Enantiospecific Syntheses of Sphingosine and Ceramide Stereoisomers with 3*S* Configuration from D-Glucose

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Utilizing the carbon framework (C3–C6) and chirality (at C4 and C5) of D-glucose, (2*S*,3*S*,4*E* and 2*R*,3*S*,4*E*)-2-amino-4-octadecene-1,3-diol (sphingosine analogues) and four stereoisomers (2*S*,3*S*,4*E*-, 2*S*,3*S*,4*Z*-, 2*R*,3*S*,4*E*-, and 2*R*,3*S*,4*Z*-) of the ceramide derivatives were synthesized in a stereocontrolled way.

During the past 20 years, glycosphingolipids (GSLs) have attracted much interest because of their wide variety of biological functions such as cell surface marking, cell recognition, cell growth regulation and oncogenesis. Many of these functions have been explained in terms of the diversity of oligosaccharide structures in GSLs.¹⁾

On the other hand, little has been known of the possible biological role of the hydrophobic backbone, ceramides or sphingosine, until the recent discovery that sphingosine and related metabolites of GSLs or sphingomyelin inhibited protein kinase C (PK-C), a pivotal enzyme in cell regulation and signal transduction.^{2,3)}

In order to discover the precise mechanism for PK-C inhibition^{4,5)} and to study the stereochemical requirement of a ceramide backbone for bioactive GSLs, pure synthetic samples of various analogues of sphingosine and ceramide are now required. It should be noted that only the 2*S*,3*R*-stereoisomer (D-erythro-sphingosine) is known to exist in natural sphingolipids. Recently, we achieved the stereocontrolled syntheses of ceramides through protected 2*S*,3*R*,4*E* (and 4*Z*)-sphinganine derived from D-glucose,⁶⁾ whereas nearly

25 other groups have reported the syntheses of D-erythro-sphingosine and the congeners based on individual ideas for stereocontrol.⁷⁾

We describe here a new synthetic route from D-glucose to the enantiomerically pure sphingosine isomers with 3*S* configuration and the *N*-tetracosanoyl derivatives (ceramides).

Results and Discussion

2,4-*O*-Benzylidene-D-erythrose **2**, readily obtainable by periodate oxidation of 4,6-*O*-benzylidene-D-glucopyranose **1**,⁸⁾ was treated with tetradecylidenetriphenylphosphorane in tetrahydrofuran to afford a mixture of *E*- and *Z*-olefins **3** in a ratio of 3.5:1 and 80% yield.

Mixture **3** was methanesulfonylated in pyridine to give a 96% yield of **4**, which was heated with sodium azide in dimethylformamide at 100–110°C for 4 days to produce an *E/Z* mixture of azido compounds with 2*S* configuration. The geometrical isomers were separable by flash chromatography to give crystalline **5E** (30.3%) and **5Z** (9%).

Major isomer **5E**, the ¹H-NMR spectrum of which showed a higher coupling constant (16.1 Hz) for the *E*-olefin, was reduced with sodium borohydride.

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The resulting amine **6E** was deprotected by acid hydrolysis with trifluoroacetic acid to give (2*S*,3*S*,4*E*)-2-amino-4-octadecene-1,3-diol **7E** (1-*threo*-sphingosine) in a moderate yield. The physical data for **7E** were in good agreement with those reported.^{7i,t,y)}

An azide displacement reaction with cyclic methanesulfonate **4** was less efficient than our previous case for 2*S*,3*R*-sphingenine, in which an acyclic substrate was used.⁶⁾ Therefore, compound **4** was converted into bis-1-ethoxyethyl ether **9** in two steps, using H⁺-resin (EtOH) and ethylvinyl ether (PPTS).

With methanesulfonate **9**, the desired azidation proceeded exclusively to give 2*S*-azide **10**, which was reduced with sodium borohydride to amine **11**. Since the geometrical isomers were inseparable at the stage of **10** or **11**, the latter was further converted to the ceramide derivative. *N*-Acylation of **11** with tetracosanoic acid was carried out under Mukaiyama's conditions,⁹⁾ and removal of the ethoxyethyl group afforded a crystalline mixture of *E/Z* isomers **13**. Acetylation of the

mixture resulted in an effective separation of the isomers, so that diacetate **14E** with an *E*-olefinic linkage (*J* = 15.4 Hz) and **14Z** with a *Z*-type (*J* = 11.0 Hz) could be isolated in 70.5% and 28% yields, respectively. Compound **14E** was deacetylated to give (2*S*,3*S*,4*E*)-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol **15E**. Similarly, minor diacetate **14Z** was converted to 4*Z*-isomer **15Z**.

For synthesis of 2*R*,3*S*-sphingenine (1-*erythro*-sphingosine), inversion of the stereogenic center at C-2 was requisite prior to azidation. Treatment of **9** with cesium acetate¹⁰⁾ in dimethylformamide afforded 2*S*-acetate **16** by *S_N2* displacement in a 70% yield. After saponifying **16**, alcohol **17** was methanesulfonylated to **18** and heated with sodium azide to give an 80% yield of an *E/Z* mixture of azide **19**, which, after hydrolyzing the ethoxyethyl group, could be separated into 4*E*-azidodiol **20E** (72%) and 4*Z*-isomer **20Z** (8%) by a combination of fractional crystallization and flash chromatography. Their structures were easily assigned by the ¹H-NMR

signals of olefinic protons with $J = 15$ Hz for *E*-isomer **20E** and $J = 11$ Hz for *Z*-isomer **20Z**. Reduction of **20E** with sodium borohydride gave (2*R*,3*S*,4*E*)-2-amino-4-octadecene-1,3-diol (*L*-erythro-sphingosine) **21E** in a 48% yield [mp 79–81°C, $[\alpha]_D + 2.5^\circ$ (lit. mp 81–82°C, $[\alpha]_D + 2.8^{(79)}$)].

To transform **20E** and **20Z** into the ceramide derivatives, reprotection of the hydroxyl groups with the 1-ethoxyethyl group was necessary, and reduction of the azido group to an amine and subsequent condensation with tetracosanoic acid was carried out. The obtained **24E** (88% yield from **20E**) and **24Z** (62% yield from **20Z**) were finally deprotected to give (2*R*,3*S*,4*E*)-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol **25E** in an 83% yield and 4*Z*-isomer **25Z** in a 77% yield. Compounds **25E** and **25Z** were indistinguishable from their enantiomers previously synthesized,⁶⁾ except for the sign of specific rotation.

In conclusion, syntheses of sphingosine analogues with 2*S*,3*S*- and 2*R*,3*S*-configurations and of the *N*-tetracosanoyl derivatives (ceramides) were achieved by inversion or double inversion of the chirality present in the starting *D*-glucose.

Experimental

General. Melting points (mp) were determined with a BÜCHI 510 melting-point apparatus and are uncorrected. Optical rotations were determined with a Jasco Model DIP-4 polarimeter for a solution in CHCl_3 at 25°C, unless noted otherwise. Flash chromatography was performed on columns of Wako gel C-200 (100–200 mesh), C-300 (200–300 mesh) or Merck Kieselgel 60 (70–230 mesh), and TLC was performed on silica gel 60 F₂₅₄ (Merck, Darmstadt). IR spectra were recorded with a Jasco IR-810 spectrophotometer, and ¹H-NMR spectra were recorded with a JNM-GX 500 NMR spectrometer. The values for δ_{H} are expressed in ppm downwards from the signal for internal TMS, with a solution in CDCl_3 , unless otherwise noted.

2,4-*O*-Benzylidene-*D*-erythrose (2). To a solution of **1** (13.4 g, 0.05 mol) in 50% aq. MeOH (150 ml) was added sodium metaperiodate (42.78 g, 0.2 mol), and the mixture was stirred for 4 hr at 0°C to room temperature. The resulting precipitate was filtered off, and washed with MeOH. The filtrate and washings were combined, and

evaporated *in vacuo*. The residue was dissolved in CHCl_3 (200 ml), washed with 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ (50 ml) and satd. brine, and dried (MgSO_4). Removal of the solvent gave crude product **2** (10.08 g, 96.9%), which was used for the next step without further purification. *R*_f 0.44 and 0.58 in 10:1 CHCl_3 -MeOH.

(2*R*,3*S*)-1,3-*O*-Benzylidene-4-octadecene-1,2,3-triol (3). To a solution of tetradecyltriphenylphosphonium bromide (21.58 g, 40 mmol, prepared by refluxing a solution of 1-bromotetradecane and triphenylphosphine in xylene for 16 hr) in THF (60 ml) in an ice-cooled methanol bath was added dropwise a 1.56 M solution of butyllithium in hexane (22.4 ml, 35 mmol), and the mixture was stirred for 1 hr at –20°C. To this mixture was added dropwise a solution of **2** (2.08 g, 10 mmol) in THF (15 ml) at –20°C, this mixture being stirred for 18 hr at –20°C to room temperature and evaporated *in vacuo*. The residue was dissolved in CHCl_3 (100 ml), washed with water (60 ml) and satd. brine, dried (MgSO_4), and evaporated *in vacuo*. Flash chromatography of the residue in 9:1 hexane-EtOAc gave **3** (3.11 g, 80.2%). *R*_f 0.55 in 8:3 hexane-AcOEt; ¹H-NMR δ_{H} : 7.33–7.51 (m, 5H, phenyl), 5.943 (dt, 0.78H, $J = 6.9$ and 15.4 Hz, H-5_{*E*-isomer}), 5.827 (dt, 0.22H, $J = 7.7$ and 11.0 Hz, H-5_{*Z*-isomer}), 5.556 (ddt, 0.78H, $J = 1.5$, 7.3, and 15.4 Hz, H-4_{*E*}), 5.565 (s, 0.22H, CHPh_2), 5.534 (s, 0.78H, CHPh_E), 5.477 (ddt, 0.22H, $J = 1.5$, 9.0 and 11.0 Hz, H-4_{*Z*}), 2.10–2.30 (m, 0.44H, H-6, 6_{*Z*}), 2.100 (q, 1.56H, $J = 7.0$ Hz, H-6, 6_{*E*}), 1.20–1.42 (m, 22H, $-\text{CH}_2-$), 0.880 (t, 3H, $J = 7.0$ Hz, CH_2CH_3).

Anal. Found: C, 77.13; H, 10.56. Calcd. for $\text{C}_{25}\text{H}_{46}\text{O}_3$: C, 77.27; H, 10.37%.

(2*R*,3*S*)-1,3-*O*-Benzylidene-2-*O*-methanesulfonyl-4-octadecene-1,2,3-triol (4). To a solution of compound **3** (1.94 g, 5 mmol) in pyridine (5 ml) was added dropwise methanesulfonyl chloride (0.58 ml, 7.5 mmol) at –15°C. The mixture was stirred for 18 hr at –15°C to room temperature, water (1 ml) was then added, and the mixture was evaporated *in vacuo*. A solution of the residue in Et_2O (50 ml) was successively washed with water and satd. brine, dried (MgSO_4) and evaporated *in vacuo*. Flash chromatography of the residue in 10:1 hexane-EtOAc gave **4** (2.23 g, 95.7%). *R*_f 0.34 in 4:1 hexane-AcOEt; ¹H-NMR δ_{H} : 7.35–7.49 (m, 5H, phenyl), 5.962 (dt, 0.75H, $J = 7.0$ and 15.4 Hz, H-5_{*E*}), 5.828 (dt, 0.25H, $J = 7.7$ and 11.0 Hz, H-5_{*Z*}), 5.537 (dd, 0.75H, $J = 7.3$ and 15.4 Hz, H-4_{*E*}), 5.577 (s, 0.25H, CHPh_2), 5.547 (s, 0.75H, CHPh_E), 5.512 (dd, 0.25H, $J = 8.8$ and 11.0 Hz, H-4_{*Z*}), 2.998 (s, 0.75H, CH_3SO_2), 2.995 (s, 2.25H, CH_3SO_2), 2.187 (m, 0.5H, H-6, 6_{*Z*}), 2.084 (q, 1.5H, $J = 6.9$ Hz, H-6, 6_{*E*}), 1.20–1.41 (m, 22H, $-\text{CH}_2-$), 0.879 (t, 3H, $J = 7.0$ Hz, CH_2CH_3).

Anal. Found: C, 66.86; H, 9.10. Calcd. for $\text{C}_{26}\text{H}_{42}\text{O}_5\text{S}$: C, 66.92; H, 9.07%.

(2*S*,3*S*,4*E*)-1,3-*O*-Benzylidene-2-azido-4-octadecene-1,3-diol (5E) and (2*S*,3*S*,4*Z*)-1,3-*O*-benzylidene-2-azido-4-octa-

decene-1,3-diol (5Z). A mixture of compound **4** (3.45 g, 7.4 mmol) and NaN_3 (2.89 g, 44.5 mmol) in DMF (35 ml) was stirred for 4 days at 100–110°C, and then evaporated *in vacuo*. A solution of the residue in Et_2O (400 ml) was successively washed with 5% aq. NaHCO_3 , water and satd. brine, dried (MgSO_4) and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 15:1 hexane–AcOEt gave **5E** (0.91 g, 30.3%) and **5Z** (0.27 g, 9.0%).

Compound 5E. mp 45–45.5°C (recrystallized from pentane); $[\alpha]_D^{25} + 81.1^\circ$ ($c=1.0$); *Rf* 0.44 in 4:1 hexane–AcOEt; $^1\text{H-NMR}$ δ_{H} : 7.36–7.55 (5H, m, phenyl), 5.908 (td, 1H, $J=6.8$ and 16.1 Hz, H-5), 5.677 (dd, 1H, $J=6.4$ and 16.1 Hz, H-4), 5.649 (s, 1H, CHPh), 4.569 (d, 1H, $J=6.4$ Hz, H-3), 4.481 (dd, 1H, $J=2.0$ and 12.2 Hz, H-1), 4.240 (dd, 1H, $J=2.0$ and 12.2 Hz, H-1'), 2.946 (br. s, 1H, H-2), 2.094 (q, 2H, $J=6.9$ Hz, H-6, 6'), 1.20–1.45 (m, 22H, $-\text{CH}_2-$), 0.878 (t, 3H, $J=6.8$ Hz, CH_2CH_3); ν_{max} (KBr) 2100 cm^{-1} (N_3).

Anal. Found: C, 72.44; H, 9.49; N, 10.19. Calcd. for $\text{C}_{25}\text{H}_{39}\text{N}_3\text{O}_2$: C, 72.60; H, 9.50; N, 10.16%.

Compound 5Z. $[\alpha]_D^{25} + 23.2^\circ$ ($c=1.0$); *Rf* 0.51 in 2:1 hexane–AcOEt; $^1\text{H-NMR}$ δ_{H} : 7.34–7.54 (m, 5H, phenyl), 5.65–5.75 (m, 2H, H-5 and H-4), 5.676 (s, 1H, CHPh), 4.882 (dd, 1H, $J=2.0$ and 6.3 Hz, H-3), 4.501 (dd, 1H, $J=1.5$ and 12.3 Hz, H-1), 4.207 (dd, 1H, $J=2.0$ and 12.3 Hz, H-1'), 2.944 (br. s, 1H, H-2), 2.09–2.19 (m, 2H, H-6, 6'), 1.26–1.46 (m, 22H, $-\text{CH}_2-$), 0.883 (t, 3H, $J=6.8$ Hz, CH_2CH_3); ν_{max} (KBr) 2100 cm^{-1} (N_3).

Anal. Found: C, 72.45; H, 9.47; N, 10.15. Calcd. for $\text{C}_{25}\text{H}_{39}\text{N}_3\text{O}_2$: C, 72.60; H, 9.50; N, 10.16%.

(2S,3S,4E)-1,3-O-Benzylidene-2-amino-4-octadecene-1,3-diol (6E). A mixture of compound **5E** (769.8 mg, 1.86 mmol) and NaBH_4 (564.1 mg, 14.9 mmol) in iso-PrOH (10 ml) was stirred for 33 hr under reflux and filtered. The excess NaBH_4 in the filtrate was decomposed by adding 30% aq. AcOH, and the mixture was evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 25:1 CHCl_3 –MeOH gave **6E** (605.1 mg, 83.9%). $[\alpha]_D^{25} - 4.4^\circ$ ($c=1.1$); *Rf* 0.46 in 19:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ δ_{H} : 7.33–7.53 (m, 5H, phenyl), 5.825 (dtd, 1H, $J=1.5$, 7.3 and 15.8 Hz, H-5), 5.586 (s, 1H, CHPh), 5.511 (ddt, 1H, $J=1.5$, 5.1 and 15.8 Hz, H-4), 4.461 (d, 1H, $J=5.1$ Hz, H-3), 4.197 (dd, 1H, $J=1.5$ and 11.4 Hz, H-1), 4.126 (dd, 1H, $J=2.2$ and 11.4 Hz, H-1'), 2.676 (dd, 1H, $J=1.7$ and 3.5 Hz, H-2), 2.085 (q, 2H, $J=7.2$ Hz, H-6, 6'), 1.647 (br. s, 2H, NH_2), 1.16–1.47 (m, 22H, $-\text{CH}_2-$), 0.879 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 77.37; H, 10.71; N, 3.64. Calcd. for $\text{C}_{25}\text{H}_{41}\text{NO}_2$: C, 77.47; H, 10.66; N, 3.61%.

(2S,3S,4E)-2-Amino-4-octadecene-1,3-diol [*L*-(–)-*threo*-sphingosine] (**7E**). To a solution of compound **6E** (331.1 mg, 0.855 mmol) in THF (3 ml) was added 80% aq. CF_3COOH (1.5 ml), and the mixture was stirred for 20 hr at room temperature. The mixture was neutralized

with 25% aq. NH_4OH and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 9:1:0.1 CHCl_3 –MeOH–25% aq. NH_4OH gave **7E** (118.2 mg, 46.2%). mp 85–87°C (recrystallized from Et_2O); $[\alpha]_D^{25} - 3.6^\circ$ ($c=1.0$) [lit. mp 88.0–88.5°C⁷¹]; mp 86–87°C, $[\alpha]_D^{25} - 2.65^\circ$;⁷¹ mp 84–85°C, $[\alpha]_D^{25} - 2.7^\circ$;⁷¹ *Rf* 0.39 in 25:5:1 CHCl_3 –MeOH–25% aq. NH_4OH ; $^1\text{H-NMR}$ δ_{H} : 5.751 (td, 1H, $J=7.2$ and 15.4 Hz, H-5), 5.449 (dd, 1H, $J=6.8$ and 15.6 Hz, H-4), 4.006 (t, 1H, $J=6.0$ Hz, H-3), 3.691 (dd, 1H, $J=4.2$ and 10.8 Hz, H-1), 3.551 (dd, 1H, $J=6.2$ and 11.0 Hz, H-1'), 2.822 (q, 1H, $J=4.4$ Hz, H-2), 2.047 (q, 2H, $J=7.0$ Hz, H-6, 6'), 1.34–1.20 (m, 20H, $-\text{CH}_2-$), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 70.72; H, 12.10; N, 4.39. Calcd. for $\text{C}_{18}\text{H}_{37}\text{NO}_2 \cdot 1/20\text{CHCl}_3$: C, 70.97; H, 12.22; N, 4.59%.

(2R,3S)-2-O-Methanesulfonyl-4-octadecene-1,2,3-triol (8). A mixture of compound **4** (13.98 g, 30 mmol) and Amberlyst 15 resin (90 g) in EtOH (300 ml) was stirred for 8 hr at 60–65°C, and filtered through Celite. To the filtrate was added glycerol (5 ml), and the mixture was evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 4:1 hexane–AcOEt gave **8** (8.14 g, 71.8%). *Rf* 0.31 in 15:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ δ_{H} : 5.803 (dtd, 0.7H, $J=1.1$, 6.8 and 15.4 Hz, H-5_E), 5.658 (dtd, 0.3H, $J=1.1$, 7.5 and 11.0 Hz, H-5_Z), 5.477 (dtd, 0.7H, $J=1.5$, 7.3 and 15.4 Hz, H-4_E), 5.401 (dtd, 0.3H, $J=1.5$, 8.8 and 11.0 Hz, H-4_Z), 4.711 (ddd, 0.3H, $J=1.0$, 4.3 and 8.8 Hz, H-3_Z), 4.607 (dt, 0.7H, $J=4.0$ and 6.6 Hz, H-2_E), 4.579 (dt, 0.3H, $J=3.8$ and 6.6 Hz, H-2_Z), 4.329 (dd, 0.7H, $J=4.0$ and 6.6 Hz, H-3_E), 3.76–3.86 (m, 2H, H-1, 1'), 3.140 (s, 2.1H, $\text{CH}_3\text{SO}_{2E}$), 3.136 (s, 0.9H, $\text{CH}_3\text{SO}_{2Z}$), 2.06–2.18 (m, 0.6H, H-6, 6'_Z), 2.059 (q, 1.4H, $J=7.0$ Hz, H-6, 6'_E), 1.34–1.20 (m, 22H, $-\text{CH}_2-$), 0.882 (t, 3H, $J=7.1$ Hz, CH_2CH_3).

Anal. Found: C, 60.21; H, 10.11. Calcd. for $\text{C}_{19}\text{H}_{38}\text{O}_5\text{S}$: C, 60.28; H, 10.12%.

(2R,3S)-1,3-Di-O-(1-ethoxyethyl)-2-O-methanesulfonyl-4-octadecene-1,2,3-triol (9). A solution of compound **8** (2.23 g, 5.9 mmol), pyridinium *p*-toluenesulfonate (0.327 g, 1.3 mmol) and ethyl vinyl ether (3.95 ml, 41.3 mmol) in CH_2Cl_2 (13 ml) was stirred for 1 hr at room temperature, before being diluted with CHCl_3 (130 ml), washed with satd. NaHCO_3 and satd. brine, dried (MgSO_4) and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 4:1 hexane–AcOEt gave **9** (2.98 g, 96.8%). *Rf* 0.30 in 4:1 hexane–AcOEt; $^1\text{H-NMR}$ δ_{H} : 5.72–5.83 (m, 1H, H-5), 5.30–5.50 (m, 1H, H-4), 3.08–3.11 (m, 3H, CH_3SO_2), 2.05–2.08 (m, 2H, H-6, 6'), 0.879 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

(2S,3S)-1,3-Di-O-(1-ethoxyethyl)-2-azido-4-octadecene-1,3-diol (10). A mixture of compound **9** (14.10 g, 27 mmol) and NaN_3 (11.70 g, 162.1 mmol) in DMF (189 ml) was stirred for 50 hr at 90–100°C, and evaporated *in vacuo*. A solution of the residue in Et_2O (1 liter) was successively washed with water and satd. brine, dried (MgSO_4) and

evaporated *in vacuo*. Flash chromatography of the residue over SiO₂ in 19:1 hexane–AcOEt gave **10** (12.03 g, 95.0%). *R_f* 0.59 in 4:1 hexane–AcOEt; ¹H-NMR δ_H: 5.61–5.76 (m, 1H, H-5), 5.27–5.46 (m, 1H, H-4), 2.04–2.08 (m, 2H, H-6, 6'), 0.880 (t, 3H, *J* = 7.0 Hz, CH₂CH₃); ν_{max} (neat) 2100 cm⁻¹ (N₃).

Anal. Found: C, 66.94; H, 11.04; N, 8.73. Calcd. for C₂₆H₅₁N₃O₄·1/5C₆H₁₄: C, 67.09; H, 11.14; N, 8.63%.

(2*S*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-2-amino-4-octadecene-1,3-diol (**11**). A mixture of compound **10** (1.30 g, 2.77 mmol) and NaBH₄ (0.839 g, 22.2 mmol) in iso-PrOH (40 ml) was stirred for 48 hr under reflux. The excess NaBH₄ was decomposed by adding 30% aq. AcOH, and the mixture was evaporated *in vacuo*. A solution of the residue in CHCl₃ (600 ml) was washed with water and satd. brine, dried (MgSO₄) and evaporated *in vacuo*. Flash chromatography of the residue over SiO₂ in 99:1 CHCl₃–Et₃N afforded **11** (1.16 g, 94.5%). *R_f* 0.35 in 12:1 CHCl₃–MeOH; ¹H-NMR δ_H: 5.60–5.70 (m, 1H, H-5), 5.21–5.45 (m, 1H, H-4), 2.053 (q, 2H, *J* = 6.9 Hz, H-6, 6'), 0.880 (t, 3H, *J* = 7.0 Hz, CH₂CH₃).

Anal. Found: C, 67.58; H, 11.84; N, 2.94. Calcd. for C₂₆H₅₃NO₄·1/6CHCl₃: C, 67.74; H, 11.55; N, 3.02%.

(2*S*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol (**12**). A mixture of compound **11** (132.9 mg, 0.30 mmol), tetracosanoic acid (132.7 mg, 0.36 mmol), 2-chloro-1-methylpyridinium iodide (115.0 mg, 0.45 mmol) and tri-*n*-butylamine (0.29 ml, 1.2 mmol) in CH₂Cl₂ (3 ml) was stirred for 1 hr under reflux, and then diluted with Et₂O (6 ml). The organic layer was washed with water and satd. brine, dried (MgSO₄) and evaporated *in vacuo*. Flash chromatography of the residue in 9:1 hexane–AcOEt gave **12** (224.9 mg, 94.5%). *R_f* 0.44 in 7:3 hexane–AcOEt; ¹H-NMR δ_H: 5.65–5.86 (m, 1H, H-5), 5.29–5.45 (m, 1H, H-4), 2.164 (m, 2H, NHCOCH₂), 2.019 (q, 2H, *J* = 7.0 Hz, H-6, 6'), 0.886 (t, 6H, *J* = 6.9 Hz, CH₂CH₃).

Anal. Found: C, 75.45; H, 12.73; N, 1.73. Calcd. for C₅₀H₉₉NO₅: C, 75.60; H, 12.56; N, 1.76%.

(2*S*,3*S*)-*N*-Tetracosanoyl-2-amino-4-octadecene-1,3-diol (**13**). A mixture of compound **12** (158.6 mg, 0.2 mmol) and Amberlyst 15 resin (0.6 g) in 1:1 CH₂Cl₂–MeOH (6.3 ml) was stirred for 21 hr at room temperature. After dissolving the insoluble product by adding CHCl₃, the mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. Recrystallization (CHCl₃) of the residue afforded **13** (112.8 mg, 86.9%). *R_f* 0.39 and 0.31 in 19:1 CHCl₃–MeOH; ¹H-NMR δ_H: 6.151 (d, 0.31H, *J* = 7.3 Hz, NH₂), 6.086 (d, 0.69H, *J* = 7.7 Hz, NH_E), 5.750 (dt, 0.69H, *J* = 6.6 and 15.4 Hz, H-5_E), 5.594 (dt, 0.31H, *J* = 7.3 and 11.0 Hz, H-5_Z), 5.477 (dd, 0.69H, *J* = 6.6 and 15.4 Hz, H-4_E), 5.438 (dd, 0.31H, *J* = 9.1 and 11.0 Hz, H-4_Z), 4.700 (m, 0.31H, H-3_Z), 4.393 (m, 0.69H, H-3_E), 3.87–3.95 (m, 1H, H-2), 3.75–3.87 (m, 2H, H-1, 1'), 2.103

(q, 0.62H, *J* = 7.3 Hz, H-6, 6'_Z), 2.029 (q, 1.38H, *J* = 7.0 Hz, H-6, 6'_E), 1.20–1.40 (m, 62H, –CH₂–), 0.880 (t, 6H, *J* = 7.0 Hz, CH₂CH₃).

Anal. Found: C, 77.37; H, 12.68; N, 2.32. Calcd. for C₄₂H₈₃NO₃: C, 77.59; H, 12.87; N, 2.15%.

(2*S*,3*S*,4*E*)-1,3-Di-*O*-acetyl-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol (**14E**) and (2*S*,3*S*,4*E*)-1,3-di-*O*-acetyl-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol (**14Z**). To a solution of compound **13** (17.19 g, 26.4 mmol) in pyridine (400 ml) was added Ac₂O (260 ml), the mixture being stirred for 2 hr at room temperature and then evaporated *in vacuo*. Flash chromatography of the residue over SiO₂ in 5:1 hexane–AcOEt gave **14E** (13.68 g, 70.5%) and **14Z** (5.44 g, 28.0%).

Compound 14E. mp 69.5–70°C (recrystallized from EtOH); [α]_D + 5.8° (*c* = 0.9); *R_f* 0.36 in 17:1 CHCl₃–Et₂O; ¹H-NMR δ_H: 5.764 (dt, 1H, *J* = 7.1 and 14.7 Hz, H-5), 5.600 (d, 1H, *J* = 9.2 Hz, NH), 5.406 (dd, 1H, *J* = 4.8 and 7.7 Hz, H-3), 5.370 (dd, 1H, *J* = 7.7 and 15.4 Hz, H-4), 4.416 (m, 1H, H-2), 4.089 (dd, 1H, *J* = 5.5 and 11.4 Hz, H-1), 4.058 (dd, 1H, *J* = 5.5 and 11.4 Hz, H-1'), 2.172 (dt, 2H, *J* = 2.6 and 7.7 Hz, NHCOCH₂), 2.071 (s, 3H, COCH₃), 2.062 (s, 3H, COCH₃), 2.018 (q, 2H, *J* = 7.0 Hz, H-6, 6'), 1.56–1.65 (m, 2H, NHCOCH₂CH₂), 1.10–1.38 (m, 62H, –CH₂–), 0.880 (t, 6H, *J* = 7.0 Hz, CH₂CH₃).

Anal. Found: C, 75.18; H, 11.88; N, 1.86. Calcd. for C₄₆H₈₉NO₅: C, 75.25; H, 11.94; N, 1.91%.

Compound 14Z. mp 71–72.5°C (recrystallized from EtOH); [α]_D + 0.9° (*c* = 1.1); *R_f* 0.43 in 17:1 CHCl₃–Et₂O; ¹H-NMR δ_H: 5.751 (dd, 1H, *J* = 6.6 and 9.2 Hz, H-3), 5.679 (dt, 1H, *J* = 7.5 and 10.6 Hz, H-5), 5.645 (d, 1H, *J* = 8.8 Hz, NH), 5.328 (dd, 1H, *J* = 9.5 and 11.0 Hz, H-4), 4.401 (m, 1H, H-2), 4.098 (dd, 1H, *J* = 4.9 and 11.3 Hz, H-1), 4.069 (dd, 1H, *J* = 5.1 and 11.3 Hz, H-1'), 2.175 (t, 2H, *J* = 7.7 Hz, NHCOCH₂), 2.067 (s, 3H, COCH₃), 2.050 (s, 3H, COCH₃), 1.57–1.65 (m, 2H, NHCOCH₂CH₂), 1.12–1.42 (m, 62H, –CH₂–), 0.880 (t, 6H, *J* = 7.0 Hz, CH₂CH₃).

Anal. Found: C, 75.46; H, 12.04; N, 1.71. Calcd. for C₄₆H₈₉NO₅: C, 75.25; H, 11.94; N, 1.91%.

(2*S*,3*S*,4*E*)-*N*-Tetracosanoyl-2-amino-4-octadecene-1,3-diol [*N*-tetracosanoyl-4*E*-L-threo-sphinganine] (**15E**). To a solution of compound **14E** (39.6 mg, 0.054 mmol) in 1:1 THF–MeOH (2 ml) was added a 1M solution of NaOMe–MeOH (0.155 ml), the mixture being stirred for 2 hr at room temperature to give a precipitated product. The clear solution obtained by adding hot CHCl₃ was neutralized with Dowex 50 (H⁺) resin, filtered through Celite and evaporated *in vacuo*. Recrystallization (CHCl₃) of the residue afforded **15E** (32.5 mg, 92.7%). mp 103–103.5°C; [α]_D – 18.0° (*c* = 1.01 in pyridine); *R_f* 0.31 in 19:1 CHCl₃–MeOH; ¹H-NMR (CDCl₃–CD₃OD, 9:1) δ_H: 5.729 (dt, 1H, *J* = 6.6 and 15.4 Hz, H-5), 5.427 (dd, 1H, *J* = 6.2 and 15.4 Hz, H-4), 4.351 (dd, 1H, *J* = 3.3 and 6.2 Hz, H-3), 3.817 (dt, 1H, *J* = 3.3 and 5.1 Hz, H-2), 3.654 (d, 2H, *J* = 5.5 Hz, H-1, 1'), 2.204 (t, 2H, *J* = 7.7 Hz, NHCOCH₂),

2.021 (q, 2H, $J=7.1$ Hz, H-6, 6'), 1.55–1.65 (m, 2H, $\text{NHCOCH}_2\text{CH}_2$), 1.20–1.44 (m, 62H, $-\text{CH}_2-$), 0.882 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 77.56; H, 12.95; N, 2.07. Calcd. for $\text{C}_{42}\text{H}_{88}\text{NO}_3$: C, 77.59; H, 12.87; N, 2.15%.

(2*S*,3*S*,4*Z*)-*N*-Tetracosanoyl-2-amino-4-octadecene-1,3-diol [*N*-tetracosanoyl-4*Z*-L-threo-sphingene] (**15Z**). Compound **14Z** (15.6 mg) was converted into **15Z** (10.7 mg, 77.5%) as described for the preparation of compound **15E**. mp 107.5–108°C (recrystallized from CHCl_3); $[\alpha]_{\text{D}} -2.0^\circ$ ($c=0.50$ in pyridine); R_f 0.39 in 19:1 CHCl_3 -MeOH; $^1\text{H-NMR}$ (CDCl_3 - CD_3OD , 9:1) δ_{H} : 5.548 (dt, 1H, $J=7.1$ and 10.6 Hz, H-5), 5.396 (dd, 1H, $J=8.8$ and 11.0 Hz, H-4), 4.671 (dd, 1H, $J=3.3$ and 8.8 Hz, H-3), 3.794 (dt, 1H, $J=3.3$ and 5.5 Hz, H-2), 3.651 (dd, 1H, $J=5.5$ and 12.1 Hz, H-1), 3.632 (dd, 1H, $J=5.5$ and 12.1 Hz, H-1'), 2.223 (t, 2H, $J=7.7$ Hz, NHCOCH_2), 2.02–2.15 (m, 2H, H-6, 6'), 1.55–1.65 (m, 2H, $\text{NHCOCH}_2\text{CH}_2$), 1.08–1.40 (m, 62H, $-\text{CH}_2-$), 0.882 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 76.43; H, 12.64; N, 2.01. Calcd. for $\text{C}_{42}\text{H}_{83}\text{NO}_3 \cdot 1/10\text{CHCl}_3$: C, 76.38; H, 12.65; N, 2.12%.

(2*S*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-2-*O*-acetyl-4-octadecene-1,2,3-triol (**16**). A mixture of compound **8** (103.6 mg, 0.198 mmol) and CsOAc (230.3 mg, 1.2 mmol) in DMF (2.5 ml) was stirred for 91 hr at 110°C. After adding further CsOAc (147 mg), the mixture was stirred for 31 hr at 110°C, before being diluted with AcOEt (40 ml), successively washed with satd. NaHCO_3 , water and satd. brine, dried (MgSO_4) and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 19:1 hexane- AcOEt gave **16** (67.0 mg, 69.5%) and **8** (10.7 mg). R_f 0.31 in 4:1 hexane- AcOEt ; $^1\text{H-NMR}$ δ_{H} : 5.68–5.74 (m, 1H, H-5), 2.075 (s, 3H, COCH_3), 2.02–2.06 (m, 2H, H-6, 6'), 1.24–1.40 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.190 (t, 6H, $J=7.1$ Hz, OCH_2CH_3), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 68.98; H, 11.07. Calcd. for $\text{C}_{28}\text{H}_{54}\text{O}_6$: C, 69.10; H, 11.18%.

(2*S*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-4-octadecene-1,2,3-triol (**17**). To a solution of compound **16** (1.999 g, 4.1 mmol) in 1:1 $\text{MeOH-CH}_2\text{Cl}_2$ (40 ml) was added a 1 M solution of NaOMe-MeOH (4.1 ml). The mixture was stirred for 4 hr at room temperature, neutralized with Amberlyst 15 resin, and filtered. After removing the solvent, crude product **17** (1.677 g, 91.9%) was obtained. The obtained crude product **17** was used for the next step without further purification. The sample for analyses was obtained by SiO_2 chromatography of a part of crude product **17** in 9:1 hexane- AcOEt . R_f 0.45 and 0.39 in 2:1 hexane- AcOEt .

$^1\text{H-NMR}$ of compound **17** (R_f 0.45) δ_{H} : 5.61–5.76 (m, 1H, H-5), 5.30–5.42 (m, 1H, H-4), 2.035 (q, 2H, $J=6.8$ Hz, H-6, 6'), 1.22–1.42 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.198 (t, 6H, $J=7.1$ Hz, OCH_2CH_3), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

$^1\text{H-NMR}$ of compound **17** (R_f 0.39) δ_{H} : 5.718 (ddd, 1H,

$J=6.3$, 13.3 and 15.3 Hz, H-5), 5.442 (dd, 1H, $J=8.4$ and 15.4 Hz, H-4), 3.85–3.89 (m, 1H, H-3), 2.056 (q, 2H, $J=6.7$ Hz, H-6, 6'), 1.22–1.41 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.197 (t, 3H, $J=7.1$ Hz, OCH_2CH_3), 1.173 (t, 3H, $J=7.0$ Hz, OCH_2CH_3), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 69.60; H, 11.66. Calcd. for $\text{C}_{26}\text{H}_{52}\text{O}_5 \cdot 1/5\text{CH}_3\text{COOC}_2\text{H}_5$: C, 69.63; H, 11.69%.

(2*S*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-2-*O*-methanesulfonyl-4-octadecene-1,2,3-triol (**18**). Compound **17** (1.650 g) was converted into **18** (1.437 g, 74.1%) as described for the synthesis of compound **4**. R_f 0.46 and 0.43 in hexane- AcOEt .

$^1\text{H-NMR}$ of compound **18** (R_f 0.46) δ_{H} : 5.734–5.830 (m, 1H, H-5), 5.284 (dd, 0.8H, $J=8.1$, 15.4 Hz, H-4), 5.290 (m, 0.2H, H-4), 3.093, 3.101, 3.104, and 3.111 (4s, 3H, CH_3SO_2), 2.066 (q, 2H, $J=6.7$ Hz, H-6, 6'), 1.22–1.42 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.18–1.21 (m, 6H, OCH_2CH_3), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

$^1\text{H-NMR}$ of compound **18** (R_f 0.43) δ_{H} : 3.077 and 3.085 (2s, 3H, CH_3SO_2), 2.059 (q, 2H, $J=6.6$ Hz, H-6, 6'), 1.22–1.41 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.15–1.21 (m, 6H, OCH_2CH_3), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 62.32; H, 10.03. Calcd. for $\text{C}_{27}\text{H}_{54}\text{O}_7\text{S}$: C, 62.03; H, 10.41%.

(2*R*,3*S*)-1,3-Di-*O*-(1-ethoxyethyl)-2-azido-4-octadecene-1,3-diol (**19**). Compound **18** (1.400 g) was converted into **19** (1.009 g, 80.2%) as described for the synthesis of compound **10**. R_f 0.48, 0.43 and 0.38 in 6:1 hexane- AcOEt ; $^1\text{H-NMR}$ δ_{H} : 2.03–2.12 (m, 2H, H-6, 6'), 1.22–1.42 (m, 28H, $-\text{CH}_2-$ and CHCH_3), 1.16–1.22 (m, 6H, OCH_2CH_3), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3); ν_{max} (neat) 2096 cm^{-1} (N_3).

Anal. Found: C, 66.94; H, 11.06; N, 8.39. Calcd. for $\text{C}_{26}\text{H}_{51}\text{N}_3\text{O}_4 \cdot 1/5\text{C}_6\text{H}_{14}$: C, 67.09; H, 11.14; N, 8.63%.

(2*R*,3*S*,4*E*)-2-Azido-4-octadecene-1,3-diol (**20E**) and (2*R*,3*S*,4*Z*)-2-azido-4-octadecene-1,3-diol (**20Z**). To a solution of compound **19** (0.998 g, 2.12 mmol) in 1:1 $\text{MeOH-CH}_2\text{Cl}_2$ (20 ml) was added dropwise CF_3COOH (0.327 ml, 4.25 mmol) at 0°C. The mixture was stirred for 6 hr at 0°C to room temperature, and then evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 3:1 hexane- AcOEt gave **20E** (78.6 mg, 11.4%), **20Z** (7.2 mg, 1.0%), and a mixture of **20E** and **20Z** (554.2 mg, 80.2%). The mixture of **20E** and **20Z** (554.2 mg) was recrystallized from hexane to give **20E** (349.6 mg, 50.6%). The mother liquor was evaporated *in vacuo*, and chromatographed over SiO_2 in 4:1 hexane- AcOEt to give **20E** (69.5 mg, 10.1%) and **20Z** (47.4 mg, 6.9%).

Compound **20E**. mp 53–54°C; $[\alpha]_{\text{D}} +34.0^\circ$ ($c=1.0$); R_f 0.34 in 1:1 hexane- AcOEt ; $^1\text{H-NMR}$ δ_{H} : 5.822 (dtd, 1H, $J=15.3$, 6.8 and 0.9 Hz, H-5), 5.540 (ddt, 1H, $J=15.3$, 7.3 and 1.5 Hz, H-4), 4.252 (t, 1H, $J=6.6$ Hz, H-3), 3.804 (dd, 1H, $J=11.7$ and 4.6 Hz, H-1), 3.768 (dd, 1H, $J=11.7$ and 5.9 Hz, H-1'), 3.509 (m, 1H, H-2), 2.073 (q, 2H, $J=7.0$ Hz,

H-6, 6'), 1.35–1.43 (m, 2H, H-7, 7'), 1.20–1.35 (m, 20H, $-\text{CH}_2-$), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3); ν_{max} (neat) 2142 cm^{-1} (N_3).

Anal. Found: C, 66.72; H, 10.79; N, 13.13. Calcd. for $\text{C}_{18}\text{H}_{35}\text{N}_3\text{O}_2$: C, 66.42; H, 10.84; N, 12.91%.

Compound 20Z. mp 43–43.5°C (recrystallized from pentane); $[\alpha]_{\text{D}} +52.3^\circ$ ($c=1.0$); R_f 0.40 in 1:1 hexane–AcOEt; $^1\text{H-NMR}$ δ_{H} : 5.695 (dt, 1H, $J=7.5$ and 11.0 Hz, H-5), 5.484 (dd, 1H, $J=9.0$ and 11.3 Hz, H-4), 4.609 (dt, 1H, $J=4.8$ and 9.3 Hz, H-3), 3.824 (dd, 1H, $J=6.6$ and 11.7 Hz, H-1), 3.777 (dd, 1H, $J=6.0$ and 11.5 Hz, H-1'), 3.528 (dd, 1H, $J=5.9$ and 10.6 Hz, H-2), 2.05–2.16 (m, 2H, H-6, 6'), 1.34–1.43 (m, 2H, H-7, 7'), 1.18–1.34 (m, 20H, $-\text{CH}_2-$), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3); ν_{max} (neat) 2134 cm^{-1} (N_3).

Anal. Found: C, 66.37; H, 10.79; N, 12.89. Calcd. for $\text{C}_{18}\text{H}_{35}\text{N}_3\text{O}_2$: C, 66.42; H, 10.84; N, 12.91%.

(2*R*,3*S*,4*E*)-2-Amino-4-octadecene-1,3-diol [*L*-(–)-erythro-sphingosine] (**21E**). A mixture of compound **20E** (27.0 mg, 0.083 mmol) and NaBH_4 (25.0 mg, 0.661 mmol) in EtOH (4 ml) was stirred for 48 hr under reflux. The excess NaBH_4 was decomposed by adding 30% aq. AcOH, and the mixture was evaporated *in vacuo*. Flash chromatography of the residue in 90:10:1 CHCl_3 –MeOH–25% aq. NH_4OH gave **21E** (11.8 mg, 47.6%). mp 79–81°C (recrystallized from Et₂O–hexane); $[\alpha]_{\text{D}} +2.5^\circ$ ($c=0.89$) [lit. mp 81–82°C; $[\alpha]_{\text{D}} +2.8^{+7\text{W}}$]; R_f 0.39 in 25:5:1 CHCl_3 –MeOH–25% aq. NH_4OH ; $^1\text{H-NMR}$ δ_{H} : 5.767 (td, 1H, $J=7.2$ and 15.4 Hz, H-5), 5.476 (dd, 1H, $J=7.3$ and 15.4 Hz, H-4), 4.074 (br. t, 1H, $J=5.6$ Hz, H-3), 3.697 (dd, 1H, $J=4.2$ and 10.8 Hz, H-1), 3.635 (dd, 1H, $J=5.9$ and 10.6 Hz, H-1'), 2.905 (br. q, 1H, $J=4.0$ Hz, H-2), 2.059 (q, 2H, $J=7.1$ Hz, H-6, 6'), 1.378 (m, 2H, H-7, 7'), 1.33–1.19 (m, 20H, $-\text{CH}_2-$), 0.881 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

(2*R*,3*S*,4*E*)-1,3-Di-*O*-(1-ethoxyethyl)-2-azido-4-octadecene-1,3-diol (**22E**). A mixture of compound **20E** (378.0 mg, 1.16 mmol), pyridinium *p*-toluenesulfonate (37.9 mg, 0.15 mmol) and ethyl vinyl ether (0.8 ml) in CH_2Cl_2 (22 ml) was stirred for 1.5 hr at room temperature and evaporated *in vacuo*. Flash chromatography of the residue over SiO_2 in 9:1 hexane–AcOEt gave crude product **22E** (540.7 mg, 99.1%). This obtained crude product **22E** was used for the next step without further purification. R_f 0.48 and 0.43 in 6:1 hexane–AcOEt.

(2*R*,3*S*,4*Z*)-1,3-Di-*O*-(1-ethoxyethyl)-2-azido-4-octadecene-1,3-diol (**22Z**). Compound **20Z** (49.9 mg) was converted into **22Z** (57.0 mg, 79.2%) as described for the synthesis of compound **22E**. The obtained crude product **22Z** was used for the next step without further purification. R_f 0.51 and 0.44 in 6:1 hexane–AcOEt.

(2*R*,3*S*,4*E*)-1,3-Di-*O*-(1-ethoxyethyl)-2-amino-4-octadecene-1,3-diol (**23E**). Compound **22E** (540.7 mg) was

converted into **23E** (458.0 mg, 89.7%) as described for the synthesis of compound **11**. R_f 0.50 in 10:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ δ_{H} : 5.65–5.73 (m, 1H, H-5), 5.438 (ddd, 0.5H, $J=2.2$, 8.4 and 15.4 Hz, H-4), 5.326 (ddt, 0.5H, $J=1.5$, 8.6 and 15.6 Hz, H-4), 2.073 (q, 2H, $J=7.0$ Hz, H-6, 6'), 1.15–1.41 (m, 34H, $-\text{CH}_2-$, OCH_2CH_3 and CHCH_3), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 70.23; H, 11.81; N, 2.99. Calcd. for $\text{C}_{26}\text{H}_{53}\text{NO}_4$: C, 70.38; H, 12.04; N, 3.16%.

(2*R*,3*S*,4*Z*)-1,3-Di-*O*-(1-ethoxyethyl)-2-Amino-4-octadecene-1,3-diol (**23Z**). Compound **22Z** (57.0 mg) was converted into **23Z** (43.2 mg, 80.3%) as described for the synthesis of compound **11**. R_f 0.53 in 12:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ δ_{H} : 5.64–5.75 (m, 1H, H-5), 5.401 (dt, 0.5H, $J=1.5$ and 10.3 Hz, H-4), 5.274 (t, 0.5H, $J=10.4$ Hz, H-4), 2.03–2.17 (m, 2H, H-6, 6'), 1.16–1.41 (m, 34H, $-\text{CH}_2-$, OCH_2CH_3 and CHCH_3), 0.880 (t, 3H, $J=7.0$ Hz, CH_2CH_3).

(2*R*,3*S*,4*E*)-1,3-Di-*O*-(1-ethoxyethyl)-*N*-tetracosanyl-2-amino-4-octadecene-1,3-diol (**24E**). Compound **23E** (440.0 mg) was converted into **24E** (783.6 mg, 99.5%) as described for the synthesis of compound **12**. R_f 0.44 and 0.37 in 7:3 hexane–AcOEt.

$^1\text{H-NMR}$ of compound **24E** (R_f 0.44) δ_{H} : 5.857 (d, 0.5H, $J=7.2$ Hz, NH), 5.840 (d, 0.5H, $J=6.5$ Hz, NH), 5.651 (m, 1H, H-5), 5.326 (m, 1H, H-4), 2.126 (m, 2H, NHCOCH_2), 2.026 (q, 2H, $J=7.0$ Hz, H-6, 6'), 1.10–1.43 (m, 74H, $-\text{CH}_2-$, OCH_2CH_3 and CHCH_3), 0.880 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

$^1\text{H-NMR}$ of compound **24E** (R_f 0.37) δ_{H} : 5.62–5.74 (m, 2H, H-5 and NH), 5.428 (m, 1H, H-4), 2.116 (m, 2H, NHCOCH_2), 2.028 (q, 2H, $J=7.1$ Hz, H-6, 6'), 1.17–1.39 (m, 74H, $-\text{CH}_2-$, OCH_2CH_3 and CHCH_3), 0.880 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 75.88; H, 12.59; N, 1.61. Calcd. for $\text{C}_{50}\text{H}_{99}\text{NO}_5$: C, 75.60; H, 12.56; N, 1.76%.

(2*R*,3*S*,4*Z*)-1,3-Di-*O*-(1-ethoxyethyl)-*N*-tetracosanoyl-2-amino-4-octadecene-1,3-diol (**24Z**). Compound **23Z** (36.6 mg) was converted into **24Z** (64.2 mg, 98.0%) as described for the synthesis of compound **12**. R_f 0.46 and 0.43 in 7:3 hexane–AcOEt; $^1\text{H-NMR}$ δ_{H} : 2.20–2.19 (m, 4H, NHCOCH_2 and H-6, 6'), 1.55–1.64 (m, 2H, $\text{NHCOCH}_2\text{CH}_2$), 1.11–1.41 (m, 74H, $-\text{CH}_2-$, OCH_2CH_3 and CHCH_3), 0.880 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 75.18; H, 12.43; N, 1.76. Calcd. for $\text{C}_{50}\text{H}_{99}\text{NO}_5$: C, 75.60; H, 12.56; N, 1.76%.

(2*R*,3*S*,4*E*)-*N*-Tetracosanoyl-2-amino-4-octadecene-1,3-diol [*N*-tetracosanoyl-4*E*-*L*-erythro-sphingenine] (**25E**). To a solution of compound **24E** (351.3 mg, 0.44 mmol) in 1:1 CH_2Cl_2 –MeOH (14 ml) was added dropwise CF_3COOH (0.068 ml, 0.88 mmol) at room temperature. The mixture was stirred for 3.5 hr at room temperature, and concentrated *in vacuo*. The residue was recrystallized from

acetone to give **25E** (238.9 mg, 83.1%). mp 97.5–99°C: $[\alpha]_D^{25} +3.2^\circ$ ($c=1.1$ in 9:1 CHCl_3 –MeOH); R_f 0.36 in 15:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ (CDCl_3 – CD_3OD , 9:1) δ_{H} : 5.740 (dt, 1H, $J=7.2$ and 15.5 Hz), 5.479 (dd, 1H, $J=6.6$ and 15.4 Hz, H-4), 4.163 (t, 1H, $J=5.5$ Hz, H-3), 3.81–3.84 (m, 2H, H-1 and H-2), 3.642 (dd, 1H, $J=5.3$ and 13.0 Hz, H-1'), 2.208 (t, 2H, $J=7.5$ Hz, NHCOCH_2), 2.041 (q, 2H, $J=7.1$ Hz, H-6, 6'), 1.610 (m, 2H, $\text{NHCOCH}_2\text{CH}_2$), 1.17–1.42 (m, 62H, $-\text{CH}_2-$), 0.883 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 77.47; H, 12.84; N, 2.04. Calcd. for $\text{C}_{42}\text{H}_{83}\text{NO}_3$: C, 77.59; H, 12.87; N, 2.15%.

(2*R*,3*S*,4*Z*)-*N*-Tetracosanoyl-2-amino-4-octadecene-1,3-diol [*N*-tetracosanoyl-4*Z*-L-erythro-sphingene] (**25Z**). Compound **24Z** (50.4 mg) was converted into **25Z** (31.6 mg, 76.7%) as described for the synthesis of compound **25E**. mp 90–91.5°C (recrystallized from acetone); $[\alpha]_D^{25} +12.7^\circ$ ($c=0.9$ in 9:1 CHCl_3 –MeOH); R_f 0.38 in 15:1 CHCl_3 –MeOH; $^1\text{H-NMR}$ (CDCl_3 – CD_3OD , 9:1) δ_{H} : 5.572 (dt, 1H, $J=7.0$ and 11.0 Hz, H-5), 5.435 (dd, 1H, $J=9.0$ and 10.8 Hz, H-4), 4.526 (dd, 1H, $J=5.3$ and 7.9 Hz, H-3), 3.864 (dd, 1H, $J=4.4$ and 11.4 Hz, H-1), 3.811 (dt, 1H, $J=3.9$ and 5.5 Hz, H-2), 3.658 (dd, 1H, $J=3.5$ and 11.2 Hz, H-1'), 2.206 (t, 2H, $J=7.7$ Hz, NHCOCH_2), 2.01–2.05 (m, 2H, H-6, 6'), 1.614 (m, 2H, $\text{NHCOCH}_2\text{CH}_2$), 1.18–1.43 (m, 62H, $-\text{CH}_2-$), 0.882 (t, 6H, $J=7.0$ Hz, CH_2CH_3).

Anal. Found: C, 76.95; H, 12.76; N, 1.99. Calcd. for $\text{C}_{42}\text{H}_{83}\text{NO}_3 \cdot 1/2(\text{CH}_3)_2\text{CO}$: C, 76.93; H, 12.76; N, 2.06%.

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