Total Synthesis of α-Cubebene, β-Cubebene, and Cubebol

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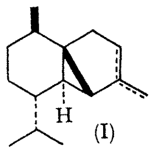
CUBEBOL (cubeb camphor), a sesquiterpenoid of cubeb oil,[1] has been assigned structure (II), the stereochemistry at C-4 and C-10 remaining unsolved.[2] Recently α-cubebene (Ia) and β-cubebene (Ib),[3] and closely related alcohols cubenol (IIIa) and *epi*-cubenol (IIIb),[4] have been isolated from the same essential oil and their structures elucidated.[5]

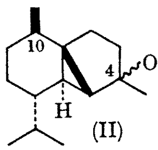
We report the total synthesis of these sesquiterpenoids.

Reaction of (—)-*trans*-caran-2-one[6] (IVa) with allylmagnesium bromide followed by hydroboration–oxidation afforded a mixture from which the crystalline diol (IVb), m.p. 143—145°, was separated in 20% yield. Oxidation of (IVb) with chromic anhydride in pyridine gave the spirolactone (IVc), m.p. 57—59°, in quantitative yield. The lactone (IVc) was pyrolysed in a sealed tube at 250—300° for a short time in the presence of pyridine, which prevented the formation of aromatic by-products, giving the unsaturated acid (Va) in 70% yield, the latter was purified and characterized as its methyl ester. After the crude carboxylic acid (Va) was converted into the diazoketone (Vb) in the usual way, without further purification, the product in cyclohexane was heated with copper powder to give a mixture consisting of (VIa), (VIIa), and (VIII) (m.p. 85—86°) in 11, 13, and 1% overall yield from (IVc), respectively.



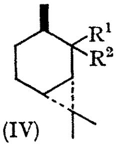
(I)

(a) *endo*-double bond
(b) *exo*-double bond



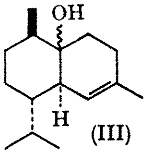
(II)

(a) α-OH
(b) β-OH



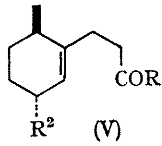
(IV)

(a) $R^1 R^2=O$
(b) $R^1=OH$, $R^2=[CH_2]_3OH$
(c) R^1, $R^2=[CH_2]_2CO_2$



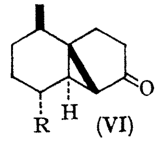
(III)

(a) α-OH
(b) β-OH



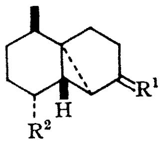
(V)

(a) $R^1=OH$, $R^2=CMe{:}CH_2$
(b) $R^1=CHN_2$, $R^2=CMe{:}CH_2$



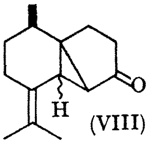
(VI)

(a) $R=CMe{:}CH_2$
(b) $R=CHMe_2$



(VII)

(a) $R^1=O$, $R^2=CMe{:}CH_2$
(b) $R^1=O$, $R^2=CHMe_2$
(c) $R^1=CH_2$, $R^2=CHMe_2$



(VIII)

The bicyclo[3,1,0]hexan-2-one moiety in these ketones was indicated by their u.v. and i.r. spectra. Upon hydrogenation with tris(triphenylphosphine)rhodium chloride as a catalyst, (VIa) gave the saturated ketone (VIb), m.p. 57—58°, identical in every respect with the norketone[3] obtained from β-cubebene (Ib). Similar treatment of (VIIa) provided the corresponding saturated ketone (VIIb). The stereoformulae assigned to (VIb) and (VIIb) were based on c.d. measurement:[7] (VIb), $[\theta]_{284} + 13{,}600$, $[\theta]_{215} - 18{,}900$; (VIIb), $[\theta_{281} - 11{,}000$; $[\theta]_{211} + 16{,}800$; *c* 0·509 in methanol). Both ketones (VIb, VIIb) were allowed to react with methylenetriphenylphosphorane in dimethyl sulphoxide, and gave β-cubebene (Ib), identical with the natural product, and its stereoisomer (VIIc), respectively.

Reaction of (VIb) with methylmagnesium iodide or methyl-lithium gave the crystalline methylcarbinol (IIa), m.p. 61—62°, $[\alpha]_D^{20} - 48{\cdot}3°$ (*c* 3·52 in chloroform), as the major product (47%), and this was identified as cubebol by a comparison of the i.r. spectra. Since preferential attack of alkylmetal reagents on the bicyclo[3,1,0]hexan-2-one system takes place from the side opposite to the cyclopropane ring,[8] the hydroxy-group in cubebol is α. Oxymercuration–demercuration[9] of α-cubebene (Ia), which would be expected to yield an epimeric methylcarbinol on the basis of the reported stereoselectivity of this reaction, afforded the liquid carbinol (IIb) as the major product (32%).

Dehydration of cubebol with thionyl chloride in pyridine under mild conditions gave a mixture of α-cubebene (Ia), β-cubebene (Ib), (7 : 2 in relative ratio) and other hydrocarbons. Successive treatment of cubebol with dimethylsulphinyl carbanion, carbon disulphide, and methyl iodide[10] gave rise to spontaneous decomposition of the resulting methyl xanthate, yielding a mixture of α-cubebene, β-cubebene, (1 : 2 in relative ratio) and other hydrocarbons. Both cubebenes were isolated by preparative g.l.c., and the synthetic α-cubebene was indistinguishable from the natural product.

Transformation of α-cubebene into cubenol and *epi*-cubenol has been reported.[11]

We thank Dr. Y. Hirose for providing authentic samples of cubebenes and Mr. Ueno for (—)-carvone; Professor V. Herout and Drs. Y. Hirose and G. L. K. Hunter for identification of cubebol, the norketone (VIa), and cubenes, respectively; and Dr. K. Kuriyama for the c.d. measurements.

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[4] Y. Ohta and Y. Hirose, *Tetrahedron Letters*, 1967, 2073.

[5] Isolation of cubebenes from citrus oils has also been reported. M. K. Veldhuis and G. L. K. Hunter, *J. Food Sci.*, 1967, **32**, 697.

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