ARTICLE

OBC
www.rsc.org/obc

New approaches to the synthesis of spiro-peroxylactones

Kevin J. McCullough,*[a] Hidekazu Tokuhara,[b] Araki Masuyama[b] and Masatomo Nojima[b]

[a] *Department of Chemistry, School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh, UK EH14 4AS*

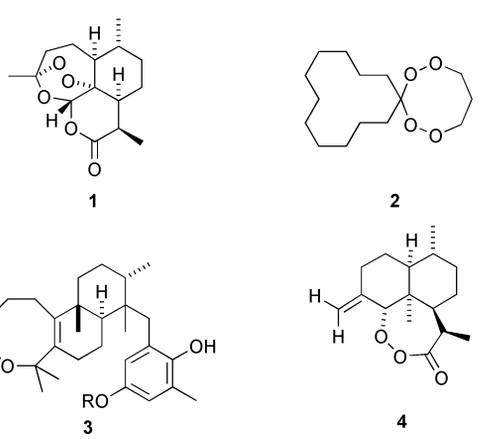
[b] *Department of Materials Chemistry & Frontier Research Center, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*

Received 14th January 2003, Accepted 10th March 2003
First published as an Advance Article on the web 27th March 2003

Ozonolysis of (alkenyldioxy)cyclododecyl hydroperoxides in trifluoroethanol gave a separable mixture of the corresponding α-hydroperoxy- and α-hydroxy-substituted spiro-tetraoxacycloalkanes with ring sizes in the range 7–12. Dehydration of the hydroperoxides or oxidation of the hydroxy-compounds afforded the corresponding peroxylactones. The solid-state structure of 1,2,6,7-tetraoxaspiro[7.11]nonadecan-3-one was determined by X-ray crystallographic analysis.

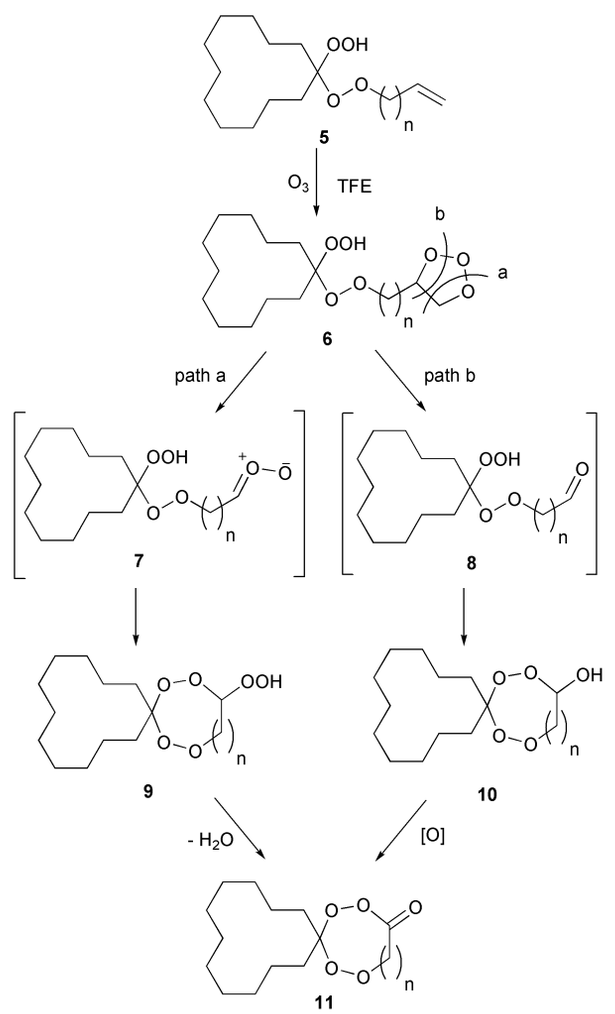
Introduction

The discovery of antimalarial activity of naturally occurring organic peroxides such as artemisinin (**1**) has stimulated recent interest in the development of methods for synthesis of new cyclic peroxide systems.[1] In this respect, we recently developed a convenient synthetic route to the spiro-peroxide, 1,2,6,7-tetraoxaspiro[7.11]nonadecane (**2**) which was found to exhibit antimalarial activities *in vitro* and *in vivo* comparable with those reported for artemisinin (**1**).[2] Although a number of natural products containing cyclic peroxide substructural units of various types have been reported to date,[1a] there are relatively few examples of molecules containing the peroxylactone moiety; noteworthy examples include the diterpenoid **3** isolated from the marine alga *Taonia atomaria*,[3] and arteannuin H (**4**) isolated from *Artemisia annua* L.[4] In the search for novel biologically active compounds, it was of interest to prepare a series of peroxylactones structurally related to the spiro-peroxide **2**.



Results and discussion

A new strategy for the synthesis of a series of spiro-peroxylactones is outlined in Scheme 1. Ozonolysis of unsaturated hydroperoxides **5**, prepared in moderate yield (37–54%) by the Ag-catalysed mono-alkenylation of 1,1-bis(hydroperoxy)cyclododecane,[5] in protic solvent would be expected to give a mixture of the corresponding α-hydroperoxy- and α-hydroxy-substituted tetraoxaspiroalkanes **9** and **10**. The ozonolysis product composition will depend on the cleavage mechanisms favoured by the respective transient primary ozonides **6**.[6] Subsequent chemical transformation of the hydroperoxyl or hydroxyl functional groups in compounds **9** and **10** should provide the desired peroxylactones **11**. In addition, since there are relatively few reliable procedures for the syntheses of macrocyclic peroxides,[7] it was of interest to investigate the scope of this particular cyclization reaction.



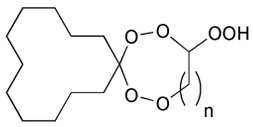
Scheme 1 Strategy for the synthesis of spiro-peroxylactones **11**.

Ozonolysis of unsaturated hydroperoxides in trifluoroethanol

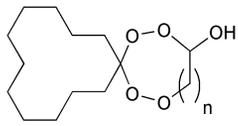
The results for the ozonolyses of alkenyldioxy-substituted cyclododecyl hydroperoxides **5a**–**e** in trifluoroethanol (TFE) are summarized in Table 1. Ozonolysis of **5a** (n = 1) afforded a

DOI: 10.1039/b300342f

Table 1 Yields of α-hydroperoxy- and α-hydroxy-substituted tetraoxacycloalkanes from **5a**–**e**



9



10

a; $n = 1$	20%	69%
b; $n = 2$	57%	24%
c; $n = 3$	47%[a]	
d; $n = 4$	18%[a]	
e; $n = 6$	9%[a]	

[a] Significant quantities of polar oligomeric products were also obtained.

mixture of the spiro-tetroxepane derivatives **9a** and **10a** in yields of 20% and 69% respectively. Under similar conditions, the reaction of **5b** (n = 2) with ozone gave a mixture of **9b** and **10b** in yields of 57% and 24%, respectively. These results demonstrate that there are two modes operating competitively in the cleavage of the primary ozonides **6a**,**b**: *viz.* the scission path **a** leading to the formation of the carbonyl oxide intermediate **7a**,**b** and formaldehyde, and the alternative path **b** providing a mixture of the aldehyde **8a**,**b** and formaldehyde *O*-oxide (Scheme 1). Subsequent intramolecular cyclisations of intermediates **7a**,**b** and **8a**,**b** proceed efficiently, thereby providing **9a**,**b** and **10a**,**b** in acceptable yields.

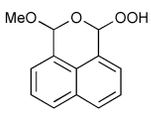
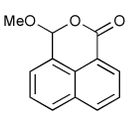
The chain length of the alkenyldioxy group in the unsaturated hydroperoxides **5** dramatically affects the efficiency of the intramolecular cyclization of the ozonolysis intermediates **7** and **8**. Thus, from **5c** was obtained the corresponding hydroperoxy-substituted tetraoxacycloalkane **9c** in 47% yield. Similarly, the hydroperoxides **9d**,**e**, albeit in low yield (18% for **9d** and 9% for **9e**), were the only readily identifiable products isolated from the ozonolysis of the unsaturated hydroperoxides **5d**,**e**. In each case, although the corresponding hydroxy compounds **10c**–**e** were not observed, significant quantities of unidentified polar oligomeric products were obtained instead. These limited results tend to suggest that (i) a carbonyl oxide, being a reactive 1,3-dipole, would be captured by a hydroperoxyl group more readily than the aldehyde group in a similar position, and (ii) in the case of particularly **7d**,**e** and/or **8d**,**e** leading to bigger rings, entropically more favoured intermolecular reactions occur predominantly.

Although the product yields were relatively low, the 10- and 12-membered cyclic peroxides **9d**,**e** were certainly obtained by the ozonolysis of the unsaturated hydroperoxides **5d**,**e** in TFE, suggesting that this methodology offers a synthetic route to novel macrocyclic peroxides.

Dehydration of α-methoxyalkyl hydroperoxides and α-hydroperoxy-substituted tetraoxacycloalkane

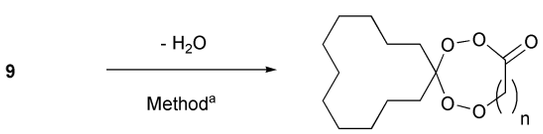
Before attempting the dehydration of α-hydroperoxy-substituted tetraoxacycloalkanes **9a**–**e**, the readily prepared α-alkoxyalkyl hydroperoxides **12a**–**c** were used as model substrates for two different dehydration procedures: method A utilising a mixture of Ac_2O–Et_3N as developed by Schreiber *et al.*,[8] and method B using PhNCO in the presence of a catalytic amount of pyridine.[9] The results, summarised in Table 2, demonstrate that the yields of esters **13a**–**c** obtained from the two procedures are fairly comparable. The major advantage of method A is the fact that the reactions generally proceeded rapidly and were complete after about 2 h. Although the reactions using method B were significantly slower, requiring about 16 h for completion, there were some advantages with this latter procedure: (a) ease of work-up: after concentration of the reaction mixture, the ester **13** was easily isolated by column chromatography on silica gel, and (b) applicability to the preparation of base-sensitive products since only a catalytic amount of pyridine was required.

Table 2 Dehydration of α-methoxy hydroperoxides

Hydroperoxide	Ester	Method[a] (% yield)
		A (84%) B (84%)
12a	**13a**	
$CH_3(CH_2)_7CH(OMe)OOH$ **12b**	$CH_3(CH_2)_7C(O)OMe$ **13b**	A (86%) B (71%)
		A (91%) B (95%)
12c	**13c**	

[a] Method A; dehydration by Ac_2O, Et_3N. Method B; dehydration by PhNCO, pyridine.

Table 3 Dehydration of α-hydroperoxy-substituted tetraoxacycloalkanes[a]



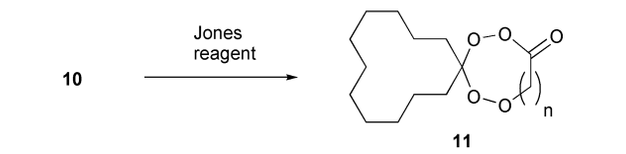
a; $n = 1$	A	0%[b]
a; $n = 1$	B	47%[b]
b; $n = 2$	A	81%
b; $n = 2$	B	77%
c; $n = 3$	A	95%
d; $n = 4$	A	80%
e; $n = 6$	A	83%

[a] Method A; dehydration by Ac_2O, Et_3N. Method B; dehydration by PhNCO, pyridine. [b] A significant amount of cyclododecanone was produced.

In the light of the results above, the dehydration of α-hydroperoxy-substituted tetraoxacycloalkanes **9a**–**e** was attempted using both methods (Table 3). It is interesting to note that under the conditions of method A, the hydroperoxide **9a** was transformed into cyclododecanone (86% yield), whereas using method B, the desired peroxylactone **11a** was obtained in 47% yield. Since the hydrogen atoms of the methylene group attached to both the peroxy and carbonyl groups are likely to be relatively acidic, it seems reasonable that the peroxylactone **11a**, if formed, would be susceptible to Et_3N-catalysed decomposition. In the case of **9b**, however, both methods A and B were used successfully, affording the corresponding peroxylactone **11b** in the acceptable yields of around 80%. Dehydration of the other hydroperoxides **9c**–**e** using method A produced the corresponding peroxylactones **11c**–**e** in yields of around 85%.

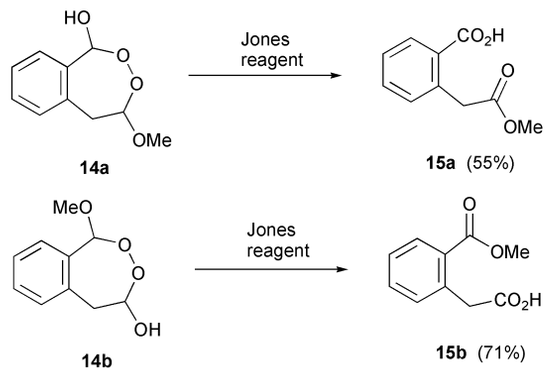
Synthesis of peroxylactones 11 by the oxidation of α-hydroxy-substituted tetraoxacycloalkanes 10

As described above, the α-hydroxy-substituted tetraoxacycloalkanes **10a**,**b** were obtained in significant quantities, in addition to the α-hydroperoxy-compounds **9a**,**b**, by the ozonolysis of the unsaturated hydroperoxides **5a**,**b**. Oxidation of **10a** by treatment with Jones reagent, followed by column chromatography on silica gel, resulted in the isolation of cyclododecanone (57%) together with the unchanged alcohol **10a** (14%) (Scheme 2). Under similar reaction conditions, oxidation of **10b**



a; n = 1	0%[a]
b; n = 2	57%

[a] Cyclododecanone was isolated in 57% yield together with unreacted **10a** (14%).



Scheme 2

proceeded smoothly to provide the peroxylactone **11b** in 57% yield. To investigate the scope of this procedure, the oxidation of hemiperacetals **14a**,**b** using Jones reagent was undertaken. The ring-opened carboxylic acids **15a**,**b** were isolated in yields of 55% and 71%, respectively.

Swern oxidation of **10b** using DMSO–oxalyl chloride also gave the peroxylactone **11b** but in a very low yield (2%) together with cyclododecanone (34%).

In general, direct oxidation of the hydroxy-substituted tetraoxacycloalkanes **10** does not provide such a convenient synthetic route to the corresponding peroxylactones **11** as does the dehydration of the analogous hydroperoxy-substituted compounds **9**.

X-ray crystallographic analysis of peroxylactone 11b

Of the various peroxylactones **11a**–**e** prepared in this study, only compound **11b** gave single crystals suitable for X-ray crystallographic analysis. The solid state structure is depicted in Fig. 1. The O–O and C–O distances around the 1,2,4,5-tetraoxocane ring lie within normal ranges, suggesting that this ring is relatively strain-free. The 1,2,4,5-tetraoxocane ring in **11b** adopts a distorted twist-boat–chair conformation similar to that observed for compound **2**[10] though, not surprisingly, there

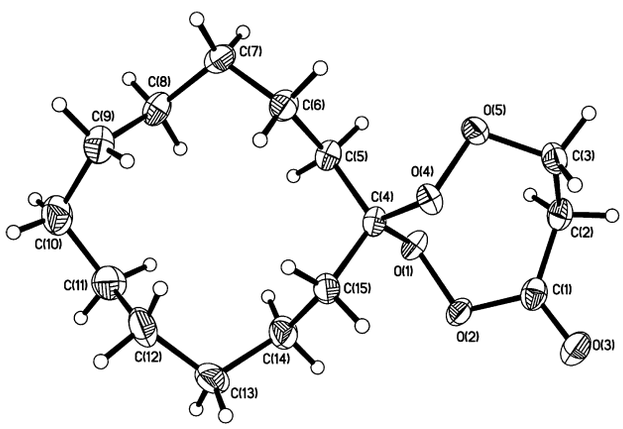


Fig. 1 Solid-state structure of peroxylactone **11b** (ORTEP,[17] 50% probability ellipsoids).

is a distinct flattening of the ring in the vicinity of the carbonyl group. In contrast to **2** and **11b**, the 8-membered peroxylactone ring in natural product **3** adopts a tub-shaped conformation presumably as a consequence of forming part of a poly-fused ring system.[3]

The relative orientations of the peroxide groups in **11b** are similar to those observed in the crystal structure of 1,1-bis(hydroperoxy)cyclododecane.[11] Such an arrangement would not only reduce steric interactions between the adjacent peroxide groups, but would also, if reproduced in carbonyl oxide intermediates **7a**–**c**, facilitate the formation of the medium-ring hydroperoxyl compounds **9a**–**c**.

In summary, a series of novel peroxylactone derivatives **11a**–**e**, with ring sizes ranging from 7–12, have been prepared from the corresponding unsaturated hydroperoxides **5a**–**e** by an ozonolysis–cyclisation–dehydration sequence. The dehydration of the cyclic hydroperoxy compounds **9a**–**e** has been accomplished using either a mixture of Ac_2O and Et_3N or PhNCO in the presence of catalytic quantities of pyridine; the latter procedure is particularly useful for the preparation of base-sensitive peroxylactones such as **11a**.

Experimental section

General

^1H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as standard. The α-alkoxyalkyl hydroperoxides, **12a**,**b**[12] and **12c**,[13] and hemiperacetals, **14a** and **14b**,[9] were prepared by literature procedures.

Ag_2O-mediated synthesis of 1-(alkenyldioxy)cyclododecyl hydroperoxides 5a–e[5]

The preparation of the hydroperoxide **5b** is representative. To a solution of Ag_2O (698 mg, 3.01 mmol) and 1,1-bis(hydroperoxy)cyclododecane (1000 mg, 4.31 mmol) in CH_2Cl_2 (10 mL) was added a solution of 4-iodobutene (783 mg, 4.31 mmol) in CH_2Cl_2 (5 mL) *via* syringe over 5 min. The reaction was stirred at room temperature for a further 15 h. After removal of the solid material by filtration through Celite, diethyl ether (100 mL) was added to the filtrate and the organic layer was washed in turn with 3% aqueous sodium thiosulfate (50 mL), aqueous $NaHCO_3$, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the components of the residue were separated by column chromatography on silica gel. The first fraction (eluting with diethyl ether–hexane, 5 : 95) gave cyclododecanone (336 mg, 43%). From the second fraction (eluting with diethyl ether–hexane, 6 : 94) was obtained the monoalkylated hydroperoxide **5b** (664 mg, 54%).

1-[(2-Propenyl)dioxy]cyclododecyl hydroperoxide (5a). (52% yield). Mp 40–42 °C (from hexane–ethyl acetate); ^1H NMR δ 1.2–1.8 (m, 22 H), 4.55 (d, J = 6.3 Hz, 2 H), 5.2–5.4 (m, 2 H), 6.08 (ddt, J = 17.2, 10.3 and 6.3 Hz, 1 H), 8.18 (s, 1 H); ^{13}C NMR δ 19.23 (2 C), 21.76 (2 C), 22.19 (2 C), 25.90 (2 C), 26.04, 26.35 (2 C), 76.16, 114.20, 119.89, 133.80. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.11. Found: C, 66.23; H, 10.36%.

1-[(3-Butenyl)dioxy]cyclododecyl hydroperoxide (5b). An oil; ^1H NMR δ 1.2–1.8 (m, 22 H), 2.43 (qt, J = 6.6 and 1.3 Hz, 2 H), 4.12 (t, J = 6.6 Hz, 2 H), 5.0–5.2 (m, 2 H), 5.85 (ddt, J = 17.2, 10.2 and 6.6 Hz, 1 H), 7.85 (s, 1 H); ^{13}C NMR δ 19.21 (2 C), 21.80 (2 C), 22.14 (2 C), 25.91 (2 C), 26.02 (2 C), 26.38, 32.38, 74.09, 113.91, 116.86, 134.61. Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.97; H, 10.62%.

1-[(4-Pentenyl)dioxy]cyclododecyl hydroperoxide (5c). (37% yield). Mp 42–43 °C (from diethyl ether–hexane); ^1H NMR δ 1.0–1.8 (m, 24 H), 1.9–2.2 (m, 2 H), 4.01 (t, J = 6.6 Hz, 2 H),

4.8–5.0 (m, 2 H), 5.72 (ddt, J = 17.0, 10.3 and 6.6 Hz, 1 H), 8.53 (s, 1 H); ^{13}C NMR δ 19.17, 21.77, 22.13, 22.43, 24.06, 24.43, 24.59, 25.90, 25.97, 26.39, 26.88, 30.05, 40.17, 74.28, 113.60, 114.74, 137.5. Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 68.17; H, 10.62%.

1-[(5-Hexenyl)dioxy]cyclododecyl hydroperoxide (5d). (53% yield). Mp 38–40 °C (from diethyl ether–hexane); ^{1}H NMR δ 1.1–1.7 (m, 26 H), 2.01 (q, J = 6.8 Hz, 2 H), 4.02 (t, J = 6.4 Hz, 2 H), 4.8–5.0 (m, 2 H), 5.72 (ddt, J = 16.8, 13.4 and 6.8 Hz, 1 H), 8.43 (br s, 1 H); ^{13}C NMR δ 19.25, 21.83, 22.20, 25.30, 25.96, 26.04, 26.47, 27.20, 33.42, 74.91, 113.73, 114.51, 138.08. Anal. Calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.94; H, 10.93%.

1-[(7-Octenyl)dioxy]cyclododecyl hydroperoxide (5e). (45% yield). An oil; ^{1}H NMR δ 1.1–1.8 (m, 30 H), 1.9–2.1 (m, 2 H), 4.03 (t, J = 6.6 Hz, 2 H), 4.8–5.0 (m, 2 H), 5.75 (ddt, J = 17.0, 10.2 and 6.8 Hz, 1 H), 8.14 (s, 1 H); ^{13}C NMR δ 19.32 (2 C), 21.89, 22.45 (2 C), 25.96, 26.02 (2 C), 26.10, 26.51 (2 C), 27.78, 28.78, 28.91, 33.70, 40.35, 75.19, 113.84, 114.14, 138.76. Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.08; H, 11.02%.

Ozonolysis of the unsaturated hydroperoxides 5a–e in TFE

The ozonolysis of the unsaturated hydroperoxide **5b** is representative. Into a solution of **5b** (373 mg, 1.3 mmol) in CH_2Cl_2 (25 mL) and 2,2,2-trifluoroethanol (TFE) (5 mL) was passed a slow stream of ozone (1.5 equiv.) at 0 °C. The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with diethyl ether (30 mL × 2). The combined organic layer was washed with 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 (5 : 95) gave cyclododecanone (15 mg, 6%). From the second fraction (eluting with diethyl ether–hexane, 15 : 85) was obtained the hydroperoxide **9b** (226 mg, 57%). Further elution with diethyl ether–hexane (20 : 80) gave the alcohol **10b** (91 mg, 24%).

1,2,5,6-Tetraoxaspiro[6.11]octadecan-3-yl hydroperoxide (9a). Mp 122–123 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.2–2.3 (m, 22 H), 4.2–4.6 (m, 2 H), 5.4–5.6 (m, 1 H), 9.20 (br s, 1 H); ^{13}C NMR δ 19.37, 21.79, 22.04, 22.37, 22.39, 25.98, 26.05, 75.09, 107.32, 116.34. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 59.73; H, 8.64%.

3-Hydroxy-1,2,5,6-tetraoxaspiro[6.11]octadecane (10a). Mp 103–104 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.2–2.0 (m, 22 H), 4.1–4.5 (m, 3 H), 5.2–5.4 (m, 1 H); ^{13}C NMR δ 19.28, 21.81, 21.97, 22.33, 25.87, 25.93, 25.98, 79.20, 97.99, 115.98. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.73; H, 8.64%.

1,2,6,7-Tetraoxaspiro[7.11]nonadecan-3-yl hydroperoxide (9b). (a 4 : 1 mixture of two diastereoisomers). Mp 108–109 °C (from diethyl ether–hexane); ^{1}H NMR (major isomer) δ 1.2–1.8 (m, 22 H), 1.97 (dt, J = 15.8 and 4.6 Hz, 1 H), 2.42 (dddd, J = 15.8, 10.9, 9.6 and 2.2 Hz, 1 H), 4.13 (ddd, J = 15.4, 4.6 and 2.2 Hz, 1 H), 4.28 (dd, J = 15.4 and 10.9 Hz, 1 H), 5.40 (dd, J = 9.6 and 4.6 Hz, 1 H), 9.04 (s, 1 H); ^{13}C NMR δ 19.02, 19.44, 21.84 (2 C), 22.21 (2 C), 25.78, 25.80, 25.83, 25.99, 26.15, 31.20, 71.07, 108.50, 112.20. The following additional signals were assigned to the minor isomer: ^{1}H NMR δ 2.0–2.2 (m, 1 H), 2.6–2.9 (m, 1 H), 3.97 (td, J = 12.7 and 3.1 Hz, 2 H), 5.38 (dd, J = 10.2 and 2.6 Hz, 2 H), 5.38 (dd, J = 10.2 and 2.6 Hz, 1 H), 9.13 (s, 1 H); ^{13}C NMR δ 19.29, 19.37, 21.65, 21.98, 22.34 (2 C), 25.44, 25.66, 25.88, 25.91, 25.94, 27.82, 70.15, 108.69, 113.11. Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27. Found: C, 59.12; H, 9.25%.

3-Hydroxy-1,2,6,7-tetraoxaspiro[7.11]nonadecane (10b). An oil (a 3 : 1 mixture of two diastereoisomers); ^{1}H NMR (major isomer) δ 1.2–1.8 (m, 22 H), 2.00 (dt, J = 17.0 and 4.8 Hz, 1 H), 2.53 (dddd, J = 17.0, 11.4, 8.9 and 1.7 Hz, 1 H), 3.75 (br s, 1 H), 4.03 (ddd, J = 15.2, 4.8 and 1.7 Hz, 1 H), 4.19 (dd, J = 15.2 and 11.4 Hz, 1 H), 5.29 (dd, J = 8.9 and 4.8 Hz, 1 H); ^{13}C NMR δ 19.09, 19.53, 21.90 (2 C), 22.16 (2 C), 25.86 (2 C), 26.00, 26.04, 26.24, 36.25, 71.44, 99.65, 111.98. The following additional signals were assigned to the minor isomer: ^{1}H NMR δ 2.1–2.2 (m, 1 H), 2.8–3.0 (m, 1 H), 3.91 (td, J = 12.7 and 3.1 Hz, 1 H); ^{13}C NMR δ 19.37, 19.46, 21.70, 21.84, 22.16 (2 C), 25.86 (2 C), 26.00, 26.04, 26.24, 36.25, 71.44, 99.65, 111.98; HRMS (CI) $[M + H]^+$ m/z Calcd for $C_{15}H_{94}O_5$ 289.2015, Found 289.2006.

1,2,7,8-Tetraoxaspiro[8.11]icosan-3-yl hydroperoxide (9c). Mp 66–67 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.1–1.8 (m, 24 H), 2.0–2.3 (m, 2 H), 3.59 (td, J = 12.6 and 4.0 Hz, 1 H), 4.22 (dd, J = 12.8 and 4.6 Hz, 1 H), 5.07 (dd, J = 10.3 and 5.0 Hz, 1 H), 9.11 (br s, 1 H); ^{13}C NMR δ 19.37, 19.42, 20.26, 20.82, 21.88, 22.18, 25.91, 26.13, 26.30, 26.49, 72.78, 109.68, 112.21. Anal. Calcd for $C_{16}H_{30}O_6$: C, 60.35; H, 9.50. Found: C, 60.51; H, 9.47%.

1,2,8,9-Tetraoxaspiro[9.11]henicosan-3-yl hydroperoxide (9d). An oil; ^{1}H NMR δ 1.2–1.8 (m, 26 H), 2.2–2.8 (m, 2 H), 3.7–4.0 (m, 1 H), 4.2–4.4 (m, 1 H), 5.1–5.3 (m, 1 H), 8.75 (s, 1 H); ^{13}C NMR δ 19.28, 19.47, 21.88, 21.92, 22.22, 25.91, 26.11, 26.42, 26.75, 76.30, 111.75, 111.89. Anal. Calcd for $C_{17}H_{32}O_6$: C, 69.19; H, 10.32. Found: C, 69.17; H, 10.25%.

1,2,10,11-Tetraoxaspiro[11.11]tricosan-3-yl hydroperoxide (9e). Mp 93–95 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.1–2.2 (m, 32 H), 3.91 (ddd, J = 12.3, 10.2 and 2.0 Hz, 1 H), 4.1–4.3 (m, 1 H), 5.5–5.7 (m, 1 H), 8.54 (s, 1 H); ^{13}C NMR δ 19.37, 19.41, 20.84, 21.89, 21.92, 22.20, 22.22, 23.89, 25.44, 25.97, 26.00, 26.20, 26.44, 26.83, 26.89, 28.85, 75.59, 110.27, 111.75, 112.72. Anal. Calcd for $C_{19}H_{36}O_6$: C, 63.31; H, 10.07. Found: C, 63.47; H, 9.95%.

Dehydration of hydroperoxides 9a–e with Ac_2O–Et_3N

The reaction of **6b** is representative. To a solution of **6b** (214 mg, 0.7 mmol) in CH_2Cl_2 (5 mL) was added a mixture of acetic anhydride (216 mg, 2.1 mmol) and triethylamine (107 mg, 1.06 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred at room temperature for 2 h. This mixture was treated with methanol (1 mL) for 15 min and then diluted with diethyl ether (50 mL). The solution was washed in turn with 5% $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The products were isolated by column chromatography on silica gel. From the fraction eluted by diethyl ether–hexane (1.5 : 98.5) was obtained cyclododecanone (6 mg, 7%). Subsequent elution with diethyl ether–hexane (5 : 95) gave the peroxylactone **11b** (162 mg, 81%).

1,2,6,7-Tetraoxaspiro[7.11]nonadecan-3-one (11b). Mp 126–127 °C (from diethyl ether–hexane); ^{1}H NMR δ 1.2–1.8 (m, 22 H), 2.51 (ddd, J = 12.7, 3.8 and 1.0 Hz, 1 H), 3.35 (ddd, J = 12.7, 11.9 and 3.8 Hz, 1 H), 4.23 (dt, J = 14.2 and 3.8 Hz, 1 H), 4.46 (ddd, J = 14.2, 11.9 and 1.0 Hz, 1 H); ^{13}C NMR δ 18.98, 19.25, 21.20 (2 C), 21.93 (2 C), 25.39, 25.54, 25.61, 25.64, 26.04, 35.24, 72.26, 117.11, 177.61. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.79; H, 9.26%.

1,2,7,8-Tetraoxaspiro[8.11]icosan-3-one (11c). Mp 105–106 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.1–1.8 (m, 22 H), 2.0–2.5 (m, 3 H), 3.3–3.7 (m, 1 H), 3.9–4.3 (m, 2 H); ^{13}C NMR δ 18.98, 19.40, 21.81, 22.17, 24.32, 24.80, 25.84, 26.08, 26.24, 26.87, 71.96, 116.65, 178.81. Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 64.04; H, 9.11%.

1,2,8,9-Tetraoxaspiro[9.11]henicosan-3-one (11d). Mp 97–98 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.1–2.4 (m, 28 H), 3.7–4.3 (m, 2 H); ^{13}C NMR δ 19.11, 21.81, 22.14, 22.60, 24.09, 24.22, 24.76, 25.82, 26.13, 26.34, 28.03, 40.38, 75.88, 114.80, 179.07. Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 65.07; H, 9.49%.

1,2,10,11-Tetraoxaspiro[11.11]tricosan-3-one (11e). Mp 88–91 °C (from hexane–diethyl ether); ^{1}H NMR δ1.1–1.9 (m, 30 H), 2.3–2.5 (m, 2 H), 4.00 (t, J = 5.0 Hz, 2 H); ^{13}C NMR δ 19.28, 21.88, 22.21, 22.34, 22.42, 25.91, 26.05, 26.78, 73.14, 113.61, 170.89. $C_{19}H_{34}O_5$: C, 66.64; H, 10.01. Found: C, 66.45; H, 9.99%.

Reaction of hydroperoxides 9a-e with phenyl isocyanate in the presence of catalytic quantities of pyridine

The reaction of hydroperoxide **9a** is representative. To a solution of hydroperoxide **9a** (76 mg, 0.26 mmol) and phenyl isocyanate (62 mg, 0.52 mmol) in benzene (20 mL), was added one drop of pyridine and the resulting reaction mixture was stirred at room temperature for 15 h. After concentration under reduced pressure, the products were separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1 : 99) gave peroxylactone **11a** (33 mg, 47%). From the second fraction (elution with diethyl ether–hexane, 5 : 95) was obtained cyclododecanone (11 mg, 23%).

1,2,5,6-Tetraoxaspiro[6.11]octadecan-3-one (11a). Mp 62–63 °C (from hexane–diethyl ether); ^{1}H NMR δ 1.2–1.9 (m, 22 H), 5.0–5.2 (m, 2 H); ^{13}C NMR δ 18.63, 19.45, 21.87, 22.23, 25.49, 25.68, 25.78, 25.95, 26.04, 75.92, 117.74, 171.44. HRMS (CI) [M + 1]+ m/z calcd for $C_{14}H_{24}O_5$ 273.1702, found 273.1703.

The reaction of hydroperoxide **12c** under similar conditions gave the lactone **13c**.

3-Methoxy-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (13c).[14] Mp 105–106 °C (from hexane–diethyl ether); ^{1}H NMR δ 3.73 (s, 3 H), 6.50 (s, 1 H), 7.5–8.5 (m, 6 H); ^{13}C NMR δ 56.32, 102.21, 119.35, 125.36, 126.45, 127.21, 128.64, 129.78, 131.61, 133.66, 163.23; IR 2950, 1740, 1250, 1090, 780 cm^{-1}. Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.70. Found: C, 72.70; H, 4.78%.

Oxidation of alcohols 10a,b by Jones reagent

The reaction of the α-hydroxy-substituted tetroxocane **10b** is representative. To a solution of CrO_3 (186 mg, 1.86 mmol) in water (0.29 mL) was added conc. H_2SO_4 (0.16 mL) at 0 °C and then, water was added to adjust the total volume to 0.7 mL. The resulting Jones reagent was added (10 min) to a solution of **10b** (268 mg, 0.93 mmol) in acetone (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for a further 3 h and then poured into aqueous sodium hydrogen sulfite, extracted with diethyl ether (5 mL × 3), and dried over anhydrous $MgSO_4$. By column chromatography on silica gel (eluting with diethyl ether–hexane, 1.25 : 98.75) was obtained cyclododecanone (15 mg, 9%). Further elution with diethyl ether–hexane (5 : 95) gave peroxylactone **11b** (152 mg, 57%).

Under similar conditions, Jones oxidation of hemiperacetals **14a** and **14b** afforded the corresponding carboxylic acids, **15a** and **15b**.

***o*-(Methoxycarbonylmethyl)benzoic acid (15a).**[15] Mp 98–100 °C (from hexane–diethyl ether); ^{1}H NMR δ 3.70 (s, 3 H), 4.05 (s, 2 H), 7.28 (dd, J = 7.6 and 1.3 Hz, 1 H), 7.39 (td, J = 7.6 and 1.3 Hz, 1 H), 7.54 (td, J = 7.6 and 1.3 Hz, 1 H), 8.14 (dd, J = 7.6 and 1.3 Hz, 1 H), 10.10 (br s, 1 H); ^{13}C NMR δ 40.63, 52.01, 127.47, 128.36, 131.80, 132.31, 133.20, 136.54, 171.99, 172.23.

***o*-(Methoxycarbonyl)phenylacetic acid (15b).**[15] Mp 146–148 °C (from hexane–diethyl ether); ^{1}H NMR δ 3.88 (s, 3 H), 4.03 (s, 2 H), 7.2–7.3 (m, 1 H), 7.37 (td, J = 7.6 and 1.4 Hz, 1 H), 7.50 (td, J = 7.6 and 1.4 Hz, 1 H), 8.02 (dd, J = 7.6 and 1.4 Hz, 1 H), 10.67 (br s, 1 H); ^{13}C NMR δ 40.76, 52.25, 127.58, 129.26, 130.98, 132.26, 132.51, 135.17, 167.60, 176.92.

Oxidation of alcohols 10 by DMSO–oxalyl chloride[16]

To a solution of oxalyl chloride (280 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) was added DMSO (375 mg, 4.8 mmol) in CH_2Cl_2 (2 mL) at −70 °C during 20 min and then, to this solution was added a solution of alcohol **10b** (288 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at −10 °C during 20 min. The mixture was cooled again to −70 °C and triethylamine (505 mg, 5 mmol) was added during 5 min. Then, the mixture was poured into water, extracted with CH_2Cl_2, washed with saturated brine, and dried over anhydrous $MgSO_4$. By column chromatography on silica gel (elution with diethyl ether–hexane, 1.5 : 98.5) was obtained cyclododecanone (56 mg, 31%). Further elution with diethyl ether–hexane (1.5 : 98.5) gave peroxylactone **11b** (6 mg, 2%). Further elution with diethyl ether–hexane (20 : 80) gave a mixture of polar, unidentified products (32 mg).

Crystal structure determination of peroxylactone 11b†

Single crystals of peroxylactone **11b** suitable for X-ray crystallographic analysis were grown from a diethyl ether–hexane solution by slow evaporation.

The X-ray diffraction data were collected on a Brucker AXS P4 diffractometer at 160 K using graphite-monochromated MoKα λ = 0.71073 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.[17]

Crystal data

$C_{15}H_{26}O_5$, M = 286.36, colorless platelets, monoclinic, space group $P2_1/c$ (No. 14), a 18.827 (4), b 5.0970 (10), c 16.083 (3) Å, β 96.99 (2)°, U 1531.9 (5) Å^3, Z = 4, D_c 1.242 g cm^{-3}, F(000) 624, μ(MoKα) 0.092 mm^{-1}, 3693 reflections measured, 2685 unique (R_{int} 0.041) which were used in all calculations. The final discrepancy factors were: $R1$ = 0.056 and $wR(F^2)$ = 0.1125 (all data).

† CCDC reference number 202065. See http://www.rsc.org/suppdata/ob/b3/b300342f/ for crystallographic files in .cif or other electronic format.

References

1 (*a*) D. A. Casteel, *Nat. Prod. Rep.*, 1992, **9**, 289; D. A. Casteel, *Nat. Prod. Rep.*, 1999, **16**, 55; (*b*) K. J. McCullough and M. Nojima, *Curr. Org. Chem.*, 2001, **5**, 601; (*c*) C. W. Jefford, in *Comprehensive Heterocyclic Chemistry*, Ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon, Oxford, 1996, Vol. 6, Chap. 20; (*d*) R. K. Haynes and S. C. Vonwiller, *Acc. Chem. Res.*, 1997, **30**, 73; (*e*) A. K. Bhattacharya and R. P. Sharma, *Heterocycles*, 1999, **51**, 1681; (*f*) Y. Dong, *Mini Rev. Med. Chem.*, 2002, **2**, 113. For the synthesis of 1,2,4-trioxan-5-ones relevant to the present work, see; (*g*) C. W. Jefford, J.-C. Rossier and G. D. Richardson, *J. Chem. Soc., Chem. Commun.*, 1983, 1064; (*h*) C. W. Jefford, J. Currie, G. D. Richardson and J.-C. Rossier, *Helv. Chim. Acta*, 1991, **74**, 1239.

2 H.-S. Kim, Y. Nagai, K. Ono, K. Begum, Y. Wataya, Y. Hamada, K. Tsuchiya, A. Masuyama, M. Nojima and K. J. McCullough, *J. Med. Chem.*, 2001, **44**, 2357.

3 A. Gonzalez, J. Martin, C. Peret, J. Rovirosa, B. Tagle and J. Clardy, *Chem. Lett.*, 1984, 1469.

4 L. Sy, G. D. Brown and R. K. Haynes, *Tetrahedron*, 1998, **54**, 4345.

5 (*a*) Y. Nonami, T. Tokuyasu, A. Masuyama, M. Nojima, K. J. McCullough, H.-S. Kim and Y. Wataya, *Tetrahedron Lett.*, 2000, **41**,

4681; (*b*) Y. Hamada, H. Tokuhara, A. Masuyama, M. Nojima, H.-J. Kim, K. Ono, N. Ogura and Y. Wataya, *J. Med. Chem.*, 2002, **45**, 1374.
6 (*a*) W. H. Bunnelle and T. A. Isbell, *J. Org. Chem.*, 1992, **57**, 729; (*b*) S. Kawamura, H. Yamakoshi and M. Nojima, *J. Org. Chem.*, 1996, **61**, 5953; (*c*) Y. Ushigoe, Y. Torao, A. Masuyama and M. Nojima, *J. Org. Chem.*, 1997, **62**, 4949; (*d*) A. Rajca, S. Rajca, S. R. Dedai and V. W. Day, *J. Org. Chem.*, 1997, **62**, 6524.
7 K. J. McCullough, T. Ito, T. Tokuyasu, A. Masuyama and M. Nojima, *Tetrahedron Lett.*, 2001, **42**, 5529 . See also C.-S. Huang, C.-C. Peng and C.-H. Chou, *Tetrahedron Lett.*, 1994, **35**, 4175 and ref. 6*c*.
8 S. L. Schreiber, R. E. Claus and J. Reagan, *Tetrahedron Lett.*, 1982, **23**, 3867.
9 K. Teshima, S. Kawamura, Y. Ushigoe, M. Nojima and K. J. McCullough, *J. Org. Chem.*, 1995, **60**, 4755.
10 K. Tsuchiya, Y. Hamada, A. Masuyama, M. Nojima, K. J. McCullough, H.-S. Kim, Y. Shibata and Y. Wataya, *Tetrahedron Lett.*, 1999, **40**, 4077.
11 P. Groth, *Acta Chem. Scand., Sect. A*, 1975, **29**, 59.
12 K. Griesbaum, W.-S. Kim, N. Nakamura, M. Mori, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, 1990, **55**, 6153.
13 T. Sugimoto, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, 1990, **55**, 3816.
14 D. Timothy, D. D. Deininger, R. Russo, N. A. Senko, A. Katz, J. M. Kitzen, R. Mitchell, G. Oshiro, A. Russo, R. Stupienski and R. J. McCaully, *J. Med. Chem.*, 1992, **35**, 823.
15 C. Kaneko and T. M. C. Naito, *Heterocycles*, 1982, **18**, 2275.
16 A. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
17 G. M. Sheldrick, SHELXTL PC (vers. 5.1), Brucker AXS: Madison, WI, USA.