The Total Synthesis of ($\pm$)-$\Delta^{1(10)}$-Aristolene (Calarene)

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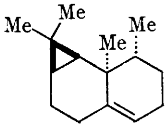
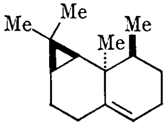
THE tricyclic sesquiterpene $\Delta^{1(10)}$-aristolene (calarene, β-gurjunene) has been assigned the structure and stereochemistry displayed in formula (I).[1,2] Here we report a total synthesis of racemic (I) and its 4-methyl epimer which fully confirms this structural and stereochemical designation.



(I)



(II)

The *cis*- and *trans*-dimethyloctalones [(IVa) b.p. 123·5°/8·5 mm.; ν_{max} 1709 and 1658 cm.$^{-1}$; τ 4·55 (m, vinyl H), 8·83 (s, Me), and 9·07 p.p.m. (d, *J* 6·2 Hz, Me): (IVb) b.p. 121·5°/8·5 mm., m.p. 45—47°, similar spectral properties]† are obtained from a 1 : 1 mixture of (IIIa) and (IIIb)[3] *via* the corresponding mono-thioketals [toluene-*p*-sulphonic acid and ethanedithiol in acetic acid, 8 hr. at 25°; ν_{max} 1713 cm.$^{-1}$, τ 4·43 p.p.m. (s, vinyl H)] followed by desulphurization with Raney nickel in absolute ethanol [30 min. at 5°, 75% from (III)]. The two isomers were separated by distillation with an annular-type spinning band column. Isomer (IVb) is more easily prepared from pure (IIIb).[3] The two dimethyloctalones (IVa) and (IVb) have been separately carried through the following synthetic scheme to (I) and (II) respectively.

Reaction of (IV) with sodium hydride and diethyl carbonate in 1,2-dimethoxyethane at 85° affords the expected β-keto-ester [(Va) (53%); mixture of keto and enol tautomers; ν_{max} 1745, 1713, 1641, and 1601 cm.$^{-1}$; τ -2·80 p.p.m. (s, *ca.* 0·2 enol H): (Vb) (77%), enol form; ν_{max} 1648 and 1609 cm.$^{-1}$; τ -2·53 p.p.m. (s, *ca.* 1·0 enol H)]. Upon treatment with methyl lithium in ether (reflux, 2 hr.), (V) gives rise to the dimethyl ketol (ν_{max} 3460 and 1702 cm.$^{-1}$) which without purification is dehydrated with 1% conc. hydrochloric acid in methanol (reflux, 2—3 hr.) to the isopropylidene derivative [(VIa) (89%), m.p. 27·5—28·5°; ν_{max} 1689, 1668 (split carbonyl) and 1626 cm.$^{-1}$; τ 4·55 (m, vinyl H), 8·19 and 8·27 (s, allylic Me), 8·94 (s, Me), and 9·08 p.p.m. (d, *J* 6·0 Hz,

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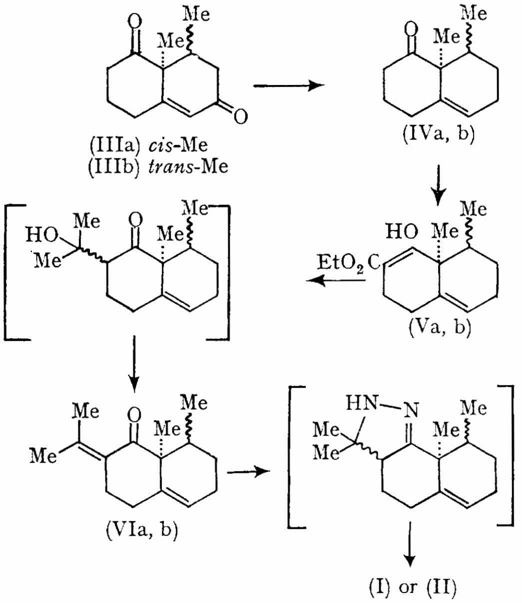
† All numbered compounds have been fully characterized by micro-analytical and spectral data. The n.m.r. and i.r. data cited refer to carbon tetrachloride solutions.

Me): (VIb) (90%), n_D^{25} 1·5260, similar spectral properties].

The unstable Δ^2-pyrazolines are readily formed from the reaction of (VI) with one equivalent of hydrazine in absolute ethanol (reflux, 1—2 hr.) and then decomposed over powdered potassium hydroxide[4] at 240—255° for 1—2 hr. From (VIb) a 3 : 1 mixture of two isomers is obtained (49% after prep. v.p.c.). The major product has been isolated in a pure state [m.p. 60·5—62°, *M* 204 (m.s.), ν_{max} 1667 cm.$^{-1}$; τ 4·69 (m, vinyl H), 8·75 and 8·96 (s, Me), 9·00 (d, *J* 6·5 Hz, Me), 9·04 (s, Me), and 9·33—9·76 p.p.m. (m, cyclopropane H)] while the minor isomer has been characterized by the properties of an enriched mixture [$C_{15}H_{24}$, *M*, 204 (m.s.); τ 4·69 (m, vinyl H), 8·66 and 8·84 (s, Me), 8·99 (s, Me), 9·04 (d, $J \sim 6$—7 Hz), and *ca.* 9·45 p.p.m. (cyclopropane H)]. The major hydrocarbon is assigned the structure and stereochemistry indicated by (II) (*i.e.*, 4-epi-$\Delta^{1(10)}$-aristolene) in view of the expected steric influence of the angular methyl group. The minor isomer is tentatively considered to have a *syn* relationship between the cyclopropane ring and the C-5 methyl group.



The pyrazoline derived from (VIa) furnished a homogenous liquid (44% after prep. v.p.c.) which proved to be identical in all respects (except optical activity) to authentic $\Delta^{1(10)}$-aristolene from two different plant sources.[2]‡ The detailed infrared (20% solution) and 100 MHz n.m.r. spectra of the natural and synthetic materials are completely superimposable and readily distinguished from the spectra of stereoisomer (II). The correspondence of the v.p.c. retention times on two different columns [under conditions which resolve (I) and (II)] and the mass spectra provides additional support. Since the stereochemistry of the isomers (IIIa) and (IIIb) has been established,[3] the synthesis constitutes a rigorous confirmation of the *cis*-relationship between the vicinal methyl groups originally assigned for (I).[1,2] The *anti*-configuration of the three-membered-ring is again consistent with the steric effect of the angular methyl group.

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