A Thesis entitled

STEREOSELECTIVITY OF ENONE EPOXIDATIONS WITH ALKALINE HYDROGEN PEROXIDE

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for the degree of Doctor of Philosophy
in the Faculty of Science

by

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CONTENTS

SUMMARY

While stereoselective epoxidation of alkenes with a hydroxyl group using peracids or peroxides in conjunction with a catalyst has been well documented and feasible mechanisms proposed, the stereochemistry of epoxidation of enones with γ-hydroxyl substituents using alkaline hydrogen peroxide is less well understood and perhaps deserves more detailed study. A thorough review of these methods for preparing epoxides from alkenes is covered in the introduction section of the thesis. Particular attention is paid to stereoselective epoxidations and the factors which influence stereoselectivity.

Previous studies have shown that 4-hydroxy-4-methylnaphthalen-1(4H)-one (48) and 1-hydroxy-1-isopropylnaphthalen-2(6H)-one (161) undergo stereospecific epoxidation with alkaline hydrogen peroxide to yield products in which the hydroxy and epoxy groups are cis and trans respectively. In an extension of these studies the synthesis of a variety of cyclic enones substituted with a hydroxyl group was undertaken and the stereochemistry of the products examined after alkaline hydrogen peroxide epoxidation. Some structurally related enones in which there was no hydroxyl group but where another functionality was present were also similarly investigated.

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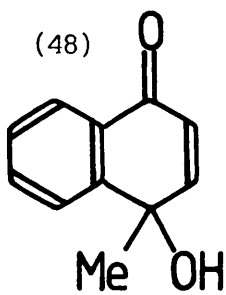

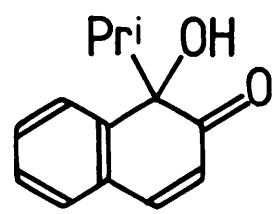

(161)

As had been established, alkaline epoxidation of the naphthalenone (48) gave exclusively the cis epoxy alcohol (49). It was shown that the

stereospecificity of epoxidation was dependent on the γ-hydroxyl group since both the methyl ether and methoxymethyl ether of (48) gave an almost equal mixture of both diastereomeric epoxides. Cleavage of the mixture of epoxy methoxymethyl ethers and separation of the resulting mixture of epoxy alcohols resulted in isolation of the previously unreported trans epoxy alcohol (247).

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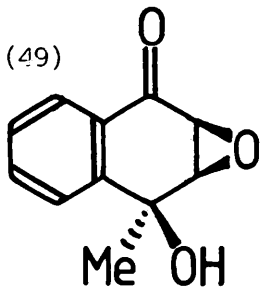

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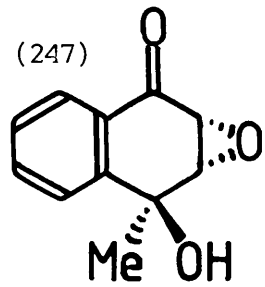
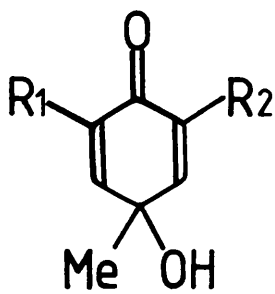


An attempt to prepare a naphthalenone with a γ-hydroxymethyl substituent for epoxidation studies was unsuccessful.

To check that the directing affect of a γ-hydroxyl group on alkaline epoxidation was not exclusive to naphthalenones a series of monocyclic p-quinols was prepared. Oxidation of p-cresol, 2,4-xylenol, mesitol, 2-t-butyl-4-methylphenol and 2,6-di-t-butyl-4-methylphenol with singlet oxygen generated <u>in situ</u> from ceric (IV) oxide and hydrogen peroxide, and



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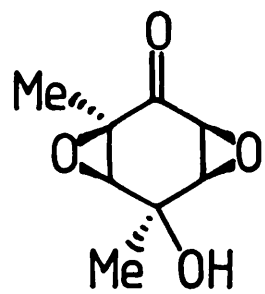


(295)

reduction of the resulting hydroperoxides with dimethyl sulphide gave the p-quinols (268)-(272). Prolonged treatment of these dienones with alkaline hydrogen peroxide gave only the cis diepoxy alcohols in all cases except (270) (R_1=R_2=Me) which refused to react under these conditions. The

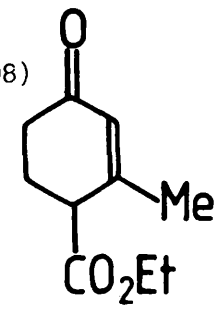
stereochemistry of the diepoxide (295) was proved by x-ray crystallography. Regioselective monoepoxidation was achieved for the unsymmetrical p-quinol (271) (R_1=H, R_2=Bu^t). While a short exposure to alkaline hydrogen peroxide resulted in cis monoepoxidation of the non-substituted double bond, reaction with mcpba oxidised the substituted double bond.

In contrast to the naphthalenone series alkaline epoxidation of 4-methoxy-4-methylcyclohexa-2,5-dienone afforded a single diepoxide. Nmr showed the epoxides were cis to one another but it was not possible to ascertain the stereochemistry of the epoxides relative to the γ-ether substituent.

To broaden the scope of the study and to try to establish whether other functional groups could effect stereospecific alkaline epoxidation of enones, a series of cyclohexenones which possessed both a hydroxyl group and carbonyl substituent in the γ-position was prepared.

Using a recently reported reaction, Hagemann's ester (308) was converted to the γ-hydroxy enone (309) by stirring an ethyl acetate

(308)



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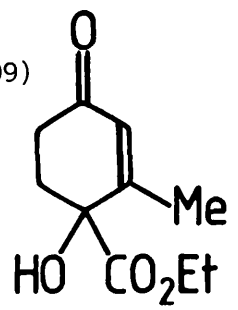

solution of the substrate with activated charcoal in the presence of air. The esters (308) and (309) proved to be versatile starting materials for investigating the epoxidation of a variety of γ-substituted cyclohexenones. Unlike the naphthalenones and p-quinols these enones did not yield simple α,β-epoxyketones on treatment with mcpba though an alternative peracid reagent, per-Amberlyst 15, proved effective for epoxidising γ-hydroxy enones such as (309). In all cases the cis epoxy alcohol was

the major epoxide isolated.

Alkaline epoxidation of the γ-hydroxy enone (309) was stereospecific affording the cis epoxy alcohol. Similar treatment of the corresponding methyl ester or N-phenyl amide (332) was also highly stereoselective though a small amount of the diastereomeric trans epoxy alcohol was formed.

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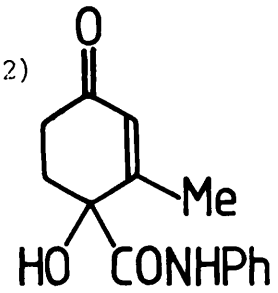

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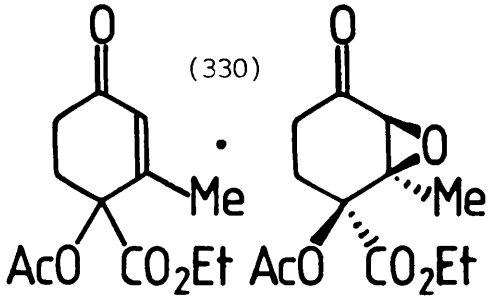

This stereoselectivity of epoxidation was lost on conversion of the alcohol (309) to its methoxymethyl ether, TBDMS ether or its acetate. In these cases both epoxides were formed in roughly equal proportions. The epoxidation of the acetate, which was worked-up prior to completion, gave an oily 1:1:1 mixture of the enone and both epoxide isomers from which the co-crystal (330), consisting of an enone molecule and an epoxide molecule in the ratio 1:1, precipitated. The structure of this compound was determined by x-ray crystallography. From this reaction it proved possible eventually to isolate and characterise the trans epoxy alcohol.

The epoxidation of structurally related enones with no γ-hydroxyl group was then studied. Alkaline epoxidation of Hagemann's ester (308) and its parent acid was stereoselective giving mainly the trans epoxy

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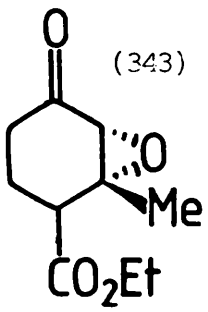

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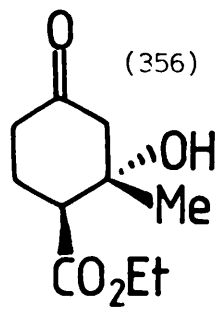
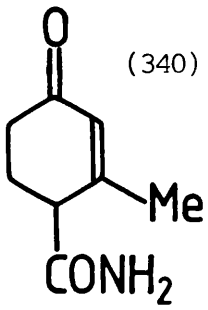


ester (343) and trans epoxy acid respectively. The stereochemistry of (343) was established by reducing the epoxide to the crystalline β-hydroxy ketone (356) whose stereochemistry was proved by x-ray crystallography. The primary amide (340) and N-phenyl amide (331) were prepared. Although these also could be epoxidised, yielding a mixture of both isomers, the stereochemistry of the products was not determined.



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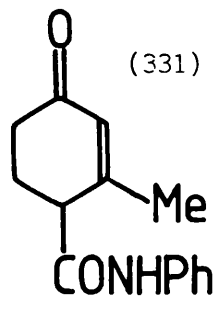
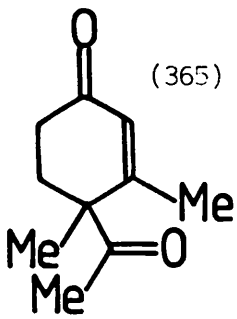


(331)

The γ-acetyl enone (365) was prepared by Michael condensation of 3-methylpentan-2,4-dione with but-3-en-2-one and cyclisation of the resulting adduct with pyrrolidinium acetate. Low temperature reaction of (365) with sodium borohydride gave the γ-hydroxyethyl enone (367). Treatment of (365) and (367) with alkaline hydrogen peroxide resulted in formation of a single epoxide in both cases. On oxidation with chromium trioxide the epoxide of (367) gave the epoxide of (365) whose stereochemistry was shown to be (369) by x-ray crystallography.



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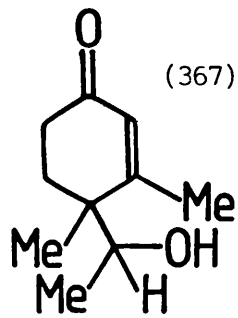

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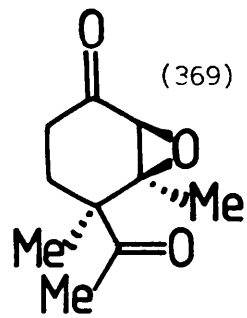


(369)

A number of α′-substituted cyclohexenones were prepared to see whether changing the position of the substituent relative to the enone affected the stereoselectivity of epoxidation. Some of these were

converted to α',α'-disubstituted cyclohexenones on reaction with lead (IV) acetate or air over activated charcoal. Treatment of these compounds with alkaline hydrogen peroxide failed to yield any epoxide products.

This work has shown that alkaline epoxidation of naphthalenones, dienones and enones bearing a γ-hydroxyl substituent is syn stereospecific or highly syn stereoselective. Conversion of the alcohol to an ether or acetate results in a loss of stereoselectivity. A number of other γ-substituents including esters, amides and ketones were also shown to exert a strong directing effect on alkaline epoxidation. It is now clear that certain substituent groups (notably hydroxyl) in the γ-position in a wide variety of cyclohexenones offer stereocontrol over alkaline epoxidations of the same order as do allylic hydroxyl groups over peracid and Sharpless epoxidations.

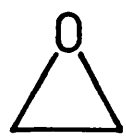
INTRODUCTION

This introduction will largely be devoted to stereoselective or stereospecific formation of epoxides from alkenes using a variety of different reagents and will conclude with a short review of chiral epoxidations.

Epoxides, formally termed oxiranes, are any substance incorporating in its structure one or more three-membered rings containing one oxygen atom and two carbon atoms. Among oxygen-containing heterocycles they are the simplest and also the most important. Their ease of formation and their readiness to undergo a large variety of reactions makes them useful synthons for other functional groups as well as for larger ring heterocycles.

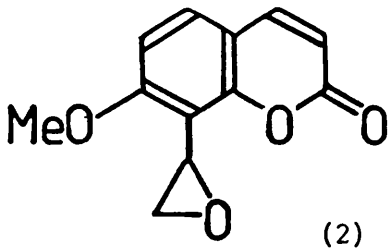
Epoxides are commercially and industrially important for the production of polyethers which can be formed by treating the epoxide with acid, base or a coordination catalyst. They are also of use when incorporated into prepolymers since the epoxide functions can be crosslinked with a difunctional amine to give thermosetting polymers which are widely employed in tool making, adhesives, insulators and tough surface coatings.

The first epoxide to be discovered was oxirane or ethylene oxide (1) which was obtained by Wurtz in 1859.[1] In 1925 it became readily available


(1)

from the treatment of ethylene chlorohydrin with caustic soda but it is now made industrially by oxidation of ethylene by air using a silver catalyst. Next to ethanol, oxirane is the most important derivative of ethylene, being extensively used in the automobile industry to make brake fluid components, solvents for finishes and resins, among others.

'Auraptin' (2) which is a coumarin derivative, was probably the first epoxide to be found in nature. The epoxide function is not uncommon among natural products.[2] It is present in arene oxides (3) which are intermediates in the hydroxylation of aromatic compounds in plants and animals and are in equilibrium with oxepins.[3] Over the past two decades arene oxides have received a great deal of interest owing to studies which have established them as being mutagenic, cytotoxic and carcinogenic. These properties are a result of the molecule covalently interacting with biopolymers such as DNA.



(2)

(3)

The overwhelming amount of literature that is now published each year on epoxides makes it impossible to give a full review of their chemistry within this introduction. For a more detailed survey of the chemistry of epoxides there have been a number of comprehensive general reviews, the most recent by Bartok and Lang[4] which updated the material contained in older publications.[5-8]

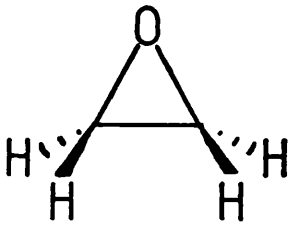
Epoxides have also been reviewed annually in 'Saturated Heterocyclic Chemistry' and 'Heterocyclic Chemistry,' two Specialist Periodical Reports published by the Royal Society of Chemistry.

Physical and Chemical Properties of Epoxides

This section gives a brief summary of some of the physical and chemical properties of epoxides primarily to show their extensive use as intermediates in organic synthesis and for comparison with the x-ray crystallographic data of some α,β-epoxy ketones presented later in this

thesis. A more comprehensive treatment of the physical properties of epoxides can be found in the reviews previously mentioned.

Oxirane (1) is a colourless liquid of b.p. 10.7°. It has a dipole moment of about 1.9 debye resulting from a non-uniform electron distribution in the σ bonds caused by the electronegative oxygen atom.



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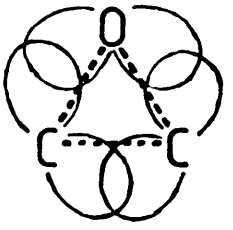


(4)

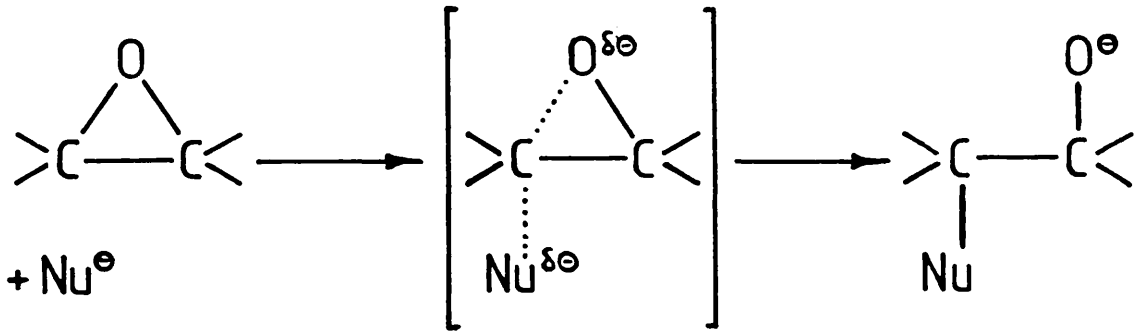
The bond lengths have been determined by a number of techniques but all have shown the C-C bond distance lies between those for a single (1.54Å) and a double (1.33Å) bond, and is typically 1.47Å. Similarly the H-C-H bond angle (~116°) lies between those for tetrahedral (109°28′) and trigonal (120°) bonding, while the C-O-C bond angle (~61°) is significantly smaller than the divalent oxygen angle of 110° for open-chain ethers. Because of this angle strain there is poor overlap of the carbon and oxygen atomic orbitals which results in the bonds being weaker than in an ordinary ether and the molecule is less stable.

Electron density maps based on x-ray studies suggest the C-C and C-O bonds are bent, as depicted in (4). Since the H-C-H bond angle is between that for an sp^2 and sp^3 hybridised carbon the orbitals used to form the C-H bonds have a fractional hybridisation state, estimated to be $sp^{2.22}$. The orbitals involved in C-C and C-O bond formation therefore have a higher p character than sp^3 with the consequence that the orbital-orbital angle is smaller than 109° but still greater than the 60° required for bond formation along the internuclear axes (shown by dotted lines) and results in the bent C-O and C-C bonds. Hence the structure is a compromise between maximum possible orbital overlap and

relief of angle strain.

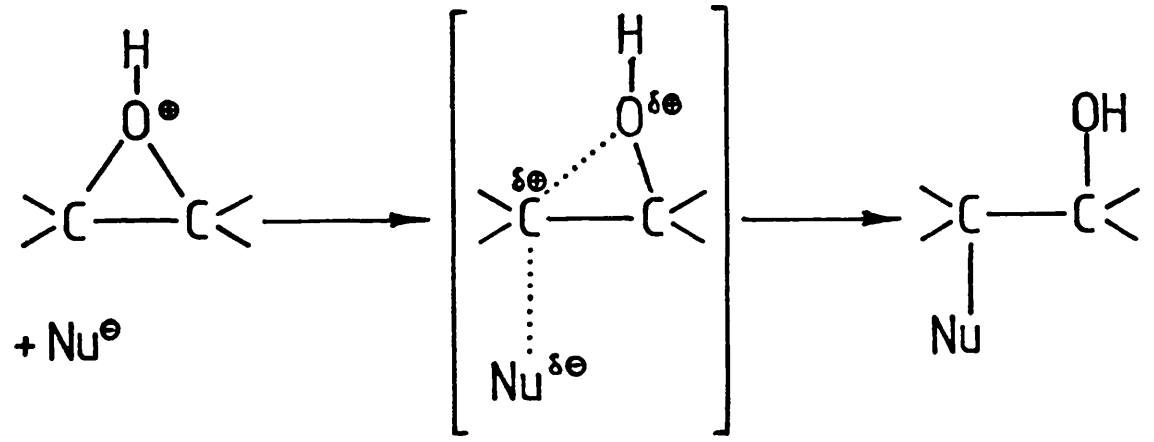
The ring strain energy, calculated as the difference between the experimental heat of formation and the calculated total bond energy, is 54.4 $kJmol^{-1}$. It is this strain which renders epoxides susceptible to ring opening with nucleophiles and makes them such versatile organic intermediates.[9,10]

When the ring-opening reaction is base-catalysed the nucleophile undergoes S_N2 attack at the less hindered carbon (Scheme 1). If however



Scheme 1

the cleavage is acid-catalysed the reaction has considerable S_N1 character. This means that in the transition state generated via the protonated epoxide intermediate carbon-oxygen bond-breaking has proceeded further than nucleophile-carbon bond-making (Scheme 2).



Scheme 2

Hence the nucleophile tends to attack the carbon that can best

accommodate the positive charge, often the one which is more hindered.

Synthesis of Epoxides

The three main laboratory methods for conversion of alkenes to epoxides are treatment with organic peroxy acids, alkaline hydrogen peroxide and alkyl peroxides in conjunction with a metal catalyst. The use of these and other less common reagents for effecting epoxidation is well known.[4,7,11-13] So, since this study is concerned with the effects of substituents on the stereoselectivity of epoxidation, this synthesis section will be largely devoted to stereospecific epoxidations or highly stereoselective epoxidations resulting from steric hindrance, angle strain, conformational factors or interaction with a charged or polar neighbouring group.

Epoxidation with Organic Peracids

Probably the most important and frequently employed method for the conversion of alkenes to epoxides is oxidation with organic peracids (peroxyacids) or a related species such as a peroxycarboximidic acid. The procedure was discovered by Prileshaev in 1909[14] and the earlier literature extensively reviewed by Swern.[15,16] More recently a number of reviews documenting the increasing range of organic peracids and their derivatives as well as the conditions, mechanism and stereochemistry of the reaction have been published.[7,13,17-21]

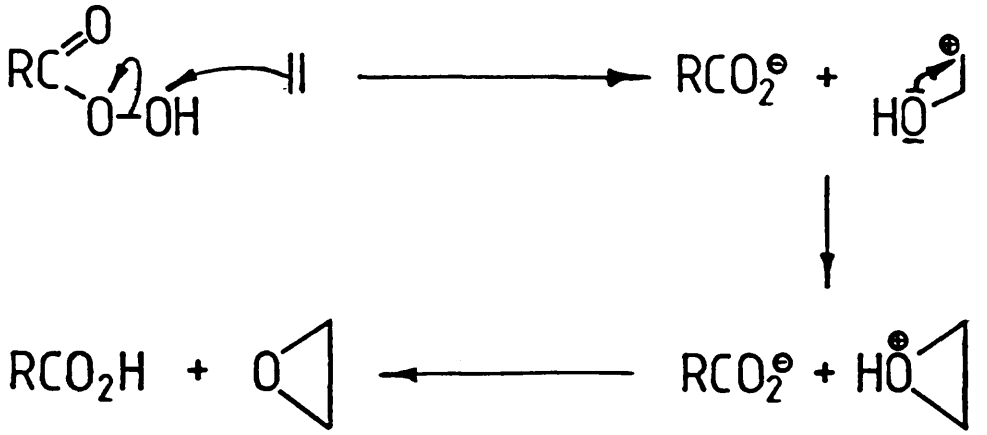
Perbenzoic acid and its substituted derivatives are the most commonly used peroxy acids for preparing epoxides. m-Chloroperbenzoic acid (mcpba) is commercially available and generally the most favoured because of its relative stability and ease of purification. The other acids are rather unstable and generally are prepared *in situ* by the addition of hydrogen peroxide to the corresponding acid. Aliphatic acids

such as peroxyacetic, trifluorperoxyacetic and peroxymaleic acid have also been used to effect epoxidation as well as peroxycarboximidic acids which are transient intermediates prepared through reaction of a nitrile (usually acetonitrile or benzonitrile) with hydrogen peroxide in weakly alkaline, buffered solution. Peroxycarboximidic acids are particularly useful for oxidising acid-sensitive alkenes though they are more susceptible to steric congestion than peracids. Among others, peroxycarbonic acids [ROC(O)OOH], peroxycarbamic acids [RNHC(O)OOH] and magnesium monoperoxyphthalate have been utilised.

Mechanism of Epoxidation of Alkenes by Peracids

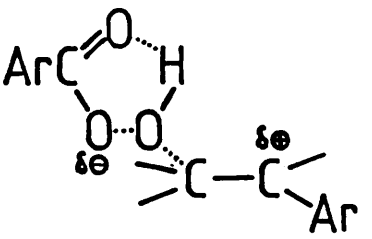
The mechanism involves attack of the electrophilic peracid on the alkene. The electrophilic nature of the peracid is confirmed from findings that such epoxidations work best with electron-rich alkenes and an electron-deficient peracid acyl group. The epoxidation kinetics have been shown to be dependent on both the nature of the peracid and the solvent. Peracids form intramolecular hydrogen bonds in inert solvents (benzene, carbon tetrachloride) and in dilute solutions. In concentrated solutions they tend to form dimers while in weakly basic solvents (ethers, alcohols, amides, ketones, etc) peracids form mainly intermolecular hydrogen bonds. Peracid epoxidations have been carried out in organic solvents, biphasic and emulsion systems, and recently mcpba was reported to give high yields of epoxides in water.[22]

A stepwise mechanism (Scheme 3) involving an initial α-hydroxy carbonium ion, an oxiranium ion, and final deprotonation is disproved by the fact that compounds resulting from rotation about the carbon-carbon bond in an α-hydroxycarbonium ion are never obtained, even in cases where electron-donating substituents could stabilise such a carbonium ion, ie peracid epoxidations are always syn stereospecific.



Scheme 3

However a kinetic isotope effect has led to the proposal of an open-chain structure (5) with strong charge separation, from which the rate of ring-closure is greater than that of rotation about the carbon-carbon bond.[23]



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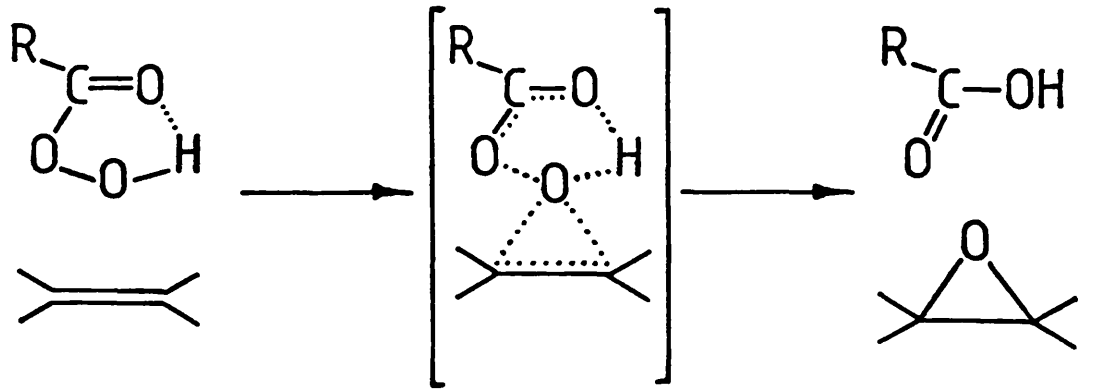
The synchronous mechanism (Scheme 4) which involves a cyclic transition state arising from attack of an intramolecularly hydrogen-bonded peracid on the alkene and was first proposed by Bartlett,[24] is now the most widely accepted.



Scheme 4

This mechanism also has its weaknesses, in that it considers only unsolvated molecules and it fails to explain, for example, the selectivity of epoxidation as a function of the nature of the peracid, induced decomposition of peracids, the specific influence of solvent, and the formation of rearranged products concurrent with epoxidation.

Even today, despite a great deal of work by Dryuk,[25] Rebek[19] and others the fine details of the mechanism have not been clarified in every respect.

Inert solvents such as dichloromethane, chloroform and benzene are most commonly employed for peracid epoxidations. In basic solvents the reaction rate decreases as the basicity increases. When the epoxide products are acid-sensitive, buffers can be used.

Peracid epoxidations are syn stereospecific. With sterically hindered alkenes the reaction takes place on the less hindered side. In other cases, the stereochemistry of the reaction is affected by polar effects or the geometry of the transition state. The stereoselectivity of peracid epoxidations was comprehensively reviewed by Berti up till 1971[7] and will be dealt with later.

Because reaction of alkenes with peracids is always syn stereospecific there is no doubt as to the relative configuration of the ring carbons on epoxidation. However often the alkene will contain one or more chiral centres, and this usually results in formation of a mixture of diastereoisomers.

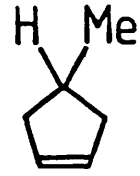
Stereoselective Peracid Epoxidations due to Steric Hindrance, Angle Strain or Conformational Factors

Generally simple acyclic alkenes show little asymmetric induction on reaction with peracids and yield an approximately equal mixture of both diastereomeric epoxides. For example the alkene (6) affords a 55:45

mixture of both diastereomeric epoxides with perbenzoic acid.[26]

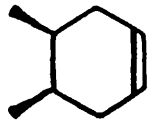
(6)

With cyclic alkenes however, steric or other effects often favour formation of a particular isomer. A purely steric effect is exhibited by 4-methylcyclopentene (7) which gave a 73:27 mixture of trans:cis epoxides with perlauric acid[27] and this ratio remained practically unaltered on changing from cyclopentane to acetonitrile as solvent.

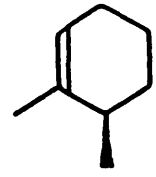


(7)

With cyclohexenes conformational or other effects often have some bearing on the epoxide distribution. Generally significant stereoselectivity is only observed if the alkyl substituent adopts an axial disposition. This is illustrated by cis-4,5-dimethylcyclohexene (8) in which one of the methyl groups must necessarily adopt an axial conformation and the result is an 87:13 ratio of trans:cis epoxides.[28]



(8)

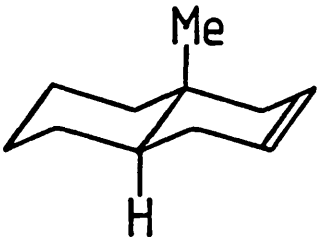


(9)

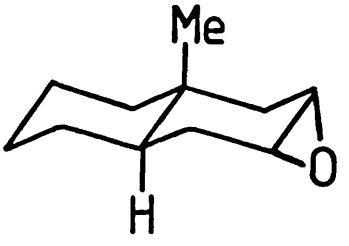
Interestingly epoxidation of 1,6-dimethylcyclohexene (9) with mcpba gave a 36:64 mixture of trans:cis epoxides.[29] This apparent exception is explained by the fact that anti attack of the peracid leading to trans epoxide formation is accompanied by an increase of eclipsing between the two methyl groups whereas syn attack leading to the cis epoxide is accompanied by a corresponding decrease, ie in this example torsional

strain between alkyl substituents is more important than the steric interaction between the alkyl substituents and the peracid reagent in determining the stereoselectivity of epoxidation.

With bicyclic and polycyclic alkenes the shielding by substituents on the two sides of the double bond usually makes it possible to predict which epoxide will be preferentially formed. For example the octalin derivative (10) affords only the epoxide (11) with p-nitroperbenzoic acid due to the methyl group which hinders approach of the peracid to the top face of the alkene.[30]



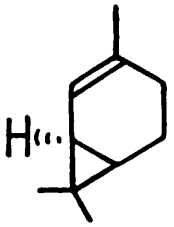
(10)



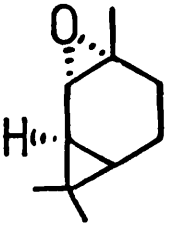
(11)

A similar situation is often found in steroids where the alkene is epoxidised on the face least hindered by the angular methyl group.

In cis-fused systems however, oxidation usually occurs cis to the substituents at the ring junction since these are generally less bulky than the other ring. Hence epoxidation of 2-carene (12), where the substituents are hydrogen atoms, gives only the epoxide trans to the cyclopropyl ring (13).[31]



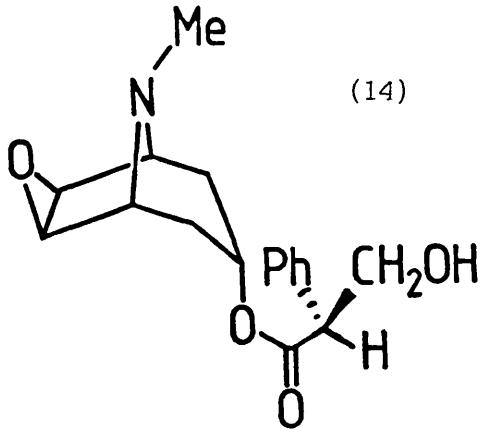
(12)



(13)

Bridged cycloalkenes are also attacked from the less hindered face. Pauling and Fletcher confirmed the exo nature of the epoxide in the tropane alkaloid scopolamine (14) by x-ray crystallography of the

hydrobromide salt.[32] Prior to this a total synthesis of the metabolite which is a powerful narcotic had been achieved.[33] This involved epoxidation of 3-acetoxytrop-6-ene (15) with formic acid and 80% hydrogen peroxide to give (16). A previous attempt with monoperphthalic acid afforded the N-oxide of (15) as the major product. Subsequent conversion of (16) into material identical with the natural product proved it was the exo-oxide formed during epoxidation.



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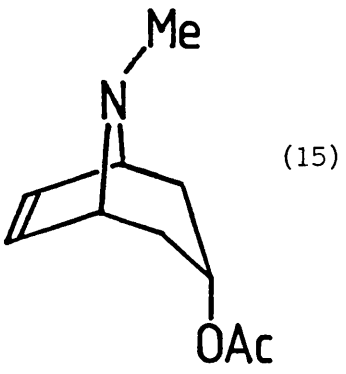

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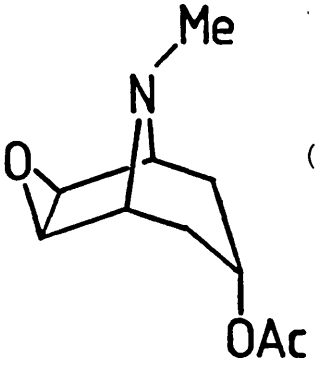
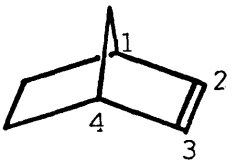


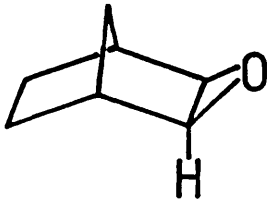
(16)

Epoxidation of norbornene (17) also gives the exo-epoxide (18).[34] As with scopolamine shielding on the endo side should favour the exo isomer. However the very high stereoselectivity led Schleyer to propose that torsional strain factors were also involved.[35] Thus while quasi-eclipsing between the C-H bonds in positions 1 and 2, and 3 and 4, is relieved in the exo-transition state, it is enhanced in the endo one, thereby favouring the exo-epoxide. For 7,7-dimethylnorbornene (19) the

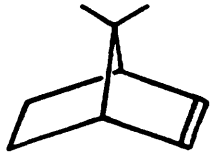
shielding effect on the double bond by one of the geminal dimethyl groups leads to a reversal in selectivity with a 94:6 ratio of the endo:exo epoxides being formed.[34]



(17)

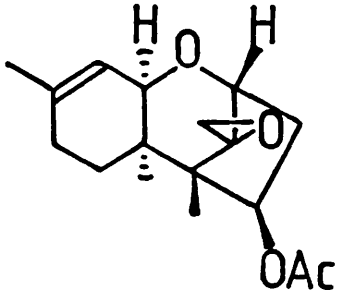


(18)

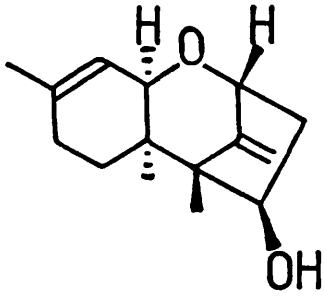


(19)

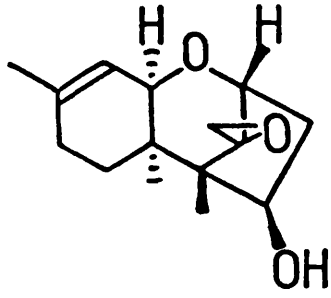
In more complex molecules the conformation around the alkene is important in determining the selectivity. For instance in the synthesis of trichodermin (20), the first total synthesis of a member of the trichothecane sesquiterpenes which show antibiotic, antifungal, cytotoxic and phytotoxic effects, epoxidation of the exocyclic alkene (21) gave exclusively the epoxide (22) which on acetylation of the alcohol gave material identical with the natural product.[36] Interestingly compound (21)



(20)



(21)

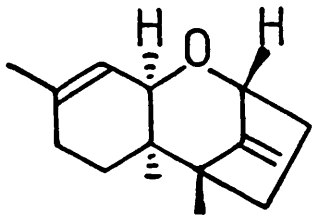


(22)

has two possible sites for epoxidation and the trisubstituted double bond would be expected to be oxidised more quickly than the exocyclic one.

However the secondary hydroxyl group is ideally placed to form a hydrogen bond with the peracid (in an analogous way to peracid epoxidation of allylic alcohols mentioned later) thereby delivering it to the exocyclic alkene and epoxidising it more quickly.

However it was subsequently shown that even in the absence of the hydroxyl group the exocyclic bond is preferentially epoxidised, as illustrated by reaction of (23) with mcpba which furnishes 30% of the naturally occuring metabolite 12,13-epoxytrichothec-9-ene (24) and 40% of recovered exocyclic alkene.[37]



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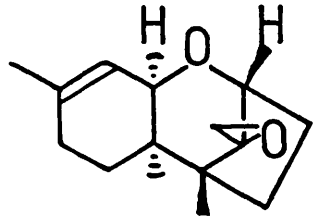
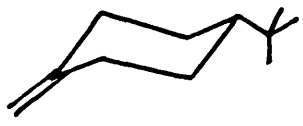


(24)

With simpler exocyclic alkenes such as (25) and other unhindered methylenecyclohexane derivatives, axial attack of the peracid generally takes place. Hence the epoxide (26) is the major isomer formed from (25) but the proportion is dependent on the solvent and peracid used.[38] This axial attack is analogous to nucleophilic attack on cyclohexanones[39] but although a number of interpretations have been proposed the actual explanation is far from totally resolved.



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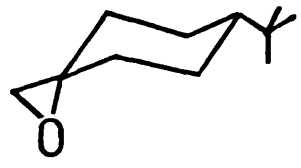
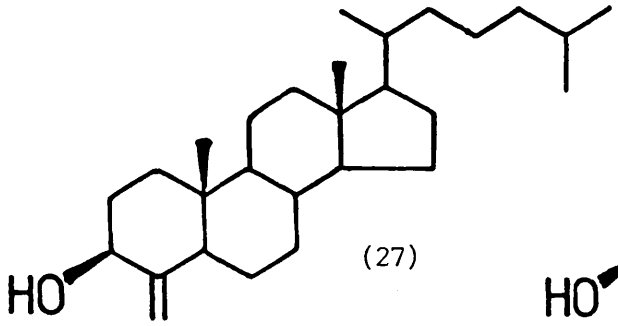


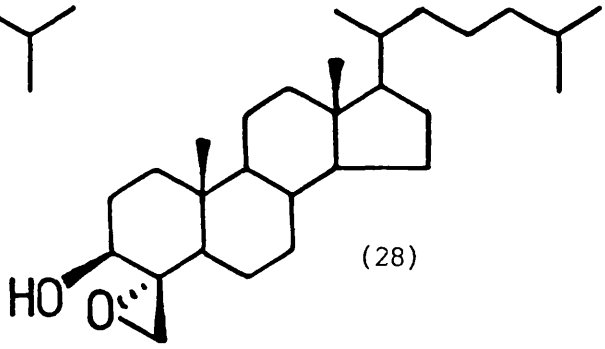
(26)

As will be shown later allylic alcohols are known to exert a cis-directing effect on epoxidation of the double bond with peracids. However Robinson[40] obtained an unusual stereochemical outcome of a peroxyacid epoxidation of the steroid (27). Treatment of the allylic

alcohol or its tetrahydropyranyl ether with mcpba led to exclusive formation of the epoxide (28). Similarly using the Sharpless asymmetric epoxidation method the only oxidation product from reaction of (27) with either (+) or (-)-diethyl tartrate in conjunction with t-butylhydroperoxide and titanium tetraisopropoxide was (28). The absence of the



(27)

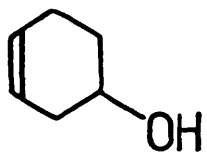


(28)

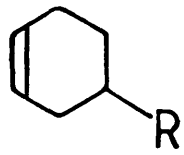
usual directive effect of the hydroxyl group in allylic epoxidation by mcpba is presumably due to the unfavourable steric interactions of a β-face peracid complex with the 19-methyl group and with the 2β and 6β-hydrogen atoms. Also (unless the A ring adopts a boat conformation) the hydroxyl group is locked in an equatorial environment and therefore is not suitably disposed to preferentially direct the peracid to either face of the alkene. X-ray crystallography confirmed that the epoxide oxygen atom was delivered to the double bond exclusively from the α-face of the steroid.

Henbest and Nicholls[41] found epoxidation of cyclohex-3-enol (29) with perbenzoic acid is slower than that of cyclohex-2-enol and gives an approximately equal ratio of both epoxide isomers. This showed the directing effect of an allylic alcohol could not be extended to a homoallylic alcohol.

(29)



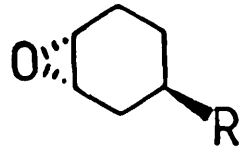
Similar epoxidation of the acetate of (29) also furnished a mixture of epoxides. The work was then extended to cyclohexenes with CH_2OH, CH_2OAc or CO_2Me substituents at the 4-position (30a-c).[42] In each case approach



(30) a R=CH_2OH

b R=CH_2OAc

c R=CO_2Me



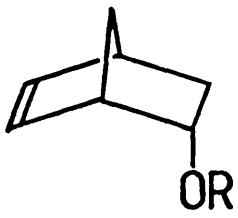
(31) a R=CH_2OH

b R=CH_2OAc

c R=CO_2Me

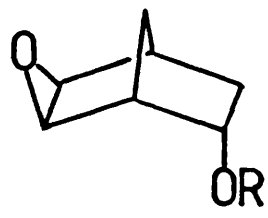
of the peracid to (30a-c) is preferentially trans to the substituent giving the epoxides (31a-c). Other workers[43] had observed a similar result with R=Ph. Since smaller substituents ie R=OH,CN were known to yield a mixture of epoxides it is likely the trans approach to (30a-c) is due to steric hindrance.

They then examined the bicyclic series (32) and (34) which may be regarded as methylene-bridged analogues of (29) and (30) respectively. With the exception of (34a) all these bicycloheptenes gave the trans epoxides (33) and (35) due to attack of the reagent from the less hindered side. This confirms there is no directing effect by the substituents.



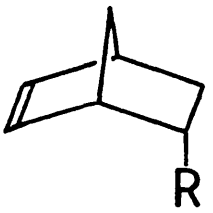
(32) a R=H

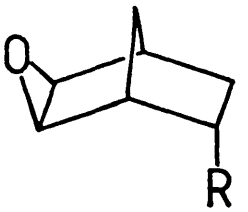
b R=Ac

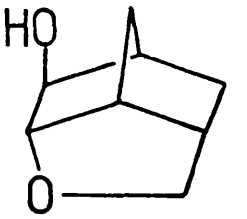


(33) a R=H

b R=Ac







(34) a $R=CH_2OH$

b $R=CH_2OAc$

c $R=CO_2Me$

(35) b $R=CH_2OAc$

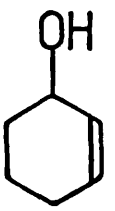
c $R=CO_2Me$

(36)

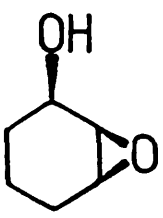
In the case of (34a) which reacted rapidly to give the furan (36) it was apparent the close proximity of the alcohol to the double bond accelerates its oxidation by aiding approach of the peracid. A similar directing effect in the analogous monocyclic case (30) is not possible since the hydroxymethyl group will preferably adopt an equatorial conformation and therefore will be well separated in space from the double bond.

Stereoselective Peracid Epoxidations explained by Interaction with a Charged or Polar Neighbouring Group

The influence of neighbouring groups on the stereochemistry of peracid epoxidations was first investigated by Henbest and Wilson.[44] In particular they studied allylic alcohols and showed that for cyclohex-2-enol (37) only the cis epoxy alcohol (38) was obtained on treatment with perbenzoic acid. Conversion of the alcohol to an acetate



(37)



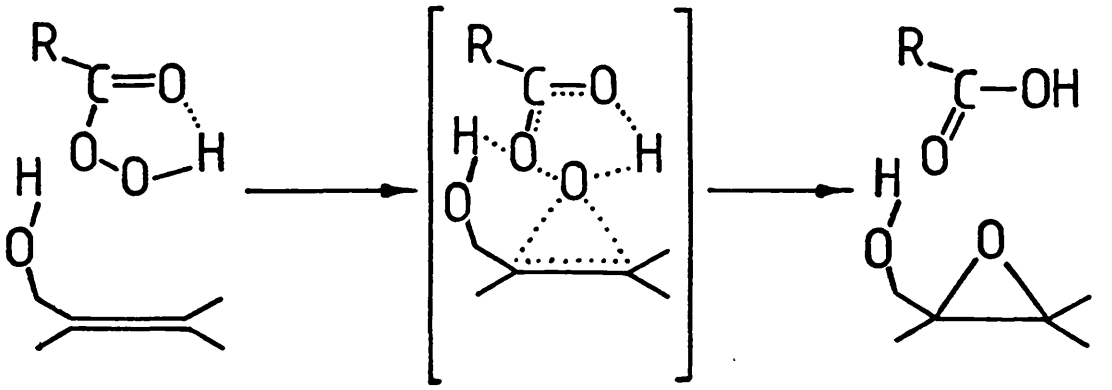
(38)

or ether results in a mixture of epoxides after similar reaction with perbenzoic acid; a 4:1 mixture of trans:cis epoxy esters being obtained

from the acetate.

As expected the epoxidation of (37) was slower than that of cyclohexene because of the electron-withdrawing property of the alcohol. However relative to other allylic O-substituents such as an acetate or ether the alcohol increases the rate of epoxidation.

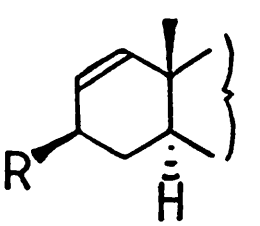
To account for this and the cis-directing effect of the allylic alcohol Henbest and Wilson proposed a mechanism involving a transition complex where the alcohol hydrogen bonds to the peracid creating a favourable intermediate for epoxidation (Scheme 5).



Scheme 5

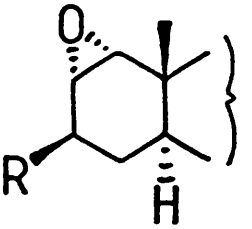
The study was extended from the monocyclic series to steroids where steric and conformational factors can also affect the product distribution.

Thus while cholest-1-ene (39a) and 3β-chlorocholest-1-ene (39b) afforded the α-epoxides (40a,b) because the relatively bulky angular methyl group on the β-side prevents approach of the peracid on this face, 3-hydroxycholest-1-ene (41) gave the cis epoxy alcohol (42).



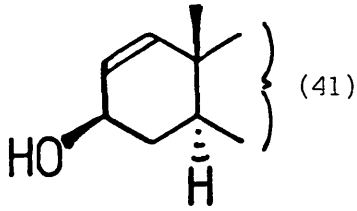
(39) a R=H

b R=Cl



(40) a R=H

b R=Cl



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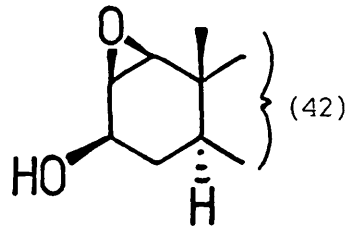
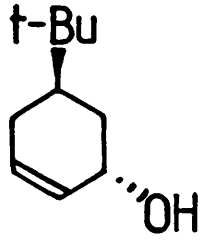


(42)

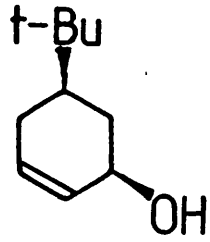
Other steroid systems were also investigated but in all cases the allylic alcohols were found to direct attack specifically at the cis side even where β-approach of reagents is normally difficult.

Whitham[45] extended the monocyclic allylic alcohol series of Henbest and Wilson by looking at the epoxidation of conformationally biassed 5-t-butylcyclohex-2-enols.

While epoxidation of (43) with perbenzoic acid is slower and less cis-stereoselective than (44), in both cases the major epoxide isomer is the cis epoxy alcohol. The work of Henbest and Wilson was repeated and



(43)



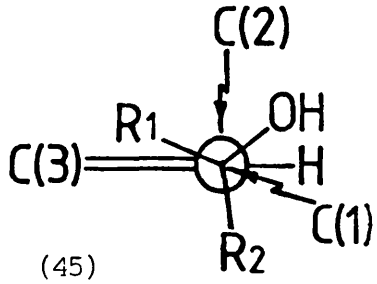
(44)

using gas-liquid chromatography (glc) for determining the product distribution, cyclohex-2-enol (37) gave a 91:9 mixture of cis:trans epoxy alcohols and its acetate gave a 43:57 mixture of cis:trans epoxy acetates.

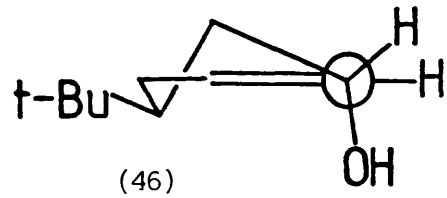
Further studies confirmed that epoxidation of cyclooct-2-enol gives exclusively the trans epoxy alcohol and acyclic allylic alcohols show a preference for formation of the threo epoxy alcohol.

These results can be interpreted consistently if it is postulated that the preferred transition state geometry of the allylic alcohol is close to that depicted in (45).

For the t-butylcyclohex-2-enols only (44), [R_1=CH_2 of ring, R_2=H] in



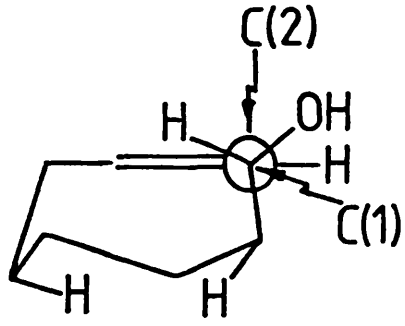
(45)



(46)

which the hydroxyl group is pseudo-equatorial, can adopt the most stable hydrogen bonded transition state with the peracid, which is considered to be positioned on the face of the double bond proximate to the hydroxyl group. Hence its epoxidation is faster and more cis-stereoselective than (43) where the hydroxyl group is pseudo-axial, as in (46), and the smaller C=C-C-O dihedral angle prevents formation of the most stable transition state.

Cyclooct-2-enol is a more flexible ring whose preferred geometry is the chair form (47). This is close to that of (45) [with R_1=H and R_2=CH_2 of ring], thereby allowing accelerated formation of the trans epoxy alcohol, which is also sterically favoured because attack of the peracid on the underside of the double bond is hindered by the α-hydrogens at C-5 and C-8.

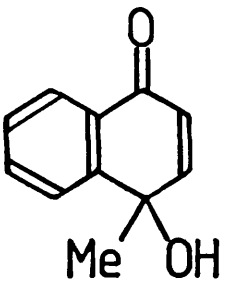


(47)

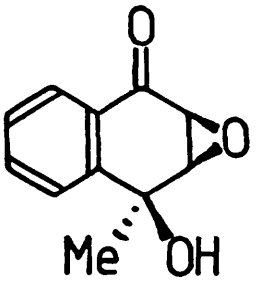
In acyclic allylic alcohols with an asymmetric C-1, the transition state with R_1=alkyl or aryl and R_2=H is of higher energy than the diastereoisomeric transition state with R_1=H and R_2=alkyl or aryl which

preferentially leads to formation of the threo epoxy alcohol.

Jefford[46] reported an unusual stereospecific epoxidation of enones substituted with a γ-hydroxyl group. Treatment of 4-methylnaphthoquinol (48) or its 5-methyl derivative with an ether solution of hydrogen peroxide and Amberlyst 15 (per-Amberlyst 15) gave exclusively the cis epoxy alcohol (49) in high yields. The epoxidation is unusual since normally peracids and hydrogen peroxide are unable to epoxidise enones except when bases or transition metal complexes are present.

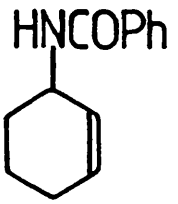


(48)

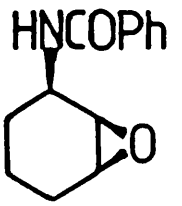


(49)

Shortly after Henbest and Wilson showed that allylic alcohols stereoselectively direct peracid epoxidations, Goodman et al[47] observed a similar effect with allylic amides. They found 3-benzamidocyclohexene (50) on treatment with peracetic acid gave only the cis epoxy amide (51).

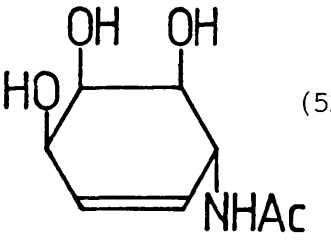


(50)

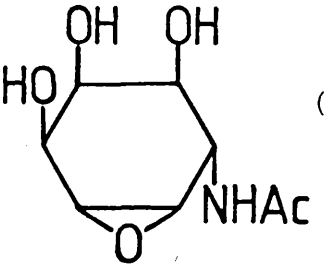


(51)

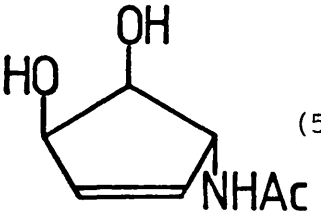
Hasegawa has shown that for cyclic systems an allylic amide is a stronger peracid directing group than an allylic alcohol.[48,49] Hence in the cyclohexane series the allylic amide (52) gave an 85% yield of the epoxy amide (53) on treatment with perbenzoic acid.[48] Similarly (54) was found to give (55) in 87% yield on treatment with mcpba and acetic anhydride.[49]



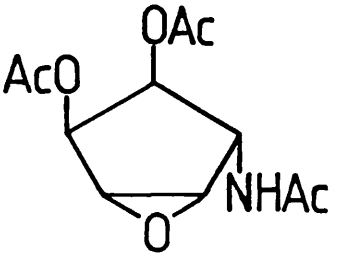
(52)



(53)

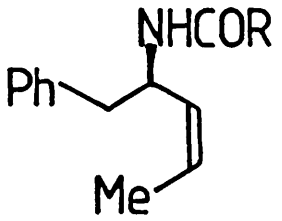


(54)

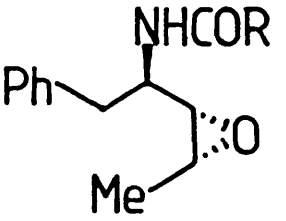


(55)

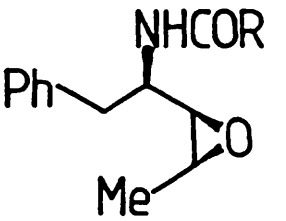
Roush recently investigated the epoxidation of acyclic allylic amides[50] and found that diastereoselectivity in the (Z)-allylic amide series was dependent on both the amide functionality and the epoxidation reagent. Reaction of (56a) with mcpba or (56b) with molybdenum hexacarbonyl and t-butylhydroperoxide gave high threo selectivity, the ratio of threo epoxide (57a,b) to erythro epoxide (58a,b) being 95:5 and 88:12 respectively.



(56) a R=NHPh
b R=CCl_3



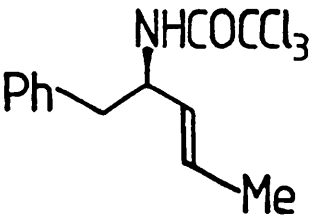
(57) a R=NHPh
b R=CCl_3



(58) a R=NHPh
b R=CCl_3

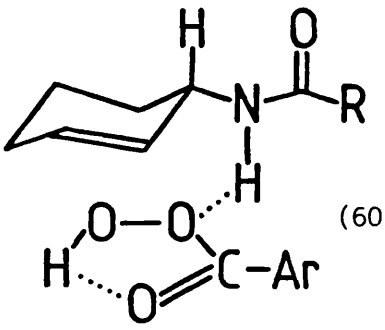
The (E)-allylic amide series is less sensitive to the reagent and amide functionality with (59) giving 76-78% threo selectivity on epoxidation with mcpba, 3,5-dinitroperbenzoic acid or molybdenum hexacarbonyl and t-butylhydroperoxide.

It was speculated that the superior performance of cyclic amides

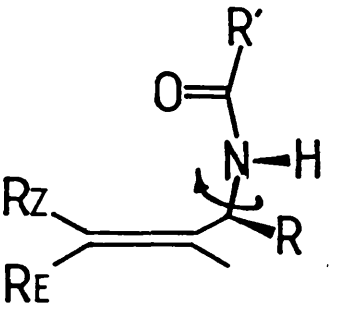


(59)

over acyclic ones in directing peracid epoxidations is related to the conformational preferences of these systems. In a cyclic allylic amide such as (60) the amide will be in a favourable position for hydrogen bonding to the peracid since (i) the s-trans conformation about the amide C-N bond is highly favoured, and (ii) the amide carbonyl will nearly eclipse the N-C-H unit. With acyclic amides the allylic C-H



(60)

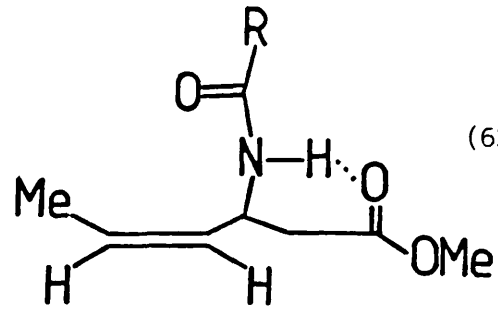


(61)

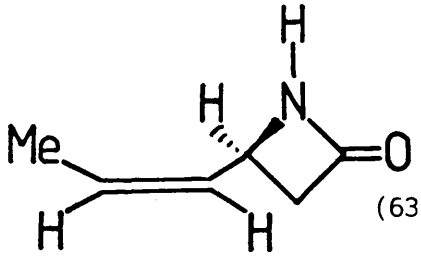
preferentially remains in the plane of the alkene which means the amide NH can direct epoxidation effectively in (61) only if rotation occurs about the allylic C-N bond such that the NH is in a better position to serve as a hydrogen bond donor to the incoming peracid.

This speculation is supported by the fact that peracid or molybdenum hexacarbonyl and t-butylhydroperoxide epoxidation of (62) occurs with low stereoselectivity. In solution the amide NH is strongly intramolecularly hydrogen bonded with the ester carbonyl thereby either preventing or competing with hydrogen bonding to the peracid. Also epoxidation of the azetidinone (63) in which the amide NH is orientated properly for directing peracids gave a high proportion (88:12) of the

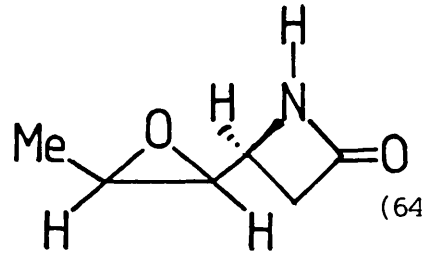
threo isomer (64).



(62)

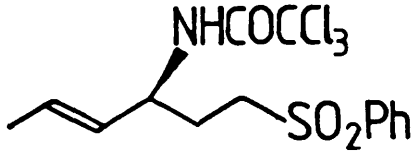


(63)

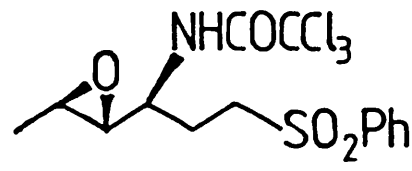


(64)

Epoxidation of (65) with mcpba was stereospecific[51] giving only the epoxy amide (66) confirming that stereoselectivity in the epoxidation of acyclic allylic amides is also dependent on other functionality within the molecule.

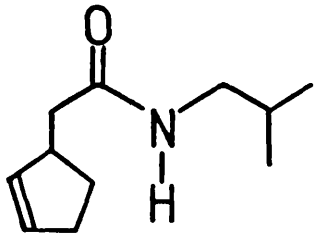


(65)

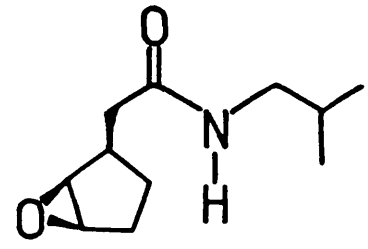


(66)

Mohamadi and Spees recently reported[52] that the amide (67) gave high stereoselectivity on epoxidation with mcpba, an excess greater than 20:1 of the cis epoxide (68) being obtained. They initially assumed this

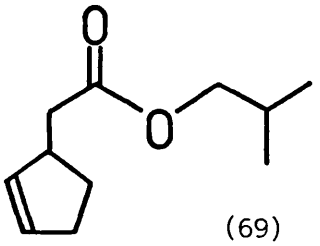


(67)

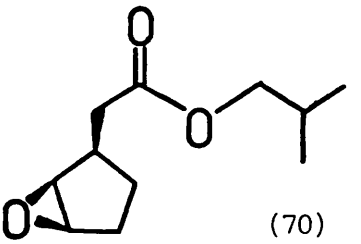


(68)

stereoselectivity was due to hydrogen bonding between the amide NH and the peracid but then found the ester (69) also directs the epoxidation, though the stereoselectivity was reduced to a 3:1 excess of the cis isomer (70). They argued that this reduced stereoselectivity is

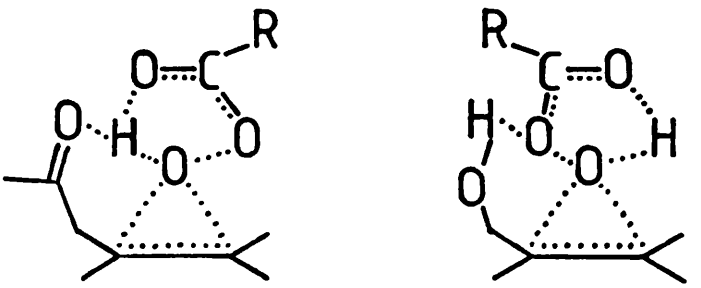


(69)



(70)

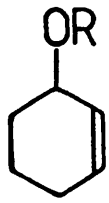
consistent with a decrease in the basicity of the oxygen of an ester with respect to the corresponding amide. Similar results were also observed on replacement of the cyclopentene ring with a cyclohexene ring. They concluded that the carbonyl group must be directing the epoxidation, forming a hydrogen bonded transition state with the peracid which has the same ring size as the analogous transition state for allylic alcohols or allylic amides (Scheme 6).

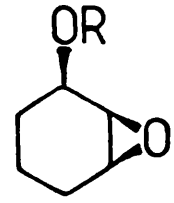


Scheme 6

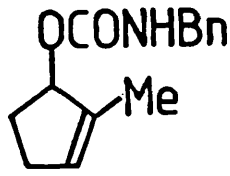
Prior to this Kočovský had found high cis-stereoselectivity in the structurally related carbamates.[53] The allylic carbamates (71a-d) and (73) were found to be oxidised from the syn side with mcpba to give cis epoxides (72a-d) and (74) respectively as the major products.

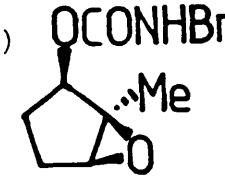
As with the allylic alcohols investigated by Henbest this effect is strong enough to overcome the steric hindrance on the β-side of steroids,





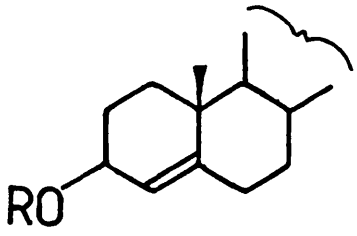
		cis:trans
(71) a R=$CONH_2$	(72) a R=$CONH_2$	3:1
b R=CONHBn	b R=CONHBn	5:1
c R=CONHTs	c R=CONHTs	3:1
d R=$CONMe_2$	d R=$CONMe_2$	10:1

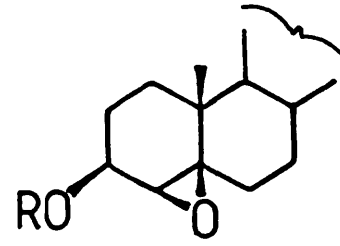
(73) 

(74) 

cis:trans 20:1

with the carbamates (75a,b) giving (76a,b) with almost total stereoselectivity.



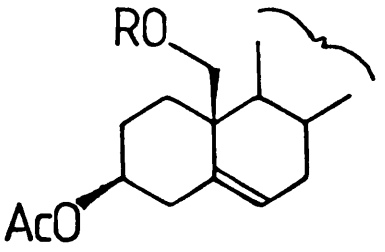


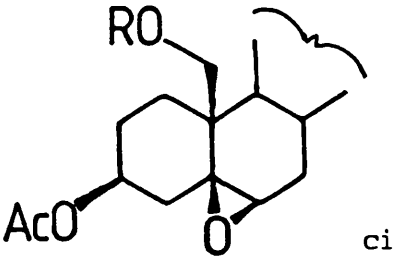
(75) a R=CONHBn
b R=$CONMe_2$

(76) a R=CONHBn
b R=$CONMe_2$

The homoallylic carbamates (77a-c) also exerted a strong directing effect giving the epoxides (78a-c) with a high cis:trans ratio. However with the N,N-dimethylcarbamate (77d) the stereoselectivity is reversed.

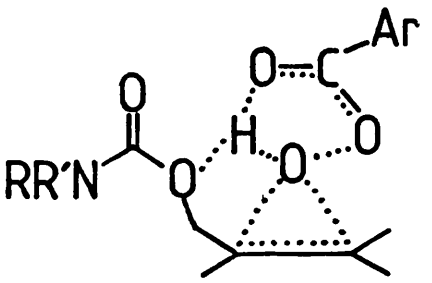
Since the N,N-dimethylcarbamates (71d) and (75b) show a strong directing effect, hydrogen bonding between the NH of the carbamate and the peracid, in an analogous way to that of allylic alcohols or allylic amides, cannot account for the observations. In trying to rationalise



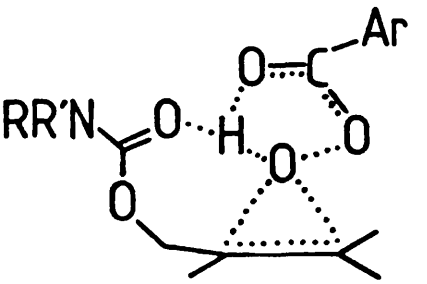


		cis:trans
(77) a R=H_2NCO	(78) a R=H_2NCO	6:1
b R=BnNHCO	b R=BnNHCO	10:1
c R=TsNHCO	c R=TsNHCO	10:1
d R=Me_2NCO	d R=Me_2NCO	1:2

the results Kočovský suggested a number of possible mechanisms which included hydrogen bonding in a reversed way ie from the peracid to either the ether oxygen as in (79), or to the carbonyl oxygen (80) which in carbamates is known to be a much stronger nucleophile.

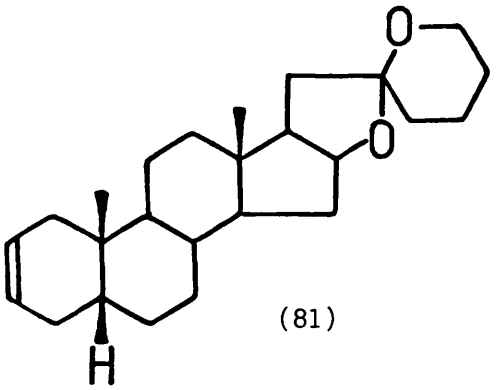


(79)

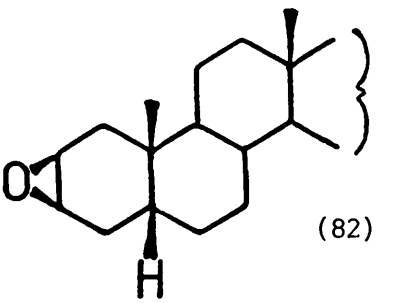


(80)

Ketones have on a small number of occasions been known to effect stereocontrolled epoxidations with peracids. Takeda et al[54] reported that while 25D,5β-spirost-2-ene (81) is known to be attacked from the β-side with peracids to give the epoxide (82), the 11α-hydroxyl (83) and

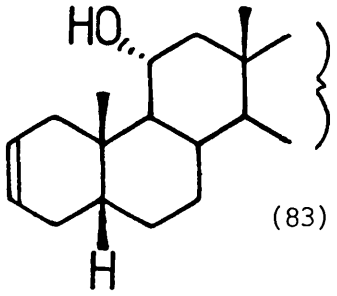


(81)

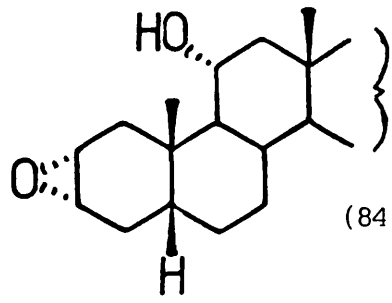


(82)

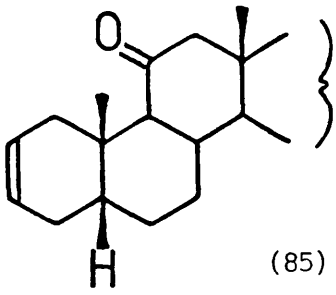
11-keto (85) derivatives give a predominance of the α-epoxides (84) and (86) respectively.



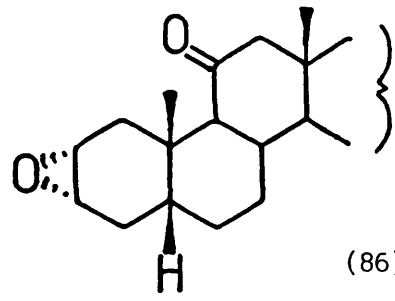
(83)



(84)

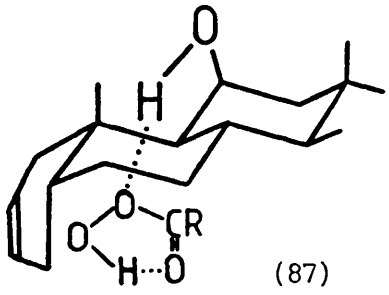


(85)

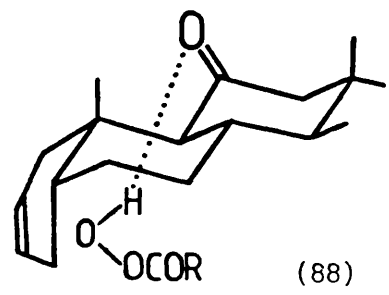


(86)

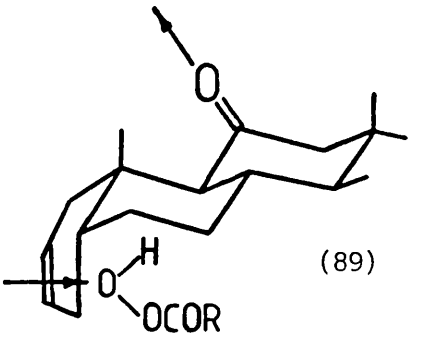
They proposed the following factors to explain these results. In the case of (83) infra-red data show there is a weak hydrogen bond between the hydroxyl group and the double bond suggesting hydrogen bond formation between the hydroxyl group and the peracid as in (87) could control the direction of attack of the reagent. This proposal is backed by the fact that while (83) and (85) give (84) and (86) with almost total stereoselectivity in cyclohexane, use of acetonitrile as solvent (whose polarity disrupts hydrogen bond formation) gives a significant proportion of the β-isomer in each case.



(87)



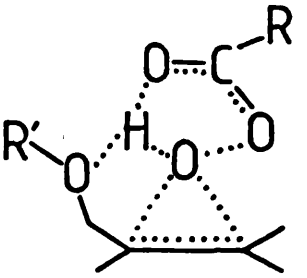
(88)



(89)

For the 11-keto compound they suggested the ketone can hydrogen bond to the peracid as in (88) thereby directing its attack. The possibilities that the dipole-dipole interaction as shown in (89) and distortion of the A ring due to the trigonal bond of the carbonyl group also favour rear-side attack, were considered as alternative explanations for the stereoselectivity.

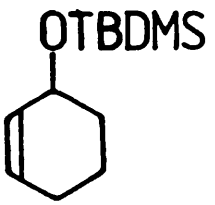
Although allylic ethers generally show a lack of directing effect on epoxidation with peracids, Ganem[55] has observed good cis-stereoselectivity on reaction of silyl ethers with highly acidic peracids. To account for the predominance of cis product the alternative transition complex (90) in which the hydrogen atom of the peracid is hydrogen bonded to the oxygen atom of the ether was proposed.



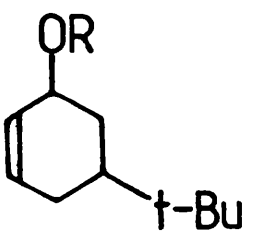
(90)

This idea is supported by the fact that (91) gave a 4.5:1 ratio of cis:trans epoxides on treatment with trifluoroperacetic acid in dichloromethane. This compares with a 1:6.7 ratio obtained with the more weakly acidic mcpba. Also when the reaction was carried out in tetrahydrofuran

to disrupt hydrogen bonding the stereoselectivity of epoxidation of (91) with trifluoroperacetic acid was reversed; a 1:7.5 ratio of cis:trans epoxides being obtained.



(91)



(92) R=α-OH

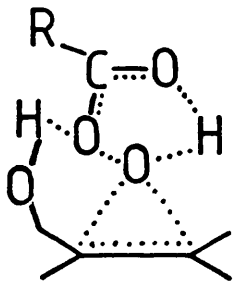
(93) R=β-OH

(94) R=α-OTBDMS

(95) R=β-OTBDMS

(96) R=α-OBn

(97) R=β-OBn

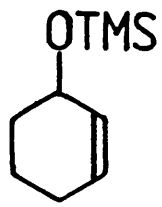


(98)

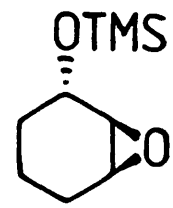
Ganem also investigated epoxidations of the conformationally biased allylic alcohols and allylic ethers (92)-(97). The results were consistent with those previously reported by Whitham but also showed the alcohols (92) and (93) are more cis-stereoselective when treated with highly acidic peracids, and the pseudoaxial ethers (94) and (96) afford mainly cis epoxides on reaction with trifluoroperacetic acid in dichloromethane. Trans epoxy ethers were predominant in all epoxidations carried out in tetrahydrofuran. These results suggest only the pseudoaxial ethers can form the favourable orientation (90) for cis epoxidation. Also since the cis epoxy alcohols were more selectively formed from reaction with trifluoroperacetic acid than with mcpba, it is likely the highly acidic trifluoroperacetic acid can hydrogen bond to the allylic hydroxyl group in either the orientation (90) or the 'classical' transition state of Henbest and Wilson,(98).

With the exception of the previous example, literature references

reporting stereoselectivity on peracid epoxidation of allylic ethers usually show the trans epoxy ether as the major product. This is a consequence of steric factors where the bulk of the ether prevents syn approach of the peracid to the double bond eg the trans epoxide (100) was formed with high selectivity (9:1) on reaction of (99) with mcpba.[56]

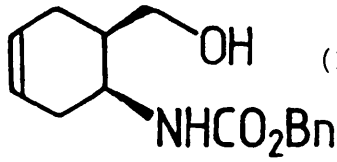


(99)

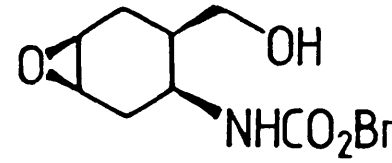


(100)

Reversed homoallylic carbamates ie those in which the N atom of the carbamate function is nearer the alkene have also been shown to effect stereospecific epoxidation of cis-disubstituted cyclohexenes with mcpba, though for steric control the N atom must occupy a pseudoaxial conformation.[57] The cis-substituted cyclohexene (101) or its acetate ester give exclusively the epoxide (102) but conversion of the alcohol to its t-butyldimethylsilyl (TBDMS) ether resulted in formation of mainly the other epoxide isomer. Rotella argued that for the TBDMS ether this was due to the carbamate function being forced to adopt a pseudo-equatorial position.



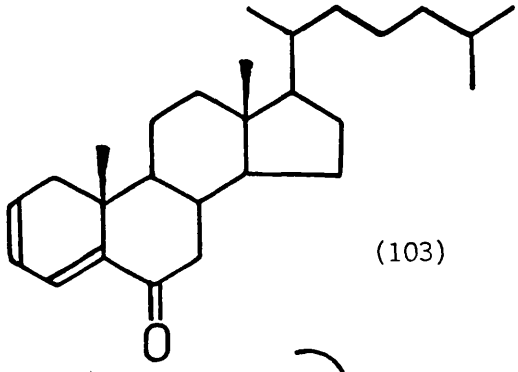
(101)



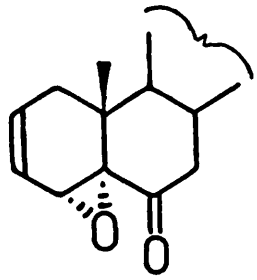
(102)

It is well established that conjugated ketones show a marked decrease in reactivity towards peracids.[58] However Černý et al[59] found dienone (103) gave the epoxide (104) as the major product. The isolation of this α,β-epoxy ketone was surprising in that linear conjugated dienones are epoxidised at the double bond more distant from the carbonyl group. They extended their study to the enones (105)-(108)

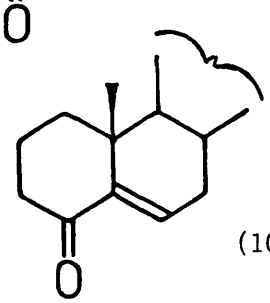
and found on treatment with mcpba that the s-cis ketones (105) and (107) show higher reactivity and furnish a higher yield of the α,β-epoxy ketones than the s-trans isomers (106) and (108). However while (105)-



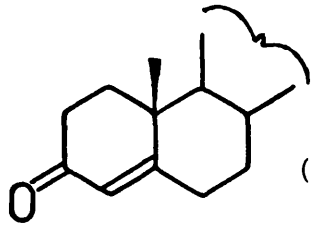
(103)



(104)

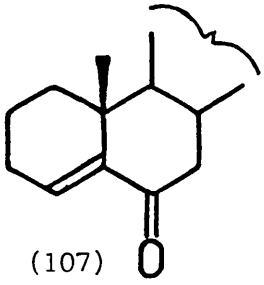


(105)

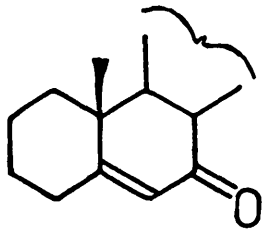


(106)

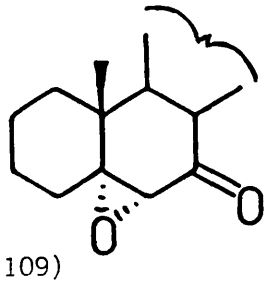
(107) show little stereoselectivity of formation of either diastereomeric epoxide, (108) gave (109) as the sole α,β-epoxy ketone product (27% yield).



(107)



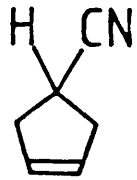
(108)



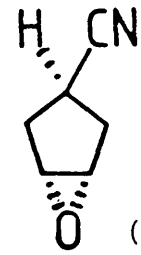
(109)

While it is generally believed that treatment of α,β-unsaturated ketones with peracids gives Baeyer-Villiger reaction products, in all of the above reactions these were formed in low yields or not at all.

A nitrile group has also been shown to induce stereoselectivity in peracid epoxidations. Henbest et al[60] have shown that, in cyclopentane, 4-cyanocyclopentene (110) gives the trans epoxide (111) in a higher ratio than 4-methylcyclopentene, despite the greater bulk of the methyl group. It was proposed that this increased selectivity must be due to a polar

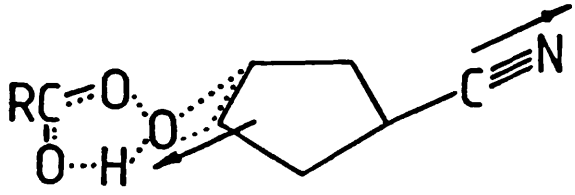


(110)

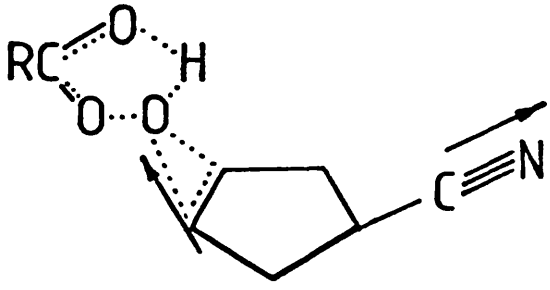


(111)

interaction. This was consistent with the facts that in polar solvents the increased selectivity was not observed and that as the distance between the nitrile group and the double bond increased, the selectivity decreased. Henbest argued that a dipole-dipole interaction between the polar substituent and the polar transition states for cis and trans attack could account for preferential formation of the trans epoxide and also fits with the above observations (Scheme 7).



Preferred interaction from trans attack

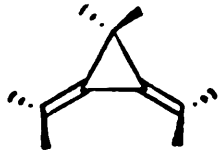


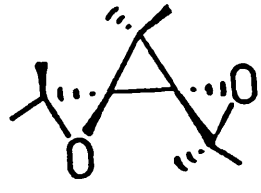
Less favourable interaction from cis attack

Scheme 7

A similar dipole-dipole interaction was proposed to account for the exclusive formation of the trans-diepoxide (113) from the diene (112) ie in the transition state leading from monoepoxide to diepoxide a trans arrangement would give a more favourable interaction.[61]

(112)





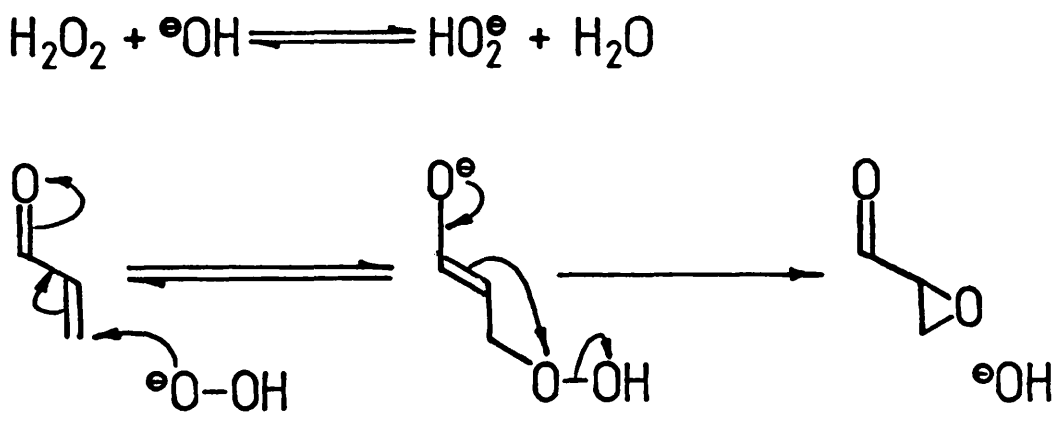
(113)

Epoxidation with Alkaline Hydrogen Peroxide

The use of alkaline hydrogen peroxide for the epoxidation of alkenes was first described by Weitz and Scheffer.[62] They proposed, and it is now well established, that the reagent is selective for alkenes with electron-withdrawing substituents, and therefore complements the peracid epoxidation procedure which tends to work only with electron-rich alkenes. The reaction has been used to prepare epoxides from α,β-unsaturated aldehydes, esters, ketones, sulphones and nitro compounds. In the case of α,β-unsaturated nitriles, epoxy amides are usually formed probably via a peroxycarboximidic acid intermediate. The alkaline hydrogen peroxide procedure was reviewed in detail by Rosowsky[5] and Berti[7], but more recent literature reviews[4,18] have been less comprehensive.

Mechanism of Epoxidation by Alkaline Hydrogen Peroxide

Kinetic studies of the oxidation of mesityl oxide and ethylideneacetone with alkaline hydrogen peroxide at 0°C showed that the reaction is first order with respect to both the α,β-unsaturated ketone and the hydroperoxide anion.[63] This is consistent with the rate-determining stage involving attack of the hydroperoxide anion on the β-carbon in a Michael-type reaction (Scheme 8). This addition is reversible. As

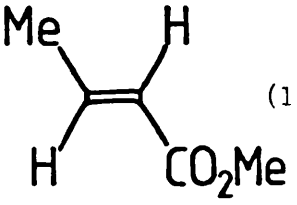


Scheme 8

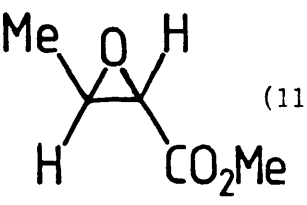
expected alkyl substituents on the β-carbon decrease the reaction rate due to their electron-releasing effect which makes the carbon-carbon double bond less susceptible to attack by the nucleophilic hydroperoxide anion.

Although enone epoxidations are usually carried out in aqueous solution, or in alcohol solvents such as methanol or ethanol, and use aqueous solutions of hydrogen peroxide, anhydrous conditions have also been utilised for effecting epoxidation. Yang and Finnegan found that t-butylhydroperoxide reacts with enones in benzene solution in the presence of a catalytic amount of benzyltrimethylammonium hydroxide (Triton-B).[64] While mesityl oxide, cyclohexenone and other unhindered enones afforded fairly good yields of the corresponding epoxides, both isophorone and 4-cholesten-3-one were inert to the same reaction conditions. This failure to react was ascribed to steric congestion as the bulky t-butylhydroperoxide anion approaches the substituted enone.

Recently Meth-Cohn et al reported another anhydrous method for epoxidising electrophilic alkenes.[65] They found acyclic α,β-unsaturated esters, sulphones, sulphoximines and amides undergo epoxidation on treatment with t-butylhydroperoxide and an alkyl lithium in dry tetrahydrofuran. In contrast to the Weitz-Scheffer epoxidation of acyclic enones which is usually highly stereoselective but not stereospecific,[66] this procedure results in stereospecific and regiospecific epoxidation. Hence treatment of methyl crotonate (114) with methyl lithium at 20° for 2 hours gave a 57% yield of the epoxide (115).



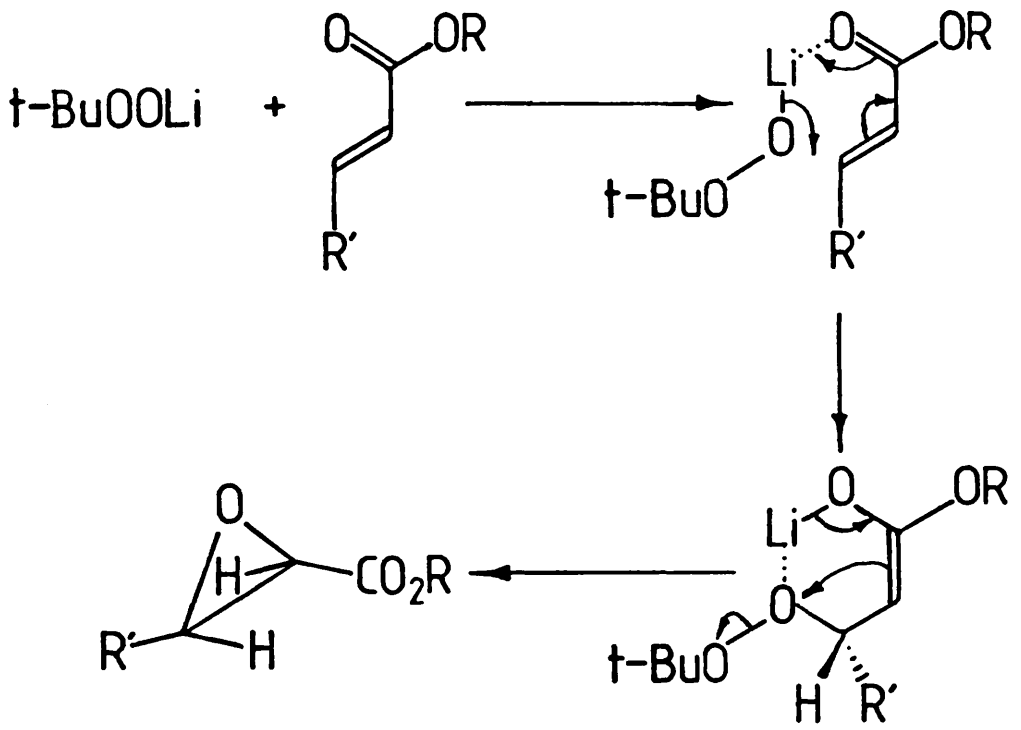
(114)



(115)

The stereospecificity of the reaction derives from a chelate-locking

mechanism (Scheme 9) in which the lithium t-butylhydroperoxide bonds to the carbonyl oxygen.



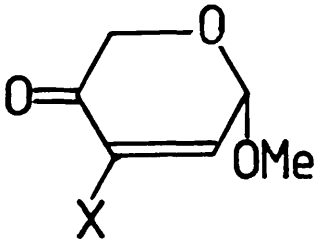
Scheme 9

When a molecule contained both an electron-rich and an electron-poor double bond only the electrophilic alkene was epoxidised, confirming the regiospecific nature of the reaction.

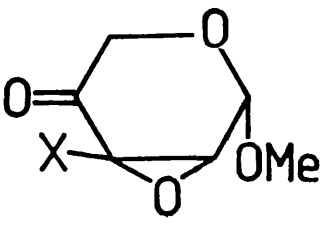
In certain cases it has been found to be advantagous to use sodium hypochlorite as an epoxidising agent for enones. While butenone (methyl vinyl ketone, MVK) gives only poor yields of 3,4-epoxybutanone with alkaline hydrogen peroxide, t-butylhydroperoxide and Triton B or from cyclisation of the bromohydrin, treatment with aqueous sodium hypochlorite which had been partially neutralised with hydrochloric acid afforded the epoxide in up to 70% yield.[67] The mechanism of epoxidation is analogous to that found for alkaline hydrogen peroxide.[68]

Interestingly similar conditions resulted in highly stereoselective epoxidation of the enones (116a,b).[69] These gave only the epoxides

(117a,b), the stereochemistry being assigned on the basis of $J_{1,2}$ coupling constant values. These were 1.0 and 1.2 Hz respectively, consistent with cis-related protons which show values in the range 0.8-2.5 Hz in 2,3-anhydro sugar derivatives while no coupling is observed when the protons are trans-related. The γ-methoxyl group is therefore capable of stereospecifically directing the epoxidation cis to itself.



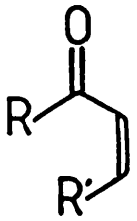
(116) a X=Cl
b X=Br

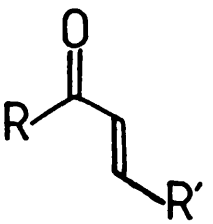


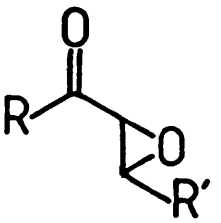
(117) a X=Cl
b X=Br

Stereoselective Alkaline Hydrogen Peroxide Epoxidations due to Steric Hindrance, Angle Strain or Conformational Factors

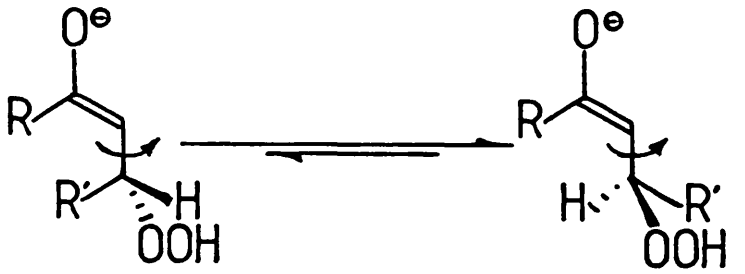
For acyclic enones the Weitz-Scheffer reaction is usually highly stereoselective but not stereospecific. Hence alkaline epoxidation of both cis or trans enones (118) and (119) usually gives mainly the epoxide (120) in which the substituents are trans.[66] This is because the hydroperoxy enolate ion can adopt whichever is the less congested conformer prior to ring closure (Scheme 10).

(118) 

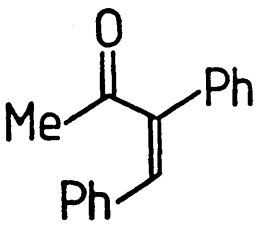
(119) 

(120) 

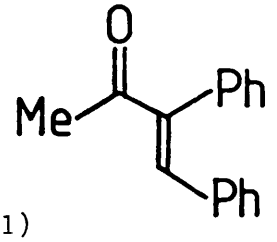
However epoxidation of α-phenylbenzalacetone (121) gave exclusively the epoxide (122) in which the phenyl substituents are cis.[66] This led to the proposal that the intermediate hydroperoxy enolate (123) is less

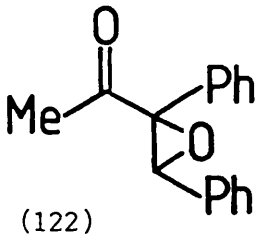


Scheme 10



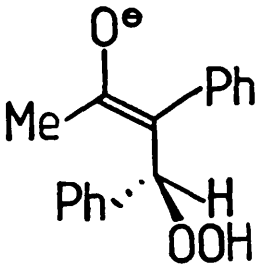
(121)



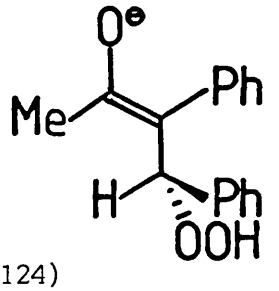


(122)

energetically favoured than (124) because the Van der Waals interaction between the enolate, which is coplanar, and the phenyl group in (123) is greater than that of the two phenyl groups in (124).

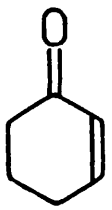


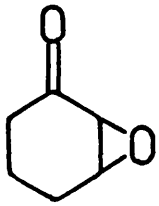
(123)



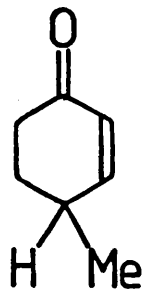
(124)

For cyclic enones in which the α,β-unsaturated bond is endocyclic the situation is more complex even though rotation about the α,β-bond in the transition state is impossible. With simple enones such as cyclohexenone (125) only one epoxide (126) is possible. However when the enone molecule possesses a chiral centre the epoxidation may be stereoselective. For example epoxidation of 4-methylcyclohexenone (127) could give either (128) or (129), the proportion of each being determined by

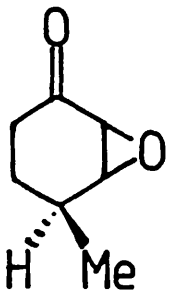
(125) 

(126) 

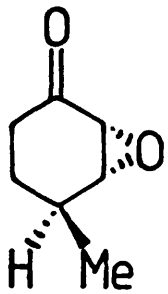
the C-4 substituent. When such an epoxidation gives exclusively one diastereomer the reaction is stereospecific.



(127)

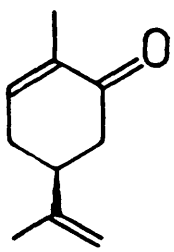


(128)

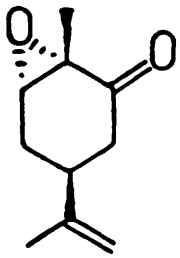


(129)

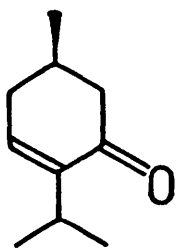
Both carvone (130) and 4-menthen-3-one (132) give only epoxides (131) and (133) respectively on alkaline epoxidation.[70] The stereo-specificity in each case is attributable to the stereo-electronic requirement that in the transition state the hydroperoxide group should



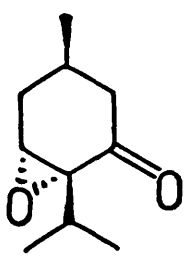
(130)



(131)



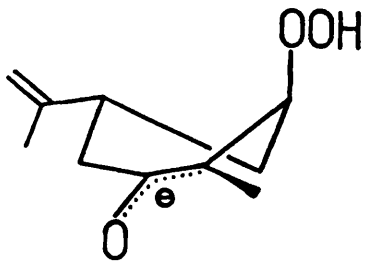
(132)



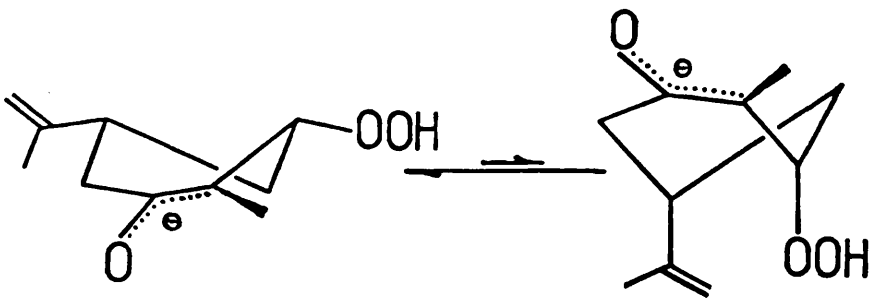
(133)

be as near to axial as possible, as depicted in (134) for carvone, thereby ensuring colinearity of the enolate π-orbital with the O-O bond for the cyclisation step. Although there are two possible axial hydroperoxy enolate diastereomers, each leading to different products, this one is far more stable and hence only one epoxide is formed. The other one (135) in which the hydroperoxy group cannot be axial is very slow to cyclise

(134)

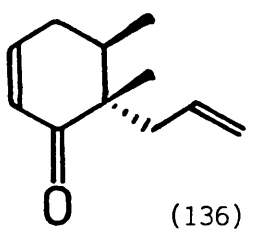


and may revert to starting materials.

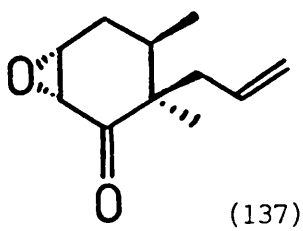


(135)

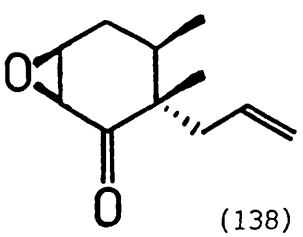
This theory of optimal overlap control was also used to explain the formation of a 3:1 mixture of the epoxides (137) and (138) respectively from the enone (136).[71] The isomeric compound (139) failed to epoxidise under the same conditions. Similarly the epoxy ketone (140) was the sole



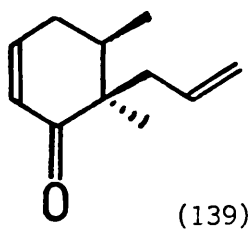
(136)



(137)



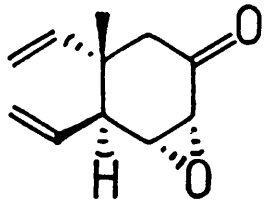
(138)



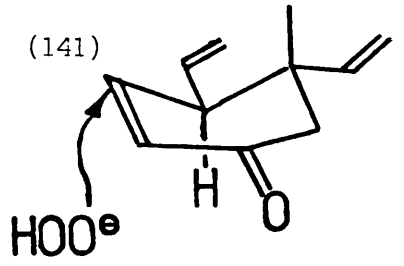
(139)

product on alkaline epoxidation of the analogous enone because of the sterically hindering axial methyl group,[72] as shown in (141).

(140)

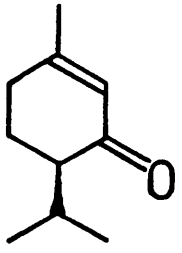


(141)

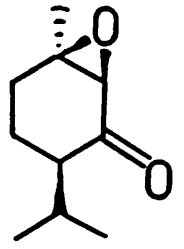


The formation of an 8:2 mixture of (143) and (144) from piperitone (142) is not due to optimal overlap control however. It is a result of the chiral centre α to the ketone in both the epoxides and the starting enone epimerising under the basic reaction conditions.[73] Epoxide (143) is the thermodynamically favoured product.

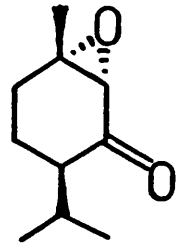
(142)



(143)

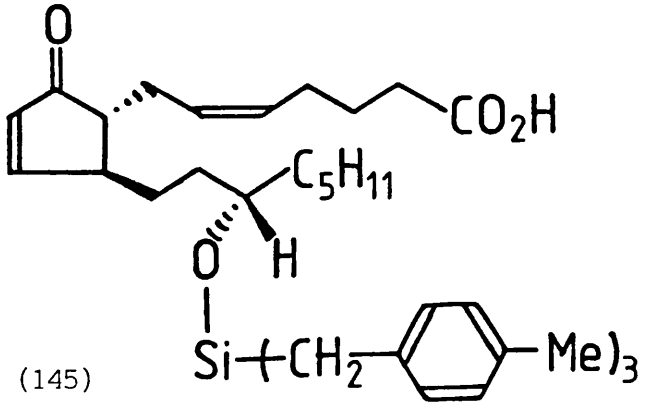


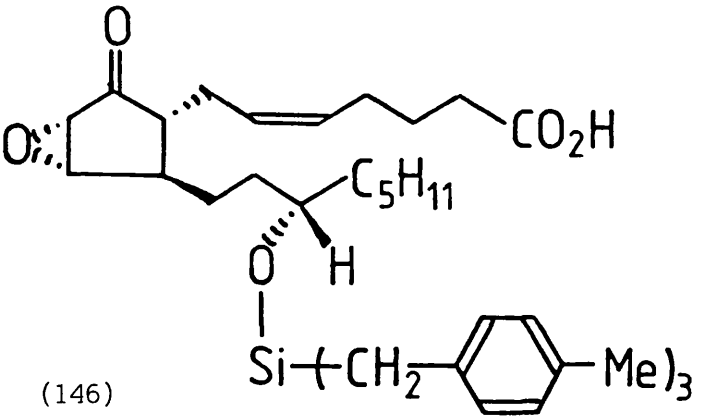
(144)



In prostaglandin work Corey has used a bulky silyl protecting group for effecting selective epoxidation.[74] The epoxide trans to the γ-substituent (146) was favoured over the cis isomer by a ratio of 94:6 on reaction of the enone (145) with alkaline hydrogen peroxide at -40°. Epoxidation of the unprotected alcohol was much less selective.

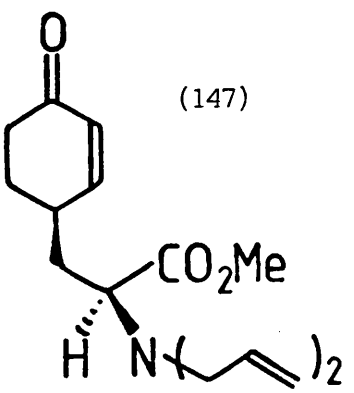
(145)



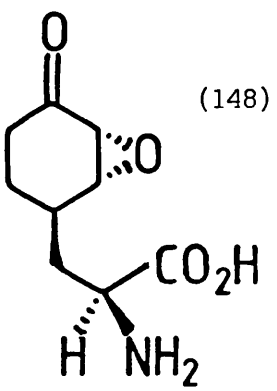


(146)

In contrast to this a synthesis of the naturally occuring antibiotic anticapsin (148) involved epoxidation of the chiral enone (147). This gave a 5:2 mixture of the cis and trans epoxides, the minor component affording the natural product after deprotection of the amine, saponification and chromatographic separation.[75]

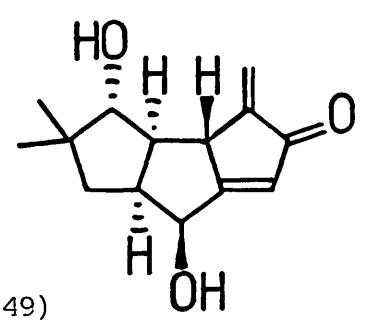


(147)

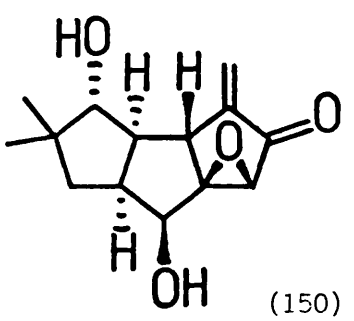


(148)

In more complex ring systems other factors such as ring junction strain can determine the stereochemistry of a Weitz-Scheffer epoxidation. For instance compound (149) gave only the epoxide (150) since only a cis ring fusion of the two cyclopentanes is strain free.[76]

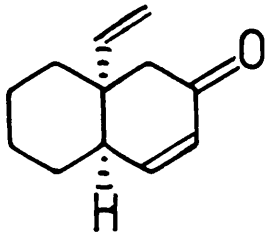


(149)

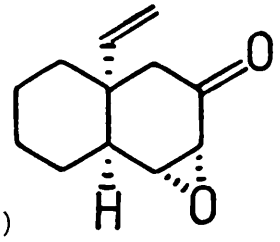


(150)

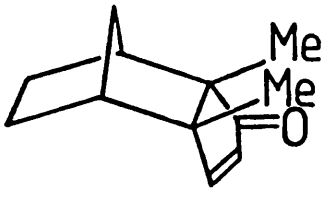
In the cis-fused enones (151) and (153), the saturated ring provides more hindrance than the angular vinyl or methyl group. Epoxides (152) and (154) are formed in 64-68% and 90% yields respectively.[77,78]



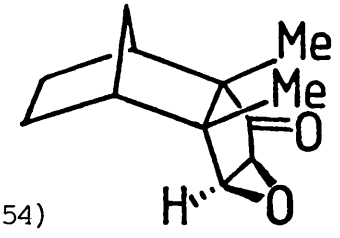
(151)



(152)



(153)

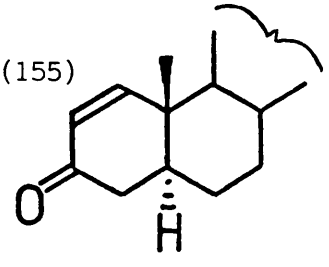


(154)

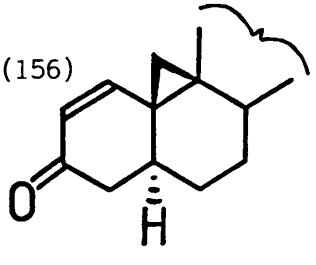
For cyclic enones in which the α,β-unsaturated bond is exocyclic, rotation about the α,β-bond in the transition state is possible and the more stable epoxide is preferred.[79]

The position with steroid enones is complex. Alkaline epoxidation of the enones (155)[80] and (156)[81] gives only the α-epoxides. In both cases the axial ring junction substituent prevents approach of the

(155)

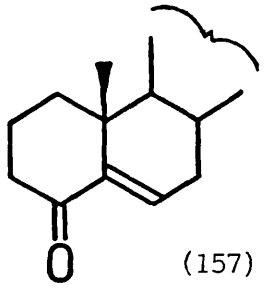


(156)

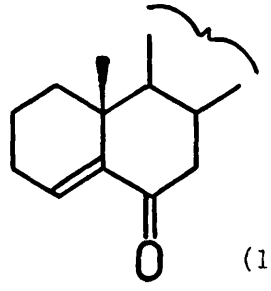


hydroperoxide anion to the β-face of the enone. However 3-keto-Δ^4-steroids where the axial methyl group is almost identically placed relative to the enone favour formation of the β-epoxide. The β-epoxides are also obtained on epoxidation of (157) and (158).[82] In this case only β-attack of the hydroperoxide anion gives an intermediate in which the

p orbitals of the enolate are suitably aligned with the hydroperoxy group for the cyclisation step ie the situation is similar to that found for carvone (130).



(157)



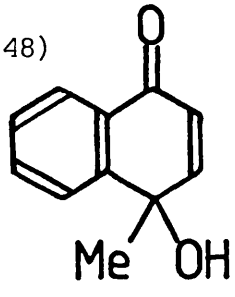
(158)

Stereoselective Alkaline Hydrogen Peroxide Epoxidations explained by Interaction with a Charged or Polar Neighbouring Group

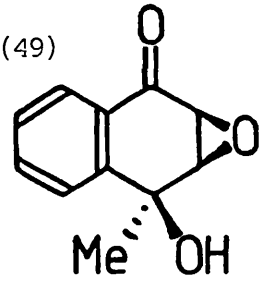
The influence of neighbouring groups on the stereoselectivity of epoxidation of enones with alkaline hydrogen peroxide has been less thoroughly investigated than the epoxidation of analogous alkenes with peracids. Despite this, a number of highly stereoselective epoxidations have been reported in the literature.

Carnduff[83] found that epoxidation of the naphthoquinol (48) with alkaline hydrogen peroxide led stereospecifically to the cis epoxy alcohol (49). This product was also obtained from base-catalysed isomerisation of the hydroperoxide (159) and from stereospecific addition of methyl lithium to naphthoquinone epoxide (160). Surprisingly (49) was obtained in good yield (64%) from prolonged treatment of (48) with mcpba.

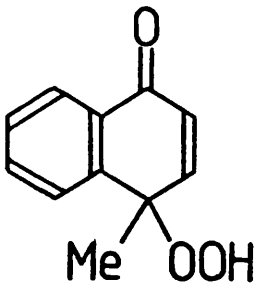
(48)

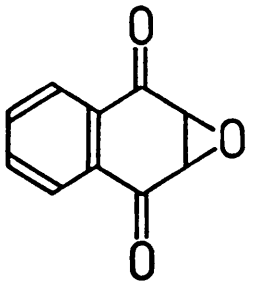


(49)

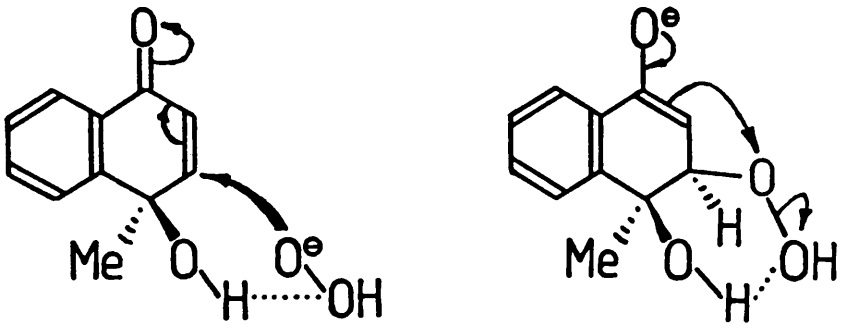


To account for the exclusive formation of the cis isomer (49) in the

(159) 

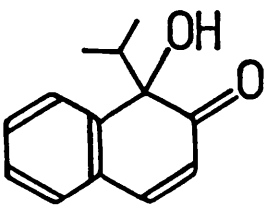
(160) 

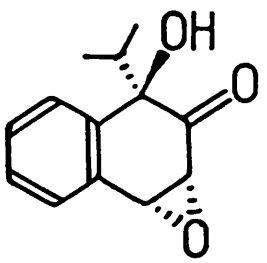
alkaline hydrogen peroxide epoxidation it was proposed that there may be an interaction of the hydroxyl group with the incoming hydroperoxide anion or with the departing hydroxide ion in the ring closure step (Scheme 11). Either of these mechanisms could result in preferential formation of (49).



Scheme 11

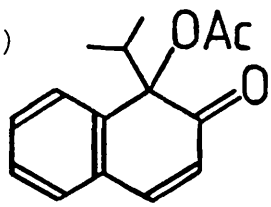
While investigating hydroperoxynaphthalenones generated by autoxidation of 1-alkyl-2-naphthols Carnduff and Leppard isolated a product which appeared to be an epoxide of the naphthalenone (161).[84,85]

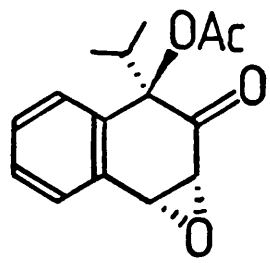
(161) 

(162) 

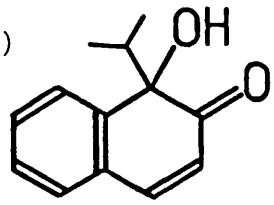
On deliberate epoxidation of the enone (161) with alkaline hydrogen peroxide they obtained the same epoxide in over 90% yield, which was shown to be (162). Similar treatment of the acetate (163) also gave only the epoxide (164) in good yield. No explanations were offered for the stereospecificity of these epoxidations but the trans epoxy alcohol

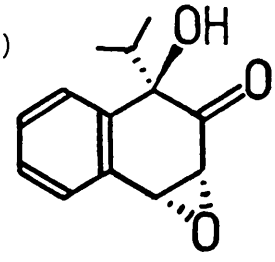
stereochemistry of (162) was confirmed by x-ray crystallography.[87]

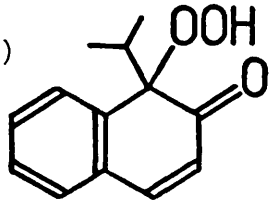
(163) 

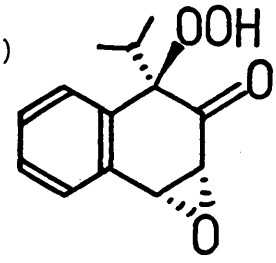
(164) 

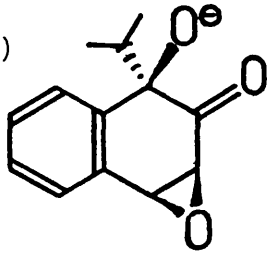
Base-catalysed rearrangement of the hydroperoxy enone (165) gave a complex mixture of products.[85] Despite this a combination of intra- and intermolecular epoxidations could explain formation of all the products.

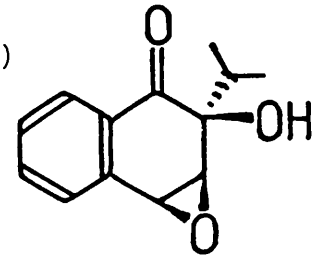
(161) 

(162) 

(165) 

(166) 

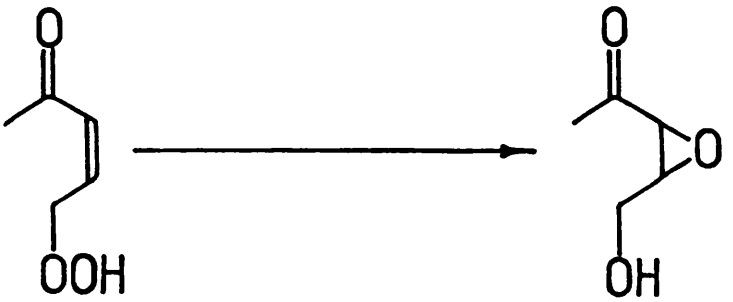
(167) 

(168) 

Since (161) is known to give exclusively the trans epoxy alcohol (162) on reaction with alkaline hydrogen peroxide,[86] it seems likely that intermolecular reaction of two molecules of (165) would lead to both (161) and (166). Epoxidation of another enone molecule by (166) would give (162). Intramolecular epoxidation of (161) should lead to the anion (167) but this is converted by ketol rearrangement into the thermodynamically more stable anion of (168). While (161), (162) and (168) were all separated

and characterised from the complex mixture, the absence of (166) and (167) could be accounted for by their subsequent transformation into other isolable products.

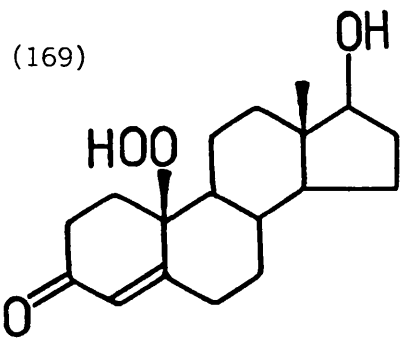
A large number of papers have appeared in the literature concerning the base-catalysed rearrangement of γ-hydroperoxy enones to α,β-epoxy-γ-hydroxyketones (Scheme 12).

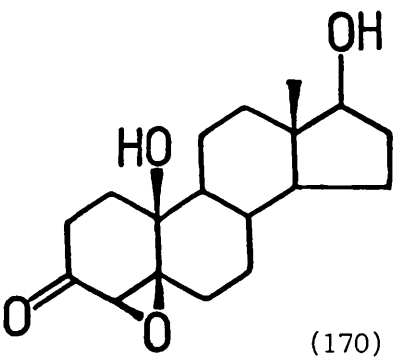


Scheme 12

When a molecule contains such a system it may either undergo intramolecular self-epoxidation giving the epoxy alcohol or may effect the epoxidation of another γ-hydroperoxy enone. In the latter case the products are an α,β-epoxy-γ-hydroperoxyketone and a γ-hydroxy enone (which could then be intermolecularly epoxidised by another hydroperoxide). For example the hydroperoxide (169) decomposed by intermolecular oxygen transfer on reaction with methanolic sodium hydroxide to give the epoxy alcohol (170) in 95% yield.[88]

(169)

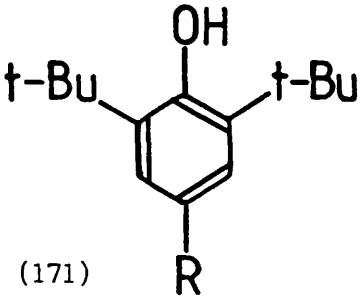




(170)

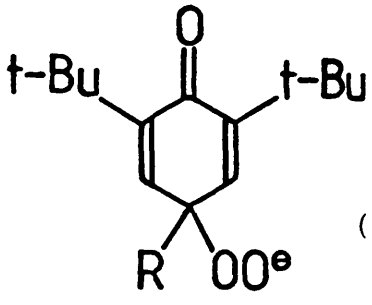
While oxygenation of phenols in the presence of base generally leads to a complex mixture resulting from the introduction of oxygen as well as

oxidative coupling of the phenolic ring, it has been shown that when t-butyl groups are in the ortho or para positions little or no coupling takes place due to steric hindrance and a less complex mixture is obtained. Nishinaga[89] found potassium t-butoxide-catalysed oxygenation of 4-alkyl-2,6-di-t-butylphenols (171) gave the p-hydroperoxy anion intermediate (172) in aprotic solvents such as N,N-dimethylformamide, dimethyl sulphoxide and hexamethylphosphoric triamide while in t-butanol addition occurs to give the isomeric o-hydroperoxy anion intermediate (173). At room temperature these intermediates undergo intramolecular

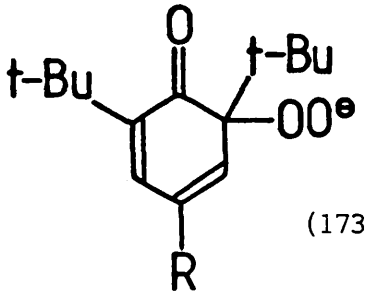


(171)

conversion to the para and ortho epoxy quinols (174) and (175) respectively. At lower temperatures however, the hydroperoxides (176) and (177) can be isolated.

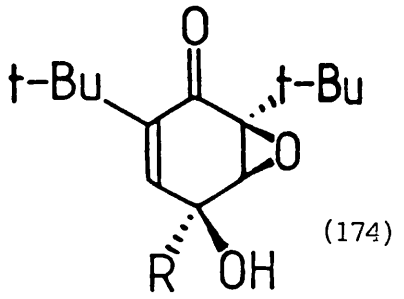


(172)

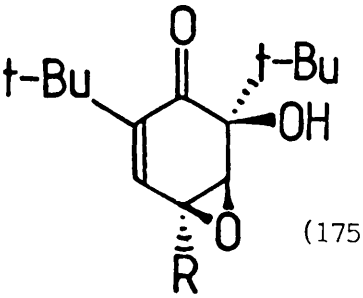


(173)

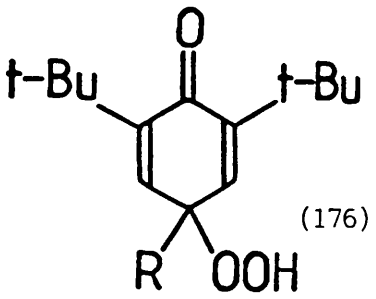
Since the proposed mechanism for formation of the epoxy quinols involves intramolecular Michael addition of the anion to the enone and then decomposition of the resulting dioxetane intermediate (Scheme 13) the epoxy and hydroxyl functions in (174) and (175) should be cis.



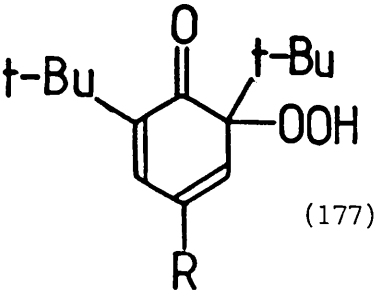
(174)



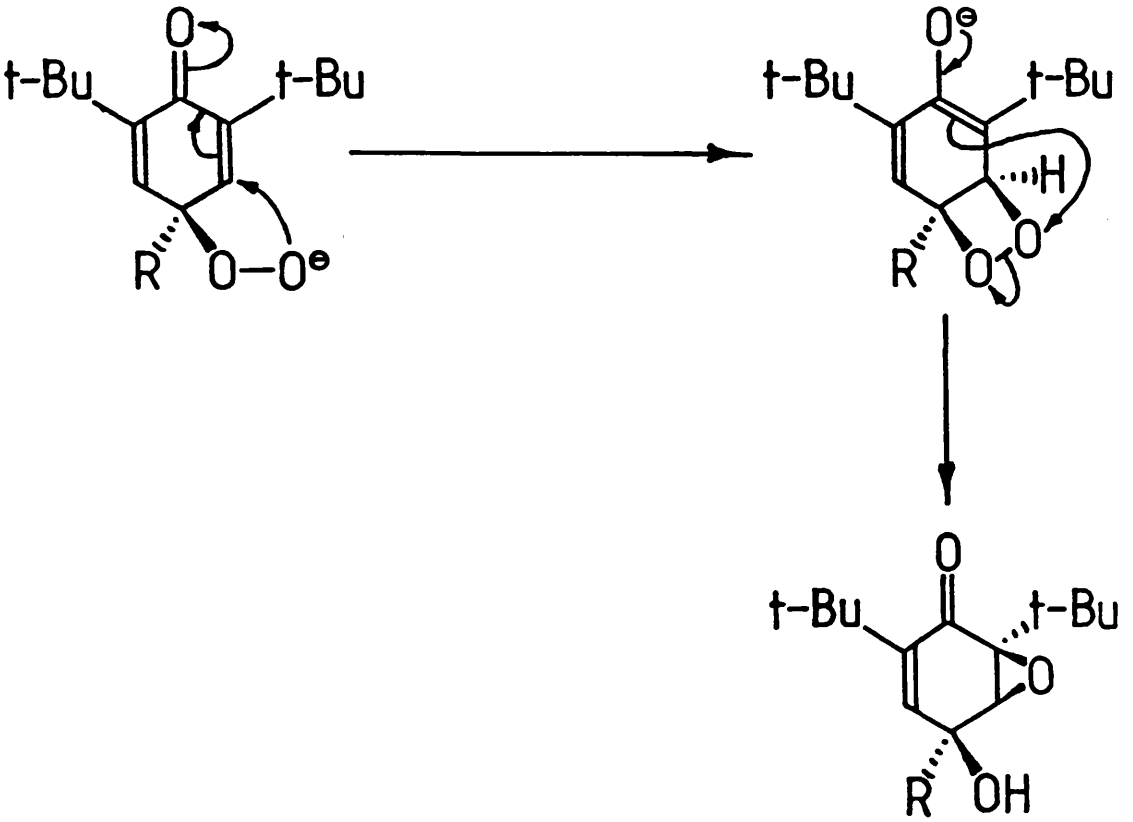
(175)



(176)



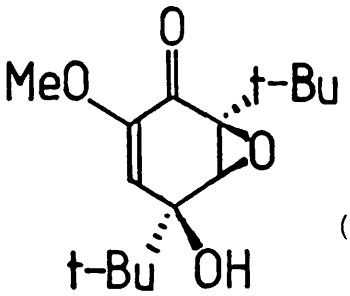
(177)



Scheme 13

For the para epoxy quinol (178) which is similarly formed by base-catalysed autoxidation of 3,5-di-t-butyl-2-hydroxyanisole the cis stereochemistry of the epoxy and hydroxyl groups was confirmed by x-ray

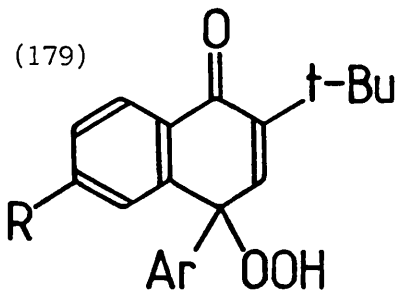
crystallography.[90,91]



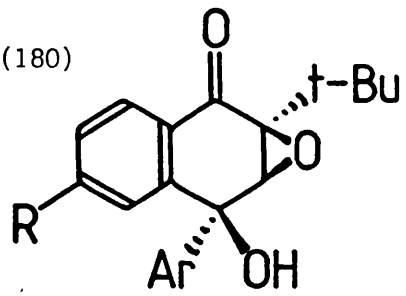
(178)

Rieker[92] reported that the para-hydroperoxide (179) yields the epoxy quinol (180) on treatment with base. Again the cis nature of the epoxy and hydroxyl functions in (178) was proved by x-ray crystallography.

(179)

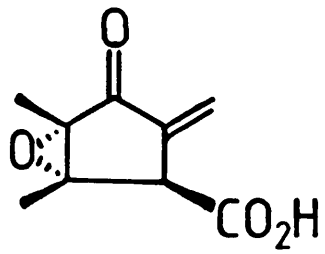


(180)

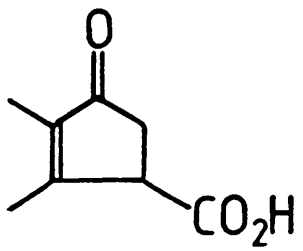


A few other cases have been reported in the literature where γ-substituted enones have undergone stereoselective Weitz-Scheffer epoxidations.

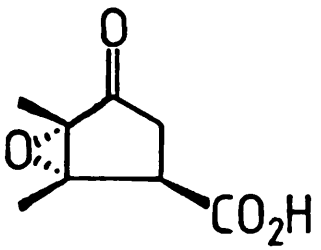
Jernow,[93] in establishing a total synthesis of the antibiotic methylenomycin A (181), treated the unsaturated acid (182) with alkaline hydrogen peroxide and reported formation of the trans epoxy acid (183).



(181)



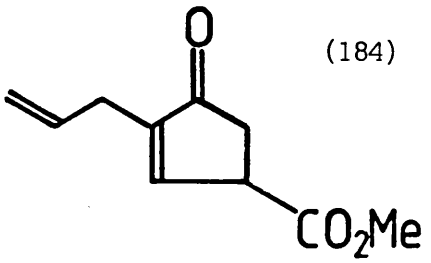
(182)



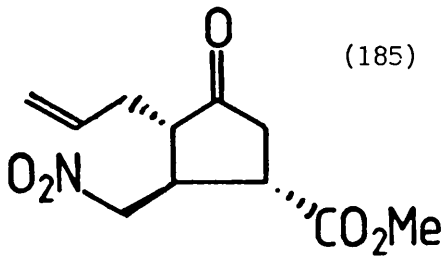
(183)

While electrostatic repulsion between the carboxylate anion of (182) and

the hydroperoxide anion would explain the formation of only the trans epoxide, the fact that treatment of the ester (184), where no carboxylate anion can be formed, with nitromethane also led to the trans Michael adduct (185)[94] means that a steric or polar repulsion between the acid carbonyl group of (182) and the hydroperoxide anion cannot be excluded.



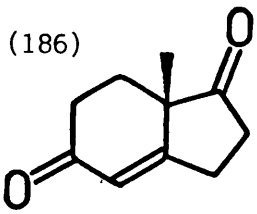
(184)



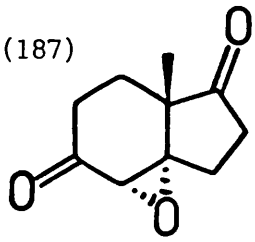
(185)

For the enone (186) which has a γ-ketone substituent, intramolecular delivery has been used to explain the stereoselectivity of epoxidation.[95]

(186)

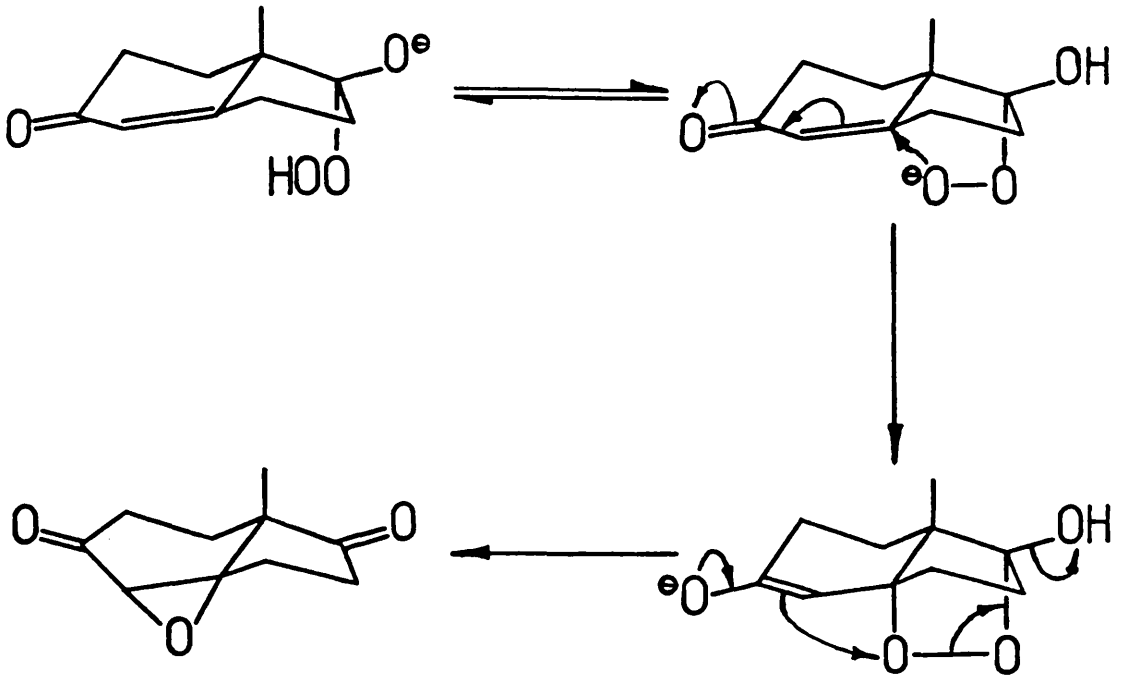


(187)



It gave only the epoxide (187) when reacted with alkaline hydrogen peroxide. The trans stereochemistry of the ring junction was confirmed by comparison with the corresponding cis epoxide which had been synthesised by a stereochemically unambiguous route. The proposed mechanism involved initial attack at the less hindered face of the non-conjugated ketone followed by intramolecular delivery of the hydroperoxide anion to the enone (Scheme 14).

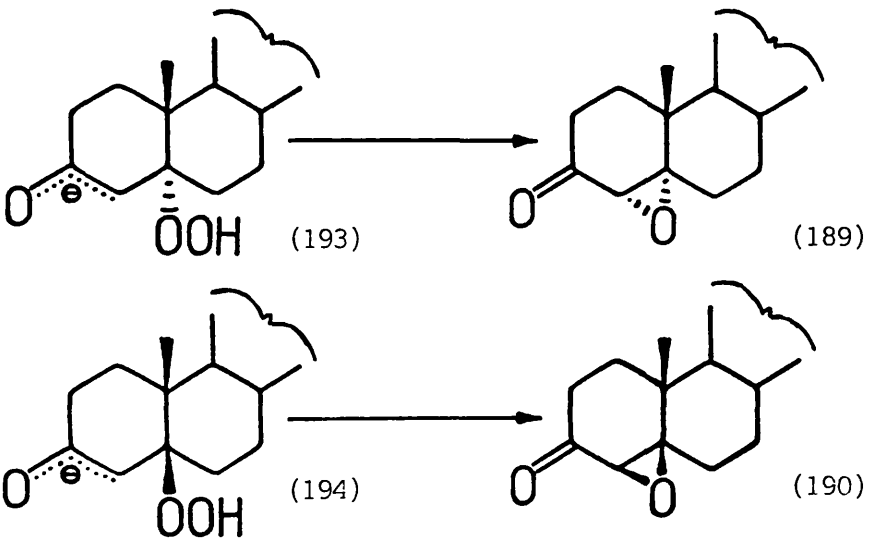
Henbest and Jackson[96] showed that even remote polar substituents have a directing effect on the alkaline epoxidation of 3-keto-Δ^4-steroids. Unlike peracids which give α-epoxides due to steric hindrance by the methyl group on the β-face, epoxidation of (188a) and (188b) with alkaline hydrogen peroxide gives exclusively the β-epoxides (190a) and (190b).



Scheme 14

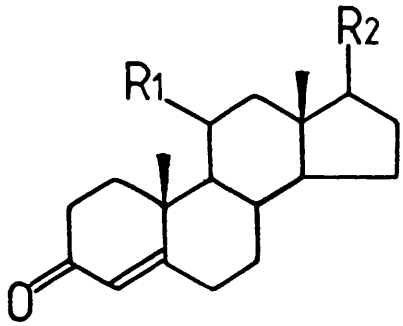
Only when polar substituents were introduced at C-11 and C-17, (188c-k) and (191c-e), was any α-epoxide (189) observed (Table 1).

To account for the formation of only the β-epoxides (188a) and (188b) they suggested the relief in steric strain and solvent compression on going from the intermediate enolate (194) to the epoxide (190) must be greater than in the analogous conversion of the enolate (193) into the epoxide (189) (Scheme 15).

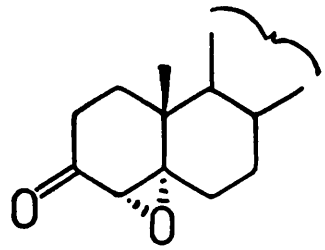


Scheme 15

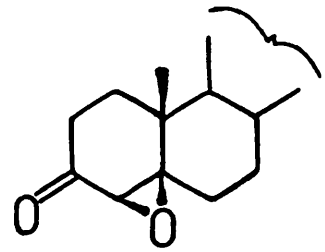
Table 1



(188),(191)



(189),(192)



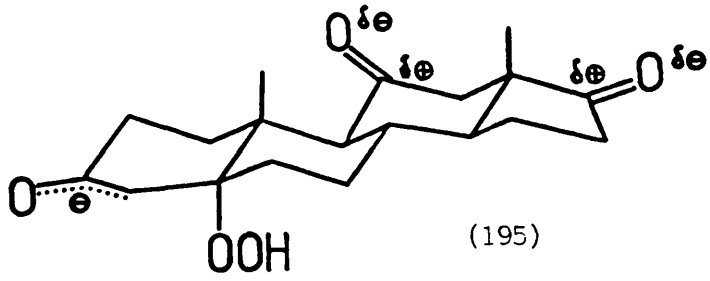
(190)

	R_1	R_2	% of (189) or (192) in total epoxide product
(188) a	H	H	(189) a 0
b	H	β-C_8H_{17}	b 0
c	H	β-CHMe$(CH_2)_2$OH	c 11
d	H	α-Br	d 26
e	H	β-COMe	e 26
f	H	α-OH	f 27
g	H	β-CN	g 28
h	H	β-CO_2Me	h 30
i	H	=O	i 30
j	H	β-OH	j 31
k	H	β-CO_2	k 60-65

	R_1	R_2	
(191) a	α-OH	β-OH	(192) a 0
b	α-OH	α-Me and β-OH	b 0
c	α-OH	COMe	c 25
d	β-OH	=O	d 51
e	=O	=O	e 86

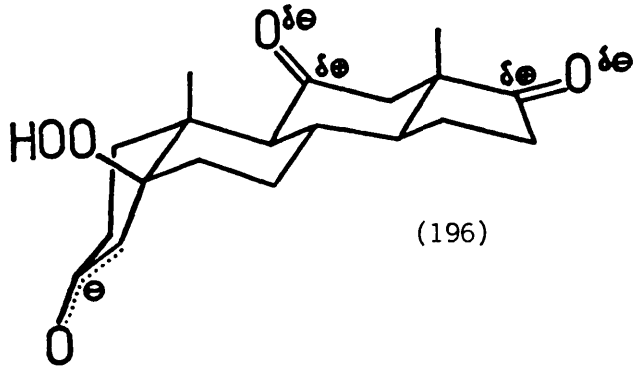
The formation of α-epoxide in the presence of some polar substituents

was rationalised by assuming there is an electrostatic interaction between the intermediate enolate and the positive end of the remote dipole(s). For example epoxidation of (191e) leads to a high yield of α-epoxide because only in the intermediate (195) can the negative enolate charge be transmitted through the steroid skeleton to the fractional positive charges of the carbonyl groups at C-11 and C-17, making the attractive forces a maximum. In the alternative intermediate (196)



(195)

leading to the β-epoxide, such an electrostatic interaction would take place through solvent and any stabilisation would be minimised or eliminated.

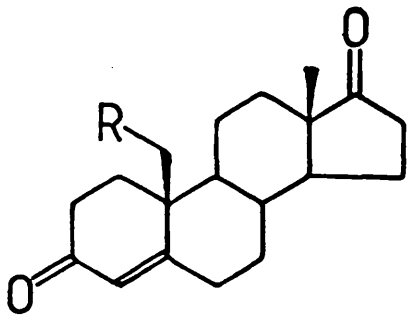


(196)

Comparison of the epoxidations of (188f,i,j) with (191a-d) indicate that a polar substituent at C-11 can have a marked effect on the epoxide distribution and can either augment or negate the effect from a substituent at C-17.

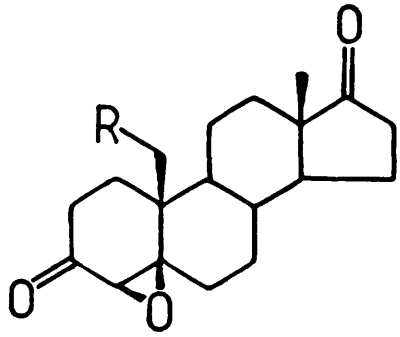
It is recently reported that alkaline epoxidation of (188i) gave a 4:1 ratio of α:β-epoxides, but that (197) gives only the β-epoxide (198).[97] This is an interesting case of a γ-hydroxymethyl group directing cis. It

also casts doubt on some of Henbest and Jackson's results since they had reported an α:β ratio of 3:7 for epoxidation of (188i).



(188) i R=H

(197) R=OH



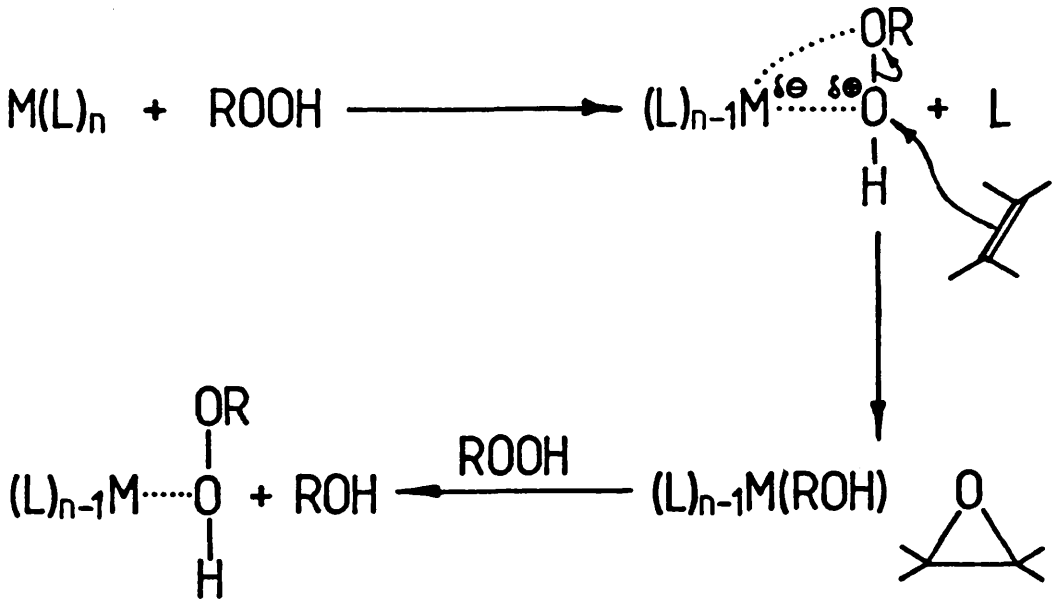
(198) R=OH

Epoxidation with Hydroperoxides in conjunction with a Metal Catalyst[98,99]

The early literature on the epoxidation of alkenes with peroxides in conjunction with a metal catalyst was reviewed by Hiatt.[100] A significant proportion of this dealt with industrial patents concerned with the conversion of propene to its epoxide. The first reaction of this type was reported by Hawkins in 1950. He found vanadium pentoxide catalysed the conversion of cyclohexene and 1-octene to their epoxides in 39% and 15% respectively. It was subsequently found that using the acetylacetonates of either vanadium, chromium or molybdenum much higher yields could be obtained. Although compounds of a large number of metals have been shown to effect the epoxidation of alkenes only vanadium, molybdenum and tungsten give consistently high yields. The choice of peroxide does not appear to matter significantly - t-butylhydroperoxide, cumene hydroperoxide and hydrogen peroxide are most commonly used. Often the alkene to be epoxidised also serves as the solvent. Since most of the early work concentrated on maximising the epoxide yield with respect to peroxide consumption, an excess of alkene to hydroperoxide, which usually results in the epoxide as the sole product, was recommended. With isolated

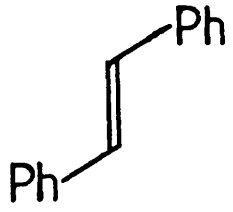
alkenes epoxidation generally occurs on the less hindered side of the double bond.

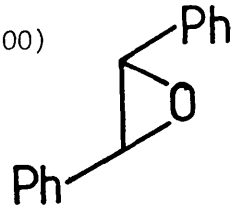
The mechanism (Scheme 16) is believed to involve displacement of a metal ligand by the hydroperoxide. This makes the hydroperoxide susceptible to attack by the nucleophilic alkene resulting in formation of the epoxide and an alcohol (from reduction of the hydroperoxide). Further exchange of this alcohol by another molecule of hydroperoxide then regenerates the epoxidising agent.



Scheme 16

A recent development in such metal-catalysed epoxidations is the introduction of a catalytic amount of amine to the system. This has been shown to have a marked effect on the epoxidation of aliphatic and aromatic alkenes with molybdenyl acetylacetonate and t-butylhydroperoxide in CCl_4.[101] In the absence of amines aliphatic alkenes did not undergo epoxidation while aromatic alkenes gave carbonyl compounds in large amounts. However on addition of amine good yields of epoxide can be achieved, eg (E)-stilbene (199) gave a 93% yield of (E)-stilbene oxide (200) when 0.01 molar equivalents of pyridine was added, though the yields change

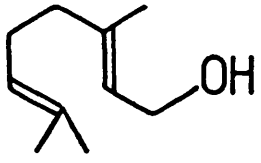
(199) 

(200) 

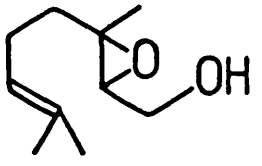
dramatically depending on the structure of the amine employed. The mechanism by which the amines assist epoxidation is not yet known.

Stereoselective Epoxidations with Hydroperoxides in conjunction with a Metal Catalyst

Sharpless[102] was the first to realise the potential of the method for complex molecule synthesis and also established that the transition metal-hydroperoxide reagents exhibit remarkable reactivity towards allylic alcohols. Hence epoxidation of geraniol (201) was selective, giving only the 2,3-epoxy alcohol (202) in 93% yield. This can be contrasted with

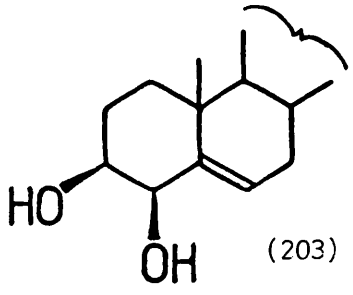


(201)

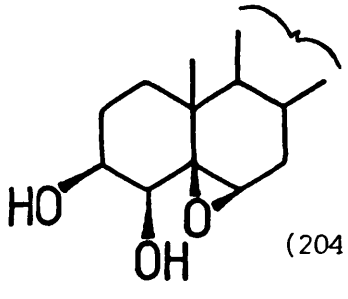


(202)

peracid epoxidation of geraniol which preferentially oxidises the double bond furthest removed from the alcohol. Also while 4β-hydroxycholesterol (203) gave only the β-epoxide (204) in 95% yield with vanadyl acetyl-acetonate and t-butylhydroperoxide, peracid treatment gives an 1:2 mixture of α:β epoxides.



(203)



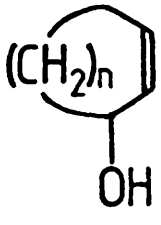
(204)

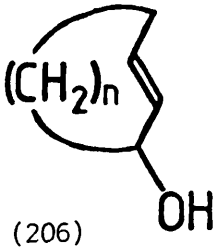
Henbest showed that allylic alcohols exhibit a cis-directing effect on epoxidation with peracids but this selectivity did not extend to homoallylic alcohols. With the present system however the rate of epoxidation of both allylic and homoallylic alcohols is greatly increased and the epoxidations are virtually totally stereoselective, giving the cis epoxy alcohols. Even 1-hydroxy(E)-4-nonene, a bishomoallylic alcohol is epoxidised over ten times faster than trans-5-decene with vanadyl acetylacetonate and t-butylhydroperoxide. However both compounds show identical reactivity on reaction with molybdenum hexacarbonyl and t-butlyhydroperoxide.

These results prompted the use of molybdenum and vanadium catalysed epoxidations in a number of complex synthetic sequences, some of which are reviewed by Sharpless and Verhoeven.[103] It is now established that while molybdenum catalysts are approximately one hundred times more reactive for isolated alkenes, vanadium catalysts are usually preferred for allylic alcohols due to the dramatic acceleration in the rate of epoxidation.

Teranishi et al[104] have studied the vanadium-catalysed epoxidation of cyclic allylic alcohols and compared the stereoselectivities with that of mcpba epoxidation. They found that the opposite direction of stereoselectivity is found for medium-ring alcohols. Hence (205a,b), (206a-c), (207) and (208) give mainly the cis epoxides on vanadium-catalysed epoxidation but mainly the trans epoxides with mcpba. The exception is

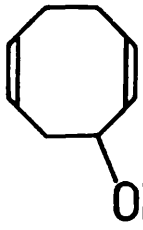
(205) a n=4
b n=5

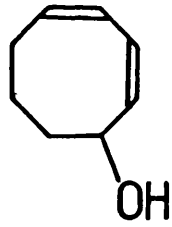




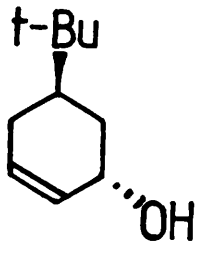
(206)

a n=4 (1RS,2RS)
b n=5
c n=8
d n=4 (1SR,2RS)

(207) 

(208) 

(206d) which gives selectively the trans epoxide with both reagents. With the conformationally biased 5-t-butylcyclohex-2-enols (43) and (44), vanadium-catalysed epoxidation gives higher cis-stereoselectivity for the pseudo-axial isomer (43) than the pseudo-equatorial one (44), though in both cases, as with peracid epoxidation, the cis isomer is highly predominant. With peracids, as mentioned earlier, Whitham[45] rationalised



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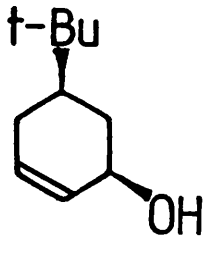
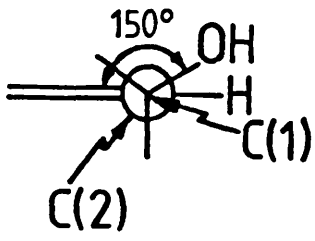


(44)

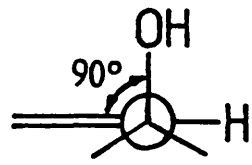
the cis to trans selectivity on moving from common cyclic allylic alcohols to medium-sized rings.

To account for the differences in selectivity observed between the peracid and vanadium-catalysed epoxidations Teranishi et al[104] proposed the following transition-state geometries (Scheme 17). The peracid

Scheme 17 Preferred transition-state geometries



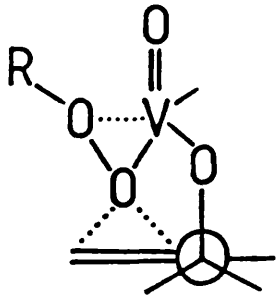
for peracid epoxidation



for vanadium epoxidation

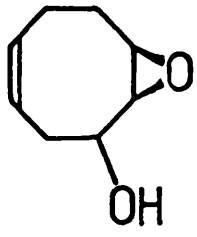
geometry is in agreement with the transition-state model of Whitham.[45]

When the proposed transition-state geometry for the vanadium-catalysed epoxidation is coupled with the mechanism proposed by Sharpless all the observed results can be rationalised. The Sharpless mechanism[103] (Scheme 18) involves coordination of both the allylic hydroxyl group and the alkyl hydroperoxide through the distal oxygen atom to the vanadium. Hence a 5-membered ring is set up and the angular requirement of the preferred transition-state outlined in Scheme 17 is fulfilled.



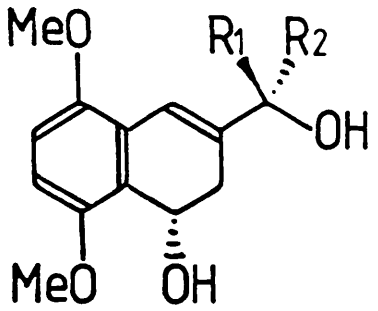
Scheme 18

When both an allylic and homoallylic group are present in a molecule it is difficult to predict which one will exert control during epoxidation. For instance vanadium-catalysed epoxidation of (207) with one mole of t-butylhydroperoxide gave only the cis-2,3-epoxy alcohol (209) with the regioselectivity of attack higher than 99%.[104] However for the



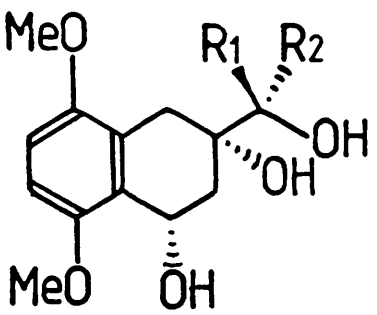
(209)

dihydronaphthalenol (210), vanadyl acetylacetonate and t-butylhydroperoxide epoxidation gave (211) after reduction of the epoxide with lithium aluminium hydride, indicating that the homoallylic hydroxyl group is more important than the stereochemistry in the side chain for controlling epoxidation.[105] Interestingly the electron-deficient alkene in (212) could also be epoxidised with vanadyl acetylacetonate and t-butylhydro-



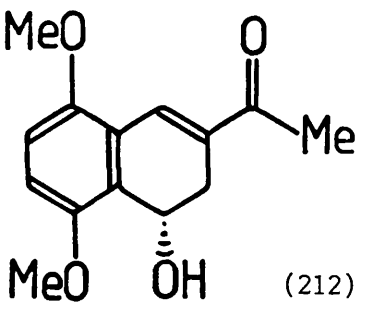
(210) a R_1=Me,R_2=H

b R_1=H,R_2=Me



(211) a R_1=Me,R_2=H

b R_1=H,R_2=Me



(212)

peroxide. Reduction of both the epoxide and the ketone then afforded (211) confirming that once again the homoallylic alcohol had directed the epoxidation. Subsequent studies by Glotter[106] have shown that the above result is more general ie α,β-unsaturated ketones possessing a hydroxyl group two or three bonds away from the β-carbon can be stereoselectively epoxidised with vanadyl acetylacetonate and t-butylhydroperoxide. In all the compounds investigated the epoxidation was syn to the hydroxyl group. A more remote hydroxyl group was found to be ineffective in triggering the epoxidation of enones.

As mentioned earlier, allylic amides, in addition to directing peracid epoxidations, are also capable of showing high stereoselectivity in metal-catalysed epoxidations.[50]

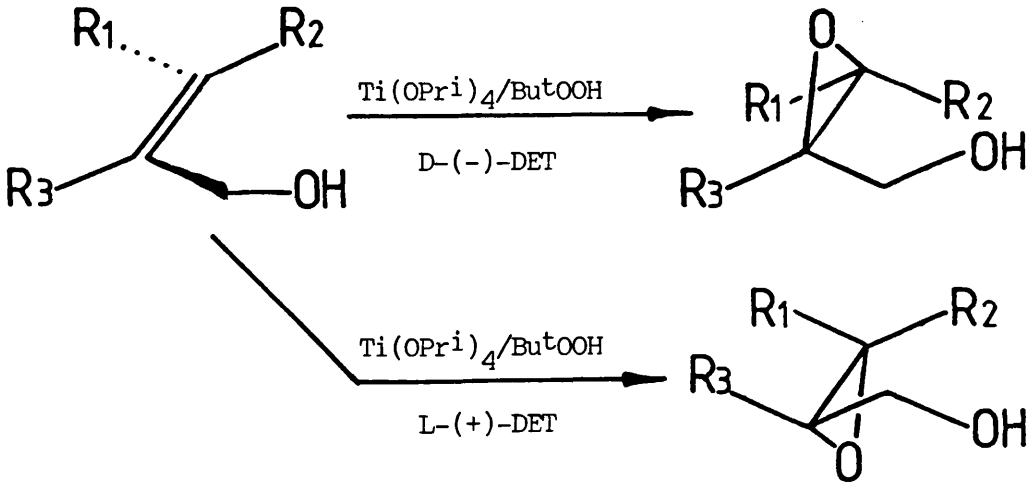
Other Epoxide Syntheses

There is a variety of other ways of forming epoxides including

treatment of alkenes with molecular oxygen in the presence or absence of a catalyst and preparation from 1,2-difunctional compounds by 1,3-elimination. Epoxides can also be synthesised from carbonyl compounds by Darzens reaction which is usually used for preparing glycidic esters, or from reaction with diazoalkanes or sulphonium ylides. Since these methods bear no relation to the work being presented in this thesis, they will not be discussed further.

Sharpless Epoxidation[107] and other Chiral Epoxidations[108]

The asymmetric epoxidation of allylic alcohols, the Sharpless epoxidation, was first reported in 1980.[109] Since then it has been extensively used for the synthesis of enantiomerically pure natural products. The reaction involves treating an allylic alcohol with t-butylhydroperoxide in the presence of titanium tetraisopropoxide and a chiral dialkyl tartrate. These conditions result in the epoxide oxygen always being delivered to the same enantioface of the alkene when a specific tartrate isomer is used (Scheme 19). Hence using D-(-)-diethyl tartrate



Scheme 19

[D-(-)-DET] the oxygen is delivered to the top face while L-(+)-diethyl tartrate [L-(+)-DET] delivers it to the bottom face. Dichloromethane is

the most commonly employed solvent.

Typically an enantiomeric excess (e.e.) of >90% is realised though this demands anhydrous reaction conditions. Sharpless[110] showed that in absence of water the e.e. for the epoxidation of (E)-α-phenylcinnamyl alcohol was 99% but this dropped to 48% on addition of one equivalent of water. The lowering of enantioselectivity and reaction rate by water is due to it interacting both reversibly and irreversibly with the catalyst.

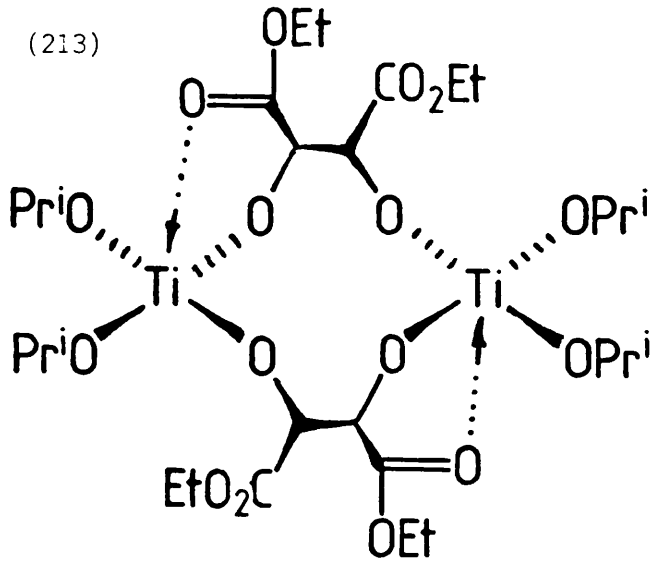
Since the experimental procedure involves an aqueous wash, poor yields were obtained for fairly water-soluble epoxy alcohols. However modification of the procedure allowed isolation of these epoxides in good yields and high e.e.[110]

Sharpless and Hanson have shown that when the reaction is performed in the presence of 3Å or 4Å molecular sieves the amounts of titanium (IV) isopropoxide and diethyl tartrate required are catalytic (<10%).[111] This new modification has the advantages of economy, mildness of conditions, ease of isolation, increased yields and the potential for in situ derivatisation of the product, though generally the products have a lower enantiomeric purity.

The mechanism of epoxidation[112] involves rapid exchange of the four isopropoxide ligands; two for the divalent chiral tartrate and one each for the allylic alcohol and t-butylhydroperoxide. The chiral catalyst (213) is believed to be responsible for the high face selectivity of the epoxidation. Exchange of two alkoxide ligands for the alcohol and peroxide than sets up the transition-state (214) in which both the oxygen atoms of the peroxide are chiral. Formation of the epoxide results from an S_N2-type reaction at oxygen in which the distal peroxo oxygen is transferred to the nucleophilic alkene.

The first commercial application of the Sharpless epoxidation was the synthesis of the female gypsy moth attractant (+)-disparlure (217)

(213)



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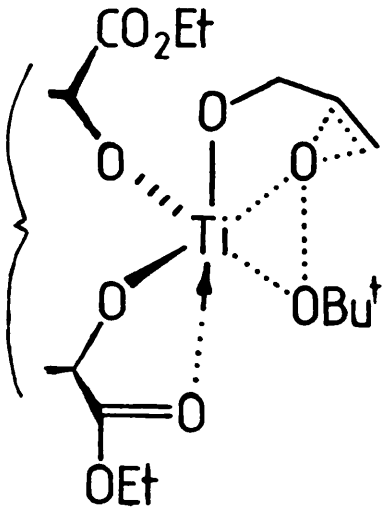

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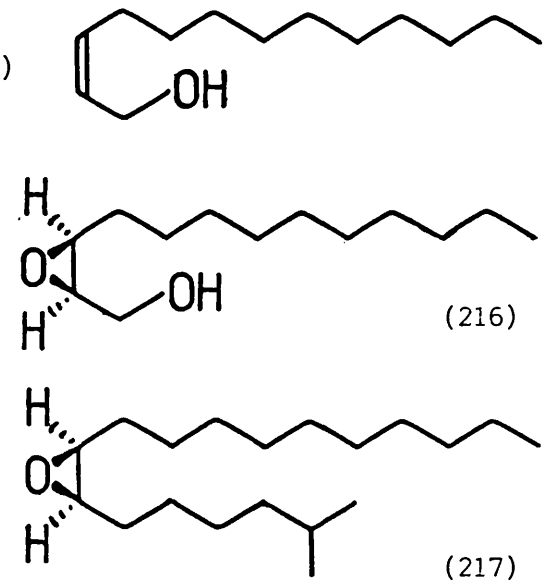


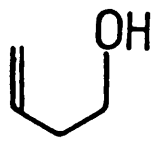
(216)

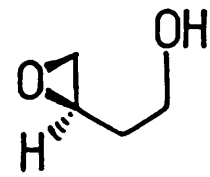
(217)

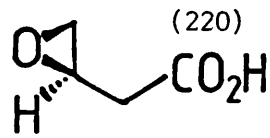
which is used by the U.S. government for insect control.[113] Epoxidation of the allylic alcohol (215) with D-(-)-DET gave the crystalline epoxide (216). This alcohol was then oxidised to the aldehyde and the second alkyl chain introduced by Wittig reaction followed by hydrogenation of the resulting double bond. The product, (+)-disparlure (217), is ten times more effective than the racemate while (-)-disparlure shows negligible activity as a moth attractant.

(+)-disparlure was also synthesised by other workers via an alternative route, though again the asymmetric epoxidation procedure was instrumental for generation of the optically active epoxide.[114]

Homoallylic alcohols can also be asymmetrically epoxidised.[115] However the enantiomeric purities are much lower and the enantiofacial selection is opposite to that found for allylic alcohols. Hence epoxidation of but-3-en-1-ol (218) with L-(+)-DET gave the epoxide (219) in 11-25% yield and 55% e.e. Oxidation of this alcohol gave the epoxy acid (220) which furnished the (-)-γ-amino-β(R)-hydroxybutyric acid (221) in 66% yield and 49% e.e. from (219) on treatment with ammonium hydroxide. This amino acid is used as an anti-epileptic and hypotensive drug.

(218) 

 (219)



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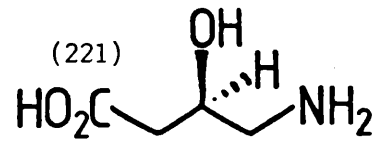
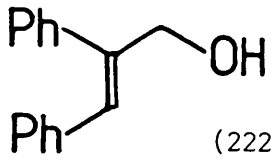
(221) 

Other applications of the Sharpless reaction include kinetic resolution of allylic alcohols[116] and β-hydroxy amines,[117] and the oxidation of sulphides to chiral sulphoxides.[118]

Prior to the discovery of the titanium-catalysed Sharpless epoxidation, vanadium catalysts bearing hydroxamic acids as ligands had been shown to give some asymmetric induction.[103] However the enantiomeric excess of products was inferior to the titanium reaction, with 80% e.e. of (223) from (222) being the best achieved.

A fairly recent development in chiral epoxidations is the highly stereoselective synthesis of optically active epoxynaphthoquinones via



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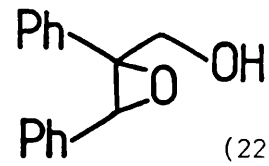
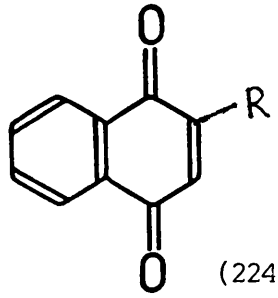


(223)

asymmetric Weitz-Scheffer epoxidation promoted by the protein bovine serum albumin (BSA).[119] Hence treatment of the naphthoquinones (224) in



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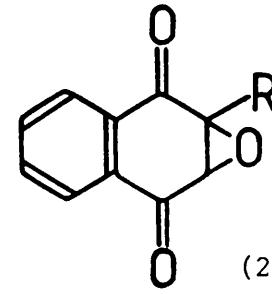


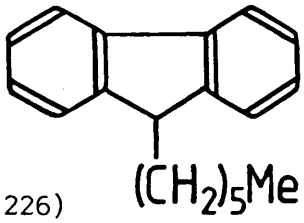
(225)

aqueous buffer solution at pH 9 with t-butylhydroperoxide and BSA afforded the epoxides (225). It was found that homogeneous conditions gave better enantioselectivity than heterogeneous conditions which had been used previously.

Although the mechanism is not fully understood the reaction is believed to involve formation of a chiral complex by binding of the substrate to the protein. This complex then undergoes oxidation to give the epoxide which is still bound to the BSA. Decomposition of this product-BSA complex gives the optically active epoxide. The stereoselection is determined by the relative accessibility of the two faces of the naphthoquinone residue to the oxidant in the substrate-BSA complex, with different binding sites having different relative accessibility. Due to competition by both the substrate and product for the same binding sites of BSA, the concentration of the substrate-BSA complex will decrease as the reaction progresses and hence the rate of formation of product will also decrease. The effect of varying the R substituent and the use of an organic cosolvent was investigated. Optimum selectivity

(100% e.e.) was obtained for the naphthoquinone with R=C_8H_{17}. This is consistent with the fact that a long alkyl chain increases the affinity for binding to the protein. In certain cases an organic cosolvent gave higher enantioselectivities eg for R=Bu^t the e.e. increased from 77% to 90% on addition of 0.05 molar equivalents of isooctane. This was attributed to specific inhibition of the product-BSA complex, thereby favouring formation of the substrate-BSA complex and thus the asymmetric reaction.

Another reported asymmetric Weitz-Scheffer epoxidation occurs when cyclohexenones are treated with 9-hexylfluorene (226) in the presence of oxygen and chiral phase transfer catalysts derived from (+)-cinchonine under basic conditions.[120] The reaction proceeds via hydroperoxyfluorene (227) which is generated <u>in situ</u> and gives epoxy-ketones in 57-85% yield and 9-54% e.e.



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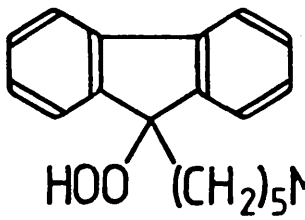
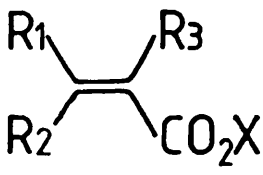


(227)

In the epoxidation of electrophilic alkenes (228) with t-butylhydroperoxide and an alkyl lithium in dry tetrahydrofuran, Meth-Cohn[65] reported diastereomeric excesses of up to 65% when X is chiral, and for the sulphoximine (229) only one epoxide was formed.



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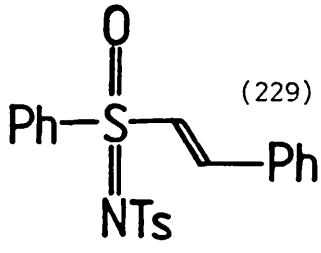


(229)

Although other asymmetric epoxidations have been reported[121,122] the

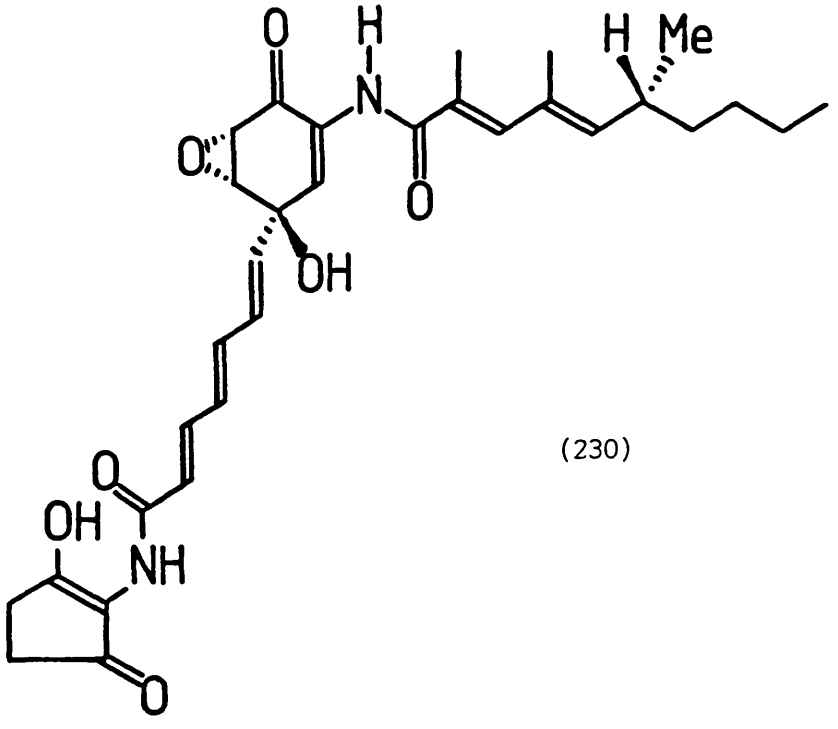
e.e. are less than 35% and typically much lower (<15%).

Some Naturally Occurring Epoxides

Throughout this Introduction a number of aspects concerning the stereochemistry of epoxidation have been reviewed. In some cases these were illustrated by total syntheses of naturally occurring epoxides which exhibit some interesting biological activity eg scopolamine, trichothecanes, anticapsin and methylenomycin A.

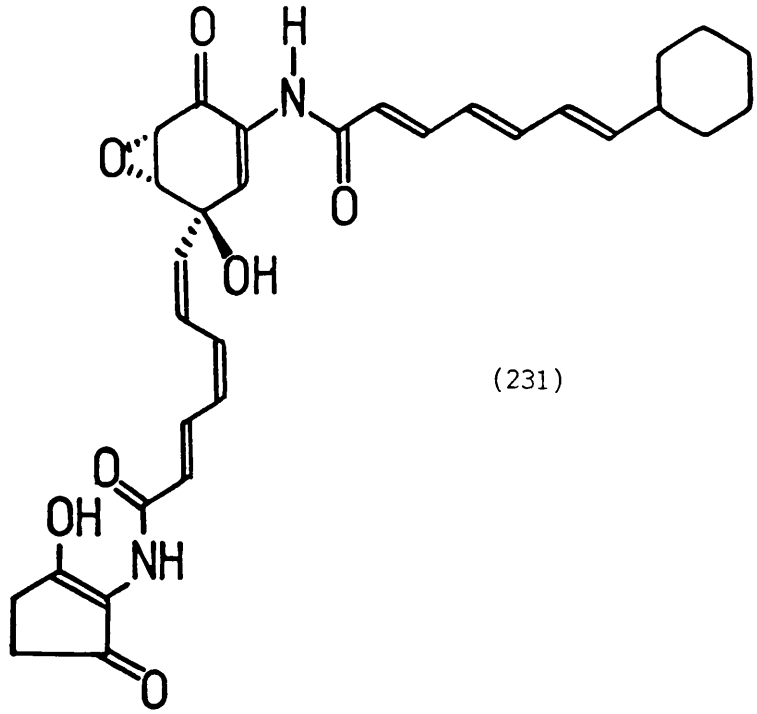
Since the Discussion is largely devoted to alkaline epoxidation of enones substituted in the γ-position with a polar functional group (often hydroxyl), it is of interest to look at some structurally related α,β-epoxyketone natural products.

The manumycin group antibiotics, manumycin (230) and asukamycin (231), which are produced by Streptomyces parvulus and Streptomyces nodosus subspecies asukaensis respectively show antimicrobial activity against Gram-positive bacteria as well as anticoccidial activity in chickens.[123]



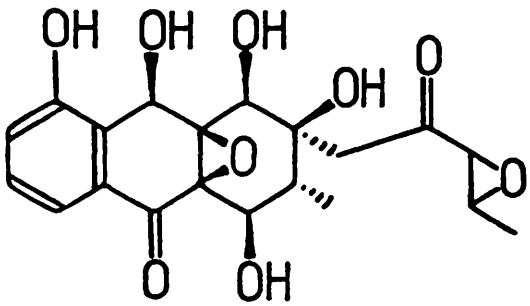
(230)

In these antibiotics the stereochemistry of the epoxy and hydroxyl substituents of the cyclohexane ring is trans.



(231)

In most other α,β-epoxy-γ-hydroxyketones the epoxy and hydroxyl groups are cis eg cervicarin (232),[124] an antitumour antibiotic produced by Streptomyces agaenis, mycochrysone (233),[125] a metabolite with no reported biological activity and epoxydon (234),[126] an antitumour compound which has been synthesised.[127,128] However the diastereomer, isoepoxydon



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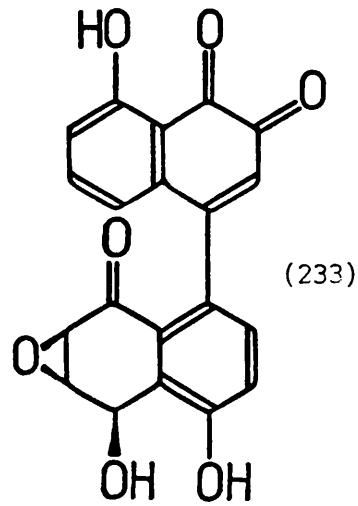

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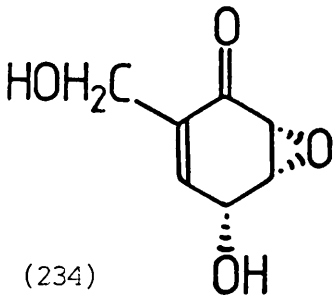

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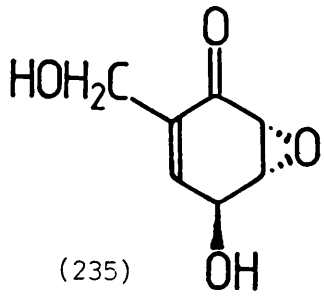
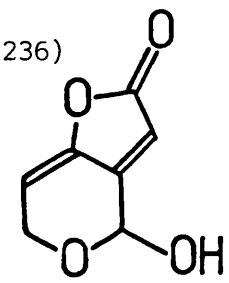


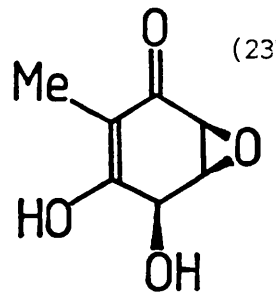
(235)

(235) has also been isolated, synthesised and shown to be an efficient precursor of patulin (236), an antibiotic produced by several fungi.[129] Terremutin (237), a structural isomer of the epoxydons, which is isolated from Aspergillus terreus has also been characterised.[130]

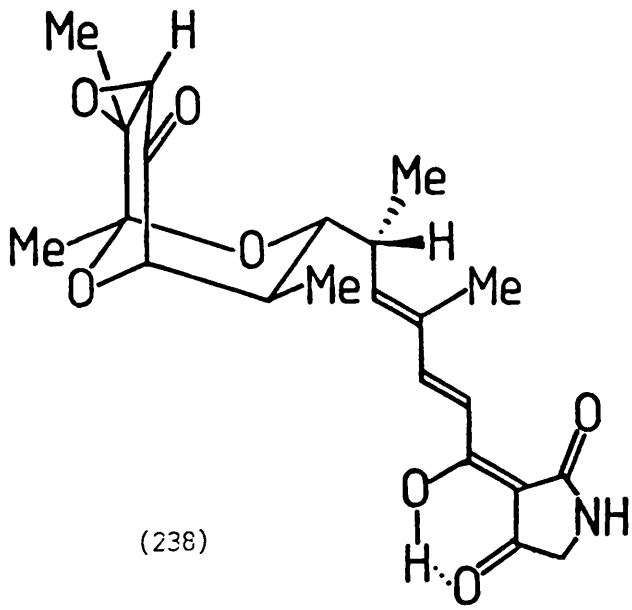
(236)



(237)



Tirandamycin (238) is a member of a small group of 3-acyltetramic acid antibiotics, isolated from Streptomyces tirandis and is a potent

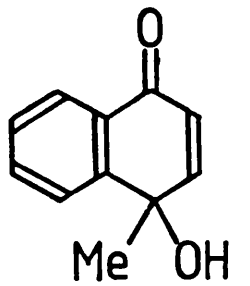


(238)

inhibitor of RNA-polymerase. The conformation of the epoxide was confirmed by an x-ray structure of the p-bromophenacyl ester of tirandamyic acid[131] which has also been made synthetically.[132]

DISCUSSION

This study of the stereoselectivity of enone epoxidations was stimulated by two previous observations in which the naphthalenones (48) and (161) were found to give stereospecifically the cis and trans epoxides (49) and (162) respectively with alkaline hydrogen peroxide.[83,86] In both these systems steric or conformational effects would not be expected to influence the stereochemistry of epoxidation. It seemed probable that a polar interaction between the hydroxyl substituent and the reagent is responsible for the stereospecific epoxidation of (48). For naphthalenone (161) however, no explanation could be offered to account for the stereospecifity on epoxidation.



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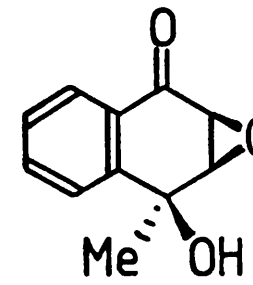
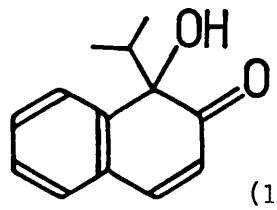


(49)



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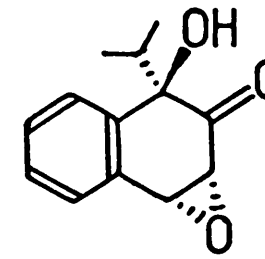
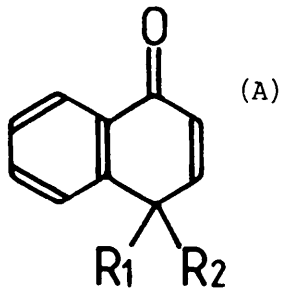


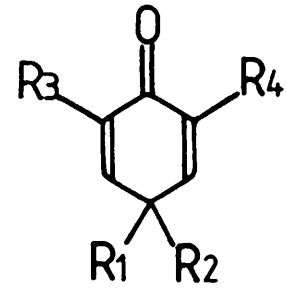
(162)

In order to see whether the above results exhibited by a γ-hydroxyl or an α-hydroxyl group were more general a variety of dienone and enone systems (A-D) were synthesised and the influence of the neighbouring substituents on the stereochemistry of epoxidation was examined.

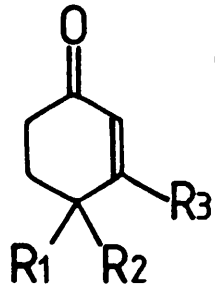
Initially in all these systems either R_1 or R_2 was a hydroxyl group (or an ether or ester derivative) though later, after the realisation



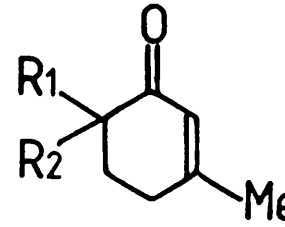
(A)



(B)



(C)



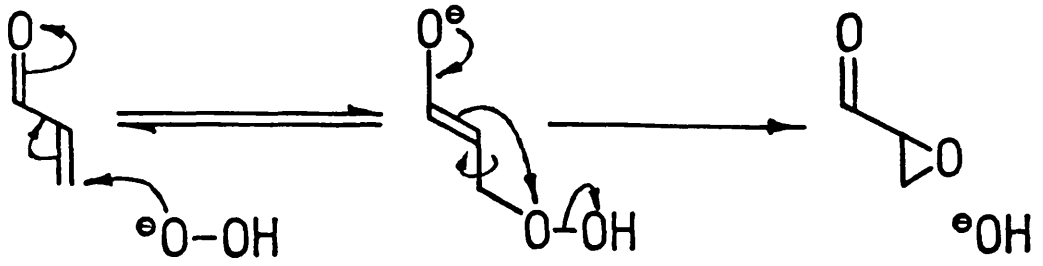
(D)

that other substituents might effect stereospecific or highly stereoselective epoxidations, the functionality of both R_1 and R_2 was more varied.

Before discussing the preparation of the starting dienones and enones and the results obtained on their epoxidation it is worth considering some properties of the various systems.

In (A-D) the enones to be epoxidised always constitute part of a ring system. This was deliberate since the mechanism for alkaline epoxidation (Scheme 8) involves Michael addition of hydroperoxide anion to the enone, generating an intermediate enolate in which the carbon-carbon double bond has shifted and there is the possibility of rotation about the 'new' carbon-carbon single bond (as shown). Hence only when the enone is part of a ring system is the possibility of rotation about this carbon-carbon bond totally excluded and the possibility of stereospecific or 'meaningful' stereoselective epoxidation necessarily maintained.

The dienone systems (A) and (B) have a number of advantages over the enone systems (C) and (D) in examining the stereoselectivity of alkaline

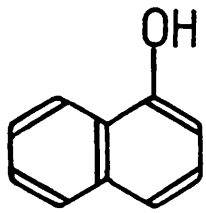


Scheme 8

epoxidation. Conformational effects in (A) and (B) are minimised since the ring is virtually planar, while in (C) and (D) it has considerably more flexibility which could influence the stereoselectivity to some extent. Since alkaline epoxidation involves attack of the nucleophilic reagent on the enone, the more electrophilic the alkene the quicker the reaction would be expected to occur. Hence epoxidation of (A) and (B) should be slower than (C) and (D) because the electron-withdrawing effect of the carbonyl group is split between the two double bonds. More importantly however this reduced electron-withdrawing effect in the dienone series means the double bonds can be epoxidised with peracids whereas simple enones usually give Baeyer-Villiger products rather than epoxides. Furthermore when there is a γ-hydroxyl group, reaction with peracids will generate cis epoxy alcohols which are useful for comparison with the products obtained from alkaline epoxidation. In system (B) both the double bonds are epoxidisable. This means that in contrast to (A), (C) and (D) where only two diastereomeric epoxide products could be formed (when $R_1 \neq R_2$) there are four possible diastereomeric epoxides for (B) (when $R_1 \neq R_2$). Another interesting facet of this series is that when $R_3 \neq R_4$ there is a regiochemical as well as a stereochemical question on epoxidation ie which double bond will be epoxidised first?

Preparation of 4-hydroxy-4-methylnaphthalen-1(4H)-one

Using the Gatterman formylation procedure adopted by Adams and Levine[133] 1-naphthol (239) on treatment with zinc cyanide and hydrogen chloride gas followed by decomposition of the iminium salt with aqueous ethanol gave 4-formyl-1-naphthol. Clemmensen reduction of the aldehyde with zinc amalgam in dilute hydrochloric acid gave, after distillation, pure 4-methyl-1-naphthol (240) in 35% overall yield. 4-Hydroxy-4-methyl-naphthalen-1(4H)-one (48), first reported by Evans,[134] was prepared from



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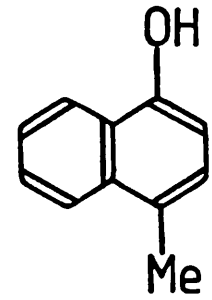

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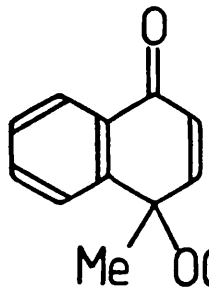

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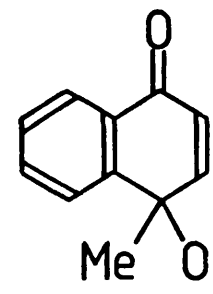


(48)

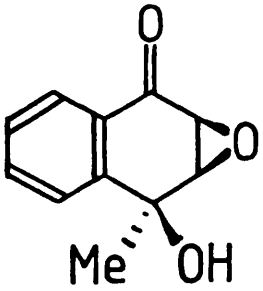
4-methyl-1-naphthol by oxidation with singlet oxygen generated *in situ* from ceric (IV) oxide and hydrogen peroxide followed by reduction of the resulting hydroperoxide (241) with dimethyl sulphide. This method for converting phenols to γ-hydroxycyclohexadienones was first used by Barton.[135] Although zinc in aqueous ammonium chloride, zinc in aqueous acetic acid and acidified aqueous iron (II) sulphate were tried as alternative reducing agents for the hydroperoxide (241) only dimethyl

sulphide, which however takes several days for complete conversion, effected clean reduction to give the alcohol (48).

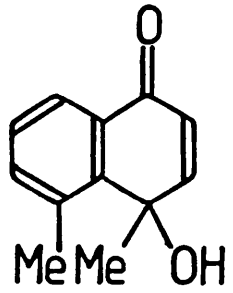
Epoxidation of 4-hydroxy-4-methylnaphthalen-1(4H)-one[83]

As mentioned earlier Carnduff found alkaline hydrogen peroxide epoxidation of the enone (48) gave a single epoxide (49).[83] The fact that mcpba epoxidation of (48) also gave only this epoxide suggests the hydroxyl and epoxy functions in (49) are cis to one another. Further evidence for this stereochemistry was found in the infra-red (ir) spectrum of (49) which showed the hydroxyl group is weakly intramolecularly hydrogen-bonded to the epoxide oxygen. Treatment of the hydroperoxide (241) with base cleanly isomerised it to the epoxide (49). Since this type of reaction is believed to be intramolecular[89] and has been shown in two cases by x-ray crystallography to give cis epoxy alcohols[91,92] the stereochemistry of (49) was confirmed.

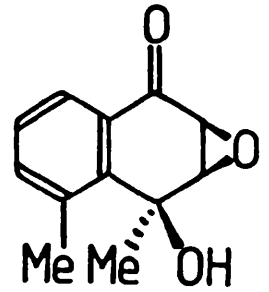
Using sodium hydroxide instead of sodium carbonate as the base, the alkaline hydrogen peroxide epoxidation of (48) was repeated. As Carnduff had previously established, no trace of a second epoxide was detected by nuclear magnetic resonance spectroscopy (nmr) or thin-layer chromatography (tlc).



(49)



(242)

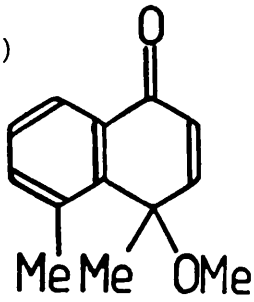


(243)

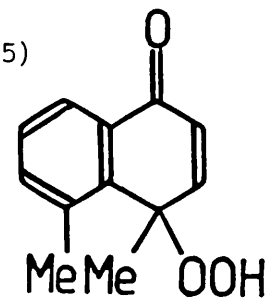
Jefford found the enone (48) and its 5-methyl derivative (242) also gave the cis epoxy alcohols (49) and (243) respectively on treatment with

per-Amberlyst 15.[46] The stereochemistry of (243) was determined by x-ray crystallography. He also showed the γ-hydroxyl function is necessary for this peracid epoxidation since both the ether (244) and hydroperoxide (245) were recovered unchanged under the same reaction conditions.

(244)



(245)

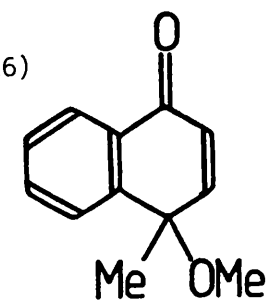


To determine whether the hydroxyl group of (48) and (242) was also a requirement for alkaline epoxidation the methyl ether of (48) was synthesised.

Preparation of 4-methoxy-4-methylnaphthalen-1(4H)-one

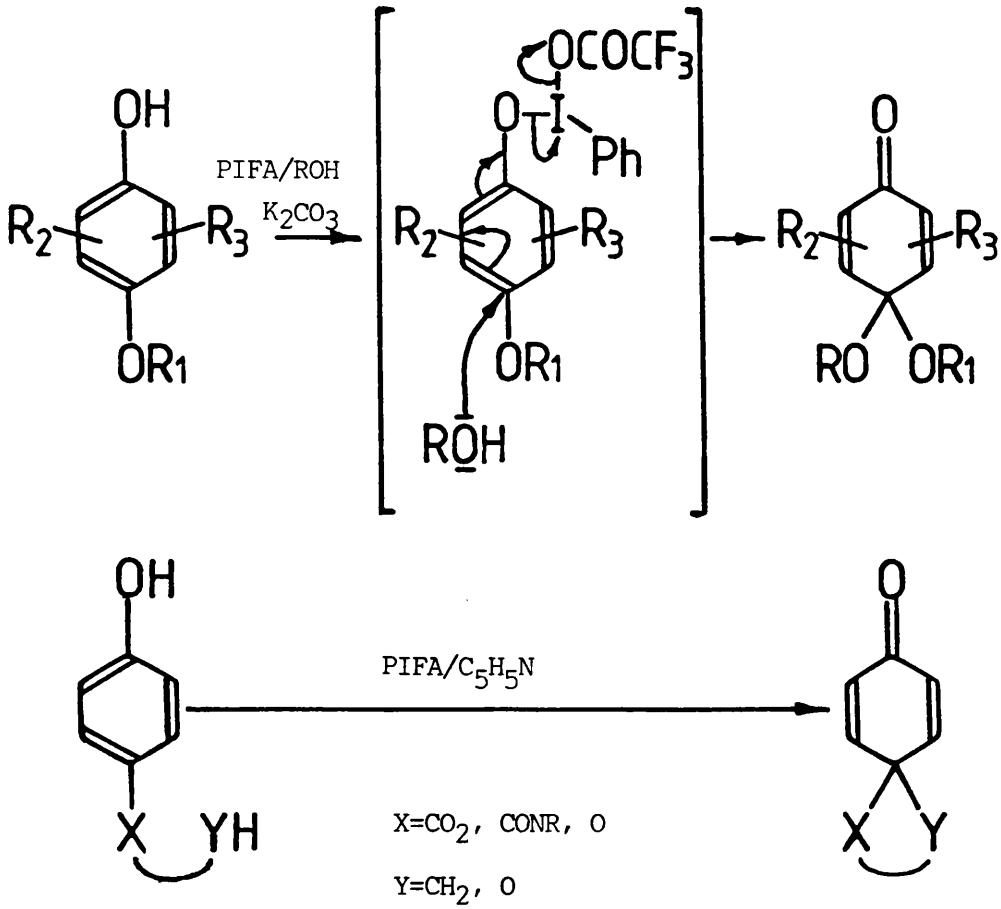
Swenton reported formation of 4-methoxy-4-methylnaphthalen-1(4H)-one (246) in 30% yield from anodic oxidation of 1-methylnaphthalene in methanolic sodium hydroxide at a platinum electrode.[136] Hafiz also obtained (246) from treatment of a methanolic solution of 4-methyl-1-naphthol with lead (IV) acetate and boron trifluoride etherate, but unlike Swenton who reported the dienone as a colourless oil, he found it to be a colourless solid, melting point (m.p.) 47-49°.[137]

(246)



The dienone (246) was prepared using the method of Hafiz and also

from treatment of a methanolic solution of 4-methyl-1-naphthol and potassium carbonate with phenyliodosyl bis(trifluoroacetate) (PIFA).[138] This reagent has been shown previously to convert p-alkylphenols and p-alkoxyphenols cleanly into p-benzoquinone monoacetals and spiro lactones (Scheme 20). The combined crude products were purified by flash chromatography affording pure dienone, m.p. 48-51°, in 78% yield.



Scheme 20

Epoxidation of 4-methoxy-4-methylnaphthalen-1(4H)-one

Hafiz had investigated alkaline epoxidation of the dienone (246) but it was not clear from his results whether he obtained a single epoxide or a mixture of both epoxy ethers.[137] In order to clarify this previous investigation it was decided to repeat this reaction.

After several days' reaction of the dienone (246) with alkaline

hydrogen peroxide, tlc still showed only a single spot of same Rf as starting material. However an ^1H nmr spectrum showed evidence of both epoxide isomers being formed. In addition to peaks associated with residual dienone, the spectrum shows four new singlets, two of which are consistent with methyl protons [chemical shifts (δ) 1.45 and 1.86] and the others with methoxyl protons (δ 2.95 and δ 3.42). The integrals of these peaks indicate the two epoxides were formed in about the ratio 4:3. There are also two new AB quartets in the region δ 3.55-3.85 due to the two epoxide protons in each product coupling with one another.

An attempt to push the reaction to completion under the same conditions only resulted in slight further conversion with the epoxides eventually comprising almost 50% of the total product. In addition to nmr evidence the presence of epoxides in the product was confirmed by the appearance of a parent peak at m/e 204 in the mass spectrum and a new carbonyl peak at 1695 cm^{-1} in the ir spectrum.

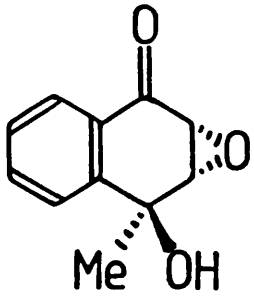
This result showed a γ-hydroxyl group is not necessary for alkaline hydrogen peroxide epoxidation of dienones but is required for stereospecific formation of a single epoxide and also appears to enhance significantly the rate of epoxidation. The naphthalenone with a γ-ether substituent (246) took about 200 hours for ~50% conversion to epoxide while the γ-hydroxy naphthalenone (48) was totally converted to the cis epoxide within 2 hours under the same conditions. The slight stereoselectivity on epoxidation of the ether (246) is almost certainly due to the greater steric bulk of the methoxyl group compared with the methyl group.

As reported for the 5-methyl derivative (244), the ether (246) was found to be inert to peracid epoxidation with mcpba, the dienone being quantitatively recovered from the reaction mixture.

Since the γ-ether group afforded a mixture of epoxides on alkaline

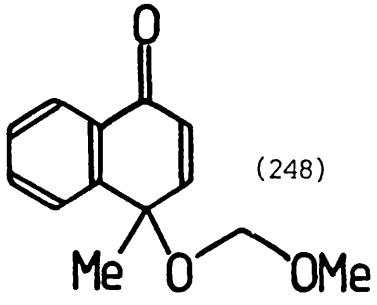
epoxidation, an ether which could be cleaved after epoxidation would provide a possible route to a mixture of both epoxy alcohols and therefore to the unknown trans epoxy alcohol (247).

(247)



Preparation of 4-methoxymethoxy-4-methylnaphthalen-1(4H)-one[139]

To a stirred solution of the alcohol (48) in methylal (dimethoxymethane) and chloroform was added phosphorus pentoxide. After 10 minutes tlc indicated the alcohol with Rf 0.5 had been converted to a single product of Rf 0.7. An ^1H nmr spectrum of this product shows a singlet at δ 3.33 and an AB quartet between δ 4.30-4.50, consistent with the methoxyl and methylene protons of the methoxymethyl (MOM) ether (248).



(248)

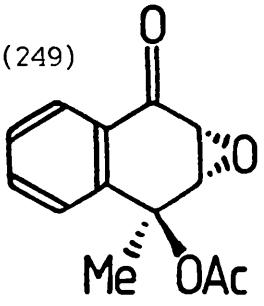
Epoxidation of 4-methoxymethoxy-4-methylnaphthalen-1(4H)-one

As with the methyl ether (246) epoxidation of the MOM ether (248) gave a mixture of diastereomeric epoxides in a 3:2 ratio and with different ^1H nmr spectra. To identify the components the cis epoxy alcohol (49) was converted to its MOM ether using methylal and phosphorus

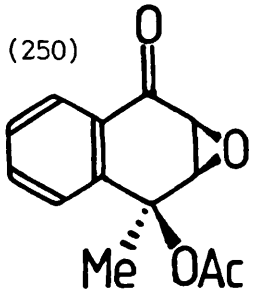
pentoxide. This cis ether has the same spectrum as the minor component formed during alkaline epoxidation.

The mixture of epoxy ethers was deprotected with p-toluenesulphonic acid in methanol and chloroform to give the cis and trans epoxy alcohols (49) and (247) which were separated by flash chromatography. Unlike the previously characterised cis isomer (49)[83] the new trans epoxy alcohol (247) did not crystallise despite several attempts. This failure to crystallise was surprising since the cis epoxy alcohol has m.p. 165-167° and tlc showed that both compounds have similar polarity. The trans isomer was eventually fully characterised as its acetate (249), a crystalline solid of m.p. 107-109° obtained from the reaction of (247) with acetic anhydride, triethylamine and N,N-dimethylaminopyridine (DMAP) in chloroform.[140] The acetate (250) of (49) was similarly prepared, but this was a viscous oil.

(249)



(250)



Although the cis and trans epoxy alcohols (49) and (247) and the cis and trans epoxy acetates (250) and (249) have similar physical and spectral properties there are sufficient distinctions, some of which are summarised in Table 2, to easily identify a particular isomer.

Only the ir solution spectrum gives any direct evidence for the cis orientation of the epoxy and hydroxyl functions in (49) and the trans orientation in (247). It is known that intramolecular hydrogen bonds between hydroxyl groups and adjacent epoxide O atoms,[141] and between hydroxyl groups and π-bonds in 1,2-benzocycloalken-3-ols and related

Table 2

	cis epoxy alcohol (49)	trans epoxy alcohol (247)
^{1}H nmr ($CDCl_3$)	δ 1.49,s,methyl protons	δ 1.87,s,methyl protons
	δ 3.72,d,epoxide proton	δ 3.62,d,epoxide proton
	δ 3.79,d,epoxide proton	δ 3.75,d,epoxide proton
ir ($CHCl_3$)	3580,3450,1690,1600,	3595,3500,1720,1690,
	1460 cm^{-1}	1600,1460 cm^{-1}
tlc (50% EtOAc/ pet. ether)	Rf 0.65	Rf 0.57
m.p.	undergoes polymorphic change with melting at ~130°; the newly formed crystals had m.p. 160-164° (lit.[83] 165-167°)	oil

	cis epoxy acetate (250)	trans epoxy acetate (249)
^{1}H nmr ($CDCl_3$)	δ 1.77,s,methyl protons	δ 1.89,s,methyl protons
	δ 2.19,s,methyl protons	δ 1.92,s,methyl protons
	δ 3.71,d,epoxide proton	δ 3.77,s,epoxide protons
	δ 4.64,d,epoxide proton	
m.p.	oil	107-109°
tlc (50% EtOAc/ pet. ether)	the Rf's of these two acetates were almost identical	

compounds[142] appear at 3580-3520 cm^{-1} and 3620-3590 cm^{-1}, respectively in the ir spectrum. Since an intramolecular hydrogen bond between the epoxy and hydroxyl groups is only possible for the cis isomer the values of 3580 cm^{-1} for (49) and 3595 cm^{-1} for (247) are consistent with the assigned structures. However because of the closeness of these values

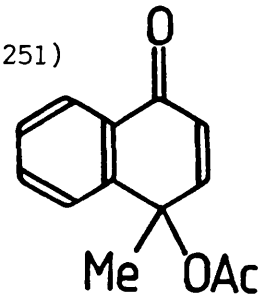
any assignment of the structures, made only from this evidence, would still be in some doubt.

Since both the epoxy acetates had been synthesised it was of interest to examine alkaline epoxidation of the γ-acetoxy enone to see whether the ester exerts any directing effect.

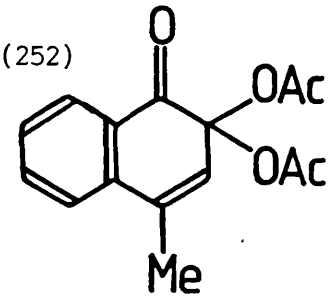
Preparation of 4-acetoxy-4-methylnaphthalen-1(4H)-one[143]

Acetylation of the γ-hydroxy naphthalenone (48) would probably have been the simplest route for making (251). However a lack of this material meant that a literature method, a one-step reaction from 4-methyl-1-naphthol, seemed more attractive.

(251)



(252)



Oxidation of 4-methyl-1-naphthol with lead (IV) acetate in acetonitrile yielded 4-acetoxy-4-methylnaphthalen-1(4H)-one (251) as the major product though, as reported,[143] the ortho diacetate (252) was also formed. It was separated from the monoacetate by base hydrolysis and (251) was further purified by flash chromatography.

Attempted epoxidation of 4-acetoxy-4-methylnaphthalen-1(4H)-one

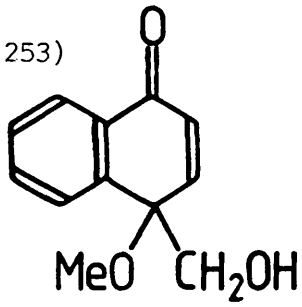
While virtually all the previous alkaline hydrogen peroxide epoxidations had employed sodium hydroxide as base, sodium carbonate was used for the acetate (251) to try to minimise hydrolysis of the ester. Despite this, apart from starting material, the only product isolated from alkaline epoxidation of (251) was the cis epoxy alcohol (49) indicating that

hydrolysis takes place prior to epoxidation.

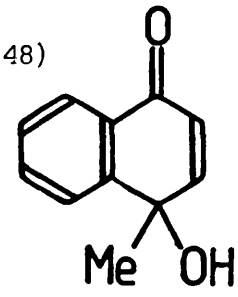
The anhydrous epoxidation conditions of Yang and Finnegan[64] which utilise benzyltrimethylammonium hydroxide (Triton B) as base and t-butyl-hydroperoxide as oxidising agent, and which epoxidised the γ-hydroxyenone (48) giving the cis epoxy alcohol (49),[83] were ineffective for the acetate (251) which was recovered unchanged.

Since of the naphthalenones examined so far only a γ-hydroxyl group resulted in totally stereoselective epoxidation it was decided to try to synthesise the dienone (253) where the alcohol is 'homoallylic' in order to determine whether this exerts a similar directing effect to the 'allylic' alcohol (48).

(253)

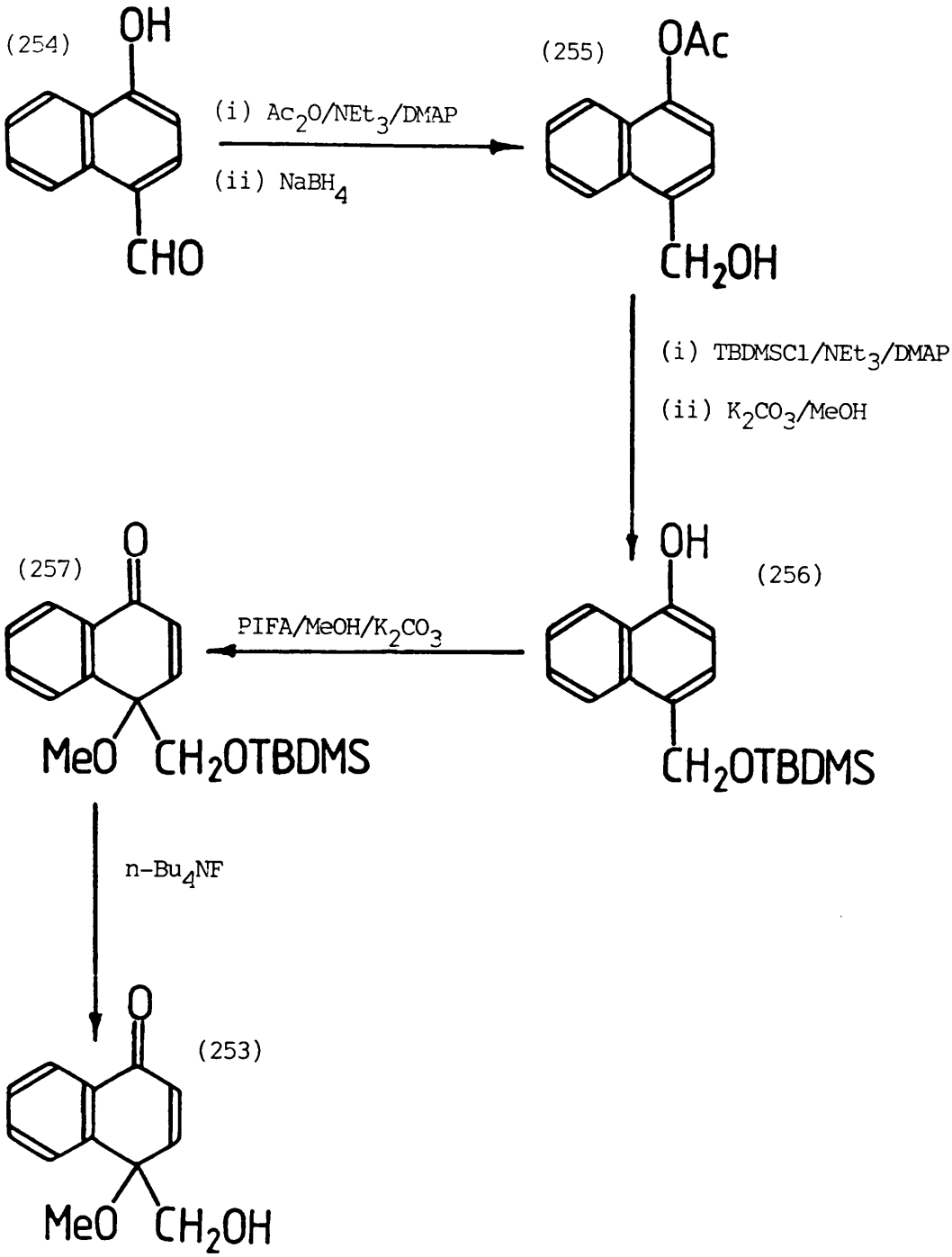


(48)



Attempted preparation of 4-hydroxymethyl-4-methoxynaphthalen-1(4H)-one

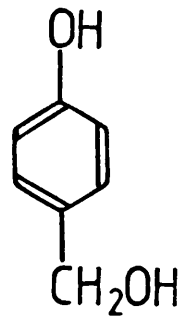
The proposed synthetic route for the preparation of the 'homoallylic' alcohol (253) is shown in Scheme 21. The key step in the route involves oxidation of the phenol (256) with PIFA.[138] The protection of the primary alcohol as its TBDMS ether prior to this oxidation seemed a necessary precaution since 4-hydroxybenzyl alcohol (258) and 4-hydroxy-1-naphthalenemethanol (260) failed to yield the dienones (259) and (253) with PIFA. The alcohol (260) was prepared by reduction of 4-formyl-1-naphthol (254) dissolved in ethyl acetate with sodium borohydride adsorbed on alumina.[144] This procedure proved quicker, the work-up simpler and gave better yields than reduction of the aldehyde with sodium borohydride

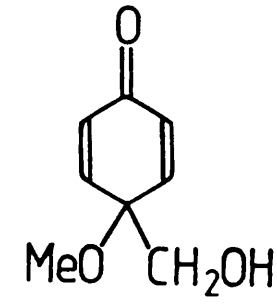


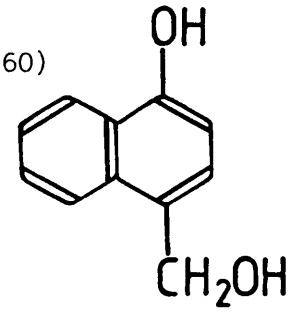
Scheme 21

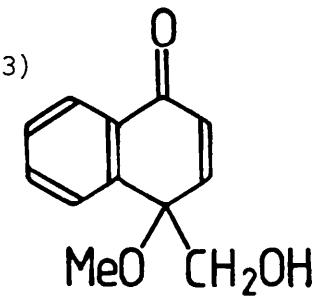
dissolved in methanol.

Treatment of (254) with acetic anhydride, triethylamine and DMAP in chloroform gave the known acetate[145] in good yield. This was subsequently reduced to the alcohol (255)[146] with sodium borohydride adsorbed on alumina. After protection of the alcohol as its TBDMS ether using TBDMS chloride, triethylamine and DMAP in chloroform,[147] the acetate was

(258) 

(259) 

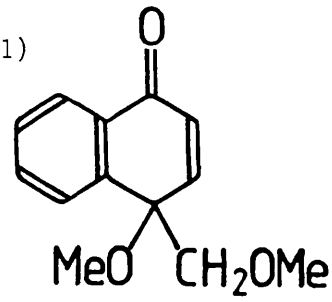
(260) 

(253) 

selectively cleaved using potassium carbonate in methanol to give the phenol (256). Using the method of Tamura[138] the phenol (256) was oxidised with PIFA in methanol. After separation of the crude product mixture by flash chromatography a compound was isolated (9% yield) whose ^{1}H nmr spectrum is consistent with the dienone (257). Although it shows a number of peaks that were uninterpretable, the presence of a new methoxyl peak at δ 3.42 and an AB quartet in the region δ 3.90-4.25 due to the non-equivalent methylene protons suggests the presence of the dienone (257). The formation of the dienone was confirmed from the mass spectrum which shows a parent peak (m/e 318) and the ir spectrum which has a new carbonyl peak at 1675 cm.$^{-1}$ Despite repeating this reaction a couple of times, no trace of the dienone (257) was isolated or even its presence detected by tlc. On one occasion the dienone (261) was formed in fairly good yield indicating the reaction conditions can cleave the TBDMS ether.

Since there was not a sufficient quantity of the dienone (257) to attempt deprotection of the TBDMS ether and then investigate reaction with alkaline hydrogen peroxide, the synthesis was abandoned.

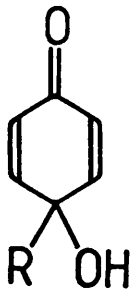
(261)



The work in this naphthalenone series has extended that found from previous investigations. In addition to confirming that a γ-hydroxyl group results in both stereospecific alkaline hydrogen peroxide epoxidation and stereospecific peracid epoxidation, it was shown that this directing effect is not observed for γ-ethers which yield a mixture of both isomers on alkaline epoxidation. By using an ether which could be cleaved after epoxidation the trans epoxy alcohol (247) was synthesised. This compound, which had defied previous attempts to prepare it, has similar physical and spectral properties to the previously characterised cis isomer (49). An attempt to synthesise the 'homoallylic' alcohol (253) to determine whether it exerts a similar effect on epoxidation to the 'allylic' alcohol (48) was unsuccessful. However later in this thesis (Chapter 3) such a 'homoallylic' alcohol was prepared and its epoxidation examined.

To check the cis-directing effect of the hydroxyl group was not exclusive to naphthalenones a series of monocyclic γ-alkyl-γ-hydroxycyclohexa-2,5-dienones was prepared for epoxidation studies.

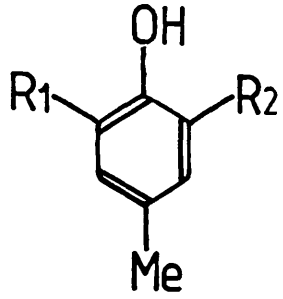
Cyclohexa-2,5-dienones have been reviewed by Waring.[148] 4-Hydroxycyclohexa-2,5-dienones (262) are often called p-quinols and are usually prepared by one of three different methods. The first two, acid-catalysed

(262) 

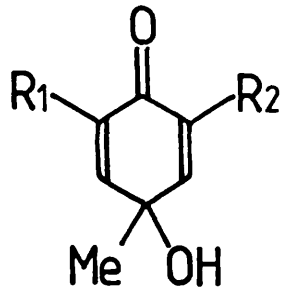
intermolecular rearrangements of aryl hydroxyamines[149] and oxidation of phenols,[135,150-153] often produce complex mixtures of products and are of limited use. The third, more recent, method which involves low temperature reaction of an organolithium or Grignard reagent with a p-benzoquinone is now preferred, affording a better yield of the p-quinol.[154]

Preparation of a series of monocyclic p-quinols

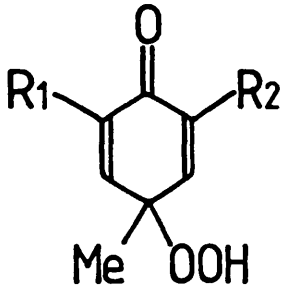
Using Barton's method[135] for converting phenols to p-quinols, which involves reaction with singlet oxygen generated *in situ* from ceric (IV) oxide and hydrogen peroxide followed by reduction of the resulting hydroperoxide with dimethyl sulphide, p-cresol (263), 2,4-xylenol (264), mesitol (265), 2-t-butyl-4-methylphenol (266) and 2,6-di-t-butyl-4-methylphenol (267) were found to give the p-quinols (268)-(272) respectively in fairly good yields. The advantages of using this route to prepare the p-quinols are that they are obtained free of the o-quinol isomer and that



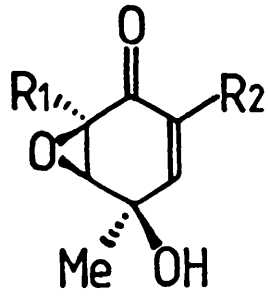
	R_1	R_2
(263)	H	H
(264)	H	Me
(265)	Me	Me
(266)	H	t-Bu
(267)	t-Bu	t-Bu



	R_1	R_2
(268)	H	H
(269)	H	Me
(270)	Me	Me
(271)	H	t-Bu
(272)	t-Bu	t-Bu



	R_1	R_2
(273)	H	H
(274)	H	Me
(275)	Me	Me
(276)	H	t-Bu
(277)	t-Bu	t-Bu



(278)

the intermediate hydroperoxides (273)-(277) could be isolated. These might prove useful when studying the epoxidation of the p-quinols, since base-catalysed isomerisation has been shown to give p-epoxy quinols (278) in which the epoxy and hydroxyl groups are cis.[83,89-92] It was found that the yield of p-quinol from phenol improved significantly as the

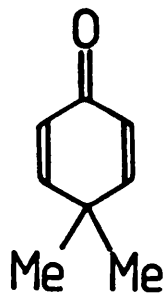
substituents R_1 and R_2 increased in size. Hence p-toluquinol (268) was isolated in poorest yield, presumably because its small size and high polarity make it more soluble in an aqueous phase than the other substituted quinols (269)-(272). Because of this, it was also prepared by addition of methyl lithium to p-benzoquinone.[155]

Epoxidation of the monocyclic p-quinols

Before investigating the quinols (268)-(272) a literature search revealed that some monocyclic dienones had previously given either monoepoxides or diepoxides with alkaline hydrogen peroxide.

4,4-Dimethylcyclohexa-2,5-dienone (279) affords both the monoepoxide (280) and diepoxide (281) in 8.1% and 3.1% yield respectively on alkaline epoxidation[156] while hexamethylcyclohexa-2,5-dienone (282) is recovered unchanged.[157] However mcpba epoxidation of (282) gave the monoepoxide (283) in good yield and this was converted to the diepoxide (284) on further treatment with the peracid. Since both these dienones have gem-dimethyl groups at C-4 the question of the stereochemistry of epoxidation

(279)



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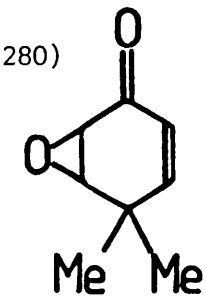

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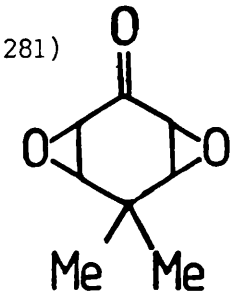

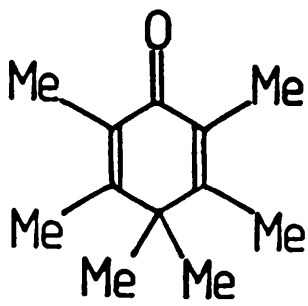

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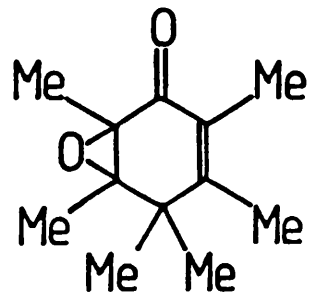

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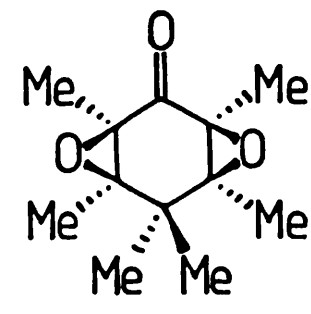
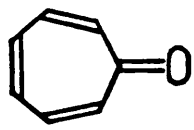


(284)

with respect to substituents does not arise until the symmetry of the molecule is destroyed ie one of the double bonds is epoxidised. Epoxidation of the remaining double bond could then occur either syn or anti to the first. While the stereochemistry of the diepoxide (281) was not examined, the monoepoxide (283) with mcpba gave exclusively the diepoxide (284) in which the epoxides are cis. The stereochemistry was assigned from the ^{1}H nmr spectrum which showed two distinct singlets for the two different methyls of the gem-dimethyl group.

A cis diepoxide (286) is also exclusively formed from tropone (285) though in this case alkaline hydrogen peroxide was used as the epoxidising reagent.[158]



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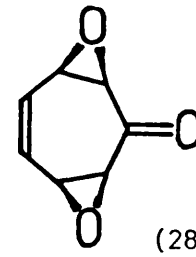
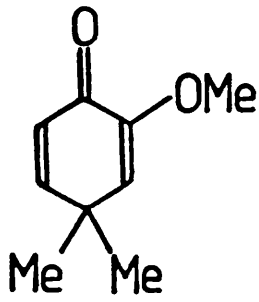
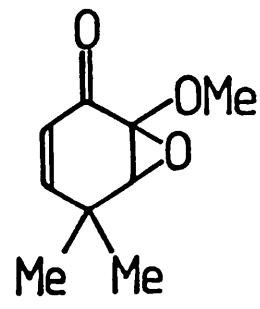


(286)

Matoba et al[159] investigated epoxidation of the dienone (287). The methoxyl substituent makes the two double bonds inequivalent and means they can be selectively epoxidised under different conditions. Treatment with mcpba results in attack at the more nucleophilic double bond giving only the monoepoxide (288) while alkaline epoxidation affects only the other double bond, affording the monoepoxide (289). Reaction of (288) with alkaline hydrogen peroxide or (289) with mcpba both failed to yield



(287)



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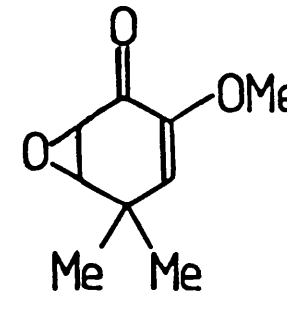
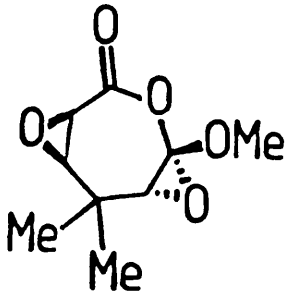


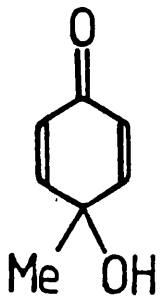
(289)

any diepoxide, the main product in each case being the diepoxy lactone (290), a result of Baeyer-Villiger oxidation and further epoxidation.

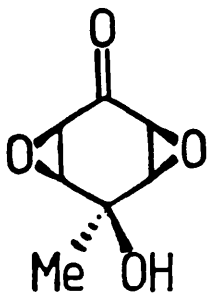
(290)



Epoxidation of 4-hydroxy-4-methylcyclohexa-2,5-dienone (p-toluquinol)[160]



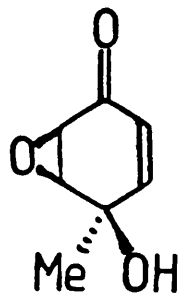
(268)



(291)

MacLachlan showed that alkaline epoxidation of toluquinol (268) with sodium carbonate and hydrogen peroxide in ethanol gave a single diepoxide.[160] This epoxide was also the major product obtained under more forcing conditions which employed sodium hydroxide as base and reduced the reaction time from 2½ hours to 1 hour. However evidence for the formation of the other two possible diastereomeric diepoxides was found in ^{13}C and ^{1}H nmr spectra of the product mixture. The major diepoxide product was assigned the stereochemistry (291). This is consistent with the facts that the four epoxide protons show a single AB quartet in the ^{1}H nmr spectrum (run in deuteriobenzene), indicating the epoxides are cis to one another and the ir spectrum shows a peak at

3570 cm^{-1} which does not decrease in size on dilution. This suggests the hydroxyl group is intramolecularly hydrogen-bonded, which is only possible if the epoxides and hydroxyl group are cis. Further support for this assignment came from the cis monoepoxy alcohol (292). Although this compound will undergo alkaline epoxidation more quickly than the dienone

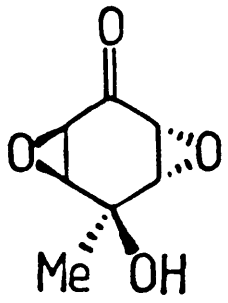


(292)

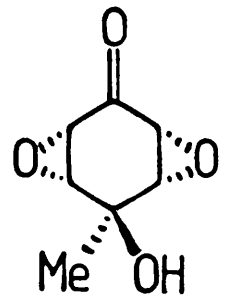
(268) because the electron-withdrawing effect of the carbonyl group is no longer split between two double bonds, thereby making the double bond more electrophilic, MacLachlan managed to isolate (292) in low yield by slow addition of hydrogen peroxide to a basic solution of the dienone. This material was identical with the monoepoxide obtained from mcpba epoxidation of the dienone. Since peracid epoxidation should yield a cis epoxy alcohol due to the directing effect of the 'allylic' alcohol the stereochemistry of (292) and diepoxide (291) was confirmed.

To try to isolate the other diastereomeric diepoxides reported by MacLachlan it was decided to repeat the alkaline epoxidation of toluquinol (268). The more vigorous reaction conditions employing sodium hydroxide as the base were tried but the reaction was left too long and after purification by flash chromatography the only product isolated and characterised was the diepoxide (291), whose spectral and physical properties were consistent with those previously reported. No trace of the diastereomeric epoxides (293) and (294) was found but the poor yield of isolated material does not exclude their formation.

Surprisingly while toluquinol and the naphthoquinol (48) readily



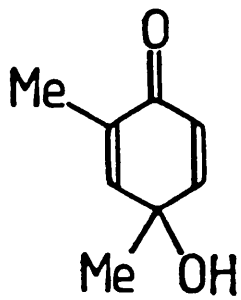
(293)



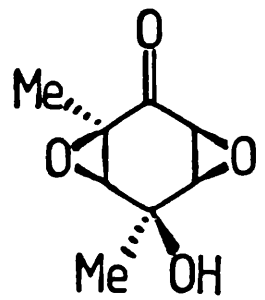
(294)

undergo peracid epoxidation with mcpba, toluquinol unlike (48) failed to epoxidise with per-Amberlyst 15, a sulphonic peracid made in situ from the ion-exchange resin Amberlyst 15 and an anhydrous ethereal solution of hydrogen peroxide.

Epoxidation of 2,4-dimethyl-4-hydroxycyclohexa-2,5-dienone



(269)



(295)

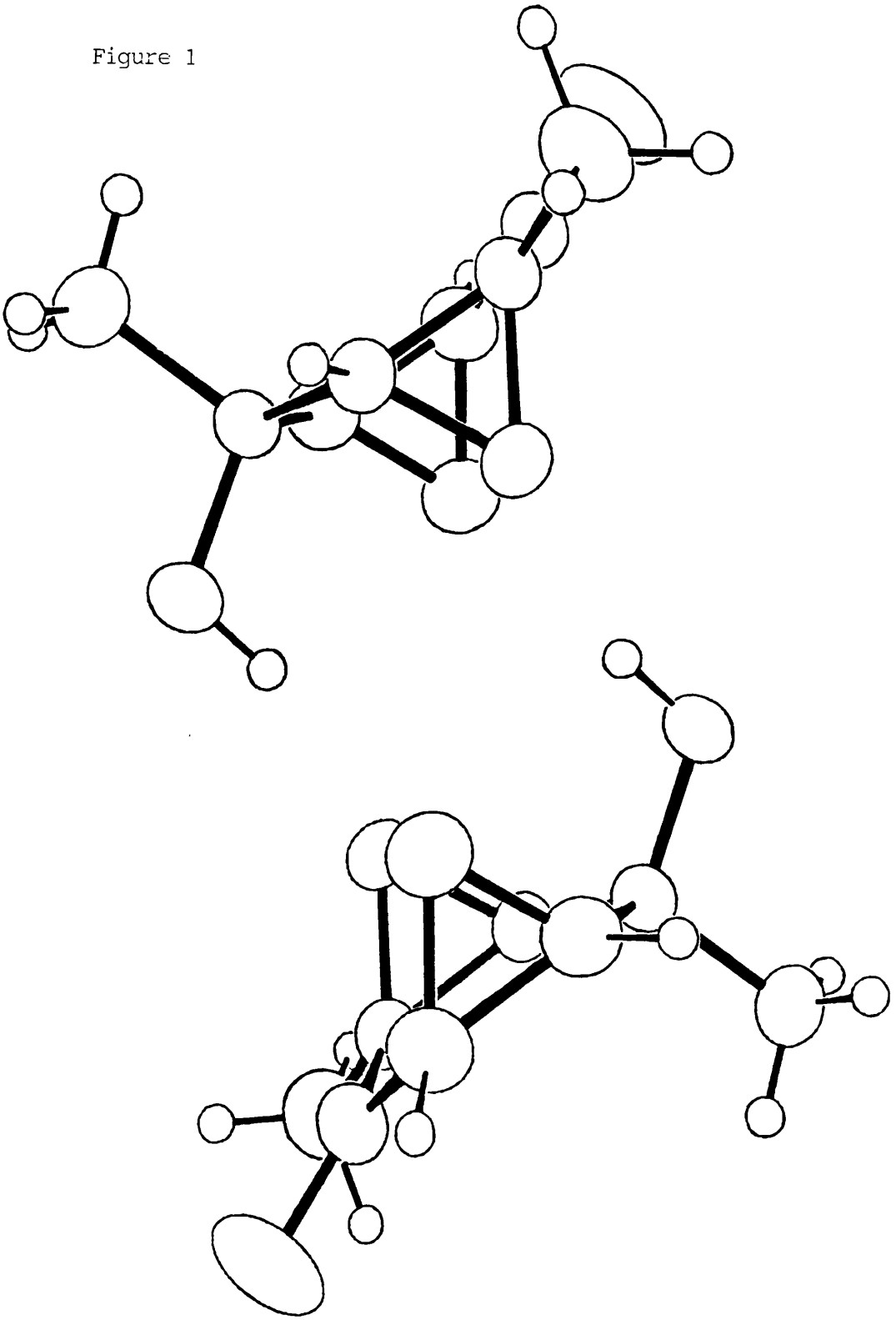
Unlike toluquinol the dienone (269) is unsymmetrical due to the methyl substituent at C-2. This increases the number of possible diastereomeric diepoxide products from three to four. Also the steric or electronic effect of the substituent may result in formation of a mono-epoxide, of which there are four possible isomers. Despite this possibility alkaline epoxidation gave a simple mixture whose 'H nmr and tlc showed it comprised only of a single diepoxide product and the starting dienone in the ratio 2:1. These components were separated by flash chromatography which afforded the crystalline diepoxide, m.p. 142-145°. As with diepoxide (291) the ir spectrum for this compound shows both an intramolecular hydrogen bond (3580 cm^{-1}) and an intermolecular

hydrogen bond (~3500 cm^{-1}) for the hydroxyl group, suggesting the likely structure for the diepoxide is (295). However unlike (291) the ^1H nmr spectrum could not confirm the stereochemistry of the epoxides as being cis or trans to one another since the methyl substituent makes the epoxide protons on either side of the molecule inequivalent. The cis hydroxy diepoxide structure of (295) was determined by x-ray analysis on a single crystal (Figures 1 and 2).

The x-ray result shows that the racemic epoxide crystallises so that a pair of enantiomeric molecules lie centrosymmetrically (as shown in Figures 1 and 2) with the hydroxyl and epoxide oxygens close together in the middle. (The distance between the epoxide oxygens and the hydrogen of the hydroxyl is 2.33Å). The hydroxyl group is also close to the two epoxide oxygens of the other molecule so that there appears to be a degree of hydrogen bonding, both intramolecularly and intermolecularly. The ir spectrum of the diepoxide suggests at least some of these interactions also take place in solution.

In addition to proving the cis stereochemistry of the epoxy and hydroxyl groups a second question concerning the conformation of the cyclohexanone ring is answered by the x-ray result. The diepoxide is capable of adopting two different boat conformations (296) and (297) but the figures show that (296) is preferred. It is well established that α,β-epoxy ketones and α,β-cyclopropyl ketones tend to adopt a conformation in which the plane of the three-membered ring lies perpendicular to the plane of the carbonyl group.[161] This geometry allows maximum interaction between the delocalised epoxide orbitals and the π orbital of the ketone, and explains why (296) in which the epoxide ring is virtually perpendicular to the plane of the carbonyl is preferred. This geometry has also been observed in previous x-ray crystal structures of α,β-epoxy ketones.[91,162,163]

Figure 1



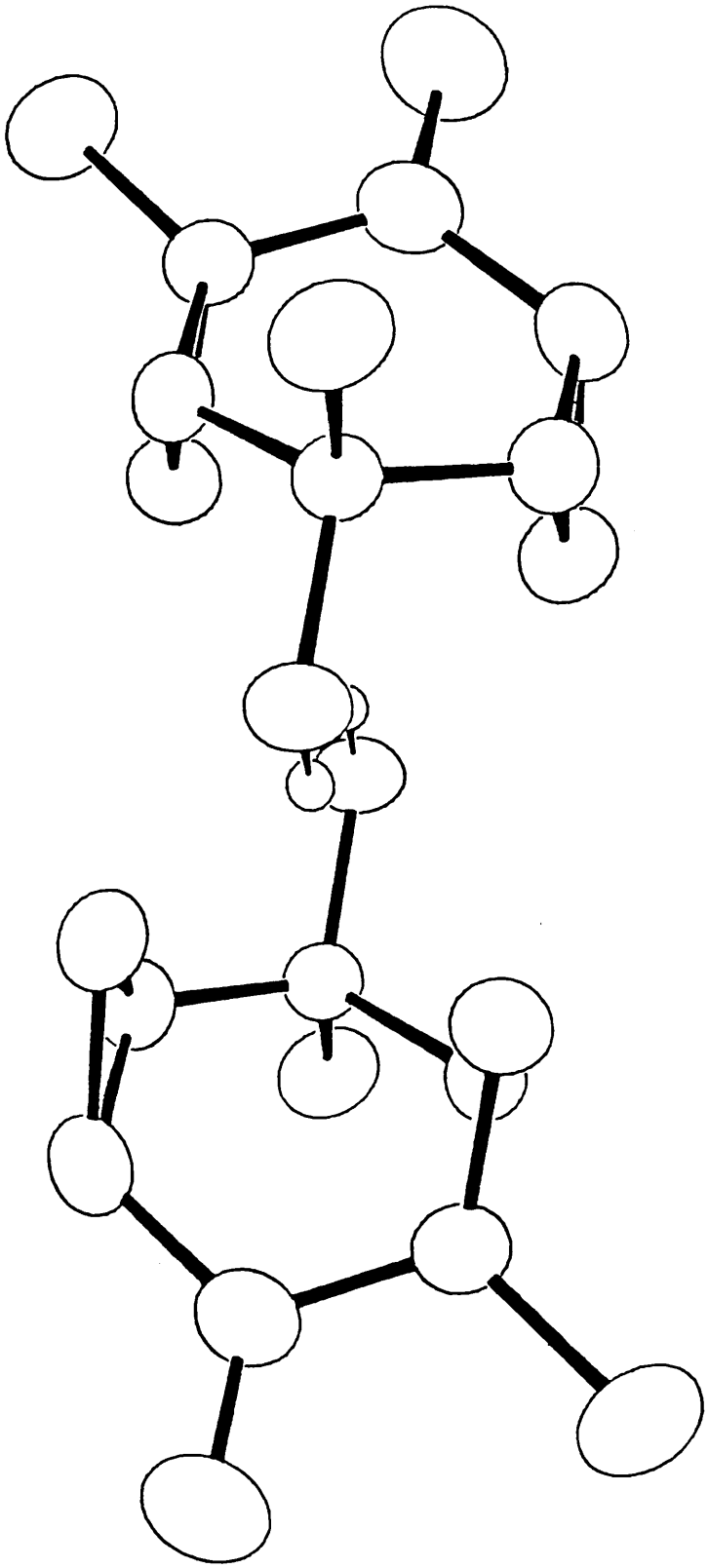
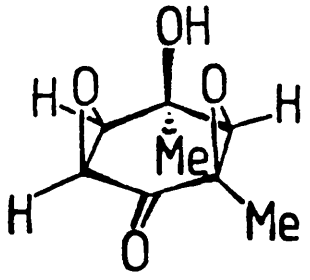
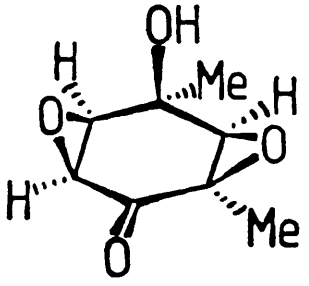


Figure 2

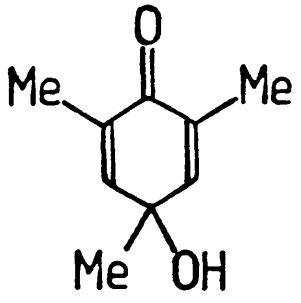
(296)



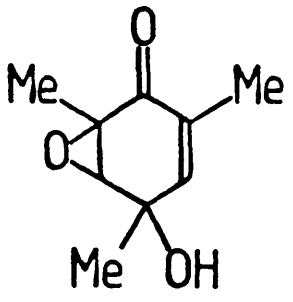
(297)



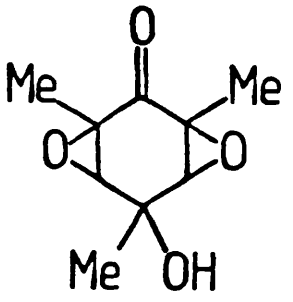
Attempted epoxidation of 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone



(270)



(298)



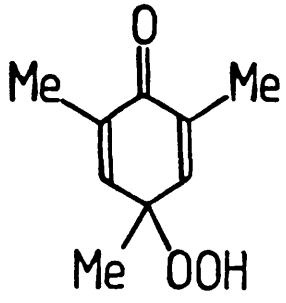
(299)

Both a monoepoxide (298) and a diepoxide (299) have been isolated from mcpba epoxidation of (270),[164] though the stereochemistry of the products was not determined. A previously attempted alkaline epoxidation of the dienone was unsuccessful, giving only recovered starting material.[165]

Although a variety of conditions was tried, treatment of the dienone (270) with alkaline hydrogen peroxide failed to yield any epoxide products.

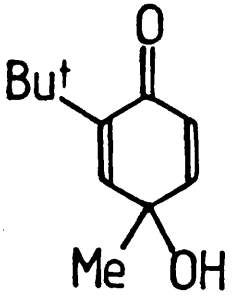
Base-catalysed rearrangement of the hydroperoxide (275) with sodium hydroxide in aqueous ethanol gave largely the alcohol (270) rather than the expected cis hydroxy monoepoxide (298) though the ^1H nmr spectrum of the product suggested this epoxide was formed in low yield. In addition to a new doublet (J ~ 3 Hz) at δ 3.44 and multiplet at δ 6.20 consistent with the protons of the newly formed epoxide and remaining enone respectively, the spectrum shows two new singlets at δ 1.25 and δ 1.48 consistent with the epoxide methyl and C-4 methyl groups. It is likely the absence of a peak for the vinyl methyl group is due to it being hidden under the much larger vinyl methyl peak of the alcohol (270). Because of the poor yield

no attempt was made to separate the monoepoxide from dienone or to establish the relative stereochemistry of the epoxy and hydroxyl groups in (298).

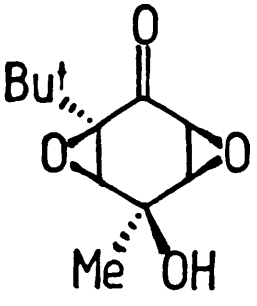


(275)

Epoxidation of 2-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone



(271)



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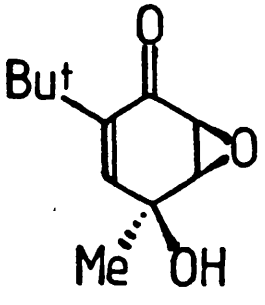


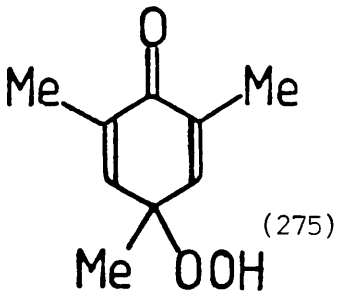
(301)

Prolonged exposure of the dienone (271) to alkaline hydrogen peroxide resulted in formation of a single diepoxide. Since this compound was also a major product from mcpba epoxidation and its ir spectrum shows an intramolecularly bonded hydroxyl group, it is clear that the epoxidation has proceeded as for the dimethyl compound (269) and that this diepoxide (300) also has its epoxy and hydroxyl groups in an all-cis conformation.

When the reaction time was shortened, tlc, using 10% ethyl acetate in petroleum ether, showed a new spot in addition to those associated with dienone and diepoxide. After separation of the products by preparative tlc, ^{1}H nmr confirmed a monoepoxide had been isolated. The spectrum for this compound shows a singlet at δ 1.27 due to the t-butyl group and a

doublet (J = 3 Hz) at δ 6.22. Since there is only a single enone peak, epoxidation must have occurred on the non-substituted side ie the mono-epoxide formed was (301). The epoxide region shows a doublet (J = 6 Hz) at δ 3.48 due to the α-epoxide proton and a doublet of doublets from δ 3.50-3.64 due to transannular coupling (J = 3 Hz) of the β-epoxide proton with the enone proton and coupling (J = 6 Hz) of the β-epoxide proton with the α-epoxide proton. Since this monoepoxide was obtained after short reaction times and the diepoxide described above was the only product from longer reaction times it is clear the monoepoxide must be an intermediate in the formation of the diepoxide. Hence the epoxy and hydroxyl groups of the monoepoxide must be cis as in (301). Also epoxidation of the dienone (271) must preferentially occur first on the non-substituted side. This could either be due to the bulk of the t-butyl group hindering approach of the hydroperoxide anion to the substituted enone or because the electron-releasing nature of the t-butyl group makes the substituted enone less electrophilic than the non-substituted one and therefore less susceptible to attack from the nucleophilic hydroperoxide anion. The isolation of the monoepoxide (301) in only low yield is consistent with epoxidation of the second double bond being quicker than the first. This is expected because, after monoepoxidation, the electron-withdrawing effect of the carbonyl group is no longer shared between two double bonds.

The monoepoxide (301) had previously been isolated from treatment of the dienone (271) with Triton B and t-butylhydroperoxide in dioxan,[166] though again the diepoxide (300) was the major product. This work also reported that unlike the hydroperoxide (275), the hydroperoxide (276) failed to yield (301) or any other epoxide products on attempted base-catalysed rearrangement. Peracid epoxidation of (271) with mcpba had also been studied and reported to give both the diepoxide (300) and the mono-



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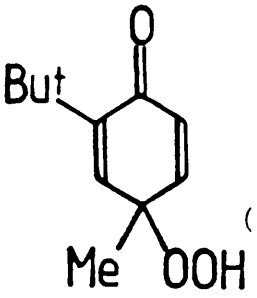
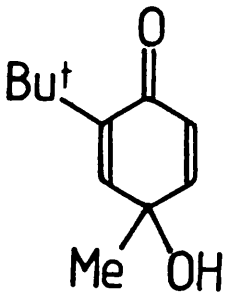
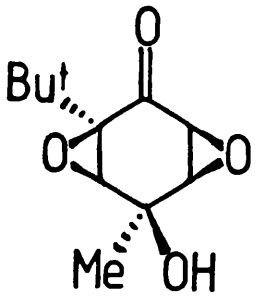


(276)

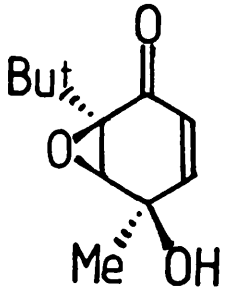
epoxide (302).[166] Since no mention was made of the relative proportions of these products it was decided to repeat this reaction.



(271)



(300)



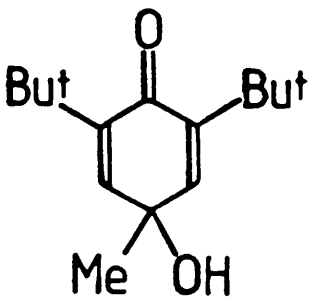
(302)

Treatment of the dienone with mcpba in dichloromethane for four days afforded the diepoxide (300) and monoepoxide (302) in a 1:2 ratio. TLC and ^1H nmr also showed there was a trace of dienone remaining. As had been previously reported these products could be separated by preparative tlc to give the diepoxide (300) and monoepoxide (302) which was still contaminated with a small proportion of dienone. The monoepoxide shows a single doublet (J = 3 Hz) at δ 3.59 for the epoxide proton and two different peaks in the enone region - a doublet (J = 11 Hz) at δ 5.71 for the α proton and a doublet of doublets (J = 11 Hz, J = 3 Hz) for the β proton. This confirms peracid epoxidation occurs on the substituted side and shows that the t-butyl substituent does not sterically hinder approach of this reagent to the double bond. The exclusive formation of a single monoepoxide, as was found for alkaline epoxidation, is therefore best explained as being due to the electron-releasing nature of the t-butyl group which makes the substituted double bond less electrophilic. Hence

while the nucleophilic hydroperoxide anion will attack only the unsubstituted side the electrophilic peracid will attack only the opposite substituted double bond. The isolation of monoepoxide (301) from alkaline epoxidation in only poor yield, while monoepoxide (302) was obtained in good yield from peracid epoxidation, is also easily explained. After monoepoxidation of the dienone (on either side) the remaining enone will be much more electrophilic than the starting dienone. Hence while alkaline epoxidation of this remaining double bond will be relatively quick affording mainly the diepoxide, it will react only slowly with mcpba, leaving mainly monoepoxide.

Attempted epoxidation of (271) with per-Amberlyst 15, as with toluquinol, was unsuccessful, with quantitative recovery of the dienone.

Epoxidation of 2,6-di-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone



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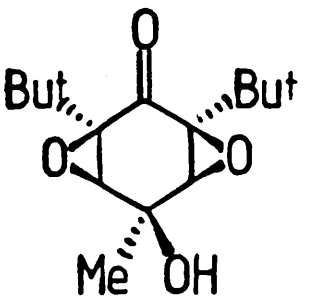
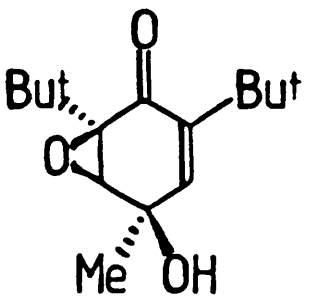


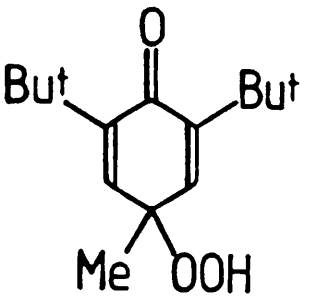
(303)



(304)

In studying the base-catalysed oxygenation of hindered phenols, Nishinaga[167] found that 2,6-di-t-butyl-4-methylphenol (267) is converted to the epoxy quinol (304) by bubbling oxygen through a solution of the phenol in an aprotic solvent such as dimethylformamide (DMF) or dimethylsulphoxide (DMSO) containing potassium t-butoxide ($KOBu^t$). The p-quinol (272) remained inert under these conditions. Further oxidation of the epoxy quinol (304) with t-butylhydroperoxide in DMF containing $KOBu^t$ afforded a diepoxide (303). The anion of hydroperoxide (277) was proposed as the intermediate in formation of the epoxy quinol (304) because (277)

(277)



when dissolved in DMF containing $KOBu^t$ reverted back to phenol and also gave some epoxy quinol (304). Although no stereochemistry was assigned to either (303) or (304) it seems likely by analogy with other base-catalysed rearrangements of γ-hydroperoxy enones that the epoxy and hydroxyl functions in both compounds are cis. The appearance of only one peak for the epoxide proton, a singlet at δ 3.41 and only one peak for the t-butyl group, a singlet at δ 1.04 in the ^1H nmr spectrum of (303) indicates the two epoxides must be cis to one another.

Monaghan also studied the quinol (272), attempting epoxidation with both alkaline hydrogen peroxide and t-butylhydroperoxide with molybdenum hexacarbonyl.[165] However as with the quinol (270) he reported only the recovery of starting dienone from the attempted alkaline epoxidation. The metal-catalysed epoxidation gave a complex mixture of products which could not be separated by preparative tlc. He argued that the presence of a doublet (J = 7 Hz) at δ 4.15 and doublet (J = 7 Hz) at δ 3.95 in the ^1H nmr spectrum of the crude product suggested an epoxide had been formed. However this interpretation is doubtful since neither of these chemical shifts or couplings is consistent with any of the peaks reported by Nishinaga for diepoxide (303) or epoxy quinol (304).[167] Despite this reported failure of the quinol (272) to undergo alkaline epoxidation it was decided to repeat this reaction.

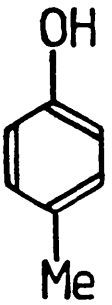
Prolonged exposure (~170 hours) of the quinol (272) to hydrogen peroxide and ethanolic sodium hydroxide resulted in about 70% conversion

to diepoxide (303). An ^1H nmr spectrum of the product showed there was no monoepoxide present indicating it must be epoxidised considerably quicker than the starting dienone. The diepoxide was separated from residual dienone by successive recrystallisations from petroleum ether, eventually affording material identical to that reported by Nishinaga.[167]

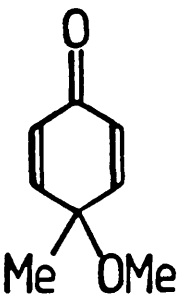
The effect of a γ-hydroxyl group in this monocyclic series has now been fairly thoroughly investigated and found to behave similarly with various epoxidising reagents to the γ-hydroxy naphthalenone (48). Because of this it was decided to check that alkaline epoxidation of a monocyclic dienone with a γ-ether substituent would show little selectivity as in the naphthalenone series.

Preparation of 4-methoxy-4-methylcyclohexa-2,5-dienone

(263)



(305)



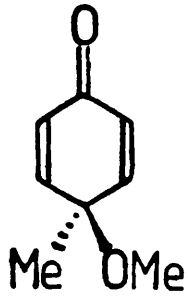
The dienone (305) was first prepared by oxidation of p-cresol (263) with lead (IV) acetate in methanolic boron trifluoride.[168] It has also been prepared by anodic oxidation of p-cresol or p-methylanisole in methanol[169-171] and oxidation of p-methylacetanilide with (diacetoxyiodo) benzene (DIAB)[172] among others.[173] Recently DIAB in methanol has been shown to effect conversion of p-alkylphenols to 4-alkyl-4-methoxycyclohexa-2,5-dienones in good yield.[174]

It was decided to prepare the dienone (305) by oxidation of p-cresol with PIFA in methanol since this had been shown to work well with 4-methyl-1-naphthol (Chapter 1). Purification of the product by flash chromato-

graphy afforded the dienone in 46% yield.

Epoxidation of 4-methoxy-4-methylcyclohexa-2,5-dienone

(305)



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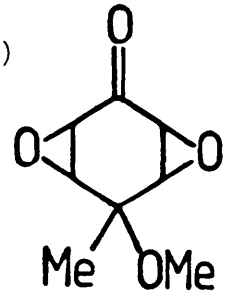
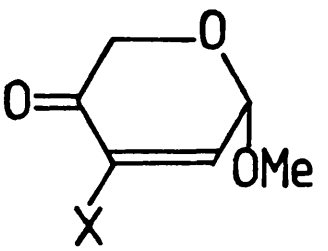


The dienone (305) was treated with alkaline hydrogen peroxide for 24 hours. Tlc after this time indicated there was no starting material left and suggested it had been largely converted to a single product of slightly lower Rf. Although the plate showed a couple of other faint spots, one of which was identified as p-cresol, an ^1H nmr spectrum confirmed the presence of only one major product. After purification of this product by flash chromatography this ^1H nmr spectrum comprised of only three peaks - two singlets at δ 1.67 and δ 3.38 and a symmetrical multiplet between δ 3.4-3.5. These peaks and their integrals are consistent with a diepoxide (306) in which the two epoxides are cis to one another, though whether they were cis or trans to the γ-ether could not be determined from the spectrum. Since this diepoxide was isolated in only poor yield (12%), it was decided to repeat the reaction and to look more closely for the formation of other epoxide products. Using sodium carbonate instead of sodium hydroxide, which drastically reduced the rate of epoxidation, the reaction was repeated with 130 mg of pure dienone. Because of the reduced rate even after 3 weeks only about 10% of the dienone had been converted to diepoxide. As before, recovery of material was poor with this mixture now totalling only 73 mg. The reaction was monitored by ^1H nmr which again showed no sign of another epoxide being formed.

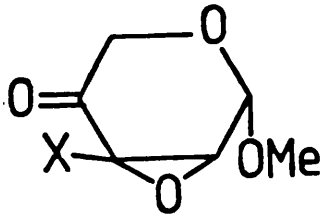
A ^{13}C nmr spectrum of the purified diepoxide obtained from the first reaction shows only six main peaks. DEPT experiments established that of these peaks two are quartets (methyl groups), two are doublets (methine groups) and two are singlets (quaternary carbons). The shifts of these peaks are consistent with the diepoxide (306), confirming that alkaline epoxidation was highly stereoselective or stereospecific. Also since only two peaks were observed for the four epoxide carbons, the spectrum shows them to be equivalent and hence cis to one another.

It has been shown that alkaline epoxidation of the enones (116a,b) gives exclusively the epoxides (117a,b) in which the epoxy and methoxy groups are cis.[69] It was hoped that using the nuclear Overhauser effect (NOE), nmr would be able to determine whether the methoxyl or the methyl group was cis to the epoxides in (306).



(116) a X=Cl

b X=Br

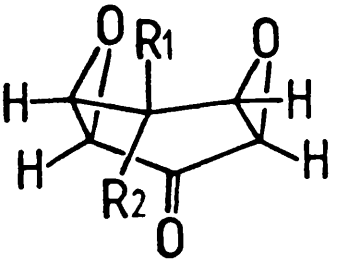


(117) a X=Cl

b X=Br

The most likely boat conformation of the diepoxide (306) is (307) since this allows the favourable interaction of the epoxide orbitals with the π orbital of the ketone, mentioned earlier. In this conformation

(307)



the dihedral angle between the β-epoxide H atoms and the two γ substituents is virtually identical, so that for R_1=OMe, R_2=Me or R_1=Me,R_2=OMe the enhancement of the β-epoxide H atoms by NOE should be the same ie this experiment would be of no use in determining the stereochemistry. However because a NOE should only be observed between R_2 and the α-epoxide H atoms, the corresponding distance from R_1 being far greater, separate irradiation of both the methoxyl and methyl groups should allow configural assignment of the γ-substituents. Irradiation of the methyl group resulted in significant enhancement of one half of the symmetrical multiplet, between δ 3.40-3.45. This half must be due to the β-epoxide H atoms which are closer to the methyl substituent. The other half at δ 3.45-3.50 appeared to have increased marginally. Although this experiment worked well, irradiation of the methoxyl group proved impossible due to its close proximity to the epoxide multiplet. Hence no comparison of the NOE's produced by irradiation of the γ-substituents could be made and the stereochemistry could not be assigned.

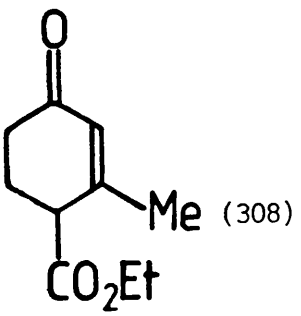
As with the naphthalenones the work done in this monocyclic series largely extended what was already established. Toluquinol had been shown to be stereospecifically epoxidised with alkaline hydrogen peroxide affording the cis diepoxy alcohol (291). This stereospecificity was shown to be general throughout the series for all the dienones that could be epoxidised. For one diepoxide the stereochemistry was proved by x-ray crystallography. The failure of 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone to be epoxidised is almost certainly due to the electron-releasing effect of the methyl substituents making the dienone less electrophilic. Steric inhibition of the double bonds to the hydro-

peroxide anion by the methyl substituents at C-2 and C-4 seems an unlikely explanation since the analogous 2,4-di-t-butyl substituted dienone can be epoxidised slowly under the same conditions. Despite the similarity in structure between this series and the naphthalenone series a number of subtle differences in reactivity were observed. Because the monocyclic quinols have two double bonds that may be epoxidised they yield diepoxides on treatment with alkaline hydrogen peroxide; monoepoxidation is slower than for the naphthoquinol (48) but the remaining double bond is epoxidised far more quickly. The quinols of both series react stereospecifically with mcpba affording epoxy or diepoxy quinols but only the naphthoquinols are oxidised with per-Amberlyst 15. The major difference between the series was that while alkaline epoxidation of a naphthalenone with a γ-ether substituent was not even appreciably stereoselective, giving both epoxy ethers, epoxidation of 4-methoxy-4-methylcyclohexa-2,5-dienone appeared to be stereospecific with a single epoxide being formed, though in low yield. An attempt to determine the stereochemistry of this epoxide by nmr using NOE was unsuccessful. For the unsymmetrical quinol (271) regioselective epoxidation was possible. Alkaline epoxidation gave mainly the diepoxide (300), but the monoepoxide (301) was also obtained, indicating oxidation occurs on the non-substituted side first. With peracids the substituted double bond is attacked first, the main product being the monoepoxide (302) which is isolated along with the diepoxide.

Chapter 3 : Epoxidation of γ-Substituted Enones (System C)

In Chapters 1 and 2 alkaline hydrogen peroxide epoxidation of dienones substituted in the γ-position with a hydroxyl group was found to be stereospecific. In all cases the dienone also had a γ-alkyl group which did not compete with the hydroxyl group in directing epoxidation. To broaden the scope of this study it was decided to investigate a new enone system that possessed both a hydroxyl and a polar functional group in the γ-position.

Stoodley recently discovered a novel hydroxylation procedure for butenoates substituted at the γ-position with an acidifying group, eg COR, CO_2R, SO_2R and $PO(OR_2)$.[175] One of the substrates he investigated was 4-ethoxycarbonyl-3-methylcyclohex-2-enone (Hagemann's ester) (308) which gave the γ-hydroxy enone (309) in 50% yield. The procedure is simple, requiring only stirring of an ethyl acetate solution of the substrate with activated charcoal for a few days in air and then filtration through celite. This led to the possibility of easily synthesising a range of cyclohexenones substituted in the γ-position with both a hydroxyl group and a carbonyl function. This new system makes it



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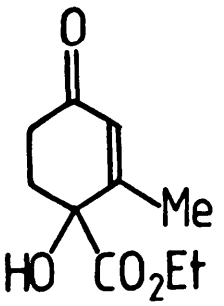
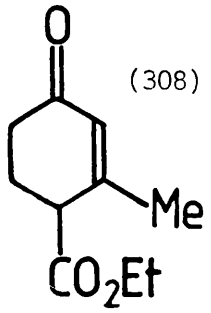


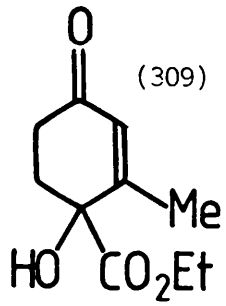
(309)

possible to study whether the stereospecificity on alkaline epoxidation is maintained in cyclohexenones, where the molecules have greater flexibility, and whether there is competition between the hydroxyl group and the carbonyl function to direct epoxidation.

Preparation of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone

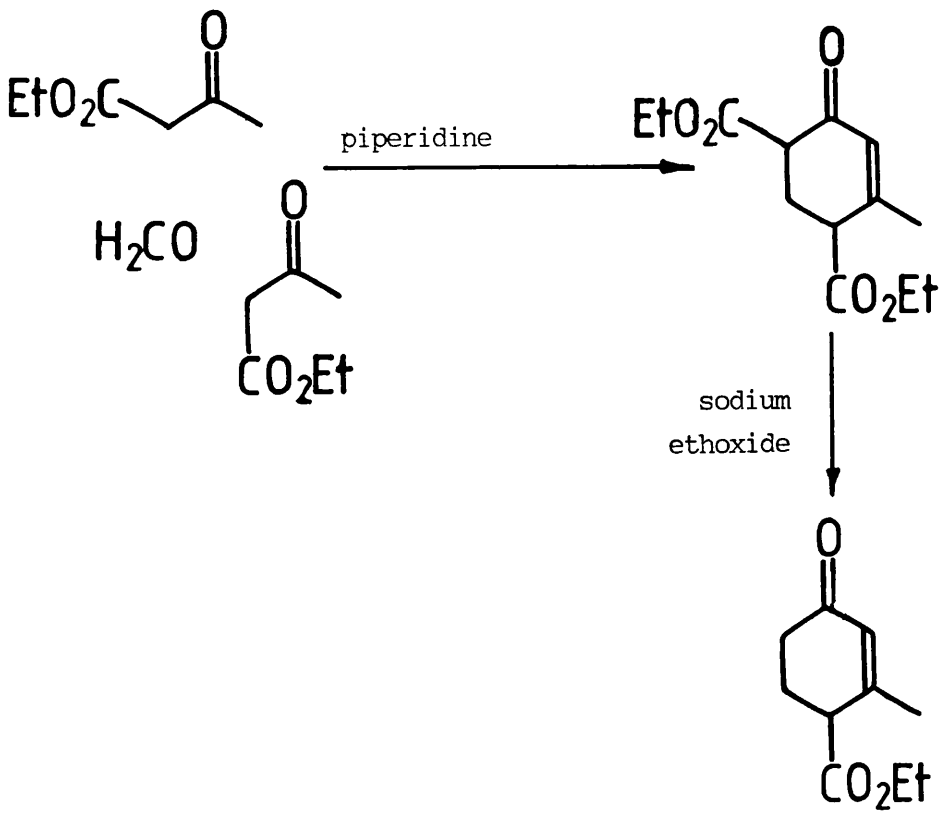


(308)



(309)

Hagemann first prepared the ester (308) from ethyl acetoacetate and methyl iodide.[176] A more convenient method was found[177] after the discovery that 4,6-diethoxycarbonyl-3-methylcyclohex-2-enone, which is prepared by condensation of two equivalents of ethyl acetoacetate with formaldehyde in the presence of piperidine, could be converted to the ester (308) on treatment with sodium ethoxide[178] (Scheme 22).

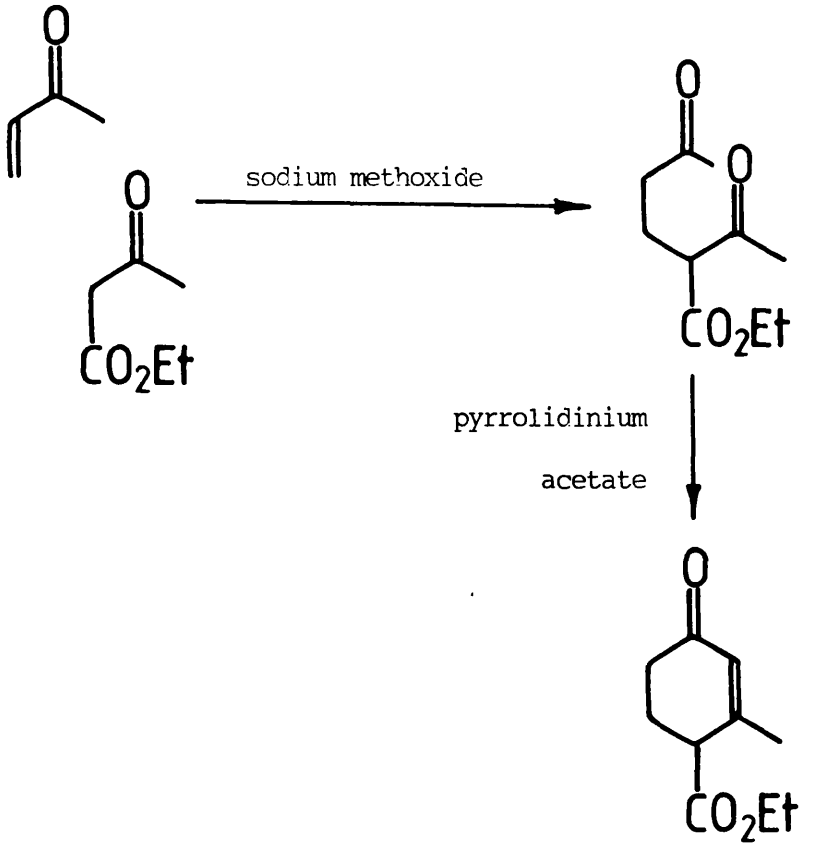


Scheme 22

Using this procedure pure Hagemann's ester was obtained after

distillation in 58% yield.

Golding[179] reported an improved method for synthesising the ester (308) (and its methyl and t-butyl analogues) which involved base-catalysed Michael addition of ethyl acetoacetate to but-3-en-2-one and subsequent cyclisation of the dioxo-ester catalysed by pyrrolidinium acetate (Scheme 23). More recently a one-pot procedure of the ester (308),



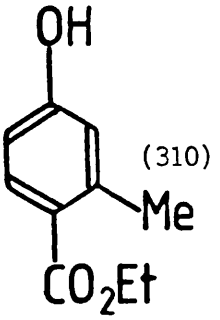
Scheme 23

involving piperidine-catalysed condensation of ethyl acetoacetate with paraformaldehyde, has been reported.[180]

Golding's method was used to prepare a stock of the ester prior to hydroxylation. Although he purified the intermediate dioxo-ester by distillation, it was found that this could be dispensed with and that a fair yield of Hagemann's ester was still obtained.

Stirring an ethyl acetate solution of the ester (308) with activated charcoal resulted in hydroxylation. This reaction was performed a

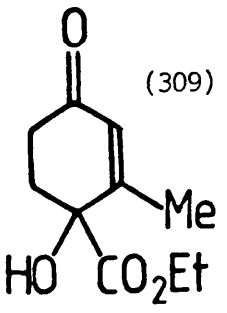
number of times, sometimes with triethylamine which, as reported, halved the amount of charcoal required and reduced the reaction time from 3 days to 1 day. The best yield of hydroxy ester (309) was 59% after purification by flash chromatography. No intermediates were ever observed by ^1H nmr or tlc which showed clean conversion of (308) (Rf 0.40) to (309) (Rf 0.25). On one occasion however, when triethylamine was used and the reaction was left longer than usual, the phenol (310) was isolated as a minor product. It presumably arises from dehydration of the alcohol.



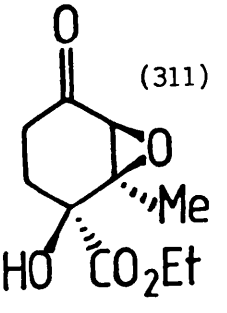
(310)

The esters (308) and (309) are both pale yellow oils with similar ^1H nmr spectra. The only significant difference is that the C-4 proton of (308) which appears as a triplet at δ 3.25 is absent in the spectrum of (309) which shows a new broad singlet, exchangeable with deuterium oxide, at δ 4.1.

Epoxidation of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone



(309)

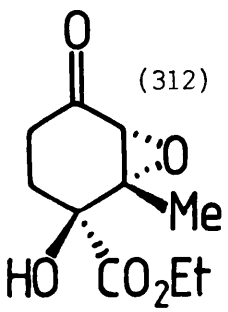


(311)

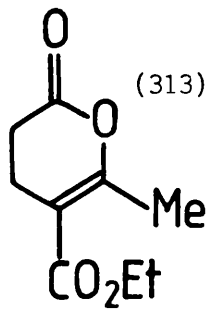
Alkaline hydrogen peroxide epoxidation of (309) in ethanol was

stereospecific affording a single low melting crystalline epoxide. Tlc showed this epoxide had slightly higher Rf than the starting enone. This same epoxide was formed in very low yield but was detected by both ^1H nmr and tlc from treatment of the enone with t-butylhydroperoxide and molybdenum hexacarbonyl. Since the γ-hydroxyl group should direct this metal-catalysed epoxidation, the stereochemistry of the epoxide formed in both reactions is likely to be (311) and this was eventually confirmed by x-ray diffraction work to be described later (p 121). None of the diastereomeric epoxide (312) (which was later synthesised) was ever detected by ^1H nmr or tlc from either of the above epoxidation procedures. (Comparison of (311) with its diastereomeric epoxide (312) will be made later).

It was hoped to obtain the epoxide (311) from peracid epoxidation. However reaction of the enone with excess mcpba in refluxing dichloromethane was slow and after one week was found by tlc to result in fairly clean conversion of the enone to a single product which proved not to be the epoxide (311). This product was purified by flash chromatography and distillation. ^{13}C, ^1H nmr, ir and mass spectral data were collected and these suggested structure (313). This compound shows a peak in its high



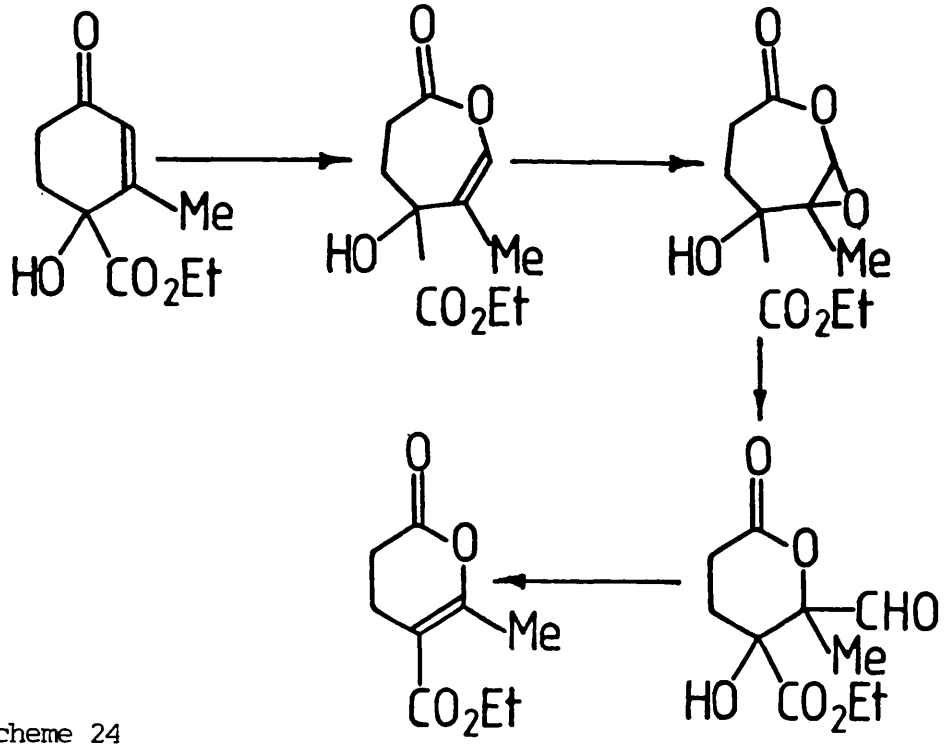
(312)



(313)

resolution mass spectrum consistent with the molecular formula $C_9H_{12}O_4$ and weight 184. It also has 9 peaks in its ^{13}C nmr spectrum whose shifts agree well with the proposed structure. The ^1H nmr spectrum with a triplet (J = 7.1 Hz) at δ 4.1 and quartet (J = 7.1 Hz) at δ 1.1 confirmed the ethyl ester is still present. Also a singlet at δ 2.0 and multiplet at

δ 2.35-2.75 are consistent with the methyl and two methylene groups respectively. Although the ir spectrum has two carbonyl peaks the frequencies, 1810 and 1760 cm^{-1}, are higher than expected for a vinyl lactone (1800-1750 cm^{-1}) and a simple α,β-unsaturated ester (1730-1715 cm^{-1}). Despite this it proved impossible to find an alternative structure that fitted the spectral data so well and could have been simply formed from the enone (309). A tentative mechanism for the formation of (313) is proposed (Scheme 24). The first two steps, Baeyer-Villiger oxidation and then epoxidation, find support from the oxidation



Scheme 24

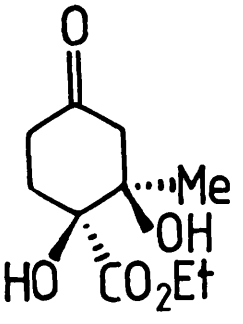
of Hagemann's ester and 3-methylcyclohex-2-enone with mcpba (see p 130). Both compounds yield epoxy lactones. Also the Baeyer-Villiger reaction is acid-catalysed and it was found that when the reaction mixture was buffered with sodium dihydrogen phosphate the enone (309) failed to react at all. This suggests Baeyer-Villiger oxidation occurs prior to epoxidation. Confirmation of this came from finding that the epoxide (311) failed to react with mcpba in refluxing dichloromethane indicating it is not an intermediate in the formation of (313). The dubious step in the

mechanism is the ring contraction of the epoxy lactone to the formyl lactone, though once formed the elimination of formic acid or carbon dioxide and water after oxidation of the aldehyde would seem quite likely. The resulting conjugation of the newly formed double bond with the ester would hinder further epoxidation with mcpba.

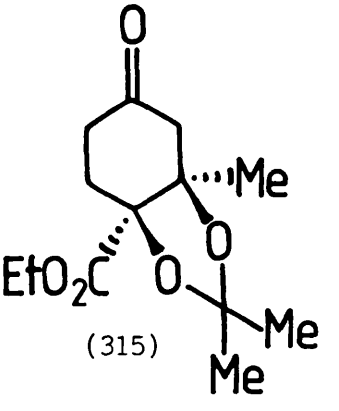
Despite the fact that oxidation of the γ-hydroxy enone (309) with mcpba gave the unexpected product (313), it could be epoxidised fairly readily with per-Amberlyst 15. Tlc and ^1H nmr showed that both the epoxides (311) and (312) were formed but that the cis hydroxy epoxide (311) predominated (~12:1 ratio).

Reduction of 2,3-epoxy-4-ethoxycarbonyl-4-hydroxy-3-methylcyclohexanone

Before the x-ray work was undertaken an attempt was made to establish the stereochemistry of the epoxy and hydroxyl groups of (311) by reducing the epoxide to the tertiary alcohol (314) and then forming the acetonide (315). Since acetonide formation would only be possible if the alcohols were cis, the isolation of (317) would therefore confirm the assignment of the epoxy and hydroxyl groups in (313) as cis.



(314)



(315)

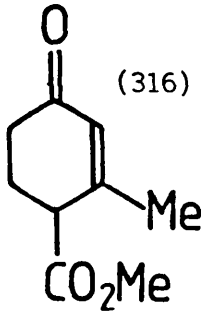
Treatment of an ethanolic solution of the cis epoxy alcohol (311) with an ethanolic solution of sodium phenylselenide (prepared by the reduction of diphenyl diselenide with sodium borohydride in ethanol[181]

containing some acetic acid) gave, after purification by flash chromatography, the diol (314) in 14% yield.[182] An attempt to improve the yield of diol using aluminium amalgam as the reducing agent[183] was unsuccessful, giving mainly unreacted epoxide, though tlc showed the diol had been formed in poor yield. As expected, the diol has lower Rf than the epoxy alcohol.

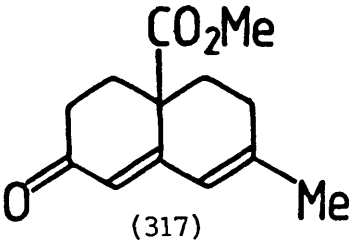
Formation of the acetonide (315) proved elusive despite attempted reactions of the diol (314) with acetone containing anhydrous copper sulphate[184] and pyridinyl p-toluenesulphonate.[185] In the first case only the diol was recovered while in the second the γ-hydroxy enone (309), resulting from dehydration of the γ-hydroxyketone, was obtained after the temperature had been raised to try to induce reaction.

Hence although all the evidence for the epoxide (311) suggests the epoxy and hydroxyl functions are cis, conclusive proof of this stereochemistry by formation of the acetonide (315) was not possible.

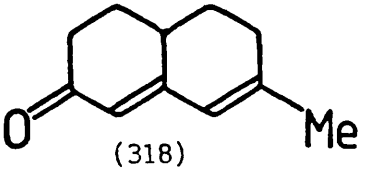
Preparation of 4-hydroxy-4-methoxycarbonyl-3-methylcyclohex-2-enone



(316)



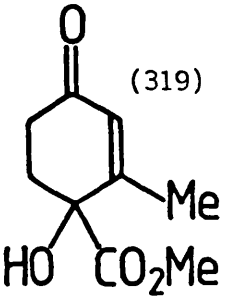
(317)



(318)

The methyl analogue of Hagemann's ester (316) was prepared according to the method of Golding.[179] In addition to the ester another higher boiling compound was formed in low yield. Separation by Kugelrohr distillation afforded pure methyl ester (316) and the minor product which crystallised on standing. Successive recrystallisations from ether gave fine white needles of m.p. 119-121° whose spectral data showed this

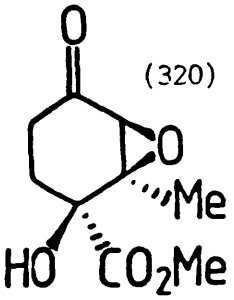
compound to be the ester (317). The ^1H nmr spectrum of (317) shows two enone protons at δ 5.81 and δ 6.10, the one of higher chemical shift being broad due to coupling with the vinyl methyl group at δ 1.88. In addition to a singlet at δ 3.71 for the methyl ester, there is a multiplet from δ 1.45-2.60 for the four methylene groups. The compound also analysed correctly for the formula $C_{13}H_{16}O_3$ and shows a large parent peak at m/e 220 in the mass spectrum. Final proof of the structure came from the uv spectrum which shows λ_{max} 290 nm (ϵ 23000) which agrees well with the model compound (318)[186] with λ_{max} 289 nm (ϵ 23000) and confirms (317) is more highly conjugated than Hagemann's ester, λ_{max} 228 nm (ϵ 10900). The yield of (317) could be significantly increased by starting with two equivalents of but-3-en-2-one for every one of methyl acetoacetate.



(319)

Hydroxylation of (316) with activated charcoal in ethyl acetate afforded (319) which, unlike the ethyl ester, is an almost colourless crystalline solid.

Epoxidation of 4-hydroxy-4-methoxycarbonyl-3-methylcyclohex-2-enone



(320)

Epoxidation of (319), not unexpectedly, gave results similar to those previously observed for the ethyl ester. Although alkaline epoxidation of (319) was not stereospecific it was highly stereoselective. ^1H nmr showed the cis:trans epoxy alcohol ratio was >20:1. High selectivity was also observed for per-Amberlyst 15 epoxidation with the cis epoxy alcohol (320) again being the major product. As with the ethyl ester, metal-catalysed epoxidation with t-butylhydroperoxide and molybdenum hexacarbonyl gave a poor yield of the cis isomer (320).

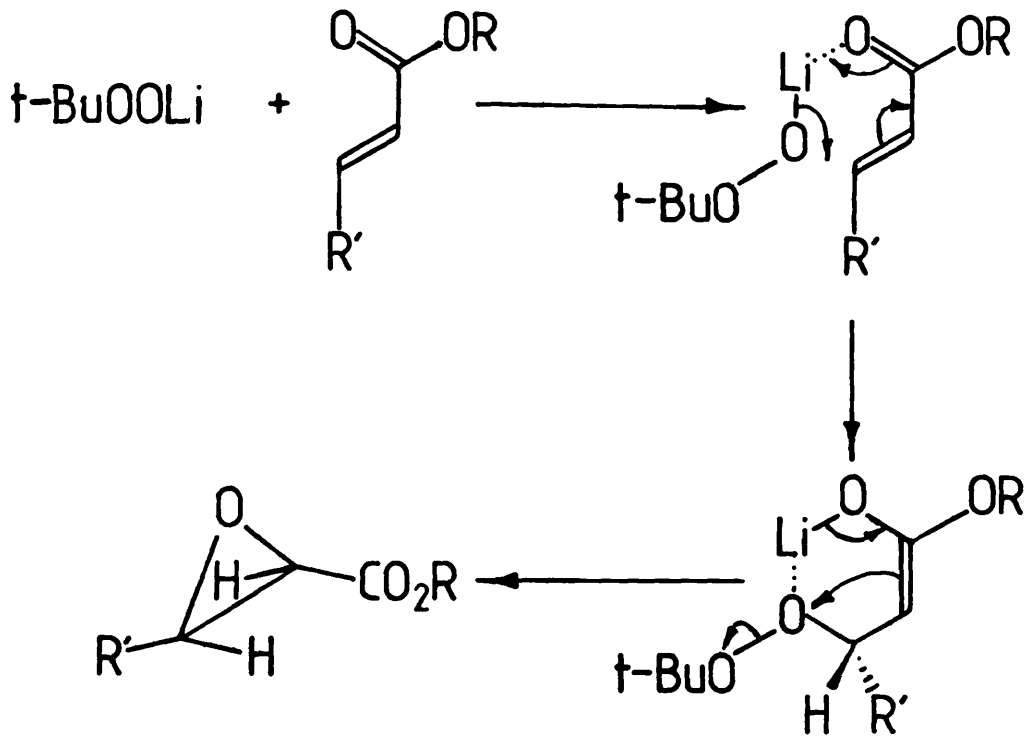
In order to check the unlikely event of the selectivity being reversed on changing from the ethyl ester (309) to the methyl ester (319) the epoxy alcohol (311) was treated with sodium cyanide, which acts as a transesterification catalyst,[187] in methanol. This gave the cis epoxy alcohol (320) confirming the selectivity on epoxidation is the same with both esters.

As mentioned earlier a new procedure for stereospecifically epoxidising acyclic electrophilic alkenes, involving treatment with an alkyl lithium and t-butylhydroperoxide in tetrahydrofuran, was reported recently.[65]

However an attempt to epoxidise (319) with lithium t-butylhydroperoxide generated <u>in situ</u> from methyl lithium and t-butylhydroperoxide gave only recovered enone (319). To check the procedure was satisfactory the reaction was repeated on methyl crotonate, one of the substrates investigated by Meth-Cohn. As reported, this gave a mixture of the α,β-epoxy ester (115) and the analogous t-butyl ester resulting from transesterification.

While the epoxidation of α,β-unsaturated ketones using this procedure has not been studied, Still[188] showed that enones can be epoxidised using the similar conditions of potassium hydride and t-butylhydroperoxide in tetrahydrofuran at -20°. However unlike the alkyl lithium procedure this

epoxidation was not stereospecific suggesting oxidation occurs via Michael addition of t-butylhydroperoxide anion to the enone rather than via the chelate-locking mechanism proposed by Meth-Cohn (Scheme 9).



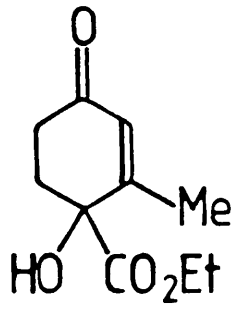
Scheme 9

It seems likely therefore that the failure of (319) to react under the alkyl lithium conditions is due to the enones inability to adopt the s-trans conformation required for the chelate-locking mechanism.

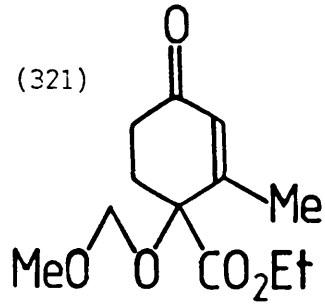
Investigation of the MOM ether of the γ-hydroxy enone (309)

Because the directing effect of a γ-hydroxyl group on alkaline hydrogen peroxide epoxidation is lost on conversion to its MOM ether (established in Chapter 1) it was envisaged that epoxidation of the analogous ether (321) in this new series would also give a mixture of both epoxy ethers and that cleavage of the ethers would then afford a mixture of the epoxy alcohols and perhaps give sufficient material to characterise the trans epoxy alcohol.

(309)

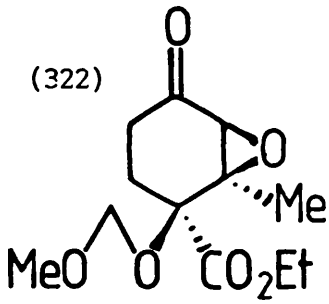


(321)

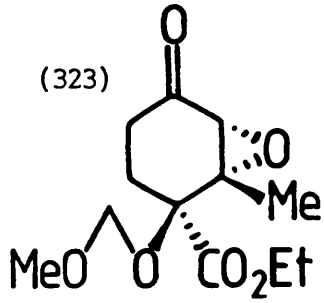


The MOM ether (321) was prepared by treating the γ-hydroxy enone (309) with methylal and phosphorus pentoxide in chloroform.[189] After 7 minutes tlc showed that the starting alcohol had been completely converted to a less polar product. The crude product was purified by flash chromatography. The formation of the MOM ether was confirmed by an ^1H nmr spectrum which shows two new singlets at δ 3.41 and δ 4.87, consistent with the methoxyl and acetal protons respectively.

(322)



(323)



The enone (321) was treated with alkaline hydrogen peroxide for 3 hours. Although tlc showed a single spot of Rf 0.45 an ^1H nmr of the product confirmed the enone had been completely converted to a mixture of the epoxides (322) and (323) in a 1:1 ratio. The spectra of the two epoxides are very similar but the methylene protons of the ether, which are inequivalent due to the chiral centre at C-4, appear as a singlet for one of the compounds and an AB quartet for the other. Identification of the ethers was achieved by converting the cis epoxy alcohol (311) to its MOM ether (322) with methylal and phosphorus pentoxide. This proved that the cis epoxy ether methylene protons give the singlet in the ^1H nmr

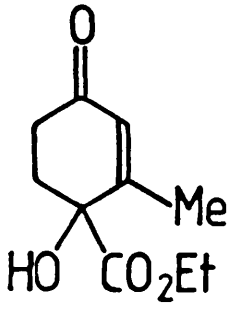
spectrum.

Unfortunately all attempts to cleave the ether mixture with p-toluenesulphonic acid in methanol or methanolic thiophenol containing boron trifluoride etherate[190] were unsuccessful. The trans hydroxy epoxide (312) remained elusive.

Investigation of the TBDMS ether of the γ-hydroxy enone (309)

Since the MOM ether (321) afforded an almost equal mixture of epoxides, ie the reaction was totally non-stereoselective, it was decided to investigate alkaline epoxidation of the bulky TBDMS ether (324). It was foreseen that this group might hinder syn approach of the hydroperoxide anion, giving only the trans epoxy ether. Another advantage of this silyl ether is that it should be possible to cleave it under relatively mild conditions, eg with tetra-n-butylammonium fluoride in tetrahydrofuran, and get the trans epoxy alcohol.

(309)



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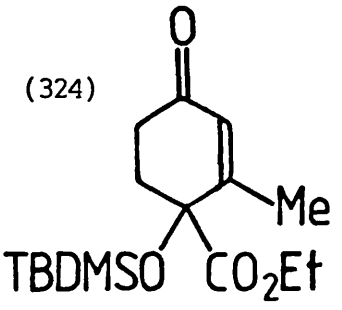
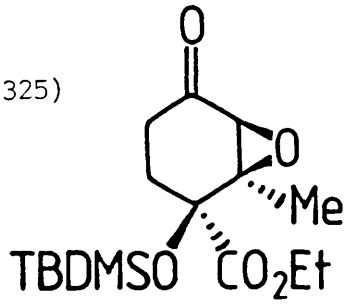


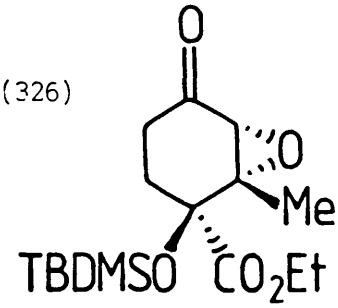
The TBDMS ether (324) was prepared by treating the alcohol (309) with TBDMS triflate in the presence of 2,6-lutidine, using dichloromethane as the solvent.[191] After purification by flash chromatography the pure silyl ether was isolated in 21% yield.

Reaction with alkaline hydrogen peroxide was complete after about 3 hours. Despite the hope that the ether would furnish only a single epoxide, an ^1H nmr of the product showed two epoxide peaks at δ 3.08 and δ 3.21. The integrals of these peaks show the two epoxides are present

(325)



(326)



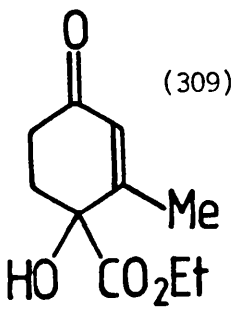
in a 3:2 ratio. Since the TBDMS ethers (325) and (326) were cleaved with tetra-n-butylammonium fluoride [192] and gave a 3:2 mixture of the trans and cis epoxy alcohols it was assumed that the cis epoxy ether (325) was the minor product from alkaline epoxidation. Hence although the bulky silyl ether does alter the selectivity to some extent, its effect is not pronounced.

An attempt to enhance the stereoselectivity using t-butylhydroperoxide instead of hydrogen peroxide as the oxidant did not appear markedly to alter the epoxide ratio, though the rate of epoxidation was significantly reduced.

Investigation of the acetate of the γ-hydroxy enone (309)

Having established that a γ-hydroxyl and γ-ether group in this series behave as in the naphthalenone series (Chapter 1) it was decided to convert the γ-hydroxy enone (309) to its acetate and try alkaline epoxidation of this ester.

(309)



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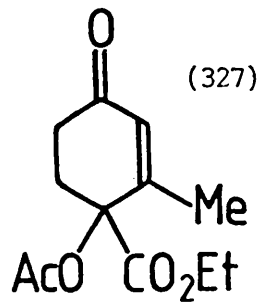
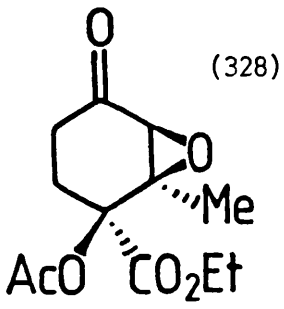


The acetate (327) was simply prepared in good yield from treatment of the alcohol with acetic anhydride, triethylamine and DMAP in chloroform. Although tlc shows the acetate is less polar than the alcohol, which is an oil, the acetate, rather surprisingly, crystallised to give a colourless solid of m.p. 72-74°.

Attempted epoxidation of (327) with t-butylhydroperoxide and Triton B in benzene for 24 hours gave only recovered starting enone, so aqueous hydrogen peroxide in the presence of sodium carbonate was tried. However in contrast to the γ-acetoxy naphthalenone (251) which underwent hydrolysis rather than epoxidation, the acetate (327) was slowly converted to a complex mixture containing acetoxy epoxides though tlc showed that some of the starting acetate had been hydroysed to the γ-hydroxy enone (309). It was decided to work up the reaction (even though enone remained) to avoid total hydrolysis, and the acetates were readily separated from hydrolysed material by flash chromatography. An ^1H nmr spectrum of this product shows an enone peak at δ 6.01 and two epoxide peaks at δ 3.17 and δ 3.24. The integrals for these peaks show that the mixture comprises the starting acetate (327) and the cis and trans epoxy acetates, (328) and (329) in an approximately 1:1:1 ratio. On standing overnight this viscous oily mixture, deposited large chunky crystals. These were



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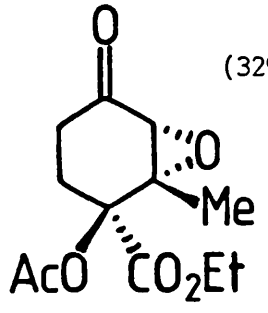
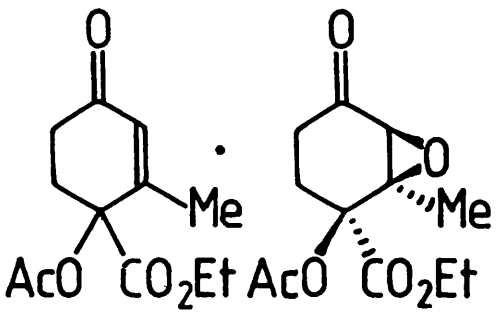


(329)

removed from the residual oil and recrystallised from chloroform/petroleum ether to give colourless platelets of m.p. 68-69°. An ^1H nmr spectrum and microanalysis of these crystals both established that they contained

the enone and one of the epoxides in exactly a 1:1 ratio. This was supported by tlc of a single crystal which showed two spots of equal intensity after development in an iodine tank. The 1:1:1 mixture thus preferentially deposited crystals containing two of these components in the ratio 1:1 and this composition is maintained on recrystallisation. Since the crystals gave these curious results, have a sharp m.p. suggesting a specific molecular structure and were of superior quality to any other crystals previously isolated in this series it was decided to examine them by x-ray diffraction.

(330)



The co-crystalline nature of the compound (330) was confirmed by x-ray analysis on a single crystal (Figures 3 and 4). The space group is $P\bar{1}$ which means the unit cell is centrosymmetric. Since each unit cell contains only two molecules, in order to be centrosymmetric they must be of opposite chirality (as depicted in Figure 4). Figure 3 shows the cis disposition of the epoxy and acetoxy functions which indicates that only epoxide (328), and not epoxide (329), is present in the co-crystal (330). It also shows the epoxide ring to be perpendicular to the plane of the carbonyl so that the carbon atoms of the cyclohexane ring are in virtually the same relative positions as those of the enone. The low R factor (R = 0.056) confirms that in the crystal the epoxide and the enone have similar conformations. The co-crystal formed from a racemic mixture and contains both enantiomers of the enone [(+)en or (-)en] and both enantiomers of the epoxide [(+)ep or (-)ep]. Figure 3 shows one of these

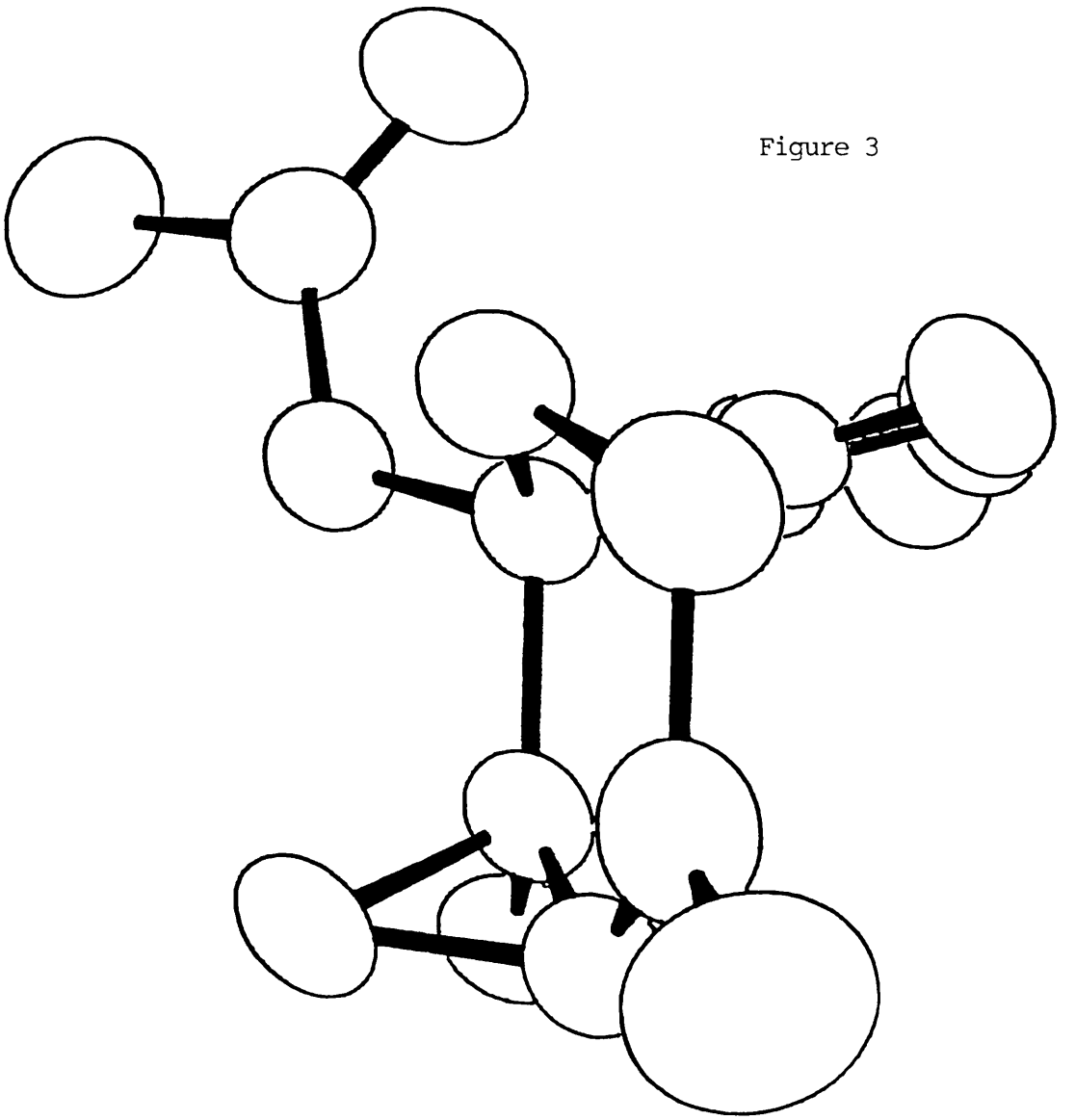
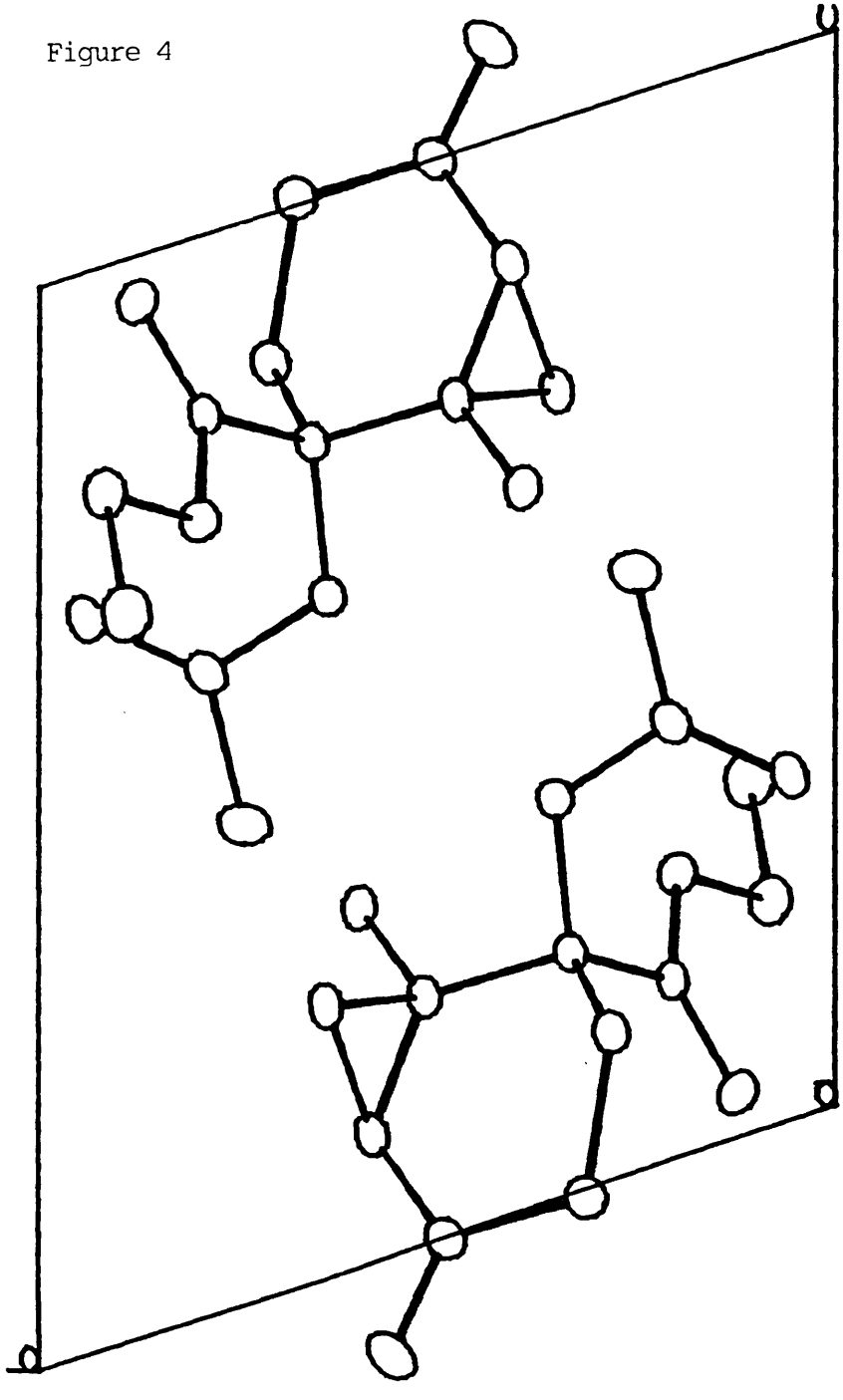


Figure 3

Figure 4



chiral units. However the Figures do not give a full representation of the crystal structure since in both Figure 3 and Figure 4 the intensity of the epoxide oxygen(s), ie the occupancy of the epoxide oxygen(s) site(s), is half that of the other atoms. The only possible interpretation is that each unit cell contains an enone and an epoxide of opposite chirality. Hence while the (+) and (-) units are always in the same half of the unit cell the (+) unit is randomly enone or epoxide (with equal likelihood) and the complementary (-) unit is epoxide or enone ie the cells are randomly

(+)en	(+)ep	(+)ep	(+)en	(+)en	(+)en	(+)ep	(+)ep
(-)ep	(-)en	(-)en	(-)ep	(-)ep	(-)ep	(-)en	(-)en

The more systematic arrangement

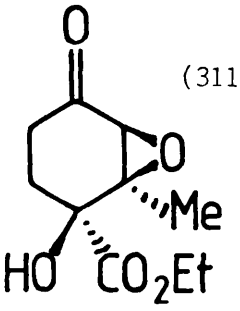
(+)en	(+)ep	(+)en	(+)ep	(+)en	(+)ep	(+)en	(+)ep
(-)ep	(-)en	(-)ep	(-)en	(-)ep	(-)en	(-)ep	(-)en

can be excluded as a possibility since it would show a four-molecule unit cell, while the random paired arrangement

(+)en	(+)ep	(+)ep	(+)en	(+)en	(+)en	(+)ep	(+)ep
(-)en	(-)ep	(-)ep	(-)en	(-)en	(-)en	(-)ep	(-)ep

would presumably permit ratios of enone to epoxide other than 1:1 and this was not found. The averaged result of the x-ray diffraction pattern (which the Figures depict) is that there is one (+) 'molecule' of composition $C_{12}H_{16}O_{5\frac{1}{2}}$ and one (-) 'molecule' of composition $C_{12}H_{16}O_{5\frac{1}{2}}$ in each unit cell.

The oil remaining after the crystals grew from the three component mixture was hydrolysed using aqueous sodium hydroxide in ethanol. As expected, after separation of the alcohols by flash chromatography, the major product was the trans epoxy alcohol (312) whose spectral characteristics and behaviour on tlc were identical to the major product obtained from cleavage of the epoxy TBDMS ether mixture. The minor epoxide product from this hydrolysis was the cis isomer (311) whose spectral character-



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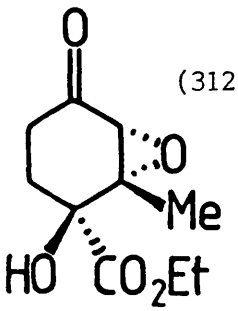


(312)

istics and behaviour on tlc were identical to the epoxide formed stereospecifically from alkaline epoxidation of the γ-hydroxy enone (309).

Conclusive proof that the stereochemistry of the epoxy and hydroxyl groups in (311) is cis came from conversion of the alcohols (311) and (312) to their acetates (328) and (329) using acetic anhydride, triethylamine and DMAP in chloroform. The acetate (328) had identical Rf and ^{1}H nmr spectrum to the epoxy acetate present in the co-crystal. As with the enone, the cis epoxy acetate has a higher melting point than the parent alcohol. The trans isomer (329), which is a viscous oil, was identical with the major component of the oil from which the co-crystals grew. Some of the physical and spectral characteristics of these compounds are summarised in Table 3.

In addition to showing that a γ-acetoxy group is incapable of directing alkaline epoxidation, treatment of the acetoxy enone (327) with alkaline hydrogen peroxide resulted in the isolation of a co-crystal (330) with unusual structure which was determined by x-ray analysis. The x-ray result also indirectly proved the stereochemistries of all α,β-epoxyketone products isolated so far in this series.

Preparation of 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone

It was thought that replacement of the ethyl ester grouping with an amide might alter the stereoselectivity on alkaline epoxidation because the NH of the amide might hydrogen bond with the hydroperoxide anion and

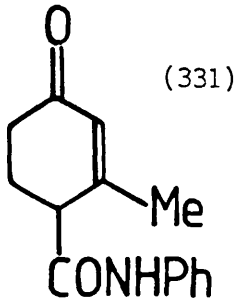
Table 3

	γ-hydroxy enone (309)	γ-acetoxy enone (327)
^{1}H nmr ($CDCl_3$)	δ 1.92 (d, 3H)	δ 2.07 (d, 3H)
	δ 4.15 (br s, 1H)	δ 2.12 (s, 3H)
	δ 5.99 (m, 1H)	δ 6.01 (m, 1H)
m.p.	oil	72-74°
tlc (50% EtOAc/ pet. ether)	Rf 0.25	Rf 0.56

	cis hydroxy epoxide (311)	trans hydroxy epoxide (312)
^{1}H nmr ($CDCl_3$)	δ 1.30 (s, 3H)	δ 1.40 (s, 3H)
	δ 3.17 (s, 1H)	δ 3.16 (s, 1H)
	δ 3.74 (br, 1H)	δ 3.82 (br, 1H)
^{13}C nmr ($CDCl_3$)	δ 13.7, 15.8, 28.1, 33.2, 62.9, 63.2, 64.5, 75.6, 173.4, 204.2.	δ 14.2, 16.2, 27.8 , 31.6, 61.5, 62.9, 63.4, 75.9, 174.5, 204.1.
m.p.	46-48°	33.5-34.5°
tlc (50% EtOAc/ pet. ether)	Rf 0.29	Rf 0.33

	cis acetoxy epoxide (328)	trans acetoxy epoxide (329)
^{1}H nmr ($CDCl_3$)	δ 1.50 (s, 3H)	δ 1.47 (s, 3H)
	δ 2.16 (s, 3H)	δ 2.12 (s, 3H)
	δ 3.23 (s, 1H)	δ 3.18 (s, 1H)
m.p.	63-65°	oil
tlc (50% EtOAc/ pet. ether)	Rf 0.58	Rf 0.59

therefore compete with the hydroxyl function in delivering the oxidising agent syn to the γ-substituent.



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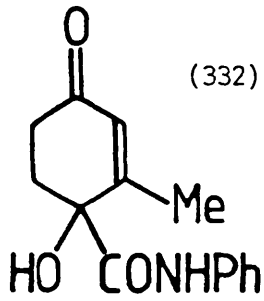
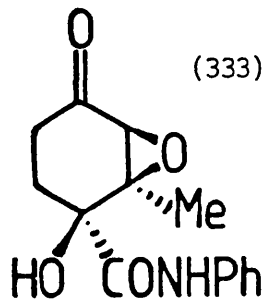


(332)

Since acetoacetanilide is cheap and readily available, the N-phenyl amide (331) was prepared in an analogous way to Hagemann's ester by condensation with but-3-en-2-one and cyclisation of the resulting Michael adduct with pyrrolidinium acetate. The amide (331) was successfully hydroxylated with air and activated charcoal in ethyl acetate, though it was not possible to monitor the reaction by tlc because the starting material and the product (332) both had the same Rf.

Epoxidation of 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone



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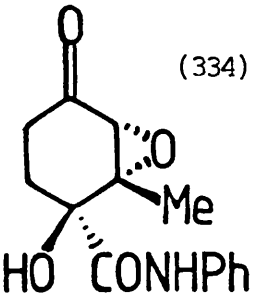
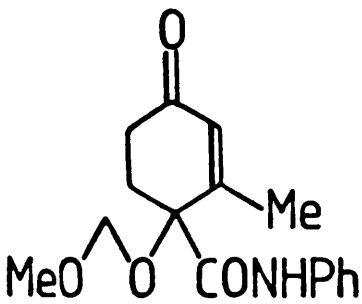


(334)

Alkaline hydrogen peroxide epoxidation of the amide (332), unlike the ethyl ester (309), was not stereospecific. The reaction, which was completed within 3 hours, gave a product whose ^1H nmr spectrum confirmed the conversion of the enone into two epoxides. The spectrum shows two peaks at δ 3.31 and δ 3.04 due to the epoxide protons of each isomer and also indicates that they are formed in about a 10:1 ratio. The major

product was isolated and purified by successive recrystallisations from chloroform/petroleum ether. An attempt to isolate the minor isomer by flash chromatographing the mother liquors from the first recrystallisation was unsuccessful, but it did give a mixture that was considerably richer in the minor isomer. Tlc established that both epoxides have higher Rf than the enone and the major product has highest Rf. Although treatment of the enone with per-Amberlyst 15 resulted in only partial conversion to epoxides, it was apparent from an ^1H nmr spectrum of the product that the ratio of the two isomers was virtually identical to that found from alkaline epoxidation. By analogy with the esters (309) and (319) this result suggests the major epoxide formed in both reactions is the cis epoxy alcohol (333). Further support for this assignment came from alkaline epoxidation of the MOM ether (335) which was prepared by treating the enone (332) with methylal and phosphorus pentoxide. Although the yield of epoxy ethers was poor, comparison of the ^1H nmr spectrum of this



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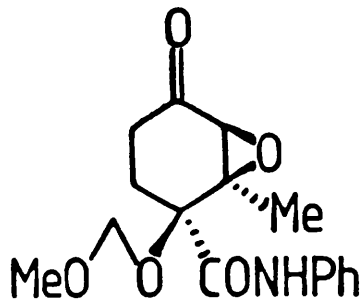

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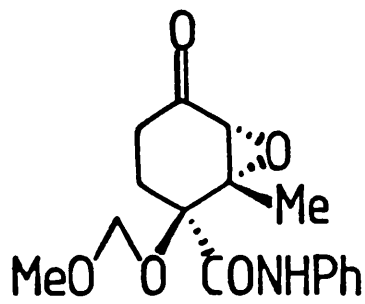
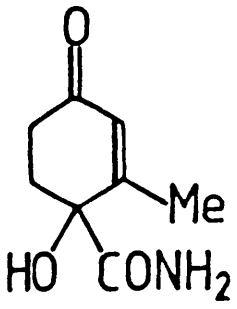


(337)

product (after purification by flash chromatography) with the epoxy ether (336), which was similarly prepared from the cis epoxy alcohol (333), showed that the trans epoxy ether (337) is formed in slight excess.

It appears from these results that for the enone (332) the stereoselectivity on alkaline epoxidation is still largely dominated by the γ-hydroxy group. However in contrast to the ester (309), the amide (332) seems to compete with the hydroxy group to a small extent since the trans epoxy alcohol (334) was formed in low yield.



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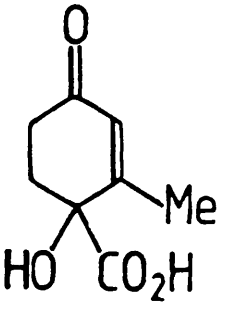

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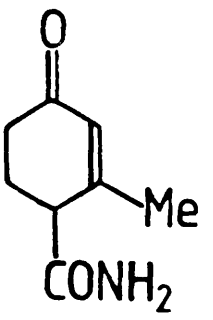

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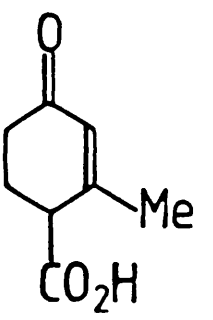


(341)

If the NH of the amide were responsible for this competition in directing epoxidation then the primary amide (338) would probably afford a better yield of the trans epoxy alcohol. Although the amide (340) and the acid (341) were synthesised (see later) attempts to hydroxylate these compounds with activated charcoal in ethyl acetate were unsuccessful. In both cases any recovered material gave uninterpretable ^{1}H nmr spectra.

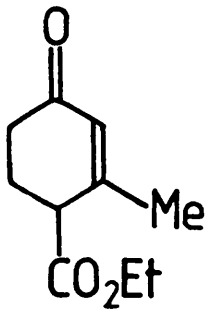
Similarly base hydrolysis of the ethyl ester (309) or treating it with concentrated aqueous ammonia failed to yield either (339) or (338).

Epoxidation of Hagemann's Ester

Having studied alkaline epoxidation of a number of γ-hydroxy enones which also contained either a γ-ester or γ-amide function it was decided to examine some structurally related compounds which do not possess the hydroxyl group. This would establish whether groups such as a γ-ester or γ-amide could exert a directing effect on epoxidation.

The epoxide of Hagemann's ester (342) has been reported twice in the literature.[193,194] The first of these references stated only that it was formed on alkaline hydrogen peroxide epoxidation of the enone (308). The stereochemistry of the epoxide in the second reference was assigned by Chemical Abstracts as (343). However no clear justification for this assignment, in which the epoxy and ester groups are trans, appeared in the paper. The method of preparation was not reported. Also, as in the previous reference, no spectral or physical characteristics of the

compound were reported.



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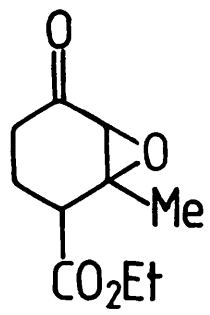

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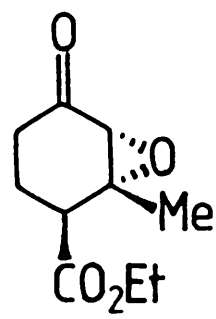
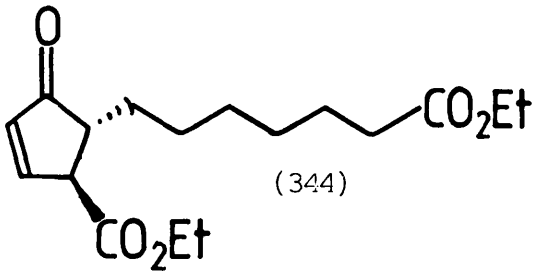


(343)

Hagemann's ester was epoxidised with alkaline hydrogen peroxide. Tlc of the crude product showed a single spot with Rf higher than the enone. The formation of the epoxide (342) was confirmed from a 90 MHz ^{1}H nmr spectrum which showed two new singlets at δ 1.35 and δ 3.10 consistent with the methyl and epoxide protons respectively. However there were no other new major peaks suggesting only one epoxide isomer was present ie the reaction was stereospecific. The product mixture was then examined using high field (200 MHz) ^{1}H and ^{13}C nmr. This showed that both epoxide isomers were present but one was highly predominant. The minor isomer constituted ~8% of the product. It shows epoxide, methyl and ethyl ester peaks in the ^{1}H nmr spectrum which are slightly offset from those of the major isomer. With this evidence in mind the product was re-examined by tlc. After prolonged development of the plate in an iodine tank a faint spot was observed whose Rf was between that of the major epoxide and the starting enone. These results indicate alkaline epoxidation of Hagemann's ester is highly stereoselective but the stereochemistry of the products could not be readily assigned from the available evidence.

Alkaline hydrogen peroxide epoxidation of the structurally related enone (344) has been shown to give a 85:15 ratio of the trans and cis epoxy esters respectively.[195] The stereochemistry of the major epoxide isomer (345) was established by ^{1}H nmr using double-irradiation techniques.



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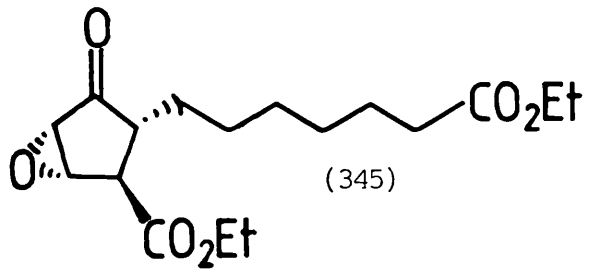


(345)

The C-11 proton appears as a doublet which, on irradiation of the C-8 proton, is converted to a singlet. The value of the coupling constant between the C-11 and C-12 protons is therefore near zero, in accord with a trans arrangement of the two protons on the cyclopentane ring.

A similar argument cannot be extended to the more flexible six-membered ring of the epoxide of Hagemann's ester (342) because there is no β-epoxide proton. Also the peak of the proton α to the ester is more complex than in compound (345) due to the two inequivalent adjacent methylene protons.

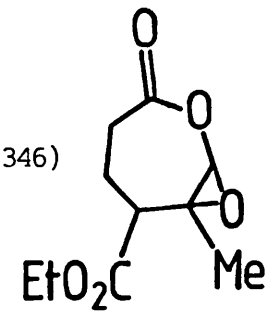
A proof that the major product from alkaline epoxidation of Hagemann's ester has the epoxy and ester groups trans to one another, ie structure (343), is described later. It therefore appears that the five- and six-membered ring systems behave similarly though the effect of the alkyl side chain of (344) on the stereoselectivity is unknown. No attempt was made to separate the two epoxides obtained from alkaline epoxidation of Hagemann's ester.

The disconcerting possibility remained that the observed stereoselectivity of the epoxidation was affected or even determined by epimerisation after epoxidation. To check that the epoxide does not epimerise at C-4 under the basic reaction conditions, a solution of the epoxide mixture in tetrahydrofuran was treated with sodium hydroxide dissolved in deuterium oxide. After 1 hour an ^1H nmr spectrum of the product showed exchange of the protons α to the ketone but not of that α to the ester.

This confirms that the 92:8 ratio of epoxides is the result of kinetic, and not thermodynamic, control.

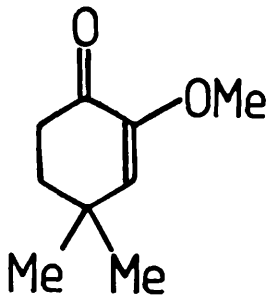
As with the γ-hydroxy enone (309) prolonged treatment of Hagemann's ester with mcpba in refluxing dichloromethane did not result in simple epoxidation of the enone. The reaction gave a single crystalline compound with Rf lower than Hagemann's ester. Recrystallisation of the product gave material, microanalysis of which suggested molecular formula $C_{10}H_{14}O_5$. This was supported by ^1H, ^{13}C nmr and ir spectral data which

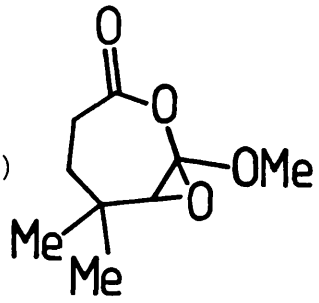
(346)



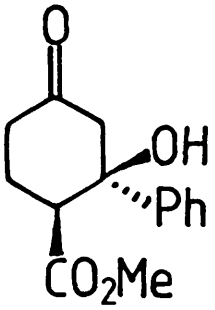
together suggested the compound has the structure (346). The 90 MHz ^1H nmr spectrum is similar to that of Hagemann's ester except that the peak due to the enone proton is replaced by a new singlet at δ 4.99 due to the acyloxy oxirane proton and the methyl resonance has shifted to δ 1.36. Interestingly a high field (200 MHz) ^1H nmr spectrum, run in deuterio-acetone, shows a complex symmetrical multiplet for the CH_2 protons of the ethyl ester which in the low field spectrum appear as a simple quartet. These two protons are inequivalent because of the chiral centre at C-4, but the difference in chemical shift (and the latent ABX_3 system) is only detectable at the higher field. A number of minor shifts due to the change in solvent were also observed. The ^{13}C nmr spectrum shows ten peaks with shifts consistent with the assigned structure. Peaks in the ir spectrum at 1760 and 1730 cm^{-1} agree well with those expected for an epoxy lactone[159] and ethyl ester respectively. Further support for the structure (346) came from a literature report of the conversion of the enone (347)

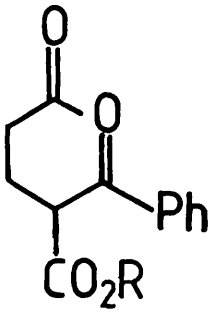
to the epoxy lactone (348) on treatment with mcpba.[159]

(347) 

(348) 

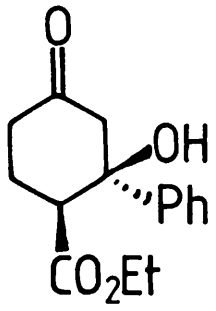
Establishing the stereochemistry of the epoxide of Hagemann's ester

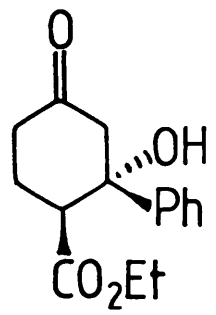
(349) 

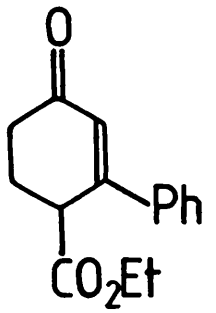
(350) 

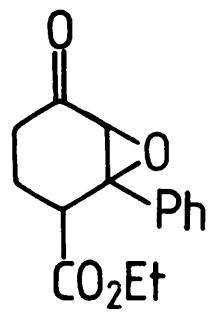
The methyl ester (349) is known and is formed exclusively from reaction of ethyl benzoylacetate with but-3-en-2-one in methanolic sodium hydroxide.[196] The reaction proceeds via Michael addition of the β-keto ester to the enone giving the intermediate (350) with R=Me. This intermediate then undergoes aldol cyclisation to (349). The aldol reaction is reversible, so the diastereomeric aldol products are in thermodynamic equilibrium. The more stable isomer is that with the bulky ester and phenyl groups trans to one another. The sole product from the reaction was therefore assigned the stereochemistry (349).

A similar aldol route should provide the analogous ethyl ester (351). It was envisaged that this β-hydroxy ketone or its diastereomer (352) might also be prepared from alkaline epoxidation of the enone (353), followed by reduction of the resulting epoxide (354). The stereochemistry of the product from this latter synthesis should be determinable by comparison

(351) 

(352) 

(353) 

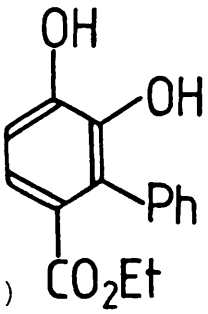
(354) 

with the aldol product, whose stereochemistry is known. Hence assuming that the stereoselectivity of epoxidation of the enone (353) is the same as for Hagemann's ester, it should be possible to establish the stereochemistry of the major epoxide isomer obtained from alkaline epoxidation of Hagemann's ester.

Michael addition of ethyl benzoylacetate to but-3-en-2-one in methanolic sodium methoxide gave the intermediate (350) with R=Et. A portion of this intermediate was purified by flash chromatography and treated with ethanolic sodium hydroxide which gave a crystalline β-hydroxy ketone which can confidently be assigned the stereochemistry (351).

The remainder of the intermediate (350) was heated with pyrrolidinium acetate which gave the enone (353). This material was purified by distillation and treated with alkaline hydrogen peroxide. However, unlike Hagemann's ester, this reaction did not result in clean conversion of the enone to epoxides. Despite this, after flash chromatographic purification, a single epoxide (354) of slightly lower Rf than the enone was isolated in 6.4% yield. Like the epoxide of Hagemann's ester this epoxide was a viscous oil. The reaction, in addition to (354) also yielded the catechol

(355) and benzoic acid.



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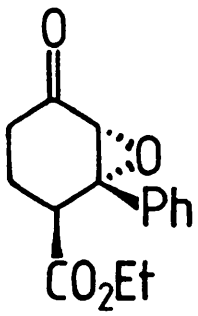

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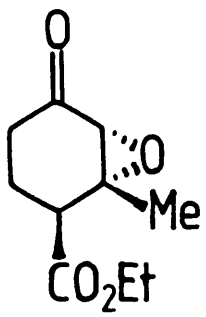
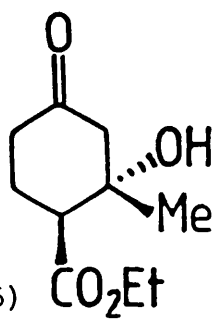


(343)

This epoxide (354) was reduced with an ethanolic solution of sodium phenylselenide.[181] This gave, after purification by flash chromatography, a new crystalline β-hydroxy ketone which is therefore (352). Comparison of the two diastereomeric β-hydroxy ketones (351) and (352) is made in Table 4. Since the reduction occurs with retention of configuration at C-3, the stereochemistry of the epoxy and ester groups in the phenyl compound (354) is trans.

This result strongly suggests the major epoxide formed on alkaline epoxidation of Hagemann's ester is the trans epoxy ester (343). This also agrees with the cited literature example in which treatment of the enone (344) with alkaline hydrogen peroxide gave mainly the trans epoxy ester (345).

The oily epoxide mixture obtained from alkaline epoxidation of Hagemann's ester was reduced with an ethanolic solution of sodium phenylselenide. This gave the β-hydroxy ketone (356), a crystalline solid of m.p. 53-54°, as the major product. However aldol cyclisation of the dione



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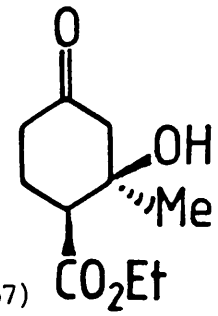

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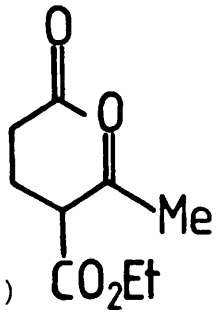


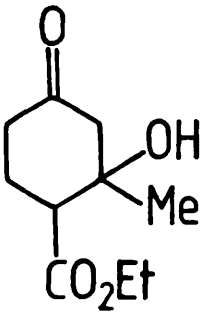
(358)

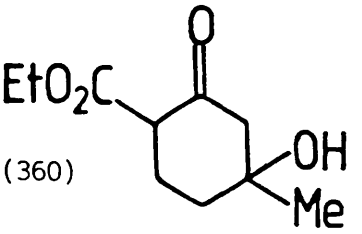
Table 4

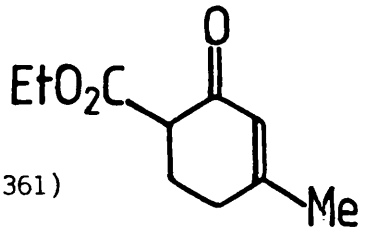
	cis hydroxy ester (351)	trans hydroxy ester (352)
^{1}H nmr ($CDCl_3$)	δ 0.91 (t, 3H)	δ 0.89 (t, 3H)
	δ 2.1-2.7 (m, 6H)	δ 1.9-2.9 (m, 5H)
	δ 3.35-3.50 (m, 1H)	δ 2.98-3.08 (m, 1H)
	δ 3.89 (dq, 2H)	δ 3.20 (br s, 1H)
	δ 4.20 (br s, 1H)	δ 3.72 (s, 1H); 3.84 (q, 2H)
	δ 7.15-7.55 (m, 5H)	δ 7.18-7.42 (m, 5H)
^{13}C nmr ($CDCl_3$)	δ 13.5 (q), 25.0 (t), 39.2 (t), 48.9 (d), 54.0 (t), 60.8 (t), 77.1 (s), 124.2 (d), 127.2 (d), 128.2 (d), 144.5 (s), 174.9 (s), 206.9 (s).	δ 13.7 (q), 24.3 (t), 37.2 (t), 49.8 (t), 50.6 (d), 60.4 (t), 77.5 (s), 125.2 (d), 128.0 (d), 128.8 (d), 144.2 (s), 172.7 (s), 210.7 (s).
ir (CCl_4)	3490, 1725, 1720, 1445 cm^{-1}	3595, 1725, 1445 cm^{-1}
m.p.	129.5-131.5°	166-167°
tlc (50% EtOAc/ pet. ether)	Rf 0.36	Rf 0.42
m/e	263 (2.3), 262 ($M^{\oplus}$; 6.2), 105 (100.0)	262 ($M^{\oplus}$; 2.3), 105 (100.0)

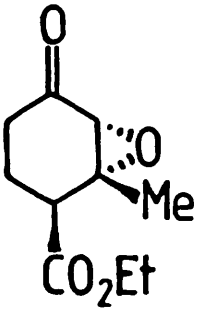
(358) gave neither this compound nor its diastereomer (357). A structurally isomeric material was isolated. In contrast to the acyclic phenyl dione (350) which can cyclise only one way, (358) can undergo intramolecular aldol condensation in two structurally different ways, affording either (359) or (360). The product from aldol cyclisation was shown to be (360) rather than (359) by mesylation of the tertiary alcohol with methanesulphonyl

chloride and triethylamine in dichloromethane, followed by elimination of methane sulphonic acid which gave the enone (361) (prepared independently later) rather than Hagemann's ester.

(359) 

(360) 

(361) 

(343) 

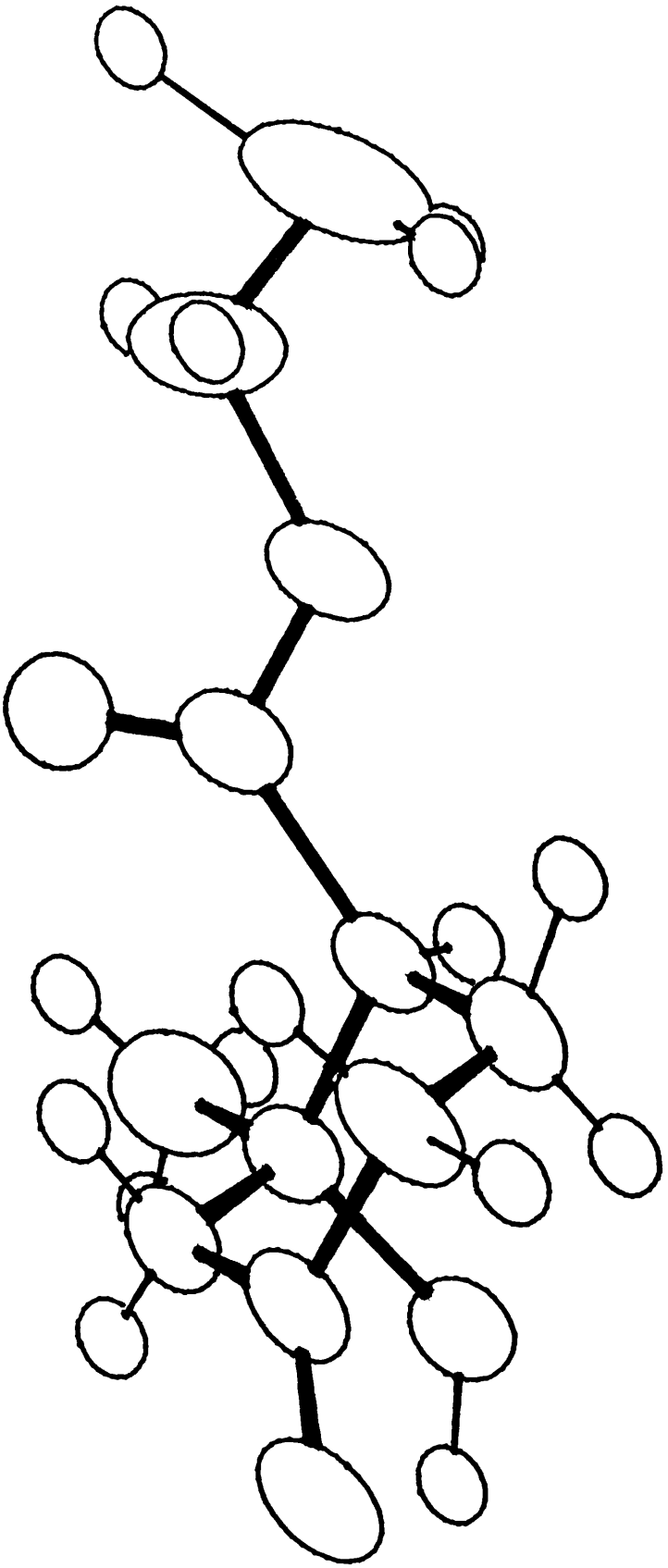
Conclusive proof of the stereochemistry of the epoxide (343) was obtained by x-ray analysis on a crystal of the tertiary alcohol (356). The result of this crystallographic work is shown in Figure 5 which clearly indicates the chair conformation of the cyclohexanone ring and the trans stereochemistry of the hydroxyl and ester groups. Both these functionalities adopt an axial conformation while the methyl group is equatorial.

This result established beyond all doubt that the major epoxide from epoxidation of Hagemann's ester was the trans epoxy ester (343). It also means that the structures of related molecules could be assigned by comparison with this standard of known stereochemistry.

Investigation of the enone (341) with a γ-carboxyl substituent

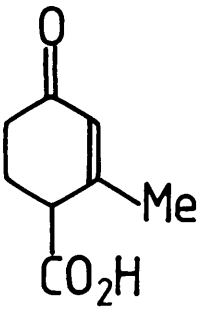
Although Hagemann's ester (308) has been known for almost a century, the parent acid (341) has never been reported. It was found that this

Figure 5

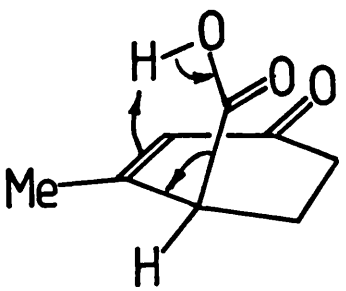


acid, which is a viscous oil, is easily prepared by base hydrolysis of the ethyl ester. The acid was characterised as its p-bromophenacyl ester.

(341)



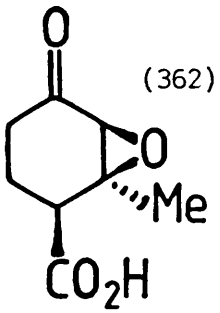
Although (341) is a 'vinylogous' β-keto acid it was relatively stable at room temperature for a few days. Only on heating to 80° or when left standing for several weeks was decarboxylation to 3-methylcyclohex-2-enone observed. The stability of the molecule is probably due to the relative positions of the carboxyl and alkene groups which are not ideally located for decarboxylation via a pericyclic mechanism (Scheme 25).



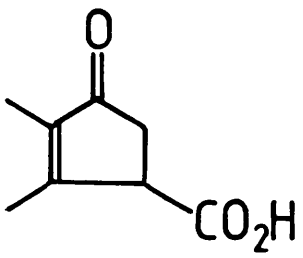
Scheme 25

Treatment of the acid (341) with alkaline hydrogen peroxide resulted in epoxidation. As with the ester a 90 MHz ^{1}H nmr spectrum of the product shows two new strong singlets at δ 1.52 and 3.26 suggesting this reaction is also highly stereoselective. In this case however, a minor singlet at δ 1.58 indicates the likely presence of the other isomer. The integrals of these peaks show the epoxy acids are produced in about the ratio 5:1. No attempt was made to separate these isomers. In order to establish the stereochemistry, base hydrolysis of the mixture obtained from alkaline epoxidation of Hagemann's ester was carried out to give mainly the trans

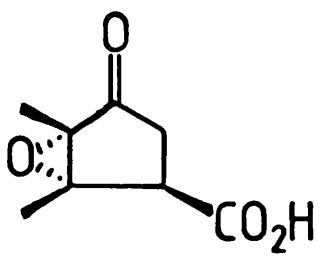
epoxy acid (362). This proved to be identical to the major epoxide formed from epoxidation of the acid (341) so the relative stereochemistries of the major epoxide isomers from both the ester and acid epoxidations is the same.



(362)



(182)

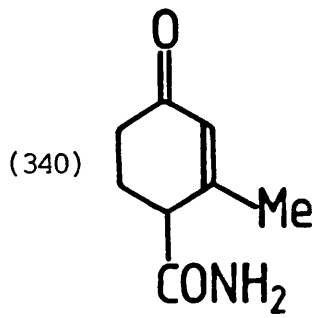


(183)

As mentioned earlier the trans epoxy acid (183) was formed in 72% yield on alkaline epoxidation of the enone (182).[93] No mention is made of any isomeric products. The new result shows that in both the cyclopentene and cyclohexene cases the stereoselectivity of epoxidation is similar.

Investigation of the primary amide (340)

As mentioned earlier, it was thought that an amide substituent in the γ-position might result in syn epoxidation due to the possibility of hydrogen bonding between the NH of the amide and the hydroperoxide anion. It was therefore of interest to examine alkaline epoxidation of the primary amide (340).



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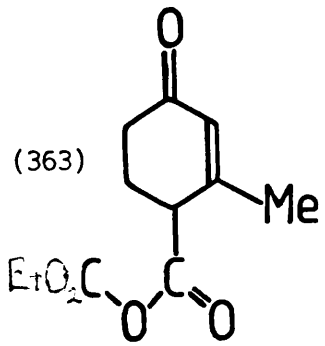


(363)

Attempts to prepare the unknown amide (340) directly from Hagemann's

ester by treatment with concentrated aqueous ammonia, liquid ammonia, urea[197] or a methanolic solution of ammonia in the presence of sodium cyanide[187] were all unsuccessful. It was eventually prepared from the parent acid (341) in low yield by forming the mixed anhydride (363) in situ using ethyl chloroformate in the presence of triethylamine and then bubbling ammonia through the solution.[198] Unlike the ethyl ester (308), methyl ester (316) and the parent acid (341), the amide is a solid of m.p. 149.5-151.5°.

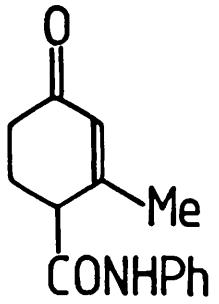
Alkaline epoxidation of the amide (340) was shown by ^{1}H nmr to give about a 5:1 ratio of the two epoxides. Recrystallisation failed to separate these compounds to any significant extent. It was hoped to establish which isomer was predominant by converting this mixture to a mixture of the two epoxy acids whose stereochemistry had already been proved. A mild non-hydrolytic method was chosen to deaminate the amide. Cleavage was achieved successfully by treating an acetonitrile solution of the amides, containing sodium acetate, with a carbon tetrachloride solution of dinitrogen tetroxide.[199] However rather than the expected 5:1 mixture of the epoxy acids, high field ^{1}H and ^{13}C nmr spectra showed that this reaction yielded an almost 1:1 ratio of these compounds. (The proton spectrum also confirmed that the cis epoxy acid's methyl resonance is of slightly higher chemical shift then the trans isomer while the epoxide protons of both isomers have virtually identical chemical shift, making resolution in the 90 MHz spectrum impossible). Hence despite the relatively mild deamination conditions, epimerisation had apparently occurred at C-4 during the cleavage and it was not possible to assign the stereochemistry of the two epoxy amides.

Because of the difficulties in obtaining the enone amide (340) and in cleaving the amide linkage after epoxidation, no further study was made but this result shows that the amide group is able to exert some control

over the epoxidation process.

Investigation of the N-phenyl amide (331)

Having examined the primary amide (340) it was of interest to look at the N-phenyl amide (331) to see whether it also exerted a directing effect on epoxidation.

(331) 

Treatment of (331) with alkaline hydrogen peroxide was shown by ^1H nmr to give a 2:1 mixture of the epoxy amides. These compounds were easily separated by crystallisation and flash chromatography. The minor component has the lower Rf on tlc. Although these compounds were purified and characterised, no attempt was made to determine the stereochemistry of the epoxy group with respect to the amide for either diastereomer. This was because the stereoselectivity was less marked than in previous cases and also because there was no obvious method of cleaving the epoxy N-phenyl amides (or synthesising them via an alternative route) without causing epimerisation at C-4 or ring-opening of the epoxide.

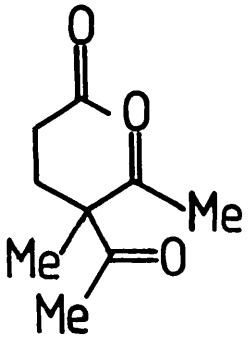
Preparation of 3,4-dimethyl-4-(1-hydroxyethyl)-cyclohex-2-enone

In Chapter 1 an unsuccessful attempt was made to synthesise a naphthalenone with a γ-hydroxymethyl substituent. In all the series (Systems A-C) a γ-hydroxy group has been shown to result in syn stereospecific or highly syn stereoselective alkaline epoxidation. To see whether this stereoselectivity is extended to a 'homoallylic' alcohol it

was decided to try again to synthesise such a compound.

Michael addition of the readily available 3-methylpentan-2,4-dione to but-3-en-2-one in methanolic sodium methoxide gave the triketone (364). Without purification this compound was heated with pyrrolidinium acetate

(364)



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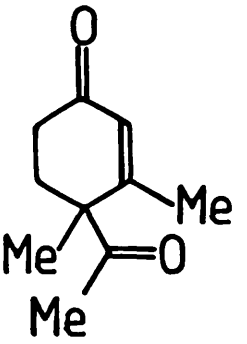
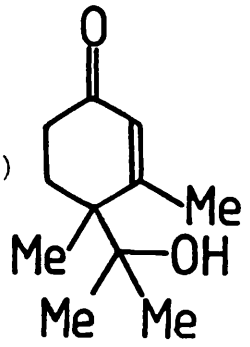


in aqueous methanol. Since in all previous cases treatment of the acyclic precursors with pyrrolidinium acetate afforded only the γ-substituted cyclohexenones, the product from this reaction was assumed to be the γ-acetyl enone (365), and not its structural isomer, 6-acetyl-3,6-dimethyl-cyclohex-2-enone. This assumption was later confirmed. Enone (365) was purified by distillation. The ^{1}H nmr spectrum of the resulting oil showed singlets at δ 1.38 and δ 2.18 associated with the γ-methyl and γ-acetyl protons. The enone methyl group appears as a doublet at δ 1.87 and the enone proton appears as a multiplet at δ 5.94.

The γ-acetyl group should be more susceptible to attack by most nucleophiles than the enone carbonyl. The original intention was to try to synthesise the tertiary alcohol (366) by selective addition of either methyl lithium or methyl magnesium bromide to the γ-acetyl group. The reason for this choice was that the alcohol (366) has only one chiral centre and therefore on epoxidation could form only one of two diastereomeric epoxides. However initial attempts with low temperature addition of methyl magnesium bromide in anhydrous ether were not promising. Although addition occurred it appeared to be non-selective and a complex mixture of

products was obtained. These had very similar Rf on tlc and proved impossible to separate. Rather than attempting addition of methyl lithium it was decided to try to reduce the ketone with sodium borohydride.

(366)



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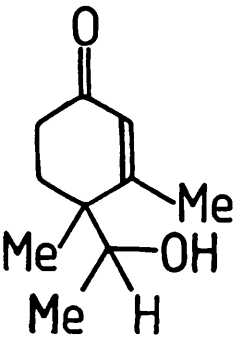


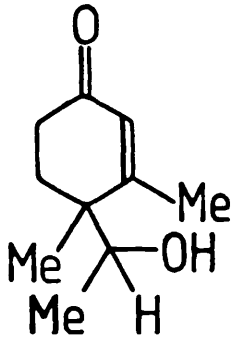
Although this was expected to generate a diastereomeric mixture of secondary alcohols (367), it was thought this complexity could be reduced by oxidising the alcohols back to the ketone after epoxidation. (It later emerged that it was a fortunate choice of reagent).

Low temperature reduction of (365) with sodium borohydride in aqueous ethanol was shown by tlc to give a complex mixture of products. In contrast to the Grignard reaction, however, the reduction was highly regioselective and one alcohol of structure (367), was the predominant product. This was easily separated from the minor components by flash chromatography. The stereochemistry of this alcohol was not established. The ^1H nmr spectrum of this product shows a broad singlet at δ 2.92 and a quartet at δ 4.0 due to the newly formed hydroxyl group and the nearby methine proton. The absence of a singlet at about δ 2 confirmed the acetyl group had been reduced.

Epoxidation of 3,4-dimethyl-4-(1-hydroxyethyl)-cyclohex-2-enone

Treatment of the enone (367) with alkaline hydrogen peroxide for 7 hours resulted in ~80% conversion to epoxide. An ^1H nmr spectrum of the crude product shows in addition to a small residual enone peak, only

(367)



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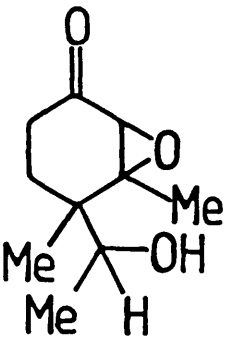


one epoxide peak at δ 2.92 and only one quartet at δ 4.0 due to the methine proton. Tlc of the product showed only two spots - one of Rf identical to the enone and one of higher Rf. These results suggest the epoxidation is stereospecific. The epoxide (368) was separated from the residual enone by flash chromatography. An ^1H nmr spectrum of the purified epoxide shows clearly the presence of only two singlets at δ 1.02 and δ 1.48 due to the C-4 and epoxide methyl groups, and a doublet at δ 1.23 due to the side chain methyl group which couples to the methine proton.

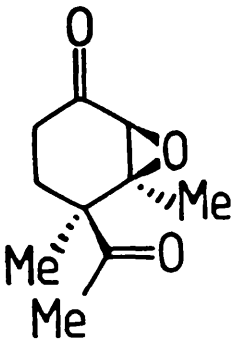
Establishing the stereochemistry of the hydroxy epoxide (368)

Having prepared the γ-acetyl enone (365) it was decided to see whether the acetyl substituent exerted any directing effect on alkaline epoxidation.

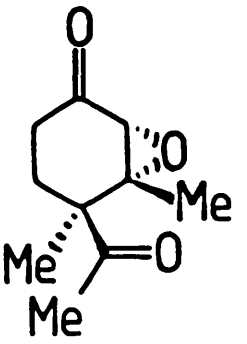
Treatment of (365) with alkaline hydrogen peroxide for 2½ hours resulted in complete conversion of the enone to epoxide. Rather surprisingly, the ^1H nmr spectrum of the product shows only four sharp singlets for the three methyl groups and the epoxide proton and tlc of the product showed only a single spot ie the epoxidation was stereospecific. Also unexpected was the fact that this product crystallised on standing, making it the only solid compound to be isolated in this γ-substituted-3,4-dimethylcyclohex-2-enone series. Recrystallisation of

the epoxide from ether/petroleum ether gave white crystals of m.p. 53-55° which were of sufficient quality to be analysed by x-ray diffraction. The result of this work is shown in Figure 6, which clearly indicates the cis stereochemistry of the epoxy and acetyl groups. As with the previous α,β-epoxyketone x-ray structures, the epoxide ring is perpendicular to the plane of the ketone, forcing the cyclohexane ring to adopt a half chair conformation in which the acetyl group adopts a pseudo-equatorial conformation and the γ-methyl group a pseudo-axial conformation. In addition to proving the cis stereochemistry of the epoxide and acetyl groups in this keto epoxide this result meant that it should be possible to establish the stereochemistry of the secondary alcohol (368), since oxidation of this functionality would afford either the above epoxide (369) or its diastereomer (370).

(369)



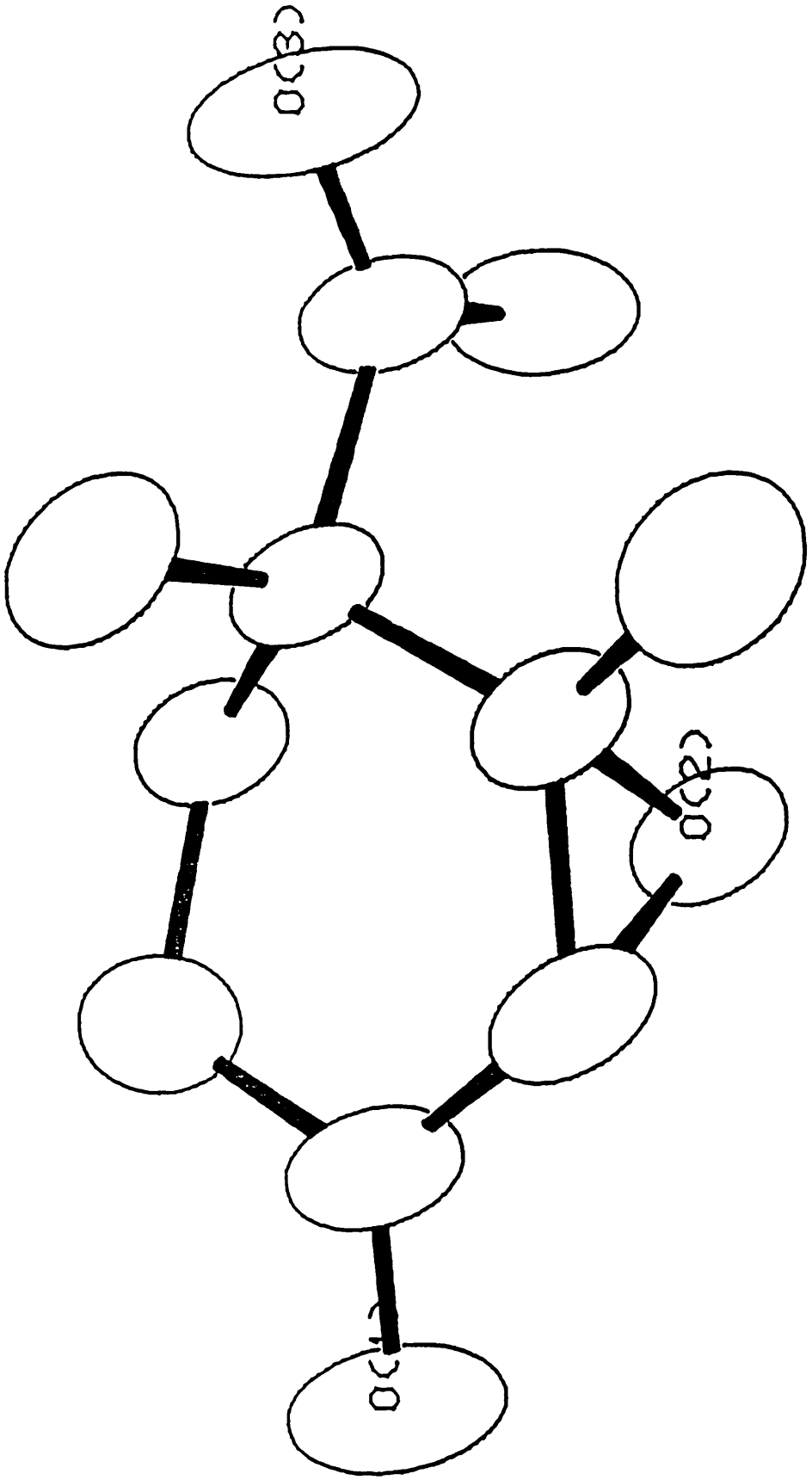
(370)



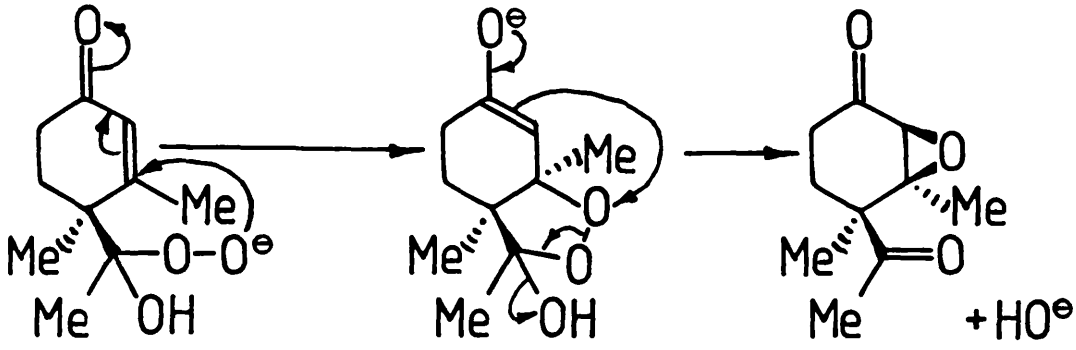
Treatment of a dichloromethane/ether solution of the alcohol (368), to which some celite had been added, with chromium trioxide resulted in oxidation to the ketone.[200] The product was an oil which had identical ^1H nmr spectrum and Rf on tlc to the ketone (369). On seeding with a crystal of (369) this oil crystallised. Recrystallisation afforded crystals with m.p. 53-55°. This proved that the hydroxyethyl substituent and epoxy group of (368) must be cis to one another.

A stereospecific alkaline epoxidation of a steroid enone with a γ-hydroxymethyl substituent has been reported (see p 53).[97] As in the

Figure 6



above case the substituent results in syn epoxidation. A γ-ketone has also been shown to effect stereospecific syn epoxidation[95] and the intramolecular delivery used to explain this selectivity (see p 50) could presumably also apply to the γ-acetyl enone (365) (Scheme 26).



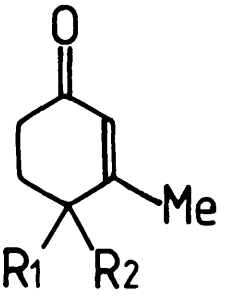
Scheme 26

In this series of γ-substituted cyclohexenones (System C) it is now clear that the stereoselectivity of alkaline epoxidation depends on the substituents R_1 and R_2. In certain cases the reaction is stereospecific affording only one epoxide, while in others the substituents apparently exert no directing effect during epoxidation and a mixture of epoxides is obtained (Table 5). The results in Table 5 are interpreted at the end of Chapter 4.

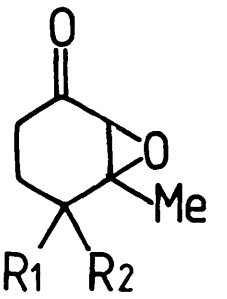
Establishment of the stereochemistry was sometimes achieved on the basis of chemical arguments but in most cases was based on x-ray evidence or firm correction with substances whose stereochemistry was known from x-ray results. No clearly general spectroscopic criteria for stereochemistry were established.

The x-ray work also adds to the growing body of evidence that epoxycyclohexanones adopt a conformation in which the plane of the epoxide ring

Table 5



Enone

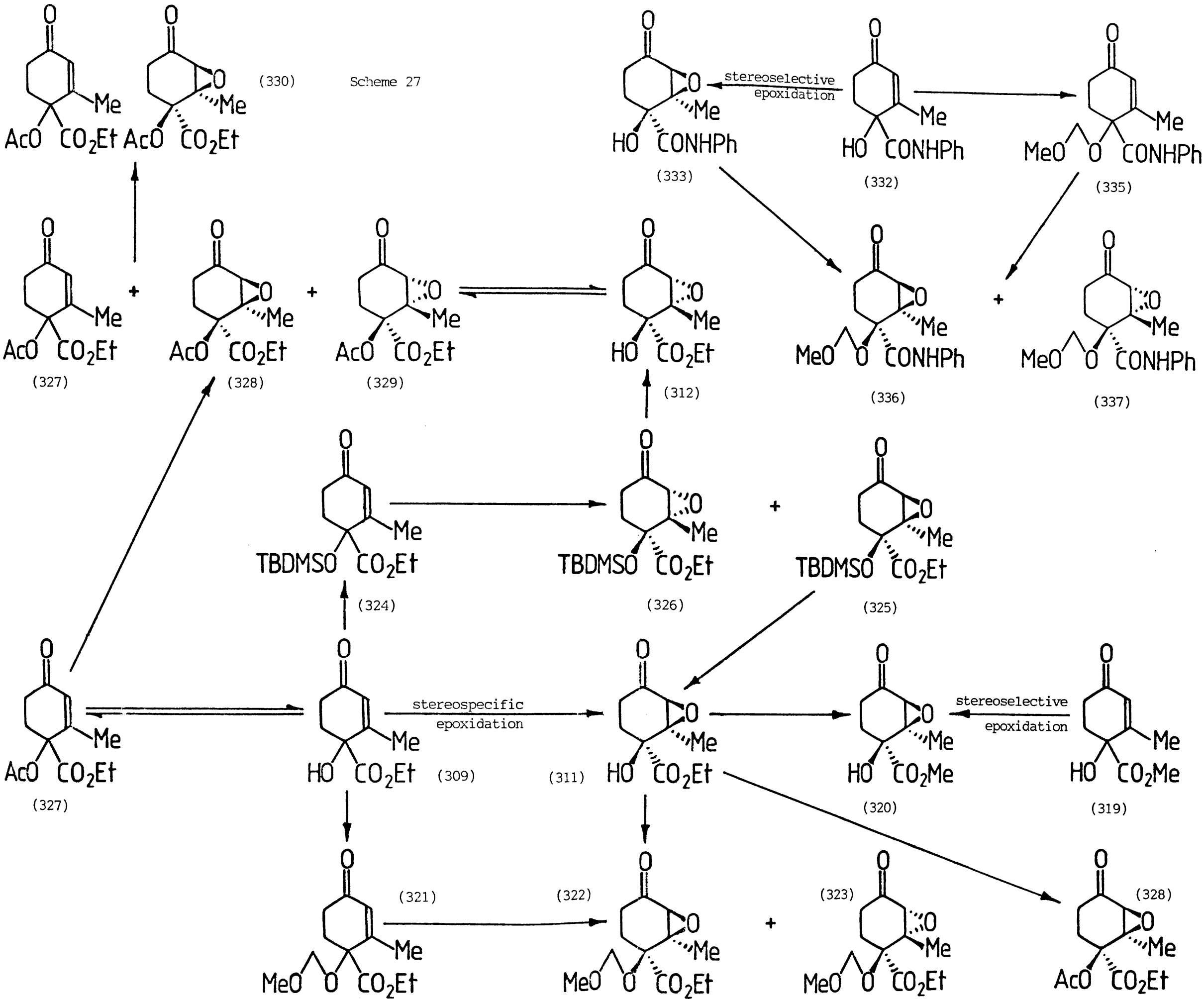


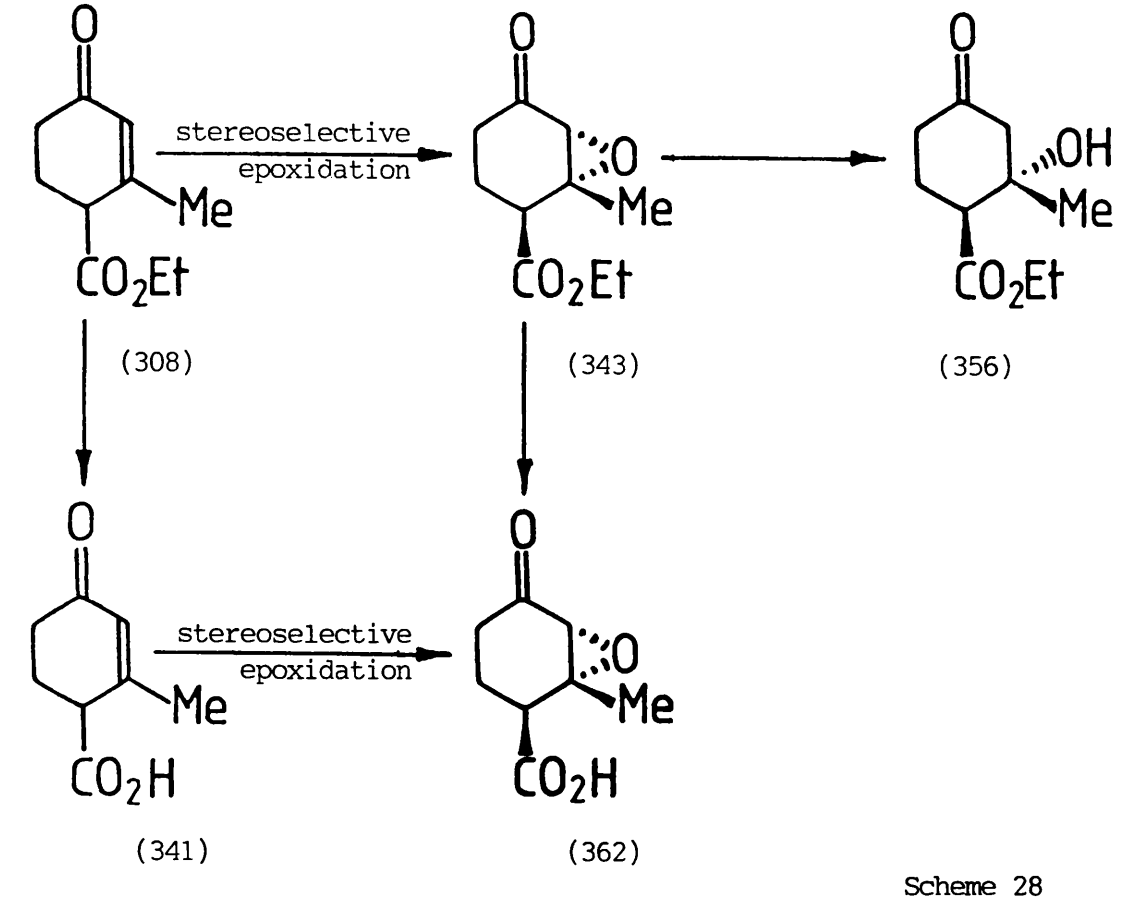
Epoxide(s)

R_1	R_2	ratio of epoxides	% cis to R_1
HO	CO_2Me	97:3	97
HO	CO_2Et	100:0	100
HO	CONHPh	10:1	91
$MeOCH_2O$	CO_2Et	1:1	50
TBDMSO	CO_2Et	2:3	40
AcO	CO_2Et	1:1	50
H	CO_2Et	8:92	8
H	$CO_2^{\ominus}$	1:5	17
H	$CONH_2$	1:5	unknown
H	CONHPh	1:2	unknown
MeCH(OH)	Me	100:0	100
MeC=O	Me	100:0	100

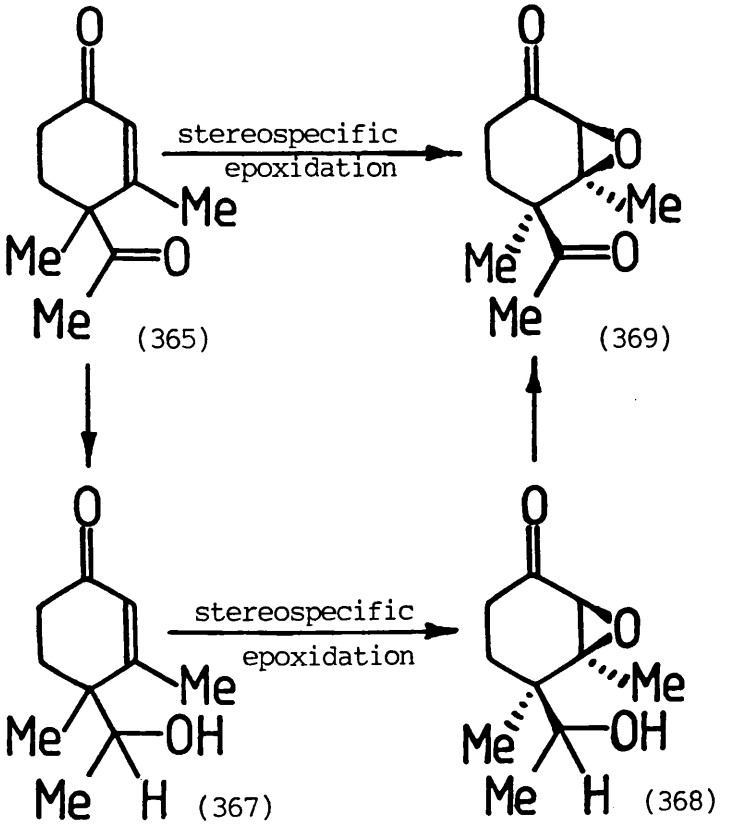
is perpendicular to the plane of the carbonyl group.

The main reactions and products reported in this chapter are summarised in Scheme 27 and Scheme 28.


(330)
Scheme 27
stereoselective epoxidation
(333)
(332)
(335)
(327)
(328)
(329)
(312)
(336)
(337)
(324)
(326)
(325)
stereospecific epoxidation
(309)
(311)
(320)
(319)
(321)
(322)
(323)
(328)


stereoselective
epoxidation
Me
CO2Et
(308)
(343)
(356)
OH
stereoselective
epoxidation
CO2H
(341)
(362)

Scheme 28

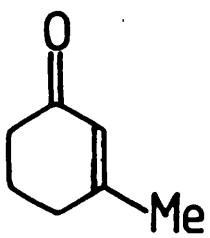

stereospecific
epoxidation
Me
Me
Me
(365)
(369)
stereospecific
epoxidation
OH
H
(367)
(368)

Chapter 4 : Attempted Epoxidation of α′-Substituted Enones (System D)

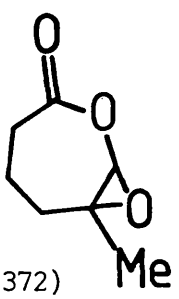
This chapter will deal with a number of α′-substituted enones that could be conveniently prepared in one or two steps from compounds (or their intermediates) that were synthesised in the previous chapter. In some cases the substituent is an α′-hydroxyl or α′-acetoxyl group and the enones therefore bear some structural resemblance to the naphthalenones (161) and (163) which underwent stereospecific alkaline epoxidation (see p 43).

Investigation of 6-acetoxy and 6-hydroxy-3-methylcyclohex-2-enone

3-Methylcyclohex-2-enone (371) was easily prepared by acid hydrolysis of Hagemann's ester (308) and purified by distillation. Its epoxidation presents no question of stereoselectivity but it was treated with alkaline hydrogen peroxide to see whether the lack of a γ-substituent affected the rate of epoxidation. For comparison (308) and the γ-hydroxy enone (309)



(371)



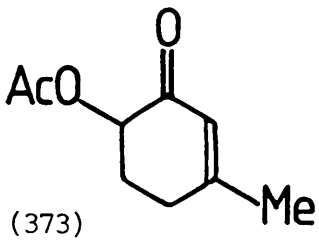
(372)

were reacted under the same conditions. In the time it took the simple enone (371) to be completely converted to epoxide only about 20% and 60% of (308) and (309) were converted to their respective epoxides. As expected, this showed a γ-substituent reduces the rate of epoxidation but that the γ-hydroxy enone (309), in which the alcohol directs the attack of the hydroperoxide anion, is oxidised more quickly than (308).

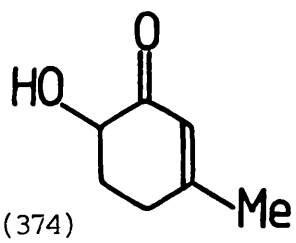
The enone (371) was also treated with mcpba, as had been done with (308), to see whether epoxidation is preceded by Baeyer-Villiger oxidation.

This proved to be the case, with the epoxy lactone (372) being isolated in good yield.

Prolonged treatment of (371) with lead (IV) acetate in refluxing benzene gave 6-acetoxy-3-methylcyclohex-2-enone (373).[201]



(373)



(374)

An attempt to epoxidise (373) with alkaline hydrogen peroxide using sodium carbonate as the base resulted only in hydrolysis of the acetate. The resulting alcohol (374) was not epoxidised under these conditions.

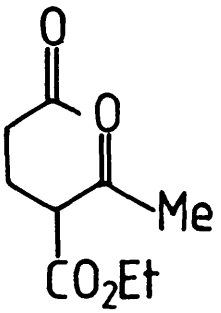
A stock of the alcohol (374) was prepared by base hydrolysis of the acetate for epoxidation studies. However treatment with alkaline hydrogen peroxide using sodium hydroxide as the base failed to yield any epoxide product. So too did reaction with mcpba, per-Amberlyst 15 and, rather surprisingly, t-butylhydroperoxide in conjunction with vanadyl acetoacetonate.[106] In all cases the products, which were usually isolated in poor yield, gave uninterpretable ^{1}H nmr spectra.

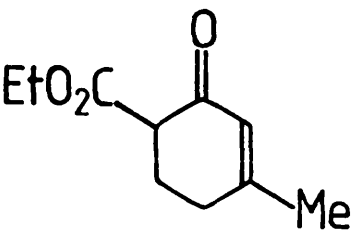
Investigation of 6-ethoxycarbonyl-3-methylcyclohex-2-enone

The intermediate (358) from which Hagemann's ester (308) was synthesised has, in fact, an alternative mode of cyclisation. It has been established that while treatment of (358) with pyrrolidinium acetate affords Hagemann's ester,[179] reaction with hydrochloric acid bubbled through a benzene solution of the intermediate and then treatment with N,N-dimethylaniline gave the isomeric compound, 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361).[202] Golding proposed that with pyrrolidinium acetate as catalyst the cyclising step involves intramolecular condensation

of an enamine with a ketone carbonyl group.[179] The preferred formation of (308) was attributed to a greater degree of steric crowding in the transition state required for cyclisation to (361). Under acidic or basic conditions the cyclisation proceeds via an enol intermediate. In these cases the major product is (361). This was thought to be due to the enol intermediate in the formation of (361) cyclising faster than that of (308).

(358)





(361)

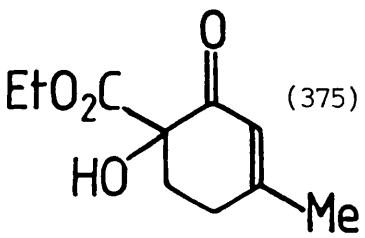
The ester (361) was prepared using the above procedure and purified by distillation. Although (361) and Hagemann's ester have virtually identical physical and spectral properties it is possible to distinguish them from their ^1H nmr spectra. While the methine proton α to the ester appears as a broad triplet for Hagemann's ester, it is a more complex multiplet in the spectrum of (361).

An attempt to epoxidise (361) with alkaline hydrogen peroxide using sodium hydroxide as the base was unsuccessful and gave only recovered enone (361). It was thought the failure of this reaction was due to abstraction of the α'proton of (361) by the base which would generate a delocalised enolate anion and prevent epoxidation. However a repeated attempt which employed sodium carbonate rather than sodium hydroxide as the base also failed to yield any epoxide products.

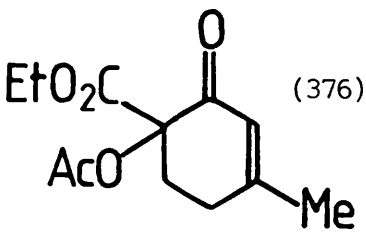
Investigation of the activated charcoal oxidation

Although it was thought that the α'-hydroxy enone (375) might be prepared from (361) by acetoxylation $\alpha'$to the ketone with lead (IV)

acetate and selective hydrolysis of the acetate (376), it was decided to try the activated charcoal hydroxylation method[175] to see whether (375) could be obtained in a single step.



(375)

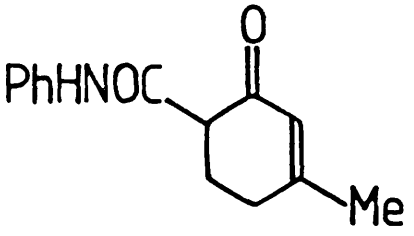


(376)

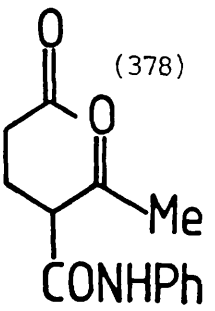
An ethyl acetate solution of the ester (361) was stirred with activated charcoal under the same conditions and using the same quantities as for the isomer (308). It appeared from an ^1H nmr spectrum of the product that no hydroxylation had occurred. However a repeated reaction in which the quantity of charcoal was trebled and the reaction time increased to two weeks resulted in the isolation of a crude product, whose ^1H nmr spectrum suggested it was a mixture of the enones (361) and (375). Although the product was flash chromatographed, it proved impossible to completely separate compound (375) from the starting ester (361) so it was decided to try to synthesise (375) by the alternative procedure outlined above (see p 151).

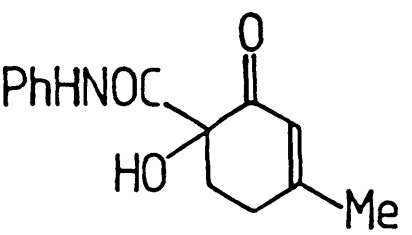
Having established that hydroxylation of the isomeric ester (361) was possible, the N-phenyl amide (377) was then examined. This compound was prepared by treating (378) [which is also the intermediate to the isomeric compound (331)] with sodium ethoxide followed by concentrated hydrochloric acid,[203] and purified by flash chromatography and recrystallisation.

In contrast to the ethyl ester, this amide was completely converted to the hydroxylated product (379) on stirring an ethyl acetate solution of (377) containing 4 mass equivalents of activated charcoal in air for 4 days.



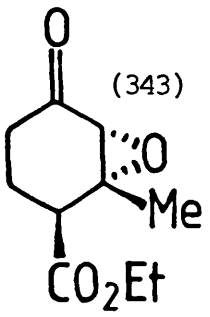
(377)

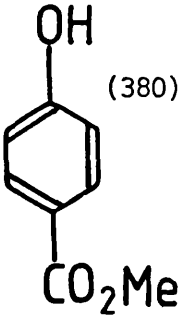


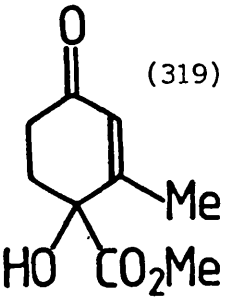


(379)

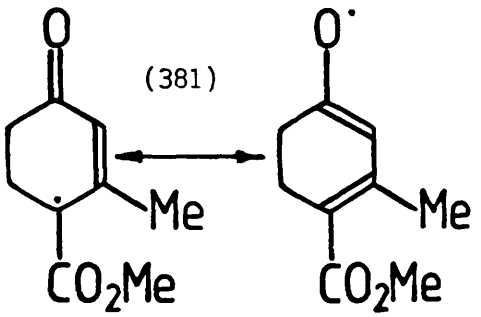
In a further exploration of the scope of the charcoal hydroxylation the epoxide (343) and acetoacetanilide, which bear strong structural resemblances to Hagemann's ester (308) and the amide (377), were both tried as potential new substrates. However in both cases the starting material was recovered unchanged indicating, as Stoodley had reported,[175] that the molecule requires a double bond for oxidation. The phenol (380)

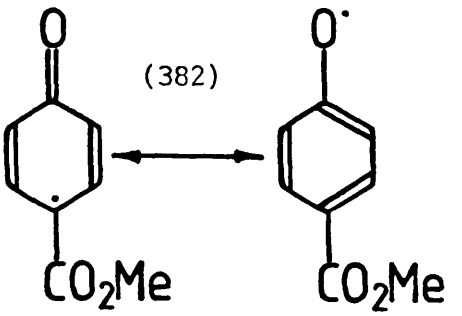






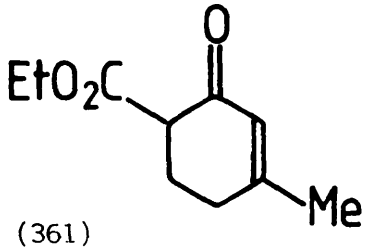
was also tried as a possible substrate. It was felt that if the oxidation proceeds via a radical mechanism then a likely intermediate in the formation of (319) would be the delocalised radical (381), resulting from abstraction of the C-4 hydrogen. A structurally similar radical (382) could feasibly be generated from the phenol (380). Despite this hope, (380) was also recovered unchanged. Hence, although the range of



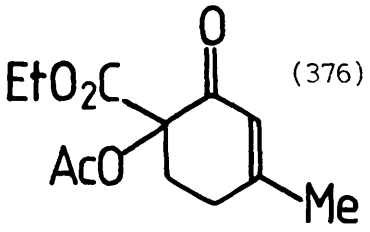


substrates capable of being oxidised was extended, further insight into the mechanism of the reaction proved elusive.

Investigation of 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone

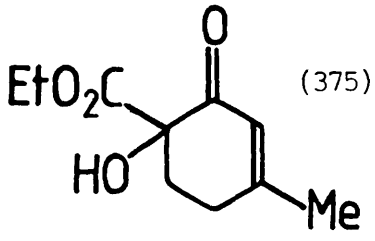


(361)



(376)

Reaction of the ester (361) with lead (IV) acetate in refluxing benzene for 72 hours gave the acetate (376). Unlike the isomeric compound (327) which is crystalline, this material, even after purification by flash chromatography, remained a viscous oil. Since the isomeric acetate (327) was cleanly converted to the γ-hydroxy enone (309) on treatment with ethanolic sodium ethoxide it was foreseen that (376) should afford (375) under the same conditions. Surprisingly this was not the case and the acetate (376) was recovered unchanged. Similarly an attempted acid-catalysed transesterification with p-toluenesulphonic acid in ethanol gave mainly recovered (376) though the presence of small multiplets at δ 6.8 and δ 7.7 suggested the presence of an aromatic compound. This minor component is presumably the phenol (383) resulting from elimination of water.



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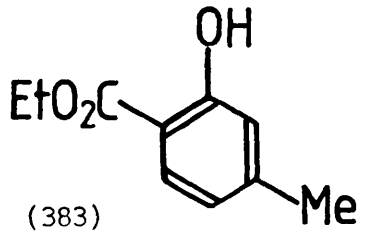

(383)

Alkaline epoxidations of (376) using both sodium carbonate and sodium hydroxide as base again gave mainly recovered starting material, and no

evidence for epoxide formation was found in the ^1H nmr spectra of the products.

Using established synthetic procedures a number of α′-substituted cyclohexenones were prepared. Some of these were converted to α′,α′-disubstituted cyclohexenones on treatment with either lead (IV) acetate or air over activated charcoal. This demonstrated that the charcoal hydroxylation procedure could be extended from cyclohexenones with a γ-substituent to their isomeric compounds with the substituent in the α′-position. Treatment of 6-acetoxy-3-methylcyclohex-2-enone (373) and 6-hydroxy-3-methylcyclohex-2-enone (374) with alkaline hydrogen peroxide failed to yield any epoxide products, while 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361) and 6-acetoxy-6-ethoxycarbonyl-3-methyl-cyclohex-2-enone (373) both proved to be inert to these conditions. It is not clear why these enones do not epoxidise; in particular, the failure of (361) and (373) was surprising given that the isomeric γ-substituted enones (Chapter 3) both gave good yields of epoxides.

To conclude, the stereoselectivity of epoxidation of a number of different enone systems was examined. α′-Substituted or α′,α′-disubstit-uted enones (System D) did not epoxidise on treatment with alkaline hydrogen peroxide. In cases where the enone possessed a γ-hydroxy group (System A-C) the epoxidation was stereospecific or highly stereoselective (irrespective of the nature of the other γ-substituent) and gave mainly the cis epoxy alcohol. A γ-hydroxyl group was also shown to markedly

increase the rate of alkaline epoxidation. Although a slight increase may be expected on the grounds that the electron-withdrawing effect of the hydroxyl group would make the enone more electrophilic, this should be largely offset by the substituent sterically hindering approach of the nucleophilic hydroperoxide anion to the enone. A plausible interpretation of both the rate increase and the syn stereoselectivity is that the hydroxyl group hydrogen bonds to the incoming hydroperoxide anion, thereby delivering it to only one face of the enone. Conversion of the γ-hydroxyl group to a γ-ether or γ-acetate resulted (with one exception) in a total loss of this directing effect. Any slight stereoselectivity can be explained on steric grounds. Even a bulky silyl ether, which was expected to hinder syn approach of the hydroperoxide anion to the enone, showed only a marginal alteration in the 1:1 ratio of products. A number of other functionalities also exerted a strong directing effect on alkaline epoxidation (System C). Both a γ-hydroxyethyl and a γ-acetyl substituent resulted in stereospecific epoxidation. In both cases the epoxide formed was cis to the substituent. The former result demonstrated that even when the hydroxyl group is one atom more remote from the β position, stereospecific epoxidation is still possible. The stereospecificity of the latter reaction might be explained by nucleophilic addition of hydroperoxide anion to the acetyl carbonyl followed by intramolecular delivery of the resulting alkyl peroxide anion to the syn face of the enone. This theory had been proposed for another enone with a γ-ketone substituent which also gave exclusively the cis epoxide. Alkaline epoxidation of enones with a γ-ester or γ-acid substituent gave mainly the trans epoxy ester and trans epoxy acid. Similar cases have been reported in the literature. Formation of the trans epoxy acid can be explained by electrostatic repulsion between the γ-carboxylate anion (formed under the alkaline conditions) and the hydroperoxide anion.

Formation of the trans epoxy ester is less easily rationalised, though steric or polar repulsion between the ester carbonyl and the hydroperoxide anion is a possible explanation. Alkaline epoxidation of an enone substituted in the γ-position with a primary amide was also highly stereoselective though similar reaction of the analogous N-phenyl amide resulted in a 2:1 mixture of both epoxide isomers. In neither case was the stereochemistry of the products established.

Stereospecific or highly stereoselective peracid and Sharpless epoxidations of hydroxy alkenes are well documented in the literature. The work presented in this thesis demonstrates that equally high selectivity can often be observed for electrophilic hydroxy alkenes (which till now have received no detailed study), where alkaline hydrogen peroxide is normally the reagent of choice. This work has also established that a number of other functional groups are capable of stereospecific or highly stereoselective alkaline epoxidations.

EXPERIMENTAL

General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected.

Routine ^{1}H nmr spectra were recorded using a Perkin Elmer R32 (90 MHz) spectrometer. ^{13}C Nmr and high field ^{1}H nmr spectra were recorded using a Varian XL-100 FT spectrometer, Bruker AM 200 SY spectrometer or Bruker WP 200 SY spectrometer. Unless otherwise stated the spectra were determined in deuteriochloroform solutions. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane, using tetramethylsilane or the δ 7.25 residual chloroform peak and the δ 77 deuteriochloroform peak as internal references for the ^{1}H and ^{13}C nmr spectra respectively.

Ir spectra were recorded using a Perkin-Elmer 580 spectrometer or a Perkin-Elmer 983 spectrometer. Uv spectra were recorded using a Perkin-Elmer 550 SE UV/VIS spectrophotometer. Mass spectra were recorded on a G.E.C.-A.E.I. M.S. 12 spectrometer (low resolution) and a G.E.C.-A.E.I. M.S. 902 spectrometer (high resolution). Elemental analyses were performed using a Carlo-Erba 1106 elemental analyser.

X-ray intensity measurements were made by 2θ-ω scan on a Nonius CAD 4 diffractometer using graphite-monochromated Mo or Cu Kα radiation. Unit cell parameters were determined by least-squares refinement of diffractometer setting angles for 25 reflections. The principal computer programs used in structure solution and refinement are: MITHRIL, A Computer Program for the Automatic Solution of Crystal Structures from X-Ray Data, C.J. Gilmore, J. Appl. Crystallogr., 1984, 17, 42; the GX Crystallographic Program System, P.R. Mallinson and K.W. Muir, J. Appl. Crystallogr., 1985, 18, 51.

Dry column flash chromatography was carried out using Merck kieselgel 60H silica and unless otherwise stated the column was eluted using an ethyl acetate/petroleum ether solvent mixture.

Petroleum ether (pet. ether) refers to the fraction boiling between 60-80° unless otherwise stated.

Thin-layer chromatography (tlc) employed plastic sheets coated with Merck kieselgel $60F_{254}$ and these were developed using 50% ethyl acetate/pet. ether, unless another solvent system is specifically stated. Preparative tlc was carried out using plates coated with 1 mm of Merck kieselgel HF_{254}.

All organic extracts were dried over anhydrous magnesium sulphate prior to removal of the solvent on a rotary evaporator, unless otherwise stated.

Abbreviations

nmr: s singlet; d doublet; t triplet; q quartet; m multiplet; br broad.

Preparation of 4-hydroxy-4-methylnaphthalen-1(4H)-one (48)

4-formyl-1-naphthol was prepared by the method of Adams and Levine.[133] A single recrystallisation of the crude product from 7:3 water:ethanol gave relatively pure material, m.p. 169-174° (lit.[204] 170-172°) in 64.1% yield.

^{1}H nmr (d-6 acetone) δ 3.45 (br s, 1H); 7.10 (d, J ~ 8 Hz, 1H); 7.47-7.83 (m, 2H); 7.95 (d, J ~ 8 Hz, 1H); 8.38 (d, J ~ 7 Hz, 1H); 9.36 (d, J ~ 8 Hz, 1H); 10.17 (s, 1H).

Clemmensen reduction of the aldehyde[204] gave, after distillation and recrystallisation from benzene/pet. ether, 4-methyl-1-naphthol in 49.5% yield, m.p. 81.5-83.5° (lit.[204] 83-84°).

^{1}H nmr ($CDCl_3$) δ 2.53 (s, 3H); 5.30 (br s, 1H); 6.60 (d, J ~ 9 Hz, 1H); 7.05 (d, J ~ 9 Hz, 1H); 7.3-7.6 (m, 2H); 7.75-8.0 (m, 1H); 8.05-8.30 (m, 1H).

4-methyl-1-naphthol (2.0 g) in ethanol (100 ml) was treated with ceric (IV) oxide (5.06 g) and hydrogen peroxide (30%, 62.5 ml).[135] This mixture was heated to reflux and the reaction monitored by tlc. After 1½ hours the reaction mixture was allowed to cool and the ceric oxide filtered off. After removal of the ethanol on a rotary evaporator the solution was diluted with water (500 ml) and extracted with 1:1 ether:pet. ether (5 x 100 ml). The combined extracts were treated with dimethyl sulphide (2.0 ml) and reduction of the intermediate hydroperoxide (241) monitored using potassium iodide/starch papers and tlc. After one week the solution was washed with water (2 x 40 ml). Evaporation of the solvent followed by recrystallisation from chloroform/pet.ether gave 4-hydroxy-4-methylnaphthalen-1(4H)-one (48) m.p. 98-100° (lit.[134] 100-102°), in 53.3% yield.

^{1}H nmr ($CDCl_3$) δ 1.58 (s, 3H); 3.12 (br s, 1H); 6.13 (d, J ~ 9 Hz, 1H); 6.95 (d, J ~ 9 Hz, 1H); 7.21-7.80 (m, 3H); 7.92 (d, J ~ 8 Hz, 1H).

Although treatment of the hydroperoxide (24) with zinc in aqueous ammonium chloride and zinc in aqueous acetic acid (both in the absence and presence of a catalytic amount of potassium iodide) resulted in complete reduction within a couple of minutes, tlc and ^{1}H nmr showed there was significant over-reduction to 4-methyl-1-naphthol. Aqueous iron (II) sulphate acidified with a few drops of concentrated sulphuric acid also effected quick reduction and tlc showed no sign of formation of 4-methyl-1-naphthol. However although ^{1}H nmr confirmed the formation of the alcohol (48), it proved far harder to purify by crystallisation than the product from dimethyl sulphide reduction, which crystallised on evaporation of the solvent.

Epoxidation of 4-hydroxy-4-methylnaphthalen-1(4H)-one (48)[83]

To a stirred solution of 4-hydroxy-4-methylnaphthalen-1(4H)-one (900 mg) in ethanol (40 ml) was added a solution of sodium hydroxide (200 mg) in water (6.0 ml) and hydrogen peroxide (30%, 4.0 ml). The reaction was monitored by tlc using several elutions with dichloromethane. After 3 hours the ethanol was removed on a rotary evaporator and the residue diluted with water (100 ml). This solution was extracted with ether (5 x 100 ml), the extracts combined and the solvent evaporated to give the cis epoxy alcohol (49) (630 mg, 65.3% yield). Recrystallisation from chloroform/pet. ether gave white needles which on heating underwent a polymorphic change along with melting at ~130°. The newly formed platelet crystals had m.p. 160-164° (lit.[83] 165-167°).

^{1}H nmr ($CDCl_3$) δ 1.49 (s, 3H); 2.72 (br s, 1H); 3.72 (d, J ~ 4 Hz, 1H); 3.79 (d, J ~ 4 Hz, 1H); 7.27-7.91 (m, 4H).

ir ($CHCl_3$) 3580, 3450, 1690, 1600, 1460 cm^{-1}.

m/e (rel. intensity) 192 (1.7), 191 (9.4), 190 ($M^{\oplus}$; 84.0), 175 (100.0).

Analysis: Found C, 69.18; H, 5.06. $C_{11}H_{10}O_5$ requires C, 69.46; H, 5.30.

Both tlc and ^{1}H nmr of the mother liquors from the recrystallisation showed no trace of the isomeric trans epoxy alcohol (247).

Preparation of 4-methoxy-4-methylnaphthalen-1(4H)-one (246)[136,137]

(a) To a stirred solution of 4-methyl-1-naphthol (2.0 g) in methanol (400 ml) was added lead (IV) acetate (8.0 g) and boron trifluoride etherate (6 ml). After 20 hours at room temperature the methanol was evaporated and the residue diluted with chloroform (100 ml). This solution was washed with saturated sodium carbonate (2 x 50 ml) and the solvent evaporated to give crude 4-methoxy-4-methylnaphthalen-1(4H)-one (246).

(b) To a stirred solution of 4-methyl-1-naphthol (790 mg) and powdered potassium carbonate (1.38 g) in anhydrous methanol at 0°C was added a solution of PIFA (2.15 g) in acetonitrile (10 ml). After 10 minutes the reaction mixture was diluted with water (100 ml) and extracted with chloroform (3 x 60 ml). Evaporation of the solvent from the combined extracts gave crude 4-methoxy-4-methylnaphthalen-1(4H)-one.

The crude products from the above reactions were combined and purified by flash chromatography giving pure 4-methoxy-4-methylnaphthalenone (2.584 g, 77.8% yield) which on recrystallisation from pet.ether had m.p. 48-51° (lit.[137] 47-49°).

^{1}H nmr ($CDCl_3$) δ 1.60 (s, 3H); 3.01 (s, 3H); 6.52 (d, J ~ 10 Hz); 6.95 (d, J ~ 10 Hz, 1H); 7.05-7.75 (m, 3H); 8.05-8.22 (m, 1H).

ir (CCl_4) 1675, 1605, 1455, 1300 cm^{-1}.

m/e 189 (2.9), 188 ($M^{\oplus}$; 23.6), 173 (100.0).

Epoxidation of 4-methoxy-4-methylnaphthalen-1(4H)-one (246)[137]

(a) To a stirred solution of 4-methoxy-4-methylnaphthalen-1(4H)-one (177 mg) in methanol (3.0 ml) was added hydrogen peroxide (30%, 0.33 ml).

Once the contents had been cooled to 15°, 3M sodium carbonate (0.086 ml) was added slowly and the reaction monitored by tlc. After about 200 hours tlc still showed only a single spot with the same Rf as the starting dienone. The reaction mixture was diluted with water (30 ml) and extracted with chloroform (4 x 25 ml). After combining the extracts, evaporation of the solvent afforded both the epoxy ethers in addition to some residual dienone. The relative proportions of these compounds was shown from the integrals in the ^1H nmr spectrum to be 8:9:22 respectively.

^1H nmr ($CDCl_3$): as well as a complex aromatic region due to the aromatic protons of all three compounds and other peaks associated with residual dienone the spectrum shows the following peaks

minor epoxide isomer: δ 1.44 (s, 3H); 2.95 (s, 3H); 3.77 (d, J ~ 2 Hz, 1H); 3.82 (d, J ~ 2 Hz, 1H).

major epoxide isomer: δ 1.86 (s, 3H); 3.42 (s, 3H); 3.65 (d, J ~ 4 Hz, 1H); 3.74 (d, J ~ 4 Hz, 1H).

Although the above mixture was treated with alkaline hydrogen peroxide under the above conditions for a further 4 weeks it was shown by ^1H nmr to result in only slight further conversion with the epoxides comprising ~ 50% of the total product. No attempt was made to separate the components of this mixture.

ir ($CHCl_3$) 1695, 1670, 1605, 1460, 1305 cm^{-1}.

m/e 204 ($M^{\oplus}$; 0.5), 203 (3.9), 188 (41.8), 172 (100.0).

(b) To a stirred solution of 4-methoxy-4-methylnaphthalen-1(4H)-one (223 mg) in dichloromethane (20 ml) was added mcpba (427 mg). After 7 days this solution was diluted with dichloromethane (80 ml) and washed with saturated aqueous sodium metabisulphite (100 ml) and saturated aqueous sodium carbonate (2 x 50 ml). Evaporation of the solvent gave a residue (288 mg) whose ^1H nmr spectrum showed dienone peaks but no evidence of any epoxide formation.

Preparation of 4-methoxymethoxy-4-methylnaphthalen-1(4H)-one (248)[139]

To a vigorously stirred solution of 4-hydroxy-4-methylnaphthalen-1(4H)-one (360 mg) in chloroform (15 ml) was added methylal (15 ml) and then phosphorus pentoxide (7.5 g) which soon became a brown gelatinous solid. The reaction was monitored by tlc which, after 10 minutes, showed a single spot of Rf 0.7 for the reaction mixture while the starting alcohol had Rf 0.5. After 15 minutes the solution was decanted from the residual solid which was washed with chloroform (2 x 30 ml). The combined organic solutions were washed with 1M potassium carbonate (4 x 150 ml). Evaporation of the solvent afforded 4-methoxymethoxy-4-methylnaphthalen-1(4H)-one (248) (380 mg, 84.3% yield).

^{1}H nmr δ 3.61 (s, 3H); 3.33 (s, 3H); 4.30-4.50 (AB quartet, 2H); 6.39 (d, J ~ 10 Hz, 1H); 7.04 (d, J ~ 10 Hz, 1H); 7.25-7.85 (m, 3H); 8.00-8.25 (m, 1H). The spectrum also shows two small singlets at δ 3.33 and δ 4.70 due to residual methylal.

Epoxidation of 4-methoxymethoxy-4-methylnaphthalen-1(4H)-one (248)

To a stirred solution of the MOM ether (248) (1061 mg) in ethanol (45 ml) and chloroform (10 ml) was added a solution of sodium hydroxide (235 mg) dissolved in water (7.0 ml) and hydrogen peroxide (30%, 4.75 ml). After 24 hours the ethanol and chloroform were evaporated and the residue diluted with water (100 ml). This solution was extracted with ether (2 x 125 ml) and chloroform (2 x 100 ml). The combined extracts were evaporated giving a 3:2 mixture of the trans and cis epoxy ethers.

cis epoxy ether: ^{1}H nmr ($CDCl_3$) δ 1.48 (s, 3H); 3.52 (s, 3H); 3.70 (d, J ~ 4 Hz, 1H); 3.94 (d, J ~ 4 Hz, 1H); 4.74 (d, J ~ 7 Hz, 1H); 4.92 (d, J ~ 7 Hz, 1H); 7.30-7.69 (m, 3H); 7.79-7.93 (m, 1H).

trans epoxy ether: ^{1}H nmr ($CDCl_3$) δ 1.88 (s, 3H); 3.22 (s, 3H); 3.67-

3.81 (AB quartet, 2H); 4.12 (d, J ~ 8 Hz, 1H); 4.35 (d, J ~ 8 Hz, 1H); 7.30-7.75 (m, 3H); 7.87-8.02 (m, 1H).

Conversion of the cis epoxy alcohol (49) to its MOM ether

The cis epoxy MOM ether of (49) was prepared in 89.9% yield using the method previously mentioned. The product has a spectrum identical to that reported above.

Cleavage of the 3:2 mixture of the trans and cis epoxy ethers

To a solution of the epoxy MOM ethers (738 mg) in ethanol (100 ml) and chloroform (20 ml) was added p-toluenesulphonic acid (100 ml). The solution was heated to reflux. The reaction was monitored by tlc. After 5 hours more p-toluenesulphonic acid (30 mg) was added to speed up the reaction. After 6½ hours the solution was allowed to cool and stand overnight. Tlc then showed the absence of any MOM ether so the solution was neutralised with aqueous sodium carbonate and the solvents evaporated. The residue was diluted with water and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts gave a mixture of the cis epoxy alcohol (49) and the trans epoxy alcohol (247). This mixture was separated by flash chromatography using dichloromethane/ ethyl acetate mixtures to elute the products from the column. This afforded (49) (139 mg, 23.2% yield), which had characteristics identical to those previously reported, and the trans epoxy alcohol (247) (103 mg, 17.2% yield) as a viscous oil.

^{1}H nmr ($CDCl_3$) δ 1.87 (s, 3H); 2.50 (br s, 1H); 3.62 (d, J ~ 4 Hz, 1H); 3.75 (d, J ~ 4 Hz, 1H); 7.25-7.70 (m, 3H); 7.75-7.95 (m, 1H).

ir ($CHCl_3$) 3595, 3500, 1720, 1690, 1600, 1460 cm^{-1}.

m/e 190 ($M^{\bullet}$; 4), 175 (8), 119 (97), 117 (100).

Acetylation of the cis epoxy alcohol (49)

To a solution of the alcohol (49) in chloroform (6 ml) was added triethylamine (0.9 ml), acetic anhydride (0.48 ml) and DMAP (33 mg).[140] This solution was allowed to stand overnight. After partitioning the reaction mixture between chloroform and 2M hydrochloric acid, the organic phase was washed with saturated aqueous sodium bicarbonate. Evaporation of the solvent gave a residue which was purified by flash chromatography. This gave the acetate (250) (668 mg, 91.2% yield) as a viscous oil.

^{1}H nmr ($CDCl_3$) δ 1.77 (s, 3H); 2.19 (s, 3H); 3.71 (d, J ~ 4 Hz, 1H); 4.64 (d, J ~ 4 Hz, 1H); 7.15-7.80 (m, 3H); 7.88 (d, J ~ 9 Hz, 1H).

ir ($CHCl_3$) 1735, 1695, 1605, 1455 cm^{-1}.

m/e 232 ($M^{\oplus}$; 2.0), 203 (6.8), 162 (33.3), 161 (53.2), 42 (100.0).

Acetylation of the trans epoxy alcohol (247)

This was prepared by the above method.[140] Flash chromatographic purification gave the acetate (56.2% yield) which on recrystallisation from ethyl acetate/pet. ether had m.p. 107-109°.

^{1}H nmr ($CDCl_3$) δ 1.89 (s, 3H); 1.92 (s, 3H); 3.77 (s, 2H); 7.15-7.75 (m, 3H); 7.79-8.10 (m, 1H).

ir ($CHCl_3$) 1730, 1685, 1495, 1450 cm^{-1}.

m/e 233 (0.4), 232 ($M^{\oplus}$; 2.6), 190 (16.2), 162 (26.2), 161 (100.0).

Analysis: Found C, 66.80; H, 5.21. $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21.

Preparation of 4-acetoxy-4-methylnaphthalen-1(4H)-one (251)[143]

To a solution of 4-methyl-1-naphthol (633 mg) in acetonitrile (50 ml) was added lead (IV) acetate (3.54 g). This heterogeneous solution was stirred with exclusion of atmospheric moisture for 16 hours at room temperature. The reaction mixture was poured into water (100 ml) and this solution extracted with ether (4 x 100 ml). The combined extracts

were washed with 1M sodium hydroxide (2 x 50 ml) and the solvent evaporated. This gave 946 mg of a 2:1 crude mixture of 4-acetoxy-4-methylnaphthalen-1(4H)-one (251) and 2,2-diacetoxy-4-methylnaphthalen-1(2H)-one (252).

To the mixture dissolved in ethanol (30 ml) was added a solution of sodium carbonate (150 mg) in water (10 ml). This solution was shaken and allowed to stand for 40 minutes. The ethanol was evaporated and the solution diluted with water (50 ml). This solution was extracted with ether (6 x 70 ml). Evaporation of the solvent left a residue (650 mg) that was now much richer in the monoacetate (251). Purification by flash chromatography and recrystallisation from chloroform/pet. ether gave 4-acetoxy-4-methylnaphthalen-1(4H)-one (251) (~ 250 mg, ~ 30% yield), m.p. 93-100° (lit.[143] 95-96°).

^{1}H nmr ($CDCl_3$) δ 1.66 (s, 3H); 2.04 (s, 3H); 6.49 (d, J ~ 10 Hz, 1H); 7.00 (d, J ~ 10 Hz, 1H); 7.27-7.73 (m, 3H); 8.01-8.21 (m, 1H).

Attempted epoxidation of 4-acetoxy-4-methylnaphthalen-1(4H)-one (251)

(a) To a stirred solution of 4-acetoxy-4-methylnaphthalen-1(4H)-one (251) (216 mg) in ethanol (5 ml) was added hydrogen peroxide (30%, 0.35 ml). Once the contents had been cooled to 15° 3M sodium carbonate (0.1 ml) was added and the reaction monitored by tlc. After about a week the reaction mixture was diluted with water (25 ml) and extracted with chloroform (4 x 25 ml). Evaporation of the solvent from the combined extracts left a residue (213 mg). Tlc and ^{1}H nmr showed this product was predominantly the cis epoxy alcohol (49) but still contained a small proportion of the starting naphthalenone (251).

(b) To a stirred solution of 4-acetoxy-4-methylnaphthalen-1(4H)-one (251) (100 mg) in dioxan (2.5 ml) containing t-butylhydroperoxide (0.8 ml) was added a 40% methanolic solution of Triton B (0.05 ml).[64] The reaction was

monitored by tlc. More Triton B (0.05 ml) was added after 24 hours. Potassium iodide/starch papers showed there was no t-butylhydroperoxide remaining after a week so brine (20 ml) was added to the reaction mixture and the resulting solution extracted with ether (4 x 20 ml). Evaporation of the solvent from the combined extracts left a residue (292 mg). Tlc and ^{1}H nmr showed this was a mixture of starting naphthalenone (251) and t-butanol.

Attempted preparation of 4-hydroxymethyl-4-methoxynaphthalen-1(4H)-one (253)

4-Acetyloxy-1-naphthalenecarboxaldehyde was prepared by acetylating the naphthol (254) with acetic anhydride, triethylamine and DMAP in chloroform.[140] Recrystallisation from ethyl acetate/pet. ether afforded pure acetate (254), m.p. 102-103.5°,[145] in 40.5% yield.

^{1}H nmr ($CDCl_3$) δ 2.49 (s, 3H); 7.38-8.10 (m, 5H); 9.22-9.37 (m, 1H); 10.33 (s, 1H).

ir (KBr disc) 1760, 1690, 1595, 1575, 1510 cm^{-1}.

m/e 215 (1.3), 214 (M⊕; 9.6), 172 (100.0).

Using the reported procedure[144] sodium borohydride was adsorbed onto alumina. Treatment of 4-acetyloxy-1-naphthalenecarboxaldehyde with this reagent gave 4-acetoxy-1-naphthalenemethanol (255) which crystallised on standing. A small portion of the product was sublimed and recrystallised from ether giving colourless needles of m.p. 87-88.5°.[146]

^{1}H nmr δ 2.25-2.75 (br s, 1H); 2.42 (s, 3H); 4.99 (s, 2H); 7.15 (d, J ~ 9 Hz, 1H), 7.35-7.68 (m, 3H); 7.80-8.15 (m, 2H).

ir (KBr disc) 3420, 1830, 1600, 1585, 1510 cm^{-1}.

m/e 218 (0.3), 217 (1.8), 216 (M⊕; 12.5), 174 (100.0).

Treatment of 4-acetyloxy-1-naphthalenemethanol (255) with TBDMS chloride, triethylamine and DMAP in chloroform according to the literature

method[147] gave the TBDMS ether. The ether was also prepared as follows: to a solution of the alcohol (2.92 g) in dichloromethane (30 ml) was added 2,6-lutidine (3.4 g) and a dichloromethane solution of TBDMS triflate (300 mg/ml, 15 ml). The reaction, from which atmospheric moisture was excluded, was monitored by tlc. After 1 hour the reaction mixture was washed with water (20 ml), saturated aqueous copper sulphate (3 x 20 ml) and brine (30 ml). Evaporation of the solvent left a residue which on flash chromatographic purification afforded the acetyloxy TBDMS ether (3.416 g) in 77.0% yield.

^{1}H nmr ($CDCl_3$) δ 0.00 (s, 6H, silyl methyl groups used as reference for remainder of spectrum); 0.82 (s, 9H); 2.32 (s, 3H); 5.07 (s, 2H); 7.18 (d, J ~ 9 Hz, 1H); 7.26-7.52 (m, 3H); 7.65-7.99 (m, 2H).

To a solution of the acetyloxy TBDMS ether (1.708 g) in anhydrous methanol (35 ml) was added potassium carbonate (2.5 g). The mixture was left to stir overnight. The reaction mixture was neutralised with dilute hydrochloric acid, diluted with water (150 ml) and extracted with chloroform until all the colour had been removed from the aqueous phase. Evaporation of the solvent gave the TBDMS ether of 4-hydroxy-1-naphthalene-methanol (256) (1.138 g, 76.1% yield).

^{1}H nmr ($CDCl_3$) δ 0.00 (s, 6H); 0.85 (s, 9H); 5.03 (s, 2H); 6.03 (br s, 1H), 6.62 (d, J ~ 9 Hz, 1H); 7.13-7.53 (m, 3H); 7.82-8.20 (m, 2H).

ir (CCl_4) 3350 (br), 1670, 1660, 1630, 1590, 1515, 1470, 1460 cm^{-1}.

m/e 288 ($M^{\oplus}$; 0.3); 75 (100.0).

To a stirred solution of the naphthol (200 mg) in anhydrous methanol (2.8 ml) was added potassium carbonate (192 mg) and a solution of PIFA (300 mg) in acetonitrile (1.4 ml).[138] After 10 minutes the reaction mixture was diluted with water (25 ml) and extracted with chloroform (4 x 20 ml). Evaporation of the solvent and purification of the product by flash chromatography gave the TBDMS ether of 4-hydroxymethyl-4-

methoxynaphthalen-1(4H)-one (257) (20 mg, 9.1% yield).

^{1}H nmr ($CDCl_3$) δ 1.01 (s); 3.41 (s); 3.97 (d, J ~ 11 Hz); 4.27 (d, J ~ 11 Hz); 6.90 (d, J ~ 10 Hz); 7.2-8.1 (m); 8.35-8.50 (m). The spectrum also showed a number of uninterpretable peaks.

ir (CCl_4) 1725, 1700, 1675, 1600, 1470, 1460 cm^{-1}.

m/e 318 (M$^{\oplus}$; 0.9), 288 (18.7), 261 (31.5), 73 (100.0).

Repetition of this reaction failed to yield any of the dienone (257). On one occasion 4-methoxy-4-methoxymethylnaphthalen-1(4H)-one (261) was isolated in 45.6% yield after flash chromatographic purification.

^{1}H nmr ($CDCl_3$) δ 3.07 (s, 3H); 3.29 (s, 3H); 3.37-3.50 (AB quartet, 2H); 6.58 (d, J ~ 11 Hz, 1H); 7.12 (d, J ~ 11 Hz, 1H); 7.38-7.80 (m, 3H); 8.07-8.22 (m, 1H).

ir (CCl_4) 1690, 1675, 1605, 1575, 1510, 1460 cm^{-1}.

m/e 262 (1.4), 231 (1.8), 220 (1.1), 219 (12.8), 218 (M$^{\oplus}$; 71.3), 173 (100.0).

Oxidation of 4-hydroxybenzyl alcohol (258) and 4-hydroxy-1-naphthalenemethanol (260) (see below) with PIFA under the above conditions also failed to yield 4-hydroxymethyl-4-methoxycyclohexa-2,5-dien-1-one (259) or 4-hydroxymethyl-4-methoxynaphthalen-1(4H)-one (253). In both cases ^{1}H nmr spectra of the products were uninterpretable.

Preparation of 4-hydroxy-1-naphthalenemethanol (260)

Reduction of 4-hydroxy-1-naphthalenecarboxaldehyde (254) with sodium borohydride by the literature method[144] gave 4-hydroxy-1-naphthalene-methanol (260) in 63.8% yield. A small portion of the crude product was sublimed giving white needles of m.p. 182-183°.

^{1}H nmr ($CDCl_3$/d-6 acetone) δ 5.02 (s, 2H); 6.24 (br s, 1H, exchanged with D_2O); 6.84 (d, J ~ 8 Hz, 1H); 7.24-7.85 (m, 3H); 8.00-8.45 (m, 2H).

ir (KBr disc) 3150 (br), 1660, 1620, 1565, 1515 cm^{-1}.

m/e 174 ($M^{\oplus}$; 0.7), 171 (100.0).

Preparation of a series of monocyclic p-quinols

Preparation of p-toluquinol (268)[155]

(a) To a stirred solution of p-benzoquinone (1.081 g) in ether (75 ml) at -78° was added an ethereal solution of methyl lithium (1.5 M, 8.7 ml) with the exclusion of atmospheric moisture. After 1 hour the solution was allowed to warm to room temperature and diluted with ether (50 ml). This solution was treated with excess saturated aqueous ammonium chloride. After separating the layers the aqueous phase was back-extracted with ether (3 x 40 ml) and the solvent evaporated from the combined organic solutions. The crude product mixture (970 mg) was purified by flash chromatography, Kugelrohr distillation and recrystallisation from chloroform/pet. ether. This gave pure p-toluquinol (326 mg, 26.3% yield).

(b) To a solution of crude 4-hydroperoxy-4-methylcyclohexa-2,5-dienone (273) (1.023 g) (prepared from p-cresol (263) according to the literature method of Barton[135]) in ether (100 ml) was added dimethyl sulphide (9 ml). The reduction of the hydroperoxide was monitored using potassium iodide/ starch papers. After about a week, the solvent was evaporated and the crude product purified by flash chromatography giving p-toluquinol (268) (434 mg, 47.9% yield). Recrystallisation from chloroform/pet. ether gave colourless crystals of m.p. 76-78° (lit.[205] 76-78°).

^1H nmr ($CDCl_3$) δ 1.48 (s, 3H); 3.80 (br s, 1H, exchanged with D_2O); 6.09 (d, J ~ 10 Hz, 2H); 6.91 (d, J ~ 10 Hz, 2H).

Preparation of 2,4-dimethyl-4-hydroxycyclohexa-2,5-dienone (269)

2,4-Dimethyl-4-hydroperoxycyclohexa-2,5-dienone (274) was prepared

from 2,4-xylenol (264) and reduced over 6 days using the same method as for the monomethyl hydroperoxide (273). The resulting crude 2,4-dimethyl-4-hydroxycyclohexa-2,5-dienone was purified by recrystallisation from chloroform/pet. ether giving white crystals (51.5% yield), m.p. 69-73° (lit.[135] 73°).

^{1}H nmr ($CDCl_3$) δ 1.44 (s, 3H); 1.84 (d, J ~ 2 Hz, 3H); 3.10 (br s, 1H, exchanged with D_2O); 6.09 (d, J ~ 10 Hz); 6.69 (m, 1H); 6.88 (dd, J ~ 10 Hz, J ~ 2 Hz, 1H).

Preparation of 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (270)

4-Hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (275) was prepared from mesitol (265) according to the literature method of Barton.[135] Recrystallisation from chloroform/pet. ether gave white crystals (76.7% yield) of m.p. 97.5-99° (lit.[135] 98-99°).

^{1}H nmr ($CDCl_3$) δ 1.35 (s, 3H); 1.88 (s, 6H); 6.66 (s, 2H); 8.84 (br s, 1H).

The hydroperoxide (275) was reduced over 7 days as before giving a virtually quantitative yield of crude 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (270). Recrystallisation from chloroform/pet. ether gave white crystals of m.p. 45-46° (lit.[206] 45.5-46°).

^{1}H nmr ($CDCl_3$) δ 1.40 (s, 3H); 1.80 (s, 6H); 3.41 (br s, 1H, exchanged with D_2O); 6.63 (s, 2H).

Preparation of 2-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (271)

2-t-Butyl-4-hydroperoxy-4-methylcyclohexa-2,5-dienone (276) was prepared from 2-t-butyl-4-methylphenol (266) in 89.8% yield using the above precedure. Recrystallisation from chloroform/pet. ether gave white crystals, m.p. 101-102°.

^{1}H nmr ($CDCl_3$) δ 1.12 (s, 9H); 1.28 (s, 3H); 6.06 (d, J ~ 11 Hz, 1H); 6.57 (d, J ~ 2 Hz, 1H); 6.71 (dd, J ~ 11 Hz, J ~ 2 Hz, 1H); 8.54 (br s, 1H).

The hydroperoxide (276) was reduced as before to give 2-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (271) in 73.5% yield with m.p. 99-100° after recrystallisation from chloroform/pet. ether.

^{1}H nmr ($CDCl_3$) δ 1.19 (s, 9H); 1.42 (s, 3H); 2.50 (br s, 1H); 5.99 (d, J ~ 10 Hz, 1H); 6.63 (d, J ~ 3 Hz, 1H); 6.76 (dd, J ~ 10 Hz, J ~ 3 Hz, 1H).

Preparation of 2,6-di-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (272)

2,6-Di-t-butyl-4-hydroperoxy-4-methylcyclohexa-2,5-dienone (277) was prepared from 2,6-di-t-butyl-4-methylphenol (267) in 67.5% yield according to the literature method of Barton.[135] Recrystallisation from pet. ether gave pale yellow crystals, m.p. 113.5-115° (lit.[135] 115-116°).

^{1}H nmr ($CDCl_3$) δ 1.24 (s, 18H); 1.37 (s, 3H); 6.58 (s, 2H); 7.71 (br s, 1H).

The hydroperoxide (277) was reduced as before to give 2,6-di-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (272) in 80% yield with m.p. 112-113° (lit.[135] 112-113°).

^{1}H nmr ($CDCl_3$) δ 1.20 (s, 18H); 1.39 (s, 3H); 2.10 (br s, 1H exchanged with D_2O); 6.54 (s, 2H).

Epoxidation of p-toluquinol (268)[160]

(a) To a stirred solution of toluquinol (1.729 g) in absolute ethanol (40 ml) at 0°C was added hydrogen peroxide (30%, 4.0 ml) and sodium hydroxide (400 mg). After 24 hours tlc suggested there was little or no toluquinol left and potassium iodide/starch papers confirmed the absence of hydrogen peroxide. The solution was decanted from the sticky solid which had precipitated and this solid washed with ethanol. The solvent was evaporated from the combined organic solutions and the dark red residue extracted with ethyl acetate (100 ml). This solution was dried over anhydrous magnesium sulphate, then filtered and the solvent evaporated. Although tlc and ^{1}H nmr showed this residue to be a complex mixture,

flash chromatography led to isolation of the diepoxide (291) (136 mg, 6.3% yield) which recrystallised from chloroform/pet. ether as colourless needles, m.p. 130-131° (lit.[160] 128-133°).

^{1}H nmr ($CDCl_3$) δ 1.45 (s, 3H); 3.24 (br s, 1H, exchanged with D_2O), 3.50 (s, 4H).

ir (CCl_4) 3575, 3400, 1725, 1705 cm^{-1}.

m/e 156 ($M^{\oplus}$; 10.5), 43 (100.0).

(b) To toluquinol (135 mg) was added an ether solution of hydrogen peroxide (1.5 M, 10 ml) and Amberlyst-15 (0.5 g) at room temperature.[46] (The ether solution of hydrogen peroxide (1.5 M, 10 ml) was prepared as follows – hydrogen peroxide (30%, 6 ml) was extracted with ether (60 ml) and the organic phase dried over anhydrous magnesium sulphate. After filtering off the solid, a portion of the filtrate was titrated with a standardised aqueous solution of acidified potassium permanganate. This showed the filtrate was 0.5 M in hydrogen peroxide. Concentration of 30 ml of the filtrate to 10 ml afforded the required solution). The reaction was monitored by tlc. After 48 hours the reaction mixture was filtered and the filtrate diluted with ether (30 ml). To this solution was added excess solid sodium sulphite and the reduction of the residual hydrogen peroxide monitored using potassium iodide/starch papers. The solid was filtered and the solvent evaporated from the filtrate. An ^{1}H nmr spectrum of the residue (108 mg) was uninterpretable and showed no evidence for the formation of any epoxide products.

Epoxidation of 2,4-dimethyl-4-hydroxycyclohexa-2,5-dienone (269)

(a) To a stirred solution of 2,4-dimethyl-4-hydroxycyclohexa-2,5-dienone (336 mg) in ethanol (5 ml) was added hydrogen peroxide (30%, 0.5 ml) and sodium hydroxide (50 mg). The reaction was monitored by tlc which still showed the presence of dienone (269) after 12 days. Despite this, the

reaction mixture was diluted with water (10 ml) and this solution extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts left a solid residue (152 mg) whose ^1H nmr spectrum showed it to be a mixture of the dienone (269) and the diepoxide (295) in the ratio 1:2. Recrystallisation from chloroform/pet. ether gave pure diepoxide (295) (42 mg, 12.4% yield), m.p. 142-145°.

^1H nmr ($CDCl_3$) δ 1.39 (s, 6H); 3.08 (br s, 1H); 3.29 (m, 1H); 3.47 (d, J ~ 2 Hz, 2H).

ir (CCl_4) 3580, 3500, 1710 cm^{-1}.

m/e 170 ($M^{\oplus}$; 5.5), 43 (100.0).

Analysis: Found C, 56.48; H, 5.87. $C_8H_{10}O_4$ requires C, 56.47; H, 5.92.

Crystal Data. $C_8H_{10}O_4$: M = 170.17, triclinic, space group $P\bar{1}$, a = 6.234, b = 7.124, c = 10.166, Å, α = 100.54°, β = 104.95 , γ = 100.59 , U = 416.0 $Å^3$, Z = 2, D_c = 1.36 g cm^{-3}. T = 293 K. R = 0.037, R′ = 0.049 for 1282 independent reflections with $F_o^2 > 2\sigma(F_o^2)$.

(b) To a stirred solution of the dienone (269) (168 mg) in ethanol (14 ml) was added hydrogen peroxide (30%, 4ml) and a solution of sodium hydroxide (112 mg) in water (2 ml). Tlc after 4 hours showed there was no dienone (269) present. The reaction mixture was diluted with water (50 ml) and extracted with chloroform (4 x 50 ml). Evaporation of the solvent from the combined extracts gave the diepoxide (295) (25 mg, 12.1% yield).

Attempted epoxidation of 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (270)[165]

To a stirred solution of 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (270) (184 mg) in ethanol (14 ml) was added hydrogen peroxide (30%, 4ml) and a solution of sodium hydroxide (112 mg) in water (2 ml). The reaction was monitored by tlc which still showed the presence of

dienone (270) after 10 days. Despite this, the reaction mixture was diluted with water (50 ml) and extracted with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts left an oily residue (60 mg) whose ^1H nmr spectrum showed it to be crude recovered dienone (270).

Base-catalysed rearrangement of 4-hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (275)

To a stirred solution of 4-hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (275) (168 mg) in ethanol (3 ml) was added a solution of sodium hydroxide (40 mg) in water (1.5 ml). The reaction was monitored by tlc using two elutions with dichloromethane. This showed the gradual disappearance of the hydroperoxide (275) while two new spots of lower Rf became visible. One of these had the same Rf as 4-hydroxy-2,4,6-trimethyl-cyclohexa-2,5-dienone (270). After 45 minutes the reaction mixture was neutralised with dilute sulphuric acid. The solution was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent gave an oil (181 mg).

^1H nmr ($CDCl_3$): this showed, in addition to prominent peaks associated with the alcohol (270) and residual chloroform, the following resonances suggesting the product contained about 15% 2,3-epoxy-4-hydroxy-2,4,6-trimethylcyclohex-5-one (298): δ 1.25 (s); 1.48 (s); 3.44 (d, J ~ 3 Hz); 6.20 (s).

Epoxidation of 2-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (271)[166]

(a) To a stirred solution of 2-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (660 mg) in ethanol (10 ml) was added hydrogen peroxide (30%, 1.0 ml) and sodium hydroxide (100 mg). The reaction was monitored by tlc which still showed the presence of dienone (271) after 6 days. Despite this, the reaction mixture was diluted with water (20 ml) and extracted

with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts left a solid residue (340 mg) whose ^{1}H nmr spectrum showed it to be a mixture of the dienone (271), monoepoxide (301) and diepoxide (300) in about the ratio 1:2:30. Recrystallisation from chloroform/pet. ether gave pure diepoxide (300), m.p. 100-103.5° (lit.[166] 112-114°).

^{1}H nmr ($CDCl_3$) δ 1.00 (s, 9H); 1.37 (s, 3H); 2.50 (br s, 1H); 3.40 (m, 3H).

ir (CCl_4) 3580, 3500, 1710, 1685 cm^{-1}.

m/e 212 ($M^{\oplus}$; 4.0), 58 (100.0).

Analysis: Found C, 62.39; H, 7.72. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60.

(b) To a stirred solution of the dienone (271) (109 mg) in ethanol (7 ml) was added hydrogen peroxide (30%, 2 ml) and a solution of sodium hydroxide (56 mg) in water (1 ml). Tlc after 4 hours showed there was no dienone (271) present. The reaction mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). Evaporation of the solvent from the combined extracts gave the diepoxide (300) (23 mg, 17.9% yield).

(c) To a stirred solution of the dienone (271) (340 mg) in methanol (6 ml) was added hydrogen peroxide (30%, 0.66 ml) and aqueous sodium carbonate (3M, 0.17 ml). After 7 days the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts left a solid residue (367 mg) whose ^{1}H nmr spectrum showed it to be a mixture of the dienone (271), monoepoxide (301) and diepoxide (300) in about the ratio 5:1:2. The components of this mixture were separated by preparative tlc. The plate was eluted several times with 10% ethyl acetate in pet. ether to effect separation. This gave the monoepoxide (301) which on recrystallisation from chloroform/pet. ether had m.p. 114-117° (lit.[166] 114-116°).

^{1}H nmr ($CDCl_3$) δ 1.27 (s, 9H); 1.42 (s, 3H); 2.35 (br s, 1H, exchanged

with D_2O); 3.48 (d, J = 6 Hz, 1H); 3.50-3.64 (dd, J = 6 Hz, J = 3 Hz, 1H); 6.22 (d, J = 3 Hz, 1H).

(d) To a stirred solution of the dienone (271) (427 mg) in dichloromethane (40 ml) was added mcpba (854 mg). After 4 days the reaction mixture was washed with saturated aqueous sodium metabisulphite (100 ml). The aqueous phase was back-extracted with dichloromethane (2 x 60 ml) and the combined organic liquors washed with saturated aqueous sodium carbonate (2 x 75 ml). Evaporation of the solvent left a solid residue (629 mg) whose ^1H nmr spectrum showed it to be a mixture of the dienone (271), monoepoxide (302) and diepoxide (300) in about the ratio 1:8:6. The components of this mixture were separated by preparative tlc. The plate was eluted several times with 10% ethyl acetate in pet. ether to effect separation. This gave the monoepoxide (302) which on recrystallisation from chloroform/pet. ether had m.p. 74-77° (lit.[166] 70-75°). ^1H nmr ($CDCl_3$) δ 1.08 (s, 9H); 2.25 (br s, 1H); 3.40 (s, 3H); 3.59 (d, J = 3 Hz, 1H); 5.71 (d, J = 11 Hz, 1H); 6.33 (dd, J = 11 Hz, J = 3 Hz, 1H).

(e) To the dienone (271) (424 mg) was added an ether solution of hydrogen peroxide (1.5 M, 20 ml) and Amberlyst-15 (1.0 g) at room temperature.[46] After 8 days the reaction mixture was filtered and the filtrate diluted with ether (30 ml). To this solution was added excess sodium sulphite and anhydrous magnesium sulphate. The reduction of the residual hydrogen peroxide was monitored using potassium iodide/starch papers. The mixture was filtered and the solvent evaporated. An ^1H nmr spectrum of the solid residue (423 mg) showed it to be starting dienone (271).

Epoxidation of 2,6-di-t-butyl-4-hydroxy-4-methylcyclohex-2,5-dienone (272)[165]

To a stirred solution of 2,6-di-t-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (272) (286 mg) in ethanol (14 ml) was added hydrogen peroxide (30%, 4 ml) and a solution of sodium hydroxide (112 mg) in water (2 ml).

The reaction was monitored by tlc which still showed the presence of dienone (272) after 10 days. Despite this, the reaction mixture was diluted with water (50 ml) and extracted with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts left a solid residue (237 mg) whose ^{1}H nmr spectrum showed it to be a mixture of the dienone (272) and diepoxide (303) in the ratio 3:7. Recrystallisation from pet. ether gave pure diepoxide (303), m.p. 140-142° (lit.[167] 141-142°).

^{1}H nmr ($CDCl_3$) δ 1.03 (s, 18H); 1.48 (s, 3H); 1.75 (br s, 1H); 3.39 (s, 2H).

ir (CCl_4) 3580, 3480, 1710, 1480, 1460, 1445 cm^{-1}.

m/e 269 (1.3), 268 ($M^{\oplus}$; 7.7), 57 (100.0).

Analysis: Found C, 66.84; H, 9.07. $C_{15}H_{24}O_4$ requires C, 67.14; H, 9.01.

Preparation of 4-methoxy-4-methylcyclohexa-2,5-dienone (305)

To a stirred solution of p-cresol (541 mg) in anhydrous methanol (20 ml) at 0°C was added powdered potassium carbonate (1.38 g) and a solution of PIFA (2.15 g) in acetonitrile.[138] After 10 minutes the reaction mixture was diluted with water (100 ml) and extracted with chloroform (3 x 60 ml). The solvent was evaporated from the combined extracts and the resulting product was purified by flash chromatography. This gave pure 4-methoxy-4-methylcyclohexa-2,5-dienone (305) (316 mg, 45.8% yield) which on recrystallisation from ether/pet. ether had m.p. 61-62.5° (lit.[168] 62-63°).

^{1}H nmr ($CDCl_3$) δ 1.41 (s, 3H); 3.18 (s, 3H); 6.28 (d, J = 11 Hz, 1H); 6.76 (d, J = 11 Hz, 1H).

Epoxidation of 4-methoxy-4-methylcyclohexa-2,5-dienone (305)

(a) To a stirred solution of 4-methoxy-4-methylcyclohexa-2,5-dienone (305) (285 mg) in methanol (1 ml) was added hydrogen peroxide (30%, 0.7 ml)

and sodium hydroxide (175 mg). The reaction was monitored by tlc. After 24 hours the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts gave the diepoxide (306) (77 mg, 16.2% yield) which, after purification by flash chromatography and recrystallisation from ether/pet. ether, had m.p. 64-65°.

^{1}H nmr ($CDCl_3$) δ 1.67 (s, 3H); 3.38 (s, 3H); 3.4-3.5 (m, 4H).

^{13}C nmr ($CDCl_3$) δ 22.3 (q); 51.7 (q); 55.9 (d); 63.4 (d); 70.4 (s); 199.5 (s). Multiplicities assigned from DEPT experiments.

ir (KBr disc) 1715, 1705 cm^{-1}.

m/e 170 ($M^{\oplus}$; 8.9), 155 (4.8), 29 (100.0).

NOE: ^{1}H nmr ($CDCl_3/C_6D_6$) - irradiation of the methyl resonance at δ 1.67 resulted in significant enhancement of only one half of the symmetrical multiplet, between δ 3.40-3.45. The other half, between δ 3.45-3.50, appeared to have increased marginally.

(b) To a stirred solution of the dienone (305) (130 mg) in methanol (3 ml) was added hydrogen peroxide (30%, 0.33 ml) and aqueous sodium carbonate (3 M, 0.086 ml). After 3 weeks the reaction mixture was diluted with water (30 ml) and extracted with chloroform (4 x 25 ml). Evaporation of the solvent from the combined extracts left a residue (73 mg) whose ^{1}H nmr spectrum showed it to be a mixture of the dienone (305) and diepoxide (306) in about the ratio 7:1. Neither this spectrum nor tlc showed evidence for the presence of another epoxide product.

Preparation of 4-ethoxycarbonyl-3-methylcyclohex-2-enone (308)[178,179]

(a) 4-Ethoxycarbonyl-3-methylcyclohex-2-enone (Hagemann's ester) (308) was prepared according to the literature method by condensing two

equivalents of ethyl acetoacetate with formaldehyde in the presence of piperidine, and treating the product with sodium ethoxide.[178] Distillation of the product afforded pure Hagemann's ester (58% yield), b.p. 100-105°/ 0.5 mm Hg.

(b) Using the method of Golding[179] pure Hagemann's ester (52.4% yield) was obtained after distillation.

^{1}H nmr ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3H); 2.00 (br s, 3H); 1.8-3.0 (m, 4H); 3.17-3.35 (br t, 1H); 4.21 (q, J = 7 Hz, 2H); 5.95 (m, 1H).

ir ($CHCl_3$) 1735, 1675, 1640 cm^{-1}

m/e 183 (1.9), 182 ($M^{\oplus}$; 14.8), 98 (100.0).

uv λ_{max} (EtOH) 228 nm (ϵ 10900).

Preparation of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309)[175]

Using the method of Stoodley[175] Hagemann's ester (308) was hydroxylated by stirring with activated charcoal (Darco G-60, 100-325 mesh powder) in ethyl acetate open to the air. The reaction was monitored by tlc which showed clean conversion of starting mixture (308), Rf 0.40, to 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309), Rf 0.25. The reaction was repeated several times, sometimes with added triethylamine which, as reported, halved the amount of charcoal required and reduced the reaction time from 3 days to 1 day. The best yield of hydroxy ester (309) obtained was 59.4% after purification by flash chromatography.

^{1}H nmr ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 3H); 1.92 (br s, 3H); 2.0-2.8 (m, 4H); 4.1 (br s, 1H, exchanged with D_2O); 4.34 (q, J = 7 Hz, 2H); 5.99 (m, 1H).

ir ($CHCl_3$) 3525, 1735, 1680, 1640, 1450 cm^{-1}.

m/e 199 (2.4); 198 ($M^{\oplus}$, 16.8), 125 (100.0).

On one occasion, ethyl 4-hydroxy-2-methylbenzoate (310) was isolated (13.6% yield) after flash chromatographing a reaction mixture which contained triethylamine and which had been stirring for 11 days.

Recrystallisation from ether/pet. ether gave (310) as white needles which on heating underwent a polymorphic change along with melting at 90.5-92°. The newly formed plate crystals had m.p. 98.5-99° (lit.[207] needles, 91-92°; plates 98-99°).

^{1}H nmr ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3H); 2.57 (s, 3H); 4.35 (q, J = 7 Hz, 2H); 6.5 (br s, 1H, exchanged with D_2O); 6.63-6.82 (m, 2H); 7.90 (d, J = 10 Hz, 1H).

ir ($CHCl_3$) 3580, 3350, 1695, 1685, 1600, 1575, 1490, 1450 cm^{-1}.

m/e 182 (0.2), 181 (3.4), 180 ($M^{\oplus}$; 31.8), 135 (100.0).

Epoxidation of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309)

(a) To a stirred solution of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) (419 mg) in ethanol (2.5 ml) was added hydrogen peroxide (30%, 0.6 ml) and aqueous sodium hydroxide (6 M, 0.16 ml). The reaction was monitored by tlc. After 2¼ hours the reaction mixture was diluted with water (20 ml) and extracted with chloroform (3 x 20 ml). Evaporation of the solvent from the combined extracts gave the cis epoxy alcohol (311) (381 mg, 84.1% yield) which on recrystallisation from ethyl acetate/pet. ether had m.p. 46-48°.

^{1}H nmr ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H); 1.30 (s, 3H); 1.62-1.81 (m, 1H); 2.12-2.53 (m, 3H); 3.17 (s, 1H); 3.74 (br s, 1H); 4.20 (q, J = 7.2 Hz, 2H).

^{13}C nmr ($CDCl_3$) δ 13.7 (q); 15.8 (q); 28.1 (t); 33.2 (t); 62.9 (t); 63.2 (d); 64.5 (s); 75.6 (s); 173.4 (s); 204.2 (s). Multiplicities assigned from DEPT experiments.

ir ($CHCl_3$) 3520, 1730, 1450, 1405 cm^{-1}.

m/e 214 ($M^{\oplus}$; 6.8), 141 (100.0).

Analysis: Found C, 56.07; H, 6.58. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.59.

Both tlc and ^{1}H nmr of the mother liquors from the above recrystallisation showed no trace of the isomeric trans epoxy alcohol (312).

(b) To the γ-hydroxy enone (309) (450 mg) was added t-butylhydroperoxide (150 mg) and molybdenum hexacarbonyl (10 mg).[100] This mixture, from which atmospheric moisture was excluded, was heated to 60°. After 2 weeks the reaction mixture was diluted with ether (50 ml) and washed with water (2 x 20 ml). Evaporation of the solvent left an oily residue (408 mg). Tlc and an ^1H nmr spectrum of this showed it was mainly unreacted enone (309) though the cis epoxy alcohol (311) had been formed in low yield (<5%).

(c) To the γ-hydroxy enone (309) (396 mg) was added an ether solution of hydrogen peroxide (1.5 M, 10 ml) and Amberlyst 15 (0.5 g).[46] The reaction was monitored by tlc which still showed the presence of enone (309) after 5 days. Despite this, the reaction mixture was diluted with ether (30 ml) and filtered. The residual hydrogen peroxide, detected by potassium iodide/starch papers, was reduced by washing the filtrate with saturated aqueous sodium sulphite (2 x 30 ml). Evaporation of the solvent left an oil (139 mg). Tlc and an ^1H nmr spectrum of the product showed it to be a mixture of the enone (309), cis epoxy alcohol (311) and trans epoxy alcohol (312) in about the ratio 16:12:1. (Physical and spectral characteristics of (312) are reported later).

(d) To a stirred solution of the γ-hydroxy enone (309) (896 mg) in dichloromethane (30 ml) was added mcpba (2.0 g) and 2,2′-thiobis(4-methyl-6-t-butylphenol) (~3 mg). This mixture was heated to reflux and the reaction monitored by tlc. After 2 days more mcpba (1.5 g) was added. After a further 3 days the reaction mixture was diluted with dichloromethane (100 ml) and washed with saturated aqueous sodium sulphite (3 x 50 ml) and saturated aqueous sodium bicarbonate (3 x 50 ml). Evaporation of the solvent gave the lactone (313) (662 mg, 79.6%). This product which is a viscous oil was purified by flash chromatography and distillation.

^{1}H nmr ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H); 1.99 (s, 3H); 2.37-2.74 (m, 4H); 4.13 (q, J = 7.1 Hz, 2H).

^{13}C nmr ($CDCl_3$) δ 13.4 (q); 20.2 (q); 26.3 (t); 30.7 (t); 62.5 (t); 100.7 (s); 165.7 (s); 168.4 (s); 173.6 (s). Multiplicities assigned from DEPT experiments.

ir ($CHCl_3$) 1810, 1760 cm^{-1}

m/e 185.0809 ($C_9H_{13}O_4$; 1.51), 184.0743 ($C_9H_{12}O_4$; M$^{\oplus}$; 1.14), 183.0670 ($C_9H_{11}O_4$; 1.53).

When the above reaction mixture was buffered with sodium dihydrogen phosphate (0.8 g) no reaction took place.

Reduction of the cis epoxy alcohol (311)

An ethanolic solution of sodium phenylselenide was prepared by reduction of diphenyl diselenide (758 mg) with sodium borohydride (185 mg) in absolute ethanol (10 ml).[181] The resulting colourless solution was immediately added to a stirred solution of the cis epoxy alcohol (345 mg) in absolute ethanol (6.5 ml) at 0°C, with the exclusion of atmospheric moisture.[182] After 5 minutes the reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (30 ml). After evaporating the solvent, the crude product mixture was flash chromatographed. This gave 3,4-dihydroxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (314) (50 mg, 14.4% yield) which on recrystallisation from chloroform/pet. ether had m.p. 77.5-79.5°.

^{1}H nmr ($CDCl_3$) δ 1.23 (s, 3H); 1.33 (t, J = 7 Hz, 3H); 1.7-3.0 (m, 6H); 3.00 (br s, 1H); 4.04 (br s, 1H); 4.34 (q, J = 7 Hz, 2H).

ir ($CHCl_3$) 3550, 3500, 1710 cm^{-1}.

m/e 217 (0.85), 216 (M$^{\oplus}$; 6.55), 43 (100.0).

Attempted formation of the acetonide (315)

(a) To a solution of the cis diol (314) (27 mg) in analar acetone (1.4 ml) was added anhydrous copper sulphate (84 mg). The mixture was heated to reflux.[184] After 48 hours tlc showed only the presence of starting material so the reaction mixture was filtered, the solvent evaporated and the diol recovered quantitatively.

(b) To a solution of the cis diol (314) (27 mg) in chloroform (2.5 ml) was added analar acetone (0.3 ml) and a few crystals of pyridinium p-toluenesulphonate.[185] The reaction was monitored by tlc which showed only the presence of starting diol after 6 days. More acetone (1 ml) was added and the solution heated to reflux. Over the following week, as a new spot of higher Rf than that of the diol became apparent, a further 5 ml of acetone was added. The solvent was evaporated and the residue dissolved in chloroform (25 ml). This solution was washed with water (15 ml) and the solvent evaporated. An ^1H nmr spectrum of the product (26 mg) showed it to be the γ-hydroxy enone (309).

Preparation of 4-methoxycarbonyl-3-methylcyclohex-2-enone (316)[179]

The methyl analogue of Hagemann's ester (316) was prepared according to the method of Golding.[179] The crude product was purified by fractional distillation using a Kugelrohr apparatus. The first fraction, b.p. 130-160°/0.1 mm Hg, was pure ester (316).

^1H nmr ($CDCl_3$) δ 1.8-3.0 (m, 6H); 2.00 (br s, 3H); 3.30 (br t, 1H); 3.75 (s, 3H); 5.94 (m, 1H).

The second fraction, b.p. 160-180°/0.1 mm Hg, was a mixture of the ester (316) and methyl 3,4,5,6-tetrahydro-2-oxo-7-methyl-4a(2H)-naphthalene-carboxylate (317). On standing crystals of (317) precipitated from this oily mixture. These were removed and washed with cold ether. Recrystallisation from ether gave (317) as fine white needles, m.p. 119-121°.

^{1}H nmr ($CDCl_3$) δ 1.45-2.60 (m, 8H); 1.88 (br s, 3H); 3.71 (s, 3H); 5.81 (s, 1H); 6.10 (br s, 1H).

ir (CCl_4) 1730, 1670, 1630, 1595, 1450, 1430 cm^{-1}.

m/e 220 (0.5), 221 (7.1), 220 ($M^{\oplus}$; 43.9), 105 (100.0).

uv λ_{max} (EtOH) 290 nm (ϵ 23000).

Analysis: Found C, 70.85; H, 7.36. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32.

When the above reaction was repeated using two equivalents of but-3-en-2-one for every one of methyl acetoacetate the proportion of this minor product (317) with respect to (316) increased to 1:2.

Preparation of 4-hydroxy-4-methoxycarbonyl-3-methylcyclohexenone (319)

4-Methoxycarbonyl-3-methylcyclohex-2-enone (316) was treated with activated charcoal in ethyl acetate as for the ethyl ester (308).[175] This gave, after purification by flash chromatography, 4-hydroxy-4-methoxycarbonyl-3-methylcyclohex-2-enone (319) in 38.7% yield, which crystallised on standing. Recrystallisation from chloroform/pet. ether gave colourless plates, m.p. 100-101°.

^{1}H nmr ($CDCl_3$) δ 1.88 (br s, 3H); 2.08-2.72 (m, 4H); 3.85 (s, 3H); 4.10 (br s, 1H); 5.97 (m, 1H).

ir ($CHCl_3$) 3500, 1725, 1665, 1430 cm^{-1}.

m/e 186 (0.4), 185 (3.0), 184 ($M^{\oplus}$; 27.2), 125 (100.0).

Analysis: Found C, 58.63; H, 6.58. $C_9H_{12}O_4$ requires C, 58.69; H, 6.57.

Epoxidation of 4-hydroxy-4-methoxycarbonyl-3-methylcyclohex-2-enone (319)

(a) To a stirred solution of 4-hydroxy-4-methoxycarbonyl-3-methylcyclohex-2-enone (319) (368 mg) in methanol (3 ml) was added hydrogen peroxide (30%, 1.2 ml) and aqueous sodium hydroxide (6 M, 0.16 ml). The reaction was monitored by tlc. After 2¾ hours the reaction mixture was diluted with water (25 ml) and extracted with chloroform (4 x 25 ml). Evaporation

of the solvent from the combined extracts gave a crystalline mixture of the cis epoxy alcohol (320) and trans epoxy alcohol (392 mg, 98.0% yield). Recrystallisation from chloroform/pet. ether afforded pure cis epoxy alcohol (320) (302 mg, 75.5% yield), m.p. 101-102.5°.

^{1}H nmr ($CDCl_3$) δ 1.38 (s, 3H); 1.68-2.67 (m, 4H); 3.26 (s, 1H); 3.72 (br s, 1H); 3.84 (s, 3H).

ir ($CHCl_3$) 3580, 3520, 1730, 1720, 1440, 1430 cm^{-1}.

m/e 200 ($M^{\oplus}$; 2.9), 125 (100.0).

Analysis: Found C, 54.04; H, 6.02. $C_9H_{12}O_5$ requires C, 53.99; H, 6.04.

^{1}H nmr spectra of the above product mixture and the evaporated mother liquors from the recrystallisation showed the trans epoxy alcohol constituted ~3% of the initial epoxide mixture. The spectrum of the evaporated mother liquors showed singlets at δ 1.51 and δ 3.13 consistent with the methyl and epoxide protons of the trans epoxy alcohol. Tlc showed the trans isomer had higher Rf.

(b) To a stirred solution of the γ-hydroxy enone (316) (237 mg) in benzene (3 ml) was added t-butylhydroperoxide (0.14 ml) and molybdenum hexacarbonyl (9.5 mg).[102] After 2 days more t-butylhydroperoxide (0.2 ml) was added. After a further 3 days the reaction mixture was diluted with ether (30 ml) and washed with saturated aqueous sodium sulphite (2 x 20 ml). Evaporation of the solvent left a residue (155 mg). Tlc and an ^{1}H nmr spectrum of the product showed it was mainly unreacted enone (316) though the cis epoxy alcohol (319) had been formed in low yield.

(c) The γ-hydroxy enone (316) was treated with per-Amberlyst 15[46] using the same method as had been employed for the ethyl ester (309). The starting enone and the cis and trans epoxy alcohols were formed in a ratio similar to that of experiment (a).

(d) To a stirred solution of t-butylhydroperoxide (0.8 ml of a 3 M toluene solution) in freshly distilled tetrahydrofuran (15 ml) at -78° was

added methyl lithium (1.2 ml of a 1.5 M ether solution) and a solution of the enone (319) (300 mg) in tetrahydrofuran (1.5 ml), with the exclusion of atmospheric moisture. The reaction mixture was allowed to slowly warm to room temperature. After 3 hours the solvent was evaporated, the residue treated with saturated aqueous ammonium sulphate (30 ml) and this solution extracted with chloroform (4 x 20 ml). Evaporation of the solvent from the combined extracts left an oily residue (358 mg). Tlc and ^{1}H nmr of this product showed it to be a mixture of starting enone (319) and 4-t-butyloxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone resulting from trans-esterification. No evidence for any epoxide formation was detected.

Under the same conditions, and as reported by Meth-Cohn,[65] methyl crotonate (114) was completely oxidised within 2 hours affording a 2:1 mixture of methyl 2,3-epoxybutanoate (115) and t-butyl 2,3-epoxybutanoate (~40% combined yield). The ratio was determined from the integrals of an ^{1}H nmr spectrum of the mixture.

^{1}H nmr ($CDCl_3$) δ 1.24-1.5 (m, methyl protons of both compounds); 1.50 (s, t-butyl ester); 3.04-3.28 (m, epoxide protons of both compounds); 3.77 (s, methyl ester).

ir (CCl_4) 1745, 1730 cm^{-1}.

Transesterification of the cis epoxy alcohol (311)

To a solution of the ethyl ester (311) (124 mg) in methanol (6 ml) was added sodium cyanide (3 mg) and the mixture heated to 50°.[187] After 3 days tlc showed complete conversion of (311) to the methyl ester (320). The methanol was evaporated and the residue dissolved in chloroform (50 ml). This solution was washed with water (50 ml). Evaporation of the solvent gave the crystalline methyl ester (320) (116 mg, 100% yield) with identical physical and spectral characteristics to those reported above.

Preparation of 4-ethoxycarbonyl-4-methoxymethoxy-3-methylcyclohex-2-enone (321)

To a stirred solution of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) (1.14 g) in chloroform (48 ml) and methylal (48 ml) was added phosphorus pentoxide (23.7 g) which rapidly became a brown gelatinous solid.[189] After 45 minutes the solution was decanted and the residual solid washed with chloroform (2 x 50 ml). The combined organic liquors were washed with aqueous potassium carbonate (0.5 M, 4 x 300 ml) and the solvent evaporated. The crude product was purified by flash chromatography affording 4-ethoxycarbonyl-4-methoxymethoxy-3-methyl-cyclohex-2-enone (321) (612 mg, 43.9% yield).

^{1}H nmr ($CDCl_3$) δ 1.29 (t, 3H, J = 7 Hz); 2.01 (br s, 3H); 2.1-2.8 (m, 4H); 3.40 (s, 3H); 4.25 (q, J = 7 Hz, 2H); 4.86 (s, 2H); 5.98 (m, 1H).

Epoxidation of 4-ethoxycarbonyl-4-methoxymethoxy-3-methylcyclohex-2-enone (321)

To a stirred solution of 4-ethoxycarbonyl-4-methoxymethoxy-3-methyl cyclohex-2-enone (321) (612 mg) in methanol (15 ml) was added hydrogen peroxide (30%, 1.5 ml) and a solution of sodium hydroxide (289 mg) in water (1.5 ml). After 3 hours the reaction mixture was diluted with water (100 ml) and extracted with chloroform (3 x 60 ml). The combined extracts were evaporated giving a 1:1 mixture of the cis and trans epoxy ethers (322) and (323) (458 mg, 70.2% yield). This crude product was purified by flash chromatography to give a clean mixture of the epoxides (322) and (323) (308 mg, 47.2% yield).

cis epoxy ether (322): ^{1}H nmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H); 1.46 (s, 3H); 1.95-2.71 (m, 4H); 3.21 (s, 1H); 3.47 (s, 3H); 4.26 (q, J = 7 Hz, 2H); 4.98 (s, 2H).

trans epoxy ether (323): ^{1}H nmr ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3H); 1.40 (s, 3H); 1.75-2.75 (m, 4H); 3.14 (s, 1H); 3.35 (s, 3H); 4.33 (q, J = 7 Hz, 2H); 4.75 (d, J = 9 Hz, 1H); 4.96 (d, J = 9 Hz, 1H).

Conversion of the cis epoxy alcohol (311) to its MOM ether (322)

The cis epoxy ether (322) was prepared from the cis epoxy alcohol (311) in 97.0% yield using the method previously mentioned. The ^{1}H nmr spectrum of the product was identical to that reported above.
m/e 258 ($M^{\oplus}$; 0.0), 45 (100.0).

Attempted cleavage of the 1:1 mixture of cis and trans epoxy ethers (322) and (323)

Depending on the conditions, treatment of the 1:1 mixture of MOM ethers (322) and (323) with p-toluenesulphonic acid in methanol or methanolic thiophenol containing boron trifluoride etherate[190] either resulted in no reaction or the isolation of a product whose ^{1}H nmr spectrum was uninterpretable. Neither reagent resulted in cleavage of the MOM ethers to the alcohols (311) and (312).

Preparation of 4-t-butyldimethylsiloxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (324)

To a stirred solution of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) (395 mg) in distilled analar dichloromethane (2 ml) was added distilled 2,6-lutidine (482 mg) and distilled TBDMS triflate (793 mg) with the exclusion of atmospheric moisture.[191] After 1½ hours the reaction mixture was diluted with ether (100 ml) and washed with saturated aqueous sodium carbonate (20 ml), saturated aqueous copper sulphate (2 x 20 ml) and brine (20 ml). The solvent was evaporated from

the organic phase and the residual mixture separated by flash chromatography. This gave recovered starting material (309) (156 mg) and its TBDMS ether (324) [130 mg, 34.5% yield (based on unrecovered alcohol)]. ^{1}H nmr ($CDCl_3$) δ 0.91 (s, 9H); 1.28 (t, J = 7 Hz, 3H); 1.98 (br s, 3H); 2.0-2.95 (m, 4H); 3.23 (q, J = 7 Hz, 2H); 5.91 (m, 1H). The methyl protons of the TBDMS ether were obscured by TMS.

Epoxidation of 4-t-butyldimethylsiloxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (324)

(a) To a stirred solution of the TBDMS ether (324) (181 mg) in ethanol (2.5 ml) was added hydrogen peroxide (30%, 0.17 ml) and aqueous sodium hydroxide (1 M, 0.27 ml). The reaction was monitored by tlc and after 3¼ hours no starting material remained. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (3 x 80 ml). Evaporation of the solvent from the combined extracts gave a clean 2:3 mixture of the cis and trans epoxy ethers (325) and (326) (44 mg, 23.1% yield). ^{1}H nmr ($CDCl_3$) δ 0.13 (s, 6H); 0.17 (s, 6H); 0.82 (s, 9H); 0.91 (s, 9H); 1.23 (t, J = 7 Hz, 3H); 1.32 (t, J = 7 Hz, 3H); 1.37 (s, 6H); 2.15-2.70 (m, 8H); 3.08 (s, 1H); 3.21 (s, 1H); 4.20 (q, J = 7 Hz, 2H); 4.29 (q, J = 7 Hz, 2H). Integration indicated the following peaks were more intense: δ 0.17; 0.82; 1.23; 1.37; 3.08; 4.29. These were provisionally attributed to the trans epoxy ether (326) and this was later confirmed by the product ratio obtained after cleavage of the ethers.

(b) To a stirred solution of the TBDMS ether (324) (130 mg) in ethanol (2 ml) was added t-butylhydroperoxide (~70%, 0.4 ml) and aqueous sodium hydroxide (1 M, 0.2 ml). After 3¼ hours the reaction mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). Evaporation of the solvent from the combined extracts left an oily residue. An ^{1}H nmr spectrum of this product showed it was >95% starting TBDMS ether (324)

though a trace amount of the epoxy ethers (325) and (326) had been formed.

Cleavage of the 2:3 mixture of cis and trans epoxy ethers (325) and (326)

To the 2:3 mixture of cis and trans epoxy ethers (325) and (326) (44 mg) at 0°C was added a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1 M, 0.27 ml).[192] After 5 minutes at 0°C the reaction mixture was left at room temperature for a further 40 minutes. It was then diluted with ether (50 ml) and washed with water (2 x 10 ml). Evaporation of the solvent gave a 2:3 mixture of the cis and trans epoxy ethers (311) and (312) in quantitative yield. The cis epoxy alcohol (311) had characteristics identical to those previously reported. The physical and spectral characteristics of the trans epoxy alcohol (312) are reported later.

Preparation of 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327)

To a solution of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) (1.14 g) in chloroform (10 ml) was added triethylamine (1.15 ml), acetic anhydride (0.87 ml) and DMAP (58 mg).[140] This solution was allowed to stand overnight. After partitioning the reaction mixture between chloroform and 2 M hydrochloric acid, the organic phase was washed with saturated aqueous sodium bicarbonate. Evaporation of the solvent gave a residue which was purified by flash chromatography. This gave 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327) (996 mg, 72.1% yield) as a solid which recrystallised from chloroform/pet. ether as plates,

m.p. 72-74°.

^{1}H nmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H); 2.07 (br s, 3H); 2.12 (s, 3H); 2.2-3.22 (m, 4H); 4.26 (q, J = 7 Hz, 2H); 6.01 (m, 1H).

ir ($CHCl_3$) 1750, 1680 cm^{-1}.

m/e 241 (0.5), 240 ($M^{\oplus}$; 4.6), 43 (100.0).

Analysis: Found C, 60.21; H, 6.82. $C_{12}H_{10}O_5$ requires C, 59.99; H, 6.71.

Epoxidation of 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327)

(a) To a stirred solution of 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327) (276 mg) in benzene (0.5 ml) containing t-butylhydroperoxide (0.075 ml) was added a 40% methanolic solution of Triton B (13 mg).[64] After 24 hours potassium iodide/starch papers showed there was no t-butylhydroperoxide remaining so brine (20 ml) was added to the reaction mixture and the resulting solution extracted with chloroform (3 x 20 ml). Evaporation of the solvent from the combined extracts left a residue (299 mg). Tlc and ^1H nmr showed this was a mixture of starting enone (327) and t-butanol.

(b) To a stirred solution of the enone (327) (5.22 g) in ethanol (65 ml) was added hydrogen peroxide (30%, 7.5 ml) and aqueous sodium carbonate (3 M, 2.0 ml). The reaction was monitored by tlc which still showed the presence of starting acetate (327) after 48 hours. Despite this, most of the ethanol was evaporated and the residue diluted with water (100 ml). This solution was then extracted with chloroform (3 x 80 ml) and the solvent evaporated from the combined extracts. Since tlc and ^1H nmr showed that a significant proportion of the starting acetate (327) had been hydrolysed to the γ-hydroxy enone (309), this product mixture was acetylated with acetic anhydride, triethylamine and DMAP in chloroform. The resulting acetate mixture was then epoxidised for 72 hours under the above conditions and worked up as before. Tlc and ^1H nmr of this product showed it was a mixture of acetates and alcohols. These were separated by flash chromatography into two fractions (a) a mixture of 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327), and the two diastereomeric 4-acetoxy-2,3-epoxy-4-ethoxycarbonyl-3-methylcyclohexanones (328) and (329) (total 4.178 g, 68.2% yield) in about a 1:1:1 ratio, and (b) a mixture of

the γ-hydroxy enone (309), the cis epoxy alcohol (311) and the trans epoxy alcohol (312) (total 714 mg). On standing overnight the acetate mixture, which was a viscous oil, deposited large chunky crystals. These crystals were removed from the residual oil and washed with a chilled 1:1 solution of ether and pet. ether. Recrystallisation from chloroform/pet. ether gave the co-crystal (330), which comprised the γ-acetoxy enone (327) and the cis epoxy acetate (328) in a 1:1 ratio, as colourless plates, m.p. 68-69°.
Tlc of a single crystal confirmed the presence of both (327) and (328).
^{1}H nmr ($CDCl_3$) δ 1.26 (s, J = 7 Hz, 3H); 1.28 (t, J = 7 Hz, 3H); 1.51 (s, 3H); 2.08 (br s, 3H); 2.0-3.2 (m, 8H); 2.13 (s, 3H); 2.17 (s, 3H); 3.23 (s, 1H); 4.26 (br q, 4H); 6.01 (m, 1H).
ir ($CHCl_3$) 1740, 1675 cm^{-1}.
m/e 256 ($M^{\oplus}$; 0.2), 240 ($M^{\oplus}$; 3.6), 43 (100.0).
Analysis: Found C, 58.36; H, 6.24. $C_{24}H_{32}O_{11}$ requires C, 58.06; H, 6.50.
Crystal Data. $C_{24}H_{32}O_{11}$: M = 496.51, triclinic, space group $P\bar{1}$, a = 8.378, b = 8.834, c = 9.976, Å, α = 102.52 , β = 82.90 , γ = 62.87 ; U = 620.1 $Å^3$, Z = 1, D_c = 1.33 g cm^{-3}. T = 293 K. R = 0.056, R′ = 0.082 for 1900 independent reflections with $F_o^2 > 2\sigma(F_o^2)$.

Preparation of the trans epoxy alcohol (312)

The oil (702 mg) from which the co-crystal (330) had precipitated [and which ^{1}H nmr showed to be mainly (~80%) the trans epoxy acetate (329)] was dissolved in ethanol (7.5 ml). To this solution was added hydrogen peroxide (30%, 0.2 ml) (to convert any residual enone to epoxide) and a solution of sodium hydroxide (50 mg) in water (1 ml). The mixture was allowed to stand so that hydrolysis occurred as well as epoxidation. The hydrolysis was monitored by tlc and when no acetate remained the solution was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts gave a mixture

which comprised mainly the trans epoxy alcohol (312) but contained a small amount of the cis epoxy alcohol (311). These were separated by flash chromatography which gave pure trans epoxy alcohol (276 mg). Recrystallisation from ether gave needles, m.p. 33.5-34.5°.

^{1}H nmr ($CDCl_3$) δ 1.39 (s, 3H); 1.39 (t, J = 7.1 Hz, 3H); 1.6-1.9 (m, 1H); 2.0-2.75 (m, 3H); 3.16 (s, 1H); 3.82 (br s, 1H); 4.40 (q, J = 7.1 Hz, 2H).

^{13}C nmr ($CDCl_3$) δ 14.2 (q); 16.2 (q); 27.8 (t); 31.6 (t); 61.5 (d); 62.9 (t); 63.4 (s); 75.9 (s); 174.5 (s); 204.1 (s). Multiplicities assigned from the off-resonance decoupled spectrum.

ir ($CHCl_3$) 3520, 1730, 1710, 1600, 1440 cm^{-1}.

m/e 215 (0.7), 214 ($M^{\oplus}$; 5.4), 43 (100.0).

Acetylation of the cis epoxy alcohol (311)

The cis epoxy alcohol (311) was acetylated with acetic anhydride, triethylamine and DMAP in chloroform, as for the γ-hydroxy enone (309).[140] The acetate (328) was isolated in quantitative yield as a crystalline solid. Recrystallisation from ether gave plates, m.p. 63-65°.

^{1}H nmr ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H); 1.50 (s, 3H); 1.9-2.9 (m, 4H); 2.16 (s, 3H); 3.23 (s, 1H); 4.25 (q, J = 7 Hz, 2H).

ir ($CHCl_3$) 1740 (br) cm^{-1}.

m/e 265 ($M^{\oplus}$; 0.1), 42 (100.0).

Acetylation of the trans epoxy alcohol (312)

The trans epoxy alcohol (312) was acetylated with acetic anhydride, triethylamine and DMAP in chloroform, as for the γ-hydroxy enone (309).[140] The acetate (329) was obtained, after flash chromatographic purification, as a viscous oil in 78.3% yield.

^{1}H nmr ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3H); 1.47 (s, 3H); 2.0-3.05 (m, 4H); 2.12 (s, 3H); 3.18 (s, 1H); 4.33 (q, J = 7 Hz, 2H).

ir ($CHCl_3$) 1740, 1715 cm^{-1}.

m/e no $M^{\oplus}$, 238 (0.2), 42 (100.0).

Preparation of 4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (331)

To a stirred solution of acetoacetanilide (18.3 g) and triethylamine (12.5 ml) in absolute ethanol (150 ml) was slowly added but-3-en-2-one (7.4 ml).[203] After 24 hours the ethanol was evaporated and the residue crystallised from ethyl acetate. 2-Acetyl-5-oxohexanilide (378) (16.49 g, 64.6% yield) was obtained and on recrystallisation from ethyl acetate/pet. ether gave fine white crystals (10.91 g, 42.7% yield), m.p. 90-94°.

^1H nmr (d-6 acetone) δ 1.80-3.35 (m, 4H); 2.07 (s, 3H); 2.20 (s, 3H); 3.60 (t, J ~ 7 Hz, 1H); 6.95-7.90 (m, 5H); 9.43 (br s, 1H).

To a solution of 2-acetyl-5-oxohexanilide (3.09 g) in methanol (5 ml) was added glacial acetic acid (0.22 ml) and pyrrolidine (0.47 ml). This mixture was heated to 80° for 1 hour. The methanol was then evaporated and the residue dissolved in ethyl acetate (100 ml). This solution was washed with saturated aqueous potassium carbonate (3 x 15 ml) and brine (3 x 15 ml). Evaporation of the solvent gave crude 4-N-phenylamino-carbonyl-3-methylcyclohex-2-enone (331) (2.54 g, 88.7% yield). Purification by flash chromatography afforded crystalline material (1.442 g, 50.3% yield). Recrystallisation from ethyl acetate gave (331) as fine white needles, m.p. 118.5-119.5°.

^1H nmr (d-6 acetone) δ 1.98 (br s, 3H); 2.15-2.40 (m, 3H); 2.40-2.70 (m, 1H); 3.49 (br t, 1H); 5.93 (m, 1H); 7.07 (br t, J = 7.5 Hz, 1H); 7.30 (br t, J = 8.1 Hz, 2H); 7.68 (br d, J = 8.1 Hz, 2H); 9.60 (br s, 1H).

^{13}C nmr (d-6 acetone) δ 22.8; 27.5; 35.1; 48.9; 120.4; 124.6; 129.0; 129.4; 139.6; 159.0; 170.8; 198.3.

ir ($CHCl_3$) 3430, 3330, 1670 (br), 1600, 1520, 1500, 1435 cm^{-1}.

m/e 231 (0.8), 230 (6.0), 229 ($M^{\oplus}$; 35.9), 110 (100.0).

Analysis: Found C, 73.21; H, 6.48; N, 6.19. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11.

Preparation of 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (332)

To a stirred solution of 4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (331) (1.00 g) in ethyl acetate (20 ml) was added activated charcoal (4.00 g).[175] After 3 days tlc (developed using 30% methanol in chloroform) of the reaction mixture showed only a single spot of the same Rf as the starting material, so triethylamine (1.0 ml) was added to the reaction mixture. After a further 7 days tlc still showed no change. Despite this, the reaction mixture was filtered through celite and the filter cake washed thoroughly with ethyl acetate. Evaporation of the solvent from the filtrate left a residue which was purified by flash chromatography. This afforded 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (332) (469 mg, 43.8% yield) which on recrystallisation from chloroform/pet. ether had m.p. 112-114.5°.

^1H nmr (d-6 acetone) δ 1.94 (br s, 3H); 2.05-2.85 (m, 4H); 5.18 (br s, 1H, exchanged with D_2O); 5.90 (m, 1H); 7.12 (br t, J = 7.4 Hz, 1H); 7.33 (br t, J = 7.3 Hz, 2H); 7.77 (br d, J = 7.5 Hz, 2H); 8.75 (br s, 1H).

^{13}C nmr (d-6 acetone) δ 18.9; 34.4; 35.5; 75.9; 120.6; 124.8; 129.5; 129.8; 139.1; 159.6; 171.5; 197.7.

ir ($CHCl_3$) 3590, 3380, 1670, 1595, 1495, 1435 cm^{-1}.

m/e 247 (0.3), 246 (0.9), 245 ($M^{\oplus}$; 4.6); 126 (100.0).

Epoxidation of 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (332)

(a) To a stirred solution of 4-hydroxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (332) (300 mg) in ethanol (5 ml) was added hydrogen peroxide (30%, 0.45 ml) and aqueous sodium hydroxide (6 M, 0.11 ml). After 3 hours the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts gave a mixture of the cis epoxy alcohol (333) and trans epoxy alcohol (334) (293 mg, 91.7% yield) in the ratio 10:1. Recrystallisation of this product mixture from chloroform/pet. ether gave the cis epoxy alcohol (333) as fine white needles, m.p. 144-148.5°.

^{1}H nmr (d-6 acetone) δ 1.42 (s, 3H); 1.85-2.85 (m, 4H); 3.30 (s, 1H); 5.61 (br s, 1H, exchanged with D_2O); 7.0-7.90 (m, 5H); 9.35 (br s, 1H, exchanged with D_2O).

ir ($CHCl_3$) 3590, 3390, 1720, 1680, 1600, 1530, 1440 cm^{-1}.

m/e 263 (2.0), 262 (10.4), 261 (M⊕; 28.9), 93 (100.0).

The mother liquors from the above recrystallisation were flash chromatographed and a 2:1 mixture of the cis epoxy alcohol (333) and the trans epoxy alcohol (334) was obtained from which the ^{1}H nmr spectrum of trans isomer could be deduced.

^{1}H nmr (d-6 acetone) δ 1.45 (s, 3H); 1.8-3.0 (m, 4H); 3.12 (s, 1H); 5.57 (br s, 1H, exchanged with D_2O); 7.0-7.9 (m, 5H); 9.35 (br s, 1H).

(b) To the γ-hydroxy enone (332) (770 mg) was added an ether solution of hydrogen peroxide (1.5 M, 15 ml) and Amberlyst 15 (0.75 g). The reaction was monitored by tlc which still showed the presence of enone (332) after 7 days. Despite this, the ether was evaporated and the residue dissolved in saturated aqueous sodium metabisulphite (100 ml). This solution was extracted with chloroform (4 x 60 ml). Evaporation of the solvent from the combined extracts left a solid (508 mg). Tlc and an ^{1}H nmr spectrum

of the product showed it to be a mixture of the enone (332), cis epoxy alcohol (333) and trans epoxy alcohol (334) in about the ratio 32:8:1.

Preparation of 4-methoxymethoxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (335)

To a stirred solution of 4-hydroxy-4-N-phenylaminocarbonyl-3-methyl-cyclohex-2-enone (332) (724 mg) in chloroform (18.5 ml) was added methylal (18.5 ml) and then phosphorus pentoxide (9.2 g) which soon became a brown gelatinous solid. After 45 minutes the solution was decanted from the residual solid which was washed with chloroform (2 x 50 ml). The combined organic solutions were washed with aqueous potassium carbonate (0.5 M, 4 x 250 ml). Evaporation of the solvent left a residue (540 mg) which was purified by flash chromatography. This afforded 4-methoxymethoxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (335) (426 mg, 48.7% yield). ^{1}H nmr ($CDCl_3$) δ 1.88 (br s, 3H); 2.2-3.05 (m, 4H); 3.50 (s, 3H); 4.82 (s, 2H); 6.17 (m, 1H); 7.0-7.7 (m, 5H); 8.79 (br s, 1H).

Epoxidation of 4-methoxymethoxy-4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (335)

To a stirred solution of the MOM ether (335) (732 mg) in methanol (8 ml) was added hydrogen peroxide (30%, 0.78 ml) and aqueous sodium carbonate (3 M, 0.8 ml). The reaction was monitored by tlc which still showed the presence of starting enone (335) after 3 days but also showed the appearance of a new spot of slightly higher Rf. The reaction mixture was diluted with water (30 ml) and extracted with chloroform (4 x 30 ml). Evaporation of the solvent from the combined extracts left a residue (350 mg). This product was flash chromatographed, affording starting material (335) (163 mg) and a mixture (52 mg, 6.7% yield) of the cis epoxy ether (336) and trans epoxy ether (337) in about a 2:3 ratio.

cis epoxy ether: ^{1}H nmr ($CDCl_3$) δ 1.40 (s, 3H); 1.65-3.0 (m, 4H); 3.26 (s, 1H); 3.53 (s, 3H); 4.94 (d, J ~ 7 Hz, 1H); 5.23 (d, J ~ 7 Hz, 1H); 7.0-7.75 (m, 5H); 8.72 (br s, 1H).

trans epoxy ether: ^{1}H nmr ($CDCl_3$) δ 1.50 (s, 3H); 1.6-3.0 (m, 4H); 3.12 (s, 1H); 3.50 (s, 3H); 4.92 (s, 2H); 7.0-7.85 (m, 5H); 8.75 (br s, 1H).

A previous attempt at epoxidising the enone (335) which employed sodium hydroxide rather than sodium carbonate as the base failed to give either the cis epoxy ether (336) or trans epoxy ether (337).

Conversion of the cis epoxy alcohol (333) to its MOM ether

The cis epoxy MOM ether of (333) was prepared in 80.2% yield using the method previously mentioned. The product has a spectrum identical to that reported above.

Epoxidation of 4-ethoxycarbonyl-3-methylcyclohex-2-enone (308)

To a stirred solution of 4-ethoxycarbonyl-3-methylcyclohex-2-enone (308) (0.84 g) in ethanol (4 ml) was added hydrogen peroxide (30%, 1.2 ml) and aqueous sodium hydroxide (6 M, 0.33 ml). The reaction was monitored by tlc which showed the gradual conversion of (308) to a compound with higher Rf. After 24 hours conversion appeared complete and the reaction mixture was diluted with water (50 ml) and extracted with ether (3 x 40 ml). Evaporation of the solvent from the combined extracts gave a mixture (550 mg, 60.2% yield) of the epoxide (343) and the diastereomeric cis epoxy ester in about a 12:1 ratio, determined from the ^{1}H nmr spectrum. The product was re-examined by tlc which, after prolonged development of the plate in an iodine tank, showed a faint spot whose Rf value was between those of the epoxide (343) and the enone (308). The mixture shows intense

spectral characteristics as follows:

^{1}H nmr ($CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H); 1.35 (s, 3H); 1.60-1.85 (m, 1H); 1.95-2.35 (m, 3H); 3.00-3.10 (m, 1H); 3.10 (s, 1H); 4.06 (q, J = 7.1 Hz, 2H).

^{13}C nmr ($CDCl_3$) δ 13.0 (q); 19.7 (t); 20.4 (q); 31.7 (t); 44.2 (d); 60.9 (t); 61.5 (s); 61.8 (d); 171.8 (s); 204.3 (s). Multiplicities assigned from DEPT experiments.

ir ($CHCl_3$) 1730 (br) cm^{-1}.

m/e 199 (0.2), 198 ($M^{\oplus}$; 2.3), 43 (100.0).

The peaks in the nmr spectra reported above are due to epoxide (343). The proton spectrum also showed the following peaks which can be attributed to the minor diastereomeric epoxide: δ 1.15 (t, J = 7.1 Hz, 3H); 1.42 (s, 3H); 3.12 (s, 1H); 4.18 (q, J = 7.1 Hz, 2H).

The above epoxide mixture (550 mg) was dissolved in tetrahydrofuran (15 ml). To this solution was added a solution of sodium hydroxide (80 mg) dissolved in deuterium oxide (1.3 ml). After 1 hour the tetrahydrofuran was evaporated and the residue diluted with water (30 ml). This solution was neutralised with dilute sulphuric acid and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts left an oil (365 mg) whose ^{1}H nmr showed deuterium exchange of the methylene protons α to the ketone but no exchange of the methine proton α to the ester.

Preparation of ethyl 1-methyl-6,8-dioxabicyclo[5.1.0]octan-5-one carboxylate (346)

To a solution of Hagemann's ester (308) (450 mg) in dichloromethane (30 ml) was added mcpba (1.0 g) and 2,2-thiobis(4-methyl-6-t-butylphenol) (~3 mg). This mixture was heated to reflux and the reaction monitored by tlc which showed complete conversion of the ester (308) to a compound with slightly lower Rf after 6 days. No intermediates were detected.

Potassium iodide/starch papers indicated there was virtually no mcpba remaining. The reaction mixture was diluted with dichloromethane (100 ml) and this solution washed with saturated aqueous sodium bicarbonate 4 x 75 ml), then brine (2 x 50 ml). Evaporation of the solvent gave crude ethyl 1-methyl-6,8-dioxabicyclo[5.1.0]octan-5-one-carboxylate (346) as a crystalline solid (572 mg). Recrystallisation from chloroform/pet ether gave the lactone (346) (214 mg, 40.5% yield) as fine white needles, m.p. 121-122.5°.

^{1}H nmr (d-6 acetone) δ 1.28 (t, J = 7.1 Hz, 3H); 1.33 (s, 3H); 2.00-2.35 (m, 2H); 2.45-2.70 (m, 2H); 2.80-3.05 (m, 1H); 4.11-4.36 (m, 2H); 5.17 (s, 1H).

In a 90 MHz ^{1}H nmr spectrum the multiplet at δ 4.11-4.36 appears as a quartet, J ~ 7 Hz.

^{13}C nmr (d-6 acetone) δ 14.4; 15.6; 22.0; 31.7; 47.2; 59.8; 61.5; 81.6; 169.8; 171.2.

ir ($CHCl_3$) 1760, 1730, 1460, 1445 cm^{-1}.

m/e no $M^{\oplus}$, 186.0810 ($C_9H_{14}O_4$; 3.5), 112 ($C_6H_8O_2$; 100.0).

Analysis: Found C, 55.93; H, 6.55. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.59.

Preparation of 4-ethoxycarbonyl-3-hydroxy-3-phenylcyclohexanone (351)

Using the method of Golding[179] crude dioxo-ester (350) was prepared (92.8% yield) by Michael condensation of ethyl benzoyl acetate with but-3-en-2-one in methanolic sodium methoxide. Part of this was purified by flash chromatography.

To a stirred solution of this ester (2.417 g), in absolute ethanol (15 ml) was added sodium hydroxide (0.1 g).[196] After 24 hours dilute aqueous ammonium chloride (100 ml) was added to the reaction mixture and this solution extracted with dichloromethane (3 x 100 ml). Evaporation of the solvent from the combined extracts gave 4-ethoxycarbonyl-3-hydroxy-

3-phenylcyclohexanone (351) (2.136 g, 88.4% yield) as a crystalline solid. Recrystallisation from ether, then chloroform/pet. ether gave (351) as flaky white crystals, m.p. 129.5-131.5°.

^{1}H nmr ($CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H); 2.05-2.70 (m, 6H); 3.35-3.50 (m, 1H); 3.89 (dq, J = 7.1 Hz, J = 2.3 Hz, 2H); 4.20 (br s, 1H, exchanged with D_2O); 7.15-7.55 (m, 5H).

^{13}C nmr ($CDCl_3$) δ 13.5 (q); 25.0 (t); 39.2 (t); 48.9 (d); 54.0 (t); 60.8 (t); 77.1 (s); 124.2 (d); 127.2 (d); 128.2 (d); 144.5 (s); 174.9 (s); 206.9 (s). Multiplicities assigned from DEPT experiments.

ir (CCl_4) 3490, 1725, 1720, 1445 cm^{-1}.

m/e 263 (2.3), 262 ($M^{\oplus}$; 6.2), 105 (100.0).

Analysis: Found C, 68.75; H, 6.98. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92.

Preparation of 4-ethoxycarbonyl-3-phenylcyclohex-2-enone (353)

Cyclisation of crude ethyl 2-benzoyl-5-oxohexanoate (350) (23.027 g) with pyrrolidinium acetate, according to the method of Golding[179], afforded crude 4-ethoxycarbonyl-3-phenylcyclohex-2-enone (353) (18.533 g). This product was purified by distillation, b.p. ~150°/0.2 mm Hg, giving enone (353) (10.299 g, 48.0% yield).

^{1}H nmr ($CDCl_3$) δ 1.08 (t, J = 7 Hz, 3H); 1.7-2.9 (m, 4H); 4.0 (m, 1H); 4.08 (q, J = 7 Hz, 2H); 6.43 (s, 1H); 7.25-7.65 (m, 5H).

Epoxidation of 4-ethoxycarbonyl-3-phenylcyclohex-2-enone (353)

To a stirred solution of 4-ethoxycarbonyl-3-phenylcyclohex-2-enone (353) (3.379 g) in ethanol (15 ml) was added hydrogen peroxide (30%, 3.6 ml) and aqueous sodium hydroxide (6 M, 1.0 ml). The reaction was monitored by tlc. After 3½ hours more hydrogen peroxide (30%, 3.5 ml) was added to the reaction mixture. Despite the fact that tlc still showed the presence of starting material after 5½ hours, the reaction mixture was

diluted with water (100 ml) and extracted with chloroform (4 x 60 ml). Evaporation of the solvent from the combined extracts left an oil (985 mg). This oil was flash chromatographed, affording the epoxide (354) (231 mg, 6.4% yield) and the catechol (355) (437 mg, 12.2% yield). The catechol (355) was purified by Kugelrohr distillation, b.p. ~230°/0.15 mm Hg.

epoxide (354): ^{1}H nmr ($CDCl_3$) δ 1.14 (t, J = 7 Hz, 3H); 1.65-2.85 (m, 4H); 3.58 (m, 1H); 3.63 (s, 1H); 4.15 (q, J = 7 Hz, 2H); 7.2-7.7 (m, 5H).

catechol (355): ^{1}H nmr ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H); 3.97 (q, J = 7 Hz, 2H); 5.27 (br s, 1H, exchanged with D_2O); 6.43 (br s, 1H, exchanged with D_2O); 6.89 (d, J = 8 Hz, 1H); 7.1-7.6 (m, 6H).

ir ($CHCl_3$) 3525, 3410, 1715, 1690, 1600, 1580 cm^{-1}.

m/e 260 (3.1), 259 (13.4), 258 ($M^{\oplus}$; 46.8) 212 (100.0).

Because of the poor yields of (354) and (355) the aqueous solution from which they were extracted was acidified to pH 2 with dilute sulphuric acid and extracted with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts left an oil (2.158 g). Although an ^{1}H nmr spectrum of this oil was uninterpretable, benzoic acid was isolated by Kugelrohr distillation of the oil. Recrystallisation from water gave benzoic acid as fine white crystals, m.p. 120-121°.

^{1}H nmr ($CDCl_3$) δ 7.2-7.7 (m, 3H); 8.0-8.2 (m, 2H); 11.65 (br s, 1H).

Reduction of the trans epoxy ester (354)

An ethanolic solution of sodium phenylselenide was prepared by reduction of diphenyl diselenide (417 mg) with sodium borohydride (102 mg) in absolute ethanol (5.5 ml).[181] The resulting colourless solution was immediately added to a stirred solution of the trans epoxy ester (334) (231 mg) in absolute ethanol (3.6 ml) at 0°C, with the exclusion of

atmospheric moisture.[182] After 5 minutes the reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (30 ml). Evaporation of the solvent gave a crystalline residue which was washed with pet. ether (2 x 20 ml). This removed the diphenyl diselenide and left 4-ethoxycarbonyl-3-hydroxy-3-phenylcyclohexanone (352) (166 mg, 71.3% yield). Recrystallisation from ether gave (352) as fine white crystals, m.p. 166-167°.

^{1}H nmr ($CDCl_3$) δ 0.89 (t, J = 7.1 Hz, 3H); 1.95-2.10 (m, 1H); 2.20-2.60 (m, 3H); 2.65-2.85 (m, 1H); 2.95-3.08 (m, 1H); 3.15-3.25 (br s, 1H); 3.65-3.90 (m, 1H); 3.84 (q, J = 7.1 Hz, 2H); 7.18-7.42 (m, 5H).

^{13}C nmr ($CDCl_3$) δ 13.7 (q); 24.3 (t); 37.2 (t); 49.8 (t); 50.6 (d); 60.4 (t); 77.5 (s); 125.2 (d); 128.0 (d); 128.8 (d); 144.2 (s); 172.7 (s); 210.7 (s). Multiplicities assigned from DEPT experiments.

ir (CCl_4) 3595, 3350, 1725, 1550, 1450 cm^{-1}.

m/e 262 ($M^{\oplus}$; 2.3), 105 (100.0).

Analysis: Found C, 68.79; H; 6.88. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92.

Preparation of 4-ethoxycarbonyl-3-hydroxy-3-methylcyclohex-2-enone (356)

An ethanolic solution of sodium phenylselenide was prepared by reduction of diphenyl diselenide (758 mg) with sodium borohydride (185 mg) in absolute ethanol (10 ml).[181] The resulting colourless solution was immediately added to a stirred solution of the epoxide mixture obtained from alkaline epoxidation of Hagemann's ester (308) (320 mg) in absolute ethanol (6.5 ml) at 0°C, with the exclusion of atmospheric moisture.[182] After 5 minutes the reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (30 ml). After evaporating the solvent, the crude product mixture was flash chromatographed. This gave 4-ethoxycarbonyl-3-hydroxy-3-methylcyclohex-2-enone (356) (263 mg, 81.4% yield) which crystallised on standing. Recrystallisation from ether/pet. ether gave

colourless crystals, m.p. 53-54°.

^{1}H nmr ($CDCl_3$) δ 1.27 (s, 3H); 1.30 (t, J = 7 Hz, 3H); 1.6-3.0 (m, 7H); 3.18 (br s, 1H); 4.24 (q, J = 7 Hz, 2H).

ir (CCl_4) 3605, 3580, 3500, 3420, 1725 (br).

m/e no $M^{\oplus}$; 185 (4.5), 43 (100.0).

Analysis: Found C, 60.03; H, 8.20. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05.

Crystal Data. $C_{10}H_{16}O_4$: M = 200.23, monoclinic, space group $P2_1/a$, a = 13.085, b = 5.613, c = 14.672, Å, α = 90.00 , β = 93.25 , γ = 90.00 , U = 1075.8 Å^3, Z = 4, D_c = 1.24 g cm^{-3}. T = 293 K. R = 0.069, R′ = 0.090 for 1505 independent reflections with $F_o^2 > 2\sigma(F_o^2)$.

Preparation of 6-ethoxycarbonyl-3-hydroxy-3-methylcyclohexanone (360)

To a stirred solution of ethyl 2-acetyl-5-oxohexanoate (358) (2.4 g) in absolute ethanol (15 ml) was added sodium hydroxide (0.1 g). After 48 hours dilute aqueous ammonium chloride (100 ml) was added to the reaction mixture and this solution extracted with dichloromethane (3 x 100 ml). Evaporation of the solvent from the combined extracts left an oil which was flash chromatographed. This gave 6-ethoxycarbonyl-3-hydroxy-3-methylcyclohexanone (360) (1.661 g, 69.2% yield).

^{1}H nmr ($CDCl_3$) δ 1.33 (s, 3H); 1.35 (t, J = 7 Hz, 3H); 1.55-3.0 (m, 7H); 4.27 (q, J = 7 Hz, 2H); 4.35 (br s, 1H, exchanged with D_2O).

Preparation of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361)

To a solution of 6-ethoxycarbonyl-3-hydroxy-3-methylcyclohex-2-enone (360) (420 mg) in dichloromethane (15 ml) was added triethylamine (0.6 ml) and then methane sulphonyl chloride (0.2 ml) with the exclusion of atmospheric moisture. After 3½ hours the reaction mixture was washed with brine (30 ml) and the washings back-extracted with chloroform (2 x 20 ml). Evaporation of the solvents from the combined organic liquors gave crude

6-ethoxycarbonyl-3-methylcyclohex-2-enone (361) (293 mg, 76.7% yield) which was purified by flash chromatography to give a major component as an oil (144 mg, 37.7% yield). This was shown by tlc and ^{1}H nmr comparison to be identical to a sample of the enone (361) prepared by another route (see later).

Preparation of 4-hydroxycarbonyl-3-methylcyclohex-2-enone

To a stirred solution of 4-ethoxycarbonyl-3-methylcyclohex-2-enone (308) (3.90 g) in methanol (15 ml) was added a solution of sodium hydroxide (1.62 g) dissolved in water (45 ml). After 1¼ hours the reaction mixture was washed with chloroform (3 x 20 ml). The aqueous phase was then acidified to pH 2 with dilute sulphuric acid and extracted with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts gave 4-hydroxycarbonyl-3-methylcyclohex-2-enone (341) (3.093 g, 93.7% yield) as a viscous oil. On standing for several weeks the acid (341) decarboxylated to 3-methylcyclohex-2-enone. Decarboxylation readily occurred on heating (341) to 80°.

^{1}H nmr ($CDCl_3$) δ 1.9-2.9 (m, 4H); 2.08 (br s, 3H); 3.2-3.45 (br t, 1H); 6.02 (m, 1H); 10.7 (br s, 1H).

ir ($CHCl_3$) 3500-2800, 1715, 1660 cm^{-1}.

m/e 155 (0.3), 154 ($M^{\oplus}$; 3.0), 39 (100.0).

The p-bromophenacyl ester, m.p. 125-130°, of acid (341) was prepared according to the literature method.[208]

^{1}H nmr ($CDCl_3$) δ 1.8-2.9 (m, 4H); 2.10 (br s, 3H); 3.35-3.53 (br t, 1H); 5.37 (s, 2H); 5.99 (m, 1H); 7.4-7.95 (m, 4H).

m/e 352 ($M^{\oplus}$; 1.0), 350 ($M^{\oplus}$; 1.0), 185 (97.3), 183 (100.0).

An attempt to prepare 4-hydroxy-4-hydroxycarbonyl-3-methylcyclohex-enone (339) by hydroxylating the acid (341) with activated charcoal in ethyl acetate, as for the ethyl ester (308),[175] was unsuccessful. Also

base hydrolysis (as above) of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) failed to yield (339). Both the reactions gave products whose ^1H nmr spectra were uninterpretable.

Epoxidation of 4-hydroxycarbonyl-3-methylcyclohex-2-enone (341)

To a stirred solution of 4-hydroxycarbonyl-3-methylcyclohex-2-enone (341) (442 mg) in methanol (2.5 ml) was added hydrogen peroxide (30%, 0.75 ml) and a solution of sodium hydroxide (165 mg) dissolved in water (0.7 ml). After 3¼ hours the reaction mixture was diluted with water (50 ml) and this solution washed with chloroform (2 x 20 ml). The aqueous phase was then acidified to pH 2 with dilute sulphuric acid and extracted with chloroform (3 x 40 ml). Evaporation of the solvent from the combined extracts gave a mixture (291 mg, 59.6% yield) of the epoxide (362) and the diastereomeric cis epoxy acid in about a 5:1 ratio.

^1H nmr ($CDCl_3$) δ 1.52 (s, 3H); 1.78-2.75 (m, 4H); 3.14-3.3 (br t, 1H); 3.26 (s, 1H); 10.4 (br s, 1H).

ir ($CHCl_3$) 3550-2400, 1710 cm^{-1}.

m/e 171 (0.7), 170 ($M^{\oplus}$; 6.4), 39 (100.0).

The peaks in the nmr spectrum reported above are due to epoxide (362). The spectrum also showed a singlet at δ 1.58 which can be attributed to the methyl group of the diastereomeric cis epoxy acid.

Hydrolysis of the epoxy ester mixture obtained from alkaline epoxidation of Hagemann's ester (308)

To a solution of the epoxy ester mixture obtained from alkaline epoxidation of Hagemann's ester (308) (143 mg) in methanol (0.5 ml) was added a solution of sodium hydroxide (50 mg) dissolved in water (1.35 ml). After 1½ hours the reaction mixture was diluted with water (40 ml) and this solution washed with chloroform (2 x 25 ml). The aqueous phase was

then acidified to pH 2 with dilute sulphuric acid and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts gave predominantly the epoxy acid (362) (77 mg, 62.7% yield). An ^{1}H nmr spectrum of this product was very similar to the spectrum reported in the preceding paragraph.

Preparation of 4-aminocarbonyl-3-methylcyclohex-2-enone (340)

To a stirred solution of freshly prepared 4-hydroxycarbonyl-3-methyl-cyclohex-2-enone (341) (3.663 g) in tetrahydrofuran (24 ml) at -15° was added triethylamine (3.30 g) and then ethyl chloroformate (2.27 ml), with the exclusion of atmospheric moisture.[198] After 5 minutes ammonia was bubbled vigorously through the solution for 10 minutes. Stirring was maintained for a further 30 minutes. The reaction mixture was left in the freezer overnight. After diluting the reaction mixture with tetrahydrofuran (50 ml) and stirring for 1 hour, the solid which had precipitated was filtered off and the solvent evaporated from the filtrate. The resulting crude product mixture was purified by flash chromatography affording crude 4-aminocarbonyl-3-methylcyclohex-2-enone (340) (830 mg, 22.8% yield). Recrystallisation from chloroform/pet. ether gave pure (340) (262 mg, 7.2% yield) as a pale yellow solid, m.p. 149.5-151.5°.

^{1}H nmr ($CDCl_3$) δ 1.7-2.8 (m, 4H); 2.01 (br s, 3H); 3.08-3.27 (br t, 1H); 6.02 (m, 1H); 6.1 (br s, 2H).

ir ($CHCl_3$) 3520, 3490, 3410, 3350, 3190, 1685, 1670, 1630, 1590 cm^{-1}.

m/e 154 (1.1), 153 (M°; 4.2), 97 (100.0).

Analysis: Found C, 62.61; H, 7.29; N, 9.10. $C_8H_{11}NO_2$ requires C, 62.72; H, 7.24; N, 9.14.

Several attempts to prepare the amide (340) directly from Hagemann's ester (308) by treatment with concentrated aqueous ammonia, liquid ammonia, urea[197] or a methanolic solution of ammonia in the presence of sodium

cyanide[187] were all unsuccessful.

Attempts to prepare 4-aminocarbonyl-4-hydroxy-3-methylcyclohex-2-enone (338) by hydroxylating the amide (340) with activated charcoal in ethyl acetate, as for the ethyl ester (308),[175] or by treating 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) with concentrated aqueous ammonia were both unsuccessful.

Epoxidation of 4-aminocarbonyl-3-methylcyclohex-2-enone (340)

To a stirred solution of 4-aminocarbonyl-3-methylcyclohex-2-enone (340) (78 mg) in methanol (1 ml) was added hydrogen peroxide (30%, 0.13 ml) and aqueous sodium hydroxide (6 M, 0.035 ml). The reaction was monitored by tlc using 20% methanol in chloroform to develop the plate. After 2½ hours the reaction was diluted with water (20 ml) and extracted with chloroform (5 x 40 ml). Evaporation of the solvent from the combined extracts gave both epoxides (72 mg, 83.6% yield) in a 5:1 ratio. Recrystallisation from chloroform/pet. ether failed to separate these diastereomers. This epoxide mixture had m.p. 167-179.5°.

^{1}H nmr (d-6 acetone) δ 1.38 (s, 3H); 1.65-1.90 (m, 1H); 2.00-2.40 (m, 3H); 3.08-3.20 (m, 1H); 3.11 (s, 1H); 6.59 (br s, 1H); 7.22 (br s, 1H).

^{13}C nmr (d-6 acetone) δ 20.5 (q); 21.4 (t); 32.6 (t); 44.7 (d); 62.0 (s); 62.6 (d); 174.5 (s); 204.8 (s). Multiplicities assigned from DEPT experiments.

ir 3540, 3380, 1705 (br), 1615, 1595, 1445 cm^{-1}.

m/e no M$^{\oplus}$, 154 (3.1), 153 (2.3), 152 (22.2), 41 (100.0).

The peaks in the nmr spectra reported above are due to the major epoxide isomer. A number of other peaks observed in the spectra can be attributed to the minor isomer.

^{1}H nmr δ 1.45 (s, 3H); 2.90 (s, 1H); 6.93 (br s, 1H).

^{13}C nmr δ 20.2 (q); 22.0 (t); 35.9 (t); 46.7 (d); 61.0 (d); 206.6 (s).

Deamination of the amide mixture obtained from alkaline epoxidation of the amide (340)

A solution of dinitrogen tetroxide (9.74 g) in carbon tetrachloride (100 ml) was prepared by bubbling dinitrogen tetroxide through carbon tetrachloride for several minutes.

To a stirred solution of the epoxy amide mixture obtained from alkaline epoxidation of the amide (340) (18 mg) in acetonitrile (0.6 ml) at 0°C was added sodium acetate (13 mg) and the above solution of dinitrogen tetroxide in carbon tetrachloride (0.2 ml).[199] After 1 hour the reaction mixture was diluted with saturated aqueous sodium carbonate (50 ml) and this solution washed with chloroform (2 x 30 ml). The aqueous phase was then acidified to pH 2 with dilute nitric acid and extracted with chloroform (3 x 40 ml). Evaporation of the solvent from the combined extracts gave a mixture (18 mg, virtually quantitative yield) of the epoxide (362) and the diastereomeric cis epoxy acid in about a 1:1 ratio.

^{1}H nmr ($CDCl_3$) δ 1.47 (s, 3H); 1.51 (s, 3H); 1.65-2.0 (m, 2H); 2.1-2.45 (m, 6H); 2.9-3.0 (m, 1H); 3.1-3.2 (m, 1H); 3.25 (s, 1H); 3.26 (s, 1H); 5.75 (br s, 1H); 6.60 (br s, 1H).

^{13}C nmr ($CDCl_3$) δ 19.8; 20.5; 20.7; 20.9; 31.9; 32.1; 44.1; 44.9; 61.7; 61.9; 62.1 (2 peaks); 175.1; 176.5; 204.5; 204.9.

ir 3550-2400, 1710 cm^{-1}.

m/e 170 ($M^{\oplus}$; 0.7); 42 (100.0).

Epoxidation of 4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (331)

To a stirred solution of 4-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (331) (528 mg) in ethanol (4 ml) was added hydrogen peroxide (30%, 0.6 ml) and aqueous sodium hydroxide (6 M, 0.16 ml). After 3 hours the reaction mixture was diluted with water (50 ml) and extracted with

chloroform (3 x 40 ml). Evaporation of the solvent from the combined extracts gave both epoxides (527 mg, 93.3% yield) in a 2:1 ratio. The mixture was recrystallised from acetone. This afforded the major epoxide isomer (87 mg) which has the lower Rf on tlc. The mother liquors were evaporated and flash chromatographed. The first fractions collected contained predominantly the minor epoxide. These were combined (201 mg, 35.6% yield) and recrystallised from chloroform/pet. ether giving fine white crystals, m.p. 156-160°. The later fractions contained predominantly the major epoxide. These were combined with the crystals which precipitated from acetone (264 mg, 46.7% yield). Recrystallisation from ethyl acetate/chloroform gave fine white needles, m.p. 217-220.5°.

minor epoxide: ^{1}H nmr ($CDCl_3$) δ 1.52 (s, 3H); 1.7-2.8 (m, 4H); 3.0-3.15 (m, 1H); 3.30 (s, 1H); 7.0-7.8 (m, 6H).

ir ($CHCl_3$) 3430, 3350, 1710, 1695, 1685, 1600, 1520, 1495, 1440 cm^{-1}.

m/e 247 (0.1), 246 (1.5), 245 ($M^{\oplus}$; 8.0), 93 (100.0).

major epoxide: ^{1}H nmr ($CDCl_3$) δ 1.59 (s, 3H); 1.8-3.0 (m, 5H); 3.19 (s, 1H); 7.0-7.8 (m, 6H).

ir ($CHCl_3$) 3410, 1720, 1690, 1600, 1530, 1500, 1440 cm^{-1}.

m/e 246 (3.2), 245 ($M^{\oplus}$; 19.0), 93 (100.0).

Preparation of 4-acetyl-3,4-dimethylcyclohex-2-enone (365)

To a stirred solution of 3-methylpentan-2,4-dione (12.8 g) in methanolic solium methoxide [prepared by dissolving sodium (0.043 g) in methanol (90 ml)] at 0°C was slowly added a solution of but-3-en-2-one (10.25 ml) in methanol (60 ml). After 24 hours the methanol was evaporated and the residue dissolved in chloroform (200 ml). This solution was washed with dilute hydrochloric acid (3 x 20 ml). Evaporation of the

solvent afforded the triketone (364) (19.85 g).

^{1}H nmr ($CDCl_3$) δ 1.31 (s, 3H); 2.09 (br s, 9H); 2.1-2.5 (m, 4H).

To a solution of the triketone (364) (19.85 g) in a 9:1 mixture of methanol and water (20 ml) was added glacial acetic acid (1.0 g) and pyrrolidine (0.9 g). This mixture was refluxed for 24 hours and then the methanol evaporated. The residue was dissolved in chloroform (100 ml) and this solution washed with hydrochloric acid (1 M, 3 x 20 ml) and aqueous sodium bicarbonate (1 M, 3 x 20 ml). The acidic washings were neutralised with aqueous sodium bicarbonate and back-extracted with chloroform (2 x 40 ml). Evaporation of the solvent from the combined organic liquors afforded a viscous oil which was distilled. This gave 4-acetyl-3,4-dimethylcyclohex-2-enone (365) (7.27 g, 40.6% yield), b.p. 90-105°/ 0.1 mm Hg.

^{1}H nmr ($CDCl_3$) δ 1.38 (s, 3H); 1.77 (br s, 3H); 1.8-2.6 (m, 4H); 2.18 (s, 3H); 5.94 (m, 1H).

Attempted preparation of 3,4-dimethyl-4(1-hydroxy-1-methylethyl)-cyclohex-2-enone (366)

To a stirred solution of 4-acetyl-3,4-dimethylcyclohex-2-enone (365) (1.328 g) in anhydrous ether (60 ml) at -78°C was added an etheral solution of methyl magnesium bromide (3 M, 3.0 ml) with the exclusion of atmospheric moisture. The reaction mixture was allowed to slowly warm to room temperature over 2½ hours. It was then diluted with saturated aqueous ammonium chloride (100 ml) and the aqueous phase back-extracted with ether (4 x 20 ml). Evaporation of the solvent from the combined organic liquors gave an oil (1.296 g) which was shown by ^{1}H nmr and tlc to be a complex mixture. Although the ^{1}H nmr spectrum confirmed addition to the acetyl group had occurred (among other things), an attempt to isolate the tertiary alcohol (366) by flash chromatographic separation was unsuccessful because

the compounds comprising the oily mixture have very similar Rf. No further attempts to isolate (366) were tried.

Preparation of 3,4-dimethyl-4(1-hydroxyethyl)-cyclohex-2-enone (367)

To a stirred solution of 4-acetyl-3,4-dimethylcyclohex-2-enone (365) (677 mg) in ethanol (10 ml) and water (5 ml) at -30°C was added sodium borohydride (38 mg). The reaction mixture was allowed to warm to room temperature over 40 minutes. It was then diluted with water (50 ml) and extracted with chloroform (3 x 50 ml). Evaporation of the solvent from the combined extracts left an oil (538 mg). Tlc of this oil indicated it was mainly a mixture of starting material (365) and a new product of lower Rf, though a number of other faint spots were also visible. These compounds were separated by flash chromatographing the oil. This gave recovered starting material (365) (336 mg) and the secondary alcohol (367) (207 mg, 60.0% yield based on unrecovered starting material) as a viscous oil. ^{1}H nmr ($CDCl_3$) δ 1.09 (s, 3H); 1.22 (d, J ~ 6 Hz, 3H); 1.3-2.65 (m, 4H); 2.02 (br s, 3H); 2.92 (br s, 1H); 4.00 (q, J ~ 6 Hz, 2H); 5.89 (m, 1H).

Epoxidation of 3,4-dimethyl-4(1-hydroxyethyl)-cyclohex-2-enone (367)

To a stirred solution of 3,4-dimethyl-4(1-hydroxyethyl)-cyclohex-2-enone (367) (207 mg) in methanol (1.5 ml) was added hydrogen peroxide (30%, 0.32 ml) and aqueous sodium hydroxide (6 M, 0.09 ml). After 7 hours the reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts left an oily residue (208 mg). ^{1}H nmr and tlc indicated this was predominantly the epoxide (368) (Rf 0.3) though there was still some starting material (367) (Rf 0.2) present. Flash chromatographic separation gave the epoxide (368) (140 mg, 61.8% yield) as a colourless oil. ^{1}H nmr ($CDCl_3$) δ 1.02 (s, 3H); 1.23 (d, J ~ 6 Hz, 3H); 1.48 (s, 3H);

1.8-2.7 (m, 4H); 2.97 (s, 1H); 3.10 (br s, 1H); 4.04 (q, J ~ 6 Hz, 2H).

ir (CCl_4) 3620, 3500, 1710 cm^{-1}.

m/e no $M^{\oplus}$, 141 (0.3), 140 (6.0); 43 (100.0).

Epoxidation of 4-acetyl-3,4-dimethylcyclohex-2-enone (365)

To a stirred solution of 4-acetyl-3,4-dimethylcyclohex-2-enone (365) (2.30 g) in methanol (16 ml) was added hydrogen peroxide (30%, 3.6 ml) and aqueous sodium hydroxide (6 M, 1.0 ml). The reaction was monitored by tlc which showed the absence of starting material (365) after 2½ hours. After 3 hours the reaction mixture was diluted with water (100 ml) and extracted with chloroform (4 x 50 ml). Evaporation of the solvent from the combined extracts gave the epoxide (369) (2.180 g, 86.5% yield) which crystallised on standing. Recrystallisation ether/pet. ether gave white crystals, m.p. 53-55°.

^1H nmr ($CDCl_3$) δ 1.01 (s, 3H); 1.13 (s, 3H); 1.8-2.4 (m, 4H); 2.11 (s, 3H); 2.91 (s).

^{13}C nmr ($CDCl_3$) δ 17.1; 17.9; 25.7; 26.0; 31.7; 51.4; 61.0; 65.0; 204.3; 209.1.

ir (CCl_4) 1715 cm^{-1}.

m/e no $M^{\oplus}$, 141 (1.9), 140 (18.6), 43 (100.0).

Analysis: Found C, 65.99; H, 7.62. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74.

Crystal Data. $C_{10}H_{14}O_3$: M = 182.22, triclinic, space group $P\bar{1}$, a = 6.623, b = 7.363, c = 10.870, Å, α = 87.07 , β = 83.25 , γ = 65.73 , U = 479.9 $Å^3$, Z = 2, D_C = 1.26 g cm^{-3}. T = 293 K. R = 0.058, R′ = 0.087 for 1633 independent reflections with $F_o^2 > 2\sigma(F_o^2)$.

Neither ^1H nmr nor tlc of the crude product showed any trace of the diastereomeric epoxide (370).

Oxidation of the epoxy alcohol (368) to the acetyl epoxide (369)

To a stirred solution of the epoxy alcohol (368) (140 mg) in chloroform (2.25 ml) and ether (0.75 ml) was added celite (0.2 g). Once this mixture had been cooled to 0°C, chromium trioxide (0.2 g) was added over a few minutes.[200] After 30 minutes more ether (2 ml) and celite (0.2 g) were added to the reaction mixture. After a further 15 minutes the reaction mixture was filtered through celite and the solvent evaporated. This gave an oil whose Rf on tlc and ^1H nmr spectrum were identical with the acetyl epoxide (369). On seeding this oil (108 mg, 78.0%) crystallised. This acetyl epoxide (369) was recrystallised from ether/pet. ether giving white crystals, m.p. 53-55°.

Preparation of 3-methylcyclohex-2-enone (371)

To 4-ethoxycarbonyl-3-methylcyclohex-2-enone (308) (11 g) was added dilute sulphuric acid (1.5 M, 1.2 l) and some powdered glass. This mixture was then refluxed for 7 hours. The reaction mixture was neutralised with dilute aqueous ammonia and then saturated with solid ammonium sulphate. This solution was extracted with ether (3 x 100 ml). Evaporation of the solvent from the combined extracts left a residue which was fractionally distilled on a Kugelrohr. This afforded relatively pure 3-methylcyclohex-2-enone (5.53 g, 83% yield).

^1H nmr ($CDCl_3$) δ 1.65-2.75 (m, 6H); 1.95 (br s, 3H); 5.87 (m, 1H).

Epoxidation of 3-methylcyclohex-2-enone (371)

To a stirred solution of 3-methylcyclohex-2-enone (371) (220 mg) in ethanol (2.5 ml) was added hydrogen peroxide (30%, 0.57 ml) and aqueous sodium hydroxide (6 M, 0.15 ml). After 1½ hours the reaction mixture was

diluted with water (20 ml) and extracted with chloroform (3 x 20 ml). Evaporation of the solvent from the combined extracts gave 2,3-epoxy-3-methylcyclohexanone (247 mg, 98.0% yield).

^{1}H nmr ($CDCl_3$) δ 1.43 (s, 3H); 1.4-2.65 (m, 6H); 3.04 (s, 1H).

4-Ethoxycarbonyl-3-methylcyclohex-2-enone (308) and 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309) were epoxidised under the above conditions. After the same reaction time, ^{1}H nmr spectra showed that there had been about 20% conversion of (308) and 60% conversion of (309) to their respective epoxides.

Preparation of 1-methyl-6,8-dioxabicyclo[5.1.0]octan-5-one (372)

To a solution of 3-methylcyclohex-2-enone (371) (900 mg) in dichloromethane (40 ml) was added mcpba (1.2 g) and 2,2'-thiobis(4-methyl-6-t-butylphenol) (~3 mg). This mixture was heated to reflux and the reaction monitored by tlc. After 24 hours potassium iodide/starch papers indicated there was no oxidising agent present, so more mcpba (1.2 g) was added to the mixture. After a further 4 days no starting material remained. The reaction mixture was washed with saturated aqueous sodium sulphite (3 x 50 ml). The organic phase was diluted with dichloromethane (100 ml) and washed with saturated sodium bicarbonate (3 x 50 ml). Evaporation of the solvent gave 1-methyl-6,8-dioxabicyclo[5.1.0]octan-5-one (372) (615 mg, 53.0% yield) as a colourless oil which was purified by Kugelrohr distillation, b.p. ~100°/0.25 mm Hg.

^{1}H nmr ($CDCl_3$) δ 1.26 (s, 3H); 1.0-2.75 (m, 6H); 4.85 (s, 1H).

^{13}C nmr ($CDCl_3$) δ 16.5 (q); 16.6 (t); 30.3 (t); 31.9 (t); 59.3 (s); 81.4 (d); 170.0 (s). Multiplicities assigned from DEPT experiments.

ir ($CHCl_3$) 1760, 1460 cm^{-1}.

m/e no $M^{\oplus}$, 125 (0.3), 113 (4.3), 43 (100.0).

Preparation of 6-acetoxy-3-methylcyclohex-2-enone (373)[209]

To a solution of 3-methylcyclohex-2-enone (373) (3.158 g) in benzene (75 ml) was added lead (IV) acetate (18.3 g).[201] This mixture was heated to reflux and the reaction monitored by tlc. After 92 hours the reaction mixture was washed once with water (50 ml), brine (50 ml), saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml). Evaporation of the solvent left an oily residue which was flash chromatographed, affording 6-acetoxy-3-methylcyclohex-2-enone (373) (2.018 g, 41.9% yield) as a viscous oil. A small proportion of this was sublimed under vacuum to give colourless crystals which recrystallised from ether as plates, m.p. 62-67° (lit.[209] 61-62°). On seeding the above oil with one of these plates it crystallised.

^{1}H nmr ($CDCl_3$) δ 1.99 (br s, 3H); 2.0-2.8 (m, 4H); 2.17 (s, 3H); 5.33 (dd, J ~ 13 Hz, J ~ 7 Hz, 1H); 5.93 (m, 1H).

ir (CCl_4) 1745, 1690, 1635 cm^{-1}.

m/e 168 ($M^{\oplus}$; 0.9), 82 (100.0).

Attempted epoxidation of 6-acetoxy-3-methylcyclohex-2-enone (373)

To a stirred solution of 6-acetoxy-3-methylcyclohex-2-enone (373) (779 mg) in ethanol (15 ml) was added hydrogen peroxide (30%, 2 ml) and a solution of sodium carbonate (159 mg) in water (0.5 ml). The reaction was monitored by tlc which still showed the presence of starting material after 6 days. The reaction mixture was diluted with water (100 ml) and extracted with chloroform (4 x 60 ml). Evaporation of the solvent from the combined extracts left an oil. An ^{1}H nmr spectrum of this oil indicated it was predominantly 6-hydroxy-3-methylcyclohex-2-enone (374) though a small amount of starting material was also present. No evidence for any epoxide formation was found.

Preparation of 6-hydroxy-3-methylcyclohex-2-enone (374)[210]

To a solution of 6-acetoxy-3-methylcyclohex-2-enone (373) (3.51 g) in methanol was added a solution of sodium hydroxide (1.50 g) in water (40 ml). After 20 minutes the reaction mixture was extracted with chloroform (3 x 30 ml). Evaporation of the solvent from the combined extracts left an oil (1.90 g) which was flash chromatographed. This gave 6-hydroxy-3-methyl-cyclohex-2-enone (374) (1.115 g, 42.4% yield) as a colourless solid which recrystallised from ether as plates, m.p.43.5-45.5° (lit.[210] oil).

^{1}H nmr ($CDCl_3$) δ 1.45-2.85 (m, 4H); 1.99 (br s, 1H); 3.82 (br s, 1H, exchanged with D_2O); 4.15 (dd, J ~ 13 Hz, J ~ 7 Hz, 1H); 5.98 (m, 1H).

ir (CCl_4) 3490, 1675, 1630 cm^{-1}.

m/e 127 (0.8), 126 ($M^{\oplus}$; 9.9), 82 (100.0).

Analysis: Found C, 66.25; H, 8.02. $C_7H_{10}O_2$ requires C, 66.65; H, 7.99.

Attempted epoxidation of 6-hydroxy-3-methylcyclohex-2-enone (374)

(a) To a stirred solution of 6-hydroxy-3-methylcyclohex-2-enone (374) (168 mg) in methanol (1.5 ml) was added hydrogen peroxide (30%, 0.4 ml) and aqueous sodium hydroxide (6 M, 0.1 ml). After 3 hours the reaction mixture was diluted with water (20 ml) and extracted with chloroform (3 x 15 ml). Evaporation of the solvent from the combined extracts left an oily residue (98 mg). An ^{1}H nmr spectrum showed this oil was predominantly starting material, though the presence of a broad singlet at δ 1.45 and two smaller singlets at δ 3.11 and 3.33 indicated one or both epoxides may have been formed. Because of the very low yield no attempt was made to determine whether the above peaks were due to epoxides and no attempt was made to separate these products from the recovered starting material.

(b) To a solution of the enone (374) (103 mg) in dichloromethane (4 ml) was added mcpba (0.12 g) and 2,2′-thiobis(4-methyl-6-t-butylphenol)

(~1 mg). This mixture was heated to reflux and the reaction monitored by tlc. After 2 days potassium iodide/starch papers showed there was no mcpba remaining so more (0.24 g) was added to the reaction mixture. After a further 5 days tlc indicated there was no enone (374) left. The reaction mixture was diluted with dichloromethane (50 ml) and this solution washed with saturated aqueous sodium sulphite (3 x 20 ml) and saturated aqueous sodium bicarbonate (3 x 20 ml). Evaporation of the solvent left a residue (25 mg) whose ^1H nmr spectrum was uninterpretable and showed no evidence of epoxide formation.

(c) To the enone (374) (50 mg) was added an ether solution of hydrogen peroxide (1.5 M, 10 ml) and Amberlyst 15 (0.5 g).[46] After 4 days this mixture was filtered. The filtrate was diluted with ether (50 ml) and washed with saturated sodium sulphite (2 x 30 ml). The washings were back-extracted with ether (2 x 20 ml) and the solvent evaporated from the combined organic liquors. The yield of recovered organic material was negligible.

(d) To a solution of the enone (374) (100 mg) in dry benzene (100 ml) was added a solution of vanadyl acetoacetonate (0.96 mg) in dry benzene (2 ml) and then a solution of t-butylhydroperoxide in toluene (3 M, 0.32 ml), with the exclusion of atmospheric moisture.[106] The reaction mixture was heated to 40° and the reaction monitored by tlc which still showed the presence of starting material after 3 days. The reaction mixture was filtered through fluorosil and the solvent evaporated. This left a residue (18 mg) whose ^1H nmr spectrum was uninterpretable and showed no evidence for epoxide formation.

Preparation of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361)[202]

6-Ethoxycarbonyl-3-methylcyclohex-2-enone (361) was prepared according to the literature method by treating a benzene solution of the

dioxo-ester (358) with gaseous hydrochloric acid and then heating this product with N,N-dimethylaniline at 140° for 2½ hours.[202] Distillation of the crude product afforded pure enone (361) (32% yield), b.p. 90-105°/ 0.5 mm Hg.

^{1}H nmr ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3H); 1.8-2.8 (m, 4H); 1.97 (br s, 1H); 3.2-3.45 (m, 1H); 4.22 (q, J = 7 Hz, 2H); 5.92 (m, 1H).

Attempted epoxidation of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361)

(a) To a stirred solution of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361) (1.55 g) in methanol (7.6 ml) was added hydrogen peroxide (30%, 2.25 ml) and aqueous sodium hydroxide (6 M, 0.62 ml). After 3¼ hours the reaction mixture was diluted with water (100 ml) and extracted with ether (3 x 50 ml). Evaporation of the solvent from the combined extracts left an oily residue (847 mg). An ^{1}H nmr spectrum of this material showed it to be fairly clean starting material. No evidence for any epoxide formation was found.

(b) The above reaction was repeated using sodium carbonate instead of sodium hydroxide as the base and the reaction time was increased to 12 days. Despite these changes, the product obtained was shown by ^{1}H nmr to be crude starting material. Again, no evidence for any epoxide formation was found.

Preparation of 6-ethoxycarbonyl-6-hydroxy-3-methylcyclohex-2-enone (375)

To a stirred solution of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361) (373 mg) in ethyl acetate (12 ml) was added activated charcoal (1.1 g).[175] After 9 days more activated charcoal (2.0 g) was added to the mixture. After a further 5 days the reaction mixture was filtered through celite and the filter cake washed thoroughly with ethyl acetate. Evaporation of the solvent gave a crude mixture (286 mg) of starting

material (361) and 6-ethoxycarbonyl-6-hydroxy-3-methylcyclohex-2-enone (375). This mixture was separated by flash chromatography into two fractions, (a) starting material (361) (97 mg), and (b) a mixture (121 mg) which was predominantly 6-ethoxycarbonyl-6-hydroxy-3-methylcyclohex-2-enone but still contained some starting material. An ^{1}H nmr spectrum of fraction (b) showed, in addition to peaks associated with residual enone (361), the following signals:

^{1}H nmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H); 2.00 (br s, 3H); 1.8-2.85 (m, 4H); 4.25 (q, J = 7 Hz, 2H); 6.0 (m, 1H).

m/e 198 ($M^{\oplus}$; 1.2), 82 (100.0).

Preparation of 6-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (377)

To 2-acetyl-5-oxohexanilide (378) (1.64 g) was added a solution of ethanolic sodium ethoxide [prepared by dissolving sodium (220 mg) in absolute ethanol (55 ml)]. The resulting solution was stirred at room temperature for 5 hours and then neutralised with 10% aqueous hydrochloric acid. This solution was concentrated on a rotary evaporator. The residue was treated with concentrated hydrochloric acid (15 ml) and left to stand for 24 hours.[203] The reaction mixture was neutralised with sodium bicarbonate and this solution extracted with ethyl acetate (3 x 30 ml). Evaporation of the solvent from the combined extracts gave crude 6-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (377) (1.375 g, 90.4% yield). Purification by flash chromatography gave crystalline material (1.185 g, 77.9% yield) which recrystallised from ethyl acetate as fine white needles, m.p. 116-117.5°.

^{1}H nmr (d-6 acetone) δ 1.97 (br s, 3H); 2.10-2.60 (m, 4H); 3.30-3.45 (m, 1H); 5.84 (m, 1H); 7.05 (br t, J = 8 Hz, 1H); 7.28 (br t, J = 8 Hz, 2H); 7.65 (br d, J = 8 Hz, 2H); 9.26 (br s, 1H).

^{13}C nmr (d-6 acetone) δ 24.2; 25.9; 30.3; 53.8; 120.1; 124.2; 126.3;

129.5; 140.1; 165.0; 168.6; 195.9.

ir ($CHCl_3$) 3350, 3260, 1680, 1645, 1595, 1535, 1495, 1435 cm^{-1}.

m/e 231 (1.0), 230 (8.6), 229 ($M^{\oplus}$; 51.5); 110 (100.0).

Analysis: Found C, 73.04; H, 6.89; N, 6.01. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11.

Preparation of 6-hydroxy-6-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (379)

To a stirred solution of 6-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (377) (330 mg) in ethyl acetate (10 ml) was added activated charcoal (1.3 g).[175] The reaction was monitored by tlc which showed a single main spot of higher Rf than that of the starting material after 4 days. The reaction mixture was filtered through celite and the filter cake washed thoroughly with ethyl acetate. Evaporation of the solvent left a viscous oil which was flash chromatographed affording 6-hydroxy-6-N-phenylaminocarbonyl-3-methylcyclohex-2-enone (379) (194 mg, 55.0% yield) as a crystalline solid. Recrystallisation from chloroform/pet. ether gave fine white crystals m.p. 81.5-84°.

^1H nmr (d-6 acetone) δ 1.90-2.20 (m, 1H); 2.01 (br s, 3H); 2.30-2.60 (m, 2H); 2.65-3.20 (m, 1H); 5.42 (br s, 1H, exchanged with D_2O); 5.96 (m, 1H); 7.07 (br t, J = 7 Hz, 1H); 7.29 (br t, J = 7 Hz, 2H); 7.70 (br d, J = 8 Hz, 2H); 9.26 (br s, 1H).

^{13}C nmr (d-6 acetone) δ 24.4 (q); 29.8 (t); 34.3 (t); 77.9 (s); 120.4 (d) 124.6 (d) (2 peaks); 129.4 (d); 139.1 (s); 166.9 (s); 170.2 (s); 196.3 (s). Multiplicities assigned from DEPT experiments.

ir ($CHCl_3$) 3440, 3380, 1665 (br), 1630, 1595, 1520, 1440 cm^{-1}

m/e 247 (0.1), 246 (1.3), 245 ($M^{\oplus}$; 6.6); 126 (100.0).

Attempts to oxidise 2,3-epoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (343), acetoacetanilide and methyl 4-hydroxybenzoate (380) with

4 mass equivalents of activated charcoal in ethyl acetate[175] were unsuccessful. In each case the starting material was recovered unchanged.

Preparation of 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone (376)

To a solution of 6-ethoxycarbonyl-3-methylcyclohex-2-enone (361) (1.532 g) in benzene (20 ml) was added lead (IV) acetate (4.06 g).[201] This mixture was heated to reflux for 72 hours. The reaction mixture was then washed once with water (20 ml), brine (20 ml), saturated aqueous sodium bicarbonate (20 ml) and brine (20 ml). Evaporation of the solvent left an oily residue which was flash chromatographed, affording 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone (376) (916 mg, 45.3% yield) as a viscous oil.

^{1}H nmr ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H); 1.65-2.85 (m, 4H); 1.99 (br s, 3H); 2.13 (s, 3H); 4.25 (q, J = 7 Hz, 2H); 5.98 (m, 1H).

ir ($CHCl_3$) 1745, 1685, 1635, 1450, 1440 cm^{-1}.

m/e no $M^{\oplus}$, 198 (0.2), 82 (100.0).

Attempted cleavage of the acetate (376)

(a) To a solution of 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone in absolute ethanol (20 ml) was added sodium ethoxide (0.02 molar equivalents) and the solution left at 0°C for 24 hours. The ethanol was evaporated and the residue dissolved in chloroform (30 ml). This solution was washed with water (2 x 10 ml). Evaporation of the solvent gave quantitative recovery of the starting material (376).

Under the same conditions the isomeric compound, 4-acetoxy-4-ethoxycarbonyl-3-methylcyclohex-2-enone (327) gave a quantitative yield of 4-ethoxycarbonyl-4-hydroxy-3-methylcyclohex-2-enone (309).

(b) To a solution of the acetate (376) (7.2 g) in ethanol (100 ml) was added p-toluenesulphonic acid (100 mg). The reaction was monitored by

tlc which showed no change after 5 days so the solution was heated to reflux. After 24 hours tlc still showed only the presence of starting material so a couple of drops of concentrated sulphuric acid was added to the solution. After a further 24 hours the ethanol was evaporated and the residue dissolved in chloroform (80 ml). This solution was washed with saturated aqueous sodium bicarbonate (2 x 30 ml). Evaporation of the solvent left an oily residue (5.718 g). An ^1H nmr spectrum of this product showed it was predominantly starting material though the complexity of the triplet and quartet regions of the ethyl ester and the presence of new multiplets at δ 6.6-6.9 and δ 7.6-7.8 indicated the phenol (380) had probably been formed in low yield.

Attempted epoxidation of 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone (376)

(a) To a stirred solution of 6-acetoxy-6-ethoxycarbonyl-3-methylcyclohex-2-enone (376) (7.18 g) in ethanol (37.5 ml) was added hydrogen peroxide (30%, 9.0 ml) and aqueous sodium carbonate (3 M, 2.4 ml). After 5 hours the reaction mixture was diluted with water (170 ml) and extracted with chloroform (4 x 60 ml). Evaporation of the solvent from the combined extracts left an oily residue (3.924 g). An ^1H nmr spectrum of this product showed it was starting material. No evidence for any epoxide formation was found.

(b) The above reaction was repeated using sodium hydroxide instead of sodium carbonate as the base. Despite this change, the product obtained was shown by ^1H nmr to be starting material. Again, no evidence for any epoxide formation was found.

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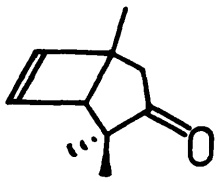
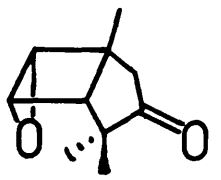
selective endo-epoxidation of (i) giving (ii). This was attributed to stereocontrol effected by the ketone carbonyl.

(i) 

(ii) 

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