Synthesis and use of cyclic peroxides

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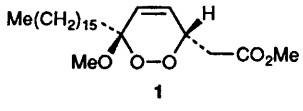
This review covers primarily the literature published between January 1992 and January 1995 inclusive although selected papers appearing in 1991 are also cited.

1 Introduction

A resurgence in the chemistry of cyclic peroxides and related compounds has been stimulated by the isolation and characterization of several natural products which not only have a cyclic peroxide unit incorporated into their structure but also possess attractive pharmacological properties.

A range of naturally occurring cyclic peroxides, as exemplified by plakortin (**1**) and muqublin (**2**), have been isolated from a variety of marine organisms; many of these compounds have considerable potential as antibiotics.[1]



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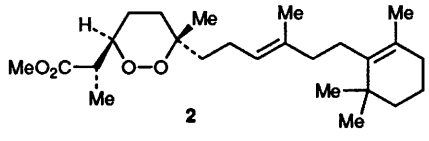

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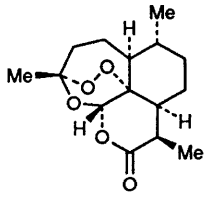
The 1,2,4-trioxane derivative (+)-artemisinin (qinghaosu) (**3**), which has been identified as the active component of a traditional Chinese herbal medicine obtained from leaves of *Atemisia annua L.*, has attracted a great deal of recent attention.[2–5] On account of their high potency and low human toxicity, artemisinin and related compounds are now being used in the treatment of some drug-resistant forms of malaria, especially *Plasmodium falciparum*. A second, lesser-known, peroxidic antimalarial agent, (+)-yinghaosu A (**4**), with an unusual dioxabicyclo[3.3.1]nonane ring system has been isolated from the leaves of *Artabotrys uncinatus* (L.) *Merr.* which are also used as the basis of a traditional Chinese herbal remedy.[5,6]



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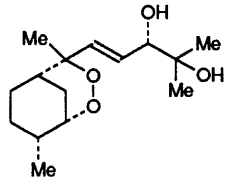

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In addition to considerations of their biological activity and structural novelty, cyclic peroxides of various types have also been employed extensively as key intermediates for the introduction of oxygen functionality into organic compounds with a high degree of stereo- and regio- selectivity.

In most of the strategies which have been developed for the synthesis of cyclic peroxides, irrespective of their structural complexity, the peroxide group is preformed, being introduced into the molecule as either molecular oxygen or hydrogen peroxide or, in some cases, ozone. Moreover, since they are intrinsically thermally labile and are highly susceptible to attack by reducing agents, the range of reagents compatible with cyclic peroxides is generally limited.

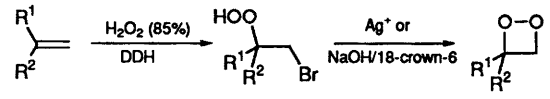
This review will attempt to highlight recent developments in the synthesis of cyclic peroxides with ring sizes from four upwards, and, where appropriate, their subsequent chemical transformation into other classes of organic compounds.

2 1,2-Dioxetanes

Although the four-membered ring 1,2-dioxetanes are highly strained and, as a consequence, hyperenergetic (*i.e.* they generate electronically excited fragments on thermal decomposition), several stable derivatives have been synthesized by either intramolecular cyclization of β-halo hydroperoxides (Kopecky method), or by [2+2] cycloaddition of singlet oxygen to alkenes.[7]

Treatment of 1,1-disubstituted alkenes with concentrated hydrogen peroxide and 1,3-dibromo-5,5-dimethylhydantoin (DDH) affords the

corresponding β-bromo hydroperoxide which subsequently undergoes base-catalysed cyclization to the 3,3-disubstituted 1,2-dioxetane **5** (**Scheme 1**).[8] 1,2-Dioxetanes derived from α-styrene derivatives have been prepared in low yield (10–15%) by a similar method.[9]

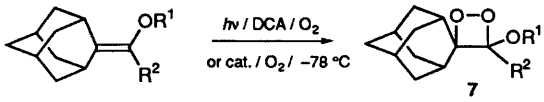


5

Scheme 1

Although the [2+2] cycloaddition of singlet oxygen to simple alkenes can provide a direct synthetic route to 1,2-dioxetanes, alternative processes, including the formation of hydroperoxides via the ene reaction or [4+2] cycloaddition, often compete readily.[7,10] The formation of dioxetanes is, however, generally more favoured with electron-rich alkenes such as enol ethers.

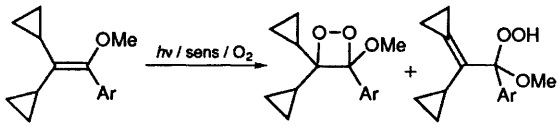
A series of thermally stable 1,2-dioxetanes **7** have been prepared in high yield by the photosensitized oxygenation of the enol ethers **6** using 9,10-dicyanoanthracene (DCA) as the sensitizer.[11] The reaction of enol ethers **6** with ground state molecular oxygen at −78°C in the presence of either tris(*p*-bromophenyl)- or tris(*o*,*p*-dibromophenyl)-ammoninium hexachloroantimonate also gives rise to 1,2-dioxetanes **7**.[12] In both cases, the reaction proceeds via the appropriate radical cation derived from **6** which is generated by single electron transfer (SET).



6 R^1 = Me, CH_2Ph, R^2 = aryl

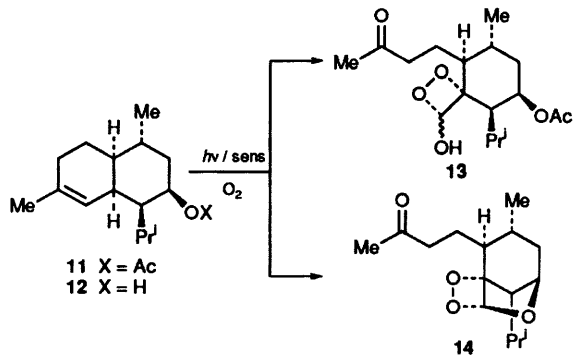
7

On photooxygenation of the dicyclopropyl enol ether **8**, the corresponding dioxetane **9** is only obtained as the major product when the reaction is carried out at −78°C. At higher reaction temperatures, the hydroperoxide **10** is the major product.[13]



8 Ar = 3-$MeOC_6H_4$ **9** **10**

Photooxygenation of the cadinene derivatives **11** and **12** has resulted in the formation of the novel ring-cleaved dioxetanes **13** and **14** respectively which exhibit modest antimalarial activity.[14]

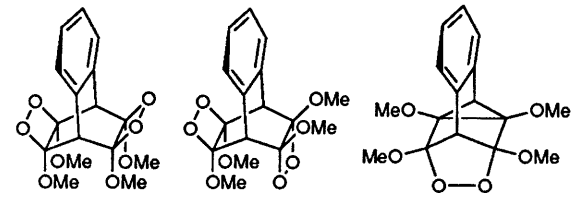


11 X = Ac
12 X = H

13

14

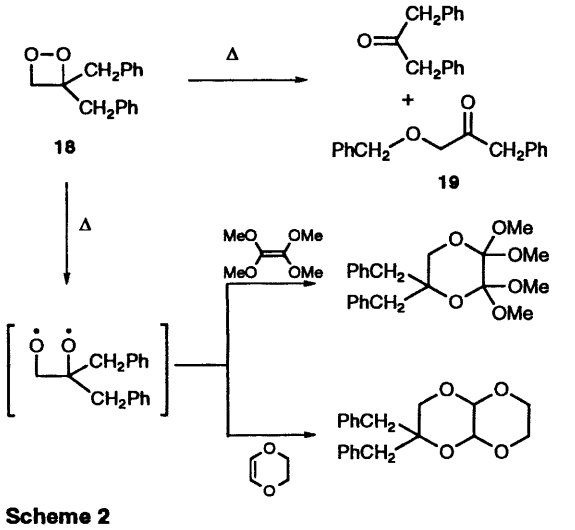
The comparatively rare diastereoisomeric bisdioxetanes **15** (68%) and **16** (20%) along with the endoperoxide **17** (12%) are obtained from the photooxygenation of the electron-rich tetramethoxybenzobarrelene at −30°C with tetraphenylporphyrin (TTP) as sensitizer.[15]



15 **16** **17**

Thermolyses of 1,2-dioxetanes, which give rise to electronically excited carbonyl fragments, have been extensively studied because of their mechanistic importance in bioluminescent processes and their potential application in molecular biology for immunoassay.[7] More recent studies have been directed towards chemical transformations of 1,2-dioxetanes.

The thermal decomposition of 3,3-dibenzyl-1,2-dioxetane **18** has afforded, in addition to the expected dibenzyl ketone (*ca.* 70%), a novel rearrangement product **19** (*ca.* 30%) which arises from a benzyl radical induced decomposition



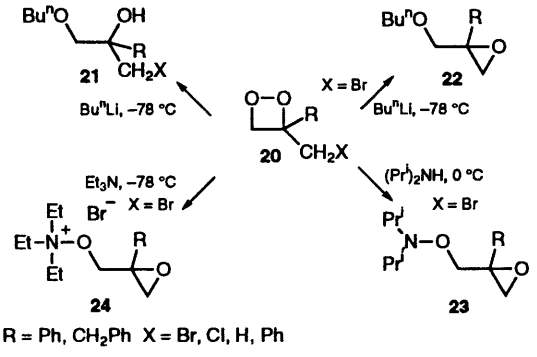
18

19

Scheme 2

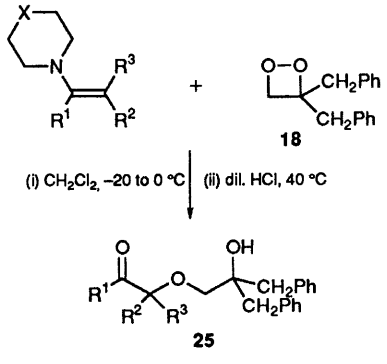
pathway.[16,17] The intermediate 1,4-dioxy diradicals from **18** and other 3,3-disubstituted dioxetanes form cycloadducts with electron-rich alkenes such as tetramethoxyethene and 1,4-dioxene (**Scheme 2**).[16,18]

In addition to appreciable quantities of ring cleavage products, 3,3-disubstituted dioxetanes **20** react with n-butyllithium, via a regioselective S_N2 displacement process on the peroxide bond, to yield the corresponding β-hydroxy ether **21** and, if X = Br or Cl, epoxy ether **22** (**Scheme 3**).[8] Heteroatom nucleophiles, including amines, sulfides, cyanide, thiocyanate, hydroxide, and halide ions, are also considered to attack the 3,3-disubstituted dioxetanes **20** at the less-hindered oxygen atom of the peroxide bond, giving rise to addition, deoxygenation, and fragmentation products.[19] With secondary amines, dioxetanes **20** are transformed into hydroxylamine derivatives **23**. Moreover, the formation of the *N*-alkoxyammonium bromide salt **24** from the reaction of **20** (X = Br) with triethylamine is consistent with the S_N2 mechanism proposed (**Scheme 3**).



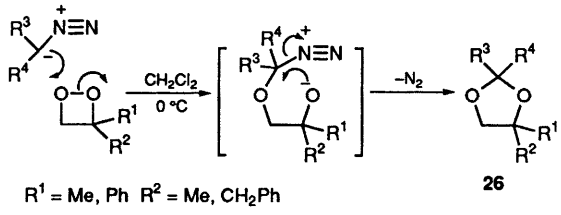
Scheme 3

In a similar fashion, enamines react with dioxetane **18** to yield, after hydrolytic work-up, α-alkoxy ketones **25** in moderate to good yield (**Scheme 4**).[20]



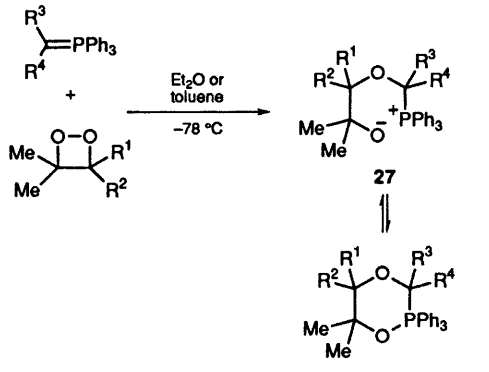
Scheme 4

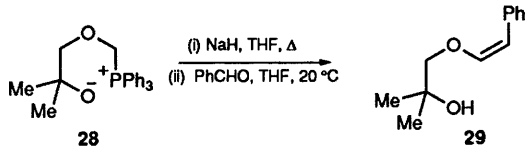
1,3-Dioxolanes **26**, which are formally products derived from carbene insertion into the peroxide bond, have been obtained from the reaction between 1,2-dioxetanes and diazoalkanes.[21] Since these reactions were carried out at low temperature, carbenes are considered unlikely to be involved. It is proposed that the reaction proceeds by an initial nucleophilic attack of the negatively charged pole of the diazoalkane on the peroxide bond followed by ring closure with concomitant elimination of nitrogen (**Scheme 5**).



Scheme 5

Triphenylalkylidenephosphoranes, being nucleophilic in character, also insert into the peroxide bond of a 1,2-dioxetane to give phosphonium alkoxides **27** which exist in equilibrium with their ring-closed isomers.[22] On deprotonation, the phosphonium alkoxide **28** participates in a Wittig reaction with benzaldehyde to give the hydroxy enol ether **29** in moderate yield.

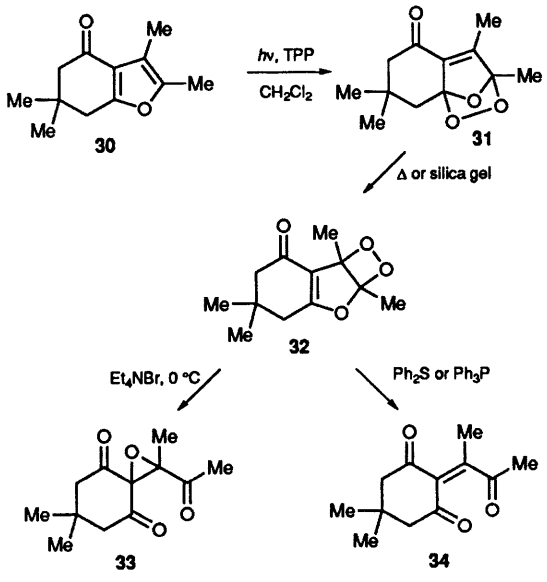




The synthesis and chemical transformation of dioxetanes derived from heterocyclic compounds, in particular benzofurans and indoles, has attracted some attention.

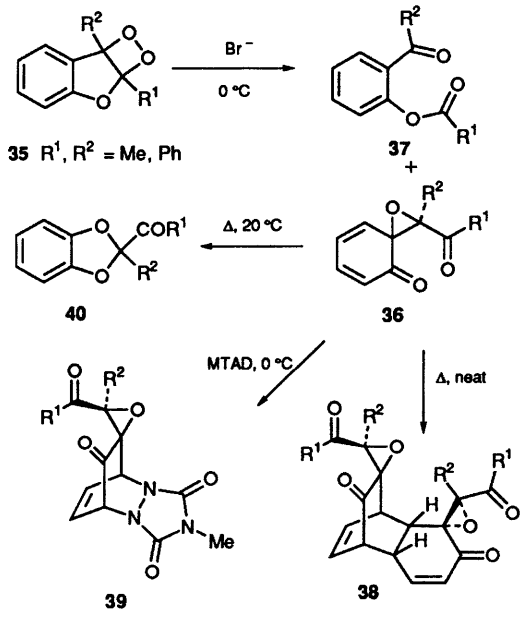
Consistent with its diene character, photooxygenation of the furan **30** affords initially the endoperoxide **31** in quantitative yield which rearranges in solution or on silica gel to give the first isolable furan derived 1,2-dioxetane **32**.[23] On treatment with catalytic quantities of

tetraethylammonium bromide, **32** rearranges cleanly to the spiroepoxide **33**. Deoxygenation of **32** using either diphenyl sulfide or triphenylphosphine gives the enedione **34** (**Scheme 6**).



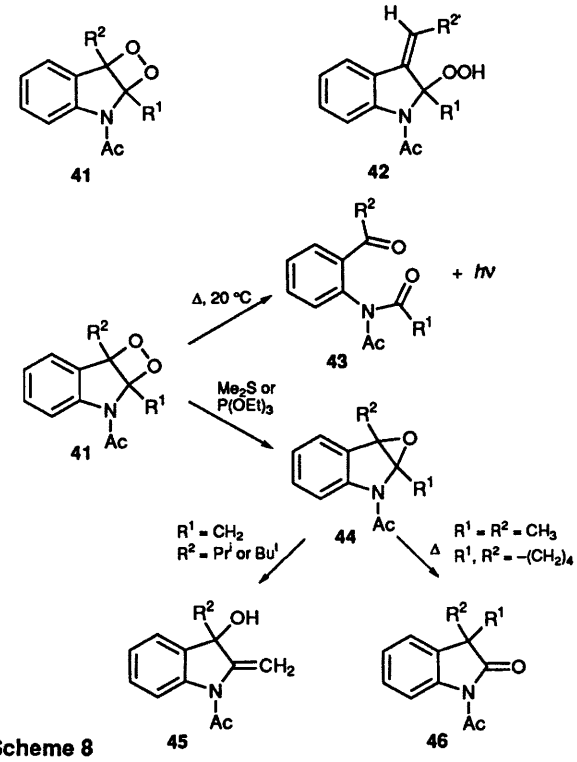
Scheme 6

Benzofuran dioxetanes **35** undergo an unprecedented bromide ion catalysed rearrangement to yield the novel spiroepoxides **36** as the major products unless either of the substituents R^1, R^2 are phenyl groups, in which case fragmentation products **37** predominate.[24] The labile epoxides **36** dimerize at low temperature in solution to give **38**, form [4+2] cycloadducts **39** with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), and rearrange to benzodioxoles **40** on thermolysis (**Scheme 7**).



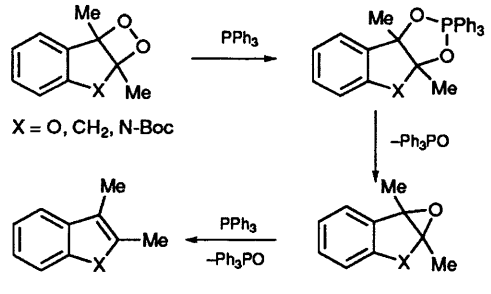
Scheme 7

Photosensitized oxygenation of N-acyl indoles results in the formation of comparatively stable 1,2-dioxetanes **41** though hydroperoxides **42** are also formed if there is an abstractable allylic hydrogen on the 3-substituent.[25–29] Since N-acylation deactivates the indole ring nitrogen, the 1,2-dioxetanes **41** are stable enough to be isolated and characterized at low temperature by spectroscopic techniques. At moderate temperatures, the 1,2-dioxetanes **41** decompose quantitatively, producing keto amides **43**, accompanied by intense chemiluminescence.[26] On treatment with dimethylsulfide or trimethyl phosphite, dioxetanes **41** are deoxygenated to the corresponding epoxides **44** which subsequently rearrange to either 2-methyleneindolines **45** or 2-indolinones **46** depending on the nature of the substituents R^1 and R^2 (**Scheme 8**).[27–29]



Scheme 8

Epoxides analogous to **44**, which are known to be highly mutagenic, have been shown to be key intermediates in the deoxygenation of dioxetanes derived from 2,3-dimethylbenzofuran, 2,3-dimethylindene, and 2,3-dimethylindole by triphenylphosphine (**Scheme 9**).[30]

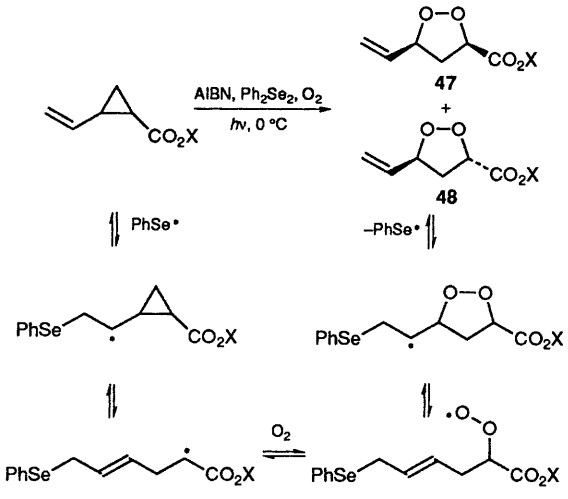


Scheme 9

3 1,2-Dioxolanes

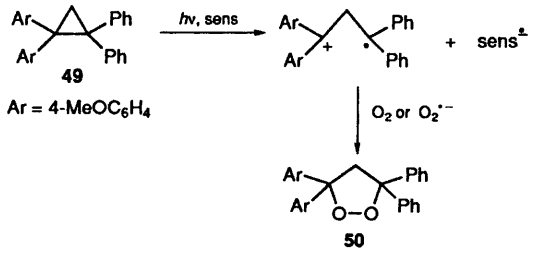
1,2-Dioxolanes are usually synthesized by a variety of radical-mediated oxygenation reactions or by intramolecular cyclization of allylic or homoallylic hydroperoxides.

Irradiation of oxygenated solutions of vinylcyclopropyl esters in the presence of diphenyl diselenide and AIBN affords mixtures of the diastereoisomeric 1,2-dioxolanes **47** and **48** via the radical-catalysed oxygenation sequence outlined in **Scheme 10**.[31] The stereoselectivity, which generally lies in favour of the *trans*-isomer **48**, is particularly pronounced when the ester group substituent is strongly electron-withdrawing [*e.g.* X = $CH(CF_3)_2$].

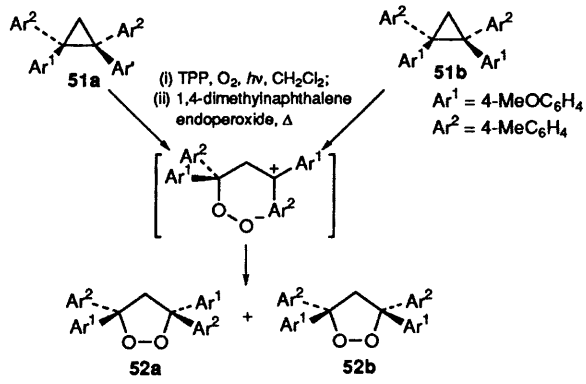


Scheme 10

1,2-Dioxolanes **50** are obtained from the photosensitized oxygenation of the electron-rich tetraaryl cyclopropanes **49** using hydroxyanthraquinones as sensitizers; DCA has also been used as a photosensitizer in analogous reactions.[32] These reactions proceed via the corresponding intermediate radical cation, generated by an electron-transfer-induced process, which subsequently combines with molecular oxygen or superoxide ($O_2^{\bullet -}$) to form **50** (**Scheme 11**). Singlet oxygen, generated thermally or photochemically, also reacts with similar cyclopropanes **51a,b** in a non-stereospecific fashion to yield the dioxolanes **52a,b** via 1,5-zwitterionic intermediates (**Scheme 12**).[33]

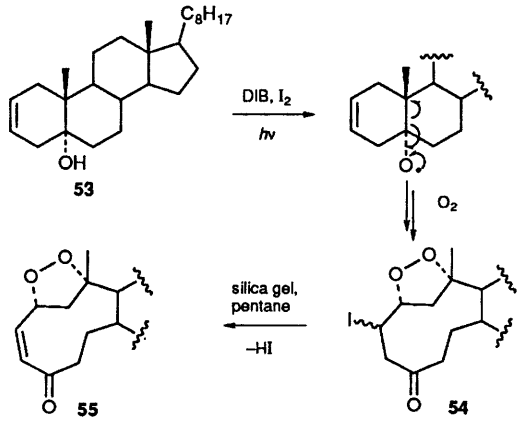


Scheme 11

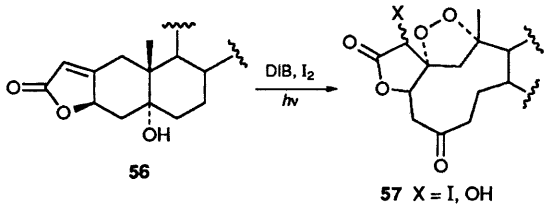


Scheme 12

When solutions of the 2-cholesten-5α-ol derivative **53** are irradiated with visible light in the presence of di(acetoxyiodo)benzene (DIB), iodine, and molecular oxygen (2–5 atm.) the resulting alkoxy radical derived from **53** undergoes β-C–C bond scission followed by cycloperoxyiodination, affording the cyclic peroxide **54** as a mixture of isomers (*ca.* 50% in total) (**Scheme 13**).[34,35] Treatment of the product mixture with silica gel yields the enone **55**. Under similar conditions, the hydroxy lactone **56** produces a mixture of iodo- and hydroxy-cyclic peroxides **57**.[35]

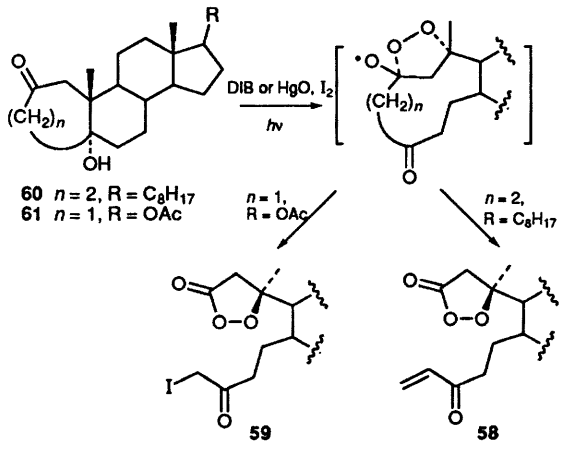


Scheme 13



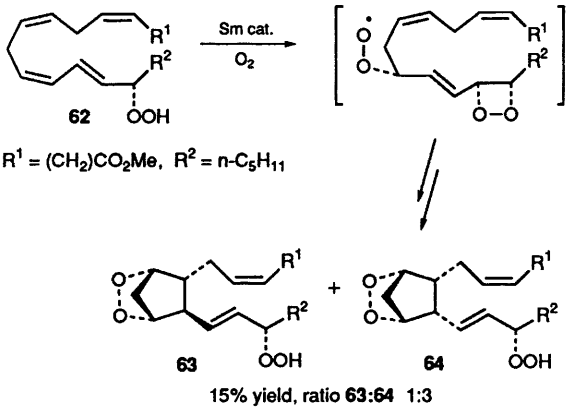
Instead of peroxides analogous to **54** and **57**, the peroxylactones **58** and **59** are obtained from the photochemical reactions of the cyclic hydroxy ketones **60** and **61** with DIB or mercury(II) oxide, iodine, and molecular oxygen.[36] Although the initial stages of the reaction mechanism are postulated to be similar to those described in **Scheme 13** the corresponding oxy radical intermediates must

undergo ring cleavage, thereby forming the peroxylactone moiety (**Scheme 14**).



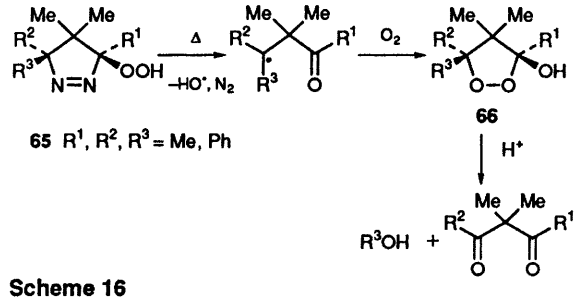
Scheme 14

The intramolecular addition of a peroxy radical to a double bond to give a 1,2-dioxolane ring is a key step in each of the sequences outlined in **Schemes 13** and **14** and also in the biosynthesis of prostaglandins and related compounds. Synthetic application of this concept has now been partially realized in the conversion of arachidonic acid, via the hydroperoxy ester **62**, into the methyl ester of PGG_2 **63** along with the 12-*epi*-isomer **64** (15%, isomer ratio 1:3) (**Scheme 15**).[37] For its success, this procedure required the development of a new catalyst, obtained from samarium(II) iodide and molecular oxygen, to effect the efficient generation of peroxy radicals from the hydroperoxide **62**. Although the overall yield is low and the product is obtained as a mixture of isomers, this procedure is commended by its inherent simplicity and represents the first biomimetic synthesis of PGG_2.



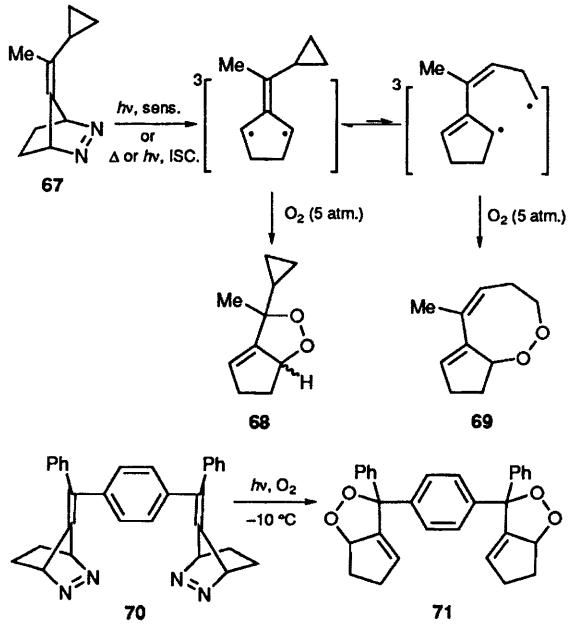
Scheme 15

Thermal decomposition of a series of pyrazoline hydroperoxides **65** in the presence of molecular oxygen (1 atm.) yields the corresponding 3-hydroxy-1,2-dioxolanes **66** in moderate yield (35–50%).[38–40] The thermally stable cyclic hemiperketals **66** do not apparently exist in equilibrium in solution with the open chain forms at room temperature but decompose under acidic conditions, particularly with phenyl groups at the 5-position, to give pentane-2,4-diones and phenols or alcohols (**Scheme 16**).[40]



Scheme 16

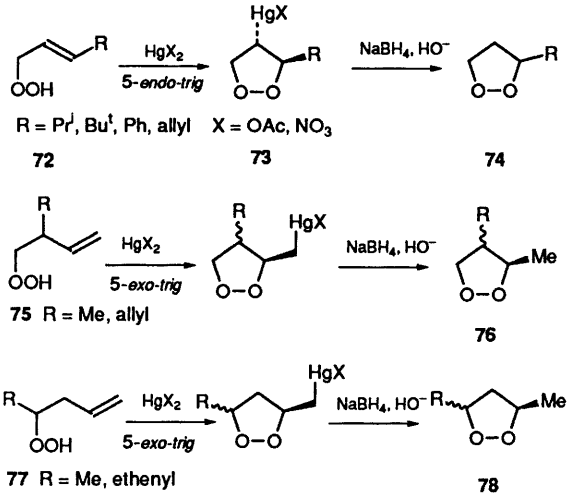
Trapping of the relatively long lived triplet diradical derived from diazoalkane **67** by molecular oxygen (5 atm.) affords the dioxolane **68** as a 1:1 mixture of diastereoisomers together with lesser quantities of the ring expanded endoperoxide **69** (**Scheme 17**).[41] Photolysis of the bis-azoalkane **70** yields in a similar fashion the structurally novel bis-dioxolane **71**.[42]



Scheme 17

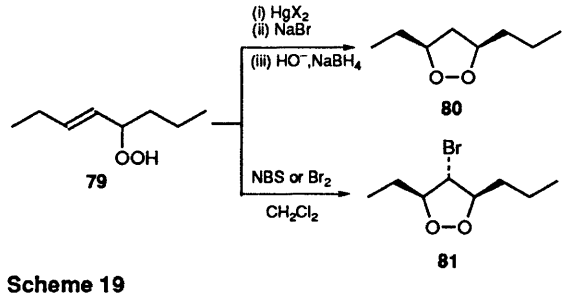
On treatment with mercury(II) acetate or nitrate, the allylic hydroperoxides **72** undergo 5-*endo* cyclization to give the intermediate mercuriated 1,2-dioxolanes **73** which are reductively demercuriated to yield in turn the 3-substituted-1,2-dioxolanes **74** (**Scheme 18**).[43] Homoallylic hydroperoxides **75** and **77** are transformed, via a similar reaction sequence, into 3,4- and 3,5-disubsituted dioxolanes **76** and **78** respectively. The cycloperoxymercuration step is highly regioselective with the mercury substituent invariably being placed on the least substituted

carbon. In the formation of 3,4- and 3,5-disubstituted dioxolanes **76** and **78**, the reaction stereoselectivity varies with the nature of the mercury(II) salt used and the steric requirements of the substituents. Generally, however, the *trans*-isomer tends to predominate for compounds **76** whereas there is a marked preference for the *cis*-isomer in **78**.



Scheme 18

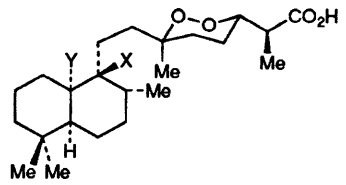
Cycloperoxymercuration–dehydridomercuration of the allylic hydroperoxide **79** affords 3-ethyl-5-n-propyl-1,2-dioxolane **80** exclusively as the *cis*-isomer in high yield (**Scheme 19**). Moreover, treatment of **79** with either NBS or bromine gives the 4-bromo derivative **81** directly (39% yield).[44]



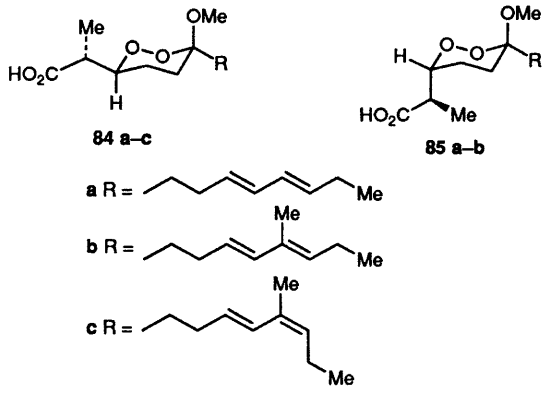
Scheme 19

4 1,2-Dioxanes and related compounds

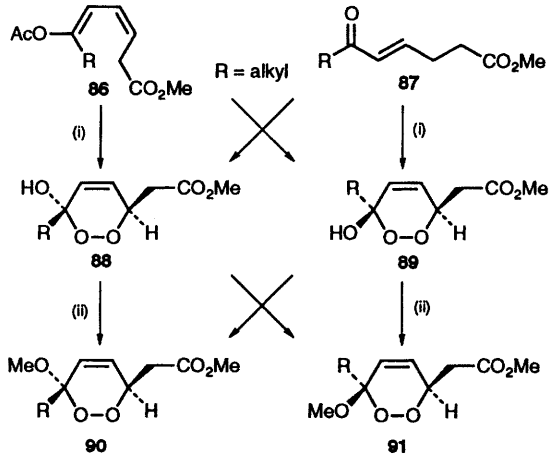
The six-membered 1,2-dioxane and 3,6-dihydrodioxine rings are found to be common structural features in many peroxy natural products.[1] Recent examples include the mycaperoxides A (**82**) and B (**83**) which have been extracted from a Thai sponge of genus *Mycale* and found to exhibit marked cytotoxicity and antiviral activity,[45] and a series of peroxyketal acids **84** and **85** which have been isolated from sponges of the *Plakortis* genus and shown to possess strong antifungal activity.[46]



82 X = Me, Y = OH
83 X = OH, Y = Me



The [4+2] cycloaddition of singlet oxygen to an acyclic 1,3-diene, which would be expected to offer the most direct synthetic route to an unsaturated six-membered cyclic peroxide, yields predominantly dioxetanes, or their fragmentation products, and/or ene-products. Nonetheless, photosentitized oxygenation of the diene **86** using a sun lamp and rose bengal (RB) as sensitizer affords a mixture of the isomeric hemiperketals **88** and **89** in moderate yield (**Scheme 20**).[47] More surprisingly, a mixture of **88** and **89** is obtained in high yield (75–85%) from the enone **87** under similar conditions using either RB or copper(II) sulfate as sensitizer. In these reactions, superoxide rather than singlet oxygen is considered to be the reactive oxygenating species. Moreover, any enone or enal capable of undergoing photoenolization to give an intermediate dienol can

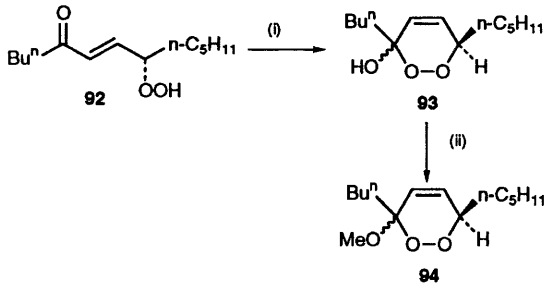


Reagents: (i) *hν* (sun lamp), RB, CH_2Cl_2-MeOH (19:1)
(ii) MeOH, TsOH, 25 °C

Scheme 20

be transformed by this latter procedure into the corresponding hemiperketal. Subsequent acid-catalysed methanolysis of **88** and **89** yields a mixture of the methoxy compounds **90** and **91** which are readily separable by chromatography. Racemic chondrillin (**90**, R = n-$C_{16}H_{33}$) and plakortin (**91**, R = n-$C_{16}H_{33}$) have been successfully synthesized by this methodology.[47]

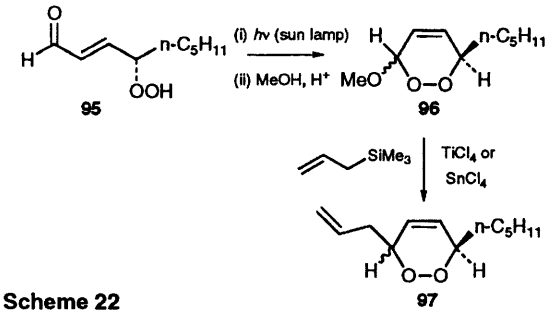
Irradiation (sun lamp) of the γ-hydroperoxy enone **92** results in double bond isomerization followed by spontaneous cyclization to produce the hemiperketal **93** (60–90%, 1:1 isomeric mixture) which on treatment with methanol and pyridinium *p*-toluenesulfonate (PPTS) affords the perketal **94** (**Scheme 21**).[48]



Reagents: (i) *hν* (sun lamp), RB, CH_2Cl_2-MeOH (19:1)
(ii) MeOH, PPTS

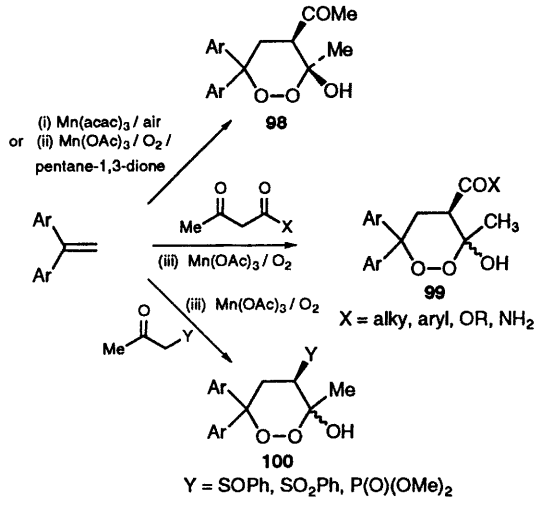
Scheme 21

Enal **95** can be transformed into perketal **96** by a similar reaction sequence. On subsequent reaction of **96** with either titanium(IV) chloride or tin(IV) chloride and allyltrimethylsilane at −78°C the 3-allyl endoperoxides **97** are obtained in moderate yield (40–59%, *cis*:*trans* ratio 3:2) (**Scheme 22**).[49]



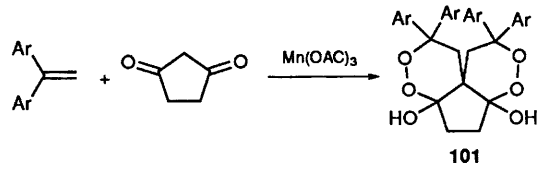
Scheme 22

The reaction of a 1,1-diarylethene with tris(2,4-pentanedionato)-manganese(III)(Mn(acac)$_3$) in the presence of air at room temperature affords the corresponding 4-acetyl-3-hydroxy-1,2-dioxane **98** in high yield.[50] More generally, oxidative free-radical cyclization reactions take place readily when Mn(acac)$_3$ is replaced by a 1,3-dicarbonyl compound and manganese(III) acetate, giving rise to a series of hemiperacetals **99** (**Scheme 23**).[50–54] Typical substrates include 1,3-diketones,[50,51] β-keto esters,[51,53] and acetoacetamides.[52] Active methylene compounds such as β-keto sulfoxides, sulfones, and phosphinates can also be employed as substrates to give dioxanes **100**.[54]

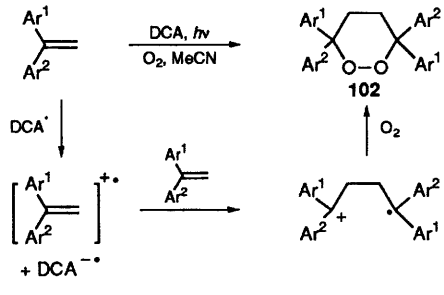


Scheme 23

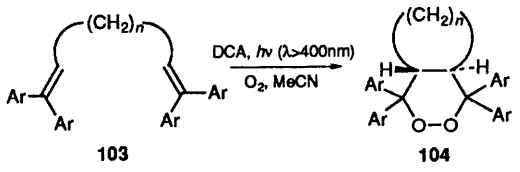
With cyclopentane-1,3-dione, the bis-hemiperketals **101** are obtained.[51] Although manganese(III) acetate is generally used as the oxidation catalyst in these reactions, manganese(II) acetate gives higher yields with active methine compounds.[53]



Photosensitized oxygenation of 1,1-diarylethenes using DCA as sensitizer affords the 3,3,6,6-tetraaryl-1,2-dioxanes **102** in high yield (>85%) providing that one of the aryl substituents has an electron-donating group at either the *para*- or *ortho*-position (**Scheme 24**).[32,55] The 1,2-dioxanes are produced in a radical chain-reaction involving the radical cation derived from the 1,1-diarylethene and ground state molecular oxygen.[55,56] Under similar conditions, the 1,ω-bis(diarylalkenyl)alkanes **103** (n = 3 or 4) are transformed into the corresponding *trans*-fused bicyclic dioxanes **104**.[57,58]

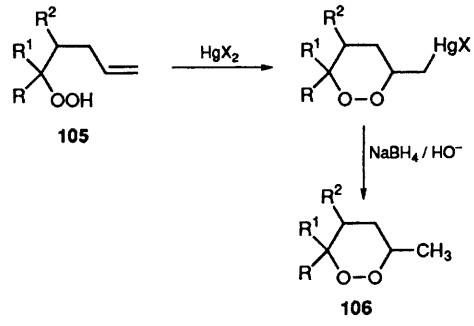


Scheme 24



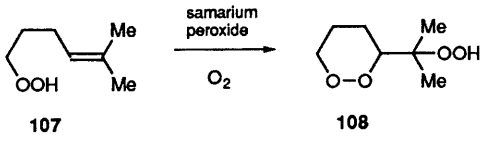
103 104

Hex-5-enyl hydroperoxide derivatives **105** have been cyclized to the 1,2-dioxane derivatives **106** by the cycloperoxymercuration/reductive demercuration sequence mentioned above for the preparation of 1,3-dioxolanes (**Scheme 25**).[43] On treatment of the hydroperoxide **107** with a recently developed samarium peroxide reagent in the presence of molecular oxygen, the dioxane **108** is obtained (70%) via a radical cyclization process.[37] The samarium peroxide reagent is claimed to be highly effective for the generation of an intermediate peroxy radical from the corresponding hydroperoxide.



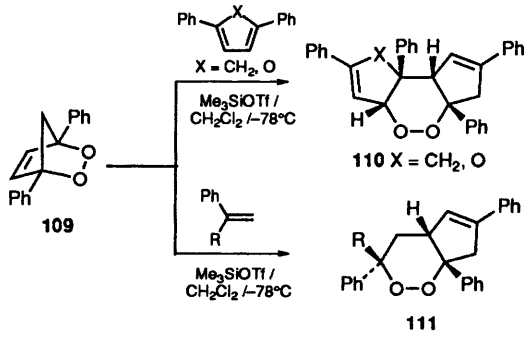
105 106

Scheme 25



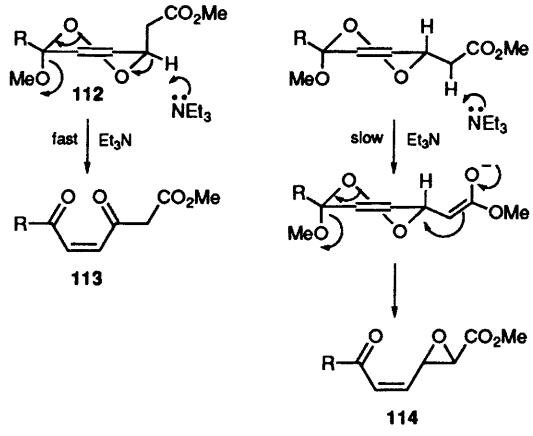
107 108

The trimethylsilyl triflate catalysed reaction between the endoperoxide **109** and either 1,4-diphenylcyclopentadiene or 2,5-diphenylfuran results in the diastereoselective formation of the tricyclic 1,2-dioxane **110** (**Scheme 26**).[59] Under similar reaction conditions, styrene and 1,2-diphenylethene produce the analogous *cis*-fused bicyclic dioxanes **111** though the acyclic olefinic moiety is incorporated with the opposite regiochemistry.



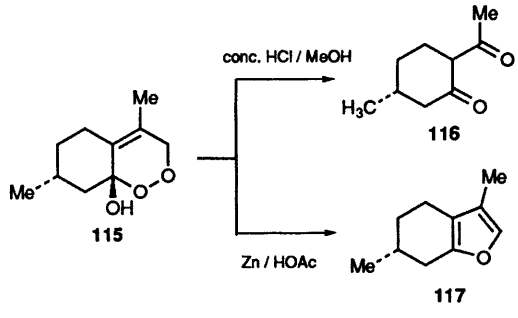
Scheme 26

3,6-Dihydrodioxines decompose under both basic and acidic conditions. The base-catalysed cleavage of peroxyketals shows a strong stereochemical dependence; thus 3,6-dihydrodioxines **112** with a hydrogen atom in a pseudo equatorial position undergo a rapid, antiperiplanar *E*2 elimination to yield initially an enedione **113** whereas the isomeric compounds with a pseudo axial hydrogen atom form the enolate which participates in an intramolecular S_N2 displacement to give an epoxide **114** (**Scheme 27**).[60]



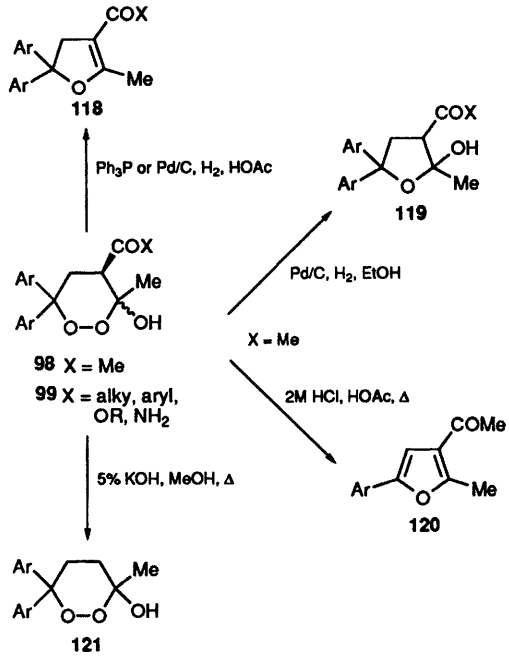
Scheme 27

In addition to the acid-catalysed formation of methyl perketals from the corresponding hemiperketals (*vide supra*), the 3,6-dihydrodioxine **115**, derived from pulegone, is transformed into the 1,3-dione **116** on treatment with concentrated hydrochloric acid in methanol (**Scheme 28**).[47] Reduction of **115** with zinc in acetic acid afforded the menthofuran **117** in 90% yield (68% overall from pulegone).[47]



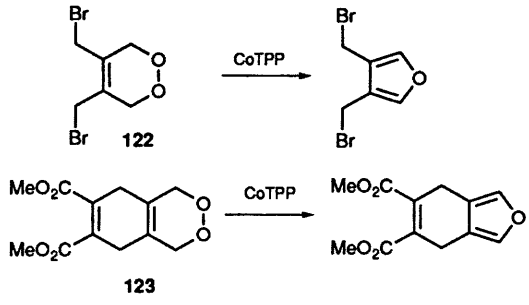
Scheme 28

The saturated hemiperketals **98** and **99** have been transformed into the corresponding dihydrofurans **118**,[50,52] tetrahydrofuranols **119**, and furans **120**[51] as outlined in **Scheme 29**. More remarkably, the dioxanes **98** were de-acylated on treatment with 5% methanolic potassium hydroxide at reflux to yield **121** (*ca.* 70–80%).[51]



Scheme 29

On treatment with cobalt(II) tetraphenylporphyrin (CoTPP), the unsaturated endoperoxides **122** and **123** rearrange to form the corresponding furan derivatives (**Scheme 30**).[61]



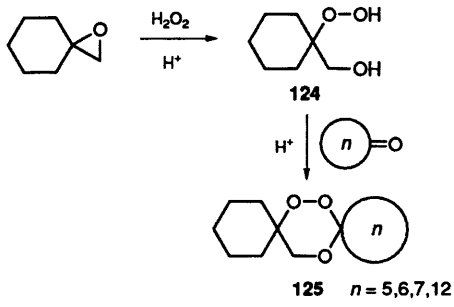
Scheme 30

5 1,2,4-Trioxanes and related compounds

Until the recognition of artemisinin (**3**) as a potent antimalarial agent, 1,2,4-trioxanes were virtually unknown as a class of compounds.[2–5] Although (+)-artemisinin (**3**) and its derivatives have proved to be attractive synthetic targets, there have also been significant developments in the chemistry of the structurally simpler monocyclic and bicyclic 1,2,4-trioxanes since several examples of these also possess attractive pharmacological properties.

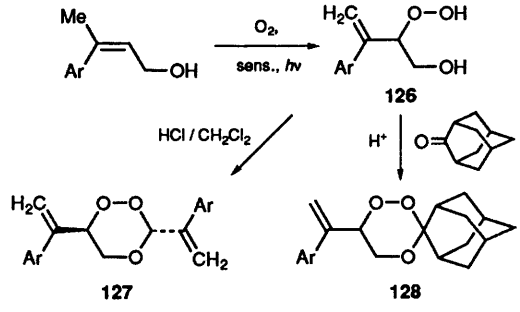
5.1 Simple 1,2,4-trioxanes

The acid catalysed perhydrolysis of methylenecyclohexane oxide under anhydrous conditions yields the β-hydroxyhydroperoxide **124** which on subsequent condensation with a cycloalkanone affords the corresponding dispiro-1,2,4-trioxane derivative **125** (**Scheme 31**).[62]



Scheme 31

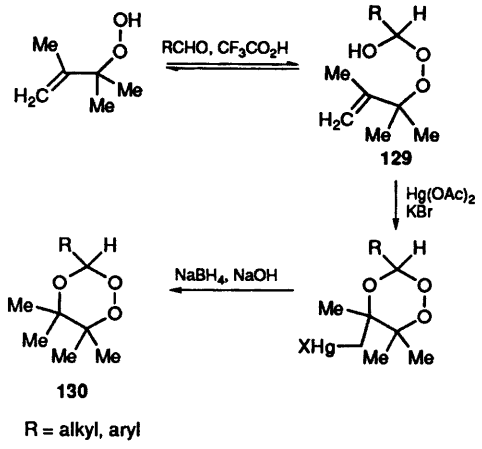
By analogy, the unsaturated β-hydroxyhydroperoxides **126**, derived from a regioselective ene reaction between singlet oxygen and the appropriate allylic alcohol, have also been transformed into the 1,2,4-trioxanes **127** which are found to be effective antimalarial agents (**Scheme 32**).[63] Treatment of **126** with concentrated hydrochloric acid in dichloromethane at room temperature results in the formation of the 3,6-bis(α-styryl) trioxane derivatives **128**, presumably via α-arylacroleins generated *in situ*.[64]



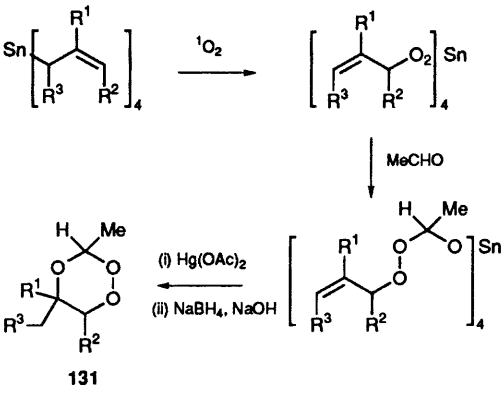
Scheme 32

In an alternative synthetic strategy, polysubstituted 1,2,4-trioxanes **130** have been conveniently prepared by the mercury(II)-mediated cyclization of hemiperacetals **129** formed *in situ* from allylic hydroperoxides and aldehydes or ketones as outlined in **Scheme 33**.[65,66]

Since tetra(allylperoxy)tin compounds, readily obtained by photooxygenation of the corresponding tetra(allyl)tin compounds via metalloene reactions, behave similarly to allyl hydroperoxides, they can be transformed into trioxanes **131** by the oxymercuration procedure (**Scheme 34**).[67] The use of intermediate tetra(allyl)tin compounds is particularly commended for the preparation of trioxanes **131** ultimately derived from gaseous alkenes.

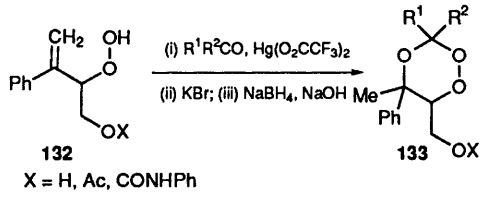


Scheme 33



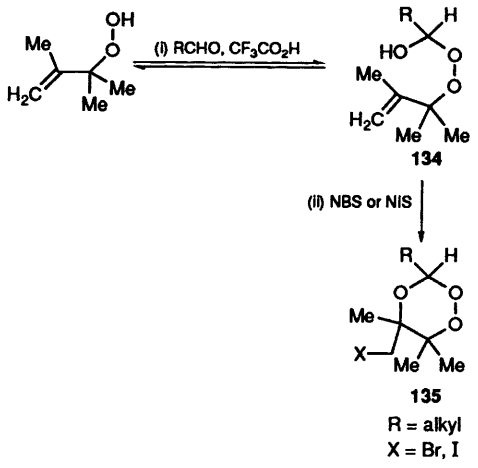
Scheme 34

When the oxymercuration reaction is carried out with the unsaturated hydroperoxides **126** (Ar = Ph) or their O-protected derivatives **132** as substrates, a series of new trioxanes **133** with an oxymethyl substituent at the 6-position is obtained (**Scheme 35**).[68]



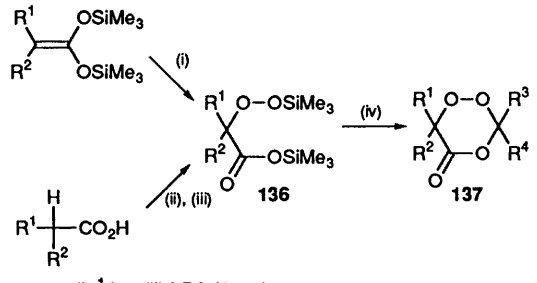
Scheme 35

Employing N-halogenosuccinimides (NIS or NBS) instead of mercury(II) salts, hemiperacetals **134** can be cyclized to give the 5-(halogenomethyl) trioxane derivatives **135** (**Scheme 36**).[69] This latter procedure is less versatile than the oxymercuration procedure because it is restricted to hemiperacetals derived from aliphatic aldehydes.



Scheme 36

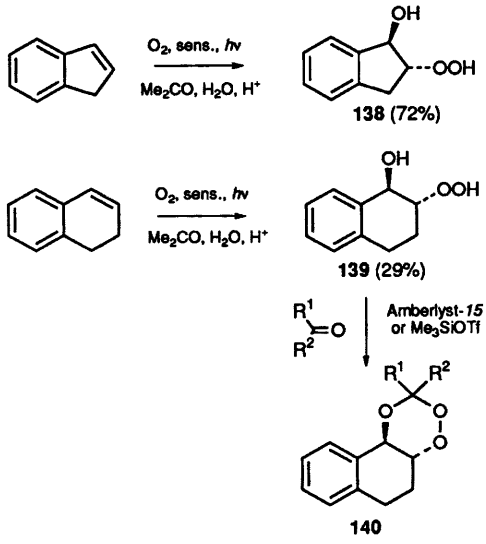
1,2,4-Trioxan-5-ones **137**, which might be expected to be relatively unstable, have been in fact readily synthesized by the trimethylsilyl triflate catalysed condensation of trimethylsilyl α[(trimethylsilyl)peroxy]alkanoates **136** with aldehydes or ketones (**Scheme 37**).[70]



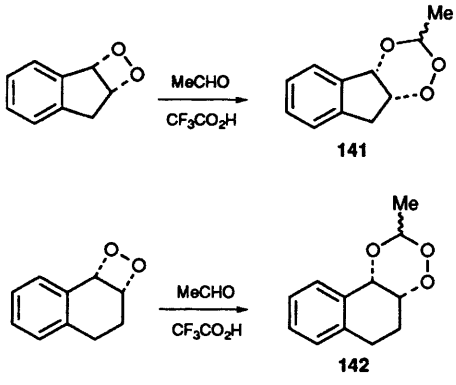
Scheme 37

Although zwitterionic intermediates, generated by the photooxygenation of electron-rich olefins, can be trapped by carbonyl compounds to yield trioxanes,[10] the analogous reactions involving either indene or 1,2-dihydronaphthalene under aqueous conditions, even in the presence of a large excess of acetaldehyde or acetone, afforded a preponderance of the *trans*-hydroxy hydroperoxides **138** and **139** respectively (**Scheme 38**).[71] Only compound **139** condensed with aldehydes or ketones to produce the *trans*-fused trioxanes **140**. *cis*-Fused trioxanes **141** and **142** have been obtained from the respective 1,2-dioxetanes derived from indene and 1,2-dihydronaphthalene.

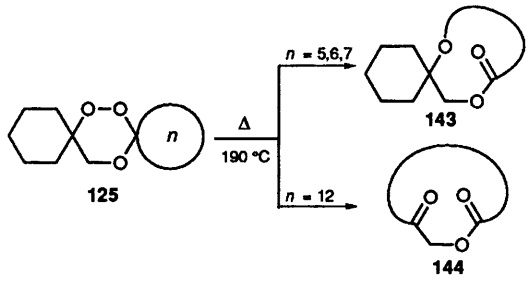
Thermolysis of 1,2,4-trioxan-5-ones **137** in solution or under flash-vacuum pyrolysis (FVP) results in extensive ring fragmentation with loss of carbon dioxide and the formation of carbonyl compounds.[72] The thermal decomposition may also be accompanied by chemiluminescence.[73]



Scheme 38

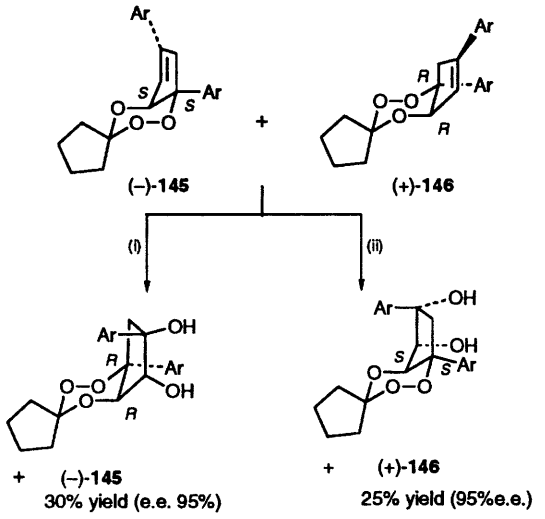


In addition to ring fragmentation, the *dispiro* trioxanes **125**, on thermolysis at 190°C in solution, undergo radical-mediated ring-expansion reactions yielding the oxalactones **143** and ketolactones **144** depending on the nature of the *spiro* substitutents (**Scheme 39**).[62]



Scheme 39

An efficient kinetic resolution of a racemic mixture of the enantiomeric *cis*-fused cyclopententeno-1,2,4-trioxanes **145** and **146** can be achieved by treatment of the respective racemic mixtures with catalytic quantities of potassium osmate, *N*-methylmorpholine-*N*-oxide (NMO), and either 1,4-bis(dihydroquinidine)phthalazine [$(DHQD)_2PHAL$] or bis(dihydroquinine)phthalazine [$(DHQ)_2PHAL$] as indicated in **Scheme 40**.[74]

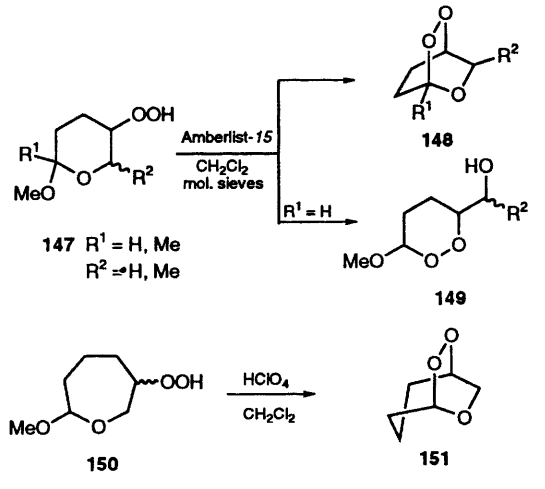


Reagents: (i) K_2OsO_4, $(DHQD)_2PHAL$, NMO, aq. Me_2CO, 20 °C, 2h
(ii) K_2OsO_4, $(DHQ)_2PHAL$, NMO, aq. Me_2CO, 20 °C, 2.7h

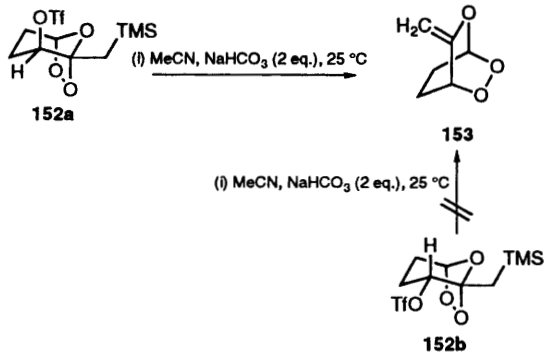
Scheme 40

5.2 Polycyclic 1,2,4-trioxanes related to artemisin

Acid-catalysed cyclization of the hydroperoxides **147**, derived from the corresponding hydrazines, has afforded the bicyclic 1,2,4-trioxanes **148** along with the 1,2-dioxanes **149** if $R^1 = H$.[75] On treatment with perchloric acid in dichloromethane, a mixture of the isomeric methoxyhydroperoxides **150** was converted quantitatively into the bicyclic ring system **151**, the putative pharmacophore of artemisinin (**3**).[76]

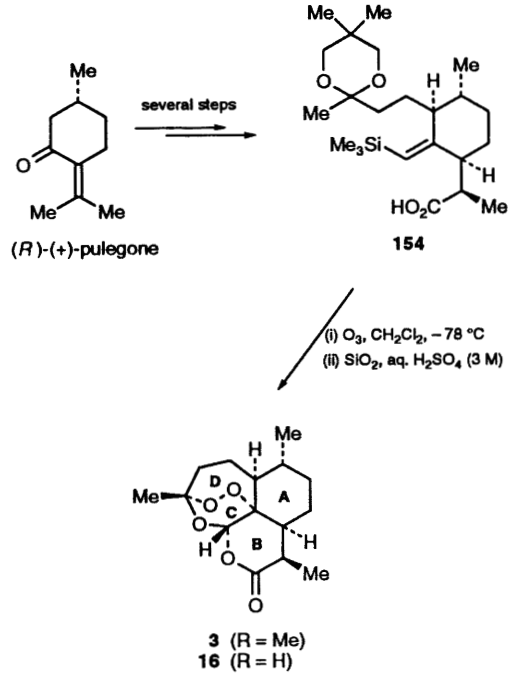


The *exo*-bicyclic ozonide **152a** rearranges smoothly into trioxabicyclo[2.2.2]octane derivative **153** (90% yield) in acetonitrile buffered with sodium hydrogen carbonate via a cationic ring-expansion process operating under stereoelectronic control; the *endo*-isomer **152b** does not rearrange under similar conditions.[77]



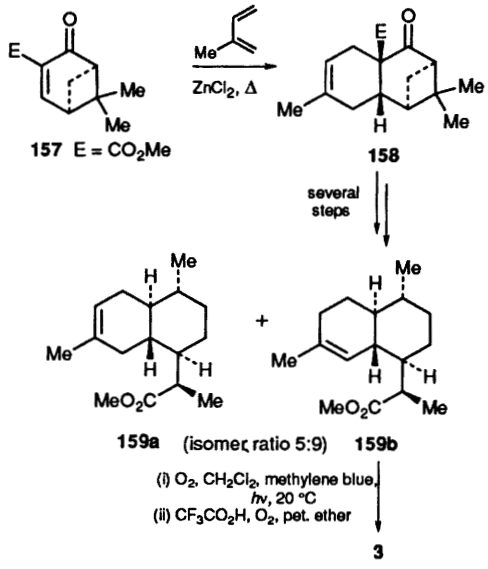
In each of the total stereoselective syntheses of (+)-artemisinin (**3**) and its derivatives, a readily available terpene, which will ultimately serve as ring A in **3**, is elaborated in a linear fashion (8–15 steps) to give a key sesquiterpene intermediate. Subsequent oxygenation of this intermediate followed by acid-catalysed rearrangement of the resulting peroxide species affords **3**. Since several of the synthetic strategies adopted have been discussed in detail elsewhere,[3,5] this review will focus on recent developments in the construction of the peroxide-containing rings C and D of **3**.

In the shortest total synthesis of **3** reported to date (ten steps), the vinyl silane **154**, obtained from (*R*)-(+)-pulegone, undergoes an anomalous ozonolysis reaction to yield an intermediate siloxy-1,2-dioxetane which rearranges on treatment with acid to give **3** in 35% yield (**Scheme 41**).[78] The 9-desmethyl derivative **156** (61%) is obtained from **155** in a similar fashion.



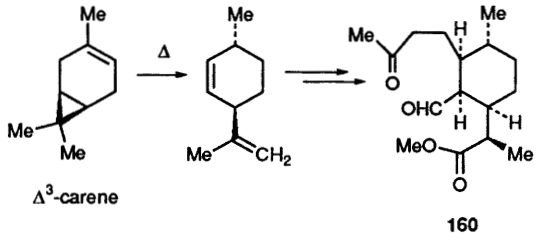
Scheme 41

The Lewis acid catalysed Diels–Alder reaction between enone ester **157**, derived from (−)-β-pinene and isoprene, yields the adduct **158** which is transformed into the regioisomeric methyl esters **159**. Photooxygenation of the inseparable mixture of regioisomers **159** followed by treatment of the crude product with trifluoroacetic acid affords **3** in 30% yield based on **159b** (**Scheme 42**).[79]



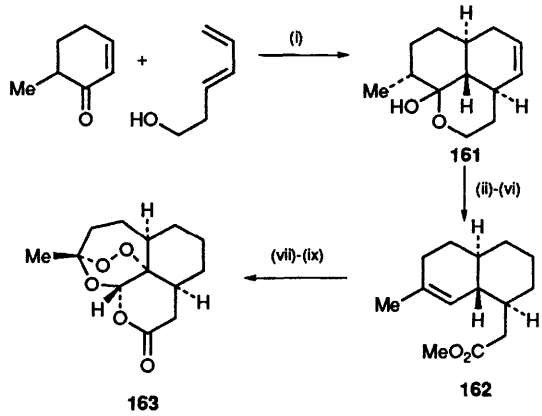
Scheme 42

A shorter, improved synthesis of a pivotal keto aldehyde (**160**) from Δ^3-carene has been reported (**Scheme 43**).[80] Artemisinin **3** can be obtained from **160** in six steps.[5]



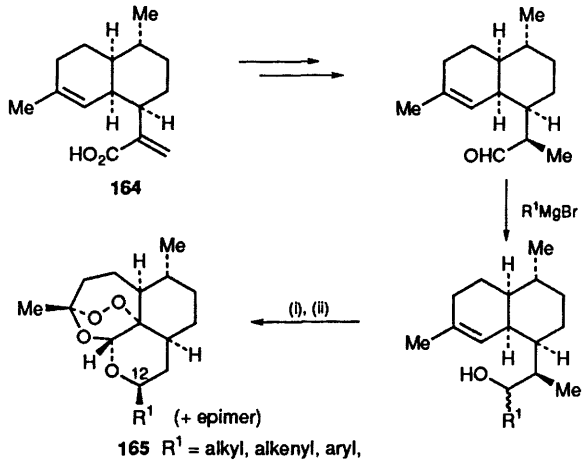
Scheme 43

Treatment of a mixture of 6-methylcyclohexenone and hexa-3,5-dien-1-ol in dichloromethane with aluminium(III) chloride or in acetonitrile with copper(II) triflate yields the tricyclic hemiacetal **161** which is readily converted into the methyl ester of desdimethyldihydroartemisinic acid (**162, Scheme 44**). Subsequent photooxygenation followed by a catalysed ring cleavage-oxygenation process provides the desdimethylartemisinin analogue **163**.[81]



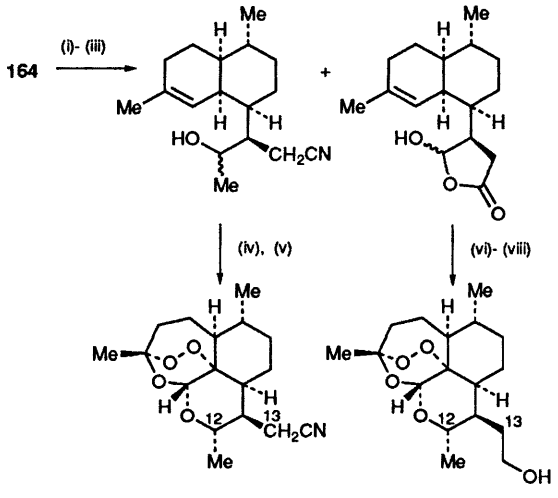
Reagents: (i)$AlCl_3$, MeCN, $Cu(OTf)_2$, –20 °C; (ii) H_2, Pd/C, EtOAc; (iii) H_2CrO_3, acetone; (iv) CH_2N_2,Et_2O; (v) $NaBH_4$, MeOH; (vi) $POCl_3$, pyridine; (vii) $^1O_2$; (viii) $Fe(phen)_3$ (0.02 eq.) then $Cu(OTf)_2$ (0.1 eq.), MeCN, O_2, –30 °C; (ix) *p*-TsOH, CH_2Cl_2

Scheme 44



Reagents: (i) O_2, MeCN, CH_2Cl_2, sens, *hv*; (ii) $Cu(OTf)_2$, MeCN, O_2, –20 °C

Scheme 45

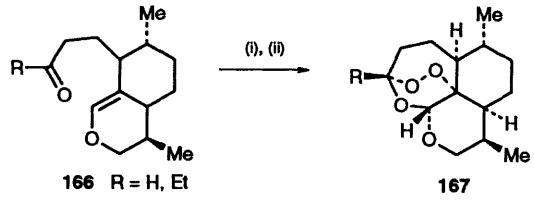


Reagents: (i) MeLi, Et_2O; (ii) KCN, NH_4Cl, aq. DMA, 120 °C; (iii) $NaBH_4$; (iv) O_2, CH_2Cl_2, sens, *hv*; (v) CF_3CO_2H, Et_2O; (vi) $LiAlH_4$, Et_2O; (vii) O_2, CH_2Cl_2, sens, *hv*; (viii) Dowex-H^+, hexane

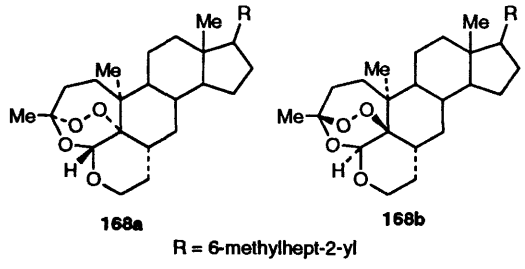
Scheme 46

Artemisinic acid **164**, which is more abundant than **3** in the plant *Artemisia annua*, has proved to be a useful precursor in the synthesis of a variety of artemisinin derivatives. Thus, several novel artemisinin derivatives functionalized at C-(12) and C-(13) have been prepared from **164** as outlined in **Schemes 45** and **46** respectively.[82–84] The 12-n-butyl derivative **165** (R^1 = n-C_4H_9) shows promising antiviral activity against HIV-1.[85]

Photooxygenation of the cyclic enol ethers **166** followed by treatment with trimethylsilyl triflate yields the corresponding desoxyartemisinin derivatives **167**.[86] Steroidal analogues **168a** and **b** are prepared in modest yield (16% and 20% respectively) by similar procedures.[87]

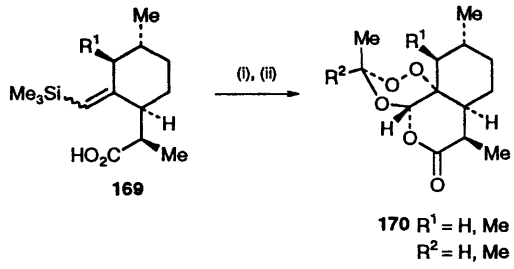


Reagents: (i) O_2, CH_2Cl_2, sens, *hv*, –78 °C; (ii) TMSOTf



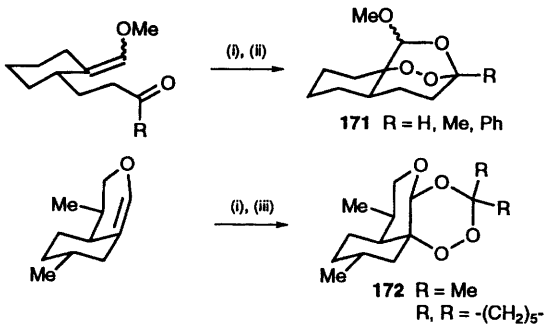
R = 6-methylhept-2-yl

By adapting a strategy used in the total synthesis of **3**,[78] low temperature ozonolysis of the vinylsilane **169** followed by treatment of the resulting product mixture with either acetone or acetaldehyde and Amberlyst-15 resin affords the tricyclic analogues **170** in which ring D is missing.[88]



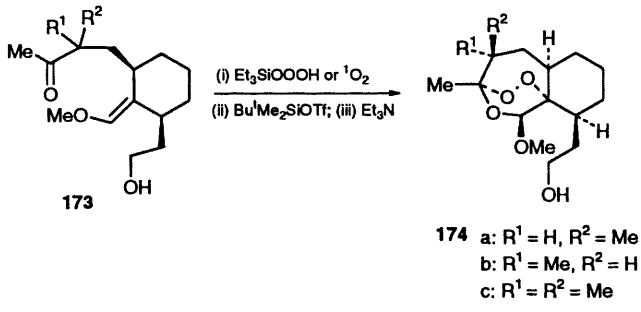
Reagents: (i) O_3, CH_2Cl_2, –78 °C
(ii) Me_2CO or MeCHO, Amberlyst-15, 22 °C

Acid-catalysed ring-opening of 1,2-dioxetanes derived from the photooxygenation of the cyclic enol ether precursors with sequential intra- or intermolecular incorporation of a carbonyl moiety yields the tricyclic analogues **171** and **172** respectively.[89]



Reagents: (i) $^1O_2$, CH_2Cl_2, –78 °C; (ii) Amberlyst-15
(iii) R_2CO, Amberlyst-15

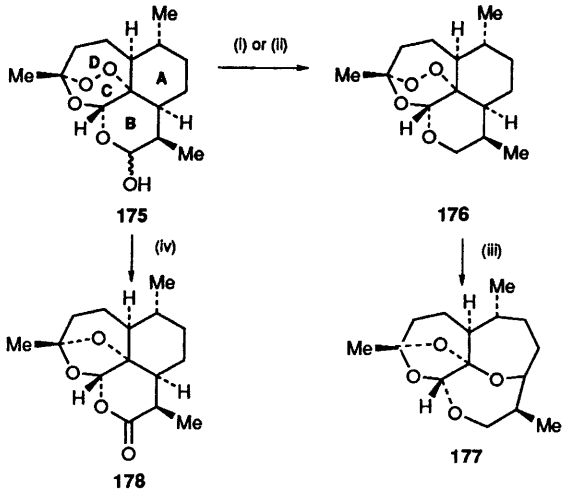
The use of triethylsilyl hydrotrioxide provides an alternative method to photooxygenation for the synthesis of 1,2-dioxetanes from electron-rich vinyl ethers.[90] Thus, the keto vinyl ethers **173** are conveniently transformed into the alkoxy tricyclic 1,2,4-trioxanes **174** as outlined in **Scheme 47**.[91,92] From structure–activity studies on the trioxane derivatives **174** it is found that only compound **174a** with a C-3 α-hydrogen atom, which is potentially available to participate in a 1,5-hydrogen abstraction process, exhibits antimalarial activity (almost twice as potent as **3**).[92]



Scheme 47

Treatment of dihydroartemisinin **175** with either triethylsilane and boron trifluoride etherate or H_3B–NEt_3 and trimethylsilyl chloride affords deoxyartemisinin **176**, a more active antimalarial than **3**, in high yield (**Scheme 48**).[93,94] Deoxyartemisinin **176** rearranges to **177** in the presence of a large excess of boron trifluoride etherate with cleavage of the peroxide bond resulting in contraction of rings C and D and concomitant expansion of rings A and B.[93] The peroxide bond of dihydroartemisinin **175** is also cleaved during its silica gel catalysed transformation into the lactone **178**.[95]

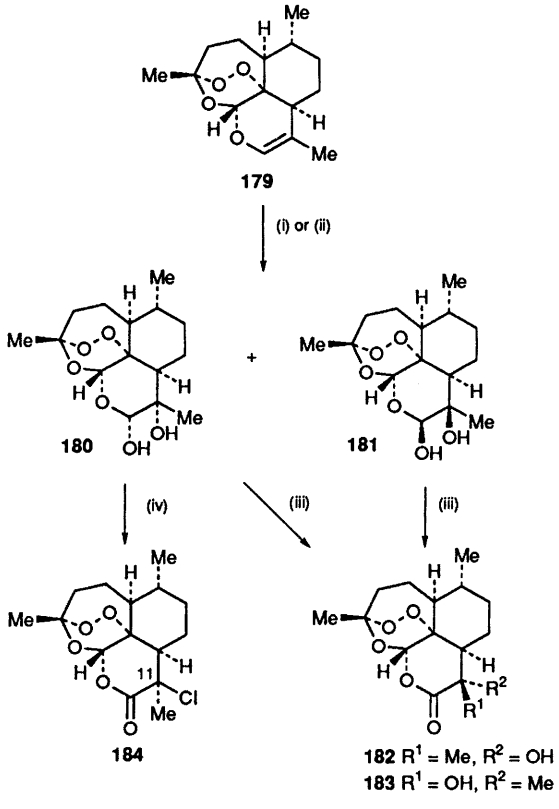
Anhydrodihydroartemisinin **179** has been found to be a useful compound for the introduction of additional functionality into ring B of **3**. Osmylation of **179** with stoichiometric quantities of osmium tetroxide in pyridine yields a 1:1 mixture of the isomeric diols **180** and **181**,[96] whereas **180** is the major isomer using catalytic quantities of osmium tetroxide with NMO as co-oxidant (**180**:**181** 7:1[97] and 10:1[98]) (**Scheme 49**). Further oxidation of **180**



Reagents: (i) Et_3SiH, BF_3-OEt_2, CH_2Cl_2, –20 °C; (ii) BH_3NEt_3, Me_3SiCl, DME, r.t.; (iii) BF_3-OEt_2 (30 eq.), MeCN, 0 °C; (iv) SiO_2, benzene, Δ, 6h.

Scheme 48

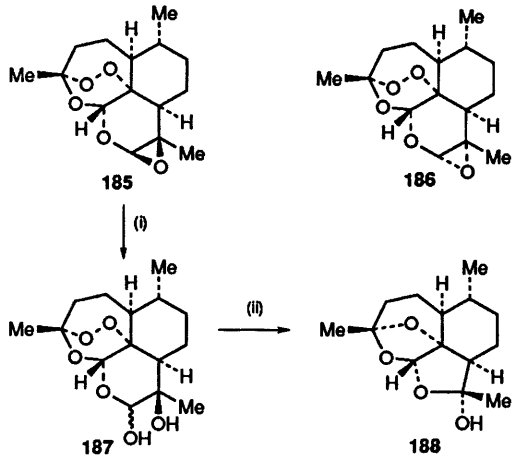
and **181** with either Jones reagent[96,98] or PCC-alumina[97] affords the corresponding 11-α- and 11-β-hydroxy derivatives **182** and **183** respectively. On treatment with thionyl chloride in pyridine, compound **180** is transformed into 11-β-chloroartemisinin **184**.[97]



Reagents: (i) OsO_4 (1 eq.), pyridine; (ii) OsO_4 (cat.), NMO, aq. acetone or Bu^tOH; (iii) Jones reagent or PCC-alumina; (iv) $SOCl_2$, pyridine

Scheme 49

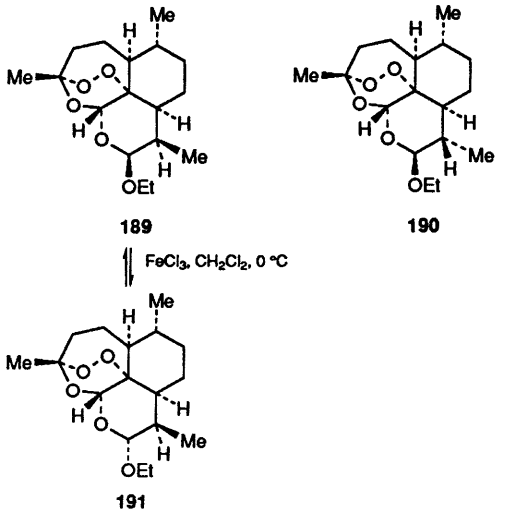
Epoxidation of **179** using either *m*-chloroperbenzoic acid (*m*CPBA) buffered with aqueous sodium hydrogen carbonate[96] or a complex of mCPBA and potassium fluoride[95,98] yields the isomeric epoxides **185/186** in various ratios depending on conditions but **185** is always the major product.[95,99] The acid-catalysed ring-opening of **185** yields 11β-hydroxy11-epihydroartemisinin **187** which rearranges in the presence of silica gel to give the ring contacted product **188** (**Scheme 50**) (*cf.* **Scheme 48**, **175**→**178** and **176**→**177**).[95]



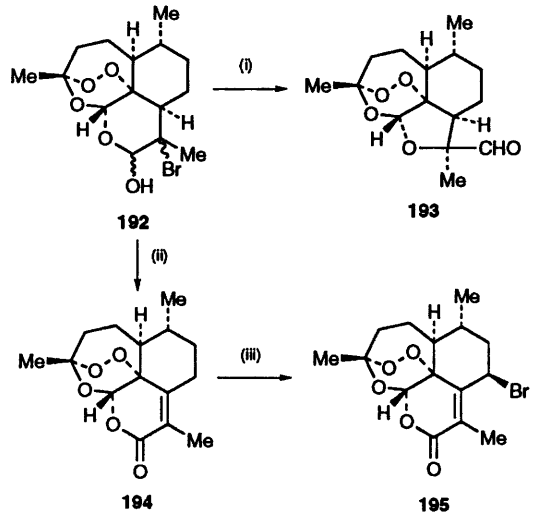
Reagents: (i) H_2SO_4 (1 M), aq. acetone; (ii) SiO_2, benzene, Δ, 10 min.

Scheme 50

The reaction of **179** with absolute ethanol in the presence of *p*-toluenesulfonic acid as catalyst yields the pharmacologically important arteether **189** together with the C-(11)-epimer **190** (3:1).[100] Surprisingly, when the reaction solvent is changed to dichloromethane, the epimeric ratio **189**:**190** inverts (1:3). Treatment of **189** with equimolar quantities of iron(III) chloride affords an equilibrium mixture of **189** and the C-(12)-epimer **191** (*ca.* 1:1).[101]



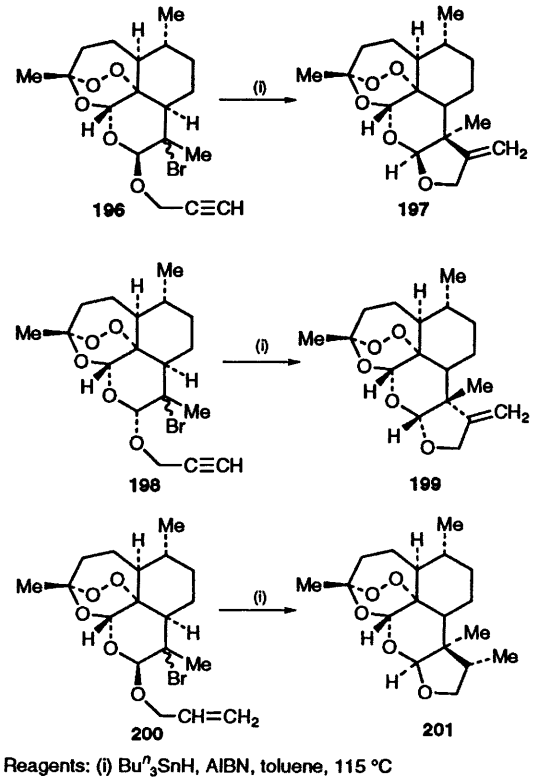
Base-catalysed dehydrobromination of the bromoacetal **192** results in ring contraction of ring B to give the aldehyde **193** (**Scheme 51**).[102] Oxidation of **192** with PCC in dichloromethane followed by treatment with DBU affords iso-artemistene **194** (overall yield of 70%) which on subsequent radical bromination with NBS gives the allylic bromo compound **195** (65% yield).[103]



Reagents: (i) DBU, CH_2Cl_2, r.t.; (ii) PCC, CH_2Cl_2 then DBU; (iii) NBS, $(PhCO_2)_2$

Scheme 51

On reduction with tri-n-butyltin hydride, the bromopropargyl ethers **196** and **198** are transformed into the *cis*-fused *exo*-methylene compounds **197** and **199** respectively via intramolecular radical

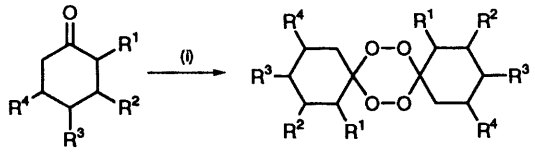


Reagents: (i) Bu^n_3SnH, AIBN, toluene, 115 °C

cyclization reactions.[104] Under similar reaction conditions, the corresponding bromoallylic ethers also undergo analogous cyclization reactions (*e.g.* **200**→**201**).

6 Ketone cyclic peroxides

The acid-catalysed peroxidation of the cyclohexanone derivatives **202** in aqueous alcohol has afforded the corresponding dimeric cyclic ketone peroxides (1,2,4,5-tetroxanes) **203** in good yield (*ca.* 70%).[105] Since such ketone peroxides are readily synthesized and exhibit antimalarial activity comparable with artemisinin **3** combined with low toxicity, they have considerable potential as inexpensive antimalarial drugs.

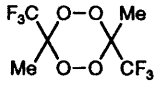


202 a: R^1 = Me, R^2 = R^3 = R^4 = H
b: R^1 = R^3 = H, R^2 = R^4 = Me
c: R^1 = R^2 = R^4 = H, R^3 = Me

203

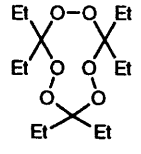
Reagents: (i) H_2O_2 (30%), H_2SO_4, aq. EtOH, 0 °C

Although tetroxanes do not usually participate in O-atom transfer reactions, trifluoroacetone diperoxide **204** is found to oxidize thioanisole to the corresponding sulfoxide and 3-methylpent-2-ene to the (*E*)-epoxide in quantitative yield.[106]



204

In addition to dimeric cyclic peroxides, peroxidation of ketones may also yield cyclic trimeric peroxides (1,2,4,5,7,8-hexoxonanes) depending on the nature of the ketone, the reaction solvent, and pH. Thus, on addition of diethyl ketone to a mixture hydrogen peroxide and sulfuric acid at −10°C, in the absence of solvent, the trimeric cyclic peroxide **205** is obtained (80% yield).[107]

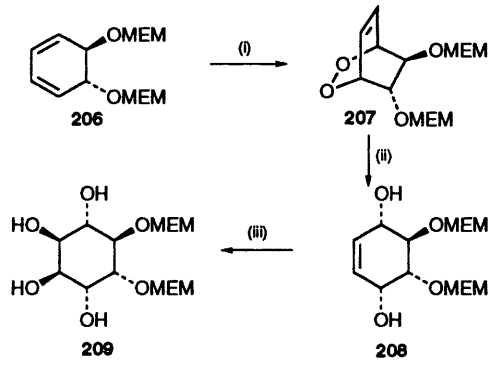


205

7 Miscellaneous endoperoxides

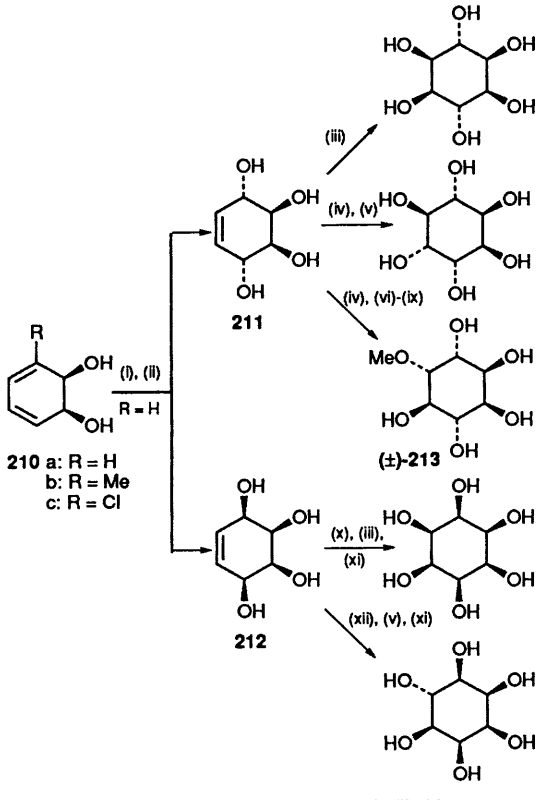
Oxygenation of cyclic conjugated dienes generally produces the corresponding bicyclic endoperoxide.[108] Although their fundamental structural and chemical properties continue to attract interest, such endoperoxides are frequently exploited as intermediates for the stereospecific introduction of *cis*-1,4-oxygen functionality into unsaturated organic molecules. Thus, several highly efficient and versatile synthetic routes to the biologically important inositols and related compounds have been developed.

Photooxygenation of the protected *trans*-cyclohexa-3,5-diene-1,2-diol **206** yields the endoperoxide **207** which is reduced by thiourea to the *cis*-1,4-diol **208** (**Scheme 52**). Osmylation of **208** affords the *chiro*-inositol derivative **209** as a single isomer.[109]



Reagents: (i) O_2, sens., *hν*, CH_2Cl_2, −70 °C; (ii) thiourea, MeOH, r. t.; (iii) OsO_4, NMO, aq. acetone, r. t.

Scheme 52

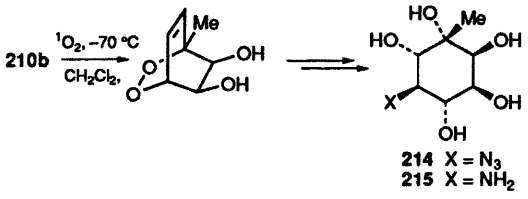


Reagents: (i) O_2, sens., *hν*, CH_2Cl_2, −70 °C; (ii) thiourea, MeOH, r. t.; (iii) OsO_4, NMO, aq. acetone, r. t.; (iv) mCPBA; (v) H_3O^+, Δ; (vi) NaH, BnBr, DMF; (vii) BnOH, NaH, DMF, 130 °C; (viii) NaH, MeI; (ix) Pd/C, H_2; (x) Ac_2O, py; (xi) K_2CO_3, MeOH; (xii) $MeCO_3H$, $MeCO_2H$

Scheme 53

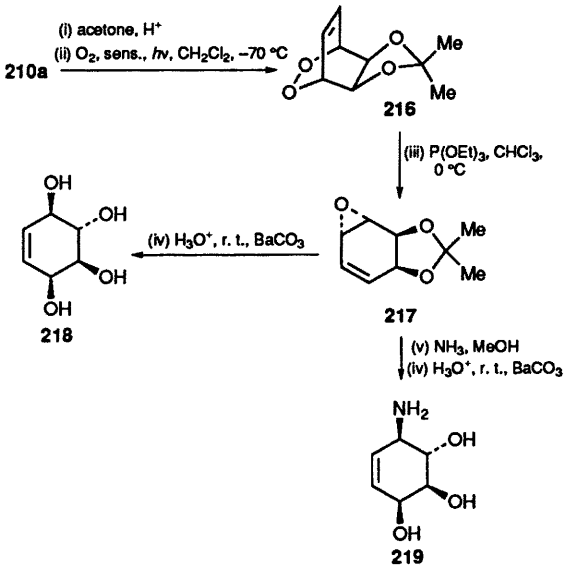
The *cis*-cyclohexa-3,5-diene-1,2-diols **210**, which are readily obtained from the microbial *cis*-dihydroxylation of the corresponding aromatic compounds, have also proved to be suitable substrates for the synthesis of a range of inositols.[110] Cycloaddition of singlet oxygen to the commercially available diol **210a** gives a readily separable mixture of the *anti*- and *syn*-endoproxides (39% and 15% yield respectively) which have been reductively cleaved to conduritol A (**211**) and conduritol D (**212**).[111] Tetrols **211** and **212** are in turn convenient precursors of a series of inositol stereoisomers and (±)-quebrachitol **213** (**Scheme 53**).

By analogous chemical steps, the homochiral azidoinosoitol **214** and aminocyclitol **215** have been enantiospecifically synthesized from the diol **210b** (**Scheme 54**).[112]



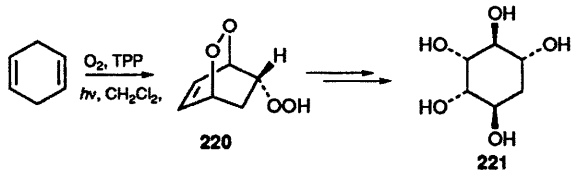
Scheme 54

Partial deoxygenation of the endoperoxide **216** with triethyl phosphite has been shown to provide the epoxide **217** (55% yield) which is a convenient precursor of conduritol F (**218**) and conduramine F_4 (**219**) (**Scheme 55**).[113]



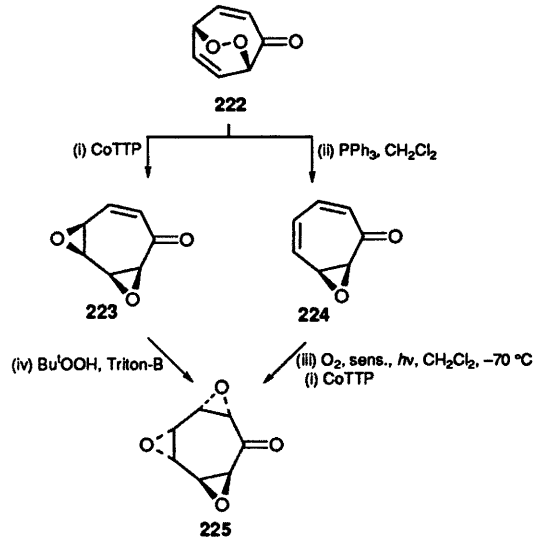
Scheme 55

Photooxygenation of 1,4-cyclohexadiene affords the hydroperoxy endoperoxide **220** (70%) which is readily transformed into the cyclohexanepentol (±)-*proto*-quercitol **221** in three simple chemical steps (**Scheme 56**).[114]



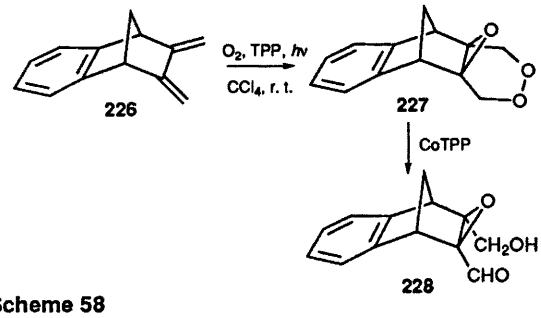
Scheme 56

Treatment of the endoperoxide **222**, derived from tropanone, with CoTPP yields the bisepoxide **223** (40%) whereas **222** is deoxygenated by triphenylphosphine to give the monoepoxide **224** (20%); both **223** and **224** can be converted into tris-epoxide **225** (**Scheme 57**).[115]



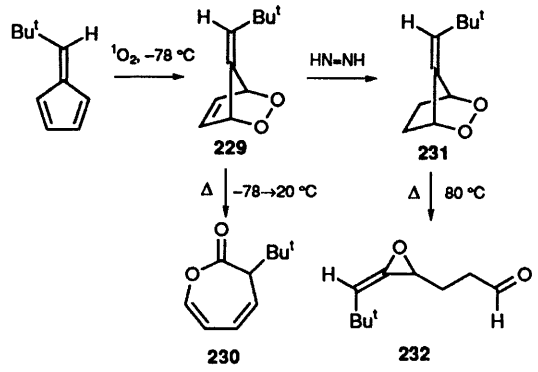
Scheme 57

Epoxy endoperoxide **227**, obtained as the sole product of the photosensitized oxygenation of **226**, undergoes CoTPP-catalysed rearrangement to give the hydroxy aldehyde **228** (**Scheme 58**).[116]



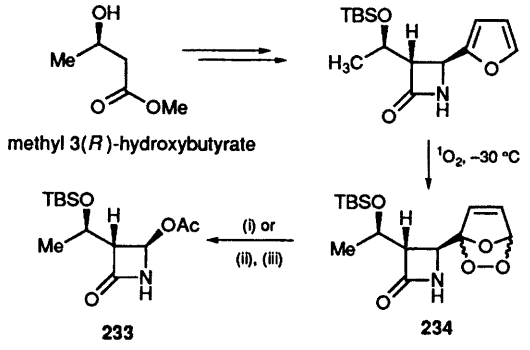
Scheme 58

Thermolysis of the fulvene endoperoxide **229** affords the oxepinone **230** as the major product whereas the mono unsaturated endoperoxide **231**, obtained by diimide reduction of **229**, rearranges to the stable allene oxide **232** on heating at 80°C (**Scheme 59**).[117]



Scheme 59

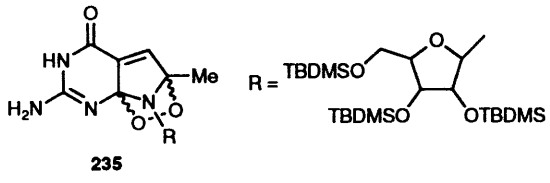
The 4-acetoxyazetidone derivative **233** has been synthesized from methyl 3(*R*)-hydroxybutyrate via the endoperoxide **234** (**Scheme 60**).[118] Although thermal rearrangement of **234** in the presence of sodium acetate provides **233** (22%), improved yields of **233** can be obtained by treatment of **234** with hydrogen peroxide followed by acetic anhydride prior to thermolysis.



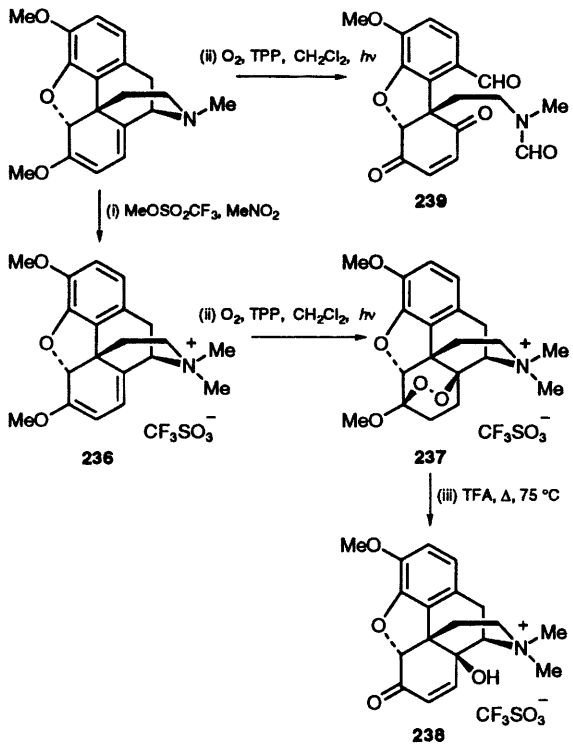
Reagents: (i) 0 °C, KOAc; (ii) H_2O_2 then Ac_2O / py; (iii) MeCN, Δ, 50 °C

Scheme 60

The [4+2] cycloaddition of singlet oxygen to a protected guanosine derivative affords the corresponding thermally labile adduct **235** as a mixture of isomers.[119] Endoperoxides related to **235** are considered to be responsible for photosensitized modifications of DNA.

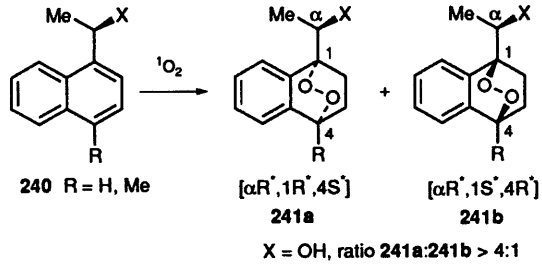


Photooxygenation of the salt **236**, derived from the quaternization of thebaine by methyl triflate, yields a stable endoperoxide **237** which on thermolysis at 75°C is converted into the 14-hydroxycodeinone salt **238** (**Scheme 61**).[120] Under similar conditions, thebaine itself produces the dihydrodibenzofuran **239** via a complex oxidative rearrangement process.

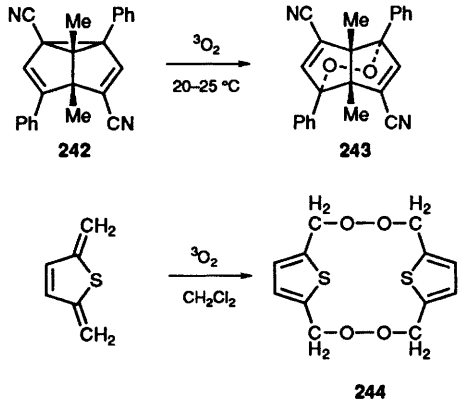


Scheme 61

In the [4+2] cycloaddition of singlet oxygen to chiral naphthalene derivatives **240**, highest diastereoisomeric ratios for adducts **241** are observed when X = OH as a result of the steering effect of the OH group on the incoming singlet oxygen species.[121]

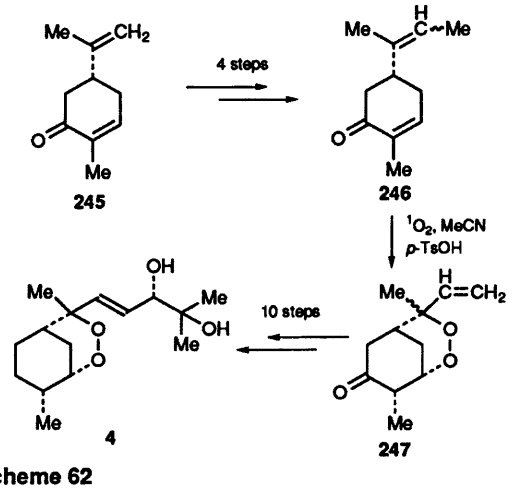


The dicyanodiphenylsemibullvalene **242** reacts readily with triplet oxygen in solution to yield the stable endoperoxide **243** (26%).[122] Oxygenation of a



solution of 2,5-dimethylene-2,5-dihydrothiophene in dichloromethane affords the macrocyclic bis-peroxide **244** in high yield.[123]

The antimalarial natural product yinghaosu A (**4**) has been synthesized from (*R*)-(−)-carvone **245** via a multi-step sequence in which the dioxabicyclo[3.3.1]nonane ring system of **4** is constructed by an ene reaction between the cyclohexenone derivative **246** and singlet oxygen followed by spontaneous cyclization of the resulting hydroperoxide in the presence of *p*-toluenesulfonic acid to yield **247** (**Scheme 62**).[5,6]

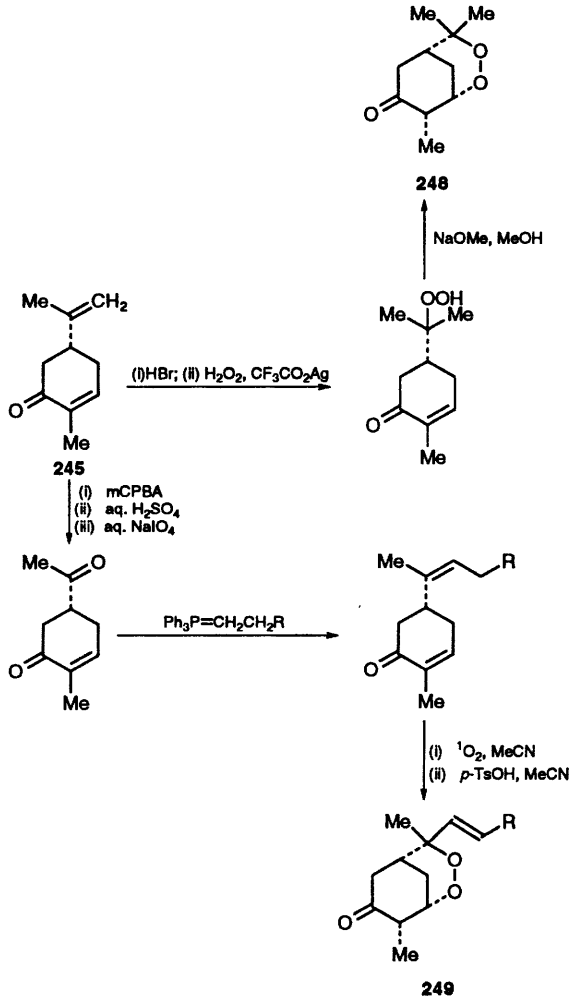


Scheme 62

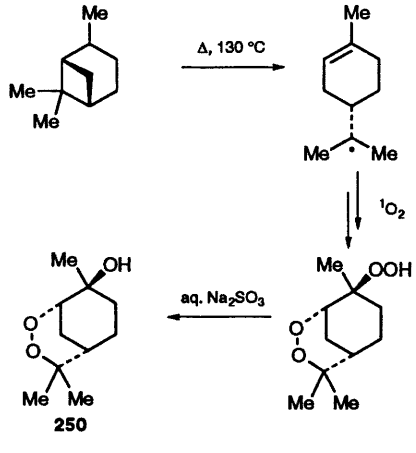
Using similar synthetic strategies, a series of enantiomeric dioxabicyclo[3.3.1]nonan-7-one analogues, *e.g.* **248** and **249**, has been prepared from **245** and its enantiomer (**Scheme 63**).[124] The structurally related compound 4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol **250** has been identified as a significant component (*ca.* 20%) of the product mixture (after treatment with sodium sulfite) arising from the autooxidation of *cis*-pinane at 130°C (**Scheme 64**).[125]

8 Cyclic peroxides derived from ozonolysis reactions

Carbonyl oxides **251**, generated *in situ* as key intermediates in the ozonolysis of alkenes and other unsaturated compounds, generally react with carbonyl compounds via [3+2] cycloaddition processes to form ozonides (1,2,4-trioxolanes) **253** or, in the presence of protic solvents (S–H), the hydroperoxides **252** (**Scheme 65**).[126,127] Although normally considered to be thermally labile and hazardous to handle, several stable ozonides have been isolated and fully characterized, including the 1,2,4-trioxolane derivative **255**, obtained by ozonolysis of alkene **254**,[128] and the polycylic ozonides **256** which have been shown to have significant antimalarial activity,[129] and the diozonide **257**, as exclusively the *endo*, *endo*-isomer, derived from hexamethyl(Dewar benzene).[130]

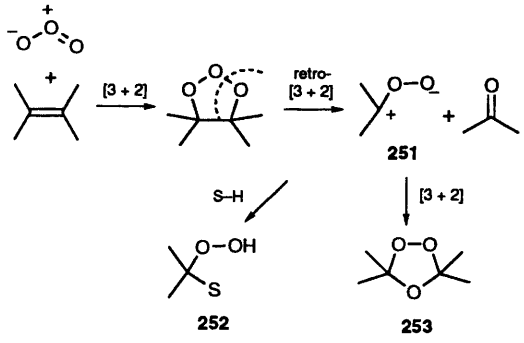


Scheme 63

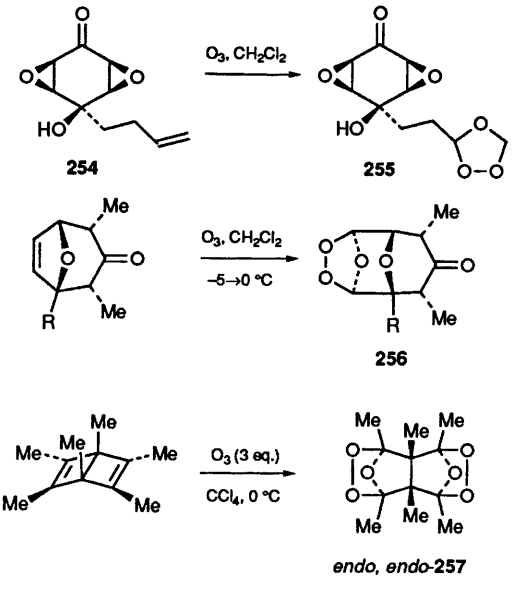


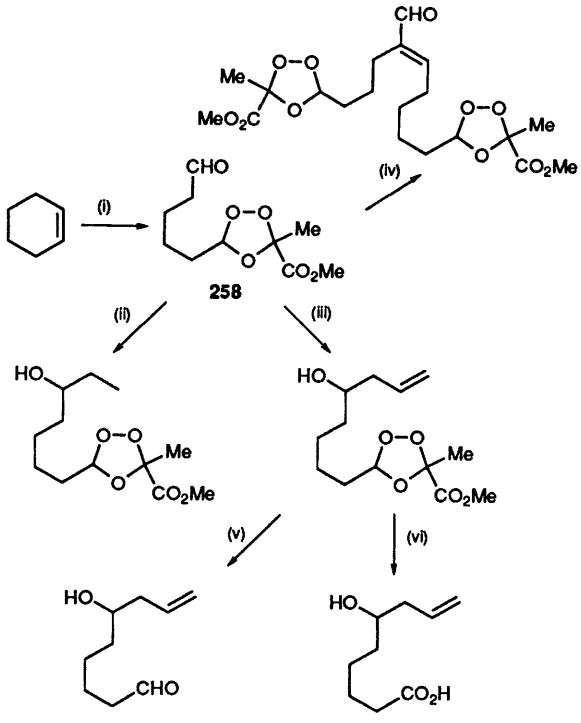
Scheme 64

Ozonolysis of cycloalkenes, illustrated by cyclohexene, in the presence of methyl pyruvate affords the corresponding trisubstituted ozonide **258**.[131,132] Since the trioxolane moiety is stable enough to function as a protected aldehyde or carboxylic acid group, the adduct **258** is terminally



Scheme 65





Reagents: (i) O_3, methyl pyruvate (1.5 eq.), CH_2Cl_2, –78 °C; (ii) Et_2Zn (1.5 eq.), BF_3-OEt_2 (1.5 eq.), CH_2Cl_2, –78 °C; (iii) CH_2=$CHCH_2SiMe_3$, $TiCl_4$ (0.5 eq.), CH_2Cl_2, –78 °C; (iv) BF_3-OEt_2 (2.3 eq.), CH_2Cl_2, r. t.; (v) Ph_3P, CH_2Cl_2, r. t.; (vi) Et_3N, CH_2Cl_2, r. t.

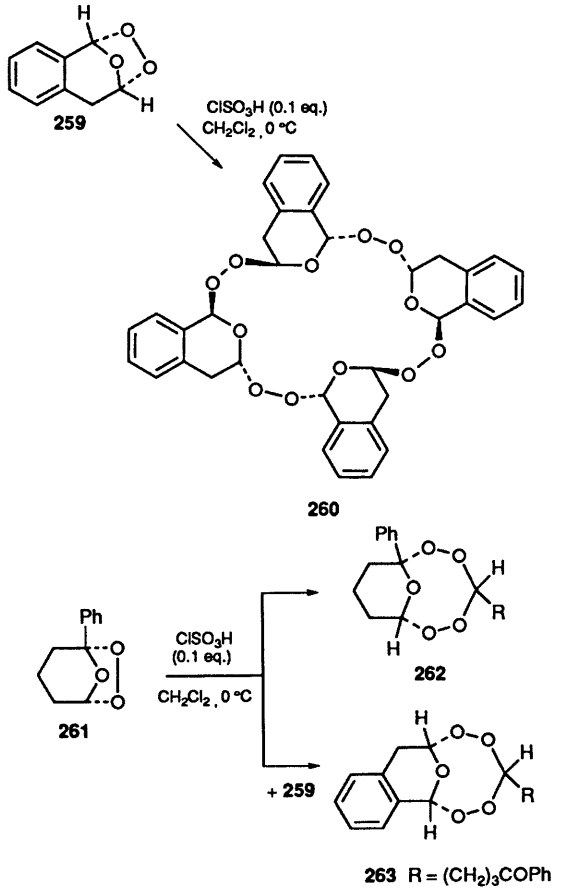
Scheme 66

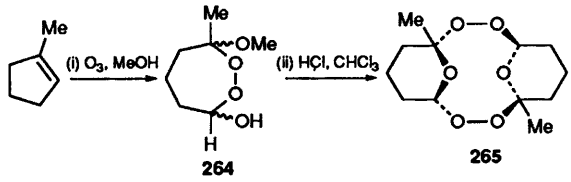
differentiated with reaction taking place selectively at the aldehyde group in a variety of subsequent chemical transformations, *e.g.* Mukaiyama-type aldol condensation reactions (**Scheme 66**).

Acidolysis of indene ozonide **259** results in formation of the crystalline cyclic tetramer **260** (20% yield) which contains a novel 20-membered dodecaoxacycloicosane ring.[133] Under similar reaction conditions, the bicyclic ozonide **261**, derived from 1-phenylcyclopentene, dimerizes to yield the 2,3,5,6,11-pentoxabicycloundecane **262** or, in the presence of **259**, forms the cross-dimerization product **263**.[133]

The tricyclic peroxide **265** is isolated in 5% yield from the acid-catalysed rearrangement of the cyclic hemiperacetal **264** obtained from the ozonolysis of 1-methylcyclopentene in methanol; dimeric bicyclic peroxides analogous to **262** have also been isolated (**Scheme 67**).[134]

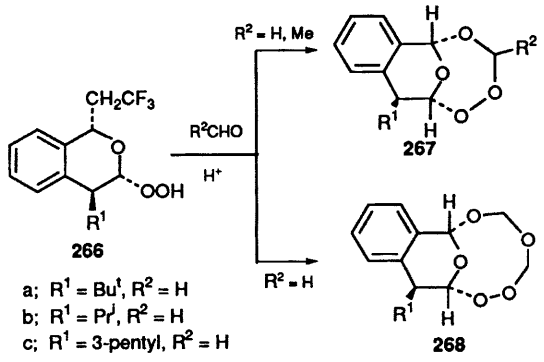
Treatment of the solvent-derived ozonolysis products, α-hydroperoxyisochromanes **266**, with formaldehyde under acidic conditions affords mixtures of the bicyclic 1,2,4,6-tetroxepanes **267** and 1,2,4,6,8-pentoxonanes **268** which have incorporated either one or two molecules of formaldehyde





Scheme 67

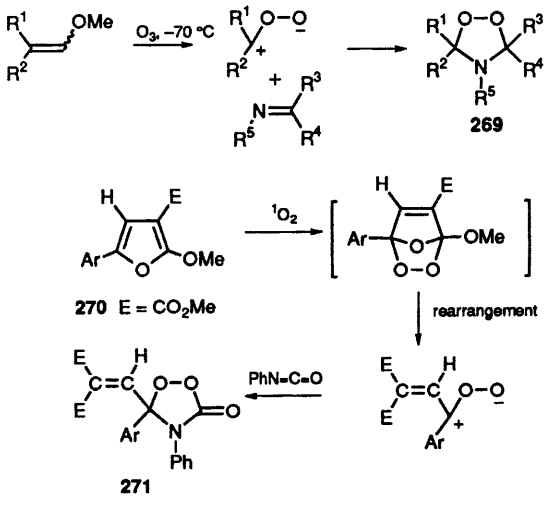
respectively.[135] When formaldehyde is replaced by acetaldehyde, only the corresponding 1,2,4,6-tetroxepanes **267** (R^2 = Me) are obtained (**Scheme 68**).



Scheme 68

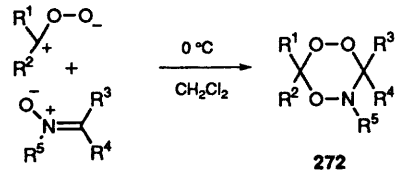
In addition to commonly observed recombination reactions with carbonyl compounds to form ozonides, carbonyl oxide intermediates may participate, with suitable co-reactants, in a variety of other cycloaddition reaction types, thus offering the prospect of alternative synthetic routes to several novel cyclic peroxide systems.[126]

Carbonyl oxides, generated by the selective ozonolysis of vinyl ethers, readily undergo [3+2] cycloaddition reactions with imines to provide the corresponding 1,2,4-dioxazolidines **269**.[136] Photooxygenation of furan derivatives **270** in the presence of phenyl isocyanate produces the 1,2,4-dioxazolidin-3-ones **271** in *ca.* 20% yield.[137] In this latter case, the required carbonyl oxides are formed by spontaneous rearrangement of the unstable ozonide intermediates (**Scheme 69**).

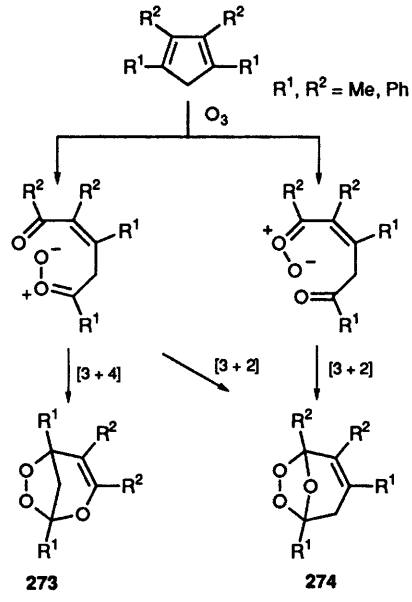


Scheme 69

The [3+3] cycloaddition reactions between carbonyl oxides and nitrones have been shown to proceed in a non-concerted fashion to yield the dihydro-1,2,4,5-trioxazines **272**.[138]

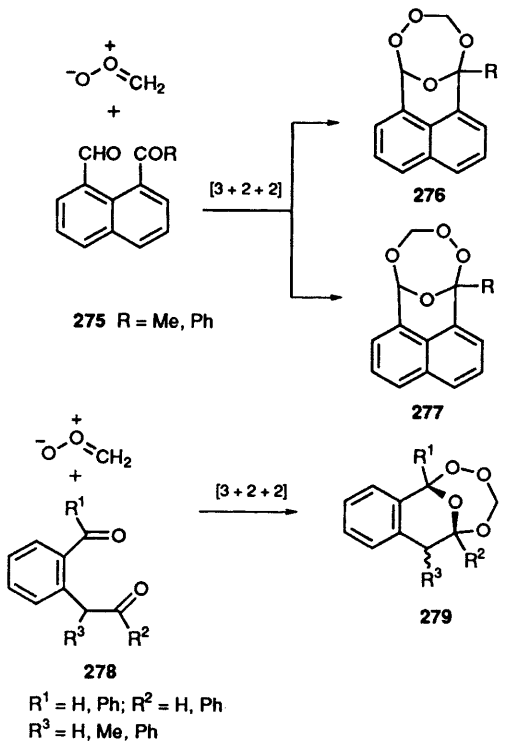


The ozonolysis of cyclopenta-1,3-dienes generally yields monomeric products consisting of either the unsaturated bicyclic endoperoxides **273** containing 1,2,4-trioxepine ring, or the unsaturated ozonides **274**, or mixtures of **273** and **274** (**Scheme 70**).[139] The bicyclic endoperoxides **273** are considered to arise from a stepwise intramolecular [3+4] cycloaddition process.



Scheme 70

Polycyclic 1,2,4,6-tetroxepane derivatives, analogous to **267**, are also obtained from reactions between formaldehyde O-oxide and 1,5-dicarbonyl compounds via extended [3+2+2] cycloaddition processes.[140] Thus, the keto aldehydes **275** and formaldehyde O-oxide yield mixtures of the regioisomeric compounds **276** and **277** whereas with the keto aldehydes **278**, the adducts **279** are obtained as mixtures of *exo*- and *endo*-isomers (**Scheme 71**).



Scheme 71

9 Conclusions

Recent developments in the chemistry of organic cyclic peroxides demonstrate that such compounds should no longer be regarded as chemical curiosities. The isolation and characterization of a range of naturally occurring cyclic peroxides with attractive pharmacological properties has provided a stimulus for the development of new synthetic methods directed towards such compounds and their analogues. In addition, cyclic peroxide systems such as 1,2-dioxetanes, 1,2,4-trioxanes and bicyclic endoperoxides offer considerable synthetic potential as intermediates for the stereospecific introduction of oxygen functionality into a range of organic molecules.

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