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Synthesis of 1,2,4-Trioxepanes and 1,2,4-Trioxocanes via Photooxygenation of Homoallylic Alcohols[1]

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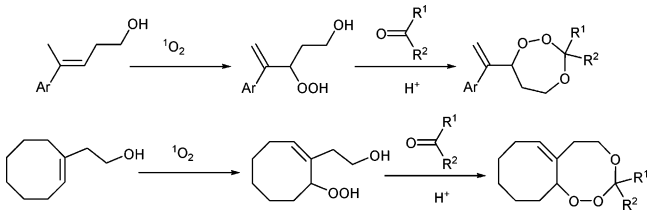
Received July 7, 2006



Homoallylic alcohols **4a**−**d**, easily accessible in two steps from cyclopropyl methyl ketone, underwent a highly regioselective reaction with singlet oxygen to yield γ-hydroxyhydroperoxides **5a**−**d** in 57−72% yield. Acid-catalyzed reaction of **5a**−**d** with acetone, cyclopentanone, and cyclohexanone furnished 1,2,4-trioxepanes **8a**−**d**, **9a**−**d**, and **10a**−**d** in good yields. Homoallylic alcohol **12** also underwent a highly regioselective photooxygenation to yield δ-hydroxyhydroperoxide **13** in 67% yield, which on reaction with acetone, cyclopentanone, and cyclohexanone, furnished 1,2,4-trioxocanes **16**−**18** in 41−55% yield.

Introduction

Ever since its isolation as the active principle of the Chinese traditional antimalarial drug, *Artemisia annua*, artemisinin (Quinghaosu **1**, Figure 1) has been a subject of intense structure activity relationship studies. Much of the early efforts were directed toward total synthesis and derivatization of artemisinin.[2] However, currently, the focus is on the synthesis and antimalarial assessment of structurally simplified 1,2,4-trioxanes, and a variety of methods of their synthesis has been reported in recent years.[3] In contrast, 1,2,4-trioxepanes and 1,2,4-trioxocanes, the next obvious candidates for SAR studies in this area, have received only limited attention. Only a few methods of their synthesis have been reported,[4−6] the number of compounds synthesized is small, and there is no report on their antimalarial activity. The crucial step in the synthesis of these oxygen heterocycles is the introduction of the hydroperoxy group. In the reported methods, this has been achieved by (i) acid-catalyzed reaction of tertiary alcohols with concentrated hydrogen peroxide,[4] (ii) cobalt-catalyzed oxygenation of cinnamyl alcohol,[5] and (iii) ozonolysis of enol ethers.[6]

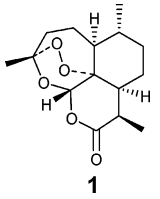


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FIGURE 1. Artemisinin.

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(1) CDRI communication no. 5408.

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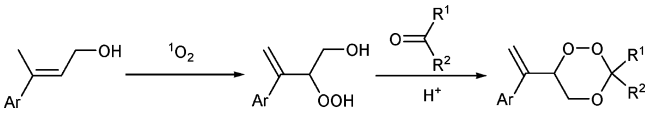
10.1021/jo061414z CCC: $33.50
Published on Web 10/26/2006

SCHEME 1



As part of our endeavor to produce synthetic substitutes for artemisinin and its derivatives, we had earlier reported a novel photooxygenation route for the synthesis of 1,2,4-trioxanes. Preparation of β-hydroxyhydroperoxides by the photooxygenation of allylic alcohols and their acid-catalyzed reaction with ketones are the key steps of this method (Scheme 1).[7] Several of the 1,2,4-trioxanes prepared by this method had shown promising antimalarial activity.[8]

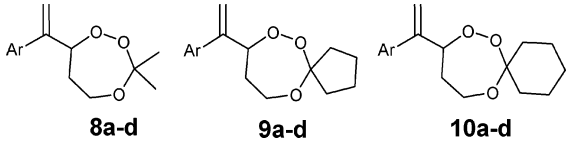


FIGURE 2. 1,2,4-Trioxepanes.

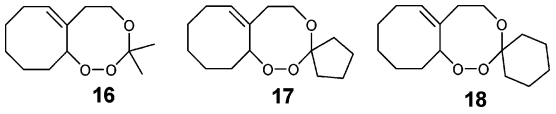


FIGURE 3. 1,2,4-Trioxocanes.

The high regioselectivity of the photooxygenation reaction of allylic alcohols[9] has prompted us to explore the scope of this reaction for the preparation of 1,2,4-trioxepanes and 1,2,4-trioxocanes. Herein, we report the preparation of γ-hydroxyhydroperoxides by regioselective photooxygenation of 4-arylpent-3-enols **4a**−**d** and their elaboration into 1,2,4-trioxepanes **8a**−**d**, **9a**−**d**, and **10a**−**d** (Figure 2). We also report the preparation of δ-hydroxyhydroperoxide **13** by the photooxygenation of 2-cyclooct-1-enyl-ethanol **12** and its elaboration into 1,2,4-trioxocanes **16**, **17**, and **18** (Figure 3). While the photooxygenation of homoallylic alcohols has been investigated earlier,[10] to the best of our knowledge, this is the first paper on elaboration of the photooxygenation products into 1,2,4-trioxepanes and 1,2,4-trixocanes.

SCHEME 2

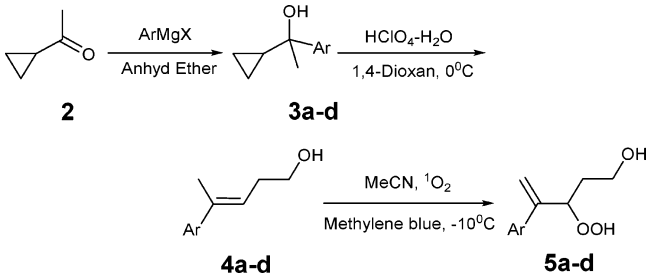
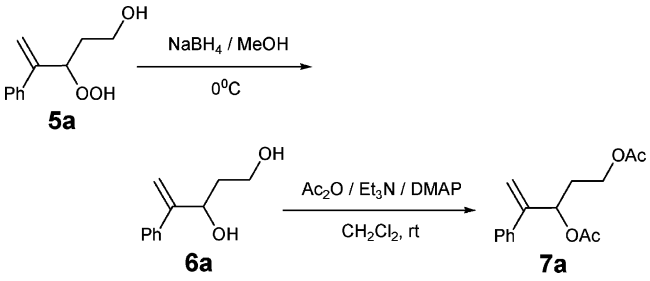


TABLE 1. Preparation of γ-Hydroxyhydroperoxides from Homoallylic Alcohols

compound	Ar	reaction time (h)	yield %
5a	phenyl	3	72
5b	4-chloro-phenyl	3	57
5c	4-biphenyl	3	62
5d	1-naphthyl	27	68

SCHEME 3



Results and Discussion

Homoallylic alcohols **4a**−**d**, easily accessible[11] in two steps from cyclopropyl methyl ketone **2**, on photooxygenation furnished γ-hydroxyhydroperoxides **5a**−**d** in 57−72% yield (Scheme 2 and Table 1). To firmly secure the structures of the γ-hydroxyhydroperoxides, compound **5a** was reduced with $NaBH_4$ to give diol **6a** (79% yield), which on acetylation with Ac_2O/Et_3N/DMAP at room temperature furnished diacetate **7a** (93% yield) that gave satisfactory ^{1}H NMR, ^{13}C NMR, and HRMS data (Scheme 3).

The regioselectivity of the photooxygenation reaction of **4a**−**d** was comparable with that of the photooxygenation of allylic alcohols (Scheme 1) and is largely due to the directing effect of the aryl group. Similar levels of regioselectivity have earlier been reported in the photooxygenation of silyl substituted homoallylic alcohol **A**, and the high level of regioselectivity has been attributed to the directing effect of the silyl group, as the structurally similar homoallylic alcohol **C** lacking the silyl group is reported to give both γ- and δ-hydroxyhydroperoxides in a 60:40 ratio (Scheme 4).[10]

γ-Hydroxyhydroperoxide **5a** on reaction with acetone, cyclopentanone, and cyclohexanone in the presence of catalytic amounts of HCl at room temperature furnished 1,2,4-trioxepanes **8a**, **9a**, and **10a** in 64, 63, and 52% yields, respectively. A similar reaction of γ-hydroxyhydroperoxide **5d** with acetone, cyclopentanone, and cyclohexanone furnished 1,2,4-trioxepanes **8d**, **9d**, and **10d** in 66, 38, and 44% yields, respectively. For the preparation of the 1,2,4-trioxepanes **8b**−**c**, **9b**−**c**, and **10b**−

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SCHEME 4

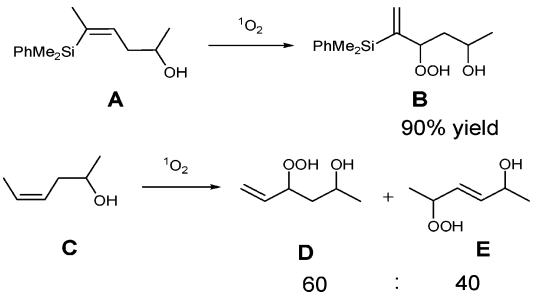
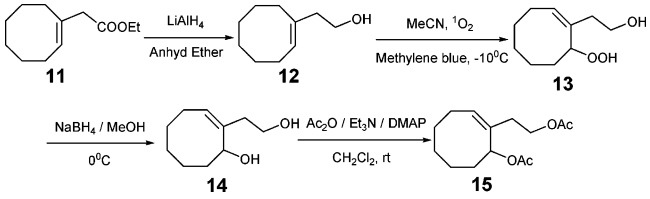


TABLE 2. Preparation of 1,2,4-Trioxepanes

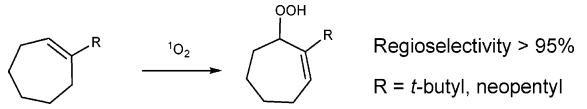
compound	Ar	yield %	mp (°C)	a/b[a]
8a	C_6H_5	64	oil	a
8b	4-Cl-C_6H_4	51	41−42	b
8c	4-biphenyl	46	81−84	b
8d	1-naphthyl	66	oil	a
9a	C_6H_5	63	oil	a
9b	4-Cl-C_6H_4	48	oil	b
9c	4-biphenyl	35	73−75	b
9d	1-naphthyl	38	oil	a
10a	C_6H_5	52	oil	a
10b	4-Cl-C_6H_4	48	oil	b
10c	4-biphenyl	43	83−86	b
10d	1-naphthyl	44	oil	a

[a] a: Yield based on γ-hydroxyhydroperoxide. b: Yield based on homoallylic alcohol.

SCHEME 5



SCHEME 6



c, γ-hydroxyhydroperoxides were not isolated and were reacted *in situ* with the appropriate ketones to furnish the 1,2,4-trioxepanes in 35−51% overall yield (Table 2 and Figure 2).

Photooxygenation of homoallylic alcohol **12**, prepared by $LiAlH_4$ reduction of ester **11**,[12] exhibited regioselectivity of a different sort and furnished δ-hydroxyhydroperoxide **13** as the sole isolable product in 67% yield. The reaction of hydroperoxide **13** with $NaBH_4$ furnished diol **14** in 73% yield, which on treatment with Ac_2O/Et_3N/DMAP furnished diacetate **15** in 85% yield (Scheme 5).

The regioselectivity observed in the photooxygenation reaction of **12** is similar to that of observed in the photooxygenation of 1-*t*-butyl and 1-neopentyl substituted cycloheptenes (Scheme 6).[13]

The acid-catalyzed reaction of δ-hydroxyhydroperoxide **13** with acetone, cyclopentanone, and cyclohexanone furnished 1,2,4-trioxocanes **16**, **17**, and **18** in 55, 41, and 48% yields, respectively (Figure 3).

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In conclusion, we have developed a highly convenient method for the preparation of γ- and δ-hydroxyhydroperoxides by the photooxygenation of homoallylic alcohols and their elaboration into 1,2,4-trioxepanes and 1,2,4-trioxocanes.[14] The method is safe and can be used for the preparation of these oxygen heterocycles on the gram scale.

Experimental Procedures

General Procedure for the Preparation of γ-Hydroxyhydroperoxides (Preparation of 3-Hydroperoxy-4-phenyl-pent-4-en-1-ol (5a) as Representative). A solution of homoallylic alcohol **4a** (2.5 g) and methylene blue (75 mg) in acetonitrile (250 mL) was irradiated with a 500 W tungsten−halogen lamp at −10 °C, while a slow stream of O_2 was bubbled into the reaction mixture. After 3 h, the reaction mixture was concentrated under vacuum at room temperature, and the crude product was purified by column chromatography over 60−120 mesh silica gel (deactivated with 12% v/w of water) using 25% ethyl acetate−hexane as an eluent to furnish 2.15 g (72% yield) of γ-hydroxyhydroperoxide **5a** as a colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85 (q, 2H, J = 5.9 Hz), 3.66−3.81 (m, 2H), 5.03 (t, 1H, J = 6.4 Hz), 5.40 and 5.46 (2 × s, 2H), 7.25−7.40 (m, 5H), 9.51 (1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.2, 59.6, 85.5, 115.2, 126.8, 127.7, 128.3, 139.3, 147.3; MS (*m*/*z*) 195 $(M + H)^+$.

4-(4-Chloro-phenyl)-3-hydroperoxy-pent-4-en-1-ol (5b). Yield 57%, oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69−1.93 (m, 3H), 3.68−3.84 (m, 2H), 5.01 (q, 1H, J = 5.3 Hz), 5.43 and 5.47 (2 × s, 2H), 7.29−7.38 (m, 4H), 9.02 (brs,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.6, 60.0, 85.9, 116.4, 128.7, 128.9, 134.2, 138.1, 146.8; MS (*m*/*z*) 211 $(M + H - H_2O)^+$, 193 $(M + H - 2H_2O)^+$.

4-Biphenyl-4-yl-3-hydroperoxy-pent-4-en-1-ol (5c). Yield 62%, mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87−1.93 (m, 2H), 2.35 (brs, 1H) 3.68−3.84 (m, 2H), 5.08 (t, 1H, J = 6.3 Hz), 5.52 and 5.43 (2 × s, 2H), 7.30−7.58 (m, 9H), 9.52 (brs,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.8, 60.2, 86.1, 115.6, 127.4, 127.5, 127.7, 129.2, 138.6, 140.9, 141.1,147.4; MS (*m*/*z*) 271 $(M + H)^+$.

3-Hydroperoxy-4-naphthyl-pent-4-en-1-ol (5d). Yield 68%, oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.81 (m, 2H), 3.59−3.69 (m, 2H), 4.92 (dd, 1H, J = 9.0, 3.2 Hz), 5.31 and 5.75 (2 × s, 2H), 7.30−7.45 (m, 5H), 7.74−7.82 (m, 2H), 8.10−8.12 (m, 1H), 9.89 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.4, 60.4, 87.4, 117.5, 125.6, 125.9, 126.2, 126.6, 128.4, 128.8, 132.0, 134.2, 138.1, 147.1; MS (*m*/*z*) 267 $(M + Na)^+$.

General Procedure for the Preparation of 1,2,4-Trioxepanes from Homoallylic Alcohols (Preparation of 9-[1-(4-Chlorophenyl)-vinyl]-7,8,12-trioxa-spiro[5.6] Dodecane (10b) as Representative). A solution of homoallylic alcohol **4b** (2 g) and methylene blue (50 mg) in acetonitrile (200 mL) was irradiated with 500 W tungsten−halogen lamp at −10 °C, while a slow stream of O_2 was bubbled into the reaction mixture. After 3 h, cyclohexanone (2.6 mL, 2.5 equiv) and conc HCl (0.5 mL) were added into the reaction mixture and stirred for 1.5 h at room temperature. After the completion of the reaction, the reaction mixture was concentrated on a rotatory evaporator at room temperature, and the crude product was purified over 60−120 mesh silica gel using 0.5% ethyl acetate−hexane as eluent to furnish 1.51 g (48% yield) of **10b** as a colorless oil.

General Procedure for the Preparation of 1,2,4-Trioxepanes from γ-Hydroxyhydroperoxides (Preparation of 8-(1-Phenyl-vinyl)-6,7,11-trioxa-spiro[4.6] Undecane (9a) as Representative). A solution of γ-hydroxyhydroperoxide **5a** (2.3 g), cyclopentanone (2.6 mL, 2.5 equiv), and conc HCl (0.5 mL) in dichloromethane (50 mL) was stirred for 1 h at room temperature. The reaction

(14) Some of these compounds have been tested for antimalarial activity in mice models and have shown moderate activity. The activity data of these compounds will be reported elsewhere.

mixture was concentrated on a rotatory evaporator at room temperature, and the crude product was purified by column chromatography over 60−120 mesh silica gel using 0.5% ethyl acetate−hexane as eluent to furnish 1.95 g (63% yield) of **9a** as a colorless oil.

3,3-Dimethyl-7-(1-phenyl-vinyl)-[1,2,4] Trioxepane (8a). Yield 64%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.51 (s, 3H), 1.80−1.87 (m, 1H), 2.09 (m, 1H,) 3.76 (td, 1H, J = 12.3, 3.3 Hz), 4.02 (t, 1H, J = 12.3 Hz), 5.06 (dd, 1H, J = 11.2, 3.2 Hz), 5.36 & 5.43 (2 × s, 2H), 7.27−7.44 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 25.3, 37.4, 61.0, 85.7, 106.9, 116.2, 127.0, 128.2, 128.8, 140.1, 146.5; MS (*m/z*) 235 $(M + H)^+$; HRMS Calcd. for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1240.

7-[1-(4-Chloro-phenyl)-vinyl]-3,3-dimethyl-[1,2,4] Trioxepane (8b). Yield 51%, mp 41−42 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.49 (s, 3H), 1.78−1.85 (m, 1H), 2.04−2.16 (m, 1H), 3.76 (td, 1H, J = 12.4, 3.2 Hz), 4.02 (t, 1H, J = 12.4 Hz), 5.00 (dd, 1H, J = 11.2, 2.8 Hz), 5.38 and 5.43 (2 × s, 2H), 7.27−7.41 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 25.3, 37.1, 60.9, 85.6, 106.9, 117.0, 128.4, 128.9, 134.1, 138.4, 145.3; MS (*m/z*) 295, 297 $(M + H)^+$; Anal. Calcd for $C_{14}H_{17}O_3Cl + 0.2H_2O$: C, 61.74; H, 6.43. Found: C, 61.43; H, 6.79.

7-(1-Biphenyl-4-yl-vinyl)-3,3-dimethyl-[1,2,4] Trioxepane (8c). Yield 46%, mp 81−84 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.53 (s, 3H), 1.84−1.92 (m, 1H), 2.14 (m, 1H,), 3.78 (td, 1H, J = 12.4, 3.4 Hz), 4.05 (t, 1H, J = 12.4 Hz), 5.11 (dd, 1H, J = 11.2, 3.3 Hz), 5.39 and 5.50 (2 × s, 2H), 7.33−7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 25.4, 37.4, 61.1, 85.6, 106.9, 116.2, 127.4, 127.5, 127.8, 129.2, 138.9, 141.1, 146.0; MS (*m/z*) 310 M^+; HRMS Calcd for $C_{20}H_{22}O_3$: 310.1569. Found: 310.1580.

3,3-Dimethyl-7-(1-naphthyl-vinyl)-[1,2,4] Trioxepane (8d). Yield 66%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.53 (s, 3H), 1.76−1.86 (m, 1H), 1.93−2.13 (m, 1H,), 3.67 (td, 1H, J = 12.4, 3.4 Hz), 3.89 (dt, 1H, J = 12.3, 1.3 Hz), 4.95 (dd, 1H, J = 11.0, 3.3 Hz), 5.28 and 5.68 (2 × s, 2H), 7.28−7.50 (m, 4H), 7.77−7.87 (m, 2H), 7.99−8.02 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 25.2, 37.8, 60.9, 86.6, 106.9, 118.4, 125.6, 126.1, 126.2, 126.3, 126.6, 128.3, 128.7, 131.9, 134.1, 138.9, 146.6; MS (*m/z*) 284 M^+; HRMS Calcd. for $C_{18}H_{20}O_3$: 284.1413. Found: 284.1417.

8-(1-Phenyl-vinyl)-6,7,11-trioxa-spiro[4.6] Undecane (9a). Yield 63%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62−1.91 (m, 8H), 2.06−2.21 (m, 2H), 3.81 (td, 1H, J = 12.2, 3.5 Hz), 3.97 (dt, 1H, J = 12.2, 1.3 Hz), 5.11 (dd, 1H, J = 11.0, 3.5 Hz), 5.36 and 5.42 (2 × s, 2H), 7.25−7.43 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 34.9, 36.4, 37.4, 62.4, 85.8, 116.2, 118.4, 127.1, 128.1, 128.8, 140.1, 146.6; MS (*m/z*) 261 $(M + H)^+$; Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.93; H, 7.94.

8-[1-(4-Chloro-phenyl)-vinyl]-6,7,11-trioxa-spiro[4.6] Undecane (9b). Yield 48%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68−1.89 (m, 8H), 2.03−2.21 (m, 2H), 3.82 (td, 1H, J = 12.1, 3.5 Hz), 3.97 (dt, 1H, J = 12.1, 1.3 Hz), 5.06 (dd, 1H, J = 11.0, 3.2 Hz), 5.39 and 5.43 (2 × s, 2H), 7.27−7.46 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 34.8, 36.4, 37.0, 62.3, 85.6, 116.9, 118.4, 128.5, 128.9, 134.1, 138.4, 145.4; MS (*m/z*) 295, 297 $(M + H)^+$; HRMS Calcd for $C_{16}H_{19}O_3Cl$: 294.1023. Found: 294.1044.

8-(1-Biphenyl-4-yl-vinyl)-6,7,11-trioxa-spiro[4.6] Undecane (9c). Yield 35%, mp 73−75 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71−1.75 (m, 8H), 1.88−1.95 (m, 1H), 2.08−2.24 (m, 1H), 3.85 (td, 1H, J = 12.3, 3.5 Hz), 4.00 (t, 1H, J = 12.3 Hz), 5.15 (dd, 1H, J = 11.2, 3.6 Hz), 5.40−5.50 (2 × s, 2H), 7.34−7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.4, 34.9, 36.5, 37.3, 62.4, 85.7, 116.2, 118.5, 127.4, 127.5, 127.8, 129.2, 138.9, 141.0, 146.2; MS (*m/z*) 337 $(M + H)^+$; Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.28; H, 7.26.

8-(1-Naphthyl-vinyl)-6,7,11-trioxa-spiro[4.6] Undecane (9d). Yield 38%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68−1.79 (m, 7H), 1.86−1.87 (m, 1H) 2.02−2.16 (m, 2H), 3.72 (td, 1H, J = 12.1, 3.6 Hz), 3.84 (dt, 1H, J = 12.1, 1.5 Hz), 5.00 (dd, 1H, J = 10.8, 3.4 Hz), 5.27 and 5.68 (2 × s, 2H), 7.29−7.50 (m, 4H), 7.76−7.86 (m, 2H), 8.00 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 34.9, 36.4, 37.7, 62.4, 86.6, 118.2, 118.4, 125.6, 126.0, 126.2, 126.3, 126.5, 128.2, 128.6, 131.9, 134.1, 138.9, 146.6; MS (*m/z*) 311 $(M + H)^+$; HRMS Calcd for $C_{20}H_{22}O_3$: 310.1569. Found: 310.1547.

9-(1-Phenyl-vinyl)-7,8,12-trioxaspiro[5.6] Dodecane (10a). Yield 52%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40−2.16 (m, 12H), 3.75 (td, 1H, J = 12.3, 3.3 Hz), 4.03 (dt, 1H, J = 12.3, 1.0 Hz), 5.04 (dd, 1H, J = 11.2, 3.4 Hz), 5.35 and 5.41 (2 × s, 2H), 7.29−7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1, 23.5, 25.8, 32.0, 34.6, 37.8, 60.7, 85.8, 107.0, 116.2, 127.1, 128.1, 128.8, 140.1, 146.8; MS (*m/z*) 275 $(M + H)^+$; Anal. Calcd for $C_{17}H_{22}O_3 + 0.1H_2O$: C, 73.93; H, 8.10. Found: C, 74.63; H, 8.58.

9-[1-(4-Chloro-phenyl)-vinyl]-7,8,12-trioxa-spiro[5.6] Dodecane (10b). Yield 48%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42−2.16 (m, 12H), 3.76 (td, 1H, J = 12.3, 3.1 Hz), 4.03 (t, 1H, J = 12.3 Hz), 5.00 (dd, 1H, J = 11.2, 3.2 Hz), 5.38 and 5.42 (2 × s, 2H), 7.31−7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1, 23.5, 25.8, 31.9, 34.6, 37.5, 60.6, 85.8, 107.1, 117.1, 128.5, 128.9, 134.1, 138.5, 145.5; MS (*m/z*) 309 $(M + H)^+$; Anal. Calcd for $C_{17}H_{21}O_3Cl + 0.1\ H_2O$: C, 65.73; H, 6.88. Found: C, 65.57; H, 6.89.

9-(1-Biphenyl-4-yl-vinyl)-7,8,12-trioxa-spiro[5.6] Dodecane (10c). Yield 43%, mp 83−86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43−2.14 (m, 12H), 3.78 (td, 1H, J = 12.3, 3.3 Hz), 4.06 (t, 1H, J = 12.3 Hz), 5.09 (dd, 1H, J = 11.2, 3.3 Hz), 5.39 and 5.49 (2 × s, 2H), 7.33−7.62 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2, 23.5, 25.8, 32.0, 34.6, 37.8, 60.6, 85.8, 107.1, 116.2, 127.4, 127.5, 127.8, 129.2, 138.9, 141.0, 146.2; MS (*m/z*) 351 $(M + H)^+$; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.82; H, 7.47. Found: C, 78.69; H, 7.76.

9-(1-Naphthyl-vinyl)-7,8,12-trioxa-spiro[5.6] Dodecane (10d). Yield 44%, oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42−1.62 (m, 10 H), 1.73−1.97 (m, 2H) 3.67 (td, 1H, J = 12.4, 3.4 Hz), 3.91 (dt, 1H, J = 12.3, 1.3 Hz), 4.94 (dd, 1H, J = 10.8, 3.1 Hz), 5.27 and 5.67 (2 × s, 2H), 7.28−7.50 (m, 4H), 7.76−7.86 (m, 2H), 8.00−8.05 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1, 23.4, 25.8, 31.9, 34.5, 38.1, 60.6, 86.6, 107.0, 118.3, 125.6, 126.2, 126.3,126.5, 128.2, 128.6, 134.1, 138.9, 146.6; MS (*m/z*) 324 M^+; HRMS Calcd for $C_{21}H_{24}O_3$: 324.1726. Found: 324.1721.

2-(8-Hydroperoxy-cyclooct-1-enyl)ethanol) (13). A solution of homoallylic alcohol **12** (3.2 g) and methylene blue (75 mg) in acetonitrile (300 mL) was irradiated with a 500 W tungsten−halogen lamp at −10 °C, while a slow stream of O_2 was bubbled into the reaction mixture. After 3 h, the reaction mixture was concentrated under vacuum at room temperature, and the crude product was purified by column chromatography over 60−120 mesh silica gel (deactivated with 12% v/w of water) using 25% ethyl acetate−hexane as eluent to furnish 2.59 g (67% yield) of δ-hydroxyhydroperoxide **13** as a colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28−1.80 (m, 6H), 2.11−2.18 (m, 4H), 2.40−2.42 (m, 2H) 3.79 (td, 1H, J = 10.0, 3.4 Hz), 3.99−4.10 (m, 1H), 5.16 (dd, 1H, J = 12.0, 4.6 Hz), 5.78 (t, 1H, J = 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.6, 27.2, 27.8, 30.9, 31.8, 64.6, 83.9, 130.9, 138.5; MS (*m/z*) 169 $(M + H - H_2O)^+$.

General Procedure for the Preparation of 1,2,4-Trioxocanes from δ-Hydroxyhydroperoxide (Preparation of 17 as Representative). A solution of δ-hydroxyhydroperoxide **13** (2.0 g), cyclopentanone (2.4 mL, 2.5 equiv), and conc HCl (0.5 mL) in dichloromethane (50 mL) was stirred for 1 h at room temperature. The reaction mixture was concentrated on a rotatory evaporator at room temperature, and the crude product was purified by column chromatography over 60−120 mesh silica gel using 0.5% ethyl acetate−hexane as eluent to furnish 1.12 g (41% yield) of **17** as a colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33−1.72 (m, 16H), 2.10 (dd, 2H, J = 14.2, 5.4 Hz), 2.17−2.43 (m, 2H), 3.40 (t, 1H, J = 10.0 Hz), 3.87 (ddd, 1H, J = 12.1, 5.5, 1.6 Hz), 5.18 (dd, 1H, J = 11.3, 4.1 Hz), 5.53 (t, 1H, J = 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2, 24.4, 24.7, 27.2, 27.6, 30.9, 34.0, 35.9, 36.8, 66.4, 80.6, 116.1, 128.5, 143.1; MS (*m/z*) 253 $(M + H)^+$; HRMS Calcd for $C_{15}H_{24}O_3$: 252.17255. Found: 252.17254.

3,3-Dimethyl-5,6,8,9,10,11,12,12a-octahydro-1,2,4-trioxa-octalene (16). Yield 55%, oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.20−1.41 (m, 4H), 1.45 (s, 3H), 1.47−1.67 (m, 4H), 2.01 (dd, 2H, J = 9.4, 3.8 Hz), 2.05−2.18 (m, 1H), 2.33−2.41 (m, 1H), 3.46 (dt, 1H, J = 12.3, 2.4 Hz), 3.74 (ddd, 1H, J = 12.6, 5.7, 1.8 Hz), 5.11 (dd, 1H, J = 11.4, 4.2 Hz), 5.49 (t, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.2, 24.6, 26.6, 27.1, 30.4, 30.5, 36.3, 64.1, 80.1, 103.6, 127.8, 142.7; MS (*m/z*) 249 $(M + Na)^+$; HRMS Calcd for $C_{13}H_{22}O_3$: 226.1569. Found: 226.1549.

1,2,4-Trioxocane 18. Yield 48%, mp 43−45 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33−1.88 (m, 18H), 2.08 (dd, 2H, J = 14.3, 5.6 Hz) 2.18−2.46 (m, 2H), 3.53 (dt, 1H, J = 11.6, 2.0 Hz), 3.76 (ddd, 1H, J = 12.3, 5.5, 1.5 Hz), 5.16 (dd, 1H, J = 11.3, 4.0 Hz), 5.52 (t, 1H, J = 8.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2, 23.4, 24.6, 25.9, 27.2, 27.6, 30.8, 30.9, 31.0, 34.2, 36.9, 63.8, 80.6, 104.4, 128.3, 143.3; MS (*m/z*) 284 $(M + NH_4)^+$; HRMS Calcd for $C_{16}H_{26}O_3$: 266.18820. Found: 266.18815.

Acknowledgment. We thank the Indian Council of Medical Research (ICMR), New Delhi, for funding a portion of these studies. We also thank SAIF, CDRI, Lucknow for providing the spectral data.

Supporting Information Available: Experimental details and characterization data of **3a**−**d**, **4a**−**d**, **6a**, **7a**, **12**, **14**, and **15**. ^{1}H NMR spectra of all the compounds and ^{13}C NMR spectra of **5a**−**d**, **6a**, **7a**, **8a**−**d**, **9a**−**d**, **10a**−**d**, and **13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061414Z