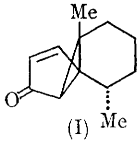
The Total Synthesis of (±)-β-Vetivone

By James A. Marshall* and Porter C. Johnson
(*Department of Chemistry, Northwestern University, Evanston, Illinois* 60201)

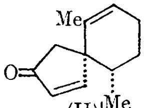
We recently presented evidence which called for revision of the long-accepted hydroazulenic structure of *β*-vetivone to a structure based on spiro[4,5]decane.[1] This new structure has now been confirmed through a straightforward total synthesis.

The known spiro-cyclopropyl ketone (I),[2] upon treatment with acetic acid–acetic anhydride containing a trace of sulphuric acid, gave the spiro[4,5]decadienone (II)[2] in 50—55% yield. Selective hydrogenation (Pd–C in ethanolic NaOH) smoothly gave the corresponding unsaturated ketone (III) [λ_{max} (film) 5·74, 7·10, 7·23, 8·56, 8·62, 11·81, 12·43 μ]. Condensation with ethyl formate ($NaH–C_6H_6$) and treatment of the resulting product with n-butanethiol and BF_3-etherate converted ketone (III) to its n-butylthiomethylene derivative[3] (IV) [λ_{max} (film) 5·87, 6·30, 8·30, 11·84, 12·31 μ; δ ($CDCl_3$) 7·30 (H_A, t, J 3), 5·38 (H-7, $W_{h/2}$ 9), 2·85 (-S-CH_2·CH_2-, t, J 7), 2·45—2·30 (C-1 CH_2, 4 lines), 1·57 (C-6 Me, d, J 2), 0·92 (CH_3·CH_2, t, J 7), 0·87 p.p.m. (C-10, d, J 6 Hz)]. The observed long-range splitting of H_A and the 4 line pattern of the C-1 methylene protons reinforce our *a priori* assumption that condensation at C-3 (*vs.* C-1) of ketone (III) would be preferred for steric reasons.

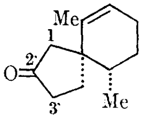
Reduction of ketone (IV) with methanolic



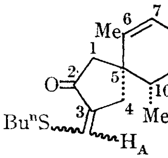
(I)



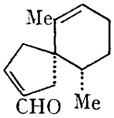
(II)



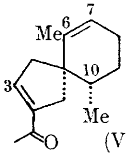
(III)



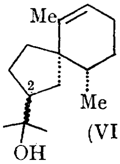
(IV)



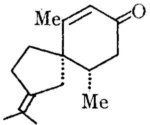
(V)



(VI)



(VII)



(VIII)

sodium borohydride followed by hydrolysis (H_2O, HCl, acetone) in the presence of mercuric chloride yielded the conjugated aldehyde[4] (V) [λ_{max} (film) 3·67, 5·95, 6·14, 7·23, 7·38, 8·44, 10·22, 11·94, 12·48, 13·72] in 73% over-all yield. This aldehyde upon treatment with ethereal methyl-lithium afforded the expected allylic alcohol mixture (epimers) which was directly oxidized (DDQ)[5] to the conjugated ketone (VI) [λ_{max} (film) 5·99, 6·14, 7·23, 8·53, 10·19, 11·95, 12·49 μ; $\delta(CDCl_3)$ 6·70 (H-3, $W_{h/2}$ 6), 5·34 (H-7, $W_{h/2}$ 8 Hz), 2·30 (CH_3CO), 1·58 (C-6 CH_3, d, J 2), 0·87 p.p.m. (C-10 CH_3, d, J 6 Hz)] in 65% over-all yield. Selective reduction of the conjugated double bond with lithium in ammonia–ethanol followed first by oxidation (CrO_3) of the resulting alcohols and then addition of methyl-lithium yielded the tertiary alcohols (VII) [λ_{max} (film) 2·91, 7·25, 8·32, 10·68, 12·02, 12·53 μ; δ ($CDCl_3$) 5·30 (H-7, $W_{h/2}$ 9 Hz), 1·67 (C-6 CH_3), 1·20 (*gem*-dimethyl), 0·92 p.p.m. (C-10 CH_3, d, J 6 Hz)] as a 60:40 mixture of C-2 epimers. One epimer must correspond to racemic hinesol[6] and the other may be racemic agarospirol.[7] The spectral properties of our synthetic alcohol mixture were entirely compatible with this assumption.

The alcohol mixture (VII) was converted to racemic β-vetivone (VIII) along the lines reported by Yoskioka and Kimura[8] for the conversion of (−)-hinesol to (+)-β-vetivone. Thus, acetylation (NaOAc–Ac_2O) followed by oxidation (CrO_3–HOAc–Ac_2O) afforded racemic 8-oxohinesyl acetate and its C-2 epimer, both of which yielded (±)-β-vetivone, m.p. 44—46°, upon treatment with BF_3 etherate. The infrared and n.m.r. spectra of material thus secured were identical with the spectra of naturally derived (−)-β-vetivone. The gas chromatographic retention time was likewise identical (peak enhancement).

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