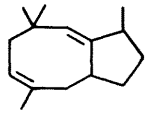
Total Synthesis of epi-Precapnelladiene

By Alan M. Birch and Gerald Pattenden*
(*Department of Chemistry, The University, Nottingham* NG7 2RD)

Summary The total synthesis of (±)-epi-precapnelladiene (**14**), containing an uncommon bicyclo[6.3.0]undecane carbon skeleton, is described; the relative stereochemistry of precapnelladiene from *Capnella imbricata* is established as that in formula (**15**).

The sesquiterpene precapnelladiene (**1**), recently isolated from the soft coral *Capnella imbricata*,[1] is thought to be the key biosynthetic precursor of the unique tricyclic ('capnellane') group of terpenes, *e.g.* (**2**) and (**3**), found in the same marine animal.[2,3] Precapnelladiene has an uncommon fused 5- and 8-membered ring system, hitherto found only in a few sester- and di-terpenoids (*e.g.* ophiobolans and fusicoccins).[4–6] In spite of numerous investigations,[7] the synthesis of a natural terpene incorporating this novel fusion of 5- and 8-rings has not previously been accomplished. We now report the total synthesis of epi-precapnelladiene, which uses a highly regio- and stereo-selective intramolecular photocycloaddition reaction to elaborate the fused 5,8-ring system in a single step.



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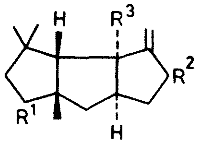
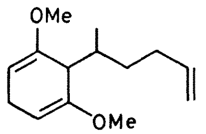


(2) $R^1 = R^2 = R^3 = H$

(3) $R^1 = R^2 =$ ◄OH, $R^3 = OH$

Alkylation (Bu^{t}Li, hexamethylphosphoric triamide) of the dihydrobenzene obtained by Birch reduction of resorcinol dimethyl ether,[8] with 5-iodohex-1-ene gave (74%) the substituted bis-ether (**4**) which on hydrolysis (1 M HCl–Me$_2$CO) and benzoylation (PhCOCl–C$_5$H$_5$N, 25 °C, 18 h) gave the enol benzoate (**5**). Irradiation of (**5**) in hexane with a 450 W medium-pressure lamp through Pyrex gave, in both a regio- and stereo-selective manner,[9] the photoadduct (**6**), ν_{max} 1720 and 1690 cm^{-1}, τ 1·8—2·1 (2H), 2·3—2·6 (3H), 7·1—9·2 (14H), and 8·97 (d, *J* 7·5 Hz, CH*Me*), in 98% isolated yield.† The stereochemistry assigned to (**6**) followed from *X*-ray analysis of the dione (**7**),[10] m.p. 66—67 °C, ν_{max} 1705 and 1695 cm^{-1}, τ 7·0—8·9 (15H) and 9·02 (d, *J* 7 Hz, CH*Me*), produced from (**6**) after saponification and retroaldolisation (KOH–EtOH, 25 °C). Treatment of the photoadduct (**6**) with lithium hexamethyldisilazide followed by MeI yielded the gem-dimethyl substituted adduct (**8**) (95%) which, on fragmentation (aq. KOH–Me$_2$SO), gave the 1,5-dione (**9**), ν_{max} 1705 and 1685 cm^{-1}, τ 7·1 (dd, *J* 8·5 and 7 Hz, COC*H*), 7·3—8·8 (12H), 8·86 (CMe$_2$), and 9·07 (d, *J* 7·5 Hz CH*Me*).



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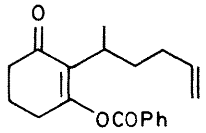

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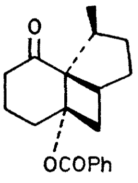

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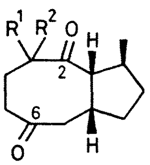
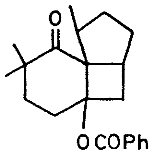


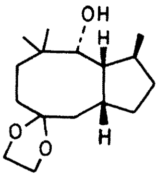
(7) $R^1 = R^2 = H$

(9) $R^1 = R^2 = Me$



(8)

After selective protection of the C-6 carbonyl group in (**9**) as the corresponding dioxolan, reduction with lithium aluminium hydride produced (90%) the *anti*-carbinol (**10**). Dehydration of (**10**) using phosphorus trichloride oxide in pyridine (25 °C, 10 days)[11] gave the bridgehead alkene (**11**) (78%), ν_{max} 1610 cm^{-1}, τ 5·13 (=C*H*), 6·04 (4H), 7·5—8·9 (12H), 9·0 (d, *J* 7 Hz, CH*Me*), and 9·02 (CMe$_2$), which on acid treatment [tetrahydrofuran(THF)–HOAc–H$_2$O, 1:3:1] gave the enone (**12**). A Wittig reaction between (**12**) and methylenetriphenylphosphoranylide (THF, 25 °C) produced the *exo*-methylene isomer (**13**) (86%), ν_{max} 1640 and 890 cm^{-1}, τ 5·03 (1H), 5·25 (1H), 5·43 (1H), 6·6 (1H), 7·4—8·9 (11H), 8·92 (Me), 8·94 (d, *J* 7 Hz, CH*Me*), and 9·03 (Me) of precapnelladiene, which on treatment with RhCl$_3$·3H$_2$O in ethanol (reflux, 0·75 h)[12] was isomerised cleanly to give (±)-precapnelladiene (**14**) (70%) showing i.r. and mass spectral data identical with the naturally derived material. Examination of the chemical-shift differences between the C-2-H (τ 5·08 synthetic; 4·94 natural) and C-11-Me (τ 9·01 synthetic; 8·97 natural) resonances in the n.m.r. spectra of the synthetic and



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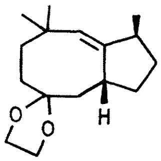

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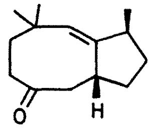

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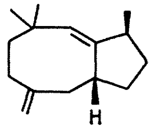

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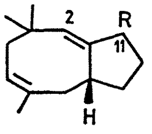

(14) R = ◄Me

(15) R = ---Me

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† Irradiation of the corresponding enol acetate derived from (**4**) was found to be less selective.

natural precapnelladienes showed that the molecules were epimeric at C-11, thereby establishing the relative stereochemistry of natural precapnelladiene as in formula (**15**).

We thank Professor Djerassi for providing spectra of natural precapnelladiene, the S.R.C. for a fellowship (to A. M. B.), and the Royal Society for an equipment grant.

(*Received*, 11*th September* 1980; *Com.* 991.)

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