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Synthesis, crystal structure and antimalarial activity of functionalized spiro-1,2,4,5-tetraoxacycloalkanes from unsaturated hydroperoxy peracetals

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Abstract

Treatment of unsaturated hydroperoxy peracetals with bis(sym-collidine)iodine(I) hexafluorophosphate affords a series of iodine-containing spiro-1,2,4,5-tetraoxacycloalkane derivatives in high yield. In addition, ozonolysis of unsaturated hydroperoxy peracetals in AcOH–CH_2Cl_2 also results in the formation of spiro-1,2,4,5-tetraoxacycloalkanes. Two of the new compounds, 3-methyl-3-methyldioxy-1,2,6,7-tetraoxaspiro[7.11]-nonadecane and dimethyl-4-iodo-1,2,6,7-tetraoxaspiro[7.11]nonadecane, exhibit significant in vitro antimalarial activity against *P. falciparum* with EC_{50} values of ca. 10^{-7} M.

In the search for novel, nonalkaloidal antimalarial compounds analogous to artemisinin,[1] we recently reported that the reaction of (cycloalkylidene)bishydroperoxides with 1,ω-dihaloalkanes in the presence of CsOH in DMF affords 1,2,4,5-tetraoxacycloalkanes such as **2** (Scheme 1).[2] Ag_2O was also found to be a good mediator for the synthesis of tetroxocane derivatives,[3] several of which (e.g. compound **3**) exhibited remarkable in vitro antimalarial activity.[2] In this respect, we now report that iodonium ion- or ozone-promoted cyclization of unsaturated hydroperoxy peracetals such as **4** afforded several new spiro-1,2,4,5-tetraoxacycloalkane derivatives in excellent yield.[†]

The Ag_2O-mediated monoalkylation of (cyclododecylidene)bishydroperoxide **1** by 4-iodo-2-methyl-1-butene gave the expected unsaturated hydroperoxide **4** in moderate yield (Scheme 2).[4] On subsequent treatment with bis(sym-collidine)iodine(I) hexafluorophosphate (BCIH) in

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† All new compounds reported in this paper gave satisfactory microanalytical and spectroscopic data.

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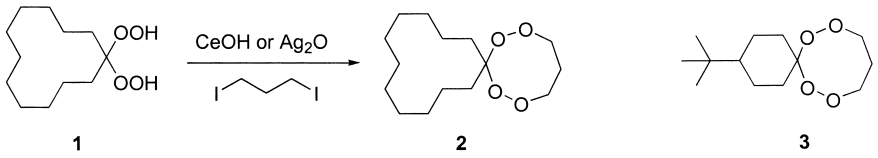
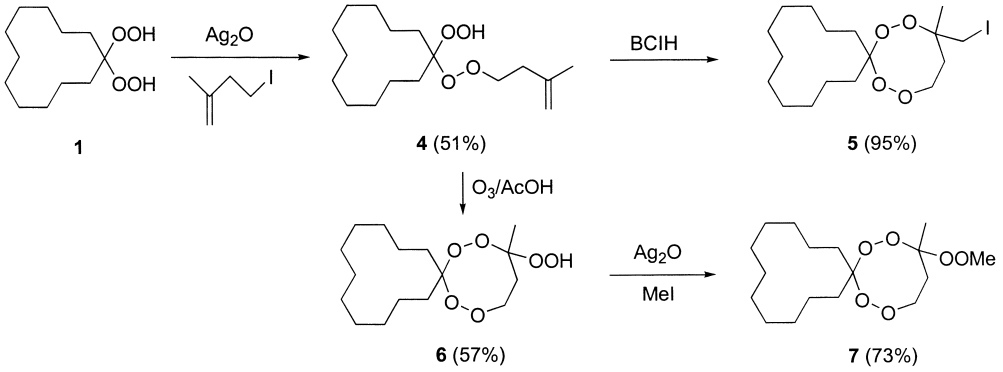


Scheme 1.

CH_2Cl_2, peracetal **4** underwent 8-*exo-trig* cyclization to give 1,2,4,5-tetroxocane **5** in high yield.[5] Ozonolysis of peracetal **4** in AcOH–CH_2Cl_2 provided a convenient method for the synthesis of the hydroperoxy-substituted 1,2,4,5-tetroxocane **6**.[6] Hydroperoxide **6** was readily methylated using methyl iodide in the presence of Ag_2O to yield **7** (Scheme 2).

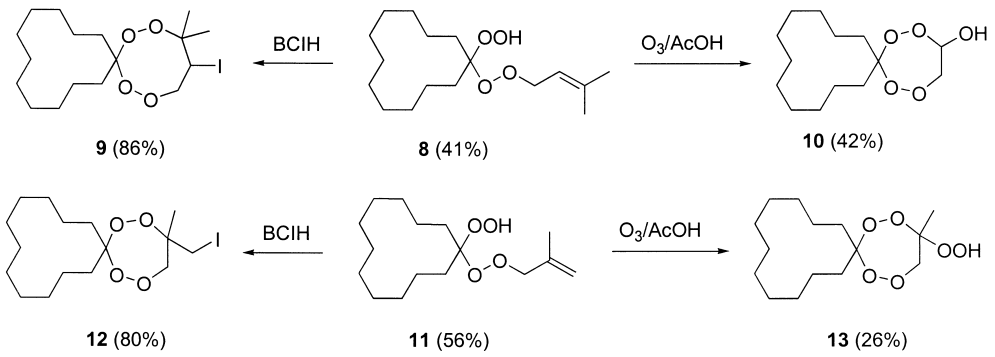


Scheme 2.

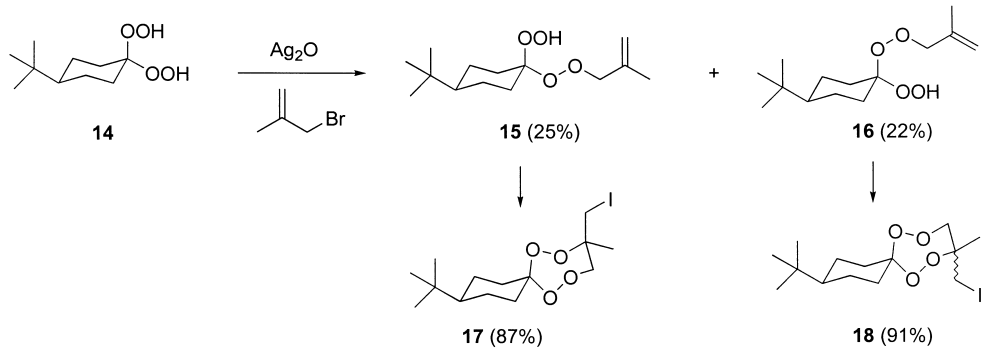
The structure of the unsaturated side-chain was found to influence the nature of the cyclization products. Thus, when the related peracetal **8** was treated with BCIH, 4-iodo-substituted 1,2,4,5-tetroxocane **9** was obtained via an 8-*endo-trig* cyclization mode. Ozonolysis of **8** in AcOH–CH_2Cl_2 provided the hydroxy-substituted 1,2,4,5-tetroxepane. Treatment of peracetal **11** with BCIH gave the expected tetroxepane derivative **12**, while ozonolysis in AcOH–CH_2Cl_2 provided the hydroperoxy-substituted tetroxepane **13** in a relatively poor yield of 26% together with cyclododecanone (55%) (Scheme 3).

Monoalkylation of the bishydroperoxide **14** with 3-bromo-2-methylpropene gave two isomeric hydroperoxides **15** and **16**, which were separated by column chromatography on silica gel. Subsequent reaction of **15** and **16** with BCIH gave in each case the corresponding tetroxepane derivatives **17** and **18** (Scheme 4). The structure of **17** was unambiguously determined by the X-ray crystallographic analysis (Fig. 1).[‡,7] The 1,2,4,5-tetroxepane ring in **17**, which adopts a twist-boat conformation, appears to be relatively strain-free with the values of the geometrical parameters generally lying within expected ranges.

[‡] The X-ray diffraction data were collected on a Bruker AXS P4 diffractometer at 160 K using graphite-monochromated Mo-K_α $\lambda = 0.71073$ Å. The structure was solved by direct methods and refined using least-squares techniques. Crystal data for **17**: $C_{14}H_{25}IO_4$, $M = 384.24$, monoclinic, $P2(1)/c$, $a = 6.1435$ (6), $b = 9.3090$ (13), $c = 28.0931$ (19) Å, $\beta = 90.963$ (6)°, $U = 1606.4$ (3) Å^3, $Z = 4$, $D_c = 1.589$ g cm^{-3}, $F(000) = 776$, μ(Mo-K_α) = 2.001 mm^{-1}. Final discrepancy factors: $R1 = 0.0345$ and $wR^2 = 0.0839$.



Scheme 3.



Scheme 4.

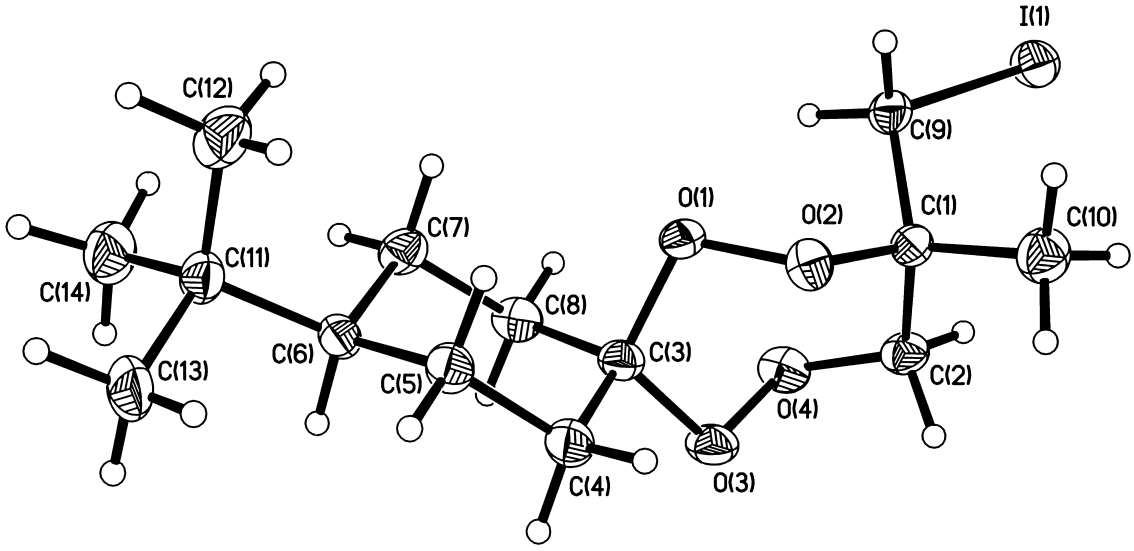


Figure 1. The X-ray crystal structure of tetroxepane derivative **17** (ORTEP, 50% probability ellipsoids for non-hydrogen atoms)[7]

Preliminary in vitro studies of the antimalarial activities of the various new cyclic peroxides prepared as described above against *P. falciparum*[8] showed that compounds **7** and **9** had EC_{50} values of 1.0×10^{-7} M and 8.0×10^{-8} M, respectively, which are approximately one tenth of the antimalarial potency of artemisinin (7.8×10^{-9} M). In contrast, none of the other cyclic peroxides, viz. **5**, **6**, **10**, **12**, **13**, **17** and **18**, showed notable antimalarial activity. These results, together with the fact that the EC_{50} value of **2** (2.5×10^{-8} M) is very similar to that of artemisinin, indicate that relatively minor changes in the structures of cyclic peroxides have a profound effect on their observed antimalarial activities.

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