Total Synthesis of (±)-$\Delta^{9(12)}$-Capnellene-8β,10α-diol

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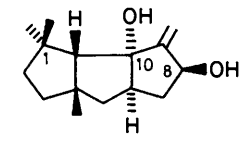
A total synthesis of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**), containing a *cis,anti,cis*-tricyclo-[6.3.0.$0^{2,6}$]undecane carbon framework, found in the marine coral *Capnella imbricata*, is described. Michael addition of the homo-allylic cuprate (**21**) to 3-methylcyclopentenone, followed by Lewis acid catalysed 'ene-type' cyclisation of the resulting specific enol ester (**22**), first provided an expeditious route to the central bicyclo[3.3.0]octanone intermediate (**24**). Alkylation of the enolate derived from (**24**) with 2-chloro-4-iodobut-2-ene (**28**) then produced compound (**29**), which was converted into the keto-acetylene (**32**) using the acetylene 'zipper' methodology. When compound (**32**) was titrated with sodium naphthalene radical anion smooth reductive cyclisation occurred producing the tricyclic allylic alcohol (**33**). Oxidation of compound (**33**) with catalytic selenium dioxide then led to the 8-*epi*-capnellenediol (**34**). Finally, displacement of the methanesulphonate derived from (**34**), with potassium superoxide in 18-crown-6, produced (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**), which showed ^{1}H- and ^{13}C-n.m.r. spectra in addition to m.s. data identical with naturally derived material.

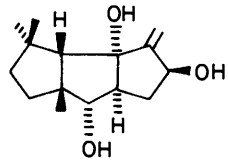
The triquinane ene-diol (**1**), designated $\Delta^{9(12)}$-capnellene-8β,10α-diol, is found along with related capnellenetriols, *e.g.* (**2**), capnellenetetrols, *e.g.* (**3**), and acetoxycapnellenes, *e.g.* (**4**) in the soft coral *Capnella imbricata*.[1] The capnellenols and their acetates also co-occur with the hydrocarbons $\Delta^{9(12)}$-capnellene (**5**) and precapnelladiene (**6**), their presumed biosynthetic precursors.[2] The members of this interesting class of marine metabolites are thought to function as chemical defence substances within the coral reef, warding off algal and microbial growth, in addition to preventing larval settlement.[3]

The 'capnellanes' possess the same linear fused triquinane carbon skeleton as that found in the 'hirsutane' family of terrestrial metabolites represented by hirsutic acid (**7**) and coriolin (**8**), but with the three methyl groups distributed differently about the tricycle.[4] $\Delta^{9(12)}$-Capnellene-8β,10α-diol (**1**) and the related oxycapnellenes (**2**), (**3**), and (**4**) show a novel and unusual ene-diol functionality associated with their ring-C portions, which is also found in isoamijiol (**9**)[5] and artolide (**10**).[6] Although a number of syntheses of the hydrocarbons $\Delta^{9(12)}$-capnellene (**5**)[7,8] and precapnelladiene (**6**)[9,10] have been accomplished, hitherto no synthesis of the more demanding oxygenated capnellenes (**1**)→(**4**) has been achieved. In this paper we describe a short total synthesis of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**) starting from 3-methylcyclopent-2-enone which features a Lewis acid catalysed 'ene-type' cyclisation, *viz.* (**22**)→(**24**), and an intramolecular reductive radical cyclisation *viz.* (**32**)→(**33**) for the regio- and stereo-specific elaboration of the tricyclic system in (**1**).[11]

We first addressed the problem of producing the novel and unusual ene-diol system present in (**1**) using the bicyclo-octanediol (**11**) as a model. An early proposal, based on the disconnection (*a*) shown in the Scheme, failed, with reductive cyclisation of (**12**) instead producing the *endo*-allylic alcohol (**14**).[12] Accordingly, we examined the 5-*exo*-dig reductive cyclisation of the corresponding acetylenic ketone (**15**), a strategy used much earlier by Stork[13] and by others[14] to elaborate the allylic alcohol functionality in gibberellins and other molecules. In the event, treatment of (**15**)[15] with sodium naphthalene radical anion proceeded smoothly leading to the required *exo*-allylic alcohol (**13**) in low, but acceptable yields. The alcohol (**13**) was most conveniently produced from (**15**) however, by cathodic reduction at a carbon electrode where yields up to 66% could be realised.[15]



(**1**)



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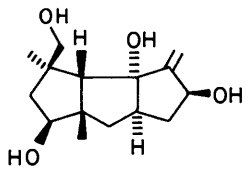
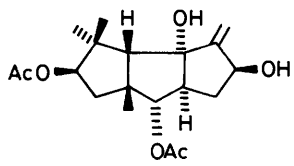


(**3**)



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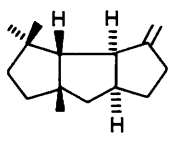

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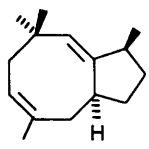
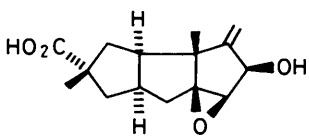
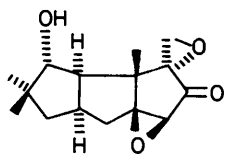


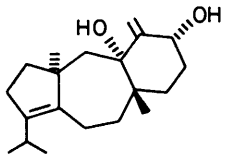
(**6**)



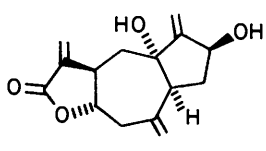
(**7**)



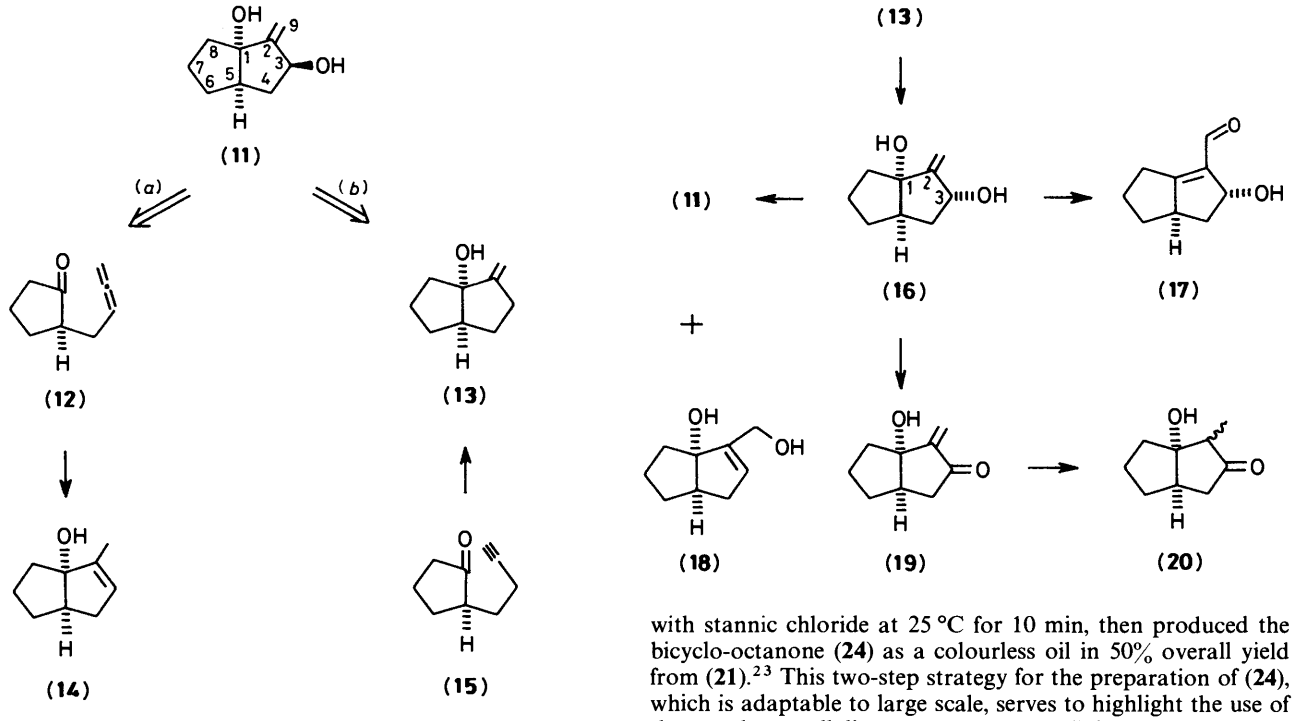
(**8**)



(**9**)



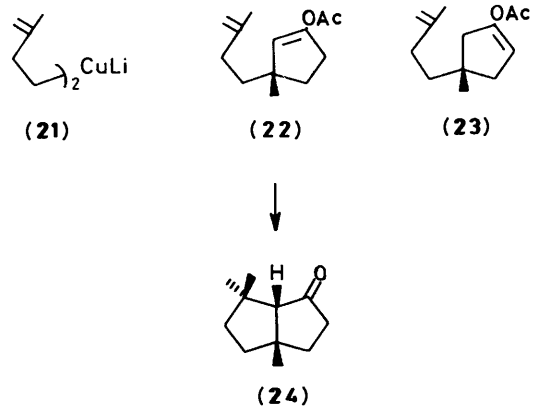
(**10**)



Scheme.

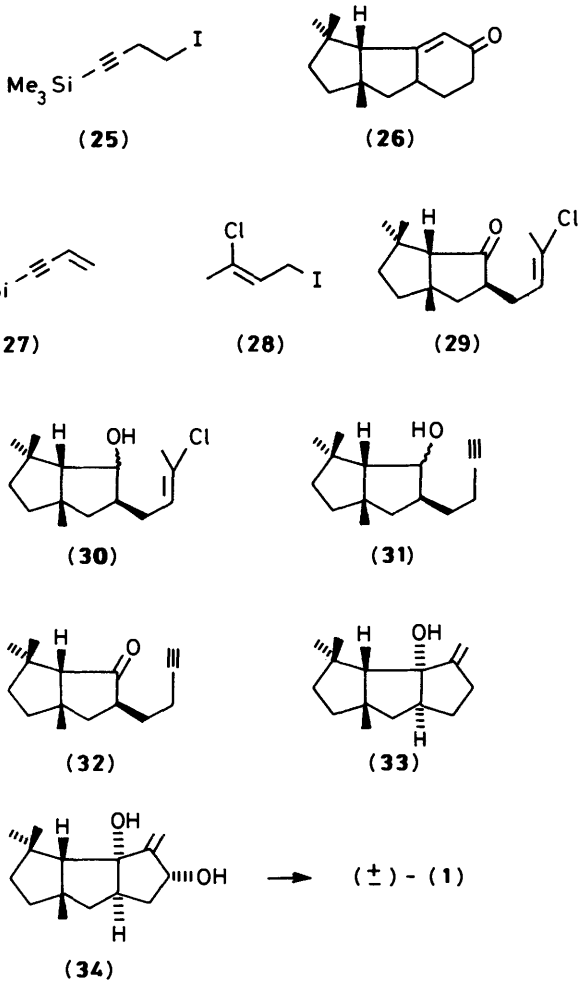
With the model bicyclo-octanol (**13**) in hand, it remained only to introduce the secondary hydroxyl functionality to produce (**11**) by allylic oxidation. Interaction between compound (**13**) and catalytic selenium dioxide in the presence of t-butylhydroperoxide,[16] proceeded in both a regio-and stereo-selective manner to produce a single crystalline ene-diol, shown to have the 1α,3α-configuration (**16**). Inversion of the 3α-configuration in the sensitive ene-diol system proved particularly difficult, and was made more so by the ease with which either of its allylic portions suffered transposition under a range of reaction conditions. Thus, attempted oxidation of (**16**) to (**19**) with chromium based reagents instead led to only the unsaturated aldehyde (**17**). In addition, although (**16**) could be oxidised to (**19**) using periodinane,[17] the reduction of compound (**19**) with di-isobutylaluminium hydride produced predominantly compound (**20**) accompanied by smaller amounts of the 1α,3α-ene-diol (**16**). The Mitsunobu method and procedures based on caesium acetate[18] proved impractical for the direct inversion of the 3α-configuration in (**16**), but eventually we found partial success with the much under-used procedure based on nucleophilic displacement with superoxide.[19] Thus, displacement of the methanesulphonate derived from compound (**16**) with potassium superoxide–18-crown-6 led to the inverted 1α,3β-ene-diol (**11**) whose formation was accompanied by varying amounts of the transposed ene-diol (**18**) depending on reaction conditions.

We next turned our attention to the synthesis of the bicyclo[3.3.0]octanone (**24**), the proposed central intermediate for elaboration to (**32**) and thence $\Delta^{9(12)}$-capnellene-8β,10α-diol. Recognising that an annulation of ring A to ring B in (**24**) must be co-ordinated with the production of two quaternary centres,[20] led us to select a retro-ene, retro-Michael disconnection from the bicyclo-octanone. Thus, addition of 3-methylcyclopent-2-enone to the cuprate (**21**) prepared from 4-lithio-2-methylbut-1-ene[21] and cuprous iodide, at −40 °C, followed by quenching with acetic anhydride first led to the enol acetate (**22**), uncontaminated by its positional isomer (**23**).[22] Treatment of the enol acetate (**22**) in moist dichloromethane with stannic chloride at 25 °C for 10 min, then produced the bicyclo-octanone (**24**) as a colourless oil in 50% overall yield from (**21**).[23] This two-step strategy for the preparation of (**24**), which is adaptable to large scale, serves to highlight the use of the rare homo-allylic cuprate reagent (**21**) in synthesis. While our work was in progress, Stevens and Paquette[8] outlined an alternative, more lengthy synthesis of (**24**) which was based on a Nazarov cyclisation.



We had intended to introduce the butynyl side-chain in compound (**32**) by either alkylation of the enolate derived from (**24**) with the acetylenic iodide (**25**) or *via* the product (**26**) obtained by Robinson annulation of (**24**) followed by an Eschenmoser fragmentation sequence. In the event, the attempted alkylation with (**25**) led to only the product of elimination (**27**), and we were not even able to make an enamine from (**24**) in order to investigate the alternative sequence. We therefore chose an alternative route to (**32**) from (**24**), based on using the vinyl chloride (**28**)[24] as a masked acetylene and alkylating agent. Thus, alkylation of the enolate derived from (**24**) in the presence of potassium hexamethyldisilazide at −78 °C, with the vinyl chloride (**28**) first led to the keto-olefin (**29**) which was shown by ^{1}H n.m.r. data [δ 1.15 (β-); δ 1.13 (α-)] to be produced as a 4:1 mixture of β- and α-C-2 epimers. Reduction of compound (**29**) with lithium aluminium hydride then gave the corresponding alcohol (**30**), as a mixture of diastereoisomers, which on treatment with potassium 3-aminopropylamide at 0 °C for 3 h provided the terminal

acetylene (**31**).[25] Oxidation of compound (**31**) using pyridinium chlorochromate in dichloromethane buffered with sodium acetate, then led to the keto-acetylene (**32**) containing less than 25% of the corresponding C-2-α-epimer. Treatment of the keto-olefin (**29**) with potassium 3-aminopropylamide gave rise to a 1:1 mixture of α- and β-epimers of (**32**) in low yield (*ca.* 10%).



The synthesis of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol (**1**) from the keto-acetylene (**32**) was completed, along parallel lines to those used in the model study, *viz.* (**15**)→(**11**), described above. Thus, titration of the keto-acetylene (**32**) with a solution of sodium naphthalene radical anion in tetrahydrofuran at 25 °C first led to the 8-deoxycapnellen-10α-ol (**33**), whose *cis, anti, cis*-geometry followed conclusively from comparison of its n.m.r. spectral data with those of natural $\Delta^{9(12)}$-capnellene (**5**) and the natural diol (**1**). Treatment of compound (**33**) with catalytic selenium dioxide in the presence of t-butyl hydroperoxide then led to the 8-*epi*-capnellenediol (**34**) in 40% yield. Finally, displacement of the methanesulphonate derived from compound (**34**) using potassium superoxide in 18-crown-6 was found to be totally specific, producing the (±)-capnellene-8β,10α-diol (**1**) as colourless crystals, m.p. 155—156 °C. The synthetic capnellenediol did not separate from naturally derived material in t.l.c. and the two samples showed completely superimposable ^{1}H- and ^{13}C-n.m.r. spectra in addition to mass spectroscopic data.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 710B spectrometer, and u.v. spectra on either a Pye Unicam SP1700 or SP800 spectrometer. ^{1}H N.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R32, or at 80 MHz on a Bruker WP 80SY PFT, or at 250 MHz on a Bruker WM 250 PFT spectrometer. ^{13}C N.m.r. spectra were recorded on a Bruker WM 250 PFT instrument, and all samples for n.m.r. analysis were dilute solutions in deuteriochloroform unless otherwise stated. The multiplicities in the n.m.r. spectra were singlets unless otherwise stated. Mass spectra were recorded on an A.E.I. MS 902, or on a VG 7070E spectrometer, and microanalytical data were obtained on a Perkin-Elmer 204B element analyser. All organic solvents were dried over $MgSO_4$, and solvents were evaporated under reduced pressure on a Büchi rotary evaporator.

2-(*But*-3-*ynyl*)*cyclopentan*-1-*one* (**15**).—Aqueous sodium hydroxide (13 ml, 6M) was added dropwise to a stirred solution of $\Delta^{1,2}$-bicyclo[4.3.0]nonan-3-one (17.5 g)[26] and hydrogen peroxide (45 ml, 30%) in methanol (250 ml). The temperature was carefully maintained in the range 15—30 °C throughout the addition. After being stirred at 15—30 °C for 3 h, the reaction mixture was evaporated to 80 ml at 12 mmHg, then diluted with water (250 ml), and extracted with ether (3 × 200 ml). The combined ether extracts were washed with water, dried, and evaporated to give a yellow oil which was distilled to give 1,2-epoxybicyclo[4.3.0]nonan-3-one (10.5 g, 65%) as a colourless oil, b.p. 60—64 °C at 1 mmHg; $\nu_{max.}$(film) 1 740 cm^{-1}; δ_H 3.18 (HCO) and 3.0—1.2 (m, 11 H) (Found: *m/z* 152.0830. $C_9H_{12}O_2$ requires *M*, 152.0837).

p-Toluenesulphonohydrazide (21 g) was added portionwise to a stirred solution of 1,2-epoxybicyclo[4.3.0]nonan-3-one (17 g) in glacial acetic acid (160 ml) and dichloromethane (160 ml) at −18 °C. The resulting yellow-coloured slurry was stirred at −18 °C for 0.5 h then at 0 °C for 2 h and finally at room temperature for 3 h. The mixture was poured into saturated sodium carbonate (500 ml), and solid sodium carbonate was added until effervescence ceased (*ca.* 200 g). Water was added to dissolve any suspended material, and the mixture was then extracted with dichloromethane (3 × 600 ml). The combined extracts were washed with saturated sodium carbonate (300 ml), dried, and evaporated to give a viscous orange oil. Careful distillation * gave the keto-acetylene (9.9 g, 53%) as a colourless oil, b.p. 60—61 °C at 1 mmHg (lit.,[15] b.p. 68—70 °C at 3.0 mmHg); $\nu_{max.}$(film) 3 100, 2 140, and 1 740 cm^{-1}; δ_H 2.5—2.0 (m, 7 H), 1.98 (t, *J* 2 Hz, ≡CH), and 2.0—1.3 (m, 2 × CH_2); δ_C 220.5, 83.6, 68.9 (d), 48.0 (d), 38.0 (t), 29.5 (t), 28.5 (t), 20.7 (t), and 16.7 (t) p.p.m. (Found: *m/z* 136.0894. $C_9H_{12}O$ requires *M*, 136.0888). The 2,4-dinitrophenylhydrazone derivative crystallised from ethanol as needles, m.p. 129 °C (Found: C, 56.9; H, 5.2; N, 18.0%. $C_{15}H_{16}N_4O_4$ requires C, 57.0; H, 5.1; N, 17.7%).

2-*Methylenebicyclo*[3.3.0]*octan*-1-*ol* (**13**).—(i) A solution of dry tetraethylammonium toluene-*p*-sulphonate (30 g) in dry dimethylformamide (DMF) (130 ml) was poured into the bridge and both sides of an electrochemical H-cell in such a way that the levels in the two sides were equal. 2-(But-3-ynyl)cyclopentan-1-one (2.3 g) was injected into the cathodic (working electrode) arm of the cell, and both sides of the cell were then purged with nitrogen for 1 h. The cell was immersed to above the level of the bridge in crushed ice (3 kg), the stirrer-bar in the cathode compartment was started, and a current of 0.3 A at 110 V was then passed for 2.5 h. The working electrode was rotated through 90° every 0.5 h in order to minimise wear. The anode compartment became a bright orange colour, and the cathode

* Violent decomposition occurs if the residue is heated after the keto-acetylene is distilled out. In one case injudicious heating resulted in an explosion.

compartment became filled with suspended graphite particles. Gases were evolved at both electrodes during the course of the electrolysis. The current was switched off, and the contents of the cathodic compartment were then poured into water (30 ml), and extracted with ether (5 × 150 ml). The cathode compartment and the electrode were carefully washed with ether, and the combined washings and extracts were then washed with water, dried, and evaporated to give a yellow oil, which was purified by chromatography (silica gel G, ether–hexane 1:2 as eluant) to give recovered keto-acetylene (0.65 g, 28%) and the required bicyclic alcohol as a colourless oil (1.0 g, 43%); $\nu_{max.}$(film) 3 500 and 1 630 cm^{-1}; δ_H 5.1—5.50 (m, =C*H*H), 5.0—4.9 (m, =CH*H*), and 2.6—1.1 (m, 12 H); δ_C 159.1, 105.2 (t), 89.9, 52.2 (d), 41.0 (t), 32.6 (t), 32.2 (t), 29.5 (t), and 25.7 (t) p.p.m. (Found: *m/z* 138.1049. $C_9H_{14}O$ requires *M*, 138.1045).

(ii) Sodium naphthalide (*ca.* 0.5M in THF) was steadily added to a stirred solution of 2-(but-3-ynyl)cyclopentan-1-one (3 g) in dry THF (400 ml) at 25 °C under nitrogen. The colour was gradually discharged until the reaction end point was reached (*ca.* 150 ml), when the solution remained a bright green colour. The excess of sodium naphthalide was quenched by opening the apparatus to the atmosphere, and the reaction mixture was evaporated to *ca.* 60 ml, to give an orange slurry, which was taken up in ether (300 ml) and washed with water (2 × 100 ml). The dried ether extract was evaporated to give a yellow slurry, which was chromatographed (Silica gel G, first with hexane as eluant until all the naphthalene had been eluted, then with ether–hexane, 1:2 as eluant), to give recovered δ-keto-acetylene (0.9 g, 30%) and then the alcohol (1.0 g, 33%) which showed spectral data identical to those previously recorded.

2-*Methylenebicyclo*[3.3.0]*octane*-1α,3α-*diol* (**16**).—A solution of t-butyl hydroperoxide (0.35 g) in dry dichloromethane (4 ml) was added to a stirred solution of 2-methylenebicyclo-[3.3.0]octan-1-ol (0.1 g), selenium dioxide (20 mg) and salicylic acid (60 mg) in dry dichloromethane (10 ml). The solution was stirred at room temperature for 4 h, benzene (50 ml) was added to the solution, and the dichloromethane was then evaporated at 12 mmHg. The yellow benzene solution was washed with aqueous potassium hydroxide (30 ml, 10%), and the aqueous washings were then back extracted with ether (2 × 20 ml). The combined extracts were dried and evaporated to give a viscous yellow oil which was purified by chromatography (silica gel G, acetone–hexane, 1:2 as eluant) to give the *diol* (0.4 g, 36%) as an amorphous cream-coloured solid, m.p. 60—62 °C (hexane); $\nu_{max.}$($CHCl_3$) 3 600, 3 300, and 1 630 (v. weak) cm^{-1}; δ_H 5.3—5.2 (two distinct multiplets, 1 H each), 4.54 (t, *H*COH), 2.7—2.6 (br, HCO*H* and HO), and 2.5—1.2 (m, 9 H); δ_C 160.6, 107.4, 88.4, 75.3 (d), 49.4 (d), 41.1 (t), 39.6 (t), 33.1 (dd), and 25.7 (t) p.p.m. (Found: C, 69.85; H, 9.3%; *m/z* 154.0995. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%; *M*, 154.0994).

2-*Methylenebicyclo*[3.3.0]*octane*-1α,3β-*diol* (**11**) *and* 2-*Hydroxymethylbicyclo*[3.3.0]*oct*-2-*en*-1α-*ol* (**18**).—A solution of freshly distilled mesyl chloride (91 mg) in dry dichloromethane (2 ml) was added dropwise over 0.5 h to a stirred solution of 2-methylenebicyclo[3.3.0]octane-1α,3α-diol (100 mg) and dry triethylamine (150 μl) in dry dichloromethane (20 ml) at −25 °C under nitrogen. The solution was stirred for 2 h at −20 °C, and then quenched with iced water (5 ml). The mixture was transferred to a cold separating funnel where it was washed successively with ice-cold hydrochloric acid (5 ml, 2M), saturated aqueous sodium hydrogen carbonate (5 ml), and brine (5 ml). The organic phase was separated and dried at 0 °C, and the solvent was then carefully evaporated to give the corresponding *allylic methanesulphonate* as a colourless oil which rapidly darkened to a purple slurry above 10 °C.

The crude methanesulphonate was taken up in ice-cold dry dimethyl sulphoxide (DMSO) (5 ml) and ice-cold dry DMF (5 ml) and then poured into a stirred solution of potassium superoxide (30 mg) and 18-crown-6 (200 mg) in ice-cold dry DMSO (5 ml). The solution was stirred for 2 h at 0 °C then for a further 1 h at 25 °C, before water (20 ml) was added and the mixture extracted with chloroform (3 × 15 ml). The combined extracts were dried for 1 h, then treated with triphenylphosphine (150 mg) and stirred at room temperature for 1 h. The solution was evaporated, and the mixture of diols isolated by chromatography (silica gel G, hexane–acetone, 3:1 as eluant) as a 50:50 mixture of (**11**) and (**18**) (80 mg, 80%); compound (**11**) showed: δ_H 5.4—5.5 (two distinct multiplets, 1 H each), 5.0—4.6 (m, *H*COH), and 2.6—1.2 (m, 11 H); compound (**18**) showed δ_H 5.8—5.9 (m, =CH), 4.2—4.3 (m, CH_2O), and 2.5—1.2 (m, 11 H).

1-*Lithio*-3-*methylbut*-3-*ene*.—*N*-Bromosuccinimide (107 g) was added portionwise to a mechanically stirred solution of 3-methylbut-3-en-1-ol (50 g) and triphenylphosphine (159 g) in dichloromethane (600 ml). After the mixture had been stirred for 2 h at room temperature, the dichloromethane was boiled off at atmospheric pressure until the distillation head temperature reached 80 °C. The crude product was then distilled out of the reaction mixture into a receiving flask, cooled to −70 °C by quickly reducing the pressure to 10 mmHg. The reaction flask contents were kept molten by vigorous stirring and heating of the black-coloured, tarry mixture. The distillation was stopped when the distillate became a deep violet colour, and the suction was then immediately released; the residue from the reaction was poured into iced-water where it set into a solid mass. The distillate was redistilled to give 1-bromo-3-methylbut-3-ene (47.7 g, 55%) as a colourless oil, b.p. 110—112 °C (lit.,[27] b.p. 107 °C); $\nu_{max.}$(film) 1 645 cm^{-1}; δ_H 4.9—4.7 (m, =CH_2), 3.50 (t, *J* 12 Hz, CH_2Br), 2.60 (t, *J* 12 Hz, CH_2), and 1.79 (Me).

1-Bromo-3-methylbut-3-ene (7 g) in dry ether (70 ml) was added dropwise to a stirred suspension of lithium chippings (1.2 g) in dry ether (30 ml) under argon at −20 °C. The grey suspension was stirred at −20 °C for 2 h, and then allowed to settle overnight at −20 °C.[21] The alkyl-lithium solution produced was titrated against diphenylacetic acid in the usual manner (113 ml, 0.41M, 70%).

3-*Methyl*-3-(3-*methylbut*-3-*enyl*)*cyclopent*-1-*en*-1-*yl Acetate* (**22**).—1-Lithio-3-methylbut-3-ene in ether (130 ml, 0.4M) was added to a stirred suspension of freshly purified copper(I) iodide (5 g)[28] in dry ether (320 ml) at −60 °C under nitrogen. The mixture was warmed to −40 °C, and then stirred at −40 °C for 2 h during which it became homogeneous and dark brown in colour. The reaction was cooled to −70 °C, and then 3-methyl-cyclopent-2-en-1-one (2.5 g)[29] in ether (20 ml) was added over 0.5 h. The solution became dark green in colour, and was stirred for a further 3 h before acetic anhydride (6 g) in ether (20 ml) was added dropwise over 0.5 h. The solution was stirred at −70 °C for 1.5 h, then warmed to −40 °C and poured into stirred saturated ammonium chloride (40 ml). The crude mixture was filtered through a Celite pad, and the ether layer was then separated. The aqueous layer was extracted with ether (2 × 200 ml), and the combined extracts were then dried and evaporated to give a pleasant smelling green oil. Chromatography (silica gel G, ether–hexane, 1:20 as eluant) gave the *enol acetate* (3.4 g, 64%) as a colourless oil; $\nu_{max.}$(film) 1 760, 1 665, and 1 645 cm^{-1}; δ_H 5.30 (app. t, *J* 2 Hz, =CH), 4.7—4.6 (m, =CH_2), 2.6—2.4 (m, CH_2), 2.08 (O_2CMe), 2.0—1.2 (m, 9 H), and 1.06 (Me); δ_C 168.4, 149.1, 146.6, 121.4 (d), 109.3 (t), 45.2, 40.4 (t), 34.7 (t), 33.7 (q), 30.7 (t), 27.1 (q), 22.7 (t), and 21.11 (q) p.p.m. [Found: *m/z* 165.1290 (*M* − MeCO). $C_{11}H_{17}O$ requires 165.1279].

5,8,8-*Trimethylbicyclo*[3.3.0]*octan*-2-*one* (**24**).—Neat tin tetrachloride (2 ml) was added in one portion to a stirred

solution of 3-methyl-3-(3-methylbut-3-enyl)cyclopent-1-en-1-ylacetate (3.5 g) in water saturated dichloromethane (175 ml, contains 0.3 g of water).[30] The mixture was stirred for 16 h at room temperature, and then water (50 ml) was added. The dichloromethane layer was separated, and the aqueous layer was then extracted with dichloromethane (2 × 50 ml). The combined extracts were dried and evaporated to give a yellow oil, which was purified by chromatography (silica gel G, ether–hexane, 1:9 as eluant) to give the *bicyclic ketone* (1.8 g, 63%) as a colourless oil; $\nu_{max.}$(film) 1 735 cm^{-1}; δ_H 2.30 (app. t, *J* 8 Hz, CH_2), 1.91—1.58 (m, 7 H) 1.22 (Me), 1.14 (Me), and 0.97 (Me); δ_C 220.6, 69.3 (d), 49.2, 44.1, 42.3 (t), 39.6 (t), 39.5 (t), 34.9 (t), 31.7 (q), 28.9 (q), and 25.7 (q) p.p.m. (Found: *m/z* 166.1343. $C_{11}H_{18}O$ requires *M*, 166.1358).

4-*Iodo*-1-*trimethylsilylbut*-1-*yne* (**25**).—Butyl-lithium (106 ml, 1.6M) was added dropwise to a stirred solution of but-3-yn-1-ol (12 g) in dry THF (50 ml) under nitrogen at 0 °C. The solution was warmed to room temperature over 0.5 h, then cooled again to 0 °C, where it was treated with trimethylsilyl chloride (18.6 g) dropwise over 10 min. After the mixture had been stirred for 0.5 h at room temperature, it was again cooled to 0 °C, where a second portion of butyl-lithium (106 ml, 1.61M) was added dropwise. When the mixture had been stirred for 0.5 h at 0 °C, and 1 h at room temperature, it was cooled again to 0 °C, treated with the second portion of trimethylsilyl chloride (18.6 g), and stirred at room temperature for 48 h. The mixture was quenched by cautious addition of cold, dilute hydrochloric acid (120 ml, 2M), and the two phase mixture was briskly shaken and separated. The organic extracts were dried and evaporated to give an orange oil, which was distilled to give 4-trimethylsilylbut-3-yn-1-ol (21 g, 86%) as a colourless oil, b.p. 86—88 °C at 0.4 mmHg; $\nu_{max.}$(film) 3 350 and 2 190 cm^{-1}; δ_H 3.68 (t, *J* 10 Hz, CH_2), 2.47 (t, *J* 10 Hz, CH_2), and 0.12 ($SiMe_3$) (Found: *m/z* 127.0573. $C_7H_{14}OSi$ requires *M*, 127.0579). Freshly prepared triphenylphosphite methiodide (21 g)[31] was transferred to the reaction vessel as a slurry in dry ether under nitrogen. The ether was evaporated under nitrogen to leave the reagent as a yellow solid. 4-Trimethylsilylbut-3-yn-1-ol (6 g) was injected, and the mixture was then stirred and warmed at 85 °C for 2 h. The homogeneous, black solution was cooled, and the crude product was distilled directly from the reaction mixture by collecting all the materials boiling below 74 °C at 2.2 mmHg. The distillate was taken up in ether (150 ml), washed successively with aqueous sodium hydroxide (2 × 50 ml, 5%) and water (50 ml), then dried and evaporated to give an orange oil, which was distilled to give the *iodide* (8.7 g, 81%) as a colourless oil, b.p. 40 °C at 0.1 mmHg; $\nu_{max.}$(film) 2 190 cm^{-1}; δ_H 3.24 (t, *J* 10 Hz, CH_2I), 2.78 (t, *J* 10 Hz, CH_2), and 0.12 ($SiMe_3$) (Found: *m/z* 251.9833. $C_7H_{13}ISi$ requires *M*, 251.9829).

(*Z*)-2-*Chloro*-4-*iodobut*-2-*ene* (**28**).—1,3-Dichlorobut-2-ene (12 g)[32] was added to a stirred solution of sodium iodide (36 g) in acetone (300 ml), and the mixture was then heated under reflux for 22 h in the dark. The black mixture was cooled to 25 °C, and then evaporated to a volume of 150 ml at 12 mmHg before it was diluted with water (40 ml) and extracted with pentane (3 × 30 ml). The combined extracts were washed successively with saturated sodium thiosulphate (200 ml), saturated sodium hydrogen carbonate (20 ml) and water (200 ml), then dried and evaporated to give the iodide as a pink-coloured, lachrymatory, photosensitive oil (15.8 g, 76%); $\nu_{max.}$(film) 1 660 cm^{-1}; δ_H 5.90 (t, *J* 10 Hz, =C*H*), 3.98 (d, *J* 10 Hz, CH_2I), 2.15 (Me) [mixed with ~15% other stereoisomer; δ_H 5.90 (t, *J* 10 Hz, =CH), 3.85 (d, *J* 10 Hz, CH_2I), 2.08 (Me)] (Found: *m/z* 215.9215. C_4H_6ClI requires *M*, 215.9025).

3-(3-*Chlorobut*-2-*enyl*)-5,8,8-*trimethylbicyclo*[3.3.0]*octan*-2-*one* (**29**).—Potassium hexamethyldisilazide (5.13 ml, 0.9M in THF)[33] was added dropwise to a stirred solution of 5,8,8-trimethylbicyclo[3.3.0]octan-2-one (0.7 g) in dry dimethoxyethane (25 ml) at −78 °C under nitrogen. The light yellow solution was stirred for 0.5 h, then 2-chloro-4-iodobut-2-ene (1.2 g) in DME (1 ml) was added dropwise, and the mixture was allowed to steadily warm to room temperature over 16 h. Water (60 ml) was added, and the mixture was then extracted with ether (3 × 30 ml). The combined, washed (H_2O) extracts were dried and evaporated to give a yellow oil which was purified by chromatography (silica gel G, hexane–ether, 20:1 as eluant) to give the *alkylated bicycle* (0.6 g, 57%) as a 4:1 mixture of β- and α-epimers; $\nu_{max.}$(film) 1 732 and 1 665 cm^{-1}; δ_H (β-epimer) 5.50 (br t, *J* 8 Hz, =CH), 2.7—1.30 (m, 10 H), 2.10 (br, =CMe), 1.23 (Me), 1.15 (Me), 0.95 (Me) (Found: *m/z* 254.1440. $C_{15}H_{23}ClO$ requires M, 254.1437).

3-(3-*Chlorobut*-2-*enyl*)-5,8,8-*trimethylbicyclo*[3.3.0]*octan*-2-*ol* (**30**).—A solution of the ketone (**29**) (0.7 g) in dry ether (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.2 g) in dry ether (30 ml). The mixture was heated under reflux for 3 h, cooled to 25 °C, and water was added dropwise to produce a white precipitate. The supernatant ether was decanted, and the precipitate was then washed with ether (2 × 30 ml). The combined extracts were dried and evaporated to give the *alcohol* (0.6 g, 86%) as a colourless oil; $\nu_{max.}$(film) 3 400 and 1 665 cm^{-1}; δ_H 5.7—5.4 (br t, *J* 8 Hz, =CH), 3.88 (app. t, *J* 9 Hz, C*H*OH), 3.40 (app. t, *J* 9 Hz, C*H*OH diastereoisomers), 2.10 (br, =CMe), 2.5—1.3 (m, 11 H), 1.24 (Me), 1.10 (Me), and 1.08 (Me) (Found: *m/z* 256.1585. $C_{15}H_{25}ClO$ requires *M*, 256.1594).

3-(*But*-3-*ynyl*)-5,8,8-*trimethylbicyclo*[3.3.0]*octan*-2-*ol* (**31**).—Potassium hydride (35% in mineral oil) was carefully washed with dry pentane and then dried by warming in a stream of nitrogen to give the oil-free hydride as a white solid (0.5 g). Dry 1,3-diaminopropane (10 ml) was injected, and the suspension was then stirred until it became homogeneous and gas evolution ceased (*ca.* 0.5 h). The solution was cooled to 0 °C and then 3-(3-chlorobut-2-enyl)-5,8,8-trimethylbicyclo[3.3.0]octan-2-ol (0.6 g) in 1,3-diaminopropane (2 ml) was added dropwise. The resulting red solution was stirred at 25 °C for 3 h, cooled to 0 °C, and ice-cold water (20 ml) was added dropwise. The crude mixture was taken up in hexane (100 ml) and the aqueous layer was separated. The hexane extract was washed with dilute hydrochloric acid (2 × 30 ml), then dried and evaporated to give a mixture of diastereoisomers of the acetylene (0.39 g, 76%) as a green oil which was used without further purification; $\nu_{max.}$(film) 3 400, 3 300, and 2 140 cm^{-1}; δ_H 4.0—3.8 (app. t, *J* 9 Hz, C*H*OH), 3.6—3.3 (app. t, *J* 9 Hz, C*H*OH diastereoisomer), 2.5—1.3 (m, 13 H), 2.00 (t, *J* 3 Hz, ≡CH), 1.22 (Me), 1.12 (Me), and 1.10 (Me) (Found: *m/z* 220.1867. $C_{15}H_{24}O$ requires *M*, 220.1827).

3-(*But*-3-*ynyl*)-5,8,8-*trimethylbicyclo*[3.3.0]*octan*-2-*one* (**32**).—A solution of 3-(but-3-ynyl)-5,8,8-trimethylbicyclo[3.3.0]octan-2-ol (0.1 g) in dichloromethane (1 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (0.2 g) and sodium acetate (15 mg) in dichloromethane (2 ml), and the resulting black suspension was then stirred at 25 °C for 2 h. The mixture was flushed through a Celite pad with ether and the black granular residue carefully triturated with dry ether (5 × 10 ml). The combined ether extracts were dried and evaporated to give the *keto-acetylene* (84 mg, 82%) as an oily 3:1 mixture of β- and α-epimers; $\nu_{max.}$ (film) 3 300, 2 140, and 1 720 cm^{-1}; δ_H(β-epimer) 2.6—1.2 (m, 12 H), 1.98 (t, *J* 3 Hz, =CH), 1.26 (Me), 1.16 (Me), and 0.94 (Me) (Found: *m/z* 218.1638. $C_{15}H_{22}O$ requires *M*, 218.1671).

$\Delta^{9(12)}$-*Capnellen*-10α-*ol* (**33**).—Sodium naphthalide (0.5M anion radical in THF) was added dropwise to a stirred solution of the ketone (**32**) (0.17 g) in dry THF (10 ml) under nitrogen. The dark green colour of the sodium naphthalide was steadily discharged to produce a red suspension. When 8 ml of the sodium naphthalide solution had been added the solution became permanently dark green, and the addition was stopped. Air was introduced into the reaction mixture, which immediately returned to a red colour. The mixture was poured into water (30 ml), extracted with ether (3 × 30 ml), and the combined extracts dried and evaporated to give a yellow gum. Chromatography (silica gel G, hexane then ether–hexane 1:2 as eluant) gave a yellow oil which consisted of a mixture of starting material and tricyclic product. Further chromatography on silica gel G impregnated with 17% silver nitrate, using 1:10 ether–hexane as eluant, gave the *tricycle* (45 mg, 30%) as a colourless oil; $\nu_{max.}$($CHCl_3$) 3 600 and 905 cm^{-1}; δ_H 5.15 and 5.05 (two distinct multiplets, =C*H*H), 2.7—2.6 (m, H_2CCH_2), 2.6—2.4 (m, $=CCH_2$), 1.92—1.39 (m, 11 H), 1.22 (Me), 1.18 (Me), and 0.98 (Me); δ_C 161.8, 107.9 (t), 90.4, 67.7 (d), 51.2 (d), 48.8, 45.2 (dd), 44.2, 43.6 (t), 42.7 (t), 32.2 (q), 31.2 (q), 29.2 (t), 27.0 (t), and 23.7 (q) p.p.m. (Found: *m/z* 220.1824. $C_{15}H_{24}O$ requires *M*, 220.1827).

$\Delta^{9(12)}$-*Capnellene*-8α,10α-*diol* (**34**).—A solution of t-butyl hydroperoxide (30 mg) in dichloromethane (0.3 ml) was added to a stirred solution of $\Delta^{9(12)}$-capnellen-10α-ol (33 mg), selenium dioxide (0.6 mg), and salicylic acid (3.5 mg) in dichloromethane (1 ml), and the solution was then stirred at 25 °C for 3 h. Benzene (15 ml) was added and the mixture was evaporated to a volume of approximately 10 ml, before it was diluted with ether (20 ml), and washed with potassium hydroxide (4 × 30 ml, 10%). The ether solution was dried and evaporated, and the residue was then chromatographed (silica gel G, hexane–acetone, 2:21 as eluant) to give the diol (13.5 mg, 40%) as a viscous, colourless oil; $\nu_{max.}$ 3 600, 3 450, 1 625, and 905 cm^{-1}; δ_H 5.39 (d, *J* 1.8 Hz, =CH*H*), 5.37 (d, *J* 2.2 Hz, =C*H*H), 4.63 (app. t, *J* 9 Hz, C*H*OH), 2.6—2.75 (m, CH), 2.17—1.35 (m, 10 H), 1.21 (Me), 1.18 (Me), and 0.97 (Me); δ_C 163.4, 111.4 (t), 89.4, 74.2 (d), 68.0 (d), 49.1, 48.9 (d), 46.5 (dd), 43.3, 43.6 (t), 42.7 (t), 38.3 (t), 32.0 (q), 31.0 (q), and 23.7 (q) p.p.m. (Found: *m/z* 236.1782. $C_{15}H_{24}O_2$ requires *M*, 236.1776).

(±)-$\Delta^{9(12)}$-*Capnellene*-8β,10α-*diol* (**1**) (with M. Ladlow).—Freshly distilled mesyl chloride (20 μl) was added over 5 min to a rapidly stirred solution of $\Delta^{9(12)}$-capnellene-8α,10α-diol (50 mg) and triethylamine (43 μl) in dry dichloromethane (1 ml) at −20 °C under argon. The mixture was stirred at −20 °C for 1 h then quenched with ice-water and washed successively with water (2 ml), ice-cold hydrochloric acid (1 ml, 2M), and saturated sodium hydrogen carbonate solution (1 ml). Evaporation of the dried organic solution left the methanesulphonate as a yellow semi-solid, which was used immediately and without further purification. The crude methanesulphonate in 1:1 DMSO–DMF (0.5 ml) was added cautiously to a rapidly stirred solution of 18-crown-6 (250 mg) and freshly powdered potassium superoxide (60 mg) in dry DMSO–DMF (1 ml, 1:1) maintained at 0—5 °C under argon. The resulting orange solution was stirred at 0—5 °C for 0.5 h and then at 20 °C for 0.5 h, before water (4 ml) was added and the mixture extracted with chloroform (3 × 5 ml). Triphenylphosphine (75 mg) was added and the chloroform solution was stirred at 25 °C for 0.5 h, then dried and evaporated. Chromatography of the resulting yellow oil (Kieselgel H; 40—60 °C light petroleum–acetone, 4:1) followed by crystallisation from hexane–ether gave the 8β,10α-diol (20 mg, 40%) as white crystals, m.p. 155—156 °C; δ_H 5.34, 5.33 ($=CH_2$), 4.8 (br, C*H*OH), 2.52 (br, 1 H), 2.38 (app. dt, *J* 5 and 2 Hz, 1 H), 1.87 (CH), 1.65—1.85 (m, 2 H), 1.46—1.6 (m, 4 H), 1.28 (dd, *J* 5 and 2 Hz, 1 H), 1.26 (Me), 1.15 (Me), and 1.08 (Me); δ_C 162.5, 109.6 (t), 90.3, 73.7 (d), 65.9 (d), 50.1 49.8 (d), 46.4 (t), 44.1, 43.3 (t), 42.1 (t), 38.0 (t), 32.4 (q), 31.5 (q), and 24.2 (q) p.p.m. (Found: C, 76.1; H, 9.9. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%). The n.m.r. data were superimposable on those of natural material, and the two compounds showed identical chromatography properties.

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