A New Method for Removal of a 4-Methyl Group from Triterpenes

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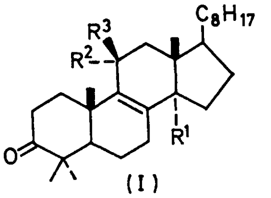
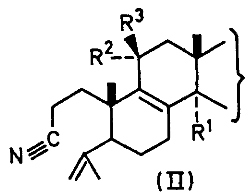
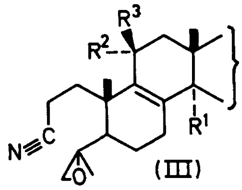
Summary A high-yielding four-step sequence for removal of a 4-methyl group from the model compound 4,4-dimethyl-5α-cholestan-3-one has been devised; the method has been applied to the synthesis of 4α,14α-dimethyl-5α-cholest-8-en-3-one and 4α,14α-dimethyl-5α-cholestane-3,11-dione from lanosterol.



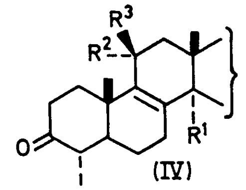
(I)



(II)

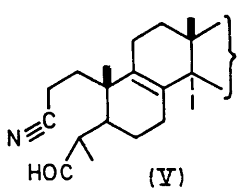


(III)

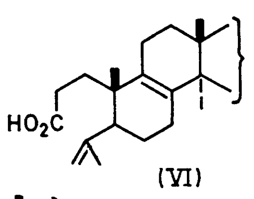


(IV)

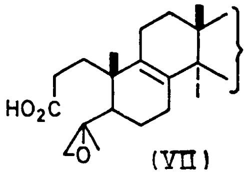
(a; 8β, 9α-dihydro, $R^1 = R^2 = R^3 =$ H)
(b; $R^1 =$ Me, $R^2 = R^3 =$ H)
(c; 8β, 9α-dihydro, $R^1 =$ Me, $R^2,R^3 =$ O)



(V)



(VI)



(VII)

ALTHOUGH considerable attention has been paid to the conversion of tetracyclic triterpenes into 4,4-bisdemethyl derivatives,[1-4] only recently has interest been shown in the removal of a single 4-methyl group.[3-5] Our object[4] has been to find a method for modifying the A ring of the fungal acids, such as eburicoic acid and tumulosic acid, to that present in the triterpenoid antibiotic, fusidic acid.[6] We now report a scheme, related to that of Holker, Jones, and Ramm,[5] which achieves the required monodemethylation at position 4 in a short, high yielding, sequence of reactions.

Initially we chose as a model compound 4,4-dimethyl-5α-cholestan-3-one (Ia), which was converted into the seco-nitrile† (IIa), m.p. 70—72°, by an 'abnormal' Beckmann rearrangement of the oxime with toluene-*p*-sulphonyl chloride in pyridine.[2,7] Treatment of (IIa) with *m*-chloroperoxybenzoic acid gave an epoxide (IIIa), m.p. 90—91° (90%), which, when heated at reflux under nitrogen in dry toluene containing BF_3–Et_2O followed by the usual work up, gave (IVa) (70%).

The reaction sequence can be readily applied to 5α-lanost-8-en-3-one (Ib) since the seco-nitrile (IIb)[2] reacts with *m*-chloroperoxybenzoic acid at 0° to afford a high yield (80%) of the epoxide (IIIb), which was a mixture (95:5) of two epimers, m.p. 89–90° (major), and 140—141°, separable by p.l.c. Treatment of the mixture of epoxides (IIIb) with BF_3 in the same way as (IIIa) gave (IVb)[4] (65%). Similarly the non-crystalline seco-nitrile (IIc), ν_{max} 2252, 1700, and 1640 cm^{-1}, obtained (75%) from the 3-oxime derivative, m.p. 202—203°, of 5α-lanostane-3,11-dione, yielded (80%) the epoxide (IIIc), which was again a mixture (95:5) of epimers, m.p. 91—93° (major), and 181—180°. Treatment of this mixture of epoxides with

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† All new compounds gave satisfactory analytical data and had the expected spectral properties.

BF_3–Et_2O in toluene afforded 4α,14α-dimethyl-5α-cholestane-3,11-dione, m.p. 119—120° (75%).

It is relevant to the mechanism of the step (III) → (IV) that reaction of (IIIb) with BF_3 for a short time gave the nitrile aldehyde (V), m.p. 92—94° (80%), ν_{max} 2250 and 1722 cm^{-1}, which the n.m.r. spectrum showed to be a *ca.* 1 : 1 mixture of C(4) epimers. Further reaction of (V) under the same conditions produced (IVb) in good yield. We have also found that toluene-*p*-sulphonic acid in toluene may be used for the ring closure, but yields were lower than for the BF_3 reaction.

In an alternative but lower yielding route to (IVb) the seco-acid (VI)[4,8] was converted cleanly (85%) with *m*-chloroperoxybenzoic acid at 0° into the epoxy-acid (VII), m.p. 160—161° (*ca.* 95 : 5 mixture of epimers by the n.m.r. spectrum). Reaction of (VII) in toluene with either BF_3–Et_2O or toluene-*p*-sulphonic acid gave (IVb) in 41 and 30% yield respectively.

(*Received, September 7th,* 1971; *Com.* 1572.)

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