

A Practical Access to 1,2-Diaminophytosphingolipids

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A practical approach to the synthesis of phytosphingolipids containing the 1,2-diamino framework is described. The methodology relies on the regioselective ring-opening of phytosphingosine-derived *N*-nosylaziridines **4** and **6** with primary or secondary amines, acylation and subsequent deprotection steps. For practical purposes, *N*-substituted ben-

zylamines were used as protected primary amine surrogates to avoid side-reactions in the course of the *N*-nosyl deprotection step.

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Introduction

The 1,2-diamino moiety is widespread in nature as part of many biologically active natural products and also as the key component of a variety of synthetic compounds with multiple applications in medicinal chemistry as therapeutically active agents or as pharmacological tools.^[1,2] As a result of our current interest in sphingolipids, we became interested in the exploration of the antifungal properties of a series of phytosphingolipid analogues encompassing different structural modifications on the sphingoid base skeleton. Among them, some 1-amino-1-deoxyphytosphingosines showed promising biological results,^[3,4] in agreement with the hypothesis that the introduction of non-natural functional groups into a sphingolipid skeleton might alter the biological profile or the metabolic stability of the resulting analogues.^[5] Despite the scarce precedents for the use of the 1,2-diamino moiety in sphingolipid chemistry, some important examples have emerged over the last few years. Thus, phosphoramidate **A** has been reported as a metabolically stable sphingosine-1-phosphate surrogate,^[6] whereas phosphoramidate **B** has been described as a sphingomyelinase inhibitor.^[7] Other examples of sphingolipid analogues containing the 1,2-diamino framework are found in the sphingosine kinase inhibitor **C**^[8] and in a series of glucosylceramide synthase inhibitors of general structure **D**.^[9] (Figure 1).

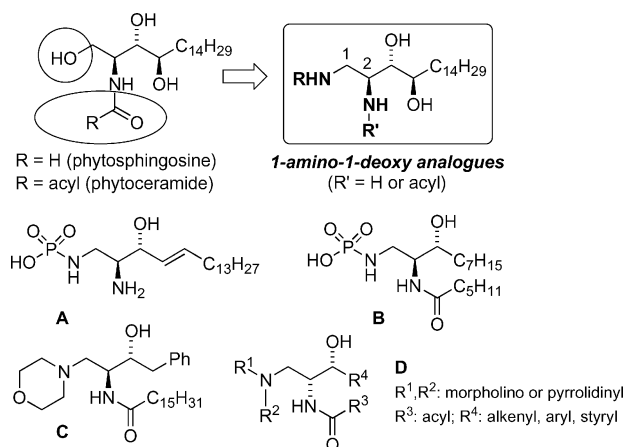


Figure 1. Phytosphingolipids and some reported sphingolipid analogues containing the 1,2-diamino framework.

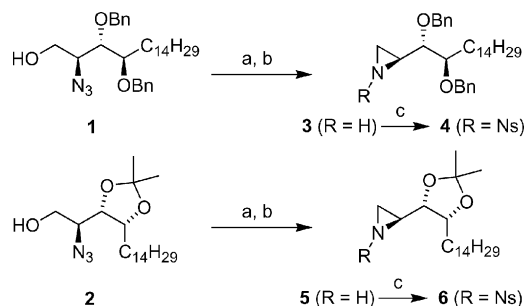
As a continuation of this work, in an attempt to widen the diversity of our previously reported analogues, we wish to report on a general approach to new phytosphingolipids, structurally related to phytosphingosine ($\text{R}' = \text{H}$) or phytoceramide ($\text{R}' = \text{acyl}$) incorporating a vicinal 1,2-diamino moiety (Figure 1).

Results and Discussion

Our methodology relies on the regiospecific nucleophilic ring-opening of *N*-nosylaziridines **4** or **6**, which arise from mesylate formation from *O,O*-diprotected 2-azidophytosphingosines **1**^[10] or **2**,^[11] azide reduction with in situ intramolecular cyclization^[12] to aziridines **3** or **5** and final sulfonylation with 2-nitrobenzenesulfonyl chloride (nosyl chloride)^[13,14] (Scheme 1).

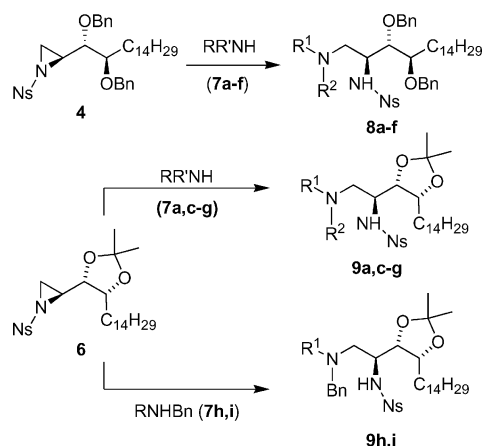
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Scheme 1. Reagents and conditions: (a) MsCl , THF, Et_3N ; (b) Ph_3P , THF, H_2O ; (c) ClSO_2R , THF, Et_3N .

To illustrate the versatility of this synthetic protocol, nosylaziridines **4** and **6** were treated with amines **7a–h** in refluxing CH_3CN .^[15] The reactions took place smoothly under the conditions shown in Scheme 2 to afford 1,2-diaminophytosphingosines **8** and **9** in good-to-excellent yields (Table 1).^[16]



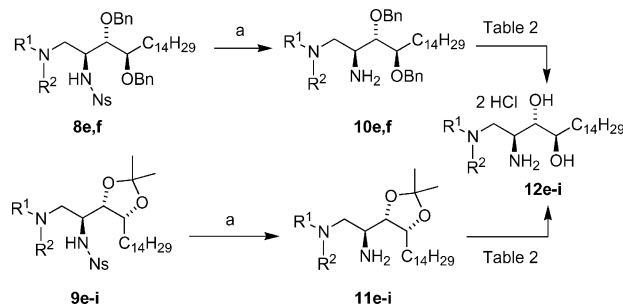
Scheme 2. Ring-opening of nosylaziridines with amines. Reaction conditions: amine (2 equiv./mol), CH_3CN , reflux, 3 h or room temp. 24 h. For compound identification and yields, see Table 1.

Table 1. Reaction of nosylaziridines **4** and **6** with amines.

Entry	Aziridine	Amine	R^1	R^2	Ad-duct	Yield ^[a] [%]
1	4	7a	<i>n</i> Bu	H	8a	81
2	4	7b	<i>n</i> Oct	H	8b	80
3	4	7c	2-hydroxyethyl	H	8c	89
4	4	7d	<i>t</i> Bu	H	8d	93
5	4	7e	Ph	H	8e	85
6	4	7f	morpholine	H	8f	89
7	6	7a	<i>n</i> Bu	H	9a	83
8	6	7c	2-hydroxyethyl	H	9c	78
9	6	7d	<i>t</i> Bu	H	9d	95
10	6	7e	Ph	H	9e	87
11	6	7f	morpholine	H	9f	97
12	6	7g	pyrrolidine	H	9g	99
13	6	7h	2-hydroxyethyl	Bn	9h	89
14	6	7i	<i>t</i> Bu	Bn	9i	82

[a] Isolated yields. For reaction conditions, see Scheme 2.

However, attempts to remove the *N*-nosyl group from phytosphingosines **8** and **9** with $\text{PhSH}/\text{Cs}_2\text{CO}_3$ ^[17] met with limited success as only the anilino (**8e**, **9e**), morpholino (**8f**, **9f**) and pyrrolidino (**9g**) analogues afforded the expected phytosphingosines **10e,f** and **11e–g** as single products in good yields (see Scheme 3 and Table 2), whereas the nosyl derivatives **8a–d** and **9a–c** afforded complex reaction mixtures. We hypothesised that a transient amide resulting from deprotonation of the C(1)NH group by the caesium salt^[18] in the above compounds would be responsible for the observed side-reactions because of an intramolecular amide displacement of the C(2)*N*-nosyl group in competition with the external thiolate.^[19] In agreement with this assumption, no side-reactions were observed with morpholines **8f** and **9f**, pyrrolidine **9g** and tertiary amines **9h** and **9i**, from which amide formation is precluded. On the other hand, the lower nucleophilicity of the caesium amide arising from anilino derivatives **8e** and **9e** would not interfere with the external thiolate in the deprotection step (see Scheme 3 and Table 2).



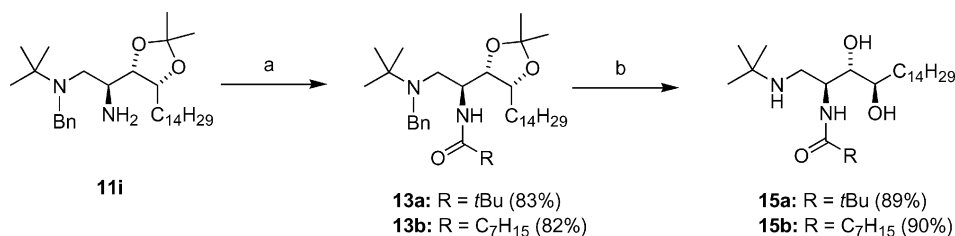
Scheme 3. Sequential deprotection of 1,2-diaminophytosphingosines. Reaction conditions: (a) PhSH (4 equiv./mol)/ Cs_2CO_3 (3 equiv./mol), CH_3CN , room temp., 20 h. For compound identification and yields, see Table 2.

Table 2. Synthesis of the phytosphingosines (see Scheme 3).

Entry	Nosylate	R^1	R^2	Amine (yield [%])	Yield ^[a,b] [%]
1	8e	Ph	H	10e (75)	12e 78 (A)
2	8f	morpholine	H	10f (83)	12f 89 (A)
3	9e	Ph	H	11e (79)	12e 99 (B)
4	9f	morpholine	H	11f (88)	12f 99 (B)
5	9g	pyrrolidine	H	11g (90)	12g 99 (B)
6	9h	2-hydroxyethyl	Bn	11h (79)	12h ($\text{R}^2 = \text{H}$) 97 (C)
7	9i	<i>t</i> Bu	Bn	11i (83)	12i ($\text{R}^2 = \text{H}$) 82 (C)

[a] Isolated yields. [b] A, B, C: deprotection methods (see text).

Acetal removal under standard acidic conditions afforded phytosphingosines **12e–g** (Method B, Table 2, entries 3–5). On the other hand, the choice of *N*-substituted benzylamines as masked precursors of secondary amines required the final simultaneous deprotection of the benzyl and acetal groups in compounds **11h** and **11i**, which was easily carried out by catalytic hydrogenation under acidic conditions to afford phytosphingosines **12h** and **12i** in excellent yields (Method C, Table 2, entries 6 and 7). Finally, BCl_3 -promoted benzyl removal^[20] from precursors **10e** and **10f** afforded phytosphingosines **12e** and **12f** in acceptable yields (Method A, Table 2, entries 1 and 2).^[21]



Scheme 4. Acylation of diamines **11** and simultaneous *N*- and *O*-deprotection. Reaction conditions: (a) RCOCl, THF, Et₃N; b) H₂, 5% Pd/C, HCl, MeOH.

This protocol was easily adapted to 1,2-diaminophytoceramide derivatives by standard acylation of intermediate amines **11** and final simultaneous *N*- and *O*-deprotection. An illustrative example is shown in Scheme 4 in which amine **11i** is acylated with two different acyl chlorides and then deprotected to afford phytoceramides **15a** and **15b** in excellent yields and purities (Scheme 4).

Conclusions

A practical protocol for the simple construction of phytosphingosine analogues bearing a vicinal 1,2-diamino moiety has been developed. The method relies on the regioselective ring-opening of *N*-nosylaziridines **4** and **6** with suitable amines and subsequent *N*-nosyl removal and deprotection. *N*-Acylation of intermediates **11** prior to final *O*- and *N*-deprotection leads to phytoceramide analogues. The versatility and simplicity of the method makes it amenable to the production of small-to-medium-sized libraries for further screening.

Experimental Section

General Methods: All moisture-sensitive reactions were carried out under argon. All the materials were obtained commercially and used without further purification. Solvents were distilled prior to use and dried by standard methods.^[22] Thin-layer chromatography (TLC) was performed on silica gel (Alugram Sil G/UV). Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. Melting points were determined with an SMP10 melting-point apparatus and are uncorrected. Chemical shifts are reported in δ (ppm) relative to the singlet at δ = 7.24 ppm of CDCl₃ and 3.31 ppm of MeOD for ¹H NMR and to the centre line of the triplet at δ = 77.0 ppm of CDCl₃ and 49.0 ppm of MeOD for ¹³C NMR. IR spectra were measured as films and were recorded with a BOMEM MB-120 instrument. $[\alpha]_D$ values are given in 10⁻¹ deg cm² g⁻¹ and were measured with a Perkin–Elmer 341 polarimeter. ESI/HRMS were recorded with a Waters LCT Premier mass spectrometer.

(*S*)-2-[(1*S*,2*R*)-1,2-Bis(benzyloxy)hexadecyl]aziridine (3**) and (*S*)-2-[(4*S*,5*R*)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl]aziridine (**5**):** Et₃N (7.5 mmol, 3 equiv.) and MsCl (5 mmol) were added to a solution of azide **1**^[10] or **2**^[11] (2.5 mmol) in THF (30 mL) at room temperature. The reaction mixture was stirred for 3 h, poured into saturated aqueous NaHCO₃ and extracted with EtOAc. The separated organic layer was washed with brine, dried with MgSO₄ and concentrated under reduced pressure. The residue was employed in

the next step without further purification. Et(*i*Pr)₂N (3.75 mmol) and Ph₃P (3.25 mmol) were added to a solution of the corresponding mesylate (2.5 mmol) in THF/H₂O (18:2). The reaction mixture was heated at 60 °C for 2 h and cooled to room temperature. The mixture was poured into brine and extracted with Et₂O (3 × 30 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (7:3 hexane/ethyl acetate) to afford the required aziridines.

Aziridine **3:** Oil, yield 960 mg, 80%. $[\alpha]_D$ = −23 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3412, 3018, 2926, 2854, 1454, 1215, 1095, 757, 669 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.32 (m, 10 H), 4.72–4.54 (m, 4 H), 3.64 (dt, *J* = 8.4, 3.6 Hz, 1 H), 3.22 (m, 1 H), 2.16 (m, 1 H), 1.78 (d, *J* = 5.6 Hz, 1 H), 1.61 (d, *J* = 3.2 Hz, 1 H), 1.73–1.51 (m, 3 H, NH, 2 CH), 1.30 (m, 24 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 138.7, 138.4, 128.3–127.5 (10 C), 81.3, 81.0, 72.6, 72.3, 31.9, 30.7, 29.8–29.3 (10 C), 25.9, 23.1, 22.7, 14.1 ppm. HRMS: calcd. for C₃₂H₄₉NO₂ [*M* + *H*]⁺ 480.3771; found 480.3767.

Aziridine **5:** Oil, yield 690 mg, 82%. $[\alpha]_D$ = +7 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3390, 3015, 2911, 2832, 1209, 1055 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 4.23 (m, 1 H), 3.57 (m, 1 H), 2.09 (m, 1 H), 1.87 (m, 1 H), 1.72 (m, 2 H), 1.58 (m, 2 H), 1.48 (s, 3 H), 1.40 (s, 3 H), 1.31 (m, 24 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 107.7, 80.3, 77.9, 31.8, 29.8–29.5 (10 C), 28.7, 27.8, 26.6, 25.1, 22.6 (2 C), 14.0 ppm.

General Procedure for the Preparation of *N*-(*o*-Nosyl)aziridines **4 and **6**:** Et₃N (3 mmol) and the sulfonyl chloride derivative (1 mmol, 1 equiv.) in THF (2 mL) was added to a solution of the corresponding aziridine **3** or **5** (1 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 2 h. Then sat. NaHCO₃ (15 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were dried with MgSO₄ and the solvents were evaporated at reduced pressure to give the crude aziridines, which were purified by column chromatography (5:1 hexanes/EtOAc).

***N*-(*o*-Nosyl)aziridine (**4**):** Oil, yield 480 mg, 81%. $[\alpha]_D$ = −23 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3012, 2933, 2824, 1412, 1577, 1368, 1189, 768 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.12 (d, *J* = 8 Hz, 1 H), 7.71 (m, 3 H), 7.30 (m, 10 H), 4.57 (m, 4 H), 3.70 (t, *J* = 3.6 Hz, 1 H), 3.5 (m, 1 H), 3.27 (m, 1 H), 2.77 (d, *J* = 7.2 Hz, 1 H), 2.54 (d, *J* = 4.8 Hz, 1 H), 1.60 (m, 2 H), 1.25 (m, 24 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 148.5, 138.3, 138.0, 134.4, 132.0, 131.6, 131.1, 128.3–127.5 (10 C), 124.3, 80.2, 76.8, 73.4, 72.2, 41.2, 32.7, 31.8, 30.3, 29.7–29.3 (9 C), 25.5, 22.6, 14.1 ppm. HRMS: calcd. for C₃₈H₅₂N₂O₆S [*M* + *H*]⁺ 665.3654; found 665.3624.

***N*-(*o*-Nosyl)aziridine (**6**):** White solid, yield 377 mg, 82%. $[\alpha]_D$ = −47 (*c* = 1, CDCl₃); m.p. 112–114 °C. IR (neat): $\tilde{\nu}$ = 2924, 2853,

1547, 1369, 1168, 752 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.21 (d, *J* = 6.4 Hz, 1 H), 7.70 (m, 3 H), 4.21 (m, *J* = 6.8 Hz, 1 H), 3.96 (t, *J* = 6 Hz, 1 H), 3.17 (m, *J* = 6.8 Hz, 1 H), 2.92 (d, *J* = 7.2 Hz, 1 H), 2.52 (d, *J* = 4.4 Hz, 1 H), 1.60 (m, 2 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.25 (m, 24 H), 0.87 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 148.4, 134.5, 132.2, 132.0, 131.3, 124.4, 108.5, 77.5, 76.9, 39.9, 33.3, 31.9, 29.7–29.3 (10 C), 27.7, 26.7, 25.2, 22.7, 14.1 ppm. HRMS: calcd. for C₂₇H₄₄N₂O₆S [M + H]⁺ 525.2998; found 525.2997.

General Procedure for the Ring-Opening of *N*-(*o*-Nosyl)aziridines 4 and 6 with Amines: The corresponding amine (1 mmol) in CH₃CN (1 mL) was added to a stirred solution of the corresponding *N*-(*o*-nosyl)aziridine (0.5 mmol) in dry CH₃CN (4 mL). The mixture was stirred at room temperature for 20 h or at reflux temperature for 2–3 h. Then the solvent was evaporated in vacuo to give a crude, which was purified by chromatography with 4:1 hexanes/EtOAc.

8a: Oil, yield 273 mg, 81%. [α]_D = +24 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3356, 2921, 2849, 1932, 1547, 1469, 1165, 875, 712, 689 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.04 (d, *J* = 7.6 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 8 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.32 (m, 10 H), 4.74–4.47 (m, 4 H), 3.80 (t, *J* = 4.8 Hz, 1 H), 3.70 (m, 1 H), 3.62 (m, 1 H), 2.93 (dd, *J* = 12.4, 5.2 Hz, 1 H), 2.35 (dd, *J* = 12.8, 4.4 Hz, 1 H), 2.25 (m, 1 H), 2.17 (m, 1 H), 1.63 (m, 2 H), 1.37 (m, 2 H), 1.27 (m, 22 H), 1.11 (m, 4 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.80 (t, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.7, 138.3, 137.9, 134.2, 133.1, 132.5, 131.0, 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 127.7, 127.5, 124.9, 81.3, 78.9, 74.0, 71.6, 54.2, 49.4, 48.5, 31.9, 31.6, 29.8–29.3 (10 C), 25.1, 22.6, 20.1, 14.1 ppm. 13.9. HRMS: calcd. for C₄₂H₆₃N₃O₆S [M + H]⁺ 738.4555; found 738.4542.

8b: Oil, yield 270 mg, 80%. [α]_D = +42 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3431, 2917, 2826, 1552, 1447, 814, 711 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 8 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.32 (m, 10 H), 4.73–4.48 (m, 4 H), 3.80 (t, *J* = 4.8 Hz, 1 H), 3.63 (m, 2 H), 2.90 (dd, *J* = 12.4, 5.2 Hz, 1 H), 2.27 (m, 2 H), 2.14 (m, 1 H), 1.64 (m, 2 H), 1.39 (m, 2 H), 1.27 (m, 36 H), 0.89 (m, 6 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.7, 138.4, 138.0, 134.2, 133.1, 132.5, 131.0, 128.4 (2 C), 128.3 (2 C), 128.1 (2 C), 127.8, 127.7 (2 C), 127.5, 125.0, 81.2, 78.9, 73.9, 71.4, 54.5, 49.8, 48.3, 31.9, 31.8, 29.8–29.3 (12 C), 27.1, 25.1, 22.6 (2 C), 20.1, 14.0 (2 C) ppm. HRMS: calcd. for C₄₆H₇₁N₃O₆S [M + H]⁺ 794.5215; found 794.5242.

8c: Oil, yield 301 mg, 89%. [α]_D = +35 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3433, 2918, 1553, 1471, 916, 762 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.01 (d, *J* = 8 Hz, 1 H), 7.80 (d, *J* = 8 Hz, 1 H), 7.65 (t, *J* = 8 Hz, 1 H), 7.54 (t, *J* = 8 Hz, 1 H), 7.33 (m, 10 H), 4.66–4.47 (m, 4 H), 3.75 (m, 1 H), 3.60 (m, 2 H), 3.36 (t, *J* = 5.6 Hz, 2 H), 2.94 (br., 1 H, OH), 2.88 (dd, *J* = 12.4, 5.6 Hz, 1 H), 2.82 (br., 1 H, NH), 2.50 (m, 1 H), 2.40 (dd, *J* = 12.8, 4.4 Hz, 1 H), 2.32 (m, 1 H), 1.60 (m, 2 H), 1.27 (m, 24 H), 0.88 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.7, 138.2, 137.8, 134.2, 133.2, 132.5, 130.8, 128.4 (2 C), 128.3 (2 C), 128.0 (2 C), 127.9, 127.8 (2 C), 127.6, 125.1, 81.3, 78.7, 73.8, 71.5, 61.0, 54.7, 51.1, 48.4, 31.9, 29.9–29.3 (10 C), 25.2, 22.6, 14.0 ppm. HRMS: calcd. for C₄₀H₅₉N₃O₇S [M + H]⁺ 586.3492; found 586.3506.

8d: Oil, yield 337 mg, 93%. [α]_D = +53 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3342, 2917, 2843, 1551, 1461, 863, 695 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.05 (d, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.33 (m, 10 H), 4.75–4.49 (m, 4 H), 3.82 (t, *J* = 4.4 Hz, 1 H), 3.62 (m, 2 H), 2.82 (dd, *J* = 12.4, 4.4 Hz, 1 H), 2.32 (dd, *J* = 12, 4.4 Hz,

1 H), 1.66 (m, 2 H), 1.44 (m, 2 H), 1.27 (m, 22 H), 0.89 (t, *J* = 7 Hz, 3 H), 0.80 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.8, 138.4, 138.0, 134.4, 133.1, 132.5, 130.8, 128.4 (2 C), 128.3 (2 C), 128.1 (2 C), 127.9 (2 C), 127.8, 127.6, 125.0, 81.5, 79.0, 73.9, 71.5, 54.8, 50.0, 41.2, 31.9, 29.9–29.3 (10 C), 28.5 (3 C), 25.2, 22.6, 14.1 ppm. HRMS: calcd. for C₄₂H₆₃N₃O₆S [M + H]⁺ 738.4555; found 738.4542.

8e: Oil, yield 347 mg, 85%. [α]_D = +53 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3331, 2914, 1517, 1463, 1127, 814, 724, 668 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.62 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.46 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.40 (m, 11 H), 6.87 (t, *J* = 8 Hz, 2 H), 6.56 (t, *J* = 7.6 Hz, 1 H), 6.15 (d, *J* = 7.6 Hz, 2 H), 5.96 (d, *J* = 7.2 Hz, 1 H), 4.74–4.51 (m, 4 H), 4.00 (m, 1 H), 3.98 (br., 1 H), 3.90 (dd, *J* = 6.4, 2.8 Hz, 1 H), 3.67 (m, *J* = 5.6 Hz, 1 H), 3.37 (dd, *J* = 14, 4 Hz, 1 H), 3.28 (dd, *J* = 13.6, 7.6 Hz, 1 H), 1.67 (m, 2 H), 1.37 (m, 2 H), 1.27 (m, 22 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.3, 147.0, 138.2, 137.7, 133.8, 133.1, 132.5, 130.6, 128.9 (2 C), 128.5 (2 C), 128.4 (2 C), 128.0 (3 C), 127.7 (2 C), 127.6, 125.2, 117.4, 112.6 (2 C), 82.1, 78.3, 74.1, 71.2, 54.1, 43.3, 31.9, 30.0–29.3 (10 C), 24.7, 22.7, 14.1 ppm. HRMS: calcd. for C₄₄H₅₉N₃O₆S [M + H]⁺ 758.4271; found 758.4253.

8f: Oil, yield 306 mg, 89%. [α]_D = +60 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 2913, 2843, 1927, 1554, 1443, 1176, 859, 772, 691 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.33 (m, 10 H), 4.92–4.40 (m, 4 H), 4.20 (dd, *J* = 6, 1.2 Hz, 1 H), 3.72 (t, *J* = 4.4 Hz, 1 H), 3.50 (m, *J* = 5.6 Hz, 1 H), 3.33 (m, 2 H), 3.22 (br., 2 H), 2.65 (t, *J* = 11 Hz, 1 H), 2.40 (dd, *J* = 13.2, 4 Hz, 1 H), 2.10 (br., 2 H), 1.97 (br., 2 H), 1.65 (m, 2 H), 1.39 (m, 2 H), 1.27 (m, 22 H), 0.89 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.8, 138.4, 138.2, 133.3, 133.2, 132.4, 131.1, 128.3 (4 C), 127.9 (2 C), 127.7 (2 C), 127.5 (2 C), 125.0, 80.7, 78.3, 74.6, 70.7, 66.3 (2 C), 56.5, 53.5, 52.5 (2 C), 31.9, 30.1–29.3 (10 C), 24.4, 22.6, 14.0 ppm. HRMS: calcd. for C₄₂H₆₁N₃O₇S [M + H]⁺ 752.4368; found 752.4334.

9a: Oil, yield 222 mg, 83%. [α]_D = +50 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3341, 2924, 2853, 1915, 1541, 1465, 1173, 853, 784 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.14 (m, 1 H), 7.88 (m, 1 H), 7.72 (m, 2 H), 4.15 (m, 1 H), 4.07 (t, *J* = 6 Hz, 1 H), 3.66 (m, 1 H), 2.88 (dd, *J* = 12.5, 3.5 Hz, 1 H), 2.38 (m, 1 H), 2.32 (dd, *J* = 12.5, 3.5 Hz, 1 H), 2.17 (m, 1 H), 1.65–1.44 (m, 4 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 1.21 (m, 26 H), 0.85 (t, *J* = 7 Hz, 3 H), 0.83 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.7, 135.5, 133.3, 132.9, 130.3, 125.3, 107.8, 77.8, 77.6, 53.9, 49.8, 49.4, 32.1, 31.9, 29.6–29.3 (10 C), 27.5, 26.6, 25.3, 22.7, 20.2, 14.1, 13.9 ppm. HRMS: calcd. for C₃₁H₅₅N₃O₆S [M + H]⁺ 598.3928; found 598.3944.

9c: Oil, yield 208 mg, 78%. [α]_D = +15 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3454, 2931, 2833, 1551, 1473, 812, 678 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.13 (m, 1 H), 7.88 (m, 1 H), 7.73 (m, 2 H), 4.13 (m, 1 H), 4.04 (t, *J* = 6 Hz, 1 H), 3.71 (m, 1 H), 3.45 (m, 1 H), 3.40 (m, 1 H), 2.98 (br., 3 H), 2.90 (dd, *J* = 12.8, 4.4 Hz, 1 H), 2.66 (m, 1 H), 2.39 (m, 2 H), 1.59 (m, 2 H), 1.38 (s, 3 H), 1.30 (s, 3 H), 1.35 (m, 24 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 147.7, 135.4, 133.5, 132.9, 132.2, 125.5, 108.0, 77.6 (2 C), 61.0, 53.9, 55.8, 51.3, 49.3, 31.9, 29.6–29.3 (10 C), 27.5, 26.6, 25.3, 22.6, 14.1 ppm. HRMS: calcd. for C₂₉H₅₁N₃O₇S [M + H]⁺ 586.3580; found 586.3572.

9d: Oil, yield 253 mg, 95%. [α]_D = +28 (*c* = 1, CDCl₃). IR (neat): $\tilde{\nu}$ = 3361, 2916, 2846, 1549, 1457, 761 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.12 (dd, *J* = 7.2, 1.6 Hz, 1 H), 7.83 (dd, *J* = 6.8,

1.2 Hz, 1 H), 7.71 (m, 2 H), 4.10 (m, 2 H), 3.71 (m, 1 H), 2.81 (dd, $J = 12$, 3.6 Hz, 1 H), 2.41 (dd, $J = 12$, 3.6 Hz, 1 H), 1.59 (m, 4 H, 2CH, 2NH), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.25 (m, 24 H), 0.86 (m, 12 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.8$, 135.6, 133.3, 132.8, 130.2, 125.1, 107.8, 77.8, 77.6, 53.9, 50.3, 42.6, 31.9, 29.7–29.3 (10 C), 28.5 (3 C), 27.5, 26.6, 25.3, 22.7, 14.1 ppm. HRMS: calcd. for $\text{C}_{31}\text{H}_{55}\text{N}_3\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 598.3928; found 598.3916.

9e: Oil, yield 241 mg, 87%. [a] $_D = +13$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3411$, 2919, 2838, 1925, 1557, 1469, 1161, 849, 681 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.07$ (m, 1 H), 7.74 (m, 1 H), 7.61 (m, 2 H), 7.01 (t, $J = 7.6$ Hz, 2 H), 6.64 (t, $J = 7.6$ Hz, 1 H), 6.32 (d, $J = 8$ Hz, 2 H), 5.88 (d, $J = 8.8$ Hz, 1 H), 4.17 (m, 2 H), 3.83 (m, 1 H), 3.27 (d, $J = 5.2$ Hz, 1 H), 1.60 (m, 2 H), 1.45 (s, 3 H), 1.32 (s, 3 H), 1.26 (m, 24 H), 0.88 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.4$ (2 C), 135.0, 133.3, 133.0, 130.1, 129.0 (2 C), 125.4, 118.0, 113.0 (2 C), 108.3, 78.5, 77.4, 54.4, 45.0, 31.9, 29.7–29.3 (10 C), 27.3, 26.5, 25.3, 22.7, 14.1 ppm. HRMS: calcd. for $\text{C}_{33}\text{H}_{51}\text{N}_3\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 618.3629; found 618.3603.

9f: Oil, yield 266 mg, 97%. [a] $_D = +18$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 2913$, 1932, 1557, 1463, 1160, 854, 777 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.12$ (m, 1 H), 7.93 (m, 1 H), 7.73 (m, 2 H), 4.32 (dd, $J = 6.4$, 5.2 Hz, 1 H), 4.18 (m, $J = 6.8$ Hz, 1 H), 3.60 (m, 1 H), 3.34 (m, 2 H), 3.27 (m, 2 H), 2.59 (dd, $J = 13.6$, 8.4 Hz, 1 H), 2.36 (dd, $J = 14$, 3.2 Hz, 1 H), 2.26 (m, 4 H), 1.56 (m, 2 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.27 (m, 24 H), 0.87 (t, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.7$, 133.4, 133.3, 132.9, 130.1, 125.4, 107.9, 78.6, 77.1, 66.5 (2 C), 58.7, 54.1, 52.7 (2 C), 31.8, 29.6–29.3 (10 C), 26.9, 26.6, 25.1, 22.6, 14.1 ppm. HRMS: calcd. for $\text{C}_{31}\text{H}_{53}\text{N}_3\text{O}_7\text{S}$ [$\text{M} + \text{H}$] $^+$ 612.3782; found 612.3769.

9g: Oil, yield 263 mg, 99%. [a] $_D = +19$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3557$, 2949, 2865, 1563, 1313, 1228, 1071 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 8.15$ (dd, $J = 7$, 2 Hz, 1 H), 7.93 (dd, $J = 7.5$, 2 Hz, 1 H), 7.71 (m, 2 H), 5.08 (br., 1 H, NHSO_2), 4.32 (t, $J = 5.5$ Hz, 1 H), 4.19 (m, 1 H), 3.52 (m, 1 H), 3.16 (t, $J = 6.5$ Hz, 2 H), 2.75 (dd, $J = 13.5$, 9 Hz, 1 H), 2.36 (dd, $J = 13.5$, 3 Hz, 1 H), 2.19 (m, 4 H), 1.90 (t, $J = 6.5$ Hz, 2 H), 1.57 (m, 2 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 1.25 (m, 24 H), 0.86 (t, $J = 6.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.1$, 135.2, 132.8, 132.6, 130.0, 125.1, 107.5, 78.6, 77.1, 55.9, 54.1, 54.0 (2 C), 44.9, 31.6, 29.4–29.1 (10 C), 26.6, 26.3, 24.9, 24.1, 23.2 (2 C), 13.8 ppm. HRMS: calcd. for $\text{C}_{31}\text{H}_{53}\text{N}_3\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 596.3677; found 596.3683.

9h: Oil, yield 272 mg, 89%. [a] $_D = -25$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3427$, 2919, 1552, 1437, 837, 698 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.12$ (m, 1 H), 7.85 (m, 1 H), 7.70 (m, 2 H), 7.29 (m, 5 H), 4.18 (t, $J = 5.6$ Hz, 1 H), 3.99 (m, 1 H), 3.82 (m, 2 H), 3.57 (m, 3 H), 2.84 (dd, $J = 14$, 8 Hz, 1 H), 2.68 (m, 2 H), 2.58 (m, 1 H), 1.45 (m, 2 H), 1.33 (s, 3 H), 1.30 (m, 27 H), 0.88 (t, $J = 6.4$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.5$, 138.1, 135.4, 133.3, 132.8, 129.9, 128.9 (2 C), 128.3 (2 C), 127.2, 125.2, 107.9, 78.3, 77.2, 59.4, 59.0, 56.1, 55.8, 53.6, 31.8, 29.6–29.3 (10 C), 26.9, 26.4, 25.2, 22.6, 14.0 ppm. HRMS: calcd. for $\text{C}_{36}\text{H}_{57}\text{N}_3\text{O}_7\text{S}$ [$\text{M} + \text{H}$] $^+$ 676.3995; found 676.3403.

9i: Oil, yield 255 mg, 82%. [a] $_D = -7.2$ ($c = 0.5$, CDCl_3). IR (neat): $\tilde{\nu} = 2917$, 1543, 1467, 835, 748 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 7.98$ (dd, $J = 7.5$, 2 Hz, 1 H), 7.86 (dd, $J = 8$, 2 Hz, 1 H), 7.67 (m, 2 H), 7.35–7.20 (m, 5 H), 6.02 (br., 1 H, NHSO_2), 4.15 (dd, $J = 6.5$, 4.5 Hz, 1 H), 3.85 (m, 2 H), 3.69 (d, $J = 15.5$ Hz, 1 H), 3.34 (m, 1 H), 3.01 (dd, $J = 14.5$, 8.5 Hz, 1 H), 2.74 (dd, $J = 14.5$, 6 Hz, 1 H), 1.40 (m, 2 H), 1.30 (s, 3 H), 1.28 (m, 24 H), 1.15 (s, 9 H), 1.11 (s, 3 H), 0.90 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.7$, 141.3, 135.7, 132.9, 132.6, 130.1, 128.4 (2 C), 128.1 (2 C), 126.7, 125.0, 107.3, 77.0, 76.7, 56.0, 55.4, 53.9, 51.1,

31.9, 30.2, 29.6–29.3 (9 C), 27.3 (3 C), 26.9, 26.6, 25.1, 22.7, 14.1 ppm. HRMS: calcd. for $\text{C}_{38}\text{H}_{61}\text{N}_3\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 688.4359; found 688.4347.

(S)-2-Azido-1-[(4S,5R)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl]-N-(o-nosyl)ethanamine (9j): NaN_3 (97 mg, 1.5 mmol) was added portionwise to a stirred solution of the corresponding *N*-(*o*-nosyl)-aziridine **6** (0.15 mmol) in 9:1 MeOH/ H_2O (10 mL). The mixture was stirred at reflux temperature for 16 h. Then saturated aqueous NaHCO_3 (30 mL) was added and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic extracts were dried with MgSO_4 , filtered and the solvents were evaporated under reduced pressure. The crude product was purified by chromatography on 4:1 hexane/EtOAc to give **9j** (72 mg, 85%) as a colourless oil: [a] $_D = +11$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3331$, 2924, 2853, 2105, 1542, 1420, 1355, 1171, 1060, 758 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.16$ (m, 1 H), 7.95 (m, 1 H), 7.77 (m, 2 H), 5.72 (d, $J = 10$ Hz, 1 H), 4.17 (m, 1 H), 4.03 (dd, $J = 8$, 6 Hz, 1 H), 3.80 (m, 1 H), 3.58 (dd, $J = 12.8$, 4.4 Hz, 1 H), 3.27 (dd, $J = 12.8$, 3.2 Hz, 1 H), 1.55 (m, 2 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 1.25 (m, 24 H), 0.87 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.6$, 135.5, 133.7, 133.2, 130.1, 125.8, 108.3, 77.4, 76.5, 53.8, 52.6, 31.9, 29.7–29.1 (10 C), 27.7, 26.5, 25.4, 22.7, 14.1 ppm. HRMS: calcd. for $\text{C}_{27}\text{H}_{46}\text{N}_5\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 568.3169; found 568.3181.

(S)-3-[(4S,5R)-2,2-Dimethyl-5-tetradecyl-1,3-dioxolan-4-yl]-3-[(o-nosyl)aminol]propanenitrile (9k): NaCN (73 mg, 1.5 mmol) was added portionwise to a stirred solution of *N*-(*o*-nosyl)aziridine **6** (0.15 mmol) in CH_3CN (10 mL) and the mixture was stirred at reflux temperature for 20 h. Saturated aqueous NaHCO_3 (30 mL) was then added and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layers were dried with MgSO_4 , filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 5:1) to give **9k** (60 mg, 87%) as a colourless oil. [a] $_D = +9.3$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3213$, 2917, 2835, 2124, 1536, 1171, 916 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 8.17$ (m, 1 H), 7.93 (m, 1 H), 7.77 (m, 2 H), 5.80 (d, $J = 8.8$ Hz, 1 H), 4.19 (m, 1 H), 4.13 (t, $J = 6$ Hz, 1 H), 3.94 (m, 1 H), 2.72 (dd, $J = 17.2$, 5.6 Hz, 1 H), 2.63 (dd, $J = 17.2$, 4 Hz, 1 H), 1.49 (m, 2 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 1.25 (m, 24 H), 0.87 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 147.6$, 134.9, 134.0, 133.3, 130.2, 125.8, 116.4, 108.7, 77.7, 77.1, 51.2, 31.9, 29.7–29.1 (10 C), 27.3, 26.6, 25.1, 22.7, 21.9, 14.1 ppm. HRMS: calcd. for $\text{C}_{28}\text{H}_{45}\text{N}_5\text{O}_6\text{S}$ [$\text{M} + \text{H}$] $^+$ 552.3107; found 552.3123.

General Procedure for Nosylate Removal: Thiophenol (0.8 mmol) and Cs_2CO_3 (0.6 mmol) were successively added to a stirred solution of the corresponding nosylate (0.2 mmol) in dry CH_3CN (2 mL). After stirring at room temperature for 24 h, saturated aqueous NaHCO_3 (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 . The combined organic extracts were dried with MgSO_4 , filtered and the solvents were evaporated under reduced pressure. The resulting crudes were purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 99:1).

10e: Oil, yield 86 mg, 75%. [a] $_D = -5$ ($c = 1$, CDCl_3). IR (neat): $\tilde{\nu} = 3381$, 2920, 2841, 1495, 1043, 769 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 7.36$ (m, 10 H), 7.15 (t, $J = 7.5$ Hz, 2 H), 6.79 (t, $J = 7$ Hz, 1 H), 6.58 (d, $J = 7.6$ Hz, 2 H), 4.80–4.59 (m, 4 H), 3.75 (m, 1 H), 3.55 (t, $J = 4$ Hz, 1 H), 3.43 (dd, $J = 12.5$, 7.5 Hz, 1 H), 3.22 (m, 1 H), 3.10 (dd, $J = 13$, 7.5 Hz, 1 H), 1.80–1.44 (m, 5 H), 2 CH, 3 NH), 1.29 (m, 24 H), 0.90 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 148.6$, 138.4, 138.3, 128.1 (2 C), 128.4 (2 C), 128.3 (2 C), 128.0 (2 C), 127.8 (2 C), 127.7, 127.6, 117.1, 113.0

(2 C), 83.3, 78.5, 73.6, 72.0, 51.7, 47.2, 31.9, 30.5, 29.8–29.3 (9 C), 25.6, 22.6, 14.1 ppm. HRMS: calcd. for $C_{38}H_{56}N_2O_2$ $[M + H]^+$ 573.4465; found 573.4439.

10f: Oil, yield 94 mg, 83%. $[a]_D = -14$ ($c = 1$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3395, 2921, 2839, 1499, 1245, 867\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (m, 10 H), 4.78–4.54 (m, 4 H), 3.68 (m, 5 H), 3.50 (m, 1 H), 3.16 (m, 1 H), 2.61 (dd, $J = 12.4, 2.8$ Hz, 1 H), 2.54 (m, 2 H), 2.30 (m, 3 H), 2.02 (br., 2 H), 1.73–1.49 (m, 4 H), 1.26 (m, 22 H), 0.89 (t, $J = 7.2$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.6, 138.5, 128.3$ (4 C), 127.9 (2 C), 127.8 (2 C), 127.6, 127.5, 82.8, 79.8, 73.7, 71.8, 67.0 (2 C), 61.8 (2 C), 53.9, 48.8, 31.9, 30.5, 29.8–29.3 (9 C), 25.7, 22.6, 14.1 ppm. HRMS: calcd. for $C_{36}H_{58}N_2O_3$ $[M + H]^+$ 567.4550; found 567.4526.

11e: Oil, yield 68 mg, 79%. $[a]_D = +10$ ($c = 1$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3581, 3386, 2918, 2847, 1499, 1220, 1054, 867\text{ cm}^{-1}$. 1H NMR (500 MHz, $CDCl_3$): $\delta = 7.20$ (t, $J = 7.5$ Hz, 2 H), 6.71 (m, 3 H), 4.19 (m, 1 H), 3.90 (dd, $J = 8, 5.5$ Hz, 1 H), 3.50 (m, 1 H), 3.10 (m, 2 H), 1.58 (m, 2 H), 1.48 (s, 3 H), 1.37 (s, 3 H), 1.27 (m, 24 H), 0.90 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.5, 129.2$ (2 C), 117.4, 113.1 (2 C), 108.1, 80.9, 77.8, 49.9, 48.5, 31.8, 29.8–29.3 (10 C), 28.3, 26.1, 25.9, 22.7, 14.1 ppm. HRMS: calcd. for $C_{27}H_{48}N_2O_2$ $[M + H]^+$ 433.3725; found 433.3741.

11f: Oil, yield 75 mg, 88%. $[a]_D = -7$ ($c = 0.5$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3541, 3363, 2915, 2858, 1448, 1368, 1223, 1012\text{ cm}^{-1}$. 1H NMR (500 MHz, $CDCl_3$): $\delta = 4.15$ (m, 1 H), 3.79 (m, 1 H), 3.72 (m, 4 H), 3.04 (m, 1 H), 2.62 (m, 3 H), 2.40 (m, 2 H), 2.30 (m, 1 H), 1.98 (br., 2 H, NH_2), 1.52 (m, 2 H), 1.41 (s, 3 H), 1.31 (s, 3 H), 1.24 (m, 24 H), 0.87 (t, $J = 7.5$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 108.1, 81.2, 78.1, 67.3$ (2 C), 62.8, 54.3, 47.0 (2 C), 32.1, 30.1–29.3 (10 C), 28.2, 26.2, 25.8, 22.6, 14.1 ppm. HRMS: calcd. for $C_{25}H_{50}N_2O_2$ $[M + H]^+$ 427.3817; found 427.3825.

11g: Oil, yield 74 mg, 90%. $[a]_D = +4$ ($c = 1$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3581, 3377, 2927, 2851, 1450, 1374, 1227, 1054\text{ cm}^{-1}$. 1H NMR (500 MHz, $CDCl_3$): $\delta = 4.14$ (m, 1 H), 3.76 (t, $J = 7$ Hz, 1 H), 3.65 (q, $J = 7.5$ Hz, 1 H), 2.67 (d, $J = 5$ Hz, 2 H), 2.59 (d, $J = 5$ Hz, 2 H), 2.50 (m, 2 H), 1.89 (br., 2 H, NH_2), 1.77 (m, 4 H), 1.53 (m, 2 H), 1.41 (s, 3 H), 1.31 (s, 3 H), 1.24 (m, 24 H), 0.88 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 107.6, 81.1, 77.9, 60.2, 55.2$ (2 C), 48.8, 31.8, 29.7–29.2 (10 C), 28.1, 26.1, 25.8, 23.4 (2 C), 22.6, 14.0 ppm. HRMS: calcd. for $C_{25}H_{50}N_2O_2$ $[M + H]^+$ 411.3883; found 411.3886.

11h: Oil, yield 77 mg, 79%. $[a]_D = -28$ ($c = 1$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3573, 3367, 2923, 1494, 1365, 665\text{ cm}^{-1}$. 1H NMR (500 MHz, $CDCl_3$): $\delta = 7.35$ (m, 5 H), 4.12 (m, 1 H), 3.84 (m, 2 H), 3.69 (m, 1 H), 3.63 (m, 2 H), 3.29 (br., 3 H), 3.00 (m, 1 H), 2.81 (m, 2 H), 2.63 (dt, $J = 13.5, 3.5$ Hz, 1 H), 2.55 (dd, $J = 13, 9.5$ Hz, 1 H), 1.51 (m, 2 H), 1.40 (s, 3 H), 1.28 (m, 27 H), 0.90 (t, $J = 7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.0, 128.9$ (2 C), 128.4 (2 C), 127.2, 108.0, 80.3, 77.7, 60.0, 59.8, 57.7, 56.6, 48.7, 31.9, 29.6–29.3 (10 C), 27.9, 26.2, 25.7, 22.6, 14.1 ppm. HRMS: calcd. for $C_{30}H_{54}N_2O_3$ $[M + H]^+$ 491.4143; found 491.4139.

11i: Oil, yield 83 mg, 83%. $[a]_D = +16$ ($c = 0.5$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3378, 2915, 2843, 1494, 998, 874\text{ cm}^{-1}$. 1H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (m, 5 H), 4.02 (m, 1 H), 3.98 (d, $J = 15$ Hz, 1 H), 3.65 (dd, $J = 8.1, 5.7$ Hz, 1 H), 3.46 (d, $J = 15$ Hz, 1 H), 2.82 (dd, $J = 13, 2.4$ Hz, 1 H), 2.59–2.41 (m, 2 H), 1.63 (br., 2 H), 1.45–1.30 (m, 2 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 1.26 (m, 24 H), 1.16 (s, 9 H), 0.88 (t, $J = 6.9$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.2, 128.1$ (2 C), 127.9 (2 C), 126.4, 107.6, 81.1, 78.0, 55.8 (2 C), 55.4, 49.0, 31.9, 29.7–29.3 (10 C), 28.2, 27.5 (3 C), 26.1, 25.9,

22.7, 14.1 ppm. HRMS: calcd. for $C_{32}H_{58}N_2O_2$ $[M + H]^+$ 503.4491; found 503.4501.

(S)-2-Azido-1-[(4S,5R)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl]-ethanamine (16): NaN_3 (325 mg, 5 mmol) was added portionwise to a stirred solution of **5** (179 mg, 0.5 mmol) in 2-ethoxyethanol (10 mL). The reaction mixture was heated at reflux temperature for 18 h. Then brine (30 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The residue was purified by chromatography on hexane/EtOAc (1:1) to give **16** (133 mg, 70%) as a colourless oil. $[a]_D = +19$ ($c = 1$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3421, 2916, 2124, 1465, 1172, 961\text{ cm}^{-1}$. 1H NMR (400 MHz, $CDCl_3$): $\delta = 4.16$ (m, 1 H), 3.84 (dd, $J = 9.2, 6$ Hz, 1 H), 3.56 (dd, $J = 12.4, 2.8$ Hz, 1 H), 3.44 (dd, $J = 12.4, 6.4$ Hz, 1 H), 2.97 (m, 1 H), 1.50 (m, 2 H), 1.40 (s, 3 H), 1.32 (s, 3 H), 1.24 (m, 24 H), 0.87 (t, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 108.1, 79.0, 77.7, 56.5, 50.3, 31.9, 29.7$ – 29.3 (10 C), 28.2, 26.1, 25.8, 22.7, 14.1 ppm.

General Procedure for N-Acylation: Et_3N (0.3 mmol) and the acid chloride (0.18 mmol) was added to a solution of the corresponding amine (0.15 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 1 h. Then saturated $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The organic layers were dried with $MgSO_4$ and the solvents evaporated at reduce pressure to give the crude amides, which were purified by column chromatography (hexanes/EtOAc, 3:1).

13a: Oil, yield 73 mg, 83%. $[a]_D = +27$ ($c = 0.5$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3523, 3354, 2926, 2863, 1557, 1451, 1312, 1231, 1009\text{ cm}^{-1}$. 1H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (m, 5 H), 5.91 (d, $J = 6.3$ Hz, 1 H), 4.32 (dd, $J = 6.6, 5.1$ Hz, 1 H), 4.02 (m, 1 H), 3.99 (d, $J = 16$ Hz, 1 H), 3.54 (d, $J = 16$ Hz, 1 H), 3.53 (m, 1 H), 3.07 (dd, $J = 14.4, 8.7$ Hz, 1 H), 2.63 (dd, $J = 14.1, 3.9$ Hz, 1 H), 1.45 (s, 3 H), 1.40–1.30 (m, 2 H), 1.25 (m, 27 H), 1.14 (s, 9 H), 1.11 (s, 9 H), 0.88 (t, $J = 6.9$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.9, 142.9, 128.2$ (2 C), 127.2 (2 C), 126.4, 107.5, 77.6, 77.2, 55.8, 55.6, 50.7, 49.4, 38.6, 31.9, 30.2, 29.6–29.3 (9 C), 27.4 (3 C), 27.3 (3 C), 27.1, 26.5, 25.3, 22.7, 14.1 ppm. HRMS: calcd. for $C_{37}H_{66}N_2O_3$ $[M + H]^+$ 587.5069; found 587.5073.

13b: Oil, yield 77 mg, 82%. $[a]_D = +21$ ($c = 0.5$, $CDCl_3$). IR (neat): $\tilde{\nu} = 3527, 3373, 2919, 2849, 1562, 1475, 1221, 987\text{ cm}^{-1}$. 1H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$ (m, 5 H), 5.42 (d, $J = 7.2$ Hz, 1 H), 4.22 (t, $J = 6$ Hz, 1 H), 4.01 (m, 1 H), 3.85 (d, $J = 15.6$ Hz, 1 H), 3.64 (m, 1 H), 3.62 (d, $J = 15.6$ Hz, 1 H), 2.94 (dd, $J = 14.4, 8.7$ Hz, 1 H), 2.74 (dd, $J = 14.4, 3.9$ Hz, 1 H), 1.92 (m, 2 H), 1.66–1.45 (m, 2 H), 1.43 (s, 3 H), 1.25 (m, 37 H), 1.13 (s, 9 H), 0.88 (t, $J = 7$ Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.8, 142.0, 128.3$ (2 C), 127.8 (2 C), 126.7, 107.6, 77.6, 77.4, 56.2, 55.8, 50.6, 49.4, 36.7, 31.8, 31.6, 29.7–29.5 (9 C), 29.3, 29.2, 29.0, 27.3, 27.2 (3 C), 26.4, 25.5, 25.3, 22.6 (2 C), 14.1 (2 C) ppm. HRMS: calcd. for $C_{40}H_{72}N_2O_3$ $[M + H]^+$ 629.5549; found 629.5545.

Synthesis of Phytosphingosines and Phytoceramides

Method A: A solution of the corresponding amine (0.1 mmol) in CH_2Cl_2 (2 mL) at -78°C was treated with BCl_3 (1 M) in heptane (2 equiv/mol for each OBn group). The reaction mixture was warmed to room temp. and stirred for an additional 16 h. The mixture was next cooled to -78°C and quenched with methanol (2 mL). The solvents were then removed under reduced pressure and EtOAc (3 mL) was next added to the oily residue. The mixture was sonicated in an ultrasonic bath for 5 min and the suspended solid was collected by filtration.

Method B: A solution of the corresponding 1-aminophytosphingosine derivative (0.1 mmol) in CH₃OH (2 mL) and conc. HCl (5 drops) was stirred for 24 h at room temperature. Then the solvent was evaporated in vacuo to afford the target compounds.

Method C: A solution of the corresponding 1-aminophytosphingosine derivative (0.1 mmol) in CH₃OH (5 mL) and concd. aqueous HCl (5 drops) was stirred under H₂ (2 atm) in the presence of 5% Pd-C (20 mg) for 24 h. Then the reaction mixture was filtered through a pad of Celite®, filtered and evaporated in vacuo to afford the target compounds.

12e: Oil, yield 46 mg, 99% (Method B); 36 mg, 78% (Method A). [α]_D = −20 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3365, 2913, 1116, 712 cm^{−1}. ¹H NMR (MeOH, 500 MHz): δ = 7.45 (m, 4 H), 7.36 (m, 1 H), 3.84 (m, 1 H), 3.73 (m, 2 H), 3.65 (m, 1 H), 3.56 (dd, *J* = 13.5, 4.5 Hz, 1 H), 1.60 (m, 1 H), 1.45 (m, 1 H), 1.18 (m, 24 H), 0.79 (t, *J* = 6.5 Hz, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 138.6, 132.3 (2 C), 131.1, 124.0 (2 C), 74.9, 74.7, 52.1, 52.0, 35.5, 33.9, 31.6–31.3 (9 C), 27.5, 24.5, 15.3 ppm. HRMS: calcd. for C₂₄H₄₄N₂O₂ [M + H]⁺ 393.3511; found 393.3491.

12f: Oil, yield 45 mg, 99% (Method B); 40 mg, 89% (Method A). [α]_D = −24 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3376, 2922, 2842, 1116 cm^{−1}. ¹H NMR (400 MHz, MeOH): δ = 4.10 (m, 1 H), 3.97 (m, 5 H), 3.66 (m, 2 H), 3.56–3.20 (m, 7 H), 1.74 (m, 1 H), 1.55 (m, 1 H), 1.27 (m, 24 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 75.4, 74.0, 66.0 (2 C), 57.6 (2 C), 50.4, 50.3, 36.0, 33.9, 31.6–31.3 (9 C), 27.2, 24.5, 15.3 ppm. HRMS: calcd. for C₂₂H₄₆N₂O₃ [M + H]⁺ 387.3581; found 387.3587

12g: Oil, yield 44 mg, 99% (Method B). [α]_D = +3 (*c* = 0.5, MeOH). IR (neat): $\tilde{\nu}$ = 3381, 2927, 2825, 1227 cm^{−1}. ¹H NMR (400 MHz, MeOH): δ = 3.90 (t, *J* = 3 Hz, 1 H), 3.77 (m, 1 H), 3.67 (m, 2 H), 3.65 (m, 2 H), 3.57 (dd, *J* = 8.5, 3.5 Hz, 1 H), 3.50 (m, 1 H), 3.42 (dd, *J* = 14, 7 Hz, 1 H), 3.12 (m, 2 H), 2.11 (m, 2 H), 1.99 (m, 2 H), 1.69 (m, 1 H), 1.48 (m, 1 H), 1.24 (m, 24 H), 0.81 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 75.2, 74.0, 57.4, 56.2, 55.3, 52.6, 36.1, 33.9, 31.6–31.3 (9 C), 27.2, 25.0, 24.9, 24.5, 15.3 ppm. HRMS: calcd. for C₂₂H₄₆N₂O₂ [M + H]⁺ 371.3564; found 371.3567

12h: Oil, yield 42 mg, 97% (Method C). [α]_D = −6 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3532, 2482, 1970, 1436, 911 cm^{−1}. ¹H NMR (500 MHz, MeOH): δ = 3.85 (br., 1 H), 3.80 (br., 2 H), 3.76 (br., 1 H), 3.67 (br., 1 H), 3.55 (d, *J* = 9 Hz, 1 H), 3.36 (d, *J* = 10.5 Hz, 1 H), 3.19 (br., 2 H), 1.63 (m, 1 H), 1.53 (m, 1 H), 1.25 (m, 24 H), 0.86 (t, *J* = 7.2 Hz, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 74.8, 74.6, 58.6, 52.5, 51.8, 48.0, 35.5, 33.9, 31.6–31.3 (9 C), 27.5, 24.5, 15.3 ppm. HRMS: calcd. for C₂₀H₄₄N₂O₃ [M + H]⁺ 361.3349; found 361.3346.

12i: Oil, yield 37 mg, 82% (Method C). [α]_D = +10 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3412, 2923, 1454, 1041 cm^{−1}. ¹H NMR (500 MHz, MeOH): δ = 3.84 (br., 1 H), 3.77 (br. d, *J* = 4.5 Hz, 1 H), 3.68 (br. m, 1 H), 3.50 (br. d, *J* = 10 Hz, 1 H), 3.25 (br. d, *J* = 10 Hz, 1 H), 1.65 (m, 1 H), 1.55 (m, 1 H), 1.42 (s, 9 H), 1.27 (m, 24 H), 0.87 (t, *J* = 7 Hz, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 74.7 (2 C), 60.2, 52.8, 42.0, 35.6, 33.7, 31.5–31.4 (8 C), 31.1, 27.4, 26.8 (3 C), 24.4, 15.1 ppm. HRMS: calcd. for C₂₂H₄₈N₂O₂ [M + H]⁺ 373.3725; found 373.3733

15a: Oil, yield 41 mg, 89%. [α]_D = +5 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3583, 3415, 2921, 2482, 1596, 1461 cm^{−1}. ¹H NMR (500 MHz, MeOH) (mixture of rotamers): δ = 5.01–5.02 (m, 1 H), 4.30–3.83 (m, 1 H), 3.63 (m, 2 H), 3.36 (m, 1 H), 3.09 (m, 1 H), 1.60–1.20 (m, 46 H), 0.90 (m, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 183.1, 77.1, 74.7, 59.2, 51.4, 45.2, 40.7, 34.8, 33.8, 31.5–31.1 (9 C),

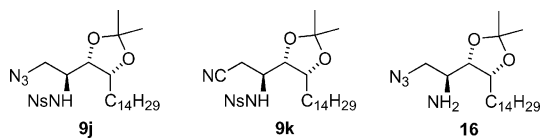
28.6 (3 C), 28.5, 28.4, 27.6, 26.8 (3 C), 24.4, 15.1 ppm. HRMS: calcd. for C₂₇H₅₆N₂O₃ [M + H]⁺ 457.4301; found 457.4307.

15b: Oil, yield 45 mg, 90%. [α]_D = +5 (*c* = 1, MeOH). IR (neat): $\tilde{\nu}$ = 3521, 2411, 2934, 1428 cm^{−1}. ¹H NMR (500 MHz, MeOH, 55 °C): δ = 5.01 (m, 1 H), 3.95 (d, *J* = 7.5 Hz, 1 H), 3.76 (d, *J* = 8.5 Hz, 1 H), 3.59 (d, *J* = 14 Hz, 1 H), 3.33 (m, 2 H), 2.44 (m, 2 H), 1.68–1.30 (m, 51 H), 0.91 (m, 3 H) ppm. ¹³C NMR (100 MHz, MeOH): δ = 176.1, 75.1, 73.8, 61.0, 52.5, 42.2, 36.3, 33.7, 33.6, 32.8, 31.5–30.8 (9 C), 26.8 (7 C), 24.4 (2 C), 15.1 (2 C) ppm. HRMS: calcd. for C₃₀H₆₂N₂O₃ [M + H]⁺ 499.4759; found 499.4762.

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