Biogenetic-type Oxidation–Cyclization in the Total Synthesis of Triterpenoid Systems

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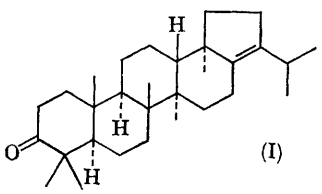
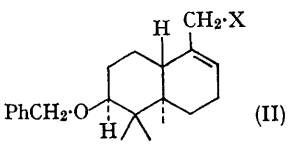
WE describe a total synthesis of the pentacyclic triterpenoid hopenone-I (I), proceeding through β- and γ-onocerin, and featuring coupling of sesquiterpenoid halves built up by oxidation–cyclization of acyclic terpene.[1,2]

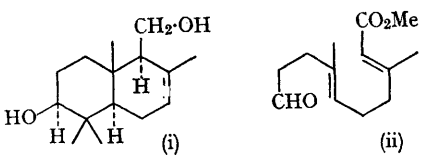


(I)

The key bicyclic intermediate (II) desired for entry into the C_{30}-series was produced most conveniently by a reaction sequence starting with cyclization of methyl *trans,trans*-farnesate 10,11-epoxide (III),[3] secured by selective terminal

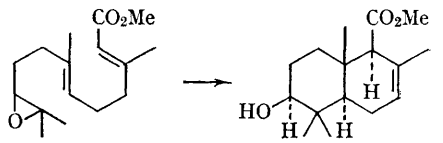


(II)



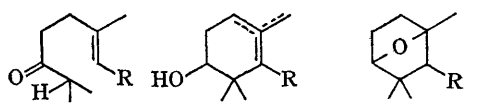
(i) (ii)

oxidation of the acyclic triene ester.[4,5] In addition to bicyclic hydroxy-ester (IV a–b) (22—28% yield), phosphoric acid (or boron trifluoride etherate) treatment of (III) gave rise to acyclic keto-ester



(III) (IVa)

(V), monocyclic hydroxy-ester (VI), and bridged ether (VII). Whereas the bicyclic ester from the phosphoric acid experiment consisted[6] of 13% axial ester (IVb), 72·5% equatorial ester (IVa)[7] and 14·5% $\alpha\beta$-unsaturated ester (VIII; R=H, R′=Me);

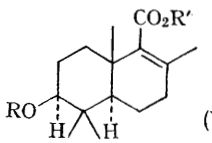


(V) (VI) (VII)

{R = $[CH_2]_2{\cdot}C(Me)=CH{\cdot}CO_2Me$}

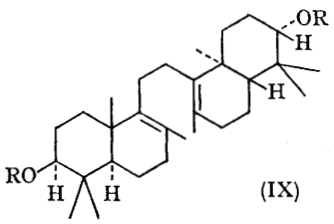
corresponding product from the boron trifluoride cyclization contained 2% axial, 91% equatorial ester along with 7% of an unknown product. Thus the boron trifluoride procedure is distinctly stereoselective, providing in one operation bicyclic system possessing the *trans–anti–trans*-stereochemistry characteristic of polycyclic terpene and steroid frameworks.

In order to prepare for the coupling process, the $\beta\gamma$-unsaturated ester was isomerized to the $\alpha\beta$-unsaturated type (VIII). For this purpose and also by reason of later chemical transformations, protection of the hydroxyl function was required; and thus *O*-benzyl ether (VIII; R = Ph·CH_2, R′ = Me) was prepared from the epimeric mixture (IV a–b) by treatment with benzyl chloride/sodium hydride in dioxan. The (non-crystalline) ether ester was equilibrated by means of sodium methoxide in dimethyl sulphoxide; the $\alpha\beta$-unsaturated ester present (16%) was enriched (39%) by chromatography, and then selectively hydrolyzed with formic acid–sulphuric acid[8,9] to give (±)-3-benzyloxy-β-bicyclofarnesic acid (VIII; R = Ph·CH_2, R′ = H), m.p. 174—176°. Lithium aluminium hydride converted the methyl ester (VIII; R = Ph·CH_2; R′ = Me) into the non-crystalline allyl alcohol (II; X = OH).

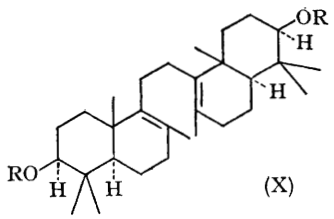


(VIII)

Coupling was effected in 52% yield by conversion of the (±)-alcohol into the corresponding bromide (II; X = Br) by means of 48% hydrobromic acid, followed by treatment with magnesium in ether. Fractional crystallization yielded (±)-β-onocerin



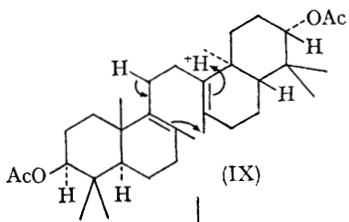
(IX)



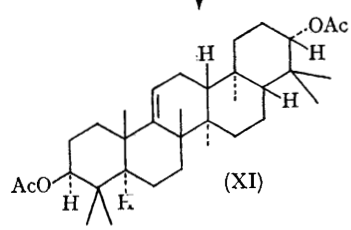
(X)

dibenzyl ether (IX; R = Ph·CH_2) and the *meso*-isomer (X; R = Ph·CH_2) m.p.'s 158—160° and 194—198°. Although spectrally indistinguishable, the isomers did not exhibit identical behaviour on thin-layer chromatography; and by such comparison with authentic (+)-β-onocerin dibenzyl ether (see below), the lower-melting isomer was shown to be the (±)-species. Cleavage of the benzyl ether groupings with sodium in liquid ammonia and subsequent acetylation of the diol afforded (±)-β-onocerin diacetate (IX; R = Ac), m.p. 180—181°. The corresponding *meso*-compound (X; R = Ac) melted at 217—220°.

Resolution of (±)-3-benzyloxy-β-bicyclofarnesic acid (VIII; R = Ph·CH_2; R′ = H) was accomplished through use of its brucine salt. The non-crystalline (+)-acid, $[\alpha]_D$ + 99·4°, was submitted to the same reaction sequence described above to yield (+)-β-onocerin dibenzyl ether (IX; R = Ph·CH_2), m.p. 135—138°, spectrally identical with the (−)-(and the *meso*-) compound. After reductive cleavage and acetylation, this dibenzyl ether gave rise to diacetate (IX; R = Ac) m.p. 235—236°, $[\alpha]_D$ + 117°, identical in all respects with authentic (+)-β-onocerin diacetate.[10]



(IX)



(XI)

As would be anticipated on the basis of earlier observations,[10] either (+)- or (±)-β-onocerin diacetate provided, on treatment with acetic–sulphuric acid at 25° for 16 hr., a modest yield of pentacyclic product, the γ-onocerin diacetate (XI). In the racemic series, γ-onocerin diacetate was obtained from benzene–methanol as colourless crystals, m.p. 320°; while in the (+)-form, the pentacycle melts at 333—336°.[10] The infrared and n.m.r. spectra of (+)- and (±)-γ-onocerin diacetate

were indistinguishable. Since (+)-γ-onocerin diacetate has been converted[11] into hopenone-I (I),[12] the above synthetic operations embrace that latter system as well.[13]

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[1] For previous work and reviews on the non-oxidative, acid-catalyzed laboratory cyclization of terpenes, see, *e.g.*, G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068; P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1373; P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *ibid.*, p. 2191.

[2] The first and only synthesis to date of a naturally occurring triterpene, α-onocerin, was achieved by G. Stork, J. E. Davies, and A. Meisels, *J. Amer. Chem. Soc.*, 1959, **81**, 5516; 1963, **85**, 3419.

[3] *Cf.* The cyclization of farnesyl acetate 10,11-epoxide to (±)-3-hydroxydrimenol (i), E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Amer. Chem. Soc.*, 1961, **83**, 3295.

[4] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.

[5] Assignment of structure (IV) rests upon (1) n.m.r. characteristics (two olefinic and two saturated *C*-methyl groups), and (2) epoxide ring-opening to glycol, which was cleaved in high yield by periodate to acetone and aldehydro-ester (ii).

[6] V.p.c. analysis of the mixture of corresponding keto-esters, obtained by chromic acid oxidation.

[7] Identified unequivocally by lithium aluminium hydride reduction to authentic (±)-3-hydroxydrimenol (ref. 3).

[8] *Cf.* A. Caliezi and H. Schinz, *Helv. Chim. Acta*, 1952, **35**, 1637.

[9] The overall 24% yield of αβ-unsaturated acid can be increased by recovering unhydrolyzed βγ-unsaturated ester and re-subjecting the latter to base-induced equilibration.

[10] D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 1955, 2639.

[11] K. Schaffner, L. Caglioti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1958, **41**, 152.

[12] H. Fazakerley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1959, 1877.

[13] Analytical and spectral properties were in all cases consistent with the assigned structures.