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Total Synthesis of Plakortide E and Biomimetic Synthesis of Plakortone B

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Xiao-Yu Sun

Total Synthesis of Plakortide E and Biomimetic Synthesis of Plakortone B

Doctoral Thesis accepted by
The Chinese University of Hong Kong

Springer

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Supervisor's Foreword

This thesis describes the first total synthesis of all possible stereoisomers of the peroxide natural product plakortide E. This includes the first confirmation of the absolute configuration of natural plakortide E, based on the conversion of plakortide E to plakortone B. This transformation also suggests a biomimetic conversion of plakortide E to plakortone B.

A new synthetic approach involving palladium-catalyzed reaction of vinyl cyclopropanes with hydrogen peroxide to form highly substituted 1,2-dioxolanes was developed. A lipase-catalyzed kinetic resolution was employed to provide optically pure 1,2-dioxolane central cores. The efficient conversion of these optically pure 1,2-dioxolane central cores into four possible 3,5-*cis*-stereoisomers of the plakortide E structure is very interesting and challenging. The successful application of the Corey-Fuchs homologation on the framework of 1,2-dioxolane, involving a metal-halogen exchange, is particularly impressive. This pathway may be the first reported example of metal-halogen exchange on cyclic peroxides. Two palladium-mediated reactions in the presence of 1,2-dioxolanes were used during the homologation sequence: a palladium-catalyzed hydrostannylation of an alkyne and Negishi olefination. Our results may widen the synthetic scope of hindered peroxide chemistry. Furthermore, these results will be of interest to scientists interested in organic peroxides as well as in the marine natural products containing five-membered cyclic peroxides.

For the following reasons I am convinced that the research presented in this thesis is outstanding and significant.

I. Plakortide E and plakortone B have attractive bioactivities and the synthetic studies toward them and their analogs will be pivotal both for the evaluation of the biological activity of these molecules and their analogs, and for drug discovery.
II. The methodology study for the syntheses of highly substituted cyclic peroxides is novel and useful, which not only extends the field of Pd-catalyzed reactions, but also provides a convenient synthetic approach to prepare 1,2-dioxolanes series.

III. It goes without saying that construction and functionalization of 1,2-dioxolanes are particularly difficult because of the low O–O bond dissociation energy, so the syntheses in the thesis are full of challenges.
IV. The convergent synthetic strategy was employed in the total synthesis of plakortide E, so the synthesis is step-economical, starting from (+)-*cis*-**137a**, the plakortide candidate structure (10*S*)-(+)-*cis*-**86a** was efficiently synthesized in ten simple chemical operations.
V. The thesis is well prepared and the chemistry inside clearly described.

Hong Kong, September 2011 Henry N. C. Wong

Acknowledgments

I would like to express my sincere thanks to my supervisor, Prof. Henry N. C. Wong, for his invaluable advice and guidance in my research work, thesis writing, and looking for a postdoctoral position.

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In addition, I give my special thanks to all the past and present members of Prof. Wong's research group, especially Dr. Jia-Qiang Dong, Dr. Xin-Gang Xie, Dr. Carole Law, Mr. Chao Cheng, Mr. Yin-Suo Lu and Mr. Xue-Song Xu for helpful discussions and co-operation.

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April 2011

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Contents

Abbreviations

[α]	Specific rotation
Å	Ångstrom (s)
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Anal.	Analytical
aq.	Aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
BDE	Bond dissociation energy
BHT	2,6-di-*tert*-butyl-4-methyl phenol
cat.	Catalytic
conc.	Concentrated
δ	Chemical shift in parts per million downfield from tetramethylsilane
d	Day (s), doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	Diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	Dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
Et	Ethyl
EI	Electron impact (in mass spectrometry)
ESI	Electrospray ionization
equiv	Equivalent
FAB	Fast atom bombardment
FT	Fourier transform

HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrum
HWE	Horner-Wadsworth-Emmons
IR	Infrared
J	Coupling constant (in NMR)
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
lit.	Literature
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
m	Multiplet (spectral),milli-
Me	Methyl
m.p	Melting point
MS	Mass spectrometry; molecular sieves
m/z	Mass to charge ratio (in mass spectrometry)
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectroscopy
PDC	Pyridinium dichromate
Ph	Phenyl
ppm	Parts per million (in NMR)
^{i}Pr	Isopropyl
q	Quartet
R_f	Retention factor
rt	Room temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	Triethylamine
tert-	Tertiary
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
p-TsOH	*p*-toluenesulfonic acid

Chapter 1
Introduction

1.1 Introduction to Organic Peroxides

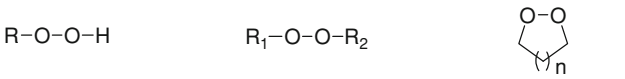
Organic peroxides are compounds containing an O–O bond. The O–O group is called the peroxide group. The peroxide bond is one of the weakest bonds in organic molecules, with BDE of approximately 34 kcal/mol (C–C: 81 kcal/mol, C–H: 98 kcal/mol, C–O: 79 kcal/mol, C–N: 66 kcal/mol) [1, 2]. The O–O bond is unstable and easily splits into reactive radicals via homolytic cleavage. For this reason, peroxides are found in nature only in small quantities, in water, atmosphere, plants, animals and man. According to the substitution patterns, organic peroxides can be classified into hydroperoxides, acyclic dialkyl peroxide and cyclic peroxides (Fig. 1.1).

1.2 Cyclic Peroxide Natural Products and Their Potential Biological Activities

Ascaridole, used as a remedy for worms, which was isolated from chenopodium oil and named by Hüthig in 1908 [3], was the first studied naturally occurring organic peroxide (Fig. 1.2). Hüthig described its explosive character and determined its chemical formula as $C_{10}H_{16}O_2$. In 1911, these results were confirmed by Nelson in his detailed study of ascaridole [3].

One of the most important medical applications of organic peroxides has been in the treatment of malarial. In the worldwide scale, there are 300–500 million clinical cases of people that are infected by malaria every year, and between one to three million deaths, mostly of children, are attributable to this disease. Every 40 s a child dies of malaria, resulting in a daily loss of more than 2,000 young lives worldwide. These estimates made malaria one of the top three killers among communicable diseases [4].

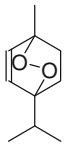
X.-Y. Sun, *Total Synthesis of Plakortide E and Biomimetic Synthesis of Plakortone B,* Springer Theses, DOI: 10.1007/978-3-642-27195-3_1,



Hydroperoxides Acyclic dialkyl peroxide Cyclic peroxides

Fig. 1.1 Categories of peroxides

Fig. 1.2 The first studied naturally occurring organic peroxide



Ascaridole

In the search for antimalarial drugs, yingzhaosu A was isolated by Liang et al. in 1979 from *Artabotrys uncinatus* (Annonaceae) [5], which was used in China as a traditional remedy for the treatment of malaria (Fig. 1.3). Further work from this lab resulted in the isolation of yingzhaosu C (Fig. 1.3) [6]. Yingzhaosus A and C both contain a 1,2-dioxane core structure. These compounds have been extensively studied for their potential antimalarial activity.

At about the same time, artemisinin, a naturally occurring organic peroxide with a 1,2,4-trioxane core, also known as qinghaosu, was isolated from the plant *Artemisia annua*, a herb described in Chinese traditional medicine by Wu and coworkers (Figs. 1.3 and 1.4) [7]. Artemisinin and its derivatives are a group of drugs that possess the most rapid action of all current drugs against falciparum malaria. The discovery of strong antimalarial activity from artemisinin and yinghaosu motivated the worldwide exploration of antimalarial cyclic peroxide drugs. Since scientists recognized the pivotal role of cyclic peroxides in various vital biological processes [8], the chemistry of cyclic peroxides has been rejuvenated in the 1970s. More and more naturally occurring cyclic peroxides have been isolated and identified.

Chondrillin, isolated from a Great Barrier Reef sponge of the genus *Chondrilla* by Wells in 1976, was the first cyclic peroxide to be isolated from marine sources [9]. Later, it was also isolated from another marine sponge *Plakortis lita* by DeGuzman and Christophersen [10, 11], and its diastereomer plakorin and a number of other alkoxydioxines were isolated from this marine sponge (Fig. 1.5) [12].

These peroxides have shown interesting biological properties. For example, chondrillin was found to have an *in vitro* IC_{50} of 5 μg/mL against P388 leukemia cells [10, 11]. Plakorin is a potent activator of sarcoplasmic reticulum calcium-ATPase, and it also has an *in vitro* $IC_{50} = 0.85$ μg/mL against murine lymphoma L1210 cells and $IC_{50} = 1.8$ μg/mL against human epidermoid carcinoma KB cells [13].

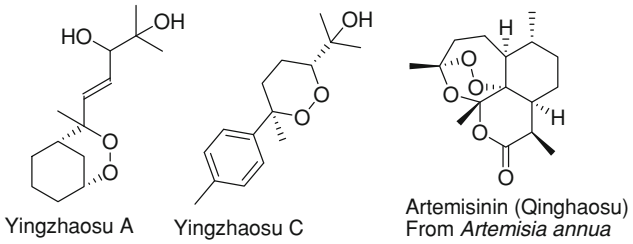
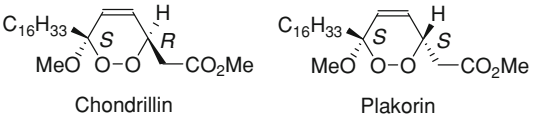


Fig. 1.3 Antimalarial natural cyclic peroxides

Fig. 1.4 *Artemisia annua*

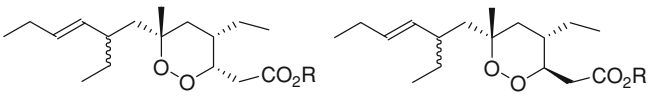
Fig. 1.5 Six-membered cyclic peroxides



Many natural peroxides with 1,2-dioxine or 1,2-dioxane subunits have been isolated from the marine sponge, *Plakortis sp.*, especially from *Plakortis halichondrioides*. For example, plakortin (**1**), 3-epi-plakortin (**2**), plakortic acid (**3**) all share a common six-membered cyclic peroxide core (Fig. 1.6). The marine cyclic peroxide plakortic acid (**3**) is a potent antifungal and antibacterial agent; however, the corresponding methyl ester, plakortin (**1**), is inactive [14, 15].

Plakinic acid A, a 3,3,5,5-tetrasubstituted 1,2-dioxolane isolated from a Caribbean sponge, was the first isolated five-membered ring peroxide among marine natural products (Fig. 1.7) [16, 17]. In the last decades, many additional plakinates have been isolated and characterized, which usually exhibited remarkable cytotoxicity against fungal and cancer cell lines [17–25]. As shown in Table 1.1, all the plakinic acids contained a 3,3,5,5-tetrasubstituted 1,2-dioxolane core.

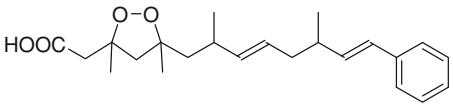
The highly unstable prostaglandin H_2 (PGH_2) and prostaglandin G_2 (PGG_2), containing a five-membered ring peroxide, were isolated and identified as key intermediates in prostaglandin's biosynthesis from arachidonic acid (Fig. 1.8) [26–28]. PGH_2 and PGG_2 were also biosynthetic precursors for many other physiological important compounds, such as prostacyclins and thromboxanes [29, 30]. Afterwards, the total syntheses of PGH_2 and PGG_2 were reported by Porter and coworkers [102] and Johnson and coworkers [110]. The early studies on prostaglandin endoperoxides and their analogs were reviewed by Nicolaou and Salomon [31, 32].



1 R = Me
3 R = H

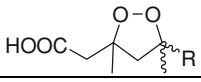
2

Fig. 1.6 Natural products with 1,2-dioxane cores



Plakinic acid A

Fig. 1.7 The first isolated five-membered ring peroxide

Table 1.1 Plakinates from marine sponge 

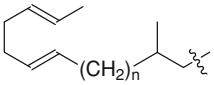
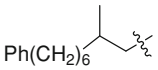
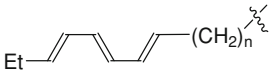
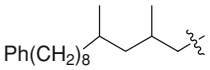
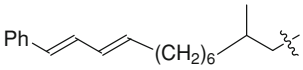
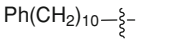
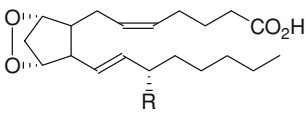
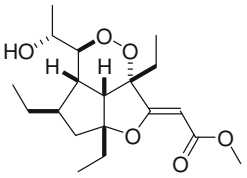
R		Plakinate	Reference
$C_{16}H_{33}$ $C_{15}H_{31}$		unnamed	[18]
	n = 4	C (3,5-*cis*); epi-C (3,5-*trans*)	[17]
	n = 2	D (3,5-*cis*); epi-D (3,5-*trans*)	[17]
		epi-E (3,5-*trans*)	[20]
		F (3,5-*cis*); epi-F (3,5-*trans*)	[21]
		G (3,5-*cis*); epi-G (3,5-*trans*)	[22]
		unnamed (3,5-cis); unnamed (3,5-trans)	[108]
		andavadoic acid (3,5-*trans*)	[24]

Fig. 1.8 Prostaglandin G_2 and H_2

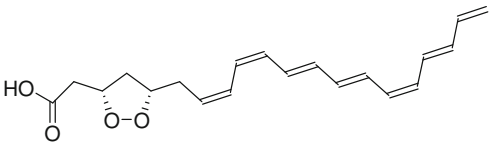


R =OOH, Prostaglandin G_2
R = OH, Prostaglandin H_2



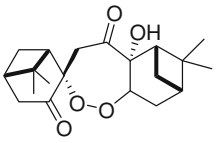
Gracilioether A

Fig. 1.9 A polycyclic natural product with 1,2-dioxane core



Mycangimycin

Fig. 1.10 A novel linear polyene peroxide



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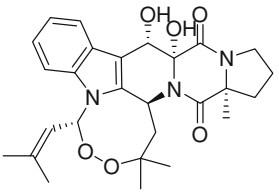


Verruculogen (**5**)

Fig. 1.11 Natural products containing medium ring cyclic peroxides

In the course of their continuing search for drug leads from Japanese marine invertebrates, Nakao and Fusetani isolated graciliorther A from the deep-sea sponge *Agelas gracilis* in 2009, which show considerable antimalarial activity (Fig. 1.9) [33]. The absolute stereochemistry of graciliorther A was confirmed by application of the modified Mosher's method.

Clardy and coworkers in their study of the southern pine beetle system, have discovered another symbiont (Streptomyces sp. SPB74) that produces a polyene peroxide, which was named mycangimycin (Fig. 1.10). It was found that mycangimycin selectively inhibits the beetle's fungal antagonist. The complete structure was fully elucidated including the absolute configuration [34, 35].

Although majority of cyclic peroxide natural products contain dioxanes or dioxolanes, some medium ring cyclic peroxides discovered in nature (Fig. 1.11). The terpenic peroxide **4** was isolated from the spice cardamom, the fruit of *Amomum krervanh* Pierre, which contained a seven-membered cyclic peroxide core. Compound **4** also exhibited moderate antimalarial activity *in vitro* against *Plasmodium falciparum* (IC_{50} = 170 nM) [36]. Verruculogen (**5**), containing a novel eight-membered cyclic peroxide core, was obtained from a strain of *Penicillium verruculosum* Peyronel isolated from peanuts, which was fully characterized by Clardy and coworkers in 1974 [37, 38].

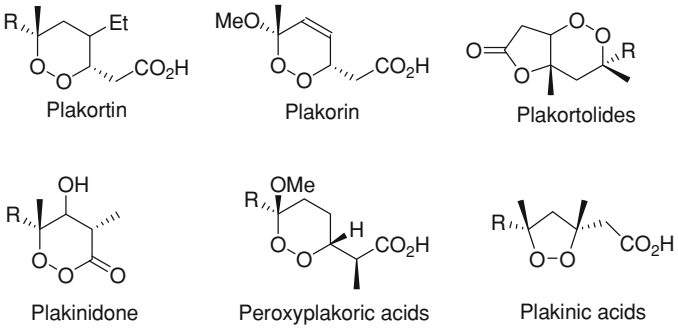


Fig. 1.12 Natural products from the genus *Plakortis*

1.3 Natural Products from Marine Sponges of the Genus Plakortis

Marine sponges have been among the most studied of marine organisms. The genus *Plakortis* has attracted particularly interests as a source of novel metabolites. Many unusual metabolites isolated from the genus *Plakortis* exhibited anti-fungal, anti-tumor, anti-bacterial and other important pharmacological activities. Based on their work, the structures, stereochemistry, pharmacological activities and selected syntheses of the *Plakortis* derived metabolites have been reviewed by Kitching and coworkers in 2004 [39–41].

Examples of cyclic peroxides isolated from the genus *Plakortis* are illustrated in Fig. 1.12. These cyclic peroxide natural products are very fascinating because of their novel structure and activities.

In their continuing search for biologically active natural products to cure cardiac disease, Patil and coworkers employed a high throughput screening to evaluate the ability of natural products to stimulate cardiac SR-Ca^{2+} ATPase [42]. A screening of over 2400 plant and marine extracts found an extract of sponge *Plakortis halichondrioides* with the ability to stimulate cardiac SR-Ca^{2+} ATPase activity. This led to the discovery of four novel polyketides, plakortones A–D, four novel acids, plakortides E–H and one known compound 3-epi-plakortin (**2**) were isolated from the sponge *Plakortis halichondrioides* (Fig. 1.13).

In 2002, Kitching and coworkers reported the first total synthesis of plakortone D, which not only confirmed the absolute stereochemistry of plakortone D, but also enabled the acquisition of other plakortones and analogs [39]. In 2010, they reported the total syntheses and configuration assignments of plakortone C and F [41]. Our group were also interested in the synthetic chemistry of the *Plakortis* derived metabolites. Our preliminary synthetic efforts towards plakortide E were recorded in 2007 [43]. In 2010, we have reported the total syntheses and configuration assignments of all four isomers of plakortone B [44], whose total synthesis was reported by Semmelhack and coworkers in 2006 [45]. In consideration that plakortone B was isolated from the same animal source together with plakortide E [42], we reasoned

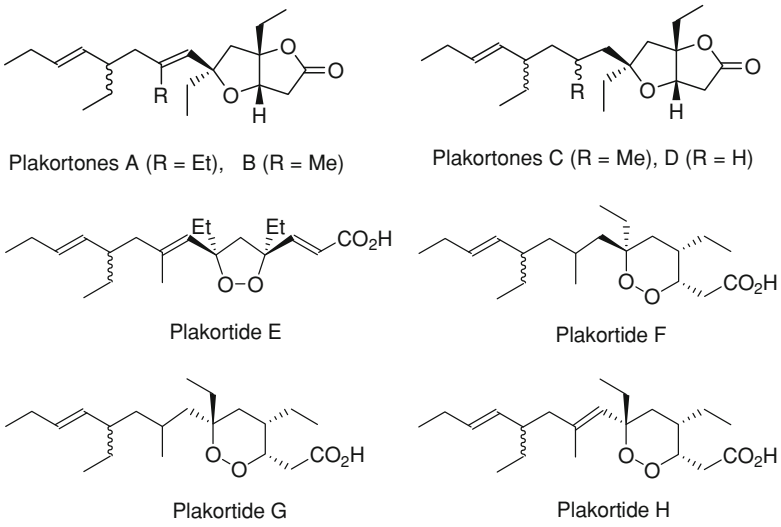
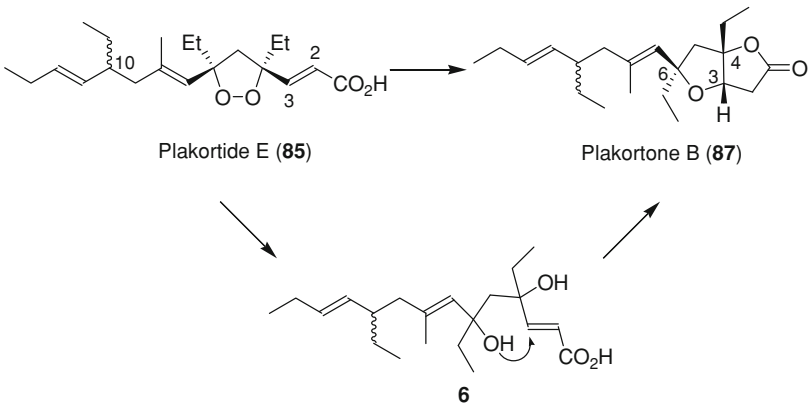


Fig. 1.13 Natural products from the sponge *Plakortis halichondrioides*

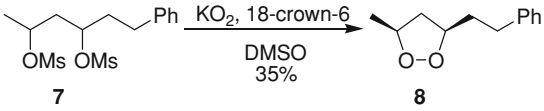


Scheme 1.1 Biosynthesis of plakortone B

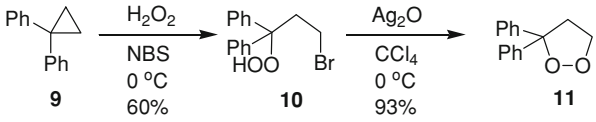
that diol **6** could be converted to plakortone B (Scheme 1.1) [109]. Kitching has also suggested that the 1,3-diol notionally derived from reductive cleavage of 1,2-dioxolane are perhaps the actual precursors of the plakortone series [40, 41].

1.4 Methodologies for Synthesis of Cyclic Peroxides

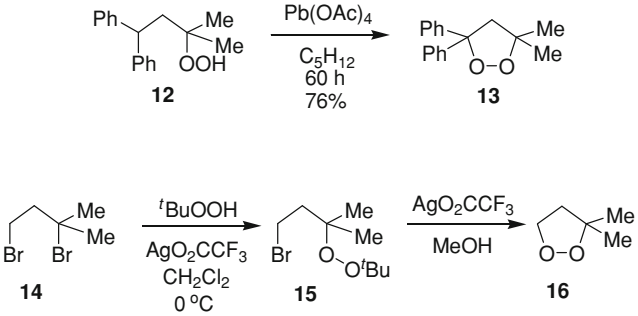
Construction of cyclic peroxides is a particularly challenging issue because of the low O–O bond dissociation energy (37 ± 1 kcal mol^{-1}) [1]. Numerous approaches have been developed in the past for the synthesis of five- and six-membered



Scheme 1.2 Corey's synthesis of 1,2-dioxolanes



Scheme 1.3 Adam's route to 1,2-dioxolanes



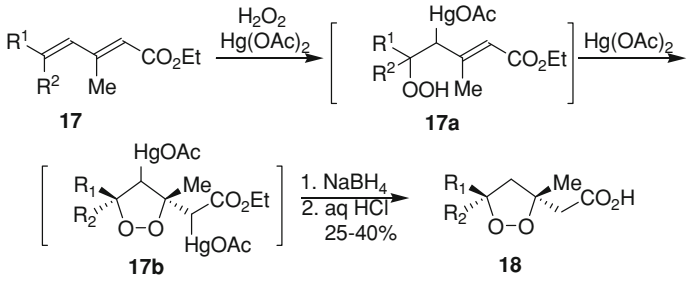
Scheme 1.4 Formations of 1,2-dioxolanes via nucleophilic reactions

ring peroxides [48–90]. Syntheses of cyclic peroxides were well-reviewed by Nojima and coworkers [46], and Bachi and coworker [47]. Many of these methodologies demand low temperature operations and mild conditions. These approaches can be categorized into three types: (1) cyclization of hydroperoxides through intramolecular nucleophilic reactions; (2) cycloaddition of triplet oxygen with radicals; (3) cycloaddition of singlet oxygen with 1,3-dienes.

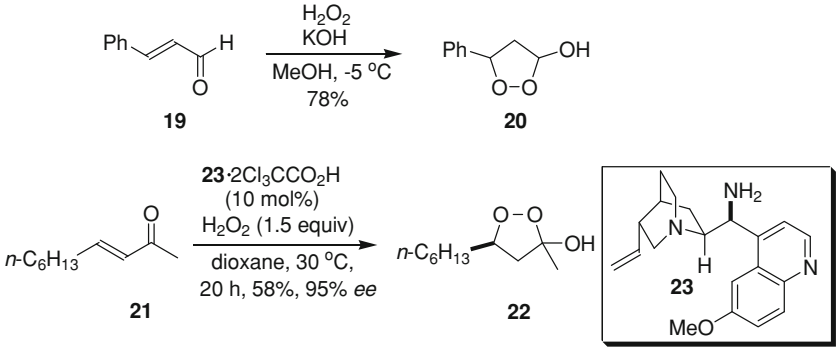
Cyclization via intramolecular nucleophilic reaction. In 1975, Corey and coworkers reported a method to obtain the 1,2-dioxolane through a intramolecular substitution. Bis (mesylate) **7** was treated with potassium superoxide to give the *cis*-disubstituted 1,2-dioxolane **8** in a moderate yield (Scheme 1.2) [87].

In 1978, Adam treated cyclopropane **9** with H_2O_2/NBS to afford β-bromohydro peroxide **10**, which was cyclized to 1,2-dioxolane **11** in the presence of silver(I) oxide in good yield (Scheme 1.3) [88].

Kropf [56] prepared 1,2-dioxolanes by treating hydroperoxides with $Pb(OAc)_4$, which involves 1,5-hydrogen abstraction by an intermediate peroxyl radical. Alternatively, the treatment of 1,3-dibromopropane **14** with *tert*-butylhydroperoxide in the presence of AgO_2CCF_3 also led to 1,2-dioxolane **16** (Scheme 1.4) [89].



Scheme 1.5 Intramolecular hydroperoxide addition to double bond



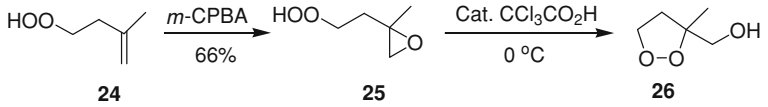
Scheme 1.6 Intramolecular hydroperoxide addition to carbonyl group

Bloodworth [66–69] prepared four non-natural plakinic acids via a peroxymercuration reaction as shown below (Scheme 1.5). A similar strategy was used by Gunstone [70] for his preparation of 1,2-dioxolanes from methyl oleate. A cycloperoxyiodination route also gave rise to 1,2-dioxolane frameworks. The difference between Bloodwoworth's and Gunstone's approach is five-*exo* vs. 5-*endo* peroxymercuration.

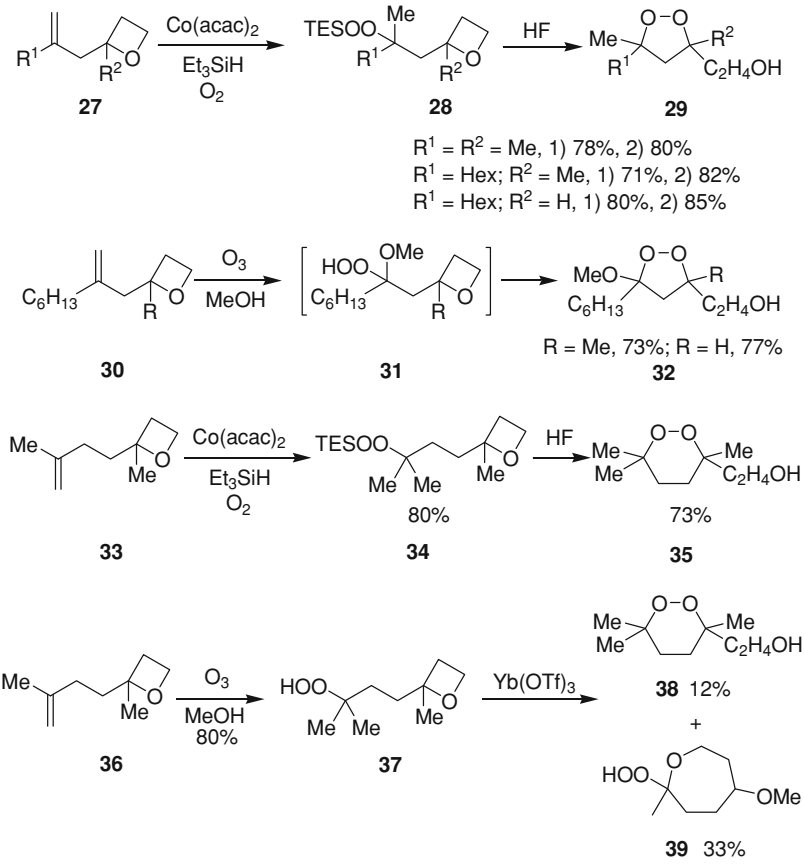
Intramolecular nucleophilic addition of hydroperoxide to a carbonyl group was one of the earliest methods to prepare cyclic peroxides. For example, the α,β-unsaturated aldehyde **19** reacted with hydrogen peroxide at room temperature in the presence of KOH to form the 1,2-dioxolane **20** in 78% yield [91–93]. An asymmetric version of this reaction was reported by List and coworkers in 2008 (Scheme 1.6) [93].

Acid-catalyzed intramolecular attack of hydroperoxide on an epoxide to form the 1,2-dioxolane was reported in 1976 (Scheme 1.7) [94]. This type of reaction was applicable to more complex substrates, and has been applied to the total syntheses of natural products [101].

Methods to synthesize the cyclic peroxides by the intramolecular opening of oxetanes with hydroperoxides have been developed by Dussault and coworkers



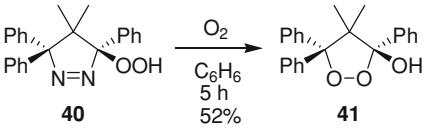
Scheme 1.7 Formation of 1,2-dioxolane via intramolecular opening of epoxide with hydroperoxide



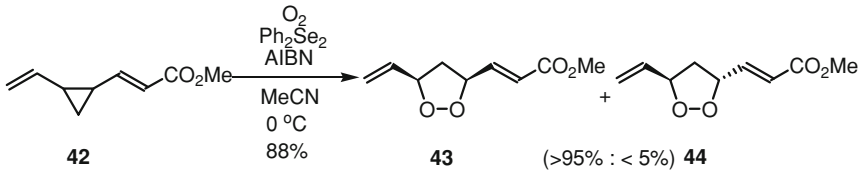
Scheme 1.8 Formations of 1,2-dioxolane via intramolecular opening of oxetanes with hydroperoxides

[78]. The method was used to synthesize the 1,2-dioxolanes, 1,2-dioxanes and 3-alkoxy-1,2-dioxolanes with good stereoselectivity and good yields (Scheme 1.8).

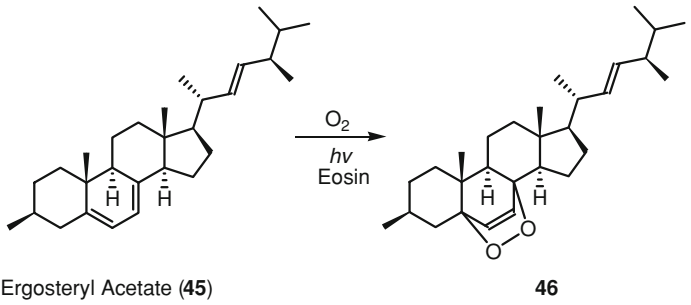
Cycloaddition of triplet oxygen with radicals. As can be seen in Scheme 1.9, pentasubstituted 3-hydroxy-1,2-dioxolanes were realized via oxygen trapping during thermolysis of cyclic α-azohydroperoxides [90].



Scheme 1.9 Cycloaddition of triplet oxygen with diradicals



Scheme 1.10 Formations of 1,2-dioxolanes reported by Feldman and coworkers



Scheme 1.11 Ergosteryl acetate oxidation with oxygen

Feldman developed a convenient approach for the formation of 1,2-dioxolanes from vinylcyclopropanes by a free radical-mediated ring expansion with oxygen as demonstrated in Scheme 1.10. In their experiments, the *cis*-1,2-dioxolanes **43** were obtained in good yield [83–86].

Cycloaddition of singlet oxygen with 1,3-dienes. Singlet oxygen ($^1O_2$) can be generated by a chemical process on a synthetically useful scale or in a photosensitized process by energy transfer from dye molecules such as rose bengal, methylene blue or porphyrins [95]. The electron occupancy of the shells of the singlet oxygen is different from those of ground state oxygen. The energy difference between ground state and singlet oxygen is 94.3 kJ/mol [96]. The damages caused by the sunlight to many organic materials are always attributed to the effects of singlet oxygen. Singlet oxygen reacting with a variety of 1,3-dienes gives the corresponding six-membered cyclic peroxides. This is one of the oldest and the most general methods to generate cyclic peroxides. Windaus and Brunken isolated the cyclic peroxide of ergosteryl acetate in 1928 [97], which was prepared through singlet oxygen cycloaddition to ergosteryl acetate (**45**) (Scheme 1.11).