A Stereocontrolled, Efficient Synthetic Route to Bioactive Sphingolipids: Synthesis of Phytosphingosine and Phytoceramides from Unsaturated Ester Precursors via Cyclic Sulfate Intermediates

Linli He, Hoe-Sup Byun, and Robert Bittman*

Department of Chemistry and Biochemistry, Queens College of The City University of New York, Flushing, New York 11367-1597

robert_bittman@qc.edu

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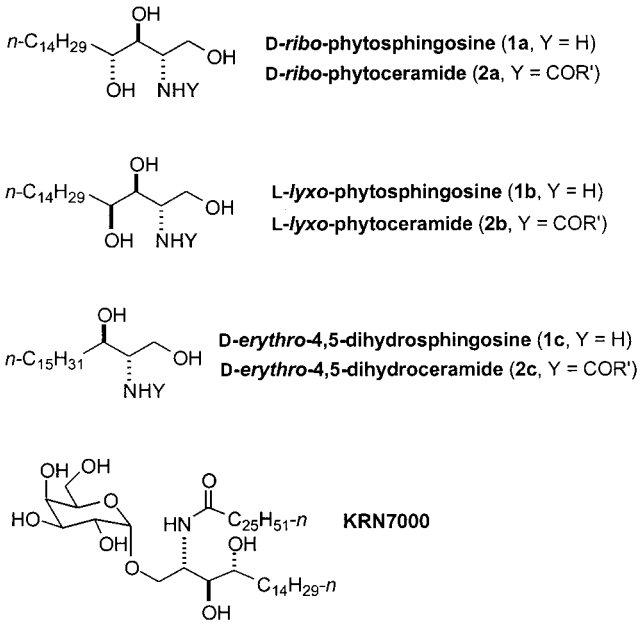
An efficient and highly enantioselective method for the preparation of D-*ribo*- and L-*lyxo*-phytosphingosines (**1a**,**b**, respectively) and phytoceramides (**2a**,**b**) has been developed. The key steps in the syntheses are as follows: (i) osmium-catalyzed asymmetric dihydroxylation of 4-*O*-protected (*E*)-α,*β*-unsaturated ester **5** (generated by dihydroxylation of 1-hexadecene, followed by oxidation to the aldehyde and Horner−Wadsworth−Emmons olefination), (ii) conversion to cyclic sulfate intermediate **7**, and (iii) regioselective α-azidation of **7**. Reduction of 4-*O*-protected 2-azido ester **8** via α-azidolactone **9** afforded phytosphingosine **1a**. Staudinger reduction of the azido group of **8**, followed by in situ *N*-acylation in aqueous media and reduction of the ester functionality with $NaBH_4$/LiBr, provided phytoceramide **2a**. By using a similar approach, phytosphingosine **1b** was synthesized. D-*erythro*-4,5-Dihydrosphingosine **1c** and D-*erythro*-4,5-dihydroceramide **2c** were synthesized in high yield from 1-hexadecanol via cyclic sulfate intermediate **15**. The desired configurations at C-2, C-3, and C-4 of the sphingoid chain can be accessed readily by the route described here.

Introduction

Phytosphingosine **1a** (Chart 1, Y = H), (2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol, one of the major long-chain components of glycosphingolipids, was first isolated from mushrooms in 1911[1] and was subsequently shown to be widely distributed as one of the molecular species of sphingolipids in microorganisms, plants, and many mammalian tissues such as brain, hair, kidney,[2a−c] skin,[2d,e] liver,[2f] uterus,[2g] and intestine,[2h] and in blood plasma.[2i] Its structure was characterized by Oda[3a] and by Carter and Hendrickson.[3b] The long-chain base of the majority of phytosphingolipids has 18 carbons; minor amounts of other chain lengths, especially C_{20}, are also present depending on the sources of origin. In addition to its structural function as the long-chain base of sphingolipids in membranes, phytosphingosine itself is a bioactive lipid; for example, phytosphingosine **1a** is a potential heat stress signal in yeast cells,[4a,b] and some of its derivatives exhibit important physiological activities. α- and *β*-Galactosyl and glucosylphytoceramides (Y = $C_{25}H_{51}CO$) possess very high tumor inhibitory potency;[4c] the α-galactosylphytoceramide KRN7000 [(2*S*,3*S*,4*R*)-1-*O*-(α-D-

Chart 1



* To whom correspondence should be addressed. Tel: (718) 997-3279. Fax: (718) 997−3349.

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(4) (a) Dickson, R. C.; Nagiec, E. E.; Skrzypek, M.; Tillman, P.; Wells, G. B.; Lester, R. L. *J. Biol. Chem*. **1997**, *272*, 30196−30200. (b) Schneiter, R. *Bioessays* **1999**, *21*, 1004−1010. (c) Kobayashi, E.; Motoki, K.; Yamaguchi, Y.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Bioorg. Med. Chem*. **1996**, *4*, 615−619. (d) Kobayashi, E.; Motoki, K.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Oncol. Res*. **1995**, *7*, 529−534.

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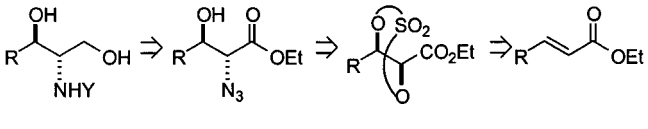
Scheme 1. Retrosynthetic Plan



Sphingosines **1a-c** (Y = H) Ceramides **2a-c** (Y = –COR') | α-Azido-β-hydroxyester | Cyclic Sulfate | (*E*)-Ester

galactopyranosyl)-2-(*N*-hexacosanoylamino)octadecane-1,3,4-triol, Chart 1] enhanced natural killer activities and strongly inhibited tumor metastasis in mice.[4d] Since it is costly to isolate these lipids from natural sources, and also not possible to obtain homogeneous material, a great deal of effort has been placed on synthetic routes to homogeneous compounds for use in biophysical, biochemical, and pharmacological studies. Most syntheses have focused on the preparation of D-*ribo*-phytosphingosine (**1a**, Y = H),[5] since its derivatives such as phytoceramides **2a**,**b** and glycosylated phytosphingolipids are accessible from **1a**,**b** by known methods. Although there exist more than 20 asymmetric synthetic routes to **1a** (see ref 5), most are lengthy syntheses that utilize derivatives of L-serine and various carbohydrates as the starting materials. Some syntheses are problematic because the starting materials are not readily accessible and the products have poor chiral purity. Therefore, the design of more efficient and improved synthetic routes to phytosphingosine continues. Herein we report an efficient enantioselective route to D-*ribo*-phytosphingosine (**1a**). This route allows the control of the stereochemistry at C-2, C-3, and C-4, as demonstrated by the synthesis of one of the diastereomers (L-*lyxo*-phytosphingosine, **1b**), as well as the facile incorporation of various hydrocarbon chains into the tail of the long-chain base (R, Scheme 1). A similar strategy provided D-*erythro*-4,5-dihydrosphingosine (**1c**) in high overall yield and chiral purity.

Synthetic Plan

Phytosphingosines **1a**,**b** (Chart 1) and 4,5-dihydrosphingosine **1c** (Chart 1) are composed of a 2-amino polyhydroxyl headgroup containing two or three chiral centers and a long-chain base. Hence, the synthesis of such a sphingosine from a readily accessible achiral starting material needs inevitably to construct both the chiral polar headgroup and the long-chain base. A *general* stereoselective synthesis should not only allow the approach to all of the possible stereoisomers in high chiral purity but also allow the incorporation of different long-chain bases, namely, a hydrocarbon chain with different chain lengths, and with or without other functional group(s).

As illustrated in the retrosynthetic analysis (Scheme 1), our syntheses of phytosphingosines **1a**,**b** and 4,5-dihydrosphingosine **1c** involve the following three major reactions: (1) asymmetric dihydroxylation of an (*E*)-α,*β*-unsaturated ester as the chiral induction stage,[6] (2) regioselective introduction of the azido group at the α position of an α,*β*-dihydroxyester, and (3) simultaneous reduction of the ester and azido functional groups. It has been well established that asymmetric dihydroxylation of an (*E*)-α,*β*-unsaturated ester provides a diol ester not only in excellent chemical yield but also with high enantioselectivity (>95% ee);[7] moreover, both enantiomers can be obtained simply by changing the chiral ligand. The reaction conditions are very mild compared with other chiral-inducing methods, e.g., asymmetric epoxidation.[8] The starting (*E*)-α,*β*-unsaturated ester is easily accessible by the Horner−Wadsworth−Emmons (HWE) reaction.[9] Moreover, we found that the assembly of the α-amino function is accomplished by regioselective α-azidation of the cyclic sulfate of the α,*β*-dihydroxyester with inversion to give the key synthetic intermediate, α-azido-*β*-hydroxyester (**8**, **8′**, **16**), a convenient precursor of sphingosine and ceramide.

Results and Discussion

A. Syntheses of Phytosphingosines 1a,b (Schemes 2−5). Preparation of 2-*O*-(Methoxymethyl)hexadecane-1,2-diol (4). On the basis of the above retrosynthetic analysis (Scheme 1), the first target for the syntheses of a phytosphingosine is the α,*β*-unsaturated ester **5**, which may be prepared by the HWE reaction of a corresponding aldehyde with a phosphonate ester. Our syntheses of phytosphingosines **1a**,**b** started with 1-hexadecene (Scheme 2). Asymmetric dihydroxylation[10] of 1-hexadecene with either AD-mix-*β* or AD-mix-α provided the desired diol **3** (85% ee)[11] and its enantiomer **3′** (79% ee, Scheme 5) in almost quantitative yields. The chiral purity of **3** and **3′** was easily enriched to >95% by recrystallization from EtOAc (at a ratio of 1 g of diol **3** or **3′** per 40 mL of solvent).

(5) Recent syntheses of D-*ribo*-phytosphingosine (**1a**): (a) Shimizu, M.; Wakioka, I.; Fujisawa, T. *Tetrahedron Lett*. **1997**, *38*, 6027−6030. (b) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2113-2116. (c) Murakami, M.; Ito, H.; Ito, Y. *Chem. Lett*. **1996**, 185−186. (d) Lin, G.-q.; Shi, Z.-c. *Tetrahedron* **1996**, *52*, 2187−2192. (e) Bettelli, E.; Chinzari, P.; D'Andrea, P.; Passacantilli, P.; Piancatelli, G.; Topai, A. *Korean J. Med. Chem*. **1996**, *6*, 339−343. (f) Li, Y.-L.; Wu, Y.-L. *Tetrahedron Lett*. **1995**, *36*, 3875−3876. (g) Li, Y.-L.; Mao, X.-H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1559−1563. (h) Matsumoto, K.; Ebata, T.; Matsushita, H.; *Carbohydr. Res*. **1995**, *279*, 93−106. (i) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett*. **1994**, *35*, 745−748. (j) Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett*. **1994**, *35*, 9573−9576. (k) Wild, R.; Schmidt, R. R. *Liebigs Ann. Chem*. **1995**, 755−764. (l) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem*. **1990**, *55*, 1439−1446. (m) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem*. **1990**, 1069−1078. (n) Schmidt, R. R.; Maier, T. *Carbohydr. Res*. **1988**, *174*, 169−179. (o) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem*. **1988**, 619−625. (p) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem*. **2000**, *65*, 3538−3541. (q) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961−5968.

(6) The Sharpless asymmetric aminohydroxylation (AA) of olefins, such as (*E*)-α,*β*-unsaturated esters **5**, is a very powerful reaction for the stereocontrolled construction of a vicinal hydroxyamido moiety. For asymmetric aminohydroxylation of olefins, see: Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1483−1486, and references therein. However, the AA reaction produces a 3-amido-2-hydroxyester instead of the desired 2-amido-3-hydroxyester. Although Morgan et al. (Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett*. **1999**, *1*, 1949−1952) demonstrated recently that AA reaction of 4-haloaryl esters provided a 2-amido-3-hydroxyester as the major product, the chemical yield and the % ee are generally unsatisfying. Furthermore, the AA reaction produces the threo instead of the desired erythro stereochemistry.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483−2547.

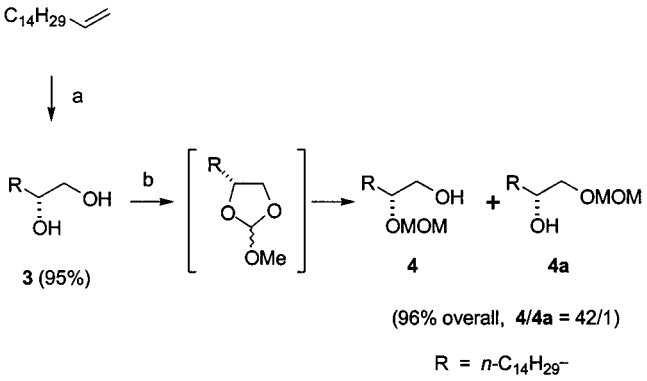
(8) For a review of catalytic asymmetric epoxidation, see: Katsuki, T.; Martin, V. *Org. React*. **1996**, *48*, 1−299.

(9) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863−927.

(10) For an optimized reaction procedure of an asymmetric dihydroxylation reaction, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768−2771.

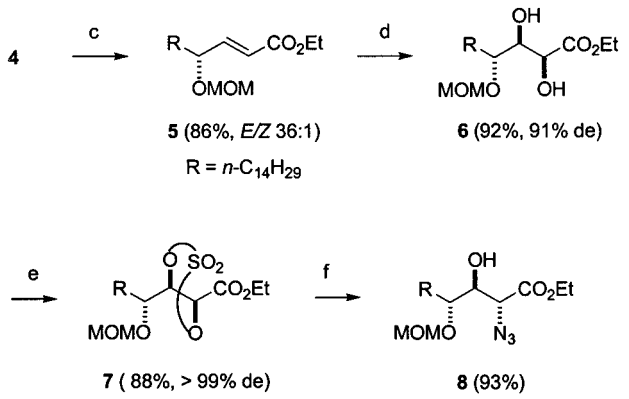
(11) The % ee of diols **3**, **3′**, and **14** was determined by ^{1}H NMR analysis of the corresponding bis-Mosher esters derived from both enantiomers.

Scheme 2. Synthesis of (*R*)-2-*O*-(Methoxymethyl)hexadecane-1,2-diol (4)[a]



[a] Reagents and conditions: (a) AD-mix-β, *t*-BuOH/H_2O 1:1, 0 °C; (b) $CH(OMe)_3$, CH_2Cl_2, D-10-camphorsufonic acid, rt; then DIBALH, −78 °C.

Scheme 3. Generation of Enantiopure (2*R*,3*S*)-Azido Ester 8 via Cyclic Sulfate 7[a]



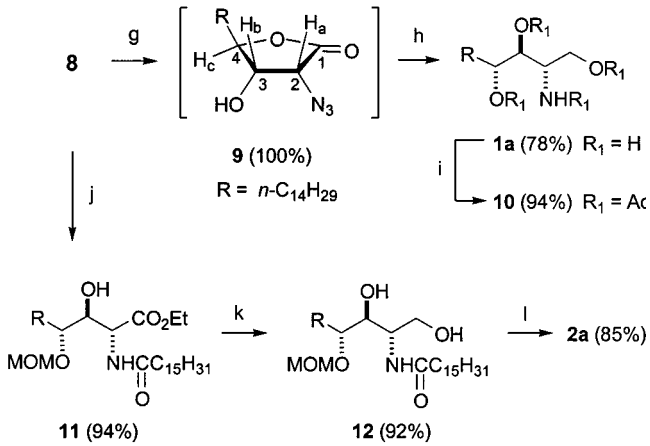
[a] Reagents and conditions: (c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −46 °C; (ii) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 °C; (e) (i) $SOCl_2$, py, CH_2Cl_2, 0 °C; (ii) $NaIO_4$, $RuCl_3$ (cat.), MeCN/H_2O 1:1, rt; (f) (i) NaN_3, Me_2CO/H_2O 1::1, rt (ii) 20% H_2SO_4 (aq)/Et_2O, rt.

Diol **3** was converted to the 2-*O*-methoxymethyl (MOM) diol **4** in one pot and in 94% yield via an unisolated ortho ester intermediate as shown in Scheme 2.[12] Transesterification of diol **3** with trimethyl orthoformate catalyzed by D-10-camphorsulfonic acid generated a mixture of two diastereomers (TLC, hexane/EtOAc 6:1, R_f 0.50, 0.45). The ratio was not determined because both diastereomers led to the desired protected alcohol **4** together with a trace of regioisomer **4a** after subsequent in situ DIBALH reduction. The regioisomer **4a** was removed by column chromatography.

Generation of Enantiomerically Pure (2*R*,3*S*)-Azido Ester 8. Ester **5** was prepared by oxidation of alcohol **4** to the corresponding aldehyde followed by HWE olefination (Scheme 3). Oxidation of alcohol **4** with PCC[13] in CH_2Cl_2 proceeded very sluggishly and was incomplete. A large excess of PCC (>10 equiv) was required for the oxidation to proceed at a reasonable rate; the maximum yield obtained was 73%. Swern oxidation of **4** provided a much better result (95% yield).[14] The aldehyde was used directly in the subsequent coupling reaction without further purification, since the aldehyde was oxidized to the corresponding acid by air. Homologation of the aldehyde by HWE olefination using lithium bromide, Et_3N, and triethyl phosphonoacetate[15a] furnished the desired unsaturated ester **5** in excellent chemical yield (85% from **4**), but in only moderate stereoselectivity (*E*/*Z* = 7:1).[15b] However, when a bulkier phosphonate such as $(i\text{-PrO})_2P(O)CH_2CO_2Et$ was used, the *E*/*Z*-selectivity was increased to 36:1.[16]

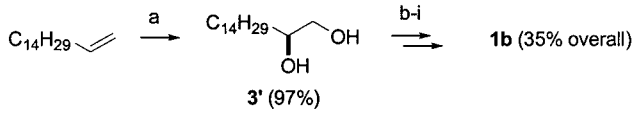
With unsaturated ester **5** in hand, the feasibility of the asymmetric dihydroxylation reaction with AD-mix-β was investigated. The enantioselectivity of an asymmetric dihydroxylation reaction is modulated by the size of the allylic substituent and the configuration at the allylic position.[7] For this reason, a small protecting group for the allylic hydroxyl group was deemed desirable. Dihydroxylation of olefin **5** proceeded much more slowly than that of the parent ester **13** (Scheme 6), probably as a consequence of the electron-withdrawing properties of the C(4)-OMOM moiety. However, the desired diol **6** was formed in 92% yield and 91% de.[17] Although the diaster-

Scheme 4. Syntheses of D-*ribo*-Phytosphingosine (1a)[a] and D-*ribo*-*N*-Palmitoylphytosphingosine (2a)



[a] Reagents and conditions: (g) concd HCl/MeOH 3:25, rt; (h) $LiAlH_4$, THF, 65 °C; (i) Ac_2O, DMAP (cat.), py, rt; (j) Ph_3P, THF/H_2O 9:1, $n\text{-}C_{15}H_{31}CO_2C_6H_4NO_2\text{-}p$, rt; (k) $NaBH_4$, LiBr, THF, rt; (l) concd HCl/MeOH 3:25, $CHCl_3$, rt.

Scheme 5. Outline of the Total Synthesis of L-*lyxo*-Phytosphingosine (1b) and L-*lyxo*-*N*-Palmitoylphytosphingosine (2b)[a]



[a] Reagents and conditions: (a) AD-mix-α, *t*-BuOH/H_2O 1:1, 0 °C; (b)−(i) see reagents and conditions in Schemes 2−4.

(12) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947−1950.

(13) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *26*, 2647−2650.

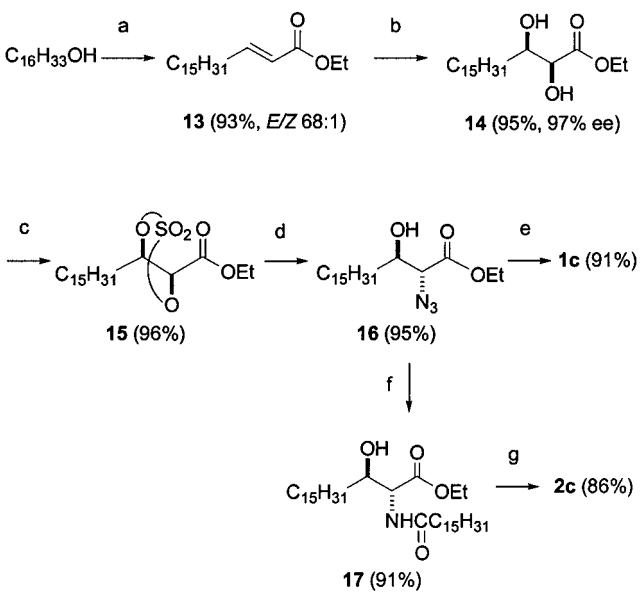
(14) For reviews of the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857−870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

(15) (a) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624−2626. (b) The *Z* and *E* stereoisomers were separated by column chromatography (elution with hexane/EtOAc 25:1) and characterized by ^1H NMR.

(16) The *E*/*Z* ratio was determined by ^1H NMR analysis. Generally, use of a larger phosphonoester reagent in the HWE reaction gives a higher *E*/*Z* ratio (Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888).

(17) The diastereomeric excess of **6** was determined by ^1H NMR.

Scheme 6. Synthesis of D-*erythro*-4,5-Dihydrosphingosine 1c and D-*erythro*-4,5-Dihydroceramide 2c[a]



[a] Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −46 °C; (ii) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt; (b) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, rt; (c) (i) $SOCl_2$, py, CH_2Cl_2, 0 °C; (ii) $NaIO_4/RuCl_3$ (cat.), MeCN−H_2O 1:1, rt; (d) (i) NaN_3, Me_2CO/H_2O 1:1, rt; (ii) 20% H_2SO_4 (aq)/Et_2O 1:1, rt; (e) $LiAlH_4$, THF, 65 °C; (f) Ph_3P, *n*-$C_{15}H_{31}CO_2C_6H_4NO_2$-*p*, THF/$H_2O$ 9:1, rt; (g) $NaBH_4$, LiBr, THF, rt.

eomers are separable by column chromatography, the resolution was arduous and was not carried out at this stage.

For regioselective α-azidation of an α,β-dihydroxyester, cyclic sulfate chemistry has unique advantages.[18] In the present synthesis, the regioselective nucleophilic ring opening of cyclic sulfate **7** is expected to be further enhanced by the electronic and steric effects of the C(4)-*O*-MOM substituent.[19] Although application of cyclic sulfate chemistry to the current synthesis may be problematical since an ether linkage such as in MOM may be oxidized by $NaIO_4/RuCl_3$ (cat.),[20] we found that this protecting group was unaffected by the oxidation conditions. Cyclic sulfate **7** was obtained in excellent yield (94%) from diol ester **6**. Application of a cyclic sulfate intermediate in the current synthesis has the following advantages, as shown in Scheme 3: (i) the diastereomeric diol esters, which were difficult to resolve at the diol ester **6** stage, are totally resolved (>99% de) by a single column chromatography step; (ii) exclusive α-azidation is achieved with excellent yield (93%); (iii) the reactions are very simple to handle; and (iv) the MOM protecting group is stable during the acidic hydrolysis after the nucleophilic ring opening. The latter observation may be ascribed to the heterogeneous nature of the reaction.

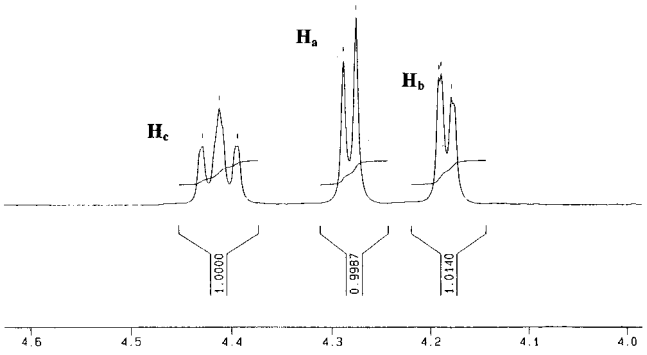


Figure 1. Partial ^1H NMR spectrum of azido lactone **9**.

Synthesis of D-*ribo*-Phytosphingosine 1a and D-*ribo*-Phytoceramide 2a. The α-azido ester **8** was converted to the corresponding D-*ribo*-phytosphingosine **1a** in one pot and in 78% yield by acid hydrolysis followed by simultaneous reduction of the azido and lactone functional groups. TLC analysis indicated a clear deprotection of the MOM group on treatment of azido ester **8** with concentrated HCl/MeOH 3:25 at room temperature for 2 h. The resulting γ-hydroxyester intermediate underwent partial cyclization to form the desired lactone **9**. Complete removal of the MOM group requires a prolonged reaction time (>6 h). However, removal of the solvents on a rotary evaporator after 1 h of reaction, followed by further drying under high vacuum (0.7 Torr) for 1∼2 h, resulted in the complete conversion of azido ester **8** to the desired lactone **9** in quantitative yield. Figure 1 shows the partial ^1H NMR spectrum of **9**. The coupling patterns between H_a and H_b (J_{ab} = 5.1 Hz) and H_b and H_c (J_{bc} = 0.8 Hz) confirmed that the desired stereochemistry was formed (see Scheme 4). Molecular modeling studies of intermediate **9** [Chem 3D Pro from CS ChemOffice (CambridgeSoft Corp.), MM2 minimization] suggested a dihedral angle of ∼94° for $H_b-C_3-C_4-H_c$ and ∼36° for that of $H_a-C_2-C_3-H_b$.[21] Simultaneous reduction of the azido and lactone functional groups with $LiAlH_4$ in THF at 67 °C furnished D-*ribo*-phytosphingosine **1a** in 45% overall yield from 1-hexadecene.[22] The structure of **1a** was further confirmed by conversion into its tetraacetyl derivative **10**. Compared with the existing syntheses,[5] our current seven-step synthesis of D-*ribo*-phytosphingosine **1a** is shorter and simpler, and the overall yield is higher.

For the synthesis of phytoceramide **2a**, reduction of azide **8** with triphenylphosphine in aqueous THF, followed by in situ *N*-acylation with 4-nitrophenyl palmitate, provided amide ester **11** in 94% yield (Scheme 4).[23] Selective reduction of the ester group of **11** was achieved in excellent yield by using $NaBH_4$/LiBr in THF at room temperature. Use of a large excess of both $NaBH_4$ (12 equiv) and LiBr (10 equiv) was required for the reaction to proceed at a reasonable rate (<24 h). Workup by

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(19) The electronic effect introduced by the electron-withdrawing methoxymethoxyl group favors α instead of β substitution. For a discussion of such an electronic effect on a S_N2 reaction, see: He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049−6055 and references therein.

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(22) The expected D-*ribo* (2*S*,3*S*,4*R*) stereochemistry of **1a** was confirmed by the agreement of the specific rotations of both **1a** and **10** with the literature values.[5a−c,g−k]

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quenching the reaction with MeOH or AcOH, followed by extraction with $CHCl_3$ or EtOAc, resulted in a lower yield (65−75%). However, addition of an equivalent volume of hexane to the reaction mixture, followed by filtration of the reaction mixture through a pad of silica gel in a sintered glass funnel and washing the pad with $CHCl_3$/MeOH 15:1 by gravity, provided the desired protected phytoceramide **12** in 92% yield. Finally, deprotection of the MOM ether with concentrated HCl in methanol gave D-*ribo*-phytoceramide **2a** in 85% yield. This nine-step synthesis afforded the desired phytoceramide **2a** from 1-hexadecene in 40% overall yield.

L-*lyxo*-Phytosphingosine **1b** and L-*lyxo*-phytoceramide **2b** were synthesized in ~35% overall yields by using the same reaction sequence; AD-mix-α was used in place of AD-mix-*β* in the dihydroxylation step of 1-hexadecene (Scheme 5; note that the corresponding enantiomers or diastereoisomers of compounds **3**−**12** are numbered as **3′**−**12′**).

B. Synthesis of D-*erythro*-4,5-Dihydrosphingosine 1c and Dihydroceramide 2c (Scheme 6). D-*erythro*-4,5-Dihydrosphingosine (Chart 1, **1c**), also known as sphinganine, is also an important bioactive sphingolipid. It has been found to inhibit protein kinase C[24a] and is an intermediate in the sphingomyelin cycle, which produces lipid second messengers participating in cell regulation and signal transduction.[24b,c] Our synthetic route for the preparation of D-*erythro*-4,5-dihydrosphingosine **1c** and the corresponding ceramide **2c** is illustrated in Scheme 6. Swern oxidation of cetyl alcohol followed by HWE coupling with triethyl phosphonoacetate provided unsaturated ester **13** in 92% overall yield (*E*/*Z* 15:1). The *E*/*Z* ratio was increased to 68:1 (93% yield) when (*i*-PrO)$_2$P(O)CH$_2$CO$_2$Et was used instead of (EtO)$_2$P(O)CH$_2$CO$_2$Et.[16] Asymmetric dihydroxylation of **13** provided diol ester **14** in very high chiral purity (97% ee)[11] and excellent chemical yield (95%). After the diol ester was converted to cyclic sulfate intermediate **15**, nucleophilic ring opening with azide ion (NaN_3, aqueous Me_2CO, room temperature) provided the desired α-azido-*β*-hydroxyester **16** in excellent yield. The azido and the ester functionalities in **16** were reduced simultaneously by $LiAlH_4$ in THF to furnish **1c** in 91% yield (Scheme 6). This five-step synthesis of D-*erythro*-sphinganine **1c** (73% overall yield from 1-hexadecanol) is superior to the known syntheses[5k,25] with respect to overall yield, chiral purity, and flexibility in the synthesis of the other stereoisomers. Furthermore, by following the same protocol as in Scheme 4, the azido ester **16** was converted to dihydroceramide **2c** in excellent yield, as shown in Scheme 6.

Conclusions

A novel and concise synthetic route for the synthesis of phytosphingosines **1a**,**b** and 4,5-dihydrosphingosine **1c** from simple achiral starting materials has been developed. Asymmetric dihydroxylation of α,*β*-unsaturated esters (**5**, **5′**, and **13**) furnished the corresponding diol ester in excellent yield and chiral purities. Cyclic sulfate intermediates (**7**, **7′**, and **15**) were used for the regioselective introduction of the azido group to the α-position with inversion. The key intermediates, α-azido-*β*-hydroxyesters (**8**, **8′**, and **16**), were converted to phytosphingosines **1a**,**b** and 4,5-dihydrosphingosine **1c** via a one-pot reduction by $LiAlH_4$ or to the corresponding ceramides **2a**−**c** via Staudinger reaction and selective reduction of the ester group with $NaBH_4$/LiBr. The seven-step synthesis of D-*ribo*-phytosphingosine **1a** proceeded in 45% overall yield and the five-step synthesis of D-*erythro*-sphinganine **1c** was achieved in 73% overall yield; this approach represents the most efficient synthetic route reported to date. This synthetic strategy is applicable to other lipids bearing skeleton-modified sphingoid base backbones.

Experimental Section

General Information. Melting points were measured on a Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400-MHz and 100-MHz on a Bruker spectrometer, respectively, and were referenced to the residual $CHCl_3$ at 7.24 (^{1}H) and 77.00 ppm (^{13}C). NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. IR spectra were recorded on a Perkin-Elmer 1600-series FT-IR spectrophotometer, and $CHCl_3$ was used as the sole solvent unless otherwise indicated. Optical rotations were measured in a 1.0-dm cell on a JASCO Model DIP-140 digital polarimeter. High-resolution mass spectra were recorded at the Michigan State University and the University of California at Riverside mass spectrometry facilities. THF was distilled from Na and benzophenone immediately before use. Pyridine, CH_2Cl_2, Et_3N, DMSO, and DMF were dried over CaH_2. Flash chromatography was carried out with Merck silica gel 60 (230−400 ASTM mesh). TLC was carried out using Merck 60F$_{254}$ (0.25-mm thick) sheets. $LiAlH_4$, $NaBH_4$, $CH(OCH_3)_3$, and AD-mix-α/*β* were purchased from Sigma-Aldrich; $SOCl_2$ and $(COCl)_2$ were from Acros; NaN_3 was from Lancaster; (*R*)-(−)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride was from Fluka. Cameo filters were purchased from Fisher Scientific.

1,2-Hexadecanediols [(+)-3] and [(−)-3′]. A solution of 14.0 g of AD-mix-*β* (or AD-mix-α) in 150 mL of *t*-BuOH/H_2O 1:1 was stirred vigorously at room temperature for 30 min. After the reaction mixture was chilled with an ice−water bath, 2.68 g (12.0 mmol) of 1-hexadecene was added, and the reaction mixture was stirred vigorously at this temperature until the disappearance of the olefin was noticed by TLC. Sodium sulfite (15.0 g, 146.0 mmol) was added to quench the reaction. Stirring was continued for another 30−60 min while the reaction mixture was allowed to warm to room temperature. The product was extracted with EtOAc (3 × 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a solid residue, which was dissolved in minimum amount of $CHCl_3$ and passed through a pad of silica gel in a sintered glass funnel to remove the ligand. The pad was washed with hexane/EtOAc 2:1 to collect the product. Concentration provided 2.95 g (95%) of **3**/**3′** as an almost pure product.[11] The chiral purities of diol **3** and its enantiomer were enriched to >95% ee by recrystallization from EtOAc at a ratio of 1 g of diol **3** or its enantiomer **3′** per 40 mL of EtOAc.

[(2*R*)-(+)-3]: mp 83.2−84.0 °C; $[\alpha]^{25}_D$ +4.12° (*c* 2.7, $CHCl_3$/MeOH 1:1); IR 3619, 3432 cm^{-1}; ^{1}H NMR *δ* 0.86 (t, 3H, *J* = 7.0 Hz), 1.15−1.50 (m, 26H), 1.41 (br s, 1H), 2.03 (br s, 1H), 3.41 (dd, 1H, *J* = 7.7, 11.0 Hz), 3.63 (dd, 1H, *J* = 11.0, 3.0 Hz), 3.69 (m, 1H); ^{13}C NMR *δ* 14.10, 22.67, 25.52, 29.34, 29.53, 29.57, 29.64, 29.67, 31.91, 33.18, 66.83, 72.33.

[(2*S*)-(−)-3′]: mp 83.0−84.0 °C; $[\alpha]^{25}_D$ −4.08° (*c* 2.9, $CHCl_3$/MeOH 1:1); the IR, ^{1}H and ^{13}C NMR spectra were identical to those of (2*R*)-(+)-**3**.

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2-*O*-(Methoxymethyl)hexadecane-1,2-diols [(−)-4] and [(+)-4′]. To a stirred suspension of 2.58 g (10.0 mmol) of diol **3** or its enantiomer **3′** and 23 mg (0.1 mmol) of D-10-camphorsulfonic acid in 120 mL of dry CH_2Cl_2 at room temperature was injected 2.2 mL (20.0 mmol) of trimethyl orthoformate under nitrogen. The suspension became clear after several minutes. The reaction mixture was stirred at room temperature under nitrogen until TLC analysis (hexane/EtOAc 6:1) showed that diol **3**/**3′** was fully consumed (∼30 min). The reaction mixture was then chilled to −78 °C, and 40 mL (60 mmol) of DIBALH (a 1.5 M solution in toluene) was injected slowly. Stirring was continued at −78 °C until the unisolated ortho ester intermediate was not detected by TLC. The reaction was quenched by dropwise addition of 1 N HCl until no bubbles were observed. The reaction mixture was then transferred to a separatory funnel with 100 mL of 1 N HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried (5.0 g of Na_2SO_4 containing 1.0 g of anhydrous K_2CO_3), decanted, and concentrated. Purification of the residue on silica gel (elution first with 100 mL of hexane/EtOAc 100:1, then with hexane/EtOAc 30:1) provided 2.83 g (94%) of product **4** as a white solid, together with 70 mg (2.3%) of regioisomer **4a**.

[(2*R*)-(−)-4]: mp 36.5−38.0 °C; $[\alpha]^{25}_D$ −33.6° (*c* 2.8, $CHCl_3$); IR 3432, 1465, 1034 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.21 (m, 22H), 1.38−1.55 (m, 4H), 2.83 (br s, 1H), 3.45 (s, 3H), 3.48−3.63 (m, 3H), 4.66 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 6.9 Hz); ^{13}C NMR δ 14.08, 22.65, 25.68, 29.33, 29.51, 29.55, 29.61, 29.65, 31.64, 31.89, 55.57, 65.66, 82.27, 96.93; HR-MS [FAB, MH^+] *m*/*z* calcd for $C_{18}H_{39}O_3$ 303.2899, found 303.2903. **4a:** ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.23 (m, 24H), 1.39 (m, 2H), 2.48 (br s, 1H), 3.33−3.41 (m, 4H), 3.60 (dd, 1H, J = 10.3, 2.8 Hz), 3.75 (m, 1H), 4.65 (m, 2H); ^{13}C NMR δ 14.11, 22.68, 25.55, 29.35, 29.55, 29.58, 29.65, 29.67, 31.92, 55.39, 70.61, 73.18, 97.02.

[(2*S*)-(+)-4′]: mp 36.9−38.1 °C; $[\alpha]^{25}_D$ +33.3° (*c* 2.3, $CHCl_3$); IR 3430, 1465, 1030 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.21 (m, 22H), 1.38−1.55 (m, 4H), 2.90 (br s, 1H), 3.45 (s, 3H), 3.48−3.63 (m, 3H), 4.66 (d, 1H, J = 6.9 Hz), 4.71 (d, 1H, J = 6.9 Hz); ^{13}C NMR δ 14.10, 22.66, 25.53, 29.34, 29.52, 29.56, 29.62, 29.66, 31.66, 31.90, 55.59, 65.71, 82.38, 96.97.

General Procedures for the Preparation of (*E*)-α,β-Unsaturated Esters from the Corresponding Alcohols. a. Swern Oxidation. To a solution of 780 mg (10.0 mmol) of DMSO in 40 mL of dry CH_2Cl_2 at −78 °C was injected 0.44 mL (5.0 mmol) of oxalyl chloride under nitrogen. The reaction mixture was stirred at this temperature for 10 min, followed by the injection of 2.0 mmol of alcohol (**4**, **4′**, or cetyl alcohol) in 5−8 mL of dry CH_2Cl_2. The reaction temperature was changed from −78 °C to −46 °C, and the reaction mixture was stirred at the latter temperature until the complete consumption of alcohol was noticed by TLC (<3 h). After 3 mL (28.0 mmol) of Et_3N was injected, the cold bath was removed. Stirring was continued while the reaction mixture was allowed to warm to room temperature. The reaction mixture was transferred to a separatory funnel containing 50 mL of saturated aqueous $NaHCO_3$ solution, and the product was extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude aldehyde was dried thoroughly under high vacuum (0.7 Torr) and used without further purification in the subsequent reaction. **b. HWE Reaction.** To a nitrogen-flushed solution of 870 mg (10.0 mmol) of LiBr in 50 mL of freshly distilled THF was injected 2.4 mmol of $(EtO)_2P(O)CH_2CO_2Et$ or $(i\text{-}PrO)_2P(O)CH_2CO_2Et$ at room temperature. After the solution was stirred at room temperature for 10 min, 0.42 mL (4.0 mmol) of Et_3N was injected, and stirring was continued for another 15 min. The solution of thoroughly dried crude aldehyde in 10 mL of dry THF was injected. A white precipitate formed several minutes after the addition of the aldehyde. The reaction mixture was stirred vigorously at room temperature until the full consumption of the aldehyde was observed (TLC). The precipitate was removed by passing the reaction mixture through a pad of silica gel in a sintered glass funnel. The pad was washed with 400 mL of hexane/EtOAc 6:1. Concentration gave a pale yellow oil that was purified by column chromatography (elution with a gradient of hexane/EtOAc 100:1−25:1).

Ethyl (2*E*,4*R*)-4-(methoxymethyloxy)octadec-2-enoate [(+)-5]: mp 31.6−32.2 °C; $[\alpha]^{25}_D$ +46.4° (*c* 2.1, $CHCl_3$); IR 1712 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, J = 7.0 Hz), 1.23−1.35 (m, 27H), 1.57 (m, 2H), 3.35 (s, 3H), 4.17 (q, 2H, J = 7.2 Hz), 4.55 (d, 1H, J = 6.8 Hz), 4.60 (d, 1H, J = 6.8 Hz), 5.94 (dd, 1H, J = 15.7, 0.9 Hz), 6.78 (dd, 1H, J = 15.7, 6.4 Hz); ^{13}C NMR δ 14.12, 14.22, 22.69, 25.17, 29.36, 29.49, 29.51, 29.59, 29.65, 29.68, 31.92, 34.89, 55.60, 60.44, 75.21, 94.58, 121.75, 147.99, 166.28.

Ethyl (2*E*,4*S*)-4-(methoxymethyloxy)octadec-2-enoate [(−)-5′]: mp 30.1−30.8 °C; $[\alpha]^{25}_D$ −45.4° (*c* 3.0, $CHCl_3$); IR 1720, 1467 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, J = 7.0 Hz), 1.23 (m, 22H), 1.27 (t, 3H, J = 7.2 Hz), 1.35 (m, 2H), 1.57 (m, 2H), 3.35 (s, 3H), 4.17 (m, 2H), 4.55 (d, 1H, J = 6.8 Hz), 4.60 (d, 1H, J = 6.8 Hz), 5.94 (dd, 1H, J = 15.8, 1.0 Hz), 6.78 (dd, 1H, J = 15.8, 6.4 Hz); ^{13}C NMR δ 14.11, 14.21, 22.67, 25.15, 29.34, 29.48, 29.50, 29.57, 29.64, 29.67, 31.91, 34.87, 55.59, 60.44, 75.18, 94.55, 121.74, 147.99, 166.27.

Ethyl (2*E*)-octadec-2-enoate (13): IR 1716, 1654 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 24H), 1.28 (t, 3H, J = 7.1 Hz), 1.45 (m, 2H), 2.17 (dt, 2H, J = 7.2, 1.3 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.78 (dt, 1H, J = 15.6, 1.2 Hz), 6.94 (dt, 1H, J = 15.6, 7.0 Hz); ^{13}C NMR δ 14.11, 14.28, 22.69, 28.01, 29.14, 29.36, 29.40, 29.52, 29.63, 29.65, 29.69, 31.92, 32.20, 60.13, 121.15, 149.55, 166.82.

General Procedures for Asymmetric Dihydroxylation of an α,β-Unsaturated Ester. A solution of 14.0 g of AD-mix-β (or AD-mix-α) in 300 mL of *t*-BuOH/H_2O 1:1 was stirred vigorously at room temperature for 1 h. Then 950 mg (10.0 mmol) of methanesulfonamide was added, and stirring was continued for another 10 min at room temperature. After the reaction mixture was chilled with an ice−water bath, the α,β-unsaturated ester (10.0 mmol) was added and the reaction mixture was stirred vigorously at this temperature until the disappearance of the α,β-unsaturated ester was noted by TLC. Sodium sulfite (15.0 g, 146 mmol) was added to quench the reaction. Stirring was continued for another 30−60 min while the reaction mixture was allowed to warm to room temperature. The product was extracted with $CHCl_3$ (3 × 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow solid residue, which was dissolved in minimum amount of $CHCl_3$ and passed through a pad of silica gel in a sintered glass funnel to remove the ligand. The pad was washed with hexane/EtOAc 3:1 to collect the product. Concentration of the eluent provided an almost pure product. The % de of diol **6** and its enantiomer **6′** was determined by ^1H and ^{13}C NMR analysis.

Ethyl (2*S*,3*S*,4*R*)-4-methoxymethyloxy-2,3-dihydroxyoctadecanoate [(−)-6]: 92% yield (91% ee); mp 39.5−40.0 °C; $[\alpha]^{25}_D$ −11.34° (*c* 1.61, $CHCl_3$); IR 3530, 1726, 1707 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.20−1.50 (m, 27H), 1.64 (m, 2H), 2.50 (br s, 2H), 3.40 (s, 3H), 3.62 (dt, 1H, J = 7.0, 4.3 Hz), 3.82 (dd, 1H, J = 7.1, 0.93 Hz), 4.26 (dq, 2H, J = 7.1, 2.0 Hz), 4.44 (d, 1H, J = 1.0 Hz), 4.64 (d, 1H, J = 6.6 Hz), 4.70 (d, 1H, J = 6.6 Hz); ^{13}C NMR δ 14.10, 14.15, 22.67, 24.63, 29.34, 29.57, 29.59, 29.64, 29.67, 29.79, 31.34, 31.90, 56.06, 62.02, 70.22, 72.98, 79.72, 97.18, 173.50; HR-MS [FAB, MH^+] *m*/*z* calcd for $C_{22}H_{45}O_6$ 405.3216, found 405.3234.

Ethyl (2*S*,3*S*,4*S*)-4-methoxymethoxy-2,3-dihydroxyoctadecanoate (6′): ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.23 (m, 22H), 1.29 (t, 3H, J = 7.2 Hz), 1.31−1.63 (m, 4H), 3.07 (d, 1H, J = 7.45 Hz), 3.40 (s, 3H), 3.59 (m, 1H), 3.68 (m, 1H), 3.79 (m, 1H), 4.16 (d, 1H, J = 7.5 Hz), 4.26 (q, 2H, J = 7.1 Hz), 4.62 (d, 1H, J = 6.6 Hz), 4.72 (d, 1H, J = 6.6 Hz); ^{13}C NMR δ 14.11, 14.16, 23.08, 25.51, 29.75, 29.95, 29.99, 30.04, 30.08, 31.76, 32.31, 55.89, 61.93, 71.03, 74.04, 82.90, 98.18, 173.09.

Ethyl (2*S*,3*R*)-2,3-dihydroxyoctadecanoate [(+)-14]: mp 67.5−68.5 °C; $[\alpha]^{25}_D$ +8.1° (*c* 1.66, $CHCl_3$/MeOH 1:1); IR 3575, 1732 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.20−1.53 (m, 28H), 1.56 (m, 3H), 1.82 (d, 1H, J = 8.0 Hz), 3.00 (d, 1H, J = 5.0 Hz), 3.86 (m, 1H), 4.05 (dd, 1H, J = 5.0, 1.9 Hz), 4.27 (q, 2H, J = 7.1 Hz); ^{13}C NMR δ 14.12, 14.16, 22.68, 25.72, 29.35,

29.49, 29.54, 29.56, 29.64, 29.68, 31.91, 33.84, 62.15, 72.51, 72.96, 173.69.

General Procedures for the Preparation of a Cyclic Sulfate Intermediate. All cyclic sulfates were prepared by using the following two-step protocol. **a. Cyclic Sulfite.** To a solution of 2.0 mmol of a vicinal diol (**6**, **6′**, or **14**) in 30 mL of dry CH_2Cl_2 was injected 0.48 mL (6.0 mmol) of pyridine at room temperature. After the mixture was stirred and chilled at 0 °C, 220 μL (3.0 mmol) of $SOCl_2$ was injected slowly. The reaction mixture was stirred for 30 min, and then filtered through a pad of silica gel in a sintered glass funnel. The pad was washed with hexane/EtOAc 6:1−4:1 until no cyclic sulfite could still be detected by TLC. The filtrate was concentrated on a rotary evaporator and further dried on a vacuum pump (0.7 Torr, 1 h). The crude sulfite was used in the subsequent oxidation without further purification. **b. Cyclic Sulfate.** To a solution of the crude cyclic sulfite in 20 mL of MeCN was added 642 mg (3.0 mmol) of $NaIO_4$. The heterogeneous mixture was stirred vigorously while 7 mg (0.02 mmol) of $RuCl_3 \cdot 3H_2O$ in 8 mL of H_2O was added quickly. The reaction was stirred at room temperature until the full consumption of the starting material was observed (∼10 min). On addition of Et_2O (60 mL) to quench the reaction, the reaction mixture separated into two layers. After the top light brown clear solution was separated from the bottom slurry, enough H_2O was added to dissolve the slurry. The aqueous phase was extracted with Et_2O (2 × 60 mL). The organic phases were combined, dried (Na_2SO_4), and passed through a small pad of silica gel in a 10-mL buret. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (elution with hexane/EtOAc 6:1).

Cyclic sulfate 7: $[\alpha]^{25}_D$ +39.58° (*c* 3.04, $CHCl_3$); IR 1747 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 24H), 1.34 (t, 3H, J = 7.2 Hz), 1.54 (m, 2H), 3.39 (s, 3H), 3.97 (dt, 1H, J = 6.4, 3.7 Hz), 4.33 (m, 2H), 4.69 (s, 2H), 5.01 (dd, 1H, J = 5.2, 3.6 Hz), 5.25 (d, 1H, J = 5.3 Hz); ^{13}C NMR δ 13.95, 14.11, 22.68, 24.87, 29.35, 29.41, 29.43, 29.50, 29.59, 29.64, 29.66, 29.67, 30.59, 31.91, 56.15, 63.29, 75.43, 75.91, 83.73, 96.96, 165.95; HR-MS (FAB, MH^+) m/z calcd for $C_{22}H_{43}O_8S$ 467.2679, found 467.2663.

Cyclic sulfate 7′: $[\alpha]^{25}_D$ +56.23° (*c* 3.0, $CHCl_3$); IR 1755 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 24H), 1.34 (t, 3H, J = 7.2 Hz), 1.68 (m, 2H), 3.39 (s, 3H), 3.83 (dt, 1H, J = 6.8, 2.8 Hz), 4.33 (q, 2H, J = 7.2 Hz), 4.69 (s, 2H), 5.01 (dd, 1H, J = 6.6, 2.9 Hz), 5.28 (d, 1H, J = 6.6 Hz); ^{13}C NMR δ 13.98, 14.11, 22.68, 25.10, 29.34, 29.41, 29.42, 29.50, 29.58, 29.63, 29.66, 30.65, 31.91, 56.27, 63.27, 75.76, 83.35, 96.83, 165.63. The diastereomer of **7′** (the enantiomer of **7**): ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 22H), 1.34 (t, 3H, J = 7.1 Hz), 1.68 (m, 2H), 3.39 (s, 3H), 3.99 (dt, 1H, J = 6.3, 0.9 Hz), 4.33 (m, 2H), 4.69 (s, 2H), 5.02 (dd, 1H, J = 5.2, 3.7 Hz), 5.25 (d, 1H, J = 5.4 Hz); ^{13}C NMR δ 13.93, 14.10, 22.66, 24.86, 29.33, 29.39, 29.41, 29.48, 29.57, 29.62, 29.65, 30.56, 31.90, 56.13, 63.27, 75.41, 75.88, 83.72, 96.94, 165.93.

Cyclic sulfate 15: mp 45.4−46.2 °C; $[\alpha]^{25}_D$ +34.6° (*c* 3.12, $CHCl_3$); IR 1777, 1742 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 23H), 1.34 (t, 3H, J = 7.2 Hz), 1.50 (m, 3H), 1.97 (m, 2H), 4.33 (q, 2H, J = 7.2 Hz), 4.82 (d, 1H, J = 7.3 Hz), 4.92 (dt, 1H, J = 7.3, 5.2 Hz); ^{13}C NMR δ 13.97, 14.10, 22.67, 24.77, 28.84, 29.21, 29.34, 29.40, 29.54, 29.60, 29.64, 29.66, 31.91, 33.00, 63.28, 79.88, 84.13, 164.89.

General Procedure for the Regioselective α-Azidation of a Cyclic Sulfate. Regioselective azidation of the cyclic sulfate intermediate was carried out according to the following protocols. To a solution of 2.0 mmol of cyclic sulfate (**7**, **7′**, or **15**) in 30 mL of acetone was added 390 mg (6.0 mmol) of NaN_3, followed by 15 mL of H_2O. The reaction mixture was stirred at room temperature until the full consumption of the cyclic sulfate was noticed (TLC, hexane/EtOAc 4:1). Most of the acetone was removed on a rotary evaporator, and the residue was dried by high vacuum for 6−10 min (0.8 Torr). Then Et_2O (100 mL) and 20% aqueous H_2SO_4 (50 mL) were added in a fume hood, and the heterogeneous mixture was stirred vigorously at room temperature until the hydrolysis was completed. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). Anhydrous K_2CO_3 (100 mg) was added to the combined organic phase to remove the dissolved H_2SO_4. After 30 min the ether solution was dried (Na_2SO_4), filtered through a small pad of silica gel in a sintered glass funnel, and concentrated to give almost pure azido derivatives.

Ethyl (2*R*,3*S*,4*R*)-2-azido-3-hydroxy-4-(methoxymethyloxy)octadecanoate [(−)-8]: $[\alpha]^{25}_D$ −7.37° (*c* 2.09, $CHCl_3$); IR 3560, 3401, 2099, 1736 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.23 (m, 23H), 1.31 (t, 3H, J = 7.1 Hz), 1.41 (m, 1H), 1.54 (m, 1H), 1.66 (m, 1H), 3.39 (s, 3H), 3.65 (m, 1H), 3.94 (br s, 2H), 4.25 (dq, 2H, J = 7.1, 1.7 Hz), 4.58 (d, 1H, J = 6.8 Hz), 4.68 (d, 1H, J = 6.8 Hz); ^{13}C NMR δ 14.11, 22.68, 25.31, 29.35, 29.53, 29.58, 29.63, 30.75, 31.91, 56.11, 61.82, 62.29, 72.90, 81.56, 97.57, 169.08; HR-MS (FAB, MH^+) m/z calcd for $C_{22}H_{44}O_5N_3$ 430.3181, found 430.3294.

Ethyl (2*R*,3*S*,4*S*)-2-azido-3-hydroxy-4-(methoxymethyloxy)octadecanoate [(+)-8′]: $[\alpha]^{25}_D$ +35.95° (*c* 3.58, $CHCl_3$); IR 3557, 3439, 2100, 1724 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.24 (m, 23H), 1.34 (t, 3H, J = 7.2 Hz), 1.61 (m, 3H), 3.40 (s, 3H), 3.70 (dt, 1H, J = 6.7, 2.9 Hz), 3.79 (dd, 1H, J = 7.5, 2.9 Hz), 3.92 (d, 1H, J = 7.5 Hz), 4.28 (q, 2H, J = 7.2 Hz), 4.68 (s, 2H); ^{13}C NMR δ 14.11, 14.16, 22.68, 25.29, 29.30, 29.35, 29.53, 29.55, 29.61, 29.62, 29.64, 29.68, 30.77, 31.91, 56.03, 62.01, 63.05, 72.61, 78.09, 96.58, 169.39; HR-MS (FAB, MH^+) m/z calcd for $C_{22}H_{44}O_5N_3$ 430.3181, found 430.3275.

Ethyl (2*R*,3*R*)-2-azido-3-hydroxyoctadecanoate [(+)-16]: mp 38.5−39.4 °C; $[\alpha]^{25}_D$ +42.03° (*c* 2.01, $CHCl_3$); IR 3616, 2113, 1736 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.23 (m, 25H), 1.32 (t, 3H, J = 7.2 Hz), 1.52 (m, 3H), 2.21 (br s, 1H), 3.91 (m, 2H), 4.28 (dq, 2H, J = 7.2, 1.2 Hz); ^{13}C NMR δ 14.12, 14.16, 22.68, 25.34, 29.35, 29.37, 29.47, 29.55, 29.62, 29.65, 29.67, 31.91, 33.01, 62.07, 66.18, 71.90, 168.99.

α-Azido-β-hydroxylactones [(+)-9] and [(+)-9′]. To a 50-mL round-bottomed flask charged with 215 mg (0.50 mmol) of ethyl (2*R*,3*S*,4*R*)-2-azido-3-hydroxy-4-(methoxymethyloxy)-octadecanoate (**8**) or ethyl (2*R*,3*S*,4*S*)-2-azido-3-hydroxy-4-(methoxymethyloxy)octadecanoate (**8′**) was added 20 mL of concd HCl/MeOH 3:25. The solution was stirred at room temperature for 1−2 h under nitrogen. TLC analysis (hexane/EtOAc 6:1) indicated that most of the starting material had disappeared and that two more polar products were formed. After the solvents were removed (2-PrOH was used to remove the residual H_2O) by rotary evaporation, the residue was further dried under high vacuum (0.7 Torr) for 1−2 h, providing 169 mg (100%) of almost pure lactone **9**/**9′** as a light pink solid.

[(+)-9]: mp 76.3−77.0 °C; $[\alpha]^{25}_D$ +107.8° (*c* 1.43, $CHCl_3$); IR 3558, 2118, 1779, 1461, 1286, 1172 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.0 Hz), 1.18−1.53 (m, 24H), 1.60 (m, 2H), 2.40 (br s, 1H), 4.19 (dd, 1H, J = 5.0, 0.8 Hz), 4.28 (d, 1H, J = 5.1 Hz), 4.41 (dt, 1H, J = 7.3, 0.8 Hz); ^{13}C NMR δ 14.10, 22.68, 25.29, 29.08, 29.34, 29.45, 29.57, 29.65, 29.67, 31.91, 32.33, 59.73, 71.68, 85.38, 171.20.

[(+)-9′]: mp 90.0−90.8 °C; $[\alpha]^{25}_D$ +62.5° (*c* 1.07, $CHCl_3$); IR 3614, 3566, 2117, 1782, 1462, 1286, 1181 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, J = 7.0 Hz), 1.18−1.50 (m, 24H), 1.77 (m, 1H), 1.88 (m, 1H), 2.21 (br s, 1H), 4.26 (d, 1H, J = 4.5 Hz), 4.32 (m, 1H), 4.37 (m, 1H); ^{13}C NMR δ 14.11, 22.68, 25.03, 28.04, 29.35, 29.39, 29.50, 29.60, 29.64, 29.66, 29.68, 31.91, 61.97, 70.02, 81.65, 171.43.

General Procedure for $LiAlH_4$ Reduction of an Azido Ester to the Corresponding Sphingosine Analogue. To an ice-cooled suspension of 57 mg (1.5 mmol) of $LiAlH_4$ in 15 mL of freshly distilled THF under nitrogen was injected a solution of 0.25 mmol of azido lactone **9**, **9′**, or azido ester **16** in 4 mL of THF. The reaction mixture was stirred at 63−65 °C until the full consumption of the azido ester was noticed by TLC (∼2 h). After being diluted with 10 mL of dry THF and chilled in an ice−water bath, the reaction mixture was filtered through a pad of silica gel (∼8 g) slurry in hexane in a sintered glass funnel (2 cm × 6 cm) to remove the salt and the excess $LiAlH_4$ by gentle suction. Note: It was found that this workup procedure was very efficient for small-scale reactions. The pad was washed with $CHCl_3$/MeOH/concen-

trated NH_4OH 130:25:4 to collect the product. After concentration, the residue was purified by column chromatography (elution with $CHCl_3$/MeOH/concentrated NH_4OH 130:25:4), providing phytosphingosine **1a** or **1b**, or 4,5-dihydrosphingosine **1c** as white solids. The product was dissolved in a minimum volume of $CHCl_3$ and passed through a Cameo filter to remove the dissolved silica gel.

D-*ribo*-Phytosphingosine [(+)-1a]: mp 98.5−101.5 °C [lit.[5h] mp 95.4−98.5 °C]; $[\alpha]^{25}_D$ +9.7° (*c* 0.7, C_5H_5N) [lit.[5h] $[\alpha]^{27}_D$ +7.3° (*c* 1.0, C_5H_5N)]; IR (C_5H_5N) 3264, 2919, 2855, 1613, 1464, 1441, 1053 cm^{-1}; ^1H NMR (pyridine-d_5) δ 0.85 (t, 3H, J = 7.0 Hz), 1.20−1.50 (m, 22H), 1.71 (m, 1H), 1.91 (m, 2H), 2.26 (m, 1H), 3.52 (m, 1H), 3.98 (t, 1H, J = 7.2 Hz), 4.23 (dd, 1H, J = 8.4, 2.8 Hz), 4.26 (dd, 1H, J = 10.4, 6.0 Hz), 4.32 (dd, 1H, J = 10.4, 4.4 Hz), 4.94 (br s, 2H), 6.33 (br s, 2H); ^{13}C NMR (pyridine-d_5) δ 14.27, 22.92, 26.17, 29.60, 29.91, 29.96, 30.00, 30.15, 30.40, 32.10, 34.70, 57.70, 65.08, 75.10, 75.76.

D-*ribo*-Phytosphingosine Tetraacetate [(+)-10]. To a solution of 20 mg (63.0 μmol) of phytosphingosine **14** in 2.0 mL of pyridine was added 120 μL (1.23 mmol) of Ac_2O and 4.0 mg (32.0 μmol) of DMAP. The light brown solution was stirred overnight at room temperature. After the solvent was removed on a rotary evaporator, the residue was further dried under high vacuum (0.7 Torr) for 20 min, dissolved in 2 mL of CH_2Cl_2, and filtered through a pad of silica gel in a buret. The pad was rinsed with 50 mL of hexane/EtOAc 4:1. Concentration gave 29 mg (94%) of the desired phytosphingosine tetraacetate **10** as a colorless syrup: $[\alpha]^{25}_D$ +27.8° (*c* 0.8, $CHCl_3$) [lit.[5p] $[\alpha]^{25}_D$ +26.2° (*c* 2.0, $CHCl_3$), lit.[5q] $[\alpha]^{25}_D$ +26.3° (*c* 2.0, $CHCl_3$)]; IR 3324, 2937, 2865, 1742, 1665 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, J = 7.2 Hz), 1.22 (m, 24H), 1.6 (m, 2H), 2.00 (s, 3H), 2.02 (s, 6H), 2.05 (s, 3H), 3.97 (dd, 1H, J = 11.6, 3.2 Hz), 4.26 (dd, 1H, J = 12.0, 4.8 Hz), 4.44 (m, 1H), 4.90 (dt, 1H, J = 9.6, 3.2 Hz), 5.07 (dd, 1H, J = 8.4, 3.2 Hz), 5.95 (d, 1H, J = 9.6 Hz); ^{13}C NMR δ 14.11, 20.73, 20.76, 21.03, 22.67, 23.29, 25.49, 28.13, 29.28, 29.34, 29.47, 29.56, 29.61, 29.67, 31.90, 47.59, 62.81, 71.94, 72.94, 169.70, 170.07, 170.85, 171.14.

L-*lyxo*-Phytosphingosine [(+)-1b]: mp 104.8−106.0 °C [lit.[5g] mp 96−98 °C]; $[\alpha]^{25}_D$ −7.4° (*c* 0.9, C_5H_5N) [lit.[5g] $[\alpha]^{20}_D$ −7.1° (*c* 1.0, C_5H_5N)]; IR (C_5H_5N) 3332, 2919, 2857, 1617, 1467, 1443, 1075 cm^{-1}; ^1H NMR (pyridine-d_5) δ 0.85 (t, 3H, J = 7.0 Hz), 1.20−1.50 (m, 22H), 1.58 (m, 1H), 1.77 (m, 1H), 1.92 (m, 1H), 2.00 (m, 1H), 3.63 (m, 1H), 3.96 (m, 1H), 4.17 (m, 1H), 4.29 (m, 2H); ^{13}C NMR (pyridine-d_5) δ 14.26, 22.92, 26.78, 29.60, 29.91, 29.97, 30.08, 30.27, 32.11, 34.60, 56.56, 65.15, 72.33, 75.12.

D-*erythro*-Sphinganine [(+)-1c]: mp 92.0−94.0 °C [lit.[25e] mp 77−78 °C]; $[\alpha]^{25}_D$ +5.7° (*c* 2.74, $CHCl_3$/MeOH 4:1) [lit.[25e] $[\alpha]^{25}_D$ +5.5° (*c* 1.1, $CHCl_3$/MeOH 10:1)]; IR 3618, 3422 cm^{-1}; ^1H NMR δ 0.85 (t, 3H, J = 7.0 Hz), 1.23 (m, 26H), 1.45 (m, 2H), 2.77 (br s, 4H), 2.57 (m, 1H), 3.67 (m, 2H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 14.11, 22.67, 26.09, 29.35, 29.65, 29.69, 31.91, 33.76, 55.67, 63.31, 74.48.

General Procedure for the One-Pot Conversion of an Azido to an Amido Group. To a solution of 1.0 mmol of α-azidoester and 944 mg (2.5 mmol) of *p*-nitrophenyl palmitate in 30 mL of THF/H_2O 9:1 was added 314 mg (1.2 mmol) of Ph_3P. The reaction mixture was stirred at room temperature under nitrogen for 48 h (96 h for a phytoceramide precursor). After the solvents were removed in vacuo (2-PrOH was used to remove the residual H_2O), the light yellow residue was dissolved in 100 mL of Et_2O and washed with 1% aqueous Na_2CO_3 solution (4 × 20 mL) to remove the 4-nitrophenol byproduct. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (elution with hexane/EtOAc 5:1).

Ethyl (2*R*,3*S*,4*R*)-2-palmitoylamido-3-hydroxy-4-(methoxymethyloxy)octadecanoate [(−)-11]: mp 58.6−59.2 °C; $[\alpha]^{25}_D$ −32.95° (*c* 1.39, $CHCl_3$); IR 3537, 1738, 1654 cm^{-1}; ^1H NMR δ 0.84 (t, 6H, J = 7.0 Hz), 1.15−1.42 (m, 51H), 1.62 (m, 4H), 2.24 (t, 2H, J = 7.6 Hz), 3.34 (s, 3H), 3.48 (m, 1H), 3.82 (br s, 1H), 4.01 (dd, 1H, J = 7.1, 2.7 Hz), 4.16 (m, 2H), 4.51 (dd, 2H, J = 12.3, 6.5 Hz), 4.67 (dd, 1H, J = 6.7, 2.8 Hz), 6.67 (d, 1H, J = 6.6 Hz); ^{13}C NMR δ 13.96, 14.06, 22.64, 24.35, 25.52, 29.20, 29.28, 29.31, 29.43, 29.56, 29.61, 29.65, 29.83, 30.64, 31.88, 36.36, 55.83, 56.10, 61.61, 73.70, 80.18, 97.13, 170.24, 174.59; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{38}H_{76}NO_6$ 642.5672, found 642.5636.

Ethyl (2*R*,3*S*,4*S*)-2-palmitoylamido-3-hydroxy-4-(methoxymethyloxy)octadecanoate [(−)-11′]: mp 58.8−59.4 °C; $[\alpha]^{25}_D$ −8.24° (*c* 1.93, $CHCl_3$); IR 3510, 1742, 1652 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, J = 7.0 Hz), 1.20−1.42 (m, 49H), 1.60 (m, 3H), 1.74 (m, 1H), 2.22 (t, 2H, J = 7.6 Hz), 2.65 (br s, 1H), 3.39 (s, 3H), 3.54 (m, 1H), 3.70 (dd, 1H, J = 6.0, 3.8 Hz), 4.20 (m, 2H), 4.63 (d, 1H, J = 6.8 Hz), 4.70 (dd, 1H, J = 8.5, 3.7 Hz), 4.72 (d, 1H, J = 6.9 Hz), 6.47 (d, 1H, J = 8.4 Hz); ^{13}C NMR δ 14.11, 22.68, 25.20, 25.55, 29.23, 29.35, 29.48, 29.57, 29.61, 29.65, 29.68, 31.15, 31.91, 36.54, 54.22, 55.94, 61.52, 74.37, 82.40, 97.86, 170.35, 174.16; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{38}H_{76}NO_6$ 642.5672, found 642.5654.

Ethyl (2*R*,3*R*)-2-palmitoylamido-3-hydroxyoctadecanoate [(−)-17]: mp 76.6−77.5 °C; $[\alpha]^{25}_D$ −23.51° (*c* 3.16, $CHCl_3$); IR 3430, 1730, 1663, 1508 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 7.1 Hz), 1.23−1.46 (m, 58H), 1.61 (m, 2H), 2.24 (t, 2H, J = 7.7 Hz), 2.88 (br s, 1H), 3.92 (dt, 1H, J = 8.4, 3.6 Hz), 4.22 (m, 2H), 4.65 (dd, 1H, J = 6.6, 3.0 Hz), 6.42 (d, 1H, J = 6.6 Hz); ^{13}C NMR δ 14.10, 14.12, 22.68, 25.58, 25.65, 29.20, 29.31, 29.35, 29.48, 29.57, 29.60, 29.65, 29.68, 31.91, 33.22, 36.40, 57.87, 61.90, 73.22, 170.44, 174.25; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{36}H_{72}NO_4$ 582.5461, found 582.5467.

General Procedure for Selective Reduction of an Ester with $NaBH_4$−LiBr in the Presence of an Amide. To a heterogeneous mixture of 1.0 mmol of α-amido ester and 868 mg (10.0 mmol) of LiBr in 40 mL of freshly distilled THF was added 454 mg (12.0 mmol) of $NaBH_4$ at 0 °C. The suspension was stirred vigorously at room temperature under nitrogen until the full consumption of starting ester was noticed (TLC). The reaction mixture was transferred to a sintered glass funnel containing a pad of silica gel. The pad was washed with 400 mL of $CHCl_3$/MeOH 15:1 by gravity to collect the product. The filtrate was concentrated, and the residue was purified by column chromatography (elution with $CHCl_3$/MeOH 50:1). The product was dissolved in $CHCl_3$ (15−25 mL) and passed through a Cameo filter to remove the dissolved silica gel.

***N*-Palmitoyl-D-*erythro*-dihydrosphingosine [(+)-2c]:** mp 106.1−107.0 °C; $[\alpha]^{25}_D$ +6.67° (*c* 2.23, $CHCl_3$/MeOH 9:1); IR 3422, 1653, 1506 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD) δ 0.82 (t, 6H, J = 7.0 Hz), 1.19 (m, 49H), 1.44 (br s, 3H), 1.57 (m, 2H), 2.17 (*t*, 2H, J = 7.8 Hz), 3.62 (dd, 2H, J = 11.4, 3.4 Hz), 3.71 (m, 1H), 3.83 (dd, 1H, J = 11.4, 3.95 Hz), 6.78 (d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 14.00, 22.59, 25.70, 25.89, 29.21, 29.27, 29.43, 29.60, 31.83, 34.13, 36.63, 53.94, 61.82, 73.19, 174.05; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{34}H_{70}NO_3$ 540.5356, found 540.5356.

4-*O*-(Methoxymethyl)-*N*-palmitoyl-D-*ribo*-phytosphingosine [(−)-12]: mp 66.9−67.5 °C; $[\alpha]^{25}_D$ −11.46° (*c* 1.48, $CHCl_3$); IR 3422, 1658, 1501 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, J = 7.0 Hz), 1.15−1.45 (m, 48H), 1.59 (m, 4H), 2.20 (t, 2H, J = 7.7 Hz), 3.01 (br s, 2H), 3.41 (s, 3H), 3.62 (dt, 1H, J = 8.26, 4.14 Hz), 3.73 (m, 2H), 3.89 (dd, 1H, J = 11.5, 3.8 Hz), 4.11 (dt, 1H, J = 4.15, 4.13 Hz), 4.61 (d, 1H, J = 6.5 Hz), 4.72 (d, 1H, J = 6.5 Hz), 6.30 (d, 1H, J = 8.4 Hz); ^{13}C NMR δ 14.09, 22.67, 25.49, 25.74, 29.29, 29.34, 29.49, 29.59, 29.65, 29.68, 30.61, 31.91, 38.81, 51.65, 56.06, 62.59, 73.90, 82.00, 97.34, 173.85; HR-MS (FAB, MH^+) *m*/*z* calcd for $C_{36}H_{74}NO_5$ 600.5567, found 600.5567.

4-*O*-(Methoxymethyl)-*N*-palmitoyl-L-*lyxo*-phytosphingosine [(+)-12′]: mp 65.0−65.8 °C; $[\alpha]^{25}_D$ +13.17° (*c* 1.4, $CHCl_3$); IR 3375, 1655, 1501 cm^{-1}; ^1H NMR δ 0.86 (t, 6H, J = 7.0 Hz), 1.23−1.41 (m, 48H), 1.56 (m, 4H), 2.19 (t, 2H, J = 7.8 Hz), 3.29 (br s, 2H), 3.39 (s, 3H), 3.49 (m, 1H), 3.67 (m, 2H), 3.90 (dd, 1H, J = 11.6, 3.6 Hz), 3.99 (dt, 1H, J = 8.0, 4.2 Hz), 4.66 (d, 1H, J = 6.6 Hz), 4.74 (d, 1H, J = 6.6 Hz), 6.44 (d, 1H, J = 8.2 Hz); ^{13}C NMR δ 14.08, 22.66, 25.19, 25.70, 29.26, 29.34, 29.48, 29.57, 29.63, 29.67, 31.27, 31.89, 36.81, 51.43, 55.94, 62.52, 74.43, 82.01, 97.79, 173.58.

General Procedure for Removal of the MOM Protecting Group. The MOM protecting group was removed by acid hydrolysis as follows. To 300 mg (0.50 mmol) of 2-palmitoyl-

amido-4-*O*-(methoxymethyl)phytoceramide (**11** or **11′**) in a 100-mL round-bottomed flask was added 28 mL of methanolic hydrochloric acid (12 N HCl/MeOH 3:25, v/v), followed by 6 mL of $CHCl_3$. The solution was stirred vigorously at room temperature until the full consumption of the starting material was detected (TLC). After most of the methanol was removed on a rotary evaporator (without heating), the residue was transferred to a 125-mL separatory funnel containing 40 mL of $CHCl_3$, and 30 mL of H_2O was added. The product was extracted with $CHCl_3$ (4 × 30 mL), and the combined extracts were treated with anhydrous K_2CO_3, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (elution with $CHCl_3$/MeOH 50:1).

***N*-Palmitoyl-D-*ribo*-phytosphingosine [(+)-2a]:** mp 124.2−125.0 °C; $[\alpha]^{25}_D$ +6.8° (*c* 0.43, $CHCl_3$/MeOH 1:1); IR 3364, 3305, 1648 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.73 (t, 6H, J = 7.0 Hz), 1.05−1.35 (m, 49H), 1.35−1.65 (m, 4H), 2.08 (t, 2H, J = 7.9 Hz), 3.40 (m, 2H), 3.54 (dd, 1H, J = 11.4, 5.3 Hz), 3.64 (dd, 1H, J = 11.5, 4.0 Hz), 3.93 (m, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 13.74, 22.41, 25.56, 29.05, 29.10, 29.13, 29.26, 29.40, 29.44, 31.67, 32.78, 36.27, 51.74, 60.84, 72.23, 75.41, 174.49; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{34}H_{70}NO_4$ 556.5304, found 556.5293.

***N*-Palmitoyl-L-*lyxo*-phytosphingosine [(+)-2b]:** mp 110.8−111.7 °C; $[\alpha]^{25}_D$ +7.0° (*c* 0.56, C_5H_5N); IR 3360, 1654 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.83 (t, 6H, J = 7.0 Hz), 1.10−1.48 (m, 50H), 1.56 (m, 3H), 2.18 (t, 2H, J = 7.7 Hz), 3.32 (d, 1H, J = 8.7 Hz), 3.45 (m, 1H), 3.57 (dd, 1H, J = 11.5, 3.8 Hz), 3.64 (dt, 1H, J = 8.7, 3.1 Hz), 3.75 (dd, 1H, J = 11.4, 2.9 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 13.63, 22.33, 25.56, 25.77, 29.04, 29.22,29.36, 31.59, 32.46, 36.08, 52.57, 60.65, 69.69, 71.66, 175.50; HR-MS (FAB, MH^+) calcd for *m*/*z* $C_{34}H_{70}NO_4$ 556.5304, found 556.5296.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **1a**−**c**, **2a**−**c**, **3**−**17**, **3′**−**12′**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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