The Total Synthesis of ($\pm$)-4-Demethylaristolone and Related Compounds

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THE sesquiterpene aristolone, isolated[1] from *Aristolochia debilis* Sieb. *et* Zucc., has been shown to possess the interesting structure[2] and absolute stereochemistry[3] depicted in (I). We report here the total synthesis of ($\pm$)-4-demethylaristolone (VII) *via* a novel synthetic sequence which should prove to be equally applicable to the natural product itself.

Reaction of the substituted cyclohexanone (II)† [b.p. 112—116°/28 mm.; ν_{max} (film) 1704 cm.$^{-1}$; τ 4·74 (1H, multiplet, vinyl H), 8·31, 8·57 (6H, doublets J 1·5, 1·2 Hz, respectively, vinyl methyls), 8·91 (3H, singlet, tertiary methyl)] with diethyl cyanomethylphosphonate[4] in the presence of methylsulphinyl carbanion in dimethyl sulphoxide[5] gave, in 88% yield, the $\alpha\beta$-unsaturated nitrile (III)‡ [b.p. 84—85°/0·15 mm.; λ_{max} 222 mμ; ν_{max} (film) 2200, 1650, 1605 cm.$^{-1}$]. The latter, upon alkaline hydrolysis, afforded in 65% yield the $\beta\gamma$-unsaturated acid (IV) b.p. 118—123°/0·05 mm. The fact that the double bond had completely isomerized into the $\beta\gamma$-position was shown clearly by the lack of an appropriate absorption in the ultraviolet and by the n.m.r. spectrum [τ 4·38 (1H, triplet, γ-vinyl H), 4·95 (1H, multiplet, vinyl H), 7·09 (2H, multiplet, $CH_2{\cdot}CO_2H$), 8·36, 8·40 (6H, doublets, J 1·5, 1·2 Hz, respectively, vinyl methyls), 8·87 (3H, singlet, tertiary methyl)].

Treatment of the sodium salt of the acid (IV) with oxalyl chloride in benzene gave the acid chloride (V) [ν_{max} (film) 1780 cm.$^{-1}$] which, due to its instability, was immediately converted, by reaction with diazomethane, into the diazo-ketone (VI) [ν_{max} (film) 2090, 1630 cm.$^{-1}$]. When the latter was heated under reflux (2 hr.) with cupric sulphate in cyclohexane and the crude product was treated with sodium hydroxide in warm methanol, a mixture of products was obtained. From the latter, by means of successive column chromatography (alumina) and preparative g.l.c., was isolated, in approximately 15% overall yield from the acid (IV), ($\pm$)-4-demethylaristolone (VII)§ [oil, λ_{max} 235 mμ (ϵ 11,600); ν_{max} ($CHCl_3$) 1645 cm.$^{-1}$; τ 4·29 (1H, broad singlet, vinyl H), 8·70, 8·77, 8·83 (9H, 3 methyl singlets)].

The stereochemistry of compound (VII) was determined unambiguously as follows. Lithium–ammonia reduction of (VIII) afforded, in 85% yield,

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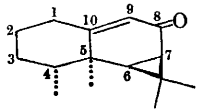
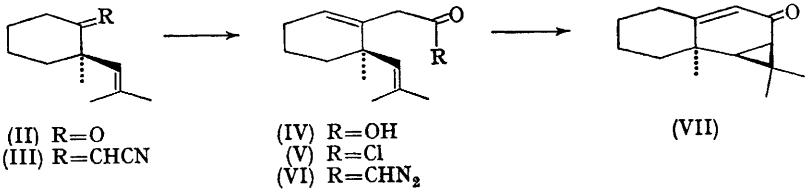
† Prepared by acid-catalysed isomerization of 2-methyl-2-methylallylcyclohexanone.

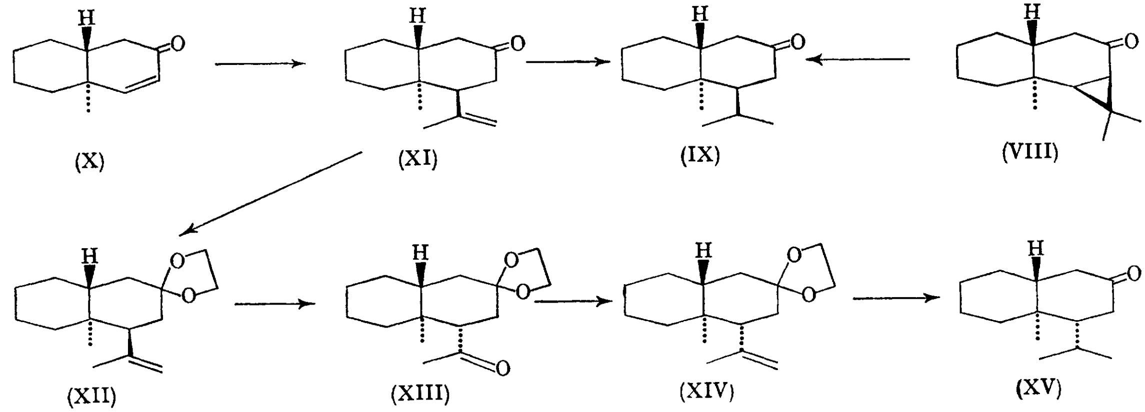
‡ Spectral data and gas–liquid chromatography (g.l.c.) indicated that this material contained approximately 20% of the corresponding $\beta\gamma$-unsaturated nitrile.

§ Also isolated from this mixture, in approximately the same yield, was ($\pm$)-5-epi-4-demethylaristolone (m.p. 88—89°). Interestingly, this compound, upon lithium–ammonia reduction, afforded ($\pm$)-5-epi-4-demethyldihydroaristolon containing *cis*-fused six-membered rings. Work on this novel observation is continuing.



(I)





(±)-4-demethyldihydroaristolone (VIII) [oil, λ_{max} 212·5 mμ (ϵ = 5200);[6] ν_{max} ($CHCl_3$) 1675 cm.$^{-1}$; τ 8·59, 8·87, 8·97 (9H, 3 methyl singlets)]. The latter, when reduced again with lithium in ammonia[7] gave, in 80% yield, the substituted decalone (IX) m.p. 49—50°.

Reaction of the known octalone (X)[8] with isopropenylmagnesium bromide in the presence of cuprous iodide[9] gave, in good yield, the decalone (XI), m.p. 83—84°; ν_{max} ($CHCl_3$) 1715, 1639, 890 cm.$^{-1}$, which, upon hydrogenation, afforded compound (IX), identical (m.p., mixed m.p., i.r., g.l.c. retention time) with (IX) obtained as described above. Although we felt confident that (XI) had the stereochemistry shown,[10] this was proved as follows. The ketal (XII), m.p. 80—81°, obtained from ketone (XI), was converted by ozonolysis and subsequent treatment with base into the keto-ketal (XIII), m.p. 74—74·5°. The latter, when treated with methylenetriphenylphosphorane in dimethyl sulphoxide, gave the ketal (XIV), m.p. 76—77° which was clearly different from (and therefore epimeric with) ketal (XII). Successive deketalization and hydrogenation of (XIV) gave decalone (XV) (b.p. 95°/0·1 mm.), which again was clearly epimeric with (IX). This overall epimerization (axial to equatorial) of the isopropenyl group (XII → XIV) unambiguously showed that the suggested stereochemistry of decalone (XI) was correct. This, in turn, proved the stereochemistry of (±)-4-demethylaristolone (XI).

Experiments directed towards the total synthesis of aristolone (I) are in progress.

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