Total Synthesis of Sesquicarene

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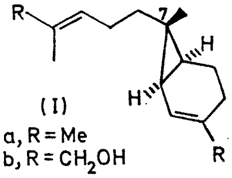
Summary Sesquicarene (Ia) has been synthesized from farnesol by two separate routes, both involving intramolecular carbenoid addition as the key step.

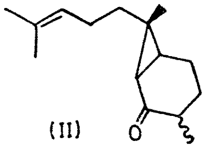
SESQUICARENE (Ia), an isoprenylogue of the well known monoterpene Δ^2-carene, represents a new structural type among sesquiterpenes.[1a] The important plant sex hormone serenin has recently shown to be a dihydroxylated version (Ib) of sesquicarene.[1b] We now report two separate syntheses of sesquicarene originating from farnesol.†

Geranylacetone (III) was obtained by retro-aldolization[2] of farnesal and reduced to the carbinol (IVa). The corresponding toluene-*p*-sulphonate (IVb) affords a mixture of the nitrile (IVc) 46%, ν_{max} 2210 cm.$^{-1}$ and the isonitrile (IVd) 11%, ν_{max} 2110 cm.$^{-1}$ upon reaction with an excess of sodium cyanide in dimethyl sulphoxide at 59°. Alkaline hydrolysis of (IVc) produced the liquid carboxylic acid (IVe) 93%, amide m.p. 76·5—77·5° from which the diazo-ketone (IVf) ν_{max} 2080 cm.$^{-1}$ was obtained by successive treatment with oxalyl chloride and diazomethane. Copper powder in tetrahydrofuran effected cyclization of (IVf) to a 1 : 1 mixture of the two sesquicarone isomers, (±)-(II) 54%, ν_{max} 1670 cm.$^{-1}$, δ C-7 Me, *cis* 1·09, *trans* 1·20.[3] Equilibration, as expected,[4] enriched the proportion of the *trans*-epimer to *ca.* 80%.

Pyrolysis of synthetic sesquicarone toluene-*p*-sulphonyl hydrazone (V) m.p. 99—100° as its sodium salt in diglyme[5] at 140° furnished a mixture of two hydrocarbons (71%). The major product (VI) 53%, ν_{max} 3300, 2100 cm.$^{-1}$, δ1·17 (d, 3H, *J* 7 Hz), 1·87 (d, 1H, *J* 2·2 Hz.) is the result of



(I)
a, R = Me
b, R = CH_2OH



(II)

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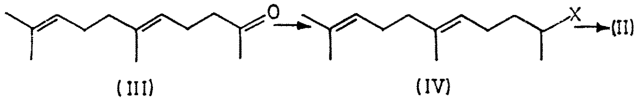
† An independent synthesis of sesquicarene has recently been reported: E. J. Corey and K. Achiwa, *Tetrahedron Letters*, 1969, 1837.

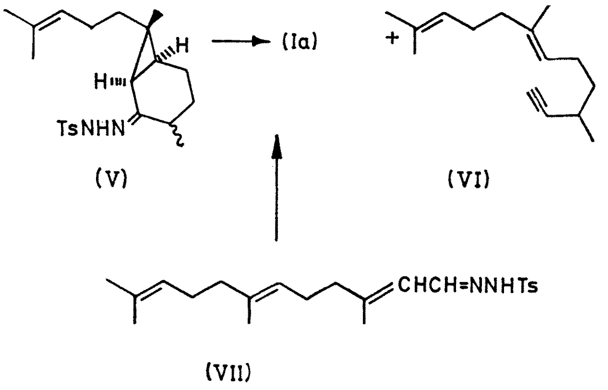
fragmentation[6] while the minor isomer is sesquicarene (Ia) (15%). The i.r., n.m.r., and mass spectral data of synthetic (±)-(Ia) are in good agreement with the literature values for the natural product.[1]

A direct, though inefficient, synthesis of sesquicarene can be accomplished by copper-catalysed cyclization of farnesal toluene-*p*-sulphonylhydrazone (VII, *cis,trans* + *trans,trans*) in the presence of sodium hydride. After chromatography on silver nitrate–silica gel, (Ia) was obtained in 5·3% yield. The intramolecular addition appears to be at least partially specific since the yield diminished to 1·5% when the *trans,trans*-(VII) was used.

As well as confirming the gross structure of sesquicarene, these syntheses also establish unequivocally the stereochemistry of the natural product at position 7 since farnesol from commercial sources is known to have a *trans*-configuration about the central 6,7-double bond.[8]



a, X=OH d, X=NC
b, X=OTs e, X=CO_2H
c, X=CN f, X=$COCHN_2$



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