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LETTERS

The synthesis and crystal structure analysis of novel macrocyclic peroxides

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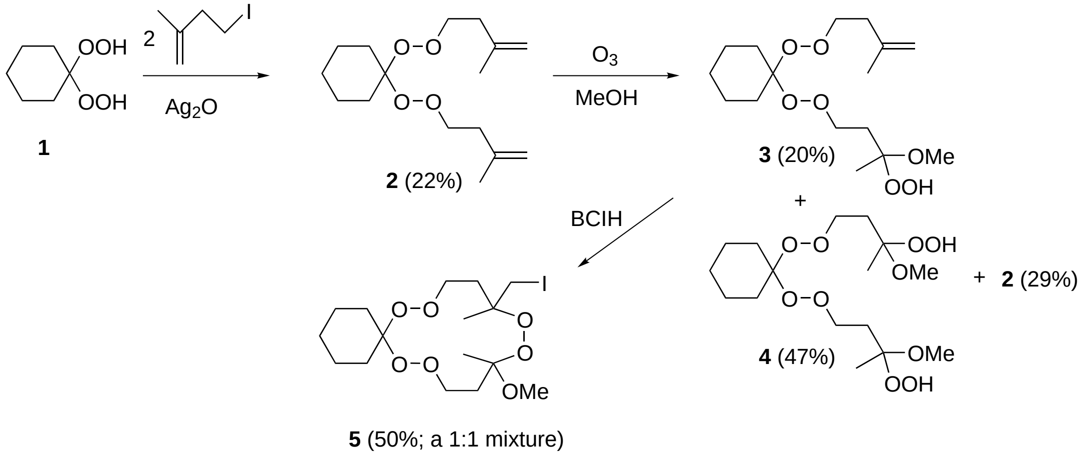
Abstract—Bis(*syn*-collidine)iodine(I) hexafluorophosphate-mediated cyclization of unsaturated hydroperoxides afforded the corresponding 11- to 16-membered macrocyclic peroxides having three peroxide units located within one ring. The crystal structures of three novel macrocyclic triperoxides were unambiguously determined by X-ray analysis. © 2001 Elsevier Science Ltd. All rights reserved.

During the last decade, the chemistry of cyclic peroxides has enjoyed a resurgence of interest with the increasing appreciation that such compounds occur widely in nature and often possess desirable pharmacological properties.[1] Thus, considerable effort has gone into developing short, efficient synthetic routes to 6- to 8-membered cyclic peroxides and identifying the key structure–activity relationships for their antimalarial activity against drug-resistant forms of malaria such as *P. falciparum*.[1–5] In contrast, examples of macrocyclic peroxides are comparatively scarce.[6–8] We now report that bis(*sym*-collidine)iodine(I) hexafluorophosphate (BCIH)-promoted cyclization of unsaturated hydroperoxides, prepared by three different methods, provides a variety of novel macrocyclic peroxides having three peroxide bonds located within one ring.[9,10]

The first approach to the synthesis of the desired unsaturated hydroperoxides was based on the mono-ozonolysis of the symmetrical bis(alkenylperoxy)cyclohexane **2**, which was prepared by alkylation of the bishydroperoxide **1** with 2 equiv. of 4-iodo-2-methylbutene in the presence of Ag_2O (Scheme 1). Subsequent reaction of diene **2** with 1.3 equiv. of ozone in MeOH-CH_2Cl_2 gave the unsaturated hydroperoxide **3** (20%) accompanied by



Scheme 1.

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di-ozonolysis product **4** (47%) and unreacted diene **2** (29%). This suggests that the rate of the reaction of the diene **2** with ozone was very similar to that of the mono-ozonolysis product **3**. Treatment of **3** with 1.5 equiv. of BCIH in CH_2Cl_2 at room temperature for 12 h gave the expected 13-membered macrocyclic triperoxide **5** in 50% yield (an equimolar mixture of two isomers). Subsequent X-ray crystallographic analysis of a suitable single crystal, obtained by fractional crystallization of the isomeric mixture from diethyl ether-hexane, unambiguously identified this material as the diastereoisomer *trans*-**5** (Fig. 1).[11] The 13-membered triperoxide ring has a triangular [553] shape with close to C_2-point group symmetry if the ring substituents are ignored. The ring atoms are disposed in a zigzag arrangement thereby minimizing Pitzer strain.

To investigate the scope of this methodology, the reactions of **7a,b** with BCIH were also carried out under similar conditions (Scheme 2). The corresponding macrocyclic peroxides **8a**,**b** were obtained in moderate yields. Although yields of the required unsaturated hydroperoxides **7** can be somewhat variable, the overall simplicity of this procedure rendered it an acceptable synthetic route to novel 11- and 13-membered cyclic peroxides.

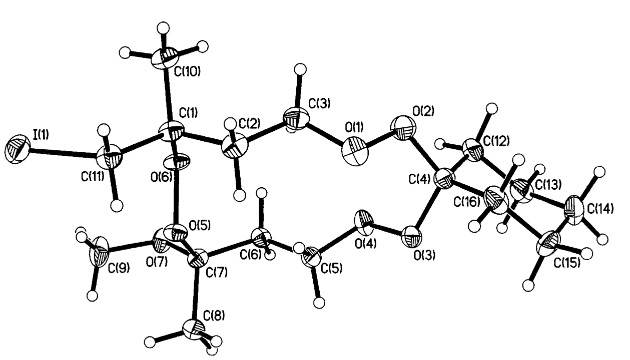
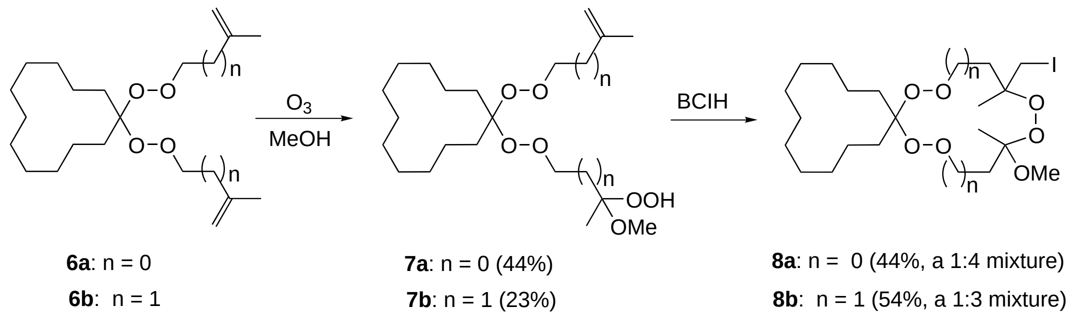


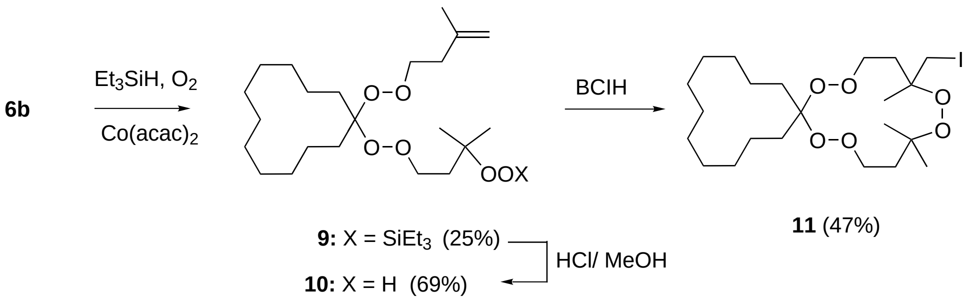
Figure 1. The crystal structure of 13-membered triperoxide **5**.[11]

In a second method for the synthesis of the required unsaturated hydroperoxides, the cobalt(II)-catalyzed triethylsilylperoxidation of diene **6b** with molecular oxygen and triethylsilane was attempted.[12–14] After a mixture of **6b**, a catalytic amount of cobalt(II) acetylacetonate, and triethylsilane in dry ethanol had been stirred at room temperature for 16 h under an oxygen atmosphere at a slightly positive pressure, the desired peroxide **9** was isolated in 25% yield after purification by column chromatography on silica gel. Subsequent removal of the triethylsilyl protecting group from **9**, followed by BCIH-mediated cyclization of hydroperoxide **10** yielded the expected 13-membered cyclic peroxide **11** in 47% yield (Scheme 3). X-Ray crystallographic analysis of compound **11** demonstrated that the 13-membered triperoxide ring of **11** adopts a similar conformation to that observed in *trans*-**5** (Fig. 2).[11]

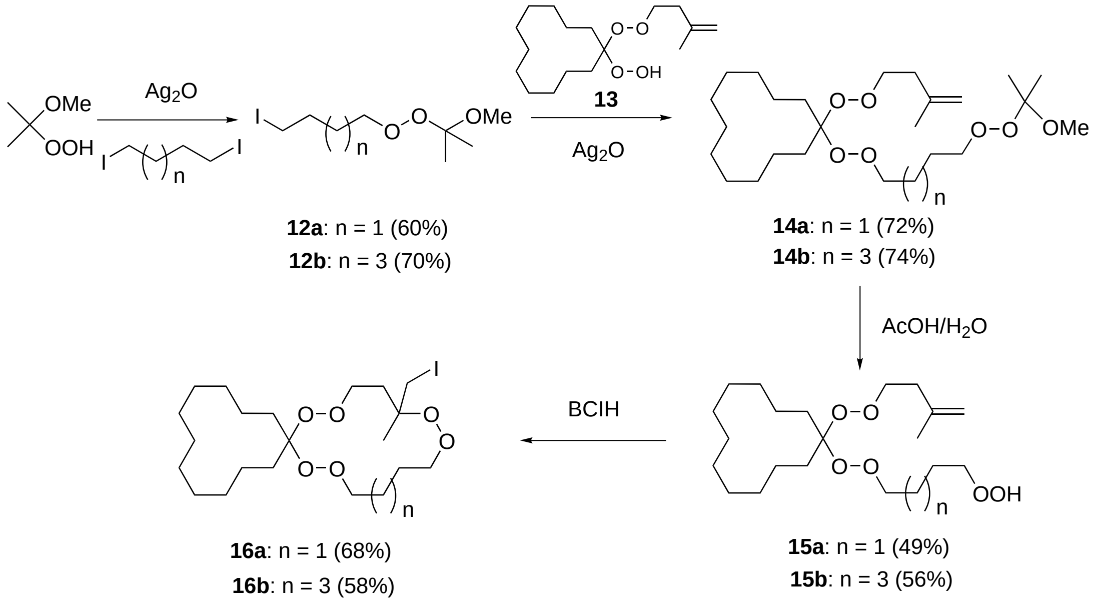
The third approach for the preparation of unsaturated hydroperoxide precursors involved the Ag_2O-catalysed alkylation of the hydroperoxide **13** with the iodoalkyl hemiperketal **12**[15] to provide the peroxide **14** in excellent yield (Scheme 4). Subsequent deprotection of **14**, followed by BCIH-promoted cyclization gave the 14- and 16-membered cyclic peroxides, **16a** and **16b** respectively (Scheme 4). The crystal structure of the novel 16-membered triperoxide **16b**, depicted in Fig. 3,[11] shows that the 16-membered ring adopts a rectangular



Scheme 2.



Scheme 3.



Scheme 4.

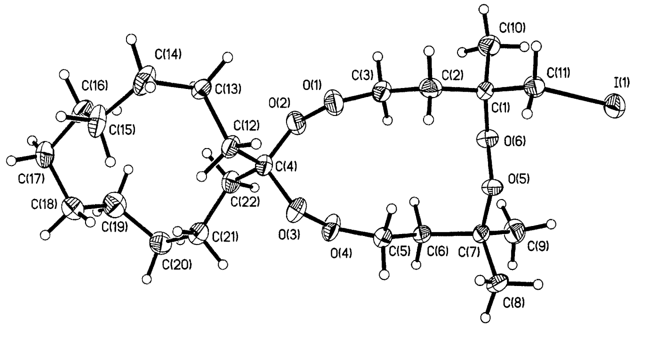


Figure 2. The crystal structure of 13-membered triperoxide **11**.[11]

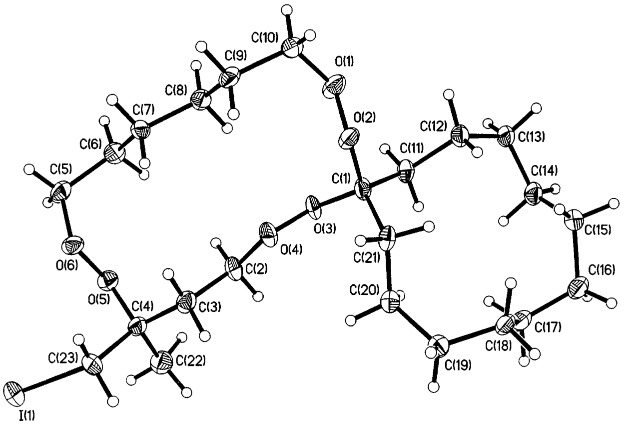


Figure 3. The crystal structure of 16-membered triperoxide **16b**.[11]

[5353] arrangement rather than the square [4444] conformation observed for cyclohexadecane.[16]

Since the product yield in each step is acceptable and, moreover, the length of the longer tether is readily variable, the latter procedure outlined in Scheme 4 should offer a convenient synthetic entry to a variety of novel macrocyclic peroxide systems.

Acknowledgements

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References

1. Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289–312; **1999**, *16*, 55–73.
2. Zhou, W. S.; Xu, X. X. *Accounts Chem. Res.* **1994**, *27*, 211–216.
3. Haynes, R. K.; Vonwiller, S. C. *Accounts Chem. Res.* **1997**, *30*, 73–79.
4. Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681–1745.
5. Meshnick, S. R.; Jefford, C. W.; Posner, G. H.; Avery, M. A.; Peters, W. *Parasitol. Today* **1996**, *12*, 79–82.
6. McCullough, K. J.; Tehsima, K.; Nojima, M. *J. Chem. Soc., Chem. Commun.* **1993**, 931–933.
7. Huang, C.-S.; Peng, C.-C.; Chou, C.-H. *Tetrahedron Lett.* **1994**, *35*, 4175–4176.
8. Rajca, A.; Rajca, S.; Dedai, S. R.; Day, V. W. *J. Org. Chem.* **1997**, *62*, 6524–6528.
9. Nonami, Y.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **2000**, *41*, 4681–4684 and the references cited therein.
10. Rousseau, G.; Homsi, F. *Chem. Soc. Rev.* **1997**, *26*, 453–461.

11. The X-ray diffraction data (Mo–K_α $\lambda = 0.71073$ Å) were collected on a Bruker AXS P4 diffractometer at 160 K. The diffraction data were corrected for Lorrentz and polarisation and absorption. The structures were solved by direct methods and refined by full least-squares techniques using anisotropic temperature factors for the non-hydrogen atoms. All crystallographic calculations and preparation of structure plots were carried out using the SHELXTL suite of progams (version 5.1; Sheldrick, G.M. Brucker AXS Inc., Madison, WI, USA.).

Crystal data for *trans*-**5**: $C_{16}H_{29}IO_7$, M = 460.29, triangular plate (data crystal dimensions 0.10×0.72×0.34 mm), monoclinic, space group $P2_1$, *a* 8.8361(10), *b* 10.2517 (15), *c* 10.5864 (19) Å, *β* 90.691 (15)°, U 958.9 (2) Å^3, $Z = 2$, D_c 1.594 g cm^{-3}, F(000) 468, μ(Mo–K_α) 0.1.702 mm^{-1}, final discrepancy factors: $R = 0.025$ and $R_w^2 = 0.064$ for $I > 2\sigma(I)$.

Crystal data for **11**: $C_{22}H_{41}IO_6$, M = 528.45, colorless block (data crystal dimensions 0.12×0.58×0.41 mm), triclinic, space group $P\bar{1}$, *a* 8.8624 (18), *b* 11.152 (2), *c* 13.425 (3) Å, *α* 83.916 (16), *β* 72.938 (17), *γ* 83.00 (2)°, U 1255.5 (4) Å^3, $Z = 2$, D_c 1.398 g cm^{-3}, F(000) 548, μ(Mo–K_α) 1.307 mm^{-1}, final discrepancy factors: $R = 0.038$ and $R_w = 0.102$ for $I > 2\sigma(I)$.

Crystal data for **16b**: $C_{23}H_{43}IO_6$, M = 542.47, colorless plate (data crystal dimensions 0.08×0.52×0.40 mm), monoclinic, space group $P2_1/c$, *a* 20.804 (5), *b* 12.357 (2), *c* 9.837 (5) Å, *β* 92.54 (2)°, U 2526.4 (15) Å^3, $Z = 4$, D_c 1.426 g cm^{-3}, F(000) 1128, μ(Mo–K_α) 1.301 mm^{-1}, final discrepancy factors: $R = 0.047$ and $R_w = 0.140$ for $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 161776, 161777 and 161778. Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

12. Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573–576.

13. Oh, C. H.; Kang, J. H. *Tetrahedron Lett.* **1998**, *39*, 2771–2774.

14. Magnus, P.; Payne, A. H.; Warning, M. J.; Scott, D. A.; Lynch, V. *Tetrahedron Lett.* **2000**, *41*, 9725–9730.

15. Dussault, P. H.; Zope, U. R.; Westermeyer, T. A. *J. Org. Chem.* **1994**, *59*, 8267–8268.

16. Anet, F. A. L.; Cheng, A. K. *J. Am. Chem. Soc.* **1975**, *97*, 2420–2424.