Syntheses of thunbergols and α- and β-cembra-2,7,11-triene-4,6-diols

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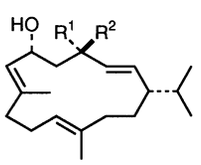
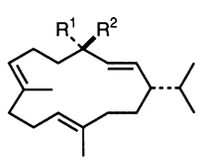
Alkylation of the racemic sulfone 25, available from the epoxide 8, using the iodide 24 followed by reduction gives the protected hydroxy acetal 27. Selective deprotection gives the alcohol 28. This is converted into the bromide 29 which is used to alkylate the keto phosphonate 33. Hydrolysis of the alkylated keto phosphonate 30 gives the aldehyde 31 which is cyclised under mild conditions (63%) and the product treated with methylmagnesium iodide, to give the racemic thunbergols 3 and 4, in a ratio of 3:4 = 10:90. The laevorotatory sulfone 25 has been prepared by regioselective ring-opening of the epoxide 38 followed by hydrogenation, selective protection and functional group modification. After alkylation of this sulfone using the iodide 24 and conversion into the aldehyde 46, an asymmetric aldol condensation gives the hydroxy amide 47 which is converted directly into the hydroxy keto phosphonate 49 by reaction with an excess of lithiated dimethyl methylphosphonate. After protection of the hydroxy group, selective hydrolysis of the acetal gives the aldehyde 51 which is cyclised as before to give the naturally occurring cembratrienediols 1 and 2 after reaction with methylmagnesium iodide and deprotection.

Introduction

The cembrenoids are a widespread group of diterpenes which have been the focus of much synthetic work.[1,2] The α- and β-cembra-2,7,11-triene-4,6-diols **1** and **2** were first isolated from



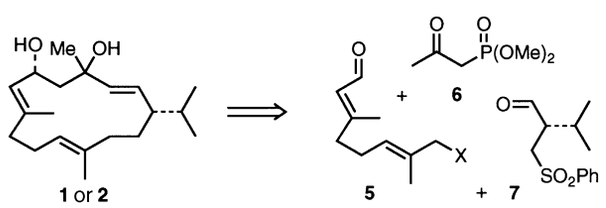
1 R^1 = OH, R^2 = Me
2 R^1 = Me, R^2 = OH



3 R^1 = Me, R^2 = OH
4 R^1 = OH, R^2 = Me

aged burley tobacco in 1962,[3,4] and are believed to give rise to volatile products during smoking which contribute to tobacco flavour.[5] It has been suggested that they act as growth regulators in the tobacco plant.[4] Tobacco leaves with high levels of cembrenoids **1** and **2** show increased resistance to certain pests and fungal infections,[6] and these cembrenoids have been found to inhibit tumour promotion in mice.[7] Both isomers have been synthesized.[8] We now report full details of a synthesis of the cembratrienediols **1** and **2** together with a synthesis of the thunbergols **3** and **4**,[9] cembrenoids isolated from pine tree resin and tobacco leaves.[10]

A convergent synthesis of the cembratrienediols was envisaged based on the long-chain halo aldehyde **5**, the keto phosphonate **6** and the sulfonyl aldehyde **7**. After preliminary

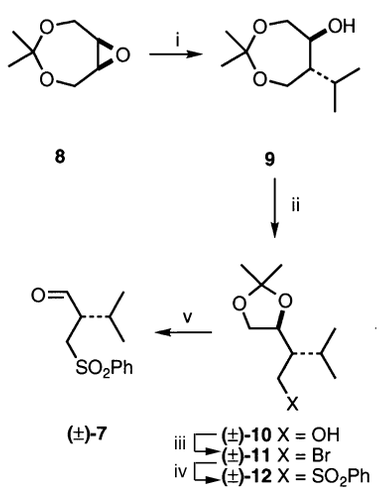


1 or **2** ⟹ **5** + **6** + **7**

investigations into alternative strategies, it was decided that alkylation of the sulfone using the long-chain halide would be followed by an aldol condensation of the product with the keto phosphonate and macrocyclisation by way of a keto phosphonate–aldehyde condensation, *vide infra*.[11] To gain experience of this chemistry, it was decided initially to develop a synthesis of the thunbergols **3** and **4**.

Results and discussion

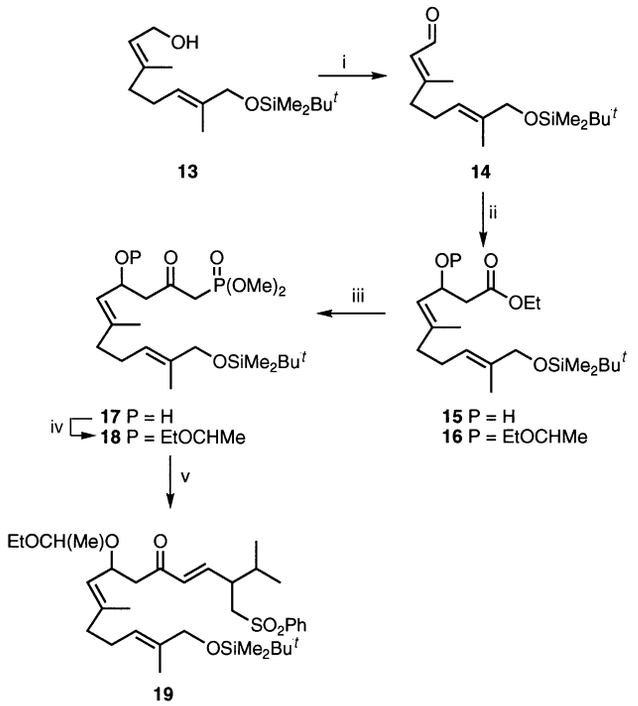
The racemic sulfone **7** was prepared as outlined in Scheme 1.



Scheme 1 *Reagents and conditions:* i, Me_2CHBr, CuI, THF, −78 °C to room temp.; ii, TsOH, acetone (70% from **8**); iii, Ph_3P, *N*-bromosuccinimide, CH_2Cl_2, pyridine (82%); iv, $PhSO_2Na$, DMF, 70 °C (75%); v, HIO_4, aqueous THF (95%)

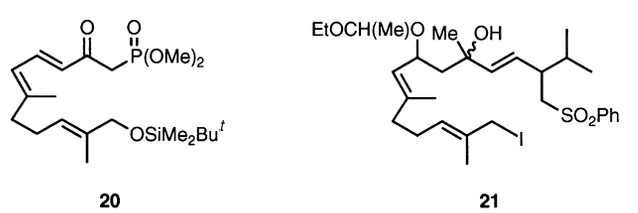
The epoxide **8**[12] underwent ring-opening on treatment with isopropylmagnesium bromide and copper(I) iodide[13] to give the alcohol **9** which rearranged under acidic conditions[12] to give the acetonide **10**. This was converted into the sulfone **12** *via* the bromide **11** and on reaction with an excess of periodic acid the acetonide was oxidatively cleaved to give the aldehyde **7**.

The viability of keto phosphonate condensations with the sulfonyl aldehyde **7** was established using the protected hydroxy keto phosphonate **18**, see Scheme 2. This was prepared from the 8-*tert*-butyldimethylsilyloxyocta-2,6-dienol **13**[14] which is readily available from geraniol. Oxidation of the alcohol[15] and aldol addition of ethyl acetate gave the racemic hydroxy ester **15** which with an excess of lithiated dimethyl methylphosphonate gave the hydroxy keto phosphonate **17**.[16] This was protected, as



Scheme 2 *Reagents and conditions:* i, pyridinium dichromate, DMF, 0 °C (78%); ii, $LiCH_2CO_2Et$, −78 °C, THF (75%); iii, $LiCH_2P(OMe)_2$, THF, −78 °C (90%); iv, CH_2=CHOEt, pyridinium toluene-*p*-sulfonate, CH_2Cl_2, 3 h (73%); v, NaH, (±)-**7** (65%)

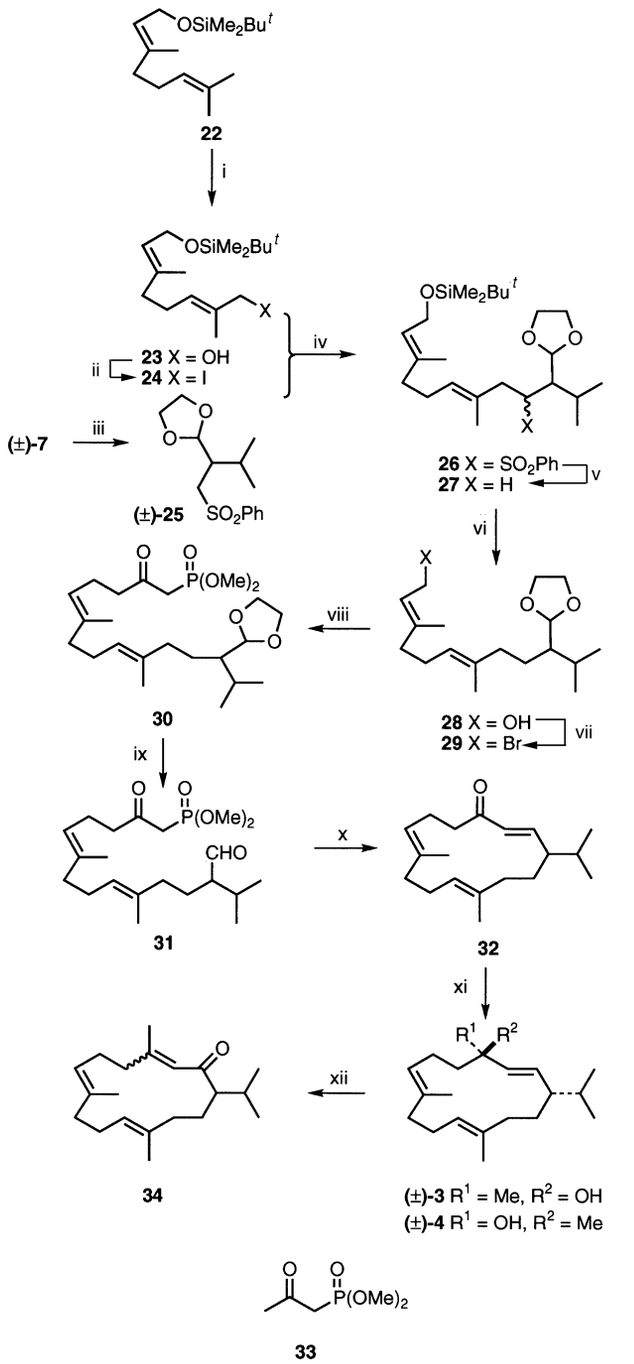
a mixture of diastereoisomers, as its ethoxyethyl derivative **18**.[17] If the order of these reactions was reversed and the aldol product protected as its ethoxyethyl derivative **16** before treatment with the lithiated dimethyl methylphosphonate, the major product was the unsaturated keto phosphonate **20**. Treatment



of the keto phosphonate **18** with a suspension of sodium hydride in 1,2-dimethoxyethane (DME) generated a red solution which reacted with the sulfonyl aldehyde **7** to give a reasonable yield, 65%, of the unsaturated ketone **19**.

This work showed that the sulfonyl aldehyde **7** can undergo condensation with keto phosphonates without, for example, loss of the phenylsulfonyl group, but preliminary attempts to convert the unsaturated ketone **19** into cembrenolides were unsuccessful. The ketone **19** was converted into the iodide **21**, as a mixture of diastereoisomers, by treatment with methylmagnesium iodide, deprotection using tetrabutylammonium fluoride and selective conversion of the primary hydroxy group into the iodide using iodine, triphenylphosphine and imidazole in diethyl ether. However, attempts to cyclise this iodide, *e.g.* using potassium hexamethyldisilazide in tetrahydrofuran under high dilution conditions,[18] were unsuccessful. It was decided at this stage to investigate the use of the keto phosphonate–aldehyde condensation reaction to form the macrocyclic ring.[11]

Geraniol *tert*-butyldimethylsilyl ether **22**[19] was oxidised[20] to the allylic alcohol **23** which was converted into the iodide **24** (Scheme 3). This iodide was found to be unstable and was used to alkylate the sulfone acetal (±)-**25** without purification. Reductive removal[21] of the phenylsulfonyl group from the alkylated product **26**, followed by desilylation using tetrabutyl-



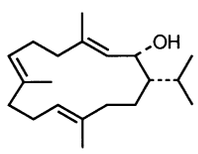
Scheme 3 *Reagents and conditions:* i, SeO_2, salicylic acid, CH_2Cl_2, Bu^tOOH (40%); ii, Ph_3P, imidazole, acetonitrile, iodine (75%); iii, ethane-1,2-diol, TsOH, benzene, heat under reflux (95%); iv, BuLi, (±)-**25** (82%); v, disodium hydrogen orthophosphate, Na–Hg, MeOH, THF (75%); vi, Bu_4NF, THF (95%); vii, dimethyl sulfide, *N*-bromosuccinimide, CH_2Cl_2 (83%); viii, sodium hydride, **33**, then add BuLi, 0 °C to room temp. (78%); ix, pyridinium toluene-*p*-sulfonate, aqueous acetone (80%); x, LiCl, acetonitrile, DBU (63%); xi, MeMgI, diethyl ether, −10 °C (65%; **3**:**4** = 10:90); xii, pyridinium chlorochromate, alumina, CH_2Cl_2 (60%)

ammonium fluoride, gave the alcohol **28**, and this was converted into the allylic bromide **29** under standard conditions. Treatment of dimethyl 2-oxopropylphosphonate **33** with sodium hydride and butyllithium followed by addition of the allyl bromide **29** resulted in regioselective monoalkylation of the keto phosphonate to give the long-chain phosphonate **30** in good yield.[22] Hydrolysis of the acetal under mildly acidic conditions[23] gave the aldehyde **31** and this was cyclised by treatment with lithium chloride and 1,8-diazabicyclo[5.4.0]undec-2-ene (DBU) in acetonitrile to give the cyclic ketone **32**[24] (63%).

The best results were obtained when the DBU was added slowly using a syringe pump to a dilute solution of the aldehyde and lithium chloride in acetonitrile at 40 °C.

The structure of this ketone was established on the basis of spectroscopic data. In particular, the geometry of the 2,3-double bond was consistent with ^{1}H NMR data, the $J_{2,3}$ coupling constant being 16 Hz. A mixture of double bond isomers containing the cyclic ketone **32** has been prepared by Dauben,[16] and the ketone **32** has been reported to be an artifact present in aged pine resin, probably arising from autoxidation of isocembrene.[2]

Treatment of the ketone **32** with methylmagnesium iodide in diethyl ether gave a mixture of thunbergol **3** and epithunbergol **4**, ratio 10:90. The structures of these were established on the basis of their spectroscopic data, the ^{13}C NMR data of the major isomer being identical to those reported for authentic epithunbergol **4**.[9,25] Moreover, oxidation of the separated thunbergols using pyridinium chlorochromate[26] in the presence of alumina gave the rearranged ketone **34**, as a mixture of 2*E*- and 2*Z*-isomers, ratio 2*E*:2*Z* = 80:20. The ^{1}H NMR spectrum of the 2*E*-isomer **34** was identical to that published both for the synthetic ketone[27] and for the ketone obtained on oxidation of mukalol **35**.[28]



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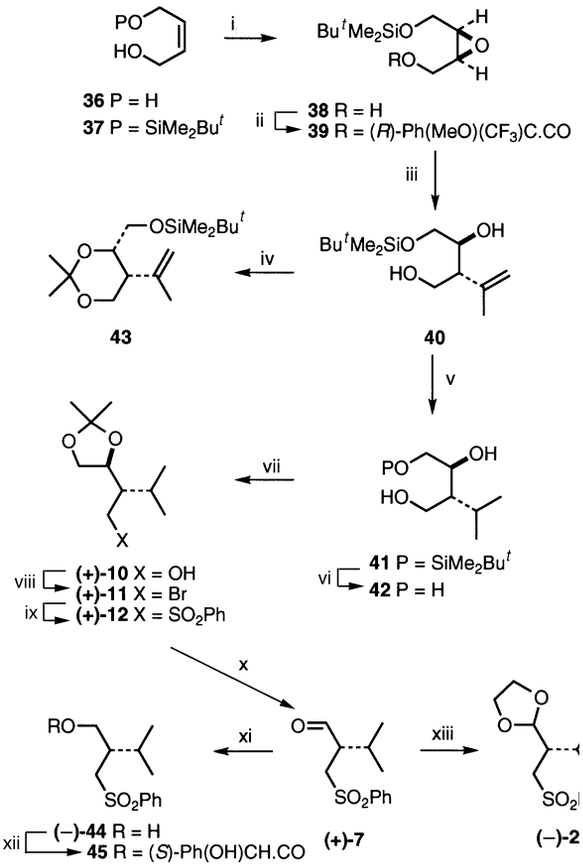
The stereoselectivity of the reaction of the ketone **32** with the Grignard reagent is consistent with preliminary molecular modelling studies which suggest that the enone system is planar with the isopropyl group pseudoequatorial. Attack on the less hindered, outside face of the enone system leads to the observed major product **4**.

To develop a stereoselective synthesis of the cembratriene-diols **1** and **2**, it was necessary to prepare the (*S*)-enantiomer of the sulfonyl acetal **25**, see Scheme 4. Monosilylation[29] of (*Z*)-but-2-ene-1,4-diol **36** followed by Sharpless epoxidation using (+)-diethyl tartrate gave the epoxy alcohol **38**.[30] This was shown to have an enantiomeric excess of *ca*. 85% by comparison of the ^{19}F NMR spectrum of its (*R*)-Mosher's ester **39** with those prepared from the racemic epoxy alcohol (available from the alkene **37** using *m*-chloroperoxybenzoic acid).[31] Copper(I) catalysed reaction of propen-2-ylmagnesium bromide with the epoxide **38** was regio- and stereo-selective and gave the 1,3-diol **40**.[32] None of the corresponding 1,2-diol was isolated and no product resulting from a Payne rearrangement of the hydroxy epoxide was detected. To check that the epoxide opening had taken place with inversion of configuration, the 1,3-diol **40** was converted into the acetonide **43** which was shown, by ^{1}H NMR spectroscopy, to have the stereochemistry indicated. Hydrogenation of the diol **40** using Wilkinson's catalyst[33] and desilylation gave the crystalline triol **42**. On acid catalysed condensation with acetone, selective acetalisation[34] gave the dextrorotatory enantiomer of the hydroxy acetal **10**. This was converted *via* the bromide **11** and sulfone **12** into the (*S*)-aldehyde (+)-**7** which gave the (*S*)-acetal (−)-**25** with ethylene glycol. The enantiomeric excess of the aldehyde (+)-**7** was estimated by reduction to the alcohol **44** which was converted into ester **45** using (*S*)-mandelic acid. Comparison of the ^{1}H NMR spectrum of the (*S*)-mandelate **45** with that of the mixture of mandelates prepared from the racemic alcohol **44**, available by reduction of the racemic aldehyde (±)-**7**, showed the enantiomeric excess of the alcohol **44**, and hence of the aldehyde (+)-**7**, to be 85%.[35]

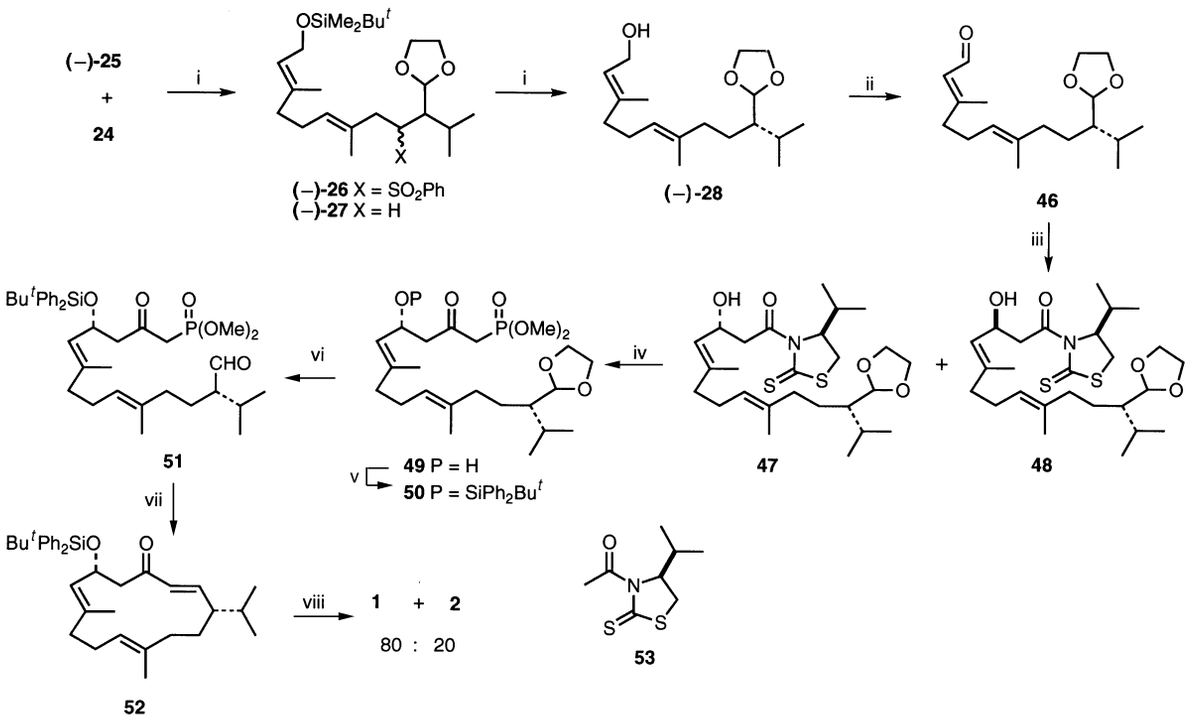
Alkylation of the sulfone (−)-**25** using the iodide **24** gave the alcohol (−)-**28** after reductive removal of the sulfur and desilylation (Scheme 5). Oxidation gave the aldehyde **46**. It was now necessary to effect an asymmetric aldol addition to introduce the chiral centres at C(6) (cembrenoid numbering) of the cembratrienediols **1** and **2** with the required configuration. This was achieved using the 1,3-thiazolidine-2-thione **53**, tin(II) trifluoromethanesulfonate and *N*-ethylpiperidine to give the aldol product **47** together with its epimer **48**, ratio 85:15.[36] These aldol products were separated and the major isomer **47** treated with an excess of the lithium salt of dimethyl methylphosphonate to give the hydroxy keto phosphonate **49** which was protected as its *tert*-butyldiphenylsilyl ether **50**. Selective hydrolysis gave the aldehyde **51** which was cyclised using lithium chloride and DBU to give the enone **52** in 31% yield.[24] This enone was found to contain *ca*. 15% of its epimer at C(1) derived from the minor enantiomer of the sulfone **25**. Reaction of the ketone **52** with methylmagnesium iodide followed by desilylation gave the cembratrienediols **1** and **2**, ratio 80:20, the stereoselectivity of the Grignard addition following that observed previously with the enone **32**. The synthetic cembratrienediols were identified on the basis of their spectroscopic data,[37] and were found to be identical by ^{1}H NMR, ^{13}C NMR and IR spectroscopy, MS and TLC, with authentic samples of the natural products.†

The modest yield (31%) found for the cyclisation of the formyl keto phosphonate **51** contrasts with the significantly better yield (63%) obtained for the cyclisation of the analogue



Scheme 4 *Reagents and conditions:* i, (+)-diethyl tartrate, Ti(OPr^i)$_4$, CH_2Cl_2, −23 °C, Bu^{t}OOH, −25 °C (90%); ii, (*R*)-Ph(MeO)(CF$_3$)C·COCl, pyridine, CH_2Cl_2, 48 h (80%); iii, propen-2-ylmagnesium bromide, THF, CuI, diethyl ether, −23 °C to room temperature (75%); iv, TsOH, 1,2-dimethoxyethane (92%); v, (Ph$_3$P)$_3$RhCl, benzene, ethanol (80%); vi, aqueous HCl, THF (90%); vii, TsOH, acetone (95%); viii, Ph$_3$P, *N*-bromosuccinimide, CH_2Cl_2, pyridine (82%); ix, PhSO$_2$Na, DMF (75%); x, HIO_4, aqueous THF (95%); xi, $NaBH_4$, MeOH, THF (90%); xii, (*S*)-(+)-mandelic acid, TsOH, benzene, heat under reflux (75%); xiii, TsOH, ethane-1,2-diol, benzene, heat under reflux (95%)

† Samples of authentic cembratrienediols were kindly provided by Dr I. Wahlberg of the Swedish Tobacco Company.



Scheme 5 *Reagents and conditions:* i, see Scheme 3; ii, pyridinium dichromate (75%); iii, *N*-ethylpiperidine, tin(II) trifluoromethanesulfonate, CH_2Cl_2, **53** (**47**, 75%; **48**, 15%); iv, $LiCH_2P(OMe)_2$, THF (77%); v, Bu^tPh_2SiCl, imidazole, DMF (70%); vi, pyridinium toluene-*p*-sulfonate, aqueous acetone (78%); vii, LiCl, DBU, acetonitrile (31%); viii, methylmagnesium iodide, diethyl ether, 0 °C (60%; **1**:**2** = 80:20)

31 which contains no *tert*-butyldiphenylsilyloxy group. To probe the factors responsible for this difference, the cyclisation of the corresponding acetal **63** was examined. This was prepared, as its racemate, as outlined in Scheme 6. Alkylation of the racemic *tert*-butyldiphenylsilyl ether **54** of the alcohol **44** using the iodide **24** gave the bis-silyl ether **56** after reductive removal of the phenylsulfonyl group. Selective deprotection[38] gave the allylic alcohol **57** which was converted into the keto ester **59** by oxidation to the aldehyde **58**, addition of lithiated ethyl acetate and oxidation. The ketone was converted into the acetal **60** using 1,2-bis(trimethylsilyloxy)ethane in the presence of trimethylsilyl trifluoromethanesulfonate,[39] and, after desilylation, reaction with an excess of lithiated dimethyl methylphosphonate gave the hydroxy keto phosphonate **62**. Oxidation gave the aldehyde **63** which was cyclised using lithium chloride and DBU, under the standard conditions, to give the cyclic enone **64** (45%). This was taken through to the hydroxy ketone **65**,[40] a known precursor of the α-cembratrienediol **1**,[37] using methylmagnesium iodide followed by pyridinium toluene-*p*-sulfonate.

It would appear that the cyclisation of the acetal **63** is somewhat more efficient than cyclisation of the siloxy ketone **51**, but neither is as efficient as cyclisation of the less complex **31**. Perhaps base-induced elimination of the oxygenated substituents β to the carbonyl group is interfering although no products formed by this elimination were isolated during the course of the present work. Notwithstanding this limitation, the cyclisation of formyl keto phosphonates does offer a reasonable procedure for formation of the 14-membered ring of cembrenoids which may be suitable for the synthesis of more complex targets in this area.

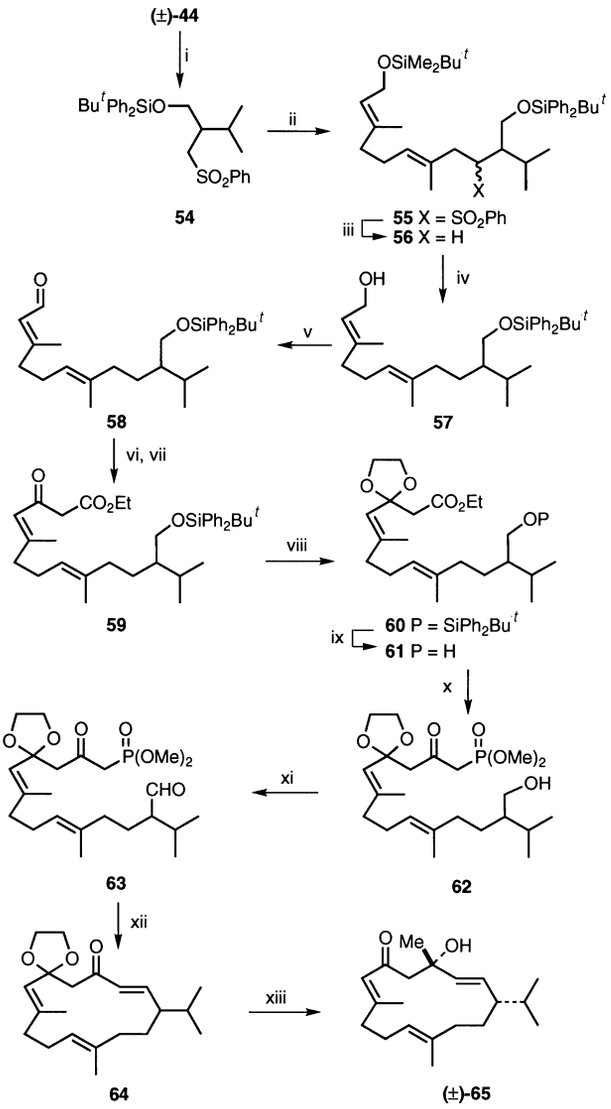
Experimental

Melting points were determined on a Buchi 510 apparatus and are uncorrected. IR Spectra were recorded on Perkin-Elmer 297 and 1710 spectrometers as liquid films unless otherwise stated. Low and high resolution mass spectra were taken on VG Micromass 16F, 30F and ZAB 1F spectrometers using electron impact (EI) and chemical ionisation (CI) modes. ^{1}H NMR Spectra were recorded at 300 Mz in [^{2}H]chloroform unless otherwise stated. *J* Values are given in Hz. Optical rotations were measured at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was carried out using Merck silica gel 60 (40–63 μm, 230–400 mesh) or May and Baker Sorbsil C60 silica gel (40–60 μm). All solvents were dried and distilled before use. Light petroleum refers to the fraction boiling in the range 40–60 °C. Ether refers to diethyl ether.

(2*SR*,3*RS*)- and (2*S*,3*R*)-3-Isopropyl-1,2-*O*-isopropylidenebutane-1,2,4-triol (±)-10 and (+)-10

Isopropylmagnesium bromide in tetrahydrofuran (400 cm^3) was added to a stirred suspension of cuprous iodide (3.8 g, 20 mmol) in ether (75 cm^3) at −78 °C over 30 min. The resultant suspension was stirred for 15 min, then the epoxide **8**[12] (14.4 g, 100 mmol) in ether (50 cm^3) was added over 10 min. The yellow suspension was allowed to warm to room temperature over 15 h and saturated aqueous ammonium chloride (10 cm^3) was added. The reaction was diluted with ether (500 cm^3), decanted and the granular salts washed with ether (2 × 50 cm^3). The combined organic extracts were washed with saturated aqueous ammonium chloride (250 cm^3; containing ammonium hydroxide so that the pH was 8) and brine (200 cm^3) and then dried ($MgSO_4$). Concentration under reduced pressure yielded a yellow oil which was taken up in acetone (100 cm^3) and stirred with toluene-*p*-sulfonic acid (380 mg, 2 mmol) for 5 h. Solid sodium carbonate (10 g) was added and after a further 30 min, the solids were filtered off. The filtrate was concentrated under reduced pressure and the residue distilled to give the *title compound* (±)-**10** (13.2 g, 70%), as a colourless oil, bp 105–110 °C/2 mmHg (Found: $M^+ + H$, 189.1490. $C_{10}H_{21}O_3$ requires *M*, 189.1491); ν_{max}/cm^{-1} 3430, 1245, 1215, 1160, 1060, 860, 790 and 730; δ_H 0.98 and 1.18 (each 3 H, d, *J* 6, Me), 1.43 and 1.49 (each 3 H, s, Me), 1.87 (2 H, m, 3-H and 3-CH), 2.28 (1 H, br s, OH), 3.73 (2 H, m, 4-H_2), 3.78 (1 H, t, *J* 8, 1-H), 4.05 (1 H, dd, *J* 8, 6, 1-H) and 4.29 (1 H, m, 2-H); *m*/*z* (CI) 189 ($M^+ + 1$, 100%) and 173 (35).

A solution of the triol **42** (0.87 g, 5.9 mmol) and toluene-*p*-



Scheme 6 *Reagents and conditions:* i, Bu^{t}Ph$_2$SiCl, imidazole, THF, DMF (75%); ii, BuLi, then add **24** (85%); iii, disodium orthophosphate, Na–Hg, MeOH, THF (73%); iv, pyridinium toluene-*p*-sulfonate, MeOH, THF (90%); v, pyridinium dichromate, DMF (70%); vi, LiCH$_2$CO$_2$Et, THF (78%); vii, pyridinium dichromate, DMF (66%); viii, 1,2-bis(trimethylsilyloxy)ethane, trimethylsilyl trifluoromethanesulfonate, CH_2Cl_2 (80%); ix, Bu_4NF, THF; x, LiCH$_2$P(OMe)$_2$ (70% from **60**); xi, pyridinium dichromate, CH_2Cl_2 (83%); xii, LiCl, acetonitrile, DBU (45%); xiii, methylmagnesium iodide, then pyridinium toluene-*p*-sulfonate (38%)

sulfonic acid (30 mg, 0.16 mmol) in acetone (30 cm^3) was stirred at 0 °C for 18 h. Solid Na_2CO_3 (1 g) was added and the mixture stirred for 30 min then filtered. After concentration under reduced pressure, the residue was distilled to give the *title compound* (+)-**10** (1.05 g, 95%), as a colourless oil, $[\alpha]_D$ +17.9 (*c* 1.0 in $CHCl_3$), with spectroscopic data identical to those of the racemic compound (±)-**10**.

(2*SR*,3*SR*)- and (2*S*,3*S*)-4-Bromo-3-isopropyl-1,2-*O*-isopropylidenebutane-1,2-diol (±)-11 and (+)-11

A solution of triphenylphosphine (21.3 g, 81 mmol) in CH_2Cl_2 (60 cm^3) was added dropwise to a stirred, cooled (0 °C) suspension of *N*-bromosuccinimide (15.5 g, 87 mmol) in CH_2Cl_2 (150 cm^3) and the resultant red solution stirred for 15 min. Pyridine (2.7 g, 34.5 mmol) was added dropwise followed by slow addition of the alcohol **10** (5.8 g, 30 mmol) in CH_2Cl_2 (60 cm^3). The reaction was stirred for 15 h at room temperature, diluted with ether (500 cm^3) and filtered through a short pad of silica gel. The filtrate was washed with saturated aqueous $NaHCO_3$ (150 cm^3), water (150 cm^3) and brine (150 cm^3). After drying ($MgSO_4$) and concentration under reduced pressure, distillation gave the *title compound* (±)-**11** (6.2 g, 82%), as a colourless oil, bp 130 °C/15 mmHg (Found: C, 47.9; H, 7.9. $C_{10}H_{19}BrO_2$ requires C, 47.8; H, 7.65%); ν_{max}/cm^{-1} 1215, 1160, 1060 and 860; δ_H 1.01 (6 H, d, *J* 6, 2 × Me), 1.38 and 1.44 (each 3 H, s, Me), 1.92 and 2.16 (each 1 H, m), 3.42 and 3.47 (each 1 H, dd, *J* 9, 5, 4-H), 3.75 (1 H, t, *J* 8, 1-H), 4.08 (1 H, dd, *J* 8, 5, 1-H) and 4.18 (1 H, m, 2-H); *m*/*z* (EI) 235, 237 (26%) and 101 (100).

Following this procedure, the (2*S*,3*S*)-enantiomer of the title compound (+)-**11**, $[\alpha]_D$ +9.9 (*c* 1.0 in $CHCl_3$), was prepared from the (2*S*,3*R*)-enantiomer of the alcohol (+)-**10**.

(2*SR*,3*SR*)- and (2*S*,3*S*)-3-Isopropyl-4-(phenylsulfonyl)-1,2-*O*-isopropylidenebutane-1,2-diol (±)-12 and (+)-12

Sodium benzenesulfinate (9.8 g, 60 mmol) was added to a solution of the bromide **11** (5.02 g, 20 mmol) in *N*,*N*-dimethylformamide (DMF) (40 cm^3) at 70 °C. After 15 h, the reaction was cooled, poured into water (100 cm^3) and extracted with ether (3 × 200 cm^3). The combined extracts were washed with water (2 × 100 cm^3) and brine (2 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (4:1) as eluent gave the *title compound* (±)-**12** (4.68 g, 75%), as a colourless solid, mp 46–47 °C (Found: C, 61.7; H, 8.0. $C_{16}H_{24}O_4S$ requires C, 61.5; H, 7.75%); $\nu_{max}(CHCl_3)$/cm^{-1} 1300, 1240, 1210, 1150, 1085, 1060, 860, 750 and 690; δ_H 1.80 and 1.93 (each 3 H, d, *J* 6, Me), 1.28 and 1.33 (each 3 H, s, Me), 2.12 (1 H, m, 3-CH), 2.27 (1 H, m, 3-H), 3.04 (2 H, d, *J* 5, 4-H$_2$), 3.58 (1 H, dd, *J* 8, 7, 1-H), 3.98 (1 H, dd, *J* 8, 5, 1-H′), 4.18 (1 H, m, 2-H), 7.59 (2 H, m, aromatic H), 7.67 (1 H, m, aromatic H) and 7.92 (2 H, m, aromatic H); *m*/*z* (CI) 330 (M^+ + 18, 100%) and 313 (M^+ + 1, 64).

Following this procedure, the (2*S*,3*S*)-enantiomer of the title compound (+)-**12**, $[\alpha]_D$ +4.72 (*c* 1.0 in $CHCl_3$), was prepared from the (2*S*,3*S*)-enantiomer of the bromide (+)-**11**.

(2*RS*)- and (2*S*)-3-Methyl-2-(phenylsulfonylmethyl)butanal (±)-7 and (+)-7

The sulfone **12** (3.1 g, 10 mmol) in tetrahydrofuran (15 cm^3) was added to a solution of periodic acid (3.4 g, 15 mmol) in tetrahydrofuran–water (30 cm^3; 1:1). The reaction was stirred for 5 h, diluted with water (30 cm^3) and extracted with ether (4 × 100 cm^3). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (3 × 50 cm^3), dried ($MgSO_4$), concentrated under reduced pressure and the residue taken up in benzene (100 cm^3). Concentration under reduced pressure gave the *title compound* (±)-**7** (2.3 g, 95%), as a pale yellow oil which was used without further purification; ν_{max}/cm^{-1} 2870, 2810, 2710, 1725, 1450, 1395, 1375, 1310, 1145, 1085, 860, 750 and 690; δ_H 0.91 and 1.00 (each 3 H, d, *J* 6, Me), 2.27 (1 H, m, 3-H), 3.00 (2 H, m, 2-H and SO$_2$C*H*H), 3.80 (1 H, dd, *J* 12, 6, SO$_2$CH*H*), 7.59 (3 H, m, aromatic H), 7.96 (2 H, m, aromatic H) and 9.64 (1 H, d, *J* 2, 1-H); *m*/*z* (CI) 258 (M^+ + 18, 100%) and 241 (M^+ + 1, 35).

Following this procedure, the (2*S*)-enantiomer of the title compound (+)-**7**, $[\alpha]_D$ +63.2 (*c* 1.0 in $CHCl_3$), was prepared from the (2*S*,3*S*)-enantiomer of the sulfone (+)-**12**.

(2*E*,6*E*)-3,7-Dimethyl-8-(*tert*-butyldimethylsilyloxy)octa-2,6-dienal 14

The alcohol **13**[14] (5.68 g, 20 mmol) in DMF (10 cm^3) was added to a stirred, cooled (0 °C) solution of pyridinium dichromate (9.4 g, 25 mmol) in DMF (20 cm^3). After 4 h, the reaction was diluted with water (200 cm^3) and extracted with ether (6 × 100 cm^3). The combined organic extracts were filtered through a short pad of Florisil and concentrated under reduced pressure to give the *title compound* **14** (4.4 g, 78%), as a pale yellow oil which was used without futher purification; ν_{max}/cm^{-1} 2845,

1675, 1630, 1610, 1250, 1194, 1115, 1070, 840 and 775; δ_H 0.06 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 1.62 (3 H, d, *J* 2, 7-Me), 2.17 (3 H, s, 3-Me), 2.28 (4 H, m, 4-H_2 and 5-H_2), 4.00 (2 H, s, 8-H_2), 5.38 (1 H, m, 6-H), 5.90 (1 H, br d, *J* 8, 2-H) and 10.00 (1 H, d, *J* 8, 1-H); *m*/*z* (CI) 283 ($M^+ + 1$, 75%), 225 (60) and 151 (100).

Ethyl (4*E*,8*E*)-5,9-dimethyl-3-hydroxy-10-(*tert*-butyldimethylsilyloxy)deca-4,8-dienoate 15

Ethyl acetate (0.97 cm^3, 10 mmol) in tetrahydrofuran (10 cm^3) was added to a solution of lithium diisopropylamide (11 mmol) in tetrahydrofuran (20 cm^3) at −78 °C over 15 min. After a further 15 min, the aldehyde **14** (2.54 g, 9 mmol) in tetrahydrofuran (5 cm^3) was added dropwise and the reaction stirred for 2 h. Water (20 cm^3) was added and the reaction extracted into ether (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (6:1) as eluent gave the *title compound* **15** (2.5 g, 75%), as a colourless oil; ν_{max}/cm^{-1} 3430, 1730, 1250, 1070, 1020, 840 and 775; δ_H 0.07 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.62 (3 H, s, 9-Me), 1.73 (3 H, s, 5-Me), 2.10 (4 H, m, 6-H_2 and 7-H_2), 2.46 (1 H, dd, *J* 16, 4, 2-H), 2.57 (1 H, dd, *J* 16, 7, 2-H), 3.74 (1 H, br s, OH), 4.00 (2 H, s, 10-H_2), 4.18 (2 H, q, *J* 7, CH_2CH_3), 4.82 (1 H, m, 3-H), 5.23 (1 H, d, *J* 10, 4-H) and 5.37 (1 H, m, 8-H); *m*/*z* (CI) 353 (25%) and 221 (100).

Dimethyl [(5*E*,9*E*)-6,10-dimethyl-4-hydroxy-2-oxo-11-(*tert*-butyldimethylsilyloxy)undeca-5,9-dienyl]phosphonate 17

Butyllithium (30 mmol) was added to a solution of dimethyl methylphosphonate (3.6 cm^3, 33 mmol) in tetrahydrofuran (60 cm^3) at −78 °C. The mixture was stirred for 1 h and the hydroxy ester **15** (3.7 g, 10 mmol) in tetrahydrofuran (10 cm^3) was added dropwise. After 1 h, water (10 cm^3) was added and the mixture poured into ether (250 cm^3). The aqueous layer was acidified to pH 2 and extracted with ether (3 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate–methanol (10:2:1) as eluent gave the *title compound* **17** (4.0 g, 90%), as a colourless oil (Found: C, 56.4; H, 9.5; P, 6.8. $C_{21}H_{41}O_6PSi$ requires C, 56.2; H, 9.2; P, 6.9%); ν_{max}/cm^{-1} 3340, 1710, 1250, 1035, 840 and 780; δ_H 0.08 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 1.60 (3 H, s, 10-Me), 1.73 (3 H, s, 6-Me), 2.05 and 2.15 (each 2 H, m, 7-H_2 and 8-H_2), 2.75 (1 H, dd, *J* 16, 3, 3-H), 2.77 (1 H, br s, OH), 2.83 (1 H, dd, *J* 16, 10, 3-H), 3.17 (2 H, d, *J* 23, 1-H_2), 3.76 and 3.81 (each 3 H, d, *J* 11, OMe), 4.00 (2 H, s, 11-H_2), 4.85 (1 H, m, 4-H), 5.22 (1 H, d, *J* 8, 5-H) and 5.37 (1 H, m, 9-H); *m*/*z* (EI) 448 (M^+).

Dimethyl [(5*E*,9*E*)-6,10-dimethyl-4-(1-ethoxyethoxy)-2-oxo-11-(*tert*-butyldimethylsilyloxy)undeca-5,9-dienyl]phosphonate 18

A mixture of the keto phosphonate **17** (3.27 g, 7.3 mmol), ethyl vinyl ether (1.2 cm^3, 22 mmol) and pyridinium toluene-*p*-sulfonate (90 mg, 0.36 mmol) in CH_2Cl_2 (7 cm^3) was stirred for 3 h at room temperature. Solid Na_2CO_3 was added and the reaction diluted with ether (50 cm^3). The solids were removed by filtration and the filtrate concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (1.5:1) as eluent gave the *title compound* **18** (1.25 g, 73%) as a pale yellow oil; ν_{max}/cm^{-1} 1720, 1250, 1035, 840 and 775; δ_H 0.07 (6 H, s, $SiMe_2$), 0.93 (9 H, s, Me_3CSi), 1.22 (6 H, m, CH_3CH_2 and CH_3CHOEt of both isomers), 1.62 (3 H, s, 10-Me), 1.70 and 1.73 (each 1.5 H, s, 6-Me), 2.03 and 2.13 (each 2 H, m, 7-H_2 and 8-H_2), 2.63 and 2.92 (each 1 H, m, 3-H), 3.18 (2 H, m, 1-H_2), 3.5 (2 H, m, CH_2CH_3), 3.80 (6 H, d, *J* 11, OMe × 2), 4.00 (2 H, s, 11-H_2), 4.63 (1 H, q, *J* 5, OCHO), 4.67 and 4.88 (each 0.5 H, m, 4-H), 5.00 and 5.17 (each 0.5 H, d, *J* 8, 5-H) and 5.35 (1 H, m, 9-H); *m*/*z* (EI) 520 (M^+).

(2*E*,6*E*,11*E*)-2,6,14-Trimethyl-8-(1-ethoxyethoxy)-10-oxo-13-(phenylsulfonylmethyl)-1-(*tert*-butyldimethylsilyloxy)pentadeca-2,6,11-triene 19

To a stirred suspension of sodium hydride (0.26 g of a 50% dispersion, 5.5 mmol, washed with 2 × 5 cm^3 DME) in DME (12 cm^3) was added a solution of the keto phosphonate **18** (2.6 g, 5 mmol) in DME (6 cm^3). The resultant dark red solution was stirred for 1 h and the aldehyde (±)-**7** (1.1 g, 4.6 mmol) in DME (5 cm^3) added dropwise. The reaction was stirred for 18 h, water (10 cm^3) was added and the mixture extracted with ether (4 × 25 cm^3). The combined ethereal extracts were washed with water (20 cm^3) and brine (20 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (4:1) as eluent gave the *title compound* **19** (3.0 g, 65%), as a pale yellow oil, a mixture of diastereoisomers; ν_{max}/cm^{-1} ($CHCl_3$) 1670, 1630, 1320, 1310, 1250, 1150, 1090, 840 and 690; δ_H 0.06 (6 H, s, $SiMe_2$), 0.90 (6 H, m, 2 × Me), 0.94 (9 H, s, Me_3CSi), 1.2 (6 H, m, 2 × Me), 1.60 (3 H, s, 2-Me), 1.70 (3 H, m, 6-Me), 1.90 (1 H, m, 14-H), 2.05 and 2.15 (each 2 H, m, 4-H_2 and 5-H_2), 2.41 and 2.49 (each 0.5 H, dd, *J* 15, 5, 9-H), 2.68 (1 H, m, 13-H), 2.78 and 2.85 (each 0.5 H, dd, *J* 15, 7.5, 9-H), 3.25 (2 H, m, SO_2CH_2), 3.51 (2 H, m, CH_2CH_3), 4.00 (2 H, s, 1-H_2), 4.67 (1 H, m, OCHO), 4.85 (1 H, m, 8-H), 5.00 (1 H, m, 7-H), 5.37 (1 H, m, 3-H), 5.97 and 6.02 (each 0.5 H, d, *J* 16, 11-H), 6.45 and 6.51 (each 0.5 H, dd, *J* 16, 5, 12-H), 7.56 (2 H, m, aromatic H), 7.62 (1 H, m, aromatic H) and 7.87 (2 H, m, aromatic H); *m*/*z* (CI) 652 ($M^+ + 18$, 75%), 562 (45), 545 (42) and 413 (100).

(2*E*,6*E*)-2,6-Dimethyl-8-(*tert*-butyldimethylsilyloxy)octa-2,6-dien-1-ol 23

To a stirred mixture of selenium dioxide (1.11 g, 10 mmol) and salicylic acid (2.76 g, 20 mmol) in CH_2Cl_2 (50 cm^3) at room temperature was added a CH_2Cl_2 extract (50 cm^3) of *tert*-butyl hydroperoxide (70%; 50 g, 0.38 mol). After 10 min, geraniol *tert*-butyldimethylsilyl ether **22**[19] (55 g, 0.2 mol) in CH_2Cl_2 (50 cm^3) was added slowly and the reaction stirred for 30 h. Aqueous KOH (10%) was added and the mixture extracted into ether (3 × 300 cm^3). The combined extracts were washed with brine (2 × 200 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The excess of *tert*-butyl hydroperoxide was removed by **careful** distillation under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (16:1 to 8:1) as eluent gave the *title compound* **23** (23 g, 40%), as a pale yellow oil; ν_{max}/cm^{-1} 3367, 1671, 1255, 1008, 837 and 777; δ_H 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Me_3CSi), 1.64 and 1.68 (each 3 H, s, Me), 2.05 and 2.15 (each 2 H, m), 4.00 (2 H, s, 1-H_2), 4.18 (2 H, d, *J* 8, 8-H_2), 5.28 (1 H, t, *J* 8, 3-H) and 5.38 (1 H, t, *J* 8, 7-H); irradiation at δ 4.00 (1-H_2) enhanced the signal at δ 5.28 (3-H) by 20%; *m*/*z* (EI) 135 (35%) and 109 (20).

(2*E*,6*E*)-2,6-Dimethyl-1-iodo-8-(*tert*-butyldimethylsilyloxy)octa-2,6-diene 24

To a stirred, cooled (0 °C) solution of the alcohol **23** (5.68 g, 20 mmol), triphenylphosphine (6.8 g, 26 mmol) and imidazole (1.8 g, 26 mmol) in ether (60 cm^3) and acetonitrile (40 cm^3) was added iodine (6.6 g, 26 mmol) in portions over 10 min. The resultant brown slurry was stirred for 1 h, diluted with ether (250 cm^3) and washed with saturated aqueous Na_2SO_3 (150 cm^3), saturated aqueous $CuSO_4$ (150 cm^3) and water (100 cm^3). The organic layer was concentrated under reduced pressure and the residue taken up in light petroleum–ether (2:1; 300 cm^3) and filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure to give the iodide **24** as a pale yellow oil (5.9 g, 75%) which was used immediately, without purification.

(2*RS*)- and (2*S*)-2-(1′,3′-Dioxolan-2′-yl)-3-methylbutyl phenyl sulfone (±)-25 and (−)-25

A mixture of the aldehyde (±)-**7** (4.8 g, 20 mmol), ethane-1,2-diol (6.0 cm^3, 100 mmol) and toluene-*p*-sulfonic acid (0.19 g, 1 mmol) in benzene (100 cm^3) was heated under reflux for 6 h using a Dean–Stark apparatus. The mixture was cooled, diluted with ether (100 cm^3) and washed with saturated aqueous $NaHCO_3$ (100 cm^3). The aqueous layer was extracted with ether (2 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (2:1) as eluent gave the *title compound* (±)-**25** (5.4 g, 95%), as a colourless solid, mp 76–77 °C (Found: M^+, 302.1427. $C_{14}H_{24}NO_4S$ requires *M*, 302.1426); $\nu_{max}(CHCl_3)/cm^{-1}$ 1290, 1235, 1130, 1080, 1020, 970, 750 and 690; δ_H 0.93 and 0.96 (each 3 H, d, *J* 6, Me), 2.12 (1 H, m, 3-H), 2.31 (1 H, m, 2-H), 3.07 (1 H, dd, *J* 16, 8, 1-H), 3.33 (1 H, dd, *J* 16, 5, 1-H), 3.80 (4 H, m, OCH_2CH_2O), 4.89 (1 H, d, *J* 3, 2′-H), 7.58 (2 H, m, aromatic H), 7.65 (1 H, m, aromatic H) and 7.92 (2 H, m, aromatic H); *m*/*z* (CI) 302 (M^+ + 18, 37%) and 285 (M^+ + 1, 72).

Following this procedure, the (2*S*)-enantiomer of the title compound (−)-**25**, $[\alpha]_D$ −3.3 (*c* 1.0 in $CHCl_3$), was prepared from the (2*S*)-enantiomer of the aldehyde (+)-**7**.

(10*RS*,2*E*,6*E*)- and (10*S*,2*E*,6*E*)-10-(1′,3′-Dioxolan-2′-yl)-3,7,11-trimethyl-1-(*tert*-butyldimethylsilyloxy)-dodeca-2,6-diene (±)-27 and (−)-27

To a solution of the sulfone **25** (4.26 g, 15 mmol) in tetrahydrofuran (60 cm^3) at −78 °C was added butyllithium (15 mmol). The reaction was allowed to warm to −30 °C over 2 h then a solution of the freshly prepared iodide **24** (5.9 g, 15 mmol) in tetrahydrofuran (20 cm^3) was added. The reaction was warmed to room temperature over 2 h, water (50 cm^3) was added and the mixture extracted with ether (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (10:1 to 6:1) as eluent gave the sulfone (±)-**26** (6.78 g, 82%), as a viscous yellow oil, a mixture of the two diastereoisomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 1305, 1260, 1145, 1110, 1085 and 840; δ_H 0.10 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 0.98 and 1.00 (each 1.5 H, d, *J* 6, Me), 1.13 (3 H, d, *J* 6, Me), 1.28 and 1.38 (each 1.5 H, s, Me), 1.60 (3 H, m, Me), 2.00 (4 H, m, 4-H_2 and 5-H_2), 2.15 (1 H, m, 11-H), 2.30 (1 H, m, 10-H), 2.43–2.70 (2 H, m, 8-H_2), 3.63 and 3.72 (each 0.5 H, m, 9-H), 3.94 (4 H, m, OCH_2CH_2O), 4.20 (2 H, m, 1-H_2), 5.13 and 5.22 (each 0.5 H, m, 6-H), 5.28 (1 H, m, 2-H), 5.38 and 5.43 (each 0.5 H, d, *J* 5, 2′-H), 7.57 (3 H, m, aromatic H) and 7.88 (2 H, m, aromatic H); *m*/*z* (CI) 568 (M^+ + 18, 10%), 454 (23), 419 (55), 277 (60) and 215 (100).

The sulfone **26** (5.5 g, 10 mmol) and disodium hydrogen orthophosphate (3.12 g, 22 mmol) in methanol (40 cm^3) and tetrahydrofuran (60 cm^3) were treated with 6% sodium amalgam (19.1 g, 50 mmol) at room temperature. The reaction was stirred vigorously for 5 h, diluted with ether (150 cm^3) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (20:1) as eluent gave the *title compound* (±)-**27** (3.1 g, 75%) as a colourless oil (Found: M^+, 410.3208. $C_{24}H_{46}SiO_3$ requires *M*, 410.3216); ν_{max}/cm^{-1} 1254, 1111, 1065, 836 and 776; δ_H 0.08 (6 H, s, $SiMe_2$), 0.90 (15 H, m, Me_3CSi and $CHMe_2$), 1.25 (1 H, m, 10-H), 1.48 (2 H, m, 9-H_2), 1.58 and 1.60 (each 3 H, s, Me), 1.94 (1 H, m, 11-H), 2.00 (6 H, m, 4-H_2, 5-H_2 and 8-H_2), 3.82 and 3.90 (each 2 H, m, 2 × CHO), 4.20 (2 H, d, *J* 7, 1-H_2), 4.82 (1 H, d, *J* 3, 2′-H), 5.10 (1 H, m, 6-H) and 5.32 (1 H, t, *J* 7, 2-H); *m*/*z* (EI) 410 (M^+, 3%) and 409 (8).

Following these procedures, the (10*S*)-enantiomer of the title compound (−)-**27**, $[\alpha]_D$ −4.7 (*c* 1.0 in $CHCl_3$), was prepared from the (2*S*)-enantiomer of the sulfone (−)-**25**.

(10*RS*,2*E*,6*E*)- and (10*S*,2*E*,6*E*)-10-(1′,3′-Dioxolan-2′-yl)-3,7,11-trimethyldodeca-2,6-dien-1-ol (±)-28 and (−)-28

Tetrabutylammonium fluoride in tetrahydrofuran (1 M; 15 cm^3, 15 mmol) was added to a solution of the silyl ether **27** (3 g, 7.3 mmol) in tetrahydrofuran (15 cm^3) and the mixture stirred for 18 h at room temperature. Water (30 cm^3) was added and the reaction extracted with ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography eluting with light petroleum–ethyl acetate (6:1) gave the *title compound* **28** (2.05 g, 95%), as a colourless oil (Found: C, 72.65; H, 11.05. $C_{18}H_{32}O_3$ requires C, 72.9; H, 10.9%); ν_{max}/cm^{-1} 3376, 1667, 1119, 1021 and 951; δ_H 0.88 and 0.92 (each 3 H, d, *J* 6, Me), 1.36 (1 H, m, 10-H), 1.52 (2 H, m, 9-H_2), 1.61 (3 H, s, 7-Me), 1.69 (3 H, s, 3-Me), 1.96 (1 H, m, 11-H), 2.10 (6 H, m, 4-H_2, 5-H_2 and 8-H_2), 3.89 (4 H, m, OCH_2CH_2O), 4.15 (2 H, m, 1-H_2), 4.82 (1 H, d, *J* 3, 2′-H), 5.10 (1 H, m, 6-H) and 5.40 (1 H, m, 2-H); *m*/*z* (CI) 296 (M^+, 15%), 279 (19), 235 (38) and 217 (65).

Following this procedure, the (10*S*)-enantiomer of the title compound (−)-**28**, $[\alpha]_D$ −3.0 (*c* 1.0 in $CHCl_3$), was prepared from the (10*S*)-enantiomer of the silyl ether (−)-**27**.

(2*E*,6*E*)-1-Bromo-10-(1′,3′-dioxolan-2′-yl)-3,7,11-trimethyl-dodeca-2,6-diene 29

Dimethyl sulfide (0.45 cm^3, 5.4 mmol) was added dropwise to a stirred, cooled (0 °C) suspension of *N*-bromosuccinimide (0.81 g, 4.5 mmol) in CH_2Cl_2 (12 cm^3). After 15 min, the reaction was cooled to −20 °C and the alcohol **28** (0.88 g, 3 mmol) was added dropwise in CH_2Cl_2 (3 cm^3). The reaction was warmed to 0 °C and stirred for 4 h before being diluted with ether (30 cm^3) and water (15 cm^3). The aqueous layer was extracted with ether (2 × 15 cm^3) and the combined extracts washed with brine (2 × 15 cm^3). The ether layer was filtered through a short plug of silica gel and concentrated under reduced pressure to give the *title compound* **29** (0.9 g, 83%), as a yellow oil which was used immediately; ν_{max}/cm^{-1} 1462, 1378, 1256, 1116, 1065, 947, 837 and 776; δ_H 0.85 and 0.90 (each 3 H, d, *J* 6, Me), 1.25 (6 H, br s, 2 × Me), 1.45 (1 H, m, 10-H), 1.65 (2 H, m, 9-H_2), 1.95 (1 H, m, 11-H), 2.10 (6 H, m, 4-H_2, 5-H_2 and 8-H_2), 3.8 (4 H, m, OCH_2CH_2O), 4.22 (2 H, d, *J* 8, 1-H_2), 4.82 (1 H, d, *J* 3, 2′-H), 5.15 (1 H, m, 6-H) and 5.30 (1 H, t, *J* 8, 2-H); *m*/*z* (CI) 279 (15%) and 217 (82).

Dimethyl [(5*E*,9*E*)-13-(1′,3′-dioxolan-2′-yl)-6,10,14-trimethyl-2-oxopentadeca-5,9-dienyl]phosphonate 30

To a stirred suspension of sodium hydride (80 mg of a 50% dispersion washed with 2 × 0.5 cm^3 tetrahydrofuran, 1.7 mmol) in tetrahydrofuran (3.5 cm^3) was added dimethyl (2-oxopropyl)phosphonate (0.21 cm^3, 1.5 mmol). The resulting white slurry was stirred vigorously for 1 h and then cooled to 0 °C. Butyllithium (1.6 mmol) was added to give a clear, yellow solution which was stirred for 30 min. The bromide **29** (0.36 g, 1 mmol) in tetrahydrofuran (2 cm^3) was added dropwise and the mixture stirred for 1 h at room temperature. Water (5 cm^3) was added and the reaction extracted with ether (10 cm^3). The aqueous layer was acidified to pH 2 and extracted with ether (2 × 10 cm^3). The combined ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography with gradient elution using light petroleum–ethyl acetate and light petroleum–ethyl acetate–methanol (10:1 to 3:1:1) gave the *title compound* **30** (0.35 g, 78%), as a pale yellow oil (Found: M^+ − H, 444.2640. $C_{23}H_{41}O_6P$ requires *M*, 444.2641); ν_{max}/cm^{-1} 1717, 1260, 1183, 1155, 1117, 1033 and 809; δ_H 0.95 (6 H, d, *J* 6, 2 × Me), 1.38 (1 H, m, 13-H), 1.48 (2 H, m, 12-H_2), 1.59 and 1.61 (each 3 H, s, Me), 1.94 (1 H, m, 14-H), 2.05 (6 H, m, 7-H_2, 8-H_2 and 11-H_2), 2.28 (2 H, q, *J* 6, 4-H_2), 2.65 (2 H, t, *J* 6, 3-H_2), 3.07 (2 H, d, *J* 23, 1-H_2), 3.78 (6 H, d, *J* 11, 2 × OMe), 3.85 (4 H, m, OCH_2CH_2O), 4.70 (1 H, d, *J* 3, 2′-H) and 5.08 (2 H, m, 5-H and 9-H); *m*/*z* (CI) 462 (M^+ + 17, 3%), 445 (M^+, 5), 401 (19), 383 (86) and 365 (100).

(5*E*,9*E*)-14-(Dimethoxyphosphinoyl)-5,9-dimethyl-2-isopropyl-13-oxotetradeca-5,9-dienal 31

A mixture of the acetal **30** (0.22 g, 0.5 mmol) and pyridinium toluene-*p*-sulfonate (15 mg, 0.06 mmol) in acetone (10 cm^3) and water (2 cm^3) was heated under reflux for 15 h. Saturated aqueous $NaHCO_3$ (1 cm^3) was added and the acetone removed under reduced pressure. The aqueous residue was extracted with ether (3 × 10 cm^3) and the combined ethereal extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate–methanol (3:1:1) as eluent gave the *title compound* **31** (1.6 g, 80%), as a colourless oil; ν_{max}/cm^{-1} 1719, 1451, 1259, 1032 and 808; δ_H 0.94 and 0.96 (each 3 H, d, *J* 6, Me), 1.60 and 1.63 (each 3 H, s, Me), 1.75 (2 H, m, 3-H_2), 2.00 (8 H, m, 2-CH, 2-H, 4-H_2, 7-H_2 and 8-H_2), 2.29 (2 H, m, 11-H_2), 2.65 (2 H, t, *J* 8, 12-H_2), 3.06 (2 H, d, *J* 23, 14-H_2), 3.77 (6 H, d, *J* 11, 2 × OMe), 5.08 (2 H, m, 6-H and 10-H) and 9.62 (1 H, d, *J* 2, 1-H); *m*/*z* (CI) 401 ($M^+ + 1$, 28%), 383 (56) and 365 (59).

(2*E*,7*E*,11*E*)-7,11-Dimethyl-4-isopropylcyclotetradeca-2,7,11-trien-1-one 32

The aldehyde **31** (150 mg, 0.37 mmol) in acetonitrile (5 cm^3) was added to a stirred suspension of lithium chloride (150 mg, 35 mmol) in acetonitrile (150 cm^3) at 40 °C. DBU (0.55 mmol) in acetonitrile (15 cm^3) was added over 15 h *via* a syringe pump. After an additional 1 h, the reaction was cooled, filtered through a short pad of silica gel and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (20:1) as eluent gave the *title compound* **32**[16] (64 mg, 63%), as a colourless oil (Found: M, 274.2288. $C_{19}H_{30}O$ requires *M*, 274.2321); ν_{max}/cm^{-1} 1687, 1664, 1621, 1444, 1385, 1369, 1240, 1129, 1078, 986 and 830; δ_H 0.83 and 0.88 (each 3 H, d, *J* 6, Me), 1.45 (2 H, m, 5-H_2), 1.52 (3 H, s, 7-Me), 1.58 (3 H, s, 11-Me), 1.80 (2 H, m, C*H*Me_2 and 4-H), 2.08 (6 H, m, 6-H_2, 9-H_2 and 10-H_2), 2.28 and 2.40 (each 1 H, m, 14-H), 2.54 (2 H, m, 13-H_2), 4.82 (1 H, m, 8-H), 5.10 (1 H, m, 12-H), 6.10 (1 H, d, *J* 16, 2-H) and 6.56 (1 H, dd, *J* 16, 8, 3-H); *m*/*z* (CI) 275 ($M^+ + 1$, 100%) and 257 (19).

(2*E*,7*E*,11*E*)-4-Isopropyl-1,7,11-trimethylcyclotetradeca-2,7,11-trien-1-ols 3 and 4

Methylmagnesium iodide (0.6 mmol) in ether (0.2 cm^3) was added to a solution of the cyclic ketone **32** (30 mg, 0.11 mmol) in ether (2 cm^3) at −10 °C. The resultant white suspension was stirred for 4 h then saturated aqueous NH_4Cl was added. Water (2 cm^3) was added and the mixture extracted with ether (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (15:1) as eluent gave a mixture of the thunbergols **3** and **4** (22 mg, 65%), **3**:**4** = 10:90. These were separated by HPLC using light petroleum–ethyl acetate (15:1) as eluent. (±)-Thunbergol **3**:[9,25] ν_{max}/cm^{-1} 3411, 1658, 1443, 1368, 1180, 1110, 1100, 1073, 1035 and 976; δ_H 0.82 and 0.86 (each 3 H, d, *J* 6, Me), 1.30 (4 H, m, 5-H_2 and 14-H_2), 1.32 (3 H, s, 1-Me), 1.52 (3 H, s, 7-Me), 1.60 (3 H, s, 11-Me), 1.65 (1 H, m, 4-CH), 1.95 (3 H, m, 6-H_2 and 4-H), 2.00–2.15 (4 H, m, 9-H_2 and 10-H_2), 2.25 and 2.40 (each 1 H, m, 13-H), 5.00 (1 H, m, 8-H), 5.2 (1 H, m, 12-H), 5.28 (1 H, dd, *J* 16, 3, 3-H) and 5.72 (1 H, d, *J* 16, 2-H);‡ *m*/*z* (CI) 289 ($M^+ - 1$, 26%), 223 (25) and 202 (26). (±)-Epithunbergol **4**:[9,25] ν_{max}/cm^{-1} 3400, 1444, 1384, 1367, 1155, 1098 and 975; δ_H 0.82 and 0.86 (each 3 H, d, *J* 6, Me), 1.30 (3 H, s, 1-Me), 1.58 (11 H, m, 4-CH, 5-H_2, 7-Me, 11-Me and 14-H_2), 1.88 (1 H, m, 4-H), 2.09 (6 H, m, 6-H_2, 9-H_2 and 10-H_2), 2.22 (2 H, m, 13-H_2), 5.03 (1 H, m, 8-H), 5.20 (1 H, t, *J* 5, 12-H), 5.28 (1 H, dd, *J* 16, 8, 3-H) and 5.56 (1 H, d, *J* 16, 2-H);‡ δ_C 14.815, 15.132, 19.373, 20.668, 23.504, 23.693, 27.966, 29.326, 33.023, 36.878, 39.031, 44.057, 46.152, 73.849, 124.848, 126.998, 127.806, 132.613, 132.889 and 138.797; (lit.,[9,25] 14.8, 15.1, 19.4, 20.7, 23.5, 23.7, 28.0, 29.3, 33.1, 36.9, 39.1, 44.1, 46.2, 73.8, 124.9, 126.9, 127.9, 132.4, 132.7 and 138.9); *m*/*z* (CI) 289 ($M^+ - 1$, 100%), 272 (47), 253 (22), 239 (35) and 223 (40).

‡ IUPAC numbering.

(2*E*,6*E*,10*E*)-14-Isopropyl-3,7,11-trimethylcyclotetradeca-2,6,10-trien-1-one 34

To a stirred suspension of pyridinium chlorochromate (110 mg, 0.51 mmol) and alumina (550 mg) in CH_2Cl_2 (1 cm^3) at room temperature was added the epithunbergol **4** (50 mg, 0.17 mmol) in CH_2Cl_2 (0.5 cm^3). The reaction was stirred for 24 h, diluted with ether (5 cm^3) and decanted. The residue was washed with ether (4 × 5 cm^3) and the combined extracts filtered through a short pad of silica gel and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (30:1) as eluent gave the ketone **34**[27,28] (30 mg, 60%), as a colourless oil; ν_{max}/cm^{-1} 1682, 1616, 1440, 1386, 1164, 1081 and 840; δ_H 0.86 and 0.88 (each 3 H, d, *J* 6, Me), 1.52 (3 H, s, 11-Me), 1.60 (3 H, s, 7-Me), 1.7 (3 H, m, 14-CH and 13-H_2), 2.07 (7 H, m, 1-H, 8-H_2, 9-H_2 and 12-H_2), 2.11 (3 H, s, 3-Me), 2.23 (4 H, m, 4-H_2 and 5-H_2), 4.83 (1 H, m, 10-H), 4.95 (1 H, m, 6-H) and 5.88 (1 H, s, 2-H); *m*/*z* (CI) 289 ($M^+ + 1$, 100%), 202 (75) and 185 (81).

(2*S*,3*R*)-2,3-Epoxy-4-(*tert*-butyldimethylsilyloxy)butan-1-ol 38

(+)-Diethyl tartrate (7.6 cm^3, 45 mmol) was added to a stirred solution of titanium(IV) isopropoxide (13 cm^3, 45 mmol) in CH_2Cl_2 (500 cm^3) at −23 °C containing powdered, flame-dried 4 Å molecular sieves. After 10 min, the alcohol **37** (10.1 g, 50 mmol) in CH_2Cl_2 (10 cm^3) was added followed by anhydrous *tert*-butyl hydroperoxide in benzene (3.75 M; 20 cm^3, 75 mmol). The reaction was stored at −25 °C for 48 h, then water (200 cm^3) was added and the resultant slurry stirred for 1 h. Aqueous NaOH (30%; 40 cm^3, saturated with NaCl) was added and the mixture stirred for 30 min. The white precipitate was removed by filtration through Celite and the aqueous layer of the filtrate extracted with CH_2Cl_2 (2 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (4:1) as eluent gave the *title compound* **38** (9.8 g, 90%), as a pale yellow oil, $[a]_D$ −14.9 (*c* 1.0 in $CHCl_3$) (Found: MH^+, 219.1414. $C_{10}H_{23}O_3Si$ requires *M*, 219.1416); ν_{max}/cm^{-1} 3390, 1360, 1255, 1155, 1095, 1040, 940, 835 and 785; δ_H 0.12 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 2.22 (1 H, t, *J* 6, OH), 3.23 (2 H, m, 2-H and 3-H), 3.78 (3 H, m) and 3.93 (1 H, dd, *J* 12, 5); *m*/*z* (CI) 219 ($MH^+ + 1$, 96%), 201 (55) and 185 (43).

A solution of the epoxy alcohol **38** (42 mg, 0.21 mmol), (*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (70 cm^3, 0.42 mmol) and pyridine (0.25 cm^3) in CH_2Cl_2 (0.7 cm^3) was stirred at room temperature for 48 h. Water (0.5 cm^3) was added and the reaction extracted with ether (2 × 5 cm^3). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (8:1) as eluent gave the ester **39** (70 mg, 80%); δ_H 0.12 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 3.32 (2 H, m, 2-H and 3-H), 3.57 (3 H, s, OMe), 3.67 (2 H, m, 4-H_2), 4.37 (1 H, dd, *J* 12, 6, 1-H), 4.52 (1 H, dd, *J* 12, 4, 1-H′) and 7.45 (5 H, m, aromatic H); δ_F −73.55 (10) and −73.63 (90) [*cf*. ester from the racemic alcohol (±)-**38**; δ_F −73.55 (50) and −73.63 (50)].

(2*S*,3*S*)-2-Isopropenyl-4-(*tert*-butyldimethylsilyloxy)butane-1,3-diol 40

Propen-2-ylmagnesium bromide (40 mmol) in tetrahydrofuran (40 cm^3) was added to a stirred suspension of cuprous iodide (0.7 g, 3.69 mmol) in ether (120 cm^3) at −23 °C over 20 min. The epoxy alcohol **38** (2.69 g, 12.3 mmol) in ether (10 cm^3) was added dropwise and the mixture stirred for 15 h. Saturated aqueous NH_4Cl was added until precipitation was complete

and the mixture decanted. The granular salts were washed with ether (3 × 50 cm^3) and the combined ethereal extracts washed with saturated aqueous NH_4Cl (adjusted to pH 8 using concentrated aqueous NH_4OH; 250 cm^3) and brine (200 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (4:1) as eluent gave the *title compound* **40** (2.40 g, 75%), as a colourless oil, $[\alpha]_D$ −4.3 (*c* 1.0 in $CHCl_3$) (Found: $M^+ + H$, 261.1891. $C_{13}H_{29}O_3Si$ requires *M*, 261.1886); ν_{max}/cm^{-1} 3380, 1255, 1120, 1090, 1040, 1005, 890, 840 and 780; δ_H 0.13 (6 H, s, $SiMe_2$), 0.95 (9 H, s, Me_3CSi), 1.67 (1 H, br s, OH), 1.83 (3 H, s, 1′-Me), 2.27 (1 H, br s, OH), 2.47 (1 H, m, 2-H), 3.73 (5 H, m, 3-H, 1-H_2 and 4-H_2) and 4.90 and 5.02 (each 1 H, br s, 1′-H); *m*/*z* (CI) 261 ($M^+ + 1$, 100%), 243 (17), 213 (39) and 192 (98).

A solution of the diol **40** (50 mg, 0.2 mmol) and toluene-*p*-sulfonic acid (2 mg) in 2,2-dimethoxyethane (1 cm^3) was stirred for 3 h. Solid Na_2CO_3 (200 mg) was added and, after a further 15 min, the mixture was filtered and the filtrate concentrated under reduced pressure to give the acetonide **43** as a colourless oil (55 mg, 92%); δ_H 0.06 and 0.07 (each 3 H, s, SiMe), 0.90 (9 H, s, Me_3CSi), 1.52 and 1.60 (each 3 H, s, Me), 1.92 (3 H, s, 1′-Me), 2.17 (1 H, m, 2-H), 3.57 (2 H, d, *J* 7, 3-CH_2), 3.80 (1 H, dd, *J* 12, 1.5, 1-H), 4.11 (1 H, m, 3-H), 4.20 (1 H, dd, *J* 12, 4, 1-H′) and 4.88 and 4.93 (each 1 H, br s, 1′-H).

(2*S*,3*S*)-2-Isopropyl-4-(*tert*-butyldimethylsilyloxy)butane-1,3-diol 41

A solution of the alkene **40** (1.05 g, 4 mmol) and tris(triphenylphosphine)rhodium(I) chloride (100 mg, 0.11 mmol) in benzene (15 cm^3)–ethanol (5 cm^3) was stirred at room temperature under an atmosphere of hydrogen for 18 h. The reaction was diluted with ether (100 cm^3), filtered through a pad of silica gel and concentrated under reduced pressure. The residue was distilled to give the *title compound* **41** (0.84 g, 80%), as a colourless oil, bp 115 °C/0.1 mmHg; $[\alpha]_D$ +10.9 (*c* 1.0 in $CHCl_3$) (Found: C, 59.6; H, 11.85. $C_{13}H_{30}O_3Si$ requires C, 59.5; H, 11.55%); ν_{max}/cm^{-1} 3380, 1255, 1110, 1090, 1040, 980, 835, 780 and 735; δ_H 0.12 (6 H, s, $SiMe_2$), 0.92 (9 H, s, Me_3CSi), 0.97 and 1.00 (each 3 H, d, *J* 6, Me), 1.61 (1 H, m, C*H*Me_2), 1.97 (1 H, m, 2-H), 2.80 (2 H, br s, 2 × OH) and 3.8 (5 H, m, 1-H_2, 3-H and 4-H_2); *m*/*z* (CI) 263 ($M^+ + 1$, 100%) and 203 (16).

(2*S*,3*S*)-3-Isopropylbutane-1,2,4-triol 42

A solution of the silyl ether **41** (1.36 g, 5.2 mmol) in tetrahydrofuran (15 cm^3) containing aqueous hydrogen chloride (10%; 3 cm^3) was stirred for 3 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ (10 cm^3) and extracted with ethyl acetate (4 × 25 cm^3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate–methanol (5:1:1) as eluent gave the *title compound* **42** (0.7 g, 90%), mp 18–20 °C; $[\alpha]_D$ +1.58 (*c* 1.0 in $CHCl_3$) (Found: $M^+ + H$, 149.1174. $C_7H_{19}O_3$ requires *M*, 149.1178); $\nu_{max}(CHCl_3)/cm^{-1}$ 3369, 1055 and 980; δ_H 0.98 and 1.06 (each 3 H, d *J* 6, Me), 1.65 (1 H, m, 3-H), 1.95 (1 H, m, C*H*Me_2), 2.85 (3 H, br s, OH) and 3.8 (5 H, m, 1-H_2, 2-H and 4-H_2); *m*/*z* (CI) 149 ($M^+ + 1$, 55%) and 113 (100).

(2*S*)-2-Isopropyl-3-(phenylsulfonyl)propan-1-ol (−)-44

Sodium borohydride (150 mg, 4 mmol) was added to a solution of the aldehyde (+)-**7** (0.24 g, 1 mmol) in tetrahydrofuran–methanol (2 cm^3). The mixture was stirred for 8 h and water (2 cm^3) and ether (10 cm^3) were added. The ethereal layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* (−)-**44** (0.22 g, 90%), as a colourless oil, $[\alpha]_D$ −13.4 (*c* 1.0 in $CHCl_3$) (Found: $M^+ + NH_4$, 260.1327. $C_{12}H_{22}NO_3S$ requires *M*, 260.1320); ν_{max}/cm^{-1} 3520, 1450, 1300, 1145, 1090, 1050, 745 and 690; δ_H 0.85 and 0.88 (each 3 H, d, *J* 6, Me), 1.92 (1 H, m, C*H*Me_2), 2.07 (1 H, m, 2-H), 2.27 (1 H, br s, OH), 3.10 (1 H, dd, *J* 15, 2, 3-H), 3.28 (1 H, dd, *J* 15, 8, 3-H), 3.73 (1 H, dd, *J* 12, 8, 1-H), 3.87 (1 H, dd, *J* 12, 6, 1-H), 7.62 (2 H, m, aromatic H), 7.7 (1 H, m, aromatic H) and 7.96 (2 H, m, aromatic H); *m*/*z* (CI) 260 ($M^+ + 18$, 100%).

A solution of the (−)-alcohol **44** (0.12 g, 0.5 mmol), (*S*)-(+)-mandelic acid (90 mg, 0.6 mmol) and toluene-*p*-sulfonic acid (5 mg, 26 mmol) in benzene (10 cm^3) was heated under reflux for 5 h using a Dean–Stark apparatus. The mixture was poured into saturated aqueous $NaHCO_3$ (10 cm^3) and the aqueous layer extracted with ether (2 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the mandelate ester **45** (140 mg, 75%), mp 90–91 °C; $[\alpha]_D$ +36.2 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3/cm^{-1}$ 3487, 1740, 1448, 1406, 1305, 1183, 1147, 1086, 1069 and 743; δ_H 0.67 and 0.80 (each 3 H, d, *J* 6, Me), 1.67 (1 H, m, C*H*Me_2), 2.17 (1 H, m, 2-H), 3.02 (2 H, d, *J* 5, 3-H_2), 4.18 (1 H, dd, *J* 12, 5, 1-H), 4.30 (1 H, dd, *J* 12, 6, 1-H), 5.15 (1 H, s, C*H*Ph) and 7.32–7.90 (10 H, m, aromatic H); *m*/*z* (CI) 395 ($M^+ + 19$, 98%), 394 ($M^+ + 18$, 44) and 376 (M^+, 32).

(10*S*,2*E*,6*E*)-3,7,11-Trimethyl-10-(1′,3′-dioxolan-2′-yl)dodeca-2,6-dienal 46

The alcohol (−)-**28** (200 mg, 0.6 mmol) was oxidised with pyridinium dichromate (240 mg) in *N*,*N*-dimethylformamide (1 cm^3) at 0 °C, following the procedure outlined for the synthesis of the aldehyde **14**, to give the *title compound* **46** (150 mg, 75%) as an oil, $[\alpha]_D$ +40.0 (*c* 1.0 in $CHCl_3$), used without further purification; ν_{max}/cm^{-1} 1704, 1673, 1630, 1414, 1373, 1335, 1237, 1178, 1120 and 956; δ_H 0.92 (6 H, d, *J* 6, 2 × Me), 1.38 (1 H, m, 10-H), 1.52 (2 H, m, 9-H_2), 1.61 (3 H, s, 7-Me), 1.95 (1 H, m, 11-H), 2.08 (4 H, m, 5-H_2 and 8-H_2), 2.23 (5 H, m, 3-Me and 4-H_2), 3.88 (4 H, m, OCH_2CH_2O), 4.81 (1 H, d, *J* 3, 2′-H), 5.10 (1 H, m, 6-H), 5.89 (1 H, d, *J* 8, 2-H) and 9.99 (1 H, d, *J* 8, 1-H); *m*/*z* (CI) 311 ($M^+ + 17$, 8%), 309 (7), 294 (M^+, 10), 293 (28), 249 (17) and 233 (18).

(4*S*)-3-[(3*R*- and 3*S*-,12*S*,4*E*,8*E*)-12-(1′,3′-Dioxolan-2′-yl)-3-hydroxy-5,9,13-trimethyltetradeca-4,8-dienoyl]-4-isopropylthiazolidine-2-thiones 47 and 48

N-Ethylpiperidine (0.66 cm^3, 4.8 mmol) was added dropwise to a suspension of tin(II) trifluoromethanesulfonate (2.0 g, 4.8 mmol) in CH_2Cl_2 (10 cm^3) at −50 to −40 °C. A solution of the thiazolidine-2-thione **53** (0.81 g, 4 mmol) in CH_2Cl_2 (5 cm^3) was added, and the reaction stirred at −50 °C to −40 °C for 4 h. After addition of the aldehyde **46** (1.2 g, 4.1 mmol) in CH_2Cl_2 (4 cm^3) at −78 °C, the reaction was stirred for 1 h and then water (10 cm^3) and ether (50 cm^3) were added. The aqueous layer was extracted with ether (3 × 15 cm^3) and the combined organic extracts filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (3:1) as eluent separated the (3′*R*)- and (3′*S*)-diastereoisomers **47** and **48**. First off the column was the less polar (3′*S*)-isomer of the *title compound* **48** (0.3 g, 15%), a yellow oil, $[\alpha]_D$ +38.0 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3466, 1701, 1367, 1335, 1195, 1150, 1119, 1013 and 957; δ_H 0.90 and 0.95 (each 3 H, d, *J* 6, Me), 0.92 (6 H, d, *J* 6, 2 × Me), 1.39 (1 H, m, 12′-H), 1.45 (2 H, m, 11′-H_2), 1.60 (3 H, s, 9′-Me), 1.68 (3 H, s, 5′-Me), 1.94 (1 H, m, 13′-H), 2.10 (6 H, m, 6′-H_2, 7′-H_2 and 10′-H_2), 2.49 (1 H, m, C*H*Me_2), 2.88 (1 H, br s, OH), 3.50 (1 H, dd, *J* 15, 3, 2′-H), 3.60 (1 H, dd, *J* 15, 8, 2′-H′), 3.82 and 3.94 (each 2 H, m, OCH_2), 4.40 (2 H, m, 5-H_2), 4.72 (1 H, m, 4-H), 4.82 (1 H, d, *J* 3, OCHO), 4.90 (1 H, dt, *J* 3, 8, 3′-H), 5.10 (1 H, m, 8′-H) and 5.22 (1 H, br d, *J* 8, 4′-H); *m*/*z* (CI) 464 (12%), 448 (18), 420 (10), 404 (100) and 386 (75). The second product off the column was the more polar (3′*R*)-isomer of the *title compound* **47** (1.49 g, 75%) as a yellow oil, $[\alpha]_D$ +92.0 (*c* 1.0 in $CHCl_3$) (Found: $M^+ + H$, 498.2795.

$C_{26}H_{44}NO_4S_2$ requires *M*, 498.2712); ν_{max}/cm^{-1} 3436, 1701, 1367, 1340, 1197, 1150, 1119, 1013 and 956; δ_H 0.90 and 0.95 (each 3 H, d, *J* 6, Me), 0.93 (6 H, d, *J* 6, 2 × Me), 1.39 (1 H, m, 12′-H), 1.45 (2 H, m, 11′-H_2), 1.60 (3 H, s, 9′-Me), 1.73 (3 H, s, 5′-Me), 1.94 (1 H, m, 13′-H), 2.10 (6 H, m, 6′-H_2, 7′-H_2 and 10′-H_2), 2.49 (1 H, m, C*H*Me$_2$), 2.64 (1 H, br s, OH), 3.45 (1 H, dd, *J* 15, 8, 2′-H), 3.60 (1 H, dd, *J* 15, 3, 2′-H′), 3.82 and 3.94 (each 2 H, m, OCH_2), 4.40 (2 H, m, 5-H_2), 4.72 (1 H, m, 4-H), 4.82 (1 H, d, *J* 3, OCHO), 4.94 (1 H, dt, *J* 3, 8, 3′-H), 5.10 (1 H, m, 8′-H) and 5.22 (1 H, br d, *J* 8, 4′-H); *m*/*z* (CI) 464 (13%), 404 (31) and 386 (17).

Dimethyl [(4*R*,13*S*,5*E*,9*E*)-13-(1′,3′-dioxolan-2′-yl)-4-hydroxy-6,10,14-trimethyl-2-oxopentadeca-5,9-dienyl]phosphonate 49

Butyllithium (5.6 mmol) in hexane was added to dimethyl methylphosphonate (0.61 cm^3, 5.6 mmol) in tetrahydrofuran (10 cm^3) at −78 °C. After 1 h at this temperature, the amide **47** (700 mg, 1.4 mmol) in tetrahydrofuran (5 cm^3) was added and the mixture stirred for 1 h. Water and ether were added and the aqueous layer was separated, acidified and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate–methanol (5:2:1) as eluent gave the *title compound* **49** (500 mg, 77%), $[\alpha]_D$ −5.2 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 1714, 1251, 1118, 1033 and 816; δ_H 0.88 (6 H, d, *J* 6, 2 × Me), 1.30 (1 H, m, 13-H), 1.45 (2 H, m, 12-H_2), 1.55 (3 H, s, 10-Me), 1.66 (3 H, s, 6-Me), 1.88 (1 H, m, 14-H), 2.02 (6 H, m, 7-H_2, 8-H_2 and 11-H_2), 2.69 (1 H, dd, *J* 8, 3, 3-H), 2.80 (1 H, dd, *J* 16, 8, 3-H), 3.12 (2 H, d, *J* 23, 1-H_2), 3.75 (6 H, d, *J* 11, 2 × OMe), 3.70 and 3.90 (each 2 H, m, OCH_2), 4.75 (2 H, m, 4-H and 2′-H), 5.05 (1 H, m, 9-H) and 5.15 (1 H, br d, *J* 8, 5-H); *m*/*z* (CI) 460 (M^+, 8%), 443 (41), 422 (19), 404 (100) and 381 (53).

Dimethyl [(4*R*,13*S*,5*E*,9*E*)-4-(*tert*-butyldiphenylsilyloxy)-13-(1′,3′-dioxolan-2′-yl)-6,10,14-trimethyl-2-oxopentadeca-5,9-dienyl]phosphonate 50

tert-Butyldiphenylsilyl chloride (0.5 cm^3, 2 mmol) was added to a solution of imidazole (0.38 g, 5.6 mmol) in *N*,*N*-dimethylformamide (2 cm^3) at room temperature and the mixture stirred for 30 min. The alcohol **49** (0.84 g, 1.8 mmol) in *N*,*N*-dimethylformamide (2 cm^3) was added dropwise and the mixture stirred for 5 h. Water (10 cm^3) and ether (20 cm^3) were added and the aqueous layer extracted with ether (3 × 20 cm^3). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **50** (70%), $[\alpha]_D$ +17.6 (*c* 1.0 in $CHCl_3$) (Found: $M^+ - C_4H_9$, 641.3079. $C_{35}H_{52}O_7PSi$ requires *M*, 641.3063); ν_{max}/cm^{-1} 1717, 1263, 1187, 1112, 1033, 944, 823, 741 and 704; δ_H 0.85 (6 H, d, *J* 6, 2 × Me), 0.92 (9 H, s, Me_3CSi), 1.25 (1 H, m, 13-H), 1.45 (2 H, m, 12-H_2), 1.46 (3 H, s, 10-Me), 1.58 (3 H, s, 6-Me), 1.85 (7 H, m, 7-H_2, 8-H_2, 11-H_2 and 14-H), 2.65 (1 H, dd, *J* 15, 6, 3-H), 2.90 (1 H, m, 3-H), 3.10 (2 H, m, 1-H_2), 3.74 (6 H, d, *J* 11, 2 × OMe), 3.85 and 3.95 (each 2 H, m, OCH_2), 4.82 (1 H, d, *J* 2, 2′-H), 4.88 (1 H, m, 4-H), 5.05 (1 H, m, 9-H), 5.13 (1 H, d, *J* 8, 5-H) and 7.38–7.67 (10 H, m, aromatic H); *m*/*z* (CI) 641 ($M^+ - 59$, 2%).

(4*S*,13*R*,2*E*,7*E*,11*E*)-7,11-Dimethyl-4-isopropyl-13-(*tert*-butyldiphenylsilyloxy)cyclotetradeca-2,7,11-trien-1-one 52

The acetal **50** (0.38 g, 0.55 mmol) in acetone–water (5:1; 12 cm^3) was heated under reflux and pyridinium toluene-*p*-sulfonate (15 mg, 0.06 mmol) was added. After 15 h, $NaHCO_3$ (3 cm^3) was added and the mixture concentrated under reduced pressure. The aqueous layer was extracted with ether (3 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (1:1) as eluent gave (2*S*,11*R*,5*E*,9*E*)-11-(*tert*-butyldiphenylsilyloxy)-14-(dimethoxyphosphinoyl)-5,9-dimethyl-2-isopropyl-13-oxotetradeca-5,9-trienal **51** (0.28 g, 78%), $[\alpha]_D$ +24.8 (*c* 1 in $CHCl_3$); ν_{max}/cm^{-1} 1721, 1262, 1111, 1034, 823, 741 and 704; δ_H 0.95 (6 H, m, 2 × Me), 1.0 (9 H, s, Me_3CSi), 1.55–2.1 (16 H, m), 2.65 (1 H, dd, *J* 15, 5, 12-H), 2.93 (1 H, dd, *J* 15, 7.5, 12-H), 3.1 (2 H, m, 14-H_2), 3.78 (6 H, d, *J* 11, 2 × OMe), 4.87 (1 H, m, 11-H), 5.0 (1 H, m, 6-H), 5.12 (1 H, m, 11-H), 7.38 (6 H, m, aromatic H), 7.68 (4 H, m, aromatic H) and 9.65 (1 H, m, 1-H); *m*/*z* (EI) 654 (M^+, 100%).

A solution of the aldehyde **51** (110 mg, 0.18 mmol) in acetonitrile (100 cm^3) containing lithium chloride (80 mg, 1.9 mmol) was heated to 40 °C and DBU (35 cm^3, 0.22 mmol) in acetonitrile (8 cm^3) added over 16 h *via* syringe pump. The reaction was cooled, filtered through a short pad of silica gel and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (30:1) as eluent gave the *title compound* **52** (30 mg, 31%) containing *ca*. 15% of its C(1)-epimer, $[\alpha]_D$ +45.6 (*c* 1.0 in $CHCl_3$) (Found: M^+, 528.3414. $C_{35}H_{48}O_2Si$ requires *M*, 528.3423); ν_{max}/cm^{-1} 1687, 1662, 1621, 1428, 1111, 1057, 823, 740 and 703; δ_H(major diastereoisomer) 0.82 and 0.86 (each 3 H, d, *J* 6, Me), 1.00 (12 H, s, Me_3CSi and Me), 1.45 (2 H, m, 5-H_2), 1.50 (3 H, s, Me), 1.65 (4 H, m, 4-H, C*H*Me$_2$ and 6-H_2), 2.00 (4 H, m, 9-H_2 and 10-H_2), 2.60 (1 H, dd, *J* 12, 3, 14-H), 3.00 (1 H, dd, *J* 12, 9, 14-H), 4.68 (1 H, m, 8-H), 4.84 (1 H, dt, *J* 3, 8, 13-H), 5.08 (1 H, d, *J* 8, 12-H), 5.75 (1 H, d, *J* 15, 2-H), 6.55 (1 H, dd, *J* 15, 8, 3-H), 7.4 (6 H, m, aromatic H) and 7.7 (4 H, m, aromatic H); *m*/*z* (CI) 529 ($M^+ + 1$, 40%) and 471 (10).

(1*R*- and 1*S*,3*R*,12*S*,4*E*,8*E*,13*E*)-12-Isopropyl-1,5,9-trimethylcyclotetradeca-4,8,13-trien-1,3-diols 1 and 2

Methylmagnesium iodide (0.19 mmol; 3 M in ether) was added to the ketone **52** (20 mg, 0.038 mmol) in ether (0.3 cm^3) at 0 °C. After 5 h, saturated aqueous NH_4Cl and water were added. The mixture was extracted into ether and the combined ethereal extracts dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran and tetrabutylammonium fluoride (0.12 mmol) in tetrahydrofuran was added. After 15 h at room temperature, water was added and the mixture extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using benzene–ethyl acetate (10:1) as eluent gave a mixture of cembratrienediols **1** and **2** (60%). The (1*S*)- and (1*R*)-diastereoisomers **1** and **2** were separated by HPLC using ethyl acetate–light petroleum (1.5:1) as eluent, ratio **1**:**2** = 80:20. The synthetic cembratrienediols had spectroscopic and chromatographic properties identical to authentic samples; synthetic α-cembratrienediol **1**, mp 69–70 °C (lit.,[3] 65–66 °C), $[\alpha]_D$ +270 (*c* 1 in $CHCl_3$) (lit.,[3] +281; lit.,[8] +173); ν_{max}/cm^{-1} 3389, 1711, 1660, 1444, 1388, 1368, 1165, 1100, 1060, 975 and 733; *m*/*z* (CI) 289 ($M^+ - 17$, 100%) and 271 (70); synthetic β-cembratrienediol **2**, $[\alpha]_D$ +170 (*c* 1.0 in $CHCl_3$) (lit.,[3] +162); ν_{max}/cm^{-1} 3339, 1465, 1430, 1390, 1370, 1170, 1145, 1120, 1097, 1083, 1038, 975 and 924; *m*/*z* (CI) 290 ($M^+ - 16$, 15%) and 273 (100).

2-(*tert*-Butyldiphenylsilyloxymethyl)-3-methylbutyl phenyl sulfone 54

A mixture of the racemic alcohol (±)-**44** (5.0 g, 21 mmol), *tert*-butyldiphenylsilyl chloride (6.5 cm^3, 25 mmol) and imidazole (3.4 g, 50 mmol) in tetrahydrofuran–DMF (25 cm^3) was stirred for 15 h at room temperature then diluted with 25 cm^3 water. The reaction was extracted with ether (4 × 50 cm^3) and the combined ethereal extracts washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (10:1) as eluent gave the *title compound* **54** (7.6 g, 75%), as a colourless oil; ν_{max}/cm^{-1} 1471, 1447, 1428, 1307, 1238, 1148, 1111, 1085, 827, 741 and 703; δ_H 0.76 and 0.80 (each 3 H, d, *J* 6, Me), 1.02 (9 H, s, Me_3CSi), 2.00 (2 H, m, 2-H and 3-H), 3.06 (1 H, dd, *J* 12, 4, SO_2CHH), 3.30 (1 H, dd, *J* 12, 6, SO_2CHH), 3.68 (2 H, d,

J 9, $SiOCH_2$) and 7.40–7.90 (15 H, m, aromatic H); *m*/*z* (CI) 481 ($M^+ + 1$, 7%), 423 (13) and 403 (43).

(2*E*,6*E*)-3,7,11-Trimethyl-1-(*tert*-butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxymethyl)dodeca-2,6-diene 56

Following the procedure outlined for the synthesis of sulfone **26**, the racemic sulfone **54** was alkylated using the freshly prepared iodide **24** to give a mixture of diastereoisomeric sulfones **55** (85%) after flash chromatography using light petroleum–ethyl acetate (15:1 to 10:1) as eluent; ν_{max}/cm^{-1} 1589, 1472, 1447, 1428, 1390, 1304, 1255, 1146, 1112, 1083, 836, 776 and 702; δ_H 0.08 (6 H, s, $SiMe_2$), 0.90 (12 H, m, Me_3CSi and Me), 1.05 (9 H, s, Me_3CSi), 1.20–2.55 (17 H, m), 3.72 (1 H, m, 9-H), 3.90 and 4.12 (each 1 H, m, $SiOCH_2$), 4.18 (2 H, d, *J* 8, 1-H_2), 5.13 (1 H, m, 6-H), 5.28 (1 H, br t, *J* 8, 2-H) and 7.40–7.90 (10 H, m, aromatic H); *m*/*z* 536 (10%), 422 (50) and 402 (55). This mixture of sulfones **55** was reduced using sodium amalgam, following the procedure outlined for the preparation of the acetal **27**, to give, after flash chromatography using light petroleum–ethyl acetate (15:1) as eluent, the *title compound* **56** (73%); ν_{max}/cm^{-1} 1472, 1428, 1389, 1362, 1255, 1112, 1070, 836, 776, 738 and 702; δ_H 0.08 (6 H, s, $SiMe_2$), 0.85 (6 H, m, 2 × Me), 0.90 and 1.05 (each 9 H, s, Me_3CSi), 1.35–2.15 (10 H, m), 1.57 and 1.65 (each 3 H, s, Me), 3.60 (2 H, m, $SiOCH_2$), 4.20 (2 H, d, *J* 7, 1-H_2), 5.05 (1 H, m, 6-H), 5.30 (1 H, m, 2-H) and 7.35–7.70 (10 H, m, aromatic H); *m*/*z* (CI) 316 (75%), 215 (50) and 198 (100).

(2*E*,6*E*)-3,7,11-Trimethyl-10-(*tert*-butyldiphenylsilyloxymethyl)-dodeca-2,6-dien-1-ol 57

A solution of the silyl ether **56** (2.0 g, 3.3 mmol) and pyridinium toluene-*p*-sulfonate (0.25 g, 1 mmol) in methanol (8 cm^3)–tetrahydrofuran (4 cm^3) was stirred at room temperature for 18 h before being concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (5:1) as eluent gave the *title compound* **57** (90%), as a colourless oil (Found: M^+, 492.3393. $C_{32}H_{48}O_2Si$ requires *M*, 492.3423); ν_{max}/cm^{-1} 3336, 1472, 1428, 1388, 1112, 999, 823, 739 and 702; δ_H 0.82 and 0.88 (each 3 H, d, *J* 6, Me), 1.05 (9 H, s, Me_3CSi), 1.30 (3 H, m, 9-H_2 and 10-H), 1.58 (3 H, s, 7-Me), 1.70 (3 H, s, 3-Me), 1.70–2.15 (8 H, m), 3.58 (2 H, t, *J* 5, $SiOCH_2$), 4.15 (2 H, m, 1-H_2), 5.03 (1 H, t, *J* 7, 6-H), 5.40 (1 H, t, *J* 8, 2-H), 7.4 (6 H, m, aromatic H) and 7.7 (4 H, m, aromatic H); *m*/*z* (CI) 492 (M^+, 4%), 476 (30), 475 (82) and 407 (55).

(2*E*,6*E*)-3,7,11-Trimethyl-10-(*tert*-butyldiphenylsilyloxymethyl)-dodeca-2,6-dienal 58

Following the procedure outlined for the preparation of the aldehyde **14**, the alcohol **57** (0.34 g, 0.69 mmol) in *N*,*N*-dimethylformamide (1.2 cm^3) was oxidised with pyridinium dichromate (0.8 mmol) at 0 °C for 4 h. Water (12 cm^3) was added and the mixture extracted into ether (6 × 25 cm^3), dried and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (10:1) as eluent gave the *title compound* **58** (240 mg, 70%); ν_{max}/cm^{-1} 2858, 1677, 1632, 1428, 1193, 1112, 1083, 824, 740 and 703; δ_H 0.82 and 0.88 (each 3 H, d, *J* 6, Me), 1.05 (9 H, s, Me_3CSi), 1.45 (3 H, m, 9-H_2 and 10-H), 1.58 (3 H, s, 7-Me), 1.90 (5 H, m, 5-H_2, 8-H_2 and 11-H), 2.18 (3 H, s, 3-Me), 2.20 (2 H, m, 4-H_2), 3.58 (2 H, m, $SiOCH_2$), 5.00 (1 H, m, 6-H), 5.86 (1 H, d, *J* 8, 2-H), 7.42 (6 H, m, aromatic H), 7.7 (4 H, m, aromatic H) and 9.98 (1 H, d, *J* 8, 1-H); *m*/*z* (CI) 508 ($M^+ + 18$, 11%), 491 (8) and 413 (82).

Ethyl (4*E*,8*E*)-5,9,13-trimethyl-3-oxo-12-(*tert*-butyldiphenylsilyloxymethyl)tetradeca-4,8-dienoate 59

Ethyl acetate (0.055 cm^3, 0.55 mmol) in tetrahydrofuran (0.8 cm^3) was added to lithium diisopropylamide (0.6 cm^3) in tetrahydrofuran (1.6 cm^3) at −78 °C over 5 min. After 20 min, the aldehyde **58** (240 mg, 0.49 mmol) in tetrahydrofuran (0.8 cm^3) was added over 5 min and the mixture stirred at −60 to −50 °C for 3 h. Water (2 cm^3) was added and the mixture allowed to warm to room temperature. Ether (20 cm^3) and water (5 cm^3) were added and the aqueous phase extracted with ether (2 × 15 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using light petroleum–ethyl acetate (6:1) as eluent gave the hydroxy esters (0.22 g, 78%); ν_{max}/cm^{-1} 3404, 1737, 1428, 1152, 1112, 1029, 824, 740 and 702; δ_H 0.82 and 0.88 (each 3 H, d, *J* 6, Me), 1.10 (9 H, s, Me_3CSi), 1.38 (3 H, t, *J* 8, CH_2CH_3), 1.45 (3 H, m, 11-H_2 and 12-H), 1.58 (3 H, s, 9-Me), 1.73 (3 H, s, 5-Me), 1.85–2.05 (7 H, m), 2.46 (2 H, m, 2-H_2), 3.57 (2 H, m, $SiOCH_2$), 4.18 (2 H, q, *J* 8, CH_2CH_3), 4.80 (1 H, m, 3-H), 5.05 (1 H, m, 8-H), 5.22 (1 H, d, *J* 8, 4-H), 7.42 (6 H, m, aromatic H) and 7.68 (4 H, m, aromatic H); *m*/*z* (CI) 596 ($M^+ + 18$, 14%), 578 (M^+, 30) and 561 (100).

Pyridinium dichromate (0.75 g, 2.0 mmol) was added to a solution of the hydroxy esters (0.6 g, 1.03 mmol) in DMF (0.2 cm^3) at 20 °C over 10 min. The reaction was stirred for 15 h, diluted with water (20 cm^3) and extracted with ether (4 × 30 cm^3). The combined ethereal extracts were filtered through a short pad of silica gel and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (12:1) as eluent gave the *title compound* **59** (0.38 g, 66%), as a colourless oil (Found: $M^+ + H$, 577.3722. $C_{36}H_{53}O_4Si$ requires *M*, 577.3713); ν_{max}/cm^{-1} 1743, 1688, 1616, 1428, 1389, 1366, 1307, 1257, 1156, 1112, 1032, 824, 740 and 703; δ_H 0.82 and 0.88 (each 3 H, d, *J* 6, Me), 1.05 (9 H, s, Me_3CSi), 1.25 (3 H, t, *J* 8, CH_2CH_3), 1.40 (3 H, m, 11-H_2 and 12-H), 1.58 (3 H, s, 9-Me), 1.85–2.05 (5 H, m, 7-H_2, 10-H_2 and 13-H), 2.15 (5 H, m, 6-H_2 and 5-Me), 3.42 (2 H, m, 2-H_2), 3.58 (2 H, m, $SiOCH_2$), 4.18 (2 H, q, *J* 8, CH_2CH_3), 5.00 (1 H, m, 8-H), 6.08 (1 H, s, 4-H), 7.44 (6 H, m, aromatic H) and 7.7 (4 H, m, aromatic H); *m*/*z* (CI) 594 ($M^+ + 18$, 29%), 577 ($M^+ + 1$, 53) and 499 (31).

Ethyl (4*E*,8*E*)-5,9,13-trimethyl-3,3-(ethylenedioxy)-12-(*tert*-butyldiphenylsilyloxymethyl)tetradeca-4,8-dienoate 60

To a solution of keto ester **59** (0.3 g, 0.52 mmol) in CH_2Cl_2 (0.5 cm^3) at −78 °C was added 1,2-bis(trimethylsilyloxy)ethane (0.25 cm^3, 1.0 mmol) and trimethylsilyl trifluoromethanesulfonate (5 cm^3, 25 mmol). The reaction was warmed to −30 °C and stirred for 18 h. Pyridine (0.1 cm^3) was added followed by saturated aqueous $NaHCO_3$ (5 cm^3) and the mixture extracted with ether (4 × 10 cm^3). The combined ethereal extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (10:1) gave the *title compound* **60** (0.25 g, 80%), as a colourless oil (Found: $M^+ - C_4H_9$, 563.3088. $C_{34}H_{47}O_5Si$ requires *M*, 563.3193); ν_{max}/cm^{-1} 1735, 1428, 1368, 1112, 1041, 947, 824, 740 and 703; δ_H 0.82 and 0.88 (each 3 H, d, *J* 6, Me), 1.05 (9 H, s, Me_3CSi), 1.28 (3 H, t, *J* 8, CH_2CH_3), 1.45 (3 H, m, 11-H_2 and 12-H), 1.58 (3 H, s, 9-Me), 1.65–2.30 (7 H, m), 1.82 (3 H, s, 5-Me), 2.80 (2 H, m, 2-H_2), 3.59 (2 H, m, $SiOCH_2$), 3.90 (4 H, m, OCH_2CH_2O), 4.14 (2 H, q, *J* 8, CH_2CH_3), 5.00 (1 H, m, 8-H), 5.27 (1 H, s, 4-H), 7.42 (6 H, m, aromatic H) and 7.67 (4 H, m, aromatic H); *m*/*z* (EI) 564 ($M^+ - 56$, 2%), 534 (30) and 199 (84).

Dimethyl [(5*E*,9*E*)-6,10,14-trimethyl-4,4-(ethylenedioxy)-13-(hydroxymethyl)-2-oxopentadeca-5,9-dienyl]phosphonate 62

Tetrabutylammonium fluoride in tetrahydrofuran (1 M; 0.5 cm^3, 0.5 mmol) was added to solution of the ester **60** (0.15 g, 0.24 mmol) in tetrahydrofuran (0.5 cm^3) and the reaction stirred for 8 h. Water (3 cm^3) was added and the reaction extracted with ether (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the alcohol **61**. This was dissolved in tetrahydrofuran (2 cm^3) and added to lithiated dimethyl methylphosphonate (1.0 mmol) in tetrahydrofuran (2 cm^3) at −78 °C. After 30 min, water and ether were added. The aqueous layer was acidified to pH 2 and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and concentrated under

reduced pressure. Flash chromatography of the residue using ethyl acetate–light petroleum (16:1) gave the *title compound* **62** (70 mg, 60%), as a pale yellow oil (Found: $M^+ + H$, 461.2659. $C_{23}H_{42}O_7P$ requires *M*, 461.2668); ν_{max}/cm^{-1} 3433, 1715, 1463, 1253, 1033 and 842; δ_H 0.88 (6 H, d, *J* 6, 2 × Me), 1.28 (3 H, m, 12-H_2 and 13-H), 1.59 (3 H, s, 10-Me), 1.60–2.10 (7 H, m), 1.77 (3 H, s, 6-Me), 3.05 (2 H, s, 3-H_2), 3.27 (2 H, d, *J* 23, 1-H_2), 3.55 (2 H, m, HOCH_2), 3.78 (6 H, d, *J* 11, 2 × OMe), 3.88 (4 H, m, OCH_2CH_2O), 5.06 (1 H, m, 9-H) and 5.18 (1 H, s, 5-H); *m*/*z* (CI) 461 ($M^+ + 1$, 29%), 417 (13) and 295 (100).

(2*E*,7*E*,11*E*)-7,11-Dimethyl-13,13-(ethylenedioxy)-4-isopropylcyclotetradeca-2,7,11-trien-1-one 64

The alcohol **62** (115 mg, 0.25 mmol) in CH_2Cl_2 (0.5 cm^3) was added to a stirred suspension of pyridinium dichromate (175 mg, 0.5 mmol) and powdered activated 3 Å molecular sieves (250 mg) in CH_2Cl_2 (2 cm^3) at 20 °C. After 2 h, the reaction was diluted with ether (20 cm^3), filtered through a short pad of Florisil and concentrated under reduced pressure to give the aldehyde **63** (95 mg, 83%). This aldehyde **63** was taken up in acetonitrile (10 cm^3) and added to a slurry of lithium chloride (85 mg, 2 mmol) in acetonitrile (100 cm^3) at 40 °C. A solution of DBU (45 cm^3, 0.3 mmol) in acetonitrile (8 cm^3) was added over 16 h *via* syringe pump and the reaction stirred at 40 °C for a further 8 h. The reaction mixture was cooled, filtered through a pad of silica gel and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ethyl acetate (20:1) as eluent gave the *title compound* **64** (30 mg, 45%), as a colourless oil (Found: $M^+ + H$, 333.2429. $C_{21}H_{33}O_3$ requires *M*, 333.2430); ν_{max}/cm^{-1} 1690, 1660, 1621, 1451, 1390, 1180, 1100, 1060 and 1041; δ_H 0.88 and 0.90 (each 3 H, d, *J* 7, Me), 1.30 (2 H, m, 5-H_2), 1.58 (3 H, s, 7-Me), 1.58–2.10 (8 H, m), 1.67 (3 H, s, 11-Me), 2.91 and 2.98 (each 1 H, d, *J* 12, 14-H), 3.97 (4 H, m, OCH_2CH_2O), 5.07 (1 H, s, 12-H), 5.11 (1 H, m, 8-H), 6.47 (1 H, d, *J* 16, 2-H) and 6.73 (1 H, dd, *J* 16, 9, 3-H); *m*/*z* (CI) 333 ($M^+ + 1$, 100%).

(10*SR*,13*SR*,2*E*,6*E*,11*E*)-13-Hydroxy-3,7,13-trimethyl-10-isopropylcyclotetradeca-2,6,11-trien-1-one 65

Methylmagnesium iodide (0.3 mmol) in ether (0.1 cm^3) was added to the cyclic ketone **64** (20 mg, 0.06 mmol) in ether (1 cm^3) at −10 °C. The mixture was stirred for 2 h then aqueous NH_4Cl (10%; 0.1 cm^3) was added. Water (2 cm^3) was added and the reaction extracted with ether (3 × 5 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (0.1 cm^3) and added to a solution of pyridinium toluene-*p*-sulfonate (1 mg) in acetone (0.5 cm^3) at 0 °C. After 5 h, solid $NaHCO_3$ (50 mg) and ether (2 cm^3) were added and the mixture was filtered and concentrated under reduced pressure. Flash chromatography followed by HPLC using light petroleum–ether (2:1) as eluent gave the hydroxy ketone **65** (7 mg, 38%); λ_{max}(EtOH)/nm 235 (ε 9600 mol^{-1} dm^3 cm^{-1}) [lit.,[40] 243 nm (ε 9300)]; ν_{max}/cm^{-1} 3435, 1676, 1613, 1443, 1390, 1367, 1255, 1168 and 980; δ_H 0.85 and 0.88 (each 3 H, d, *J* 8, Me), 1.20–2.24 (10 H, m), 1.30 (3 H, s, 13-Me), 1.55 (3 H, s, 7-Me), 2.06 (3 H, s, 3-Me), 2.46 and 2.74 (each 1 H, d, *J* 12, 14-H), 4.90 (1 H, m, 6-H), 5.45 (1 H, d, *J* 16, 12-H), 5.57 (2 H, dd, *J* 16, 7, 11-H) and 6.04 (1 H, s, 2-H); *m*/*z* (CI) 305 ($M^+ + 1$, 32%), 303 (14), 287 (28), 242 (10) and 206 (100).

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