1,2,4,5-Tetraoxacycloalkanes: Synthesis and Antimalarial Activity

A. Masuyama[*,1], J.-M. Wu[1], M. Nojima[1], H.-S. Kim[2] and Y. Wataya[2]

[1] *Department of Materials Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan*

[2] *Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-Naka, Okayama 700-8530, Japan*

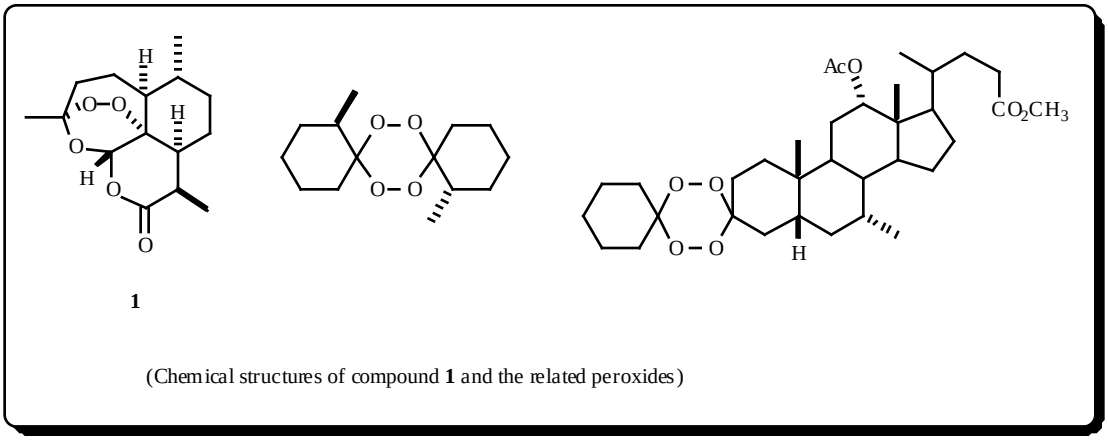
Abstract: In this short review the methods of preparation of novel 1,2,4,5-tetraoxacycloalkanes and the related peroxides are summarized, with the emphasis on the usefulness of 1,1-bishydroperoxides as the precursor. Also, their antimalarial activities *in vitro* and *in vivo* are discussed.

Keywords: 1,2,4,5-tetraoxacycloalkanes, 1,2,5,6-tetraoxacycloalkanes, 1,2,6,7-tetraoxaspiro[7.11]nonadecane, antimalarial activity, medium-sized cyclic peroxides, cyclization methods, *P. falciparum, P. berghei.*

1. INTRODUCTION

Because malaria parasites are rapidly developing multidrug resistance to the most common chemotherapeutic alkaloidal drugs, interest in the antimalarial properties of nonalkaloidal compounds such as the sesquiterpene 1,2,4-trioxane artemisinin (**1**) and the related endoperoxides is rapidly growing [1]. Particularly interesting is the fact that dispiro-1,2,4,5-tetroxanes, easily prepared by the acid-catalyzed condensation of cycloalkanones and hydrogen peroxide, exhibit remarkable anti-malarial activities *in vitro* and *in vivo* [2]. Very recently Dong reviewed the advancement in the synthesis and drug design of antimalarial 1,2,4,5-tetroxanes, with an emphasis on mixed 1,2,4,5-tetroxanes derived from the cyclocondensation of ketones with 1,1-bishydroperoxides [3a]. This and the related papers [3b-f] led us to deduce that medium-sized cyclic peroxides having two peroxide groups in the ring would be also potent candidates for antimalarial drugs.

We review herein our trial to develop several strategies for the synthesis of the unprecedented spiro-1,2,4,5-tetraoxacycloalkanes and the related cyclic and acyclic peroxides. Some of the cyclic peroxides show notable *in vitro* and *in vivo* antimalarial activities comparable to artemisinin **1**.



(Chemical structures of compound **1** and the related peroxides)

2. SYNTHETIC METHODOLOGIES

Three strategies have been developed for the synthesis of the spiro-1,2,4,5-tetraoxacycloalkanes as shown in Scheme 1; *i.e.*, (i) CsOH- or Ag_2O-mediated cyclization of (alkylidene)bishydroperoxides and 1,n-dihaloalkanes, (ii) electrophile-promoted cyclization of unsaturated hydroperoxides, and (iii) TMSOTf-catalyzed cyclocondensation of 1,n-bishydroperoxides with cycloalkanones.

2.1. CsOH- or Ag_2O-Mediated Cyclization of (Alkylidene)-1,1-Bishydroperoxides and 1,n-Dihaloalkanes

CsOH or Ag_2O is well known to promote nucleophilic substitution of alkyl halides with hydroperoxides [4,5]. Therefore, we considered that nucleophilic substitution of 1,n-diiodoalkane with readily available (alkylidene)-1,1-bishydroperoxides [3] would provide the desired 1,2,4,5-tetraoxacycloalkanes. Consistent with this expectation, treatment of a mixture of **2a** and 1,3-diiodoalkane(s) (1.5 mol equiv.) with CsOH•H_2O (2 mol equiv.) in DMF for 15 h gives the expected 1,2,4,5-tetroxocane derivative **3a** in 40% yield. Alternatively, the cyclization reaction in the

*Address correspondence to this author at the Department of Materials Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565-0871, Japan; Fax: +81-6-6879-7930; E-mail: toratora@chem.eng.osaka-u.ac.jp

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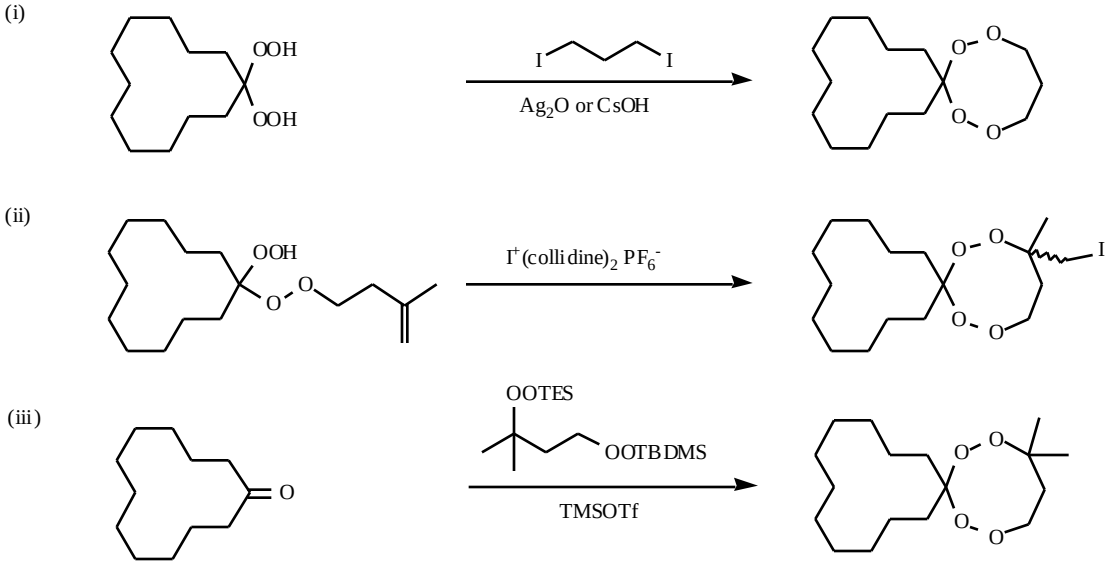
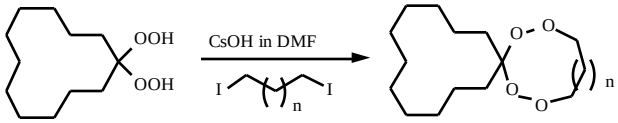


Scheme 1.

presence of freshly prepared Ag_2O (2 mol equiv.) in ethyl acetate also gives **3a** in the highest yield of 61% (Table **1**) [6].

Table 1. Synthesis of 1,2,4,5-tetraoxacycloalkanes by the Reaction of Bishydroperoxides and Diiodoalkanes



2a **3a-7a**

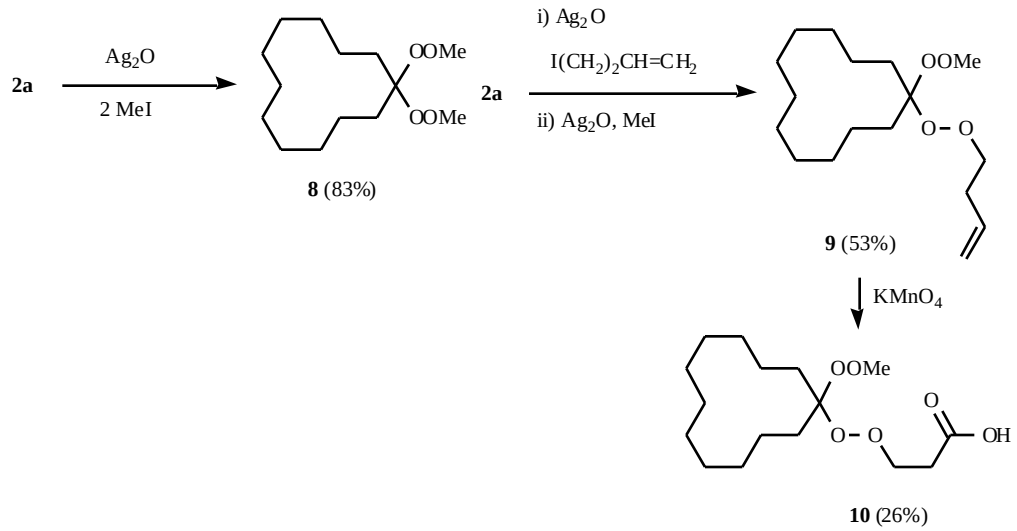
3a-7a	mediator	solvent	% yield[a]
3a: n = 1	CsOH[b]	DMF	40
3a: n = 1	Cs_2CO_3	DMF	31
3a: n = 1	Ag_2O	CH_2Cl_2	42
3a: n = 1	Ag_2O[b]	CH_2Cl_2	56
3a: n = 1	Ag_2O[b]	$MeCO_2Et$	61
4a: n = 2	CsOH[b]	DMF	30
4a: n = 2	Ag_2O[b]	$MeCO_2Et$	12
5a: n = 3	CsOH[b]	DMF	17
6a: n = 4	CsOH[b]	DMF	18
7a: n = 6	CsOH[b]	DMF	18
7a: n = 6	Ag_2O[b]	$MeCO_2Et$	0

[a]Considerable amount of cyclododecanone was also isolated.
[b]Two-mol equiv. of a promoter was used.

The chain length in the 1,n-diiodoalkanes plays an important role in the CsOH-promoted cyclization (Table **1**). First, 1,3-, 1,4-, 1,5-, 1,6-, and 1,8-diiodoalkanes could be used as the partner in the nucleophilic substitution with the 1,1-bishydroperoxide **2a**, thereby providing the corresponding 1,2,4,5-tetraoxacycloalkanes **3a**-**7a**. Second, a high dilution procedure is required for the preparation of the 10- to 13-membered tetraoxacyclolalkanes **5a**-**7a**. Under normal conditions, only a complex mixture of products containing cyclododecanone is obtained. Finally, the Ag_2O-promoted cyclization is inefficient for the synthesis of the 9- to 13-membered tetraoxacycloalkanes **4a**-**7a**. The reaction of **1a** with 1,4-diiodobutane gives **4a** albeit in a low yield of 12%, while the reaction with 1,6-diiodohenae is ineffective.

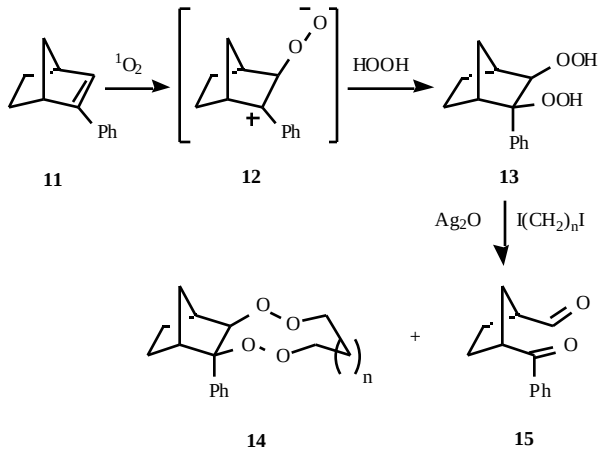
As will be shown later, the 1,2,4,5-tetroxocane derivatives **3a** shows a remarkable antimalarial activity *in vitro* and *in vivo*. Therefore, we have been interested in the synthesis and the antimalarial activity of the acyclic analogues. 1,1-Bis(methyldioxy)cyclododecane **8** is prepared by treatment of **2a** with 2 equiv of MeI in the presence of Ag_2O in ethyl acetate in high yield (Scheme **2**) [7]. Unsymmetrically substituted peroxide is also easily prepared by the consecutive alkylation of 1,1-bishydroperoxide by two different alkyl iodides. For example, treatment of **2a** with 1.2 equiv. of 4-iodobutene in the presence of Ag_2O gives the monoalkylated product. Subsequent methylation provides an unsaturated peroxide **9**, which in turn is oxidized by $KMnO_4$ to give the carboxylic acid **10** (Scheme **2**) [7].

As a reasonable extension, we have challenged the preparation of labile 1,2-bishydroperoxide as the precursor of cyclic peroxides with a different structure [8]. In this respect, 2-phenylnorbornene **11** is known to react with singlet oxygen to generate a zwitterionic intermediate **12** which can be efficiently trapped by methanol to form the corresponding methoxy-substituted hydroperoxide [9]. By analogy, photooxygenation of a solution of the alkene **11** in acetonitrile containing 30% aqueous hydrogen peroxide affords the 1,2-bishydroperoxide **13** in essentially quantitative yield (Table **2**) [10]. Treatment of a mixture of **13** and 1,3-diiodopropane with Ag_2O in CH_2Cl_2 gives the desired tricyclic peroxide **14a** containing a 1,2,5,6-tetroxonane ring, though the major product is the keto aldehyde **15** (48%). The 1,2,5,6-tetroxecane derivative **14b** is obtained, also in relatively low yield, from the analogous cycloalkylation reaction involving 1,4-diiodobutane (Table **2**) [10].



Scheme 2.

Table 2. Synthesis of 1,2,5,6-tetraoxacycloalkanes



	% yield of 14	% yield of 15
a: n = 1	9	48
b: n = 2	7	53

2.2. Iodonium Ion- or Ozone-Promoted Cyclization of Unsaturated Hydroperoxy Peracetals

Electrophile-promoted cyclization of unsaturated hydroperoxide is well known to be an efficient procedure for the synthesis of cyclic peroxides [11]. In this respect, Dussault and we independently have found that iodonium ion promotes cyclization of unsaturated hydroperoxy acetals thereby providing the iodo-substituted cyclic peroxides [12].

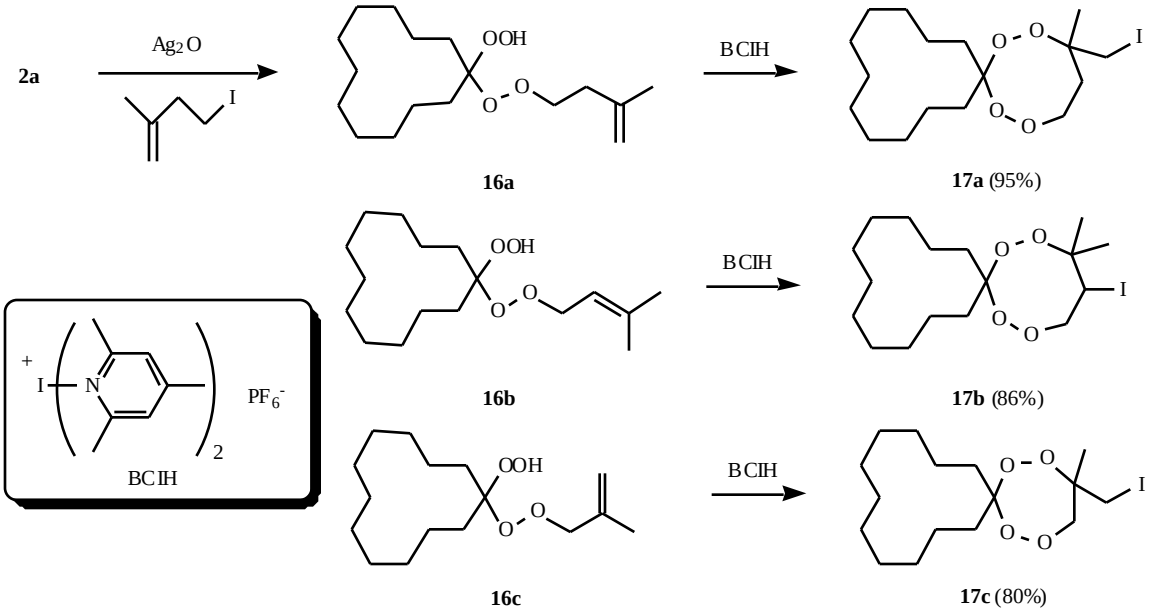
It is easily noticed that the unsaturated hydroperoxide **16a,** prepared by the Ag_2O-mediated monoalkylation of 1,1-bishydroperoxide **2a** with 4-iodo-2-methyl-1-butene, is a proper precursor for the synthesis of the 1,2,4,5-tetraoxacycloalkanes by the electrophile-promoted cyclization (Scheme 3). On subsequent treatment with bis(*sym*-collidine)-iodine(I) hexafluorophosphate (BCIH) [13] in CH_2Cl_2, peracetal **16a** undergoes 8-*exo-trig* cyclization to give 1,2,4,5-tetroxocane **17a** in high yield [14]. The structure of the unsaturated side-chain has been found to influence the nature of the cyclization products. Thus, when the related peracetal **16b** is treated with BCIH, 4-iodo-substituted 1,2,4,5-tetroxocane **17b** is obtained *via* an 8-*endo-trig* cyclization mode, while treatment of peracetal **16c** gives the tetroxepane derivative **17c** (Scheme **3**).

To obtain information for the scope and limitations of BCIH-promoted cyclization of unsaturated hydroperoxide, we have prepared alternative unsaturated hydroperoxides **18**. The reactions result in the formation of novel macrocyclic peroxides **19** with ring sizes in the range 14-20 in moderate yields of 50-58% (Scheme **4**) [15]. These results imply that BCIH is a highly efficient promoter for the synthesis of medium- and large-membered cyclic peroxides from a variety of unsaturated hydroperoxides.

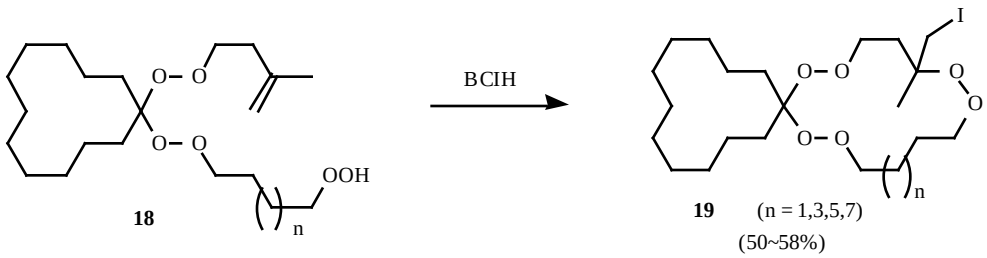
In the former section was described trapping of the zwitterionic intermediate **12** from 2-phenylnorbornene **11** by aqueous H_2O_2. The same intermediate **12** can be trapped by unsaturated hydroperoxide or unsaturated alcohols thereby providing the corresponding unsaturated hydroperoxides **20**-**22** albeit in low yield (12-25%) (Scheme **5**). The reactions of **20**-**22** with BCIH give in each case the corresponding 1,2,5,6-tetroxonane **23**, 1,2,4-trioxepane **24** and 1,2,5-trioxocane **25**, respectively (Scheme **5**) [10].

Ozone is also a good promoter for the synthesis of cyclic peroxides from unsaturated hydroperoxides. The key is the efficient intramolecular trapping of the derived carbonyl oxide intermediate by the remote hydroperoxy group, which is assisted by AcOH or trifluoroethanol, protic solvent with a low nucleophilicity [16]. Thus, ozonolysis of peracetal **16a** in AcOH-CH_2Cl_2 provides the hydroperoxy-substituted 1,2,4,5-tetroxocane **26**, which is readily methylated using methyl iodide in the presence of Ag_2O to yield **27** (Scheme **6**) [13].

Ozonolysis of (alkenyldioxy)cyclododecyl hydroperoxides **28** in trifluoroethanol gives α-hydroperoxy-substituted spiro-tetraoxacycloalkanes **29** with ring sizes in the range 7-12. Dehydration of the hydoperoxides affords the corresponding peroxylactones **30** (Scheme **6**) [17].



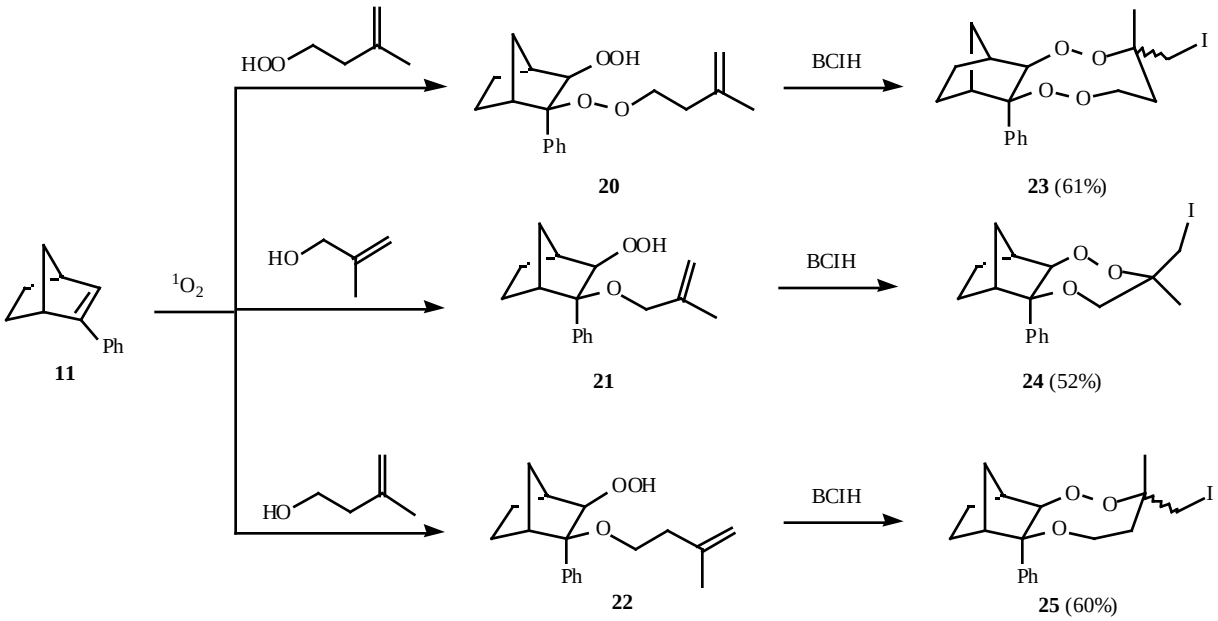
Scheme 3.



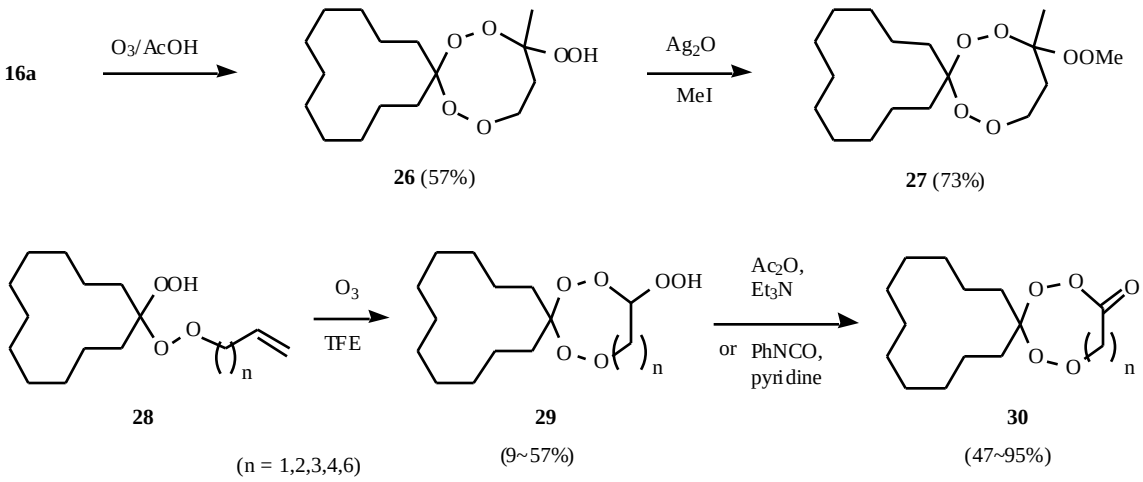
Scheme 4.

2.3. Acid-Catalyzed Cyclocondensation of 1,n-Bishydroperoxides with Ketones

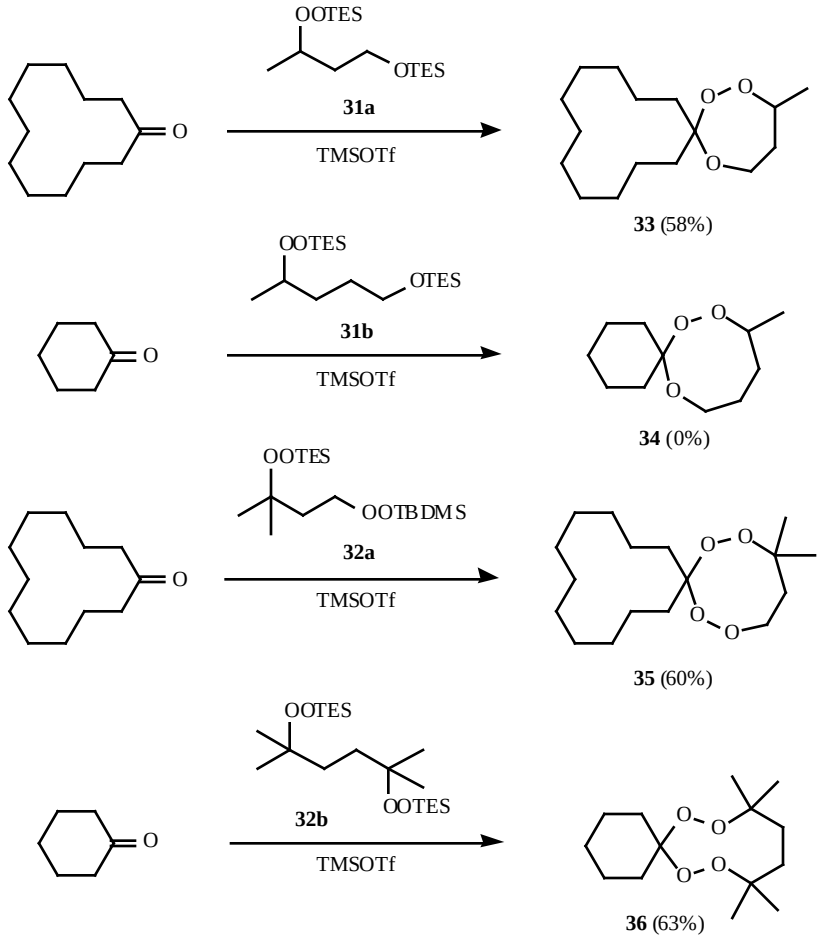
Oh, Dussault, and O'Neill have found independently that acid-catalyzed cyclocondensation of carbonyl compounds with 3-hydroxypropyl hydroperoxides (or their protected form such as **31a**) is an attractive method for the synthesis of 1,2,4-trioxepane derivatives [18,19]. However, this reaction does not seem to work well for the preparation of 1,2,4-trioxocane **34** (Scheme **7**). In contrast, TMSOTf-



Scheme 5.



Scheme 6.



Scheme 7.

catalyzed cyclocondensation of trialkylsilyl-protected bishydroperoxide **32a** with cyclododecanone provides a spiro-1,2,4,5-tetroxocane derivative **35**. From the bisperoxide **32b** is obtained the spiro-1,2,4,5-tetroxonane derivative **36** (Scheme **7**)*.

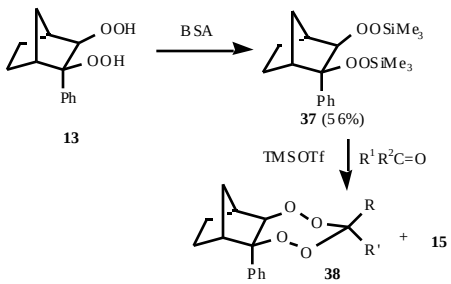
1,2-Bishydroperoxide **13** is successfully transformed using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) into the corresponding bis-trimethylsilylated derivative **37**. TMSOTf-catalyzed cyclocondensation of **37** with carbonyl compounds provides a series of 1,2,4,5-tetroxepane derivatives **38a-e** (Table **3**) [10].

3. ANTIMALARIAL ACTIVITY *IN VITRO*

With a series of 1,2,4,5-tetraoxacycloalkanes in hand, we tested the antimalarial activities against *P. falciparum*

*Tokuhara, H.; Masuyama, A.; Nojima, M. unpublished results

Table 3. Cyclocondensation of 1,2-bisperoxide 37 with Aldehyde or Ketone



	% yield of 38	% yield of 15
a: R^1 = Ph, R^2 = H	23	36
b: R^1 = 4-FC_6H_4, R^2 = H	13	33
c: R^1 = cyclohexyl, R^2 = H	12	29
d: R^1, R^2 = -$(CH_2)_5$-	19	41
e: R^1, R^2 = -$CH(CH_3)$-$(CH_2)_4$-	11	45

(chloroquine sensitive FCR-3 strain) and cytotoxicities against mouse tumor mammary FM3A cell (Table **4**) [6b,7]. Selectivity shows the mean of EC_{50} value for FM3A cells/the mean of EC_{50} value for *P. falciparum*. That is, high selectivity would mean effective attack of malaria parasite by the peroxide without significant damage of host cells.

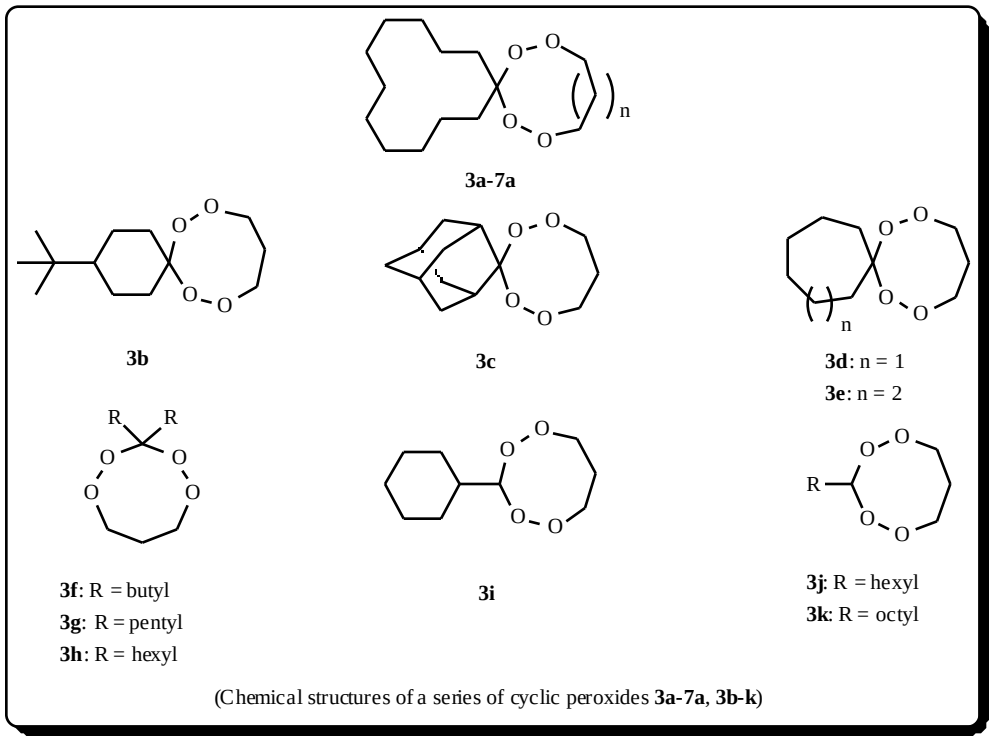
The results are summarized as follows: (a) all the tetroxocanes **3a-i** showed substantial antimalarial activity. The EC_{50} values against *P. falciparum* were in the ranges of 0.003-0.31 μM and the selectivity was in the range of 95-10,000. It is worth noting that the antimalarial activities of **3a-c** are comparable to that of artemisinin. (b) For a series of cyclic peroxides **3a-7a**, the ring size exerts a substantial influence on the EC_{50} values, the activity decreasing in the order **6a** > **3a** > **4a** > **5a** > **7a**. (c) The activity of the acyclic peroxide **8** was only one tenth of that of artemisinin and the selectivity was significantly poor than that of artemisinin. However, this is, to our knowledge, the first example to demonstrate that acyclic peroxide has certainly a substantial antimalarial activity.

The *in vitro* antimalarial activities of 1,2,5,6-tetraoxycycloalkanes and 1,2,5-trioxacycloalkanes from 1,2-bishydroperoxide **13** were also determined (Table **5**) [10]. A

Table 4. *In Vitro* Antimalarial Activities of 1,2,4,5-tetraoxacycloalkanes and the Related Peroxides Against *P. falciparum* and Cytotoxicities Against FM3A Cells

	EC_{50} values (μM)		
peroxide	***P. falciparum*[a]**	**FM3A[b]**	**selectivity[c]**
3a (n = 1)	0.025	8.0	320
4a (n = 2)	0.1	17	170
5a (n = 3)	0.28	12	43
6a (n = 4)	0.01	16	1600
7a (n = 6)	1.7	29	17
3b	0.003	30	10000
3c	0.05	58	1160
3d	0.20	32	160
3e	0.20	110	550
3f	0.28	56	200
3g	0.31	34	110
3h	0.20	19	95
3i	0.20	19	95
3j	NA[d]		
3k	NA[d]		
8	0.086	1.5	17
9	0.38	6.0	16
10	5.0	0.45	11
17a	0.51	5.6	11
17b	0.08	9.3	116
17c	1.3	1.7	1.3
27	0.1	1.2	12
30 (n = 2)	NA[d]		
35	0.7	9.0	13
artemisinin	0.01	10	1000

[a]Chloroquine sensitive (FCR-3 strain).
[b]Mouse mammary tumor FM3A cells in culture as a control for mammalian cell cytotoxicity.
[c]Selectivity = mean of EC_{50} value for FM3A cells/mean of EC_{50} value for *P. falciparum*.
[d]NA: no activity at 10 μM.



(Chemical structures of a series of cyclic peroxides **3a-7a**, **3b-k**)

series of tetraoxacycloalkanes, **14a**, **23** and **38c-e** showed antimalarial activity against *P. falciparum* with EC_{50} values in the range 0.13-0.45 μM, and the selectivity in the range 24-237. As judged from a combination of their respective activity and selectivity, compounds **14a** and **38c** were found to be most attractive. For trioxacycloalkane derivatives **24** and **25**, it is noted that the antimalarial activity of compound **25** was comparable to that of artemisinin (Table **5**).

4. ANTIMALARIAL ACTIVITY *IN VIVO*

As shown in the former section, some of the medium-sized cyclic peroxides and the related acyclic one show attractive antimalarial activity *in vitro*. Therefore, *in vivo* antimalarial activities of these peroxides were determined against *P. berghei* NK 65 strain *via* intraperitoneal (ip) administration in infected mice [6b,7]. Results shown in Table **6** indicate that the 1,2,4,5-tetroxocanes, **3a** and **3b** had potent antimalarial activities (ED_{50}: 12-15 mg/kg), although slightly less potent compared with artemisinin (ED_{50}: 5.0 mg/kg), on treatment with intraperitoneal (ip) administration. More important is the fact that the peroxide **3a** was orally active. The cyclic peroxides **4a** and **6a**, which showed similar activities *in vitro*, were found to exert only moderate activities *in vivo* (ED_{50}: 48-160 mg/kg).

It should be noticed that by the administration with **3a** (ip; 50 mg/kg/day; 4 days), malaria parasites could not be

Table 5. ***In Vitro*** **Antimalarial Activities of 1,2,5,6-tetraoxacycloalkanes and 1,2,5-trioxacycloalkanes Against** ***P. falciparum*** **and Cytotoxicities Against FM3A Cells**

	EC_{50} values (μM)		
peroxide	***P. falciparum*** **[a]**	**FM3A [b]**	**selectivity [c]**
14a	0.19	45	237
23	0.15	11	73
24	1.0	11	11
25	0.005	15	3000
38a	1.5	13	9
38b	1.0	11	11
38c	0.21	11	52
38d	0.45	11	24
38e	0.13	5.9	45

Table 6. *In Vivo* Antimalarial Activities (ip and p.o.) of Peroxides Against *P. berghei* Infected Mice

peroxide	method of administration	ED_{50} (mg/kg)[a]	ED_{90} (mg/kg)[a]
artemisinin	ip	5.4	32
	p.o.	13	89
3a	ip	12	20
	p.o.	20	40
4a	ip	48	65
6a	ip	160	
3b	ip	15	30
	p.o.	52	84
3c	ip	100	
3e	ip	21	75
3g	ip	30	58
8	ip	13	20
	p.o.	30	60
14a	ip	13	50
38c	ip	70	

[a]The test compounds dissolved in olive oil were administered to groups of five mice once a day starting on day 0 and continued on day 1, day 2, and day 3. Parasitemia levels were determined on the day following the last treatment (on day 4).

observed in blood stream after the 4-day suppressive test. Consistent with this result, all five infected mice were cured; no cytotoxic effects were observed over a 60-day monitoring period. Furthermore, all five infected mice treated with a 3-day oral regiment of **3a** (160 mg/kg/day) beginning on the day of 1% parasitemia were cured; no parasite reoccurrence or treatment-induced toxicity was observed. In contrast, *P. Berghei* parasites were still observed in the blood stream of infected mice following a corresponding administration of artemisinin (p.o., 160 mg/kg/day, 3 days), and all five infected mice died within 18 days. Also interesting is the remarkably low toxicity of the tetroxocane **3a**; no death or no cytotoxicity was observed at 1600 mg/kg/day (ip). This new and easily prepared tetroxocane **3a** is, therefore, a promising compound appropriate for clinical evaluation.

It is interesting to note that the ED_{50} value of the most promising acyclic peroxide, 1,1-bis(methyldioxy)cyclododecane **8** on ip administration was only twice of that of artemisinin. Consistent with this, on administration of **8** (ip; 20 mg/kg; 4 days), malaria parasites could not be observed in blood stream after the 4-day suppressive test.

As indicated in Table **6**, the ED_{50} value of **14a** on ip administration was 2.4 times of that of artemisinin, whereas **38c** showed only moderate activity. Most disappointing is the fact that the tricyclic peroxide **25**, the very active compound *in vitro*, was found to be inactive *in vivo* (ED_{50}: ip; 100 mg/kg) [10].

CONCLUSION

We have developed several synthetic pathways of medium-sized 1,2,4,5- and 1,2,5,6-tetraxacycloalkanes. Judged from the data *in vitro* and *in vivo*, it may be concluded that 1,2,6,7-tetraoxaspiro[7.11]nonadecane **3a**, efficiently prepared from cheap compounds by only two steps, is highly attractive as the candidate of antimalarial drugs. We are now in progress to clarify the mode of action of **3a** on malaria parasite and modify **3a** to develop a compound for intravenous administration.

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REFERENCES

[1] (a) Borstnik, K.; Paik, I.-H.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661-1667; (b) McCullough, K. J.; Nojima, M. *Current Org. Chem*. **2001**, *5*, 601-636; (c) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res*. **2004**, *37*, 397-404; (d) Haynes, R. K.; Ho, W.-Y.; Chan, H.-W.; Fugmann, B.; Stetter, J.; Croft, S. L.; Vivas, L.; Peters. W.; Robinson, B. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1381-1385.

[2] Dong, Y. *Mini Rev. Med. Chem.* **2002**, *2*, 113-123.

[3] (a) Dong, Y. *Mini Rev. Med. Chem.* in press; (b) Jefford, C. W.; Li, Y.; Jaber, A.; Boukouvalas, J. *Synth. Commun*. **1990**, *20*, 2589-2596; (c) Kim, H.-S.; Tsuchiya, K.; Shibata, Y.; Wataya, Y.; Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1867-1870; (d) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron Lett*. **2003**, *44*, 7359-7363; (e) Iskra, J.; Bonnet-

Delpon, D.; Begue, J.-P. *Tetrahedron Lett.* **2003**, *44*, 6309-6312; (f) Solaja, B.; A. Terzic, N.; Pocsfalvi, G.; Gerena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. *J. Med. Chem.* **2002**, *45*, 3331-3336.

[4] (a) Dussault, P. H.; Sahli, A. *J. Org. Chem*. **1992**, *57*, 1009-1012; (b) Dussault, P. H.; Zope, U. R. *J. Org. Chem*. **1995**, *60*, 8218-8222.

[5] (a) Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3272-3278; (b) Adam, W.; Birke, A.; Cadiz, C.: Diaz, S.; Rodoriguez, A. *J. Org. Chem*. **1978**, *43*, 1154-1158.

[6] (a) Tsuchiya, K.; Hamada, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Shibata, Y.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 4077-4080; (b) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357-2361.

[7] Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Ono, K.; Ogura, N.; Wataya, Y. *J. Med. Chem.* **2002**, *45*, 1374-1378.

[8] Adam, W.; Bruenker, H.-G.; Kumar, A. S.; Peters, K.; Schneider, U.; Von Schnering, H.G. *J. Am. Chem. Soc*. **1996**, *118*, 1899-1905.

[9] Jefford, C. W. *Chem. Soc. Rev*. **1993**, 59-66.

[10] (a) McCullough, K. J.; Nonami, Y.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 9151-9155; (b) Kim, H.-S.; Begum, K.; Ogura, N.; Wataya, Y.; Nonami, Y.; Ito, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2003**, *46*, 1957-1961.

[11] (a) Bloodworth, A. J.; Shah. A. *Tetrahedron Lett*. **1993**, *34*, 6643-6646; (b) Bloodworth, A. J.; Bothwell, B. D.; Collins, A. N.; Maidwell, N. L. *Tetrahedron Lett.* **1996**, *37*, 1885-1888.

[12] (a) Dussault, P. H.; Davies, D. R. *Tetrahedron Lett.*, **1996**, *37*, 463-466; (b) Ushigoe, Y.: Kano, Y.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 5-10; (c) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Org. Chem*. **2000**, *65*, 1069-1075.

[13] Rousseau, G.; Homsi, F. *Chem. Soc. Rev*. **1997**, *26*, 453-461.

[14] Nonami, Y.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett*. **1999**, *40*, 4681-4684.

[15] (a) McCullough, K. J.; Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M. *Tetrahedron Lett.* **2001**, *42*, 5529-5532; (b) Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525-536.

[16] (a) Ushigoe, Y.: Torao, Y.; Masuyama, A.; Nojima. M. *J. Org. Chem*. **1997**, *62*, 4949-4954; (b) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron* **2001**, *57*, 5979-5989.

[17] McCullough, K. J.; Tokuhara, H.; Masuyama, A.; Nojima, M. *Org. Biomol. Chem.* **2003**, *1*, 1522-1527.

[18] (a) Oh, C. H.; Kang, J. H. *Tetrahedron Lett*. **1998**, *39*, 2771-2774; (b) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591-4593.

[19] (a) Oh, C. H.; Kim, H. J.; Wu, S. H.; Won, H. S. *Tetrahedron Lett*. **1999**, *40*, 8391-8394; (b) O'Neill, P. M.; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, *44*, 8135-8139.