Total Synthesis of Symbioramide, a Novel Ca^{2+}-ATPase Activator from *Symbiodinium* sp.

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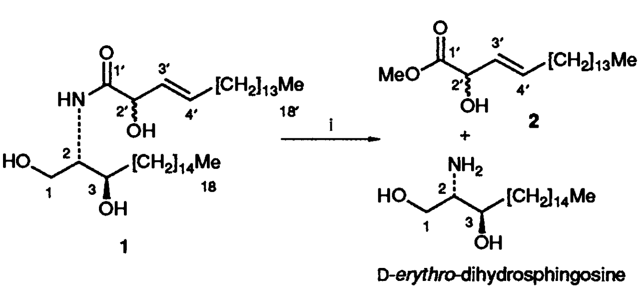
The first total synthesis of symbioramide **1** has been accomplished by the coupling of D-*erythro*-dihydrosphingosine with an unusual, chiral α-hydroxy-β,γ-unsaturated fatty acid prepared from L-ascorbic acid, and simultaneously established the complete stereostructure of **1** to be (2*S*,2′*R*,3*R*,3′*E*)-*N*-(2′-hydroxyoctadec-3′-enoyl)dihydrosphingosine.

Sphingosine is the basic skeleton of sphingolipids and glycosphingolipids which are known to be constituents of biomembranes, and plays an important role in biological systems.[1] Diverse classes of biologically important ceramides and cerebrosides has been obtained from various natural sources. More recently, a new type of bioactive ceramide, symbioramide **1**, has been isolated from the insides of gill cells of an Okinawan bivalve (*Fragum* sp.), which is the first example of a sarcoplasimic reticulum Ca^{2+}-ATPase activator of marine sources and also exhibits antileukaemic activity.[2] Its low abundance in natural sources and its intriguing structural features, coupled with significant biological activities, made it the target for synthesis in connection with our synthetic studies on sphingolipids.[3] The chemical structure **1** for symbioramide has been established from the fact that methanolysis gave methyl 2-hydroxyoctadec-3*E*-enoate **2** {$[\alpha]_D^{28}$ −16° (*c* 1, $CHCl_3$)} and D-*erythro*-dihydrosphingosine, which was identified as its triacetyl derivative {$[\alpha]_D^{22}$ +14° (*c* 0.1, $CHCl_3$)} (Scheme 1).[2]

However, the stereochemistry of the 2′-hydroxy group of the unusual fatty acid remained to be defined. We report here a full account[4] of the first asymmetric total synthesis of symbioramide **1** (by the strategy shown in Schemes 2–5), using optically active aldehydes **6** as a chiral synthon, which unequivocally established the absolute configuration of compound **1**.



Scheme 1 *Reagents:* i, H_2SO_4, MeOH

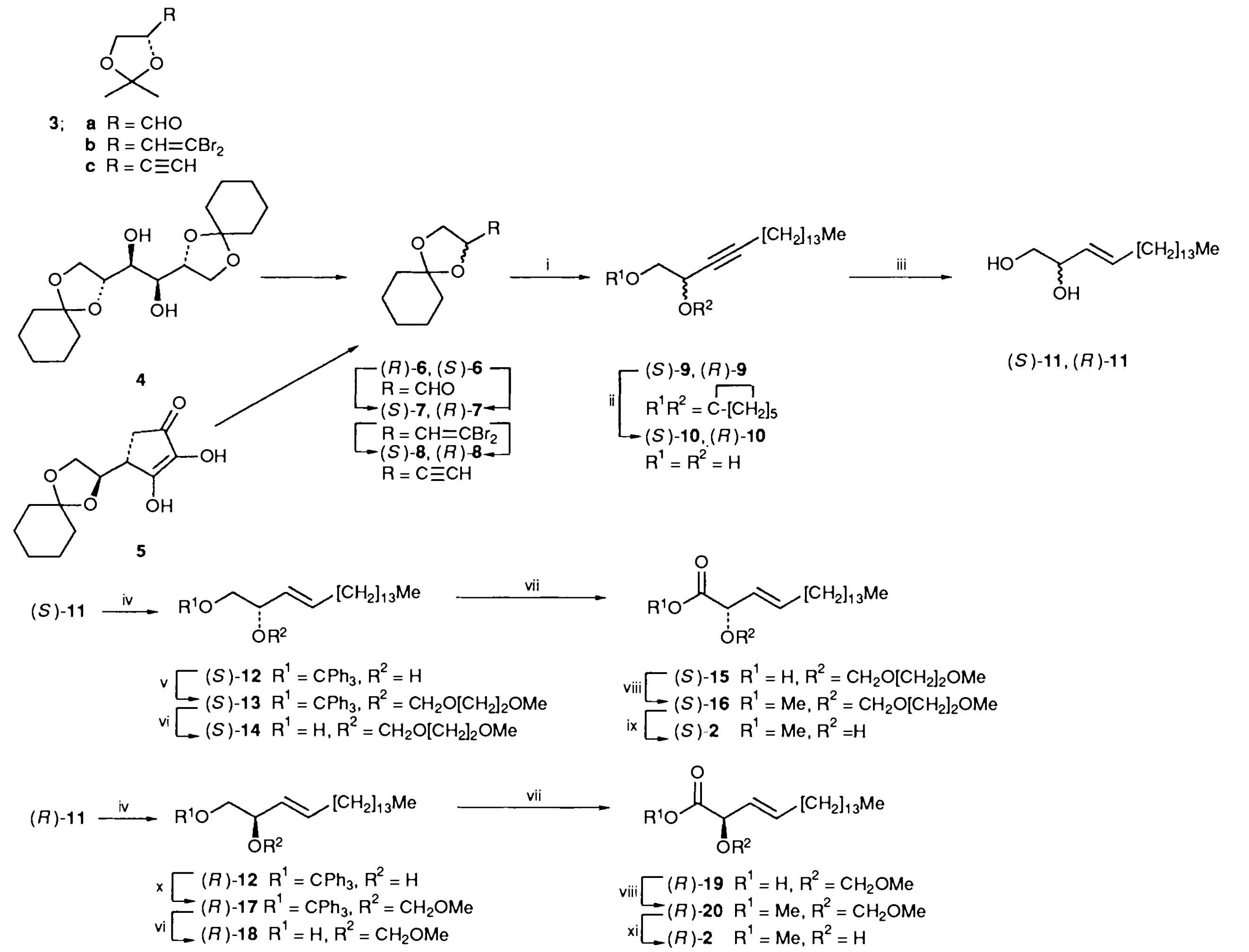
Results and Discussion

Our studies began with the synthesis of a pair of enantiomeric esters **2**. Our original plan was to start with readily accessible optically active aldehyde **3a**. However, difficulties were encountered in our initial efforts to synthesize compound **2** from aldehyde **3a** owing to the instability of the dioxolanes **3a**, **3b** and **3c**. We pursued our original plan by replacing the protecting group with a cyclohexylidene group which improved the yields markedly (Scheme 2). The corresponding aldehydes (*R*)- and (*S*)-**6** can be conveniently prepared from 1,2;5,6-di-*O*-dicyclohexylidene-D-mannitol **4**[5] and cyclohexylidene-L-ascorbic acid **5**,[6] respectively. $NaIO_4$ oxidation of compound **4** gave the enantiomerically pure aldehyde (*R*)-**6** (49%). Chain extention of the aldehyde (*R*)-**6** by one carbon to form the dibromoolefin (*S*)-**7** was accomplished in 73% yield by reaction with carbon tetrabromide–triphenylphosphine reagent in methylene dichloride.[7] Treatment of dibromide (*S*)-**7** with 2 mol equiv. of BuLi in tetrahydrofuran (THF) provided the corresponding terminal acetylene (*S*)-**8** (61%; $[\alpha]_D$ +39.3°), which was alkylated with tetradecyl tosylate to afford the octadecyne derivative (*S*)-**9** (64%). The acetylene (*S*)-**9** was hydrolysed to the diol (*S*)-**10** by using conc. HCl in EtOH (69% yield), and diol **10** was converted stereoselectively by $LiAlH_4$ reduction[8] in 1,2-dimethoxyethane (DME) into the *E*-alkene diol (*S*)-**11** (63%; $[\alpha]_D$ +9.05°). Tritylation of (*S*)-**11**, followed by protection of the secondary alcohol (*S*)-**12** with a β-methoxyethoxymethyl group, gave tris-ether (*S*)-**13** (66%, 2 steps), which on selective detritylation by TsOH afforded the primary alcohol (*S*)-**14** (82%; $[\alpha]_D$ +73.2°). Subsequent oxidation of (*S*)-**14** with pyridinium dichromate (PDC) provided the carboxylic acid (*S*)-**15**, which was isolated as its methyl ester (*S*)-**16** (41%, 2 steps). Finally, deprotection of bis-ether (*S*)-**16** with excess of $ZnBr_2$ yielded methyl (2*S*,3*E*)-2-hydroxyoctadec-3-enoate (*S*)-**2** {73%; $[\alpha]_D^{19}$ +46.4° (*c* 0.278, $CHCl_3$)}.

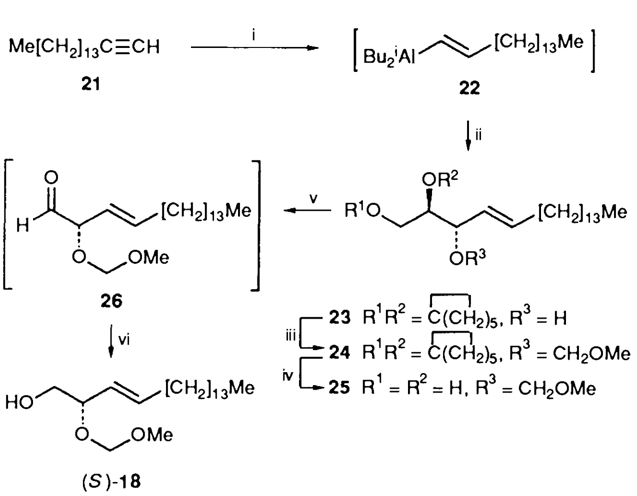
Synthesis of ester (*R*)-**2** followed the same procedure as used for the (*S*)-enantiomer, starting with (*S*)-**6**† *via* (*R*)-**8** ($[\alpha]_D$ −37.4°), (*R*)-**11** ($[\alpha]_D$ −8.97°), and (*R*)-**18** ($[\alpha]_D$ −73.7°). Oxidation (PDC) of primary alcohol (*R*)-**18** and subsequent methylation gave methyl ester (*R*)-**20**. Deprotection of ester (*R*)-**20** with $BF_3{\cdot}Et_2O$–EtSH yielded the enantiomeric methyl ester (*R*)-**2** {$[\alpha]_D^{19}$ −44.7° (*c* 0.257, $CHCl_3$)}.‡ Both synthetic enantiomers of compound **2** showed identical spectral data with those of the ester obtained from natural symbioramide **1**. However, (*R*)-**2** had the same optical rotation sign as that of the natural compound, confirming the absolute stereochemistry at the C-2′ position to be *R*.

† Attempts to purify aldehyde (*S*)-**6** prepared from lactone **5** led only to decomposition.

‡ The $[\alpha]_D$ value of the methyl ester **2** obtained by acidic hydrolysis of the natural product **1** is smaller, probably due to partial racemization. The optical purity of the synthetic products (*R*)-**2** and (*S*)-**2** was determined from their ^1H NMR spectra by use of a shift reagent. The ^1H NMR spectra of (*R*)-**2** and (*S*)-**2** in the presence of tris[3-heptafluoropropyl(hydroxy)methylene-(+)-camphorato]europium(III) in $CDCl_3$ showed the absence of the other enantiomer by comparison with those of (±)-**2**. By a similar method, compounds **23** and **29** were shown not to contain their enantiomers.



Scheme 2 *Reagents and conditions:* i, BuLi, hexane, THF, −78 °C; then $CH_3[CH_2]_{13}OTs$, HMPA, −10 to 0 °C; ii, TsOH, MeOH, room temp.; iii, $LiAlH_4$, DMF, reflux; iv, Ph_3CCl, DMAP, pyridine, reflux; v, MEMCl, Pr^i_2NEt, CH_2Cl_2, room temp.; vi, TsOH, MeOH, CH_2Cl_2, room temp.; vii, PDC, DMF, 40–50 °C; viii, CH_3I, Pr^i_2NEt, CH_2Cl_2, room temp.; ix, $ZnBr_2$ (excess), CH_2Cl_2, reflux; x, MOMCl, Pr^i_2NEt, CH_2Cl_2, reflux; xi, $BF_3\cdot Et_2O$, EtSH, room temp.



Scheme 3 *Reagents and conditions:* i, DIBAH, hexane, 50 °C; ii, (*R*)-**6**, Et_2O–toluene, 0 °C to room temp.; iii, MOMCl, Pr^i_2NEt, CH_2Cl_2; iv, PPTS, MeOH–CH_2Cl_2, room temp.; v, $Pb(OAc)_4$, benzene, room temp.; vi, $NaBH_4$, MeOH, 0 °C to room temp.

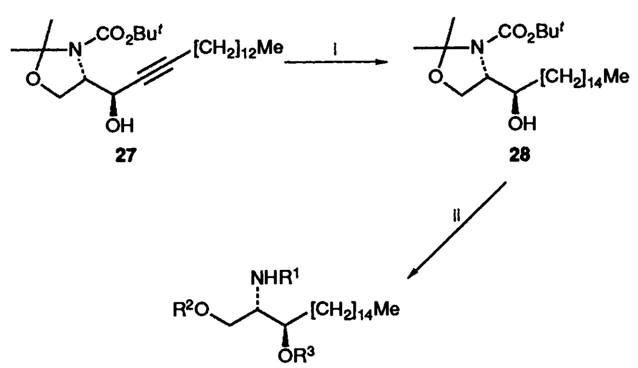
Having established the absolute configuration of compound **2** by an unambiguous method, we next turned our attention to a more expedient procedure for compound **2** starting from the chiral synthon (*R*)-**6** (Scheme 3). Towards this end, we examined the stereoselective reaction of aldehyde (*R*)-**6** with the alanate **22**. The requisite alanate **22** was prepared in quantitative yield by the reaction of hexadec-1-yne **21** with diisobutylaluminium hydride (DIBAH) in hexane.[9] Freshly prepared alanate **22** was treated with aldehyde (*R*)-**6** to afford readily the optically active allyl alcohol **23** as a single adduct (64%; $[\alpha]_D$ +10.9°).* The *anti*-selectivity observed in the conversion of (*R*)-**6** into **23** was expected according to the general sequence *via* the β-chelation-controlled addition of organometallic compounds to aldehydes.[10] Protection of the secondary alcohol in compound **23** with a methoxymethyl group gave tetrakis-ether **24**, which on selective deprotection of the cyclohexylidene group by pyridinium toluene-*p*-sulfonate (PPTS) afforded the diol **25** (56%, 2 steps; $[\alpha]_D$ +64.5°).

Unfortunately, despite considerable experimentation with conditions and oxidants such as $RuCl_4\cdot xH_2O$–$NaIO_4$,[11] we were unable to effect selective oxidation of the primary alcohol in **25** to furnish the corresponding acid **19**: only decomposition of the starting material was observed. On the other hand, oxidation of diol **25** with $Pb(OAc)_4$ gave the aldehyde **26**, which was reduced by $NaBH_4$ without purification, affording the alcohol **18** in 75% yield. Except for the sign of its optical rotation, this alcohol **18** had identical spectral and physical

* See footnote ‡ on page 343.

properties with those of the product prepared from (*R*)-**6**, indicating that the reaction of alanate **22** and (*R*)-**6** gave *anti*-product **23**.

According to the stereoselective synthesis of sphingosine developed by Liotta,[12] D-*erythro*-dihydrosphingosine was readily prepared by catalytic hydrogenation of the oxazolidine **27** ($[\alpha]_D$ −41.3°), obtained from L-serine and 1-lithiopentadec-1-yne, followed by deprotection, and was isolated as its acetonide **30** {80%, 4 steps; $[\alpha]_D^{22}$ +29.5° (*c* 1.178, $CHCl_3$)} (Scheme 4).



29 $R^1 = CO_2Bu^t$, $R^2 = R^3 = H$ (iii)
$R^1 = R^2 = R^3 = H$ D-*erythro*-dihydrosphingosine (iv)
30 $R^1 = H$, $R^2R^3 = CMe_2$

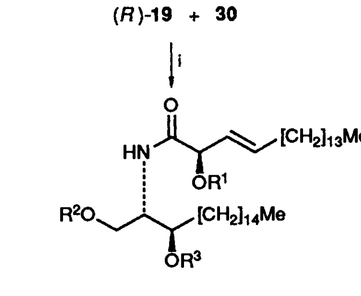
Scheme 4 *Reagents and conditions:* i, PtO_2, H_2, AcOEt, room temp.; ii, TsOH, MeOH, room temp.; iii, conc. HCl, AcOEt, room temp.; iv, dimethoxypropane, CSA, reflux.

With both segments [(*R*)-**19** and **30**] in hand, the stage was then set for the final conjunction of each component to give the target symbioramide **1**. The desired condensation of primary amine **30** with acid (*R*)-**19**, which was prepared from primary alcohol (*R*)-**18** as mentioned above, was successfully accomplished by the conventional method using dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxybenzotriazole (HOBt) to give the amide **31**. Subsequent deacetonization of compound **31** afforded diol **32** in 38% overall yield from amine **30**. Finally, careful deprotection of the alcohol function in diol **32** with $BF_3 \cdot Et_2O$–EtSH at room temperature yielded symbioramide **1** in 63% yield {m.p. 112–113 °C (from acetone–benzene); $[\alpha]_D^{19}$ +2.65° (*c* 0.378, $CHCl_3$)}. Acetylation of symbioramide **1** gave its triacetate **33** (97%, m.p. 75–78 °C) (Scheme 5). Synthetic symbioramide **1** and its triacetate **33** displayed identical IR, ^1H NMR, MS, and optical rotation data with those of the natural product and its triacetate, respectively.

In conclusion, the present synthesis established the absolute configuration of symbioramide **1** as (2*S*,2′*R*,3*R*,3′*E*)-*N*-(2′-hydroxyoctadec-3′-enoyl)dihydrosphingosine.

Experimental

M.p.s were determined with a Yamato MP-1 apparatus, and are uncorrected. IR spectra were measured with a Hitachi 260-10 spectrophotometer. Mass spectra were obtained with a Hitachi M-60 or a JMS-HX 100 mass spectrometer, and high-resolution mass spectra were recorded on a JEOL JMS-HX110 instrument. ^1H NMR spectra were taken on a JEOL GSX-400 or GSX-500 instrument for $CDCl_3$ solutions with Me_4Si as internal standard. Chemical shifts are reported in ppm, coupling constants in Hz. Optical rotations were recorded with a JASCO DIP-140 polarimeter. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were



(ii) 31 $R^1 = CH_2OMe$, $R^2R^3 = CMe_2$
(iii) 32 $R^1 = CH_2OMe$, $R^2 = R^3 = H$
(iv) 1 $R^1 = R^2 = R^3 = H$
33 $R^1 = R^2 = R^3 = Ac$

Scheme 5 *Reagents and conditions:* i, DCC, HOBt, CH_2Cl_2, room temp.; ii, TsOH, MeOH, room temp.; iii, $BF_3 \cdot Et_2O$, EtSH, room temp.; iv, Ac_2O, pyridine, room temp.

performed on a Perkin-Elmer 240 C,H,N analyser. Column chromatography was performed on silica gel (Merck, Kieselgel 60 Art. 7734; Fuji Davison silica gel BW-300 for flash column chromatography).

4,4-Dibromo-1,2-cyclohexylidenedioxybut-3-ene (S)-**7**.—To a cold (0 °C), stirred solution of triphenylphosphine (6.50 g, 24.8 mmol) in methylene dichloride (16 cm^3) were added dropwise a solution of carbon tetrabromide (4.11 g, 12.4 mmol) in methylene dichloride (8 cm^3) and a solution of cyclohexylidene-D-glyceraldehyde[5] (1.055 g, 6.20 mmol) in methylene dichloride (8 cm^3) under argon. After the reaction mixture had been stirred for 15 min at 0 °C, cold water (30 cm^3) was added and the mixture was stirred for another 10 min. The organic layer was decanted, dried (Na_2SO_4), and concentrated. Chromatography of the oily residue [SiO_2 (160 g); (1:1) diethyl ether–hexane] yielded dibromoolefin (*S*)-**7** as an oil (1.47 g, 73%), $[\alpha]_D^{23}$ −5.23 (*c* 0.968, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1620, 1280, 1160, 1040, 930 and 810 (C–Br); δ_H 1.41–1.64 (10 H, m, CH_2), 3.68 (1 H, dd, *J* 8.3 and 6.6, CH*H*O), 4.18 (1 H, dd, *J* 8.5 and 6.3, C*H*HO), 4.73 (1 H, td-like, CHO) and 6.53 (1 H, d, *J* 7.4, olefinic H); *m/z* (EI) 328 (15.7%), 326 (30.8), 283 (68.3), 281 (34.3), 214 (50.0) and 212 (100).

5,6-O-Cyclohexylidene-L-ascorbic Acid **5**.—A white suspension of L-ascorbic acid (20.00 g, 0.114 mmol), triethyl orthoformate (5.6 cm^3, 0.07 mmol), and boron trifluoride–diethyl ether (0.56 cm^3, 0.01 mmol) in cyclohexanone (120 cm^3) was stirred overnight at room temperature under argon. The resulting clear solution was concentrated (20 Torr; external temperature 80 °C) to give a solid. Recrystallization from acetone–hexane yielded compound **5** as a powdery solid (25.56 g, 88%), m.p. 184–185 °C (Found: C, 56.3; H, 6.3. Calc. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29%); $[\alpha]_D^{25}$ +46.3 (*c* 1.08, MeOH); ν_{max}(KBr)/cm^{-1} 3220 (OH), 1740 (C=O) and 1660 (C=C); δ_H 1.33–1.40 and 1.53–1.63 (10 H, m, cyclohexyl CH_2), 4.03 (1 H, dd, *J* 8.6 and 6.7, C*H*HOC), 4.12 (1 H, dd, *J* 8.5 and 6.6, CH*H*OC), 4.24 (1 H, dt, *J* 6.7 and 4.4, CHOC), 4.52 (1 H, d, *J* 4.4, CHOCO), 8.07 (1 H, s, OH, exch.) and 10.5 (1 H, s, OH, exch.); *m/z* (EI) 256 (M^+, 23.5%) and 213 (100).

4,4-Dibromo-1,2-cyclohexylidenedioxybut-3-ene (R)-**7**.—The reaction was carried out as described above for (*S*)-**7**, using compound **5** (5.00 g, 19.5 mmol) and lithium aluminium hydride (2.22 g, 58.5 mmol) followed by oxidation ($NaIO_4$) to give compound (*S*)-**6** (2.87 g), which was followed by treatment with triphenylphosphine (20.5 g, 78.2 mmol) and carbon tetrabromide (12.9 g, 38.9 mmol) to give compound (*R*)-**7** as an oil (1.17 g, 18%), $[\alpha]_D^{21}$ +6.53 (*c* 1.026, $CHCl_3$).

1,2-*Cyclohexylidenedioxybut*-3-*yne* (S)-**8**.—To a stirred solution of dibromide (*S*)-**7** (1.278 g, 3.92 mmol) in THF (20 cm^3) at −78 °C under argon was added dropwise a 1.62 mol dm^{-3} solution of butyllithium in hexane (5.8 cm^3, 9.4 mmol). The mixture was stirred for 30 min at −78 °C, and for an additional 40 min at 0 °C. The resulting mixture was quenched by the addition of cold water (15 cm^3) and extracted with (1:2) diethyl ether–hexane. The combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated to give a pale yellow oil (0.93 g). Purification by chromatography [SiO_2 (60 g); (1:3) diethyl ether–hexane] yielded alkyne (*S*)-**8** as an oil (0.395 g, 61%), $[\alpha]_D^{24}$ +39.3 (*c* 0.890, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3290 (C≡C–H), 1040 and 920; δ_H 1.40–1.67 (10 H, m, CH_2), 2.48 (1 H, d, *J* 1.9, CCH), 3.94 (1 H, dd, *J* 8.0 and 6.1, C*H*HO), 4.16 (1 H, dd, *J* 8.0 and 6.3, CH*HO*), and 4.71 (1 H, td, *J* 6.3 and 2.2, CHO); *m*/*z* (EI) 166 (M^+, 18.4%) and 123 (100).

1,2-*Cyclohexylidenedioxybut*-3-*yne* (R)-**8**.—The title compound was prepared from dibromide (*R*)-**7** (4.06 g, 12.5 mmol) according to the method described for (*S*)-**8**, to yield *alkyne* (*R*)-**8** as an oil (1.73 g, 83%), $[\alpha]_D^{18}$ −37.4 (*c* 0.924, $CHCl_3$).

(S)-1,2-*Cyclohexylidenedioxyoctadec-3-yne* (S)-**9**.—To a stirred solution of alkyne (*S*)-**8** (308 mg, 1.85 mmol) in THF (5 cm^3) at −23 °C under argon was added dropwise a 1.62 mol dm^{-3} solution of butyllithium in hexane (1.6 cm^3, 2.6 mmol) and a solution of tetradecyl toluene-*p*-sulfonate (683 mg, 1.85 mmol) in hexamethylphosphoric triamide (HMPA) (2 cm^3). The mixture was warmed up to room temperature and stirred for 1 h. The resulting mixture was poured into ice-cooled water (5 cm^3), and extracted with diethyl ether. The extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated. The residue (brown oil, 1.23 g) was purified by flash chromatography [SiO_2 (50 g); (1:1) methylene dichloride–hexane] to give the acetylene (*S*)-**9** as an oil (429 mg, 64%), $[\alpha]_D^{25}$ +22.7 (c 1.020, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1160, 1100, 1040 (C–O–C) and 925; δ_H 0.88 (3 H, t-like, Me), 1.26 (24 H, br s, CH_2), 1.48–1.75 (10 H, m, cyclohexyl CH_2), 2.20 (2 H, td, *J* 7.2 and 1.9, 5-H_2), 3.82 (1 H, dd-like, C*H*HO), 4.12 (1 H, dd-like, CH*HO*) and 4.70 (1 H, dd-like, CHO); *m*/*z* (EI) 362 (M^+, 18.2%), 319 (22.1), 137 (21.3) and 55 (100). High-resolution FAB-MS: Found: *m*/*z* 363.3204. Calc. for $C_{24}H_{43}O_2$ (M + H)$^+$, 363.3263.

(R)-1,2-*Cyclohexylidenedioxyoctadec*-3-*yne* (R)-**9**.—The reaction was carried out as described above, using alkyne (*R*)-**8** (1.377 g, 8.28 mmol), to give compound (*R*)-**9** as an oil (2.448 g, 82%), $[\alpha]_D^{18}$ −21.6 (*c* 0.983, $CHCl_3$).

(S)-3-*Octadec*-3-*yne*-1,2-*diol* (S)-**10**.—To a solution of compound (*S*)-**9** (380 mg, 1.05 mmol) in ethanol (10 cm^3) were added a few drops of conc. hydrochloric acid and the mixture was refluxed for 4 h. The resulting mixture was then concentrated and the residue was dissolved in ethyl acetate. The organic layer was washed successively with saturated aq. sodium hydrogen carbonate and saturated brine, dried (Na_2SO_4), and evaporated to give a powdery solid. Recrystallization from hexane yielded *diol* (*S*)-**10** as leaflets (203 mg, 69%), m.p. 74.5–75.0 °C (Found: C, 76.7; H, 12.0. $C_{18}H_{34}O_2$ requires C, 76.54; H, 12.13%); $[\alpha]_D^{24}$ +11.2 (*c* 0.920, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3380 (OH), 3200 (OH), 1090, 1045 and 720; δ_H 0.88 (3 H, t, 7.0, Me), 1.26 (24 H, br s, CH_2), 2.00 (1 H, dd, *J* 8.3, 5.0, CH_2O*H*, exch.), 2.15 (1 H, d, *J* 6.1, CHO*H*, exch.), 2.21 (2 H, t, *J* 7.2, 5-H_2), 3.64 (1 H, m, C*H*HOH), 3.70 (1 H, m, CH*H*OH) and.4.44 (1 H, m, C*H*OH); *m*/*z* (EI) 282 (M^+, 3.6%), 251 (M^+ − CH_2OH, 76.7), 111 (83.3) and 43 (100).

(R)-*Octadec*-3-*yne*-1,2-*diol* (R)-**10**.—The reaction was carried out as described above, using alkyne (*R*)-**9** (1.718 g, 4.74 mmol) to give *diol* (*R*)-**10** as leaflets (0.747 g, 56%), m.p. 74.0–75.0 °C (from hexane) (Found: C, 76.6; H, 12.1%); $[\alpha]_D^{18}$ −11.6 (*c* 1.100, $CHCl_3$).

(2S,3E)-*Octadec*-3-*ene*-1,2-*diol* (S)-**11**.—To a stirred solution of ynol (*S*)-**10** (1.578 g, 5.59 mmol) in DME (50 cm^3) at 0 °C was added lithium aluminium hydride (0.64 g, 16.8 mmol) in portions and the mixture was then refluxed for 3 h under argon. After the mixture had been quenched by slow addition of 5% aq. sodium hydroxide, it was diluted with chloroform and filtered over Celite. The filtrate was washed with saturated brine, dried ($MgSO_4$), and evaporated to give a powdery solid. Recrystallization from hexane yielded *enediol* (*S*)-**11** as leaflets (1.002 g, 63%), m.p. 60–60.5 °C (Found: C, 75.8; H, 12.7. $C_{18}H_{36}O_2$ requires C, 76.00; H, 12.75%); $[\alpha]_D^{29}$ +9.05 (*c* 0.398, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3400 (OH), 3300 (OH), 1080 and 970 (*E*-C=C); δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.25–1.32 (24 H, m, CH_2), 1.87 (1 H, dd, *J* 7.0 and 5.2, CH_2O*H*, exch.), 1.98 (1 H, d, *J* 3.8, CHO*H*, exch.), 2.04 (2 H, q, *J* 7.1, 5-H_2), 3.50 (1 H, ddd, *J* 11.2, 7.5, and 5.0, C*H*HOH), 3.64 (1 H, ddd, *J* 11.2, 7.1, and 3.8, CH*H*OH), 4.20 (1 H, m, C*H*OH), 5.45 (1 H, dd, *J* 15.4 and 6.8, 3-H) and 5.78 (1 H, dt, *J* 15.4 and 6.8, 4-H); *m*/*z* (EI) 284 (M^+, 0.57%) and 253 (M^+ − CH_2OH, 100).

(2R,3E)-*Octadec*-3-*ene*-1,2-*diol* (R)-**11**.—The reaction was carried out as described above, using diol (*R*)-**10** (1.450 g, 5.13 mmol) to give enediol (*R*)-**11** as leaflets (1.071 g, 73%), m.p. 60–60.5 °C (from hexane) (Found: C, 76.2; H, 12.8%); $[\alpha]_D^{15}$ −8.97 (*c* 0.858, $CHCl_3$).

(2S,3E)-1-*Trityloxyoctadec*-3-*en*-2-*ol* (S)-**12**.—A solution of diol (*S*)-**11** (330 mg, 1.16 mmol), trityl chloride (970 mg, 3.48 mmol), and 4-(dimethylamino)pyridine (DMAP) (570 mg, 4.67 mmol) in pyridine (10 cm^3) was gently refluxed for 2 h. The mixture was then diluted with ethyl acetate, and washed successively with saturated aq. copper sulfate, saturated aq. sodium hydrogen carbonate, and saturated brine. The organic layer was dried (Na_2SO_4) and evaporated to give a yellow oil. Purification by flash column chromatography [SiO_2 (180 g); (2:1) methylene dichloride–hexane] yielded enol (*S*)-**12** as an oil (493 mg, 81%), $[\alpha]_D^{23}$ +10.2 (*c* 1.128, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH), 1070 and 970 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.23–1.35 (24 H, m, CH_2), 1.98 (2 H, q-like, 5-H_2), 2.35 (1 H, d, *J* 3.3, OH, exch.), 3.08 (1 H, dd, *J* 9.3 and 8.0, C*H*HOC), 3.17 (1 H, dd, *J* 9.3 and 3.6, CH*H*OC), 4.20–4.23 (1 H, m, C*H*OH), 5.37 (1 H, dd-like, 3-H), 5.70 (1 H, td-like, 4-H) and 7.22–7.33 and 7.42–7.47 (15 H, m, Ph); *m*/*z* (EI) 253 (M^+ − Ph_3COCH_2, 5.2%) and 243 (Ph_3C^+, 100).

(2R,3E)-1-*Trityloxyoctadec*-3-*en*-2-*ol* (R)-**12**.—Tritylation of diol (*R*)-**11** (1.023 g, 3.60 mmol) was carried out according to the method described above to give enol (*R*)-**12** as a pale yellow oil (1.807 g, 95%).

(2S,3E)-2-(2-*Methoxyethoxymethoxy*)-1-*trityloxyoctadec*-3-*ene* (S)-**13**.—A solution of enol (*S*)-**12** (483 mg, 0.917 mmol), β-methoxyethoxymethyl chloride (MEMCl) (0.31 cm^3, 2.7 mmol), and *N*,*N*-diisopropylethylamine (0.80 cm^3, 4.6 mmol) in methylene dichloride (4 cm^3) was stirred for 18 h at room temperature under argon, diluted with chloroform, washed with saturated aq. sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give a brown oil (598mg). Purification by flash column chromatography [SiO_2 (60 g);

(2:1) methylene dichloride–hexane] yielded compound (*S*)-**13** as an oil (455 mg, 81%), $[\alpha]_D^{23}$ +34.1 (*c* 0.983, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1090 and 970 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.24–1.35 (24 H, m, CH_2), 2.00 (2 H, q-like, 5-H_2), 3.05 (1 H, dd, *J* 9.8 and 4.3, C*H*HOCPh$_3$), 3.23 (1 H, dd, *J* 9.6 and 7.2, CH*H*OCPh$_3$), 3.38 (3 H, s, MeO), 3.51–3.58 (2 H, m, MeOC*H*$_2$), 3.62–3.66 (1 H, m, MeOCH$_2$C*H*H), 3.86 (1 H, ddd, *J* 10.4, 5.2, and 3.3, MeOCH$_2$CH*H*), 4.23 (1 H, td-like, C*H*OMEM), 4.75 (1 H, d, *J* 6.9, OC*H*HO), 4.81 (1 H, d, *J* 6.6, OCH*H*O), 5.27 (1 H, dd, *J* 15.5 and 7.9, 3-H), 5.68 (1 H, dt, *J* 15.4 and 6.8, 4-H) and 7.20–7.31 and 7.44–7.48 (15 H, m, Ph); *m/z* (EI) 508 (0.4%), 341 (41.4) and 243 (Ph_3C^+, 100).

(2S,3E)-2-(2-*Methoxyethoxymethoxy*)*octadec*-3-*en*-1-*ol* (S)-**14**.—A solution of trityl ether (*S*)-**13** (86.0 mg, 0.140 mmol) and toluene-*p*-sulfonic acid monohydrate (30 mg, 0.15 mmol) in methylene dichloride (2.5 cm^3)–methanol (2.5 cm^3) was stirred for 30 min at room temperature before being diluted with chloroform, washed with saturated aq. sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. The residual oil (91 mg) was purified by flash column chromatography [SiO_2 (10 g); (1:1) ethyl acetate–hexane] to give enol (*S*)-**14** as an oil (42.8 mg, 82%), $[\alpha]_D^{21}$ +73.2 (*c* 1.242, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH), 1070, 1025, and 960 (*E*-C=C); δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.26–1.36 (24 H, m, CH_2), 2.03 (2 H, q-like, 5-H_2), 2.63 (1 H, dd-like, OH, exch.), 3.40 (3 H, s, MeO), 3.49–3.62 (4 H, m, MeOC*H*$_2$ and C*H*$_2$OH), 3.66 (1 H, dt-like, MeOCH$_2$C*H*H), 3.85 (1 H, dt-like, MeOCH$_2$CH*H*), 4.13 (1 H, dt-like, C*H*OMEM), 4.72 (1 H, d, *J* 6.9, OC*H*HO), 4.80 (1 H, d, *J* 7.2, OCH*H*O), 5.31 (1 H, dd, *J* 15.4 and 7.7, 3-H) and 5.75 (1 H, dt-like, 4-H); *m/z* (EI) 341 (M$^+$ − CH$_2$OH, 1.1%), 266 (2.2) and 89 (100). High-resolution FAB-MS: Found: *m/z* 373.3299. Calc. for $C_{22}H_{45}O_4$: (M + H)$^+$, 373.3318.

Methyl (2S,3E)-2-(2-*Methoxyethoxymethoxy*)*octadec*-3-*enoate* (S)-**16** via *Acid* (S)-**15**.—A mixture of enol (*S*)-**14** (114.2 mg, 0.307 mmol) and PDC (690 mg, 1.83 mmol) in *N,N*-dimethylformamide (DMF) (2 cm^3) was stirred for 3 h at 40–50 °C under N_2. The resulting mixture was diluted with water and extracted with ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give the acid (*S*)-**15** as a brown oil (121 mg). This oil was dissolved in methylene dichloride (5 cm^3), to which *N,N*-diisopropylethylamine (0.53 cm^3, 3.0 mmol) and methyl iodide (1.7 cm^3, 27 mmol) were added and the mixture was stirred overnight at room temperature under N_2. The resulting brown suspension was diluted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to give a brown oil (156 mg). Purification by flash column chromatography [SiO_2 (20 g); (1:4) ethyl acetate–hexane] yielded ester (*S*)-**16** as an oil (50.0 mg, 41%), $[\alpha]_D^{20}$ +68.0 (*c* 0.500, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O), 1200, 1170, 1100, 1030 and 970 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.25–1.39 (24 H, m, CH_2), 2.06 (2 H, q-like, 5-H_2), 3.38 (3 H, s, *Me*OCH$_2$), 3.53 (2 H, t-like, MeOC*H*$_2$), 3.68 (1 H, dt-like, MeOCH$_2$C*H*H), 3.75 (3 H, s, CO$_2$Me), 3.79 (1 H, dt, *J* 110.0 and 4.4, MeOCH$_2$CH*H*), 4.64 (1 H, d, *J* 7.4, C*H*OMEM), 4.77 (1 H, d, *J* 7.1, OC*H*HO), 4.81 (1 H, d, *J* 7.1, OCH*H*O), 5.47 (1 H, dd, *J* 15.4 and 7.4, 3-H) and 5.88 (1 H, dt-like, 4-H); *m/z* (EI) 341 (M$^+$ − MeOCO, 1.6%), 295 (1.9) and 89 (100). High-resolution FAB-MS; Found: *m/z* 401.3264. Calc. for $C_{23}H_{45}O_5$ (M + H)$^+$, 401.3267.

Methyl (2S,3E)-2-*Hydroxyoctadec*-3-*enoate* (S)-**2**.—A solution of compound (*S*)-**16** (47.5 mg, 0.119 mmol) and zinc bromide (267 mg, 1.19 mmol) in methylene dichloride (3 cm^3) was refluxed for 8 h. The resulting mixture was then partitioned between chloroform and water. The organic layer was dried (Na_2SO_4) and evaporated to give a waxy solid (49 mg). Purification by flash column chromatography [SiO_2 (10 g); (4:15) ethyl acetate–hexane] gave compound (*S*)-**2** as a waxy solid (27.1 mg, 73%), R_f 0.53 [AcOEt–hexane (1:3)]; $[\alpha]_D^{19}$ +46.4 (*c* 0.278, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH), 1740 (C=O), 1250, 1210 and 970; δ_H 0.88 (3 H, t-like, Me), 1.25–1.38 (24 H, m, CH_2), 2.06 (2 H, q-like, 5-H_2), 2.83 (1 H, d, *J* 5.8, OH, exch.), 3.80 (3 H, s, CO$_2$Me), 4.60 (1 H, t-like, C*H*OH), 5.50 (1 H, dd, *J* 15.4 and 6.3), and 5.88 (1 H, dt, *J* 15.4 and 6.9, 4-H); *m/z* (EI) 312 (M$^+$, 1.1%) and 253 (M$^+$ − CO$_2$Me, 100).

(2R,3E)-2-(*Methoxymethoxy*)-1-*trityloxyoctadec*-3-*ene* (R)-**17**.—A solution of compound (*R*)-**12** (1.785 g, 3.39 mmol), methoxymethyl chloride (1.0 cm^3, 13.2 mmol), and *N,N*-diisopropylethylamine (2.9 cm^3, 16.7 mmol) in methylene dichloride (5 cm^3) was refluxed for 30 min under argon. The mixture was diluted with methylene dichloride, washed with saturated aq. sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give a brown oil (2.50 g). Purification by flash column chromatography [SiO_2 (180 g); (1:1) methylene dichloride–hexane] gave alkene (*R*)-**17** as an oil (1.765 g, 91%), ν_{max}(neat)/cm^{-1} 1150, 1095 and 970 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.23–1.36 (24 H, m, CH_2), 2.01 (2 H, q, *J* 6.9, 5-H_2), 3.07 (1 H, dd, *J* 9.6 and 4.4, C*H*HO), 3.23 (1 H, dd-like, CH*H*O), 3.39 (3 H, s, MeO), 4.16–4.18 (1 H, m, C*H*OMOM), 4.64 (1 H, d, *J* 6.6, OC*H*HO), 4.73 (1 H, d, *J* 6.6, OCH*H*O), 5.29 (1 H, dd, *J* 15.4 and 7.7, 3-H), 5.67 (1 H, dt-like, 4-H) and 7.20–7.30 and 7.45–7.47 (15 H, m, Ph); *m/z* (EI) 297 (M$^+$ − CH$_2$OCPh$_3$, 25.4%) and 243 (Ph_3C^+, 100).

(2R,3E)-2-(*Methoxymethoxy*)*octadec*-3-*en*-1-*ol* (R)-**18**.—Detritylation of compound (*R*)-**17** (1.753 g, 3.07 mmol) was carried out according to the method described for compound (*S*)-**14** from trityl ether (*S*)-**13** to give enol (*R*)-**18** as a solid (0.892 g, 88%), $[\alpha]_D^{15}$ −73.7 (*c* 0.0904, $CHCl_3$).

Methyl (2R,3E)-2-(*Methoxymethoxy*)*octadec*-3-*enoate* (R)-**20**.—The reaction was carried out as described as above, using the primary alcohol (*R*)-**18** (95.2 mg, 0.290 mmol) to give ester (*R*)-**20** as a pale yellow oil (37.5 mg, 36%), $[\alpha]_D^{19}$ −66.6 (*c* 0.335, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O) and 960 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.25–1.31 (22 H, m, CH_2), 1.37–1.40 (2 H, m, 6-H_2), 2.07 (2 H, q-like, 5-H_2), 3.39 (3 H, s, *Me*OCH$_2$), 3.76 (3 H, s, CO$_2$Me), 4.59 (1 H, d, *J* 7.4, C*H*OMOM), 4.67 (1 H, d, *J* 6.6, OC*H*HO), 4.73 (1 H, d, *J* 6.9, OCH*H*O), 5.49 (1 H, dd, *J* 15.4 and 7.4, 3-H) and 5.88 (1 H, dt-like, 4-H); *m/z* (EI) 311 (M$^+$ − MeOCH$_2$, 0.7%), 297 (M$^+$ − CO$_2$Me, 21.1), and 45 (MeOCH$_2^+$, 100). High-resolution FAB-MS; Found: *m/z* 357.2998. Calc. for $C_{21}H_{41}O_4$: (M + H)$^+$, 357.3005.

Methyl (2R,3E)-2-*Hydroxyoctadec*-3-*enoate* (R)-**2**.—To a stirred solution of ester (*R*)-**20** (32.1 mg, 0.09 mmol) in ethanethiol (2 cm^3) was added a few drops of boron trifluoride–diethyl ether under argon and the mixture was stirred for 40 min at room temperature, quenched by the addition of saturated aq. sodium hydrogen carbonate, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give an oil (40 mg). Purification by flash column chromatography [SiO_2 (10 g); (1:4) ethyl acetate–hexane] gave hydroxy ester (*R*)-**2** as a solid (25.7 mg, 91%), $[\alpha]_D^{19}$ −44.7 (*c* 0.257, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3350 (OH), 1760 (C=O), 1740, 1260, 1200, 1140 and 970 (*E*-C=O); δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.26–1.31 (22 H, m, CH_2), 1.37–1.40 (2 H, m, 6-H_2), 2.06 (2 H, q-like, 5-H_2), 2.83 (1 H, d, *J* 5.8, OH, exch.), 3.80 (3 H, s, CO$_2$Me), 4.61 (1 H, t, *J* 6.1, C*H*OH), 5.50 (1 H, dd, *J* 15.4 and 6.3, 3-H) and 5.88 (1 H, dt, *J* 15.4 and 6.9, 4-H); *m/z* (EI) 312 (M^+, 0.9%) and 253 ($M^+ - CO_2Me$, 100). High-resolution FAB-MS; Found: *m/z* 313.2746. Calc. for $C_{19}H_{37}O_3$ $(M + H)^+$, 313.2743.

(2R,3S,4E)-1,2-*Cyclohexylidenedioxynonadec*-4-*en*-3-*ol* **23**.—To a solution of hexadec-1-yne **21** (1.53 g, 6.88 mmol) in hexane (6 cm^3) was added a 1.0 mol dm^{-3} solution of di-isobutylaluminium hydride (DIBAH) in hexane (6.9 cm^3, 6.88 mmol) under argon, and the mixture was stirred for 3 h at 50 °C to give a solution of the alanate in hexane. To a cooled (0 °C), stirred solution of the alanate was added dropwise a solution of cyclohexylidene-D-glyceraldehyde **6** (1.19 g, 7.02 mmol) in diethyl ether (4.5 cm^3)–toluene (1.5 cm^3), and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into saturated aq. potassium oxalate (250 cm^3) and extracted with ethyl acetate (200 cm^3 × 1, 100 cm^3 × 1). Combined organic extracts were washed with half-saturated aq. sodium chloride, dried (Na_2SO_4), and evaporated to give an oil (2.72 g). Purification by flash column chromatography [SiO_2 (300 g); (1:5) ethyl acetate–hexane] gave compound **23** as an oil (1.136 g, 64%), $[\alpha]_D^{23}$ +10.9 (*c* 1.013, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH) and 970 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.25–1.41 (24 H, m, CH_2), 1.52–1.65 (10 H, m, cyclohexyl CH_2), 2.02–2.05 (3 H, m, 6-H_2 and OH, exch.), 3.87–3.96 (2 H, m, CH_2OC), 4.09 (1 H, td, *J* 6.7 and 4.1, CHOC), 4.27 (1 H, br s, C*H*OH), 5.38 (1 H, dd, *J* 15.5 and 6.5, 4-H) and 5.77 (1 H, dt-like, 5-H); *m/z* (EI) 394 (M^+, 1.8%), 253 (1.0) and 141 (100).

(2R,3S,4E)-1,2-*Cyclohexylidenedioxy*-3-(*methoxymethoxy*)-*nonadec*-4-*ene* **24**.—Methoxymethylation of the alcohol **23** (763 mg, 1.93 mmol) was carried out by a similar method as described for the preparation of compound (*R*)-**17** to yield title compound **24** as an oil (840 mg, 99%), ν_{max}(neat)/cm^{-1} 1275, 1150, 1100, 1025 and 960 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.25–1.38 (24 H, m, CH_2), 1.56–1.62 (10 H, m, cyclohexyl CH_2), 2.07 (2 H, q-like, 6-H_2), 3.37 (3 H, s, MeO), 3.84 (1 H, dd, *J* 8.3 and 6.3, C*H*HOC), 4.00 (1 H, dd, *J* 8.0 and 5.2, C*H*OMOM), 4.04 (1 H, dd-like, CH*H*OC), 4.10–4.14 (1 H, m, CHOC), 4.55 (1 H, d, *J* 6.6, OC*H*HO), 4.73 (1 H, d, *J* 6.6, OCH*H*O), 5.33 (1 H, dd-like, 4-H) and 5.71 (1 H, dt-like, 5-H); *m/z* (EI) 438 (M^+, 1.6%), 297 (8.5) and 141 (100).

(2R,3S,4E)-3-(*Methoxymethoxy*)*nonadec*-4-*ene*-1,2-*diol* **25**.—The mixture of compound **24** (490 mg, 1.12 mmol) and PPTS (281 mg, 1.12 mmol) in methanol (20 cm^3)–methylene dichloride (6 cm^3) was stirred for 48 h at room temperature under argon and was then concentrated. The residue was dissolved in methylene dichloride, washed with brine, dried (Na_2SO_4), and evaporated to give an oil (650 mg). Purification by flash column chromatography [SiO_2 (50 g); (1:40) methanol–methylene dichloride] gave diol **25** as an oil (229 mg, 57%), $[\alpha]_D^{23}$ +64.5 (*c* 1.100, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH), 1660 (C=C), 970 (*E*-C=C) and 915; δ_H 0.88 (3 H, t-like, Me), 1.26–1.39 (24 H, m, CH_2), 2.05–2.10 (2 H, m, 6-H_2), 2.11 (1 H, m, CH_2O*H*, exch.), 2.43 (1 H, d, *J* 5.5, CHO*H*, exch.), 3.39 (3 H, s, MeO), 3.67–3.74 (3 H, m, C*H*OH and C*H*$_2$OH), 4.09 (1 H, dd, *J* 8.2 and 5.0, C*H*OMOM), 4.56 (1 H, d, *J* 6.6, CH*H*HO), 4.71 (1 H, d, *J* 6.6, OCH*H*O), 5.36 (1 H, dd-like, 4-H) and 5.78 (1 H, dt-like, 5-H); *m/z* (EI) 341 (M^+ − OH, 0.2%), 297 ($M^+ - CHOHCH_2OH$, 40.3) and 45 ($MeOCH_2^+$, 100).

(2S,3E)-2-(*Methoxymethoxy*)*octadec*-3-*en*-1-*ol* (S)-**18**.—To a stirred solution of diol **25** (115 mg, 0.321 mmol) in benzene (5 cm^3) was added lead tetraacetate (156 mg, 0.353 mmol) in portions under argon. The mixture was stirred at room temperature for 20 min and was filtered over Celite. The filtrate was stirred with anhydrous potassium carbonate for 30 min at room temperature, and was then filtered and evaporated to give crude aldehyde **26** as an oil (98 mg).

To a stirred solution of crude aldehyde **26** in methanol (4 cm^3) at 0 °C was added sodium borohydride (24 mg, 0.634 mmol) in portions, and the mixture was stirred for 5 min at 0 °C and for an additional 10 min at room temperature. After being cooled to 0 °C, the mixture was quenched by the slow addition of 5% aq. citric acid to pH 4–5. The resulting mixture was diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give an oil (130 mg). Purification by flash column chromatography [SiO_2 (18 g); (1:2) ethyl acetate–hexane] gave primary alcohol (*S*)-**18** as an oil (78.8 mg, 75%), $[\alpha]_D^{25}$ +61.4 (*c* 0.788, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300 and 965 (*E*-C=C); δ_H 0.88 (3 H, t-like, Me), 1.25–1.37 (24 H, m, CH_2), 2.05 (2 H, q-like, 5-H_2), 2.31 (1 H, br s, OH, exch.), 3.40 (3 H, s, MeO), 3.57–3.59 (2 H, m, C*H*$_2$OH), 4.07–4.11 (1 H, m, C*H*OMOM), 4.61 (1 H, d, *J* 6.6, OC*H*HO), 4.75 (1 H, d, *J* 6.6, OCH*H*O), 5.31 (1 H, dd, *J* 15.4 and 7.7, 3-H) and 5.76 (1 H, dt-like, 4-H); *m/z* (EI) 297 (M^+ − CH_2OH, 100%), 267 ($M^+ - MeOCH_2O$, 31.6), 251 (37.6) and 45 ($MeOCH_2^+$, 99.9).

t-*Butyl* 4-(1-*Hydroxyhexadecyl*)-2,2-*dimethyloxazolidine*-3-*carboxylate* **28**.—To a solution of the propargyl alcohol **27** (3.65 g, 8.34 mmol) in ethyl acetate (40 cm^3) was added a catalytic amount of $PtO_2 \cdot 1\text{–}3H_2O$ (0.09 g), and the mixture was stirred for 1 h at room temperature under H_2. The reaction mixture was filtered over Celite and evaporated to give a brown oil (4.30 g). Purification by chromatography [SiO_2 (40 g); (1:2) ethyl acetate–hexane] gave compound **28** as an oil (3.71 g, 100%), $[\alpha]_D^{20}$ −12.7 (*c* 1.090, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3420 (OH) and 1695 (amide C=O); δ_H 0.88 (3 H, t-like, Me), 1.25–1.41 (28 H, m, CH_2), 1.49 (12 H, br s, *Me*CMe, CMe_3), 1.58 (3 H, s, MeC*Me*), 3.49 (1 H, br s, OH, exch.) and 3.74–4.08 (4 H, m, CH_2OC, CHN, C*H*OH); *m/z* (EI) 441 (M^+, 0.2%), 426 (M^+ − Me, 3.3), 368 (M^+ − Bu^{t}O, 9.0) and 200 (100). High-resolution FAB-MS; Found: *m/z* 442.3912. Calc. for $C_{26}H_{52}NO_4$: $(M + H)^+$, 442.3899.

N-t-*Butoxycarbonyl*-D-*erythro*-*dihydrosphingosine* **29**.—A solution of the oxazolidine **28** (3.52 g, 7.97 mmol) and toluene-*p*-sulfonic acid monohydrate (0.18 g, 0.96 mmol) in methanol (50 cm^3) was stirred for 4 h at room temperature and was concentrated. The residue was dissolved in ethyl acetate, washed successively with aq. saturated sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to give a solid. Recrystallization from (2:1) hexane–diethyl ether yielded *compound* **29** as a powdery solid (2.66 g, 83%), m.p. 82.5–83.5 °C (Found: C, 68.4; H, 11.8; N, 3.5. $C_{23}H_{47}NO_4$ requires C, 68.78; H, 11.79; N, 3.49%); $[\alpha]_D^{21}$ +8.20 (*c* 1.000, $CHCl_3$);* ν_{max}(KBr)/cm^{-1} 3330 (OH, NH), 1690, 1530 (amide C=O), 1175 and 1050; δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.26–1.33 (24 H, m, CH_2), 1.46 (9 H, s, Bu^t), 1.48–1.58 (4 H, m, 4- and 5-H_2), 2.34 (1 H, br s, OH, exch.), 2.44 (1 H, br s, OH, exch.), 3.53 (1 H, m, C*H*OH), 3.76 (1 H, dd-like, C*H*HOH), 3.80 (1 H, m, C*H*NH), 4.00 (1 H, dd, *J* 11.3 and 3.3, CH*H*OH) and 5.38 (1 H, m, NH, exch.); *m/z* (EI) 386 (M^+ − Me, 0.2%), 326 (10.6), 144 (37.6) and 100 (100).

1,3-O-*Isopropylidene*-D-erythro-*dihydrosphingosine* **30**.—To a stirred solution of ester **29** (2.65 g, 6.60 mmol) in ethyl acetate (100 cm^3) was added conc. hydrochloric acid (30 cm^3), and the mixture was then stirred for 25 min at room temperature. The cooled (0 °C) mixture was basified with 25% aq. sodium

* See footnote ‡ on page 343.

hydroxide and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give crude D-*erythro*-dihydrosphingosine as a powdery solid. A solution of crude D-*erythro*-dihydrosphingosine and camphorsulfonic acid monohydrate (1.82 g, 7.3 mmol) in 2,2-dimethoxypropane (150 cm^3) was refluxed for 1 h and concentrated. The residue was dissolved in ethyl acetate, washed successively with aq. saturated sodium hydrogen carbonate, water, and saturated brine. The organic layer was dried (Na_2SO_4) and was evaporated to give a dark yellow oil (2.42 g). Purification by chromatography [SiO_2 (120 g); (40:1) chloroform–methanol] gave compound **30** as a brown oil (2.18 g, 97%), $[\alpha]_D^{22}$ +29.5 (*c* 1.178, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3360 (NH), 1200 and 1070; δ_H 0.88 (3 H, t-like, Me), 0.90–1.20 (2 H, m, NH_2, exch.), 1.23–1.28 (26 H, m, CH_2), 1.39 (3 H, s, *Me*CMe), 1.44 (3 H, s, MeC*Me*), 1.46–1.52 (1 H, m, 4-H), 1.69–1.75 (1 H, m, 4-H), 2.64 (1 H, td, *J* 9.6 and 5.2, C*H*NH_2), 3.39 (1 H, td, *J* 9.0 and 2.6, CHOC), 3.45 (1 H, dd, *J* 11.3 and 9.9, C*H*HOC) and 3.81 (1 H, dd, *J* 11.4 and 5.4, CH*H*OC); *m/z* (EI) 341 (M^+, 0.5%), 340 (M^+ − H, 0.5), 326 (15.3), 101 (39.4) and 43 (100). High-resolution FAB-MS; Found: *m/z* 342.3381. Calc. for $C_{21}H_{44}NO_2$: $(M + H)^+$, 342.3372.

2′-O-(*Methoxymethyl*)*symbioramide* **32**.—To a stirred suspension of crude acid (*R*)-**19** prepared from the alcohol (*R*)-**18** (768 mg, 2.34 mmol), DCC (483 mg, 2.34 mmol), and HOBt (316 mg, 2.34 mmol) in methylene dichloride (20 cm^3) was added dropwise a solution of primary amine **30** (799 mg, 2.34 mmol) in methylene dichloride (10 cm^3), and the mixture was stirred for 6 h at room temperature. The resulting suspension was filtered and concentrated to give a waxy solid. Purification by flash column chromatography [SiO_2 (250 g); (3:5) ethyl acetate–hexane] afforded a mixture of unchanged alcohol (*R*)-**18** and amide **31** as a waxy solid (791 mg).

A solution of this mixture and toluene-*p*-sulfonic acid monohydrate (30 mg) in methylene dichloride (5 cm^3)–methanol (5 cm^3) was stirred for 1 h at room temperature, and concentrated. The residue was dissolved in chloroform, washed with saturated aq. sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give a solid. Purification by flash column chromatography [SiO_2 (80 g); (40:1) methylene dichloride–methanol] gave the unchanged alcohol (*R*)-**18** (95.2 mg, recovery 12%) and diol **32** as a powdery solid [560 mg, 38% from (*R*)-**30**], $[\alpha]_D^{23}$ −27.1 (*c* 0.981, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3275 (OH, NH), 1645, 1530 (amide C=O), 1150, 1100, 1070, 1030 and 970 (*E*-C=C); δ_H 0.88 (6 H, t-like, Me and 18′-H_3), 1.26–1.31 (48 H, m, CH_2), 1.36–1.39 (2 H, m, 6′-H_2), 1.49–1.53 (2 H, m, 4-H_2), 2.04–2.10 (2 H, m, 5′-H_2), 2.49 (1 H, d, *J* 6.1, CHO*H*, exch.), 2.66–2.68 (1 H, m, CH_2O*H*, exch.), 3.40 (3 H, s, MeO), 3.77–3.82 (3 H, m, C*H*$_2$OH and C*H*NH), 4.02–4.04 (1 H, m, C*H*OH), 4.51 (1 H, d, *J* 7.4, C*H*OMOM), 4.67 (1 H, d, *J* 6.6, OC*H*HO), 4.75 (1 H, d, *J* 6.6, OCH*H*O), 5.43 (1 H, dd, *J* 15.4 and 7.2, 3′-H), 5.88 (1 H, dt-like, 4′-H) and 7.35 (1 H, d, *J* 7.7, NH, exch.); *m/z* (EI) 626 (M^+, 0.2%), 625 (M^+ − H, 0.7), 328 (15.8), 297 (41.8) and 45 (100). High-resolution FAB-MS; Found: *m/z* 626.5731. Calc. for $C_{38}H_{76}NO_5$: $(M + H)^+$, 626.5724.

Symbioramide **1**.—To a stirred suspension of diol **32** (80.9 mg, 0.129 mmol) in ethanethiol (9 cm^3) was added a few drops of boron trifluoride–diethyl ether under argon and the mixture was stirred for 45 min at room temperature. The resulting clear solution was poured into saturated aq. sodium hydrogen carbonate (10 cm^3) and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to give a powdery solid (75 mg). Recrystallization from (1:2) acetone–benzene gave symbioramide **1** as a powder (47.6 mg, 63%), m.p. 112–113 °C (lit.,[2] 105–107 °C) (Found: C, 74.5; H, 12.3; N, 2.4. Calc. for $C_{36}H_{71}NO_4$: C, 74.30; H, 12.30; N, 2.41%); $[\alpha]_D^{19}$ +2.65 (*c* 0.378, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300 (OH, NH), 1640, 1530 (amide C=O), 1250, 1060 and 960 (*E*-C=C); δ_H 0.88 (6 H, t, *J* 6.9, Me), 1.26–1.31 (48 H, m, CH_2), 1.36–1.41 (2 H, m, 6′-H_2), 1.50–1.55 (2 H, m, 4-H_2), 2.08 (2 H, q-like, 5′-H_2), 2.51 (1 H, d, *J* 6.0, CHO*H*, exch.), 2.64 (1 H, br s, CH_2O*H*, exch.), 3.15 (1 H, d, *J* 3.3, CHO*H*, exch.), 3.76–3.83 (3 H, m, C*H*HOH, C*H*NH, C*H*OH), 4.03 (1 H, dt, *J* 11.6 and 3.6, CH*H*OH), 4.53 (1 H, dd, *J* 7.2 and 3.6, 2′-H), 5.56 (1 H, dd-like, 3′-H), 5.90 (1 H, dt-like, 4′-H) and 7.02 (1 H, d, *J* 7.7, NH, exch.); *m/z* (EI) 581 (M^+, 1.2%), 563 (M^+ − H_2O, 16.9), 328 (40.2), 280 (46.6), 253 (45.9) and 43 (100).

Symbioramide Triacetate **33**.—A solution of symbioramide **1** (18.2 mg, 0.031 mmol) and acetic anhydride (0.5 cm^3) in pyridine (2.5 cm^3) was stirred overnight at room temperature, and was then diluted with ethyl acetate, washed successively with saturated aq. copper sulfate and water, dried ($MgSO_4$), and evaporated to give a solid. Purification by flash chromatography [SiO_2 (8 g); (1:2) ethyl acetate–hexane] gave triacetate **33** as a solid (21.4 mg, 97%), m.p. 75–78 °C (lit.,[2] 75–78 °C); ν_{max}(KBr)/cm^{-1} 3300 (NH), 1730 (CO), 1660 (CONH), 1540 (amide II band), 1270, 1240, 1030 and 950 (*E*-C=C); δ_H 0.88 (6 H, t-like, Me), 1.25–1.31 (48 H, m, CH_2), 1.35–1.39 (2 H, m, 6′-H_2), 1.57–1.62 (2 H, m, 4-H_2), 2.04–2.08 (2 H, m, 5′-H_2), 2.04 (3 H, s, Ac), 2.07 (3 H, s, Ac), 2.18 (3 H, s, Ac), 4.04 (1 H, dd, *J* 11.3 and 3.3, C*H*HOAc), 4.31 (1 H, dd, *J* 11.3 and 6.9, CH*H*OAc), 4.33–4.38 (1 H, m, C*H*NH), 4.90 (1 H, dt, *J* 8.3 and 5.0, C*H*OAc), 5.49 (1 H, d, *J* 7.2, C*H*OAc), 5.52 (1 H, dd, *J* 15.4 and 7.2, 3′-H), 5.90 (1 H, dt-like, 4′-H) and 6.52 (1 H, d, *J* 8.8, NH); *m/z* (EI) 708 (M^+, 1.0%), 707 (M^+ − H, 2.3), 648 (M^+ − AcOH, 19.7) and 370 (100). High-resolution FAB-MS; Found: *m/z* 708.578. Calc. for $C_{42}H_{78}NO_7$: $(M + H)^+$, 708.5778.

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