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TOTAL SYNTHESIS OF $\Delta^{9(12)}$-CAPNELLENE-8α,10α-DIOL

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Summary: A total synthesis of (11), the 8-epimer of $\Delta^{9(12)}$-capnellene-8β,10α-diol (1,R=H) found in the soft coral *Capnella imbricata* is described.

The tricyclic diol (1,R=H), designated $\Delta^{9(12)}$-capnellene-8β,10α-diol, is found along with related alcohols (1,R=H or OH) and the hydrocarbons (2) and (3) in the soft coral *Capnella imbricata*.[1] The 'capnellanes' (*i.e.* 1 and 2) are related to the 'hirsutane' family of triquinane sesquiterpenes e.g. hirsutic acid and coriolin, but with the three methyl groups distributed differently about the tricycle.[2] A unique feature of the capnellenols (1) is the presence of an unusual *bis*-allylic alcohol functionality associated with ring C. In previous studies we have described the total synthesis of the novel hydrocarbon (3) and its biogentically patterned transannular cyclisation to the capnellane carbon framework.[3] We now report a total synthesis of $\Delta^{9(12)}$-capnellene-8α,10α-diol (11), *i.e*. 8-epi-(1,R=H), which uses the overall strategy summarised in the Scheme.[†]

Recognition that the annulation of ring A to ring B in (1) must be co-ordinated with the production of two quaternary centres,[4] led us to select a retro-ene, retro-Michael disconnection from the key bicyclic intermediate (6); this strategy proved to be particularly facile for the preparation of large quantities of this bicyclooctanone.[5] Thus, addition of 3-methylcyclopent-2-enone to lithium bis(3-methylbut-3-enyl) cuprate (4) (prepared from 4-lithio-2-methylbut-1-ene[6] and cuprous iodide) at -40°C, followed by quenching with acetic anhydride first led to the enol acetate (5)(46%) uncontaminated by its positional isomer.[7] Treatment of the enol

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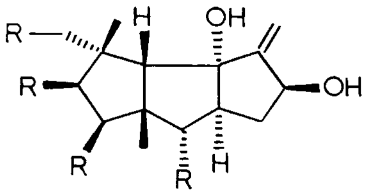
[†] This work was first reported at the IVth IUPAC International Symposium on Marine Natural Products, Tenerife, Canary Islands, Spain, July 1982.

acetate (5) in moist dichloromethane with stannic chloride (1 equiv.)[8] at 25°C for 10 min. then gave the bicyclooctanone (6) (63%) as a colourless oil, ν_{max} (film) 1735 cm.$^{-1}$, δ2.3(t, separations 8.4 Hz, CH$_2$), 1.9 - 1.58(m,7H), 1.22(Me) 1.14(Me), 0.97(Me), δ_{carbon} 220.6, 69.3d, 49.2, 44.1, 42.3t, 39.6t, 39.5t, 34.96, 31.7q, 28.9q, 25.7q p.p.m.

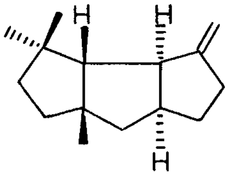
Ring C was to be annulated to (6) *via* the keto-acetylene precursor (9) using the reductive cyclisation method first described by Stork.[9] To this end, alkylation of the enolate derived from (6) |KN(SiMe$_3$)$_2$ in DME at -78°C| with 3-chloro-1-iodobut-2-ene[10] led to the keto-olefin (7) obtained as a 4:1 mixture of β- and α-epimers.[11] Reduction of (7) with lithium aluminium hydride in ether then gave the corresponding carbinol (87%, mixture of isomers) which on treatment with potassium 3-aminopropylamide (0°C, 3h) provided the acetylene (8) (82%).[12] Oxidation of (8) using pyridinium chlorochromate in dichloromethane buffered with sodium acetate, then led to the keto-acetylene (9)(80%) containing 25 - 30% of the α-epimer.[13]

The critical cyclisation step (9 → 10) was best accomplished by titration with sodium naphthalene radical anion in tetrahydrofuran at 25°.[14] This procedure led to the 8-deoxycapnellen-10α-ol (10) in 26% yield (not optimised).[15] The *cis*, *anti*, *cis*-stereochemistry for (10) followed conclusively from comparison of n.m.r. spectral data[16] with those of natural capnellene (2) and the capnellenediol (1,R=H). Treatment of 8-deoxycapnellen-10α-ol (10) with *t*-butyl hydroperoxide in the presence of catalytic selenium dioxide[17] then gave the capnellenediol (11)(40%), ν_{max} 3600, 3450, 1625, 905 cm.$^{-1}$, δ 5.39 (d, *J* 1.8, :C$\underline{H}$H), 5.37 (d, *J* 2.2, :CH$\underline{H}$), 4.63 (t, separations 9 Hz, C$\underline{H}$OH), 2.6-2.75 (m, C$\underline{H}$), 2.17 - 1.35 (m,10H), 1.21(Me), 1.18(Me), 0.97(Me), δ_{carbon} 163.4, 111.4t, 89.4, 74.2d, 68.0d, 49.1, 48.9d, 46.5dd, 43.3, 43.6t, 42.7t, 38.3t, 32.0q, 31.0q, 23.7q p.p.m., the 8-epimer of natural $\Delta^{9(12)}$-capnellene-8β,10α-diol (1,R=H). Studies are now in progress to extend the overall strategy described above to the synthesis of (1,R=H) and related capnellenols (1,R=H or OH).

We thank the S.E.R.C. for a studentship (to S.J.T.).



(1)



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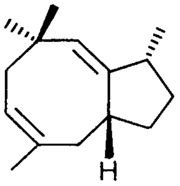

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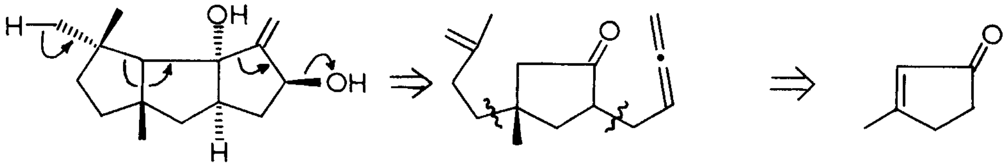
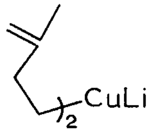


Scheme



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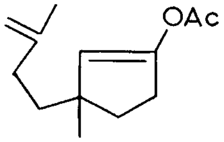

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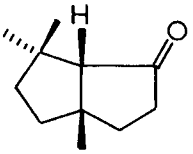
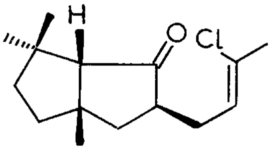


(6)



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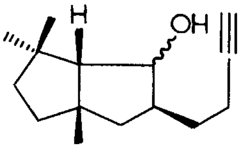

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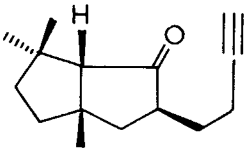
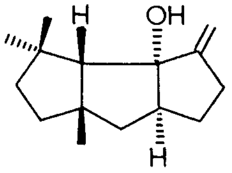


(9)



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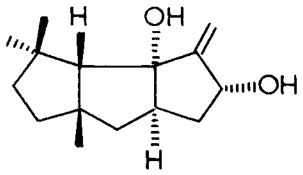

(11)

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5. A less efficient synthesis of this bicyclooctanone has been described recently, see: K.E. Stevens and L.A. Paquette, Tetrahedron Lett., 1981, 4393.
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11. The epimer ratio followed from inspection of spectra data. We are currently investigating a range of alternative reaction conditions to optimise the stereoselectivity, cf ref.2, and P.T. Lansbury, N.Y. Wang and J.E. Rhodes, Tetrahedron Lett., 1971, 1829.
12. cf. C.A. Brown, J. Org. Chem., 1978, **43**, 3083.
13. Treatment of (7) with potassium 3-aminopropylamide led to a 1:1 mixture of α- and β- epimers of the keto-acetylene (9) in low yield (∿ 10%). β-Epimer: δ_{carbon} 219.7, 83.6, 69.5d, 68.8, 48.4d, 46.0, 44.5, 42.3t, 40.4t, 31.5t, 30.4t, 28.6d, 28.1q, 25.3q, 16.6q p.p.m. α-Epimer: δ_{carbon} 220.9, 83.5, 69.6d, 68.8, 48.6d, 46.8, 44.0, 42.4t, 39.4t, 31.5t, 30.4t, 29.7d, 28.2q, 26.1q, 16.7q.
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15. Substantial amounts of starting material were recovered due to competitive enolate ion formation; n.m.r. data, cf. ref. 13, showed that this was composed of a 1:1 mixture of α- and β-epimers.
16. The deoxycapnellen-10α-ol showed: δ 5.14 (t, J 2.4, :C*H*H), 5.04 (t, J 2.1, :CH*H*), 2.58 - 2.7 (m, C*H*), 2.4 - 2.55 (m, CH_2C:), 1.92 - 1.39 (m, 10H), 1.22 (Me), 1.18(Me), 0.98(Me), δ_{carbon} 161.8, 107.9t, 90.4, 67.6d, 51.2d, 48.8, 45.2 dd, 44.2, 43.6t, 42.7t, 32.2q, 31.3q, 29.2t, 27.0t, 23.7q, p.p.m.
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