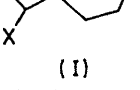
Total Synthesis of Zizaane-type Sesquiterpenoids

By FUSAO KIDO, HISASHI UDA, and AKIRA YOSHIKOSHI*
(*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai, Japan*)

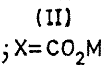
Summary Zizaane-type sesquiterpenoids have been synthesised from methyl (+)-camphene carboxylate.

ZIZAANE-TYPE sesquiterpenoids, *e.g.* zizaene (tricyclovetivene)[1] (Ia), khusimol[2] (Ib), zizanoic acid[2] (Ic), and epizizanoic acid[3] (Id), occur in vetiver oil. We report their total synthesis.

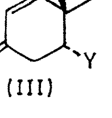
Lithium aluminium hydride reduction of methyl (+)-camphene carboxylate[4] (IIa) gave the alcohol (IIb), m.p. 31°, which was then oxidised to the aldehyde (IIc) by dicyclohexylcarbodi-imide–dimethyl sulphoxide–phosphoric acid[5] in 80% yield. In the presence of sodium ethoxide, (IIc) condensed with acetone to give the *trans*-enone (IId), λ_{max} 230 nm. (ϵ 9900), ν_{max} 1692 cm.$^{-1}$, δ 6·01, 6·94 (d., 1H each, J 16 Hz.), in 76% yield. Hydrocyanation of (IId) with potassium cyanide–ammonium chloride[6] and subsequent ozonisation of the resulting cyano-ketone led to the cyano-diketone (IIe), ν_{max} 2240, 1738, and 1721 cm.$^{-1}$, shown to be homogeneous on t.l.c. and n.m.r., in 45% overall yield from (IId). Benzoic acid-piperidine catalysed the cyclisation of (IIe) to the tricyclic ketone (IIIa), m.p. 62—62·5°, λ_{max} 240 nm. (ϵ 13,300) (62% yield), and the n.m.r. coupling pattern of the latter at δ 2·66 (d., 1H, J 7·4 Hz.) was suggestive of an α-cyano-group. Attempted desulphurisation of the ethylenethioacetal of (IIIa) and hydrolysis of its cyano-group to a carboxy-group were unsuccessful, while a hydroxy-compound obtained by sodium borohydride reduction of (IIIa) underwent smooth hydrolysis in boiling methanolic potassium hydroxide giving a carboxylic acid, and esterification of the crude hydrolysis product with diazomethane followed by Jones oxidation afforded the desired keto-ester (IIIb), m.p. 91—92°, λ_{max} 241 nm. (ϵ 15,400), ν_{max} 1730 and 1659 cm.$^{-1}$, in 70% yield from (IIIa). The unsaturated ester (IIIc) was obtained by desulphurisation of the ethylenethioacetal of (IIIb) with Raney nickel.



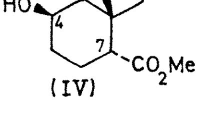
(I)
a; X = β-Me
b; X = β-CH_2OH
c; X = β-CO_2H
d; X = α-CO_2H



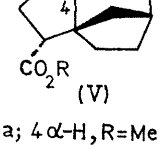
(II)
a; X = CO_2Me, Y = CH_2
b; X = CH_2OH, Y = CH_2
c; X = CHO, Y = CH_2
d; X = CH:CHCOMe, Y = CH_2
e; X = CH(CN)CH_2COMe
Y = O



(III)
a; X = O, Y = CN
b; X = O, Y = CO_2Me
c; X = H_2, Y = CO_2Me



(IV)



(V)
a; 4α-H, R=Me
b; 4β-H, R=Me
c; 4β-H, R=H

The coupling pattern of (IIIc) at δ 2·63 (q., 1H, J 4 and 10 Hz.) indicated an equatorial ester group; however its orientation depends on the conformation of the cyclohexene ring. Assuming that a chair conformation is preferable for the cyclohexene ring, the ester group would be α.

Osmic acid oxidation of (IIIc) yielded the dihydroxy-ester (IV), δ 3·07 and 4·21 (m., 1H each, $W_{\frac{1}{2}}$ = 18·2 and 19·3 Hz., respectively; assigned to the axial protons on C-4 and C-7), whose monomesylate was treated with potassium t-butoxide at room temperature for 15 min., causing pinacol rearrangement to the keto-ester (Va), m.p. 92—93°, ν_{max} 1726 and 1692 cm.$^{-1}$, o.r.d. $[\phi]_{310}$ −639. Prolonged treatment with the base in the above rearrangement gave a 2 : 3 equilibrium mixture of (Va) and its epimer (Vb), m.p. 78—78·5°, ν_{max} 1737 and 1709 cm.$^{-1}$, o.r.d. $[\phi]_{312}$ +6925, $[\phi]_{259}$ −9425, and the keto-esters were separated by silica gel column chromatography. Identity of (Va) and (Vb) with authentic specimens[3] derived from the methyl ester of epizizanoic acid (Id) was shown by a comparison of i.r., n.m.r., and o.r.d. On lithium aluminium hydride reduction followed by Jones oxidation, (Vb) afforded the keto-carboxylic acid (Vc), whose sodium salt was treated with a large excess of methylenetriphenylphosphorane in dimethyl sulphoxide at 58° for several days, giving an unsaturated carboxylic acid, indistinguishable from epizizanoic acid (Id) by a comparison of the i.r. spectra, in approximately 10% yield.

Transformation of epizizanoic acid into zizanoic acid (Ic), khusimol (Ib), and zizaene (Ia) has been reported.[2,3]

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