Total Synthesis of the Marine Natural Product (±)-Precapnelladiene

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A stereo-controlled total synthesis of the novel sesquiterpene precapnelladiene (**1**), isolated from the soft coral *Capnella imbricata,* is reported; the synthesis unequivocally establishes the stereochemistry of the natural product as (**1**).

In recent years, several molecular arrays composed of fused 5–8 and 5–8–5 rings have been obtained from natural sources. Prominent among these are the sesquiterpene precapnelladiene (**1**) from a marine organism,[1] the diterpene basemenone (**2**) from tobacco,[2] and the sesterterpene ophiobolin F (**3**) of fungal origin.[3] The uncommon assembly of carbocyclic rings in these compounds, with a high degree of functionalisation and chiral centres, has attracted the attention of synthetic chemists,[4,5] and requires new synthetic strategies. In this communication, we offer a solution to the problem and report the first total synthesis of (±)-precapnelladiene (**1**) which also firmly establishes its stereochemistry.[1]†

The key concept in our synthetic strategy to the 5–8 system of precapnelladiene was the use of the bicyclo[3.3.0]oct-1(5)-

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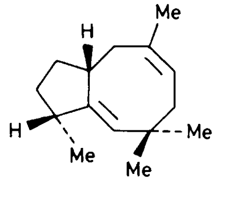
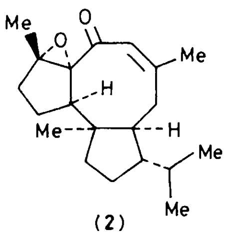
† Birch and Pattenden, reporting[5] the synthesis of (±)-*epi*-precapnelladiene, correctly predicted the relative stereochemistry of the natural product as (**1**).



(1)



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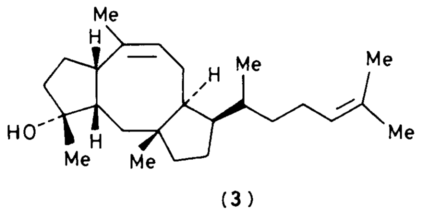

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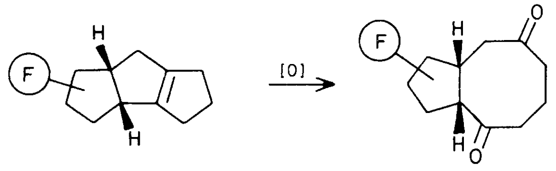
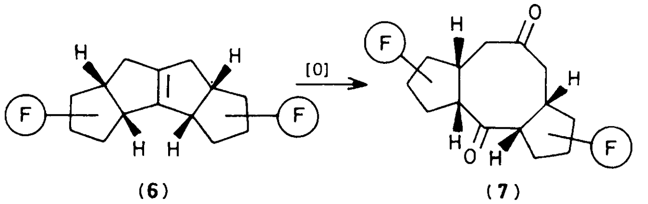
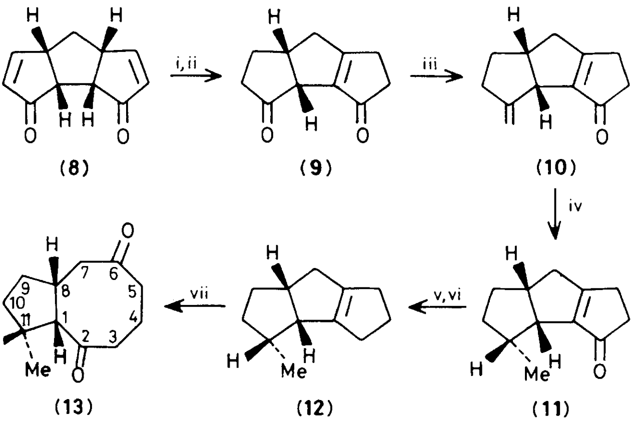


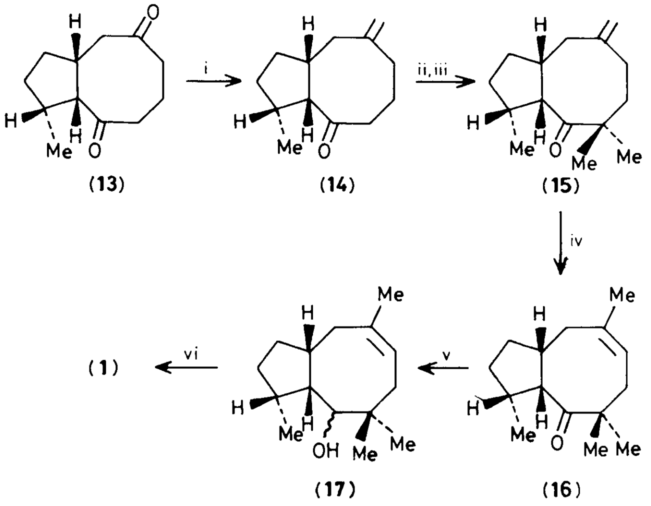
(4) (5)



(6) (7)



Scheme 1. i, $RhCl_3\cdot3H_2O$–EtOH, 70%; ii, H_2–10% Pd/C–EtOAc, quantitative; iii, $Ph_3P^+MeI^-$–t-$C_5H_{11}O^-Na^+$–toluene, 85%; iv, H_2–5% Rh/C–EtOH, 90%; v, $HSCH_2CH_2SH$-*p*-$MeC_6H_4SO_3H$–benzene, 80%; vi, Na–liq.NH_3, 65%; vii, RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, 80%.



Scheme 2. i, $Ph_3P^+MeI^-$–t-$C_5H_{11}O^-Na^+$–toluene, 81%; ii, $(Me_3Si)_2NH$–Bu^{n}Li–MeI, −78 °C, tetrahydrofuran, 92%; iii, Pr^i_2NH–Bu^{n}Li–MeI, −78 °C, tetrahydrofuran, 67%; iv, $RhCl_3\cdot3H_2O$–EtOH, 80%; v, $LiAlH_4$–Et_2O, 80%; vi, $POCl_3$–1,8-diazabicyclo[5.4.0]undec-7-ene–pyridine, 70%.

ene moiety present in triquinane (**4**) as a cyclo-octane-1,5-dione (**5**) equivalent; the *exo*-preference of (**4**) could be exploited for generating the requisite stereochemistry. An extension [(**6**) → (**7**)] of this general theme should provide an entry into the 5–8–5 ring system of fisicoccins[6] and ophiobolins.[7]

The readily available[8] tricyclic bis-enone (**8**) served as the starting material for the synthesis of (**1**) (Scheme 1). Relocation of one of the enone moieties in (**8**) and partial hydrogenation of the disubstituted double bond produced (**9**) in high yield. Selective Wittig olefination of the more reactive saturated carbonyl group of (**9**) proceeded smoothly to yield (**10**). Stereoselective hydrogenation of (**10**) from the convex face, over rhodium–carbon catalyst, furnished the crystalline enone (**11**), m.p. 51—52 °C, with the desired *endo*-methyl group. The enone (**11**) was deoxygenated *via* the thioacetalisation–desulphurisation sequence to yield the pivotal olefin (**12**) in *ca.* 30% overall yield from (**8**). Catalytic ruthenium dioxide oxidation of (**12**) employing the Sharpless conditions[9] gave the required bicyclic dione (**13**), m.p. 39—40 °C, i.r. (neat): 1695 cm^{-1}, ^1H n.m.r. (100 MHz): δ 3.10 (1-H, dd, *J* 6 Hz), 1.6—2.6 (14H, m), and 0.90 (11-Me, d, *J* 7 Hz); ^{13}C n.m.r. (25 MHz): δ 215.2, 213.9, 56.1, 47.3, 44.9, 43.9 (2C), 39.5, 31.5, 30.9, 23.1, and 15.9.

The next stage involved the introduction of methyl groups and double bonds into the eight-membered ring of (**13**). Chemoselective Wittig olefination of the less hindered C-6 carbonyl group furnished the keto-olefin (**14**), i.r. (neat): 1695, 1640, and 890 cm^{-1}; ^1H n.m.r. (100 MHz): δ 4.88 (1H, s), 4.72 (1H, s), 3.24 (1-H, dd, *J* 6 Hz), and 0.96 (11-Me, d, *J* 7 Hz). Two successive, kinetically controlled, regioselective methylations of (**14**) with lithium hexamethyldisilazide–methyl iodide and lithium di-isopropylamide–methyl iodide, respectively, produced the *gem*-dimethylated compound (**15**), m.p. 66—67 °C, i.r. (KBr): 3075, 1690, 1635, and 880 cm^{-1}; ^1H n.m.r. (100 MHz): δ 4.84 (1H, s), 4.68 (1H, d, *J* 3 Hz), 3.34 (1-H, dd, *J* 6 Hz), 1.08 (3-Me, s), 1.94 (3-Me, s), and 0.90 (11-Me, d, *J* 7 Hz); ^{13}C n.m.r. (25 MHz): δ 218.4, 148.5, 114.5, 51.6, 49.0, 48.3, 40.6, 40.0, 37.9, 35.2, 31.9, 30.5, 27.2, 21.4, and 16.3. Rhodium catalysed isomerisation of the terminal olefinic moiety into the endocyclic position readily gave (**16**), i.r. (neat): 3050, 1695, and 1660 cm^{-1}; ^1H n.m.r. (100 MHz): δ 5.44 (5-H, t, *J* 8 Hz), 3.24 (1-H, dd, *J* 6Hz), 1.76 (6-Me, s), 1.2 (3-Me, s), 1.08 (3-Me, s), and 0.88 (11-Me, d, *J* 7 Hz). The final step in the precapnelladiene synthesis required conversion of the C-2 carbonyl group into a C-1–C-2 double bond, and this was achieved through metal hydride reduction of (**16**) to give (**17**) followed by dehydration as shown in Scheme 2. The synthetic sample of (**1**) was identical (i.r.; ^{1}H n.m.r.) with the natural product.[1]

We thank Professors C. Djerassi and G. Pattenden for comparison spectra. This research was supported through a U.G.C. Special Assistance Programme in Organic Chemistry.

Received, 21st May 1984; Com. 704

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