Synthesis of *erythro*-18,19-Dihydroxysqualene 2,3-Oxide and Other Internally Oxidized Squalene Derivatives

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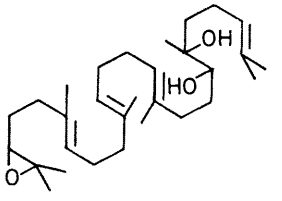
Summary In addition to the title compound, the preparation of the four possible internal monodiols and of the four possible internal monoepoxides of squalene are described; trisubstituted aliphatic epoxides were found to be readily deoxygenated by zinc dust/acetic acid.

THE discovery by van Tamelen and Curphey[1] of the selective oxidation of the terminal double bonds of squalene led to the establishment of squalene 2,3-oxide as the precursor of lanosterol.[2] I now report the conversion of the intact squalene molecule into specific internal oxidation products. One such derivative, *erythro*-18,19-dihydroxysqualene 2,3-oxide (**1**) has been transformed by nonenzymic cyclization to (±)-malabaricanediol.[3]



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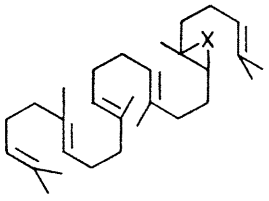
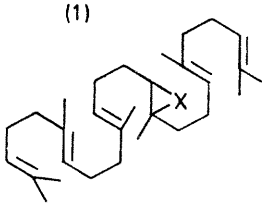


(2a) and (2b) X = O
(4a) and (4b) X = OH,OH

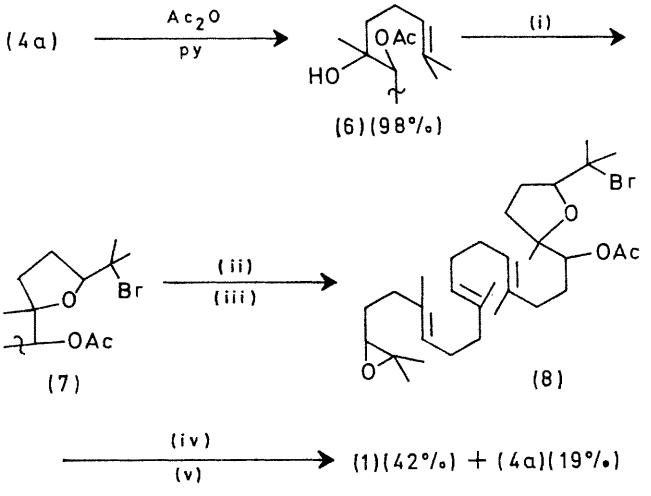


(3a) and (3b) X = O
(5a) and (5b) X = OH,OH

Epoxidation of squalene (200 g) with peracetic acid (1·3 equiv.) in methylene chloride afforded squalene 2,3-oxide and the two *trans* internal oxides (**2a**) and (**3a**) in roughly equal amounts. Controlled acidic hydrolysis allowed selective opening of the terminal epoxide moiety in the presence of the internal oxides. The resulting partial hydrolysis mixture was subjected to thiourea clathrate formation and only contaminating squalene and oxides (**2a**) and (**3a**) formed the complex—the terminal diol was excluded. Removal of the squalene by filtration through silica gel with hexane left 53 g (26% overall yield) of the two internal *trans*-oxides (**2a**) and (**3a**). This epoxide mixture was readily hydrolysed to a mixture of the corresponding *erythro*-diols (**4a**) and (**5a**) by treatment with aqueous perchloric acid in t-butyl alcohol.

Although squalene 2,3-oxide and squalene 2,3-diol separate on silica gel chromatography from their internal analogues, the internal isomers do not separate from each other. However, on silver nitrate-impregnated silica gel the mono-internal diols (**4a**) and (**5a**), but not the corresponding oxides (**2a**) and (**3a**), separate dramatically. The faster moving isomer is (**4a**), as demonstrated by periodate cleavage to the expected C_8 and C_{22} fragments; the slower isomer (**5a**) is cleaved by periodate to the predicted C_{13} and C_{17} components. The diols are eluted from either column chromatography or t.l.c. as crystalline silver nitrate complexes. Decomposition of these complexes with aqueous ammonia releases the pure diols (**4a**) and (**5a**), which are easily transformed back to the corresponding oxides (**2a**) and (**3a**) by sequential treatment with an excess of toluene-*p*-sulphonyl chloride in pyridine, ice, and finally potassium hydroxide—all in the same vessel.

Pure samples of the *cis* internal oxides (**2b**) and (**3b**) and their corresponding *threo*-diols (**4b**) and (**5b**) were also prepared. In this case squalene was randomly *cis*-hydroxylated with osmium tetroxide in pyridine and the terminal



SCHEME. Reagents: (i) *N*-bromosuccinimide (1·1 equiv), Bu^{t}OH, 2 h; (ii) H_2O, then NBS (1·2 equiv.) 1 h; (iii) CO_3^{2-} (10 equiv.), 2 h; (iv) HOAc (12 equiv.)/Zn dust, 10 min.; (v) KOH–MeOH (50 min.).

mono-diol was separated from the internal pair (**4b** and **5b**) by silica gel chromatography. As with their *erythro*-analogues, the *threo*-diols separated readily from each other on silver nitrate-impregnated silica gel and the faster moving isomer was (**4b**). The separated *threo*-diols were quantitatively transformed to the corresponding *cis*-oxides (**2b** and **3b**) by the toluene-*p*-sulphonyl chloride/pyridine procedure. The *cis*-oxides (**2b**) and (**3b**) reveal a single oxiran methyl resonance at δ 1·32 and the corresponding resonance for the *trans*-oxides (**2a**) and (**3a**) appears at δ 1·26.

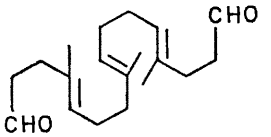
Starting from *erythro*-diol (**4a**) the required epoxy-diol (**1**) was prepared in 41% overall yield (Scheme). The only significant by-product (19%) was the starting diol (**4a**). Following the initial acetylation, the remaining five steps were effected in the same reaction vessel over the course of 4 h. The individual steps were monitored by t.l.c.

The key reaction involves protection of one terminal double bond by formation of the cyclic bromo-ether (**7**).[4,5]

It was necessary to acetylate the secondary OH group of (**4a**) to prevent formation of a bromo-ether involving the adjacent internal double bond. The bromo-ether (**7**) was accompanied by 3—4% of the 6-membered-ring bromo-ether resulting from Markownikoff opening of the intermediate bromonium ion. Both the 5- and 6-membered-ring bromo-ethers serve the necessary protective function and are reduced by zinc dust to the desired product.

The zinc dust reduction of epoxy-bromo-ether (**8**) requires only a trace of acetic acid catalyst. If a large quantity of acetic acid is introduced, the 2,3-oxide function is rapidly reduced to the corresponding olefin. Controls with squalene 2,3-oxide revealed that this unusual reduction is complete in 10—15 min at room temperature in glacial acetic acid; squalene is the exclusive product. Perhydrosqualene 2,3-oxide was reduced at a comparable rate. Reduction of the pure *trans*-internal oxide (**2a**) produced *cis*- and *trans*-olefin in almost equal amounts. This deoxygenation of purely aliphatic epoxides by zinc dust/acetic acid does not appear to have been reported previously.

After the final saponification (Scheme) the required epoxy-diol (**1**) was easily separated from the starting diol (**4a**) by preparative silica gel t.l.c. Diol (**1**) gave the correct elemental analysis and consonant i.r. and n.m.r. spectra. That (**1**) was not contaminated by isomeric diols was demonstrated by hydrolysis to the corresponding tetraol followed by periodate cleavage. G.l.c. analysis revealed the sole fragments to be the C_{19} dialdehyde (**9**) (M^+, m/e = 290) and the known C_8-ketone (**10**).



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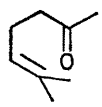

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[2] E. E. Tamelen, *Accounts Chem. Res.*, 1968, **1**, 111.
[3] K. B. Sharpless, *J. Amer. Chem. Soc.*, in the press.
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[5] O. Tanaka, N. Tanaka, T. Ohsawa, Y. Iitaka, and S. Shibota, *Tetrahedron Letters*, 1968, 4235; E. Demole and P. Enggist, *Chem. Comm.*, 1969, 264.