Total Synthesis of Solamin and Reticulatacin

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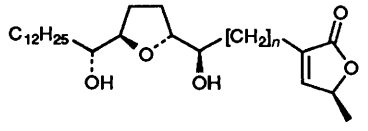
A total synthesis of the natural products, solamin **1** and reticulatacin **2** is described. The monotetrahydrofuran moiety **12a** of compounds **1** and **2** was constructed by an eight-step reaction sequence, starting from (−)-muricatacin **5**, an acetogenin derivative. The γ-lactone moieties **26** and **27** of compounds **1** and **2** were prepared by a multi-stage procedure, starting from (*S*)-(−)-ethyl lactate. A palladium-catalysed cross coupling reaction of compound **12a** with either compound **26** or compound **27** gave the products **28** and **29** which by a three-step sequence were converted into compounds **1** and **2** respectively. Similarly, 15,16-di-*epi*-solamin **3** and 17,18-di-*epi*-reticulatacin **4** were synthesized.

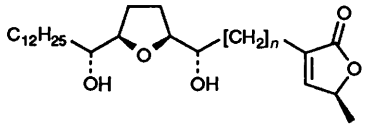
Annonaceous acetogenins, isolated from a number of plants belonging to the Annonaceae, show a broad spectrum of potent biological activity[1] by inhibiting electron-transport in mitocondria. Although more than 90 members of this family have been reported since isolation of the first in 1982,[1-3] few have been synthesized, probably because little is known of their absolute configuration. Sinha *et al.*, achieved a total synthesis of natural solamin **1** and reticulatacin **2**,[4] just prior to the completion of our synthetic study. A non-natural diastereoisomer of uvalicin,[5] a diastereoisomer of dihydro-4-oxomurisolin,[6] a diastereoisomer of corossoline[7] and an enantiomer of (+)-bullatacin[8] have also been synthesized.

Here, we report a total synthesis of natural solamin **1**,[9] 15,16-di-*epi*-solamin **3**, natural reticulatacin **2**[10] and 17,18-di-*epi*-reticulatacin **4**. Our synthetic strategy is outlined in Fig. 2.

As shown in Schemes 1 and 2, tetrahydrofuran moiety **12a** of compounds **1** and **2** was constructed from (−)-muricatacin **5**,[11] an acetogenin derivative which we have previously synthesized in an enantiomerically pure state.[12] The hydroxy group of the alcohol **5** was protected as a methoxymethyl ether (MOM ether) to give compound **6**. Reduction of compound **6** with diisobutylaluminium hyride (DIBAL) gave the hemiacetal **7**, which was then submitted to Wittig reaction with pent-4-ynylidenetriphenylphosphorane[13] to afford the acyclic compound **8**. Epoxidation of compound **8** with *m*-chloroperbenzoic acid (MCPBA) and subsequent acid-catalysed cyclization with camphorsulfonic acid (CSA) gave an inseparable mixture of the diastereoisomers **9a** and **9b**. At this stage, we could not determine the stereochemistry nor the ratio of **9a** and **9b**, since all the ^{1}H NMR signals for **9a** and **9b** overlapped. Recently, Cassady *et al.*, have reported that since the isomers of different relative stereochemistry for the bis(2,4,6-trimethylbenzoate) esters of 1,1′-(tetrahydrofuran-2,5-diyl)bis(pentan-1-ol) showed unique chemical-shift patterns in deuteriobenzene, it was possible to assign the relative stereochemistry of the monotetrahydrofuranyl moiety of annonaceous acetogenins. Thus, the chemical shift for the tetrahydrofuran ring methine protons of the *threo-trans-threo* model was δ 4.09, while that of the *threo-cis-threo* model was δ 3.97.[14] In order to apply this method in our work, the diastereoisomers **9a** and **9b** were converted into the bis(2,4,6-trimethylbenzoates) **10a** and **10b** as follows: removal of the MOM protecting group of the inseparable mixture **9a** and **9b**, subsequent hydrogenation with 5%-palladium carbon as catalyst and treatment with 2,4,6-trimethylbenzoyl chloride (Fig. 3). The ^{1}H NMR spectra of the diastereoisomers **10a** and **10b** in deuteriobenzene showed a 3:2 ratio of signals at δ 4.10 and 3.98 for the tetrahydrofuran



Solamin 1: $n = 12$
Reticulatacin 2: $n = 14$



15,16-Di-*epi*-solamin 3: $n = 12$
17,18-Di-*epi*-reticulatacin 4: $n = 14$

Fig. 1

ring methine protons, thus indicating that isomer **9a** with the desired stereochemistry (*threo-trans-threo*) was the major product in the epoxidation–cyclization of compound **8**. For the epoxidation of compound **8**, use of the vanadyl acetylacetonate–*tert*-butyl hydroperoxide system instead of MCPBA gave the *threo-trans-threo* and *threo-cis-threo* products in a 1:4 ratio, an unfavourable result compared to that for the MCPBA oxidation. Fortunately, isomers **9a** and **9b** were separable by preparative thin-layer chromatography (TLC) (benzene–AcOEt = 20:1) after the hydroxy group of compounds **9a** and **9b** had been protected as a benzoate ester (**11a** and **11b**). Hydrolysis of benzoate ester and removal of the MOM protecting group afforded compound **12a** and its diastereoisomer **12b**.

As shown in Scheme 3, the γ-lactone moieties **26** and **27** of compounds **1** and **2** were constructed as follows. The γ-lactone **13** was prepared by White's method,[15] starting from (*S*)-(−)-ethyl lactate. Alternatively, the vinyl iodide moieties **24** and **25** were prepared through a seven-step reaction sequence, starting from prop-2-yn-1-ol and either 1-bromopentane or 1-bromoheptane. The acetylenic alcohols **14** and **15**, prepared by the reported procedure[16] were subjected to the acetylene zipper reaction with potassium 3-aminopropylamide (KAPA) in 3-aminopropylamine to give the terminal acetylenes **16** and **17**.[17] The primary hydroxy group of compounds **16** and **17** were protected as a *tert*-butyldimethylsilyl ether (TBS ether) to give compounds **18** and **19** which, on treatment with tributyltin hydride and subsequently with iodine, afforded an *EZ* mixture

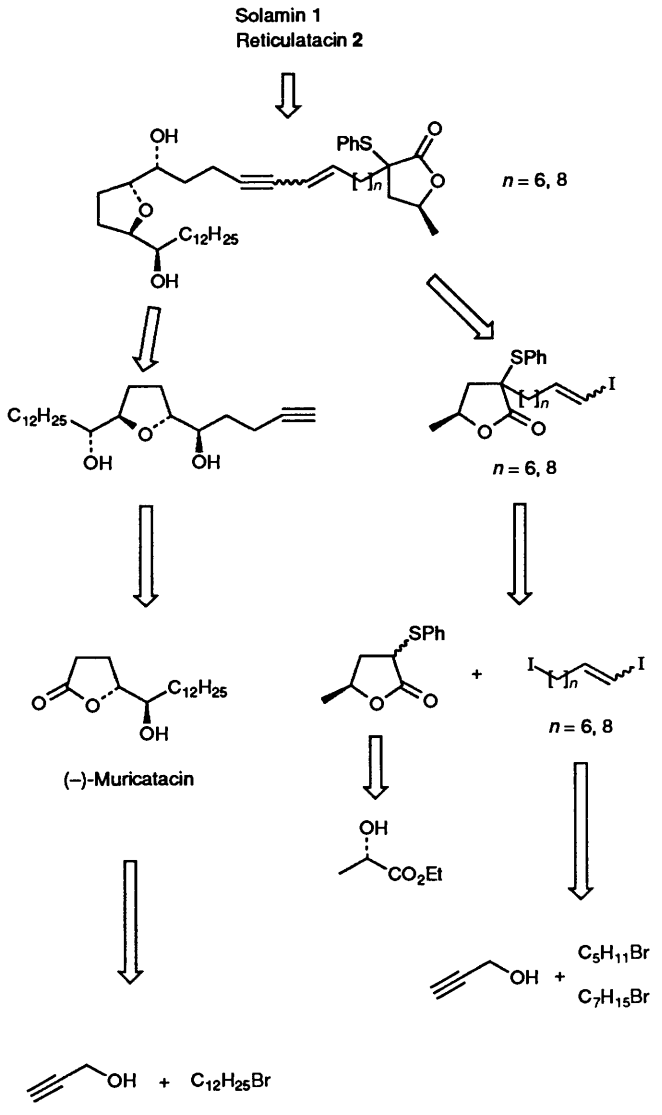


Fig. 2 Retro synthesis

of compounds **20** and **21** in a good yield.[18] After removal of the TBS protecting group of **20** ($E:Z$ = 3:1) and **21** ($E:Z$ = 1:1) with tetrabutylammonium fluoride (TBAF), compounds **22** and **23** were transformed into the diiodides **24** and **25** in two steps *via* tosylation followed by iodination. The diiodides **24** and **25** were then subjected to alkylation with the sodium enolate of compound **13** to afford the furanones **26** and **27** in 50% yield.

As shown in Scheme 4, completion of the carbon skeleton to give the coupled products **28** and **29** was achieved by application of Hoye's method.[5] A $Pd^{(0)}$-catalysed cross coupling reaction of compound **12a** with the iodides **26** or **27** gave compounds **28** and **29**, respectively. Catalytic hydrogenation of compounds **28** and **29** using Wilkinson's catalyst afforded the saturated products **30** and **31**. Oxidation of the sulfur with MCPBA, followed by thermal elimination afforded compounds **1** and **2**.

The synthetic solamin **1** was identical with the natural sample kindly supplied by Dr. B. Figadère in terms of its optical rotation and ^{1}H NMR, IR and MS spectral data. The optical rotation, ^{1}H NMR, IR and MS spectra and melting point of synthetic reticulatacin **2** were in good agreement with reported values.[10]

Similarly, 15,16-di-*epi*-solamin **3** and 17,18-di-*epi*-reticulatacin **4** were synthesized (Scheme 5).

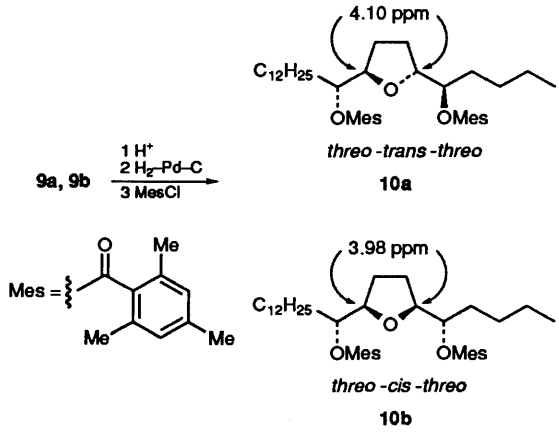
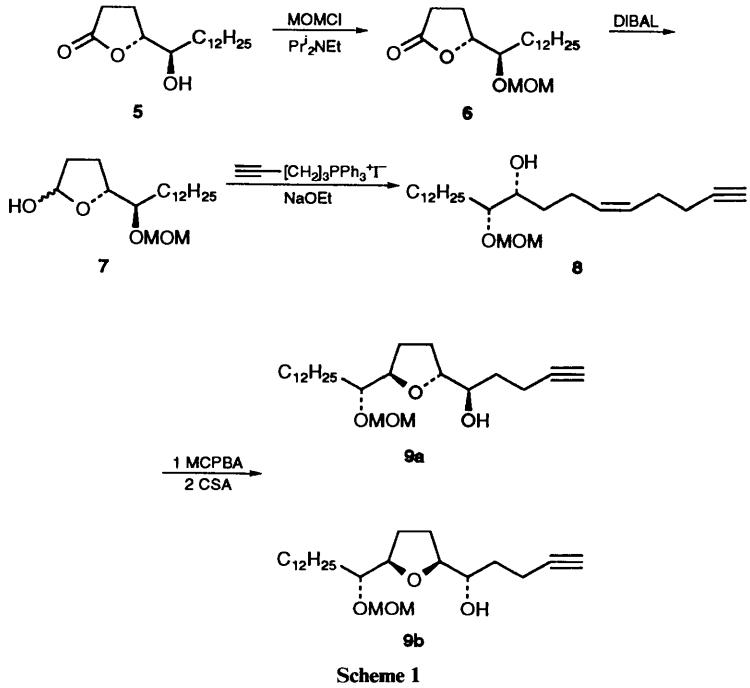
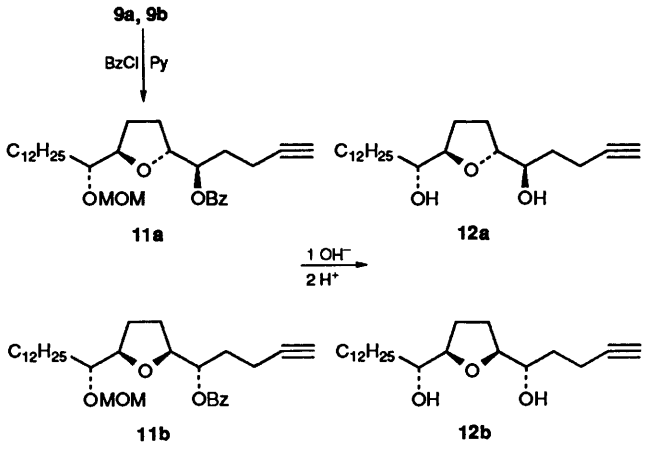


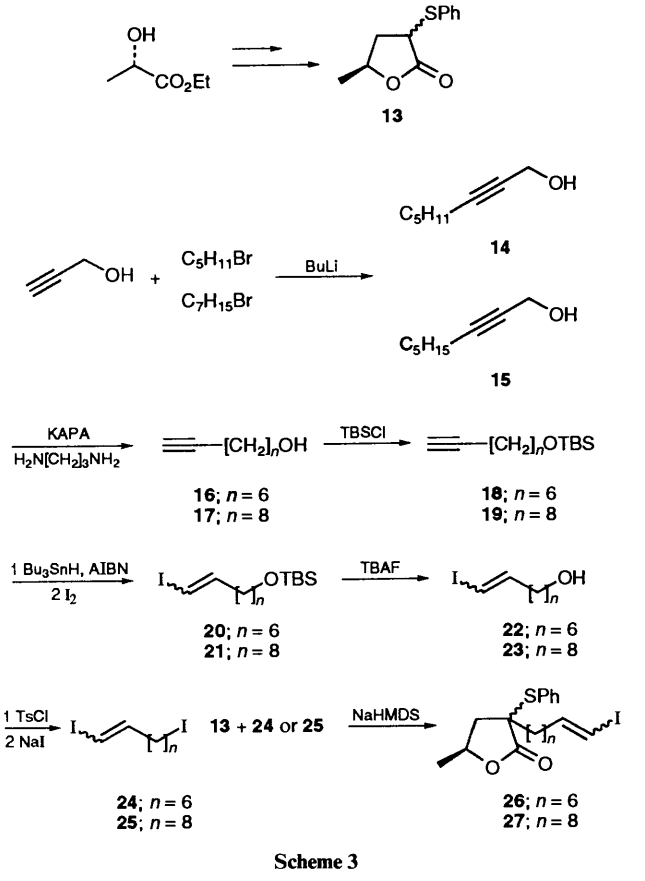
Fig. 3



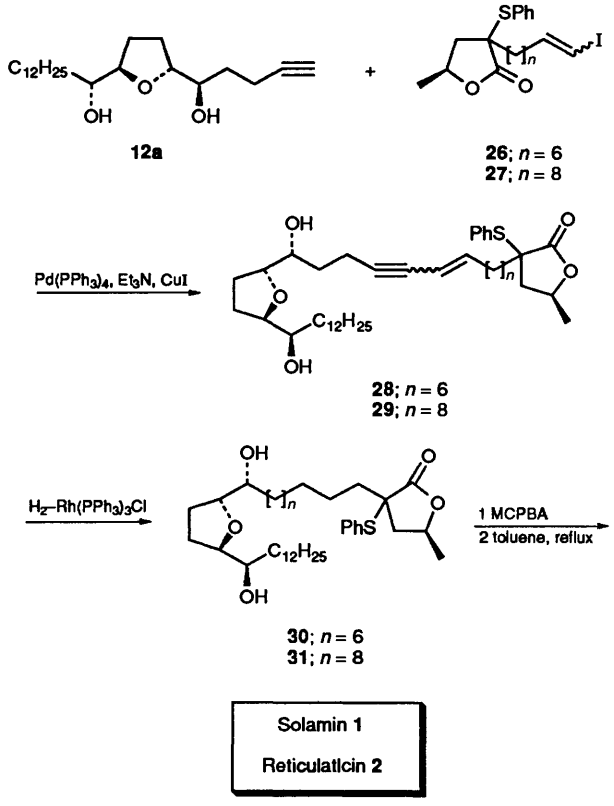
Scheme 1



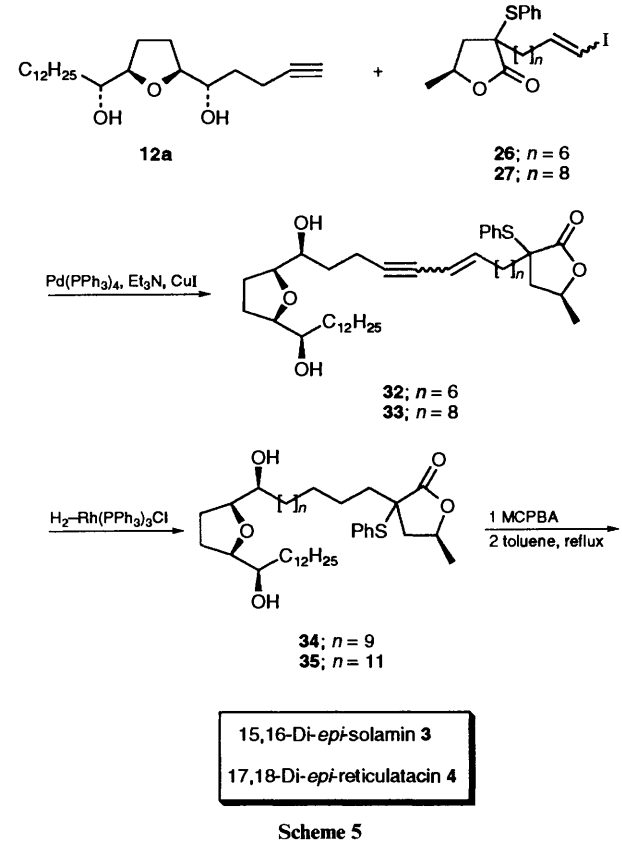
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Experimental

All m.p. values are uncorrected. Optical rotation was measured with a JASCO DIP-4 spectrometer and are quoted in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a JASCO IR-810 infrared spectrometer, and ^{1}H NMR spectra were measured with JEOL GSX-270 (270 MHz) spectrometer and J values are reported in Hz. MS spectra were recorded with a JEOL JMS-DX-300 and JMS-DX-303 instruments.

(5R,5'R)-(2',4'-*Dioxaheptadecan-5'-yl*)*tetrahydrofuran-2-one* **6**.—An ice-cooled mixture of (−)-muricatacin **5** (1.95 g, 6.69 mmol) and chloromethyl methyl ether (**CAUTION**) (5.39 g, 67 mmol) in CH_2Cl_2 (20 cm^3) was treated with Pr^i_2NEt (2.20 g, 17 mmol) and the resultant mixture was warmed to room temp. and stirred for 30 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and Et_3N (6.01 g, 60 mmol) and water (10 cm^3) were added to it. The mixture was acidified to pH 6 and extracted with diethyl ether. The extract was dried and evaporated to give crude compound **6**, which was purified using silica gel column chromatography, eluted with hexane–AcOEt (20:1), to give compound **6** (2.10 g, 94%) as a colourless oil,

$[\alpha]_D^{22}$ −17.4 (*c* 1.14, $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 2850, 1780, 1465, 1360, 1215, 1180, 1150, 1100, 1040, 990 and 920; δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.7), 1.26–1.68 (22 H, m), 2.08 (1 H, m), 2.24 (1 H, m), 2.43–2.67 (2 H, m), 3.40 (3 H, s), 3.60 (1 H, m), 4.56 (1 H, dt, *J* 7.2 and 5.1) and 4.71 (2 H, s) (Found: C, 69.4; H, 10.8. Calc. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05%).

(5R,5′R)-(2′,4′-*Dioxaheptadecan-5′-yl*)*tetrahydrofuran-2-ol* **7**.—To a solution of compound **6** (2.10 g, 6.38 mmol) in CH_2Cl_2 (20 cm^3) was added a diisobutylaluminium hydride solution in hexane (1.0 mol dm^{-3}; 6.38 cm^3, 6.38 mmol) at −78 °C. After the mixture had been stirred for 20 min, MeOH (5.0 cm^3) was added to it and the whole allowed to warm to room temp. Filtration through plug of Celite followed by evaporation gave compound **7** as a colourless oil, which was used in the next step without further purification.

(Z,9R,10R)-10-(*Methoxymethoxy*)*docos-5-en-1-yn-9-ol* **8**.—*N*,*N*-Dimethylformamide (DMF) (100 cm^3) was added to NaOEt (4.12 g, 60.4 mmol) with cooling in an ice-bath and the mixture was stirred until homogeneous. Pent-4-yn-1-yltriphenylphosphonium iodide (27.5 g, 60.4 mmol) was added to the mixture which was then stirred at 0 °C for 2 h. To the solution, maintained at 0–5 °C, a solution of compound **7** (1.97 g, 5.97 mmol) in DMF (20 cm^3) was added dropwise over a period of 1 h. After the usual work-up, the crude product was chromatographed over silica gel and eluted with hexane–AcOEt (4:1) to give the alcohol **8** as a colourless oil, $[\alpha]_D^{24}$ −9.4 (*c* 1.34, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 3300, 3000, 2920, 2850, 2100, 1650, 1470, 1455, 1145, 1100, 1040, 920, 720 and 630; δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.6), 1.26–1.58 (24 H, m), 1.95 (1 H, t, *J* 2.7), 2.21–2.32 (6 H, m), 2.29 (1 H, d, *J* 4.4, OH), 3.35 (1 H, m), 3.41 (3 H, s), 3.52 (1 H, m), 4.70 (2 H, s) and 5.47 (2 H, m) (Found: C, 75.3; H, 11.6. Calc. for $C_{24}H_{44}O_3$: C, 75.74; H, 11.65%).

(2R,5R,1′R,1″R)- *and* (2S,5R,1′S,1″R)-2-(1′-*Hydroxypent*-4′-*ynyl*)-5-(2″,4″-*dioxaheptadecan-5″-yl*)*tetrahydrofuran* **9a** *and* **9b**.—To a solution of compound **8** (1.17 g, 3.09 mmol) in CH_2Cl_2 (20 cm^3) was added MCPBA (2.18 g, 12.6 mmol) at 0 °C. After the mixture had been stirred for 2 h, sat. $Na_2S_2O_3$ (10 cm^3) and $NaHCO_3$ (10 cm^3) were added to it and the whole was extracted with CH_2Cl_2. Drying ($MgSO_4$) and subsequent evaporation of the mixture gave a colourless oil, which was dissolved in CH_2Cl_2 (20 cm^3) and the solution was added camphorsulfonic acid (50 mg) at 0 °C. After the mixture had been stirred for 2 h at this temperature, it was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated to afford an inseparable mixture of compounds **9a** and **9b** as a colourless oil, which was used in the next step without further purification.

Determination of the Ratio of **9a** *and* **9b**.—To a solution of the mixture of compounds **9a** and **9b** (40 mg, 0.1 mmol) in MeOH (2 cm^3) was added a trace of conc. HCl. After the mixture had been stirred for 6 h, the solvent was evaporated. Purification of the residue by preparative TLC (hexane–AcOEt, 3:1) gave a colourless oil, which was dissolved in EtOH and hydrogenated over 5% Pd–C for 3 h. Filtration and evaporation of the reaction mixture provided an oil, which was dissolved in pyridine (0.5 cm^3) and treated with 2,4,6-trimethylbenzoyl chloride (18 mg, 0.1 mmol) at 0 °C. After the mixture had been stirred for 3 h, it was diluted with diethyl ether (10 cm^3) and washed with dilute hydrochloric acid and brine. Drying ($MgSO_4$) and evaporation provided an oil. Purification by preparative TLC (hexane–AcOEt, 10:1) gave a mixture of compounds **10a** and **10b** (36 mg, 56%). The ^1H NMR spectrum showed that the ratio of **10a**:**10b** was 3:2. δ_H(C_6D_6) 0.85 (3 H, t, *J* 6.6), 0.91 (3 H, t, *J* 6.6), 1.15–1.80 (32 H, m), 2.04 (6 H, br), 2.46 (12 H, br), 3.98 (0.8 H, m, *threo-cis-threo*), 4.10 (1.2 H, m, *threo-trans-threo*), 5.27–5.38 (2 H, m) and 6.65 (4 H, br).

(2R,5R,1′R,1″R)- *and* (2S,5R,1′S,1″R)-2-(1′-*Benzyloxypent*-4′-*ynyl*)-5-(2″,4″-*dioxaheptadecan-5″-yl*)*tetrahydrofuran* **11a** *and* **11b**.—To a solution of the mixture of compounds **9a** and **9b** (670 mg, 1.69 mmol) in pyridine (10 cm^3) was added benzoyl chloride (261 mg, 1.86 mmol) at 0 °C. After being stirred in an ice-bath for 1 h and then at room temp. for 5 h, the mixture was poured into sat. aqueous $NaHCO_3$ and extracted with diethyl ether. Drying ($MgSO_4$) and subsequent evaporation of the extract afforded a crude product, which was chromatographed over silica gel with hexane–AcOEt (20:1) as eluent to give a colourless oil (769 mg, 91%). Further purification by preparative TLC (benzene–AcOEt, 20:1) gave the *threo-trans-threo* isomer **11a** (438 mg, 0.876 mmol) and the *threo-cis-threo* isomer **11b** (331 mg, 0.662 mmol). Data for **11a**; $[\alpha]_D^{26}$ +34.8 (*c* 2.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3300, 3060, 2920, 2850, 2100, 1715, 1600, 1445, 1360, 1310, 1270, 1105, 1040, 915 and 705; δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.6), 1.20–1.51 (22 H, m), 1.71–2.09 (6 H, m), 1.94 (1 H, t, *J* 2.6), 2.35 (2 H, m), 3.35 (3 H, s), 3.46 (1 H, m), 4.07 (1 H, m), 4.18 (1 H, m), 4.62 (1 H, d, *J* 6.7), 4.77 (1 H, d, *J* 6.7), 5.27 (1 H, m), 7.36–7.56 (3 H, m), 8.04–8.07 (2 H, m) (Found: C, 74.0; H, 9.6. Calc. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Data for **11b**; $[\alpha]_D^{26}$ −4.6 (*c* 1.20, $CHCl_3$). The IR spectrum was similar to that of compound **11a**. δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.7), 1.20–1.51 (22 H, m), 1.70–2.11 (6 H, m), 1.94 (1 H, t, *J* 2.7), 2.30 (2 H, m), 3.37 (3 H, s), 3.55 (1 H, m), 3.90 (1 H, m), 4.15 (1 H, m), 4.65 (1 H, d, *J* 6.8), 4.83 (1 H, d, *J* 6.8), 5.32 (1 H, m), 7.36–7.61 (3 H, m) and 8.05–8.09 (2 H, m) (Found: C, 73.9; H, 9.5. Calc. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66%).

(2R,5R,1′R,1″R)-2-(1′-*Hydroxypent*-4′-*ynyl*)-5-(1″-*hydroxytridecanyl*)*tetrahydrofuran* **12a**.—To a solution of the alcohol **11a** (438 mg, 0.876 mmol) in MeOH (5 cm^3) was added NaOH (50 mg). After the mixture had been stirred for 5 h, the solvent was evaporated and the mixture was extracted with diethyl ether. Subsequent evaporation of the extract gave a colourless oil, which was dissolved in MeOH (5 cm^3) and treated with a trace of conc. HCl. After the mixture had been stirred for 6 h, the solvent was evaporated and the crude product was chromatographed over silica gel with hexane–AcOEt (2:1) as eluent to give compound **12a** (243 mg, 79%) as colourless needles, m.p. 35–37 °C; $[\alpha]_D^{26}$ +21.5 (*c* 1.28, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 3320, 2950, 2930, 2850, 2120, 1460, 1070 and 620; δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.7), 1.20–2.02 (28 H, m), 1.96 (1 H, t, *J* 2.6), 2.26 (1 H, d, *J* 4.2, OH), 2.34 (1 H, br, OH), 2.36 (2 H, m), 3.41 (1 H, m), 3.56 (1 H, m) and 3.82 (2 H, m) (Found: C, 74.7; H, 11.4. Calc. for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44%).

(2S,5R,1′S,1″R)-1-(1′-*Hydroxypent*-4′-*ynyl*)-5-(1″-*hydroxytridecanyl*)*tetrahydrofuran* **12b**.—In the same manner as described above, compound **11b** (331 mg, 0.662 mmol), afforded compound **12b** (182 mg, 78%) as colourless needles, m.p. 29–33 °C; $[\alpha]_D^{24}$ −9.3 (*c* 0.60, $CHCl_3$). The IR spectrum of compound **12b** was similar to that of compound **12a**; δ_H($CDCl_3$) 0.88 (3 H, t, *J* 6.7), 1.20–2.02 (28 H, m), 1.97 (1 H, t, *J* 2.6), 2.28 (1 H, br, OH), 2.39 (2 H, dt, *J* 7.3 and 2.6), 2.42 (1 H, br, OH), 3.42 (1 H, m), 3.60 (1 H, m) and 3.85 (2 H, m) (Found: C, 75.1; H, 11.2. Calc. for $C_{22}H_{40}O_3$: C, 74.95; H, 11.44%).

(3RS,5S)-5-*Methyl*-2-(*phenylsulfanyl*)*tetrahydrofuran-2-one* **13**.—According to the reported procedure,[15] (*S*)-(−)-ethyl lactate (29.5 g, 0.25 mol) afforded compound **13** (9.5 g, 19%) as a colourless oil. Its IR and NMR spectra were identical with those reported.[15]

Oct-2-yn-1-ol **14**.—According to the reported procedure,[16] prop-2-yn-1-ol (1.0 g, 16 mmol) afforded compound **14** (1.17 g, 58%) as a colourless oil. Its IR and NMR spectra were identical with those reported.[19]

Dec-2-yn-1-ol **15**.—In the same manner as just described, prop-2-yn-1-ol 1.0 g, 16 mmol) afforded compound **15** (1.65 g, 67%) as a colourless oil. Its IR and NMR spectra were identical with those reported.[16]

Oct-7-yn-1-ol **16**.—According to the reported procedure, compound **14** (0.85 g, 6.8 mmol) afforded compound **16** (0.60 g, 71%) as a colourless oil. Its IR and NMR spectra were identical with those reported.[20]

Dec-9-yn-1-ol **17**.—In the same manner as just described, compound **15** (1.05 g, 6.8 mmol) afforded compound **17** (0.88 g, 84%) as a colourless oil. Its IR and NMR spectra were identical with those reported.[16]

8-(tert-*Butyldimethylsilyloxy*)*oct-1-yne* **18**.—To a solution of compound **16** (0.60 g, 4.8 mmol) in DMF (10 cm^3) were added imidazole (0.81 g, 11.9 mmol) and *tert*-butyldimethylchlorosilane (0.79 g, 5.2 mmol). After the mixture had been stirred for 2 h, it was diluted with diethyl ether and washed with water and brine. Drying ($MgSO_4$) and evaporation gave compound **18** as a colourless oil (1.05 g, *ca.* 92%), which was used in the next step without further purification; ν_{max}(film)/cm^{-1} 3400, 2960, 2850, 2120, 1460, 1250, 1100, 835, 770 and 620. δ_H($CDCl_3$) 0.05 (6 H, s), 0.90 (9 H, s), 1.30–1.60 (8 H, m), 1.94 (1 H, t, *J* 2.6), 2.19 (2 H, tt, *J* 7.1 and 2.6) and 3.60 (2 H, t, *J* 6.5).

10-(tert-*Butyldimethylsilyloxy*)*dec-1-yne* **19**.—In the same manner as just described, the alcohol **17** (0.88 g, 5.7 mmol) afforded compound **19** (1.40 g, *ca.* 91%) as a colourless oil. The IR spectrum was similar to that of compound **18**. δ_H($CDCl_3$) 0.05 (6 H, s), 0.89 (9 H, s), 1.28–1.60 (12 H, m), 1.94 (1 H, t, *J* 2.6), 2.18 (2 H, tt, *J* 7.0 and 2.6) and 3.60 (2 H, t, *J* 6.6).

(EZ)-8-(tert-*Butyldimethylsilyloxy*)-1-*iodooct*-1-*ene* **20**.—According to the reported procedure,[18] the allcyne **18** (1.03 g, 4.3 mmol) afforded the vinyl iodide **20** (1.23 g, *ca.* 70%, *E*:*Z* = 3:1) as a colourless oil, which was used in the next step without further purification. ν_{max}(film)/cm^{-1} 2930, 2850, 1600, 1460, 1250, 1100, 840 and 770. δ_H($CDCl_3$) 0.05 (6 H, s), 0.90 (9 H, s), 1.20–1.60 (8 H, m), 2.00–2.18 (2 H, m), 3.59 (2 H, t, *J* 6.0), 5.94–5.98 (0.75 H, dt, *J* 14.4 and 1.2, *E*), 6.17 (0.5 H, m, *Z*) and 6.45–6.56 (0.75 H, dt, *J* 14.4 and 7.1, *E*).

(EZ)-10-(tert-*Butyldimethylsilyloxy*)-1-*iododec*-1-*ene* **21**.—In the same manner as just described, the allcyne **19** (1.08 g, 4.0 mmol) afforded the vinyl iodide **21** (1.12 g, *ca.* 71%, *E*:*Z* = 1:1) as a colourless oil, which was used in the next step without further purification. The IR spectrum was similar to that of compound **20**. δ_H($CDCl_3$) 0.05 (6 H, s), 0.89 (9 H, s), 1.20–1.60 (12 H, m), 2.00–2.17 (2 H, m), 3.60 (2 H, t, *J* 6.5), 5.95–5.99 (0.5 H, dt, *J* 14.4 and 1.2, *E*), 6.17 (1 H, m, *Z*) and 6.45–6.56 (0.5 H, dt, *J* 14.4 and 7.2, *E*).

(E,Z)-8-*Iodooct*-7-*en*-1-*ol* **22**.—To an ice-cooled solution of compound **20** (570 mg, 1.55 mmol) in THF (15 cm^3) was added Bu_4NF (1.0 mol dm^{-3} solution in THF; 3.0 cm^3). The mixture was allowed to warm to room temp. and then stirred for a further 5 h. After completion of the reaction, the mixture was diluted with diethyl ether and washed with water and brine. Drying ($MgSO_4$) and evaporation afforded the crude alcohol **22**, which was chromatographed over silica gel (hexane–AcOEt = 4:1) to afford the pure alcohol **22** (334 mg, 85%, *E*:*Z* = 3:1) as a colourless oil; ν_{max}(film)/cm^{-1} 3370, 2940, 2860, 1600, 1460, 1060 and 845; δ_H($CDCl_3$) 1.21 (1 H, t, *J* 4.9, OH), 1.25–1.60 (8 H, m), 2.02–2.20 (2 H, m), 3.63 (2 H, td, *J* 6.6 and 4.9), 5.94–5.98 (0.75 H, dt, *J* 14.4 and 1.2, *E*), 6.18 (0.5 H, m, *Z*) and 6.45–6.56 (0.75 H, dt, *J* 14.4 and 7.2, *E*) (Found: 254.0140. Calc. for $C_8H_{15}IO$, 254.0168).

(E,Z)-10-*Iododec*-9-*en*-1-*ol* **23**.—In the same manner as just described, compound **21** (1.12 g, 2.83 mmol) afforded the alcohol **23** (686 mg, 86%, *E*:*Z* = 1:1) as a colourless oil. The IR spectrum was similar to that of compound **22**. δ_H($CDCl_3$) 1.21 (1 H, t, *J* 5.2, OH), 1.25–1.60 (12 H, m), 2.01–2.21 (2 H, m), 3.61–3.68 (2 H, td, *J* 6.4 and 5.2), 5.94–5.99 (0.5 H, dt, *J* 14.4 and 1.2, *E*), 6.17 (1 H, m, *Z*) and 6.45–6.56 (0.5 H, dt, *J* 14.4 and 7.2, *E*) (Found: 283.0557. Calc. for ($C_{10}H_{19}IO$ + 1), 283.0559).

(E,Z)-1,8-*Diiodooct*-1-*ene* **24**.—To an ice-cooled solution of the alcohol **22** (254 mg, 1.0 mmol) in pyridine (5 cm^3) was added *p*-TsCl (210 mg, 1.1 mmol). After being stirred in an ice-bath for 1 h and then at room temp. for 5 h, the mixture was diluted with diethyl ether and washed with 1 mol dm^{-3} HCl and water. Drying ($MgSO_4$) and subsequent evaporation gave the crude tosylate as a colourless oil, which was then dissolved in acetone (10 cm^3) and NaI (0.75 g, 5.0 mmol) was added to the solution. After being stirred at room temp. for 3 h, the mixture was filtered and the filtrate was evaporated. The residue was chromatographed over silica gel, with hexane–AcOEt (20:1) as eluent to give the diiodide **24** (295 mg, 81%, *E*:*Z* = 3:1) as a colourless oil; ν_{max}(film)/cm^{-1} 3050, 2920, 2850, 1600, 1460, 1430, 1280, 1200, 945 and 720; δ_H($CDCl_3$) 1.25–1.90 (8 H, m), 2.02–2.18 (2 H, m), 3.18 (2 H, m), 5.96–6.01 (0.75 H, dt, *J* 14.4 and 1.5, *E*), 6.19 (0.5 H, m, *Z*) and 6.45–6.55 (0.75 H, dt, *J* 14.4 and 7.2, *E*) (Found: 363.9204. Calc. for $C_8H_{14}I_2$, 363.9185).

(E,Z)-1,10-*Diiododec*-1-*ene* **25**.—In the same manner as just described, the alcohol **23** (680 mg, 2.4 mmol) afforded the diiodide **25** (677 mg, 72%, *E*:*Z* = 1:1) as a colourless oil. The IR spectrum was similar to that of compound **24**. δ_H($CDCl_3$) 1.20–1.90 (12 H, m), 2.01–2.17 (2 H, m), 3.19 (2 H, t, *J* 7.1), 5.94–6.00 (0.5 H, dt, *J* 14.4 and 1.2, *E*), 6.17 (1 H, m, *Z*) and 6.45–6.56 (0.5 H, dt, *J* 14.4 and 7.2, *E*) (Found: 391.9506. Calc. for $C_{10}H_{18}I_2$, 391.9498).

(E,Z,3RS,5S)-3-(8′-*Iodooct*-7′-*enyl*)-5-*methyl*-3-(*phenylsulfanyl*)*tetrahydrofuran*-2-*one* **26**.—To an ice-cooled solution of compound **13** (200 mg, 1.0 mmol) in THF (5 cm^3) was added sodium bis(trimethylsilyl)amide (1.0 mol dm^{-3} solution in THF; 1.0 cm^3). After the mixture had been stirred at 0 °C for 30 min, the diiodide **24** (382 mg, 1.0 mmol) in HMPA (2 cm^3) was added to it and the whole was allowed to warm to room temperature. The reaction mixture was then poured into sat. aqueous NH_4Cl and extracted with diethyl ether. Drying ($MgSO_4$) and subsequent evaporation gave the crude iodofuranone **26** which was chromatographed over silica gel (hexane–AcOEt, 8:1) to give the pure iodofuranone **26** (22 mg, 51%; *E*:*Z*, 3:1) ν_{max}(film)/cm^{-1} 3050, 2975, 2925, 2850, 1760, 1600, 1440, 1380, 1340, 1190, 945, 750 and 695; δ_H($CDCl_3$) 1.19 (2.4 H, d, *J* 6.4), 1.38 (0.6 H, d, *J* 6.2), 1.20–1.80 (10 H, m), 1.96 (1 H, m), 2.02–2.20 (2 H, m), 2.31–2.35 (0.2 H, dd, *J* 13.7 and 5.4), 2.48–2.53 (0.8 H, dd, *J* 14.9 and 7.6), 4.45–4.53 (0.8 H, m), 4.57–4.63 (0.2 H, m), 5.95–6.00 (0.75 H, dt, *J* 14.4 and 1.2, *E*), 6.18 (0.5 H, m, *Z*), 6.44–6.55 (0.75 H, dt, *J* 14.4 and 7.2, *E*), 7.32–7.43 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 444.0605. Calc. for $C_{19}H_{25}IO_2S$, 444.0620).

(E,Z,2RS,4S)-3-(10′-*Iododec*-9′-*enyl*)-5-*methyl*-3-(*phenylsulfanyl*)*tetrahydrofuran*-2-*one* **27**.—In the same manner as

just described, compounds **13** (296 mg, 1.48 mmol) and **25** (519 mg, 1.48 mmol) afforded the iodofuranone **27** (342 mg, 49%, $E:Z$ = 1:1) as a colourless oil. The IR spectrum was similar to that of compound **23**; $\delta_H(CDCl_3)$ 1.19 (2.4 H, d, *J* 6.4), 1.38 (0.6 H, d, *J* 6.2), 1.20–1.81 (14 H, m), 1.96 (1 H, m), 2.00–2.20 (2 H, m), 2.31–2.35 (0.2 H, dd, *J* 13.8 and 5.5), 2.48–2.53 (0.8 H, dd, *J* 14.9 and 7.6), 4.42–4.53 (0.8 H, m), 4.56–4.64 (0.2 H, m), 5.94–6.00 (0.5 H, dt, *J* 14.4 and 1.5, *E*), 6.17 (1 H, m, *Z*), 6.45–6.56 (0.5 H, dt, *J* 14.4 and 7.2, *E*), 7.32–7.43 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 472.0915. Calc. for $C_{21}H_{29}IO_2S$, 472.0933).

(1‴R,2″R,3RS,5″R,13′S)-3-{13′-*Hydroxy*-13′-[5″-(1‴-*hydroxytridecanyl*)-2″-*furyl*]*tridec*-7′-*en*-9′-*ynyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **28**.—To a solution of the vinyl iodide **26** (21 mg, 0.048 mmol) in benzene (0.5 cm^3) was added Et_3N (8 mg, 0.08 mmol) and $Pd(PPh_3)_4$ (17 mg, 2.4 μmol) and the resulting solution was stirred for 45 min. The acetylenic diol **12a** (17 mg, 0.048 mmol) along with CuI (1 mg) were then added to the mixture which after being stirred for a further 3 h was treated with saturated aqueous NH_4Cl and extracted with diethyl ether. The extract was dried ($MgSO_4$) and evaporated to give crude compound **28** which was purified by preparative TLC (hexane–AcOEt, 2:1) to afford pure compound (20 mg, 61%) as a colourless oil; ν_{max}(film)/cm^{-1} 3450, 3060, 3020, 2930, 2850, 2230, 1765, 1460, 1440, 1190, 1070, 950, 750 and 695; $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.6), 1.19 (2.4 H, *J* 6.4), 1.38 (0.6 H, d, *J* 6.1), 1.20–1.80 (36 H, m), 1.93–2.12 (5 H, m), 2.26 (1 H, d, *J* 3.7, OH), 2.33 (1 H, d, *J* 5.1, OH), 2.31–2.54 (3 H, m), 3.40 (1 H, m), 3.55 (1 H, m), 3.82 (2 H, m), 4.49–4.57 (1 H, m), 5.40–5.46 (1 H, m), 5.97–6.08 (1 H, m), 7.37–7.42 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 668.4454. Calc. for $C_{41}H_{64}O_5S$, 668.4474).

(1‴R,2″S,3RS,5″R,13′R)-3-{13′*Hydroxy*-13′-[5″-(1‴*hydroxytridecanyl*)-2″-*furyl*]*tridec*-7′-*en*-9′-*ynyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **32**.—In the same manner as just described, the vinyl iodide **26** (24 mg, 0.054 mmol) and the acetylenic diol **12b** (19 mg, 0.054 mmol) afforded compound **32** (18 mg, 50%) as a colourless oil. The IR spectrum was similar to that of compound **28**; $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.7), 1.19 (2.4 H, t, *J* 6.4), 1.38 (0.6 H, *J* 6.1), 1.18–1.81 (36 H, m), 1.93–2.12 (5 H, m), 2.30 (2 H, br, OH), 2.31–2.55 (3 H, m), 3.43 (1 H, m), 3.59 (1 H, m), 3.85 (2 H, m), 4.45–4.57 (1 H, m), 5.40–5.46 (1 H, m), 6.00–6.06 (1 H, m), 7.32–7.42 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 668.4493. Calc. for $C_{41}H_{64}O_5S$, 668.4474).

(1‴R,2″R,3RS,5″R,15′S)-3-{15′-*Hydroxy*-15′-[5″-(1‴-*hydroxytridecanyl*)-2″-*furyl*]*pentadec*-9′-*en*-11′-*ynyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **29**.—In the same manner as previously described, the vinyl iodide **27** (42 mg, 0.089 mmol) and the acetylenic diol **12a** (31 mg, 0.089 mmol) afforded compound **29** (32 mg, 52%) as a colourless oil. The IR spectrum was similar to that of compound **28**. $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.7), 1.18 (2.4 H, d, *J* 6.1), 1.38 (0.6 H, d, *J* 6.1), 1.20–1.80 (40 H, m), 1.89–2.28 (5 H, m), 2.30 (2 H, br, OH), 2.31–2.56 (3 H, m), 3.41 (1 H, m), 3.56 (1 H, m), 3.80 (2 H, m), 4.45–4.60 (1 H, m), 5.41–5.47 (1 H, m), 5.81–6.10 (1 H, m), 7.32–7.43 (3 H, m) and 7.51–7.59 (2 H, m) (Found: 696.4811. Calc. for $C_{43}H_{68}O_5S$, 696.4788).

(1‴R,2″S,3RS,5″R,15′R)-3-{15′-*Hydroxy*-15′-[5″-(1‴*hydroxytridecanyl*)-2″-*furyl*]*pentadec*-9′-*en*-11′-*ynyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **33**.—In the same manner as described above, the vinyl iodide **27** (22 mg, 0.047 mmol) and the acetylenic diol **12b** (16 mmol) afforded compound **33** (18 mg, 55%) as a colourless oil. The IR spectrum was similar to that of compound **28**; $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.7), 1.18 (2.4 H, d, *J* 6.2), 1.38 (0.6 H, *J* 6.1), 1.20–1.83 (40 H, m), 1.87–2.29 (5 H, m), 2.31–2.64 (3 H, m), 2.50 (2 H, br, OH), 3.45 (1 H, m), 3.61 (1 H, m), 3.83 (2 H, m), 4.43–4.64 (1 H, m), 5.41–5.47 (1 H, m), 5.81–6.14 (1 H, m), 7.32–7.44 (3 H, m) and 7.51–7.71 (2 H, m) (Found: 696.4774. Calc. for $C_{43}H_{68}O_5S$, 696.4788).

(1‴R,2″R,3RS,5″R,13′S)-3-{13′-*Hydroxy*-13′-[5″-(1‴-*hydroxytridecanyl*)-2″-*furyl*]*tridecanyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **30**.—A solution of compound **28** (10 mg, 0.015 mmol) in benzene (0.3 cm^3) was hydrogenated over chlorotris(triphenylphosphine)rhodium (2 mg) for 2 d. Filtration and evaporation provided an oil, which was purified by preparative TLC (hexane–AcOEt = 2:1) to give compound **30** (6 mg, 60%) as a colourless oil; ν_{max}(film)/cm^{-1} 3420, 3050, 2920, 2850, 1760, 1460, 1180, 1070, 960, 750 and 690; $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.6), 1.18 (2.4 H, d, *J* 6.1), 1.38 (0.6 H, d, *J* 6.1), 1.20–1.80 (47 H, m), 1.98 (4 H, m), 2.32 (2 H, br, OH), 2.33 (0.2 H, dd, *J* 13.8 and 5.5), 2.52 (0.8 H, dd, *J* 13.9 and 7.6), 3.41 (2 H, br), 3.79 (2 H, q, *J* 6.6), 4.45–4.64 (1 H, m), 7.32–7.43 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 672.4822. Calc. for $C_{41}H_{70}O_5S$ − 2, 672.4788).

(1‴R,2″S,3RS,5″R,13′R)-3-{13′-*Hydroxy*-13′-[5″-(1‴-*hydroxytridecanyl*)-2″-*furyl*]*tridecanyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **34**.—In the same manner as just described, compound **32** (12 mg, 0.018 mmol) afforded compound **34** (8 mg, 67%) as a colourless oil. The IR and ^1H NMR spectra were similar to those of compound **30** (Found: 672.4813. Calc. for ($C_{41}H_{70}O_5S$ − 2), 672.4788).

(1‴R,2″R,3RS,S″R,15′S)-3-{15′-*Hydroxy*-15′-[5″-(1‴-*hydroxytridecanyl*)-2″-*furyl*]*pentadecanyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **31**.—In the same manner as described above, compound **29** (8 mg, 0.011 mmol) afforded compound **31** (6 mg, 75%) as a colourless oil. The IR spectrum was similar to that of compound **30**; $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.7), 1.18 (2.4 H, d, *J* 6.4), 1.38 (0.6 H, d, *J* 6.1), 1.21–1.81 (51 H, m), 1.98 (4 H, m), 2.32 (2 H, br, OH), 2.31 (0.2 H, dd, *J* 13.8 and 5.5), 2.54 (0.8 H, dd, *J* 13.9 and 7.6), 3.40 (2 H, br), 3.80 (2 H, q, *J* 6.5), 4.45–4.53 (1 H, m), 7.32–7.43 (3 H, m) and 7.51–7.57 (2 H, m) (Found: 700.5087. Calc. for ($C_{43}H_{74}O_5S$ − 2), 700.5101).

(1‴R,2″S,3RS,5″R,15′R)-3-{15′-*Hydroxy*-15′-[5″-(1-*hydroxytridecanyl*)-2″-*furyl*]*pentadecanyl*}-5-*methyl*-3-(*phenylsulfanyl*)*furan*-2-*one* **35**.—In the same manner as mentioned above, compound **33** (6 mg, 0.009 mmol) afforded compound **35** (3 mg, 50%) as a colourless oil. The IR and ^1H NMR spectrum were similar to those of compound **31** (Found: 700.5096. Calc. for ($C_{43}H_{74}O_5S$ − 2), 700.5101).

Solamin **1**.—To a solution of compound **30** (6 mg, 8.9 μmol) in MeOH (0.1 cm^3) was added MCPBA (2 mg) at 0 °C. After the mixture had been stirred at this temperature for 15 min, filtration afforded a yellow solid, which was used in the next step without further purification. The solid was dissolved in toluene (0.5 cm^3) and the solution was refluxed for 1 h. After completion of the reaction, evaporation of the mixture gave crude compound **1**, which upon recrystallisation gave pure compound **1** (2 mg, 40%) as colourless needles, m.p. 66—69 °C (lit.,[9] 64–68 °C); $[\alpha]_D^{24}$ 22 (*c* 0.1, MeOH), [lit.,[9] 21.2 (*c* 0.16, MeOH)]. The IR, ^1H NMR and MS spectra were identical with those of the natural sample.

Reticulatacin **2**.—In the same manner as just described, compound **31** (4 mg, 5.7 μmol) afforded compound **2** (1 mg, 30%) as colourless needles, m.p. 79–81 °C (lit.,[10] 80–80.5 °C); $[\alpha]_D^{24}$ 24 (*c* 0.05, $CHCl_3$) [lit.,[10] 26 (*c* 0.5, $CHCl_3$)]. The IR, ^1H NMR and MS spectra were identical with those reported.[10]

15,16-*Di*-epi-*solamin* **3**.—In the same manner as described above, compound **34** (4 mg, 0.0057 mmol) afforded compound **3** (1 mg, 30%) as colourless needles. The IR and ^{1}H NMR spectra were similar to those of compound **1** (Found: 562.4612. Calc. for ($C_{35}H_{64}O_5$ − 2), 562.4597).

17,18-*Di*-epi-*reticulatacin* **4**.—In the same manner described above, compound **35** (3 mg, 4.3 μmol) afforded compound **4** (1 mg, 40%) as colourless needles. The IR and ^{1}H NMR spectra were similar to those of compound **2** [Found: 590.4942. Calc. for ($C_{37}H_{68}O_5$ − 2), 590.4910].

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