Synthesis and Notable Antimalarial Activity of Acyclic Peroxides, 1-(Alkyldioxy)-1-(methyldioxy)cyclododecanes

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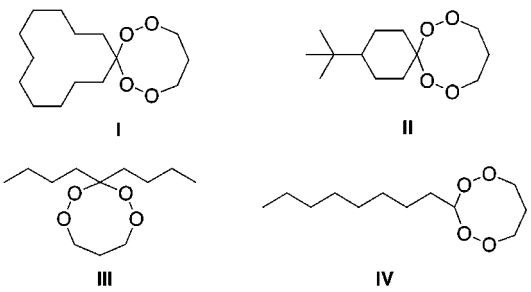
Of several bis(alkyldioxy)alkanes and the related acyclic peroxides prepared in this study, 1,1-bis(methyldioxy)cyclododecane showed the most notable antimalarial activity particularly in vivo (almost a half of that of artemisinin).

Introduction

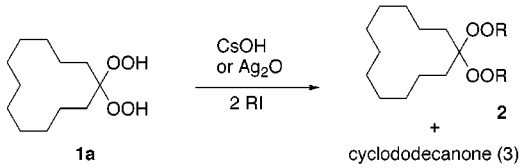
Because malaria parasites are rapidly developing multidrug resistance to the most common chemotherapeutic alkaloidal drugs, interest in the antimalarial properties of nonalkaloidal compounds such as artemisinin and the related endoperoxides is rapidly growing.[1] In connection with this, we also have found that 3,3-dialkyl-substituted 1,2,4,5-tetroxocanes **I**−**III** show moderate to remarkable antimalarial activities in vitro (EC_{50}: 0.025 μM, 0.0030 μM, and 0.16 μM, respectively), while the 3-alkyl-substituted one (**IV**) is ineffective.[2] In contrast, only small attention has been paid to the potential of acyclic peroxides.[3] We report herein that acyclic analogues of the endoperoxides **I**−**IV** with a variety of functional groups can be conveniently prepared by the dialkylation of bis(hydroperoxide)s **1**. Moreover, 1,1-bis(methyldioxy)cyclododecane (**2a**), an acyclic analogue of endoperoxide **I**, exerts a notable antimalarial activity not only in vitro but also in vivo.



Results and Discussion

Synthesis of Symmetrically Substituted Bis(alkyldioxy)alkanes. We first examined the synthesis of symmetrically substituted bis(alkyldioxy)alkanes. Treatment of a bis(hydroperoxide) **1a** with 3 equiv of MeI in the presence of Ag_2O[4] in ethyl acetate gave the expected 1,1-bis(methyldioxy)cyclododecane **2a** in 83% yield. Alternatively, the CsOH-promoted reaction[5] in DMF resulted in the formation of **2a** (56%) together with cyclododecanone **3** (12%). The bis(alkyldioxy)alkanes **2b**−**f** with longer alkyl chains were obtained in poor to excellent yield depending on the nature of the alkyl halides and of the promoter (Scheme 1). The reaction of the bis(hydroperoxide)s **1b**,**c** with MeI gave the corresponding peroxides **2g**,**h** in excellent yield (Scheme 2).

Scheme 1



R	promoter[a]	peroxide (% yield)	ketone **3** (% yield)
Me	CsOH	**2a** (57%)	12%
Me	Ag_2O	**2a** (83%)	
Et	CsOH	**2b** (46%)	30%
Et	Ag_2O	**2b** (87%)	
Pr	CsOH	**2c** (25%)	54%
Bu	CsOH	**2d** (33%)	48%
Bu	Ag_2O	**2d** (13%)[c]	
$CH_2CH{=}CH_2$[b]	Ag_2O	**2e** (24%)[d]	51%
$CH_2C(CH_3){=}CH_2$[b]	Ag_2O	**2f** (35%)[e]	45%

Synthesis of Unsymmetrically Substituted Bis(alkyldioxy)alkanes. Treatment of the bis(hydroperoxide) **1a** with 1.2 equiv of alkyl iodides in the presence of Ag_2O gave in each case the monoalkylated products **4a**−**c** in moderate yield. Subsequent methylation provided the unsymmetrically substituted peroxides **5a**−**c**. Similarly, the peroxide **5h** was obtained from **1c** (Scheme 2). For the preparation of the iodoalkyl-substituted peroxides **5d**,**e**, Ag_2O-promoted reaction of 1-(methyldioxy)cyclododecyl hydroperoxide (**4d**) with diiodoalkanes was found to be effective. α-Alkoxyalkyl-substituted peroxides **5f**,**g** were prepared by the reactions of the same starting material **4d** and vinyl ethers[6] (Scheme 2).

The hydroxyalkyl-substituted peroxide **5j** was prepared by the procedure illustrated in Scheme 3. The key step was the alkylation of bis(hydroperoxide) **1a** with 2-(6-iodohexyloxy)tetrahydropyran. Subsequent oxidation of **5j** with Jones reagent gave the corresponding

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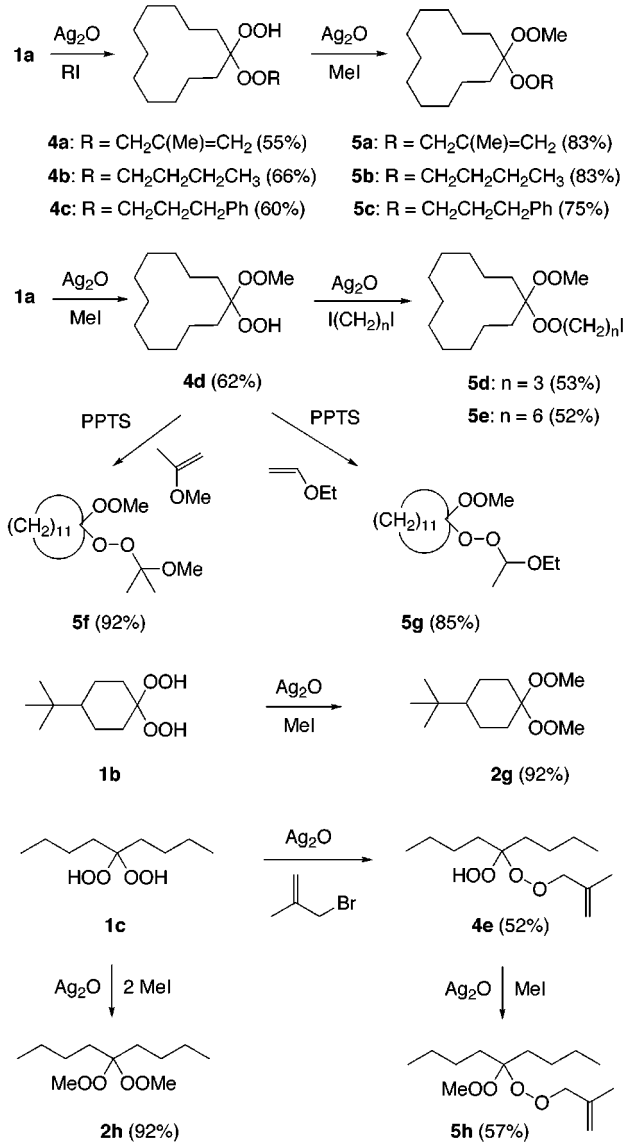
Scheme 2

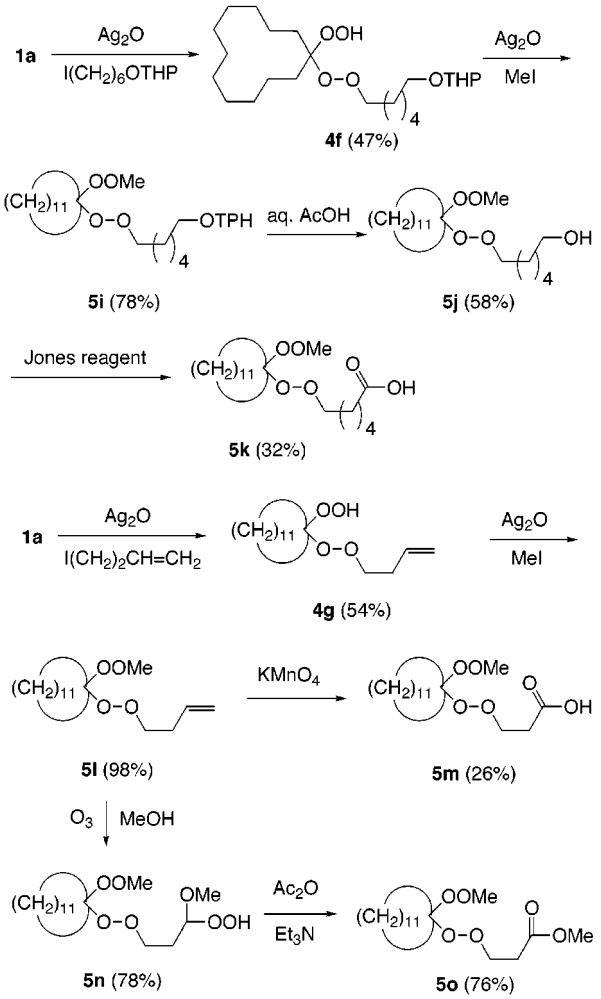


carboxylic acid **5k**. As an alternative way for the synthesis of the similar acyclic peroxide having a carboxylic acid group in the side chain, oxidation of the unsaturated peroxide **5l** with $KMnO_4$ was undertaken (Scheme 4). The carboxylic acid **5m** was certainly obtained albeit in a low yield of 26%, together with cyclododecanone (36%) and the unreacted peroxide **5l** (26%). Ozonolysis of **5l** in methanol, followed by dehydration gave the corresponding ester **5o**.

Synthesis of α-Methoxy-Substituted Dialkyl Peroxides. To obtain the acyclic peroxides with a different structure, we next conducted the ozonolysis of alkenes in methanol to give the α-methoxy-substituted hydroperoxides **9**. By the subsequent Ag_2O-promoted alkylation, α-methoxy-substituted peroxides **10a**−**f** were prepared (Scheme 4). These compounds would be considered as the acyclic analogue of 1,2,4-trioxacycloalkanes.

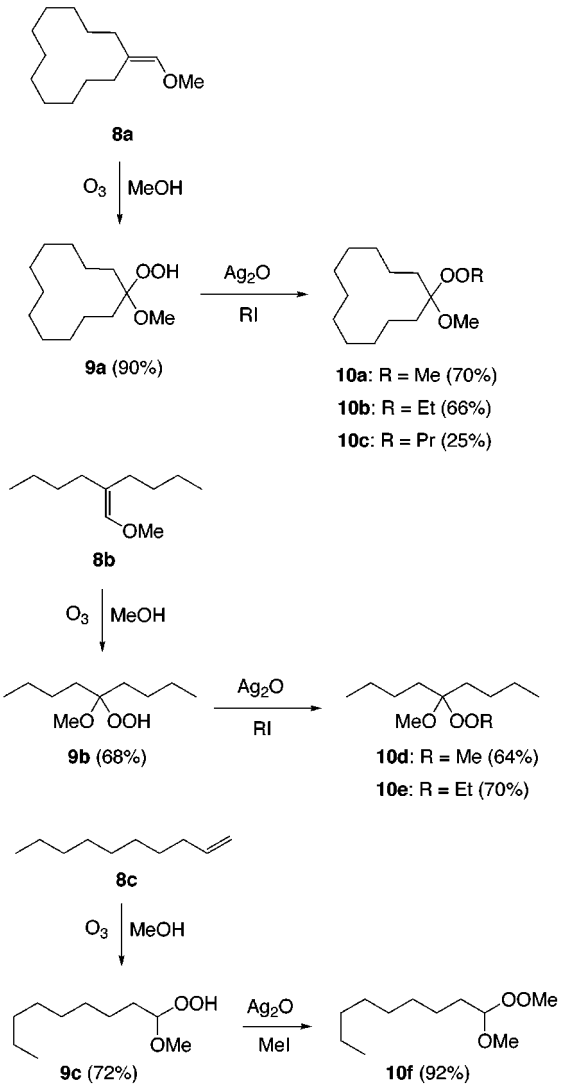
Antimalarial Activity of Acyclic Peroxides in Vitro. With a series of acyclic peroxides **2**, **5**, and **10** in hand, we tested the antimalarial activities against *P. falciparum* and cytotoxicities against FM3A cell (Table 1).[7] The results are summarized as follows. (a) For a series of symmetrically substituted peroxides **2a**−**f**, the

Scheme 3



bis(methyldioxy)-substituted one **2a** was the most promising. Regretfully, the activity of **2a** (IC_{50} = 0.086 μM) was only one tenth of that of artemisinin (IC_{50} = 0.01 μM), and the selectivity was significantly poor (17) compared to than that of artemisinin (1000). However, this is, to our knowledge, the first example to demonstrate that acyclic peroxide has certainly a substantial antimalarial activity. (b) The characteristics of 1-(butyldioxy)-1-(methyldioxy)cyclododecane (**5b**) were notable. The IC_{50} value (0.22 μM) was comparable to that of **2a**. Moreover, a better selectivity (91) was observed. In contrast, the antimalarial activity of 1,1-bis(butyldioxy)cyclododecane (**2d**) was very low. These results suggest that the minor change of the structure of peroxides would exert a meaningful influence on the nature of the medicinal action. Also, some functionalized peroxides, **5e**−**g** and **5i**−**l**,**o**, showed significant activities. (c) When the antimalarial activities of a series of bis(methyldioxy)alkanes **2a**, **2g**, and **2h** were compared, it was noted that the structure of the alkyl groups exerts a remarkable influence. A similar trend was observed for a series of α-methoxy-substituted peroxides, **10a**, **10d**, and **10f**. This implies that in the case of acyclic peroxides the presence of the cyclododecane ring would be an important factor for the appearance of a significant antimalarial activity. (d) The effect of alkyl chain observed for a series of α-methoxy-substituted peroxides **10a**−**c** was very similar to that for 1,1-bis(alkyldioxy)-

Scheme 4



cyclododecanes **2a**−**c**. Thus, the IC_{50} value of **10a** (0.080 μM) was comparable to that of **2a** (0.086 μM). In addition, the selectivity of **10a** (238) was much better than that of **2a** (17). The same trend was observed between the ethyl-substituted ones, **2b** and **10b**.

Antimalarial Activity of Acyclic Peroxides in Vivo. In vivo antimalarial activities against *P. berghei* NK 65 strain[7] were then determined for the acyclic peroxides, **2a**,**b**, **5b**,**j**, and **10a**,**b**, which had shown notable activities in vitro. Results shown in Table 2 indicate that the ED_{50} value of 1,1-bis(methyldioxy)-cyclododecane (**2a**) (ED_{50}: 13 mg/kg) on intraperitoneal administration (ip) was only twice of that of artemisinin (ED_{50}: 5.4 mg/kg). In contrast, 1-(methyldioxy)-1-methoxycyclododecane (**10a**), which had a similar activity and a better selectivity in vitro, showed only moderate activity in vivo (ED_{50}: 30 mg/kg). A similar difference of the activity in vivo was also observed between **2b** and **10b**. Thus, the ED_{50} value of bis(ethyldioxy)cyclododecane (**2b**) was moderate (41 mg/kg), while 1-(ethyldioxy)-1-methoxycyclododecane (**10b**) showed no activity against *P. berghei* NK 65 strain. The activities of unsymmetrically substituted peroxides **5b**,**j** were found to be only moderate. It is also interesting to note that the peroxide **2a** was found to be orally active (ED_{50}: 30 mg/kg) (Table 2).

Table 1. In Vitro Antimalarial Activities of Peroxides against *P. falciparum* and Cytotoxicities against FM3A Cells[a]

	EC_{50} values (μM)		
peroxide	*P. falciparum*[b]	FM3A[c]	selectivity[d]
2a	0.086	1.5	17
2b	0.20	10	50
2c	1.8	12	7
2d	2.1	8.5	4
2e	1.6	14	9
2f	1.5	38	25
2g	25	25	1
2h	4.8	>45	>9
5a	1.3	17	13
5b	0.22	20	91
5c	1.0	34	34
5d	NA[e]		
5e	0.74	86	116
5f	0.24	7.3	30
5g	0.29	12	41
5h	1.6	15	9
5i	0.90	7.6	8
5j	0.072	1.6	22
5k	0.27	14	52
5l	0.38	6.0	16
5m	5.0	0.45	
5o	0.23	1.4	6
10a	0.080	19	238
10b	0.23	26	113
10c	0.62	>37	>60
10d	NA[e]		
10e	8.6	>48	>6
10f	NA[e]		
artemisinin	0.01	10	1000

[a] In vitro antimalarial activities and cytotoxicities were determined by the previously reported protocol.[7] [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*. [e] NA: no activity at 10 μM.

Table 2. In Vivo Antimalarial Activities (ip and po) of Peroxides against *P. berghei* Infected Mice

	intraperitoneal		oral	
peroxides	ED_{50}, mg/kg[a]	ED_{90}, mg/kg[a]	ED_{50}, mg/kg[a]	ED_{90}, mg/kg[a]
artemisinin	5.4	32	13	89
2a	13	20	30	60
2b	41	64		
5b	35	80		
5j	30	60		
10a	30	68		
10b	>100			

[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.[7]

On administration of the most active acyclic peroxide **2a** (ip; 20 mg/kg; 4 days), malaria parasites could not be observed in blood stream after the 4 day suppressive test. Consistent with this, one (by administration of 20 mg/kg; 4 days) and two (50 mg/kg; 4 days) of five infected mice were cured, and they had no cytotoxicities more than 60 days.

Summary

We could demonstrate that some acyclic peroxides show substantial antimalarial activity even in vivo. This is certainly a new finding and suggests that further

investigation on the antimalarial activity for a wide range of acyclic peroxides would be promising to find a new candidate of antimalarial drugs.

Experimental Section

General Procedure. ^{1}H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard. The bis(hydroperoxide)s **1a**−**c** were prepared by the reported methods.[2b,8] The detailed procedures for the determination of antimalarial activities of peroxides in vitro and in vivo have been previously described.[7]

CsOH-Mediated Synthesis of 1,1-Bis(alkyldioxy)alkanes. The preparation of **2a** is representative. To a stirred solution of a bis(hydroperoxide), **1a** (464 mg, 2.00 mmol), and CsOH−H_2O (672 mg, 4.00 mmol) in DMF (25 mL) was added methyl iodide (568 mg, 4.00 mmol) via a syringe over 10 min at 0 °C, and the mixture was stirred at room temperature for 16 h. To the reaction mixture was added ether (150 mL), and the organic layer was washed with aqueous sodium thiosulfate, aqueous $NaHCO_3$, and saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography on silica gel. Elution with ether−hexane (1.25:98.75) gave the peroxide **2a** (296 mg, 57%). Subsequent elution with ether−hexane (2:98) gave cyclododecanone (**3**) (44 mg, 12%).

1,1-Bis(methyldioxy)cyclododecane (2a): Mp 38−39 °C (from hexane); ^{1}H NMR δ 1.3−1.5 (m, 18 H), 1.63 (t, J = 9.6 Hz, 4 H), 3.92 (s, 6 H); ^{13}C NMR δ 19.30, 21.78, 22.44, 26.04, 26.09, 26.83, 63.18, 113.33. Anal. ($C_{14}H_{28}O_4$) C, H.

Preparation of Functionalized Peroxides, 5i−k. To a solution of Ag_2O (650 mg, 2.8 mmol) and the bis(hydroperoxide) **1a** (928 mg, 4.0 mmol) in ethyl acetate (10 mL) was added a solution of 1-iodo-6-(2-tetrahydropyranyloxy)hexane[9] (1.25 g, 4.0 mmol) in ethyl acetate (5 mL) via a syringe over 5 min at 0 °C, and the reaction was continued at room temperature for 15 h. After filtration of the solid material over Celite, 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. From the first fraction (elution with ether−hexane, 5:95) was obtained cyclododecanone (102 mg, 14%). Subsequent elution with ether−hexane (12.5:87.5) gave 1-[6-(2-tetrahydropyranyloxy)hexyldioxy]cyclododecyl hydroperoxide (**4f**) in 47% yield (780 mg). To a solution of Ag_2O (232 mg, 1.00 mmol) and the hydroperoxide **4f** (416 mg, 1.00 mmol) in ethyl acetate (10 mL) was added a solution of methyl iodide (284 mg, 2.00 mmol) in ethyl acetate (5 mL) via a syringe over 5 min at 0 °C, and the reaction was continued at room temperature for 15 h. By column chromatography on silica gel (elution with ether−hexane, 6:94), the desired peroxide **5i** was obtained in 78% yield (337 mg). Then, the peroxide **5i** (215 mg, 0.5 mmol) in acetic acid (4 mL)−THF (2 mL)−H_2O (1 mL) was stirred at room temperature for 15 h. Then, the products were separated by column chromatography on silica gel. Elution with ether−hexane (10:90) gave the unreacted peroxide **5i** (77 mg, 36%). Subsequent elution with ether−hexane (27:73) gave the alcohol **5j** (100 mg, 58%).

6-[(1-Methyldioxy)cyclododecyldioxy]hexan-1-ol (5j): An oil; ^{1}H NMR δ 1.2−1.7 (m, 30 H), 1.95 (br s, 1 H), 3.63 (t, J = 6.6 Hz, 2 H), 3.90 (s, 3 H), 4.08 (t, J = 6.6 Hz, 2 H); ^{13}C NMR δ 19.21, 21.78, 22.16, 25.45, 25.86, 25.95, 26.81, 27.69, 32.49, 32.63, 62.63, 63.02, 74.83, 113.15. Anal. ($C_{19}H_{38}O_5$) C, H.

To a stirred solution of an alcohol **5j** (450 mg, 1.30 mmol) in acetone (5 mL) was added Jones reagent (prepared from CrO_3 (260 mg, 2.6 mmol), concentrated H_2SO_4 (0.23 mL), and 1.4 mL of H_2O) at 0 °C, and the mixture was stirred at room temperature for 3 h. After addition of ether (150 mL), the organic layer was washed with aqueous HCl and saturated brine and dried over anhydrous $MgSO_4$. The products were separated by column chromatography on silica gel. Elution with ether−hexane (10:90) gave cyclododecanone (48 mg, 20%). Subsequent elution with ether−hexane (25:75) gave the carboxylic acid **5k** (150 mg, 32%).

6-[(1-Methyldioxy)cyclododecyldioxy]hexanoic acid (5k): Mp 37−38 °C (from hexane−ether); ^{1}H NMR δ 1.3−1.8 (m, 28 H), 2.37 (t, J = 7.3 Hz, 2 H), 3.90 (s, 3 H), 4.08 (t, J = 6.3 Hz, 2 H), 11.06 (br s, 1 H); ^{13}C NMR δ 19.21, 21.76, 22.14, 24.33, 25.55, 25.93, 25.99, 26.78, 27.42, 33.86, 63.00, 74.57, 113.15, 180.16. Anal. ($C_{19}H_{36}O_6$) C, H.

Synthesis of 3-[(1-Methyldioxy)cyclododecyldioxy]-propionic Acid (5m). To a stirred solution of an alkene **5l** (129 mg, 0.43 mmol) and $NaHCO_3$ (18.1 mg, 0.22 mmol) in acetone (1 mL) was added $KMnO_4$ (197 mg, 1.25 mmol) dissolved in acetone (5 mL) at 0 °C. After 1 h, the mixture was concentrated under vacuum, and the residue was dissolved in ether and washed with aqueous $NaHSO_3$. After filtration of MnO_2 over Celite, the aqueous layer acidified by 1 N HCl (pH 4) was extracted with ether. The combined organic layer was washed with saturated brine and dried over anhydrous $MgSO_4$. The residue was separated by column chromatography on silica gel. Elution with ether−hexane (1:99) gave the unreacted alkene (34 mg, 26%). Subsequent elution with ether−hexane (2:98) gave cyclododecanone (28 mg, 36%). From the final fraction (elution with ether−hexane; 60:40) was obtained the carboxylic acid **5n** (36 mg, 26%).

3-[(1-Methyldioxy)cyclododecyldioxy]propionic acid (5m): Mp 69−70 °C (from ether−hexane); ^{1}H NMR δ 1.2−1.8 (m, 22 H), 2.78 (t, J = 6.3 Hz, 2 H), 3.88 (s, 3 H), 4.35 (t, J = 6.3 Hz, 2 H); ^{13}C NMR δ 19.25 (2 C), 21.87 (2 C), 22.21 (2 C), 25.99 (2 C), 26.06, 26.79 (2 C), 33.26, 63.06, 70.01, 113.48, 177.25. Anal. ($C_{16}H_{30}O_6$).

Ozonolysis of Methoxymethylenecyclododecane in Methanol. To a solution of vinyl ether **8a** (630 mg, 3 mmol) in MeOH−ethyl acetate (35 mL, 3:4) was passed a slow stream of ozone (1 equiv; flow for 9 min) at −70 °C. By evaporation of the solvent under vacuum, followed by crystallization from hexane, pure hydroperoxide **9a** was obtained (620 mg, 90%).

1-Methoxycyclododecan-1-yl hydroperoxide (9a): Mp 88−90 °C (from ether−hexane); ^{1}H NMR δ 1.4−1.8 (m, 22 H), 3.31 (s, 3 H), 7.55 (s, 1 H); ^{13}C NMR δ 19.61, 22.12, 22.55, 26.33, 27.93, 48.90, 110.17. Anal. ($C_{13}H_{26}O_3$) C, H.

Ag_2O-Promoted Alkylation of α-Methoxyalkyl Hydroperoxides. The preparation of peroxide **10a** is representative. To a solution of Ag_2O (580 mg, 2.5 mmol) and **9a** (575 mg, 2.5 mmol) in ethyl acetate (20 mL) was added a solution of methyl iodide (710 mg, 5 mmol) in ethyl acetate (10 mL) via a syringe over 5 min at 0 °C, and the reaction was continued at room temperature for 15 h. By column chromatography on silica gel (elution with ether−hexane, 1:49), peroxide **10a** (430 mg, 70%) was obtained.

1-Methoxy-1-(methyldioxy)cyclododecane (10a): An oil; ^{1}H NMR δ 1.2−1.8 (m, 22 H), 3.31 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR δ 13.32, 21.89, 26.02, 26.11, 28.11, 48.56, 62.86, 109.11. Anal. ($C_{14}H_{28}O_3$) C, H.

Supporting Information Available: Synthetic methods of α-(alkyldioxy)alkyl hydroperoxide **4b** and of unsymmetrically substituted peroxides **5a**, **5g**, and **5o** and the spectroscopic and elemental analysis data for all new compounds **2a**−**h**, **4a**−**g**, **5a**−**o**, **9a**−**c**, and **10a**−**f** are available free of charge via the Internet at http://pubs.acs.org.

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