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An efficient synthesis of D-*ribo*-C_{18}-phytosphingosine and L-*arabino*-C_{18}-phytosphingosine from D-fructose

Ramu Sridhar Perali *, Suresh Mandava, Sudharani Chalapala

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

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ABSTRACT

D-*ribo*-C_{18}-phytosphingosine and L-*arabino*-C_{18}-phytosphingosine were synthesised starting from commercially inexpensive D-fructose. Metal-mediated fragmentation and stereoselective reduction were used as key steps to provide the hydrophilic portion of D-*ribo* and L-*arabino* phytosphingosines. Grubbs' cross-metathesis and hydrogenation allowed the incorporation of hydrophobic tail.

1. Introduction

Sphingolipids are ubiquitous structural motifs influencing several biological machineries.[1] They play important roles in cellular adhesion, molecular recognition, signal transduction, immune response and apoptosis.[2] The significant involvement of sphingolipids in physiological process makes them critical for the diagnosis of most common human diseases like diabetes,[3] cancer,[4] Alzheimer's,[5] infectious[6] and several neurological syndromes.[7] Recent studies revealed that some of the sphingosine analogues are capable of bringing about morphological changes in neuronal cells[8] and behaving as like enzyme inhibitors.[9] Due to their multiple biological activities, a great deal of effort has been made towards the asymmetric synthesis of aminodiol sphingoid bases (sphingosines)[10] in the last decade and several methods for their preparations have been reported. However enantioselective methods for the synthesis of aminotriol sphingoid bases (phytosphingosines)[11] have increased in the recent years due to their growing biological relevance. It is also evident that a majority of phytosphingolipids has 18-carbon long-chain base. Out of several synthetic methods for phytosphingosines, the chiral-pool approaches particularly from L-serine[12] and carbohydrates[13] are noteworthy. Novel methods for the enantioselective synthesis of sphingolipids and phytosphingosine analogues involving fewer synthetic steps and commercially inexpensive raw materials are still in demand. Thus, in addition to the existing methods, herein we report a convenient enantioselective synthesis of D-*ribo*-C_{18}-phytosphingosine and L-*arabino*-C_{18}-phytosphingosine starting from grape sugar, fructose.

2. Results and discussion

D-Fructose **1** was converted to the known diacetonide **2** in an overall yield of 39% over four steps.[14] Compound **2** was treated with I_2/Ph_3P/imidazole under reflux in toluene to provide iodo diacetonide **3** in 95% yield. Zinc-mediated fragmentation of **3** gave alcohol that was protected with TBDMSCl without isolation of the α-hydroxy ketone to produce ketone **4**[15] in good yield (85%, over two steps). Reduction of ketone **4** with $NaBH_4$ at −78 °C in ethanol[16] provided 2,3-*syn* alcohol **5**[17] and 2,3-*anti* alcohol **6**[18] in a ratio of 1:24, respectively. Interestingly, when $LiAlH(O\text{-}^tBu)_3$[16] was employed for the reduction the ratio of **5** and **6** was 7:3, respectively with 70% combined yield. The 2,3-*syn* relationship in compound **5** was assigned based on the coupling constant $J_{3,2}$=3.2 Hz where as in the case of compound **6** the 2,3-*anti* relationship was assigned by observing the coupling constant $J_{3,2}$=8.8 Hz. The stereochemistry at 2-position was further confirmed by comparing the NMR spectral data with the reported values.[17,18] Both the diastereomers can be isolated in pure form by conventional silica gel column chromatography. It is noteworthy that key intermediates **5** and **6** can be synthesised on gram scale from D-fructose in a series of eight steps involving only three column chromatographic purifications (Scheme 1).

* Corresponding author. Tel.: +91 40 6679 4823; fax: +91 40 2301 2460; e-mail address: prssc@uohyd.ernet.in (R.S. Perali).

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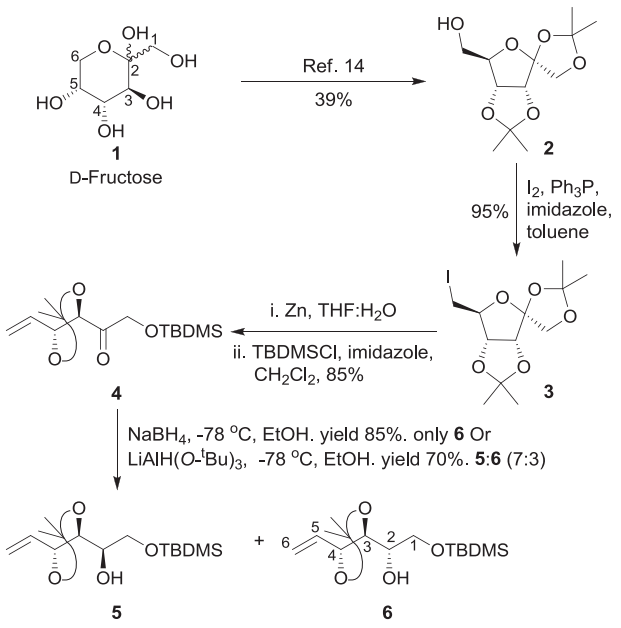
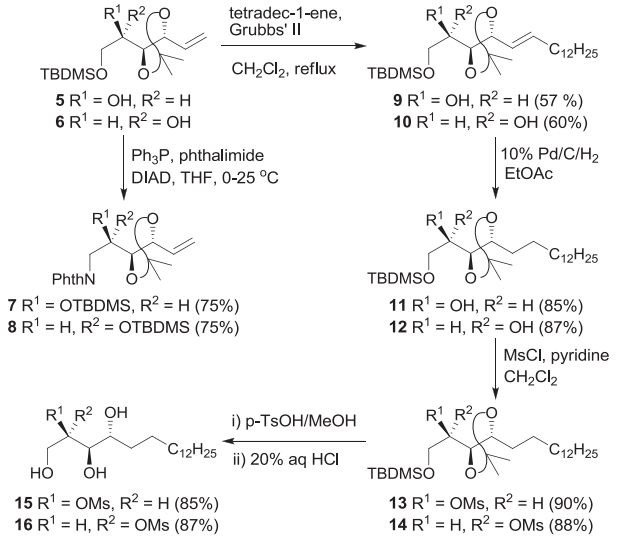


Scheme 1. Preparation of key intermediates **5** and **6**.

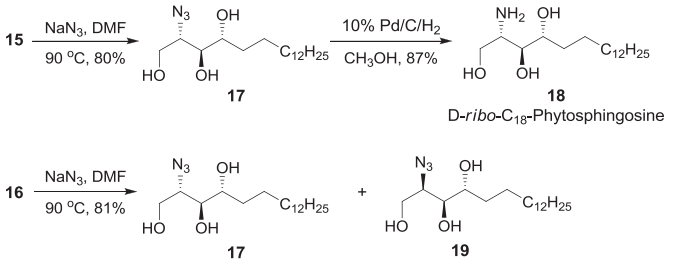
Attempts to incorporate the amino group in the form of phthalimide, to resemble the phytosphingosine skeleton, via a Mitsunobu reaction provided compounds **7** and **8**. The unexpected formation of the rearranged products **7** and **8** can be visualized through a 1,4 O→O silyl migration followed by substitution at C-1 (Scheme 2).[19] Activation of alcohol function in **5** or **6** by reacting with CH_3SO_2Cl/pyridine in CH_2Cl_2 followed by S_N2 substitution with NaN_3/DMF was not successful. We reasoned that the steric bulk present on both sides of the alcohol probably hinders the incoming nucleophile for substitution. To overcome this problem the substitution reaction was postponed to a later stage in which the activated alcohol will be less hindered.



Scheme 2. Synthesis of 2-*O*-methanesulfonyl D-*ribo*- and L-*arabino*-C_{18}-phytosphingosine.

Towards this, cross-metathesis of alcohols **5** and **6** with tetradec-1-ene using Grubbs' II generation catalyst provided the alkenols **9** and **10**, which were further hydrogenated with 10% Pd/C under hydrogen to give alcohols **11**[20] and **12**, respectively, in good yield. Even though quite a few methods for the preparation of sphingosines through the incorporation of the lipid chain via a cross-metathesis have been reported,[21] to the best of our knowledge, very few reports were observed for the synthesis of phytosphingosines.[22] Activation of the secondary alcohol in **11** or **12** using CH_3SO_2Cl/pyridine in CH_2Cl_2 provided sulfonates **13**[20] and **14**. A one-pot deprotection of TBDMS and acetonide protective groups using *p*-TsOH/MeOH/20% aqueous HCl provided the C-2-*O*-methanesulfonated triols **15**[13g,23] and **16** (Scheme 2).

Substitution of mesylate **15** with NaN_3 provided the azido-D-*ribo*-phytosphingosine **17**[24] that was further hydrogenated to give pure D-*ribo*-C_{18}-phytosphingosine **18**[22] in good yield. However, under similar reaction conditions mesylate **16** provided an inseparable 1:1 mixture of azido-D-*ribo*-phytosphingosine **17** and azido-L-*arabino*-phytosphingosine **19** (Scheme 3). The structure of **19** was confirmed by comparing the ^{13}C NMR with the reported enantiomer of **19**, i.e., azido-D-*arabino*-phytosphingosine.[25]



Scheme 3. Stereoselective synthesis of D-*ribo*-C_{18}-phytosphingosine.

The formation of only **17** from **15** and a mixture of **17** and **19** from **16** could be justified by considering the energy-minimised conformation of **15**, which adopts like a chair conformation and **16** adopting like a twist-boat conformation. As shown in Fig. 1 both the conformations possess an intramolecular hydrogen-bond between C1—OH and C3—OH forming a six-membered ring. Presence of an axial methanesulfonate in compound **15** facilitates an S_N2 type substitution reaction with azide. However, compound **16** to undergo S_N2 substitution reaction suffers with steric hindrance due to the ring oxygen as well as axial substituent at C3. Probably due to this reason compound **16** will undergo S_N1 type substitution reaction that leads to the formation of **17** and **19.**

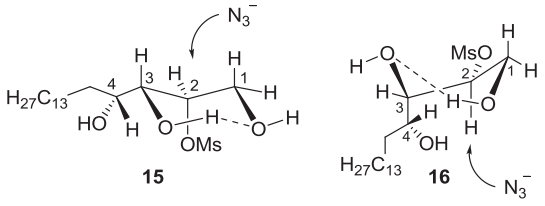
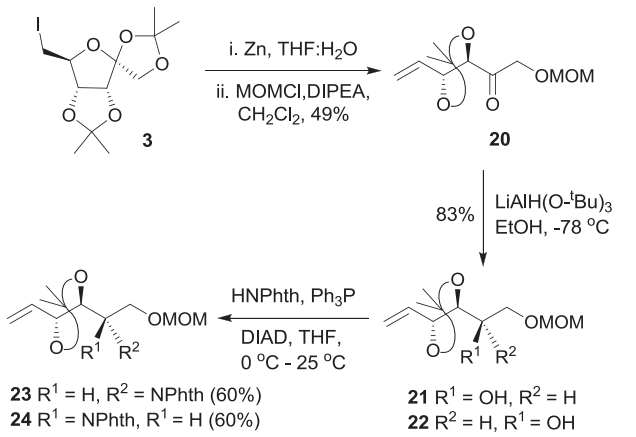


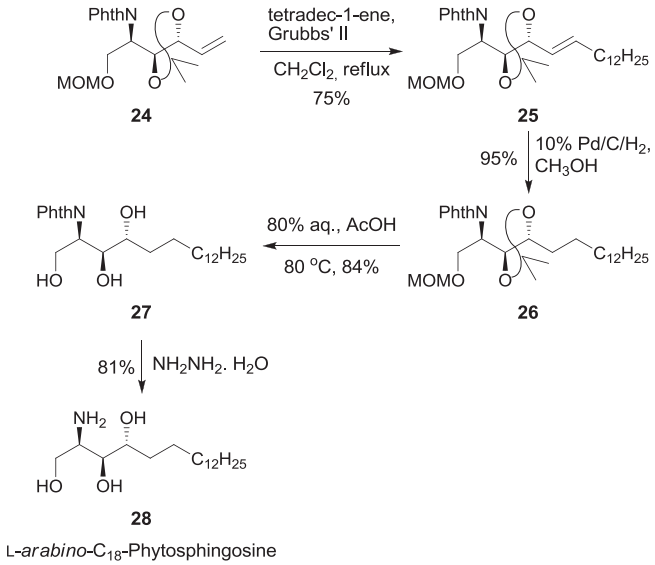
Fig. 1. Energy-minimised conformation for **15** and **16**.

Towards the enantioselective synthesis of L-*arabino*-phytosphingosine, the alcohol derived from Zn-mediated fragmentation of **3** was protected in situ with methoxymethyl (MOM) protective group using MOMCl/DIPEA to give ketone **20**. Interestingly, treatment of ketone with LiAlH(*O*-^{t}Bu)$_3$ in EtOH at −78 °C provided an inseparable mixture of *syn* and *anti* alcohols **21** and **22** in 3:7 ratio, respectively. Treatment of this diastereomeric alcohol mixture with Ph_3P/DIAD/phthalimide in dry THF at 0 °C followed by warming it to 25 °C provided Mitsunobu inversion products **23** and **24** again in 3:7 ratio in good yield (Scheme 4). The stereochemistry for **24** was found to be 2,3-*syn* configuration by observing the coupling constant $J_{3,2}$=4.4 Hz and based on this the other diastereomer was assigned to be 2,3-*anti* compound **23**.



Scheme 4. Preparation of key intermediate for the synthesis of L-*arabino*-phytosphingosine.

Cross-metathesis of olefin **24** with tetradec-1-ene using Grubbs' II generation catalyst provided olefin **25**, which upon hydrogenation using 10% Pd/C/H_2 provided compound **26**. A one-pot deprotection of acid-sensitive MOM and acetonide protective groups by heating the reaction mixture in 80% aqueous CH_3COOH at 80 °C provided the triol **27** in excellent yield. Final deprotection of phthalimide was achieved by stirring the reaction mixture in $H_2NNH_2 \cdot H_2O$/MeOH provided the expected L-*arabino*-C_{18}-phytosphingosine[22b,26] **28** as a white solid (Scheme 5). A similar procedure can also be applied to compound **23** to synthesise D-*ribo*-C_{18}-phytosphingosine **18**.



Scheme 5. Stereoselective synthesis of L-*arabino*-C_{18}-phytosphingosine.

3. Conclusion

In conclusion, an efficient method for the stereoselective synthesis of D-*ribo*-C_{18}-phytosphingosine involving a total of 13 steps with an overall yield 6% and L-*arabino*-C_{18}-phytosphingosine involving a total of 11 steps with an overall yield of 4.4% has been developed starting from commercially inexpensive D-fructose. Further, the present methodology will also provide an access to the synthesis of phytosphingosine analogues with variable alkyl chain lengths. Further application of the key intermediates **5**, **6**, **23** and **24** in the total synthesis of biologically active natural products is under progress.

4. Experimental section

4.1. General

All the reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. Acetone was distilled from potassium permanganate, CH_2Cl_2 was distilled from calcium hydride, ethanol was distilled from sodium ethoxide followed by distillation from magnesium ethoxide, pyridine was distilled from KOH and toluene was distilled from sodium. TLC was run on Silica Gel 60 F_{254} (Merck) and the spots were detected by staining with H_2SO_4 in methanol (5%, v/v) or phosphomolybdic acid in ethanol (5%, w/v) and heat. Silica gel (100–200 mesh) was used as a stationary phase for column chromatography. NMR spectra were recorded at 25 °C on a Bruker Avance III 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) or 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) instrument with $CDCl_3$ or CD_3OD or DMSO-d_6 as solvent and residual $CHCl_3$ (δ_H 7.26 ppm) or CH_3OH (δ_H 3.31 ppm) or $(CH_3)_2SO$ (δ_H 2.50 ppm) as internal standard for ^{1}H and $CDCl_3$ (δC 77.0 ppm) or CD_3OD (δC 49.0 ppm) or DMSO-d_6 (δC 39.5 ppm) as internal standard for ^{13}C. Chemical shifts are given in δ (ppm) and coupling constants (J) in hertz. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on a Shimadzu-LCMS-2010A mass spectrometer.

4.2. (4*S*,5*R*)-1-(2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy)-1(*R*)-ethan-1-ol (5)[17] and (4*S*,5*R*)-1-(2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy)-1(*S*)-ethan-1-ol (6)[18]

Reduction with $NaBH_4$: A solution of ketone **4** (4.0 g, 13.3 mmol) in EtOH (40 mL) was added dropwise for a period of 1 h to a solution of $NaBH_4$ (1.0 g, 26.6 mmol) in EtOH (80 mL) at −78 °C. After 2 h the reaction was quenched with saturated NH_4Cl solution (10 mL) and allowed it to warm to 25 °C. The reaction mixture was concentrated under reduced pressure to give a thick semi solid. EtOAc (150 mL) and water (50 mL) were added and the organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane (3:97) to give alcohol **6** (3.4 g, 85%) as a colourless liquid. R_f (10% EtOAc/hexane) 0.58; IR (neat): 3562, 2986, 2934, 2858, 1645, 1464, 1371 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 6.01–6.09 (m, H-5, 1H), 5.41 (dt, J=1.6, 17.2 Hz, H-6$_a$, 1H), 5.28 (d, J=10.4 Hz, H-6$_b$, 1H), 4.68 (t, J=6.4 Hz, H-4, 1H), 4.05 (dd, J=6.4, 8.8 Hz, H-3, 1H), 3.80 (dd, J=2.8, 9.6 Hz, H-1$_a$, 1H), 3.61–3.70 (m, H-1$_b$, H-2, 2H), 2.51 (d, J=5.2 Hz, 2-OH, 1H), 1.46 (s, CH_3 (isopropylidine), 3H), 1.35 (s, CH_3 (isopropylidine), 3H), 0.91 (s, Si–^{t}Bu, 9H), 0.08 (br s, Si–$(CH_3)_2$, 6H). δ_C (100 MHz, $CDCl_3$): 134.1, 117.5, 108.7, 78.7, 77.4, 69.5, 64.3, 27.8, 25.8, 25.4, 18.3, −5.4, −5.5. Low-resolution MS (EI): m/z: 303 (M^++1). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.38, 10.12.

Reduction with LiAlH(*O*-^{t}Bu)$_3$: A solution of ketone **4** (1.5 g, 5.0 mmol) in EtOH (30 mL) was added dropwise for a period of 1 h to a solution of LiAlH(*O*-^{t}Bu)$_3$ (3.2 g, 12.5 mmol) in EtOH (40 mL) at −78 °C. After stirring for 2 h at same temperature, the reaction was quenched with 5% aqueous NaOH solution (1 mL) and water (15 mL). After allowing the reaction mixture to warm to 25 °C it was filtered through a pad of Celite and the filter cake was washed with MeOH/EtOAc (1:1, 400 mL). Evaporation of the solvents under reduced pressure gave a thick syrup to which EtOAc (100 mL) and water (40 mL) were added. The organic

layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a 7:3 mixture of **5** and **6**, respectively. The crude product was purified by column chromatography using EtOAc/hexane (3:97) to give alcohol **5** (735 mg) and **6** (315 mg) as colourless liquids. Yield 70% (combined yield): **5**: R_f (10% EtOAc/hexane) 0.53; IR (neat): 3564, 2928, 2856, 1647, 1464, 1379 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 6.00–6.09 (m, H-5, 1H), 5.35 (d, J=17.2 Hz, H-6_a, 1H), 5.30 (d, J=10.4 Hz, H-6_b, 1H), 4.59 (t, J=7.2 Hz, H-4, 1H), 4.24 (dd, J=3.2, 6.8 Hz, H-3, 1H), 3.59–3.63 (br s, H-1_a, H-1_b, H-2, 3H), 2.35 (d, J=5.6 Hz, 2-OH, 1H), 1.53 (s, CH_3 (isopropylidine), 3H), 1.39 (s, CH_3 (isopropylidine), 3H), 0.89 (s, Si–^{t}Bu, 9H), 0.06 (br s, Si–$(CH_3)_2$, 6H). δ_C (100 MHz, $CDCl_3$): 134.4, 119.3, 108.6, 79.1, 77.3, 69.9, 64.1, 27.2, 25.8, 24.9, 18.3, −5.4, −5.4. Low-resolution MS (EI): m/z: 303 (M^++1). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.41; H, 10.22.

4.3. 2-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethyl)isoindoline-1,3-dione (7)[19]

To a stirred solution of alcohol **5** (300 mg, 1.0 mmol), Ph_3P (782 mg, 3.0 mmol) and phthalimide (176 mg, 1.2 mmol) in dry THF (8 mL) at 0 °C was injected DIAD (602 mg, 3.0 mmol) dropwise for a period of 10 min. The reaction mixture was allowed to stir at 25 °C for 6 h. After completion of reaction (by TLC) the mixture was concentrated and the product was purified by column chromatography using EtOAc/hexane (1:9) to give compound **7** (322 mg, 75%) as colourless needles. R_f (10% EtOAc/hexane) 0.39; IR (KBr): 2984, 2932, 2854, 1772, 1718, 1616, 1469, 1394 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.83 (dd, J=3.6, 5.6 Hz, phthalimide Ar–H, 2H), 7.70 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 5.99–6.08 (m, H-5, 1H), 5.33 (d, J=16.0 Hz, H-6_a, 1H), 5.32 (d, J=11.6 Hz, H-6_b, 1H), 4.58 (dd, J=6.0, 8.4 Hz, H-4, 1H), 4.14–4.20 (m, H-2, 1H), 4.08 (dd, J=5.6, 8.0 Hz, H-3, 1H), 3.78 (dd, J=3.2, 14.0 Hz, H-1_a, 1H), 3.71 (dd, J=3.6, 14.0 Hz, H-1_b, 1H), 1.49 (s, CH_3 (isopropylidine), 3H), 1.34 (s, CH_3 (isopropylidine), 3H), 0.76 (s, Si–^{t}Bu, 9H), 0.04 (s, Si–CH_3, 3H), −0.13 (s, Si–CH_3, 3H). δ_C (100 MHz, $CDCl_3$): 168.3, 134.3, 133.9, 132.1, 123.1, 119.3, 108.5, 80.1, 78.7, 69.0, 40.1, 27.9, 25.6, 25.4, 18.1, −4.4, −4.8. Low-resolution MS (EI): m/z: 432 (M^++1). Anal. Calcd for $C_{23}H_{33}NO_5Si$: C, 64.01; H, 7.71; N, 3.25. Found: C, 64.12; H, 7.62; N, 3.36.

4.4. 2-((*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethyl)isoindoline-1,3-dione (8)[19]

Compound **8** was synthesised following the procedure described for compound **7** as a colourless liquid. Yield 75%. R_f (10% EtOAc/hexane) 0.43; IR (neat): 2986, 2932, 2858, 1774, 1718, 1616, 1469, 1394 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.82 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.70 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 6.06–6.15 (m, H-5, 1H), 5.38 (d, J=16.8 Hz, H-6_a, 1H), 5.31 (d, J=10.4 Hz, H-6_b, 1H), 4.64 (t, J=7.2 Hz, H-4, 1H), 4.18–4.23, (m, H-2, 1H), 4.13 (dd, J=4.8, 6.4 Hz, H-3, 1H), 3.87 (dd, J=6.8, 14.4 Hz, H-1_a, 1H), 3.76 (dd, J=6.8, 14.4 Hz, H-1_b, 1H), 1.27 (s, CH_3 (isopropylidine), 3H), 1.25 (s, CH_3 (isopropylidine), 3H), 0.83 (s, Si–^{t}Bu, 9H), 0.03 (s, Si–CH_3, 3H), −0.02 (s, Si–CH_3, 3H). δ_C (100 MHz, $CDCl_3$): 168.3, 134.5, 133.8, 132.1, 123.0, 119.0, 108.3, 80.3, 79.1, 68.2, 41.4, 27.0, 25.7, 24.6, 17.8, −4.3, −4.5. Low-resolution MS (EI): m/z: 432 (M^++1). Anal. Calcd for $C_{23}H_{33}NO_5Si$: C, 64.01; H, 7.71; N, 3.25. Found: C, 64.12; H, 7.68; N, 3.36.

4.5. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*S*,5*S*)-2,2-dimethyl-5-((*E*)-tetradec-1-enyl)-1,3-dioxolan-4-yl)ethanol (9)

Compound **5** (0.35 g, 1.2 mmol) and 1-tetradecene (0.91 g, 4.6 mmol) were dissolved in CH_2Cl_2 (25 mL) at room temperature. Grubbs' II generation catalyst (4 mol %) was added to the solution and then the reaction mixture was refluxed under nitrogen for 24 h. After completion of reaction it was allowed to warm to 25 °C and the solvent was evaporated. Purification of the residue by column chromatography with EtOAc/hexane: (4:96) afforded compound **9** (310 mg, 57%) as a colourless liquid. R_f (10% EtOAc/hexane) 0.63; IR (neat): 3562, 2926, 2854, 1464, 1379 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 5.75 (dt, J=6.4, 15.2 Hz, H-6, 1H), 5.64 (dd, J=8.4, 15.2 Hz, H-5, 1H), 4.55 (dd, J=7.2, 8.4 Hz, H-4, 1H), 4.15 (dd, J=3.2, 6.8 Hz, H-3, 1H), 3.57 (br s, H-2, H-1_a, H-1_b, 3H), 2.36 (d, J=4.8 Hz, 2-OH, 1H), 2.01–2.05 (m, 7-CH_2, 2H), 1.48 (s, CH_3 (isopropylidine), 3H), 1.35 (s, CH_3 (isopropylidine), 3H), 1.22 (br s, 8 to 17-$(CH_2)_{10}$, 20H), 0.86 (s, Si–^{t}Bu, 9H), 0.84 (t, J=6.8 Hz, 18-CH_3, 3H), 0.03 (s, Si–$(CH_3)_2$, 6H). δ_C (100 MHz, $CDCl_3$): 137.2, 125.6, 108.1, 78.9, 76.9, 70.1, 64.1, 32.2, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 27.1, 25.8, 24.8, 22.6, 18.2, 14.0, −5.4. Low-resolution MS (EI): m/z: 471 (M^++1). Anal. Calcd for $C_{27}H_{54}O_4Si$: C, 68.88; H, 11.56. Found: C, 68.75; H, 11.48.

4.6. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*S*,5*S*)-2,2-dimethyl-5-((*E*)-tetradec-1-enyl)-1,3-dioxolan-4-yl)ethanol (10)

Compound **10** was synthesised following the procedure described for compound **9**. Yield 60%. R_f (10% EtOAc/hexane) 0.67; IR (neat): 3560, 2928, 2856, 1464, 1369 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 5.80 (dt, J=6.8, 15.2 Hz, H-6, 1H), 5.60 (tdd, J=1.5, 7.6, 16.0 Hz, H-5, 1H), 4.63 (t, J=6.8 Hz, H-4, 1H), 4.00 (dd, J=6.4, 8.8 Hz, H-3, 1H), 3.78–3.82 (m, H-1_a, 1H), 3.67–3.70 (m, H-2, H-1_b, 2H), 2.46 (d, J=4.4 Hz, 2-OH, 1H), 2.03–2.10 (m, 7-CH_2, 2H), 1.44 (s, CH_3 (isopropylidine), 3H), 1.36–1.40 (m, 8-CH_2, 2H), 1.33 (s, CH_3 (isopropylidine), 3H), 1.24–1.29 (m, 9 to 17-$(CH_2)_9$, 18H), 0.90 (s, Si–^{t}Bu, 9H), 0.87 (t, J=7.2 Hz, 18-CH_3, 3H), 0.98 (s, Si–$(CH_3)_2$, 6H). δ_C (100 MHz, $CDCl_3$): 135.5, 125.3, 108.3, 78.9, 77.5, 69.6, 64.4, 32.3, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 27.9, 25.8, 25.4, 22.7, 18.3, 14.1, −5.3, −5.4. Low-resolution MS (EI): m/z: 471 (M^++1). Anal. Calcd for $C_{27}H_{54}O_4Si$: C, 68.59; H, 11.94. Found: C, 68.71; H, 11.68.

4.7. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*S*,5*S*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)ethanol (11)[20]

To a stirred solution of compound **9** (140 mg, 0.3 mmol) in EtOAc (5 mL) was added 10% palladium on charcoal (30 mg). Then the mixture was degassed and stirred under the hydrogen atmosphere at 25 °C overnight. After completion of the reaction (by TLC) the suspension was filtered through a pad of Celite and concentrated. The crude product was purified by column chromatography using hexane/EtOAc (19:1) to afford compound **11** (120 mg, 85%) as a colourless liquid. R_f (5% EtOAc/hexane) 0.54; IR (neat): 3468, 2924, 2854, 1464, 1379 cm^{-1}. δ_H (500 MHz, $CDCl_3$): 4.14–4.18 (m, H-4, 1H), 4.10 (dd, J=3.0, 6.5 Hz, H-3, 1H), 3.65 (dd, J=3.0, 6.0 Hz, H-2, 1H), 3.62 (dd, J=6.0, 9.5 Hz, H-1_a, 1H), 3.57 (dd, J=6.0, 9.5 Hz, H-1_b, 1H), 2.31 (d, J=5.5 Hz, 2-OH, 1H), 1.73–1.77 (m, 5-CH_a, 1H), 1.53–1.54 (m, 5-CH_b, 1H), 1.48 (s, CH_3 (isopropylidine), 3H), 1.36 (s, CH_3 (isopropylidine), 3H), 1.25 (br m, 6 to 17-$(CH_2)_9$, 24H), 0.89 (s, Si–^{t}Bu, 9H), 0.87 (t, J=5.6 Hz, 18-CH_3, 3H), 0.06 (s, Si–$(CH_3)_2$, 6H). δ_C (125 MHz, $CDCl_3$): 107.6, 77.5, 76.4, 69.9, 64.5, 31.9, 29.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 27.2, 26.7, 25.8, 25.1, 22.6, 18.3, 14.0, −5.3. Low-resolution MS (EI): m/z: 473 (M^++1). Anal. Calcd for $C_{27}H_{56}O_4Si$: C, 68.59; H, 11.94. Found: C, 68.51; H, 11.89.

4.8. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*S*,5*S*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)ethanol (12)

Compound **12** was synthesised following the procedure described for compound **11**. Yield 87%. R_f (5% EtOAc/hexane) 0.61; IR (neat): 3562, 2926, 2854, 1464, 1379 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 4.13–4.17 (m, H-4, 1H), 3.89 (dd, *J*=5.6, 8.8 Hz, H-3, 1H), 3.81 (dd, *J*=5.6, 12.4 Hz, H-1_a, 1H), 3.62–3.69 (m, H-2, H-1_b, 2H), 2.57 (d, *J*=4.8 Hz, 2-OH, 1H), 1.68–1.75 (m, 6-CH_a, 1H), 1.49–1.58 (m, 5-CH_2, 2H), 1.38 (s, CH_3 (isopropylidine), 3H), 1.30 (s, CH_3 (isopropylidine), 3H), 1.24 (br s, 7 to 17-$(CH_2)_{11}$, 6-CH_b, 23H), 0.90 (s, Si–^{t}Bu, 9H), 0.86 (t, *J*=6.4 Hz, 18-CH_3, 3H), 0.08 (s, Si–$(CH_3)_2$, 6H). δ_C (100 MHz, $CDCl_3$): 107.8, 78.2, 77.1, 69.2, 64.6, 31.9, 29.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 28.3, 26.4, 25.8, 25.7, 22.6, 18.3, 14.1, −5.3, −5.4. Low-resolution MS (EI): *m*/*z*: 473 (M^++1). Anal. Calcd for $C_{27}H_{56}O_4Si$: C, 68.88; H, 11.56. Found: C, 68.45; H, 11.89.

4.9. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*R*,5*S*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)ethyl methanesulfonate (13)[20]

To a stirred solution of compound **11** (90 mg, 0.2 mmol) in CH_2Cl_2 (2.5 mL) were added pyridine (0.57 mL) and methanesulfonyl chloride (38 μL, 0.5 mmol), respectively, at 25 °C. The resultant mixture was stirred for 4 h, then was diluted with CH_2Cl_2 (40 mL). The solution was washed with saturated aqueous $CuSO_4$ solution (2×10 mL) to remove the pyridine. CH_2Cl_2 was dried under anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (EtOAc/hexane (1:40)) of crude afforded compound **13** (95 mg, 90%) as a viscous oil. R_f (5% EtOAc/hexane) 0.37; IR (neat): 2926, 2858, 1647, 1460, 1363, 1255 cm^{-1}. δ_H (500 MHz, $CDCl_3$): 4.67 (dt, *J*=5.5, 6.5 Hz, H-2, 1H), 4.25 (t, *J*=6.0 Hz, H-3, 1H), 4.10–4.14 (m, H-4, 1H), 3.88 (dd, *J*=5.5, 11.0 Hz, H-1_a, 1H), 3.82 (dd, *J*=5.5, 11.5 Hz, H-1_b, 1H), 3.08 (s, 3H), 1.48–1.56 (m, 5-CH_2, 2H), 1.45 (s, CH_3 (isopropylidine), 3H), 1.34 (s, CH_3 (isopropylidine), 3H), 1.24 (br s, 6 to 17-$(CH_2)_{12}$, 24H), 0.88 (s, Si–^{t}Bu, 9H), 0.87 (t, *J*=7.0 Hz, 18-CH_3, 3H), 0.08 (s, Si–CH_3, 3H), 0.07 (s, Si–CH_3, 3H). δ_C (125 MHz, $CDCl_3$): 108.2, 80.7, 77.1, 75.9, 63.0, 38.9, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.3, 27.7, 26.1, 25.9, 25.8, 22.6, 18.2, 14.1, −5.4, −5.5. Low-resolution MS (EI): *m*/*z*: 551 (M^++1). Anal. Calcd for $C_{28}H_{58}O_6SSi$: C, 61.04; H, 10.61. Found: C, 61.15; H, 10.52.

4.10. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*R*,5*S*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)ethyl methanesulfonate (14)

Compound **14** was synthesised following the procedure described for compound **13**. Yield 88%. R_f (5% EtOAc/hexane) 0.39; IR (neat): 2926, 2854, 1464, 1361, 1255, 1179, 1109 cm^{-1}. δ_H (500 MHz, $CDCl_3$): 4.66 (td, *J*=2.0, 6.0 Hz, H-2, 1H), 4.24 (t, *J*=6.0 Hz, H-3, 1H), 4.17–4.21 (m, H-4, 1H), 3.96 (dd, *J*=2.0, 12.0 Hz, H-1_a, 1H), 3.87 (dd, *J*=6.0, 12.0 Hz, H-1_b, 1H), 3.09 (s, SO_2CH_3, 3H), 1.55–1.65 (m, 5-CH_2, 2H), 1.40 (s, CH_3 (isopropylidine), 3H), 1.31 (s, CH_3 (isopropylidine), 3H), 1.24 (br s, 6 to 17-$(CH_2)_{12}$, 24H), 0.89 (s, Si–^{t}Bu, 9H), 0.86 (t, *J*=7.0 Hz, 18-CH_3, 3H), 0.08 (s, Si–CH_3, 3H), 0.07 (s, Si–CH_3, 3H). δ_C (125 MHz, $CDCl_3$): 108.1, 82.6, 77.2, 76.1, 62.9, 39.1, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 27.3, 26.6, 25.8, 25.1, 22.6, 18.3, 14.1, −5.4, −5.5. Low-resolution MS (EI): *m*/*z*: 551 (M^++1). Anal. Calcd for $C_{28}H_{58}O_6SSi$: C, 61.04; H, 10.61. Found: C, 61.15; H, 10.58.

4.11. (2*R*,3*R*,4*R*)-1,3,4-Trihydroxyoctadecan-2-yl methanesulfonate (15)[13g,23]

To a stirred solution of **13** (120 mg, 0.2 mmol) in methanol (2 mL) was added *p*-toluenesulfonic acid (63 mg, 0.3 mmol). The resultant mixture was stirred at 25 °C for 2 h. Then 20% aqueous HCl (3 mL) was added to the mixture and stirred at 25 °C for another 2 h. Removal of the solvents under reduced pressure provided a viscous residue. To the residue were added EtOAc (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. Column chromatography of the crude product using CH_2Cl_2/MeOH (19:1) provided compound **15** (74 mg, 85%) as a white solid. R_f (hexane/EtOAc/MeOH 10:10:1) 0.44; IR (KBr): 3504, 3383, 3225, 2918, 2851, 1471, 1439, 1359 cm^{-1}. δ_H (500 MHz, DMSO-d_6): 5.03 (t, *J*=5.5 Hz, 1-OH, 1H), 4.93 (d, *J*=7.0 Hz, 3-OH, 1H), 4.73 (dt, *J*=1.5, 6.5 Hz, H-2, 1H), 4.49 (d, *J*=6.5 Hz, 4-OH, 1H), 3.59–3.67 (m, H-1_a, 1H), 3.33–3.36 (m, H-1_b, H-3, H-4, 3H), 3.17 (s, $-SO_2CH_3$, 3H), 1.65–1.69 (m, H-5_a, 1H), 1.43–1.45 (m, H-5_b, 1H), 1.24 (br s, 6 to 17-$(CH_2)_{12}$, 24H), 0.85 (t, *J*=7 Hz, 18-CH_3, 3H). δ_C (125 MHz, DMSO-d_6): 83.1, 71.9, 69.6, 60.6, 38.3, 33.9, 31.7, 29.7, 29.6, 29.5, 29.4, 29.1, 25.2, 22.5, 14.4. Low-resolution MS (EI): *m*/*z*: 397 (M^++1). Anal. Calcd for $C_{19}H_{40}O_6S$: C, 57.54; H, 10.17. Found: C, 57.71; H, 10.08.

4.12. (2*S*,3*R*,4*R*)-1,3,4-Trihydroxyoctadecan-2-yl methanesulfonate (16)

Compound **16** was synthesised following the procedure described for compound **15**. Yield 87%. White solid. R_f (hexane/EtOAc/MeOH 10:10:1) 0.39; IR (KBr): 3526, 3402, 2920, 2851, 1473, 1431, 1350 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 4.90 (dt, *J*=4.5, 8.5 Hz, H-2, 1H), 4.06–4.09 (m, H-3, 1H), 3.91–3.97 (m, H-1_a and H1_b, 2H), 3.74–3.77 (m, H-4, 1H), 3.13 (s, $-SO_2CH_3$, 3H), 2.98–3.02 (m, −OH, 2H), 2.43 (br s, −OH, 1H), 1.47–1.51 (m, 5-CH_2, 2H), 1.25–1.30 (br m, 6 to 17-$(CH_2)_{12}$, 24H), 0.87 (t, *J*=7.0 Hz, 18-CH_3, 3H). δ_C (100 MHz, $CDCl_3$): 82.5, 74.9, 72.4, 61.2, 38.6, 32.7, 31.9, 29.7, 29.6, 29.5, 29.5, 29.5, 29.3, 25.6, 22.6, 14.1. Low-resolution MS (EI): *m*/*z*: 397 (M^++1). Anal. Calcd for $C_{19}H_{40}O_6S$: C, 57.54; H, 10.17. Found: C, 57.45; H, 10.21.

4.13. (2*S*,3*S*,4*R*)-2-Azidooctadecane-1,3,4-triol (17)[13g,23]

To a stirred solution of compound **15** (60 mg, 0.15 mmol) in dry DMF, sodium azide (50 mg, 0.75 mmol) was added. The resultant mixture was stirred for 48 h at 90 °C. The reaction mixture was brought to 25 °C and CH_2Cl_2 (5 mL) was added. The excess amount of sodium azide was filtered and the filtrate was concentrated to give a thick gummy residue, which was purified by column chromatography using CH_2Cl_2/MeOH (19:1) to afford compound **17** (42 mg, 80%) as a white solid. R_f (hexane/EtOAc/MeOH 10:10:1) 0.62; IR (KBr): 3396, 2918, 2849, 2118, 1738, 1464 cm^{-1}. δ_H (500 MHz, $CDCl_3$): 3.99 (dd, *J*=5.5, 11.5 Hz, H-1_a, 1H), 3.87–3.89 (m, H-1_b, 1H), 3.76–3.81 (m, H-3, H-4, 2H), 3.66 (dd, *J*=5.0, 10.0 Hz, H-2, 1H), 2.84 (br s, −OH, 1H), 2.67 (br s, −OH, 1H), 2.35 (br s, −OH, 1H), 1.48–1.57 (m, 5-CH_2, 2H), 1.25–1.33 (br m, 6 to 17-$(CH_2)_{12}$, 24H), 0.87 (t, *J*=7 Hz, 18-CH_3, 3H). δ_C (125 MHz, $CDCl_3$): 74.7, 72.5, 63.1, 61.7, 32.0, 31.9, 29.7, 29.6, 29.5, 29.3, 25.7, 22.6, 14.0. Low-resolution MS (EI): *m*/*z*: 344 (M^++1). Anal. Calcd for $C_{18}H_{37}N_3O_3$: C, 62.94; H, 10.86; N, 12.23. Found: C, 62.85; H, 10.76; N, 12.31.

4.14. (2*S*,3*S*,4*R*)-2-Aminooctadecane-1,3,4-triol (D-*ribo*-C_{18}-Phytosphingosine) (18)[22]

To a stirred solution of compound **17** (40 mg, 0.1 mmol) in MeOH (3 mL) was added 10% palladium on charcoal (15 mg). Then the mixture was degassed and stirred under the hydrogen atmosphere at 25 °C for 3 h. After completion of the reaction (by TLC) the suspension was filtered through a pad of Celite and concentrated. The crude product was purified by flash column chromatography using CH_2Cl_2/MeOH/NH_4OH (80:20:1) to afford compound **18** (32 mg, 87%) as a white solid. R_f (CH_2Cl_2/MeOH/NH_4OH 85:15:1) 0.15; IR (KBr): 3369, 2918, 2851, 1469 cm^{-1}. δ_H (500 MHz, CD_3OD):

3.79 (dd, J=4.0, 11.0 Hz, H-1$_a$, 1H), 3.59 (dd, J=7.0, 11.0 Hz, H-1$_b$, 1H), 3.51–3.54 (m, H-4, 1H), 3.37 (dd, J=5.5, 8.0 Hz, H-3, 1H), 3.00–3.03 (m, H-2, 1H), 1.74–1.78 (m, 5-CH$_a$, 1H), 1.56–1.58 (m, 5-CH$_b$, 1H), 1.30–1.37 (br m, 6 to 17-(CH$_2$)$_{12}$, 24H), 0.91 (t, J=7.0 Hz, 18-CH$_3$, 3H). δ_C (125 MHz, CD$_3$OD): 74.8, 73.0, 62.3, 54.5, 33.4, 31.6, 29.5, 29.4, 29.3, 29.0, 25.1, 22.3, 13.0. Low-resolution MS (EI): m/z: 318 (M$^+$+1). Anal. Calcd for $C_{18}H_{39}NO_3$: C, 68.09; H, 12.38; N, 4.41. Found: C, 68.15; H, 12.31; N, 4.38.

4.15. (2*S*,3*S*,4*R*)-2-Azidooctadecane-1,3,4-triol (17) and (2*R*,3*S*,4*R*)-2-azido-1,3,4-octadecane triol (19) (mixture)

Compounds **17** and **19** were synthesised following the procedure described for compound **17**. Yield 81% (1:1). White solid. R_f (hexane/EtOAc/MeOH 10:10:1) 0.62; IR (KBr): 3354, 2918, 2851, 2139, 2104, 1471, 1354 cm^{-1}. δ_C (100 MHz, CDCl$_3$): 74.6, 74.3, 72.6, 72.5, 63.8, 63.1, 62.8, 61.7, 33.4, 31.9, 29.7, 29.6, 29.3, 25.7, 25.5, 22.7, 14.1, 14.0. Low-resolution MS (EI): m/z: 344 (M$^+$+1). Anal. Calcd for $C_{18}H_{37}N_3O_3$: C, 68.09; H, 12.38; N, 12.23. Found: C, 68.12; H, 12.47; N, 12.45.

4.16. 1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethoxy)ethanone (20)

The crude oily residue (800 mg, 4.3 mmol) obtained after zinc-mediated fragmentation reaction of iodide **3** was dissolved in dichloromethane (30 mL) and cooled to 0 °C. To this *N*,*N*-diisopropylethylamine (5.5 g, 43.0 mmol) was added followed by methoxymethylchloride (3.5 g, 43.0 mmol) dropwise over 30 min. The mixture was allowed to warm to 25 °C and stirred for 24 h. The solvent was evaporated and the residue was diluted with EtOAc (50 mL). The resultant solution was washed with water (30 mL) and the aqueous layer was extracted with EtOAc (2×30 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography using EtOAc/hexane (1:24) to afford pure ketone **20** (485 mg, 13.8 mmol) as a pale yellow liquid. Yield (49% from **3**). R_f (20% EtOAc/hexane) 0.52; IR (neat): 3086, 2989, 2895, 1738, 1614, 1456, 1377 cm^{-1}. δ_H (400 MHz, CDCl$_3$): 5.79–5.88 (m, H-5, 1H), 5.35 (d, J=17.2 Hz, H-6$_a$, 1H), 5.23 (d, J=10.4 Hz, H-6$_b$, 1H), 4.62 (s, –OCH$_2$O–, 2H), 4.44 (m, carbonyl–CH$_2$O–, 2H), 4.39 (t, J=7.6 Hz, H-4, 1H), 4.13 (d, J=8.0 Hz, H-2, 1H), 3.31 (s, –OCH$_3$, 3H), 1.39 (s, CH$_3$ (isopropylidine), 3H), 1.38 (s, CH$_3$ (isopropylidine), 3H). δ_C (100 MHz, CDCl$_3$): 204.4, 134.3, 118.7, 111.0, 96.4, 83.5, 79.1, 69.6, 55.7, 26.7, 26.2. Low-resolution MS (EI): m/z: 231 (M$^+$+1). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.19; H, 7.91.

4.17. (*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethyloxy)ethanol (21) and (*S*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethyloxy) ethanol (22)

To a solution of LiAlH(*O*-^{t}Bu)$_3$ (1.2 g, 4.7 mmol) in EtOH (18 mL) at −78 °C was added a solution of ketone **20** (540 mg, 2.3 mmol) in EtOH (18 mL) dropwise for a period of 45 min. After stirring for 2 h at same temperature, the reaction was quenched with 5% aqueous NaOH solution (0.5 mL) and water (5 mL). After allowing the reaction mixture to warm to 25 °C it was filtered through a pad of Celite and filter cake was washed with MeOH/EtOAc (1:1, 200 mL). Evaporation of the solvents under reduced pressure gave thick syrup to which EtOAc (50 mL) and water (25 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to give compounds **21** and **22** (450 mg, 83%) as a 7:3 diastereomeric mixture, respectively.

4.18. 2-((*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethyloxy)ethyl)isoindoline-1,3-dione (23) and 2-((*R*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethyloxy)ethyl)isoindoline-1,3-dione (24)

To a stirred solution of diastereomeric alcohol mixture **21** and **22** (390 mg, 1.7 mmol), Ph$_3$P (1.3 g, 5.0 mmol) and phthalimide (296 mg, 2.0 mmol) in dry THF (25 mL) at 0 °C was injected DIAD (1.0 g, 5.0 mmol) dropwise for a period of 20 min. The reaction mixture was allowed to stir at 25 °C for 6 h. After completion of reaction (by TLC) the mixture was concentrated and the product was purified by column chromatography using EtOAc/hexane to give compounds **23** (110 mg) and **24** (256 mg) as semisolids in 60% combined yield. Compound **23**: R_f (20% EtOAc/hexane) 0.58; IR (neat): 2988, 2934, 1776, 1714, 1614, 1467, 1383 cm^{-1}. δ_H (400 MHz, CDCl$_3$): 7.84 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.71 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 5.84–5.92 (m, H-5, 1H), 5.48 (d, J=16.8 Hz, H-6$_a$, 1H), 5.33 (d, J=10.4 Hz, H-6$_b$, 1H), 4.51–4.59 (m, H-2, –OCH$_2$O–, 3H), 4.32 (dd, H-3, J=7.2, 9.6 Hz, 1H), 4.27–4.34 (m, H-3, H-4, 2H), 4.14 (dd, J=9.6, 10.4 Hz, H-1$_a$, 1H), 3.80 (dd, J=5.2, 10.4 Hz, H-1$_b$, 1H), 3.24 (s, –OCH$_3$, 3H), 1.35 (s, CH$_3$ (isopropylidine), 3H), 1.32 (s, CH$_3$ (isopropylidine), 3H). δ_C (100 MHz, CDCl$_3$): 168.3, 135.2, 133.9, 131.9, 123.5, 119.8, 109.6, 96.4, 80.8, 78.1, 64.3, 55.4, 53.6, 27.0, 26.8. Low-resolution MS (EI): m/z: 362 (M$^+$+1). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.25; H, 6.37; N, 3.81. Compound **24**: R_f (20% EtOAc/hexane) 0.52; IR (neat): 2988, 2935, 2891, 1776, 1714 cm^{-1}; δ_H (400 MHz, CDCl$_3$): 7.81 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.71 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 5.57–5.65 (m, H-5, 1H), 4.96 (d, J=16.8 Hz, H-6$_a$, 1H), 4.76 (d, J=10.4 Hz, H-6$_b$, 1H), 4.50–4.57 (m, H-2, –OCH$_2$O–, 3H), 4.31 (dd, J=4.4, 9.6 Hz, H-3, 1H), 4.29 (dd, J=8.0, 9.6 Hz, H-1$_a$, 1H), 4.18 (t, J=8.4 Hz, H-4, 1H), 4.00 (dd, J=4.0, 10.4 Hz, H-1$_b$, 1H), 3.22 (s, O–CH$_3$, 3H), 1.43 (s, CH$_3$ (isopropylidine), 3H), 1.41 (s, CH$_3$ (isopropylidine), 3H). δ_C (100 MHz, CDCl$_3$): 168.4, 134.9, 134.0, 131.5, 123.3, 119.1, 109.8, 96.4, 82.1, 76.2, 64.9, 55.3, 53.6, 27.0, 26.9. Low-resolution MS (EI): m/z: 362 (M$^+$+1). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.81. Found: C, 63.31; H, 6.38; N, 3.82.

4.19. 2-((*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-((*E*)-tetradec-1-enyl)-1,3-dioxolan-4-yl)-2-(methoxymethyloxy)ethyl)isoindoline-1,3-dione (25)

Compound **24** (200 mg, 0.55 mmol) and 1-tetradecene (430 mg, 2.2 mmol) were dissolved in CH_2Cl_2 (20 mL) at room temperature. Grubbs' II generation catalyst (4 mol%) was added to the solution and then the reaction mixture was refluxed under nitrogen for 24 h. After cooling the reaction mixture was concentrated and purified by column chromatography with EtOAc/hexane (1:9) to afford compound **25** (220 mg, 75%) as a colourless liquid. R_f (20% EtOAc/hexane) 0.64; IR (neat): 3053, 2926, 2847, 1776, 1714, 1614, 1467, 1385 cm^{-1}. δ_H (400 MHz, CDCl$_3$): 7.81 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.70 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 5.43 (dt, J=6.4, 15.6 Hz, H-6, 1H), 5.23 (dd, J=7.6, 15.6 Hz, H-5, 1H), 4.58 (d, J=6.4 Hz, –OCH$_a$O–, 1H), 4.54 (dd, J=3.6, 10.8 Hz, H-2, 1H), 4.52 (d, J=6.4 Hz, –OCH$_b$O–, 1H), 4.31 (t, J=10.8 Hz, H-1$_a$, 1H), 4.25 (dd, J=8.4, 10.0 Hz, H-3, 1H), 4.15 (t, J=8.4 Hz, H-4, 1H), 4.01 (dd, J=4.0, 10.4 Hz, H-1$_b$, 1H), 3.22 (s, –OCH$_3$, 3H), 1.43 (s, CH$_3$ (isopropylidine), 3H), 1.40 (s, CH$_3$ (isopropylidine), 3H), 0.92–1.33 (br m, 8 to 17-(CH$_2$)$_{10}$, 20H), 0.87 (t, J=5.2 Hz, 18-CH$_3$, 3H), 0.65–0.79 (m, 7-CH$_2$, 2H). δ_C (100 MHz, CDCl$_3$): 168.3, 137.4, 134.0, 131.7, 125.9, 123.2, 109.3, 96.4, 82.1, 75.7, 65.0, 55.3, 53.6, 31.9, 31.7, 29.6, 29.4, 29.3, 29.3, 29.1, 28.2, 27.1, 26.9, 22.6, 14.1. Low-resolution MS (EI): m/z: 529 (M$^+$). Anal. Calcd for $C_{31}H_{47}NO_6$: C, 70.29; H, 8.94; N, 2.64. Found: C, 70.15; H, 8.89; N, 2.71.

4.20. 2-((*R*)-1-(4*S*,5*S*)-2,2-(Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2-(methoxymethyloxy)ethyl)isoindoline-1,3-dione (26)

To a stirred solution of compound **25** (200 mg, 0.38 mmol) in MeOH (6 mL) was added 10% palladium on charcoal (40 mg). Then the mixture was degassed and stirred under the hydrogen atmosphere at 25 °C for overnight. After completion of the reaction (by TLC) the suspension was filtered through a pad of Celite and concentrated to give compound **26** (190 mg, 95%) as a colourless liquid. R_f (10% EtOAc/toluene) 0.53; IR (neat): 2926, 2854, 1776, 1716, 1467, 1383 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.85 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.73 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 4.57 (d, J=6.8 Hz, $-OCH_aO-$, 1H), 4.53–4.56 (m, H-2, 1H), 4.52 (d, J=6.4 Hz, $-OCH_bO-$, 1H), 4.31 (t, J=10.4 Hz, H-1_a, 1H), 4.21 (dd, J=7.2, 9.6 Hz, H-3, 1H), 4.02 (dd, J=4.4, 10.4 Hz, H-1_b, 1H), 3.89 (td, J=2.8, 7.6 Hz, H-4, 1H), 3.22 (s, $-OCH_3$, 3H), 1.43 (s, CH_3 (isopropylidine), 3H), 1.40 (s, CH_3 (isopropylidine), 3H), 1.09–1.25 (m, 5 to 17-$(CH_2)_{13}$, 26H), 0.89 (t, J=6.8 Hz, 18-CH_3, 3H). δ_C (100 MHz, $CDCl_3$): 168.4, 134.2, 131.5, 123.4, 109.2, 96.4, 80.0, 64.7, 55.3, 55.4, 33.7, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 27.4, 27.1, 25.4, 22.6, 14.1. Low-resolution MS (EI): m/z: 531 (M^+). Anal. Calcd for $C_{31}H_{49}NO_6$: C, 70.02; H, 9.29; N, 2.63. Found: C, 70.12; H, 9.23; N, 2.55.

4.21. 2-((2*R*,3*S*,4*R*)-1,3,4-Trihydroxyoctadecan-2-yl) isoindoline-1,3-dione (27)

A solution of compound **26** (170 mg, 0.32 mmol) in 80% aqueous acetic acid (6 mL) was stirred at 80 °C for 24 h. After completion of the reaction (by TLC) the reaction mixture was cooled to 25 °C and the solvent was removed under reduced pressure. The residual acetic acid was co-evaporated with toluene to give a white solid. Flash column chromatography of this residue with EtOAc/hexane (1:1) provided compound **27** (120 mg, 84%) as a white solid. R_f (40% EtOAc/toluene) 0.2; IR (KBr): 3564, 3620, 3414, 2918, 2849, 1778, 1705, 1466, 1386 cm^{-1}. δ_H (400 MHz, $CDCl_3$): 7.88 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 7.78 (dd, J=3.2, 5.6 Hz, phthalimide Ar–H, 2H), 4.48–4.52 (m, H-2, 1H), 4.24 (dd, J=4.4, 12.0 Hz, H-1_a, 1H), 4.14 (dd, J=6.0, 12.0 Hz, H-1_b, 1H), 4.06 (d, J=7.2 Hz, H-3, 1H), 3.50–3.5 (m, H-4, 1H), 1.62–1.65 (m, 5-H_a, 1H), 1.50–1.54 (m, 5-H_b, 1H), 1.27 (br s, 6 to 17-$(CH_2)_{12}$, 24H), 0.89 (t, J=6.8 Hz, 18-CH_3, 3H). δ_C (100 MHz, $CDCl_3$): 169.2, 134.5, 131.5, 123.7, 72.3, 71.0, 61.5, 54.9, 33.6, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 25.8, 22.7, 14.1. Low-resolution MS (EI): m/z: 448 (M^++1). Anal. Calcd for $C_{26}H_{41}NO_5$: C, 69.77; H, 9.23, N; 3.13. Found: C, 69.85; H, 9.18; N, 3.25.

4.22. (2*R*,3*S*,4*R*)-2-Aminooctadecane-1,3,4-triol (L-*arabino*-C_{18}-phytosphingosine) (28)

To a stirred solution of compound **27** (40 mg, 0.10 mmol) in dry CH_3OH (3 mL) was added hydrazine hydrate (9.0 mg, 0.18 mmol) at 25 °C. The resulting mixture was stirred for 24 h. After completion of the reaction the solvent was evaporated under reduced pressure. The obtained residue was purified by flash column chromatography using $CHCl_3$/MeOH/NH_4OH (85:15:1) to give compound **28** (23 mg, 81%) as a white solid. R_f ($CHCl_3$/MeOH/NH_4OH (80:20:1)) 0.48; IR (KBr): 3462, 2924, 2854, 1466 cm^{-1}. δ_H (400 MHz, CD_3OD): 3.80 (dd, J=4.0, 10.8 Hz, H-1_a, 1H), 3.67–3.71 (m, H-4, 1H), 3.55 (dd, J=5.2, 10.8 Hz, H-1_b, 1H), 3.36 (dd, J=2.4, 6.8 Hz, H-3, 1H), 2.94–2.99 (m, H-2, 1H), 1.50–1.60 (m, 2H), 1.31 (br s, 6 to 17-$(CH_2)_{12}$, 24H), 0.92 (t, J=6.8 Hz, 18-CH_3, 3H). δ_C (100 MHz, CD_3OD): 73.7, 70.8, 63.1, 54.2, 33.2, 31.6, 29.5, 29.4, 29.3, 29.0, 25.6, 22.3, 13.0. Low-resolution MS (EI): m/z: 318 (M^++1). Anal. Calcd for $C_{18}H_{39}NO_3$: C, 68.09; H, 12.38; N, 4.41. Found: C, 68.15; H, 12.31; N, 4.38.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.003.

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