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A NEW SYNTHESIS OF (±)-CEDRENE USING SEQUENTIAL INTER- AND INTRA-MOLECULAR MICHAEL REACTIONS

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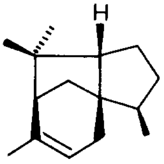
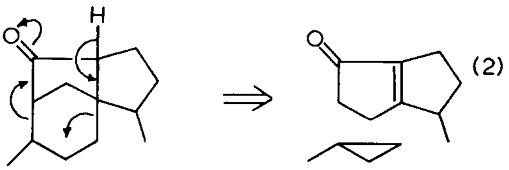
Summary: A synthesis of (±)-cedrene(1), which features sequential intermolecular i.e.(2) → (7), and intramolecular i.e. (8) → (9), Michael reactions using the bicyclo[3.3.0]octenone(2) as key intermediate, is described.

The tricyclic sesquiterpene cedrene(1), which is found in *Juniperus* oil, has been the focal point of many inspired syntheses of fused ring carbocycles. First synthesised by Stork in 1955[1], the molecule has since been elaborated by a number of diverse routes[2], the most recent of which is based on intramolecular 1,3-photocycloaddition of an olefin to a substituted anisole[3]. In this *Letter* we outline an alternative synthesis of (±)-cedrene which features sequential inter- and intra-molecular Michael reactions using the bicyclo[3.3.0] octenone(2) as key intermediate.

Our initial plan was to elaborate the tricyclic ring system in cedrene, using a single step tandem Michael addition sequence involving the kinetic enolate derived from (2) and an activated cyclopropane (see Scheme)[4]. In a model study however, the bicyclooctenone(3a) was recovered unchanged after deprotonation at -78°C (LDA, THF) followed by treatment with the cyclopropane(4) (-78°C to 0°C). Furthermore, although the enolate derived from the corresponding β-ketoester(3b) (NaH, DME, 25°C) added smoothly to (4), producing the adduct(5), ν_{max}(film) 1800, 1750, 1705, 1645 cm^{-1}; δ 1.76, 1.84 ($-OCMe_2O-$), 2.0 - 3.3(m, 12H), 3.74(CO_2Me), we were unable to induce this substrate, either



(1)



Scheme

in situ or in a separate operation, to undergo a second (intramolecular) Michael reaction leading to (6).

The problems above were overcome when we used 2-nitrobut-2-ene instead of an activated cyclopropane, as the three-carbon annulation reagent in the Scheme. Thus, Michael addition of the enolate derived from (2)[5] (LDA, HMPA, -78°C) to 2-nitrobut-2-ene, followed by quenching at -60°C led to a mixture of diastereomers of the nitroketone(7) in a combined yield of 90%. Hydrolysis of (7), using sodium nitrite and *n*-propyl nitrite in dimethylsulphoxide (25°C, 5 days) then produced the 1,4-dione(8) (44%), ν_{max} 1710, 1695, 1640 cm^{-1}.

In a highly regioselective process, treatment of (8) with potassium *t*-butoxide in *t*-butanol (25°C, 15 min) resulted in smooth intramolecular Michael reaction leading to the tricyclo[5.3.1.0^{1,5}]undecanedione(9)[6] (73%), ν_{max} 1740, 1715 cm^{-1}; δ0.86, 1.0(d, *J* 7, 2:1 α,β-CHMe isomers), δ_{carbon} 217.9, 209.8, 56.4(d), 54.8(d), 52.3(t), 49.9, 49.4(d), 41.3(d), 33.8(t), 32.5(t), 25.7(t), 16.5(q), 12.6(q)p.p.m. (major α-isomer). After selective protection of the 6-ring carbonyl group in (9) as the corresponding dioxolan [$(HOCH_2)_2$ $HC(OEt)_3$, *p*-TSA], a Wittig reaction with methylenetriphenylphosphorane provided the alkene(10), ν_{max} 1660 cm^{-1}; δ4.88(m :CH$_2$) as a colourless oil. In order to optimise yields in the Simmons-Smith reaction leading to (12), it was found expedient to next convert the dioxolan group in (10) to the axial carbinol(11) *via* reduction of the corresponding ketone using L-selectride.

Cyclopropanation of the hydroxy-alkene(11) using $Et_2Zn-CH_2I_2$ in the presence of catalytic oxygen, then led to (12) (68%) which on hydrogenation (Rh/PtO$_2$; HOAc-NaOAc) provided the cedranol (13) whose p.m.r. spectral data, δ4.03(m, CHOH), 1.29(CMeMe), 1.18(d, *J* 7, CHMe.CHOH), 0.91(CMeMe), 0.84(d, *J* 6, CHMe), could be correlated with those reported for isomers of the cedranol derived from natural cedrene[7]. Dehydration of the carbinol(13), using phosphorus oxychloride in hot benzene containing pyridine, finally produced (±)-cedrene(1) and the corresponding Me-epimer as a colourless oil; the synthetic cedrene showed chromatographic and spectral data indistinguishable from naturally derived material.

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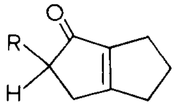
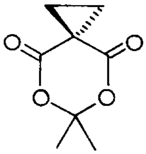


(3)

a R = H

b R = CO_2Me



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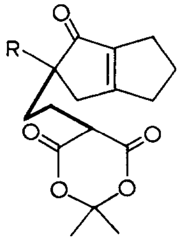

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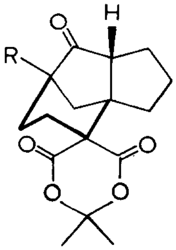

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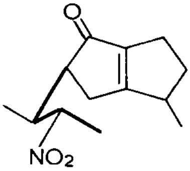

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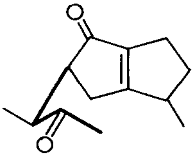

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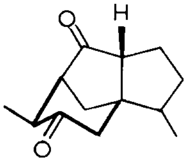

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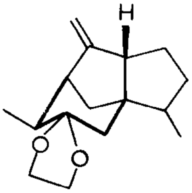

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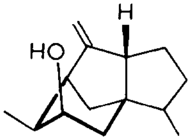

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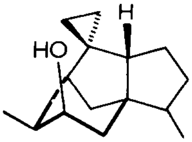

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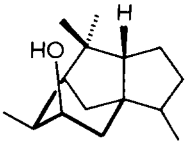

(13)

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3. P.A. Wender and J.J. Howbert, *J. Am. Chem. Soc.*, 1981, **103**, 688.

4. For illustrations of the use of activated cyclopropanes in Michael reactions leading to fused ring carbocycles and heterocycles see: S. Danishefsky, *Acc. Chem. Res.*, 1979, **12**, 66.

5. The bicyclooctenone(2) showed b.p. 50°C at 0.1 mm., ν_{max} 1700, 1640 cm^{-1}; δ1.16(d, *J* 7, CH*Me*), 1.75 - 2.05(m,1H), 2.2 - 3.15(m,8H), δ_{carbon} 204.2, 190.5, 147.6, 40.9(d), 38.9(t), 37.0(dd), 23.9(t), 23.8(t), 18.3(q) p.p.m. It was obtained from 3-methylcyclopent-1-enaldehyde following Grignard reaction with vinylmagnesium bromide, oxidation to 3-methyl-1-(1-oxoprop-2-enyl)cyclopent-1-ene using MnO$_2$, and Nazarov cyclisation (polyphosphoric acid, 60°C, 3 min).

6. Although the intramolecular Michael reaction is not widely used in synthesis, recent publications attest its enormous preparative value. See: G. Stork, J.D. Winkler and N.A. Saccomano, *Tetrahedron Lett.*, 1983, **24**, 465 and refs. cited therein; S.D. Burke, C.W. Murtiashan and M.S. Dike, *J. Org. Chem.*, 1982, **47**, 1349; I.A. Blair, L.N. Mander, P.H.C. Mundill and S.G. Pyne, *Aust. J. Chem.*, 1981, **34**, 1887 and refs. cited therein; B.M. Trost, C.D. Suey and F. DiNinno, *J. Am. Chem. Soc.*, 1979, **101**, 1284.

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