A Practical and Cost-Effective Synthesis of D-*erythro*-Sphingosine from D-*ribo*-Phytosphingosine via a Cyclic Sulfate Intermediate

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Abstract: The practical and efficient synthesis of D-*erythro*-sphingosine from commercially available D-*ribo*-phytosphingosine is described. An important feature of this synthesis is the selective transformation of the 3,4-vicinal diol of phytosphingosine into the characteristic *E*-allylic alcohol of sphingosine via a cyclic sulfate intermediate that contains a non-nucleophilic trifluoroacetamide protecting group.

Key words: cyclic sulfates, protecting groups, reactive intermediates, sphingolipids, synthetic methods

Sphingolipids are a structurally diverse class of lipids that contain long-chain aliphatic amino alcohols. They are important structural components of the plasma membranes of essentially all eukaryotic cells and play critical roles in many biological processes.[1] Growing interest in the biological functions of sphingolipids has generated a desire to develop efficient methods for their synthesis. One of the important factors for the successful synthesis of natural and non-natural sphingolipids is the acquisition of the appropriate sphingoid bases, which are the principal backbone of sphingolipids.

Among the naturally occurring sphingoid bases, D-*erythro*-sphingosine (**1**; Figure 1) and D-*ribo*-phytosphingosine (**2**) are the most important and common species.[2] While D-*ribo*-phytosphingosine is readily obtainable on an industrial scale from a yeast fermentation process,[3,4] D-*erythro*-sphingosine is rather expensive and available only from laborious animal tissue extraction or chemical synthesis.

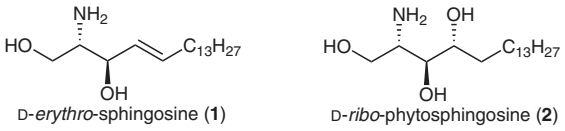
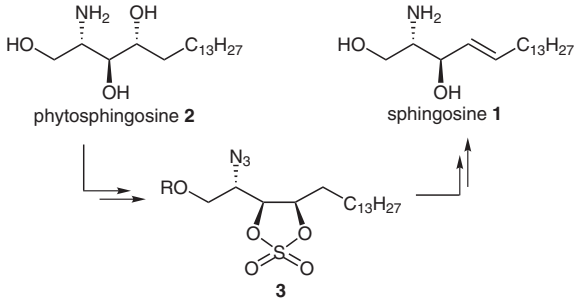


Figure 1 Chemical structures of compounds **1** and **2**

A great deal of effort has been devoted to the synthesis of D-*erythro*-sphingosine.[5,6] To install the absolute stereochemistry of sphingosine **1**, many synthetic approaches have involved asymmetric induction such as Sharpless asymmetric epoxidation and asymmetric aldol reaction. A second popular approach involves the use of chiral starting materials, such as carbohydrates and amino acids. The relatively inexpensive phytosphingosine **2** has been also employed as a starting material for the facile synthesis of sphingosine **1**.[6,7] The key requirement of this synthetic approach is the selective transformation of the C-4 hydroxy group of phytosphingosine into the characteristic 4,5-*trans* double bond of sphingosine.

We have previously reported a convenient synthetic route to sphingosine **1** from phytosphingosine **2**.[7] The key step in the reaction sequence, as depicted in Scheme 1, comprises the selective elimination reaction of cyclic sulfate **3** for the transformation of the 3,4-vicinal diol of phytosphingosine into the *E*-allylic alcohol of sphingosine. The advantage of the use of a cyclic sulfate is that it eliminates the need for selective activation of only one vicinal hydroxy group. The non-nucleophilic azide was chosen as the amino protecting group because a nucleophilic protecting group might react with the cyclic sulfate in an intramolecular manner. Regrettably, the possibility of scaling up the process is limited due to the explosive potential of organic azide[8] and the cost-ineffective transformation of the amino group of phytosphingosine into an azide. Thus, we sought to identify an alternative amino protecting group that is compatible with the reactive cyclic sulfate functional group. Herein, we wish to report our studies on this subject and to describe a cost-effective, efficient synthetic route to sphingosine **1**.



Scheme 1 Synthesis of sphingosine **1** via azido-phytosphingosine **3**

A great many protecting groups have been used to protect amino groups, including carbamates, sulfonamides, and amides.[9] Amino protecting groups for our synthetic needs should be non-nucleophilic and stable during both cyclic sulfate formation and under the cyclic sulfate-mediated elimination conditions. In addition, these protecting groups should be readily cleaved under mild conditions

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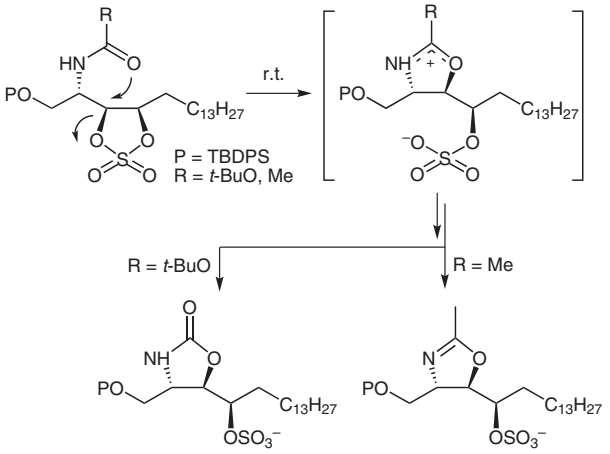
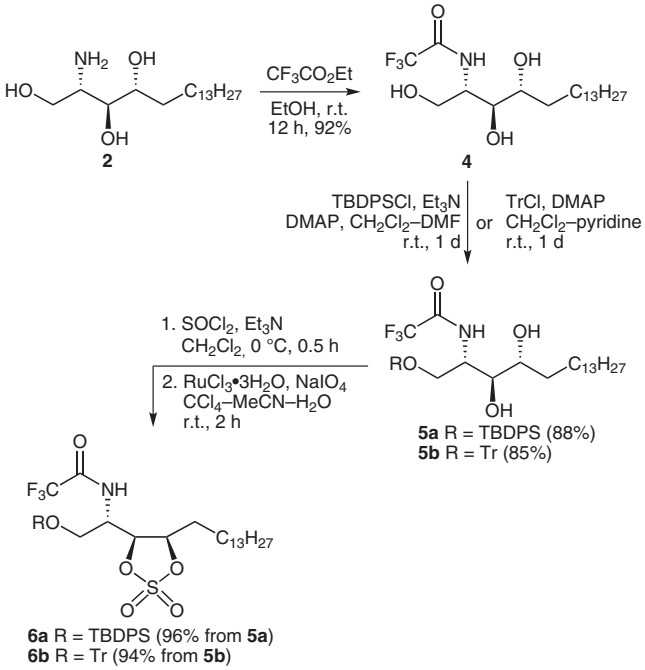
because sphingosine is not very stable due to the presence of the reactive allylic alcohol functional group.

Sulfonamide is one of the most stable nitrogen protecting groups, and the oxygen atoms of sulfonamide are poor intramolecular nucleophiles.[10] However, cleavage of sulfonamide generally requires harsh conditions. Although some sulfonamide protecting groups, such as 2- or 4-nitro- and 2,4-dinitrobenzenesulfonamides can be removed under relatively mild conditions,[11] they are somewhat expensive. Thus, sulfonamides were not considered to be the protecting group of choice. Carbamates and amides have been used widely as protecting groups for amines, however, due to the high nucleophilicity of the oxygen atoms, the electron-rich carbamates and amides would not be suitable nitrogen protecting groups for our synthetic needs. These protecting groups have been utilized in the intramolecular inversion of activated hydroxy groups.[12] The cyclic sulfates derived from *N*-Boc or *N*-acetyl protected *ribo*-phytosphingosine (Scheme 2), in our hands, were rather unstable and decomposed into the polar sulfate esters upon standing in solution at room temperature, as a result of nucleophilic substitution of the cyclic sulfate functional group by the oxygen atom of the protecting group.[13]



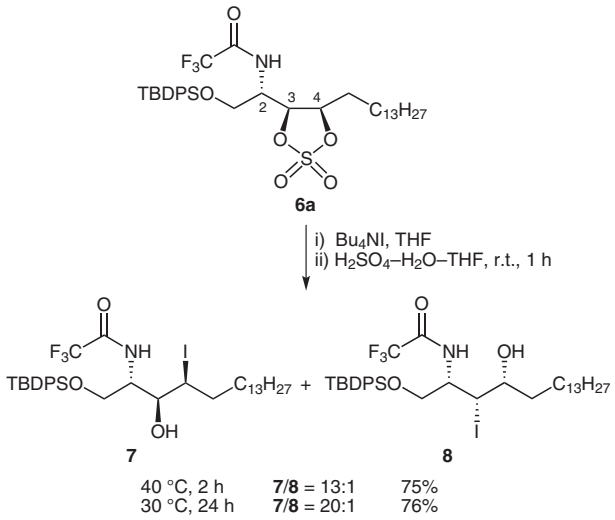
Scheme 2 Thermolysis of the cyclic sulfate

It occurred to us that protection of the 2-amino functionality of *ribo*-phytosphingosine (**2**) with electron-deficient amides would present an attractive alternative to our initial azide approach. Among electron-deficient amide protecting groups, trifluoroacetamide was chosen due to its low cost, efficient introduction, and convenient removal under mild conditions. Thus, known trifluoroacetamide derivative **4**[14] was prepared in high yield (92%) by treatment of **2** with CF_3CO_2Et in ethanol at room temperature (Scheme 3). The primary alcohol of **4** was protected selectively either as its silyl or trityl ether to produce **5a** (88%) or **5b** (85%), respectively. Conversion of 3,4-vicinal diol **5** into its cyclic sulfite with thionyl chloride in the presence of triethylamine followed by oxidation with $RuCl_3$/$NaIO_4$, provided cyclic sulfate **6** in high yield (96% for **6a** and 94% for **6b**). Both cyclic sulfates **6a** and **6b** were stable enough at room temperature to allow proper use for several days.



Scheme 3 Synthesis of cyclic sulfate **6**

With multigram quantities of cyclic sulfate **6** available, we attempted to apply our previous reaction process[7] for the transformation of a cyclic sulfate into an allylic alcohol, which involves the regioselective ring opening of the cyclic sulfate by iodide and a subsequent dehydrohalogenation reaction. Thus, we first examined the regioselectivity of the nucleophilic ring opening of cyclic sulfate by iodide (Scheme 4).

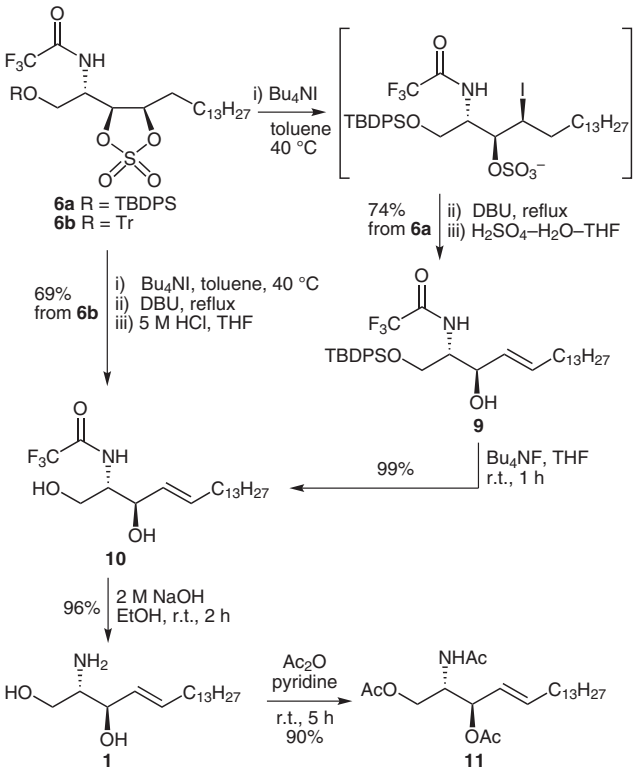


Scheme 4 Nucleophilic ring opening of cyclic sulfate **6a**

We found that the treatment of cyclic sulfate **6a** with tetrabutylammonium iodide (Bu_4NI) in tetrahydrofuran at 40 °C for two hours, followed by acidic hydrolysis of the

intermediate O-sulfate, afforded a 13:1 mixture of iodo alcohols **7** and **8** in 75% combined yield. The regioselectivity could be improved to 20:1 when the reactions were carried out at lower temperature (30 °C) for one day (76%). When the solvent was changed from tetrahydrofuran to toluene, similar regioselectivities and yields were observed. The regioselectivity attained was high enough, but slightly lower than, that for the azide-protected cyclic sulfate **3** (Scheme 1).

After studying the ring opening of cyclic sulfate **6a** by iodide, we examined the direct one-pot ring opening/dehydrohalogenation sequence (Scheme 5). The treatment of cyclic sulfate **6a** with Bu_4NI in toluene at 40 °C led to the disappearance of the starting material and to the formation of polar material in two hours. Then, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added and the reaction temperature was raised to reflux, where it was held for one hour. This treatment, followed by acidic hydrolysis of the resulting sulfate ester intermediate with aqueous sulfuric acid, successfully furnished the desired *E*-allylic alcohol **9** in high yield (74%). When the reaction was carried out in tetrahydrofuran, the yield was slightly decreased (70%).



Scheme 5 Synthesis of D-*erythro*-sphingosine (**1**)

With a facile route to the large-scale preparation of 1,2-protected D-*erythro*-sphingosine **9** established, efforts were then directed toward the deprotection steps. Removal of the silyl protecting group in **9** with Bu_4NF in tetrahydrofuran furnished the known 2-acyl-protected sphingosine **10**[15] in high yield. Finally, the trifluoroacetyl group was easily removed under alkaline conditions to afford the desired D-*erythro*-sphingosine **1** in 96% yield. The analytical and spectroscopic data of both the synthetic **1** and its triacetate derivative **11**[16] were in good agreement with literature data.[5,6b,17]

The above sequence could be also successfully applied to the cyclic sulfate **6b** (Scheme 5), which contains the less expensive trityl group as the protecting group of the primary hydroxy group. The cyclic sulfate **6b** was submitted to the aforementioned one-pot ring opening/dehydrohalogenation conditions. Exposure of the resulting reaction mixture to hydrochloric acid in tetrahydrofuran resulted in simultaneous hydrolysis of the sulfate ester intermediate and removal of the trityl protecting group to give the 2-acyl-protected sphingosine **10** with a 69% overall yield. It is worth noting that it was possible to prepare compound **10** from phytosphingosine **2** through this sequence with a similar overall yield without the need for column chromatographic purification of the intermediates.

In summary, we have developed an efficient and practical route for the synthesis of D-*erythro*-sphingosine (**1**) from the low cost phytosphingosine **2** with a high overall yield (ca. 55%). The 3,4-vicinal diol of phytosphingosine was transformed into the characteristic *E*-allylic alcohol of sphingosine via a cyclic sulfate. An important feature of this synthesis is the use of the non-nucleophilic trifluoroacetamide protecting group for the 2-amino functionality in phytosphingosine to avoid complications caused by the participation of the neighboring group in the cyclic sulfate-mediated elimination reactions. The process is highly selective and seems to be readily amenable to large-scale synthesis.

All chemicals were reagent grade and used as purchased. All reactions were performed in an inert atmosphere of anhydrous argon or nitrogen using distilled anhydrous solvents. Reactions were monitored by TLC analysis using silica gel 60 F-254 TLC plates. Melting points are uncorrected. Flash column chromatography was carried out with silica gel (230–400 mesh). Optical rotations were measured using sodium light (D line at 589.3 nm). ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded in δ units relative to the non-deuterated solvent as an internal reference. IR spectra were measured with a Fourier transform infrared spectrometer. High-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB).

2,2,2-Trifluoro-*N*-[(2*S*,3*S*,4*R*)-1,3,4-trihydroxyoctadecan-2-yl]acetamide (4)

To a solution of phytosphingosine **2** (4.00 g, 12.6 mmol) in EtOH (25 mL), was slowly added ethyl trifluoroacetate (2.30 mL, 19.3 mmol). After stirring for 12 h at r.t., the reaction mixture was poured into brine (80 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 1:1) to give trifluoroacetamide **4**.

Yield: 4.79 g (92%); white solid; mp 98–102 °C; $[\alpha]_D^{25}$ –1.7 (*c* 0.9, EtOH).

IR (neat): 3303, 2918, 2850, 1700 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.27 (s, 24 H), 1.48–1.70 (m, 2 H), 3.45–3.54 (m, 1 H), 3.59 (t, *J* = 5.7 Hz,

1 H), 3.72 (dd, *J* = 7.2, 11.7 Hz, 1 H), 3.86 (dd, *J* = 4.2, 11.7 Hz, 1 H), 4.16–4.24 (m, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 15.3, 24.5, 27.6, 31.3, 31.52, 31.56, 31.6, 33.9, 34.2, 55.6, 62.0, 73.9, 76.2, 120.2 (q, $^1J_{C–F}$ = 285.2 Hz, CF_3), 159.8 (q, $^2J_{C–F}$ = 36.8 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{39}F_3NO_4$: 414.2831; found: 414.2828.

_N_-[(2_S_,3_S_,4_R_)-1-(*tert*-Butyldiphenylsilyloxy)-3,4-dihydroxyoctadecan-2-yl]-2,2,2-trifluoroacetamide (5a)

To a solution of **4** (2.00 g, 4.84 mmol) in CH_2Cl_2 (20 mL) and DMF (7 mL), were added Et_3N (1.00 mL, 7.17 mmol), DMAP (58 mg, 0.47 mmol), and TBDPSCl (1.80 mL, 7.03 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 24 h, and then diluted with EtOAc (100 mL). The organic layer was washed with brine (2 × 80 mL), dried over $MgSO_4$, and concentrated. Purification of the crude product by silica gel column chromatography (hexane–EtOAc, 6:1) afforded diol **5a**.

Yield: 2.78 g (88%); colorless oil; $[\alpha]_D^{25}$ +30.3 (*c* 0.7, $CHCl_3$).

IR (neat): 3423, 2926, 2855, 1714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.6 Hz, 3 H), 1.06 (s, 9 H), 1.25 (s, 23 H), 1.38–1.55 (m, 2 H), 1.68–1.78 (m, 1 H), 2.10 (br s, 1 H), 3.11 (br s, 1 H), 3.58–3.68 (m, 2 H), 3.83 (dd, *J* = 4.2, 10.9 Hz, 1 H), 4.04 (dd, *J* = 3.1, 11.0 Hz, 1 H), 4.18–4.26 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 7.35–7.48 (m, 6 H), 7.51–7.66 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.0, 22.6, 25.6, 26.7, 29.3, 29.5, 29.56, 29.6, 29.64, 29.7, 31.9, 33.3, 51.3, 63.1, 73.0, 75.2, 117.2 (q, $^1J_{C–F}$ = 286.3 Hz), 128.0, 130.27, 130.3, 131.77, 131.8, 135.39, 135.5, 156.9 (q, $^2J_{C–F}$ = 37.0 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{57}F_3NO_4Si$: 652.4009; found: 652.4003.

_N_-[(2_S_,3_S_,4_R_)-3,4-Dihydroxy-1-(trityloxy)octadecan-2-yl]-2,2,2-trifluoroacetamide (5b)

To a solution of **4** (1.70 g, 4.11 mmol) in pyridine (8 mL) and CH_2Cl_2 (15 mL), were added DMAP (50 mg, 0.41 mmol) and triphenyl methyl chloride (1.40 g, 5.02 mmol). This reaction mixture was stirred for 24 h at r.t., then quenched with 0.5 M HCl (10 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with brine (2 × 80 mL), dried over $MgSO_4$, and concentrated. Purification of the crude product by silica gel column chromatography (hexane–EtOAc, 4:1) afforded diol **5b**.

Yield: 2.30 g (85%); colorless oil; $[\alpha]_D^{25}$ +39.7 (*c* 0.7, $CHCl_3$).

IR (neat): 3420, 2924, 2853, 1712 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.9 Hz, 3 H), 1.22–1.54 (m, 26 H), 1.62–1.74 (m 1 H), 2.44 (br s, 1 H), 3.26 (br s, 1 H), 3.34–3.42 (m, 1 H), 3.46–3.56 (m, 2 H), 3.63 (br s, 1 H), 4.32–4.40 (m, 1 H), 7.26–7.37 (m, 10 H), 7.40–7.47 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.5, 29.3, 29.4, 29.5, 29.6, 29.64, 31.9, 33.0, 50.7, 62.1, 72.5, 74.9, 87.8, 117.7 (q, $^1J_{C–F}$ = 286.3 Hz), 127.4, 127.8, 128.1, 128.3, 142.8, 157.0 (q, $^2J_{C–F}$ = 37.0 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{53}F_3NO_4$: 656.3927; found: 656.3921.

Synthesis of Cyclic Sulfates 6a and 6b; General Procedure

To a solution of diol **5** (2.50 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (1.20 mL, 8.61 mmol) and thionyl chloride (0.24 mL, 2.77 mmol) at 0 °C. After 30 min, this reaction mixture was poured into brine (50 mL) and extracted with EtOAc (2 × 80 mL). The organic layer was dried over $MgSO_4$ and concentrated. This crude cyclic sulfite was dried in vacuo for 3 h, then dissolved in CCl_4–MeCN–H_2O (1:1:1, 21 mL). To the resulting solution were added $RuCl_3·3H_2O$ (26.0 mg, 0.13 mmol) and $NaIO_4$ (1.60 g, 7.48 mmol), and the reaction mixture was stirred at r.t. for 2 h, diluted with EtOAc (100 mL) and washed with saturated $NaHSO_3$ (2 × 80 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give cyclic sulfate **6**.

(2_S_,3_S_,4_S_)-1-(*tert*-Butyldiphenylsilyloxy)-2-[*N*-(trifluoroacetyl)amino]octadecan-3,4-cyclic Sulfate (6a)

Yield: 1.71 g (96% from **5a**); colorless oil; $[\alpha]_D^{25}$ +4.0 (*c* 0.6, $CHCl_3$).

IR (neat): 3420, 2926, 2855, 1789, 1216 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H), 1.15–1.44 (m, 22 H), 1.45–1.60 (m, 1 H), 1.61–1.74 (m, 2 H), 1.78–1.92 (m, 1 H), 3.73 (dd, *J* = 2.8, 10.9 Hz, 1 H), 4.00 (dd, *J* = 3.2, 10.9 Hz, 1 H), 4.35–4.43 (m, 1 H), 4.92–4.99 (m, 1 H), 5.10 (dd, *J* = 5.1, 8.9 Hz, 1 H), 6.76 (d, *J* = 9.1 Hz, 1 H), 7.31–7.50 (m, 6 H), 7.56–7.67 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.2, 22.7, 25.1, 26.5, 26.7, 27.7, 28.7, 29.1, 29.3, 29.4, 29.5, 29.60, 29.63, 29.7, 31.9, 49.2, 62.1, 80.9, 86.0, 117.4 (q, $^1J_{C–F}$ = 286.3 Hz), 127.7, 128.1, 129.6, 130.3, 131.5, 131.9, 134.8, 135.3, 135.4, 135.5, 157.2 (q, $^2J_{C–F}$ = 37.8 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{55}F_3NO_4SSi$: 714.3471; found: 714.3470.

(2_S_,3_S_,4_S_)-1-(Trityloxy)-2-[*N*-(trifluoroacetyl)amino]octadecan-3,4-cyclic Sulfate (6b)

Yield: 1.69 g (94% from **5b**); colorless oil; $[\alpha]_D^{25}$ –15.1 (*c* 0.9, $CHCl_3$).

IR (neat): 3476, 2918, 2849, 1445, 1158 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.0 Hz, 3 H), 1.16–1.44 (m, 23 H), 1.46–1.74 (m, 2 H), 1.78–1.94 (m, 1 H), 3.28 (dd, *J* = 2.7, 10.2 Hz, 1 H), 3.64 (dd, *J* = 3.9, 10.2 Hz, 1 H), 4.34–4.46 (m, 1 H), 4.92–5.00 (m, 1 H), 5.16 (dd, *J* = 5.4, 8.7 Hz, 1 H), 6.52 (d, *J* = 9.0 Hz, 1 H), 7.22–7.40 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.2, 27.7, 28.7, 29.1, 29.3, 29.4, 29.5, 29.61, 29.64, 31.9, 48.4, 61.4, 81.6, 85.9, 87.6, 117.3 (q, $^1J_{C–F}$ = 286.3 Hz), 127.2, 127.6, 127.9, 128.2, 128.3, 142.7, 146.8, 157.2 (q, $^2J_{C–F}$ = 37.8 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{51}F_3NO_6S$: 718.3389; found: 718.3387.

Synthesis of Iodo Alcohols 7 and 8

To a solution of cyclic sulfate **6a** (200 mg, 0.26 mmol) in THF (3 mL) was added Bu_4NI (140 mg, 0.38 mmol). The reaction mixture was heated for 2 h at 40 °C, then cooled to r.t. and concentrated H_2SO_4 (5 μL), H_2O (6 μL), and THF (80 μL) were added. The mixture was stirred for 1 h at r.t. and then diluted with EtOAc (20 mL), washed with sat. aq $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to provide a mixture of iodo alcohols **7** and **8** in a ratio of 13:1 according to ^{1}H NMR analysis in $CDCl_3$. Purification of the crude material by column chromatography on silica gel (hexane–EtOAc, 15:1) gave iodo alcohols **7** and **8**.

_N_-[(2_S_,3_S_,4_S_)-1-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-4-iodooctadecan-2-yl]-2,2,2-trifluoroacetamide (7)

Yield: 138 mg (69%); colorless oil; $[\alpha]_D^{25}$ +2.1 (*c* 0.7, $CHCl_3$).

IR (neat): 3419, 2926, 2855, 1709, 1169 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3 H), 1.06 (s, 9 H), 1.16–1.40 (m, 23 H), 1.45–1.56 (m, 1 H), 1.62–1.73 (m, 1 H), 1.87–1.98 (m, 1 H), 2.35 (d, *J* = 8.0 Hz, 1 H), 3.24–3.31 (m, 1 H),

3.74 (dd, *J* = 3.8, 10.7 Hz, 1 H), 4.03 (dd, *J* = 3.9, 10.7 Hz, 1 H), 4.12–4.19 (m, 1 H), 4.22 (dt, *J* = 4.6, 9.3 Hz, 1 H), 6.8 (d, *J* = 8.9 Hz, 1 H), 7.34–7.48 (m, 6 H), 7.58–7.67 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.2, 22.7, 26.5, 26.8, 28.7, 29.3, 29.4, 29.5, 29.6, 29.64, 29.67, 29.68, 29.7, 31.9, 37.3, 44.6, 54.2, 61.6, 73.8, 117.2 (q, $^1J_{C-F}$ = 286.5 Hz), 127.7, 127.98, 128.0, 129.6, 130.17, 130.2, 132.2, 134.8, 135.2, 135.4, 135.5, 157.0 (q, $^2J_{C-F}$ = 37.1 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{56}F_3INO_3Si$: 762.3026; found: 762.3022.

N-[(2*S*,3*R*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-3-iodooctadecan-2-yl]-2,2,2-trifluoroacetamide (8)

Yield: 11 mg (6%); colorless oil.

IR (neat): 3421, 2926, 2855, 1726, 1169 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.3 Hz, 3 H), 1.08 (s, 9 H), 1.20–1.41 (m, 22 H), 1.74–1.90 (m, 1 H), 1.90–2.24 (m, 1 H), 3.18 (d, *J* = 8.4 Hz, 1 H), 3.87 (dd, *J* = 2.4, 11.1 Hz, 1 H), 3.90–4.0 (m, 1 H), 4.01–4.09 (m, 1 H), 4.12 (dd, *J* = 2.1, 11.1 Hz, 1 H), 4.42–4.50 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 7.36–7.50 (m, 6 H), 7.54–7.66 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.2, 22.7, 26.8, 26.9, 28.7, 29.36, 29.4, 29.5, 29.6, 29.62, 29.68, 31.9, 34.5, 38.5, 52.1, 63.1, 76.3, 117.2, 128.0, 128.1, 128.2, 130.2, 130.4, 131.5, 131.7, 135.3, 135.4, 156.8.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{56}F_3INO_3Si$: 762.3026; found: 762.3030.

N-[(2*S*,3*R*,*E*)-1-(*tert*-Butyldiphenylsilyloxy)-3-hydroxyoctadec-4-en-2-yl]-2,2,2-trifluoroacetamide (9)

To a solution of cyclic sulfate **6a** (1.70 g, 2.38 mmol) in toluene (25 mL) was added Bu_4NI (1.00 g, 2.71 mmol). The reaction mixture was heated for 3 h at 40 °C. After the reaction was complete, DBU (0.50 mL, 3.40 mmol) was added and the reaction mixture was heated to reflux for 2 h. The reaction was cooled to r.t. and concentrated H_2SO_4 (34 μL), H_2O (30 μL), and THF (546 μL) were added. The mixture was stirred for 1 h at r.t., then diluted with EtOAc (80 mL) and washed with sat. aq $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude product by silica gel column chromatography (hexane–EtOAc, 25:1) afforded **9**.

Yield: 1.11 g (74%); colorless oil; $[\alpha]_D^{25}$ +26.0 (*c* 0.7, $CHCl_3$).

IR (neat): 3427, 2926, 2855, 1722, 1168 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3 H), 1.06 (s, 9 H), 1.15–1.40 (m, 24 H), 2.03 (dd, *J* = 6.6, 13.6 Hz, 2 H), 2.69 (d, *J* = 7.4 Hz, 1 H), 3.76 (dd, *J* = 3.0, 10.7 Hz, 1 H), 3.90–3.98 (m, 1 H), 4.01 (dd, *J* = 2.9, 10.7 Hz, 1 H), 4.23–4.30 (m, 1 H), 5.46 (dd, *J* = 6.0, 15.4 Hz, 1 H), 5.81 (app. dt, *J* = 6.6, 14.6 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 7.33–7.47 (m, 6 H), 7.55–7.65 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.1, 22.7, 26.8, 29.0, 29.2, 29.4, 29.5, 29.6, 29.7, 31.9, 32.2, 54.0, 62.7, 71.5, 73.3, 117.8 (q, $^1J_{C-F}$ = 286.3 Hz), 127.6, 127.7, 127.8, 127.97, 128.0, 128.1, 130.2, 130.24, 131.9, 132.1, 134.7, 135.4, 135.42, 135.6, 157.0 (q, $^2J_{C-F}$ = 37 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{55}F_3INO_3Si$: 634.3903; found: 634.3902.

N-[(2*S*,3*R*,*E*)-1,3-Dihydroxyoctadec-4-en-2-yl]-2,2,2-trifluoroacetamide (10)

From ***9***: To a solution of **9** (1.10 g, 1.74 mmol) in THF (25 mL) was added Bu_4NF (2.60 mL, 2.60 mmol, 1.0 M in THF) at r.t. The reaction mixture was stirred for 1 h, then diluted with H_2O (80 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine (2 × 100 mL), dried over Na_2SO_4, and concentrated. Purification of the crude product by silica gel column chromatography (hexane–EtOAc, 3:1) afforded **10** (681 mg, 99%) as a white solid.

From ***6b***: To a solution of crude cyclic sulfate **6b** (3.00 g, 4.18 mmol) in toluene (60 mL) was added Bu_4NI (1.71 g, 4.62 mmol). The reaction mixture was heated for 3 h at 40 °C. After the reaction was complete, DBU (0.90 mL, 6.00 mmol) was added and the reaction mixture was heated to reflux for 2 h. The reaction mixture was then cooled to r.t. and 5.0 M HCl (40 mL) and toluene (30 mL) were added. The resulting mixture was stirred for 2 h at r.t. and then diluted with EtOAc (100 mL) and washed with sat. aq $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude product by silica gel column chromatography (hexane–EtOAc, 3:1) afforded **10** (1.14 g, 69% from **6b**) as a white solid.

Mp 89–91 °C; $[\alpha]_D^{25}$ –28.7 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$): 3280, 2916, 2850, 1699, 1181 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.5 Hz, 3 H), 1.24 (s, 20 H), 1.30–1.41 (m, 2 H), 2.04 (dd, *J* = 6.8, 13.9 Hz, 2 H), 3.71 (dd, *J* = 3.4, 11.6 Hz, 1 H), 3.87–3.94 (m, 1 H), 4.07 (dd, *J* = 2.7, 8.7 Hz, 1 H), 4.35 (t, *J* = 5.2 Hz, 1 H), 5.50 (dd, *J* = 6.5, 15.4 Hz, 1 H), 5.80 (app. dt, *J* = 6.7, 14.7 Hz, 1 H), 7.16 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.0, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 32.2, 54.1, 61.1, 74.0, 117.7 (q, $^1J_{C-F}$ = 286.0 Hz), 127.9, 135.3, 157.4 (q, $^2J_{C-F}$ = 36.8 Hz).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{37}F_3NO_3$: 396.2726; found: 396.2724.

(2*S*,3*R*)-(*E*)-2-Aminooctadec-4-ene-1,4-diol (D-*erythro*-Sphingosine) (1)

To a solution of **10** (1.53 g, 4.68 mmol) in EtOH (90 mL) was added 2 M NaOH (75 mL) at r.t. The reaction mixture was stirred for 2 h and then diluted with H_2O (80 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine (2 × 100 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel ($CHCl_3$–MeOH–NH_4OH, 135:25:4) to give sphingosine **1**.

Yield: 1.33 g (96%); white waxy solid; mp 76–77 °C (Lit.[17a] 79–82 °C); $[\alpha]_D^{25}$ –3.0 (*c* 1.0, $CHCl_3$) (Optical rotation values[5–7,17a] of sphingosine **1** range from –1.4 to –2.9); R_f = 0.15 ($CHCl_3$–MeOH–NH_4OH, 135:25:4).

IR (neat): 3240, 2919, 2851, 1467, 1032, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.5 Hz, 3 H), 1.24 (s, 20 H), 1.33–1.38 (m, 2 H), 2.05 (q, *J* = 6.6 Hz, 2 H), 2.56–2.58 (m, 1 H), 3.60 (dd, *J* = 6.0, 10.8 Hz, 1 H), 3.67 (dd, *J* = 4.6, 10.8 Hz, 1 H), 4.06 (t, *J* = 6.4 Hz, 1 H), 5.47 (dd, *J* = 7.2, 15.4 Hz, 1 H), 5.76 (td, *J* = 6.7, 14.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.2, 29.25, 29.34, 29.5, 29.7, 31.9, 32.3, 56.2, 63.7, 75.1, 129.0, 134.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{38}O_2N$: 300.2903; found: 300.2907.

(2*S*,3*R*)-(*E*)-2-Acetamidooctadec-4-ene-1,3-diyl Diacetate (11)

To a solution of sphingosine **1** (300 mg, 1.00 mmol) in pyridine (9 mL) was added Ac_2O (578 μL, 6.12 mmol) at 0 °C. After stirring at r.t. for 5 h, the reaction mixture was poured into H_2O (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to give sphingosine triacetate **11**.

Yield: 386 mg (90%); white solid; mp 102–104 °C (Lit. 100–102 °C,[5g] 101–102 °C,[17a] 104.6–106.0 °C[17b]); $[\alpha]_D^{25}$ –14.4 (*c* 1.2,

$CHCl_3$) (Optical rotation values[5g,6b,17a] of sphingosine triacetate **11** range from –13.0 to –13.2).

IR (neat): 3290, 1736, 1657, 1552 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.6 Hz, 3 H), 1.25 (s, 22 H), 1.98 (s, 3 H), 2.01–2.04 (m, 2 H), 2.056 (s, 3 H), 2.062 (s, 3 H), 4.03 (dd, *J* = 3.9, 11.4 Hz, 1 H), 4.29 (dd, *J* = 6.0, 11.4 Hz, 1 H), 4.39–4.46 (m, 1 H), 5.27 (app. t, *J* = 6.5 Hz, 1 H), 5.38 (dd, *J* = 7.5, 15.3 Hz, 1 H), 5.66 (br d, *J* = 9.0 Hz, 1 H), 5.78 (td, *J* = 6.9, 15.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.8, 21.1, 22.7, 23.3, 28.9, 29.1, 29.3, 29.4, 29.57, 29.64, 31.9, 32.3, 50.7, 62.6, 73.8, 124.1, 137.4, 169.6, 170.0, 170.9.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{24}H_{44}O_5N$: 426.3219; found: 426.3230.

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