Synthesis and Antimalarial Activity of 1,2,4,5-Tetraoxanes

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Abstract: Methods for formation of 1,2,4,5-tetraoxanes are summarized and antimalarial activities of 1,2,4,5-tetraoxanes are discussed.

1 INTRODUCTION

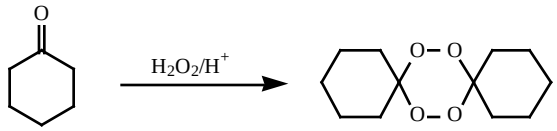
Ketone and aldehyde diperoxides (1,2,4,5-tetraoxanes) contain two peroxy groups in a six-membered heterocycle and are readily formed by acid-catalyzed oxidation of carbonyl compounds with hydrogen peroxide. Carbonyl oxide dimers are also used to describe these compounds since they can be generated by dimerization of a carbonyl oxide intermediate derived from ozonolysis of olefins. Both 1,2,4,5-tetroxanes and 1,2,4,5-tetraoxanes appear as formal names in the literature; 1,2,4,5-tetraoxanes, or more simply tetraoxanes, are used in this article. Readers are asked to check these terms in their search of the literature [1].

Thermolysis of tetraoxanes derived from cycloalkanones finds industrial use in the production of macrocyclic hydrocarbons and lactones [2]. Although this method is simple, its application to the synthesis of functionalized macrocyclic compounds remains to be explored. Tetraoxanes are capable of initiating polymerization of olefins and their utility as high-temperature initiators is under examination [3]. More recently, tetraoxanes have been found to possess impressive antimalarial activity [4]. Their useful antimalarial activities have attracted considerable attention. The antimalarial mode of action of tetraoxanes is believed to parallel that of artemisinin, a potent 1,2,4-trioxane antimalarial of natural origin [5]. In each case, peroxide bond scission leads to reactions that produce cytotoxic carbon-radicals [6]. This article will cover both synthetic methods and antimalarial activities of tetraoxanes.

2 SYNTHETIC METHODS

A number of useful procedures have been developed for the preparation of tetraoxanes. The key steps involve introduction of the peroxide group and, where appropriate, transformation of hydroperoxide intermediates into cyclic peroxides. Since peroxides, especially hydroperoxide intermediates, are both thermally and chemically labile, the choice of reagents and reaction conditions compatible with them is generally limited. This restriction poses additional challenges in stereochemical control and subsequent functionalization. Tetraoxane synthetic methods will be summarized based on the source of the peroxide bond.

The most general method for formation of the tetraoxane heterocycle involves acid-catalyzed addition of hydrogen peroxide to a carbonyl compound and subsequent cyclization of the hydroperoxide intermediates [7]. The direct synthesis is usually carried out in the presence of either sulfuric, or perchloric or methanesulfonic acids (Scheme 1).



1A **1B**

Scheme 1.

Early studies suggested that tetraoxanes (diperoxides) are thermodynamically controlled products whereas hexaoxonanes (triperoxides) are products of kinetic control [8]. While it is clear that tetraoxanes are more thermodynamically stable than hexaoxonanes, more recent work revealed whether tetraoxanes or hexaoxonanes are kinetically preferred depends on the relative rates of several steps involved in their formation [7]. Virtually, all of the hydroperoxide intermediates listed in the Scheme 2 have been isolated under various conditions. Indeed, ketone structure, reaction solvent, temperature, pH, and addition mode play significant roles in product distribution outcome. Recently, an NMR-based method has been developed to differentiate between tetraoxanes and hexaoxonanes [9].

Since most methods for selective formation of tetraoxanes vs. hexaoxonanes were developed using cyclohexanone, application of these methods to other ketones has been uncertain [10]. In many cases, tetraoxanes are often contaminated with hexaoxonanes and open-chain hydroperoxides. The following procedures can be used to purify the crude product when modification of reaction conditions fails to afford a pure tetraoxane. Selective removal of more reactive hydroperoxides can be achieved using dimethyl sulfide, or the more strongly reducing agent, potassium iodide. If recrystallization fails to remove residual hexaoxonanes, heating the mixture with perchloric acid in acetic acid can convert hexaoxonanes to tetraoxanes (Scheme 3) [8]. In this procedure, decomposition of the

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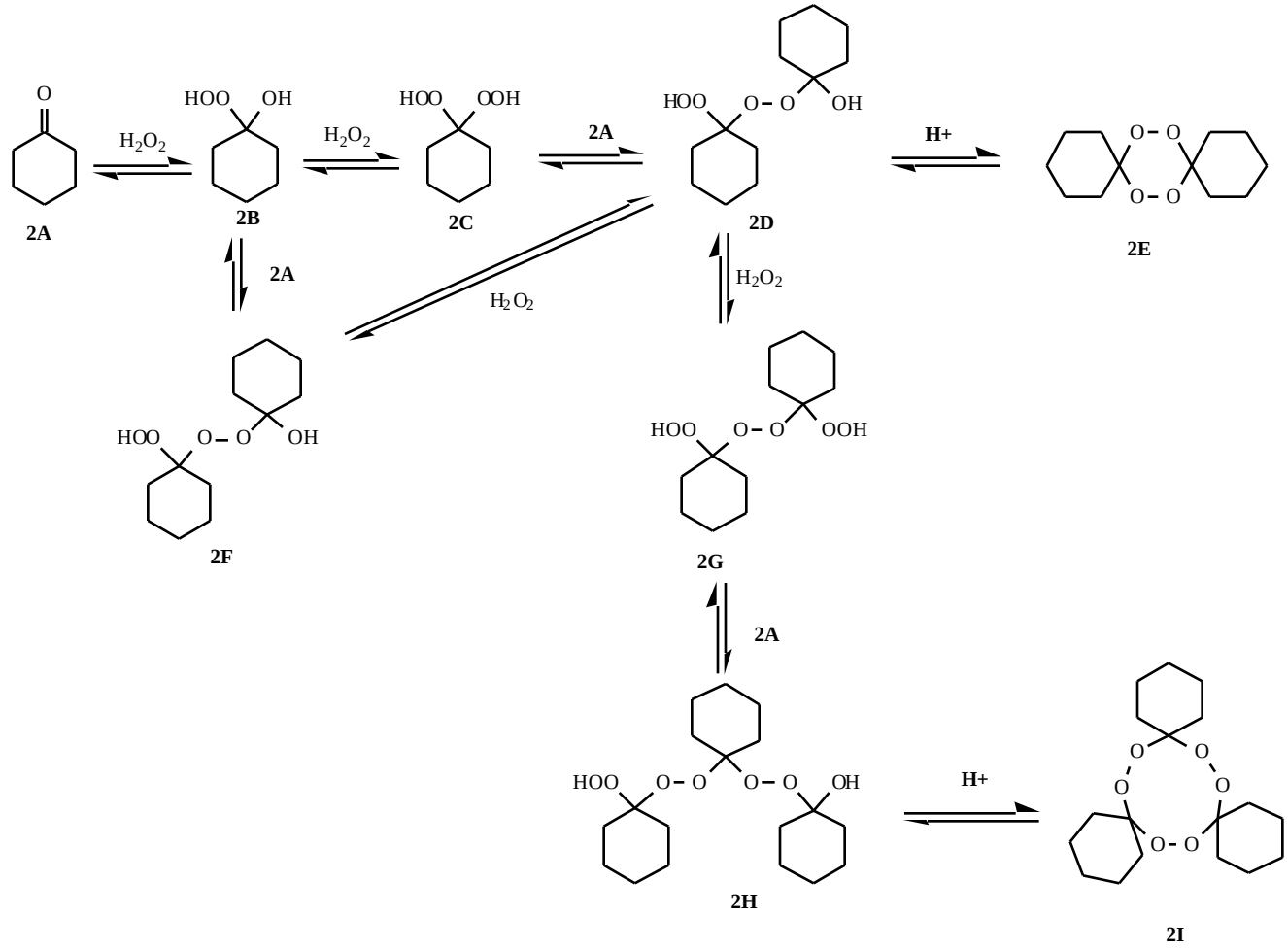
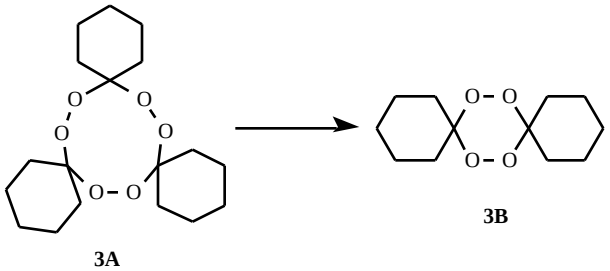


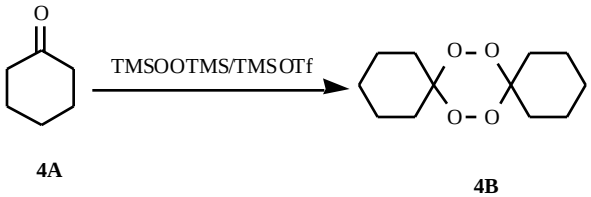
Scheme 2.

thermodynamically less stable hexaoxonanes to the more water-soluble lactones may also facilitate the purification process. Indeed, both tetraoxanes and hexaoxonanes derived from cyclohexanone can be converted into 6-formyloxyhexanoic acid in high yield on treatment with formic acid at ca. 90 ºC [11]. Furthermore, in many cases, only one tetraoxane isomer is reported, although several diastereomers can form from aldehydes and substituted ketones. On the one hand, one isomer can be more stable than the others and predominate in the crude product; on the other hand, the isolated isomer could be the least soluble and therefore readily precipitate from the reaction solvent while the other isomers remain in solution. Caution should be exercised in the discussion of stereoselectivity based solely on isolated tetraoxane products.



Scheme 3.

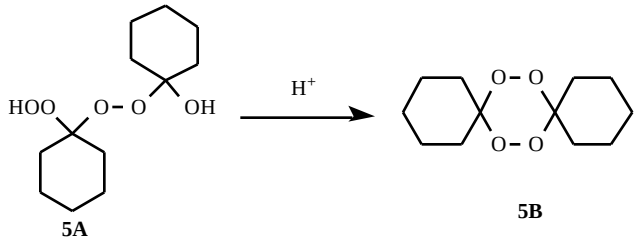
A closely related reaction employs bis (trimethylsilyl) peroxide in the presence of trimethylsilyl trifluoromethanesulfonate (Scheme 4) [12]. Bis (trimethylsilyl) peroxide has been reported to a safer oxidizing agent than 100% hydrogen peroxide, a reagent that is no longer commercially available. This procedure works efficiently with various aldehydes and ketones to give high yields of tetraoxanes. Traces of byproducts such as lactones and trimeric peroxides can easily be removed by recrystallization.



Scheme 4.

α-Hydroperoxy-α'-hydroxy-dialkylperoxides undergo cyclization in the presence of perchloric acid to give tetraoxanes (Scheme 5) [13]. Indeed, this constitutes a two-step procedure for the synthesis of tetraoxanes, namely hydroperoxidation of ketones to give open-chain dimeric peroxides **5A**, followed by their conversion to tetraoxanes **5B**. This method is especially useful when the direct

synthetic method fails and dimeric peroxides **5A** readily precipitate from the reaction solution. The success of the two-step method probably derives from the fact that formation of open-chain hydroperoxides and cyclization to tetraoxanes occur optimally under different reaction conditions.



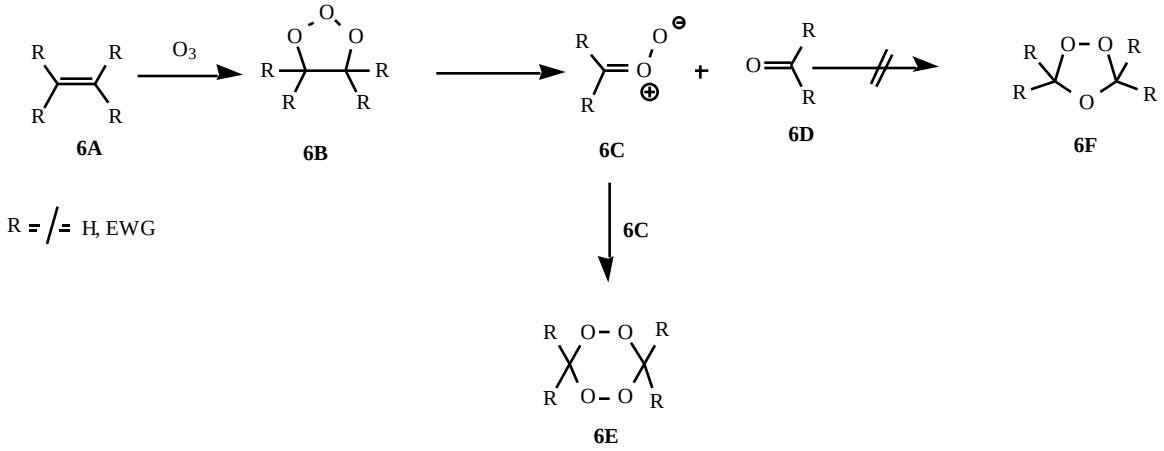
5A **5B**

Scheme 5.

Formation of tetraoxanes **6E** is well known when ozonolysis of alkenes **6A** is carried out in an aprotic solvent (Scheme 6) [14]. Preferred substrates are tetrasubstitued

Ozonolysis of vinyl ethers **7A** has been an efficient process for the formation of carbonyl oxides **7C** due to the directed fragmentation of the primary ozonide intermediate **7B** (Scheme 7) [15]. Carbonyl oxides **7C** undergo dimerization to form tetraoxanes **7E** when the reaction is carried out in aprotic solvents. However, this method has not been optimized with the specific aim to synthesize tetraoxanes. In fact, ozonolysis of vinyl ethers in the presence of alcohols has been widely used to obtain hydroperoxide intermediates that are subsequently converted to cyclic peroxides other than tetraoxanes [16].

The ozonolysis method has also been applied to *O*-methyl ketone oximes that are easily accessible from a variety of ketones (Scheme 8) [17]. Although the mechanistic details have yet to be elucidated, carbonyl oxides **8C** are believed to result from the ozonolysis of oxime ethers **8A**. In the absence of carbonyl compounds or protic solvents, carbonyl oxides **8C** give tetraoxanes **8E**. The method has been extended to the synthesis of dispiro tetraoxanes devoid of the usual hexaoxonane byproducts that

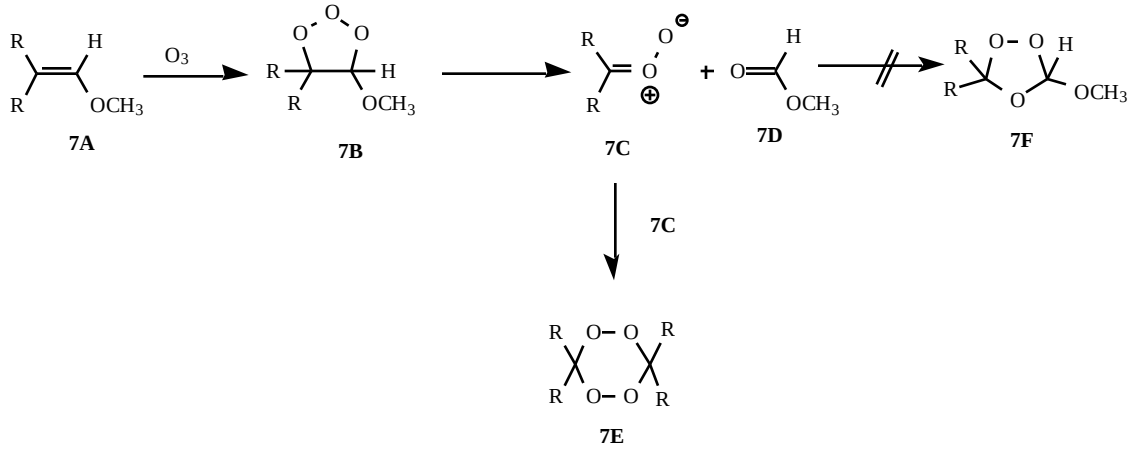


6A **6B** **6C** **6D** **6F** **6E**

Scheme 6.

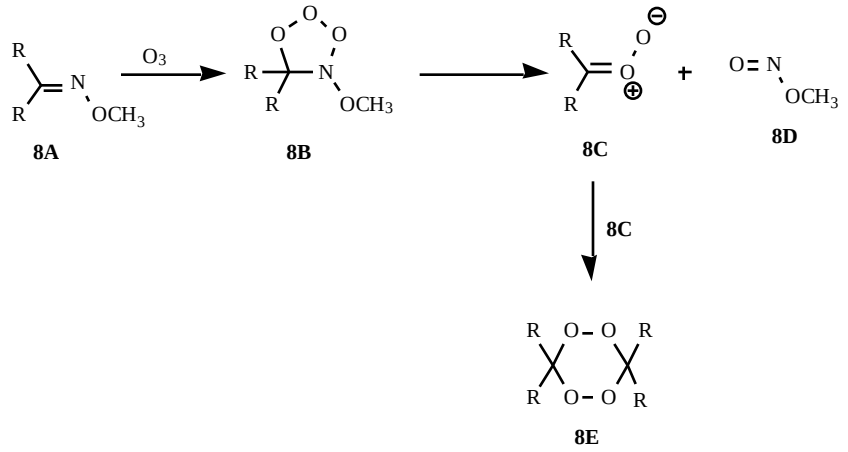
alkenes because ketone oxide intermediates **6C** tend to dimerize rather than undergo cycloaddition with the less reactive ketones **6D** to produce ozonides **6F**.

are often seen in acidic peroxidation reactions [18]. In general, tetraoxanes formally derived from aromatic ketones and strained polycyclic ketones are best obtained via



7A **7B** **7C** **7D** **7F** **7E**

Scheme 7.



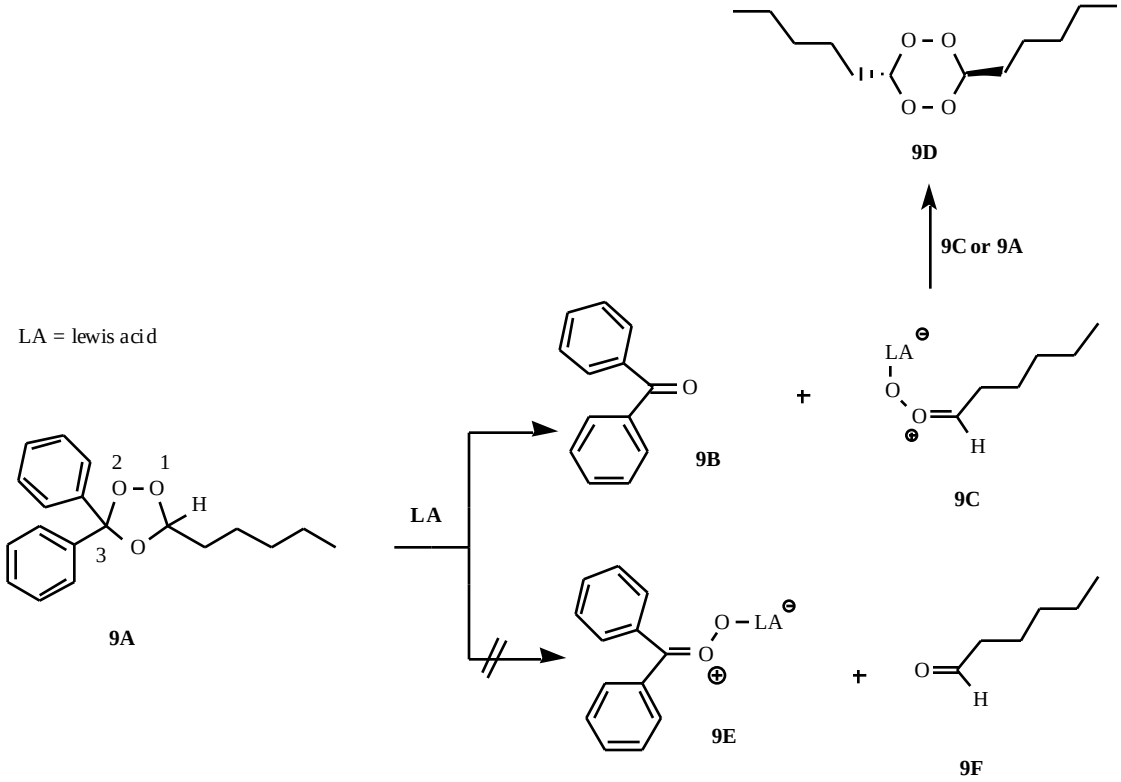
Scheme 8.

ozonolysis procedures described above, since these ketones preferentially undergo Baeyer-Villiger oxidation when reacting with acidic hydrogen peroxide.

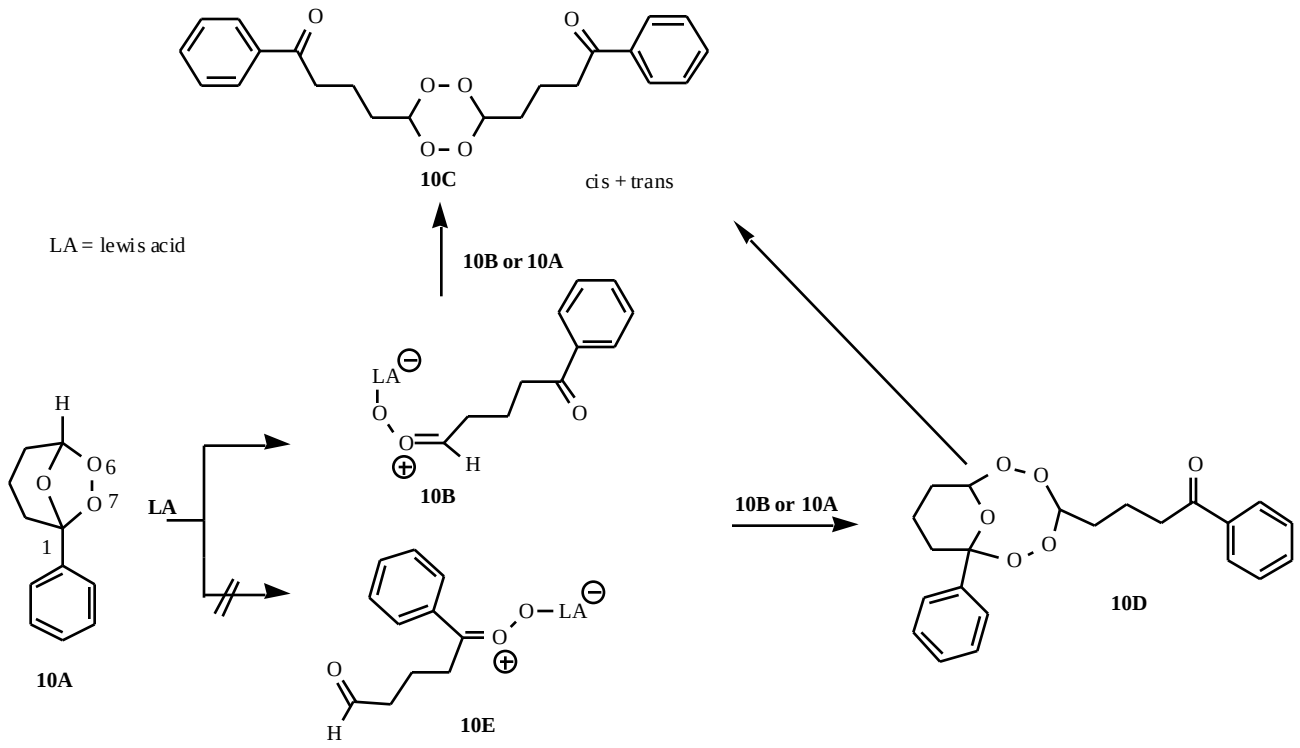
Another useful method that can be traced back to ozonolysis involves treatment of ozonides with $ClSO_3H$ or $SbCl_5$ (Scheme 9) [19]. The key intermediate is an interesting zwitterionic carbonyl oxide **9C** masked by the acid catalyst. The formation of tetraoxanes **9D** is explained by self-reaction of **9C** and/or attack of **9C** on another ozonide **9A**. It is interesting to note that less-substituted masked carbonyl oxide **9C** is formed instead of the more substituted one **9E** that is preferred in the ozonolysis of the parent alkene of **9A**. It appears that the cleavage of C(3)-O(2)-bond (development of an oxycarbenium ion) is the rate-limiting step although the O(2) is more sterically hindered.

Bicyclic ozonides undergo similar reactions that result in formation of tetraoxanes and 1,2,4,5,7-pentoxocanes (Scheme 10) [20]. Acidolysis of **10A** leads to masked carbonyl oxide **10B**, which reacts with itself and/or parent ozonide **10A** to produce tetraoxane **10C** and pentoxocane **10D**.

Transformation of readily accessible tetraoxanes **11A** into other tetraoxanes **11B** that are otherwise difficult to obtain



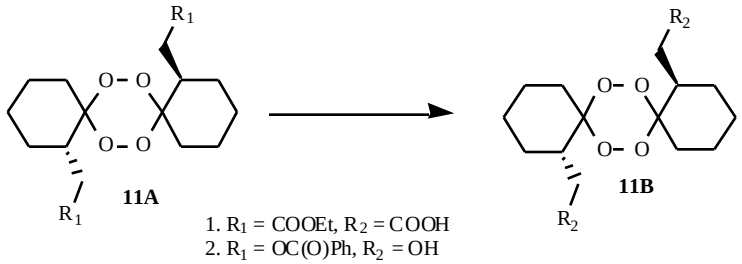
Scheme 9.



Scheme 10.

has been demonstrated (Scheme 11) [21]. This depends on availability of parent tetraoxanes with appropriate functional groups and identification of feasible reactions and compatible reagents.

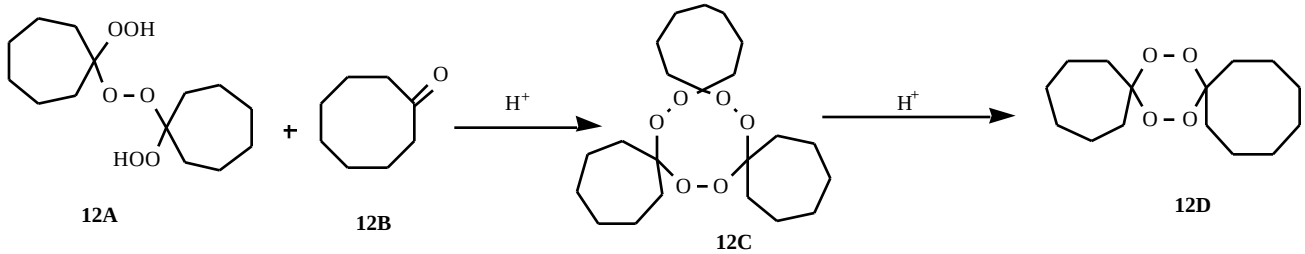
depend on careful selection of suitable substrates and efficient separation of the desired mixed tetraoxanes from the undesired products. The first indirect method to access unsymmetrical tetraoxanes involves heating mixed



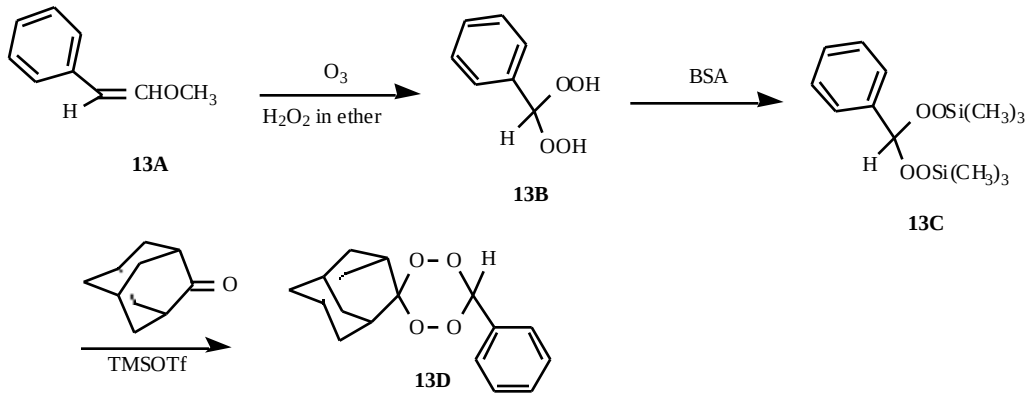
Scheme 11.

Little is known about unsymmetrical tetraoxanes, although they can, conceptually, be directly prepared by acidic peroxidation of two ketones or by ozonolysis of two enol ethers, two oxime ethers or an unsymmetrical alkene, or even two symmetric alkenes. Success of this strategy would

hexaoxonanes in the presence of perchloric acid [2a], in a similar manner to the conversion of hexaoxonanes to symmetrical tetraoxanes (Scheme 12). The origin of the dimerization selectivity is not clear.

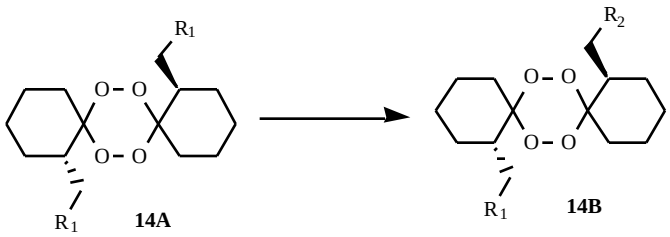


Scheme 12.



Scheme 13.

An elegant approach to unsymmetrical tetraoxanes has been developed that involves ozonolysis of vinyl ethers in presence of hydrogen peroxide to give 1,1-bis(hydroperoxides) (Scheme 13) [22]. Subsequent trimethysilylation is required to effect an efficient TMSOTf-catalyzed cyclocondensation with carbonyl compounds. Indeed, this is the first general procedure for the synthesis of tetraoxanes possess antimalarial activity in *P. berghei*-infected mice. To the best of our knowledge, this is the earliest known attempt to synthesize structurally simple peroxidic antimalarials. However, the *in vitro* antimalarial activities of these tetraoxanes against *P. falciparum* were not confirmed until two decades later [4]. Since then, tetraoxanes have received growing attention. Here, we present *in vitro*



Scheme 14.

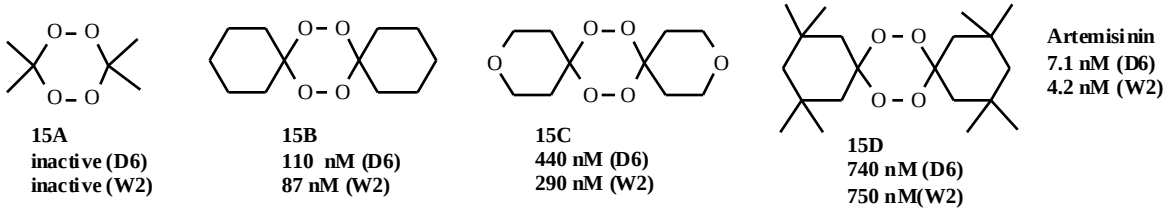
unsymmetrical tetraoxanes with a well-defined reaction sequence.

Transformation of functionalized symmetrical tetraoxanes **14A** to unsymmetrical tetraoxanes **14B** seems possible, and holds great potential to rapidly access structurally diverse functionalized tetraoxanes, although this kind of extension has yet to be explored (Scheme 14).

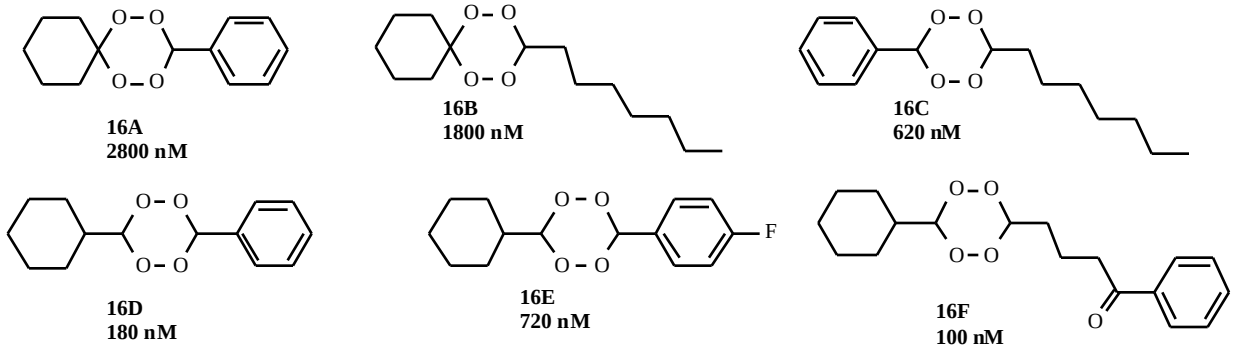
3 ANTIMALARIAL ACTIVITY

Shortly after the discovery of artemisinin, it should be noted that unpublished data [23], showed that several antimalarial activities for all of the reported tetraoxanes in order of increasing structural complexity. Since *in vivo* antimalarial activities for some of the tetraoxanes were evaluated using different methods, it is difficult to use these data to make effective comparisons between the various tetraoxanes.

Antimalarial activities of several structurally simple tetraoxanes were determined using two *P. falciparum* malaria parasite clones D6 (chloroquine-sensitive but mefloquine-resistant) and W2 (chloroquine-resistant but mefloquine-sensitive) [24]. The simplest tetrasubstitued tetraoxane **15A** is inactive whereas simple dispiro-tetraoxane **15B** has an *in vitro* activity of ca. 100 nM, 15 times less



Scheme 15.

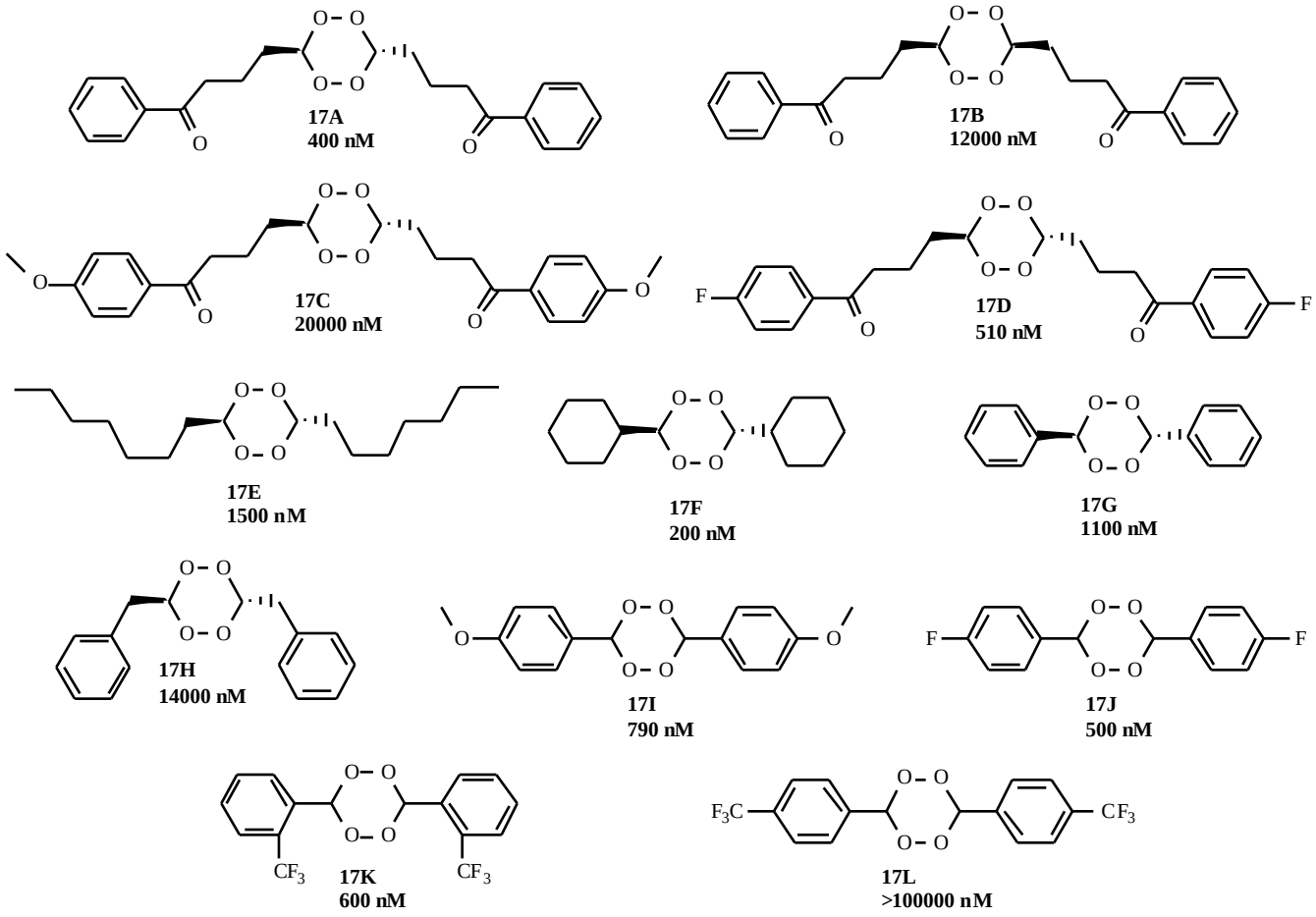


Scheme 16.

active than artemisinin. Insertion of an oxygen atom in the cyclohexane ring (**15C**) diminishes activity 4-fold. Introduction of four pairs of geminal methyl groups on the cyclohexane rings (**15D**) results in a striking decrease in activity compared to that of the unsubstituted tetraoxane **15B**, confirming an independent finding that showed **15D** is entirely inactive, due presumably to excessive steric hindrance about the peroxide bond preventing a suitable interaction with heme, the putative "receptor" for antimalarial peroxides. However, it is arguable that the protection of the peroxide bond is equally important to avoid premature cleavage by drug metabolizing enzymes. Therefore, both tetraoxane reductive activation in the parasite and tetraoxane metabolic inactivation by CYP P450s may be a function of peroxide bond accessibility.

A variety of 3,3,6-trisubstituted and 3,6-disubstituted unsymmetrical tetraoxanes were evaluated for antimalarial activity against chloroquine-sensitive *P. falciparum* (FCR-3) [22]. Generally, they are moderately active. It is interesting to note that disubstituted tetraoxanes **16C** and **16D** are more active than more substituted monospiro-tetraoxanes **16A** and **16B** in this series, and the two most active compounds **16D** and **16F** bear a cyclohexyl substituent.

Antimalarial activities of twelve 3,6-disubstitued symmetrical 1,2,4,5-tetraoxanes against *P. falciparum* (FCR-3) have been examined [20]. It is surprising to note that *cis*-isomer **17B** is 40 times less active than *trans*-isomer **17A**. The reason for that is not clear although it is not uncommon that two diastereomers differ significantly in



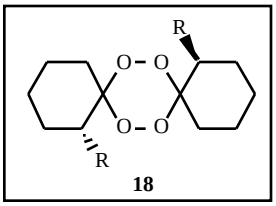
Scheme 17.

activity, especially in cases where the diastereomeric substituents are in proximity to the peroxide bonds and therefore could differently modulate the interaction with heme. More surprisingly, remote substituents (**17C** vs. **17D**, **17J** vs. **17L**) exert a remarkable effect on the antimalarial activity although similarly remotely located substituents in the artemisinin family generally do not affect *in vitro* antimalarial activity significantly [25]. The most active compound (**17F**) in this series is also cyclohexyl-substitued, like the most acive compounds **16E** and **16F** in the previous series, indicating the cyclohexyl radical that might be formed from these compounds may contribute to their antimalarial activities. A substituted cyclohexyl radical has been proposed to be associated with good antimalarial activity in arteflene [26].

As illustrated by the activity of **18B** (WR148999) [27], dispiro tetraoxanes represent a unique class of antimalarials. An extensive survey on the effect of dispiro tetraoxane substitution on antimalarial activity has been conducted and is discussed here in more detail.

Due to synthetic limitations, only symmetrically-substituted dispiro tetraoxanes can be prepared by acid-catalyzed peroxidation or by ozonolysis of *O*-methyl oximes. With regard to the effect of side chain length for 1,10-dialkylated tetraoxanes **18A-18E** (Table 1), extension of the alkyl side chain results in an initial slight increase and then a slight decrease in activity. Introduction of bulky *tert*-butyl groups at the 1 and 10 postions decreases activity significantly [28, 29].

Table 1. ***In vitro*** **Antimalarial Activity of 1,10-Dialkyl-Substituted Tetraoxanes Against** ***P. falciparum***

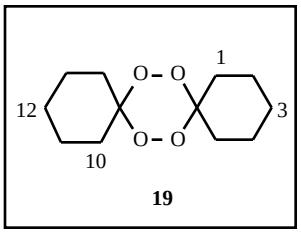


18

compd	R	IC_{50} (nM)	
		D6	W2
18A	H	38	26
18B	CH_3	55	32
18C	C_2H_5	23	19
18D	C_3H_7	84	39
18E	$C(CH_3)_3$	>300	160
artemisinin	-----	8.4	7.3

The effect of position and number of substituents on antimalarial activity was further examined (Table 2) [29]. Antimalarial potency does not diminish for **19A** and **19B**, isomers of **18B**, but drops off 4-fold for di-*tert*-butylated tetraoxane **19C**. For eight tetramethyl tetraoxanes **19D**-**19K**, potency is maintained for 1,2,10,11-tetramethyl **19D**, decreased slightly for 1,3,10,12-tetramethyl **19E**, enhanced 2-4 fold for 1,4,10,13-tetramethyl **19F**, 2,3,11,12-tetramethyl **19H**, and 2,4,11,13-tetramethyl **19I**, and lost entirely for 1,5,10,14-tetramethyl **19G** and bis-geminally-substituted 3,3,12,12-tetramethyl **19K**. This dramatic potency loss may occur because of severe steric hindrance preventing peroxide bond access to parasite heme. Menthone diperoxide **19L**, also a tetrasubstituted analogue, is equipotent to the 1,10-dimethyl tetraoxane **18B**, indicating the size of two isopropyl groups at the 1 and 10 positions is tolerated. Interchange of isopropyl and methyl groups within the same cyclohexane ring (**19M** vs. **19L**) results in a 3-fold decrease in activity. More heavily substituted tetraoxanes **19N** and **19O** containing geminal substituents are inactive as expected. Furthermore, there is no correlation between hydrophobicity and antimalarial potency among these tetraoxane derivatives.

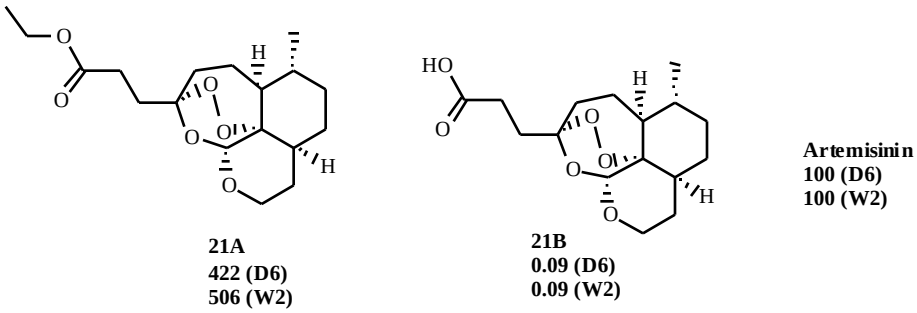
Table 2. ***In vitro*** **Antimalarial Activity of Alkyl-Substituted Tetraoxanes Against** ***P. falciparum***



19

compd	R	IC_{50} (nM)	
		D6	W2
19A	2,11-dimethyl	76	51
19B	3,12-dimethyl	23	21
19C	3,12-di-*tert*-butyl	200	100
19D	1,2,10,11-tetramethyl	50	43
19E	1,3,10,12-tetramethyl	110	49
19F	1,4,10,13-tetramethyl	15	19
19G	1,5,10,14-tetramethyl	>1000	>1000
19H	2,3,11,12-tetramethyl	12	10
19I	2,4,11,13-tetramethyl	30	15
19J	1,1,10,10-tetramethyl	>1000	>1000
19K	3,3,12,12-tetramethyl	>1000	>1000
19L	1,10-diisopropyl-4,13-dimethyl	47	37
19M	4,13-diisopropyl-1,10-dimethyl	140	94
19N	1,3,3,10,12,12-hexamethyl	>1000	>1000
19O	2,2,4,4,11,11,13,13-octamethyl	>1000	>1000
artemisinin	-----	8.4	7.3

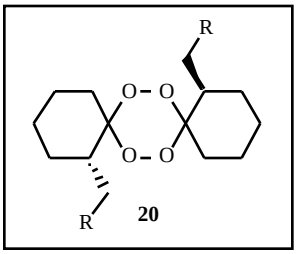
To improve the water solubility of these very lipophilic tetraoxanes, a variety of unsaturated and polar functional groups were incorporated at the 1 and 10 positions (Table 3) [21]. The NF54 (chloroquine-sensitive) and K1 (chloroquine-



Scheme 18. Relative antimalarial activity.

resistant) *P. falciparum* strains were employed to determine antimalarial activity. The presence of alkene (**20A**), alkyne (**20B**), and ether moieties (**20J**, **20K**) maintains or enhances antimalarial activity relative to the parent **18B**, whereas alcohol **20H** and its benzoate ester **20I** are inactive. Tetraoxane carboxylic acids **20F** and **20G** demonstrate a complete lack of antimalarial activity in contrast to their corresponding ethyl esters **20D** and **20E**, which are 2- to 5-fold more potent than prototype tetraoxane **18B**. The diminished potency of peroxy carboxylic acids has been previously seen in the artemisinin series [30]; for example, ester **21A** is 4-5 times more active than artemisinin, and **21B**, its carboxylic acid, is virtually devoid of antimalarial activity (Scheme 18). The presence of two carboxylic acid functionalities in **20F** and **20G** seems to be responsible for their lack of activity. Subsequent *in vivo* evaluations revealed that tetraoxane esters **20D** and **20E** are inactive orally, due presumably to rapid metabolism that converts them to inactive tetraoxane acids **20F** and **20G**. Also disappointingly, other compounds with improved water solubility fail to display improved oral activity compared to dimethyl tetraoxane **18B**. This illustrates that improving tetraoxane antimalarial activity is somewhat hindered by most of the currently available synthetic methods that provide only symmetrically-substituted tetraoxanes, a limitation that makes fine-tuning of physicochemical properties more difficult.

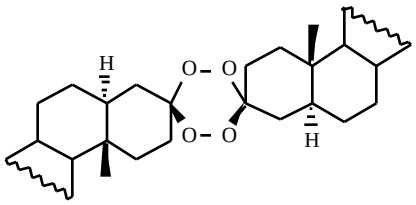
Table 3. ***In vitro*** **Antimalarial Activity of Functionalized Tetraoxanes Against** ***P. falciparum***



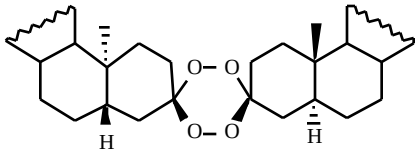
compd	R	IC_{50} (nM)	
		NF54	K1
20A	$CH{=}CH_2$	23	19
20B	$C{\equiv}CH$	13	13
20C	C_6H_5	>200	>200
20D	$CH_2COOC_2H_5$	16	14
20E	$COOC_2H_5$	6.5	6.2
20F	CH_2COOH	>200	>200
20G	COOH	>200	>200
20H	OH	>200	>200
20I	$OCOC_6H_5$	>200	>200
20J	OCH_3	16	15
20K	$OCH_2C_6H_5$	26	18
18B	H	39	28
artemisinin	-----	12	10

Steroidal 1,2,4,5-tetraoxanes **22A** and **22B** (presumable *trans* and *cis* isomers) are synthesized by acid-catalyzed peroxidation of 5α-cholestan-3-one, a formally densely substituted cyclohexanone (Scheme 19) [31]. In general, predictability of product selectivity and stereochemical outcome is low because of the complexity of reactions involved (vide supra). The proposed *cis* isomer **22B** is inactive against both D6 and W2 clones while the proposed *trans* isomer **22A** has a modest antimalarial activity (IC_{50} = 155 nM) against the D6 clone. The poor antimalarial activity could be explained in terms of strong steric shielding provided by overcrowded ring systems and/or apparently extremely poor water solubility.

Several cholic acid-derived tetraoxanes were designed to explore the influence of steroid carrier on the antimalarial activity (Table 4) [32]. Diester and diamide tetraoxanes are directly synthesized using H_2O_2/H_2SO_4 and TMSOOTMS/TMSOTf methods, respectively. In each case, two isomers (presumably *cis* and *trans*) are formed and isolated. It is interesting to note that the tetraoxane ring in **23A** adopts a twisted conformation based on the X-ray crystallographic analysis. The *cis* series was found to be more active than the *trans* series, and the tetraoxanes containing amide moieties outperform tetraoxanes bearing ester or acid functionalities. It is somewhat surprising that diester tetraoxanes are completely inactive *in vitro*, in marked contrast to diester tetraoxane **20E**, the most active compound in that series. Compared to steroidal tetraoxanes **22A** and **22B**, potency improves for this series, as illustrated by **23C** with an IC_{50} of 9.3 nM against the D6 clone. This



22A

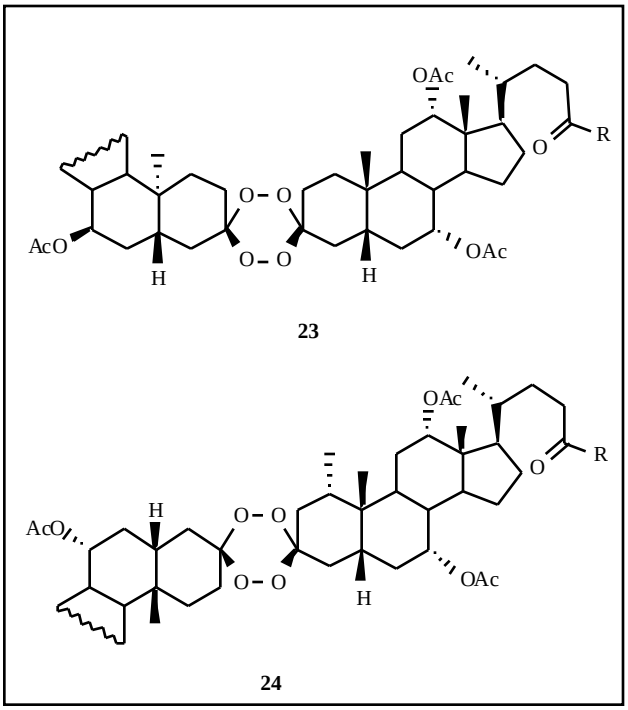


22B

Scheme 19.

improvement in potency might result from the presence of suitable water-soluble functional groups and/or difference in stereochemical framework.

Table 4. ***In vitro*** **Antimalarial Activity of Cholic Acid-Derived Tetraoxanes Against** ***P. falciparum***



23

24

compd	R	IC_{50} (nM)	
		D6	W2
23A	OCH_3	>96	>96
24A	OCH_3	>96	>96
23B	NH_2	24	19
24B	NH_2	130	59
23C	$NHCH_2CH_2CH_3$	9.3	60
24C	$NHCH_2CH_2CH_3$	20	30
23D	OH	>99	>99
24D	OH	>99	>99

Although the peroxide group is the essential pharmacophore in peroxidic antimalarials, the mere presence of a peroxide bond in a structure is insufficient to endow it with good antimalarial activity. In tetraoxanes, the presence of a second peroxide bond apparently has no significant advantage beyond a consideration of synthetic simplicity. To achieve the level of antimalarial activity displayed by artemisinin or more potent semisynthetic artemisinins such as artemether is a challenging task. Antimalarial potency is determined by several factors including lipophilicity, thermal and metabolic stability of the peroxide group, accessibility of the peroxide bond by heme (steric effect), and efficiency of cytotoxic carbon-radical formation (reaction rate and radical type). Future attempts to delineate these complex relationships are highly desirable. It is hoped that what has been learned about tetraoxanes, in combination with the wealth of knowledge generated from the research on artemisinins and other peroxides, can be used to identify structurally simple, affordable, and effective antimalarials.

4 CONCLUSION

Acid-catalyzed peroxidation of ketones and ozonolysis of alkenes, enol ethers or oxime ethers are two of the most useful methods for the synthesis of symmetrically-substituted tetraoxanes. Recently, cyclocondensation of 1,1-bis(trimethylsilylperoxy)alkanes and carbonyl compounds has evolved as a highly general method for the preparation of unsymmetrical tetraoxanes. Functional group transformation of readily available tetraoxanes provides a rapid access to diverse tetraoxanes that might otherwise be difficult to obtain. However, challenging problems remain that include low reaction yields, a limited array of accessible functional groups, and lack of stereochemical control. In contrast to dispiro tetraoxanes, which often possess good *in vitro* antimalarial activity comparable to that of artemisinin, monocyclic and monospiro tetraoxanes examined so far are generally poor antimalarials. It is predicted that tetraoxane oral activity will improve by gaining a better understanding of tetraoxane metabolism and by application of an expanded design strategy made possible by the recently discovered synthetic method to access unsymmetrical tetraoxanes.

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