Antimalarial Activity of Novel 1,2,5,6-Tetraoxacycloalkanes and 1,2,5-Trioxacycloalkanes

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Photooxygenation of 2-phenylnorbornene **1** in the presence of 30% aqueous hydrogen peroxide afforded 1,2-bishydroperoxide **3**, which could be cycloalkylated on treatment with silver oxide and a 1,*ω*-diiodoalkane to provide the tricyclic peroxides **12**. Trimethylsilylation of **3** followed by TMSOTf-catalyzed cyclocondensation with carbonyl compounds led to the formation of the tricyclic peroxides **14** containing a 1,2,4,5-tetroxepane structure. Photooxygenation of **1** in the presence of either unsaturated hydroperoxides or unsaturated alcohols followed by bis(collidine)-iodine hexafluorophosphate promoted cyclization gave the corresponding cyclic peroxides **15**−**17**. Several of these cyclic peroxides showed substantial antimalarial activity particularly in vitro.

Introduction

Since malaria parasites are rapidly developing resistance to the most commonly used chemotherapeutic alkaloidal drugs, the antimalarial properties of nonalkaloidal compounds such as artemisinin and the related endoperoxides have attracted considerable attention.[1] We have recently reported that treatment of (alkylidene)-1,1-bishydroperoxides with 1,*ω*-dihaloalkanes in the presence of CsOH in DMF[2] or Ag_2O in CH_2Cl_2[3] affords a series of novel 1,2,4,5-tetraoxacycloalkanes that exhibit remarkable antimalarial activity not only in vitro but also in vivo.[3] In the development of new synthetic routes to cyclic peroxides containing two peroxide groups within the same ring, the comparatively rare *vic*-dihydroperoxide was identified as a promising precursor.[4] We report herein details of (i) the synthesis of the tetraoxacycloalkanes, (ii) extension of this methodology to the synthesis of novel 1,2,5-trioxacycloalkanes, and (iii) the antimalarial activities of the respective peroxidic compounds.

Results and Discussion

Preparation of a 1,2-Bishydroperoxide and the Related Unsaturated Hydroperoxides. 2-Phenylnorbornene **1** is known to react with singlet oxygen to generate a zwitterionic intermediate that can be efficiently trapped by methanol to form **2**.[5] By analogy, photooxygenation of a solution of **1** in acetonitrile containing 30% aqueous hydrogen peroxide afforded the 1,2-bishydroperoxide **3** in essentially quantitative yield (Scheme 1). Compound **3** was successfully transformed using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) into the corresponding bis-trimethylsilylated derivative **5**,[6] which could be isolated by column chromatography on silica gel.

Since we had previously found that bis(collidine)-iodine hexafluorophosphate (BCIH) promoted cyclization of unsaturated hydroperoxides provided a versatile method for the synthesis of a variety of cyclic peroxides,[7] we tried to prepare the appropriate unsaturated hydroperoxides. Photooxygenation of **1** in the presence of either the unsaturated hydroperoxide **6** or unsaturated alcohols **7** and **8** afforded the corresponding labile unsaturated hydroperoxides **9**−**11**, which could be isolated in low yield (12−25%) by rapid chromatography on silica gel but needed to be used without further purification (Scheme 2).

Synthesis of 1,2,5,6-Tetraoxycycloalkanes and 1,2,5-Trioxacycloalkanes. With these starting materials in hand, the synthesis of cyclic peroxides was attempted. Treatment of a mixture of **3** and 1,3-diiodopropane with Ag_2O in CH_2Cl_2[3] gave the desired tricyclic peroxide **12a**, containing a 1,2,5,6-tetroxonane ring, though the major product was again the keto aldehyde **13** (48%). The 1,2,5,6-tetroxecane derivative **12b** was obtained from the analogous cycloalkylation reaction involving 1,4-diiodobutane (Scheme 3). In the crystal structure of **12a**, as determined by the X-ray analysis, the nine-membered tetroxonane ring was found to adopt the symmetrical boat−chair conformation.[4]

TMSOTf-catalyzed cyclocondensation of trimethylsilyl-protected bishydroperoxide **5** with carbonyl compounds[6] provided a series of novel 1,2,4,5-tetroxepane derivatives **14a**−**e** (Scheme 4). The crystal structure of **14a**, as determined by X-ray analysis, had demonstrated that the seven-membered 1,2,4,5-tetroxepane ring of **14a** is in a classical chair conformation as a consequence of the structural rigidity imposed by the fused bicyclo-[2.2.1]heptane ring system.[4]

Treatment of the unsaturated hydroperoxide **9** with BCIH afforded the tricyclic peroxide **15**, containing a 1,2,5,6-tetroxonane ring, in 61% yield. Similarly, the tricyclic peroxides **16** and **17**, each containing a 1,2,5-trioxacycloalkane ring, were prepared from the unsaturated hydroperoxides **10** and **11** in yields of 52% and

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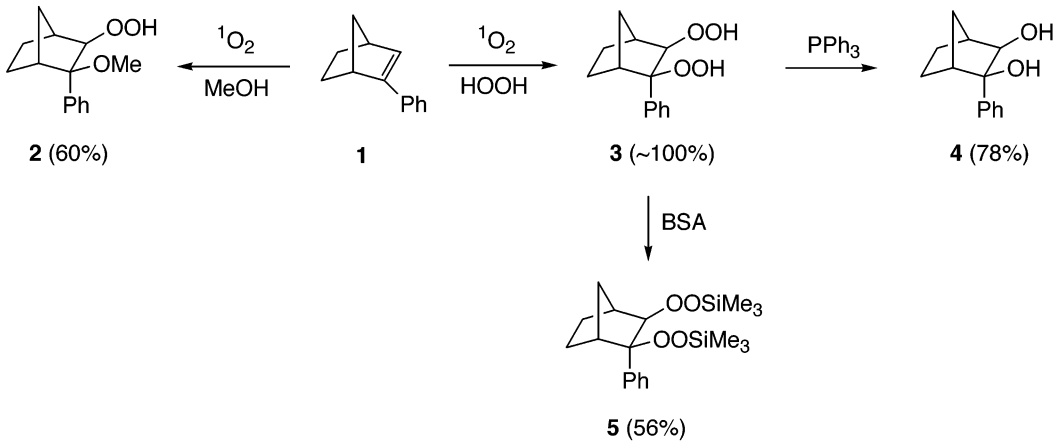
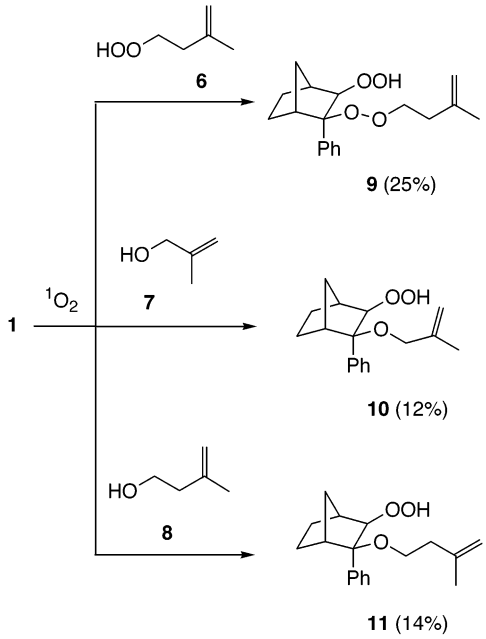
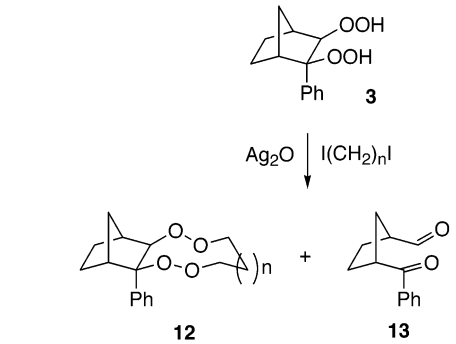
Scheme 1



Scheme 2

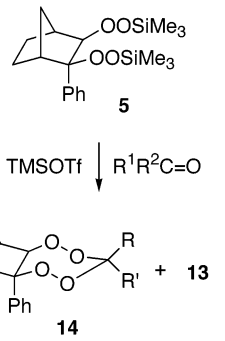


Scheme 3



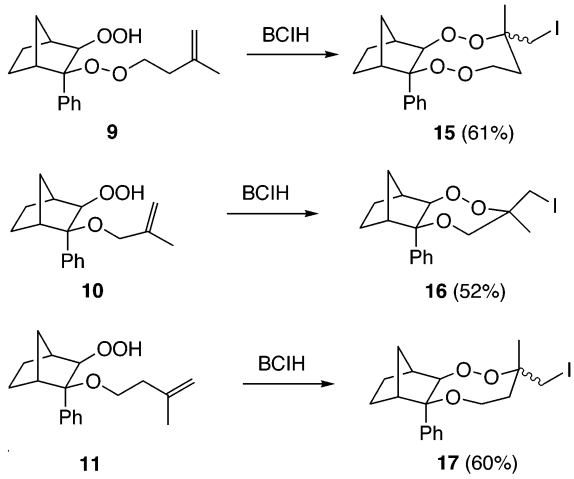
	12	13
a; n = 1	9%	48%
b; n = 2	7%	53%

Scheme 4



a; R^1 = Ph, R^2 = H	23%	36%
b; R^1 = 4-FC_6H_4, R^2 = H	13%	33%
c; R^1 = cyclohexyl, R^2 = H	12%	29%
d; R^1, R^2 = -$(CH_2)_5$-	19%	41%
e; R^1, R^2 = -CH($CH_2)_4$-CH$_3$	11%	45%

Scheme 5



60%, respectively (Scheme 5). Although tricyclic peroxide **16** provided weakly diffracting crystals, its structure was unambiguously determined by X-ray crystallographic analysis (Figure 1). The central 1,2,5-trioxepane ring adopts a classical chair conformation similar to that of the peroxide ring in **14a**. The phenyl group at C(4) is endo, and the iodomethyl group is in an axial position and is syn to the bridging methine group of the norbornane moiety.

Antimalarial Activity of 1,2,5,6-Tetraoxycycloalkanes and 1,2,5-Trioxacycloalkanes. The antimalarial activities of the derived cyclic peroxides in vitro

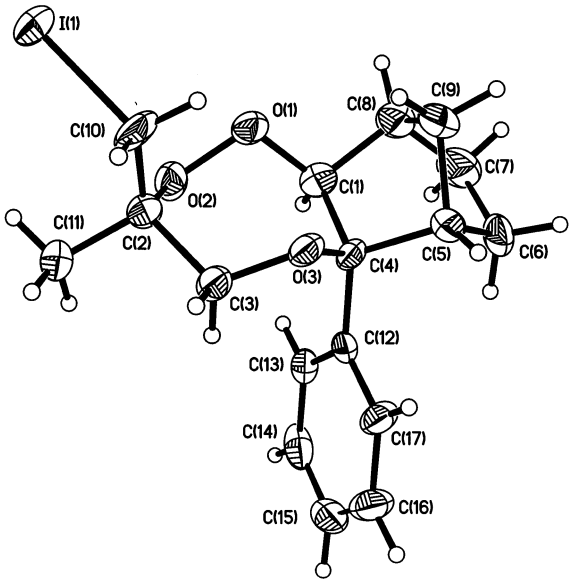


Figure 1. Crystal structure of compound **16** (two molecules per asymmetric unit; only molecule one shown for clarity).

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

	EC_{50} (μM)		
peroxide	*P. falciparum*[b]	FM3A[c]	selectivity[d]
12a	0.19	45	237
14a	1.5	13	9
14b	1.0	11	11
14c	0.21	11	52
14d	0.45	11	24
14e	0.13	5.9	45
15	0.15	11	73
16	1.0	11	11
17	0.005	15	3000
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} for FM3A cells)/(mean of EC_{50} for *P. falciparum*).

were determined against *P. falciparum* (FCR-3 strain).[3] A series of tetraoxacycloalkanes, **12a**, **14a**−**e**, and **15**, showed antimalarial activity against *P. falciparum* with EC_{50} values in the range 1.5×10^{-6} to 1.3×10^{-7} M, and the selectivity determined by the 50% inhibitory concentration against mouse mammary FM3A cells were in the range 9−237. As judged from a combination of their respective activity and selectivity, compounds **12a** and **14c** were found to be the most attractive. For trioxacycloalkane derivatives **16** and **17**, it is noted that the antimalarial activity of compound **17** (5.0×10^{-9} M) was comparable to that of artemisinin (Table 1).

In vivo antimalarial activities against *P. berghei* NK 65 strain[3] were then determined for the peroxides **12a**, **14c**, and **17**, which had shown significant activities in vitro. As indicated in Table 2, the ED_{50} value of **12a** (ED_{50} = 13 mg/kg) on intraperitoneal administration (ip) was 2.4 times of that of artemisinin (ED_{50} = 5.4 mg/kg) whereas **14c** showed only moderate activity (ED_{50} = 70 mg/kg). However, **12a** showed weak antimalarial activity on oral administration (po) ($ED_{50} \approx 100$ mg/kg). Most disappointing is the fact that the tricyclic peroxide **17**, the most active compound in vitro, was found to be inactive in vivo (ip, 100 mg/kg). Thus, it is evident that significant modification of the functionalization would be required in order to produce a significant antimalarial drug candidate based on the novel structure of the tricyclic peroxides prepared in this study.

Table 2. In Vivo Antimalarial Activities of Peroxides against *P. berghei* Infected Mice[a]

	ip		po	
peroxide	ED_{50}, mg/kg	ED_{90}, mg/kg	ED_{50}, mg/kg	ED_{90}, mg/kg
artemisinin	5.4	13	32	89
12a	13	50	>100 (45%[b])	
14c	70	>100 (70%[b])		

[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 days 1−3. 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.[3] [b] The value in parentheses shows the growth inhibition in each dose.

Summary

Trapping of the zwitterionic intermediate, generated from the reaction of 2-phenylnorbornene **1** and singlet oxygen, by aqueous H_2O_2, unsaturated hydroperoxides, or unsaturated alcohols provides a series of useful precursors for the synthesis of novel cyclic peroxides containing the 1,2,5,6-tetraoxacycloalkane and 1,2,5-trioxacycloalkane ring systems. Several of the cyclic peroxides prepared in this study showed significant antimalarial activity particularly in vitro.

Experimental Section

General Procedures. ^1H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the internal standard. Bis(collidine)iodine(I) hexafluorophosphate (BCIH) was prepared by the method reported by Simonot and Rousseau.[8]

Photooxidation of 2-Phenylnorbornene 1 in the Presence of Hydrogen Peroxide. A cooled (0 °C), oxygenated solution of **1** (290 mg, 1.71 mmol), 30% aqueous H_2O_2 (10 g), and tetraphenylporphine (1 mg) in CH_3CN (20 mL) was irradiated for 1.5 h with a 350 W high-pressure mercury lamp filtered through an aqueous $CuSO_4$ solution (>400 m). After extraction with Et_2O (50 mL), the organic layer was washed in turn with aqueous $NaHCO_3$ and saturated brine. Removal of solvent (room temp, 15 mmHg) yielded the crude 1,2-bishydroperoxide **3** as the sole product. Treatment of a solution of **3** in CH_2Cl_2 (404 mg, 1.71 mmol) with 3 equiv of triphenylphosphine (1344 mg, 5.13 mmol) at room temperature for 3 h followed by column chromatography on silica gel (elution with Et_2O−hexane, 40:60) gave the diol **4** (272 mg, 78%).

3-Hydroperoxy-2-phenyl-2-norbornyl hydroperoxide, 3: an oil; ^1H NMR δ 0.8−1.5 (m, 5 H), 2.1−2.2 (m, 1 H), 2.4−2.5 (m, 1 H), 2.5−2.6 (m, 1 H), 4.77 (s, 1 H), 7.1−7.5 (m, 5 H), 8.52 (br s, 1 H), 10.12 (br s, 1 H); ^{13}C NMR δ 23.56, 25.12, 34.81, 41.71, 46.18, 91.16, 95.65, 128.09, 128.27 (2 C), 128.52 (2 C), 138.54.

Reaction of Bishydroperoxide 3 with Diiodoalkanes. The reaction with 1,3-diiodopropane is representative. To a stirred solution of 1,3-diiodopropane (888 mg, 3 mmol) and Ag_2O (510 mg, 2.2 mmol) in CH_2Cl_2 (25 mL), was added bishydroperoxide **3** (472 mg, 2.0 mmol) by syringe over 1 h. The resulting mixture was stirred at room temperature for 16 h. After filtration of the solid material through Celite, Et_2O (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 was dried over anhydrous

$MgSO_4$. After evaporation of the solvent under vacuum, the products were isolated by column chromatography on silica gel, eluting initially with Et_2O−hexane (4:96) to give tetroxane **12a** (50 mg, 9%) followed by Et_2O−hexane (3:7) to give *cis*-3-benzoylcyclopentanecarbaldehyde **13**[9] (194 mg, 48%): an oil; ^{1}H NMR δ 1.9−2.4 (m, 6 H), 2.8−2.9 (m, 1 H), 3.8−3.9 (m, 1 H), 7.4−7.5 (m, 3 H), 7.9−8.0 (m, 2 H), 9.67 (s, 1 H); ^{13}C NMR δ 26.38, 29.63, 30.01, 46.11, 51.66, 128.39 (2 C), 128.59 (2 C), 133.06, 136.17, 201.24, 203.27.

2-Phenyl-3,4,8,9-tetraoxatricyclo[9.2.1.0^{2,10}]tetradecane, 12a: mp 140−142 °C (from methanol); ^{1}H NMR δ 1.1−1.6 (m, 6 H), 2.18 (d, J = 10.2 Hz, 1 H), 2.3−2.4 (m, 1 H), 2.4−2.5 (m, 1 H), 2.9−3.0 (m, 1 H), 3.93 (d × t, J = 10.2 and 10.2 Hz, 2 H), 4.42 (d, J = 10.2 Hz, 2 H), 4.74 (s, 1 H), 7.2−7.6 (m, 5 H); ^{13}C NMR δ 24.03, 24.82, 25.27, 35.65, 42.81, 47.93, 73.66, 73.96, 87.17, 93.82, 127.39 (2 C), 128.30 (2 C), 128.37, 140.17. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.10; H, 7.26.

TMSOTf-Catalyzed Cyclocondensation of Bisperoxide 5 with Carbonyl Compounds. The reaction with benzaldehyde is representative. Under an argon atmosphere, a solution of BSA (1218 mg, 6 mmol) in THF was added to a CH_2Cl_2 solution of bishydroperoxide **3** (708 mg, 3 mmol) at 0 °C for 10 min, and the mixture was stirred at room temperature for an additional 5 min. After concentration under reduced pressure, the residue was separated by column chromatography on silica gel. Elution with Et_2O−hexane (2:98) gave the bisperoxide 2,3-bis[(trimethylsilyl)dioxy]-2-phenylnorbornane **5** (638 mg, 56%): an oil; ^{1}H NMR δ 0.15 (s, 9 H), 0.27 (s, 9 H), 1.0−1.6 (m, 5 H), 2.3−2.4 (m, 1 H), 2.6 (m, 1 H), 3.0−3.1 (m, 1 H), 4.48 (s, 1 H), 7.2−7.6 (m, 5 H); ^{13}C NMR δ −1.62 (3 C), −1.26 (3 C), 23.36, 25.70, 34.05, 40.30, 42.19, 94.56, 95.02, 127.30 (2 C), 127,44, 130.08 (2 C), 139.34.

To a stirred solution of bisperoxide **5** (322 mg, 0.85 mmol) and benzaldehyde (180 mg, 1.70 mmol) in CH_2Cl_2 (25 mL) was added TMSOTf (111 mg, 0.5 mmol) by syringe over 10 min at −70 °C. Stirring was continued at 0 °C for an additional 1.5 h. The products were isolated by column chromatography on silica gel, eluting initially with Et_2O−hexane (1:25) to give the tetroxepane **14a** (64 mg, 23%) and subsequently with Et_2O−hexane (1:9) to give keto aldehyde **13** (62 mg, 36%).

2,5-Diphenyl-3,4,6,7-tetraoxatricyclo[7.2.1.0^{2,8}]dodecane, 14a: mp 133 °C (from ethyl acetate−hexane); ^{1}H NMR δ 0.9−1.0 (m, 1 H), 1.1−1.4 (m, 3 H), 1.5−1.6 (m, 1 H), 2.3−2.4 (m, 2 H), 2.5−2.6 (m, 1 H), 5.21 (s, 1 H), 6.65 (s, 1 H), 7.1−7.7 (m, 10 H); ^{13}C C NMR δ 23.76 (CH), 23.87 (CH), 35.08 (CH), 41.42 (CH), 47.12 (CH), 91.45 (CH), 98.62, 109.33 (CH), 127.12 (2C, CH), 127.42 (CH), 127.48 (CH), 127.69 (CH), 128.21 (CH), 128.41 (2 C, CH), 128.79 (CH), 130.05 (CH), 130.67, 139.87. Anal. ($C_{20}H_{20}O_4$) C, H.

Preparation of Cyclic Peroxide 15. By the procedure described before, a solution of 2-phenylindene **1** (550 mg, 3.2 mmol), 3-methyl-3-butenyl hydroperoxide **6** (2.0 g, 20 mmol), and rose bengal (5 mg) in CH_3CN (10 mL) was irradiated at 0 °C for 5 h under oxygen atmosphere. After workup, the products were separated by column chromatography on silica gel. Elution with Et_2O−hexane (5:95) gave the unsaturated hydroperoxide 3-[(3-methyl-3-butenyl)dioxy]-3-phenyl-2-norbornyl hydroperoxide **9** (241 mg, 25%): an oil; ^{1}H NMR δ 0.9−1.4 (m, 5 H), 1.39 (s, 3 H), 1.9−2.0 (m, 3 H), 2.1−2.2 (m, 1 H), 2.5−2.6 (m, 1H), 3.5−3.6 (m, 1 H), 3.7−3.8 (m, 1 H), 4.44 (s, 1 H), 4.56 (s, 1 H), 4.70 (s, 1 H), 7.2−7.7 (m, 5 H), 10.2 (s, 1 H); ^{13}C NMR δ 22.0, 23.6, 26.0, 34.9, 35.7, 42.2, 46.2, 72.6, 91.2, 95.0, 112.0, 127.8, 127.9 (2 C), 129.1 (2 C), 138.9, 141.4.

To CH_2Cl_2 (5 mL) were concurrently added a CH_2Cl_2 (5 mL) solution of the unsaturated hydroperoxide **9** (140 mg, 0.46 mmol) and a CH_2Cl_2 (5 mL) solution of BCIH (473 mg, 0.92 mmol) over 30 min, and then the reaction mixture was stirred at room temperature for 1 h (the flask was covered with aluminum foil). The reaction mixture was poured into aqueous $Na_2S_2O_3$ (20 mL) and extracted with Et_2O (30 mL × 2). The combined organic layer was washed with 0.2 N HCl (50 mL) and aqueous sodium bicarbonate (30 mL) and was dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the product was isolated by column chromatography on silica gel. Elution with Et_2O−hexane (4:96) gave the cyclic peroxide **15** (120 mg, 61%).

7-Iodomethyl-7-methyl-2-phenyl-3,4,8,9-tetraoxatricyclo[9.2.1.0^{2,10}]tetradecane, 15: mp 150−152 °C (from hexane); ^{1}H NMR δ 0.8−1.4 (m, 5 H), 1.42 (s, 3 H), 2.0−2.1 (m, 1 H), 2.2−2.3 (m, 1 H), 2.4−2.5 (m, 1 H), 2.9−3.1 (m, 2 H), 2.94 (d, J = 10.2 Hz, 1 H), 2.99 (d, J = 10.2 Hz, 1 H), 3.6−3.7 (m, 1 H), 4.1−4.2 (m, 1 H), 4.63 (br s, 1 H), 7.2−7.5 (m, 5 H); ^{13}C NMR δ 8.2, 24.0, 25.1, 25.4, 31.3, 35.4, 42.4, 47.7, 68.9, 81.6, 87.4, 93.6, 127.3, 128.0, 128.2, 128.4, 128.9, 139.6. Anal. ($C_{18}H_{23}IO_4$) C, H, I.

Preparation of Unsaturated Hydroperoxides 10 and 11. The preparation of **10** is representative. A solution of 2-phenylindene **1** (340 mg, 2.0 mmol), methallyl alcohol **7** (2.9 g, 40 mmol), and rose bengal (5 mg) in CH_3CN (10 mL) was irradiated at 0 °C for 5 h under an oxygen atmosphere. After workup, the reaction products were isolated by column chromatography on silica gel. Elution with Et_2O−hexane (5:95) gave **10** (66 mg, 12%).

3-(2-Methyl-2-propenyloxy)-3-phenyl-2-norbornyl hydroperoxide, 10: an oil; ^{1}H NMR δ 1.1−1.4 (m, 3 H), 1.5−1.7 (m, 2 H), 1.59 (s, 3 H), 2.3−2.4 (m, 2 H), 3.0−3.1 (m, 1 H), 3.24 (d, J = 11.6 Hz, 1 H), 3.79 (d, J = 11.6 Hz, 1 H), 4.53 (s, 1 H), 4.67 (s, 1 H), 4.88 (s, 1 H), 7.2−7.4 (m, 3 H), 7.6−7.7 (m, 2 H), 9.94 (s, 1 H); ^{13}C NMR δ 19.79, 23.92, 25.48, 34.32, 40.18, 40.95, 66.52, 90.23, 93.26, 111.70, 128.03 (2 C), 127.91, 130.28 (2 C), 138.28, 141.96.

3-(3-Methyl-3-butenyloxy)-3-phenyl-2-norbornyl hydroperoxide, 11: an oil; ^{1}H NMR δ 0.9−2.1 (m, 9 H), 1.33 (s, 3 H), 2.9−3.0 (m, 2 H), 3.4−3.6 (m, 1 H), 4.46 (br s, 1 H), 4.63 (s, 1 H), 4.69 (s, 1 H), 7.2−7.4 (m, 3 H), 7.6−7.7 (m, 2 H), 9.94 (s, 1 H); ^{13}C NMR δ 21.2, 24.1, 25.7, 34.2, 38.3, 39.9, 41.0, 59.0, 89.9, 92.9, 112.2, 127.7, 127.8 (2 C), 130.3 (2 C), 138.2, 143.1.

Reaction of Unsaturated Hydroperoxides 10 and 11 with BCIH. The reaction of **10** is representative. A solution of the unsaturated hydroperoxide **10** (160 mg, 0.58 mmol) and BCIH (600 mg, 1.2 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 1 h. After workup, the products were separated by column chromatography on silica gel. Elution with Et_2O−hexane (2:98) gave peroxide **16** (120 mg, 52%).

5-Iodomethyl-5-methyl-8-phenyl-3,4,7-trioxabicyclo-[7.2.1.0^{2,8}]dodecane, 16: mp 89−90 °C (from hexanes−Et_2O); ^{1}H NMR δ 0.6−1.6 (m, 5 H), 0.90 (s, 3 H), 2.2−2.5 (m, 3 H), 3.36 (d, J = 13.5 Hz, 1 H), 3.53 (d, J = 10.4 Hz, 1 H), 3.66 (d, J = 13.5 Hz, 1 H), 4.46 (d, J = 10.4 Hz, 1 H), 4.89 (br s, 1 H), 7.5−7.5 (m, 5 H); ^{13}C NMR δ 12.5, 20.8, 23.4, 24.0, 35.3, 41.7, 49.8, 71.3, 82.1, 90.7, 91.7, 127.5, 127.7, 127.9, 128.1, 129.1, 139.9. Anal. ($C_{17}H_{21}IO_3$) C, H.

5-Iodomethyl-5-methyl-9-phenyl-3,4,8-trioxatircyclo-[8.2.1.0^{2,9}]tridecane, 17: an oil (ca. 1:1 mixture of isomers); ^{1}H NMR δ 0.7−1.6 (m, 5 H), 0.97 (s, 3 H), 2.2−2.5 (m, 3 H), 2.77 (d, J = 10.4 Hz, 1 H), 2.89 (d, J = 10.4 Hz, 1 H), 3.0−3.1 (m, 1 H), 3.3−3.4 (m, 1 H), 3.36 (d, J = 10.2 Hz, 1 H), 3.62 (d, J = 10.2 Hz, 1 H), 4.66 (br s, 1 H), 7.3−7.5 (m, 5 H); ^{13}C NMR δ 10.7, 15.6, 22.6, 23.7, 25.2, 26.6, 35.1, 39.1, 41.3, 41.4, 50.7, 50.8, 60.6, 61.3, 80.0, 80.3, 86.5, 86.7, 91.7, 91.8, 127.36, 127.42, 127.44, 127.51, 128.32, 128.47, 128.51, 128.67, 128.71, 140.73. HRMS (EI, M^+) m/z calcd for $C_{18}H_{23}IO_3$: 414.0692. Found: 414.0699. Anal. ($C_{18}H_{23}IO_3$) C, H.

Determination of the X-ray Crystal Structure of Compound 16. The X-ray diffraction data were collected on a Brucker AXS P4 diffractometer at 160 K using graphite-monochromated Mo Kα, λ = 0.710 73 Å. The structure was solved by direct methods and refined using least-squares techniques. All crystallographic calculations and preparation of structure plots and tables were carried out using the SHELXTL PC suite of programs.[10]

Crystal Data for Compound 16: $C_{17}H_{21}IO_3$, MW = 400.24, colorless needles, triclinic, space group $P\bar{1}$ (No. 2), a = 8.287(3) Å, b = 9.460(4) Å, c = 22.137(8) Å, α = 80.54(3)°, β = 84.27(3)°, γ = 74.81(4)°, U = 1649.1(11) Å^3, Z = 4, D_c = 1.612 g cm^{-3}, $F(000)$ = 800, μ(Mo Kα) = 1.949 mm^{-1}, final discrepancy factors R1 = 0.084 and wR2 = 0.240.

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Supporting Information Available: Physical properties of compounds **4**, **12b**, and **14b**−**e**, elemental analysis data for all new cyclic peroxides, and X-ray crystallographic data for compound **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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