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A HIGHLY STEREOSELECTIVE SYNTHESIS OF 2(S), 3(R), 4*E*- AND 2(S), 3(R), 4*Z*-*N*-TETRACOSANOYLSPHINGENINE FROM D-GLUCOSE*

KATSUYA KOIKE, MASAAKI NUMATA, MAMORU SUGIMOTO, YOSHIAKI NAKAHARA, AND TOMOYA OGAWA**

RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama, 351-01 (Japan)

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ABSTRACT

The synthesis of 4-*E*- and 4-*Z*-D-*erythro*-ceramide was achieved in 10 steps in ~20–30% overall yield, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. *E*- and *Z*-5-Deoxy-1,2-*O*-isopropylidene-5-*C*-tetradecylidene-α-D-xylofuranose were used as key intermediates.

INTRODUCTION

In view of the crucial importance of sphingoglycolipids as regulatory molecules in many aspects of cell biology, such as cell growth, cell adhesion, and cell recognition[2], we planned a project on the synthesis of these molecules. Even though several synthetic approaches to the hydrophobic part of the sphingoglycolipids, racemic[3] and optically active ceramide[4], have been reported, a practical route suitable for a large-scale synthesis of **1** and related compounds has remained to be established.

In an earlier paper[5], we described preliminarily a practical and stereoselective route for the synthesis of D-*erythro*-ceramides **1**, **2**, and **3**, based on the chiron approach[6], by using 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**) as starting material (see Scheme 1), and now describe the work in detail.

RESULTS AND DISCUSSION

Treatment of aldehyde **5**, readily obtainable[7] from compound **4** with tetradecylidenetriphenylphosphorane in tetrahydrofuran, afforded a mixture of *E*-olefin **6** and its *Z* isomer (**9**) in 42 and 48% yield, respectively. In our hands, the *E*/*Z* ratio of the Wittig olefination could not be controlled in favor of the *E* isomer **6**. However, irradiation[8] of the *Z*-olefin **9** in 1:19 1,4-dioxane–cyclohexane in the presence of diphenyl disulfide with an Eikosha EHS-W-300 high-pressure mercury lamp (300

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**To whom enquiries should be addressed.

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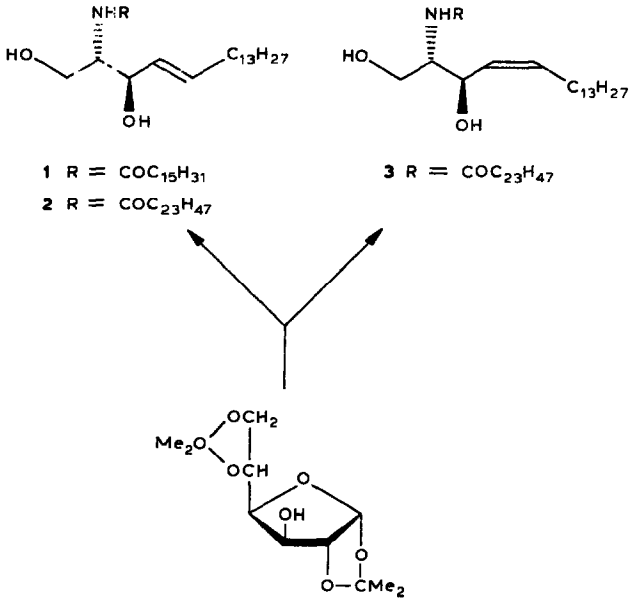
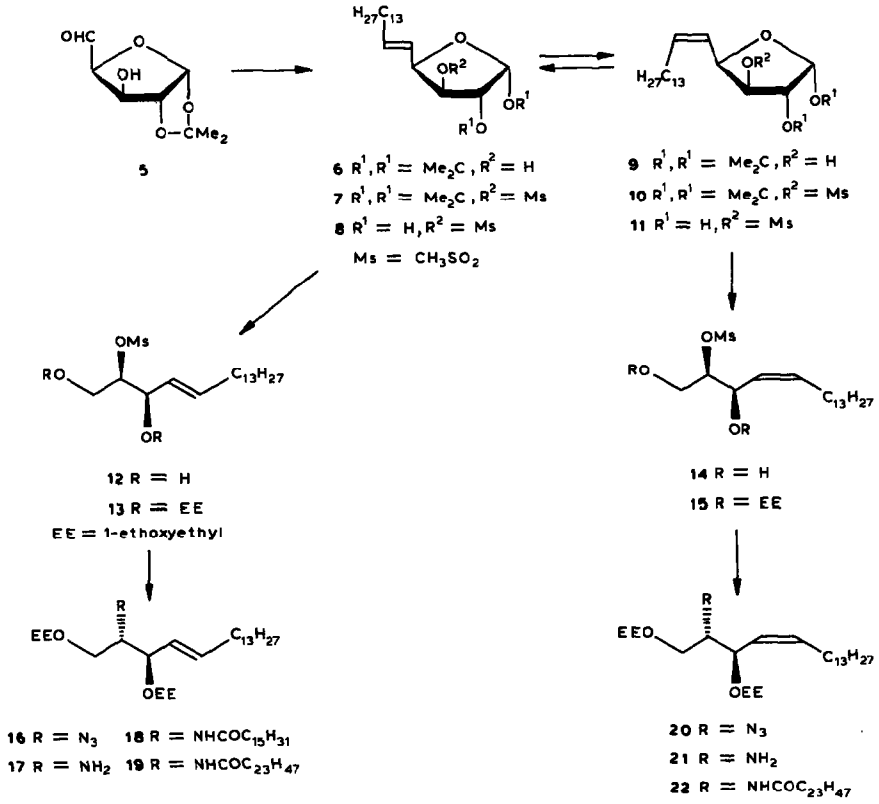


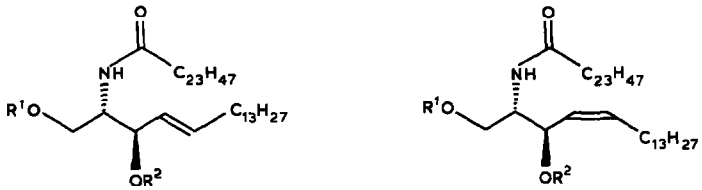
Scheme I.

W) under an atmosphere of nitrogen afforded an equilibrium mixture of **6** and **9** in the ratio of 14.5:1, from which pure *E*-olefin **6** could be isolated in 93% yield. Thus, transformation of aldehyde **5** into *E*-olefin **6** was achieved in 87% yield in two steps. Treatment of compound **6** with methanesulfonyl chloride, to give mesylate **7** in 92% yield, and hydrolysis of compound **7** in aqueous acetic acid, afforded a 63% yield of crystalline diol **8**. Oxidation of **8** with sodium metaperiodate in aqueous ethanol, and reduction of the product with sodium borohydride afforded an 86% yield of crystalline compound **12**. Protection of the diol grouping of **12** with a 1-ethoxyethyl group[9], and SN2 displacement of the mesylate group in the product with sodium azide afforded the desired azide **16** in 65% overall yield. The reduction of azide **16** to amine **17** was achieved by use of either sodium borohydride or Lindlar catalyst[10] in high yield. Acylation of amine **17** to **18** or **19** could be achieved without difficulty by using either hexadecanoyl chloride or tetracosanoic acid, 2-chloro-1-methylpyridinium iodide, and tributylamine[11]. Removal of the 1-ethoxyethyl group of **18** and **19** with Amberlyst A 15 resin in methanol–dichloromethane gave crystalline 4-*E*-D-*erythro*-ceramides **1** and **2**. The isomeric 4-*Z*-D-*erythro*-ceramide **3** could be obtained, by use of the same sequence of reactions from *Z*-olefin **9** in 27% overall yield in seven steps. Both 4-*E*-D-*erythro*-ceramide (**2**) and the 4-*Z* isomer **3** were converted into the glycosyl acceptors **25** and **28** in three steps in the conventional way.

In conclusion, based on the concept of a carbohydrate template[6], stereoselective synthesis of ceramides **1**, **2**, and **3**, and their derivatives, could be achieved in an efficient manner.



Scheme 2.



EXPERIMENTAL

General. — Melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$ at 25°, unless noted otherwise. Column chromatography was performed on columns of

silica gel (Merck, 70–230 mesh). Flash chromatography was performed on columns of Wako gel C-300 (200–300 mesh). T.l.c. and high-performance t.l.c. were performed on silica gel 60 F_{254} (Merck, Darmstadt). Molecular sieves were purchased from Nakarai Chemicals, Ltd. I.r. spectra were recorded with an EPI-G2 Hitachi spectrophotometer, using KBr pellets for the crystalline samples, and films for the liquid samples. ^{1}H-N.m.r. spectra were recorded with either a JNM-GX400 or a JNM-FX90Q n.m.r. spectrometer. ^{13}C-N.m.r. spectra were recorded with a JNM-FX 100FT n.m.r. spectrometer operated at 25.05 MHz. The values of δ_C and δ_H are expressed in p.p.m. downwards from the signal for internal Me_4Si, for solutions in $CDCl_3$, unless noted otherwise. Values of δ_H (D_2O) and δ_C (D_2O) are expressed in p.p.m. downward from Me_4Si, by reference to internal standards of Me_2CO (2.225) or Me_3COH (1.230), and 1,4-dioxane (67.4) or MeOH (49.8), respectively.

(E) *and* (Z)-*5-Deoxy-1,2-O-isopropylidene-5-C-tetradecylidene-α-*D-*xylo-furanose* (**6** *and* **9**). — To a solution of tetradecyltriphenylphosphonium bromide (9.9 g, 18.3 mmol, prepared by refluxing a solution of 1-bromotetradecane and triphenylphosphine in xylene for 16 h) in THF (150 mL) cooled in an ice–methanol bath was added dropwise a 1.5M solution of butyllithium in hexane (8.9 mL, 13.3 mmol), and the mixture was stirred for 1 h at −15 to +10°. To this mixture was added dropwise a solution of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**5**; 1.0 g, 5.1 mmol) in THF (10 mL) at −10°. The mixture was stirred for 2 h at −10 to +20° and evaporated *in vacuo*. The residue was dissolved in 3:7 H_2O–MeOH (100 mL) and extracted with hexane (200 mL × 3), and the extracts were combined, successively washed with water and saturated saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue in 9:1 hexane–EtOAc gave **6** (784 mg, 42%) and **7** (890 mg, 47%).

Compound **6**: recrystallised from hexane, m.p. 72–73°, $[\alpha]_D$ −39.4° (*c* 1.2); R_F 0.63 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 5.971 (ddt, 1 H, *J* 1.2, 15.6, and 6.8 Hz, H-6), 5.928 (d, 1 H, *J* 3.9 Hz, H-1), 5.491 (ddt, 1 H, *J* 5.8, 15.6, and 1.4 Hz, H-5), 4.696 (bd, 1 H, *J* 5.6 Hz, H-4), 4.571 (d, 1 H, *J* 3.9 Hz, H-2), 4.036 (bs, 1 H, H-3), 2.109 (t, 1 H, *J* 6.8 Hz, H-7), 2.090 (t, 1 H, *J* 6.8 Hz, H-7'), 1.511 (s, 3 H, C*H*$_3$C), 1.324 (s, 3 H, C*H*$_3$C), and 0.880 (t, 3 H, *J* 6.8 Hz, *CH*$_3$CH$_2$); δ_C 137.1 (C-5), 122.3 (C-6), 111.6 (Me$_2$*C*), 104.6 (C-1), and 85.0 (C-4).

Anal. Calc. for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94. Found: C, 71.73; H, 10.88.

Compound **9**: recrystallised from hexane, m.p. 73–74°, $[\alpha]_D$ −32.8° (*c* 1.1); R_F 0.55 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 5.946 (d, 1 H, *J* 3.9 Hz, H-1), 5.743 (ddt, 1 H, *J* 2.4, 9.8, and 6.1 Hz, H-6), 5.483 (ddt, 1 H, *J* 7.5, 11.2, and 2.0 Hz, H-5), 4.943 (ddd, 1 H, *J* 1.2, 2.6, and 7.3 Hz, H-4), 4.568 (d, 1 H, *J* 3.9 Hz, H-2), 4.075 (dd, 1 H, *J* 2.7 and 4.4 Hz, H-3), 2.2–2.05 (m, 2 H, C*H*$_2$CH=), 1.526 (s, 3 H, C*H*$_3$C), 1.326 (s, 3 H, C*H*$_3$C), and 0.881 (t, 3 H, *J* 6.6 Hz, C*H*$_3$CH$_2$); δ_C 136.3 (C-5), 122.8 (C-6), 111.4 (Me$_2$*C*), 104.5 (C-1), and 85.2 (C-4).

Anal. Calc. for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94. Found: C, 71.73; H, 10.88.

Isomerization of compound **9** *into compound* **6**. — A solution of compound **9**

(104 mg, 0.28 mmol) and diphenyl disulfide (65 mg, 0.30 mmol) in 1:19 1,4-dioxane–cyclohexane (5 mL) was stirred for 1 h at 20° under irradiation with an Eikosha EHS-W-300 high-pressure mercury lamp (300 W) under an atmosphere of N_2, and then evaporated *in vacuo*. Chromatography of the residue over Lober column (LiChroprep Si60 size B) in 17:3 hexane–EtOAc afforded **6** (96.4 mg, 93%) and **9** (6.7 mg, 6%).

(E)-*5-Deoxy-1,2-O-isopropylidene-3-O-(methylsulfonyl)-5-C-tetradecylidene-α-D-xylofuranose* (**7**). — To a solution of compound **6** (6.3 g, 17 mmol) in pyridine (100 mL) was added dropwise methanesulfonyl chloride (2 mL, 26 mmol) at −5 to 0°. The mixture was stirred for 16 h at 20°, water (3 mL) was added at −5 to 0°, and the mixture was evaporated *in vacuo*. A solution of the residue in Et_2O (300 mL) was successively washed with water, aq. $NaHCO_3$, and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 9:1 hexane–EtOAc gave **7** (7.1 g, 92%). An analytical sample was recrystallized from hexane; m.p. 59–60°, $[\alpha]_D$ −32.1° (*c* 1.1); R_F 0.58 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 5.960 (d, 1 H, *J* 3.9 Hz, H-1), 5.940 (ddt, 1 H, *J* 2.0, 14.0, and 7.0 Hz, H-6), 5.497 (ddt, 1 H, *J* 7.3, 15.3, and 2.0 Hz, H-5), 4.901 (d, 1 H, *J* 2.9 Hz, H-3), 4.796 (d, 1 H, *J* 3.9 Hz, H-2), 4.727 (dd, 1 H, *J* 2.9 and 4.7 Hz, H-4), 3.025 (s, 3 H, CH_3SO_2), 2.093 (t, 1 H, *J* 7.1 Hz), 2.076 (t, 1 H, *J* 6.8 Hz, CH_2CH=), 1.523, 1.325 (2 s, 6 H, CH_3C), and 0.880 (t, 3 H, CH_3CH_2); δ_C 138.2 (C-5), 121.7 (C-6), 112.3 (Me_2C), 104.4 (C-1), 83.7 (C-4), 83.6 (C-3), and 79.8 (C-2).

Anal. Calc. for $C_{23}H_{42}O_6S$: C, 61.85; H, 9.48; S, 7.18. Found: C, 61.81; H, 9.47; S, 7.10.

(E)-*5-Deoxy-3-O-(methylsulfonyl)-5-C-tetradecylidene-α-D-xylofuranose* (**8**). — A solution of compound **7** (1.59 g, 3.6 mmol) in 1:4 H_2O–AcOH (5 mL) was stirred for 2 h at 80°, diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (150 mL). The extract was successively washed with H_2O, aq. $NaHCO_3$, and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue in 7:3 hexane–EtOAc afforded **8** (0.9 g, 63%); recrystallized from hexane, m.p. 57–59°, $[\alpha]_D$ +9.1° (*c* 1.7); R_F 0.34 in 1:1 hexane–EtOAc; n.m.r. data: δ_H 5.869 (dt, 1 H, *J* 15.4 and 6.8 Hz, H-6), 5.531 (bs, 1 H, H-1), 5.465 (dd, 1 H, *J* 7.8 and 15.4 Hz, H-5), 4.945 (dd, 1 H, *J* 3.2 and 4.9 Hz, H-3), 4.824 (dd, 1 H, *J* 4.4 and 7.3 Hz, H-4), 4.416 (bs, 1 H, H-2), 3.851 (bs, 1 H, OH-1), 3.295 (d, 1 H, *J* 4.5 Hz, OH-2), 3.060 (s, 3 H, CH_3SO_2), 2.087 (t, 1 H, *J* 6.8 Hz), 2.070 (t, 1 H, *J* 7.0 Hz, CH_2–CH=), and 0.880 (t, 3 H, CH_3CH_2); δ_C 137.9 (C-5), 122.9 (C-6), 95.1 (C-1), 85.7 (C-3 and C-4), and 76.3 (C-2).

Anal. Calc. for $C_{20}H_{38}O_6S \cdot 0.25\ H_2O$: C, 58.44; H, 9.44; S, 7.80. Found: C, 58.19; H, 9.30; S, 7.84.

(Z)-*5-Deoxy-1,2-O-isopropylidene-3-O-(methylsulfonyl)-5-C-tetradecylidene-α-D-xylofuranose* (**10**). — Compound **9** (5.0 g) was treated as described for **6**, to give compound **10** (5.5 g, 91%); recrystallized from hexane, m.p. 50–57°, $[\alpha]_D$ −58.0° (*c* 1.0); R_F 0.58 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 5.985 (d, 1 H, *J* 3.9 Hz, H-1), 5.773 (dt, 1 H, *J* 11.0 and 6.8 Hz, H-6), 5.472 (dd, 1 H, *J* 8.1 and 11.0

Hz, H-5), 5.071 (dd, 1 H, *J* 2.0 and 8.0 Hz, H-4), 4.903 (d, 1 H, *J* 3.0 Hz, H-3), 4.817 (d, 1 H, *J* 3.9 Hz, H-2), 3.034 (s, 3 H, CH_3SO_2), 2.20–2.05 (m, 2 H, CH_2CH=), 1.544, 1.338 [2 s, 6 H, $(CH_3)_2C$], and 0.882 (t, 3 H, *J* 6.6 Hz, CH_3CH_2).

Anal. Calc. for $C_{23}H_{42}O_6S$: C, 61.85; H, 9.48; S, 7.18. Found: C, 61.90; H, 9.52; S, 7.17.

*(Z)-5-Deoxy-3-O-(methylsulfonyl)-5-C-tetradecylidene-α-*D*-xylofuranose* (**11**). — Compound **10** (0.30 g) was treated as described for compound **7**, to give compound **11** (0.19 g, 69%); recrystallized from 1:3 Et_2O–hexane, m.p. 78–79°, $[\alpha]_D$ −38.9° (*c* 1.1); R_F 0.28 in 4:1 hexane–EtOAc; n.m.r. data: δ_H 5.762 (ddt, 1 H, *J* 1.5, 11.0, and 6.8 Hz, H-6), 5.567 (t, 1 H, *J* 4.7 Hz, H-1), 5.433 (ddt, 1 H, *J* 8.6, 11.0, and 1.5 Hz, H-5), 5.205 (ddd, 1 H, *J* 1.5, 4.6, and 8.8 Hz, H-4), 4.951 (dd, 1 H, *J* 2.7 and 4.6 Hz, H-3), 4.451 (ddd, 1 H, *J* 2.9, 4.4, and 5.8 Hz, H-2), 3.464 (d, 1 H, *J* 5.1 Hz, OH-1), 3.014 (d, 1 H, *J* 5.8 Hz, OH-2), and 1.881 (t, 3 H, *J* 6.6 Hz, CH_3CH_2).

Anal. Calc. for $C_{20}H_{38}O_6S$: C, 59.08; H, 9.42; S, 7.89. Found: C, 59.51; H, 9.10; S, 7.82.

*1,3-Dihydroxy-2-(methylsulfonyloxy)-4-*E-D-threo*-octadec-4-ene* (**12**). — To a stirred solution of compound **8** (1.56 g, 3.83 mmol) in 4:1 EtOH–H_2O (100 mL) was added portionswise $NaIO_4$ (1.96 g, 9.2 mmol) at −5 to 0°. The mixture was stirred for 30 min at −5 to 0° and then for 1 h at 20°, and filtered. To the filtrate was added dropwise a solution of $NaBH_4$ (540 mg, 14.3 mmol) in EtOH (10 mL) at −5 to 0° with stirring. The mixture was stirred for 30 min at −5 to 0° and for 15 min at 20°, and filtered through Celite. To the filtrate was dropwise added acetic acid until no more hydrogen was evolved. The mixture was poured into Et_2O (1 L), and the ether layer was washed successively with 5% aq. $Na_2S_2O_3$ (200 mL), 5% $NaHCO_3$ (200 mL), H_2O (200 mL), and satd. saline (200 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 1:1 hexane–EtOAc gave **12** (1.24 g, 86%); crystallized from hexane, m.p. 60–62°, $[\alpha]_D$ −0.7° (*c* 0.6); R_F 0.30 in 1:1 hexane–EtOAc; n.m.r. data: δ_H 5.861 (ddt, 1 H, *J* 1.0, 15.4, and 6.8 Hz, H-5), 5.487 (ddt, 1 H, *J* 7.2, 15.4, and 1.4 Hz, H-4), 4.604 (dt, 1 H, *J* 3.2 and 5.9 Hz, H-2), 4.347 (t, 1 H, *J* 7.1 Hz, H-3), 3.937 (dd, 1 H, *J* 3.2 and 12.7 Hz, H-1), 3.814 (dd, 1 H, *J* 5.6 and 12.7 Hz, H-1′), 3.152 (s, 3 H, CH_3SO_2), 2.076 (t, 1 H, *J* 7.1 Hz, H-6), 2.059 (t, 1 H, *J* 6.8 Hz, H-6′), and 0.881 (t, 3 H, *J* 6.8 Hz, CH_3CH_2); δ_C 136.3 (C-4), 126.9 (C-5), 85.8 (C-2), 72.1 (C-3), 62.4 (C-1), and 38.7 (CH_3SO_2).

Anal. Calc. for $C_{19}H_{38}O_5S$: C, 60.28; H, 10.12; S, 8.47. Found: C, 60.27; H, 10.10; S, 8.35.

*1,3-Bis(1-ethoxyethoxy)-2-(methylsulfonyloxy)-4-*E-D-threo*-octadec-4-ene* (**13**). — A solution of compound **12** (507 mg, 1.34 mmol), pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol), and ethyl vinyl ether (0.8 mL, 8.4 mmol) in CH_2Cl_2 (5 mL) was stirred for 1 h at 20°, and then diluted with CH_2Cl_2 (50 mL), washed successively with 5% aq. $NaHCO_3$ and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 70:30:1 hexane–EtOAc–

Et_3N gave **13** (848 mg, 85%); $[\alpha]_D$ −12° (*c* 1.8); R_F 0.61 and 0.57 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 3.104, 3.095, 3.088, and 3.080 (4 s of equal intensity, CH_3SO_2 of 4 diastereoisomers); δ_C 100.1, 99.9, 99.7, and 97.4 [4 $CH_3CH(O–)_2$].

*2-Azido-1,3-bis(1-ethoxyethoxy)-4-*E-D-erythro-*octadec-4-ene* (**16**). — A mixture of compound **13** (486 mg, 0.93 mmol) and NaN_3 (366 mg, 5.63 mmol) in DMF (6 mL) was stirred for 5 days at 80–85°, and evaporated *in vacuo*. A solution of the residue in Et_2O (100 mL) was successively washed with H_2O and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 90:10:1 hexane–EtOAc–Et_3N gave **16** (330 mg, 76%); $[\alpha]_D$ −21° (*c* 1.6); R_F 0.66 and 0.62 in 4:1 hexane–EtOAc; n.m.r. data: δ_H no signals for CH_3SO_2; δ_C 99.9, 99.6, 99.1, and 96.7 [4 $CH_3CH(O–)_2$]; ν_{max} 2100 cm^{-1}.

Anal. Calc. for $C_{26}H_{51}N_3O_4$: C, 66.49; H, 10.95; N, 8.95. Found: C, 66.82; H, 10.83; N, 8.65.

*2-Amino-1,3-bis(1-ethoxyethoxy)-4-*E-D-erythro-*octadec-4-ene* (**17**). — A mixture of compound **16** (330 mg, 0.70 mmol) and $NaBH_4$ (162 mg, 4.3 mmol) in *i*PrOH (10 mL) was stirred for 2 days under reflux. After addition of further $NaBH_4$ (50 mg), the mixture was stirred for 1 day under reflux. The excess of $NaBH_4$ was decomposed by addition of acetic acid, and the mixture was evaporated *in vacuo*. A solution of the residue in $CHCl_3$ (100 mL) was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 95:5:1 $CHCl_3$–MeOH–Et_3N afforded **17** (287 mg, 90%); $[\alpha]_D$ −9.5° (*c* 6.0); R_F 0.63 in 9:1 CH_2Cl_2–MeOH; n.m.r. data: δ_C 99.9, 99.6, 98.8, 96.8 [4 $CH_3CH(O–)_2$], and 54.5 (C-2).

Anal. Calc. for $C_{26}H_{32}NO_4$: C, 70.73; H, 12.45; N, 3.08. Found: C, 70.38; H, 12.04; N, 3.16.

*1,3-Bis(1-ethoxyethoxy)-2-hexadecanamido-4-*E-D-erythro-*octadec-4-ene* (**18**). — A mixture of compound **17** (232 mg, 0.63 mmol), hexadecanoyl chloride (218 mg, 0.79 mmol), and 4-dimethylaminopyridine (DMAP; 12 mg) in pyridine (3 mL) was stirred for 1 h at 20°. After addition of 3 drops of H_2O, the mixture was stirred for 30 min at 20°, and evaporated *in vacuo*. A solution of the residue in Et_2O (100 mL) was washed successively with 5% aq. $NaHCO_3$, H_2O, and satd. saline, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 80:20:1 hexane–EtOAc–Et_3N afforded **18** (288 mg, 81%); $[\alpha]_D$ −14° (*c* 0.6); R_F 0.48 and 0.54 in 4:1 hexane–EtOAc; n.m.r. data: δ_C 100.5, 99.9, 97.7, 97.5 [4 $CH_3CH(O–)_2$], and 52.2 (C-2); ν_{max} 1630 and 1530 cm^{-1}.

Anal. Calc. for $C_{42}H_{83}NO_5$: C, 73.95; H, 12.27; N, 2.05. Found: C, 74.34; H, 12.17; N, 2.09.

*1,3-Bis(1-ethoxyethoxy)-2-tetracosanamido-4-*E-D-erythro-*octadec-4-ene* (**19**) *from compound* **16**. — A mixture of compound **16** (1.75 g, 3.7 mmol) and Lindlar catalyst (640 mg) in EtOH (100 mL) was stirred for 6.5 h under H_2, and filtered through Celite. Evaporation of the filtrate afforded crude **17** (1.68 g). A mixture of **17** (1.68 g), tetracosanoic acid (1.64 g, 4.4 mmol), 2-chloro-1-methylpyridinium iodide (1.34 g, 5.2 mmol), and tributylamine (2.37 mL, 9.96 mmol) in

CH_2Cl_2 (26 mL) was stirred for 1 h under reflux under an atmosphere of Ar, and diluted with Et_2O (500 mL). The organic layer was successively washed with water and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 80:20:1 hexane–EtOAc–Et_3N afforded **19** (2.3 g, 80% from **16**); R_F 0.41 and 0.35 in 4:1 hexane–EtOAc; ν_{max} 1630 and 1530 cm^{-1}.

Anal. Calc. for $C_{50}H_{99}NO_5$: C, 75.60; H, 12.56; N, 1.76. Found: C, 75.67; H, 12.50; N, 1.73.

N-*Hexadecanoyl-4*-E-D-erythro-*sphingenine* (**1**). — A solution of compound **18** (163 mg, 0.24 mmol) and pyridinium *p*-toluenesulfonate (33 mg, 0.13 mmol) in MeOH (8 mL) was stirred for 47 h at 20°, diluted with CH_2Cl_2 (100 mL), and successively washed with aq. $NaHCO_3$ and satd. saline, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography over SiO_2 in 9:1 $CHCl_3$–MeOH afforded **1** (117 mg, 91%); recrystallized from MeOH, m.p. 93–94°, $[\alpha]_D$ −4.1° (*c* 0.66); R_F 0.40 in 9:1 $CHCl_3$–MeOH; n.m.r. data: δ_H (1:1 $CDCl_3$–CD_3OD), 5.729 (dt, 1 H, *J* 15.2 and 6.8 Hz, H-5), 5.477 (dd, 1 H, *J* 7.1 and 15.2 Hz, H-4), 4.126 (t, 1 H, *J* 6.6 Hz, H-3), 3.855 (dt, 1 H, *J* 6.1 and 4.4 Hz, H-2), 3.787 (dd, 1 H, *J* 4.8 and 11.2 Hz, H-1), 3.658 (dd, 1 H, *J* 4.2 and 11.2 Hz, H-1′), 2.209 (t, 2 H, *J* 7.7 Hz, $COCH_2CH_2$), 2.054 (t, 1 H, *J* 7.1 Hz, H-6), 2.037 (t, 1 H, *J* 7.1 Hz, H-6′), and 0.889 (t, 6 H, *J* 6.6 Hz, CH_3CH_2); δ_C 174.0 (C=O), 134.3 (C-4), 129.1 (C-5), 74.6 (C-3), 62.6 (C-1), and 54.8 (C-2).

Anal. Calc. for $C_{34}H_{67}NO_3$: C, 75.92; H, 12.56; N, 2.60. Found: C, 75.91; H, 12.94; N, 2.50.

N-*Tetracosanoyl-4*-E-D-erythro-*sphingenine* (**2**). — A mixture of compound **19** (1.307 g, 1.64 mmol) and Amberlyst **15** resin (4.8 g) in 1:1 CH_2Cl_2–MeOH (52 mL) was stirred for 2 h at 20°, to give some precipitated product. A clear solution was obtained by addition of $CHCl_3$ (50 mL), and filtered through Celite, and the filtrate was evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 20:1 $CHCl_3$–MeOH gave **2** (853 mg, 80%). An analytical sample was obtained by recrystallization from benzene; m.p. 91–92°, $[\alpha]_D$ −2.0° (*c* 0.8, 9:1 $CHCl_3$–MeOH); R_F 0.48 in 9:1 $CHCl_3$–MeOH; n.m.r. data: δ_H (9:1 $CDCl_3$–CD_3OD) 5.744 (dt, 1 H, *J* 15.4 and 6.6 Hz, H-5), 5.478 (dd, 1 H, *J* 6.6 and 15.4 Hz, H-4), 4.170 (t, 1 H, *J* 5.1 Hz, H-3), 2.209 (t, 2 H, *J* 7.1 Hz, $COCH_2CH_2$), 2.049 (t, 1 H, *J* 6.6 Hz, H-6), 2.031 (t, 1 H, *J* 7.1 Hz, H-6′), and 0.882 (t, 6 H, *J* 7.1 Hz, CH_3CH_2); δ_C (9:1 $CDCl_3$–CD_3OD) 174.7 (C=O), 134.1 (C-4), 128.9 (C-5), 73.5 (C-3), 61.8 (C-1), and 54.8 (C-2).

Anal. Calc. for $C_{42}H_{83}NO_3$: C, 77.60; H, 12.87; N, 2.15. Found: C, 77.72; H, 12.71; N, 2.15.

1,3-Dihydroxy-2-(methylsulfonyloxy)-4-Z-D-threo-*octadec-4-ene* (**14**). — Compound **11** (1.0 g) was processed as described for **8**, to give **14** (870 mg, 93%); recrystallized from 1:7 Et_2O–hexane, m.p. 57–58°, $[\alpha]_D$ −12.5° (*c* 1.0); R_F 0.30 in 1:1 hexane–EtOAc; n.m.r. data: δ_H 5.704 (dt, 1 H, *J* 11.4 and 8.1 Hz, H-5), 5.408 (bt, 1 H, *J* 10.0 Hz, H-4), 4.691 (bt, 1 H, *J* 7.8 Hz, H-3), 4.598 (m, 1 H, H-2), 3.172 (s, 3 H, CH_3SO_2), and 0.881 (t, 3 H, *J* 6.4 Hz, CH_3CH_2).

Anal. Calc. for $C_{19}H_{38}O_5S$: C, 60.28; H, 10.12; S, 8.47. Found: C, 60.49; H, 10.18; S, 8.40.

*1,3-Bis(1-ethoxyethoxy)-2-methylsulfonyloxy)-4-*Z-D-threo-*octadec-4-ene* (**15**). — Compound **14** (4.6 g) was transformed, as decribed for compound **12**, into **15** (5.9 g, 94%); $[\alpha]_D$ −1.7° (*c* 1.1); R_F 0.45 in 7:3 hexane–EtOAc; n.m.r. data: δ_H 5.710 (ddt, 1 H, *J* 1.8, 11.3, and 6.7 Hz, H-5), 5.544 (ddt, 1 H, *J* 7.6, 11.3, and 1.8 Hz, H-4), 4.861 (q, 1 H, *J* 5.2 Hz, O_2CHCH_3), 4.693 (q, 1 H, *J* 5.5 Hz, O_2CHCH_3), 4.629 (dt, 1 H, *J* 7.6 and 1.8 Hz, H-3), 4.441 (q, 1 H, *J* 1.8 Hz, H-2), 4.361 (dd, 1 H, *J* 1.8 and 13.1 Hz, H-1), 3.979 (dd, 1 H, *J* 1.6 and 13.4 Hz, H-1'), 3.710 (q, 2 H, *J* 7.0 Hz, OCH_2CH_3), 3.646 (dq, 1 H, *J* 9.5 and 7.0 Hz, OCH_2CH_3), 3.488 (dq, 1 H, *J* 9.5 and 7.0 Hz, OCH_2CH_3), 3.102 (s, 3 H, CH_3SO_2), 1.398 (d, 3 H, *J* 5.2 Hz, $CHCH_3$), 1.313 (d, 3 H, *J* 5.2 Hz, $CHCH_3$), and 0.880 (t, 3 H, *J* 6.7 Hz, CH_3CH_2).

*2-Azido-1,3-bis(1-ethoxyethoxy)-4-*Z-D-erythro-*octadec-4-ene* (**20**). — Compound **15** (1.0 g) was processed as for compound **13**, to give **20** (819 mg, 90%); $[\alpha]_D$ −48.5° (*c* 1.1); R_F 0.69 and 0.64 in 4:1 hexane–EtOAc; ν_{max} 2100 cm^{-1} (N_3).

Anal. Calc. for $C_{26}H_{49}N_3O_4$: C, 66.77; H, 10.56; N, 8.98. Found: C, 66.46; H, 10.86; N, 8.71.

*2-Amino-1,3-bis(1-ethoxyethoxy)-4-*Z-D-erythro-*octadec-4-ene* (**21**). — A mixture of compound **20** (910 mg) and Lindlar catalyst (360 mg) in EtOH (60 mL) was stirred for 5 h at 20° under H_2, and then filtered through Celite. The filtrate was evaporated *in vacuo*, and chromatography of the residue over SiO_2 in 90:6:1 $CHCl_3$–MeOH–Et_3N gave **21** (822 mg, 96%); $[\alpha]_D$ −6.8° (*c* 1.1); R_F 0.77 in 9:1 $CHCl_3$–MeOH; ν_{max} 2900 cm^{-1} (NH_2); n.m.r. data: δ_C 99.9, 99.6, 98.8, and 96.7 (4 O_2CHCH_3).

Anal. Calc. for $C_{26}H_{53}NO_4$: C, 70.38; H, 12.04; N, 3.16. Found: C, 70.14; H, 12.20; N, 2.85.

*1,3-Bis(1-ethoxyethoxy)-2-tetracosanamido-4-*Z-D-erythro-*octadec-4-ene* (**22**). — Compound **21** (2.0 g) was converted into **22** (2.72 g, 78%) as described for the synthesis of compound **19**. Compound **22** was a white solid, precipitated from $CHCl_3$–MeOH; m.p. 77–78°, $[\alpha]_D$ −22.3° (*c* 1.0); R_F 0.39 in 4:1 hexane–EtOAc; ν_{max} 1540 and 1630 cm^{-1}.

Anal. Calc. for $C_{50}H_{99}NO_5$: C, 75.60; H, 12.56; N, 1.76. Found: C, 75.62; H, 12.60; N, 1.72.

N-*Tetracosanoyl-4-*Z-D-erythro-*sphingenine* (**3**). — Compound **22** (1.0 g) was converted into compound **3** (595 mg, 73%) as described for the preparation of compound **2**.

Compound **3** was recrystallized from benzene; m.p. 85–86°, $[\alpha]_D$ −9.0° (*c* 1.0, 9:1 $CHCl_3$–MeOH); R_F 0.48 in 9:1 $CHCl_3$–MeOH; n.m.r. data: δ_H (9:1 $CDCl_3$–CD_3OD), 6.954 (d, 1 H, *J* 7.8 Hz, N*H*), 5.572 (dt, 1 H, *J* 11.0 and 7.1 Hz, H-5), 5.425 (dd, 1 H, *J* 9.0 and 11.0 Hz, H-4), 4.509 (dd, 1 H, *J* 5.4 and 8.8 Hz, H-3), and 0.885 (t, 6 H, *J* 6.6 Hz, CH_3CH_2); δ_C 174.3 (C=O), 133.1 (C-4), 128.6 (C-5), 67.2 (C-3), 60.8 (C-1), and 54.8 (C-2).

Anal. Calc. for $C_{42}H_{83}NO_3$: C, 77.59; H, 12.87; N, 2.15. Found: C, 77.50; H, 12.77; N, 2.11.

2-N-*Tetracosanoyl-1*-O-*trityl-4*-E-D-erythro-*sphingenine* (**23**). — A mixture of compound **2** (325 mg, 0.5 mmol) and trityl chloride (278 mg, 1.0 mmol) in pyridine (5 mL) was stirred for 24 h at 20°, and then for 4 h at 55°, cooled, and evaporated *in vacuo*; a solution of the residue in $CHCl_3$ was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 4:1 hexane–EtOAc afforded **23** (297 mg, 67%); $[\alpha]_D$ −0.9° (*c* 1.0); R_F 0.34 in 4:1 hexane–EtOAc; n.m.r. data: δ_H 6.081 (d, 1 H, *J* 7.8 Hz, N*H*), 5.629 (ddt, 1 H, *J* 1.5, 15.4, and 6.6 Hz, H-5), 5.246 (dd, 1 H, *J* 6.3 and 15.6 Hz, H-4), 4.052 (m, 1 H, H-2), 3.405 (t, 1 H, *J* 8.3 Hz, H-3), 3.388 (dd, 1 H, *J* 3.7 and 9.8 Hz, H-1), 3.292 (dd, 1 H, *J* 3.9 and 9.8 Hz, H-1'), 2.200 (t, 2 H, *J* 7.6 Hz, $COCH_2CH_2$), 1.905 (m, 2 H, H-6,6'), 1.636 (m, 2 H, $COCH_2CH_2$), and 0.876 (t, 6 H, *J* 6.4 Hz, CH_3CH_2); δ_C 87.4 (CPh_3), 74.4 (C-3), 63.1 (C-1), and 53.4 (C-2).

Anal. Calc. for $C_{61}H_{97}NO_3$: C, 82.09; H, 10.96; N, 1.57. Found: C, 82.00; H, 11.17; N, 1.49.

3-O-*Benzoyl-2*-N-*tetracosanoyl-1*-O-*trityl-4*-E-D-erythro-*sphingenine* (**24**). — A mixture of compound **23** (224 mg, 250 μmol), benzoyl chloride (70 mg, 500 μmol), 4-dimethylaminopyridine (DMAP; 30 mg) in pyridine (2 mL) was stirred for 24 h at 20°, and then for 1 h at 55°. Processing and chromatography over a Lobar column (LiChroprep Si60 size A) in 4:1 hexane–EtOAc afforded **24** (183 mg, 88%) and recovered **23** (38 mg).

Compound **24**: $[\alpha]_D$ +5.9° (*c* 0.9); R_F 0.61 in 4:1 hexane–EtOAc; n.m.r. data: δ_H 5.879 (dt, 1 H, *J* 15.1 and 6.8 Hz, H-5), 5.709 (t, 1 H, *J* 7.6 Hz, H-3), 5.697 (d, 1 H, *J* 9.4 Hz, N*H*), 5.451 (dd, 1 H, *J* 7.6 and 15.4 Hz, H-4), 4.496 (ddd, 1 H, *J* 4.4, 6.9, and 10.0 Hz, H-2), 3.453 (dd, 1 H, *J* 3.4 and 9.5 Hz, H-1), 3.190 (dd, 1 H, *J* 4.2 and 9.5 Hz, H-1'), 2.107 (t, 2 H, *J* 7.6 Hz, $COCH_2CH_2$), and 1.992 (q, 2 H, *J* 7.1 Hz, H-6,6'); δ_C 86.9 (CPh_3), 74.4 (C-3), 61.8 (C-1), and 51.4 (C-2).

Anal. Calc. for $C_{68}H_{101}NO_4$: C, 81.96; H, 10.22; N, 1.41. Found: C, 82.01; H, 10.17; N, 1.36.

3-O-*Benzoyl-2*-N-*tetracosanoyl-4*-E-D-erythro-*sphingenine* (**25**). — A solution of compound **24** (163 mg, 164 μmol) and *p*-TsOH · H_2O (16 mg) in 2:1 CH_2Cl_2–MeOH (7.5 mL) was stirred for 24 h at 20°, and then evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 97:3 $CHCl_3$–MeOH afforded **25** (104 mg, 84%); $[\alpha]_D$ +16.5° (*c* 1.1); R_F 0.54 in 10:1 $CHCl_3$–MeOH; n.m.r. data: δ_H 6.107 (d, 1 H, *J* 8.8 Hz, N*H*), 5.846 (dt, 1 H, *J* 14.8 and 6.9 Hz, H-5), 5.609 (dd, 1 H, *J* 7.6 and 15.1 Hz, H-4), 5.533 (t, 1 H, *J* 7.6 Hz, H-3), 4.279 (m, 1 H, H-2), 3.740 (dd, 1 H, *J* 3.6 and 11.9 Hz, H-1), and 3.690 (dd, 1 H, *J* 3.2 and 12.2 Hz, H-1').

Anal. Calc. for $C_{49}H_{87}NO_4$: C, 78.03; H, 11.63; N, 1.86. Found: C, 77.85; H, 11.54; N, 1.84.

3-O-*Benzoyl-2*-N-*tetracosanoyl-4*-Z-D-erythro-*sphingenine* (**28**). — A mixture of compound **3** (650 mg) and trityl chloride (417 mg) in pyridine (10 mL) was stirred for 5 h at 55°. To this mixture was added benzoyl chloride (210 mg) and DMAP (122 mg), and the mixture was stirred for 18 h at 20° and evaporated *in vacuo*. A

solution of the residue in EtOAc (200 mL) was successively washed with aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. A solution of the residue and *p*-TsOH·H_2O (67 mg) in CH_2Cl_2 (10 mL) was stirred for 16 h at 20°, and evaporated *in vacuo*. Chromatography of the residue over SiO_2 in 15:1 $CHCl_3$–MeOH afforded **28** (398 mg, 54%); recrystallized from $CHCl_3$, it had m.p. 104.5–105°, $[\alpha]_D$ +32.9° (*c* 1.0); R_F 0.54 in 10:1 $CHCl_3$–MeOH; n.m.r. data: δ_H 6.066 (d, 1 H, *J* 9.0 Hz, N*H*), 5.885 (t, 1 H, *J* 9.0 Hz, H-3), 5.723 (dt, 1 H, *J* 11.0 and 7.8 Hz, H-5), 5.614 (dd, 1 H, *J* 9.0 and 10.8 Hz, H-4), 4.283 (m, 1 H, H-2), 3.754 (dt, 1 H, *J* 12.5 and 3.7 Hz, H-1), 3.667 (ddd, 1 H, *J* 3.0, 8.7, and 12.5 Hz, H-1′), and 2.993 (dd, 1 H, *J* 4.6 and 8.8 Hz, OH-1): δ_C 69.7 (C-3), 61.8 (C-1), and 53.7 (C-2).

Anal. Calc. for $C_{49}H_{87}NO_4$: C, 78.03; H, 11.62; N, 1.86. Found: C, 78.20; H, 11.68; N, 1.92.

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