Chirospecific Synthesis of D-*erythro*- and L-*threo*-Sphinganines from Sugars

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D-*erythro*-sphinganine **1** and L-*threo*-sphinganine **2** have been prepared in the enantiomerically pure form by the chirospecific manner. Key intermediates, 2-amino-3-hydroxy-4-pentenoates **8** and **12**, were obtained from L-glucono-1,5-lactone and L-gulonic acid g-lactone via a simultaneous dealkoxyhalogenation.

Key Words : D-*erythro*-Sphinganine, L-*threo*-Sphinganine, Simultaneous dealkoxyhalogenation, L-Glucono-1,5-lactone, L-Gulonic acid γ-lactone

Introduction

Dihydrosphingosine, called sphinganine, is an intermediate of the biosynthesis of sphingolipids (*e.g.* ceramides, cerebrosides, sphingomycelin, gangliosides),[1] which plays an important role in a wide range of physiological activities such as immune response, signaling and cell recognition.[2] D-*erythro*-Sphinganine **1** is the important components of cellular membranes and is known as an inhibitor of protein kinase C.[3] Quite a number of syntheses of sphingosine and its derivatives have been reported.[4] Although many synthetic routes from noncarbohydrates through a chiral induction step have been proven as useful methods,[4c,5] chirospecific routes from carbohydrates have low overall yields owing to a tedious number of steps.[6] This encouraged us to explore an efficient synthetic route to sphingosine derivatives starting from carbohydrates. Planning use of carbohydrate derivatives as an enantiomerically pure building block, we focused on the transformation of C6-unit sugars into a multifunctionalized β-hydroxy-α-amino acid derivatives that can easily approach sphingosine derivatives. For example, we reported the synthetic route of 2-amino-3-hydroxy-4-pentenoic acid derivatives via a simultaneous dealkoxyhalogenation.[7] Here, we describe the synthesis of D-*erythro*-sphinganine **1** and L-*threo*-sphinganine **2** by homochiral synthetic techniques from L-glucono-1,5-lactone and L-gulonic acid γ-lactone. Our general retrosynthesis of target molecules **1** and **2** is outlined in Figure 1.

Results and Discussion

As our chiral source, we chose L-glucono-1,5-lactone and L-gulonic acid γ-lactone, which have the two stereocenters required for the target molecules **1** and **2**, respectively. (Figure 1) Thus, the stereochemistry of C2 and C3 in L-glucono-1,5-lactone was used for compound **1**, while that of C2 and C3 in L-gulonic acid γ-lactone was used for compound **2**.

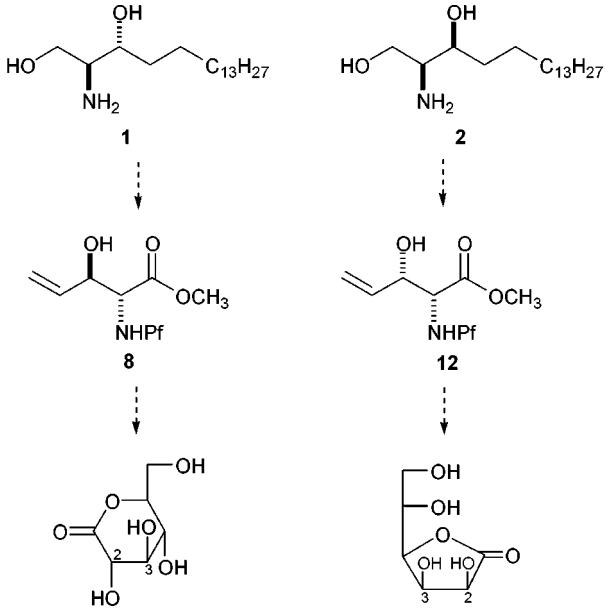

Figure 1. Retrosynthesis of compounds **1** and **2**.

D-*erythro*-Sphinganine 1. Our synthesis commenced with the synthesis of the known diisopropylidenemannonate **3** which was easily accessible via known procedures[8] from D-glucono-δ-lactone. We chose the 9-phenyl-9-fluorenyl (Pf) group for protection of the amine since the protecting group has been shown to inhibit deprotonation at the α-position of an α-amino ester.[9]

For regioselective hydrolysis of the terminal *O*-isopropylidene group in diisopropylidene **3** under acidic condition, Dowex 50W-X8 was treated to **3** in 90% methanol to give the diol **4** in 95% yield. The diol **4** was oxidized in the presence of $NaIO_4$; this was followed by $NaBH_4$ reduction of the resulting aldehyde, which led to the formation of alcohol **5** in quantitative yield. After mesylation of alcohol **5**, the resulting mesylate was treated with LiI to give 2,3-isopropylidene iodide **7** in 97% yield. Treatment of 2,3-isopropylidene iodide **7** with *n*-BuLi at –40 °C gave the (2*R*,3*R*)-2-amino-3-hydroxy-4-pentenoate **8** {$[\alpha]_D^{20}$ +278.2 (*c* 1.00, $CHCl_3$)} in 84% yield, through a simultaneous dealkoxy-

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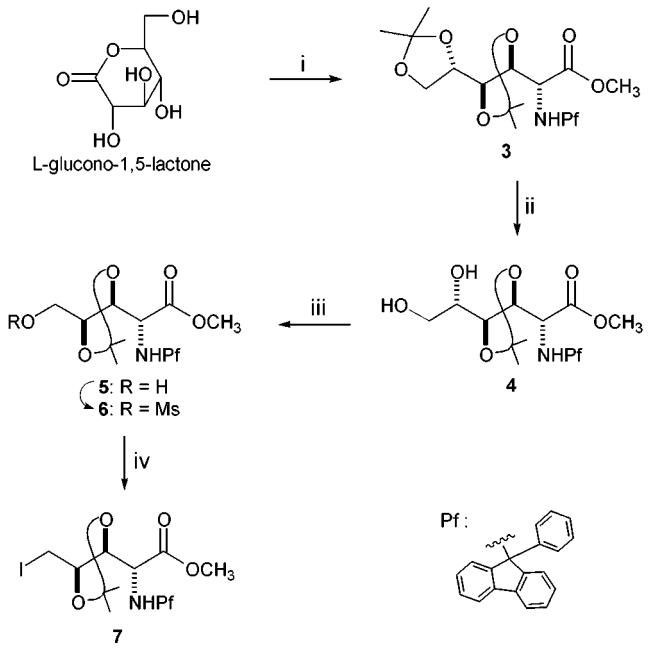
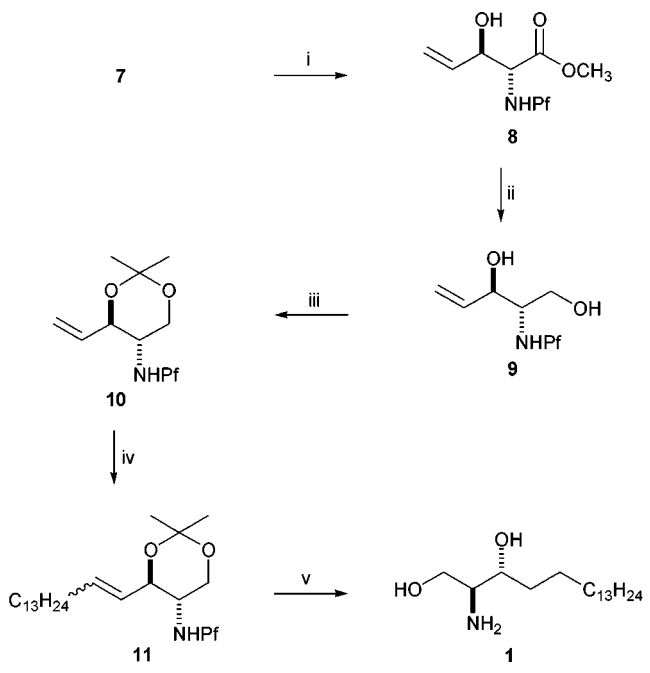


Scheme 1. Reagents and conditions; i) ref 8, 10; ii) Dowex 50W-X8, MeOH, rt, 95%; iii) $NaIO_4$, $NaBH_4$, EtOH-H_2O (2/1), rt to 0 °C, 98%, MsCl, Et_3N, THF, 0 °C, 97%; iv) LiI, DMF, 80 °C, 97%.

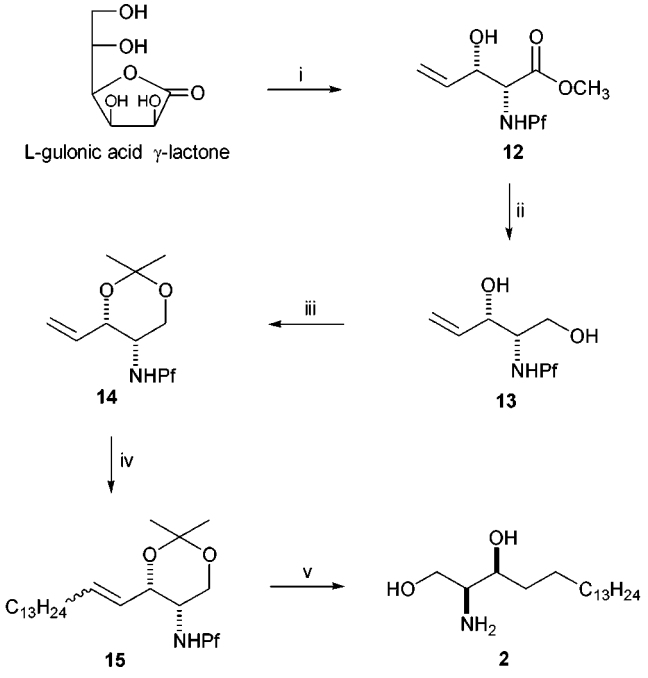
halogenation. This 2-amino-3-hydroxy-4-pentenoate **8** is an important chiral building block for an asymmetric synthesis of bioactive β-hydroxy-α-amino acids. The ester group of pentenoate **8** was reduced by LAH at 0 °C to give compound **9** in 94% yield. The compound **9** was treated with 2,2-dimethoxypropane in acetone to give the isopropylidene pentene **10** in 89% yield. After ozonolysis of pentene compound **10** in CH_2Cl_2 at –78 °C, the resulting aldehyde was treated with tetradecyltriphenylphosphonium bromide to give octadecen-1,3-diol mixture compound **11** (*Z*/*E* 16 : 1, 68% yield). After reduction of Pf group and olefin with 10% Pd/C, the remaining isopropylidene group was completely hydrolyzed with Dowex 50W-X8 in 90% MeOH. The mixture was filtered and the resin was washed with MeOH, and then eluted with 3N aqueous NH_4OH to afford the free base form of D-*erythro*-sphinganine **1** (76% yield) without further purification.

L-*threo*-Sphinganine 2. To further demonstrate the versatility of the synthetic strategy, we have prepared the L-*threo*-sphinganine **2**. The (2*R*,3*S*)-2-amino-3-hydroxy-4-pentenoate **12** was easily obtained from L-gulonic acid γ-lactone as described;[7] the overall yield for this conversion was 59%.

The ester group of (2*R*,3*S*)-2-amino-3-hydroxy-4-pentenoate **12** was reduced by LAH at 0 °C to give compound **13** in 92% yield. The diol compound **13** was treated with 2,2-dimethoxypropane in acetone to give isopropylidene pentene **14**. Ozonolysis of compound **14** in CH_2Cl_2 at –78 °C gave the aldehyde, which was immediately condensed with the ylide, obtained from the tetradecyltriphenylphosphonium bromide, to get **15** as an isomer mixture (*Z*/*E* 20 : 1, 66% yield). The compound **15** was treated with H_2, 10% Pd/C, and Dowex 50W-X8 sequentially, the same procedure for compound **1** to give L-*threo*-sphinganine **2** $[\alpha]_D^{20}$ –2.6 (*c* 2.00, CH_3OH) (79% yield).



Scheme 2. Reagents and conditions; i) *n*-BuLi, THF, –40 °C, 84%; ii) LAH, THF, 0 °C, 94%; iii) Acetone, TsOH, MeOH, 2,2-dimethoxypropane, 50 °C, 89%; iv) O_3, CH_2Cl_2, –78 °C, $CH_3(CH_2)_{12}CH_2PPh_3Br$, *n*-BuLi, THF, –40 °C to rt, 68%; v) H_2, 10% Pd/C, MeOH, 60 °C, 85%, Dowex 50W-X8, MeOH, rt, 76%.



Scheme 3. Reagents and conditions; i) ref 7; ii) LAH, THF, 0 °C, 92%; iii) TsOH, Acetone, MeOH, 2,2-dimethoxypropane, 50 °C, 86%; iv) O_3, CH_2Cl_2, –78 °C, $CH_3(CH_2)_{12}CH_2PPh_3Br$, *n*-BuLi, THF, –40 °C to rt, 66%; v) H_2, 10% Pd/C, MeOH, 60 °C, 82%, Dowex 50W-X8, MeOH, rt, 79%.

Conclusions

We have described the chirospecific synthesis of D-*erythro*-sphinganine **1** and L-*threo*-sphinganine 2 via a simultaneous dealkoxyhalogenation. The developed synthetic routes should be valuable for vicinal aminoalcohol like sphingosine derivatives.

Experimental Section

General. All non-aqueous reactions were carried out under an inert nitrogen atmosphere. THF was distilled from Na/benzophenone; 2,2-dimethoxypropane, DMF, and methylene chloride were distilled from CaH_2. Column chromatography was carried out using 230-400 mesh silica gel. The final solution before evaporation was washed with brine and dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR experiments were conducted on Brucker AW-500 spectrometer. HREIMS were obtained on a JEOLJMS-700 mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Methyl 2-deoxy-3,4;5,6-di-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-L-mannonate 3. The mannonate **3** was prepared from L-glucono-1,5-lactone, using a method to the described one.[8,10] solid, 80% (overall yield) $[\alpha]_D^{20}$ +77.2 (*c* 2.00, $CHCl_3$); IR (KBr): 2987, 2935, 1735 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.08 (s, 3H), 1.29 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 2.83 (dd, *J* = 7.2, 9.2 Hz, 1H), 3.20 (d, *J* = 9.3 Hz, 1H), 3.23 (s, 3H), 3.95 (m, 3H), 4.09 (m, 2H), and 7.18-7.69 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 25.4, 26.4, 27.2, 27.5, 51.6, 58.8, 66.9, 72.9, 77.3, 79.5, 82.0, 109.7, 110.3, 119.3, 120.1, 125.2, 126.2, 127.3, 127.5, 128.1, 128.2, 128.4, 128.5, 140.4, 141.1, 144.2, 148.5, 148.7, and 174.0. Anal. calcd. for $C_{32}H_{35}NO_6$: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.59; H, 6.69; N, 2.64.

Methyl 2-deoxy-3,4-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-L-mannonate 4. To a solution of the compound (3.00 g, 5.66 mmol) in 90% MeOH (20 mL) was added Dowex 50W-X8 resin (0.5 g). The reaction mixture was stirred for 24 h at room temperature, filtered, and the filtrate was evaporated. The crude residue was chromatographed on silica gel [hexane-EtOAc (1 : 1)] to give compound **4** (2.63 g, 95%) as a solid, mp 68-70 °C; $[\alpha]_D^{20}$ (*c* 1.3, $CHCl_3$); IR (KBr): 3020, 2360, 2341, 1731 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.07 (s, 3H), 1.25 (s, 3H), 2.32 (br, 1H), 2.59 (d, *J* = 9.5 Hz, 1H), 3.25 (s, 3H), 3.50 (t, *J* = 7.7 Hz, 1H), 3.66 (m, 1H), 3.70 (m, 1H), 3.84 (dd, *J* = 3.2, 11.2 Hz, 1H), 3.90 (dd, *J* = 7.3, 9.3 Hz, 1H), and 7.06-7.73 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 26.2, 26.6, 52.2, 58.6, 64.5, 72.7, 72.9, 77.3, 80.2, 81.6, 109.9, 120.3, 120.4, 125.6, 126.0, 126.3, 127.6, 127.6, 128.4, 128.7, 128.9, 129.3, 140.7, 141.1, 142.2, 147.4, and 174.6. Anal. calcd. for $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86. Found: C, 71.20; H, 6.39; N, 2.88.

Methyl 2-deoxy-3,4-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-L-lyxonate 5. To a solution of diol **4** (2.50 g, 5.11 mmol) in EtOH : H_2O (40 mL : 20 mL) was added $NaIO_4$ (1.31 g, 6.12 mmol) at room temperature. After stirring for 2 h, the mixture was cooled to 0 °C, and then $NaBH_4$ (0.23 g, 6.12 mmol) was added and stirred for 10 min. After evaporation of EtOH, the mixture was poured into an excess of H_2O and extracted with EtOAc (40 mL × 3). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (2 : 1)] to give compound **5** (2.30 g, 98%) as a solid, mp 65-66 °C; $[\alpha]_D^{20}$ +150 (*c* 1.1, $CHCl_3$); IR (KBr): 3500, 3410, 2990, 2945, 1730 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.09 (s, 3H), 1.28 (s, 3H), 2.63 (d, *J* = 8.9 Hz, 1H), 3.23 (s, 3H), 3.34 (br, 1H, OH), 3.78 (m, 1H), 3.85 (m, 2H), and 7.09-7.72 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 26.4, 26.8, 51.9, 58.7, 63.8, 72.7, 76.8, 80.2, 80.3, 109.6, 120.2, 120.2, 125.6, 125.8, 126.2, 127.4, 127.5, 128.3, 128.5, 128.7, 128.9, 140.4, 141.2, 143.2, 148.0, and 174.7. Anal. calcd. for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.20; H, 6.38; N, 3.06.

Methyl 2-deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl-2-[(9-phenyl-9-fluorenyl)-amino]-L-lyxonate 6. To a solution of alcohol **5** (2.20 g, 4.79 mmol) in THF (25 mL) were added triethylamine (1.3 mL, 9.58 mmol) and methanesulfonyl chloride (0.56 mL, 7.18 mmol) at 0 °C. After stirring for 15 min, the mixture was poured into saturated aqueous $NaHCO_3$ (25 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (20 mL × 3). After concentration of combined extracts, the resulting residue was chromatographed on silica gel [hexane-EtOAc (4 : 1)] to give compound **6** (2.50 g, 97%) as a solid, mp 154-157 °C; $[\alpha]_D^{20}$ +202 (*c* 0.95, $CHCl_3$); IR (KBr): 3400, 2990, 2950, 1753 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.10 (s, 3H), 1.30 (s, 3H), 2.63 (br, 1H), 3.03 (d, *J* = 4.9 Hz, 1H), 3.11 (s, 3H), 3.24 (s, 3H), 3.82 (dd, *J* = 7.3, 8.8 Hz, 1H), 4.00 (ddd, *J* = 2.4, 7.1, 9.3 Hz, 1H), 4.45 (dd, *J* = 6.2, 10.9 Hz, 1H), 4.74 (dd, *J* = 2.5, 10.9 Hz, 1H), and 7.13-7.71 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 26.6, 26.9, 37.9, 51.9, 58.8, 70.3, 72.7, 78.2, 78.2, 110.6, 120.2, 120.3, 125.1, 125.9, 126.2, 127.5, 127.6, 128.4, 128.5, 128.6, 128.8, 140.2, 141.3, 143.5, 148.0, 148.3, and 174.4. Anal. calcd. for $C_{29}H_{31}NO_7S$: C, 64.79; H, 5.81; N, 2.61. Found: C, 64.82; H, 5.79; N, 2.60.

Methyl 2,5-dideoxy-3,4-*O*-isopropylidene-5-iodo-2-[(9-phenyl-9-fluorenyl)-amino]-L-lyxonate 7. To a solution of mesylate **6** (2.00 g, 3.72 mmol) in dried DMF (19 mL) was added LiI (1.99 g, 14.88 mmol). After stirring of the mixture overnight at 80 °C, saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (20 mL × 3). The extract was evaporated and the remaining residue was chromatographed on silica gel [hexane-EtOAc (10 : 1)] to give compound **7** (2.05 g, 97%) as a solid, mp 63-66 °C; $[\alpha]_D^{20}$ +160.0 (*c* 1.5, $CHCl_3$); IR (KBr): 3300, 2950, 1715 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.07 (s, 3H), 1.34 (s, 3H), 2.63 (t, *J* = 8.1 Hz, 1H), 3.04 (d, *J* = 10.4 Hz, 1H), 3.23 (s, 3H), 3.44 (m, 1H), 3.67 (dd, *J* = 3.2, 10.1 Hz, 1H), 3.77 (m, 2H), and 7.13-7.70 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 8.4, 27.1, 27.6, 51.8, 58.6, 72.6, 79.6, 82.3, 110.2, 120.2, 120.3, 125.2, 126.0, 126.1, 127.5, 127.5, 128.4, 128.5, 128.6, 128.8,

140.2, 141.3, 143.7, 148.2, 148.3, and 174.5. Anal. calcd. for $C_{28}H_{28}INO_4$: C, 59.06; H, 4.96; N, 2.46. Found: C, 59.06; H, 4.97; N, 2.45.

Methyl (2*R*,3*R*)-3-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 8. A solution of iodide **7** (1.50 g, 2.63 mmol) in THF (15 mL) was cooled to –40 °C, 2.5 M *n*-BuLi (4.21 mL, 10.54 mmol, 400 mol%) was added dropwise over 5 min via syringe pump. The reaction mixture was stirred an additional 10 min at –40 °C, then quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (20 mL × 3) and combined extracts were concentrated. The resulting residue was chromatographed on silica gel [hexane-EtOAc (4 : 1)] to give compound **8** (0.85 g, 84%) as a solid, mp 120-122 °C; $[\alpha]_D^{20}$ +278.2 (*c* 1.00, $CHCl_3$); IR (KBr): 3500, 3055, 1740 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 2.77 (d, *J* = 5.5 Hz, 1H), 3.28 (s, 3H), 4.01 (t, *J* = 5.5 Hz, 1H), 4.69 (s, 1H, NH), 5.15 (d, *J* = 10.6 Hz, 1H) 5.25 (d, *J* = 14.7 Hz, 1H), 5.74 (ddd, *J* = 16.3, 10.5, 5.5 Hz, 1H), and 7.20-7.67 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 50.4, 58.8, 71.4, 72.0, 115.2, 118.8, 118.9, 124.0, 124.8, 125.1, 126.2, 126.2, 127.0, 127.2, 127.3, 127.5, 135.6, 139.0, 139.9, 142.9, 146.9, 147.3 and 172.7. Anal. calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found; C, 77.70; H, 6.03; N, 3.60.

(2*S*,3*R*)-1,3-Dihydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentene 9. To an ice-cooled solution of LAH (0.12 g, 3.11 mmol) in THF (8 mL) was added a solution of compound **8** (0.80 g, 2.08 mmol) in THF (4 mL). The reaction mixture was warmed to room temperature, stirred for 30 min, then quenched by the sequential addition of water (0.8 mL), 15% aqueous NaOH (0.8 mL), and water (2.4 mL). The mixture was filtered and evaporated. The resulting residue was chromatographed on silica gel [hexane-EtOAc (2 : 1)] to give compound **9** (0.70 g, 94%) as an oil, $[\alpha]_D^{20}$ +183.6 (*c* 2.00, $CHCl_3$); IR (neat): 3424, 3310, 3063, 3013, 2929, 2857 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 2.10 (ddd, *J* = 1.6, 4.4, 6.0 Hz, 1H), 2.73 (dd, *J* = 4.4, 11.1 Hz, 2H), 3.17 (dd, *J* = 1.6, 11.1 Hz, 1H), 4.03 (t, *J* = 6.1 Hz, 1H), 5.13 (m, 1H), 5.27 (m, 1H), 5.57 (ddd, *J* = 6.1, 10.4, 16.8 Hz, 1H), and 7.21-7.69 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 57.3, 62.1, 72.7, 74.7, 117.4, 120.3, 120.5, 125.1, 126.2, 126.3, 127.7, 128.4, 128.5, 128.8, 128.9, 129.0, 138.7, 140.5, 141.1, 145.2, 149.1, and 150.8. Anal. calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.66; H, 6.48; N, 3.90.

(2*S*,3*R*)-1,3-*O*-Isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentene 10. Solution of compound **9** (0.65 g, 1.82 mmol), 2,2-dimethoxypropane (0.67 mL, 5.46 mmol) and *p*-toluenesulfonic acid (20 mg) in dry acetone (20 mL) was stirred at 50 °C overnight. After evaporation of acetone, the mixture was poured into saturated aqeous $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL × 2). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (8:1)] to give compound **10** (0.64 g, 89%) as a solid, mp 136-138 °C; $[\alpha]_D^{20}$ –43.3 (*c* 2.00, $CHCl_3$); IR (KBr): 3302, 3064, 2994, 2938, 2875, 1447 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.21 (s, 3H), 1.41 (s, 3H), 2.04 (br, 1H), 2.22 (ddd, *J* = 5.2, 9.7, 9.7 Hz, 1H), 2.86 (dd, *J* = 5.2, 11.7 Hz, 1H), 3.29 (dd, *J* = 9.7, 11.7 Hz, 1H), 4.01 (dd, *J* = 7.7, 9.7 Hz, 1H), 5.31 (m, 1H), 5.41 (m, 1H), 5.62 (ddd, *J* = 7.7, 10.1, 17.5 Hz, 1H), and 7.16-7.69 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 19.2, 29.0, 50.9, 66.1, 72.4, 75.9, 97.9, 119.6, 120.1, 120.2, 125.3, 125.6, 126.0, 127.2, 127.8, 127.8, 128.3, 128.5, 128.6, 136.8, 139.8, 140.9, 145.3, and 148.7. Anal. calcd. for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.59; H, 6.83; N, 3.52.

(2*S*,3*R*,4*Z*)-1,3-*O*-Isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-4-octadecen-1,3-diol 11. A solution of the isopropylidene pentene **10** (0.50 g, 1.26 mmol) in CH_2Cl_2 (10 mL) was ozonized at –78 °C until the solution turned blue, and then the residue ozone was removed with N_2 gas. To the reaction mixture was added dimethyl sulfide (0.28 mL, 3.78 mmol) and it was stirred for overnight at room temperature. The residue mixture was evaporated to give aldehyde, which was in the used next step without further purification. To a suspension of the tetradecyltriphenylphosphonium bromide (1.17 g, 2.10 mmol) in THF (12 mL) was added dropwise 2.5 M *n*-BuLi (0.84 mL, 2.10 mmol, 200 mol%) at –40 °C. After stirring for 2 h, a solution of the crude aldehyde in THF (2 mL) was added. The reaction mixture was warmed to room temperature, stirred for 30 min, then quenched with water (20 mL). The mixture was extracted with EtOAc (20 mL × 4) and combined extracts were concentrated. The remaining residue was chromatographed on silica gel [hexane-EtOAc (10 : 1)] to give compound **11** (0.50 g, 68%) as an oil; $[\alpha]_D^{20}$ +176.7 (*c* 3.00, $CHCl_3$); IR (neat): 3336, 3062, 2992, 2925, 2854, 1453 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 0.88 (t, *J* = 6.9 Hz, 3H), 1.26 (m, 22H), 1.36 (s, 3H), 1.42 (s, 3H), 1.76 (m, 1H), 1.89 (m, 1H), 1.94 (br, 1H), 2.93 (dd, *J* = 2.0, 11.9 Hz, 1H), 2.96 (m, 1H), 3.39 (dd, *J* = 1.8, 11.9 Hz, 1H), 4.44 (dd, *J* = 0.7, 7.6 Hz, 1H), 5.57 (ddd, *J* = 7.6, 7.6, 11.2 Hz, 1H), 6.00 (m, 1H), and 7.11-7.66 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 14.5, 19.2, 23.1, 28.3, 29.6, 29.8, 29.9, 29.9, 30.0, 30.1, 30.1, 30.2, 32.3, 50.7, 64.4, 70.5, 72.7, 99.1, 120.0, 120.2, 125.7, 126.7, 127.4, 128.0, 128.4, 128.4, 128.6, 128.6, 129.0, 133.2, 140.2, 141.0, 146.3, 149.4, and 152.1. Anal. calcd. for $C_{40}H_{53}NO_2$: C, 82.85; H, 9.21; N, 2.42. Found: C, 82.82; H, 9.23; N, 2.40.

(2*S*,3*R*)-2-Amino-1,3-dihydroxy-4-octadecane (D-*erythro*-sphinganine) 1. The protected octadecen-1,3-diol **11** (0.20 g, 0.34 mmol) and 10% Pd/C (0.07 g) were placed in MeOH (10 mL) under an atmosphere of hydrogen at 60 °C for 3 h. The reaction mixture was filtered through Celite, and the filtrate concentrated. The residue was chromatographed on silica gel [CH_2Cl_2-IPA (6 : 1)] to give octadecane compound (0.10 g, 85%) as an oil. A solution of octadecane compound (0.09 g, 0.26 mmol) and Dowex 50W-X8 resin (0.05 g) in 90% MeOH (5 mL) was stirred for 12 h at 50 °C. The mixture was filtered, and then the insoluble material was washed with CH_3OH (20 mL). The remaining residue was eluted with 3N NH_4OH. The ammoniacal solution was evaporated, then co-evaporation with toluene to give compound **1** (0.06 g, 76%) as a solid, mp 125-127 °C; $[\alpha]_D^{20}$ –3.5 (*c* 3.00, CH_3OH); IR (KBr): 3261, 2918, 2850 cm^{-1}; δ_H

(500 MHz; CD_3OD) 0.90 (t, J = 6.9 Hz, 3H), 1.28 (m, 26H), 1.49 (m, 3H), 1.93 (br, 3H), 3.16 (m, 1H), and 3.68-3.83 (m, 3H); δ_C (125 MHz; CD_3OD) 14.9, 24.2, 24.5, 27.5, 30.9, 31.0, 31.1, 31.2, 31.2, 31.2, 33.5, 34.6, 58.8, 59.8, and 71.0; MS m/z: 284, 270, 252 (M^+); Anal. calcd. for $C_{18}H_{39}NO_2$: C, 71.70; H, 13.04; N, 4.65. Found: C, 71.72; H, 13.01; N, 4.65.

Methyl (2*R*,3*S*)-3-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 12. This was prepared from L-gulonic acid γ-lactone as described;[11] mp 117-120.

(2*S*,3*S*)-1,3-Dihydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentene 13. To an ice-cooled solution of LAH (0.13 g, 3.50 mmol) in THF (10 mL) was added a solution of compound **12** (0.90 g, 2.33 mmol) in THF (5 mL). The reaction mixture was warmed to room temperature, stirred for 30 min, then quenched by the sequential addition of water (0.9 mL), 15% aqueous NaOH (0.9 mL), and water (2.7 mL). The mixture was filtered and evaporated. The residue was chromatographed on silica gel [hexane-EtOAc (2:1)] to give compound **13** (0.77 g, 92%) as an oil, $[\alpha]_D^{20}$ +94.6 (*c* 1.30, $CHCl_3$); IR (neat): 3468, 3318, 3063, 3016, 2929, 2857, 1447 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 2.30 (m, 1H), 2.94 (br, 1H), 3.26 (ddd, J = 5.4, 10.1 Hz, 1H), 3.41 (dd, J = 5.4, 10.1 Hz, 1H), 3.49 (br, 1H), 3.71 (m, 1H), 5.08 (ddd, J = 1.6, 1.6, 10.6 Hz, 1H), 5.14-5.18 (m, 1H), 5.67 (ddd, J = 5.1, 10.6, 16.2 Hz, 1H), and 7.25-7.75 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 57.0, 63.9, 72.5, 73.4, 114.9, 119.9, 120.0, 125.4, 126.0, 127.2, 127.8, 128.1, 128.3, 128.5, 137.9, 140.1, 140.7, 145.2, 149.6, and 150.4. Anal. calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.63; H, 6.47; N, 3.93.

(2*S*,3*S*)-1,3-*O*-Isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentene 14. A solution of diol **13** (0.70 g, 1.96 mmol), 2,2-dimethoxypropane (0.72 mL, 5.88 mmol) and *p*-toluenesulfonic acid (22 mg) in dry acetone (22 mL) was stirred at 50 °C overnight. After evaporation of acetone, the mixture was poured into saturated aqeous $NaHCO_3$ (20 mL) and extracted with EtOAc (15 mL × 3). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane-EtOAc (8 : 1)] to give compound **14** (0.67 g, 86%) as a solid, mp 48-50 °C; $[\alpha]_D^{20}$ +215.8 (*c* 2.00, $CHCl_3$); IR (KBr): 3337, 3062, 2992, 2938, 2868, 1452 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.33 (s, 3H), 1.44 (s, 3H), 2.00 (d, J = 1.9 Hz, 1H), 2.94 (dd, J = 2.0, 11.9 Hz, 1H), 3.39 (dd, J = 1.8, 11.9 Hz, 1H), 4.14 (m, 1H), 5.18-5.24 (m, 2H), 6.11 (ddd, J = 5.9, 10.7, 17.0, Hz, 1H), and 7.19-7.66 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 19.2, 30.1, 50.7, 64.4, 72.7, 75.3, 99.1, 116.2, 120.0, 120.3, 125.8, 126.6, 126.7, 127.4, 127.9, 128.4, 128.5, 128.6, 128.7, 138.1, 140.3, 140.9, 146.2, 149.5, and 151.8 Anal. calcd. for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.61; H, 6.85; N, 3.51.

(2*S*,3*S*,4*Z*)-1,3-*O*-Isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-4-octadecen-1,3-diol 15. A solution of the isopropylidene pentene **14** (0.60 g, 1.51 mmol) in CH_2Cl_2 (12 mL) was ozonized at −78 °C until the solution turned blue, and then the residue ozone was removed with N_2 gas. To the reaction mixture was added dimethyl sulfide (0.33 mL, 4.53 mmol) and it was stirred overnight at room temperature. The residue mixture was evaporated to give aldehyde, which was used in the next step without further purification. To a suspension of the tetradecyltriphenylphosphonium bromide (1.45 g, 2.60 mmol) in THF (15 mL) was added dropwise 2.5 M *n*-BuLi (1.04 mL, 2.60 mmol, 200 mol%) at −40 °C. After stirring for 2 h, a solution of the crude aldehyde in THF (7 mL) was added. The reaction mixture was warmed to room temperature, stirred for 30 min, then quenched with water (22 mL). The mixture was extracted with EtOAc (25 mL × 3) and the combined extracts were concentrated. The remaining residue was chromatographed on silica gel [hexane-EtOAc (10 : 1)] to give compound **15** (0.58 g, 66%) as an oil, $[\alpha]_D^{20}$ −60.9 (*c* 3.00, $CHCl_3$); IR (KBr): 3301, 3062, 2992, 2925, 2854, 1449 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 0.88 (t, J = 6.9 Hz, 3H), 1.21 (s, 3H), 1.28 (m, 22H), 1.43 (s, 3H), 2.05 (br, 1H), 2.23 (m, 2H), 2.24 (ddd, J = 5.1, 9.2, 10.3 Hz, 1H), 2.80 (dd, J = 5.1, 11.7 Hz, 1H), 3.31 (dd, J = 10.3, 11.7 Hz, 1H), 4.43 (dd, J = 9.2, 9.2 Hz, 1H), 5.12 (dd, J = 9.2, 10.7 Hz, 1H), and 5.76 (ddd, J = 7.5, 7.5, 10.8 Hz, 1H) 7.17-7.69 (m, 13H, Pf); δ_C (125 MHz; $CDCl_3$) 14.6, 19.5, 23.1, 28.6, 29.6, 29.8, 29.9, 30.0, 30.0, 30.1, 30.1, 32.4, 51.9, 66.7, 69.4, 72.8, 98.3, 120.5, 120.6, 125.7, 126.3, 127.6, 128.2, 128.2, 128.7, 128.8, 128.9, 137.3, 140.0, 141.5, 145.8, 149.3, and 151.2. Anal. calcd. for $C_{40}H_{53}NO_2$: C, 82.85; H, 9.21; N, 2.42. Found: C, 82.84; H, 9.21; N, 2.44.

(2*S*,3*S*)-2-Amino-1,3-dihydroxy-4-octadecane (L-*threo*-sphinganine) 2. The protected octadecen-1,3-diol **15** (0.25 g, 0.43 mmol) and 10% Pd/C (0.08 g) were in MeOH (10 mL) under an atmosphere of hydrogen at 60 °C for 3 h. The reaction mixture was filtered through Celite, and the filtrate concentrated. The residue was chromatographed on silica gel [CH_2Cl_2-IPA (6 : 1)] to give octadecane compound (0.12 g, 82%) as a solid. To a solution of amine compound (0.10 g, 0.29 mmol) in 90% MeOH (5 mL) was added Dowex 50W-X8 resin (0.05 g). The reaction mixture was stirred 12 h at 50 °C. The mixture was filtered, and then the insoluble material was washed with CH_3OH (20 mL). The remaining residue was eluted with 3N NH_4OH. The NH_3 solution was evaporated to give compound **2** (0.07 g, 79%) as a solid, mp 126-128 °C; $[\alpha]_D^{20}$ 2.6 (*c* 2.00, CH_3OH); IR (KBr): 3241, 2919, 2850 cm^{-1}; δ_H (500 MHz; CD_3OD) 0.90 (t, J = 6.9 Hz, 3H), 1.29 (m, 26H), 1.49 (m, 3H), 1.91 (br, 3H), 3.14 (m, 1H), 3.69 (dd, J = 8.4, 11.4 Hz, 1H), 3.77 (m, 1H), and 3.82 (dd, J = 3.7, 11.4 Hz, 1H); δ_C (125 MHz; CD_3OD) 14.8, 24.1, 27.4, 30.9, 31.0, 31.1, 31.1, 31.2, 33.5, 34.6, 58.8, 59.9, and 71.1; MS m/z: 284, 270, 252 (M^+); Anal. calcd. for $C_{18}H_{39}NO_2$: C, 71.70; H, 13.04; N, 4.65. Found: C, 71.70; H, 13.05; N, 4.63.

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