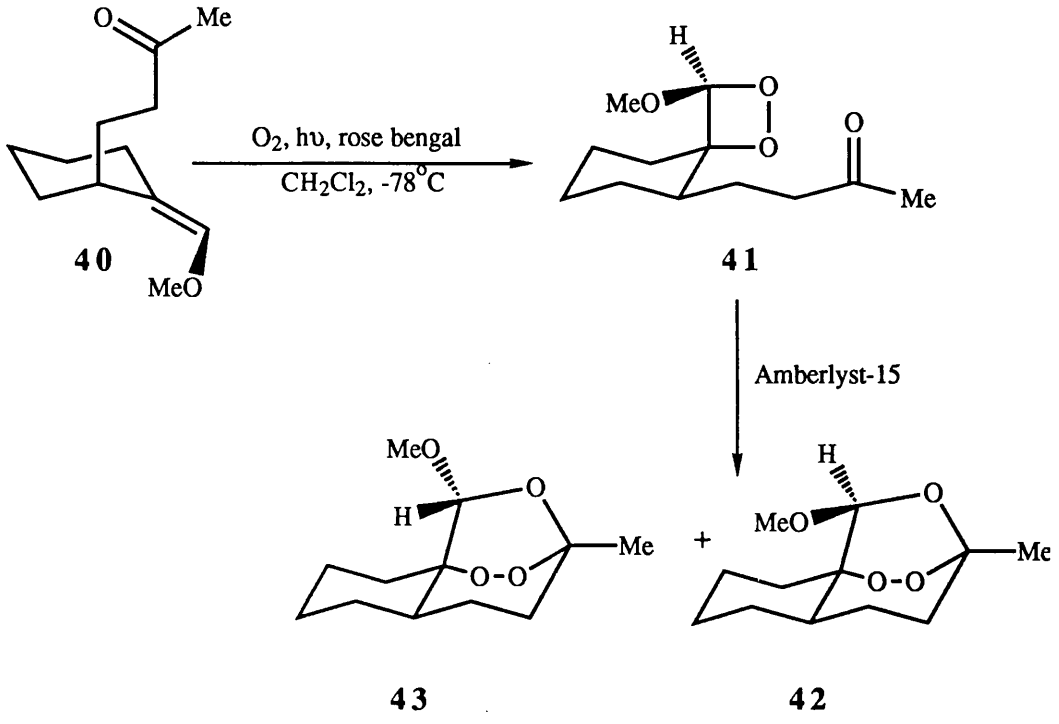
Scheme 15

Subsequently it was discovered that endoperoxide (**37**), when treated with acetaldehyde in the presence of an acid catalyst gave the *cis*-fused 1,2,4-trioxane (**39**) presumably *via* hydroperoxy cation (**38**) (Scheme 16)[23]. The reaction was found to proceed much more efficiently with the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyst[21].



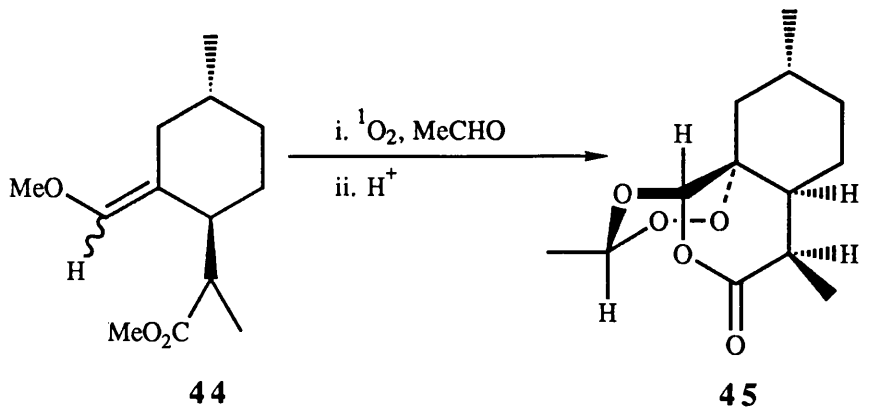
Scheme 16

Jefford *et al*[27] provided an intramolecular example of trioxane formation by photo-oxygenation and subsequent acid catalysis of the Z-methoxylidene derivative (**40**) (Scheme 17). The intermediate dioxetane (**41**) underwent cyclisation on treatment with amberlyst-15 to give mainly *endo*-methoxy tricyclic trioxane (**42**) in 48% yield together with its *exo* epimer (**43**) in 19% yield.



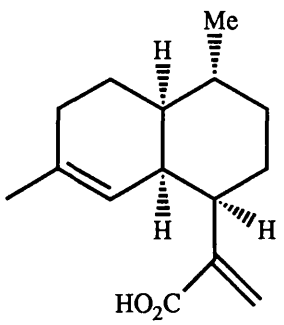
Scheme 17

Many of the total syntheses of complex artemisinin-like 1,2,4-trioxanes are also based on the principle of trapping β-peroxycarbocations by carbonyl compounds (method 5a). An early example of this type of reaction was carried out by McPhail *et al*[28] in the synthesis of desethanoqinghaosu (**45**). Singlet oxygenation of methyl enol ether (**44**) in the presence of acetaldehyde gave **45** in 15% yield (Scheme 18).

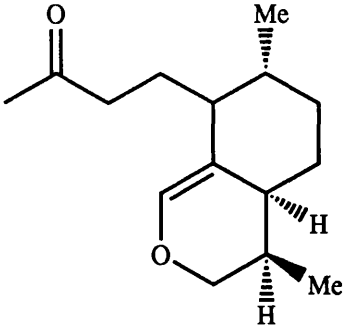


Scheme 18

Arteannuic acid (**46**) is a relatively abundant constituent of *artemisia annua*[5]. Bin Ye *et al*[29] devised an efficient conversion of **46** to **5** *via* the intermediate cyclic enol ether (**47**) (Scheme 19).

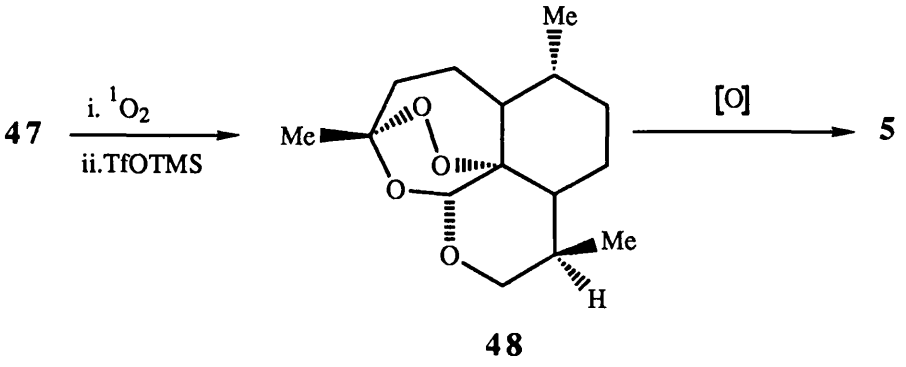


46



47

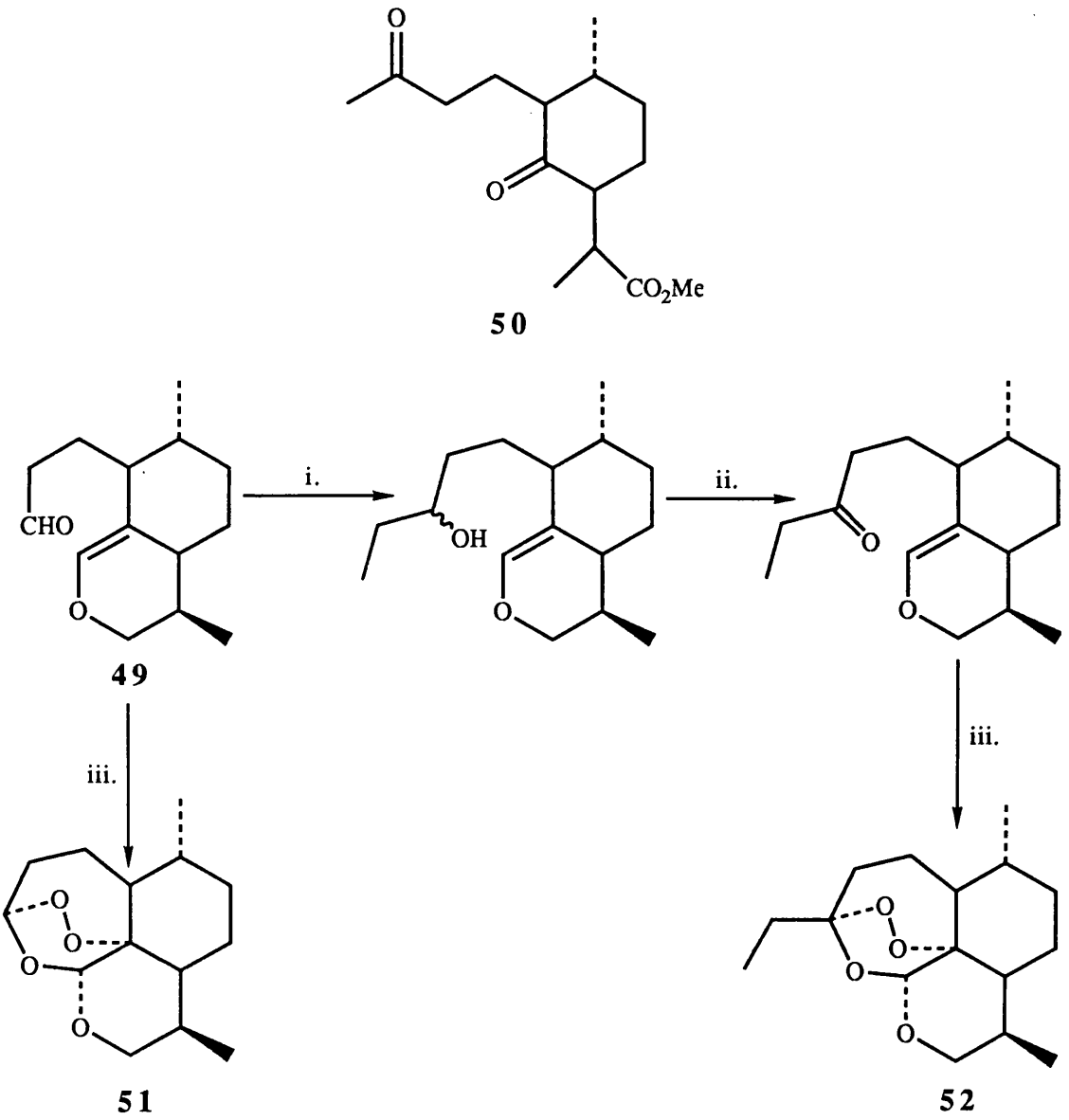
Photooxgenation of **47** in methylene blue at -78 °C followed by treatment with trimethylsilyl trifluoromethanesulfonate (TfOTMS) gave deoxoqinghaosu (**48**) in 62% yield by a process based on general method 5a. Oxidation of **48** with $RuCl_3$-$NaIO_4$ gave **5** in 96% yield.



48

Scheme 19

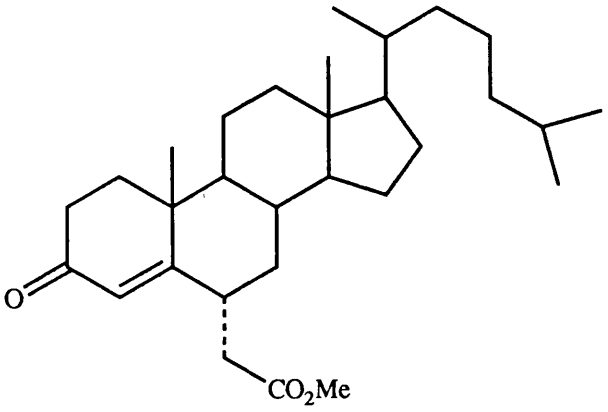
A cyclic enol ether (**49**) was also the key intermediate in the syntheses of artemisinin analogues (**51**) and (**52**) from diketone (**50**) (Scheme 20)[30].



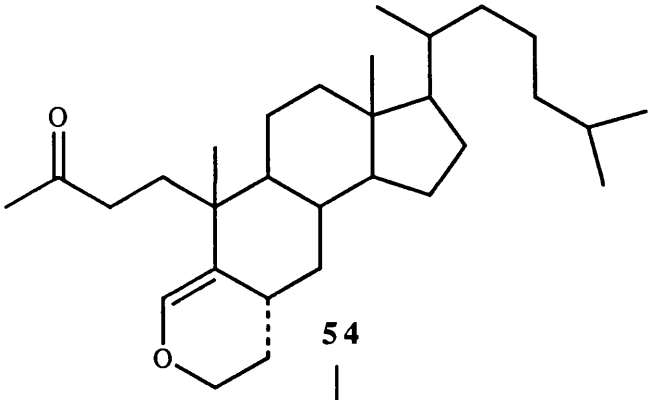
i. EtMgBr, Et_2O
ii. DMSO, $(COCl)_2$
iii. $^1O_2$, methylene blue, -78 °C then TMSOTf

Scheme 20

The proposal that the high affinity of **5** for plasmodium membranes may be because of its similarity with cholesterol led Rong *et al*[31] to combine in one compound, the 1,2,4-trioxane structure with that of cholesterol. In this example also, photooxygenation of a suitable cyclic enol ether (**54**) led to the formation of 1,2,4-trioxanes (**55a**) and (**55b**) (Scheme 21).

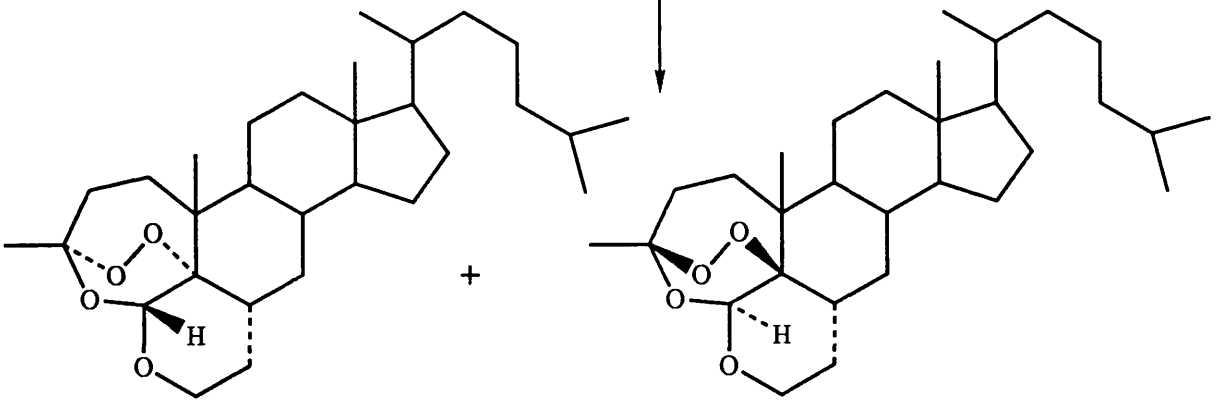


53



54

$^1O_2$, methylene blue
-78 °C then TMSOTf



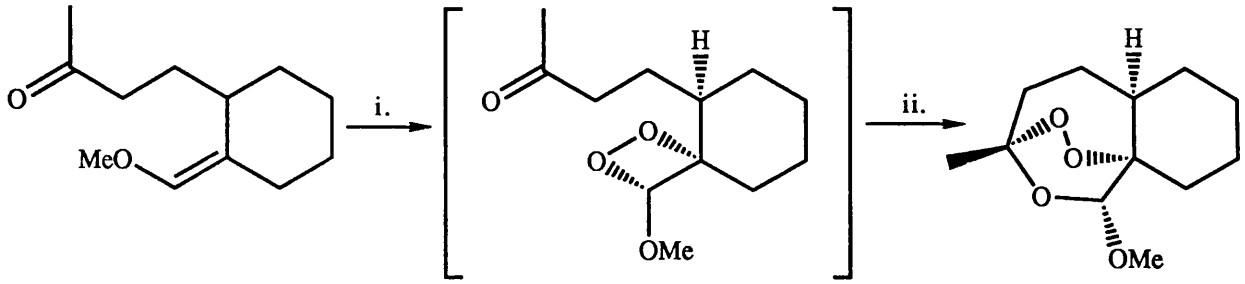
55a
16%

55b
20%

Scheme 21

In preliminary testing **55a** and **55b** were found to be more effective than **5** *in vitro* against *P. berghei* malaria.

Posner's[32] approach involved using triethylsilyl hydrotrioxide to generate methoxy dioxetanes (**57**) from methyl enol ethers (**56**). These then gave 1,2,4-trioxanes on treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (Scheme 22).

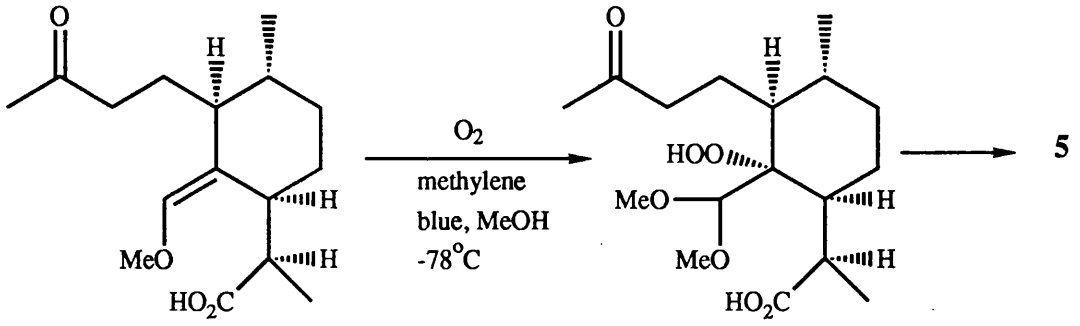


56 **57**

i. $Et_3SiOOOH$, -78 °C, CH_2Cl_2
ii. ^{t}-$BuMe_2SiOTf$

Scheme 22

Most literature methods for the synthesis of **5** and closely related 1,2,4-trioxanes are based on intramolecular electrophilic addition (method 5b). The earliest example of this type of total synthesis was provided by Schmid and Hofheinz[33] who synthesized enol ether (**58**) from (-)-isopulegol. Photooxygenation of **58** in methanol gave hydroperoxide (**59**), a masked α-hydroperoxy aldehyde, which when treated with acid gave **5** in 30% yield (Scheme 23).

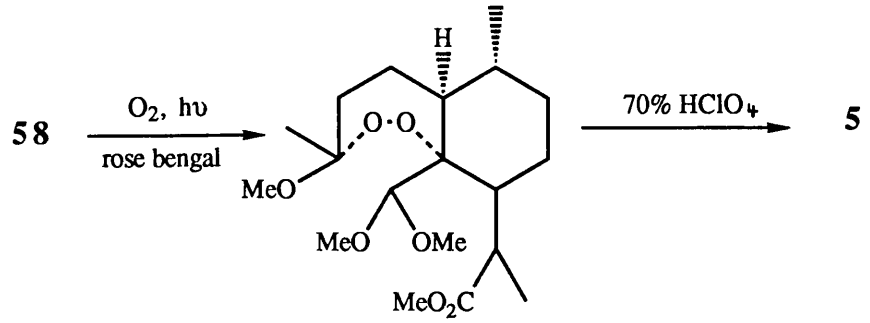


58 **59**

Scheme 23

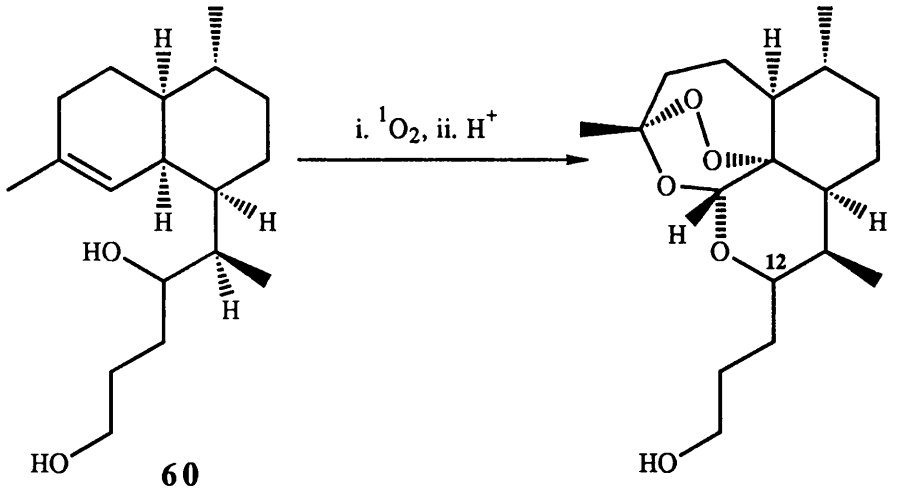
Ravindranathan *et al*[34] synthesized **5** from (+)-isolimenene. The key intermediate in this synthesis was also enol ether **(58)**.

Zhou[35] introduced the 1,2,4-trioxane group by a procedure identical to the Schmid and Hofheinz[33] method. The starting (+)-citronellal was converted to **58**, which on singlet oxygenation gave **5** (Scheme 24).



Scheme 24

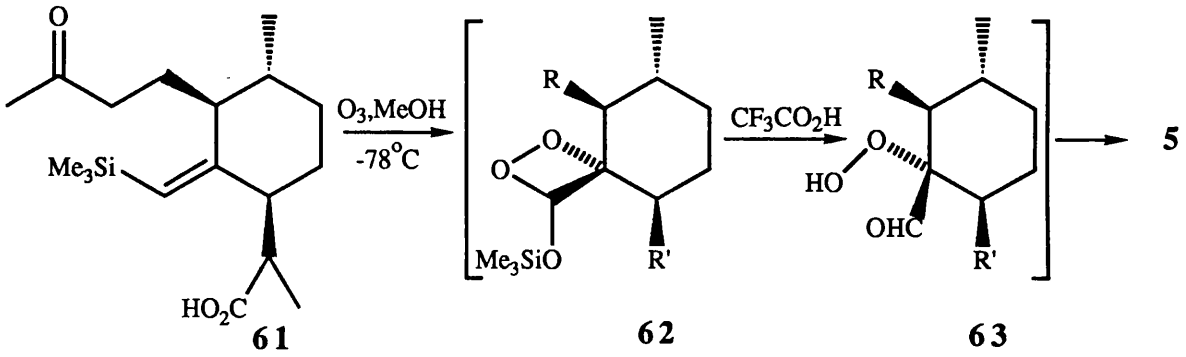
Jung *et al*[36] converted (+)-artemisinic acid into an artemisinin-like 1,2,4-trioxane. The key step in this synthesis was the formation of diol **(60)**. Photooxygenation of **60** with oxygen [irradiation with 45-W medium mercury arc lamp at -78 °C, methylene blue (cat)], followed by acidic dowex-resin catalysed cyclisation of the oxygenation intermediates afforded 1,2,4-trioxanes in 11-12% yield (Scheme 25).



Scheme 25

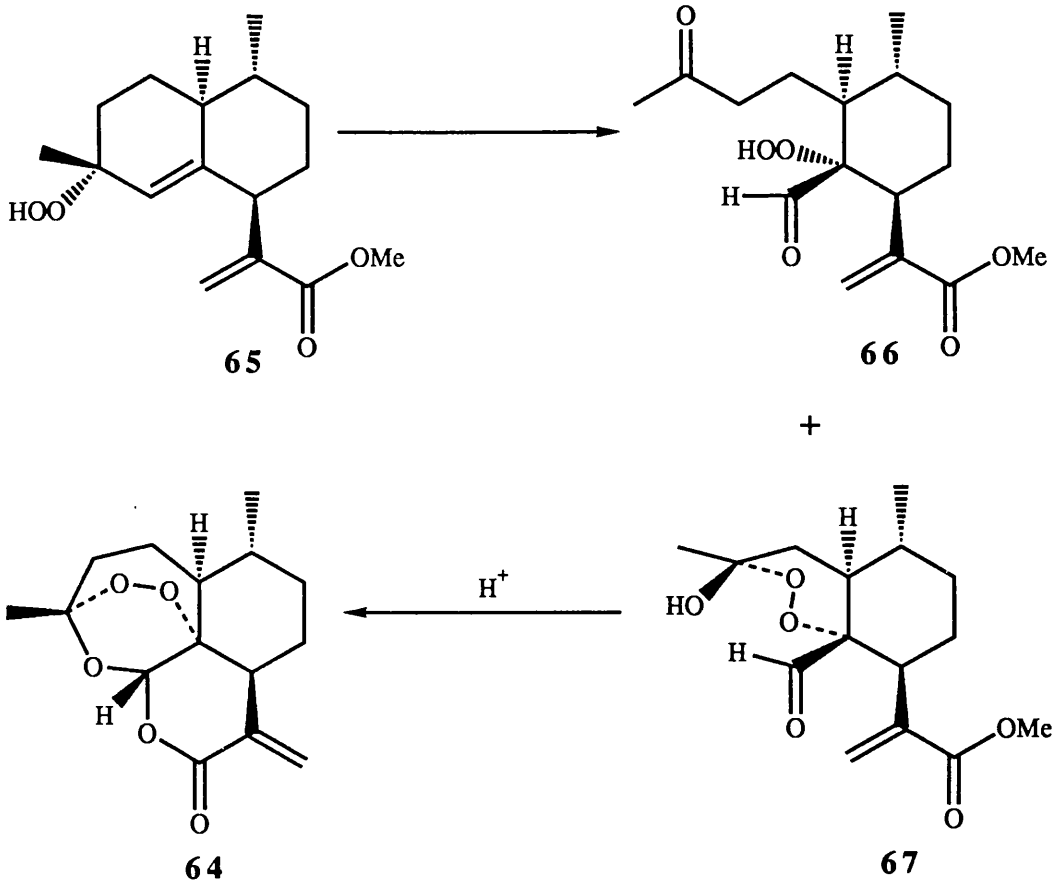
Avery *et al*[37-40] used a different approach for the introduction of the peroxy

group. Their method involved taking a vinylsilane (**61**), which on reaction with ozone formed a transient silyloxydioxetane (**62**). Treatment of **62** with acid caused ring opening to labile α-hydroperoxy aldehyde (**63**), (cf. **58**, an α-hydroperoxy dimethyl acetal), which undergoes further selective cyclisation to give the desired product (Scheme 26).



61 **62** **63**

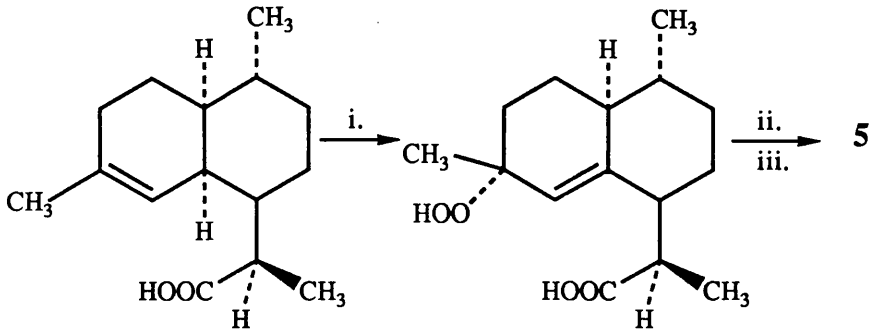
Scheme 26



Scheme 27

Haynes *et al*[41] started with arteannuic acid **46**, in the total syntheses of dehydroqinghaosu (**64**). They converted **46** to ester (**65**), which when treated with Fe(phenanthroline)$_3$(PF$_6$)$_3$ followed by Cu(OSO$_2$CF$_3$)$_2$ in acetonitrile under oxygen, gave a mixture of the dicarbonyl hydroperoxide (**66**) and peroxyhemiacetal (**67**). Subsequent treatment with acid gave **64** (Scheme 27).

Acton and Roth[42] carried out a similar conversion of **46** to **5** (Scheme 28). However they used trifluoroacetic acid instead of a copper catalyst.



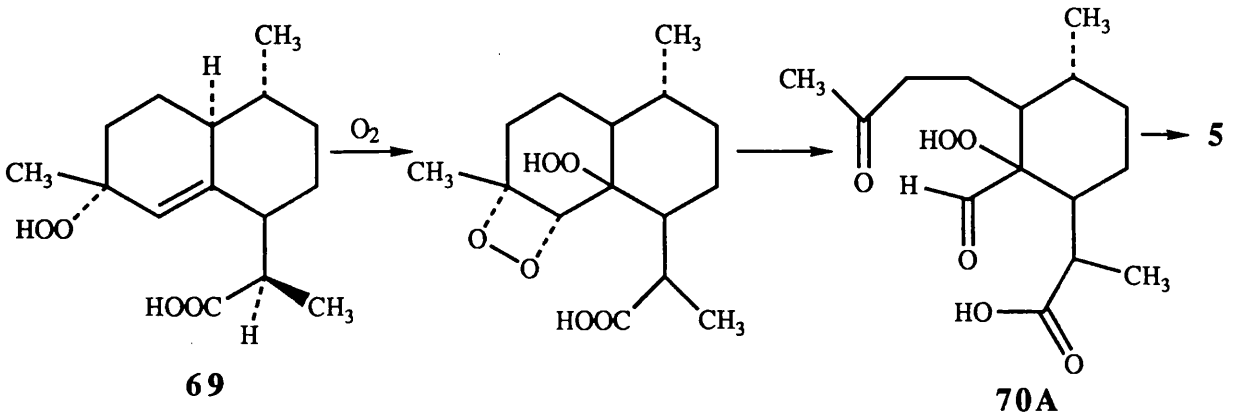
68 **69**

i. $^1O_2$
ii. $^3O_2$
iii. CF_3CO_2H

Scheme 28

Several mechanistic pathways can be envisaged for the air (triplet oxygen) oxidation of compound (**69**) to **5** (Scheme 29). The oxygens introduced in the second step of the transformation of compound (**68**) to **5** were located by using oxygen-18 in the triplet oxygen oxidation and determining the ^{18}O-induced shifts in the ^{13}C nmr spectrum of **5**. In the ^{13}C nmr spectrum of **5** the peak at δ 105.3 is due to C-3 and the peak at δ 79.4 is due to C-12a. A 2: 1 mixture of **5** and **5**-$^{18}O_2$ showed upfield shifts for these two peaks which demonstrated that the labelled oxygen was exclusively in the endoperoxide bridge. This result ruled out the mechanisms in which the endoperoxide bridge of **5** came from the singlet oxygen reaction (mechanisms 2 and 3). The use of $^{18}O_2$ in the photooxidative conversion of **68** to **69** followed by air oxidation resulted in artemisinin labelled in two of the non peroxide portions. Of the three suggested mechanisms then, mechanism 1 was most likely. The conversion of (**70A**) to **5** occurs via (**70B**) (Scheme 30).

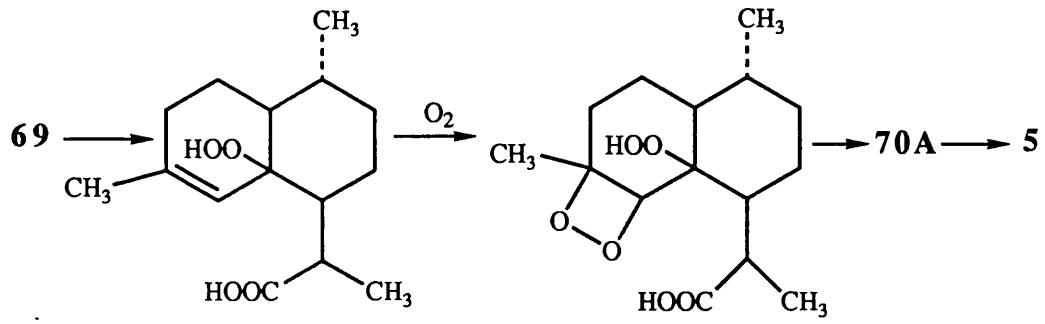
Mechanism 1



69 70A

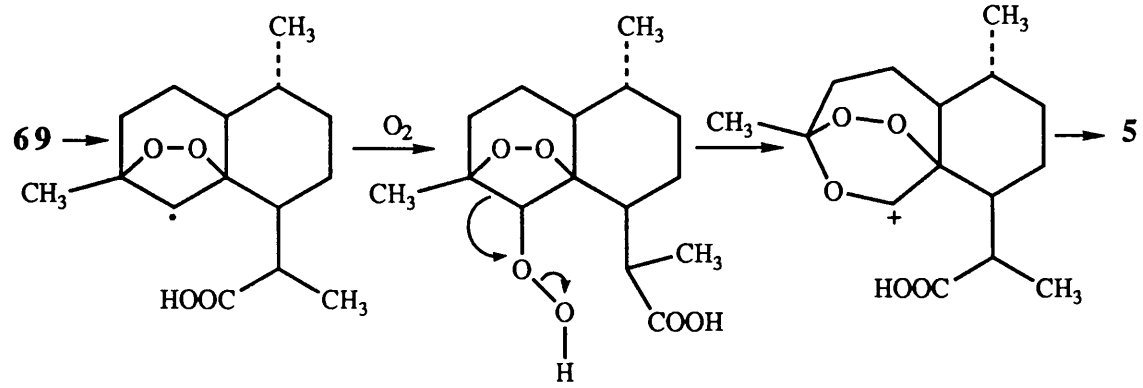
This mechanism requires that the oxygen in the endoperoxide bridge of **5** originate in the triplet oxygen step.

Mechanism 2



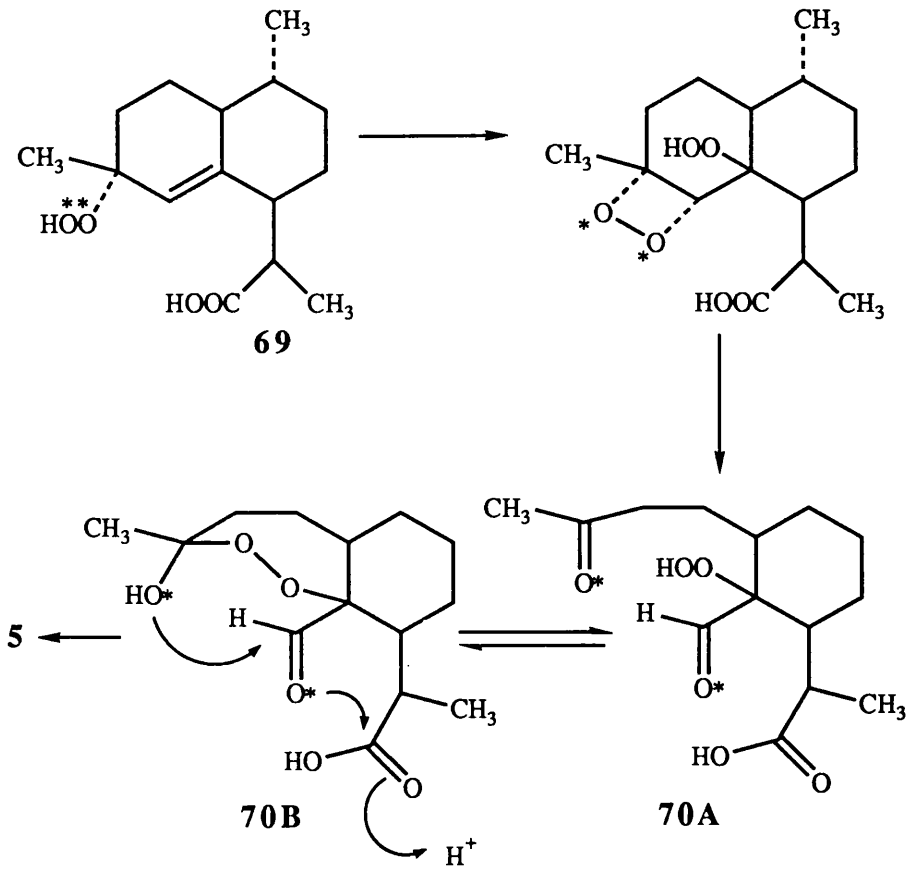
This mechanism differs from mechanism 1 in that the endoperoxide bridge of 5 comes from the singlet oxygen oxidation of **68**.

Mechanism 3



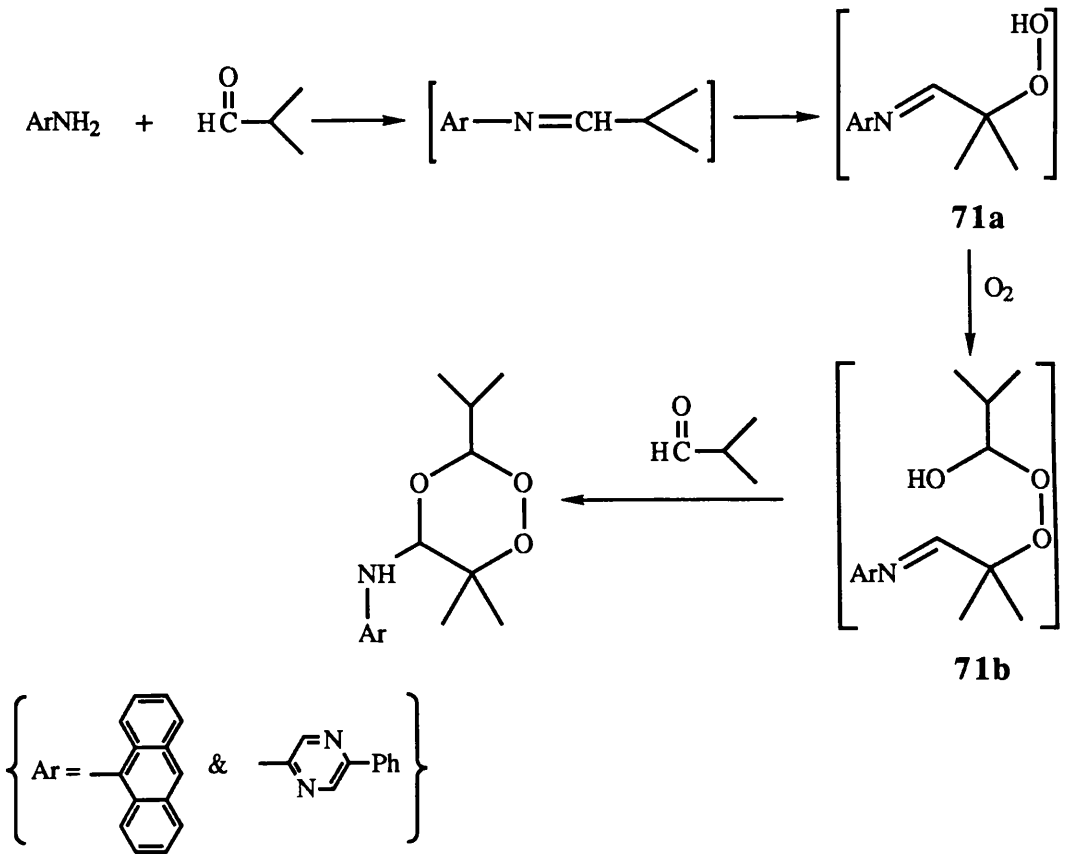
In this mechanism, the endoperoxide bridge of 5 also comes from the singlet oxygen oxidation step.

Scheme 29

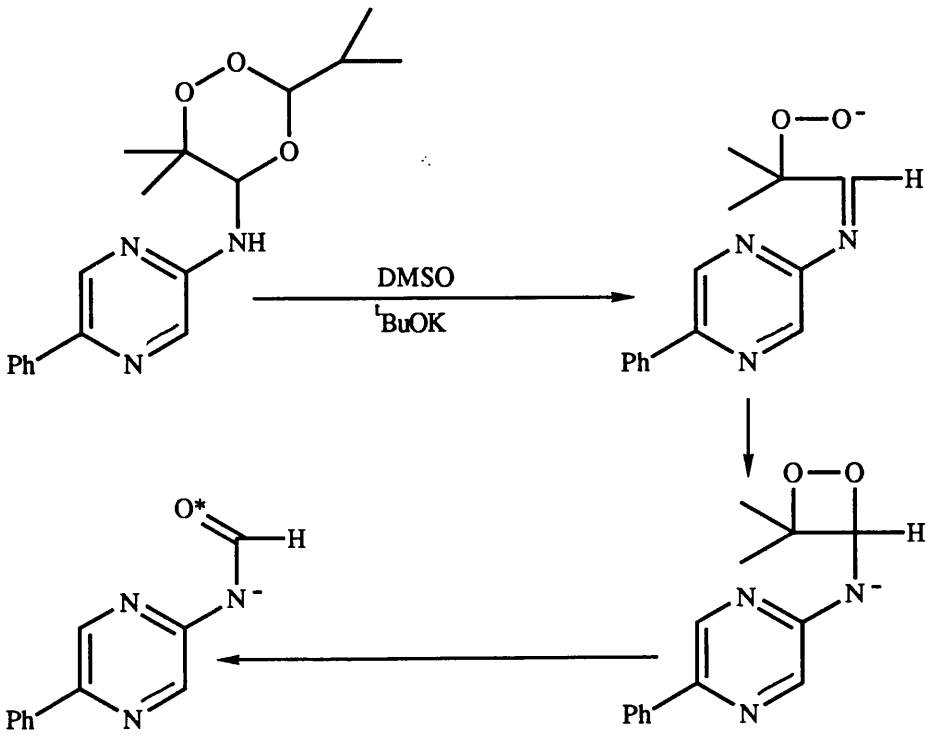


Scheme 30

Intramolecular electrophilic addition (method 5b, X=NR), has also been exploited in the synthesis of arylamino-1,2,4-trioxanes. Goto *et al*[43] produced chemiluminescent 5-arylamino-1,2,4-trioxanes by the autoxidation of imines, which gave α-hydroperoxyimines (**71a**), (cf. **59**, an α-hydroperoxy dimethyl acetal and **63**, an α-hydroperoxy aldehyde) (Scheme 31). Chemiluminescence of these compounds was observed in aprotic polar solvents in the presence of base. The products isolated were found to be the corresponding amides (Scheme 32).

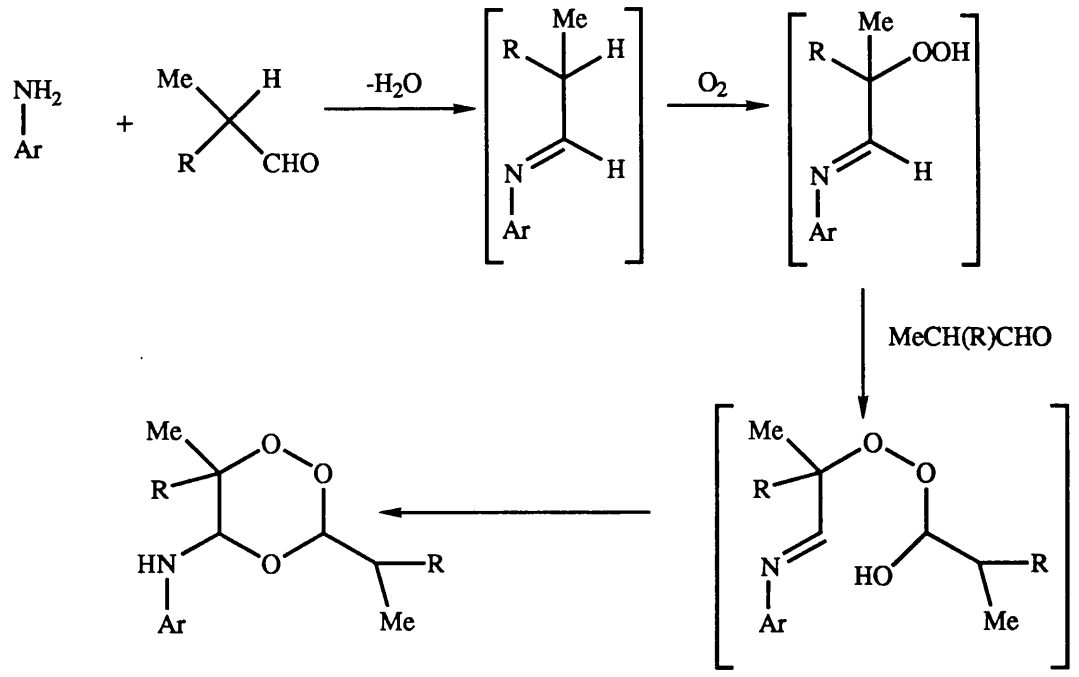


Scheme 31



Scheme 32

Yamamoto *et al* [44] also synthesized 5-arylamino-1,2,4-trioxanes by this method (Scheme 32) by using aniline, toludine, xylidine and mesitylamine starting materials.

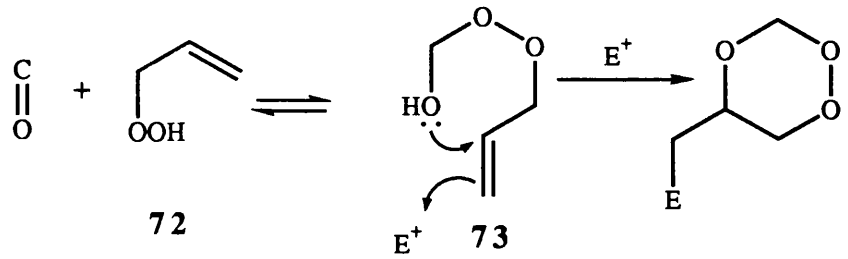


Scheme 33

All the methods for the synthesis of 1,2,4-trioxanes discussed so far have limitations and none can claim to be a general route. In the condensation of β-hydroperoxy alcohols with aldehydes and ketones[8-11] an epoxide must be stirred with potentially dangerous 98% hydrogen peroxide for several days to produce the starting hydroperoxide whereas Singh's regiospecific photo-oxygenation method[12] only produces 6-(1-methylenealkyl)-1,2,4-trioxanes. The trapping of Paterno-Buchi triplet 1,4-diradicals by molecular oxygen[14-16] is very restrictive and involves the use of expensive equipment. Another restrictive method is the singlet oxygenation of α-pyrans[18] of which only one example was found in the literature. There is only one example of the ring expansion of an ozonide[19] to a 1,2,4-trioxane and the desired rearrangement only occurs if the starting ozonide is substituted in a particular fashion. The autoxidation of imines[43,44] only produces 5-arylamino-1,2,4-trioxanes. The methods involving the singlet oxygenation of methyl enol ethers[33,35,34,28], cyclic enol ethers[29,30,31] and diols[36] have only been applied to the synthesis of complex, polycyclic, artemisinin-like trioxanes. The ozonolysis of vinyl silanes[37-40] has only been useful in the synthesis of artemisinin-like trioxanes as has the Haynes synthesis[41]

which involves treatment of an ester with Fe(phenanthroline)$_3$(PF$_6$)$_3$ followed by Cu(OSO$_2$CF$_3$)$_2$. Posner's approach using triethylsilyl hydrotrioxide and an enol ether is also limited as it only leads to complex multicyclic 1,2,4-trioxanes[32]. Although the Jefford[27] approach has produced a wide variety of 1,2,4-trioxanes in good yields, it is also somewhat limited because only bicyclic endoperoxides or their equivalents are used as starting materials, so all trioxanes formed have fused ring systems.

Given the limitations of existing routes to 1,2,4-trioxanes, there is clearly a need to develop new, less restrictive methodology for their synthesis. We decided to exploit the principle of electrophilic addition (method 5b), in the development of a new, potentially general route to 1,2,4-trioxanes (Scheme 34).



Scheme 34

The important intermediate in the scheme is allylic hemiperoxyacetal (**73**) (cf. **71b**), which is formed in the reaction of allylic hydroperoxides (**72**) with carbonyl compounds. The hydroxyl group in **73** acts as the internal nucleophile and electrophilic addition across the double bond therefore leads to the formation of 1,2,4-trioxanes. We envisaged using a variety of electrophiles and in particular mercury(II) salts [45].

1.6 Aims of Thesis

The aims of the present work were as follows.

1. To see if the principle outlined in scheme 34 could be translated into a viable synthesis of 1,2,4-trioxanes.

2. To investigate the effects upon the yields of 1,2,4-trioxanes by,

a) varying the starting aldehydes and ketones to observe,
(i) *electronic* effects, as electron-withdrawing R groups in the aldehydes and ketone starting materials should favour hemiperoxyacetal (**73**) formation, but should also reduce the nucleophilicity of the OH group.
(ii) *steric* effects, as bulky R groups in the starting aldehydes and ketones may disfavour formation of **73**. In addition hemiperoxyacetal formation would be expected to be less favourable for ketones than for aldehydes.

b) varying the allylic hydroperoxide **72**.

c) varying the electrophile.

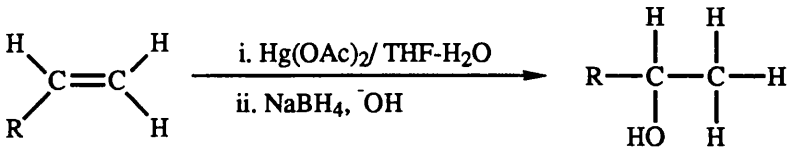
3. To see if the resultant 1,2,4-trioxanes displayed antimalarial activity.

4. To investigate the reactions of the new 1,2,4-trioxanes obtained, with particular interest in those that might underpin their antimalarial activity or provide a potential role in organic synthesis.

ALDEHYDE-DERIVED 1,2,4-TRIOXANES *VIA* INTRAMOLECULAR OXYMERCURIATION

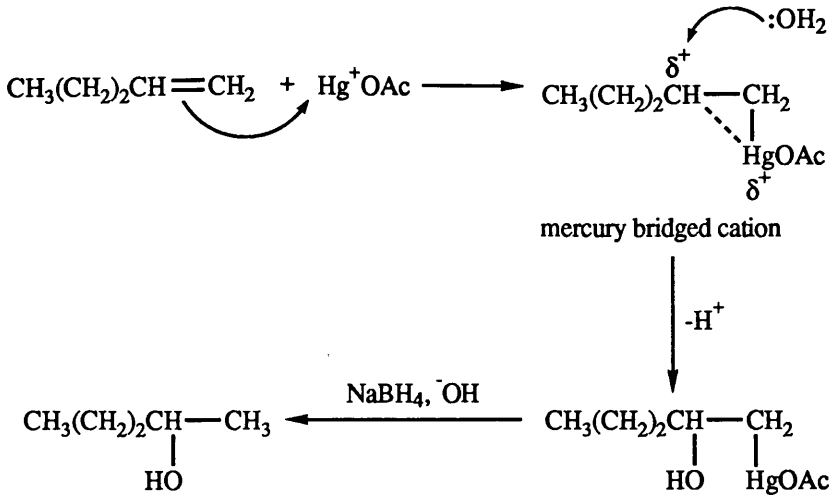
2.1 Introduction

Alkenes readily undergo addition reactions with mercury(II) salts in the presence of appropriate nucleophiles to produce organomercury compounds[45]. Brown *et al*[46] combined the oxymercuriation of alkenes with sodium borohydride reduction as a new route to alcohols (Scheme 35).



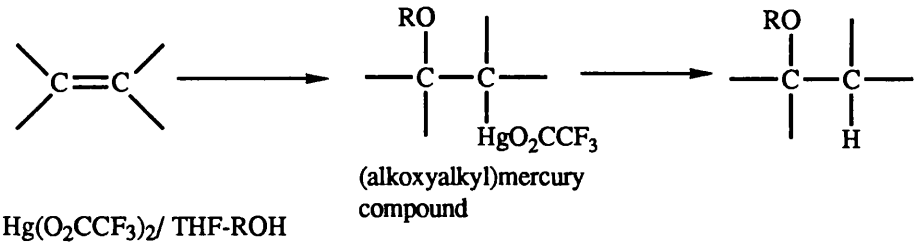
Scheme 35

In the first *oxymercuriation* step, water and mercury acetate add to the double bond. The second *demercuriation* step involves sodium borohydride reduction of the mercury acetate group which is replaced with hydrogen. This *oxymercuriation-demercuriation* process is highly regioselective as the net orientation of the addition of -H and-OH is in accordance with Markovnikov's rule. The orientation of addition in the *oxymercuriation* stage and the general lack of accompanying rearrangements is accounted for by the intermediacy of a mercury bridged cation (Scheme 36).



Scheme 36

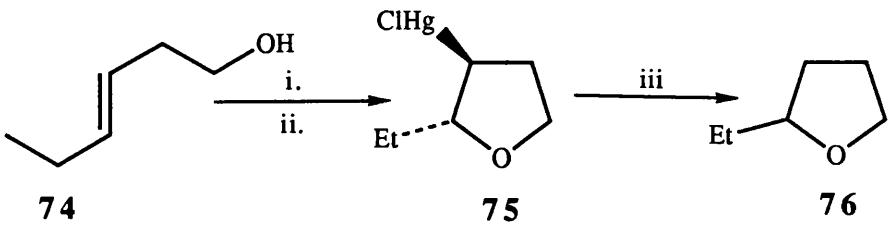
A similar reaction occurred with mercury trifluoroacetate in tetrahydrofuran containing alcohol. Alkoxyalkyl-mercury compounds were formed, which when treated with basic sodium borohydride give ethers (Scheme 37)[47].



i. $Hg(O_2CCF_3)_2$/ THF-ROH
ii. $NaBH_4$, ^-OH

Scheme 37

Intramolecular oxymercuration of suitably unsaturated alcohols can lead to the formation of cyclic ethers[48,49,50]. An early example of this type of reaction was provided by Henbest and Nicholls (Scheme 38)[48]. Treatment of *trans*-hex-3-enol (**74**) with mercury(II) acetate in methanol followed by anion exchange with aqueous sodium chloride gave (**75**), which on reduction with hydrazine gave 2-ethyltetrahydrofuran (**76**).

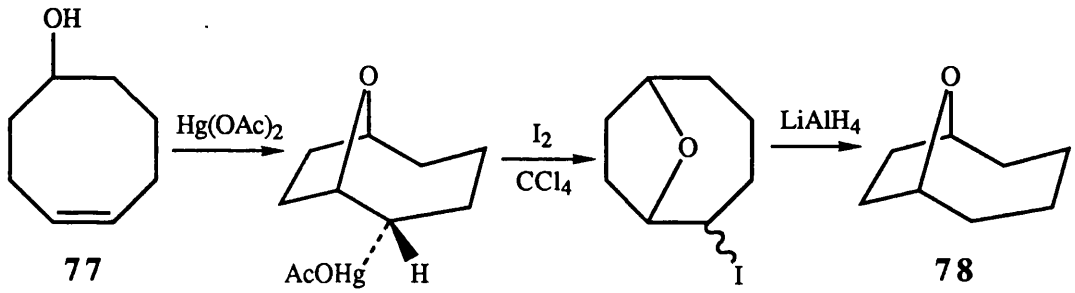


74 75 76

i. $Hg(OAc)_2$
ii. NaCl
iii. hydrazine

Scheme 38

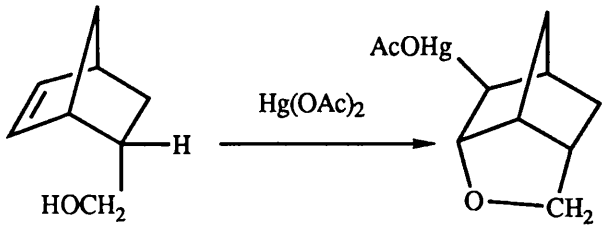
Paquette and Strom[50] used a similar method to form bicyclic ether (**78**) from the oxymercuration of 4-cycloocten-1-ol (**77**) (Scheme 39).



77 78

Scheme 39

Fractor and Taylor[49] provided a further example of the use of intramolecular oxymercuration for the formation of 5-membered rings. Bicyclo[2.2.1]hept-2-en-5-*endo*-yl methanol (**79**) was treated with mercury acetate to give (**80**) (Scheme 40).

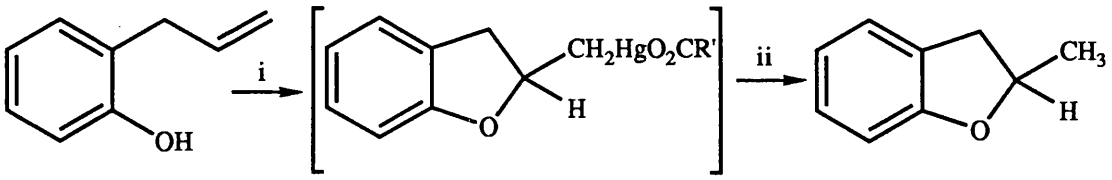


79 80

Scheme 40

In order for cyclisation to occur with norbornene derivatives, the hydroxymethyl group must be in either the *endo*-5 or *syn*-7 position[45]. Grundon *et al*[51]

carried out an early example of this type of reaction by treating *o*-allylphenol with mercury(II) salts of a range of chiral carboxylic acids. This was followed by reductive demercuration to give optically active 2,3-dihydro-2-methylbenzofuran (**81**) (Scheme 41).

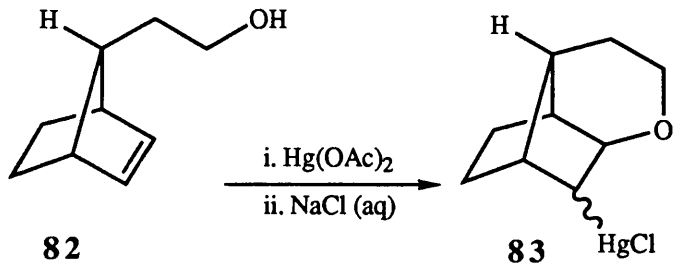


81

i. $Hg(O_2CR')_2$
ii. $NaBH_4$, ^-OH

Scheme 41

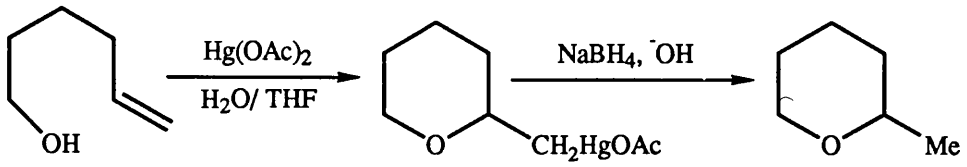
Bly *et al*[52] treated bicyclic alcohol (**82**) with mercury acetate in methanol. Intramolecular addition of the *syn*-hydroxyl oxygen and mercuric acetate across the double bond occurred to give tricyclic ether (**83**) (Scheme 42)



82 **83**

Scheme 42

Brown *et al* formed six membered ring (**85**) by combining oxymercuration of hex-5-en-1-ol (**84**) with sodium borohydride reduction (Scheme 43)[45].

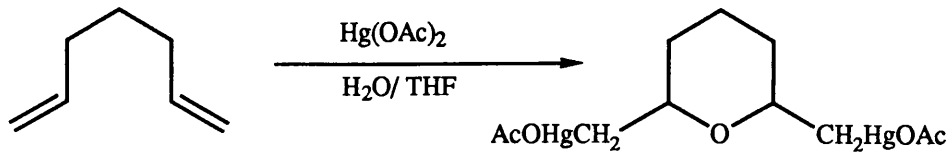


84 **85**

Scheme 43

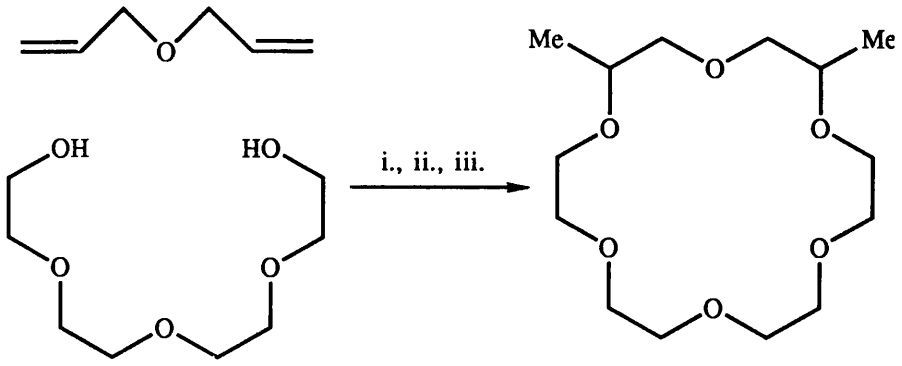
Brown and co-workers also generated starting alcohols for oxymercuration by

hydroxymercuriation of an appropriate diene (Scheme 44)[45].



Scheme 44

Bloodworth *et al*[53] exploited the Brown[47] combination of cyclooxymercuriation followed by sodium borohydride reduction in the synthesis of phase transfer catalyst 2,6-dimethyl-18-crown-6 (**86**) (Scheme 45).

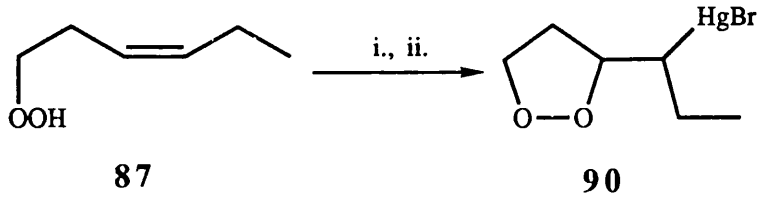


86

i. $Hg(OAc)_2$-$KClO_4$-$HClO_4$
ii. KCl
iii. $NaBH_4$-NaOH

Scheme 45

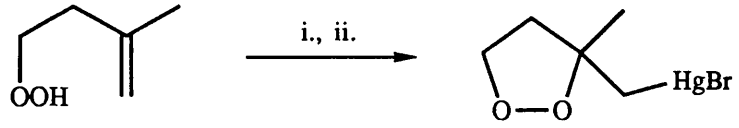
Intramolecular oxymercuriation of unsaturated hydroperoxides has been useful in the synthesis of cyclic peroxides. Porter *et al*[54] treated unsaturated hydroperoxides (**87**), (**88**) and (**89**) with mercuric acetate to form five-membered cyclic peroxides (**90**), (**91**) and (**92**) respectively (Schemes 46, 47 and 48).



87 90

i. $Hg(OAc)_2$
ii. $KBr_{(aq)}$

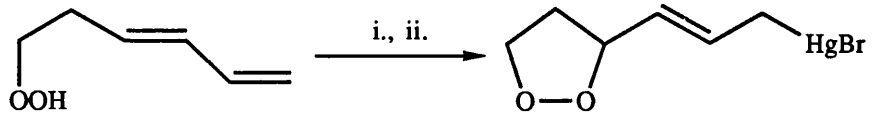
Scheme 46



88 91

i. $Hg(OAc)_2$
ii. $KBr_{(aq)}$

Scheme 47

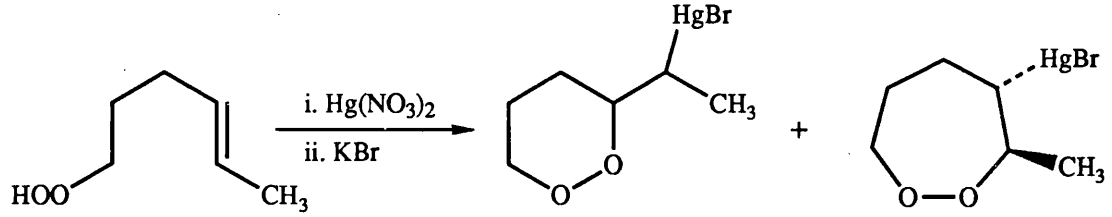


89 92

i. $Hg(OAc)_2$
ii. $KBr_{(aq)}$

Scheme 48

Peroxide **(93)** gave a mixture of two ring peroxides **(94)** and **(95)** on reaction with $Hg(NO_3)_2.H_2O$ (Scheme 49)[54].

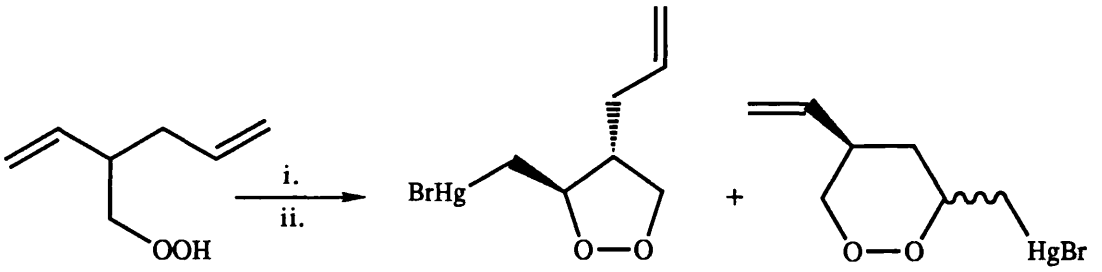


93 94 95

Scheme 49

Bloodworth *et al*[55] found that mercury-salt-induced cyclisation of diene

hydroperoxide (**96**) was not regiospecific. High stereoselectivity with respect to dioxolane (**97**) was observed (Scheme 50)

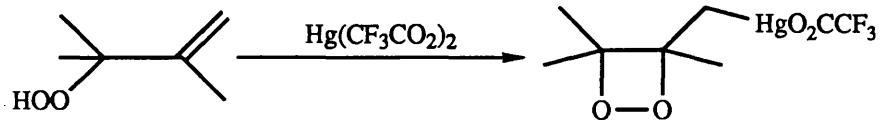


96 **97**

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

Scheme 50

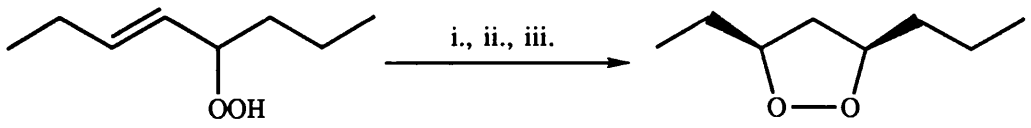
Allylic hydroperoxides are expected to cyclise less readily. However, depending on the structure of the hydroperoxide used and under suitable conditions both 4-*exo* (Scheme 51)[56] and 5-*endo* (Scheme 52)[57] cyclisations have been observed. Adam *et al*[56] detected the 4-*exo* cyclisation product, dioxetan (**99**) from the cycloperoxymercuriation of (**98**) (Scheme 51).



98 **99**
(minor product)

Scheme 51

Courtneidge *et al*[57] achieved a 5-*endo* ring closure of allylic hydroperoxide (**100**) by reaction with mercury(II) acetate to give dioxolane (**101**) (Scheme 52).

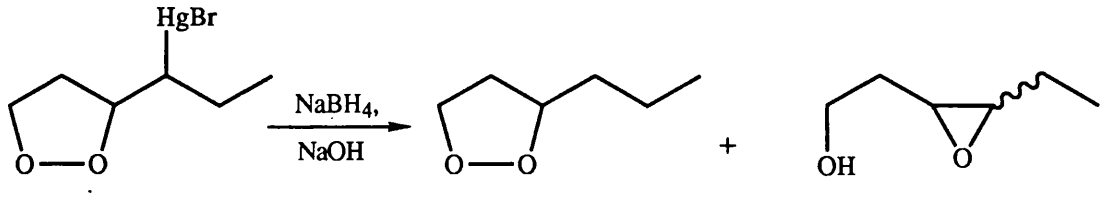


100 **101**

i. $Hg(OAc)_2$
ii. NaBr
iii. $NaBH_4$, NaOH

Scheme 52

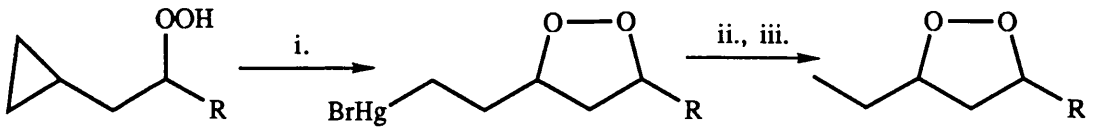
Although mercury(II)-mediated cyclisation of alkenyl hydroperoxides is a useful route to cyclic peroxides, the demercuration step can lead to two possible products. The desired cyclic peroxide (**102**) can be formed from **90**, by a free radical mechanism involving hydrogen abstraction by the β-peroxyalkyl radical, alternatively intramolecular homolytic displacement at oxygen may occur followed by hydrogen abstraction to give hydroxyalkyloxirane (**103**) (Scheme 53).



90 **102** **103**

Scheme 53

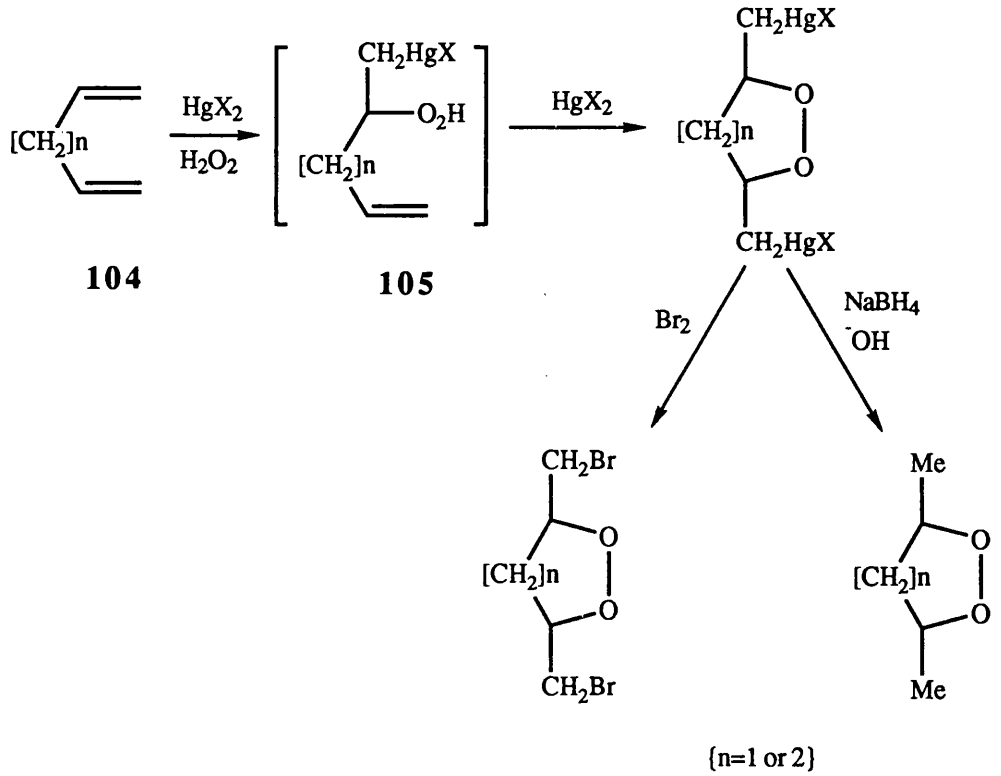
In certain cases the extent of hydroxyalkyloxirane formation can even become predominant. To overcome this problem Bloodworth and Korkodilos[58] developed the peroxymercuration of cyclopropanes as a new route to cyclic peroxides. This method afforded starting peroxides with the mercurio substituent one carbon atom further removed from the O-O bond than those derived from alkenes, thereby reducing the possibility of intramolecular homolytic substitution at oxygen (Scheme 54).



i. $Hg(OAc)_2$, 0.2 $HClO_4$
ii. KBr, H_2O
iii. $NaBH_4$, NaOH

Scheme 54

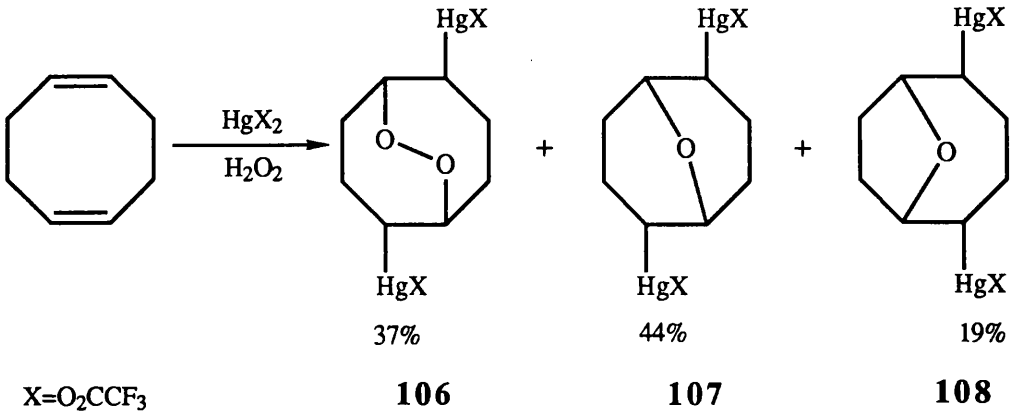
The hydroperoxymercuriation of suitable dienes **(104)** affords unsaturated hydroperoxides **(105)** capable of cyclising by subsequent intramolecular peroxymercuriation (Scheme 55)[59-64]. The reaction was rationalized by hydroperoxymercuriation of one double bond followed by mercury(II)-salt-induced cyclisation. Only 5- or 6-membered ring formation was observed.



Scheme 55

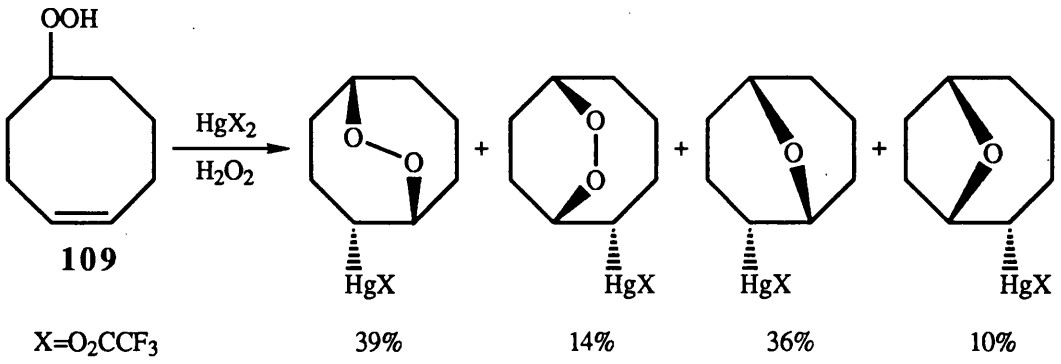
Peroxymercuriation of cyclic dienes leads to the formation of bicyclic peroxides **(106)** and bicyclic ethers **(107)** and **(108)** (Scheme 56)[62,63,64]. These compounds

were also assumed to arise *via* hydroperoxymercuration of one double bond, followed by a mercury(II)-salt-induced cyclisation reaction.



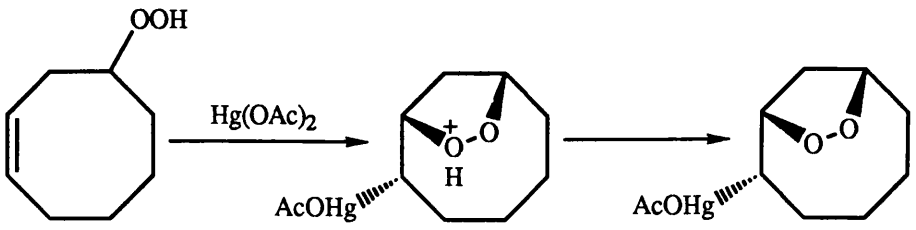
Scheme 56

To investigate the cyclisation step further, Courtneidge[65] treated 4-cyclooctenyl hydroperoxide (**109**) with mercury(II) trifluoroacetate to give bicyclic ethers and bicyclic peroxides (Scheme 57).



Scheme 57

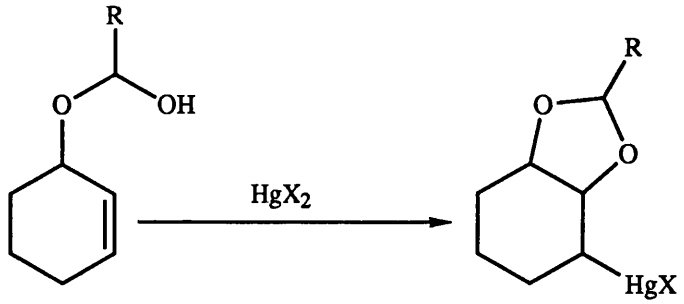
Spencer[66] treated cyclo-oct-3-en-1-yl hydroperoxide (**110**) with mercury acetate to give bicyclic peroxides only. The reason for this was thought to be the sterically favoured formation of *vic*-dialkylperoxonium ions (**111**) (Scheme 58).



110 **111**

Scheme 58

Overman *et al*[67] developed a route to cyclic acetals by mercury(II)-mediated cyclisation of hemiacetals (**112**) (Scheme 59). This reaction will be discussed in greater detail later on in the chapter.



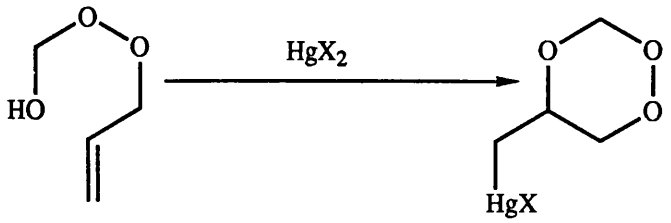
112

X=O_2CCF_3

(The -OH group acts as the internal nucleophile)

Scheme 59

We decided to base a new synthesis of 1,2,4-trioxanes on mercury(II)-mediated cyclisation of hemiperoxyacetals **73** (Scheme 60).



73

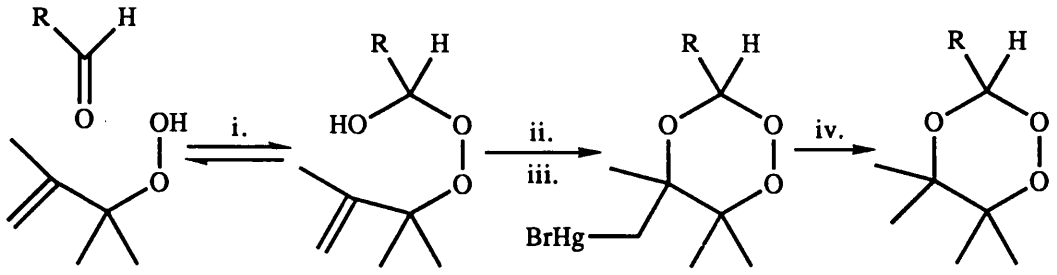
(The -OH group acts as the internal nucleophile)

Scheme 60

2.2 Results and Discussion

2.2.1 An intramolecular oxymercuriation route to 1,2,4-trioxanes

We applied the principle of intramolecular oxymercuriation to the synthesis of 1,2,4-trioxanes (Scheme 61)[68].



113 114 115 116

i. cat. CF_3COOH, CH_2Cl_2
ii. $Hg(OAc)_2$, 6 mol% $HClO_4$
iii. KBr
iv. $NaBH_4$, NaOH

Scheme 61

The starting 2,3-dimethylbut-1-en-3-yl hydroperoxide (**113**), was obtained in up to 90% yield by tetraphenylporphine-sensitised photooxygenation of 2,3-dimethylbut-2-ene[69]. Hemiperoxyacetal (**114**), was generated by the trifluoroacetic acid-catalysed addition reaction of crude **113** with aldehyde in dichloromethane solvent.

The formation of **114** was confirmed by ^1H nmr spectroscopy from the HOCHR proton signal of appropriate muliplicity at δ 4.8-5.2 where R was aliphatic and at δ 6.2-6.3 where R was aromatic. The extent of formation of **114** as determined

by ^1H nmr spectroscopy was 90-95% where aliphatic aldehydes were used and as little as 5% where the starting aldehydes were aromatic. Generally the intermediate hemiperoxyacetals were not isolated and were treated *in situ* with mercury acetate and perchloric acid catalyst. The oxymercurations (5-20 mmol scale) were completed in 1-3 hrs as judged by the time taken for the solid mercury acetate to dissolve, although there were no deleterious effects if the reactions were allowed to run overnight. In the examples where aliphatic aldehydes were used, the organomercury(II) bromides (**115**), were obtained as a pair of diastereoisomers after anion exchange with potassium bromide. Isolation by simple column chromatography (SiO_2, CH_2Cl_2) gave the pure componds in yields ranging from 56-86% (Table 2).

Table 2

Yields for 1,2,4-trioxanes derived from aldehydes (Scheme 59).

Compound	**R**	**115**% yield	**116**% yield
a	Me	60	62[x]
b	Et	62	54[x]
c	Pr	80	85[x]
d	^iPr	56	55[+]
e	^tBu	59	58[+]
f	CCl_3	86	not isolated
g	2-$NO_2C_6H_4$	20	27[x]
h	4-ClC_6H_4	21	23[x]
i	C_6H_5	not isolated	38[x]

(Where **x** is the overall yield calculated from **113** by 'one-pot' method
and **+** is the overall yield calculated from **113** by the reduction of **115**)

The sodium borohydride reductions[70] proceeded in over 90% yield with little or no side products and the 3-alkyl-1,2,4-trioxanes (**116**, R=alkyl) were purified by simple column chromatography (SiO_2, CH_2Cl_2) followed by bulb-to-bulb distillation under reduced pressure if necessary. In the examples where aromatic aldehydes were used, the crude organomercury(II) bromides (**115**, R=aryl) contained appreciable amounts of starting aldehyde, which could not be removed by simple column chromatography. However separation of the 5-(bromomercuriomethyl)-3-(aryl)-1,2,4-trioxanes **115**, from unreacted aromatic aldehydes was achieved by treating the mixture with a sodium chlorite-hydrogen peroxide system buffered with sodium phosphate

(Scheme 62)[71]. The net result of this reaction was oxidation of the aromatic aldehyde impurity to the corresponding carboxylic acid which was subsequently converted to the sodium salt and washed out in the aqueous layer, leaving **115** (R=aryl) dissolved in the organic layer.

$$NaClO_2 + H_2O \rightleftharpoons HClO_2 + NaOH$$

$$RCHO + HClO_2 \longrightarrow RCOOH + HOCl$$

The purpose of the hydrogen peroxide was to scavenge the HOCl

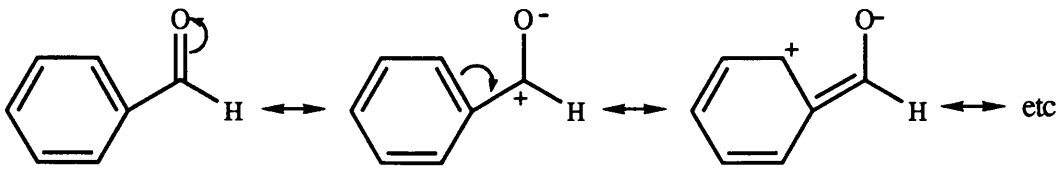
$$HOCl + H_2O_2 \longrightarrow HCl + H_2O + O_2$$

Scheme 62

The aromatic organomercury(II) bromides **115**, were then purified by column chromatography (SiO_2, CH_2Cl_2) and obtained in yields ranging from 20-21% (Table 2).

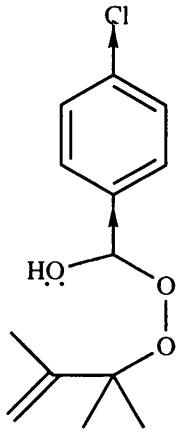
The low yields for aromatic 1,2,4-trioxanes **115** and **116** may be due to a very low extent of hemiperoxyacetal **114** formation (about 5% as judged from ^1H nmr spectroscopy). Low formation of **114** was attributed to the low reactivity of aromatic aldehydes with compounds like **113**, because of resonance stabilisation (Fig 1).

Figure 1



In addition the electron-withdrawing effect of substituents like -Cl on the aryl group would tend to reduce the nucleophilicity of the internal nucleophile (-OH) in **114** (Fig 2) making trioxane formation by intramolecular oxymercuriation less likely.

Figure 2



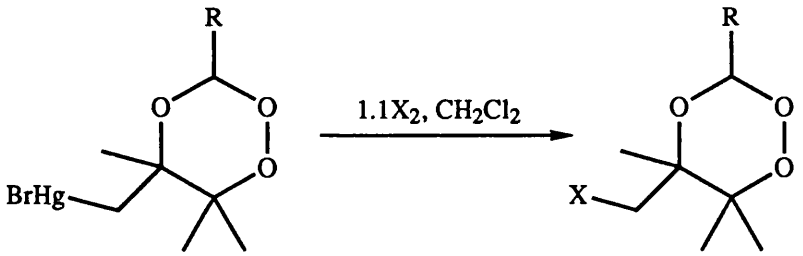
nucleophilicity of -OH is decreased by the electron-withdrawing effect of aryl group

The three steps of the syntheses (Scheme 59) could also be carried out consecutively in the same reaction vessel. In this 'one-pot' procedure, the anion exchange was omitted and the solution was washed with 5% aqueous sodium bicarbonate before commencing the sodium borohyride reduction. The 'one-pot' procedure for the aromatic compounds involved using ethanolic rather than aqueous sodium borohydride for the reductions. In this way the unreacted aldehydes present were converted into their corresponding alcohols, which were readily separated from **116** (R=aryl) by chromatography (SiO_2, CH_2Cl_2). The 'one-pot' method is fast and convenient as it avoids handling the intermediate mercurials **115**. The overall yields of the mercury-free 1,2,4-trioxanes were improved by the 'one-pot' method by up to 10%. For example compound **116a** was isolated in 55% yield after reduction of **115a**, but by using the 'one-pot' procedure the yield was improved to 62%. Similarly compound **116c**, obtained by reduction of compound **115c** was isolated in 80% yield, but this overall yield was improved to 85% by omitting the anion exchange step and following the 'one-pot' route.

All new 1,2,4-trioxanes gave satisfactory C and H analyses and positive peroxide tests with acidic iron(II) thiocyanate. The high field proton and carbon-13 nmr spectra were consistent with their structures. The organomercurials **115** were each obtained as a pair of diastereoisomers and isomerism was removed by reduction to compounds **116**.

2.2.2 Halogenodemercurations of organomercurial 1,2,4-trioxanes

Halogenodemercurations were carried out in subdued lighting by the dropwise addition of a solution of bromine or iodine to **115**. The halogen-substituted 1,2,4-trioxanes (**117**) thus formed were isolated by column chromatography (SiO_2, CH_2Cl_2) in high yields (Scheme 63).



115

117
a. R=Me, X=Br, 90%
f. R=Et, X=I, 98%

Scheme 63

2.2.3 NMR Studies and Determination of Stereochemistry

The presence of the 1,2,4-trioxane ring in compounds **115**, **116** and **117** was confirmed by the ^{13}C nmr signals observed for the ring-carbon atoms at δ 94-99 (C-3), δ 80-84 (C-6) and δ 75-79 (C-5) and by the ^{1}H nmr signals of appropriate multiplicity observed for the CHR proton at δ 5.0-5.5 (R=alkyl), or δ 6.3-6.8 (R=aryl) (see spectra at the end of this chapter).

The spectra of the organomercurials **115**, additionally showed characteristic signals for the CH_2HgBr group at δ_C 45-46 [$^{1}J(^{13}C\text{-}^{199}Hg)$ *ca.* 1550 Hz] and δ_H 2.0-2.3 (AB pattern with the downfield doublet showing long range coupling to the *gem* methyl group). This suggested restricted rotation about the $BrHgCH_2$-ring bond, as a result of steric effects or due to attractive interactions between the mercurial group and the O^{4} atom of the trioxane ring.

The halogeno compounds, **117** were formed as a pair of diastereoisomers as expected from the presence of chiral centres at C-3 and C-5. The key nmr features were very similar to the starting organomercurials. The ^{1}H nmr spectra of the major isomer showed the characteristic H^3 signals of appropriate multiplicity. The spectra differed from those of the precursor **115**, in the chemical shifts of the H^AH^B doublets which appeared between δ 3.1-3.4. Here again as for compounds **115**, the downfield doublet of the AB pattern showed long range coupling to the *gem* methyl group. This implied that restriction about the CH_2-ring bond could not be due to attractive interactions and

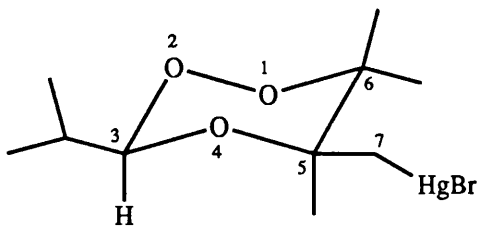
was therefore probably steric in origin. Another distinctive feature in the carbon spectra of **117**, was the signal due to CH_2X (X=Br or I) which was observed at δ 14.38 for **117f** (X=I) and at δ 38.6 for **117a** (X=Br).

Nuclear Overhauser effect (NOE) experiments were carried out to determine the stereochemistries of the major and minor diastereoisomers of organomercurial compounds **115**. NOE works by the principle that two protons close in space will interact. Saturation of the signal due to one proton will therefore cause rapid relaxation of the second proton's signal resulting in an enhancement of that signal. Compound **115d** (R=^{i}Pr) was used for the NOE measurements. The R group attached to C-3 was reasonably assumed to lie in the equatorial position so H^3 had to be axial, therefore any proton exhibiting an NOE to H^3 must also be axial or in an axial group.

Table 3 NOE measurements

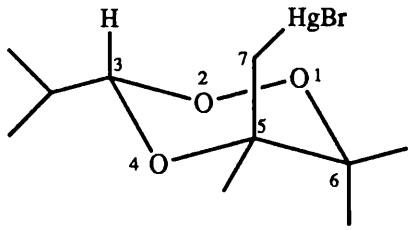
Isomers	**H^i**	**H^o**	**% enhancement of H^o**
Major	Me on C-6	H^7	4.3
	H^7	Me on C-6	4.0
	Me on C-5	H^3	7.2
Minor	H^7	H^3	4.2

H^i-proton irradiated, H^o-proton observed



MAJOR

Figure 3



MINOR

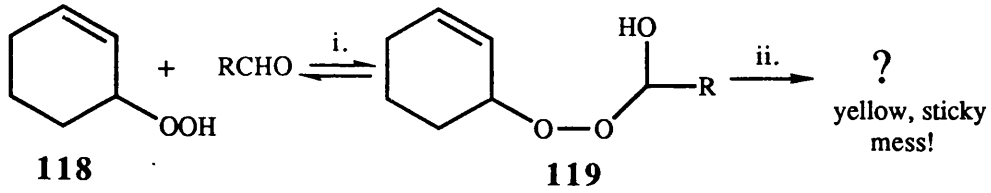
Figure 4

The results (Table 3) show that in the major isomer (Figure 3), the CH_2HgBr group must lie in the equatorial position as there is a key NOE measurement of 7.2% between H^3 and the protons of the axial methyl group on C-5. In the minor isomer (Figure 4), the CH_2HgBr group must therefore lie in the axial position. This was confirmed by irradiation of the downfield H^7 signal which resulted in a 4.2% enhancement at H^3 (the upfield H^7 signal overlaps with the major isomer). All the methyl group signals were

irradiated but table 3 shows only those cases where an NOE was observed.

2.2.4 Other hydroperoxides

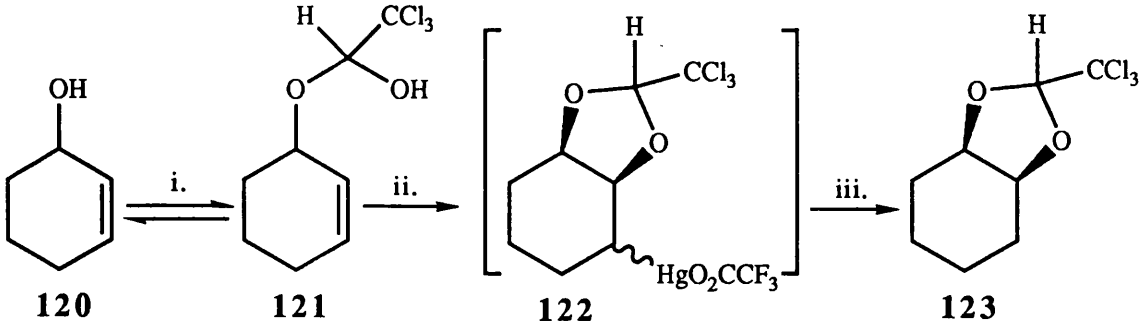
The trifluoroacetic acid catalysed reaction of cyclohexenyl hydroperoxide (**118**) with aldehydes gave hemiperoxyacetals (**119**). However subsequent reaction of **119** with mercury(II) acetate did not give 1,2,4-trioxanes, even after 12 hrs reaction time (Scheme 64). The ^{1}H and ^{13}C nmr spectra of the end products were very complicated and but clearly showed that unsaturation was still present. We were unable to identify the products.



i. cat. CF_3CO_2H, CH_2Cl_2
ii. $Hg(OAc)_2$

Scheme 64

Overman *et al*[67] formed hemiacetal (**121**) by reacting 2-cyclohexen-1-ol (**120**) with chloral. Treatment of **121** with mercury(II) trifluoroacetate for a critical 48 hrs followed by demercuration with alkaline sodium borohydride afforded the cyclic chloral adduct (**123**) in 62% yield (Scheme 65).

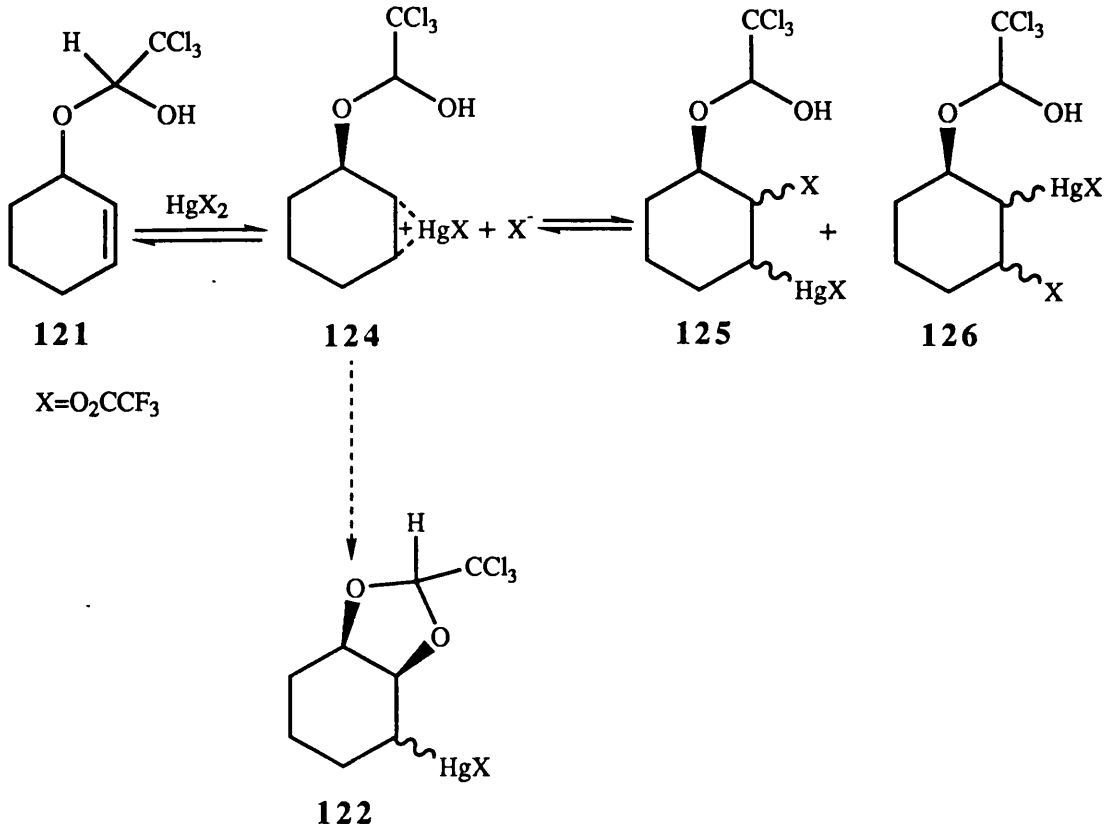


i. $2CCl_3CHO$, THF
ii. $Hg(O_2CCF_3)_2$
iii. $NaBH_4$, NaOH

Scheme 65

The time course of cyclic acetal formation was studied in detail. Build up of **122**

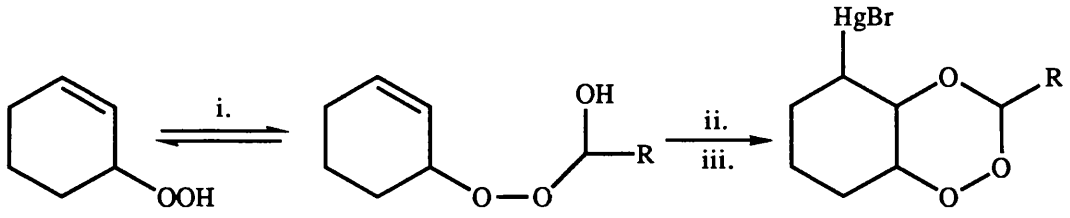
(characterised after demercuriation to **123**) occurred slowly and reached a maximum only after 50 hrs. However, the hemiacetal **121**, disappeared rapidly and was present to an extent of only 22% 15 minutes after the addition of mercury(II) trifluoroacetate. The slow build up of **122** coupled with the rapid disappearance of **121** was attributed to the initial reversible formation of adducts **(125)** and **(126)**. However, the thermodynamically favoured capture of an intermediate mercurinium ion **(124)** at C-2 by the hydroxyl group could dominate leading to **122** formation (Scheme 66).



Scheme 66

Mercury(II) trifluoroacetate was presumably used instead of mercury(II) acetate because of its greater solubility in organic solvents and because the trifluoroacetate anion is much more labile than the acetate anion[72].

We decided to apply Overman's[67] conditions to our hemiperoxyacetals **119** (Scheme 67).



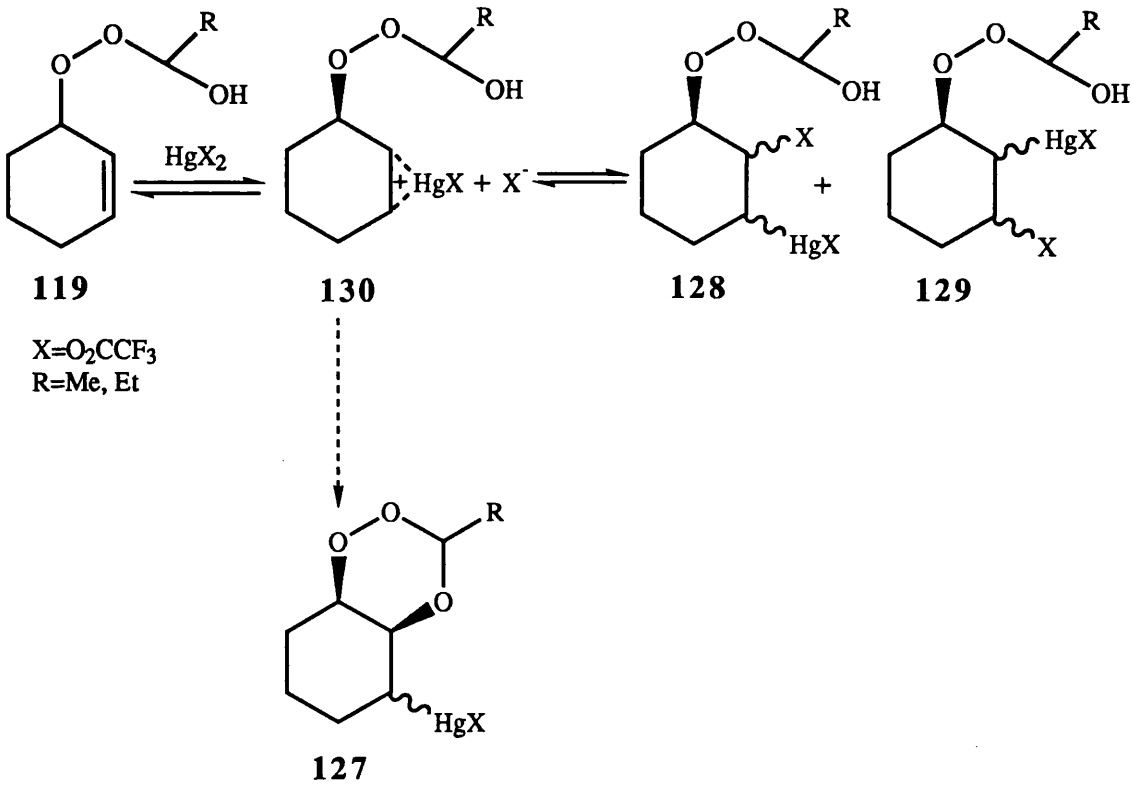
118 **119** **127**

a. R=Me 12%
b. R=Et 15%

i. 2RCHO, CH_2Cl_2
ii. $Hg(O_2CCF_3)_2$, 48hrs
iii. KBr (aq)

Scheme 67

After 12 hrs, a sample of mixture was removed from the reaction vessel in order to collect some ^{13}C nmr data. At this stage the spectrum was complicated and did not contain the characteristic signals for trioxane-ring-carbons. In fact a critical 48 hrs reaction time with mercury(II) trifluoroacetate was needed for the desired reaction to occur. The reason for this long reaction time was thought to be the initial formation of adducts **(128)** and **(129)** (cf. **125** and **126**). As in Overman's[67] examples, the adducts were presumed to exist in equilibrium with an intermediate mercurinium ion **(130)**. The thermodynamically favoured capture at C-2 of **130** by the hydroxyl group led to the formation of **127** (Scheme 68). Purification was carried out by simple column chromatography (SiO_2, CH_2Cl_2), followed by HPLC. Two isomers of **127a** (R=Me) and a single isomer of **127b** (R=Et) were isolated.



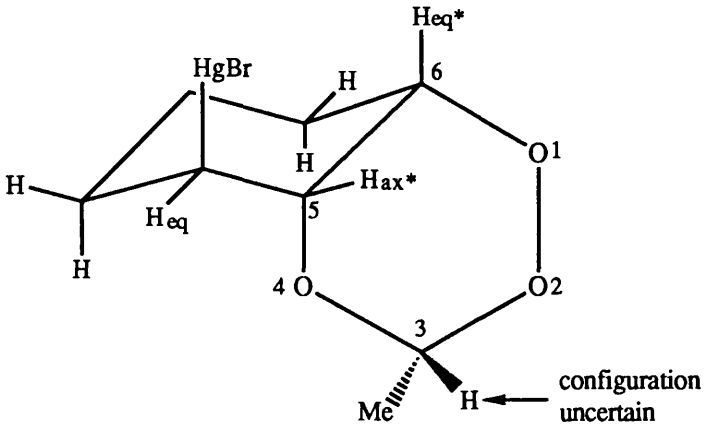
Scheme 68

The presence of the trioxane ring in **127a** (major isomer) and **127b** was confirmed by the ^{13}C nmr signals for ring-carbons at δ 101-105 (C-3), δ 79-80 (C-6) and δ 74 (C-5). The ring-carbons for **127a** (minor isomer) were observed slightly downfield at around δ 103 (C-3), δ 85 (C-6) and δ 82 (C-5). The normal stereochemical outcome of peroxymercuration is *trans*-addition, but this could not be assumed in this case since equilibrium conditions applied. However the ^1H nmr spectrum of the major isomer of **127a** was consistent for a *cis*-fused (*trans*-added) product as shown in figure 5. Therefore as expected, the quartet due to H^3 was observed at δ 5.32. The H^6 proton (next to O-O) has one *anti* coupling (to the axial proton of the adjacent CH_2 group of the cyclohexane ring) and two *gauche* couplings (to the equitorial proton of the adjacent CH_2 group of the cyclohexane ring and to H^5). *Anti* couplings are generally large and *gauche* couplings are small therefore, the signal appeared as a broad multiplet (ddd) at δ 3.99. The H^5 proton (next to O) has two *gauche* couplings (to H^6 and to CHHgBr) and was observed as a sharp triplet downfield of the H^6 signal at δ 4.29. The CHHgBr proton has three *gauche* couplings (to H^5 and to the adjacent CH_2 protons) and appeared as an apparent quintet at δ 3.34;

presumably one of the protons was not coupled to it. This signal also showed that the position of the HgBr group corresponds to *trans*-addition. The observation of the H^6 signal upfield of H^5 seems somewhat unusual, however this may be due to the fact that H^6 is equatorial and H^5 is axial with respect to the trioxane ring. Heteronuclear correlation nmr established that the signal at δ 3.99 was due to a proton attached to C-OO (ie H^6) and that the signal at δ 4.29 was due to a proton attached to C-O (ie H^5) (see the Hetcor pulse sequence ^1H / ^{13}C nmr signal correlations at the end of this chapter). The ^1H nmr spectrum for **127b** was very similar to **127a**. The only significant difference was in the multiplicity of the H^3 signal which was observed as a triplet at δ 5.13 for compound **127b**.

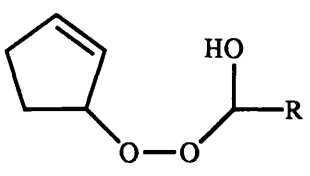
Figure 5

cis-fused (*trans*-added product)

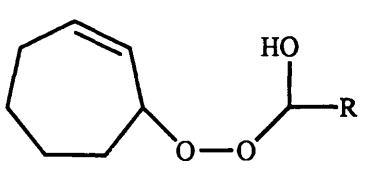


eq*-in equatorial position with respect to trioxane ring
ax*- in axial position with respect to trioxane ring
eq-in equatorial position with respect to cyclohexane ring

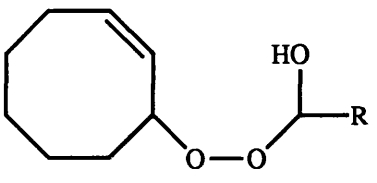
It has since been shown by others that the mercury(II) trifluoroacetate reaction cannot be extended to 5-, 7- or 8-membered ring systems. Hemiperoxyacetals **131**, **132** and **133** were treated with mercury(II) trifluoroacetate for up to 60 hrs. However no 1,2,4-trioxane formation was observed, although trifluoroacetate incorporation was detected by infra-red spectroscopy[73].



131



132



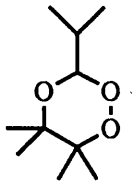
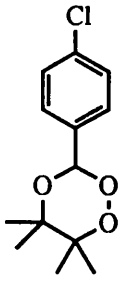
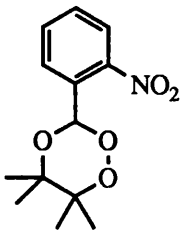
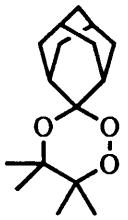
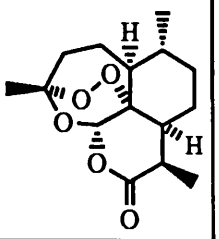
133

2.2.5 Antimalarial activity of 1,2,4-trioxanes

Some of the new 1,2,4-trioxanes were tested for biological activity by Dr Warhurst of the London School of Tropical Medicine and Hygiene.

Ethanolic extracts of 1,2,4-trioxanes **116d, 116g, 116h** and **149d** (synthesis to be discussed in chapter 3), were tested for antimalarial activity *in vitro* by assessing their ability to inhibit the uptake of the dye [G^3-H]-hypoxanthine, into *P. falciparum* (the chloroquine-resistant strain) cultured in human blood. The IC_{50} values were determined on the basis of 10-fold dilutions followed by 2-fold dilutions within selected ranges of concentrations (the ethanol concentration for tested dilutions was not more than 0.1%). Table 4, shows the IC_{50} value of artemisinin **5** along with IC_{50} values obtained for some new 1,2,4-trioxanes.

Table 4. Antimalarial activity (*in vitro*) of artemisinin and some new 1,2,4-trioxanes

					
Trioxanes	**116d**	**116h**	**116g**	**149d**	**5**
IC_{50} nmol l^{-1}	90, 000	5140	1310	9.7	10-30

Of all the new 1,2,4-trioxanes tested, the simple alkyl compound **116d** showed the lowest antimalarial activity. The aromatic compounds **116g** and **116h**, were significantly more active than compound **116d** and the *ortho*-nitro-substituted aromatic trioxane **116g** was four times as active as the *para*-chloro counterpart **116g**. The most striking result was observed for the adamantyl-substituted compound **149d** (synthesis to be discussed in next chapter), which was found to have antimalarial potency of similar magnitude to that of artemisinin **5**. However, many more compounds need to be tested before a general structure-activity pattern emerges.

2.3 Conclusion

The new synthesis of 1,2,4-trioxanes *via* intramolecular oxymercuriation utilises readily available starting materials, is easy to carry out and is potentially very general. Starting allylic hydroperoxide **113** was obtained in good yield by singlet oxygenation[69] of the appropriate alkene and the crude product was used for the reversible addition reaction with aldehydes to form hemiperoxyacetals **114.** The overall 1,2,4-trioxane yields seem to be dependent in part, on the extent of hemiperoxyacetal formation. Where aliphatic aldehydes were used the extent of **114** formation was high (90-95%) and reaction with mercury(II) acetate resulted in good yields of **115** (60-86%). The extent of formation of **114** where aromatic aldehydes were used was very low and this was reflected in poor 1,2,4-trioxane yields (20-25%). The alkaline sodium borohydride reductions of **115** to **116** proceeded efficiently, but the 'one-pot' method for **116** formation gave overall better yields.

Nuclear Overhauser effect measurements on organomercurial compound **115d** (R=^{i}Pr) confirmed that in the major diastereoisomer the CH_2HgBr group was equatorial, whereas in the minor isomer it was in the axial position.

Halogenodemercuriation of compounds **115** made available the corresponding halogen-containing 1,2,4-trioxanes **117** (X=I or Br) in very good yields (90-98%). As with compounds **115**, the halogeno-1,2,4-trioxanes **117** were observed as a pair of diastereoisomers.

Bicyclic 1,2,4-trioxanes **127**, were made available by treating hemiperoxyacetal **119** with mercury(II) trifluoroacetate for a critical 48 hrs. The long reaction time was thought to be due to the initial incorporation of trifluoroacetate to give adducts **128** and **129**, which were in equilibrium with an intermediate mercurinium ion **130**. 1,2,4-Trioxane formation could then only occur by the thermodynamically favoured capture at C-2 of **130** by the -OH group.

Finally some 1,2,4-trioxanes synthesised by the new intramolecular oxymercuriation route, were found to be significantly active *in vitro* against *P. falciparum* (the chloroquine-resistant strain of malaria).

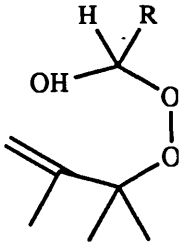
2.4 Experimental

2,3-Dimethylbut-1-en-3-yl hydroperoxide (113)[69]

2,3-Dimethylbut-2-ene (0.2mol; 16g) in dichloromethane (350ml) containing the sensitiser, tetraphenylporphine (20mg) was irradiated with a 400w sodium lamp in an immersion cell apparatus. Oxygen gas was bubbled through. After 5h, the lamp was switched off. The dichloromethane solvent was removed under reduced pressure to give the crude product as an oil in 95% yield.

^{1}H nmr (60 MHz) : δ 1.6 (s, 6H), 2.1 (s,3H), 5.2 (m, 2H, CH_2=C), 8.2 (bs, OOH) ppm.
^{13}C nmr (100 MHz) : δ 147.98 (CH_2=C), 111.66 (CH_2=C), 84.14 (C-OOH), 23.74 (2C), 18.55 (CH_2=CCH_3) ppm.

Hemiperoxyacetal formation (114)



114a (R=Me)

A solution of **113** (10mmol; 1.16g) in dichloromethane (15ml) was treated with acetaldehyde (20mmol; 0.88g) and trifluoroacetic acid catalyst (4 drops). The mixture was stirred at room temperature for 5mins after which the solvent was removed under reduced pressure. The extent of formation of **114a** was 90-95% (as determined from ^{1}H nmr spectroscopy).

^{1}H nmr (60 MHz) : δ 1.1 (d, 3H, CHC**H$_3$**), 1.4 (s, 6H), 1.8 (s, 3H, CH_2CC**H$_3$**), 4.9 (m, 2H, **CH_2**=C), 5.3 (q, 1H, **CH**OH), 5.8 (bs, **OH**) ppm.
^{13}C nmr (100 MHz) : δ 148.16 (CH_2=**C**), 111.49 (**CH_2**=C), 97.09 (**C**HOH), 83.84 (**C**Me_2), 24.30 ($CHCH_3$), 24.0 (2C), 18.64 (CH_2=CCH_3) ppm.

Hemiperoxyactals were similarly obtained using a one molar equivalent of chloral, propanal, butanal, 2-methyl-propanal, 2,2-dimethyl-propanal, 4-chlorobenzaldehyde and 2-nitrobenzaldehyde in place of acetaldehyde. Where aliphatic aldehydes were used, the extent of formation of **114** as calculated from the ^{1}H nmr spectrum was 90-95%. For the aromatic aldehydes the extent of formation of **114** was as little as 5%.

114b (R=Et)

^{1}H nmr (60 MHz) : δ 1.0–1.4 (m, 5H, CH_2CH_3, overlap of separate proton signals), 1.5 (s, 6H), 1.9 (s, 3H, $CH_2=CCH_3$), 4.8 (m, 2H, $CH_2=C$), 5.2 (m, 1H, CHEt) ppm.

114c (R=Pr)

^{1}H nmr (60 MHz) : δ 0.6–1.0 (m, 7H, $CH_2CH_2CH_3$, overlap of separate proton signals), 1.2 (s, 6H), 1.7 (s, 3H, $CH_2=C-CH_3$), 4.7 (m, 2H, $CH_2=C$), 5.1 (m, 1H, CHOH) ppm.

114d (R=^{i}Pr)

^{1}H nmr (60 MHz) : δ 0.8–1.2 (m, 7H, $CH(CH_3)_2$), 1.3 (s, 6H), 1.85 (s, 3H, $CH_2=C-CH_3$), 4.9 (m, 3H, $CH_2=C$ and CHOH), 5.2 (bs, OH) ppm.

114e (R=^{t}Bu)

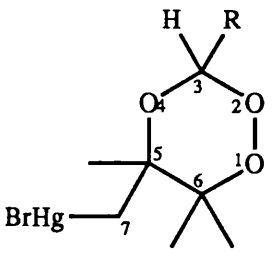
^{1}H nmr (60 MHz) :δ 0.98 (s, 9H, ^{t}Bu), 1.4 (s, 6H), 1.8 (s, 3H, $CH_2=C-CH_3$), 4.9-5.1 (m, 3H, $CH_2=C$ and CHOH), 6.2 (bs, OH) ppm.

114f (R=CCl_3)

^{1}H nmr (60 MHz) : δ 1.6 (s, 6H, $C(CH_3)_3$), 1.9 (s, 3H, CH_2CCH_3), 4.8 (bs, OH), 5.0 (m, 2H, $CH_2=C$), 5.3 (bs, 1H, CHOH) ppm.

^{13}C nmr (100 MHz) : δ 147.41 ($CH_2=C$), 112.18 ($CH_2=C$), 102.05 (CHOH), 97.18 (CCl_3), 85.62 (CMe_2), 24.34, 24.27, 18.60 ($CH_2=CCH_3$) ppm.

3-(Alkyl / Aryl)-5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxanes (115)



115a (R=Me)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g) in dichloromethane (20ml) was treated with acetaldehyde (20mmol; 0.88g) followed by catalytic trifluoroacetic acid (4 drops). The mixture was stirred at room temperature for 5-15min. Solid mercury(II) acetate (10mmol; 3.18g) was added in one portion with perchloric acid catalyst (6 mol%, 6 drops). The reaction was assumed to reach completion once all the solid mercury acetate had dissolved (0.5-1hr). The reaction mixture was washed with 5% aqueous sodium bicarbonate solution (10ml) to remove acid. Subsequent anion exchange of the acetate group for bromide was carried out by stirring with aqueous potassium bromide (10mmol; 1.19g in 10ml.H_2O) for 0.5hrs. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x15ml). The combined organic extracts were dried ($MgSO_4$). Removal of the dichloromethane solvent under reduced pressure gave the crude product. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.69) gave the pure product as a white solid (2.64g; 60%).

^{1}H nmr (200 MHz) Major isomer : δ 5.51 (q, J=5.25 Hz, 1H, **CH**CH_3), 2.22 (broad doublet, J=11.65 Hz, 1H, **CH^{a}H^b**HgBr, shows long range coupling to C5-Me), 2.01 (d, J=11.65 Hz, 1H, CH^a**H^b**HgBr), 1.49 (s, 3H), 1.45 (s, 3H), 1.23 (d, J=5.25 Hz, 3H, **CH**CH_3), 1.02 (s, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 95.72 (C-3), 83.38 (C-6), 78.0 (C-5), 45.79 ($^1J(^{13}C\text{-}^{199}Hg)$=1556.7 Hz, **C**$H_2$HgBr), 23.79 ($^3J(^{13}C\text{-}^{199}Hg)$=87.4 Hz, BrHg$CH_2$**C**$CH_3$), 21.80, 21.29, 18.15 ppm. Minor isomer :δ 95.45, 83.38, 76.94, 44.11, 27.14, 22.45, 21.54, 18.23 ppm.
Major:Minor isomer ratio 3.8:1
Found: C, 21.85; H, 3.44% $C_8H_{15}BrHgO_3$ requires: C, 22.03; H, 3.50%

A similar procedure was followed for compounds **115b-115f.**

115b (R=Et)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), propanal (10mmol; 0.58g), trifluoroacetic acid (2 drops), mercury acetate (5mmol; 1.59g), perchloric acid (3 drops), potassium bromide (5mmol; 0.6g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.77) gave the pure product as a white solid (1.40g, 62%).

^{1}H nmr (400 MHz) Major isomer : δ 5.26 (t, J=5.20 Hz, 1H, **CH**CH_2CH_3), 2.17 (bd, J=11.51 Hz, 1H, **CH^{a}H^b**HgBr, shows long range coupling to C5-Me), 2.02 (d,

J=11.51 Hz, 1H, CH^aH^bHgBr), 1.48-1.40 (m, 2H, CH_2CH_3), 1.45 (s, 3H), 1.40 (s, 3H), 0.97 (s, 3H), 0.84 (t, J=7.61Hz, 3H, CH_2CH_3) ppm. Minor isomer : δ 5.44 (t, J=5.33 Hz, 1H, $CHCH_2CH_3$), 3.10 (bd, J=11.63 Hz, 1H, CH^aH^bHgBr), 2.30 (d, J=11.63 Hz, 1H, CH^aH^bHgBr), 1.48-1.40 (m, 8H overlaps with major isomer), 0.89 (t, J=7.58 Hz, 3H, CH_2CH_3 overlaps with major isomer) ppm.

^{13}C nmr (100 MHz) Major isomer : δ 99.20 (C-3), 83.43 (C-6), 77.74 (C-5), 45.89 ($^1J(^{13}C\text{-}^{199}Hg)$=1553.6 Hz, CH_2HgBr), 25.21, 23.56, 21.71, 21.24, 7.74 ppm. Minor isomer : δ 99.01 (C-3), 83.43 (C-6, overlaps with major isomer), 77.49 (C-5), 44.50 (CH_2HgBr), 26.89, 25.21 (overlaps with major isomer), 22.31, 21.45, 8.03 ppm.

Major:Minor isomer ratio 4.8:1

Found: C, 24.10; H, 3.68% $C_9H_{17}BrHgO_3$ requires: C, 23.82; H, 3.78%

115c (R=Pr)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (14mmol; 1.63g), butanal (14mmol; 1.1g), trifluoroacetic acid (5 drops), mercury acetate (14mmol; 4.46g), perchloric acid (8 drops), potassium bromide (14mmol; 1.67g).

Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.82) gave the pure white solid product (5.24g, 80%).

^{1}H nmr (400 MHz) Major isomer : δ 5.40 (t, J=4.96 Hz, 1H, CHPr), 2.24 (bd, J=11.65 Hz, 1H, CH^aH^bHgBr, shows long range coupling to C5-Me), 2.06 (d, J=11.65 Hz, 1H, CH^aH^bHgBr), 1.53 (s, 3H), 1.47 (s, 3H), 1.35-1.40 (m, 4H, $CH_2CH_2CH_3$), 1.04 (s, 3H), 0.90 (t, J=7.3Hz, 3H, $CH_2CH_2CH_3$) ppm. Minor isomer : δ 5.47 (t, J=4.96 Hz, 1H, CHPr), 3.06 (bd,J=11.65 Hz, 1H, CH^aH^bHgBr), 2.25 (d, J=11.65 Hz, 1H, CH^aH^bHgBr), 1.55 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.35-1.42 (m, 7H, overlaps with major isomer) ppm.

^{13}C nmr (100 MHz) Major isomer : δ 98.74 (C-3), 83.71 (C-6), 78.05 (C-5), 45.77 (CH_2HgBr), 34.13 ($BrHgCH_2CCH_3$), 23.86, 21.92, 21.44, 17.04, 13.95 ppm. Minor isomer : δ 98.70, 83.71, 78.05 (overlaps with major isomer), 45.76, 34.18, 23.86 (overlaps), 21.92 (overlaps), 21.44 (overlaps), 17.19, 13.95 (overlaps) ppm.

Major:Minor isomer ratio 9:1

Found: C, 25.74; H, 3.99% $C_{10}H_{19}BrHgO_3$ requires: C, 25.68; H, 4.09%

115d (R=^{i}Pr)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (20mmol; 2.32g), 2-methyl-propanal (20mmol; 1.44g), trifluoroacetic acid (8 drops), mercury acetate (20mmol; 6.37g),

perchloric acid (12 drops), potassium bromide (20mmol; 2.38g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.88) gave the pure white solid product (5.24g, 56%).

^{1}H nmr (400 MHz) Major isomer : δ 5.13 (d, J=5.02 Hz, 1H, C**H**^{i}Pr), 2.24 (bd, J=11.65 Hz, 1H, C**H**^{a}H^{b}HgBr, shows long range coupling to C5-Me), 2.06 (d, J=11.65 Hz, 1H, CH^a**H**^{b}HgBr), 1.80 (m, J=1.9 Hz, 1H, C**H**$(CH_3)_2$), 1.51 (s, 3H), 1.45 (s, 3H), 1.03 (s, 3H), 0.92 (d, J=4.27 Hz, 3H), 0.89 (d, J=4.27 Hz, 3H) ppm. Minor isomer : δ 5.24 (d, J=5.12 Hz, 1H, C**H**^{i}Pr), 3.06 (bd, J=12.18 Hz, 1H, C**H**^{a}H^{b}HgBr), 2.25 (d, J=12.18 Hz, 1H, CH^a**H**^{b}HgBr), 1.8 (m, 1H, C**H**$(CH_2)_3$, overlaps with major isomer), 1.47 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 0.98 (m, 6H, CH$(\mathbf{CH_3})_2$) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 101.77 (C-3), 83.55 (C-6), 77.96 (C-5), 45.78 ($^1J(^{13}C\text{-}^{199}Hg)$=1541.4 Hz, $\mathbf{CH_2}$HgBr), 30.81(C**H**$(CH_3)_2$), 23.67, 21.86, 21.40, 16.82, 16.63 ppm. Minor isomer : δ 101.81, 83.61, 77.61, 44.42 ($\mathbf{CH_2}$HgBr), 30.93 (C**H**$(CH_3)_2$), 27.10, 22.45, 21.57, 17.18, 16.69 ppm.
Major:Minor isomer ratio 6.3:1
Found: C, 25.89; H, 3.91% $C_{10}H_{19}BrHgO_3$ requires: C, 25.68; H, 4.09%

115e (R=^{t}Bu)
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (20mmol; 2.32g), 2,2-dimethyl-propanal (20mmol; 1.72g), trifluoroacetic acid (8 drops), mercury acetate (20mmol; 6.37g),.perchloric acid (12 drops), potassium bromide (20mmol; 2.38g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.95) gave the pure white solid product (6.37g, 59%).

^{1}H nmr (400 MHz) Major isomer : δ 5.0 (s, 1H, C**H**^{t}Bu), 2.20 (bd, J=11.7 Hz, 1H, C**H**^{a}H^{b}HgBr), 2.07 (d, 11.7 Hz, 1H, CH^a**H**^{b}HgBr), 1.5 (s, 6H), 1.03 (s, 3H), 0.9 (s, 9H, C$(\mathbf{CH_3})_3$) ppm. Minor isomer : δ 5.07 (s, 1H, C**H**^{t}Bu), 3.06 (d, J=11.7 Hz, 1H, C**H**^{a}H^{b}HgBr), 2.2 (d, J=11.7 Hz, 1H, CH^a**H**^{b}HgBr, overlaps with major isomer), 1.26 (s, 6H), 1.02 (s, 3H), 0.93 (s, 9H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 103.48 (C-3), 83.44 (C-6), 78.08 (C-5), 45.83 ($^1J(^{13}C\text{-}^{199}Hg)$=1558.84 Hz, $\mathbf{CH_2}$HgBr), 34.44 (C$(\mathbf{CH_3})_3$), 24.60 (3C, C$(\mathbf{CH_3})_3$), 23.62, 21.90, 21.42 ppm. Minor isomer : δ 103.11, 83.44 (overlaps with major isomer), 78.08 (overlaps), 44.43, 34.76 (C$(\mathbf{CH_3})_3$), 25.15, 24.73 (3C, C$(\mathbf{CH_3})_3$), 22.50, 21.56 ppm.
Major:Minor isomer ratio 3.3:1
Found: C, 27.87; H, 4.34% $C_{11}H_{21}BrHgO_3$ requires: C, 27.42; H, 4.39%

115f (R=CCl_3)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (20mmol; 2.32g), chloral (20mmol), trifluoroacetic acid (8 drops), mercury acetate (20mmol; 6.37g),.perchloric acid (12 drops), potassium bromide (20mmol; 2.38g). The crude product was obtained in 83% yield.

^{1}H nmr (60 MHz) : δ 5.48 (s, 1H, $CHCCl_3$), 2.6 (bd, J=12.14 Hz, 1H, CH^aH^bHgBr, shows long range coupling to C5-Me), 2.46 (d, J=12.14 Hz, 1H, CH^aH^bHgBr), 2.2 (s, 3H), 2.0 (s, 3H), 1.5 (s, 3H) ppm.

115g (R_1=2-$NO_2C_6H_4$)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g) dissolved in dichloromethane (20ml) was treated with 2-nitrobenzaldehyde (10mmol; 1.51g) followed by catalytic trifluoroacetic acid (4 drops) at room temperature. The mixture was stirred for 5-15min. Solid mercury(II) acetate (10mmol; 3.18g) was added in one portion with perchloric acid catalyst (6 drops). The reaction mixture was stirred at room temperature for 1.5-2hrs (some solid assumed to be unreacted mercury acetate was still present in the reaction mixture). The mixture washed with 5% aqueous sodium bicarbonate solution (10ml) to remove acid. Subsequent anion exchange of the acetate group for bromide was carried out by stirring with aqueous potassium bromide (10mmol; 1.19g in 10ml.H_2O). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x15ml). The combined organic extracts were dried ($MgSO_4$). Removal of the dichloromethane solvent under reduced pressure gave a mixture of crude **115g** and unreacted aldehyde. Separation of **115g** from the aldehyde impurity was impossible by simple column chromatography. The mixture was dissolved in acetonitrile (15ml) and sodium phosphate monobasic hydrate (2.66mmol; 0.41g) in water (10ml) and 35% hydrogen peroxide (10.37mmol; 0.35g) were added at 0 °C (ice) with stirring. A cooled aqueous solution of sodium chlorite (13.99mmol; 1.27g) in water (10ml) was added dropwise to this cooled mixture. Sodium sulfite (5mmol; 0.4g) was then added in one portion followed by 5% aqueous sodium bicarbonate until the solution was sufficiently basic to produce the sodium salt of the carboxylic acid formed from the excess aromatic aldehyde. Crude **115g** was extracted from the mixture with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$), and concentrated by the removal of solvent under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.83) gave **115g** as a white solid product (1.09g, 20%).

^{1}H nmr (400 MHz) Major isomer : δ 7.86 (dd, J=1.16 Hz, 8.06 Hz, 1H, aromatic), 7.74

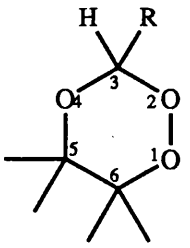
(dd, J=1.51 Hz, 7.78 Hz, 1H, aromatic), 7.63 (dt, J=1.27 Hz, 7.66 Hz, 1H, aromatic), 7.52 (dt, J=1.48 Hz, 7.78 Hz, 1H, aromatic), 6.92 (s, 1H, $CHC_6H_4NO_2$), 2.25 (bd, J=11.81 Hz, 1H, CH^aH^bHgBr, shows long range coupling to C5-Me), 2.11 (d, J=11.81 Hz, 1H, $CH_2H^aH^bHgBr$), 1.64 (s, 3H), 1.61 (s, 3H), 1.12 (s, 3H) ppm. Minor isomer : δ 7.90 (dd, J=1.16 Hz, 8.06 Hz, 1H, aromatic), 7.81 (dd, J=1.51 Hz, 7.78 Hz, 1H, aromatic), 7.63 (dt, J=1.27 Hz, 7.66 Hz, 1H, aromatic, overlaps with major isomer), 7.52 (dt, J=1.48 Hz, 7.78 Hz, 1H, aromatic, overlaps with major isomer), 7.02 (s, 1H,$CHC_6H_4NO_2$), 3.16 (bd, J=11.79 Hz, 1H,CH^aH^bHgBr), 2.26 (d, J=11.79 Hz, 1H, CH^aH^bHgBr), 1.64 (s, 3H, overlaps with major isomer), 1.62 (s, 3H), 1.35 (s, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 148.34 ($C-NO_2$), 132.98, 130.42, 128.64, 127.99 and 124.31 (aromatic), 94.14 (C-3), 84.57 (C-6), 79.95 (C-5), 45.08 (CH_2HgBr), 23.35, 22.05, 21.33 ppm. Minor isomer : δ 148.34 (overlaps with major isomer), 133.45, 130.64, 128.64 (overlaps), 127.99 (overlaps), 124.49, 93.83, 84.52, 79.95 (overlaps), 45.08 (overlaps), 22.99, 22.05 (overlaps),
21.33 (overlaps) ppm.
Major:Minor isomer ratio 8:1
Found: C, 28.81; H, 2.79% $C_{13}H_{16}BrHgNO_5$ requires: C, 28.56; H, 2.95%

115h (R=4-ClC_6H_4)
Procedure as for **115g**
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), 4-chlorobenzaldehyde (10mmol; 1.16g), trifluoroacetic acid (4 drops), mercury(II) acetate (10mmol; 3.18g), perchloric acid (6 drops), potassium bromide solution (10mmol; 1.19g in 10ml.H_2O), sodium phosphate monobasic hydrate (2.66mmol; 0.41g) in water (10ml), 35% hydrogen peroxide (10.37mmol; 0.35g), sodium chlorite (13.99mmol; 1.27g), sodium sulfite (5mmol; 0.4g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.79) gave the pure white solid product (1.12g, 21%).

^{1}H nmr (400 MHz) Major isomer : δ 7.39 (d, J=8.55 Hz, 2H, aromatic), 7.32 (d, J=8.55 Hz, 2H, aromatic), 6.29 (s, 1H, CHC_6H_4Cl), 2.29 (bd, J=11.78 Hz, 1H, CH^aH^bHgBr, shows long range coupling to C5-Me), 2.08 (d, J=11.78 Hz, 1H, CH^aH^bHgBr), 1.59 (s, 3H), 1.56 (s, 3H), 1.09 (s, 3H) ppm. Minor isomer: δ 7.40 (d, J=8.29 Hz, 2H, aromatic), 7.32 (d, J=8.29 Hz, 2H, aromatic), 6.40 (s, 1H, CHC_6H_4Cl), 3.37 (bd, J=11.52Hz, 1H, CH^aH^bHgBr), 2.26 (d, J=11.52 Hz, 1H, CH^aH^bHgBr), 1.32 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 135.63, 132.87, 128.55 (2C), 128.47 (2C), 97.86 (C-3), 83.75 (C-6), 79.06 (C-5), 44.49 (CH_2HgBr), 23.59, 21.93, 21.29 ppm. Minor

isomer: δ 135.66, 132.94, 128.61 (2C), 128.37 (2C), 97.54, 83.75 (overlaps with major isomer), 78.78, 42.78, 27.09, 22.59, 21.58 ppm.
Major:Minor isomer ratio 7.3:1
Found: C, 28.98; H, 3.44%, $C_{13}H_{16}BrClHgO_3$ requires: C, 29.12; H, 3.01%

3-(Alkyl / Aryl)-5,5,6,6-tetramethyl-1,2,4-trioxanes (116)



116a (R=Me), 'one-pot' procedure

2,3-Dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g) in dichloromethane (20ml) was treated with acetaldehyde (20mmol; 0.88g) and catalyic trifluoroacetic acid (4 drops) at room temperature. The mixture was stirred for 5-15min. Solid mercury(II) acetate (10mmol; 3.18g) was added in one portion followed by perchloric acid catalyst (6 drops). The reaction was assumed to reach completion once all the solid mercury acetate had dissolved (0.5-1hr). The reaction mixture was washed with 5% aqueous sodium bicarbonate solution (10ml) to remove acid. The organic layer was cooled with stirring (ice). To this cooled solution was added dropwise over 10mins, a cooled solution of sodium borohydride (10mmol; 0.38g) in aqueous sodium hydroxide (2M, 5ml). A grey/ black mercury by-product was seen to precipitate out. The reaction mixture was stirred for a further 20min., with cooling, before being filtered through phase separation paper. The aqueous layer was extracted with dichloromethane (3x5ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.79) gave the pure product as a colourless liquid (0.99g; 62%).

^{1}H nmr (400 MHz) : δ 5.55 (q, J=5.27 Hz, 1H, CHMe), 1.22 (s, 3H), 1.21 (s, 3H), 1.19 (d, 5.27 Hz, 3H, $CHCH_3$), 1.12 (s, 3H), 0.98 (s, 3H) ppm.
^{13}C nmr (100 MHz) : δ 95.52 (C-3), 81.92 (C-6), 75.23 (C-5), 24.65, 21.33, 21.06, 20.12, 18.15 ppm.
Found: C, 59.81; H, 10.03% $C_8H_{16}O_3$ requires: C, 59.98; H, 10.07%
Accurate mass spectrum. Found m / z: 160.1096 $C_8H_{16}O_3$ requires: 160.2132

116b (R=Et), 'one-pot' procedure

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), propanal (10mmol; 0.58g), trifluoroacetic acid (4 drops), mercury acetate (10mmol; 3.18g), perchloric acid catalyst (6 drops), sodium borohydride (10mmol; 0.37g) in 2M NaOH (7ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.73) gave the pure product as a colourless liquid (0.94g, 54%).

^{1}H nmr (400 MHz) : δ 5.31 (t, J=5.06 Hz, 1H, CHEt), 1.60 (m, 2H, CH_2CH_3), 1.46 (s, 3H), 1.35 (s, 3H), 1.12 (s, 3H), 0.98 (s, 3H), 0.91 (t, J=7.58Hz, 3H, CH_2CH_3) ppm.
^{13}C nmr (100 MHz) : δ 99.35 (C-3), 82.11 (C-6), 75.04 (C-5), 25.62, 24.63, 21.35, 21.09, 20.16, 7.92 ppm.
Found: C, 62.84; H, 10.71% $C_9H_{18}O_3$ requires: C, 62.04; H, 10.41%

116c (R=Pr), 'one-pot' procedure

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), butanal (10mmol; 0.72g), trifluoroacetic acid (4 drops), mercury acetate (10mmol; 3.18g), perchloric acid catalyst (6 drops), sodium borohydride (10mmol; 0.37g) in 2M NaOH (7ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.72) followed by trap-to-trap reduced pressure distillation at room temperature, gave the pure product as a colourless liquid (1.61g, 85%).

^{1}H nmr (400 MHz) : δ 5.39 (t, J=5.05 Hz, 1H, CHPr), 1.46-1.39 (m, 4H, $CH_2CH_2CH_3$), 1.45 (s, 3H), 1.34 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.88 (t, J=7.25 Hz, 3H, $CH_2CH_2CH_3$) ppm.
^{13}C nmr (100 MHz) : δ 98.44 (C-3), 82.11 (C-6), 75.04 (C-5), 34.38, 24.66, 21.38, 21.09, 20.14, 17.03, 13.92 ppm.
FAB mass spectrum m / z : 189 (MH^+)
Found: C, 64.08; H, 11.13% $C_{10}H_{20}O_3$ requires: C, 63.80; H, 10.71%

116d (R=^{i}Pr), reduction of 115d

A solution of **115d** (5.3mmol; 2.5g) in dichloromethane (20ml) was cooled with stirring (ice). A cooled solution of sodium borohydride (5.3mmol; 0.2g), in aqueous sodium hydroxide (2M, 5ml) was added dropwise over 10mins. A grey/ black mercury precipitate was observed. The reaction mixture was stirred for a further 20mins before being filtered through phase separation paper. The residual aqueous layer was extracted with dichloromethane (3x5ml). The combined organic extracts were dried ($MgSO_4$) and the dichloromethane solvent was removed under reduced pressure. Purification by simple

column chromatography (SiO_2, CH_2Cl_2, R_f 0.85) followed by trap-to-trap distillation under reduced pressure, at room temperature, gave the pure product as a colourless liquid (0.54g, 55%).

^{1}H nmr (400 MHz) : δ 5.15 (d, J=5.00 Hz, 1H, CH^iPr), 1.74 (dsept., J=5.00 Hz, 6.87 Hz, 1H, $CH(CH_3)_2$), 1.46 (s, 3H), 1.34 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.92 (d, J=6.87 Hz, 3H), 0.91 (d, 6.87 Hz, 3H) ppm.
^{13}C nmr (100 MHz) : δ 101.54 (C-3), 82.06 (C-6), 74.84 (C-5), 31.07($CH(CH_3)_2$), 24.57, 21.34, 21.06, 20.13, 16.81, 16.57 ppm.
Found: C, 63.70; H=10.58% $C_{10}H_{20}O_3$ requires: C, 63.80; H, 10.71%

116e (R=^{t}Bu), reduction of 115e

Starting materials : **115e** (5mmol; 2.5g), sodium borohydride (5mmol; 0.19g) in 2M NaOH (5ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.92) gave the pure white solid product (0.59g, 58%).

^{1}H nmr (400 MHz) : δ 5.02 (s, 1H, CH^tBu), 1.45 (s, 3H), 1.34 (s, 3H),
1.12 (s, 3H), 0.99 (s, 3H), 0.91 (s, 9H, $C(CH_3)_3$)ppm.
^{13}C nmr (100 MHz) : δ 103.04 (C-3), 81.87 (C-6), 74.69 (C-5), 34.43 ($C(CH_3)_3$), 24.52, 24.51 (3C, $C(CH_3)_3$), 21.34, 20.99, 20.06 ppm.
Found: C, 65.44; H, 11.27% $C_{11}H_{22}O_3$ requires: C, 65.31; H, 10.96%

116g (R=2-$NO_2C_6H_4$), 'One-pot' procedure

2,3-Dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g) in dichloromethane (20ml) was treated with 2-nitrobenzaldehyde (10mmol; 1.51g) and catalytic trifluoroacetic acid (4 drops) at room temperature. The mixture was stirred for 5-15min. Solid mercury(II) acetate (10mmol; 3.18g) was added in one portion followed by perchloric acid catalyst (6 drops). The reaction mixture was stirred at room temperature for 5hrs. Solid unreacted mercury acetate still present in the mixture was filtered off. The filtrate was washed with 5% aqueous sodium bicarbonate solution (10ml) to remove acid. The organic layer was cooled with stirring (ice) and aqueous sodium hydroxide (2M, 5ml) was added. A cooled solution of sodium borohydride (10mmol; 0.38g) in ethanol (10ml) was added dropwise over a period of ten minutes. A grey/ black mercury by-product was seen to precipitate out. The reaction mixture was stirred for a further 20mins with cooling, before being filtered through phase separation paper. The aqueous layer was extracted with dichloromethane (3x5ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.79) gave the pure product as a colourless

liquid (0.72g; 27%).

^{1}H nmr (400 MHz) : δ 7.86 (dd, J=1.28 Hz, 8.11 Hz, 1H, aromatic), 7.82 (dd, J=1.18 Hz, 7.86 Hz, 1H, aromatic), 7.62 (dt, J=1.12 Hz, 7.64 Hz, 1H, aromatic), 7.50 (dt, J=0.1.26 Hz, 7.82 Hz, 1H, aromatic), 6.93 (s, 1H, $CHC_6H_4NO_2$), 1.56(s, 3H), 1.52 (s, 3H), 1.22 (s, 3H), 1.07 (s, 3H) ppm.
^{13}C nmr (100 MHz) : δ 148.32 (C-NO_2), 133.01, 130.19, 129.38, 128.39, 124.23, 93.80 (C-3), 82.88 (C-6), 77.01 (C-5), 24.51, 21.54, 21.03, 19.72 ppm.
Found: C, 57.98; H, 6.25; N, 5.13% $C_{13}H_{17}NO_5$ requires: C, 58.42; H, 6.41; N, 5.24%

116h (R=4-ClC_6H_4), 'One-pot' procedure
Procedure as for **116g**.
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), 4-chlorobenzaldehyde (10mmol; 1.16g), trifluoroacetic acid (4 drops), mercury(II) acetate (10mmol; 3.18g), 6 mol% perchloric acid catalyst (6 drops), aqueous sodium hydroxide (2M, 5ml), sodium borohydride (10mmol; 0.38g) in ethanol (10ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.86) gave the pure product as a colourless liquid (0.59g, 23%).

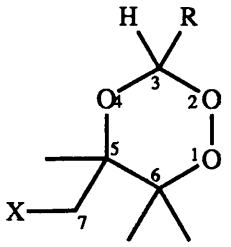
^{1}H nmr (400 MHz) : δ 7.44 (d, J=8.56 Hz, 2H, aromatic), 7.43 (d, J=8.56 Hz, 2H, aromatic), 6.33 (s, 1H, CHC_6H_4Cl), 1.59 (s, 3H), 1.50 (s, 3H), 1.24 (s, 3H), 1.07 (s, 3H) ppm.
^{13}C nmr (100 MHz) : δ 135.53, 133.63, 128.53 (2C), 128.49 (2C), 97.78 (C-3), 82.32 (C-6), 76.25 (C-5), 24.58, 21.47, 21.06, 19.98 ppm.
FAB mass spectrum m / z : 257 (MH^+)
Found: C, 60.82; H, 6.67% $C_{13}H_{17}ClO_3$ requires: C, 60.80; H, 6.41%

116i (R=C_6H_5), 'One-pot' procedure
Procedure as for **116g**.
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), benzaldehyde (10mmol; 1.06g), trifluoroacetic acid (4 drops), mercury(II) acetate (10mmol; 3.18g), 6 mol% perchloric acid catalyst (6 drops), aqueous sodium hydroxide (2M, 5ml), sodium borohydride (10mmol; 0.38g) in ethanol (10ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.78) gave the pure product as a colourless liquid (0.84g, 37.8%).

^{1}H nmr (400 MHz) : δ 7.55-7.53 (m, 2H, aromatic), 7.40-7.73 (m, 3H, aromatic), 6.40

(s, 1H, CHC_6H_5), 1.65 (s, 3H), 1.54 (s, 3H), 1.28 (s, 3H), 1.11 (s, 3H) ppm.
^{13}C nmr (100 MHz) : δ 135.08, 129.62, 128.25 (2C), 127.02 (2C), 98.48 (C-3), 82.14 (C-6), 75.98 (C-5), 24.56, 21.44, 21.03, 19.94 ppm.
Nmr data from a separate synthesis of **116i** by Karen Johnson[73]: ^1H nmr δ 7.5 (m, 2H), 7.4 (m, 3H), 6.4 (s, 1H, CHC_6H_5), 1.6 (s, 3H), 1.5 (s, 3H), 1.3 (s, 3H), 1.1 (s, 3H) ppm. ^{13}C nmr : δ 135.0, 128.4, 124.6 (2C), 123.4 (2C), 92.0, 83.6, 76.3, 24.1, 21.3, 21.1, 19.5 ppm.

3-Alkyl-5-(halomethyl)-5,6,6-trimethyl-1,2,4-trioxanes (117)



117a (R=Me, X=Br)

The reaction was carried out in subdued lighting (reaction vessel was covered in aluminium foil). Bromine (5.5mmol; 0.82g) in dichloromethane (15ml) was added dropwise to a stirred solution of **115a** (5mmol; 2.13g) in dichloromethane (20ml). The mixture was stirred at room temperature for 3hrs. The solvent was removed under reduced pressure to give a creamy white, wet looking solid which was extracted with light petroleum (2x15ml). The light petroleum was removed from the crude product under reduced pressure. Purification by column chromatography (SiO_2, CH_2Cl_2, R_f 0.88) gave the pure product as a clear liquid (1.01g, 90%).

^1H nmr (400 MHz) Major isomer : δ 5.52 (q, J=5.21 Hz, 1H, **CH**Me), 3.41 (bd, J=10.67 Hz, 1H, CH^aH^bBr, shows long range coupling to C5-Me), 3.28 (d, J=10.67 Hz, 1H, CH^aH^bBr), 1.51 (s, 3H), 1.49 (s, 3H), 1.24 (d, J=5.21 Hz, 3H), 1.09 (s, 3H) ppm. Minor isomer : δ 5.40 (q, J=5.17 Hz, 1H), 4.18 (bd, J=11.02 Hz, 1H, CH^aH^bBr), 3.39 (d, J=11.02 Hz, 1H, CH^aH^bBr), 1.55 (s, 3H), 1.26 (d, J=5.17 Hz, 3H), 1.21 (s, 3H), 1.04 (s, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 96.04 (C-3), 81.1 (C-6) , 76.1 (C-5), 38.6 (CH_2Br), 21.5, 21.1, 17.9, 17.7 ppm. Minor isomer : δ 96.07, 81.10 (overlaps with major isomer), 76.12 (overlaps), 38.59 (CH_2Br), 22.40, 21.52, 17.99, 17.94 (overlaps) ppm.
Major: Minor isomer ratio 4.6: 1
Found: C, 40.76; H, 6.64; Br, 34.10% $C_8H_{15}BrO_3$ required: C, 40.18; H, 6.32; Br,

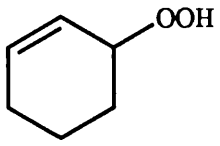
34.42%

117f (R=Et, X=I)

The reaction was carried out in subdued lighting (aluminium foil covered reaction vessel). Iodine (0.41mmol; 0.05g) in dichloromethane (10ml) was added dropwise to a stirred solution of **115b** (0.37mmol; 0.17g) in dichloromethane (10ml). The mixture was stirred at room temperature (5-5.5hrs) before washing with 20% sodium thiosulfate solution (10ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (2x5ml). The combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure to give a viscous liquid which was extracted with light petroleum (2x10ml). Removal of the solvent from the extract under reduced pressure gave the crude product (0.1g).

^{1}H nmr (400 MHz) Major isomer : δ 5.27 (t, J=5.11 Hz, 1H, **CH**Et), 3.31 (bd, J=10.33 Hz, 1H, **CH^{a}H^b**I, shows long range coupling to C5-Me), 3.12 (d, J=10.33 Hz, 1H, CH^a**H^b**I), 1.49 (m, 5H), 1.07 (s, 6H), 0.92 (t, J=7.58 Hz, 3H, CH_2**CH_3**) ppm. Minor isomer : δ 5.10 (t, J=5.10 Hz, 1H), 4.06 (bd, J=10.55 Hz, 1H, **CH^{a}H^b**I), 3.23 (d, J=10.55 Hz, 1H, CH^a**H^b**I), 1.49 (m, 5H overlaps with major isomer), 1.03 (s, 3H), 1.02 (s, 3H), 0.98 (t, J=7.58 Hz, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 99.99 (C-3), 80.53 (C-6), 74.81 (C-5), 25.24, 21.34(2C), 20.53, 14.38 (**C**-I), 7.86 ppm. Minor isomer : δ 99.55, 80.44, 74.81 (overlaps), 28.19, 22.77, 22.10, 20.80, 13.65 (**C**-I), 7.98 ppm.

Cyclohex-2-enyl hydroperoxide (118)[69]

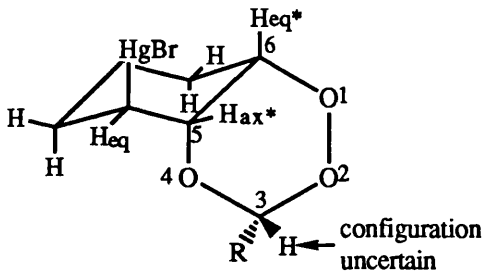


Cyclohexene (0.18mol; 14.98g) in dichloromethane (350ml) containing the sensitiser, tetraphenylporphine (27mg) was irradiated with a 400w sodium lamp in an immersion cell apparatus. Oxygen gas was bubbled through. After 5h, the lamp was switched off. The dichloromethane solvent was removed under reduced pressure to give the crude product as an oil in 55% yield.

^{1}H nmr (60 MHz) : δ 1.5-2.4 (m, 6H), 4.5 (m, 1H, **CH**COOH), 5.2 (m, 2H, **CH=CH**), 8.2 (bs, **OOH**) ppm.
^{13}C nmr (100 MHz) : δ 134.19 (HOOC**C**H=CH), 123.97 (HOOCCH=**C**H), 78.31 (**C**-

OOH), 26.22, 25.18, 18.23 ppm.

Bicyclic 1,2,4-trioxanes (127)



eq*-in equatorial position with respect to trioxane ring
ax*- in axial position with respect to trioxane ring
eq-in equatorial position with respect to cyclohexane ring

127a (R=Me)

Cyclohex-2-enyl hydroperoxide, **118** (10mmol; 0.98g) dissolved in dichloromethane (20ml), was treated with acetaldehyde (20mmol; 0.88g) with stirring. After 5mins mercury(II) trifluoroacetate (10mmol; 4.26g) was added in one portion and the mixture was stirred at room temperature for 48 hrs. The mixture was washed with water (15ml) and stirred for 0.5 hrs with aqueous potassium bromide (10mmol; 1.19g in 5ml H_2O). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$) and concentrated by removal of the solvent under reduced pressure. Isolation of **127a** was carried out by simple column chromatography (SiO_2, CH_2Cl_2 major isomer R_f 0.54, minor isomer R_f 0.65) followed by HPLC (column: 250mm x 10mm kromasil silica gel 5μm; mobile phase: 10% ethyl acetate + 90% hexane fraction; detector: refractive index R20 setting; flow rate: 5.0 cm^3/ min; chart speed: 5mm/ min), to give two isomers of the white, solid product. Major isomer (0.66g, 15%), minor isomer (0.13g, 3%).

^{1}H nmr (400 MHz) Major isomer : δ 5.32 (q, J=5.33 Hz, 1H, $CHCH_3$), 4.29 (t, J=2.85 Hz; $^3J(^1H\text{-}^{199}Hg)$=72 Hz, 1H, proton attached to C-O ie, **H^5**. The signal is sharp because it has two *gauche* couplings- to H^6 and to CHHgBr), 3.99 (ddd, J=2.85 Hz, 5.70 Hz, 11.40 Hz, 1H, proton attached to C-OO ie, **H^6**. The signal appears broad because it has one *anti* coupling- to the axial proton of the adjacent CH_2 group, as well as two *gauche* couplings- to the equatorial proton of the adjacent CH_2 group and to the H^5 proton of the trioxane ring), 3.34 (approx quintet with apparent J of 2.81 Hz; $^2J(^1H\text{-}^{199}Hg)$=228 Hz, CHHgBr), 2.02-1.54 (m, 6H), 1.29 (d, J=5.33 Hz, 3H, $CHCH_3$) ppm. Minor isomer : δ 5.45 (q, J=5.38 Hz, 1H, $CHCH_3$), 4.0-3.92 (complex multiplet, 1H), 3.58 (m, 1H), 2.45 (m), 1.95-1.6 (m), 1.28 (d, J=5.38 Hz, 3H, $CHCH_3$), 1.26-1.23 (m) ppm.

^{13}C nmr (100 MHz) Major isomer δ 101.65 (C-3), 79.49 (C-6), 74.11 (C-5), 59.16 (CHHgBr), 27.46, 25.59, 24.69, 18.06 ppm. Minor isomer δ 102.82 (C-3), 85.30 (C-6), 81.99 (C-5), 30.85, 26.46, 26.34, 18.00 ppm. (The CHHgBr carbon is probably too broad to be seen in this spectrum).

Hecor pulse sequence was used to obtain ^{1}H/ ^{13}C signal correlations which showed that the peak at δ_H 4.29 (H^5) correlates with δ_C 74.11 and the peak at δ_H 3.99 (H^6) correlates at δ_C 79.49 in the major isomer (see hetcor pulse sequence ^{1}H / ^{13}C signal correlation spectrum at the end of this chapter).

Found: C, 21.91; H, 3.05% required $C_8H_{13}BrHgO_3$: C, 21.95; H, 2.99%

127b (R=Et)

Procedure as for **127a**

Starting materials : Cyclohexenyl hydroperoxide **118** (5mmol; 0.49g), Propanal (10mmol; 0.59g), mercury(II) trifluoroacetate (5mmol; 2.13g). Purification by simple column chromatography (SiO_2, CH_2Cl_2 R_f 0.51) followed by HPLC (column: 250mm x 10mm kromasil silica gel 5μm; mobile phase: 10% ethyl acetate + 90% hexane fraction; detector: refractive index R20 setting; flow rate: 5.0 cm^3/ min; chart speed: 5mm/ min) gave a single isomer of the pure product as a white solid (0.34g, 15%).

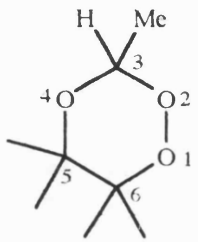
^{1}H nmr (400 MHz) : δ 5.13 (t, J=5.06 Hz, 1H, $CHCH_2CH_3$), 4.28 (t, 2.68 Hz; $^{3}J(^{1}H\text{-}^{199}Hg)$=76 Hz, 1H, proton attached to C-O ie, **H^5**. The signal appears as a sharp triplet due to two *gauche* couplings- to H^6 and to CHHgBr), 4.04 (ddd, J=2.68 Hz, 5.35 Hz, 11.77 Hz, 1H, proton attached to C-OO ie, **H^6**. The signal is broad as a result of one *anti* coupling- to the axial proton of the adjacent CH_2 group and two *gauche* couplings- to the equatorial proton of the adjacent CH_2 group and to the H^5 proton of the trioxane ring), 3.36 (approx quintet with J of 2.68 Hz; $^{2}J(^{1}H\text{-}^{199}Hg)$=246 Hz, 1H, CHHgBr), 2.42-1.58 (m, 8H), 0.94 (t, J=7.44 Hz, 3H, CH_2CH_3) ppm.

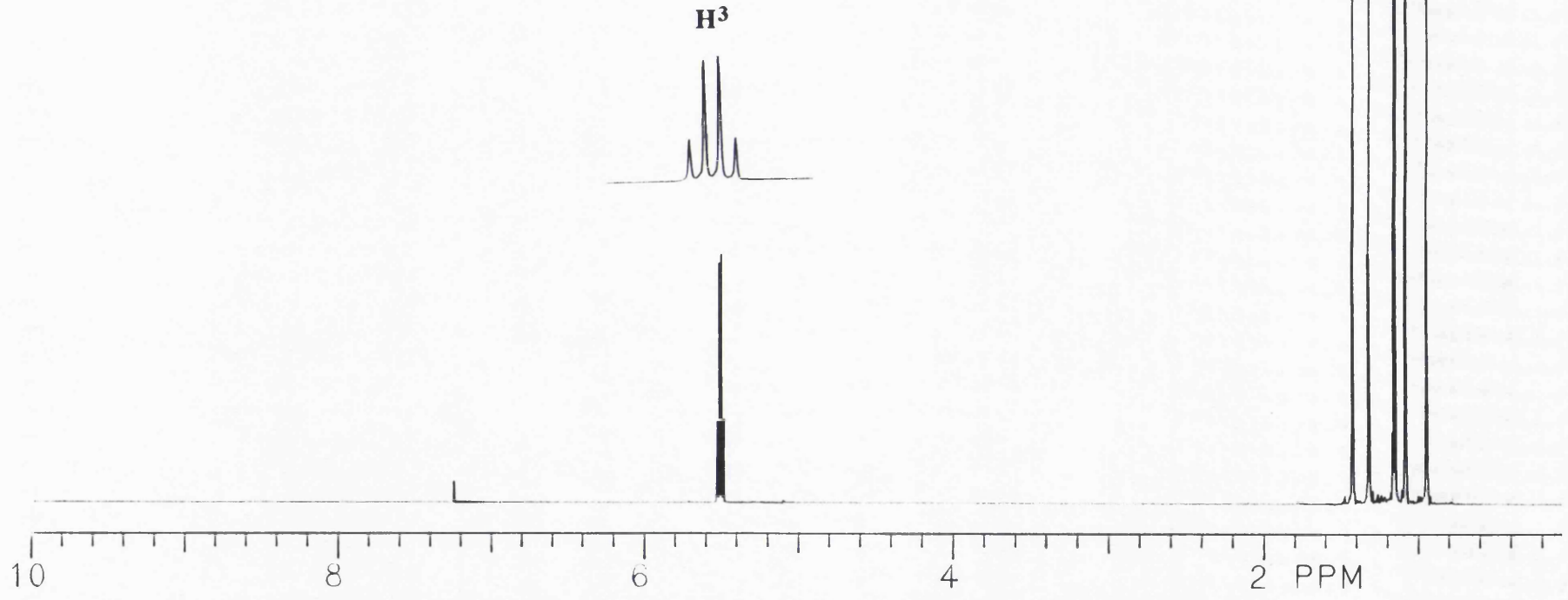
^{13}C nmr (100 MHz) δ 105.28 (C-3), 79.63 (C-6), 74.06 (C-5), 59.20 (CH_2HgBr), 27.43, 25.66, 25.64, 24.74, 7.85 ppm.

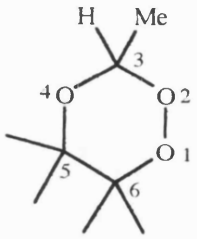
Found: C, 24.25; H, 3.12% $C_9H_{15}BrHgO_3$ requires: C, 23.93; H, 3.35%

See p219

2.5.1 ^{1}H nmr spectrum of 3,5,5,6,6-pentamethyl-1,2,4-trioxane (**116a**)



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Me
3
4O
O2
O1
5
6

C6
C3
C5
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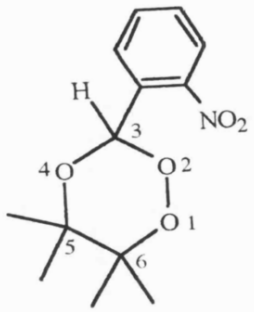
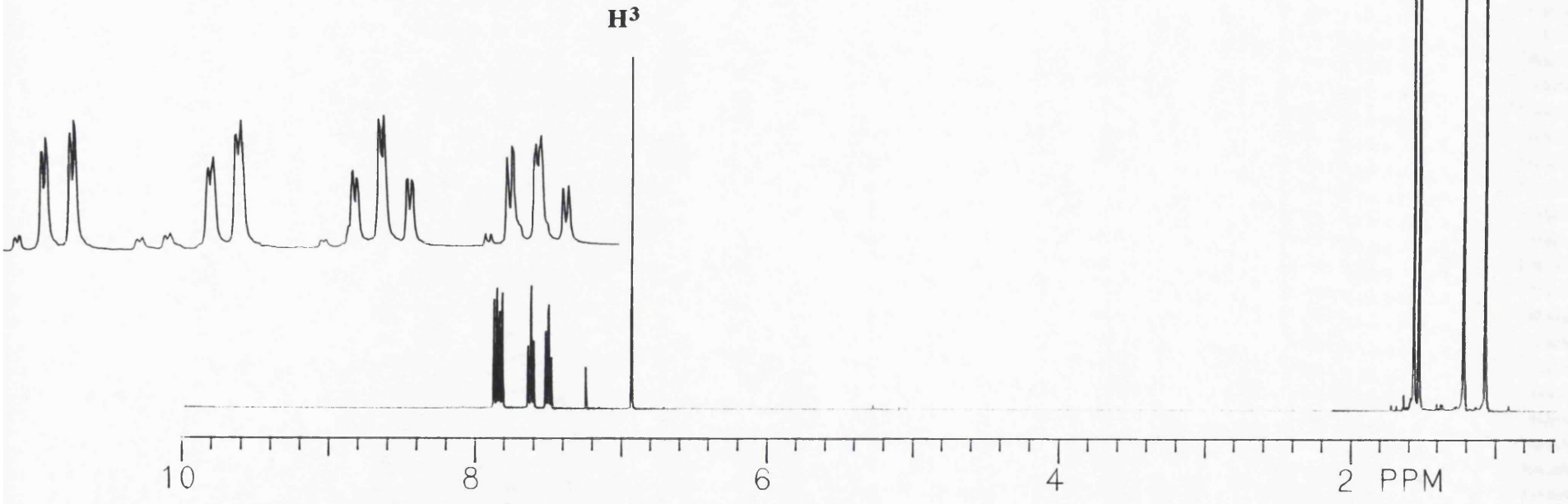
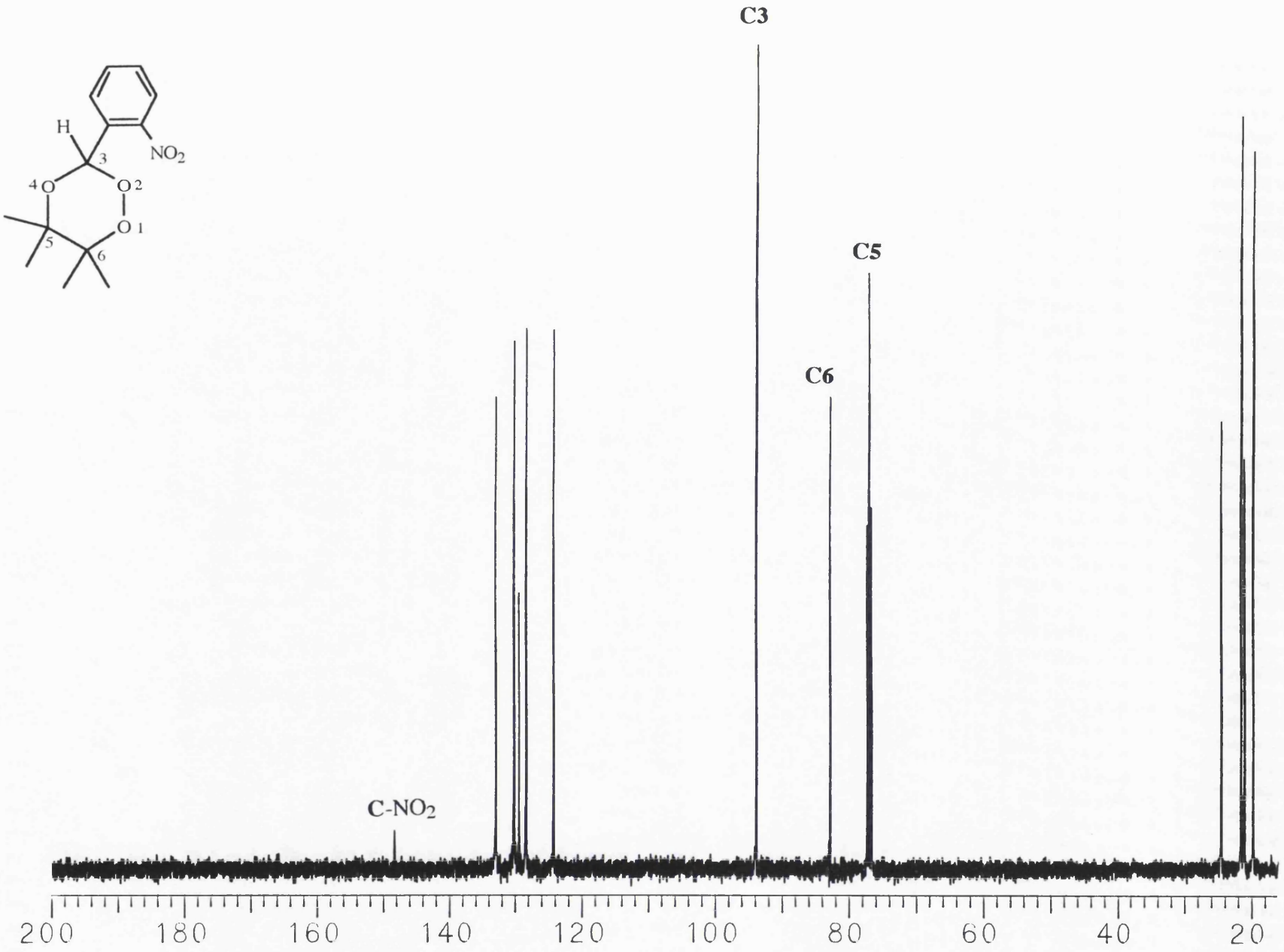
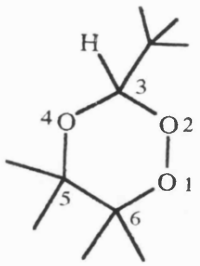
180
160
140
120
100
80
60
40
20
PPM


H
3
NO2
4O
O2
O1
5
6

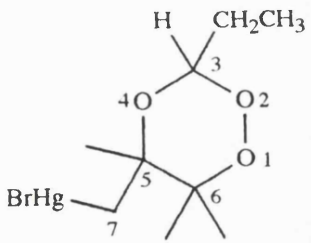

H3
10
8
6
4
2 PPM


C3
C5
C6
C-NO2
H
NO2
3
4 O
O 2
O 1
5
6
200
180
160
140
120
100
80
60
40
20

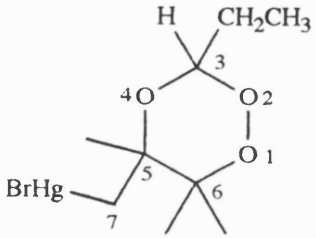


3C, $C(\mathbf{C}H_3)_3$

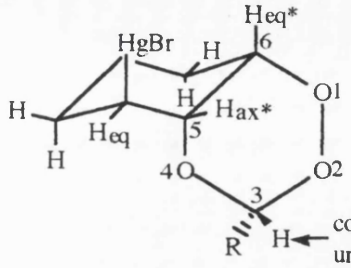
2.5.6 ^{1}H NMR spectrum of 3-ethyl-5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxane (115b)



2.5.7 ^{13}C nmr spectrum of 3-ethyl-5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxane (**115b**)

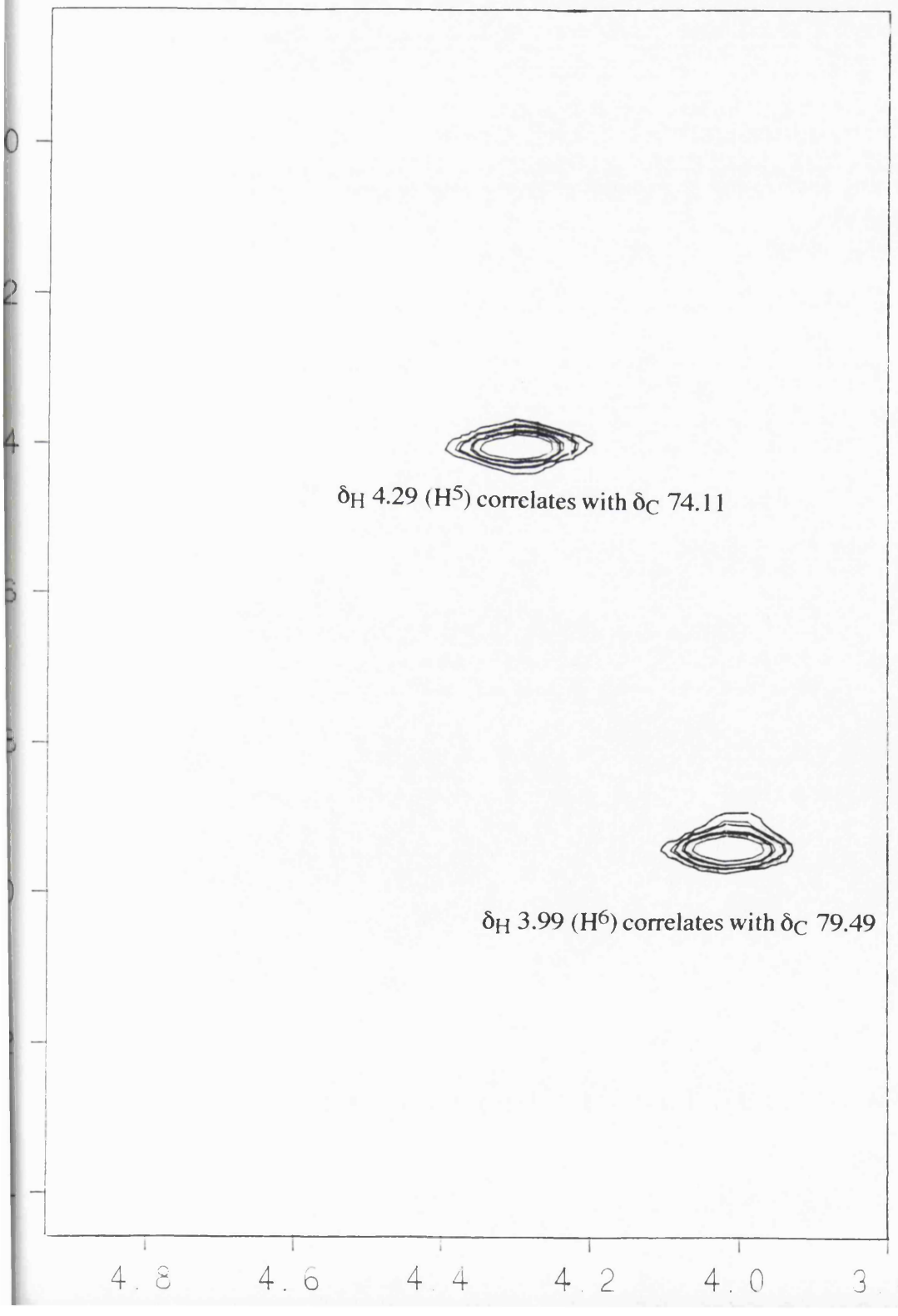


2.5.8 Hetcor pulse sequence ^{1}H / ^{13}C signal correlations for compound **127a**



eq*-in equatorial position with respect to trioxane ring
ax*- in axial position with respect to trioxane ring
eq-in equatorial position with respect to cyclohexane ring

(PPM)



δ_H 4.29 (H^5) correlates with δ_C 74.11

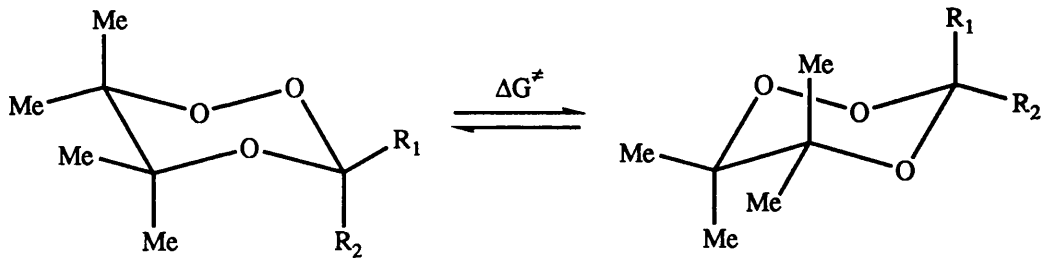
δ_H 3.99 (H^6) correlates with δ_C 79.49

THE SYNTHESIS OF SOME TETRA- AND HEXA-ALKYL-1,2,4-TRIOXANES AND DYNAMIC NMR STUDIES OF THEIR CONFORMATIONAL MOBILITY

3.1 Introduction

An obvious extension of the intramolecular oxymercuriation route to 1,2,4-trioxanes, is the use of ketones (R_1COR_2) instead of aldehydes (RCHO) in the first step (see scheme 61, chapter 2). 1,2,4-Trioxane compounds synthesised from ketones in which R_1=R_2, are no longer conformationally locked can undergo ring inversion (Fig 6).

Figure 6



{where $R_1 = R_2$ and $\Delta G^{\neq}$= barrier to ring inversion}

The barriers to ring inversion in these ketone-derived 1,2,4-trioxanes may be determined from dynamic nmr studies of their conformational mobility.

3.1.1 Dynamic nmr spectroscopy[74]

$$\underset{n_A}{A} \rightleftharpoons \underset{n_B}{B} \qquad \text{(eqn i)}$$

{where n_A and n_B are the mole fractions of A and B}

For a molecule interconverting between two states A and B or a nucleus exchanging between two molecules A and B (equation i), any equilibrium can be characterised by two parameters.

a). *The position* of the equilibrium, which is determined by ΔG, the free energy of the

process (equation ii),

$$n_A / n_B = \exp(-\Delta G / RT) \qquad \text{(eqn ii)}$$

$$\text{and } n_A + n_B = 1$$

b). *The rate* of interconversion, which is determined by the free energy of activation ($\Delta G^{\neq}$) ie, the rate constant of the reaction A → B, is given by equation iii,

$$k = RT/Nh \exp(-\Delta G^{\neq}/ RT) \qquad \text{(eqn iii)}$$

{where h = Planck's constant and N = number of particles}

A nucleus in state A will have a chemical shift υ_A and a coupling J_A; in state B the shift will be υ_B and the coupling J_B (in hertz). The spectrum of such a sample may be observed under the following three conditions.

1. Slow exchange (low temperature)

If the rate of interconversion of A and B is slow on the nmr timescale, then the spectra of both species A and B will be observed separately ie, signals at shifts υA and υB with couplings J_A and J_B will be detected. A direct measurement of the relative intensities of the signals will give n_A and n_B values and therefore ΔG.

2. Fast exchange (high temperature)

If the rate of interconversion is fast, the nmr spectrum observed will be an 'averaged' spectrum in which the chemical shifts and couplings are the weighted averages of the values in states A and B. Therefore the nucleus will give rise to one signal with a position (υ_{av}) given by,

$$\upsilon_{av} = n_A\upsilon_A + n_B\upsilon_B$$

and coupling (J_{av}) given by, $J_{av} = n_AJ_A + n_BJ_B$.

3. Intermediate exchange (intermediate temperature)

In this case lines broaden in the nmr spectrum, as the separate signals for species A and B begin to merge. When the two environments (which cause the two separate signals at low temperature) are equally populated, the rate constant (s^{-1}) for the exchange at the coalescence point is given by equation iv,

$$k = \pi\Delta\upsilon / 2^{1/2}\, s^{-1} \qquad \text{(eqn iv)}$$

{where $\Delta\upsilon$ is the frequency separation of the initially sharp lines}

The rate constant at the coalescence temperature for the AB spectrum where the nuclei are coupled (J), ie H_AH_B is given by equation v,

$$k = \pi\{0.5[(\Delta\upsilon)^2 + 6J_{AB}^2]\}^{1/2} \qquad \text{(eqn v)}$$

{where $\Delta\upsilon = (\Delta^2 - J_{AB}^2)^{1/2}$ and Δ= distance in Hz between the centres of the doublets}

Rate constants obtained at one specific temperature may be of interest. However in most cases, much more interesting information can be obtained from an analysis of the energy quantities involved in the process. An early approach in this direction resulted in the Arrhenius activation theory[74]. This theory is based on the assumption that molecules require a certain excess energy known as the activation energy E_A, in order to react. In addition, the activated and unactivated molecules are in equilibrium (equation vi),

$$k = Ae^{-E_A/RT} \qquad \text{(eqn vi)}$$

The pre-exponential or frequency factor A, and activation energy E_A, are customarily obtained from a linear plot of ln k vs T^{-1}, when k is known from at least two different temperatures. The frequency factor A, has been interpreted as the number of 'effective' collisions per unit volume and unit time. Equation v, rests on over simplified assumptions, in fact a more realistic treatment would have to be based on statistical thermodynamics.

The absolute rate theory developed by Eyring[74] is better suited to the types of problems of interest in the present context. The fundamental equation in this theory is the so called Eyring equation (vii),

$$k = \kappa k_B T/h e^{-\Delta G^{\neq}/RT} \qquad \text{(eqn viia)}$$

$$k = \kappa k_B T/h e^{(\Delta H^{\neq} - T\Delta S^{\neq})/RT} \qquad \text{(eqn viib)}$$

{where κ= transmission coefficient ie, fraction of all reacting molecules reaching the transition state that proceed to deactivated product molecules}.

In adiabatic reactions (those proceeding without electronic excitation), the magnitude of κ is determined by the capacity of the activated complex to transfer the activation energy to other molecules. Normally this proceeds smoothly with polyatomic molecules, so that κ can be assumed to be equal to unity. In non-adiabatic reactions (those involving singlet-triplet transitions), κ may be as low as 10^{-7}. A transmission coefficient of 0.5 is used in cases where two equivalent transition states are separated by one or more energy minima. The probability for foreward and reverse reactions from an intermediate energy minimum are equal (eg cyclohexane in Figure 7).

$\Delta H^{\neq}$ and $\Delta S^{\neq}$ can be calculated from Arrhenius parameters at a given temperature (equations viii and ix),

$$\Delta H^{\neq} = E_A - RT \qquad \text{(eqn viii)}$$

$$\Delta S^{\neq} = R\,(\ln A - \ln e\, k_B T/\, h) \qquad \text{(eqn ix)}$$

The Eyring equation can be used to calculate $\Delta G^{\neq}$ when K and T are known. The free energy of activation $\Delta G^{\neq}$, can be obtained at the coalescence temperature T_c (equation x),

$$\Delta G^{\neq} = RT_c\,[\,2.3 + \ln\,(T_c/\,\Delta\upsilon)]\ \text{cal mol}^{-1} \qquad \text{(eqn x)}$$

{if κ is unity}

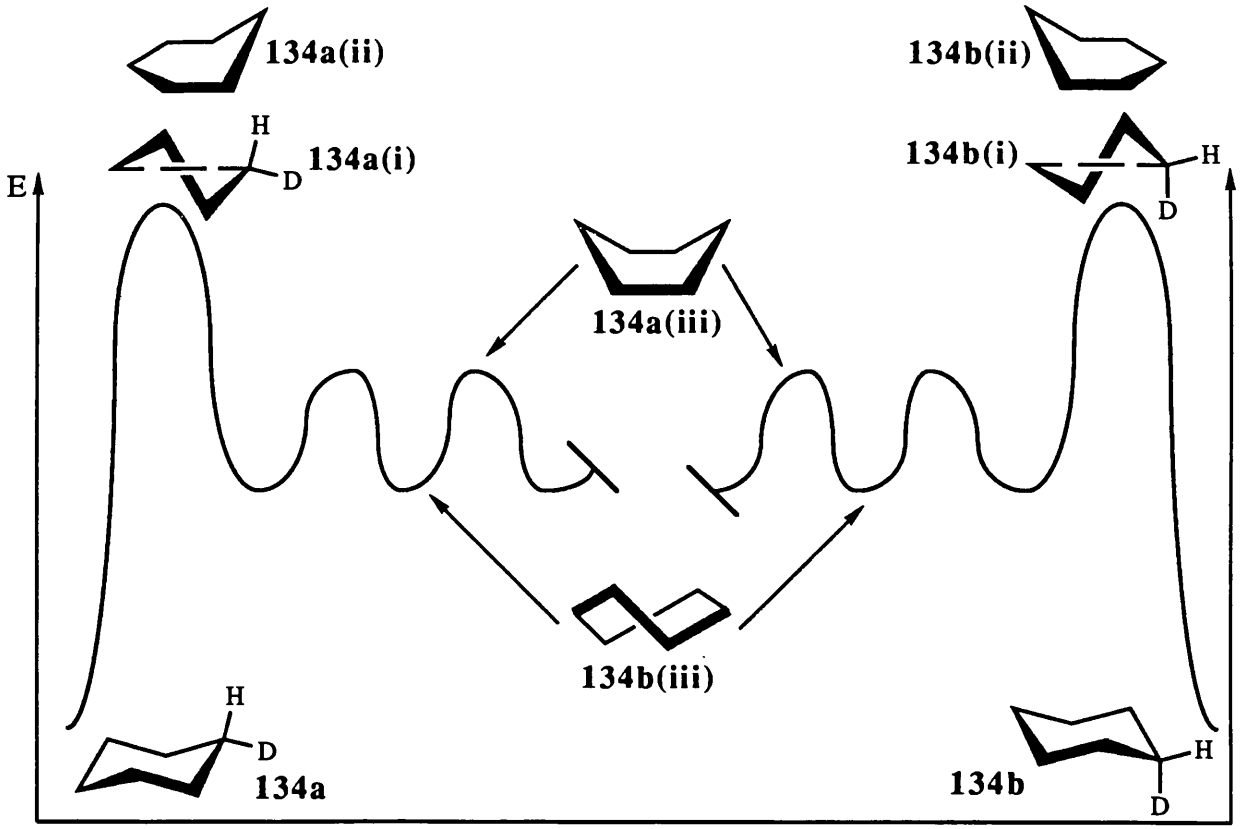
However, for a coalescing AB system equation xi, is much more appropriate,

$$\Delta G^{\neq} = RT_c\,[\,2.3 + \ln\,(T_c/\{\Delta\upsilon^2 + 6J_{AB}^2\}^{1/2})]\ \text{cal mol}^{-1} \qquad \text{(eqn xi)}$$

Statistical contributions to activation entropies must also be considered and it is important to define the process to which $\Delta S^{\neq}$ applies.

Figure 7

The chair-twist boat-chair energy diagram



Reaction coordinate

The rate constant found for the exchange of the proton in cyclohexane-d_{11}[74] between the equatorial and axial sites is for a chair-chair inversion (Fig 7). The interconversion of the two chair conformations **(134a)** and **(134b)** requires passage through a high energy conformation **134a(i)** or **134a(ii)** to a series of intermediate energy twist-boat **134b(iii)** and boat **134a(iii)** conformations. Subsequent passage through other high energy forms such as **134b(i)** or **134b(ii)** then leads to **134b**. It is important to recognise that in the case of cyclohexane and by extension of other six-membered rings, the equilibrium ground-state conformation is not an ideal chair with dihedral angles of 60° and carbon-carbon-carbon angles of 109.5°. The ring is flattened a little so that dihedral angles are less than 60° and bond angles are greater than 109.5°. The rate constant is only half that for the chair to twist-boat exchange, since half the molecules that reach the twist-boat state will revert to the initial chair and only half will continue to the inverted chair. Equation xii was derived from equation viib,

$$\ln (K/T) = -\Delta H^{\neq}/ RT + \Delta S^{\neq}/ R + \ln (k_B/ h) \qquad \text{(eqn xii)}$$

From equation xii, we see that the rate constants at all temperatures are multiplied by a common factor r and that $\Delta S^{\neq}$ increases by a factor R ln r. The statistical contribution to $\Delta S^{\neq}$ for the chair-chair process is only R ln 3 and this result can also be obtained by using a transmission coefficient $\kappa = 0.5$. The $\Delta G^{\neq}$ value for such a case will be given using this correction (equation xiii),

$$\Delta G^{\neq} = 2.3RT_c (\ln K/h + \ln T_c - \ln K_c - \ln 0.5) \qquad \text{(eqn xiii)}$$
$$= 4.575\, T_c (10.02 + \ln T_c - \ln K_c)\ \text{cal mol}^{-1}$$

{where K = Boltzmann's constant and h = Planck's constant}

3.1.2 Chair-Chair interconversion of six-membered rings

The chair-chair interconversion of saturated six-membered rings and particularly the effect of substitution both on the ring and in the ring skeleton have been much studied[75]. The barriers for ring inversion of cyclohexane (10.1 kcal mol^{-1}) and other six-membered rings can be measured indirectly from their coalescence temperature nmr spectra[75]. There are generally considered to be three principal contributions to conformational energies of structures **134** (Fig 7).

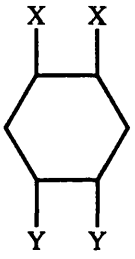
a). *Bayer strain,* arising from deformation of bond angles away from their preferred lowest energy value.
b). *Torsional (Pitzer) strain,* arising from 1,2-interactions between groups attached to contiguous carbon atoms.
c). *Van der Waals* interactions.

In so far as a half chair of type **134a(i)** and **134b(i)** has been postulated as the transition state for the chair-chair interconversion (Fig 7), its relative enthalpy represents the barrier to this interconversion and the values of Bayer-, tortional- and van der Waals-strain for this form represent the contribution from these factors to the barrier. An important point about transition states **134a(i)** and **134b(i)**, is that they have six kinds of substitution positions (pseudo-equatorial and pseudo-axial at three kinds of carbon atom), compared with only two for the chair form. This is important when inversion of substituted cyclohexanes are under consideration, as there are now several possible pathways each of differing energy. As a result when a single substituent designed to raise the barrier to ring inversion is introduced, inversion will take place preferentially by way of the transition state of lowest energy and this may

result in any constraint due to the substituent being avoided. If any substituent is made which would tend to lower the barrier, inversion will prefer to take place by the lowest energy pathway and therefore a lower barrier will be observed experimentally.

1,2-Interactions (Pitzer strain)

A large, perhaps predominant part of the inversion barrier of cyclohexane occurs as a result of enhanced 1,2-interactions in the transition state ie, due to the barrier opposing rotation about individual bonds in the ring skeleton. In the case of 1,2,4,5-tetrasubstituted cyclohexanes (**135**), in which there are necessarily increased eclipsing interactions in the transition state, barriers tend to be larger than in cyclohexane[75].

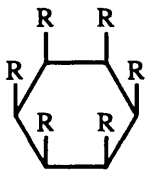


135

a. X= CH_3, Y= $COOCH_3$, barrier= 11.5 kcal mol^{-1}

b. X= Cl, Y= $COOCH_3$, barrier= 12.8 kcal mol^{-1}

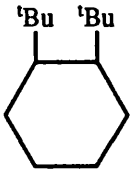
c. X= OH, Y= $COOCH_3$, barrier= 11.6 kcal mol^{-1}



136

a. R= $OCOCH_3$ (30 °C) barrier= 15.3 kcal mol^{-1}

b. R= CH_3 (60 °C) barrier= 17.0 kcal mol^{-1}



137

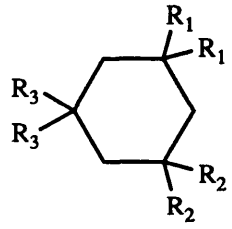
barrier= 16.3 kcal mol^{-1}

The increased eclipsing interactions are steric and electrostatic in origin since the substituents are more or less polar. A greater number of substituents than in compound **135** will cause 1,2-interactions which produce even higher barriers. Compound (**136a**)[76], with all substituents on the same side of the ring, has a barrier to inversion at 30 °C of about 15.3 kcal mol^{-1}. Compound (**136b**)[75] has one of the highest barriers yet found for a substituted cyclohexane (17.0 kcal mol^{-1}). The high ring inversion barrier for *cis*-1,2-di-*t-butyl* cyclohexane (**137**)[77] (16.3 kcal mol^{-1}), can be explained in terms of the t-butyl groups being eclipsed or nearly eclipsed in the transition state.

Van der Waals' interactions

There is no unequivocal evidence of the role and relative importance of Van der Waals' interactions. Barriers to ring inversion in 1,1,3,3-tetrasubstituted

cyclohexanes[75] such as compound (**138a**) are slightly lower than in cyclohexanes, while those of 1,1,3,3,5,5-hexasubstituted cyclohexanes[75] (**138b**) are substantially lower.



138a, R_1=R_2=Me, R_3=H, barrier= 8.7 kcal mol^{-1}
138b, R_1=R_2=R_3=Me, barrier= 8.0 kcal mol^{-1}

It is thought that 1,3-syn-diaxial interactions in the ground state may produce a preferred chair conformation that is somewhat flattened[75]. The transition state for ring inversion is undoubtedly flatter than a chair conformation. Compounds **138a** and **138b** have a ground state conformation nearer that of the transition state and this is reflected in their lower ring inversion barriers. This point is further borne out by results for heterocyclic rings to be discussed later.

Bond angle strain (Bayer strain)

Calculations point to Bayer strain being greater in the transition state than in the ground state. Molecular mechanics calculations[78] and molecular models which allow mechanical rotation about carbon-carbon linkages suggest the importance of bond angle strain for inversion of six-membered rings. If a 5-, 7-, 8-, or greater-membered ring is constructed, there is a great deal of flexibility in the model even though bond angles are constrained to 109.5°. In contrast, the chair conformation of cyclohexane is inflexible and to invert the ring of a model molecule requires exertion of force. Table 5[75] shows the results for barriers to ring inversion in some cycloalkanes $(CH_2)n$.

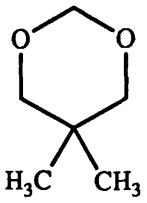
Table 5

n	$\Delta G^{\neq}$/ kcal mol^{-1}
5	<RT
6	10.1
7	<5.3
8	8.1
9	6
10	5.7

Bayer strain is also relevant to the discussion of spiro compounds.

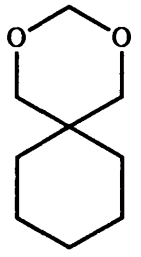
Dipolar effects

Dipole-dipole interactions play an important role in conformational analysis. However when one or more heteroatoms replace carbon atoms in the cyclohexane skeleton, large changes in other interactions take place which may obscure effects due to dipole-dipole interactions. Examples which illustrate the effect of dipole interactions do exist. Compounds **(139d)** and **(140)** have very similar inversion barriers, whereas the barrier in compound **(141)** is much lower[79].



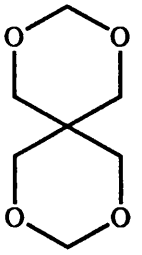
139d

$\Delta G^{\neq}$ = 10.9 kcal mol^{-1}



140

$\Delta G^{\neq}$ = 10.9 kcal mol^{-1}



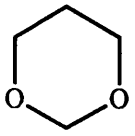
141

$\Delta G^{\neq}$ = 9.7 kcal mol^{-1}

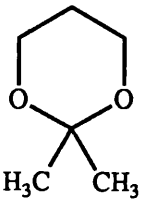
{The effect of adding a six-membered ring (**139d** → **140**) is negligible, but the effect of polar groups in that ring is substantial (**140** → **141**)}

Heterocyclic six-membered rings

A generally applicable effect observed in heterocyclic systems can be demonstrated by considering 1,3-dioxane **(139a)** and the 2,2-dimethyl derivative **(139b)**. The barrier to inversion of **139a** was found to be 9.9 kcal mol^{-1}, whereas the value for **139b** was 7.8 kcal mol^{-1}.



139a



139b

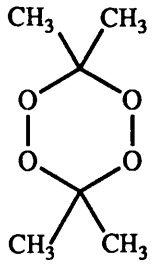
The reason for this is that the axial methyl groups in **139b** interact particularly strongly with axial hydrogen atoms in the 4- and 6-positions[75]. This interaction probably produces a flatter chair-conformation, which is much more like the relatively flat half-chair transition state conformation and this results in a reduced barrier to ring inversion.

Many examples of this effect have been observed. Table 6[75] shows barriers to ring inversion of some oxygen heterocycles.

Table 6
Ring inversion barriers of some oxygen heterocycles

compound	$\Delta G^{\neq}$ kcal mol^{-1}
 **142**	9.4
 **143**	12.9
 **139a**	9.6
 **144**	9.4 - 9.7
 **145**	10.2

From table 6 it is evident that the substitution of one oxygen atom **(142)** lowers the barrier. This is thought to be a reflection of both the flattening of the six-membered ring and the ease of rotation about the relatively long carbon-oxygen bonds. Similar arguments may also be applicable for compounds **139a**, **(144)** and **(145)**, although 1,3-diaxial repulsion between lone pairs on the oxygens in **139a** and **145** may also be of some importance. The oxygen-oxygen bond has a much higher barrier to rotation than either a carbon-carbon or carbon-oxygen bond. This effect is observed in compound **(143)** which has the highest barrier in table 6. The high barrier observed for compound **(146)**[80,81] provides a further striking illustration of this effect.



146

$\Delta G^{\neq}$ =15.4 kcal mol^{-1}

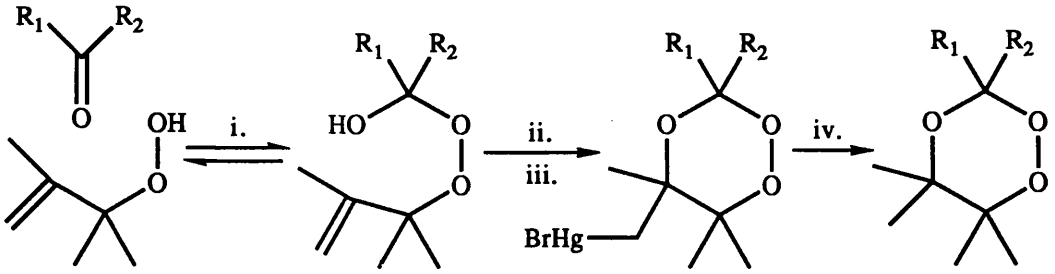
No ring inversion barriers for 1,2,4-trioxanes have been recorded in the literature. The extension of our new synthesis of 1,2,4-trioxanes (chapter 2) to formaldehyde and to ketones afforded compounds suitable for such a study. Accordingly, a dynamic nmr determination of barriers for chair-chair interconversion in some tetra- and hexa-substituted 1,2,4-trioxanes was carried out[82]. The ring inversion barriers for 1,2,4-trioxanes were then compared with those for equivalently substituted 1,3-dioxanes (Fig 8).

Figure 8

3.2 Results and discussion

3.2.1 The synthesis of 5,5,6,6-tetramethyl- and 3,3,5,5,6,6-hexa-alkyl-1,2,4-trioxanes by intramolecular oxymercuriation

5,5,6,6-tetramethyl-1,2,4-trioxane (**149a**) and some 3,3,5,5,6,6-hexa-alkyl-1,2,4-trioxanes (**149b-149h**), were prepared by an intramolecular oxymercuriation[68] procedure (Scheme 69).



113 **147** **148** **149**

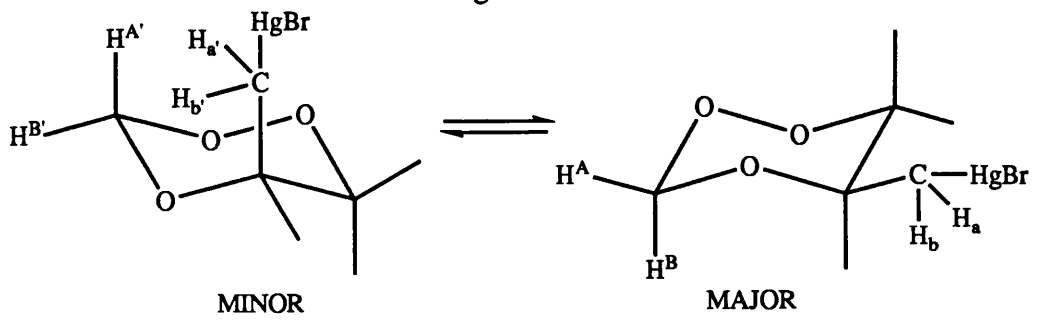
i. cat. CF_3COOH, CH_2Cl_2
ii. $Hg(OAc)_2$, 6 mol% $HClO_4$
iii. KBr
iv. $NaBH_4$, NaOH

Scheme 69

Hemiperoxyacetals (**147**) derived from allylic hydroperoxide (**113**) and the appropriate ketone (or paraformaldehyde for example **149a**), were treated *in situ* with mercury(II) acetate and perchloric acid catalyst. The oxymercuriations (5-20mmol scale) were complete in 1-3 hrs. Organomercury(II) bromides (**148**) obtained after anion exchange with potassium bromide were purified by simple column chromatography (SiO_2, CH_2Cl_2) and isolated in yields ranging from 0.53% (for **148h**, R_1=Me, R_2= p-$NO_2C_6H_4$) to 34% (for **148b**), see table 7.

The low temperature (-48 °C) proton nmr spectrum of 5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxane **148a**, suggests an equilibrium between two conformations (Fig 9).

Figure 9



MINOR MAJOR

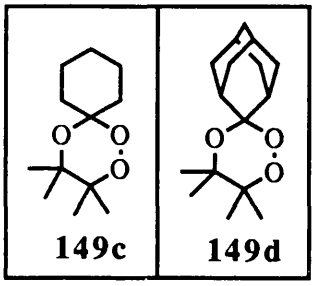
40 : 60

At low temperatures the rate of interconversion between the two conformations was slow enough for each to be detected and separate signals were observed for the $\mathbf{H^A}$, $\mathbf{H^B}$, $\mathbf{H^{A'}}$, $\mathbf{H^{B'}}$, $\mathbf{H_a}$, $\mathbf{H_b}$, $\mathbf{H_{a'}}$ and $\mathbf{H_{b'}}$ protons. Thus $\mathbf{H^A}$ appeared at δ 5.55 (d, J=10.4 Hz), $\mathbf{H^B}$ at δ 4.99 (d, J=10.4 Hz), $\mathbf{H^{A'}}$ at δ 5.64 (d, J=10.5 Hz) and $\mathbf{H^{B'}}$ at δ 5.08 (d, J=10.5 Hz). In addition $\mathbf{H_a}$ was observed at δ 2.26 (d, J=11.6 Hz), $\mathbf{H_b}$ at δ 2.08 (d, J=11.6 Hz), $\mathbf{H_{a'}}$ at δ 3.02 (d, J=12.0 Hz) and $\mathbf{H_{b'}}$ at δ 2.30 (d, J=12.0 Hz). When the temperature was raised (+65 °C), the $\mathbf{H^A}$ signal merged with the $\mathbf{H^{A'}}$ signal to give a new 'averaged' signal at δ 5.4 (d, J=11.2 Hz) and the $\mathbf{H^B}$ signal merged with the $\mathbf{H^{B'}}$ to give a new 'averaged' signal at δ 5.24 (d, J=11.2 Hz). Similarly the $\mathbf{H_a}$ signal merged with the $\mathbf{H_{a'}}$ signal to give a new broad doublet at δ 2.55 (J=12.0 Hz), while the $\mathbf{H_b}$ signal merged with the $\mathbf{H_{b'}}$ signal to give a sharp doublet at δ 2.15 (J=12.0 Hz).

The sodium borohydride reductions[70] proceeded in over 90% yield and the mercury-free 1,2,4-trioxanes **149**, were purified by column chromatography (see table 7 for yields). The relatively lower yields for compounds **149**, as compared with yields for the aldehyde-derived compounds **116** (discussed in chapter 2), were attributed to hemiperoxyketal **147**, formation being less favourable than hemiperoxyacetal **114** formation, as a result of steric hindrance (Fig 10).

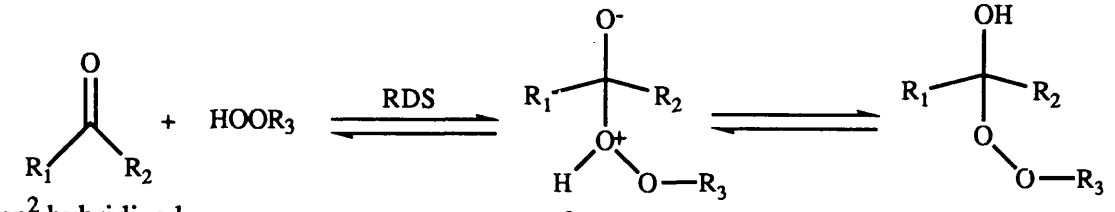
Table 7. Percentage yields of ketone-derived 1,2,4-trioxanes

compound	R_1	R_2	**148**/ %yield	**149**/ %yield
a	H	H	24	22[x]
b	Me	Me	34	30[x]
c	see below	see below	not isolated	42[x]
d	see below	see below	25	25+
e	CH_2Cl	CH_2Cl	30	30[x]
f	Me	^iPr	13	
g	Me	^tBu	not isolated	8[x]
h	Me	p-$NO_2C_6H_4$	0.53	



(Where x is the overall yield calculated from **113** by 'one-pot' method and + is the overall yield calculated from **113** after reduction of **148**)

Figure 10



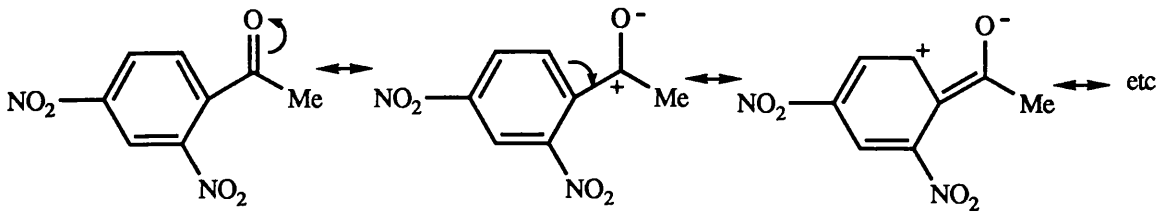
sp^2 hybridized

sp^3 hybridized

{RDS= rate determining step}

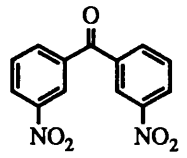
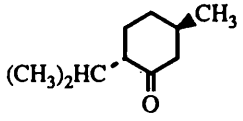
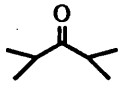
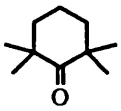
In general ketones with bulky R groups gave 1,2,4-trioxanes **149**, in relatively lower yields eg, compound **149g** (R_1=Me, R_2=^tBu) was formed in 8% yield, whereas compound **149b** (R_1=R_2=Me) was formed in 30% yield. Where the starting ketone was aromatic (p-$NO_2C_6H_4$), trioxane (**148h**) was formed in just 0.53% yield. This very low yield was attributed to very low hemiperoxyacetal **147** formation, as a result of resonance stabilisation in the ground state (Fig 11).

Figure 11



The ketones shown in table 8 did not afford 1,2,4-trioxanes *via* the oxymercuriation route (Scheme 69) and starting materials were recovered. This lack of reactivity was attributed to both steric and electronic factors.

Table 8.
Ketones which did not yield 1,2,4-trioxanes

 A	 B
 C	 D

3.2.2 **Dynamic nmr studies**

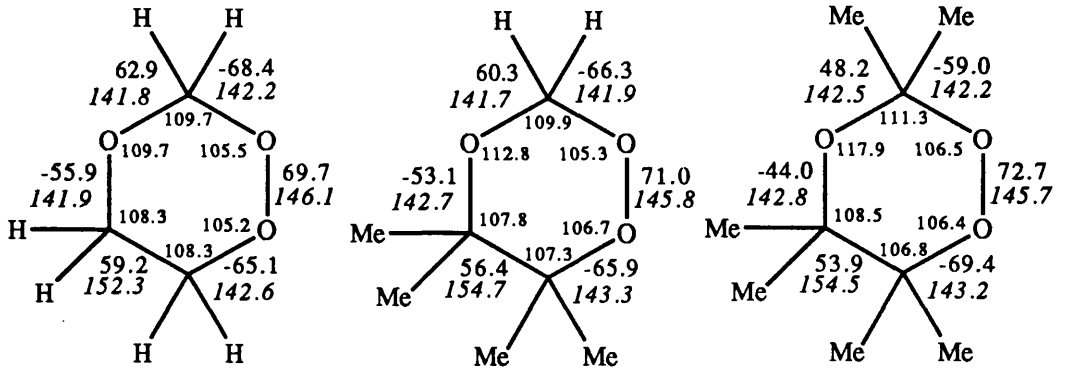
1,2,4-Trioxanes with R_1=R_2 are not conformationally locked (unlike the aldehyde-derived 1,2,4-trioxanes discussed in chapter 2) and undergo inversion at a rate which is slow enough to be detected on the nmr timescale. Conformational processes in the trioxane ring should be hindered by the high rotational barriers of the oxygen-oxygen bond and the hexasubstituted carbon-carbon bonds[75]. Ring inversion barriers for 1,2,4-trioxanes **149a**, **149b**, **149c** and **149d**, were determined from the temperature-dependence of nmr spectra and are shown in table 9[82], along with barriers for some similarly substituted 1,3-dioxanes (**139**) and relevant cyclohexanes (**150**).

The nmr behaviour of compound **149b** is typical (see nmr spectra at the end of this chapter). At -48 °C six methyl group signals are present in both proton and carbon-13 nmr spectra, showing that interchange of axial and equatorial methyl groups by ring inversion is slow on the nmr timescale. As the temperature is raised, methyl signals broaden and at about 0 °C depending on the relative chemical shift, coalesce to give a

single peak for the two methyl groups at each ring position, then finally become narrow again. The rate constant for ring inversion at the coalescence temperature was determined from the low temperature shift of exchanging signals by Dr J.E. Anderson[74]. The free energy of activation for ring inversion at this temperature was then calculated as discussed in the introduction, by assuming a transmission coefficient of 0.5, since the set of twist conformations form an unstable intermediate minimum, symetrically placed between the two chair conformations on the potential energy surface (Fig 7).

Allinger's MM3 molecular mechanics program[83,84] which is parametrised for the peroxide bond confirmed that the chair conformation is more stable than any boat conformation by several kcal mol^{-1} for compounds **139e**, **139h** and **139i** and for compounds **149a** and **149b**. Calculations in the 1,2,4-trioxane series have not previously been reported, so some bond lengths, bond angles and torsion angles are shown in fig 12.

Figure 12



Scheme. Bond lengths (pm; italic numbers), internal bond angles (small numbers) and torsional angles for bonds in 1,2,4-trioxanes rings as calculated by MM3.

The succession of oxygen-carbon and oxygen-oxygen bonds, short compared with carbon-carbon bonds, induces ring-puckering, that is torsion angles greater than 60°. Substitution with geminal methyl groups produces slight bond lengthening and closing down of bond angles internal to the ring. In the hexamethyl compound, methyl-methyl 1,3-diaxial interactions flatten one part of the ring as shown by noticeably reduced torsion angles and increased puckering in the rest of the ring.

Table 9. Barriers to ring inversion in a series of 1,2,4-trioxanes (**149**), 1,3-dioxanes (**139**) and cyclohexanes (**150**).

Substituents	Coalescence temperature T_c (°C)	Barrier at T_c (kcal mol^{-1})
1,2,4-Trioxanes		
149a 5,5,6,6-Me_4	+2	12.2
149b 3,3,5,5,6,6-Me_6	-5	12.3
149c 5,5,6,6,-Me_4-3,3(-CH_2-)$_5$	-18	11.6
149d 5,5,6,6-Me_4-3,3-Ad[a]	-17	11.6
1,3-Dioxanes		
139a none	-70	9.9
139b 2,2-Me_2	-70	7.8
139c 4,4-Me_2	-70	8.6
139d 5,5-Me_2	-70	11.2
139e 2,2,4,4-Me_4	<-150	<5.5
139f 2,2,5,5-Me_4	-70	8.9
139g 4,4,6,6-Me_4	-148	5.9
139h 4,4,5,5-Me_4	-73	10.1
139i 2,2,4,4,5,5-Me_6	-133	6.5
Cyclohexanes		
cyclohexane		10.1
150a 1,1-Me_2		10.3
150b 1,1,4,4-Me_4		11.4
150c 1,1,3,3-Me_4		8.7

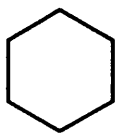
[a] Ad=spiro[2.2]adamantyl.

The results in table 9 for simple 1,3-dioxanes show clearly from several comparisons how introducing axial substituents in the 2, 4 or 6-positions produces substantial lowering of barriers. Syn-diaxial interactions are particularly marked because of the four short carbon-oxygen bonds in 1,3-dioxanes compared with the equivalent carbon-carbon bonds of cyclohexanes, and produce these barrier reductions. This effect is further depicted by considering compounds **139h** and **139i** (compare **139h** with **139d** and **139i** with **139h** or **139f**) but the results also illustrate a contrasting effect. Introducing a hexasubstituted bond in the 4-5 position leads to ring

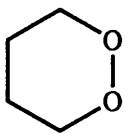
inversion barriers higher by more than 1 kcal mol^{-1} in **139h** and **139i** compared with **139c** and **139e** respectively.

The barriers to ring inversion for each of the 1,2,4-trioxanes **149a-149d** are surprisingly similar, and higher than any in the 1,3-dioxane series. The extra substituents at the OCO position in **149b-149d** compared with **149a** have little effect on the barrier although the equivalent substitution in the 1,3-dioxane series lowers the barrier by more than 3 kcal mol^{-1}. The slightly lower barriers in **149c** and **149d** compared with **149a** and **149b** may reflect the cyclic substituents being less able to distort to accomodate strain in the ground state.

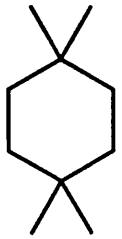
Comparisons between the 1,2,4-trioxanes and equivalently substituted 1,3-dioxanes are striking. The barrier in **149a** is 2.1 kcal mol^{-1} higher than in **139h**, while that in **149b** is 5.8 kcal mol^{-1} higher than in **139i**. In both cases a CH_2, group in the dioxane has been replaced by an oxygen atom in the trioxane. It is difficult to predict whether the replacement increases or decreases transannular interactions, as the parent 1,3-dioxane (9.9) and cyclohexane (10.1) barriers are very similar, but it does introduce an oxygen-oxygen bond which has a high rotational barrier and this is thought to be the cause of the contrasting high barriers in the 1,2,4-trioxanes. As the 1,3-dioxanes **139h** and **139i** have substituents located in the 5,6,1,2-part of the molecule, the 'low barrier' rate-determining rotation step of the ring inversion is presumably in the 5,6,1,2-part. The introduction of an oxygen atom into the 6-position to give 1,2,4-trioxanes **149a** and **149b** with a high barrier oxygen-oxygen bond, removes the 'low barrier' section of the molecule which therefore leads to high barriers regardless of the substitution pattern. There is a precedent for enhanced barriers when oxygen-oxygen bonds are introduced as shown by comparison of the ring inversion barrier for cyclohexane of 10.1 kcal mol^{-1} with the higher barrier for 1,2-dioxane **143** (12.9 kcal mol^{-1}, see table 6). This is further illustrated by comparison of the ring inverson barrier for 1,1,4,4-tetramethylcyclohexane **150b**[85,86] of 11.4 kcal mol^{-1} with the higher barriers for both 3,3,6,6-tetramethyl-1,2-dioxane **151**[87] (14.6 kcal mol^{-1}) and 3,3,6,6-tetramethyl-1,2,4,5-tetroxane **146**[80,81] (15.4 kcal mol^{-1}).



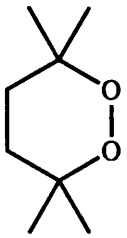
Cyclohexane
10.1 kcal mol^{-1}



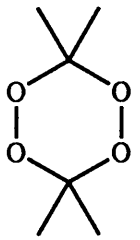
143
12.9 kcal mol^{-1}



150b
11.4 kcal mol^{-1}



151
14.6 kcal mol^{-1}



146
15.4 kcal mol^{-1}

Rotation about individual bonds and the overall flatness of the ground state ring conformation must be the dominating influences on the barrier sizes for the 1,2,4-trioxanes, but these effects operate in opposite directions and their relative importance when all carbons are substituted, is too complicated to elucidate.

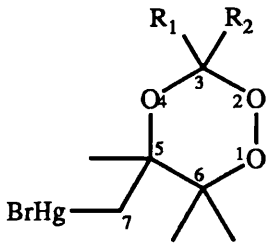
3.3 Conclusion

The overall yields for ketone-derived (and paraformaldehyde-derived) 1,2,4-trioxanes **149**, were lower than for the aldehyde-derived compounds **116**, as a result of poor hemiperoxyketal **147** formation. The oxymercuriation route (Scheme 69) could not be fully developed to include aromatic ketones (only a 0.53% yield was obtained for compound **148h**, R_1=Me, R_2=p-$NO_2C_6H_4$). This lack of reactivity was attributed to both steric and electronic factors in the ground state (cf. aromatic aldehydes-chapter 2).

In general 1,2,4-trioxanes where R_1=R_2 **149a-d**, had significantly higher ring inversion barriers than those for structurally related 1,3-dioxanes **139**. This difference was attributed to the presence of high rotational barrier oxygen-oxygen bonds in the 1,2,4-trioxane series, the absence of which in the 1,3-dioxane series enabled them to rotate about the 'low barrier' 5,6,1,2-part of the ring in the rate determining step.

3.4 Experimental

5-(Bromomercuriomethyl)-3,3-(alkyl/aryl)-5,6,6-trimethyl-1,2,4-trioxanes (148)



148a (R_1=R_2=H)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g) in acetonitrile (20ml), was treated with paraformaldehyde (11.67mmol; 1.05g) and catalytic trifluoroacetic acid (2 drops). The mixture was stirred at room temperature (10 minutes). Mercury(II) acetate (5mmol; 1.59g), was added in one portion with 6 mol % perchloric acid catalyst (3 drops). The reaction mixture was stirred for a further 45min-1hr. The mixture was washed with 5% sodium bicarbonate (10ml). Anion exchange of the acetate group for bromide was carried out by stirring with aqueous potassium bromide (5mmol; 0.59g in 10ml water). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.94), gave the pure product as a white solid (0.18g, 24%).

^{1}H nmr (400MHz) -58 °C Major isomer : d 5.55 (d, J=10.4 Hz, 1H, CH^AH^B), 4.99 (d, J=10.4 Hz, 1H, CH^AH^B), 2.26 (d, J=11.6 Hz, 1H, CH_aH_bHgBr), 2.08 (d, J=11.6 Hz, 1H, CH_aH_bHgBr), 1.58 (s, 3H), 1.47 (s, 3H), 1.05 (s, 3H).
Minor isomer : d 5.64 (d, J=10.5 Hz, 1H, $CH^{A'}H^{B'}$), 5.08 (d, J=10.5 Hz, 1H, $CH^{A'}H^{B'}$), 3.02 (d, J=12.0 Hz, 1H, $CH_{a'}H_{b'}HgBr$), 2.3 (d, J=12.0 Hz, 1H, $CH_{a'}H_{b'}HgBr$), 1.55 (s, 3H), 1.29 (s, 3H), 1.05 (s, 3H) ppm.
+65 °C : d 5.4 (d, J=11.2 Hz, 1H,CH^AH^B), 5.24 (d, J=11.2 Hz, 1H, CH^AH^B), 2.55 (bd, J=12.0 Hz, 1H, CH_aH_bHgBr), 2.15 (d, J=12.0 Hz, 1H, CH_aH_bHgBr), 1.46 (s, 3H), 1.41 (s, 3H), 1.25 (s, 3H) ppm.
^{13}C nmr (100MHz) +25 °C : d 91.24 (C-3), 85.30 (C-6), 77.40 (C-5), 44.00 (broad signal, CH_2HgBr), 21.99, 21.92, 21.86 ppm.
Found: C, 19.53; H, 2.93% $C_7H_{13}O_3BrHg$ requires: C, 19.75; H, 3.08%

148b (R_1=R_2=Me)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g) in dichloromethane (25ml) was treated with acetone (10mmol; 0.58g) and catalytic trifluoroacetic acid (4 drops). The mixture was stirred at room temperature (10 minutes). Mercury(II) acetate (10mmol; 3.18g) was added with 6 mol % perchloric acid catalyst (6 drops). The reaction mixture was stirred for a further 45min-1hr until most of the solid mercury acetate was consumed. The mixture was washed with 5% sodium bicarbonate (20ml). Anion exchange of the acetate group for bromide was carried out by stirring with aqueous potassium bromide (10mmol; 1.19g in 15ml water) for 0.5hrs. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x15ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.8), gave the pure product as a white solid (0.59g, 34%).

^{1}H nmr (400MHz) +25 °C : d 2.35 (bd, 1H, CH_aH_bHgBr), 2.05 (d, J=11.08 Hz, 1H, CH_aH_bHgBr), 1.50 (bs, 3H), 1.39 (bs, 6H), 1.37 (s, 3H), 1.20 (bs, 3H) ppm.
^{13}C nmr (100MHz) +25 °C : d 102.19 (C-3), 82.79 (C-6), 77.82 (C-5), 48.02 (CH_2HgBr), 29.0, 27.32, 25.94, 22.32, 22.12 ppm.
Found: C, 24.04; H,3.66% $C_9H_{17}O_3BrHg$ requires: C, 23.82; H, 3.78%

148d (R_1=R_2=3,3-Ad[a])

Procedure as for **148b**.
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (6mmol; 0.58g), adamantanone (6mmol; 0.9g), trifluoroacetic acid (2 drops), mercury acetate (6mmol; 1.9g), perchloric acid catalyst (3 drops), potassium bromide (6mmol; 0.71g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.79), gave the pure product as a white solid (0.84g, 25%).
([a] Ad=spiro[2.2]adamantyl)

^{1}H nmr (400MHz) +25 °C : d 2.6 (bd, 1H, CH_aH_bHgBr), 2.30 (d, J=11.23 Hz, 1H, CH_aH_bHgBr), 2.09-1.49 (m, 20H), 1.12 (s, 3H) ppm.
^{13}C nmr (100MHz) +25 °C : d 104.82 (C-3), 82.98 (C-6), 78.46 (C-5), 48.04(bs, CH_2HgBr), 37.53, 37.18, 34.59, 34.34, 34.13, 34.03, 33.69, 28.38, 27.23 (9C, C3-'adamantyl'), 26.69 (C5-Me), 22.65 and 21.79 (C6-Me_2) ppm.
Found: C, 35.20; H, 4.58% $C_{16}H_{25}O_3BrHg$ requires: C, 35.08; H, 4.97%

148e (R_1=R_2=CH_2Cl)

Procedure as for **148b**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), 1,3-dichloroacetone (5mmol; 0.64g), trifluoroacetic acid (2 drops), mercury acetate (5mmol; 1.59g), perchloric acid catalyst (3 drops), potassium bromide (5mmol; 0.6g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.91), gave the pure product as a white solid (1.57g, 30%).

^{1}H nmr (400MHz) +25 °C : d 3.79 (m, 4H, $2CH_2Cl$), 2.45 (bd, 1H, CH_aH_bHgBr), 2.08 (d, J=12.13Hz, 1H, CH_aH_bHgBr), 1.44 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H) ppm.

^{13}C nmr (100MHz) +25 °C : d 101.07 (C-3), 84.03 (C-6), 79.87 (C-5), 45.51 (CH_2Cl), 44.22 (bs, CH_2HgBr), 43.83 (CH_2Cl), 28.40, 22.30 (2C) ppm.

Found: C, 20.86; H, 2.76% $C_9H_{15}Cl_2O_3BrHg$ requires: C, 20.68; H, 2.89%

148f (R_1=Me, R_2=^{i}Pr)

Procedure as for **148b**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), 3-methyl-2-butan-2-one (5mmol; 0.43g), trifluoroacetic acid (2 drops), mercury acetate (5mmol; 1.59g), perchloric acid catalyst (3 drops), potassium bromide (5mmol; 0.6g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.82), gave the pure product as a white solid (0.09g, 9%).

^{1}H nmr (400MHz) +25 °C : d 2.24 (d, J=11.99 Hz, 1H, CH_aH_bHgBr), 1.98 (d, J=11.99 Hz, 1H, CH_aH_bHgBr), 1.75-1.8 (m, 1H, CH^iPr), 1.55 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.11 (s, 3H), 0.95 (m, 6H, CH-Me_2) ppm.

Found: C, 27.23; H, 3.67% $C_{11}H_{21}O_3BrHg$ requires: C, 27.42; H, 4.39%

148h (R_1=Me, R_2=p-$NO_2C_6H_4$)

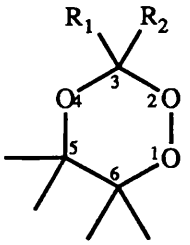
Procedure as for **148b**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (15mmol; 1.74g), 4-nitroacetophenone (20mmol; 2.48g), trifluoroacetic acid (6 drops), mercury acetate (15mmol; 4.77g), perchloric acid catalyst (9 drops), potassium bromide (15mmol; 1.78g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.75), gave the pure product as a white solid (0.03g, 0.53%).

^{1}H nmr (60MHz) +25 °C : d 7.8-7.7 (m, 4H, p-$NO_2C_6H_4$), 2.26 (d, J=10.5 Hz, 1H,

CH_aH_bHgBr), 2.10 (d, J=10.5 Hz, 1H, CH_aH_bHgBr), 1.6 (s, 3H), 1.44 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H) ppm.

3,3-(Dialkyl)-5,5,6,6-tetramethyl-1,2,4-trioxanes (149)



149a (R_1=R_2=H), 'one-pot' procedure

2,3-Dimethylbut-1-en-3-yl hydroperoxide (14mmol; 1.64g) in acetonitrile (30ml) was treated with paraformaldehyde (27.78mmol; 2.5g) and catalytic trifluoroacetic acid (6 drops). The mixture was stirred (10 minutes) before treating with mercury(II) acetate (14mmol; 4.5g) and 6 mol % perchloric acid catalyst (9 drops). After stirring (45min-1hr), the mixture was washed with 5% sodium bicarbonate (15ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were cooled with stirring (ice). A cooled solution of sodium borohydride (14mmol; 0.53g) in 2M aqueous sodium hydroxide (5ml), was added dropwise and a black precipitate was observed. The mixture was stirred for a further 20-30mins., before being filtered through phase separation paper. The aqueous layer was extracted with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.85), gave the pure product as a colourless liquid (0.45g, 22%).

^{1}H nmr (400MHz) +42 °C : d 5.20 (very broad doublet, 2H, C3-$\mathbf{H_2}$), 1.28 (s, 12H, C5-$\mathbf{Me_2}$ and C6-$\mathbf{Me_2}$) ppm.
+25 °C : d 5.28 (2H, C3-H_2), 1.22 and 1.27 (12H, C5-$\mathbf{Me_2}$ and C6-$\mathbf{Me_2}$) ppm.
-58 °C.: d 5.55 (d, J=8.36 Hz, 1H), 4.94 (d, J=8.36 Hz, 1H), 1.99 (s, 3H),
1.35 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H) ppm.
^{13}C nmr (100MHz) +46 °C : d 91.25 (C-3), 83.59 (C-6), 74.53 (C-5), 21.77 (broad, due to two far apart methyl signals collapsing together), 21.29 (sharp, due to two adjacent methyl signals collapsing together) ppm.
+25 °C : d 91.16, 83.56, 74.46, 21.21 (4C) ppm.
-58 °C.: d 91.08, 83.56, 74.38, 24.14*, 21.11**, 19.22**, 19.18* ppm.

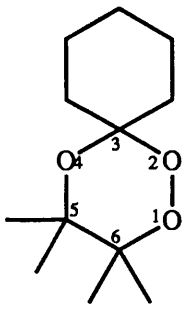
+25 °C (carbon-proton coupled) : d 91.14 [t, $^1J(^{13}C-^1H)$=164.55 Hz, H_2 coupled to C3], 83.8 (m), 74.0 (m), 21.20 [q, $^1J(^{13}C-^1H)$=123.4 Hz] ppm.
(* and** methyl signals which merge at high temperature).
Found: C, 57.59; H, 9.47% $C_7H_{14}O_3$ requires: C, 57.51; H, 9.65%

149b (R_1=R_2=Me), 'one-pot' procedure

2,3-Dimethylbut-1-en-3-yl hydroperoxide (14mmol; 1.64g) in dichloromethane (25ml) was treated with acetone (28mmol; 1.6g) and catalytic trifluoroacetic acid (4 drops). The mixture was stirred (10 minutes) before adding mercury(II) acetate (14mmol; 4,5g) with 6 mol % perchloric acid catalyst (6 drops). The reaction mixture was stirred for a further 45min-1hr until most of the solid mercury acetate was consumed. The mixture was washed with 5% sodium bicarbonate (20ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (2x10ml). The combined organic extracts were cooled with stirring (ice). A cooled solution of sodium borohydride (14mmol; 0.53g) in 2M aqueous sodium hydroxide (5ml) was added dropwise and a black precipitate was observed. The mixture was stirred for a further 20-30mins., before filtering through phase separation paper. The aqueous layer was extracted with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.8), gave the pure product as a white solid (0.72g, 30%).

^{1}H nmr (400MHz) +42 °C : d 1.46 (s, 6H, C3-**Me_2**), 1.24 (s, 12H, C5-**Me_2** and C6-**Me_2**) ppm.
-48 °C : d 1.62 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H) ppm.
^{13}C nmr (100MHz) +42 °C : d 101.74 (C-3), 81.38 (C-6), 74.78 (C-5), 26.47 (2C, C3-**Me_2**), 25.76 and 21.56 (4C, C5-**Me_2**, C6-**Me_2**) ppm.
-49 °C : d 101.62, 81.31, 74.31, 27.37, 26.04, 25.08(2C), 24.40, 21.04 ppm.
Found: C, 61.78; H, 9.97% $C_9H_{18}O_3$ requires: C, 62.04; H, 10.41%

149c (R_1=R_2=3,3{-CH_2-}$_5$), 'one-pot' procedure



Procedure as for **149b**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), cyclohexanone (10mmol; 0.98g), trifluoroacetic acid (4 drops), mercury acetate (10mmol; 3.18g), perchloric acid catalyst (6 drops), sodium borohydride (10mmol; 0.37g) in 2M aqueous sodium hydroxide (5ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.89), gave the pure product as a colourless liquid (0.89g, 42%).

^{1}H nmr (400MHz) +25 °C : d 1.23 (s, 12H, C5-**Me$_2$** and C6-**Me$_2$**), 1.42-1.65 (m,10H, C3-'cyclohexyl') ppm.

-58 °C : d 1.06 (s, 3H), 1.09 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.38-1.90 (m, 10H, C3-'cyclohexyl') ppm.

^{13}C nmr (100MHz) +25 °C : d 101.98 (C-3), 81.57 (C-6), 74.65 (C-5), 35.35(broad), 26.09, 25.43 (5C, C3-'cyclohexyl'), 22.90 and 21.66 (4C, C5-**Me$_2$** and C6-**Me$_2$**) ppm.

-58 °C : d 101.95, 81.52, 74.58, 36.19, 33.36, 26.34, 26.28, 24.98 (5C, C3-'cyclohexyl'), 22.94, 22.45, 21.90 and 21.05 (4C, C5-**Me$_2$** and C6-**Me$_2$**) ppm.

Found: C, 66.83; H, 10.18% $C_{12}H_{22}O_3$ requires: C, 67.26; H, 10.35%

149e (R_1=R_2=CH_2Cl), 'one-pot' procedure

Procedure as for **149b**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), 1,3-dichloroacetone (10mmol; 1.27g), trifluoroacetic acid (4 drops), mercury acetate (10mmol; 3.18g), perchloric acid catalyst (6 drops), sodium borohydride (10mmol; 0.37g) in 2M aqueous sodium hydroxide (5ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.78), gave the pure product as a white solid (0.73g, 30%).

^{1}H nmr (400MHz) +25 °C : d 2.83 (m, 4H, 2CH_2Cl_2), 1.31 (s, 6H),
1.28 (s, 6H) ppm.

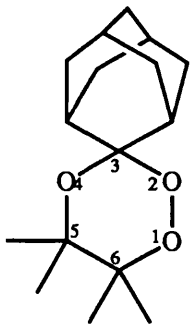
^{13}C nmr (100MHz) +25 °C : d 100.92 (C-3), 82.60 (C-6), 76.69 (C-5),

43.99 (2C, $2CH_2Cl_2$), 25.13 and 21.50 (4C, C5-Me_2 and C6-Me_2) ppm.
Found: C, 44.39; H, 6.54% $C_9H_{16}Cl_2O_3$ requires: C, 44.46; H, 6.63%

149g (R_1=Me, R_2=^{t}Bu), 'one-pot' procedure
Procedure as for **149b**.
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), 3,3-dimethylbutan-2-one (5mmol; 0.5g), trifluoroacetic acid (2 drops), mercury acetate (5mmol; 1.59g), perchloric acid catalyst (3 drops), sodium borohydride (5mmol; 0.19g) in 2M aqueous sodium hydroxide (5ml). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.86), gave the pure product as a white solid (0.08g, 8%).

^{13}C nmr (100MHz) +25 °C : d 101.71 (C-3), 81.35 (C-6), 74.74 (C-5), 35.05 (C^{t}Bu), 26.35, 25.72, 24.88 (2C), 22.32 and 21.51 (3C, ^{t}Bu) ppm.
Found: C, 65.43; H, 10.92% $C_{12}H_{24}O_3$ requires: C, 64.67; H, 11.84%

149d (R_1=R_2=3,3-spiro[2.2]adamantyl), reduction of 148d.



5-(Bromomercuriomethyl)-5,6,6-trimethyl-3, 3-spiro[2.2]adamantyl-1,2,4-trioxane **148d** (1.5mmol; 0.82g), in dichloromethane (10ml) was stirred with cooling (ice). Cooled sodium borohydride (1.5mmol; 0.06g) in aqueous 2M sodium hydroxide (1ml), was added dropwise and a black mercury precipitate was observed. The mixture was stirred for a further 20-30mins., before being filtered through phase separation paper. The aqueous layer was extracted with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure.and purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.75), gave the pure product as a white solid (0.39g, 89%).

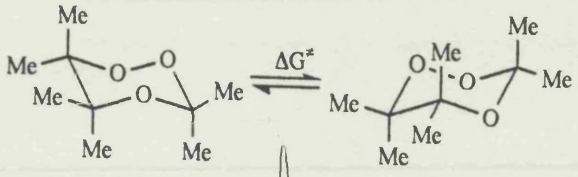
^{1}H nmr (400MHz) +25 °C : d 1.51-2.11 (m, 14H, C3-'adamantyl'), 1.24 (s, 12H, C5-Me_2 and C6-Me_2) ppm.
-58 °C : d 1.43-2.04 (m, 14H, C3-'adamantyl'), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (s, 3H),

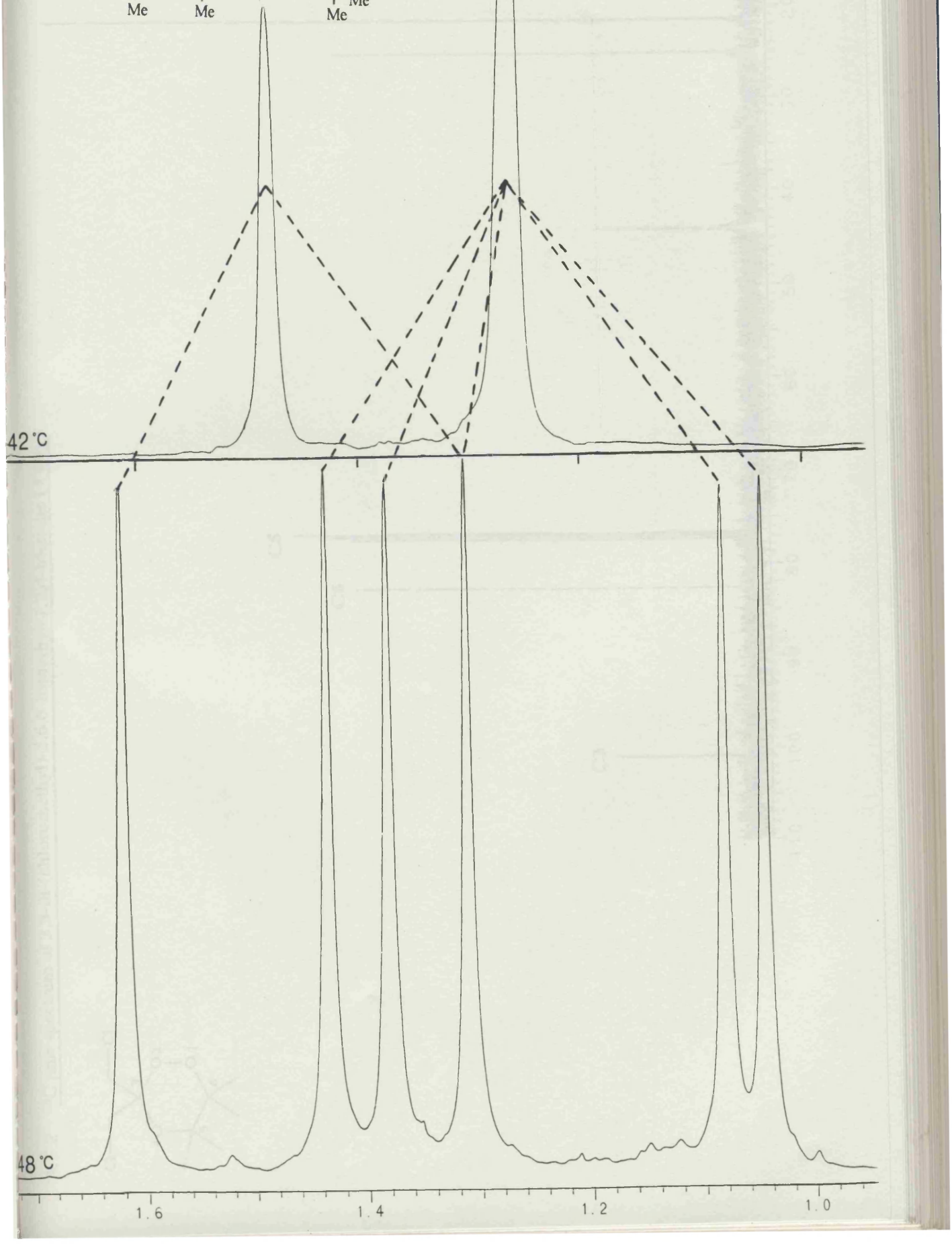
0.98 (s, 3H) ppm.
^{13}C nmr (100MHz) +25 °C : d 103.89 (C-3), 81.39 (C-6), 74.89 (C-5), 37.33, 36.07, 33.91, 33.83, 27.41, 26.80 (9C, C3-'adamantyl'), 25.69 and 21.69 (4C, C5-**Me$_2$** and C6-**Me$_2$**) ppm.
-58 °C : d 103.81 (C-3), 81.32 (C-3), 74.68 (C-5), 37.13, 36.90, 36.78, 33.80, 33.44, 33.37, 33.28, 26.86, 26.26(9C, C3-'adamantyl'), 26.39, 24.59, 21.95 and 21.11 (4C, C5-**Me$_2$** and C6-**Me$_2$**) ppm.
Found: C, 72.07; H, 9.76% $C_{16}H_{26}O_3$ requires: C, 71.98; H, 10.01%

All the dynamic nmr experiments were carried out by J. E. Anderson. The nmr spectra were for approximately 0.1 mol dm^{-3} solutions in deuteriochloroform for spectra at temperatures above -60 °C. The barriers were calculated[74] from the coalescence of appropriate nmr signals as the temperature varied.

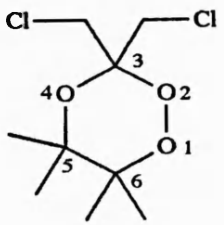
3.5 NMR Spectra

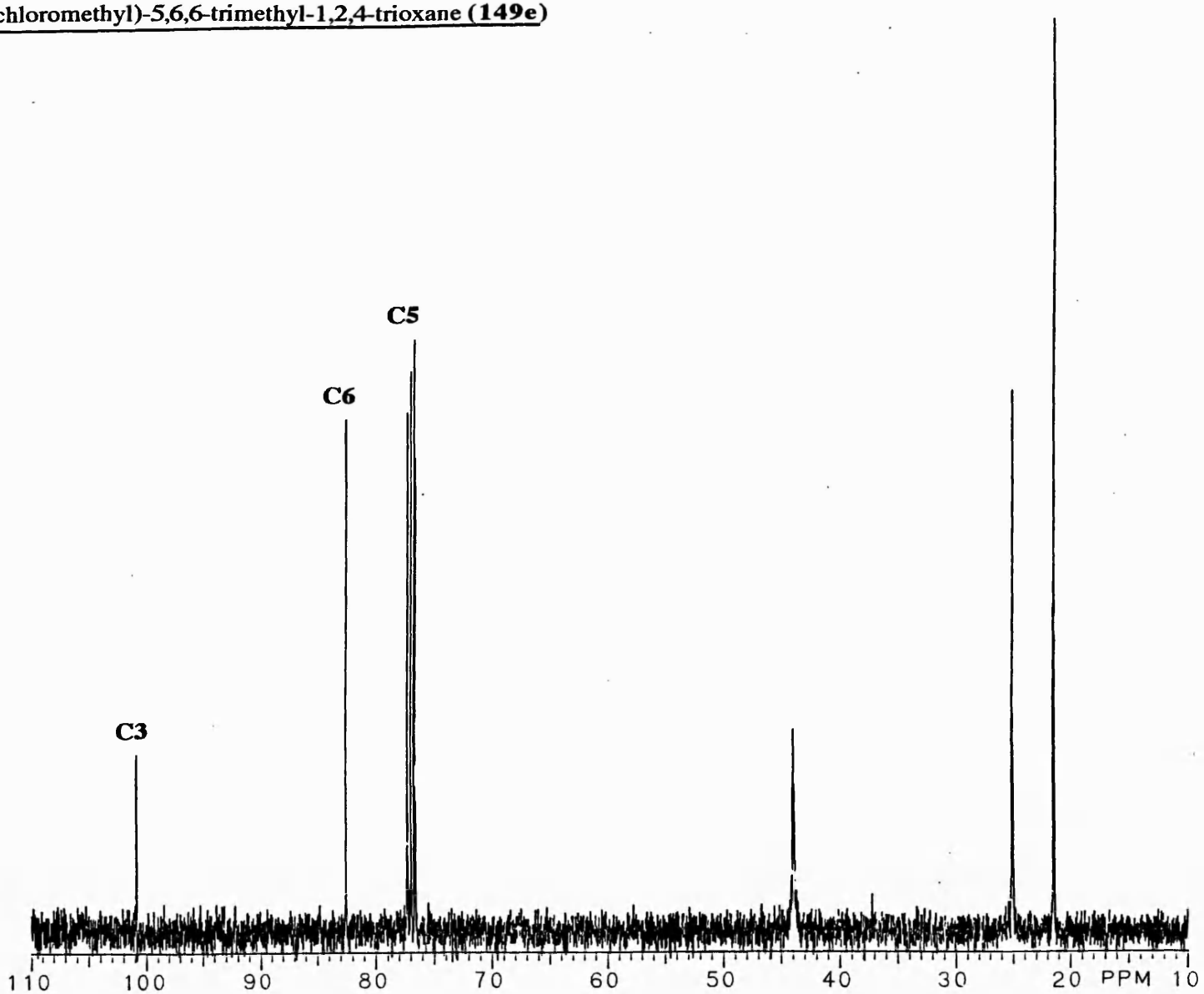
3.5.1 Variable temperature ^1H nmr for 3,3,5,5,6,6-hexamethyl-1,2,4-trioxane (**149b**)



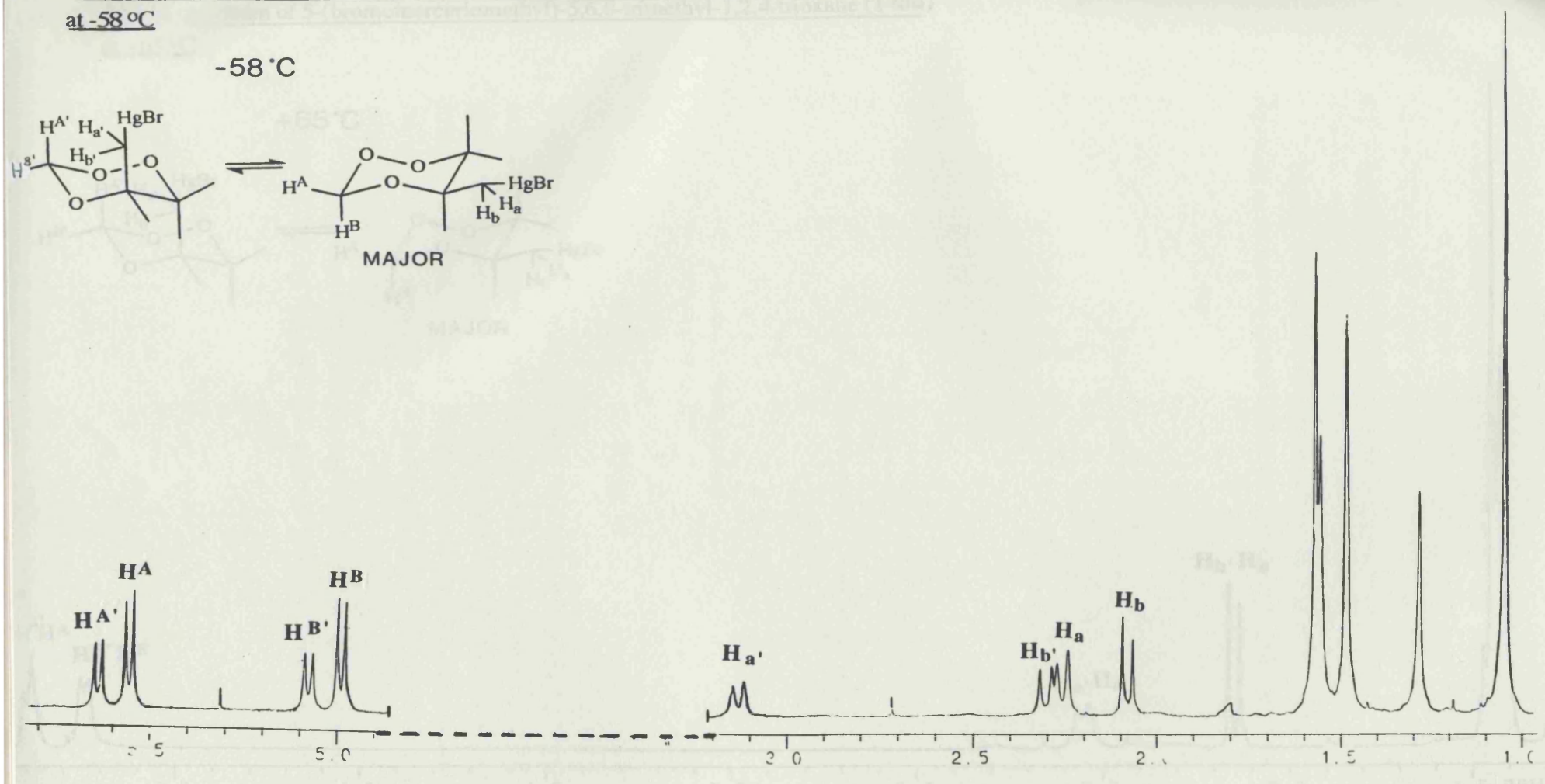


3.5.2 ^{13}C nmr spectrum of 3,3-di-(chloromethyl)-5,6,6-trimethyl-1,2,4-trioxane (**149e**)

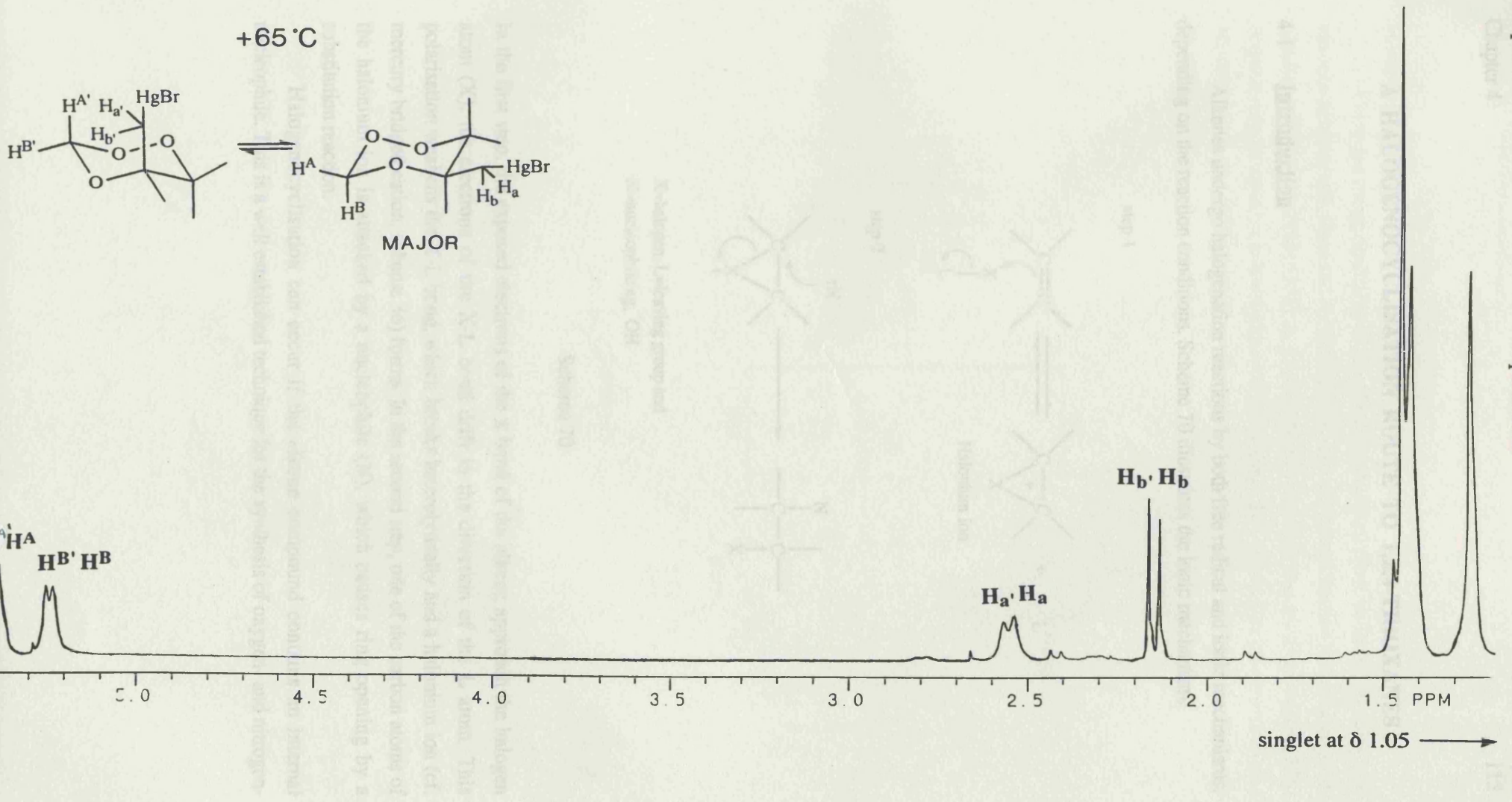




.5.3 ^{1}H nmr spectrum of 5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxane (**148a**) at -58 °C



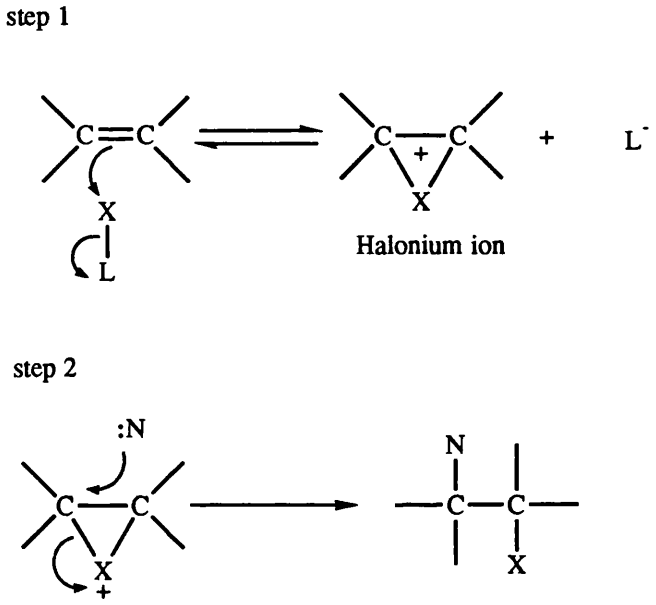
3.5.4 ^{1}H nmr spectrum of 5-(bromomercuriomethyl)-5,6,6-trimethyl-1,2,4-trioxane (**148a**) at +65 °C



A HALOGENOCYCLISATION ROUTE TO 1,2,4-TRIOXANES

4.1 Introduction

Alkenes undergo halogenation reactions by both free radical and ionic mechanisms, depending on the reaction conditions. Scheme 70 illustrates the ionic mechanism.



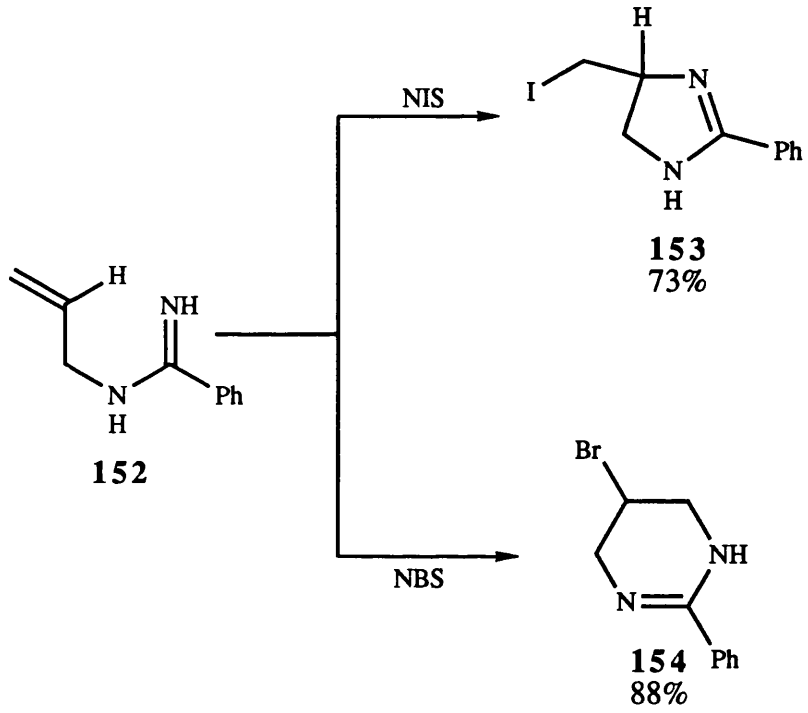
Scheme 70

In the first step, the exposed electrons of the π bond of the alkene approach the halogen atom (X), the electrons of the X-L bond drift in the direction of the L atom. This polarisation weakens the X-L bond, which breaks heterolytically and a halonium ion (cf. mercury bridged cation, scheme 36) forms. In the second step, one of the carbon atoms of the halonium ion is attacked by a nucleophile (N), which causes ring opening by a substitution reaction.

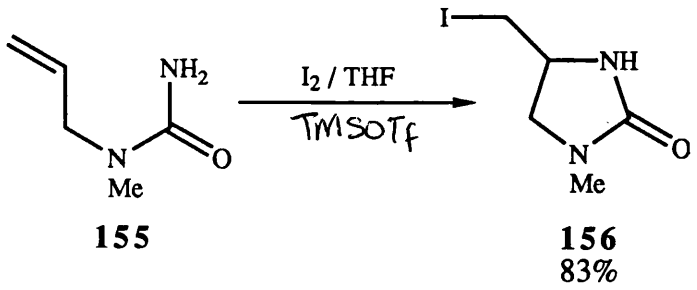
Halogenocyclisation can occur if the alkene compound contains an internal nucleophile. This is a well established technique for the synthesis of oxygen- and nitrogen-

containing heterocycles[88].

There are many examples of the use of halogenocyclisation in the formation of nitrogen heterocycles. Hunt and co-workers[89] carried out iodocyclisation reactions on allyl-amidines (**152**) and -ureas (**155**) to give imidazolines (**153**) and imidazolinones (**156**) respectively. In contrast bromocyclisation of amidine **152** resulted in the formation of a six-membered ring (**154**), possibly indicating a change in reaction mechanism (Schemes 71 and 72).



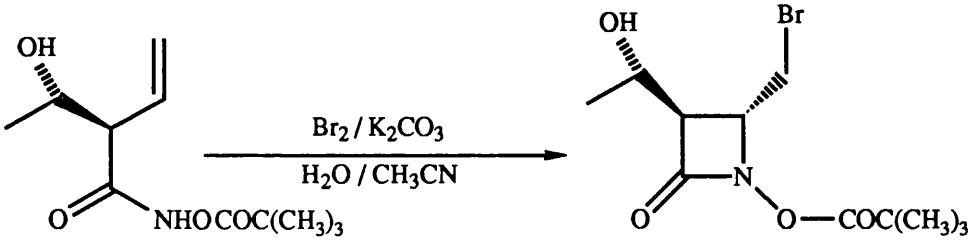
Scheme 71



Scheme 72

In order to convert compound (**155**) to (**156**), prior silylation was necessary to prevent cyclisation occurring on the oxygen.

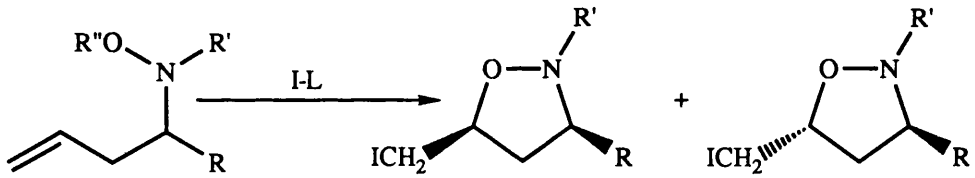
Ma and Miller[90] used bromocyclisation in the final step of an asymmetric synthesis of potentially antibiotic compound (**157**). (Scheme 73).



157

Scheme 73

Isoxazolidines are important intermediates in the synthesis of many naturally occurring substances. Mancini *et al*[91] devised a new route to 3,5-disubstituted isoxazolidines. (**159**) *via* iodocyclisation of homoallylic hydroxylamines (**158**) (Scheme 74).



158 **159a** **159b**

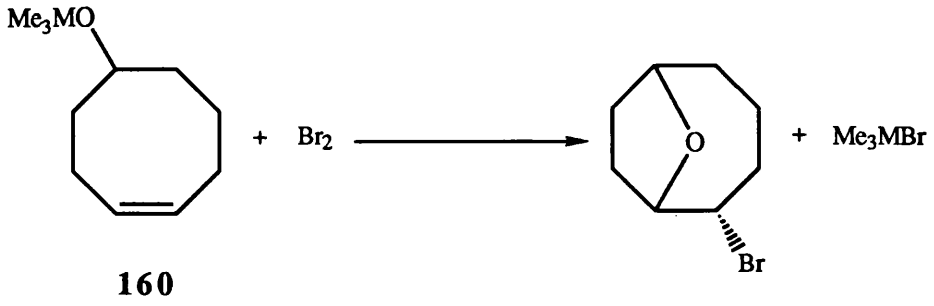
Where I-L = I_2 or N-iodosuccinimide

Scheme 74

Hydroxylamine **158**, was iodocyclised by treatment with iodine in dichloromethane or with N-iodosuccinimide (NIS) and tetrahydrofuran (THF) in chloroform at 0-20 °C. Under these conditions, cyclisation proceeded in a strictly Markovnikov fashion to yield products of 5-*exo-trig* -heterocyclisation. The major product was the *cis* isomer **159a**.

Halogenocyclisation has also been widely used in the synthesis of cyclic ethers. Bloodworth and Eggelte[92] treated cyclo-oct-4-enol derivatives (**160**), with bromine in carbon tetrachloride to yield a bicyclic ether, presumably by a polar mechanism (Scheme

75).

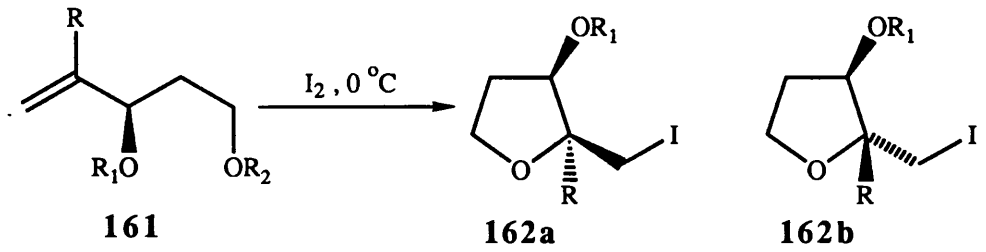


160

Where M = Si or C

Scheme 75

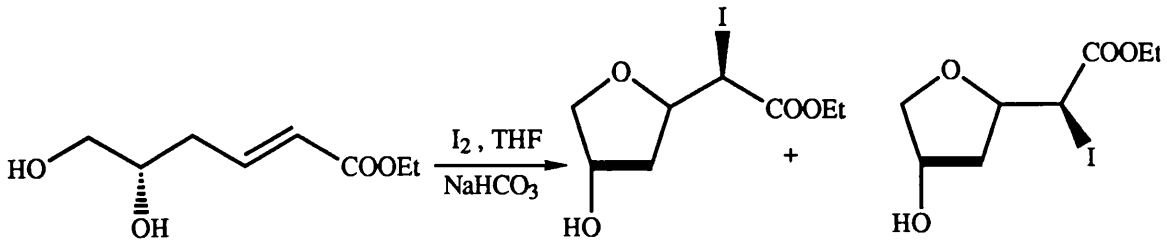
Tetrahydropyran and tetrahydrofuran units are found in a wide range of biologically important natural products. Kim *et al*[93] used iodocyclisation of 4-alkene-1,3-diol drivatives **(161)** in a stereoselective synthesis of hydroxy-substituted tetrahydrofurans **(162)** (Scheme 76). The *cis* **(162a)**, and *trans* **(162b)** isomers, were separated by chromatography.



161 **162a** **162b**

Scheme 76

Chiral induction generating two new stereogenic centres was observed by the iodoetherification of optically active ethyl 5,6-dihydroxyhexenoate **(163)**[94]. Of the four possible isomeric tetrahydrofuran products only compounds **(164a)** and **(164b)** were obtained (Scheme 77).

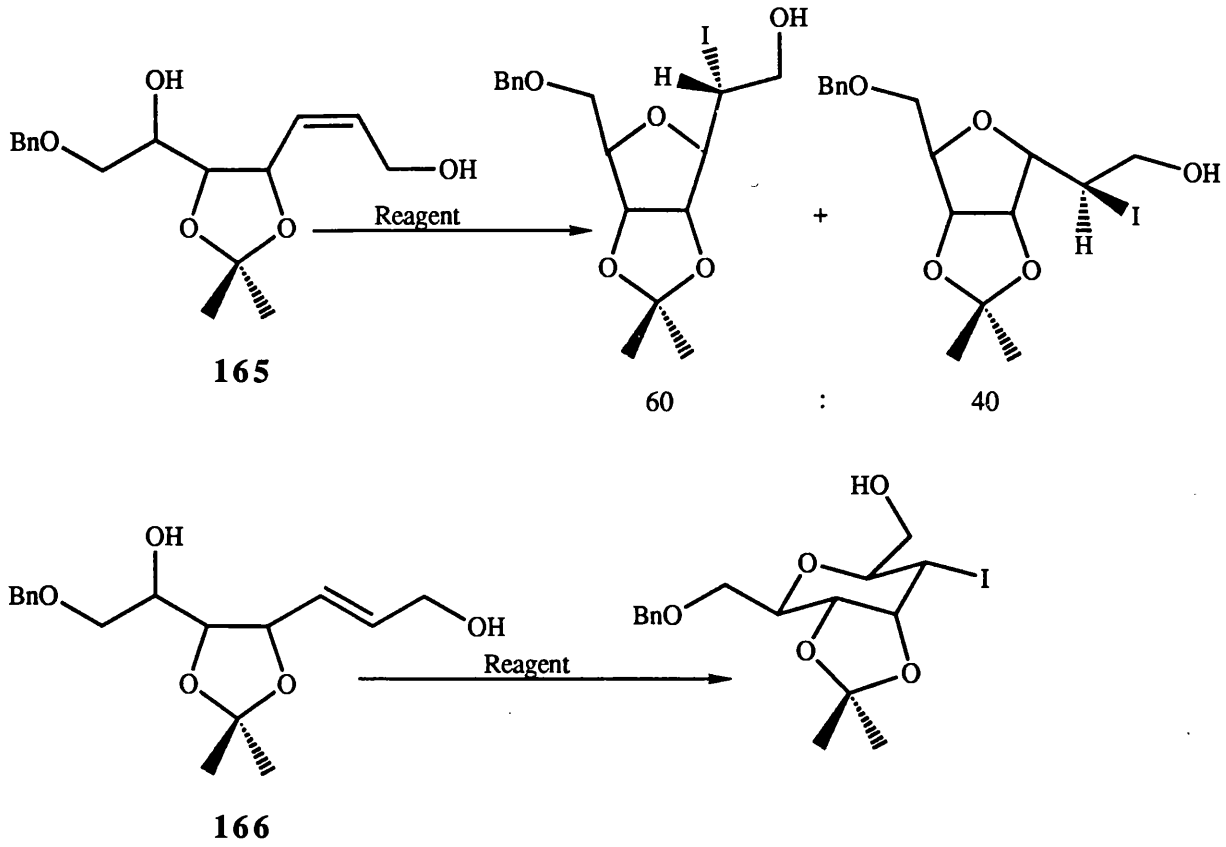


163 **164a** **164b**

12 : 1

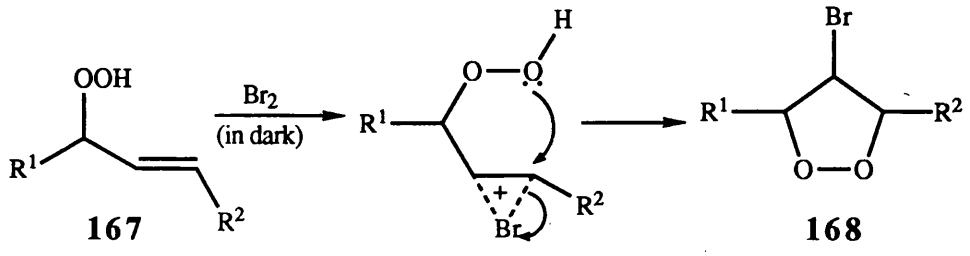
Scheme 77

Double bond geometry plays a significant role in determining the regiochemistry of halogenocyclisation. For example (Z)-olefin **(165)** gave 5-*exo* closure with low β: α selectivity, whereas (E)-olefin **(166)** showed 6-*endo* closure exclusively (Scheme 78)[88].



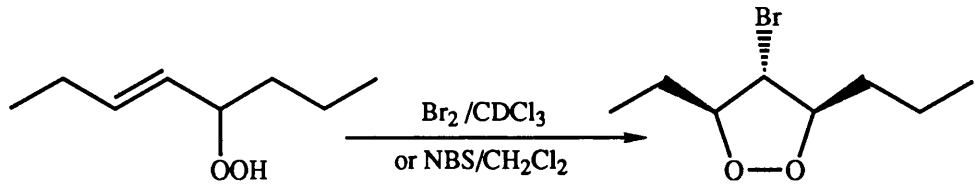
Scheme 78

Halogenocyclisation may also be applied to allylic hydroperoxides, as a route to cyclic peroxides. Bascetta *et al*[95], found that direct bromination of allylic hydroperoxides **(167)** afforded bromosubstituted cyclic peroxides **(168)** in almost quantitative yield, presumably *via* a bromonium ion intermediate (Scheme 79).



Scheme 79

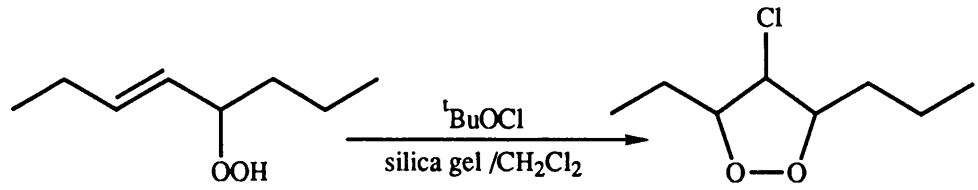
Courtneidge *et al*[57] carried out 5-*endo* ring closures of some simple allylic hydroperoxides with electrophilic halogen reagents (NBS, Br_2 and ^tBuOCl) to give substituted 1,2-dioxolanes.



100 **169**

Scheme 80

Bromodioxolane (**169**), was obtained by reaction of *E*-allylic hydroperoxide **100**, with either *N*-bromosuccinimide (NBS) in dichloromethane or with elemental bromine in deuteriochloroform (Scheme 80). The latter probably involved a polar bromonium ion-mediated reaction, which in stereochemical outcome parallels the intramolecular peroxymercuriations discussed in chapter 2 (see scheme 52). The reaction with *N*-bromosuccinimide however, was probably mechanistically more complex. Allylic hydroperoxide **100**, also reacted with *tert*-butyl hypochlorite (^tBuOCl) in dichloromethane to give a complex set of products from which a mixture of 4-chloro-1,2-dioxolanes (**170**) were isolated (Scheme 81).

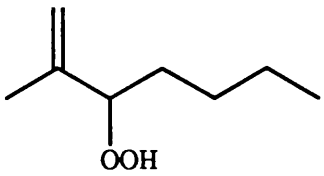


100 **170**

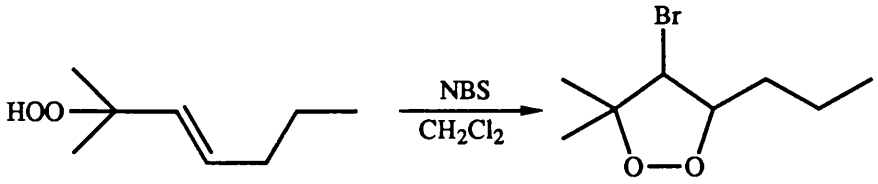
Scheme 81

The treatment of tertiary hydroperoxide (**172**) with *N*-bromosuccinimide resulted in a cyclisation reaction which gave 4-bromo-1,2-dioxolane (**173**) (Scheme 82). However

under the same reaction conditions, secondary hydroperoxide (**171**) was cleaved to a selection of products.



171

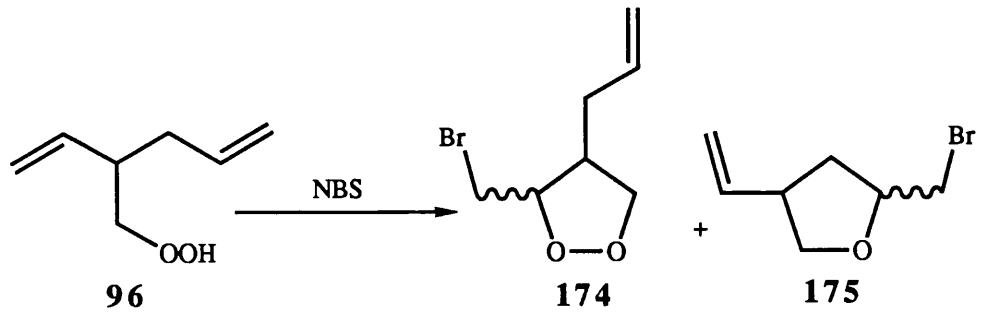


172 **173**

Scheme 82

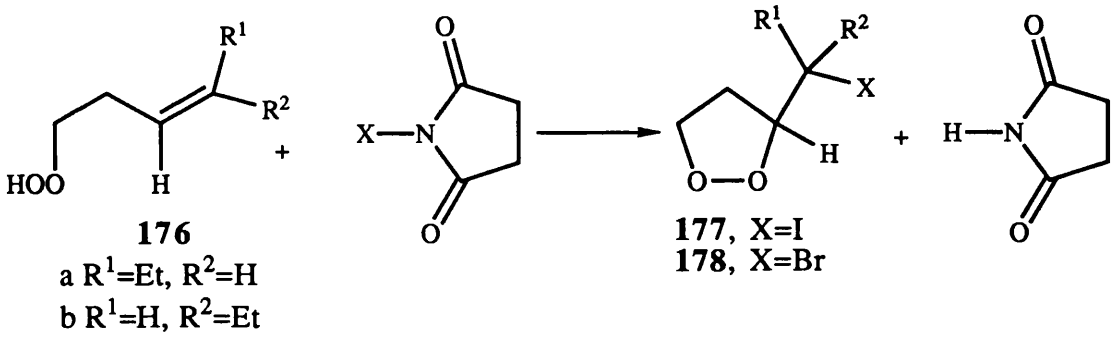
The facility with which the tertiary isomer **172**, underwent 1,2-dioxolane formation (in comparison with the inertness of isomer **171** was rationalised by appreciating the general observation that in polar oxybromination, attack of the nucleophile on the intermediate cyclic cation occurs at the least substituted carbon atom (Markovnikov-type addition). For secondary isomer **171**, this would involve the apparently unfavourable formation of 1,2-dioxetanes, although these compounds were synthesised from allylic peroxides by reaction with mercury(II) trifluoroacetate as discussed in chapter 2 (see scheme 51)[56].

Cycloperoxybromination of diene hydroperoxide **96**, by reaction with *N*-bromosuccinimide also occurred by a polar process. Consistent with this **96** yielded not only dioxolane (**174**) (cf **97**, chapter 2), but also tetrahydrofuran derivative (**175**) in a ratio of *ca.* 2:1, both products being mixtures of *cis*- and *trans*-isomers (Scheme 83)[55]. The formation of cyclic ether **175**, was rationalised by the intermediacy of a *gem*-dialkyl peroxonium ion ($R_1R_2O^+OH$)[96].



Scheme 83

Bloodworth and Curtis[97] treated alk-3-enyl hydroperoxides (**176**), with *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) to give iodo- (**177**), or bromo-alkyl 1,2-dioxolanes (**178**), with no (iodides) or partial (bromides) stereospecificity (Scheme 84).

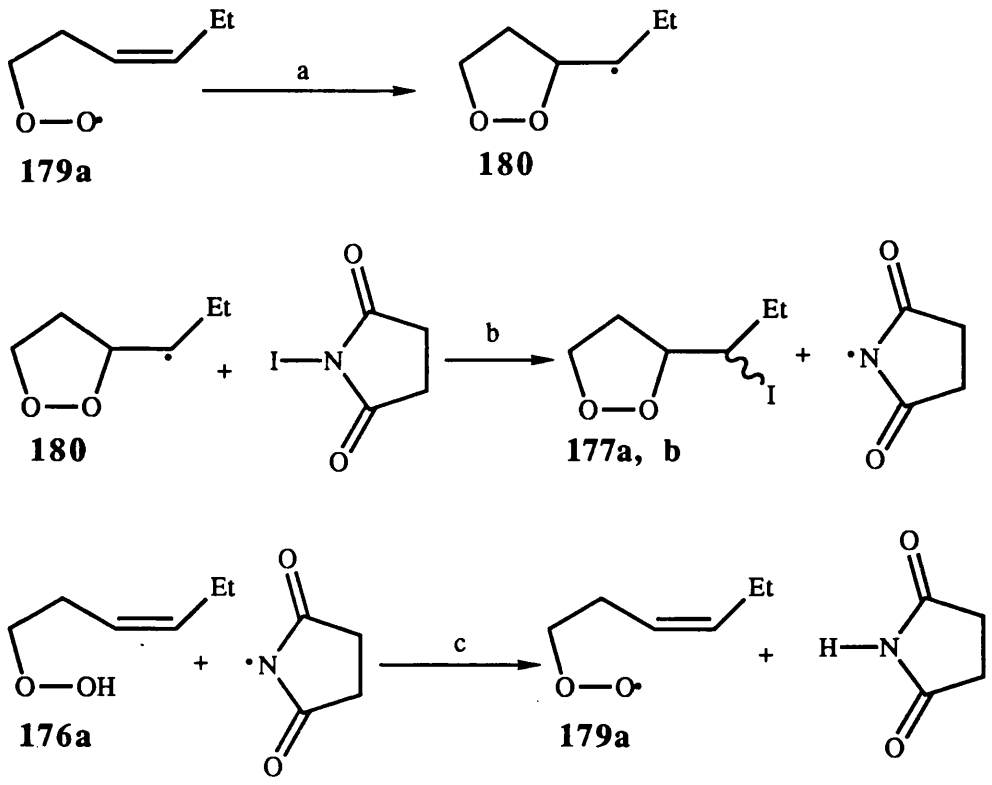


176
a R^1=Et, R^2=H
b R^1=H, R^2=Et

177, X=I
178, X=Br

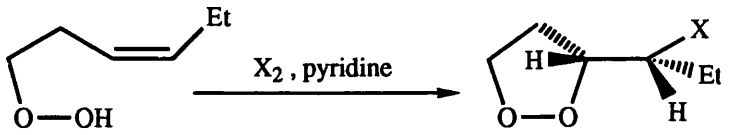
Scheme 84

Cyclisation was not stereospecific and hydroperoxides **176a** and **176b** each gave the same *ca.* 1:1, mixture of diastereoisomeric iodides **177a** and **177b**. A common intermediate was indicated in the iodocyclisations, as neither the starting hydroperoxides nor product iodides underwent isomerisation under reaction conditions. A free radical chain mechanism was proposed for these reactions and the propagation steps (illustrated for the *Z*-isomer) are shown in scheme 85.



Scheme 85

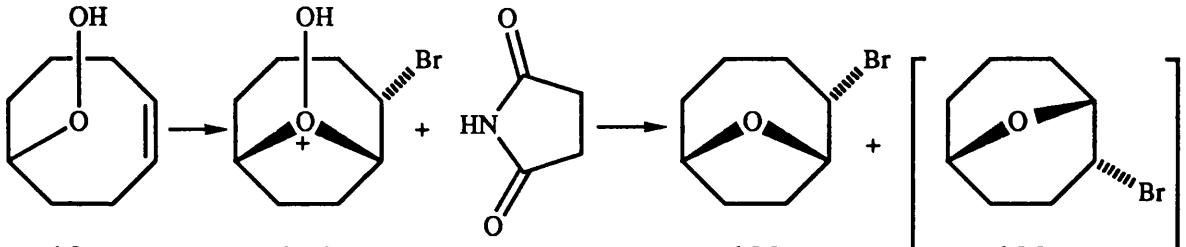
Mixtures of diastereoisomeric dioxolanes were also produced in the corresponding *N*-bromosuccinimide reactions. *E*-hydroperoxide **176a**, gave predominantly (*ca.* 75%) the *threo*-isomer and *Z*-hydroperoxide **176b**, gave mainly (*ca.* 80%) the *erythro*-isomer, thereby indicating that stereospecific *trans* addition *via* the bromonium ion here competes with the free radical chain process, presumably because of a smaller rate constant for reaction of alkyl radical **(180)** with NBS compared with that for reaction with NIS (Scheme 85, step b). Stereospecific cyclisation was achieved by treating hydroperoxides **176a** and **176b** with molecular iodine or bromine and pyridine in dichloromethane (Scheme 86).



176a **177a, X=I** **178a, X=Br**

Scheme 86

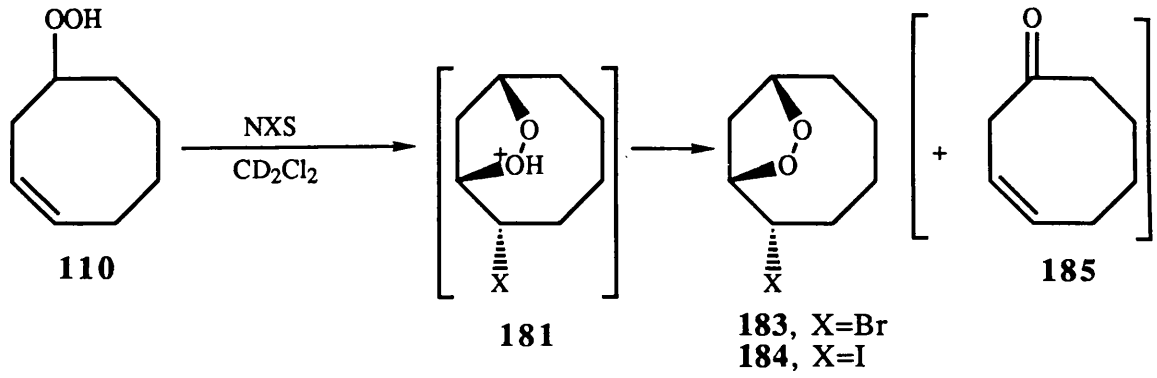
Treatment of cyclo-oct-4-en-1-yl hydroperoxide **109**, with N-bromosuccinimide resulted in the formation of bicyclic ether (**182a**) via *gem*-peroxonium ion (**181**). Some (**182b**) was also formed as a result of electrophilic attack at the other unsaturated carbon in **109** (Scheme 87)[96]. No peroxidic material was isolated in this reaction, in contrast the reaction of **109** with mercury(II) trifluoroacetate gives both bicyclic ethers and peroxides (see chapter 2, scheme 57).



109 **181** **182a** **182b**

Scheme 87

Bloodworth and Spencer[66] treated cyclo-oct-3-en-1-yl hydroperoxide **110**, with *N*-bromosuccinimide, *N*-iodosuccinimide and molecular iodine. The reactions with NBS and with NIS in CD_2Cl_2 afforded single isomers of 2-substituted[5.2.1]-peroxides (**183**) and (**184**), but cyclo-oct-3-en-1-one (**185**) was also obtained (Scheme 88).

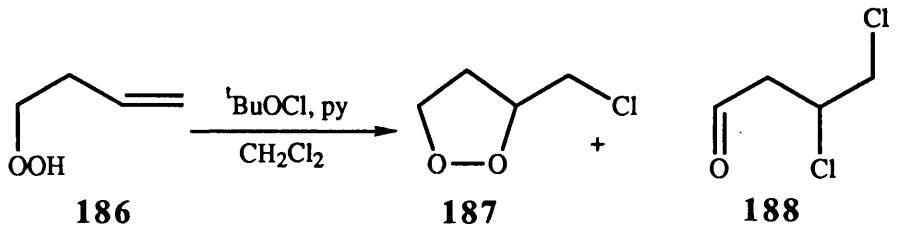


110 **181** **183**, X=Br **184**, X=I **185**

Scheme 88

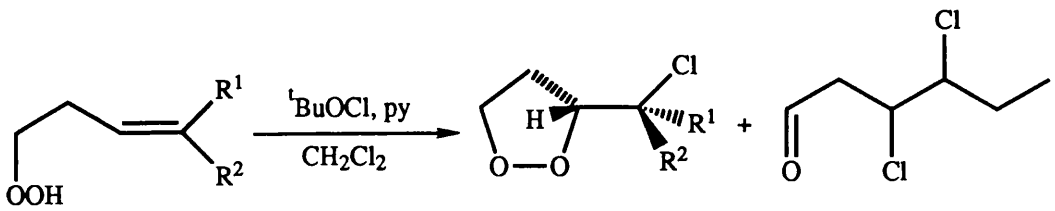
Compound **185** was thought to arise by a radical mechanism and by changing to a more polar solvent CD_3OD, ketone formation was completely (NBS) or largely (NIS) suppressed and high yields of cyclic peroxides **183** and **184** were obtained. The yield of iodide **184**, was also markedly improved by treating hydroperoxide **110** with molecular iodine rather than NIS in CD_2Cl_2. The absence of ketone **185** formation was consistent with this reaction proceeding by a wholly polar mechanism.

Bloodworth and Tallant[98] treated alkyl-3-en-1-yl hydroperoxides with t-butyl hypochlorite (^tBuOCl) to give chloroalkyl-1,2-dioxolanes (Schemes 89 and 90).



186 **187** **188**

Scheme 89



189 R^1=Et, R^2=H
190 R^1=H, R^2=Et

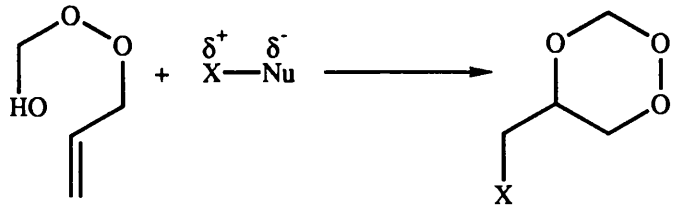
191 R^1=Et, R^2=H
192 R^1=H, R^2=Et

193

Scheme 90

But-3-en-1-yl hydroperoxide (**186**), afforded the expected 3-chloromethyl-1,2-dioxolane (**187**), together with one major by-product (**188**). Reactions with *Z*- and *E*-hex-3-en-1-yl hydroperoxides provided information about the stereoselectivity of cycloperoxychlorination. The *Z*-isomer (**189**) and the *E*-isomer (**190**) gave *threo*-and *erythro*-3-(1-chloropropyl)-1,2-dioxolanes (**191**) and (**192**), with a single diastereoisomer of 3,4-dichlorohexanal (**193**). The stereoselectivity observed with the hydroperoxides **189** and **190**, suggested that cycloperoxychlorination proceeded predominantly by a polar mechanism.

As far as we are aware there are no examples of the application of halogenocyclisation to the preparation of 1,2,4-trioxanes. Accordingly, we decided to apply the technique to unsaturated hemiperoxyacetals **73**, as a second variant of our electrophile-mediated cyclisation route to 1,2,4-trioxanes (Scheme 91).



73

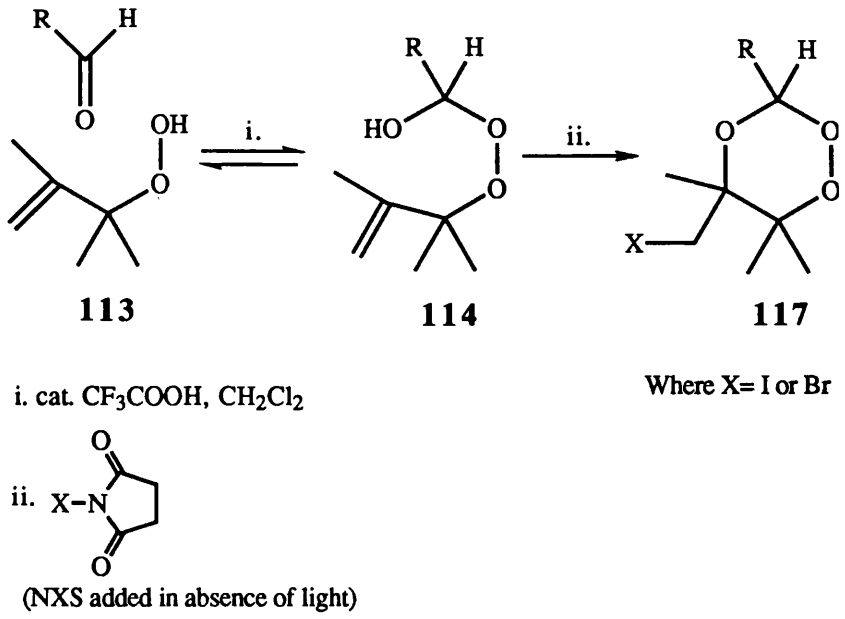
The -OH group acts as the internal nucleophile. (X=halogen)

Scheme 91

4.2 Results and Discussion

4.2.1 A halogenocyclisation route to 1,2,4-trioxanes

Scheme 92 illustrates the new halogenocyclisation route to 1,2,4-trioxanes[99].



Scheme 92

The reaction was carried out in a flask protected from light by aluminium foil. The crude hydroperoxide **113**[68] and aldehyde in dichloromethane solvent were stirred with trifluoroacetic acid catalyst for 10 minutes before treating with freshly recrystallised N-halogenosuccinimide (NXS). After 90-120 minutes, the reaction mixture was washed with 20% sodium thiosulfate (NIS reactions) or water (NBS reactions). The organic layer was dried and the solvent removed under reduced pressure to give crude 1,2,4-trioxanes **117**, which were isolated as a pair of diastereoisomers by simple column chromatography (SiO_2, CH_2Cl_2). The iodides obtained by this method were a pale pink colour, suggesting the presence of iodine. They were isolated as analytically pure, colourless liquids after treatment with silver acetate in dichloromethane.

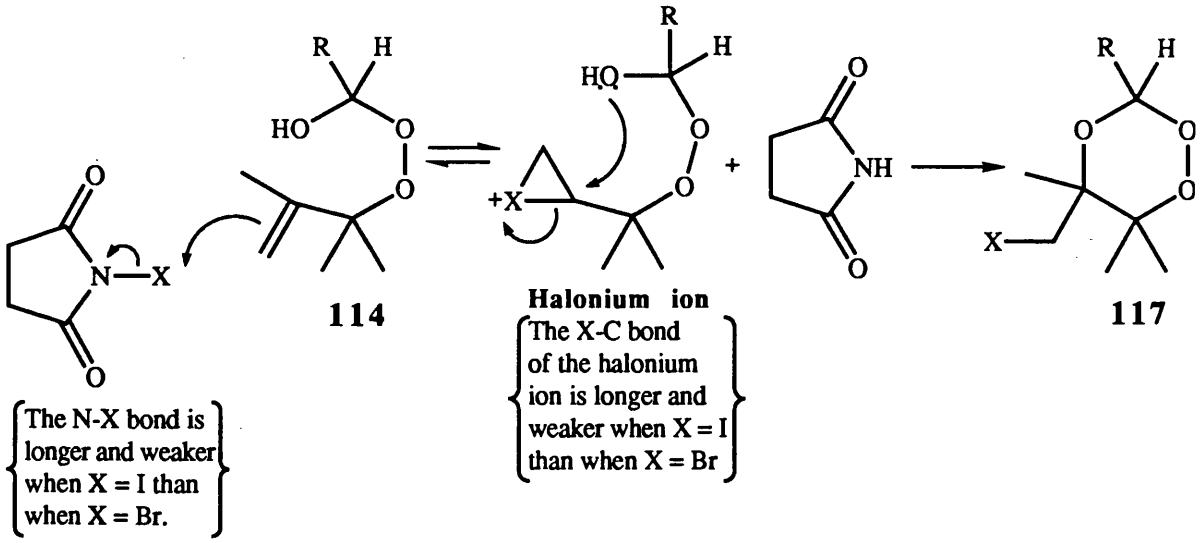
The new halogeno-1,2,4-trioxanes **117**, were obtained in yields ranging from 15-65% (Table 10).

Table 10. Percentage yields of 5-halogeno-1,2,4-trioxanes

Compound	R group	X group	Yield (%)
117a	Me	Br	30
117b	Et	Br	35
117c	Pr	Br	25
117d	^{t}Bu	Br	15
117e	Me	I	65
117f	Et	I	62
117g	C_6H_{13}	I	32
117h	^{i}Pr	I	25
117i	^{t}Bu	I	20

In general the NIS reactions gave higher 1,2,4-trioxane yields than the corresponding NBS reactions, for example compound **117a** (R=Me, X=Br), was obtained in just 30% yield, whereas compound **117e** (R=Me, X=I) was isolated in 65% yield. This reflects a greater reactivity of NIS compared to NBS attributed to weaker N-halogen and C-halogen bonds (Fig 13).

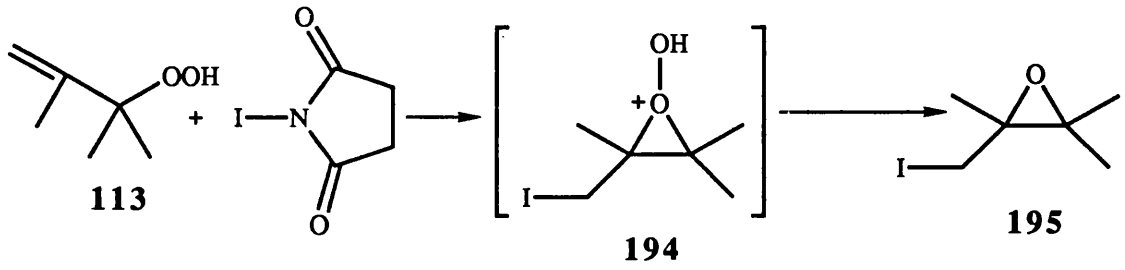
Figure 13



The halogen-containing compounds **117**, rapidly oxidised acidified iron(II)

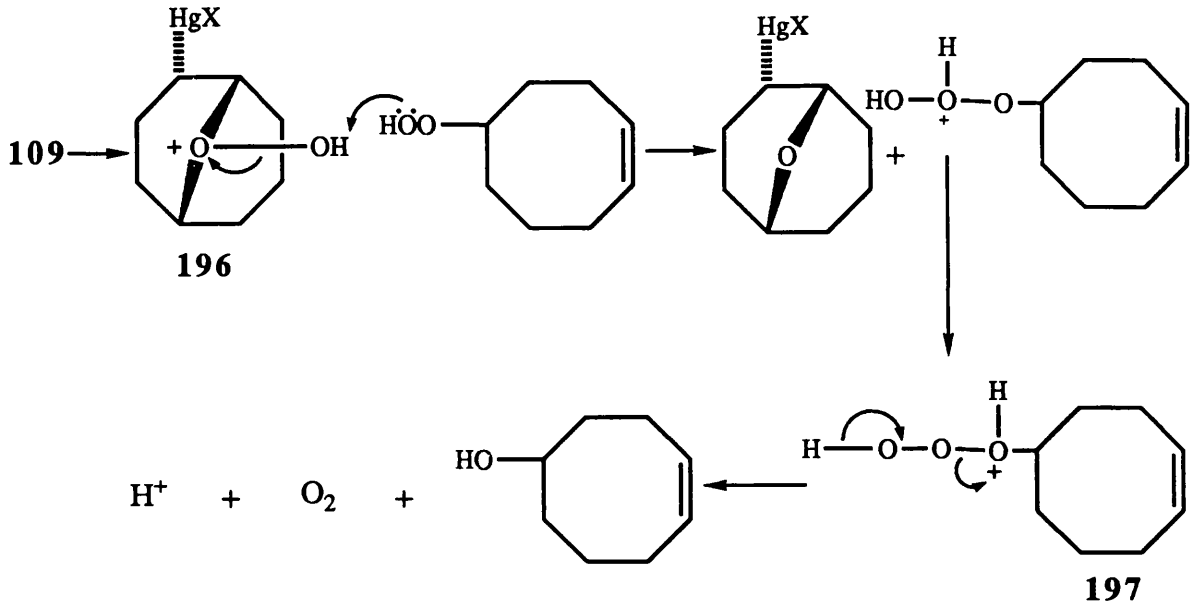
thiocyanate as expected for cyclic peroxides and their structures were confirmed by consistent elemental analysis and ^{1}H and ^{13}C nmr spectra. In addition compounds **117a** and **117f**, were independently synthesised by halogenodemercuriation of the corresponding 5-bromomercuriomethyl-1,2,4-trioxanes **115** (see chapter 2, section 2.2.2).

The halogenocyclisation route to 1,2,4-trioxanes proved less versatile than that based on cyclooxymercuriation. The NIS and NBS reactions could not be extended to aromatic aldehydes or to ketones. With these substrates, where there is much less hemiperoxyacetal present at equilibrium (see chapters 2 and 3) and therefore competing reactions predominate. The NIS reactions with acetone, cyclohexanone and adamantanone all gave the same major product, which was isolated and identified by nmr and mass spectrometry as 1-iodomethyl-1,2,2-trimethyloxirane (**195**). Epoxide **195**, was also formed when the allylic hydroperoxide **113** alone was treated with NIS (Scheme 93) and although the yield was low (26% after chromatography), no other products were detected.



Scheme 93

The reaction was envisaged to proceed through the protonated perepoxide (**194**), which must transfer its electrophilic -OH group to a nucleophile in the process of forming epoxide **195**. Previous evidence shows that related *gem*-dialkylperoxonium ions such as (**196**) derived from cyclooct-4-enyl hydroperoxide **109**, transfer their electrophilic -OH groups to the precursor hydroperoxide to form protonated hydrotrioxides (**197**) which then undergo deoxygenation to give the corresponding alcohol (Scheme 94)[100].



Scheme 94

However, we were unable to demonstrate a parallel reaction between protonated perepoxide **194** and hydroperoxide **113**. Thus 2,3-dimethylbut-3-en-2-ol which would result from such a reaction, was not detected and an authentic sample of this alcohol reacted with NIS to give a mixture of unidentified products rather than epoxide **195**.

4.2.2 NMR Studies and Stereochemistry

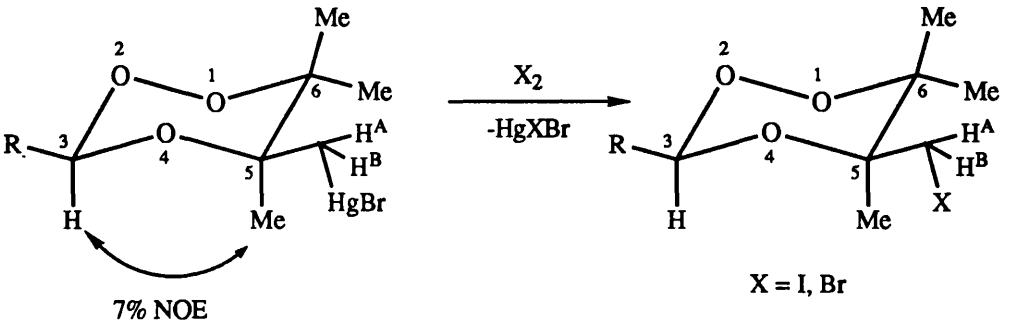
The halogenocyclisations had much in common with the earlier cyclooxymercuriations (chapter 2). The stereoselectivities were comparable and the key nmr features of the 1,2,4-trioxanes were very similar (see nmr spectra at the end of this chapter).

The ^1H nmr spectra for the predominant isomer showed the characteristic C-3 proton signal of appropriate multiplicity at δ 4.9-5.5 (δ 5.0-5.5 for the corresponding organomercurials). As in the corresponding organomercurial compounds **115**, the downfield doublet of the AB pattern for the C-5 methylene group showed long range coupling to the *gem* methyl group and the downfield doublet of the minor isomer was considerably deshielded (δ 4.0-4.8). These features suggest that there is restricted rotation about the XCH_2-ring bond in both *cis* and *trans* isomers (as in the organomercury compounds **115**, where this was supported by NOE, see chapter 2). The similarity of the

halogeno- and bromomercurio-1,2,4-trioxanes (Fig 14), indicates that the restricted rotation is a steric rather than an electronic effect. The ring-carbon signals in the ^{13}C nmr spectra appeared at δ 95-104 (C-3), δ 80-81 (C-6) and δ 75-76 (C-5), (virtually the same shifts as in the related 5-bromomercuriomethyl-1,2,4-trioxanes, **115**). The distinctive feature of the 5-halogenomethyl compounds **117**, was the CH_2X signal which appeared at δ 14-15 (X=I) and at δ 39-40 (X=Br).

Each of the halogen-containing compounds **117**, consisted of a pair of diastereoisomers as expected from the presence of chiral centres at C-3 and C-5. The reactions were stereoselective with isomer ratios, as determined by nmr spectroscopy, ranging from 4:1 to 13:1. The major isomer had the alkyl group at C-3 and the CH_2X group at C-5 *cis* to one another so that they were both in the equatorial position. This was shown by the identity of the major isomer with that from halogenodemercuriation (Fig 14), where the stereochemistry of the precursor mercurial **115**, was established by NOE experiments (see chapter 2, section 2.2.2).

Figure 14



115 **117**

4.3 Conclusion

The halogenocyclisation route to 1,2,4-trioxanes proved to be less general than the intramolecular oxymercuriation method discussed in chapters 2 and 3. Moderate yields for compounds **117**, were obtained where aliphatic aldehydes were used, but the NBS and NIS reactions could not be extended to include aromatic aldehydes or ketones. The NIS reactions with ketone substrates, all gave the same major product which was identified as

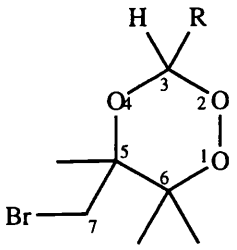
epoxide **195**.

The stereoselectivities and key nmr features for the halogen-containing compounds **117**, were very similar to the corresponding bromomercurial compounds **115**. Restricted rotation was suggested by the appearance of long range coupling between the downfield doublet of the AB pattern (CH_2X) and the *gem* methyl group attached to C5. As a similar pattern was observed in the earlier organomercurial compounds **115**, we were able to conclude that this restriction to rotation was steric in origin rather than electronic.

The major diastereoisomer of **117**, was thought to have a *cis* configuration by analogy with the earlier organomercurials **115** and further evidence for this was obtained by independent synthesis of halogeno compounds **117** by halogenodemercuriation of the parent organomercurials **115**.

4.4 Experimental

3-(Alkyl)-5-(bromomethyl)-5,6,6-trimethyl-1,2,4-trioxanes



117a (R=Me)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), dissolved in dichloromethane (20ml) was treated with acetaldehyde (10mmol; 0.44g) and catalytic trifluoroacetic acid (2 drops). The reaction vessel was covered with aluminium foil and the mixture was stirred (10 minutes). N-Bromosuccinimide (5mmol; 0.88g) was added in one portion and the mixture was stirred at room temperature (1.5-2hrs). The reaction mixture was washed with water (10ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.88), gave the pure product (0.36g, 30%).

^{1}H nmr (400MHz) Major isomer : δ 5.45 (q, J=5.27 Hz, 1H, **CH**CH_3), 3.40 (bd, J=10.68 Hz, 1H, **CH^{a}H^b**Br, shows long range coupling to C5-Me), 3.36 (d, J=10.68 Hz, 1H, CH^a**H^b**Br), 1.47 (s, 3H), 1.45 (s, 3H), 1.23 (d, J=5.27 Hz, 3H, CH**CH$_3$**), 1.13 (s, 3H) ppm. Minor isomer : δ 5.42 (q, J=5.19 Hz, 1H, **CH**CH_3), 4.21 (bd, J=10.68 Hz, 1H, **CH^{a}H^b**Br, shows long range coupling to C5-Me), 3.41 (d, J=10.68 Hz, 1H, CH^a**H^b**Br), 1.49 (s, 3H), 1.31 (d, J=5.19 Hz, 3H, CH**CH$_3$**), 1.24 (s, 3H), 1.01 (s, 3H) ppm.
^{13}C nmr (100MHz) Major isomer : δ 96.07 (C-3), 81.32 (C-6), 75.98 (C-5), 38.55 (**CH_2**Br), 21.45, 21.11, 17.83, 17.64 ppm. Minor isomer : δ 96.07 (C-3, overlaps with major isomer), 80.36 (C-6), 76.10 (C-5), 39.40 (**CH_2**Br), 21.98, 20.51, 18.03, 17.54 ppm.
Major: Minor isomer ratio 5: 1

An independent synthesis of this compound was carried out by halogenodemercuriation of 5-(bromomercuriomethyl)-3,5,6,6-tetramethyl-1,2,4-trioxane as described in chapter 2. The nmr data from the independent synthesis were as follows.
^{1}H nmr (400 MHz) Major isomer : δ 5.52 (q, J=5.21 Hz, 1H, **CH**Me), 3.41 (bd, J=10.67

Hz, 1H, CH^aH^bBr, shows long range coupling to C5-Me), 3.28 (d, J=10.67 Hz, 1H, CH^aH^bBr), 1.51 (s, 3H), 1.49 (s, 3H), 1.24 (d, J=5.21 Hz, 3H), 1.09 (s, 3H) ppm. Minor isomer : δ 5.40 (q, J=5.17 Hz, 1H), 4.18 (bd, J=11.02 Hz, 1H, CH^aH^bBr), 3.39 (d, J=11.02 Hz, 1H, CH^aH^bBr), 1.55 (s, 3H), 1.26 (d, J=5.17 Hz, 3H), 1.21 (s, 3H), 1.04 (s, 3H) ppm.

^{13}C nmr (100 MHz) Major isomer : δ 96.04 (C-3), 81.1 (C-6) , 76.1 (C-5), 38.6 (CH_2Br), 21.5, 21.1, 17.9, 17.7 ppm. Minor isomer : δ 96.07, 81.10 (overlaps with major isomer), 76.12 (overlaps), 38.59, 22.40, 21.52, 17.99, 17.94 (overlaps) ppm.

Major: Minor isomer ratio 4.6: 1

Found: C, 40.76; H, 6.64; Br, 34.10% $C_8H_{15}BrO_3$ requires: C, 40.18; H, 6.32; Br, 34.42%

117b (R=Et)

Procedure as for formation of **117a**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5.60mmol; 0.65g), propanal (16.8mmol; 0.97g), trifluoroacetic acid (2 drops), N-Bromosuccinimide (5.60mmol; 0.99g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.86) gave the pure product (0.39g, 30%).

^{1}H nmr (400 MHz) Major isomer : δ 5.28 (t, J=5.18 Hz, 1H, $CHCH_2CH_3$), 3.39 (bd, J=10.64 Hz, 1H, CH^aH^bBr, shows long range coupling to C5-Me), 3.26 (d, J=10.64 Hz, 1H, CH^aH^bBr), 1.78-1.52 (m, 2H), 1.49 (s, 3H), 1.46 (s, 3H), 1.07 (s, 3H), 0.90 (t, J=7.57 Hz, 3H, CH_2CH_3) ppm. Minor isomer : δ 5.18 (t, J=5.21 Hz, 1H, $CHCH_2CH_3$), 4.26 (bd, J=10.64 Hz, 1H, CH^aH^bBr, shows long range coupling to C5-Me), 3.40 (d, J=10.64 Hz, 1H, CH^aH^bBr), 1.78-1.52 (m, 2H, overlaps with major isomer), 1.19 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.94 (t, J=7.30 Hz, 3H, CH_2CH_3) ppm

^{13}C nmr (100 MHz) Major isomer : δ 99.66 (C-3), 81.22 (C-6) , 75.84 (C-5), 38.54 (CH_2Br), 25.31, 21.51, 21.02, 17.60, 7.79 ppm. Minor isomer : δ 99.45, 81.58, 75.84 (overlaps with major isomer), 38.83, 25.28, 22.35, 21.56, 20.65, 8.72 ppm.

Major: Minor isomer ratio 7: 1

Found: C, 42.66; H, 6.58% $C_9H_{17}BrO_3$ requires: C, 42.70; H, 6.77%

117c (R=Pr)

Procedure as for formation of **117a**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), butanal (5mmol; 0.36g), trifluoroacetic acid (2 drops), N-Bromosuccinimide (5mmol; 0.89g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.85) gave the pure

product (0.33g, 25%).

^{1}H nmr (400MHz) Major isomer : δ 5.35 (t, J=5.16 Hz, 1H, C**H**$CH_2CH_2CH_3$), 3.39 (bd, J=10.62 Hz, 1H, C**H**^{a}H^{b}Br, shows long range coupling to C5-Me), 3.26 (d, J=10.62 Hz, 1H, CH^a**H**^{b}Br), 1.49 (s, 3H), 1.42-1.39 (m, 7H, $CH_2CH_2CH_3$), 1.32 (s, 3H), 0.88 (s, 3H) ppm. Minor isomer δ 5.10 (t, J=5.02 Hz, 1H, C**H**$CH_2CH_2CH_3$), 3.68 (bd, J=10.62 Hz, 1H, C**H**^{a}H^{b}Br, shows long range coupling to C5-Me), 3.37 (d, J=10.62 Hz, 1H, CH^a**H**^{b}Br), 1.53 (s, 3H), 1.42-1.39 (m, 7H, $CH_2CH_2CH_3$, overlaps with major isomer), 1.07 (s, 3H), 0.89 (s, 3H) ppm

^{13}C nmr (100MHz) Major isomer : δ 98.80 (C-3), 81.24 (C-6), 75.85 (C-5), 38.57 (C-Br), 27.95, 21.51, 21.05, 17.59, 16.96, 13.84 ppm. Minor isomer : δ 98.98, 81.59, 74.40, 35.83, 34.05, 24.41, 22.37, 20.55, 17.55, 13.94 ppm.

Major:Minor isomer ratio 6:1

Found: C, 44.89; H, 7.52% $C_{10}H_{19}BrO_3$ requires: C, 44.94; H, 7.12%

117d (R=^{t}Bu)

Procedure as for formation of **117a**.

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), 2,2-dimethylpropanal (5mmol; 0.43g), trifluoroacetic acid (2 drops), N-Bromosuccinimide (5mmol; 0.89g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.93) gave the pure product (0.21g, 15%).

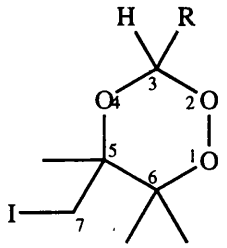
^{1}H nmr (400MHz) Major isomer : δ 4.97 (s, 1H, C**H**^{t}Bu), 3.41 (bd, J=11.98 Hz, 1H, C**H**^{a}H^{b}Br, shows long range coupling to C5-Me), 3.28 (d, J=11.98 Hz, 1H, CH^a**H**^{b}Br), 1.48 (s, 3H), 1.46 (s, 3H), 1.08 (s, 3H), 0.91 (s, 9H, C(CH_3)$_3$) ppm. Minor isomer δ 4.97 (s, 1H, C**H**^{t}Bu, overlaps with major isomer), 3.98 (bd, J=11.88 Hz, 1H, C**H**^{a}H^{b}Br, shows long range coupling to C5-Me), 3.38 (d, J=11.88 Hz, 1H, CH^a**H**^{b}Br), 1.34 (s, 3H), 1.21 (s, 3H), 0.94 (s, 3H), 0.92 (s, 9H, C(CH_3)$_3$) ppm

^{13}C nmr (100MHz) Major isomer : δ 103.39 (C-3), 81.19 (C-6), 75.71(C-5), 38.65 (C-Br), 34.70 (**C**(CH_3)$_3$), 25.12, 24.48 (3C, C(CH_3)$_3$), 21.12, 17.55 ppm. Minor isomer : δ 103.20 (C-3), 81.19 (C-6, overlaps with major isomer), 71.06 (C-5), 38.65 (C-Br, overlaps with major isomer), 36.01 (**C**(CH_3)$_3$), 28.64, 25.72, 24.60, 21.53 (3C, C(CH_3)$_3$) ppm.

Major:Minor isomer ratio 11:1

Found: C, 47.09; H, 7.54% $C_{11}H_{21}BrO_3$ requires: C, 46.98; H, 7.47%

3-(Alkyl)-5-(iodomethyl)-5,6,6-trimethyl-1,2,4-trioxanes



117e (R=Me)

2,3-Dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g) dissolved in dichloromethane (20ml), was treated with acetaldehyde (10mmol; 0.44g) and trifluoroacetic acid catalyst (2 drops). The reaction vessel was covered with aluminium foil and the mixture was stirred (10 minutes). N-Iodosuccinimide (5mmol; 1.13g) was added in one portion and the mixture was stirred at room temperature (1.5-2hrs). The reaction mixture was washed with 20% sodium thiosulphate (10ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.95), gave the pure product (0.93g, 65%).

^{1}H nmr (400MHz) Major isomer : δ 5.38 (q, J=5.38 Hz, 1H, **CH**CH_3), 3.30 (bd, J=10.34 Hz, 1H, C**H**^{a}H^{b}I, shows long range coupling to C5-Me), 3.12 (d, J=10.34 Hz, 1H, CH^a**H**^{b}I), 1.50 (s, 3H), 1.49 (s, 3H), 1.22 (d, J=5.38 Hz, 3H, CH**CH$_3$**), 1.06 (s, 3H) ppm. Minor isomer : δ 5.28 (q, J=5.28 Hz, 1H, **CH**CH_3), 4.11 (bd, J=10.34 Hz, 1H), 3.21 (d, J=10.34 Hz, 1H), 1.56 (s, 3H), 1.25 (d, J=5.28 Hz, 3H, CH**CH$_3$**), 1.16 (s, 3H), 1.16 (s, 3H) ppm.
^{13}C nmr (100MHz) Major isomer : δ 95.26 (C-3), 80.27 (C-6), 75.03 (C-5), 21.30 (2C), 20.56, 17.87, 14.19 (**C**-I) ppm. Minor isomer : δ 95.76 (C-3), 80.27 (C-6, overlaps with major isomer), 75.03 (C-5, overlaps with major isomer), 22.69, 22.22, 20.97, 17.77, 13.19 (**C**-I) ppm.
Major:Minor isomer ratio 8:1
Found: C, 33.53; H, 5.22% $C_8H_{15}IO_3$ requires: C, 33.58; H, 5.28%

117f (R=Et)
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10.67mmol; 1.24g), propanal (21mmol; 1.24g), trifluoroacetic acid (4 drops), N-iodosuccinimide (10.67mmol; 2.42g).

Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.79) gave the pure product (1.98g, 62%).

^{1}H nmr (400MHz) Major isomer : δ 5.27 (t, J=5.11 Hz, 1H, C**H**Et), 3.31 (bd, J=10.36 Hz, 1H, C**H**^{a}H^{b}I, shows long range coupling to C5-Me), 3.10 (d, J=10.36 Hz, 1H, CH^a**H**^{b}I), 1.57-1.52 (m, 2H). 1.49 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.84 (t, J=7.56 Hz, 3H, $CH_2C\mathbf{H_3}$) ppm. Minor isomer δ 5.10 (t, J=5.11 Hz, 1H, C**H**Et), 4.08 (bd, J=10.37 Hz, 1H), 3.27 (d, J=10.37 Hz, 1H), 1.57-1.52 (m, 2H, overlaps with major isomer), 1.30 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H), 0.91-0.89 (m, 3H, $CH_2C\mathbf{H_3}$) ppm.
^{13}C nmr (100MHz) : Major isomer δ 99.88 (C-3), 80.43 (C-6), 74.73 (C-5), 25.18, 21.29 (2C), 20.47, 14.33 (**C**-I), 7.82 ppm. Minor isomer δ 99.16 (C-3), 80.44 (C-6), 74.73 (C-5, overlaps with major isomer), 28.19, 22.65, 22.09, 20.80, 13.40 (**C**-I), 7.99 ppm.
Major:Minor isomer ratio 4.5:1
Found: C, 36.18; H, 5.82% $C_9H_{17}IO_3$ requires: C, 36.02; H, 5.71%

An independent synthesis of this compound was carried out by halogenodemercuriation of 5-(bromomercuriomethyl)-3-ethyl-5,6,6-trimethyl-1,2,4-trioxane as described in chapter 2. The nmr data from the independent synthesis is as follows.
^{1}H nmr (400 MHz) Major isomer : δ 5.27 (t, J=5.11 Hz, 1H, C**H**Et), 3.31 (bd, J=10.33 Hz, 1H, C**H**^{a}H^{b}I, shows long range coupling to C5-Me), 3.12 (d, J=10.33 Hz, 1H, CH^a**H**^{b}I), 1.49 (m, 5H), 1.07 (s, 6H), 0.92 (t, J=7.58 Hz, 3H, $CH_2C\mathbf{H_3}$) ppm. Minor isomer : δ 5.10 (t, J=5.10 Hz, 1H), 4.06 (bd, J=10.55 Hz, 1H, C**H**^{a}H^{b}I, shoes long range coupling to C5-Me), 3.23 (d, J=10.55 Hz, 1H, CH^a**H**^{b}I), 1.49 (m, 5H overlaps with major isomer), 1.03 (s, 3H), 1.02 (s, 3H), 0.98 (t, J=7.58 Hz, 3H) ppm.
^{13}C nmr (100 MHz) Major isomer : δ 99.99 (C-3), 80.53 (C-6), 74.81 (C-5), 25.24, 21.34(2C), 20.53, 14.38 (**C**-I), 7.86 ppm. Minor isomer : δ 99.55, 80.44, 74.81 (overlaps), 28.19, 22.77, 22.10, 20.80, 13.65 (**C**-I), 7.98 ppm.

117g (R=hexyl)
Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), heptanal (20mmol; 2.28g), trifluoroacetic acid (4 drops), N-iodosuccinimide (10mmol; 2.26g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.77) gave the pure product (1.14g, 32%).

^{1}H nmr (400MHz) Major isomer : δ 5.31 (t, J=5.98 Hz, 1H, C**H**hexyl), 3.31 (bd, J=11.99 Hz, 1H, C**H**^{a}H^{b}I, shows long range coupling to C5-Me), 3.12 (d, J=11.99 Hz,

1H, CH^aH^bI), 1.49 (s, 3H), 1.40-1.25 (m, 11H), 1.07 (s, 3H), 0.84 (t, J=7.06 Hz, 3H, terminal CH_3 group of hexyl chain) ppm. Minor isomer : δ 5.18 (t, J=5.99Hz, 1H, CHhexyl), 4.11 (bd, J=11.99 Hz, 1H, CH^aH^bI, shows long range coupling to C5-Me), 3.30 (d, J=11.99 Hz, 1H, CH^aH^bI), 1.38 (s, 3H), 1.40-1.25 (m, 11H, overlaps with major isomer), 1.10 (s, 3H), 0.84 (t, J=7.06 Hz, 3H, terminal CH_3 group of hexyl chain, overlaps with major isomer) ppm.

^{13}C nmr (100MHz) Major isomer : δ 99.33 (C-3), 80.56 (C-6), 74.87 (C-5), 31.88, 31.65, 28.99, 23.57, 22.59, 22.53, 21.39, 20.53, 19.35, 14.06 (C-I) ppm. Minor isomer : δ 98.80 (C-3), 80.52 (C-6), 74.87 (C-5, overlaps with major isomer), 32.14, 31.82, 30.97, 29.18, 29.07, 23.65, 22.76, 22.33, 19.01, 13.89 (C-I) ppm.

Major:Minor isomer ratio 3.8:1

Found: C, 43.98; H, 6.13% $C_{13}H_{23}IO_3$ requires: C, 44.08; H, 6.54%

117h (R=^{i}Pr)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), 2-methylpropanal (5mmol; 0.43g), trifluoroacetic acid (2 drops), N-iodosuccinimide (5mmol; 1.13g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.88) gave the pure product (0.39g, 25%).

^1H nmr (400MHz) Major isomer : δ 5.03 (d, J=5.41 Hz, 1H, CH^iPr)), 3.31(bd, J=10.52 Hz, 1H, CH^aH^bI, shows long range coupling to C5-Me), 3.11 (d, J=10.52 Hz, 1H, CH^aH^bI), 1.58-1.57 (m, 1H, $CH(CH_3)_2$), 1.47 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.91 (d, J=4.97 Hz, 3H), 0.85 (d, J=4.97 Hz, 3H) ppm. Minor isomer : δ 4.92 (d, J=5.40Hz, 1H, CH^iPr), 4.80 (bd, J=10.62 Hz, 1H, CH^aH^bI, shows long range coupling to C5-Me), 3.28 (d, J=10.62 Hz, 1H, CH^aH^bI), 1.58-1.57 (m, 1H, $CH(CH_3)_2$, overlaps with major isomer), 1.45 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 0.98-0.95 (m, 6H, $CH(CH_3)_2$) ppm.

^{13}C nmr (100MHz) Major isomer : δ 102.24 (C-3), 80.46 (C-6), 74.60 (C-5), 30.85 ($CH(CH_3)_2$), 21.37, 21.31, 20.42, 16.88, 16.59, 14.53 (C-I) ppm. Minor isomer : δ 101.60 (C-3), 80.46 (C-6, overlaps with major isomer), 71.64 (C-5), 31.07 ($CH(CH_3)_2$), 22.72, 22.56, 21.07, 17.01, 16.60, 13.16 (C-I) ppm.

Major:Minor isomer ratio 4:1

Found: C, 38.56; H, 6.25% $C_{10}H_{19}IO_3$ requires: C, 38.23; H, 6.10%

117i (R=^{t}Bu)

Starting materials : 2,3-dimethylbut-1-en-3-yl hydroperoxide (10mmol; 1.16g), 2,2-dimethylpropanal (10mmol; 0.86g), trifluoroacetic acid (4 drops), N-iodosuccinimide (10mmol; 2.26g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.93)

gave the pure product (0.64g, 20%).

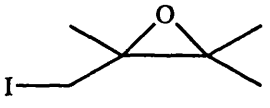
^{1}H nmr (400MHz) Major isomer : δ 4.93 (s, 1H, C**H**^{t}Bu), 3.33 (bd, J=10.17 Hz, 1H, CH^{a}H^{b}I, shows long range coupling to C5-Me), 3.11 (d, J=10.17 Hz, 1H, CH^a**H**^{b}I), 1.47 (s, 3H), 1.45 (s, 3H), 1.05 (s, 3H), 0.91 (s, 9H, C(C**H$_3$**)$_3$) ppm. Minor isomer δ 4.82 (s, 1H, C**H**^{t}Bu, overlaps with major isomer), 3.98 (bd, J=11.99 Hz, 1H, CH^{a}H^{b}I, shows long range coupling to C5-Me), 3.29 (d, J=11.99 Hz, 1H, CH^a**H**^{b}I), 1.53 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H, C(C**H$_3$**)$_3$) ppm

^{13}C nmr (100MHz) Major isomer : δ 103.60 (C-3), 80.38 (C-6), 74.58 (C-5), 38.68 (**C**(CH$_3$)$_3$), 24.45 (3C, C(**C**H$_3$)$_3$), 21.42, 21.29, 20.29, 14.53 (**C**-I) ppm. Minor isomer : δ 102.84 (C-3), 80.40 (C-6), 72.77 (C-5), 34.68 (**C**(CH$_3$)$_3$, overlaps with major isomer), 24.90 (3C, C(**C**H$_3$)$_3$), 24.55, 22.34, 21.08, 12.98 (**C**-I) ppm.

Major:Minor isomer ratio 12.7:1

Found: C, 40.63; H, 6.13% $C_{11}H_{21}IO_3$ requires: C, 40.26; H, 6.45%

Formation of 1-iodomethyl-1,2,2-trimethyloxirane (195) by reaction of 2,3-dimethylbut-1-en-3-yl hydroperoxide with N-iodosuccinimide



2,3-Dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), was dissolved in dichloromethane (20ml). N-Iodosuccinimide (5mmol; 1.13g) was added in one portion and the mixture was stirred at room temperature (1.5-2hrs). The reaction mixture was washed with 20% sodium thiosulfate (10ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.78), was used to isolate the major product (0.30g, 26%).

^{1}H nmr (400MHz) : δ 3.34 (d, J=10.19 Hz, 1H, CH^{a}H^{b}I), 3.07 (d, J=10.19 Hz, 1H, CH^a**H**^{b}I), 1.50 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H) ppm.

^{13}C nmr (100MHz) : δ 64.79 (epoxide carbon), 63.39 (epoxide carbon), 21.12, 20.37, 17.91, 10.59 (**C**-I) ppm.

FAB mass spectrum m / z calculated for $C_6H_{12}IO^+$ (MH^+): 227

Reaction of 2,3-dimethylbut-1-en-3-yl hydroperoxide and adamantanone and N-Iodosuccinimide

2,3-Dimethylbut-1-en-3-yl hydroperoxide (5mmol; 0.58g), was dissolved in dichloromethane (20ml). Adamantanone (5mmol; 0.75g), was added with stirring at room temperature followed by a catalytic amount of trifluoroacetic acid (2 drops). The reaction vessel was covered with aluminium foil and the mixture was stirred (10 minutes). N-Iodosuccinimide (5mmol; 1.13g) was added in one portion and the mixture was stirred at room temperature (1.5-2hrs). The reaction mixture was washed with 20% sodium thiosulfate (10ml). The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3x10ml). The combined organic extracts were dried ($MgSO_4$). Removal of the solvent was carried out under reduced pressure. Simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.78), was used to isolate the major product (0.31g).

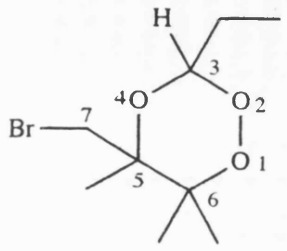
^{1}H nmr (400MHz) : δ 3.30 (d, J=9.96 Hz, 1H, CH^aH^bI), 3.03 (d, J=9.96 Hz, 1H, CH^aH^bI), 1.46 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H) ppm.
^{13}C nmr (100MHz) : δ 64.65 (epoxide carbon), 63.24 (epoxide carbon), 21.04, 20.28, 17.82, 10.56 (**C**-I) ppm.

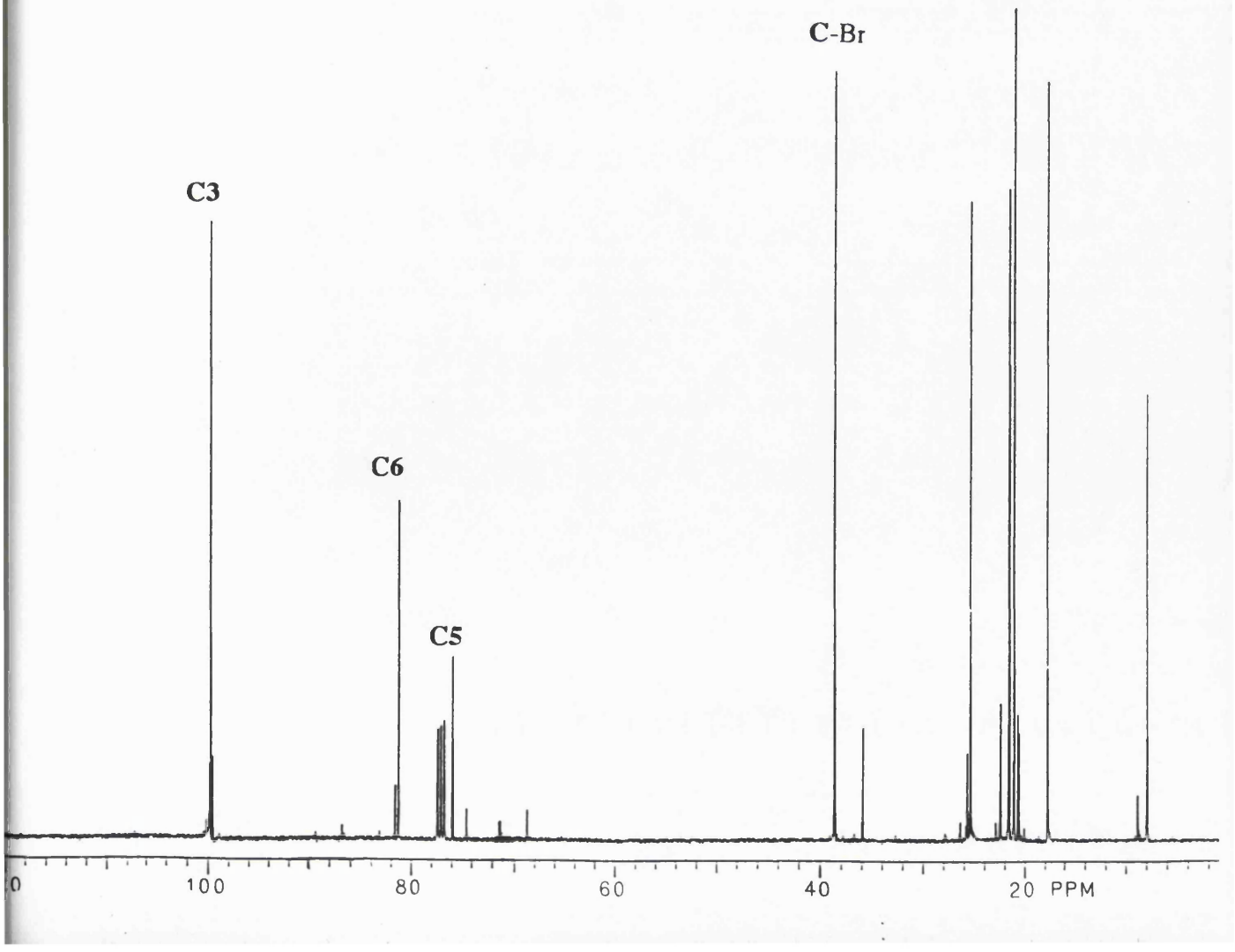
This reaction was also carried out with cyclohexanone and acetone in place of adamantanone. A similar pattern was observed in the nmr spectra.

See p219

4.5 NMR Spectra

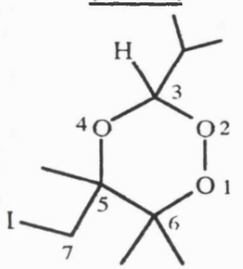
4.5.1 Nmr spectra of 3-ethyl-5-(bromomethyl)-5,6,6-trimethyl-1,2,4-trioxane (**117b**)

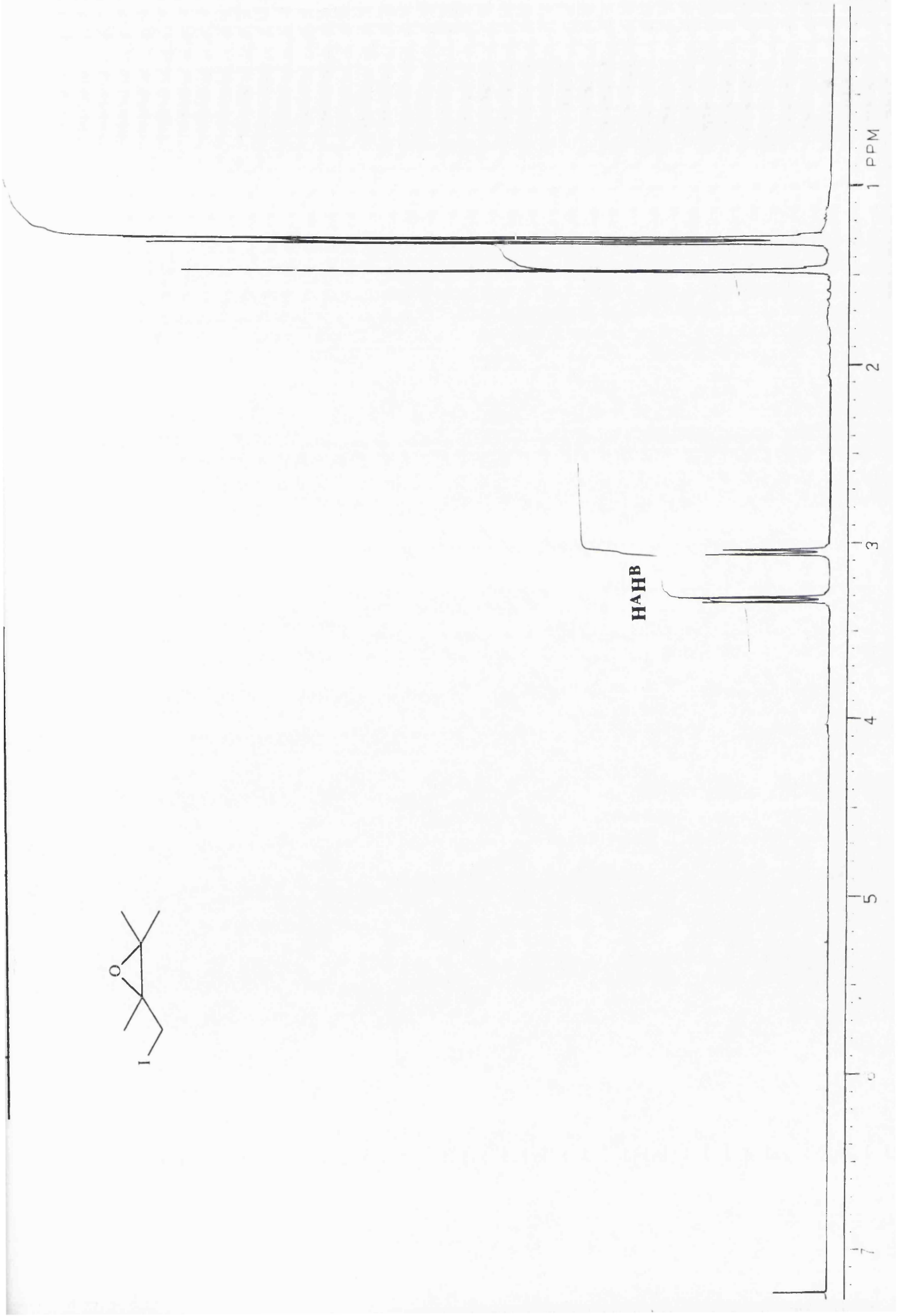




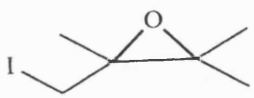
4.5.2 ^{13}C nmr spectrum of 3-(2-methylethyl)-5-(iodomethyl)-5,6,6-trimethyl-1,2,4-trioxane

(117h)




1 PPM
2
3
4
5
6
7
H^AH^B
O
I

4.5.4 ^{13}C nmr spectrum of 1-iodomethyl-1,2,2-trimethyloxirane (**195**)

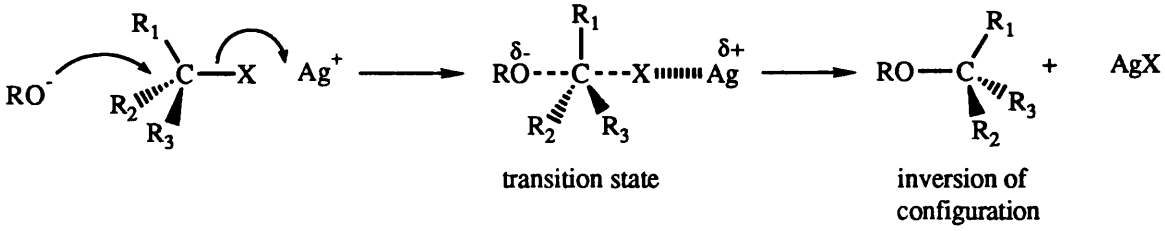


A SILVER-SALT-ASSISTED CYCLISATION ROUTE TO 1,2,4-TRIOXANES

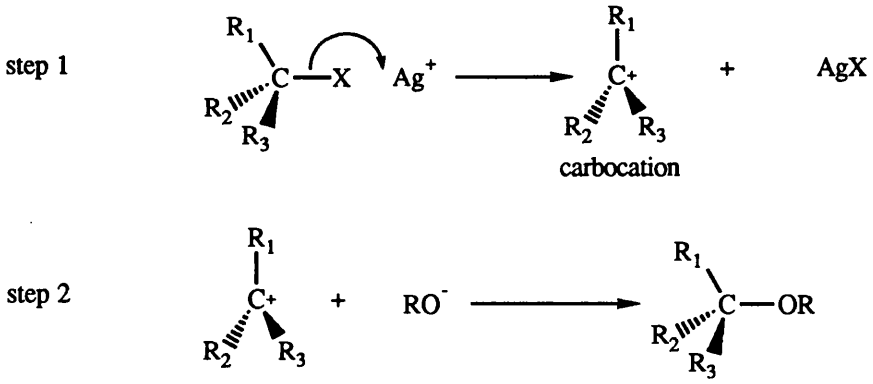
5.1 Introduction

Silver-salt-assisted ether formation is a well established technique. The reaction can occur by either a S_N2 or a S_N1 mechanism, depending on the reaction conditions (Scheme 95).

S_N2



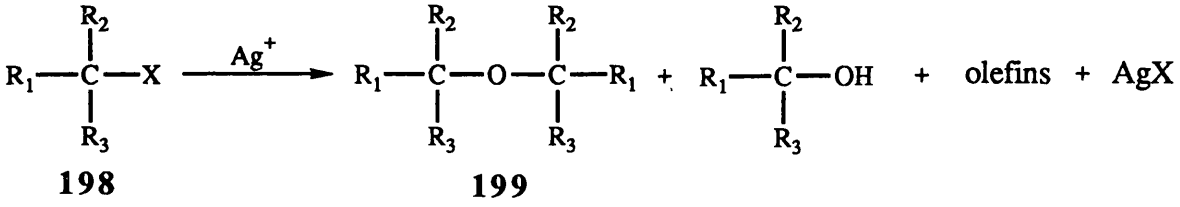
S_N1



X = halogen
RO⁻ = an oxy-nucleophile

Scheme 95

Masada and Sakajiri[101] prepared some di-*t*-alkyl ethers (**199**) in high yields (63-73%), by reaction of *t*-butyl halides (**198**) with silver carbonate or silver oxide (Scheme 96).

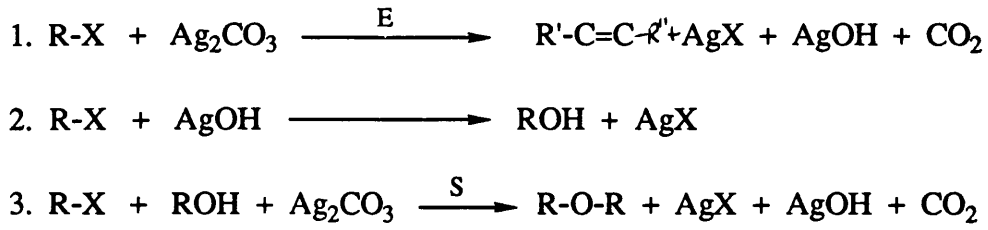


198 199

X=halogen

Scheme 96

The yields decreased as the alkyl groups became bulkier. The following pathways were proposed for the mechanism (Scheme 97).

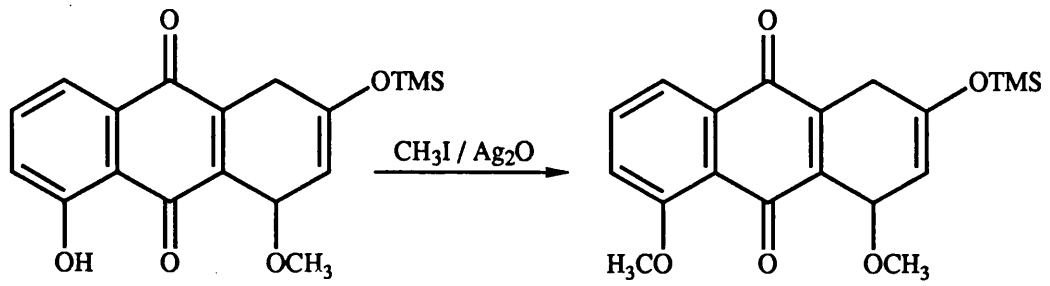


X=halogen

Scheme 97

The reaction was carried out in a non-polar solvent and ether formation occurred by bimolecular nucleophilic substitution (S_N2).

Manning *el al* carried out a silver oxide/ methyl iodide methylation of a hydroxyl group in the anthroquinone **(200)** (Scheme 98)[102].



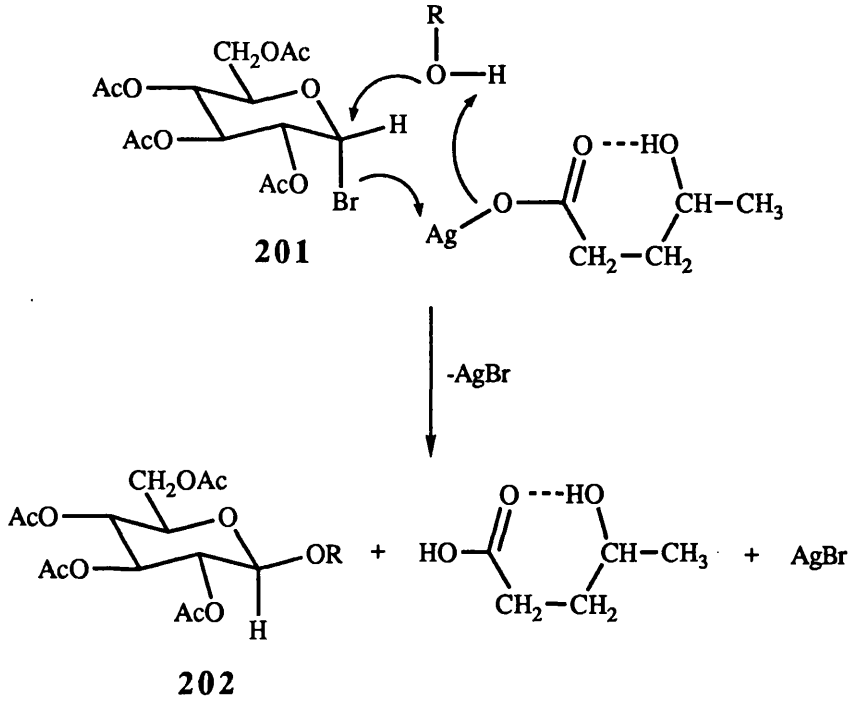
200

TMS = tetramethylsilane

Scheme 98

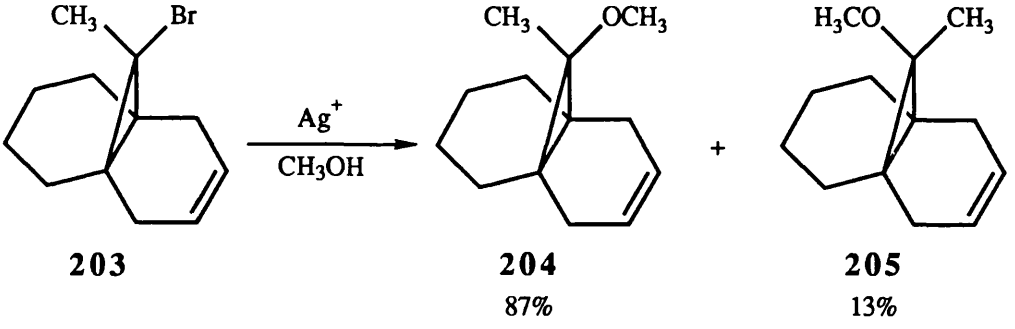
A further example of silver-salt-assisted substitution involving an oxy-nucleophile was provided by Wulff and co-workers[103]. Glucopyranosyl bromides

(**201**) were treated with appropriate salts of dicarboxylic or hydroxycarboxylic acids to give compounds (**202**). The reaction sequence was thought to follow a trimolecular synchronous mechanism (Scheme 99).



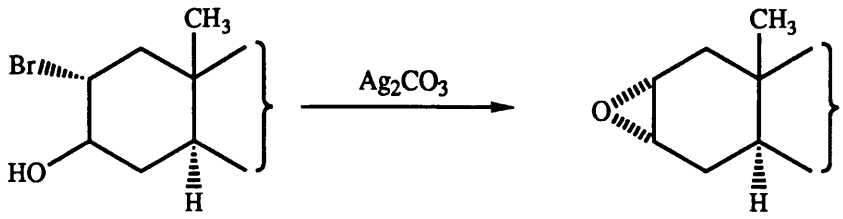
Scheme 99

The silver salt-assisted methanolysis of compound (**203**) gave ethers (**204**) and (**205**) (Scheme 100)[102]



Scheme 100

Silver-salt-assisted cyclisation of bromohydrins (**206**) was used in the formation of epoxides (Scheme 101)[102].



206

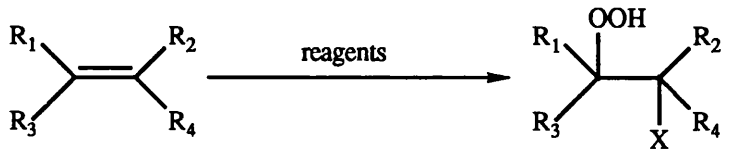
Scheme 101

This reaction was the only example of silver-salt-assisted cyclic ether formation that we were able to find in the literature.

Dialkyl peroxides may be obtained by the alkylation of alkyl halides. Davies *et al*[104] showed that mild conditions could be achieved by assisting the departure of the halide ion with the aid of a suitable silver salt (Scheme 102)[104,105].

Scheme 102

Kopecky and co-workers[106,107] carried out an intramolecular variation of this method by treating β-halohydroperoxides (**207**), with silver salts to give cyclic peroxides. Compounds **207**, were prepared in good yields by the reaction between olefins, N-chloroacetamide, 1,3-dibromo-5,5-dimethylhydantoin or 1,3-diiodo-5,5-dimethylhydantoin and hydrogen peroxide (Scheme 103)[106].

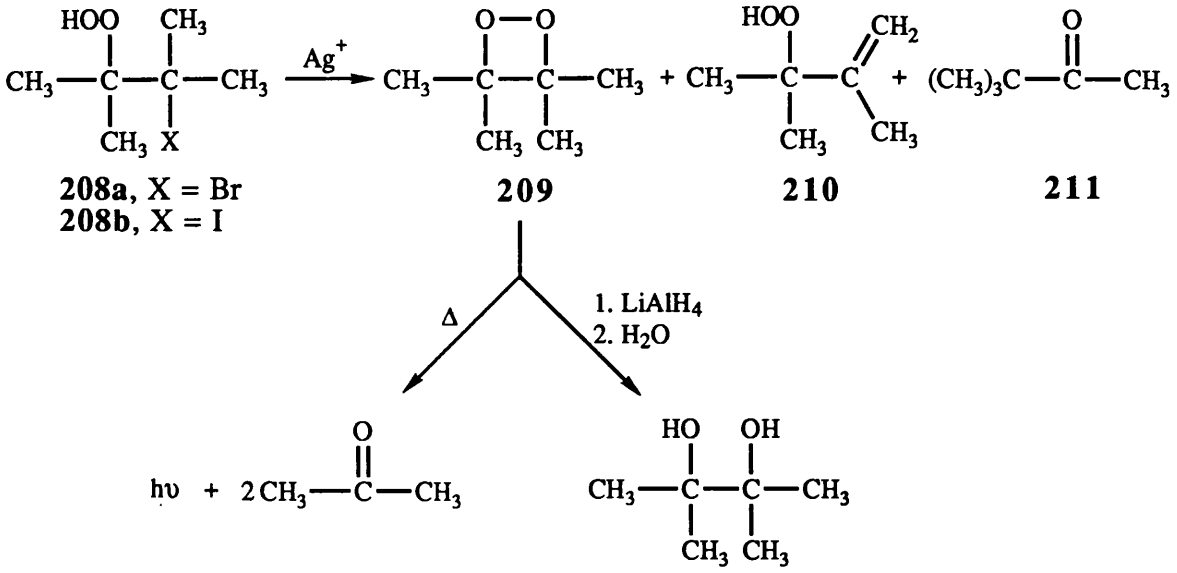


207

X = halogen
reagents: N-chloroacetamide or
1,3-dihalo-5,5-dimethylhydantoin
and H_2O_2 (98%)

Scheme 103

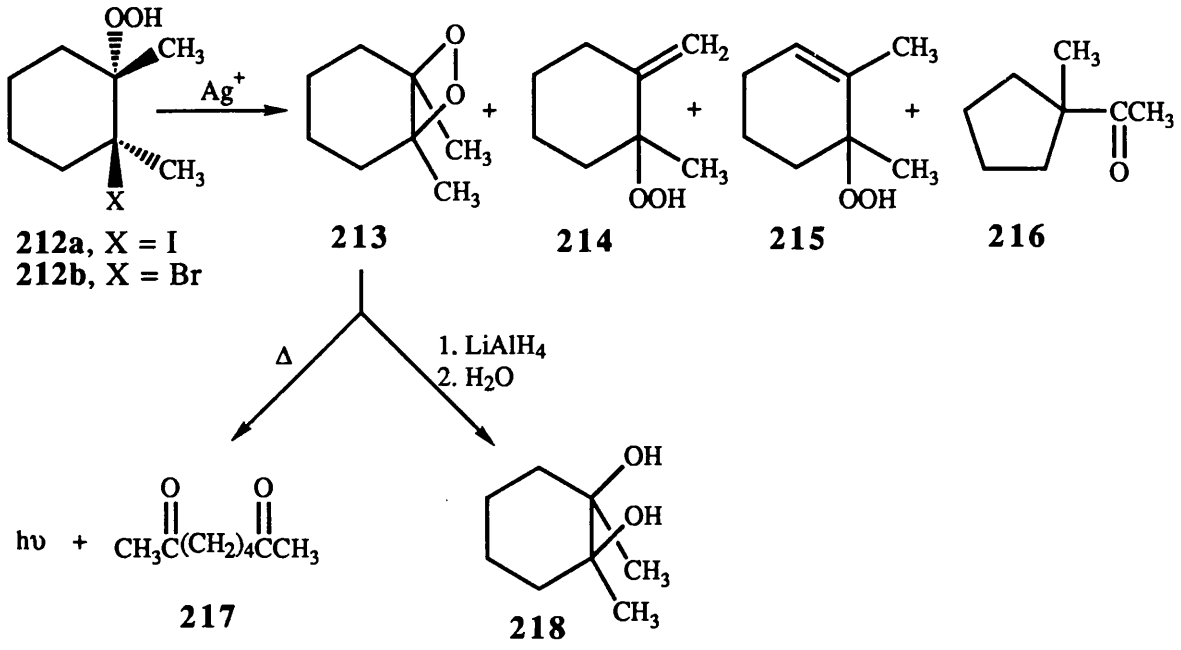
β-Haloperoxides (**208a**) and (**208b**), were treated with either silver acetate or silver benzoate to give a mixture of 1,2-dioxetanes (**209**), 3-hydroperoxy-2,3-dimethyl-1-butene (**210**) and pinacolone (**211**), in ratios of 1:4:1 to 3:3:1 depending on reaction conditions (Scheme 104)[107].



Scheme 104

The formation of dioxetane **209**, was confirmed by reduction to pinacol (98% yield) with lithium aluminium hydride. Thermolysis of **209** in benzene or carbon tetrachloride gave acetone (98% yield).

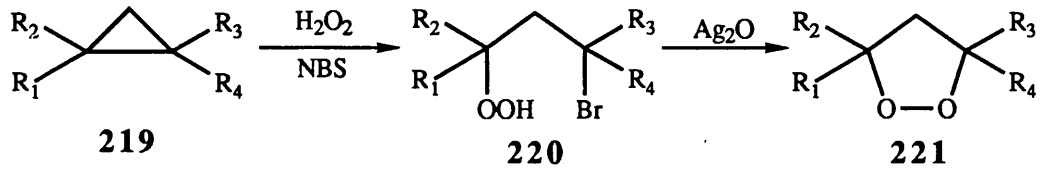
Trans-2-halo-1,2-dimethylcyclohexyl hydroperoxides (**212a**, X=I) and (**212b**, X=Br), were also treated with silver acetate in order to assess the generality of this synthesis of 1,2-dioxetanes. A mixture of four products (**213**), (**214**), (**215**) and (**216**), was obtained. The formation of dioxetane **213** was confirmed by reduction to diol (**218**) and by thermolysis to (**217**) (Scheme 105)[107].



Scheme 105

Compounds **214** and **215** were formed by the elimination of hydrogen halide and compound **216** was formed by a ring contraction. 1,2-dioxolane **213**, was isolated in 25% yield as a crystalline solid. Consistently higher yields of **213** were obtained from iodohydroperoxide starting compounds.

Adam *et al*[108] investigated the conversion of cyclopropanes (**219**) into 1,2-dioxolanes (**221**), by a silver oxide-assisted cyclisation route (Scheme 106).

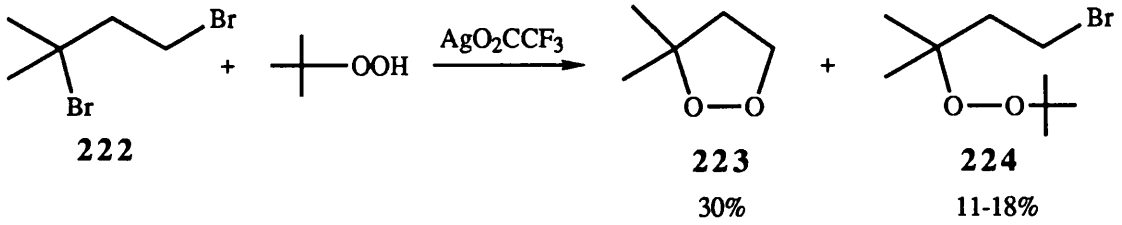


Scheme 106

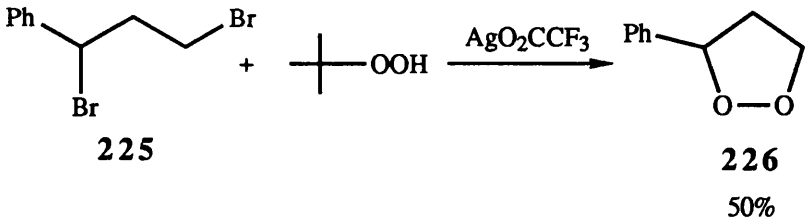
This method proved to be problematic as the hydroperoxybromination of cyclopropanes **219** to give γ-hydroperoxybromides (**220**), only proceeded at an acceptable rate when the cyclopropanes possessed at least one aryl substituent. Furthermore, the hydroperoxybromination was subject to unpredictable amounts of competing aromatic bromination.

Dibromides (**222**) and (**225**), underwent silver-salt-induced cyclisation

reactions to give 1,2-dioxolanes (**223**) and (**226**) respectively (Schemes 107 and 108)[109].

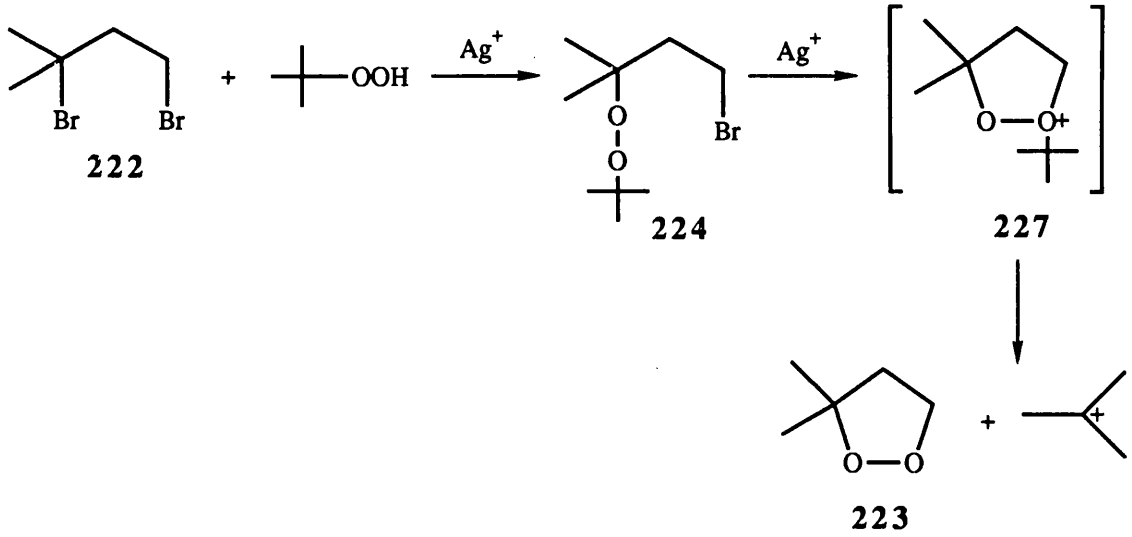


Scheme 107



Scheme 108

The isolation of bromoperoxide (**224**) along with **223** (Scheme 107), suggested that **224** was an intermediate in the conversion of **222** to **223**. The mechanism proposed for this conversion is illustrated in scheme 109.

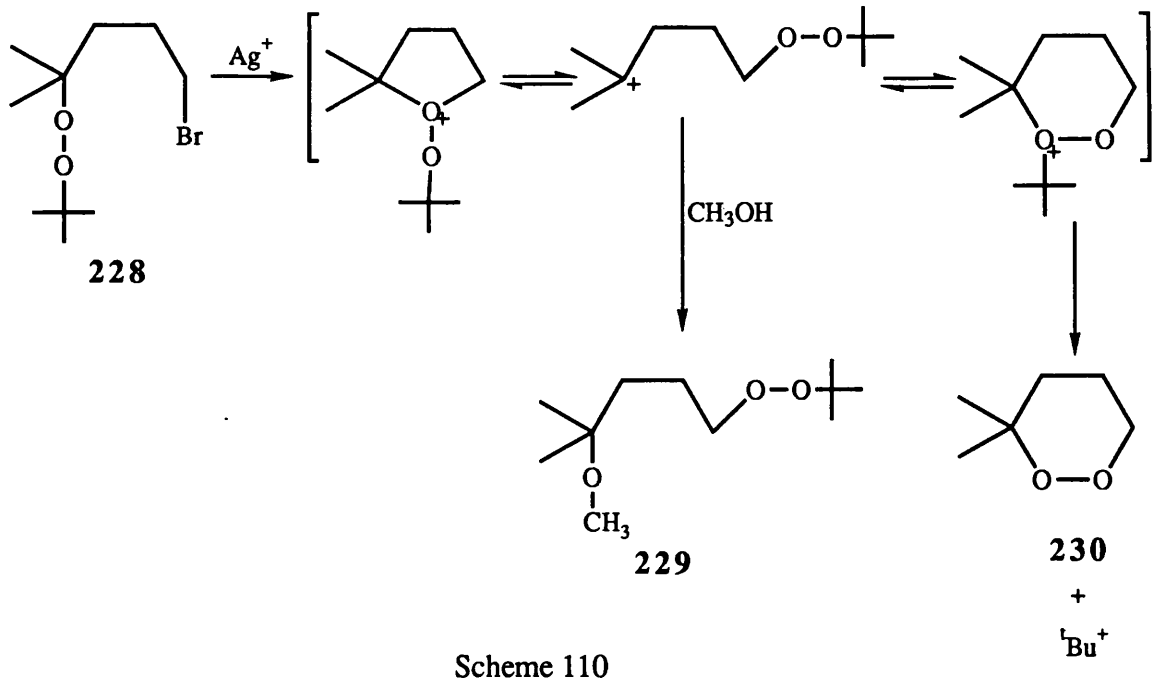


Scheme 109

The proposed mechanism involved the intramolecular alkylation of a dialkyl peroxide, with the formation of an intermediate peroxonium ion (**227**).

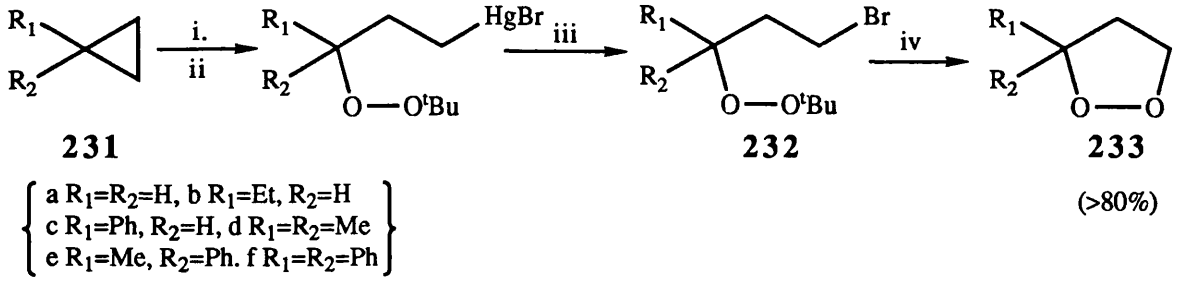
Peroxy-bromide (**228**), was similarly converted to 3,3-dimethyl-1,2-dioxane

(230) in 70% yield by treatment with silver tetrafluoroborate in dichloromethane. However the same reaction in methanol resulted in the formation of peroxy-transfer product (229). A mechanism to account for this product-solvent dependence is shown in scheme 110[109].



Scheme 110

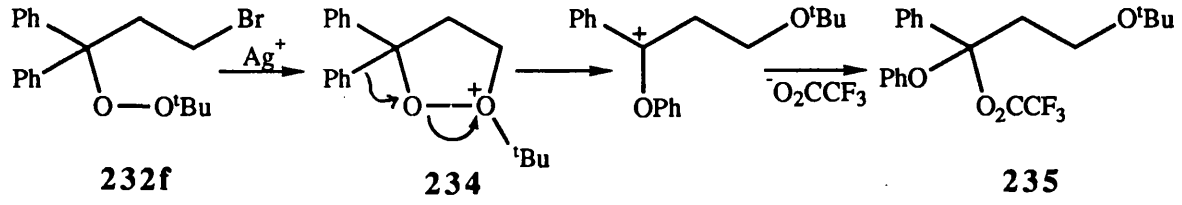
As an alternative to Adam's problematic method for the synthesis of 1,2-dioxolanes from cyclopropanes *via* hydroperoxides (see scheme 106), Bloodworth *et al*[110,111] devised an efficient alternative. As with Porter's route[109], the important intermediates were γ-bromoalkyl *tert*-butyl peroxides (232), but these were made available from cyclopropanes (231) by peroxymercuriation followed by bromodemercuriation (Scheme 111).



i. 2*t*-BuOOH, $Hg(OAc)_2$, 20 mol% $HClO_4$, CH_2Cl_2
ii. KBr, H_2O
iii. Br_2, NaBr, MeOH
iv. AgO_2CCF_3, CH_2Cl_2

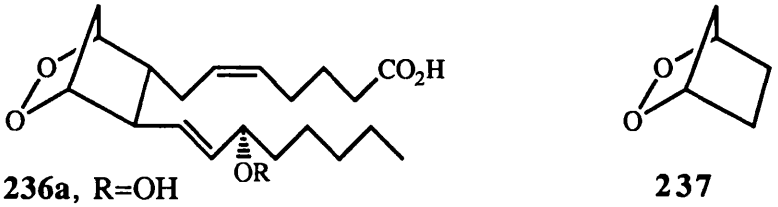
Scheme 111

Dioxolanes (**233**) were obtained in over 80% yield from cyclopropanes **231a-231e**. The exception was with 1,1-diphenylcyclopropane **231f**, which formed a γ-bromoalkyl *tert*-butyl peroxide **232f**. When treated with silver trifluoroacetate **232f** gave compound (**235**), presumably *via* a cyclic trialkylperoxonium intermediate (**234**). Compound **234** can be enviseged to undergo rearrangement by 1,2-phenyl migration and accompanying O-O cleavage to give **235** (Scheme 112).



Scheme 112

The isolation of two prostaglandin endoperoxides (**236a**) and (**236b**), inspired considerable interest in the synthesis of the bicyclic peroxide structure (**237**).

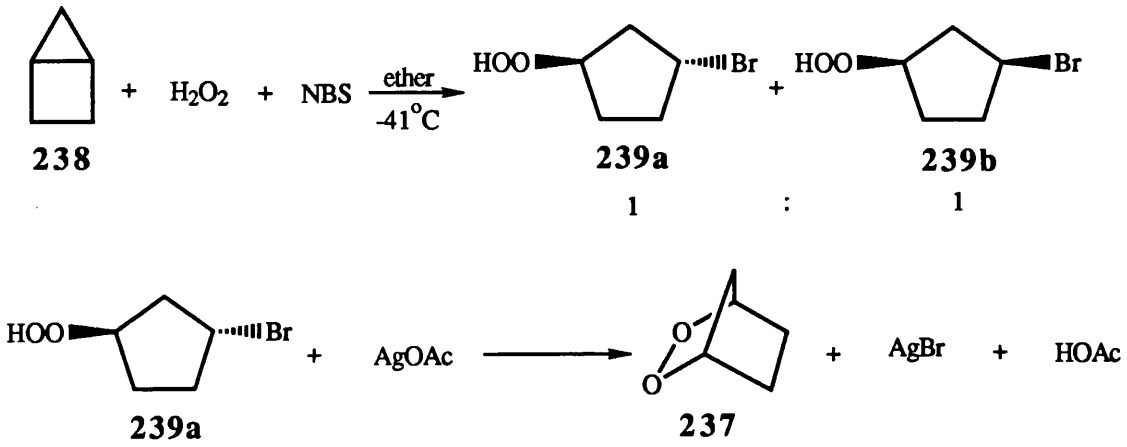


236a, R=OH
236b, R=H

237

Porter and Gilmore[112] used a silver salt-assisted method in one of the first syntheses of compound **237** (Scheme 113). This method actually precedes Adam's[108] similar

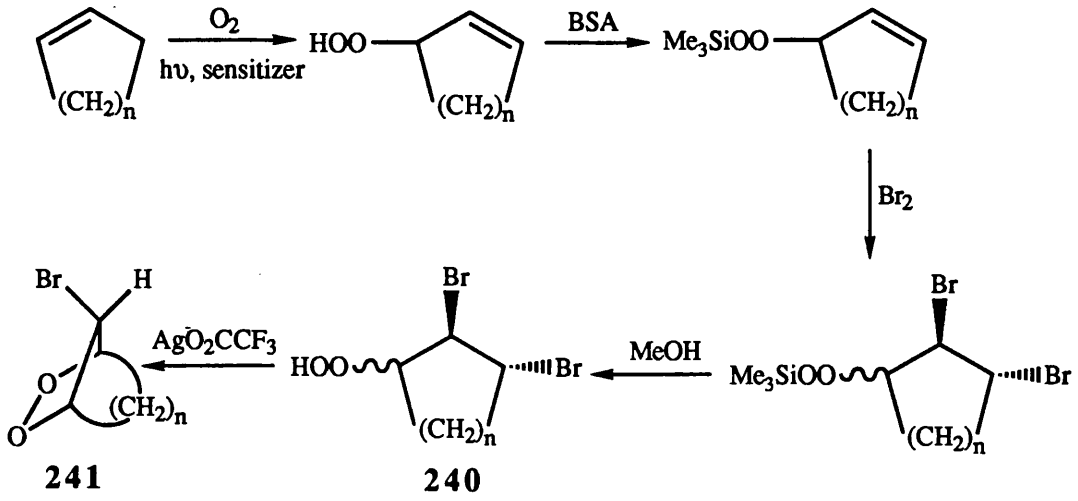
conversion of cyclopropanes into 1,2-dioxolanes which was discussed earlier (see scheme 106).



Scheme 113

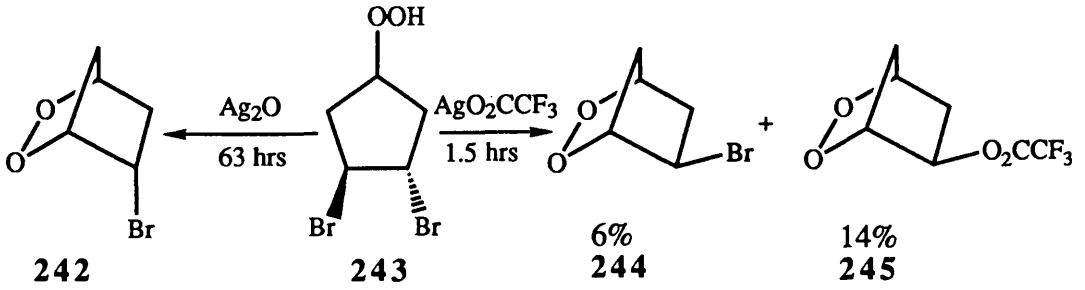
The reaction of **238** with 98% H_2O_2 and N-bromosuccinimide (NBS) in ether (-41 °C), afforded a 1:1 mixture of the *cis*- (**239b**) and *trans* (**239a**)-3-bromopentyl hydroperoxides, which were separated by silica chromatography at -10 °C. The *trans* isomer **239a**, was then treated with silver acetate for 30 mins to give **237** in quantitative yield.

Bloodworth and Eggelte[113] incorporated silver-salt-assisted substitution into a sequence of reactions that provide a general route to [n.2.1]-peroxides (**241**) from commercially available C5-C8 cycloalkanes (Scheme 114).



Scheme 114

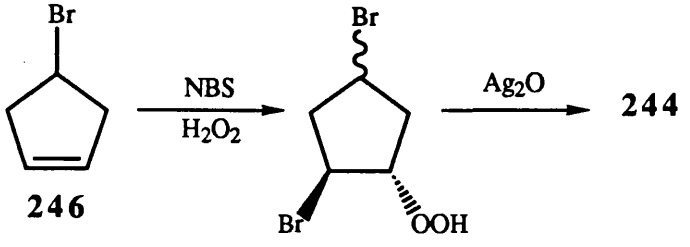
The silver-salt-induced dioxabicyclisation of 3,4-dibromocyclopentyl hydroperoxide (**243**) gave the products of both S_N1 and S_N2 reactions with differing stereochemical consequences (Scheme 115)[114,115].



242 **243** **244** **245**

Scheme 115

Treatment of **243** with silver trifluoroacetate gave a 5-bromo-2,3-dioxabicyclo[2.2.1]heptane (**244**) and a 5-trifluoroacetoxy-2,3-dioxabicyclo[2.2.1]heptane (**245**). An independent experiment showed that **244** could be converted into **245** with silver trifluoroacetate. To avoid the trifluoroacetate for bromide substitution that accompanied and competed with the dioxabicyclisation reaction, compound **243** was treated with silver oxide to give an isomeric 5-bromo-2,3-dioxabicylo[2.2.1]heptane (**242**). On the basis of the known preference for displacement of a *trans*-3-bromine with inversion[112,113], it was originally wrongly assumed that **244** had an *endo*-configuration and so an *exo*-configuration was assigned to **242**, the suggestion being that **242** was the product of equilibrium control. The correct assignments were established by an independent synthesis of the *exo*-isomer **244** *via trans*-hydroperoxybromination of 3-cyclopentenyl bromide (**246**) and ring closure with silver oxide (Scheme 116)[114].



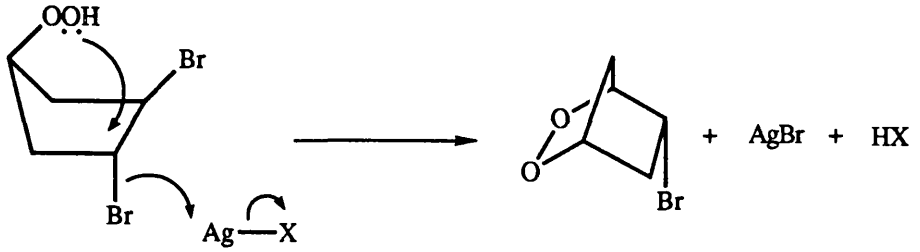
246

Scheme 116

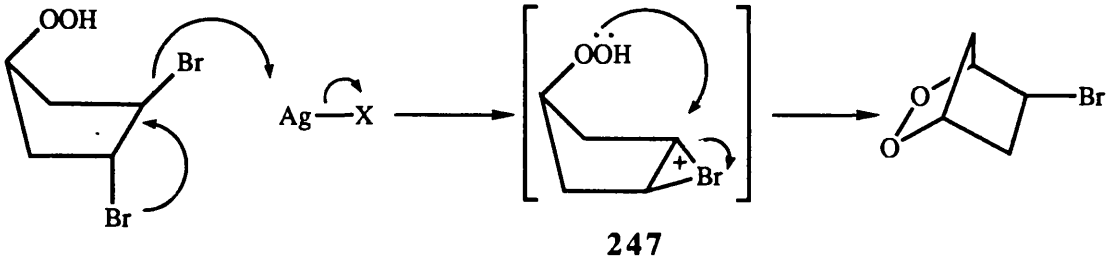
The possibility that **244** and **245** were derived from **243** *via* **242**, was eliminated by

the observation that **242** did not react with silver trifluoroacetate. It was therefore concluded, that in contradistinction to the reactions of **139a**[112] and **240** (n=2)[113], the AgO_2CCF_3-induced dioxabicyclisation of **243** involved preferential displacement of the *cis*-3-bromine. It seemed highly probable that the process was assisted by the *vicinal* bromine, ie that a *trans* bromonium ion (**247**) was an intermediate (Scheme 117).

S_N2

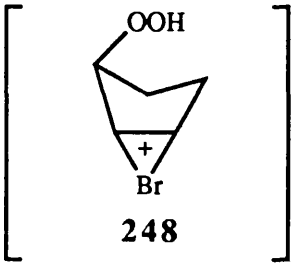


S_N1



247

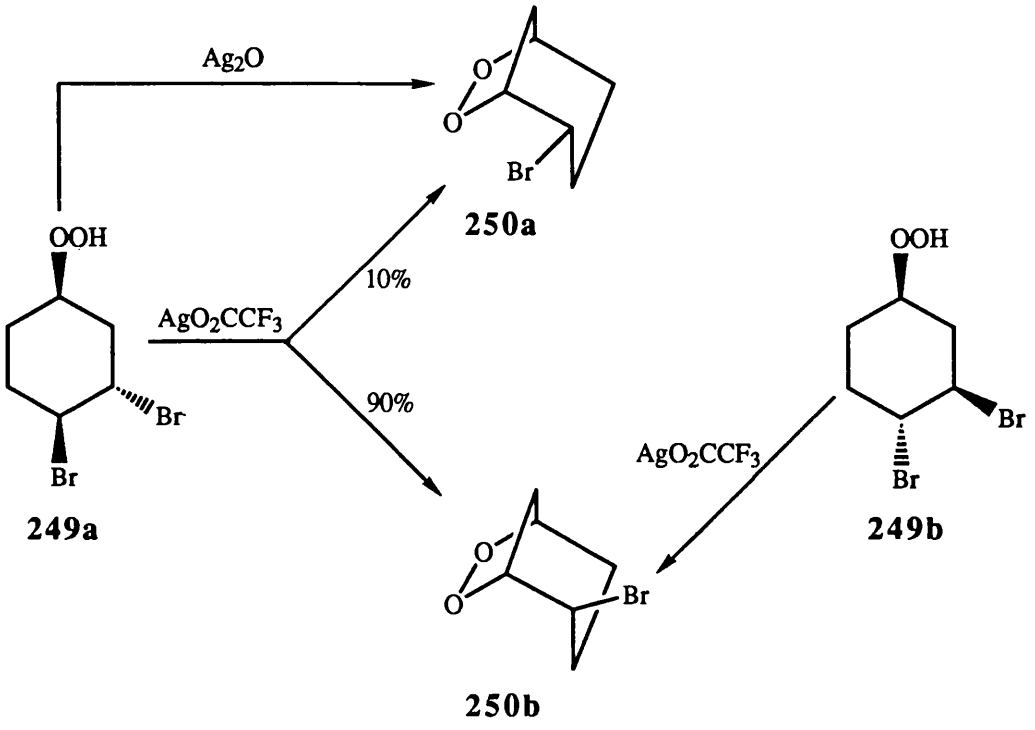
Scheme 117



248

Such a mechanism would not have been available to compound **139a** and formation of a [2.2.1]-endoperoxide from **240** *via* the corresponding species **248**, would require a disfavoured 5-*endo* mode of ring closure.

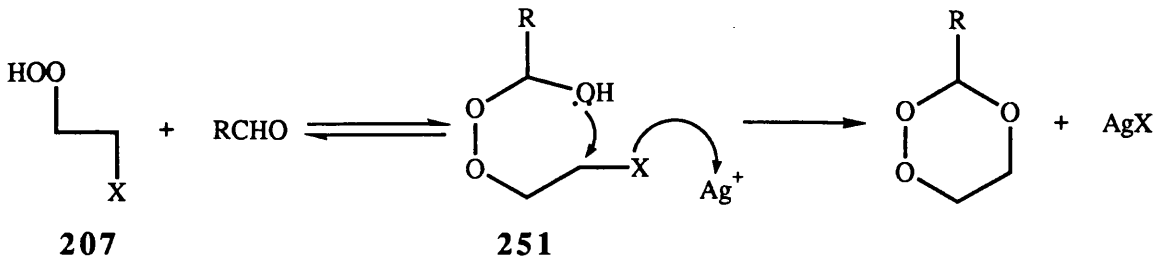
Investigations were also carried out into the reactions of *trans*-3-*cis*-4-dibromocyclohexyl hydroperoxide (**249a**) and *cis*-3-*trans*-4-dibromocyclohexyl hydroperoxide (**249b**) with silver trifluoroacetate as further evidence for a bromonium ion-mediated dioxabicyclisation (Scheme 118)[116].



Scheme 118

The behaviour of the *trans*-3-bromide **249a** closely resembled that of its cyclopentyl analogue **243**[114,115]. Thus with silver oxide only the *cis*-2-bromo-[3.2.1]peroxide (**250a**) was obtained as expected for a S_N2 ring closure. With silver trifluoroacetate some **250a** was formed, but the predominant (90%) bicyclic peroxide was **250b** ie, the [3.2.1]peroxide available *via* a bromonium ion mechanism. The *trans*-4-bromide **249b**, did not react with silver oxide and **250b** was the only bicyclic peroxide formed with silver trifluoroactate. These results supported the existence of a bromonium ion pathway for dioxabicyclisation of 3,4-dibromocycloalkyl hydroperoxides and confirmed a dependence of mechanism upon the choice of silver salt.

We decided to attempt to apply the principle of silver-salt-assisted cyclisation to the synthesis of 1,2,4-trioxanes (Scheme 119).



207 251

Where X = halogen and -OH is the internal oxy-nucleophile

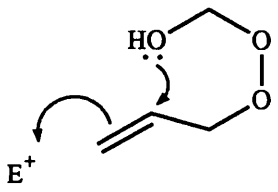
Scheme 119

We envisaged reacting β-halohydroperoxides (**207**)[106] with aldehydes to give halogen-substituted-hemiperoxyacetals (**251**). The subsequent treatment of **251** with silver salts would then hopefully result in 1,2,4-trioxane formation.

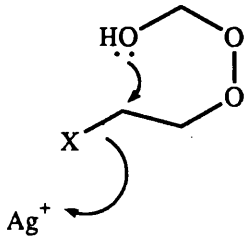
The proposed silver salt-assisted cyclisation is mechanistically similar to the earlier intramolecular electrophilic addition routes discussed in chapters 2, 3 and 4 (Fig 15).

Figure 15

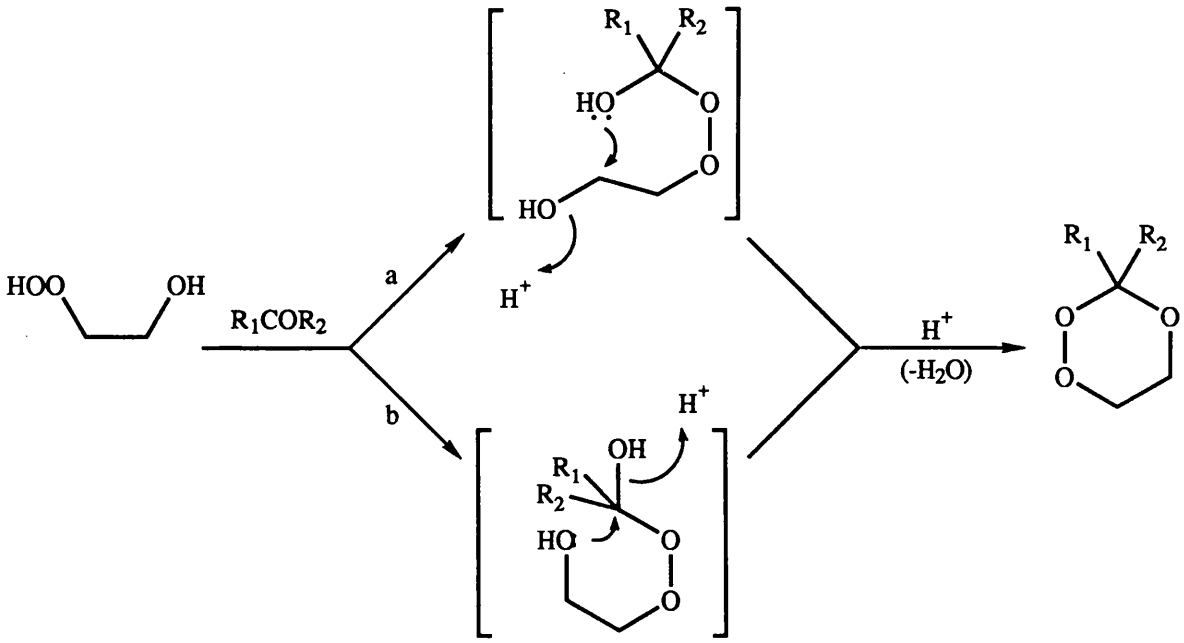
Intramolecular electrophilic addition



Silver-salt-assisted substitution

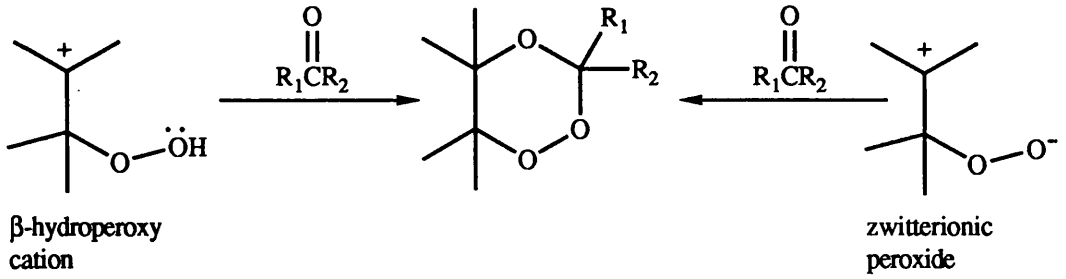


The silver-salt-assisted substitution method has superficial similarities with the synthesis of these compounds by the dehydration of peroxy diols[8-12] (see chapter 1, method 1). In both cases cyclisation to the 1,2,4-trioxanes structure occurs as a result of intramolecular substitution by an oxy-nucleophile (-OH). However in the case of peroxy diol dehydration, the oxy-nucleophile (-OH) could either be from the hemiperoxyacetal (Scheme 120a) or from the substituent (Scheme 120b).



Scheme 120

The trapping of β-hydroperoxycations and zwitterionic peroxides by aldehydes and ketones (Scheme 121)[27] may also be compared to a silver-salt-assisted synthesis of 1,2,4-trioxanes by a S_N1 mechanism (see chapter 1, method 5a for further elaboration).



β-hydroperoxy cation

zwitterionic peroxide

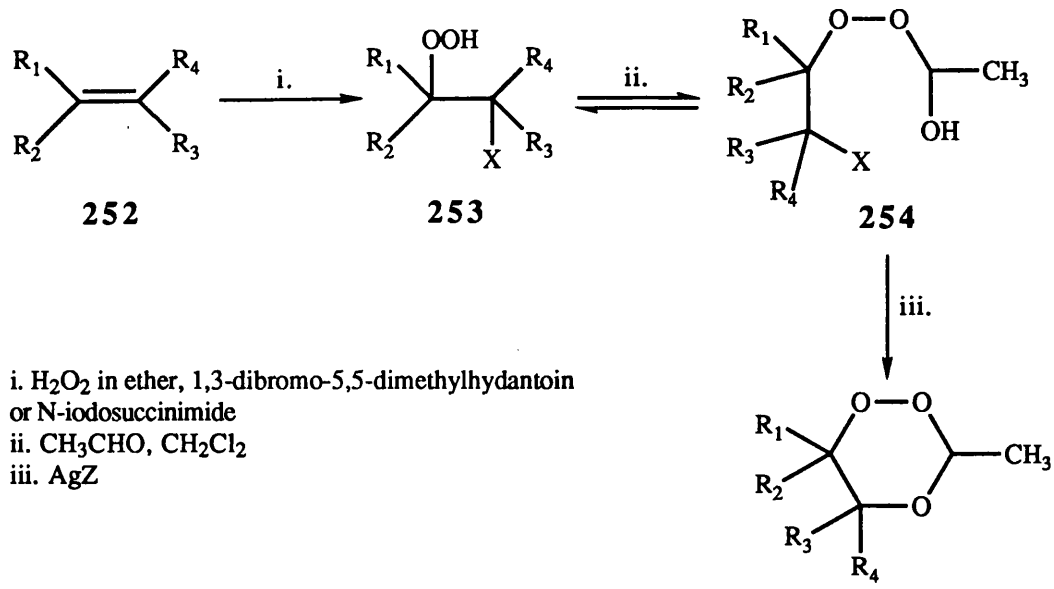
Scheme 121

Scheme 125 illustrates a possible new synthesis of 1,2,4-trioxanes by intramolecular, silver-salt-assisted nucleophilic substitution.

5.2 Results and Discussion

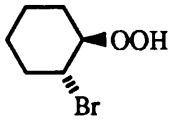
5.2.1 An attempt at a silver-salt-assisted substitution route to 1,2,4-trioxanes

Scheme 122 shows in more detail the reactions which we studied in our attempt to provide a new synthesis of 1,2,4-trioxanes by intramolecular silver-salt-assisted nucleophilic substitution.



253a $R_1=R_2=R_3=R_4=Me$, X=Br, **253bi** $R_1=R_2=R_3=Me$, $R_4=H$, X=Br,
253bii $R_1=R_2=R_3=Me$, $R_4=H$, X=I, **253ci** $R_1=R_3=R_4=H$, $R_2=C_6H_5$, X=Br,
253cii $R_1=R_3=R_4=H$, $R_2=C_6H_5$, X=I, **253d** $R_1=Me$, $R_2=CH(CH_3)_2$, $R_3=R_4=H$, X=Br

253e



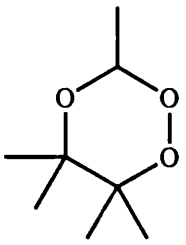
Scheme 122

The starting β-halohydroperoxides (**253**) were prepared according to Kopecky's method[106] in good yields (70-80%). The proton nmr spectra of crude compounds **253** compared favourably with the literature and we also obtained some carbon-13 nmr data which were not previously reported. The key signals were at δ 85-87 (C-OOH), δ 31-38 (C-Br) and at δ 13-14 (C-I). The crude hydroperoxides **253** dissolved in dichloromethane, were treated with excess acetaldehyde and a silver(I) salt for 45mins-1hr. From past experience (see chapters 2 and 4) we expected **253** to react with acetaldehyde to give hemiperoxyacetals (**254**). Compounds **254** were not generally

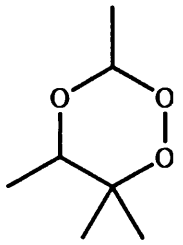
isolated but were treated *in situ* with the silver compounds. The crude products were obtained as yellow oils after filtering through Celite and concentrating.

5.2.1.2 The 3-bromo-2,3-dimethyl-2-butyl hydroperoxide system

3-Bromo-2,3-dimethyl-2-butyl hydroperoxide (**253a**) reacted with acetaldehyde and silver trifluoroacetate in the desired fashion to give 3,5,5,6,6-pentamethyl-1,2,4-trioxane **116a** in 21% yield. However the synthesis of **116a** by intramolecular oxymercuriation (chapter 2) was much more efficient (62% yield). The proton and carbon-13 nmr spectra of **116a** obtained by the silver salt method were in good agreement with spectra obtained from the earlier oxymercuriation route. Thus C-3 was observed at δ 95.60; C-6 at δ 82.03 and C-5 at δ 74.45. In the proton spectrum, $CHCH_3$ proton was observed as a quartet at δ 5.56 whilst the $CHCH_3$ protons gave the expected doublet signal at δ 1.21.



116a



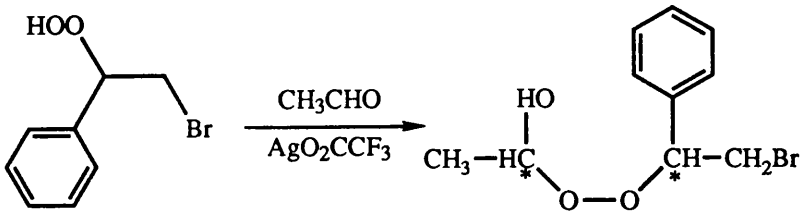
255

5.2.1.3 The 3-halo-2-methyl-2-butyl hydroperoxide system

3,5,6,6-Tetramethyl-1,2,4-trioxane (**255**), was also synthesised by the new silver-salt-assisted route (Scheme 122). The reaction of β-bromohydroperoxide **253bi** with acetaldehyde and either silver trifluoroacetate or silver tetrafluoroborate gave **255** in 10% yield. The yield was improved slightly to 12%, by treating β-iodohydroperoxide **253bii** with acetaldehyde and silver trifluoroacetate. Purification was carried out by simple column chromatography followed by HPLC to give pure **255** as a colourless liquid. The key signals in the ^{13}C nmr spectrum were observed at δ 96.07 (C-3), δ 82.73 (C-6) and δ 76.64 (C-5). In the proton spectrum the CH_3CHOO proton gave a quartet signal at δ 5.55 and the CH_3CHO proton was also observed as a quartet at δ 4.21. The other important signals were at δ 1.21 (d, 3H, CH_3CH-OO) and at δ 0.99 (d, 3H, CH_3CH-O). The new 1,2,4-trioxane **255** gave satisfactory C/H analyses and a positive test with acidic iron(II) thiocyanate.

5.2.1.4 The 2-halo-1-phenylethyl hydroperoxide system

The reaction of **253ci** with a 2-fold excess of acetaldehyde and an equivalent amount of silver trifluoroacetate in dichloromethane did not produce a 1,2,4-trioxane even after 12hrs reaction time. ^{1}H and ^{13}C nmr spectroscopy showed that the products were a 1:1 mixture of starting **253ci** and hemiperoxyacetal **254ci** (2 diastereoisomers) (Scheme 123). The silver trifluoroacetate did not take part in the reaction at all and was fully recovered at the end.



253ci **254ci**

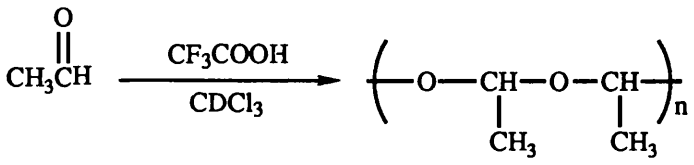
Scheme 123

The signals in the proton spectrum to confirm the presence of **254ci**, were observed in duplicate for two diastereoisomers. The key signals were at δ 5.52, 5.47 (q, $CHCH_3$) and at δ 5.31, 5.24 (dd, CHC_6H_5). The CH_2Br signals for starting **253ci** overlapped with the CH_2Br signals for one of the diastereoisomers of **254ci**. Thus the H^aH^bBr signal (dd) appeared at δ 3.74 and the signal for the H^aH^bBr proton (dd) was observed at δ 3.63, for both **253ci** and one diastereoisomer of **254ci**. In the other diastereoisomer the H^aH^bBr signal (dd) was observed at δ 3.70, whilst the H^aH^bBr signal (dd) appeared at δ 3.64. The other key signals to support **254ci** formation were at δ 1.63, 1.62 (s, OH) and at δ 1.27, 1.23 (d, $CHCH_3$). In the ^{13}C nmr spectrum the $CHCH_3$ signal was observed at δ 97.79, 97.24 (2 diastereoisomers); the CHC_6H_5 signal at δ 86.53, 85.23; the CH_2Br signal at δ 32.66, 32.40 and finally the CH_3 signal at δ 18.72, 18.46. Hetcor pulse sequence by ^{1}H/ ^{13}C signal correlations carried out by Chris Cooksey (UCL), were used to confirm that hemiperoxyacetal **254ci** was the main product. In an independent reaction, we treated 2-bromo-1-phenylethyl hydroperoxide **253ci**, with a two-fold excess of acetaldehyde in deuteriochloroform. The ^{13}C nmr spectrum recorded after 20 mins at room temperature, confirmed the formation of **254ci** as a pair of diastereoisomers.

We decided to apply more forcing conditions to the **253ci**, acetaldehyde and silver trifluoroacetate reaction. Under reflux conditions in dichloromethane a brown oil was obtained after 45mins-1hr. ^{1}H and ^{13}C nmr spectroscopy showed a complex

set of signals. No 1,2,4-trioxane formation was detected, although signals corresponding to some starting **253ci** and hemiperoxyacetal **254ci** were present.

The reaction of **253ci** with a large excess of acetaldehyde (as solvent), and an equivalent amount of silver trifluoroacetate, gave acetaldehyde polymer (**256**) as the major product. Thus in the proton spectrum the $CHCH_3$ proton signal was observed as a quartet (δ 5.13), whilst the signal for the $CHCH_3$ protons was a doublet (δ 1.47). In the ^{13}C nmr spectrum, the $CHCH_3$ signal appeared at δ 98.45 and the $CHCH_3$ signal was observed at δ 21.60. No 1,2,4-trioxane formation was detected, in fact starting **253ci** did not appear to react at all. The presence of trifluoroacetic acid, available from the decomposition of silver trifluoroacetate, was thought to catalyse the polymerisation of acetaldehyde. In an independent reaction we treated acetaldehyde with trifluoroacetic acid and as expected acetaldehyde polymer was found to be the major product (Scheme 124).

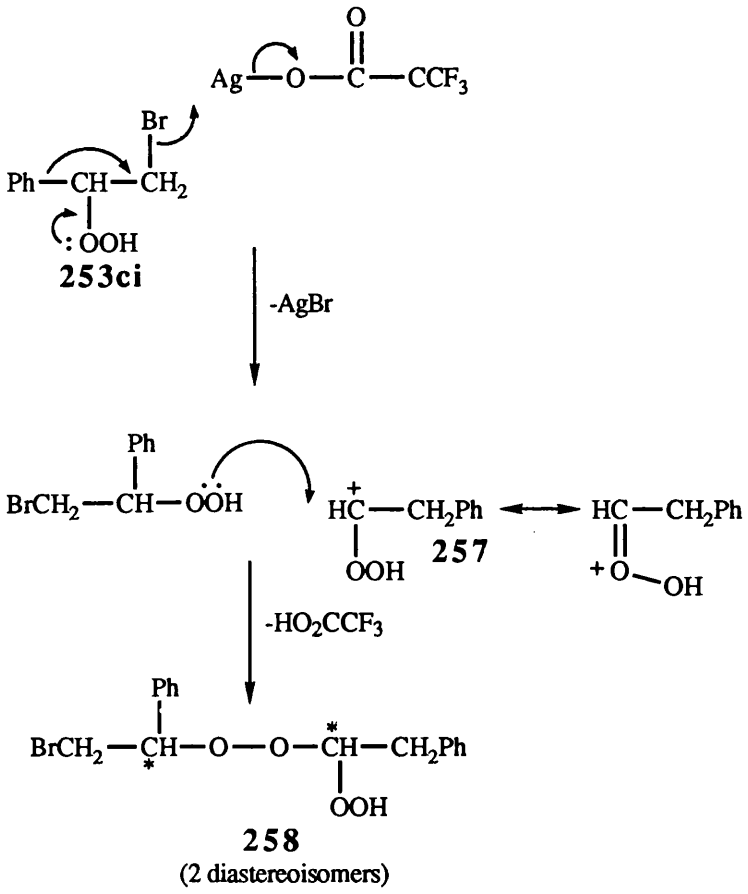


256

Scheme 124

As we had so little success with silver trifluoroacetate, we decided to vary the silver salt. Thus we treated **253ci** with acetaldehyde and silver tetrafluoroborate at room temperature. The reaction did not produce a 1,2,4-trioxane. The ^1H nmr spectrum was quite complicated but some signals corresponding to **253ci** and **254ci** were present.

We decided to investigate the reaction of silver trifluoroacetate with **253ci** in the absence of acetaldehyde to see if the products of this reaction were also present in any of the earlier **253ci** / acetaldehyde/ silver salt reactions. Thus we treated **253ci** with an equivalent amount of silver trifluoroacetate in dichloromethane solvent for 45mins-1hr. We obtained a 1:1 mixture of starting **253ci** and compound (**258**), which had not been detected in the previous **253ci** / acetaldehyde/ silver salt reactions. Scheme 125 illustrates the procedure by which **258** was thought to arise.



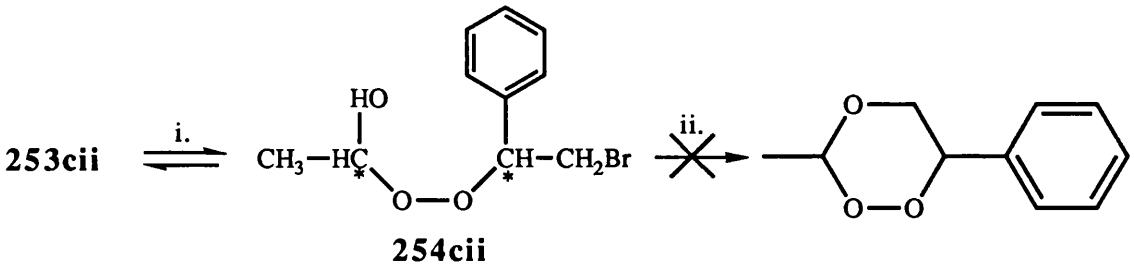
Scheme 125

The silver-salt-assisted loss of bromine from **253ci**, coupled with a 1,2-phenyl group migration was thought to result in structure (**257**), which reacted with a further molecule of **253ci** to give **258** as two diastereoisomers. The proton spectrum was particularly complicated but peaks were observed at reasonable chemical shifts for CHOOH (δ-5.51-5.45), CHC_6H_5 (δ 5.25-5.10), CH_2Br (δ 3.80-3.50) and $CH_2C_6H_5$ (δ 3.00-2.85). In the ^{13}C spectrum, the key signals were due to CHOOH (δ 101.03 and 100.65), CHC_6H_5 (δ 85.49 and 85.42), $CH_2C_6H_5$ (δ 39.57 and 39.31) and finally CH_2Br (δ 32.43 and 32.19).

As iodine is thought to be a better leaving group than bromine, we decided to treat the iodo-equivalent of **253ci** with acetaldehyde and a silver salt in the hope that 1,2,4-trioxane formation would be more likely to occur. Thus we treated the β-iodohydroperoxide **253cii**, with a 2-fold equivalent of acetaldehyde and an equivalent amount of silver trifluoroacetate. No 1,2,4-trioxane formation was detected and the reaction was 'messy'. The only products observed by nmr spectroscopy were unchanged **253cii** and hemiperoxyacetal **254cii** (2 diastereoisomers). The main

difference in the nmr spectra of **254cii** and **254ci** was in the chemical shift for the carbon attached directly to the halogen (δ 13-14 for C-I and δ 33-35 for C-Br). We repeated the reaction of **253cii** and acetaldehyde with silver(I) oxide but we were still not able to produce any 1,2,4-trioxanes. The reaction was very 'messy' and we were unable to identify any of the products.

We hoped that in the presence of a strong base, the OH group in hemiperoxyacetal **254cii** would be converted to O^-, which is a more powerful nucleophile. Thus we had a final attempt at effecting cyclisation of **254cii** to give the desired 1,2,4-trioxane by treating **253cii** and acetaldehyde with sodium hydride (Scheme 126).



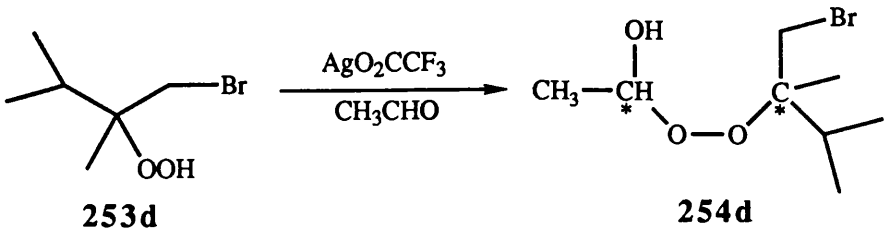
i. $2CH_3CHO$
ii. NaH, THF, under N_2

Scheme 126

However the ^1H and ^{13}C nmr spectra were very complicated and we were unable to identify any of the products.

5.2.1.5 The 1-bromo-2,3-dimethyl-2-butyl hydroperoxide system

1-Bromo-2,3-dimethyl-2-butyl hydroperoxide **253d**, was treated with acetaldehyde and silver trifluoroacetate. However no 1,2,4-trioxane formation was detected and the silver trifluoroacetate was fully recovered. The main product appeared to be hemiperoxyacetal **254d** (2 diastereoisomers) (Scheme 127).



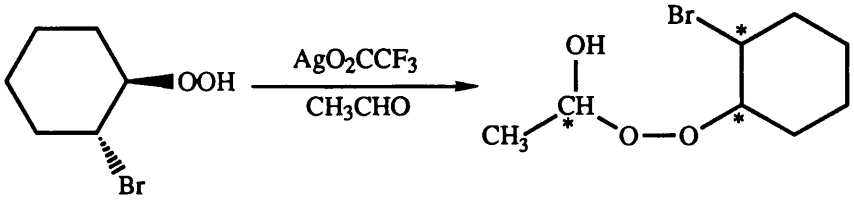
253d **254d**

Scheme 127

The formation of two diasterioisomers of **254d** was supported by the observation of duplicate signals for $CHCH_3$ (δ 97.09, 96.95), CCH_2Br (δ 84.98, 84.64), CH_2Br (δ 39.75, 39.45) and $CH(CH_3)_2$ (δ 31.72, 31.58).

5.2.1.6 The *trans*-2-bromocyclohexyl hydroperoxide system

trans-2-Bromocyclohexyl hydroperoxide **253e**, was treated with acetaldehyde and silver trifluoroacetate. Again no 1,2,4-trioxane formation was detected by nmr spectroscopy although signals were observed to support the formation of at least two isomers of hemiperoxyacetal **254e** (Scheme 128).



253e **254e**

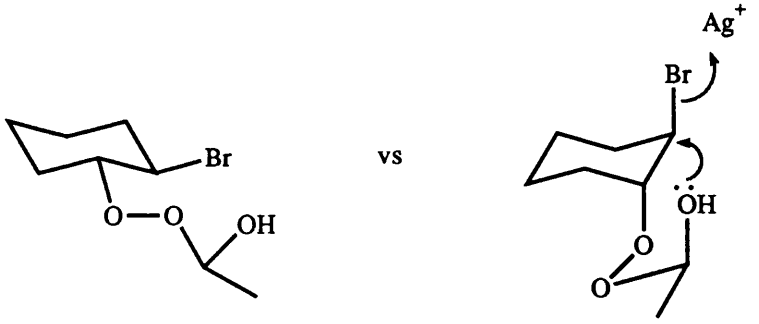
Scheme 128

The key signals in the proton spectrum to support **254e** formation (2 isomers) was the appearance of two quartets due to the $CHCH_3$ proton (δ 5.48, 5.43). A complex multiplet between δ 4.21-3.92 could have contained signals for CHBr and $C_{ring}HOO$ protons. In the ^{13}C nmr spectrum duplicate signals were observed for $CHCH_3$ (δ 97.62, 96.69), $C_{ring}HOO$ (δ 84.54, 85.79), CHBr (δ 35.49, 34.99) and CH_3 (δ 18.57, 18.39).

The silver-salt-assisted route to 1,2,4-trioxanes did not work for any of the hydroperoxide systems with primary alkyl halide groups. However 1,2,4-trioxanes were obtained in modest yields from tertiary (**253a**) and secondary (**253b**) hydroperoxides. This implys that the silver-salt-assisted substitution occurs by an S_N1 reaction. The failure of hydroperoxide **253e** (also 2 ry) to form a 1,2,4-trioxane was thought to be because of unfavourable conformational preference for *trans*-diequatorial

in the hemiperoxyacetal (Fig 16).

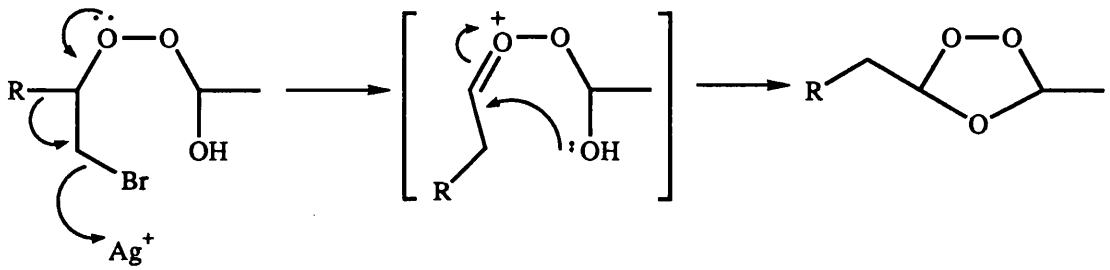
Figure 16



trans-diequatorial

trans-diaxial
(more likely to cyclise in the desired fashion)

In the cases where we were unable to identify any of the reaction products, we considered the possibility of ozonide formation by a process illustrated in scheme 129.



1,2-Me migration
(cf Scheme 125)

Scheme 129

In fact we found no evidence for this reaction occurring.

5.3 Conclusion

The silver-salt-assisted route to 1,2,4-trioxanes was not very successful. Compound **116a**, was obtained in just 21% yield from β-halohydroperoxide **253a** (**116a** was obtained in 62% yield by intramolecular oxymercuriation, chapter 2). A new 1,2,4-trioxane **255**, with just one methyl group at position C-5 was also produced by this silver salt route in 10-12% yield from compounds **253b**. The β-halohydroperoxides **253c-253e** reacted with acetaldehyde to give hemiperoxyacetals

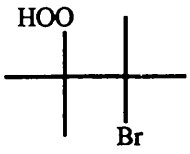
253, but the desired cyclisation reaction with silver salts did not occur and no 1,2,4-trioxanes were isolated. Thus a silver-salt-assisted route to 1,2,4-trioxanes is not really synthetically useful.

5.4 Experimental

Silver trifluoroacetate[117]

Trifluoroacetic acid (0.19mol) was added to a stirred suspension of silver oxide (0.1mol) in water (50ml). The resulting solution was filtered. The filtrate was evaporated to dryness under reduced pressure. The crude silver trifluoroacetate was purified by extraction with ether from a Soxhlet thimble to give a powdery white solid (21.65g, 96%).

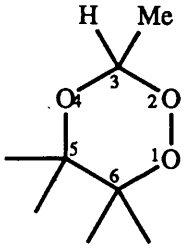
3-Bromo-2,3-dimethyl-2-butyl hydroperoxide (253a)[106]



1,3-Dibromo-5,5-dimethylhydantoin (5mmol; 1.43g) was added to a stirred solution of 2,3-dimethyl-2-butene (10mmol; 0.84g) and H_2O_2 in ether (25mmol-1ml 85% H_2O_2 in 10ml ether dried over $MgSO_4$) at -40 °C (CO_2, acetone). The reaction vessel was protected with a calcium chloride tube and allowed to come to room temperature (20-30mins). The mixture was washed with cold saturated sodium bicarbonate solution (20ml) and several times with water before being dried ($MgSO_4$). Ether was removed under reduced pressure to give the crude product as an orange/ yellow solid (1.59g, 81%).

^{1}H nmr (400MHz) δ : 1.79 (s, 6H), 1.43 (s, 6H) ppm.
^{13}C nmr (100MHz) δ : 86.95 (C-OOH), 71.81 (C-Br), 30.56 (2C), 21.27 (2C) ppm.
Literature data[106]: ^{1}H nmr δ : 8.2-7.7 (broad singlet for hydroperoxy proton), 1.81 (singlet) and 1.45 (singlet) for the protons of the two *gem*-dimethyl groups.

Formation of 3,5,5,6,6-pentamethyl-1,2,4-trioxane 116a, by reaction of 253a with acetaldehyde and silver trifluoroacetate

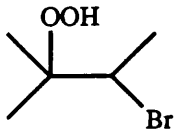


Acetaldehyde (23mmol; 1.02g) was added to a stirred solution of 3-bromo-2,3-dimethyl-2-

butyl hydroperoxide (7.72mmol; 1.52g) in dichloromethane (20ml). Silver trifluoroacetate (7.72mmol; 1.7g) was added in one portion and the mixture was stirred at room temperature (45min-1hr). The mixture was filtered through Celite. The crude product was concentrated by the removal of solvent under reduced pressure (0.25g, 21%).

^{1}H nmr (400MHz) δ : 5.56 (q, J=5.23 Hz, 1H, $CHCH_3$), 1.47 (s, 3H), 1.37 (s, 3H), 1.21 (d, J=5.23 Hz, 3H, $CHCH_3$), 1.13 (s, 3H), 0.99 (s, 3H) ppm.
^{13}C nmr (100MHz) δ : 95.60 (C-3), 82.03 (C-6), 75.45 (C-5), 24.62, 21.33, 21.05, 20.14, 18.12 ppm.
Nmr data from intramolecular oxymercuriation synthesis of **116a** (see chapter 2):
^{1}H nmr (400 MHz) : δ 5.55 (q, J=5.27 Hz, 1H, CHMe), 1.22 (s, 3H), 1.21 (s, 3H), 1.19 (d, 5.27 Hz, 3H, $CHCH_3$), 1.12 (s, 3H), 0.98 (s, 3H) ppm.
^{13}C nmr (100 MHz) : δ 95.52 (C-3), 81.92 (C-6), 75.23 (C-5), 24.65, 21.33, 21.06, 20.12, 18.15 ppm.

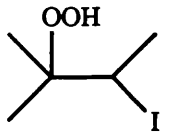
3-Bromo-2-methyl-2-butyl hydroperoxide (253bi)[106]



Procedure as for **253a**, except that in this case the gaseous alkene was condensed into ether (10ml) at -40 °C (CO_2, acetone) before beginning the reaction.
Starting materials : 2-methylbut-2-ene (15mmol; 1.05g), 1,3-dibromo-5,5-dimethyl hydantoin (2.5mmol; 0.71g), H_2O_2 in ether (25mmol). The reaction gave the crude product as a yellow oil (0.82g, 90%).

^{1}H nmr (60MHz) δ : 8.2 (bs, OOH), 4.94 (q, J=6.13 Hz, 1H, CHBr), 2.21 (d, J=6.13 Hz, 3H, CH_3CHBr), 1.64 (s, 6H) ppm.
Literature data[106]: ^{1}H nmr δ : 8.6 (broad singlet for hydroperoxy proton), 4.44 (q, J=7 Hz, for methine proton), 1.68 (d, J=7 Hz, for terminal methyl protons), 1.37 (s, 3H) and 1.28 (s, 3H) for the protons of the two non-equivalent *gem*-dimethyl groups.

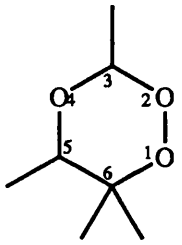
3-Iodo-2-methyl-2-butyl hydroperoxide (253bii)



Gaseous 2-methylbut-2-ene (15mmol; 1.05g) was condensed into ether (10ml) at -40°C (CO_2, acetone). H_2O_2 in ether (25mmol-1ml 85% H_2O_2 in 10ml ether dried over $MgSO_4$) was added to this cooled solution. The reaction vessel was covered (aluminium foil). N-iodosuccinimide (5mmol; 1.33g) was added with stirring in small portions over 5mins. The reaction vessel was protected by a calcium chloride tube and the mixture was allowed to come to room temperature (20-30mins). The mixture was washed with water (3x20ml). The organic extract was washed with 20% sodium thiosulphate solution (10ml) before being dried ($MgSO_4$). Ether was removed under reduced pressure to give the crude product as a yellow oil (0.8g, 70%).

^{1}H nmr (60MHz) δ : 4.64 (q, J=6.28 Hz, 1H, **CH**I), 2.03 (d, J=6.28 Hz, 3H, **CH_3**CHI), 1.52 (s, 6H) ppm.

Formation of 3,5,6,6-tetramethyl-1,2,4-trioxane (255)



a) Reaction of 253bi with acetaldehyde and silver trifluoroacetate.
Procedure as for the formation of **116a** from **253a**.
Starting materials : 3-bromo-2-methyl-2-butyl hydroperoxide (5.13mmol; 0.94g), acetaldehyde (20mmol; 0.88g), silver trifluoroacetate (5.13mmol; 1.13g). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.54) followed by HPLC (column: 2 x 250mm silica gel 5μm, mobile phase: 10% ethyl acetate + 90% hexane, flow rate: 5.0cm^3/ min) gave the pure product as a colourless liquid (0.07g, 10%).

^{1}H nmr (400MHz) δ : 5.55 (q, J=5.31 Hz, 1H, **CH**-OO), 4.21 (q, J=6.77 Hz, 1H, **CH**-O), 1.26 (s, 3H), 1.21 (d, J=5.31 Hz, 3H, **CH_3**CH-OO), 1.17 (s, 3H), 0.99 (d, J=6.77 Hz, 3H, **CH_3**CH-O) ppm.
^{13}C nmr (100MHz) δ : 96.07 (C-3), 82.73 (C-6), 76.64 (C-5), 25.58, 18.24, 17.03, 13.08 ppm.
Found: C, 57.81; H, 9.55% $C_7H_{14}O_3$ requires: C, 57.51; H, 9.66%

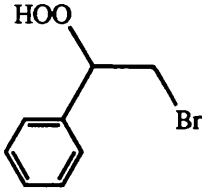
b) Reaction of 253bi with acetaldehyde and silver tetrafluoroborate.
Acetaldehyde (35mmol; 1.58g) was added to a stirred solution of 3-bromo-2-methyl-2-butyl hydroperoxide (12mmol; 2.2g) in dichloromethane (20ml). Silver tetrafluoroborate (12mmol; 2.34g) was added in one portion at -70 °C (CO_2, acetone). The solution was allowed to come to room temperature with stirring (45min-1hr). The mixture was filtered through Celite and washed several times with water. The organic layer was dried ($MgSO_4$) and concentrated to give the crude product as a yellow oil (0.18g, 10%).

^{1}H nmr (400MHz) δ : 5.56 (q, J=5.30 Hz, 1H, CH-OO), 4.20 (q, J=6.76 Hz, 1H, CH-O), 1.25 (s, 3H), 1.20 (d, J=5.30 Hz, 3H, CH_3CH-OO), 1.15 (s, 3H), 0.98 (d, J=6.76 Hz, 3H, CH_3CH-O) ppm.
^{13}C nmr (100MHz) δ : 96.01 (C-3), 82.71 (C-6), 77.27 (C-5), 25.56, 18.23, 17.56, 13.02 ppm.

c) Reaction of 253bii with acetaldehyde and silver trifluoroacetate.
Acetaldehyde (7mmol; 0.3g) was added to a stirred solution of 3-iodo-2-methyl-2-butyl hydroperoxide (3.48mmol; 0.8g) in dichloromethane (15ml). Silver trifluoroacetate (3.48mmol; 0.77g) was added in one portion. The mixture was stirred at room temperature (30-45min.) before being filtered through Celite. The filtrate was washed with 20% sodium thiosulphate solution (10ml). The organic layer was dried ($MgSO_4$) and concentrated by the removal of solvent under reduced pressure to give the crude product as a yellow oil (0.08g, 12%).

^{1}H nmr (400MHz) δ : 5.48 (q, J=5.30 Hz, 1H, CH-OO), 4.20 (q, J=6.69 Hz, 1H, CH-O), 1.24 (s, 3H), 1.19 (d, J=5.30 Hz, 3H, CH_3CH-OO), 1.11 (s, 3H), 1.01 (d, J=6.69 Hz, 3H, CH_3CH-O) ppm.
^{13}C nmr (100MHz) δ : 95.04 (C-3), 81.98 (C-6), 76.94 (C-5), 24.38, 18.21, 17.63, 13.09 ppm.

2-Bromo-1-phenylethyl hydroperoxide (253ci)[106]

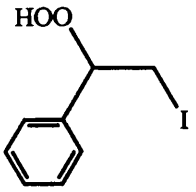


Procedure as for **253a**.
Starting materials : styrene (4mmol; 0.42g), 1,3-Dibromo-5,5-dimethylhydantoin (2mmol;

0.57g), H_2O_2 in ether (20mmol). The reaction gave the crude product as a yellow oil (0.53g, 61%).

^{1}H nmr (200MHz) δ : 8.50 (bs, 1H, **OOH**), 7.39 (s, 5H, aromatic protons), 5.15 (t, J=7.52 Hz, 1H, CHC_6H_5. The signal was expected to be a dd, as this proton is part of an ABX system), 3.73 (dd, J=6.99 Hz, 10.84 Hz, 1H, **H^{a}H^{b}Br**), 3.59 (dd, J=5.75 Hz, 10.84 Hz, 1H, H^a**H^b**Br) ppm.
^{13}C nmr (100MHz) δ : 129.05, 128.67 (2C), 128.62, 127.03 (2C), 86.64 (**C**-OOH), 31.83 (**C**-Br) ppm.
Literature data[106]: ^{1}H nmr δ : 9.0 (hydroperoxy proton), 7.2 (s, phenyl protons), 4.93 (t, methine proton), 3.52 (d, methylene proton), 3.47 (d, methylene proton) ppm.

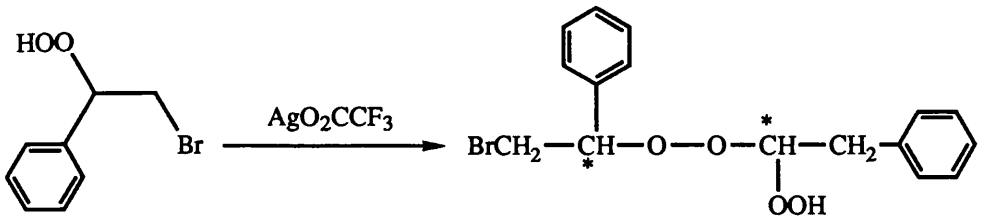
2-Iodo-1-phenylethyl hydroperoxide (253cii)



A solution of styrene (4mmol; 0.42g) and H_2O_2 in ether (25mmol-1ml 85% H_2O_2 in 10ml ether dried over $MgSO_4$) was cooled to -40 °C (CO_2, acetone). The reaction vessel was covered (aluminium foil). N-iodosuccinimide (4mmol; 0.89g) was added with stirring in small portions over 5mins. The reaction vessel was protected by a calcium chloride tube and the mixture was allowed to come to room temperature (20-30min). The mixture was washed with water (3x20ml). The organic extract was washed with 20% sodium thiosulphate solution (10ml) before being dried ($MgSO_4$). Ether was removed under reduced pressure to give the crude product as a yellow oil (0.38g, 36%).

^{1}H nmr (200MHz) δ : 8.30 (bs, 1H, **OOH**), 7.45 (s, 5H, aromatic protons), 5.05 (t, J=7.20 Hz, 1H, CHC_6H_5. The signal was expected to be a dd, as this proton is part of an ABX system), 3.65 (dd, J=6.09Hz, 10.93 Hz, 1H, **H^{a}H^{b}I**), 3.41 (dd, J=5.56 Hz, 10.93 Hz, 1H, H^a**H^b**I) ppm.
^{13}C nmr (100MHz) δ : 128.20 (2C), 127.60, 126.08, 126.00 (2C), 84.84 (**C**-OOH), 14.81 (**C**-I) ppm.

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci, with silver trifluoroacetate

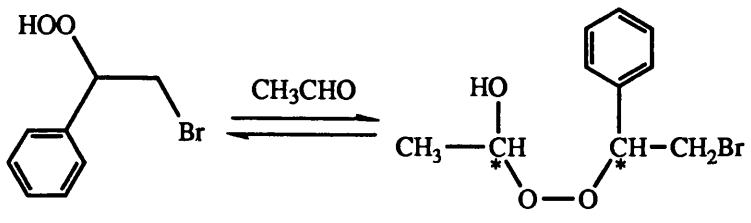


258

2-Bromo-1-phenylethyl hydroperoxide **253ci** (3mmol; 0.8g) in dichloromethane (20ml), was stirred at room temperature for 5-10 mins. Silver trifluoroacetate (3mmol; 0.66g) was added in one portion and the mixture was stirred for a further 45-60 mins. The mixture was filtered through Celite and the filtrate was washed with water (5ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.52) to give a pale yellow liquid. ^1H and ^{13}C nmr spectroscopy indicated that the product was a 1: 1 mixture of starting **253ci** and compound **258**. Further purification by HPLC (column: 2 x 250mm silica gel 5μm, mobile phase: 10% ethyl acetate + 90% hexane, flow rate: 5.0cm^3/ min), gave pure **258** as a creamy coloured solid (0.10g, 9.5%).

nmr signals for 258 (2 diastereoisomers in approx 1:1 ratio)
^1H nmr (400MHz) δ : 7.49-7.15 (m, 10H, aromatic protons), 5.51-5.45 (m, 1H, CH-OOH), 5.25-5.10 (m, 1H, CHC_6H_5), 3.80-3.50 (m, 2H, CH_2Br), 3.00-2.85 (m, 2H, $CH_2C_6H_5$) ppm.
^{13}C nmr (100MHz) δ : 137.01-126.71 (aromatic carbons), [101.03 (CH-OOH) and 100.65 (CH-OOH)], [85.49 (CHC_6H_5) and 85.42 (CHC_6H_5)], [39.57 ($CH_2C_6H_5$) and 39.31 ($CH_2C_6H_5$)], [32.43 (CH_2Br) and 32.19 (CH_2Br)] ppm.
Found: C, 54.03; H, 4.21; Br, 22.03% $C_{16}H_{17}BrO_4$ required: C, 54.41; H, 4.82; Br, 22.64%

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci, with acetaldehyde



254ci

2-Bromo-1-phenylethyl hydroperoxide (3.73mmol; 0.81g) dissolved in $CDCl_3$ (2ml), was treated with acetaldehyde (7.46mmol; 0.33g). The mixture was stirred for 20mins at room temperature and a ^{13}C nmr spectrum was recorded. The product appeared to be a 1: 1 mixture of unchanged **253ci** and two diastereoisomers of hemiperoxyacetal **254ci**.

nmr signals for 253ci
^{13}C nmr (100MHz) δ : 128.91, 128.65 (2C), 128.59, 127.43 (2C), 85.19 (C-OOH), 31.29 (C-Br) ppm.
nmr signals for 254ci (2 diastereoisomers)
^{13}C nmr (100MHz) δ : [129.69 and 128.60], [128.37 and 128.35 (2C)], [128.29 and 128.47], [126.97 and 126.93 (2C)], [97.45 and 97.11 ($CHCH_3$)], [85.27 and 85.25 (CHC_6H_5)], [32.11 and 32.09 (CH_2Br)], [18.39 and 18.24 (CH_3)] ppm.

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci with acetaldehyde and silver trifluoroacetate at room temperature
Acetaldehyde (6.5mmol; 0.29g) was added to a stirred solution of 2-bromo-1-phenylethyl hydroperoxide (3.27mmol; 0.71g) in dichloromethane (20ml). Silver trifluoroacetate (3.27mmol; 0.72g) was added in one portion. The mixture was stirred at room temperature (45min-12hrs). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product as a yellow oil (0.98g). ^1H and ^{13}C nmr spectroscopy showed that no 1,2,4-trioxane formation had occurred and that the main products were a 1: 1 mixture of unchanged **253ci** and two diastereoisomers of hemiperoxyacetal **254ci**.

nmr signals for 253ci
^1H nmr (400MHz) δ : 7.45-7.27 (m, containing signal for 5H, aromatic protons-overlap with other products), 5.18 (dd, J=5.57 Hz, 7.22 Hz, 1H, CHC_6H_5), 3.74 (dd, J=7.22 Hz, 10.92 Hz, 1H, H^aH^bBr, overlaps with one of the diastereoisomers of **254ci**), 3.63 (dd, J=5.57 Hz, 10.92 Hz, 1H, H^aH^bBr, overlaps with one of the diastereoisomers of **254ci**) ppm.
^{13}C nmr (100MHz) δ : 129.03, 128.65 (2C), 128.62, 126.94 (2C), 85.32 (C-OOH), 33.21 (C-Br) ppm.
nmr signals for 254ci (2 diastereoisomers)
^1H nmr (400MHz) δ : [8.21 (s, 1H, OOH) and 8.20 (s, 1H, OOH)], 7.45-7.27 (m, aromatic protons), [5.52 (q, J=5.48 Hz, 1H, $CHCH_3$) and 5.47 (q, J=5.33 Hz 1H, $CHCH_3$)], [5.31 (dd, J=5.26 Hz, 7.79 Hz, 1H, CHC_6H_5) and 5.24 (dd, J=5.75 Hz, 7.18 Hz, 1H, CHC_6H_5)], [3.74 (dd, J=7.22 Hz, 10.92 Hz, 1H, H^aH^bBr, overlaps with

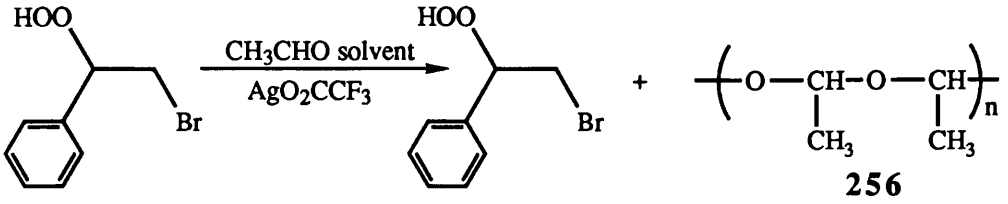
starting **253ci**), 3.63 (dd, J=5.60 Hz, 10.92 Hz, 1H, H^aH^bBr, overlaps with starting **253ci**) and 3.70 (dd, J=7.22 Hz, 10.95 Hz, 1H, H^aH^bBr), 3.64 (dd, J=5.73 Hz, 10.95 Hz, 1H, H^aH^bBr], [1.63 (s, 1H, OH) and 1.62 (s, 1H, OH)], [1.27 (d, J=5.48 Hz, 3H, $CHCH_3$) and 1.23 (d, J=5.33 Hz) 3H, $CHCH_3$)] ppm.
^{13}C nmr (100MHz) δ : [129.48 and 129.07], [128.93 and 128.79 (2C)], [128.73 and 128.48], [126.90 and 126.83 (2C)], [97.79 and 97.24 ($CHCH_3$)], [86.53 and 85.23 (CHPh)], [32.66 and 32.40 (CH_2Br)][18.72 and 18.46 (CH_3)] ppm.
Hetcor pulse sequence was used to confirm these assignments by ^1H/ ^{13}C signal correlations which showed that peaks at δ_H 1.27 and 1.23 correlate with δ_C 18.72 and 18.46; δ_H 5.31 and 5.24 correlate with δ_C 86.53 and 85.23; δ_H 5.52 and 5.47 correlate with δ_C 97.79 and 97.24 and δ_H 3.63-3.74 correlate with δ_C 32.66 and 32.40.

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci with acetaldehyde and silver trifluoroacetate under reflux conditions

Acetaldehyde (12mmol; 0.53g) was added to a stirred solution of 2-bromo-1-phenylethyl hydroperoxide (4mmol; 0.87g) in dichloromethane (20ml). Silver trifluoroacetate (4mmol; 0.83g) was added in one portion and the mixture was heated to reflux with stirring (45min-1hr.). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product as a brown oil (1.05g). ^1H and ^{13}C nmr spectroscopy showed that the reaction was very 'messy' under reflux conditions and a complicated set of signals were obtained. No 1,2,4-trioxane formation was observed although some peaks in the ^1H and ^{13}C nmr spectra did correspond to starting **253ci** and hemiperoxyacetal **254ci**.

^1H nmr (400MHz) main peaks δ : 8.13 (bs, may be due to OOH), 7.41-7.19 (m, aromatic protons), 5.70-5.00 (m, may contain signals for $CHCH_2Br$ of **253ci** and CHC_6H_5 of **254ci**), 3.80-3.65 (m, may contain CH^aH^bBr signals), 3.15-2.75 (m, may contain CH^aH^bBr signals), 1.60 (bs, may be due to OH), 1.50-1.20 (m) ppm.
^{13}C nmr (100MHz) main peaks δ : 129.49-126.47 (aromatic carbons), 104.24-101.47 (may contain the $CHCH_2$ signal for **254ci**), 79.09, 66.13-66.04, 50.58, 39.03-32.54 (may contain signals for CH_2Br), 17.59, 16.29 ppm.

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci with silver trifluoroacetate in acetaldehyde solvent



256

Acetaldehyde (20ml) was added to 2-bromo-1-phenylethyl hydroperoxide (4mmol; 0.87g) at room temperature. Silver trifluoroacetate (4mmol; 0.83g) was added in one portion and the mixture was stirred (45min-1hr.). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure. No 1,2,4-trioxane formation was detected from nmr spectroscopy. The main products of the reaction were acetaldehyde polymer **256** and some unchanged hydroperoxide **253ci**.

nmr signals for 253ci

^{1}H nmr (200MHz) δ : 8.61 (bs, **OOH**), 7.45 (s, 5H, aromatic protons), 5.13 (t, J=7.46 Hz, 1H, **CH**C_6H_5. The signal was expected to be a dd, as this proton is part of an ABX system), 3.69 (dd, J=6.85Hz, 10.93 Hz, 1H, **H^{a}H^{b}Br**), 3.52 (dd, J=5.35 Hz, 10.93 Hz, 1H, H^a**H^b**Br) ppm.

^{13}C nmr (100MHz) δ : 129.15, 128.87 (2C), 128.72, 127.13 (2C), 86.44 (C-OOH), 32.83 (C-Br) ppm.

nmr signals for acetaldehyde polymer 256

^{1}H nmr (200MHz) δ : 5.03 (q, J=5.15 Hz, 1H, **CH**CH_3), 1.37 (d, J=5.15 Hz, 3H, $CHCH_3$)

^{13}C nmr (100MHz) δ : 99.35 ($CHCH_3$), 20.50 ($CHCH_3$) ppm.

Treatment of acetaldehyde with trifluoroacetic acid

Acetaldehyde (0.2g) was dissolved in $CDCl_3$ (3ml) in an nmr tube. A drop of trifluoroacetic acid was added and the mixture was shaken in the tube. After 10 mins ^{1}H and ^{13}C nmr spectra were recorded. The main product was acetaldehyde polymer **256**.

^{1}H nmr (400MHz) δ : 5.13 (q, J=5.22 Hz, 1H, **CH**CH_3), 1.47 (d, J=5.22 Hz, 3H, $CHCH_3$)

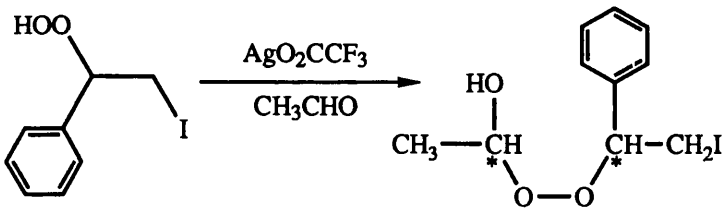
^{13}C nmr (100MHz) δ : 98.45 ($CHCH_3$), 21.60 ($CHCH_3$) ppm.

Reaction of 2-bromo-1-phenylethyl hydroperoxide 253ci with acetaldehyde and silver tetrafluoroborate at room temperature

Acetaldehyde (4mmol; 0.18g) was added to a stirred solution of 2-bromo-1-phenylethyl hydroperoxide (1.87mmol; 0.4g) in dichloromethane (15ml). Silver tetrafluoroborate (1.87mmol; 0.36g) was added in one portion at -70 °C (CO_2, acetone). The mixture was allowed to come to room temperature with stirring (45min-1hr). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil (0.5g). The reaction did not produce a 1,2,4-trioxane and the ^1H nmr spectrum showed a complicated set of signals which may have contained peaks corresponding to **253ci** and some hemiperoxyacetal **254ci** (2 diastereoisomers).

^1H nmr (200MHz) main peaks δ : 8.12 (bs, **OOH**), 7.61-7.20 (m, aromatic protons), 5.55-5.10 (m, may contain signals for $CHCH_2Br$ of starting **253ci** and CHC_6H_5, $CHCH_3$ of hemiperoxyacetal **254ci**), 3.88-3.30 (m, signals for CH_2Br for both **253ci** and **254ci**), 1.50-1.10 (m), 1.72 (s, may be **OH**) ppm.

Reaction of 2-iodo-1-phenylethyl hydroperoxide 253cii with acetaldehyde and silver trifluoroacetate at room temperature



254cii

Acetaldehyde (4.32mmol; 0.19g) was added to a stirred solution of 2-iodo-1-phenylethyl hydroperoxide (1.44mmol; 0.38g) in dichloromethane (15ml).The reaction vessel was covered (aluminium foil). Silver trifluoroacetate (1.44mmol; 0.32g) was added in one portion. The mixture was stirred at room temperature (45min-1hr). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure. From ^{13}C nmr spectroscopy, the main products detected appeared to be a 1: 1 mixture of unchanged **253cii** and two diastereoisomers of hemiperoxyacetal **254cii**. No 1,2,4-trioxane formation was observed.

nmr signals for 253cii

^{13}C nmr (100MHz) δ : 129.42-126.88 (aromatic carbons), 86.85 (**C**-OOH), 14.21 (**C**-I)

ppm.

nmr signals for 254cii (2 diastereoisomers)

^{13}C nmr (100MHz) δ : 129.42-126.88 (aromatic carbons), [96.45 ($CHCH_3$) and 96.39 ($CHCH_3$)], [85.49 (CHC_6H_5) and 85.21 (CHC_6H_5)], [18.72 (CH_3) and 18.43 (CH_3)], [13.66 (CH_2I) and 14.05 (CH_2I)] ppm.

Reaction of 2-iodo-1-phenylethyl hydroperoxide 253cii with acetaldehyde and silver tetrafluoroborate at room temperature

Procedure as for reaction of 2-bromo-1-phenylethyl hydroperoxide with acetaldehyde and silver tetrafluoroborate.

Starting materials : 2-iodo-1-phenylethyl hydroperoxide (1.5mmol; 0.39g), acetaldehyde (4mmol; 0.18g), silver tetrafluoroborate (1.5mmol; 0.3g). The crude product was obtained as a yellow oil (0.53g). The reaction was 'messy' and a complicated set of peaks were observed in the ^{13}C nmr spectrum. No 1,2,4-trioxane formation was detected, but signals corresponding to two diastereoisomers of hemiperoxyacetal **254cii** were present.

^{13}C nmr (100MHz) main peaks δ : 129.39-127.39 (aromatic carbons), [96.35 ($CHCH_3$) and 96.25 ($CHCH_3$)], [85.37 (CHC_6H_5) and 85.24 (CHC_6H_5)], [18.81 (CH_3) and 18.72 (CH_3)], [13.92 (CH_2I) and 14.22 (CH_2I)] ppm.

Reaction of 2-iodo-1-phenylethyl hydroperoxide 253cii with acetaldehyde and silver(I) oxide at room temperature

Acetaldehyde (3.4mmol; 0.15g) was added to a stirred solution of 2-iodo-1-phenylethyl hydroperoxide (1.17mmol; 0.31g) in dichloromethane (15ml).The reaction vessel was covered (aluminium foil). Silver(I) oxide (1.17mmol; 0.27g) was added in one portion. The mixture was stirred at room temperature (12hrs). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure. The ^{13}C and ^{1}H nmr spectra were complicated and we were unable to identify the products.

^{1}H nmr (400MHz) main peaks δ : 7.35-7.26 (m, aromatic protons), 5.02 (m), 3.80-3.83 (m), 2.67 (s), 1.36 (d, J=5.12 Hz), 1.2-1.3 (m) ppm.

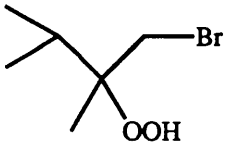
^{13}C nmr (100MHz) main peaks δ : 134.43-125.39 (aromatic carbons), 86.79 (may be CHPh), 74.56, 67.93, 52.33, 51.17, 29.44, 20.47, 5.13 ppm.

Reaction of 2-iodo-1-phenylethyl hydroperoxide 253cii with acetaldehyde and sodium hydride at room temperature

Acetaldehyde (4.5mmol; 0.2g) was added to a stirred solution of 2-iodo-1-phenylethyl hydroperoxide (1.5mmol; 0.39g) in dichloromethane (15ml).The reaction vessel was covered (aluminium foil). Nitrogen gas was bubbled through the reaction vessel. Sodium hydride in tetrahydrofuran (5ml) was transferred to the reaction vessel. The mixture was stirred at room temperature (45min-1hr). The mixture was filtered through celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil (0.5g). The ^1H and ^{13}C nmr spectra were complicated. No 1,2,4-trioxane formation was detected and we were unable to identify any of the products.

^1H nmr (400MHz) main peaks δ : 7.26-7.22 (m, aromatic protons), 5.16 (s), 4.98 (m), 3.37-3.25 (m), 1.26 (d, J=5.18 Hz), 1.16 (d, J=5.46 Hz), 1.12 (d, J=5.52 Hz) ppm.
^{13}C nmr (100MHz) main peaks δ : 141.12-125.69 (aromatic carbons), 73.96, 29.65, 15.29 ppm.

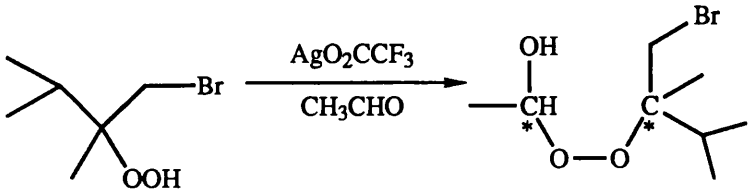
1-Bromo-2,3-dimethyl-2-butyl hydroperoxide (253d)



Procedure as for **253a**.
Starting materials : 2,3-dimethylbut-1-ene (5mmol; 0.42g), 1,3-dibromo-5,5-dimethylhydantoin (2.5mmol; 0.71g), H_2O_2 in ether (25mmol). The reaction gave the crude product as a yellow oil (0.84g, 85%).

^1H nmr (200MHz) δ : 7.23 (bs, OOH), 3.45 (d, J=6.55 Hz, 1H, H^aH^bBr), 3.61 (d, J=6.55 Hz, 1H, H^aH^bBr), 2.04 (m, 1H, $CH(CH_3)_2$), 1.14 (s, 3H, CH_3COOH), 0,93 (d, J=6.91 Hz, 3H), 0,86 (d, J=6.91 Hz, 3H) ppm.
^{13}C nmr (100MHz) δ : 84.82 (C-OOH), 38.34 (C-Br), 31.40 ($CH(CH_3)_2$), 17.64, 16.78, 15.34 ppm.

Reaction of 1-bromo-2,3-dimethyl-2-butyl hydroperoxide 253d, with acetaldehyde and silver trifluoroacetate at room temperature

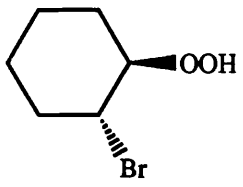


254d

Procedure as for the reaction of **253a** with acetaldehyde and silver trifluoroacetate.
Starting materials : 1-bromo-2,3-dimethyl-2-butyl hydroperoxide (3.3mmol; 0.65g), acetaldehyde (6.6mmol; 0.3g), silver trifluoroacetate (3.3mmol; 0.72g). The crude product was obtained as a yellow oil (0.7g). No 1,2,4-trioxane formation was detected by ^{13}C nmr spectroscopy and the main products appeared to be two diastereoisomers of hemiperoxyacetal **254d** and some starting **253d**.

nmr signals for 253d
^{13}C nmr (100MHz) δ : 84.60 (**C**-OOH), 39.44 (**C**-Br), 31.78 ($CH(CH_3)_2$), 17.55, 16.82, 15.95 ppm.
nmr signals for 254d (2 diastereoisomers)
^{13}C nmr (100MHz) δ : [97.09 ($CHCH_3$) and 96.95 ($CHCH_3$)], [84.98 (CCH_2Br) and 84.64 (CCH_2Br)], [39.75 (CH_2Br) and 39.45 (CH_2Br)], [31.71 ($CH(CH_3)_2$ and 31.58 ($CH(CH_3)_2$], [20.63 and 20.44], [18.61 and 18.51], [16.69 and 16.51], [15.71 and 15.30] ppm.

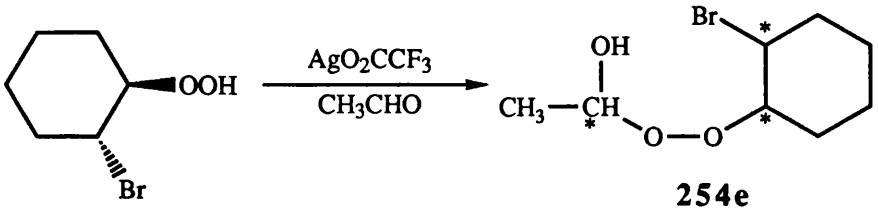
***trans*-2-Bromocyclohexyl hydroperoxide (253e)**[106]



Procedure as for **253a**
Starting materials : cyclohexene (5mmol; 0.41g), 1,3-dibromo-5,5-dimethylhydantoin (2.5mmol; 0.71g), H_2O_2 in ether (25mmol). The reaction gave the crude product as a yellow oil (0.83g, 85%).
^{1}H nmr (200MHz) δ : 8.25 (bs, OOH), 4.15-3.54 (m, 2H, CHOOH, CHBr), 2.51-1.31 (broad, multiplet, 8H, protons of ring) ppm.

Literature data[106]: ^{1}H nmr δ : 8.96 (broad singlet for hydroperoxy proton), 4.2 (m, methine protons), 2.6-1.0 (broad multiplet for methylene protons of ring) ppm.

Reaction of trans-2-bromocyclohexyl hydroperoxide 253e with acetaldehyde and silver trifluoroacetate at room temperature



254e

Acetaldehyde (35mmol; 1.56g) was added to a stirred solution of trans-2-bromocyclohexyl hydroperoxide (8mmol; 1.56g) in dichloromethane (20ml). Silver trifluoroacetate (8mmol; 1.77g) was added in one portion. The mixture was stirred at room temperature (45min-1hr). The mixture was filtered through Celite and washed with water (10ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil (2.1g). The ^{13}C and ^{1}H nmr spectra were very complicated. No 1,2,4-trioxane formation was detected but the appearance of at least two isomers of hemiperoxyacetal **254e** was thought to be observed.

^{1}H nmr (400MHz) δ : [5.48 (q, J=5.46 Hz, 1H, **C**HCH$_3$) and 5.43 (q, J=5.46 Hz, 1H, **C**HCH$_3$)], 4.21-3.92 (complex multiplet which may contain signals for **C**HBr and C_{ring}HOO), 2.40-2.15 (complex multiplet containing signals for ring protons), 1.85-1.10 (complex multiplet containing signals for ring protons) ppm.
^{13}C nmr (100MHz) δ : main peaks 131.29 (suggests some unsaturation), [97.66 (**C**HCH$_3$) and 96.69 (**C**HCH$_3$)], [86.54 and 85.79 (C_{ring}O-O)], 51.55, [35.49 (**C**-Br) and 34.99 (**C**-Br)], 29.04, 25.27, 25.19, 24.92, 23.15, 23.04, 22.98, 21.59, 20.71, 20.54, [18.57 and 18.39 (CH$_3$)] ppm.

See p219

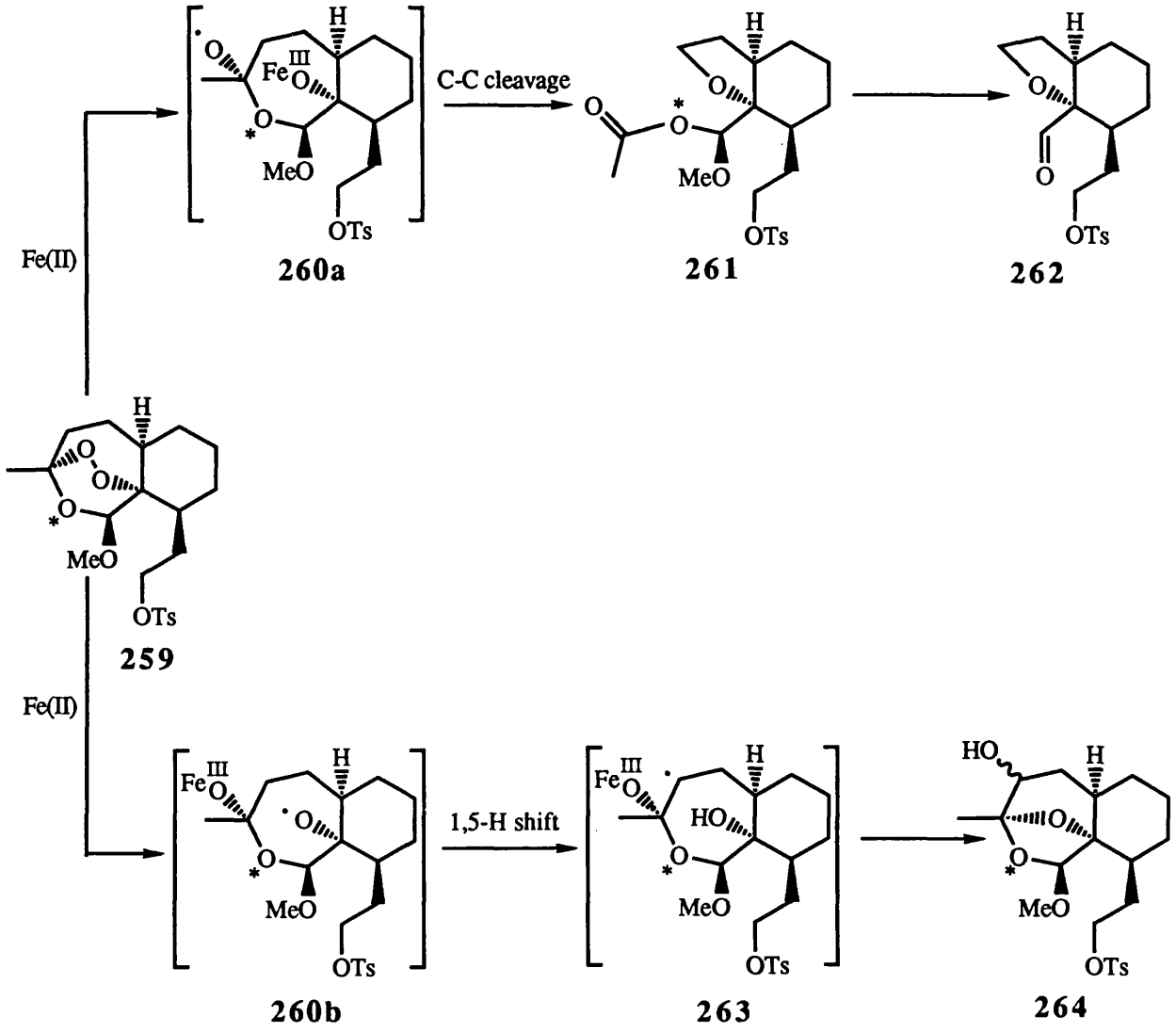
SOME REACTIONS OF 1,2,4-TRIOXANES: PHOTOLYSIS AND REACTION WITH IRON(II) SULFATE

6.1 Introduction

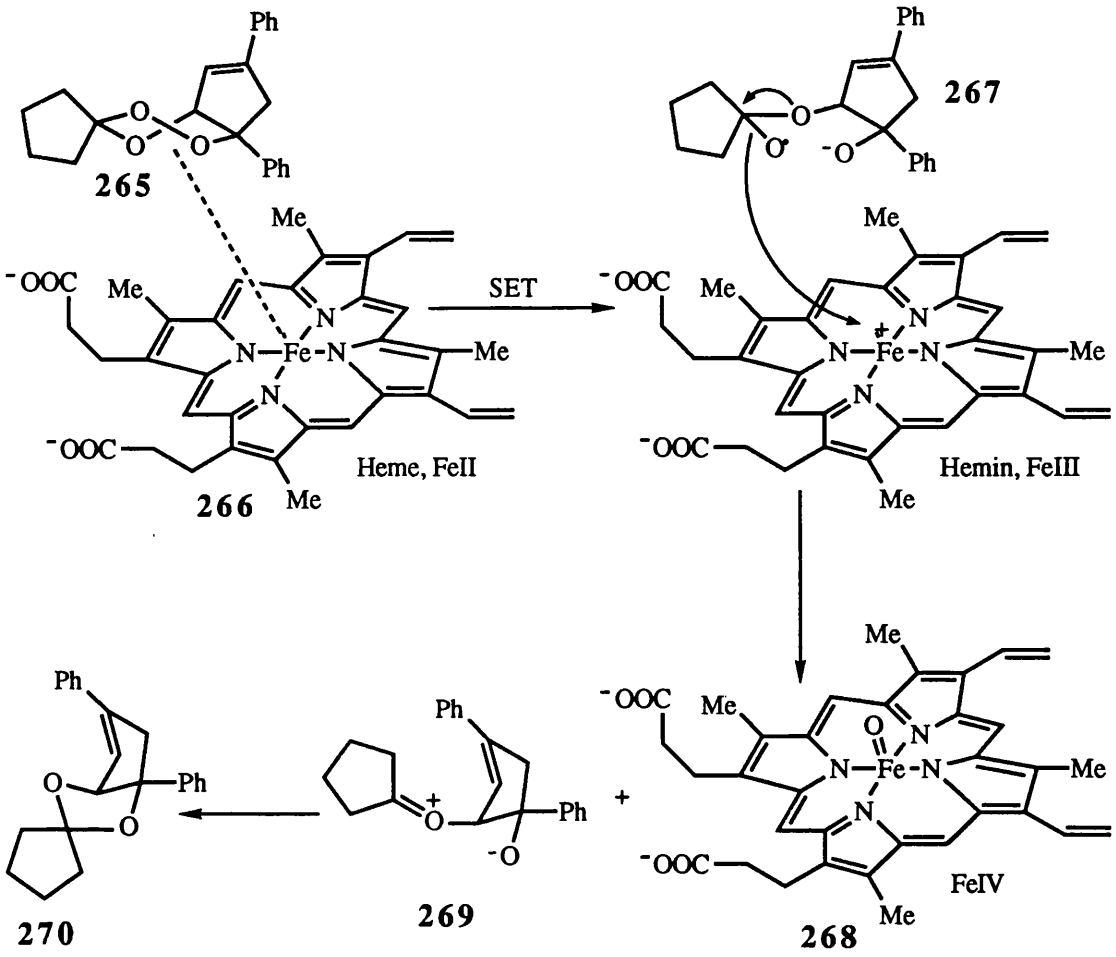
Intraerythrocytic malaria parasites digest hemoglobin as a food source. The discarded prosthetic group heme, is soluble and toxic to the host. Normally detoxification is effected by oxidative polymerisation to innocuous hemozoin. Antimalarial drugs such as chloroquine, quinine and artemisinin seem to act by potentiating the toxicity of heme (see chapter 1). Current understanding of artemisinin activity invokes hemin-catalysed reduction of the trioxane unit as the key step converting it into one or more cytotoxic compounds that kill malaria parasites[118]. It has been suggested that these cytotoxic compounds could be oxygen-centred radicals[3]. Accordingly there is much interest in studying the reaction of model 1,2,4-trioxanes with iron(II) reagents.

Posner *et al*[7] treated trioxane tosylate (**259**) with two different sources of ferrous ions to simulate the hemin-catalysed cleavage of the trioxane unit in artemisinin. Iron(II)-induced cleavage of the peroxide bond in **259** led to radical intermediates (**260a**) and (**260b**) in about a 2:1 ratio. Carbon-carbon bond cleavage of **260a** initially produced labile ring-contracted tetrahydrofuran acetal (**261**) with ^{18}O located in the acetoxy group and then produced stable electrophilic tetrahydrofuran aldehyde (**262**) lacking ^{18}O. 1,5-Hydrogen atom abstraction in radical intermediate **260b** ultimately led to stable dioxolane alcohol (**264**), as a mixture of the two diastereoisomers *via* (**263**) (Scheme 130).

Jefford *et al*[27] investigated the reaction of 1,2,4-trioxane (**265**) with heme. They proposed that the antimalarial potency of **265**, was due to its ability to adopt a twist conformation so that it could efficiently complex with the ferrous ion of heme (**266**) (Scheme 131). Subsequent single electron transfer (SET) from the ferrous ion to the low-lying σ^* O-O bond of **265** resulted in its cleavage to the radical anion (**267**), which then transferred an atom of oxygen to the new ferric ion to create the ferryl iron-oxene intermediate (**268**). Meanwhile the deoxygenated intermediate (**269**) closed to the 1,3-dioxolane (**270**).

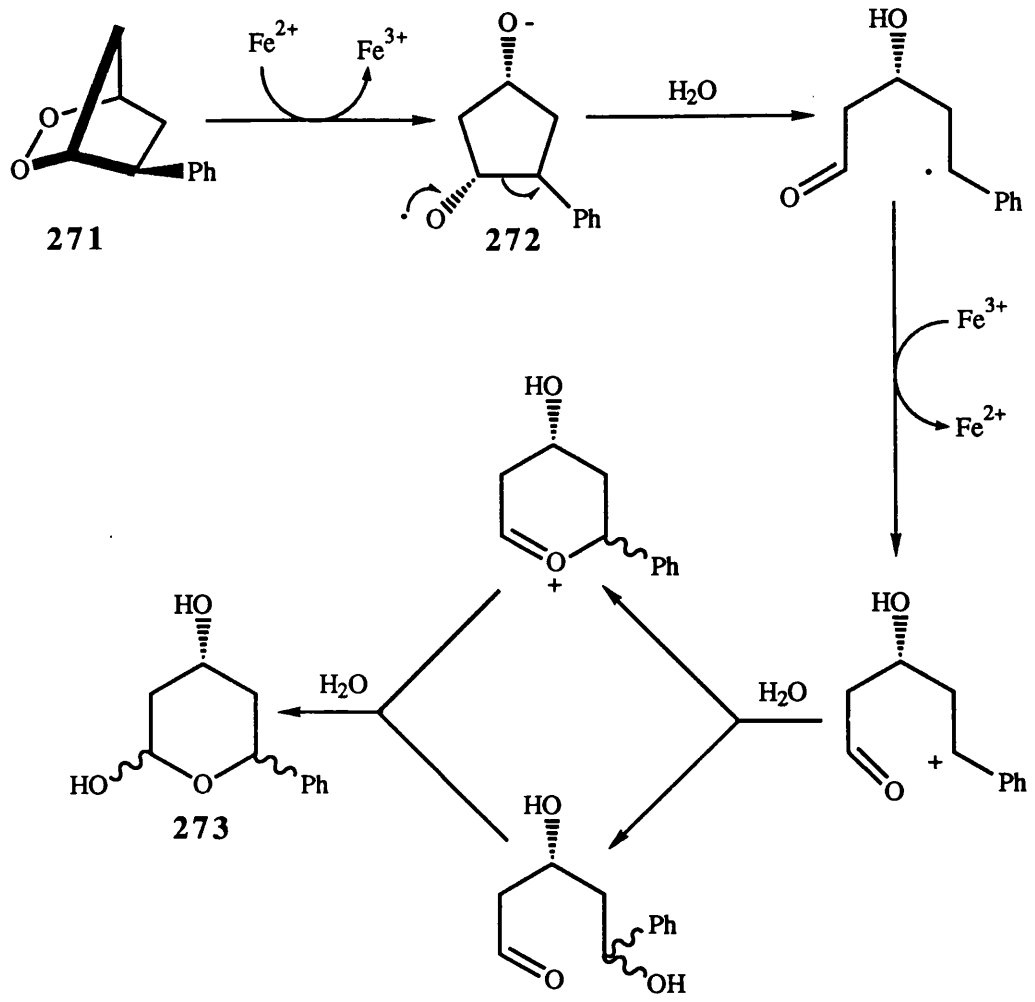

C-C cleavage
Fe(II)
Fe(II)
1,5-H shift
MeO
OTs
HO
260a
261
262
259
260b
263
264
{where *O = 18O}

Scheme 130



Scheme 131

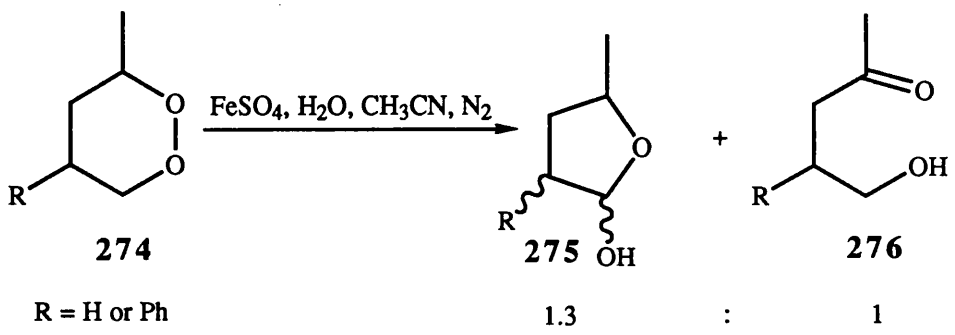
The reactions of other cyclic peroxides with electron transfer reagents such as iron(II) salts, have been extensively studied and provide useful background information. An example of such a reaction was carried out by Kishi and Takahashi[119, 120]. They treated endoperoxide (**271**) with iron(II) sulfate in aqueous acetonitrile under nitrogen (Scheme 132).



Scheme 132

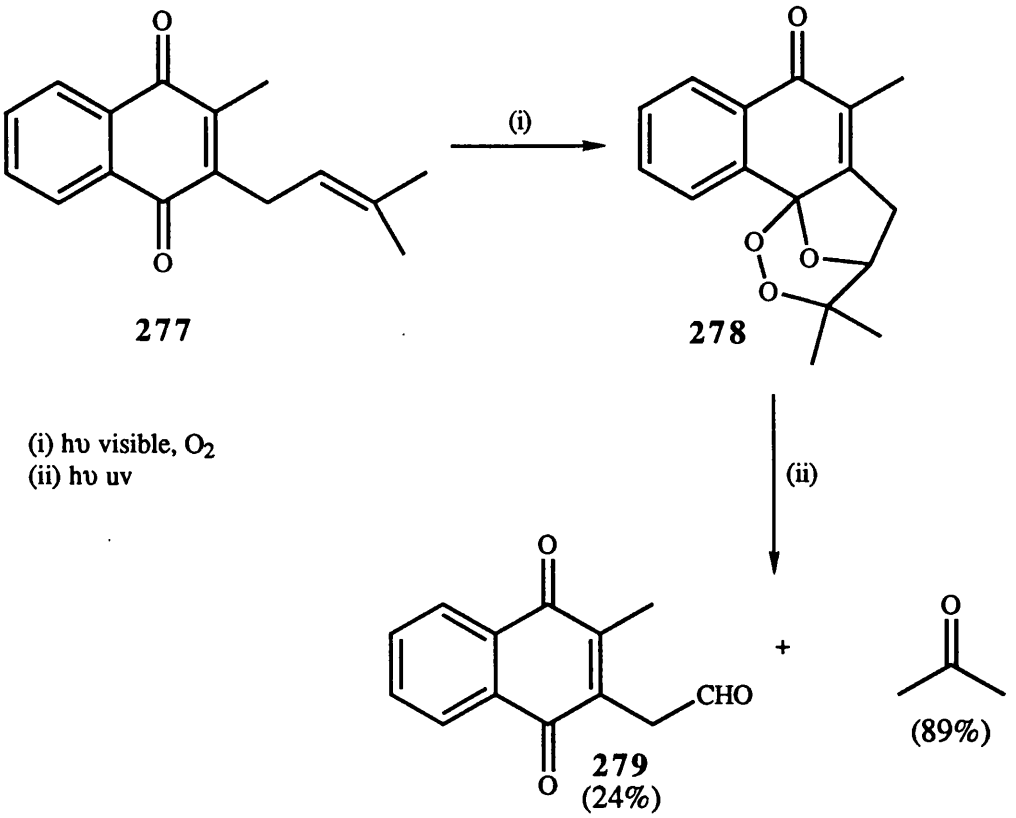
The reaction was initiated by electron supply from Fe^{II} to **271**. The formation of **(273)** involved the prior formation of radical anion **(272)** by a Fe^{II}-Fe^{III} process initially hypothesised by Turner and Hertz[121].

Under similar conditions Curtis[122] treated monocyclic 1,2-dioxanes **(274)** with iron(II) sulfate. In this case a mixture of two 1,5-hydrogen transfer products **(275)** and **(276)** were isolated in approx 1:1 ratio (Scheme 133).



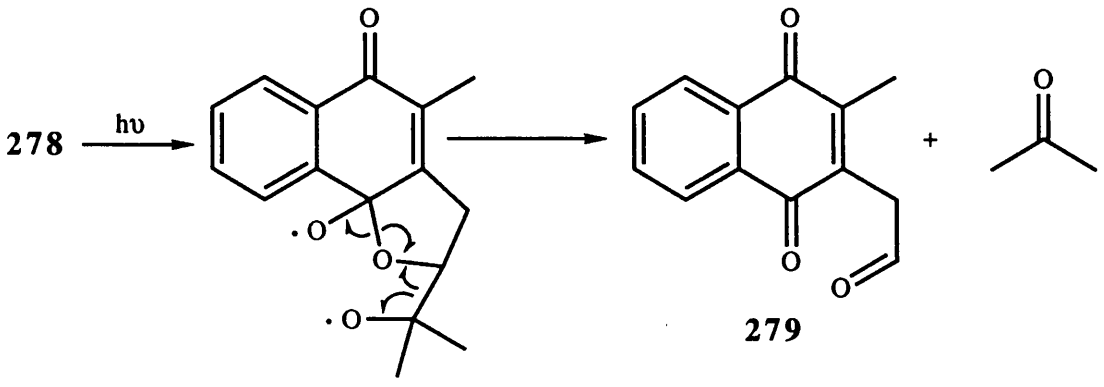
Scheme 133

Studies on the thermal decomposition reactions of artemisinin have shown it to be surprisingly stable when heated neat up to 200 °C[123,124], and when heated in neutral solvents up to 150 °C[125]. Beyond these temperatures thermal decomposition was observed as a result of cleavage of the peroxide bridge. Very little work has been carried out on the photolysis reactions of these types of compounds. In fact only one example of 1,2,4-trioxane photolysis was found in the literature[14]. Wilson and coworkers[14] isolated 1,2,4-trioxane (**278**) from the photooxidation reaction of menaquinone-1, a vitamin K homologue (see chapter 1, method 2). Irradiation of **278** with the ultraviolet output of an argon laser resulted in the formation of acetone and aldehyde (**279**) (Scheme 134).

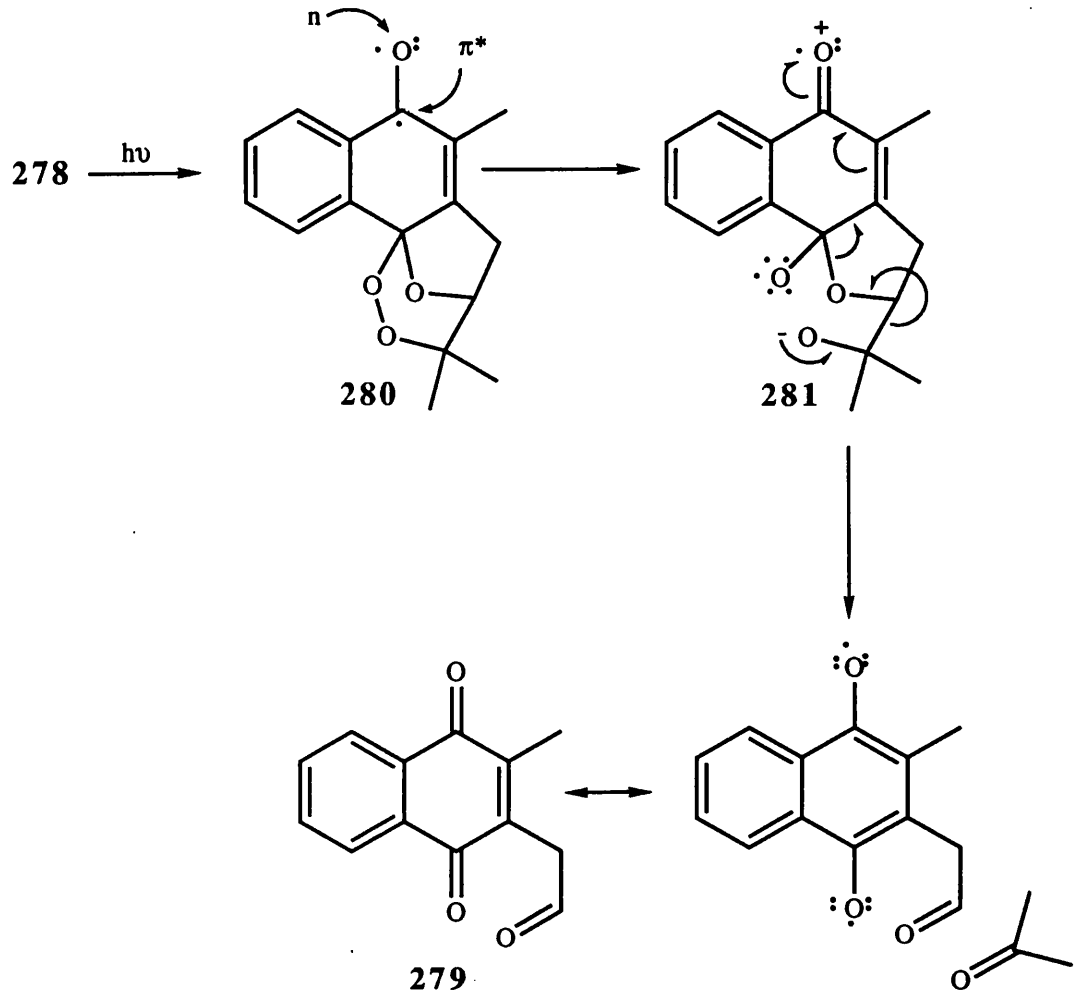


Scheme 134

The products of this photodecomposition may have arisen by a simple six-centred fragmentation (Scheme 135) or an electron-transfer process (Scheme 136).



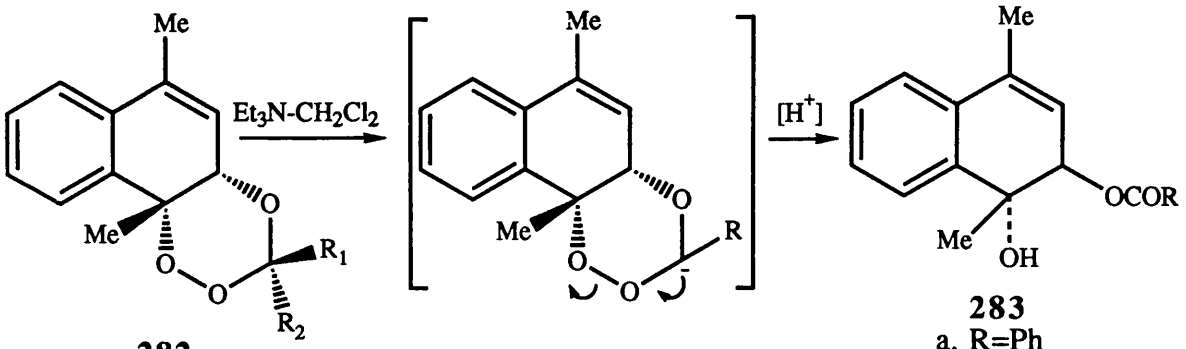
Scheme 135



Scheme 136

Thus, excitation of the dienone chromophore to the n,π* excited state (**280**) might provide a readily available π* electron for donation to the peroxide. Electron transfer from the excited carbonyl to the peroxide linkage would result in the charge separated species (**281**), which would be expected to fragment to quinone aldehyde compound **279**. These results clearly established 1,2,4-trioxanes as intermediates in the photodegradation of vitamin K.

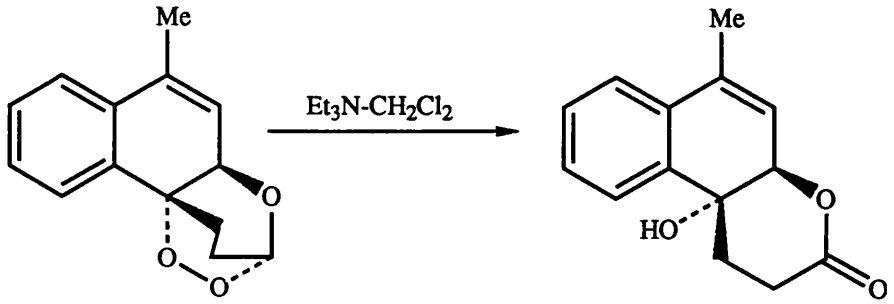
Jefford *et al*[126] reported a further reagent-induced cleavage reaction of 1,2,4-trioxanes. They found that compounds (**282**) and (**284**) with a hydrogen at the C-3 position, underwent scission of the O-O bond on treatment with triethylamine to give potentially useful 1,2-diol monoesters (**283**) (Scheme 137) and lactones (**285**) (Scheme 138). The reactions proceeded by abstraction of the C-3 proton followed by carbonyl-forming elimination. This is just a new example of the well known Kornblum-de la Mare[127] reaction of secondary alkyl peroxides with base.



282
a. R_1=H, R_2=Ph
b. R_1=Me, R_2=H
c. R_1=R_2=H

283
a. R=Ph
b. R=Me
c. R=H

Scheme 137



284 **285**

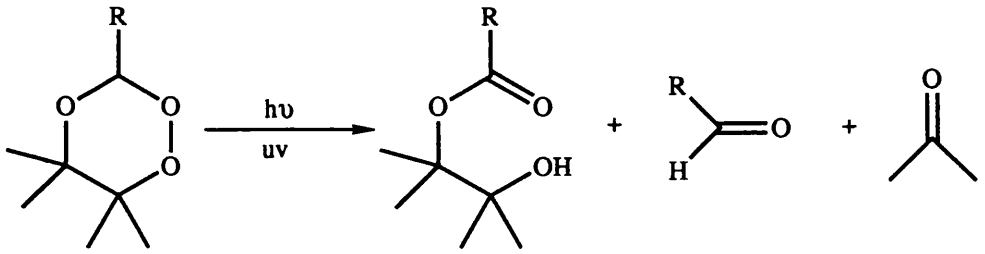
Scheme 138

We decided to investigate the photolysis of our new 1,2,4-trioxanes and also their reactions with iron(II) sulfate to simulate the biologically important hemin-catalysed cleavage of the 1,2,4-trioxane ring in artemisinin[118].

6.2 Results and Discussion

6.2.1 Photolysis of 1,2,4-trioxanes

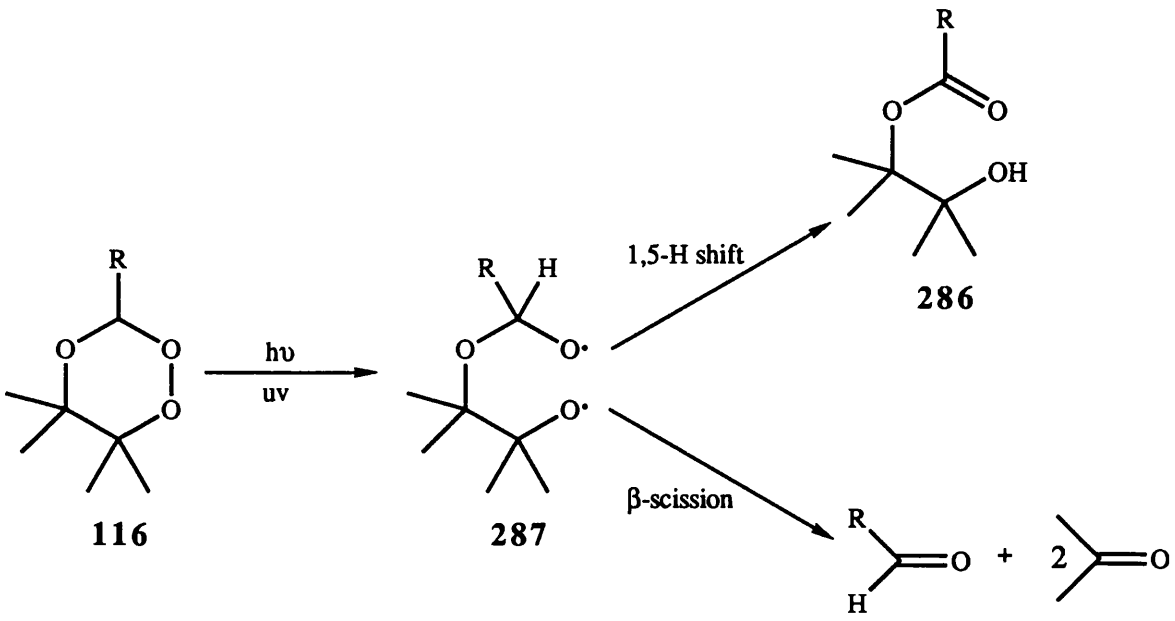
Scheme 139 shows the products obtained upon photodecomposition of some 1,2,4-trioxanes **116** which were synthesised by the intramolecular oxymercuriation route (chapter 2).



116 **286**

Scheme 139

1,2,4-Trioxanes **116** were dissolved in deuteriochloroform and placed in nmr tubes. The tubes were attached directly to a Hanovia medium vapour mercury lamp with a uv output of 2.8W. The samples were all irradiated simultaneously so that comparitive reaction times are meaningful. The tubes were moved to different positions around the mercury lamp at hourly intervals to ensure uniform irradiation. Direct photolysis of compounds **116**, was followed by ^{1}H nmr spectroscopy until all of the starting 1,2,4-trioxanes were consumed. The main products of the photodecomposition reactions were 2,3-dimethylbutan-2,3-diol monoesters (**286**) (see table 11). Some acetone and aldehyde side products were also detected. The ratio of **286**: acetone: aldehyde formation, as judged by ^{1}H nmr spectroscopy, was found to be approximately 10:1:0.5. Thus 1,5-hydrogen shift as opposed to β-scission was the major pathway for the demise of dioxyl radicals (**287**) formed by the O-O homolysis of **116** (Scheme 140).



Scheme 140

The time taken for complete consumption of starting material varied according to the nature of the R group in the starting 1,2,4-trioxanes **116**. The aromatic compound **116i** required the longest irradiation time and compounds with larger R groups seemed to require longer exposures than those with smaller R groups. Pure 2,3-dimethylbutan-2,3-diol monoesters **286** were isolated analytically pure by simple column chromatography (SiO_2, CH_2Cl_2) in yields ranging from 16-28.6% (table 11).

Table 11

Percentage yields and reaction times for **286** formation by photolysis

Starting 1,2,4-trioxanes	R group	Reaction time (hrs) *	Percentage yields for **286** (%) +
116a	Me	2	28.6
116b	Et	3	22
116c	Pr	6	16
116i	C_6H_5	10	22

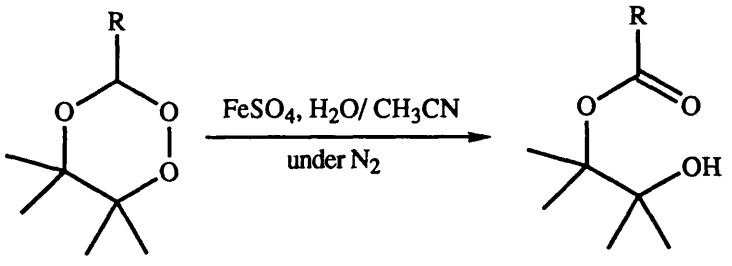
* For complete consumption of starting 1,2,4-trioxane.

+ Isolated and pure.

As far as we are aware, the photodecomposition of Wilson's[14] Menaquinone-1-derived 1,2,4-trioxane **278** (see scheme 134) and the photolysis of our 1,2,4-trioxanes are the only studies of such reactions. The cleavage of 1,2,4-trioxanes by photolysis is a viable alternative to Jefford's[126] earlier base-induced cleavage (see scheme 137).

6.2.2 The reaction of 1,2,4-trioxanes with iron(II) sulfate

Scheme 143 shows the products obtained from the reaction of some 1,2,4-trioxanes with iron(II) sulfate under conditions similar to those applied previously to 1,2-dioxanes[119,120,122].



116 **286**

Scheme 141

The only products detected were 2,3-dimethylbutan-2,3-diol monoesters **286**, which were isolated analytically pure by simple column chromatogaphy (SiO_2, CH_2Cl_2) in yields ranging from 35-50% (table 12). The times taken for the complete consumption of starting material were considerably longer than in the previous photodecomposition reactions, eg **286c** was obtained after 12 hrs by the iron(II) sulfate route but was formed in just 6 hrs by the photodecomposition method. However the overall yields of **286** were much improved by the iron(II) method, eg for **286c** from 16% (photolysis route) to 35% (iron(II) sulfate route).

Table 12

Percentage yields and reaction times for **286** formation by iron(II) sulfate route

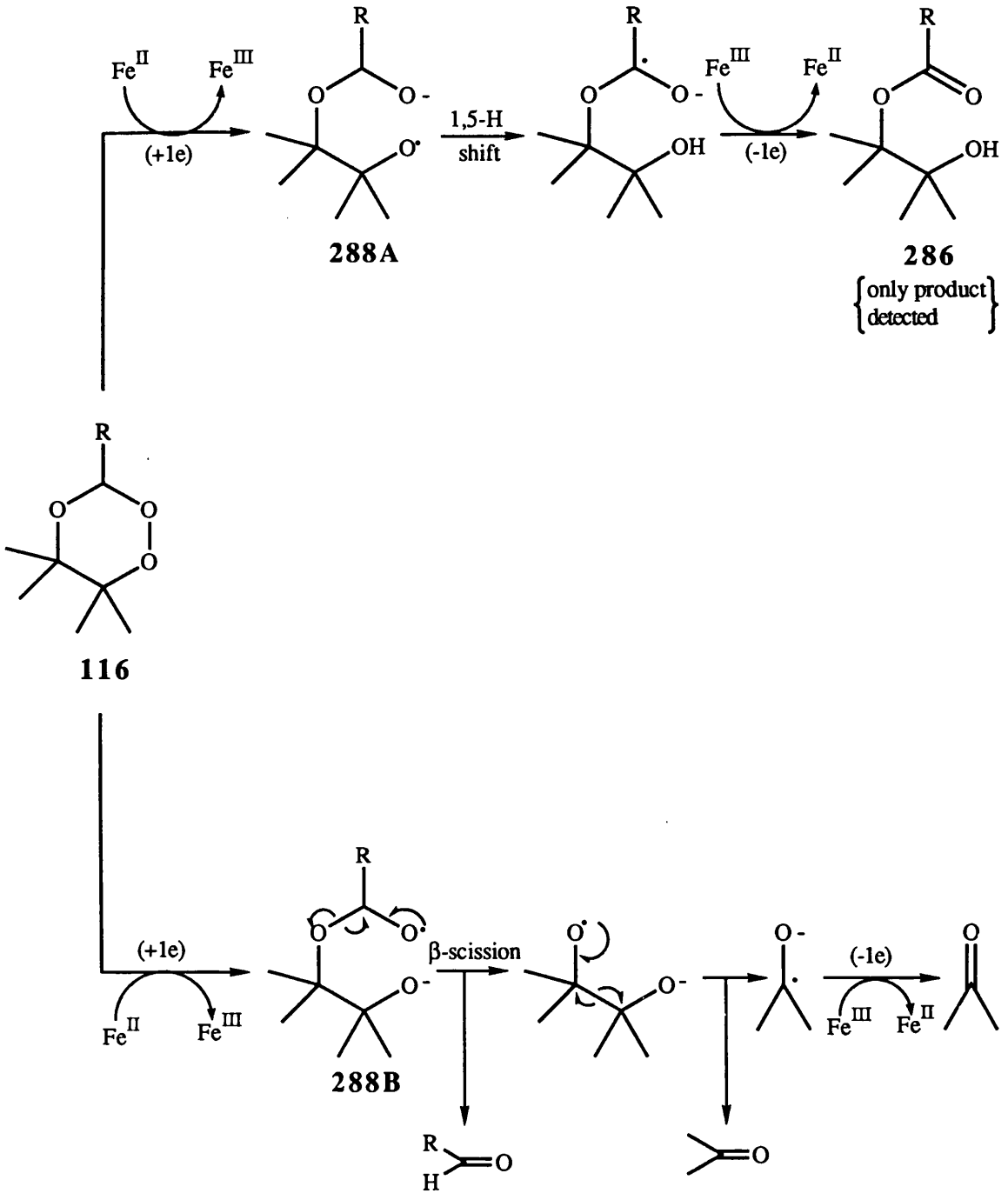
Starting 1,2,4-trioxanes	R group	Reaction time (hrs) *	Percentage yields of **286** (%) +
116a	Me	12	73[a]
116c	Pr	12	35
116e	^{t}Bu	72	50
116g	2-$NO_2C_6H_4$	48	50
116h	4-ClC_6H_4	48	50

[a] Crude product.

+ Isolated and pure.

* For complete consumption of starting 1,2,4-trioxane.

The iron(II)-induced decompositions were probably initiated by electron transfer from Fe^{II} to **116** resulting in the formation of intermediate radical anion **(288)** (Scheme 142). Volatile products which could have resulted by a β-scission route (also illustrated in scheme 142), such as acetone and an aldehyde, were not detected at all, although they may have been lost in the work-up procedure. However as no aromatic aldehydes were detected from the reaction of aromatic 1,2,4-trioxanes with iron(II) sulfate, we concluded that no β-scission had occurred, as aromatic aldehydes are not volatile and would not have been lost in the work-up procedure.



Scheme 142

It should be noted that the radical anion **288B** cannot give 1,5-H shift although **288A** can give competitive β-scission. 1,5-Hydrogen shift as opposed to β-scission was the major pathway.

6.2.3 Key nmr features for 2,3-dimethylbutan-2,3-diol monoesters

The formation of diol monoesters **286** by both the photolysis and iron(II)-induced routes was confirmed by ^{1}H and ^{13}C nmr spectroscopy. The key signals for **286** in the proton spectrum were a broad singlet between δ 3.80-3.30 for the **OH** group and the appearance of two sharp singlets between δ 1.64-1.38 and δ 1.30-1.09 for the two **Me_2** groups. In the ^{13}C nmr spectrum the **C**=O signal appeared at δ 174.79–164.28 and the **C**-O-C=O signal was observed at δ 91,45–88.80. Another key signal due to **C**-OH appeared between δ 75.05-74.48.

6.3 Conclusion

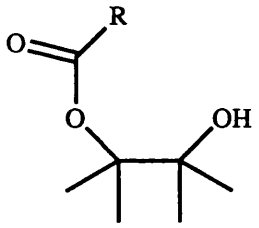
The iron(II)-induced route to 2,3-dimethylbutan-2,3-diol monoesters **286** gave much higher yields and fewer side products than the photolysis route.

Many natural products contain diol monoester[126] entities, but with the exception of Jefford's[126] synthesis of 1,2-diol monoesters by the base-induced cleavage of bicyclic 1,2,4-trioxanes, very few useful routes to these compounds were found in the literature. Thus both photolysis and iron(II)-induced cleavage reactions of 1,2,4-trioxanes offer a potentially useful approach to diol monoester compounds.

These preliminary experiments confirm that simple 1,2,4-trioxanes react with an inorganic iron(II) salt, albeit slowly, to give products that can be rationalised as arising by an electron transfer process. Much more work will have to be done to establish if this observation is relevant to the antimalarial activity of these compounds.

6.4 Experimental

Preparation of 2,3-dimethylbutan-2,3-diol monoesters (286) from 1,2,4-trioxanes



286a (R=Me)

1) Photodecomposition of 116a

A solution of **116a** (4.38mmol; 0.70g) dissolved in deuteriochloroform (2.5ml), was placed in an nmr tube. The tube was irradiated at 20 °C with a Hanovia medium vapour mercury lamp of uv output 2-8W. The tube was moved to different positions around the mercury lamp at hourly intervals to ensure uniform irradiation. The reaction was followed by proton nmr spectroscopy (60MHz) until all the trioxane was consumed (2hrs). The solvent was removed under reduced pressure to give the crude product as a yellow oil. Purification by simple column chromatography (SiO_2, CH_2Cl_2 R_f 0.54) gave the pure product as a colourless liquid (0.20g, 28.6%).

^{1}H nmr (400 MHz) : δ 3.40 (bs, 1H, **OH**), 1.96 (s, 3H, **CH_3**C=O), 1.41 (s, 6H, **Me_2**), 1.13 (s, 6H, **Me_2**) ppm.
^{13}C nmr (100 MHz) : δ 171.24 (**C**=O), 89.04 (**C**-O-C=O), 74.48 (**C**-OH), 24.78 (2C), 22.29, 21.49 (2C) ppm.
Literature data[128]: ^{1}H nmr δ 3.26 (s, 1H, D_2O exchange), 1.95 (s, 3H), 1.4 (s, 6H), 1.3 (s, 6H) ppm.
Found: C, 59.44; H, 10.25% $C_8H_{16}O_3$ requires: C, 59.98; H, 10.07%

2) Reaction of 116a with iron(II) sulfate

Iron(II) sulfate (5.12mmol; 0.78g) in water (6ml) was added under N_2 with stirring to a chilled (ice) solution of 1,2,4-trioxane **116a** (2.56mmol; 0.41g) dissolved in a 1:1 mixture of H_20 and acetonitrile (2ml). The reaction mixture was allowed to come to room temperature and was stirred for a further 12hrs. The mixture was then extracted with dichloromethane (2 x 5ml) and the extract was dried ($MgSO_4$) and concentrated (rotary evaporator) to give the crude product (0.30g, 73%).

^{1}H nmr (400 MHz) : δ 3.35 (bs, 1H, **OH**), 1.93 (s, 3H, CH_3C=O), 1.38 (s, 6H, **Me_2**), 1.09 (s, 6H, **Me_2**) ppm.

286b (R=Et)

1) Photodecomposition of 116b

Procedure as for photodecomposition of **116a**.

Starting materials : 1,2,4-trioxane **116b** (2.19mmol; 0.38g), deuteriochloroform (2ml). The reaction was followed by proton nmr spectroscopy (60MHz) until all the trioxane was consumed (3hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.55) gave the pure product as a colourless liquid (0.08g, 22%).

^{1}H nmr (400 MHz) : δ 3.50 (bs, 1H, **OH**), 2.26 (q, J=7.25 Hz, 2H, CH_3CH_2), 1.43 (s, 6H, **Me_2**), 1.14 (s, 6H, **Me_2**), 1.09 (t, J=7.25 Hz, 3H, CH_3CH_2) ppm.
^{13}C nmr (100 MHz) : δ 174.79 (**C**=O), 88.80 (**C**-O-C=O), 74.81 (**C**-OH), 28.72, 25.00 (2C), 21.60 (2C), 10.09 ppm.
Found: C, 61.99; H, 10.56% $C_9H_{18}O_3$ requires: C, 62.04; H, 10.41%

286c (R=Pr)

1) Photodecomposition of 116c

Procedure as for photodecomposition of **116a**.

Starting materials : 1,2,4-trioxane **116c** (1.96mmol; 0.37g), deuteriochloroform (2ml). The reaction was followed by proton nmr spectroscopy (60MHz) until all the trioxane was consumed (6hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.52) gave the pure product as a colourless liquid (0.06g, 16%).

^{1}H nmr (400 MHz) : δ 3.41 (bs, 1H, **OH**), 2.22 (t, J=7.36 Hz, 2H, CH_2C=O), 1.59-1.57 (m, 2H, $CH_3CH_2CH_2$), 1.43 (s, 6H, **Me_2**), 1.16 (s, 6H, **Me_2**), 0.90 (t, J=7.36 Hz, 3H, CH_3CH_2) ppm.
^{13}C nmr (100 MHz) : δ 173.89 (**C**=O), 88.97 (**C**-O-C=O), 74.53 (**C**-OH), 37.44 (O_2CCH_2), 24.87 (2C, **Me_2**), 21.66 (2C, **Me_2**), 18.55, 13.51 ppm
FAB mass spectrum m / z : 189 (MH^+)

2) Reaction of 116c with iron(II) sulfate

Procedure as for reaction of **116a** with iron(II) sulfate.

Starting materials : 1,2,4-trioxane **116c** (1.54mmol; 0.29g) in 1: 1 H_20/ acetonitrile (3ml), iron(II) sulfate (3.08mmol; 0.47g) in water (6ml); reaction time (12hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.52) gave the pure product as a

colourless liquid (0.10g, 35%).

^{1}H nmr (400 MHz) : δ 3.45 (bs, 1H, **OH**), 2.23 (t, J=7.52 Hz, 2H, **CH_2**C=O), 1.69-1.50 (m, 2H, CH_3**CH_2**CH_2), 1.45 (s, 6H, **Me_2**), 1.16 (s, 6H, **Me_2**), 0.91 (t, J=7.52 Hz, 3H, **CH_3**CH_2) ppm.
^{13}C nmr (100 MHz) : δ 173.93 (**C**=O), 89.04 (**C**-O-C=O), 74.57 (**C**-OH), 37.49 (O_2**C**CH_2), 24.92 (2C, **Me_2**), 21.73 (2C, **Me_2**), 18.59, 13.56 ppm
Found: C, 64.01; H, 10.73% $C_{10}H_{20}O_3$ requires: C, 63.80; H, 10.71%

286e (R=^{t}Bu)

2) Reaction of 116e with iron(II) sulfate

Procedure as for reaction of **116a** with iron(II) sulfate.
Starting materials : 1,2,4-trioxane **116e** (0.99mmol; 0.20g) in 1: 1 H_20/ acetonitrile (2ml), iron(II) sulfate (0.99mmol; 0.30g) in water (3ml); reaction time (72hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.53) gave the pure product as a colourless liquid (0.10g, 50%).

^{1}H nmr (400 MHz) : δ 3.60 (bs, 1H, **OH**), 1.50 (s, 6H, **Me_2**), 1.20 (s, 6H, **Me_2**), 1.19 (s, 9H, **^{t}Bu** group) ppm.
^{13}C nmr (100 MHz) : δ 169.93 (**C**=O), 89.16 (**C**-O-C=O), 75.05 (**C**-OH), 31.90 (**C**$(CH_3)_3$), 24.78 (3C, C$(CH_3)_3$), 24.68 (2C, **Me_2**), 21.76 (2C, **Me_2**) ppm.
FAB mass spectrum m / z : 201 (MH^+)

286g (R=2-$NO_2C_6H_4$)

2) Reaction of 116g with iron(II) sulfate

Procedure as for reaction of **116a** with iron(II) sulfate.
Starting materials : 1,2,4-trioxane **116g** (0.45mmol; 0.12g) in 1: 1 H_20/ acetonitrile (2ml), iron(II) sulfate (0.89mmol; 0.14g) in water (2ml); reaction time (48hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.67) gave the pure product as a colourless liquid (0.26g, 50%).

^{1}H nmr (400 MHz) : δ 8.75 (dd, J=1.38 Hz, 8.45 Hz, 1H, aromatic), 8.29 (dd, J=1.21 Hz, 7.72 Hz, 1H, aromatic), 7.65 (dt, J=1.12 Hz, 7.64 Hz, 1H, aromatic), 7.61 (dt, J=1.13 Hz, 8.05 Hz, 1H), 3.35 (bs, 1H, **OH**), 1.64 (s, 6H, **Me_2**), 1.30 (s, 6H, **Me_2**) ppm.
^{13}C nmr (100 MHz) : δ 164.28 (**C**=O), 148.03 (**C**-NO_2), 135.09, 129.61, 127.28, 124.46, 124.41, 91.45 (**C**-O-C=O), 74.82 (**C**-OH), 25.28 (2C, **Me_2**), 21.75 (2C, **Me_2**)

ppm
Found: C, 58.48; H, 5.91% $C_{13}H_{17}NO_5$ requires: C, 58.42; H, 6.41%

286h (R=4-ClC_6H_4)

2) Reaction of 116h with iron(II) sulfate

Procedure as for reaction of **116a** with iron(II) sulfate.
Starting materials : 1,2,4-trioxane **116h** (2.03mmol; 0.52g) in 1: 1 H_20/ acetonitrile (4ml), iron(II) sulfate (4.06mmol; 0.62g) in water (4ml); reaction time (48hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.67) gave the pure product as a colourless liquid (0.26g, 50%).

^{1}H nmr (400 MHz) : δ 7.88 (d, J=8.67 Hz, 2H, aromatic), 7.38 (d, J=8.67 Hz, 2H, aromatic), 3.30 (bs, 1H, **OH**), 1.60 (s, 6H, **Me_2**), 1.27 (s, 6H, **Me_2**) ppm.
^{13}C nmr (100 MHz) : δ 165.68 (**C**=O), 139.38 (**C**-Cl), 130.88 (2C), 129.75, 128.70 (2C), 90.49 (**C**-O-C=O), 74.84 (**C**-OH), 25.26 (2C, **Me_2**), 21.89 (2C, **Me_2**) ppm
Found: C, 61.01; H, 6.72% $C_{13}H_{17}ClO_3$ requires: C, 60.92; H, 6.67%
FAB mass spectrum m / z : 257 (MH^+) also (MH^+ for ^{37}Cl) in approx 3:1 ratio.

286i (R=C_6H_5)

1) Photodecomposition of 116i

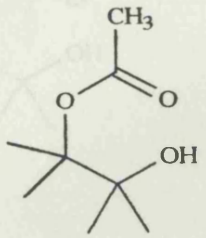
Procedure as for photodecomposition of **116a.**
Starting materials : 1,2,4-trioxane **116i** (2.19mmol; 0.38g), deuteriochloroform (2ml). The reaction was followed by proton nmr spectroscopy (60MHz) until all the trioxane was consumed (10hrs). Purification by simple column chromatography (SiO_2, CH_2Cl_2, R_f 0.62) gave the pure product as a colourless liquid (0.08g, 22%).

^{1}H nmr (400 MHz) : δ 7.85 (m, 2H), 7.60-7.45 (m, 3H), 3.80 (bs, 1H, **OH**), 1.59 (s, 6H, **Me_2**), 1.26 (s, 6H, **Me_2**) ppm.
^{13}C nmr (100 MHz) : δ 164.98 (**C**=O), 134.21, 129.21, 127.93 (2C), 126.31 (2C), 89.82 (**C**-O-C=O), 74.97 (C-OH), 25.13 (2C, **Me_2**), 21.03 (2C, **Me_2**) ppm.
Johnson[73] prepared this compound previously by a photolysis method and obtained analysis for it.

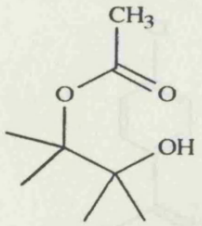
See p219

6.5 NMR Spectra

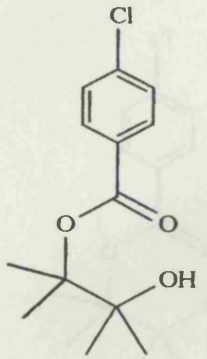
6.5.1 ^{1}H nmr spectrum of 2,3-dimethylbutan-2,3-diol monoacetate (**286a**)



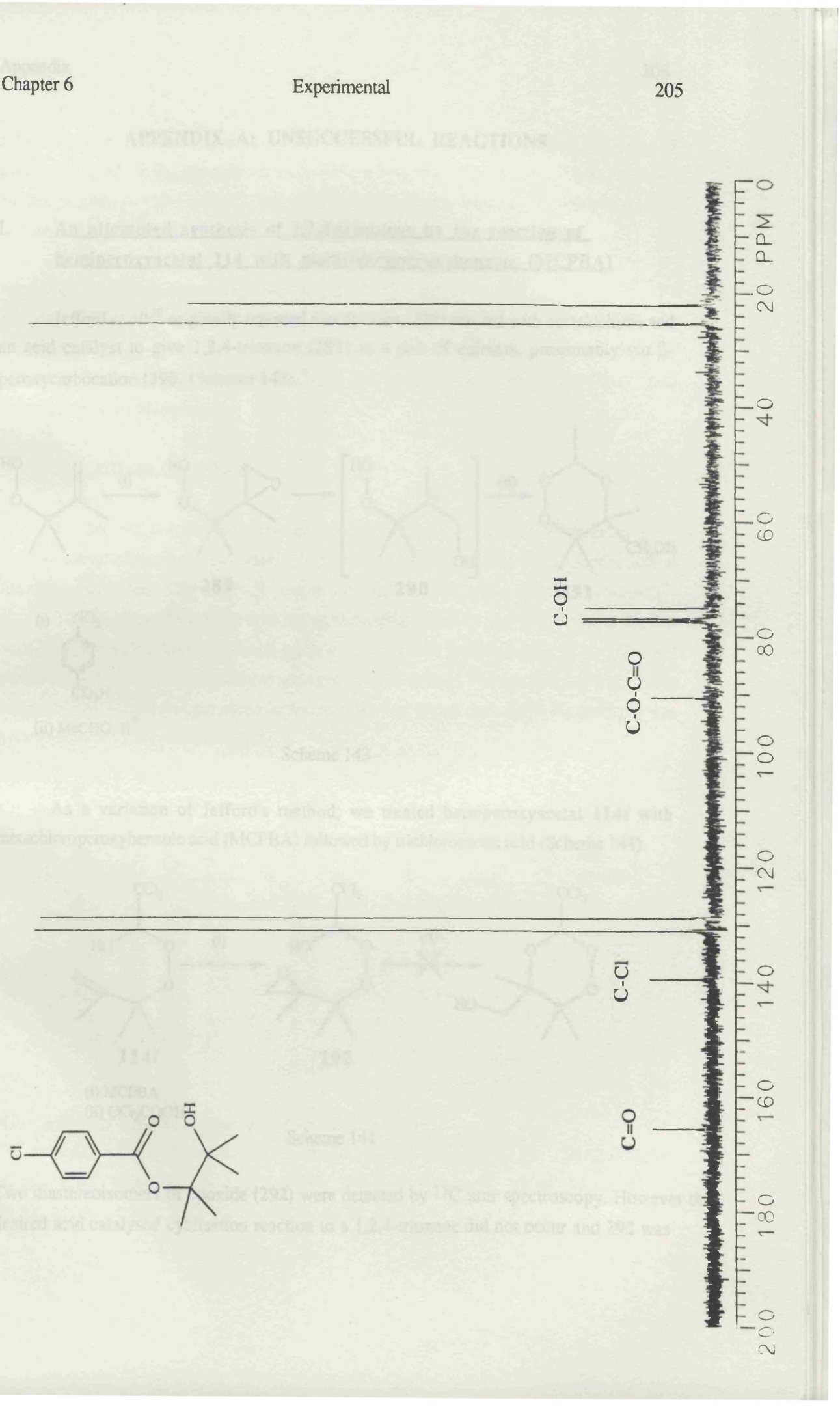
6.5.2 ^{13}C nmr spectrum of 2,3-dimethylbutan-2,3-diol monoacetate (**286a**)



6.5.3 ^{1}H nmr spectrum of 2,3-dimethylbutan-2,3-diol mono(4-chlorobenzoate) (**286h**)



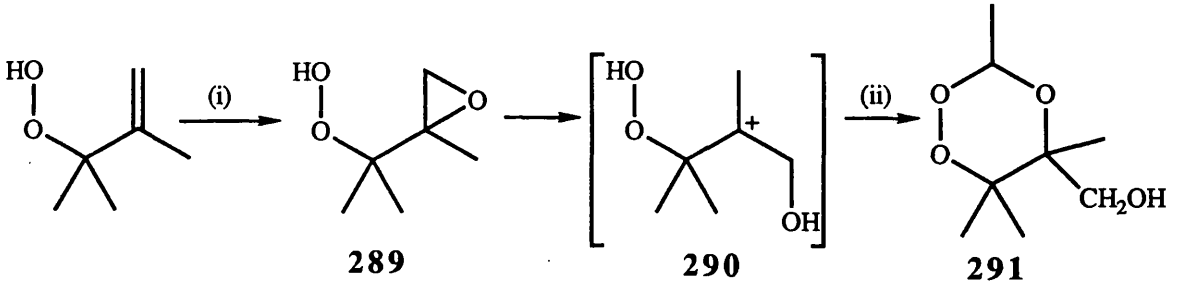
6.5.4 ^{13}C nmr spectrum of 2,3-dimethylbutan-2,3-diol mono(4-chlorobenzoate) (**286h**)



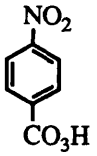
APPENDIX A: UNSUCCESSFUL REACTIONS

I. An attempted synthesis of 1,2,4-trioxanes by the reaction of hemiperoxyacetal 114 with metachloroperoxybenzoic (MCPBA)

Jefford *et al*[129] originally reported that epoxide (**289**) reacted with acetaldehyde and an acid catalyst to give 1,2,4-trioxane (**291**) as a pair of epimers, presumably *via* β-peroxycarbocation (**290**) (Scheme 143).



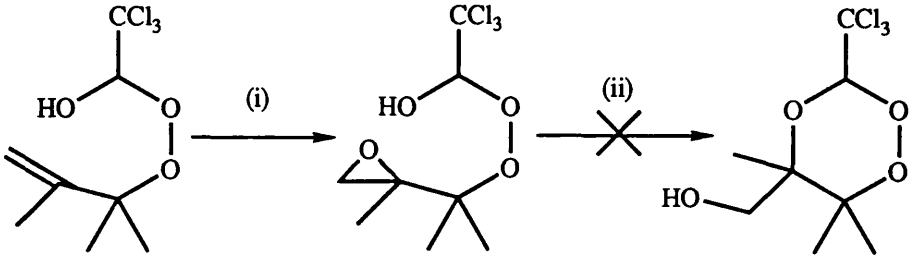
289 **290** **291**

(i) 

(ii) MeCHO, H^+

Scheme 143

As a variation of Jefford's method, we treated hemiperoxyacetal **114f** with metachloroperoxybenzoic acid (MCPBA) followed by trichloroacetic acid (Scheme 144).



114f **292**

(i) MCPBA
(ii) CCl_3COOH

Scheme 144

Two diastereoisomers of epoxide (**292**) were detected by ^{13}C nmr spectroscopy. However the desired acid catalysed cyclisation reaction to a 1,2,4-trioxane did not occur and **292** was

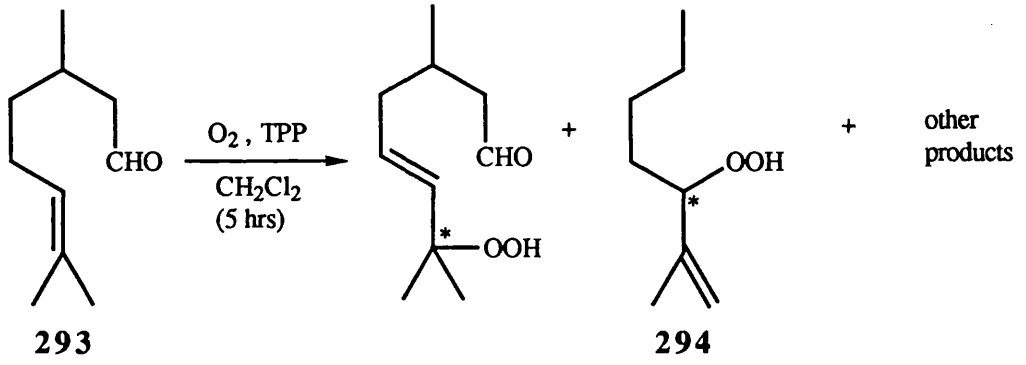
fully recovered. This lack of reactivity was attributed to reduced nucleophilicity of the -OH group as a result of the strongly electron-withdrawing trichloro- group in **114f**. However the reaction works with $Hg(OAc)_2$ (see chapter 2) presumably because a mercurinium ion is a much stronger electrophile than a protonated epoxide.

Nmr data for 292 (2 diastereoisomers in approx 1: 1 ratio).
^{13}C nmr (100 MHz): δ 101.96 and 101.92 (C-OH), 96.89 and 96.87 (CCl_3), 84.56 and 84.49 ($C(CH_3)_2$), 59.96 and 59.87 ($C(CH_3)$ of epoxide), 51.74 and 51.71 (CH_2 of epoxide), 21.24 and 21.19 (CH_3), 20.90 and 20.83 (CH_3), 17.48 ($C(CH_3)$, two diastereoisomers overlap) ppm.

II. The citronellal system

We decided to extend our oxymercuriation route to 1,2,4-trioxanes (chapters 2 and 3) to an intramolecular system which contained the hydroperoxide, aldehyde and alkene functions. We hoped to form bicyclic artemisinin-like 1,2,4-trioxanes from such a system.

The singlet oxygenation reaction of citronellal (**293**) in dichloromethane solvent with tetraphenylporphine sensitiser, gave a very viscous brown liquid. A complicated mixture of peroxide positive products appeared to have formed. The mixture was impossible to separate by simple column chromatography. We had hoped that one of the products was hydroperoxide (**294**) (Scheme 145).



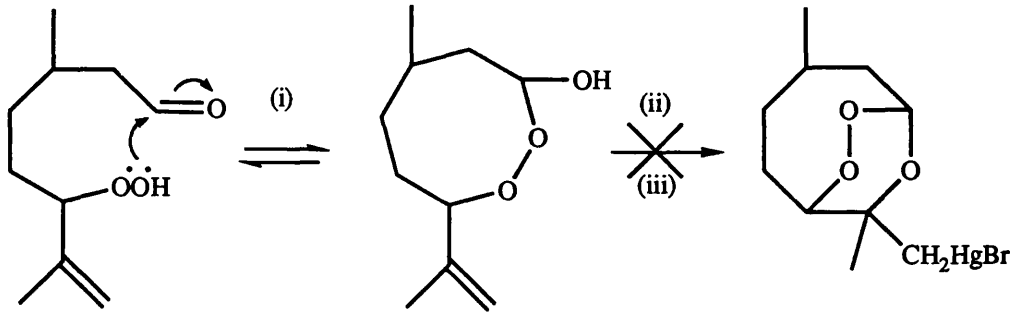
293 **294**

TPP = tetraphenylporphine

Scheme 145

Nmr data for singlet oxygenation reaction of 293
^{13}C nmr (100 MHz) major signals: δ 190.01 (CHO), 136.16, 135.83, 128.60, 112.87, 99.15, 98.93, 89.44, 53.40, 50.24, 39.63, 39.52, 39.44, 33.76, 32.59, 32.56, 28.97, 27.83, 24.80, 24.23, 20.02, 19.92, 19.78, 16.90 ppm.

The mixture of singlet oxygenation products was dissolved in dichloromethane and treated with catalytic trifluoroacetic acid followed by mercury(II) acetate for 2 hrs (see chapter 2). We hoped that if the mixture contained hydroperoxide **294**, some hemiperoxyacetal (**295**) would form in the presence of an acid catalyst. The reaction of **295** with mercury(II) acetate would then hopefully give bicyclic 1,2,4-trioxane (**296**) (Scheme 146).



294 **295** **296**

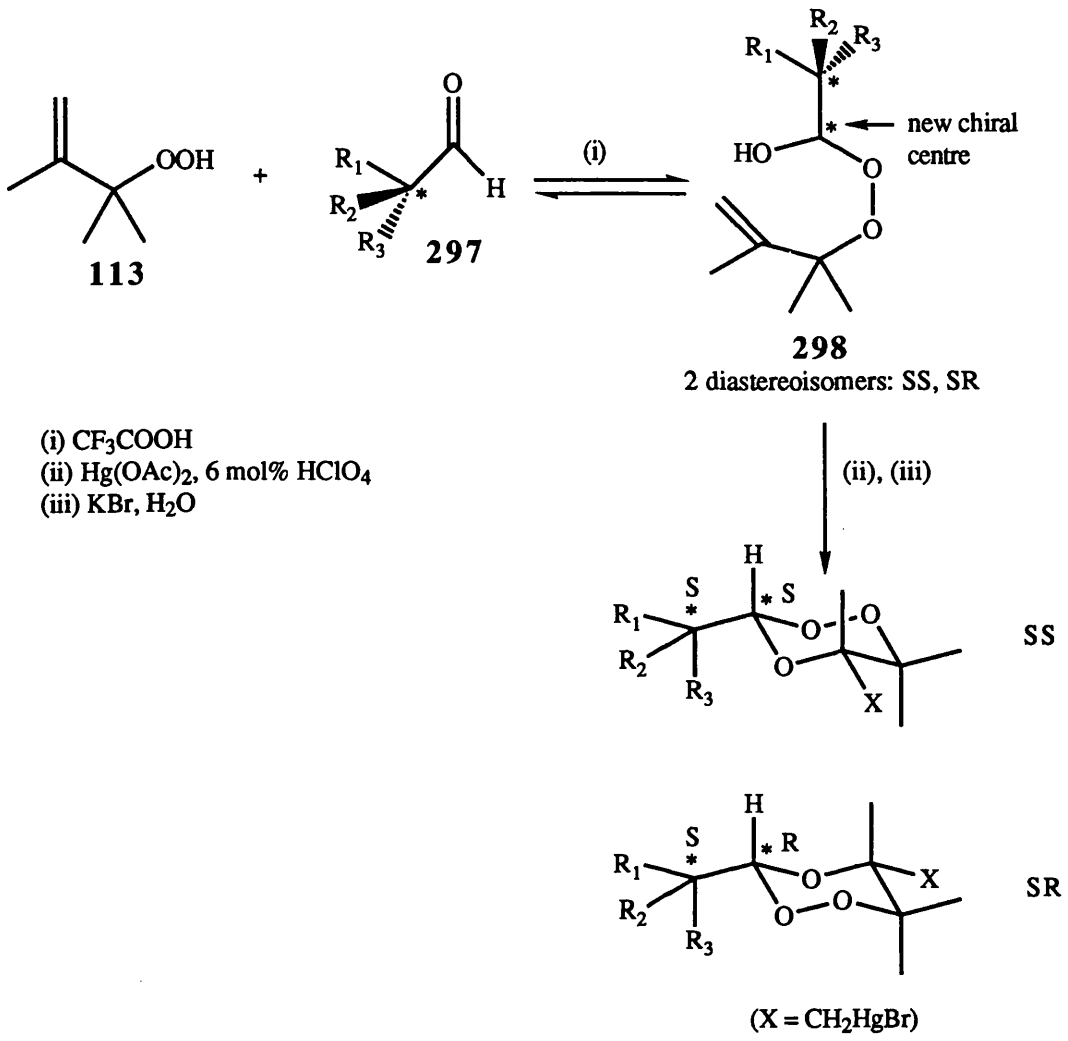
(i) H^+
(ii) $Hg(OAc)_2$, $HClO_4$
(iii) KBr

Scheme 146

The nmr spectra of the products of this attempted intramolecular oxymercuriation reaction were very complicated. We were unable to identify or isolate any of the products. 1,2,4-Trioxane formation did not appear to have occurred.

III. Attempted asymmetric synthesis of 1,2,4-trioxanes

One of the ways to introduce asymmetry in the trioxane ring is to use a chiral aldehyde (**297**) (Scheme 147). Treatment of starting hydroperoxide **113** with say an S-aldehyde would lead to the formation of two diastereomeric hemiperoxyacetals (**298**, SS and SR). 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 we would hope to observe upon cyclisation a predominance of the 1,2,4-trioxane derived from that isomer. We would hope to be able to separate the individual, optically pure 1,2,4-trioxane isomers and hence begin to investigate the influence of the ring configuration upon antimalarial activity. We were aware of the dangers of racemisation in the chiral aldehyde (HC-C=O) *via* the enol or enolate.

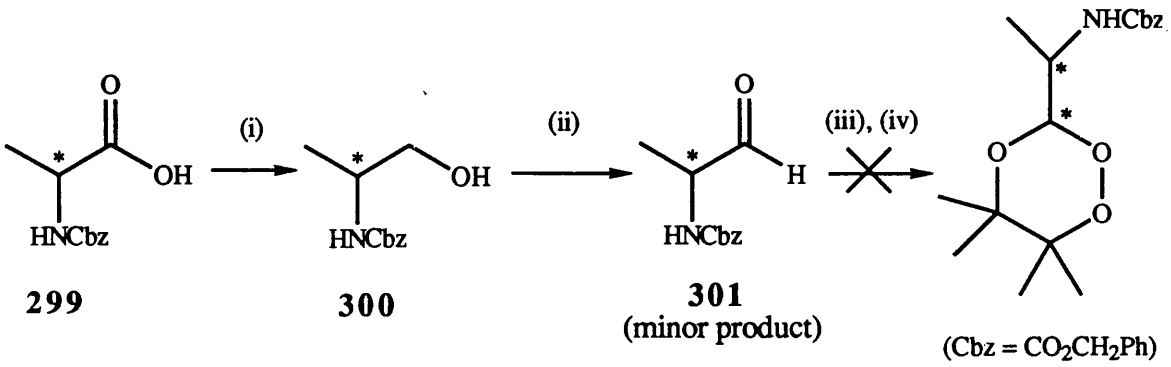


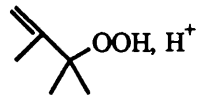
Scheme 147

We decided to use α-amino aldehydes **(302)**[130] and **(303)**[131] which were available from α-amino acids.

(i) *N*-CbZ-DL-alanal **(301)**[130]

Commerially available N-benzyloxy-DL-alanine **(299)** was reduced to the corresponding alcohol **(300)** with borane-tetrahydrofuran complex. Oxidation of **300** with activated DMSO[132] was very complicated. The desired aldehyde **(301)** appeared to be a minor product and we were unable to identify the other products. The impure aldehyde was treated with hydroperoxide **113** and mercury(II) acetate but no 1,2,4-trioxane formation was observed. We were unable to identify the products (Scheme 148).



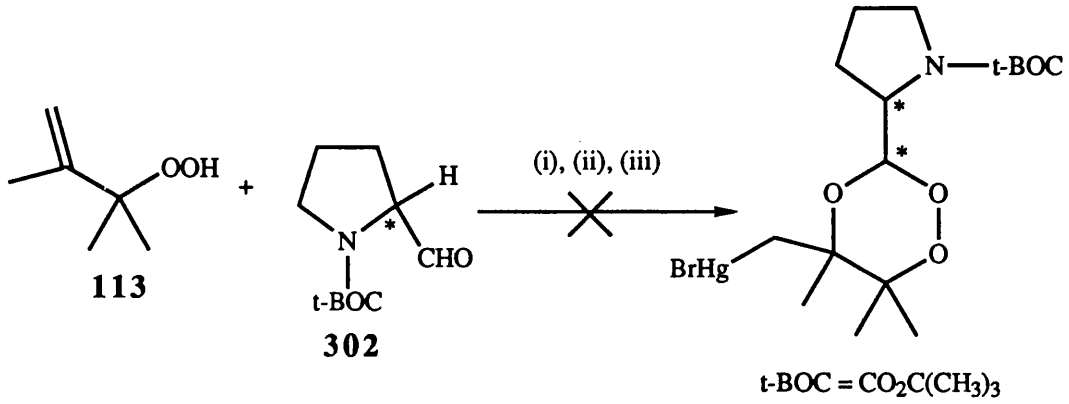
(i) BH_3.THF
(ii) DMSO, $(COCl)_2$
(iii) 

(iv) $Hg(OAc)_2$, 6 mol% $HClO_4$ followed by KBr

Scheme 148

(i) *N*-t-BOC-L-prolinal (302)[131]

N-t-butoxycarbonyl-L-prolinal (**302**) was prepared according to the literature[131]. However the reaction of **302** with hydroperoxide **113** and trifluoroacetic acid followed by intramolecular oxymercuriation did not result in 1,2,4-trioxane formation (Scheme 149).



(i) CF_3COOH
(ii) $Hg(OAc)_2$, 6 mol% $HClO_4$
(iii) KBr

Scheme 149

APPENDIX B: GENERAL EXPERIMENTAL

NMR Spectroscopy

Unless otherwise indicated, all nmr spectra were recorded at 400 MHz (^1H) or 100 MHz (^{13}C) as solutions in $CDCl_3$ and referenced to $CHCl_3$ (δ 7.24 ppm ^1H, δ 77 ppm for ^{13}C) using a varian VXR400 spectrometer. 200 MHz ^1H (50 MHz ^{13}C) nmr spectra were similarly recorded on a varian XL200 spectrometer, and 60 MHz spectra on a Jeol PMX6O spectrometer.

Mass Spectroscopy

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

Unless otherwise indicated all solvents were used as received. Diethyl ether was dried over sodium wire. Dichloromethane was distilled over calcium hydride.

All reagents for which syntheses are not given were available from commercial sources.

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, 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.

Analytical and semi-preparative HPLC was carried out by using a waters M600 pump and R401 refractometer with a Rheodyne 7125 infection valve. Preparative HPLC was performed on a waters prep LC system 500 with a refractometer.

APPENDIX C: LIST OF ABBREVIATIONS

TBMS	*tert*-butyldimethylsilyl
TMSOTf	trimethylsilyl trifluormethanesulfonate
$Et_3SiOOOH$	triethylsilyl hydrotrioxide
CF_3CO_2H	trifluoroacetic acid
CCl_3CO_2H	trichloroacetic acid
$CDCl_3$	deuteriochloroform
CH_2Cl_2	dichloromethane
NIS	N-iodosuccinimide
NBS	N-bromosuccinimide
THF	tetrahydrofuran
CH_3CN	acetonitrile
^tBuOCl	tert-butyl hypochlorite
TMS	tetramethylsilane
DMSO	dimethyl sulphoxide
BSA	bistrimethylsilylacetamide
MCPBA	metachloroperoxybenzoic acid
TPP	5,10,15,20-teraphenyl-21H,23H-porphine
FAB	Fast atom bombardment
ISC	inter-system crossing
NOE	Nuclear Overhauser effect

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Synthesis of 1,2,4-Trioxanes *via* Intramolecular Oxymercuriation

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Synthesis of 1,2,4-Trioxanes *via* Intramolecular Oxymercuriation

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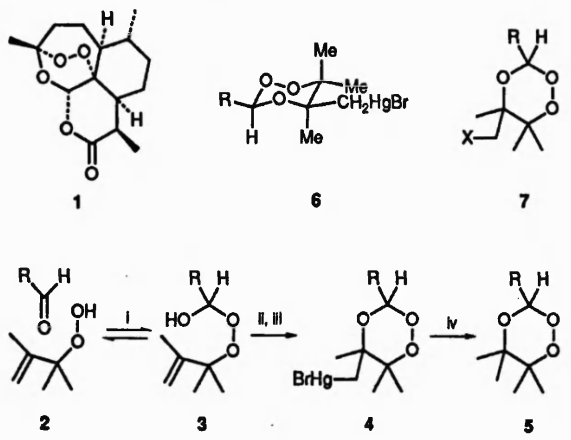
3-Alkyl- and 3-aryl-5,5,6,6-tetramethyl-1,2,4-trioxanes **5** are prepared by reduction of the corresponding 5-bromomercuriomethyl compounds **4** obtained, after anion exchange, by intramolecular oxymercuriation of the hemiperacetals **3** formed from aldehydes and 2,3-dimethylbut-1-en-3-yl hydroperoxide **2**; a 'one pot' procedure omitting the anion exchange and isolation of the organomercury(II) bromide **4** may be used.

Since it became clear that the antimalarial activity of the plant extract qinghaosu **1**[1] is associated with the peroxide moiety it contains, much effort has gone into developing new preparative routes to 1,2,4-trioxanes.[2] We now report the first application of intramolecular oxymercuriation to this synthetic problem. The new method described here utilises readily available starting materials, is easy to carry out, gives good yields, and is potentially very general.

The three-step sequence used to convert allylic hydroperoxide **2** into the 1,2,4-trioxanes **5** is shown in Scheme 1. Hydroperoxide **2** was obtained by tetraphenylporphine-sensitised photooxygenation of 2,3-dimethylbut-2-ene[3] and the crude product, still containing sensitiser, could be used without deleterious effect. The oxymercuriations (5–20 mmol scale) were complete in 1–3 h as judged by the time taken for all the mercury(II) acetate to dissolve, but there were no adverse effects if the reactions were allowed to run overnight. For the aliphatic aldehydes, the organomercury(II) bromides **4**,† obtained after anion exchange,[4] were readily purified by column chromatography (SiO_2, CH_2Cl_2) and were isolated in yields of 35–62%. The reductions[4] proceeded in over 90% yield with little or no side-products, and the 3-alkyl-1,2,4-trioxanes (**5**, R = alkyl)† were purified by column chromatography (SiO_2, CH_2Cl_2) followed by bulb-to-bulb distillation under reduced pressure. For the aromatic aldehydes, however, the crude organomercury(II) bromides **4** contained appreciable amounts of starting aldehyde which could not be removed by simple column chromatography.

† All new 1,2,4-trioxanes gave satisfactory C and H analyses and positive peroxide tests with acidic iron(II) thiocyanate.



R = Me, Et, Pr, Pr^i, Bu^t, 2-$NO_2C_6H_4$, 4-ClC_6H_4

Scheme 1 *Reagents*: i, cat. CF_3CO_2H; ii, $Hg(OAc)_2$, 6 mol% $HClO_4$; iii, KBr; iv, $NaBH_4$, NaOH

We have shown that the three steps of the synthesis can be carried out consecutively in the same reaction vessel. In this 'one pot' procedure, the anion exchange was omitted and the solution of organomercury(II) acetate in dichloromethane was treated with NaOH (2 mol dm^{-3}) before commencing the reduction. By reducing the aromatic compounds with ethanolic rather than aqueous $NaBH_4$, the unreacted aldehydes present were converted into the corresponding alcohols which were readily removed by chromatography (SiO_2, CH_2Cl_2), thereby allowing the 3-aryl-1,2,4-trioxanes (**5**, R = aryl)† to be purified. The 'one pot' method is fast and convenient, avoids handling the intermediate organomercurial and gives better overall yields of the mercury-free 1,2,4-trioxanes **5**.

Consistent with the proposed structures, the organomercurials **4** were each obtained as a pair of diastereoisomers and the isomerism was removed by reduction. For each organomercurial **4** there was a predominant isomer (80–90%) which presumably has the *cis* configuration, since this can adopt a conformation **6** with both R and CH_2HgBr groups equatorial.

The presence of the 1,2,4-trioxane ring in compounds **4** and **5** was confirmed by the ^{13}C NMR signals observed for the ring-carbon atoms at δ 94–99 (C-3), 80–84 (C-6) and 75–79 (C-5), and by the ^1H NMR signals of appropriate multiplicity observed for the CHR proton at δ 5.0–5.5 (R = alkyl) or 6.3–6.8 (R = aryl). The spectra of the organomercurials **4** additionally showed characteristic signals for the CH_2HgBr group at δ_c 45–46 [$^1J(^{199}Hg)$ *ca.* 1550 Hz] and δ_H 2.0–2.3 (AB pattern with the downfield doublet showing long range coupling to the *gem* methyl group).

Halogenodemercuriation of compounds **4** should make available the corresponding halogen-containing 1,2,4-trioxanes (**7**, X = halogen). We have confirmed the efficacy of this route by preparing 5-bromomethyl-3,5,6,6-tetramethyl-1,2,4-trioxane (**7**, R = Me, X = Br) in 90% yield by brominolysis of the corresponding organomercurial in dichloromethane.

We are currently investigating the scope of the method with respect to both the unsaturated hydroperoxide and the multiply bonded acceptor which together afford the substrate for mercury(II)-induced cyclisation. We envisage the possibility not only of preparing 1,2,4-trioxanes with a wide range of substituents at the 3-, 5- and 6-positions, but also of preparing larger rings and rings with nitrogen atoms incorporated at the 4-position.

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Chair–Chair Interconversion in Some Highly Substituted 1,2,4-Trioxanes and 1,3-Dioxanes. A Dynamic NMR Study of a Striking Effect of Skeletal Substitution

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A dynamic NMR determination of barriers to chair–chair interconversion in some tetra- and hexa-substituted 1,2,4-trioxanes and 1,3-dioxanes is reported. Two comparisons of trioxanes and equivalently substituted dioxanes show that trioxane barriers are strikingly higher, and this is attributed to the high barrier to rotation about the oxygen–oxygen bond in the trioxane series.

The chair–chair interconversion of saturated six-membered rings and particularly the effect of substitution, both on the ring and in the ring skeleton, have been much studied.[1] In the first, rate-determining step, concerted rotation, constrained by the ring, takes place about several adjacent bonds to attain a set of twist conformations of relatively high energy. Some connection, albeit not simple, between ring inversion barriers and rotational barriers for molecules R–X–Y–R′, the acyclic equivalents of the various X–Y bonds in the ring is thus expected. The twist conformations are more flexible, so further bond rotations little constrained by the ring and so reflecting mainly the substituents on the bond take place relatively easily, until a reversal of the original concerted rotation leads to the original or to an inverted chair. The barrier in cyclohexane[2,3] is 10.1 kcal mol^{-1} and most simple substitutions have little effect on, or lower, this barrier, since statistically molecules choose rotation about the lowest-barrier bonds in the rate-determining step. We now report ring inversion studies where comparisons show how introducing bonds with high rotational barriers can lead to high ring inversion barriers.

High inversion barriers are already known in highly substituted molecules, with no 'low-barrier' bonds. For example, all *cis*-1,2,3,4,5,6-hexamethylcyclohexane[4] has a barrier of 17.4 kcal mol^{-1}, while that for dodecamethylcyclohexane[5] is 16.4 kcal mol^{-1}. Interactions between 1,3-diaxial methyl groups flatten the ring and lead to a lower ring inversion barrier in the latter case, even though all skeletal bonds, being hexa-substituted, have higher intrinsic rotational barriers. With ring flattening, skeletal bonds are already significantly rotated away from the staggered towards the eclipsed conformation even in the ground state.

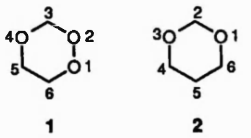
Results and Discussion

We treat two sets of compounds with an intermediate degree of substitution, from the recently available[6] 1,2,4-trioxane **1** and the structurally similar 1,3-dioxane **2** series. To the best of our knowledge there is no previous information on the solution phase conformations of 1,2,4-trioxanes and the present results may have a wider significance, given the current interest in these compounds as potential antimalarial drugs.[7] Ring inversion barriers as determined from the temperature-dependence of NMR spectra are shown in Table 1 along with those previously reported for some other 1,3-dioxanes and relevant cyclohexanes. The NMR behaviour of compound **1b** is typical. At −48 °C six methyl group signals are seen in both the proton and carbon-13 NMR spectra, showing that interchange of axial and equatorial methyl groups by ring inversion is slow on the NMR timescale. As the temperature is raised, methyl signals broaden and at about 0 °C, depending on the relative chemical shift, coalesce to give a single peak for the two methyl groups at each ring position, then finally become narrow again. From the low temperature relative shift of exchanging signals, the rate constant for ring inversion at the coalescence temperature can be determined.[8] The free energy of activation for ring inversion at this temperature can then be calculated,[8] assuming a transmission coefficient of 0.5, since the set of twist conformations form an unstable intermediate minimum symmetrically placed between the two chair conformations on the potential energy surface.

Table 1 Barriers (kcal mol^{-1}) to ring inversion in series of 1,2,4-trioxanes **1**, 1,3-dioxanes **2** and cyclohexanes **3**

Substituents	Coalescence temperature T_c/°C	Barrier at T_c	Ref.
1,2,4-Trioxanes			
1a 5,5,6,6-Me	+2	12.2	*a*
1b 3,3,5,5,6,6-Me$_6$	−5	12.3	*a*
1c 5,5,6,6-Me$_4$-3,3(–CH$_2$–)$_5$	−18	11.6	*a*
1c 5,5,6,6-Me$_4$-3,3,Ad[b]	−17	11.6	*a*
1,3-Dioxanes			
2a None	−70	9.9	9
2b 2,2-Me$_2$	−70	7.8	10
2c 4,4-Me$_2$	−70	8.6	9
2d 5,5-Me$_2$	−70	11.2	9
2e 2,2,4,4-Me$_4$	< −150	< 5.5	11
2f 2,2,5,5-Me$_4$	−70	8.9	9
2g 4,4,6,6-Me$_4$	−148	5.9	11
2h 4,4,5,5-Me$_4$	−73	10.1	*a*
2i 2,2,4,4,5,5-Me$_6$	−133	6.5	*a*
Cyclohexanes			
3a None		10.1	2,3
3b 1,1-Me$_2$		10.3	20
3c 1,1,4,4-Me$_4$		11.4	14, 16
3d 1,1,3,3-Me$_4$		8.7	14

[a] This work. [b] Ad = spiro[2.2]adamantyl.



1 **2**

Some polymethyl-1,3-dioxanes have been shown by molecular mechanics[12] calculations to prefer twist-boat conformations. However, we confirmed using Allinger's MM3 molecular mechanics program[13] which is parametrised for the peroxide bond, that the chair conformation is more stable than any boat conformation by several kcal mol^{-1} for the compounds

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A Halogenocyclisation Route to 1,2,4-Trioxanes

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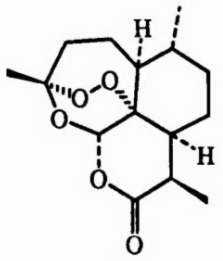
Abstract: Hemiperoxyacetals derived from 2,3-dimethylbut-1-en-3-yl hydroperoxide and aliphatic aldehydes undergo cyclisation with NIS or NBS to afford the corresponding 3-alkyl-5-halogenomethyl-5,6,6-trimethyl-1,2,4-trioxanes in yields of 20-65%.

The natural product artemisinin (qinghaosu) **1** has become a lead compound in the search for new antimalarial drugs[1]. Artemisinin contains the unusual structural feature of a 1,2,4-trioxane ring and this has provided the focus for the synthesis of analogues. New methods for preparing 1,2,4-trioxanes have appeared in response to this stimulus, including (i) the trapping of Paterno-Buchi triplet 1,4-diradicals with molecular oxygen[2], (ii) the trapping of β-peroxy carbocations or equivalents with aldehydes and ketones[3], and (iii) our own contribution, the cyclooxymercuriation of hemiperoxyacetals derived from allylic hydroperoxides followed by reductive demercuriation[4,5]. Halogenocyclisation is a well established technique for the synthesis of oxygen- and nitrogen- containing heterocycles[6] but, as far as we are aware, it has not been applied to the preparation of 1,2,4-trioxanes. Such an approach is the subject of this communication and it represents a second variant of a general strategy for preparing 1,2,4-trioxanes by the electrophile-mediated cyclisation of unsaturated hemiperoxyacetals.



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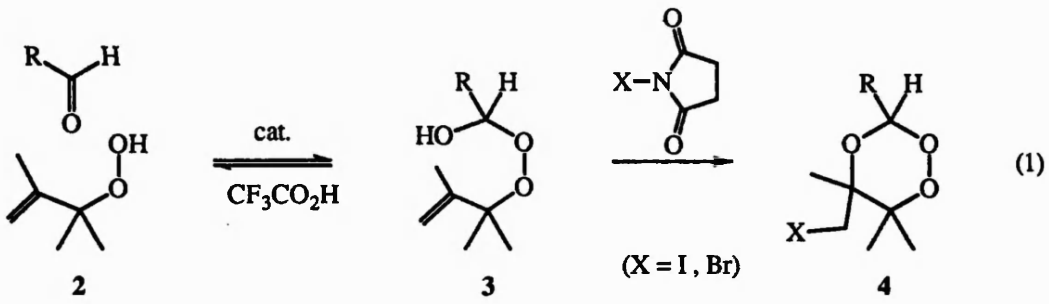
The reaction (equation 1) was carried out as follows. In a flask protected from light by aluminium foil, the hydroperoxide **2**[4] (5 mmol) and aldehyde (5-10 mmol) in dichloromethane (20 ml) were stirred with trifluoroacetic acid (2 drops) for 10 min before adding freshly recrystallised *N*-halogenosuccinimide (5 mmol). After 90-120 min, the reaction mixture was washed with 20% sodium thiosulfate (NIS reactions) or water (NBS reactions). The organic layer was dried, the solvent removed under reduced pressure and the 1,2,4-trioxane **4** isolated by chromatography (SiO_2, CH_2Cl_2). The iodides so obtained were pink, suggesting the presence of iodine, but were isolated as analytically pure colourless liquids after treatment with silver acetate in dichloromethane.

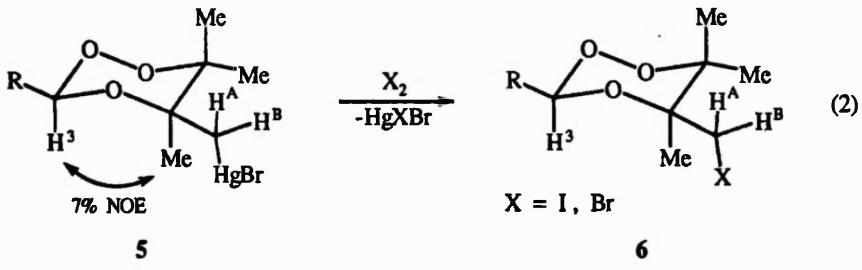


The peroxides prepared are shown in the Table. The compounds rapidly oxidised acidified iron(II) thiocyanate as expected for cyclic peroxides and their structures were confirmed by consistent elemental analysis and ^1H and ^{13}C NMR spectra. For compounds **4b** and **4f**, further proof was afforded by identity with authentic samples prepared independently by halogenodemercuriation of the corresponding 5-bromomercuriomethyl-1,2,4-trioxanes[4].

Table. 5-Halogenomethyl-1,2,4-trioxanes 4

Compound	R	X	Yield (%)	Compound	R	X	Yield (%)
4a	Me	I	65	**4e**	Bu^t	I	20
4b	Et	I	62	**4f**	Me	Br	30
4c	C_6H_{13}	I	32	**4g**	Et	Br	35
4d	Pr^i	I	25	**4h**	Pr	Br	25

Each product consisted of a pair of diastereoisomers as expected from the presence of chiral centres at C-3 and C-5. The reactions are stereoselective with the isomer ratios, as determined by NMR, ranging from 4:1 to 13:1. The major isomer has the alkyl group at C-3 and the CH_2X group at C-5 *cis* to one another so that they are both equatorial in the preferred conformation (**6**). This was shown by the identity of the major isomer with that from halogenodemercuriation (equation 2) where the stereochemistry of the precursor mercurial (**5**) was established by NOE experiments. Thus, for the major peroxymercurial derived from 2-methylpropanal (**5**, R=^{i}Pr), irradiation of the singlet at δ 1.45 (C^5-Me) produced an NOE of 7% in the doublet at δ 5.13 (H^3) whereas irradiation of the doublets at δ 2.06 and 2.24 (CH^AH^BHgBr) had no effect upon the H^3 signal. These results show that the CH_2HgBr group is equatorial. It is inconceivable that the major products derived from other aldehydes do not have the same stereochemistry and the observed spectroscopic similarities support this.

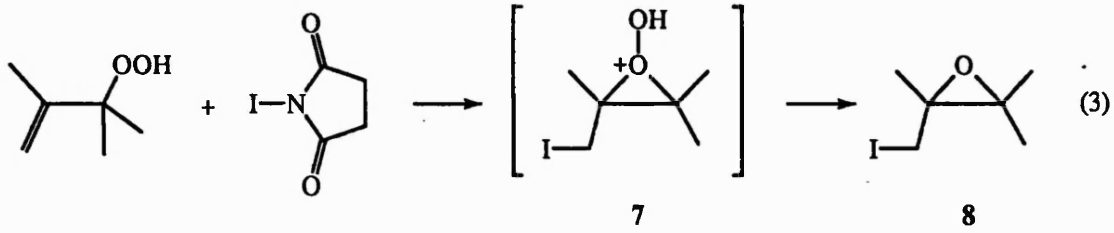


5 6 (2)

The present halogenocyclisations have much in common with the earlier cyclooxymercuriations[4]. The stereoselectivities are comparable and the key NMR features of the 1,2,4-trioxanes are very similar. Thus, the ^{1}H NMR spectra show, for the major isomers **6**, characteristic H^3 signals of appropriate multiplicity at δ 4.9 - 5.5 (5.0 - 5.5 for the corresponding organomercurials[4]) and H^AH^B doublets at δ 3.1 - 3.4 (2.0 - 2.3 for the organomercurials[4]). Again like the corresponding organomercurials, the downfield doublet of the AB pattern shows long range coupling to the *gem* methyl group and the downfield doublet of the AB pattern for the minor isomer is considerably deshielded (δ 4.0 - 4.8). These features suggest that there is restricted rotation about the XCH_2-ring bond in both *cis* and *trans* isomers, and in the organomercury compounds this is supported by NOE studies. The similarity of the halogeno and bromomercurio compounds (*e.g.* **5** and **6**) indicates that the restricted rotation has its origin in a steric rather than an electronic effect. In the ^{13}C NMR spectra, the ring-carbon signals appear at δ 95-104 (C-3), 80-81 (C-6) and 75-76 (C-5), virtually the same as in the related 5-bromomercuriomethyl 1,2,4-trioxanes[4]. The distinctive feature of the 5-halogenomethyl compounds is the CH_2X signal at δ 14-15 (X = I) or 39-40 (X = Br).

The halogenocyclisation route to 1,2,4-trioxanes has, however, proved less versatile than that based on cyclooxymercuriation. Thus, we were unable to extend the NIS and NBS reactions to aromatic aldehydes or to ketones. With these substrates, where there is much less hemiperoxyacetal present at equilibrium, competing reactions predominated. The NIS reactions all gave the same major product which was isolated and identified by NMR and mass spectrometry as 1-iodomethyl-1,2,2-trimethyloxirane **8**. Epoxide **8** was also formed when the allylic hydroperoxide **2** alone was treated with NIS (equation 3) and although the yield was low (26% after chromatography), no other products were detected.

The reaction can be envisaged to proceed through the protonated perepoxide **7**, which must transfer its electrophilic OH group to a nucleophile in the process of forming epoxide **8**. We have previously provided evidence that related *gem*-dialkylperoxonium ions derived from *trans*-4,5-



7 8

epoxycyclooctyl hydroperoxide transfer their electrophilic OH groups to the precursor hydroperoxide and its *cis* isomer to form protonated hydrotrioxides which then undergo deoxygenation to give the corresponding alcohols[7]. However, we were unable to demonstrate that a parallel reaction occurs here between protonated perepoxide **7** and hydroperoxide **2**. Thus, 2,3-dimethylbut-3-en-2-ol, which would result from such a reaction, was not detected and an authentic sample of this alcohol reacted with NIS to give not epoxide **8** but rather a mixture of unidentified products.

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EXPERIMENTAL APPENDIX

Chapter 2

Compound **113** was obtained crude as a green oil (22g, 95%).
Compounds **114a-114f** were obtained crude as green oils.
Compound **115f** was obtained crude as a yellow solid (9g, 83%).
Compound **118** was obtained crude as a green oil (9.7g, 55%).

Chapter 4

Compounds **117a-117d** were obtained pure as creamy, white solids.
Compounds **117e-117i** were obtained pure as white solids.
Compound **195** was obtained pure as a white solid.

Chapter 5

Compound **116a** was obtained crude as a yellow solid.
Compound **254ci** was obtained crude as a yellow oil.
Compound **256** was obtained crude as a yellow solid.
Compound **254cii** was obtained crude as a yellow oil.
Compound **254d** was obtained crude as a yellow oil.
Compound **254e** was obtained crude as a yellow oil.

Chapter 6

Compound **286a** was obtained crude as a yellow oil.