

Simple Conversion of Cycloalkenes into Bromo-substituted Prostanoid Endoperoxides (Dioxabicyclo[*n*.2.1]alkanes)

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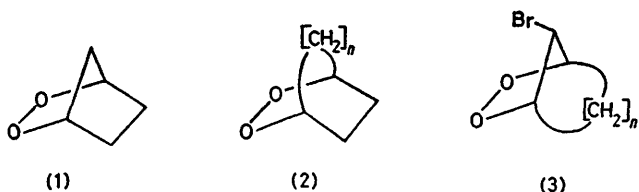
Summary Dioxabicyclo[*n*.2.1]alkanes bearing a *cis*-bromine on the one-carbon bridge are readily prepared from cycloalkenes by the sequence singlet oxygenation, bromination, and treatment with silver trifluoroacetate.

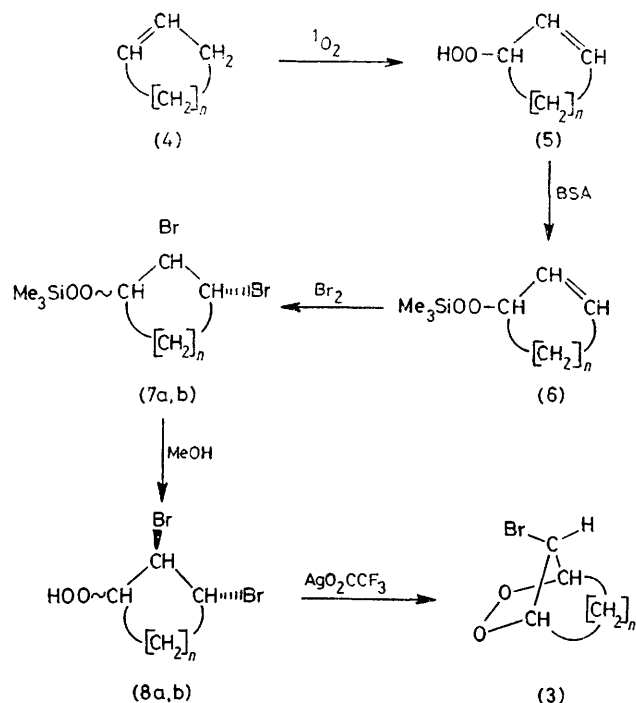
CHEMICAL lability associated with the 2,3-dioxabicyclo[2.2.1]heptane (1) nucleus of prostaglandin endoperoxides is important in the biosynthesis of prostaglandins.¹ To establish which structural features of this nucleus, if any, are necessary to observe the type of chemistry associated with prostaglandin endoperoxides, it is desirable to study the behaviour of a variety of related bicyclic peroxides. Of particular interest are comparisons within homologous series where some features of structure (1) are retained by

each member while others are varied systematically. The recently discovered combination of singlet oxygenation of cycloalka-1,3-dienes and di-imide reduction provides a general route to dioxabicyclo[*n*.2.2]alkanes (2),² a series in which each homologue retains the type of 1,2-dioxacyclohexane ring present in (1). We now describe the preparation of a new homologous series of endoperoxides that are substituted dioxabicyclo[*n*.2.1]alkanes (3), where the 5-membered peroxide ring is the prostanoid feature that is preserved throughout.

Our strategy is outlined in the Scheme. Commercially available reagents are used throughout and each step of the procedure is easy to carry out. First, the 2-cycloalkenyl hydroperoxide (5) was prepared by photo-oxygenation of the cycloalkene (4), neat or in dichloromethane solution, using tetraphenylporphine as sensitizer and a 140 W sodium lamp as light source. The reaction was slow but also clean at the 5–25% conversions obtained after 3–5 days' irradiation. Pure hydroperoxides were thus obtained simply by removing unchanged cycloalkene (and dichloromethane if used) followed by short-path distillation under reduced pressure.

Next, the hydroperoxide was silylated using bis(trimethylsilyl)acetamide (BSA) before carrying out bromine addition in carbon tetrachloride at 0 °C. Methanolysis





SCHEME

then afforded the crude 2,3-dibromocycloalkyl hydroperoxide as a mixture of *cis-trans* (**8a**) and *trans-trans* (**8b**) diastereoisomers. Intermediates (**6**) and (**7**) were not isolated and an almost quantitative conversion of (**5**) into (**8**) was achieved. Purification of (**8**) by column chromatography ($SiO_2-CH_2Cl_2$) also effected partial separation of the diastereoisomers.

The advantages of adding bromine to the trimethylsilyl peroxide (**6**) rather than directly to the hydroperoxide (**5**) are twofold. First it reduces the formation of side products

arising from (mainly intermolecular) attack of peroxide upon the intermediate bromonium ion, and secondly it increases the fraction obtained of *cis-trans*-2,3-dibromocycloalkyl hydroperoxide (**8a**) which is the isomer that ring-closes to give endoperoxide in the final step. Both effects were particularly dramatic with the cyclohexenyl system.

The ring closure was carried out by stirring (**8**) with silver trifluoroacetate in dichloromethane for 1 h at room temperature. The endoperoxide (**3**) was readily separated from the more polar components of the mixture, including unchanged hydroperoxide and products of trifluoroacetate-for-bromine substitution, by low temperature column chromatography ($SiO_2-CH_2Cl_2$; *ca.* $-35^\circ C$) and was purified by recrystallisation (light petroleum- CH_2Cl_2) at low temperature.

TABLE. Prostanoid endoperoxides (**3**)^a

<i>n</i>	M.p./ $^\circ C$	Yield/% ^b	^{13}C n.m.r. ^c	$\delta(Me_4Si)/p.p.m.$
2	52–53	13	82.36, 55.12, 27.85	
3	72–74	27	82.89, 60.39, 32.07, 16.06	
4	76–77	38	87.50, 57.40, 32.57, 22.63	
5	64–65	13	88.59, 62.04, 32.28, 25.83, 25.31	

^a Satisfactory C, H, and Br analyses were obtained for each compound, and mass spectra showed the expected M^+ and $(M+2)^+$ ions. ^b Of isolated peroxide. Based on cycloalkenyl hydroperoxide (**5**). ^c $CDCl_3$ solution.

The bicyclic peroxides obtained are shown in the Table. Further evidence of structure was provided by 1H n.m.r. spectroscopy. For the [2.2.1]-endoperoxide the absence of long range W-plan coupling for the $CHBr$ proton shows that the bromine is *cis* to the peroxide linkage and confirms that, as expected,³ the dioxabicyclization takes place with inversion of configuration. It is assumed that this holds also for the other three systems.

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¹ K. H. Gibson, *Chem. Soc. Rev.*, 1977, **6**, 489; K. C. Nicolaou, G. P. Gasic, and W. E. Barnette, *Angew. Chem. Internat. Edn.*, 1978, **17**, 293.

² D. J. Coughlin, R. S. Brown, and R. G. Salomon, *J. Amer. Chem. Soc.*, 1979, **101**, 1533, and references therein.

³ N. A. Porter and D. W. Gilmore, *J. Amer. Chem. Soc.*, 1977, **99**, 3503.