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# Stereoselective synthesis of D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine

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**Abstract**—An alternative synthetic route to D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine was developed, utilizing chiral β-lactam **3** obtained from D-(−)-tartaric acid as a starting material. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Sphingolipids are ubiquitous membrane components of eukaryotic cells. D-*erythro*-Sphingosine is a structural unit common to almost all sphingolipids in eukaryotic cells,[1] and a lipophilic component of glycosphingolipids and ceramides. It exhibits potent inhibitory activity against protein kinase C, and blocks human polymorphonuclear leukocyte phagocytosis through inhibition of mitogen-activated protein kinase activation.[2] On the other hand, it is a novel activator of 3-phosphoinositide-dependent kinase.[3] Sphingosines, ceramides, and glycosphingolipids have been shown to play a role in inter- and intracellular signaling along with other secondary messenger molecules.[4] Simultaneously, they play key roles in the regulation of cell growth, differentiation and apoptosis. Phytosphingosines[5] constitute the major base component of higher plants, protozoa, yeast, and fungi, and are found in human kidney cerebrosides (Fig. 1).

Due to the importance of these compounds, a great deal of effort has been devoted to the synthesis of the chiral sphingosines and various synthetic routes are still being investigated to produce them more effectively. Here we report an alternative stereoselective route for the synthesis of D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine.

Our synthesis is shown by retroanalysis in Fig. 2.

Thus, we designed the ketone **9** as a key intermediate of the alternative synthesis of both D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine. The C4–C5 *E*-double bond moiety in sphingosine should be constructed by hydride reduction of the enol triflate **10**, which is obtained by *Z*-selective enolization of the ketone **9**. On the other hand, the C4 hydroxy group of phytosphingosine could be introduced by the stereoselective hydride reduction of the carbonyl moiety of the ketone **9**. The disconnection of the C4–C5 bond of the ketone **9** leads to the alkyl sulfone **7** and the chiral β-lactam **6**. The β-lactam **6** is easily derived from chiral β-lactam **3** obtained from D-(−)-tartaric acid according to the reported method.[6]

## 2. Results and discussion

The synthesis of the ketone **9** was performed by conversion of the chiral β-lactam **3** ($[\alpha]_D^{24}=-29.5°$, *c* 1.2, $CHCl_3$) obtained from D-(−)-tartaric acid according to a previously reported method (Scheme 1). Compound **3** was converted to alcohol **4** by sodium borohydride reduction, and was then treated with triisopropylsilyl chloride in DMF using imidazole as a base to give the silyl ether **5**. Treatment of a solution of **5** in $CH_2Cl_2$ with di-*tert*-butyl dicarbonate and triethyl amine gave *N*-Boc-protected β-lactam **6**. Treatment of **6** with 4-tolyl tetradecylsulfone **7** and *n*-butyllithium in THF at −78°C yielded α-sulfonyl ketone **8** as a 1:1 mixture

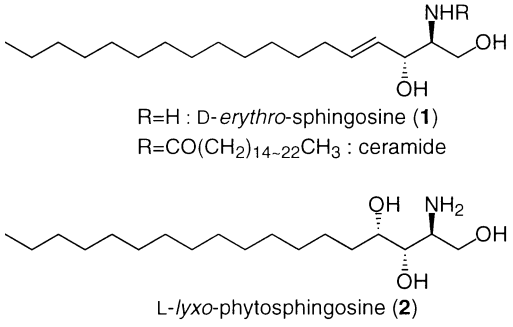


**Figure 1.** Structures of D-*erythro*-sphingosine, ceramide and L-*lyxo*-phytosphingosine.

*Keywords*: stereoselective synthesis; D-*erythro*-sphingosine; L-*lyxo*-phytosphingosine.

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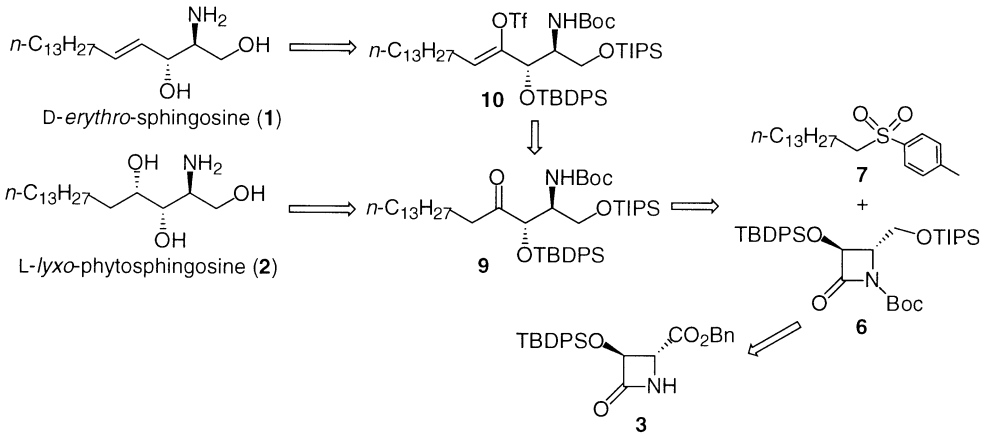
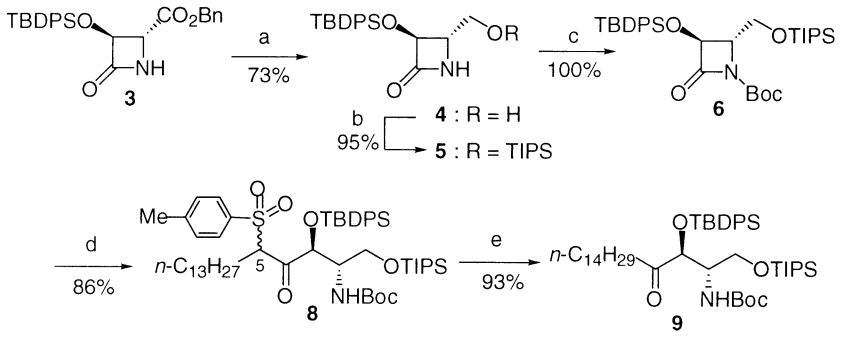
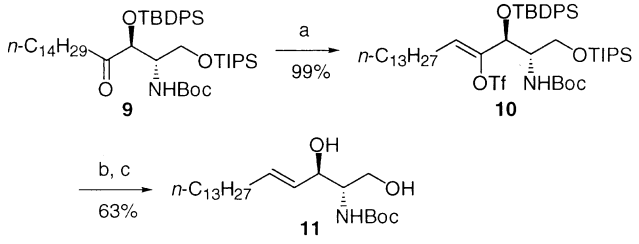



**Figure 2.** Retrosynthesis of D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine.




**Scheme 1.** *Reagents and conditions*: (a) $NaBH_4$, EtOH, rt, 1 h; (b) TIPSCl, imidazole, DMF, rt, 4 h; (c) $(Boc)_2O$, $Et_3N$, cat. DMAP, $CH_2Cl_2$, rt, 1 h; (d) *n*-$C_{14}H_{29}SO_2C_6H_4Me$ (**7**), *n*-BuLi, THF, −78°C, 1 h; (e) lithium naphthalenide, THF, −78°C, 20 min.

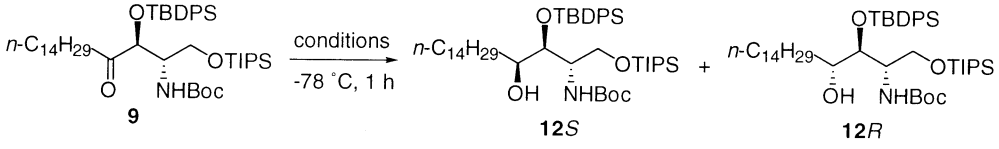



**Scheme 2.** *Reagents and conditions*: (a) $KN(TMS)_2$, THF, −78°C, 1 h then $PhN(Tf)_2$, THF, −23°C, 20 min; (b) $HCO_2H$, $Et_3N$, cat. $Pd(OAc)_2(PPh_3)_2$, DMF, 60°C, 7 h; (c) TBAF, THF, rt, 2 h.

of two diastereomers at the C5 position.[7] The *p*-toluenesulfonyl moiety of **8** was eliminated with lithium naphthalenide in THF to give **9** in good yield.[8]

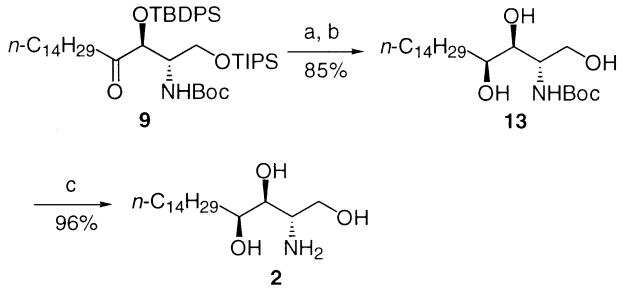
The synthesis of the *N*-Boc sphingosine **11** is depicted in Scheme 2. Deprotonation of **9** with potassium bis(trimethylsilyl)amide and successive sulfonylation with *N*-phenyltrifluoromethanesulfonimide gave enol triflate **10**, exclusively.[9] At this stage, the geometry of **10** was not clear. The reductive elimination of the trifluoromethanesulfonate group from the enol triflate by formic acid and triethylamine using bis(acetato)bis(triphenylphosphine)palladium(II) as a catalyst[10] and successive deprotection of the two silyl

**Table 1.** Hydride reduction of ketone **9**




| Entry | Conditions | Results[a] (**12***S*/**12***R*, % yield) |
|---|---|---|
| 1 | DIBAL, toluene | 54:46, 86 |
| 2 | $LiEt_3BH$, THF | 92:8, 86 |
| 3 | $Li(s\text{-}Bu)_3BH$, THF | No reaction |

[a] The diastereomeric ratio was determined by $^1H$ NMR.




**Scheme 3.** *Reagents and conditions*: (a) $LiEt_3BH$, THF, −78°C, 2 h; (b) TBAF, THF, rt, 2 h; (c) 10% HCl in MeOH (w/v), 40°C, 9 h.

groups with tetrabutylammonium fluoride in THF exclusively gave *trans*-olefinated *N*-Boc sphingosine **11**, and conversion into D-*erythro*-sphingosine by deprotection have already been reported.[11]

Hydride reduction of the ketone **9** to introduce the C4 hydroxy group of phytosphingosine **2** is summarized in Table 1. The hydride reduction using DIBAL in toluene gave no selective results (entry 1). The reduction using $LiEt_3BH$ in THF at −78°C gave satisfactory results in yield and stereoselectivity (entry 2). The reduction using L-selectride gave no reducing products, which may have been due to the bulkiness of the reducing agent (entry 3). The diastereomeric ratio of these compounds was determined by $^1H$ NMR. However, the stereochemistry was not identified at this stage. Therefore, we converted the major compound **12** obtained in this reduction to a deprotected compound by treatment with TBAF, and then 10% HCl in MeOH (Scheme 3). That compound was the same as the one in the reported data of **2**.[12] It then became clear that the configuration of the major product obtained from $LiEt_3BH$ reduction of **9** was the compound **12***S*.

## 3. Summary

In summary, we have developed an alternative method, which allows the total synthesis of D-*erythro* sphingosine and L-*lyxo* phytosphingosine from the same precursor ketone **9**. Thus, the C4–C5 *E*-double bond moiety of sphingosine could be constructed by hydride reduction of the enol triflate **10**, which is obtained by *Z*-selective enolization of the ketone **9**. The C4 hydroxy group of phytosphingosine was also constructed by stereoselective reduction of the carbonyl moiety of the ketone **9**.

## 4. Experimental

### 4.1. General

$^1H$ NMR spectra were recorded on a JEOL JNM-EX270 at 270 MHz using tetramethylsilane as an internal reference. $^{13}C$ NMR spectra were recorded on a JEOL JNM-GSX400 at 100 MHz. IR absorption spectra were recorded on a Jasco IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-O1SG mass spectrometer. Separation of the compounds by column chromatography was carried out with Silica Gel 60 (Merck, 230–400 mesh ASTM).

**4.1.1. (3*S*,4*S*)-3-*tert*-Butyldiphenylsilyloxy-4-hydroxymethylazetidin-2-one (4).** To a solution of **3** (1.6 g, 3.5 mmol) in EtOH (8.0 ml) was added $NaBH_4$ (0.26 g, 7.0 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with 10% AcOH aqueous solution. After removal of solvents under reduced pressure, the mixture was added to $H_2O$ (20 ml) and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:1, then 7:3) afforded **4** (0.90 g, 73%) as a colorless oil. $[\alpha]^{24}_D=-45.2°$ (*c* 0.37, $CHCl_3$). IR ($CHCl_3$) 3623, 3417, 1770 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (s, 9H), 3.02 (dd, 1H, *J*=11.8, 6.3 Hz), 3.27 (dd, 1H, *J*=11.8, 3.5 Hz), 3.52–3.60 (m, 1H), 4.51–4.57 (m, 1H), 6.40–6.50 (brs, 1H), 7.30–7.50 (m, 6H), 7.62–7.80 (m, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.09, 26.62 (3C), 60.54, 61.62, 78.17, 127.95 (4C), 130.14, 130.26, 131.99, 133.02, 135.57 (2C), 135.69 (2C), 169.15. HRMS (FAB, positive), calcd for $C_{20}H_{25}NNaO_3Si$: $(M+Na)^+$ 378.1501; found 378.1521. Anal. calcd for $C_{20}H_{25}NO_3Si$; C, 67.57; H, 7.09; N, 3.94. Found; C, 67.17; H, 6.91; N, 3.73.

**4.1.2. (3*S*,4*S*)-3-*tert*-Butyldiphenylsilyloxy-4-triisopropylsilyloxymethylazetidin-2-one (5).** To a solution of **4** (0.49 g, 1.4 mmol) and imidazole (0.28 g, 4.1 mmol) in DMF (3.0 ml) was added TIPSCl (0.45 ml, 2.1 mmol). After stirring for 4 h at room temperature, the reaction mixture was treated with sat. $NaHCO_3$ (0.5 ml) and poured into $H_2O$ (20 ml). After extraction with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The crude product was concentrated in vacuo and purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9, then 1:4) afforded **5** (0.67 g, 95%) as a colorless oil. $[\alpha]^{24}_D=-53.1°$ (*c* 0.35, $CHCl_3$). IR ($CHCl_3$) 3237, 3072, 3051, 1767 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 0.92 (s, 21H), 1.08 (s, 9H), 3.16 (dd, 1H, *J*=11.9, 8.2 Hz), 3.31 (dd, 1H, *J*=11.9, 3.8 Hz), 3.59 (ddd, 1H, *J*=8.2, 3.8, 3.1 Hz), 4.56 (t, 1H, *J*=3.1 Hz), 5.95 (brs, 1H), 7.32–7.50 (m, 6H), 7.65–7.80 (m, 4H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.72 (3C), 17.85 (6C), 19.13, 26.63 (3C), 60.63, 63.27, 78.46, 127.88 (4C), 130.03, 130.03, 130.14, 132.03, 133.21, 135.58 (2C), 135.75 (2C), 168.09. HRMS (FAB, positive), calcd for $C_{29}H_{45}NNaO_3Si_2$: $(M+Na)^+$ 534.2836; found 534.2832.

**4.1.3. (3*S*,4*S*)-*N*-*tert*-Butoxycarbonyl-3-*tert*-butyldiphenylsilyloxy-4-(triisopropylsilyloxy)methylazetidin-2-one (6).** To a solution of **5** (0.63 g, 1.23 mmol), DMAP (10 mg, 0.082 mmol) and $Et_3N$ (0.52 ml, 3.7 mmol) in $CH_2Cl_2$ (3.0 ml) was added di-*tert*-butyl dicarbonate (0.32 ml, 1.8 mmol). After stirring for 1 h at room temperature, the reaction mixture was treated with sat. $NaHCO_3$ (0.50 ml) and poured into $H_2O$ (20 ml). After extraction with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The crude product was concentrated in vacuo and purified by silica gel column chromatography. Elution with EtOAc/hexane (1:9) afforded **6** (0.77 g, 100%) as a colorless oil. $[\alpha]^{24}_D=+1.2°$ (*c* 0.35, $CHCl_3$). IR ($CHCl_3$) 1805, 1719 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 0.77–0.90 (m, 21H), 1.08 (s, 9H), 1.51 (s, 9H), 3.38 (dd, 1H, *J*=11.4, 1.6 Hz), 3.85 (ddd, 1H, *J*=1.8, 1.6, 2.3 Hz), 4.96 (d, 1H, *J*=2.3 Hz), 7.33–7.50 (m, 6H), 7.63–7.80 (m, 4H).

$^{13}$C NMR ($CDCl_3$) $\delta$ 11.73 (3C), 17.78 (6C), 19.24, 26.62 (3C), 28.05 (3C), 58.53, 60.38, 63.29, 76.47, 83.15, 127.91 (4C), 130.09, 130.14, 131.90, 133.06, 135.51 (2C), 135.76 (2C), 148.60, 165.36. HRMS (FAB, positive), calcd for $C_{34}H_{53}NNaO_5Si_2$: $(M+Na)^+$ 612.3541; found 612.3565. Anal. calcd for $C_{34}H_{53}NO_5Si_2$; C, 66.73; H, 8.73; N, 2.29. Found; C, 66.33; H, 8.33; N, 2.24.

**4.1.4. 4-Tolyl tetradecylsulfone (7).** To a solution of *p*-toluenesulfinic acid sodium salt (1.1 g, 6.0 mmol) in MeOH (7 ml) was added 1-bromotetradecane (1.5 ml, 5.0 mmol). The reaction mixture was refluxed for 24 h and cooled and the solvent evaporated. The crude mixture was added to $H_2O$ (5.0 ml), and extracted with AcOEt. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the removal of solvents, recrystallization from hexane gave **7** (1.0 g, 73%) as a white crystalline solid. mp 61–63°C. IR ($CHCl_3$) 1316, 1303, 1288, 1144 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 0.87 (t, 3H, $J$=5.7 Hz),1.20–1.40 (m, 22H), 1.60–1.75 (m, 2H), 2.45 (s, 3H), 3.00–3.09 (m, 2H), 7.36 (d, 2H, $J$=8.7 Hz), 7.79 (d, 2H, $J$=8.7 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 14.12, 21.62, 22.73 (2C), 28.29, 29.02, 29.26, 29.36, 29.48, 29.58, 29.66 (2C), 31.94, 56.46, 77.05, 128.11 (2C), 129.87 (2C), 136.40, 144.51. HRMS (FAB, positive), calcd for $C_{21}H_{37}O_2S$: $(M+H)^+$ 353.2514; found 353.2534. Anal. calcd for $C_{21}H_{36}O_2S$; C, 71.54; H, 10.29; S, 9.09. Found; C, 71.14; H, 10.39; S, 9.07.

**4.1.5. (2*S*,3*S*,5*RS*)-2-*tert*-Butoxycarbonylamino-3-*tert*-butyldiphenylsilyloxy-5-*p*-tolylsulfonyl-1-triisopropylsilyloxyoctadecan-4-one (8).** To a solution of **7** (33.8 mg, 0.096 mmol) in THF (0.80 ml) cooled to 0°C was added 1.5 M *n*-BuLi/hexane solution (0.12 ml, 0.19 mmol). After stirring for 5 min, the reaction mixture was cooled to −78°C, and added to a solution of **6** (30 mg, 0.048 mmol) in THF (0.50 ml) via cannula. After stirring for 1 h at −78°C, the reaction mixture was treated with sat. $NH_4Cl$ (0.10 ml) and poured into $H_2O$ (10 ml). After extraction with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and purified by silica gel column chromatography. Elution with EtOAc/hexane (3:97, then 5:95) afforded **8** (40 mg, 86%) as a colorless oil. $[\alpha]^{24}_D$=+7.5° ($c$ 1.0, $CHCl_3$). IR ($CHCl_3$) 3420, 1712, 1598, 1319, 1305, 1290 cm$^{-1}$. $^1$H NMR ($CDCl_3$) (1:1 diastereomeric mixture) $\delta$ 0.80–1.50 (m, 66H), 2.42 (s, 3H), 3.62–3.71 (m, 1H), 3.77–3.87 (m, 1H), 4.10–4.50 (m, 1.5H), 4.71 (t, 0.5H, $J$=7.2 Hz), 4.80–5.05 (m, 2H), 7.20–7.80 (m, 14H). HRMS (FAB, positive), calcd for $C_{55}H_{89}KNO_7Si_2$: $(M+K)^+$ 1002.5535; found 1002.5539. Anal. calcd for $C_{55}H_{91}NO_7SSi_2$; C, 68.35; H, 9.49; N, 1.45; S, 3.32. Found; C, 68.75; H, 9.70; N, 1.50; S, 3.40.

**4.1.6. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-*tert*-butyldiphenylsilyloxy-1-triisopropylsilyloxyoctadecan-4-one (9).** To a solution of lithium-naphthalenide, prepared from naphthalene (64 mg, 0.50 mmol) in THF (1.0 ml) and Li wire (4.3 mg, 0.62 mmol) was added a solution of **7** (0.12 g, 0.12 mmol) in THF (0.50 ml) via cannula. The mixture was stirred for 20 min at −78°C. The reaction mixture was treated with sat. $NH_4Cl$ (0.50 ml) and poured into $H_2O$ (10 ml). After extraction with ether, the organic layer was diluted with brine and dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (0:100, then 5:95) afforded **9** (93 mg, 93%) as a colorless oil. $[\alpha]^{24}_D$=+4.9° ($c$ 1.0, $CHCl_3$). IR ($CHCl_3$) 3445, 1709, 1501 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (t, 3H, $J$=6.5 Hz), 0.94–1.32 (m, 63H), 2.08 (dt, 1H, $J$=17.6, 5.8 Hz), 2.30 (dt, 1H, $J$=17.6, 6.4 Hz), 3.69 (dd, 1H, $J$=9.9, 8.0 Hz), 3.77 (dd, 1H, $J$=9.9, 5.8 Hz), 4.08 (m, 1H), 4.39 (d, 1H, $J$=4.8 Hz), 4.82 (d, 1H, $J$=9.0 Hz), 7.30–7.66 (m, 10H). $^{13}$C NMR ($CDCl_3$) $\delta$ 11.92 (3C), 14.13, 17.96 (6C), 19.60, 22.72 (2C), 27.06 (3C), 28.33 (3C), 29.00, 29.40 (3C), 29.69 (3C), 31.61, 31.95 (3C), 39.29, 55.01, 61.96, 77.87, 79.25, 127.61 (2C), 127.73 (2C), 129.86, 129.90, 133.04, 133.09, 135.91 (2C), 136.04 (2C), 155.38, 209.40. HRMS (FAB, positive), calcd for $C_{48}H_{83}NNaO_5Si_2$: $(M+Na)^+$ 832.5708; found 832.5697. Anal. calcd for $C_{48}H_{85}NO_5Si_2$; C, 70.97; H, 10.55; N, 1.72. Found; C, 71.37; H, 10.15; N, 1.58.

**4.1.7. (2*S*,3*S*,4*Z*)-2-*tert*-Butoxycarbonylamino-3-*tert*-butyldiphenylsilyloxy-4-trifluoromethanesulfonyloxy-1-triisopropylsilyloxyoctadec-4-ene (10).** A solution of **9** (93 mg, 0.11 mmol) in THF (0.3 ml) was cooled to −78°C, treated with 0.5 M KHMDS/toluene solution (0.70 ml, 0.35 mmol) and stirred for 1 h. The reaction mixture was warmed up to −23°C, and *N*-phenylbistrifluoromethanesulfonamide (0.10 g, 0.34 mmol) was added. After stirring for 20 min, the reaction mixture was treated with sat. $NH_4Cl$ (0.10 ml) and poured into $H_2O$ (10 ml). After extraction with ether, the organic layer was diluted with brine and dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (0:10, then 1:49) afforded **10** (107 mg, 99%) as a colorless oil. $[\alpha]^{24}_D$=−1.1° ($c$ 1.0, $CHCl_3$). IR ($CHCl_3$) 3447, 1712, 1503 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 0.82–1.43 (m, 64H), 1.60 (m, 1H), 2.04 (m, 1H), 3.57–3.92 (m, 3H), 4.52 (d, 1H, $J$=5.3 Hz), 4.65 (d, 1H, $J$=8.4 Hz), 5.51 (t, 1H, $J$=8.0 Hz), 7.23–7.80 (m, 10H). $^{13}$C NMR ($CDCl_3$) $\delta$ 11.87 (3C), 14.14, 17.97 (6C), 19.40, 22.68, 22.73, 25.59, 29.63, 27.01 (3C), 28.30 (3C), 28.44, 28.90, 29.26, 29.37, 29.54, 29.70 (2C), 31.63, 31.97, 55.43, 62.28, 72.84, 78.82, 125.30, 127.59 (2C), 127.81 (2C), 129.91, 130.02, 132.84 (2C), 136.02 (2C), 136.13 (2C), 146.30, 155.14. HRMS (FAB, positive), calcd for $C_{49}H_{82}F_3NNaO_7SSi_2$: $(M+Na)^+$ 964.5200; found 964.5198. Anal. calcd for $C_{49}H_{82}F_3NO_7SSi_2$; C, 62.45; H, 8.77; N, 1.49; S, 3.40. Found; C, 62.85; H, 8.73; N, 1.49; S, 3.03.

**4.1.8. (2*S*,3*R*,4*E*)-2-*tert*-Butoxycarbonylaminooctadec-4-ene-1,3-diol (11).** To a stirred solution of **10** (53 mg, 0.056 mmol) and tributylamine (41 μl, 0.17 mmol), bis-(acetato)bis(triphenylphosphine)palladium (4.5 mg, 0.006 mmol) in DMF (0.3 ml) was added formic acid (4.3 μl, 0.11 mmol) at room temperature. After stirring for 7 h at 60°C, the reaction mixture was treated with sat. $NaHCO_3$ (0.20 ml) and extracted with ether. The ether layer was evaporated in vacuo. The crude mixture was dissolved in THF (0.10 ml) and added to 1.0 M TBAF/THF solution (0.12 ml, 0.12 mmol). After stirring for 2 h at room temperature, the reaction mixture was treated with sat. $NaHCO_3$ (0.20 ml) and poured into $H_2O$ (10 ml). After

extraction with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (3:7–2:3) afforded **11** (14 mg, 63%) as a white crystalline solid. Mp 61–64°C; $[\alpha]^{24}_D$=−1.4° (*c* 1.0, $CHCl_3$). IR (KBr) 3364, 1687, 1668, 1533 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (t, 3H, *J*=5.5 Hz), 1.20–1.54 (m, 33H), 2.05 (q, 2H, *J*=7.5 Hz), 3.5–3.67 (m, 1H), 3.72 (dd, 1H, *J*=8.3, 4.5 Hz), 4.32 (t, 1H, *J*=6.7 Hz), 5.30 (brs, 1H), 5.53 (dd, 1H, *J*=16.3, 6.7 Hz), 5.78 (dt, 1H, *J*=16.3, 7.2 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.13, 22.71 (2C), 27.72, 28.11, 28.41 (3C), 28.56, 29.14, 29.24, 29.39, 29.51, 29.71, 31.95, 32.33, 55.49, 62.66, 74.77, 79.81, 128.98, 134.15, 156.28. HRMS (FAB, positive), calcd for $C_{23}H_{46}NO_4$: $(M+H)^+$ 400.3427; found 400.3432. Anal. calcd for $C_{23}H_{45}NO_4$; C, 69.13; H, 11.35; N, 3.51; S, 3.32. Found; C, 68.73; H, 10.95; N, 3.44.

**4.1.9. (2*S*,3*S*,4*S*)-2-*tert*-Butoxycarbonylaminooctadecane-1,3,4-triol (13).** To a solution of **9** (55 mg, 0.068 mmol) in THF (0.30 ml) cooled to −78°C was added 1.0 M lithium triethylborohydride (0.21 ml, 0.21 mmol). After stirring for 2 h, the reaction mixture was treated with sat. $Na_2CO_3$ (0.20 ml) and 30% aqueous $H_2O_2$ (0.10 ml) and warmed to room temperature. The aqueous layer was extracted with ether, and the ether layer was evaporated in vacuo. The crude mixture was dissolved in THF (0.20 ml) and treated with 1.0 M TBAF/THF solution (0.13 ml, 0.13 mmol). After stirring for 2 h at room temperature, the reaction mixture was treated with sat. $NaHCO_3$ (0.20 ml). After extraction with ether, the organic layer was washed with brine and dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was purified by silica gel column chromatography. Elution with EtOAc/hexane (1:1–3:2) afforded **13** (24 mg, 85%) as a white crystalline solid. Mp 142–145°C. $[\alpha]^{24}_D$=−7.7° (*c* 0.10, $CHCl_3$). IR (KBr) 3351, 3255, 1672, 1544 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (t, 3H, *J*=6.9 Hz), 1.19–1.75 (m, 35H), 3.40 (d, 1H, *J*=9.5 Hz), 3.48–3.70 (m, 2H), 3.75 (dd, 1H, *J*=11.0, 4.0 Hz), 4.06 (dd, 1H, *J*=11.0, 2.6 Hz), 5.24 (d, 1H, *J*=8.6 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.14, 22.71, 26.10, 28.35 (3C), 29.38 (2C), 29.57, 29.70 (5C), 31.96, 32.81, 53.51, 62.04, 69.68, 72.91, 77.62, 80.42, 157.20. HRMS (FAB, positive), calcd for $C_{23}H_{48}NO_5$: $(M+H)^+$ 418.3532; found 418.3525.

**4.1.10. (2*S*,3*S*,4*S*)-2-Aminooctadecane-1,3,4-triol (2).** To a solution of **13** (6.6 mg, 0.016 mmol) in MeOH (0.1 ml) was added 10% (w/v) HCl/MeOH (0.1 ml) and the mixture was stirred for 9 h at 40°C. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography. Elution with $CHCl_3$/MeOH/aq. $NH_3$ (40:10:1) afforded **2** (4.8 mg, 96%) as a white crystalline solid. Mp 92–95°C. $[\alpha]^{24}_D$=−2.6° (*c* 0.21, pyridine). IR (KBr) 3374, 3318, 3267, 3054 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) $\delta$ 0.90 (t, 3H, *J*=7.4 Hz), 1.20–1.60 (m, 26H), 3.20–3.33 (m, 1H), 3.54–3.67 (m, 2H), 3.70 (dd, 1H, *J*=11.6, 7.4 Hz), 3.84 (dd, 1H, *J*=11.6, 5.0 Hz); $^1H$ NMR (DMSO-d6) $\delta$ 0.86 (t, 3H, *J*=6.5 Hz), 1.15–1.35 (m, 24H), 1.35–1.50 (m, 2H), 3.06–3.08 (m, 1H), 3.40–3.51 (m, 6H), 3.68 (dd, 1H, *J*= 3.9, 11.4 Hz). HRMS (FAB, positive), calcd for $C_{18}H_{40}NO_3$: $(M+H)^+$ 318.3008; found 318.3026.

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