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SYNTHESIS OF (±)-8,9-DEOXYALLIACOL B

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ABSTRACT: The first elaboration of the novel framework of the alliacane group of sesquiterpene lactones is exemplified by the synthesis of (±)-8,9-deoxyalliacol B (13).

The novel carbon skeleton of the group of sesquiterpene lactones[1] isolated from Marasmius alliaceus is exemplified by alliacol B (12-hydroxydehydroalliacolide) (1) which has been chemically interconverted into the other members of the group. We report the first synthetic entry into this area by describing the synthesis of (±)-8,9-deoxyalliacol B (13).

Interaction of 5-nitropentan-2-one and 5,5-dimethylcyclopent-2-en-1-one (NBu_4F, THF 20°C, 20 hr) gave the adduct (2; 95%) which by acid-catalysed internal aldol cyclisation (p-toluenesulphonic acid, toluene reflux, 5 hr.) produced the bicyclic nitroketone (3; 96%). Subjection of (3) to the Nef reaction (EtONa/EtOH, 20°, 1 hr. followed by HCl acidification) gave the four products (4), (5), (6) and (7); heating the mixture of the three last compounds with p-toluenesulphonic acid gave the single required conjugated diketone (7; 74%).

Selective interaction of the less sterically congested carbonyl group of (7) with dimethyl malonate ($TiCl_4$[2], pyridine, THF, 20°, 17 hr.) yielded the expected diester (8; 74%). Sodium borohydride reduction of (8) in the presence of cerium (III) chloride[3] produced a single hydroxyester (9; 91%) whose stereochemistry is plausibly assigned on the basis of hydride attack at the face opposite to that hindered by the methyl group of the cyclohexene ring. This was confirmed by the n.m.r. shifts induced by the reagent $Eu(fod)_3$

in the resonances of the three methyl groups a, b and c which were considerably greater for a and b than for c.[5] The epimeric hydroxydiester (10) obtained from (9) by treatment with aqueous sulphuric acid in THF (68%) showed the expected opposite effect, the shift for c being greater than that for a and b.[5] The required configuration about the exocyclic double bond was achieved by operating selectively on the less sterically hindered methoxycarbonyl group. Thus treatment of the hydroxydiester (9) with aqueous methanolic sodium hydroxide for 10 hr. at room temperature gave the ester-acid (11; 88%) which was first converted into the corresponding imidazolide[4] (N,N'-carbonyldiimidazole, THF) and then reduced with lithium borohydride to yield the ester diol (12; 55%). Prolonged base hydrolysis of (12) for two days followed by acidification gave a mixture of (±)-8,9-deoxyalliacol B (13) m.p. 108-109 °C and the diastereoisomeric lactone (14) m.p. 103.5-104.5 °C in the undesirable ratio of 1:3 (combined yield 63%). The stereochemistry of (13) was rigidly established by X-ray crystallography.[6] An exactly cognate sequence performed on the epimeric hydroxydiester (10) gave a similar 1:3 ratio of the lactones (13) and (14).

The more nucleophilic nature of the 8,9-double bond in (13) seems to render it a prime candidate for selective peracid attack; in the event its congested steric environment has proved a hindrance to this desirable result. Studies on other epoxidation methods are in train. Confirmatory analytical and spectroscopic data were obtained for all the above new compounds.[7]

We thank SERC and Roche Products Ltd for support and Dr J R Hanson and Dr V Thaller for their helpful interest.

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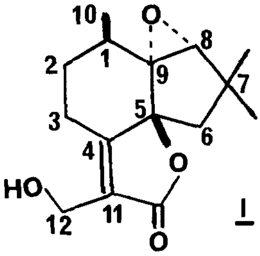

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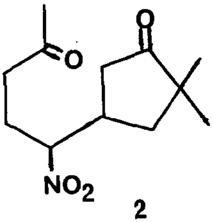

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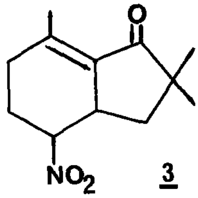

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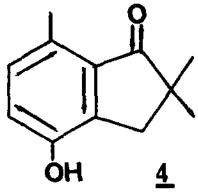

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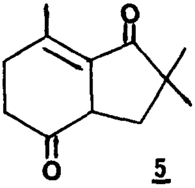

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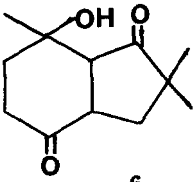

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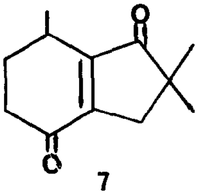

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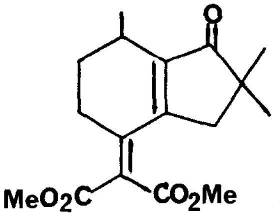

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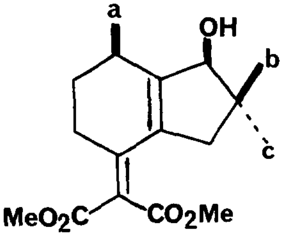

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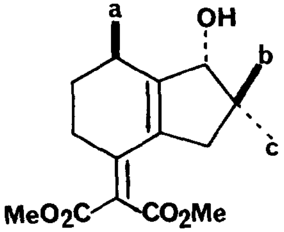

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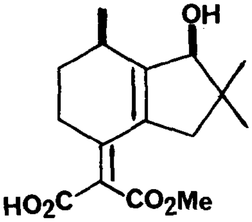

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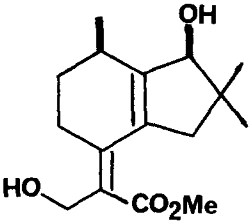

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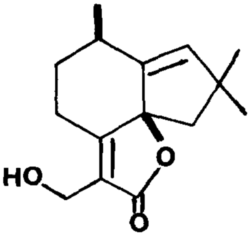

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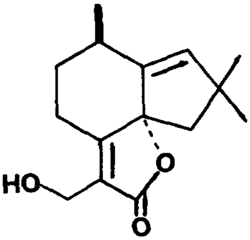

14

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4. H.A. Staab, *Angew. Chem. Int. Ed. Engl.*, 1962, *1*, 351.
5. Methyl resonances (δ) of (9): *a* 1.19 (d, J = 7.0 Hz), *b* 1.02, *c* 0.96; with $Eu(fod)_3$ [8 mg for 5 mg of (9)] *a* 2.09, *b* 2.27, *c* 1.58.

   Methyl resonances (δ) of (10): *a* 1.14 (d, J = 7.1 Hz), *b* 0.99, *c* 1.08; with $Eu(fod)_3$ [8 mg for 5 mg of (10)] *a* 1.73, *b* 1.86, *c* 2.57.
6. We are grateful to Dr P R Raithby for this determination.

   Crystal data: $C_{15}H_{19}O_3$, M = 247.30, monoclinic, space group $\underline{P}2_1/\underline{n}$ (non-standard setting of $P2_1/c$, no:14), *a* = 6.423 (1), *b* = 12.807 (2), *c* = 16.857 (2) Å, β = 90.01 (1)°, *U* = 1386.6 (3) Å, Z = 4, $\underline{D}_m$ = not measured, $\underline{D}_c$ = 1.184 g cm^{-3}, graphite-monochromated Cu-$\underline{K}_\alpha$ radiation, λ = 1.5418 Å, μ (Cu - K_α) = 5.78 cm^{-1}, F(000) = 532.2682 intensities measured on a Syntex $P2_1$ diffractometer, and averaged to give 2011 unique observed reflections [*f* > 4 σ *F*]. Final residuals for 178 refined parameters are *R* = 0.068 and R_w = 0.087 (C,O refined anisotropically, CH_2, CH_3, and OH hydrogens each with a common isotropic temperature factor). The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this work.
7. PMR spectrum of 8,9-deoxyalliacol B (13);

   δ($CDCl_3$, 250 MHz) 5.81 (1H, s, 8-H), 4.40 (2H, s, 12-H), 2.82 (1H, 'dd', *J* = 7.3 and 12.3 Hz, 3-H_1), 2.67 (1H, m, 1-H), 2.31 (1H, m, 2-H_1), 2.13 (1H, m, 3-H_2), 2.07 (1H, d, *J* = 13.2 Hz, 6-H_1), 1.85 (1H, d, *J* = 13.2 Hz, 6-H_2), 1.52 (1H, m, 2-H_2), 1.32 (3H, s, 14-H), 1.14 (3H, s, 15-H) and 0.86 (3H, d, *J* = 7.4 Hz, 10-H).

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