Synthetic methods for unsymmetrically-substituted 1,2,4,5-tetroxanes and of 1,2,4,5,7-pentoxocanes

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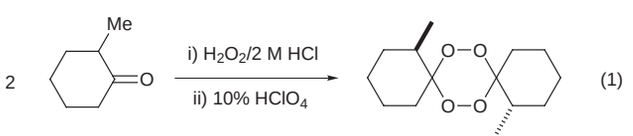
Ozonolysis of vinyl ethers **1a**–**c** in the presence of hydrogen peroxide in diethyl ether gave the corresponding 1,1-bis(hydroperoxide)s **2a**–**c**. Subsequent trimethylsilylation, followed by the TMSOTf-catalyzed cyclocondensation with carbonyl compounds gave the unsymmetrically-substituted 1,2,4,5-tetroxanes **5**–**14**. Similarly, the 1,2,4,5,7-pentoxocanes **18**, **19** were prepared by the reaction of an α,α′-bis(trimethylsilylperoxy) ether **17** and carbonyl compounds. The tetroxane **14** showed notable antimalarial activity *in vitro* and *in vivo*.

The discovery of pharmacologically active six-membered ring peroxides has provoked a renewed interest in the development of new synthetic methods of such structures.[1] Particularly interesting is the fact that symmetrically-substituted 1,2,4,5-tetroxanes, easily prepared by the acid-catalyzed condensation of carbonyl compounds and hydrogen peroxide, exhibit remarkable antimalarial activities *in vitro* and *in vivo* [eqn. (1)].[2] In



(1)

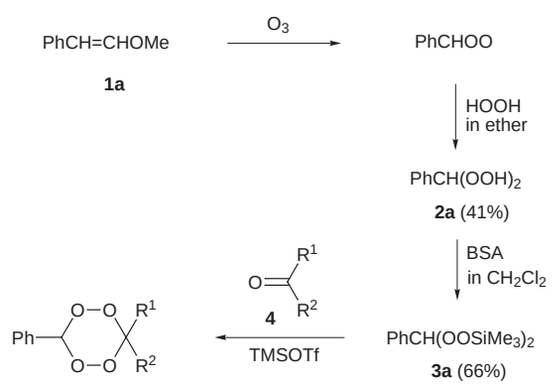
connection with this, Jefford and co-workers[3] have found that the TMSOTf-catalyzed condensation of an aldehyde and bis-(trimethylsilyl peroxide) provides the symmetrically substituted 3,6-dialkyl-1,2,4,5-tetroxane in high yield. We report herein that under similar conditions unsymmetrically substituted 1,2,4,5-tetroxanes can be prepared from 1,1-bis(trimethylsilyl-dioxy)alkanes and carbonyl compounds. Also, cyclocondensation of an α,α′-bis(trimethylsilylperoxy) ether and carbonyl compounds gives the corresponding 1,2,4,5,7-pentoxocanes.

Results and discussion

Synthesis of unsymmetrically substituted 1,2,4,5-tetroxanes

The first question to address was whether it was possible to prepare monoalkyl-substituted bis(hydroperoxide)s without trouble.[4] In reality, the desired bis(hydroperoxide)s **2a**–**c** were prepared in moderate yields by the ozonolysis of vinyl ethers **1a**–**c** in the presence of excess H_2O_2 in diethyl ether[5] at −70 °C (Schemes 1 and 2). By column chromatography on silica gel, pure bis(peroxide)s were easily isolated. Although a variety of dialkyl-substituted bis(hydroperoxide)s such as cyclohexylidene bisperoxide have been prepared,[4] this is, to our knowledge, the first example of isolation of monoalkyl-substituted bis(hydroperoxide)s.

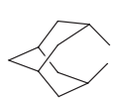
With the starting materials **2a**–**c** in hand, we then tried the cyclocondensation with carbonyl compounds. When the bis(hydroperoxide) **2a** was treated with cyclohexanone **4b** in the presence of 1 equiv. of trimethylsilyl trifluoromethanesulfonate



5; $R^1 = R^2$ = Me (26%)

6; R^1, R^2 = -$(CH_2)_5$- (33%)

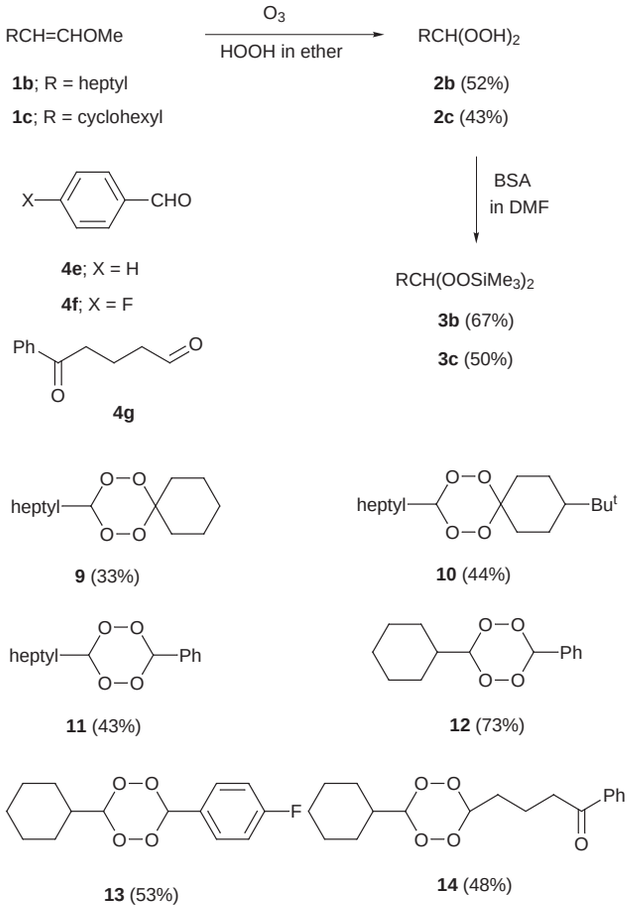
7; R^1, R^2 = -$CH_2CH_2CH(t\text{-Bu})CH_2CH_2$- (14%)

8; R^1, R^2 =  (30%)

Scheme 1

(TMSOTf), however, only a complex mixture of unidentified products were obtained.

Therefore, we next tried protection of the hydroperoxy groups. Treatment of bis(hydroperoxides) **2a**–**c** with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) in CH_2Cl_2 gave the corresponding bis(trimethylsilylated) products **3a**–**c** in good yield.[6] Subsequent cyclocondensation of the protected peroxide **3a** with carbonyl compounds **4a**–**d** (2 equiv.) in the presence of 1 equiv. of TMSOTf in CH_2Cl_2 gave the corresponding unsymmetrically-substituted 1,2,4,5-tetroxanes **5**–**8**. Although the yields of **5**–**8** were poor (Scheme 1), it was interesting to note that symmetrically substituted tetroxanes such as 3,6-diphenyl-1,2,4,5-tetroxane were not isolated at all. The by-products were the carbonyl compound that was used in excess and also highly polar oligomers. Thus, the unsymmetrically-substituted tetroxanes, as the most nonpolar product, were easily isolated by the column chromatography on silica gel.



Scheme 2

Similarly, cyclocondensations of **3b**,**c** and carbonyl compounds **4b**,**c**,**e**,**f**,**g** gave in each case the corresponding tetroxanes **9**–**14** in moderate yields (Scheme 2). These results suggest that the cyclocondensation reaction developed in this study is a highly general method for the synthesis of unsymmetrically-substituted 1,2,4,5-tetroxanes. Moreover, this reveals the new chemical methodology of using bis(hydroperoxide)s as the construction unit of cyclic peroxides.

Synthesis of 1,2,4,5,7-pentoxocanes

Since a carbonyl oxide moiety had been found to be efficiently trapped by H_2O_2 in diethyl ether, we considered that the carbonyl oxide intermediate from an indene derivative would be also captured by H_2O_2, but by a different mode, giving the bis(hydroperoxy) substituted isochromane derivative.[7] This was confirmed to be true for the ozonolysis of an indene **15**. Subsequent silylation of the derived bis(hydroperoxide) **16** led to the formation of the bis-silylated isochromane derivative **17**, which was isolated by column chromatography on silica gel.

Treatment of a mixture of the peroxide **17** and benzaldehyde **4e** with TMSOTf provided the expected 1,2,4,5,7-pentoxocane derivative **19**[8] in 15% yield, together with the corresponding ozonide **20**[7] (14%). From the reaction with acetone, a pentoxocane **18** was obtained in 20% yield (Scheme 3).

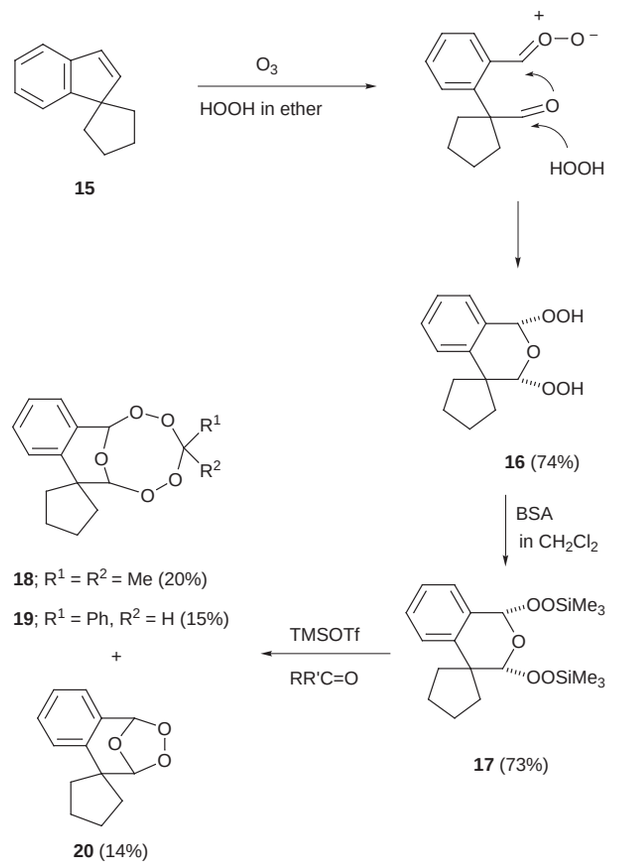
Antimalarial activities of 1,2,4,5-tetroxanes and 1,2,4,5,7-pentoxocanes

A brief comment is made concerning the antimalarial activity of the tetroxanes and pentoxocanes. Antimalarial activities against *P. falciparum* and cytotoxicities against FM3A cells, of some unsymmetrically-substituted tetroxanes and of pentoxocanes have been examined.[9] The EC_{50} values of 3,6-dialkyl-substituted tetroxanes, **11**, **12**, and **14** were in the range of 1.1×10^{-7}–7.2×10^{-7} M and moreover, the selectivity was notable (Table 1). In contrast, pentoxocanes **18**, **19** were found to be ineffective.

Table 1 Antimalarial activities of 1,2,4,5-tetroxanes against *P. falciparum* and cytotoxicities against FM3A

Tetroxane	*P. falciparum* EC_{50}/M	FM3A EC_{50}/M	Selectivity[a]
6	2.8×10^{-6}	1.5×10^{-5}	5
9	1.8×10^{-6}	1.7×10^{-5}	9
11	6.2×10^{-7}	1.9×10^{-5}	30
12	1.8×10^{-7}	6.5×10^{-6}	36
13	7.2×10^{-7}	4.8×10^{-6}	7
14	1.0×10^{-7}	1.1×10^{-5}	110
Artemisinin	7.8×10^{-9}	1.0×10^{-5}	1280

[a] Selectivity = cytotoxicity/antimalarial activity.



Scheme 3

Since the antimalarial activity of the tetroxane **14** *in vitro* was particularly remarkable, the *in vivo* antimalarial activity against *P. berghei*, NK 65 strain, in the multiple-dose Peter's method[10] was also determined. The result showed that **14** is a potent antimalarial agent against *P. berghei*, the ED_{50} value being 35 mg kg^{-1}.

Experimental

General

^1H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard. Coupling constants J are measured in Hz. β-Methoxystyrene **1a**, 1-methoxynonene **1b**, and 2-cyclohexyl-1-methoxyethene **1c** were prepared by the reported method.[11]

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.

Ozonolysis of vinyl ethers 1a–c in the presence of hydrogen peroxide in diethyl ether

The procedure for ozonolysis of β-methoxystyrene **1a** is representative.[4b,7] A diethyl ether solution (2.5 M) of anhydrous H_2O_2 was prepared by extraction of 30% aqueous H_2O_2 solution with diethyl ether.[5] The diethyl ether extracts were dried over anhydrous $MgSO_4$ and titrated iodometrically. To the diethyl ether solution (25 cm^3) of H_2O_2, the vinyl ether **1a** (670 mg, 5.0 mmol) was added and then, a slow stream of ozone (1 equiv.; flow for 15 min) was passed at −70 °C. After adding diethyl ether (70 cm^3), the organic layer was washed with ice-cold potassium dihydrogen phosphate, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (2 : 8) gave a bis(hydroperoxide) **2a** (317 mg, 41%).

α-Hydroperoxybenzyl hydroperoxide 2a. An oil (41%) (Found: C, 54.0; H, 5.4. $C_7H_8O_4$ requires: C, 53.85; H, 5.1%); δ_H 6.33 (1 H, s), 7.3–7.5 (5 H, m), 9.42 (2 H, s); δ_C 110.06, 126.91, 128.49, 129.80, 132.18.

1-Hydroperoxyoctyl hydroperoxide 2b. An oil (52%) (Found: C, 54.0; H, 10.4. $C_8H_{18}O_4$ requires: C, 53.9; H, 10.2%); δ_H 0.88 (3 H, t, *J* 6), 1.3–1.8 (12 H, m), 5.28 (1 H, t, *J* 6), 10.02 (2 H, br s); δ_C 13.98, 22.54, 24.62, 28.43, 29.00, 29.15, 31.65, 111.14.

Cyclohexyl(hydroperoxy)methyl hydroperoxide 2c. Mp 81–82 °C (43%) (from hexane) (Found: C, 52.0; H, 8.6. $C_7H_{14}O_4$ requires: C, 51.8; H, 8.7%); δ_H 1.1–1.8 (11 H, m), 4.96 (1 H, d, *J* 8), 9.80 (2 H, br s); δ_C 25.48 (2 C, CH_2), 26.04 (CH_2), 28.34 (2 C, CH_2), 37.39 (CH), 114.32 (OOCHOO).

Trimethylsilylation of bis(hydroperoxide)s

The preparation of **3a** is representative. To a stirred solution of a bis(hydroperoxide) **2a** (515 mg, 3.30 mmol) in CH_2Cl_2 (25 cm^3), was added BSA (1340 mg, 6.60 mmol) *via* syringe over 10 min at 0 °C.[6] After stirring for more than 2.5 h at room temperature, the solvent was evaporated under vacuum and the residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1 : 50) gave the trimethylsilylated peroxide **3a** (658 mg, 66%).

α,α-Bis(trimethylsilyldioxy)toluene 3a. An oil (66%) (Found: C, 51.7; H, 7.9. $C_{13}H_{24}O_4Si_2$ requires: C, 52.0; H, 8.05%); δ_H 0.21 (18 H, s), 6.13 (1 H, s), 7.3–7.5 (5 H, m); δ_C 1.37, 110.26, 127.42, 128.14, 129.36, 134.03.

1,1-Bis(trimethylsilyldioxy)octane 3b. An oil (67%) (Found: C, 52.6; H, 10.8. $C_{14}H_{34}O_4Si_2$ requires: C, 52.1; H, 10.6%); δ_H 0.21 (18 H, s), 0.86 (3 H, t, *J* 7), 1.3–1.8 (12 H, m), 5.13 (1 H, t, *J* 6); δ_C 1.27, 14.05, 22.59, 25.03, 29.02, 29.33, 29.77, 31.72, 101.96.

[Bis(trimethylsilyldioxy)methyl]cyclohexane 3c. An oil (50%) (Found: C, 51.4; H, 9.6. $C_{13}H_{30}O_4Si_2$ requires: C, 50.9; H, 9.9%); δ_H 0.23 (18 H, s), 1.1–1.8 (11 H, m), 4.89 (1 H, d, *J* 7); δ_C 0.00 (6 C, CH_3), 27.49 (2 C, CH_2), 28.00 (CH_2), 30.35 (2 C, CH_2), 40.09 (CH), 115.45 (OOCHOO).

Cyclocondensation of 3 with a carbonyl compound

The synthesis of the tetroxane **6** is representative.[3] To a stirred solution of the peroxide **3a** (150 mg, 0.5 mmol) and cyclohexanone **4b** (98 mg, 1.0 mmol) in CH_2Cl_2 (25 cm^3), was added TMSOTf (111 mg, 0.5 mmol) *via* a syringe over 10 min at −70 °C. After stirring for more than 2 h at 0 °C, the mixture was poured into diethyl ether (70 cm^3). Then, the organic layer was washed with ice-cold $NaHCO_3$, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1 : 25) gave the tetroxane **6** (39 mg, 33%). From the second fraction (elution with diethyl ether–hexane, 1 : 9), a mixture of cyclohexanone **4b** (7 mg, 7%) and benzaldehyde **4e** (4 mg, 8%) was obtained. Elution with diethyl ether gave the unidentified oligomeric products (17 mg).

3,3-Dimethyl-6-phenyl-1,2,4,5-tetroxane 5. Mp 43–44 °C (26%) (from MeOH) (Found: C, 60.85; H, 6.1. $C_{10}H_{12}O_4$ requires: C, 61.2; H, 6.2%); δ_H 1.43 (3 H, s), 1.97 (3 H, s), 6.65 (1 H, s), 7.4–7.5 (5 H, m); δ_C 21.35, 21.56, 108.35, 108.61, 127.83, 128.07, 129.11, 131.07.

3-Phenyl-1,2,4,5-tetraoxaspiro[5.5]undecane 6. Mp 103–104 °C (33%) (from diethyl ether–hexane) (Found: C, 66.1; H, 6.75. $C_{13}H_{16}O_4$ requires: C, 66.1; H, 6.8%); δ_H 1.4–1.7 (10 H, m), 6.67 (1 H, s), 7.4–7.5 (5 H, m); δ_C 19.61, 19.97, 23.09, 27.89, 29.56, 105.63, 106.47, 125.30, 126.43, 128.79, 129.79.

9-*tert*-Butyl-3-phenyl-1,2,4,5-tetraoxaspiro[5.5]undecane 7. Mp 139–140 °C (14%) (from diethyl ether–hexane) (Found: C, 69.6; H, 8.3. $C_{17}H_{24}O_4$ requires: C, 69.8; H, 8.3%); δ_H 0.89 (9 H, s), 1.2–1.8 (9 H, m), 6.67 (1 H, s), 7.4–7.5 (5 H, m); δ_C 22.73, 23.16, 27.58 (3 C, CH_3), 30.28, 32.02, 32.34 (C), 47.42 (CH), 107.85 (CH), 108.70 (C), 127.53, 128.70, 129.56, 131.05.

Tetroxane 8. Mp 123–124 °C (30%) (from methanol) (Found: C, 70.6; H, 7.1. $C_{17}H_{20}O_4$ requires: C, 70.8; H, 7.0%); δ_H 1.6–2.1 (14 H, m), 6.68 (1 H, s), 7.4–7.5 (5 H, m); δ_C 26.99 (2 C), 30.84, 33.08 (2 C), 33.21 (2 C), 34.45, 36.89, 107.67 (CH), 110.76 (C), 127.53 (2 C), 128.66 (2 C), 131.00, 131.57.

3-Heptyl-1,2,4,5-tetraoxaspiro[5.5]undecane 9. An oil (33%) (Found: C, 65.1; H, 10.1. $C_{14}H_{26}O_4$ requires: C, 65.6; H, 10.2%); δ_H 0.88 (3 H, t, *J* 6), 1.2–1.7 (22 H, m), 5.80 (1 H, t, *J* 5).

9-*tert*-Butyl-3-heptyl-1,2,4,5-tetraoxaspiro[5.5]undecane 10. An oil (44%) (Found: C, 68.6; H, 10.7. $C_{18}H_{34}O_4$ requires: C, 68.75; H, 10.9%); δ_H 0.87 (12 H, br s), 1.2–1.7 (21 H, m), 5.80 (1 H, t, *J* 5); δ_C 14.04, 22.57, 23.09, 23.45, 27.55 (3 C), 28.92, 29.20, 29.72, 30.03, 31.61, 32.06, 32.29, 47.42, 108.43, 108.61.

3-Heptyl-6-phenyl-1,2,4,5-tetroxane 11. An oil (43%) (Found: C, 67.25; H, 8.5. $C_{15}H_{22}O_4$ requires: C, 67.65; H, 8.3%); δ_H 0.87 (3 H, t, *J* 6), 1.3–1.7 (12 H, m), 6.06 (1 H, t, *J* 5), 6.74 (1 H, s), 7.3–7.5 (5 H, m); δ_C 14.05, 22.57, 23.56, 28.88, 29.20, 29.56, 31.61, 108.16, 108.71, 127.66, 128.68, 130.96, 131.16.

3-Cyclohexyl-6-phenyl-1,2,4,5-tetroxane 12. Mp 67–68 °C (73%) (from methanol) (Found: C, 67.1; H, 7.25. $C_{14}H_{17}O_4$ requires: C, 67.2; H, 7.25%); δ_H 1.2–1.8 (11 H, m), 5.87 (1 H, d, *J* 5.9), 6.73 (1 H, s), 7.3–7.5 (5 H, m); δ_C 25.43, 25.93, 26.97, 39.14, 108.26, 110.96, 127.67, 128.70, 131.05, 131.66.

3-Cyclohexyl-6-(4-fluorophenyl)-1,2,4,5-tetroxane 13. Mp 82–83 °C (53%) (from methanol) (Found: C, 62.5; H, 6.3. $C_{14}H_{17}FO_4$ requires: C, 62.7; H, 6.4%); δ_H 1.2–1.8 (11 H, m), 5.84 (1 H, d, *J* 5.9), 6.70 (1 H, s), 7.09 (2 H, t, *J* 8.9), 7.43 (2 H t, *J* 8.9); δ_C 25.43 (2 C), 25.91, 26.97 (2 C), 39.12, 107.49, 110.98, 115.92 (2 C, d, *J* 21.9), 127.13, 129.94 (2 C), 164.29 (d, *J* 251.4).

3-(3-Benzoylpropyl)-6-cyclohexyl-1,2,4,5-tetroxane 14. Mp 82–83 °C (48%) (from methanol) (Found: C, 67.6; H, 7.6. $C_{18}H_{24}O_5$ requires: C, 67.5; H, 7.55%); δ_H 1.2–2.0 (15 H, m),

3.02 (2 H, t, *J* 7), 5.67 (1 H, d, *J* 6), 5.92 (1 H, t, *J* 6), 7.4–7.5 (5 H, m); δ_C 18.04 (CH_2), 25.37 (2 C, CH_2), 25.91 (CH_2), 26.86 (2 C, CH_2), 29.07 (CH_2), 37.68 (CH_2), 39.07 (CH), 108.52 (OOCHOO), 110.05 (OOCHOO), 127.98 (2 C), 128.61 (2 C), 133.12, 136.71, 199.01 (C=O).

Ozonolysis of indene 15 in the presence of hydrogen peroxide in diethyl ether, followed by trimethylsilylation

To a diethyl ether solution (25 cm^3) of H_2O_2 and indene derivative **15** (850 mg, 5.0 mmol) was passed a slow stream of ozone (1 equiv.; flow for 15 min) at −70 °C. After adding ether (70 cm^3), the organic layer was washed with ice-cold $NaHCO_3$, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (3:7) gave the bis(hydroperoxide) **16** (930 mg, 74%). Subsequent silylation of **16** (604 mg, 2.40 mmol) by 2 equiv. of BSA (976 mg) in CH_2Cl_2 (25 cm^3) at room temperature for 2.5 h, followed by column chromatography on silica gel (elution with diethyl ether–hexane, 1:50) gave the trimethylsilylated compound **17** (692 mg, 73%). Although the ^1H and ^{13}C NMR spectra were consistent with the structure, the labile peroxide **17** did not give the correct elemental analysis data.

1,3-Bis(hydroperoxy)spiro[1*H*-2-benzopyran-4(3*H*),1′-cyclopentane] 16. An oil (74%) (Found: C, 62.35; H, 6.6. $C_{13}H_{16}O_5$ requires: C, 61.9; H, 6.4%); δ_H 1.5–2.1 (8 H, m), 5.27 (1 H, s), 6.18 (1 H, s), 7.2–7.4 (4 H, m), 9.45 (1 H, br s), 9.76 (1 H, br s); δ_C 24.85, 26.07, 33.61, 41.60, 47.69, 99.53, 105.57, 125.07, 126.29, 126.85, 127.13, 129.87, 140.97.

1,3-Bis(trimethylsilyldioxy)spiro[1*H*-2-benzopyran-4(3*H*),1′-cyclopentane] 17. An oil (73%); δ_H 0.26 (9 H, s), 0.29 (9 H, s), 1.5–2.1 (8 H, m), 5.25 (1 H, s), 6.21 (1 H, s), 7.2–7.4 (4 H, m); δ_C 0.00, 0.11, 26.59, 28.91, 37.81, 40.04, 50.69, 101.85, 107.47, 126.75, 127.44, 128.03, 129.43, 130.42, 131.88.

Cyclocondensation of 17 and a carbonyl compound

The cyclocondensation with benzaldehyde is representative. To a stirred solution of the peroxide **17** (334 mg, 0.84 mmol) and benzaldehyde **4e** (78 mg, 1.68 mmol) in CH_2Cl_2 (25 cm^3), was added TMSOTf (86 mg, 0.84 mmol) *via* a syringe over 10 min at −70 °C and the reaction was continued for more than 2 h at 0 °C. After treatment of the reaction mixture as described in the previous cyclocondensation procedure, the residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1:25) gave an ozonide **20**[7] (25 mg, 14%). Subsequent elution with diethyl ether–hexane (1:25) gave a pentoxocane **19** (43 mg, 15%).

4′,4′-Dimethylspiro[cyclopentane-1,8′(7′*H*)-1′,7′-epoxy-1′*H*-[2,3,5,6]benzotetroxecine] 18. Mp 118–119 °C (20%) (from diethyl ether–hexane) (Found: C, 65.65; H, 6.9. $C_{16}H_{20}O_5$ requires: C, 65.7; H, 6.9%); δ_H 1.20 (3 H, s), 1.39 (3 H, s), 1.5–2.2 (8 H, m), 5.28 (1 H, s), 6.14 (1 H, s), 7.3–7.5 (5 H, m).

4′-Phenylspiro[cyclopentane-1,8′(7′*H*)-1′,7′-epoxy-1′*H*-[2,3,5,6]benzotetroxecine] 19. Mp 118–119 °C (15%) (from methanol) (Found: C, 70.6; H, 5.9. $C_{20}H_{20}O_5$ requires: C, 70.6; H, 5.9%); δ_H 1.5–2.3 (8 H, m), 5.46 (1 H, s), 6.29 (1 H, s), 6.49 (1 H, s), 7.2–7.5 (9 H, m); δ_C 25.14, 26.90, 33.44, 44.02, 46.97, 97.27, 103.50, 108.59, 125.89, 126.23, 126.92, 127.24, 128.59, 130.22, 130.56, 140.73.

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