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A STEREOSELECTIVE TOTAL SYNTHESIS OF dl 1β 4aα-DIMETHYL-cis-1, 1a, 2, 3, 4, 4a-HEXAHYDROFLUOREN-9-ONE-1α-CARBOXYLIC ACID

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The close structural and biogenetic relationship between the gibberellins[1] with some diterpenoids[1,2] directed attention towards the conversion in the hydrophenanthrene diterpenoid skeleton to B-nor compounds[3], with the characteristic hydrofluorene ring system of these plant growth substahces. The first successful transformation of the enantiomer of methyl 6,7-diketo-5-isodesoxy podocarpate[4] to the hydroxy acid I, through benzillic acid rearrangement was realised by two groups[3a,b,c]. On controlled oxidation the acid I was converted to the keto acid II[3a,b,c]. We now report the first streoselective total synthesis of the dl 1β 4aα-dimethyl-cis-1,1a,2,3,4,4a-hexahydrofluoren-9-one-1α-carboxylic acid (II)*.

2-Benzyl-3-methyl-Δ^2-cyclohexenone (III)[5], b.p. 130-132°/0.4 mm., λ_{max} 242 mμ (log ε 4.0), was prepared in 85% yield through the condensation of Hagemann's ester with

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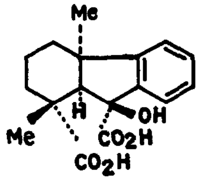
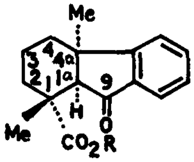
* Although formulas of only one enantiomer are drawn, they are taken to represent a racemate except where indicated. All new compounds for which melting and boiling points are reported have been characterised by microanalytical data and the homogeneity of the solid compounds have been checked by thin layer chromatography. Infra-red spectra were determined in chloroform solution and the ultraviolet spectra in 95% ethanol solution.

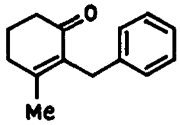


I



II, R= H

IIa, R= Me



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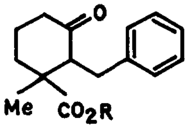
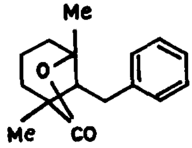


IV, R= H

V, R= Me



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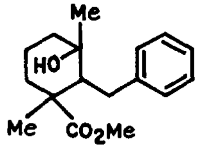
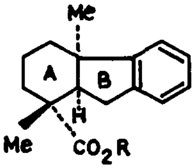
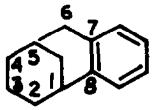


VII



VIII, R = H

IX, R = Me



X

benzylchloride in the presence of potassium-*t*-butoxide followed by alkaline hydrolytic decarboxylation. Conjugate addition of hydrogen cyanide[6] to the unsaturated ketone III and subsequent alkaline hydrolysis yielded 2-benzyl-3-methyl-3-carboxy*cyclo*hexanone (IV), m.p. 153.5-154°, in satisfactory yield. The methyl ester V, b.p. 142-145°/0.4 mm.; yellow 2:4-dinitrophenylhydrazone, m.p. 230°, on reaction with methylmagnesiumiodide yielded the γ-lactone VI, m.p. 106°, ν_{max} 1765 cm^{-1}, and the hydroxy ester VII, m.p. 73°, ν_{max} 1722 cm^{-1} and 3550 cm^{-1}, in a ratio of about 1:8, beside small amount of a liquid (γ-lactone and ester mixture) which was not characterised further. The cyclisation of the hydroxy-ester VII, with polyphosphoric acid[6] at 80-82° for 1 hr. followed by alkaline hydrolysis of the resulting liquid product yielded a single crystalline acid VIII, m.p. 170-171°, ν_{max} 1700 cm^{-1}, λ_{max} 260 mμ (log ϵ 2.94), 266 mμ (log ϵ 3.14), 273 mμ (log ϵ 3.14) in about 50% yield; methyl ester IX, (diazomethane, m.p. 48°, ν_{max} 1730 cm^{-1}; λ_{max} 259 mμ (log ϵ 2.71), 262 mμ (log ϵ 2.70), 265 mμ (log ϵ 2.75) and 272 mμ (log ϵ 2.75). On dehydrogenation with Pd-C (10%) the acid VIII, yielded 1-methylfluorene, m.p. 84-85°, alone or mixed with an authentic sample. The cyclisation of γ-lactone VI with polyphosphoric acid under various conditions either led to the recovery of the starting material or a neutral hydrocarbon which revealed the absence of carbonyl band in the infra-red, and on dehydrogenation with Pd-C (10%) yielded 1-methylfluorene, thus confirming that cyclisation had proceeded through the loss of carboxyl group[6,7].

The inherent difficulty encountered in Bogert-Cook acid-catalysed cyclisation of benzylcyclohexene (with or without substitution in the cyclohexene and benzene ring) to the hydrofluorene system, in preference to the facile cyclisation to 7,8-benzobicyclo (3,3,1) nonane system (X) has been adequately demonstrated[8,5a]. It is of importance to note here that in the present studies both the hydroxy ester VII, and the lactone VI, yielded the hydrofluorene system with polyphosphoric acid, though in the latter case with complete elimination of the carboxyl group**.

Remarkable degree of stereoselectivity through the generation of the angular C-10 asymmetric centre containing the methyl group, with respect to the C-4 *gem*-methyl-carboxyl group, by the acid catalysed closure of the 9,10-bond in an aromatic alkylation process has been utilised for the synthesis of resin acids[6,7,9]. It has been established that only podocarpic acid system[6] (for an exception however, see ref. 10), i.e., *cis*-orientation of the C-4 carboxyl with respect to the C-10 methyl group, with both *trans* and *cis* A/B-ring junction is generated by this process. Similar steric control in the cyclisation of the hydroxy ester VII would be expected to give rise to the *cis*-orientation of the angular methyl group (at C-4a) with respect to C-1 carboxyl group, and since a single acid was obtained in this case stereochemistry VIII may be reasonably

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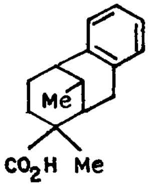
** The cyclisation of the γ-lactone VI, with $AlCl_3$ however yielded the acid (i) in about 48% yield. Further studies on this type of cyclisation will be reported in a separate communication.



(i)

assigned to this, with stable cis A/B-ring fused hexahydrofluorene system[11].

On oxidation with chromic acid[6], the methyl ester IX afforded the liquid keto ester (IIa), ν_{max} 1709 cm^{-1} and 1725 cm^{-1}; λ_{max} 247 mμ (logϵ 4.15), 292 mμ (logϵ 3.41), in 30% yield, after purification through chromatography over acid-washed alumina, which on refluxing with excess of methanolic sodium methoxide solution yielded only a single crystalline compound, the keto acid II, m.p. 123-124°, λ_{max} 245 mμ (logϵ 4.11) and 290 mμ (logϵ 3.38), in 80% yield. The infrared spectra of this synthetic keto acid II is identical with that of the authentic l-isomer and the methylesters (diazomethane) of both the acids showed identical retention time in V.P.C., which conclusively establishes the stereochemistry assigned to the acid VIII, except for the ring junction. The catalytic (Pd-C) reduction of the keto acid II in ethanol in presence of perchloric acid yielded the acid VIII, which correlates the stereochemistry of these two acids at the ring junction. Since the keto acid II was derived from the methyl ester IIa through equilibriating condition, it most probably has cis-ring junction[11], but no rigorous proof could yet be advanced.

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