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Novel, efficient and stereospecific synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-sphingosine☆

Sadagopan Raghavan,* A. Rajender and J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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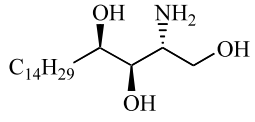
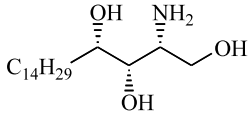
Abstract—The stereo- and regioselective elaboration of a bromohydrin from an olefinic precursor and Pummerer ene reaction for carbon–carbon bond formation are the key steps in a novel and flexible synthesis of *xylo*-phytosphingosine and *threo*-sphingosine.

1. Introduction

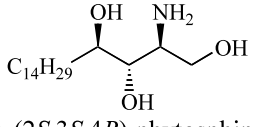
Sphingosines, dihydrosphingosines and phytosphingosines (Fig. 1) are long-chain bases that form the backbone of sphingolipids, which are important membrane components. Sphingolipids are involved in a number of cellular events including cell growth, differentiation, adhesion and neuronal repair. They have also been shown to play a critical role as secondary messengers in cell signaling.[1] The phytosphingosines[2a] and their derivatives[2b] also exhibit important physiological activities. The majority of phytosphingosines have eighteen carbons, minor amounts of other chain lengths; especially C_{20}, are also present depending on the sources of origin. Phytosphingosine was first isolated from mushrooms in 1911[3] and was subsequently shown to be widely distributed in yeast,[4] fungi,[5] plants,[6] marine organisms[7] and mammalian tissues.[8] Since it is not



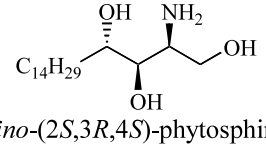
lyxo-(2*R*,3*R*,4*R*)-phytosphingosine



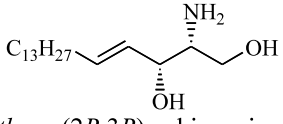
xylo-(2*R*,3*S*,4*S*)-phytosphingosine



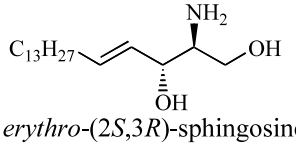
ribo-(2*S*,3*S*,4*R*)-phytosphingosine



arabino-(2*S*,3*R*,4*S*)-phytosphingosine



threo-(2*R*,3*R*)-sphingosine



erythro-(2*S*,3*R*)-sphingosine

Figure 1.

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* Corresponding author. E-mail: purush101@yahoo.com

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possible to obtain homogenous material from natural sources and it is expensive to isolate these lipids, a great deal of synthetic effort has been made to obtain homogenous compounds for biological studies. Most syntheses have focused on the preparation of *ribo*-(2*S*,3*S*,4*R*)-phytosphingosine starting with compounds from a chiral pool[9,10] or approaches involving asymmetric induction.[11] It is therefore of great interest to synthesize other phytosphingosine diastereomers to learn about the precise function of individual sphingolipids in vivo. The design of an efficient and improved route to phytosphingosines therefore continues to be important.

2. Results and discussion

A general synthesis that would allow syntheses of phytosphingosine diastereomers in high purity and incorporation of different hydrocarbon chain lengths is required. We recently disclosed stereoselective bromohydration of β-hydroxy-γ,δ-unsaturated sulfoxides π-complexed to a bromonium ion via intramolecular nucleophilic attack by the sulfinyl moiety.[12] The potential of this methodology is illustrated by the enantioselective synthesis of *xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytoshingosine[13a,b] and *threo*-(2*R*,3*R*)-C_{18}-sphingosine.[13c] The retrosynthetic analysis is illustrated in Scheme 1. The phytosphingosine **1**, can be elaborated from the sulfide **2**, which in turn can be obtained eventually by a ene reaction from the bromohydrin **3**. The bromohydrin **3** can be readily obtained from the olefin **4** by the methodology disclosed by us.

2.1. Synthesis of *xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine

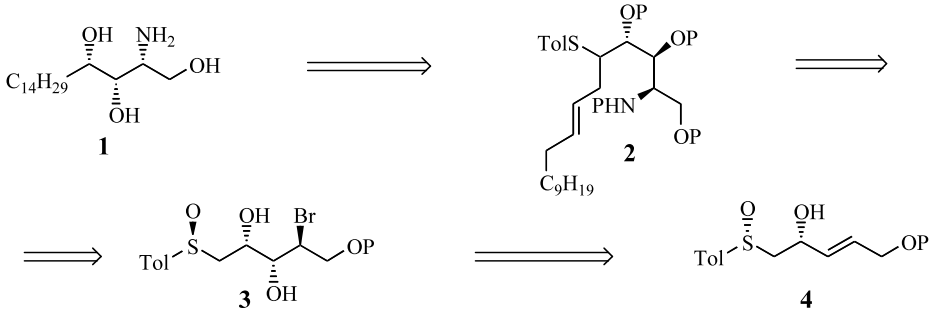
On the basis of the retrosynthetic analysis (Scheme 1), the first target for the synthesis is the β-hydroxy-γ,δ-unsaturated sulfoxide **6**, which was prepared by the reduction of the keto sulfoxide **5**[14] with DIBAL-H/$ZnCl_2$.[15] Treatment of the olefin **6**, with NBS in toluene in the presence of water, afforded the bromohydrin **8** as the sole product. The *syn*-disposition of the two hydroxy groups at C_2 and C_3 was proven by acetonide formation **9** and the ^{13}C NMR[16] spectrum, which revealed signals at δ 27.0 and 27.4 for the methyl groups. The orientation, as indicated for the hydroxy group and bromine at C_3 and C_4 respectively, is expected from a overall anti addition across the double bond. The observed stereo- and regioselectivity can be rationalized through the intermediacy of a sulfoxonium salt **7** (Scheme 2).

The 5-*exo* nucleophilic attack by the sulfinyl group onto the olefin π-complexed to the bromonium ion results in the formation of the sulfoxonium salt **7**, which upon hydrolysis by attack of water on sulfur in an S_N2 fashion, yields the bromohydrin **8**, with inversion of the sulfur configuration.[17] The acetonide **9**, was converted readily to the azido sulfoxide **10** by treatment with sodium azide in DMSO. The C_{13} hydrocarbon chain was introduced by the Pummerer ene reaction.[18] Thus treatment of the sulfoxide **10** with TFAA in DCM, afforded the Pummerer intermediate **11** which was then reacted in the same pot with 1-tridecene and $SnCl_4$ to afford the sulfide **12**. The ^1H NMR and ^{13}C spectrum of **12** revealed the presence of only one isomer although four isomers are theoretically expected; two that differ due to the configuration at the newly created stereogenic center and two geometrical isomers. The structure of the sulfide **12**, was not rigorously established since the configuration at the newly created stereogenic center was of no consequence for the synthesis of the target molecule. The synthesis of the target was accomplished as depicted in Scheme 3.

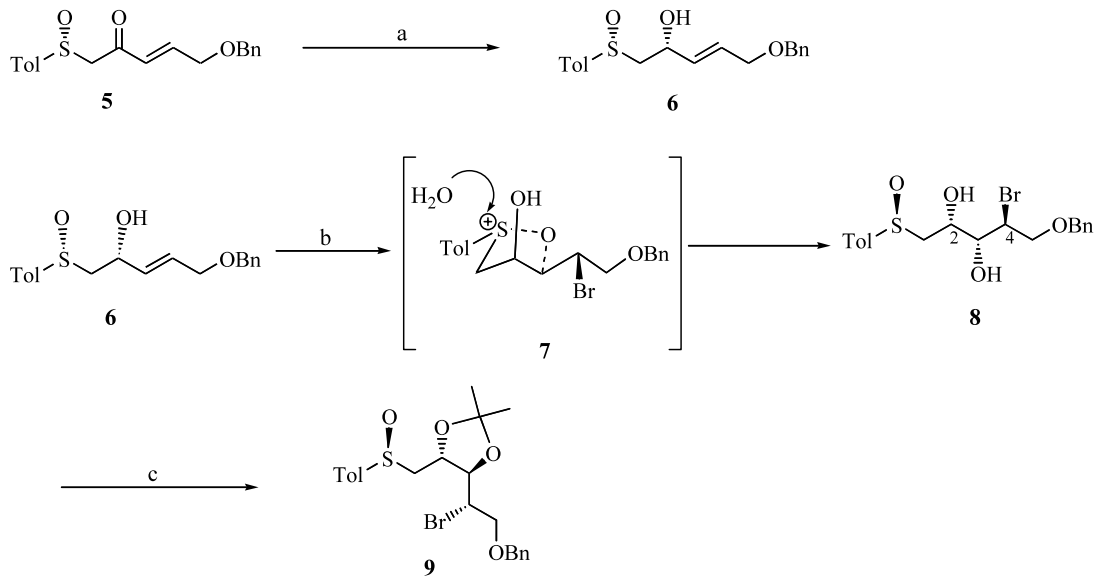
Five transformations were effected in a one pot operation, by treatment of the sulfide **12**, with Ra-Ni in methanol in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen to yield the acetonide **13**. The double bond and the azide were reduced with the resulting amine transformed into a urethane and the toluene thio group and benzyl ether hydrogenolysed under the reaction conditions. The acetonide **13** was then deprotected to give the triol **14**, which when acetylated, afforded the tetraacetate **15** with physical characteristics identical (except for the sign of rotation) to that reported in the literature.[13d]

2.2. Synthesis of *threo*-(2*R*,3*R*)-C_{18}-sphingosine

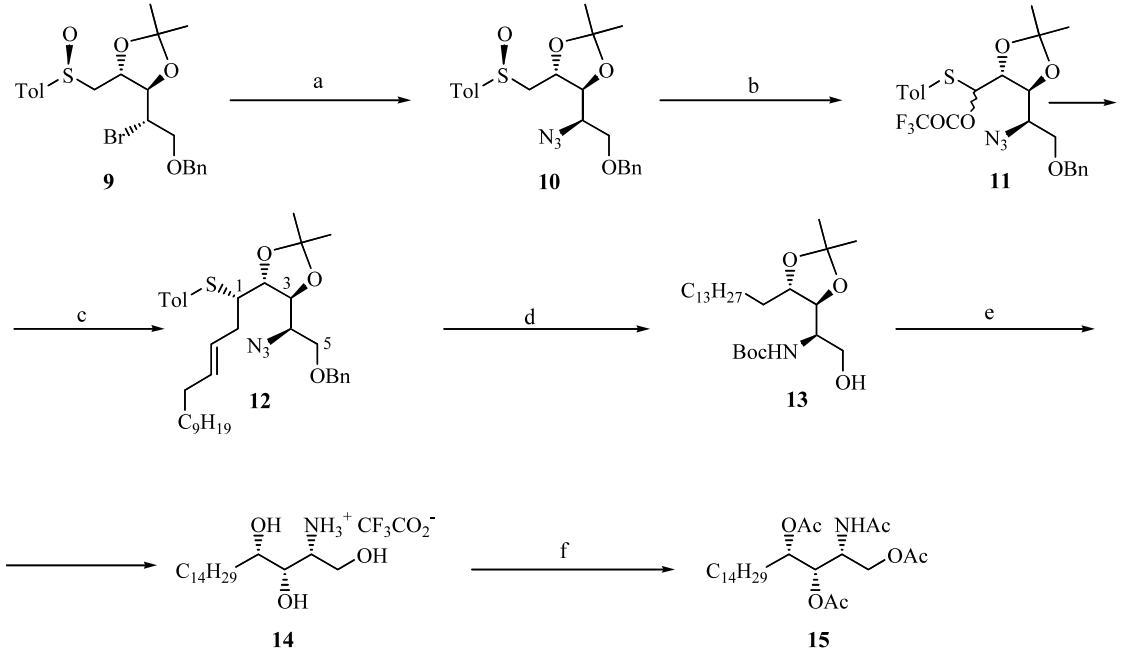
threo-Sphingosine and their derivatives are reversible inhibitors of protein kinase C.[19] Herein we report the synthesis of *threo*-(2*R*,3*R*)-sphingosine from the azido



Scheme 1.



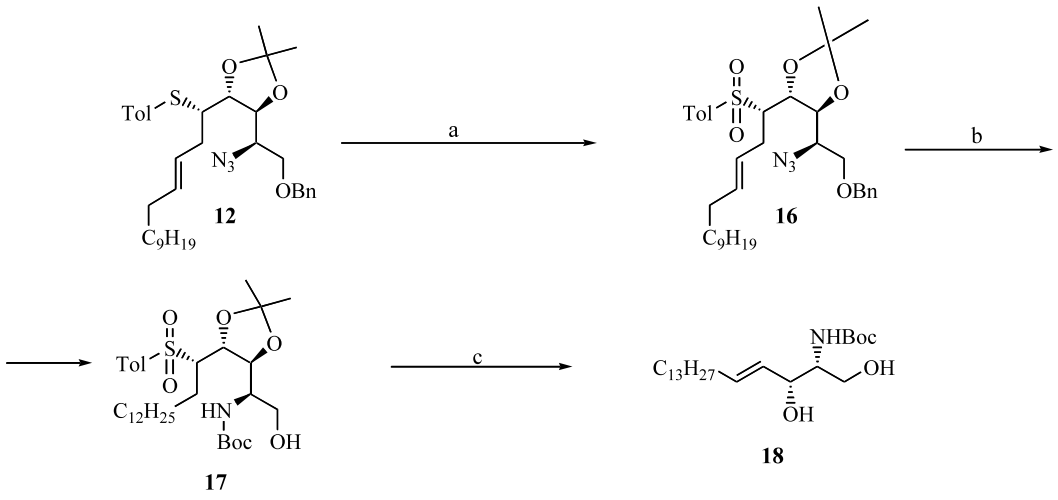
Scheme 2. *Reagents and conditions*: (a) DIBAL, THF, −78°C, 91%; (b) NBS, H_2O, toluene, rt, 88%; (c) 2,2-DMP, acetone, CSA (cat.), rt, 86%.



Scheme 3. *Reagents and conditions*: (a) NaN_3, DMSO, 85°C, 75%; (b) TFAA, CH_2Cl_2, 0°C; (c) $C_{13}H_{26}$, $SnCl_4$, 0°C, 65% for the two steps; (d) Ra-Ni, H_2, $(Boc)_2O$, MeOH, rt–reflux, 68%; (e) TFA:H_2O, 0°C; (f) Ac_2O, DMAP (cat.), pyridine, rt, 78%.

sulfide **12** (Scheme 4). Oxidation of the sulfide **12**, with oxone[20] afforded the sulfone **16**, which was transformed into the urethane **17**, in a one pot, four step transformation by treatment with $Pd(OH)_2/C$ in methanol under an atmosphere of hydrogen. Treatment of the sulfone **17**, with Na/Hg[21] in methanol yielded the *threo*-sphingosine derivative **18** (Scheme 4) with physical characteristics identical to that reported in the literature.[22] The crude ^1H NMR spectrum of **18** revealed the presence of the *trans*-olefin only.

In conclusion, we have described a flexible (use of different olefins in the Pummerer ene reaction permits the introduction of variable carbon chains), stereoselective synthesis of *xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine and *threo*-(2*R*,3*R*)-C_{18}-sphingosine. The key steps of the syntheses are i) asymmetric induction from sulfur to C_2 in the transformation of **5** to **6**, ii) asymmetric induction from C_2 to C_3 and C_4 in the transformation of **6** to **8**, iii) ene reaction for the introduction of the hydrocarbon chain (of varying lengths if desired), iv)



Scheme 4. *Reagents and conditions*: (a) $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, MeOH:$H_2O$:THF, 0°C–rt, 82%; (b) $Pd(OH)_2/C$, $(Boc)_2O$, H_2, EtOH, rt, 71%; (c) Na-Hg, Na_2HPO_4, MeOH, 20°C, rt, 65%.

one pot multi step transformation of **12** to **13** and **16** to **17**, v) transformation of the sulfone **17** into sphingosine **18** cleanly using Na-Hg. It is pertinent to mention that starting from the C_2 diastereomer of alcohol **6**, the *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine can be synthesized, essentially following an identical reaction sequence.

3. Experimental

3.1. 5-Benzyloxy-1-(S_R)-(4-methylphenylsulfinyl)-(2*R*,3*E*)-penten-2-ol 6

The β-ketosulfoxide **5** (1.56 g, 4.76 mmol) was stirred for 15 min with $ZnCl_2$ (935 mg, 5.7 mmol) in THF (48 mL). The reaction mixture was cooled to −78°C, and DIBAL (2M solution in toluene, 3.6 mL, 7.2 mmol) added dropwise over a period of 10 min. After 30 min while stirring at the same temperature, methanol (48 mL) was added and the reaction mixture allowed to return to rt. The solvent was evaporated under reduced pressure. The residue was diluted with 5% aq. HCl solution and extracted into CH_2Cl_2. The organic layer was washed with 5% aq. NaOH solution, brine and dried over Na_2SO_4. The crude product was purified by column chromatography using 50% EtOAc/petroleum ether as the eluent to afford the hydroxysulfoxide **6** (1.41 g, 4.3 mmol) as a single diastereomer in 91% yield. Pale yellow liquid. $R_f=0.27$ (50% petroleum ether/AcOEt), $[\alpha]_D^{25}=118.9$ (*c* 0.75, $CHCl_3$), LSIMS *m*/*z*: 331 $[M+H]^+$, ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.53$ (d, $J=8.2$ Hz, 2H), 7.36–7.22 (m, 7H), 5.87 (dt, $J=14.9$, 5.9 Hz, 1H), 5.72 (dd, $J=14.9$, 4.6 Hz, 1H), 4.79 (m, 1H), 4.52 (s, 2H), 4.06 (d, $J=4.6$ Hz, 2H), 2.94 (dd, $J=13.4$, 9.6 Hz, 1H), 2.76 (dd, $J=13.4$, 3.0 Hz, 1H), 2.43 (s, 3H).

3.2. 5-Benzyloxy-4-bromo-1-(S_S)-(4-methylphenylsulfinyl)-(2*R*,3*R*,4*S*)-pentane-2,3-diol 8

To a solution of the sulfoxide **6** (1.32 g, 4 mmol) in dry toluene, (16 mL) water (144 mg, 8 mmol) was added, followed by *N*-bromosuccinimide (850 mg, 4.8 mmol) and the reaction mixture stirred at room temperature for 15 min. The reaction mixture was quenched by the addition of an aq. saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer extracted with ethylacetate. The combined organic layers were successively washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent afforded the crude product, which was purified by column chromatography using AcOEt/petroleum ether (2:3) as the eluent to yield the bromohydrin **8** (1.5 g, 3.52 mmol) in 88% yield as a white solid. Mp 136–137°C, $R_f=0.26$ (60% petroleum ether/AcOEt), $[\alpha]_D^{25}=-129.5$ (*c* 1.0, $CHCl_3$), LSIMS *m*/*z*: 427 $[M+H]^+$, ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, $J=8.2$ Hz, 2H), 7.35–7.27 (m, 7H), 4.64–4.56 (m, 3H), 4.17 (dt, $J=7.6$, 4.8 Hz, 1H), 3.98 (dd, $J=10.3$, 4.8 Hz, 1H), 3.85 (dd, $J=10.3$, 4.8 Hz, 1H), 3.61 (dt, $J=7.6$, 4.8 Hz, 1H), 3.38–3.17 (m, 2H), 2.66 (dd, $J=13.4$, 1.88 Hz, 1H), 2.43 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=21.3$, 51.2, 61.0, 65.9, 71.6, 73.3, 75.1, 124.0, 127.6, 127.7, 128.4, 130.0, 137.5, 139.6, 141.6.

3.3. 4-[2-Benzyloxy-1-bromo-(1*S*)-ethyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinylmethyl)-(4*R*,5*R*)-1,3-dioxolane 9

To a solution of the diol **8** (1.45 g, 3.4 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 13 mL) was added CSA (32 mg, 0.14 mmol) and the reaction mixture stirred at ambient temperature for 2 h. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography using 20% AcOEt/petroleum ether as the eluent to yield the acetonide **9** (1.35 g, 2.92 mmol) as colourless crystalline solid in 86% yield. Mp 147–149°C, $R_f=0.64$ (50% petroleum ether/AcOEt), $[\alpha]_D^{25}=-152.4$ (*c* 1.0, $CHCl_3$), LSIMS *m*/*z*: 467 $[M+H]^+$, ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.56$ (d, $J=8.2$ Hz, 2H), 7.37–7.27 (m, 7H), 4.65–4.53 (m, 3H), 4.12–3.96 (m, 2H), 3.80–3.70 (m, 2H), 3.35 (dd, $J=13.2$, 2.9 Hz, 1H), 2.84 (dd, $J=13.2$, 10.3 Hz, 1H), 2.41 (s, 3H), 1.40

(s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.3$, 27.0, 27.4, 51.9, 63.6, 71.1, 73.3, 74.9, 79.8, 110.5, 123.9, 127.6, 127.7, 128.3, 130.0, 137.6, 141.4, 141.5.

3.4. 4-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-(S_S)-(4-methylphenylsulfinylmethyl)-(4*S*,5*R*)-1,3-dioxolane 10

To a solution of acetonide **9** (1.33 g, 2.85 mmol) in DMSO, (12 mL) NaN_3 (925 mg, 14.2 mmol) was added. The reaction mixture was stirred at 85°C for 8 h. Once the reaction mixture returned to room temperature, it was diluted with ether. The organic layer was washed successively with water, brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification of the crude product by column chromatography using 20% AcOEt/petroleum ether as the eluent afforded azido acetonide **10** (915 mg, 2.14 mmol) in 75% yield. White solid. Mp 82–84°C, $R_f = 0.66$ (50% petroleum ether/AcOEt), $[\alpha]_D^{25} = -49.5$ (*c* 0.65, $CHCl_3$), LSIMS *m*/*z*: 430 $[M+H]^+$, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.52$ (d, $J = 8.2$ Hz, 2H), 7.33–7.26 (m, 7H), 4.60–4.50 (m, 3H), 3.88 (dd, $J = 7.4$, 4.6 Hz, 1H), 3.74–3.61 (m, 2H), 3.56 (m, 1H), 2.95 (dd, $J = 13.4$, 3.7 Hz, 1H), 2.81 (dd, $J = 13.4$, 8.2 Hz, 1H), 2.43 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), ^{13}C NMR (50MHz, $CDCl_3$): $\delta = 21.4$, 26.6, 27.2, 60.1, 62.2, 69.6, 72.0, 73.4, 80.0, 110.4, 123.8, 127.7, 127.8, 128.9, 130.0, 137.4, 141.1, 141.7.

3.5. 2-Azido-2-[2,2-dimethyl-5-[1-(4-methylphenylsulfanyl)-(*E*)-3-tetradecenyl]-(4*S*,5*R*)-1,3-dioxolan-4-yl]ethylbenzylether 12

Trifluoroacetic anhydride (1.3 g, 6.15 mmol) was added dropwise over 5 min to a mixture of the acetonide **10** (880 mg, 2.05 mmol) and 1-tridecene (560 mg, 3.08 mmol) in dichloromethane (16 mL) cooled at 0°C and stirred for 1 h at the same temperature. $SnCl_4$ (550 mg, 2.05 mmol) was then added and after 10 min at 0°C, the reaction mixture was quenched by the slow addition of aq. saturated Na_2CO_3 solution. Extraction into diethylether followed by purification by column chromatography using 2% AcOEt/petroleum ether afforded **12** (790 mg, 1.33 mmol) in 65% yield as a pale yellow liquid. $R_f = 0.51$ (10% petroleum ether/AcOEt), $[\alpha]_D^{25} = 13.1$ (*c* 0.2, $CHCl_3$), LSIMS *m*/*z*: 594 $[M+H]^+$, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.31$–7.16 (m, 7H), 6.95 (d, $J = 8.2$ Hz, 2H), 5.50–5.20 (m, 2H), 4.50 (s, 2H), 4.25–4.10 (m, 2H), 3.7–3.45 (m, 3H), 2.90 (td, $J = 7.4$, 2.2 Hz, 1H), 2.56–2.24 (m, 2H), 2.22 (s, 3H), 1.96–1.82 (m, 2H), 1.36 (s, 3H), 1.32 (s, 3H), 1.24–1.11 (m, 16H), 0.78 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 21.0 22.6, 26.7, 27.1, 29.1, 29.3, 29.5, 29.6, 31.9, 32.5, 35.6, 60.8, 70.4, 73.5, 76.7, 77.0, 77.3, 109.7, 126.4, 127.7, 127.8, 128.3, 128.4, 129, 129.7, 132.2, 132.4, 133.0, 137.0.

3.6. 2-(*N*-*tert*-Butoxycarbonyl)amino-2-(2,2-dimethyl-5-tetradecyl-(4*S*,5*R*)-1,3-dioxalan-4-yl)-1-ethanol 13

To a mixture of **12** (118 mg, 0.2 mmol), $(Boc)_2O$ (87 mg, 1 mmol) in methanol (2 mL) Ra-Ni (1 g) was added. The reaction mixture was stirred under H_2 pressure for 2 h at room temperature. The reaction mixture was then refluxed for 6 h upon which TLC revealed the completion of reaction. The reaction mixture was allowed to return to room temperature and then filtered through a small pad of Celite. The Celite pad was repeatedly washed with methanol (10×5). Evaporation of the solvent under reduced pressure followed by purificaion by column chromatography using 20% AcOEt/petroleum ether afforded the *N*-Boc aminoalcohol **13** (62 mg, 0.14 mmol) as a pale yellow liquid in 68% yield. $R_f = 0.26$ (20% petroleum ether/AcOEt), $[\alpha]_D^{25} = -9.1$ (*c* 0.6, $CHCl_3$), LSIMS *m*/*z*: 458 $[M+H]^+$, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.04$ (d, $J = 6.9$ Hz, 1H, NH), 3.82–3.55 (m, 5H), 1.95 (bs, 1H, OH), 1.60–1.43 (m, 2H), 1.41–1.10 (m, 39H), 0.86 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 22.6, 25.6, 26.1, 26.7, 27.2, 28.2, 29.3, 29.6, 30.8, 31.8, 32.4, 33.2, 52.9, 63.0, 71.3, 80.0, 81.2, 108.7, 156.4.

3.7. 3,4-Di(methylcarbonyloxy)-2-methylcarboxamido-(2*R*,3*S*,4*S*)-octadecylacetate 15

To the protected aminoalcohol **13** (40 mg, 0.09 mmol) in dichloromethane (0.1 mL) a 20:1 solution of TFA/Water (0.4 mL) was added and stirred at 0°C for 3 h. The solvent was evaporated under reduced pressure and then azeotroped with benzene. The aminotriol was directly taken to the step without further purification. Pyridine (0.9 mL), and acetic anhydride (0.1 mL) were added to the reaction vessel. The resulting mixture was stirred overnight at rt. The reaction mixture was then concentrated, and the residue chromatographed on a silica gel column using 30% EtOAc/petroleum ether system as the eluent to give the tetraacetylderivative **15** (34 mg, 0.07 mmol) in 78% yield as a viscous liquid. $R_f = 0.23$ (30% petroleum ether/AcOEt), $[\alpha]_D^{25} = -6.9$ (*c* 0.9, $CHCl_3$) (Lit. $[\alpha]_D^{21} = +7.0$ (*c* 0.86, $CHCl_3$) for the enantiomer),[13d] LSIMS *m*/*z*: 485 $[M+H]^+$, ^{1}H NMR(300 MHz, $CDCl_3$): $\delta = 5.73$ (d, $J = 9.5$ Hz, 1H, NH), 5.11 (dd, $J = 6.5$, 4.3 Hz, 1H), 5.03 (dd, $J = 12.7$, 6.5 Hz, 1H), 4.49 (m, 1H), 4.03 (dd, $J = 11.3$, 6.0 Hz, 1H), 3.97 (dd, $J = 11.3$, 5.9 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 6H), 2.01 (s, 3H), 1.67–1.51 (m, 2H), 1.39–1.15 (m, 24H), 0.88 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 20.6, 20.7, 20.9, 22.7, 23.2, 24.8, 29.2, 29.3, 29.5, 29.6, 30.5, 31.9, 48.0, 62.9, 71.9, 72.2, 169.9.

3.8. 1-[5-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)-(*E*)-3-tetradecenyl]-(4*S*,5*R*)-1,3-dioxolane 16

To a solution of sulfide **12** (296 mg, 0.5 mmol) in a mixture of MeOH:water:tetrahydrofuran (1:1:2, 0.5 mL) Oxone® (153 mg, 1.0 mmol) was added at 0°C for 30 min after which the mixture was allowed to return to room temperature. After complete conversion to the sulfone, which was revealed by TLC examination (ca. 4 h), the solvent was evaporated under reduced pressure and the residue extracted into ethylacetate. Column

chromatography using 15% AcOEt/petroleum ether afforded sulfone **16** (250 mg, 0.4 mmol) in 82% yield. Viscous liquid. $R_f = 0.52$ (20% petroleum ether/AcOEt), $[\alpha]_D^{25} = -12.7$ (*c* 1.6, $CHCl_3$), LSIMS *m/z*: 626 $[M+H]^+$, ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 8.2$ Hz, 2H), 7.39–7.22 (m, 7H), 5.35 (dt, $J = 13.4$, 6.7 Hz, 1H), 5.16 (dt, $J = 13.4$, 6.7 Hz, 1H), 4.58 (s, 2H), 4.50 (dd, $J = 8.2$, 3.7 Hz, 1H), 4.28 (dd, $J = 8.2$, 2.2 Hz, 1H), 3.85–3.68 (m, 3H), 3.28 (m, 1H), 2.60–2.40 (m, 5H), 1.96–1.76 (m, 2H), 1.55–1.15 (m, 22H), 0.88 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 21.6, 22.6, 26.5, 26.9, 28.8, 29.1, 29.2, 29.3, 29.5, 29.6, 31.9, 32.3, 59.6, 65.4, 70.5, 73.3, 74.4, 77.2, 109.5, 124.8, 127.7, 127.8, 128.4, 128.9, 129.5, 134.7, 136.4, 137.7, 144.7, 144.8.

3.9. 2-(*N*-*tert*-Butoxycarbonyl)amino-2-{2,2-dimethyl-5-[1-(4-methylphenylsulfonyl)tetracetyl]-(4*S*,5*S*)-1,3-dioxalan-4-yl}-1-ethanol 17

To a mixture of sulfone **16** (188 mg, 0.3 mmol) and $(Boc)_2O$ (130 mg, 0.60 mmol) in abs. ethanol (0.6 mL), $Pd(OH)_2/C$ (200 mg, 0.03 mmol, 10 mol%) was added. After evacuating, the reaction mixture was then stirred under H_2 atmosphere for 16 h. The reaction mixture was then filtered through a small pad of Celite and repeatedly washed with ethanol. Evaporation of the solvent afforded the crude product which was purified by column chromatography using 30% AcOEt/petroleum ether as the eluent to give **17** (134 mg, 0.22 mmol) in 71%. Low melting oily solid. $R_f = 0.16$ (20% petroleum ether/AcOEt), $[\alpha]_D^{25} = -3.4$ (*c* 2.4, $CHCl_3$), LSIMS *m/z*: 612 $[M+H]^+$, ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.78$ (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 5.09 (d, $J = 8.9$ Hz, NH, 1H), 4.7 (d, $J = 8.3$ Hz, 1H), 4.04 (dd, $J = 8.3$, 3.8 Hz, 1H), 3.93 (dd, $J = 9.7$, 4.5 Hz, 1H), 3.83 (m, 1H), 3.69 (dd, $J = 11.1$, 4.5 Hz, 1H), 3.29 (m, 1H), 2.45 (s, 3H), 1.76–1.63 (m, 2H), 1.44–1.16 (m, 37H), 0.88 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.2$, 21.7, 22.7, 26.8, 28.4, 29.2, 29.4, 29.7, 32.0, 50.1, 65.0, 75.2, 78.7, 79.9, 109.1, 129.1, 129.5, 136.9, 144.4, 155.9.

3.10. 2-(*N*-*tert*-Butoxycarbonyl)amino-(2*R*,3*R*,4*E*)-4-octadecene-1,3-diol 18

6% Na-Hg (250 mg) was added to a solution of **17** (100 mg, 0.16 mmol) and Na_2HPO_4 (29 mg, 0.32 mmol) in methanol (3.2 mL) at −20°C for 30 min after which the reaction mixture was allowed to return to room temperature. After stirring for another 2 h, the reaction mixture was diluted with water (3.2 mL) and evaporated under reduced pressure. The residue was extracted with ethylacetate to afford the crude product mixture. Purification by column chromatography using 25% AcOEt/petroleum ether afforded the sphingosine **18** (41 mg, 0.104 mmol) in 65% yield. Low melting solid. $[\alpha]_D^{25} = +0.4$ (*c* 0.9, $CHCl_3$) (Lit. $[\alpha]_D^{25} = -0.4$ (*c* 1.0, $CHCl_3$) for the enantiomer),[22] LSIMS *m/z*: 400 $[M+H]^+$, ^1H NMR (200 MHz, $CDCl_3$): $\delta = 5.71$ (dt, $J = 15.6$, 6.7 Hz, 1H), 5.46 (dd, $J = 15.6$, 6.7 Hz, 1H), 5.1 (bs, 1H, NH), 4.29 (dd, $J = 5.9$, 3.7 Hz, 1H), 3.80–3.71 (m, 2H), 3.58 (m, 1H), 2.08–1.88 (m, 2H), 1.44–1.12 (m, 31H), 0.85 (t, $J = 6.5$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 22.7, 28.3, 29.1, 29.2, 29.3, 29.5, 29.7, 31.9, 32.3, 55.6, 64.5, 73.6, 79.8, 129.0, 134.2, 156.4.

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