Total Synthesis of (2*S*,3*S*,4*R*)-2-[(2'*R*)-2-Benzoyloxydocosanoylamino]-16-methylheptadecane-1,3,4,-triol 3,4-Dibenzoate, a Partially Protected Ceramide Part of Sponge Cerebrosides[1]

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(2*S*,3*S*,4*R*)-2-[(2'*R*)-2-Benzoyloxydocosanoylamino]-16-methylheptadecane-1,3,4-triol 3,4-dibenzoate **32**, a partially protected ceramide part of a cerebroside from the marine sponge *Halichondria japonica*, has been synthesized from L-ascorbic acid, and its absolute stereochemistry has been determined. The key steps in the synthesis include the regioselective ring opening of chiral epoxide **5** with a 2-alkyl-2-lithio-1,3-dithiane and the introduction of a hydroxymethylene synthon using Dondoni's protocol to assemble C(1) and C(2) functionality.

Sponges are known to have remarkable powers of regeneration and self-recognition.[2] The cell-recognition processes have been assumed to be related to the sugar chains of cell-surface glycolipids and glycoproteins.

In 1991, Hayashi *et al.*,[3] showed that the main glycosphingolipid of the sponge *Halichondria japonica* was a ceramide digalactoside, Galα1→4Galβ1→1Cer, by using (FAB/MS), IR and ^{1}H NMR spectroscopy. The ceramide moiety was composed mainly of *cis* 4-hydroxyoctadecasphingosine and 2-hydroxydocosanoic acid. In the original paper, the stereochemistry of the lipid was not clear but it was inferred as having structure **1** from analogy with many cerebrosides isolated from marine organisms. Our continuing interest in the synthesis of naturally occurring lipids, coupled with our desire to establish the absolute structural assignment, led us to undertake the synthesis of the ceramide moiety **2**. Although many synthetic methods for phytosphingosines have been described,[4] this is the first report of the synthesis of ceramide **2** in optically pure form from L-ascorbic acid.

Results and Discussion

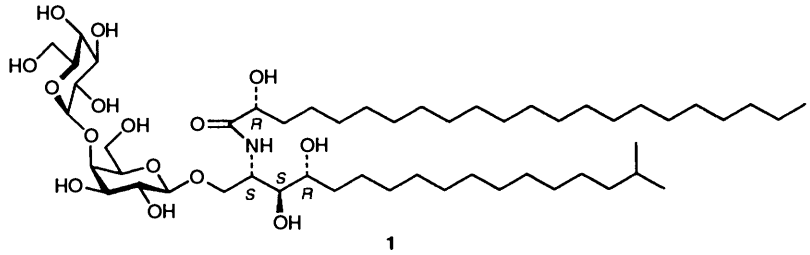
The synthetic strategy for assembling an appropriately functionalized precursor of phytosphingosine **3** was stereoselective ring opening of the epoxide **5** with a 2-alkyl-2-lithio-1,3-dithiane **C**. For the later stages of the synthesis, the requisite consecutive stereochemistry **A** could be obtained by means of Dondoni's protocol[5] *via* the thiazole **4**. In our previous communication,[6] we also reported the synthesis of optically active 2-hydroxy fatty acid **6** from the epoxide **5**. A combination of substrates **3** and **6** can eventually yield the ceramide **2** (Scheme 1).

The achiral portion of compound **3** was synthesized from octane-1,8-diol **7**. Treatment of diol **7** with 47% hydrobromic acid in refluxing benzene[7] led to the monobromide **8**. Subsequent protection of the alcohol **8** with dihydropyran (DHP) and pyridinium toluene-*p*-sulfonate (PPTS) yielded the pyranyl ether **9**. Coupling of bromide **9** with isobutylmagnesium bromide in the presence of dilithium tetrachlorocuprate(II) (0 °C to room temp.),[8] followed by hydrolysis with toluene-*p*-sulfonic acid (PTSA) in methanol, provided the alcohol **10** in 75% yield from diol **7**. Mesylation and bromination under standard conditions led to the bromide **11** in 87% yield from alcohol **10**. Treatment of bromide **11** with 2-lithio-1,3-dithiane in the presence of hexamethylphosphoric triamide (HMPA) at −78 °C[9] led to the 2-alkyl-1,3-dithiane **12** in 90% yield (Scheme 2).

3,4-Anhydro-1,2-*O*-isopropylidene-D-erythritol **5** was prepared by a modification of Abushanab's protocol[10] from the diol **13**, which was derived from L-ascorbic acid. The sequence began with the protection of the primary hydroxy group of diol **13** with pivaloyl chloride to give the pivalate **14**, which was then sulfonylated with *m*-nitrobenzenesulfonyl chloride (NsCl) to give the nisyl ester **15**. By subsequent treatment with base, diester **15** was converted into the epoxide **5** in 39% overall yield from diol **13**. The stereoisomeric purity (>99%) of epoxide **5** was confirmed by both ^{1}H NMR spectroscopy and the optical-rotation value[11] (Scheme 3).

Treatment of epoxide **5** with the 2-alkyl-2-lithio-1,3-dithiane derived from compound **12** at −78 °C led to the 2,2-dialkylated 1,3-dithiane **16** in 80% yield. Reductive desulfurization of compound **16** with Raney Ni afforded the alcohol **17**. Transacetalization of this compound was carried out by a reaction sequence (1, acidic hydrolysis; 2, protection of primary hydroxy group; 3, ketalization; and 4, basic hydrolysis of the pivalate) which gave the primary alcohol **18** in 55% yield from compound **16**. Swern oxidation[12] of primary alcohol **18** afforded the aldehyde **19** in 97% yield (Scheme 4).

With the aldehyde **19** in hand, we focused our efforts on creating a new chiral hydroxymethylene centre according to the Dondoni protocol.[5] Treatment of aldehyde **19** with 2-(trimethylsilyl)thiazole (2-TST) **4** afforded the highly diastereoselective adduct, which on desilylation gave (Scheme 5) the pure *anti*-2-(α-hydroxyalkyl)thiazole **20** (d.e. > 98% from ^{1}H NMR



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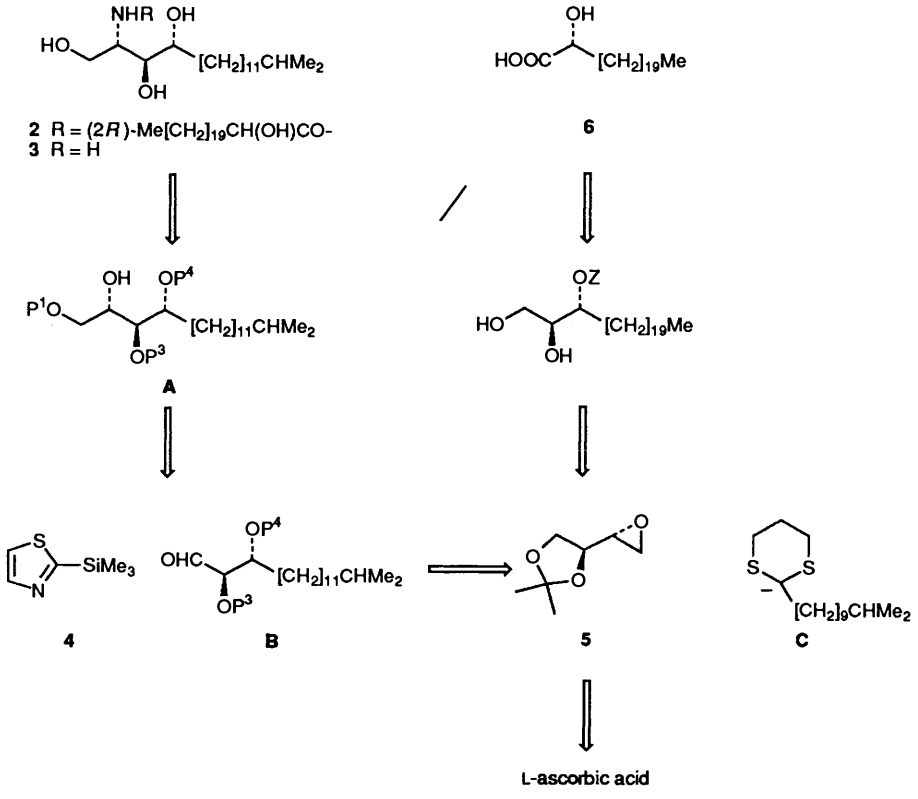
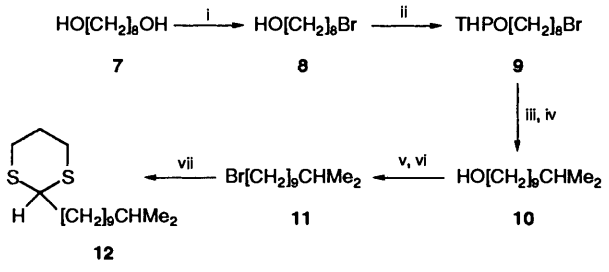
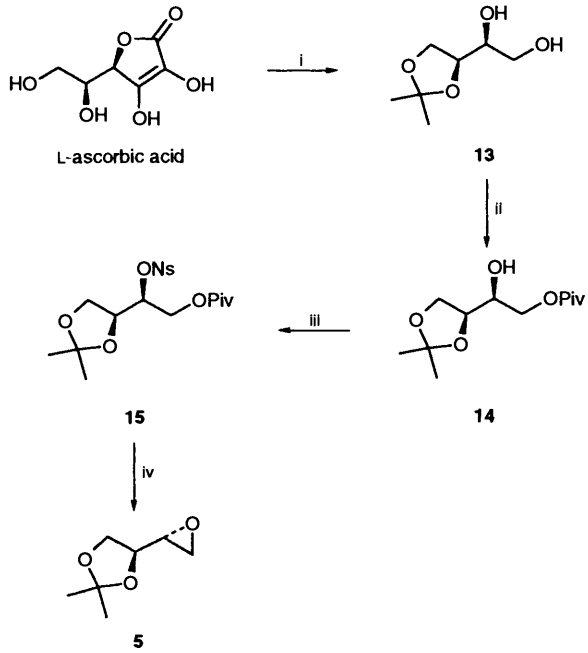


Scheme 1



Scheme 2 *Reagents:* i, 47% HBr, PhH; ii, DHP, PPTS; iii, Bu^{t}MgBr, Li_2CuCl_4, THF; iv, PTSA, MeOH; v, MsCl, py, DMAP; vi, LiBr, Me_2CO; vii, 1,3-dithiane, BuLi, HMPA, THF

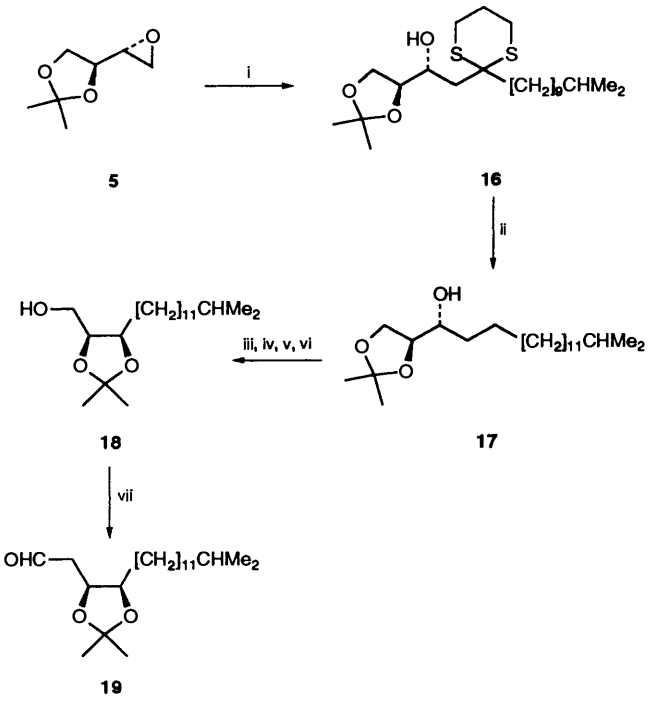


Scheme 3 *Reagents:* i, ref. 9; ii, PivCl, py, CH_2Cl_2; iii, NsCl, py, DMAP; iv, KOH, MeOH. Piv = Me_3CCO-; Ns = *m*-nitrobenzenesulfonyl

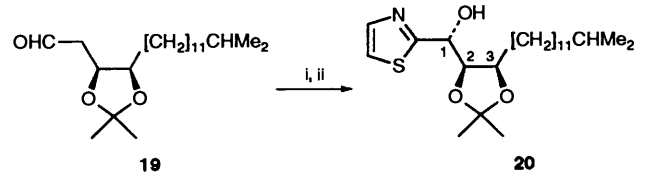
spectroscopy). This high diastereoselectivity (d.e. = diastereoisomeric excess) is attributed to the tight transition state **D** which discriminates the diastereotopic face of the aldehyde.[5] The stereochemistry of compound **20** was assigned as being C(1)–C(2) *anti* from the proposed mechanism and the coupling constants ($J_{1,2}$ 8.5 Hz, $J_{2,3}$ 5.5 Hz). Unfortunately, this compound possessed an undesirable configuration at C(1) which prevented continuation of the synthetic procedure. Initial attempts to invert the configuration by a modified Mitsunobu reagent[13] (*m*-nitrobenzoic acid–Ph_3P–diisopropyl azodicarboxylate) were fruitless, owing to severe steric hindrance to the incoming carboxylate anion **E**.

We therefore adopted a more lengthy strategy involving oxidation and reduction. The alcohol **20** was oxidized to the ketone **21** by using Swern conditions.[12] Reduction of ketone **21** with various metal hydrides in methanol was tried, and the results are shown in Table 1. The best result was obtained by reduction with $NaBH_4$ (0.5 molar equiv.) in the presence of cerium(III) chloride (2 molar equiv.) (**22**:**20** 85:15) (Scheme 6). The formation of the C(1)–C(2) *syn*-product **22** can be rationalized based on the transition-state model **F** by assuming that complexation of cerium ion occurs between the O atom of the isopropylidene group and the N atom of the thiazole ring and that the hydride attacks from the less hindered side.

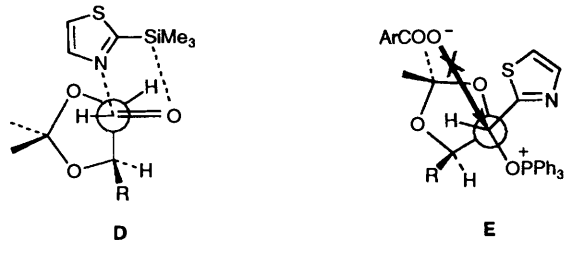
It is noteworthy that the addition of strontium chloride completely reversed the selectivity (**22**:**20** 7:93). In this case, the transition model **G** is the more favoured because strontium ion would have less affinity towards the nitrogen atom compared with the oxygen atom. The hydride would attack the carbonyl carbon atom from the direction shown by the arrow.

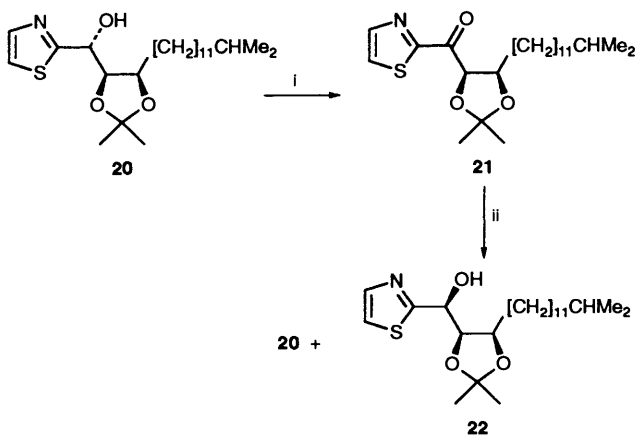


Scheme 4 *Reagents:* i, BuLi, HMPA, THF, **12**, −78 °C; ii, Raney Ni, EtOH; iii, PTSA, MeOH; iv, PivCl, py; v, $Me_2C(OMe)_2$, PPTS, PhH; vi, LiOH, MeOH; vii, $(COCl)_2$, DMSO, Et_3N



Scheme 5 *Reagents:* i, 2-(trimethylsilyl)thiazole **4**, THF; ii, TBAF, THF





Scheme 6 *Reagents:* i, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH

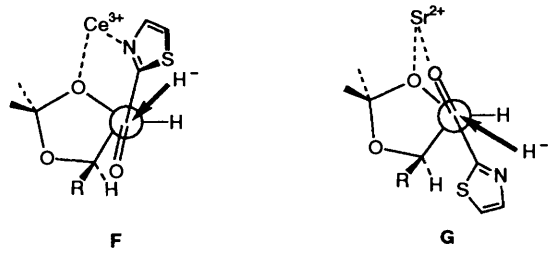


Table 1 Reduction of compound **21** with various metal hydrides *

Reagent	Product ratio **22**:**20**	Combined yield (%)
$NaBH_4$–$SrCl_2$	7:93	89
K-Selectride	13:87	94
$NaBH_4$	28:72	100
$LiBH_4$	29:71	79
L-Selectride–$CaCl_2$	46:54	43
$NaBH_4$–$CaCl_2$ (−15 °C)	49:51	93
$Zn(BH_4)_2$	53:46	72
L-Selectride	54:46	82
$NaBH_4$–$CaCl_2$ (0° C)	67:33	99
$NaBH_4$–$CeCl_3 \cdot 7H_2O$	85:15	96

* Reactions were carried out at room temperature, unless otherwise stated, in methanol. Product ratios were estimated from NMR spectra.

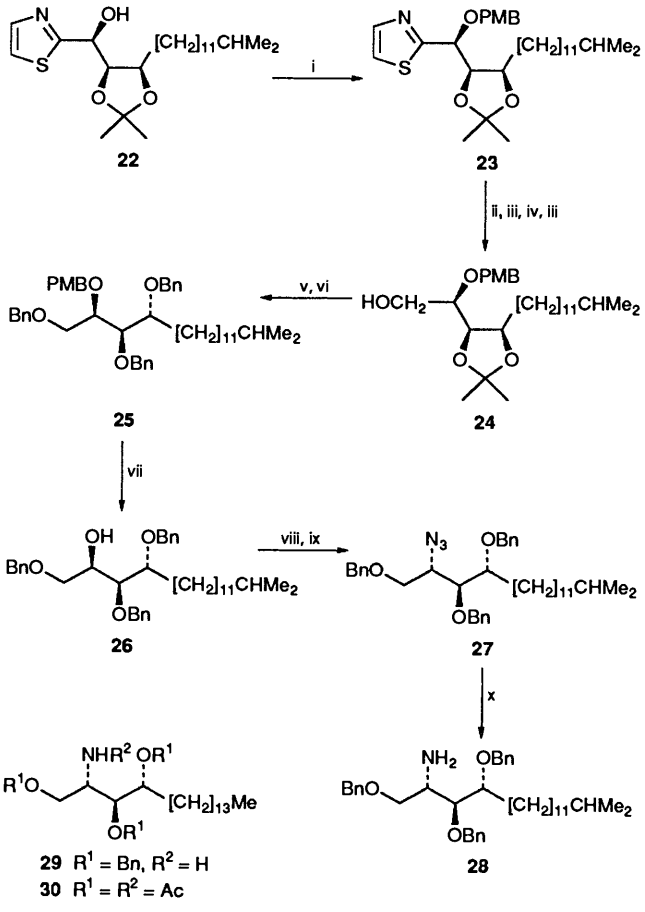
These two diastereoisomers could be easily separated by flash chromatography. That the major product had the desired configuration at C(1) was finally confirmed by derivation to the phytosphingosine **30** and by the ^1H NMR spectrum of compound **22** ($J_{1,2}$ 2.7 Hz: *syn*).

The remaining task of introducing the nitrogen function was achieved by the following sequence of reactions. Protection of the alcohol **22** as the *p*-methoxybenzyl (PMB) ether **23**, and subsequent methylation, reduction and hydrolysis of the thiazole moiety[14] provided an aldehyde, which on reduction with sodium boranuide (sodium borohydride, $NaBH_4$) afforded the alcohol **24** in 61% yield from the heterocycle **22**. Deprotection of compound **24** with PTSA in methanol followed by standard benzylation afforded the tris(benzyl ether) **25** (96%). Selective debenzylation of tetraether **25** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in CH_2Cl_2–water (20:1) led to the monoalcohol **26** (84%). Final conversion of the alcohol **26** into the phytosphingosine **28** commenced with mesylation and azidation [LiN_3, dimethylformamide (DMF), 90–100 °C] to afford the azide **27** in 80% yield. Reduction of azide **27** with lithium aluminium hydride in tetrahydrofuran (THF) afforded the amine **28** in 71% yield (Scheme 7). We are convinced that our synthetic product **28** is identical in stereochemistry with that of the natural lipid but were unable to secure a sample or the original spectra of compound **1** and could not make a direct comparison. We next prepared the well documented, structurally similar phytosphingosine **29** *via* similar methodology. Reductive deprotection of compound **29** with sodamide (sodium in liquid ammonia), followed by acetylation provided the acetamide triacetate **30** identical in all respects with the reported data ($[\alpha]_D$, IR, ^1H NMR and ^{13}C NMR).[15] Based on the congruity of the spectral data in Table 2 and the assumed biogenesis of phytosphingosines, we propose that the absolute stereochemistry of the 4-hydroxyisooctadecasphingosine should be that of compound **28**.

Having successfully prepared compound **28**, we proceeded to complete the synthesis of our target ceramide by amidation of compound **28** with (2*R*)-benzoyloxydocosanoic acid, which had been prepared from L-ascorbic acid.[6] Treatment of the mixture

Table 2 Spectral data for compounds **28** and **29**

	28	**29**
$[\alpha]_D^{20}$	−6.50 (*c* 1.02, $CHCl_3$)	−6.66 (*c* 0.90, $CHCl_3$)
^{1}H NMR 2-H	3.15 (ddd, *J* 7.0, 6.8, 3.0)	3.19 (ddd, *J* 7.5, 6.5, 3.5)
1-H	3.48 (dd, *J* 8.9, 7.0)	3.51 (dd, *J* 9.0, 7.5)
3-H	3.55 (dd, *J* 6.8, 3.2)	3.59 (dd, *J* 6.5, 3.5)
1′-H	3.68 (dd, *J* 8.9, 3.0)	3.71 (dd, *J* 9.0, 3.5)
4-H	3.68–3.75 (m)	3.71–3.74 (m)
EI-MS (% Int.)	587 (0.13) $[M]^+$	587 (0.23) $[M]^+$
	522 (0.44)	522 (0.62)
	496 (5.58)	496 (6.46)
	466 (3.22)	466 (3.48)
	388 (12.45)	388 (15.53)
	239 (7.11)	239 (8.52)
	150 (46.59)	150 (49.84)
	91 (100)	91 (100)



Scheme 7 *Reagents:* i, PMBCl, NaH, DMF; ii, MeI, MeCN; iii, $NaBH_4$, MeOH; iv, $CuCl_2$, CuO, aq. MeCN; v, PTSA, MeOH; vi, BnBr, NaH, Bu_4NI, DMF; vii, DDQ, CH_2Cl_2–water; viii, MsCl, DMAP, py, CH_2Cl_2; ix, LiN_3, DMF; x, $LiAlH_4$, THF. PMB = 4-methoxybenzyl.

of amine **28** and (2*R*)-benzoyloxydocosanoic acid with *N*-[3-(dimethylamino)propyl] *N*′-ethyl carbodiimide hydrochloride (EDC·HCl)[16] led to the ceramide **31** in 95% yield. Catalytic hydrogenation followed by tritylation, benzoylation and partial hydrolysis afforded the tribenzoate **32** (Scheme 8). The physical properties of compound **32** showed close similarity to those of the ceramide **33**, which was obtained from the starfish *Acanthaster planci*.[17]

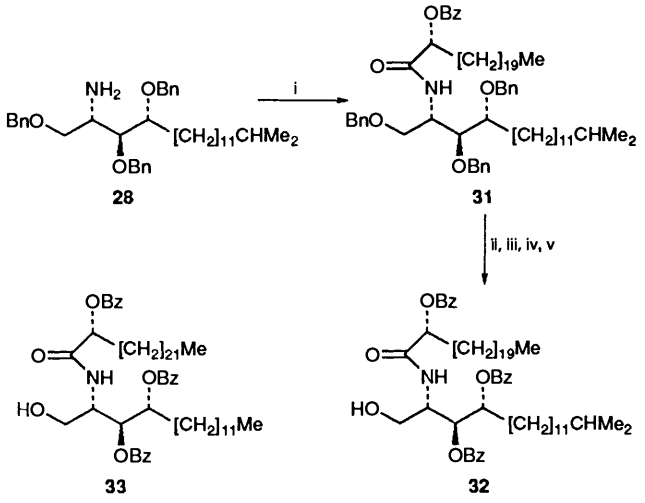
In conclusion, we believe that we have determined the absolute stereochemistry of the ceramide **1** as being that of compound **2** by means of its total synthesis, although direct comparison with the authentic sample could not be done. The present synthesis should provide a versatile method for elaborating all possible stereoisomers by changing the starting material from L-ascorbic acid to D-isoascorbic acid.

Experimental

M.p.s were measured on a Yanagimoto apparatus (MP-S2) and are uncorrected. IR and UV spectra were recorded with a JASCO A-100 or Shimadzu FTIR-8100 spectrophotometer and a Shimadzu UV-2200 spectrophotometer, respectively. Optical rotations were taken on a Horiba SEPA-200 polarimeter, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 60, 270 and 500, and 68 and 126 MHz, respectively, on a Hitachi R-600L JEOL GSX270 and GX500 instrument. Tetramethylsilane was the internal standard, and *J* values are given in Hz. Merck silica gel (70–230 mesh) was used for column chromatography. Merck Fertigplatten F 254 were used for TLC. All moisture-sensitive reactions were carried out using standard syringe-septum techniques under argon. Benzene, THF and diethyl ether were distilled from benzophenone ketyl. Dry acetonitrile and CH_2Cl_2 were obtained by distillation over P_2O_5. DMF and dimethyl sulfoxide (DMSO) were distilled over calcium hydride. Pyridine, Et_3N and diisopropylamine were distilled over KOH. Solutions were dried over $MgSO_4$.

8-Bromooctan-1-ol **8**.—A mixture of octane-1,8-diol **7** (7.31 g, 50.0 mmol) and 47% hydrobromic acid (6.25 cm^3) in benzene (100 cm^3) was heated under reflux using a Dean–Stark water separator for 2 days with addition of 47% hydrobromic acid every 12 h (3 × 6.25 cm^3). The reaction mixture was washed successively with water and aq. sodium hydrogen carbonate, dried, and evaporated. The crude product was purified by distillation under reduced pressure to afford monobromide **8** (8.87 g, 85%) as an oil, b.p. 72.5–78.0 °C/266 N m^{-2}; ν_{max}(film)/cm^{-1} 3330, 1462, 1440, 1245, 1055 and 720; δ_H(60 MHz; $CDCl_3$) 1.14–2.17 (13 H, m), 3.40 (2 H, t, *J* 6.6) and 3.63 (2 H, t, *J* 6.0).

1-Bromo-8-(tetrahydropyran-2-yloxy)octane **9**.—To a solution of monoalcohol **8** (8.87 g, 42.4 mmol) and PPTS (0.25 g, 0.995 mmol) in dichloromethane (40 cm^3) was added a solution of 3,4-dihydro-2*H*-pyran (DHP) (4.64 cm^3, 50.9 mmol) in dichloromethane (20 cm^3). After being stirred at room temperature for 2 h, the solution was washed successively with saturated aq. sodium hydrogen carbonate and brine, dried, and evaporated. The crude product was purified by column chromatography on silica gel [elution with benzene–AcOEt (98:2)] to give bromo ether **9** as an oil (11.3 g, 91%);



Scheme 8 *Reagents:* i, (2*R*)-benzoyloxydocosanoic acid, EDC·HCl, CH_2Cl_2; ii, H_2, 10% Pd–C, H^+, THF; iii, Ph_3CCl, py, DMAP; iv, PhCOCl, py; v, PTSA, $CHCl_3$–MeOH (1 : 1)

ν_{max}(film)/cm^{-1} 1470, 1460, 1445, 1390, 1370, 1360, 1140, 1125, 1080, 1070, 1040, 990, 980, 910, 875, 820, 730 and 680; δ_H(60 MHz; $CDCl_3$) 1.17–2.00 (18 H, m), 3.17–4.05 (6 H, m) and 4.42–4.67 (1 H, m).

10-*Methylundecan*-1-*ol* **10**.—To a solution of isobutylmagnesium bromide prepared from isobutyl bromide (1.67 cm^3, 15.4 mmol) and Mg (0.373 g, 15.4 mmol) in THF (2 cm^3) was added a 0.1 mol dm^{-3} solution of Li_2CuCl_4 in THF (1.0 cm^3) at room temperature followed by addition of a solution of bromo ether **9** (3.00 g, 10.2 mmol) in THF (15 cm^3). The reaction mixture was stirred for 12 h at room temperature and was then quenched with aq. NH_4Cl. The resulting mixture was extracted with hexane–diethyl ether (1 : 1). The organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in methanol (15 cm^3), PTSA (0.189 g, 0.996 mmol) was added, and the resulting mixture was stirred at room temperature for 6 h. After addition of dichloromethane, the mixture was washed with aq. sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure. After stripping with toluene, the residue was purified by chromatography on silica gel with benzene–AcOEt (98 : 2) as the eluent to leave the alcohol **10** (1.86 g, 97%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3340, 1470, 1385, 1370, 1060, 1040, 820 and 720; δ_H(60 MHz; $CDCl_3$) 0.88 (6 H, d, *J* 5.4), 1.25–2.00 (17 H, m) and 3.65 (2 H, t, *J* 6.0).

1-*Bromo*-10-*methylundecane* **11**.—Methanesulfonyl chloride (1.3 cm^3, 16.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the alcohol **10** (2.41 g, 13.0 mmol) and pyridine (3.1 cm^3, 39.0 mmol) in dry dichloromethane (13 cm^3). The solution was stirred at room temperature for 12 h. The reaction mixture was quenched with water and extracted with dichloromethane. The organic phase was washed successively with hydrochloric acid (1 mol dm^{-3}), aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to leave a mesyl ester as a pale yellow oil (4.23 g, 98%).

A solution of the above mesyl ester (3.42 g, 13.0 mmol) and $LiBr·H_2O$ (2.72 g, 25.9 mmol) in acetone (57 cm^3) was heated under reflux for 12 h. After removal of the solvent under reduced pressure, aq. sodium hydrogen carbonate was added and the mixture was extracted with hexane. The organic phase was dried and evaporated. Chromatography on silica gel with hexane as the eluent yielded the bromide **11** (2.86 g, 89%) as an oil; ν_{max}(film)/cm^{-1} 1485, 1440, 1380, 1360, 1260, 1250, 1170, 1070, 1040, 720 and 675; δ_H(60 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 5.4), 1.25–1.94 (17 H, m) and 3.39 (2 H, t, *J* 6.6).

2-(10′-*Methylundecyl*)-1,3-*dithiane* **12**.—A solution of BuLi (1.63 mol dm^{-3} in hexane; 7.4 cm^3, 12.0 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of 1,3-dithiane (1.38 g, 11.5 mmol) in dry THF (26 cm^3) under argon. The resulting solution was maintained at −20 °C for 2 h and was then re-cooled to −70 °C. To the mixture was added HMPA (2.4 cm^3; 13.7 mmol), followed by a solution of the bromide **11** (2.86 g, 11.5 mmol) in THF (12 cm^3). The resulting suspension was allowed to warm to room temperature and was stirred for 12 h. Saturated aq. NH_4Cl was added to the suspension and the resulting mixture was then extracted with hexane. The organic phase was dried and evaporated to leave a yellow liquid. Chromatography on silica gel with hexane–benzene (9 : 1) as the eluent yielded the dithiane **12** (2.99 g, 90%) as an oil; ν_{max}(film)/cm^{-1} 1465, 1420, 1380, 1360, 1275, 1240, 1180, 1170, 905, 860 and 720; δ_H(60 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 5.4), 1.25–2.10 (21 H, m), 2.76–2.91 (4 H, m) and 4.03 (1 H, t, *J* 6.6).

1,2-O-*Isopropylidene*-4-O-*pivaloyl*-L-*threitol* **14**.—Pivaloyl chloride (3.9 cm^3, 31.6 mmol) was added dropwise to a stirred and cooled (−15 °C) solution of the diol **13**[9] (4.87 g, 30.1 mmol) and dry pyridine (2.7 cm^3) in dry dichloromethane (9 cm^3). After being stirred for 2 h at ambient temperature, the reaction mixture was diluted with dichloromethane and then was washed with aq. sodium hydrogen carbonate, dried and evaporated under reduced pressure to leave a liquid. Chromatography on silica gel with benzene–AcOEt (9 : 1) as the eluent yielded title compound **14** (5.68 g, 77%) as an oil; ν_{max}(film)/cm^{-1} 3475, 1720, 1480, 1460, 1380, 1370, 1280, 1210, 1160 and 850; δ_H(60 MHz; $CDCl_3$) 1.22 (9 H, s), 1.38 (3 H, s), 1.43 (3 H, s), 2.60 (1 H, br s, exchangeable with D_2O) and 3.5–4.3 (6 H, m).

1,2-O-*Isopropylidene*-3-O-(m-*nitrobenzenesulfonyl*)-4-O-*pivaloyl*-L-*threitol* **15**.—A solution of *m*-nitrobenzenesulfonyl chloride (6.13 g, 27.7 mmol) in dry dichloromethane (6.4 cm^3) was added to a stirred solution of the pivalate **14** (5.68 g, 23.1 mmol) 4-(dimethylamino)pyridine (DMAP) (1.41 g, 11.5 mmol) and dry pyridine (2.2 cm^3) in dry dichloromethane (11 cm^3). The resulting suspension was stirred at room temperature for 24 h. The resulting solution was washed with aq. sodium hydrogen carbonate, dried, and concentrated under reduced pressure. After stripping with toluene, diester **15** (9.95 g, 100%) was obtained as a yellow oil; ν_{max}(film)/cm^{-1} 3170, 1720, 1600, 1520, 1470, 1450, 1340, 1270, 1200, 1180, 1140, 1060, 910, 720 and 650; δ_H(60 MHz; $CDCl_3$) 1.21 (9 H, s), 1.25 (6 H, s), 3.5–4.5 (5 H, m), 4.7–5.1 (1 H, m) and 7.6–8.9 (4 H, m).

1,2-*Anhydro*-3,4-O-*isopropylidene*-D-*erythritol* **5**.—A solution of diester **15** (18.6 g, 45.2 mmol) in dry methanol (20 cm^3) was added to a stirred and cooled (0 °C) solution of KOH (2.98 g, 43.0 mmol) in dry methanol (40 cm^3). The mixture was stirred at room temperature for 2 h and was then evaporated under reduced pressure. The residue was triturated with diethyl ether and the resulting suspension was filtered. The organic phase was evaporated to leave a liquid. This was purified by distillation under reduced pressure to give epoxide **5** (3.13 g, 51%) as an oil; b.p. 85.6–90.0 °C/3200–3466 N m^{-2}; $[\alpha]_D^{16}$ −9.47 (*c* 1.13, EtOH); ν_{max}(film)/cm^{-1} 1380, 1370, 1220, 1160, 1060, 900 and 845; δ_H(270 MHz; $CDCl_3$) 1.38 (3 H, s), 1.46 (3 H, s), 2.66 (1 H, dd, *J* 4.9 and 2.6, 1-H), 2.85 (1 H, dd, *J* 4.9 and 4.0, 1-H′), 3.03 (1 H, ddd, *J* 5.8, 4.0 and 2.6, 2-H), 3.86 (1 H, ddd, *J* 6.2, 5.8 and 5.6, 3-H), 3.93 (1 H, dd, *J* 8.1 and 5.6, 4-H) and 4.13 (1 H, dd, *J* 8.1 and 6.2, 4-H′).

(2S,3R)-3-*Hydroxy*-1,2-*isopropylidenedioxy*-15-*methylhexadecan*-5-*one Trimethylene Dithioketal* **16**.—A solution of BuLi (1.63 mol dm^{-3} in hexane; 7.2 cm^3, 11.7 mmol) was added to a stirred and cooled (−78 °C) solution of the dithioacetal **12** (3.10 g, 10.7 mmol) in dry THF (95 cm^3) under argon. The mixture was allowed to warm to −20 °C over a period of 2 h. The solution was then cooled to −40 °C. To the mixture were added HMPA (2.0 cm^3, 11.7 mmol) and a solution of epoxide **5** (1.41 g, 9.75 mmol) in dry THF (15 cm^3). The resulting suspension was allowed to warm to room temperature and was stirred for 12 h. Aq. NH_4Cl was added to the suspension and the resulting mixture was extracted with hexane. The organic phase was dried and evaporated to leave a yellow liquid. Chromatography on silica gel with benzene–AcOEt (95:5) as the eluent yielded *title compound* **16** (3.36 g, 80%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3450, 1460, 1420, 1380, 1365, 1250, 1210 and 845; δ_H(60 MHz; $CDCl_3$) 0.87 (6 H, d, *J* 5.4), 1.25–2.27 (23 H, m), 1.36 (3 H, s), 1.41 (3 H, s), 2.76–3.05 (4 H, m), 3.44 (1 H, br s) and 3.74–4.10 (4 H, m); *m/z* (EI) 432 (M^+, 27%), 417 (26), 331 (7.6), 287 (100), 263 (26), 231 (8.3), 205 (9.5), 187 (8.3), 175 (14), 130 (36), 101 (14) and 59 (27) (Found: M^+, 432.2708. $C_{23}H_{44}O_3S_2$ requires M, 432.2734).

(2S,3R)-1,2-*Isopropylidenedioxy*-15-*methylhexdecan*-3-*ol* **17**.—A stirred suspension of freshly prepared Raney Ni (W-2, 23.0 g) and the dithioketal **16** in ethanol (60 cm^3) was heated under reflux for 1 h and was then filtered through a pad of silica gel. The filtrate was evaporated to dryness under reduced pressure to leave the *alcohol* **17** (1.43 g, 89%) as needles; m.p. 41.0–42.2 °C; $[\alpha]_D^{22}$ −8.74 (*c* 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3511, 1471, 1383, 1371, 1266, 1215, 1051, 862 and 722; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 5.4), 1.10–1.60 (23 H, m), 1.37 (3 H, s), 1.43 (3 H, s), 2.01 (1 H, br s, exchangeable with D_2O), 3.74–3.82 (1 H, m, 3-H) and 3.86–4.07 (3 H, m, 1-H_2 and 2-H); δ_C(68 MHz; $CDCl_3$) 22.63, 25.28, 26.46, 27.40, 27.95, 29.50, 29.56, 29.64, 29.69, 29.92, 32.60, 39.05, 64.45, 70.61, 78.67 and 108.88; *m/z* (EI) 327 (M^+ − 1, 3%), 313 (52), 285 (7.1), 169 (7.1), 101 (100), 59 (32) and 43 (14) (Found: M^+, 328.2937. $C_{20}H_{40}O_3$ requires M, 328.2980).

(2S,3R)-2,3-*Isopropylidenedioxy*-15-*methylhexadecan*-1-*ol* **18**.—A solution of the acetonide **17** (2.24 g, 8.82 mmol) and PTSA (0.259 g, 1.36 mmol) in methanol (15 cm^3) was stirred at room temperature for 3 h. The resulting solution was evaporated to dryness under reduced pressure and the residue was recrystallized from methanol to yield the corresponding triol (1.86 g).

Pivaloyl chloride (0.87 g, 7.09 mmol) was added dropwise to a stirred and cooled (−17 °C) solution of the above triol in pyridine (16 cm^3). The mixture was stirred at 0 °C for 5 h, when brine was added. The mixture was extracted with diethyl ether and the organic phase was washed with hydrochloric acid (1 mol dm^{-3}), dried, and evaporated. The residue was purified by column chromatography on silica gel with $CHCl_3$–MeOH (98:2) as the eluent to yield the corresponding 1-*O*-pivalate (1.64 g, 66%); $[\alpha]_D^{23}$ +6.35 (*c* 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3428, 1732, 1698, 1482, 1321, 1304, 1200, 1167, 1073, 924 and 722; δ_H(500 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.23 (9 H, s), 1.10–1.58 (23 H, m), 2.30 (1 H, br s), 2.60 (1 H, br s), 3.65 (1 H, ddd, *J* 9.0, 5.0 and 3.5, 3-H), 3.75 (1 H, ddd, *J* 6.0, 5.0 and 4.5, 2-H), 4.23 (1 H, dd, *J* 12.0 and 6.0, 1-H) and 4.26 (1 H, dd, *J* 12.0 and 4.5, 1-H′); δ_C(126 MHz; $CDCl_3$) 22.64, 25.82, 27.18, 27.40, 27.96, 29.55, 29.58, 29.65, 29.70, 29.93, 32.34, 38.89, 39.05, 65.51, 72.51 and 179.24.

To a solution of the above 1-*O*-pivalate (2.51 g, 6.73 mmol) and 2,2-dimethoxypropane (2.5 cm^3, 20.2 mmol) in benzene (45 cm^3) was added a catalytic amount of PPTS. The resulting solution was stirred and heated under reflux for 30 min before aq. sodium hydrogen carbonate was added. The mixture was extracted with hexane–diethyl ether, dried, and evaporated to yield the corresponding 2,3-*O*-*isopropylidene*-1-*O*-*pivalate* (2.68 g, 97%) as an oil; $[\alpha]_D^{22}$ −10.07 (*c* 1.25, $CHCl_3$); ν_{max}(film)/cm^{-1} 1735, 1460, 1380, 1370, 1160 and 860; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.21 (9 H, s), 1.11–1.64 (23 H, m), 1.35 (3 H, s), 1.44 (3 H, s), 4.05 (1 H, dd, *J* 10.8 and 6.5, 1-H), 4.10 (1 H, dd, *J* 10.8 and 5.4, 1-H′), 4.10–4.18 (1 H, m, 2-H) and 4.21 (1 H, dt, *J* 11.3 and 5.4, 3-H); δ_C(68 MHz; $CDCl_3$) 22.65, 25.61, 26.62, 27.17, 27.41, 27.96, 28.15, 29.08, 29.47, 29.56, 29.63, 29.70, 29.93, 38.72, 39.06, 63.03, 75.27, 77.27, 108.14, 128.32 and 178.24 [Found: (EI) M^+, 412.3570. $C_{25}H_{48}O_4$ requires M, 412.3555].

A solution of above 2,3-*O*-isopropylidene-1-*O*-pivalate (2.68 g, 6.49 mmol) and $LiOH{\cdot}H_2O$ (0.409 g, 9.47 mmol) in methanol (30 cm^3) was stirred and heated at 50 °C for 3 h. The resulting mixture was evaporated to dryness under reduced pressure to leave the *alcohol* **18** (2.12 g, 100%) as an oil; $[\alpha]_D^{23}$ −18.84 (*c* 2.50, $CHCl_3$); ν_{max}(film)/cm^{-1} 3420, 1460, 1375, 1360, 1240, 1210, 1040 and 840; δ_H(500 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.12–1.62 (23 H, m), 1.36 (3 H, s), 1.47 (3 H, s), 1.97 (1 H, dd, *J* 7.5 and 5.0, OH), 3.56–3.64 (2 H, m, 1-H_2) and 4.11–4.18 (2 H, m, 2- and 3-H); δ_C(126 MHz; $CDCl_3$) 22.62, 25.53, 26.66, 27.39, 27.94, 28.26, 28.86, 29.48, 29.54, 29.61, 29.64, 29.68, 29.92, 39.04, 61.83, 77.95, 107.99 and 128.29 [Found: (EI) (M^+ − 1) 327.2869. $C_{20}H_{39}O_3$ requires *m/z* 327.2899].

(2R,3R)-2,3-*Isopropylidenedioxy*-15-*methylhexadecanal* **19**.—To a solution of oxalyl dichloride (0.35 cm^3, 3.65 mmol) in dry dichloromethane (6 cm^3) maintained at −78 °C was added dropwise a solution of DMSO (0.84 cm^3, 11.9 mmol) in dichloromethane (3 cm^3) and the mixture was stirred for 15 min. The above alcohol **18** (1.00 g, 3.04 mmol), dissolved in dichloromethane (5.5 cm^3), was added dropwise and the mixture was stirred for 15 min. Triethylamine (2.1 cm^3, 15.2 mmol) was added at −50 °C and the mixture was stirred for 2 h, after which time it was allowed to warm to room temperature. The reaction mixture was then quenched with water and extracted with hexane–diethyl ether. The organic phase was dried, and evaporated under reduced pressure to leave the aldehyde **19** (0.973 g, 97%) as a pale yellow oil.

(1R,2S,3R)-2,3-*Isopropylidenedioxy*-15-*methyl*-1-*thiazol*-2′-*yl*)*hexadecan*-1-*ol* **20**.—To a stirred solution of the aldehyde **19** (0.973 g, 2.98 mmol) in dry THF (10 cm^3) was added a solution of 2-(trimethylsilyl)thiazole **4** (0.61 cm^3, 3.87 mmol) in dry THF (6.0 cm^3) at room temperature under argon. After the mixture had been stirred for 2 h, a solution of tetrabutylammonium fluoride (TBAF) (0.935 g, 3.58 mmol) in THF (5 cm^3) was added and the mixture was stirred for 30 min. The reaction mixture was poured into aq. sodium hydrogen carbonate and extracted with hexane–diethyl ether. The combined extracts were dried and evaporated to dryness. Chromatography on silica gel with benzene–AcOEt (95:1) as the eluent yielded *title compound* **20** (1.06 g, 86%) as an oil; $[\alpha]_D^{23}$ −11.63 (*c* 1.01, $CHCl_3$); ν_{max}(film)/cm^{-1} 3300, 1500, 1460, 1375, 1360, 1215, 1050, 860 and 720; δ_H(500 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.10–1.80 (23 H, m), 1.35 (3 H, s), 1.50 (3 H, s), 4.02 (1 H, br s), 4.16 (1 H, dd, *J* 8.5 and 5.5, 2-H), 4.28 (1 H, ddd, *J* 9.0, 5.5 and 4.0, 3-H), 4.96 (1 H, d, *J* 8.5, 1-H), 7.34 (1 H, d, *J* 3.5, 5′-H) and 7.74 (1 H, d, *J* 3.5, 4′-H); δ_C(126 MHz; $CDCl_3$) 22.64, 25.53, 26.79, 27.40, 27.96, 28.22, 29.22, 29.57, 29.60, 29.62, 29.65, 29.71, 29.93, 39.05, 70.23, 78.40, 79.35, 108.22, 120.21, 128.31, 141.16 and 170.89 [Found: (EI) M^+ 411.2819 (0.7%). $C_{23}H_{41}NO_3S$ requires M, 411.2807].

(2R,3R)-2,3-*Isopropylidenedioxy*-15-*methyl*-1-(*thiazol*-2′-*yl*)-*heptadecan*-1-*one* **21**.—To a solution of oxalyl dichloride (0.61

cm^3, 6.32 mmol) in dry dichloromethane (10.5 cm^3) maintained at −78 °C was added a solution of DMSO (1.5 cm^3, 21.1 mmol) in dichloromethane (4 cm^3) and the mixture was stirred for 15 min. The above alcohol **20** (2.17 g, 5.27 mmol), dissolved in dichloromethane (4 cm^3), was added dropwise and the mixture was stirred for 45 min. Triethylamine (3.7 cm^3, 26.3 mmol) was added at −50 °C and stirring was continued for 30 min. The reaction mixture was quenched with water and extracted with hexane–diethyl ether. The organic phase was dried, filtered through a pad of silica gel, and evaporated under reduced pressure to leave the ketone **21** as a pale yellow oil (2.13 g, 99%); ν_{max}(film)/cm^{-1} 1700, 1480, 1380, 1370, 1240, 1220, 1100, 870 and 750; δ_H(60 MHz; $CDCl_3$) 0.85 (6 H, d, *J* 6.0), 1.10–1.60 (23 H, m), 1.45 (3 H, s), 1.66 (3 H, s), 4.47–4.70 (1 H, m), 5.82 (1 H, d, *J* 7.2), 7.72 (1 H, d, *J* 3.0) and 8.03 (1 H, d, *J* 3.0).

(1S,2S,3R)-2,3-*Isopropylidenedioxy*-15-*methyl*-1-(*thiazol*-2′-*yl*)*hexadecan*-1-*ol* **22**.—To a stirred suspension of the ketone **21** (0.279 g, 0.678 mmol) and cerium(III) chloride (0.505 g, 1.36 mmol) in methanol (5 cm^3) was added $NaBH_4$ (0.0128 g, 0.339 mmol) portionwise and the resulting solution was stirred for 10 min at room temperature. The reaction was quenched by addition of 5% aq. citric acid and the resulting mixture was extracted with hexane–diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to dryness. Chromatography on silica gel with benzene–AcOEt (9:1) yielded the (1S)-*alcohol* **22** (0.226 g, 96%) as a pale yellow oil; $[\alpha]_D^{25}$ −31.67 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 3520, 3400, 3200, 1500, 1460, 1380, 1360, 1215, 1040, 870 and 720; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.10–1.90 (23 H, m), 1.38 (3 H, s), 1.55 (3 H, s), 3.35 (1 H, d, *J* 5.9, OH), 4.30 (1 H, ddd, *J* 9.5, 6.2 and 4.1, 3-H), 4.59 (1 H, dd, *J* 6.2 and 2.7, 2-H), 5.01 (1 H, dd, *J* 5.9 and 2.7, 1-H), 7.30 (1 H, d, *J* 3.0, 5′-H) and 7.75 (1 H, d, *J* 3.0, 4′-H); δ_C(68 MHz; $CDCl_3$) 22.62, 24.78, 26.79, 27.11, 27.37, 27.92, 29.44, 29.51, 29.60, 29.64, 29.67, 29.90, 39.02, 70.49, 77.59, 79.65, 108.24, 119.33, 142.54 and 173.11 [Found: (EI) M^+, 411.2818. $C_{23}H_{41}NO_3S$ requires M, 411.2807].

(1S,2R,3R)-2,3-*Isopropylidenedioxy*-1-(p-*methoxybenzyl*-*oxy*)-15-*methyl*-1-(*thiazol*-2′-*yl*)*hexadecane* **23**.—To a stirred suspension of sodium hydride (60% dispersion; 0.0864 g, 3.59 mmol, washed twice with dry hexane) in dry DMF (2.5 cm^3) was added a solution of the alcohol **22** (1.23 g, 2.99 mmol) in dry DMF (3.6 cm^3) under argon. After the mixture had been stirred for 30 min at room temperature, PMBCl (0.49 cm^3, 3.59 mmol) was added at 0 °C. The resulting suspension was stirred at ambient temperature for 2 h. Aq. sodium hydrogen carbonate was added dropwise to the suspension and the resulting mixture was extracted with hexane–diethyl ether. The organic phase was washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Chromatography on silica gel with benzene–AcOEt (95:5) as the eluent yielded *compound* **23** as an oil; $[\alpha]_D^{24}$ −59.24 (*c* 1.11, $CHCl_3$); ν_{max}(film)/cm^{-1} 1610, 1515, 1465, 1380, 1365, 1245, 1060, 1040, 820 and 720; δ_H(270 MHz; $CDCl_3$) 0.86 (5 H, d, *J* 6.8), 1.08–1.80 (23 H, m), 1.38 (3 H, s), 1.53 (3 H, s), 3.79 (3 H, s), 3.99–4.18 (1 H, m, 3-H), 4.33 (1 H, dd, *J* 5.9 and 4.3, 2-H), 4.42 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.55 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.80 (1 H, d, *J* 4.3, 1-H), 6.86 (2 H, d, *J* 8.6, ArH), 7.28 (2 H, d, *J* 8.6, ArH), 7.37 (1 H, d, *J* 3.0, 5′-H) and 7.76 (1 H, d, *J* 3.0, 4′-H); δ_C(68 MHz; $CDCl_3$) 22.62, 25.94, 26.55, 27.15, 27.37, 27.92, 29.15, 29.41, 29.50, 29.53, 29.62, 29.68, 29.90, 39.02, 55.16, 70.94, 77.37, 77.61, 79.97, 108.79, 113.63, 120.37, 128.27, 129.47, 129.55, 141.94, 159.20 and 170.37 [Found: (EI) M^+, 531.3420. $C_{31}H_{49}NO_4S$ requires M, 531.3385].

(2R,3R,4R)-3,4-*Isopropylidenedioxy*-2-(p-*methoxybenzyl*-*oxy*)-16-*methylheptadecan*-1-*ol* **24**.—Methyl iodide (1.7 cm^3, 2.71 mmol) was added to a stirred solution of the thiazole **23** (1.44 g, 2.71 mmol) in dry acetonitrile (22 cm^3) under argon. The mixture was heated at 50 °C for 48 h and was then evaporated to dryness under reduced pressure to leave a brown oil.

Sodium boranuide (0.205 g, 3.25 mmol) was added portionwise to a stirred and cooled (0 °C) solution of the crude *N*-methylthiazolium salt in dry methanol (20 cm^3) and the resulting solution was stirred at room temperature for 30 min. The excess of reagent was destroyed by addition of acetone. The resulting suspension was evaporated to dryness to give an oily residue.

The crude product was dissolved in acetonitrile (5 cm^3) and to this solution was added a solution of $CuCl_2 \cdot 2H_2O$ (0.546 g, 3.20 mmol) and CuO (0.255 g, 3.20 mmol) in a mixture of acetonitrile (15 cm^3) and water (1.5 cm^3). The mixture was stirred for 30 min at room temperature, filtered through a pad of Celite, and then extracted with hexane–diethyl ether. The organic phase was washed with brine, dried, and evaporated to give the crude aldehyde (0.965 g).

A solution of the above aldehyde in methanol (5 cm^3) was treated with $NaBH_4$ (0.115 g, 3.04 mmol) at room temperature. After 30 min, the reaction was quenched by addition of 5% aq. citric acid, and the solvent was evaporated off. The residue was extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel with benzene–AcOEt (95:5) as the eluent yielded the alcohol **24** (0.806 g, 61%) as a yellow oil; $[\alpha]_D^{22}$ +17.45 (*c* 1.03, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440, 1610, 1505, 1460, 1370, 1360, 1240, 1210, 1030 and 820; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.10–1.70 (23 H, m), 1.36 (3 H, s), 1.49 (3 H, s), 2.34–2.41 (1 H, m, OH), 3.50–3.64 (2 H, m, 1- and 2-H), 3.70–3.80 (1 H, m, 1-H′), 3.80 (3 H, s), 4.06 (1 H, ddd, *J* 10.0, 5.7 and 3.0, 4-H), 4.19 (1 H, dd, *J* 5.7, 3-H), 4.62 (1 H, A part of ABq, *J* 10.8, benzylic H), 4.72 (1 H, B part of ABq, *J* 10.8, benzylic H), 6.88 (2 H, d, *J* 8.4, ArH) and 7.31 (2 H, d, *J* 8.4, ArH); δ_C(68 MHz; $CDCl_3$) 22.63, 25.92, 26.23, 27.38, 27.71, 27.93, 29.53, 29.56, 29.63, 29.66, 29.69, 29.90, 39.03, 55.20, 62.34, 72.00, 77.14, 77.26, 79.09, 108.32, 113.77, 128.29, 129.37, 130.55 and 159.19.

(2R,3R,4R)-1,2,3-*Tribenzyloxy*-2-(p-*methoxybenzyloxy*)-*octadecane* **25**.—A mixture of the alcohol **24** (0.806 g, 1.68 mmol) and PTSA (0.032 g, 0.168 mmol) in methanol (8.5 cm^3) was stirred at room temperature for 3 h. After removal of the solvent, methanol (5 cm^3) was added to the mixture and this was stirred for 1 h. The resulting mixture was evaporated to dryness under reduced pressure and the residue was partitioned between diethyl ether and aq. sodium hydrogen carbonate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to dryness. Chromatography on silica gel with chloroform–methanol (95:5) as the eluent yielded a triol (0.705 g, 96%); $[\alpha]_D^{25}$ −21.81 (*c* 1.10, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3320, 1615, 1588, 1512, 1470, 1246, 1076, 1040 and 819; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 7.0), 1.10–1.60 (23 H, m), 2.50 (1 H, br s), 2.98 (1 H, br s), 3.07 (1 H, br s), 3.50–3.64 (2 H, m, 1- and 2-H), 3.67–3.80 (2 H, m, 4-H and 1-H′), 3.80 (3 H, s), 3.92 (1 H, dd, *J* 11.3 and 5.1, 3-H), 4.49 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.68 (1 H, B part of ABq, *J* 11.1, benzylic H), 6.88 (2 H, d, *J* 8.6, ArH) and 7.27 (2 H, d, *J* 8.6, ArH); δ_C(68 MHz; $CDCl_3$) 22.62, 25.68, 27.38, 27.93, 29.59, 29.62, 29.64, 29.68, 29.70, 29.92, 39.02, 55.23, 62.07, 71.62, 73.23, 74.51, 77.39, 114.00, 129.58, 129.86 and 159.56.

To a stirred suspension of sodium hydride (60% dispersion; 0.091 g, 2.27 mmol, washed twice with dry hexane) in dry DMF (2.6 cm^3) was added a solution of the above alcohol (0.331 g, 0.755 mmol) in dry DMF (2.6 cm^3) under argon. After being stirred for 1 h at 50 °C, the mixture was allowed to cool to room

temperature and then tetrabutylammonium iodide (TBAI) (0.084 g, 0.226 mmol) and benzyl bromide (0.36 cm^3, 3.02 mmol) were added in one portion to the mixture. The resulting suspension was stirred at ambient temperature for 5 h. Aq. sodium hydrogen carbonate was added dropwise to the suspension and the resulting mixture was then extracted with hexane–diethyl ether. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness. Chromatography on silica gel with benzene as the eluent yielded the tris(benzyl ether) **25** (0.481 g, 90%) as a pale yellow oil; $[\alpha]_D^{24}$ +3.84 (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 3050, 3010, 1600, 1504, 1460, 1445, 1240, 1080, 1060, 1020, 815, 730 and 690; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.8), 1.10–1.74 (23 H, m), 3.48–3.68 (3 H, m, 1-H_2 and 4-H), 3.70–3.84 (2 H, m, 2- and 3-H), 3.77 (3 H, s), 4.41 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.47 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.46 (2 H, s, benzylic H), 4.54 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.61 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.64 (1 H, A part of ABq, *J* 11.1, benzylic H), 6.80 (2 H, d, *J* 8.4, ArH), 7.22 (2 H, d, *J* 8.4, ArH) and 7.24–7.36 (15 H, m, 3 × Ph); δ_C(68 MHz; $CDCl_3$) 22.65, 25.71, 27.42, 27.95, 29.59, 29.64, 29.69, 29.80, 29.94, 30.38, 39.05, 55.18, 70.18, 71.51, 72.77, 73.34, 74.25, 78.48. 79.98, 113.60, 127.38, 127.58, 127.73, 127.75, 128.04, 128.17, 128.22, 128.32, 129.57, 130.88, 138.12, 138.78, 138.84 and 159.07; *m/z* (EI) 617 ($M^+ - C_6H_5CH_2$, 2.3%), 587 (0.6), 509 (4.5), 481 (2.7), 356 (17), 267 (20), 211 (17), 181 (37), 163 (17), 137 (20), 121 (76) and 91 (100).

(2R,3S,4R)-1,3,4-*Tribenzyloxy*-16-*methylheptadecan*-2-*ol* **26**.—DDQ (0.200 g, 0.883 mmol) was added to a stirred and cooled (0 °C) solution of the *p*-methoxybenzyl ether **25** (0.481 g, 0.679 mmol) in a mixture of dichloromethane (5.2 cm^3) and water (0.3 cm^3). The resulting mixture was stirred at 0 °C for 2 h. The mixture was diluted with dichloromethane and washed successively with aq. sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to dryness. In order to remove the resulting *p*-methoxybenzaldehyde, the residue was reduced with $NaBH_4$ in methanol before purification. Chromatography on silica gel with benzene–AcOEt (98:2) as the eluent yielded the monoalcohol **26** (0.337 g, 84%) as an oil; $[\alpha]_D^{23}$ −10.22 (*c* 1.06, $CHCl_3$); ν_{max}(film)/cm^{-1} 3460, 3055, 3020, 1495, 1460, 1450, 1360, 1100, 1060, 730 and 690; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 1.11–1.70 (24 H, m), 3.17 (1 H, d, *J* 4.9, OH), 3.54 (2 H, d, *J* 5.7, 1-H_2), 3.60 (1 H, dd, *J* 4.3 and 3.0, 3-H), 3.68 (1 H, ddd, *J* 7.3 and 4.3, 4-H), 4.04 (1 H, tdd, *J* 5.7, 4.9 and 3.0, 2-H), 4.47 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.53 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.52 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.69 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.54 (1 H, A part of ABq, *J* 11.1, benzylic H) and 7.23–7.34 (15 H, m, 3 × Ph); δ_C(68 MHz; $CDCl_3$) 22.65, 25.58, 27.41, 27.95, 29.59, 29.67, 29.70, 29.93, 30.98, 39.05, 69.83, 71.07, 72.78, 73.34, 73.52, 79.03, 79.91, 127.64, 127.81, 127.91, 128.07, 128.30, 128.33, 128.37, 138.08, 138.12 and 138.27; *m/z* (EI) 587 (M^+ − 1, 0.2%), 497 (0.9), 391 (8), 359 (10), 299 (30), 253 (38), 181 (100), 153 (99), 148 (62), 104 (50) and 91 (99).

(2S,3S,4R)-2-*Azido*-1,2,3-*tribenzyloxy*-16-*methylheptadecane* **27**.—Methanesulfonyl chloride (0.053 g, 0.687 mmol) was injected dropwise into a stirred and cooled (0 °C) solution of the monoalcohol **26** (0.337 g, 0.572 mmol) and DMAP (0.035 g, 0.286 mmol) in dry pyridine (3.0 cm^3). The resulting solution was stirred for 3 h at room temperature. Aq. sodium hydrogen carbonate was added to this mixture and the resulting mixture was extracted with hexane–diethyl ether. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. After stripping with toluene, the mesyl ester (0.382 g, 100%) was obtained as a pale yellow oil.

A mixture of the above mesyl ester (0.382 g, 0.572 mmol) and lithium azide (0.140 g, 2.86 mmol) in dry DMF (40 cm^3) was heated at 90–100 °C for 48 h under argon. The cooled mixture was partitioned between hexane–diethyl ether and water. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure to leave a liquid. Chromatography on silica gel with hexane–benzene (1:1) as the eluent yielded the azide **27** (0.283 g, 80%) as an oil; $[\alpha]_D^{22}$ +8.87 (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 3025, 2095, 1460, 1450, 1260, 1100, 1020, 730 and 690; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.2), 1.11–1.70 (23 H, m), 3.60 (1 H, dt, *J* 7.3 and 3.8, 2-H), 3.63–3.82 (4 H, m, 1-H_2 and 3- and 4-H), 4.50 (1 H, A part of ABq, *J* 10.8, benzylic H), 4.55 (1 H, B part of ABq, *J* 10.8, benzylic H), 4.51 (2 H, s, benzylic H), 4.59 (1 H, A part of ABq, *J* 10.8, benzylic H), 4.69 (1 H, B part of ABq, *J* 10.8, benzylic H) and 7.23–7.37 (15 H, m, 3 × Ph); δ_C(68 MHz; $CDCl_3$) 22.65, 25.28, 27.41, 27.95, 29.57, 29.60, 29.67, 29.72, 29.75, 29.82, 29.93, 39.05, 62.05, 70.16, 71.99, 73.31, 73.78, 79.11, 79.19, 127.60, 127.64, 127.67, 127.71, 127.88, 127.99, 128.39, 128.88, 138.02 and 138.32; *m/z* (EI) 585 (M^+ − N_2, 0.7%), 571 (M^+ − N_3, 0.6), 494 (17), 464 (17), 386 (11), 268 (13), 181 (18), 163 (42), 148 (14) and 91 (100).

(2S,3S,4R)-2-*Amino*-1,3,4-*tribenzyloxy*-16-*methylheptadecane* **28**.—A solution of the azide **27** (0.283 g, 0.460 mmol) in dry THF (3.0 cm^3) was added to a suspension of $LiAlH_4$ (0.042 g, 1.11 mmol) in dry THF (3.0 cm^3). The resulting suspension was stirred for 30 min and was then heated under reflux for 1 h. The reaction was quenched by addition of a small amount of water (**CARE**!) and the resulting mixture was filtered. The filtrate was dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica gel with chloroform–methanol (95:5) as the eluent yielded the *amine* **28** (0.193 g, 71%) as an oil; $[\alpha]_D^{20}$ −6.50 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 3360, 3300, 3020, 1495, 1460, 1450, 1360, 1090, 1065, 730 and 690; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.8), 1.11–1.25 (25 H, m), 3.15 (1 H, ddd, *J* 7.0, 6.8 and 3.0, 2-H), 3.48 (1 H, dd, *J* 8.9 and 7.0, 1-H), 3.68–3.15 (1 H, m, 4-H), 3.55 (1 H, dd, *J* 6.8 and 3.2, 3-H), 3.68 (1 H, dd, *J* 8.9 and 3.0, 1-H′), 4.48 (2 H, s, benzylic H), 4.52 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.68 (1 H, B part of ABq, *J* 11.1, benzylic H), 4.53 (1 H, A part of ABq, *J* 11.1, benzylic H), 4.74 (1 H, B, part of ABq, *J* 11.1, benzylic H) and 7.26–7.37 (15 H, m, 3 × Ph); δ_C(68 MHz; $CDCl_3$) 22.65, 25.83, 26.55, 27.40, 27.95, 29.63, 29.67, 29.70, 29.82, 29.93, 30.38, 39.05, 52.55, 71.95, 72.87, 73.23, 73.56, 77.21, 80.07, 81,67, 126.89, 127.47, 127.52, 127.58, 127.75, 127.80, 127.87, 128.28, 128.34, 128.49, 138.35, 138.61 and 138.69 [Found: (EI) M^+, 587.4307. $C_{39}H_{57}NO_3$ requires M, 587.4339].

(2S,3S,4R)-2-*Amino*-1,3,4-*tribenzyloxyoctadecane* **29**.—By a similar sequence of reactions to those described for the preparation of compound **28**, the *amine* **29** was obtained as an oil; $[\alpha]_D^{21}$ −6.66 (*c* 0.90, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3370, 3300, 3060, 1495, 1470, 1455, 1360, 1090, 1070 and 1025; δ_H(500 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.5), 1.20–1.74 (26 H, m), 2.07 (2 H, br s, NH_2), 3.19 (1 H, ddd, *J* 7.5, 6.5 and 3.5, 2-H), 3.51 (1 H, dd, *J* 9.0 and 7.5, 1-H), 3.59 (1 H, dd, *J* 6.5 and 3.5, 3-H), 3.71 (1 H, dd, *J* 9.0 and 3.5, 1-H′), 3.71–3.74 (1 H, m, 4-H), 4.47 (1 H, A part of ABq, *J* 11.3, benzylic H), 4.49 (1 H, B part of ABq, *J* 11.3, benzylic H), 4.52 (1 H, A part of ABq, *J* 11.3, benzylic H), 4.62 (1 H, B part of ABq, *J* 11.3, benzylic H), 4.54 (1 H, A part of ABq, *J* 11.3, benzylic H) 4.73 (1 H, B part of ABq, *J* 11.3, benzylic H) and 7.26–7.37 (15 H, m, 3 × Ph); δ_C(126 MHz; $CDCl_3$) 14.10, 22.67, 25.79, 29.62, 29.68, 29.81, 30.41, 31.90, 52.65, 72.00, 72.41, 73.26, 73.58, 77.21, 80.06, 81.43, 127.50, 127.56, 127.62, 127.78, 127.83, 127.88, 128.22, 128.31, 128.37, 128.53, 138.29, 138.54 and 138.64 [Found: (EI) M^+, 587.4341].

(2S,3S,4R)-2-[(2′R)-*Benzyloxydocosanoylamino*]-1,3,4-*tribenzyloxy*-16-*methylheptadecane* **31**.—A solution of EDC

hydrochloride (0.0378 g, 0.197 mmol) in dry dichloromethane (1.0 cm^3) was added to a solution of the amine **28** (0.105 g, 0.179 mmol) and (2*R*)-benzoyloxydocosanoic acid (0.0909 g, 0.197 mmol) in the same solvent (2.0 cm^3) at room temperature under argon. After being stirred for 3 days, the mixture was evaporated to dryness. Chromatography on silica gel with benzene–AcOEt (98:2) as the eluent yielded amido ester **31** (0.175 g, 95%) as needles; m.p. 49.0–50.0 °C; $[\alpha]_D^{18}$ +5.33 (*c* 1.16, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3318, 1734, 1663, 1551, 1468, 1452, 1273, 1253, 1117, 1102, 739, 708 and 696; δ_H(270 MHz; $CDCl_3$) 0.86 (6 H, d, *J* 6.5), 0.87 (3 H, t, *J* 7.0), 1.20–1.70 (59 H, m), 1.88–2.00 (2 H, m), 3.44 (1 H, m, NH), 3.54 (1 H, dd, *J* 9.2 and 3.8, 1-H), 3.75 (1 H, dd, *J* 7.8 and 2.2, 3-H), 3.84 (1 H, dd, *J* 9.2 and 4.1, 1-H′), 4.25 (1 H, dddd, *J* 9.2, 7.8, 4.1 and 3.8, 2-H), 4.35–4.50 (5 H, m, benzylic H), 4.75 (1 H, d, *J* 9.2 benzylic H), 5.37 (1 H, t, *J* 5.7, 2′-H), 6.58 (1 H, d, *J* 9.2, ArH), 7.15–7.41 (16 H, m, ArH), 7.73 (1 H, m, ArH) and 7.98–8.04 (2 H, m, ArH); δ_C(68 MHz; $CDCl_3$) 14.11, 22.66, 24.85, 26.10, 27.43, 27.95, 29.28, 29.34, 29.41, 29.58, 29.62, 29.69, 29.75, 29.82, 29.96, 31.80, 31.90, 39.06, 49.30, 68.71, 71.92, 73.03, 73.70, 74.73, 76.38, 78.70, 80.50, 127.44, 127.65, 127.74, 128.20, 128.37, 128.65, 129.24, 129.64, 133.51, 138.01, 138.45, 138.65, 165.28 and 169.52; *m/z* (EI) 1029 (M^+, 0.6%). 938 (2.2), 830 (5.0), 712 (28), 622 (32), 443 (21), 335 (6.2), 169 (11) and 91 (100) [Found: (FAB, +ve) 1030.7880 (M^+ + 1) $C_{68}H_{104}NO_6$ requires *m/z*, 1030.7896].

(2S,3S,4R)-2-[(2′R)-*Benzoyloxydocosanoylamino*]-3,4-*dibenzoyloxy*-16-*methylheptadecan*-1-*ol* **32**.—A mixture of compound **31** (0.175 g, 0.170 mmol), 10% Pd on carbon (0.044 g) and a trace of hydrochloric acid in THF (4 cm^3) was hydrogenated under hydrogen. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated to dryness. Chromatography on silica gel with chloroform–methanol (95:5) as the eluent yielded a crystalline residue (0.114 g, 88%).

A mixture of the above residue (0.070 g, 0.0921 mmol), trityl chloride (0.257 g, 0.928 mmol) and DMAP (0.011 g, 0.0921 mmol) in dry pyridine (5.4 cm^3) was stirred at 65 °C for 2.5 h. After the mixture had cooled it was stirred while benzoyl chloride (0.13 cm^3) was added. The resulting suspension was stirred at room temperature for 18 h. The reaction was then quenched by addition of methanol (0.3 cm^3). After dilution with chloroform, the mixture was washed with water, dried ($MgSO_4$), and evaporated. After stripping with toluene, the residue was dissolved in chloroform–methanol (1:1; 3 cm^3), PTSA (0.035 g) and water (1 drop) were added and the resulting mixture was stirred at ambient temperature for 18 h. The resulting solution was washed with aq. sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to dryness. Chromatography on silica gel with benzene–AcOEt (9:1) yielded the *alcohol* **32** (0.073 g, 82%) as an oil; $[\alpha]_D^{21}$ +43.23 (*c* 0.657, $CHCl_3$): ν_{max}(film)/cm^{-1} 3300, 1730, 1651, 1551, 1468, 1285, 1246, 1120, 1070 and 706; δ_H(270 MHz; $CDCl_3$) 0.85 (6 H, d, *J* 6.5), 0.88 (3 H, t, *J* 7.0), 1.6–1.06 (58 H, m), 1.8–2.1 (4 H, m), 2.85 (1 H, t, *J* 6.5, OH), 3.70 (2 H, br t, and 1-H_2), 4.44 (1 H, tdd, *J* 9.2, 8.6 and 3.0, 2-H), 5.32 (1 H, dt, *J* 6.2 and 2.4, 4-H), 5.38 (1 H, t, *J* 5.7, 2′-H), 5.44 (1 H, dd, *J* 8.6 and 2.4, 3-H), 7.10 (1 H, d, *J* 9.2, NH), 7.30–7.64 (9 H, m, ArH) and 7.84–8.15 (6 H, m, ArH); δ_C(68 MHz; $CDCl_3$) 14.09, 22.61, 22.63, 24.98, 25.70, 27.40, 27.93, 28.92, 29.27, 29.33, 29.39, 29.49, 29.53, 29.60, 29.67, 29.92, 31.89, 31.98, 39.03, 50.32, 61.52, 73.66, 73.85, 74.75, 77.20, 128.30, 128.42, 128.59, 128.96, 129.41, 129.63, 129.76, 129.90, 129.94, 133.02, 133.31, 133.69, 165.69, 166.07, 166.72 and 170.49 [Found: (FAB, +ve) (M^+ + 1), 968.6972. $C_{61}H_{94}NO_8$ requires *m/z*, 968.6965].

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