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Graphical Abstract

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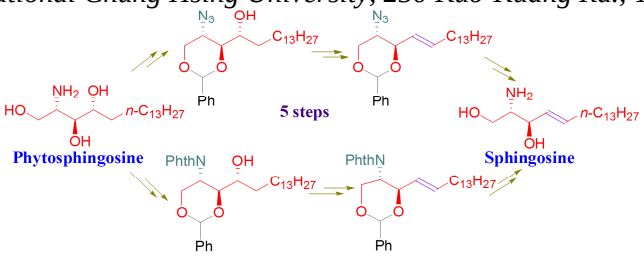

A Rapid Synthesis of Sphingosine from Phytosphingosine

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1. Abstract

A simple and efficient protocol for the synthesis of a sphingosine starting from cost-effective phytosphingosine has been described. Two alternative synthetic pathway have been disclosed based on the use of two different kinds of protective groups for the protection of the amino group in the phytosphingosine. The protected phytosphingosine was subsequently transformed into sphingosine in 5 steps i.e. protection of the amine group, protection of 1,3-diol, leaving group insertion, elimination, and one-pot deprotection.

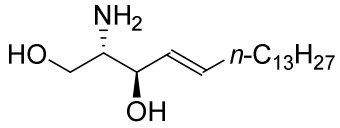
Key words: Phytosphingosine, Sphingosine, Regioselective, Protection, Elimination, Deprotection

2. Introduction

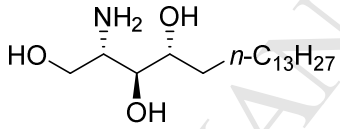
Sphingosine and its derivatives are collectively called sphingolipids and these are key signaling molecules and also play an important role in biological activities. As these molecules are the potentially specific inhibitor of protein kinase C which shows an important role for transduction.[1-4] Metabolites of their family like ceramide, sphingosine and sphingosine-1-phosphate are the important component in the cell process.[5-8] Has its hydrophobic moieties are inside the membrane layer while its hydrophilic moieties are along the cell surface.[9] It plays important role in regulating fundamental and diverse cell processes that include survival, adhesion, cell growth, differentiation, migration, apoptosis[10] etc... Sphingolipids are associated with common diseases such as cancer,[11] heart disease,[12] Alzheimer's disease[13] etc., and are unique markers that indicate the existence of metabolic disorders arising from deletion, duplication and point mutations in the gene encoding to the enzymes.[14] Sphingosine is an important building block for several biologically important molecules like ceramides, which has a long chain 2-amino-1,3-diol, C-4 and C-5 trans double bond and a polar head group at a C-1 position through ester linkage.[15]

Hence their need for large-scale to understand its biological properties in depth has been prompted the development of various synthetic procedures including from phytosphingosine to sphingosine.[16-17] Among them, carbohydrates like D-mannose[18-19] and D-glucose[19-20] were efficient precursors to sphingosine. However, these methods needed more than 10 steps. In another method, sphingosine was derived from serine by the reduction of N-PMP and Boc-N-PMP by the diastereoselective method. Even though in that last step PMP de-protection had some problems and the lengthy procedure was employed.[21] Among them, Recently Panza et al reported the synthesis of sphingosine in excellent yield by the way of approaching proper protecting groups and it led less number of protection and deprotection steps.[22] On the other hand, Chung et al reported the synthesis of four diastereomers of sphingosine by using of N-trityl protecting group.[23] In 2006 Kim's group also reported synthesis of sphingosine from phytosphingosine with less number of steps.[24] It was a convenient way to access to all four diastereomers. We envisioned that Panza et al approach is a convenient protocol which will

offer a facile access to the sphingosine. Herein, we report a facile protocol for the synthesis of sphingosine from phytosphingosine with a major thrust on developing an efficient route with fewer reaction steps and improved yields. We have selected phytosphingosine as starting materials because of both sphingosine and phytosphingosine are structurally related to each other and the removal of C4-OH of phytosphingosine and arising of C4 and C5 double bond will lead to sphingosine (Figure 1).



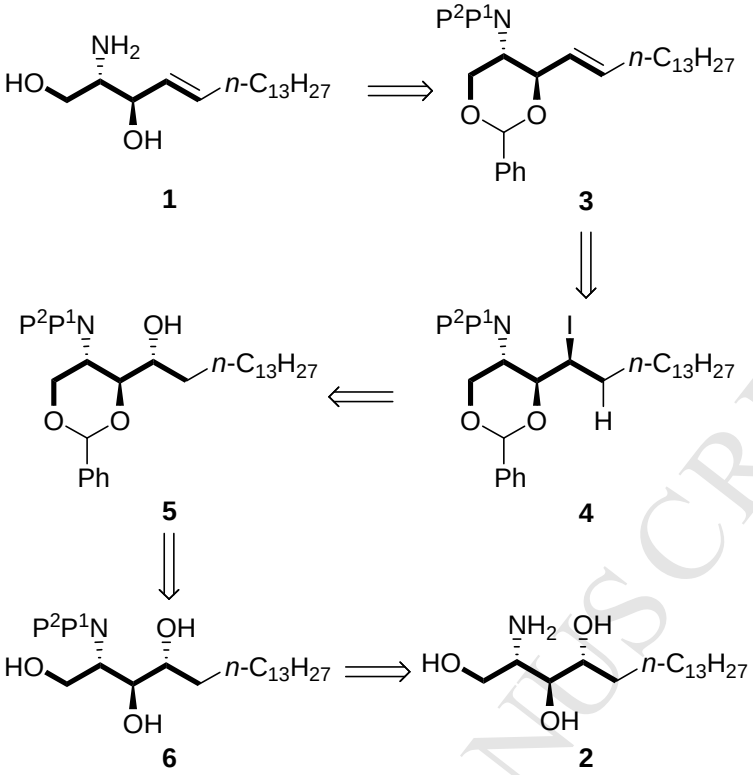
Sphingosine **1**



Phytosphingosine **2**

Figure 1. Structures of sphingosine **1** and phytosphingosine **2**.

Based on our experience on this kind of chemistry, we envisaged that commercially available phytosphingosine **2** would serve as appropriate starting material for the synthesis of sphingosine **1**. As shown in the retrosynthetic strategy (Scheme 1) the sphingosine **1** would be obtained from fully protected olefin intermediate **3** via *N*-deprotection and benzylidene deprotection. The intermediate **3** would be obtained via deiodination at C4 of intermediate **4** which would be derived from **5** by Appel's reaction (S_N2). The mono-ol **5** would be generated from the triol **6** by stereo and regio-selective protection of 1,3-diol by using 1-(dimethoxymethyl)benzene. The triol **6** would be synthesized from phytosphingosine **2** by the protection of different protecting groups.



Scheme 1. Retrosynthetic strategy for the synthesis of sphingosine **1**.

3. Results and Discussion

Accordingly, initially, the protection of amine group of phytosphingosine **2** was carried out by using phthalic anhydride (1.8 equiv.) at reflux condition for 16 hours, provided **6a** in 76% yield.[22] The **6a** was treated with benzaldehyde dimethyl acetal (2.0 equiv.) and camphorsulfonic acid (CSA, 1.0 equiv.) in acetonitrile at room temperature for the regioselective synthesis of benzylidene **5a** in 77% yield.[22] The regioselective ring formation between C1 and C3-OH is the key step which led to a stable thermodynamic six-member ring of **5a** and left the C4-OH free for further smooth reactions. The ring formation between C3 and C4 not only would lead us to extra steps but also the formed ring is kinetic five-member.

Since alcohol is a poor leaving group to form the double bond, we have introduced a known leaving group at C4 position in order to get olefin. At first, we treated **5a** with methanesulfonyl chloride which would provide C4 methanesulfonate derivative in 92% yield. We expected that the -OMs

(methanesulfonate) group would serve as a good leaving group to obtain olefin **3a**. However, while we tried to eliminate -OMs from C4-position, we only obtained desired olefin product **3a** in 18% yield. In order to enhance the yield of olefin **3a**, our task was to introduce a good leaving group at C4 position. Accordingly, we have tried to introduce the iodine to replace C4-OH by Appel's reaction which was a good leaving group at C4 position. Though iodine is a bulky moiety compare to that of Br and Cl to fit in the C4 secondary alcohol position but it has good leaving property than any other halogen. For Appel's reaction, we have treated **5a** with PPh_3 (2.0 equiv.), imidazole (5.0 equiv.), I_2 (2.0 equiv.) in toluene at 80 ^oC for overnight and **4a** was obtained in 99% yield.[22] Then **4a** was the treated with DBU (4.0 equiv.) in toluene to afford trans-olefin **3a** in 93% yield.[22] The trans selectivity might be attributed to the steric hindrances of the bulky group on double bond at C4 and C5 carbons which in principle try to be far apart from each other and therefore presumably this reaction occurs via anti-coplanar. Also, DBU is a bulky base; hence it takes the proton from a less hindered side and produced the selectively trans olefin **3a** desired product in good yield.

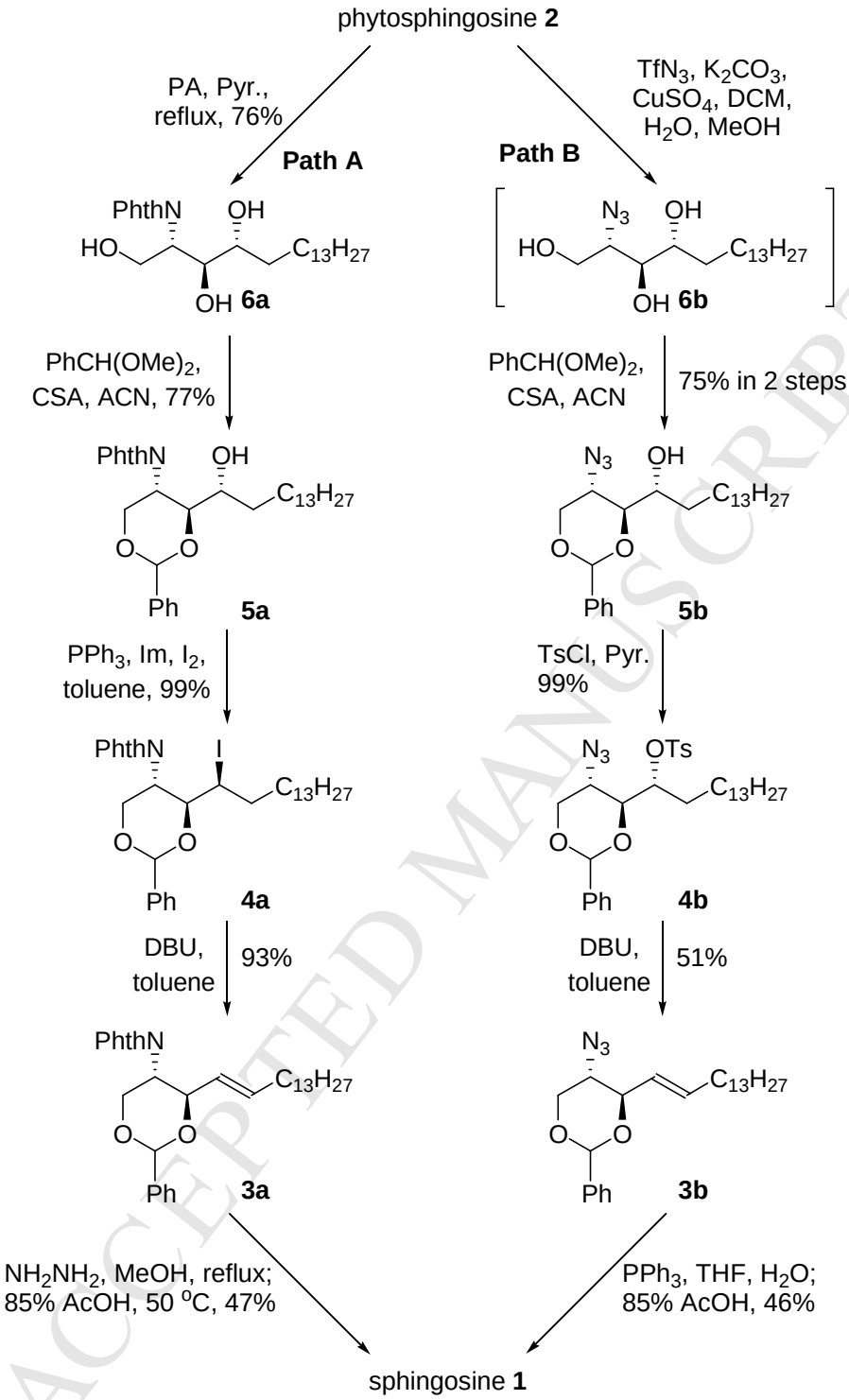
Next, in order to achieve our target, we have tried different approaches to remove the -Phth and benzylidene groups from **3a.** The first approach was involved that selective deprotection of the benzylidene group from **3a** by using 85% TFA and water at 50 ^oC provided the precursor for sphingosine and treatment of this precursor with hydrazine (1.5 equiv.) in methanol at reflux condition resulted into our desired product sphingosine **1** in 61% yield[22] in two steps. In another approach, we have tried this deprotection process in one-pot operation. For that, firstly **3a** was treated with hydrazine (1.5 equiv.) in methanol at reflux condition to deprotect the Phth-group and after the completion of the reaction, the crude product was then treated with 85% AcOH in water at 50 ^oC to afford the sphingosine **1** in 47% yield in two steps (Path A, Scheme 2).

We have also established an alternative synthetic pathway for the synthesis of sphingosine **1** by using the same phytosphingosine **2** as our starting material. It was shown in Path B (Scheme 2). The azido compound **6b** was obtained via the reaction of phytosphingosine **2** with in situ prepared trifluoromethane sulfonyl azide (TfN_3, 2.0 equiv.), under the influence of copper sulphate (0.016 equiv.)

and potassium carbonate (5.0 equiv.) by using the mixture of dichloromethane, water and methanol as the solvent system.[25] Without further purification **6b** was then treated with benzaldehyde dimethyl acetal (2.0 equiv.) and CSA (1.0 equiv.) in acetonitrile at room temperature provided benzylidene **5b** in 75% yield for two steps.[22] By Appel's reaction the mono-ol **5b** could not convert to the iodinated desired product and instead of that amine derivative was obtained. A little modification was made where **5b** was treated with TsCl (3.6 equiv.) in pyridine which provided tosylation at C4 position **(4b)** in 99% yield. The **4b** was then treated with DBU (4 equiv.) in toluene to afford trans-olefin **3b** in 51% yield. It was then deprotected by using Staudinger's reaction (PPh_3, THF and water) followed by de-benzylidene reaction with 85% AcOH resulted in sphingosine **1** in 46% yield.

4. Conclusions

In conclusion, we have successfully developed two alternative synthetic methodologies for the synthesis of biologically important sphingosine 1 from commercially available phytosphingosine 2. Both azido and phthalic group were used as potent protecting groups for amine in phytosphingosine **2.** In two alternative strategies were lead to facile transformation to sphingosine over 5 steps which include protection, leaving group insertion, elimination and finally one pot deprotection. The developed protocol is superior as it effectively reduces the number of steps providing the sphingosine **1** in overall 25% and 17% yield.



Scheme 2. Synthesis of sphingosine from phytosphingosine.

4. Experimental Section

4.1. General Information.

Some reactions were conducted in flame-dried glassware, under the nitrogen atmosphere. Acetonitrile and toluene were purified and dried from a safe purification system containing activated Al_2O_3 (PubChem CID: 9989226); All reagents obtained from commercial sources were used without purification unless otherwise mentioned. Phytosphingosine (PubChem CID: 122121); was purchased from Tokyo Chemical Industry Co. Ltd, Japan. Flash column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$ (0.5 g), $(NH_4)_6Mo_7O_{24}$ (24.0 g) and H_2SO_4 (28.0 mL) in water (500.0 mL) and subsequent heating on a hot plate. Optical rotations were measured at 589 nm (Na), ^1H, ^{13}C NMR, DEPT, ^1H-^1H COSY, ^1H-^{13}C COSY, and NOESY spectra were recorded with 400 and 600 MHz instruments. Chemical shifts are in ppm from Me_4Si generated from the $CDCl_3$ lock signal at δ7.26. IR spectra were taken with a FT-IR spectrometer using KBr plates. Mass spectra were analyzed on Orbitrap instrument with an ESI source.

4.2. (2*S*,3*S*,4*R*)-2-(Phthalimido)-octadecane-1,3,4-triol (6a).

To a solution was added phytosphingosine **2** (1.00 g, 3.15 mmol) and phthalic anhydride (840 mg, 5.67 mmol) in pyridine (50 mL). The resulting mixture was immersed in a preheated oil bath to reflux and stirred for 16 hours at the same temperature until TLC indicated the complete disappearance of starting material. Then the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to afford triol **6a** (2.11 g, 76%) as a white solid. R_f 0.62 (EtOAc/Hex = 2/1); mp 85-86 ^oC; $[\alpha]^{25}_D$ -33.46 (*c* 1.00, Pyridine). IR (KBr): 3513, 3317, 2918, 2853, 1770, 1704, 1613, 1465, 1391 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H, ArH), 7.76 (dd, *J* = 5.4, 3.1 Hz, 2H, ArH), 4.66 (dd, *J* = 9.6, 4.9 Hz, 1H, H-2) 4.18 (dd, *J* = 12.1, 4.9 Hz, 1H, H-1a), 4.09-3.95 (dd, *J* = 8.8, 3.2 Hz, 2H, H-1b, H-3), 3.76 (dd, *J* = 8.7, 3.5 Hz, 1H, H-4), 1.62-1.18 (m, 26H, CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4 (C × 2), 134.4 (CH × 2), 131.6 (C × 2), 123.6 (CH × 2), 101.0 (CH_2), 75.0 (CH), 72.9 (CH), 60.9 (CH_2), 53.8 (CH), 32.6 (CH_2), 31.9 (CH_2), 29.7

146 (CH_2 × 2), 29.65 (CH_2), 29.63 (CH_2), 29.6 (CH_2), 29.5 (CH_2 × 2), 29.3 (CH_2), 25.7 (CH_2), 22.7 (CH_2),

147 14.1 (CH_3).

148 HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{41}O_5NNa$ 470.2882; found 470.2892.

149 **4.3. (2*S*,3*S*,4*R*)-2-(Phthalimido)-1,3-benzylidene-octadecan-1,3,4-triol (5a).**

150 To a solution of the triol **6a** (2.11 g, 4.7 mmol) and benzaldehyde dimethyl acetal (1.4 mL, 9.4 mmol)

151 in anhydrous acetonitrile (21.0 mL) was treated with camphorsulfonic acid (1.09 g, 4.7 mmol) at room

152 temperature under nitrogen atmosphere. After completion of the reaction, the reaction mixture was

153 quenched by trimethylamine and extracted by water (10 mL) and dichloromethane (20 mL × 3). The

154 combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and

155 concentrated under reduced pressure. The crude was purified by column chromatography on silica gel

156 to afford **5a** (2.84 g, 77%) as a white solid. R_f 0.47 (EtOAc/Hex = 1/4); mp 68-72 °C; $[\alpha]^{25}_D$ +15.97 (*c*

157 0.86, CH_2Cl_2). IR (KBr): 3467, 2922, 2851, 1708, 1646, 1502, 1467, 1387, 1120, 1012 cm^{-1}. ^1H NMR

158 ($CDCl_3$, 400 MHz): δ = 7.88-7.80 (m, 2H, ArH), 7.78-7.68 (m, 2H, ArH), 7.57-7.46 (m, 2H, ArH),

159 7.45-7.30 (m, 3H, ArH), 5.70 (s, 1H, CHPh), 4.72 (dd, *J* = 9.9, 4.4 Hz, 1H, H-2), 4.68-4.60 (m, 1H,

160 H-3), 4.56 (t, *J* = 10.5 Hz, 1H, H-4), 4.10 (dd, *J* = 10.1, 4.6 Hz, 2H, H-1a, H-1b), 1.85-1.11 (m, 26H,

161 CH_2), 0.86 (t, *J* = 6.9 Hz, 3H, CH_3).

162 ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.0 (C), 137.55 (C × 2), 134.2 (CH × 2), 131.6 (C × 2), 129.1

163 (CH), 128.3 (CH × 2), 126.2 (CH × 2), 123.5 (CH × 2), 101.2 (CH), 78.0 (CH), 78.9 (CH), 66.2 (CH_2),

164 45.7 (CH), 32.03 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.63 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2),

165 29.45 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI): *m*/*z* $[M+H]^+$

166 calcd for $C_{33}H_{46}NO_5$ 536.3370; found 536.3366.

167 **4.4. (*2S,3S,4S*)-2-(Phthalimido)-1,3-benzylidene-4-iodooctadecane-1,3-diol (4a).**

168 To a solution of compound **5a** (2.84 g, 5.3 mmol) in dry toluene (28.4 mL) under nitrogen condition

169 triphenylphosphine (2.78 g, 10.6 mmol), imidazole (1.80 g, 26.5 mmol) and iodine (2.69 g, 10.6 mmol)

170 were added sequentially and the reaction mixture was stirred at 80 °C for 4 h. The resulting solution

171 was washed with saturated aq. $Na_2S_2O_3$ and extracted by water (30 mL) and dichloromethane (30 mL ×

3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford iodine **4a** (3.38 g, 99%) as colorless viscous liquid. R_f 0.52 (EtOAc/Hex = 1/4); $[\alpha]^{25}_D$ +9.75 (c 0.93, CH_2Cl_2); IR (KBr) *v* 3747, 2923, 2853, 2107, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H, ArH), 7.78-7.76 (m, 2H, ArH), 7.58-7.55 (m, 2H, ArH), 7.42-7.38 (m, 3H, ArH), 5.83 (s, 1H, CHPh), 4.82 (ddd, *J* = 10.9, 9.9, 5.1 Hz, 1H, H-3), 4.49 (t, *J* = 10.8 Hz, 1H, H-1a), 4.32 (dd, *J* = 9.8, 1.7 Hz, 1H, H-2), 4.14 (dd, *J* = 10.5, 5.1 Hz, 1H, H-1b), 4.02 (ddd, *J* = 9.2, 5.4, 1.7 Hz, 1H, H-4), 1.39-1.15 (m, 26H, CH_2), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C), 137.5 (C × 2), 134.4 (CH × 2), 131.5 (C × 2), 129.1 (CH), 128.3 (CH × 2), 126.3 (CH × 2), 123.6 (CH × 2), 101.1 (CH), 77.0 (CH) 65.9 (CH_2), 49.3 (CH), 37.0 (CH_2), 34.5 (CH), 31.9 (CH_2), 29.74 (CH_2), 29.7 (CH_2), 29.64 (CH_2), 29.62 (CH_2 × 2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{33}H_{44}IO_4NNa$ 668.2207, found 668.2188.

4.5. (*2S,3R,4E*)-2-(Phthalimido)-1,3-benzylidene-octadec-4-ene-1,3-diol (3a).

To a solution of the iodo compound **4a** (3.38 g, 5.23 mmol) in anhydrous toluene (34 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.1 mL, 3.19 mmol) under nitrogen atmosphere. The resulting mixture was kept at 110 °C for 2 hours, after the disappearance of the starting material in TLC. It was allowed to room temperature and the mixture was neutralized with 2M HCl, then the reaction mixture was extracted by water (30 mL) and dichloromethane (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide **3a** (2.53 g, 93%) as a white solid. R_f 0.63 (EtOAc/Hex = 1/4); mp 66-70 ^oC; $[\alpha]^{25}_D$ +4.80 (c 0.93, CH_2Cl_2); IR (KBr) *v* 2922, 2852, 1774, 1715, 1468, 1454, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H, ArH), 7.76-7.69 (m, 2H, ArH), 7.56-7.52 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 5.79-5.63 (m, 2H, CHPh, H-5), 5.46 (dd, *J* = 15.4, 8.3 Hz, 1H, H-4), 5.06 (dd, *J* = 9.6, 8.4 Hz, 1H, H-3), 4.62 (t, *J* = 10.8 Hz, 1H, H-1a), 4.52-4.40 (m, 1H, H-2), 4.18 (dd, *J* = 10.4, 4.8 Hz, 1H, H-1b), 1.97-1.76 (m, 2H, CH_2), 1.35-0.92 (m, 22H, CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (CH),

134.2 (CH), 133.3 (C), 132.4 (C × 2), 132.3 (CH), 132.2 (CH), 131.53 (CH), 131.5 (CH), 131.47 (C × 2), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.3 (CH), 123.4 (CH), 101.1 (CH), 78.2 (CH), 66.4 (CH2), 48.8 (CH), 32.1 (CH_2), 31.9 (CH_2), 29.7 (CH_2 × 2), 29.6 (CH_2 × 2), 29.35 (CH_2), 29.33 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{33}H_{43}O_4NNa$ 540.3084, found 540.3075.

4.6. (2S,3S,4R)-2-(Azido)-1,3-benzylidene-octadecan-1,3,4-triol (5b).

A solution of NaN_3 (2.04 g, 31.5 mmol), DCM/H_2O (5.0 mL/5.0 mL) was cooled to 0 ^oC and Tf_2O (1.10 mL, 6.30 mmol) was added dropwise to the reaction mixture for 20 min, under nitrogen atmosphere. The reaction mixture was kept at the same temperature for 3 hours. The mixture was extracted with water and dichloromethane (10 mL × 2). The combined organic layer was washed with saturated $NaHCO_3$ (16 mL) and the organic layer was used to produce azido group in phytosphingosine **2**. To the suspension of phytosphingosine (1.00 g, 3.15 mmol), K_2CO_3 (2.14 g, 15.8 mmol) and $CuSO_4$•$5H_2O$ (16.0 mg, 0.01 mmol) in the mixture of methanol and water (4.0 mL/3.0 mL) was added the combined organic layer which contained TfN_3. After reaction completion, the resulting solution was concentrated to remove the organic solvent under *vacuo*. The mixture was extracted by water (10 mL) and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was used in the next step reaction without further purification.[24] A suspension of triol (1.08 g, 3.15 mmol) and benzaldehyde dimethyl acetal (1.0 mL, 6.3 mmol) in anhydrous acetonitrile (10.8 mL) was treated with camphorsulfonic acid (0.73 g, 3.15 mmol) in nitrigen atmosphere. The reaction stirred at room temperature for 1 hour. The residue was purified by column chromatography on silica gel to afford the compound **5b** (1.02 g, 75%) as a colorless liquid. R_f 0.67 (EtOAc/Hex = 1/3); $[\alpha]^{25}_D$ +34.34 (*c* = 1.0, CH_2Cl_2); IR (KBr) *v* 3475, 3068, 3038, 2848, 2122, 1466, 1398 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H, ArH), 7.39-7.36 (m, 3H, ArH), 5.46 (s, 1H, CHPh), 4.38 (dd, *J* = 8.4, 3.0 Hz, 1H, H-2), 3.88 (s, 1H, H-4), 3.67 (m, 3H, H-1a, H-1b, H-3), 1.62 (dd, *J* = 13.8, 7.2 Hz, 2H, H-5a, H-5b), 1.56-1.26 (m, 24H, CH_2), 0.88 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C),

129.0 (CH), 128.1 (CH × 2), 125.9 (CH × 2), 100.8 (CH), 82.1 (CH), 72.1 (CH), 68.5 (CH2), 52.9 (CH), 31.8 (CH_2), 31.6 (CH_2), 29.6 (CH_2 × 2), 29.5 (CH_2 × 3) 29.4 (CH_2 × 2), 29.2 (CH_2 × 2), 25.9 (CH_2), 22.5 (CH_2), 13.9 (CH_3); HRMS (ESI, M+Na^+) calcd for $C_{25}H_{41}N_3O_3Na$ 454.3046, found 454.3040.

4.7. (*2S,3S,4S*)-2-Azido-1,3-benzylidene-4-*O*-(toluenesulfonyl)-octadeca-ne-1,3-diol (4b).

To a solution of the compound **5b** (2.51 g, 5.83 mmol) in pyridine (24.5 mL) was added 4-toluenesulfonyl chloride (3.97 g, 21.0 mmol) and stirred at room temperature for 24 hours. The starting material was completely consumed as judged by TLC. Then the mixture was washed with saturated aqueous $Na_2S_2O_3$, extracted with dichloromethane (30 mL× 3) and water. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford iodine **4b** (3.38 g, 99%) as the colorless viscous liquid. R_f 0.43 (EtOAc/Hex = 1/8); $[\alpha]^{25}D$ +28.18 (c 0.93, CH_2Cl_2); IR (KBr) *v* 3747, 2923, 2853, 2107, 1460, 1367, 1189, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 12.6 Hz, 2H, ArH), 7.40-7.32 (m, 5H, ArH), 7.29-7.23 (m, 2H, ArH), 5.36 (s, 1H, CHPh), 4.78 (ddd, *J* = 9.6, 3.6, 1.8 Hz, 1H, H-2), 4.37 (dd, *J* = 10.9, 5.2 Hz, 1H, H-4), 3.80 (dd, *J* = 10.1, 1.8 Hz, 1H, H-3), 3.68 (t, *J* = 10.7 Hz, 3H, H-1a), 3.49 (td, *J* = 10.3, 5.2 Hz, 1H, H-1b), 2.41 (s, 3H, CH_3), 1.89 (m, 1H, H-5a), 1.63 (m, 1H, H-5b), 1.36-1.11 (m, 24H, CH_2), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C), 129.0 (CH), 128.1 (CH × 2), 125.9 (CH × 2), 100.8 (CH), 82.1 (CH), 72.1 (CH), 68.5 (CH_2), 52.9 (CH), 31.8 (CH_2), 31.6 (CH_2), 29.6 (CH_2 × 2), 29.5 (CH_2 × 3) 29.4 (CH_2 × 2), 29.2 (CH_2 × 2), 25.9 (CH_2), 22.5 (CH_2), 13.9 (CH_3); HRMS (ESI, M+H^+) calcd for $C_{32}H_{48}N_3O_5S$ 586.3309, found 586.3527.

4.8. (*2S,3R,4E*)-2-Azido-1,3-benzylidene-octadec-4-ene-1,3-diol (3b).

To a solution of compound **4b** (606.1 mg, 1.03 mmol) were dissolved in toluene (6.0 mL) and DBU (6.0 mL, 4.10 mmol) was added under nitrogen atmosphere. Then the reaction allowed to stir at 120 ^oC for overnight. It was allowed to room temperature and the mixture was neutralized with 2M HCl, then the reaction mixture was extracted by water (50 mL) and dichloromethane (50 mL). The combined

organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **3b** (416.2 mg, 51%) as solid. R_f 0.82 (EtOAc/Hex = 1/8); $[\alpha]^{25}_{D}$ +13.38 (c = 1.0, CH_2Cl_2); IR (KBr) *v* 2924, 2853, 2107, 1643, 1459, 1397 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 12.6 Hz, 1H, ArH), 7.41-7.27 (m, 3H, ArH), 7.20-7.17 (m, 1H, ArH), 5.91 (dt, *J* = 10.5, 10.2 Hz, 1H, H-5), 5.51 (dd, *J* = 11.4, 10.8 Hz, 1H, H-4), 5.41 (s, 1H, CHPh), 4.33 (m, 1H, H-2), 4.25 (dd, *J* = 7.8, 7.2 Hz, 1H, H-4), 3.82 (d, *J* = 15.0 Hz, 1H, H-3), 3.97 (t, *J* = 12.3 Hz, 1H, H-1a), 3.44-3.35 (m, 1H, H-1b), 1.18 (m, 24H, CH_2), 0.8 (t, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (C), 129.1 (CH × 2), 128.6 (CH × 2), 127.8 (CH × 2), 101.0 (CH), 81.8 (CH), 68.9 (CH), 57.3 (CH), 32.4 (CH_2), 31.9 (CH_2), 29.65 (CH_2 × 2), 29.63 (CH_2 × 2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.6 (24H, CH_2), 22.7 (CH_2), 13.9 (CH_3); HRMS (ESI, M^+H^+) calcd for $C_{25}H_{40}O_2N_3$ 414.3115, found 414.3348.

4.9. (*2S,3R,4E*)-2-Aminooctadec-4-ene-1,3-diol (1).

Method A: To a solution of compound **3a** (241.0 mg, 0.54 mmol) in methanol (2.40 mL) was added hydrazine (0.81 mL, 0.81 mmol) and the resulting mixture was stirred at preheated oil bath to reflux. Upon completion of the reaction, as indicated by TLC (6 hours) cooled to room temperature and concentrated. Then it dissolved in 85% TFA/EtOH (1.5 mL/0.2 mL) and the temperature was raised to 50 ^oC. After completion of the reaction, the residue was chromatographed on silica gel to provide **1** (104 mg, 61%) as a white solid. *Method B*: To a solution of compound 3b (210.mg, 0.051 mmol) dissolved in THF/H_2O (1.8/0.2 mL) and kept it in 0 ^oC for 5 minutes. Then PPh_3 (266.0 mg, 1.015 mmol) added and the reaction mixture was stirred for 15 minutes at same temperature after that, it was allowed to stir at rt for 5-6 hours. After completion of the reaction judged by TLC, the solvent was concentrated and the crude amine derivative was used to next step without further purification. The amine derivative was dissolved in 85% AcOH/EtOH (1.3/0.2 mL) and it put into preheated oil bath at 50-60 ^oC and stirred for 24 hours at same temperature. After completion of the reaction the solvent removed under vacuum and extracted with water and EtOAc (3 × 10) the organic layer dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The crude product purified by column

chromatography to afford (70.0 mg, 46%) as a yield. R_f 0.37 (MeOH/DCM = 1/5); $[\alpha]^{25}_D$ -1.62 (*c* 0.9, $CHCl_3$) (lit.[9] $[\alpha]^{25}_D$ -1.6); mp 70-72 ^oC (lit.[9] 72-75 ^oC); IR (KBr) *v* 3747, 3351, 2918, 2850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dtd, *J* = 15.4, 6.8, 1.2 Hz, 1H), 5.45 (dd, *J* = 15.4, 6.9 Hz, 1H), 4.06 (t, *J* = 5.9 Hz, 1H), 3.67 (dd, *J* = 10.6, 4.6 Hz, 2H), 2.88 (dd, *J* = 13.8, 3.9 Hz, 6H), 2.05 (dd, *J* = 14.1, 6.9 Hz, 2H), 1.36 (dd, *J* = 12.1, 5.4 Hz, 2H), 1.32-1.26 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7 (CH), 129.2 (CH), 75.2 (CH), 75.0 (CH), 63.7 (CH_2), 56.3 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.7 (CH_2 × 2), 29.59 (CH_2 × 3), 29.4 (CH_2 × 2), 22.8 (CH_2), 14.3 (CH_3); HRMS (ESI, M^+H^+) calcd for $C_{18}H_{38}O_2N$ 300.2903, found 300.2904.

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Highlights

- Sphingosine plays an important role in biological activities.
- We used two kinds of protecting groups (Phthalic anhydride and azide) for amino group in commercially available phytosphingosine.
- This is the direct and simple synthetic strategy including C1 and C3-OH protection, leaving group installing at C4, elimination and the global de-protection.
- We have reported a facile protocol for the synthesis of sphingosine from phytosphingosine with developing an efficient route with fewer reaction steps and improved yields.