CHEMICAL COMMUNICATIONS, 1968

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

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THE sesquiterpene aristolone, isolated¹ from Aristolochia debilis Sieb. et Zucc., has been shown to possess the interesting structure² and absolute stereochemistry³ 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.; v_{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 cyanomethylphosphonate⁴ in the presence of methylsulphinyl carbanion in dimethyl sulphoxide⁵ gave, in 88% yield, the $\alpha\beta$ -unsaturated nitrile (III)[‡] [b.p. 84—85°/0·15 mm.; λ_{max} 222 m μ ; 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 [$\tau 4.38$ (1H,

triplet, γ -vinyl H), 4.95 (1H, multiplet, vinyl H), 7.09 (2H, multiplet, $CH_2 \cdot CO_2 H$), 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) $[v_{max} \text{ (film) } 1780 \text{ cm.}^{-1}]$ which, due to its instability, was immediately converted, by reaction with diazomethane, into the diazo-ketone (VI) $[v_{max} \text{ (film) } 2090, 1630 \text{ cm}.^{-1}]$. 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, $\lambda_{\max} 235 \text{ m}\mu \ (\epsilon \ 11,600); \ \nu_{\max} \ (\text{CHCl}_3) \ 1645 \text{ cm}.^{-1};$ 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. Lithiumammonia reduction of (VIII) afforded, in 85% yield,

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

 $[\]pm$ 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.

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 (\pm) -4-demethyldihydroaristolone (VIII) [oil, λ_{\max} 212.5 m μ ($\epsilon = 5200$);⁶ ν_{max} (CHCl₃) 1675 cm.⁻¹; τ 8.59, 8.87, 8.97 (9H, 3 methyl singlets)]. The latter, when reduced again with lithium in ammonia? 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 iodide⁹ gave, in good yield, the decalone (XI), m.p. 83-84°; v_{max} (CHCl₃) 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 ketoketal (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 \rightarrow XIV) unambiguously showed that the suggested stereochemistry of decalone (XI) was correct. This, in turn, proved the stereochemistry of (\pm) -4-demethylaristolone (XI).

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

Financial support from the National Research Council of Canada, and a National Research Council of Canada Studentship (to W. de W.) are gratefully acknowledged.

(Received, January 1st, 1968; Com. 003.)

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