The Total Synthesis of (±)-Lindestrene

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A FURANOSESQUITERPENE, lindestrene,[1] was isolated as a component of *Lindera strychnifolia* Vill., and its structure has been established as (I).

This is an unstable oil and rapidly autoxidised in air at room temperature to give a resinous substance. The synthesis of racemic lindestrene provides additional confirmation of its structure.

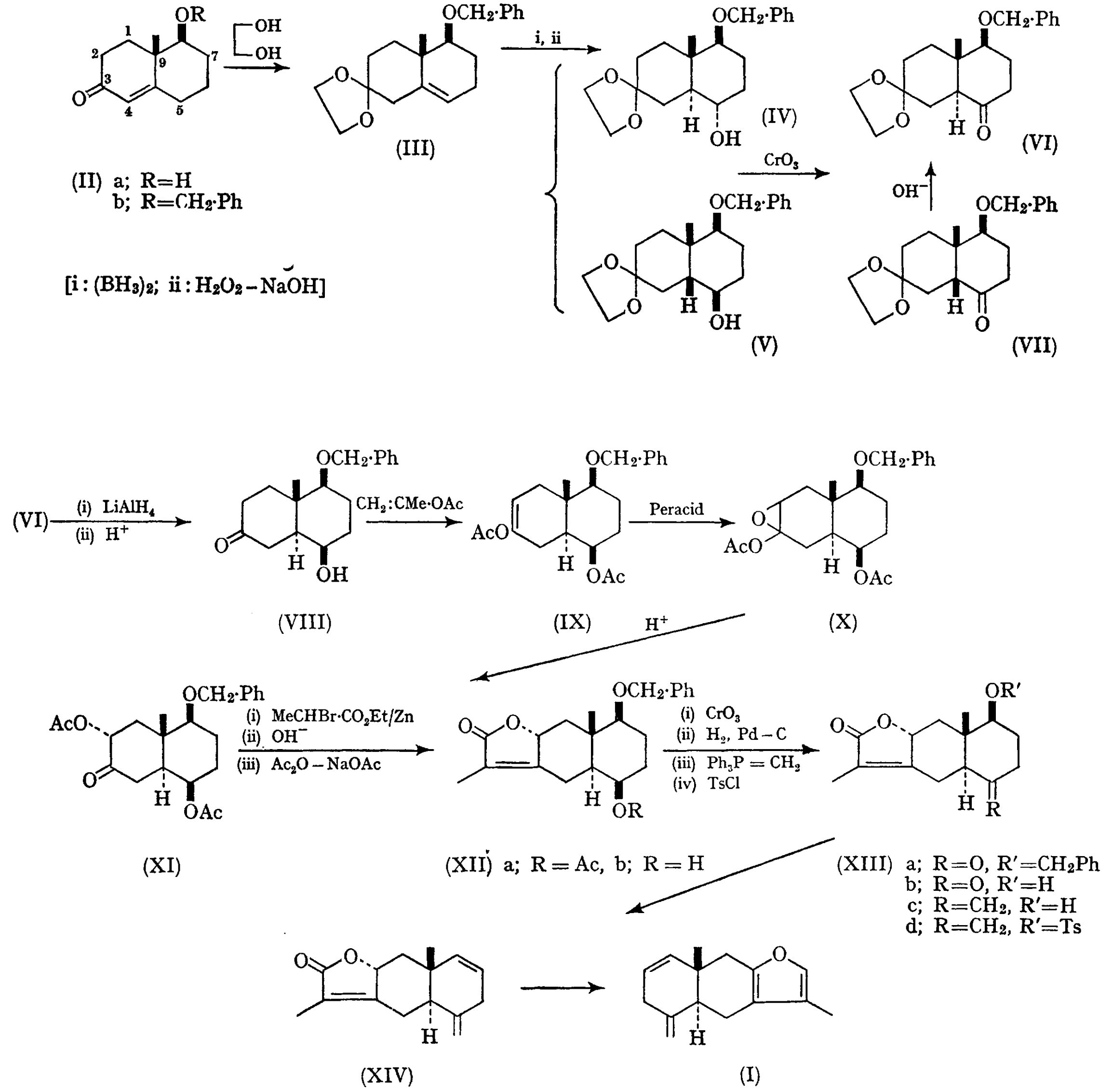
The starting material for synthesis was the readily available hydroxy-octalone[2] (IIa), the benzyl ether (IIb) of which was converted into the ketal (III), m.p. 92·5—94°. Hydroboration of (III) gave a mixture[*] of a crystalline compound (IV), m.p. 90—92°, and an oily hydroxy-derivative (V) at 1 : 1 in 62% yield.

Oxidation of (IV) or (V) with chromium trioxide in pyridine afforded a ketone (VI), m.p. 89—90°, or (VII), m.p. 115—116°, respectively. The latter was epimerised to the former by treatment with an alkali. Compound (VI) gave a 5β-hydroxy-*trans*-decalone (VIII), m.p. 96—97°, by reduction with lithium aluminium hydride followed by deketalisation with 75% acetic acid, in quantitative yield.

Treatment of (VIII) with isopropenyl acetate and toluene-*p*-sulphonic acid furnished its enol-acetate[†] (IX), ν_{max} 1750 and 1745 cm.$^{-1}$ in 82% yield. This is converted into a 2-acetoxy-3-keto-derivative by the conventional method.[3]

[*] As n.m.r. spectra of (IV) and (V) show 9-angular methyl at τ 9·08 and 8·83, and 5-hydrogen at τ 6·66 and 6·08, respectively, (IV) is a *trans*-conformer and (V) a *cis*-conformer.

[†] As this ketone (VIII) is a *trans*-3-decalone, enolization of this ketone occurs preferentially at C-2.



The epoxide (X) which was obtained on treatment of (IX) with *m*-chloroperbenzoic acid, was transformed into an α-acetoxy-ketone (XI) by the action of perchloric acid in acetic acid in 40% yield.

The Reformatsky reaction product of (XI) with ethyl α-bromopropionate was immediately hydrolysed, and an acid product was lactonised under reflux in acetic anhydride–sodium acetate, to give an αβ-unsaturated lactone (XIIa), m.p. 152—153°, in 53% overall yield.

On hydrolysis with 5% hydrochloric acid in methanol, it gave in 92% yield a 5β-hydroxy-compound (XIIb), m.p. 174—175°, which was oxidised with chromium trioxide–pyridine, to give a 5-oxo-derivative (XIIIa), m.p. 217—219° in 87% yield.

Debenzylation of (XIIIa) by hydrogenation gave in quantitative yield (XIIIb), m.p. 228—231°, which was converted into (XIIIc), m.p. 206—208°, in 63% yield, by the Wittig reaction with methyltriphenylphosphonium bromide. Its tosylate

(XIIId) was heated under reflux in dimethylformamide for 24 hr., to give (XIV),‡ ν_{max} 1765, 1695, 1655, 890, 770, 753, 730 cm.$^{-1}$, and the corresponding formate, m.p. 189—191°, in 37% and 30% yield, respectively.

The γ-lactone function in (XIV) was reduced[4] with di-isobutylaluminium hydride, to give racemic oily compound (I), which was shown to be identical with lindestrene by comparison of the infrared spectrum and gas-chromatographic retention time.

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‡ This compound was shown to be identical with the peracid oxidation product (ref. 1) of lindestrene (I) by comparison of the infrared spectra.

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