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STUDIES TOWARDS THE SYNTHESIS OF TRANS-CLERODANE DITERPENES AND CONGENERS: STEREOSELECTIVE SYNTHESIS OF (±)-4aβ,7β,8aβ,-TRIMETHYL-8α-BENZYL-4β-HYDROXY-TRANS-DECALIN

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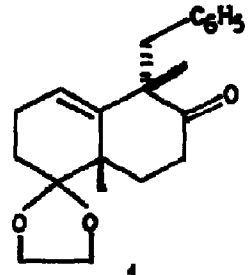
Abstract: A stereoselective synthesis of the title compound (5), by a route which allows flexibility for an approach to trans-clerodane diterpenes and congeners, is described.

The bicyclic skeleton with its characteristic array of asymmetric centers present in trans-clerodane diterpenes has also been identified in a few sesquiterpenoids[1]. In a comprehensive synthetic study towards these compounds, many of which possess important biological activity, we have recently completed a stereoselective synthesis of the title compound (5)[2], by a route which allows sufficient flexibility to prepare other analogues. We wish to communicate these results, prompted by a recent report[3] on the first total synthesis of a trans-clerodane diterpene via an intermediate (7), also envisaged[4] by us (vide infra).

Initial attempts to synthesise the desired trans-decalone of 1 were foiled by an unusual carbon- carbon bond cleavage during catalytic hydrogenation of 1[5]. However, 3 could be prepared through reductive alkylation of the ketol (2)[6] with benzyl chloride, following the procedure of Heathcock and co-workers[6], and was obtained in 40% yield after extensive chromatographic purification over alumina; m.p. 71-72° C; δ (CCl_4): 7.1 (m,5H,aromatic), 3.46-2.66 (apparent q, 2H, benzylic methylene), 1.06 and 0.94 (each: s,3H, tert. methyl). Based on well-documented studies[7], the stereochemistry of this product was assumed. Wittig reaction of 3 with methylenetriphenylphosphorane afforded the olefin (4) in 80% yield; b.p. 135° C (bath temp.) at 0.01 mm; δ (CCl_4): 7.05 (s,5H, aromatic), 4.7 (d,d,2H, $=CH_2$), 2.8-2.53 (d,2H, benzylic methylene), 1.0 and 0.9 (each: s,3H, tert. methyl). Catalytic hydrogenation of the olefinic moiety in 4 (in EtOH or DMF with 10% Pd-C at room temp. & press.) afforded a diastereomeric mixture of the corresponding methyl derivative in a ratio of 4:1 (g.l.c.). The major isomer, m.p. 132-33° C, was separated through column chromatography on silicagel. Molecular models clearly suggest that this should correspond to the desired isomer (5) in view of the steric factors present in 4. This was also evident from the ^1H NMR spectra of 5 and the corresponding acetate(viscous liquid), revealing one of the two tertiary methyl singlets at ~δ 0.8 as observed in the



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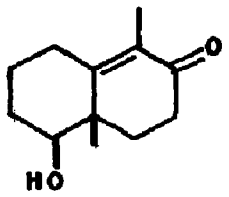

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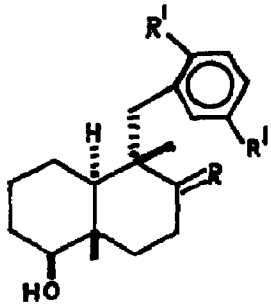
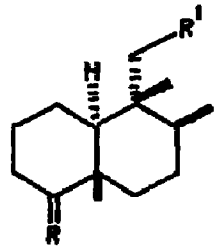


3: R = O ; R' = H
4: R = CH_2 ; R' = H
5: R = β-Me, α-H ; R' = H
6: R = β-Me, α-H ; R' = OH



7: R = $\begin{matrix}-O\\-O\end{matrix}$; R' = CHO
8: R = O ; R' = COOH

related compounds.[1,3] In case of a trans orientation of the C-7 and C-8 methyl groups, this signal is expected[3] to appear around δ 1.0. With a view to confirming this stereochemistry and also to gain an access to the desired precursor (7) for trans- clerodane series, an attempt was made to prepare the known acid (8)[1] through oxidative cleavage[4] of the aromatic ring in 5 with RuO_4. The desired acid (8) could not be isolated from the resulting mixture of acidic products, obtained in a very poor yield. We expect to realise these objectives with the synthon (6) during the synthesis of avarol, which is under investigation.

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References and Notes

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2. The synthetic compounds described herein are racemic. All new compounds gave expected elemental analyses and spectral data.
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