Divergent Synthesis of Diastereomeric Sphingosines from a Chiral Aziridine

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All four stereoisomers of sphingosines were synthesized starting from a single intermediate, chiral aziridine (**2**), which was efficiently prepared by enzymatic desymmetrization in an enatiopure form. Aziridine (**2**) was converted to **3**, which was used for the synthesis of **4**. Both the advanced key intermediates, vinylaziridines **3** and **4**, were successfully converted to *threo*-sphingosines **1a** and **1b**, respectively. Ring-closing metathesis (RCM) using the Grubbs II catalyst was the key reaction in the synthesis. Two *erythro*-sphingosines **1c** and **1d** were synthesized by the ring-expansion reactions of vinylaziridines **3** and **4**, followed by RCM reactions. The successful divergent synthesis confirmed that chiral vinylaziridine **2** can be used as a key intermediate for the synthesis of sphingosine-related natural products.

Keywords: Sphingosine, Divergent synthesis, Aziridine, Ring opening, Ring expansion

Introduction

Glycosphingolipids (GSLs), a part of the larger family of sphingolipids, are found in the membranes of all eukaryotic cells. GSL has a hydrophobic core and hydrophilic extracellular oligosaccharide chain. They are responsible for diverse biological functions such as cellular communication and the regulation of cell behavior. The core structure of GSLs, called ceramide, consists of a long-chain amino alcohol, sphingosine, which is linked to a fatty acid (usually a chain of 18–20 carbon atoms) through an amide bond. Sphingosine, the backbone of sphingolipids, therefore, bears a 2-amino-1,3-diol moiety at the one end, and because of the presence of two stereocenters at these positions, a total of four isomeric structures are possible, even though D-*erythro*-sphingosine is the most abundant form in nature (Figure 1). Substitution with diverse glycans and phosphate groups at the hydroxy group present at the end of the sphingosine base affords structurally diverse sphingolipids.

The synthesis of sphingosines and their analogs has been interesting because of their important biological activities and unique structural features, leading to better activities and efficient synthetic strategies.[1,2] Previously, an enantiomerically pure chiral aziridine (**2**, Scheme 1) was easily prepared by enzymatic desymmetrization, and it was successfully used as a starting material for the asymmetric synthesis of oseltamivir.[3] During this synthetic study, alkenylaziridines exhibited excellent regio- and stereoselectivity in the ring-opening reactions with various heteroatom nucleophiles, including oxygen[4] and nitrogen nucleophiles.[5] We have also been intrigued by the potential of enantiomerically pure *cis*-3-substituted-2-vinylaziridines that are easily prepared from *cis*-2,3-bis(hydroxymethyl) aziridine for the synthesis of diverse nitrogen-containing natural products. Here we report the synthesis of all the possible sphingosines from this chiral vinylaziridine.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance III 400 and a Bruker Avance 500 NMR spectrometer (Bruker corporation, Billerica, MA, USA) at ambient temperature using $CDCl_3$ as the solvent unless otherwise stated. The chemical shifts are reported in ppm downfield from TMS, and the signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. IR spectra were recorded using a Jasco FT/IR-300E spectrometer (Jasco corporation, Easton, MD, USA). Optical rotations were measured using a Jasco DIP-1000 digital polarimeter in solutions in a 1-dm cell. High-resolution mass spectra (HRMS) were recorded using a maXis 4G spectrometer (Bruker corporation, Billerica, MA, USA) using the ESI (electrospray ionization) method. All the reagents and solvents were of appropriate grade and used as received unless specified otherwise. Technical-grade ethyl acetate, hexane, and pentane used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether, when used as the solvents for reactions, were freshly distilled from sodium-benzophenone ketyl. Dimethylformamide (DMF) was stored over 4-Å molecular sieves before use. Flash chromatography was carried out using Merck 60 silica packed in glass columns.

(2*S*,3*S*)-*t*-Butyl 3-(acetoxymethyl)-2-vinylaziridine-1-carboxylate (3). Dess–Martin periodinane (DMP) (3.41 g, 8.04 mmol) was added to a solution of alcohol **2** (987 mg,

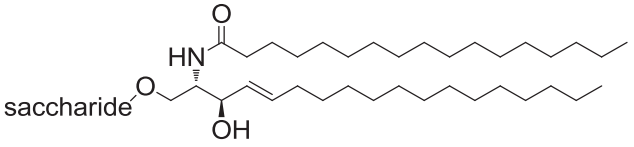
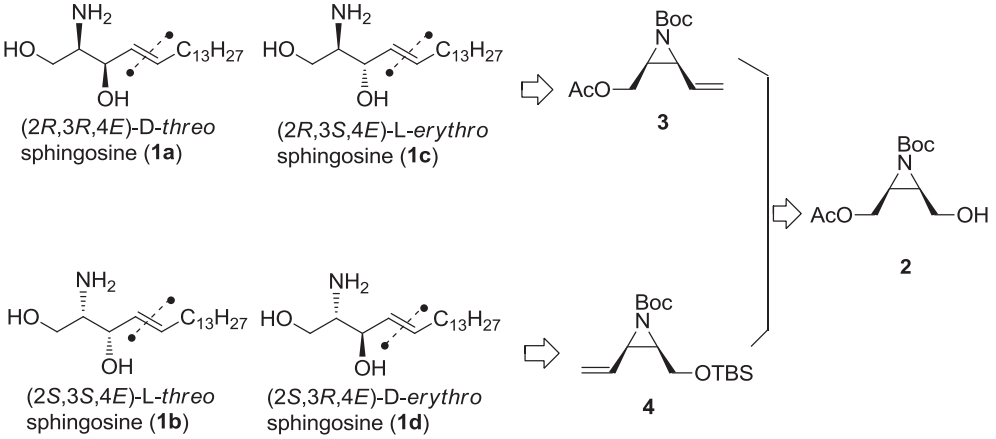


Figure 1. General structure of sphingolipids.

4.02 mmol) in CH_2Cl_2 (30 mL), according to the reported procedure.[3] The resulting solution was stirred at room temperature for 2 h. After the reaction was completed, saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (15 mL) solutions were added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 5:1) afforded the desired aldehyde (586 mg, 2.40 mmol, 60%) as a colorless oil: $[\alpha]_D^{26}$ + 48.5 (*c* 1.25, $CHCl_3$); IR (film): 2979, 2936, 1714, 1516, 1367, 1245, 1167, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, 1 H, *J* = 4.9 Hz, -CHC*H*O), 4.34 (dd, 1 H, *J* = 9.8, 4.5 Hz, -OC*H*HCH–), 4.19 (dd, 1 H, *J* = 9.8, 4.5 Hz, -OCH*H*CH–), 3.11–3.04 (m, 2 H, -NC*H*CH_2-, -C*H*CHCHO), 2.07 (s, 3 H, –C(O)CH_3), 1.46 (s, 9 H, -NC(O)OC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 170.3, 159.6, 83.0, 61.1, 44.8, 41.4, 27.7, 20.5; HRMS (ESI) calcd. for $C_{11}H_{17}NO_5$ + Na 266.1004, found 266.1001.

Potassium bis(trimethylsilyl)amide (KHMDS) [10.2 mL (0.7 M in toluene), 7.20 mmol] was added to methyltriphenylphosphonium bromide (2.57 g, 7.20 mmol) in THF (15 mL), and the resulting mixture was stirred at –20°C for 30 min. A solution of the aldehyde prepared from the previous procedure (586 mg, 2.40 mmol) in THF (5 mL) was added dropwise to the above solution using a cannula, and the reaction mixture was stirred at −20°C for 1 h. After the reaction was completed, a saturated aqueous NH_4Cl solution (15 mL) was added. The mixture was extracted with ether (3 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) provided the desired vinylaziridine **3** (475 mg, 1.96 mmol, 82%) as a colorless oil: $[\alpha]_D^{28}$ + 50.9 (*c* 1.44, $CHCl_3$); IR (film) 2979, 1725, 1448, 1370, 1300, 1231, 1160, 1040, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (ddd, 1 H, *J* = 17.0, 10.4, 6.2 Hz, -C*H*CH_2), 5.48 (dd, 1 H, *J* = 17.0, 1.3 Hz, -CHC*H*H), 5.32 (bd, 1 H, *J* = 10.4 Hz, -CHCH*H*), 4.11 (dd, 1 H, *J* = 12.0, 5.8 Hz, -OC*H*HCH–), 4.05 (dd, 1 H, *J* = 11.8, 6.8 Hz, -OCH*H*CH–), 3.07 (t, 1 H, *J* = 6.3 Hz, -C*H*CHCH_2), 2.84 (q, 1 H, *J* = 6.6 Hz, -NC*H*CH_2–), 2.09 (s, 3 H, –C(O)CH_3), 1.46 (s, 9 H, -NC(O)OC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 161.6, 131.1, 120.2, 81.6, 62.1, 42.3, 40.5, 28.3, 27.8, 20.8; HRMS (ESI) calcd. for $C_{12}H_{19}NO_4$ + Na 264.1211, found 264.1205.

(2*R*,3*R*)-2-(*t*-Butoxycarbonylamino)-3-(*p*-methoxybenzyloxy)pent-4-en-1-yl acetate (7). To a solution of vinylaziridine **3** (283 mg, 1.17 mmol) in dry CH_2Cl_2 (10 mL) was added *p*-methoxybenzyl alcohol (728 μL, 5.85 mmol) and $BF_3{\cdot}OEt_2$ (7.21 μL, 0.0585 mmol) at −20°C. The reaction mixture was stirred at −20°C for 30 min. After the reaction was completed, a saturated aqueous $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) furnished the desired compound **7** (399 mg, 1.05 mmol, 90%) as a colorless oil: $[\alpha]_D^{25}$ –19.6 (*c* 0.60, $CHCl_3$); IR (film) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (bd, 2 H, *J* = 8.6 Hz, -OCH_2*Ph*–), 6.87 (dd, 2 H, *J* = 8.6, 2.0 Hz, -OCH_2*Ph*–), 5.80 (ddd, 1 H, *J* = 17.8, 10.3, 7.3 Hz, -C*H*CH_2), 5.35 (bd, 1 H, *J* = 17.8 Hz, -CHC*H*H), 5.32 (bd, 1 H, *J* = 10.3 Hz, -CHCH*H*), 4.92–4.79 (m, 1 H, -N*H*CHCH_2–), 4.54 (d, 1 H, *J* = 11.4 Hz, -OC*H*HPh–), 4.24 (d, 1 H, *J* = 11.4 Hz, -OCH*H*Ph–), 4.11 (dd, 1 H, *J* = 10.8, 7.1 Hz, -OC*H*HCH–), 4.06 (dd, 1 H, *J* = 10.8, 6.2 Hz, -OCH*H*CH–), 3.97–3.85 (m, 2 H, -OC*H*CH-, -NHC*H*CH_2–), 3.81 (s, 3 H, -C(O)CH_3), 1.97 (s, 3 H, –PhOCH_3), 1.42 (s, 9 H, -NC(O)OC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 159.3, 155.7, 134.8, 129.9, 129.6, 119.1, 113.8, 79.4, 70.1, 63.5, 60.4, 55.2, 52.6, 28.3, 20.8; HRMS (ESI) calcd. for $C_{20}H_{29}NO_6$ + Na 402.1892, found 402.1887.



Scheme 1. Structures and retrosynthetic analysis of four diastereomers of sphingosines.

(2*R*,3*R*)-2-(*t*-Butoxycarbonylamino)-3-hydroxypent-4-en-1-yl acetate (8). To a solution of **7** (165 mg, 0.434 mmol) in CH_2Cl_2/H_2O (4:1) (10 mL) was added DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 147 mg, 0.651 mmol). The reaction mixture was stirred at room temperature for 18 h. After the reaction was completed, a saturated aqueous $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/EtOAc = 3:1) afforded the desired alcohol **8** (68 mg, 0.262 mmol, 60%) as a colorless oil: $[\alpha]_D^{24}$ +23.1 (*c* 0.60, $CHCl_3$); IR (film) 3443, 3398, 2976, 2925, 2856, 1739, 1715, 1510, 1367, 1242, 1168, 1045, 928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, 1 H, *J* = 17.2, 10.6, 5.6 Hz, -C*H*CH_2), 5.33 (dd, 1 H, *J* = 17.2, 1.4 Hz, -CHC*H*H), 5.21 (bd, 1 H, *J* = 10.6 Hz, -CHCH*H*), 5.01–4.89 (m, 1 H, -N*H*CHCH_2–), 4.26–4.23 (m, 1 H, -OC*H*CH–), 4.22 (dd, 1 H, *J* = 11.0, 6.8 Hz, -OC*H*HCH–), 4.11 (dd, 1 H, *J* = 11.3, 6.8 Hz, -OCH*H*CH–), 3.92–3.79 (m, 1 H, -NHC*H*CH_2–), 2.81 (bs, 1 H, -CHCHO*H*), 2.06 (s, 3 H, -C(O)CH_3), 1.41 (s, 9 H, -NC(O)OC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 156.0, 137.1, 116.7, 79.8, 71.2, 63.5, 53.2, 28.2, 20.8; HRMS (ESI) calcd. for $C_{12}H_{21}NO_5$ + Na 282.1317, found 282.1311.

(2*R*,3*R*,4*E*)-2-(*t*-Butoxycarbonylamino)-3-hydroxyoctadec-4-en-1-yl acetate (9). To a stirred solution of alcohol **8** (125 mg, 0.482 mmol) in dry CH_2Cl_2 (10 mL) at room temperature were added 1-pentadecene (520 μL, 1.92 mmol) and Grubbs catalyst (second generation, 40 mg, 0.0482 mmol), producing a light brown solution. This solution was stirred at 40°C for 16 h. After the mixture was concentrated, purification by flash chromatography (hexane/EtOAc = 4:1) provided the desired alcohol **9** (114 mg, 0.258 mmol, 53%, *E*/*Z* = 12:1, ^1H NMR analysis) as a brown oil: $[\alpha]_D^{23}$ +4.6 (*c* 0.86, $CHCl_3$); IR (film) 3444, 3368, 2924, 2853, 1745, 1720, 1503, 1460, 1366, 1240, 1170, 1045, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, 1 H, *J* = 15.4, 6.1 Hz, –CHC*H*CH_2–), 5.48 (dd, 1 H, *J* = 15.4, 6.6 Hz, -C*H*CHOH), 4.95–4.83 (m, 1 H, -CHN*H*C(O)–), 4.22 (dd, 1 H, *J* = 11.2, 6.4 Hz, -NHCHC*H*H–), 4.02–4.14 (m, 1 H, -CHC*H*OH), 4.11 (dd, 1 H, *J* = 11.1, 6.0 Hz, -NHCHCH*H*–), 3.89–3.75 (m, 1 H, -NHC*H*CH–), 2.32–2.22 (b, 1 H, -CHCHO*H*), 2.08 (s, 3 H, C(O)CH_3), 2.03 (q, 2 H, *J* = 6.9 Hz, -CHCHCH_2–), 1.44 (s, 9 H, -NC(O)OC(CH_3)$_3$), 1.37–1.33 (m, 2 H, -C$H_2$$CH_3$), 1.29–1.23 (m, 20 H, -$C_{10}H_{20}$$CH_2$$CH_3$), 0.88 (t, 3 H, *J* = 6.6 Hz, -CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.9, 134.4, 128.5, 79.7, 71.4, 63.7, 53.5, 32.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.3, 22.6, 20.8, 14.1; HRMS (ESI) calcd. for $C_{25}H_{47}NO_5$ + H 442.3532, found 442.3527.

(2*R*,3*R*,4*E*)-2-(*t*-Butoxycarbonylamino)octadec-4-en-1,3-diol (10). To a solution of alcohol **9** (14 mg, 0.033 mmol) in methanol (3 mL) was added potassium carbonate (K_2CO_3) (6.8 mg, 0.050 mmol) at room temperature, and the solution was stirred at room temperature for 25 min. After the reaction was completed, a saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with ether (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 3:1) afforded the desired product **10**[6] (10 mg, 0.026 mmol, 81%) as a white solid: mp. 56–59°C, $[\alpha]_D^{24}$ +0.67 (*c* 0.80, $CHCl_3$; IR (film) 3416, 2924, 2853, 1690, 1504, 1461, 1366, 1248, 1171, 1057, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dt, 1 H, *J* = 15.4, 6.6 Hz, -CHC*H*CH_2–), 5.51 (dd, 1 H, *J* = 15.4, 6.6 Hz, -C*H*CHOH), 5.24–5.09 (m, 1 H, -CHN*H*C(O)–), 4.34 (dd, 1 H, *J* = 6.3, 3.4 Hz, -CHC*H*OH), 3.79 (d, 2 H, *J* = 4.5 Hz, -CH_2OH), 3.68–3.56 (m, 1 H, -NHC*H*CH–), 2.40–2.21 (b, 2 H, -CH_2O*H*, -CHCHO*H*), 2.03 (q, 2 H, *J* = 6.8 Hz, -CHCHCH_2–), 1.44 (s, 9 H, -NC(O)OC(CH_3)$_3$), 1.39–1.33 (m, 2 H, -C$H_2$$CH_3$), 1.31–1.22 (m, 20 H, -$C_{10}H_{20}$$CH_2$$CH_3$), 0.88 (t, 3 H, *J* = 6.6 Hz, -CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 134.1, 128.9, 79.7, 73.5, 64.4, 55.5, 32.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.3, 22.6, 14.1; HRMS (ESI) calcd. for $C_{23}H_{45}NO_4$ + Na 422.3246, found 422.3240.

(2*R*,3*R*,4*E*)-D-*threo*-Sphingosine (1a). Compound **10** (22 mg, 0.055 mmol) was dissolved in CH_2Cl_2 (1 mL) at 0°C. To this solution was added TFA (0.5 mL, mmol), and the solution was stirred at room temperature for 12 h. After the reaction was completed, a solution of 33% aqueous ammonia was added until the pH of the solution reached 8–9. The mixture was extracted with $CHCl_3$ (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography ($CHCl_3$/MeOH/NH_4OH = 135:25:4)[7] produced pure D-*threo*-sphingosine (**1a**)[8] (14 mg, 0.046 mmol, 87%) as a white solid: mp. 80–83°C, $[\alpha]_D^{28}$ +2.9 (*c* 0.8, $CHCl_3$); IR (film) 3350, 3297, 2920, 2849, 1673, 1595, 1463, 1038, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (dt, 1 H, *J* = 15.4, 6.6 Hz, -CHC*H*CH_2–), 5.45 (dd, 1 H, *J* = 15.4, 7.0 Hz, -C*H*CHOH), 4.02 (bt, 1 H, *J* = 6.1 Hz, -CHC*H*OH), 3.69 (dd, 1 H, *J* = 10.6, 3.5 Hz, -C*H*HOH), 3.56 (dd, 1 H, *J* = 10.7, 6.3 Hz, -CH*H*OH), 2.87–2.79 (m, 1 H, -C*H*NH_2), 2.52–2.36 (b, 4 H, -CH_2O*H*, -CHNH_2, -CHO*H*), 2.04 (q, 2 H, *J* = 7.0 Hz, -CHCHCH_2–), 1.43–1.33 (m, 2 H, –C$H_2$$CH_3$), 1.30–1.24 (m, 20 H, -$C_{10}H_{20}$$CH_2$$CH_3$), 0.88 (t, 3 H, *J* = 6.6 Hz, -CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1 129.7, 73.8, 64.6, 56.5, 32.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 22.7, 14.1; HRMS (ESI) calcd. for $C_{18}H_{37}NO_2$ + H 300.2903, found 300.2897.

(2*R*,3*R*)-*t*-Butyl 3-((*t*-butyldimethylsilyloxy)methyl)-2-vinylaziridine-1-carboxylate (4). To a solution of methyltriphenylphosphonium bromide (2.56 g, 7.17 mmol) in THF (15 mL) was added potassium bis(trimethylsilyl) amide (KHMDS) (10.2 mL (0.7 M in toluene), 7.17 mmol). The resulting mixture was stirred at −20°C for 30 min. A solution of aldehyde **6** prepared according to the

published procedure[3] (756 mg, 2.39 mmol) in THF (5 mL) was added dropwise to the above solution using a cannula, and the reaction mixture was stirred at −20°C for 30 min. After the reaction was completed, a saturated aqueous NH_4Cl solution (15 mL) was added. The mixture was extracted with ether (3 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) provided the desired vinylaziridine **4** (608 mg, 1.93 mmol, 81%) as a colorless oil: $[\alpha]_D^{21}$ –28.8 (*c* 1.15, $CHCl_3$); IR (film) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (ddd, 1 H, *J* = 17.0, 10.4, 6.3 Hz, -C*H*CH_2), 5.43 (bd, 1 H, *J* = 17.1 Hz, -CHC*H*H), 5.28 (bd, 1 H, *J* = 10.4 Hz, -CHCH*H*), 3.79 (dd, 1 H, *J* = 11.2, 5.4 Hz, -OC*H*HCH–), 3.52 (dd, 1 H, *J* = 11.2, 6.6 Hz, -OCH*H*CH–), 3.02 (t, 1 H, *J* = 6.4 Hz, -C*H*CHCH$_2$), 2.84 (q, 1 H, *J* = 6.5 Hz, -NC*H*CH_2–), 1.45 (s, 9 H, -NC(O)OC(C*H*$_3$)$_3$), 0.89 (s, 9 H, -OSi(CH$_3$)$_2$C(C*H*$_3$)), 0.061 (d, 6 H, -OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 131.7, 119.5, 81.2, 61.0, 44.1, 42.6, 27.9, 25.9, 18.3, −5.2, −5.3; HRMS (ESI) calcd. for $C_{16}H_{31}NO_3Si$ + Na 336.1971, found 336.1965.

(3*S*,4*S*)-5-(*t*-Butyldimethylsilyloxy)-4-(*t*-butoxycarbonylamino)-3-(*p*-methoxybenzyloxy)pent-1-ene (11). To a solution of vinylaziridine **4** (608 mg, 1.93 mmol) in anhydrous CH_2Cl_2 (20 mL) were added *p*-methoxybenzyl alcohol (1.19 mL, 9.65 mmol) and $BF_3{\cdot}OEt_2$ (12 μL, 0.096 mmol) at –20°C. The reaction mixture was stirred at −20°C for 1 h. After the reaction was completed, a saturated aqueous $NaHCO_3$ solution (15 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 7:1) afforded the desired alkene **11** (661 mg, 1.46 mmol, 76%) as a colorless oil: $[\alpha]_D^{23}$ + 5.23 (*c* 1.06, $CHCl_3$); IR (film) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (bd, 2 H, *J* = 8. Hz, -OCH$_2$*Ph*–), 6.87 (bd, 2 H, *J* = 8.6 Hz, -OCH$_2$*Ph*–), 5.84 (ddd, 1 H, *J* = 17.5, 10.5, 7.3 Hz, –C*H*CH_2), 5.31 (bd, 1 H, *J* = 17.5 Hz, –CHC*H*H), 5.29–5.26 (m, 1 H, –CHCH*H*), 4.89–4.76 (m, 1 H, –CHN*H*C(O)–), 4.53 (d, 1 H, *J* = 11.1 Hz, –OC*H*HPh–), 3.52 (d, 1 H, *J* = 11.2 Hz, –OCH*H*Ph–), 4.15–4.07 (m, 1 H, -OC*H*CH–), 3.80 (s, 3 H, –PhOC*H*$_3$), 3.75–3.66 (m, 1 H, –NHC*H*CH_2–), 3.65–3.57 (m, 2 H, –OC*H*$_2$CH–), 1.42 (s, 9 H, –NC(O)OC(C*H*$_3$)$_3$), 0.87 (s, 9 H, –OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.044 (d, 6 H, –OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 155.4, 135.6, 130.2, 129.4, 129.2, 129.0, 128.5, 117.8, 113.5, 113.4, 113.3, 78.7, 70.1, 65.2, 63.4, 61.3, 54.9, 54.9, 28.0, 25.5, 17.8, −5.7, −5.8; HRMS (ESI) calcd. for $C_{24}H_{41}NO_5Si$ + Na 474.2651, found 474.2646.

(3*S*,4*S*)-5-(*t*-Butyldimethylsilyloxy)-4-(*t*-butoxycarbonylamino)-3-hydroxypent-1-ene (12). To a solution of alkene **11** (660 mg, 1.46 mmol) in CH_2Cl_2/H_2O (4:1) (20 mL) was added DDQ (497 mg, 2.19 mmol). The reaction mixture was stirred at room temperature for 18 h. After the reaction was completed, a saturated aqueous $NaHCO_3$ (20 mL) solution was added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer separated, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/EtOAc = 3:1) afforded the desired allyl alcohol **12** (305 mg, 0.920 mmol, 63%) as a colorless oil: $[\alpha]_D^{23}$ + 4.99 (*c* 1.02, $CHCl_3$); IR (film) 3402, 3363, 2976, 2926, 1686, 1511, 1366, 1251, 1168, 1043, 923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddd, 1 H, *J* = 17.1 10.6, 5.4 Hz, –C*H*CH_2), 5.33 (dd, 1 H, *J* = 17.2, 1.6 Hz, –CHC*H*H), 5.18 (dd, 1 H, *J* = 10.6, 1.4 Hz, –CHCH*H*), 5.15–5.04 (m, 1 H, –CHN*H*C(O)–), 4.54–4.37 (m, 1 H, –OC*H*CH–), 3.92–3.77 (m, 2 H, –OC*H*$_2$CH–), 3.68–3.54 (m, 1 H, –NHC*H*CH_2), 3.40 (bs, 1 H, –CHCHO*H*), 1.42 (s, 9 H, –NC(O)OC(C*H*$_3$)$_3$), 0.89 (s, 9 H, –OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.07 (s, 6 H, –OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 137.4, 116.0, 9.4, 73.5, 65.1, 54.4, 28.3, 25.8, 18.1, −5.6; HRMS (ESI) calcd. for $C_{16}H_{33}NO_4Si$ + H 332.2257, found 332.2251.

(2*S*,3*S*,4*E*)-1-(*t*-Butyldimethylsilyloxy)-2-(*t*-butoxycarbonylamino)-3-hydroxyoctadec-4-ene (13). To a stirred solution of allyl alcohol **12** (87 mg, 0.26 mmol) in dry CH_2Cl_2 (5 mL) at room temperature were added 1-pentadecene (280 μL, 1.04 mmol) and Grubbs catalyst (second generation, 22 mg, 0.026 mmol) producing a light brown solution. The resulting solution was stirred at 40°C for 16 h. The mixture was then concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) produced the desired compound **13** (85 mg, 0.165 mmol, 63%, *E*/*Z* = 12:1, ^1H NMR analysis) as a brown oil: $[\alpha]_D^{23}$ +10.3 (*c* 1.04, $CHCl_3$); IR (film) 3446, 2925, 2854, 1718, 1696, 1499, 1465, 1365, 1253, 1171, 1106, 968, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (dt, 1 H, *J* = 15.4, 6.7 Hz, –CHC*H*CH_2–), 5.46 (dd, 1 H, *J* = 15.4, 6.3 Hz, –C*H*CHOH), 5.17–5.02 (m, 1 H, –CHN*H*C(O)–), 4.42–4.32 (m, 1 H, –CHC*H*OH), 3.83 (dd, 1 H, *J* = 10.4, 4.0 Hz, –NHCHC*H*H–), 3.79 (dd, 1 H, *J* = 10.1, 2.8 Hz, –NHCHCH*H*–), 3.68–3.51 (m, 1 H, –NHC*H*CH_2–), 3.24 (bs, 1 H, –CHCHO*H*), 2.02 (q, 2 H, *J* = 6.9 Hz, –CHCHC*H*$_2$–), 1.44 (s, 9 H, –NC(O)OC(C*H*$_3$)$_3$), 1.40–1.33 (m, 2 H, –C*H*$_2$CH$_3$), 1.32–1.20 (m, 20 H, –C$_{10}$*H*$_{20}$CH$_2$CH$_3$), 0.90 (s, 9 H, –OSi(CH$_3$)$_2$C(C*H*$_3$)$_3$), 0.86 (t, 3 H, *J* = 7.0 Hz, –CH$_2$C*H*$_3$), 0.07 (s, 6 H, –OSi(C*H*$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 133.4, 128.9, 79.3, 73.6, 65.1, 57.8, 32.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.4, 25.8, 22.7, 18.1, 14.1, −5.6; HRMS (ESI) calcd. for $C_{29}H_{59}NO_4Si$ + H 514.4292, found 514.4286.

(2*S*,3*S*,4*E*)-L-*threo*-Sphingosine (1b). To a solution of compound **13** (76 mg, 0.15 mmol) was dissolved in EtOH (3 mL) at 0°C. A solution of aqueous 2.0 M HCl (2 mL) was added. The solution was stirred for 30 min at room temperature. After the reaction was completed, the solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and the organic layer was washed with $NaHCO_3$, brine, and dried ($MgSO_4$). The organic solution was concentrated to afford the desired diol

as a colorless oil, which was used in the next step without further purification.

To a solution of crude diol, prepared as described in the previous procedure, in dry CH_2Cl_2 (4 mL) was added TFA (2 mL) at 0°C. The resulting solution was stirred at room temperature for 12 h. After the reaction was completed, a solution of 33% aqueous ammonia was added until the pH of the solution reached to 8–9. The mixture was extracted with $CHCl_3$ (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography ($CHCl_3$/MeOH/NH_4OH = 135:25:4)[7] provided pure L-*thre*o-sphingosine (**1b**)[8a,9] (39 mg, 0.13 mmol, 88%) as a white solid: mp. 84–86°C, $[\alpha]_D^{24}$ −2.8 (*c* 0.82, $CHCl_3$); IR (film) 3400, 3336, 2922, 2853, 1675, 1462, 1035, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (dt, 1 H, *J* = 15.4, 6.7 Hz, −CHC*H*CH_2–), 5.44 (dd, 1 H, *J* = 15.4, 6.8 Hz, −C*H*CHOH), 4.01 (bt, 1 H, *J* = 5.9 Hz, −CHC*H*OH), 3.68 (dd, 1 H, *J* = 10.8, 3.9 Hz, −C*H*HOH), 3.54 (dd, 1 H, *J* = 10.1, 6.2 Hz, −CH*H*OH), 2.86–2.73 (m, 1 H, −C*H*NH_2), 2.71–2.49 (b, 4 H, −CH_2O*H*, −CHNH_2, −CHO*H*), 2.04 (q, 2 H, *J* = 6.9 Hz, −CHCHCH_2–), 1.43–1.33 (m, 2 H, −CH_2CH_3), 1.32–1.28 (m, 20 H, −$C_{10}H_{20}CH_2CH_3$), 0.88 (t, 3 H, *J* = 6.5 Hz, −CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 129.6, 73.6, 64.4, 56.5, 32.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 22.7, 14.1; HRMS (ESI) calcd. for $C_{18}H_{37}NO_2$ + H 300.2903, found 300.2897.

(4*R*,5*S*)-4-(Acetoxymethyl)-5-vinyloxazolidin-2-one (14c). To a stirred solution of vinylaziridine **3** (197 mg, 0.816 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (302 μL, 2.44 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h. After the reaction was completed, a saturated aqueous Na_2CO_3 (10 mL) solution was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/EtOAc = 3:1) furnished the desired *cis*-oxazolidinone **14c** (92 mg, 0.496 mmol, 60%) and *trans*-oxazolidinone **14t** (22 mg, 0.118 mmol, 14%) as colorless oils: **14c**: $[\alpha]_D^{23}$ +63.7 (*c* 1.50, $CHCl_3$); IR (film) 3281, 2961, 2924, 2855, 1739, 1375, 1260, 1096, 1019, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (bs, 1 H, −C(O)N*H*CH–), 5.88 (ddd, 1 H, *J* = 17.3, 10.5, 6.9 Hz, −C*H*CH_2), 5.48 (bd, 1 H, *J* = 17.2 Hz, −CHC*H*H), 5.42 (bd, 1 H, *J* = 10.6 Hz, −CHCH*H*), 5.13 (t, 1 H, *J* = 7.5 Hz, −C*H*CHCH_2), 4.18 (dd, 1 H, *J* = 11.3, 4.0 Hz, −OC*H*HCH–), 4.08 (td, 1 H, *J* = 7.8, 4.1 Hz, −OCH_2C*H*–), 3.95 (dd, 1 H, *J* = 11.3, 7.4 Hz, −OCH*H*CH–), 2.08 (s, 3 H, −C(O)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.8, 129.7, 120.9, 78.6, 63.1, 54.2, 20.6; HRMS (ESI) calcd. for $C_8H_{11}NO_4$ + H 186.0766, found 186.0763. **14t**: $[\alpha]_D^{23}$ + 71.5 (*c* 1.40, $CHCl_3$); IR (film) 3388, 2924, 2854, 1739, 1644, 1391, 1231, 1044, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, 1 H, *J* = 17.1, 10.4, 6.7 Hz, −C*H*CH_2), 5.47 (bd, 1 H, *J* = 17.1 Hz, −CHC*H*H), 5.37 (bd, 1 H, *J* = 10.4 Hz, −CHCH*H*), 5.39–5.28 (bs, 1 H, −C(O)N*H*CH–), 4.72 (t, 1 H, *J* = 6.6 Hz, −C*H*CHCH_2), 4.29 (dd, 1 H, *J* = 11.6, 4.1 Hz, −OC*H*HCH–), 4.04 (dd, 1 H, *J* = 11.6, 6.0 Hz, −OCH*H*CH–), 3.79 (td, 1 H, *J* = 5.9, 4.4 Hz, −OCH_2C*H*–), 2.11 (s, 3 H, −C(O)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 157.9, 133.4, 119.6, 79.2, 64.2, 56.8, 20.6; HRMS (ESI) calcd. for $C_8H_{11}NO_4$ + H 186.0766, found 186.0760.

(4*R*,5*S*)-4-(Acetoxymethyl)-5-(pentadec-1-en-1-yl)oxazolidin-2-one (16). To a stirred solution of oxazolidinone **14c** (111 mg, 0.599 mmol) in dry CH_2Cl_2 (15 mL) at room temperature were added 1-pentadecene (644 μL, 2.39 mmol) and Grubbs catalyst (second generation) (50 mg, 0.0599 mmol), producing a light brown solution. The resulting solution was stirred at 40°C for 22 h. The mixture was then concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) afforded the desired compound **16** (128 mg, 0.348 mmol, 58%, *E*/*Z* = 14:1, ^1H NMR analysis) as a brown oil: $[\alpha]_D^{23}$ + 22.5 (*c* 1.10, $CHCl_3$); IR (film) 3258, 2952, 2913, 284, 1727, 1466, 1380, 1243, 1036, 982, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (bs, 1 H, −C(O)N*H*CH–), 5.91 (dt, 1 H, *J* = 15.2, 6.9 Hz, −CHC*H*CH_2–), 5.49 (dd, 1 H, *J* = 15.4, 8.2 Hz, −C*H*CHOH), 5.07 (t, 1 H, *J* = 8.1 Hz, −OC*H*CH–), 4.18 (dd, 1 H, *J* = 11.2, 3.7 Hz, −OC*H*HCH–), 4.02 (td, 1 H, *J* = 7.9, 3.7 Hz, −OCH_2C*H*–), 3.95 (dd, 1 H, *J* = 11.2, 7.6 Hz, −OCH*H*CH–), 2.11–2.06 (m, 5 H, −C(O)CH_3, −CHCHCH_2–), 1.41–1.33 (m, 2 H, −CH_2CH_3), 1.29–1.20 (m, 20 H, −$C_{10}H_{20}CH_2CH_3$), 0.86 (t, 3 H, *J* = 6.7 Hz, −CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.1, 139.2, 121.3, 79.1, 63.2, 54.4, 32.2, 31.8, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 28.6, 22.6, 20.6, 14.0; HRMS (ESI) calcd. for $C_{21}H_{37}NO_4$ + Na 390.2620, found 390.2614.

(4*R*,5*S*)-4-(Hydroxymethyl)-5-(pentadec-1-en-1-yl)oxazolidin-2-one (17). To a solution of compound **16** (42 mg, 0.114 mmol) in methanol (5 mL) was added potassium carbonate (K_2CO_3) (19 mg, 0.136 mmol) at room temperature. The resulting solution was stirred at room temperature for 25 min. After the reaction was completed, a saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with ether (3 × 5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 1:1) produced the desired alcohol **17** (31 mg, 0.095 mmol, 88%)[10] as a white solid: mp. 98–100°C, $[\alpha]_D^{23}$ +12.1 (*c* 0.60, $CHCl_3$); IR (film) 3420, 3326, 2918, 2850, 1740, 1707, 1465, 1241, 1105, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (bs, 1 H, −C(O)N*H*CH–), 5.83 (dt, 1 H, *J* = 15.4, 6.7 Hz, −CHC*H*CH_2–), 5.37 (dd, 1 H, *J* = 15.4, 6.8 Hz, −C*H*CHOH), 4.38 (dd, 1 H, *J* = 17.5, 8.8 Hz, −OC*H*HCH–), 4.33 (dd, 1 H, *J* = 8.8, 5.2 Hz, −OCH*H*CH–), 4.12 (bt, 1 H, *J* = 5.2 Hz, −OC*H*CH–), 3.86 (dt, 1 H, *J* = 8.7, 5.0 Hz, −OCH_2C*H*–), 2.94 (bs, 1 H, −CH_2O*H*), 2.04 (q, 2 H, *J* = 6.9 Hz, −CHCHCH_2–), 1.40–1.32 (m, 2 H, −CH_2CH_3), 1.30–1.20 (m, 20 H, −$C_{10}H_{20}CH_2CH_3$), 0.87 (t, 3 H, *J* = 6.7 Hz, −CH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 136.4, 126.4, 73.1, 66.3, 56.3, 32.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 22.7, 14.1; HRMS (ESI) calcd. for $C_{19}H_{35}NO_3$ + Na 348.2514, found 348.2509.

(2*R*,3*S*,4*E*)-L-*erythro*-Sphingosine (1c). To a solution of alcohol **17** (30 mg, 0.092 mmol) in EtOH (1 mL) at room temperature was added an aqueous 2 M NaOH (0.5 mL) solution. The resulting solution was stirred at 80°C for 2 h. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with diethyl ether (10 mL), and washed with 2 M NaOH (3 × 2 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography ($CHCl_3$/MeOH/NH_4OH = 135:25:4)[7] provided pure L-*erythro*-sphingosine (**1c**)[8] (26 mg, 0.0868 mmol, 96%) as a white solid: mp. 79–80°C, $[\alpha]_D^{28}$ +1.9 (*c* 0.40, $CHCl_3$); IR (film) 3430, 3377, 2921, 2852, 1584, 1462, 1096, 971 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, 1 H, *J* = 15.3, 6.6 Hz, –CHC*H*CH_2–), 5.46 (dd, 1 H, *J* = 15.4, 6.4 Hz, –C*H*CHOH), 4.22–4.06 (m, 1 H, –CHC*H*OH), 3.80–3.57 (m, 2 H, –CH_2OH), 3.31–3.01 (b, 4 H, –CH_2O*H*, –CHNH_2, –CHO*H*), 3.0–2.85 (brm, 1 H, –C*H*NH_2), 2.04 (q, 2 H, *J* = 6.8 Hz, –CHCHCH_2–), 1.40–1.34 (m, 2 H, –C$H_2$$CH_3$), 1.31–1.23 (m, 20 H, –$C_{10}H_{20}CH_2CH_3$), 0.88 (t, 3 H, *J* = 6.6 Hz, –CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 129.0, 75.1, 63.7, 56.2, 32.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 22.7, 14.1; HRMS (ESI) calcd. for $C_{18}H_{37}NO_2$ + H 300.2903, found 300.2897.

(4*S*,5*R*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-5-vinyloxazolidin-2-one (15c). To a stirred solution of vinylaziridine **4** (75 mg, 0.239 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}Et_2O$ (88 μL, 0.717 mmol) at room temperature. The reaction mixture was stirred at room temperature for 7 h. After the reaction was completed, a saturated aqueous Na_2CO_3 (5 mL) solution was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/EtOAc = 2:1) furnished the desired *cis*-oxazolidinone **15c** (53 mg, 0.205 mmol, 53%) and *trans*-oxazolidinone **15t** (8 mg, 0.0310 mmol, 15%) as colorless oils: **15c:** $[\alpha]_D^{23}$ –57.3 (*c* 1.00, $CHCl_3$); IR (film) 3274, 2929, 2857, 1756, 1466, 1390, 1253, 1222, 1132, 1099, 1057, 1006, 936, 887, 838, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, 1 H, *J* = 17.3, 10.6, 6.8 Hz, –C*H*CH_2), 5.48 (dd, 1 H, *J* = 17.2, 1.2 Hz, –CHC*H*H), 5.47–5.42 (b, 1 H, –C(O)N*H*CH–), 5.37 (dd, 1 H, *J* = 10.5, 1.1 Hz, –CHCH*H*), 5.09 (t, 1 H, *J* = 7.5 Hz, –C*H*CHCH_2), 3.89 (td, 1 H, *J* = 7.7, 4.5 Hz, –OCH_2C*H*–), 3.58 (dd, 1 H, *J* = 10.3, 4.5 Hz, –OC*H*HCH–), 3.53 (dd, 1 H, *J* = 10.3, 7.3 Hz, –OCH*H*CH–), 0.88 (s, 9 H, –OSi$(CH_3)_2$C$(CH_3)_3$), 0.055 (d, 6 H, –OSi$(CH_3)_2$C$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 130.3, 120.1, 78.8, 62.3, 56.9, 25.7, 18.1, –5.5; HRMS (ESI) calcd. for $C_{12}H_{23}NO_3Si$ + H 258.1525, found 258.1521. **15t**: $[\alpha]_D^{21}$ –65.9 (*c* 1.40, $CHCl_3$); IR (film) 3283, 2933, 2895, 2858, 1756, 1466, 1397, 1255, 1221, 1121, 1013, 934, 840, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, 1 H, *J* = 17.0, 10.5, 6.4 Hz, –C*H*CH_2), 5.81 (bs, 1 H, –C(O)N*H*CH–), 5.41 (dd, 1 H, *J* = 17.1, 1.1 Hz, –CHC*H*H), 5.30 (dd, 1 H, *J* = 10.4, 1.0 Hz, –CHCH*H*), 4.73 (td, 1 H, *J* = 5.6, 1.3 Hz, –C*H*CHCH_2), 3.67–3.58 (m, 3 H, –OCH_2C*H*-, –OCH_2CH–), 0.88 (s, 9 H, –OSi$(CH_3)_2$C$(CH_3)_3$), 0.069 (s, 6 H, OSi$(CH_3)_2$C$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 134.5, 118.3, 79.3, 64.3, 59.3, 25.7, 18.1, –5.5; HRMS (ESI) calcd. for $C_{12}H_{23}NO_3Si$ + H 258.1525, found 258.1519.

(4*S*,5*R*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-5-(pentadec-1-en-1-yl)oxazolidin-2-one (18). To a stirred solution of oxazolidinone **15c** (22 mg, 0.0854 mmol) in dry CH_2Cl_2 (10 mL) at room temperature were added 1-pentadecene (92 μL, 0.341 mmol) and Grubbs catalyst (second generation) (7.2 mg, 0.0085 mmol), producing a light brown solution. The resulting solution was stirred at 40°C for 12 h. The mixture was then concentrated. Purification by flash chromatography (hexane/EtOAc = 4:1) afforded the desired compound **18** (28 mg, 0.0636 mmol, 75%, *E*/*Z* = 12:1, ^{1}H NMR analysis) as a brown oil: $[\alpha]_D^{23}$ –22.6 (*c* 0.90, MeOH); IR (film) 3481, 3278, 3135, 2923, 2853, 1737, 1465, 1402, 1365, 1254, 1225, 1136, 1102, 1054, 976, 888, 840, 777, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.8 (dt, 1 H, *J* = 15.4, 6.4 Hz, –CHC*H*CH_2–), 5.51 (dd, 1 H, *J* = 15.4, 8.1 Hz, –C*H*CHOH), 5.22 (bs, 1 H, -C(O)N*H*CH–), 5.04 (t, 1 H, *J* = 8.0 Hz, –OC*H*CH–), 3.83 (td, 1 H, *J* = 7.4, 4.6 Hz, –OCH_2C*H*–), 3.61–3.52 (m, 2 H, -OCH_2CH–), 2.08 (q, 2 H, *J* = 7.0 Hz, –CHCHCH_2–), 1.45–1.34 (m, 2 H, –C$H_2$$CH_3$), 1.32–1.23 (m, 20 H, –$C_{10}H_{20}CH_2CH_3$), 0.92–0.84 (brm, 12 H, –OSi$(CH_3)_2$C$(CH_3)_3$, –CH_2CH_3), 0.063 (d, 6 H, –OSi$(CH_3)_2$C$(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 138.4, 121.9, 79.2, 62.5, 57.2, 32.2, 31.9, 29.7, 29.6, 29.4, 29.3, 29.1, 28.7, 25.7, 22.7, 18.1, 14.1, –5.5; HRMS (ESI) calcd. for $C_{25}H_{49}NO_3Si$ + Na 462.3379, found 462.3338.

(4*S*,5*R*)-4-(Hydroxymethyl)-5-(pentadec-1-en-1-yl)oxazolidin-2-one (19). To a stirred solution of compound **18** (26 mg, 0.0591 mmol) in dry THF (4 mL) at room temperature was added tetrabutylammonium fluoride (TBAF) [60 μL (1.0 M in THF), 0.0602 mmol]. After 1.5 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane/EtOAc = 1:1) offered the desired alcohol **19** (16 mg, 0.049 mmol, 84%) as a white solid: mp. 98–100°C, $[\alpha]_D^{21}$ –11.9 (*c* 0.53, MeOH)[10]; IR (film) 3285, 2918, 2850, 1700, 1467, 1405, 1094, 1022, 970, 934, 869, 777, 725 cm^{-1}; ^{1}H NMR 5.92 (dt, 1 H, *J* = 15.2, 6.8 Hz, –CHC*H*CH_2–), 5.73 (bs, 1 H, –C(O)N*H*CH–), 5.56 (dd, 1 H, *J* = 15.4, 8.1 Hz, –C*H*CHOH), 5.08 (t, 1 H, *J* = 8.1 Hz, –OC*H*CH–), 3.89 (td, 1 H, *J* = 7.4, 3.9 Hz, –OCH_2C*H*–), 3.68 (dd, 1 H, *J* = 11.2, 3.9 Hz, –OC*H*HCH–), 3.63 (dd, 1 H, *J* = 11.2, 7.1 Hz, –OCH*H*CH–), 2.40–2.15 (b, 1 H, –CH_2O*H*), 2.09 (q, 2 H, *J* = 7.1 Hz, –CHCHCH_2–), 1.41–1.36 (m, 2 H, –C$H_2$$CH_3$),

1.28–1.24 (m, 20 H, $-C_{10}H_{20}CH_2CH_3$), 0.88 (t, 3 H, J = 6.8 Hz, $-CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.9, 121.9, 79.5, 62.1, 56.9, 32.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.7, 22.7, 14.1; HRMS (ESI) calcd. for $C_{19}H_{35}NO_3$ + Na 348.2515, found 348.2506.

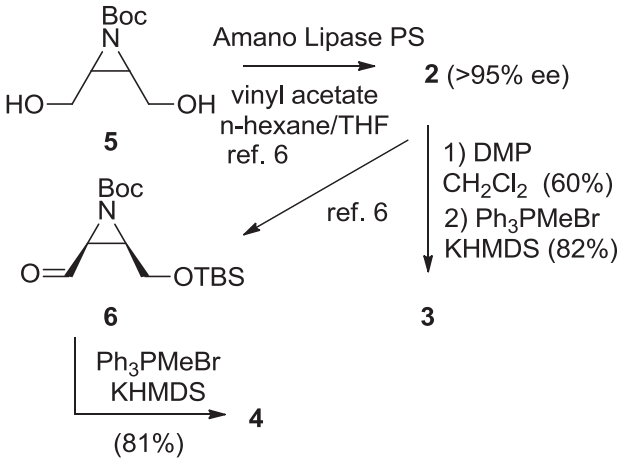
(2*S*,3*R*,4*E*)-D-*erythro*-Sphingosine (1d). To a solution of alcohol **19** (20 mg, 0.061 mmol) in EtOH (1 mL) was added an aqueous 2 M NaOH (0.5 mL) solution at room temperature. The resulting solution was stirred at 80°C for 2 h. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with diethyl ether (10 mL), and washed with an 2 M NaOH (3 × 2 mL) solution. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography ($CHCl_3$/MeOH/NH_4OH = 135:25:4) furnished pure D-*erythro*-sphingosine (**1d**)[8a,b,11](17 mg, 0.056 mmol, 92%) as a white solid: mp. 76–77°C, $[\alpha]_D^{28}$ –1.70 (*c* 0.41, $CHCl_3$); IR (film) 3400, 3370, 2920, 2850, 1582, 1462, 1096, 970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, 1 H, J = 15.4, 6.7 Hz, $-CHCHCH_2-$), 5.47 (dd, 1 H, J = 15.4, 7.0 Hz, $-CHCHOH$), 4.15–4.02 (m, 1 H, $-CHCHOH$), 3.79–3.55 (m, 2 H, $-CH_2OH$), 3.01–2.77 (brm, 1 H, $-CHNH_2$), 2.40–2.19 (b, 4 H, $-CH_2OH$, $-CHNH_2$, $-CHOH$), 2.05 (q, 2 H, J = 6.8 Hz, $-CHCHCH_2-$), 1.41–1.34 (m, 2 H, $-CH_2CH_3$), 1.29–1.23 (m, 20 H, $-C_{10}H_{20}CH_2CH_3$), 0.88 (t, 3 H, J = 6.6 Hz, $-CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 129.3, 75.4, 63.9, 56.1, 32.3, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 22.7, 14.1; HRMS (ESI) calcd. for $C_{18}H_{37}NO_2$ + H 300.2903, found 300.2895.

Results and Discussion

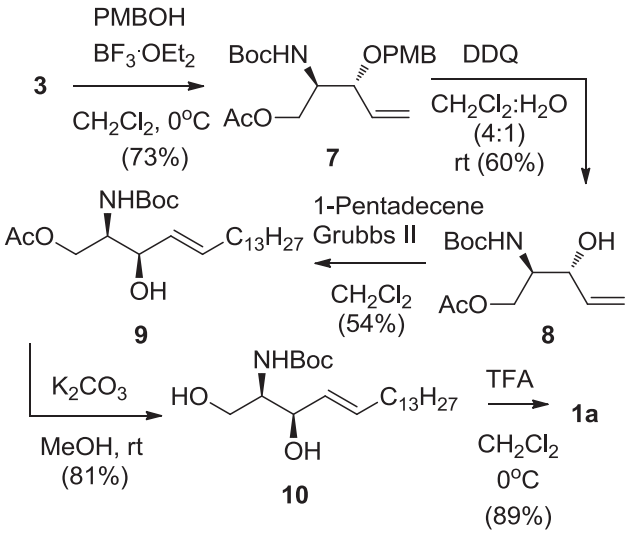
Synthesis of all four sphingosines started from enantiomerically pure *cis*-3-substituted-2-vinylaziridines, i.e., **3** and **4**, which can be easily prepared from a common chiral aziridine, *cis*-2-acetoxymethyl-3-hydroxymethylaziridine (**2**) (Scheme 1). (2*R*,3*R*,4*E*)-D-*threo*-Sphingosine (**1a**) and (2*R*,3*S*,4*E*)-L-*erythro*-sphingosine (**1c**) could be derived from chiral vinylaziridine **3**. Similarly, (2*S*,3*S*,4*E*)-L-*threo*-sphingosine (**1b**) and (2*S*,3*R*,4*E*)-D-*erythro*-sphingosine (**1d**), in turn, could be prepared from chiral vinylaziridine **4**.

Vinylaziridines **3** and **4** became important intermediates for the synthesis of all four possible sphingosines **1a–1d**. Preparation of chiral vinylaziridines **3** and **4** was achieved using the Wittig reaction of the corresponding aldehydes (Scheme 2).[3,4] Enzymatic desymmetrization of *meso*-diol **5** provided **2** in an enantiomerically pure form. Oxidation followed by the Wittig olefination provided chiral vinylaziridine **3**. The synthesis of **4** was achieved successfully by conversion of **2** into aldehyde **6**, according to the previously reported procedure,[3] followed by the Wittig olefination.

First, we investigated the synthesis of (2*R*,3*R*,4*E*)-D-*threo*-sphingosine **1a**, and the synthetic sequence is summarized in Scheme 3.



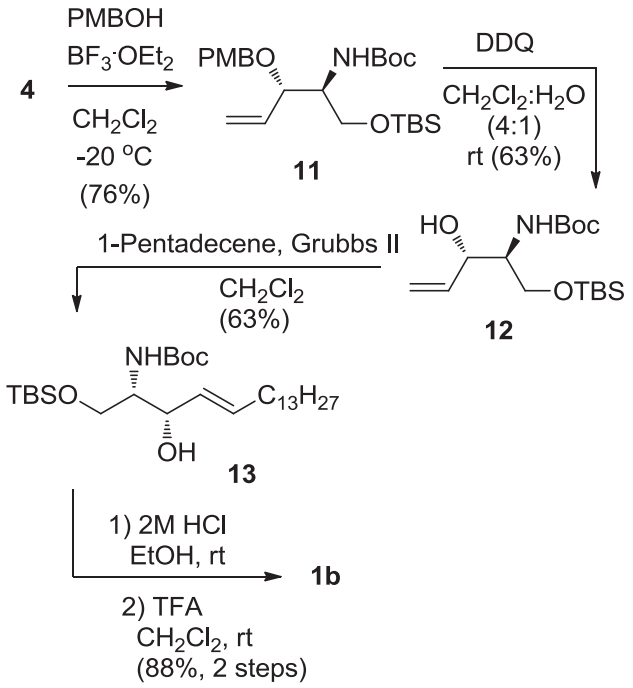
Scheme 2. Preparation of the starting chiral vinylaziridines **3** and **4**.



Scheme 3. Synthesis of (2*R*,3*R*,4*E*)-D-*threo*-Sphingosine (**1a**).

As reported previously,[4] the Lewis acid-catalyzed ring opening of aziridine **3** with *p*-methoxybenzyl alcohol (PMBOH) produced **7** in good yield with excellent regio- and stereoselectivity. Deprotection of the PMB group followed by the cross-metathesis reaction of **8** with 1-pentadecene in the presence of the Grubbs II catalyst successfully afforded the protected sphingosine **9** with a good *E*/*Z* selectivity (12:1, confirmed by ^{1}H NMR). The target (2*R*,3*R*,4*E*)-L-*threo*-sphingosine (**1a**) was obtained through a sequential deprotection of the acetyl group (K_2CO_3, MeOH) in **9** and the Boc group in **10** (TFA, CH_2Cl_2). Sphingosine **1a** showed identical spectra as those reported in the literature.[8]

For the synthesis of the corresponding enantiomeric isomer of sphingosine, i.e., (2*S*,3*S*,4*E*)-D-*threo*-sphingosine (**1b**), it is required to start with aziridine **4** bearing the opposite stereochemistry to **3** (Scheme 4). The selective ring opening of aziridine **4** with PMBOH in the presence of $BF_3.OEt_2$ followed by deprotection produced the protected

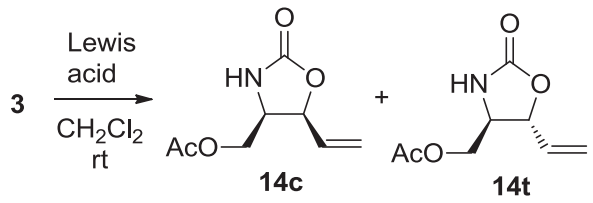


Scheme 4. Synthesis of (2*S*,3*S*,4*E*)-D-*threo*-sphingosine (**1b**).

allylic alcohol **12**. The cross-metathesis reaction provided the desired sphingosine **13** in a protected form (*E*/*Z* selectivity = 12:1 by ^{1}H NMR). After deprotection of TBS (HCl, EtOH) and Boc (TFA, CH_2Cl_2) groups, the desired (2*S*,3*S*,4*E*)-L-*threo*-sphingosine (**1b**) was obtained. The spectra matched with those reported previously.[8]

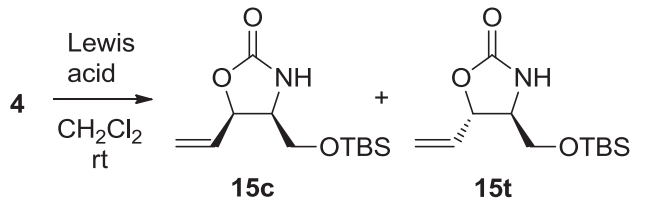
Next, the synthesis of *erythro*-sphingosines was investigated. A straight and simple strategy would require the corresponding trans isomers of **3** and **4**. Because the corresponding trans isomers in enantiopure forms are not readily accessible, we searched for another possibility. The ring expansion of *N*-Boc-substituted aziridines to the corresponding oxazolidinones has been well known.[12,13] This ring-expansion reaction occurs regioselectively in the case of vinylaziridines in an S_N1 fashion, providing 2-oxazolidinones. The ring-expansion reactions of **3** and **4** were

Table 1. Ring-expansion reactions of vinylaziridines **3.**



Entry	Lewis acid (equiv)	Yield (%)	Ratio (14c/14t)
1	$BF_3.OEt_2$ (0.5)	75	4:1
2	$Sc(OTf)_3$ (0.1)	78	2:1
3	$Cu(OTf)_2$ (0.1)	72	2:1
4	$Sn(OTf)_2$ (0.1)	79	2:1

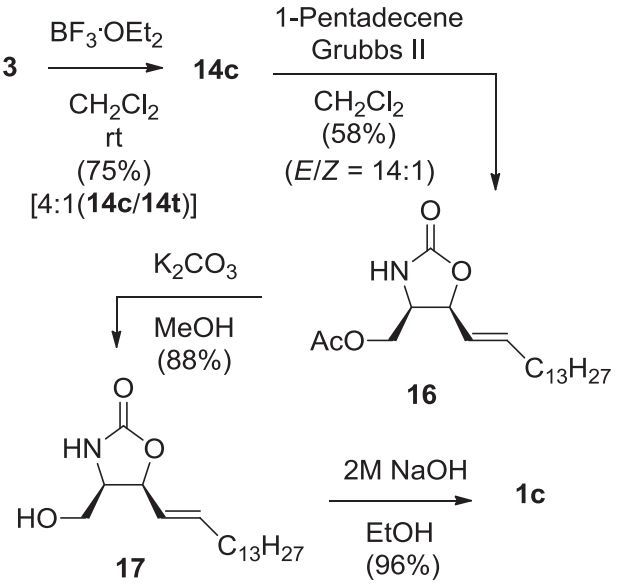
Table 2. Ring-expansion reactions of vinylaziridines **4**.



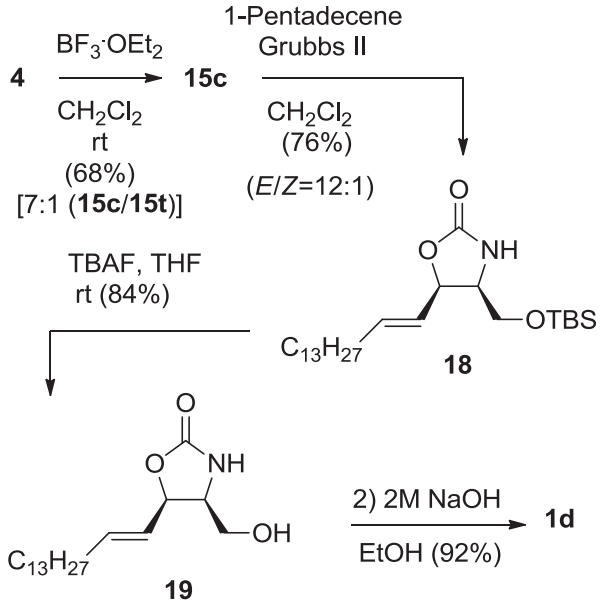
Entry	Lewis acid (equiv)	Yield (%)	Ratio (15c/15t)
1	$BF_3.OEt_2$ (0.5)	68	7:1
2	$Sc(OTf)_3$ (0.1)	72	2:1
3	$Cu(OTf)_2$ (0.1)	70	2:1
4	$Sn(OTf)_2$ (0.1)	70	2:1

investigated using various Lewis-acids. The results are summarized in Tables 1 and 2. In the case of the chiral aziridine **3**, Lewis acids such as $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $Cu(OTf)_2$, and $Sn(OTf)_2$ were tested because these acids had been used for the ring-expansion reactions previously (Table 1).[12b,c,13] All the Lewis acids examined afforded mixtures of 4,5-*cis* (**14c**) and 4,5-*trans* (**14t**) isomers, and $BF_3.OEt_2$ provided the best result. Employing 0.5 equiv of this Lewis acid resulted in 75% combined yield with a ratio of 4:1 (**14c/14t**). The results of the ring-expansion reaction of chiral aziridine **4** exhibited a similar trend (Table 2). $BF_3{\cdot}OEt_2$ also produced the best results [0.5 equiv of $BF_3{\cdot}OEt_2$, 68% combined yield with a ratio of 7:1 (**15c/15t**)]. After the separation, the cis compounds **14c** and **15c** were used for the next reactions.

Having the desired intermediates **14c** and **15c** in our hand, we were in the position of pursuing the synthesis of *erythro*-sphingosines. The synthesis of one of the *erythro*-isomer, i.e., (2*R*,3*S*,4*E*)-L-*erythro*-sphingosine (**1c**) is shown in Scheme 5. Oxazolidinone **14c**, obtained from the



Scheme 5. Synthesis of (2*R*,3*S*,4*E*)-L-*erythro*-sphingosine (**1c**).



Scheme 6. Synthesis of (2*S*,3*R*,4*E*)-D-*erythro*-sphingosine (**1d**).

ring-expansion reaction of chiral aziridine **3** in the presence of a Lewis acid ($BF_3{\cdot}OEt_2$), was subjected to the cross-metathesis reaction with 1-pentadecene in the presence of the Grubbs II catalyst, providing the desired extended olefin **16**. The *E*/*Z* ratio of the product was measured to be 14:1 by ^{1}H NMR. Hydrolysis of acetate group (K_2CO_3, MeOH) followed by hydrolysis of the carbamate by treating with methanolic NaOH finally provided the target (2*R*,3*S*,4*E*)-L-*erythro*-sphingosine (**1c**). The spectra of **1c** are identical to those reported in the literature.[8]

The remaining *erythro*-isomer, (2*S*,3*R*,4*E*)-D-*erythro*-sphingosine (**1d**), was synthesized according to the route shown in Scheme 6. After the Lewis acid-catalyzed ring-expansion reaction of **4**, cross-metathesis of **15c** was carried out smoothly to afford **18** (*E*/*Z* ratio of 12:1 by ^{1}H NMR analysis). Deprotection of TBS group by TBAF produced **19**, and, finally, the carbamate was subjected to basic hydrolysis to provide (2*S*,3*R*,4*E*)-D-*erythro*-sphingosine (**1d**).[8,11]

Conclusion

Chiral aziridine **2**, readily available through the enzymatic desymmetrization of aziridinediol **5**, is a useful starting material for the synthesis of all four diastereomers of sphingosines. Vinylaziridines **3** and **4** were prepared from chiral aziridine **2**. The *threo*-isomers of sphingosine were synthesized from **3** and **4** by selective ring-opening reactions using an oxygen nucleophile and the cross-metathesis reaction as key reactions. To synthesize the *erythro*-isomers, a Lewis acid-catalyzed ring-expansion reaction of *N*-Boc-aziridines was exploited. Similar cross-metathesis reactions of the resulting oxazolidinones provided the sphingosines with the required stereochemistries. This divergent synthesis of all enantiomers of sphingosine has confirmed that chiral vinylaziridnes such as **3** and **4** are versatile intermediates for the synthesis of sphingosines and related natural products.

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Supporting Information. Additional supporting information is available in the online version of this article.

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