Total synthesis of (+)-curacin A, a novel antimitotic metabolite from a cyanobacterium

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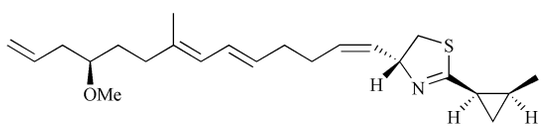
A concise total synthesis of (+)-curacin A, a potent antimitotic agent isolated from the cyanobacterium *Lyngbya majuscula*, is described. The synthesis features a new strategy to the 2-cyclopropyl-4-alkenyl substituted thiazoline unit in the natural product involving facile and selective thioacylation of the amino-alcohol **10** with the benzotriazole derived thioamide **11**, leading to **28**, as a key step. Cyclodehydration of **28** using Burgess' reagent then completed the synthesis of curacin A **1**.

Curacin A **1** is a potent antimitotic agent which was isolated from the cyanobacterium *Lyngbya majuscula* collected off the coast of Curaçao. Its gross structure was reported by Gerwick *et al.* in 1994,[1] and its absolute configuration was determined by White *et al.*[2] a year later, during studies which also described the first total synthesis of the novel metabolite.[3] Curacin A shows antiproliferative activity which has been associated with its capacity to inhibit tubulin polymerisation at the colchicin site.[4] The cyanobacterium *L. majuscula* is a rich source of several important secondary metabolites, but its biological activity is usually associated with the powerful tumour promoters lyngbyatoxin[5] and debromoaplysiatoxin.[6] Curacin A has an unusual structure which features a novel cyclopropane-substituted thiazoline as a key feature. Because of its novel structural features and interesting biological activity, the compound has attracted the attentions of medicinal[7] and synthetic chemists, and several total syntheses of curacin A have now been reported in the primary literature.[3,8–12] In contemporaneous studies we have earlier described the total syntheses of a range of biologically important thiazoline-based natural products, *e.g.* lissoclinamide 4 (**2**) from the sea squirt *Lissoclinum patella*[13] and thiagazole **3** from the gliding bacterium *Polyangium* sp.[14] Curacin A provided us with an opportunity to develop our synthetic studies with novel thiazoline-based compounds and complement our long-standing interests in cyclopropane-containing secondary metabolites of biological significance, *e.g.* chrysanthemic acid,[15] presqualene,[16] and casbene.[17]

Nearly all of the synthetic strategies described towards curacin A have differed from each other largely according to the manner adopted towards the chiral thiazoline moiety in the molecule. Thus, White *et al.*[3] and later Iwasaki *et al.*[10] used the cyclisation of an amino-thioester as the key step, *viz.* **4** to **6**, whereas Aubé *et al.*[8] and Falck *et al.*[12] utilised the hydroxy thioamide **5**, and Wipf *et al.*[11] applied the oxazoline–thiazoline conversion **7** to **6**. In contrast, Kobayashi *et al.*[9] found that the condensation between the cysteine derivative **8** and a cyclopropane imino ether **9** provided direct access to the thiazoline ring in curacin A (Scheme 1). Our own contemporaneous studies towards the synthesis of the thiazoline ring in curacin A, do not differ significantly from the aforementioned strategy of Aubé and Falck *et al*. However, we did encounter practical difficulties in synthesising the key hydroxy thioamide precursor **5** which led us to develop a new strategy and featured the facile and selective thioacylation of the amino alcohol **10** with the benzotriazole-derived thioamide **11** as the key step.[18] This chemistry, leading to a concise synthesis of (+)-curacin A, is now described in this paper.[19]



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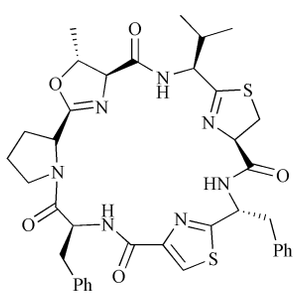

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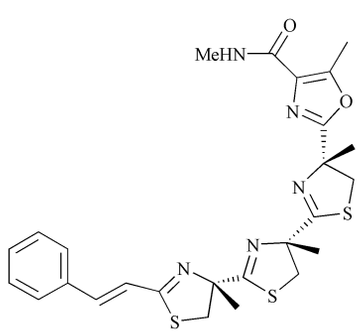

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Our strategy for the synthesis of curacin A **1** required a synthesis of the polyene substituted 1,2-amino alcohol **10** which we planned to synthesise *via* a Wittig condensation between the phosphonium salt **17c** and Garners' aldehyde **18**,[20] leading to **19**, followed by removal of the Boc protection (Scheme 2). Thus, the salt **17c** was first elaborated starting from pent-4-yn-1-ol **12** and featured: i, a Suzuki cross-coupling reaction[21] between the vinyl iodide **14** and the vinyl boronic acid **13** to access the *E*,*E*-1,3-diene intermediate **15**, and ii, an

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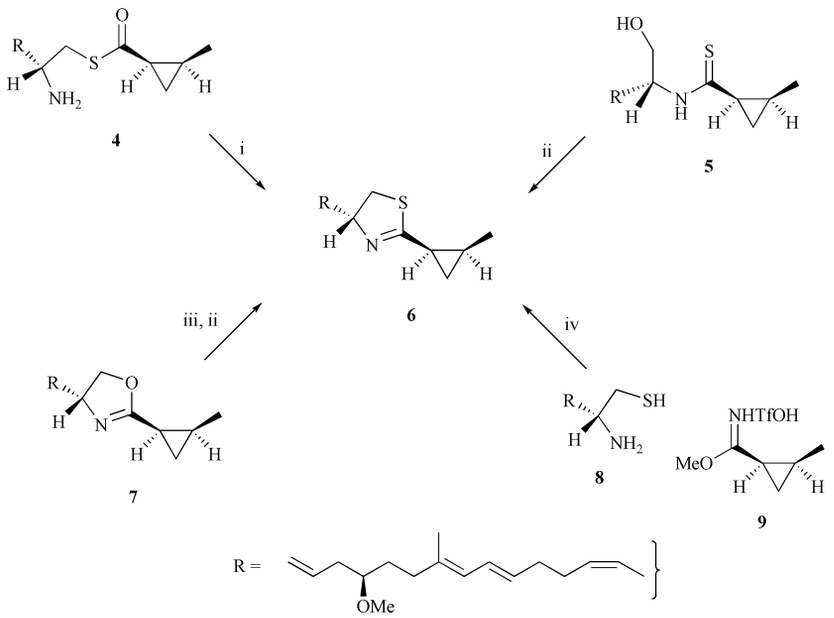
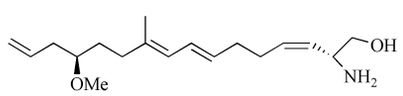


Scheme 1 *Reagents*: i, heat, C_6H_6; ii, Burgess' reagent, THF or Me_3P, ADDP, −45 °C; iii, H_2S, TEA, MeOH; iv, MeOH, 55 °C.



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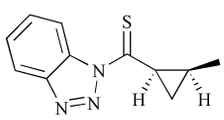

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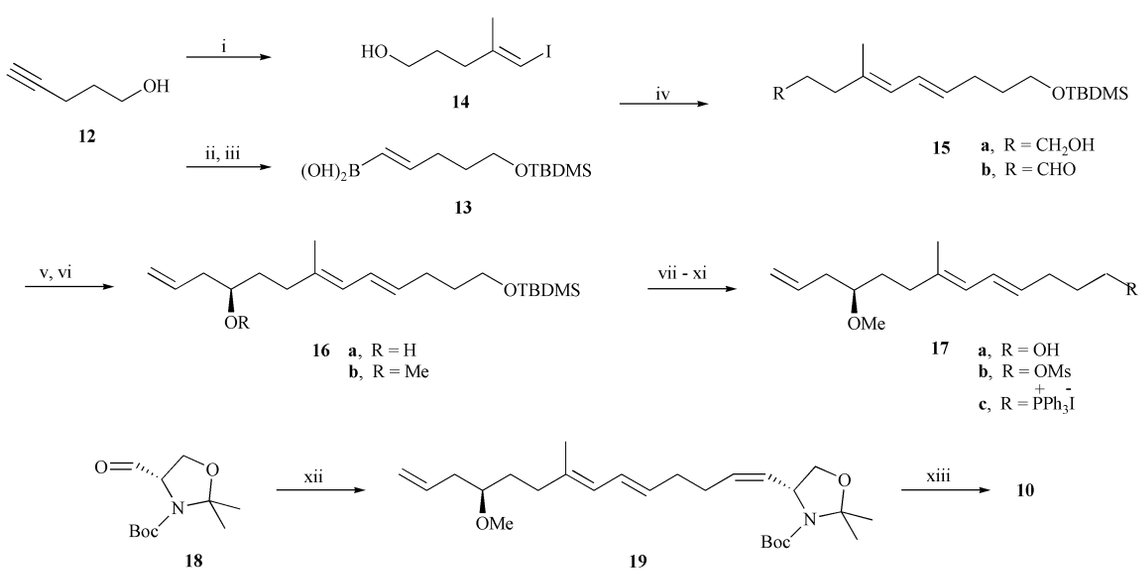
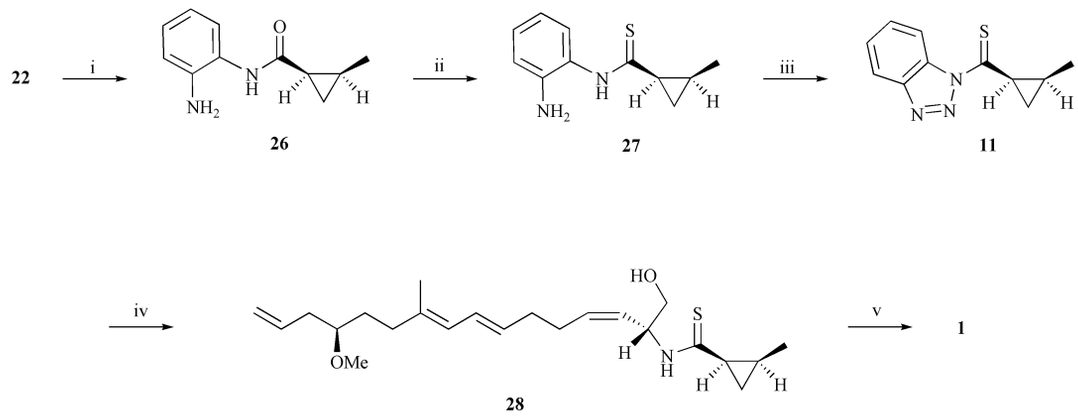
asymmetric allylation reaction[22] to introduce the chiral secondary alcohol centre in the triene **16** (Scheme 2). Protection of pent-4-yn-1-ol as its TBDMS ether, followed by hydroboration using catechol–borane and hydrolysis of the boronate ester first gave the *E*-boronic acid **13** in good yield.[23] Carbozirconation[24] of pent-4-yn-1-ol, followed by iodination led to the *E*-vinyl iodide **14** which, by Suzuki coupling to **13**, next produced the *E*,*E*-diene **15a**. Oxidation of **15a** using Dess–Martin periodinane,[25] followed by allylboration of the resulting aldehyde with the borane derived from (−)-*B*-methoxy-(diisopinocampheyl)borane[22] next led to the carbinol **16a** in 96% ee as measured by NMR analysis of the corresponding methoxy(trifluoromethyl)phenyl ester.[26] *O*-Methylation of **16a**, followed by cleavage of the silyl ether, mesylation, conversion into the corresponding iodide and treatment with triphenylphosphine finally provided the known phosphonium salt **17c**, prepared earlier by White *et al.*[3] using a slightly different route. A *Z*-selective Wittig reaction between Garner's aldehyde **18** and the ylide produced from **17c** in the presence of sodium hexamethyldisilazide[27] in THF at −78 °C next produced the *Z,E,E*-tetraene **19**,[3] in 82% yield, which was then hydrolysed to the 1,2-amino alcohol **10** using 10% HCl in MeOH.[28]

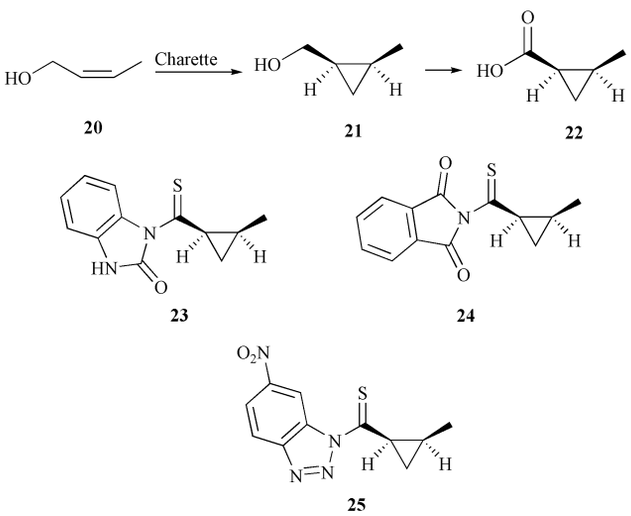
cis-2-Methylcyclopropane carboxylic acid **22** was smoothly synthesised from *Z*-crotyl alcohol **20** using an asymmetric Charette cyclopropanation[29] followed by ruthenium-catalysed oxidation[30] of the resulting cyclopropane methanol **21**. After several abortive attempts to couple the acid **22** to the amine **10**,[31] *en route* to curacin A, we altered our strategy and examined a range of thioacylating agents derived from the cyclopropane carboxylic acid **22** with a view to synthesising the



Scheme 2 *Reagents*: i, Me_3Al, Cp_2ZrCl_2, I_2; ii, TBDMSCl, Et_3N, DMAP, CH_2Cl_2; iii, catechol–borane, H_2O; iv, $Pd(OAc)_2$, PPh_3; v, Dess–Martin periodinane; vi, (−)-β-allyl(diisopinocampheyl)borane, MeOH, NaOH, H_2O_2; vii, NaH, MeI, THF; ix, MsCl, Et_3N; x, NaI, acetone; xi, PPh_3, CH_3CN; xii, **17c**, NaHMDS, −78 °C to 0 °C, THF; xiii, 10% HCl, MeOH, 40 °C.



Scheme 3 ***Reagents***: i, phenylene-1,2-diamine, pyBOP, Et_3N; ii, P_4S_{10}, Na_2CO_3; iii, $NaNO_2$, AcOH–H_2O; iv, **10**, DMF, 0 °C; v, Burgess' reagent, THF.



corresponding thioamide precursor, *viz.* **28**, to our target.[32] Thus, we examined the scope for the thiobenzimidazolone **23**,[33] the phthalimide **24**[34] and the nitrobenzotriazole **25**[35] derived thioamides as thioacylating agents for the amine **10**, but each had their distinctive disadvantages. Ultimately we found that the benzotriazole cyclopropyl thioamide **11**, derived from the carboxylic acid **22** following amide **26** formation with 1,3-diaminobenzene, thionation, and diazotisation of the resulting thioamide **27** (Scheme 3), reacted cleanly with the amino-alcohol **10** to produce the polyene substituted thioamide **28** in 87% yield. Treatment of **28** with Burgess' reagent[36] then effected cyclodehydration to give (+)-curacin A (**1**) as a colourless oil which exhibited ^{1}H NMR and ^{13}C NMR spectroscopic data, together with optical rotation data, which were identical to those recorded for the natural product isolated from *L. majuscula*.

Experimental

General details

Melting point determinations were made on a Reichert Kofler micro hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1720 or 1600 series FT-IR instrument and were calibrated using a standard polystyrene film; the spectra were recorded for samples as either liquid films or dilute solutions in spectroscopic grade chloroform. UV spectra were recorded for solutions in spectroscopic grade ethanol using a Philips PU 8720 or a Perkin-Elmer Lambda 16 spectrophotometer. Specific rotations were measured on a JASCO DIPA-370 polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}. Proton NMR spectra were recorded on a Bruker DPX 360 (360 MHz), a Bruker AM 400 (400 MHz) or a Bruker DRX 500 (500 MHz) spectrometer. The chemical shifts are recorded relative to tetramethylsilane or to chloroform and the multiplicity of a signal is designated by one of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; and m, multiplet. All *J* values are in Hertz. Carbon-13 NMR spectra were recorded on a Bruker AM 400 (100.4 MHz), a Bruker DPX 360 (90.6 MHz), a Bruker DRX 500 (125.8 MHz) or a Jeol EX-270 (67.8 MHz) spectrometer. The spectra were recorded for dilute solutions in deuteriated solvents with chemical shifts reported relative to tetramethylsilane or chloroform on a broad band decoupled mode, and the multiplicities obtained using a DEPT sequence. The following abbreviations are used for the multiplicities: q, primary methyl; t, secondary methylene; d, tertiary methine and s, quaternary.

Mass spectra were recorded on a VG Autospec, MM-701CF or a VG Micromass 70E spectometer using electron ionisation (EI), fast atom bombardment (FAB) or chemical ionisation (CI) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed using Merck silica gel 60 as the stationary phase and light petroleum (bp 40–60 °C) was distilled before use. All reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated aluminium plates, which were visualised with ultraviolet light and then developed with vanillin solution, basic potassium permanganate solution or phosphomolybdic acid solution.

Routinely, dry organic solvents were stored under nitrogen, and benzene, diethyl ether and toluene solvents were dried over sodium wire. Other organic solvents were dried by distillation as follows: THF (sodium benzophenone ketyl), dichloromethane (calcium hydride), methanol (magnesium). Other organic solvents and reagents were purified by the accepted literature procedures. Organic extracts were dried over anhydrous magnesium sulfate, filtered under gravity and the solvent removed under reduced pressure on a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in flame- or oven-dried apparatus under a nitrogen or argon atmosphere.

(*E*)-[5-(*tert*-Butyldimethylsilyloxy)pent-1-enyl]boronic acid 13

A solution of *tert*-butyldimethylsilyl chloride (9.4 g, 62.4 mmol) in dry DMF (50 ml) was added dropwise over 10 min to a stirred mixture of pent-4-yn-1-ol (5.0 g, 59.4 mmol) and imidazole (10.1 g, 148.60 mmol) in dry DMF (100 ml) at 0 °C under an atmosphere of nitrogen. The solution was allowed to warm to room temperature and stirred at this temperature for 12 h. Water (300 ml) was added and the mixture was then extracted with ether (3 × 200 ml). The combined organic extracts were washed with brine (100 ml), then dried and evaporated *in vacuo* to leave a pale yellow oil. The oil was purified by chromato-

graphy on silica gel using 10% ether–light petroleum as eluant to give 1-(*tert*-butyldimethylsilyloxy)-pent-4-yne (11.6 g, 97%) as a colourless oil; ν_{max} (film) 2954, 2929, 2857, 1256, 1107 and 835 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 3.70 (2H, t, *J* 6.0 Hz, CH_2OSi), 2.28 (2H, td, *J* 7.1, 2.7 Hz, CCH_2CH_2), 1.93 (1H, t, *J* 2.7 Hz, CCH), 1.73 (2H, tt, *J* 6.0 Hz, $CH_2CH_2CH_2$), 0.90 [9H, s, $(CH_3)_3CSi$], 0.06 [6H, s, $OSi(CH_3)_2$]; δ_C (67.8 MHz; $CDCl_3$) 83.95 (d), 68.27 (s), 61.26 (t), 31.47 (t), 25.86 (q), 18.22 (s), 14.74 (t), −5.46 (q).

Catechol–borane (10.50 ml, 98.48 mmol) was added dropwise over 5 min to a stirred solution of the pent-4-yne (16.3 g, 82.1 mmol) in dry THF (30 ml) under an atmosphere of nitrogen. The resulting mixture was heated under reflux for 12 h and then evaporated *in vacuo* to leave a cloudy oil. The oil was purified by distillation under reduced pressure to give the corresponding boronate ester (24.5 g, 94%) as a colourless oil; bp 142 °C at 0.6 mmHg (lit.,[37] bp 164 °C at 1.0 mmHg); ν_{max} (film) 2953, 2929, 2857, 1638, 1473, 1374, 1333, 1236 and 1105 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.24–7.20 (2H, m, ArC*H*), 7.12–7.06 (3H, m, 2 × ArC*H* and BCH:C*H*CH_2), 5.83 (1H, dt, *J* 18.0, 1.6 Hz, BC*H*:CH), 3.68 (2H, t, *J* 6.3 Hz, CH_2OSi), 2.41–2.34 (2H, m, $CHCH_2CH_2$), 1.74 (2H, tt, *J* 6.9, 6.9 Hz, $CH_2CH_2CH_2$), 0.92 [9H, s, $(CH_3)_3CSi$], 0.08 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 157.24 (d), 148.22 (s), 122.40 (d), 116.20 (d, br), 112.18 (d), 62.26 (t), 32.37 (t), 31.22 (t), 25.91 (q), 18.26 (s), −5.34 (q).

The boronate ester (24.5 g, 76.9 mmol) was added in one portion to water (350 ml) and the mixture was then stirred vigorously for 4 h. The precipitate was filtered and then washed with water (2 × 50 ml). Recrystallisation from water gave a solid which was dissolved in ether (500 ml) and washed with brine (100 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the boronic acid (16.3 g, 87%) as a colourless solid; mp 67 °C (H_2O) [lit.,[37] m.p. 68 °C (H_2O)]; ν_{max} (film) 2953, 2929, 2857, 1634, 1367, 1255 and 1106 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.99 (1H, dt, *J* 17.6, 6.5 Hz, BCH:C*H*CH_2), 5.56 (1H, d, *J* 17.6 Hz, BC*H*:CH), 3.65 (2H, t, *J* 6.4 Hz, CH_2OSi), 2.29 (2H, dt, *J* 6.8, 6.8 Hz, $CHCH_2CH_2$), 1.69 (2H, tt, *J* 6.8, 6.8 Hz, $CH_2CH_2CH_2$), 0.91 [9H, s, $(CH_3)_3CSi$], 0.06 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 157.16 (d), 122.44 (d, br), 62.45 (t), 31.96 (t), 31.32 (t), 25.94 (q), 18.28 (s), −5.31 (q).

(*E*) 5-Iodo-4-methylpent-4-en-1-ol 14

A solution of trimethylaluminium (2.0 M) in hexanes (90.0 ml, 180 mmol) was added dropwise over 15 min to a stirred solution of zirconocene dichloride (4.34 g, 15 mmol) in dry dichloromethane (150 ml) under an atmosphere of nitrogen. The mixture was stirred for 15 min, then cooled to 0 °C and a solution of pent-4-yn-1-ol (5.0 g, 60 mmol) in dry dichloromethane (40 ml) was added dropwise over 30 min. The mixture was stirred at room temperature for 20 h, then cooled to −30 °C and a solution of iodine (18.1 g, 71 mmol) in dry THF (70 ml) was added dropwise over 1 h, keeping the internal temperature at −30 °C. The mixture was allowed to warm to 0 °C over 2 h and then saturated potassium carbonate solution (20 ml) was added cautiously. The resulting slurry was stirred for a further 30 min, then diluted with ether (500 ml), dried and filtered through a pad of Celite. The filtrate was evaporated *in vacuo* to leave a pale yellow oil. The oil was purified by chromatography on silica gel using 30% ethyl acetate–light petroleum as eluant to give the vinyl iodide (9.8 g, 73%)[24] as a colourless viscous oil; ν_{max} (film) 3298, 3056, 2939, 1267 and 1061 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.9 (1H, s, CHI), 3.55 (2H, t, *J* 6.5 Hz, $HOCH_2$), 2.57 (1H, br s, OH), 2.25 (2H, t, *J* 6.5 Hz, CH_2CH_2C), 1.81 (3H, s, CH_3), 1.64 (2H, tt, *J* 6.5, 6.5 Hz, $CH_2CH_2CH_2$); δ_C (67.8 MHz; $CDCl_3$) 147.03 (s), 74.90 (d), 61.26 (t), 35.38 (t), 30.12 (t), 23.63 (q).

(4*E*,6*E*)-10-(*tert*-Butyldimethylsilyloxy)-4-methyldeca-4,6-dien-1-ol 15a

Triphenylphosphine (1.7 g, 6.4 mmol) was added in one portion to a stirred solution of palladium(II) acetate (0.36 g, 1.6 mmol) in degassed THF (25 ml) under an atmosphere of nitrogen, and the mixture was then stirred for 20 min. The yellow solution was added dropwise over 10 min to a stirred mixture of the vinyl iodide **14** (7.2 g, 32 mmol), the vinyl boronic acid **13** (10.9 g, 45 mmol) and degassed aqueous lithium hydroxide solution (225 ml, 446 mmol) in degassed THF (425 ml) under an atmosphere of nitrogen. The mixture was stirred at 40 °C (bath temp.) for 16 h, then cooled and partitioned between ether (1000 ml) and water (200 ml). The separated aqueous layer was extracted with ether (3 × 500 ml), and the combined organic extracts were then washed successively with saturated ammonium chloride solution (1000 ml), water (750 ml) and brine (500 ml), dried and evaporated *in vacuo* to leave a pale brown oil. The oil was purified by column chromatography on silica gel using 15 to 20% ethyl acetate–light petroleum as eluant to give the *diene* (5.6 g, 59%) as a pale yellow oil; (Found C, 68.2; H, 11.6. $C_{17}H_{34}O_2Si$ requires C, 68.4; H, 11.5%); λ_{max} (EtOH) 222 (541) nm; ν_{max} (film) 3388, 2929, 2857, 1255 and 1099 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.83 (1H, d, *J* 10.8 Hz, C:C*H*CH), 5.59 (1H, dt, *J* 15.0, 7.0 Hz, CH:C*H*CH_2), 3.66–3.60 (4H, m, 2 × CH_2), 2.18–2.10 (4H, m, 2 × CH_2), 1.75 (3H, s, CH_3), 1.71 (2H, tt, *J* 7.2, 7.2 Hz, $CH_2CH_2CH_2$), 1.62 (2H, tt, *J* 7.0, 7.0 Hz, $CH_2CH_2CH_2$), 1.44 (1H, br s, OH), 0.90 [9H, s, $(CH_3)_3CSi$], 0.05 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 135.76 (s), 132.15 (d), 126.76 (d), 125.02 (d), 62.69 (t), 62.54 (t), 36.03 (t), 32.56 (t), 30.71 (t), 29.14 (t), 25.94 (q), 18.33 (s), 16.40 (q), −5.30 (q); *m*/*z* (FAB) 299.2397 (MH^+, 17%, $C_{17}H_{35}O_2Si$ requires 299.2406), 241 (15), 167 (30), 149 (49), 136 (18), 121 (21), 107 (54), 93 (43).

(4*R*,7*E*,9*E*)-13-(*tert*-Butyldimethylsilyloxy)-7-methyltrideca-1,7,9-trien-4-ol 16a

A solution of the alcohol **15a** (1.0 g, 3.4 mmol) in dry dichloromethane (5 ml) was added dropwise over 2 min to a stirred suspension of Dess–Martin periodinane (3.6 g, 8.4 mmol) in dry dichloromethane (10 ml) at 0 °C under an atmosphere of nitrogen. The mixture was allowed to warm to room temperature and then stirred at that temperature for 1.5 h. Sodium thiosulfate solution (10%, 10 ml) and saturated $NaHCO_3$ solution (10 ml) were added slowly, and the mixture was then stirred vigorously for 1 h. The mixture was extracted with ether (3 × 200 ml) and the combined organic extracts were then dried (Na_2SO_4) and evaporated *in vacuo* to leave a pale yellow oil. The oil was purified by column chromatography on silica gel using 10% ether–light petroleum as eluant to give the corresponding aldehyde **15b** (0.97 g, 98%) as a colourless oil; (Found C, 68.6; H, 11.2; $C_{17}H_{32}O_2Si$ requires C, 68.9; H, 10.9%); λ_{max} (EtOH) 206 (6698), 237 (13 903) nm; ν_{max} (film) 3021, 2929, 2856, 1727, 1255 and 1102 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 9.78 (1H, t, *J* 1.8 Hz, CHO), 6.23 (1H, dd, *J* 15.0, 10.7 Hz, CHC*H*:CH), 5.81 (1H, d, *J* 10.7 Hz, C:C*H*CH), 5.61 (1H, dt, *J* 15.0, 7.0 Hz, CH:C*H*CH_2), 3.62 (2H, t, *J* 6.4 Hz, CH_2OSi), 2.56 (2H, td, *J* 7.5, 1.8 Hz, $OHCCH_2CH_2$), 2.38 (2H, t, *J* 7.5 Hz, CH_2CH_2C), 2.16 (2H, dt, *J* 7.0, 7.0 Hz, $CHCH_2CH_2$), 1.75 (3H, s, CH_3), 1.61 (2H, m, $CH_2CH_2CH_2$), 0.90 [9H, s, $(CH_3)_3CSi$], 0.05 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 202.22 (d), 133.73 (s), 132.98 (d), 126.46 (d), 125.51 (d), 62.48 (t), 42.03 (t), 32.49 (t), 31.84 (t), 29.14 (t), 25.93 (q), 18.31 (s), 16.54 (q), −5.31 (q); *m*/*z* (FAB) 297.2230 (MH^+, 5%, $C_{17}H_{33}O_2Si$ requires 297.2250), 279 (5), 239 (15), 165 (11), 147 (35), 136 (29), 121 (43), 105 (31), 93 (57).

A solution of allylmagnesium bromide (1.0 M) in diethyl ether (18 ml, 18.2 mmol) was added dropwise over 15 min to a stirred solution of (−)-*B*-methoxy(diisopinocampheyl)borane (5.7 g, 18 mmol) in dry diethyl ether (35 ml) at 0 °C under an atmosphere of argon. The resulting slurry was allowed to warm to room temperature and then stirred at that temperature for 2.5 h. The solvents were removed *in vacuo* (10 mmHg, 0.5 h then

1 mmHg, 0.5 h) to leave a colourless residue. The residue was extracted with pentane (3 × 30 ml) under an atmosphere of argon and the extracts were then filtered through a Schlenk filter. The filtrate was evaporated *in vacuo* (10 mmHg, 0.5 h then 1 mmHg, 1 h) to leave the corresponding *B*-allylborane as a colourless viscous oil which was used immediately in the next step without further purification.

A solution of the aldehyde **15b** (4.2 g, 14.0 mmol) in dry diethyl ether (35 ml) maintained at −78 °C and under an atmosphere of argon, was added dropwise along the side of the flask, *via* a cannula, to a stirred solution of the *B*-allylborane in dry diethyl ether (35 ml) at −100 °C under an atmosphere of argon, over 1 h while keeping the internal temperature at −100 °C. The mixture was stirred at −100 °C for 1 h and then dry methanol (3.6 ml) was added dropwise over 10 min. The mixture was allowed to warm to room temperature over 1 h, and then 3 M sodium hydroxide solution (7.5 ml) and aqueous hydrogen peroxide solution (30%, 15 ml) were added over 10 min. The mixture was stirred vigorously overnight and then partitioned between ether (200 ml) and brine (75 ml). The separated aqueous layer was extracted with ether (3 × 200 ml) and the combined organic extracts were dried and evaporated *in vacuo* to leave a pale yellow oil. The oil was purified by column chromatography on silica gel using 10% ethyl acetate–light petroleum as eluant to give the secondary *alcohol* (3.75 g, 79%) as a colourless viscous oil; $[\alpha]_D^{20}$ + 1.72 (*c* 1.57 in $CHCl_3$); (Found C, 70.7; H, 11.6; $C_{20}H_{38}O_2Si$ requires C, 70.9; H, 11.3%); λ_{max} (EtOH) 239 (3881) nm; ν_{max} (film) 3362, 3075, 2929, 2856, 1255 and 1103 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.89–5.77 (1H, m, CH_2:C*H*CH_2), 5.84 (1H, d, *J* 10.8 Hz, C:C*H*CH), 5.58 (1H, dt, *J* 15.0, 7.0 Hz, CH:CHCH_2), 5.16–5.12 (2H, m, CH_2:CH), 3.64–3.60 [1H, m, CH(OH)], 3.62 (2H, t, *J* 6.4 Hz, CH_2OSi), 2.34–2.07 (6H, m, 3 × CH_2), 1.75 (3H, s, CH_3), 1.67–1.54 (5H, m, 2 × CH_2, OH), 0.90 [9H, s, $(CH_3)_3CSi$], 0.05 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 135.96 (s), 134.72 (d), 132.12 (d), 126.77 (d), 124.98 (d), 118.13 (t), 70.37 (d), 62.53 (t), 41.93 (t), 35.95 (t), 34.79 (t), 32.56 (t), 29.14 (t), 25.94 (q), 18.32 (s), 16.47 (q), −5.30 (q); *m*/*z* (FAB) 339.2700 (MH^+, 4%, $C_{20}H_{39}O_2Si$ requires 339.2719), 281 (5), 207 (10), 189 (11), 147 (21), 133 (7), 121 (27), 107 (31), 93 (47).

A solution of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (51 mg, 0.20 mmol) in dry dichloromethane (0.5 ml) was added dropwise over 1 min to a stirred mixture of the alcohol **16a** (34 mg, 0.10 mmol) and DMAP (1 mg, 8.2 μmol) in dry pyridine (0.5 ml) at 0 °C under an atmosphere of nitrogen. The mixture was allowed to warm to room temperature and then stirred at that temperature overnight. The solvents were removed *in vacuo* to leave a pale brown residue which was purified by column chromatography on silica gel using 5% ether–light petroleum as eluant to give the corresponding *Mosher ester* (40 mg, 72%) as a colourless viscous oil; ν_{max} (film) 3076, 2952, 2929, 2856, 1746, 1256, 1169 and 1106 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.57–7.55 (2H, m, ArC*H*), 7.43–7.39 (3H, m, ArC*H*), 6.23 (1H, dd, *J* 15.0, 10.7 Hz, CHC*H*:CH), 5.77 (1H, d, *J* 10.7 Hz, C:C*H*CH), 5.71–5.56 (2H, m, 2 × CH), 5.13 [1H, tt, *J* 6.0, 6.0 Hz, CH(OCO-)], 5.06–5.02 (2H, m, CH_2:CH), 3.63 (2H, t, *J* 6.4 Hz, CH_2OSi), 3.56 [3H, d, *J* 1.1 Hz, $C(OCH_3)$], 2.38 (2H, dd, *J* 6.0, 6.0 Hz, CHCH_2CH), 2.16 (2H, dt, *J* 7.0, 7.0 Hz, CH:CHCH_2CH_2), 2.09–2.03 (2H, m, CH_2CH_2C), 1.81–1.74 [2H, m, CH(O)CH_2CH_2], 1.72 (3H, s, CH_3), 1.66–1.58 (2H, m, $CH_2CH_2CH_2$), 0.91 [9H, s, $(CH_3)_3CSi$], 0.06 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 166.11 (s), 134.63 (s), 132.63 (d), 132.58 (d), 132.25 (s), 129.53 (d), 128.33 (d), 127.44 (2 × d), 126.63 (d), 125.39 (2 × d), 123.21 (q, *J* 285.5 Hz, s), 118.47 (t), 84.35 (q, *J* 21.3 Hz, s), 76.23 (d), 62.54 (t), 55.41 (q), 37.91 (t), 35.23 (t), 32.55 (t), 31.55 (t), 29.16 (t), 25.95 (q), 18.34 (s), 16.40 (q), −5.29 (q); *m*/*z* (FAB) 497.2377 ($MH^+ - C_4H_9$, 3%, $C_{26}H_{36}O_4F_3Si$ requires 497.2335), 422 (10), 291 (21), 189 (44), 147 (31), 133 (19), 121 (35), 105 (38), 93 (43).

tert-Butyl[(4*E*,6*E*,10*R*)-10-methoxy-7-methyltrideca-4,6,12-trienyloxy]dimethylsilane 16b

A solution of the alcohol **16a** (2.0 g, 6 mmol) in dry THF (15 ml) was added dropwise over 10 min to a stirred suspension of sodium hydride (0.47 g, 12 mmol) in dry THF (10 ml) at 0 °C under an atmosphere of argon. The mixture was stirred at room temperature for 3 h, then cooled to 0 °C and methyl iodide (3.7 ml, 59 mmol) was added dropwise over 10 min. The mixture was allowed to warm to room temperature and then stirred at that temperature for 6 h. Water (30 ml) was added dropwise over 5 min and the mixture was then extracted with ether (3 × 100 ml). The combined organic extracts were dried and evaporated *in vacuo* to leave a colourless oil. The oil was purified by column chromatography on silica gel using 5% ether–light petroleum as eluant to give the corresponding *methyl ether* (2.1 g, 99%) as a colourless oil; $[\alpha]_D^{20}$ −1.5 (*c* 2.80 in $CHCl_3$); (Found C, 71.6; H, 11.7; $C_{21}H_{40}O_2Si$ requires C, 71.5; H, 11.4%); λ_{max} (EtOH) 217 (4634), 237 (5448) nm; ν_{max}(film) 3076, 2929, 2856, 1255 and 1100 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.87–5.76 (2H, m, 2 × CH), 5.58 (1H, dt, *J* 15.0, 7.0 Hz, CH:C*H*CH_2), 5.12–5.05 (2H, m, CH_2:CH), 3.62 (2H, t, *J* 6.4 Hz, CH_2OSi), 3.35 (3H, s, OCH_3), 3.20 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.30–2.26 (2H, m, CHCH_2CH), 2.18–2.04 (4H, m, 2 × CH_2), 1.73 (3H, s, CH_3), 1.66–1.57 (4H, m, 2 × CH_2), 0.90 [9H, s, $(CH_3)_3CSi$], 0.05 [6H, s, $OSi(CH_3)_2$]; δ_C (90.6 MHz; $CDCl_3$) 136.15 (s), 134.75 (d), 131.85 (d), 126.90 (d), 124.77 (d), 116.93 (t), 79.87 (d), 62.55 (t), 56.53 (q), 37.64 (t), 35.34 (t), 32.59 (t), 31.56 (t), 29.15 (t), 25.95 (q), 18.33 (s), 16.50 (q), −5.29 (q); *m*/*z* (FAB) 353.2848 (MH^+, 6%, $C_{21}H_{41}O_2Si$ requires 353.2876), 295 (10), 220 (11), 189 (27), 161 (13), 147 (39), 133 (21), 121 (59), 107 (37), 93 (58).

(4*E*,6*E*,10*R*)-10-Methoxy-7-methyltrideca-4,6,12-trien-1-ol 17a

TBAF (0.9 g, 3.4 mmol) was added in one portion to a stirred solution of the silyl ether **16b** (1.1 g, 3.1 mmol) in dry THF (15 ml) at 0 °C under an atmosphere of nitrogen. The mixture was allowed to warm to room temperature and then stirred at that temperature for 3 h. Water (20 ml) was added and the mixture was extracted with ether (3 × 100 ml). The combined organic extracts were dried and evaporated *in vacuo* to leave a colourless oil. The oil was purified by column chromatography on silica gel using 50% ether–light petroleum as eluant to give the *alcohol* (0.72 g, 98%) as a colourless viscous oil; $[\alpha]_D^{20}$ −2.2 (*c* 1.90 in $CHCl_3$); (Found C, 75.5; H, 11.6; $C_{15}H_{27}O_2$ requires C, 75.3; H, 11.4%); λ_{max} (EtOH) 234 (5 264) nm; ν_{max}(film) 3377, 2932 and 1095 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.28 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.87–5.76 (2H, m, 2 × CH), 5.59 (1H, dt, *J* 15.0, 7.0 Hz, CH:C*H*CH_2), 5.12–5.05 (2H, m, CH_2:CH), 3.69–3.65 (2H, m, CH_2OH), 3.35 (3H, s, OCH_3), 3.20 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.30–2.05 (6H, m, 3 × CH_2), 1.74 (3H, s, CH_3), 1.72–1.44 (4H, m, 2 × CH_2), 1.37 (1H, br s, OH); δ_C (90.6 MHz; $CDCl_3$) 136.46 (s), 134.63 (d), 131.35 (d), 127.12 (d), 124.56 (d), 116.91 (t), 79.83 (d), 62.29 (t), 56.45 (q), 37.55 (t), 35.27 (t), 32.37 (t), 31.48 (t), 29.14 (t), 16.46 (q); *m*/*z* (EI) 238.1934 (M^+, 32%, $C_{15}H_{27}O_2$ requires 238.1933), 206 (15), 165 (84), 147 (36), 121 (41), 105 (78), 93 (75), 85 (100).

Methanesulfonic acid (4*E*,6*E*,10*R*)-10-Methoxy-7-methyltrideca-4,6,12-trienyl ester 17b

Methanesulfonyl chloride (0.4 ml, 4.6 mmol) was added dropwise over 5 min to a stirred solution of the alcohol **17a** (0.9 g, 3.6 mmol) and triethylamine (1.0 ml, 7.2 mmol) in dry dichloromethane (20 ml) at −30 °C under an atmosphere of nitrogen. The mixture was stirred at −20 °C for 1 h, then at room temperature for 1 h and concentrated *in vacuo* to leave a residue. The residue was purified by column chromatography on silica gel using 50% ether–light petroleum as eluant to give the corresponding *mesylate* (1.11 g, 99%) as a colourless viscous

oil; $[\alpha]_D^{20}$ −0.9 (*c* 2.58 in $CHCl_3$); (Found C, 61.0; H, 9.2; $C_{16}H_{28}SO_4$ requires C, 60.7; H, 8.9%); ν_{max} (film) 2933, 1356, 1175 and 1095 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.28 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.86–5.75 (2H, m, 2 × CH), 5.51 (1H, dt, *J* 15.0, 7.1 Hz, CH:C*H*CH_2), 5.11–5.04 (2H, m, CH_2:CH), 4.23 [2H, t, *J* 6.5 Hz, $CH_2(OSO_2CH_3)$], 3.34 (3H, s, OCH_3), 3.19 [1H, tt, *J* 5.8, 5.8 Hz, $CH(OCH_3)$], 3.00 (3H, s, OSO_2CH_3), 2.31–2.03 (6H, m, 3 × CH_2), 1.85 (2H, tt, *J* 6.5, 6.5 Hz, $CH_2CH_2CH_2$), 1.73 (3H, s, CH_3), 1.62–1.56 (2H, m, $CHCH_2CH_2$); δ_C (90.6 MHz; $CDCl_3$) 137.34 (s), 134.66 (d), 129.35 (d), 128.18 (d), 124.28 (d), 116.92 (t), 79.81 (d), 69.36 (t), 56.48 (q), 37.58 (t), 37.28 (q), 35.29 (t), 31.51 (t), 28.84 (t), 28.56 (t), 16.52 (q); *m*/*z* (FAB) 317.1783 (MH^+, 52%, $C_{16}H_{29}SO_4$ requires 317.1787), 307 (21), 284 (48), 275 (19), 243 (23), 154 (100), 149 (32), 136 (74), 121 (34), 107 (49), 91 (51).

[(4*E*,6*E*,10*R*)-10-Methoxy-7-methyltrideca-4,6,12-trienyl]-triphenylphosphonium iodide 17c

Sodium iodide (1. 9 g, 12.6 mmol) was added in one portion to a stirred solution of the mesylate **17b** (0.8 g, 2.5 mmol) in dry acetone (10 ml) under an atmosphere of nitrogen. The mixture was stirred for 24 h in the dark and the solvents were then removed *in vacuo* to leave a residue. The residue was diluted with ether–hexane (1:1, 25 ml) and filtered through a short pad of silica gel. The solvents were removed *in vacuo* to leave a pale yellow oil which was purified by column chromatography on silica gel using 5% ether–light petroleum as eluant to give the corresponding *iodide* (0.85 g, 98%) as a colourless oil; $[\alpha]_D^{20}$ −1.6 (*c* 4.28 in $CHCl_3$); (Found C, 52.0; H, 7.5; $C_{15}H_{25}IO$ requires C, 51.7; H, 7.2%); λ_{max} (EtOH) 237 (6812) nm; ν_{max} (film) 2926, 1440, 1096, 963 and 911 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.30 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.87–5.76 (2H, m, 2 × CH), 5.50 (1H, dt, *J* 15.0, 7.1 Hz, CH:C*H*CH_2), 5.12–5.05 (2H, m, CH_2:CH), 3.35 (3H, s, OCH_3), 3.24–3.17 [1H, m, C*H*(OCH_3)], 3.20 (2H, t, *J* 7.0 Hz, CH_2I), 2.31–2.02 (6H, m, 3 × CH_2), 1.92 (2H, tt, *J* 7.0, 7.0 Hz, $CH_2CH_2CH_2$), 1.75 (3H, s, CH_3), 1.60 (2H, td, *J* 7.9, 5.9 Hz, $CHCH_2CH_2$); δ_C (90.6 MHz; $CDCl_3$) 137.14 (s), 134.73 (d), 129.51 (d), 128.11 (d), 124.46 (d), 116.97 (t), 79.88 (d), 56.55 (q), 37.64 (t), 35.35 (t), 33.44 (t), 33.06 (t), 31.56 (t), 16.59 (q), 6.58 (t); *m*/*z* (FAB) 349.1018 (MH^+, 47%, $C_{15}H_{25}IO$ requires 349.1028), 348 (71), 316 (44), 307 (51), 275 (45), 249 (35), 154 (100), 136 (62), 119 (35), 107 (53), 93 (54).

Triphenylphosphine (0.6 g, 2.4 mmol) was added in one portion to a stirred solution of the iodide (0.74 g, 2.1 mmol) in dry acetonitrile (10 ml) under an atmosphere of argon. The mixture was heated under reflux for 16 h and then concentrated *in vacuo* to leave a residue. The residue was purified by column chromatography on silica gel using dichloromethane to 10% methanol–dichloromethane as eluant to give the *phosphonium salt* (1.2 g, 92%) as a colourless foam; $[\alpha]_D^{20}$ +0.4 (*c* 11.30 in $CHCl_3$); (Found C, 65.0; H, 6.7; $C_{33}H_{40}IPO$ requires C, 64.9; H, 6.6%); λ_{max} (EtOH) 229 (32 283) nm; ν_{max} (film) 2926, 1438, 1112, 996, 968, 914, 734, 723 and 690 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 7.78–7.72 (9H, m, 9 × ArC*H*), 7.68–7.64 (6H, m, 6 × ArC*H*), 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.77–5.68 (2H, m, 2 × CH), 5.36 (1H, dt, *J* 15.0, 7.2 Hz, CH:C*H*CH_2), 5.03–4.97 (2H, m, CH_2:CH), 3.60–3.54 (2H, m, CH_2P), 3.26 (3H, s, OCH_3), 3.13 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.41 (2H, dt, *J* 7.2, 7.2 Hz, :$CHCH_2CH_2$), 2.23–2.16 (2H, m, CH_2CH_2C), 2.08–1.93 (2H, m, $CHCH_2CH$), 1.73–1.65 (2H, m, $CH_2CH_2CH_2$), 1.65 (3H, s, CH_3), 1.53–1.48 (2H, m, $CHCH_2CH_2$); δ_C (125.8 MHz; $CDCl_3$) 137.65 (s), 134.94 (d), 134.41 (d), 133.38 (d, *J* 10 Hz, d), 130.36 (d, *J* 13 Hz, d), 128.80 (d, *J* 24 Hz, d), 123.98 (d), 118.05 (d), 117.37 (s), 116.71 (t), 79.55 (d), 56.27 (q), 37.32 (t), 35.08 (t), 32.88 (d, *J* 16 Hz, t), 31.29 (t), 22.35 (d, *J* 12 Hz, t), 21.90 (t), 16.49 (q); *m*/*z* (FAB) 483.2819 (M^+ − I, 100%, $C_{33}H_{40}PO$ requires 483.2817), 289 (12), 262 (20), 154 (17), 136 (12), 97 (18).

(4*R*)-*N*-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-[(1*Z*,5*E*,7*E*,11*R*)-11-methoxy-8-methyltetradeca-1,5,7,13-tetraen-1-yl]oxazolidine 19

A solution of sodium hexamethyldisilazide (1.0 M) in THF (1.6 ml, 1.6 mmol) was added dropwise over 30 min to a stirred solution of the phosphonium salt **17c** (1.0 g, 1.6 mmol) in dry THF (10 ml) at −78 °C under an atmosphere of argon. The orange mixture was stirred at −78 °C for 1 h and a solution of the aldehyde 18 (0.45 g, 2.0 mmol) in dry THF (10 ml) was added dropwise over 1 h. The mixture was stirred at −78 °C for a further 1 h and then allowed to warm to 0 °C over 1 h. Water (30 ml) was added and the mixture was then extracted with ether (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave an oil. The oil was purified by column chromatography on silica gel using 15% ether–light petroleum as eluant to give the tetraene (0.58 g, 82%) as a colourless viscous oil; $[\alpha]_D^{20}$ + 73.6 (*c* 1.10 in $CHCl_3$); (Found C, 72.0; H, 10.2; N, 3.2; $C_{26}H_{43}O_4N$ requires C, 72.0; H, 10.0; N, 3.2%); λ_{max} (EtOH) 205 (10 761), 236 (19 958) nm; ν_{max} (film) 2978, 2931, 1698, 1384 and 1095 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.24 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.87–5.76 (2H, m, 2 × CH), 5.56–5.40 (3H, m, 3 × CH), 5.12–5.05 (2H, m, CH_2:CH), 4.72–4.53 (1H, m, NCH), 4.04 (1H, dd, *J* 8.7, 6.2 Hz, OC*H*HCH), 3.63 (1H, dd, *J* 8.7, 3.2 Hz, OCH*H*CH), 3.35 (3H, s, OCH_3), 3.20 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.30–2.07 (8H, m, 4 × CH_2), 1.74 (3H, s, CH_3), 1.63–1.52 (8H, m, 2 × CH_3, CH_2), 1.45 [9H, s, $(CH_3)_3CO$]; δ_C (90.6 MHz; $CDCl_3$) 151.93 (s), 136.58 (s), 134.69 (d), 130.94 (d), 130.82 (d), 129.61 (d), 127.31 (d), 124.57 (d), 116.90 (t), 93.61 (s), 79.83 (d), 79.61 (s), 68.93 (t), 56.50 (q), 54.47 (d), 37.60 (t), 35.33 (t), 32.83 (t), 31.56 (t), 28.45 (q), 27.42 (t), 26.39 (q), 24.05 (q), 16.50 (q); *m*/*z* (EI) 433.3191 (M^+, 1%, $C_{26}H_{43}O_4N$ requires 433.3192), 333 (19), 286 (7), 234 (6), 144 (19), 107 (14), 85 (28).

(2*R*,3*Z*,7*E*,9*E*,13*R*)-13-Methoxy-10-methyl-2-aminohexadeca-3,7,9,15-tetraen-1-ol 10

10% Aqueous HCl solution (16 ml) was added dropwise over 5 min to a stirred solution of the oxazolidine **19** (325 mg, 0.7 mmol) in methanol (32 ml). The mixture was heated at 40 °C (bath temperature) for 3 h and then neutralised with saturated $NaHCO_3$ solution. The mixture was extracted with dichloromethane (3 × 50 ml) and the combined organic extracts were then dried (Na_2SO_4) and evaporated *in vacuo* to leave the crude amino-alcohol (200 mg, 91%) as a colourless viscous oil; ν_{max} (film) 3356, 2922, 1443, 1097, 963 and 913 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.87–5.76 (2H, m, 2 × CH), 5.59–5.55 (2H, m, 2 × CH), 5.27 [1H, dd, *J* 9.9, 9.9 Hz, CH:C*H*$CH(NH_2)$], 5.12–5.05 (2H, m, CH_2:CH), 3.74–3.73 [1H, m, $CH(NH_2)$], 3.50 [1H, dd, *J* 10.4, 4.5 Hz, C*H*H(OH)], 3.37–3.29 [1H, m, CH*H*(OH)], 3.35 (3H, s, OCH_3), 3.20 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.30–2.08 (9H, m, 4 × CH_2, OH), 1.74 (3H, s, CH_3), 1.74–1.68 (2H, br m, NH_2), 1.60 [2H, td, *J* 7.9, 6.0 Hz, $CH(OCH_3)CH_2CH_2$];δ_C (90.6 MHz; $CDCl_3$) 136.88 (s), 134.74 (d), 131.60 (d), 130.95 (d), 127.44 (d), 124.53 (d), 116.95 (t), 79.88 (d), 77.20 (d), 66.43 (t), 56.53 (q), 50.11 (d), 37.64 (t), 35.36 (t), 32.88 (t), 31.58 (t), 27.83 (t), 16.56 (q); *m*/*z* (EI) 293.2343 (M^+, 9%, $C_{18}H_{31}O_2N$ requires 293.2355), 262 (35), 220 (13), 185 (5), 145 (15), 119 (42), 107 (40), 93 (52), 85 (100), which was used without further purification.

(1*R*,2*S*)-2-Methylcyclopropanecarboxylic acid (2-aminophenyl)-amide 26

Benzotriazol-1-yloxy(tripyrrolidino)phosphonium hexafluorophosphate (2.40 g, 4.6 mmol) was added in one portion to a stirred mixture of *cis*-2-methylcyclopropane carboxylic acid **22** (420 mg, 4.2 mmol), phenylene-1,2-diamine (454 mg, 4.2 mmol) and triethylamine (1.2 ml, 8.4 mmol) in dry dichloromethane (30 ml) at 0 °C and under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 3 h and then at room temperature

overnight. Water (50 ml) was added and the mixture was extracted with ethyl acetate (3 × 200 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave a brown oil. The oil was purified by column chromatography on silica gel using 80% ether–light petroleum as eluant to give the *amide* (482 mg, 60%) as a white solid. Recrystallisation from dichloromethane–light petroleum gave white crystals; mp 142–145 °C; $[\alpha]_D^{20}$ +8.2 (*c* 0.8 in $CHCl_3$); (Found C, 69.8; H, 7.4; N, 14.9; $C_{11}H_{14}ON_2$ requires C, 69.5; H, 7.4; N, 14.7%); λ_{max} (EtOH) 221 (12 672), 236 (8777), 292 (3295) nm; ν_{max} ($CHCl_3$) 3421, 3004, 2400, 1670, 1621, 1501 and 1453 cm^{-1}; δ_H (360 MHz; d_6-DMSO) 9.36 [1H, s, NH(CO)], 7.21 (1H, d, *J* 7.7 Hz, ArC*H*), 6.90 (1H, dd, *J* 7.7, 7.7 Hz, ArC*H*), 6.75 (1H, d, *J* 7.7 Hz, ArC*H*), 6.57 (1H, dd, *J* 7.7, 7.7 Hz, ArC*H*), 4.83 (2H, s, NH_2), 1.91–1.85 [1H, m, (NH)COC*H*], 1.29–1.19 (1H, m, CHC*H*HCH), 1.15 (3H, d, *J* 6.0 Hz, CH_3), 1.01 (1H, ddd, *J* 8.0, 8.0, 3.8 Hz, CHCH*H*CH), 0.80–0.76 (1H, m, C*H*CH_3); δ_C (90.6 MHz; d_6-DMSO) 169.66 (s), 141.76 (s), 125.67 (d), 125.17 (d), 124.20 (s), 116.46 (d), 116.21 (d), 20.12 (d), 14.60 (d), 12.44 (t), 12.08 (q); *m*/*z* (EI) 190.1105 (M^+, 68%, $C_{11}H_{14}ON_2$ requires 190.1106), 172 (15), 157 (5), 145 (5), 108 (100), 83 (73).

(1*R*,2*S*)-2-Methylcyclopropanecarbothioic acid (2-aminophenyl)-amide 27

Phosphorus pentasulfide (449 mg, 1.0 mmol) was added in one portion to a stirred suspension of sodium carbonate (107 mg, 1.0 mmol) in dry THF (6.5 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. The amide **26** (120 mg, 0.63 mmol) was added in one portion and the resulting mixture was stirred at 0 °C for 5 h and then at room temperature for 12 h. Sodium phosphate tribasic solution (12%, 10 ml) was added and the mixture was stirred vigorously for 2 h. The mixture was extracted with ether (3 × 75 ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave a colourless solid. The solid was purified by column chromatography on silica gel using 70% ether–light petroleum as eluant to give the *thioamide* (77 mg, 58%) as a waxy solid; $[\alpha]_D^{20}$ +213.5 (*c* 0.95 in $CHCl_3$); λ_{max} (EtOH) 234 (11 822), 276 (10 047) nm; ν_{max} ($CHCl_3$) 3369, 2960, 1621, 1502, 1453, 1383 and 1352 cm^{-1}; δ_H (360 MHz; d_6-DMSO, 353 K) 10.73 [1H, br s, NH(CS)], 7.08–7.02 (2H, m, 2 × ArC*H*), 6.81 (1H, d, *J* 7.9 Hz, ArC*H*), 6.65–6.61 (1H, ddd, *J* 7.5, 7.5, 1.3 Hz, ArC*H*), 2.42–2.36 [1H, m, (NH)CSC*H*], 1.34–1.29 (2H, m, CHC*H*HCH and C*H*CH_3), 1.25 (3H, d, *J* 5.2 Hz, CH_3), 1.10–1.06 (1H, m, CHCH*H*CH); δ_C (90.6 MHz; d_6-DMSO, 353 K) 201.52 (s), 142.98 (s), 127.29 (d), 127.23 (d), 125.32 (s), 116.20 (d), 116.60 (d), 29.35 (d), 15.69 (d), 14.72 (t), 11.25 (q); *m*/*z* (EI) 206.0876 (M^+, 49%, $C_{11}H_{14}SN_2$ requires 206.0878), 173 (100), 157 (11), 145 (13), 108 (20), 99 (15).

Benzotriazol-1-yl-[(1*R*,2*S*)-2-methylcyclopropyl]-methanethione 11

Sodium nitrite (126 mg, 1.8 mmol) was added in three portions over 3 min to a stirred solution of the thioamide **27** (252 mg, 1.2 mmol) in aqueous acetic acid solution (95%, 15 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Ice-cold water (20 ml) was added and the mixture was then extracted with cold dichloromethane (150 ml). The separated organic layer was washed with ice-cold water (3 × 50 ml), dried (Na_2SO_4) and evaporated *in vacuo* (bath temp. < 5 °C) to leave the crude *benzotriazole* as a yellow oil; δ_H (360 MHz; $CDCl_3$) 8.89 (1H, d, *J* 8.3 Hz, ArC*H*), 8.16 (1H, d, *J* 8.3 Hz, ArC*H*), 7.68 (1H, ddd, *J* 8.3, 8.3, 1.0 Hz, ArC*H*), 7.54 (1H, ddd, *J* 8.3, 8.3, 1.0 Hz, ArC*H*), 3.98–3.92 [1H, m, (CS)CH], 1.92–1.87 (1H, m, CHC*H*HCH), 1.76–1.71 (1H, m, C*H*CH_3), 1.51–1.45 (1H, m, CHCH*H*CH), 1.22 (3H, d, *J* 6.2 Hz, CH_3) which was used immediately in the next reaction without further purification.

(1*R*,2*S*)-2-Methylcyclopropanecarbothioic acid [(1*R*,2*Z*,6*E*,8*E*,12*R*)-1-(Hydroxymethyl)-12-methoxy-9-methylpentadeca-2,6,8,14-tetraenyl]amide 28

A solution of the benzotriazole **11** in dry DMF (2 ml) maintained at 0 °C, was added dropwise over 1 min to a stirred solution of the amino alcohol **10** (325 mg, 1.1 mmol) in dry DMF (1 ml) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 2 h and then water (15 ml) was added. The mixture was extracted with ether (3 × 100 ml) and the combined organic extracts were then washed with brine (75 ml), dried (Na_2SO_4) and evaporated *in vacuo* to leave an orange oil. The oil was purified by column chromatography on silica gel using 40% ether–light petroleum as eluant to give the *thioamide* (379 mg, 87%) as a colourless viscous oil; $[\alpha]_D^{20}$ + 62.8 (*c* 2.76 in $CHCl_3$); ν_{max} (film) 3261, 3073, 3007, 2927, 1641, 1518, 1444, 1408, 1387, 1334, 1078 and 964 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 7.38 (1H, d, *J* 7.2 Hz, NH), 6.25 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.85–5.77 (2H, m, 2 × CH), 5.72–5.67 (1H, m, C*H*NH), 5.60–5.52 (2H, m, 2 × CH), 5.46–5.42 [1H, m, CH_2C*H*:CHCH(NH)], 5.11–5.05 (2H, m, CH_2:CH), 3.84 [1H, dd, *J* 10.8, 4.0 Hz, C*H*H(OH)], 3.72 [1H, dd, *J* 10.8, 5.3 Hz, CH*H*(OH)], 3.34 (3H, s, OCH_3), 3.20 [1H, tt, *J* 5.9, 5.9 Hz, C*H*(OCH_3)], 2.32–2.02 (10H, m, 4 × CH_2, CH, OH), 1.73 (3H, s, CH_3), 1.59 [2H, td, *J* 7.8, 6.1 Hz, CH(OCH_3)C$H_2$$CH_2$], 1.34–1.28 (1H, m, CHC*H*HCH), 1.19–1.13 (1H, m, C*H*CH_3), 1.14 (3H, d, *J* 6.3 Hz, CHCH_3), 1.05 (1H, ddd, *J* 8.0, 8.0, 5.1 Hz, CHCH*H*CH); δ_C (90.6 MHz; $CDCl_3$) 201.79 (s), 136.77 (s), 135.68 (d), 134.70 (d), 130.80 (d), 127.55 (d), 124.83 (d), 124.58 (d), 116.95 (t), 79.86 (d), 65.44 (t), 56.49 (q), 54.34 (d), 37.61 (t), 35.34 (t), 32.58 (t), 31. 54 (t), 30.82 (d), 28.38 (t), 16.56 (q), 16.16 (d), 14.54 (t), 11.94 (q); *m*/*z* (EI) 391.2529 (M^+, 14%, $C_{23}H_{37}SO_2N$ requires 391.2545), 360 (11), 316 (21), 274 (17), 198 (80), 180 (88), 166 (24).

(+)-Curacin A (1)

Burgess' reagent (13.4 mg, 0.1 mmol) was added in one portion to a stirred solution of the thioamide **28** (11.0 mg, 0.1 mmol) in dry THF (2 ml) under an atmosphere of nitrogen. The mixture was stirred for 2 h and the solvents were then removed *in vacuo* to leave a pale yellow residue. The residue was purified by column chromatography on silica gel using 10% ether–light petroleum as eluant to give *curacin A* (5.2 mg, 50%) as a colourless viscous oil; $[\alpha]_D^{20}$ +61.3 (*c* 0.75 in $CHCl_3$) {naturally occurring curacin A showed $[\alpha]_D^{20}$ +60.0 (*c* 1.1 in $CHCl_3$)}; ν_{max} (film) 2924, 1616, 1440, 1097 and 963 cm^{-1}; δ_H (500 MHz; C_6D_6) 6.34 (1H, dd, *J* 15.0, 10.8 Hz, CHC*H*:CH), 5.98 (1H, d, *J* 10.8 Hz, C:C*H*CH), 5.83 (1H, ddt, *J* 16.9, 10.4, 7.1 Hz, CH_2:CH), 5.65 (1H, dd, *J* 10.7, 9.2 Hz, CH:C*H*CHN), 5.53 (1H, dt, *J* 15.0, 6.4 Hz, CH:C*H*CH_2), 5.41 (1H, dt, *J* 10.7, 6.6 Hz, CH_2C*H*:CHCH), 5.08–5.03 (3H, m, CH_2, CH), 3.14 (3H, s, OCH_3), 3.09–3.01 [1H, m, C*H*(OCH_3)], 3.05 (1H, dd, *J* 10.8, 8.1 Hz, C*H*HS), 2.75 (1H, dd, *J* 10.8, 10.8 Hz, CH*H*S), 2.24–2.03 (8H, m, 4 × CH_2), 1.69–1.57 (3H, m, CH, CH_2), 1.66 (3H, s, CH_3), 1.19–1.16 (1H, m, CHC*H*HCH), 1.18 (3H, d, *J* 6.2 Hz, CHCH_3), 0.95–0.91 (1H, m, C*H*CH_3), 0.71 (1H, ddd, *J* 8.2, 8.2, 4.4 Hz, CHCH*H*CH); δ_C (125.8 MHz; C_6D_6) 168.45 (s), 136.47 (s), 135.35 (d), 131.38 (d), 131.33 (d), 130.87 (d), 127.51 (d), 125.56 (d), 116.84 (t), 79.93 (d), 74.34 (d), 56.34 (q), 39.98 (t), 38.06 (t), 35.82 (t), 33.16 (t), 32.18 (t), 28.16 (t), 20.14 (d), 16.61 (q), 16.04 (d), 14.25 (t), 12.36 (q); *m*/*z* (FAB) 374.2499 (MH^+, 100%, $C_{23}H_{36}SON$ requires 374.2518), 342 (3), 274 (4), 180 (14), 166 (7), 140 (9), 119 (11), 105 (14), 93 (27).

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