The Stereoselective Synthesis of *meso–trans*-1,3-Dimethylcyclohexane-2-acetic-1,3-dicarboxylic Acid

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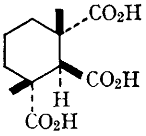
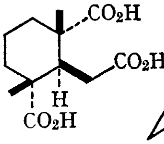
THE key to the stereochemistry of ring A of most diterpenoid resin acids was furnished by their drastic oxidation to yield two *meso*-acids (I) and (II).[1] The establishment by Barton and Schmeidler[2] of the *meso–trans*-structure (I) for the C_{11}-acid provided the first solid evidence of the *trans*-fusion between ring A and its neighbours. The degradation conditions are so drastic, however, that the possibility of stereomutation of an initially-formed isomer *via* the epimerisable 2-carboxylic acid function cannot be entirely ruled out. We now report the synthesis of the non-epimerisable *trans–meso*-C_{12}-acid (II) by a route which unambiguously defines the stereochemistry at the three centres.[3]

1,5-Dimethylbicyclo[3,3,1]non-2-en-9-one (III)[4] in which the two methyl groups are necessarily *cis*-related, was treated with sodium acetylide in dimethylformamide[5] to yield a mixture of the epimeric carbinols (IV; R = H). Pyrolysis of the corresponding mixture of acetates (IV; R = COMe) in the presence of zinc oxide[6] proceeded smoothly to give the allene acetate (V), which was hydrolysed by mild acid treatment to the $\alpha\beta$-unsaturated aldehyde (VI). Specific saturation of the conjugated carbon–carbon double bond of (VI) with lithium in ammonia, followed by chromium trioxide oxidation and diazomethane esterification led to a mixture of two esters epimeric at C-9 (VII shows the axial isomer). Separation by gas–liquid chromatography gave a liquid ester (35%) and a crystalline isomer, m.p. 29° (65%). That the more abundant, crystalline ester was in fact the desired axial isomer (VII) was shown unequivocally by the spectroscopic properties of the liquid equatorial isomer, and the derived acid and primary alcohol. For example, in the high-dilution infrared spectrum of the last compound, OH · · · π-bonding gives rise to a weak bonded-hydroxyl stretching absorption at 3538 $cm.^{-1}$ in addition to the free hydroxyl band at 3636 $cm.^{-1}$; this is possible only if the hydroxyethyl side-chain at C-9 is equatorial. The axial primary alcohol derived from (VII) exhibited a single, free-hydroxyl absorption at 3638 $cm.^{-1}$ under these conditions.

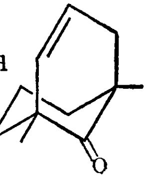
This assignment was confirmed by the very sluggish reaction of the liquid equatorial ester with selenium dioxide in acetic acid, whereas the



(I)



(II)



(III)

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[2] D. H. R. Barton and G. A. Schmeidler, *J. Chem. Soc.*, 1948, 1197.

[3] For previous unsuccessful attempts to synthesize these C_{11} and C_{12}-acids see B. Arbusow and O. Schapschinskaja, *Ber.*, 1935, **68**, 437; S. M. Mukherjee, *J. Indian Chem. Soc.*, 1947, **24**, 495; P. N. Rao and P. Bagchi, *J. Org. Chem.*, 1958, **23**, 169; D. K. Banerjee and S. N. Mahapatra, *Teterahedron*, 1960, **11**, 234.

[4] J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 1964, 289.

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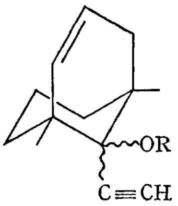
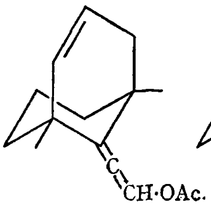
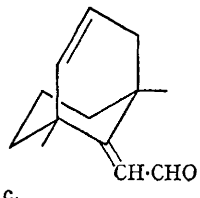


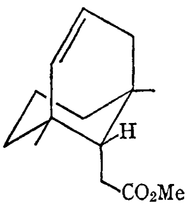
(IV)



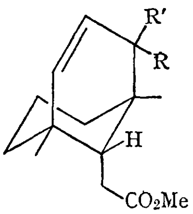
(V)



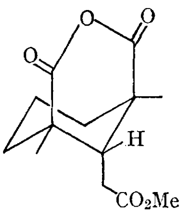
(VI)



(VII)



(VIII)



(IX)

less-hindered solid axial isomer (VII) underwent rapid oxidation with this reagent to furnish the corresponding allylic acetate (VIII; R = H; R′ = OCOMe). Hydrolysis and manganese dioxide oxidation produced the conjugated ketone (VIII; R,R′ = O) λ_{max} (EtOH) 233 mμ (ε, 6850); m.p. 59·5—60°. Finally, the two *cis*-1,3-dicarboxylic acid groupings of the acid (II) were created by mild acid potassium permanganate oxidation of this conjugated ketone. This yielded the 1,3-anhydride ester (IX) and the corresponding dicarboxylic acid, both of which were converted by mild base treatment into the *meso–trans*-C_{12}-tricarboxylic acid (II) m.p. 208—212° (wide range due to anhydride formation) identical in physical and spectroscopic properties with an authentic sample of the diterpene degradation product kindly provided by Professor L. Ruzicka and Professor O. Jeger. A more precise comparison of the trimethyl esters of the synthetic and naturally-derived acids could detect no difference in their infrared, n.m.r., and mass-spectral properties and they were inseparable under several conditions of gas–liquid chromatography.

Satisfactory microanalytical and mass-spectral data were obtained for all compounds reported and infrared and n.m.r. spectra were completely consistent with the structures formulated.

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