

The Total Synthesis of Racemic Nootkatone

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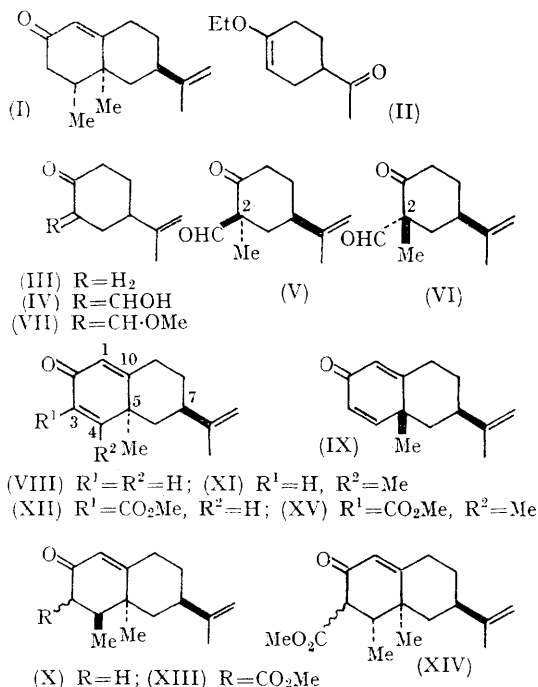
NOOTKATONE, a sesquiterpene ketone first isolated¹ from the heartwood of Alaska yellow cedar (*Chamaecyparis nootkatensis*) and later also found² in grapefruit (*Citrus paradisi*) and other citrus species has been assigned the structure (I).³ A partial synthesis of nootkatone starting from the parent hydrocarbon valencene has been described.⁴ We report a total synthesis of racemic nootkatone beginning with 4-acetyl-1-ethoxycyclohexene⁵ (II).

Reaction of the ketone (II) with triphenylmethylphosphonium iodide in tetrahydrofuran in the presence of n-butyl-lithium, followed by mild acid hydrolysis, yielded 4-isopropenylcyclohexanone (III) [b.p. 102—103°/20 mm.; ν_{\max} 1710 (CO), 1645, and 900 cm^{-1} (C=CH₂)].[†] Sodium methoxide-catalysed condensation of (III) with ethyl formate⁶ leads to the hydroxymethylene derivative (IV) [b.p. 55—60°/0.005 mm.; λ_{\max}

[†] The spectral data quoted refer to ethanol solutions for the u.v., carbon tetrachloride solutions for the i.r., and deuteriochloroform solutions for the n.m.r.

312 $m\mu$ (ϵ 11,800); ν_{\max} 1660, 1620, 895 cm^{-1}], which was treated with methyl iodide in acetone to give a mixture of the keto-aldehydes (V) and (VI) and the enol ether (VII) [(V):(VI):(VII) *ca.* 55:18:27]. The keto-aldehydes (V) and (VI) could be separated by preparative gas chromatography [(V): b.p. 55–65°/0.01 mm.; ν_{\max} 2725, 1730, 1710, 1645, 895 cm^{-1} ; δ 9.76 (s, CHO), 1.40 p.p.m. (s, Me at C-2); (VI): b.p. 55–65°/0.01 mm.; ν_{\max} 2700, 1715, 1650, 895 cm^{-1} ; δ 9.45 (s, CHO), 1.23 p.p.m. (s, Me at C-2)]. Condensation of (V) and (VI) with acetone⁷ in the presence of piperidine–acetic acid and subsequent treatment of the reaction product with methanolic potassium hydroxide yielded the dienones (VIII) and (IX) respectively [(VIII): m.p. 39–40°; λ_{\max} 242 $m\mu$ (ϵ 15,500); ν_{\max} 1665, 1635, 1608, 895 cm^{-1} ; δ 1.33 p.p.m. (s, Me at C-5); (IX): b.p. 122–124°/0.01 mm.; λ_{\max} 242 $m\mu$ (ϵ 13200); ν_{\max} 1660, 1630, 1608, 895 cm^{-1} ; δ 1.30 p.p.m. (s, Me at C-5)]. For preparative purposes the mixture of (V), (VI), and (VII) was similarly treated to give the dienones (VIII) and (IX) in a ratio of 5:1. Separation of (VIII) from (IX) was by crystallization.

The reductive methylation of (VIII) with lithium dimethylcuprate(I) ($Li^+Me_2Cu^-$)⁸ in absolute ether



at 0°, gave in about 85% yield almost exclusively 4-epi-nootkatone (X) [b.p. 75–80°/0.004 mm.; λ_{\max} 241 $m\mu$ (ϵ 14,400); ν_{\max} 1682, 1650, 1630, 895 cm^{-1} ; δ 1.33 (s, Me at C-5), 1.02 p.p.m. (d, *J* 7 c./sec., Me at C-4)] and only traces of nootkatone (I), detectable by capillary g.l.c. The dehydrogenation of (X) with 2,3-dichloro-5,6-dicyanobenzoquinone in toluene⁹ led to racemic 3,4-dehydro-nootkatone (XI) [b.p. 100–105°/0.001 mm.; λ_{\max} 243 $m\mu$ (ϵ 17,500); ν_{\max} 1672, 1635, 1620, 895 cm^{-1} ; δ 2.01 (s, Me at C-4), 1.37 p.p.m. (s, Me at C-5)], spectral properties and g.l.c. behaviour identical with those of a specimen similarly obtained from natural nootkatone. This proves that the configuration of the isopropenyl and angular methyl groups in (XI), (X), (VIII), and (V) is the same as in natural nootkatone.† Consequently (X) differs from nootkatone (I) only in its opposite configuration at C-4.

In order to transform dehydro-nootkatone (XI) into nootkatone (I), we attempted to reduce the 3,4-double bond under various conditions. However, the 1,10-double bond in (XI) was attacked, preferentially, and again only minor quantities of nootkatone were obtained.

The tetra-substituted conjugated double bond in the keto-ester (XV) might be expected to be reduced more easily than the corresponding tri-substituted one. Therefore the dienone (XII) was prepared from the mixture of (V), (VI), and (VII), by condensation with methyl acetoacetate in the presence of piperidine–acetic acid,¹⁰ followed by treatment with potassium hydroxide and re-esterification with diazomethane. Pure (XII) [m.p. 78–79°; λ_{\max} 244 $m\mu$ (ϵ 11600); ν_{\max} 1760, 1730, 1680, 1655, 895 cm^{-1} ; δ 3.88 (s, OCH_3), 1.38 p.p.m. (s, Me at C-5)] could be isolated from the crude reaction product by chromatography on silica gel. The methylation of (XII) under similar conditions to (VIII), led almost exclusively (>80% yield) to the crystalline keto-ester (XIII) [m.p. 94–95°, λ_{\max} 239 $m\mu$ (ϵ 13500); ν_{\max} 1740, 1675, 1645, 1625, 895 cm^{-1} ; δ 3.80 (s, OCH_3), 1.32 (s, Me at C-5), 0.99 p.p.m. (d, *J* 7 c./sec., Me at C-4)] with traces of the epimeric keto-ester (XIV) [m.p. 132–133°, λ_{\max} 237 $m\mu$ (ϵ 15000); ν_{\max} 1745, 1675, 1645, 1625, 895 cm^{-1} ; δ 3.80 (s, OCH_3), 1.16 (s, Me at C-5), 0.97 p.p.m. (d, *J* 7 c./sec., Me at C-4)], separable by silica gel column chromatography. Because the saponification of (XIII) followed by decarboxylation leads to 4-epi-nootkatone (X) the relative configuration of the isopropenyl and

† Under the assumption that the isopropenyl group in the ketones (V) and (VI) preferentially occupies an equatorial position of a cyclohexanone chair conformation, attention has to be drawn to the fact that the chemical shift of the formyl proton in (V) and (VI) is opposite to previously observed corresponding δ -values of equatorial and axial formyl groups (G. W. Buchanan and J. B. Stothers, *Chem. Comm.*, 1967, 179). Investigations relevant to this are in progress.

angular methyl groups in (XII) must be the same as in (X). Dehydrogenation of (XIII) under similar conditions to those described for (X) yielded the dienone-ester (XV) [b.p. 135—140°/0.005 mm.; λ_{\max} 244 m μ (ϵ 14000); ν_{\max} 1750, 1678, 1652, 895 cm.⁻¹; δ 3.86 (s, OCH₃), 2.02 (s, Me at C-4), 1.40 p.p.m. (s, Me at C-5)], which could easily be reduced with

sodium borohydride in pyridine¹¹ to give mainly the keto-ester (XIV). Subsequent saponification followed by decarboxylation gave crystalline racemic nootkatone (I) [m.p. 45—46°, u.v., i.r., and n.m.r. spectra and chromatographic behaviour on a polar and a non-polar glass capillary column identical with those of natural nootkatone].§

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