Stereoselective synthesis of *N,O,O,O*-tetraacetyl-D-*ribo*-phytosphingosine, *N,O,O*-triacetyl-D-*erythro*-sphingosine and *N,O,O*-triacetyl sphingonine from a common chiral intermediate derived from D-mannitol

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Abstract

An efficient protocol for the stereoselective synthesis of tetraacetyl-D-*ribo*-phytosphingosine, triacetyl-D-*erythro*-sphingosine and triacetyl sphinganine has been devised from a common chiral intermediate derived from commercially available D-mannitol. The key steps involved are Sharpless epoxidation, Miyashita C(2) selective *endo* mode azide opening of 2,3-epoxy alcohol, and selective *E*-Wittig olefination.

Keywords: Sphingolipids, D-mannitol, epoxidation, regioselective, Wittig olefination

Introduction

Sphingoid bases are long-chain aliphatic compounds typically possessing 2-amino-1,3-diol and 2-amino-1,3,4-triol functionality (Figure 1).[1] They are the structural backbone of sphingolipids (cerebrosides, sphingomyelins, gangliosides and ceramides), which are an important membrane constituents of eukaryotic cells, plasma membranes and intracellular organelles, and responsible for many physiological processes including cell growth, adhesion, differentiation and also play a prominent role in cell signaling.[2] Apart from this, many sphingolipids from marine organisms display pronounced antifungal, antitumor, antiviral, immunostimulatory, neuritogentic, antidiabetic, cytotoxic, and protein kinase inhibitor activities.[3]

Among the naturally occurring sphingoid bases D-*erythro*-sphingosine **2** is the first isolated compound from human brain by Thudichum in 1884.[4] In addition to **2**, several sphingoid bases were isolated, among them C_{18}-phytosphingosines are the more biologically active sphingoid bases have that been isolated from plants, yeast, fungi, marine organisms[5] and mammalian tissues[6] such as brain, hair, intestine, uterus, liver, skin and blood plasma. D-*ribo*-

Phytosphingosine (**1**) is the most frequently occurring phytosphingosine in nature and has been shown to play an important role as a potential heat stress signal in yeast cells[7] and as a cytotoxic agent against human leukemic cell lines[8] Furthermore, D-*erythro*-sphingosine[9] and D-*ribo*-phytosphingosines[10] are essential part of more complex bioactive molecules such as GalCer (**4**) and KRN7000 (**5**) respectively.

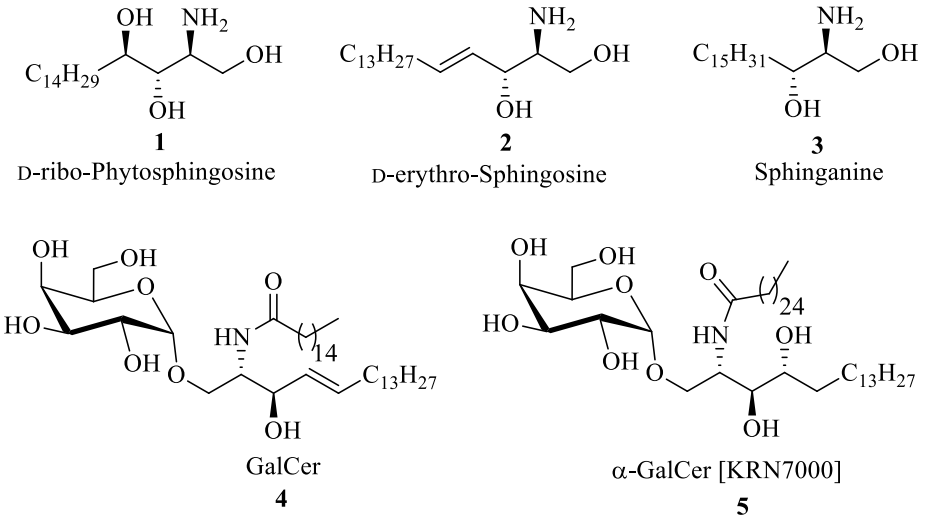
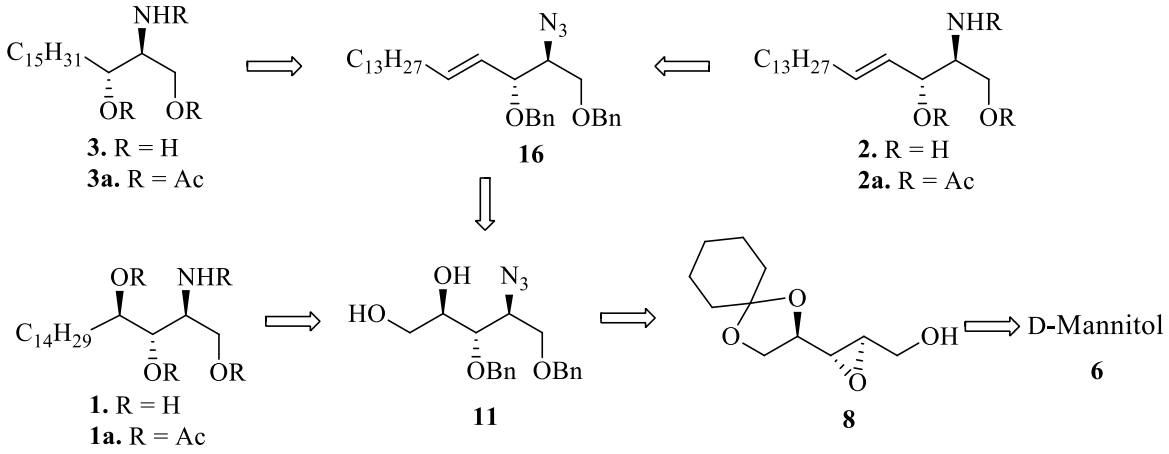


Figure 1. Sphingolipids and glycolipids.

Sphingolipids are available only in limited amounts from natural sources, and their isolation and purification from natural sources is expensive and difficult task. Because of the interesting biological properties of sphingolipids, there is growing interest in developing efficient methods for their synthesis.[1,11] Although, many methods for the synthesis of sphingolipids have been reported, a simple and straight forward synthesis from inexpensive starting material with high level of stereocontrol is always in demand. In continuation of our efforts on natural product synthesis[12] and development of new methodologies[13] we herein, disclose a simple and convenient new approach for the asymmetric synthesis of title compounds **1**, **2**, and **3** from D-mannitol (**6**), involving the steps with high stereocontrol approach.

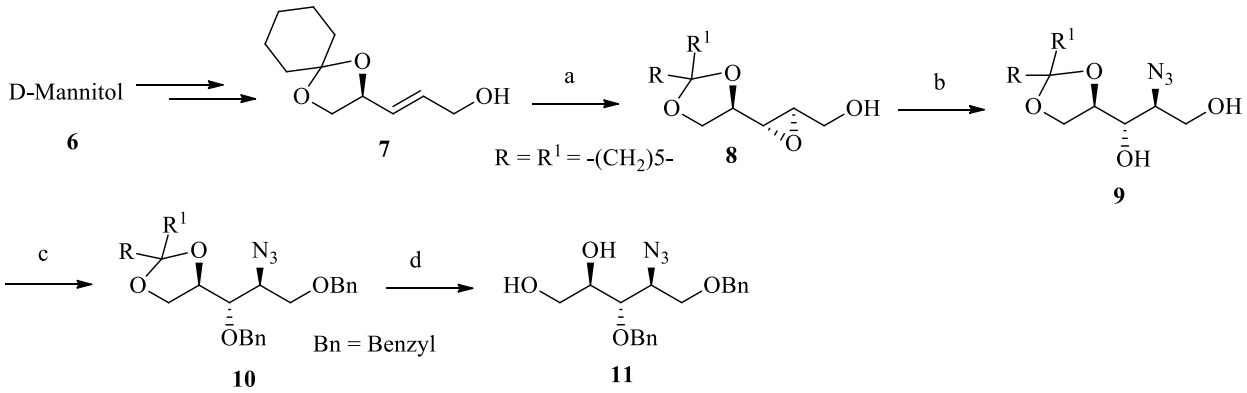
Results and Discussion

Our retrosynthetic analysis for target compounds **1, 2,** and **3** is depicted in Scheme 1. Retrosynthetically, it was envisioned that, all the three titled sphingolipids **1, 2** and **3** to be obtained from a common intermediate **11,** could be acquired by regioselective epoxide opening with azide nucleophile followed by protection of 1,3-diol as their benzylethers and consequent deprotection of cyclohexylidene group of epoxy alcohol **8** derived from the D-mannitol (**6**).



Scheme 1. Retrosynthetic plan for the synthesis of targeted sphingolipids.

According to the above retrosynthetic analysis, the first target is to be synthesis of diastereomerically pure azido diol intermediate **11** (Scheme 2). Towards that object, the allylic alcohol **7**, which was easily prepared from D-mannitol according to known procedures,[14] was subjected to Sharpless catalytic asymmetric epoxidation[15] using diethyl D-tartrate, $Ti(O^iPr)_4$ and cumene hydroperoxide to afford epoxy alcohol **8** in 95% yield with high diastereoselectivity, (98% *de*, determined by NMR and GC-MS analysis).



(a) Diethyl D-tartrate, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, -20 °C, 72 h, 95%, 98% *de*; (b) $(MeO)_3B$, NaN_3, DMF, 50 °C, 8 h, then $NaIO_4$ treatment 96%; (c) Benzyl bromide, NaH, THF, *n*-Bu_4NI (TBAI), 0 °C-rt, overnight, 92%; (d) 10% HCl, CH_3CN, rt, 4 h, 93%.

Scheme 2. Synthesis of key intermediate **11.**

The next crucial step in our strategy is C(2) regioselective opening of the epoxy alcohol **8** by azide nucleophile. This was accomplished by using NaN_3-$(CH_3O)_3B$ system developed by Miyashita and co-workers.[16] This reaction proceeds *via* an intramolecular boron chelate through

a novel *endo-mode* epoxide opening with extremely high C(2) selectivity. The same thing was observed in our case. Under Miyashita conditions, the azide nucleophile selectively opening epoxy alcohol **8** at C(2) rather than C(3) position, which is sterically hindered by neighbouring protected *vicinal* diol moiety (>95% *de*, based on crude ^{1}H-NMR analysis). Furthermore, we have treated the crude product with $NaIO_4$ to remove the C(3) opened compound easily in the form of aldehyde by the column chromatography. Gratifyingly, the desired azido diol **9** was isolated in 96% yield, and as a single diastereomer after purification. Benzyl ether protection of azido diol **9** followed by selective deprotection of cyclohexylidene group by treating with 10% HCl in CH_3CN gave the desired intermediate 4-azido 1,2-diol **11** in 93% yield.

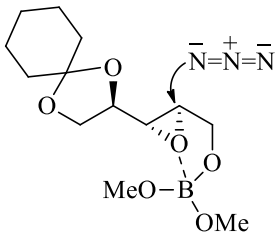
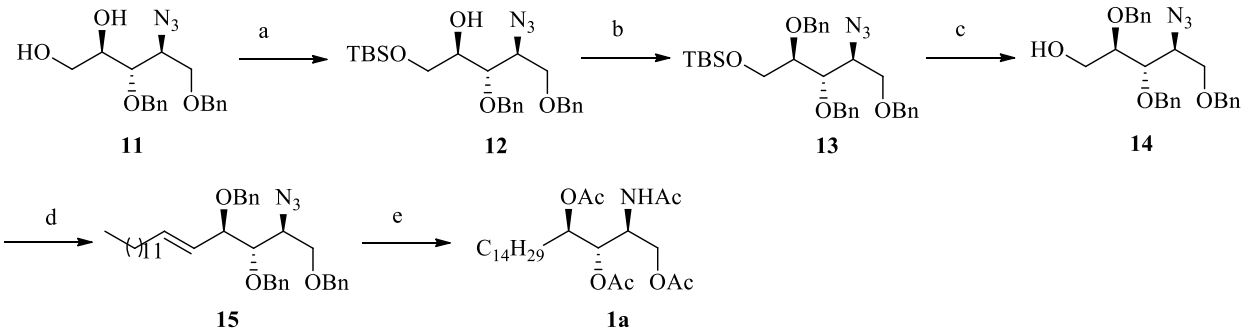


Figure 2. C(2) Selective azide nucleophile opening of epoxy alcohol borate complex.

After successful synthesis of the key intermediate **11,** next we turned our attention towards the synthesis of D-*ribo*-phytosphingosine (**1**) from intermediate **11** (Scheme 3). Toward this objective, the primary alcohol of **11** was selectively protected as TBS ether and the secondary alcohol group was protected as benzyl ether to afford compound **13**. At this juncture, it becomes necessary to free the compound **13** from the TBS group and it was removed by stirring a solution of **13** in dry THF in the presence of *n*-Bu_4NF (TBAF), gave the compound **14** in 96% yield. The primary alcohol functionality of **14** was converted to the corresponding aldehyde moiety using 2-Iodoxybenzoic acid (IBX), and the obtained aldehyde was rather labile to column purification and therefore it was quickly subjected to Wittig olefination[17] using *n*-$C_{13}H_{27}P^+Ph_3Br^-$ ylide in presence of *n*-BuLi to afford alkene **15** as a mixture of *trans* and *cis* isomers (*E/Z*, 19:1; determined by ^{1}H-NMR spectra) in 81% yield. The geometrical isomer ratio is no relevance to the planned synthetic sequence as the double bond will be reduced in the next step.

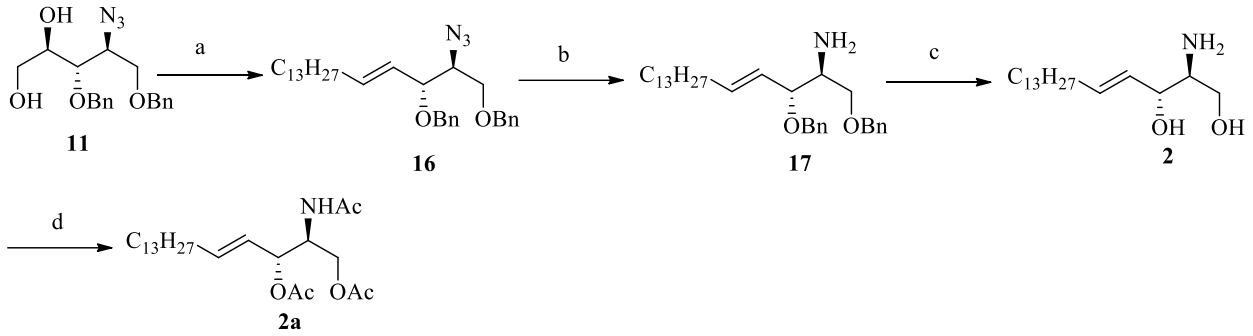
Having the desired compound at the penultimate stage, attention was focused on the final deprotection and reduction step. One-pot reduction of azide group, saturation of double bond, and deprotection of the benzyl ethers was carried out by hydrogenation using $Pd(OH)_2/C$ on **15** affording the crude residue of target molecule **1** which was difficult to purify by column chromatography and was therefore converted it into its acetyl derivative using Ac_2O and pyridine to afford tetraacetyl D-*ribo*-phytosphingosine (**1a**) in good yield. The analytical and spectroscopic data of this compound is in good agreement with the reported data.[18]



(a) TBSCl (TBS = (*t*-Bu)Me_2Si), imidazole, 4-(dimethylamino)-pyridine (DMAP), CH_2Cl_2, 0 ^oC- rt, overnight, 95%. (b) Benzyl bromide, NaH, THF, *n*-Bu_4NI (TBAI), 0 ^oC-rt, 16 h, 93%. (c). *n*-Bu_4NF (TBAF), THF, rt, 4 h, 96%. (d) i. 2-Iodoxybenzoic acid (IBX), DMSO, CH_3CN, rt, 24 h. ii. *n*-$C_{13}H_{27}P^+Ph_3Br^-$, *n*-BuLi, THF, -78 ^oC-rt, 14 h, 81%. (e) i. $Pd(OH)_2/C/H_2$ (ballons), EtOAc:MeOH (1:1), rt; ii. Pyridine, Ac_2O, DMAP, rt, 24 h, 80%.

Scheme 3. Synthesis of tetraacetyl D-*ribo*-phytosphingosine (**1a**).

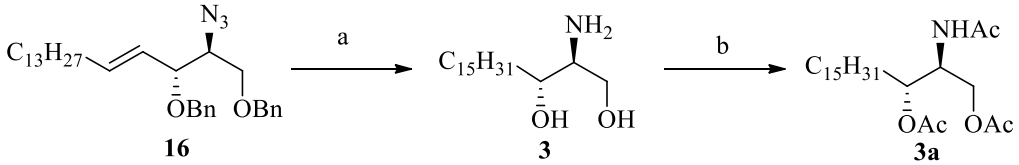
After successful synthesis of compound **1**, then we turned our attention towards the synthesis of compounds **2** and **3.** As per the Scheme 4, oxidative cleavage of the diol **11** with $NaIO_4$ yielded corresponding aldehyde and without column purification it was subjected to the Wittig olefination[17] by using *n*-$C_{14}H_{29}P^+Ph_3Br^-$ ylide in the presence *n*-BuLi to afford alkene **16** as a inseparable mixture of *trans and cis* isomers (*E/Z*, 20:1, determined by ^{1}H-NMR spectra). The selective reduction of azide group of the compound **16** with Lindlar's catalyst[19] under hydrogen atmosphere provided the amine **17** in 83% yield. Deprotection of the benzyl groups in **17** by means of *Birch* reduction[20a] gave the title compound D-*erythro*-sphingosine (**2**). For analytical purpose, compound **2** was acetylated with acetic anhydride in presence of pyridine and catalytic amount of DMAP to obtain triacetyl D-*erythro*-sphingosine (**2a**) in good yield. The analytical and spectroscopic data of both **2** and **2a** were in good agreement with the reported data.[9a-c,18b, 20]



(a) i. $NaIO_4$, aq. CH_3CN (60%), rt, 30 min; ii. *n*-$C_{14}H_{29}P^+Ph_3Br^-$, *n*-BuLi, THF, -78 °C- rt, 14 h, 85%. (b) $Pd/CaCO_3/H_2$ (ballons), EtOAc, rt, 8 h, 83%. (c) Na/NH_3, THF, -78 °C, 45 min, 80%. (d) Ac_2O, Pyridine, rt, DMAP, 16 h, 85%.

Scheme 4. Synthesis of triacetyl D-*erythro*-sphingosine (**2a**).

The third desired sphingoid base, sphinganine (**3**) was synthesized (Scheme 5) from compound **16** in a single step through the one-pot reduction of azide, hydrogenation of double bond, and deprotection of the benzyl ethers by catalytic hydrogenation using Pearlman's catalyst. For analytical reasons, compound **3** was acetylated with acetic anhydride in presence of pyridine and DMAP (catalytic) to obtain *N,O,O*-triacetyl sphinganine (**3a**) in good yield. The analytical and spectroscopic data of **3** and **3a** were in good agreement with the reported data of the respective natural product.[21]



(a) $Pd(OH)_2/C/H_2$ (balloons), EtOAc:MeOH (1:1), rt, 48 h, 87%. (b) Ac_2O, Pyridine, DMAP, rt, 16 h, 81%.

Scheme 5. Synthesis of triacetyl sphinganine **3a**.

Conclusions

In conclusion, a stereoselective total synthesis of *N,O,O,O*-tetraacetyl D-*ribo*-phytosphingosine, *N,O,O*-triacetyl D-*erythro*-sphingosine and *N,O,O*-triacetyl sphinganine were accomplished by versatile strategy from a common intermediate derived from D-mannitol. A combination of

Sharpless epoxidation, Miyashita C(2) selective endo mode azide opening of epoxy alcohol, and preferential *E*-Wittig olefination were effectively utilized in accomplishing the synthesis. We believed that the key intermediate reported in this paper serves as a good synthon for making of other natural products.

Experimental Section

General. The solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from Aldrich and Lancaster, and were used without further purification unless otherwise stated. All moistrure-sensitive reactions were carried out under N_2 atmosphere. Column chromatography: silica gel (SiO_2; Acme's 60-120 mesh). Optical rotations: Perkin-Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 ^oC, IR spectra: Perkin-Elmer IR-683 spectrophotometer. NMR: Recorded on Varian Gemini 200 or Bruker Avance 300 or Varian Unity 400 MHz spectrometer depends on their availability, using TMS as an internal standard for ^1H NMR, and $CDCl_3$ for ^{13}C NMR (chemical shift values in δ, J in Hz). MS: Recorded either on Thermo-Finnigan MAT1020B or Micromass 7070H spectrometer operating at 70 eV using direct inlet system. All high resolution mass spectra (HRMS) were recorded on QSTAR XL hybrid MS/MS system equipped with an ESI source. GC-MS were recorded on Agilent 6890 series GC-MS system, GC (Agilent Technologies, Palo Alto, CA) equipped with a model 5973N mass selective detector and a HP-5MS capillary column (5% phenyl, 95% PDMS, 30 m x 0.25 mm i.d. x 0.25 μm film thickness).

(2*S*,3*S*,4*R*)-2,3-Epoxy-4,5-(cyclohexylidenedioxy)-pentan-1-ol (8). To activated 4Å molecular sieves powder (2.8 g, 35% (*wt/wt*)) in dry CH_2Cl_2 (175 mL) under N_2 were sequentially added $Ti(O^iPr)_4$ (0.95 mL, 3.2 mmol) and diethyl D-tartrate (0.67 mL, 4 mmol) at -20 ^oC, and the mixture was stirred for 30 min. A solution of **7** (8 g, 40.4 mmol) in CH_2Cl_2 (50 mL) was added, and the resulting mixture was stirred at -20 ^oC for 30 min. Cumene hydroperoxide (11.8 mL, 80.8 mmol) was added dropwise to the reaction mixture, and the resulting solution was stored at -20 ^oC in freezer for 72 h. Aq. tartaric acid (10%, 40 mL) was added slowly at -20 ^oC, and the whole mass was allowed to warm to r.t. After being stirred for 1 h, the reaction mixture was filtered, and the filtrate was extracted with CH_2Cl_2 (50 mL). The combined org. layers were treated with a pre-cooled (0^o C) soln. of 25 mL of 30% NaOH (*w/v*) in brine at 0 ^oC [25 mL of 30% NaOH soln. in brine are prepared by adding 1.25 g of NaCl to a soln. of 7.5 g of NaOH in 22.5 mL of H_2O] and stirred for 20 min. The two layers were separated and the aq. layer was extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with brine, dried (anh. Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 1:4) to give **8** as colorless oil (8.2 g, 95%, 98% *de*). $[\alpha]_D^{25}$ +27.5 (c 1.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 4.09 (dt, 1H, *J* 3.2, 8.6 Hz), 3.93-3.80 (m, 3H), 3.64 (brd, 1H, *J* 12.4 Hz), 3.04 (dd, 1H, *J* 2.2, 3.9 Hz), 3.01 (dd, 1H, *J* 2.0, 5.8 Hz),

2.34 (brs, 1H), 1.62-1.51 (m, 8H), 1.41 (brs, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 110.5, 74.8, 66.4, 61.0, 57.2, 55.4, 36.0, 34.6, 24.9, 23.8, 23.7. IR (neat) (ν_{max}, cm^{-1}): 3444, 2935, 2860, 1449, 1367, 1162, 1098. ESI-MS: *m/z* 237 $[M+Na]^+$. HRMS calculated for $C_{11}H_{18}O_4Na$: 237.1102 $[M+Na]^+$, found: 237.1100. GC-MS data: The inlet and GC-MS interface temperatures were kept at 280 ºC, Helium was used as the carrier gas at flow rate of 1 mL/min., and the sample was injected in split mode 1:10 ratio. Oven program was 80 ºC for 2 min; raised temperature 10 ºC/min to 280 ºC; hold 5 min; a single peak was found at the retention time of 13.77 min with mass m/z 214 $[M+H]^+$

(2*S*,3*S*,4*R*)-2-Azido-4,5-(cyclohexylidenedioxy)-pentane-1,3-diol (9). A mixture of epoxy alcohol **8** (7.92 g, 37 mmol), $B(OMe)_3$ (6.3 mL, 55.5 mmol), and NaN_3 (4.81 g, 74 mmol) in DMF (60 mL) under N_2 atmosphere were stirred at 50 ºC for 8 h. After cooling to 0 ºC, saturated $NaHCO_3$ (50 mL) was added, and the mixture was stirred for 30 min at the same temp. The mixture was separated, and the aq. layer was extracted with Et_2O (3x75 mL). The combined organic layers were successively washed with H_2O (25 mL), brine (45 mL), and dried (Na_2SO_4). Concentration under reduced pressure gave oily residue, was dissolved in CH_3CN (60 mL) and treated with $NaIO_4$ (3.96 g, 18.5 mmol) dissolved in 40 mL water at r.t. for 30 min. and filtered. The filtrate was mixed with H_2O (10 mL) and extracted with EtOAc (3x70 mL). The combined org. layers were washed with H_2O (20 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 1:4) to afford the azido diol **9** as colorless oil (9.12 g, 96%). $[\alpha]_D^{25}$ +26.7 (c 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.18 (dd, 1H, *J* 6.0, 12.0 Hz), 4.09 (dd, 1H, *J* 6.0, 8.3 Hz), 3.96-3.91 (m, 3H), 3.83 (dd, 1H, *J* 5.2, 9.8 Hz) 3.61 (dd, 1H, *J* 4.5, 9.8 Hz), 2.77 (brd, 1H, *J* 4.5 Hz), 2.54 (brs, 1H), 1.60-1.55 (m, 8H), 1.41 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 110.2, 74.9, 72.5, 65.7, 63.9, 62.3, 36.2, 34.5, 24.9, 23.9, 23.6. IR (neat) (ν_{max}, cm^{-1}) :3405, 2937, 2857, 2105, 1447, 1275, 1101. ESI-MS: *m/z* 280 $[M+Na]^+$. HRMS calculated for $C_{11}H_{19}N_3O_4Na$: 280.1273 $[M+Na]^+$, found: 280.1271.

(2*S*,3*S*,4*R*)-2-Azido-4,5-(cyclohexylidenedioxy)-1,3-(dibenzyloxy)-pentane (10). To a well stirred soln. of NaH (60% dispersion in mineral oil, 2.4 g, 60 mmol) in dry THF (75 mL) under nitrogen was added azido diol **9** (5.14 g, 20 mmol) dissolved in THF (30 mL) *via* syringe very slowly at 0 ºC and allowed to stir at same temp. for 20 min. TBAI (50 mg, cat.) followed by benzyl bromide (6 mL, 50 mmol) were added at 0 ºC and allowed to stir at r.t. for overnight. The reaction mixture was quenched by addition of H_2O until clear soln. results. THF was removed under reduced pressure, the residue was diluted with H_2O (20 mL) and extracted with Et_2O (3x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; hexane 100%, followed by EtOAc/hexane, 1:19) to give **10** as a colorless oil (8.04 g, 92 %). $[\alpha]_D^{25}$ +26.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.30-7.23 (m, 10H), 4.69 (dd, 2H, *J* 11.3, 22.3 Hz), 4.57 (dd, 2H, *J* 12.0, 13.9 Hz), 4.15 (dd, 1H, *J* 6.2, 12.6 Hz), 4.00 (dd, 1H, *J* 6.4, 8.3 Hz), 3.86-3.75 (m, 2H), 3.72-3.59 (m, 3H), 1.56-1.53 (m, 8H), 1.38 (brs, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.7, 137.6, 128.4, 127.9, 127.7, 127.6, 109.8, 79.3, 74.6, 73.8, 73.3, 69.6, 66.2, 62.5, 36.2, 34.7, 25.1,

23.9, 23.7. IR (neat) (ν_{max}, cm^{-1}): 2936, 2861, 2097, 1451, 1275, 1101. ESI-MS: *m/z* 460 $[M+Na]^+$. HRMS calculated for $C_{25}H_{31}N_3O_4Na$: 460.2212 $[M+Na]^+$, found: 460.2222.

(2*R*,3*S*,4*S*)-4-Azido-3,5-(dibenzyloxy)-pentane-1,2-diol (11). To a cooled (0 ºC) solution of compound **10 (**7 g, 16 mmol**)** in CH_3CN (85 mL) was added 10% HCl (85 mL) and allowed to stir at r.t. for 4 h. The reaction was quenched with solid $NaHCO_3$ until neutralized at r.t. The CH_3CN was removed under *vacuum*, then it was diluted with EtOAc (70 mL) and after separation of the layers, the aq. layer was further extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 1:4) to give **11** as colorless oil (5.31 g, 93%). $[\alpha]_D^{25}$ +38.8 (c 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.34-7.25 (m, 10H), 4.68 (d, 1H, *J* 10.9 Hz), 4.59 (d, 1H, *J* 10.9 Hz), 4.55 (s, 2H), 3.90 (dt, 1H, *J* 4.4, 6.6 Hz), 3.80-3.72 (m, 2H), 3.70-3.66 (m, 3H), 3.64 (m, 1H) 2.82 (brs, 1H), 2.00 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.4, 137.3, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 79.2, 73.9, 73.5, 71.2, 69.3, 63.3, 61.9. IR (neat) (ν_{max}, cm^{-1}): 3405, 2872, 2100, 1455, 1267, 1090. ESI-MS: *m/z* 380 $[M+Na]^+$. HRMS calculated for $C_{19}H_{23}N_3O_4Na$: 380.1586 $[M+Na]^+$, found: 380.1597.

(2*R*,3*S*,4*S*)-1-(tert-Butyldimethylsilyloxy)-4-azido-3,5-(dibenzyloxy)-pentan-2-ol (12). To a well stirred soln. of diol **11** (3.57 g, 10 mmol) in dry CH_2Cl_2 (75 mL) was added imidazole (1.36g, 20 mmol) TBSCl (1.73 g, 11.5 mmol) and DMAP (122 mg, 10 mol%) at 0 ºC. After 30 min, the reaction mixture was left to warm to r.t., and stirred for overnight. The reaction mixture was treated with saturated aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2x40 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; hexane 100%, followed by EtOAc/hexane, 1:99) to give **12** as a colorless oil (4.47 g, 95%). $[\alpha]_D^{25}$ +22.9 (c 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.32-7.23 (m, 10H), 4.72 (d, 1H, *J* 11.3 Hz), 4.55 (s, 2H), 4.54 (d, 1H, *J* 11.3 Hz), 4.01-3.96 (m, 1H), 3.81 (dd, 1H, *J* 3.7, 9.8 Hz), 3.72-3.63 (m, 3H), 3.59-3.54 (m, 2H), 2.43 (brd, 1H, *J* 4.7 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.8, 137.7, 128.4, 127.9, 127.8, 127.7, 127.6, 79.1, 73.8, 73.3, 70.9, 69.6, 63.6, 62.3, 25.8, 18.2, -5.4. IR (neat) (ν_{max}, cm^{-1}): 3456, 2928, 2857, 2097, 1461, 1256, 1096. ESI-MS: *m/z* 494 $[M+Na]^+$. HRMS calculated for $C_{25}H_{37}N_3O_4SiNa$: 494.2451 $[M+Na]^+$, found: 494.2465.

(2*R*,3*S*,4*S*)-1-(tert-Butyldimethylsilyloxy)-4-azido-2,3,5-(tribenzyloxy)-pentane (13). To a well stirred soln. of NaH (60% dispersion in mineral oil, 1.04 g, 26.1 mmol) in dry THF (75 mL) under nitrogen was added compound **12** (4.1 g, 8.7 mmol) dissolved in THF (30 mL) *via* syringe very slowly at 0 ºC and allowed to stir for 20 min. Then it was added *n*-Bu_4NI (50 mg cat.) followed by benzyl bromide (3.1 mL, 26.1 mmol) drop wise with help of syringe and allowed to stir for overnight. The reaction mixture was quenched by addition of water until clear soln. results. THF was removed under reduced pressure, the residue was diluted with H_2O (40 mL) and extracted with Et_2O (3x35 mL). The combined organic layers was dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2; hexane 100%,

followed by EtOAc/hexane 1:19) to give **13** as a pale yellow oil (4.53 g, 93 %). $[\alpha]_D^{25}$ -2.6 (c 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.26-7.22 (m, 15H), 4.68 (d, 1H, *J* 12.0 Hz), 4.59 (s, 2H), 4.53 (d, 1H, *J* 12.0 Hz), 4.45 (s, 2H), 3.92-3.82 (m, 2H), 3.74-3.66 (m, 2H), 3.64-3.56 (m, 3H), 0.89 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 138.2, 137.9, 137.8, 128.3, 127.9, 127.8, 127.7, 127.5, 79.3, 78.2, 73.8, 73.2, 72.4, 69.9, 62.2, 62.0, 25.9, 18.2, -5.4. IR (neat) (ν_{max}, cm^{-1}): 2931, 2859, 2097, 1458, 1256, 1098. ESI-MS: *m/z* 584 $[M+Na]^+$; HRMS calculated for $C_{32}H_{42}N_3O_4SiNa$: 584.2920 $[M+Na]^+$, found: 584.2912.

(2*R*,3*S*,4*S*)-4-Azido-2,3,5-(tribenzyloxy)-pentan-1-ol (14). To a stirred soln. of **13** (4.1 g, 7.3 mmol) in dry THF (80 mL) under nitrogen was added TBAF (1M in THF, 14.6 mL, 14.6 mmol) at 0°. The reaction mixture was allowed to warm gradually to rt., and stirred for 4 h. THF was removed under reduced pressure, the residue was diluted with H_2O (5 mL) and extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2; hexane 100%, followed by EtOAc/hexane 1:9) to give **14** as a pale yellow oil (3.26 g, 96 %). $[\alpha]_D^{25}$ +13.8 (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.34-7.24 (m, 15H), 4.65 (s, 2H), 4.60 (dd, 2H, *J* 11.5, 22.0 Hz), 4.48 (d, 2H, *J* 3.0 Hz), 3.90 (dd, 1H, *J* 4.9, 10.0 Hz), 3.80-3.69 (m, 3H), 3.63-3.58 (m, 3H), 1.91 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.7, 137.6, 137.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 78.5, 78.1, 74.1, 73.3, 71.9, 69.6, 62.2, 60.5. IR (neat) (ν_{max}, cm^{-1}): 3452, 3031, 2923, 2866, 2096, 1454, 1095. ESI-MS: *m/z* 470 $[M+Na]^+$; HRMS calculated for $C_{26}H_{29}N_3O_4Na$: 470.2055 $[M+Na]^+$, found: 470.2043.

(2*S*,3*S*,4*R*,5*E*)-2-Azido-1,3,4-(tribenzyloxy)-octdeca-5-ene (15). To a stirred soln. of IBX (4.7 g, 16.8 mmol) in DMSO (8 mL) was added alcohol **14 (**2.5 g, 5.6 mmol**)** dissolved in CH_3CN (32 mL) at rt., and stirred until completion of the reaction (24 h). Filtered the reaction mixture through pad of *celite* and repeatedly washed with Et_2O (50 mL). The combined org. filtrates were washed with ice cold water (2x25 mL) followed by saturated hypo soln. (50 mL), dried and concentrated under reduced pressure to give corresponding aldehyde as a colourless *viscous* oil (2.36 g, 95%), that was used without purification for further step.

n-BuLi (1.6M in hexane, 13 mL, 21.8 mmol) was added dropwise *via* syringe to a stirred soln. of (1-tridecyl)-triphenylphosphonium bromide (11.06 g, 21.1 mmol) in dry THF (150 mL) at -78 °C. After 30 min, hexane (100 mL) was added, followed by the dropwise addition of a soln. of above freshly prepared aldehyde (2.36 g, 5.28 mmol) in THF (50 mL) *via* syringe. The reaction mixture was stirred at -78 °C for 2 h before the addition of MeOH (50 mL). The reaction mixture was allowed to warm to rt. over further 12 h and quenched with saturated aq. NH_4Cl (100 mL). Brine soln. (50 mL) was added, the organic layer was separated and the aq. layer was extracted with Et_2O (3x75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2; hexane 100%, followed by EtOAc/hexane 1:99) to give **15** as a colourless oil (2.61 g, 81%). $[\alpha]_D^{25}$ –23.9 (c 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.32-7.25 (m, 15H), 5.79 (dt, 1H, *J* 6.7, 15.4 Hz), 5.51 (dd, 1H, *J* 8.5, 15.3 Hz), 4.78 (dd, 1H, *J* 3.7, 11.1 Hz), 4.62 (dd, 2H, *J* 5.8, 11.8 Hz), 4.51 (d, 2H, *J* 4.5 Hz), 4.34 (dd, 1H, *J* 2.4, 11.8 Hz), 3.96 (dd, 1H, *J* 3.7, 8.3 Hz), 3.77-3.63 (m, 4H),

2.13 (dt, 2H, *J* 6.9, 13.5 Hz), 1.41-1.25 (m, 20H), 0.89 (t, 3H, *J* 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 138.4, 138.1, 137.9, 137.8, 136.8, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 126.1, 125.7, 80.7, 74.4, 73.2, 69.9, 69.8, 69.7, 61.9, 32.5, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.0, 22.7, 14.1. IR (neat) (ν_{max}, cm^{-1}): 2924, 2854, 2098, 1456, 109. ESI-MS: *m/z* 634 $[M+Na]^+$. HRMS calculated for $C_{39}H_{53}N_3O_3Na$: 634.3984 $[M+Na]^+$, found: 634.3971.

***N,O,O,O*-Tetracetyl-D-ribo-phytosphingosine ((2*S*,3*S*,4*R*)-2-acetamino-1,3,4-(triacetoxy)-octadecane) (1a).** A mixture of olefin **15** (1.22 g, 2 mmol) and $Pd(OH)_2/C$ (20% content, 30% (*wt/wt*), 0.366 g) in EtOAc (40 mL) containing trace amount of HCl (5 µl) was stirred for 48 h at r.t. under H_2 atmosphere (balloons). The catalyst was filtered through pad of *celite*, repeatedly washed with EtOAc (20 mL) and filtrate was concentrated in *vacuo* to give crude phytosphingosine. This crude product was dissolved in pyridine (15 mL), DMAP (0.1 g, cat.) and acetic anhydride (3 mL, excess) were added under N_2, and allowed to stir overnight. The solvent was removed under reduced pressure, saturated aq. $NaHCO_3$ (10 mL) was added to the residue and the mixture was extracted with Et_2O (3x30 mL). The combined organic layers were sequentially washed with saturated aq. $CuSO_4$ (2x15 mL), H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2; EtOAc/hexane 1:7) to afford compound **1a** as a semi solid (0.8 g, 80%). $[\alpha]_D^{25}$ +19.1 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.98 (d, 1H, *J* 9.3 Hz), 5.05 (dd, 1H, *J* 3.1, 8.5 Hz), 4.88 (td, 1H, *J* 3.8, 7.0 Hz), 4.33-4.37 (m, 1H), 4.28 (dd, 1H, *J* 5.4, 11.6 Hz), 3.95 (dd, 1H, *J* 3.1, 11.6 Hz), 2.01 (s, 3H), 1.97 (s, 6H), 1.95 (s, 3H), 1.59-1.52 (m, 2H), 1.24-1.18 (m, 24H), 0.82 (t, 3H, *J* 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 171.1, 170.8, 170.1, 169.7, 72.9, 71.8, 62.8, 47.5, 31.8, 31.3, 30.1, 29.6, 29.4, 29.3, 29.2, 28.0, 25.4, 23.2, 22.6, 20.9, 20.6, 20.7, 14.0. IR (neat) (ν_{max}, cm^{-1}): 2925, 2854, 1745, 1660, 1371, 1279. ESI-MS: *m/z* 508 $[M+Na]^+$. HRMS calculated for $C_{26}H_{47}NO_7Na$: 508.3250 $[M+Na]^+$, found: 508.3274.

(2*S*,3*R*,4*E*)-2-Azido-1,3-(dibenzyloxy)-octadeca-4-ene (16). To a stirred soln. of **11** (2.5 g, 7 mmol) in 30 mL of CH_3CN at r.t. was added $NaIO_4$ (3 g, 14 mmol) dissolved in H_2O 20 mL over a period of 10 min. The mixture was stirred about 30 min, filtered through pad of *celite* and repeatedly washed with Et_2O. The filtrate was mixed with H_2O (20 mL) and extracted with EtOAc (3x50 mL). The combined organic layers were washed with H_2O (20 mL), brine soln. (25 mL) and dried (Na_2SO_4). Solvent removal under reduced pressure afforded the corresponding aldehyde in almost quantitative yield (2.2 g, 98%). This was sufficiently pure and hence used as such for the next step. $[\alpha]_D^{25}$ -16.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.56 (d, 1H, *J* 1.5 Hz), 7.32-7.21 (m, 10H), 4.72 (d, 1H, *J* 11.3 Hz), 4.65 (d, 1H, *J* 12.1 Hz), 4.49 (s, 2H), 3.91 (dd, 1H, *J* 1.5, 3.7 Hz), 3.87 (dt, 1H, *J* 3.7, 6.0 Hz), 3.71 (dd, 1H, *J* 6.7, 9.8 Hz), 3.63 (dd, 1H, *J* 6.0, 9.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 200.7, 137.2, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 82.5, 73.4, 67.6, 61.4. IR (neat) (ν_{max}, cm^{-1}): 2923, 2867, 2101, 1731, 1454, 1267, 1100. ESI-MS: *m/z* 380 $[M+Na]^+$.

n-BuLi (1.6M in hexanes, 16.9 mL, 27 mmol) was added dropwise *via* syringe to a stirred soln. of (1-tetradecyl)triphenylphosphonium bromide (14.7 g, 27 mmol) in dry THF (150 mL) at -78 °C. After 30 min, hexane (150 mL) was added, followed by the dropwise addition of a soln. of

above freshly prepared aldehyde (2.2 g, 6.76 mmol) in THF (30 mL) *via* syringe. The reaction mixture was stirred at -78 ºC for 2 h before the addition of MeOH (50 mL). The reaction mixture was allowed to warm to r.t. over further 12 h and quenched with saturated aq. NH_4Cl (75 mL). Brine (50 mL) was added, the organic layer was separated and the aq. layer was extracted with Et_2O (3x50 mL). The combined org. extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2; hexane 100%, followed by EtOAc/hexane 1: 99) to give **16** as a pale yellow oil (2.9 g, 85%, mixture of *E* and *Z* isomers). $[\alpha]_D^{25}$ -33.7 (c 1.3, $CHCl_3$,). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.30-7.23 (m, 10H), 5.72 (dt, 1H, *J* 7.2, 15.6 Hz), 5.41 (dd, 1H, *J* 8.3, 15.6 Hz), 4.58 (d, 1H, *J* 12.2 Hz), 4.54 (d, 1H, *J* 12.2 Hz), 4.50 (d, 1H, *J* 11.3 Hz) 4.32 (d, 1H, *J* 11.3 Hz), 3.88 (dd, 1H, *J* 5.2, 8.3 Hz), 3.61-3.53 (m, 3H), 2.10 (dd, 2H, *J* 7.2, 14.5 Hz), 1.41-1.25 (m, 22H), 0.89 (t, 3H, *J* 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 138.1, 137.9, 137.8, 128.4, 128.3, 127.7, 127.6, 127.5, 125.9, 79.4, 73.3, 69.9, 69.4, 64.4, 32.3, 31.9, 29.6, 29.4, 29.3, 29.1, 29.0, 27.9, 22.6, 14.1. IR (neat) (ν_{max}, cm^{-1}): 2924, 2854, 2098, 1457, 1098. ESI-MS: *m/z* 528 $[M+Na]^+$. HRMS calculated for $C_{32}H_{47}N_3O_2Na$: 528.3565 $[M+Na]^+$, found: 528.3548.

(2*S*,3*R*,4*E*)-2-Amino-1,3-(dibenzyloxy)-octadeca-4-ene (17). A mixture of olefin **16** (1.01 g, 2 mmol) and *Lindlar's* catalyst ($Pd/CaCO_3$, 20% content, 35% (*wt/wt*), 0.353 g) in EtOAc (30 mL) was stirred for 8 h at r.t. under H_2 atmosphere (balloons). The catalyst was filtered through pad of *celite*, repeatedly washed with EtOAc (20 mL) and filtrate was concentrated *in vacuo* to give crude amino compound which was purified by column chromatography (SiO_2; EtOAc/hexane 1:9) to give **17** as colourless oil (0.795 g, 83%). $[\alpha]_D^{25}$ -28.4 (c 0.68, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.28-7.21 (m, 10H), 5.70 (dt, 1H, *J* 6.8, 15.6 Hz), 5.38 (dd, 1H, *J* 7.8, 15.6 Hz), 4.54 (d, 1H, *J* 11.7 Hz), 4.47 (s, 2H), 4.28 (d, 1H, *J* 11.7 Hz), 3.69 (t, 1H, *J* 7.8 Hz), 3.56 (dd, 1H, *J* 3.9, 8.7 Hz), 3.46 (dd, 1H, *J* 7.8, 15.6 Hz), 3.03 (q-like, 1H, *J* 3.9 Hz), 2.11 (dd, 2H, *J* 6.8, 13.6 Hz), 1.39-1.25 (m, 22H), 0.89 (t, 3H, *J* 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 138.4, 138.1, 137.9, 128.3, 128.2, 127.7, 127.6, 127.4, 126.5, 80.6, 73.2, 70.5, 70.0, 54.4, 32.4, 31.9, 29.7, 29.5, 29.3, 29.2, 29.1, 28.0, 22.7, 14.1. IR (neat) (ν_{max}, cm^{-1}): 3386, 3062, 3030**,** 2924, 2855, 1457, 1093. ESI-MS: *m/z* 480 $[M+H]^+$. HRMS calculated for $C_{32}H_{50}NO_2$: 480.3841 $[M+H]^+$, found: 480.3865.

D-erythro-Sphingosine ((2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol (2). A soln. of compound **17** (410 mg, 0.860 mmol) in dry THF (10 mL) was added dropwise to a soln. of Na (198 mg, 8.60 mmol) in dry liq. NH_3 (ca. 40 mL) at -78 ºC. After 45 min, solid NH_4Cl was added, and the mixture was allowed to warm to r.t. (ammonia evaporated). The resulting solid residue was stirred with EtOAc (30 mL), filtered and washed with EtOAc (25 mL). The combined organic phases were dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (SiO_2; MeOH/EtOAc, 1:9) gave compound **2** as a white waxy compound (205 mg, 80%). m.p. 72-74 ºC, $[\alpha]_D^{25}$ -3.1 (c 1.0, $CHCl_3$), {[lit.[20a] mp 73-75 ºC, $[\alpha]^{25}_D$ -2.86 (*c* 1.1, $CHCl_3$)] and [lit.[20b] mp 76-77 ºC, $[\alpha]^{24}_D$ -3.0 (*c* 1.0, $CHCl_3$)]}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 6.54 (brd, 1H, *J* 7.5 Hz), 6.51 (brd, 1H, *J* 7.5 Hz), 5.83 (dt, 1H, *J* 6.6, 14.3 Hz), 5.56 (dd, 1H, *J* 6.2, 15.1 Hz), 4.31 (brs, 1H), 3.97-3.68 (m, 4H), 3.00 (brs, 1H), 2.06-1.98 (m, 2H), 1.36-1.10 (m,

22H), 0.88 (t, 3H, *J* 6.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 134.1, 128.6, 74.3, 62.2, 54.5, 32.2, 31.8, 30.68, 29.6, 29.4, 29.3, 29.2, 29.1, 27.8, 23.3, 22.6, 14.1. IR (KBr) (ν_{max}, cm^{-1}): 3292, 2919, 2850, 1649, 1552, 1464, 1050, 722. ESI-MS: *m/z* 300 $[M+H]^+$

***N,O,O*-Triacetyl D-erythro-Sphingosine ((2*S*,3*R*,4*E*)-1,3-diacetoxy-2-acetamido-octadec-4-ene (2a).** The compound **2 (**100 mg, 0.33 mmol) was dissolved in pyridine (6 mL) and Ac_2O (0.5 mL) and DMAP (3 mg, cat.) were added sequentially. The reaction mixture was stirred overnight and the solvent removed under reduced pressure. Et_2O (30 mL) was added to the residue and washed sequentially with saturated aq. $CuSO_4$ (2x5 mL), H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 1: 6) to afford triacetyl derivative **2a** as a white solid (120 mg, 85%). m.p. 97-99 ^oC; $[\alpha]_D^{25}$ -11.8 (c 1.0, $CHCl_3$); {[lit.[9a] mp 99-101 ^oC, $[\alpha]^{20}_D$ -12.0 (*c* 1.0, $CHCl_3$)] and [lit.[9c] mp 99-101 ^oC, $[\alpha]^{20}_D$ -12.1 (*c* 1.0, $CHCl_3$)]}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.84 (dt, 1H, *J* 6.6, 15.3 Hz), 5.66 (d, 1H, *J* 8.8 Hz), 5.41 (dd, 1H, *J* 7.3, 15.3 Hz), 5.29 (t, 1H, *J* 6.6 Hz), 4.46-4.40 (m, 1H), 4.32 (dd, 1H, *J* 11.7, 5.9 Hz), 4.06 (dd, 1H, *J* 3.6, 11.7 Hz), 2.07 (s, 3H), 2.06 (s, 3H), 2.04-1.99 (m, 2H), 1.98 (s, 3H), 1.34-1.25 (m, 22H), 0.89 (t, 3H, *J* 5.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 171.0, 170.0, 169.6, 137.5, 124.1, 73.8, 62.5, 50.6, 32.2, 31.9, 29.7, 29.6, 29.4, 29.3, 29.1, 28.9, 23.3, 22.6, 21.1, 20.7, 14.1. IR (KBr) (ν_{max}, cm^{-1}): 3289, 2919, 2852, 1736, 1654, 1549, 1230. ESI-MS: *m/z* 448 $[M+Na]^+$; HRMS calculated for $C_{24}H_{43}NO_5Na$: 448.3038 $[M+Na]^+$, found: 448.3034.

Sphinganine ((2*S*,3*R*)-2-amino-octadecane-1,3-diol (3). A mixture of olefin **16** (252 mg, 0.5 mmol) and $Pd(OH)_2/C$ (20% content, 30% (*wt/wt*), 76 mg) in EtOAc:MeOH (1:1, 30 mL) containing trace amount of HCl (5 µl) was stirred for 48 h at r.t. under H_2 atmosphere (balloons). The catalyst was filtered through pad of *celite,* repeatedly washed with aq. MeOH and filtrate was concentrated in *vacuo* to give the solid compound which on recrystallization from CH_3CN afforded compound **3** as a white solid (130 mg, 87%). m.p. 70-73 ^oC; $[\alpha]_D^{25}$ +4.5 (c 0.5, MeOH), {[lit.[21a] $[\alpha]^{25}_D$ +8.1 (*c* 1.0, MeOH) and [lit.[21b] mp 71-73 ^oC, $[\alpha]^{25}_D$ +1.83 (*c* 1.0, pyridine). ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6,): δ_H 8.10 (brs, 2H), 4.86 (brs, 1H), 3.87 (brs, 1H), 3.78 (brs, 2H), 3.12 (brs, 1H), 1.48-1.25 (m, 28H), 0.89 (t, 3H, *J* 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 70.2, 58.6, 57.7, 34.0, 32.8, 30.5, 30.4, 30.2, 26.8, 23.5, 14.7. IR (KBr) (ν_{max}, cm^{-1}): 3387, 2918, 2849, 1599, 1507, 1466, 1058. ESI-MS: *m/z* 302 $[M+H]^+$; HRMS calculated for $C_{18}H_{40}NO_2$**:** 302.3059 $[M+H]^+$, found: 302.3060.

***N,O,O*-Triacetyl sphinganine ((2*S*,3*R*)-1,3-diacetoxy-2-acetamido-octadecane (3a).** The compound **3** (100 mg, 33.2 mmol) was dissolved in pyridine (6 mL) and Ac_2O (0.5 mL) and DMAP (3 mg, cat.) were added sequentially. The reaction mixture was stirred overnight and removed the solvent under *vacuo*. Et_2O (30 mL) was added to the residue and washed sequentially with saturated aq. $CuSO_4$ (2x5 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2; EtOAc/hexane, 1:6) to afford pure compound **3a** as a white solid (114 mg, 81%). m.p. 92-95 ^oC, $[\alpha]_D^{25}$ +14.6 ^oC (c 0.5, $CHCl_3$) {[lit.[21c] mp 90-93 ^oC, $[\alpha]^{19}_D$ +16.0 (*c* 0.5, $CHCl_3$) and lit.[21d] $[\alpha]^{27.5}_D$ +13.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.90 (brs, 1H), 4.85 (dd, 1H, *J* 5.8, 12.6 Hz), 4.34-4.31

(m, 1H), 4.24 (dd, 1H, *J* 6.8, 11.7 Hz), 4.02 (dd, 1H, *J* 3.9, 11.7 Hz), 2.06 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H), 1.59-1.54 (m, 2H), 1.25 (brs, 26H), 0.89 (t, 3H, *J* 7.12 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.9, 170.8, 169.6, 73.9, 62.5, 50.4, 31.8, 31.6, 31.5, 29.6, 29.5, 29.4, 29.3, 25.8, 25.3, 23.3, 22.6, 20.9, 20.8, 14.1. IR (KBr) (ν_{max}, cm^{-1}): 3292, 2918, 2850, 1734, 1648, 1546, 1241. ESI-MS: *m/z* 428 $[M+H]^+$; HRMS calculated for $C_{24}H_{46}NO_5$: 428.3375, $[M+H]^+$ found: 428.3392.

General procedure for the synthesis of tridecyl and tetradecyl triphenyl phosphonium bromides, 1-Bromotridecane or 1-bromotetradecane (30 mmol) and triphenyl phosphine (30 mmol) were refluxed in 125 mL dry CH_3CN for overnight. The solvent was removed under reduced pressure and the residue was repeatedly washed with hexane or diethyl ether until the compound precipitate out. Further, it was recrystallized with benzene, ether (1:1) mixture to give white solid.

Data of n-tridecyl triphenyl phosphonium bromide[22a]: (13.05 g, 83%); mp 83-87 ^oC. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.96-7.64 (m, 15H), 4.02-3.93 (m, 2H), 1.60 (brs, 4H), 1.22 (brd, 18H), 0.89 (t, 3H, *J* 6.7 Hz); ESI-MS: *m/z* 445 $[M-Br]^+$.

Data of n-tetradecyl triphenyl phosphonium bromide[22b]: (14.2 g, 88%). mp 82-85 ^oC. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.96-7.67 (m, 15H), 4.01-3.96 (m, 2H), 1.60 (brs, 4H), 1.28-1.17 (m, 20H), 0.89 (t, 3H, *J* 6.7 Hz); ESI-MS: *m/z* 459 $[M-Br]^+$.

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