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An Enantiospecific Synthesis of D-*erythro*-Sphingosine from D-Tartaric Acid#

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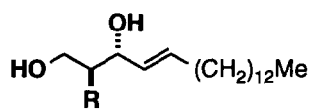
Abstract: An efficient enantiospecific synthesis of D-*erythro*-sphingosine (**1**) via azidosphingosine (**2**) is described, the absolute stereochemistry being derived from D-tartaric acid.

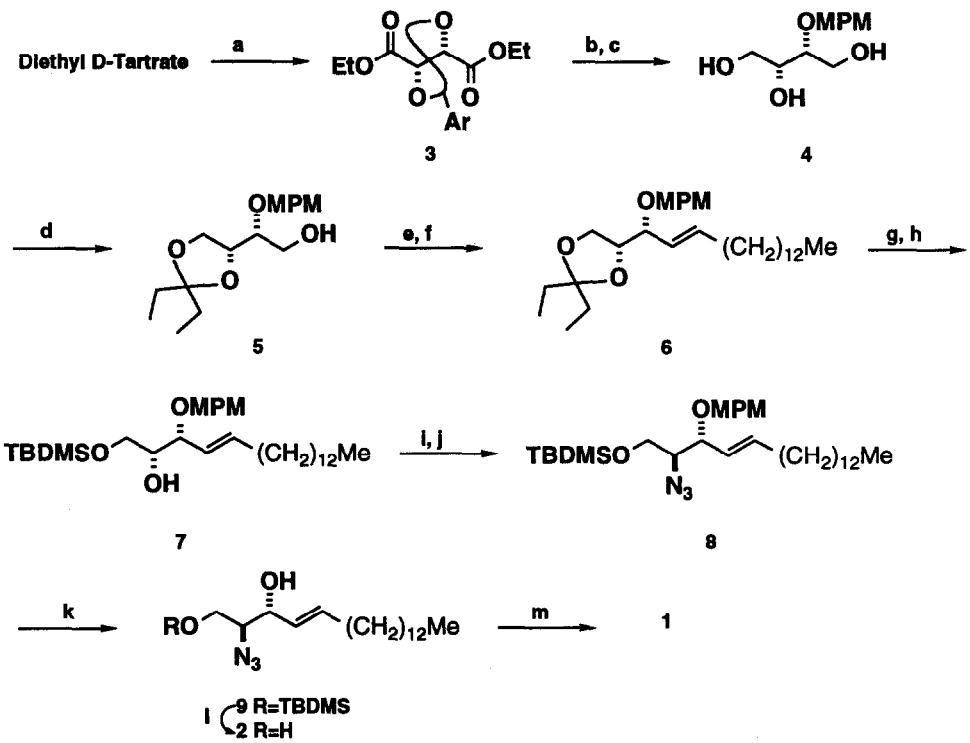
D-*erythro*-Sphingosine (**1**) is an important component of all sphingolipids of the glycosphingolipid and phosphosphingolipid types. Recently it has been shown that glycosphingosines, as well as sphingosine itself, are important in such diverse biological phenomena as cell-cell-recognition and signalling within and between cells[1]. Traditionally, glycosphingolipids have been prepared by glycosylation of a suitably protected ceramide derivative with an appropriate glycosyl donor and, thus, a large number of total syntheses of compound **1** that are compatible with this approach has been developed[2]. Generally, however, such glycosylation reactions suffer from inferior yields. In an attempt to overcome this problem Schmidt and co-workers[3] developed an alternative strategy to glycosphingolipids based on glycosylation of a 3-O-protected derivative of azidosphingosine (**2**), prepared from D-galactose, followed by reduction of the azide group and N-acylation. Herein we report an enantiospecific synthesis of azidosphingosine (**2**) from diethyl-D-tartrate. Since the azidoderivative **2** can be reduced to D-*erythro*-sphingosine (**1**) in high yield[3] this work also constitutes a formal total synthesis of the title compound. In addition, we also describe a new and easily accessible 3-O-protected azidosphingosine derivative (**10**) that should have potential as a coupling partner in glycosphingosine synthesis.



1 R=NH_2
2 R=N_3

The synthesis starts with conversion of diethyl-D-tartrate into the corresponding *p*-methoxybenzylidene acetal **3** in high yield (Scheme). Direct reduction of acetal **3** to the 2-O-MPM-protected D-threitol derivative **4**, as described for the corresponding benzylidene acetal[4], proved somewhat capricious and the product was always contaminated with various amounts of the corresponding primary protected MPM ether. After considerable experimentation it was found that the desired transformation could be accomplished *via* a two-

Dedicated to Professor Satoru Masamune on the occasion of his 65th birthday.

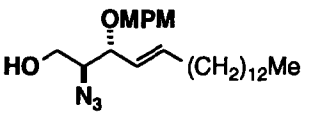


Scheme. Ar=*p*-$MeOC_6H_4$, MPM=*p*-$MeOC_6H_4CH_2$, TBDMS=^{t}BuMe$_2$Si; (a) *p*-$MeOC_6H_4CH(OMe)_2$, *p*-TsOH, DMF, 99% (b) $NaBH_4$, LiCl, THF, EtOH, 100% (c) BH_3·THF, THF, reflux, 94% (d) 3-pentanone, *p*-TsOH, THF, 89% (e) DMSO, $(COCl)_2$, Et_3N, -78°C (f) $Ph_3PCH_2(CH_2)_{12}MeBr$, PhLi, THF, toluene, -30°C, 1h, then MeOH, H_2O, 62% (two steps) (g) 2% aq. H_2SO_4, MeOH, 93% (h) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 91% (i) MsCl, pyridine, 0°C (j) NaN_3, 18-crown-6, DMF, 75°C, 87%, (k) DDQ, CH_2Cl_2, H_2O, 87%(l) Bu_4NF, THF, 94% (m) see ref. 3b.

step procedure involving (i) $LiBH_4$-reduction of the ester groups in **3** followed by (ii) BH_3·THF-induced reductive opening of the acetal moiety[5] to furnish compound **4** in excellent yield (94%, two steps). Selective protection of the 1,2-diol moiety in compound **4** was effected by exposure to 3-pentanone and *p*-TsOH (cat.) affording the five-membered ring acetal **5** as a single isomer in 89% yield[6]. Swern oxidation[7] of acetal **5** then gave the corresponding aldehyde that proved to be prone to epimerization[8] upon attempted purification. This problem was simply overcome by subjecting the crude aldehyde to a Schlosser modification of the Wittig olefination[3b, 9] furnishing alkene **6** as a single isomer in good yield (62%, two steps). It is noteworthy that attempts to accomplish this olefination by means of a Julia-Lythgoe coupling[10] afforded alkene **6** in low yield as a mixture of E/Z-isomers. The acetal moiety of **6** was removed by mild acidic hydrolysis[11] and selective protection of the resultant 1,2-diol at the primary hydroxyl group[12] then furnished silyl ether **7**. Mesylation of the secondary hydroxyl group in **7** followed by displacement with NaN_3 (cat. 18-crown-6) proceeded smoothly, furnishing the fully protected azidosphingosine derivative **8** in high yield (87%, two steps). Oxidative cleavage (DDQ) of the MPM-ether[13] gave alcohol **9** and, finally, dismantling the silyl ether gave D-*erythro*-azidosphingosine (**2**) with spectral and physical data in excellent accord with those reported previously[3]. It is noteworthy that the removal of the MPM protecting group in compound **8** proceeded

without any concomitant oxidation of the allylic alcohol, a serious problem that has been observed previously[14]. Since the azido group in **2** has been reduced to the corresponding amine[3], this work constitutes a formal total synthesis of D-*erythro*-sphingosine (**1**).

Altenatively, removal of the silyl group in **8** gave the 3-O-MPM protected sphingosine derivative **10** which should have potential as a coupling partner in glycosphingosine synthesis.



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In summary, a novel and enantiospecific synthesis of D-*erythro*-azidosphingosine (**2**) from diethyl D-tartrate has been accomplished in 12 steps and 31% overall yield. Since there is a current interest in using 3-O-protected azidosphingosine derivatives as coupling partners in glycosphingosine synthesis, we believe that compound **10** should be an interesting alternative to the previously described derivatives.

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EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as solvent. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks (ν, cm^{-1}) are listed. Optical rotations, $[\alpha]_D$, were measured on a Perkin Elmer 141 polarimeter at the sodium D line and at ambient temperatures. Flash chromatography employed Grace Amicon silica gel 60 (0.035-0.070 mm). Methylene chloride and dimethylformamide (DMF) was distilled from calcium hydride immediately before use; tetrahydrofuran (THF) and toluene were distilled from sodium-benzophenone ketyl. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven dried syringes.

(2S,3S)-2,3-O-(4-Methoxybenzylidene)-diethyl tartrate (3). A solution of diethyl-D-tartrate (7 ml, 41 mmol), 4-methoxybenzaldehyde dimethyl acetal (12 ml, 70 mmol) and *p*-toluenesulfonic acid (100 mg) in DMF (20 ml) was stirred under reduced pressure (10 mm Hg) at 50 °C for 5 h. The reaction mixture was then poured into Et_2O-saturated aq. $NaHCO_3$. The phases were separated and the organics washed with water, then 10% aq. $NaHSO_3$, and dried ($MgSO_4$). Removal of the solvents and flash-chromatography (heptane/EtOAc 9/1→1/1) afforded compound **3** (13.1g, 99%) as white crystals (mp 35,°C). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (2H, d, J=8.8), 6.90 (2H, d, J=8.8), 6.11 (1H, s), 4.92 (1H, d, J=4.0), 4.81 (1H, d, J=4.0), 4.32 (2H, q, J=7.0), 4.29 (2H, q, J=7.0), 3.81 (3H, s), 1.35 (3H, t, J=7.0), 1.32 (3H, t, J=7.0); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.2, 160.9, 128.8, 127.6, 113.8, 106.7, 77.5, 77.2, 62.0, 55.3, 14.2, 14.1; IR (KBr) 3080, 2910, 1750, 1610 cm^{-1}; $[\alpha]_D$=+23.6 (c 1.99, $CHCl_3$).

(2R,3R)-2-O-(4-Methoxybenzyl)-1,2,3,4-butanetetrol (4). A mixture of $NaBH_4$ (466 mg, 12.3 mmol) and LiCl (510 mg, 12.3 mmol) in THF (10 ml) was stirred vigorously for 10 min. and then compound **3** was added. After 30 min. EtOH (20 ml) was added and the resultant mixture was stirred at ambient temperature for 24 h. The reaction was quenched by addition of acetone (1 ml), then filtered through a pad of celite, and

the filter-cake was washed with EtOH (2 x10 ml). Removal of the solvents and flash-chromatography (EtOAc) yielded the corresponding 1,4-diol (370 mg, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$), 300 MHz) δ 7.41 (2H, d, J=8.8), 6.90 (2H, d, J=8.8), 6.11 (1H, s), 4.12 (2H, m), 3.81 (3H, s), 3.80 (4H, m), 2.51 (2H, m, 2x -OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 129.3, 128.0, 113.9, 103.8, 79.3, 78.4, 62.4, 62.3, 55.3; IR (film) 3400, 3000, 2930, 1610, 1590 cm^{-1}; $[\alpha]_D$=-10.9 (c 1.99, $CHCl_3$).
To a stirred solution of the 1,4-diol from above (2.0 g, 8.3 mmol) in THF (30 ml) at -20,°C was added BH_3·THF (30 ml, 30 mmol, 1M in THF) dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and then heated to refluxed. After 6 h the reaction mixture was cooled to 0,°C and MeOH (5 ml) was added carefully followed by removal of the solvents. The residue was triturated with MeOH (10 ml), the solvents stripped down and this procedure was repeated five times. Flash-chromatography (EtOAc→EtOAc/MeOH 19/1) gave MPM-ether **4** (1.90g, 94%) as white crystals (mp 54-55 °C). ^{1}H NMR ($CDCl_3$), 300 MHz) δ 7.26 (2H, d, J=8.9), 6.89 (2H, d, J=8.9), 4.64 (1H, d, J=11.5), 4.51 (1H, d, J=11.5), 3.89-3.61 (5H, m), 3.81(3H, s), 3.52 (1H, m), 2.97 (1H, br s, -OH), 2.73 (1H, br s, -OH), 2.56 (1H, br s, -OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 129.7, 129.6, 114.0, 78.8, 72.1, 71.7, 63.1, 60.8, 55.3; IR (KBr) 3430, 1960, 1610 cm^{-1}; $[\alpha]_D$=-29.6 (c 0.71, $CHCl_3$).

(2R,3R)-1,2-O-3-Pentylidene-3-(4-methoxybenzyl)-1,2,3,4-butanetetrol (5). To a stirred solution of compound **4** (955 mg, 3.95 mmol) in THF (10 ml) was added 3-pentanone (6 ml, 58 mmol) and *p*-toluenesulphonic acid (100 mg). The resultant mixture was stirred until TLC indicated that there was no starting material left and then $NaHCO_3$ (s) was added until neutral pH. Filtration, removal of the solvents and flash-chromatography (heptane/EtOAc 3/2) gave acetal **5** (1.09 g, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (2H, d, J=8.9 Hz), 6.88 (2H, d, J=8.9 Hz), 4.75 (1H, d, J=11.5 Hz), 4.62 (1H, d, J=11.5 Hz), 4.26 (1H, dt, J=8.1, 5.9 Hz), 4.02 (1H, dd, J=8.0, 6.2 Hz), 3.81 (3H, s), 3.71-3.63 (2H, m), 3.59-3.49 (2H, m), 1.71-1.62 (m, 4H), 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ159.4, 130.4, 129.6, 113.9, 113.4, 79.1, 77.3, 72.5, 66.2, 61.9, 55.3, 29.6, 29.2, 8.2, 8.1; IR (film) 3450, 2930, 1620 cm^{-1}; $[\alpha]_D$=+24.0 (c 1.48, $CHCl_3$); HRMS $[M]^+$ calcd for $C_{17}H_{26}O_5$: 310.1780, found: 310.1767.

(2R,3R,4E)-1,2-O-Pentylidene-3-(4-methoxybenzyl)-4-octadecen-1,2,3-triol (6). To a solution of DMSO (461 µl, 6.50 mmol) in CH_2Cl_2 (10 ml) at -78 °C was added oxalyl chloride (279 µl, 3.25 mmol) and the mixture was stirred for 15 min. before addition of alcohol **5** (0.672 g, 2.17 mmol) in CH_2Cl_2 (2 ml). After 2 h at -78 °C, triethylamine (1.22 ml, 8.67 mmol) was added. After an additional 30 min. the reaction was quenched by addition of phosphate buffer (pH 7), the phases were separated and the organics washed three times with water (3 x 5 ml). Drying ($MgSO_4$) and removal of the solvents gave the corresponding aldehyde as a yellow oil that was carried on directly to the next step.

To a stirred slurry of tetradecyltriphenylphosphonium bromide (1.75 g, 3.25 mmol) in toluene (60 ml) at 0 °C was added freshly prepared PhLi (3.14 ml, 6.50 mmol, 2.07 M in Et_2O) and the resultant solution was stirred at 0 °C for 20 min., then cooled to -30 °C followed by dropwise addition of the crude aldehyde from above in THF (3 ml). After stirring at -30 °C for 1 h MeOH (2ml) was added followed by H_2O (3ml). After allowing the reaction mixture to warm to room temperature the phases were separated, the aqueous phase extracted with CH_2Cl_2 (2 x 5 ml) and the combined organics dried ($MgSO_4$). Removal of the solvents and flash-chromatography (heptane/EtOAc 19/1) gave compound **6** (659 mg, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (2H, d, J=8.8 Hz), 6.88 (2H, d, 8.8 Hz), 5.69 (1H, dtr, J=15.5, 7.0 Hz), 5.27 (1H, dd, J=15.5, 8.0 Hz), 4.61 (1H, d, J=11.9 Hz), 4.40 (1H, d, J=11.9 Hz), 4.18 (1H, dt, J=7.5, 6.3 Hz), 3.86 (1H, dd, J=8.0, 6.3 Hz), 3.80 (3H, s), 3.74 (1H, t, J=7.5 Hz), 3.58 (1H, tr, J=7.5 Hz), 2.08 (2H, m) 1.69-1.52 (4H, m), 1.40-1.12 (22H, m), 0.96-0.77 (9H, m); IR (film) 3045, 2920, 1620 cm^{-1}; $[\alpha]_D$=-22.1 (c 0.53, $CHCl_3$); HRMS $[M+NH_4]^+$ calcd for $C_{31}H_{56}O_4N$: 506.4209, found: 506.4209.

(2R,3R,4E)-1-tert-Butyldimetylsilyloxy-3-(4-methoxybenzyl)-4-octadecen-2,3-diol (7). To a solution of acetal **6** (198 mg, 0.405 mmol) in MeOH (4 ml) was added 2% aq. H_2SO_4 (5 drops) and the resultant mixture was stirred at ambient temperature until TLC indicated that all the starting material was consumed. Then solid K_2CO_3 (200 mg) was added, the mixture was filtered and the solvents removed. Flash-chromatography (hexane/EtOAc 9/1→3/7) gave the corresponding 1,2-diol (158 mg, 93%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (2H, d, J=8.8 Hz), 6.88 (2H, d, 8.8 Hz), 5.78 (1H, dt, J=15.5, 6.7 Hz), 5.35 (1H, dd, J=15.5, 8.5 Hz), 4.56 (1H, d, J=11.0 Hz), 4.26 (1H, d, J=11.0 Hz), 3.81 (3H, s), 3.80-3.49 (4H, m), 2.95 (1H, br s), 2.28 (1H, br s), 2.10 (2H, m), 1.45-1.12 (22H, m) 0.88 (3H, m); IR (film) 3400, 3050, 2920, 1610 cm^{-1}; $[\alpha]_D$=-24.2 (c 1.69, $CHCl_3$).
To a solution of the 1,2-diol from above (154 mg, 0.367 mmol) in CH_2Cl_2 (5 ml) was added tert-butyldimethylsilyl chloride (61 mg, 0.404 mmol), triethylamine (153 µl, 1.101 mmol) and DMAP (cat.). The mixture was stirred overnight, then poured into water-methylene chloride and the phases separated. The aq. phase was extracted once with methylene chloride and the combined organics dried ($MgSO_4$) and stripped down. Flash-chromatography (hexane/EtOAc 20/1→3/1) yielded compound **7** (179 mg, 91%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 5.72 (1H, dt, J=15.5, 6.7 Hz), 5.40 (1H, dd, J=15.5, 8.5 Hz), 4.66 (1H, d, J=11.0 Hz) 4.29 (1H, d, J=11.0 Hz), 3.80 (3H, s), 3.78-3.52 (4H, m), 2.55 (1H, br s), 2.10 (2H, m), 1.47-1.13 (22H, m), 0.88 (12H, m), 0.10 (6H, s); IR (film) 3500, 3050, 2950, 1610, 1590 cm^{-1}; $[\alpha]_D$=-17.0 (c 1.71, $CHCl_3$).

(2S,3R,4E)-2-Azido-1-tert-butyldimetylsilyloxy-3-(4-methoxybenzyl)-4-octadecen-3-ol (8). To a solution of alcohol **7** (170 mg, 0.318 mmol) in CH_2Cl_2 (5 ml) at -20 °C was added methanesulfonyl chloride (37 µl, 0.478 mmol), triethylamine (88 µl, 0.637 mmol) and DMAP (cat.). The mixture was warmed to 0°C and stirred overnight, then poured into Et_2O-water and the phases separated. The aq. phase was extracted once with Et_2O and the combined organicis washed with brine, dried ($MgSO_4$) and stripped down to yield a slighty yellow oil that was processed in the next step.
To a solution of the crude mesylate in DMF (3 ml) was added sodium azide (620 mg, 9.54 mmol) and 18-crown-6 (cat.) and the mixture was warmed to 75 °C. After 20 h the reaction mixture was poured into Et_2O-water and the phases were separated. The aq. phase was extracted thrice with Et_2O, the combined organics washed with brine, dried ($MgSO_4$) followed by removal of the solvents. Flash-chromatography (hexane/EtOAc 99/1→9/1) gave azide **8** (155 mg, 87%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.5 Hz), 5.74 (1H, dt, J=15.5, 6.7 Hz), 5.41 (1H, dd, J=15.5, 8.5 Hz), 4.54 (1H, d, J=11.4 Hz), 4.27 (1H, d, J=11.4 Hz), 3.85 (1H, dd, J=8.5, 6.1 Hz), 3.80 (3H, s), 3.77-3.66 (2H, m), 3.46-3.39 (1H, m), 2.09 (2H, m), 1.31-1.12 (22H, m), 0.89-0.83 (12H, m), 0.08 (3H, s), 0.06 (3H, s); IR (film) 2920, 2090, 1610 cm^{-1}; $[\alpha]_D$=-29.5 (c 0.607, $CHCl_3$); HRMS $[M+NH_4]^+$ calcd for $C_{32}H_{61}N_4O_3Si$: 577.4513, found: 577.4522.

(2S,3R,4E)-2-Azido-1-tert-butyldimetylsilyloxy-4-octadecen-3-ol (9). To a solution of compound **8** (50 mg, 0.089 mmol) in CH_2Cl_2 (2 ml) at 0 °C was added water (2 drops) and DDQ (26 mg, 0.116 mmol). The mixture was stirred at 0 °C for 2 h and then sat. $NaHCO_3$ was added, the phases were separated and the aq. phase extracted twice with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$) and the solvent stipped down. Flash-chromatography (hexane/EtOAc 9/1→4/1) gave compound **9** (34 mg, 87%) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78 (1H, dt, J=15.5, 7.5 Hz), 5.49 (1H, dd, J=15.5, 8.0 Hz), 4.22 (1H, m), 3.81 (2H, m), 3.42 (1H, m), 2.33 (1H, d, J=4.9 Hz, -OH), 2.06 (2H, m), 1.43-1.17 (22H, m), 0.97-0.82 (12H, m), 0.09 (6H, s); IR (film) 3410, 2920, 2095 cm^{-1}; $[\alpha]_D$= -3.10 (c 0.607, $CHCl_3$).

(2S,3R,4E)-2-Azido-4-octadecen-1,3-diol (2). To a stirred solution of silyl ether **9** (31 mg, 0.071 mmol) in THF was added tetrabutylammonium fluoride trihydrate (29 mg, 0.092 mmol). After 1 h the reaction mixture

was poured into Et_2O-water, the phases separated and the aq. phase extracted with Et_2O (2 x 5 ml). The combined organics were washed with brine, dried ($MgSO_4$) and concentrated. Flash-chromatography (hexane/EtOAc 3/1→3/2) gave compound **2** (21.5 mg, 94%) as a low-melting solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.83 (1H, dt, J=15.5, 6.1 Hz), 5.54 (1H, dd, J=15.5, 7.2 Hz), 4.42 (1H, br m), 3.77 (2H, br m), 3.51 (1H, m), 2.13-1.96 (4H, m, $CHCH_2$ and 2 x -OH), 1.43-1.05 (22H, m), 0.87 (3H, t, J=6.9 Hz); IR (film) 34000, 2920, 2100, 1610 cm^{-1}; $[\alpha]_D$=-32.1 (c 3.47, $CHCl_3$) [lit. [3b] $[\alpha]_D$=-32.9 (c 4, $CHCl_3$)].

(2S,3R,4E)-2-Azido-3-(4-methoxybenzyl)-4-octadecen-1,3-diol (10). The silyl ether was removed as described above using tetrabutylammonium fluoride trihydrate. From 102 mg (0.182 mmol) of silyl ether **8** there was obtained 76 mg (94%) of alcohol **10**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (2H, d, J=8.5 Hz), 6.88 (2H, d, 8.5 Hz), 5.79 (1H, dt, J=15.5, 6.5 Hz), 5.44 (1H, dd, J=15.5, 8.3 Hz), 4.56 (1H, d, J=11.4 Hz), 4.29 (1H, d, J=11.4 Hz), 3.88 (1H, dd, J=8.3, 5.9 Hz), 3.80 (3H, s), 3.72 (2H, m), 3.46 (1H, m), 2.16-2.07 (3H, m), 1.44-1.13 (22H, m), 0.88 (3H, t, J=7.0 Hz); IR (film) 3400, 2920, 2095, 1610 cm^{-1}; $[\alpha]_D$=-65.4 (c 2.08, $CHCl_3$); HRMS $[M+NH_4]^+$ calcd for $C_{26}H_{47}N_4O_3$: 463.3648, found: 463.3643.

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