Synthesis and Antimalarial Activity of Novel Medium-Sized 1,2,4,5-Tetraoxacycloalkanes

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CsOH- or Ag_2O-mediated cycloalkylation of (alkylidene)bisperoxides **3** and 1,*n*-dihaloalkanes (n = 3−8) provided the corresponding medium-sized 1,2,4,5-tetraoxacycloalkanes **4**−**8** in moderate yields. Subsequent evaluation of the antimalarial activity of the cyclic peroxides **4**−**8** in vitro and in vivo revealed that 1,2,6,7-tetraoxaspiro[7.11]nonadecane **4a** has considerable potential as a new, inexpensive, and potent antimalarial drug.

Introduction

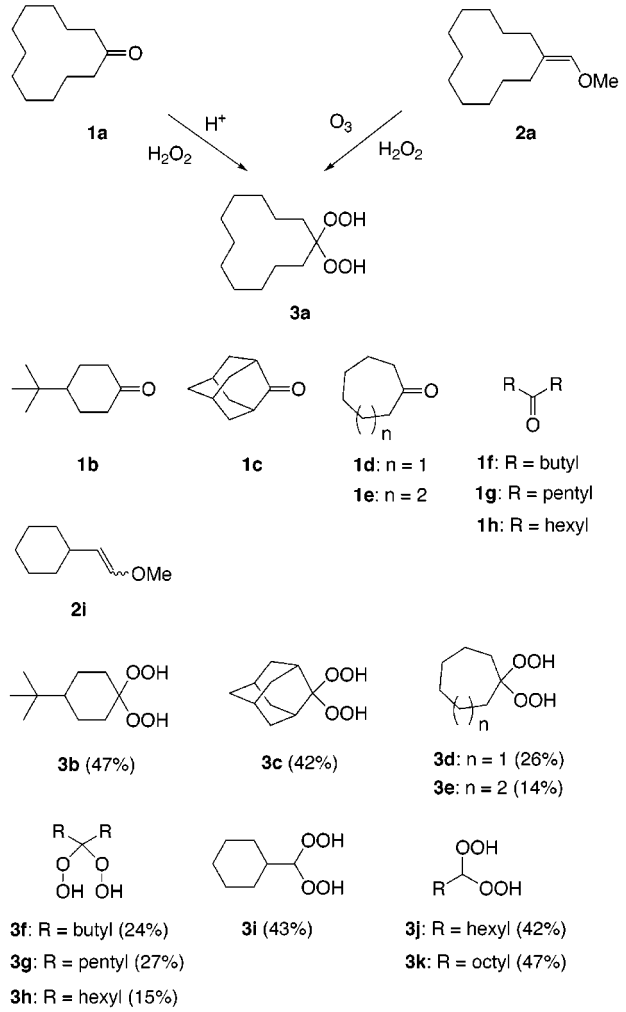
Because malaria parasites are rapidly developing multidrug resistance to the more common chemotherapeutic alkaloidal drugs, interest in the antimalarial properties of nonalkaloidal compounds such as the sesquiterpene artemisinin and the related endoperoxides is rapidly growing.[1] Particularly interesting is the fact that dispiro-1,2,4,5-tetroxanes, easily prepared by the acid-catalyzed condensation of cycloalkanones and hydrogen peroxide, exhibit remarkable antimalarial activities in vitro and in vivo.[2] This observation had led us to speculate that other cyclic peroxide systems having two peroxide groups within the same ring could also possess significant antimalarial activity.[3] In this respect, we now report that CsOH- or Ag_2O-mediated cyclization of (alkylidene)bishydroperoxides **3** and 1,*n*-dihaloalkanes offers a promising procedure for the synthesis of novel 1,2,4,5-tetraoxacycloalkanes **4**−**8**.[4] Moreover, these cyclic peroxides have been found to show remarkable antimalarial activity not only in vitro but also in vivo.

Results and Discussion

Synthesis of 1,2,4,5-Tetraoxacycloalkanes. Ozonolysis of the vinyl ethers **2a**,**i** in the presence of excess hydrogen peroxide (ca. 2 equiv) in diethyl ether[5] at −70 °C, followed by column chromatography on silica gel, gave the expected bis(hydroperoxide)s **3a**,**i** in yields of 33 and 43%, respectively (Scheme 1).[3b] The bis(hydroperoxide)s, **3j** and **3k**, were prepared by the ozonolysis of 1-octene and 1-decene, respectively, under similar reaction conditions. Alternatively, bis(hydroperoxide) **3a** could be prepared by the reaction of cyclododecanone and 30% aqueous hydrogen peroxide in formic acid (ca. 50%).[6] By using the latter method, the bis(hydroperoxide)s **3b**−**h** were also prepared (Scheme 1).

Cycloalkylation of the bis(hydroperoxide)s **3a**−**k** was attempted by treatment with 1,*n*-diiodoalkanes in the presence of cesium hydroxide monohydrate in DMF.[7] Thus the reaction of **3a** with 1,3-diiodopropane (1.5 mol equiv) and CsOH·H_2O (2 mol equiv) in DMF for 15 h, followed by column chromatography on silica gel, afforded the desired 1,2,4,5-tetroxocane derivative **4a** (40% yield) as the first fraction. Cyclododecanone **1a** was obtained subsequently (40%) (Scheme 2). Bis(hydrop-

Scheme 1



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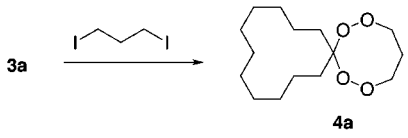
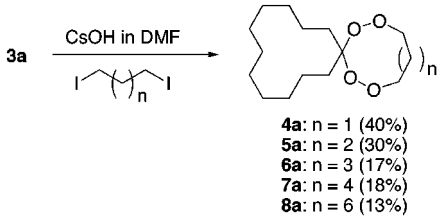
Scheme 2[a]



mediator	solvent	% yield[a]
CsOH[b]	DMF	40
Cs_2CO_3	DMF	31
Ag_2O	CH_2Cl_2	42
Ag_2O[b]	CH_2Cl_2	56
Ag_2O[b]	$MeCO_2Et$	61

[a] A considerable amount of cyclododecanone was also isolated. [b] A total of 2 mol equiv of promoter was used.

Scheme 3



eroxide) **3a** was found to be labile toward $CsOH·H_2O$ because treatment of **3a** with $CsOH·H_2O$ in DMF for 15 h resulted in its complete decomposition into **1a**. Cs_2CO_3 was found to be a less efficient promoter than CsOH in the synthesis of **4a**.

Since Ag_2O is reported to be an excellent catalyst for the synthesis of dialkyl peroxides by the alkylation of organic hydroperoxides,[8] the cycloalkylation reaction between **3a** and 1,3-diiodopropane was attempted in the presence of freshly prepared Ag_2O in dichloromethane (Scheme 2). The ratio of **3a** to Ag_2O exerts a small but important influence on the efficiency of the reaction: using equimolar amounts of Ag_2O provided tetroxocane **4a** in 42% yield, whereas with 2 mol equiv of Ag_2O, **4a** was isolated in an improved 56% yield. Changing the solvent from dichloromethane to ethyl acetate resulted in a further increase in the yield of peroxide **4a** (61%).

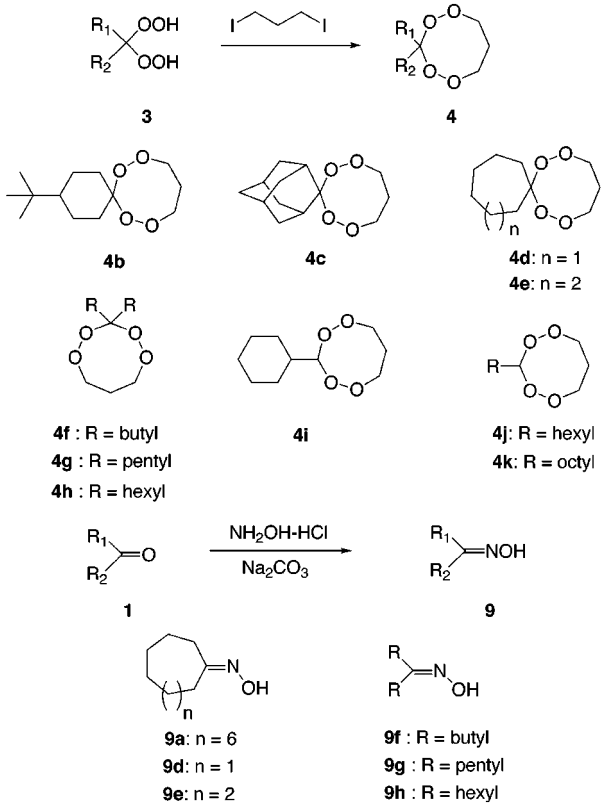
The chain length in the 1,*n*-diiodoalkanes plays an important role in the CsOH-promoted cyclization reaction (Scheme 3). First, 1,*n*-diiodoalkanes (n = 3−6, 8) could be used for cycloalkylation of the bis(hydroperoxide) **3a**, thereby providing the corresponding 1,2,4,5-tetraoxacycloalkanes **4a**−**8a**. The analogous reaction with 1,2-diiodoethane yielded only cyclododecanone **1a** rather than the expected 1,2,4,5-tetroxepane derivative. Second, under normal conditions, the cyclization reaction between **3a** and the longer chain 1,*n*-diiodoalkanes (n = 5, 6, and 8) produced only a complex mixture of products containing cyclododecanone. Simultaneous addition of more dilute solutions of the reactants over extended addition times resulted in the preparation of the 10- to 13-membered tetraoxacyclolalkanes **6a**−**8a** albeit in moderate to low yields (see Experimental Section). Finally, the Ag_2O-promoted cyclization was less successful for the synthesis of the 9- to 13-membered tetraoxacycloalkanes **5a**−**8a**. For example, the reaction of **3a** with 1,4-diiodobutane gave **5a** in a low yield of 12% together with **1a** (70%), whereas the

Table 1. Synthesis of 1,2,4,5-Tetroxocanes by the Reaction of Bishydroperoxides and 1,3-Diiodopropane

tetroxocane	promoter[a]	solvent	% yield
4b	CsOH	DMF	26
4b	Cs_2CO_3	DMF	18
4b	Ag_2O	CH_2Cl_2	54
4c	CsOH	DMF	19
4d	Ag_2O	$MeCO_2Et$	53
4e	Ag_2O	$MeCO_2Et$	54
4f	Ag_2O	$MeCO_2Et$	69
4g	Ag_2O	$MeCO_2Et$	58
4h	Ag_2O	$MeCO_2Et$	63
4i	CsOH	DMF	19
4i	Ag_2O	CH_2Cl_2	21
4j	Ag_2O	$MeCO_2Et$	32
4k	Ag_2O	$MeCO_2Et$	27

[a] Except for Cs_2CO_3, 2 mol equiv of a promoter was used.

Scheme 4



analogous reaction with 1,6-diiodohexane resulted in the production of only oligomeric products.

The procedures used for the synthesis of a variety of 1,2,4,5-tetroxocane derivatives **4b**−**k** are summarized in Table 1 and Scheme 4. A slight modification of the procedure is required for the synthesis of **4d**−**h** because of difficulties in separating the desired tetroxocane from the reaction byproducts by column chromatography on silica gel column. Thus, a mixture of **4g** and **1g** was treated with $NH_2OH·HCl$ to convert **1g** to the highly polar oxime **9g** (Scheme 4). On subsequent column chromatography of this mixture on silica gel, the tetroxocane **4g** was easily isolated (58%). The teraoxecanes **4d**−**f**,**h** were isolated in a similar fashion. It was found that it was difficult to separate the cyclic peroxide **8a** from ketone **1a** and unreacted 1,8-diiodooctane. By using only 0.7 equiv of the diiodide in the reaction with **3a**, and subsequent treatment of the product mixture with $NH_2OH·HCl$, 13-membered 1,2,4,5-tetraoxacyclotridecane derivative **8a** was conveniently purified by column chromatography on silica gel.

Table 2. In Vitro Antimalarial Activities of Peroxides **4**−**8** against *P. falciparum* and Cytotoxicities against FM3A Cells[a]

peroxide	EC_{50} values (M) *P. falciparum*[b]	FM3A[c]	selectivity[d]
3a	1.0×10^{-4}	4.4×10^{-5}	
4a	2.5×10^{-8}	8.0×10^{-6}	320
5a	1.0×10^{-7}	1.7×10^{-5}	170
6a	2.8×10^{-7}	1.2×10^{-5}	43
7a	1.0×10^{-8}	1.6×10^{-5}	1600
8a	1.7×10^{-6}	2.9×10^{-5}	17
4b	3.0×10^{-9}	3.0×10^{-5}	10000
4c	5.0×10^{-8}	5.8×10^{-5}	1160
4d	2.0×10^{-7}	3.2×10^{-5}	160
4e	2.0×10^{-7}	1.1×10^{-4}	550
4f	2.8×10^{-7}	5.6×10^{-5}	200
4g	3.1×10^{-7}	3.4×10^{-5}	110
4h	2.0×10^{-7}	1.9×10^{-5}	95
4i	2.0×10^{-7}	1.9×10^{-5}	95
artemisinin	1.0×10^{-8}	1.0×10^{-5}	1000

[a] In vitro antimalarial activities and cytotoxicities were reported previously.[3a] [b] Chloroquine sensitive (FCR-3 strain). [c] Mouse mammary tumor FM3A cells in culture as a control for mammalian cell cytotoxicity. [d] Selectivity = mean of EC_{50} value for FM3A cells/mean of EC_{50} value for *P. falciparum*.

Antimalarial Activity of 1,2,4,5-Tetraoxacycloalkanes in Vitro. With a series of 1,2,4,5-tetraoxacycloalkanes **4**−**8** in hand, we tested their antimalarial activities and cytotoxicities against *P. falciparum* and FM3A cells, respectively (Table 2).[3a] The results are summarized as follows: (a) All the tetroxocanes **4a**−**i** showed substantial antimalarial activity with EC_{50} values against *P. falciparum* in the range 3.1×10^{-7}−3.0×10^{-9} M, and the selectivity was determined by the 50% inhibitory concentration against mouse mammary FM3A cells in the range 43−10000. It is worth noting that the antimalarial activities of **4a**−**c** are comparable to that of artemisinin (the EC_{50} value against *P. falciparum* and the selectivity are 1.0×10^{-8} M and 1000, respectively).[1e,9] (b) For the series of cyclic peroxides **4a**−**8a**, the peroxide ring size exerts a remarkable influence on the EC_{50} values, the activity decreasing in the order **7a** > **4a** > **5a** > **6a** > **8a**. (c) 3,3-Dialkyl-substituted 1,2,4,5-tetroxocanes **4f**−**h** with different alkyl chains showed moderate antimalarial activity. (d) In contrast, the antimalarial activity of the monoalkyl-substituted 1,2,4,5-tetroxocanes **4i** was very low. Tetroxocanes **4j**−**k** exhibited no significant cytotoxicity at 5×10^{-5} M for *P. falciparum*. These results suggest that minor changes in the structure of the cyclic peroxides **4**−**8** exerts a remarkable influence on the antimalarial activity in vitro.

Antimalarial Activity of 1,2,4,5-Tetraoxacycloalkanes in Vivo. In vivo antimalarial activities for peroxides against the *P. berghei* NK 65 strain were also determined.[3a] The results compiled in Table 3 indicate that the 1,2,4,5-tetroxocanes, **4a** and **4b**, exhibited potent antimalarial activity (ED_{50}: 12−15 mg/kg), although their potency is lower than that of artemisinin (ED_{50}: 5.0 mg/kg) on intraperitoneal administration. More important is the fact that the peroxide **4a** was found to be orally active (ED_{50}: 20 mg/kg) whereas cyclic peroxides **7a** and **4c**, which showed similar activities in vitro, were found to exert only moderate activities even in intraperitoneal administration (ED_{50}: 100−160 mg/kg).

On administration of **4a** to infected mice by intraperitoneal injection (ip) (50 mg/kg/day; 4 days), the malaria parasites could not be observed in their bloodstreams after the 4 day suppressive test. Consistent with this, five out of the five infected mice were cured and experienced no cytotoxic effects for more than 60 days afterward. Furthermore, all infected mice, treated orally (po) with **4a** (160 mg/kg/day) once a day for three consecutive days beginning on the day of 1% parasitemia were cured with no parasite reincrease or toxicity. Conversely, on similar treatment of infected mice with artemisinin, the malaria parasites were still observed in their blood streams, and as a result, five out of the five mice treated with artemisinin died during 18 days due to *P. berghei* infection (po, 160 mg/kg/day; 3 days). The low toxicity of the tetroxocane **4a** is also noteworthy; no death or no cytotoxicity was observed at dose levels of 1600 mg/kg/day (ip). It is concluded, therefore, that this new and easily prepared tetroxocane **4a** represents a promising candidate for further clinical evaluation.

Table 3. In Vivo Antimalarial Activities of Peroxides against *P. berghei* Infected Mice

peroxides	intraperitoneal ED_{50}, mg/kg[a]	intraperitoneal ED_{90}, mg/kg[a]	oral ED_{50}, mg/kg[a]	oral ED_{90}, mg/kg[a]
4a	12	20	20	40
5a	48	65		
7a	160	>200		
4b	15	30	52	84
4c	100			
4d	72	>100		
4e	21	75		
4f	50	90		
4g	30	58		
4h	60	91		
artemisinin	5	32	13	89

[a] Various concentrations of the test compounds were prepared in olive oil. The test compounds 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), and ED values of the antimalarial activities indicated above were determined by the previously reported protocol.[3a]

Experimental Section

General Procedure. ^1H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard. The bis(hydroperoxide) **3i**[3b] and Ag_2O[10] were prepared by literature methods.

Caution: Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, mechanical shock, oxidizable organic materials, or transition metal ions.

Preparation of Bis(hydroperoxide)s by the Ozonolysis of a Vinyl Ether in the Presence of Hydrogen Peroxide in Diethyl Ether. Ozonolysis of methoxymethylenecyclododecane (**2a**) is representative. The diethyl ether solution (2.5 M) of anhydrous H_2O_2 was prepared by extraction of the 30% aqueous H_2O_2 solution with diethyl ether. The diethyl ether extracts were dried over anhydrous $MgSO_4$ and standardized iodometrically. To the solution of H_2O_2 in diethyl ether (25 mL) was added vinyl ether **2a** (630 mg, 3.0 mmol), and then a slow stream of ozone (1 equiv; flow for 9 min) was passed into the resulting reaction mixture at −70 °C. After adding diethyl ether (70 mL), the organic layer was washed with ice-cold potassium dihydrogen phosphate and saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:10) gave cyclododecanone **1a** (215 mg, 39%). Subsequent elution with diethyl ether−hexane (3:7) gave the bis(hydroperoxide) **3a** (232 mg, 33%).

(Cyclododecylidene)bishydroperoxide 3a:[6] mp 140−141 °C (from benzene); ^1H NMR δ 1.2−1.8 (m, 22 H), 8.06 (s, 2 H); ^{13}C NMR δ 19.28, 21.86, 22.15, 26.02, 26.19, 26.29, 112.64.

α-Hydroperoxyheptyl hydroperoxide 3j: an oil; ^{1}H NMR δ 0.88 (t, J = 5.2 Hz, 3 H), 1.2−1.8 (m, 10 H), 5.29 (t, J = 6.1 Hz, 1 H), 9.40 (br s, 2 H); ^{13}C NMR δ 14.02, 22.48, 24.64, 28.56, 28.61, 31.52, 111.36. Anal. ($C_7H_{16}O_4$) C, H.

α-Hydroperoxynonyl hydroperoxide 3k: an oil; ^{1}H NMR δ 0.87 (t, J = 6.6 Hz, 3 H), 1.2−1.9 (m, 14 H), 5.28 (t, J = 6.1 Hz, 1 H), 9.44 (br s, 2 H); ^{13}C NMR δ 14.07, 22.63, 24.67, 28.54, 29.15, 29.22, 29.29, 31.79, 111.32. Anal. ($C_9H_{20}O_4$) C, H.

Preparation of Bis(hydroperoxide)s by the Reaction of a Ketone with 30% Aqueous Hydrogen Peroxide in Formic Acid. The preparation of **3g** is representative. To a stirred solution of 6-undecanone **1g** (5.10 g, 30 mmol) in formic acid (20 mL) was added 30% aqueous hydrogen peroxide (10 mL), and the mixture was stirred at room temperature for 3 min. The mixture was then poured into ice-cold water, and the organic products were extracted by diethyl ether (300 mL). After conventional workup, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:20) gave the unreacted undecanone **1g** (3.00 g). Elution with diethyl ether−hexane (1:9) gave a bis(hydroperoxide) **3g** (1.76 g, 27%).

6,6-Dihydroperoxyundecane 3g: mp 85−86 °C (from methanol); ^{1}H NMR δ 0.90 (t, J = 6.1 Hz, 6 H), 1.3−1.7 (m, 16 H), 8.83 (br s, 2 H); ^{13}C NMR δ 13.95, 22.39, 23,22, 29.44, 31.79, 114.72. Anal. ($C_{11}H_{24}O_4$) C, H.

1,1-Dihydroperoxy-(4-*tert*-butyl)cyclohexane 3b: mp 83−84 °C (from ether−hexane); ^{1}H NMR δ 0.87 (s, 9 H), 1.1−1.8 (m, 9 H), 9.27 (s, 2 H); ^{13}C NMR δ 23.32, 27.58, 29.70, 32.31, 47.39, 110.00. Anal. ($C_{10}H_{20}O_4$) C, H.

4,4-Dihydroperoxyadamantane 3c: mp 144−145 °C (from ether−hexane); ^{1}H NMR δ 1.7−2.1 (m, 14 H), 8.82 (s, 2 H); ^{13}C NMR δ 26.94, 31.14, 33.68, 36.98, 112.88. Anal. ($C_{10}H_{16}O_4$) C, H.

(Cycloheptylidene)bishydroperoxide 3d: an oil; ^{1}H NMR δ 1.5−1.6 (m, 8 H), 1.9−2.0 (m, 4 H), 9.39 (s, 2 H); ^{13}C NMR δ 22.59, 29.96, 32.46, 115.98. Anal. ($C_7H_{14}O_4$) C, H.

(Cyclooctylidene)bishydroperoxide 3e: an oil; ^{1}H NMR δ 1.4−2.0 (m, 14 H), 9.35 (s, 2 H); ^{13}C NMR δ 21.69, 24.82, 27.12, 27.82, 115.08. Anal. ($C_8H_{16}O_4$) C, H.

5,5-Dihydroperoxynonane 3f: an oil; ^{1}H NMR δ 0.92 (t, J = 6.6 Hz, 6 H), 1.2−1.5 (m, 8 H), 1.69 (t, J = 7.4 Hz, 4 H), 9.39 (s, 2 H); ^{13}C NMR δ 13.86, 22.77, 25.59, 28.88, 114.77. Anal. ($C_9H_{20}O_4$) C, H.

7,7-Dihydroperoxytridecane 3h: an oil; ^{1}H NMR δ 0.89 (t, J = 6.3 Hz, 6 H), 1.2−1.4 (m, 16 H), 1.6−1.7 (m, 4 H), 9.20 (br s, 2 H); ^{13}C NMR δ 14.02, 22.55, 23.47, 29.18, 29.36, 31.59, 114.59. Anal. ($C_{13}H_{28}O_4$) C, H.

CsOH-Mediated Synthesis of 1,2,4,5-Tetraoxacycloalkanes 4a, 5a, 4b, 4c, and 4i. The synthesis of tetroxocane **4a** is representative. To a stirred solution of the bis(hydroperoxide) **3a** (348 mg, 1.50 mmol) and CsOH·H_2O (504 mg, 3 mmol) in DMF (25 mL) was added 1,3-diiodopropane (666 mg, 2.25 mmol) by syringe over 10 min. The resulting reaction mixture was stirred for 16 h at room temperature under argon atmosphere. The mixture was then poured into diethyl ether (100 mL), and the organic layer was washed in turn with 3% aqueous sodium thiosulfate (50 mL), aqueous $NaHCO_3$, and saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was separated by column chromatography on silica gel. Initial elution with diethyl ether−hexane (1:49) gave the tetroxocane **4a** (164 mg, 40%). Further elution with diethyl ether−hexane (1:20) gave cyclododecanone **1a** (122 mg, 45%).

1,2,6,7-Tetraoxaspiro[7.11]nonadecane 4a: mp 83−84 °C (from hexane); ^{1}H NMR δ 1.3−1.7 (m, 22 H), 2.1−2.2 (m, 2 H), 4.12 (dt, J = 12.5 and 5.6 Hz, 2 H), 4.31 (dt, J = 12.5 and 4.7 Hz, 2 H); ^{13}C NMR δ 19.36, 21.90, 22.17, 25.91, 26.07, 26.25, 30.40, 73.94, 112.13. Anal. ($C_{15}H_{28}O_4$) C, H.

1,2,7,8-Tetraoxaspiro[8.11]icosane 5a: mp 97−98 °C (from hexane); ^{1}H NMR δ 1.3−1.7 (m, 24 H), 2.2−2.3 (m, 2 H), 3.66 (t, J = 12.2 Hz, 2 H), 4.26 (dd, J = 12.2 and 3.9 Hz, 2 H); ^{13}C NMR δ 19.30, 21.89, 22.17, 25.95, 26.11, 26.43, 30.93, 32.51, 73.85, 111.82. Anal. ($C_{16}H_{30}O_4$) C, H.

4-*tert*-Butyl-7,8,12,13-tetraoxaspiro[5.7]tridecane 4b: mp 58−59 °C (from hexane); ^{1}H NMR δ 0.86 (s, 9 H), 1.1−1.8 (m, 9 H), 2.18 (m, 2 H), 4.10 (m, 2 H), 4.35 (m, 2 H); ^{13}C NMR δ 23.34, 23.61, 27.64, 28.59, 30.35, 31.93, 32.37, 47.44, 73.76, 74.02, 107.92. Anal. ($C_{13}H_{24}O_4$) C, H.

Spiro[tricyclo[3.3.1.1^{3,7}]decane-2,3′-[1,2,4,5]tetroxocane] 4c: mp 34−35 °C (from hexane); ^{1}H NMR δ 1.6−2.3 (m, 16 H), 4.12 (dt, J = 12.9, 5.6 Hz, 2 H), 4.35 (dt, J = 12.5, 4.8 Hz, 2 H); ^{13}C NMR δ 27.06, 30.30, 31.81, 33.67, 33.98, 37.25, 73.94, 109.95. Anal. ($C_{13}H_{20}O_4$) C, H.

3-Cyclohexyl-1,2,4,5-tetroxocane 4i: an oil; ^{1}H NMR δ 1.1−1.8 (m, 12 H), 2.6−2.8 (m, 1 H), 4.0−4.2 (m, 2 H), 4.43 (dd, J = 12.9 and 3.6 Hz, 2 H), 5.12 (d, J = 6.3 Hz, 1 H). Anal. ($C_{10}H_{18}O_4$) C, H.

CsOH-Mediated Synthesis of 1,2,4,5-Tetraoxacycloalkanes 6a and 7a. The synthesis of **7a** is representative. To a stirred solution of CsOH·H_2O (1008 mg, 6.00 mmol) in DMF (20 mL) were added a solution of bis(hydroperoxide) **3a** (696 mg, 3.00 mmol) in DMF (20 mL) and a solution of 1,6-diiodohexane (1521 mg, 4.50 mmol) in DMF (20 mL) simultaneously via syringe over 1 h at room temperature. The reaction was continued for more than 16 h. The products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:100) gave the cyclic peroxide **7a** (168 mg, 18%).

1,2,8,9-Tetraoxaspiro[9.11]henicosane 6a: mp 51−52 °C (from hexane); ^{1}H NMR δ 1.3−1.8 (m, 24 H), 2.0−2.1 (m, 4 H), 4.1−4.2 (m, 4 H); ^{13}C NMR δ 19.26, 21.92, 22.25, 24.89, 25.97, 26.06, 26.65, 28.45, 76.64, 110.89. Anal. ($C_{17}H_{32}O_4$) C, H.

1,2,9,10-Tetraoxaspiro[10.11]docosane 7a: mp 48−49 °C (from hexane); ^{1}H NMR δ 1.3−1.8 (m, 30 H), 4.02 (t, J = 4.8 Hz, 4 H); ^{13}C NMR δ 19.35, 21.89, 22.23, 25.00, 26.02, 26.13, 26.43, 26.99, 74.63, 112.06. Anal. ($C_{18}H_{34}O_4$) C, H.

CsOH-Mediated Synthesis of 1,2,4,5-Tetraoxacyclotridecane 8a. To a stirred solution of CsOH·H_2O (1220 mg, 7.14 mmol) in DMF (25 mL) were added a solution of **3a** (829 mg, 3.57 mmol) in DMF (20 mL) and a solution of 1,8-diiodooctane (915 mg, 2.50 mmol) simultaneously via syringe over 1 h at room temperature. The reaction was continued for more than 16 h under argon atmosphere. After workup as described above, the residue was separated by column chromatography on silica gel (elution with diethyl ether−hexane (1:20)) to give a mixture of **8a** and **1a** (714 mg), which was reacted with a mixture of NH_2OH·HCl (300 mg, 4.31 mmol) and Na_2CO_3 (300 mg, 2.83 mmol) in 70% aqueous ethanol (10 mL) at room temperature for 15 h. After conventional workup, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:90) gave the tetraoxacyclotridecane **8a** (112 mg, 13% based on diiodooctane).

13,14,23,24-Tetraoxaspiro[11.12]tetracosane 8a: mp 37 °C (from hexane); ^{1}H NMR δ 1.3−1.7 (m, 34 H), 4.11 (t, J = 5.6 Hz, 4 H); ^{13}C NMR δ 19.27, 21.85, 22.18, 24.17, 26.00, 26.15, 26.56, 26.97, 74.84, 112.79. HRMS [M^+] m/z calcd for $C_{20}H_{38}O_4$, 342.2770; found, 342.2768.

Cs_2CO_3-Mediated Synthesis of 1,2,4,5-Tetraoxacycloalkanes 4a and 4b. The synthesis of a tetroxocane **4a** is representative. To a stirred solution of Cs_2CO_3 (652 mg, 2.00 mmol) and **3a** (464 mg, 2.00 mmol) in DMF (20 mL) was added a solution of 1,3-diiodopropane (888 mg, 3.00 mmol) in DMF (10 mL) via syringe over 5 min at 0 °C. The reaction was continued for a further 16 h at room temperature. After workup as described above, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:100) gave the cyclic peroxide **4a** (166 mg, 31%).

Ag_2O-Mediated Synthesis of 1,2,4,5-Tetroxocanes. The preparation of a tetroxocane **4g** is representative. To a solution of Ag_2O (1392 mg, 6 mmol) and a bis(hydroperoxide) **3g** (660 mg, 3.00 mmol) in dichloromethane (20 mL) was added a solution of 1,3-diiodopropane (1332 mg, 4.5 mmol) in dichloromethane (10 mL) via a syringe over 5 min at 0 °C. The reaction was continued at room temperature for more than 15 h. After filtration of the solid material over Celite, diethyl

ether (100 mL) was added to the filtrate, and the organic layer was washed with 3% aqueous sodium thiosulfate (50 mL), aqueous $NaHCO_3$, and saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:20) gave a 5:2 mixture of a peroxide **4g** and undecanone **1g** (562 mg), which was reacted with a mixture of $NH_2OH·HCl$ (104 mg, 1.50 mmol) and Na_2CO_3 (212 mg, 2.00 mmol) in 70% aqueous ethanol (10 mL) at room temperature for 15 h. After conventional workup, the residue was separated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:90) gave the tetroxocane **4g** (447 mg, 57%).

3,3-Dipentyl-1,2,4,5-tetroxocane 4g: an oil; ^{1}H NMR δ 0.84 (t, J = 5.4 Hz, 6 H), 1.2−1.7 (m, 16 H), 2.0−2.1 (m, 2 H), 4.0−4.3 (m, 4 H); ^{13}C NMR δ 13.89, 22.45, 23.22, 29.49, 60.41, 31.88, 73.53, 113.34; EIMS m/z 342 (M^+, 1), 183 (100). Anal. ($C_{14}H_{28}O_4$) C, H.

8,9,13,14-Tetraoxaspiro[6.7]tetradecane 4d: an oil; ^{1}H NMR δ 1.4−2.3 (m, 14 H), 4.07 (dt, J = 12.9 and 5.9 Hz, 2 H), 4.34 (dt, J = 12.9 and 4.7 Hz, 2 H); ^{13}C NMR δ 22.57, 30.12, 30.46, 32.28, 73.42, 113.19. Anal. ($C_{10}H_{18}O_4$) C, H.

1,2,6,7-Tetraoxaspiro[7.7]pentadecane 4e: an oil; ^{1}H NMR δ 1.2−2.4 (m, 16 H), 4.07 (dt, J = 12.9 and 5.7 Hz, 2 H), 4.34 (dt, J = 12.9 and 5.2 Hz, 2 H); ^{13}C NMR δ 21.85, 24.89, 27.53, 27.93, 30.48, 73.48, 112.18. Anal. ($C_{11}H_{20}O_4$) C, H.

3,3-Dibutyl-1,2,4,5-tetroxocane 4f: an oil; ^{1}H NMR δ 0.91 (t, J = 6.9 Hz, 6 H), 1.2−1.8 (m, 12 H), 2.0−2.2 (m, 2 H), 4.08 (dt, J = 12.9 and 5.8 Hz, 2 H), 4.33 (dt, J = 12.9 and 4.7 Hz, 2 H); ^{13}C NMR δ 13.91, 22.86, 25.72, 29.33, 73.60, 111.41. Anal. ($C_{12}H_{24}O_4$) C, H.

3,3-Dihexyl-1,2,4,5-tetroxocane 4h: an oil; ^{1}H NMR δ 0.88 (t, J = 5.8 Hz, 6 H), 1.2−1.8 (m, 20 H), 2.1−2.2 (m, 2 H), 4.08 (dt, J = 12.5 and 5.8 Hz, 2 H), 4.33 (dt, J = 12.9 and 4.6 Hz, 2 H); ^{13}C NMR δ 14.05, 22.57, 23.58, 29.45, 29.63, 30.44, 31.66, 73.64, 111.47. Anal. ($C_{16}H_{32}O_4$) C, H.

3-Hexyl-1,2,4,5-tetroxocane 4j: an oil; ^{1}H NMR δ 0.87 (t, J = 6.5 Hz, 3 H), 1.2−1.8 (m, 11 H), 2.6−2.8 (m, 1 H), 4.13 (ddd, J = 2.8, 7.6, 11.9 Hz, 2 H), 4.44 (ddd, J = 3.5, 3.8, 13.3 Hz, 2 H), 5.37 (t, J = 5.6 Hz, 1 H); ^{13}C NMR δ 14.00, 22.45, 24.64, 26.54, 28.77, 28.92, 31.47, 74.22 (2C), 108.21. Anal. ($C_{10}H_{20}O_4$) C, H.

3-Octyl-1,2,4,5-tetroxocane 4k: an oil; ^{1}H NMR δ 0.86 (t, J = 6.6 Hz, 3 H), 1.2−1.8 (m, 15 H), 2.6−2.8 (m, 1 H), 4.13 (ddd, J = 2.9, 12.0, 12.0 Hz, 2 H), 4.43 (ddd, J = 3.5, 3.5, 12.0 Hz, 2 H), 5.36 (t, J = 5.8 Hz, 1 H); ^{13}C NMR δ 14.07, 22.61, 24.71, 26.60, 28.79, 29.11, 29.26 (2 C), 31.79, 74.25 (2 C), 108.25. Anal. ($C_{12}H_{24}O_4$) C, H.

In Vitro and In Vivo Antimalarial Activity. In vitro antimalarial activity against *P. falciparum* (FCR-3 strain) and cytotoxicity against mouse mammary cell (FM3A) was determined as described previously.[3a] In vivo antimalarial activity was assessed using ICR mice infected with *P. berghei* (NK 65 strain) following the protocol described previously.[3a] Various concentrations of the test compounds, prepared in olive oil, were administered daily via two routes, either ip or po, to groups of five mice for four consecutive days beginning on the day of infection (to determine the ED value and survival time). To determine the curative effect, the test compounds were administered to the mice orally once a day for 3 consecutive days beginning on the day of 1% parasitemia in the infected mice. Parasitemia levels were monitored every day for 2 months. Treatment was considered to be curative when no parasites were detected after 60 days. On average, mice in the control group survived for 6.5 days after infection.

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