Natural Furanocembranoids. A Synthetic Approach to Lophotoxin based on an Acyl Radical Macrocyclisation Strategy

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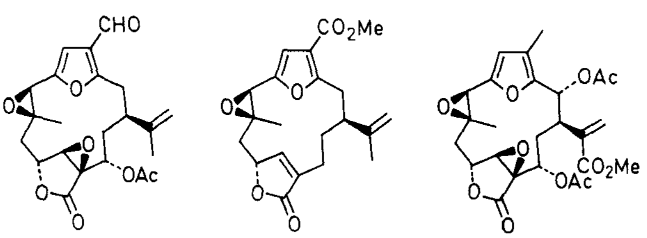
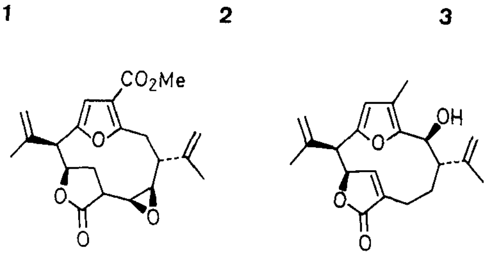
A concise synthesis of the furan-containing macrocyclic (cembranoid) ring system **8** (10-isopropenyl-3,7,13-trimethyl-15-oxabicyclo[10.2.1]pentadeca-2,6,12,14-tetraene) found in lophotoxin **(1)** and other members of this family of irreversible nicotinic receptor antagonists, is described. The synthesis features a 14-*endo* trig cyclisation from an unsaturated acyl radical intermediate incorporating a terminal conjugated enone moiety, viz **10**, leading to the macrocycle (5*E*,9*E*)-13-isopropenyl-2,6,10-trimethylcyclotetradeca-5,9-diene-2,4-dione **(9)**, followed by acid-catalysed furan ring formation from the resulting 1,4-dione system in **9** (Scheme 1).

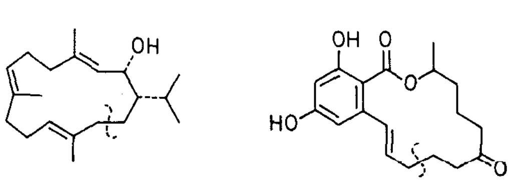
Lophotoxin **(1)**, which has been isolated from gorgonium (soft) corals,[1] is a potent neurotoxic substance that binds selectively and irreversibly to acetylcholine recognition sites in nicotinic acetylcholine receptors.[2] This binding prevents acetylcholine from activating the receptors, thereby leading to paralysis and asphixiation. Like the related pukalide **(2)**[3] and bipinnatin **(3)**[4] produced by corals, lophotoxin shows a structure based on a 14-carbon macrocyclic (cembranoid) ring which incorporates an unusual trisubstituted furan ring system. Twelve-membered carbon macrocyclic furanocembranoids are also known, and include pseudopterolide **4**[5] and kallolide **5**.[6] Lophotoxin **(1)** and the related oxygen-functionalised furanocembranoids **2** → **5** offer a significant challenge to the synthetic chemist.[7,8] With a view to developing and expanding the scope for radical macrocyclisation reactions to highly functionalised molecules,[9] and at the same time contribute to an understanding of the modus operandi of lophotoxin and relatives *in vivo*,[10] we have examined a strategy towards the synthesis of the core furanocembrane unit **8** common to these neurotoxic substances.



1 **2** **3**

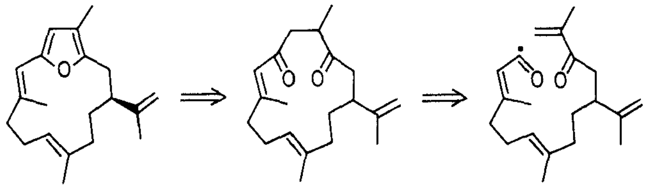


4 **5**



6 **7**

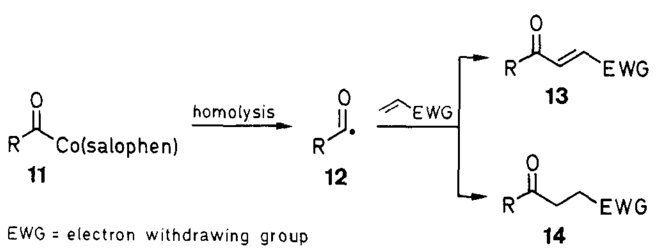
In earlier work, we have described concise syntheses of the 14-ring macrocyclic compounds mukulol **(6)**[11] and zearalenone **(7)**,[12] which were based on novel 14-*endo* trig intramolecular cyclisations of appropriate allylic radical intermediates onto conjugated enone electrophores. Our idea in the present study was to extend this radical macrocyclisation strategy to α,β-unsaturated *acyl* radical intermediates and to elaborate the furanocembranoid **8** via a 14-*endo* trig cyclisation from **10**, leading to the macrocycle **9**, followed by acid-catalysed furan ring formation from the 1,4-dione system in **9** (Scheme 1).[13]



8 **9** **10**

Scheme 1

During an extensive program of research, developing and probing the potential for organocobalt complexes as precursors to carbon-centred radical intermediates, we have earlier described the synthesis of acylcobalt salophen reagents, viz **11**, and their homolytic cleavage leading to acyl radical intermediates.[14] Furthermore, we have shown that these acyl radical intermediates **12** undergo both inter- and intramolecular addition reactions to activated carbon-to-carbon double bonds leading to the two types of products **13** and **14**, shown in Scheme 2, according to the constitution of the substrates and the reaction conditions. In contemporaneous studies of the synthesis of acyl radicals, other researchers have highlighted the uses of *Se*-phenyl selenoesters[15] and *S*-acyl xanthates[16] as precursors to these intermediates. In addition, whilst our own work was in progress, Boger and his colleagues[17] have evaluated the use of certain saturated acyl selenoesters in the synthesis of 11 → 20 membered cyclic γ-keto esters.



Scheme 2

Our attempts to use acylcobalt complexes as intermediates in the elaboration of oxygen functionalised carbocyclic ketones of the type represented by structure **9**, proved problematic, whereas model studies with selenoester intermediates as precursors to acyl radicals for macrocyclic ketone formation were encouraging. Accordingly, we decided to make the C_{25}-α,β-unsaturated selenoester **23** as the precursor to the acyl radical intermediate **10** in our projected synthesis of the furanocembranoid **8**. The selenoester **23** was synthesised in nine steps starting from methyl (*E,E*)-farnesoate.[18] Thus, treatment of methyl (*E,E*)-farnesoate with catalytic selenium dioxide in the presence of *tert*-butyl hydroperoxide was found to be regioselective and led exclusively to the all-*E* allyl alcohol **15**.[19] The allyl alcohol **15** was next converted into the vinyl ether **16** which then underwent a smooth Claisen rearrangement at 160 °C producing the γ,δ-unsaturated aldehyde **17** in almost quantitative yield. The aldehyde **17** was now treated with isopropenylmagnesium bromide leading to a 3:2 mixture of diastereoisomeric carbinols **18**. Although the diasteroisomers of the carbinol **18** could be separated and fully characterised, the synthesis of the selenoester **23** did not require us to use a single diastereomer, and the 3:2 mixture of carbinols **18** was used in the next stages of the synthesis.

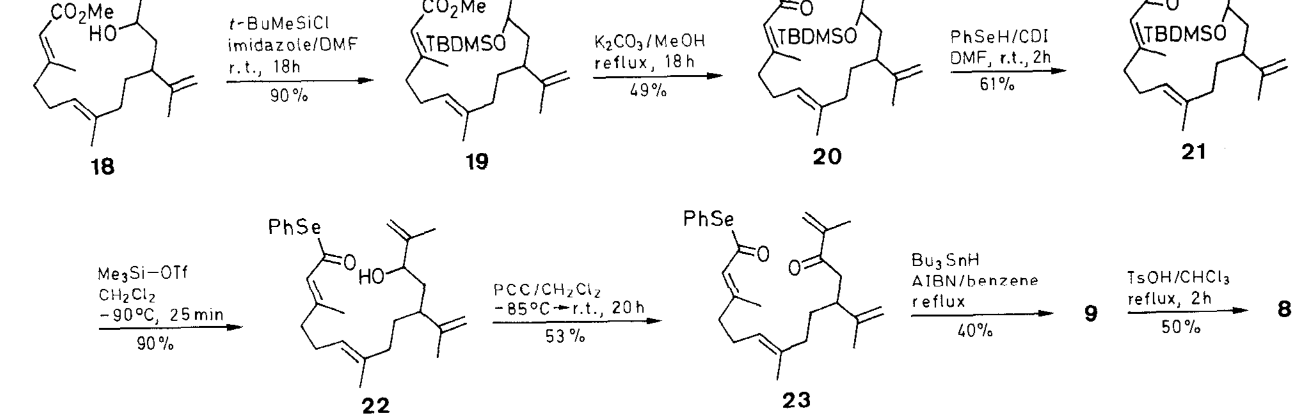
Following protection of the carbinol **18** as the corresponding TBDMS ether **19**, saponification in the presence of aqueous methanolic potassium carbonate next led to the carboxylic acid **20**. The carboxylic acid **20** was reacted immediately with benzeneselenol in dimethylformamide in the presence of 1,1′-carbonyldiimidazole (CDI)[20] producing the selenoester **21**, which was then deprotected using trimethylsilyl triflate in dichloromethane[21] at − 90 °C leading to **22**. Finally, oxidation of the alcohol **22** with pyridinium chlorochromate at −85 °C to 25 °C, provided the key selenoester intermediate **23** as a pale yellow oil.

When a solution of the selenoester **23** in benzene was heated under reflux and treated with tributylstannane in the presence of AIBN over 1.5 hours, work-up and chromatography separated the macrocyclic triene 1,4-dione **9** as an inseparable 1:1 mixture of diastereoisomers in a combined yield of 40 %. Treatment of the 1,4-dione **9** with a catalytic amount of *p*-toluenesulphonic acid in hot chloroform then resulted in smooth intramolecular cyclodehydration producing the furanocembranoid **8**. The furanocembranoid **8** displayed spectroscopic features consistent with the all-*E* triene 2,3,5-trisubstituted furan cembrane structure, and showed spectroscopic data which overlapped with similar data reported for synthetic model furanoterpenes and natural furanocembranoids. Further work is now in progress to extend this tandem intramolecular cyclisation strategy, shown in Scheme 1, to lophotoxin and related naturally occurring furanocembranoids.

Kugelrohr bulb-to-bulb distillations were performed on a Büchi GKR-50 rotating bulb apparatus. IR spectra were recorded on a Perkin-Elmer 1220 spectrometer. Spectra were recorded as thin liquid films on sodium chloride discs. UV absorption spectra were obtained on a Philips PU 8720 UV/visible scanning spectrophotometer as dilute solutions in the stated solvent. ^{1}H NMR spectra were recorded on a Bruker WP80SY PFT, a Bruker WM250 PFT, or a Bruker AM400 PFT spectrometer at 80 MHz, 250 MHz and 400 MHz respectively. ^{13}C NMR spectra were also recorded on these instruments at 22.5 MHz, 62.9 MHz and 100.6 MHz respectively. All NMR measurements were obtained for dilute solutions in $CDCl_3$ containing TMS or $CHCl_3$ as an internal standard. For ^{13}C NMR spectra, designations were determined by distortionless enhancement by polarisation transfer (DEPTA) pulse sequences in conjunction with broad-band decoupled CMR.

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

All organic solutions were dried over $MgSO_4$ or Na_2SO_4 and solvents were removed under reduced pressure on a Büchi rotary evaporator. Analytical TLC was performed on Merck Kieselgel 60



F254 aluminium backed plates which were visualised with UV light (254 nm) or alternatively with basic potassium permanganate.

Methyl (2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trienoate (15):

A solution of methyl farnesoate (4.41 g, 17.6 mmol)[18] in CH_2Cl_2 (10 mL) was added in one portion to a stirred mixture of SeO_2 (980 mg, 8.8 mmol) and 70% aq *t*-BuOOH (4.8 mL, 35 mmol) in CH_2Cl_2 (90 mL) at 0 °C. After 10 min at this temperature the mixture was allowed to warm to r.t. over 45 min. Water (50 mL) was added, and the two phases were then separated. The organic phase was washed with brine (30 mL), then dried, and evaporated to dryness in vacuo. Chromatography on silica gel using hexanes/Et_2O (70:30 and 60:40) as eluent gave the alcohol **15** as a pale yellow oil; yield: 1.99 g (42%; 75% based on recovered starting material).

$C_{16}H_{26}O_3$	calc.	C 72.14	H 9.84
(266.4)	found	72.09	10.10

HRMS: calc. for $C_{16}H_{26}O_3$ (M^+ $-H_2O$): 248.1775, found: 248.1766.

IR (film): ν = 3426 (OH), 1719 (C=O), 1650 cm^{-1} (C=C).

UV (EtOH): λ = 216 nm.

^1H NMR ($CDCl_3$, 80 MHz): δ = 1.62, 1.68 (2 s, 3 H each, 2 × CH_3), 2.17 (d, 3 H, J = 1 Hz, C$\underline{H}_3$C=CHC=O), 1.8–2.3 (m, 8 H, 4 × CH_2), 3.67 (s, 3 H, OCH_3), 3.96 (s, 2 H, C$\underline{H}_2$OH), 5.1–5.38 (2 br, 1 H each, 2 × C=CH), 5.66 (br s, 1 H, C=CHC=O).

^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 13.1 (q), 15.6 (q), 18.3 (q), 25.5 (t), 25.85 (t), 38.9 (t), 40.4 (t), 50.2 (q), 67.9 (t), 115.0 (d), 122.7 (d), 124.8 (d), 134.6 (s), 135.45 (s), 159.45 (s), 166.8 (s).

Methyl (2*E*,6*E*,10*E*)-12-Ethenyloxy-3,7,11-trimethyldodeca-2,6,10-trienoate (16):

A solution of the alcohol **15** (2.95 g, 11.0 mmol) and mercuric acetate (105 mg, 0.33 mmol) in ethyl vinyl ether (10.6 mL, 110 mmol) was heated under reflux for 16 h. The excess ethyl vinyl ether was removed by distillation, and the residue was then purified by chromatography on silica gel using hexanes/Et_2O (90:10 and 50:50) as eluent to give the vinyl ether **16** as a colourless oil; yield: 2.53 g (79%; 95% based on recovered starting material).

$C_{18}H_{28}O_3$	calc.	C 73.93	H 9.65
(292.4)	found	74.16	10.02

HRMS: calc. for $C_{17}H_{24}O_2$ (M^+ $-$MeOH): 260.1805, found: 260.1790.

IR (film): ν = 1720 (C=O), 1651 cm^{-1} (C=C).

UV (EtOH): λ = 218 nm.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.61, 1.68 (2 s, 3 H each, 2 × CH_3), 2.17 (s, 3 H, CH_3C=CC=O), 1.8–2.2 (m, 8 h, 4 × CH_2), 3.70 (s, 3 H, OCH_3), 3.99 (dd, 1 H, J = 1 and 7 Hz, $\underline{H}$HC=CH), 4.08 (s, 2 H, OCH_2), 4.22 (dd, 1 H, J = 1 and 14 Hz, H$\underline{H}$C=CH), 5.09, 5.42 (2 br, 1 H each, 2 × C=CH), 5.68 (s, 1 H, C=CHC=O), 6.46 (dd, 1 H, J = 7 and 14 Hz, HHC=C$\underline{H}$).

^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 13.4 (q), 15.7 (q), 18.4 (q), 25.7 (t), 26.0 (t), 38.9 (t), 40.6 (t), 50.2 (q), 74.2 (t), 86.6 (t), 115.2 (d), 123.15 (d), 128.0 (d), 131.0 (s), 135.3 (s), 151.3 (d), 159.2 (s), 166.6 (s).

Methyl (*RS*)(2*E*,6*E*)-3,7-Dimethyl-10-(1-methylethenyl)-12-oxo-dodeca-2,6-dienoate (17):

The vinyl ether **16** (1.69 g, 5.78 mmol) was heated in a sealed tube at 140 °C for 2 h, to give the aldehyde **17** as a pale yellow oil, which was used without further purification. A small sample was purified by chromatography on silica gel using hexanes/Et_2O (65:35) as eluent; yield: 1.65 g (97%).

$C_{18}H_{28}O_3$	calc.	C 73.93	H 9.65
(292.4)	found	74.11	9.95

IR (film): ν = 1723 (C=O), 1650 cm^{-1} (C=C).

UV (EtOH): λ = 219 nm.

^1H NMR ($CDCl_3$, 80 MHz): δ = 1.59, 1.67 (2 s, 3 H each, 2 × CH_3), 2.18 (d, 3 H, J = 1 Hz, C$\underline{H}_3$C=CHC=O), 1.8–2.6 (m, 11 H, HCC=C and 5 × CH_2), 3.69 (s, 3 H, OCH_3), 4.8 (m, 2 H, H_2C=C), 5.1 (br, 1 H, C=CH), 5.68 (br s, 1 H, C=CHC=O), 9.67 (t, 1 H, J = 2 Hz, CH_2C$\underline{H}$O).

^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 15.3 (q), 18.05 (q), 18.3 (q), 25.4 (t), 30.9 (t), 36.5 (t), 40.3 (t), 40.5 (d), 47.0 (t), 49.9 (q), 111.8 (t), 115.0 (d), 122.9 (d), 135.1 (s), 145.5 (s), 166.2 (s), 200.7 (d).

Methyl (12*RS*,10*RS*)(2*E*,6*E*)-12-Hydroxy-3,7,13-trimethyl-10-(1-methylethenyl)tetradeca-2,6,13-trienoate (18):

2-Bromopropene (2.33 mL, 26.2 mmol) was added dropwise over 10 min to a stirred suspension of magnesium turnings (640 mg, 26.2 mmol) under dry THF (45 mL) with cautious warming. When the magnesium had been consumed the solution was cooled to 0 °C, and a solution of the aldehyde **17** (6.39 g, 21.9 mmol) in dry THF (5 mL) added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, and then quenched by the careful addition of sat. aq NH_4Cl (20 mL). Water (50 mL) was added and the mixture was extracted with EtOAc (2 × 40 mL). The combined extracts were washed with brine (30 mL), then dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexanes/Et_2O (75:25) as eluent to give:

(i) a minor diastereoisomer of the secondary alcohol (eluted first) as a colourless oil; yield: 2.60 g (35%).

$C_{21}H_{34}O_3$	calc.	C 75.41	H 10.25
(334.5)	found	75.74	10.69

IR (film): ν = 3446 (OH), 1722 (C=O), 1650 cm^{-1} (C=C).

UV (EtOH): λ = 219 nm.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.58, 1.62, 1.72 (3 s, 3 H each, 3 × CH_3), 2.16 (s, 3 H, CH_3C=CC=O), 1.4–2.2 (m, 10 H, 5 × CH_2), 2.31 (m, 1 H, CH_2C$\underline{H}$$CH_2$), 3.68 (s, 3 H, OCH_3), 3.98 (dd, 1 H, J = 3.3 and 8.8 Hz, HOC$\underline{H}$CHH), 4.78, 4.80, 4.83, 4.94 (4 s, 1 H each, 4 × $\underline{H}$HC=C), 5.06 (br, 1 H, C=CH), 5.67 (s, 1 H, C=CHC=O).

^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 15.9 (q), 17.7 (q), 17.8 (q), 18.6 (q), 25.8 (t), 32.0 (t), 37.3 (t), 39.2 (t), 40.75 (t), 43.3 (d), 50.45 (q), 73.2 (d), 109.8 (t), 112.5 (t), 115.2 (d), 122.7 (d), 136.15 (s), 146.8 (s), 148.3 (s), 159.7 (s), 167.0 (s).

(ii) a major diastereoisomer of the secondary alcohol (eluted second) as a colourless oil; yield: 3.41 g (47%).

$C_{21}H_{34}O_3$	calc.	C 75.41	H 10.25
(334.5)	found	75.55	10.54

IR (film): ν = 3435 (OH), 1722 (C=O), 1650 cm^{-1} (C=C).

UV (EtOH): λ = 219 nm.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.58, 1.66, 1.72 (3 s, 3 H each, 3 × CH_3), 2.16 (s, 3 H, CH_3C=CC=O), 1.4–2.2 (m, 11 H, C=CCH and 5 × CH_2), 3.68 (s, 3 H, OCH_3), 4.07 (t, 1 H, J = 6.7 Hz, HOC$\underline{H}$$CH_2$), 4.73, 4.78, 4.83, 4.91 (4 s, 1 H each, 4 × $\underline{H}$HC=C), 5.06 (br s, 1 H, C=CH), 5.66 (s, 1 H, C=CHC=O).

^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 15.9 (q), 16.9 (q), 18.1 (q), 18.65 (q), 25.8 (t), 31.65 (t), 37.1 (t), 38.6 (t), 40.75 (t), 43.7 (d), 50.5 (q), 74.45 (d), 111.45 (t), 111.9 (t), 115.2 (d), 122.8 (d), 136.1 (s), 147.1 (s), 147.6 (s), 157.7 (s), 167.0 (s).

Methyl (10*RS*,12*RS*)(2*E*,6*E*)-12-*tert*-Butyldimethylsiloxy-3,7,13-trimethyl-10-(1-methylethenyl)tetradeca-2,6,13-trienoate (19):

Imidazole (435 mg, 6.39 mmol) and *tert*-butyldimethylsilyl chloride (500 mg, 3.32 mmol) were added to a solution of the diastereoisomerically pure alcohol **18** (852 mg, 2.55 mmol) in dry DMF (5 mL). The solution was stirred at r.t. for 18 h, and then quenched by the addition of water (25 mL). The mixture was extracted with EtOAc (2 × 20 mL) and the combined extracts were then washed with brine (20 mL), dried, and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexanes/Et_2O (90:10) as eluent to give the silyl ether **19** as a colourless oil; yield: 1.035 g (90%). The silyl ether from the major diastereoisomer of the alcohol **18** shows:

$C_{27}H_{48}O_3Si$	calc.	C 72.26	H 10.78
(448.8)	found	72.68	11.12

IR (film): ν = 1724 (C=C), 1650 cm^{-1} (C=O).

UV (EtOH): λ = 218 nm.

^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.01$, 0.03 (2 s, 3 H each, 2 × CH_3Si), 0.88 (s, 9 H, 3 × CH_3CSi), 1.58, 1.62, 1.67 (3 s, 3 H each, 3 × CH_3), 2.17 (d, 3 H, J = 1 Hz, C$\underline{H}_3$C=CHC=O), 1.3–2.2 (m, 11 H, C=CCH and 5 × CH_2), 3.68 (s, 3 H, OCH_3), 4.02 (t, 1 H, J = 7 Hz, SiOC$\underline{H}$$CH_2$), 4.64 (m, 1 H, $\underline{H}$HC=C), 4.76 (m, 2 H, 2 × H$\underline{H}$C=C), 4.80 (m, 1 H, $\underline{H}$HC=C), 5.06 (m, 1 H, C=CH), 5.67 (d, 1 H, J = 1 Hz, C=C$\underline{H}$C=O).

^{13}C NMR ($CDCl_3$, 22.05 MHz): $\delta = -5.0$ (q), −4.7 (q), 16.0 (q), 16.3 (q), 18.1 (s), 18.4 (q), 18.75 (q), 25.85 (t and 3 × q), 31.9 (t), 37.45 (t), 39.8 (t), 40.9 (t), 42.9 (d), 50.55 (q), 75.15 (d), 111.7 (2 × t), 115.4 (d), 122.8 (d), 136.4 (s), 147.2 (2 × s), 159.7 (s), 167.0 (s).

Whereas the silyl ether from the minor diastereoisomer of the alcohol **18** shows:

$C_{27}H_{48}O_3Si$	calc.	C 72.26	H 10.78
(448.8)	found	72.70	11.22

IR (film): ν = 1724 (C=O), 1650 cm^{-1} (C=C).

UV (EtOH): λ = 219 nm.

^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = -0.02$, 0.02 (2 s, 3 H each, 2 × CH_3Si), 0.89 (s, 9 H, 3 × CH_3CSi), 1.59, 1.60, 1.68, 2.17 (4 s, 3 H each, 4 × CH_3), 1.4–2.2 (m, 11 H, C=CCH and 5 × CH_2), 3.69 (s, 3 H, OCH_3), 3.96 (dd, 1 H, J = 3.5 and 8.5 Hz, SiOC$\underline{H}$CHH), 4.71, 4.81 (2 s, 2 H each, 4 × $\underline{H}$HC=C), 5.07 (s, 1 H, C=CH), 5.67 (s, 1 H, C=CHC=O).

^{13}C NMR ($CDCl_3$, 22.5 MHz): $\delta = -5.0$ (q), −4.5 (q), 16.0 (q), 18.1 (s and q), 18.75 (q), 25.9 (t and 3 × q), 32.1 (t), 37.4 (t), 40.9 (2 × t), 43.1 (d), 50.5 (q), 75.1 (d), 110.4 (t), 112.3 (t), 115.35 (d), 122.8 (d), 136.3 (s), 146.9 (s), 148.0 (s), 159.7 (s), 167.0 (s).

(10*RS*,12*RS*)(2*E*,6*E*)-12-*tert*-Butyldimethylsiloxy-3,7,13-trimethyl-10-(1-methylethenyl)tetradeca-2,6,13-trienoic Acid (20):
K_2CO_3 (4.3 g, 31 mmol) was added to a solution of the mixture of diastereoisomeric esters **19** (2.8 g, 6.2 mmol) in 7% MeOH (43 mL), and the mixture was then heated under reflux for 18 h. After cooling, the solution was acidified with 2 N HCl, and then extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (40 mL), then dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexanes/Et_2O (85:15) as eluent to give the acid **20** as a colourless oil; yield: 1.31 g (49%).

Major diastereoisomer:

IR (film): ν = 3400–2800 (OH), 1693 (C=O), 1643 cm^{-1} (C=C).

^{13}C NMR ($CDCl_3$, 22.5 MHz): $\delta = -4.9$ (q), −4.65 (q), 16.1 (q), 16.4 (q), 18.2 (s), 18.5 (q), 19.1 (q), 25.9 (t and 3 × q), 26.1 (t), 31.9 (t), 37.5 (t), 39.9 (t), 41.2 (t), 43.0 (d), 75.2 (d), 111.55 (t), 111.7 (t), 115.6 (d), 122.7 (d), 136.6 (s), 147.3 (2 × s), 162.6 (s), 172.5 (s).

Minor diastereoisomer:

IR (film): ν = 3300–2700 (OH), 1693 (C=O), 1643 cm^{-1} (C=C).

UV (EtOH): λ = 209 nm.

^{13}C NMR ($CDCl_3$, 22.5 MHz): $\delta = -4.9$ (q), −4.4 (q), 16.1 (q), 16.9 (q), 18.2 (s and q), 19.2 (q), 26.0 (t and 3 × q), 32.2 (t), 37.45 (t), 40.9 (t), 41.3 (t), 43.2 (d), 75.3 (d), 110.5 (t), 112.4 (t), 115.5 (d), 122.8 (d), 136.5 (s), 147.0 (s), 148.8 (s), 162.6 (s), 172.5 (s).

***Se*-Phenyl (10*RS*,12*RS*)(2*E*,6*E*)-12-*tert*-Butyldimethylsiloxy-3,7,13-trimethyl-10-(1-methylethenyl)tetradeca-2,6,13-trienselenoate (21):**
1,1′-Carbonyldiimidazole (463 mg, 2.86 mmol) was added in one portion to a stirred solution of the acid **20** (1.183 g, 2.72 mmol) in dry DMF (18 mL) at 0 °C. After 10 min at this temperature, the mixture was stirred at r.t. for 1.5 h. Benzeneselenol (375 µl, 3.53 mmol) was added dropwise, and the yellow solution was then stirred at r.t. for 2.25 h. The mixture was quenched with water (50 mL) and then extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), and then dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexanes and hexanes/Et_2O (90:10) as eluent to give the selenoester **21** as a pale yellow oil; yield: 960 mg (61%).

Major diastereoisomer:

IR (film): ν = 1703 (C=O), 1616 cm^{-1} (C=C).

^{13}C NMR ($CDCl_3$, 22.5 MHz): $\delta = -4.9$ (q), −4.6 (q9, 16.2 (q), 16.4 (q), 18.2 (s), 18.5 (q), 20.3 8q), 25.9 (t and 3 × q9, 32.0 (t), 37.5 (t), 39.9 (t), 40.75 (t), 43.0 (d), 75.15 (d), 111,55 (2 × t), 122.4 (d), 124.55 (d), 127.5 (s), 128.6 (d), 129.2 (2 × d), 135.8 (2 × d), 136.85 (s), 147.25 (2 × s), 157.5 (s), 189.3 (s).

Minor diastereoisomer:

IR (film): ν = 1703 (C=O), 1616 cm^{-1} (C=C).

^{13}C NMR ($CDCl_3$, 22.5 MHz): $\delta = -4.9$ (q), −4.4 (q), 16.2 (q), 16.9 (q), 18.2 (s and q), 20.3 (q), 26.0 (t and 3 × q), 32.2 (t), 37.45 (t), 40.8 (2 × t), 43.2 (d), 75.2 (d), 110.5 (t), 112.3 (t), 122.5 (d), 124.6 (d), 127.1 (s), 128.5 (d), 129.2 (2 × d), 135.8 (2 × d), 136.7 (s), 147.0 (s), 148.7 (s), 157.3 (s), 189.1 (s).

***Se*-Phenyl (10*RS*,12*RS*)(2*E*,6*E*)-12-Hydroxy-3,7,13-trimethyl-10-(1-methylethenyl)tetradeca-2,6,13-trienselenoate (22):**
Trimethylsilyl triflate (460 µl, 2.38 mmol) was added dropwise over 5 min to a stirred solution of the silyl ether **21** (390 mg, 0.68 mmol) in dry CH_2Cl_2 (8 mL) at −90 °C. After 25 min at this temperature, MeOH (1 mL) was added dropwise and the mixture was stirred for 5 min. The solution was poured into water (10 mL), and the two phases were separated. The organic phase was washed with brine (10 mL), and then dried and evaporated in vacuo. The residue was purified by chromatography on silica gel using hexanes/Et_2O (90:10 and 80:20) as eluent to give the alcohol **22** as a pale yellow oil; yield: 165 mg (53%, 95% based on recovered starting material).

Major diastereoisomer:

IR (film): ν = 3426 (OH), 1702 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.59, 1.66, 1.71 (3 s, 3 H each, 3 × CH_3), 1.3–1.9 (m, 8 H, 4 × CH_2), 2.07 (d, 3 H, J = 0.7 Hz, C$\underline{H}_3$C=CHC=O), 2.1 (m, 3 H, CH and CH_2), 4.06 (m, 1 H, HOC$\underline{H}$$CH_2$), 4.73 (m, 1 H, $\underline{H}$HC=C), 4.76 (m, 2 H, 2 × H$\underline{H}$C=C), 4.90 (m, 1 H, $\underline{H}$HC=C), 5.06 (t, 1 H, J = 6.7 Hz, C=C$\underline{H}$$CH_2$), 6.08 (s, 1 H, C=CHC=O), 7.36 (m, 3 H, 3 × H-Ar), 7.51 (m, 2 H, 2 × H-Ar).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (q), 17.0 q), 18.1 (q), 20.3 (q), 25.7 (t), 31.7 (t), 37.2 (t), 38.5 (t), 40.7 (t), 44.0 (d), 74.8 (d), 111.9 (t), 112.3 (t), 122.5 (d), 124.5 (d), 127.2 (s), 128.6 (d), 129.2 (2 × d), 135.8 (2 × d), 136.6 (s), 146.9 (s), 147.6 (s), 157.7 (s), 189.4 (s).

Minor diastereoisomer:

IR (film): ν = 3429 (OH), 1702 (C=O), 1615 cm^{-1} (C=C).

UV (EtOH): λ = 233 nm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.59, 1.63 (2 s, 3 H each, 2 × CH_3), 1.4–1.65 (m, 4 H, 2 × CH_2), 1.70 (s, 3 H, CH_3), 1.8–1.9 (m, 3 H, CH_2 and C$\underline{H}$HCHOH), 2.07 (d, 3 H, J = 1 Hz, CH_3C=CHC=O), 2.1–2.2 (m, 3 H, CH_2 and CH$\underline{H}$CHOH), 2.33 (m, 1 H, C=CCH), 3.98 (dd, 1 H, J = 3 × 9 Hz, HOC$\underline{H}$CHH), 4.79 (br m, 2 H, 2 × $\underline{H}$HC=C), 4.83, 4.93 (2 s, 1 H each, H$\underline{H}$C=C), 5.05 (t, 1 H, J = 6 Hz, C=C$\underline{H}$$CH_2$), 6.08 (s, 1 H, C=CHC=O), 7.35 (m, 3 H, 3 × H–Ar), 7.5 (m, 2 H, 2 × H–Ar).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1 (q), 17.7 (q), 18.1 (q), 20.3 (q), 25.7 (t), 32.0 (t), 37.4 (t), 39.0 (t), 40.7 (t), 43.4 (d), 73.3 (d), 110.0 (t), 112.85 (t), 122.4 (d), 124.45 (d), 127.3 (s), 128.6 (d), 129.2 (2 × d), 135.75 (2 × d), 136.6 (s), 146.75 (s), 148.2 (157.8 (s), 189.4 (s).

***Se*-Phenyl (10*RS*)(2*E*,6*E*)-3,7,13-Trimethyl-10-(1-methylethenyl)-12-oxotetradeca-2,6,13-trienselenoate (23):**
PCC (50 mg, 0.23 mmol) was added to a stirred solution of the alcohol **22** (96 mg, 0.21 mmol) in dry CH_2Cl_2 (4 mL) at −85 °C, and the suspension was then allowed to slowly warm to r.t. over 20 h. Celite was added, and the suspension was filtered through Florisil in Et_2O. The ether is evaporated in vacuo and the residue was purified by chromatography on silica gel using hexanes/Et_2O (85:15) as eluent to give the enone **23** as a pale yellow oil; yield: 25 mg (26%, 41% based on recovered starting material).

IR (film): ν = 1700 (C=O), 1677 (C=O), 1615 cm^{-1} (C=C).

UV (EtOH): λ = 228 nm.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.2–1.9 (m, 8 H, 4 × CH_2), 1.60, 1.68 (2 s, 3 H each, 2 × CH_3), 1.87 (s, 3 H, CH_3CC=O), 2.08 (s, 3 H, CH_3C=CC=O), 2.15 (br m, 1 H, $CH_2C\underline{H}CH_2$), 2.6–2.8 (m, 2 H, CH_2C=O), 4.70, 4.76 (2 s, 1 H each, 2 × $\underline{H}$HC=O), 5.06 (br, 1 H, C=C$\underline{H}CH_2$), 5.75, 5.92 (2 s, 1 H each, 2 × $\underline{H}$HC=CC=O), 6.09 (s, 1 H, C=CHC=O), 7.38 (m, 3 H, 3 × H–Ar), 7.53 (m, 2 H, 2 × H–Ar).

(2*RS*,13*RS*)(5*E*,9*E*)-13-2,6,10-Trimethyl-(1-methylethenyl)cyclotetradeca-5,9-diene-1,14-dione (9):

AIBN (6 mg, 0.04 mmol) was added to a solution of the selenoester **23** (172 mg, 0.38 mmol) in dry, deoxygenated benzene (68 mL) and the solution was heated under reflux. A solution of Bu_3SnH (136 µl, 0.51 mmol) in dry benzene (7 mL) was added, via syringe pump, over 1.5 h and the mixture was heated under reflux for a further 1.3 h. The mixture was cooled and the solvent was removed by evaporation in vacuo. The residue was purified by chromatography on silica gel using hexanes and hexanes/Et_2O (90:10 and 80:20) as eluent to give the dione **9** as a 1:1 mixture of diastereoisomers which were not separated; yield: 46 mg (40%).

HRMS: calc. for $C_{20}H_{30}O_2$: 302.2246, found: 302.2241.

IR (film): ν = 1708 (C=O), 1680 (C=O), 1613 cm^{-1} (C=C).

UV (EtOH): λ = 238 nm.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.09, 1.10 (2 d, 1.5 H each, J = 7 Hz, 2 × 0.5 $C\underline{H}_3CH$), 1.3–1.8 (m, 8 H, 4 × CH_2), 1.55, 1.73 (2 s, 3 H each, 2 × CH_3), 2.05 (m, 1 H, $CH_2C\underline{H}CH_2$), 2.09, 2.10 (2 d, 1.5 H each, J = 1 Hz, 2 × 0.5 $C\underline{H}_3C$=CHC=O), 2.3 (m, 4 H, 2 × $C\underline{H}_2C$=O), 2.55 (m, 1 H, $C\underline{H}CH_3$), 4.65, 4.70, 4.75, 4.80 (4 s, 0.5 H each, 4 × $\underline{H}$HC=C), 4.96 (br, 1 H, C=C$\underline{H}CH_2$), 5.87, 6.02 (2 s, 0,5 H each, 2 × 0.5 C=CHC=O).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.8 (d), 40.9 (d), 42.2 (d), 43.9 (d), 110.25 (t), 112.4 (t), 123.5 (d), 124.0 (d), 124.4 (d), 124.6 (d), 135.2 (s), 147.1 (s), 149.9 (s), 159.1 (s), 199.65 (s), 199.9 (s), 212.1 (s), 212.4 (s).

(2*E*,6*E*)-3,7,13-Trimethyl-10-(1-methylethenyl)-15-oxabicyclo-[10.2.1]pentadeca-2,6,12,14-tetraene (8):

A solution of the dione **9** (4 mg, 0.013 mmol) in $CHCl_3$ (5 mL) containing TsOH (1 mg) was heated under reflux for 3.5 h, then cooled and evaporated to dryness in vacuo. The residue was purified by chromatography on silica gel using hexanes as eluent to give the furan **8** as a colourless oil; yield: 2 mg (50%).

HRMS: calc. for $C_{20}H_{28}O$: 284.2140, found: 284.2136.

UV (EtOH): λ = 284 nm.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.3–2.1 (m, 11 H, $CH_2C\underline{H}CH_2$ and 5 × CH_2), 1.60, 1.75, 1.89, 1.92 (4 s, 3 H each, 4 × CH_3), 4.65–4.85 (br m, 3 H, C=C$\underline{H}CH_2$ and $\underline{H}$HC=C), 5.88, 5.90 (2 s, 1 H each, C=CH).

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(1) Fenical, W.; Okuda, R.K.; Bandurraga, M.M.; Culver, P.; Jacobs, R.S. *Science* **1981**, *212*, 1512.

(2) Culver, P.; Burch, M.; Potenza, C.; Wasserman, L.; Fenical, W.; Taylor P. *Mol. Pharmacol.* **1985**, *28*, 436.
Sorenson, E.M.; Culver, P.; Chiappinelli, V.A. *Neuroscience* **1987**, *20*, 875.

(3) Missakian, M.G.; Burreson, B.J.; Scheuer, P.J. *Tetrahedron* **1975**, *31*, 2513.

(4) Wright, A.E.; Burres, N.S.; Schulte, G.E. *Tetrahedron Lett.* **1989**, *30*, 3491.

(5) Bandurraga, M.M.; Fenical, W.; Donovan, S.F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.

(6) Look, S.A.; Burch, M.T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.

(7) For other approaches to furanocembranoids, see:
Marshall, J.A.; Robinson, E.D. *J. Org. Chem.* **1990**, *55*, 3450.
Kondo, A.; Ochi, T.; Iio, H.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, 1491.
Paterson, I.; Gardner, M. *Tetrahedron* **1989**, *45*, 5283.
Paquette, L.A.; Rayner, C.M.; Doherty, A.M. *J. Am. Chem. Soc.* **1990**, *112*, 4078.
Paquette, L.A.; Astles, P.C. *Tetrahedron Lett.* **1990**, *31*, 6505.

(8) For a review on cembranoid synthesis see:
Tius, M.A. *Chem. Rev.* **1988**, *88*, 719.

(9) For fundamental studies of radical macrocyclisations see:
Porter, N.A.; Magnin, D.R.; Wright, B.T. *J. Am. Chem. Soc.* **1986**, *108*, 2787.
Porter, N.A.; Chang, V.H.; Magnin, D.R.; Wright, B.T. *Ibid.* **1988**, *110*, 3554.

(10) Abramson, S.N.; Trischman, J.A.; Tapiolas, D.M.; Harold, E.E.; Fenical, W.; Taylor, P. *J. Med. Chem.* **1991**, *34*, 1798.

(11) Cox, N.J.G.; Pattenden, G.; Mills, S.D. *Tetrahedron Lett.* **1989**, *30*, 621.

(12) Hitchcock, S.A.; Pattenden, G. *Tetrahedron Lett.* **1990**, *31*, 3641.

(13) Preliminary publication: Astley, M.P.; Pattenden, G. *Synlett* **1991**, 335.

(14) Coveney, D.J.; Patel, V.F.; Pattenen, G.; Thompson, D.M. *J. Chem. Soc., Perkin Trans 1* **1990**, *2721*; and references therein.

(15) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328.
Crich, D.; Fortt, S.M. *Tetrahedron Lett.* **1987**, *28*, 2895.
Crich, D.; Fortt, S.M. *Tetrahedron* **1988**, *29*, 2585.
Crich, D.; Fortt, S.M. *Tetrahedron* **1989**, *45*, 6581.
Boger, D.L.; Mathvink, R.J. *J. Org. Chem.* **1988**, *53*, 3377.
Boger, D.L.; Mathvink, R.S. *J. Org. Chem.* **1989**, *54*, 1777.
Bachi, M.D.; Denenmark, D. *Heterocycles* **1989**, *28*, 583.

(16) Delduc, P.; Tailhan, C.; Zard, S.Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308.
Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6127.
Barton, D.H.R.; Crich, D.; Löbberding, A.; Zard, S.Z. *Tetrahedron* **1986**, *42*, 2329.
Barton, D.H.R.; Crich, D. *J. Chem. Soc., Perkin Trans 1* **1986**, 1603.

(17) Boger, D.L.; Mathvink, R.J. *J. Am. Chem. Soc.* **1990**, *112*, 4008.

(18) Corey, E.J.; Gilman, N.W.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(19) Sum, F.W.; Weiler, L. *J. Am. Chem. Soc.* **1979**, *101*, 4401.

(20) Gais, H.-J. *Angew. Chem.* **1977**, *89*, 251; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 244.

(21) Bou, V.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 567.