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RESOLUTION OF SQUALENE 2,3-EPOXIDE

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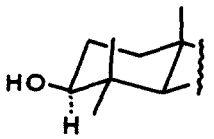
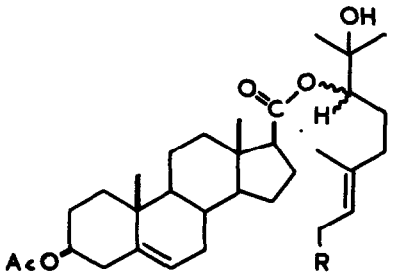
The intermediacy of squalene 2,3-epoxide in the biosynthesis of 3-oxygenated triterpenes (and derived compounds) in mammalian tissue,[1] micro-organisms,[2] and plants[3] is now firmly established. The frequently made assumption that (3S)-squalene 2,3-epoxide (I) acts as a specific precursor of 3β-oxygenated triterpenes (as II) has, however, received only indirect experimental support.[4] We here report a convenient resolution of this important precursor. Biochemical results which fully confirm the validity of the above assumption are presented elsewhere.[5] The interesting possibility that some 3α-hydroxy triterpenes might be formed via (3R)-squalene 2,3-epoxide remains to be tested.[6]

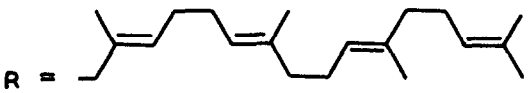
(I)



(II)



(III)



Treatment of squalene 2,3-diol[7] with 3β-acetoxy-17β-chloroformylandrost-5-ene[8] in dry pyridine gave the diastereoisomeric esters (III) (85%) as a gum, $[\alpha]_D$ -14.9°. P.l.c. on silica gel GF_{254} then readily afforded the individual isomers, $[\alpha]_D$ -6.5° and -23.5°, which on reduction with lithium aluminium hydride gave optically pure squalene 2,3-diols (70%), $[\alpha]_D$ + and -10.7°. Application of Horeau's procedure[9] showed these diols to have the (3R) and (3S) configurations respectively, in agreement with molecular rotation requirements[10] and CD results.[4] Treatment of the diols with p-toluenesulphonyl chloride in pyridine followed by the addition of ethanolic potassium hydroxide solution gave (3S)- and (3R)-squalene 2,3-epoxides respectively (80%), $[\alpha]_D$ approximately -1.8° and +2.0° (MeOH). The absolute configuration and essential optical purity of each isomer was established by (a) reconversion, with overall inversion, into squalene 2,3-diol, (b) model experiments with the 24,25-epoxides and 24,25-diols derived from lanosteryl acetate,[10] and (c) biosynthetic experiments.[5]

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Footnotes and References

All new compounds gave satisfactory analytical and spectroscopic data. Rotations are for chloroform solutions except as indicated.

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