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

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Review

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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

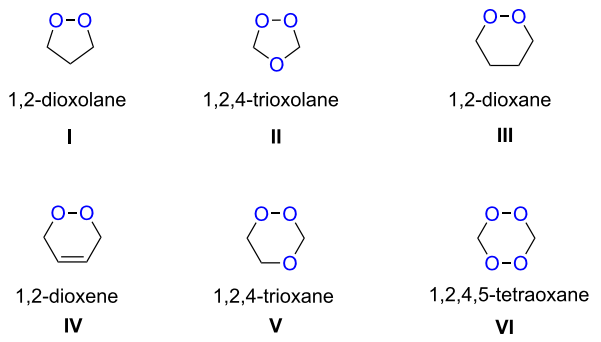


Figure 1: Five and six-membered cyclic peroxides.

appeared: Tang et al. [3], O'Neill, Posner and colleagues [4,5], Masuyama et al. [6], Van Ornum et al. [7], Jefford [8,9], Dembitsky et al. [10-15], Opsenica and Šolaja [16], Muraleedharan and Avery [17], and other [18-27] including dissertations [28-32].

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 peroxycarbenium 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 **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].

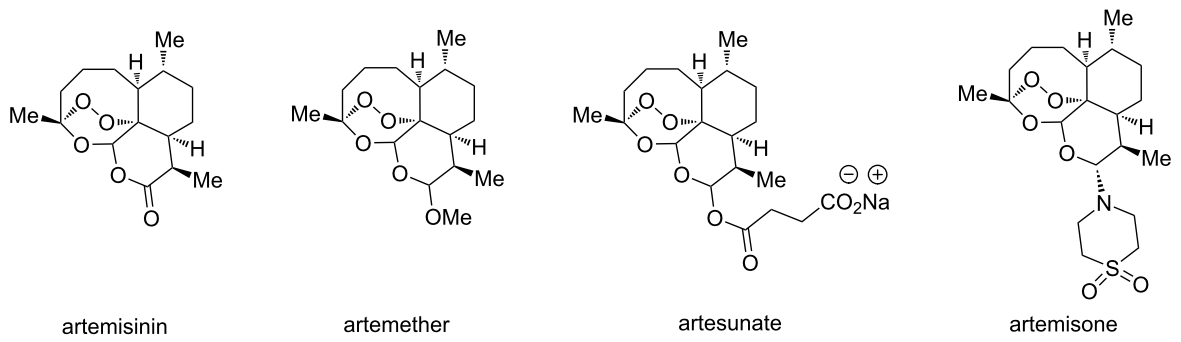


Figure 2: Artemisinin and semi-synthetic derivatives.

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-dioxane [10-15,112,178-181], 1,2-dioxene [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 peroxycarbenium ions. Syntheses employing hydrogen peroxide and the intramolecular Kobayashi cyclization are less frequently used.

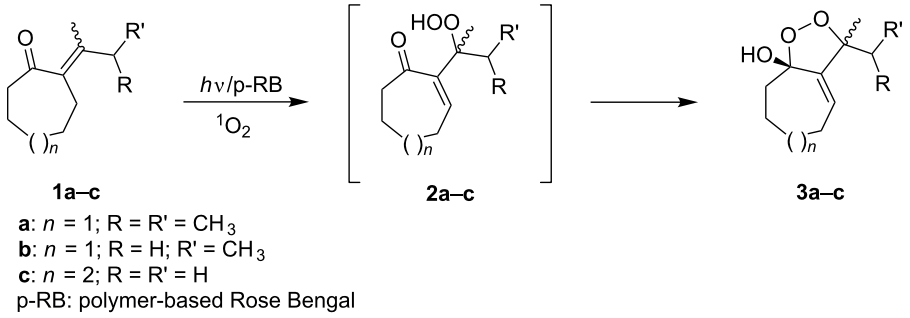
1.1. Use of oxygen for the peroxide ring formation

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].

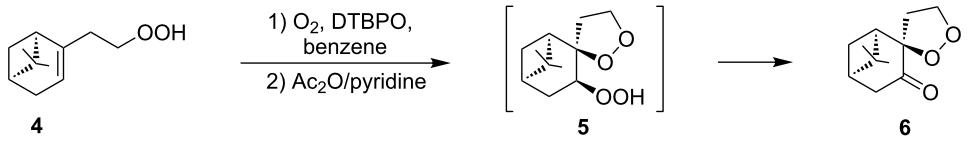
Dioxolane **6** was synthesized in 36% yield by the reaction of oxygen with hydroperoxide **4** in the presence of di-*tert*-butyl peroxalate (DTBPO) followed by the treatment of the reaction mixture with acetic anhydride and pyridine at room temperature (Scheme 2).

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].

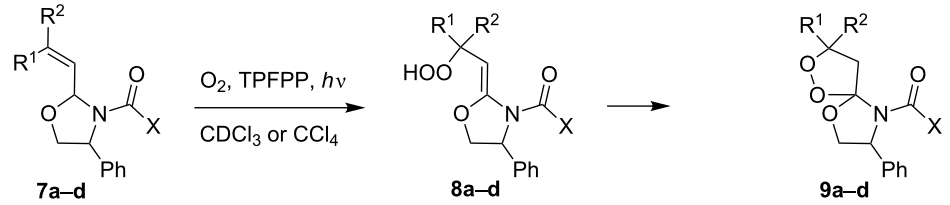
The photooxygenation of oxazolidines **7a–d** through the formation of hydroperoxides **8a–d** gives spiro-fused oxazolidine-containing dioxolanes **9a–d** in low yields (12–30%) (Scheme 3) [233].



Scheme 1: Synthesis of 3-hydroxy-1,2-dioxolanes **3a–c**.



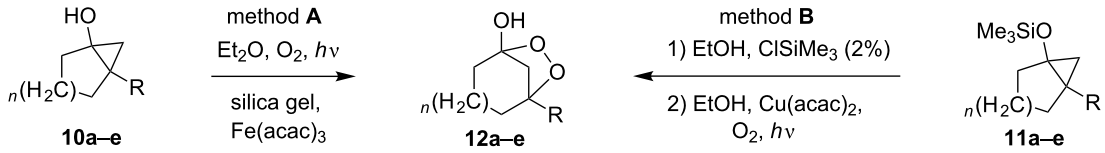
Scheme 2: Synthesis of dioxolane **6**.



Scheme 3: Photooxygenation of oxazolidines **7a–d** with formation of spiro-fused oxazolidine-containing dioxolanes **9a–d**.

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].



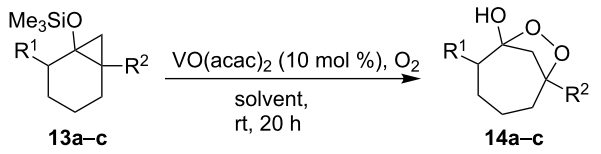
Scheme 4: Oxidation of cyclopropanes **10a–e** and **11a–e** with preparation of 1,2-dioxolanes **12a–e**.

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_4H_9	1	3	55	3.5	84
c	C_6H_{13}	1	3	68	–	–
d	CH_2Ph	1	3	50	5	78
e	CH_3	2	36	54	6	80

[a]Et_2O, O_2, *hν*, silica gel, $Fe(acac)_3$ (4 mol %).
[b]EtOH, O_2, *hν*, $Cu(acac)_2$ (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].



Scheme 5: $VO(acac)_2$-catalyzed oxidation of silylated bicycloalkanols **13a**–**c**.

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
			CF_3CH_2OH	86
b	H	Bn	CF_3CH_2OH	43
c	Me	Me	CF_3CH_2OH	43

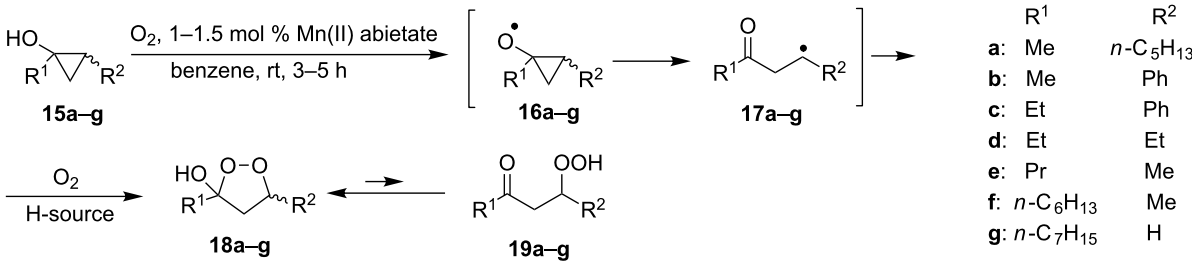
This reaction gives β-hydroxyketones as by-products that are formed as a result of the decomposition of dioxolanes **14**.

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 $[(phen)_3Fe(III)(PF_6)_3]$ or equimolar amounts of benzoyl peroxide or di-*tert*-butyl peroxide. The possible mechanism of the oxidation is shown in Scheme 7 [237].

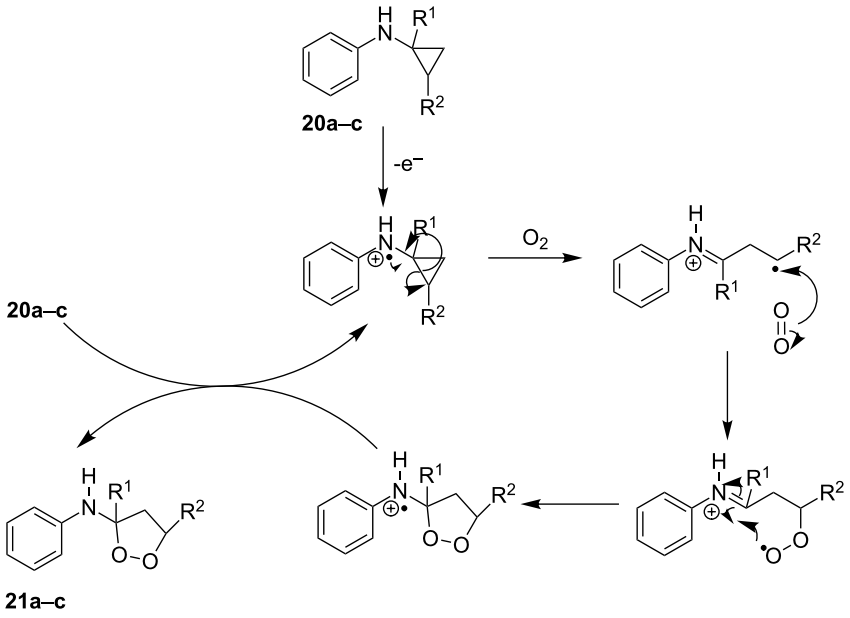
According to the ^1H NMR data, dioxolanes **21a–c** are formed under the above-mentioned conditions in almost quantitative yields; the yields based on the isolated product were not higher than 80% [237].



Scheme 6: Mn(II)-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 °C, 3 days. 2. (t-$BuO)_2$ (1 mol/1 mol **20a**), $CHCl_3$, UV (254 nm), ambient temperature, aerobic, 2 h. 3. $[(phen)_3Fe(III)(PF_6)_3]$ (0.6 % mol), $CHCl_3$, ambient temperature, aerobic, 1 h.
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. 2. $[(phen)_3Fe(III)(PF_6)_3]$ (0.6 % mol), $CHCl_3$, ambient temperature, aerobic, 1 h.



Scheme 7: Oxidation of aminocyclopropanes **20a–c**.

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].

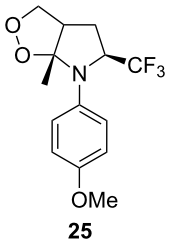
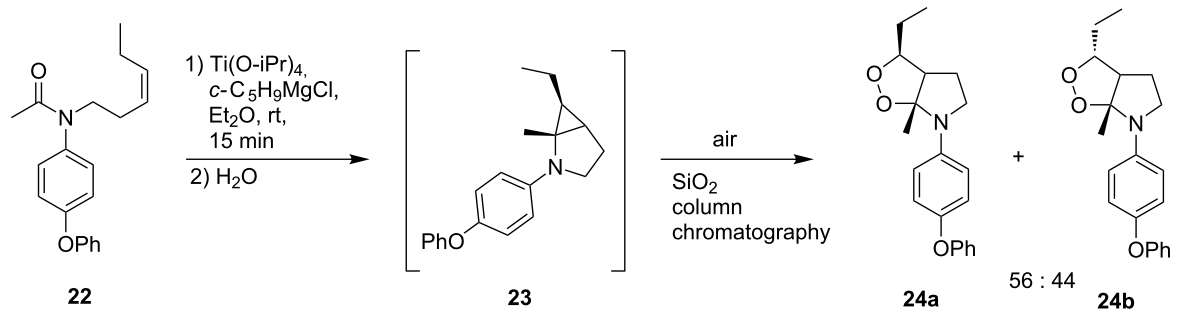


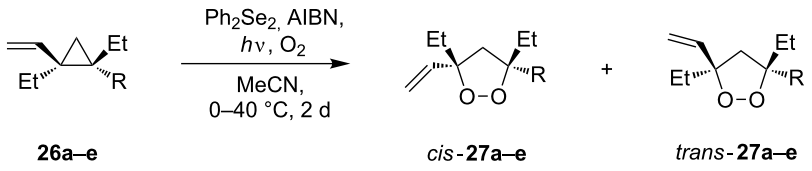
Figure 3: Trifluoromethyl-containing dioxolane **25**.

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 Ph_2Se_2 (10 mol %) and azobisisobutyronitrile (AIBN, 8 mol %) in air under irradiation for two days. The product was purified by



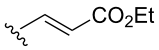
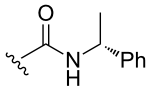
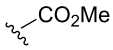
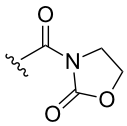
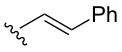
Scheme 8: Synthesis of aminodioxolanes **24**.



26a–e *cis*-**27a–e** *trans*-**27a–e**

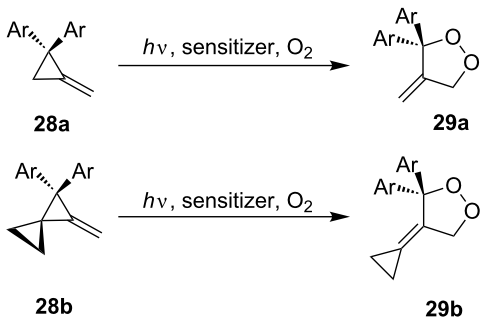
Scheme 9: Synthesis of 1,2-dioxolanes **27a–e** by the oxidation of cyclopropanes **26a–e**.

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

Dioxolane **27a–e**	R	Yield (*cis* + *trans*), %	Ratio (*cis*/*trans*)
a		88	1/7
b		100	*trans* isomer
c		75	1/22
d		100	1/13
e		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).



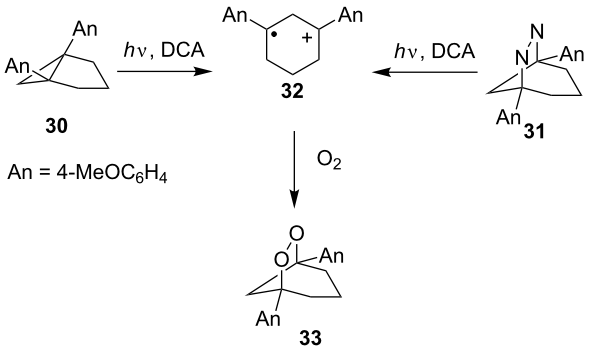
28a **29a**

28b **29b**

Scheme 10: Photoinduced oxidation of methylenecyclopropanes **28**.

The reaction was performed in acetonitrile or in a mixture of toluene and acetonitrile with the use of 9,10-dicyanoanthracene (DCA), 1,2,4,5-tetracyanobenzene (TCNB), or *N*-methyl-quinolinium tetrafluoroborate ($NMQ^+BF_4^-$) as sensitizers. Under these conditions, 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).



30 **32** **31**

An = 4-MeOC$_6$H$_4$

33

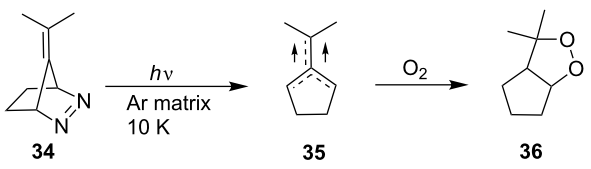
Scheme 11: Irradiation-mediated oxidation.

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].

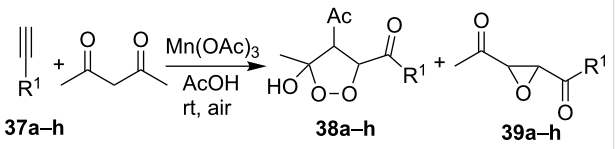
Bicyclic peroxide 2-heptyl-3,4-dioxabicyclo[3.3.0]oct-1(8)-ene was prepared by a similar process [244].

The oxidation of arylacetylenes **37a**–**h** with atmospheric oxygen in the presence of catalytic amounts of $Mn(OAc)_3$ in an



Scheme 12: Application of diazene **34** for dioxolane synthesis.

excess of acetylacetone afforded dioxolanes **38a**–**h** in moderate yields (34–64%) (Scheme 13, Table 5) [245].



Scheme 13: $Mn(OAc)_3$-catalyzed cooxidation of arylacetylenes **37a–h** and acetylacetone with atmospheric oxygen.

Table 5: Structures and yields of dioxolanes **38a–h** and epoxides **39a–h**.

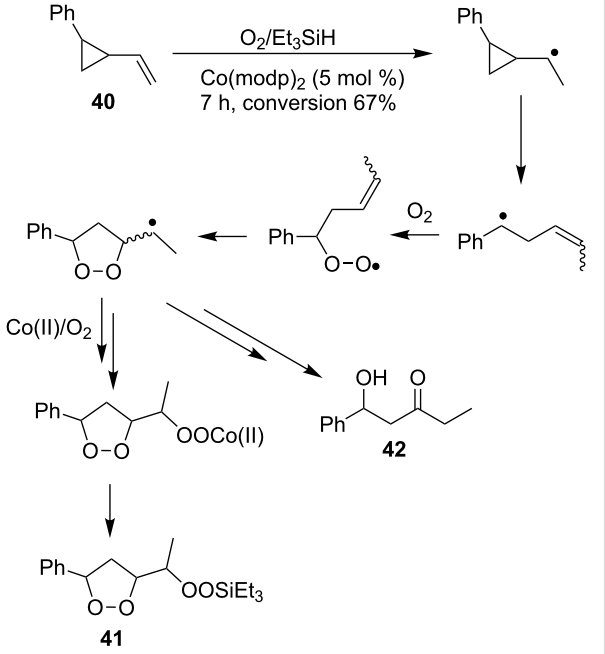
37a–h	R^1	Yield **38a–h**, %	Yield **39a–h**, %
a	Ph	45	5
b	4-MeC_6H_4	52	7
c	4-$MeOC_6H_4$	64	2
d	4-ClC_6H_4	38	2
e	4-FC_6H_4	41	6
F	1-naphthyl	54	6
g	2-naphthyl	52	8
h	3,4-$(MeO)_2C_6H_3$	34	11

The reaction was performed at 23 °C in glacial acetic acid in air; the **37**/acetylacetone/$Mn(OAc)_3$ 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].

1.2. Peroxidation of alkenes with the Co(II)/Et_3SiH/O_2 system (Isayama–Mukaiyama reaction)

Peroxysilylation of alkenes with molecular oxygen in the presence of triethylsilane catalyzed by cobalt(II) diketonates was described for the first time by S. Isayama and T. Mukaiyama in 1989 [246,247]. Currently, this approach is one of the main methods for the preparation of peroxides from alkenes.

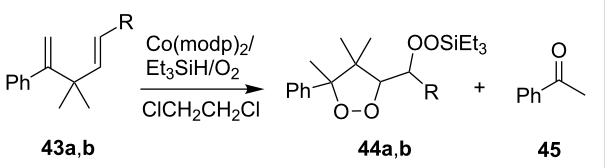
Compounds (oxidized by the Isayama–Mukaiyama reaction) containing a reaction center that can be subjected to the attack by a peroxide radical, are able to undergo intramolecular cyclization to form the 1,2-dioxolane ring. For example, the $Co(modp)_2$-catalyzed peroxysilylation (modp = 1-morpholino-5,5-dimethyl-1,2,4-hexanetrionate) of (2-vinylcyclopropyl)benzene (**40**) affords triethyl(1-(5-phenyl-1,2-dioxolan-3-yl)ethylperoxy)silane (**41**) in 37% yield (Scheme 14).



Scheme 14: Peroxidation of (2-vinylcyclopropyl)benzene (**40**).

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].

The peroxidation of 1,4-dienes **43a**,**b** with the $Co(modp)_2$/Et_3SiH/O_2 system according to a similar reaction scheme gave dioxolanes **44a**,**b**. Acetophenone (**45**) was obtained as the by-product (Scheme 15, Table 6) [249].



Scheme 15: Peroxidation of 1,4-dienes **43a**,**b**.

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

Table 6: Synthesis of dioxolanes **44a**,**b**.

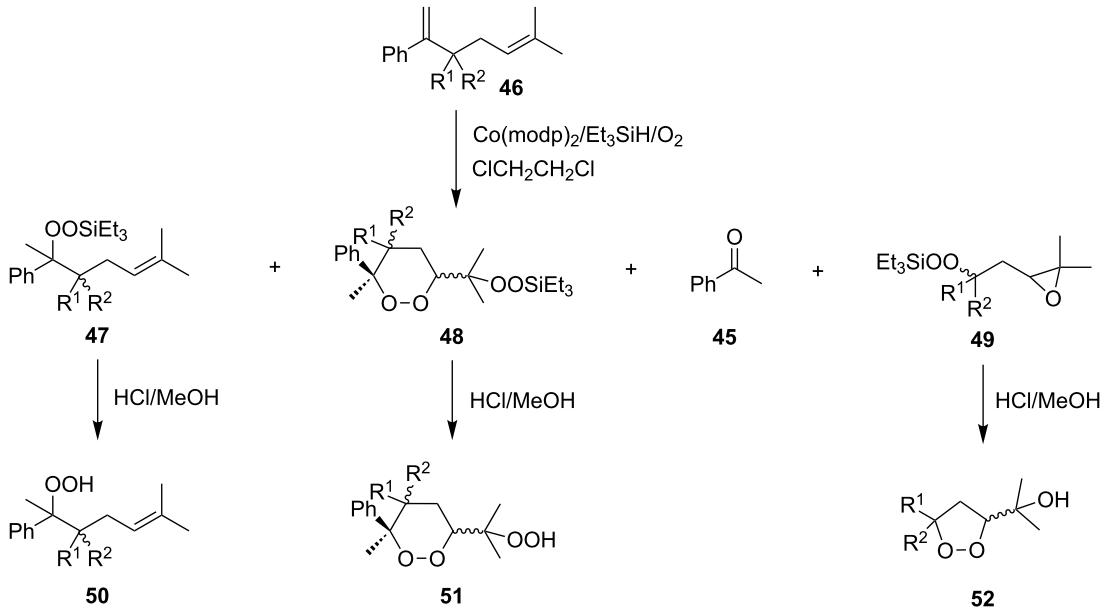
1,4-Diene **43**	R	Reaction time, h	Conversion, %	Yield, %	
				44	**45**
a	H	4.5	47	27	49
b	COOEt	2	44	56	22

of the Isayama–Mukaiyama reaction for the synthesis of cyclic peroxides. In some cases, the reaction with 1,5-dienes **46a–d** produces, along with 1,2-dioxanes **51** (desilylation products of the corresponding 1,2-dioxanes **48**), 1,2-dioxolanes (**52b**,**d**) as a result of cyclization of the corresponding peroxysilyl epoxides **49**. In these reactions, unsaturated triethylsilyl peroxides **47** are formed as by-products, which are desilylated during hydrolysis to give the unsaturated hydroperoxides **50** (Scheme 16, Table 7) [249].

1,2-Dioxolanes can be produced from oxetanes **53a,b** containing a double bond in the side chain according to a similar scheme. The first step afforded peroxysilanes **54a**,**b**, which upon treatment with aqueous HF gave the target dioxolanes **55a**,**b** (Scheme 17) [250].

A similar way to 1,2-dioxolanes used an oxirane cycle for the stages of ring opening followed by 1,2-dioxolane ring closing [251].

The synthesis of spirodioxolane **59** involved the peroxysilylation of 1,3-dicyclohexenylpropan-2-yl acetate (**56**) catalyzed by cobalt complexed with 2,2,6,6-tetramethylheptane-3,5-dione ($Co(THD)_2$) as the first step giving 1,3-bis(1-(triethylsilylperoxy)cyclohexyl)propan-2-yl acetate (**57**) that was subse-

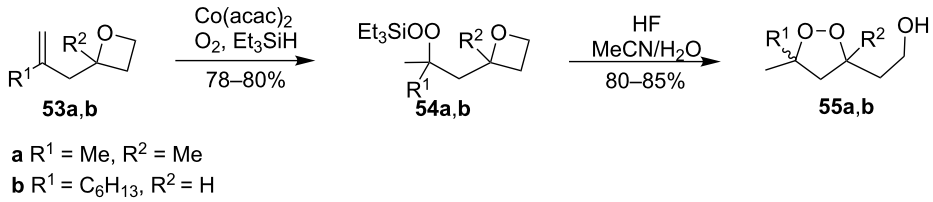


Scheme 16: Peroxidation of 1,5-dienes **46**.

Table 7: Peroxidation of 1,5-dienes **46**.

Diene **46**	R^1	R^2	Reaction time, h	Conversion, %	Yield[a], %				
					45	**49**	**50**	**51**	**52**
a	H	H	6	82	4	–	13	31	–
b	H	Me	2.5	83	36	–	12	13	33
c	H	Ph	3.5	75	57	38	7	27	–
d	Me	Me	3	84	51	–	–	31	26

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



Scheme 17: Peroxidation of oxetanes **53a**,**b**.

quently 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].

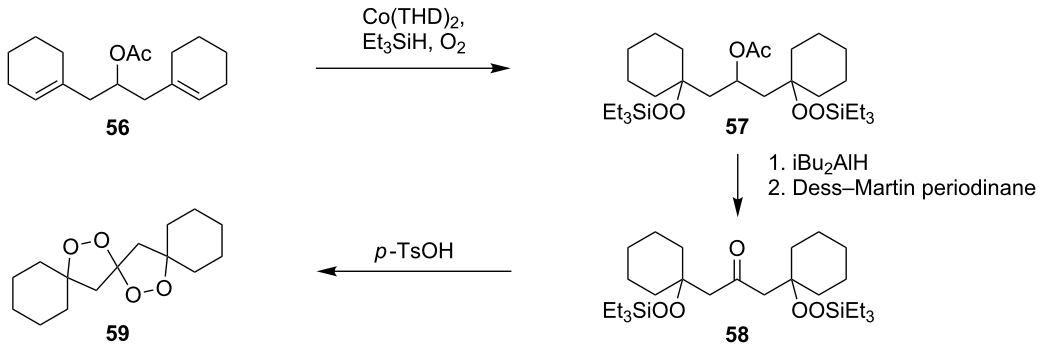
1.3. The use of ozone. Peroxycarbenium ions in the 1,2-dioxolanes synthesis

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.

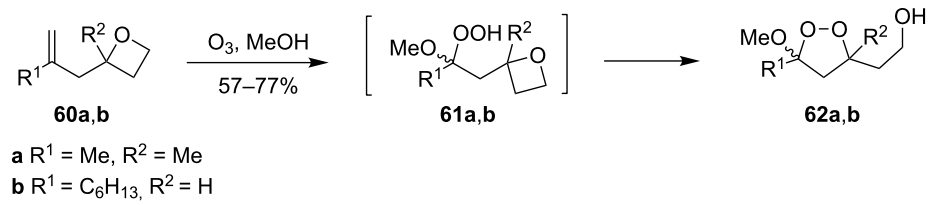
The reaction of oxetanes **60a**,**b** with ozone in methanol produced 3-alkoxy-1,2-dioxolanes **62a,b**. The analysis of the reaction mixture (TLC, NMR) confirmed that cyclic peroxides are formed immediately in the reaction mixture rather than in the course of the treatment or purification of the reaction 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-diyl-bis(methanesulfonate) (**63**) gave 9-oxoheptadecane-7,11-diyl-bis(methanesulfonate) (**64**). The latter reacted with H_2O_2 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].

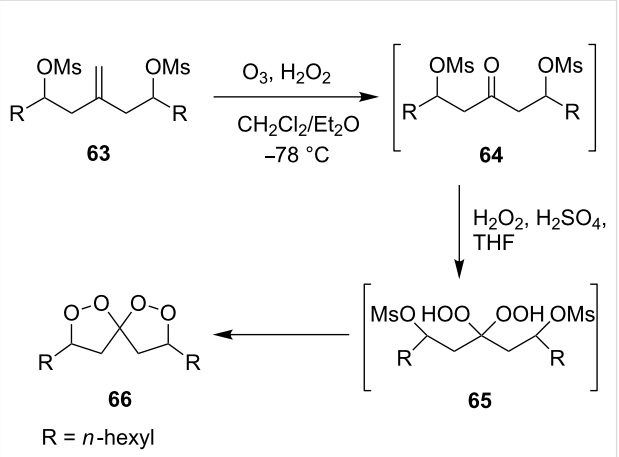
The treatment of 3,3'-(cyclohexa-3,6-diene-1,3-diyl)dipropan-1-ol (**67**) and 4,4'-(cyclohexa-3,6-diene-1,3-diyl)dibutan-2-ol (**69**)



Scheme 18: Peroxidation of 1,6-diene **56**.



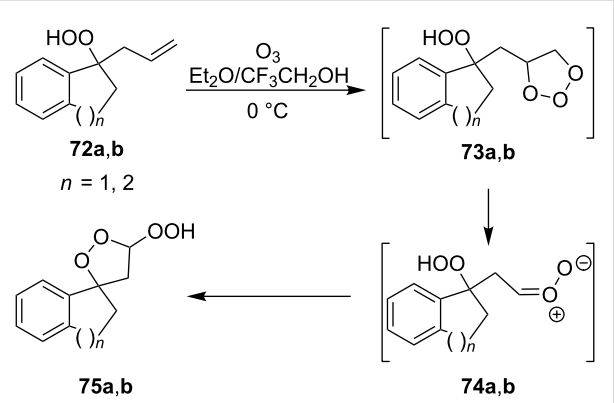
Scheme 19: Synthesis of 3-alkoxy-1,2-dioxolanes **62a**,**b**.



Scheme 20: Synthesis of spiro-bis(1,2-dioxolane) **66**.

with ozone in MeOH/CH_2Cl_2 followed by the addition of a catalytic amount of *p*-TsOH lead to the intramolecular peroxyketalization that proceeds through the formation of the peroxycarbenium 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-1*H*-indene (**72a**) and 1-allyl-1-hydroperoxy-1,2,3,4-tetrahydronaphthalene (**72b**), respectively, in an Et_2O/CF_3CH_2OH 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].



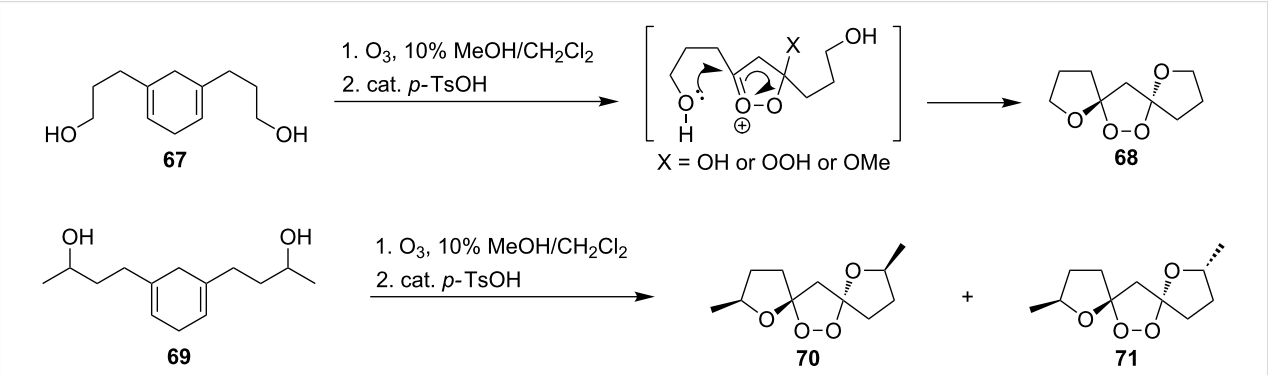
Scheme 22: Synthesis of spirohydroperoxydioxolanes **75a,b**.

Spirohydroperoxydioxolane **75a** (*n* = 1) was obtained in 71% yield (the diastereoisomeric ratio was 1:1); the yield of **75b** (*n* = 2) was 21% (the diastereoisomeric ratio was 1:1).

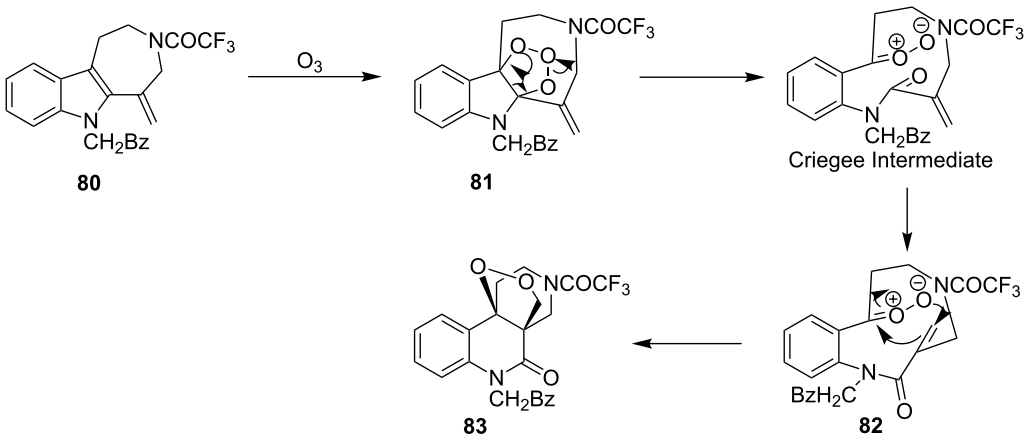
5'-Hydroperoxyspiro[chromane-2,3'-[1,2]dioxolane] (**77**, yield 18%) and (3*S*,5*S*)-3,5-dihydroperoxy-3-(3-phenylpropyl)-1,2-dioxolane (**79**, yield 22%) (Scheme 23) were synthesized in a similar way starting from 2-allyl-2-hydroperoxychromane (**76**) and (4,4-dihydroperoxyhept-6-enyl)benzene (**78**), respectively [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 (molozonide **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].

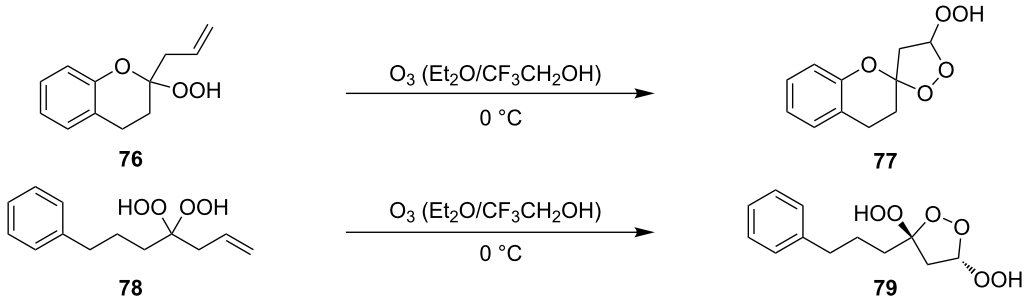
The peroxycarbenium ions produced by the decomposition of 1,2,4-trioxolanes can be trapped with allyltrimethylsilane. For example, the $SnCl_4$-mediated fragmentation of ozonides **84a–l**



Scheme 21: Synthesis of dispiro-1,2-dioxolanes **68**, **70**, **71**.



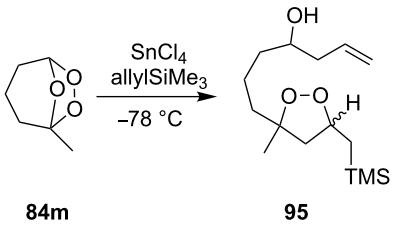
Scheme 24: Ozonolysis of azepino[4,5-*b*]indole **80**.



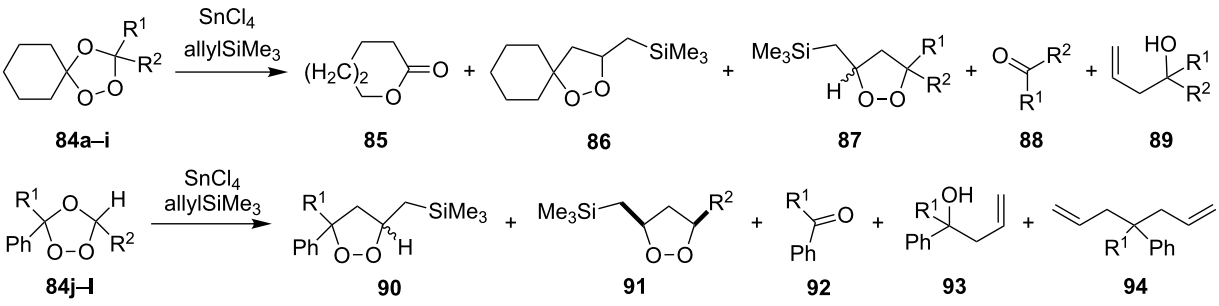
Scheme 23: Synthesis of spirohydroperoxydioxolane **77** and dihydroperoxydioxolane **79**.

in the presence of allyltrimethylsilane in dichloromethane gives a complex mixture of products **85**–**94**, including dioxolanes **86a–i**, **87i**, **90j–l**, and **91j** (Scheme 25, Table 8) [256].

Treatment of the bicyclic ozonide 1-methyl-6,7,8-trioxabicyclo[3.2.1]octane **84m**, with $SnCl_4$ 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].



Scheme 26: $SnCl_4$-mediated fragmentation of bicyclic ozonide **84m** in the presence of allyltrimethylsilane.



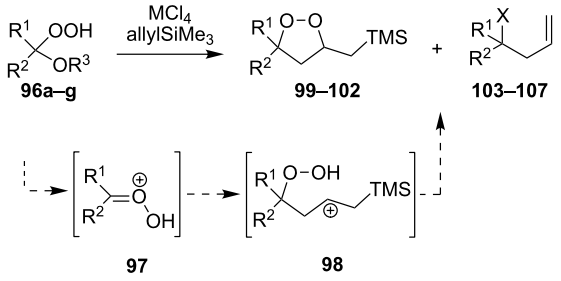
Scheme 25: $SnCl_4$-mediated fragmentation of ozonides **84a–l** in the presence of allyltrimethylsilane.

Table 8: The $SnCl_4$-mediated fragmentation of ozonides **84a–l** in the presence of allyltrimethylsilane.

				Yield, %				
Ozonide **84**	R^1	R^2	*T*, °C	Lactone **85**	Dioxolane **86**	Dioxolane **87**	Ketone **88**	Alcohol **89**
a	$-(CH_2)_4-$		−78 to 0	11	50	–	**88a** (traces)	–
b	$-(CH_2)_5-$		−78 to 0	17	57	–	**88b** (traces)	–
c	$-(CH_2)_6-$		−78 to 0	39	24	–	**88c** (traces)	–
d	CH_3	Ph	−78 to 0	25	61	–	**88d** (93%)	–
e	C_4H_9	C_4H_9	−78 to 0	40	14	–	**88e** (70%)	75
f	H	C_8H_{17}	−78	–	56	–	–	50
g	H	Ph	−78	–	79	–	–	13
h	H	H	−78	–	10	–	–	–
i	CH_3	$C(CH_3)_3$	−78 to 0	31	21	9 (*cis*)	–	–
Ozonide **84**	R^1	R^2	*T*, °C	Dioxolane **90** (*cis*:*trans*)	Dioxolane **91**	Carbonyl compound **92**	Alcohol **93**	Alkene **94**
j	H	C_3H_7	−78	15 (1:1)	7	39	**93j** (20%)	–
k	H	H	−78	15 (1:1)	–	22	**93j** (24%)	–
l	CH_3	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.

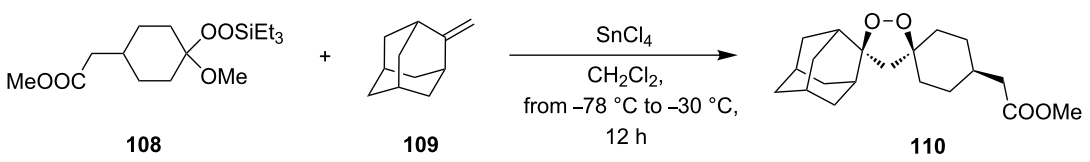
Dioxolanes **99–102** are produced from alkoxyhydroperoxides **96a–g** (ozonolysis products of alkenes) in a similar way. The first step results in the formation of peroxycarbenium ions **97**, which are trapped with allyltrimethylsilane under the formation of intermediate hydroperoxides **98**. Then 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].



Scheme 27: MCl_4-mediated fragmentation of alkoxyhydroperoxides **96** in the presence of allyltrimethylsilane.

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

Hydroperoxide **96**	R^1	R^2	R^3	M	Dioxolane **99–102** (yield, %)	Alkene **103–107** (X, yield, %)
a	Me	Me	Me	Ti	**99** (31)	–
b	Me	Me	$(CH_2)_2OMe$	Sn	**99** (56)	–
b	Me	Me	$(CH_2)_2OMe$	Ti	**99** (12)	**103** (–OOH, 23)
c	4-*tert*-butyl-cyclohexylidene		Me	Ti	–	**104** ($–O_2–$, 31)
c	4-*tert*-butyl-cyclohexylidene		Me	Sn	**100** (42)	–
d	4-*tert*-butyl-cyclohexylidene		$(CH_2)_2OMe$	Sn	**100** (59)	–
e	Me	$BnOCH_2$	Me	Ti	**101** (12)	**105** (=O, 62)
f	Bu	H	Me	Ti	**102** (7)	**106** (OMe, 63)
g	Bu	H	$(CH_2)_2OMe$	Ti	**102** (15)	**107** ($O(CH_2)_2OMe$, the yield was not determined)



108 109 110

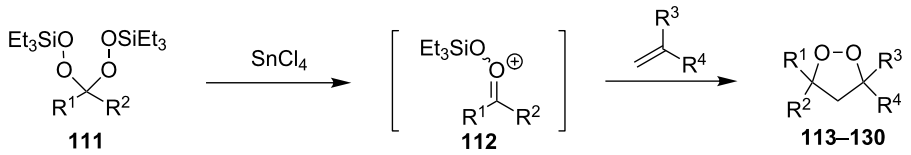
Scheme 28: $SnCl_4$-catalyzed reaction of monotriethylsilylperoxyacetal **108** with alkene **109**.

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'-dioxa-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



111 112 113–130

Scheme 29: $SnCl_4$-catalyzed reaction of triethylsilylperoxyacetals **111** with alkenes.

Table 10: Structures and yields of 1,2-dioxolanes **113–130**.

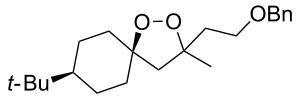
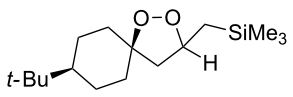
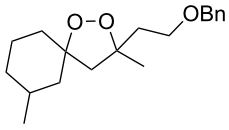
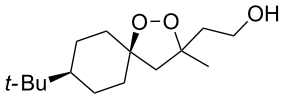
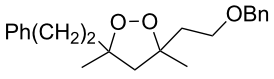
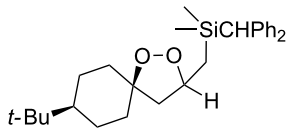
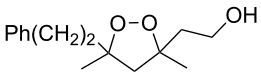
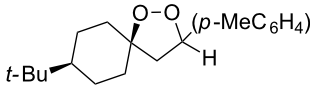
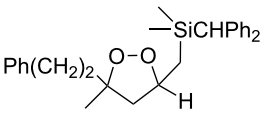
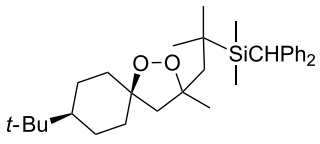
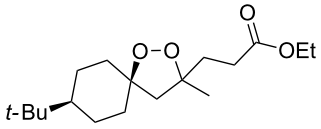
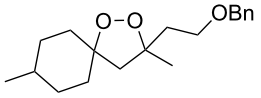
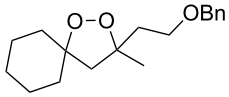
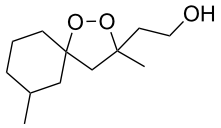
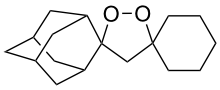
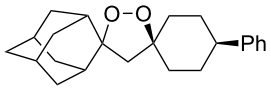
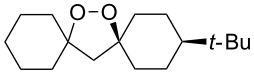
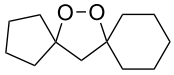
Product	Structure	Yield[a], %	Product	Structure	Yield[a], %
113		80	**122**		92
114		72	**123**		47
115		57	**124**		72
116		67	**125**		28
117		57	**126**		48

Table 10: Structures and yields of 1,2-dioxolanes **113–130**. (continued)

118		34	**127**		59
119		46	**128**		51
120		74	**129**		68
121		94	**130**		90

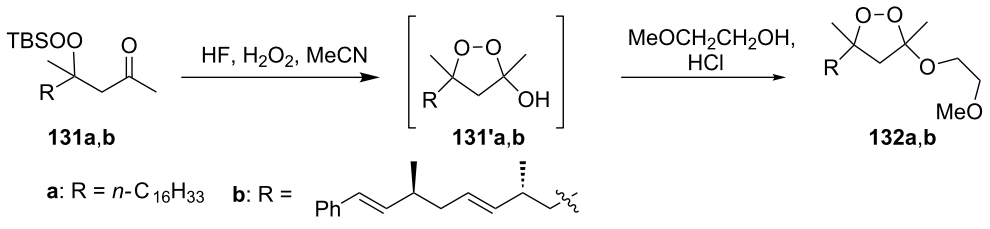
[a]Reagents and conditions: $SnCl_4$ (1.0–2.0 equiv), alkene (1.0–3.0 equiv), CH_2Cl_2, from −78 °C to 25 °C, 2–24 h.

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

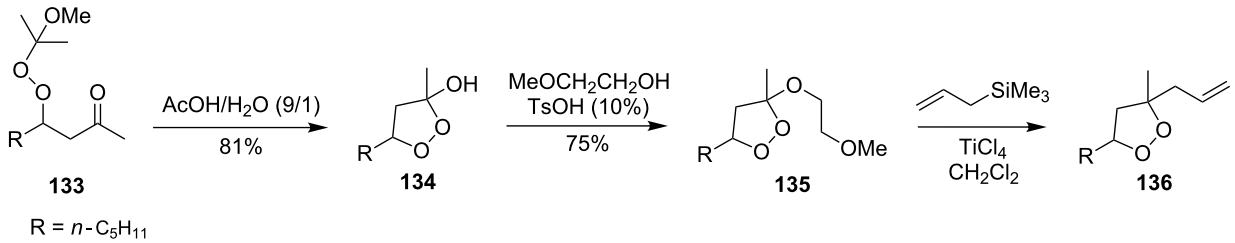
The desilylation of *tert*-butyldimethylsilylperoxy ketones **131a**,**b** with HF followed by cyclization and subsequent reaction with monomethylethylene glycol afforded dioxolanes **132a**,**b** in 75 and 88% yield, respectively. The intermediate hydroxydioxolanes **131'a**,**b** were used in the second 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].

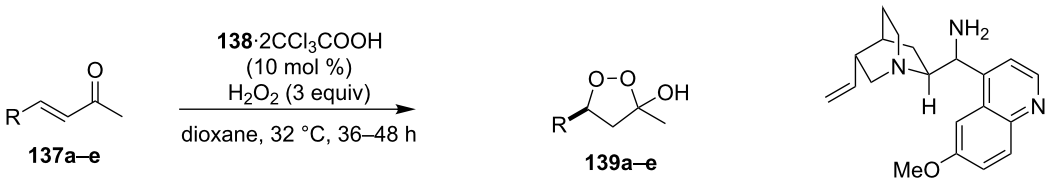
The asymmetric peroxidation of methyl vinyl ketones **137a–e** with 9-amino-9-deoxyepiquinine **138** and CCl_3COOH afforded



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



Scheme 31: Deprotection of peroxide **133** followed by cyclization.



	R	Yield, %
139a	iC_6H_{13}	65
139b	$PhCH_2CH_2$	68
139c	$CH_2=CHCH_2$	69
139d	iBu	61
139e	cyclohexyl	54

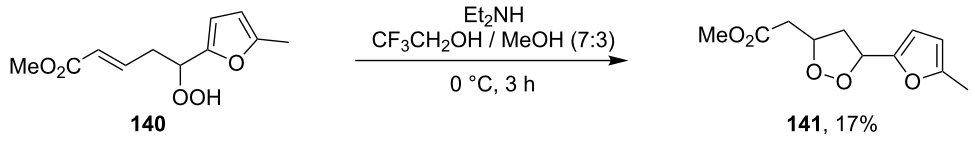
Scheme 32: Asymmetric peroxidation of methyl vinyl ketones **137a–e**.

hydroxydioxolanes **139a–e** with high enantiomeric excess (ee 94–95%) (Scheme 32) [262].

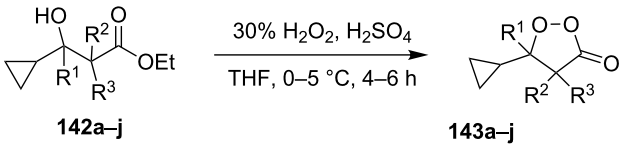
The Kobayashi synthesis of 1,2-dioxolanes represents an intramolecular version of the Michael reaction, in which the hydroperoxide group acts as the nucleophile. Generally, the reaction is performed in fluorinated alcohols (CF_3CH_2OH or $(CF_3)_2CHOH$) in the presence of diethylamine or, in some cases, 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.



Scheme 33: Et_2NH-catalyzed intramolecular cyclization.



	R^1	R^2	R^3	Yield, %
143a	Me	H	H	80
143b	Me	H	Me	38
143c	cyclopropyl	H	H	69
143d	cyclopropyl	H	Me	39
143e	cyclopropyl	H	Et	35

	R^1	R^2	R^3	Yield, %
143f	Ph	H	H	42
143g	4-chlorophenyl	H	H	55
143h	Me	H	Et	52
143i	Me	Me	Me	33
143j	cyclopropyl	Me	Me	30

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-tetrahydronapthalene (**145**) gives hydroperoxide-containing bromonium cation **147** as the intermediate, which undergoes cyclization to form 1,2-dioxolane-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

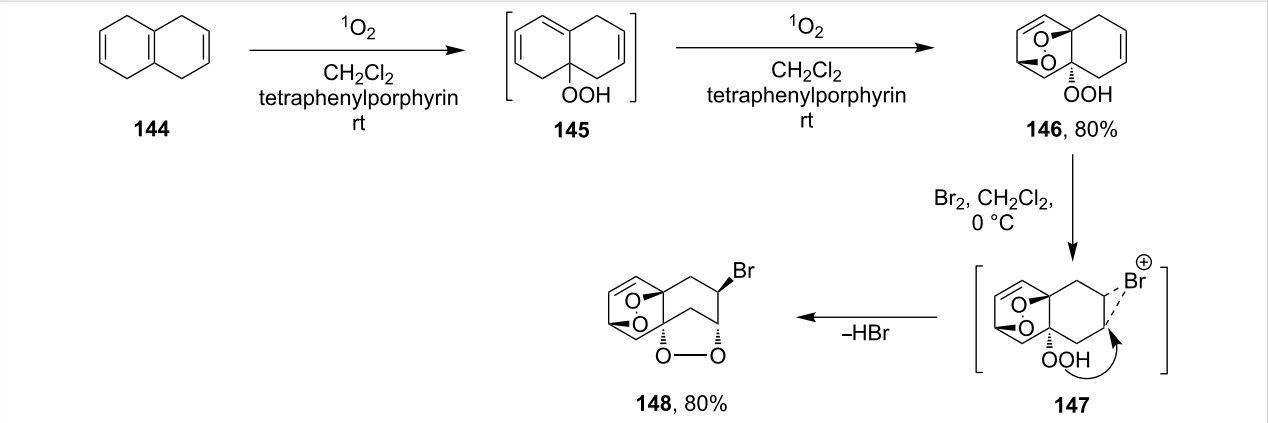
1,2-Dioxolane-containing compounds **150a–d** were synthesized by the oxidation of triterpenes **149a–d** with $Na_2Cr_2O_7$/*N*-hydroxysuccinimide (Scheme 36). The resulting compounds exhibit antitumor activity comparable with that of betulinic acid [175-177].

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

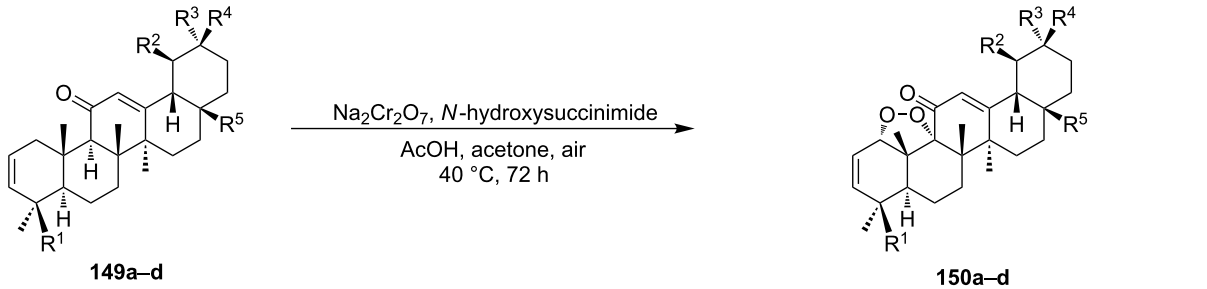
The possibility of performing the Curtius and Wolff rearrangements to form 1,2-dioxolane ring-retaining products was exemplified by the synthesis of ethyl (3,5,5-trimethyl-1,2-dioxolan-3-yl)methylcarbamate (**152**) and methyl 3-(3,5,5-trimethyl-1,2-dioxolan-3-yl)propanoate (**154**) (through formation of stable diazodioxolane **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_4NF and H_2O_2 (Scheme 38) [259].

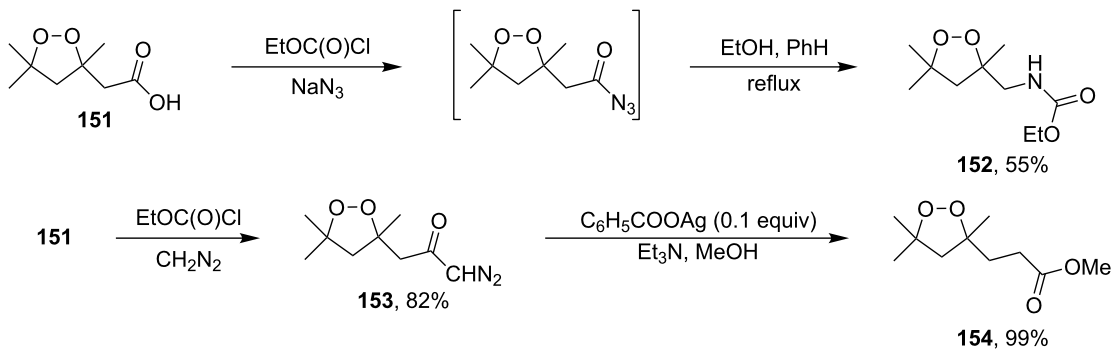
Dioxolane **158** with the aminoquinoline antimalarial pharmacophore was synthesized in two steps by the oxidation of alcohol **156** with $H_5IO_6/RuCl_3$ followed by amidation of the



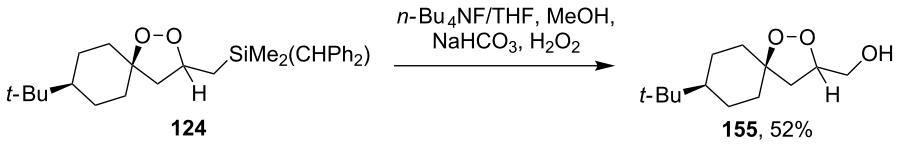
Scheme 35: Haloperoxidation accompanied by intramolecular ring closure.



Scheme 36: Oxidation of triterpenes **149a–d** with $Na_2Cr_2O_7$/*N*-hydroxysuccinimide.



Scheme 37: Curtius and Wolff rearrangements to form 1,2-dioxolane ring-retaining products.



Scheme 38: Oxidative desilylation of peroxide **124**.

acid **157** (Scheme 39) [88]. It was shown that compound **158** exhibits antimalarial activity comparable with that of artemisinin [88].

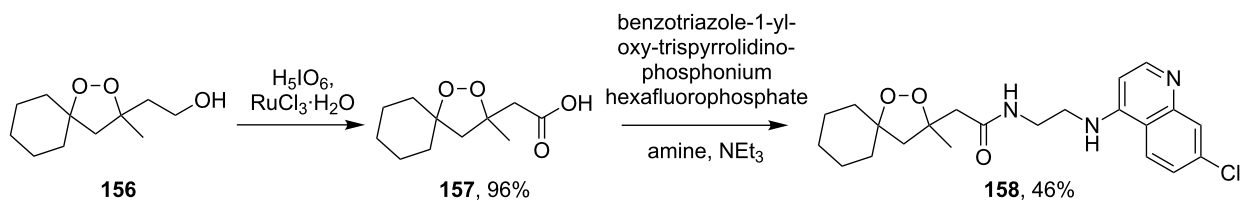
Plakinic acids belong to a large family of natural products, which were shown to be highly cytotoxic toward cancer cells and fungi. Diastereomers of plakinic acid A, **162a** and **162b** were synthesized starting from dioxolane ((*R*)-3-((2*R*,3*E*,6*S*,7*E*)-2,6-dimethyl-8-phenylocta-3,7-dienyl)-5-(2-methoxyethoxy)-3,5-dimethyl-1,2-dioxolane) (**159**) [260]. In the first step, dioxolane **159** was treated with (1-(ethylthio)vinyloxy)-trimethylsilane in the presence of $TiCl_4$ to obtain *S*-ethyl 2-((*R*)-5-((2*R*,3*E*,6*S*,7*E*)-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)

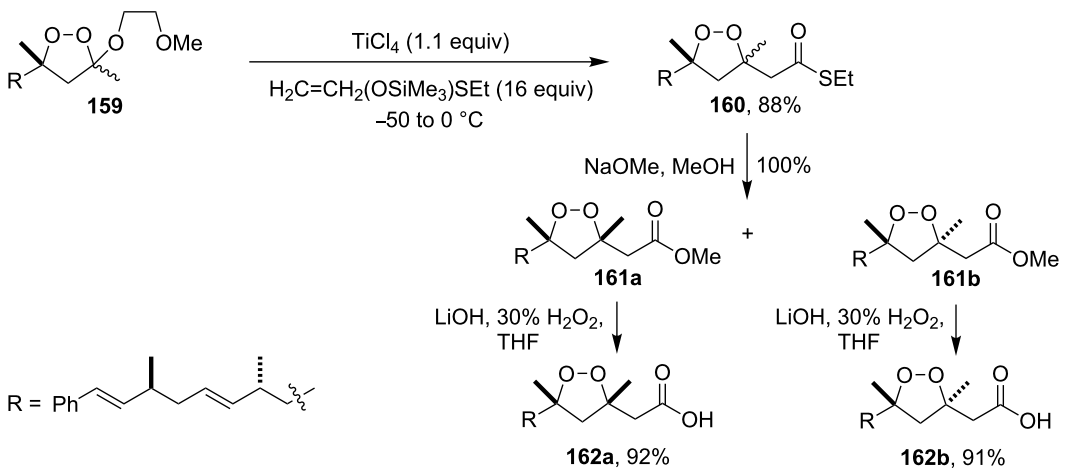
The currently most widely used methods for the synthesis of 1,2,4-trioxolanes are based on reactions of ozone with unsaturated compounds, such as the ozonolysis of alkenes, the cross-ozonolysis of alkenes with carbonyl compounds, and the cross-ozonolysis of O-alkylated oximes in the presence of carbonyl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

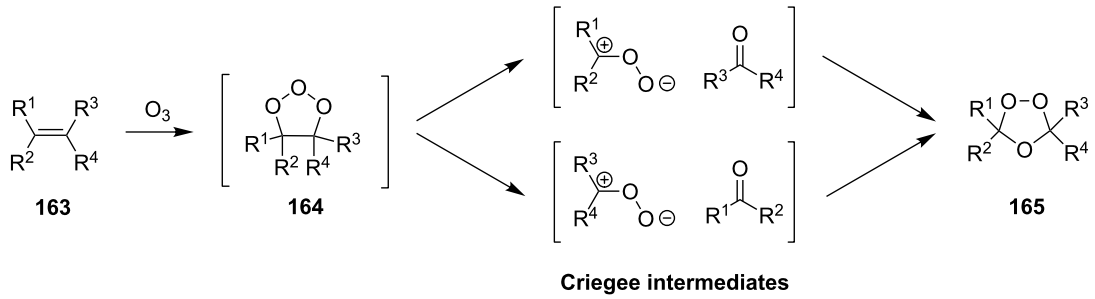


Scheme 39: Synthesis of dioxolane **158**, a compound containing the aminoquinoline antimalarial pharmacophore.



Scheme 40: Diastereomers of plakinic acid A, **162a** and **162b**.

unstable 1,2,3-trioxolane **164** (so-called molozonide) that is followed by its decomposition to a peroxycarbenium 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.



Scheme 41: Ozonolysis of alkenes.

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

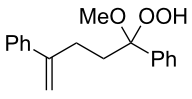
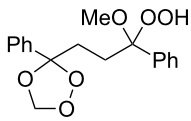
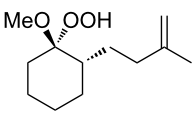
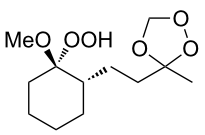
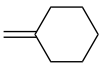
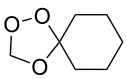
Alkene **163**	Ozonolysis conditions	1,2,4-Trioxolane **165**	Yield, %	Reference
	Et_2O, −70 °C		24	[270]
	Et_2O, −70 °C		27	[270]
	hexane, −78 °C		78	[256]

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

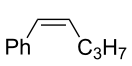
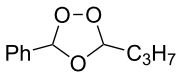
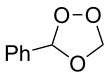
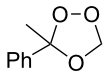
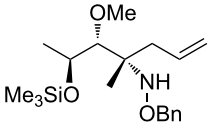
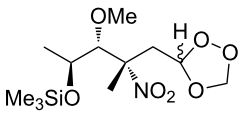
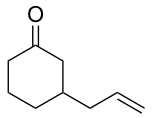
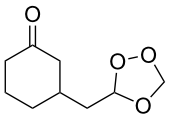
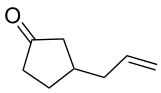
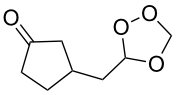
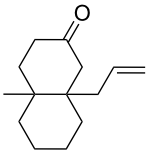
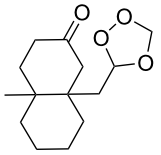
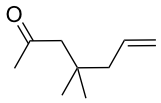
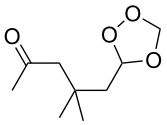
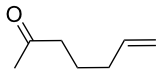
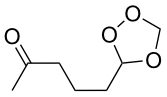
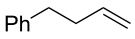
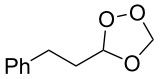
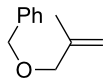
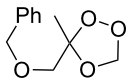
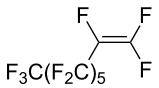
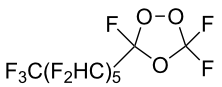
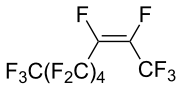
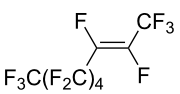
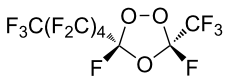
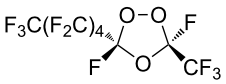
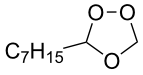
	hexane, −78 °C		73	[256]
	hexane, −78 °C		77	[256]
	hexane, −78 °C		61	[256]
	isooctane/CCl_4, −78 °C, 1 h		>82	[271]
	CH_2Cl_2, −78 °C		95	[272]
	CH_2Cl_2, −78 °C		90	[272]
	CH_2Cl_2, −78 °C		92	[272]
	CH_2Cl_2, −78 °C		93	[272]
	CH_2Cl_2, −78 °C		93	[272]
	CH_2Cl_2, −78 °C		94	[272]
	pentane, −78 °C		63	[272]
	freon-113, 15–20 °C, 2 h		The yield was not determined	[273,274]
 	freon-113, 15–20 °C, 2 h	 	The yield was not determined	[273]
	CH_2Cl_2, −78 °C		96	[275]

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

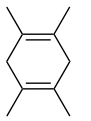
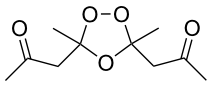
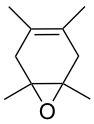
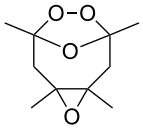
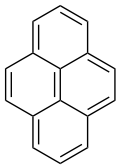
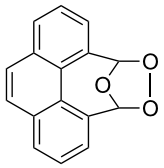
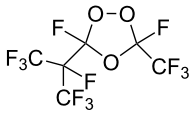
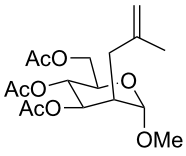
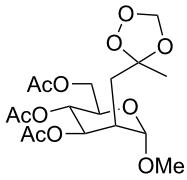
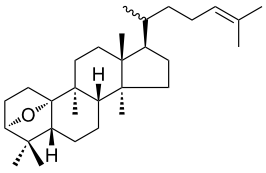
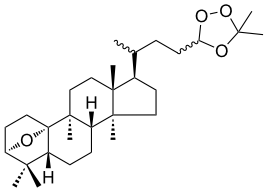
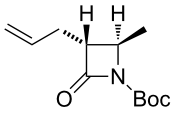
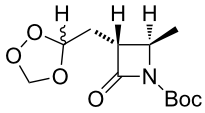
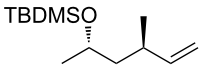
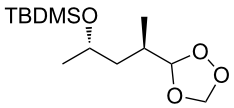
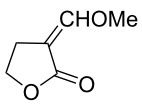
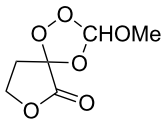
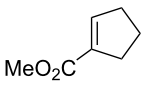
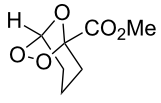
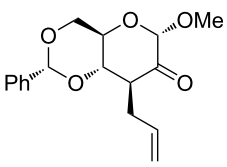
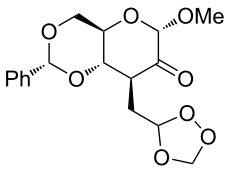
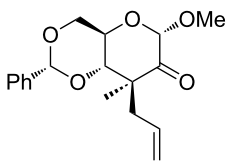
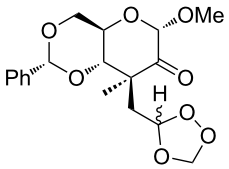
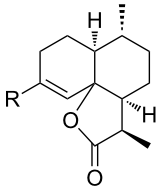
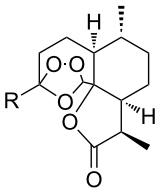
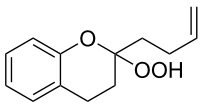
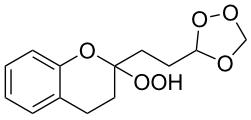
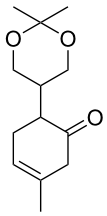
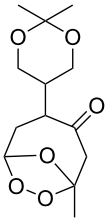
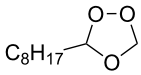
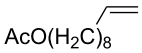
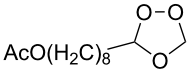
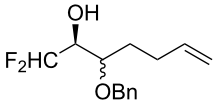
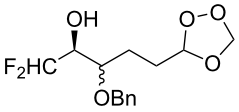
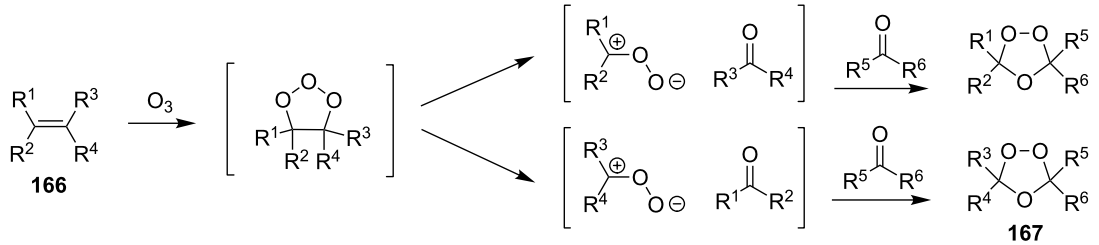
	polymer-based, −78 °C, 8 h		23	[276]
	polymer-based, −78 °C, 3 h		38	[276]
	CH_2Cl_2, −70 °C		48	[277]
$(F_3C)_2FCFC{=}CFCF_3$	without solvent, −133 to −43 °C		100	[278]
	1) CH_2Cl_2, −78 °C, 15 min. 2) Me_2S, rt, 6 h		71	[279]
	hexane, −78 °C, 30 min		6	[280]
	CH_2Cl_2, −78 °C, 20 min		The yield was not determined	[281]
	CH_2Cl_2, −78 °C, 2 h		>97	[282]
	$CDCl_3$, −65 °C		88	[283]
	$CFCl_3$, −70 °C		100	[283]
	CH_2Cl_2, −78 °C, 1 h		85	[284]

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

	CH_2Cl_2, −78 °C, 1 h		70	[285]
 R = Me, Et, Pr, iPr, iBu, E	pentane, −78 °C	 R = Me, Et, Pr, iPr, iBu, E	10-30	[148-152]
	Et_2O/CH_3OH, −78 °C		12	[254]
	CH_2Cl_2, −78 °C		92	[286]
	CH_2Cl_2, 0 °C		95	[287,288]
	H_2O/CH_2Cl_2, 0 °C		72	[289]
	1) SiO_2, −78 °C; 2) Me_2S, MeOH		30	[290]

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).



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

Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds.

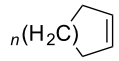
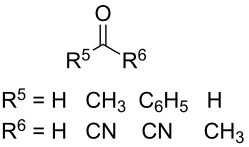
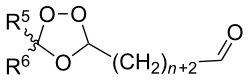
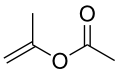
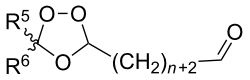
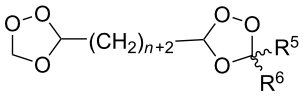
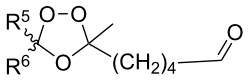
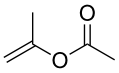
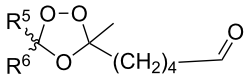
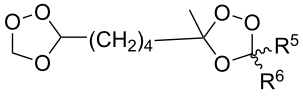
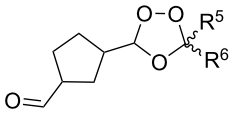
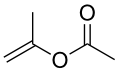
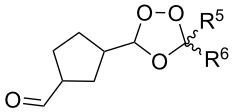
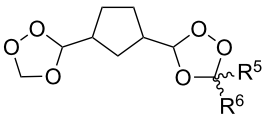
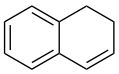
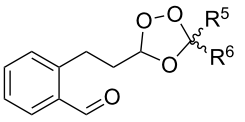
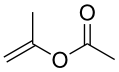
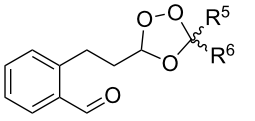
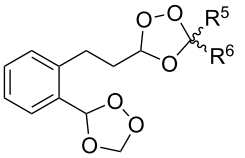
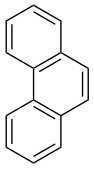
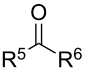
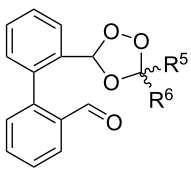
Alkene **166**	Carbonyl compound	Ozonolysis conditions	1,2,4-Trioxolane **167**	Yield, %	Reference
 *n* = 1, 2, 3, 4, 8	 R^5 = H CH$_3$ C$_6$H$_5$ H R^6 = H CN CN CH$_3$	CH_2Cl_2, −78 °C		17–74	[291]
	 R^5 = H CH$_3$ C$_6$H$_5$ H R^6 = H CN CN CH$_3$	CH_2Cl_2, −78 °C		9–57	[291]
	 R^5 = H CH$_3$ R^6 = H CN	CH_2Cl_2, −78 °C		50 42	[291]
	 R^5 = H CH$_3$ R^6 = H CN	CH_2Cl_2, −78 °C		38 32	[291]
	 R^5 = CH$_3$ C$_6$H$_5$ H R^6 = CN CN CH$_3$	CH_2Cl_2, −78 °C		18–48	[291]
	 R^5 = CH$_3$ C$_6$H$_5$ H R^6 = CN CN CH$_3$	CH_2Cl_2, −78 °C		25–37	[291]
	 R^5 = H CH$_3$ C$_6$H$_5$ H R^6 = H CN CN CH$_3$	CH_2Cl_2, −78 °C		63–80	[291]
	 R^5 = H CH$_3$ C$_6$H$_5$ H R^6 = H CN CN CH$_3$	CH_2Cl_2, −78 °C		55–77	[291]
	 R^5 = H CH$_3$ C$_6$H$_5$ R^6 = H CN CN	CH_2Cl_2, −78 °C		49–74	[291]

Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds. (continued)

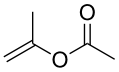
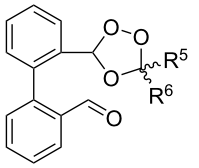
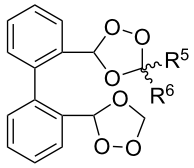
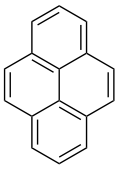
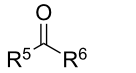
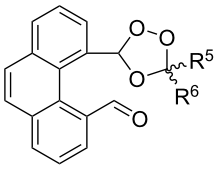
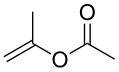
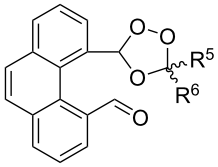
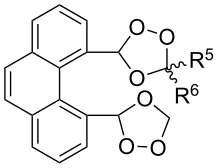
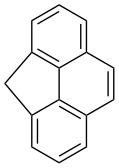
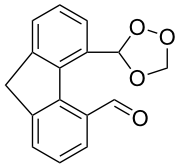
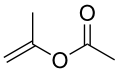
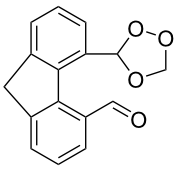
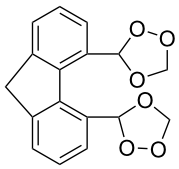
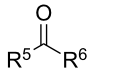
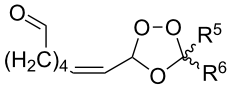
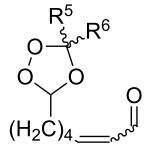
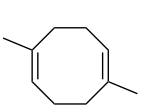
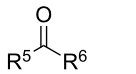
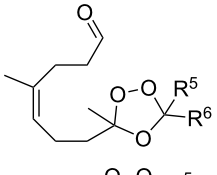
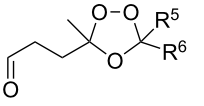
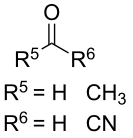
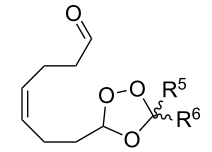
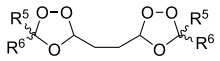
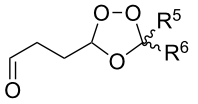
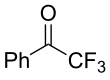
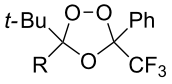
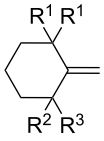
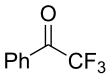
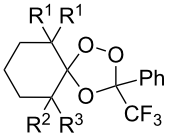
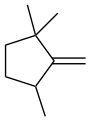
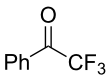
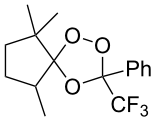
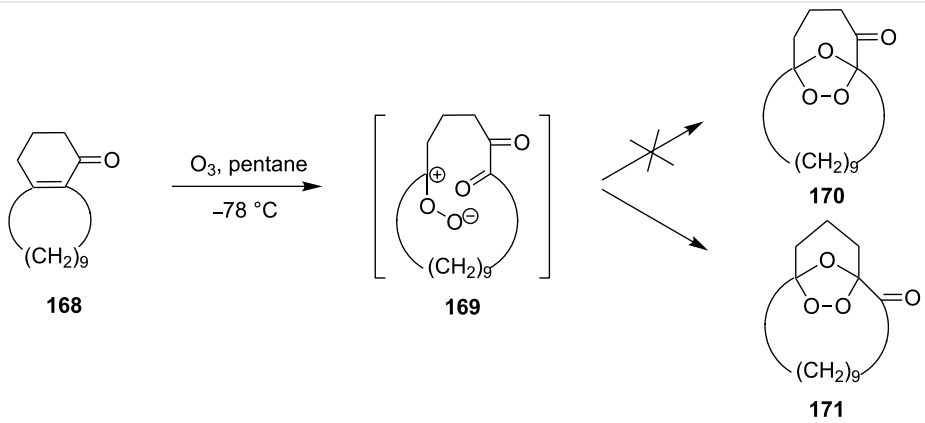
	 R^5 = H CH_3 C_6H_5 R^6 = H CN CN	CH_2Cl_2, −78 °C		63–66	[291]
	 R^5 = H CH_3 R^6 = H CN	CH_2Cl_2, −78 °C		52 62	[291]
	 R^5 = H CH_3 R^6 = H CN	CH_2Cl_2, −78 °C		41 46	[291]
		CH_2Cl_2, −78 °C		82	[291]
		CH_2Cl_2, −78 °C		26	[291]
	 R^5 = H CH_3 R^6 = H CN	CH_2Cl_2, −78 °C	 	58 53 21 21	[292] [292]
	 R^5 = H CH_3 R^6 = H CN	CH_2Cl_2, −78 °C	 	23 25 68 60	[292] [292]

Table 12: Examples of 1,2,4-trioxolanes synthesized by the cross-ozonolysis of alkenes in the presence of carbonyl compounds. (continued)

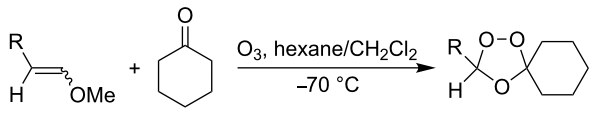
		CH_2Cl_2, −78 °C		30 25	[292]
				15 14	[292]
				25 27	[292]
 R = Me, iPr		Et_2O, −70 °C		60 56	[293]
 **a** R^1 = H; R^2 = H; R^3 = H **b** R^1 = H; R^2 = -$(CH_2)_4$- = R^3		Et_2O, −70 °C		59 65	[293]
		Et_2O, −70 °C		59	[293]

For the ozonolysis of the bicyclic cyclohexenone, 2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-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**.



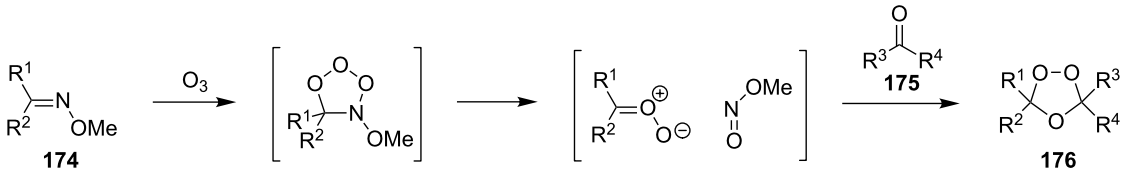
172a R = C_8H_{17}
172b R = Ph

173a, 47%
173b, 65%

Scheme 44: Cross-ozonolysis of enol ethers **172a**,**b** with cyclohexanone.

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 tetrasubstituted 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 45: Griesbaum co-ozonolysis.

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

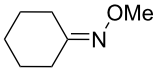
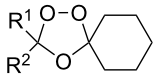
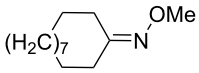
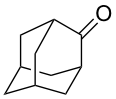
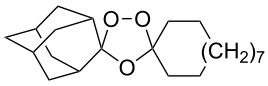
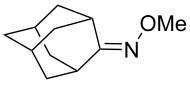
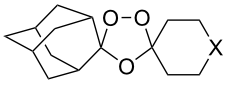
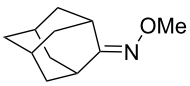
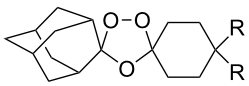
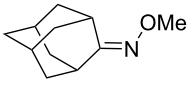
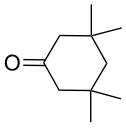
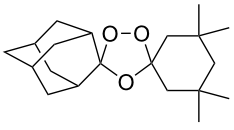
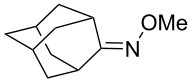
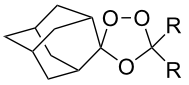
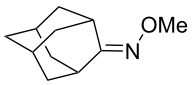
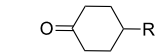
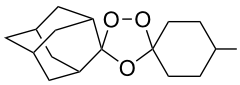
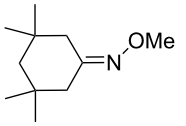
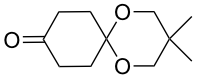
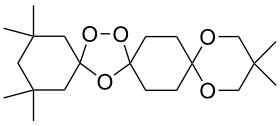
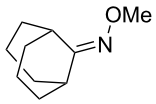
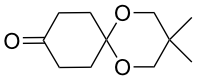
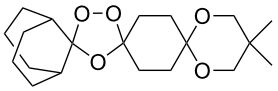
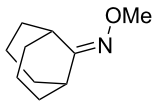
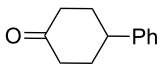
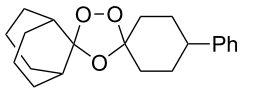
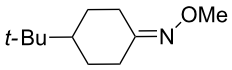
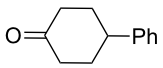
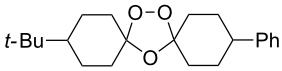
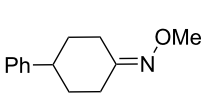
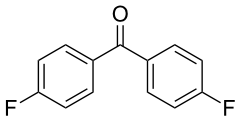
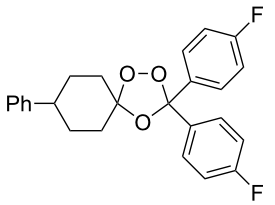
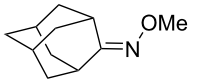
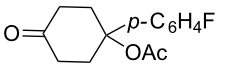
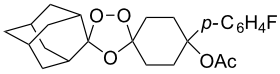
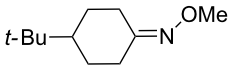
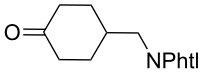
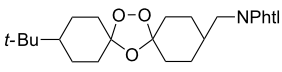
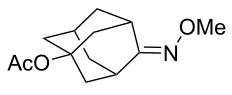
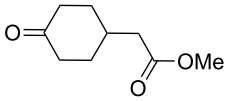
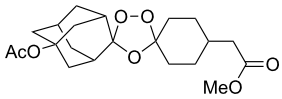
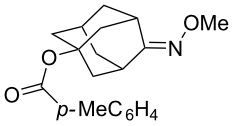
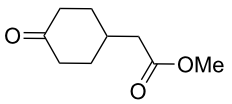
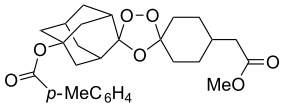
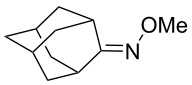
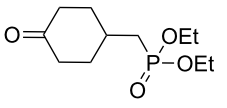
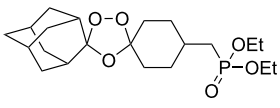
Oxime **174**	Ketone **175**	Ozonolysis conditions	1,2,4-Trioxolane **176**	Yield, %	Ref.
	 R^1 = -$(CH_2)_4$- = R^2 R^1 = -$(CH_2)_5$- = R^2 R^1 = -$(CH_2)_6$- = R^2 R^1 = CH_3; R^2 = Ph R^1 = C_4H_9; R^2 = C_4H_9	hexane, −78 °C		47–67	[256]
		pentane, CH_2Cl_2, 0 °C		54	[91]
	 X = CH_2, C=O, O, NCO_2Et, SO_2, NCO_2t-Bu NCOR, NSO_2R R = Alk, Ar	pentane, CH_2Cl_2, 0 °C		10–75	[91,94] [95,296]
	 R = $OCH_2C(CH_3)_2CH_2O$, Me, Ph, CO_2Et	pentane, CH_2Cl_2, 0 °C		23–50	[91-93]
		pentane, 0 °C		48	[92,93]

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

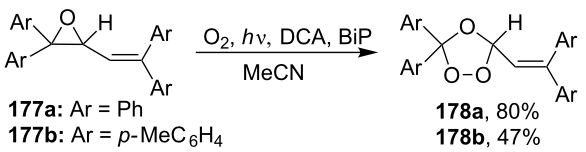
	 R = Ph, Bn, *p*-$C_6H_4CO_2Et$, 2-pyridyl	pentane, CH_2Cl_2, 0 °C		32–58	[91-93]
	 R = *n*-Pr, iPr, *t*-Bu, *p*-C_6H_4OA phthalimido, CH_2OAc, CH_2COOEt, $CH_2SO_2C_6H_5$, phthalimidomethyl, COOEt $COOCH_2C(CH_3)_3$, $COON(CH_2CH_3)_2$, *p*-$C_6H_4SO_2Me$, *p*-C_6H_4F *p*-$C_6H_4CO_2Et$	pentane, CH_2Cl_2, 0 °C		20–70	[91-93,96] [97,297]
		pentane, 0 °C		38	[91]
		pentane, 0 °C		41	[91]
		pentane, CH_2Cl_2, 0 °C		33	[91]
		hexane, CH_2Cl_2, 0 °C		17	[91]
		pentane, CH_2Cl_2, 0 °C		27	[91]
		pentane, CH_2Cl_2, 0 °C		53	[92,93]
		pentane, CH_2Cl_2, 0 °C		n.d.[a]	[96,97]
		cyclohexane CH_2Cl_2, 0 °C		30	[298]
		cyclohexane CH_2Cl_2, 0 °C		54	[298]
		cyclohexane, CH_2Cl_2, 0 °C		78	[258]

[a]Yield 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

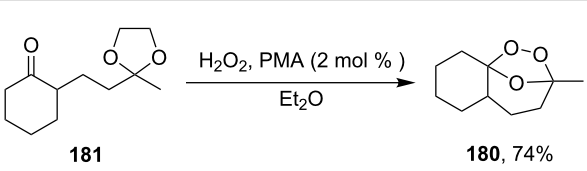
The reactions of aryloxiranes **177a**,**b** with oxygen in the presence of 9,10-dicyanoanthracene (DCA) and biphenyl (BiP) under irradiation produced 1,2,4-trioxolanes **178a** and **178b** (Scheme 46). It should be noted that the oxirane moiety is oxidized rather than the double bond in these reactions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



Scheme 46: Reactions of aryloxiranes **177a**,**b** with oxygen.

This unusual result was obtained upon treatment of the hydroxydioxepane, 3-methoxy-3-methyloctahydro-3*H*-benzo[*c*][1,2]dioxepin-9a-ol (**179**) with TMSOTf/Et_3SiH. Thus, the peroxide moiety was not reduced with Et_3SiH, and the reaction produced the bicyclic peroxide, 1-methyl-10,11,12-trioxatricyclo[7.2.1.$0^{4,9}$]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].



Scheme 48: Formation of 1,2,4-trioxolane **180** by the reaction of 1,5-ketoacetal **181** with H_2O_2.

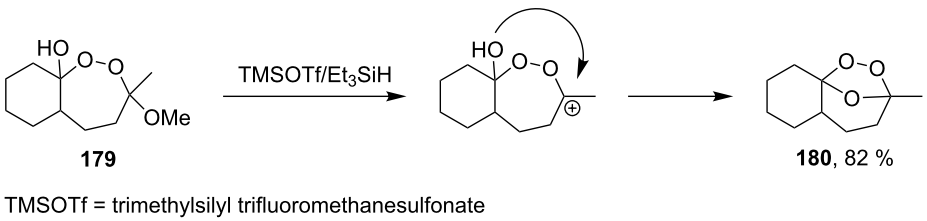
2.5. Structural modifications, in which 1,2,4-trioxolane ring remains intact

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

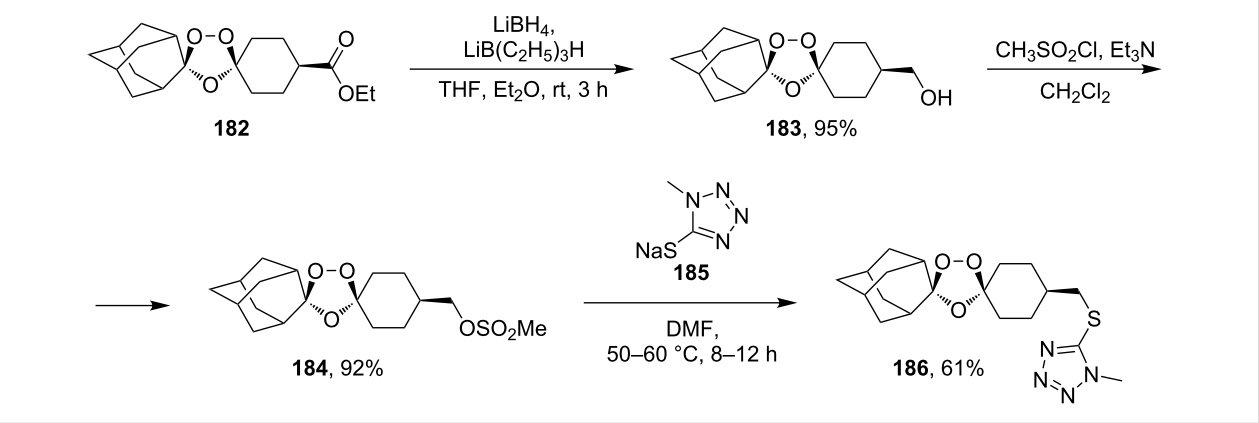
Ozonide **188** was synthesized by Mitsunobu reaction of alcohol **183** with pyridin-4-ol (**187**) (Scheme 50) [93]. It should be emphasized that this method can be applied in spite of the use of triphenylphosphine, which is a strong reducing agent for peroxides.

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].

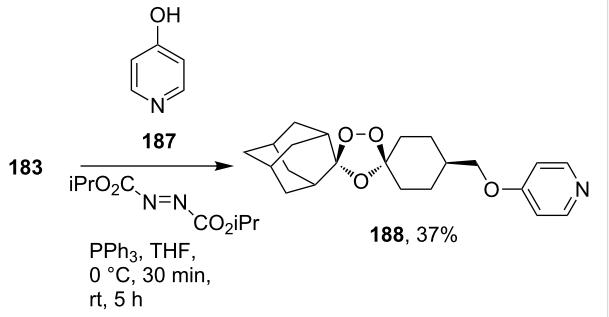
Aminoquinoline-containing 1,2,4-trioxalane **191** was synthesized by reductive amination of adamantane-2-spiro-3'-8'-oxo-



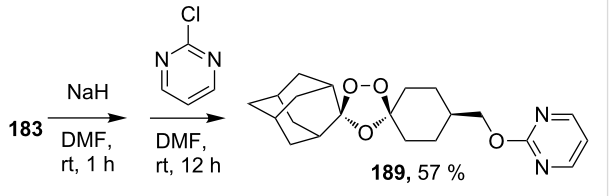
Scheme 47: Intramolecular formation of 1,2,4-trioxolane **180**.



Scheme 49: 1,2,4-Trioxolane **186** with tetrazole fragment.



Scheme 50: 1,2,4-Trioxolane **188** with a pyridine fragment.



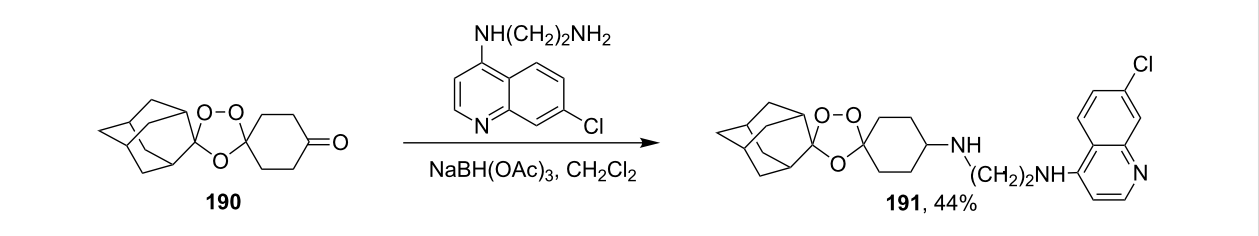
Scheme 51: 1,2,4-Trioxolane **189** with pyrimidine fragment.

1’,2’,4’-trioxaspiro[4.5]-decane **190** (Scheme 52). Ozonide **191** is an example of a combination of two known antiparasitic pharmacophores, viz. a peroxide and an aminoquinoline moiety [296].

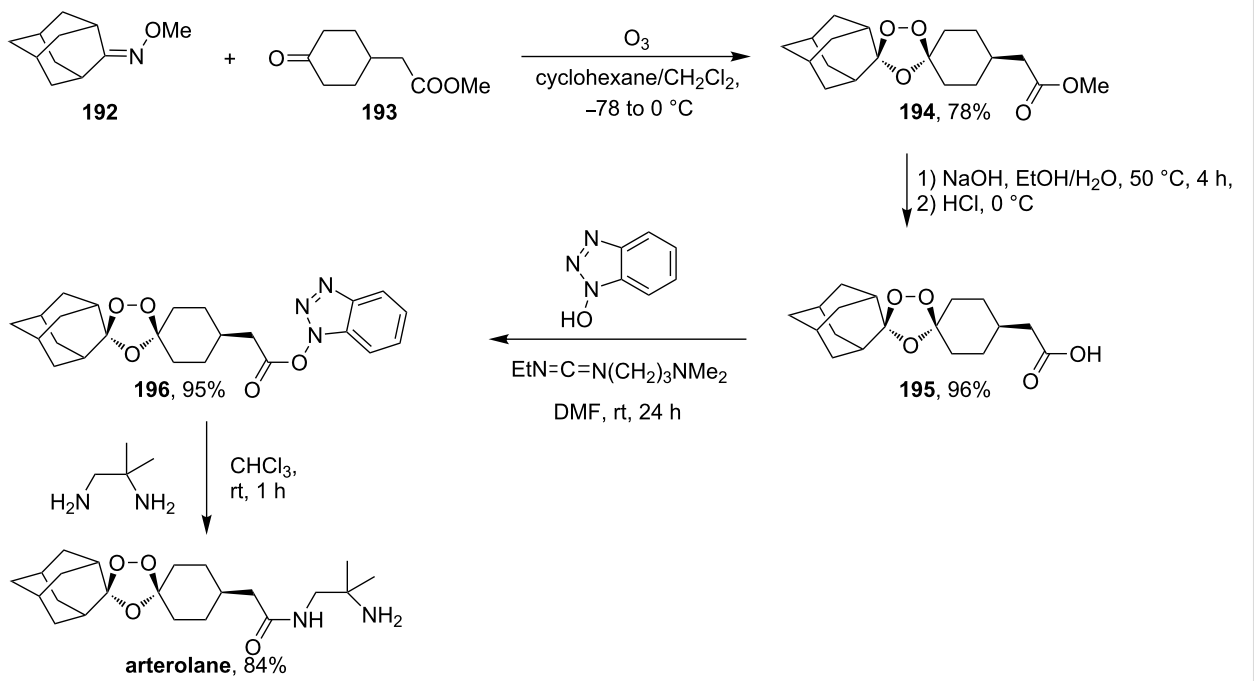
Arterolane is a fully synthetic 1,2,4-trioxalane, also known as OZ277. It has high antimalarial activity and is currently in the final stage of clinical trials. As drug, this compound is used in combination with piperaquine. The synthesis of arterolane is based on the Griesbaum coozonolysis of a mixture of adamantan-2-one *O*-methyloxime (**192**) and 4-carbomethoxycyclohexanone **193** to form *cis*-adamantane-2-spiro-3’-8’-methoxycarbonylmethyl-1’,2’,4’-trioxaspiro[4.5]decane **194**. The latter is hydrolyzed to *cis*-adamantane-2-spiro-3’-8’-carboxymethyl-1’,2’,4’-trioxaspiro[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 52: Synthesis of aminoquinoline-containing 1,2,4-trioxalane **191**.

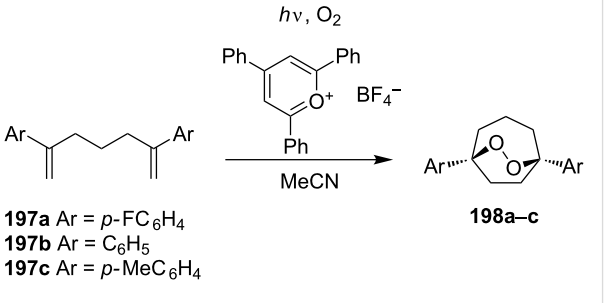


Scheme 53: Synthesis of arterolane.

pation of halogenonium ion donors, acid-mediated rearrangements of peroxides, the palladium-catalyzed cyclization of compounds with C=C and –O–O– groups, and reactions with the participation of peroxycarbenium ions.

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

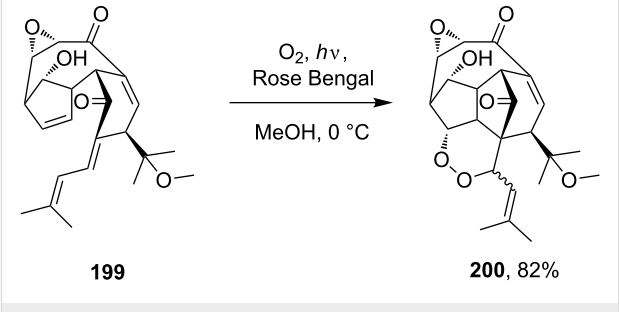
The oxidation of diarylheptadienes **197a–c** with singlet oxygen in acetonitrile afforded bicyclic peroxides **198a–c** in 33–58% yields. 2,4,6-Triphenylpyrylium tetrafluoroborate was used as the sensitizer for singlet oxygen generation (Scheme 54) [301].



Scheme 54: Oxidation of diarylheptadienes **197a–c** with singlet oxygen.

It was found that tris(bipyrazyl)ruthenium(II) [$(Ru(bpz)_3(PF_6)_2$] is an excellent photocatalyst for the synthesis of 1,2-dioxanes by aerobic photooxygenation of α,ω-dienes [302].

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

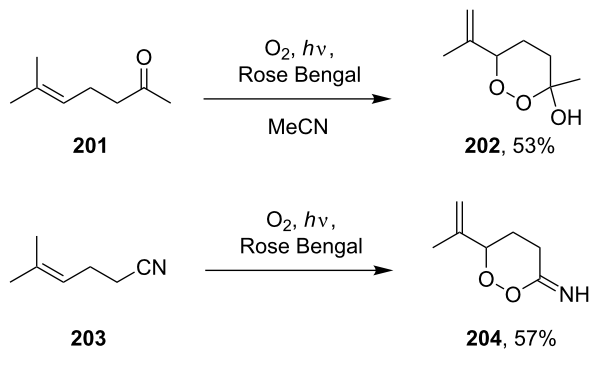


Scheme 55: Synthesis of hexacyclinol peroxide **200**.

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].

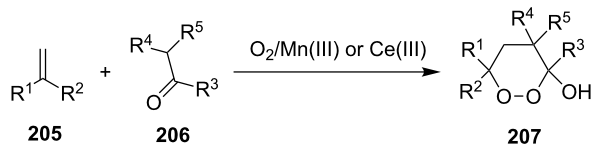
3.2. Oxidative coupling of carbonyl compounds and alkenes in the presence of manganese or cerium salts

The synthesis of 1,2-dioxanes **207** is based on the addition of alkene **205** and oxygen to carbonyl compound **206** via the inter-



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

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).

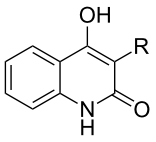
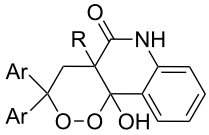
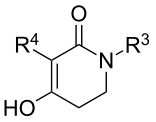
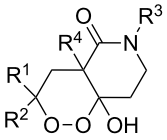
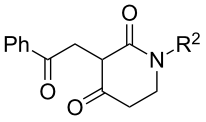
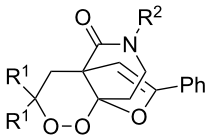
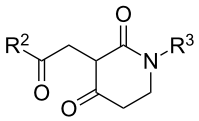
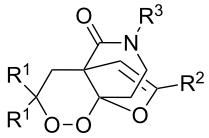


Scheme 57: Synthesis of 1,2-dioxanes **207** by oxidative coupling of carbonyl compounds **206** and alkenes **205**.

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	O	$Mn(OAc)_2$, O_2, AcOH, 80 °C, 10 h	Ph, O–O, OH	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	$Mn(OAc)_3$, air, AcOH, 23 °C, 0.5–24 h	CO_2R^4, R^1, R^2, O–O, OH	20–84	[306]
R, Ph R = H, Me	Y = OEt, OMe *n* = 0, 1, 2	$CeCl_3{\times}7H_2O$, air, iPrOH, rt, 16 h	HO, Ph, COY	42–87	[307]
R, Ph R = H, Me	X = O, NCH_2Ph	$CeCl_3{\times}7H_2O$, air, iPrOH, rt, 16 h	R, Ph, X, O–O, OH	5–73	[307]
Ph	*n* = 1, 2	$CeCl_3{\times}7H_2O$, air, iPrOH, rt, 14–16 h	$n(H_2C)$, Me, HO, Ph, O–O	19 (*n* = 1), 33 (*n* = 2)	[308]
Ph	OEt	$CeCl_3{\times}7H_2O$, air, iPrOH, rt, 14–16 h	EtO_2C, Ph, O–O, OH	18	[308]

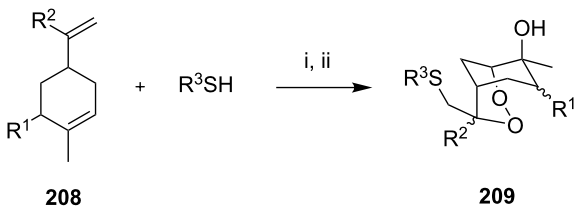
Table 14: Examples of 1,2-dioxanes **207** synthesized by oxidative coupling of carbonyl compounds **206** and alkenes **205**. (continued)

 Ar = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$	 R = Me, Pr, Bu, Ph	Mn(OAc)$_3$, air, AcOH, 23 °C, 15–18 h		22–89	[309]
 R^1 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, Et, Me, *n*-C$_7$H$_{15}$ R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, Et, Me, H	 R^3 = Me, Et, Pr, iPr, Ph, PhCH$_2$ R^4 = CO$_2$Et, CO$_2$iPr, H	Mn(OAc)$_3$, air, AcOH, 23 °C, 9–18 h		17–99	[310]
 R^1 = Ph, 4-ClC$_6$H$_4$	 R^2 = PhCH$_2$, Et	Mn(OAc)$_3$, air, AcOH, reflux, 10 min		9–11	[311]
 R^1 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 2-naphthyl	 R^2 = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, *t*-Bu R^3 = Me, Et, Pr, iPr, *t*-Bu, Ph, PhCH$_2$,	Mn(OAc)$_3$, air, AcOH, rt, 3.5–7.5 h		8–75	[312]

3.3. Oxidation of 1,5-dienes in the presence of thiols

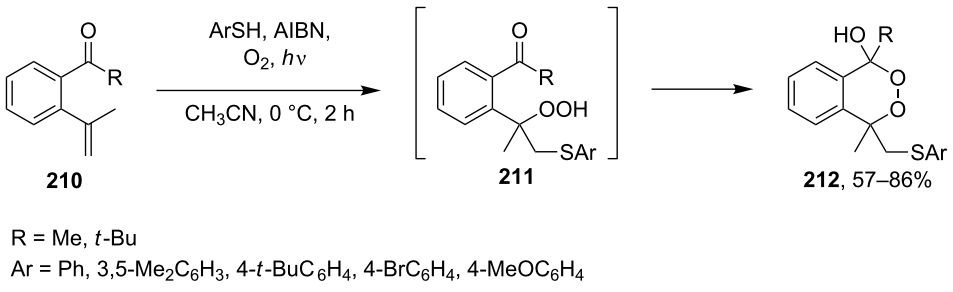
The co-oxidation of 1,4-dienes and thiols (thiol–olefin co-oxygenation, TOCO reaction) was described for the first time by Beckwith and Wagner as a method for the synthesis of sulfur-containing 1,2-dioxolanes [313,314]. More recently, it has been shown that under similar conditions, the oxidation of 1,5-dienes **208** affords the corresponding sulfur-containing 1,2-dioxanes **209**. The reaction proceeds under oxygen atmosphere in the presence of azobisisobutyronitrile (AIBN) or di*tert*-butyl peroxalate (DBPO) as radical initiators. The resulting unstable hydroperoxides are reduced with triphenylphosphine to hydroxy derivatives **209** (Scheme 58, Table 15).

The oxidation of acetophenones **210** produces bicyclic 1,2-dioxanes **212** (Scheme 59). It is hypothesized that the reaction gives hydroperoxide **211** as the intermediate, that undergoes rapid cyclization to form the target 1,2-dioxane **212** [317].



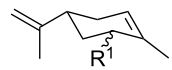
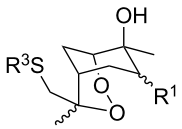
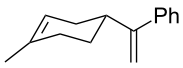
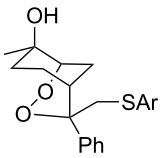
208 **209**

Scheme 58: 1,2-Dioxanes **209** synthesis by co-oxidation of 1,5-dienes **208** and thiols.



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.

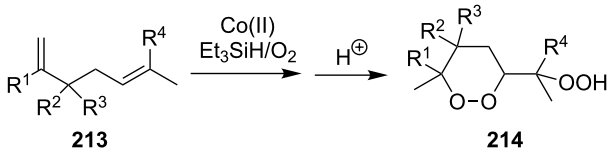
Diene **208**	Thiol	Reaction conditions	1,2-Dioxane **209**	Yield, %	Reference
 R^1 = H, PhCOO, OH	R^3SH R^3 = Ph, 4-FC_6H_4, *n*-Bu, *t*-Bu, MeO_2CCH_2, cyclohexyl, Ph_3C	1) O_2, DBPO, benzene/heptane, rt, 10 h or O_2, AIBN, *hν*, MeCN, 4 °C, 10 h 2) Ph_3P, CH_2Cl_2, 0–5 °C, 2 h, rt, 1 h		6–54	[107,179,315]
	PhSH 4-ClC_6H_4SH	1) O_2, AIBN, *hν*, MeCN, 0 °C, 2 h 2) Ph_3P, CH_2Cl_2, 0 °C to rt		70 (Ar = Ph), 21 (Ar = 4-ClC_6H_4)	[102,316]

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

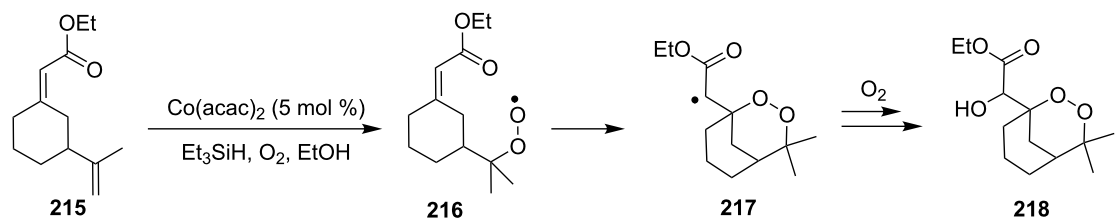
The Isayama–Mukaiyama peroxysilylation of 1,5-dienes **213** followed by desilylation under acidic conditions gives hydroperoxide-containing 1,2-dioxanes **214** (Scheme 60, Table 16).

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].

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

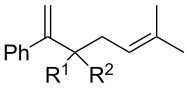
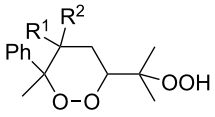
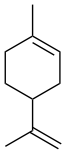
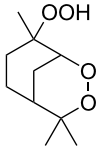


Scheme 60: Isayama–Mukaiyama peroxysilylation of 1,5-dienes **213** followed by desilylation under acidic conditions.



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

Table 16: Synthesis of 1,2-dioxanes by the Isayama–Mukaiyama method.

1,5-Diene **213**	Reaction conditions[a]	1,2-Dioxane **214**	Yield, %	Reference
 R^1, R^2 = H, Me, Ph	1) $Co(modp)_2$, O_2, Et_3SiH, $ClCH_2CH_2Cl$, 2–6 h 2) HCl/MeOH		13–64	[249]
	1) $Co(modp)_2$, O_2, Et_3SiH, $ClCH_2CH_2Cl$, 1 h 2) HCl/MeOH		22	[318,319]

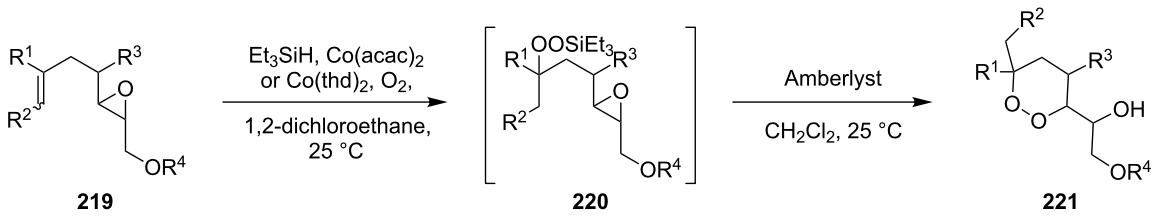
[a]modp = 1-morpholino-5,5-dimethyl-1,2,4-hexanetrionate.

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].

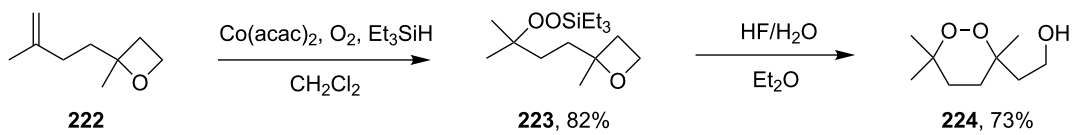
2-(3,6,6-Trimethyl-1,2-dioxan-3-yl)ethanol (**224**) was synthesized in a similar way starting with the peroxidation of 2-methyl-2-(3-methylbut-3-enyl)oxetane (**222**), followed by oxetane-ring opening in triethyl(2-methyl-4-(2-methyloxetan-2-yl)butan-2-ylperoxy)silane (**223**) (Scheme 63) [250].

Dioxanes can also be synthesized by inramolecular cyclizations with the attack on a keto group. The peroxysilylation of the unsaturated ketone 1,5-dicyclohexenylpentan-3-one (**225**), with the $Co(thd)_2/Et_3SiH/O_2$ system produced 1,5-bis(1-(triethylsi-

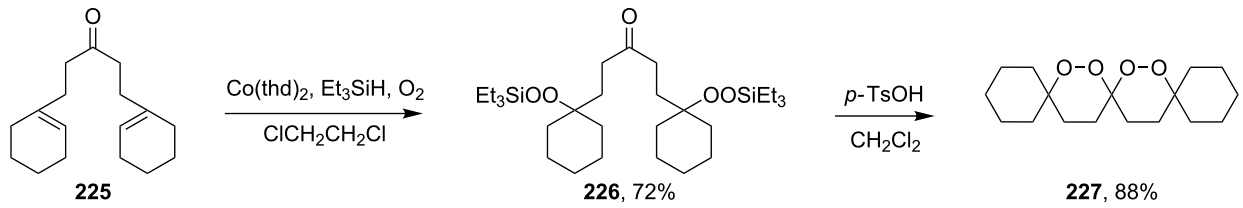


221a R^1 = Me, R^2 = H, R^3 = Et, R^4 = Ac, 75%
221b R^1 = Me, R^2 = H, R^3 = Et, R^4 = CH_3SO_2, 45%
221c,**d** R^1 = Me, R^2 = Me, Et, R^3 = H, R^4 = Ac, 58–65%
221e,**f**,**g** R^1 = Me, R^2 = *n*-BuCHEt, EtCHEt, Et, R^3 = Et, R^4 = Ac, 36–45%

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



Scheme 63: Inramolecular cyclization with the oxetane-ring opening.

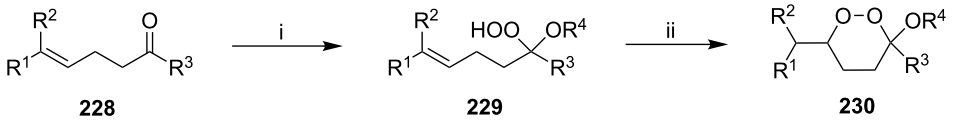


Scheme 64: Intramolecular cyclization with the attack on a keto group.

lylperoxy)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[5.2.2.5.2.2]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_2O_2–H_2NCONH_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).



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.

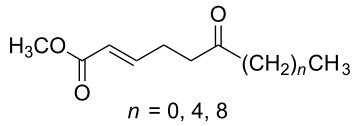
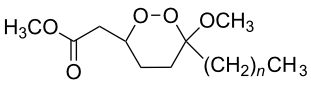
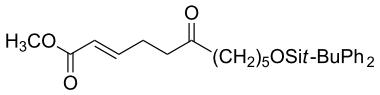
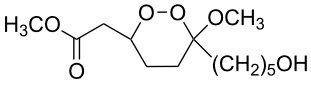
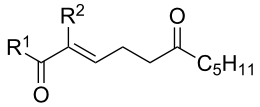
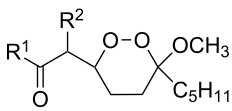
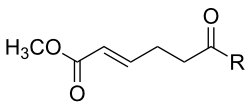
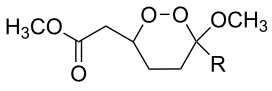
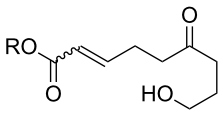
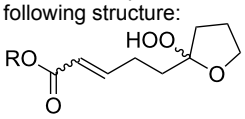
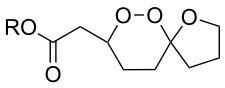
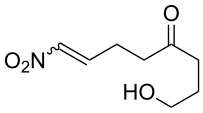
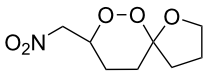
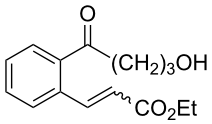
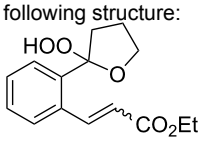
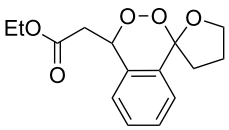
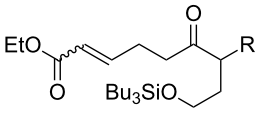
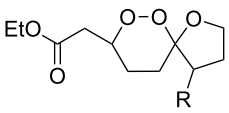
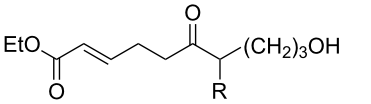
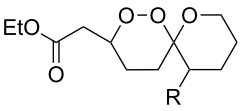
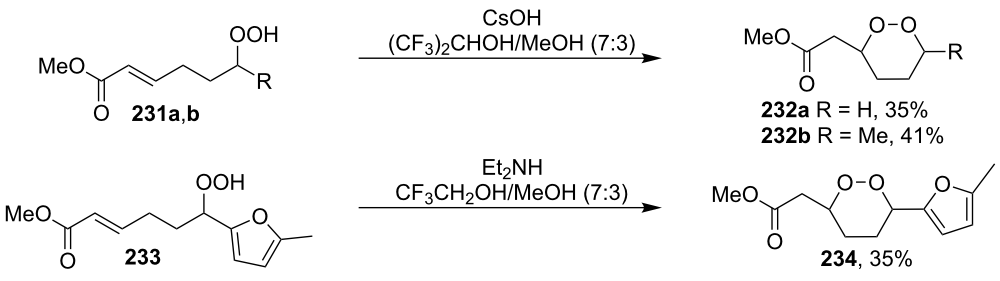
Unsaturated ketone **228**	Reaction conditions	1,2-Dioxane **230**	Yield, %	Reference
 *n* = 0, 4, 8	1) $H_2O_2{\cdot}H_2NCONH_2$, $Sc(OTf)_3$, MeOH 2) Et_2NH, CF_3CH_2OH, 0 °C, 2 d		1) 67–83 2) 60–72	[322,323]
	1) $H_2O_2{\cdot}H_2NCONH_2$, $Sc(OTf)_3$, MeOH 2) Et_2NH, CF_3CH_2OH 3) HF, pyridine, THF		1) 52 2) 87 3) 100	[324]
 R^1 = OMe, O*t*-Bu, Me, Ph R^2 = Me, H	1) $H_2O_2{\cdot}H_2NCONH_2$, $Sc(OTf)_3$, MeOH 2) Et_2NH, CF_3CH_2OH		8–38	[104-106]
 R = Ph, $PhCH_2$, CH_2=$CHCH_2CH_2CH_2$, $(CH_3)_2C$=$CHCH_2CH_2CH(CH_3)CH_2CH_2$	1) $H_2O_2{\cdot}H_2NCONH_2$, $Sc(OTf)_3$, MeOH 2) Et_2NH, CF_3CH_2OH		28–58	[104-106]

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

 R = Et, $PhCH_2$ Intermediate product **229** has the following structure: 	1) $H_2O_2{\cdot}H_2NCONH_2$, *p*-TsOH, MeOH, rt, 20 h 2) Et_2NH, CF_3CH_2OH, rt, 24 h		1) 54–82 2) 52	[325-327]
	H_2O_2–H_2NCONH_2, *p*-TsOH, 1,2-dimethoxyethane, rt, 11 h		35	[325-327]
 Intermediate product **229** has the following structure: 	1) $H_2O_2{\cdot}H_2NCONH_2$, 10-camphorsulfonic acid, 1,2-dimethoxyethane, rt, 18 h 2) Et_2NH, CF_3CH_2OH, rt, 2 h		1) 86 2) 54	[325-327]
 R = Me, $CH_3OCH_2OCH_2CH_2CH_2$	1) $H_2O_2{\cdot}H_2NCONH_2$, *p*-TsOH, EtOH, rt, 10 h 2) Et_2NH, CF_3CH_2OH, rt, 12 h		1) 72–80 2) 40–52	[328]
 R = H, Me, $EtOOCCH_2$, $AcOCH_2CH_2$	1) $H_2O_2{\cdot}H_2NCONH_2$, *p*-TsOH, EtOH, rt, 12 h 2) Et_2NH, CF_3CH_2OH, 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]. Et_3N in MeOH can also be used as catalyst for this type of cyclization [263].



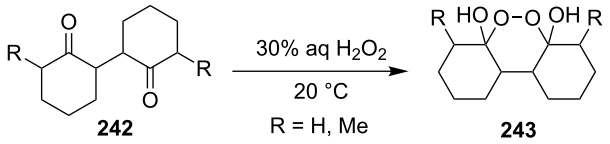
Scheme 66: CsOH and Et_2NH-catalyzed cyclization.

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).

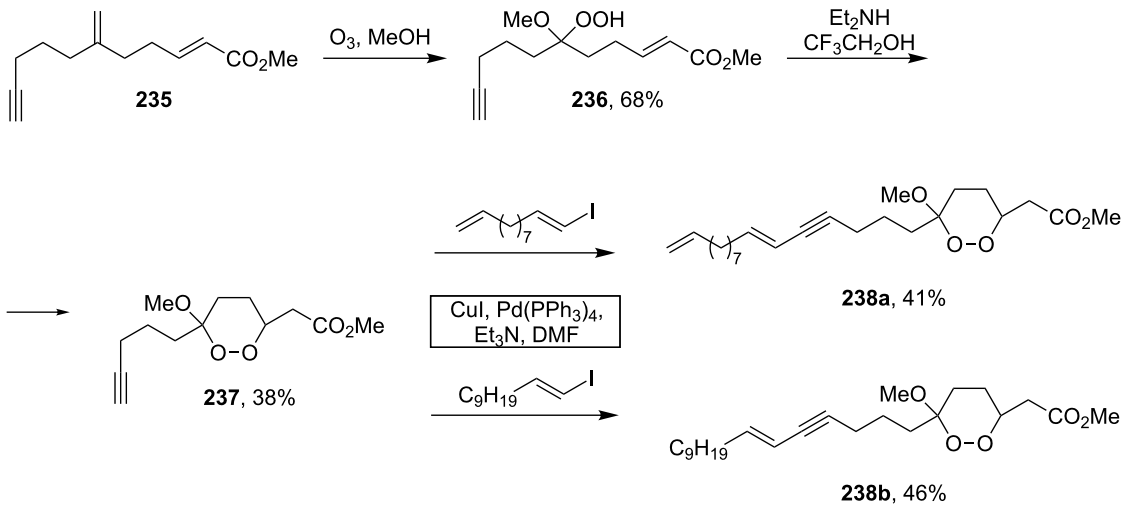
Initially, an attempt was made to synthesize diethyl 2,2'-(1,2,7,8-tetraoxaspiro[5.5]undecane-3,9-diyl)diacetate (**241**) by cyclization of (2*E*,9*E*)-diethyl 6,6-dihydroperoxyundeca-2,9-dienedioate bis(hydroperoxide) (**240**) (the bishydroperoxidation product of (2*E*,9*E*)-diethyl 6,6-dimethoxyundeca-2,9-dienedioate (**239**)) with Et_2NH in CF_3CH_2OH. 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 peroxide produced by the cyclization of bis(hydroperoxide) **240** was reduced with $NaBH_4$ in an alkaline medium [331].

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

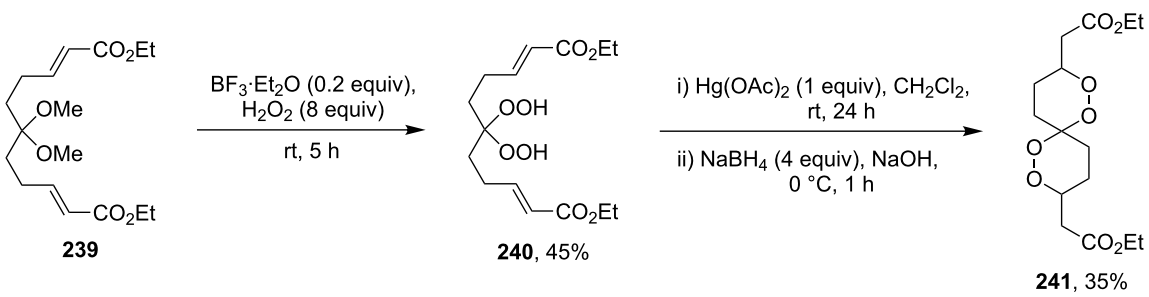
The reaction of 1,4-diketones **242** (cyclohexanone derivatives) with hydrogen peroxide in a neutral medium produced 3,6-dihydroxydioxanes **243** albeit without reported yields (Scheme 69). The resulting compounds exhibit a broad spectrum of antiparasitic activities against causative agents of malaria,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



Scheme 69: Reaction of 1,4-diketones **242** with hydrogen peroxide.



Scheme 67: Preparation of peroxyplakoric acid methyl ethers A and D.



Scheme 68: $Hg(OAc)_2$ in 1,2-dioxane synthesis.

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-dimethyloxepane (**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].

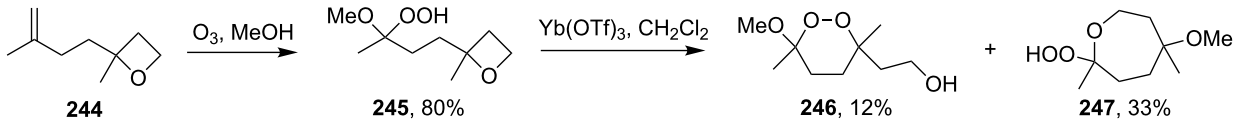
An approach to the cyclization based on an intramolecular nucleophilic substitution was used also for the synthesis of diastereomers of dioxanes **252a**,**b** containing triple bonds. Hydroperoxides **251a**,**b** that were synthesized by the ozonolysis of **250** were treated with potassium *tert*-butoxide. 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

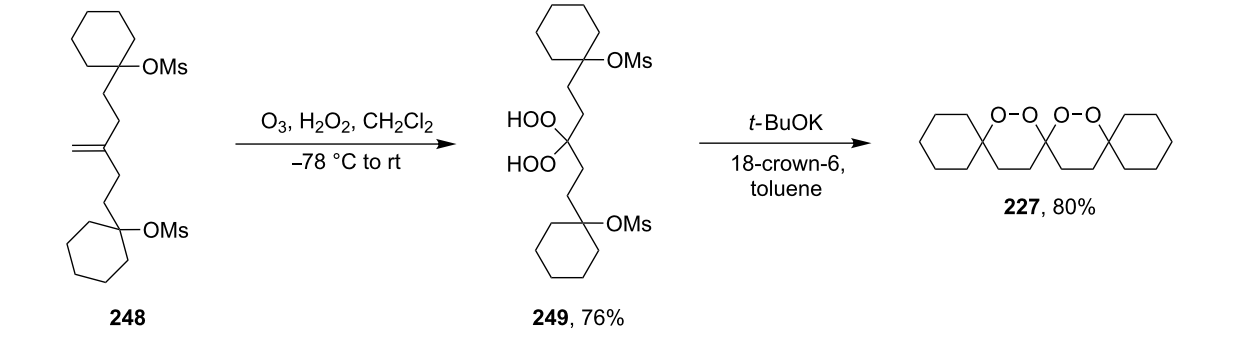
This approach to the synthesis of 1,2-dioxane rings is based on the intramolecular cyclization of hydroperoxides containing a C=C group. In the first step, the addition of a halonium ion to the double bond results in the formation of a carbocation, which is subjected to the intramolecular attack of the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

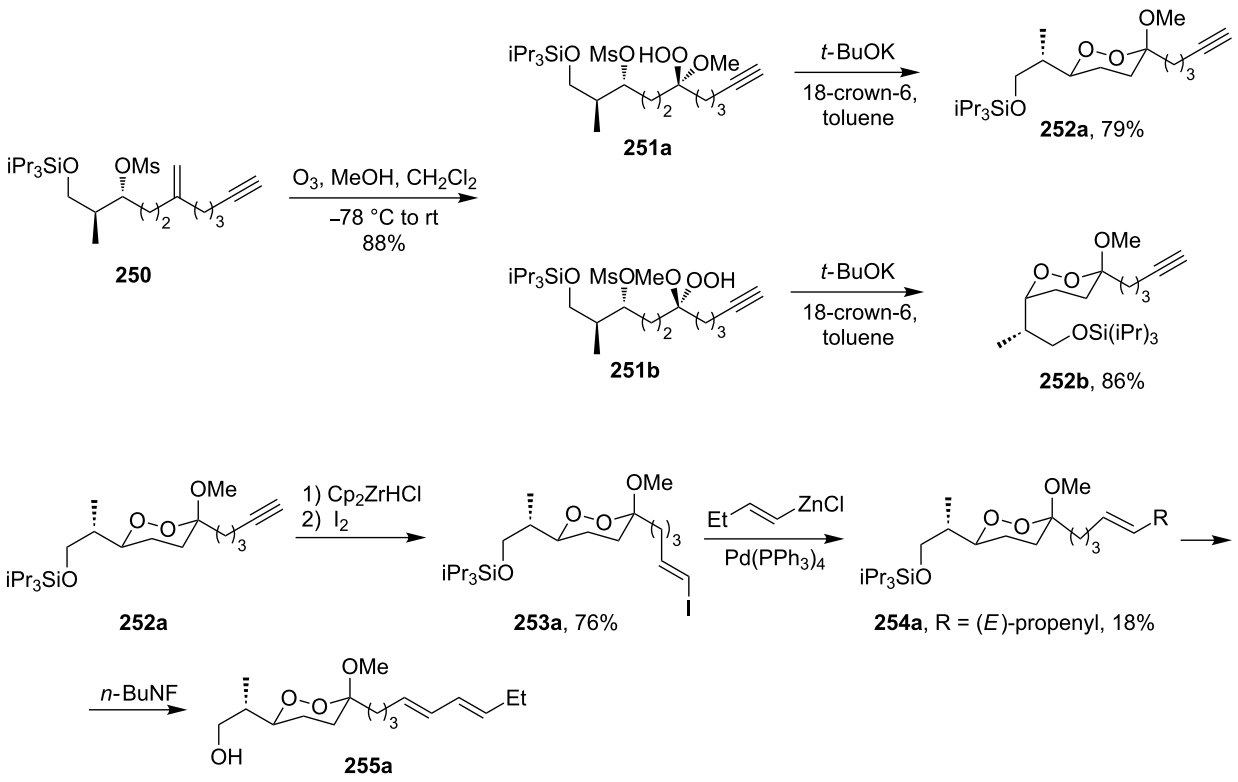
In the studies [334,335] iodine-containing 1,2-dioxanes **266a–c**, **268**, and **270a**,**b** were synthesized from the corresponding hydroperoxyalkenes **265a–c**, **267**, and **269a**,**b** with bis(sym-collidine)iodonium hexaflulorophosphate (BCIH) in the cyclization step (Scheme 74).



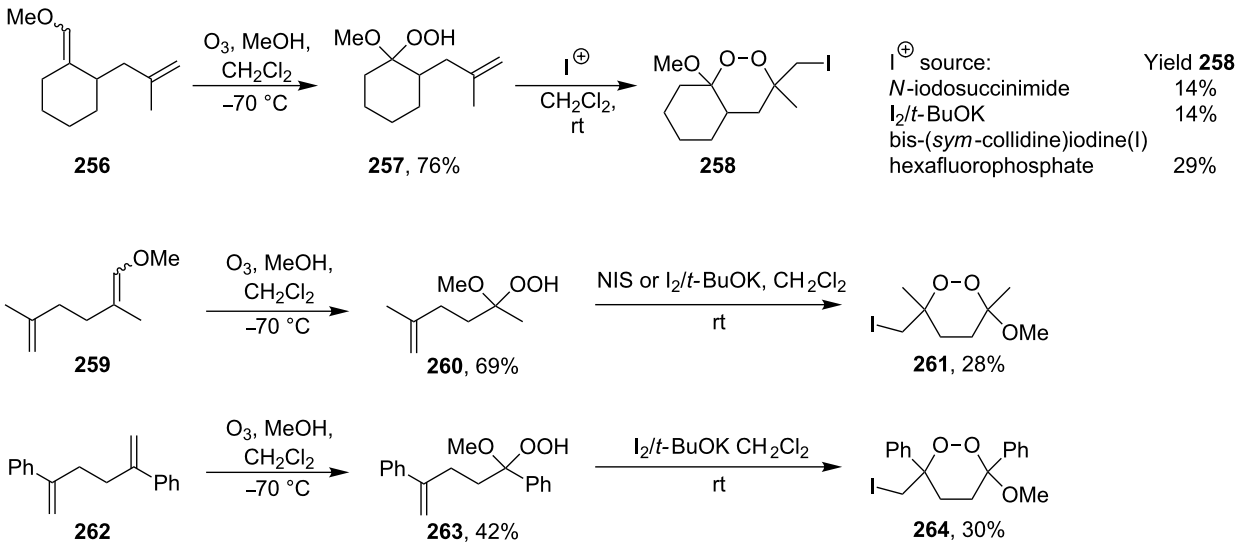
Scheme 70: Inramolecular cyclization with oxetane-ring opening.



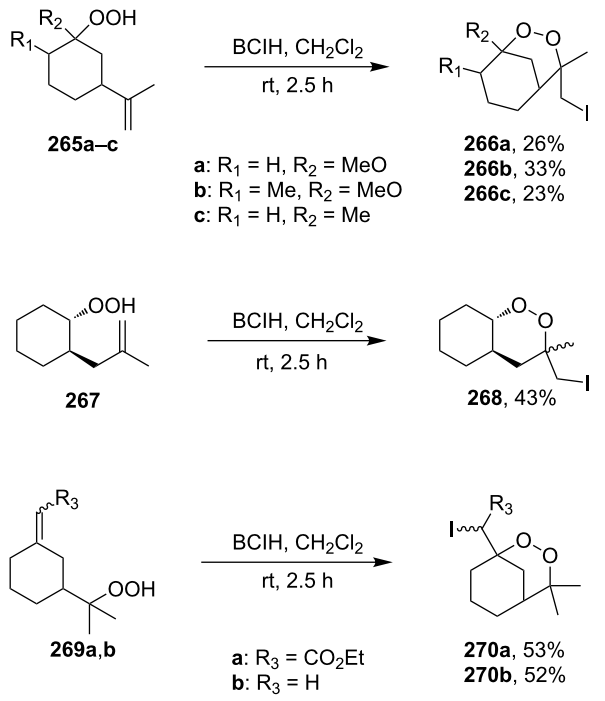
Scheme 71: Inramolecular cyclization with MsO fragment substitution.



Scheme 72: Synthesis of 1,2-dioxane **255a**, a structurally similar compound to natural peroxyplakoric acids.



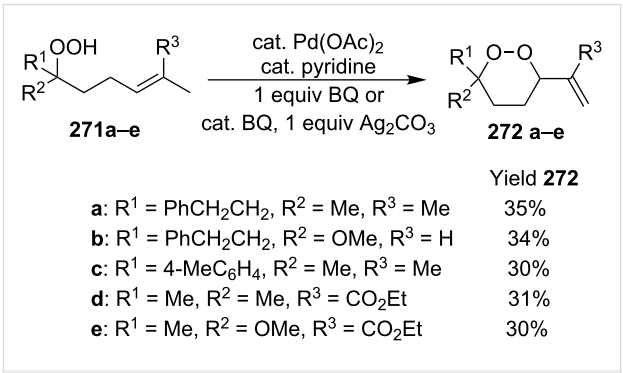
Scheme 73: Synthesis of 1,2-dioxanes based on the intramolecular cyclization of hydroperoxides containing C=C groups.



Scheme 74: Use of BCIH in the intramolecular cyclization.

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].

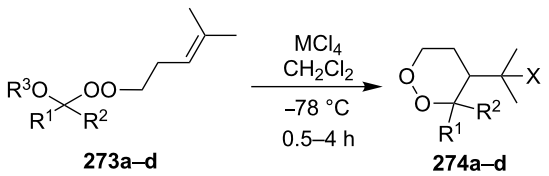


Scheme 75: Palladium-catalyzed cyclization of δ-unsaturated hydroperoxides **271a–e**.

3.10. Acid-mediated cyclizations of peroxides

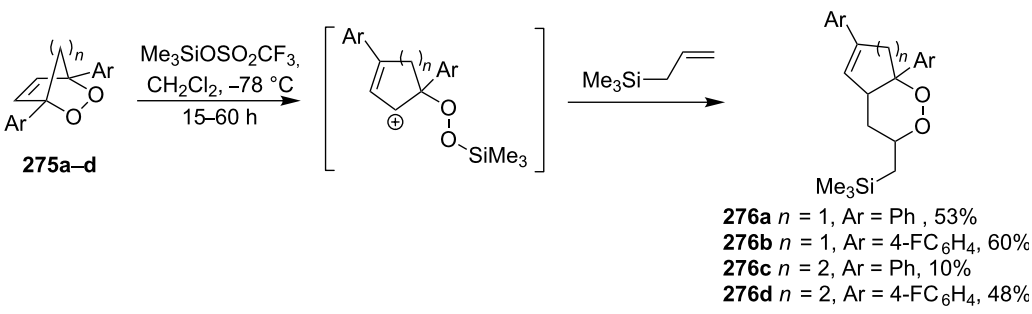
The intramolecular cyclization of unsaturated peroxyacetals **273a–d** in the presence of $TiCl_4$ or $SnCl_4$ occurs via formation of peroxycarbenium ions to give methoxy- and chlorine-containing dioxanes **274a–d** as the reaction products (Scheme 76) [257].

The treatment of endoperoxides **275a–d** with allyltrimethylsilane in the presence of catalytic amounts of trimethylsilyl triflate or $SnCl_4$ gave bicyclic 1,2-dioxanes **276a–d** (Scheme 77) [337].



	R1	R2	R3	M	X	Yield **274**
a:	Me	Me	Me	Sn	Cl	73%
b:	Me	Me	Et	Ti	Cl	46%
c:	Bu	H	Me	Sn	OMe	68%
d:	$PhCH_2$	H	Me	Ti	OMe	20%

Scheme 76: Intramolecular cyclization of unsaturated peroxyacetals **273a–d**.

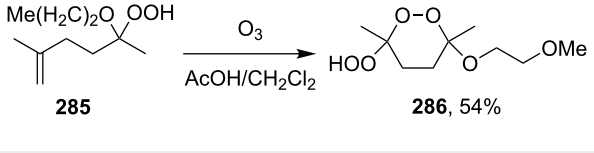


Scheme 77: Allyltrimethylsilane in the synthesis of 1,2-dioxanes **276a–d**.

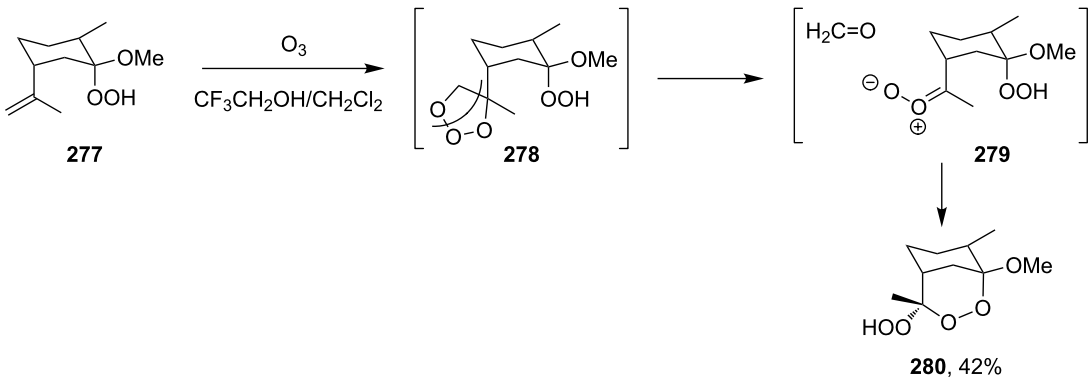
The electrophilic center of the peroxycarbenium ion produced by the decomposition of molozonide can be trapped by the hydroperoxide group of the molecule. This type of cyclization was used as the basis for the synthesis of hydroperoxide-containing 1,2-dioxanes. The ozonolysis of 1-hydroperoxy-1-methoxy-2-methyl-5-(prop-1-en-2-yl)cyclohexane (**277**) in a trifluoroethanol/dichloromethane mixture through formation of molozonide **278** and peroxycarbenium ion **279** finally afforded (6*S*)-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, (1*S*,5*S*)-1-hydroperoxy-4,4-dimethyl-2,3-dioxabicyclo[3.3.1]nonane (**282**), (1*S*,4*S*,5*S*)-1-hydroperoxy-4-methoxy-4-methyl-2,3-dioxabicyclo[3.3.1]nonane (**284a**), and (1*S*,4*R*,5*S*)-1-hydroperoxy-4-methoxy-4-methyl-2,3-dioxabicyclo[3.3.1]nonane (**284b**) (Scheme 79) [338].

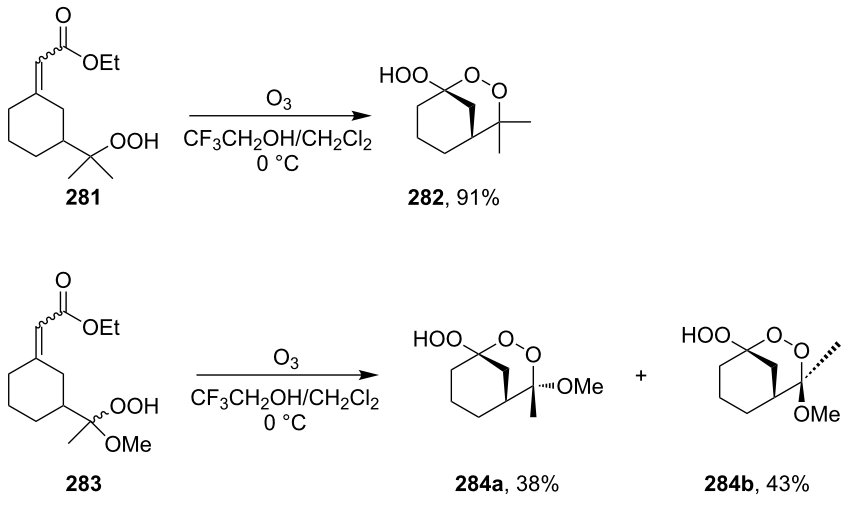
Under similar conditions, the reaction of 5-hydroperoxy-5-(2-methoxyethoxy)-2-methylhex-1-ene (**285**) in $AcOH/CH_2Cl_2$ produced 3-hydroperoxy-6-(2-methoxyethoxy)-3,6-dimethyl-1,2-dioxane (**286**) (Scheme 80) [270].



Scheme 80: Preparation of 1,2-dioxane **286**.



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



Scheme 79: Synthesis of bicyclic 1,2-dioxanes.

3.11. Other methods for the synthesis of 1,2-dioxanes

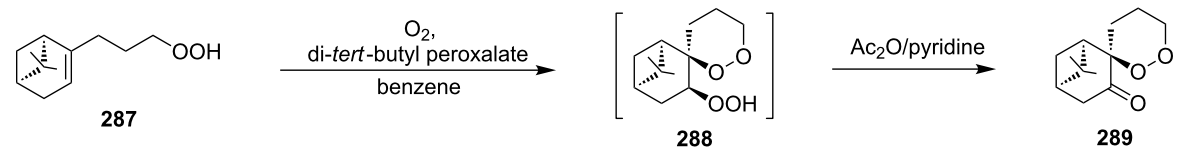
The di(*tert*-butyl)peroxalate-initiated radical cyclization of unsaturated 2-(3-hydroperoxypropyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene hydroperoxide (**287**) in the presence of oxygen gave 1,2-dioxane (**289**). The reaction proceeds through formation of compound **288** containing a hydroperoxide group, which is transformed into a carbonyl group by treatment with Ac_2O/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].

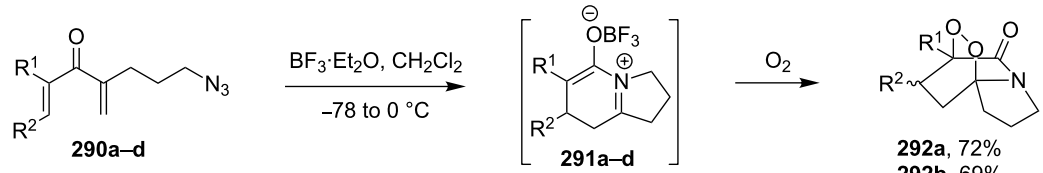
3.12. Structural modifications, in which 1,2-dioxane ring remains intact

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

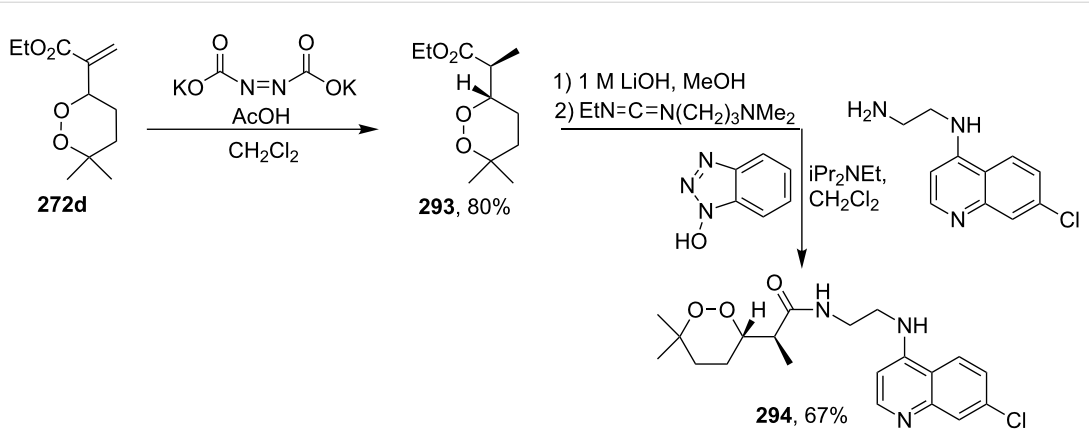
N-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-((*S*)-6,6-dimethyl-1,2-dioxan-3-yl)propanamide (**294**) containing the aminoquinoline moiety that is characteristic for antiparasitic compounds was synthesized by the following series of steps: reduction of the double bond in the presence of the peroxide group (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**.



Scheme 82: Oxidation of 1,4-betaines **291a–d**.



Scheme 83: Synthesis of aminoquinoline-containing 1,2-dioxane **294**.

The synthesis of the sulfonyl-containing 1,2-dioxane 2-(benzyloxy)-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 (6*R*)-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].

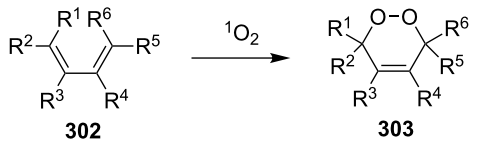
Methyl 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetate (**298**) was enzymatically hydrolyzed to 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetic acid (**299**). The next step in the synthesis of target compound **301** involved the two-step amidation via the intermediate formation of perfluorophenyl 2-(6-methoxy-6-pentyl-1,2-dioxan-3-yl)acetate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

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

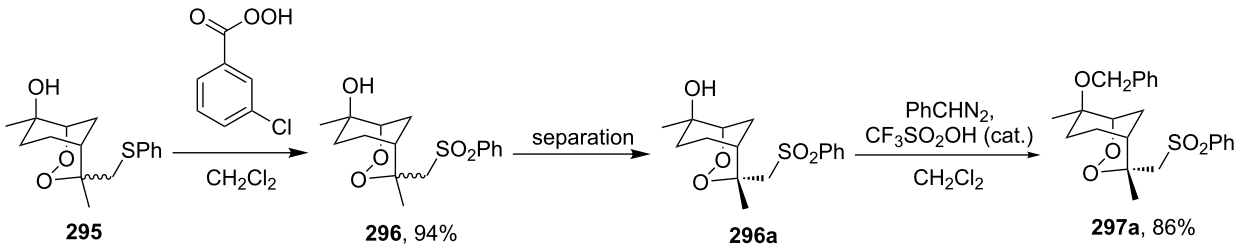
4. Synthesis of 1,2-dioxenes

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

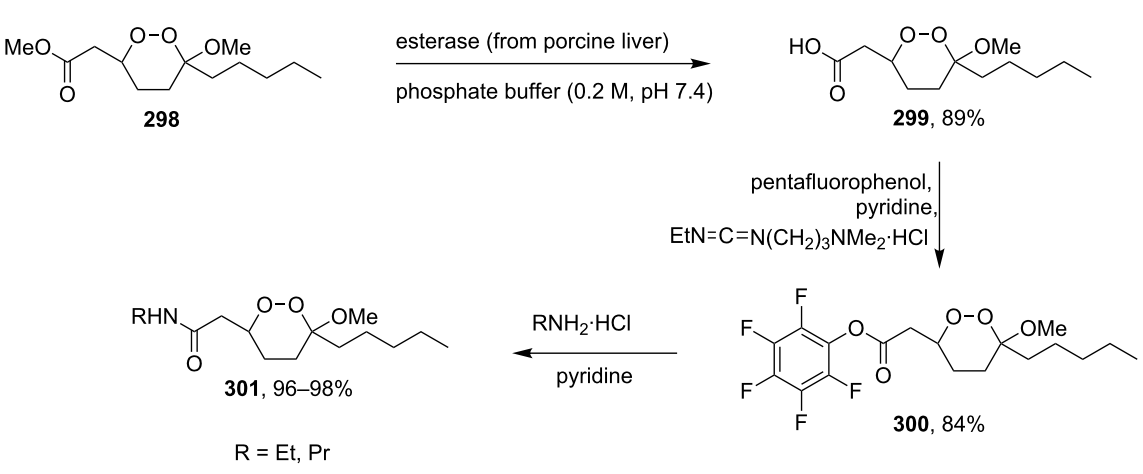
The reaction of singlet oxygen with the 1,3-diene system can proceed by the following pathways: the [4 + 2]-cycloaddition, the singlet-oxygen–ene reaction, and the [2 + 2]-cycloaddition to form dioxetanes. The reaction pathway depends on the nature of the solvent, and on electronic and steric factors. However, the [4 + 2]-cycloaddition (**302** + $^1O_2$) occurs in most cases, and this reaction is frequently used for the synthesis of the 1,2-dioxene 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 84: Synthesis of the sulfonyl-containing 1,2-dioxane.



Scheme 85: Synthesis of the amido-containing 1,2-dioxane **301**.

Table 18: Examples of the use of $^1O_2$ in the synthesis of 1,2-dioxenes.

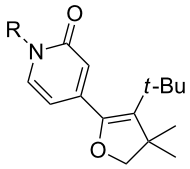
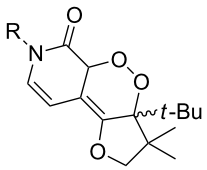
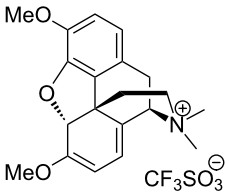
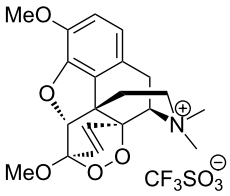
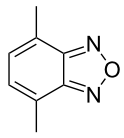
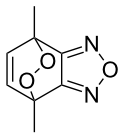
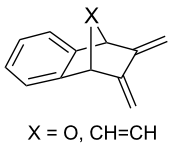
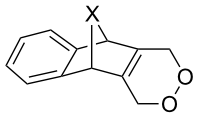
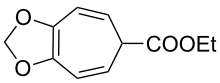
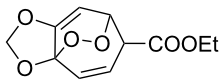
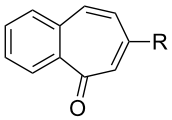
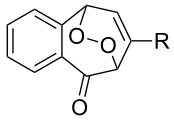
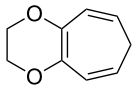
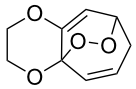
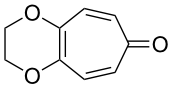
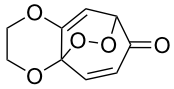
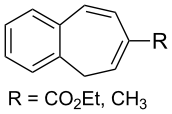
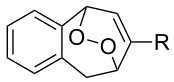
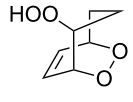
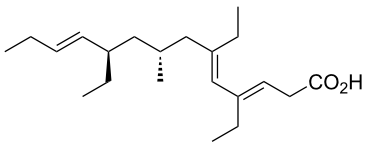
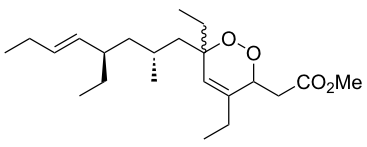
Alkene **302**	Reaction conditions	1,2-Dioxene **303**	Yield, %	Reference
 R = $PhCH_2$, H, Me	O_2, *hv*, tetraphenylporphyrin, CH_2Cl_2, −78 °C, 1 h		100	[340]
	O_2, *hv*, tetraphenylporphyrin, CH_2Cl_2, −78 °C, 2 h		85	[341]
	O_2, hv, fullerene C_{60}, $CDCl_3$, 0 °C, 2 h		93	[342]
 X = O, CH=CH	O_2, *hv*, tetraphenylporphyrin, CCl_4		75	[343]
	O_2, *hv*, tetraphenylporphyrin, CCl_4, rt, 30 min		90	[344]
 R = H, CO_2Et	O_2, *hv*, tetraphenylporphyrin, CCl_4, rt, 18–20 h		74 95	[345]
	O_2, *hv*, tetraphenylporphyrin, CCl_4, 10 °C, 1.5 h		73	[346]
	O_2, *hv*, tetraphenylporphyrin, $CHCl_3$, 10 °C, 45 min		94	[346]
 R = CO_2Et, CH_3	O_2, *hv*, tetraphenylporphyrin, CCl_4, rt, 24 h to 9 d		94 36	[347]
	O_2, *hv*, tetraphenylporphyrin, CH_2Cl_2, −10 °C, 6 h		54	[348]
	1) O_2, *hv*, Rose Bengal, MeOH/CH_2Cl_2 (1/19), 0 °C, 8 h 2) CH_2N_2		40	[182,183]

Table 18: Examples of the use of $^1O_2$ in the synthesis of 1,2-dioxenes. (continued)

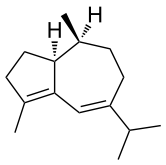
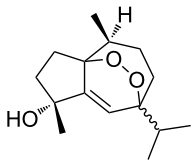
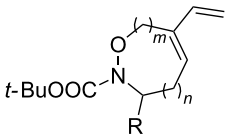
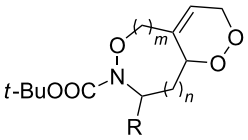
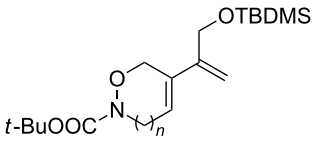
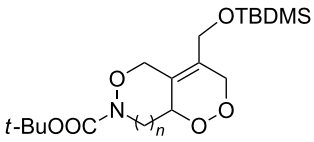
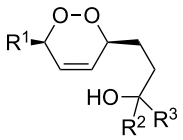
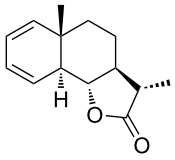
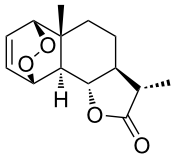
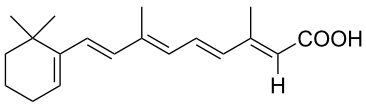
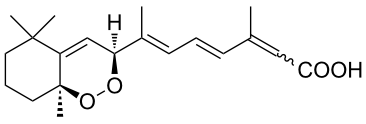
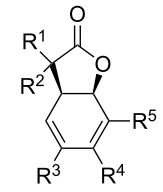
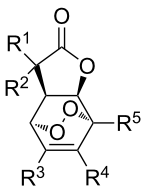
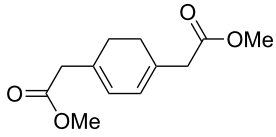
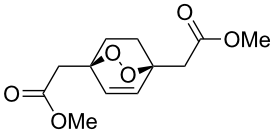
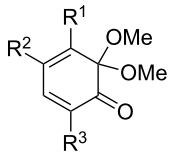
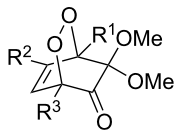
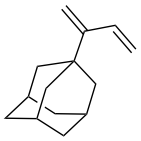
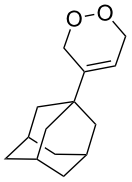
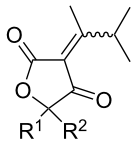
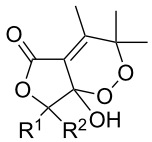
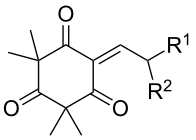
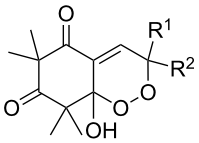
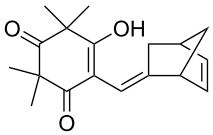
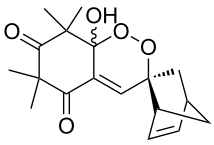
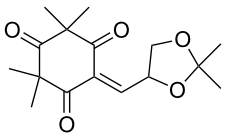
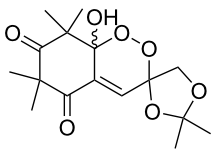
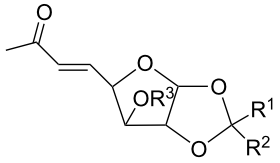
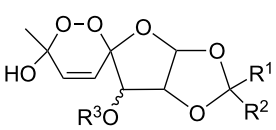
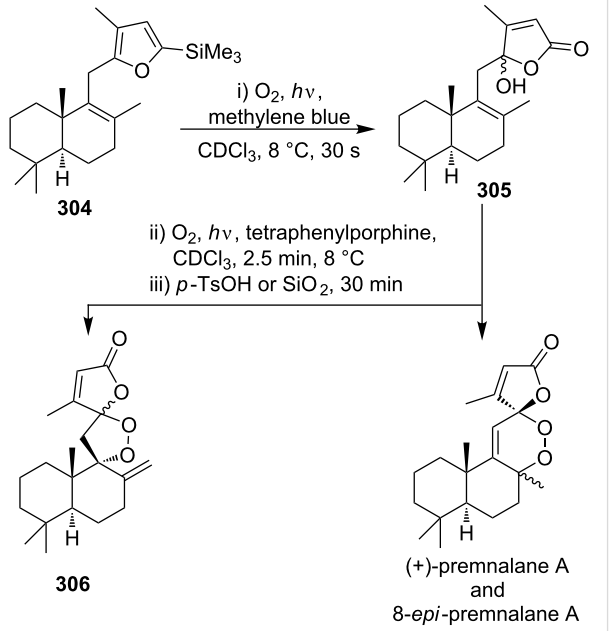
	1) O_2, *hv*, methylene blue, CH_2Cl_2, 15 °C, 30 min 2) PPh_3, acetone, rt, 40 min		50	[349]
 *m* = 1, 2 *n* = 0, 1, 2 R = H, Me, Ph, $PhCH_2OCH_2$	O_2, *hv*, Rose Bengal, MeCN, 0 °C, 6–16 h		54–82	[350]
 *n* = 1, 2	O_2, *hv*, Rose Bengal, $MeOH/CH_2Cl_2$ (1/19), 0 °C, 6 h	 *n* = 1, 2	42 66	[351]
 R^1 = Ph, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, naphthyl R^2 = H, Me, Ph R^3 = H, Me, Ph	O_2, *hv*, Rose Bengal, CH_2Cl_2, 6 h		23–70	[352]
	O_2, *hv*, tetraphenylporphyrin, benzene, 18 h		28	[353]
 retinoic acid	O_2, *hv*, Rose Bengal, EtOH, 10 °C, 70 min		56	[186-190]
 R^1, R^2 = -$(CH_2)_5$-, CH_3 R^3 = H, iPr, *t*-Bu, PhO R^4 = Me_3Si R^5 = H, PhO	O_2, *hv*, tetraphenylporphyrin, CH_2Cl_2		13–95	[191-195]
	O_2, *hv*, Rose Bengal, CH_2Cl_2		89	[354]

Table 18: Examples of the use of $^1O_2$ in the synthesis of 1,2-dioxenes. (continued)

 R^1 = H, Me, MeO R^2 = H, iPr, *t*-Bu, $(OCH_2C(CH_3)_2CH_2O)CH$ R^3 = H, Me, *t*-Bu	O_2, *hv*, tetraphenylporphyrin, $CHCl_3$ or Rose Bengal, MeOH, −15 to 0 °C, 1–4 h		70–92	[355]
	O_2, *hv*, Rose Bengal, CH_2Cl_2, 6 h		91	[356]
 R^1,R^2 = -$(CH_2)_5$- R^1,R^2 = -$(CH_2)_4$- R^1,R^2 = Ph, H	air, sunlight, $CHCl_3$, rt, 5 d or O_2, *hv*, CH_2Cl_2, $CuSO_4$, TsOH, 1 h		53–80	[357,358]
 R^1 = Me, CH_2OSi*t*-Bu$(Ph)_2$ R^2 = Me, Ph, CH_2OSi*t*-Bu$(Ph)_2$	air, sunlight, $CHCl_3$, rt, 3 d		60–85	[113-116] [359,360]
	air, sunlight, $CHCl_3$, rt, 3 d		23	[119]
	air, sunlight, $CHCl_3$, rt, 6 d		15	[119]
 R^1 = Me, CCl_3, H R^2 = Me, CCl_3, H R^3 = Ac, Me	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].



Scheme 87: Synthesis of (+)-premnalane A and 8-epi-premnalane A.

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

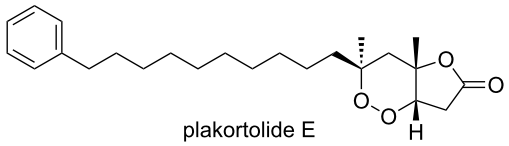
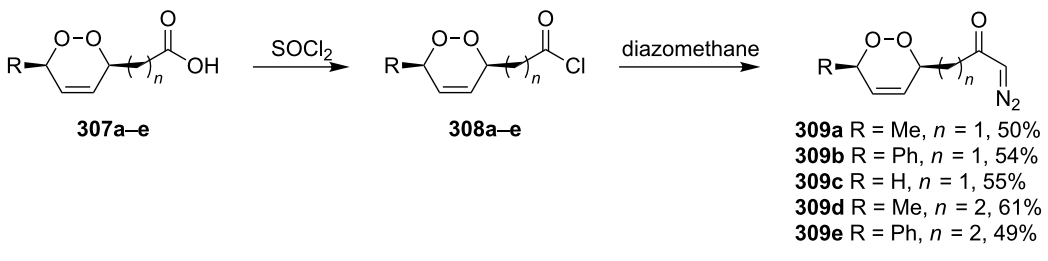


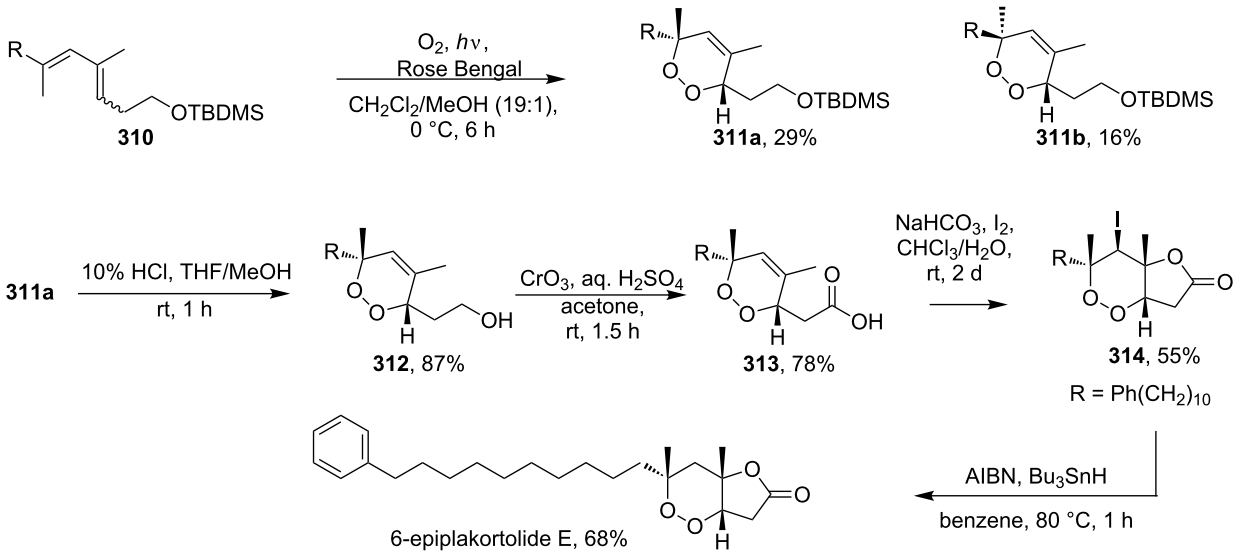
Figure 4: Plakortolide E.

6-Epiplakortolide E 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 I^+-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].

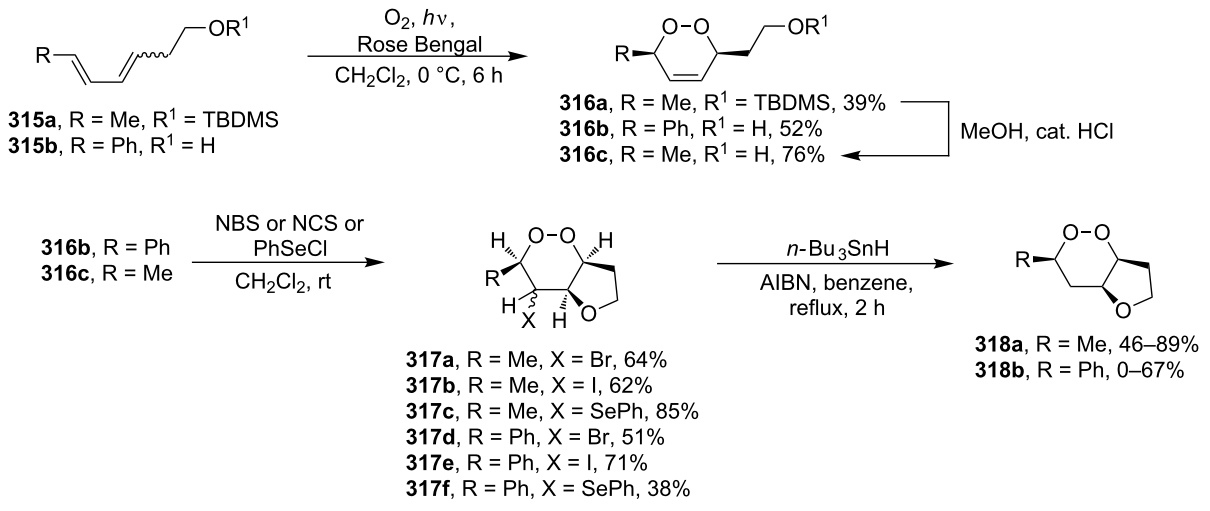
More recently, a similar approach was used for the preparation of tetrahydrofuran-containing bicyclic peroxides **318a**,**b**. It involves the synthesis of 1,2-dioxenes **316** from dienes **315**, the cation-initiated cyclization to give bicyclic compounds **317**, and the reduction with Bu_3SnH. *N*-Bromo- and iodosuccinimides (NBS and NIS, respectively) were used as donors of halogenide ions. Additionallay, the cyclization was successfully performed with the use of phenylselenyl chloride as the donor of $PhSe^+$ cation (Scheme 90) [364].



Scheme 88: Synthesis of the diazo group containing 1,2-dioxenes **309a–e**.



Scheme 89: Synthesis of 6-epiplakortolide E.

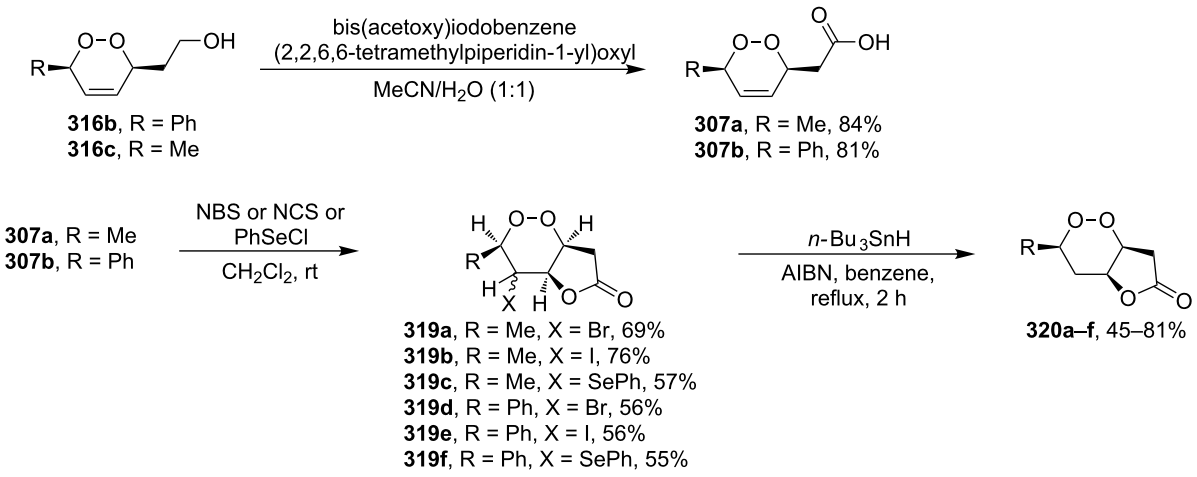


Scheme 90: Application of Bu_3SnH for the preparation of tetrahydrofuran-containing bicyclic peroxides **318a**,**b**.

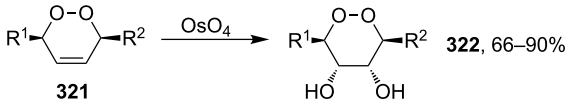
Acids **307a** and **307b** were synthesized by oxidation of the corresponding alcohols with the bis(acetoxy)iodobenzene/2,2,6,6-tetramethyl-1-piperidinyl oxyl (BAIB/TEMPO) system. The cyclization to bicyclic peroxides **319a–f** containing the lactone ring was performed with the use of N-bromo- and 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 Bu_3SnH [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 $K_2OsO_2(OH)_4$ (catalytic amounts, a source of OsO_4) and $K_3Fe(CN)_6$ (oxidizer), was employed for this purpose. In this reaction, K_2OsO_4 (0.5 mol %) combined with oxidizers ($K_3Fe(CN)_6$, *N*-methylmorpholine *N*-oxide, citric acid, or $KClO_3$) 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



Scheme 91: Application of Bu_3SnH for the preparation of lactone-containing bicyclic peroxides **320a–f**.



Scheme 92: Dihydroxylation of the double bond in the 1,2-dioxene ring **321** with OsO_4.

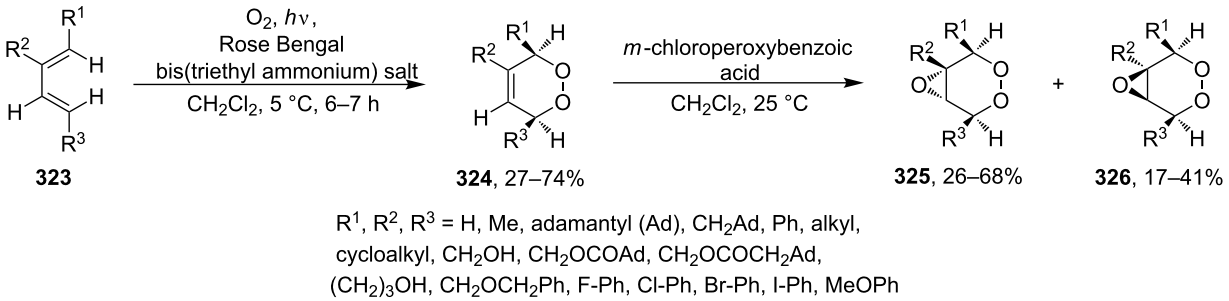
inhibiting activity against the causative agents of candidiasis infections *Candida albicans*, *Candida krusei*, and *Candida tropicalis*, that are in some cases comparable with the activity of the currently used amphotericin B, ketonazole, and nystatin [218-228]. In addition, these compounds exhibit 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].

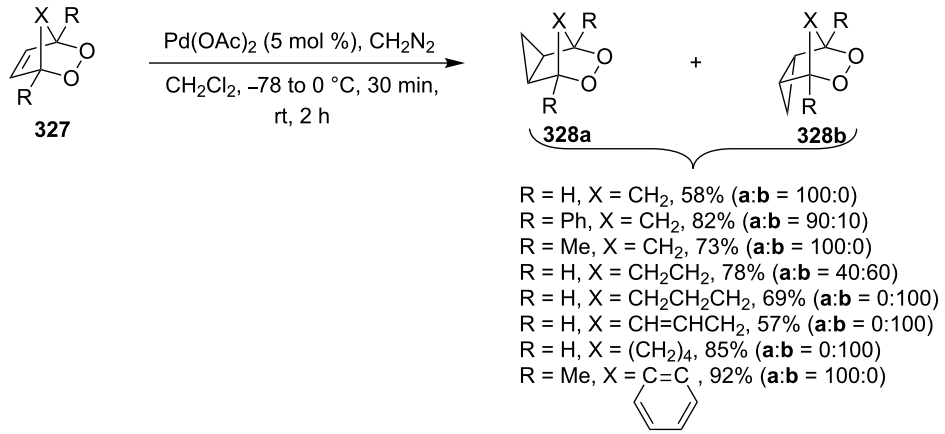
Pyridazine-containing bicyclic endoperoxides **334a–c** were synthesized by the inverse-electron-demand Diels–Alder cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**329**) to 1,2-dioxenes **330** followed by the elimination of dinitrogen from **331a–c** to give **332a–c**, the isomerization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

5. Synthesis of 1,2,4-trioxanes

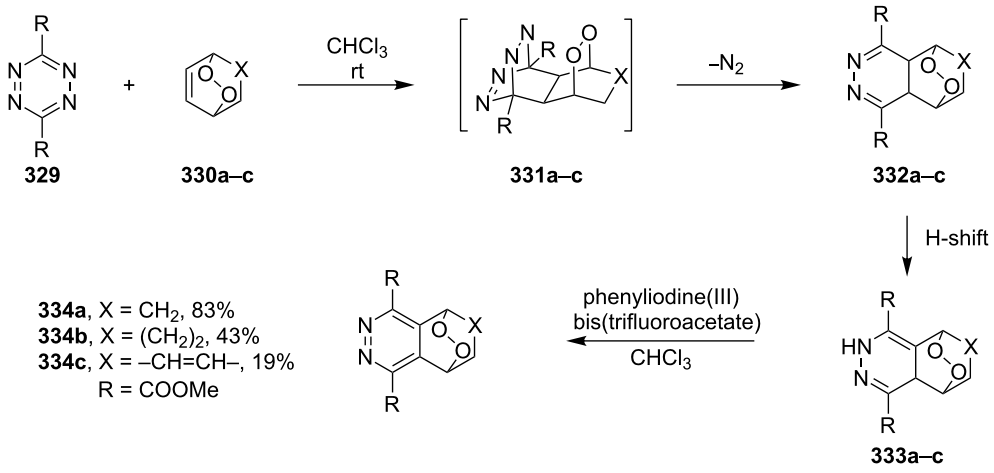
This part is devoted to methods for the synthesis of the 1,2,4-trioxane ring by the singlet-oxygen ene reaction with unsaturated alcohols, the photooxidation of enol ethers and vinyl sulfides, the [4+2]-cycloaddition of singlet oxygen to the pyran system, the Isayama-Mukaiyama peroxysilylation of unsatu-



Scheme 93: Epoxidation of 1,2-dioxenes **324**.



Scheme 94: Cyclopropanation of the double bond in endoperoxides **327**.



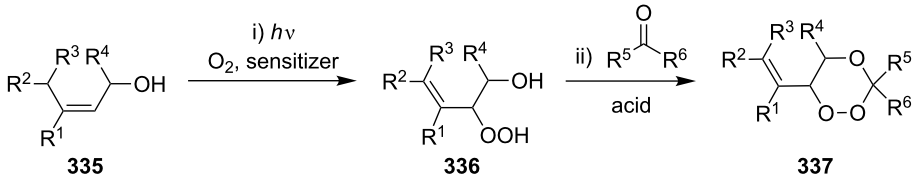
Scheme 95: Preparation of pyridazine-containing bicyclic endoperoxides **334a–c**.

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 hydroxy 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.



Scheme 96: Synthesis of 1,2,4-trioxanes **337** by the hydroperoxidation of unsaturated alcohols **335** with $^1O_2$ and the condensation of the hydroxy hydroperoxides **336** with carbonyl compounds.

Table 19: Examples of 1,2,4-trioxanes synthesized by the singlet oxygen ene reaction.

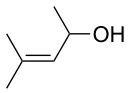
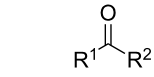
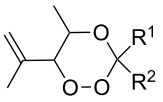
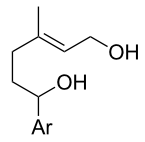
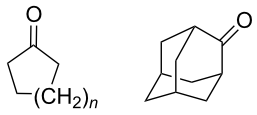
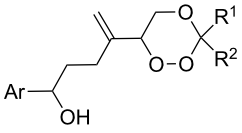
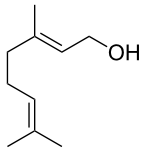
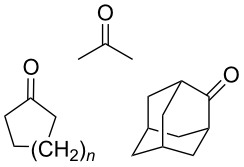
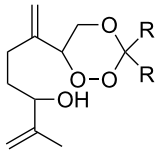
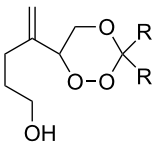
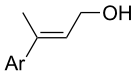
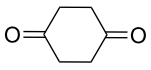
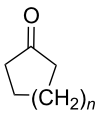
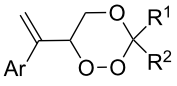
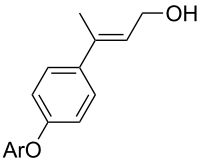
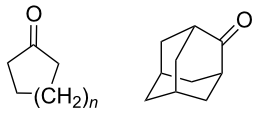
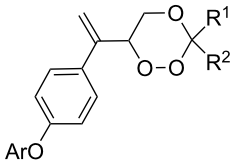
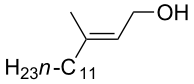
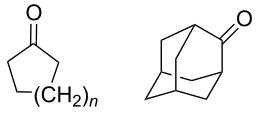
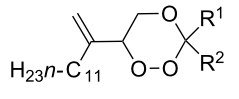
Alkene **335**	Carbonyl compound	Reaction conditions[a]	Product **337**	Yield i) **336**, % ii) **337**, %	Reference
	 $R^1 = R^2$ = Me, Et, *c*-C_5H_9, *c*-C_6H_{11} R^1 = Me, R^2 = Et, OMe; R^1 = H, R^2 = Me, Et, Ph	1) O_2, *h*ν, TPP 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2		i) 88–94 ii) 63–78	[371]
 Ar = Ph, 4-ClC_6H_4, 1-naphthyl, 4-PhC_6H_4	 *n* = 1, 2	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 4–6 h 2) TsOH, CH_2Cl_2, rt, 1 h		i) 30–45 ii) 50–74	[372]
	 *n* = 1, 2	1) O_2, *h*ν, methylene blue, MeCN, −10 °C 2) acid 3) $NaBH_4$, MeOH	 	The yield was not determined	[373]
 Ar = Ph, 4-PhC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$ 1-naphthyl, 2-naphthyl, 2-phenanthrenyl, 3-phenanthrenyl, 2-fluorenyl	  *n* = 1, 2	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 4–6 h 2) HCl, 5°C, 18 h		22–51	[374-379]
 Ar = Ph, 1-naphthyl, 2-naphthyl	 *n* = 1, 2	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 4–6 h 2) HCl, rt, 1 h		45–70	[380]
	 *n* = 1, 2	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH_2Cl_2, rt, 1 h		i) 43 ii) 65–76	[381]

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

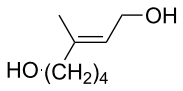
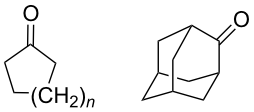
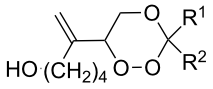
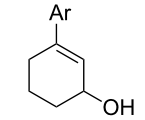
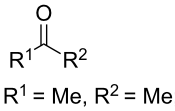
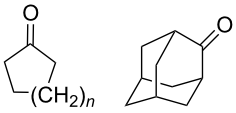
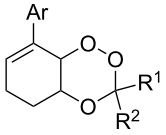
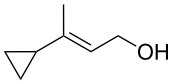
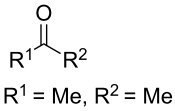
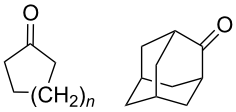
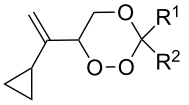
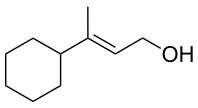
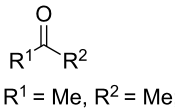
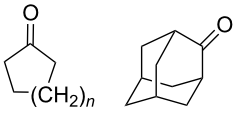
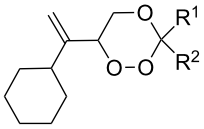
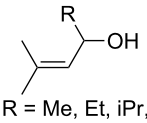
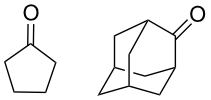
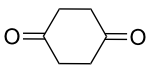
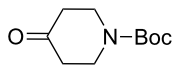
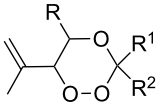
	 *n* = 1, 2	1) O_2, *hν*, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH_2Cl_2, rt, 1 h		i) 37 ii) 46–59	[381]
 Ar = Ph, 4-ClC_6H_4, 4-PhC_6H_4	 R^1 = Me, R^2 = Me; R^1 = Ph, R^2 = H  *n* = 1, 2	1) O_2, *hν*, methylene blue, MeCN, 0 °C, 18 h 2) HCl, CH_2Cl_2, 0 °C, 3–6 h		i) 22–35 ii) 12–37	[382]
	 R^1 = Me, R^2 = Me; R^1 = Ph, R^2 = H  *n* = 1, 2	1) O_2, *hν*, methylene blue, MeCN, 0 °C, 6 h 2) TsOH, CH_2Cl_2, rt, 2 h		i) 50 ii) 31–75	[383]
	 R^1 = Me, R^2 = Me; R^1 = Ph, R^2 = H  *n* = 1, 2	1) O_2, *hν*, methylene blue, MeCN, 0 °C, 6 h; 2) TsOH, CH_2Cl_2, rt, 2 h		i) 35 ii) 57–83	[383]
 R = Me, Et, iPr, *t*-Bu, *n*-Pr, CH_2-iPr, *c*-Pr, cyclohexyl	 R^1 = Et, R^2 = Me; R^1 = Et, R^2 = H; R^1 = β-naphthyl, R^2 = H; R^1 = 2-Fu, R^2 = H; R^1 = Ph, R^2 = H; R^1 = *o*-ClPh, R^2 = H; $HC(OEt)_3$   	1) O_2, *hν*, TPP 2) $BF_3{\cdot}Et_2O$, Et_2O, 0 °C		i) 54–97 ii) 8–78	[384-387]

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

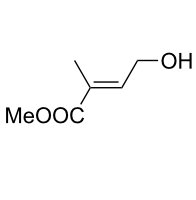
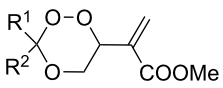
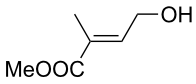
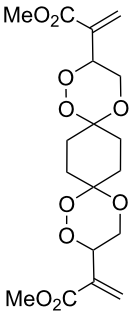
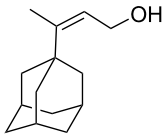
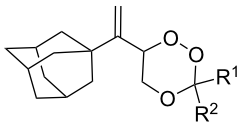
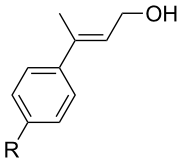
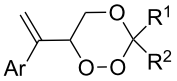
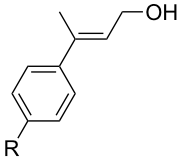
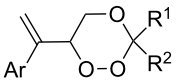
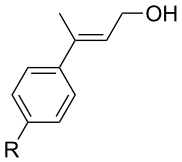
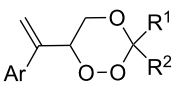
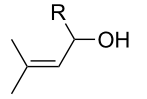
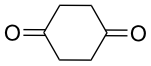
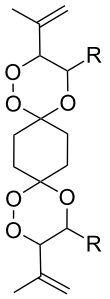
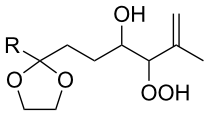
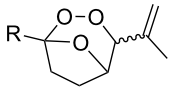
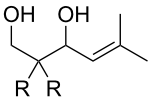
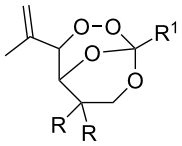
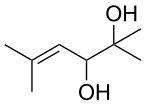
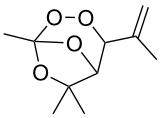
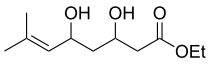
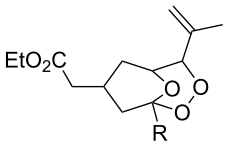
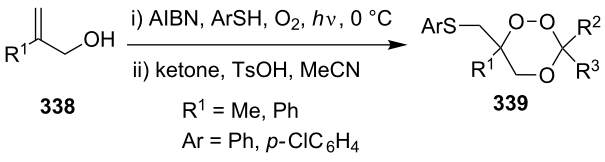
	1) O_2, *h*ν, TTP, polystyrene 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2		20–86	[385,387, 388]
	1) O_2, *h*ν, TTP or TPP PS-DVB-based 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2		20	[389]
	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 4–5 h 2) HCl, CH_2Cl_2, rt, 1 h		38–54	[390]
 R = H, OMe, Me, F, Cl, Br	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 5 h 2) HCl, MeCN, rt, 3 h		23-69	[125-127]
 R = H, OMe, Me, F, Cl, Br	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 5 h 2) HCl, MeCN, rt, 3 h		40–87	[125-127]
 R = H, OMe, Me, F, Cl, Br	1) O_2, *h*ν, methylene blue, MeCN, 0 °C, 5 h 2) HCl, MeCN, rt, 3 h		35–55	[125-127]

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

 R = *n*-Bu, *n*-Pr iPr, iBu, allyl		1) O_2, *h*ν, TTP or TPP PS-DVB-based 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2		4–19	[389]
 R = Me, Et	Intramolecular process	1) O_2, *h*ν, TTP or TPP PS-DVB-based 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2		i) 84–91 ii) 12–19	[391]
 R = Me, H	$R^1C(OMe)_3$ R^1 = Me, Et, *n*-Pr, Ph	1) O_2, *h*ν, TPP, CCl_4, 10 °C 2) PPTS, CH_2Cl_2		i) 94–99 ii) 21–30	[391]
	$MeC(OMe)_3$	1) O_2, *h*ν, TPP, CCl_4, 10 °C 2) PPTS, CH_2Cl_2		i) 83 ii) 19	[391]
	$RC(OMe)_3$ R = Me, Et, *n*-Pr	1) O_2, *h*ν, TPP, CCl_4, rt 2) TsOH, CH_2Cl_2, rt		i) 83 ii) 18–55	[392]

[a]TPP is tetraphenylporphyrin; TTP is tetratolylporphyrin; PPTS is pyridinium *para*-toluenesulfonate.

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



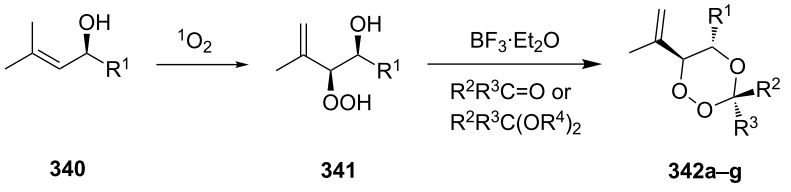
Scheme 97: Synthesis of sulfur-containing 1,2,4-trioxanes **339**.

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

The formation of peroxyketals **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].

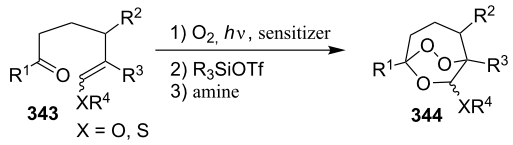
The approach to the synthesis of 1,2,4-trioxanes proposed by Jefford and co-workers in 1993 [394] is based on the photooxidation of enol ethers or vinyl sulfides **343** with oxygen followed by the rearrangement of the resulting 1,2-dioxetanes in the presence of trialkylsilyl triflates. The resulting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

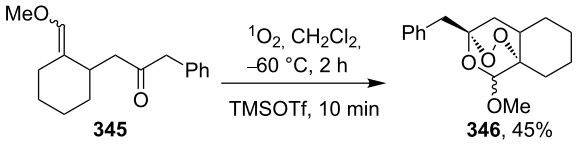


	R^1	R^2	R^3	R^4	Yield, %
a	*n*-Bu	Ph	H	Me	48
b	iBu	β–Naph	H	–	21
c	Me	–Ada–		–	10
d	iBu	–Ada–		–	12
e	Me	2-Fu	H	–	34
f	Et	*o*-Cl-Ph	H	–	22
g	Me	OEt	H	OEt	70

Scheme 98: $BF_3{\cdot}Et_2O$-catalyzed synthesis of the 1,2,4-trioxanes **342a–g**.

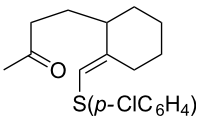
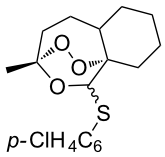
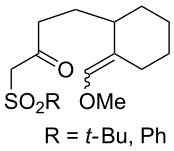
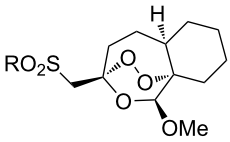
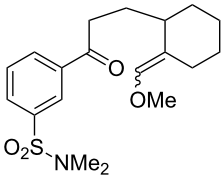
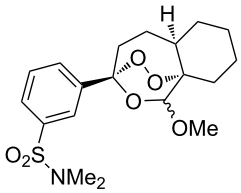
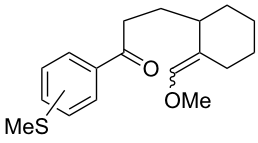
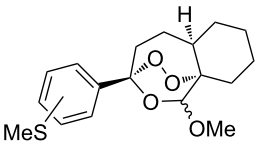
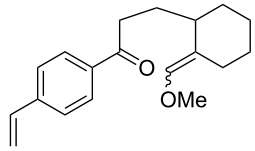
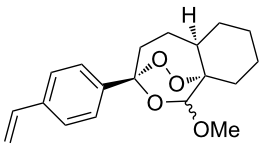
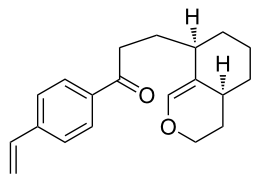
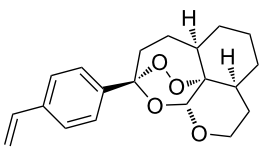


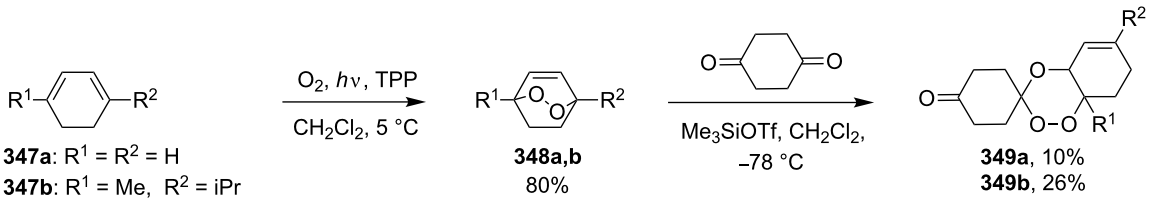
Scheme 99: Photooxidation of enol ethers or vinyl sulfides **343**.



Scheme 100: Synthesis of tricyclic peroxide **346**.

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
	1) O_2, *h*v, methylene blue, CH_2Cl_2, −78 °C 2) TBDMSOTf, CH_2Cl_2, −78 °C 3) Et_3N, CH_2Cl_2, −78 °C to −15 °C		47 (12-α) 47 (12-β)	[395]
	1) O_3, $(PhO)_3P$, CH_2Cl_2, −78 °C 2) Et_3SiOTf, CH_2Cl_2, −78 °C 3) Et_3N, CH_2Cl_2, −78 °C to rt		30–38	[395]
	1) O_3, $(PhO)_3P$, CH_2Cl_2, −78 °C 2) Me_3SiOTf, CH_2Cl_2, −78 °C 3) Et_3N, CH_2Cl_2, −78 °C to rt		7	[395]
	1) O_3, $(PhO)_3P$, CH_2Cl_2, −78 °C 2) Me_3SiOTf, CH_2Cl_2, −78 °C 3) Et_3N, CH_2Cl_2, −78 °C to rt		3 (12-α) 11 (12-β)	[395]
	1) Air, *h*v, methylene blue, CH_2Cl_2, −90 °C 2) Me_3SiOTf, CH_2Cl_2, −90 °C, 1 h 3) 1- ethylpiperidine, CH_2Cl_2, −78 °C to rt		36 (12-α) 15 (12-β)	[396]
	1) Air, *h*v, methylene blue, CH_2Cl_2, −78 °C, 1 h 2) Me_3SiOTf, CH_2Cl_2, −78 °C, 2 h 3) 1-ethylpiperidine, CH_2Cl_2, −78 °C to rt		33	[397]



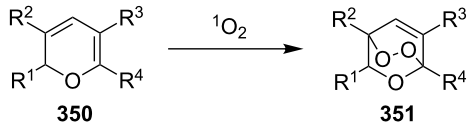
347a: $R^1 = R^2 = H$
347b: R^1 = Me, R^2 = iPr

348a,b 80%

349a, 10%
349b, 26%

Scheme 101: Reaction of endoperoxides **348a**,**b** derived from cyclohexadienes **347a**,**b** with 1,4-cyclohexanedione.

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].



350 **351**

Scheme 102: [4 + 2]-Cycloaddition of singlet oxygen to 2*H*-pyrans **350**.

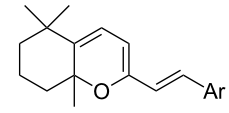
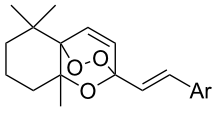
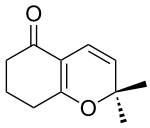
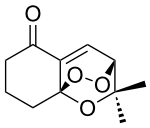
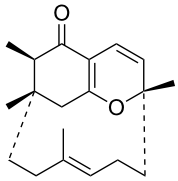
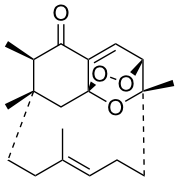
Unsaturated bicyclic trioxanes **351** are [4 + 2]-cycloaddition products of singlet oxygen to the pyran moiety in **350** (Scheme 102, Table 21).

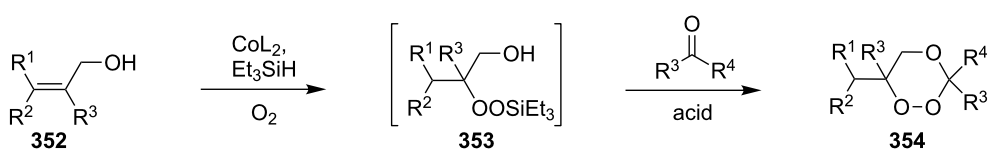
It was shown that in this reaction the starting pyran can serve as the sensitizer for the formation of singlet oxygen [402].

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 21: Examples of 1,2,4-trioxanes synthesized by oxidation of 2*H*-pyrans.

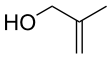
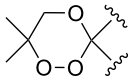
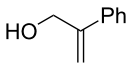
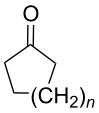
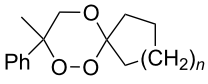
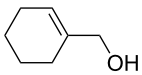
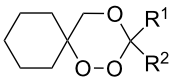
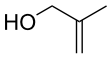
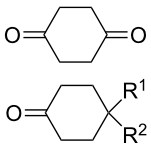
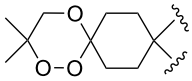
Pyran **350**	Reaction conditions	1,2,4-Trioxane **351**	Yield, %	Reference
 Ar = Ph, *p*-MeC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$	O_2, *hv*, benzene		85–90	[399]
	Air, Rose Bengal, *hv*, THF, −78 °C		94	[400]
	Air, Rose Bengal, *hv*, CH_2Cl_2, −78 °C		65	[401]



352 **353** **354**

Scheme 103: Synthesis of 1,2,4-trioxanes **354** using peroxysilylation stage.

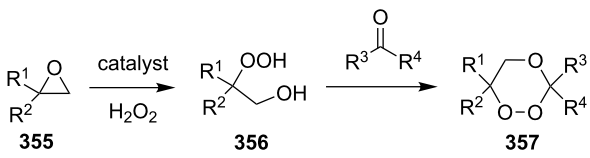
Table 22: Examples of 1,2,4-trioxanes synthesized through the Isayama–Mukaiyama peroxysilylation.

Unsaturated alcohol **352**	Carbonyl compound	Reaction conditions[a]	1,2,4-Trioxane **354**	Yield, %	Reference
	 R^1 = Ph, *p*-FC_6H_4, *p*-$O_2NC_6H_4$, *p*-PhC_6H_4, furanyl  R^2, R^3 = Me, Ph, *p*-FC_6H_4, -$(CH_2)_5$-, $PhCH_2CH_2$	1) $Co(acac)_2$, Et_3SiH, O_2, rt 2) TsOH		1) 60 2) 40–90	[403]
	 n = 1, 2	1) $Co(acac)_2$, Et_3SiH, O_2, rt 2) TsOH		42 54	[403]
	 R^1 = R^2 = Me R^1 = R^2 = -$(CH_2)_5$- R^1 = R^2 = -$(CH_2)_{11}$- R^1 = H, R^2 = 9-phenanthryl R^1 = H, R^2 = *p*-FC_6H_4 R^1 = H, R^2 = *p*-$CF_3C_6H_4$ R^1 = CH_3, R^2 = Ph R^1 = CH_3, R^2 = *p*-$CF_3C_6H_4$	1) $Co(thd)_2$, Et_3SiH, O_2, rt 2) TsOH		40–85	[404]
	 R^1 = H, R^2 = CO_2Et R^1 = Me, R^2 = CO_2Et R^1 = F, R^2 = CO_2Et	1) $Co(acac)_2$, Et_3SiH, O_2, EtOH, 4 h 2) TsOH, $CHCl_3$, 45 min to 3.5 h		1) 36 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

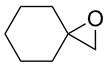
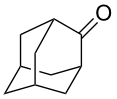
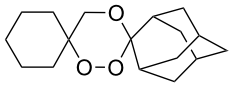
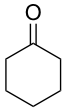
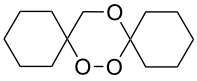
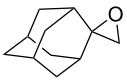
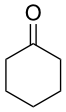
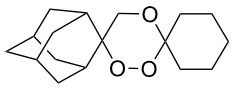
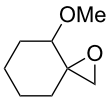
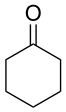
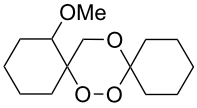
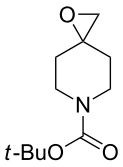
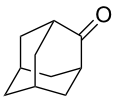
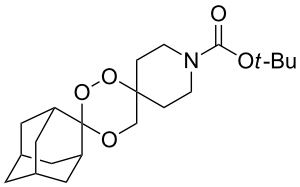
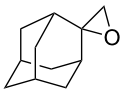
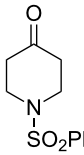
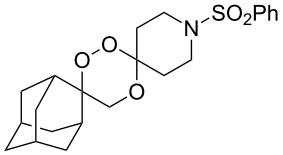
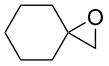
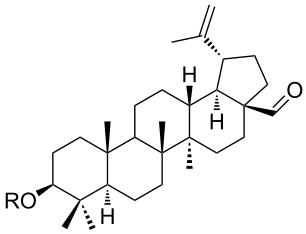
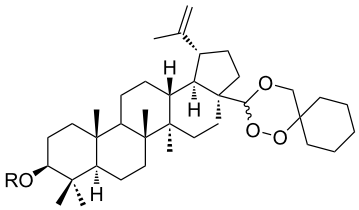
An important approach to the synthesis of 1,2,4-trioxanes **357** is based on the epoxide-ring opening in **355** with hydrogen peroxide in the presence of a catalyst followed by the condensation of the vicinal hydroxy hydroperoxides **356** with ketones (Scheme 104, Table 23). The drawbacks of this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

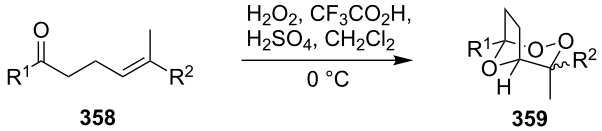


Scheme 104: Epoxide-ring opening in **355** with H_2O_2 followed by the condensation of hydroxy hydroperoxides **356** with ketones.

The reaction of unsaturated ketones **358** with $H_2O_2/CF_3COOH/H_2SO_4$ 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].

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.
		1) $MoO_2(acac)_2$, H_2O_2 , Et_2O, $MgSO_4$ 2) TsOH, CH_2Cl_2, rt		i) 59 ii) 95	[405]
				i) 59 ii) 69	[405]
		1) $MoO_2(acac)_2$, H_2O_2, THF, $MgSO_4$ 2) 10-camphor-sulfonic acid, CH_2Cl_2, rt		i) 29 ii) 46	[405]
		1) H_2O_2, Et_2O, 0 °C, 4 h 2) H_2SO_4, CH_2Cl_2, rt, 4 d		i) 8 ii) 28	[406]
		1) $MoO_2(acac)_2$, H_2O_2, Et_2O, $MgSO_4$, rt, 22 h 2) TsOH, CH_2Cl_2, rt, 5 h		i) 98 ii) 92	[407]
		1) $MoO_2(acac)_2$, H_2O_2, Et_2O 2) 10-camphor-sulfonic acid, CH_2Cl_2		i) 25 ii) 39	[407]
	 R= Ac, Me	1) $MoO_2(acac)_2$, H_2O_2 , Et_2O, $MgSO_4$ 2) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C to 0 °C, 5 h	 R= Ac, Me	i) - ii) 27–35	[175] [176]



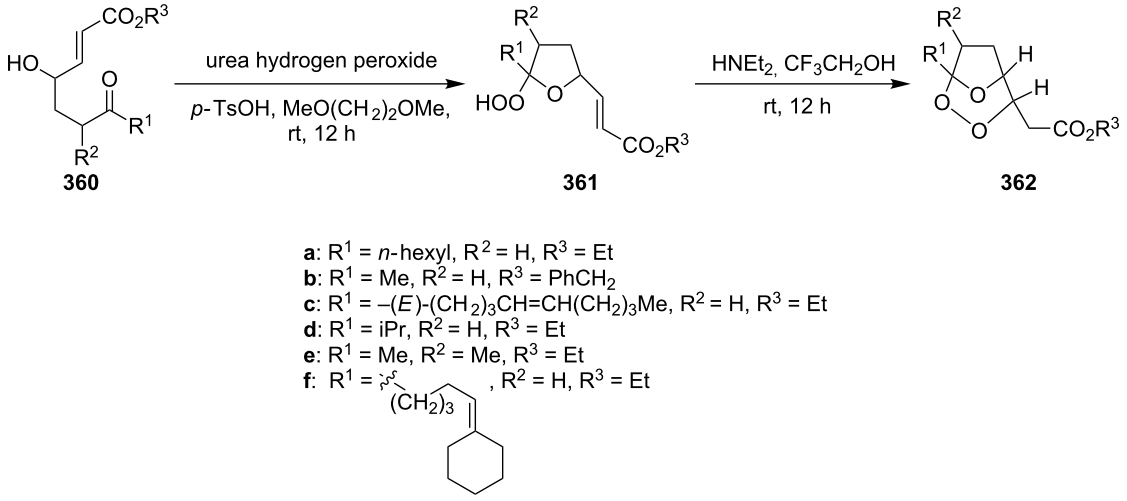
358 **359**

R^1 = Me, Et, *n*-Pr, allylCH_2, $PhCH_2OCH_2CH_2CH_2$
R^2 = Me, CH_2OH

Scheme 105: Peroxidation of unsaturated ketones **358** with the H_2O_2/CF_3COOH/H_2SO_4 system.

5.4. Synthesis of 1,2,4-trioxanes by the Kobayashi method

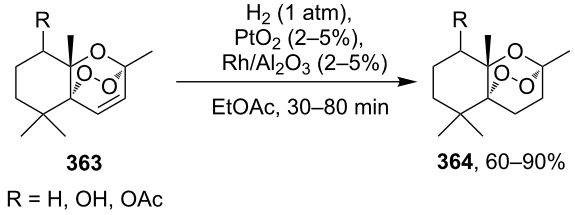
A convenient method for the synthesis of bicyclic trioxanes **362** was developed based on the hydroperoxidation of polyfunctional compounds **360** with the urea–hydrogen peroxide complex followed by the base-mediated intramolecular cyclization of **361** (Scheme 106). The yield of hydroperoxides **361** 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].



Scheme 106: Synthesis of 1,2,4-trioxanes **362** through Et_2NH-catalyzed intramolecular cyclization.

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].



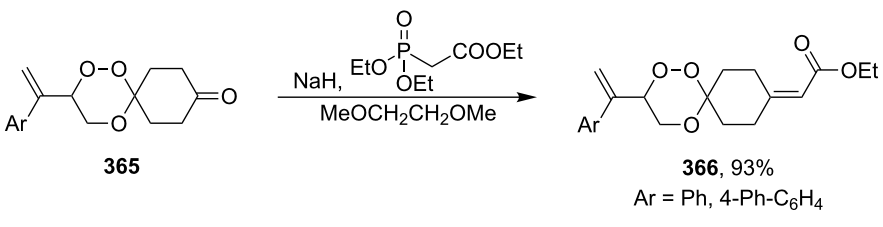
Scheme 107: Reduction of the double bond in tricyclic peroxides **363**.

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.

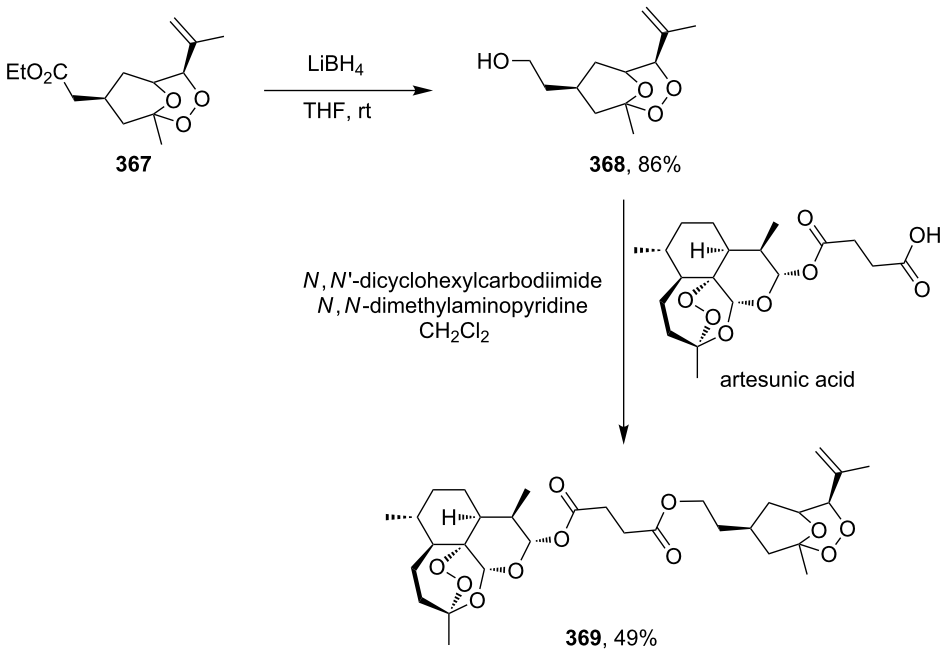
Peroxide dyad **369** consisting of 1,2,4-trioxane moieties of different types was synthesized by the esterification of artesunic acid with 2-((3*S*,6*R*)-1-methyl-6-(prop-1-en-2-yl)-7,8,9-trioxabicyclo[3.3.1]nonan-3-yl)ethanol (**368**) (obtained by the reduction of ethyl 2-((3*S*,6*R*)-1-methyl-6-(prop-1-en-2-yl)-7,8,9-trioxabicyclo[3.3.1]nonan-3-yl)acetate (**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 N^1-(7-chloroquin-4-yl)cyclohexane-1,4-diamine (**371**) (Scheme 110) [86].

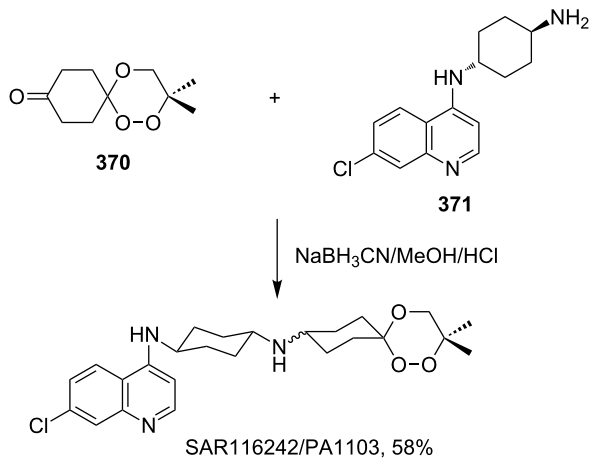
Trioxaferroquines, ferrocene-containing compounds, belong to a new type of hybrid molecules exhibiting high antimalarial activity. The last step of the synthesis of one of these com-



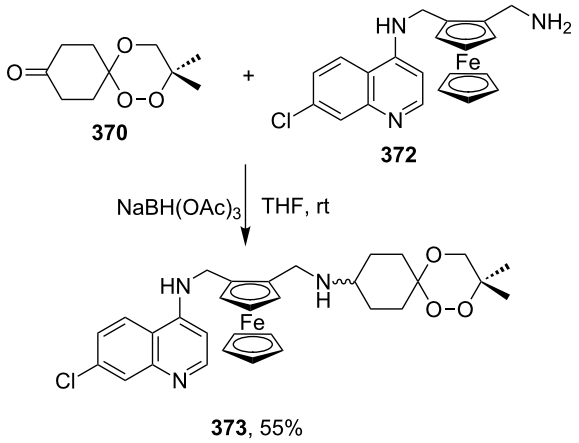
Scheme 108: Horner–Wadsworth–Emmons reaction in the presence of peroxide group.



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 **370**.



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

pounds (**373**) based on the reductive amination of ketone **370** with amine **372** is shown in Scheme 111. The unusual fact is that compound **373** bearing the peroxide bond and a Fe-containing moiety is stable [412].

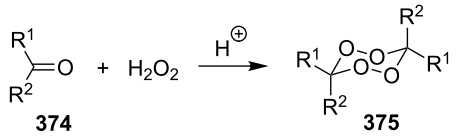
6. Synthesis fo 1,2,4,5-tetraoxanes

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_2O_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.



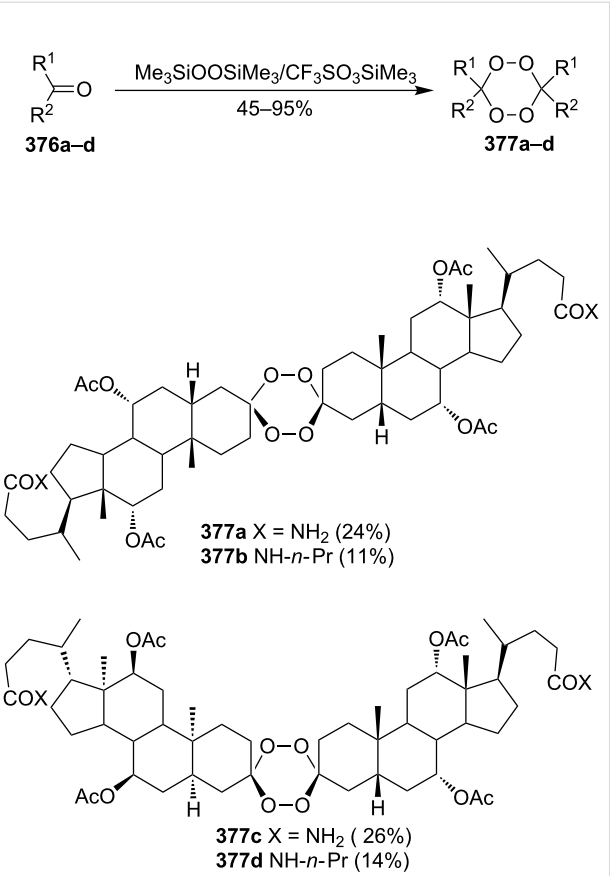
Scheme 112: Acid-catalyzed reactions of H_2O_2 with ketones and aldehydes **374**.

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

The cyclocondensation of carbonyl compounds **376a–d** with $Me_3SiOOSiMe_3/CF_3SO_3SiMe_3$ afforded steroidal tetraoxanes **377a–d** (Scheme 113) [417,418]. The cyclocondensation of ketones **376** was performed at 0 °C in acetonitrile using a 1.5-fold molar excess of $Me_3SiOOSiMe_3$ and $CF_3SO_3SiMe_3$ with respect to ketone **376** [417,418].

6.3. $MeReO_3$-catalyzed peroxidation of ketones

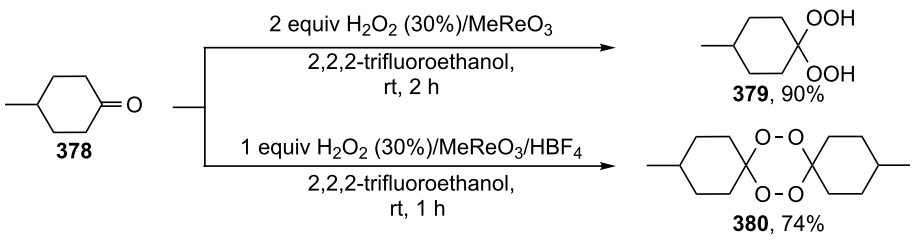
1,1-Dihydroperoxy-4-methylcyclohexane (**379**) and symmetrical tetraoxane **380** were selectively synthesized in high yields from 4-methylcyclohexanone (**378**) with the use of the 30% $H_2O_2/MeReO_3$/fluorinated alcohol system (Scheme 114) [419].



Scheme 113: Cyclocondensation of carbonyl compounds **376a–d** using $Me_3SiOOSiMe_3/CF_3SO_3SiMe_3$.

Table 24: Examples of symmetrical 1,2,4,5-tetraoxanes **375** synthesized by the acid-catalyzed cyclocondensation of ketones and aldehydes with H_2O_2.

Tetraoxane **375**; R^1, R^2	Reaction conditions	Yield, %	Reference
–CH(Et)$(CH_2)_4$–	H_2O_2, MeCN, H_2SO_4, −20 °C, 48 h	24	[413]
–CH(Pr)$(CH_2)_4$–		7	
–CH_2CH(Me)$(CH_2)_3$–		32	
–CH(Me)CH(Me)$(CH_2)_3$–		4	
–CH(Me)CH_2CH(Me)$(CH_2)_2$–		20	
–CH(Me)$(CH_2)_2$CH(Me)CH_2–		26	
–$(CH_2)_2$C(Me)$_2(CH_2)_2$–		29	
–CH(iPr)$(CH_2)_2$CH(Me)CH_2–		20	
–CH(Me)$(CH_2)_2$CH(iPr)CH_2–		26	
–CH(Me)CH_2C(Me)$_2(CH_2)_2$–		34	
–CH_2C(Me)$_2CH_2$C(Me)$_2CH_2$–		68	
–C(Me)$_2(CH_2)_4$–		26	
–CH(Me)$(CH_2)_3$CH(Me)–	H_2O_2, EtOH/H_2O, H_2SO_4, 0 °C	18	[414]
–$(CH_2)_5$–		90	
–$(CH_2)_5$–	H_2O_2, $(CF_3)_2$CHOH	≈100	[415]
H, –$(CH_2)_3$CHO	H_2O_2, EtOH/H_2O, H_2SO_4, −10°C, 1 h	80	[416]



Scheme 114: Peroxidation of 4-methylcyclohexanone (**378**).

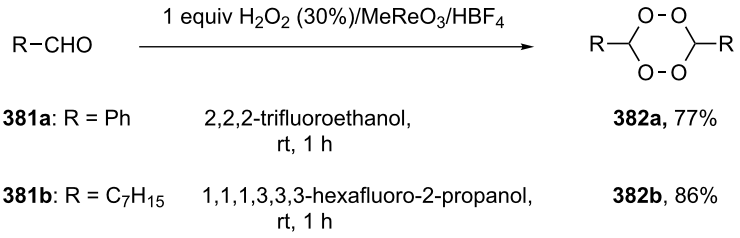
The use of fluorinated alcohols as the solvent results in an increase in the selectivity of the synthesis. Under similar conditions, symmetrical 3,6-diphenyl- and 3,6-di-(*n*-heptyl)-1,2,4,5-tetraoxanes **382a**,**b** were synthesized from benzaldehyde (**381a**) and *n*-octanal (**381b**), respectively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

Unsymmetrical tetraoxanes **383a–d** were prepared from 4-methylcyclohexanone (**378**) by the reaction with ketones (R^1COR^2) using of 1 equiv of HBF_4, 2 equiv of H_2O_2, and 0.1 mol % $MeReO_3$ in CF_3CH_2OH (TFE) at room temperature. The unsymmetrical tetraoxane, 3,3-dibutyl-6-heptyl-1,2,4,5-tetraoxane (**384**), was synthesized from octanal (**381b**) with the use of $CH_3CHOHCF_3$ (HFIP) (Scheme 116) [419].

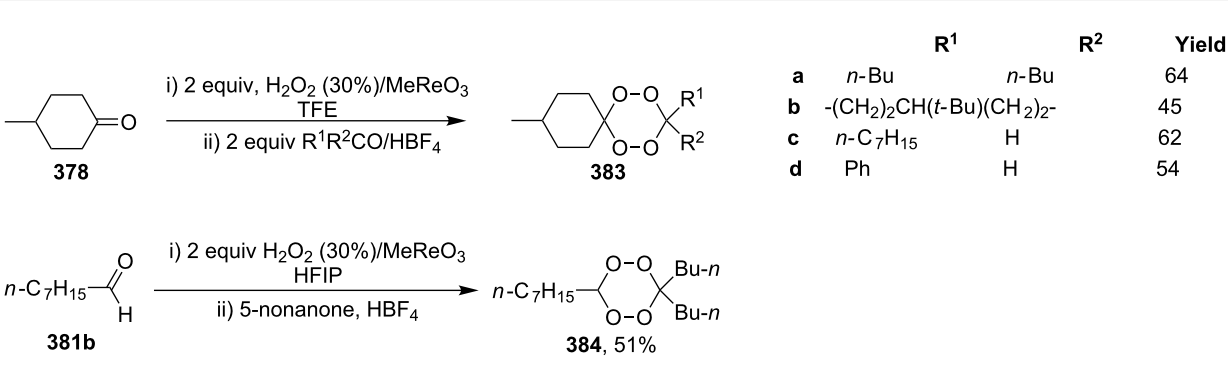
This method was applied to the synthesis of 3,3,6,6-tetraalkyl-1,2,4,5-tetraoxanes **386a–c** and **388a–i** from cyclic **385a–c** and acyclic ketones **387a–i** (Scheme 117) [420], as well as of dispiro-1,2,4,5-tetraoxanes **390a–c** from 4-substituted cyclohexanones **389a–c** (Scheme 118) [421].

The use of the 30% H_2O_2/$MeReO_3$ (MTO)/fluorinated alcohol system enabled the synthesis of symmetrical compounds **392** from aldehydes **391** and unsymmetrical tetraoxanes **393** containing aryl (peroxide-destabilizing) substituents from aldehydes **391** (and cycloalkanones) (Scheme 119) [422].

Unsymmmetrical 1,2,4,5-tetraoxanes containing adamantane (**395a–i**) and cyclodecane moieties (**396a–d**) exhibiting high

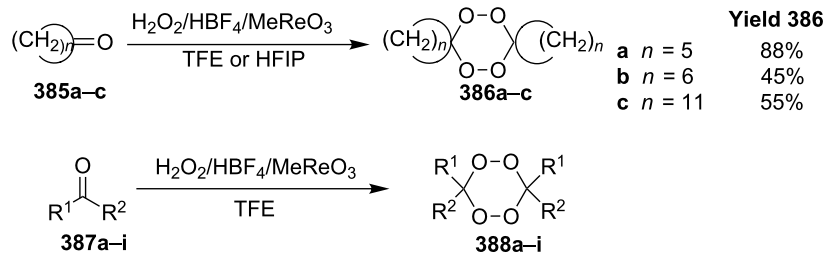


Scheme 115: Synthesis of symmetrical tetraoxanes **382a**,**b** from aldehydes **381a**,**b**.



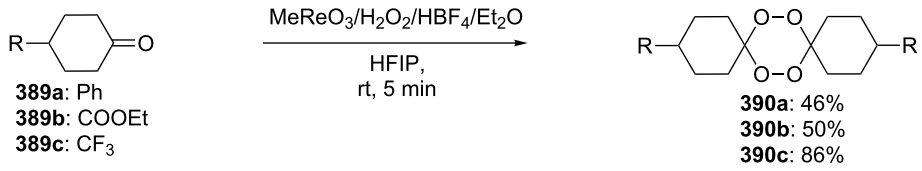
	R^1	R^2	Yield
a	*n*-Bu	*n*-Bu	64
b	-$(CH_2)_2$CH(*t*-Bu)$(CH_2)_2$-		45
c	*n*-C_7H_{15}	H	62
d	Ph	H	54

Scheme 116: Synthesis of unsymmetrical tetraoxanes using of $MeReO_3$.

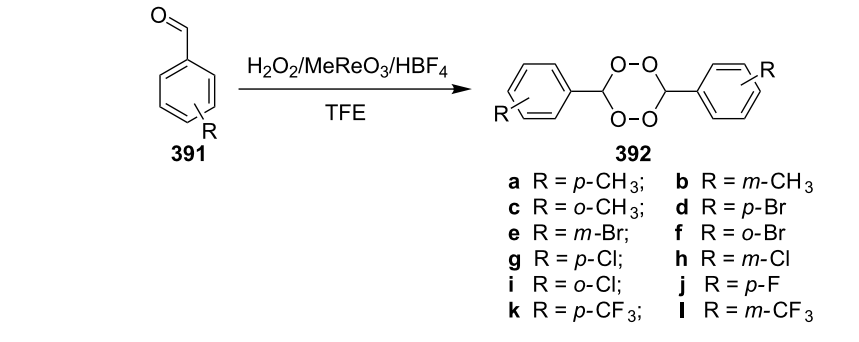


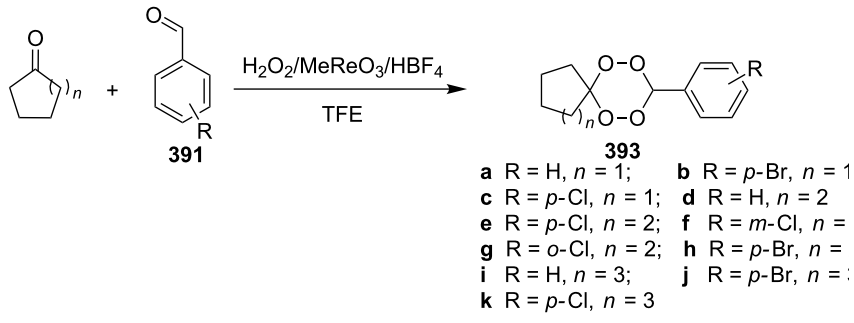
	Yield 388		Yield 388
a R^1 = Et, R^2 = Et	57 %	**f** R^1 = Et, R^2 = *n*-C_5H_{11}	59%
b R^1 = *n*-Pr, R^2 = *n*-Pr	45 %	**g** R^1 = Et, R^2 = *n*-C_6H_{13}	55%
c R^1 = *n*-Bu, R^2 = *n*-Bu	44 %	**h** R^1 = Et, R^2 = *n*-C_7H_{15}	57%
d R^1 = Et, R^2 = *n*-Pr	56 %	**i** R^1 = Me, R^2 = *n*-C_7H_{15}	72%
e R^1 = Et, R^2 = *n*=Bu	55 %		

Scheme 117: Synthesis of symmetrical tetraoxanes using of $MeReO_3$.

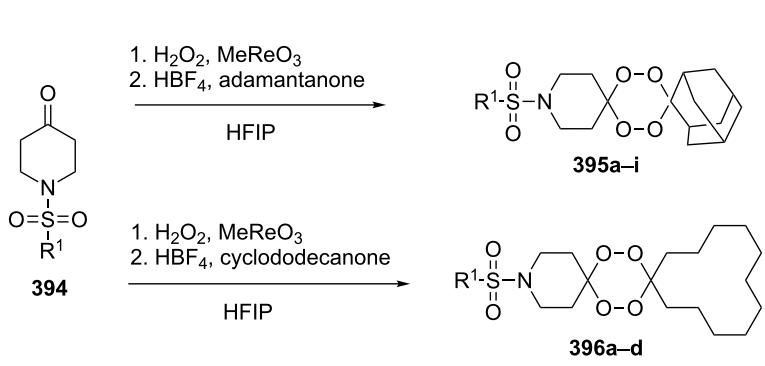


Scheme 118: Synthesis of symmetrical tetraoxanes using of $MeReO_3$.





Scheme 119: $MeReO_3$ in the synthesis of symmetrical tetraoxanes with the use of aldehydes.



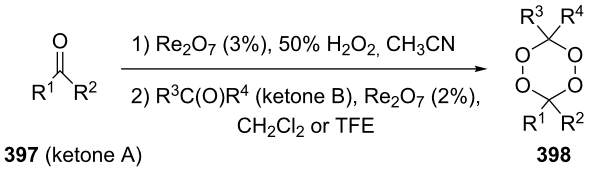
	Yield
395a R^1 = Me	61%
395b R^1 = Et	60%
395c R^1 = iPr	56%
395d R^1 = Cp	53%
395e R^1 = CF_3CH_2	51%
395f R^1 = Ph	36%
395g R^1 = 4-ClC_6H_4	41%
395h R^1 = 4-FC_6H_4	38%
395i R^1 = 4-$CF_3C_6H_4$	25%
396a R^1 = Me	36%
396b R^1 = Et	32%
396c R^1 = iPr	38%
396d R^1 = Ph	20%

Scheme 120: Preparation of unsymmmetrical 1,2,4,5-tetraoxanes with high antimalarial activity.

antimalarial activity (Scheme 120) were prepared from sulfonylpiperidones **394** [138].

6.4. Re_2O_7-Catalyzed cyclocondensation of *gem*-bishydroperoxides with ketones

Re_2O_7 is an efficient catalyst for the addition of hydroperoxide groups to ketones and aldehydes. Due to these properties, Re_2O_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].



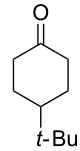
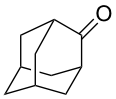
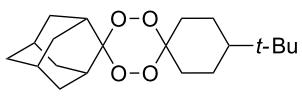
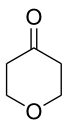
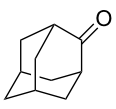
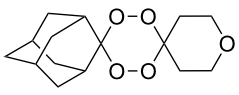
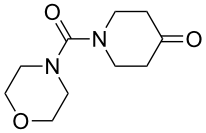
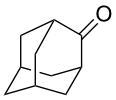
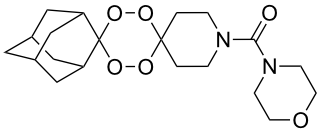
Scheme 121: Re_2O_7-Catalyzed synthesis of tetraoxanes **398**.

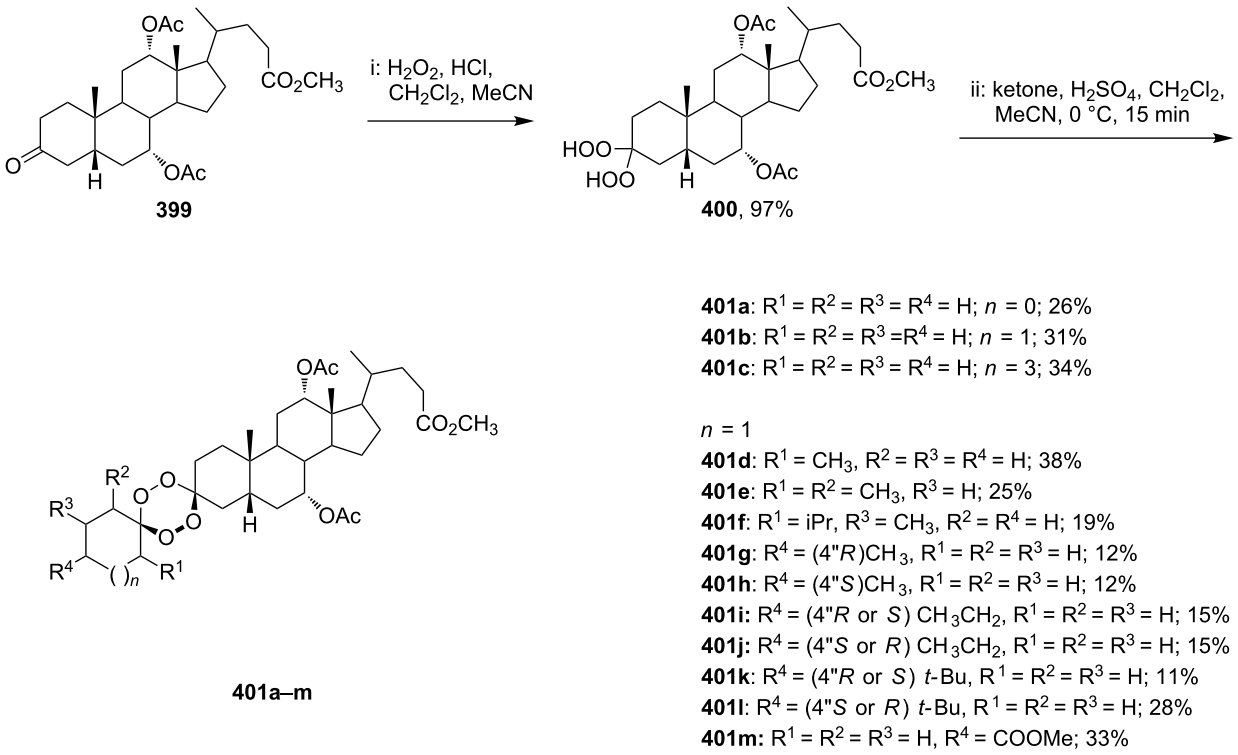
6.5. Protic acid-catalyzed cyclocondensation of *gem*-bishydroperoxides with ketones

Unsymmetrical steroidal tetraoxanes **401** were synthesized by the hydroperoxidation of methyl 3-oxo-7α,12α-diacetoxy-5β-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_2SO_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_2O_7-Catalyzed synthesis of tetraoxanes **398**.

Ketone A, **397**	Ketone B	Reaction conditions	Tetraoxane **398**	Yield, %
		1) H_2O_2 (2 equiv), 0.5 h, 0 °C 2) Ketone B (2 equiv), CH_2Cl_2, 1 h, rt		67
		1) H_2O_2 (4 equiv), 0.5 h, rt 2) Ketone B (4 equiv), 2,2,2-trifluoroethanol, Re_2O_7, 0.5 h, rt		69
		1) H_2O_2 (4 equiv), 6 h, rt 2) Ketone B (4 equiv), 2,2,2-trifluoroethanol, Re_2O_7, 2 h, rt		49



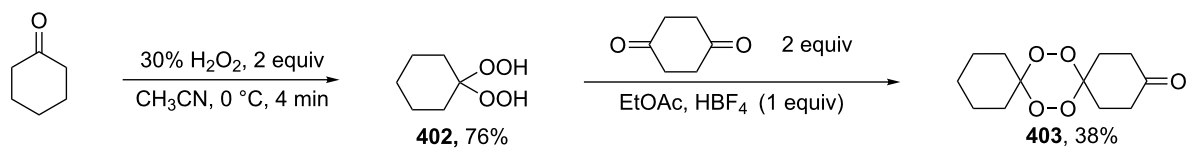
Scheme 122: H_2SO_4-Catalyzed synthesis of steroidal tetraoxanes **401**.

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-cyclohexanedione was carried out in the presence of HBF_4 (Scheme 123).

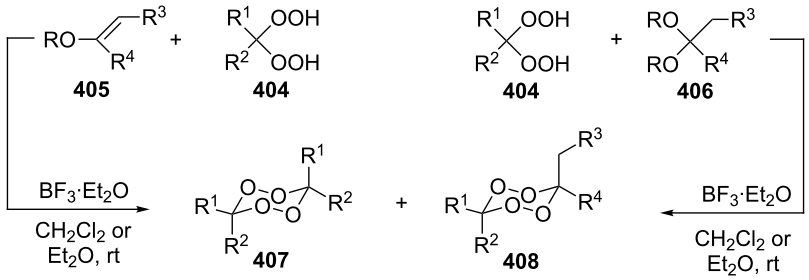
6.6. Cyclocondensation of bishydroperoxides with acetals and enol ethers

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].

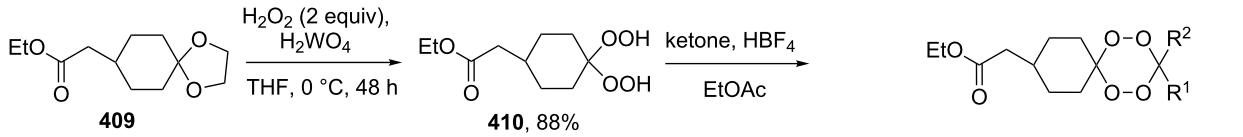
The bishydroperoxidation of 1,3-dioxolane **409** was carried out in the presence of H_2WO_4. The following HBF_4-catalyzed condensation of bishydroperoxide **410** with ketones gave 1,2,4,5-tetraoxanes **411a–c** containing the ester group (Scheme 125) [144].



Scheme 123: HBF_4-Catalyzed condensation of bishydroperoxide **402** with 1,4-cyclohexanedione.



Scheme 124: $BF_3{\cdot}Et_2O$-Catalyzed reaction of *gem*-bishydroperoxides **404** with enol ethers **405** and acetals **406**.



411a $R^1 = R^2 = -(CH_2)_5-$, 75%
411b $R^1 = R^2 = -(CH_2)_{11}-$, 66%
411c $R^1 = R^2$ = adamantylidene, 87%

Scheme 125: HBF_4-Catalyzed cyclocondensation of bishydroperoxide **410** with ketones.

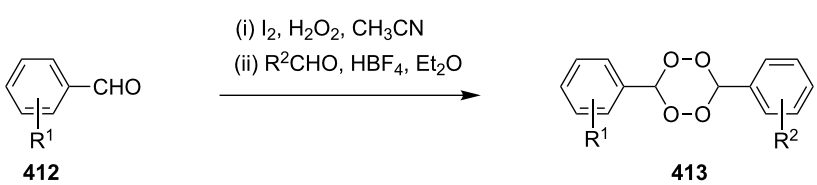
6.7. Iodine-catalyzed one-pot synthesis of symmetrical and unsymmetrical tetraoxanes

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 β-diketones with hydrogen peroxide

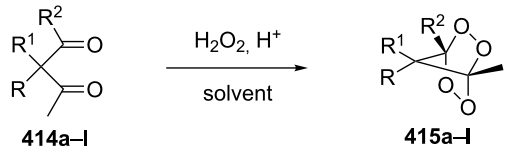
The acid-catalyzed condensation of β-diketones **414a–l** with hydrogen peroxide is a simple and facile method for the synthesis of bridged 1,2,4,5-tetraoxanes **415a–l**. This method enables the synthesis of these compounds on the multigram scale in 47–77% yields (Scheme 127). The high concentration of a strong acid, such as H_2SO_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.



Scheme 126: Synthesis of symmetrical and unsymmetrical tetraoxanes **413** from benzaldehydes **412**.

Table 26: Iodine-catalyzed one-pot synthesis of tetraoxanes **413**.

Tetraoxane **413**		Yield, %	Tetraoxane **413**		Yield, %
R^1	R^2		R^1	R^2	
o-Me	*o*-Me	42	*p*-(*t*-Bu)	*p*-(*n*-Pr)	32
o-Me	*m*-Me	33	*p*-(*t*-Bu)	*p*-(iPr)	38
p-Me	*p*-Me	54	*p*-(*n*-Pr)	*p*-(iPr)	28
p-Me	*p*-(iPr)	33	*p*-(*t*-Bu)	*p*-OMe	22
p-Me	*p*-(*t*-Bu)	46	*p*-(iPr)	*p*-OMe	24
p-Me	*p*-OMe	25	*p*-Et	*p*-Me	41
p-Me	*p*-CO_2Me	37	*p*-Et	*m*-Me	39
p-Me	*o*-Me	25	*p*-Et	*p*-(iPr)	37
p-Me	*m*-Me	38	*p*-Et	*p*-(*t*-Bu)	25
p-Me	*p*-(*n*-Pr)	37	*p*-(*n*-Pr)	*p*-OMe	24
p-Me	H	43	*p*-Cl	*p*-Cl	25
p-Me	*p*-CHO	31	*p*-Br	*p*-Br	22
p-(*n*-Bu)	*p*-(*n*-Bu)	40	*p*-F	*p*-F	29
p-(*t*-Bu)	*p*-(*t*-Bu)	53	*p*-OMe	*p*-OMe	27
m-Me	*m*-Me	51	*p*-Et	*p*-Et	44
m-Me	H	30	*p*-(*n*-Pr)	*p*-(*n*-Pr)	38
m-Me	*p*-OMe	29	*p*- (iPr)	*p*-(iPr)	41



414a–l **415a–l**

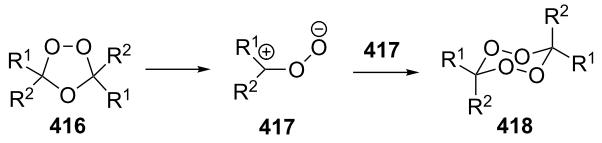
	yield **415**
a: R = Bu, R^1 = H, R^2 = Me	77%
b: R = Bu, R^1 = Me, R^2 = Me	73%
c: R = CH_2-CH=CH_2, R^1 = H; R^2 = Me	62%
d: R = CH_2CH_2CN, R^1 = H; R^2 = Me	47%
e: R = CH_2CH_2COOEt, R^1 = H, R^2 = Me	55%
f: R = 1-adamantyl, R^1 = H, R^2 = Me	67%
g: R = CH_2Ph, R^1 = H, R^2 = Me	69%
h: R = *m*-$MePhCH_2$, R^1 = H, R^2 = Me	75%
i: R = *p*-$MePhCH_2$, R^1 = H, R^2 = Me	77%
j: R = *o*-$MeOPhCH_2$, R^1 = H, R^2 = Me	54%
k: R = *p*-NO_2PhCH_2, R^1 = *H*, R^2 = Me	58%
l: R = R^2 = -$(CH_2)_4$-, R^1 = H	48%

Scheme 127: Synthesis of bridged 1,2,4,5-tetraoxanes **415a–l** from β-diketones **414a–l** and H_2O_2.

It was found that phosphomolybdic acid and phosphotungstic acid efficiently catalyze the addition of H_2O_2 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

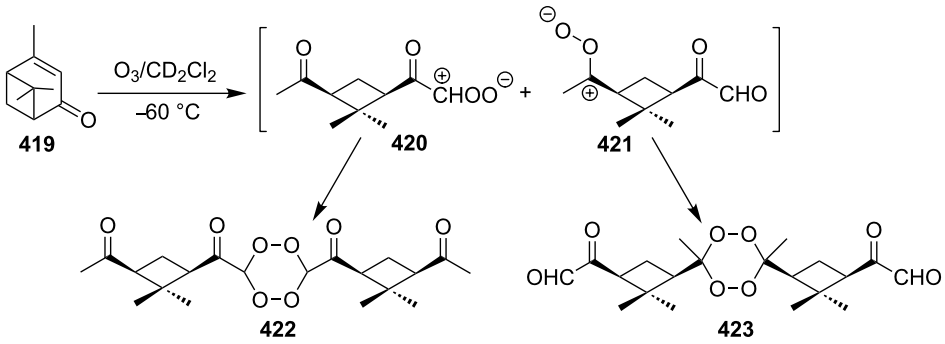
The dimerization of zwitterions **417** produced by decomposition of ozonides **416** affords symmetrical tetraoxanes **418** (Scheme 128).



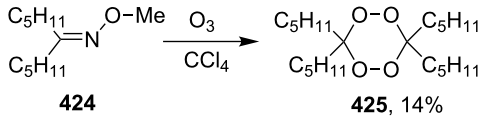
Scheme 128: Dimerization of zwitterions **417**.

For example, the ozonolysis of verbenone **419** via the formation of zwitterioninc 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.



Scheme 129: Ozonolysis of verbenone **419**.



Scheme 130: Ozonolysis of O-methyl oxime **424**.

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].

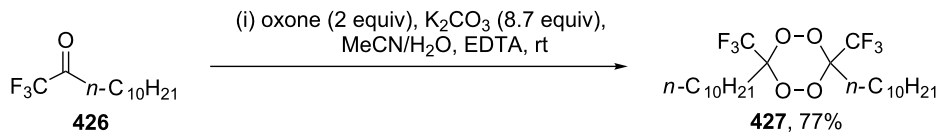
The synthesis of unsymmetrical steroidal tetraoxane **429** in 19% yield was performed by the intramolecular cyclization of dialdehyde **428** with hydrogen peroxide under acidic conditions (Scheme 132) [434].

In the synthesis of geminal bishydroperoxides by $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}$MeOH-catalyzed reactions of ketals **430–432** with hydrogen peroxide in Et_2O tetraoxanes **433–435** (Scheme 133) are obtained as by-products in 12%, 6%, and 19% yields, respectively [435].

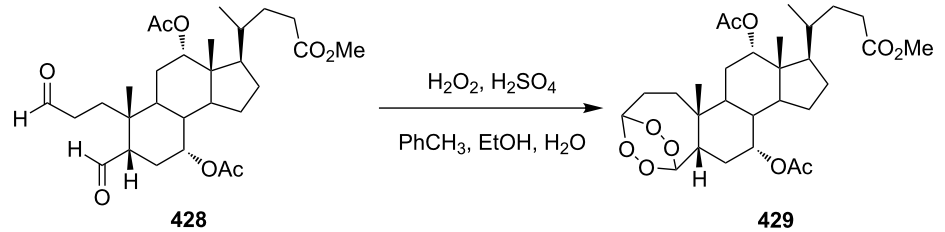
Scheme 134 shows the synthesis of 3,3,6,6-tetramethyl-1,2,4,5-tetraoxane (**437**) in 90% yield by the transformation of the intermediate 3,3,6,6,9,9-hexamethyl-1,2,4,5,7,8-hexaoxononane (**436**) in acetone [436]. This method is suitable for the preparation of the target product in amounts of only several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

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

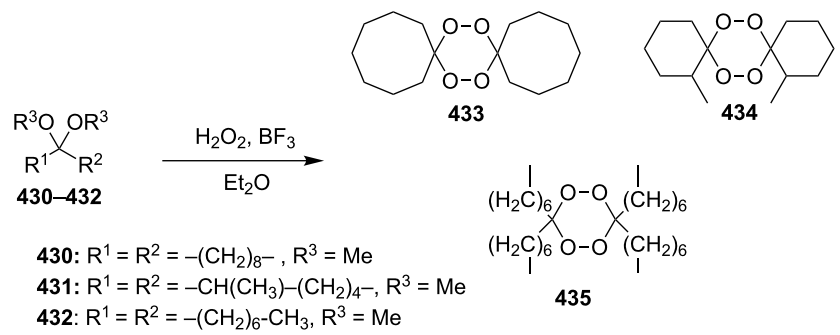
In the last two decades, 1,2,4,5-tetraoxanes were considered as the most promising compounds for the design of antiparasitic drugs. This is due, first, to the high activity of their derivatives



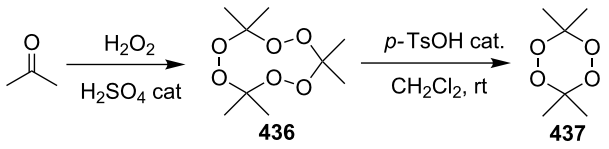
Scheme 131: Peroxidation of 1,1,1-trifluorododecan-2-one **426** with oxone.



Scheme 132: Intramolecular cyclization of dialdehyde **428** with H_2O_2.



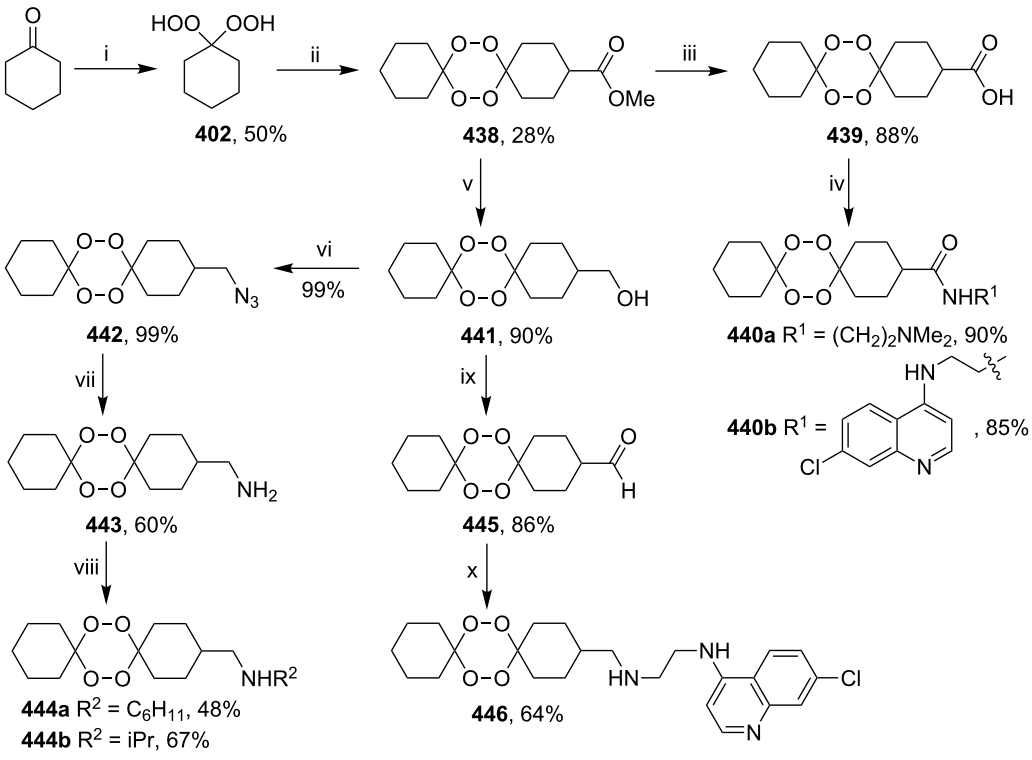
Scheme 133: Tetraoxanes **433**–**435** as by-products in peroxidation of ketals **430**–**432**.



Scheme 134: Transformation of triperoxide **436** in diperoxide **437**.

and, second, to a wide scope of structural modifications, in which the tetraoxane ring remains intact.

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



Scheme 135: Preparation and structural modifications of tetraoxanes.

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 $LiAlH_4$ and $NaBH(OAc)_3$, with the products retaining the peroxide ring.

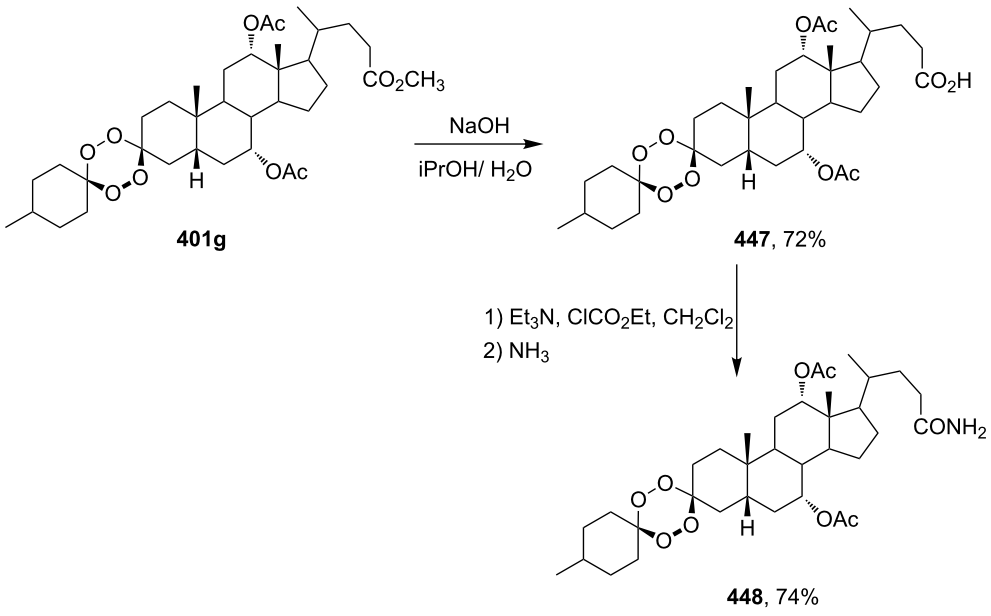
Steroidal tetraoxane **448**, which is approximately six times more active that Artelinic acid and 2.4 times as active as arteether against *P. falciparum*, was also synthesized by the alkaline hydrolysis of ester **401g** followed by the amidation of acid **447** (Scheme 136) [128].

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-methylbenzo[*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].

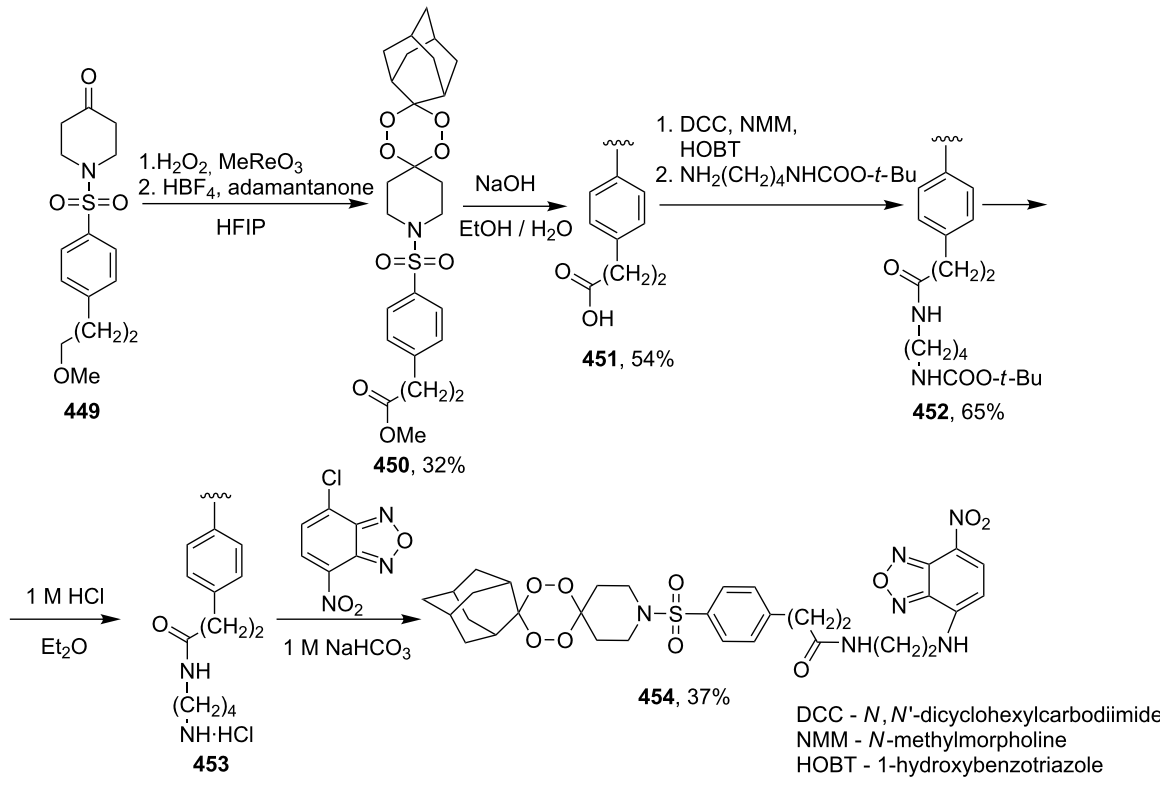
The synthesis of tetraoxane **458** (RKA182) exhibiting the in vitro and in vivo activity comparable with that of artemisinin was performed on the kilogram scale according to Scheme 138. This compound is a promising malaria drug candidate [82,83]. The key steps in this synthesis are the preparation of 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

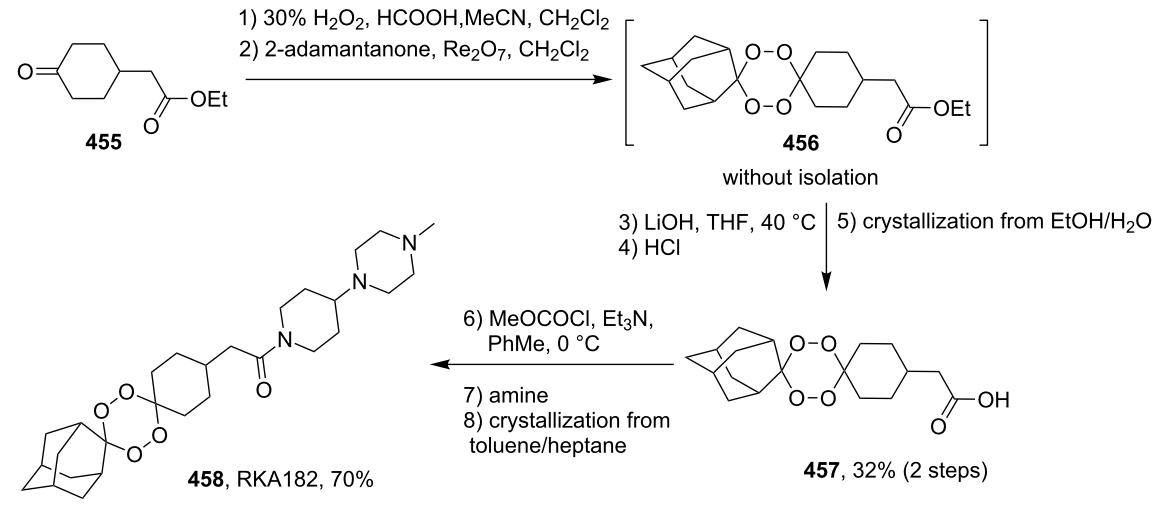
The review summarizes and generalizes studies on the synthesis of five- and six-membered cyclic peroxides published last decade (since 2000 to present). Most of the currently established methods for the synthesis of these compounds are based on the use of such key oxidizing agents as oxygen, ozone, and 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.



Scheme 136: Structural modifications of steroidal tetraoxanes.



Scheme 137: Synthesis of 1,2,4,5-tetraoxane **454** containing the fluorescent moiety.



Scheme 138: Synthesis of tetraoxane **458** (RKA182).

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 dialkyloxy derivatives with hydrogen peroxide or *gem*-bishydroperoxides catalyzed by protic and aprotic acids, such as $MeReO_3$, Re_2O_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.

Acknowledgements

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