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Regioselective Inversion of the Hydroxyl Group in D-*ribo*-Phytosphingosine via a Cyclic Sulfate and Bis-Sulfonate Intermediate

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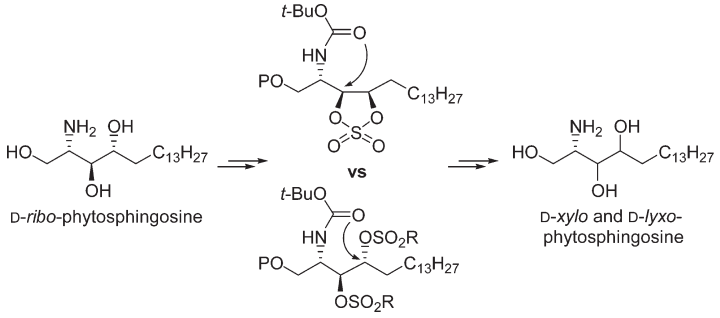

The selective synthesis of D-*xylo*- and D-*lyxo*-phytosphingosines from commercially available D-*ribo*-phytosphingosine is described. Thermolysis of the *N*-carbonyl protected cyclic sulfate led to an inversion of configuration of the proximal hydroxyl group to give the *xylo*-isomer, whereas the corresponding bis-sulfonate resulted in an inversion of configuration of the distal hydroxyl group to give the *lyxo*-isomer. This study allowed the comparison between a cyclic sulfate and a bis-sulfonate in an intramolecular substitution reaction involving a carbonyl oxygen nucleophile.

Introduction

The 1-amino-2,3-diol subunit is found in many natural and synthetic compounds with a wide range of interesting bioactivities.[1] Consequently, efficient routes for the stereoselective preparation of this subunit are of continuing interest and significant value. To establish the desired stereochemistry of consecutive stereocenters of vicinal amino diols, most syntheses rely on chiral pools, such as carbohydrates and amino acids, or asymmetric induction, such as Sharpless asymmetric dihydroxylation and aminohydroxylation.[2] Depending on the target, substrate- or reagent-controlled diastereo- and enantioselective reactions can be additionally applied to install the remaining stereocenters of the vicinal amino diol moiety. However, these strategies sometimes suffer from low selectivity due to a mismatch in asymmetric induction between the substrate control and reagent control. Thus, in some cases, the selective configurational inversion of a hydroxyl group of the 1-amino-2,3-diol is necessary. The selective configurational inversion of such a hydroxyl group has been well studied in cyclic systems. However, it has been less widely explored in acyclic systems.[3]

Phytosphingosines are long-chain, aliphatic natural compounds possessing a 1-amino-2,3-diol subunit. They are the principal structural backbone of biologically important sphingolipids and are widely distributed in plants, yeasts,

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(1) For selected examples, see: (a) Rosenberg, S. H.; et al. *J. Med. Chem.* **1993**, *36*, 449–459. (b) Ocain, T. D.; Abou-Gharbia, M. *Drugs Future* **1991**, *16*, 37–51. (c) Greenlee, W. J.; Siegl, P. K. S. *Annu. Rep. Med. Chem.* **1991**, *26*, 63–72. (d) Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173–236.

(2) For selected examples, see: (a) Enomoto, M.; Kuwahara, S. *J. Org. Chem.* **2009**, *74*, 7566–7569. (b) Zhou, X.; Liu, W.-J.; Ye, J.-L.; Huang, P.-Q. *J. Org. Chem.* **2007**, *72*, 8904–8909. (c) Patel, S. K.; Murat, K.; Py, S.; Vallée, Y. *Org. Lett.* **2003**, *5*, 4081–4084. (d) Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poe, R. W.; Sobieray, D. M.; Vusse, J. V. D. *J. Org. Chem.* **1996**, *61*, 9564–9568. (e) Chan, M. F.; Hsiao, C.-N. *Tetrahedron Lett.* **1992**, *33*, 3567–3570.

(3) For selected examples, see: (a) Curti, C.; Zanardi, F.; Battistini, L.; Sartori, A.; Rassu, G.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2006**, *71*, 8552–8558. (b) Dong, H.; Pei, Z.; Ramström, O. *J. Org. Chem.* **2006**, *71*, 3306–3309. (c) Chang, C.-W. T.; Hui, Y.; Elchert, B. *Tetrahedron Lett.* **2001**, *42*, 7019–7023. (d) Weinges, K.; Haremsa, S.; Maurer, W. *Carbohydr. Res.* **1987**, *164*, 453–458. (e) Lattrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901–920.

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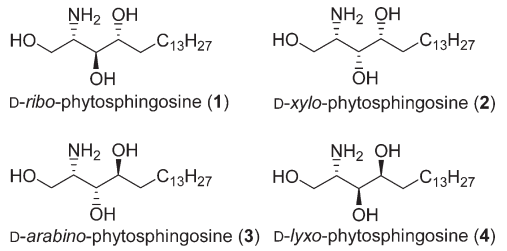


FIGURE 1. D-*ribo*-Phytosphingosine (**1**) and its stereoisomers **2**−**4**.

fungi, and even mammalian tissues.[4] In nature, the most predominant stereoisomer of phytosphingosines is D-*ribo*-phytosphingosine (**1**, Figure 1). The growing interest in the biological functions of sphingolipids has generated a need to develop efficient methods for the preparation of D-*ribo*-phytosphingosine (**1**) and other stereoisomers, such as D-*xylo*- (**2**), D-*arabino*- (**3**), and D-*lyxo*-phytosphingosines (**4**), which are shown in Figure 1.[5,6]

In this regard, we have previously reported a high-yield approach to the stereoselective synthesis of D-*xylo*-, D-*arabino*-, and D-*lyxo*-phytosphingosines from inexpensive D-*ribo*-phytosphingosine (**1**).[7] Our synthetic strategy was not based on stereochemical induction; it was rather based on a selective configurational inversion of pre-existing stereocenters. The hydroxyl group of phytosphingosines was inverted via the regioselective activation/acylation of vicinal hydroxyl groups and a neighboring-group participation. The amino group was protected as a non-nucleophilic azide to avoid complications caused by multiple anchimeric assistances during the inversion of activated hydroxyl groups.

Results and Discussion

In the course of our ongoing sphingolipid research, we have explored an alternative and efficient route for the transformation of cheap, commercially available D-*ribo*-phytosphingosine (**1**) into other stereoisomers. As shown in Figure 2, our new strategy is based on the use of a cyclic sulfate **5** or bis-sulfonate **6** for the activation of the vicinal hydroxyl groups of **1**. One of the advantages of this approach is that a selective activation of only one vicinal hydroxyl group is not required. For the regioselective configurational inversion of activated hydroxyl groups, we decided to utilize nucleophilic amino protecting groups, such as carbamates, to allow a nucleophilic intramolecular substitution at C-3 or C-4.

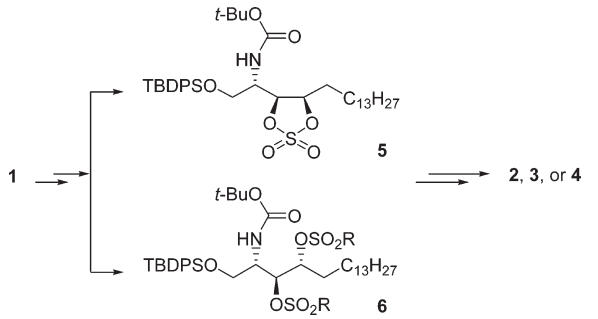


FIGURE 2. Synthesis of stereoisomers of D-*ribo*-phytosphingosine (**1**) via a cyclic sulfate or a bis-sulfonate.

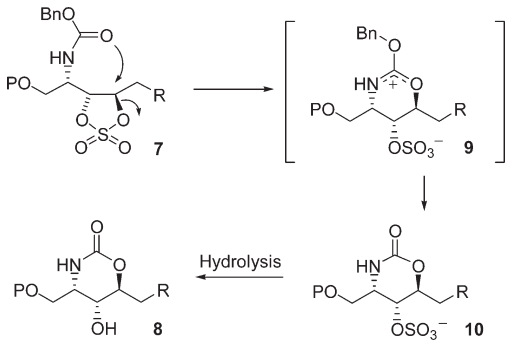


FIGURE 3. Pedersen's inversion of a hydroxyl group in *xylo*-phytosphingosine via a cyclic sulfate.

In fact, Pedersen and co-workers have previously reported a similar approach; a cyclic sulfate was used for the configurational inversion of hydroxyl groups in vicinal amino diols.[8] As shown in Figure 3, the Cbz-protected *xylo*-phytosphingosine was converted into its stereoisomer via a cyclic sulfate intermediate with the aid of a carbamate protecting group. Thermolysis of the cyclic sulfate **7** in acetonitrile led to an inversion of configuration of the distal hydroxyl group to form a 1,3-oxazinan-2-one **8**. As discussed by Pedersen, the thermolytic formation of the oxazinanone **8** proceeded via an initial nucleophilic substitution of the cyclic sulfate function by the oxygen atom of the carbamate to give the intermediate oxonium ion **9**, followed by an irreversible fragmentation step that led to the oxazinanone sulfate **10**. Hydrolysis of the sulfate ester group of **10** finally afforded **8**.

Conceptually, the nucleophilic carbonyl of the carbamate in the *ribo*-phytosphingosine-derived cyclic sulfate **5** could attack either the C-3 or C-4 position to give the 5-membered oxazolidinone **11** or the 6-membered oxazinanone **12**, respectively (Figure 4). On the basis of the literature demonstrating the rearrangement of cyclic sulfate **13** into more stable isomeric cyclic sulfate **15** via hemisulfate anion/oxonium intermediate **14** (Figure 5),[9] we speculated that the first nucleophilic substitution

(4) (a) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715–4733. (b) Muralidhar, P.; Radhika, P.; Krishna, N.; Rao, D. V.; Rao, Ch. B. *Nat. Prod. Sci.* **2003**, *9*, 117–142. (c) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365–391.

(5) Selected publications for recent syntheses of phytosphingosines, see: (a) Liu, Z.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2010**, *75*, 4356–4364. (b) Pandey, G.; Tiwari, D. K. *Tetrahedron Lett.* **2009**, *50*, 3296–3298. (c) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844–6848. (d) Yoon, H. J.; Kim, Y.-W.; Lee, B. K.; Lee, W. K.; Kim, Y.; Ha, H.-J. *Chem. Commun.* **2007**, 79–81. (e) Righi, G.; Ciambrone, S.; Achille, C. D.; Leonelli, A.; Bonini, C. *Tetrahedron* **2006**, *62*, 11821–11826. (f) Lombardo, M.; Capdevila, M. G.; Pasi, F.; Trombini, C. *Org. Lett.* **2006**, *8*, 3303–3305. (g) Lu, X.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2004**, *65*, 5433–5438. (h) Raghavan, S.; Rajender, A. *J. Org. Chem.* **2003**, *68*, 7094–7097. (i) Ndakala, A. J.; Hashemzadeh, M.; So, R. C.; Howell, A. R. *Org. Lett.* **2002**, *4*, 1719–1722.

(6) For the synthesis of more than one stereoisomer of phytosphingosine, see: (a) Dubey, A.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 3425–3427. (b) Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Org. Lett.* **2009**, *11*, 205–208. (c) Enders, D.; Paleček, J.; Grondal, C. *Chem. Commun.* **2006**, 655–657. (d) Cai, Y.; Ling, C. C.; Bundle, D. R. *Org. Biomol. Chem.* **2006**, *4*, 1140–1146. (e) Lu, X.; Bittman, R. *Tetrahedron Lett.* **2005**, *46*, 3165–3168. (f) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618–7626. (g) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657–10670.

(7) Kim, S.; Lee, N.; Lee, S.; Lee, T.; Lee, Y. M. *J. Org. Chem.* **2008**, *73*, 1379–1385.

(8) Kemp, S. J.; Bao, J.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 7162–7167.

(9) Leurquin, F.; Ozturk, T.; Pilkington, M.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3173–3177.

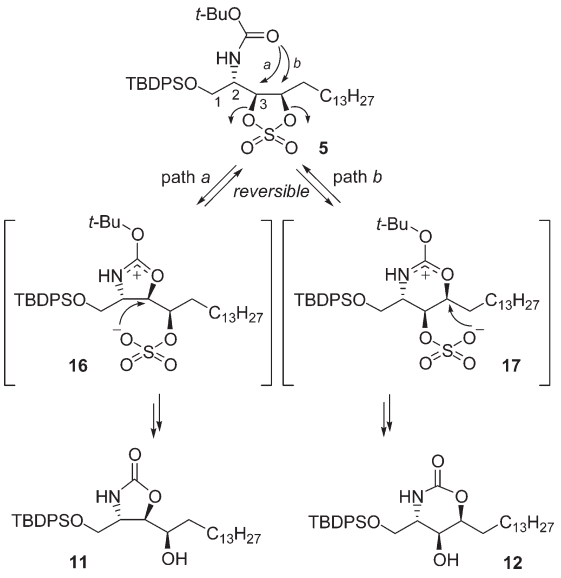


FIGURE 4. Plan for inversion of the hydroxyl groups in *ribo*-phytosphingosine via a cyclic sulfate.

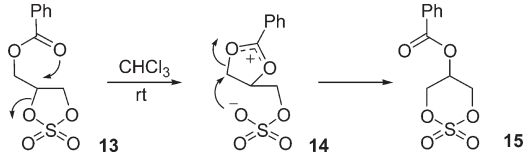


FIGURE 5. Rearrangement of cyclic sulfate **13** to the six-membered isomeric cyclic sulfate **15**.[9]

step of **5** could be reversible leading to the thermodynamically more stable oxonium intermediate.

Our computational studies suggested that the oxazolidinone yielding intermediate **16** is more stable than the oxazinanone yielding intermediate **17**. Density functional calculations at the PBE/DNP level on the truncated system of **16** and **17**, shown in Figure 6 as **A** and **B**, respectively, revealed that **A** is more stable than **B** by 0.9 kcal/mol. In the case of the cyclic sulfate **7** derived from the *xylo*-isomer, calculations on the modified systems **C** and **D** indicated that the oxazolidinone yielding intermediate **C** is less stable than the oxazinanone yielding intermediate **D** by 8.7 kcal/mol. This energy difference correlated well with the result obtained by Pedersen. Thus, we envisioned that the regiochemical outcome of the *ribo*-phytosphingosine-derived cyclic sulfate **5** would be different from that of the *xylo*-phytosphingosine-derived cyclic sulfate **7**; we expected that the cyclic sulfate **5** would mainly be transformed into the 5-membered oxazolidinone **11**.

The known *N*-Boc- and 1-*O*-silyl-protected phytosphingosine **18**[10] was easily prepared from D-*ribo*-phytosphingosine (**1**) with a high overall yield (Scheme 1). The 3,4-vicinal diol **18** was converted into the cyclic sulfate **5** by treatment with thionyl chloride followed by oxidation with $RuCl_3$/$NaIO_4$. The obtained cyclic sulfate **5** was found to be rather unstable and decomposed into a polar material on standing in acetonitrile solution at room temperature; only trace

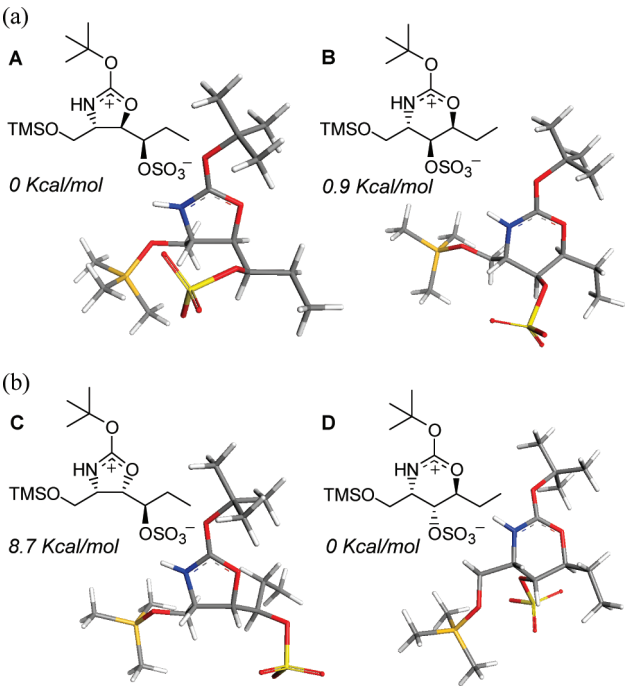


FIGURE 6. Density functional calculations at the PBE/DNP level on the conformers of hemisulfate anion/oxonium intermediates. (a) Truncated systems of the *ribo*-phytosphingosine-derived intermediates **16** and **17**. (b) Modified systems of the *xylo*-phytosphingosine-derived intermediate **9** and its isomeric form.

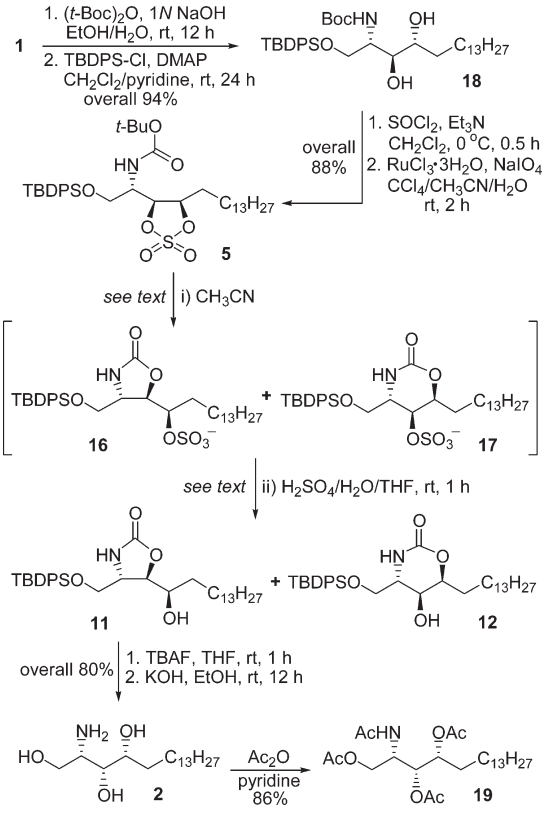
amounts of **5** could be detected after 12 h. The polar material was deduced to be the sulfate esters **16** and/or **17**. Thus, the resulting solution was treated with aqueous H_2SO_4 for hydrolysis of the sulfate ester group. This treatment provided oxazolidinone **11** and oxazinanone **12** in a ratio of 5.1:1 and in 65% yield. When the cyclic sulfate **5** was heated at 45 °C (oil bath temperature) in acetonitrile for 2 h and treated with acid, oxazolidinone **11** and oxazinanone **12** were obtained in a 3.9:1 ratio with a combined yield of 66%. When the solvent was changed to THF (45 °C, 2 h), oxazolidinone **11** was also obtained as a major product along with the minor oxazinanone **12** in a similar ratio (4.8:1) in combined 68% yield. As expected, the observed regioselectivity of the cyclic sulfate **5** during the thermolysis reaction was opposite to that obtained with the cyclic sulfate **7** that was derived from the *xylo*-isomer. Although more systematic studies are needed, these results led us to believe that the different regioselectivities could be due to the stability of the intermediate oxonium ions and a thermodynamic control. The obtained major isomer **11** was deprotected to afford D-*xylo*-phytosphingosine (**2**) in two steps. For analytical reasons, **2** was peracetylated with Ac_2O/pyridine to provide the tetraacetate derivative **19**. The analytical and spectroscopic data of both the synthetic D-*xylo*-phytosphingosine (**2**) and its tetraacetate **19** were in agreement with those reported in the literature.[5b,h,11]

To examine the effect of other amino protecting groups on the regioselectivity and product distribution, a *N*-acetyl-protected cyclic sulfate was examined. For the synthesis of

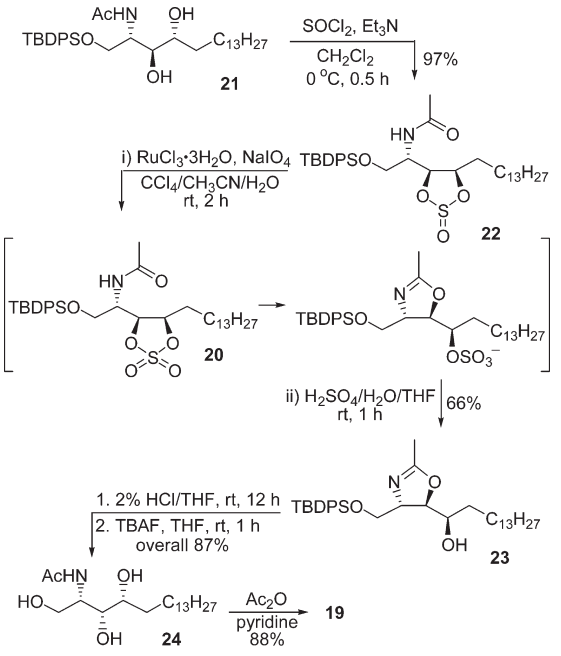
(10) (a) Yoshimitsu, Y.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2010**, *75*, 3843–3846. (b) Veerapen, N.; Leadbetter, E. A.; Brenner, M. B.; Cox, L. R.; Besra, G. S. *Bioconjugate Chem.* **2010**, *21*, 741–747.

(11) (a) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643–13658. (b) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1990**, *11*, 1069–1078.

SCHEME 1. Synthesis of D-*xylo*-Phytosphingosine (2) via Cyclic Sulfate 5

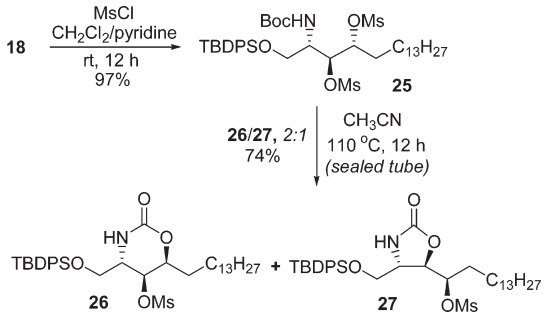


SCHEME 2. Synthesis of *N*-Acetyl D-*xylo*-Phytosphingosine 24



the *N*-acetyl-protected cyclic sulfate **20** (Scheme 2), the 3,4-vicinal diol **21** was first converted into the cyclic sulfite **22** by treatment with thionyl chloride. When the cyclic sulfite **22** was treated with $RuCl_3/NaIO_4$ at room temperature for its oxidation into a cyclic sulfate, it was found that the generated cyclic sulfate was reactive enough to undergo cyclization

SCHEME 3. Synthesis of Oxazinanone 26 and Oxazolidinone 27 via Bis-Mesylate 25



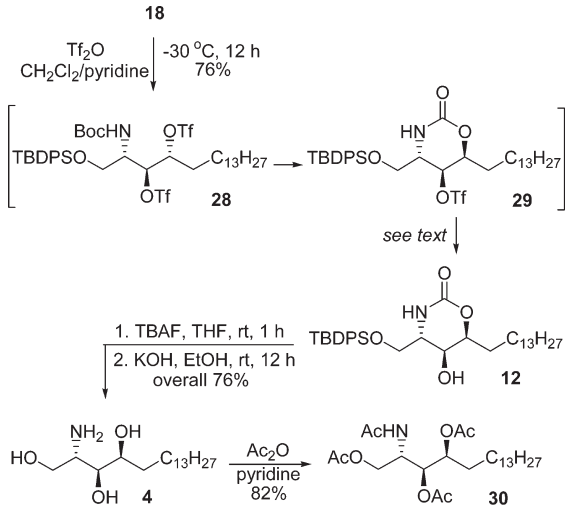
with the electron-rich amide group under the reaction conditions. The only obtained product after acidic hydrolysis was the 5-membered oxazoline **23** (66%). No 6-membered isomer was detected in the crude ^1H NMR spectra. The cyclization followed a pattern similar to that of the *N*-Boc-protected cyclic sulfate **5** in that the 5-membered isomer was preferentially formed over the 6-membered isomer with the configurational inversion occurring at C-3. The exposure of oxazoline **23** to HCl/THF followed by treatment of the resulting compound with Bu_4NF provided the known *N*-acetyl D-*xylo*-phytosphingosine **24**[12] in 87% overall yield. The identity of **24** was further confirmed by its conversion to tetraacetate **19**.

After obtaining the results with the cyclic sulfate, we examined the use of a bis-sulfonate as a diol activating group. Cyclic sulfates and bis-sulfonates could be regarded as synthetic equivalents in that they both activate vicinal hydroxyl groups. However, they could display different chemical behaviors in the substitution reaction with the oxygen atom of a carbonyl group since they could have different transition state conformations and reactivities. We envisaged that the first substitution step of the bis-sulfonate **6** (Figure 2) might be irreversible, unlike that of the cyclic sulfate **5**. In the cyclic sulfate system (Figure 4), the hemisulfate anions **16** and **17**, generated from the cyclic sulfate **5**, could have a great chance to intramolecularly attack the nearby reactive C-3 and C-4 positions to reform the starting compound and thus lead to a thermodynamical equilibrium. On the other hand, in the acyclic bis-sulfonate system, the nucleophilic substitution generates the oxonium ion intermediate and the dissociated sulfonate anion. The two separated species would have a low chance to intermolecularly react with each other to give the starting compound. Thus, its substitution step is less likely reversible and the product would be formed under kinetic control. With these considerations in mind, studies were made to compare the chemistry of a bis-sulfonate with that of its corresponding cyclic sulfate.

First, the vicinal bis-mesylate **25** was prepared from the 3,4-vicinal diol **18** and thermolyzed (Scheme 3). Bis-mesylate **25** was found to be stable during heating; it was even stable in acetonitrile at reflux. Thus, thermolysis of **25** in acetonitrile was conducted in a sealed tube at 110 °C for 12 h. In contrast to the corresponding cyclic sulfate **5**, the bis-mesylate **25** gave the 6-membered oxazinanone **26** as the major product and oxazolidinone **27** as the minor product (2:1 ratio; 74% combined yield).

(12) Sugiyama, S.; Honda, M.; Higuchi, R.; Komori, T. *Liebigs Ann. Chem.* **1991**, *4*, 349–356.

SCHEME 4. Synthesis of D-*lyxo*-Phytosphingosine (4) via Bis-Triflate 28



We next attempted to prepare the bis-triflate **28** (Scheme 4). When the 3,4-vicinal diol **18** was treated with an excess (3 equiv) of triflic anhydride in CH_2Cl_2/pyridine at low temperature (−30 °C), the obtained product was not the anticipated bis-triflate **28** but the 6-membered oxazinanone **12** (76%) after column chromatography. No 5-membered oxazolidinone product was detected in the crude ^{1}H NMR spectra. Intermediate **29**, the C-3 triflate derivative of **12**, could be obtained after rapid purification. However, it was too unstable to be fully characterized, and rapidly underwent hydrolysis to give **12** on standing at room temperature. The presence of the C-3 triflate **29** implied that the formation of **12** proceeded via the bis-triflate **28**. These experiments provided a facile route for the selective configurational inversion of the C-4 hydroxyl group of *ribo*-phytosphingosine. The selectively obtained **12** was deprotected to afford D-*lyxo*-phytosphingosine (**4**) in two steps. For analytical reasons, **4** was also peracetylated to provide tetraacetate **30**, of which spectroscopic data were identical with those reported.[5f,6f,11,13]

The *N*-acetyl-protected 3,4-vicinal diol **21** was also treated with an excess of triflic anhydride to examine the effect of the acetyl protecting group on the regioselectivity (Scheme 5). The reaction of **21** under the same conditions as for **18** provided the 6-membered oxazine **31** (64%) as the only identifiable regioisomer. No trace of the other possible regioisomer **23** was observed in the crude ^{1}H NMR spectra. The cyclization followed the same pattern as that observed in the case of *N*-Boc-protected **18**. These results once again demonstrate that cyclic sulfates and bis-sulfonates display different chemical behaviors in the substitution reaction with the oxygen atom of a carbonyl group. The exposure of oxazine **31** to HCl/THF followed by treatment of the resulting compound with Bu_4NF provided the known *N*-acetyl D-*lyxo*-phytosphingosine **32**[12] in 70% overall yield. The identity of **32** was further confirmed by its conversion to tetraacetate **30**.

To our knowledge, the direct comparison between a cyclic sulfate and a bis-sulfonate in an intramolecular substitution reaction with a carbonyl oxygen nucleophile has not yet been reported in the literature. Our study could therefore be the first example of such a comparison. The reasons for the significant change in the position of the nucleophilic attack depending on the structure of the leaving group (cyclic sulfate vs bis-sulfonate) are not yet completely understood. We suggested that the different outcomes might be the result of a thermodynamic or kinetic control of the reaction pathways. However, more systematic experimental and computational studies are needed.

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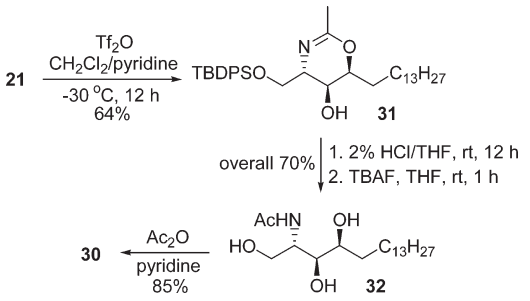
SCHEME 5. Synthesis of *N*-Acetyl D-*lyxo*-Phytosphingosine 32



Conclusion

In summary, we describe herein a synthesis of D-*xylo*- (**2**) and D-*lyxo*-phytosphingosines (**4**) from the low-cost D-*ribo*-phytosphingosine (**1**) based on the configurational inversion of the stereocenter via a regioselective nucleophilic substitution of a cyclic sulfate and bis-sulfonate. The synthetic methodology also provided protected isomers of phytosphingosines that could be synthetically useful in the preparation of various sphingolipid derivatives. We found that the thermolysis of the cyclic sulfates **5** and **20** led to an inversion of configuration of the proximal hydroxyl group, whereas the bis-sulfonates **25** and **28** led to an inversion of configuration of the distal hydroxyl group. This study allowed us to compare a cyclic sulfate and a bis-sulfonate in an intramolecular substitution reaction that involved an oxonium ion intermediate. In addition, this study demonstrated that the cyclic sulfate **5** that was obtained from *ribo*-phytosphingosine exhibited a regiochemical behavior that was substantially different from that observed for the *xylo*-phytosphingosine-derived cyclic sulfate **7**. Finally, we anticipate the regioselective inversion of a hydroxyl group of the 1-amino-2,3-diol with *ribo* configuration by the approach presented in this paper is of practical interest since it allows easy access to *xylo*- and *lyxo*-configured vicinal amino diols that are less readily available than the *ribo*-type system.

Experimental Section

(2*S*,3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-[*N*-(*tert*-butyloxycarbonyl)amino]octadecan-3,4-diol (18). To a solution of compound **1** (1.50 g, 4.72 mmol) in EtOH/H_2O (1:1, 12 mL) was added 1 N NaOH (6 mL) and di-*tert*-butyl dicarbonate (1.6 mL, 6.96 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (hexane/EtOAc, 1:1) afforded the *N*-Boc-protected compound (1.89 g, 96%). Triethylamine (0.9 mL, 6.46 mmol), DMAP (45 mg, 0.37 mmol), and TBDPS-Cl (1.5 mL, 5.86 mmol) were added at 0 °C to a solution of the *N*-Boc-protected compound (1.80 g, 4.31 mmol) in CH_2Cl_2/DMF (1:1, 10 mL). The reaction mixture was stirred at

room temperature for 24 h. It was then diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography on silica gel (hexane/EtOAc, 10:1) afforded the diol **18** (2.77 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ +13.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.06 (s, 9H), 1.25 (s, 23H), 1.41 (s, 9H), 1.46−1.56 (m, 2H), 1.62−1.74 (m, 1H), 2.62 (br s, 1-OH), 3.11 (d, J = 6.9 Hz, 1-OH), 3.58−3.68 (m, 2H), 3.76−3.89 (m, 2H), 3.92−4.02 (m, 1H), 5.17 (d, J = 8.4 Hz, 1-NH), 7.34−7.46 (m, 6H), 7.60−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.7, 25.9, 26.8 (3C), 28.3 (3C), 29.3, 29.5, 29.6 (3C), 29.7 (4C), 31.9, 33.1, 52.0, 64.0, 73.4, 75.6, 79.6, 127.9 (4C), 129.97, 127.98, 132.3, 132.5, 135.5 (2C), 135.5 (2C), 155.7; IR ($CHCl_3$) υ_{max} 3443, 2925, 2854, 1693, 1112 (cm^{-1}); MS (FAB) m/z 656 ($[M + H]^+$, 16), 556 (100), 199 (50); HRMS (FAB) calcd for $C_{39}H_{66}NO_5Si$ 656.4710 ($[M + H]^+$), found 656.4708.

(2*S*,3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-[*N*-(*tert*-butyloxycarbonyl)amino]octadecan-3,4-cyclic Sulfate (5). To a solution of diol **18** (0.35 g, 0.53 mmol) in CH_2Cl_2 (6 mL) were added triethylamine (0.20 mL, 1.43 mmol) and thionyl chloride (0.06 mL, 0.69 mmol) at 0 °C. After 30 min, the reaction mixture was poured into brine and extracted with EtOAc twice. The organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 15:1) to give a diastereomeric mixture of cyclic sulfites (0.36 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two diastereomers) δ 0.89 (t, J = 6.9 Hz, 6H, both diastereomers), 1.07 (s, 18H, both diastereomers), 1.26 (s, 48H, both diastereomers), 1.46 (s, 18H, both diastereomers), 1.50−1.58 (m, 2H, both diastereomers), 1.60−1.76 (m, 2H, both diastereomers), 1.76−1.90 (m, 1H, diastereomer 1), 1.98−2.22 (m, 1H, diastereomer 2), 3.66−3.98 (m, 3H, both diastereomers), 3.85 (dd, J = 3.0, 10.2 Hz, 1H, diastereomer 1), 4.10−4.26 (m, 1H, diastereomer 2), 4.54−4.70 (m, 2H, both diastereomers), 4.86−5.60 (m, 3H, both diastereomers), 7.36−7.49 (m, 12H, both diastereomers), 7.61−7.68 (m, 8H, both diastereomers); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of two diastereomers) δ 14.1 (2C, both diastereomers), 19.3 (diastereomer 1), 19.4 (diastereomer 2), 22.7 (2C, both diastereomers), 25.8 (diastereomer 1), 25.9 (diastereomer 2), 26.8 (3C, diastereomer 1), 26.9 (3C, diastereomer 2), 28.3 (6C, both diastereomers), 29.3 (2C, both diastereomers), 29.5 (2C, both diastereomers), 29.56 (diastereomer 1), 29.6 (diastereomer 2), 29.63 (6C, both diastereomers), 29.7 (8C, both diastereomers), 31.9 (2C, both diastereomers), 50.2 (diastereomer 1), 50.8 (diastereomer 2), 63.4 (diastereomer 1), 63.9 (diastereomer 2), 78.7 (diastereomer 1), 80.2 (diastereomer 2), 81.2 (diastereomer 1), 83.5 (diastereomer 2), 85.2 (2C, both diastereomers), 127.8 (8C, both diastereomers), 129.9 (2C, diastereomer 1), 129.94 (2C, diastereomer 1), 132.5 (diastereomer 1), 132.7 (diastereomer 2), 132.9 (diastereomer 1), 132.95 (diastereomer 2), 135.43 (2C, diastereomer 1), 135.47 (2C, diastereomer 2), 135.5 (2C, diastereomer 1), 135.6 (2C, diastereomer 2), 154.7 (diastereomer 1), 154.9 (diastereomer 2); MS (FAB) m/z 702 ($[M + H]^+$, 5), 588 (47), 199 (66), 57 (100); HRMS (FAB) calcd for $C_{39}H_{64}NO_6SSi$ 702.4224 ($[M + H]^+$), found 702.4234.

To a solution of cyclic sulfite (0.25 g, 0.36 mmol) in CCl_4/CH_3CN/H_2O (6 mL, 1:1:1) were added $RuCl_3 \cdot 3H_2O$ (6 mg, 0.03 mmol) and $NaIO_4$ (280 mg, 1.31 mmol). After the reaction mixture was stirred at room temperature for 2 h, it was diluted with EtOAc and washed with a saturated $NaHSO_3$ solution. The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give the cyclic sulfate **5** (0.35 g, 92%) as a colorless oil.

The isolated cyclic sulfate **5** was unstable in NMR solvents and underwent facile cyclization to give the sulfate esters **16** and **17**, as described above. Thus, its full characterization was not performed.

Procedure for the Thermolysis of the Cyclic Sulfate 5. A solution of the cyclic sulfate **5** (0.15 mmol) in dry CH_3CN (5 mL) was heated to 45 °C until the disappearance of the starting material on TLC (2 h). The reaction was cooled to room temperature, and concentrated H_2SO_4 (4 μL), H_2O (5 μL), and THF (70 μL) were added. The mixture was stirred for 1 h at room temperature. It was then diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to provide a crude mixture. The crude isomer ratio of 3.9:1 was determined from the ^{1}H NMR spectrum in $CDCl_3$. Purification of the crude material by column chromatography on silica gel (hexane/EtOAc, 2:1) afforded oxazolidinone **11** (47 mg, 53%) and oxazinanone **12** (12 mg, 13%).

(4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-5-((*R*)-1-hydroxypentadecyl)oxazolidin-2-one (11). As a colorless oil: R_f 0.45 (hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ −38.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.05 (s, 9H), 1.26 (s, 23H), 1.40−1.60 (m, 3H), 2.38 (br s, 1-OH), 3.49−3.57 (m, 1H), 3.58−3.69 (m, 2H), 3.85 (dd, J = 4.8, 10.2 Hz, 1H), 4.22 (dd, J = 4.2, 5.1 Hz, 1H), 5.66 (s, 1-NH), 7.36−7.48 (m, 6H), 7.60−7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.7, 25.5, 26.7 (3C), 29.3, 29.4, 29.5, 29.6, 29.63 (2C), 29.7 (3C), 31.9, 32.6, 55.4, 65.3, 72.3, 81.3, 127.9 (4C), 130.1 (2C), 132.5, 132.6, 135.46 (2C), 135.5 (2C), 158.8; IR ($CHCl_3$) υ_{max} 3303, 2925, 2854, 1756, 2098, 1114 (cm^{-1}); MS (FAB) m/z 582 ($[M + H]^+$, 28), 265 (30), 199 (71), 135 (100); HRMS (FAB) calcd for $C_{35}H_{56}NO_4Si$ 582.3979 ($[M + H]^+$), found 582.3971.

(4*S*,5*S*,6*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-5-hydroxy-6-tetradecyl-1,3-oxazinan-2-one (12). As a colorless oil: R_f 0.23 (hexane/EtOAc, 2:1); $[\alpha]^{25}_D$ −44.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 6.3 Hz, 3H), 1.02 (s, 9H), 1.25 (s, 22H), 1.37−1.47 (m, 1H), 1.55−1.66 (m, 1H), 1.70−1.84 (m, 2H), 3.45−3.58 (m, 2H), 3.63 (dd, J = 4.5, 9.6 Hz, 1H), 3.79 (br s, 1H), 3.88 (br s, 1-OH), 4.09 (t, J = 6.5 Hz, 1H), 6.71 (s, 1-NH), 7.30−7.45 (m, 6H), 7.55−7.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.1, 22.7, 25.2, 26.8 (3C), 29.4, 29.5, 29.6 (2C), 29.65 (2C), 29.7 (3C), 30.3, 31.9, 58.3, 63.9, 65.3, 77.7, 127.9 (4C), 129.9, 130.0, 132.55, 132.6, 135.49 (2C), 135.5 (2C), 155.1; IR ($CHCl_3$) υ_{max} 3358, 2925, 2854, 1710, 1113 (cm^{-1}); MS (FAB) m/z 582 ($[M + H]^+$, 64), 199 (65), 135 (100); HRMS (FAB) calcd for $C_{35}H_{56}NO_4Si$ 582.3979 ($[M + H]^+$), found 582.3976.

(2*S*,3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-[*N*-(acetyl)amino]-octadecan-3,4-diol (21). To a solution of tetraacetyl-D-*ribo*-phytosphingosine (3.00 g, 6.18 mmol) in anhydrous methanol (20 mL) was added sodium methoxide (5 mL, 21.9 mmol, 25 wt % solution in MeOH). After being stirred at room temperature for 30 min, the reaction mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude *N*-acetyl-phytosphingosine (2.20 g, 6.11 mmol) was dissolved in CH_2Cl_2/DMF (15 mL, 1:1) and triethylamine (1.5 mL, 10.8 mmol), DMAP (70.0 mg, 0.57 mmol), and TBDPS-Cl (2.5 mL, 9.61 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 24 h. It was then diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the diol **21** (3.60 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +19.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.08 (s, 9H), 1.26 (s, 23H), 1.40−1.58 (m, 2H), 1.68−1.80 (m, 1H), 1.90 (s, 3H), 2.56 (d, J = 7.5 Hz, 1-OH), 3.32 (d, J = 8.1 Hz, 1-OH), 3.54−3.68 (m, 2H), 3.80 (dd, J = 5.1, 10.8 Hz, 1H), 4.02 (dd, J = 3.3, 10.5 Hz, 1H), 3.97 (dt, J = 4.2, 8.4 Hz, 1H), 6.08 (d, J = 8.7 Hz, 1-NH), 7.36−7.50 (m, 6H), 7.60−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 22.7, 23.3, 25.8, 26.9 (3C), 29.3 (3C), 29.6, 29.64 (2C), 29.7 (3C), 31.9, 33.4, 51.1, 63.7, 73.3, 75.7, 128.0 (4C), 130.2 (2C), 132.0, 132.4, 135.5 (2C), 135.53 (2C), 169.9; IR ($CHCl_3$) υ_{max} 3334, 2925, 2854, 1653, 1113 (cm^{-1}); MS (FAB) m/z 598 ($[M + H]^+$, 72), 342 (100), 199 (80), 135 (92); HRMS (FAB) calcd for $C_{36}H_{60}NO_4Si$ 598.4249 ($[M + H]^+$), found 598.4287.

(2*S*,3*S*,4*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-[*N*-(acetyl)amino]-octadecan-3,4-cyclic Sulfite (22). To a solution of diol **21** (1.00 g,

1.67 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (0.8 mL, 5.74 mmol) and thionyl chloride (0.2 mL, 2.31 mmol) at 0 °C. After 30 min, the reaction mixture was poured into brine and extracted with EtOAc twice. The organic layers were dried over $MgSO_4$ and concentrated. It was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to give a diastereomeric mixture of cyclic sulfite **22** (1.05 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two diastereomers) δ 0.88 (t, J = 6.9 Hz, 6H, both diastereomers), 1.08 (s, 18H, both diastereomers), 1.26 (s, 44H, both diastereomers), 1.42−1.68 (m, 5H, both diastereomers), 1.68−1.82 (m, 3H, both diastereomers), 1.92 (s, 3H, diastereomer 1), 1.94 (s, 3H, diastereomer 2), 3.70 (dd, J = 3.0, 10.5 Hz, 1H, diastereomer 1), 3.76 (dd, J = 2.7, 10.8 Hz, 1H, diastereomer 2), 3.87 (dd, J = 3.3, 10.5 Hz, 1H, diastereomer 1), 4.11 (dd, J = 2.4, 10.5 Hz, 1H, diastereomer 2), 4.24 (dt, J = 3.3, 8.7 Hz, 1H, diastereomer 1), 4.44−4.54 (m, 1H, diastereomer 2), 4.54−4.60 (m, 1H diastereomer 1), 4.60−4.66 (m, 1H diastereomer 2), 4.91 (ddd, J = 3.3, 5.1, 9.3 Hz, 1H, diastereomer 1), 5.05 (dd, J = 5.4, 8.1 Hz, 1H, diastereomer 2), 5.78 (d, J = 9.3 Hz, 1-NH, diastereomer 1), 5.86 (d, J = 9.6 Hz, 1-NH, diastereomer 2), 7.36−7.49 (m, 12H, both diastereomers), 7.60−7.67 (m, 8H, both diastereomers); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of two diastereomers) δ 14.1 (2C, both diastereomers), 19.3 (diastereomer 1), 19.4 (diastereomer 2), 22.7 (2C, both diastereomers), 23.3 (diastereomer 1), 23.33 (diastereomer 2), 25.7 (diastereomer 1), 25.8 (diastereomer 2), 26.8 (3C, diastereomer 1), 26.9 (3C, diastereomer 2), 28.2 (2C, both diastereomers), 28.97 (diastereomer 1), 29.0 (diastereomer 2), 29.3 (4C, both diastereomers), 29.4 (diastereomer 1), 29.41 (diastereomer 2), 29.47 (diastereomer 1), 29.5 (diastereomer 2), 29.6 (4C, both diastereomers), 29.63 (4C, both diastereomers), 31.9 (2C, both diastereomers), 48.7 (diastereomer 1), 49.2 (diastereomer 2), 63.1 (diastereomer 1), 63.9 (diastereomer 2), 79.1 (diastereomer 1), 81.3 (diastereomer 2), 83.1 (diastereomer 1), 84.8 (diastereomer 2), 127.87 (2C, both diastereomers), 127.89 (3C, both diastereomers), 127.9 (3C, both diastereomers), 130.0 (4C, both diastereomers), 132.4 (diastereomer 1), 132.6 (diastereomer 2), 132.8 (diastereomer 1), 132.9 (diastereomer 2), 135.4 (2C, diastereomer 1), 135.44 (2C, diastereomer 2), 135.46 (2C, diastereomer 1), 135.5 (2C, diastereomer 2), 169.3 (diastereomer 1), 169.5 (diastereomer 2); MS (FAB) m/z 644 ([M + H]$^+$, 22), 586 (65), 199 (77), 135 (100); HRMS (FAB) calcd for $C_{36}H_{58}NO_5SSi$ 644.3805 ([M + H]$^+$), found 644.3807.

(*R*)-1-((4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methyl-4,5-dihydrooxazol-5-yl)pentadecan-1-ol (23). To a solution of cyclic sulfite **22** (590 mg, 0.92 mmol) in $CCl_4/CH_3CN/H_2O$ (9 mL, 1:1:1) were added $RuCl_3 \cdot 3H_2O$ (9.5 mg, 0.05 mmol) and $NaIO_4$ (560 mg, 2.62 mmol). After the reaction mixture was stirred at room temperature for 2 h, concentrated H_2SO_4 (24 μL), H_2O (30 μL), and THF (430 μL) were added. The mixture was further stirred for 1 h at room temperature. It was then diluted with EtOAc and washed with a saturated $NaHSO_3$ solution. The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to give the oxazoline **23** (350 mg, 66%) as a colorless oil: $[\alpha]^{25}_D$ −0.9 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.05 (s, 9H), 1.25 (s, 26H), 1.58−1.75 (m, 1H), 2.03 (s, 3H), 3.50−3.61 (m, 1H), 3.64−3.87 (m, 2H), 4.40−4.58 (m, 1H), 5.34 (s, 1H), 7.24−7.42 (m, 6H), 7.60−7.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 19.1, 20.5, 22.7, 25.0, 26.8 (3C), 29.4 (2C), 29.48, 29.6, 29.66 (2C), 29.7 (3C), 31.9, 32.5, 55.6, 61.1, 66.8, 80.3, 127.99 (2C), 128.0 (2C), 130.0, 130.2, 131.7 (2C), 135.5 (2C), 135.7 (2C), 170.1; IR ($CHCl_3$) υ_{max} 3418, 2926, 2855, 1755, 1217, 1113 (cm^{-1}); MS (FAB) m/z 580 ([M + H]$^+$, 13), 135 (100), 199 (65); HRMS (FAB) calcd for $C_{36}H_{58}NO_3Si$ 580.4186 ([M + H]$^+$), found 580.4194.

(2*S*,3*S*,4*R*)-2-(*tert*-Butoxycarbonylamino)-1-(*tert*-butyldiphenylsilyloxy)octadecane-3,4-diol Dimethanesulfonate (25). To a solution of diol **18** (100 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) and pyridine (0.3 mL) was added MsCl (36 μL, 0.46 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (hexane/EtOAc, 15:1) afforded bis-mesylate **25** (118 mg, 97%) as a colorless oil: $[\alpha]^{25}_D$ −5.7 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.4 Hz, 3H), 1.11 (br s, 9H), 1.21−1.27 (m, 24H), 1.44 (br s, 9H), 1.70−1.77 (m, 2H), 3.03 (s, 3H), 3.09 (s, 3H), 3.66−3.74 (m, 1H), 3.81−3.93 (m, 2H), 4.90−4.97 (m, 2H), 5.25 (d, J = 9.4 Hz, 1-NH), 7.32−7.47 (m, 6H), 7.62−7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.5, 22.9, 25.6, 26.7 (2C), 27.0, 28.4, 29.5, 29.7 (2C), 29.8 (2C), 29.9 (2C), 31.4, 32.1, 38.6, 38.7, 38.9, 39.0, 39.2, 39.5, 51.8, 62.3, 80.5, 80.8, 81.3, 128.1 (2C), 128.2 (2C), 130.2, 130.4, 132.7 (2C), 135.8 (2C), 135.9 (2C), 155.3; IR ($CHCl_3$) υ_{max} 3418, 2926, 2855, 1712, 1467, 1361, 1176 (cm^{-1}); MS (FAB) m/z 812 ([M + H]$^+$, 35), 588 (55), 135 (25); HRMS (FAB) calcd for $C_{41}H_{70}NO_9S_2Si$ 812.4261 ([M + H]$^+$), found 812.4258.

Procedure for the Themolysis of Bis-Mesylate 25. Bis-mesylate **25** (100 mg, 0.12 mmol) was dissolved in CH_3CN (3 mL). The resulting solution was transferred to a sealed tube, degassed with N_2 gas, and heated at 110 °C (oil bath) for 12 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to provide a mixture of oxazinanone **26** and oxazolidinone **27** in a ratio of 2.0:1 according to ^{1}H NMR in $CDCl_3$. Purification of the crude material by column chromatography on silica gel (hexane/EtOAc, 2:1) gave oxazinanone **26** (39 mg, 49%) and oxazolidinone **27** (20 mg, 25%).

(4*S*,5*S*,6*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-oxo-6-tetradecyl-1,3-oxazinan-5-yl Methanesulfonate (26). As a colorless oil: R_f 0.15 (hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ −30.0 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 6.3 Hz, 3H), 1.00 (s, 9H), 1.19 (s, 22H), 1.32−1.54 (m, 2H), 1.62−1.78 (m, 2H), 3.02 (s, 3H), 3.47−3.54 (dd, J = 6.8, 10.4 Hz, 1H), 3.62−3.68 (dd, J = 5.1, 10.6 Hz, 1H), 3.75−3.79 (m, 1H), 4.14−4.20 (m, 1H), 4.86 (br s, 1H), 5.29 (br s, 1-NH), 7.32−7.40 (m, 6H), 7.53−7.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 18.9, 20.8, 22.5, 24.6, 26.6 29.0, 29.1, 29.2, 29.3, 29.4 (2C), 29.5 (3C), 30.4, 31.7, 38.9, 56.3, 64.4, 71.6, 74.7, 127.0, 127.1, 127.8, 127.82, 129.9, 130.0, 132.0, 132.1, 135.3 (2C), 135.4 (2C), 153.4; IR (CH_3Cl) υ_{max} 3289, 2925, 2849, 2855, 1715, 1465, 1361, 1177, 1113 (cm^{-1}); MS (FAB) m/z 660 ([M + H]$^+$, 43), 243 (100), 154 (15); HRMS (FAB) calcd for $C_{36}H_{58}NO_6SSi$ 660.3754 ([M + H]$^+$), found 660.3750.

(*R*)-1-((4*S*,5*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-oxo-oxazolidin-5-yl)pentadecyl Methanesulfonate (27). As a colorless oil: R_f 0.31 (hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ −21.1 (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J = 6.6 Hz, 3H), 0.99 (s, 9H), 1.19 (s, 22H), 1.48−1.50 (m, 2H), 1.63−1.67 (m, 2H), 3.02 (s, 3H), 3.57 (d, J = 4.9 Hz, 2H), 3.70−3.76 (m, 1H), 4.38−4.40 (m, 1H), 4.58−4.62 (m, 1H), 4.92 (s, 1-NH), 7.40−7.37 (m, 6H), 7.50−7.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.3, 22.8 (2C), 25.2, 26.9 (2C), 29.4, 29.5 (2C), 29.7 (2C), 29.8 (3C), 30.5, 32.0 (2C), 39.5, 55.4, 65.3, 78.1, 81.5, 128.2 (4C), 130.3, 130.34, 132.5, 135.66, 135.7 (4C), 163.8; IR ($CHCl_3$) υ_{max} 3289, 2925, 2854, 1762, 1464, 1354, 1174, 1113 (cm^{-1}); MS (FAB) m/z 660 ([M + H]$^+$, 37), 428 (100), 344 (45); HRMS (FAB) calcd for $C_{36}H_{58}NO_6SSi$ 660.3754 ([M + H]$^+$), found 660.3756.

Procedure for Cyclization via Bis-Triflate. To a solution of diol **18** or **21** (0.20 mmol) in CH_2Cl_2 (3 mL) and pyridine (1 mL) was added triflic anhydride (0.60 mmol) at −30 °C. After being stirred for 12 h at −30 °C, the reaction mixture was poured into water and extracted with CH_2Cl_2 twice. The organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the obtained crude material by column chromatography on silica gel (hexane/EtOAc, 2:1) gave oxazinanone **12** (109 mg, 76%) or oxazine **31** (74 mg, 64%), respectively.

The concentration of the reaction mixture followed by the rapid purification of the obtained residue by column chromatography on silica gel provided **29**. Compound **29** was too

unstable to be fully characterized, and rapidly underwent hydrolysis to give **12** on standing at room temperature. Thus, its full characterization was not performed.

(4*S*,5*S*,6*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-oxo-6-tetradecyl-1,3-oxazinan-5-yl Trifluoromethanesulfonate (29). As a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J = 6.7 Hz, 3H), 0.99 (s, 9H), 1.20 (s, 22H), 1.27−1.50 (m, 2H), 1.69−1.75 (m, 2H), 3.44 (dd, J = 7.7, 10.4 Hz, 1H), 3.68−3.78 (m, 2H), 4.01−4.10 (m, 1H), 5.04 (s, 1H), 6.08 (s, 1-NH), 7.30−7.43 (m, 6H), 7.50−7.56 (m, 4H); MS (FAB) m/z 714 ([M + H]$^+$, 40), 586 (40), 538 (100), 220 (57), 199 (43), 135 (78); HRMS (FAB) calcd for $C_{36}H_{55}F_3NO_6SSi$ 714.3471 ([M + H]$^+$), found 714.3459.

(4*S*,5*S*,6*S*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methyl-6-tetradecyl-5,6-dihydro-4*H*-1,3-oxazin-5-ol (31). As a colorless oil (74 mg, 64%); $[\alpha]^{25}_D$ −4.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 6.8 Hz, 3H), 1.04 (s, 9H), 1.24 (s, 22H), 1.42−1.50 (m, 2H), 1.52−1.68 (m, 2H), 1.88 (s, 3H), 3.43−3.49 (m, 2H), 3.90−3.94 (m, 1H), 3.97 (d, 1H, J = 6.4 Hz), 3.99−4.02 (m, 1H), 7.35−7.42 (m, 6H), 7.62−7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.2, 21.4, 22.7, 25.4, 26.8 (2C), 26.9, 29.3 (2C), 29.5, 29.6 (3C), 29.7, 31.9, 32.7, 58.2, 62.8, 66.6, 74.6, 127.8 (2C), 127.9, 128.0, 129.9 (2C), 130.1, 130.2, 135.5 (2C), 135.6, 135.8, 171.6; IR ($CHCl_3$) υ_{max} 3347, 3071, 2925, 2854, 1667, 1466, 1240, 1112 (cm^{-1}); MS (FAB) m/z 580 ([M + H]$^+$, 22), 557 (12), 301 (89), 279 (100); HRMS (FAB) calcd for $C_{36}H_{58}NO_3Si$ 580.4186 ([M + H]$^+$), found 580.4142

General Procedure for the Removal of the Protecting Groups of Compounds 11 and 12. To a solution of **11** or **12** (100 mg, 0.17 mmol) in THF (0.1 M) was added TBAF (2 equiv, 1.0 M solution in THF) at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification of the crude product by silica gel column chromatography (hexane/EtOAc, 2:1) led to the desilylated compound. A solution of the desilylated compound (30.0 mg, 0.09 mmol) in 1 N KOH (EtOH/H_2O 2:1) was refluxed for 2 h. The reaction mixture was cooled to room temperature and a 10% HCl solution (2 mL) was added. The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OH, 40:10:1) gave the D-phytosphingosine **2** or **4**.

(2*S*,3*R*,4*R*)-2-Aminooctadecane-1,3,4-triol (D-*xylo*-Phytosphingosine, 2). As a white solid (43 mg, 80%): mp 99−100 °C (lit.[5h] mp 98−99 °C); $[\alpha]^{25}_D$ +12.9 (c 0.5, pyridine) {lit.[5h] $[\alpha]^{27}_D$ +11.8 (c 0.45, pyridine)}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 0.85 (t, J = 6.0 Hz, 3H), 1.23 (s, 22H), 1.51−1.58 (m, 1H), 1.70−1.75 (m, 1H), 1.80−1.90 (m, 1H), 1.96−2.02 (m, 1H), 3.55 (dt, J = 3.3, 6.6 Hz, 1H), 4.06−4.09 (m, 2H), 4.08−4.22 (m, 2H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 14.2, 22.8, 26.5, 29.5, 29.8 (2C), 29.9 (3C), 30.1 (3C), 32.0, 34.7, 57.9, 60.7, 70.8, 72.8; IR (KBr) υ_{max} 3372, 2920, 2851, 2361, 1734, 1470, 1057 (cm^{-1}); MS (FAB) m/z 318 ([M + H]$^+$, 25), 60 (93), 154 (38), 643 (53); HRMS (FAB) calcd for $C_{18}H_{40}NO_3$ 318.3008 ([M + H]$^+$), found 318.3007.

(2*S*,3*S*,4*S*)-2-Aminooctadecane-1,3,4-triol (D-*lyxo*-Phytosphingosine, 4). As a white solid (41 mg, 76%): mp 104−105 °C (lit.[5f] mp 104.2−105.5 °C, lit.[6f] mp 104.8−106.0 °C, lit.[13a] mp 92−95 °C, lit.[13b] mp 95 °C,); $[\alpha]^{25}_D$ −6.7 (c 0.9, pyridine) {lit.[5f] $[\alpha]^{25}_D$ −7.5 (c 1.0, pyridine), lit.[6f] $[\alpha]^{25}_D$ −7.4 (c 0.9, pyridine), lit.[13a] $[\alpha]^{24}_D$ −2.6 (c 0.2, pyridine), lit.[13b] $[\alpha]^{23}_D$ −6.2 (c 1.0, pyridine)}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 0.85 (t, J = 6.3 Hz, 3H), 1.23 (s, 22H), 1.50−1.63 (m, 1H), 1.70−1.92 (m, 1H), 1.93−2.13 (m, 2H), 3.64 (ddd, J = 4.5, 6.6, 11.4 Hz, 1H), 3.96 (dd, J = 2.1, 6.6 Hz, 1H), 4.17 (dd, J = 6.6, 10.2 Hz, 1H), 4.22−4.39 (m, 2H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 14.3, 22.9, 26.8, 29.6 (2C), 30.0 (3C), 30.3 (4C), 32.1, 34.6, 56.5, 65.2, 72.3, 75.1; IR (KBr) υ_{max} 3358, 2924, 2853, 2361, 1645, 1468, 1119 (cm^{-1}); MS (FAB) m/z 318 ([M + H]$^+$, 25), 43 (100), 60 (97), 81 (22), 282 (17); HRMS (FAB) calcd for $C_{18}H_{40}NO_3$ 318.3008 ([M + H]$^+$), found 318.3011.

General Procedure for the Removal of the Protecting Groups of Compounds 23 and 31. To a solution of oxazoline **23** or oxazine **31** (0.17 mmol) in THF (5 mL) was added 2% HCl solution (5 mL). After being stirred for 12 h at room temperature, this reaction mixture was poured into 10% aqueous $NaHCO_3$ solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude compound was dissolved in THF (5 mL) and TBAF (0.25 mmol, 1.0 M solution in THF) was added at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) afforded the compounds **24** or **32**, respectively.

***N*-((2*S*,3*R*,4*R*)-1,3,4-Trihydroxyoctadecan-2-yl)acetamide (24).** As a white solid (84 mg, 91%): mp 100−103 °C (lit.[12] mp 104−106 °C); $[\alpha]^{25}_D$ +10.2 (c 0.7, pyridine) {lit.[12] $[\alpha]^{27}_D$ +3.4 (c 1.0, MeOH)}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 0.85 (t, J = 6.0 Hz, 3H), 1.23 (s, 22H), 1.57−1.71 (m, 1H), 1.73−1.92 (m, 2H), 1.94−2.08 (m, 1H), 2.11 (s, 3H), 4.12−4.20 (m, 1H), 4.21−4.34 (m, 2H), 4.41 (dd, J = 2.7, 6.3 Hz, 1H), 4.84−4.92 (m, 1H), 8.25 (d, J = 8.4 Hz, 1H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 14.3, 22.9, 23.2, 26.3, 29.6 (3C), 29.9 (3C), 30.1 (3C), 32.1, 34.2, 53.7, 62.7, 72.2, 73.5, 170.4; IR (KBr) υ_{max} 3381, 2905, 2891, 1604, 1570, 1114 (cm^{-1}); MS (FAB) m/z 360 ([M + H]$^+$, 65), 282 (50), 60 (100); HRMS (FAB) calcd for $C_{20}H_{42}NO_4$ 360.3114 ([M + H]$^+$), found 360.3110.

***N*-((2*S*,3*S*,4*S*)-1,3,4-Trihydroxyoctadecan-2-yl)acetamide (32).** As a white solid (43 mg, 70%): mp 114.6−115.0 °C (lit.[12] mp 114−115 °C); $[\alpha]^{25}_D$ +8.4 (c 1.0, pyridine) {lit.[12] $[\alpha]^{27}_D$ +1.02 (c 1.0, MeOH)}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 0.85 (t, J = 6.9 Hz, 3H), 1.23 (s, 20H), 1.49−1.53 (m, 1H), 1.65−1.70 (m, 1H), 1.79−1.96 (m, 1H), 2.05−2.12 (m, 2H), 2.14 (s, 3H), 4.06 (dd, J = 1.8, 8.4 Hz, 1H), 4.10−4.17 (m, 1H), 4.33 (dd, J = 4.2, 11.1 Hz, 1H), 4.53 (dd, J = 4.5, 11.1 Hz, 1H), 4.69−4.76 (m, 1H), 8.67 (d, J = 8.7 Hz, 1H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 14.3, 22.9, 23.2, 26.8, 29.6 (3C), 29.9 (3C), 30.1 (3C), 32.1, 34.3, 54.8, 61.9, 71.1, 73.5, 171.6; IR (KBr) υ_{max} 3381, 2905, 1605, 1565, 1114 (cm^{-1}); MS (FAB) m/z 360 ([M + H]$^+$, 40), 282 (50), 60 (100); HRMS (FAB) calcd for $C_{20}H_{42}NO_4$ 360.3114 ([M + H]$^+$), found 360.3110.

General Procedure for Acetylation of D-Phytosphingosine. To a solution of **2**, **4**, **24**, or **32** (0.06 mmol) in pyridine (1 mL) was added Ac_2O (1 mL). After being stirred at room temperature overnight, this reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 1:1) to give tetraacetate **19** or **30**.

(2*S*,3*R*,4*R*)-2-Acetamidooctadecane-1,3,4-triol Triacetate (Tetraacetyl-D-*xylo*-phytosphingosine, 19). As a white solid (from **2**: 25 mg, 86%; from **24**: 19 mg, 88%): mp 45.5−46.5 °C (lit.[5b] mp 44−46 °C); $[\alpha]^{25}_D$ +10.5 (c 0.75, $CHCl_3$) {lit.[5b] $[\alpha]^{27}_D$ +6.5 (c 0.9, $CHCl_3$), lit.[11b] $[\alpha]^{27}_D$ +6.1 (c 0.6, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.20−1.34 (m, 24H), 1.53−1.64 (m, 2H), 2.02 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 4.00 (dd, J = 5.7, 11.4 Hz, 1H), 4.05 (dd, J = 6.3, 11.3 Hz, 1H), 4.52 (m, 1H), 5.05 (dd, J = 6.6, 12.9 Hz, 1H), 5.16 (dd, J = 4.2, 6.3 Hz, 1H), 5.72 (d, J = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.6, 20.7, 20.9, 22.7, 23.2, 24.8, 29.2, 29.3, 29.4 (2C), 29.5 (2C), 29.69 (3C), 30.5, 31.9, 47.9, 62.9, 71.9, 72.2, 169.8, 170.1, 170.5 (2C); IR (KBr) υ_{max} 3295, 2926, 2855, 1746, 1663, 1541, 1227 (cm^{-1}); MS (FAB) m/z 486 ([M + H]$^+$, 77), 426 (100), 508 (63); HRMS (FAB) calcd for $C_{26}H_{48}NO_7$ 486.3431([M + H]$^+$), found 486.3445.

(2*S*,3*S*,4*S*)-2-Acetamidooctadecane-1,3,4-triol Triacetate (Tetraacetyl-D-*lyxo*-phytosphingosine, 30). As a white solid (from **4**: 24 mg,

82%; from **32**: 18 mg, 85%): mp 73.5−74.1 °C; $[\alpha]^{25}_{D}$ −8.5 (*c* 0.8, $CHCl_3$) {lit.[11a] $[\alpha]^{22}_{D}$ −3.1 (*c* 1.1, $CHCl_3$), lit.[11b] $[\alpha]^{28}_{D}$ −3.3 (*c* 0.5, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.3 Hz, 3H), 1.16−1.36 (m, 24H), 1.36−1.59 (m, 2H), 1.96 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 4.21 (dd, J = 4.5, 11.4 Hz, 1H), 4.50−459 (m, 1H), 5.08 (m, 2H), 5.77 (d, J = 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.57, 20.65, 20.9, 22.6, 23.1, 25.1, 29.25, 29.30, 29.38, 29.43, 29.51, 29.55 (2C), 29.58 (2C), 30.8, 31.8, 47.3, 63.1, 71.0, 71.7, 169.6, 170.2, 170.5, 170.6; IR (KBr) υ_{max} 2924, 2845, 1746, 1655, 1559, 1223 (cm^{-1}); MS (FAB) m/z 486 ($[M + H]^+$, 100), 426 (70), 508 (50); HRMS (FAB) calcd for $C_{26}H_{48}NO_7$ 486.3431 ($[M + H]^+$), found 486.3433.

Theoretical Calculations. Theoretical calculations of the truncated conformers **A**, **B**, **C**, and **D** were performed by using the density functional theory (DFT) method as implemented in the DMol3 package,[14] which is available as part of the Material Studio 5.0 package. In the DFT calculations, we employed the Perdew, Burke, and Ernzerhof (PBE) function[15] for the exchange-correlation interaction within a generalized gradient approximation (GGA) and a double numerical basis set including d-polarization functions (DNP) as implemented in the DMol3.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**, **4**, **11**, **12**, **18**−**19**, **21**−**27**, **29**−**32**, and cyclic sulfite derivative from diol **18**. This material is available free of charge via the Internet at http://pubs.acs.org.