Synthesis of Hydroxy(or Hydroperoxy)-Substituted 1,2,4-Trioxacycloalkanes by the Ozonolysis of Unsaturated Hydroperoxy Acetals

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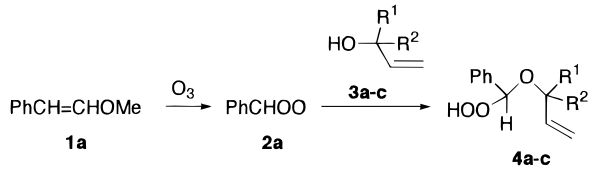
Ozonolyses of unsaturated hydroperoxy acetals **4a**−**k** gave in each case the mixtures of products containing the corresponding trioxanes **8a**−**f** and **12e,f**, trioxepanes **12g**−**i**, trioxocane **12j**, and trioxonane **12k**. By choosing the proper conditions of the ozonolysis, the desired cyclic peroxide was selectively obtained in moderate to good yield. Alternatively, acid-catalyzed cyclization of the methanol-derived ozonolysis products **13h** and **13j** provided the corresponding trioxepane **12h** and trioxocane **12j**, respectively.

The discovery of pharmacologically active six- and seven-membered-ring peroxides has given a renewed interest in the development of new synthetic methods of such structures.[1] Because of the potential ease of modification, functionalized trioxanes and trioxepanes would be very attractive.[2] In this respect, Dussault[3] and our group[4] independently discovered that electrophilic cyclization of unsaturated hydroperoxy acetals, derived from capture of carbonyl oxide with unsaturated alcohol, would be promising. Thus, a variety of halo-substituted 1,2,4-trioxanes and 1,2,4-trioxepanes have been prepared by I_2- or *N*-halosuccinimide-mediated cyclization. During our continuing search for efficient transformation of unsaturated hydroperoxy acetals to cyclic peroxides, we have found that the ozonolysis is convenient for the synthesis of not only 1,2,4-trioxanes and 1,2,4-trioxepanes but also novel 1,2,4-trioxocanes and 1,2,4-trioxononanes in which a hydroxy or hydroperoxy group is directly attached to the ring.

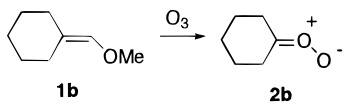
Results and Discussion

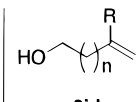
Preparation of Unsaturated Hydroperoxy Acetals. We previously reported that trapping of carbonyl oxides with primary unsaturated allylic or homoallylic alcohols proceeds well to give the corresponding unsaturated hydroperoxy acetals **4d**−**h** in good yields.[4] To obtain an information for the structural effect of allylic alcohols on the efficiency, we conducted ozonolyses of *β*-methoxystyrene (**1a**) in the presence of a series of allylic alcohols **3a**−**c** (3 equiv) in CH_2Cl_2 at −70 °C (Scheme 1). The yields of hydroperoxides decreased in the order **4a** (51%) > **4b** (43%) > **4c** (13%), suggesting that the steric bulk of the alcohols affects remarkably the efficiency. As potent precursors of medium-sized cyclic peroxides, hydroperoxides **4i**−**k** were also prepared in moderate yields (Scheme 1).

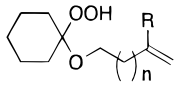
Scheme 1



	R^1	R^2	**4**, % yield
a	H	H	51
b	Me	H	43
c	Me	Me	13







	n	R	**4**, % yield
i	1	H	67
j	2	Me	55
k	3	Me	64

Synthesis of 1,2,4-Trioxanes. With unsaturated hydroperoxy acetals **4a**−**f** in hand, we then conducted the ozonolyses under several conditions. Treatment of **4a** with ozone in MeOH−ether at −78 °C gave the expected 6-hydroxy-1,2,4-trioxane **8a** almost quantitatively (Scheme 2). Moreover, it was obtained as a single isomer.

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(1) (a) Casteel, D. A. *Nat. Prod. Rep.* **1992**, 289. (b) Posner, G. H.; Cumming, J. N. Ploypradith, P.; Chang, H. O. *J. Am. Chem. Soc.* **1995**, *117*, 5885. (c) Posner, G. H.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 722.

(2) (a) Jefford, C. W.; McGoran, E. C.; Boukouvalas, J.; Richardson, G.; Robinson, B.; Peters, W. *Helv. Chim. Acta* **1988**, *71*, 1805. (b) Bloodworth, A. J.; Johnson, K. A.*Tetrahedron Lett.* **1994**, *35*, 8057. (c) Bloodworth, A. J.; Hagen, T.; Johnson, K. A.; LeNoir, I.; Mousay, C. *Tetrahedron Lett.* **1997**, *38*, 635. For the synthesis of 1,2,4-trioxanes, see: (a) Bunnelle, W. H.; Isbell, T. A.; Barnes, C. L.; Qualls, S. *J. Am. Chem. Soc.* **1991**, *113*, 8168. (b) Bloodworh, A. J.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.* **1992**, 428. (c) Fujisaka, T.; Miura, M.; Nojima, M.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1031. (d) Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211 and the references therein. For the synthesis of trioxepane, see: (a) Adam, W.; Duran, N. *J. Chem. Soc., Chem. Commun.* **1972**, 798.

(3) (a) Dussault, P. H.; Davies, D. R. *Tetrahedron Lett.* **1996**, *37*, 463. (b) Dussault, P. H.; Lee, H.-J.; Niu, Q. J. *J. Org. Chem.* **1995**, *60*, 784.

(4) Ushigoe, Y.; Kano, Y.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 5.

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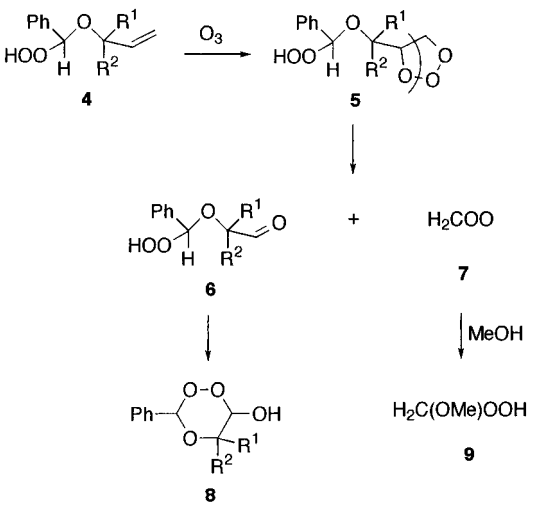
Scheme 2



	R^1	R^2	**8**, % yield
a	H	H	80[a] (87)[b]
b	Me	H	64[c] (92)[d]
c	Me	Me	94[a] (94)[b]

[a] Isolated yield after column chormatography on silica gel (elution with methylene chloride); the *trans/cis* ratio = 1:3. [b] The yield determined by the ^{1}H NMR spectrum of the crude product; only the *trans* isomer was obtained. [c] Isolated yield. [d] The yield from the crude reaction mixture.

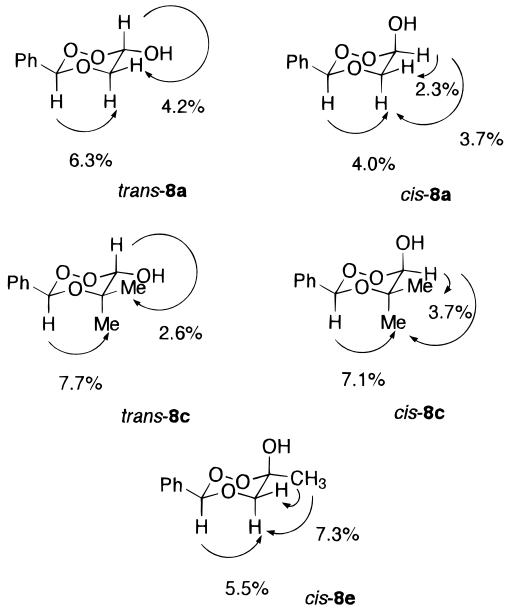
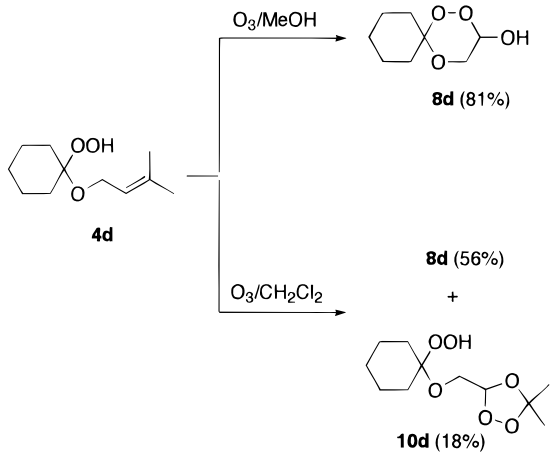


Figure 1. NOE of 6-hydroxy-1,2,4-trioxanes **8a**,**c**,**e**.

To confirm the structure, the NOE was measured (Figure 1). The data clearly demonstrated that the isolated trioxane was *trans*-**8a** with the hydroxy group occupying an equatorial position. The ^{1}H coupling constants also supported the assigned stereochemistry of **8a**. This is in marked contrast to the fact that, in the case of *trans*-3,6-dimethoxy-1,2,4,5-tetroxane,[5] both of the methoxy groups have been found to occupy the axial positions; this novel stereochemistry has been rationalized in terms

(5) Chiang, C.-Y.; Butler, W.; Kuczkowski, R. L. *J. Chem. Soc., Chem. Commun.* **1988**, 465.

Scheme 3



of the *exo*-anomeric effect. The same trend holds for 3-methoxy-6-hydroxy-1,2-dioxane.[6a] Trioxane **8a** was, however, labile on silica gel, and during column chromatography equilibration between two stereoisomers occurred very easily. Thus, although no indication of decomposition of **8a** was observed, elution of *trans*-**8a** with CH_2Cl_2 gave a 3:1 mixture of *cis*- and *trans*-**8a**. In marked contrast, elution of the 3:1 mixture of *cis*- and *trans*-**8a** with ether resulted in the isolation of a 1:2 mixture of *cis*- and *trans*-**8a**. This may imply that the relative stability is very similar between *trans*- and *cis*-**8a** and, moreover, the ratio in equilibrium is solvent dependent. Exactly the same trends were observed for the ozonolysis of **4c** and the behavior of the derived product **8c**. The ^{1}H NMR spectrum of trioxane **8b** showed that it exists as a mixture of three isomer. In connection with facile production of **8a**−**c** from **4a**−**c**, DeNinno[7] has found that ozonolyses of cyclic allylic alcohols give labile bicyclic peroxides containing a 6-hydroxy-substituted 1,2,4-trioxane structure.

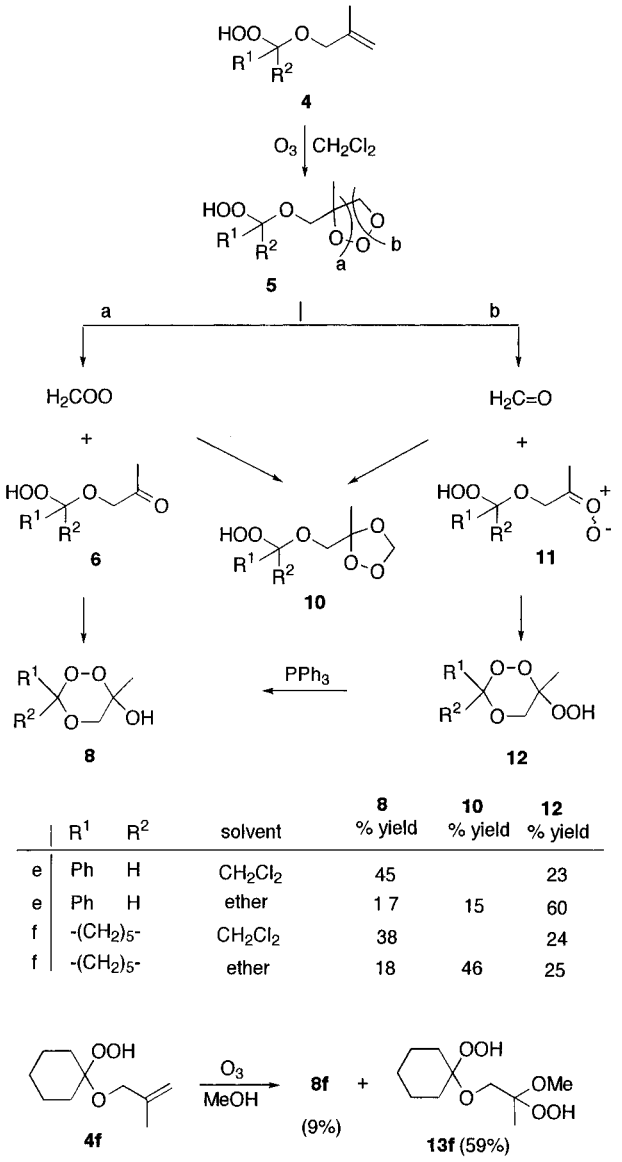
A plausible mechanism for the formation of trioxane **8a** is illustrated in Scheme 2. Reflecting the directive effect of alkoxymethyl group,[8] cleavage of primary ozonide **5a** is highly selective, yielding exclusively formaldehyde oxide **7** and ω-oxo hydroperoxide **6a**. In methanol **7** is transformed into water-soluble hydroperoxide **9**. Thus, after workup with water, only trioxane **8a** is left in the organic layer. Efficient production of **8a** implies that intramolecular hemiperacetalization of ω-oxo hydroperoxide **6a** leading to trioxane **8a** is a rapid process.[6]

Reaction of **4d** with ozone in MeOH−ether gave trioxane **8d** in the isolated yield of 81%. When the same reaction was repeated in CH_2Cl_2, the corresponding ozonide **10d** was obtained in 18% yield, together with **8d** (56%) (Scheme 3), suggesting that the intramolecular cyclization of keto hydroperoxide **6d** is significantly faster than the intermolecular cycloaddition with acetone *O*-oxide.

Treatment of hydroperoxy acetal **4f** with ozone in CH_2Cl_2 gave a mixture of 6-hydroxy-1,2,4-trioxane **8f** (38%) and 6-hydroperoxy-1,2,4-trioxane **12f** (24%) (Scheme 4). In the reaction in ether, however, the corresponding

(6) (a) Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* **1989**, *30*, 461. (b) Voss. T.; Prinzbach, H. *Tetrahedron Lett.* **1994**, *35*, 1535.
(7) DeNinno, M. P. *J. Am. Chem. Soc.* **1995**, *117*, 9927.
(8) (a) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729. (b) Hayes, H.; Wallace, T. W. *Tetrahedron Lett.* **1990**, *31*, 3355. (c) Arjona, O.; Martin-Domenech, A.; Plumet, J. *J. Org. Chem.* **1993**, *58*, 7929. (d) Kawamura, S.; Yamakoshi, H.; Nojima, M. *J. Org. Chem.* **1996**, *61*, 5953.

Scheme 4



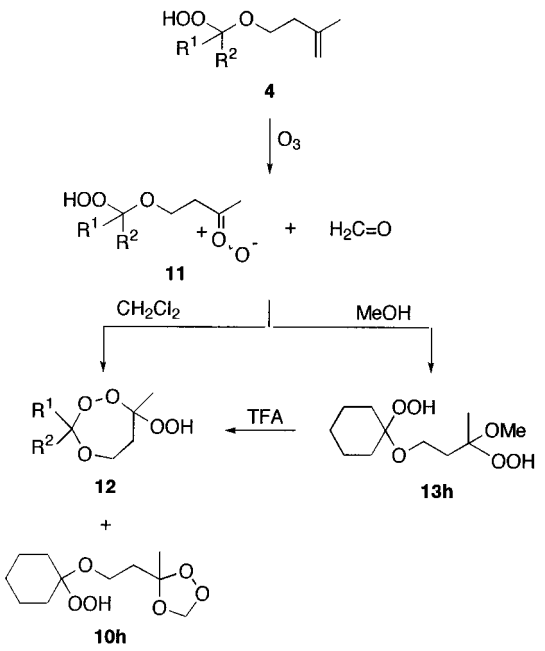
	R^1	R^2	solvent	8 % yield	10 % yield	12 % yield
e	Ph	H	CH_2Cl_2	45		23
e	Ph	H	ether	17	15	60
f	-$(CH_2)_5$-		CH_2Cl_2	38		24
f	-$(CH_2)_5$-		ether	18	46	25

ozonide **10f** was the major product (46%). To obtain an information for the identity of the ozonolysis intermediate, reaction of **4f** was conducted in MeOH−ether. From the reaction mixture, α-alkoxyalkyl hydroperoxide **13f** was isolated in 59% yield, together with 9% of **8f**. This clearly suggests that the direction of cleavage of primary ozonide (PO) **5f** is selective; pathway b (Scheme 4) providing carbonyl oxide intermediate **11f** predominates. Probably, the directive effect of the electron-donating methyl group is much stronger than the opposite directive effect of the electron-withdrawing alkoxymethyl substituent.[9] Then, formation of a significant amount of **8f** in CH_2Cl_2 (38%) implies that in this solvent loss of an oxygen atom from **11f** may occur very easily (Scheme 4). From the ozonolysis of **4e** in CH_2Cl_2, **8e** and **12e** were isolated in moderate yields (Scheme 4). The NOE of hydroxy-substituted 1,2,4-trioxane **8e** suggested that the trioxane ring adopts a chair conformation with the hydoxy substituent occupying the axial position (Figure 1).

Synthesis of 1,2,4-Trioxepanes. To see if seven-membered-ring peroxide could be produced by intramolecular cyclization of carbonyl oxide intermediate **11h** or not, we then conducted ozonolysis of hydroperoxide **4h** in CH_2Cl_2. The product was a mixture of the expected 7-hydroperoxy-substituted 1,2,4-trioxepane **12h** (28%) and ozonide **10h** (6%). When the same reaction was repeated in ether, a significant increase in the yield of peroxidic products was certainly observed. However, the major product was ozonide **10h** (46%), which could not be separated from the contaminated **12h** by column chromatography on silica gel. Ozonolysis of **4h** in MeOH−ether did not give trioxepane **12h** but instead afforded α-alkoxyalkyl hydroperoxide **13h** in high yield (Scheme 5). This implies that, because of the substituent electronic effect,[9] only the carbonyl oxide intermediate **11h** is produced from **4h**. Moreover, in aprotic solvent intermolecular cycloaddition with formaldehyde leading to ozonide **10h** competes well with intramolecular cyclization leading to trioxepane **12h**. As an alternative route for the synthesis of **12h**, we conducted acidolysis of the easily obtainable **13h**. Certainly, treatment with 1 equiv of trifluoroacetic acid (TFA) in CH_2Cl_2 gave **12h** albeit in a low yield of 24% (Scheme 5).

From the view of selective synthesis of trioxepane **12h**, it was, therefore, important to suppress the formation of **10h**. As an approach to overcoming this problem, we considered that ozonolysis in trifluoroethanol would be promising, since this protic solvent with a lower nucleophilicity may not capture carbonyl oxide and, nevertheless, it may solvate strongly formaldehyde.[10] Consistent with this expectation, ozonolysis of hydroperoxide **4h** in trifluoroethanol−ether resulted in exclusive isolation of trioxepane **12h** in 65% yield. From ozonolysis of **4i** under

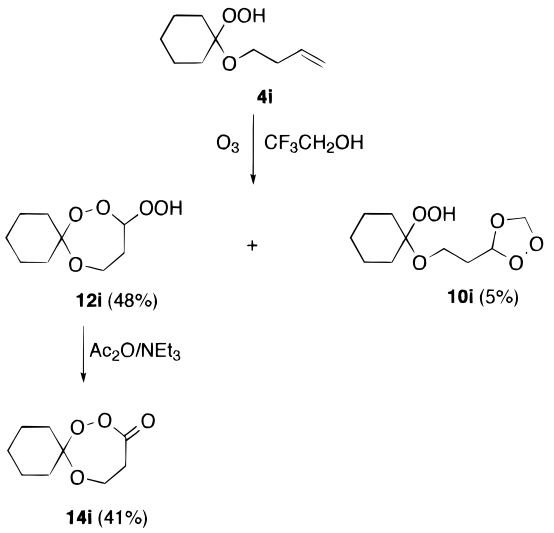
Scheme 5



	R^1	R^2	solvent	products (% yield)
g	Ph	H	CF_3CH_2OH	**12g** (28)
h	-$(CH_2)_5$-		CH_2Cl_2	**10h** (6), **12h** (28)
h	-$(CH_2)_5$-		ether	**10h** (46), **12h** (17)
h	-$(CH_2)_5$-		MeOH	**13h** (75)
h	-$(CH_2)_5$-		CF_3CH_2OH	**12h** (62)
h	-$(CH_2)_5$-		CH_3CO_2H	**12h** (62)

(9) (a) Fliszar, S.; Belzecki, C.; Chylinska, J. B. *Can. J. Chem.* **1967**, *45*, 221. (b) Griesbaum, K.; Kiesel, G. *Chem. Ber.* **1989**, *122*, 145. (c) Bunnelle, W. H.; Lee, S.-G. *J. Am. Chem. Soc.* **1992**, *114*, 7577.

Scheme 6



the same conditions, trioxepane **12i** was obtained as a sole isolable product (28%) (Scheme 6).

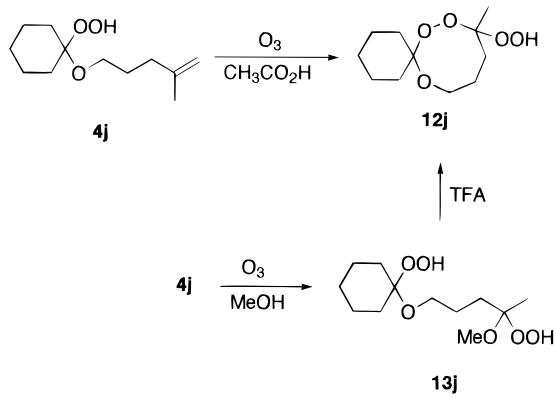
Treatment of unsaturated hydroperoxy acetal **4i** with ozone in CF_3CH_2OH−ether resulted in the production of a 9:1 mixture of trioxepane **12i** and ozonide **10i**, which could not be separated by column chromatography on silica gel. However, dehydration of **12i** occurred very easily. Thus, treatment of the mixture with acetic anhydride−triethylamine,[11] followed by column chromatography, gave pure peroxy lactone **14i** in 41% yield.

Synthesis of 1,2,4-Trioxocane and 1,2,4-Trioxonane. Particularly interesting was to see if the entropically-disfavored[12] eight-membered cyclic peroxide, trioxocane derivative **12j**, could be produced by intramolecular cyclization of the ozonolysis intermediate from hydroperoxide **4j**. Treatment of **4j** with ozone in CF_3CH_2OH−ether resulted in the formation of a complex mixture of unidentified products. When the ozonolysis of **4j** was conducted in acetic acid−methylene chloride, however, the expected trioxocane derivative **12j** was produced in 33% yield, suggesting that the more acidic protic solvent, acetic acid, facilitates the intramolecular cyclization of the corresponding carbonyl oxide intermediate. Treatment of α-alkoxyalkyl hydroperoxide **13j**, obtained from the ozonolysis of **4j** in MeOH, with trifluoroacetic acid also provided the desired trioxocane **4j** in 38% yield (Scheme 7).

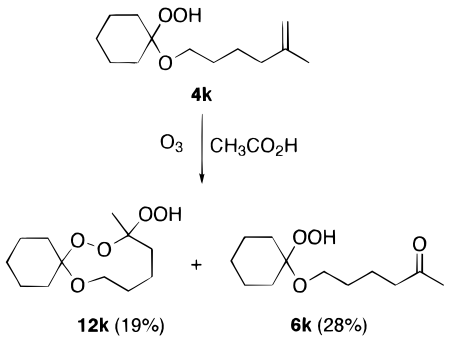
In light of these results, we next attempted the synthesis of the 1,2,4-trioxonane derivative. Although the yield was very low (19%), ozonolysis of hydroperoxide **4k** in acetic acid−methylene chloride gave certainly the trioxonane derivative **12k**, together with *ω*-oxo hydroperoxide **6k** (28%) (Scheme 8).

Conclusion. As a new and convenient synthetic method of hydroxy(or hydroperoxy)-substituted 1,2,4-trioxacycloalkanes, we have found that ozonolysis of unsaturated hydroperoxy acetals is quite promising. Proper choice of ozonolysis conditions is essential for the selective production of desired cyclic peroxides. Particularly interesting is the fact that by the ozonolysis of hydroperoxide **4j** in acetic acid or the acidolysis of solvent-derived ozonolysis product **13j**, novel eight-membered cyclic peroxide **12j** is produced. Also, 1,2,4-trioxonane derivative **12k** is obtained from the ozonolysis of **4k** in acetic acid. These results clearly demonstrate the wide scope of this methodology for the synthesis of 6−9-membered cyclic peroxides.

Scheme 7



Scheme 8



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 method of ozonolysis was previously described.[13] *β*-Methoxystyrene (**1a**) and (methoxymethylene)cyclohexane (**1b**) were prepared by the reported method.[14]

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. No particular difficulties were experienced in handling any of the new peroxides synthesized in this work using the reaction scales and procedures described below together with the safeguard mentioned above.

Ozonolysis of Vinyl Ethers 1a,b in the Presence of the Unsaturated Alcohols 3a−c,i,j. Ozonolysis of *β*-methoxystyrene (**1a**) in the presence of allyl alcohol (**3a**) is representative. To a CH_2Cl_2 solution (15 mL) of vinyl ether **1a** (330 mg, 2.94 mmol) and allyl alcohol (**3a**) (330 mg, 3 equiv) was passed a slow stream of ozone (1 equiv; flow for 8.8 min[13]) at −70 °C. After addition of 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 vacuum, the residue was separated by

(10) Ozonolysis of *β*-methoxystyrene in trifluoroethanol−ether gives a complex mixture of products including 3,6-diphenyl-1,2,4,5-tetraoxane and benzaldehyde; no evidence is obtained for the formation of the products derived from capture of benzaldehyde oxide by trifluoroethanol. Ushigoe, Y.; Nojima, M. Unpublished result.

(11) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(12) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, FL, 1994.

(13) McCullough, K. J.; Nakamura, N.; Fujisaka, T.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1991**, *113*, 1786.

(14) Griesbaum, K.; Kim, W.-S.; Nakamura, N.; Mori, M.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1990**, *55*, 6153.

column chromatography on silica gel. Elution with ether−hexane (1:9) gave hydroperoxide **4a** (220 mg, 51%).

α-Propenoxybenzyl hydroperoxide (4a): oil; ^{1}H NMR δ 4.29 (dd, J = 5.6 and 1.3 Hz, 1 H), 4.37 (dd, J = 5.6 and 1.3 Hz, 1 H), 5.23 (dd, J = 11.5 and 1.3 Hz, 1 H), 5.36 (dd, J = 15.7 and 1.7 Hz, 1 H), 5.87 (s, 1 H), 5.9−6.1 (m, 1 H), 7.3−7.5 (m, 5 H), 8.56 (s, 1 H); ^{13}C NMR δ 69.7, 105.9, 117.6, 126.9, 127.9, 128.3, 128.9, 129.2, 133.9, 135.5. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.64; H, 6.85.

α-(1-Methylpropenoxy)benzyl hydroperoxide (4b): oil (a 2:1 mixture of two isomers); ^{1}H NMR δ 1.32 (d, J = 6.6 Hz, 1 H), 1.42 (d, J = 6.6 Hz, 2 H), 4.24 (quintet, J = 6.6 Hz, 0.34 H), 4.56 (quintet, J = 6.6 Hz, 0.66 H), 5.1−5.3 (m, 2 H), 5.7−5.8 (m, 0.66 H), 5.90 (s, 1 H), 5.9−6.1 (m, 0.34 H), 7.3−7.6 (m, 5 H), 8.6−8.7 (br s, 0.66 H), 8.0−8.1 (br s, 0.34 H); ^{13}C NMR δ 21.0, 21.4, 75.5, 76.0, 103.9, 105.1, 115.9, 116.9, 126.9, 127.1, 128.1, 128.3, 128.9, 129.2, 135.7, 136.2, 139.1, 139.8. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.45; H, 7.40.

α-(1,1-Dimethylpropenoxy)benzyl hydroperoxide (4c): oil; ^{1}H NMR δ 1.38 (s, 3H), 1.49 (s, 3H), 5.15 (dd, J = 10.5 and 1.0 Hz, 1 H), 5.22 (dd, J = 17.5 and 1.0 Hz, 1 H), 5.94 (s, 1 H), 5.97 (dd, J = 17.5 and 10.5 Hz, 1 H), 7.2−7.6 (m, 5 H), 8.14 (s, 1 H); ^{13}C NMR δ 26.42 (Me), 27.1, 77.6, 101.5, 114.7, 127.0, 128.2, 128.8, 137.5, 143.1. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.11; H, 7.43.

1-(3-Butenoxy)cyclohexyl hydroperoxide (4i): oil; ^{1}H NMR δ 1.4−1.8 (m, 10 H), 2.36 (q, J = 6.6 Hz, 2 H), 3.58 (t, J = 6.6 Hz, 2 H), 5.14 (dq, J = 19.8 and 1.0 Hz, 1 H), 5.19 (dq, J = 11.7 and 1.0 Hz, 1 H), 5.8−6.0 (m, 1 H), 7.85 (br s, 1 H); ^{13}C NMR δ 22.6, 25.4, 31.4, 34.2, 59.8, 105.5, 117.4, 136.2. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.59; H, 9.52.

1-(4-Methyl-4-pentenoxy)cyclohexyl hydroperoxide (4j): oil; ^{1}H NMR δ 1.3−1.7 (m, 12 H), 1.72 (s, 3 H), 2.10 (t, J = 7.6 Hz, 2 H), 3.48 (t, J = 6.6 Hz, 2 H), 4.71 (br s, 2 H), 7.79 (s, 1 H); ^{13}C NMR δ 22.3, 22.7, 25.4, 27.6, 30.9, 31.5, 34.4, 59.7, 105.3, 110.1, 145.8. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.92; H, 10.25.

1-(5-Methyl-5-hexenoxy)cyclohexyl hydroperoxide (4k): oil; ^{1}H NMR δ 1.3−1.7 (m, 14 H), 1.71 (s, 3 H), 2.10 (t, J = 7.6 Hz, 2 H), 3.51 (t, J = 6.3 Hz, 2 H), 4.68 (s, 1 H), 4.71 (s, 1 H), 7.36 (s, 1 H); ^{13}C NMR δ 22.3, 22.7, 24.2, 25.4, 29.5, 31.5, 37.4, 60.3, 105.4, 110.0, 145.7. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.58; H, 10.49.

Ozonolysis of Unsaturated Hydroperoxy Acetals 4a−d,f,h,j in MeOH−Ether. The reaction of hydroperoxide **4f** is representative. A solution of unsaturated hydroperoxy acetal **4f** (290 mg, 1.57 mmol) in methanol (15 mL) and ether (15 mL) was cooled to −78 °C, and ozone (1.0 equiv) was bubbled through it at −78 °C. Aqueous KH_2PO_4 was added, and the mixture was extracted with ether (70 mL), washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (25:75) gave **13f** (220 mg, 59%).

2-((1-Hydroperoxycyclohexyl)oxy)-1-methoxy-1-methylethyl hydroperoxide (13f): oil; ^{1}H NMR δ 1.40 (s, 3 H), 1.4−1.8 (m, 10 H), 3.42 (s, 3 H), 3.61 (d, J = 10.4 Hz, 1 H), 3.80 (d, J =10.4 Hz, 1 H), 8.64 (s, 1 H), 9.36 (s, 1 H); ^{13}C NMR δ 16.8, 22.7, 25.4, 31.2, 32.0, 49.3, 62.4, 105.9, 106.1. Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.84; H, 8.86. Found: C, 50.62; H, 8.86.

3-((1-Hydroperoxycyclohexyl)oxy)-1-methoxy-1-methylpropyl hydroperoxide (13h): oil; ^{1}H NMR δ 1.42 (s, 3 H), 1.4−2.1 (m, 11 H), 2.3−2.4 (m, 1 H), 3.38 (s, 3 H), 3.6−3.9 (m, 2 H), 9.19 (s, 1 H), 9.77 (s, 1 H); ^{13}C NMR δ 18.4, 22.6, 24.3, 25.4, 31.3, 31.5, 31.7, 48.9, 59.6, 105.3, 107.2. Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.79; H, 8.86. Found: C, 53.52; H, 9.1

4-((1-Hydroperoxycyclohexyl)oxy)-1-methoxy-1-methylbutyl hydroperoxide (13j): oil; ^{1}H NMR δ 1.32 (s, 3 H), 1.3−2.0 (m, 14 H), 3.35 (s, 3 H), 3.5−3.6 (m, 2 H), 8.77 (s, 1 H), 9.06 (s, 1 H); ^{13}C NMR δ 18.4, 22.6, 24.3, 25.4, 31.3, 31.5, 31.7, 48.9, 59.6, 105.3, 107.2. Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53; H,9.15. Found: C, 54.95; H, 9.16.

6-Hydroxy-3-phenyl-1,2,4-trioxane (*trans*-8a): oil (crude product); ^{1}H NMR δ 3.64 (dd, J = 11.2 and 8.6 Hz, 1 H), 4.15 (dd, J = 11.2 and 2.3 Hz, 1 H), 4.97 (s, 1 H; H−D exchange in D_2O), 5.48 (dd, J = 8.6 and 2.3 Hz, 1 H), 5.99 (s, 1 H), 7.3−7.5 (m, 5 H); ^{13}C NMR δ 68.4, 93.7, 103.1, 127.0, 128.4, 130.0, 132.9.

6-Hydroxy-5-methyl-3-phenyl-1,2,4-trioxane (8b): oil (a mixture of three isomers); ^{1}H NMR δ 1.32 (d, J = 6.9 Hz) + 1.34 (d, J = 6.3 Hz) + 1.46 (d, J = 6.9 Hz) (3 H), 3.4−4.2 (m, 1 H), 4.6−5.3 (m, 1 H), 6.01 (s) + 6.28 (s) + 6.41 (s) (1 H), 7.3−7.5 (m, 5 H); ^{13}C NMR δ 12.5, 15.0, 15.6, 96.3, 97.2, 97.8, 98.7, 98.9, 103.6, 126.9, 128.1, 128.3, 129.3, 129.9, 133.2, 134.1, 134.4. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.11; H, 6.35.

5,5-Dimethyl-6-hydroxy-3-phenyl-1,2,4-trioxane (*trans*-8c): oil (crude product); ^{1}H NMR δ 1.38 (s, 3 H), 1.42 (s, 3 H), 3.41 (s, 1 H), 5.30 (s, 1 H), 6.29 (s, 1 H), 7.3-7.5 (m, 5 H); ^{13}C NMR δ 15.4, 24.7, 75.0, 98.7, 100.1, 127.2, 128.4, 30.0, 133.6.

Treatment of Trioxanes *trans*-8a,c with Silica Gel in CH_2Cl_2. Reaction of *trans*-**8c** is representative. A mixture of *trans*-**8c** (40 mg, 0.20 mmol) and silica gel (5 g) in CH_2Cl_2 (10 mL) was stirred at rt for 10 h. Column chromatography on silica gel (elution with CH_2Cl_2) gave a 3:1 mixture of *cis*- and *trans*-**8a** (39 mg, 94%). The structure of the major isomer was confirmed as *cis*-**8a** by the NOE measurement.

6-Hydroxy-3-phenyl-1,2,4-trioxane (*cis*-8a): oil (in admixture with 25% of *trans*-**8a**); ^{1}H NMR δ 4.09 (dd, J = 11.2 and 10.7 Hz, 1 H), 4.19 (dd, J = 11.2 and 2.0 Hz, 1 H), 4.97 (s, 1 H), 5.20 (dd, J = 10.2 and 2.0 Hz, 1 H), 6.22 (s, 1 H), 7.3−7.5 (m, 5 H). ^{13}C NMR δ 68.0, 93.8, 104.1, 126.7, 128.4, 130.2, 133.6. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.28; H, 5.81.

5,5-Dimethyl-6-hydroxy-3-phenyl-1,2,4-trioxane (*cis*-8c): oil (in admixture with 50% of *trans*-**8c**); ^{1}H NMR δ 1.56 (s, 3 H), 1.57 (s, 3 H), 3.80 (d, J = 11.3 Hz, 1 H), 4.79 (d, J = 11.3 Hz, 1 H), 6.43 (s, 1 H), 7.3−7.6 (m, 5 H). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.59; H, 6.77.

Ozonolysis of Unsaturated Hydroperoxy Acetal 4d in CH_2Cl_2. A solution of unsaturated hydroperoxy acetal **4d** (310 mg, 1.57 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C, and ozone (1.5 equiv) was bubbled through it at −78 °C. Aqueous KH_2PO_4 was added, and the mixture was extracted with diethyl ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (10:90) gave ozonide **10d** (70 mg, 18%). Subsequent elution with diethyl ether−hexane (20:80) gave trioxane **8d** (150 mg, 56%).

3-Hydroxy-1,2,5-trioxaspiro[5.5]undecane (8d): oil: ^{1}H NMR δ 1.3−1.7 (m, 10 H), 3.63 (dd, J = 3.0 and 11.9 Hz, 1 H), 3.82 (d, J = 9.6 Hz, 1 H; H-D exchange in D_2O), 4.08 (dd, J = 3.0 and 11.9 Hz, 1 H), 5.15 (dt, J = 9.6 and 3.0 Hz, 1 H); ^{13}C NMR δ 22.1, 22.5, 25.3, 61.3, 94.4, 103.5. Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.04; H, 8.41.

α-[(5,5-Dimethyl-1,2,4-trioxolan-3-yl)methoxy]cyclohexyl hydroperoxide (10d): oil; ^{1}H NMR δ 1.3−1.9 (m, 10 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 3.61 (dd, J = 4.3 and 11.4 Hz, 1 H), 3.70 (dd, J = 4.3 and 11.4 Hz, 1 H), 5.42 (t, J = 4.3 Hz, 1 H), 8.99 (s, 1 H); ^{13}C NMR δ 22.6, 23.8, 23.9, 25.3, 31.52, 58.8, 102.2, 106.0, 109.6. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.34; H, 8.29.

Ozonolysis of Unsaturated Hydroperoxy Acetals 4e,f in CH_2Cl_2. Reaction of hydroperoxide **4e** is representative. A solution of unsaturated hydroperoxy acetal **4e** (776 mg, 4.00 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C, and ozone (1.5 equiv) was bubbled through it at -78 °C. Aqueous KH_2PO_4 was added, and the mixture was extracted with ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude products were separated by column chromatography on silica gel. Elution with ether−hexane (15:85) gave **12e** (196 mg, 23%). Subsequent elution with ether−hexane (20:80) gave **8e** (349 mg, 45%).

1-Methyl-4-phenyl-2,3,5-trioxanyl hydroperoxide (12e): oil; ^{1}H NMR δ 1.61 (s, 3 H), 3.88 (d, J = 11.5 Hz, 1 H), 3.98 (d, J = 11.5 Hz, 1 H), 6.12 (s, 1 H), 7.3−7.6 (m, 5 H), 8.40 (s, 1

H); ^{13}C NMR δ 18.3, 65.0, 102.2, 105.9, 127.0, 128.2, 129.7, 134.1. Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 57.47; H, 6.04.

6-Hydroxy-6-methyl-3-phenyl-1,2,4-trioxane (8e): mp 95−97 °C (from ethyl acetate−hexane); ^{1}H NMR δ 1.39 (s, 3 H), 3.95 (d, J = 11.5 Hz, 1 H), 4.02 (d, J = 11.5 Hz, 1 H), 4.40 (s, 1 H), 6.12 (s, 1 H), 7.3−7.6 (m, 5 H); ^{13}C NMR δ 15.1, 65.9, 97.4, 103.7, 126.7, 129.9, 130.2, 133.3. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.01; H, 6.18.

3-Methyl-1,2,5-trioxaspiro[5.5]undecan-3-yl hydroperoxide (12f): mp 85 °C (from ethyl acetate−hexane); ^{1}H NMR δ 1.44 (s, 3 H), 1.4−2.1 (m, 10 H), 3.67 (d, J = 12.2 Hz, 1 H), 3.78 (d, J = 12.2 Hz, 1 H), 8.31 (s, 1 H); ^{13}C NMR δ 19.9, 22.3, 22.5, 25.3, 30.0, 32.7, 61.1, 103.1, 106.0. Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.95; H, 7.92.

3-Hydroxy-3-methyl-1,2,5-trioxaspiro[5.5]undecane (8f): oil; ^{1}H NMR δ 1.31 (s, 3 H), 1.4−2.2 (m, 10 H), 3.55 (d, J = 11.6 Hz, 1 H), 3.91 (d, J = 11.6 Hz, 1 H), 4.30 (s, 1 H); ^{13}C NMR δ 20.5, 22.1, 22.3, 25.4, 28.0, 34.2, 65.3, 97.3, 102.6. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.72; H, 8.53.

Ozonolysis of Unsaturated Hydroperoxy Acetals 4e,f,h in Ether. The reaction of hydroperoxide **4h** is representative. A solution of unsaturated hydroperoxy acetal **4h** (233 mg, 1.17 mmol) in ether (15 mL) was cooled to −78 °C, and ozone (1.5 equiv) was bubbled through it at −78 °C. Aqueous KH_2PO_4 was added, and the mixture was extracted with diethyl ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (15:85) gave a 3:1 mixture of **10h** and **12h** (177 mg, 63%). Two products could not be separated by repeated column chromatography on silica gel.

α-[2-(3-Methyl-1,2,4-trioxan-3-yl)ethoxy]cyclohexyl hydroperoxide (10h): oil (in admixture with 25% of **12h**); ^{1}H NMR δ 1.44 (s, 3 H), 1.4−1.8 (m, 10 H), 2.0−2.2 (m, 2 H), 3.6−3.7 (m, 2 H), 5.15 (s, 1 H), 5.21 (s, 1 H), 8.73 (s, 1 H); ^{13}C NMR δ 20.5, 22.4, 22.9, 23.6, 31.1, 31.7, 36.9, 58.1, 94.0, 105.3, 109.3.

α-[(3-Methyl-1,2,4-trioxan-3-yl)methoxy]cyclohexyl hydroperoxide (10f): oil (in admixture with 30% of **12f**); ^{1}H NMR δ 1.57 (s, 3 H), 1.2−1.7 (m, 10 H), 3.56 (s, 1 H), 3.57 (s, 1 H), 5.12 (s, 1 H), 5.31 (s, 1 H), 8.03 (s, 1 H); ^{13}C NMR δ 19.1, 22.6, 25.3, 31.4, 62.1, 94.3, 105.0, 108.8.

Ozonolysis of Unsaturated Hydroperoxy Acetals 4g−i in CF_3CH_2OH/Ether. The reaction of hydroperoxide **4i** is representative. A solution of unsaturated hydroperoxy acetal **4i** (293 mg, 1.58 mmol) in trifluoroethanol/ether (1:2 v/v; 15 mL) was cooled to 0 °C, and ozone (1.5 equiv) was bubbled through it at −0 °C. Aqueous KH_2PO_4 was added, and the mixture was extracted with diethyl ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (2:8) gave a 9:1 mixture of **12i** and **10i** (174 mg, 53%), which could not be separated by column chromatography on silica gel. Therefore, the mixture was treated with acetic anhydride and triethylamine. After the ozonolysis as above, the residue (an 8:1 mixture of **12i** and **10i** from 1.23 mmol of **4i**) was taken up in CH_2Cl_2 (4 mL) and cooled to 0 °C. Acetic anhydride (225 mg, 3 equiv) and triethylamine (112 mg, 1.5 equiv) were added, and the solution was stirred at rt for 20 h. This mixture was treated with methanol (1 mL) for 15 min and then diluted with ether (50 mL). The solution was washed with 5% H_2SO_4 and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude products were separated by column chromatography on silica gel. From the fraction eluted by ether−hexane (15:85) was obtained 1,2,4-trioxepane derivative **14i** (57 mg, 41% based on **4i**).

1-Methyl-4-phenyl-2,3,5-trioxepanyl hydroperoxide (12g): oil (a 1:1 mixture of two isomers); ^{1}H NMR δ 1.43 (s) + 1.51 (s) (3 H), 2.1−2.6 (m, 2 H), 3.9−4.2 (m, 2 H), 5.98 (s) + 6.13(s) (1 H), 7.3−7.6 (m, 5 H), 8.27 (s) + 8.41 (s) (1 H); ^{13}C NMR δ 20.3, 20.8, 39.6, 40.3, 62.7, 65.0, 105.7, 108.5, 110.7, 112.5, 126.7, 126.8, 128.2, 128.4, 129.1, 129.6, 134.6. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.56; H, 6.47.

9-Methyl-7,8,12-trioxaspiro[5.6]dodecan-9-yl hydroperoxide (12h): oil; ^{1}H NMR δ 1.59 (s, 3 H), 1.5−1.8 (m, 10 H), 1.9−2.1 (m, 2 H), 3.6−3.7 (m, 1 H), 3.8−4.0 (m, 1 H), 8.07 (s, 1 H); ^{13}C NMR δ 20.20 (Me), 22.3, 22.8, 25.3, 31.8, 32.6, 39.9, 58.1, 107.1, 110.4. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.25; H, 8.57.

7,8,12-Trioxaspiro[5,6]dodecan-9-yl hydroperoxide (12i): oil (in admixture with 10% of **10i**); ^{1}H NMR δ 1.2−1.8 (m, 10 H), 1.9−2.1 (m, 2 H), 3.7−3.8 (m, 2 H), 5.37 (t, J = 4.8 Hz, 1 H), 9.42 (s, 1 H); ^{13}C NMR δ 22.3, 22.8, 25.2, 31.2, 33.1, 34.1, 58.3, 107.0, 107.8.

9-Oxo-7,8,12-trioxaspiro[5.6]dodecane (14i): oil; ^{1}H NMR δ 1.4−2.0 (m, 10 H), 2.6−2.7 (m, 1 H), 3.4−3.5 (m, 1 H), 3.8−4.0 (m, 2 H); ^{13}C NMR δ 22.2, 22.5, 25.1, 29.4, 33.0, 35.3, 54.9, 108.5, 176.0; IR 3000, 1750, 1200, 1080 cm^{-1}. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.17; H, 7.40.

Ozonolysis of Unsaturated Hydroperoxy Acetals 4j,k in CH_3CO_2H/CH_2Cl_2. The reaction of **4j** is representative. To a solution of **4j** (166 mg, 0.78 mmol) in AcOH-CH_2Cl_2 (1:2, 30 mL) was passed a slow stream of ozone−O_2 at 0 °C. After the reaction, the mixture was poured into aqueous $NaHCO_3$ and the products were extracted with ether. Then, the ether layer was washed with saturated brine, dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography on silica gel. Elution with ether−hexane (15:85) gave **12j** (60 mg, 33%).

9-Methyl-7,8,13-trioxaspiro[5.7]tridecan-9-yl hydroperoxide (12j): mp 123 °C (from ether−hexane); ^{1}H NMR δ 1.44 (s, 3 H), 1.3−1.9 (m, 14 H), 3.63 (ddd, J = 12.9, 7.9 and 3.0 Hz, 1 H), 3.81 (ddd, J = 12.9, 5.9 and 3.0 Hz, 1 H), 7.99 (s, 1 H); ^{13}C NMR δ 18.7, 22.8, 25.2, 25.5, 30.0, 32.4, 33.3, 62.9, 104.5, 110.8. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.89; H, 8.62.

9-Methyl-7,8,14-trioxaspiro[5.8]tetradecan-9-yl hydroperoxide (12k): oil; ^{1}H NMR δ 1.37 (s, 3 H), 1.3−2.0 (m, 16 H), 3.4−3.5 (m, 1 H), 3.84 (ddd, J = 23.8, 10.9 and 3.6 Hz, 1 H), 8.44 (s, 1 H); ^{13}C NMR δ 15.7, 18.8, 22.8, 22.9, 25.4, 26.6, 28.0, 31.1, 33.2, 56.3, 105.6, 114.5. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.84; H, 9.09.

α-(5-Oxohexoxy)cyclohexyl hydroperoxide (6k): oil; ^{1}H NMR δ 1.3−1.9 (m, 14 H), 2.16 (s, 3 H), 2.51 (t, J = 6.9 Hz, 2 H), 3.51 (t, J = 6.9 Hz, 2 H), 8.15 (s, 1 H); ^{13}C NMR δ 20.4, 22.7, 25.4, 29.4, 30.0, 31.5, 43.3, 59.8, 105.3, 209.9; MASS (CI; isobutane) 231 (M^+ + 1), 215, 197, 171, 115, 99.

Acidolysis of α-Methoxyalkyl Hydroperoxides 13h,j. Acidolysis of **13h** is representative. To a solution of **13h** (210 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added TFA (97 mg, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C. This solution was stirred at rt for 2 h. Aqueous KH_2PO_4 was added, and the mixture was extracted with ether, washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (15:85) gave **12h** (40 mg, 24%).

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