Macrocyclisations using Allylic Radical Intermediates. A New Synthetic Approach to Natural 14-Membered Cembranoids

Nicholas J. G. Cox,[a] Stuart D. Mills[b] and Gerald Pattenden*[,a]
[a] *Department of Chemistry, The University, Nottingham NG7 2RD, UK*
[b] *ICI Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield SK10 4TG, UK*

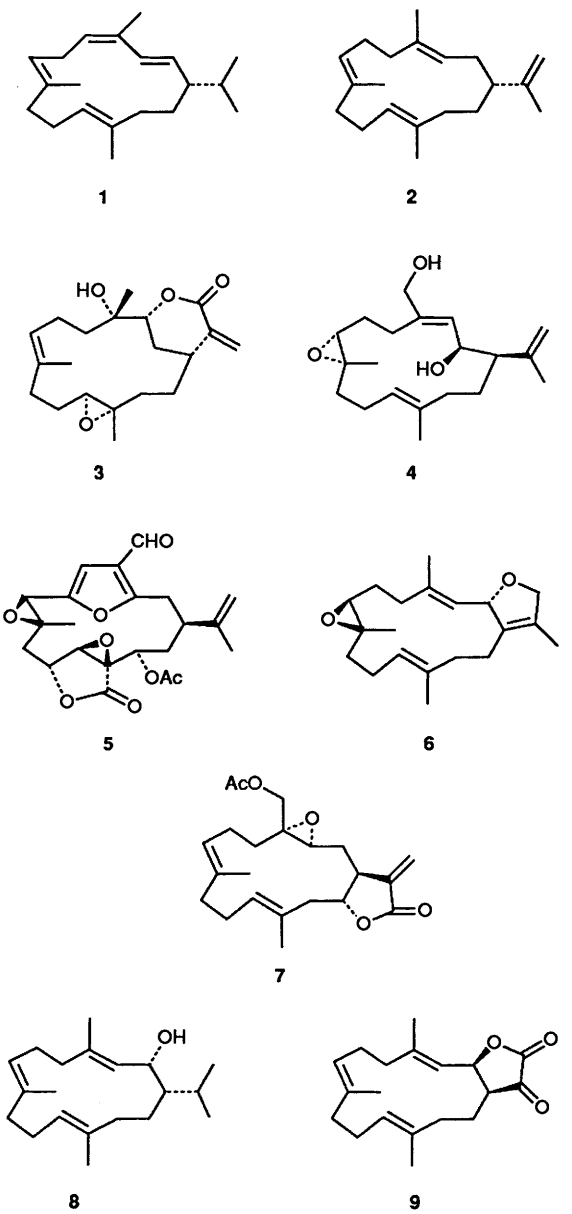
A range of alternative radical macrocyclisation approaches to cembranoids have been evaluated. Radical macrocyclisations involving the allylic radicals **11** generated from the corresponding allylic iodides, **15b** and **20b**, in the presence of Bu_3SnH–AIBN,† are shown to lead to 14-membered trienones, *viz* **10**, *via* selective 14-*endo*-*trig* processes. Both **10a** and **10b** can then be elaborated to the natural marine cembranoids **8** (mukulol) and **9** respectively, by straightforward functional group interconversions.

Concise syntheses of the α,ω-dial **28**, the terminal acetylenic aldehyde **27** and the allylic iodide enal **37** were developed, but neither was found to undergo radical mediated cyclisation to the corresponding 14-membered carbocycles **29**, **30** and **38** respectively. Instead, only the products of reduction, *e.g.* **39**, or intermolecular pinacolisation, *e.g.* **34** were produced.

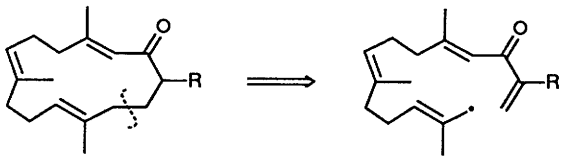
Ever since the determination of the structures of the 14-membered diterpene hydrocarbon cembrene **1** from *Pinus albicaulis* in 1962,[1] a very wide range of cembranoids have been found in higher plants of the genus *Pinus*[2] and *Nicotiana*,[3] in particular, and also from marine soft corals.[4] Cembranoids have attracted a great deal of interest from both synthetic chemists and biologists, largely as a result of their unusual structures and their diverse range of biological properties. For example, the simplest cembrane, neocembrane **2**, is used as a trail pheromone of the Australian termite *Nasutitermis excitiosus*,[5] and sinularin **3** produced by the soft *Sinularis flexibilis* is an antineoplastic agent.[6] Asperdiol **4** is active against tumor cells at the μg cm^{-3} level,[7] and lophotoxin **5** is a neuromuscular toxin (LD_{50} in mice 8 μg g^{-1}) isolated from the gorgonium of the genus *Lophogorgonia*.[8] Finally, 16-deoxysarcophine **6** found in the coral *Sarcophytum trocheliophorum* has been found to possess interesting calcium antagonistic activity[9] and lobalide **7** from *Lobophytum crassum* shows ichthyotoxic properties.[10]

In spite of considerable effort there remains a dearth of flexible macrocyclisation methodology for the elaboration of 14-membered diterpenes of the type represented by formulae **1**–**7** which accommodate a range of sensitive oxygen-containing functionality distributed in a predetermined geometrical manner.[11,12] We have examined a number of complementary methods for the synthesis of oxygenated cembranoids which have as their focus the intramolecular macrocyclisation of carbon centred radical precursor molecules.[13] In this paper we describe the development of this chemistry and the total synthesis of mukulol **8** found in *Comiphora mukul*[14] and a new approach to the cembranolide lactone **9** isolated from the soft coral *Sinularia mayi*.[15,16]

Although radical cyclisations have now acquired a status of immense importance in the design of synthesis of five- and six-membered (and some medium) carbo- and hetero-cyclic compounds, before the fundamental studies published by Porter *et al.*[17] in 1986, and before the start of our own work, illustrations of their use in the elaboration of large ring compounds were extremely sparse indeed. Our idea in the work described here was to elaborate the 14-ring macrocyclic ketones **10a** and **10b** *via* 14-*endo*-*trig* cyclisations of the novel allyl radical intermediates **11a** and **11b** respectively as the key step, and then to



† AIBN = Azoisobutyronitrile.

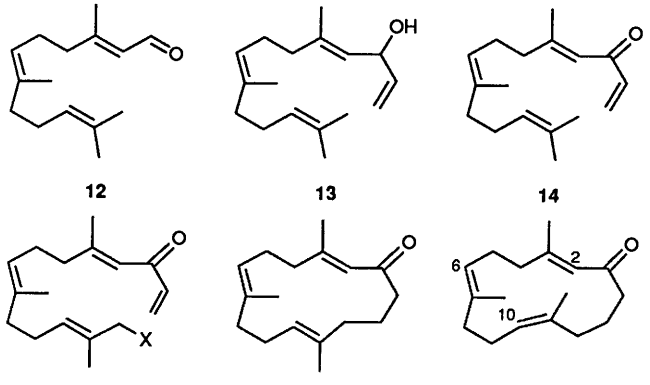


10a R = H
b R = $CHMe_2$

11

produce the cembranoids **8** and **9** by appropriate functional group manipulation of the macrocycles. At the outset of our work there were no illustrations of the scope for allyl radicals in ring synthesis[18] and no demonstrations of the use of radical macrocyclisations in target natural product synthesis.[19]

Thus, in our synthesis of the 14-membered trienone precursor **10a** to the cembranolide lactone **9**, farnesal **12** was first treated with vinylmagnesium bromide in tetrahydrofuran (THF) at 0 °C leading to the bis-allylic alcohol **13**, which was then smoothly oxidised to the corresponding tetraenone **14** in the presence of manganese dioxide. The elaboration of **14** to the allylic alcohol **15a** was next effected, in a regio- and stereoselective manner, using catalytic selenium dioxide in the presence of *tert*-butyl hydroperoxide.[20] The *E*-stereochemistry of the allylic alcohol double bond in **15a** followed from NOE experiments, where irradiation at δ 3.98 (CH_2OH) in the ^1H NMR spectrum was shown to enhance the signal at δ 5.37 (CH_2CH=$CMeCH_2OH$) by 10%.



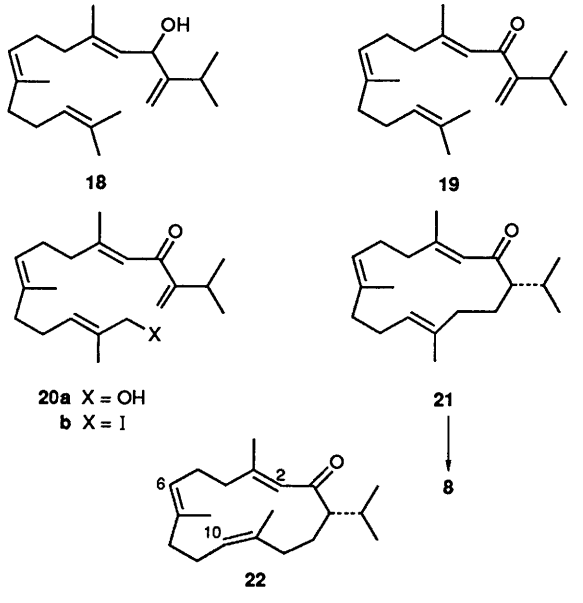
12 **13** **14**

15a X = OH
b X = I

16 **17**

Treatment of **15a** with iodine in the presence of triphenylphosphine and imidazole[21] next led to the allylic iodide **15b**, precursor to the allyl radical intermediate of **11a** for the projected macrocyclisation to **16**. To our satisfaction when a solution of the iodide **15b** in dry deaerated benzene was heated under reflux for 3 h in the presence of tributyltin hydride and AIBN, work-up led to a 3:1 mixture of the (10*E*) **16** and the (10*Z*) **17** isomers of the anticipated cyclotetradecatrienone, which were easily separated by chromatography, in a combined yield of 52%.

The first obvious sign that macrocyclisation of **15b** had occurred was the loss of the characteristic signals for the ethenyl group in the ^1H NMR spectrum of the product, and the shift in the positions of the other (non-conjugated) vinyl hydrogen signals from δ 5.1–5.4 to δ 4.8–4.9 in (*E*) **16**. These shifts in the vinyl signals, which are presumably associated with transannular interactions and/or ring strain, are typical of many cembranoids.[22] Interestingly, the 10-H of the 10(*Z*) isomer **17** is significantly deshielded in comparison with the same signal in the *E*-isomer (δ 5.96 *vs.* δ 4.79) presumably because this vinylic hydrogen is directed out of the macrocycle ring rather than inwards (see data in Experimental section). The full structure and stereochemistry of the all-*E*-macrocyclic trienone **16** followed from inspection and comparison of its ^1H NMR and ^{13}C NMR spectral data with those reported by Kato *et al.*[23] for the same compound prepared by an alternative route. Confirmation of the (10*Z*) stereochemistry of the minor product **17** resulting from radical macrocyclisation of **15b** was obtained by comparison of ^1H and ^{13}C NMR data with those of the (10*E*) isomer **16**, *e.g.* the pronounced γ-effect observed at C-12 in the ^{13}C NMR spectrum of **17**; δ 23.0 *vs.* δ 15.0. The isomer **17** is clearly the result of isomerisation, *via* allylic transposition, of the radical intermediate **11a** produced from **15b** prior to the observed 14-*endo* cyclisation. No additional products, whose formation could be accounted for as a result of competitive 8-*exo*, 10-*exo* or 12-*endo* cyclisation modes, were isolated from the cyclisation of **15b**. The all-*E*-trienone **16** has been used by Kato *et al.*[23] in a synthesis of the cembranolide lactone **9**, following: (i) deprotonation and alkylation with ethyl iodoacetate; (ii) reduction of the resulting γ-keto ester with sodium borohydride; (iii) acid-catalysed cyclisation to the corresponding *cis*-butyrolactone; and finally (iv) α-methylenation. Our synthesis of **16**, therefore, constitutes a formal synthesis of this cembranolide which is found in the coral *Sinularia maji*.[15]



18 **19**

20a X = OH
b X = I

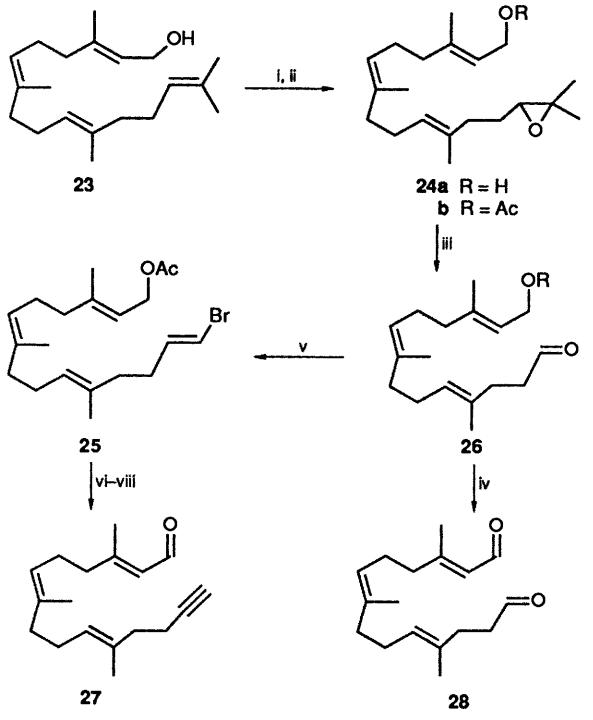
21

8

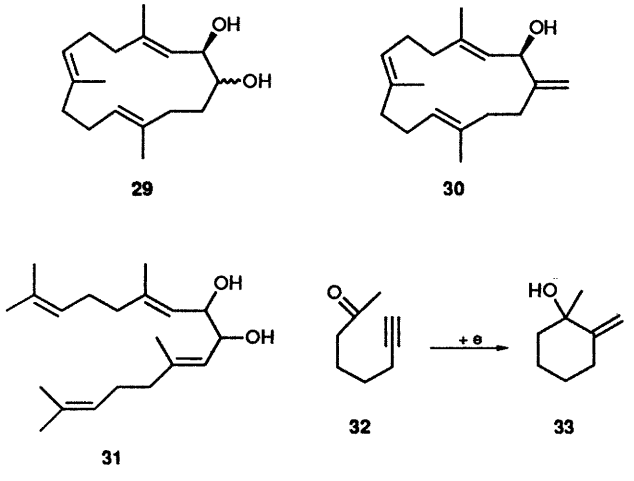
22

Using an identical sequence of reactions to those described above, we also effected a new total synthesis of mukulol **8** a metabolite which was first isolated from the gum resin of the Indian tree *Comiphora mukul*.[14] Thus, elaboration of farnesal to the iodotetraenone **20b**, *via* **18**, **19** and **20a**, followed by stannane-induced radical cyclisation led to a 4:1 mixture of the macrocyclic trienones **21** and **22** in a combined yield of 40%. After separation of the all-*E* isomer **21**, by chromatography, reduction in the presence of lithium aluminium hydride then gave (±)-mukulol **8** which showed spectroscopic data identical with those reported for the natural product. This second synthesis of the 14-membered ring system found in cembranoids, therefore fully endorsed the potential for radical macrocyclisation reactions *via* allylic radical intermediates in this demanding area of synthesis.

In contemporaneous investigations we also examined a number of complementary routes to cembranoids, each of which involved radical macrocyclisation as the key stratagem.[13] For example, both the α,ω-dialdehyde **28** and the corresponding terminal acetylenic aldehyde **27** were synthesised from geranyl-



Scheme 1 *Reagents:* i, Ref. 29; ii, Ac_2O–C_5H_5N; iii, HIO_4; iv, MnO_2; v, $Ph_3\overset{+}{P}CH_2Br\ \bar{B}r$–KOBu^t (R = Ac); vi, K_2CO_3–MeOH; vii, KOBu^t; viii, MnO_2



geraniol **23**, (Scheme 1), with a view to effecting their intramolecular reductive coupling (pinacol-type) to the diol **29** and the allylic alcohol **30** respectively. However, although model work with *E*-citral (producing **31**; 12%) and literature precedent[24,25] were encouraging, the attempted electrochemical reductive pinacolisation of the dialdehyde **28**, to **29**, under a range of conditions, *e.g.* in the presence of chromium(III) trichloride[24] to first complex the aldehyde or in the presence of diethyl malonate as a proton source,[25] met with failure, and only starting material was recovered. Furthermore, although Shono *et al.*[26] and others,[27,28] have demonstrated that terminal acetylenic ketones undergo smooth intramolecular reductive coupling to the corresponding cyclic allylic alcohols, *viz* **32**—→**33**, under a range of conditions *e.g.* electrochemistry, sodium naphthalene radical anion, reducing metals, the only product we were able to obtain from electrochemical reductive coupling of the acetylenic aldehyde **27** was the pinacol dimer **34** in 11% yield.

Finally, in other investigations we synthesised the allylic iodide—α,β-unsaturated aldehyde substrate **37**, with a view to effecting its radical-mediated cyclisation to the 14-membered aldehyde **38** (Scheme 2). These attempts also met with failure however, and only the product of reduction, *i.e.* **39**, was isolated on treatment of **37** with tributyltin hydride and catalytic azoisobutyronitrile.

Experimental

General Details.—M.p.s were determined using a Köfler hot-stage instrument and are uncorrected, and Kugelrohr bulb-to-bulb distillations were performed on a Büchi GKR-50 rotating bulb apparatus.

Infrared spectra were recorded on a Pye-Unicam SP3-100 spectrometer; spectra were recorded as thin liquid films on sodium chloride discs or as solutions in the stated solvent. Ultraviolet absorption spectra were obtained on a Philips PV 8720 UV/Visible scanning spectrophotometer as dilute solutions in the stated solvent (ε follows λ_{max} in parentheses).

Proton magnetic resonance spectra were recorded at 90 MHz unless otherwise stated and were recorded as either continuous wave spectra at 90 MHz on a Perkin Elmer R32 instrument or as pulsed Fourier transform spectra on a Bruker WP80SY PFT, a JEOL FX90Q PFT, a Bruker WM250 PFY, or a Bruker AM400 PFT spectrometer at 80 MHz, 90 MHz, 250 MHz and 400 MHz respectively. ^{13}C Nuclear magnetic resonance spectra were also recorded on these instruments at 20.15 MHz, 22.5 MHz, 62.9 MHz and 100.6 MHz respectively as stated. All NMR measurements were obtained for dilute solutions in deuteriochloroform containing tetramethylsilane (TMS) or chloroform as an internal standard and chemical shifts (δ) are reported in ppm from TMS. Line separations (J) are given in Hertz and multiplicities are designated as follows: no designation, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For ^{13}C NMR, designations were determined by distortionless enhancement by polarisation transfer (DEPT) pulse sequences in conjunction with broad-band decoupled ^{13}C NMR.

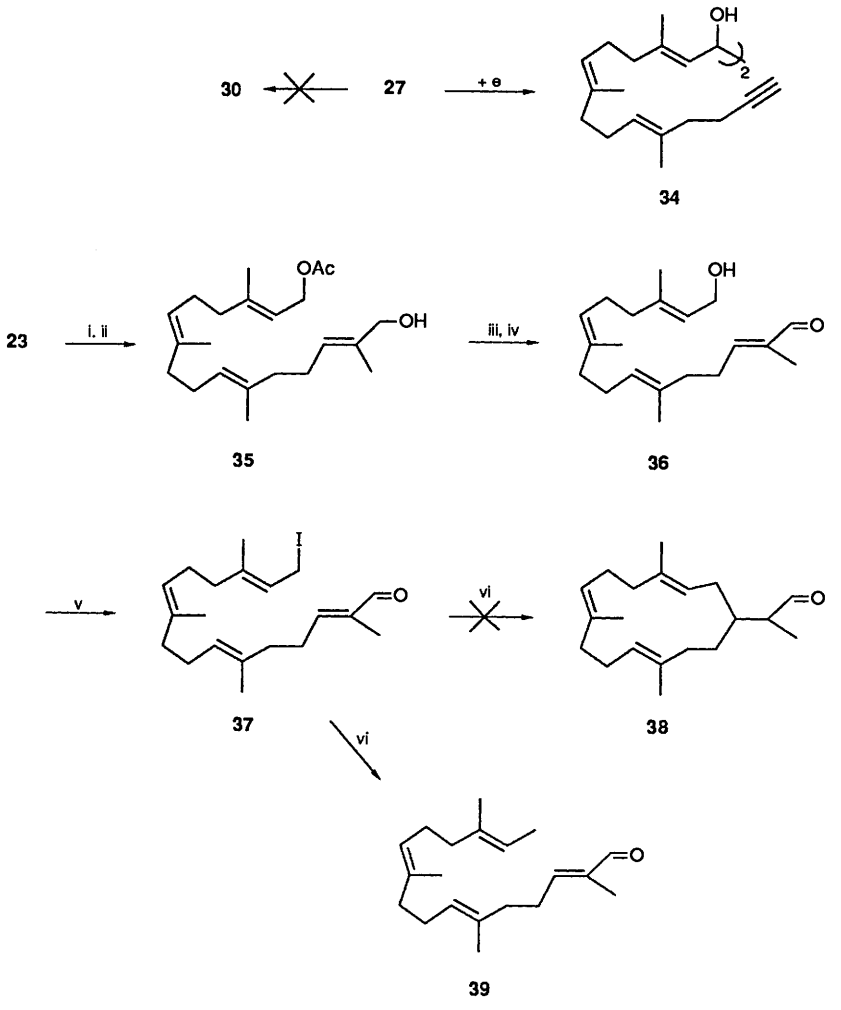
Mass spectra were recorded on an AEI MS902 or on a VG 7070E instrument using either electron impact or chemical ionisation (CI) techniques. Microanalyses were performed using a Perkin Elmer 240B elemental analyser.

All organic solutions were dried over magnesium sulfate or sodium sulfate and solvents were removed under reduced pressure on a Büchi rotary evaporator. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F254 aluminium backed plates which were visualised with UV light (254 nm) or alternatively with basic potassium permanganate, acidic alcoholic 2,4-dinitrophenylhydrazine, dilute aqueous sulfuric acid or acidic alcoholic vanillin spray reagents. Silica refers to Silica gel 60.

Gas-liquid chromatography was performed on a Pye-Unicam GCD chromatograph with flame-ionisation detection using a nitrogen flow rate of 40 $cm^3\ min^{-1}$.

High pressure liquid chromatography was performed on a Waters Associates Liquid Chromatograph equipped with a 30 cm column (internal diameter 7.8 mm) packed with μPorasil.

3,7,11-*Trimethyldodeca*-2(E),6(E),10-*trienal* **12**.—A solution of (*E,E*)-farnesol (10.0 g) in dichloromethane (20 cm^3) was added in a single portion to a stirred suspension of manganese dioxide (40.0 g) in dichloromethane (400 cm^3). The mixture was stirred at room temperature for 16 h and then filtered under suction. Evaporation of the filtrate left the enal (9.12 g, 95%) as a pale yellow oil, b.p. (oven) 190–194 °C (11 mmHg) [lit.,[30] b.p. 98–118 °C (0.5 mmHg)]; λ_{max} (EtOH)/nm 238 (11 000); ν_{max}(film)/cm^{-1} 2770, 1685, 1635 and 1615; δ_H(250 MHz) 9.99 (d, *J* 8, CHO), 5.89 (d, *J* 8, =C*H*CHO), 5.08 (br m, 2 × =CH), 2.3–1.9 (m, 4 × CH_2, CH_3), 1.64 (CH_3) and 1.58 (2 × CH_3); δ_C(22.5



Scheme 2 *Reagents:* i, Ac_2O–C_5H_5N; ii, SeO_2 – Bu^tO_2H; iii, MnO_2, $CHCl_3$; iv, K_2CO_3–MeOH; v, PPh_3, I_2, imidazole; vi, Bu_3SnH–AIBN

MHz) 189.7 (d), 162.1, 135.7, 130.5, 126.9 (d), 123.8 (d), 122.2 (d), 40.0 (t), 39.2 (t), 26.2 (t), 25.3 (t), 25.0 (q), 17.0 (q), 16.8 (q) and 15.4 (q).

5,9,13-*Trimethyltetradeca*-1,4(E),8(E),12-*tetraen*-3-*ol* **13**.—A solution of the enal **12** (9.10 g) in dry ether (15 cm^3) was added dropwise over 15 min to a stirred solution of vinylmagnesium bromide (0.1 mol dm^{-3}) in THF (100 cm^3), under nitrogen at 0 °C. The solution was stirred at 0 °C for 20 min and then quenched by the addition of saturated ammonium chloride solution (30 cm^3). The mixture was diluted further with brine (500 cm^3) and then extracted with diethyl ether (4 × 150 cm^3). The combined extracts were washed with water (200 cm^3) and then with brine (150 cm^3). Evaporation of the dried extracts left the *alcohol* (9.45 g, 92%) as a pale yellow oil which was comparatively pure. A small sample was purified by chromatography on silica to give a colourless oil; ν_{max}(film)/cm^{-1} 3330br, 1665, 1005 and 905; δ_H(250 MHz) 5.90 (ddd, *J* 18, 10 and 8, H_2C=C*H*), 5.23 (d, *J* 18, =C*H*H), 5.25–5.0 (m, 3 × =CH), 5.12 (d, *J* 10, =CH*H*), 4.87 (br dd, *J* 8, 8, C*H*OH), 2.15–1.9 (m, 4 × CH_2), 1.70 (CH_3), 1.67 (CH_3), 1.58 (2 × CH_3) and 1.45 (br, OH); δ_C(20 MHz) 140.2 (d), 138.9, 135.4, 131.3, 126.0 (d), 124.4 (d), 123.8 (d), 113.9 (t), 69.9 (d), 39.7 (t), 39.6 (t), 26.8 (t), 26.3 (t), 25.7 (q), 17.7 (q), 16.7 (q) and 16.0 (q) (Found M^+, 248.2110; C, 81.8; H, 11.4; $C_{17}H_{28}O$ requires *M*, 248.2140; C, 82.2; H, 11.4%).

5,9,13-*Trimethyltetradeca*-1,4(E),8(E),12-*tetraen*-3-*one* **14**.—A solution of the alcohol **13** (9.20 g) in dichloromethane (20 cm^3) was added in a single portion to a stirred suspension of manganese dioxide (92.0 g) in dichloromethane (500 cm^3). The mixture was stirred at room temperature for 16h and then filtered under suction. Evaporation of the filtrate left the *tetraenone* (7.03 g, 77%) as a pale yellow oil, b.p. (oven) 178–180 °C (7 mmHg) which was used without further purification; λ_{max}(EtOH)/cm^{-1} 250 (5 500); ν_{max}(film)/cm^{-1} 1680, 1670, 1630, 1610 and 980; δ_H(250 MHz) 6.52 (dd, *J* 18 and 11, H_2C=C*H*C=O), 6,35 (=CHC=O), 6.29 (dd, *J* 18, 2, =C*H*H), 5.83 (dd, *J* 11, 2, =CH*H*), 5.18 (br, 2 × =CH), 2.35–2.0 (m, 4 × CH_2, CH_3C=CC=O), 1.78 (CH_3) and 1.70 (2 × CH_3) (M^+, 246.1988. *M*, 246.1984).

14-*Hydroxy*-5,9,13-*trimethyltetradeca*-1,4(E),8(E),12(E)-*tetraen*-3-*one* **15a**.—A solution of the tetraenone **14** (6.80 g) in dichloromethane (10 cm^3) was added in a single portion to a stirred mixture of selenium dioxide (1.50 g) and *tert*-butyl hydroperoxide (80% solution, 6.0 cm^3) in dichloromethane (90 cm^3) at 0 °C. The stirred mixture was allowed to warm to room temperature over 2 h before it was concentrated to leave a yellow residue which was immediately taken up in diethyl ether (50 cm^3). The solution was washed with sodium hydroxide solution (10%, 2 × 50 cm^3) and then with brine (50 cm^3). Evaporation of the dried extracts left a yellow residue. The residue was purified by chromatography on silica using pentane–diethyl ether (2:1, 3:2, 1:1) as eluent to give the *hydroxy tetraenone* (2.03 g, 28%) as a pale yellow oil; λ_{max}(EtOH)/nm 264 (9 800); ν_{max}(film)/cm^{-1} 3420br, 1660, 1628, 1604 and 990; δ_H(250 MHz) 6.42 (dd, *J* 15, 10, H_2C=C*H*C=O), 6.28 (=CHC=O), 6.23 (dd, *J* 15, 2, =C*H*H), 5.75

(dd, *J* 10, 2, =CH*H*), 5.37 (t, *J* 5, =CH), 5.10 (br, =CH), 3.98 (CH_2OH), 2.3–1.9 (m, 4 × CH_2), 2.14 (d, *J* 1, CH_3C=CC=O), 1.68 (CH_3) and 1.62 (CH_3); irradiation at δ 3.98 gave an NOE of 10% at δ 5.37; δ_C(22.5 MHz) 190.6, 160.1, 138.4, 135.9, 134.9, 126.9 (t), 125.7 (t), 123.2 (d), 121.7 (d), 68.9 (t), 41.3 (t), 39.3 (t), 26.2 (t), 26.1 (t), 19.7 (q), 16.0 (q) and 13.7 (q) [Found: M^+ (CI) 263; C, 77.4; H, 9.9. $C_{17}H_{26}O_2$ requires *M* + H, 263; C, 77.8; H, 10.0%].

14-*Iodo*-5,9,13-*trimethyltetradeca*-1,4(E),8(E),12(E)-*trien*-3-*one* **15b**.—Triphenylphosphine (200 mg) and a solution of imidazole (60 mg) in acetonitrile (0.5 cm^3) was added to a stirred solution of the hydroxy tetraenone **15a** (100 mg) in dry diethyl ether (1 cm^3). The resulting pink solution was stirred under nitrogen at 0 °C for 10 min and then iodine (240 mg) was added in 12 × 20 mg portions. The solution was stirred at 0 °C for 30 min and then was diluted with pentane (15 cm^3). The extracts were washed successively with saturated aqueous sodium thiosulfate (5 cm^3), saturated cupric sulfate solution (5 cm^3) and water (5 cm^3). Evaporation of the dried extracts left the *iodo tetraenone* (106 mg, 75%) as a highly labile pale yellow oil which was used immediately without further purification; ν_{max}(film)/cm^{-1} 1655, 1620, 1598 and 990; δ_H 6.8–6.1 (m, 3 × =CH), 5.9–5.6 (m, 2 × =CH), 4.9–4.65 (br, =CH), 3.99 (CH_2I), 2.35–2.0 (m, 4 × CH_2, CH_3), 1.80 (CH_3) and 1.64 (CH_3) (M^+ − I, 245. *M* − I, 245).

3,7,11-*Trimethylcyclotetradeca*-2(E),6(E),10(E)-*trienone* **16** *and* 3,7,11-*Trimethylcyclotetradeca*-2(E),6(E),10(Z)-*trienone* **17**.—Tributyltin hydride (0.54 cm^3) and AIBN (50 mg) were added to a solution of the iodo tetraenone **15b** (720 mg) in dry, deaerated benzene (650 cm^3) under nitrogen. The solution was heated to reflux and held at reflux for 3 h. The solution was then allowed to cool to room temperature before it was concentrated under reduced pressure to leave a colourless residue (2.0 g). The residue was purified by chromatography on silica using diethyl ether–hexane (1:30, 1:20) as eluent to give a mixture of the two isomers **16** and **17** (230 mg, 48%) inseparable by column chromatography. Separation was achieved by HPLC eluting with diethyl ether–hexane (1:40) which gave the major isomer (72%), the all-*E* *cyclic ketone* **16** as a colourless oil; λ_{max}(EtOH)/nm 240 (10 800); ν_{max}($CHCl_3$)/cm^{-1} 1680 and 1610; δ_H(400 MHz) 5.93 (=CHC=O), 4.87 (br m, =CH), 4.79 (br m, =CH), 2.30–1.78 (m, 7 × CH_2), 2.08 (d, *J* 0.8, CH_3C=CC=O), 1.59 (CH_3) and 1.54 (d, *J* 0.7, CH_3); δ_C(101 MHz) 202.4, 155.8, 134.6, 133.4, 125.9 (2 × d), 125.0 (d), 40.4 (t), 39.5 (t), 39.1 (t), 37.3 (t), 24.5 (t), 24.2 (t), 21.9 (t), 19.3 (q), 15.1 (q) and 15.0 (q) (Found: M^+, 246.1974. *M*, 246.1984). And the minor isomer (28%) the 2(*E*),6(*E*),10(*Z*) *cyclic ketone* **17** as a colourless oil; λ_{max}(EtOH)/nm 241 (9 400); ν_{max}($CHCl_3$)/cm^{-1} 1675, 1615; δ_H(400 MHz) 5.98 (=CHC=O), 5.16 [t, *J* 6.5, =CH(*Z*)], 4.92 [br m, =CH(*E*)], 2.40–1.90 (m, 7 × CH_2), 2.07 (d, *J* 1.2, CH_3C=CC=O), 1.66 (d, *J* 1.2, CH_3) and 1.59 (d, *J* 1.1, CH_3); δ_C(101 MHz) 201.8, 157.4, 137.5, 134.6, 126.4 (d), 124.5 (d), 123.6 (d), 44.2 (t), 40.6 (2 × t), 31.0 (t), 29.5 (t), 24.0 (2 × t), 23.4 (q), 18.6 (q) and 16.2 (q) (M^+, 246.1975. *M*, 246.1984).

2,6,10,14-*Tetramethyl*-3-*methylenepentadeca*-5(E),9(E),13-*trien*-4-*ol* **18**.—A solution of a 2:1 mixture of 2-bromo-3-methylbut-1-ene and its positional isomer 1-bromo-3-methylbut-1-ene[31] (4.88 g) in dry THF (25 cm^3) was added dropwise over 15 min to a stirred mixture of dry magnesium turnings (880 mg) under dry THF (25 cm^3) at room temperature under nitrogen. When the magnesium turnings had all been consumed, the solution was cooled to 0 °C and the aldehyde **12** (6.57 g) in dry THF (10 cm^3) was then added dropwise over 10 min. The solution was stirred at room temperature for 16 h and then quenched by the addition of saturated aqueous ammonium chloride (20 cm^3) and extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3) and then with brine (50 cm^3). Evaporation of the dried extracts left a yellow residue (8.03 g). The residue was purified by chromatography on silica using hexane–diethyl ether (5:1) as eluent to give the *alcohol* (3.11 g, 54%) as a colourless oil; ν_{max}(film)/cm^{-1} 3550br, 1660, 1640 and 910; δ_H 5.25–4.75 (m, 2 × =CHR, C*H*OH), 5.12 (=C*H*H), 4.88 (=CH*H*), 2.2–1.8 (m, 4 × CH_2, $CHMe_2$), 1.73 (d, *J* 1.3, CH_3), 1.68 (CH_3), 1.60 (2 × CH_3), 1.07 (d, *J* 6.8, CH_3) and 1.05 (d, *J* 6.8, CH_3); δ_C(22.5 MHz) 158.0, 138.0, 135.0, 130.7, 127.3 (d), 124.3 (d), 123.7 (d), 106.0 (t), 70.4 (d), 39.6 (2 × t), 29.9 (d), 26.7 (t), 26.2 (t), 25.4 (q), 22.9 (q), 22.4 (q), 17.4 (q), 16.4 (q) and 15.8 (q) (Found M^+, 290.2615; C, 83.0, H, 11.85. $C_{20}H_{34}O$ requires *M*, 290.2610; C, 82.70; H, 11.80%).

2,6,10,14-*Tetramethyl*-3-*methylenepentadeca*-5(E),9(E),13-*trien*-4-*one* **19**.—A solution of the alcohol **18** (180 mg) in dichloromethane (1 cm^3) was added in a single portion to a stirred suspension of manganese dioxide (2.0 g) in dichloromethane (25 cm^3). The mixture was stirred at room temperature for 17 h and then filtered under suction. Evaporation of the filtrate left the *trienone* (170 mg, 95%) as a pale yellow oil, b.p. 224–226 °C (12 mmHg); λ_{max}(EtOH)/cm^{-1} 243 (7 800) and 258 (8 350); ν_{max}(film)/cm^{-1} 1660, 1605 and 930; δ_H 6.39 (=CHC=O), 5.83 (=C*H*H), 5.57 (=CH*H*), 5.12 (br, 2 × =CH), 3.16–2.76 (m, $CHMe_2$), 2.2–2.0 (m, 4 × CH_2, CH_3C=CC=O), 1.67 (CH_3), 1.60 (2 × CH_3) and 1.04 [dt, *J* 6.8, 1.6, $CH(CH_3)_2$]; δ_C(22.5 MHz) 193.8, 157.2, 156.7, 135.8, 131.0, 124.2 (d), 123.0 (d), 121.4 (d), 118.9 (t), 41.0 (t), 39.6 (t), 28.0 (d), 26.7 (t), 26.0 (t), 25.5 (q), 21.7 (2 × q), 19.2 (q), 17.5 (q) and 15.9 (q) (Found: M^+, 288.2457; C, 83.45; H, 11.2. $C_{20}H_{32}O$ requires *M*, 288.2453; C, 83.27; H, 11.18%).

15-*Hydroxy*-2,6,10,14-*tetramethyl*-3-*methylenepentadeca*-5(E),9(E),13(E)-*trien*-4-*one* **20a**.—A solution of the trienone **19** (100 mg) in dichloromethane (1 cm^3) was added in a single portion to a stirred mixture of selenium dioxide (18 mg) and *tert*-butyl hydroperoxide (90% solution; 0.1 cm^3) in dichloromethane (4 cm^3) at 0 °C.[32] The stirred mixture was allowed to warm to room temperature over 2 h before it was concentrated to leave a yellow residue which was taken up immediately in diethyl ether (5 cm^3). The solution was washed with aqueous sodium hydroxide (10%, 2 × 5 cm^3) and then with brine (5 cm^3). Evaporation of the dried extracts left a yellow residue (40 mg). The residue was purified by chromatography on silica using hexane–diethyl ether (2:1) as eluent to give the *hydroxy trienone* (20.1 mg, 19%) as a pale yellow oil; λ_{max}(EtOH)/nm 237 (8 800) and 258 (10 500); ν_{max}(film)/cm^{-1} 3400br, 1665, 1615 and 930; δ_H(250 MHz) 6.37 (d, *J* 1, =CHC=O), 5.84 (=C*H*H), 5.59 (=CH*H*), 5.38 (t, *J* 1.3, *H*C=CMeCH$_2$OH), 5.12 (br, =CH), 3.99 (CH_2OH), 2.95 (septet, *J* 6, $CHMe_2$), 2.3–2.0 (m, 4 × CH_2), 2.08 (d, *J* 1, CH_3C=CC=O), 1.66 (CH_3), 1.62 (CH_3) and 1.04 [d, *J* 6, $CH(CH_3)_2$]; irradiation at δ 3.99 gave an NOE of −6% at δ 5.38; δ_C(22.5 MHz) 194.1, 157.1, 156.8, 135.6, 134.9, 125.2 (d), 123.1 (d), 121.5 (d), 119.2 (t), 68.4 (t), 40.9 (t), 39.2 (t), 28.0 (d), 26.1 (t), 25.9 (t), 21.7 (2 × q), 19.2 (q), 15.9 (q) and 13.4 (q) [Found: M^+ + H (CI), 305; C, 79.1; H, 11.0. $C_{20}H_{32}O_2$ requires *M* + H, 305; C, 78.90; H, 10.59%].

15-*Iodo*-2,6,10.14-*tetramethyl*-3-*methylenepentadeca*-5(E),9(E),13(E)-*trien*-4-*one* **20b**.—Triphenylphosphine (260 mg) and a solution of imidazole (67 mg) in acetonitrile (1 cm^3) were added to a stirred solution of the hydroxy trienone **20a** (150 mg) in dry diethyl ether (1.5 cm^3) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 10 min and then

iodine (250 mg) was added in 10 portions over 5 min. The solution was stirred at 0 °C for 30 min and was then diluted with pentane (10 cm^3). The extracts were washed successively with saturated aqueous sodium thiosulfate (5 cm^3), saturated aqueous cupric sulfate (5 cm^3) and water (5 cm^3). Evaporation of the dried extracts left the iodo trienone (150 mg, 74%) as a highly labile pale yellow oil which was used immediately without further purification; ν_{max}(film)/cm^3 1655 and 1605; δ_H 6.38 (=CHC=O), 5.85 (=C*H*H), 5.65 (br, *H*C=CMeCH$_2$I), 5.58 (=CH*H*), 5.12 (br, =CH), 3.93 (CH$_2$I), 3.15–2.75 (m, CHMe$_2$), 2.3–1.95 (m, 4 × CH$_2$), 2.08 (d, *J* 1.5, C*H*$_3$C=CHC=O), 1.60 (CH$_3$), 1.54 (CH$_3$) and 1.04 (d, *J* 6.4, C*H*Me$_2$) (M^+, 414. *M*, 414).

14-*Isopropyl*-3,7,11-*trimethylcyclotetradeca*-2(E),6(E),10(E)-*trienone* **21** and 14-*Isopropyl*-3,7,11-*trimethylcyclotetradeca*-2(E),6(E),10(*Z*)-*trienone* **22**.—Tributyltin hydride (0.1 cm^3) and AIBN (6 mg) were added to a solution of the iodo trienone **20b** (150 mg) in dry, deaerated benzene (125 cm^3) under nitrogen. The solution was heated under reflux for 3 h. The solution was then allowed to cool to room temperature before it was concentrated to give a colourless residue. The residue was purified by column chromatography on silica using diethyl ether-hexane (1:50) as eluent to give a mixture of the two isomers **21** and **22** (50 mg, 35%) inseparable by column chromatography. Separation was achieved by HPLC eluting with diethyl ether–hexane (1:100) which gave the major isomer (79%), the all-*E cyclic ketone* **21** as a colourless oil; λ_{max}(EtOH)/nm 241 (6 200), ν_{max}($CHCl_3$)/cm^{-1} 1675 and 1610; δ_H(400 MHz) 5.89 (=CHC=O), 4.94 (br m, =CH), 4.83 (br m, =CH), 2.36–1.65 (m, 6 × CH$_2$, 2 × CH), 2.11 (C*H*$_3$C=CC=O), 1.60 (CH$_3$), 1.52 (CH$_3$), 0.89 [d, *J* 6.8, CH(C*H*$_3$)Me] and 0.87 [d, *J* 6.8, CHMe(C*H*$_3$)]; δ_C(101 MHz) 205.5, 155.8, 134.5, 133.7, 126.5 (d), 125.9 (d), 125.2 (d), 56.7 (d), 39.5 (t), 38.9 (t), 37.2 (t), 31.2 (d), 26.0 (t), 24.4 (t), 24.0 (t), 21.2 (q), 20.3 (q), 19.5 (q), 15.3 (q) and 14.6 (q) (M^+, 288.2449. *M*, 288.2453). And the minor isomer (21%) the 2(*E*),6(*E*),10(*Z*) *cyclic ketone* **22** as a colourless oil; λ_{max}(EtOH)/nm 236 (5 500); ν_{max}($CHCl_3$)/cm^{-1} 1670 and 1610; δ_H(400 MHz) 5.97 (=CHC=O), 5.15 [t, *J* 7, =CH(*Z*)], 4.90 [br m, =CH(*E*)], 2.30–1.70 (m, 6 × CH$_2$, 2 × CH), 2.11 (d, *J* 1.0, CH$_3$C=CC=O), 1.66 (d, *J* 0.7, CH$_3$), 1.60 (CH$_3$), 0.93 [d, *J* 6.7, CH(CH$_3$)Me] and 0.87 [d, *J* 6.6, CHMe(C*H*$_3$)]; δ_C(101 MHz) 204.0, 157.8, 137.5, 134.8, 126.1 (d), 123.9 (d), 123.4 (d), 60.8 (d), 40.8 (t), 40.4 (t), 29.7 (t), 29.5 (t), 29.4 (d), 27.7 (t), 24.0 (t), 23.1 (q), 21.5 (q), 20.1 (q), 18.9 (q) and 16.4 (q) (M^+, 288.2442. *M*, 288.2453).

(±)-*Mukulol* **8**.—Lithium aluminium hydride (1.0 mg) was added in a single portion to a stirred solution of the cyclic ketone **21** (4.5 mg) in dry diethyl ether (1 cm^3) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min then quenched by the addition of water (0.5 cm^3) and then extracted with diethyl ether (2 × 2 cm^3). Evaporation of the dried organic extracts left a colourless residue (3.0 mg). The residue was purified by chromatography on silica using pentane–diethyl ether (5:1) as eluent to give the saturated ketone (1.5 mg, 33%), resulting from 1,4-reduction, as a colourless oil; δ_H(400 MHz) 5.02 (m, =CH), 4.91 (m, =CH), 2.3–1.65 (7 × CH$_2$, 3 × CH), 1.50 (2 × CH$_3$) and 0.95–0.75 (m, 3 × CH$_3$) (M^+, 290.2607. *M*, 290.2610). And then (±)-*mukulol* (14-*isopropyl*-3,7,11-*trimethylcyclotetradeca*-2(E),6(E),10(E)-*trienol*) (1.0 mg, 22%) as a colourless oil; δ_H(400 MHz) 5.33 (d, *J* 8.8, =CHCHOH), 5.04 (t, *J* 6.1, =CH), 4.92 (t, *J* 6.5, =CH), 4.60 (d, *J* 8.8, C*H*OH), 2.3–1.7 (m, 6 × CH$_2$, 2 × CH), 1.60 (d, *J* 4.3, CH$_3$), 1.57 (2 × CH$_3$), 1.00 [d, *J* 6.8, CHMe(C*H*$_3$)] and 0.96 [d, *J* 6.8, CH(C*H*$_3$)Me] (M^+, 290.2588. *M*, 290.2610).

14-*Hydroxy*-4,8,12-*trimethyltetradeca*-4(E),8(E),12(E)-*trienal* **26a**.—Periodic acid dihydrate (500 mg) was added in a single portion to a vigorously stirred solution of 14,15-epoxy-3,7,11,15-tetramethylhexadeca-2(*E*),6(*E*),10(*E*)-triene-1-ol **24a**[29] (650 mg) in THF (8 cm^3) and diethyl ether (2 cm^3) at 0 °C. The solution was allowed to warm to room temperature over 1 h before it was diluted with water (30 cm^3) and extracted with diethyl ether (3 × 20 cm^3). The combined ether extracts were washed successively with saturated aqueous sodium hydrogen carbonate (20 cm^3), water (20 cm^3) and brine (2 × 20 cm^3). Evaporation of the dried extracts left the *hydroxy aldehyde* (550 mg, 98%) as a pale yellow oil which was comparatively pure. A small sample was purified by chromatography on silica; ν_{max}(film)/cm^{-1} 3400br, 2720, 1720 and 1665; δ_H 9.73 (t, *J* 1.8, *H*C=O), 5.41 (t, *J* 6.9, =C*H*CH$_2$O), 4.13 (d, *J* 6.9, 2 × =CH), 2.6–1.8 (m, 6 × CH$_2$), 1.67 (CH$_3$) and 1.60 (2 × CH$_3$); δ_C (22.5 MHz) 202.5 (d), 139.2, 135.0, 133.0, 125.5 (d), 124.2 (d), 123.8 (d), 59.3 (t), 42.2 (t), 39.5 (2 × t), 31.9 (t), 26.6 (t), 26.4 (t), 16.3 (q), 16.1 (q) and 16.0 (q) (Found: M^+, 246.1988; C, 77.1; H, 10.95. $C_{17}H_{28}O_2$ requires: *M*, 246.1984; C, 77.2; H, 10.7%).

3,7,11-*Trimethyltetradeca*-2(E),6(E),10(E)-*triene*-1,14-*dial* **28**.—A solution of the hydroxy aldehyde **26a** (410 mg) in chloroform (2 cm^3) was added in a single portion to a stirred suspension of manganese dioxide (4.0 g) in chloroform (40 cm^3). The mixture was stirred at room temperature for 3 h and then filtered under suction. Evaporation of the filtrate left a yellow residue which was purified by chromatography on silica using hexane–diethyl ether (3:2) as eluent to give the *dialdehyde* (160 mg, 37%) as a pale yellow oil; λ_{max}(EtOH)/nm 238 (25 500); ν_{max}(film)/cm^{-1} 2730, 1730, 1675, 1635 and 1615; δ_H 10.11 (d, *J* 8, CH*H*C=O), 9.86 (t, *J* 1.8, CH$_2$*H*C=O), 5.97 (d, *J* 8, =C*H*HC=O), 2.65–1.95 (m, 6 × CH$_2$), 2.20 (CH$_3$C=CC=O) and 1.64 (2 × CH$_3$); δ_C(22.5 MHz) 202.3 (d), 191.0 (d), 163.4, 136.2, 133.1, 127.5 (d), 125.2 (d), 122.8 (d), 42.1 (d), 40.6 (d), 39.4 (d), 31.9 (d), 26.5 (d), 25.7 (d), 17.6 (q) and 16.0 (2 × q) ($M^+ - H_2O$, 244.1817. *M* − H_2O, 244.1827).

14,15-*Epoxy*-3,7,11,15-*tetramethylhexadeca*-2(E),6(E),10(E)-*trienyl Ethanoate* **24b**.—Acetic anhydride (10 cm^3) was added in a single portion to a stirred solution of the alcohol **24a** (2.40 g) in pyridine (30 cm^3). The solution was stirred at room temperature for 20 h, then quenched with water (150 cm^3) and extracted with hexane (3 × 100 cm^3). The combined extracts were washed successively with dilute hydrochloric acid (5%, 4 × 50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). Evaporation of the dried extracts left the *epoxy ethanoate* **24b** (2.39 g, 88%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1735, 1665 and 1025; δ_H 5.34 (t, *J* 7.2, =CHCH$_2$O), 5.12 (br m, 2 × =CH), 4.58 (d, *J* 7.2, CH$_2$O), 2.69 [t, *J* 6.0, HCO (epoxy)], 2.2–1.9 (m, 6 × CH$_2$), 2.04 (CH$_3$C=O), 1.70 (CH$_3$), 1.60 (2 × CH$_3$), 1.29 [Me(C*H*$_3$)CO] and 1.25 [CH$_3$(Me)CO] ($M^+ - C_2H_4O_2$, 288.2440. *M* − $C_2H_4O_2$, 288.2453).

13-*Formyl*-3,7,11-*trimethyltrideca*-2(E),6(E),10(E)-*trienyl Ethanoate* **26b**.—Periodic acid dihydrate (880 mg) was added in a single portion to a vigorously stirred solution of the epoxy acetate **24b** (1.25 g) in THF (15 cm^3) and diethyl ether (2 cm^3) at 0 °C. The solution was allowed to warm to room temperature over 1 h before it was diluted with water (30 cm^3) and extracted with diethyl ether (3 × 20 cm^3) and brine (20 cm^3). Evaporation of the dried extracts left the *acetoxyaldehyde* (1.03 g, 94%) as a pale yellow oil which was comparatively pure. A small sample was purified by chromatography on silica to give a colourless oil which showed: ν_{max}(film)/cm^{-1} 2720, 1740 and 1665; δ_H 9.72 (t, *J* 1.7, *H*C=O), 5.34 (br t, *J* 7.3, =CHCH$_2$O), 5.10 (br m, 2 × =CH), 4.56 (d, *J* 7.3, CH$_2$O), 2.6–1.9 (m, 6 × CH$_2$),

2.02 (CH_3C=C), 1.69 (CH_3) and 1.59 (2 × CH_3); δ_C(22.5 MHz) 201.6 (d), 170.4, 141.6, 134.8, 132.8, 125.1 (d), 123.7 (d), 118.4 (d), 61.0 (t), 41.9 (t), 39.2 (2 × t), 31.6 (t), 26.3 (t), 26.0 (t), 20.6 (q), 16.2 (q) and 15.8 (2 × q) ($M^+ - C_2H_4O_2$, 246.1983. $M - C_2H_4O_2$, 246.1984).

15-*Bromo*-3,7,11-*trimethylpentadeca*-2(E),6(E),10(E),14-*tetraenyl Ethanoate* **25**.—Potassium *tert*-butoxide (600 mg) was added in a single portion to a stirred solution of bromomethyltriphenylphosphonium bromide[33] (1.28 g) in dry THF (50 cm^3) at −78 °C under nitrogen for 1 h. The acetoxy aldehyde **26b** (820 mg) was then added dropwise over 5 min to the resulting bright yellow solution and the solution was stirred at −78 °C for a further 1.5 h, after which time TLC analysis showed complete consumption of the oxo acetate. The mixture was quenched by the dropwise addition of water (20 cm^3) and the solution was then allowed to warm to room temperature where it was extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3) and then with brine (2 × 50 cm^3). Evaporation of the dried extracts left a yellow residue (1.21 g) which was purified by chromatography on silica using hexane–diethyl ether (20:1) as eluent to give the *vinyl bromide* (14*E*,14*Z* mixture, 330 mg, 32%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1670, 1620 and 1605; δ_H 6.25–6.0 (m, =CHBr, *H*C=CHBr), 5.37 (br t, *J* 7, =C*H*CH_2O), 5.15 (br m, 2 × =CH), 4.60 (d, *J* 7, CH_2O), 2.4–2.0 (m, 6 × CH_2), 2.05 (CH_3C=O), 1.73 (CH_3) and 1.63 (2 × CH_3); δ_C(22.5 MHz) 170.9, 142.1, 135.3, 134.5 (d), 133.8, 125.2 (d), 123.9 (d), 118.5 (d), 107.7 (d), 61.3 (t), 39.6 (2 × t), 37.9 (t), 28.3 (t), 26.7 (t), 26.3 (t), 21.0 (q), 16.5 (q), 16.0 (q) and 15.9 (q) ($M^+ - C_2H_4O_2$, 324.1248 and 322.1274. $M - C_2H_4O_2$ 324.1276 and 322.1296).

3,7,11-*Trimethylpentadeca*-2(E),6(E),10(E)-*trien*-14-*ynal* **27**.—Potassium carbonate (200 mg) was added in a single portion to a stirred solution of the vinyl bromide **25** (160 mg) in methanol (10 cm^3) and the mixture was then stirred at room temperature for 18 h. The mixture was diluted with water (20 cm^3) and then extracted with hexane (4 × 50 cm^3). The combined hexane extracts were washed with water (20 cm^3) and then with brine (20 cm^3). Evaporation of the dried extracts left the corresponding *hydroxyvinyl bromide* (14*E*,14*Z* mixture, 120 mg, 85%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450br, 1665, 1620 and 1605; δ_H 6.15–5.8 (m, =CHBr, *H*CBr), 5.34 (t, *J* 7, =C*H*CH_2O), 5.05 (br m, =CH), 4.07 (d, *J* 7, CH_2O), 2.4–2.95 (m, 6 × CH_2), 1.61 (d, *J* 0.7, CH_3) and 1.53 (2 × CH_3); δ_C(22.5 MHz) 139.6, 135.2, 134.6 (d), 133.9, 125.2 (d), 124.0 (d), 123.6 (d), 107.7 (d), 59.4 (t), 39.6 (2 × t), 37.0 (t), 28.3 (t), 26.7 (t), 26.4 (t), 16.3 (q), 16.0 (q) and 15.9 (q) ($M^+ - H_2O$, 324.1283 and 322.1288. $M - H_2O$, 324.1276 and 322.1296).

A solution of the hydroxyvinyl bromide (70 mg) in dry THF was added rapidly to a stirred solution of potassium *tert*-butoxide (70 mg)[34] in dry THF (15 cm^3) at −23 °C for 20 min. The mixture was quenched by the dropwise addition of dilute hydrochloric acid (5%, 10 cm^3) and then allowed to warm to room temperature where it was extracted with hexane (4 × 20 cm^3). The combined extracts were washed with water (20 cm^3) and then with brine (20 cm^3). Evaporation of the dried extracts left a yellow residue which was purified by chromatography using hexane–diethyl ether (5:1, 2:1) as eluent to give 3,7,11-*trimethylhexadeca*-2(E),6(E),10(E)-*trien*-14-*yn*-1-*ol* (40 mg, 75%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3430br, 3310, 2120 and 1670; δ_H 5.33 (t, *J* 7.0, =C*H*CH_2O), 5.03 (br m, 2 × =CH), 4.06 (d, *J* 7.0, CH_2), 2.2–1.8 (m, 6 × CH_2, =CH), 1.60 (CH_3) and 1.53 (2 × CH_3); δ_C(22.5 MHz) 139.6, 135.2, 133.2, 125.6 (d), 124.0 (d), 123.5 (d), 84.4, 68.4 (d), 59.4 (t), 39.6 (2 × t), 38.5 (t), 26.7 (t), 26.4 (t), 17.7 (t), 16.3 (q), 16.0 (q) and 15.8 (q) ($M^+ - H_2O$, 242.205. $M - H_2O$, 242.2035).

A solution of the trien-14-ynol (90 mg) in chloroform (1 cm^3) was added in a single portion to a stirred suspension of managanese dioxide (900 mg) in chloroform (10 cm^3). The mixture was stirred at room temperature for 4 h and then filtered under suction. Evaporation of the filtrate left the *aldehyde* **27** (73.6 mg, 82%) as a colourless oil; λ_{max}(EtOH)/nm 238 (7 200); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320, 2790, 2130, 1665, 1635 and 1610; δ_H(400 MHz) 10.00 (d, *J* 8.1, HC=O), 5.89 (dd, *J* 8.1, *J* 1.1, =CHC=O), 5.16 (t, *J* 6.8, =CH), 5.09 (m, =CH), 2.3–1.9 (m, 6 × CH_2), 2.17 (d, *J* 1.1, CH_3C=CC=O), 1.94 (t, *J* 2.5, =CH) and 1.61 (2 × CH_3); δ_C(101 MHz) 197.3 (d), 163.8, 136.5, 133.4, 127.5 (d), 125.4 (d), 122.7 (d), 84.4, 68.4 (d), 40.7 (t), 39.6 (t), 38.5 (t), 26.6 (t), 25.8 (t), 17.7 (t), 17.7 (q), 16.1 (q) and 15.9 (q) (M^+, 258.1958. M, 258.1984).

Attempted Electrochemical Cyclisation of Trienynal **27**.—A solution of the aldehyde **27** (51 mg) in dry dimethylformamide (DMF) (5 cm^3) was added dropwise by syringe-pump over 9 h to the catholyte solution [consisting of a solution of anhydrous $NaClO_4$ (18.4 g) in dry DMF (150 cm^3)][13] whilst maintaining a cathodic potential of −1.7 V. This potential was maintained for a further 1 h, by which time the current had fallen to zero. The catholyte was poured into water (60 cm^3) and extracted with diethyl ether (6 × 50 cm^3). The combined ether extracts were washed with water (4 × 50 cm^3) and then with brine (2 × 50 cm^3). Evaporation of the dried extracts left a yellow residue (35.1 mg) which was purified by chromatography on silica using hexane–diethyl ether (1:1) as eluent to give 5,9,13,18,22,26-hexamethyltriaconta-5,9,13,17,21,25-hexen-1,29-diyn-15,16-diol **34** (5.4 mg, 11%) as a colourless oil; δ_H 5.18 (m, 4 × =CH), 4.4–4.1 (m, C*H*OH), 2.3–1.9 (m, 12 × CH_2, 2 × =CH), 1.71 (2 × CH_3) and 1.60 (4 × CH_3) ($M^+ - H_2O$, 500.4014. M-H_2O, 500.4018).

16-*Hydroxy*-3,7,11,15-*tetramethylhexadeca*-2(E),6(E),10(E),14(E)-*tetraenyl Ethanoate* **35**.—Geranylgeranyl ethanoate* (10.75 g) was added dropwise over 10 min to a stirred mixture of selenium dioxide (250 mg), salicylic acid (500 mg) and *tert*-butyl hydroperoxide (70% solution; 17 cm^3) in dichloromethane (17 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and then stirred for 60 h before it was evaporated under reduced pressure to leave a yellow residue which was immediately taken up in diethyl ether (50 cm^3). The ether solution was washed with aqueous sodium hydroxide (10%; 2 × 25 cm^3) and then with brine (2 × 25 cm^3). Evaporation of the dried extracts left a yellow residue (8.15 g), which was purified by chromatography on silica using hexane–diethyl ether (5:1, 4:1, 3:1, 5:2) as eluent to give the aldehyde corresponding to **35** (see below) (220 mg, 2%) as a colourless oil and then the *hydroxy ethanoate* (1.21 g, 11%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400br, 1725, 1675 and 1605; δ_H(400 MHz) 5.41 (tq, *J* 6.9, 1.4, C*H*CH_2OAc), 5.34 (tq, *J* 7.1, 1.2 *H*C=CCH_2OH), 5.11 (m, 2 × =CH), 4.59 (d, *J* 7.1, CH_2OAc), 3.99 (CH_2OH), 2.2–1.95 (m, 6 × CH_2), 2.05 (CH_3C=O), 1.71 (CH_3), 1.67 (CH_3) and 1.60 (2 × CH_3); irradiation at δ 3.99 gave an NOE of −6% at δ 5.41; δ_C(101 MHz) 171.1, 142.3, 135.5, 134.9, 134.8, 126.1 (d), 124.6 (d), 123.8 (d), 118.5 (d), 69.0 (t), 61.5 (t), 39.8 (t), 39.7 (t), 26.7 (t), 26.4 (t), 21.1 (q), 16.6 (q), 16.1 (2 × q) and 13.9 (q) ($M^+ - C_2H_4O_2$, 288.2435. $M - C_2H_4O_2$, 288.2453).

16-*Hydroxy*-2,6,10,14-*tetramethylhexadeca*-2(E),6(E),10(E),14(E)-*tetraenal* **36**.—A solution of the alcohol **35** (1.21 g) in dichloromethane (3 cm^3) was added in a single portion to a stirred suspension of manganese dioxide (12.0 g) in chloroform

* (*E*,*E*,*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenyl ethanoate.

(100 cm^3). The mixture was stirred at room temperature for 18 h and then filtered under suction. Evaporation of the filtrate left the corresponding enal (1.09 g, 91%) as a colourless oil; λ_{max}(EtOH)/nm 224 (26 800); ν_{max}(film)/cm^{-1} 2720, 1750, 1690 and 1640; δ_H 9.37 (HC=O), 6.46 (br t, *J* 7, HC=CC=O), 5.34 (br t, *J* 7.2, =C*H*CH_2OAc), 5.12 (br m, 2 × =CH), 4.57 (d, *J* 7.2, CH_2O), 2.55–1.85 (m, 6 × CH_2), 2.53 (CH_3C=O), 1.73 (CH_3), 1.71 (CH_3) and 1.59 (2 × CH_3) ($M^+ - C_2H_4O_2$, 286.2298. *M* − $C_2H_4O_2$, 286.2297).

Potassium carbonate (60 mg) was added in a single portion to a stirred solution of the above enal (70 mg) in methanol (25 cm^3) and the mixture was then stirred at room temperature for 18 h. The mixture was diluted with water (10 cm^3) and then extracted with hexane (3 × 15 cm^3). The combined hexane extracts were washed with water (10 cm^3) and then with brine (10 cm^3). Evaporation of the dried extracts left the *hydroxy tetraenal* (43.4 mg, 82%) as a colourless oil; λ_{max}(EtOH)/nm 224 (16 600); ν_{max}($CHCl_3$)/cm^{-1} 2730, 3460br, 1675 and 1640; δ_H 9.37 (HC=O), 6.47 (t, *J* 7.0, HC=CC=O), 5.41 (t, *J* 6.9, =C*H*CH_2O), 5.15 (m, 2 × =CH), 4.15 (d, *J* 6.9, CH_2O), 2.55–1.9 (m, 6 × CH_2), 1.75 (CH_3), 1.68 (CH_3) and 1.61 (2 × CH_3); δ_C(22.5 MHz) 195.1 (d), 154.2 (d), 139.7, 139.2, 135.2, 133.4, 125.7 (d), 124.1 (d), 123.6 (d), 59.4 (t), 39.6 (2 × t), 38.0 (t), 27.5 (t), 26.7 (t), 26.4 (t), 16.3 (q), 15.9 (2 × q) and 9.2 (q) (M^+ − OH, 287.2331. *M* − OH, 287.2375).

16-*Iodo*-2,6,10,14-*tetramethylhexadeca*-2(E),6(E),10(E),14(E)-*tetraenal* **37**.—Triphenylphosphine (300 mg) and a solution of imidazole (87 mg) in acetonitrile (1 cm^3) were added to a stirred solution of the hydroxy tetraenal **36** (150 mg) in dry diethyl ether (1.5 cm^3). The solution was stirred under nitrogen at 0 °C for 10 min and then iodine (350 mg) was added in portions over 2 min. The solution was stirred at 0 °C for 30 min and then diluted with pentane (15 cm^3). The extracts were washed successively with saturated aqueous sodium thiosulfate (5 cm^3), saturated aqueous cupric sulfate (5 cm^3) and water (5 cm^3). Evaporation of the dried extracts left the *iodo tetraenal* (100 mg, 47%) as a highly labile yellow oil which was contaminated with a small amount of triphenylphosphine oxide and was used immediately without further purification; δ_H 9.39 (HC=O), 6.48 (t, *J* 7, =C*H*C=O), 5.15 (m, 3 × =CH), 3.48 (d, *J* 9.9, CH_2I), 2.6–1.8 (m, 6 × CH_2) and 1.64 (br, 4 × CH_3).

Attempted Radical Cyclisation of the Tetraenal **37**.—Tributyltin hydride (60 mm^3) and AIBN (5 mg) were added to a solution of the iodotetraenal **37** (92 mg) in dry, deaerated benzene (50 cm^3 under nitrogen. The solution was heated to reflux and held at reflux for 3 h. The solution was allowed to cool to room temperature before it was concentrated to leave a colourless residue. The residue was purified by chromatography on silica using hexane–diethyl ether (50:1, 20:1, 10:1) as eluent to give 2,6,10,14-*tetramethylhexadeca*-2(E),6(E),10(E),14(E)-*tetraenal* (5 mg, 8%) as a colourless oil; λ_{max}(EtOH)/nm 228 (10 700); ν_{max}($CHCl_3$)/cm^{-1} 2730, 1675, 1640 and 1600; δ_H(400 MHz) 9.38 (HC=O), 6.47 (t, *J* 7.2, HC=CC=O), 5.16 (m, 3 × =CH), 2.5–1.9 (m, 6 × CH_2) and 1.75–1.55 (m, 5 × CH_3) (M^+, 288.2449. *M*, 288.2453).

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References

1 W. G. Dauben, W. E. Thiessen and P. R. Resnick, *J. Am. Chem. Soc.*, 1962, **84**, 2015; W. G. Dauben, W. E. Thiessen and P. R. Resnick, *J. Org. Chem.*, 1965, **30**, 1693.
2 S. Akiyoshi, *Imp. Ind. Res. Inst. Rept. Jap.*, 1937, **17**, 1 (*Chem. Abstr.* 1937, **31**, 8172); H. Kobayashi and S. Akiyoshi, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1044; H. Kobayashi and S. Akiyoshi, *Bull. Chem. Soc. Jpn.*, 1963, **36**, 823; N. T. Mirov, *The Genus Pinus*, Ronald Press, N.Y., 1967; P. M. Iloff Jr. and N. T. Mirov, *U.S. Dep. Agric. Tech. Bull.*, 1961, No. 1239; R. Mayer, V. A. Pentegova and N. K. Kashtanova, *Khim. Prir. Soedin.*, 1965, **1**, 223; G. I. Shibanova, V. A. Pentegova and L. N. Vol'skii, *Khim. Prir. Soedin.*, 1971, **7**, 214; W. G. Dauben. G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle and C. Suter, *J. Am. Chem. Soc.*, 1974, **96**, 4724; V. A. Raldugin, A. I. Rezvukhin and V. A. Pentegova, *Khim. Prir. Soedin.*, 1971, 598 (*Chem. Abstr.*, 1972, **77**, 5630e); B. Kimland and T. Norin, *Acta Chem. Scand.*, 1968, **22**, 943.
3 For a review and discussion of the chemistry and biological transformations of tobacco cembranoids, see I. Wahlberg and C. R. Enzell, *Beiträge zur Tabakforschung International*, 1984, **12**, 93; I. Wahlberg and C. R. Enzell, *Nat. Prod. Rep.*, 1987, 237.
4 For reviews, see B. Tursch, *Pure Appl. Chem.*, 1976, **48**, 1; D. J. Faulkner, *Tetrahedron*, 1977, **33**, 1421; D. J. Faulkner, *Nat. Prod. Rep.*, 1991, **8**, 97; and earlier reviews in this series.
5 A. J. Birch, W. V. Brown, J.E.T. Corrie and B. P. Moore, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2653.
6 A. J. Weinheimer, J. A. Matson, M. B. Hossain and D. van der Helm, *Tetrahedron Lett.*, 1977, 2923.
7 A. J. Weinheimer, J. A. Matson, D. van der Helm and M. Poling, *Tetrahedron Lett.*, 1977, 1295.
8 P. Culver, M. Burch, C. Potenza, L. Wasserman, W. Fenical and P. Taylor, *Mol. Pharmacol.*, 1985, **28**, 436: S. N. Abramson, J. A. Trischman, D. M. Tapiolas, E. E. Harold, W. Fenical and P. Taylor, *J. Med. Chem.*, 1991, **34**, 1798.
9 J. Kobayashi, Y. Ohizumi, H. Nakamura, T. Yamakado, T. Matsuzaki and Y. Hirata, *Experientia*, 1983, **39**, 67.
10 Y. Kashman and A. Groweiss, *Tetrahedron Lett.*, 1977, 1159.
11 For a recent review of cembranoid synthesis, see M. A. Tius, *Chem. Rev.*, 1988, **88**, 719.
12 Methods that have been developed for macrocyclisation in the cembranoid field include: Ni^0-mediated intramolecular coupling of bis-allylic bromides; W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle and C. Suter, *J. Am. Chem. Soc.*, 1975, **97**, 4973; L. Crombie, G. Kneen, G. Pattenden and D. Whybrow, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1711. Intramolecular Warsworth–Emmons olefinations; M. A. Tius and A. H. Fauq, *J. Am. Chem. Soc.*, 1986, **108**, 1035; J. A. Marshall and B. S. DeHoff, *Tetrahedron Lett.*, 1986, **27**, 4873. Sulfide/sulfone carbanion alkylations; M. Kodama, Y. Matsuki and S. Ito, *Tetrahedron Lett.*, 1975, 3065; H. Takayanagi, T. Uyehara and T. Kato, *J. Chem. Soc., Chem. Commun.*, 1978, 359; W. G. Dauben, R. K. Saugier and I. Fleischhauer, *J. Org. Chem.*, 1985, **50**, 3767; J. A. Marshall and D. G. Cleary, *J. Org. Chem.*, 1986, **51**, 858. Intramolecular Friedel–Crafts acylations; Y. Kitahara, T. Kato, T. Kobayashi and B. P. Moore, *Chem. Lett.*, 1976, 219; T. Kato, M. Suzuki, T. Kobayashi and B. P. Moore, *J. Org. Chem.*, 1980, **45**, 1126. Additions of allyl organometallics to aldehydes; W. C. Still and D. Mobilio, *J. Org. Chem.*, 1983, **48**, 4785; J. A. Marshall, B. S. DeHoff and S. L. Crooks, *Tetrahedron Lett.*, 1987, **28**, 527; L. A. Paquette, C. M. Rayner and A. M. Doherty, *J. Am. Chem. Soc.*, **1990**, **112**, 4078. [5,5]-Sigmatropic ring expansion reactions; P. A. Wender and D. A. Holt, *J. Am. Chem. Soc.*, 1985, **107**, 7771. Ring contraction by stereoselective Wittig rearrangements; J. A. Marshall, T. M. Jenson and B. S. DeHoff, *J. Org. Chem.*, 1986, **51**, 4316; 1987, **52**, 3860; J. A. Marshall and D. J. Nelson, *Tetrahedron Lett.*, 1988, **29**, 741.
13 N. J. G. Cox, PhD Thesis, University of Nottingham, 1988. See also ref. 19.
14 V. D. Patil, U. R. Nayak and S. Dev, *Tetrahedron*, 1973, **29**, 341; R. S. Prasad and S. Dev, *Tetrahedron*, 1976, **32**, 1437.
15 Y. Uchio, S. Eguchi, M. Nakayama and T. Hase, *Chem. Lett.*, 1982, 277. The same metabolite has also been isolated from *Lobophytum michaelae*, see J. C. Coll, S. J. Mitchell and G. J. Stokie, *Aust. J. Chem.*, 1977, **30**, 1859.
16 Preliminary communication, N. J. G. Cox, G. Pattenden and S. D. Mills, *Tetrahedron Lett.*, 1989, **30**, 621.
17 N. A. Porter, D. R. Magnin and B. T. Wright, *J. Am. Chem. Soc.*, 1986, **108**, 2787; see also, N. A. Porter, V. H.-T. Chang, D. R. Magnin and B. T. Wright, *J. Am. Chem. Soc.*, 1988, **110**, 3554.
18 For early fundamental studies on allyl radical intermediates see, R. Sustmann, in *Substituent Effects in Radical Chemistry; Allylic Radicals—An ESR Spectroscopical Study*, eds. H. G. Viehe, R. Merenyi and Z. Janousek; D. Reidel, Boston, 1986, p. 143; R. J.

Crawford, J. Hamelin and B. Strehlke, *J. Am. Chem. Soc.*, 1971, **93**, 3810; D. M. Golden, *Int. J. Chem. Kinet.*, 1969, **1**, 127; D. B. Denney, R. M. Hoyte and P. T. MacGregor, *J. Chem. Soc., Chem. Commun.*, 1967, 1241; R. M. Hoyte and D. B. Denney, *J. Org. Chem.*, 1974, **39**, 2607. For contemporaneous studies of the uses of allylic radicals in synthesis, see G. Stork and M. E. Reynolds, *J. Am. Chem. Soc.*, 1988, **110**, 6911.

19 For an approach to the mycotoxin zearalenone based on a 14-*endo-trig* macrocylisation from an allylic radical, see S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1990, **31**, 3641 and immediately following paper. For an example of acyl radical macrocyclisations in furanocembrane synthesis, see M. A. Astley and G. Pattenden, *Synlett.*, 1991, **5**, 335.

20 M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.

21 See E. J. Corey, S. G. Pyne and W. Su, *Tetrahedron Lett.*, 1983, **24**, 4883.

22 See Y. Uchio, S. Eguchi, M. Nakayama and T. Hase, *Chem. Lett.*, 1982, 277.

23 M. Aoki, T. Uyehara and T. Kato, *Chem. Lett.*, 1984, 695.

24 D. W. Sopher and J. H. P. Utley, *J. Chem. Soc., Chem. Commun.*, 1979, 1087; D. W. Sopher and J. H. P. Utley, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1361.

25 L. A. Powell and R. M. Wightman, *J. Am. Chem. Soc.*, 1979, **101**, 4412; L. A. Powell and R. M. Wightman, *J. Electroanal. Chem.*, 1980, **106**, 377; B. Czochralska, M. Szweykowska, N. A. Dencher and D. Shugar, *Bioelectrochem. Bioenerg.*, 1978, **5**, 713.

26 T. Shono, I. Nishiguchi and H. Omizu, *Chem. Lett.*, 1976, 1233; T. Shono, I. Nishiguchi, H. Omizu and M. Mitani, *J. Am. Chem. Soc.*, 1978, **100**, 545.

27 Reductive cyclisations have been reported under a range of conditions, see D. P. Fox, R. D. Little and M. M. Baizer, *J. Org. Chem.*, 1985, **50**, 2202; S. K. Pradhan, T. V. Radhakrishnan and R. Subramanian, *J. Org. Chem.*, 1976, **41**, 1943; E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821; S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani and V. B. Thaker, *J. Org. Chem.*, 1981, **46**, 2622; J. Ardisson, J. P. Férézou, M. Julia and A. Pancrazi, *Tetrahedron Lett.*, 1987, **28**, 2001.

28 G. Pattenden and S. J. Teague, *Tetrahedron Lett.*, 1982, **23**, 5471; G. Pattenden and S. J. Teague, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1077; G. Pattenden and G. M. Robertson, *Tetrahedron Lett.*, 1986, **27**, 399; M. J. Begley, G. Pattenden and G. M. Robertson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1085.

29 E. E. van Tamelen and R. G. Nadeau, *Bioorg. Chem.*, 1982, **11**, 197.

30 For a review, see N. Rabjohn, *Org. React.* (N.Y.), 1976, **24**, 261.

31 B. Gredy, *Bull. Soc. Chim. Fr.*, 1935, **2**, 1951; Z. Goldschmidt and D. Finkel, *J. Chem. Soc., Perkin Trans. 1*, 1983, 45.

32 M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 5526.

33 J. Wolinsky and K. L. Erickson, *J. Org. Chem.*, 1965, **30**, 2208.

34 M. Matsumoto and K. Kuroda, *Tetrahedron Lett.*, 1980, **21**, 4021; N. Harada, Y. Tamai and H. Uda, *J. Org. Chem.*, 1984, **49**, 4266.

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