Synthesis of five- and six-membered cyclic organic peroxides: Key transformations into peroxide ring-retaining products

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Abstract
The present review describes the current status of synthetic five and six-membered cyclic peroxides such as 1,2-dioxolanes, 1,2,4-trioxolanes (ozonides), 1,2-dioxanes, 1,2-dioxenes, 1,2,4-trioxanes, and 1,2,4,5-tetraoxanes. The literature from 2000 onwards is surveyed to provide an update on synthesis of cyclic peroxides. The indicated period of time is, on the whole, characterized by the development of new efficient and scale-up methods for the preparation of these cyclic compounds. It was shown that cyclic peroxides remain unchanged throughout the course of a wide range of fundamental organic reactions. Due to these properties, the molecular structures can be greatly modified to give peroxide ring-retaining products. The chemistry of cyclic peroxides has attracted considerable attention, because these compounds are used in medicine for the design of antimalarial, antihelminthic, and antitumor agents.

Introduction
Approaches to the synthesis of five and six-membered cyclic peroxides, such as 1,2-dioxolanes I, 1,2,4-trioxolanes (ozonides) II, 1,2-dioxanes III, 1,2-dioxenes IV, 1,2,4-trioxanes V, and 1,2,4,5-tetraoxanes VI, published from 2000 to present are reviewed. These compounds are widely used in synthetic and medicinal chemistry (Figure 1).

In the last decade, two reviews on this rapidly progressing field were published by McCullough and Nojima [1] and Korshin and Bachi [2] covering earlier studies. There are several review articles on medicinal chemistry of peroxides, where the problems of their synthesis are briefly considered. In addition to these reviews other publications dealing with this subject
Reviews published earlier on the chemistry of ozone [33-36] and on the chemistry and biological activity of natural peroxides, and cyclic peroxides [37-46] are closely related to this review. Generally speaking, state-of-the-art approaches to the synthesis of cyclic peroxides are based on three key reagents: oxygen, ozone, and hydrogen peroxide. These reagents and their derivatives are used in the main methods for the introduction of the peroxide group, such as the singlet-oxygen ene reaction with alkenes, the [4 + 2]-cycloaddition of singlet oxygen to dienes, the Mukaiyama–Isayama peroxysilylation of unsaturated compounds, the Kobayashi cyclization, the nucleophilic addition of hydrogen peroxide to carbonyl compounds, the ozonolysis, and reactions with the involvement of peroxycarbonyl ions.

Each part of the review deals with a particular class of the above-mentioned peroxides in accordance with an increase in the number of oxygen atoms and the ring size. In the individual sections, the data are arranged mainly according to the common key step in the synthesis of the cyclic peroxides. Examples of the synthesis of peroxide derivatives via modifications of functional groups, with the peroxide bond remaining unbroken, are given in the end of each chapter. In most cases, the syntheses of compounds having high biological activity are considered.

Currently, the rapid progress in chemistry of organic peroxides is to a large degree determined by their high biological activity. In medicinal chemistry of peroxides, particular emphasis is given to the design of compounds having activity against causative agents of malaria and helminth infections. The World Health Organization (WHO) considers malaria as one of the most dangerous social diseases. Worldwide, 300–500 million cases of malaria occur each year, and 2 million people die from it [47,48].

Due to a high degree of resistance in malaria to traditional drugs as quinine, chloroquine, and mefloquine, an active search for other classes of new drugs is performed. In this respect, organic peroxides play a considerable role. In medicinal chemistry of peroxides, artemisinin a natural peroxide exhibiting high antimalarial activity, is the most important drug in use for approximately 30 years. Artemisinin was isolated in 1971 from leaves of annual wormwood (Artemesia annua) [49-51]; the 1,2,4-trioxane ring \( \text{V} \) is the key pharmacophore of these drugs. A series of semi-synthetic derivatives of artemisinin were synthesized: artesunate, artemether, and artemisone (Figure 2). Currently, drugs based on these compounds are considered as the most efficacious for the treatment of malaria [52-76].

The discovery of arterolane, a synthetic 1,2,4-trioxolane, is a considerable success in the search for easily available synthetic peroxides capable of replacing artemisinin and its derivatives in medical practice. Currently, this compound is currently in phase III clinical trials [77-81].
The mechanism of antimalarial action of peroxides is unusual for pharmaceutical chemistry. According to the commonly accepted mechanism, peroxides diffuse into Plasmodium-infected erythrocytes, and the heme iron ion of the latter reduces the peroxide bond to form a separated oxygen-centered radical anion, which rearranges to the C-centered radical having a toxic effect on Plasmodium [82-87].

In the course of the large-scale search for synthetically accessible and cheap antimalarial peroxides (compared with natural and semi-synthetic structures), it was found that structures containing 1,2-dioxolane [88-90], 1,2,4-trioxolane [91-101], 1,2-dioxane [102-112], 1,2-dioxene [113-119], 1,2,4-trioxane [120-127] or 1,2,4,5-tetraoxane rings [128-146] exhibit pronounced activity, and in some cases, even superior to that of artemisinin.

Another important field of medicinal chemistry of organic peroxides includes the search for antihelminthic drugs. For example, compounds containing 1,2-dioxolane [147], 1,2,4-trioxolane [148-152], 1,2,4-trioxane [153-158] or bridged 1,2,4,5-tetraoxane [159] moieties show activity against Schistosoma. Schistosomiasis is one of the most widespread helminthic diseases; 800 million people are at risk of acquiring this infection [160-174].

Additionally, based on synthetic peroxides, several compounds exhibiting antitumor activity were synthesized. These compounds contain 1,2-dioxolane [10-15,175-178], 1,2-dioxene [10-15,112,178-181], 1,2-dioxane [114,182-185] or 1,2,4-trioxane [10-15,175,176] rings. More than 300 peroxides are known to have a toxic effect on cancer cells [10-15,73,186-206].

Synthetic peroxides exhibit also other activities. For example, compounds containing the 1,2,4-trioxane ring are active against Trichomonas [207], compounds with the 1,2-dioxane ring show antitrypanosomal and antileishmanial activities [208-212], and compounds containing the 1,2-dioxene ring possess fungicidal [210,213-224] and antimycobacterial activities [128-131,225-228]. The present review covers literature relating to 5- and 6-membered cyclic peroxide chemistry published between 2000 and 2013.

Review
1. Synthesis of 1,2-dioxolanes
The modern approaches to the synthesis of 1,2-dioxolanes are based on the use of oxygen and ozone for the formation of the peroxide moiety, the Isayama–Mukaiyama peroxysilylation, and reactions involving peroxyxycarbenium ions. Syntheses employing hydrogen peroxide and the intramolecular Kobayashi cyclization are less frequently used.

1.1. Use of oxygen for the peroxide ring formation
The singlet-oxygen ene reaction with alkenes provides an efficient tool for introducing the hydroperoxide function. The reaction starts with the coordination of oxygen to the double bond followed by the formation of hydroperoxides presumably by a stepwise or concerted mechanism [229,230]. The oxidation of α,β-unsaturated ketones 1a–c by singlet oxygen affords 3-hydroxy-1,2-dioxolanes 3a–c via the formation of β-hydroperoxy ketones 2a–c (Scheme 1) [231].

Dioxolane 6 was synthesized in 36% yield by the reaction of oxygen with hydroperoxide 4 in the presence of di-tert-butyl peroxyxalate (DTBPO) followed by the treatment of the reaction mixture with acetic anhydride and pyridine at room temperature (Scheme 2).

It should be emphasized that a mixture of dioxolanes 5 and 6 in a ratio of 7:3 is formed already in the first step [232].

The photooxygenation of oxazolidines 7a–d through the formation of hydroperoxides 8a–d gives spiro-fused oxazolidine-containing dioxolanes 9a–d in low yields (12-30%) (Scheme 3) [233].

![Scheme 1: Synthesis of 3-hydroxy-1,2-dioxolanes 3a–c.](image-url)
The reaction was performed in a temperature range from −10 to −5 °C. The conversion of oxazolidines 7 and the yields of dioxolanes 9 were determined by $^1$H NMR spectroscopy.

An efficient method for the synthesis of 1,2-dioxolanes is based on the oxidation of cyclopropanes by oxygen in the presence of transition-metal salts as the catalysts. The reactions of bicycloalkanols 10a–e with singlet oxygen in the presence of catalytic amounts of Fe(III) acetylacetonate produce peroxides 12a–e, which can also be synthesized starting from silylated bicycloalkanols 11a–e with the use of Cu(II) acetylacetonate (Scheme 4, Table 1) [234].

Table 1: Structures and yields of dioxolanes 12a–e.

| Bicycloalkanol 10a–e, silylated bicycloalkanol 11a–e | 1,2-Dioxolane 12a–e | Method A$^a$ | Method B$^b$ |
|---------------------------------------------------|---------------------|-------------|-------------|
| R        | n   | Reaction time, h | Yield, % | Reaction time, h | Yield, % |
| a        | CH$_3$ | 1   | 3       | 35    | 5   | 54   |
| b        | C$_4$H$_9$ | 1  | 3       | 55    | 3.5  | 84   |
| c        | C$_6$H$_{13}$ | 1 | 3     | 68    | –    | –    |
| d        | CH$_2$Ph | 1  | 3       | 50    | 5    | 78   |
| e        | CH$_3$ | 2   | 36      | 54    | 6    | 80   |

$^a$Et$_2$O, O$_2$, hv, silica gel, Fe(acac)$_3$ (4 mol %).

$^b$EtOH, O$_2$, hv, Cu(acac)$_2$ (4 mol %).
Similarly, the reactions of silylated bicycloalkanols 13a–c with oxygen in the presence of the catalyst VO(acac)$_2$ yielded dioxolanes 14a–c, which made it possible to perform the oxidation without irradiation (Scheme 5, Table 2) [235].

This reaction gives β-hydroxyketones as by-products that are formed as a result of the decomposition of dioxolanes 14.

Cyclopropanols 15a–g are readily oxidized by molecular oxygen in the presence of Mn(II) abietate or acetylacetonate (Scheme 6) [236].

Presumably, the reaction proceeds via the intermediate formation of O- and C-centered radicals 16a–g and 17a–g, respectively. According to this method, dioxolanes 18a–g (exist in equilibrium with the open form 19a–g) were synthesized in 60–80% yields.

Like hydroxycyclopropanes, aminocyclopropanes are transformed into 1,2-dioxolanes. For example, N-cyclopropyl-N-phenylamines 20a–c form dioxolanes 21a–c in the presence of atmospheric oxygen (Table 3). It was found that the reaction rate substantially increases in the presence of catalytic amounts of [(phen)$_3$Fe(III)(PF$_6$)$_3$] or equimolar amounts of benzoyl peroxide or di-tert-butyl peroxide. The possible mechanism of the oxidation is shown in Scheme 7 [237].

According to the $^1$H NMR data, dioxolanes 21a–c are formed under the above-mentioned conditions in almost quantitative yields; the yields based on the isolated product were not higher than 80% [237].

\[
\begin{align*}
\text{HO} & \quad \text{O}_2, \quad \text{1.5 mol % Mn(II) abietate} \\
R^1 & \quad \text{benzene, rt, 3–5 h} \\
R^2 & \\
15a–g & \\
& \quad \text{O}_2 \quad \text{H-source} \\
& \quad \text{rt, 3–5 h} \\
& \quad \text{18a–g} \\
& \\
& \quad \text{19a–g} \\
& \quad \text{16a–g} \\
& \quad \text{17a–g} \\
& \quad \text{R}^1 \quad \text{R}^2 \\
\end{align*}
\]

**Scheme 6: Mn(III)-catalyzed oxidation of cyclopropanols 15a–g.**

| Table 3: Peroxidation of N-cyclopropyl-N-phenylamines 20a–c to form 3-(1,2-dioxalanyl)-N-phenylamines 21a–c. |
|---|---|---|
| **Dioxolane 21a–c** | **R$^1$** | **R$^2$** | **Reaction conditions** |
| a | H | H | 1. (BzO)$_2$ (1 mol/1 mol 20a), CHCl$_3$, dark, $-20^\circ$C, 3 days. |
| b | Me | H | 1. (t-BuO)$_2$ (1 mol/1 mol 20b), CHCl$_3$, UV (254 nm), ambient temperature, aerobic, 2 h. |
| c | H | Me | 1. (t-BuO)$_2$ (1 mol/1 mol 20c), CHCl$_3$, UV (254 nm), ambient temperature, aerobic, 2 h. |

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**Table 2: Structures and yields of dioxolanes 14a–c.**

| Silylated bicycloalkanol 13a–c | **R$^1$** | **R$^2$** | **Solvent** | **Yield 14a–c, %** |
|---|---|---|---|---|
| a | H | Me | EtOH | 45 |
| b | H | Bn | CF$_3$CH$_2$OH | 43 |
| c | Me | Me | CF$_3$CH$_2$OH | 43 |
Structurally similar 3-ethyl-6a-methyl-6-(4-phenoxyphenyl)hexahydro[1,2]dioxolo[3,4-b]pyrroles 24a and 24b were synthesized from (Z)-N-(hex-3-enyl)-N-(4-phenoxyphenyl)acetamide (22). It was suggested that aminocyclopropane 23 is formed in situ, which is subsequently oxidized in air on silica gel (Scheme 8) [238]. The total yield of both isomers 24 was 31%.

Trifluoromethyl-containing dioxolane 25 (Figure 3) was synthesized according to this method in 40% yield [239].

A series of 1,2-dioxolanes 27a–e containing various functional groups R were prepared by the oxidation of cyclopropanes 26a–e (Scheme 9, Table 4).

The reaction was performed in the presence of Ph2Se2 (10 mol %) and azobisisobutyronitrile (AIBN, 8 mol %) in air under irradiation for two days. The product was purified by
Scheme 9: Synthesis of 1,2-dioxolanes 27a–e by the oxidation of cyclopropanes 26a–e.

Table 4: Structures and yields of dioxolanes 27a–e.

| Dioxolane 27a–e | R            | Yield (cis + trans), % | Ratio (cis/trans) |
|-----------------|--------------|------------------------|-------------------|
| a               | CO₂Et        | 88                     | 1/7               |
| b               | Ph           | 100                    | trans isomer      |
| c               | CO₂Me        | 75                     | 1/22              |
| d               | N            | 100                    | 1/13              |
| e               | Ph           | 82                     | 1/2.8             |

flash chromatography to obtain a mixture of cis and trans isomers, whose ratio depends primarily on the nature of the substituent in cyclopropanes 26a–e [240].

The oxidation of methylenecyclopropanes 28a and 28b under photoinduced electron-transfer conditions is described by a similar scheme (Scheme 10).

Dioxolane 29a was obtained in quantitative yield (\(^1\)H NMR data), the yield of 29b was not reported [241].

Under irradiation in the presence of oxygen, 1,5-bis(4-methoxyphenyl)bicyclo[3.1.0]hexane (30) and 1,5-bis(4-methoxyphenyl)-6,7-diazabicyclo[3.2.1]oct-6-ene (31) were transformed into bicyclic dioxolane 33. It was suggested that both reactions proceed via the formation of 1,3-radical cation 32 (Scheme 11).

Dioxolane 33 was synthesized in the highest yields (91% from 30 and 100% from 31) in acetonitrile with the use of 9,10-dicyanoanthracene (DCA) as the sensitizer [242].

After irradiation of diazene 34 in an argon matrix at 10 K, biradical 35 was detected by IR spectroscopy and the reaction of the latter with oxygen at 10 K proceeded regioselectively to give dioxolane 36 (Scheme 12) [243].

Bicyclic peroxide 2-heptyl-3,4-dioxabicyclo[3.3.0]oct-1(8)-ene was prepared by a similar process [244].

The oxidation of arylacetylenes 37a–h with atmospheric oxygen in the presence of catalytic amounts of Mn(OAc)₃ in an
excess of acetylacetone afforded dioxolanes 38a–h in moderate yields (34–64%) (Scheme 13, Table 5) [245].

The reaction was performed at 23 °C in glacial acetic acid in air; the 37/acetacetylone/Mn(OAc)₃ molar ratio was 1/10/10. The reaction gave oxiranes 39 as by-products, which can also be synthesized in quantitative yields by the treatment of dioxolanes 38 with silica gel in methanol [245].

The peroxidation of 1,4-dienes 43a,b with the Co(modp)₂/Et₃SiH/O₂ system according to a similar reaction scheme gave dioxolanes 44a,b. Acetophenone (45) was obtained as the by-product (Scheme 15, Table 6) [249].

The desilylation of the initially formed silicon peroxide followed by cyclization of the hydroperoxide accompanied by the attack on the electrophilic center is another example of the use of a peroxide radical, are able to undergo intramolecular cyclization to form the 1,2-dioxolane ring. For example, the Co(modp)₂-catalyzed peroxysilylation (modp = 1-morpholino-5,5-dimethyl-1,2,4-hexanetrionate) of (2-vinylcyclopropyl)benzene (40) affords triethyl(1-(5-phenyl-1,2-dioxolan-3-yl)ethylperoxy)silane (41) in 37% yield (Scheme 14).

The reaction was carried out in 1,2-dichloroethane at room temperature, and the reaction products were separated by column chromatography. 1-Hydroxy-1-phenylpentan-3-one (42) was isolated as a by-product in 16% yield [248].
Table 7: Peroxidation of 1,5-dienes

| Diene | R<sub>1</sub> | R<sub>2</sub> | Reaction time, h | Conversion, % | Yield, % | a |
|-------|------------|------------|-----------------|--------------|---------|---|
| a     | H          | H          | 6               | 45           | 82      | 82|
| b     | H          | Me         | 2.5             | 36           | 83      | 43|
| c     | Me         | H          | 3.5             | 57           | 75      | 37|
| d     | Ph         | Ph         | 3.5             | 54           | 38      | 27|

*The yields are given based on the converted dienes 46a–d.*

A similar way to 1,2-dioxanes used an oxime cycle for the stages of ring opening followed by 1,2-dioxide ring closing of the Isoyama-Mukaiyama reaction for the synthesis of cyclic peroxides. In some cases, 1,2-dioxanes 48, 1,2-dioxide 51, and perfluorocarboxylic acid peroxides 47 are obtained as by-products, which are desylated during hydrolysis to give the unsaturated hydroperoxides 50 (Scheme 16, Table 7) [249].

table 6. Synthesis of dioxolanes 44a,b

| 1,4-Diene | R | Reaction time, h | Conversion, % | Yield, % |
|-----------|---|------------------|--------------|---------|
| a         | H | 4.5              | 47           | 27      | 49 |
| b         | COOEt | 2          | 44           | 56      | 22 |

The synthesis of spirodioxolane 59 involved the peroxysilylation of 1,3-dicyclohexyl-2,2-diacetate (CoTDA) as the first step, followed by aqueous NaOH treatment to give the target dioxolane 55a,b (Scheme 17) [250].
Scheme 17: Peroxidation of oxetanes 53a,b.

...subsequently transformed into the carbonyl-containing diperoxide (1,3-bis(1-(triethylsilylperoxy)cyclohexyl)propan-2-one) (58) in two steps. The latter was treated with p-TsOH to give the target peroxide 59 (Scheme 18) [252].

1.3. The use of ozone. Peroxy carbene ions in the 1,2-dioxolanes synthesis

The ozonolysis of unsaturated compounds is a reliable and facile method for the introduction of the peroxide functional group. As in the above-considered studies, the intramolecular cyclization of ozonolysis products can be performed with the use of the hydroperoxide group provided that there is an appropriate electrophilic center.

The reaction of oxetanes 60a,b with ozone in methanol produced 3-alkoxy-1,2-dioxolanes 62a,b. The analysis of the reaction mixture (TLC, NMR) confirmed that cyclic peroxides are formed immediately in the reaction mixture rather than in the course of the treatment or purification of the reaction products. It was suggested that the reaction proceeds via the formation of hydroperoxy acetals 61a,b (Scheme 19) [250].

The ozonolysis of 9-methyleneheptadecane-7,11-diylbis(methanesulfonate) (63) gave 9-oxoheptadecane-7,11-diylbis(methanesulfonate) (64). The latter reacted with H2O2 in the presence of sulfuric acid (or iodine) as the catalyst to form 9,9-dihydroperoxyheptadecane-7,11-diyl-bis(methanesulfonate) 65, and the replacement of the mesyl groups in the latter compound afforded 3,8-dihexyl-1,2,6,7-tetraoxaspiro[4.4]nonane (66, Scheme 20). The yield of dioxolane 66 was 36% based on 63 [252].

The treatment of 3,3’-(cyclohexa-3,6-diene-1,3-diyl)dipropan-1-ol (67) and 4,4’-(cyclohexa-3,6-diene-1,3-diyl)dibutan-2-ol (69) ...
with ozone in MeOH/CH$_2$Cl$_2$ followed by the addition of a catalytic amount of p-TsOH lead to the intramolecular peroxycyclization that proceeds through the formation of the peroxy-carbenium ion (shown in Scheme 21 for the ozonolysis of 67 as an example) to give finally dispiro-1,2-dioxolanes: 1,8,12,13-tetra-oxadispiro-[4.1.4.2]tridecane 68 (yield 67%) and two isomers of 2,9-dimethyl-1,8,12,13-tetraoxadispiro[4.1.4.2]tridecane 70 and 71 (combined yield 72%) (Scheme 21) [253].

The spirohydroperoxydioxolanes, 5-hydroperoxy-2',3'-dihydrospiro[1,2]dioxolane-3,1'-indene (75a) and 5-hydroperoxy-3',4'-dihydro-2'H-spiro[1,2]dioxolane-3,1'-naphthalene (75b), were synthesized by the ozonolysis of 1-allyl-1-hydroperoxy-2,3-dihydro-1H-indene (72a) and 1-allyl-1-hydroperoxy-1,2,3,4-tetrahydronaphthalene (72b), respectively, in an Et$_2$O/CF$_3$CH$_2$OH system (2:1). The reaction proceeds via the formation of ozonide 73 followed by elimination of formaldehyde to give peroxycarbenium ion 74 that undergoes cyclization via the attack of the hydroperoxide group on the carbon center of peroxycarbenium ion 74 (Scheme 22) [254].

An oxidative rearrangement takes place in the reaction of azepino[4,5-b]indole 80 with ozone. The addition of ozone to the endocyclic double bond (molozone 81) and the formation of the Criegee intermediate are followed by a 1,3-dipolar interaction of the peroxycarbenium ion with the double bond (82) to form dioxolane 83. The yield was not lower than 48% but no exact yield was reported (Scheme 24) [255].
in the presence of allyltrimethylsilane in dichloromethane gives a complex mixture of products 85–94, including dioxolanes 86–88, 90–92, and 93 (Scheme 25, Table 8) [256].

Treatment of the bicyclic ozonide 1-methyl-6,7,8-trioxabicyclo[3.2.1]octane 84m, with SnCl₄ in the presence of allyltrimethylsilane produces a mixture of two cis diastereomers and two trans diastereomers (in a ratio of 35:35:15:15) of 7-(3-methyl-5-((trimethylsilyl)methyl)-1,2-dioxolan-3-yl)hept-1-en-4-ol 95 in a total yield of 48% (Scheme 26) [256].
Table 8: The SnCl₄-mediated fragmentation of ozonides 84a–l in the presence of allyltrimethylsilane.

| Ozonide 84 | R¹ | R² | T, °C | Lactone 85 | Dioxolane 86 | Dioxolane 87 | Ketone 88 | Alcohol 89 | Yield, % |
|------------|----|----|-------|------------|--------------|--------------|-----------|----------|----------|
| a          | -(CH₂)₄- |    | -78 to 0 | 11         | 50           | -            | 88a (traces) | -        |          |
| b          | -(CH₂)₅- |    | -78 to 0 | 17         | 57           | -            | 88b (traces) | -        |          |
| c          | -(CH₂)₆- |    | -78 to 0 | 39         | 24           | -            | 88c (traces) | -        |          |
| d          | CH₃   | Ph | -78 to 0 | 25         | 61           | -            | 88d (93%)  | -        |          |
| e          | C₆H₅ | C₆H₅| -78 to 0 | 40         | 14           | -            | 88e (70%)  | 75       |          |
| f          | H     | C₆H₁₇| -78     | -          | 56           | -            | -         | 50       |          |
| g          | H     | Ph | -78     | -          | 79           | -            | -         | -        | 13       |
| h          | H     | H | -78     | -          | 10           | -            | -         | -        | -        |
| i          | CH₃   | C(CH₃)₃| -78 to 0 | 31         | 21           | 9 (cis)     | -         | -        |          |

| Ozonide 84 | R¹ | R² | T, °C | Dioxolane 90 (cis:trans) | Dioxolane 91 | Carbonyl compound 92 | Alcohol 93 | Alkene 94 | Yield, % |
|------------|----|----|-------|--------------------------|--------------|----------------------|-----------|----------|----------|
| j          | H  | C₃H₇| -78   | 15 (1:1)                 | 7            | -                    | 93j 20%   | -        |          |
| k          | H  | C₃H₇| -78   | 15 (1:1)                 | -            | 22                   | 93j 24%   | -        |          |
| l          | CH₃| H   | -78   | 9 (1:1)                  | -            | 43                   | -         | 2.5      |          |

These syntheses of dioxolanes involve the formation of the peroxycarbenium ion as the key step. The reaction of the latter with allyltrimethylsilane followed by the intramolecular cyclization finally leads to the dioxolane ring.

Dioxolanes 99–102 are produced from alkoxyhydroperoxides 96a–g (ozonolysis products of alkenes) in a similar way. The first step results in the formation of peroxycarbenium ions 97, which are trapped with allyltrimethylsilane under the formation of intermediate hydroperoxides 98. Then either cyclic dioxolanes 99–102 or unsaturated compounds 103–107 are formed as the major reaction products depending on the nature of the substituents and the Lewis acid (Scheme 27, Table 9) [257].

Table 9: Synthesis of 1,2-dioxolanes 99–102.

| Hydroperoxide 96 | R¹ | R² | R³ | M   | Dioxolane 99–102 (yield, %) | Alkene 103–107 (X, yield, %) |
|------------------|----|----|----|-----|-----------------------------|-------------------------------|
| a                | Me | Me | Me | Ti  | 99 (31)                      | -                             |
| b                | Me | Me | (CH₂)₂OMe | Sn | 99 (56)                      | -                             |
| b                | Me | Me | (CH₂)₂OMe | Ti | 99 (12)                      | 103 (=OOH, 23)                |
| c                | 4-tert-butyl-cyclohexylidene | Me | Ti | -   | 104 (=O₂⁻, 31)              |
| c                | 4-tert-butyl-cyclohexylidene | Me | Sn | 100 (42) | -                  |
| d                | 4-tert-butyl-cyclohexylidene | (CH₂)₂OMe | Sn | 100 (59) | -                        |
| e                | Me | BrOCH₂ | Me | Ti  | 101 (12)                      | 105 (=O, 62)                  |
| f                | Bu | H  | Me | Ti  | 102 (7)                       | 106 (OMe, 63)                 |
| g                | Bu | H  | (CH₂)₂OMe | Ti | 102 (15)                      | 107 (O(CH₂)₂OMe, the yield was not determined) |

Scheme 27: MCl₄-mediated fragmentation of alkoxyhydroperoxides 96 in the presence of allyltrimethylsilane.
The reaction of trialkylsilylperoxyacetals with alkenes in the presence of Lewis acids also proceeds through the formation of peroxycarbenium ions. For example, the reaction of methyl 2-(4-methoxy-4-(triethylsilylperoxy)cyclohexyl)acetate (108) with 2-methyleneadamantane (109) produced adamantane-2-spiro-3',8'-methoxycarbonylmethyl-1',2'-dioxo-spiro[4.5]decane (110) in 40% yield (Scheme 28) [258].

The use of easily accessible triethylsilylperoxyacetals 111 as the starting materials for the generation of silylperoxycarbenium ions 112 enabled the synthesis of 1,2-dioxolanes containing various functional groups 113–130 in good yields by the reactions with alkenes (Scheme 29, Table 10) [88,90,259].

1.4. Methods for the synthesis of 1,2-dioxolanes from hydrogen peroxide and hydroperoxides

This section deals with reactions, in which hydrogen peroxide or hydroperoxides are used for the construction of the five-membered peroxide ring. In all syntheses, the final (key) step involves the intramolecular cyclization of hydroperoxide with

| Product | Structure | Yielda, % | Product | Structure | Yielda, % |
|---------|-----------|-----------|---------|-----------|-----------|
| 113     | ![Structure 113](image1) | 80        | 122     | ![Structure 122](image2) | 92        |
| 114     | ![Structure 114](image3) | 72        | 123     | ![Structure 123](image4) | 47        |
| 115     | ![Structure 115](image5) | 57        | 124     | ![Structure 124](image6) | 72        |
| 116     | ![Structure 116](image7) | 67        | 125     | ![Structure 125](image8) | 28        |
| 117     | ![Structure 117](image9) | 57        | 126     | ![Structure 126](image10) | 48        |
Table 10: Structures and yields of 1,2-dioxolanes 113–130. (continued)

| 118 | t-Bu | O-O | COEt | 34 | 127 | O-O | OBn | 59 |
|-----|------|-----|------|----|-----|-----|-----|----|
| 119 |       | O-O | OBn  | 46 | 128 | O-O | OH  | 51 |
| 120 |       | O-O |      | 74 | 129 | O-O | Ph  | 68 |
| 121 |     t-Bu | O-O |      | 94 | 130 | O-O |     | 90 |

*aReagents and conditions: SnCl4 (1.0–2.0 equiv), alkene (1.0–3.0 equiv), CH2Cl2, from −78 °C to 25 °C, 2–24 h.

The attack on the electrophilic center (an activated double bond or a carbon atom of a keto or ester group).

The desilylation of tert-butylidemethylsilylperoxy ketones 131a,b with HF followed by cyclization and subsequent reaction with monomethylethylene glycol afforded dioxolanes 132a,b in 75 and 88% yield, respectively. The intermediate hydroxydioxolanes 131'a,b were used in the second step without isolation (Scheme 30) [260]. A series of analogues of plakinic acids were synthesized by the modification of the peroxyketal moiety of dioxolanes 132a and 132b [260].

The monoperoxy ketal moiety of 4-(2-methoxypropan-2-ylperoxy)nonan-2-one (133) was used for the generation of the hydroperoxide group. The intramolecular cyclization afforded 3-methyl-5-pentyl-1,2-dioxolan-3-ol (134), which could be easily reacted with monomethylethylene glycol to form 3-(2-methoxyethoxy)-3-methyl-5-pentyl-1,2-dioxolane (135). Allylation of the latter produced 3-allyl-3-methyl-5-pentyl-1,2-dioxolane (136) in 47% yield (Scheme 31) [261].

The asymmetric peroxidation of methyl vinyl ketones 137a–e with 9-amino-9-deoxyepiquinine 138 and CCl3COOH afforded

Scheme 30: Desilylation of tert-butylidemethylsilylperoxy ketones 131a,b followed by cyclization.

Scheme 31: Deprotection of peroxide 133 followed by cyclization.
hydroxydioxolanes 139a–e with high enantiomeric excess (ee 94–95%) (Scheme 32) [262].

The Kobayashi synthesis of 1,2-dioxolanes represents an intramolecular version of the Michael reaction, in which the hydroperoxide group acts as the nucleophile. Generally, the reaction is performed in fluorinated alcohols (CF<sub>3</sub>CH<sub>2</sub>OH or (CF<sub>3</sub>)<sub>2</sub>CHOH) in the presence of diethylamine or, in some cases, of cesium hydroxide. Initially, the method was proposed for the synthesis of the 1,2-dioxane moiety (examples are considered in the corresponding section) [263]. However, it was shown that this method is also applicable to the preparation of structurally complex 1,2-dioxolanes, such as methyl 2-(5-(5-methylfuran-2-yl)-1,2-dioxolan-3-yl)acetate (141) from the furan derivative (E)-methyl 5-hydroperoxy-5-(5-methylfuran-2-yl)pent-2-enoate (140) (Scheme 33) [264].

A simple method was developed for the synthesis of cyclopropane-containing oxodioxolanes 143a–j and is based on the hydroperoxidation of tertiary alcohols 142a–j in an acidic medium followed by cyclization of the intermediate hydroperoxides through the ester group (Scheme 34) [265].

This method allows for the use of a nonhazardous 30% hydrogen peroxide solution. However, the authors mentioned that structurally similar tertiary alcohols, without a cyclopropane substituent, are inert under the reported conditions.

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**Scheme 32:** Asymmetric peroxidation of methyl vinyl ketones 137a–e.

**Scheme 33:** Et<sub>2</sub>NH-catalyzed intramolecular cyclization.

**Scheme 34:** Synthesis of oxodioxolanes 143a–j.
Haloperoxidation reaction that is accompanied by intramolecular ring closure represents another version of the cyclization reaction. For example, the reaction of bromine with unsaturated hydroperoxide 146 (produced by reaction of 1,4,5,8-tetrahydronaphthalene (144) with singlet oxygen via the formation of 4a-hydroperoxy-1,4,4a,5-tetrahydronaphthalene (145) gives hydroperoxide-containing bromonium cation 147 as the intermediate, which undergoes cyclization to form 1,2-dioxolanc-containing 7-bromo-4,5,10,11-tetraoxatetracyclo[7.2.2.1^{3,6}.0^{3,9}]tetradec-12-ene (148) (Scheme 35).

The cyclization occurs selectively because the hydroperoxide group in intermediate 147 attacks only one of two possible electrophilic carbon centers [266].

1.5. 1,2-Dioxolane ring formation through oxidation of the allylic position

1,2-Dioxolane-containing compounds 150a–d were synthesized by the oxidation of triterpenes 149a–d with Na$_2$Cr$_2$O$_7$/N-hydroxysuccinimide (Scheme 36). The resulting compounds exhibit antitumor activity comparable with that of betulinic acid [175-177].

1.6. Structural modifications, in which the 1,2-dioxolane ring remains intact

The possibility of performing the Curtius and Wolff rearrangements to form 1,2-dioxolane ring-retaining products was exemplified by the synthesis of ethyl (3,5,5-trimethyl-1,2-dioxolan-3-yl)methylcarbamate (152) and methyl 3-(3,5,5-trimethyl-1,2-dioxolan-3-yl)propanoate (154) (through formation of stable dixiodoxolane 153) from 2-(3,5,5-trimethyl-1,2-dioxolan-3-yl)acetic acid (151) (Scheme 37) [267].

Dioxolane 155 that contains a free hydroxy group was synthesized by the oxidative desilylation of silicon-containing peroxide 124 with n-Bu$_4$NF and H$_2$O$_2$ (Scheme 38) [259].

Dioxolane 158 with the aminoquinoline antimalarial pharmacophore was synthesized in two steps by the oxidation of alcohol 156 with H$_2$O$_2$/RuCl$_3$ followed by amidation of the
Plakinic acids belong to a large family of natural products, which were shown to be highly cytotoxic toward cancer cells and fungi. Diastereomers of plakinic acid A, 162a and 162b were synthesized starting from dioxolane (R)-3-(((2R,3E,6S,7E)-2,6-dimethyl-8-phenylocta-3,7-dienyl)-5-(2-methoxyethoxy)-3,5-dimethyl-1,2-dioxolane) (159) [260]. In the first step, dioxolane 159 was treated with 1-(ethylthio)vinyloxytrimethylsilane in the presence of TiCl₄ to obtain S-ethyl 2-(((2R,3E,6S,7E)-2,6-dimethyl-8-phenylocta-3,7-dienyl)-3,5-dimethyl-1,2-dioxolan-3-yl)-ethanethioate (160). The subsequent reaction with sodium methoxide in methanol produced the corresponding esters 161a and 161b, which were hydrolyzed to prepare the target plakinic acids (Scheme 40).

2. Synthesis of 1,2,4-trioxolanes (ozonides)

The currently most widely used methods for the synthesis of 1,2,4-trioxolanes are based on reactions of ozone with unsaturated compounds, such as the ozonolysis of alkenes, the cross-ozonolysis of alkenes with carbonyl compounds, and the cross-ozonolysis of O-alkylated oximes in the presence of carbonyl compounds (Griesbaum coozonolysis).

2.1. Ozonolysis of alkenes

According to the mechanism proposed by R. Criegee [268,269] the ozonolysis of alkenes 163 involves several steps: the 1,3-dipolar cycloaddition of ozone to the double bond to form...
unstable 1,2,3-trioxolane 164 (so-called molozonide) that is followed by its decomposition to a peroxycarbene ion and a carbonyl compound (Criegee intermediates). The 1,3-dipolar cycloaddition of the intermediates with each other form the 1,2,4-trioxolane 165 (Scheme 41, Table 11). Generally, the ozonolysis is performed in aprotic solvents at low temperatures and in some cases, on polymeric substrates. Since various compounds containing a C=C group are easily available, a wide range of functionalized 1,2,4-trioxolanes can be synthesized in moderate to high yields.

Table 11: Examples of 1,2,4-trioxolanes produced by the ozonolysis of alkenes.

| Alkene 163 | Ozonolysis conditions | 1,2,4-Trioxolane 165 | Yield, % | Reference |
|------------|-----------------------|----------------------|----------|-----------|
| Et₂O, −70 °C | 24 [270] |
| MeO - Ph | 27 [270] |
| hexane, −78 °C | 78 [256] |
Table 11: Examples of 1,2,4-trioxolanes produced by the ozonolysis of alkenes. (continued)

| Structure | Reaction Conditions | Yield | Source |
|-----------|--------------------|-------|--------|
| ![Structure](image1) | hexane, $-78 ^\circ C$ | 73 | [256] |
| ![Structure](image2) | hexane, $-78 ^\circ C$ | 77 | [256] |
| ![Structure](image3) | hexane, $-78 ^\circ C$ | 61 | [256] |
| ![Structure](image4) | isoctane/CCl$_4$, $-78 ^\circ C$, 1 h | $>82$ | [271] |
| ![Structure](image5) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 95 | [272] |
| ![Structure](image6) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 90 | [272] |
| ![Structure](image7) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 92 | [272] |
| ![Structure](image8) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 93 | [272] |
| ![Structure](image9) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 93 | [272] |
| ![Structure](image10) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 94 | [272] |
| ![Structure](image11) | pentane, $-78 ^\circ C$ | 63 | [272] |
| ![Structure](image12) | Freon-113, 15–20 $^\circ C$, 2 h | The yield was not determined | [273,274] |
| ![Structure](image13) | Freon-113, 15–20 $^\circ C$, 2 h | The yield was not determined | [273] |
| ![Structure](image14) | CH$_2$Cl$_2$, $-78 ^\circ C$ | 96 | [275] |
Table 11: Examples of 1,2,4-trioxolanes produced by the ozonolysis of alkenes. (continued)

| Compound | Reaction Conditions | Yield | Reference |
|----------|---------------------|-------|-----------|
| Polymer-based, −78 °C, 8 h | | 23 | [276] |
| Polymer-based, −78 °C, 3 h | | 38 | [276] |
| CH₂Cl₂, −70 °C | | 48 | [277] |
| (F₃C)₂FCFC=CFCF₃ | without solvent, −133 to −43 °C | 100 | [278] |
| | 1) CH₂Cl₂, −78 °C, 15 min. 2) Me₂S, rt, 6 h | 71 | [279] |
| | hexane, −78 °C, 30 min | 6 | [280] |
| | CH₂Cl₂, −78 °C, 20 min | The yield was not determined | [281] |
| | CH₂Cl₂, −78 °C, 2 h | >97 | [282] |
| | CDCl₃, −65 °C | 88 | [283] |
| | CFCl₃, −70 °C | 100 | [283] |
| | CH₂Cl₂, −78 °C, 1 h | 85 | [284] |
Table 11: Examples of 1,2,4-trioxolanes produced by the ozonolysis of alkenes. (continued)

| R = Me, Et, Pr, iPr, iBu, t | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C}, 1 \text{ h} \] | \[ \text{pentane, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \] | \[ \text{Et}_2\text{O/CH}_3\text{OH, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{H}_2\text{O/CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{AcO}()_2\text{C}_8, 0 ^\circ \text{C} \] | \[ \text{F}_2\text{H}_2\text{C}()_3\text{OBn} \] |
|-----------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| \[ \text{Ph}^+ \text{O}^\text{-} \text{OMe} \] | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C}, 1 \text{ h} \] | \[ \text{pentane, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \] | \[ \text{Et}_2\text{O/CH}_3\text{OH, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{H}_2\text{O/CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{AcO}()_2\text{C}_8, 0 ^\circ \text{C} \] | \[ \text{F}_2\text{H}_2\text{C}()_3\text{OBn} \] |

| R = Me, Et, Pr, iPr, iBu, t | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C}, 1 \text{ h} \] | \[ \text{pentane, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, -78 ^\circ \text{C} \] | \[ \text{Et}_2\text{O/CH}_3\text{OH, } -78 ^\circ \text{C} \] | \[ \text{CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{H}_2\text{O/CH}_2\text{Cl}_2, 0 ^\circ \text{C} \] | \[ \text{AcO}()_2\text{C}_8, 0 ^\circ \text{C} \] | \[ \text{F}_2\text{H}_2\text{C}()_3\text{OBn} \] |

Scheme 42: Cross-ozonolysis of alkenes 166 with carbonyl compounds.

2.2. Cross-ozonolysis of alkenes with carbonyl compounds

The peroxycarbenium ion produced by the decomposition of 1,2,3-trioxolane (molozonide) can react with externally introduced carbonyl compounds to form the corresponding 1,2,4-trioxolanes. The pathway of decomposition of 1,2,3-trioxolanes is determined by the structure of the starting alkene 166. In some cases, a high selectivity of the formation of cross-ozonolysis products 1,2,4-trioxolanes (ozonides) 167, can be achieved (Scheme 42, Table 12).
Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds.

| Alkene | Carbonyl compound | Ozonolysis conditions | 1,2,4-Trioxolane | Yield, % | Reference |
|--------|-------------------|-----------------------|------------------|----------|-----------|
| \(n(H_2C)\) \(n = 1, 2, 3, 4, 8\) | \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 17–74 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 9–57 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 50 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 38 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 18–48 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 25–37 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 63–80 | [291] |
| \(O\) | CH\(_2\)Cl\(_2\), \(-78 \, ^\circC\) | \(R^5 = H\) CH\(_3\) C\(_6\)H\(_5\) H | 55–77 | [291] |
Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds. (continued)

| Chemical Structure | Reaction Conditions | Yield | Reference |
|--------------------|--------------------|-------|-----------|
| ![Chemical Structure 1](image1) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 63–66 | [291] |
| ![Chemical Structure 2](image2) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 52 62 | [291] |
| ![Chemical Structure 3](image3) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 41 46 | [291] |
| ![Chemical Structure 4](image4) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 82 | [291] |
| ![Chemical Structure 5](image5) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 26 | [291] |
| ![Chemical Structure 6](image6) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 58 53 | [292] |
| ![Chemical Structure 7](image7) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 21 21 | [292] |
| ![Chemical Structure 8](image8) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 23 25 | [292] |
| ![Chemical Structure 9](image9) | CH<sub>2</sub>Cl<sub>2</sub>, −78 °C | 68 60 | [292] |
Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds. (continued)

| R² | R³ | R⁴ | CH₂Cl₂, °C | [Reference] |
|----|----|----|-----------|-------------|
| H  | H  | R⁵ | −78 °C     | 30:25 [292] |
| H  | CN | R⁶ |           |             |

For the ozonolysis of the bicyclic cyclohexenone, 2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-benzo[13]annulen-1-one (168), two reaction pathways can be proposed through intermediate 169 to form ozonides 170 and 171. It appeared that the reaction gave only 16,17,18-trioxatricyclo[10.3.2.11,12]octadecan-2-one 171 as two isomers, with the anti isomer in 60% and the syn isomer in 10% yield (Scheme 43) [294]. The structures of these compounds were established by X-ray diffraction [294].

The cross-ozonolysis of enol ethers 172a,b with cyclohexanone enabled the synthesis of 1,2,4-trioxolanes 173a,b containing the easily oxidizable C–H fragment in the third position (Scheme 44) [256].

Scheme 43: Ozonolysis of the bicyclic cyclohexenone 168.
2.3. Cross-ozonolysis of O-alkyl oximes in the presence of carbonyl compounds (Griesbaum co-ozonolysis)

In 1995, K. Griesbaum and co-workers reported a new type of cross-ozonolysis [295]. This method enables the synthesis of tetrastituted ozonides \( 176 \) by an ozone-mediated reaction of O-alkyl oximes \( 174 \) with ketones \( 175 \) (Scheme 45, Table 13). The selective synthesis of ozonides has attracted great interest because it allows the preparation of compounds exhibiting high antiparasitic activity.

**Scheme 44:** Cross-ozonolysis of enol ethers 172a, b with cyclohexa-none.

**Scheme 45:** Griesbaum co-ozonolysis.

**Table 13:** Examples of ozonides (1,2,4-trioxolanes) synthesized by the Griesbaum method.

| Oxime 174 | Ketone 175 | Ozonolysis conditions | 1,2,4-Trioxolane 176 | Yield, % | Ref. |
|-----------|-----------|-----------------------|---------------------|----------|------|
| \( \text{Ome} \) | \( \text{R}^1 \text{O} \text{O} \text{R}^2 \) | hexane, \(-78{}^\circ\text{C}\) | \( \text{Ome} \) | 47–67 | [256] |
| \( \text{Me} \) | \( \text{R}^1 \text{O} \text{O} \text{R}^2 \) | pentane, \( \text{CH}_2\text{Cl}_2, 0{}^\circ\text{C} \) | \( \text{Ome} \) | 54 | [91] |
| \( \text{X} \) | \( \text{R}^1 \text{O} \text{O} \text{R}^2 \) | pentane, \( \text{CH}_2\text{Cl}_2, 0{}^\circ\text{C} \) | \( \text{Ome} \) | 10–75 | [91,94,95,296] |
| \( \text{Me} \) | \( \text{R}^1 \text{O} \text{O} \text{R}^2 \) | pentane, \( \text{CH}_2\text{Cl}_2, 0{}^\circ\text{C} \) | \( \text{Ome} \) | 23–50 | [91-93] |
| \( \text{Me} \) | \( \text{R}^1 \text{O} \text{O} \text{R}^2 \) | pentane, \( 0{}^\circ\text{C} \) | \( \text{Ome} \) | 48 | [92,93] |
Table 13: Examples of ozonides (1,2,4-trioxolanes) synthesized by the Griesbaum method. (continued)

| R = Ph, Bn, p-C₆H₄CO₂Et, 2-pyridyl | pentane, CH₂Cl₂, 0 °C | 32–58 [91-93] |
| R = n-Pr, iPr, t-Bu, p-C₆H₄OA, phthalimido, CH₂OAc, CH₂COOEt, CH₃SO₂C₆H₄, phthalimidomethyl, COOEt, COOCH₂(CH₃)₂, COON(CH₂)CH₃, p-C₆H₄SO₂Me, p-C₆H₄F, p-C₆H₄CO₂Et | pentane, CH₂Cl₂, 0 °C | 20–70 [91-93,96,97,297] |
| R | pentane, 0 °C | 38 [91] |
| R | pentane, 0 °C | 41 [91] |
| R | pentane, CH₂Cl₂, 0 °C | 33 [91] |
| R | hexane, CH₂Cl₂, 0 °C | 17 [91] |
| R | pentane, CH₂Cl₂, 0 °C | 27 [91] |
| R | pentane, CH₂Cl₂, 0 °C | 53 [92,93] |
| R | pentane, CH₂Cl₂, 0 °C | n.d. [96,97] |
| R | cyclohexane CH₂Cl₂, 0 °C | 30 [298] |
| R | cyclohexane CH₂Cl₂, 0 °C | 54 [298] |
| R | cyclohexane, CH₂Cl₂, 0 °C | 78 [258] |

*aYield was not determined*
The Griesbaum method is widely applicable and allows the selective synthesis of symmetrical and unsymmetrical 1,2,4-trioxolanes, which are not accessible by direct ozonolysis of alkenes or the cross-ozonolysis of alkenes or enol ethers in the presence of carbonyl compounds. In addition, this method does not need tetrasubstituted alkenes or enol ethers as starting materials, which are difficult to prepare. Taking into account a wide range of commercially available ketones, it can be concluded that this is the most universal method for the synthesis of 1,2,4-trioxolanes in terms of selectivity and structural diversity of the final products.

2.4. Other methods for the synthesis of 1,2,4-trioxolanes

The reactions of aryloxiranes 177a,b with oxygen in the presence of 9,10-dicyanoanthracene (DCA) and biphenyl (BiP) under irradiation produced 1,2,4-trioxolanes 178a and 178b (Scheme 46). It should be noted that the oxirane moiety is oxidized rather than the double bond in these reactions [299].

This unusual result was obtained upon treatment of the hydroxydioxepane, 3-methoxy-3-methyloctahydro-3H-benzo[c][1,2]dioxepin-9a-ol (179) with TMSOTf/Et3SiH. Thus, the peroxide moiety was not reduced with Et3SiH, and the reaction produced the bicyclic peroxide, 1-methyl-10,11,12-trioxa-tricyclo[7.2.1.0⁴,⁹]dodecane (180) containing the 1,2,4-trioxolane moiety, as the major product (Scheme 47) [270].

The same bicyclic peroxide 180 was synthesized in good yield by the reaction of 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclohexanone (181) with hydrogen peroxide in the presence of phosphomolybdic acid (PMA) (Scheme 48) [300].

2.5. Structural modifications, in which 1,2,4-trioxolane ring remains intact

Scheme 49 shows possible modifications of substituents at the ozonide ring by the reduction of the ester group in cis-adamantan-2-spiro-3’-8’-ethoxycarbonyl-1’,2’,4’-triaxaspiro[4.5]decane 182 to form the alcohol cis-adamantan-2-spiro-3’-8’-hydroxymethyl-1’,2’,4’-triaxaspiro[4.5]decane 183. The latter was mesylated to 184 (cis-adamantan-2-spiro-3’-8’-methanesulfonylmethyl-1’,2’,4’-triaxaspiro[4.5]decane), and used in the reaction with sodium 1-methyl-1H-tetrazole-5-thiolate 185 for the synthesis of cis-adamantan-2-spiro-3’-8’-[[1’-methyl-1’H-tetrazol-5’-yl]thio]methyl]-1’,2’,4’-triaxaspiro[4.5]decane 186 through nucleophilic substitution of the mesyl group by the thio group of tetrazole 185 (Scheme 49) [297].

Ozonide 188 was synthesized by Mitsunobu reaction of alcohol 183 with pyridin-4-ol (187) (Scheme 50) [93]. It should be emphasized that this method can be applied in spite of the use of triphenylphosphine, which is a strong reducing agent for peroxides.

The alkylation of the sodium salt of alcohol 183 with 2-chloropyrimidine in dimethylformamide gave ozonide 189 (Scheme 51). In this reaction, neither sodium hydride nor sodium salt 183 cleave the ozonide ring to a substantial degree. The resulting 1,2,4-trioxolanes 188 and 189 exhibit high in vitro antimalarial activity comparable with that of artemisinin and in vivo even higher activity than that of artemisinin [93].

Aminoquinoline-containing 1,2,4-trioxalane 191 was synthesized by reductive amination of adamantane-2-spiro-3’-8’-oxo-
Arterolane is a fully synthetic 1,2,4-trioxalane, also known as OZ277. It has high antimalarial activity and is currently in the final stage of clinical trials. As drug, this compound is used in combination with piperaquine. The synthesis of arterolane is based on the Griesbaum coozonolysis of a mixture of adamantan-2-one O-methyloxime (192) and 4-carbomethoxycyclohexanone 193 to form cis-adamantane-2-spiro-3'-8'-methoxy carbonylmethyl-1',2',4'-trioxsapio[4,5]decane 194. The latter is hydrolyzed to cis-adamantane-2-spiro-3'-8'-carboxymethyl-1',2',4'-trioxsapio[4,5]decane 195, followed by mild amidation with the formation of the intermediate ozonide 196 that on treatment with 2-methylpropane-1,2-diamine finally gives the target compound (Scheme 53). The in vitro and in vivo studies showed that arterolane is more active against causative agents of malaria than artemisinin, chloroquine, and mefloquine [77,78,81].

3. Synthesis of 1,2-dioxanes
Modern approaches to the synthesis of 1,2-dioxanes are based on reactions with singlet oxygen, the oxidative coupling of carbonyl compounds and alkenes in the presence of manganese and cerium salts, the co-oxidation of alkenes and thiols with oxygen, the Isayama–Mukaiyama peroxidation, the Kobayashi cyclization of hydroperoxides, the reaction of 1,4-diketones with hydrogen peroxide, the intramolecular nucleophilic substitution by the hydroperoxide group, the cyclization with partici-
Scheme 53: Synthesis of arterolane.

The addition of singlet oxygen to substrate 199 occurs in the last step of the synthesis of natural hexacyclinol peroxide 200 (Scheme 55) [303].

3.1. Methods for the synthesis of 1,2-dioxanes using singlet oxygen

The oxidation of diarylheptadienes 197a–c with singlet oxygen in acetonitrile afforded bicyclic peroxides 198a–c in 33–58% yields. 2,4,6-Triphenylpyrylium tetrafluoroborate was used as the sensitizer for singlet oxygen generation (Scheme 54) [301].

The reactions of 6-methylhept-5-en-2-one (201) and 5-methylhex-4-enenitrile (203) with singlet oxygen produced 1,2-dioxanes, 3-methyl-6-(prop-1-en-2-yl)-1,2-dioxan-3-ol (202) and 6-(prop-1-en-2-yl)-1,2-dioxane-3-imine (204), containing the hydroxy and imine groups, respectively (Scheme 56) [304].

3.2. Oxidative coupling of carbonyl compounds and alkenes in the presence of manganese or cerium salts

The synthesis of 1,2-dioxanes 207 is based on the addition of alkene 205 and oxygen to carbonyl compound 206 via the inter-
mediate formation of carbon-centered peroxide radicals. The reaction occurs in the presence of catalytic amounts of manganese or cerium salts, which are involved in a redox cycle. It is assumed that the oxidation of β-dicarbonyl compounds proceeds through a formation of an enol-containing complex with a metal ion (Scheme 57, Table 14).

**Scheme 56:** Oxidation of enone 201 and enenitrile 203 with singlet oxygen.

**Scheme 57:** Synthesis of 1,2-dioxanes 207 by oxidative coupling of carbonyl compounds 206 and alkenes 205.

**Table 14:** Examples of 1,2-dioxanes 207 synthesized by oxidative coupling of carbonyl compounds 206 and alkenes 205.

| Alkene 205 | Carbonyl compound 206 | Reaction conditions | 1,2-Dioxane 207 | Yield, % | Ref. |
|------------|-----------------------|--------------------|-----------------|----------|-----|
| Ph         | Ethyl ketone          | Mn(OAc)_2, O_2, AcOH, 80 °C, 10 h | 1,2-Dioxane     | 67       | [305] |
| R^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, Et | R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, Et, Me, H | | | |
| R^3 = Ph, Me, Et, Et_2N | R^4 = Et, Bu | Mn(OAc)_2, air, AcOH, 23 °C, 0.5–24 h | 207 | 20–84 | [306] |
| Ph         | Y = OEt, OMe n = 0, 1, 2 | CeCl_3×7H_2O, air, iPrOH, rt, 16 h | | 42–87 | [307] |
| R = H, Me | X = O, NCH_2Ph | CeCl_3×7H_2O, air, iPrOH, rt, 16 h | | 5–73 | [307] |
| Ph         | | CeCl_3×7H_2O, air, iPrOH, rt, 14–16 h | | 19 (n = 1), 33 (n = 2) | [308] |
| Ph         | | CeCl_3×7H_2O, air, iPrOH, rt, 14–16 h | | 18 | [308] |
3.3. Oxidation of 1,5-dienes in the presence of thiols
The co-oxidation of 1,4-dienes and thiols (thiol–olefin co-oxygenation, TOCO reaction) was described for the first time by Beckwith and Wagner as a method for the synthesis of sulfur-containing 1,2-dioxolanes [313,314]. More recently, it has been shown that under similar conditions, the oxidation of 1,5-dienes affords the corresponding sulfur-containing 1,2-dioxanes. The reaction proceeds under oxygen atmosphere in the presence of azobisisobutyronitrile (AIBN) or di-tert-butyloperoxalate (DBPO) as radical initiators. The resulting unstable hydroperoxides are reduced with triphenylphosphine to hydroxy derivatives [317].

The oxidation of acetophenones produces bicyclic 1,2-dioxanes (Scheme 58, Table 15).

![Scheme 58: 1,2-Dioxanes synthesis by co-oxidation of 1,5-dienes and thiols.](image)

**Table 14: Examples of 1,2-dioxanes synthesized by oxidative coupling of carbonyl compounds and alkenes.** (continued)
Scheme 59: Synthesis of bicyclic 1,2-dioxanes 212 with aryl substituents.

Table 15: Examples of 1,2-dioxanes synthesized by co-oxidation of 1,5-dienes and thiols.

| Diene | Thiol | Reaction conditions | 1,2-Dioxane | Yield, % | Reference |
|-------|-------|---------------------|-------------|----------|-----------|
| R₃SH | R⁴ = Ph, 4-FC₆H₄, n-Bu, t-Bu, MeO₂C(CH₂)₂, cyclohexyl, Ph₃C | 1) O₂, DBPO, benzene/heptane, rt, 10 h or O₂, AIBN, hv, MeCN, 4 °C, 10 h 2) Ph₃P, CH₂Cl₂, 0–5 °C, 2 h, rt, 1 h | | 6–54 | [107,179,315] |
| PhSH | 4-ClC₆H₄SH | 1) O₂, AIBN, hv, MeCN, 0 °C, 2 h 2) Ph₃P, CH₂Cl₂, 0 °C to rt | | 70 (Ar = Ph), 21 (Ar = 4-ClC₆H₄) | [102,316] |

Scheme 60: Isayama–Mukaiyama peroxysilylation of 1,5-dienes followed by desilylation under acidic conditions.

An alternative synthesis of a 1,2-dioxane by the Isayama–Mukaiyama method includes the following sequence of reactions: peroxysilylation, desilylation, and recyclization.

Scheme 61: Synthesis of bicycle 218 with an 1,2-dioxane ring.

3.4. Synthesis of 1,2-dioxanes by the Isayama–Mukaiyama method

The Isayama–Mukaiyama peroxysilylation of 1,5-dienes 213 followed by desilylation under acidic conditions gives hydroperoxide-containing 1,2-dioxanes 214 (Scheme 60, Table 16).

The oxidation of (Z)-ethyl 2-(3-(prop-1-en-2-yl)cyclohexylidene)acetate (215) gives ethyl 2-(4,4-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-1-yl)-2-hydroxyacetate (218) in 29% yield. The oxidative reaction proceeds presumably with formation of an O-centered radical 216, then a C-centered radical 217 and the latter adds oxygen and is reduced to the hydroxy derivative of 1,2-dioxane 218 (Scheme 61) [318].
Table 16: Synthesis of 1,2-dioxanes by the Isayama–Mukaiyama method.

| 1,5-Diene 213 | Reaction conditionsa | 1,2-Dioxane 214 | Yield, % | Reference |
|---------------|----------------------|-----------------|----------|-----------|
| ![1,5-Diene](image) | 1) Co(modp)2, O2, Et3SiH, CICH2CH2Cl, 2–6 h 2) HCl/MeOH | ![1,2-Dioxane](image) | 13–64 | [249] |
| ![1,5-Diene](image) | 1) Co(modp)2, O2, Et3SiH, CICH2CH2Cl, 1 h 2) HCl/MeOH | ![1,2-Dioxane](image) | 22 | [318,319] |

*a*modp = 1-morpholino-5,5-dimethyl-1,2,4-hexanetronate.

accompanied by a ring opening of oxirane or oxetane (Scheme 62 and Scheme 63).

Cobalt(II) acetylacetonate (acac) or bis-2,2,6,6-tetramethylheptane-3,5-dienoate (thd) were used as the catalyst for the peroxidation of 219. The cyclization of the intermediate peroxide 220 was performed with Amberlyst-15 ion-exchange resin. This approach was used in the multistep synthesis of the natural endoperoxide 9,10-dihydroplakortin, which exhibits antimalarial and anticancer activities as do its structural analogues [320,321].

2-(3,6,6-Trimethyl-1,2-dioxan-3-yl)ethanol (224) was synthesized in a similar way starting with the peroxidation of 2-methyl-2-(3-methylbut-3-enyl)oxetane (222), followed by oxetane-ring opening in triethyl(2-methyl-4-(2-methyloxetan-2-y1)butan-2-ylperoxy)silane (223) (Scheme 63) [250].

Dioxanes can also be synthesized by inramolecular cyclizations with the attack on a keto group. The peroxyisilylation of the unsaturated ketone 1,5-dicyclohexenylpentan-3-one (225), with the Co(thd)2/ Et3SiH/O2 system produced 1,5-bis(1-triethyls"

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Scheme 62: Intramolecular cyclization with an oxirane-ring opening.

Scheme 63: Intramolecular cyclization with the oxetane-ring opening.
lyl(peroxy)cyclohexyl)pentan-3-one (226), which underwent cyclization in the presence of $p$-toluenesulfonic acid to give the spiro-fused 7,8,10,11-tetraoxatrispiro[5.2.5.2.2]henicosane 227 (Scheme 64) [252].

3.5. Synthesis of 1,2-dioxanes by the Kobayashi method

The synthesis is based on the peroxidation of the carbonyl group of unsaturated ketones 228 with the urea–hydrogen peroxide complex followed by a Michael cyclization of the hydroperoxy acetals 229 under basic conditions. This method is suitable for the efficient synthesis of functionalized 1,2-dioxanes 230 in moderate to high yields (Scheme 65, Table 17). In early studies, scandium(III) triflate was used as the catalyst for the hydroperoxidation of ketones with the H$_2$O$_2$–H$_2$NCONH$_2$ complex. More recently, it was shown that in some cases, cheaper catalysts such as $p$-toluenesulfonic and 10-camphorsulfonic acid can be used for this purpose (Table 17).

### Table 17: Examples of 1,2-dioxanes synthesized by the Kobayashi method.

| Unsaturated ketone 228 | Reaction conditions | 1,2-Dioxane 230 | Yield, % | Reference |
|------------------------|---------------------|-----------------|----------|-----------|
| $\text{H}_2$CO$\cdots$ $\cdots$ $\text{H}_2$NCONH$_2$ | 1) H$_2$O$_2$, H$_2$NCONH$_2$, Sc(OTf)$_3$, MeOH, $0^\circ$C, 2 d | $\text{H}_2$CO$\cdots$ $\cdots$ $\text{OCH}_3$ | 1) 67–83 | [322,323] |
| $\text{H}_2$CO$\cdots$ $\cdots$ $\text{H}_2$NCONH$_2$ | 2) Et$_2$NH, CF$_3$CH$_2$OH | $\text{H}_2$CO$\cdots$ $\cdots$ $\text{OCH}_3$ | 2) 60–72 | |
| $\text{H}_2$CO$\cdots$ $\cdots$ $\text{H}_2$NCONH$_2$ | 3) HF, pyridine, THF | $\text{H}_2$CO$\cdots$ $\cdots$ $\text{OCH}_3$ | 3) 100 | |
| $\text{H}_2$CO$\cdots$ $\cdots$ $\text{H}_2$NCONH$_2$ | 2) Et$_2$NH, CF$_3$CH$_2$OH | $\text{H}_2$CO$\cdots$ $\cdots$ $\text{OCH}_3$ | 1) 52 | [324] |
| $\text{H}_2$CO$\cdots$ $\cdots$ $\text{H}_2$NCONH$_2$ | 3) HF, pyridine, THF | $\text{H}_2$CO$\cdots$ $\cdots$ $\text{OCH}_3$ | 2) 87 | |

Scheme 64: Intramolecular cyclization with the attack on a keto group.

Scheme 65: Peroxidation of the carbonyl group in unsaturated ketones 228 followed by cyclization of hydroperoxy acetals 229.
Table 17: Examples of 1,2-dioxanes synthesized by the Kobayashi method. (continued)

| Intermediate product | Reaction Conditions | Yields | References |
|----------------------|--------------------|--------|------------|
| 229                  | 1) \( \text{MeOH, p-TsOH, rt, 20 h} \)  
2) \( \text{Et}_2\text{NH, CF}_3\text{CH}_2\text{OH, rt, 24 h} \) | 1) 54–82  
2) 52 | [325-327] |
| 229                  | 1) \( \text{1,2-dimethoxyethane, p-TsOH, rt, 11 h} \)  
2) \( \text{Et}_2\text{NH, CF}_3\text{CH}_2\text{OH, rt, 2 h} \) | 35 | [325-327] |
| 229                  | 1) \( \text{1,2-dimethoxyethane, 10-camphorsulfonic acid, rt, 18 h} \)  
2) \( \text{Et}_2\text{NH, CF}_3\text{CH}_2\text{OH, rt, 2 h} \) | 1) 86  
2) 54 | [325-327] |
| 229                  | 1) \( \text{1,2-dimethoxyethane, p-TsOH, EtOH, rt, 12 h} \)  
2) \( \text{Et}_2\text{NH, CF}_3\text{CH}_2\text{OH, rt} \) | 1) 70–93  
2) 42–65 | [328] |

It was found that cesium hydroxide can be used as a base for the cyclization to give 232 and 234. Compared to Scheme 65, the method is suitable for the cyclization of hydroperoxides 231 and 233, which are no ketone derivatives (Scheme 66) [264]. \( \text{Et}_3\text{N} \) in MeOH can also be used as catalyst for this type of cyclization [263].

Scheme 66: \( \text{CsOH} \) and \( \text{Et}_2\text{NH} \)-catalyzed cyclization.
The synthesis of peroxyplakoric acid methyl ethers A and D 238a and 238b, which are natural peroxides isolated from marine sponges exhibiting fungicidal and antitumor activities [329,330] is an interesting example of the synthesis of complex structures. The polyunsaturated compound (E)-methyl 6-methyleneundec-2-en-10-ynoate (235) was subjected to ozonolysis to obtain methoxyhydroperoxide, (E)-methyl 6-hydroperoxy-6-methoxyundec-2-en-10-ynoate (236), whose cyclization afforded methyl 2-(6-methoxy-6-(pent-4-inyl)-1,2-dioxan-3-yl)acetate (237), in which the triple bond is easily modified by palladium-catalyzed cross-coupling reactions to form the target 1,2-dioxanes 238a,b (Scheme 67).

Initially, an attempt was made to synthesize diethyl 2,2'-((1,2,7,8-tetraoxaspiro[5.5]undecane-3,9-diyl))diacetate (241) by cyclization of (2E,9E)-diethyl 6,6-dihydroperoxyundeca-2,9-dienedioate bis(hydroperoxide) (240) (the bishydroperoxidation product of (2E,9E)-diethyl 6,6-dimethoxyundeca-2,9-dienedioate (239)) with Et₂NH in CF₃CH₂OH. However, these attempts failed. Spiroperoxide 241 was prepared in satisfactory yield by reaction of 240 with the use of mercury (II) acetate (Scheme 68) [331]. The intermediate mercury-containing peroxy produced by the cyclization of bis(hydroperoxide) 240 was reduced with NaBH₄ in an alkaline medium [331].

3.6. Synthesis of 1,2-dioxanes from 1,4-dicarbonyl compounds

The reaction of 1,4-diketones 242 (cyclohexanone derivatives) with hydrogen peroxide in a neutral medium produced 3,6-dihydroxydioxanes 243 albeit without reported yields (Scheme 69). The resulting compounds exhibit a broad spectrum of antiparasitic activities against causative agents of malaria, trypanosomiasis, and leishmaniasis [208-212].
3.7. Methods for the synthesis of 1,2-dioxanes from hydroperoxides

Compounds containing a C=C group and an oxygen-containing ring are convenient starting materials for the synthesis of cyclic peroxides [250-252,332]. For example, the ozonolysis of the double bond in the oxetane-containing compound, 2-methyl-2-(3-methylbut-3-enyl)oxetane (244) afforded 2-(3-hydroperoxy-3-methoxybutyl)-2-methyloxetane (245), which underwent recyclization in the presence of ytterbium triflate to give 2-(6-methoxy-3,6-dimethyl-1,2-dioxan-3-yl)ethanol (246) along with the seven-membered compound 2-hydroperoxy-5-methoxy-2,5-dimethylloxepane (247) (Scheme 70) [250].

Spirodioxane 227, whose synthesis by the Isayama–Mukaiyama method was described above (Scheme 64), could also be synthesized via the ozonolysis of alkene 248 in the presence of hydrogen peroxide followed by the cyclization of bis(hydroperoxide) 249 with potassium tert-butoxide (Scheme 71) [252].

An approach to the cyclization based on an intramolecular nucleophilic substitution was used also for the synthesis of diastereomers of dioxanes 252a,b containing triple bonds. Hydroperoxides 251a,b that were synthesized by the ozonolysis of 250 were treated with potassium tert-butoxide. One of the diastereomers, 252a, was then modified first via the stereoselective hydrozirconation and iodination to 253a and then by the Negishi cross coupling to produce silylated product 254a, which was desilylated to obtain alcohol 255a (Scheme 72). 1,2-Dioxane 255a is structurally similar to natural peroxyplakoric acids having fungicidal and antimalarial activities [332].

3.8. Use of halonium ions in the cyclization

This approach to the synthesis of 1,2-dioxane rings is based on the intramolecular cyclization of hydroperoxides containing a C=C group. In the first step, the addition of a halonium ion to the double bond results in the formation of a carbocation, which is subjected to the intramolecular attack of the hydroperoxide group.

The treatment of unsaturated monoperoxyketals 257, 260, and 263 (prepared by ozonolysis of 256, 259, and 262 in methanol, respectively) with such donors of halonium ions such as N-iodosuccinimide (NIS), I$_2$/t-BuOK, or bis(sym-collidine)iodonium hexafluorophosphate gave iodine-containing 1,2-dioxanes 258, 261, and 264, in moderated yields (Scheme 73) [333]. It should be noted that attempts to synthesize related peroxides with N-bromosuccinimide failed [333].

In the studies [334,335] iodine-containing 1,2-dioxanes 266a–c, 268, and 270a,b were synthesized from the corresponding hydroperoxyalkenes 265a–c, 267, and 269a,b with bis(sym-collidine)iodonium hexafluorophosphate (BCIH) in the cyclization step (Scheme 74).
Scheme 72: Synthesis of 1,2-dioxane 255a, a structurally similar compound to natural peroxyplakoric acids.

Cp₂ZrHCl - zirconocene chloride hydride (Schwartz's reagent)

Scheme 73: Synthesis of 1,2-dioxanes based on the intramolecular cyclization of hydroperoxides containing C=C groups.
3.9. Pd(II)-catalyzed cyclization

The palladium-catalyzed cyclization of δ-unsaturated hydroperoxides 271 represents a new route to 1,2-dioxane cyclic compounds 272 (Scheme 75). The cyclization was performed in toluene, 1,4-dioxane, or 1,2-dichloroethane at 80 °C for 3 h in the presence of p-benzoquinone or silver carbonate as the oxidizing agent for Pd(0) that was formed in the catalytic cycle. To the best of our knowledge, this method is the first example of a palladium acetate-catalyzed synthesis of cyclic peroxides [336].

3.10. Acid-mediated cyclizations of peroxides

The intramolecular cyclization of unsaturated peroxyacetals 273a–d in the presence of TiCl₄ or SnCl₄ occurs via formation of peroxycarbenium ions to give methoxy- and chlorine-containing dioxanes 274a–d as the reaction products (Scheme 76) [257].

The treatment of endoperoxides 275a–d with allyltrimethylsilane in the presence of catalytic amounts of trimethylsilyl triflate or SnCl₄ gave bicyclic 1,2-dioxanes 276a–d (Scheme 77) [337].
The electrophilic center of the peroxyperbenium ion produced by the decomposition of molozonide can be trapped by the hydroperoxide group of the molecule. This type of cyclization was used as the basis for the synthesis of hydroperoxide-containing 1,2-dioxanes. The ozonolysis of 1-hydroperoxy-1-methoxy-5-(prop-1-en-2-yl)cyclohexane (277) in a trifluoroethanol/dichloromethane mixture through formation of molozonide 278 and peroxyperbenium ion 279 finally afforded (6S)-6-hydroperoxy-1-methoxy-2,6-dimethyl-7,8-dioxabicyclo[3.3.1]nonane (280) (Scheme 78) [334]. The intramolecular cyclization of intermediate 279 is only possible if the hydroperoxide group is in a particular spatial arrangement [334].

Under these conditions, ethyl 2-(3-(2-hydroperoxypropan-2-yl)cyclohexylidene)acetate hydroperoxide (281) and ethyl 2-(3-(1-hydroperoxy-1-methoxyethyl)cyclohexylidene)acetate hydroperoxide (283) react to form dioxanes, (1S,5S)-1-hydroperoxy-4,4-dimethyl-2,3-dioxabicyclo[3.3.1]nonane (282), (1S,4S,5S)-1-hydroperoxy-4-methoxy-2,3-dioxabicyclo[3.3.1]nonane (284a), and (1S,4R,5S)-1-hydroperoxy-4-methoxy-2,3-dioxabicyclo[3.3.1]nonane (284b) (Scheme 79) [338].

Under similar conditions, the reaction of 5-hydroperoxy-5-(2-methoxyethoxy)-2-methylhex-1-ene (285) in AcOH/CH₂Cl₂ produced 3-hydroperoxy-6-(2-methoxyethoxy)-3,6-dimethyl-1,2-dioxane (286) (Scheme 80) [270].

Scheme 78: Intramolecular cyclization using the electrophilic center of the peroxyperbenium ion 279.

Scheme 79: Synthesis of bicyclic 1,2-dioxanes.
3.11. Other methods for the synthesis of 1,2-dioxanes

The di(tert-butyl)peroxalate-initiated radical cyclization of unsaturated 2-(3-hydroperoxypropyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene hydroperoxide (287) in the presence of oxygen gave 1,2-dioxane (289). The reaction proceeds through formation of compound 288 containing a hydroperoxide group, which is transformed into a carbonyl group by treatment with Ac₂O/pyridine (Scheme 81) [232]. The yield of 289 was 14% based on 287.

The original cyclization occurs during the oxidation of 1,4-betaines 291a–d prepared from dienones 290a–d containing an azide group in the side chain. The reaction yields peroxide-bridged indolizinediones 292a–d (Scheme 82) [339].

3.12. Structural modifications, in which 1,2-dioxane ring remains intact

This section deals with syntheses of compounds exhibiting high antimalarial activity that is comparable with or higher than that of artemisinin.

N-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-((S)-6,6-dimethyl-1,2-dioxan-3-yl)propanamide (294) containing the aminoquinoline moiety that is characteristic for antiparasitic compounds was synthesized by the following series of steps: reduction of the double bond in the presence of the peroxide group (transformation of ethyl 2-(6,6-dimethyl-1,2-dioxan-3-yl)acrylate (272d) into ethyl 2-((S)-6,6-dimethyl-1,2-dioxan-3-yl)propanoate (293)), alkaline hydrolysis, and amidation (Scheme 83) [336].

![Scheme 81: Di(tert-butyl)peroxalate-initiated radical cyclization of unsaturated hydroperoxide 287.](image1)

![Scheme 82: Oxidation of 1,4-betaines 291a–d.](image2)

![Scheme 83: Synthesis of aminoquinoline-containing 1,2-dioxane 294.](image3)
The synthesis of the sulfonyl-containing 1,2-dioxane 2-(benzyl-oxo)-2,6-dimethyl-6-(phenylsulfonylmethyl)-7,8-dioxabicyclo[3.3.1]nonane \(297a\), included the following steps: oxidation of the sulfide group in 2,6-dimethyl-6-(phenylthiomethyl)-7,8-dioxabicyclo[3.3.1]nonan-2-ol \(295\) to form 2,6-dimethyl-6-(phenylsulfonylmethyl)-7,8-dioxabicyclo[3.3.1]nonan-2-ol \(296\) followed by the isolation of the isomer \(6R\)-2,6-dimethyl-6-(phenylsulfonylmethyl)-7,8-dioxabicyclo[3.3.1]nonan-2-ol \(296a\) and benzylation of the latter to obtain the target peroxide \(297a\) (Scheme 84) [107].

Methyl 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetate \(298\) was enzymatically hydrolyzed to 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetic acid \(299\). The next step in the synthesis of target compound \(301\) involved the two-step amidation via the intermediate formation of perfluorophenyl 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetate \(300\) (Scheme 85) [110].

The enzymatic hydrolysis step was necessary because attempts to hydrolyze ester \(298\) under alkaline conditions (LiOH in dimethyl sulfoxide) failed and led to peroxide ring-opening [110].

### Scheme 84: Synthesis of the sulfonyl-containing 1,2-dioxide.

4. Synthesis of 1,2-dioxenes

#### 4.1. Reaction of 1,3-dienes with singlet oxygen

The reaction of singlet oxygen with the 1,3-diene system can proceed by the following pathways: the \([4 + 2]\)-cycloaddition, the singlet-oxygen–ene reaction, and the \([2 + 2]\)-cycloaddition to form dioxetanes. The reaction pathway depends on the nature of the solvent, and on electronic and steric factors. However, the \([4 + 2]\)-cycloaddition \((302 + \mathbf{1}_2\mathbf{O}_2)\) occurs in most cases, and this reaction is frequently used for the synthesis of the 1,2-dioxide system \(303\) (Scheme 86). Table 18 gives examples of 1,2-dioxenes synthesized by the reaction of singlet oxygen with 1,3-diene systems.

#### Scheme 86: Reaction of singlet oxygen with the 1,3-diene system \(302\).

### Scheme 85: Synthesis of the amido-containing 1,2-dioxide \(301\).
Table 18: Examples of the use of $^1$O$_2$ in the synthesis of 1,2-dioxenes.

| Alkene 302 | Reaction conditions | 1,2-Dioxene 303 | Yield, % | Reference |
|------------|--------------------|-----------------|----------|-----------|
| ![Alkene 302](image1) | O$_2$, hv, tetraphenylporphyrin, CH$_2$Cl$_2$, −78 °C, 1 h | ![1,2-Dioxene 303](image2) | 100 | [340] |
| ![Alkene 302](image3) | O$_2$, hv, tetraphenylporphyrin, CH$_2$Cl$_2$, −78 °C, 2 h | ![1,2-Dioxene 303](image4) | 85 | [341] |
| ![Alkene 302](image5) | O$_2$, hv, fullerene C$_{60}$, CDCl$_3$, 0 °C, 2 h | ![1,2-Dioxene 303](image6) | 93 | [342] |
| ![Alkene 302](image7) | O$_2$, hv, tetraphenylporphyrin, CCl$_4$ | ![1,2-Dioxene 303](image8) | 75 | [343] |
| ![Alkene 302](image9) | O$_2$, hv, tetraphenylporphyrin, CCl$_4$, rt, 30 min | ![1,2-Dioxene 303](image10) | 90 | [344] |
| ![Alkene 302](image11) | O$_2$, hv, tetraphenylporphyrin, CCl$_4$, rt, 18–20 h | ![1,2-Dioxene 303](image12) | 74 | [345] |
| ![Alkene 302](image13) | O$_2$, hv, tetraphenylporphyrin, CCl$_4$, 10 °C, 1.5 h | ![1,2-Dioxene 303](image14) | 73 | [346] |
| ![Alkene 302](image15) | O$_2$, hv, tetraphenylporphyrin, CHCl$_3$, 10 °C, 45 min | ![1,2-Dioxene 303](image16) | 94 | [346] |
| ![Alkene 302](image17) | O$_2$, hv, tetraphenylporphyrin, CCl$_4$, rt, 24 h to 9 d | ![1,2-Dioxene 303](image18) | 94 | [347] |
| ![Alkene 302](image19) | O$_2$, hv, tetraphenylporphyrin, CH$_2$Cl$_2$, −10 °C, 6 h | ![1,2-Dioxene 303](image20) | 54 | [348] |

1) O$_2$, hv, Rose Bengal, MeOH/CH$_2$Cl$_2$ (1/19), 0 °C, 8 h
2) CH$_2$N$_2$
| Reaction Conditions | Product Structure | Yield | Source |
|---------------------|------------------|-------|--------|
| 1) \( \text{O}_2, \text{hv}, \text{methylene blue, CH}_2\text{Cl}_2, 15 ^\circ \text{C}, 30 \text{ min} \) | ![Product Structure](image1) | 50 | [349] |
| 2) \( \text{PPh}_3, \text{acetone, rt, 40 min} \) | ![Product Structure](image2) | | |
| \( \text{O}_2, \text{hv}, \text{Rose Bengal, MeCN, 0 ^\circ \text{C, 6–16 h}} \) | ![Product Structure](image3) | 54–82 | [350] |
| \( \text{O}_2, \text{hv}, \text{Rose Bengal, MeOH/CH}_2\text{Cl}_2 (1/19), 0 ^\circ \text{C, 6 h} \) | ![Product Structure](image4) | 42 | [351] |
| \( \text{O}_2, \text{hv}, \text{Rose Bengal, CH}_2\text{Cl}_2, 6 \text{ h} \) | ![Product Structure](image5) | 23–70 | [352] |
| \( \text{O}_2, \text{hv}, \text{tetraphenylporphyrin, benzene, 18 h} \) | ![Product Structure](image6) | 28 | [353] |
| \( \text{O}_2, \text{hv, retinoic acid, EtOH, 10 ^\circ \text{C, 70 min}} \) | ![Product Structure](image7) | 56 | [186-190] |
| \( \text{O}_2, \text{hv, tetraphenylporphyrin, CH}_2\text{Cl}_2 \) | ![Product Structure](image8) | 13–95 | [191-195] |

*Table 18: Examples of the use of \( ^1\text{O}_2 \) in the synthesis of 1,2-dioxenes. (continued)*
Table 18: Examples of the use of $^1\text{O}_2$ in the synthesis of 1,2-dioxenes. (continued)

| R$^1$, R$^2$, R$^3$ | Reagents | Yield | Reference |
|---------------------|-----------|--------|-----------|
| H, Me, MeO, (OCH$_2$C(CH$_3$)$_2$CH$_2$O)CH, H, Me, f-Bu | O$_2$, hv, tetraphenylporphyrin, CHCl$_3$ or Rose Bengal, MeOH, $-15$ to $0 \, ^\circ$C, 1–4 h | 70–92 | [355] |
| | O$_2$, hv, Rose Bengal, CH$_2$Cl$_2$, 6 h | 91 | [356] |
| R$^1$, R$^2$ = -(CH$_2$)$_n$ | air, sunlight, CHCl$_3$, rt, 5 d or O$_2$, hv, CH$_2$Cl$_2$, CuSO$_4$, TsOH, 1 h | 53–80 | [357,358] |
| R$^1$, R$^2$, R$^3$ = -(CH$_2$)$_4$ | air, sunlight, CHCl$_3$, rt, 3 d | 60–85 | [113-116] [359,360] |
| R$^1$, R$^2$, R$^3$ = Ph, H | air, sunlight, CHCl$_3$, rt, 3 d | 23 | [119] |
| R$^1$, R$^2$, R$^3$ = Me, CH$_3$OSi-Bu(Ph)$_2$, Me, Ph, CH$_3$OSi-Bu(Ph)$_2$ | air, sunlight, CHCl$_3$, rt, 6 d | 15 | [119] |
| R$^1$, R$^2$, R$^3$ = Me, CCl$_3$, H | air, sunlight, CCl$_4$, rt, 160 h | 55–80 | [361] |
(+)-Premnalane A is a natural compound of plant origin exhibiting pronounced antimicrobial activity. The synthesis of this compound includes the following steps: oxidation of the furan ring of compound 304, the singlet-oxygen–ene reaction of the double bond-containing bicyclic compound 305, and acid-induced ketalization (Scheme 87) [362].

This synthesis produced a 1:1 mixture of diastereomeric (+)-premnalane A and 8-epi-premnalane A in 24% combined yield and diastereomeric 1,2-dioxolanes 306 in 49% yield. Pure (+)-premnalane A was isolated by column chromatography.

4.2. Structural modifications, in which 1,2-dioxene ring remains intact
Diazo-containing 1,2-dioxenes 309a–e were synthesized starting from the corresponding acids 307a–e, which were transformed into acid chlorides 308a–e and then subjected to diazotization (Scheme 88) [363]. The 1,2-dioxenes 309a–e were used for the intramolecular insertion of carbenes, that were produced by decomposition of the diazo group, into the –O–O–bond [363].

6-Epiplakortolide Е is a bicyclic peroxylactone that was isolated in low yield (0.0003%) from the marine sponge Plakortis sp. The structurally related plakortolide Е (Figure 4) exhibits high cytotoxicity against cancer cells and shows also activity against Toxoplasma gondii, which is the causative agent of toxoplasmosis [184,185].

6-Epiplakortolide Е was synthesized by the multistep synthesis involving the oxidation of diene 310 with singlet oxygen to give two isomeric 1,2-dioxenes 311a,b, the isolation of dioxene 311a, its silyl deprotection to form alcohol 312, the oxidation of the latter to 1,2-dioxenic acid 313, the t+ induced lactonization to produce 314, and the deiodination to obtain the target product (Scheme 89) [184,185]. It should be noted that the cyclic peroxide compound 314 remains intact under the reductive conditions in the presence of tributylstannane; this step occurs in good yield (68%) [184,185].

More recently, a similar approach was used for the preparation of tetrahydrofuran-containing bicyclic peroxides 318a,b. It involves the synthesis of 1,2-dioxenes 316 from dienes 315, the cation-initiated cyclization to give bicyclic compounds 317, and the reduction with Bu3SnH. N-Bromo- and iodosuccinimides (NBS and NIS, respectively) were used as donors of halogenide ions. Additionally, the cyclization was successfully performed with the use of phenylselenyl chloride as the donor of PhSe+ cation (Scheme 90) [364].
Acids 307a and 307b were synthesized by oxidation of the corresponding alcohols with the bis(acetoxy)iodobenzene/2,2,6,6-tetramethyl-1-piperidinyl oxyl (BAIB/TEMPO) system. The cyclization to bicyclic peroxides 319a–f containing the lactone ring was performed with the use of N-bromo- and iodosuccinimides and PhSeCl (Scheme 91) [364]. As in the above-considered case, the peroxide ring remains unchanged upon the reduction of the C–X bond in compounds 319a–f with Bu3SnH [364].

The double bond in the 1,2-dioxene ring of 321 was subjected to dihydroxylation with osmium tetroxide (Scheme 92) [354,365]. The reaction was performed in aqueous tert-butanol, acetone, or acetonitrile at room temperature. Several methods were used for the oxidation. For example, the commercially available AD-mix, a mixture consisting of K2OsO4(OH)4 (catalytic amounts, a source of OsO4) and K3Fe(CN)6 (oxidizer), was employed for this purpose. In this reaction, K2OsO4 (0.5 mol %) combined with oxidizers (K3Fe(CN)6, N-methylmorpholine N-oxide, citric acid, or KClO3) was also used [354,365].

The epoxidation of 1,2-dioxenes 324 produced by the addition of singlet oxygen to dienes 323 was performed by treatment with m-chlorobenzoic acid (Scheme 93). It was shown that epoxidized dioxanes 325 and 326, as well as dioxenes 324, have...
inhibiting activity against the causative agents of candidiasis infections *Candida albicans*, *Candida krusei*, and *Candida tropicalis*, that are in some cases comparable with the activity of the currently used amphotericin B, ketoconazole, and nystatin [218-228]. In addition, these compounds exhibit pronounced antimalarial activity, although lower than that of artemisinin [366,367].

The cyclopropanation of the double bond in endoperoxides 327 was performed by the reaction with diazomethane in the presence of Pd(OAc)$_2$ to produce 328a,b (Scheme 94) [368].

Pyridazine-containing bicyclic endoperoxides 334a–c were synthesized by the inverse-electron-demand Diels–Alder cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (329) to 1,2-dioxenes 330 followed by the elimination of dinitrogen from 331a–c to give 332a–c, the isomerization to 333a–c, and the oxidation (Scheme 95) [369].

5. **Synthesis of 1,2,4-trioxanes**

This part is devoted to methods for the synthesis of the 1,2,4-trioxane ring by the singlet-oxygen ene reaction with unsaturated alcohols, the photooxidation of enol ethers and vinyl sulfides, the [4+2]-cycloaddition of singlet oxygen to the pyran system, the Isayama-Mukaiyama peroxysilylation of unsatu-
rated alcohols, reactions with hydrogen peroxide, and the intramolecular Kobayashi cyclization.

5.1. Use of singlet oxygen in the synthesis of 1,2,4-trioxane
One of the widely used approaches to the synthesis of the 1,2,4-trioxane ring 337 is based on the hydroperoxidation of unsaturated alcohols 335 with singlet oxygen (the singlet-oxygen ene reaction) and the acid-catalyzed condensation of the resulting vicinal hydroxyl hydroperoxides 336 with ketones or aldehydes (acetals, orthoesters) (Scheme 96, Table 19).

The method was described for the first time by Singh in 1990 [370]. Due to a wide structural series of prepared 1,2,4-trioxane systems and the use of readily available inexpensive reagents, this is an efficient method for their synthesis.
Table 19: Examples of 1,2,4-trioxanes synthesized by the singlet oxygen ene reaction.

| Alkene | Carbonyl compound | Reaction conditions | Product | Yield | Reference |
|--------|-------------------|---------------------|---------|-------|-----------|
|        |                   |                     |         | i)    |           |
|        |                   |                     |         | 336,  %|           |
|        |                   |                     |         | ii)   | 337, %    |
|        |                   |                     |         |       |           |
|        |                   |                     |         |       |           |
|        |                   | 1) O₂, hv, TPP      |         | i) 88–94 | [371]    |
|        |                   | 2) BF₃·Et₂O, CH₂Cl₂|         | ii) 63–78 |           |
|        |                   | Ar = Ph, 4-ClC₆H₄, 1-naphthyl, 4-PhC₆H₄ | n = 1, 2 |       |           |
|        |                   |                     |         |       |           |
|        |                   | 1) O₂, hv, methylene blue, MeCN, 0 °C, 4–6 h 2) TsOH, CH₂Cl₂, rt, 1 h |         | i) 30–45 | [372]    |
|        |                   |                     |         | ii) 50–74 |           |
|        |                   | Ar = Ph, 4-ClC₆H₄, 4-ClC₆H₄, 4-MeOC₆H₄, 1-naphthyl, 2-naphthyl, 3-phenanthenyl, 2-fluorenyl | n = 1, 2 |       |           |
|        |                   |                     |         |       |           |
|        |                   | 1) O₂, hv, methylene blue, MeCN, 0 °C, 4–6 h 2) HCl, 5°C, 18 h |         |        | [374-379] |
|        |                   | Ar = Ph, 1-naphthyl, 2-naphthyl | n = 1, 2 |       |           |
|        |                   |                     |         |       |           |
|        |                   | 1) O₂, hv, methylene blue, MeCN, 0 °C, 4–6 h 2) HCl, rt, 1 h |         | 45–70  | [380]    |
|        |                   | Ar = Ph, 1-naphthyl, 2-naphthyl | n = 1, 2 |       |           |
|        |                   |                     |         |       |           |
|        |                   | 1) O₂, hv, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH₂Cl₂, rt, 1 h |         | i) 43  | [381]    |
|        |                   |                     |         | ii) 65–76 |           |
Table 19: Examples of 1,2,4-trioxanes synthesized by the singlet oxygen ene reaction. (continued)

| Structure | Reaction Conditions | Products |
|-----------|---------------------|----------|
| ![Structure 1](image1.png) | 1) O$_2$, hv, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH$_2$Cl$_2$, rt, 1 h | ![Product 1](image2.png) i) 37 ii) 46–59 [381] |
| ![Structure 2](image3.png) | 1) O$_2$, hv, methylene blue, MeCN, 0 °C, 18 h 2) HCl, CH$_2$Cl$_2$, 0 °C, 3–6 h | ![Product 2](image4.png) i) 22–35 ii) 12–37 [382] |
| ![Structure 3](image5.png) | 1) O$_2$, hv, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH$_2$Cl$_2$, rt, 2 h | ![Product 3](image6.png) i) 50 ii) 31–75 [383] |
| ![Structure 4](image7.png) | 1) O$_2$, hv, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH$_2$Cl$_2$, rt, 2 h | ![Product 4](image8.png) i) 35 ii) 57–83 [383] |
| ![Structure 5](image9.png) | 1) O$_2$, hv, TPP 2) BF$_3$·Et$_2$O, Et$_2$O, 0 °C | ![Product 5](image10.png) i) 54–97 ii) 8–78 [384-387] |
Table 19: Examples of 1,2,4-trioxanes synthesized by the singlet oxygen ene reaction. (continued)

1. $O_2$, hv, TTP, polystyrene
2. $BF_3\cdot Et_2O$, $CH_2Cl_2$

MeOOC

1. $O_2$, hv, TTP or TPP
   PS-DVB-based
2. $BF_3\cdot Et_2O$, $CH_2Cl_2$

MeOOC

1. $O_2$, hv, methylene blue, MeCN, 0 °C, 4–5 h
2. HCl, $CH_2Cl_2$, rt, 1 h

$R = H, OMe, Me, F, Cl, Br$

1. $O_2$, hv, methylene blue, MeCN, 0 °C, 5 h
2. HCl, MeCN, rt, 3 h

$R = H, OMe, Me, F, Cl, Br$

1. $O_2$, hv, methylene blue, MeCN, 0 °C, 5 h
2. HCl, MeCN, rt, 3 h

$Ar$
Table 19: Examples of 1,2,4-trioxanes synthesized by the singlet oxygen ene reaction. (continued)

| R = n-Bu, n-Pr, iPr, iBu, allyl | R = Me, Et | R = Me, H | R = Me, Et, n-Pr, Ph | R = Me, Et, n-Pr |
|---------------------------------|----------|---------|----------------|-------------|
| 1) O₂, hv, TTP or TTP PS-DVB-based 2) BF₃·Et₂O, CH₂Cl₂ | 1) O₂, hv, TTP or TTP PS-DVB-based 2) BF₃·Et₂O, CH₂Cl₂ | 1) O₂, hv, TTP, CCl₄, 10 °C 2) PPTS, CH₂Cl₂ | 1) O₂, hv, TTP, CCl₄, 10 °C 2) PPTS, CH₂Cl₂ | 1) O₂, hv, TTP, CCl₄, rt 2) TsOH, CH₂Cl₂, rt |
| 4–19 [389] | i) 84–91 ii) 12–19 [391] | i) 94–99 ii) 21–30 [391] | i) 83 ii) 19 [391] | i) 83 ii) 18–55 [392] |

A similar approach based on the co-oxidation of hydroxalkenes 338 and thiols (TOCO-reaction, thiol–olefin co-oxygenation) was applied to the synthesis of sulfur-containing 1,2,4-trioxanes 339 (Scheme 97).

The formation of peroxyketais 342a–g from vicinal hydroxyhydroperoxides 341 (oxidation products of unsaturated alcohols 340) in the presence of boron trifluoride is a convenient approach to the synthesis of the 1,2,4-trioxane ring (Scheme 98) [385].

The approach to the synthesis of 1,2,4-trioxanes proposed by Jefford and co-workers in 1993 [394] is based on the photooxidation of enol ethers or vinyl sulfides 343 with oxygen followed by the rearrangement of the resulting 1,2-dioxetanes in the presence of trialkylsilyl triflates. The resulting bicyclic compound 344 is structurally similar to artemisinin. Another version of this synthesis is based on the use of the ozone/triphenylphosphate in the oxidation step 1) (Scheme 99, Table 20).

This method was applied to the synthesis of tricyclic peroxide 346 (containing one carbon atom less in the mono-oxygen ring compared to structures 344) from the enol ether, 1-(2-(methoxymethylene)cyclohexyl)-3-phenylpropan-2-one (345) (Scheme 100) [207].

Azobisisobutyronitrile (AIBN) was used as the initiator of the radical reaction. In the second step (condensation), cyclopentanone, cyclohexanone, tert-butylcyclohexanone, 1,4-cyclohexanediene, cyclodecanone, and adamantanone were employed. 1,2,4-Trioxanes 339 were prepared in 25–68% yields in two steps [120,393].

aTPP is tetraphenylporphyrin; TTP is tetratolylporphyrin; PPTS is pyridinium para-toluenesulfonate.

Scheme 97: Synthesis of sulfur-containing 1,2,4-trioxanes 339.

![Scheme 97: Synthesis of sulfur-containing 1,2,4-trioxanes 339.](image-url)
Scheme 98: BF₃·Et₂O-catalyzed synthesis of the 1,2,4-trioxanes 342a–g.

Table 20: Examples of 1,2,4-trioxanes synthesized by oxidation of enol ethers or vinyl sulfides.

| Enol ether or vinyl sulfide 343 | Reaction conditions | Product 344 | Yield, % | Reference |
|---------------------------------|---------------------|-------------|----------|-----------|
| ![Enol ether or vinyl sulfide](image1) | 1) O₂, hv, methylene blue, CH₂Cl₂, −78 °C 2) TBDMSOTf, CH₂Cl₂, −78 °C 3) Et₃N, CH₂Cl₂, −78 °C to −15 °C | ![Product 344](image2) | 47 (12-α) 47 (12-β) | [395] |
| ![Enol ether or vinyl sulfide](image3) | 1) O₂, (PhO)₃P, CH₂Cl₂, −78 °C 2) Et₃SiOTf, CH₂Cl₂, −78 °C 3) Et₃N, CH₂Cl₂, −78 °C to rt | ![Product 344](image4) | 30–38 | [395] |
| ![Enol ether or vinyl sulfide](image5) | 1) O₂, (PhO)₃P, CH₂Cl₂, −78 °C 2) Me₃SiOTf, CH₂Cl₂, −78 °C 3) Et₃N, CH₂Cl₂, −78 °C to rt | ![Product 344](image6) | 7 | [395] |
| ![Enol ether or vinyl sulfide](image7) | 1) O₂, (PhO)₃P, CH₂Cl₂, −78 °C 2) Me₃SiOTf, CH₂Cl₂, −78 °C 3) Et₃N, CH₂Cl₂, −78 °C to rt | ![Product 344](image8) | 3 (12-α) 11 (12-β) | [395] |
| ![Enol ether or vinyl sulfide](image9) | 1) O₂, (PhO)₃P, CH₂Cl₂, −90 °C 2) Me₃SiOTf, CH₂Cl₂, −90 °C, 1 h 3) 1-ethylpiperidine, CH₂Cl₂, −78 °C to rt | ![Product 344](image10) | 36 (12-α) 15 (12-β) | [396] |
| ![Enol ether or vinyl sulfide](image11) | 1) Air, hv, methylene blue, CH₂Cl₂, −78 °C, 1 h 2) Me₃SiOTf, CH₂Cl₂, −78 °C, 2 h 3) 1-ethylpiperidine, CH₂Cl₂, −78 °C to rt | ![Product 344](image12) | 33 | [397] |
The reaction of endoperoxides 348a,b derived from cyclohexadienes 347a,b with 1,4-cyclohexanedione produced trioxanes 349a,b containing a keto group which is useful for further transformations (Scheme 101) [398].

Unsaturated bicyclic trioxanes 351 are [4 + 2]-cycloaddition products of singlet oxygen to the pyran moiety in 350 (Scheme 102, Table 21).

It was shown that in this reaction the starting pyran can serve as the sensitizer for the formation of singlet oxygen [402].

### 5.2. Synthesis of 1,2,4-trioxanes by the Isayama–Mukaiyama method

The Isayama–Mukaiyama peroxysilylation of unsaturated alcohols 352 is a new route to hydroxy silyl peroxides 353, whose condensation with ketones in an acidic medium affords 1,2,4-trioxanes 354 (Scheme 103, Table 22).
Table 22: Examples of 1,2,4-trioxanes synthesized through the Isayama–Mukaiyama peroxyisilylation.

| Unsaturated alcohol 352 | Carbonyl compound | Reaction conditionsa | 1,2,4-Trioxane 354 | Yield, % | Reference |
|------------------------|-------------------|----------------------|-------------------|---------|-----------|
| HO                      | R'                  | 1) Co(acac), Et3SiH, O2, rt  
|                        | R'                  | 2) TsOH              |       | 1) 60   | [403]     |
|                        | R'                  | 1) Co(acac), Et3SiH, O2, rt  
|                        | R'                  | 2) TsOH              |       | 2) 40–90 | [403]     |
|                        | R'                  | 1) Co(thd), Et3SiH, O2, rt  
|                        | R'                  | 2) TsOH              |       | 40–85   | [404]     |
|                        | R'                  | 1) Co(acac), Et3SiH, O2, rt  
|                        | R'                  | 2) TsOH              |       | 1) 36   | [153-158] |
|                        | R'                  | 1) Co(acac), Et3SiH, O2, rt  
|                        | R'                  | 2) TsOH              |       | 2) 57–100 | [153-158] |

a (Co(II)(thd)2) is bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt (II).

5.3. Use of epoxides as starting reagents in the synthesis of 1,2,4-trioxanes

An important approach to the synthesis of 1,2,4-trioxanes 357 is based on the epoxide-ring opening in 355 with hydrogen peroxide in the presence of a catalyst followed by the condensation of the vicinal hydroxy hydroperoxides 356 with ketones (Scheme 104, Table 23). The drawbacks of this method are generally low yields of 356 in the step of the epoxide–ring opening and difficulties of their isolation from the reaction mixture.

The reaction of unsaturated ketones 358 with H2O2/CF3COOH/H2SO4 in dichloromethane produced 1,2,4-trioxanes 359 in 25–95% yields (Scheme 105). It is assumed that in the first step, the hydroperoxidation of the keto group in 358 and the epoxidation of the double bond occur followed by the acid-induced intramolecular cyclization to form bicyclic compound 359 [408].
5.4. Synthesis of 1,2,4-trioxanes by the Kobayashi method

A convenient method for the synthesis of bicyclic trioxanes 362 was developed based on the hydroperoxidation of polyfunctional compounds 360 with the urea–hydrogen peroxide complex followed by the base-mediated intramolecular cyclization of 361 (Scheme 106). The yield of hydroperoxides 361 was 86–90%. In the second step, the intramolecular cyclization was performed in the presence of a catalytic amount of diethylamine. The yields of trioxanes 362 are in the range of 10–35% [409,410].

### Table 23: Examples of 1,2,4-trioxanes 357 synthesized based on epoxides 355.

| Epoxide 355 | Carbonyl compound | Reaction conditions | 1,2,4-Trioxane 357 | Yield i) 356 ii) 357, % | Ref. |
|-------------|-------------------|---------------------|-------------------|------------------------|------|
| ![Epoxide](image1) | ![Carbonyl compound](image2) | 1) MoO$_2$(acac)$_2$, H$_2$O$_2$, Et$_2$O, MgSO$_4$, 2) TsOH, CH$_2$Cl$_2$, rt | ![1,2,4-Trioxane](image3) | i) 59 ii) 95 | [405] |
| ![Epoxide](image4) | ![Carbonyl compound](image5) | 1) MoO$_2$(acac)$_2$, H$_2$O$_2$, THF, MgSO$_4$, 2) 10-camphor-sulfonic acid, CH$_2$Cl$_2$, rt | ![1,2,4-Trioxane](image6) | i) 69 ii) 29 | [405] |
| ![Epoxide](image7) | ![Carbonyl compound](image8) | 1) H$_2$O$_2$, Et$_2$O, 0 °C, 4 h, 2) H$_2$SO$_4$, CH$_2$Cl$_2$, rt, 4 d | ![1,2,4-Trioxane](image9) | i) 8 ii) 28 | [406] |
| ![Epoxide](image10) | ![Carbonyl compound](image11) | 1) MoO$_2$(acac)$_2$, H$_2$O$_2$, Et$_2$O, MgSO$_4$, rt, 22 h, 2) TsOH, CH$_2$Cl$_2$, rt, 5 h | ![1,2,4-Trioxane](image12) | i) 98 ii) 92 | [407] |
| ![Epoxide](image13) | ![Carbonyl compound](image14) | 1) MoO$_2$(acac)$_2$, H$_2$O$_2$, Et$_2$O, 2) 10-camphor-sulfonic acid, CH$_2$Cl$_2$ | ![1,2,4-Trioxane](image15) | i) 25 ii) 39 | [407] |
| ![Epoxide](image16) | ![Carbonyl compound](image17) | 1) MoO$_2$(acac)$_2$, H$_2$O$_2$, Et$_2$O, MgSO$_4$, 2) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, −78 °C to 0 °C, 5 h | ![1,2,4-Trioxane](image18) | i) - ii) 27–35 | [175] [176] |

**Scheme 105:** Peroxidation of unsaturated ketones 358 with the H$_2$O$_2$/CF$_3$COOH/H$_2$SO$_4$ system.
5.5. Structural modifications, in which 1,2,4-trioxane ring remains intact

The possibility of the reduction of the double bond in tricyclic peroxides 363 by hydrogen with the use of the mixed platinum–rhodium catalyst to form products, in which the 1,2,4-trioxane moiety remains intact, was exemplified by the synthesis of peroxides 364 (Scheme 107) [411].

1,2,4-Trioxane esters 366 were synthesized in high yield from 1,2,4-trioxane ketones 365 by the Horner–Wadsworth–Emmons reaction in the presence of sodium hydride as the base (Scheme 108) [375]. Compounds 366 exhibit antimalarial activity comparable with that of artemisinin.

Peroxide dyad 369 consisting of 1,2,4-trioxane moieties of different types was synthesized by the esterification of artesunic acid with 2-((3S,6R)-1-methyl-6-(prop-1-en-2-yl)-7,8,9-trioxabicyclo[3.3.1]nonan-3-yl)ethanol (368) (obtained by the reduction of ethyl 2-((3S,6R)-1-methyl-6-(prop-1-en-2-yl)-7,8,9-trioxabicyclo[3.3.1]nonan-3-yl)acetate (367)) in the presence of N,N′-dicyclohexylcarbodiimide (DCC) (Scheme 109) [392]. The particular structural feature of compound 369 is that it contains a natural peroxide moiety (artesunic acid) combined with the synthetic 1,2,4-trioxane moiety.

Trioxaquines are hybrid compounds containing the 1,2,4-trioxane and aminoquinoline moieties. They attracted interest because of a dual mode of action on Plasmodium. One of these compounds, PA1103/SAR116242, was selected as a drug candidate. The final step of its synthesis involves the reductive amination of keto-containing 1,2,4-trioxane 370 with N1-(7-chloroquin-4-yl)cyclohexane-1,4-diamine (371) (Scheme 110) [86].

Trioxaferroquines, ferrocene-containing compounds, belong to a new type of hybrid molecules exhibiting high antimalarial activity. The last step of the synthesis of one of these com-
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Scheme 109: Reduction of ester group by LiBH$_4$ in the presence of 1,2,4-trioxane moiety.

Scheme 110: Reductive amination of keto-containing 1,2,4-trioxane and a Fe-containing moiety.

Scheme 111: Reductive amination of keto-containing 1,2,4-trioxane and a Fe-containing moiety.

6. Synthesis of 1,2,4,5-tetraoxanes

The most widely used approaches to the synthesis of 1,2,4,5-tetraoxanes are based on the reaction of ketones and aldehydes with hydrogen peroxide or gem-bishydroperoxides catalyzed by protic or aprotic acids, MeReO$_3$, Re$_2$O$_7$, and iodine. These methods were used for the synthesis of a wide range of symmetrical and unsymmetrical 1,2,4,5-tetraoxanes.

6.1. Acid-catalyzed cyclocondensation of ketones and aldehydes with hydrogen peroxide

This cyclocondensation is the simplest route to some symmetrical (containing identical substituents in positions 3 and 6) 1,2,4,5-tetraoxanes 375 starting from ketones 374 (Scheme 112, Table 24). The acid-catalyzed reactions of hydrogen peroxide with dialkyl ketones, cycloalkanones, and substituted medium-size cycloalkanones produce symmetrical 1,2,4,5-tetraoxanes in...
moderate to high yields. The drawback of this method is the high sensitivity of the yields of the target peroxides to the structure of the starting carbonyl compounds.

### 6.2. Use of the bis(trimethylsilyl)peroxide/trimethylsilyltrifluoromethanesulfonate system in the cyclocondensation of carbonyl compounds

The cyclocondensation of carbonyl compounds with $\text{Me}_3\text{SiOOSiMe}_3/\text{CF}_3\text{SO}_3\text{SiMe}_3$ afforded steroidal tetraoxanes (Scheme 113) [417,418]. The cyclocondensation of ketones was performed at 0 °C in acetonitrile using a 1.5-fold molar excess of $\text{Me}_3\text{SiOOSiMe}_3$ and $\text{CF}_3\text{SO}_3\text{SiMe}_3$ with respect to ketone [417,418].

### 6.3. MeReO$_3$-catalyzed peroxidation of ketones

1,1-Dihydroperoxy-4-methylcyclohexane (379) and symmetrical tetraoxane were selectively synthesized in high yields from 4-methylcyclohexanone (378) with the use of the 30% $\text{H}_2\text{O}_2/\text{MeReO}_3$/fluorinated alcohol system (Scheme 114) [419].

| Tetraoxane 375: $R^1, R^2$ | Reaction conditions | Yield, % | Reference |
|-----------------------------|---------------------|----------|-----------|
| $-\text{CH}($Et$)(\text{CH}_2)_4$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 24 | [413] |
| $-\text{CH}($Pr$)(\text{CH}_2)_4$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 7 | |
| $-\text{CH}_2\text{CH}($Me$)($CH$_2)_3$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 32 | |
| $-\text{CH}($Me$)($Me$)($CH$_2)_3$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 4 | |
| $-\text{CH}($Me$)($CH$_2)($CH)(Me)$($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 29 | |
| $-\text{CH}($Me$)($CH$_2)($CH($Me$)($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 20 | |
| $-\text{CH}($Me$)($CH$_2)($CH($Pr$)($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 26 | |
| $-\text{CH}($Me$)($CH$_2)($CH($Me$)($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 34 | |
| $-\text{CH}_2\text{C}($Me$)($Me$)($CH$_2)($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 68 | |
| $-\text{C}($Me$)($Me$)($CH$_2)_4$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 26 | |
| $-\text{CH}($Me$)($CH$_2)($CH($Me$)($CH$_2)_2$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 18 | |
| $-\text{CH}($Me$)($CH$_2)_3$ | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 90 | |
| $-\text{CH}_2$ | $\text{H}_2\text{O}_2$, $\text{MeReO}_3$ | 100 | |
| H, $-(\text{CH}_2)$CHO | $\text{H}_2\text{O}_2$, MeCN, $\text{H}_2\text{SO}_4$, -20 °C, 48 h | 80 | |

Scheme 112: Acid-catalyzed reactions of $\text{H}_2\text{O}_2$ with ketones and aldehydes 374.

Scheme 113: Cyclocondensation of carbonyl compounds 376a–d using $\text{Me}_3\text{SiOOSiMe}_3/\text{CF}_3\text{SO}_3\text{SiMe}_3$. 

Table 24: Examples of symmetrical 1,2,4,5-tetraoxanes 375 synthesized by the acid-catalyzed cyclocondensation of ketones and aldehydes with $\text{H}_2\text{O}_2$. 

Scheme 114: Cyclocondensation of carbonyl compounds 376a–d using $\text{Me}_3\text{SiOOSiMe}_3/\text{CF}_3\text{SO}_3\text{SiMe}_3$. 

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`Table 24`
The use of fluorinated alcohols as the solvent results in an increase in the selectivity of the synthesis. Under similar conditions, symmetrical 3,6-diphenyl- and 3,6-di-(n-heptyl)-1,2,4,5-tetraoxanes 382a,b were synthesized from benzaldehyde (381a) and n-octanal (381b), respectively (Scheme 115) [419].

Unsymmetrical tetraoxanes 383a–d were prepared from 4-methylcyclohexanone (378) by the reaction with ketones (R¹COR²) using 1 equiv of HBF₄, 2 equiv of H₂O₂, and 0.1 mol % MeReO₃ in CF₃CH₂OH (TFE) at room temperature. The unsymmetrical tetraoxane, 3,3-dibutyl-6-heptyl-1,2,4,5-tetraoxide (384), was synthesized from octanal (381b) with the use of CH₃CHOHCF₃ (HFIP) (Scheme 116) [419].

This method was applied to the synthesis of 3,3,6,6-tetraalkyl-1,2,4,5-tetraoxanes 386a–c and 388a–i from cyclic 385a–c and acyclic ketones 387a–i (Scheme 117) [420], as well as of dispiro-1,2,4,5-tetraoxanes 390a–c from 4-substituted cyclohexanones 389a–c (Scheme 118) [421].

Unsymmetrical tetraoxanes containing adamantane (395a–i) and cycloalkane moieties (396a–d) exhibiting high...
Scheme 117: Synthesis of symmetrical tetraoxanes using MeReO₃.

Scheme 118: Synthesis of symmetrical tetraoxanes using MeReO₃.

Scheme 119: MeReO₃ in the synthesis of symmetrical tetraoxanes with the use of aldehydes.
antimalarial activity (Scheme 120) were prepared from sulfonylpyperidones 394 [138].

6.4. Re$_2$O$_7$-Catalyzed cyclocondensation of gem-bishydroperoxides with ketones

Re$_2$O$_7$ is an efficient catalyst for the addition of hydroperoxide groups to ketones and aldehydes. Due to these properties, Re$_2$O$_7$ can be used in the one-pot synthesis of unsymmetrical 1,2,4,5-tetraoxanes 398 from ketones 397 in good yields (Scheme 121, Table 25) [423].

6.5. Protic acid-catalyzed cyclocondensation of gem-bishydroperoxides with ketones

Unsymmetrical steroidal tetraoxanes 401 were synthesized by the hydroperoxidation of methyl 3-oxo-7a,12a-diacetoxy-5b-cholan-24-oate (399) in the presence of HCl followed by the condensation of bishydroperoxide 400 with the corresponding ketone in the presence of H$_2$SO$_4$ (Scheme 122) [128,132,141,142]. Structurally more simple ketones, for example, acetone, are also involved in the cyclocondensation with bishydroperoxide 400 [141].

Table 25: Re$_2$O$_7$-Catalyzed synthesis of tetraoxanes 398.

| Ketone A, 397 | Ketone B | Reaction conditions | Tetraoxane 398 | Yield, % |
|--------------|----------|---------------------|----------------|---------|
| O           | O       | 1) H$_2$O$_2$ (2 equiv), 0.5 h, 0 °C  
2) Ketone B (2 equiv), CH$_2$Cl$_2$, 1 h, rt | ![Tetraoxane 398](image) | 67 |
| O           | O       | 1) H$_2$O$_2$ (4 equiv), 0.5 h, rt  
2) Ketone B (4 equiv), 2,2,2-trifluoroethanol, Re$_2$O$_7$, 0.5 h, rt | ![Tetraoxane 398](image) | 69 |
| N=S=O      | O       | 1) H$_2$O$_2$ (4 equiv), 6 h, rt  
2) Ketone B (4 equiv), 2,2,2-trifluoroethanol, Re$_2$O$_7$, 2 h, rt | ![Tetraoxane 398](image) | 49 |
The synthesis of keto-containing tetraoxane 403 was also performed in two steps [144]. Thus the intermediate 1,1-dihydroperoxycyclohexane 402 was prepared from cyclohexanone in a neutral medium, and its condensation with 1,4-cyclohexanone was carried out in the presence of HBF₄ (Scheme 123).

### 6.6. Cyclocondensation of bishydroperoxides with acetals and enol ethers

The method for the synthesis of 1,2,4,5-tetraoxanes 407 and 408 is based on the boron trifluoride etherate-catalyzed reaction of gem-bishydroperoxides 404 with enol ethers 405 and acetals 406 under mild conditions. More than two dozens of tetraoxanes were synthesized in yields from 45 to 95% according to this method (Scheme 124). The advantage of this method is the use of readily available starting compounds, such as acetals, enol ethers, and boron trifluoride etherate [424,425].

The bishydroperoxidation of 1,3-dioxolane 409 was carried out in the presence of H₂WO₄. The following HBF₄-catalyzed condensation of bishydroperoxide 410 with ketones gave 1,2,4,5-tetraoxanes 411a–c containing the ester group (Scheme 125) [144].

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**Scheme 122:** H₂SO₄-Catalyzed synthesis of steroidal tetraoxanes 401.

The synthesis of keto-containing tetraoxane 403 was also performed in two steps [144]. Thus the intermediate 1,1-dihydroperoxycyclohexane 402 was prepared from cyclohexanone in a neutral medium, and its condensation with 1,4-cyclohexanone was carried out in the presence of HBF₄ (Scheme 123).

### 6.6. Cyclocondensation of bishydroperoxides with acetals and enol ethers

The method for the synthesis of 1,2,4,5-tetraoxanes 407 and 408 is based on the boron trifluoride etherate-catalyzed reaction of gem-bishydroperoxides 404 with enol ethers 405 and acetals 406 under mild conditions. More than two dozens of tetraoxanes were synthesized in yields from 45 to 95% according to this method (Scheme 124). The advantage of this method is the use of readily available starting compounds, such as acetals, enol ethers, and boron trifluoride etherate [424,425].

The bishydroperoxidation of 1,3-dioxolane 409 was carried out in the presence of H₂WO₄. The following HBF₄-catalyzed condensation of bishydroperoxide 410 with ketones gave 1,2,4,5-tetraoxanes 411a–c containing the ester group (Scheme 125) [144].

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**Scheme 123:** HBF₄-Catalyzed condensation of bishydroperoxide 402 with 1,4-cyclohexanone.
6.7. Iodine-catalyzed one-pot synthesis of symmetrical and unsymmetrical tetraoxanes

The reaction of substituted benzaldehyde 412 with hydrogen peroxide in the presence of the Lewis acid I\(_2\) produced geminal bishydroperoxide, whose condensation with the starting or another substituted benzaldehyde gave tetraoxane 413 (Scheme 126, Table 26) [426,427].

The iodine-catalyzed one-pot synthesis of symmetrical and unsymmetrical tetraoxanes from substituted benzaldehydes has some advantages over other methods. Thus, it can be performed with the use of mild reagents (which do not decompose peroxide) and it does not need an excess of hydrogen peroxide and substituted benzaldehyde.

6.8. Acid-catalyzed condensation of \(\beta\)-diketones with hydrogen peroxide

The acid-catalyzed condensation of \(\beta\)-diketones 414a–l with hydrogen peroxide is a simple and facile method for the synthesis of bridged 1,2,4,5-tetraoxanes 415a–l. This method enables the synthesis of these compounds on the multigram scale in 47–77% yields (Scheme 127). The high concentration of a strong acid, such as H\(_2\)SO\(_4\), HBF\(_4\), or HClO\(_4\) (2 g of the acid per 5 mL of the solvent) is the key factor determining the yield and selectivity of the synthesis of 1,2,4,5-tetraoxanes. Under these conditions, the targeted compounds are produced selectively even in the presence of an excess of hydrogen peroxide [428]. Unlike many compounds with the O–O bond, which are rearranged in acidic media, the resulting cyclic peroxides are fairly stable under these reaction conditions.
Table 26: Iodine-catalyzed one-pot synthesis of tetraoxanes 413.

| Tetraoxane 413 | Yield, % | Tetraoxane 413 | Yield, % |
|---------------|----------|---------------|----------|
| R1            | R2       | R1            | R2       |
| o-Me          | o-Me     | 42            | p-(t-Bu) | 32        |
| o-Me          | m-Me     | 33            | p-(t-Bu) | 38        |
| p-Me          | p-Me     | 54            | p-(t-Bu) | 28        |
| p-Me          | p-(i-Pr) | 33            | p-(t-Bu) | 22        |
| p-Me          | p-(t-Bu) | 46            | p-(i-Pr) | 24        |
| p-Me          | p-Ome    | 25            | p-Et     | 41        |
| p-Me          | p-CO2Me  | 37            | p-Et     | 39        |
| p-Me          | o-Me     | 25            | p-Et     | 37        |
| p-Me          | m-Me     | 38            | p-Et     | 25        |
| p-Me          | p-(n-Pr) | 37            | p-(n-Pr) | 24        |
| p-Me          | H        | 43            | p-Cl     | 25        |
| p-Me          | p-CHO    | 31            | p-Br     | 22        |
| p-Me          | p-(n-Bu) | 40            | p-F      | 29        |
| p-(n-Bu)      | p-(n-Bu) | 53            | p-OMe    | 27        |
| m-Me          | m-Me     | 51            | p-Et     | 44        |
| m-Me          | H        | 30            | p-(n-Pr) | 38        |
| m-Me          | p-OMe    | 29            | p-(i-Pr) | 41        |

Scheme 127: Synthesis of bridged 1,2,4,5-tetraoxanes 415a–l from β-diketones 414a–l and H2O2.

It was found that phosphomolybdic acid and phosphotungstic acid efficiently catalyze the addition of H2O2 to β-diketones resulting in the selective formation of bridged 1,2,4,5-tetraoxanes. The use of these catalysts made it possible to obtain bridged tetraoxanes from easily oxidizable benzoylacetone derivatives and α-unsubstituted β-diketones [429].

6.9. Synthesis of symmetrical 1,2,4,5-tetraoxanes by the ozonolysis of unsaturated compounds

The dimerization of zwitterions produced by decomposition of ozonides 416 affords symmetrical tetraoxanes (Scheme 128).

For example, the ozonolysis of verbenone 419 via the formation of zwitterionic structures 420 and 421 gives a mixture of two symmetrical 1,2,4,5-tetraoxanes 422 and 423 (Scheme 129) [430]. Peroxides 422 and 423 are unstable due to the presence of carbonyl groups adjacent to the O–O group, and they almost completely decompose as the temperature is raised.

3,3,6,6-Tetrapentyl-1,2,4,5-tetraoxane (425) was synthesized in a similar way by the ozonolysis of undecan-6-one O-methyl oxime (424) (Scheme 130) [431,432]. It should be noted that this approach is not widely used because of a limited number of appropriate structures and low yields of the target products.
6.10. Other methods for the synthesis of 1,2,4,5-tetraoxanes

The peroxidation of 1,1,1-trifluorododecan-2-one (426) with oxone afforded the symmetrical tetraoxane, 3,6-didecyl-3,6-bis(trifluoromethyl)-1,2,4,5-tetraoxane (427) (Scheme 131) [433].

The synthesis of unsymmetrical steroidal tetraoxane 429 in 19% yield was performed by the intramolecular cyclization of dialdehyde 428 with hydrogen peroxide under acidic conditions (Scheme 132) [434].

In the synthesis of geminal bishydroperoxides by BF₃·Et₂O or BF₃·MeOH-catalyzed reactions of ketals 430–432 with hydrogen peroxide in Et₂O tetraoxanes 433–435 (Scheme 133) are obtained as by-products in 12%, 6%, and 19% yields, respectively [435].

Scheme 134 shows the synthesis of 3,3,6,6-tetramethyl-1,2,4,5-tetraoxane (437) in 90% yield by the transformation of the intermediate 3,3,6,6,9,9-hexamethyl-1,2,4,5,7,8-hexamoxonanone (436) in acetone [436]. This method is suitable for the preparation of the target product in amounts of only several hundred milligrams.

6.11. Structural modifications, in which 1,2,4,5-tetraoxane ring remains intact

In the last two decades, 1,2,4,5-tetraoxanes were considered as the most promising compounds for the design of antiparasitic drugs. This is due, first, to the high activity of their derivatives...
Amides 440a, b and amines 444a, b, and 446 active against various strains of *P. falciparum* were synthesized from methyl 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane-3-carboxylate (438) containing the ester group (Scheme 135) [135,437]. To prepare aminoquinoline derivatives 440a, b, ester 438 was
hydrolyzed to 7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane-3-carboxylic acid (439) followed by the amidation of the latter. The synthesis of products 444a,b and 446 was performed with a wide range of classical reagents for organic synthesis with the intermediate formation of compounds containing such groups as hydroxy 441, azide 442, amino 443, and aldehyde 445.

An interesting feature of the synthesis according to Scheme 135 is the use of such strong reducing agents as LiAlH₄ and NaBH₄(OAc)₃, with the products retaining the peroxide ring.

Steroidal tetraoxane 448, which is approximately six times more active that Artelinic acid and 2.4 times as active as arteether against P. falciparum, was also synthesized by the alkaline hydrolysis of ester 401g followed by the amidation of acid 447 (Scheme 136) [128].

Compounds containing a fluorescent moiety are of interest in terms of the mechanism of antiparasitic action of peroxides. For example, 1,2,4,5-tetraoxane 454 containing the 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole moiety was synthesized according to Scheme 137. In the first step, ketone 449 was transformed in tetraoxane 450, whose ester group was subjected to the alkaline hydrolysis to form acid 451 followed by the amidation to give 452 and the hydrolysis to obtain hydrochloride 453. Then the reaction of the latter with 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole afforded the target compound 454 [138].

The synthesis of tetraoxane 458 (RKA182) exhibiting the in vitro and in vivo activity comparable with that of artemisinin was performed on the kilogram scale according to Scheme 138. This compound is a promising malaria drug candidate [82,83]. The key steps in this synthesis are the preparation of adamantane-containing tetraoxane 456 from ethyl 2-(4-oxocyclohexyl)acetate (455), the hydrolysis of 456, and the purification to obtain acid 457. The amidation of the latter affords target product 458.

### Conclusion

The review summarizes and generalizes studies on the synthesis of five- and six-membered cyclic peroxides published last decade (since 2000 to present). Most of the currently established methods for the synthesis of these compounds are based on the use of such key oxidizing agents as oxygen, ozone, and hydrogen peroxide. The Isayama–Mukaiyama and Kobayashi methods are widely used in the synthesis of 1,2-dioxolanes, 1,2-dioxanes, and 1,2,4-trioxanes. The reactions with the participation of peroxycarbenium ions play an important role in the synthesis of peroxides.
The Griesbaum coozonolysis of ketones and O-alkyl oximes is the most flexible and efficient method for the synthesis of unsymmetrical 1,2,4-trioxolanes. The [4 + 2]-cycloaddition of oxygen to a 1,3-diene system is, in fact, the only route to 1,2-dioxenes.

Methods for the synthesis of 1,2,4,5-tetraoxanes are based on reactions of ketones, aldehydes, and their dialkyl oximes with hydrogen peroxide or *gem*-bishydroperoxides catalyzed by protic and aprotic acids, such as MeReO$_3$, Re$_2$O$_7$, and iodine.
Modifications of functional groups to form peroxide ring-retaining products are applicable to the synthesis of cyclic peroxides of various structural types. This approach can be used to prepare complex peroxides exhibiting antiparasitic and anti-tumor activities.

Carbonyl compound are generally employed as the starting reagents in the synthesis of cyclic peroxides. These methods can be used for the selective peroxidation of monocarbonyl compounds. In the case of dicarbonyl compounds, there are a limited number of efficient procedures for the synthesis of cyclic peroxides.

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