α-Substituted organic peroxides: synthetic strategies for a biologically important class of *gem*-dihydroperoxide and perketal derivatives

Katja Žmitek,[a] Marko Zupan[a,b] and Jernej Iskra*[a]

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In this paper we review the recent developments in the synthesis of α-substituted hydroperoxides. α-Substituted hydroperoxides are interesting compounds due to their chemistry and bioactivity and as intermediates for the synthesis of other peroxides, of which cyclic peroxides are of major importance. Although the emphasis of this report will be on the derivatives of *gem*-dihydroperoxides, perketals, as well as the less studied nitrogen and sulfur derivatives, will also be covered.

1. Introduction

Oxidation is one of the basic reactions in nature and is used by most life forms to transform food into energy. However, although oxidation has an important role in an organism's defence system, it can also be damaging to cells, where peroxides play a crucial role. This dual nature of oxidation points to the importance and the complexity of the oxidation reaction in biochemical pathways.[1] In chemistry, the situation is similar with oxidation being a fundamental reaction with hydrogen peroxide and molecular oxygen as basic oxidants. They became very important reagents due to their potential in "green" chemistry applications.[2,3] Organic hydroperoxides and peroxides are also important reagents, intermediates and products in various fields of organic chemistry ranging from radical processes, polymerizations to oxidations.[4–6] More important is their function in nature and many hydroperoxides have bioactive properties or play an important role as reactive intermediates in natural processes.[7–10] Hydroperoxides are intermediates in the auto-oxidative transformation of polyunsaturated fatty acids and DNA leading to various diseases.[11–14] Some examples of bioactive hydroperoxides include contact allergens (**1**, **2**), naturally occurring litseaverticillols as anti-HIV activity compounds (**3**), and important compounds for the defence system of plants (**4**) (Fig. 1).[7,15–19]

Within organic peroxides, cyclic peroxides are an important class. Their chemistry and bioactivity evolved largely after it was realized that naturally occurring artemisinin (**5**) and yingzhaosu (**6**) (Fig. 2) were, due to their endoperoxide functionality and chemistry, potent antimalarial agents active against resistant strains of *Plasmodium*. This has led to the antimalarial activity of cyclic peroxides being extensively reviewed in recent years.[20–25]

[a]*Laboratory of Organic and Bioorganic Chemistry, Department of Physical and Organic Chemistry, "Jožef Stefan" Institute, Jamova 39, 1000 Ljubljana, Slovenia. E-mail: jernej.iskra@ijs.si; Fax: +386 1 4773 822; Tel: +386 1 4773 631*
[b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*

Katja Žmitek

Katja Žmitek received her Diploma in Chemistry with honours from the Faculty of Chemistry and Chemical Technology at the University of Ljubljana, Slovenia in 2003 and was awarded the Krka Prize. After graduation, she was employed by the Jožef Stefan Institute, Ljubljana, Slovenia as a researcher where she is working towards her PhD thesis in the field of organic peroxides.

Jernej Iskra

Jernej Iskra studied chemistry at the University of Ljubljana (Slovenia), from where he received his Bachelor of Science degree in 1993 and doctorate in 1998 under the guidance of Professor Marko Zupan. In that year he joined the team of Dr S. Stavber and Prof. M. Zupan at the "Jožef Stefan" Institute in Ljubljana and in 2000 obtained a Marie Curie fellowship for two years' postdoctoral research in the group of Dr J.-P. Bégué and Dr D. Bonnet-Delpon at the Université Paris-Sud. In 2002, he returned to the "Jožef Stefan" Institute in Ljubljana, where he now works on the synthesis of organic peroxides and their application as antimalarial agents as well as on "green" methods for halogenation and oxidation reactions.

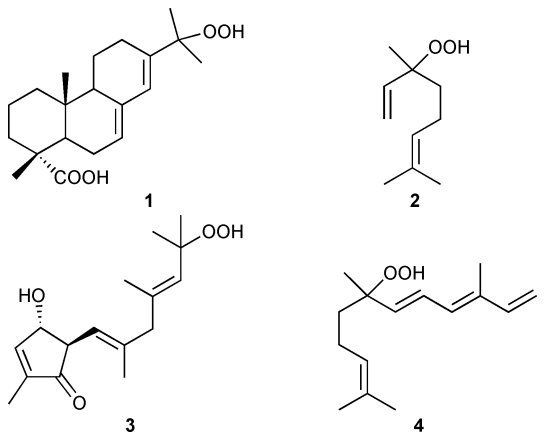


Fig. 1 Bioactive hydroperoxides **1**–**4**.

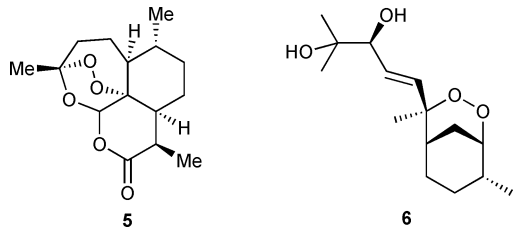
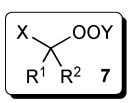


Fig. 2 Naturally occurring artemisinin (**5**) and yingzhaosu (**6**).

Recent developments in the preparation of α-heteroatom substituted hydroperoxides **7** (*gem*-dihydroperoxides, perketals and their derivatives) are interesting due to their diverse bioactivity including: as allergens, antimalarials, mycotoxins, anti-fungal and anti-tumour agents, inhibitors of enzymes, and their function in the defence system of plants and their fragrance. Furthermore they are synthetic intermediates for the preparation of various cyclic peroxides *via* cyclization reactions. In this paper we will review more fully the various strategies for the conversion of ketones or C–C double bonds with hydrogen peroxide, ozone, singlet oxygen and oxygen into various classes of α-substituted peroxides (Fig. 3) that have appeared in the literature mostly within the last ten years.

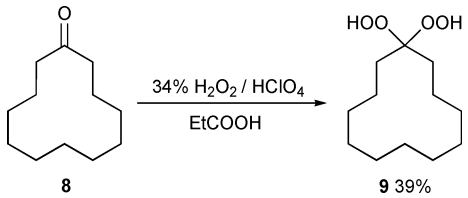


7A: X = OOH, Y = H
7B: X = OOR, Y = R
7C: X = OH, Y = H, R
7D: X = OR, Y = H, R
7E: X = NR_2, SR, Y = H, R

Fig. 3 *gem*-Dihydroperoxides **7A** and their corresponding perethers **7B**, peroxy hemiketals **7C**, peroxy ketals **7D**, together with examples of nitrogen and sulfur derivatives **7E**.

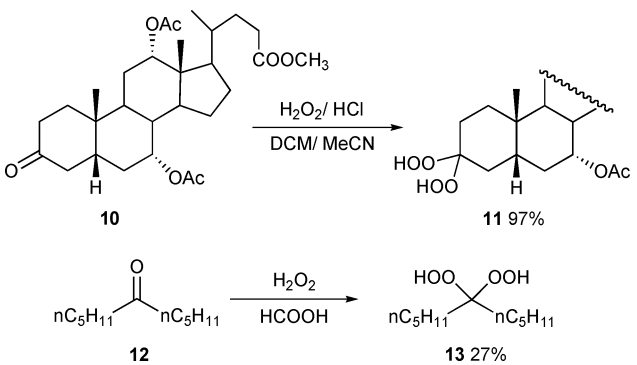
2. *gem*-Dihydroperoxides 7A

The most direct way for preparing *gem*-dihydroperoxides (DHP) is the addition of hydrogen peroxide to ketones. However, treatment of cyclohexanone with hydrogen peroxide in neutral media results in a mixture of peroxidic products, generally called cyclohexanone peroxide.[26] Selected cyclic ketones have been converted to DHPs with 30% H_2O_2, as demonstrated by Ledaal and Solbjor, who managed to isolate cyclododecanone DHP **9** under acidic conditions (Scheme 1).[27]



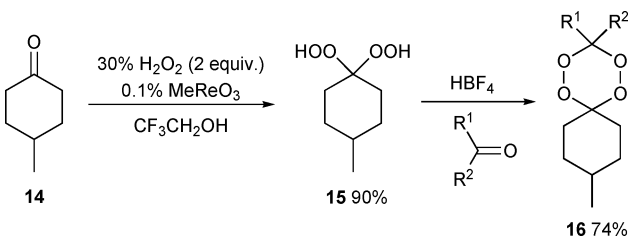
Scheme 1

This is exemplified in the preparation of the steroid DHP, where the use of HCl in a catalytic amount enabled the selective conversion of the steroidal ketone **10** to DHP **11** (Scheme 2).[28–30] For synthesis of DHPs from other ketones, and from acyclic ones, formic acid was used as a solvent and DHPs were isolated in lower yields.[31] The lower yields are a result of the acid promoted further cyclization of DHP to tetraoxanes or other cyclic products. In general, acid is employed in these reactions to improve selectivity and the yield of DHP formation. Recently, in a study on the synthesis of orally active dispiro 1,2,4,5-tetraoxanes as antimalarials, formic acid was used a solvent for the preparation of 1,1-dihydroperoxy cyclohexane as the intermediate product in 76% yield at 0 °C in 4 minutes.[32]



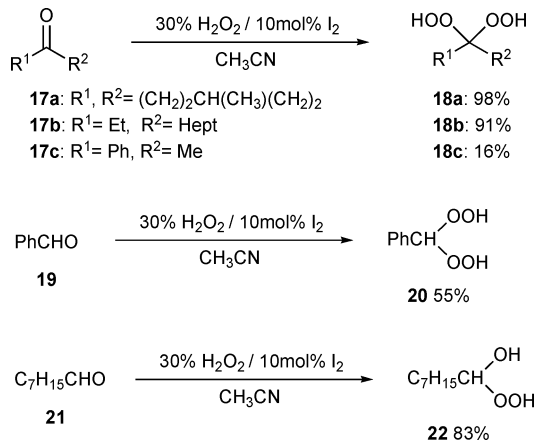
Scheme 2

Another type of catalysis was reported with methyltrioxorhenium, whose active form in reactions with hydrogen peroxide is peroxo and diperoxo complex. Therefore the acid was replaced by the methyltrioxorhenium catalyst and 4-methylcyclohexanone **14** was converted under neutral conditions in trifluoroethanol to DHP **15** in a yield of 90% (Scheme 3).[33] Further addition of ketone and acid leads to cyclization to symmetric or non-symmetric tetraoxanes **16** where fluorinated alcohol is crucial for the selective formation of **16** over other cyclic or acyclic peroxides.[34,35]



Scheme 3

A more general way of preparing DHPs **7A** under neutral conditions is with the use of 30% aqueous H_2O_2 with iodine as a catalyst. This system is effective for the preparation of various DHPs from cyclic and acyclic ketones, acetophenone and also from benzaldehyde (Scheme 4).[36,37] The yield of hydroperoxidation of various cyclic ketones was 60–98% including androstane-3,17-dione while acyclic ketones were converted with a similar efficiency. Even acetophenone **17c** was converted to the DHP **18c** albeit in a lower yield. Benzaldehydes were converted with yields of 55–76% and this is the only reported synthesis of primary *gem*-DHPs by dihydroperoxidation with H_2O_2. The reactivity of aliphatic aldehydes was the same as in non-catalyzed reactions, yielding hydroxyhydroperoxides **22**.



Scheme 4

The mechanism of iodine catalysis was studied using the relative kinetics of the substituted benzaldehydes giving a Hammett reaction constant (ρ) of −2.76. This suggests the development of a strong positive charge in the transition state of dihydroperoxidation (Fig. 4).[37]

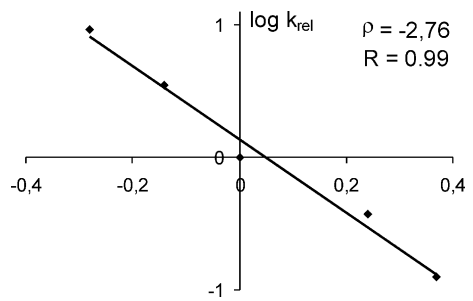
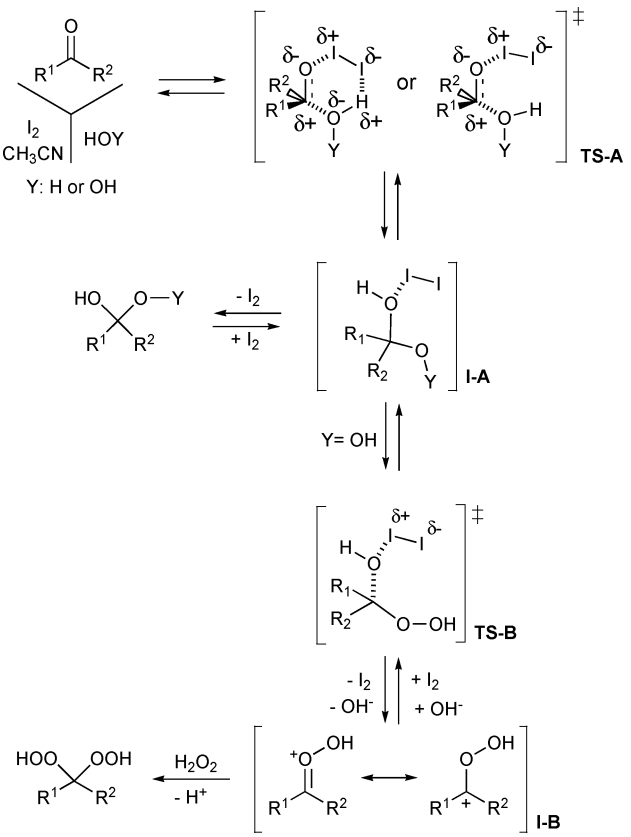


Fig. 4 Relative kinetics of the iodine-catalyzed reaction of benzaldehydes with 30% H_2O_2.

The mechanism of catalysis with I_2 is thought to be a two-step reaction, with iodine being essential in each step and possibly playing a double role as a catalyst. The iodine enhances the electrophilic character of the carbonyl C-atom and secondly it enhances the nucleophilic character of hydrogen peroxide. It also assists in the rehybridization of the sp^3 C-atom into the sp^2-one in the second step, which enables the further addition of a nucleophile (Scheme 5). It is evident that iodine is able to discriminate between

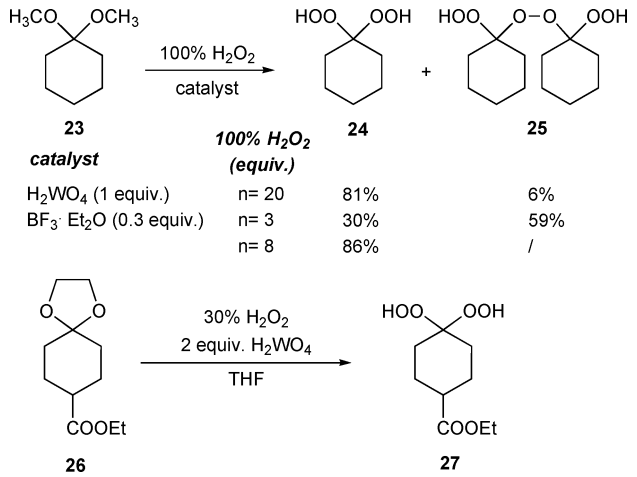


Scheme 5

the elimination of the hydroxy and hydroperoxy group and the addition of water or H_2O_2 to the carbonyl group.

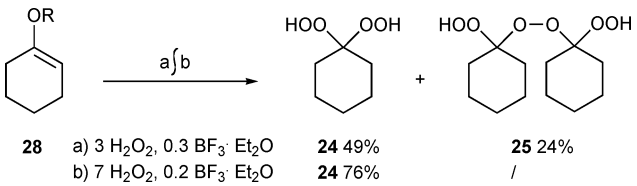
The synthesis of dihydroperoxides is limited by their stability and it depends on their structure. 2,2-Dihydroperoxypropane is difficult to handle because it readily decomposes, however, an interesting stabilization of this DHP was reported by the interaction with the diphosphinoyl donors, which prevents cyclo-oligomerization of the corresponding DHP and its decomposition.[38,39] Intermolecular interaction between the hydroperoxide group and the O-atom of the bis(diphenylphosphinoyl)ethane was confirmed by X-ray crystallography. The formation of an adduct can also be accelerated by using R_2SnCl_2 (R = Me or Bu).

An alternative method to synthesize DHPs by H_2O_2 employs ketals or enol ethers as starting compounds, although acid conditions are necessary and consequently dimeric dihydroperoxides **25** are formed along with DHPs **24**. Ketals can be perhydrolyzed with 20 equivalents of anhydrous H_2O_2 and 1 equivalent of H_2WO_4 (Scheme 6).[40] Alternatively, the use of an anhydrous solution of H_2O_2 and $BF_3{\cdot}OEt_2$ was also reported. To avoid the formation of the dimeric product **25**, a higher amount of H_2O_2 is required for the selective formation of DHPs from cyclic and acyclic ketals with yields varying from 44% to 91% (Scheme 6).[41,42] Anhydrous H_2O_2 as well as its aqueous solutions of higher concentration are hazardous chemicals and safety precautions should be employed. A safer alternative is the use of a 30% aqueous solution of H_2O_2 that is commercially available. In this respect, **27** was synthesized by a modified procedure with 30% H_2O_2 and tungstic acid.[32]



Scheme 6

In addition, a Lewis acid was used to transform enol ethers into the corresponding DHPs (Scheme 7).[42] Again, using a higher quantity of peroxide increases selectivity.



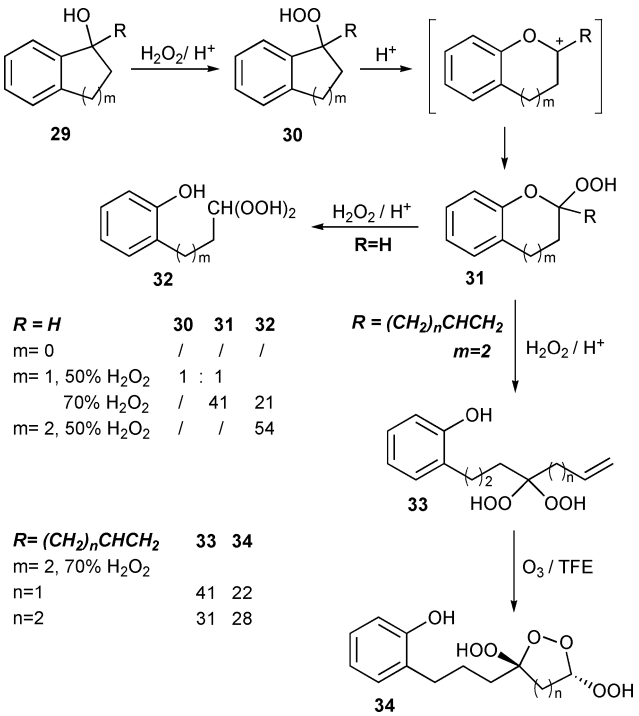
Scheme 7

Aliphatic aldehydes are less reactive than ketones for dihydroperoxidation and could not be converted to DHPs with H_2O_2 (Scheme 4). Primary DHPs **32** can be obtained from secondary alcohol **29** by H_2O_2 and acid induced rearrangement of intermediate tertiary hydroperoxide **30** (Scheme 8).[43] The size of the ring in **30** determines the ease of rearrangement and formation of the products. Tertiary alcohols gave, after rearrangement, DHP **33** that was further cyclised by ozone in fluorinated alcohol to yield a product with a dihydroperoxy, dioxolane or a dioxane structure **34**.[44,45]

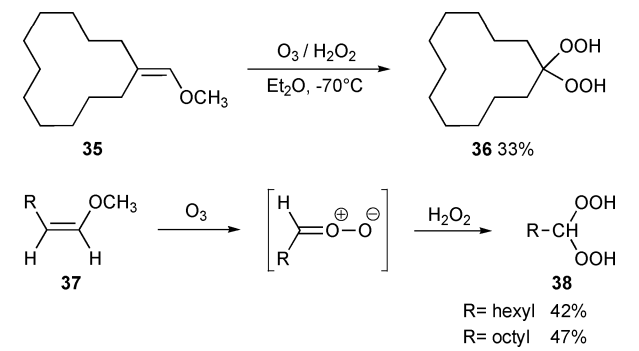
The ozonolysis of enol ethers or α-olephins has been widely used as a synthetic pathway for preparing DHPs when selective reactions with H_2O_2 were not available (Scheme 9).[31,46] Ozonolysis of enol ethers proceeds in the presence of an excess of H_2O_2 in diethyl ether at −70 °C. Yields are low to moderate. However, it still remains the only general synthetic procedure for the synthesis of primary *gem*-DHPs.

3. *gem*-Bisperethers 7B

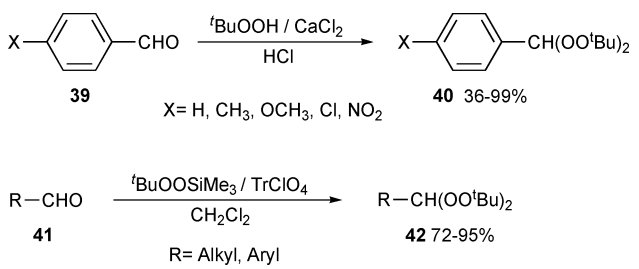
DHPs are precursors for various cyclic peroxides with the main transformation being cyclization into spiro bisperethers, dispiro compounds—1,2,4,5-tetraoxanes or macrocyclic 1,2,4,5-tetraoxacycloalkanes. The initial step for preparing bisperethers is the direct conversion of carbonyl compounds with ^{t}BuOOH accomplished in the presence of an acid and a dessicant.[47] Substituted benzaldehydes do react with ^{t}BuOOH in the presence of HCl and calcium dichloride as a desiccant with good yields (Scheme 10).[48] Aldehydes were transformed to bisperethers **42**



Scheme 8



Scheme 9

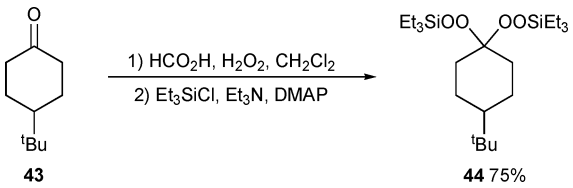


Scheme 10

using ^{t}Bu-trimethylsilyl peroxide and trityl perchlorate ($TrClO_4$) as the catalyst.[49]

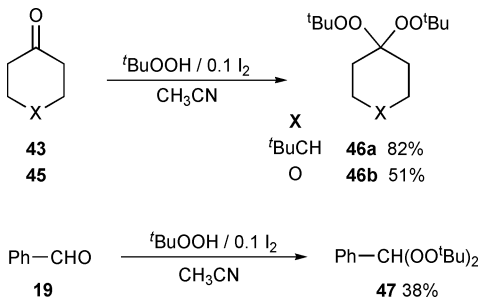
Silyl derivatives **44** were synthesized from cyclic and acyclic ketones in a two-step reaction with DHP as intermediate product. This intermediate product was further silylated to isolate silylperoxyethers **44** (Scheme 11), which were then used as a source of peroxycarbenium ion for annulation reactions.[50]

A more recent method was reported for the peroxidation of carbonyl compounds under neutral conditions with ^{t}BuOOH



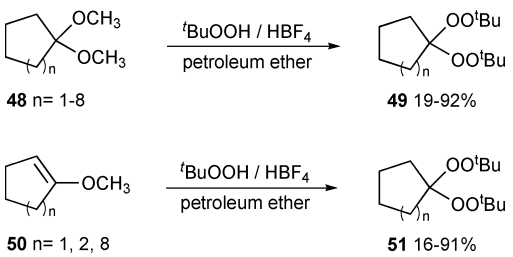
Scheme 11

using iodine as a catalyst. Bisperethers were formed with 10 mol% of iodine directly from benzaldehyde **19**, ^{t}Bu-cyclohexanone **43** and tetrahydro-4*H*-pyranone **45**. The use of a desiccant was unnecessary and the bisperethers **46** and **47** were isolated with moderate to good yields (Scheme 12).[37]



Scheme 12

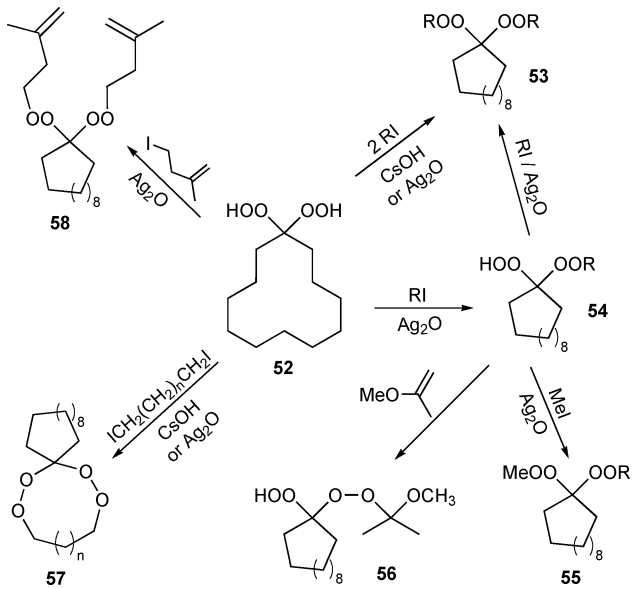
Another possibility to convert ketones to *gem*-bisperethers was reported by the Terent'ev group and involves transforming ketones to ketals or enol ethers followed by reaction with ^{t}BuOOH.[51] The group were successful in transforming cyclic as well as acyclic substrates to their perether derivatives. Their reactions require the presence of protic or Lewis acids and the use of a desiccant was in some cases inevitable (Scheme 13).



Scheme 13

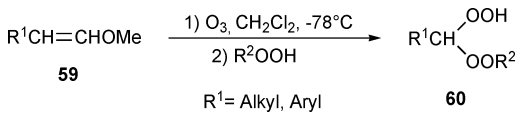
Methods for the synthesis of more complex bisperethers proceed from *gem*-dihydroperoxides as starting compounds (Scheme 14). Using alkyl iodides with Ag_2O or CsOH as promoters, **52** can be transformed directly to the bisperether **53** and **58** with two equivalents of alkyl iodide or stepwise through the monoalkylated hydroperoxide **54** to symmetrical **53** and unsymmetrical substituted bisperethers **55**.[52,53] **54** can be transformed also into α-alkoxyalkyl-substituted peroxide **56** by a reaction with vinyl ether.[54] Cycloalkylation of **52** was achieved by treating it with 1,*n*-diiodoalkanes (n = 3–8) in the presence of Ag_2O or CsOH and provided the medium-sized 1,2,4,5-tetraoxacycloalkanes **57** in moderate yields.[31]

Ozonolysis is an important method for the selective synthesis of DHPs from enol ethers with H_2O_2 as a nucleophile. The reaction of



Scheme 14

ketones with ROOH leads to bisperethers, while ozonolysis of enol ethers in the presence of alkylhydroperoxide as a nucleophile can result in the formation of hydroperoxy peracetals **60** (Scheme 15).[55]

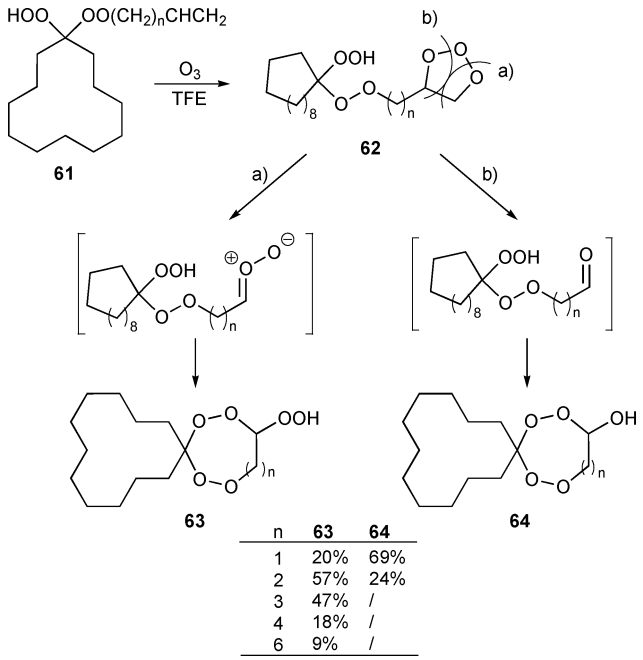


Scheme 15

Unsaturated hydroperoxy perketal **61** reacts further with ozone to yield perethers. The composition of ozonolysis products depends on the cleavage mechanisms favoured by the respective transient primary ozonide **62**. The group of McCullough studied ozonolysis in trifluoroethanol (TFE) and found that there are two modes of cleaving the primary ozonide each operating competitively depending on the length of the alkyl chain (Scheme 16); the scission path **a** leading to the formation of the carbonyl oxide intermediate and formaldehyde and path **b**, which results in a mixture of the aldehyde and formaldehyde *O*-oxide.[56] Subsequent intramolecular cyclization of the intermediates proceeds efficiently, providing α-hydroperoxy **63** and/or α-hydroxy **64** substituted perethers.

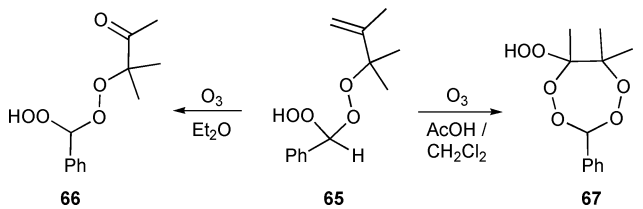
The cleavage of the primary ozonide from the unsaturated hydroperoxy peracetals is affected by reaction conditions. In diethyl ether or in a mixture of CH_2Cl_2–acetic acid, the reaction proceeds through path **a**. But in diethyl ether, the reaction produces the keto hydroperoxide **66** and not, as expected, the α-hydroperoxy substituted perether **67**. The latter is formed in acidic media (Scheme 17). This notable diversion of the reaction pathway was attributed to the solvation of the carbonyl oxide moiety by the acidic solvent, thereby enhancing the electrophilicity of the carbon atom of carbonyl oxide.[55] This is also supported by the formation of hydroperoxides in fluorinated alcohol (TFE) that is a known solvent with expressed Lewis acid character.[57–59]

Cyclic bisperethers were also obtained by photooxygenation with singlet oxygen in the presence of tetraphenylporphine (TPP). Photooxygenation of 2-phenylnorbornene **68**, which is known



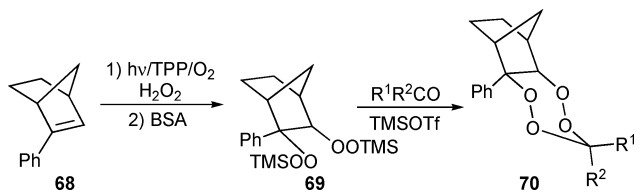
n	63	64
1	20%	69%
2	57%	24%
3	47%	/
4	18%	/
6	9%	/

Scheme 16



Scheme 17

to react with singlet oxygen to form a zwitterionic intermediate, in the presence of 30% H_2O_2 in acetonitrile, afforded the labile 1,2-bis-hydroperoxide, that was further trimethylsilylated by bis(trimethylsilyl)acetamide (BSA) into **69** and converted to cyclic bisperethers **70** by cyclocondensation catalyzed by TMSOTf (Scheme 18).[60,61]

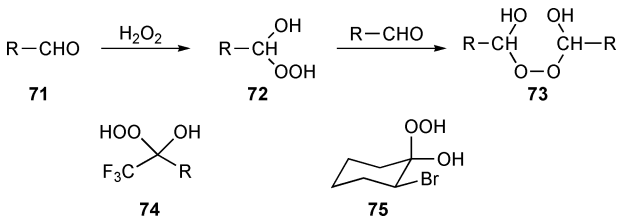


Scheme 18

4. Perketal derivatives 7C and 7D

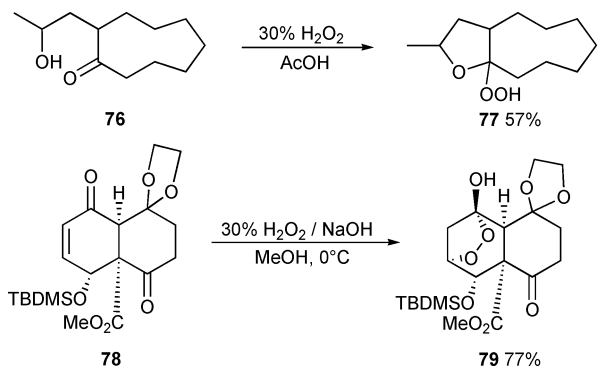
4.1. Oxidation with H_2O_2

Addition of hydrogen peroxide to carbonyl compounds produces hydroperoxy hemiketals **7C**, also named as perhydrates. Aldehydes **71** form, during the reaction with H_2O_2, hydroperoxy hemiacetals **72**, which are sufficiently stable to be isolated. However, hydroperoxy hemiacetals **72** are difficult to obtain selectively because they are readily converted with another molecule of aldehyde to bis(hydroxyalkyl)peroxide **73** (Scheme 19).[62] The reactivity of ketones is different. Hydroperoxy ketal is not stable and is transformed into a complex mixture of peroxidic products named ketone peroxide.[26] Only exceptionally can hydroperoxy hemiketal be isolated. This is the case with electron deficient ketones like trifluoromethyl ketones, which form stable hydroperoxy hemiketals **74** and are important and powerful oxygen transfer agents.[63] 2-Bromocyclohexanone when reacting with H_2O_2 does form a stable perhydrate **75**, but in this case it is stabilized by intramolecular interaction; this fact was confirmed by a full structural characterisation of the perhydrate by X-ray crystallography.[64]



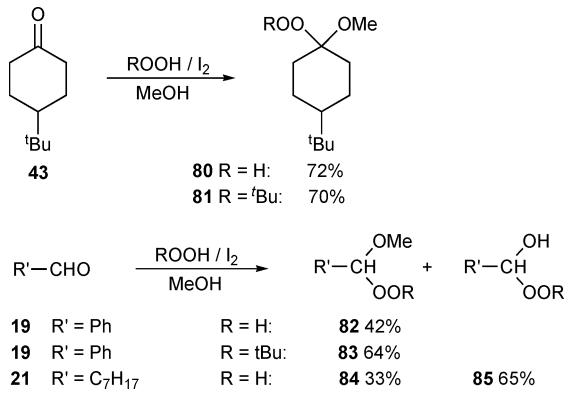
Scheme 19

Although hydroperoxy hemiketals **7C** are unstable, their perether or ether derivatives are stable and can be isolated. In addition, perketals were used as a protecting group. Perketals can be directly obtained by adding H_2O_2 to the carbonyl group and its subsequent acid or base catalyzed etherification. An older example of forming α-alkoxy hydroperoxide or hydroperoxy ketal **77** involves the addition of H_2O_2 in acetic acid to γ-hydroxy ketone **76**, whose alcohol group serves as internal nucleophile.[65] The base catalyzed reaction of α,β-unsaturated ketone **78** with H_2O_2 leads to the formation of α-hydroxy endoperoxide or peroxy hemiketal **79** with the hydroperoxy group serving as an internal nucleophile (Scheme 20).[66,67]



Scheme 20

The direct conversion of the ketone to the perketal derivative was accomplished with iodine as a catalyst. By using methanol as a solvent for the addition of H_2O_2 to 4-*tert*-butylcyclohexanone **43**, hydroperoxy ketal **80** was isolated in a 72% yield (Scheme 21).[36,37] Interestingly, iodine was able to discriminate between nucleophiles with only methanol acting as a nucleophile, although an aqueous solution of H_2O_2 was used. Perketal **81** was directly obtained by using ^{t}BuOOH instead of H_2O_2. Benzaldehyde reacted similarly giving hydroperoxy ketal **82** or perketal **83** when reacted with H_2O_2 or ^{t}BuOOH, respectively. Aliphatic aldehyde **21** was also peroxidised, however any discrimination between MeOH and H_2O

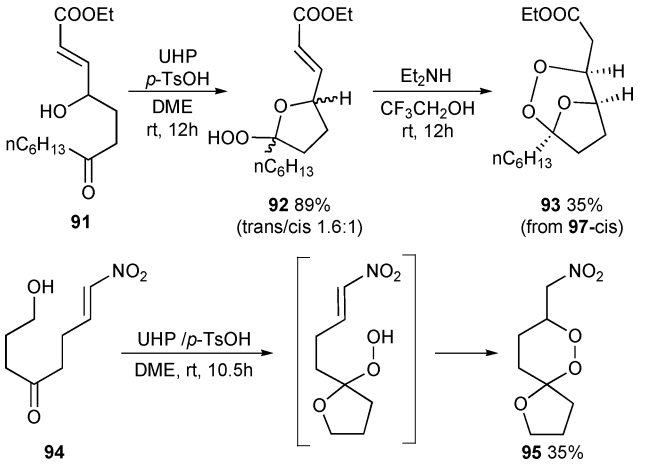


Scheme 21

nucleophiles was lost and the two products **84** and **85** were formed (Scheme 21).[37]

Without the iodine catalyst, direct conversion of ketones into hydroperoxy ketals **7D** requires acidic conditions, while a complex of urea and hydrogen peroxide (UHP) is an alternative to the anhydrous hydrogen peroxide. This strategy that avoids using ozone or singlet oxygen was used when preparing a derivative of the naturally occurring spongean peroxyplakoric acid **90** with antimalarial activity. For the synthesis of 3-methoxy-1,2-dioxane **90** by peroxyhemiacetalization of the ketone **86** followed by intramolecular conjugate addition, UHP was used as a source for the peroxide unit. Both the acid and reaction conditions play an important role in the distribution of the products (Scheme 22).[68,69] The latter product could be formed through intramolecular addition of the hydroperoxy group. The best selectivity for hydroperoxy ketal **87** was obtained when using $Sc(OTf)_3$ as a catalyst in a more diluted medium. Similar sensitivity to reaction conditions was also found in the intramolecular conjugate addition in **87**, where the acid catalyst transformed **87** back into the starting ketone **86**, sodium methoxide catalyst cleaved the peroxy bond to form epoxide **89**, while diethylamine catalyst was able to form 3-methoxy-1,2-dioxane **90** and the best results were obtained in fluorinated alcohol.

The following methodology was further elaborated in **91** by joining peroxidation with the addition of an internal nucleophile instead of methanol to yield **92**, while further cyclization leads to the formation of the trioxane ring **93** (Scheme 23). This reaction is also possible by involving a nitro group instead of an ester one and in this case activation was improved requiring no amine for cyclization into the spiroperoxide **95**.[70–72]

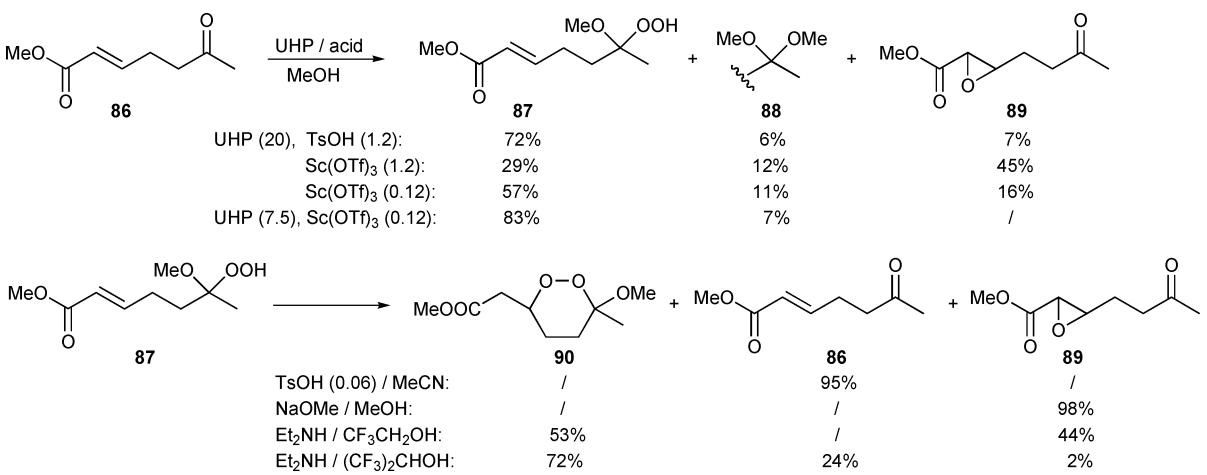


Scheme 23

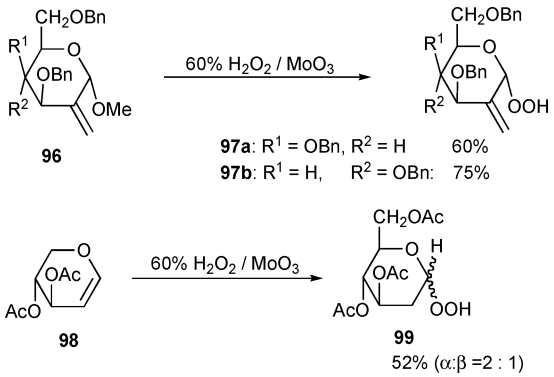
Part of the research on the synthesis of hydroperoxides is concentrated on developing agents for enantioselective oxygen transfer reactions. Naturally occurring sugars are part of a chiral pool and thus are "natural" candidates. Unsaturated glycoside **96** was oxidized with H_2O_2 in the presence of a MoO_3 catalyst into the corresponding α-anomeric hydroperoxides **97** (Scheme 24). A similar reaction of glucal **98** afforded anomeric hydroperoxide **99** with an α–β-anomer ratio of 2 : 1.[73,74] These hydroperoxides were used as a chiral oxygen transfer agent for the oxidation of allyl alcohols and sulfides with moderate enantioselective excess.

4.2. Ozonolysis

The driving force in the research within the area of organic peroxides has been the pharmacological importance of their products, especially in the case of 1,2,4-trioxanes. These compounds are obtained from hydroperoxy ketals **7D** formed by the addition of alcohol to the peroxycarbenium ion. Ozonolysis of the sp^2

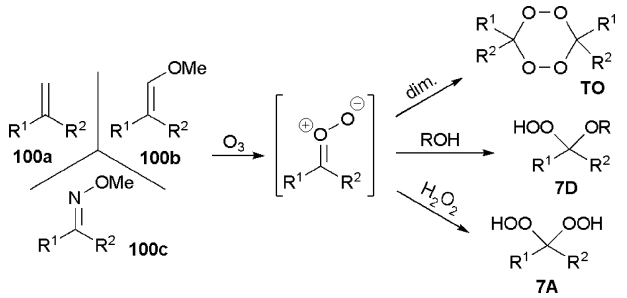


Scheme 22



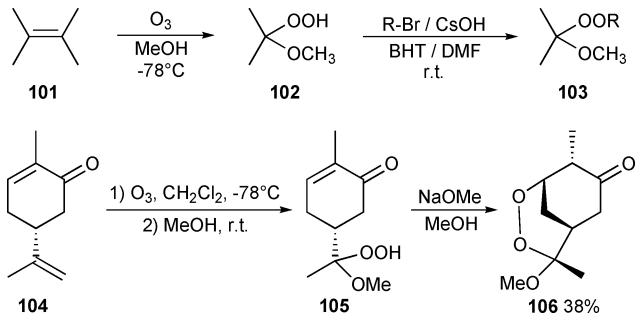
Scheme 24

C-atom in **100** is the main pathway for the formation of the peroxycarbenium ion, which is a reactive intermediate for various hydroperoxides and tetraoxanes (TO) (Scheme 25).[31,46,75,76]



Scheme 25

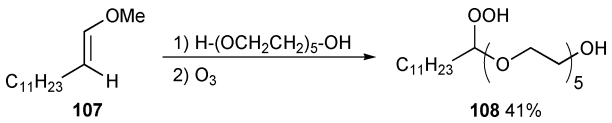
Therefore, the most widely used method for preparing perketals proceeds *via* hydroperoxy ketals **7D** formed by ozonolysis of the alkene at −78 °C. The perketal is then formed either by an external nucleophile in the presence of butylated hydroxytoluene (BHT) in DMF as in **102** or by an internal one as in **105** (Scheme 26).[77,78]



Scheme 26

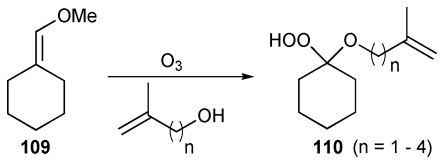
Polyethylene glycols are very important in pharmaceutical, cleaning, laundry and cosmetic products. It is known that on exposure to air PEGs show contact allergenic activity. The explanation for this is based on the formation of hydroperoxides as primary autooxidation products. This has now been confirmed by isolating the hydroperoxy ketals of PEG (pentaethylene glycol) with a lipophilic chain **108** using ozonolysis (Scheme 27).[79]

The ozonolysis of enol ether **109** in the presence of unsaturated alcohol forms a hydroperoxy ketal **110** with an unsaturated bond, which is a potential starting point for further ozonolysis



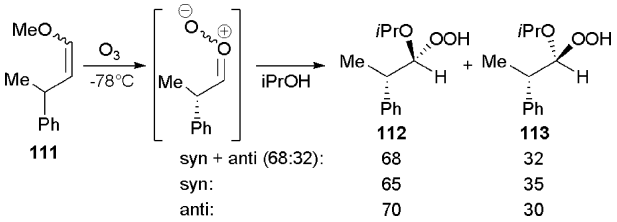
Scheme 27

with concomitant cyclization to a variety of cyclic peroxides (Scheme 28).[80,81]



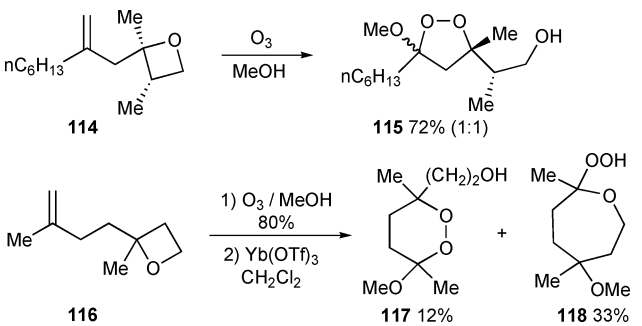
Scheme 28

The stereochemistry of addition of nucleophiles to aldehydes and ketones is well researched, however, little is known about the stereochemical outcome of the addition of nucleophiles to carbonyl oxides. Dussault's group has studied diastereoselectivity of additions to acyclic carbonyl oxides and found that carbonyl oxide and aldehyde affect similarly the stereoselectivity of the addition of a nucleophile. Furthermore, they synthesized *syn* and *anti* carbonyl oxides by ozonolysis of the (*E*) and (*Z*) enol ether **111** and they observed only a small effect of the geometry of the carbonyl oxide on the diastereoselectivity of addition of i-PrOH (Scheme 29).[82]



Scheme 29

Stereoselectivity was observed when using a different approach, where ozonolysis of the alkene **114** was coupled by intramolecular 5-*exo* cyclization to give the stereo specific 1,2-dioxolane **115** with a 1 : 1 mixture of two diastereoisomers out of a possible four (Scheme 30).[83] The ease of cyclization is surprising although no acid catalyst was present in the reaction. The 6-*exo* cyclization in **116** is less pronounced and in this case it was only possible to isolate the perketal **117** as a mixture of diastereoisomers together with

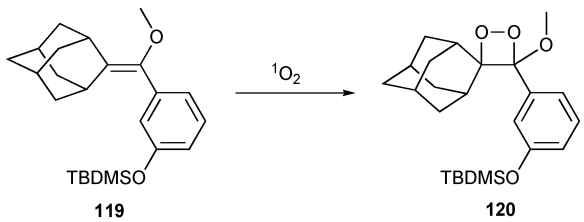


Scheme 30

the formation of a hydroperoxy oxepan derivative **118**. However, cyclization can be achieved with an acid catalyst.

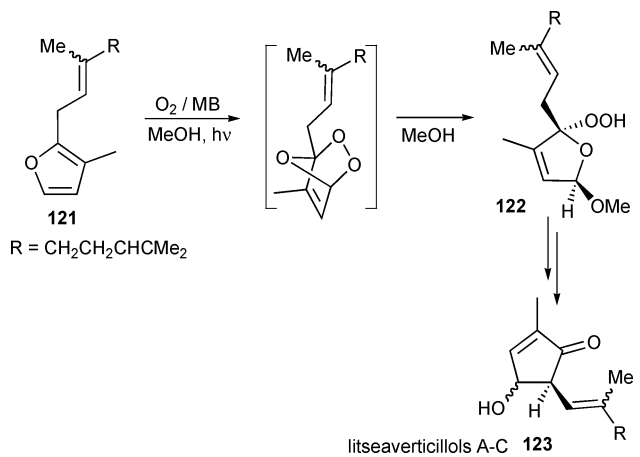
4.3. Singlet oxygen

Besides hydrogen peroxide and ozone, singlet oxygen is also an efficient reagent for generating perketal derivatives. A recent example shows the synthesis of spiroadamantyl-1,2-dioxetane **120**, prepared from **119** with the hydroxy group protected with a *tert*-butyldimethylsilyl group (TBDMS), by the photochemical generation of the singlet oxygen in the presence of PPh_3 or alternatively by calcium peroxide diperoxohydrate (Scheme 31).[84] **120** is a stable 1-methoxy-1,2-dioxetane that is a source of luminescence that bears some similarities with bioluminescence. The reaction was used as a trap for a singlet oxygen to determine its quantity through the decomposition of **120** by a chemically induced electron exchange mechanism (CIEEL) that generates a chemiluminescent signal.[85]



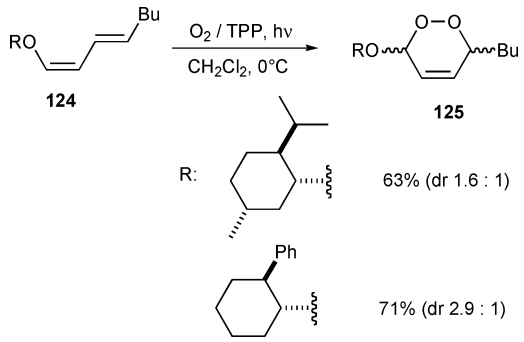
Scheme 31

Singlet oxygen, although problematic in biochemistry as a reactive oxygen species, is also an agent in biosynthesis as shown by the [4 + 2] cycloaddition of $^1O_2$, generated by methylene blue (MB) assisted photoexcitation of aerial oxygen, to naturally occurring furans **121**, where the hydroperoxy ketal **122** acts as an intermediate product in the biosynthesis of litseaverticillols **123**, a family of potent anti-HIV natural products (Scheme 32).[10,19] Furthermore, the corrected structure of the litseaverticillol E has an allyl hydroperoxide group.[18]



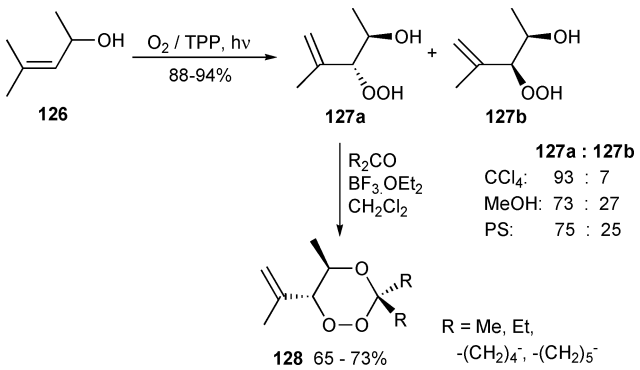
Scheme 32

In order to have a route to enantiomerically enriched perketals to form a family of 3-methoxy-1,2-dioxanes, cycloaddition of $^1O_2$ to chiral dienol ethers was studied.[86] The geometry of the olefin and substituents affects the mode of reaction, where three types of reaction were observed: Diels–Alder, [2 + 2] cycloaddition and the ene reaction. The (1*Z*,3*E*)-dienol ether **124** reacted *via* [4 + 2] cycloaddition to yield the desired perketal **125** and had the highest diastereoselectivity of tested dienols (Scheme 33).



Scheme 33

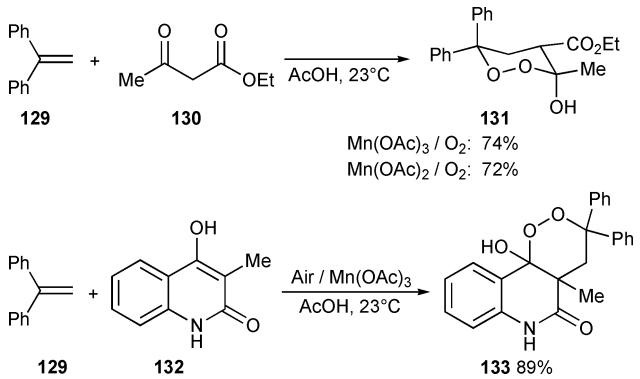
Cyclic perketals—1,2,4-trioxanes are usually synthesized by cyclization of open perketal derivatives (hydroperoxy ketals **7D** or peroxy hemiketals **7C**). However, an ene reaction of the allyl alcohol **126** with singlet oxygen yields 2-hydroperoxy alcohol **127** and the diastereoselectivity drops significantly in MeOH and polystyrene (PS). The acid-catalyzed cyclization of the **127**, obtained in CCl_4, with a ketone gives *trans*-5,6-disubstituted 1,2,4-trioxane **128** (Scheme 34).[87–89] It is also possible to obtain 2-hydroperoxy alcohols by opening up the epoxide with H_2O_2.[90]



Scheme 34

4.4. Molecular oxygen

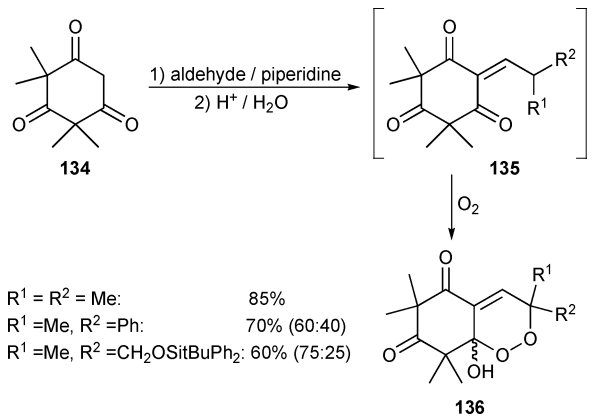
Oxygen is a powerful oxidant, but it usually needs activation for efficient reactivity. When preparing perketals, oxygen is mainly used for the synthesis of 3-hydroxy-1,2-dioxanes. One possibility is to use [2 + 2 + 2] cycloaddition of oxygen, olefin **129** and diketone **130**, where the reaction system is activated electrochemically.[91] This reaction was modified to use manganese(III) salts in order to activate the oxygenation (Scheme 35).[92–95] The manganese salt generates a carbon radical species from the dicarbonyl compound, which reacts with alkene to form a stable radical that traps the oxygen to give a dioxane product **131**. Instead of a dicarbonyl compound, other β-substituted ketones with sulfur, phosphorous or cyano groups can be used,[96–98] while pyrrolidinediones **132**



Scheme 35

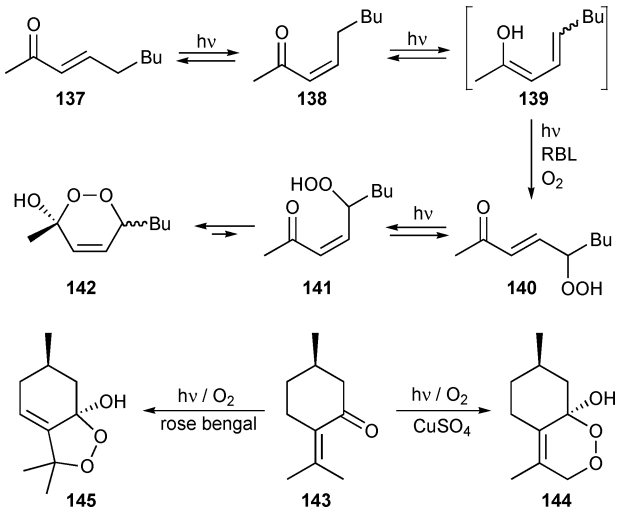
or 4-piperidone-3-carboxylates give azabicyclic peroxides **133** (Scheme 35).[99–104]

G-factors, that have also a 3-hydroxy-1,2-dioxane structural element, are a phytohormone and a growth regulator in plants that possess also antimalarial activity. In nature, G-factors are toxic for the plant yet they are formed in plants on demand for their action by facile autooxidation of syncarpic acid. Formation of the Mannich base between syncarpic acid **134**, piperidine and aldehyde followed by further acid-catalyzed hydrolysis gives an unstable product **135** that readily reacts with oxygen to form analogues of G-factors **136** (Scheme 36).[105,106] This reaction opened the gate to facile synthesis of G-factor analogues and offers an insight into the role that the peroxide bond plays in the activity of G-factor analogues against resistant strains of *Plasmodium falciparum*.[107–111]



Scheme 36

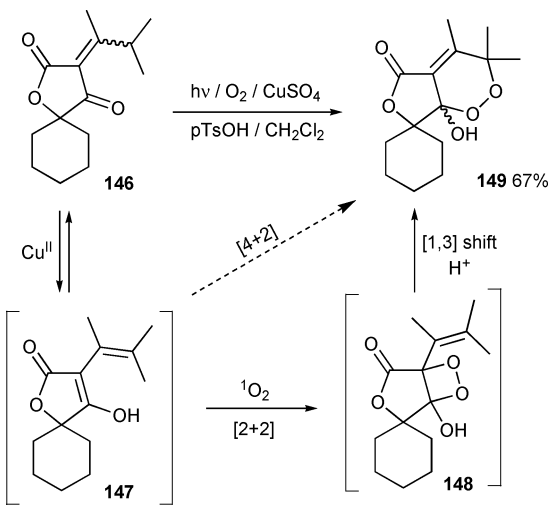
Another case of a naturally occurring 3-alkoxy-1,2-dioxene structural unit was present in the first isolated marine derived cyclic peroxides known as chondrillins and plakorins. They are active against tumor and leukemia cells. Synthetic pathways to these natural compounds consist in part of photo-induced enolization of unsaturated ketones **137** in the presence of copper(II) sulfate or rose bengal lactone (RBL) and subsequent oxygenation (Scheme 37).[112–115] This so called Snider method became a major route to the synthesis of 1,2-dioxanes using oxygen, but its mechanism is not clear. Initial results point to radical oxygenation because a radical quencher inhibited the reaction, while the singlet oxygen quencher DABCO had no effect. Furthermore, the reaction of pulegon **143** yielded different products; **145** and



Scheme 37

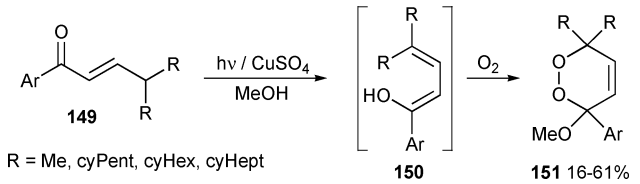
144 with singlet oxygen and copper(II) sulfate induced enolization and photooxygenation by oxygen respectively.[112] Dussault *et al.* reported the stereoselective preparation of chondrillin and plakorin *via* singlet oxygenation and radical rearrangement.[116]

Schobert *et al.* showed another aspect of Snider's protocol in the case of 2,5-dihydrofuran-2,4-dione **146**—an important structural element in bioactive compounds that is prone to oxidation when it has an alkylidene group at position 3 (Scheme 38).[117,118] Reaction was activated by copper(II) sulfate that acts as a photosensitizer and promoter of enolization and proceeds under acidic conditions. Results point to the involvement of a singlet oxygen with [2 + 2] cycloaddition to the enol double bond and [1,3] O-shift to form the dioxen cycle. An alternative path involving [4 + 2] cycloaddition is less probable.



Scheme 38

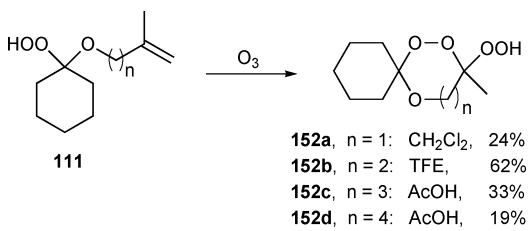
A photoenolization and oxygenation strategy was applied for the synthesis of antimalarial 3-methoxy-1,2-dioxane derivatives. The reaction of α,β-unsaturated ketone **149** in methanol led to the formation of 3-methoxy-1,2-dioxane derivatives **151** with significant antimalarial activity (Scheme 39).[119,120]



Scheme 39

4.5. Hydroperoxy ketals as synthons

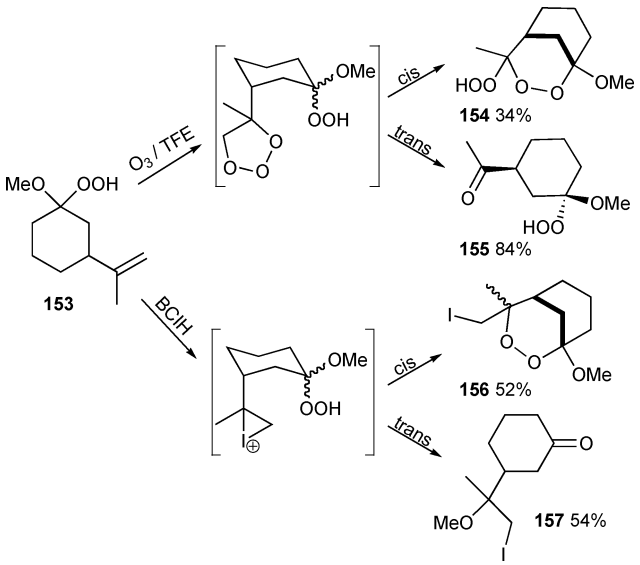
As already pointed out, hydroperoxy ketals **7C** and **7D** serve as starting compounds for various peroxides *via* etherification or peretherification reactions. Another transformation includes alkenyl substituted hydroperoxy ketals **7D**, where ozonolysis of the C–C double bond enables intramolecular cyclization into various macrocyclic peroxides. A study of cyclization of unsaturated hydroperoxy ketals **111** revealed that the cleavage of the primary ozonide that is formed in ozonolysis depends on the structure of the ozonide and on the reaction conditions with the solvent playing a crucial role. For example, 1,2,4-trioxane **152a** was formed in a 24% yield in CH_2Cl_2 and it was accompanied by the formation of 38% of corresponding alcohol, whereas the 7-membered ring peroxide-1,2,4-trioxepane **152b** was formed in a better yield, however TFE was necessary for its selective formation (Scheme 40). Eight- and even nine-membered ring peroxides **152c** and **152d** were formed when a more acidic solvent was used although in lower yields.[121]



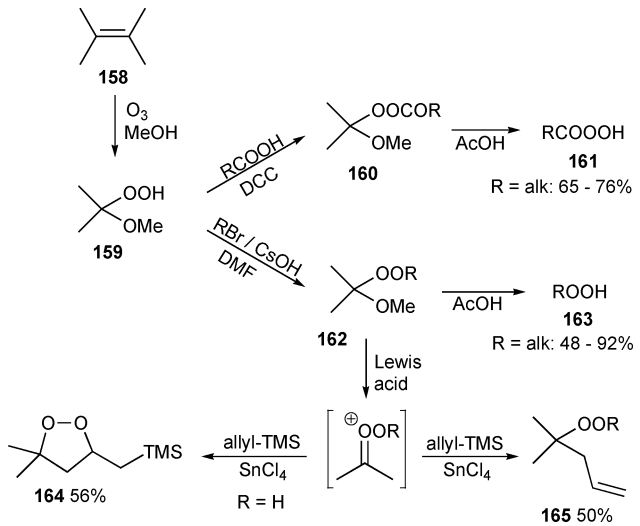
Scheme 40

Among the solvents studied, trifluoroethanol had an important effect in the cyclization reactions by enhancing the cyclization step by activating carbonyl oxides to react with nucleophiles and prevent side reactions like cycloaddition to occur. Transformation in TFE depends on the geometry of the hydroperoxy ketal **153** (Scheme 41). When the hydroperoxy group is in the *cis* position, the endoperoxide **154** is formed due to the proximity of the hydroperoxy group and the carbonyl oxide, while the *trans* isomer cannot form the desired product and **155** is formed instead. An alternative cyclization strategy involves halonium mediated cyclization with bis(collidine)iodine(I) hexafluorophosphate (BCIH) and similar results on the effect of geometry of the molecule on the type of product were observed. Again, the isomer with the hydroperoxy group in the *cis* position gives endoperoxide **156** while the *trans*-one gives **157**.[122]

By ozonolysis of tetramethylethene **158** in methanol, 2-hydroperoxy-2-methoxypropane **159** was obtained and it was used as a building block for hydroperoxides **163** or peracids **161** by alkylation/acylation and subsequent hydrolysis in acetic acid (Scheme 42).[75,123] Furthermore, peroxy ketals **162** were converted



Scheme 41



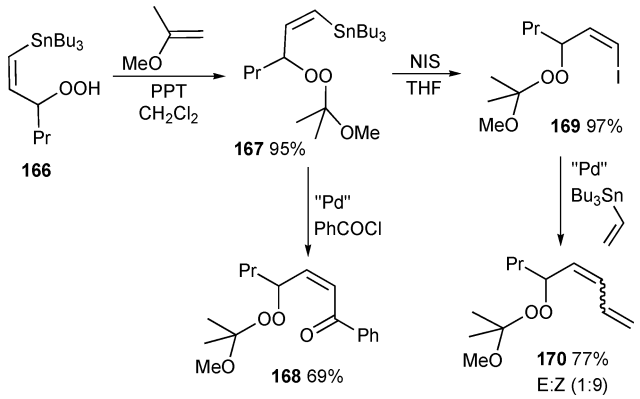
Scheme 42

by Lewis acid to the peroxycarbenium intermediate which reacts with nucleophiles to form various peroxides.[81,124,125] Even the stereoselective version of this reaction with chiral silyl enol ethers was studied.[126]

Perketals were also used as a protecting group for hydroperoxides. As a result, the hydroperoxides could be subjected to iodination, Wittig olefination, reductions and palladium-catalyzed C–C bond forming reactions (Scheme 43).[127–129]

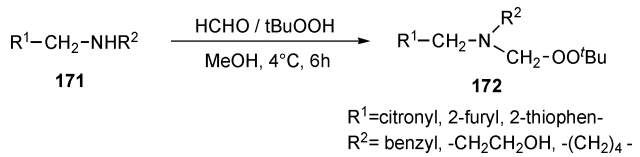
5. α-Heteroatom hydroperoxides 7E

The perketal derivatives **7C** and **7D** are the main constituents of a group of α-heteroatom substituted peroxides, while there are only limited examples of nitrogen and sulfur derivatives **7E**, although heterocyclic nitrogen derivatives of **7E** are important in biochemical oxygenation as exemplified by the role of 4*a*-hydroperoxyflavin.[130] A series of model amine peroxides **172** as



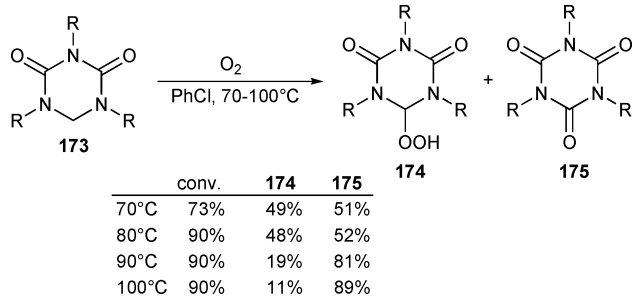
Scheme 43

targeted antimalarials containing a ^{t}Bu-peroxy function were synthesized from secondary amines **171** by treating them with formaldehyde and ^{t}Bu-hydroperoxide in methanol (Scheme 44).[131]



Scheme 44

Derivatives of dioxohexahydrotriazine **173** readily undergo oxidation in air to form cyanuric acid derivatives. During the reaction in chlorobenzene at lower temperatures, hydroperoxidic products **174** occur and decomposition to trimethylcyanuric acid **175** begins with increasing the temperature (Scheme 45).[132]

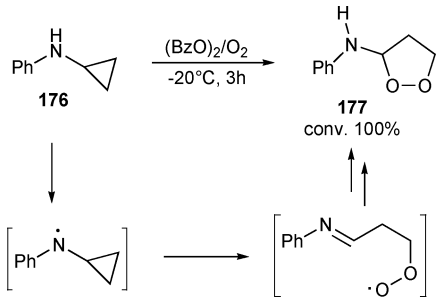


	conv.	174	175
70°C	73%	49%	51%
80°C	90%	48%	52%
90°C	90%	19%	81%
100°C	90%	11%	89%

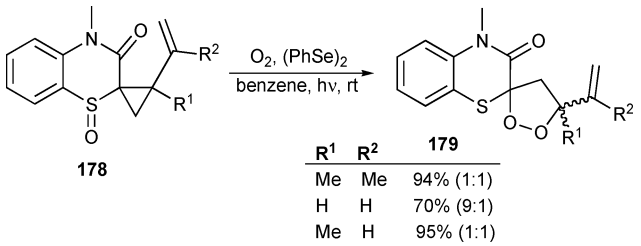
Scheme 45

N-Cyclopropyl-*N*-phenylamine derivative **176** undergoes aerobic oxidative ring opening to produce the relatively stable 3-amino-1,2-dioxolane derivative **177** (Scheme 46). An autocatalytic oxygenation mechanism was proposed for the formation of the 1,2-dioxolane product.[133]

Sulfur containing hydroperoxide was formed in a photochemical [3 + 2] oxygen cycloaddition to a cyclopropane ring in benzothiazinone spirocyclopropanes **178** (Scheme 47). Substrates were irradiated under a tungsten lamp in the presence of catalytic amounts of diphenyl diselenide and dioxolanes **179** were formed as a mixture of diastereomers in good yields.[134]



Scheme 46



R1	R2	179
Me	Me	94% (1:1)
H	H	70% (9:1)
Me	H	95% (1:1)

Scheme 47

6. Conclusion

An increasing need for organic peroxides as industrial chemicals and especially as bioactive compounds generates a demand for their effective synthesis. Direct conversion of carbon–carbon or carbon–heteroatom bonds into *gem*-dihydroperoxides and perketal derivatives with hydrogen peroxide, ozone and less frequently with singlet or triplet oxygen presents a basic synthetic pathway, while further cyclization provides a synthetic route to various cyclic peroxides of different size and structure. With increasing knowledge about peroxidation reactions we can expect that targeted organic peroxides will be more available and significant advancement in their properties and activity will be achieved.

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