Halonium Ion-Mediated Reaction of Unsaturated Hydroperoxy Acetals. Competition between the Formation of Cyclic Peroxides and the Migration of the Methoxy (or Hydroxy) Group

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Monoozonolyses of dienes **2** in methanol gave in each case the corresponding unsaturated α-methoxy hydroperoxides **3**. Capture of 2-alkyl-substituted cyclohexanone oxides by methanol was highly diastereoselective, thereby providing exclusively the hydroperoxides derived from attack by methanol from the less hindered face of the carbonyl oxide intermediates. Halonium ion-mediated reactions of the hydroperoxides **3** gave the novel methoxy- or hydroxy-migrated products, together with the expected halogen-substituted 1,2-dioxanes and/or 1,2-dioxepanes, the composition of the product mixture being a function of the halogenating agent utilized and the structure of **3**.

The discovery of antimalarial activity of artemisinin and various other 1,2,4-trioxane derivatives has stimulated recent interest in the development of new methods for synthesis of analogous cyclic peroxide systems.[1] In this respect, we[2] and Dussault[3] reported independently that halonium ion-mediated cyclization of unsaturated hydroperoxy acetals provided a convenient synthetic route to 1,2,4-trioxanes and related 1,2,4-trioxepanes. Since 1,2-dioxanes, for example, arteflene and yingzhaosu C, and 1,2-dioxepanes also exhibit significant antimalarial activity,[4−6] we describe herein the results of some recent investigations into the synthesis of new 1,2-dioxane and 1,2-dioxepane derivatives via halonium ion-mediated cyclization of the unsaturated hydroperoxy acetals **3** derived from the trapping of unsaturated carbonyl oxides by methanol.

Results and Discussion

Preparation of Unsaturated Hydroperoxy Acetals. The required unsaturated hydroperoxy acetals **3** were synthesized by monoozonolysis of the appropriate diene **2** in MeOH−CH_2Cl_2. With the exception of **2c**, the diene substrates **2** were enol ether derivatives, obtained from the corresponding unsaturated ketones as outlined in Scheme 1. Taking advantage of the known chemoselectivity of ozone toward electron-rich enol ethers, the reaction of diene **2a** with 1 equiv of ozone in MeOH−CH_2Cl_2 at −70 °C, followed by column chromatography on silica gel, gave exclusively 1-methoxy-2-(2-methyl-2-propenyl)cyclohexyl hydroperoxide **(3a)**. Ozonolyses of dienes **2b**−**f** under similar conditions afforded the corresponding α-methoxyalkyl hydroperoxides **3b**−**f** in moderate to good yield (Scheme 1). Although they were spectroscopically pure on isolation, the hydroperoxides **3a**−**c**, obtained as oils, were found to be too thermally labile to provide satisfactory elemental analysis data.

It is interesting to note that the hydroperoxides **3a**,**d**,**f** were isolated as single isomers, which implies that capture of corresponding 2-alkyl-substituted cyclohexanone *O*-oxide by methanol must show a high degree of diastereofacial selectivity. Since in the ^{1}H NMR spectra of these hydroperoxides **3a**,**d**,**f** the signal of the methine hydrogen at C-2 overlapped with methylene signals, the stereochemistry of these compounds could not be readily determined. On the other hand, NOE measurements obtained from a related compound, **3g**, isolated in 95% yield as a single isomer from the ozonolysis of 1-methoxymethylene-2-phenylcyclohexane (**2g**) in methanol, indicated that the phenyl group and the hydroperoxy

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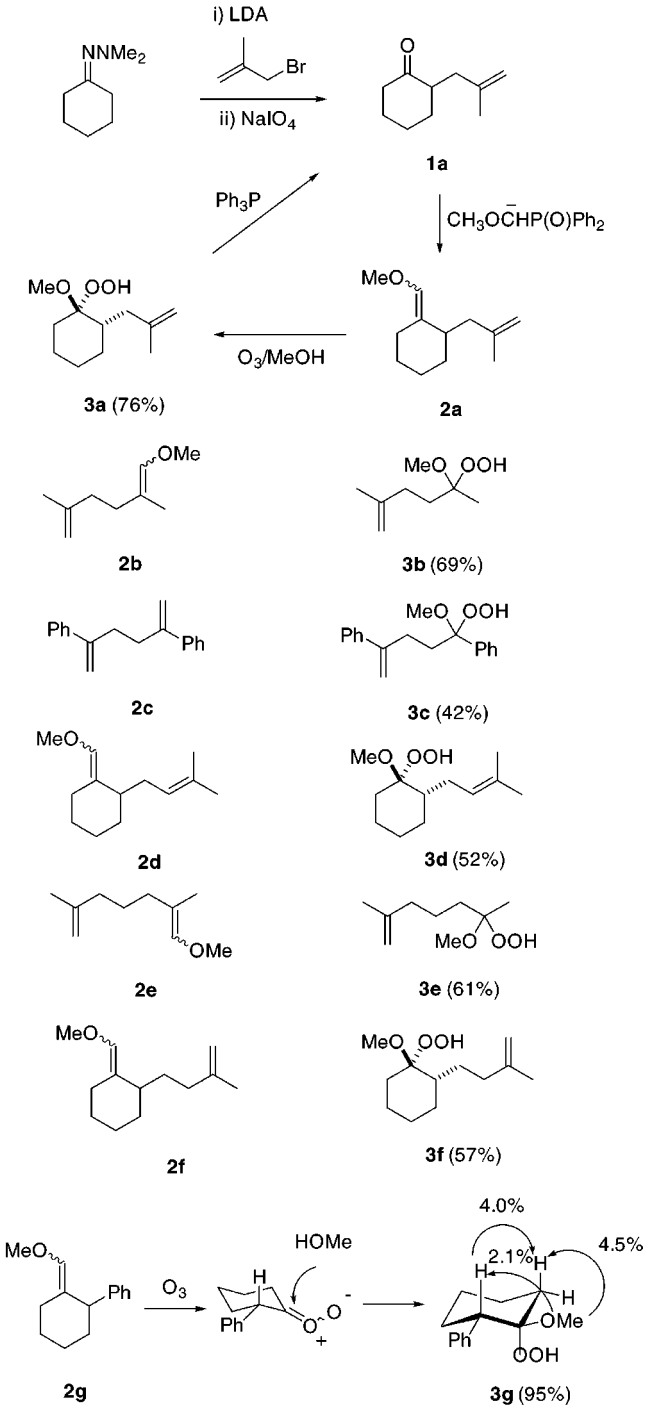
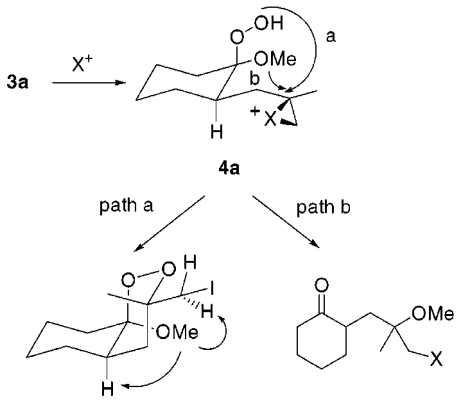
Scheme 1



were cis (Experimental Section), suggesting that methanol attacked the carbonyl oxide moiety from the less hindered face anti to the phenyl substituent. By analogy, similar configurations have been tentatively assigned for compounds **3a**,**d**,**f** (Scheme 1).[7] Dussault and Zope[8] have reported that addition of *tert*-butyl alcohol to an acyclic carbonyl oxide was highly diastereoselective although the addition of the sterically less hindered methanol and 2-propanol exhibited only moderate diastereoselectivity.

Scheme 2



NIS	**5a**; X = I (14%)	**6a**; X = I (25%)
NIS[a]	**5a** (8%)	**6a** (20%)
I_2/KOBu^t	**5a** (14%)	**6a** (40%)
BCIH	**5a** (29%)[b]	**6a** (20%)
NBS		**7a**; X = Br (48%)

[a] The reaction in the presence of 1.2 equiv. of CD_3OD.

[b] A 3:2 mixture of two stereoisomers.

Halonium Ion-Mediated Cyclization of Unsaturated Hydroperoxy Acetals. With the starting materials **3** in hand, a series of iodonium ion-mediated cyclizations were conducted using three different reagents: *N*-iodosuccinimide (NIS)−$NaHCO_3$,[2] I_2−KOBu^t,[3] and bis(*sym*-collidine)iodine(I) hexafluorophosphate (BCIH).[9a] Although NIS−$NaHCO_3$ and I_2−KOBu^t have been used previously in the preparation of cyclic peroxides,[2,3] the effectiveness of BCIH for the synthesis of 1,2-dioxanes and 1,2-dioxepanes from the corresponding unsaturated hydroperoxides was of particular interest because this reagent is known to promote cyclization reactions leading to the entropically less favored medium-sized cyclic ethers and lactones.[9a]

Treatment of the methoxy hydroperoxide **3a** with NIS afforded the corresponding 1,2-dioxane **5a** (14% yield; a single stereoisomer) and the iodo ketone **6a** (25% yield), arising from the unexpected migration of the methoxy group.[10] The NOE measurement of the isolated dioxane **5a** suggested that the methoxy and iodomethyl groups were cis (Scheme 2 and the Experimental Section). The reaction of **3a** with I_2−KOBu^t gave similar results. Under the reaction conditions described above for **3a**, the hydroperoxide **3b** also provided similar mixtures of the corresponding 1,2-dioxane **5b** and ketone **6b**. When the hydroperoxide **3c** was treated with NIS, however, only a ketone, **6c**, was isolated in 31% yield, whereas a mixture of the 1,2-dioxane **5c** and ketone **6c** was obtained from the reaction with I_2−KOBu^t (Scheme 3).

The structure of the crystalline 1,2-dioxane **5c** was determined by X-ray crystallographic analysis (Figure 1).[11] The central 1,2-dioxane ring adopts a slightly distorted chair conformation with the sterically more

(7) The related singlet oxygenation of 1-methoxymethylene-2-(2-cycanoethyl)cyclohexane also shows the same diastereoselectivity: (a) Hamzaoui, M.; Provot, O.; Camuzat-Dedenis, B.; Moskowitz, H.; Mayrargue, J.; Ciceron, L.; Gay, F. *Tetrahedron Lett*. **1998**, *39*, 4029. (b) Cumming, J. N.; Wang, D.; Park, S. B.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem*. **1998**, *41*, 952.

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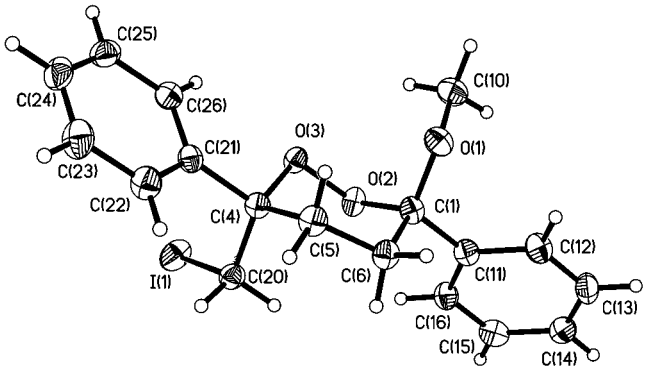
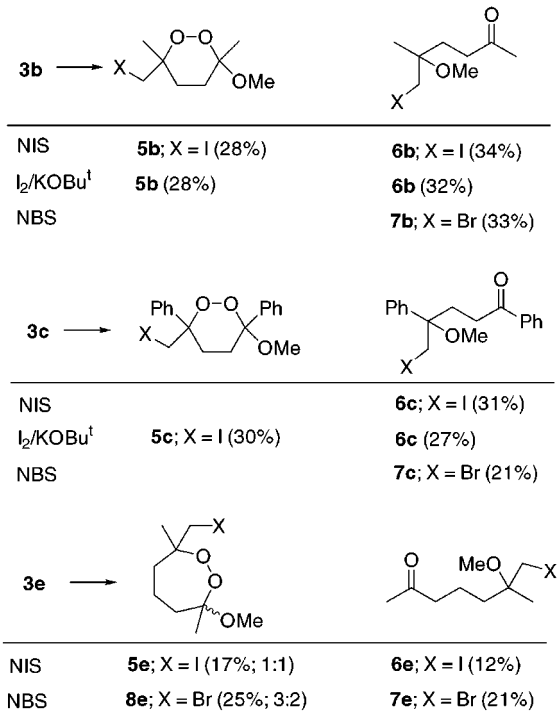


Figure 1. Molecular structure of 1,2-dioxane derivative **5c** (ORTEP[9]).

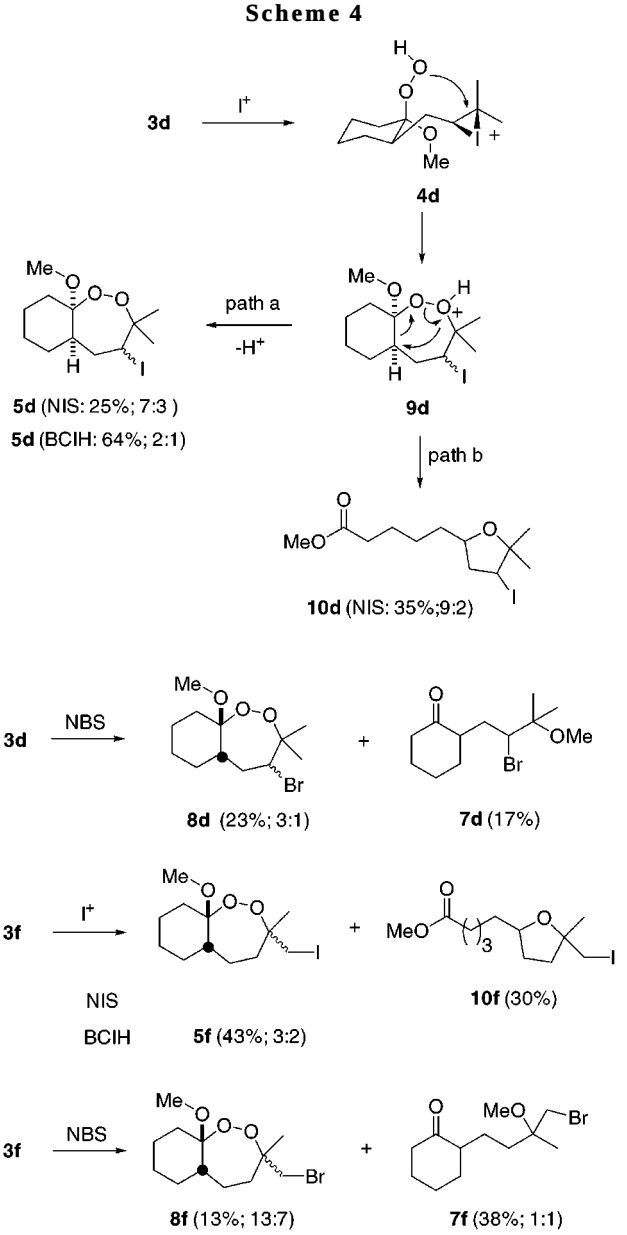
Scheme 3



demanding phenyl groups equatorial and the methoxy and iodomethyl groups axial.

Consistent with its reported ability to promote the formation of the entropically disfavored seven- and eight-membered cyclic ethers from unsaturated alcohols,[9a] BCIH has proved to be the most effective reagent for the production of the cyclic peroxides from the unsaturated hydroperoxy acetals **3** (Schemes 2 and 4). For example, the reaction of **3a** with BCIH gave the corresponding dioxane **5a** in 29% yield together with the rearrangement

Scheme 4

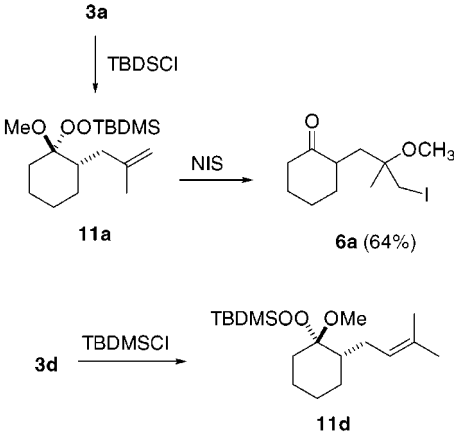


product **6a** (20%). The dioxane **5a** was obtained as a 3:2 mixture of cis and trans stereoisomers, in marked contrast to the fact that **5a** was isolated as a single isomer from the reaction with NIS or I_2–KOBu^t (the ratios of products, if formed as mixtures of isomers, are shown in the schemes). On the basis of the structure of the starting material **3a**, the relation of the methoxy and iodomethyl groups in the minor isomer is considered to be trans.

Thus, in the iodonium ion-mediated reactions of **3a**–**c**, two alternative processes (paths a and b, Scheme 2) can compete, with the relative contributions of each being a marked function of the structure of **3** and the nature of the iodonium ion reagents. Attack of the hydroperoxy group on the electron-deficient carbon of the iodonium ion intermediate **4a** yields the 1,2-dioxane **5a** after deprotonation (path a). Alternatively, the formation of ketone **6a** requires an intramolecular migration of the methoxy group,[10] followed by heterolytic O–O bond fission (path b). Consistent with the proposed intramolecular process, reaction of **3a** with NIS in the presence of 1.2 equiv of CD_3OD gave the product **6a**, which did

(11) Crystal data for **5c**: $C_{18}H_{19}IO_3$, $M = 410.23$, colorless needles, triclinic, space group $P\bar{1}$ (no. 2), $a = 8.7230(10)$ Å, $b = 10.006(2)$ Å, $c = 10.780(2)$ Å, $\alpha = 64.410(10)°$, $\beta = 82.83(2)°$, $\gamma = 77.24(2)°$, $V = 827.2(2)$ Å^3, $Z = 2$, $D_c = 1.647$ g cm^{-3}, $F(000) = 408$, μ(Mo Kα) = 1.945 mm^{-1}, final discrepancy factors $R = 0.025$ and $R_w = 0.067$. Crystal data for **8d**: $C_{12}H_{21}BrO_3$, $M = 293.20$, colorless needles, monoclinic, space group $P2_1/c$ (no. 14), $a = 12.399(4)$ Å, $b = 9.849(4)$ Å, $c = 10.699(3)$ Å, $\beta = 100.18(2)°$, $V = 1286.0(7)$ Å^3, $Z = 4$, $D_c = 1.514$ g cm^{-3}, $F(000) = 608$, μ(Mo Kα) = 3.188 mm^{-1}, final discrepancy factors $R = 0.036$ and $R_w = 0.084$. The X-ray diffraction data were collected on a Siemens P4 diffractometer using graphite-monochromated Mo Kα ($\lambda = 0.710\,73$ Å) at $T = 160$ K and corrected for absorption, and the structure was solved by direct methods. All crystallographic calculations were carried out using SHELXTL (version 5.1) (Sheldrick, G. M., Brucker AXS Inc., Madison, WI).

Scheme 5



not contain any deuterium (Scheme 2). Assuming that the methoxy group and the side chain were 1,2-diequatorial in **3a**, then path b (5-exo attack) would be entropically favorable. Molecular models suggest that in **4a** the electron-deficient carbon could be placed in close proximity to the methoxy group. Moreover, C=O bond formation in the final step could provide an additional driving force.

Treatment of the methoxy hydroperoxide **3d** with BCIH gave the desired 1,2-dioxepane **5d** in 64% yield as the sole isolable product. The analogous reaction between **3d** and NIS, however, produced a mixture of the 1,2-dioxepane **5d** (25% yield) and the unexpected furan derivative **10d** (35% yield) (Scheme 4). The furan **10d** was found to be the kinetically controlled product, since treatment of **5d** with NIS resulted in the quantitative recovery of **5d**. The analogous reaction of **3f** with NIS afforded the corresponding furan derivative **10f** in 30% yield but apparently none of the 1,2-dioxepane **5f**, whereas **5f** was isolated in 43% yield on reaction of **3f** with BCIH (Scheme 4). The reaction of hydroperoxides **3d**,**f** with I_2−KOBu^t resulted in the formation of a complex mixture of unidentified products.

Although the hydroperoxides **3a** and **3d** form the corresponding cyclic peroxides **5a** and **5d**, respectively, when treated with NIS, the disparate structures of the nonperoxidic products **6a** and **10d** indicate that they have been formed by distinctly different pathways, the former by methoxy group migration (vide supra) and the latter by cleavage of the O−O bond of the cyclic intermediate **9d**. Thus, reaction of **11a**, the *tert*-butyldimethylsilyl-protected derivative of **3a**, with NIS gave the methoxy-migration product **6a** in enhanced yield consistent with total suppression of the cyclization process involving the peroxide group (Scheme 5). Under similar conditions, the reaction of the TBDMS compound **11d** with NIS produced only a complex mixture of unidentified products. This is in reasonable agreement with the notion that dioxepane **5d** and furan **10d** are both derived from the cyclic intermediate **9d** arising from attack of the terminal oxygen of the hydroperoxy group on the carbocation center of the iodonium ion **4d** (Scheme 4).

Thus, (1) the reaction of **3d** seems to proceed exclusively via the cyclic intermediate **9d**, while the methoxy migration is important in the case of **3a**, and (2) the reaction of **3d** with BCIH gives predominantly the dioxepane **5d**, while the formation of the furan **10d** is important in the reaction with NIS. Although methoxy group migration (6-endo attack) should also be entropically favorable in the case of the halonium ion **4d**, molecular models suggest that, as a consequence of the longer side chain in **4d**, approach of the electron-deficient carbon to the methoxy group directly attached to the cyclohexane ring suffers significant steric congestion. The alternative attack by the hydroperoxy group with a lesser steric demand (7-endo attack) predominantly occurs to give the cyclic intermediate **9d**. Subsequent deprotonation, which would be assisted by collidine in the case of BCIH, results in the formation of the 1,2-dioxepane **5d** (path a in Scheme 4). In the case of NIS, the succinimide anion, which is probably strongly coordinated to the iodonium ion, does not seem to work as an efficient base, and as a result, the alternative bond reorganization involving O−O bond scission[12] (path b in Scheme 4) can compete, thereby providing the furan derivative **10d**. In the case of **3a** having a shorter side chain, a process similar to path b in Scheme 4 does not seem to be important, since the expected product would be the ring-strained oxetane derivative.

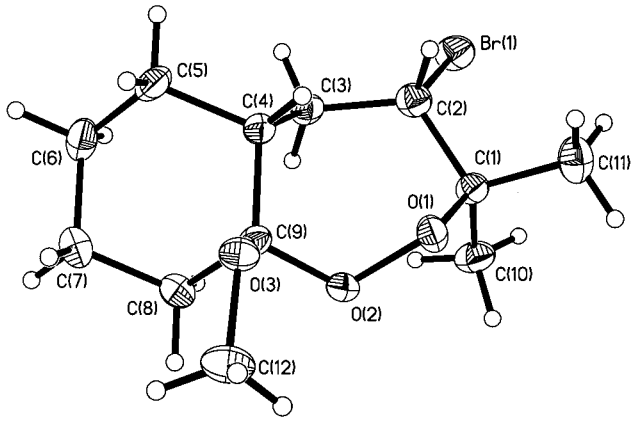


Figure 2. Molecular structure of 1,2-dioxepane derivative **8d** (ORTEP[9]).

The reaction of hydroperoxide **3a** with *N*-bromosuccinimide (NBS) in the presence of $NaHCO_3$ afforded the methoxy-migrated ketone **7a** in 48% yield rather than the expected 1,2-dioxane (Scheme 2). Similar trends were observed for **3b**,**c** (Scheme 3). In contrast, the analogous reactions of hydroperoxides **3d**−**f** with NBS did provide the expected dioxepanes **8d**−**f** together with the ketones **7d**−**f**, demonstrating again that the substrate with a longer side chain favors the formation of the cyclic peroxide, reflecting the ease in approach of the hydroperoxide group to the electron-deficient carbon of the halonium ion intermediate (Schemes 3 and 4).

The structure of the major isomer of compound **8d**, as determined by X-ray crystallographic analysis, consists of a chairlike cyclohexane ring cis-fused to a 1,2-dioxepane ring which adopts a twist-chair conformation (Figure 2).[11] Moreover, the structural features of this isomer of **8d** are entirely consistent with (a) the syn relationship established between the hydroperoxy and the 3-methyl-2-butenyl groups in the substrate **3d** as discussed above (Scheme 1) and (b) the ring closure mechanism proposed in Scheme 4, which should result in the terminal peroxide oxygen and the bromine in **8d** being antiperiplanar

(12) A similar C−O bond formation with the concomitant O−O bond fission has been proposed for the formation of 2-bromo-9-oxabicyclo-[4.2.1]nonane from the reaction of 5-hydroperoxycyclooctene with NBS: Bloodworth, A. J.; Curtis, R. J.; Spencer, M. D.; Tallant, N. A. *Tetrahedron* **1993**, *49*, 2729.

(observed torsion angle: O(1)−C(1)−C(2)−Br(1) 174.1-(2)°).

It is remarkable that the reaction of **3f** with NIS gives exclusively the furan derivative **10f**, while the reaction of the same substrate with NBS results in the formation of the ketone **7f** together with a small amount of the dioxepane **8f**. Thus, a difference in nature (e.g., electronegativity and polarizability) between the halonium ions, **4f** (X = I) and **4f** (X = Br), seems to play an important role in determining the course of the reaction. Thus, the harder, more electrophilic Br^+ may promote the methoxy migration via the kinetically favored 1,4-shift. In this respect, NBS is well-known to be the reagent of choice for the cyclofunctionalization reactions of unsaturated acetals.[10]

Conclusion

By the appropriate choice of halogenating agent and unsaturated hydroperoxide substrate **3**, several new 1,2-dioxanes or 1,2-dioxepanes could be synthesized. BCIH seems to be the best reagent for the synthesis of these peroxides, particularly 1,2-dioxepane because of the absence of a reactive counteranion[9a] and the expected role of collidine as a nonnucleophilic base. In the halocyclization reactions the unexpected migration of either a methoxy or a hydroxy group was also found to compete strongly, thereby providing the corresponding ketone or furan derivatives. The variation in reaction outcome can be rationalized from the results in terms of the difference in (a) the structure of unsaturated hydroperoxide substrates **3** and (b) the intrinsic nature of the halogenating agents.

Experimental Section

General Procedures. ^{1}H (270 MHz; 400 MHz for NOE studies) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the standard. Unsaturated ketones **1a**,**b**,**d**−**f**[13] and the derived dienes **2a**,**b**,**d**−**f**[14] were prepared by the reported methods. The vinyl ether **2g** was prepared from 2-phenylcyclohexanone in a similar way. 2,5-Diphenyl-1,5-hexadiene (**1c**) was synthesized from 1,2-dibenzoylethane by the conventional Wittig reaction.[15] BCIH was prepared by the method of Simonot and Rousseau.[16]

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.

Monoozonolysis of Dienes in MeOH−CH_2Cl_2. Ozonolysis of a vinyl ether, **2b**, is representative. Into a solution of **2b** (445 mg, 3.2 mmol) in CH_2Cl_2 (25 mL) and methanol (5 mL) was passed a slow stream of ozone (1 equiv) at −70 °C. After extraction with ether (70 mL), the organic layer was washed with ice-cold sodium bicarbonate and saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the products were isolated by column chromatography on silica gel. Elution with diethyl ether−hexane (1:9) gave the unsaturated hydroperoxide **3b** (350 mg, 69%).

2-Methoxy-5-methyl-5-hexen-2-yl hydroperoxide (3b): oil; ^{1}H NMR δ 1.36 (s, 3 H), 1.75 (s, 3 H), 1.8−1.9 (m, 2 H), 2.0−2.1 (m, 2 H), 3.33 (s, 3 H), 4.71 (s, 2 H), 8.36 (s, 1 H); ^{13}C NMR δ 19.10, 22.66, 32.06, 33.14, 48.98, 107.02, 109.88, 145.32.

1-Methoxy-2-phenylcyclohexyl hydroperoxide (3g): mp 88−90 °C (from ethyl acetate−hexane); ^{1}H NMR δ 1.3−1.5 (m, 1 H), 1.5−1.6 (m, 1 H), 1.6−1.9 (m, 4 H), 1.9−2.1 (m, 1 H), 2.38 (dt, J = 13.2 and 4.0 Hz, 1 H), 2.98 (dd, J = 11.4 and 3.7 Hz, 1 H), 3.22 (s, 3 H), 7.2−7.4 (m, 5 H), 7.58 (s, 1 H); ^{13}C NMR δ 22.84, 25.12, 30.19, 31.02, 51.00, 51.12, 106.58, 126.51, 127.89, 129.54, 141.15. Anal. Calcd for $C_{13}H_{18}0_3$: C, 70.25; H, 8.16. Found: C, 70.07; H, 8.12. In the NOE measurement, irradiation of the signal due to the methoxy group resulted in the enhancement of the hydrogen at C-2 (δ 2.9−3.0, m) (2%) and two hydrogens at C-6 (δ 1.5−1.6 (m) and 2.38 (dt)) (4.5% to each). By the irradiation of the signal of the hydrogen at C-2, an enhancement of the signal due to one of the hydrogens at C-6 (δ 1.5−1.6 (m)) (4.0%) was induced. No NOE was observed between the hydroperoxy group and the hydrogen at C-2.

Reaction of Hydroperoxides 3b,e with *N*-Iodosuccinimide. Reaction of a hydroperoxide, **3b**, with NIS is representative. To a CH_2Cl_2 solution (25 mL) of **3b** (110 mg, 0.69 mmol) were added NIS (320 mg, 1.4 mmol) and then $NaHCO_3$ (56 mg, 0.67 mmol). The mixture was stirred at room temperature for 15 h (the flask was covered by aluminum foil) and then diluted with hexanes−ether (30 mL; 8:2). The precipitated succinimide was removed by filtration and washed with hexane (3 × 5 mL), and the combined filtrate and washings were washed with aqueous $Na_2S_2O_3$ and saturated brine and dried ($MgSO_4$). The organic layer was concentrated by a rotatory evaporator to leave the oily residue, which was subjected to column chromatography on silica gel. Elution with ether−hexane (5:95) gave a dioxane, **5b** (54 mg, 28%). Subsequent elution with ether−hexane (15:85) gave a ketone, **6b** (64 mg, 34%).

3-Iodomethyl-6-methoxy-3,6-dimethyl-1,2-dioxane (5b): oil; ^{1}H NMR δ 1.27 (s, 3 H), 1.28 (s, 3 H), 1.7−1.8 (m, 3 H), 1.9−2.1 (m, 1 H), 3.32 (s, 3 H), 3.50 (s, 2 H); ^{13}C NMR δ 12.54, 19.73, 24.40, 27.60, 30.51, 49.06, 78.08, 101.87. Anal. Calcd for $C_8H_{15}IO_3$: C, 33.58; H, 5.28. Found: C, 33.69; H, 5.25.

6-Iodo-5-methoxy-5-methyl-2-hexanone (6b): oil; ^{1}H NMR δ 1.27 (s, 3 H), 1.8−2.1 (m, 2 H), 2.18 (s, 3 H), 2.50 (t, J = 7.9 Hz, 2 H), 3.17 (s, 3 H), 3.23 (d, J = 10.9 Hz, 1 H), 3.30 (d, J = 10.9 Hz, 1 H); ^{13}C NMR δ 15.06, 22.50, 30.01, 30.08, 37.89, 49.54, 73.82, 208.05. Anal. Calcd for $C_8H_{15}IO_2$: C, 35.57; H, 5.60. Found: C, 35.58; H, 5.59.

Reaction of Hydroperoxides 3d,f with *N*-Iodosuccinimide. Reaction of a hydroperoxide, **3d**, with NIS is representative. To a CH_2Cl_2 solution (25 mL) of **3d** (310 mg, 1.5 mmol) were added NIS (633 mg, 2.9 mmol) and then $NaHCO_3$ (122 mg, 1.5 mmol). The mixture was stirred at room temperature for 15 h (the flask was covered by aluminum foil). After workup as described above, the oily residue was subjected to column chromatography on silica gel. Elution with ether−hexane (5:95) gave a dioxepane, **5d** (84 mg, 25%, a 7:3 mixture of two isomers). Subsequent elution with diethyl ether−hexane (10:90) gave a tetrahydrofuran derivative, **10d** (132 mg, 35%, a 9:2 mixture of two isomers). Treatment of **10d** (100 mg) with NIS (128 mg) for 15 h, followed by column chromatography on silica gel, resulted in the recovery of **10d** (95 mg).

5-Iodo-1-methoxy-4,4-dimethyl-2,3-dioxabicyclo[5.4.0]-undecane (5d) (major isomer): mp 82−83 °C; ^{1}H NMR δ 1.1−2.7 (m, 11 H), 1.28 (s, 3 H), 1.43 (s, 3 H), 3.17 (s, 3 H), 4.54 (dd, J = 8.6 and 4.6 Hz, 1 H); ^{13}C NMR δ 20.54 (CH_2), 22.05 (CH_3), 22.18 (CH_2), 25.12 (CH_3), 25.59 (CH_2), 28.74 (CH_2), 38.56 (CH_2), 39.82 (CH), 44.31 (CH), 48.23 (CH_3), 84.67 (C), 107.55 (C). Anal. Calcd for $C_{12}H_{21}IO_3$: C, 42.37; H, 6.22; I, 37.30. Found: C, 42.69; H, 5.94; I, 37.34. The minor isomer was obtained as an admixture with 70% of the major one (oil). The following additional signals were assigned to this isomer: ^{1}H NMR δ 1.50 (s, 3 H), 1.52 (s, 3 H), 3.23 (s, 3 H), 4.03 (dd, J = 12.1 and 6.3 Hz, 1 H); ^{13}C NMR δ 21.31 (CH_2), 22.30 (CH_2),

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24.93 (CH_2), 26.65 (CH_3), 27.48 (CH_3), 30.55 (CH_2), 40.58 (CH), 41.49 (CH_2), 41.60 (CH), 48.38 (CH_3), 84.96 (C), 107.01 (C).

Methyl 5-[2-(4-iodo-5,5-dimethyltetrahydrofuranyl)]-valerate (10d): oil (a 9:2 mixture of two isomers); ^{1}H NMR (major isomer) δ 1.3−1.8 (m, 6 H), 1.32 (s, 3 H), 1.39 (s, 3 H), 2.0−2.2 (m, 1 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.58 (dt, J = 12.6 and 6.3 Hz, 1 H), 3.67 (s, 3 H), 3.8−3.9 (m, 1 H), 4.01 (dd, J = 11.2 and 6.6 Hz, 1 H); ^{13}C NMR (major isomer) δ 24.78 (CH_2), 25.43 (CH_2), 25.72 (CH_3), 29.17 (CH_3), 30.50 (CH), 33.84 (CH_2), 36.61 (CH_2), 43.74 (CH_2), 51.43 (CH_3), 77.72 (CH), 81.80 (C), 173.96 (C); ^{1}H NMR (minor isomer) δ 1.33 (s, 3 H), 1.36 (s, 3 H), 2.32 (t, J = 7.4 Hz, 2 H), 3.67 (s, 3 H); ^{13}C NMR (minor isomer) (only the characteristic signals are shown) δ 24.15 (CH_2), 25.05 (CH_2), 25.88 (CH_3), 25.99 (CH_3), 31.11 (CH), 36.07 (CH_2), 42.91 (CH_2), 51.45 (CH_3), 74.74 (CH), 82.52 (C); MS (EI) m/z (rel intens) 225 [$M^+ - (CH_2)_4CO_2Me$] (89), 213 ($M^+ - I$) (83), 74 (25); HRMS [$(M + H)^+$] m/z calcd for $C_{12}H_{22}IO_3$ 314.0614, found 314.0615.

Reaction of Hydroperoxides 3a with *N*-Iodosuccinimide in the Presence of CD_3OD. To a CH_2Cl_2 solution (25 mL) of **3a** (250 mg, 1.2 mmol) and CD_3OD (70 μL) were added NIS (566 mg, 2.5 mmol) and then $NaHCO_3$ (110 mg, 1.3 mmol). The mixture was stirred at room temperature for 15 h. After the workup as described above, the residue was separated by column chromatography on silica gel. Elution with ether−hexane (5:95) gave a dioxane, **5a** (32 mg, 8%). Further elution with ether−hexane (10:90) gave a ketone, **6a** (80 mg, 20%).

4-Iodomethyl-1-methoxy-4-hydroxy-1,2-dioxabicyclo-[4.4.0]decane (5a): oil; ^{1}H NMR δ 1.2−2.1 (m, 10 H), 2.1−2.2 (m, 1 H), 1.31 (s, 3 H), 3.32 (s, 3 H), 3.41 (d, J = 9.7 Hz, 1 H), 3.44 (d, J = 9.7 Hz, 1 H); ^{13}C NMR δ 15.46, 21.37, 21.66, 22.07, 25.20, 27.03, 34.54, 36.07, 48.90, 81.21, 106.07. Anal. Calcd for $C_{11}H_{19}IO_3$: C, 40.51; H, 5.87. Found: C, 40.88; H, 5.79. Irradiation of the methoxy group (δ 3.32) resulted in the enhancement of the signals due to the iodomethyl group (δ 3.44) (the exact extent of the enhancement was not determined, because two signals resonated at very near positions) and the bridgehead hydrogen at C-6 (δ 2.1−2.2) (1.0%). No enhancement of the methyl signal (δ 1.31) was observed. Also, a small enhancement of the signal of H-6 was observed by the irradiation of the iodomethyl hydrogen at δ 3.44 (1%). In the reaction with BCIP, **5a** was obtained as a 3:2 mixture of two isomers. The following additional signals were assigned to the minor isomer: ^{1}H NMR δ 1.41 (s, 3 H), 3.34 (s, 3 H); ^{13}C NMR δ 11.61, 20.38, 22.18, 24.87, 25.84, 26.96, 33.93, 34.77, 49.22, 79.44, 105.19.

2-(3-Iodo-2-methoxy-2-methylpropyl)cyclohexanone (6a): oil; ^{1}H NMR δ 1.2−2.6 (m, 11 H), 1.25 (s, 3 H), 3.11 (s, 3 H), 3.20 (s, 1 H), 3.21 (s, 1 H); ^{13}C NMR δ 16.66, 23.74, 25.02, 28.23, 34.54, 36.48, 41.89, 46.44, 49.62, 74.29, 212.25. Anal. Calcd for $C_{11}H_{19}IO_2$: C, 42.60; H, 6.17. Found: C, 42.71; H, 5.95.

Reaction of the Hydroperoxide 3c with I_2−KOBu^t. To a THF solution (25 mL) of the hydroperoxide **3c** (230 mg, 0.80 mmol) and KOBu^t (92 mg, 0.82 mmol) was added I_2 (610 mg, 2.4 mmol) over 5 min at 0 °C, and then the mixture was stirred at room temperature for 13 h (the flask was covered by aluminum foil). Ether (70 mL) was added, and the organic layer was separated, washed with aqueous $Na_2S_2O_3$ followed by saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel. Elution with diethyl ether−hexane (3:97) gave a dioxane, **5c** (101 mg, 30%). Subsequent elution with diethyl ether−hexane (5:95) gave a ketone, **6c** (87 mg, 27%).

3-Iodomethyl-6-methoxy-3,6-diphenyl-1,2-dioxane (5c): mp 141−142 °C (from ether−hexane); ^{1}H NMR δ 1.9−2.2 (m, 2 H), 2.2−2.4 (m, 1 H), 2.4−2.6 (m, 1H), 3.22 (s, 3 H), 3.96 (s, 2 H), 7.3−7.5 (m, 10 H); ^{13}C NMR δ 12.10, 27.44, 32.13, 50.53, 81.06, 102.95, 125.36, 125.59, 128.32, 128.50, 128.61, 139.26, 141.06. Anal. Calcd for $C_{18}H_{19}IO_3$: C, 52.70; H, 4.67; I, 30.93. Found: C, 52.66; H, 4.56; I, 30.69.

5-Iodo-4-methoxy-1,4-diphenyl-1-pentanone (6c): mp 82−83 °C (from ether−hexane); ^{1}H NMR δ 2.2−2.4 (m, 1 H), 2.4−2.8 (m, 2 H), 2.8−3.0 (m, 1 H), 3.25 (s, 3 H), 3.60 (d, J = 10.9 Hz, 1 H), 3.75 (d, J = 10.9 Hz, 1 H), 7.2−7.8 (m, 8 H), 7.85 (m, 2 H); ^{13}C NMR δ 14.88, 30.39, 33.25, 50.08, 78.53, 126.22, 127.98, 128.34, 128.50, 133.06, 141.26, 199.25; MS m/z (rel intens) 261 ($M^+ - CH_2CH_2COPh$) (100), 253 ($M^+ - CH_2I$) (87), 105 [$M^+ - CH_2CH_2C(CH_2I)(OMe)Ph$] (74). Anal. Calcd for $C_{18}H_{19}IO_2$: C, 54.84; H, 4.86. Found: C, 54.65; H, 4.64.

Reaction of the Hydroperoxide 3a,d,f with BCIH. The reaction of **3f** is representative. To a CH_2Cl_2 solution (25 mL) of the hydroperoxide **3f** (310 mg, 1.4 mmol) were added BCIH (1.5 g, 2.9 mmol) and $NaHCO_3$ (130 mg, 1.5 mmol), and then the mixture was stirred at room temperature for 15 h (the flask was covered by aluminum foil). After the workup as described above, the components of the crude product mixture were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (4:96) gave a dioxepane, **5f** (210 mg, 43%, a 3:2 mixture of two isomers).

4-Iodomethyl-1-methoxy-4-methyl-2,3-dioxabicylco-[5.4.0]undecane (5f): oil; ^{1}H NMR δ 1.1−2.3 (m, 13 H), 1.28 (s, major) + 1.43 (s) (3 H), 3.17 (s, major) + 3.18 (s, major) + 3.43 (d, J = 10.2 Hz) + 3.59 (d, J = 10.2 Hz) (2 H), 3.29 (s) + 3.30 (s, major) (3 H); ^{13}C NMR δ 13.50 (CH_2), 13.80 (CH_2), 21.03 (CH_2), 22.28 (CH_2), 22.41 (CH_2), 22.59 (CH_3), 24.89 (CH_2), 24.93 (CH_2), 26.15 (CH_3), 26.60 (CH_2), 26.90 (CH_2), 30.12 (CH_2), 30.53 (CH_2), 36.95 (CH_2), 38.82 (CH_2), 41.69 (CH), 48.20 (CH_3), 48.47 (CH_3), 81.80 (C), 82.66 (C), 107.55 (C), 108.00 (C). Anal. Calcd for $C_{12}H_{21}IO_3$: C, 42.37; H, 6.22. Found: C, 42.00; H, 6.31.

Protection of the Hydroperoxides 3 by *tert*-Butyldimethylsilyl Group. The synthesis of **11a** is representative.[17] To a CH_2Cl_2 solution (35 mL) of TBDMSCl (460 mg, 3.0 mmol) and the hydroperoxide **3a** (300 mg, 1.5 mmol) was added a CH_2Cl_2 solution (15 mL) of imidazole (210 mg, 3.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 15 h. After removal of the precipitate by filtration, the organic layer was washed with aqueous NH_4Cl followed by saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with ether−hexane (2:98) gave the peroxide **11a** (300 mg, 64%).

1-Methoxy-2-(2-methyl-2-propenyl)cyclohexyl *tert*-butyldimethylsilyl peroxide (11a): oil; ^{1}H NMR δ 0.18 (s, 6 H), 0.96 (s, 9 H), 1.2−1.7 (m, 8 H), 1.69 (s, 3 H), 2.0−2.4 (m, 3 H), 3.31 (s, 3 H), 4.67 (s, 1 H), 4.74 (s, 1 H); ^{13}C NMR δ −5.75, −5.68, 18.31, 20.42, 21.75, 22.43, 24.60, 26.00, 26.18 (3C), 35.40, 37.50, 48.45, 106.65, 111.64, 144.58. Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 65.20; H, 10.72.

Reaction of the Peroxide 11a with NIS. To a CH_2Cl_2 solution (25 mL) of **12a** (290 mg, 0.91 mmol) were added NIS (420 mg, 1.9 mmol) and then $NaHCO_3$ (80 mg, 0.95 mmol). The mixture was stirred at room temperature for 15 h (the flask was covered by aluminum foil) and then diluted with hexane (30 mL). After the conventional workup, the residue was subjected to column chromatography on silica gel. Elution with ether−hexane (10:90) gave a ketone, **6a** (180 mg, 64%, a 3:1 mixture of two isomers).

Reaction of Hydroperoxides 3a−f with *N*-Bromosuccinimide. Reaction of a hydroperoxide, **3d**, is representative. To a CH_2Cl_2 solution (25 mL) of **3d** (310 mg, 1.4 mmol) were added NBS (510 mg, 2.9 mmol) and then $NaHCO_3$ (130 mg, 1.5 mmol). The mixture was stirred at room temperature for 15 h (the flask was covered by aluminum foil). After conventional workup, the oily residue was subjected to column chromatography on silica gel. Elution with ether−hexane (3:97) gave a dioxepane, **8d** (95 mg, 23%, a 3:1 mixture of two isomers), which on recrystallization from ethyl acetate−hexane afforded the major isomer. Subsequent elution with ether−hexane (8:92) gave a ketone, **7d** (66 mg, 17%), which was contaminated by inseparable impurities (ca. 10%).

5-Bromo-1-methoxy-4,4-dimethyl-2,3-dioxabicyclo[5.4.0]-undecane (8d) (major isomer): mp 96−97 °C (from hexanes−ethyl acetate); ^{1}H NMR δ 1.2−2.5 (m, 11 H), 1.34 (s, 3 H), 1.51 (s, 3 H), 3.28 (s, 3 H), 3.95 (dd, J = 12.0 and 3.5 Hz,

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1 H); ^{13}C NMR δ 19.86 (CH_3), 21.31 (CH_2), 22.25 (CH_2), 24.89 (CH_2), 25.10 (CH_3), 30.71 (CH_2), 38.96 (CH_2), 42.17 (CH), 48.39 (CH_3), 59.77 (CH), 84.89 (C), 106.95 (C). Anal. Calcd for $C_{12}H_{21}BrO_3$: C, 49.16; H, 7.22. Found: C, 48.98; H, 7.17. The minor isomer was obtained in an admixture with 67% of the major one (oil). The following additional signals were assigned to this isomer: ^{1}H NMR 1.32 (s, 3 H), 1.50 (s, 3 H), 3.39 (s, 3 H), 4.41 (dd, J = 7.3 and 4.0 Hz, 1 H); ^{13}C NMR δ 20.77 (CH_2), 25.03 (CH_3), 25.10 (CH_3), 25.34 (CH_2), 26.00 (CH_3), 29.34 (CH_2), 36.37 (CH_2), 37.45 (CH), 38.60 (CH_2), 48.32 (CH_3), 60.66 (CH), 84.69 (C), 107.62 (C).

2-(2-Bromo-3-methoxy-3-methylbutyl)cyclohexanone (7d): oil (ca. 90% purity); ^{1}H NMR δ 1.2−2.2 (m, 7 H), 1.34 (s, 6 H), 2.2−2.4 (m, 3 H), 2.7−2.8 (m, 1 H), 3.29 (s, 3 H), 4.32 (dd, J = 11.9 and 1.7 Hz, 1 H); ^{13}C NMR δ 22.50 (CH_3), 23.36 (CH_3), 25.44 (CH_2), 28.37 (CH_2), 34.39 (CH_2), 35.72 (CH_2), 42.57 (CH_2), 49.18 (CH), 49.52 (CH_3), 63.27 (CH), 76.66 (C), 213.15 (C).

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Supporting Information Available: Preparation methods and the physical properties of dienes **2a**−**f**, hydroperoxides **3a**,**c**−**f**, products **5e**, **6e**, **7a**−**c**,**e**,**f**, and **8a**−**c**,**e**,**f**, and a TBDMS-protected peroxide, **12d**, and crystal data, atomic coordinates, bond lengths and angles, and displacement parameters for **5c** and **8d**. This material is available free of charge via the Internet at http//pubs.acs.org.

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