Synthesis of L-*lyxo*-Phytosphingosine and Its 1-Phosphonate Analogue Using a Threitol Acetal Synthon

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The first synthesis of an isosteric phosphonate analogue of the aminotriol lipid phytosphingosine (**3**), together with an improved synthesis of (2*S*,3*S*,4*S*)-phytosphingosine (**2**), are described. A key intermediate is 3-pentylidene acetal **9**, which was prepared in two steps from dimethyl 2,3-*O*-benzylidene-D-tartrate (**7**).

Introduction

The trihydroxy sphingoid base phytosphingosine (4D-hydroxysphinganine, PHS) consists of an aliphatic chain (predominantly octadecyl) bearing a 2-amino-1,3,4-triol headgroup. PHS differs from sphingosine in that it possesses an additional hydroxy group (at C4) but does not possess a 4,5-trans double bond. PHS is the major sphingoid base in fungi, plants, and several mammalian tissues.[1] In addition to its structural role in membranes, PHS has a number of physiological roles, many of which remain to be elucidated. PHS is involved in the heat stress response of yeast cells[2] and induces apoptosis in cancer cells.[3] Amide-linked derivatives of PHS, which constitute $\sim$30% of the total ceramide content of the stratum corneum (the water permeability barrier of human skin),[4] self-associate extensively via hydrogen bonds even in the hydrated state and have different chain-packing properties than ceramides with a sphingosine backbone.[4d] PHS is also the backbone of (a) KRN7000, an α-galactosylsphingolipid that stimulates natural killer cells to produce cytokines and strongly inhibits tumor metastasis in mice[5] and (b) the glycosylphosphatidylinositol (GPI) of the membrane-anchored proteins in yeast.[6]

The construction of the aminotriol moiety of the phytosphingosines represents a synthetic challenge. A number of routes to naturally occurring (2*S*,3*S*,4*R* or D-ribo)-PHS (Chart 1, **1**) and some of its diastereomers have been reported.[7] The chiral centers of the PHS molecule have generally been derived from carbohydrate[8] and serine precursors.[9] In addition, chiral induction into PHS has been achieved by the Sharpless asymmetric epoxidation[10] and asymmetric dihydroxylation reactions,[11] asymmetric aldol reactions,[12] and other stereoselective methods.[13] In this paper, we describe an efficient method for the preparation of L-*lyxo*-PHS (**2**)[11,14] that utilizes a pentylidene group to protect the 1,2-diol moiety of 3-*O*-protected-D-threitol **8** as an acetal. To further illustrate the utility of this method, we synthesized an

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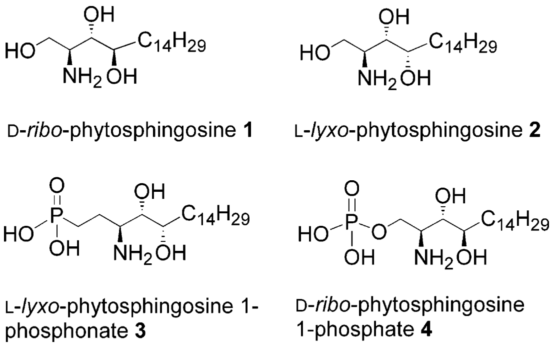
CHART 1. Structures of D-*ribo*-PHS (1) and Its Phosphate Ester (4) and of L-*lyxo*-PHS (2) and Its Isosteric 1-Phosphonate Derivative (3)

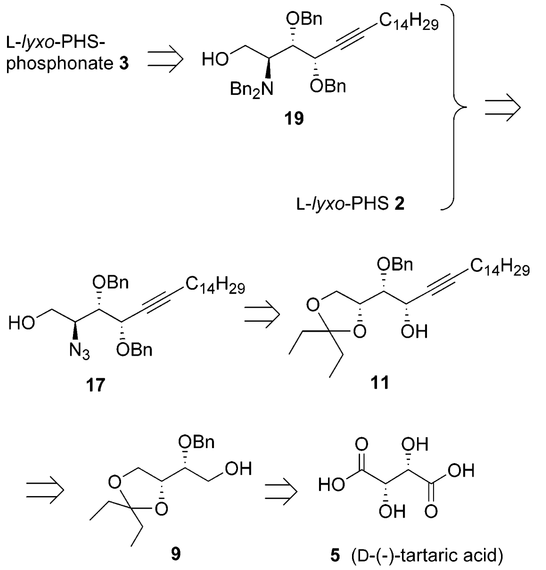


isosteric phosphonate derivative of **2**, L-*lyxo*-phytosphingosine 1-phosphonate (**3**). Our interest in the latter compound arises from the recent finding that a phosphate ester of PHS, D-*ribo*-phytosphingosine 1-phosphate (**4**), possesses a higher affinity than sphingosine-1-phosphate for a widely distributed cell-surface G protein coupled receptor.[15] Since the carbon−phosphorus bond is resistant to the action of lipid phosphohydrolases, a phosphonate derivative[16] of a bioactive lysosphingolipid such as **4**, in which the phosphate oxygen at C1 of **4** is replaced with a methylene group, is expected to have a long half-life in cells and thus be a valuable pharmacological tool to probe receptor-specific interactions. In previous work, we have found that isosteric phosphonate analogues of glycerophospholipids retain the biological activity of the parent phosphate esters.[17] It should also be noted that nonhydrolyzable phosphonolipids with a 2-amino-3,4-dihydroxy headgroup are found in some bacteria[18] and mollusks.[19]

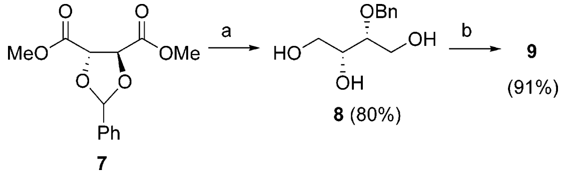
Results and Discussion

As illustrated in the retrosynthetic analysis (Scheme 1), our syntheses of L-*lyxo*-phytosphingolipids **2** and **3** started with readily available D-(−)-tartaric acid (**5**), which was converted to pentylidene-protected D-threitol derivative **9** (see Scheme 2). After Dess−Martin oxidation,[20] the aliphatic chain was installed with concomitant construction of the third chiral center, the acetal of tetrol **11** was released, and regioselective azidation of the secondary hydroxy group of the resultant 1,2-diol with inversion of configuration was accomplished, affording azido alcohol **17**. For the synthesis of L-lyxo-PHS (**2**), the azido group and triple bond of **17** were reduced, and the protecting groups at C3 and C4 were removed in a one-pot reaction. For the synthesis of the isosteric phosphonate analogue **3**, azide **17** was converted to protected α-(*N*,*N*-dibenzyl)amino alcohol **19**. Condensation of the aldehyde derived from **19** with tetramethyl methylenediphosphonate, followed by ester hydrolysis, reduction of the unsaturation, and hydrogenolysis of the protecting groups, afforded PHS-phosphonate **3**.

SCHEME 1. Retrosynthetic Plan



SCHEME 2. Preparation of Threitol Derivative 9[a]



[a] Reagents and conditions: (a) LiAlH$_4$, AlCl$_3$, Et$_2$O, reflux and (b) pentanone, HClO$_4$, MS (method A), or 3,3-dimethoxypentane, 10% CSA, THF, reflux, 30 min, then K$_2$CO$_3$ (method B).

Synthesis of Threitol Derivative 9. D-(−)-Tartaric acid (**5**) has been used extensively as a chiral precursor of many natural products.[21] Scheme 2 shows a short synthesis of the protected threitol derivative **9**. Benzylidene acetal **7** is commercially available or can be readily prepared by esterification of **5** (SOCl$_2$, MeOH) to give dimethyl ester **6**, followed by acetal protection of the hydroxy groups (PhCHO, *p*-TsOH, cyclohexane, reflux; see Supporting Information); alternatively, **7** is accessible from **5** in a one-pot reaction.[22] Both ester and acetal functionalities of **7** were reduced with LiAlH$_4$ in the presence of AlCl$_3$,[23] affording triol **8** in 80% yield. We found that the 1,2-isopropylidene-protected derivative of **8**, which is a widely used building block,[24] was unstable on storage, especially as a solution in chloroform. Therefore, we converted triol **8** to pentylidene acetal **9**, which

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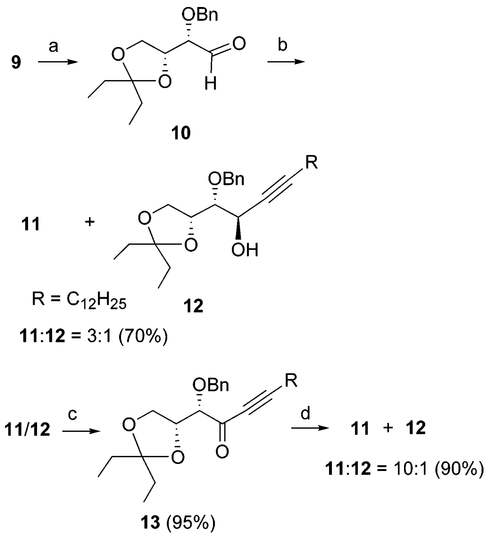
SCHEME 3. Preparation of Propargyl Alcohol 11[a]

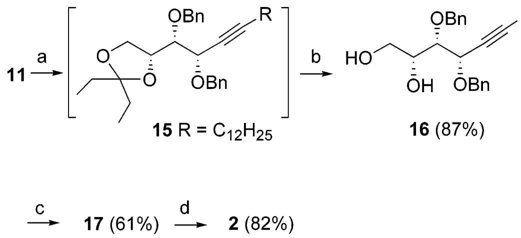


[a] Reagents and conditions: (a) PCC, NaOAc, CH_2Cl_2, MS; (b) *n*-BuLi, 1-tetradecyne, Et_2O, $ZnBr_2$, −20 °C to rt; (c) Dess−Martin periodinane, CH_2Cl_2, 1 h, rt; and (d) L-Selectride, THF, −78 °C to rt.

is less acid sensitive and thus more stable than the isopropylidene acetal. The most suitable conditions for the formation of this new acetal derivative entail the brief heating of **8** with 3,3-dimethoxypentane[25] (1.2 equiv) with a catalytic amount of 10-camphorsulfonic acid (CSA) in THF (reflux, 30 min; overall yield for the four steps >50%).

Synthesis of Propargyl Alcohol 11. Alcohol **9** was oxidized to the corresponding aldehyde **10** with PCC in the presence of NaOAc and molecular sieves (Scheme 3).[26] A chelation-controlled addition of tetradecynyllithium to aldehyde **10** in the presence of anhydrous $ZnBr_2$ in Et_2O afforded a mixture of **11** and **12** in a ratio of only 3:1. The mild selectivity may be a result of 2,3-chelation of Zn^{2+} to give the undesired diastereomer **12**.[27] In an attempt to increase the yield of **11**, the mixture of **11** and **12** was oxidized to the propargylic ketone and then reduced diastereoselectively. Although PCC oxidation gave a disappointing result,[28] oxidation of the mixture of propargyl alcohols **11** and **12** with the Dess−Martin periodinane reagent afforded ketone **13** exclusively. Unfortunately, during the purification of crude **13** by silica gel column chromatography, some loss of configuration at C3 took place. Therefore, the crude ketone **13** was used directly in the next step. Reduction of **13** with L-Selectride (−78 °C, THF) afforded propargyl alcohol **11** as the major product (C3,C4 syn). The ratio of **11**:**12** was 10:1, and the overall yield of the isolated products was 90%. Pure propargyl alcohol **11** was obtained by column chromatography (elution with hexane/EtOAc 6:1).[29]

SCHEME 4. Conversion of 11 to L-*lyxo*-PHS (2)[a]



[a] Reagents and conditions: (a) BnBr, TBAB, NaH, THF, reflux, 3 h; (b) 5% H_2SO_4, MeOH, rt; (c) (i) PPh_3, DIAD, CH_2Cl_2, 0 °C, (ii) $TMSN_3$, 0 °C to rt, and (iii) TBAF, THF, rt; and (d) $Pd(OH)_2/C$, H_2, MeOH.

Synthesis of L-*lyxo*-PHS (2). Scheme 4 outlines the synthesis of product **2** from alcohol **11**. After the hydroxy group of **11** was protected as a benzyl ether (BnBr, NaH, catalytic *n*-Bu_4NBr (TBAB)), selective deprotection of **15** with 5% H_2SO_4 provided 1,2-diol **16** in 87% yield for the two steps. Diol **16** was converted to azido alcohol **17** in a one-pot reaction.[30a] This was accomplished by adding the diol to a mixture of diisopropyl azodicarboxylate (DIAD) and Ph_3P at 0 °C. After 3 h, $TMSN_3$ was added to accomplish the azide substitution reaction.[30b] Hydrolysis of the silyl ether of the primary hydroxy group and purification by column chromatography provided azido alcohol **17** in 61% yield. Simultaneous reduction of the azido group and the triple bond, together with hydrogenolysis of the benzyl groups in the presence of Pearlman's catalyst ($Pd(OH)_2/C$), gave L-*lyxo*-PHS **2** in 82% yield. The NMR spectra and rotation data were in full accord with previously reported data.[11]

Synthesis of L-*lyxo*-PHS 1-Phosphonate (3). We used a Horner−Wadsworth−Emmons reaction to introduce an (*E*)-enephosphonate moiety (Scheme 5). A low yield was obtained in the reaction of tetramethyl methylenediphosphonate with the aldehyde derived by oxida-

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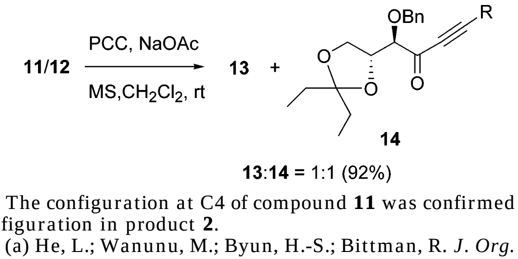
[24] For examples, see: (a) Backstrom, A. D.; Austin, R.; McMordie, A. S.; Begley, T. P. *J. Carbohydr. Chem.* **1995**, *14*, 171−175. (b) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239−10252. (c) Matsumura, R.; Suzuki, T.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 1543−1546.

[25] See the Experimental Procedures for an alternative method to prepare **9**. For methods to prepare 3,3′-dimethoxypentane, see: (a) Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* **1986**, 122−125. (b) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821−1826.

[26] The ^1H and ^{13}C NMR spectra of **10** indicate that epimerization did not occur at C2. Furthermore, the configuration at C2 was not altered on PCC oxidation of chiral 2-*O*-benzyl-3,4-*O*-isopropylidene-1-butanol to the isopropylidene aldehyde analogue of **10**: (a) Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869−872. (b) Valverde, S.; Herradon, B.; Martin-Lomas, M. *Tetrahedron Lett.* **1985**, *26*, 3731−3734. (c) Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209−3246.

[27] Recent advances in enantioselective additions of alkynylmetals to aldehydes (for a recent review, see Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886) suggest that it will be possible to improve the ratio of **11**:**12**. On the other hand, **12** may predominate when the addition is carried out under nonchelating conditions, thereby providing the stereochemistry leading to the D-*ribo*-PHS backbone.

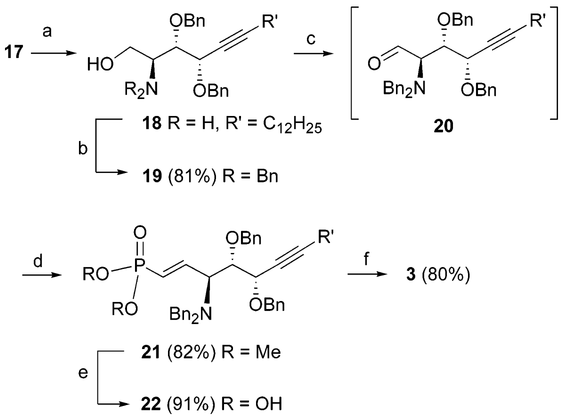
[28] PCC oxidation of the mixture of compounds **11** and **12** gave a mixture of diastereomers **13** and **14** in a 1:1 ratio.



[29] The configuration at C4 of compound **11** was confirmed by the 4*S* configuration in product **2**.

[30] (a) He, L.; Wanunu, M.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1999**, *64*, 6049−6055. (b) For a postulated mechanism to account for the conversion of a 1,2-diol to a 2-azido-1-ol with inversion, see: Scheme 1 of ref 30a and Mathieu-Pelta, I.; Evans, S. A., Jr. *J. Org. Chem.* **1992**, *57*, 3409−3413.

SCHEME 5. Conversion of 17 to L-*lyxo*-PHS 1-Phosphonate (3)[a]



[a] Reagents and conditions: (a) PPh_3, THF/H_2O 9:1, rt, 48 h; (b) K_2CO_3, BnBr, H_2O, NaOH; (c) Dess–Martin periodinane, CH_2Cl_2, rt; (d) tetramethyl methylenediphosphonate, THF, NaH; (e) TMSBr, CH_2Cl_2; and (f) $Pd(OH)_2/C$, H_2, MeOH.

tion of azido alcohol **17**. Therefore, the azido group was first reduced to an amino group with PPh_3 in THF/H_2O (9:1) to afford 2-amino alcohol **18**. Reaction of the amino group with excess benzyl bromide in K_2CO_3/NaOH (1:1) in water gave *N*,*N*-dibenzyl amino alcohol **19** (81% yield for the two steps). Oxidation of **19** with the Dess–Martin reagent afforded aldehyde 20,[31] which reacted with the anion derived from tetramethyl methylenediphosphonate to provide unsaturated phosphonate ester **21** (82% for the two steps). Treatment of **21** with trimethylsilyl bromide, followed by 5% aqueous MeOH, afforded phosphonic acid **22** in 91% yield. Finally, reduction of the double and triple bonds and deprotection of the *N*- and *O*-benzyl groups all at the same time gave the desired (2*S*,3*S*,4*S*)-PHS-phosphonate analogue **3** in 80% yield.

Conclusion

A novel synthesis of L-*lyxo*-PHS (**2**) and the first synthesis of L-*lyxo*-PHS 1-phosphonate (**3**) via the new D-threitol acetal derivative **9** have been reported here. Coupling of 1-tetradecyne with aldehyde **10** gave a mixture of alcohols **11** and **12**, which were oxidized and then reduced with L-Selectride to install the third chiral center. After protection of the 4-hydroxy group and deprotection of the 1,2-hydroxy groups, the 2-hydroxy group was converted to an azido group with inversion of configuration. Hydrogenolysis gave L-*lyxo*-PHS (**2**). An unsaturated phosphonate moiety was introduced by reaction of tetramethyl methylenediphosphonate with aldehyde **20**. Ester hydrolysis, followed by deprotection and reduction of the double and triple bonds, gave L-*lyxo*-PHS 1-phosphonate **3** in high yield. If L-tartaric acid is used as the starting material, the methods shown here can be used to prepare the enantiomers of these phytosphingolipids. The availability of 1-phosphonate derivatives of PHS diastereomers is expected to spur analysis of the bioactivities of these lysolipids.

Experimental Procedures[32]

(2*R*,3*R*)-2-*O*-Benzyl-3,4-*O*-(3′-pentylidene)-1-butanol [(+)-9]. Two methods were used to prepare acetal **9**. In method A, triol **8** underwent reaction with 3-pentanone, whereas in method B it reacted with 3,3-dimethoxypentane. Method A: a slurry of 8.4 g (39.6 mmol) of triol **8**, 25.2 g of 4 Å molecular sieves, and 42 mL (396 mmol) of 3-pentanone in 300 mL of dry THF was treated with 4.1 mL (41 mmol) of concentrated $HClO_4$. The mixture was stirred overnight and then quenched by adding 40 g (290 mmol) of anhydrous K_2CO_3. The solid residue was removed by filtration and washed with Et_2O (2 × 100 mL). The solvent was evaporated, and the residue was purified by column chromatography (elution with EtOAc/hexane 1:3) to give **9** (9.8 g, 88%) as a colorless liquid. Method B: to a solution of 8.4 g (39.6 mmol) of triol **8** and 930 mg (4.0 mmol) of CSA in 300 mL of dry THF was added 6.3 g (47.5 mmol) of 3,3-dimethoxypentane. The solution was stirred at reflux for 2 h and then quenched by adding 4.0 g (29 mmol) of anhydrous K_2CO_3. The solid residue was removed by filtration and washed with Et_2O (2 × 100 mL). The solvent was evaporated, and the residue was purified by chromatography (EtOAc/hexane 1:3) to give 10.2 g (91%) of **9** as a colorless liquid: $[\alpha]^{25}_{D}$ +15.4° (*c* 3.75, $CHCl_3$); R_f 0.30 (EtOAc/hexane 1:3); ^1H NMR (C_6D_6) δ 1.00–1.07 (m, 6H), 1.68–1.79 (m, 4H), 1.90 (s, 1H), 3.36 (m, 1H), 3.43 (m, 1H), 3.57 (m, 2H), 3.84 (t, 1H, J = 6.4 Hz), 4.24 (m, 1H), 4.65 (d, 1H, J = 12.0 Hz), 4.74 (d, 1H, J = 12.0 Hz), 7.18 (m, 1H), 7.27 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (C_6D_6) δ 8.36, 8.42, 29.7, 30.1, 62.3, 66.4, 72.8, 78.1, 80.0, 113.2, 128.0, 139.2; HR-MS (FAB, MNa^+) *m*/*z* calcd for $C_{16}H_{24}O_4Na^+$ 303.1568, found 303.1574.

(2*R*,3*S*)-2-*O*-Benzyl-3,4-*O*-(3′-pentylidene)-2,3,4-trihydroxybutanal (10). A mixture of 5.6 g (20.0 mmol) of triol **8** and 5 g of 3 Å molecular sieves in 200 mL of dry CH_2Cl_2 was stirred at room temperature for 2 h (mixture A). A slurry of 11.5 g (140 mmol) of NaOAc, 15.8 g (73.3 mmol) of PCC, and 5 g of 3 Å molecular sieves in 200 mL of CH_2Cl_2 was stirred at room temperature for 2 h (mixture B). Mixture B was added to mixture A, with stirring at room temperature for 4 h. After 400 mL of dry Et_2O was added, stirring was continued for 30 min. The resulting precipitate was removed by filtration over a short pad of silica gel and thoroughly washed with Et_2O. The solvent was evaporated, and the residue was dried to give 5.0 g (91%) of **10** as a pale yellow liquid, which was used in the next reaction without further purification. A pure sample of aldehyde **10** was obtained by flash chromatography (3:1 hexane/EtOAc); R_f 0.59 (EtOAc/hexane 1:3); ^1H NMR ($CDCl_3$) δ 0.84–0.92 (m, 6H), 1.58–1.72 (m, 4H), 3.85 (m, 2H), 4.05 (t, 1H, J = 6.8 Hz), 4.34 (m, 1H), 4.68 (d, 1H, J = 12.0 Hz), 4.78 (d, 1H, J = 12.0 Hz), 7.25–7.40 (m, 5H), 9.70 (d, 1H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 8.09, 8.14, 28.7, 39.3, 65.8, 73.4, 75.6, 83.1, 113.7, 128.1, 128.2, 128.4, 128.5, 137.1, 202.0.

(2*R*,3*R*,4*S*)- and (2*S*,3*R*,4*R*)-3-*O*-Benzyl-1,2-*O*-(3′-pentylidene)-5-octadecyn-1,2,3,4-tetrol (11) and (12). To a solution of 1.6 g (8.2 mmol) of 1-tetradecyne in 100 mL of dry Et_2O at −20 °C was added dropwise 3.3 mL (8.2 mmol) of *n*-BuLi (a 2.89 M solution in hexane) under nitrogen. The white suspension was stirred at −20 °C for 1 h, and then 2.15 g (9.5 mmol) of anhydrous $ZnBr_2$ was added at 0 °C. After 1 h at 0 °C and 1 h at room temperature, a solution of 1.9 g (6.8 mmol) of aldehyde **10** in 20 mL of dry Et_2O was added dropwise at −20 °C. The mixture was allowed to warm to room temperature overnight and then quenched by the addition of 20 mL of saturated aqueous NH_4Cl solution at −20 °C. After the mixture was diluted with 80 mL of water, the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was purified by chromatography (EtOAc/hexane 1:3) to give a 3:1 mixture of **11**/**12** (2.2 g, 70%) as a colorless liquid.

(2*R*,3*R*)-3-*O*-Benzyl-1,2-*O*-(3′-pentylidene)-4-oxo-5-octadecyn-1,2,3-triol [(−)-13]. A solution of 2.00 g (5.0 mmol) of the 3:1 mixture of **11**/**12** in 100 mL of dry CH_2Cl_2 at room

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[31] For the Dess–Martin oxidation of a *N*,*N*-dibenzyl-α-amino alcohol, see: Cooke, J. W. B.; Davies, S. G.; Naylor, A. *Tetrahedron* **1993**, *49*, 7955–7966.

[32] See the Supporting Information for general methods.

temperature was treated with 2.00 g (5.5 mmol) of Dess−Martin periodinane. After 1 h, TLC analysis indicated the complete consumption of starting material. An aqueous solution of 10% $Na_2S_2O_3$ (50 mL, 20.2 mmol) was added. The mixture was stirred until both layers became clear. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution, water, and brine and dried ($MgSO_4$). The solvent was evaporated, and the residue was dried to afford 1.89 g (95%) of ketone **13** as a colorless liquid. A pure sample of **13** was obtained by flash chromatography (hexane/EtOAc 3:1); $[\alpha]^{25}_D$ −28.4° (*c* 13.0, $CHCl_3$); R_f 0.87 (hexane/EtOAc 3:1); ^1H NMR (C_6D_6) δ 1.01 (m, 6H), 1.27 (t, 3H, J = 6.0 Hz) 1.26−1.40 (m, 20H), 1.68 (q, 2H, J = 7.2 Hz), 1.82 (q, 2H, J = 7.2 Hz), 2.02 (t, 2H, J = 6.8 Hz), 4.05 (m, 3H), 4.35 (d, 1H, J = 12.0 Hz), 4.66 (m, 2H), 7.17−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.56, 14.3, 19.0, 22.2, 27.8, 29.1, 29.4, 29.5, 29.8, 30.0, 30.1, 33.8, 66.9, 72.1, 73.4, 76.8, 85.9, 97.2, 114.0, 128.0, 128.1, 128.5, 137.8, 186.3; HR-MS (FAB, MNa^+) m/z calcd for $C_{30}H_{46}O_4Na^+$ 493.3288, found 493.3288.

(2*R*,3*S*)-3-*O*-Benzyl-1,2-*O*-(3′-pentylidene)-4-oxo-5-octadecyn-1,2,3-triol [(−)-14]. PCC oxidation of a mixture of **11**/**12** gave a 1:1 mixture of **13**/**14** in 92% total yield. A pure sample of **14** was obtained by flash chromatography (hexane/EtOAc 3:1); $[\alpha]^{25}_D$ −14.4° (*c* 2.5, $CHCl_3$); R_f 0.93 (hexane/EtOAc 3:1); ^1H NMR (C_6D_6) δ 1.03−1.18 (m, 9H), 1.26−1.43 (m, 20H), 1.70 (q, 2H, J = 7.2 Hz), 1.85 (q, 2H, J = 7.2 Hz), 2.02 (t, 2H, J = 6.8 Hz), 3.91 (d, 1H, J = 5.2 Hz), 4.05 (m, 2H), 4.48 (d, 1H, J = 12.0 Hz), 4.64 (m, 1H), 4.85 (d, 1H, J = 12.0 Hz), 7.25−7.29 (m, 3H), 7.45 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 8.31, 8.36, 8.44, 14.4, 19.1, 23.1, 27.8, 29.1, 29.4, 29.5, 29.8, 30.0, 30.1, 32.3, 66.2, 73.2, 76.9, 81.0, 85.5, 97.4, 113.8, 128.0, 128.1, 128.5, 138.2, 186.6; MS (ESI) m/z 488.3 (MNH_4^+).

(2*R*,3*R*,4*S*)-3-*O*-Benzyl-1,2-*O*-(3′-pentylidene)-5-octadecyn-1,2,3,4-tetrol [(+)-11]. To a solution of 543 mg (1.19 mmol) of ketone **13** in 50 mL of dry THF was added 2.38 mL (2.4 mmol) of L-Selectride (a 1 M solution in THF) dropwise at −78 °C under nitrogen. The reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature for 0.5 h. The mixture was diluted with 100 mL of EtOAc and filtered through a pad of silica gel, which was rinsed with 100 mL of EtOAc. The filtrate was concentrated, and the residue was purified by chromatography (hexane/EtOAc 6:1) to give 445 mg (82%) of propargyl alcohol **11** as a colorless oil; $[\alpha]^{25}_D$ +11.2° (*c* 6.3, $CHCl_3$); R_f 0.75 (hexane/EtOAc 3:1); ^1H NMR (C_6D_6) δ 1.03−1.10 (m, 9H), 1.35−1.55 (m, 20H), 1.72−1.82 (m, 4H), 2.18 (m, 2H), 2.37 (d, 1H, J = 6.8 Hz), 3.58 (m, 1H), 3.77 (d, 1H, J = 8.4 Hz), 4.01 (m, 1H), 4.55 (m, 2H), 4.94 (m, 2H), 7.20−7.32 (m, 3H), 7.52 (d, 2H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 8.43, 14.4, 19.0, 23.1, 28.9, 29.3, 29.5, 29.8, 29.9, 30.0, 30.1, 32.3, 63.8, 66.8, 74.8, 78.0, 80.0, 83.0, 86.4, 113.0, 127.4, 127.7, 127.9, 128.0, 128.1, 128.5, 139.1; HR-MS (FAB, MNa^+) m/z calcd for $C_{30}H_{48}O_4Na^+$ 495.3445, found 495.3437.

(2*R*,3*R*,4*S*)-3,4-Benzyloxy-5-octadecyn-1,2,3,4-tetrol [(+)-16]. To a mixture of 272 mg (6.78 mmol) of NaH (60%) and 1.60 g (3.39 mmol) of **11** in 100 mL of THF were added 870 mg (5.09 mmol) of benzyl bromide and 32 mg (0.10 mmol) of TBAB. The mixture was heated at reflux for 3 h and then quenched by the addition of 50 mL of water. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, water, and then dried ($MgSO_4$); and concentrated. To the dry residue of **15** in 100 mL of MeOH was added 5 mL of 5% aqueous H_2SO_4. The mixture was stirred at room temperature overnight. After 5.0 g (36 mmol) of solid K_2CO_3 was added, the mixture was filtered. The filtrate was evaporated to provide a residue that was purified by chromatography (hexane/EtOAc 3:1), affording 1.46 g of **16** (87% for two steps) as a colorless oil; $[\alpha]^{25}_D$ +8.9° (*c* 2.7, $CHCl_3$); R_f 0.24 (hexane/EtOAc 3:1); ^1H NMR (C_6D_6) δ 1.03 (t, 3H, J = 6.8 Hz), 1.33−1.53 (m, 20H), 2.14 (m, 2H), 2.82 (s, 1H), 3.54 (d, 1H, J = 4.4 Hz), 3.98 (m, 3H), 4.44 (m, 1H), 4.58 (d, 1H, J = 11.6 Hz), 4.65 (m, 1H), 4.70 (d, 1H, J = 11.6 Hz), 4.89 (d, 1H, J = 11.6 Hz), 4.95 (d, 1H, J = 11.6 Hz), 7.17−7.22 (m, 6H), 7.44 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.0, 23.1, 28.9, 29.0, 29.3, 29.5, 29.8, 29.9, 30.0, 30.1, 32.3, 63.5, 70.8, 71.0, 72.1, 74.2, 77.1, 81.4, 89.2, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.6, 128.7, 138.2, 138.9; HR-MS (FAB, MNa^+) m/z calcd for $C_{32}H_{46}O_4Na^+$ 517.3288, found 517.3303.

(2*S*,3*S*,4*S*)-2-Azido-3,4-benzyloxy-5-octadecyn-1,3,4-triol [(+)-17]. To a solution of 1.63 g (3.4 mmol) of **16** and 1.34 g (5.1 mmol) of Ph_3P (both thoroughly dried overnight at 0.7 Torr) in 150 mL of dry CH_2Cl_2 was added 1.06 mL (5.1 mmol) of DIAD at 0 °C. After the yellow reaction mixture was stirred at 0 °C for 3 h under nitrogen, 592 mL (4.4 mmol) of Me_3SiN_3 was added. The reaction mixture was stirred at 0 °C for 3 h and then allowed to warm to room temperature overnight. After removal of the solvent, the residue was dissolved in 10 mL of THF and treated with 8.5 mL (8.5 mmol) of n-Bu_4NF (TBAF) (a 1 M solution in THF containing 5 wt % H_2O). The brown reaction mixture was stirred at room temperature until the silyloxy azides were consumed completely (TLC). Concentration gave a slurry that was dissolved in CH_2Cl_2 and passed through a pad of silica gel in a sintered glass funnel to remove $Ph_3P(O)$ and salts. The pad was washed with a mixture of hexanes−EtOAc (6:1). The crude products were purified by silica gel chromatography (hexanes/EtOAc 3:1) to give **17** (1.04 g, 61%) as a colorless oil; $[\alpha]^{25}_D$ +28.9° (*c* 1.75, $CHCl_3$); R_f 0.70 (hexane/EtOAc 3:1); ^1H NMR (C_6D_6) δ 1.03 (t, 3H, J = 6.8 Hz), 1.33−1.53 (m, 20H), 1.73 (t, 1H, J = 4.4 Hz), 2.14 (m, 2H), 3.83 (m, 2H), 3.91 (m, 1H), 3.96 (m, 1H), 4.52 (m, 1H), 4.60 (d, 1H, J = 11.6 Hz), 4.68 (d, 1H, J = 11.6 Hz), 4.95 (d, 1H, J = 11.6 Hz), 5.01 (d, 1H, J = 11.6 Hz), 7.17−7.32 (m, 6H), 7.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.0, 23.1, 28.9, 29.2, 29.5, 29.8, 30.0, 30.1, 32.3, 62.4, 63.8, 70.4, 71.1, 75.1, 76.9, 81.8, 89.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 138.3, 138.6; HR-MS (FAB, MNa^+) m/z calcd for $C_{32}H_{45}N_3O_3Na^+$ 542.3353, found 542.3328.

(2*S*,3*S*,4*S*)-Phytosphingosine [(−)-2]. To a solution of 63 mg (0.12 mmol) of **17** in 90 mL of MeOH was added 12.7 mg (0.024 mmol) of 20% $Pd(OH)_2/C$. The resulting suspension was purged with H_2 for approximately 10 min and then stirred with a balloon filled with H_2 overnight, when TLC indicated the complete consumption of the starting material. The crude reaction mixture was filtered through a short pad of Celite, and the solvent was evaporated to provide 32 mg (82%) of **2** as a white solid; mp 104.2−105.5 °C [lit.[11] mp 104.8−106.0 °C]; $[\alpha]^{25}_D$ −7.5° (*c* 1.00, C_5H_5N) [lit.[11] $[\alpha]^{25}_D$ −7.4° (*c* 0.9, C_5H_5N)]; R_f 0.56 ($CHCl_3$/MeOH/NH_4OH 130:25:4); ^1H NMR (CD_3OD) δ 0.89 (t, 3H, J = 6.4 Hz), 1.27−1.53 (m, 24H), 2.98 (m, 1H), 3.39 (m, 1H), 3.40 (m, 1H), 3.59 (m, 1H), 3.67 (m, 1H), 3.76 (m, 1H); ^{13}C NMR (CD_3OD) δ 15.0, 23.9, 27.2, 30.6, 30.9, 31.0, 33.2, 34.5, 34.7, 55.9, 64.4, 72.6, 75.1; HR-MS (FAB, MNa^+) m/z calcd for $C_{18}H_{39}NO_3Na^+$ 340.2822, found 340.2828.

(2*S*,3*S*,4*S*)-2-*N*,*N*-Dibenzylamino-3,4-benzyloxy-5-octadecyn-1,3,4-triol [(−)-19]. To a solution of 0.94 g (1.86 mmol) of **17** in 30 mL of THF/H_2O 9:1 was added 0.63 g (2.3 mmol) of Ph_3P. The reaction mixture was stirred at room temperature under nitrogen for 48 h. After the solvents were removed, a solution of 520 mg (3.72 mmol) of K_2CO_3 and 150 mg (3.72 mmol) of NaOH in 10 mL of water was added. The solution was heated at reflux with stirring for 30 min. To the refluxing mixture was added 0.96 g (5.58 mmol) of benzyl bromide. The mixture was heated for an additional 2 h and then cooled to room temperature. The organic phase was separated, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (hexane/EtOAc 3:1) to give 0.99 g (81% for two steps) of **19** as a colorless oil; $[\alpha]^{25}_D$ −25.5° (*c* 2.15, $CHCl_3$); R_f 0.74 (hexane/EtOAc 3:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.22−1.47 (m, 20H), 2.12 (m, 2H), 2.72 (s, 1H), 3.30 (m, 1H), 3.44 (d, 2H, J = 13.6 Hz), 3.71 (m, 1H), 3.86 (d, 1H, J = 8.8 Hz), 3.90 (d, 2H, J = 13.6 Hz), 4.04 (m, 1H), 4.35 (m, 1H), 4.39 (d, 1H, J = 11.6 Hz), 4.64 (d, 1H, J = 11.2 Hz), 4.79 (d, 1H, J = 11.6 Hz), 5.01 (d, 1H, J = 11.2 Hz), 7.17−7.35 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.9, 22.7, 28.5, 29.0, 29.1, 29.4, 29.6, 29.7, 30.3, 31.9, 54.0, 58.4, 59.9, 71.0, 71.1, 72.1, 73.2, 76.4, 78.9, 89.4, 127.0, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 129.0, 130.1, 132.4, 137.9, 138.3, 139.6; HR-MS (FAB, MNa$^+$) *m/z* calcd for $C_{46}H_{59}NO_3Na^+$ 696.4387, found 696.4414.

Dimethyl (3*S*,4*S*,4*S*)-3-*N*,*N*-Dibenzylamino-4,5-dibenzyloxy-6-octadecyn-(1*E*)-enephosphonate [(+)-21]. A solution of 336 mg (0.50 mmol) of alcohol **19** in 50 mL of dry CH_2Cl_2 at room temperature was treated with 252 mg (0.60 mmol) of Dess–Martin periodinane. After 1 h, TLC analysis indicated the complete consumption of starting material. An aqueous solution of 10% $Na_2S_2O_3$ (50 mL) was added. The mixture was stirred until both layers became clear. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution, water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was dried to afford crude aldehyde **20** as a colorless liquid. To a mixture of 36 mg (1.5 mmol) of NaH and 50 mL of THF was added 348 mg (1.5 mmol) of tetramethyl methylenediphosphonate in 10 mL of THF at 0 °C. After the mixture was stirred for 10 min, a solution of aldehyde **20** in 10 mL of THF was added. The reaction mixture was stirred for 2 h, diluted with Et_2O (20 mL), and extracted in successive order with 1 M NaOH/MeOH (7:3) (2 × 30 mL) to remove the excess diphosphonate, H_2O/brine (1:1) (1 × 30 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexane/EtOAc 1:1) to give 318 mg (82% for the two steps) of **21** as a colorless oil; $[\alpha]^{25}_D$ +22.8° (*c* 1.3, $CHCl_3$); R_f 0.73 (hexane/EtOAc 1:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.22–1.35 (m, 20H), 1.99 (m, 2H), 3.56–3.68 (m, 8H), 3.86 (m, 3H), 4.08 (m, 1H), 4.30 (d, 1H, J = 6.4 Hz), 4.37 (d, 1H, J = 11.2 Hz), 4.67 (d, 1H, J = 10.8 Hz), 4.73 (d, 1H, J = 11.2 Hz), 5.03 (d, 1H, J = 10.8 Hz), 5.85 (dd, 1H, J = 17.2, 22.0 Hz), 6.98 (m, 1H), 7.17–7.35 (m, 20H); ^{13}C NMR ($CDCl_3$) 14.1, 18.6, 22.7, 28.4, 29.0, 29.2, 29.4, 29.6, 29.7, 31.9, 52.2, 54.9, 61.6 (d, J_{CP} = 22.0 Hz), 70.9, 74.2, 76.2, 89.4, 126.4, 126.9, 127.1, 127.3, 127.5, 127.7, 127.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.9, 129.0, 137.9, 138.3; HR-MS (FAB, MNa$^+$) *m/z* calcd for $C_{49}H_{64}NO_5PNa^+$ 800.4414, found 800.4408.

(3*S*,4*S*,4*S*)-3-*N*,*N*-Dibenzylamino-4,5-benzyloxy-6-octadecyn-(1*E*)-enephosphonic acid [(+)-22]. To a solution of 200 mg (0.22 mmol) of dimethyl phosphonate **21** in 10 mL of dry CH_2Cl_2 at room temperature was added 0.29 mL (2.2 mmol) of bromotrimethylsilane. The reaction mixture was stirred for 4 h, at which time TLC indicated that all of the reactant had been consumed. The solvent was removed, and the residue was dried. A solution of the residue in 1 mL of 95% MeOH was stirred for 1 h, and the solvent was removed to afford 174 mg (91%) of **22** as a white solid, mp 65.1–65.7 °C; $[\alpha]^{25}_D$ +40.9° (*c* 1.6, $CHCl_3$/MeOH 1:1); R_f 0.76 ($CHCl_3$/MeOH 1:1); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.22–1.35 (m, 20H), 1.84 (m, 2H), 4.30 (m, 3H), 4.37 (d, 1H, J = 11.2 Hz), 4.48 (m, 2H), 4.65 (d, 1H, J = 11.2 Hz), 4.75 (d, 1H, J = 11.6 Hz), 4.85 (d, 1H, J = 11.2 Hz), 4.96 (m, 1H), 5.19 (m, 1H), 6.45 (m, 1H), 7.07–7.60 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.7, 22.7, 28.3, 29.0, 29.1, 29.4, 29.6, 29.7, 31.9, 56.1, 64.7 (d, J_{CP} = 22.0 Hz), 71.3, 71.4, 72.6, 73.9, 74.6, 91.5, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.3, 129.7, 130.9, 131.6, 135.6, 137.2; ^{31}P NMR ($CDCl_3$) δ 13.1; HR-MS (FAB, MNa$^+$) *m/z* calcd for $C_{47}H_{60}NO_5PNa^+$ 772.4101, found 772.4132.

(2*S*,3*S*,4*S*)-Phytosphingosine 1-Phosphonate [(−)-3]. To a solution of 116 mg (0.17 mmol) of unsaturated phosphonic acid **22** in 90 mL of MeOH was added 18 mg (0.034 mmol) of 20% $Pd(OH)_2$/C. The resulting suspension was purged with H_2 for approximately 10 min and then stirred with a balloon filled with H_2 overnight, when TLC indicated the complete consumption of the starting material. The crude reaction mixture was filtered through a short pad of Celite, and the solvent was evaporated to provide 49 mg (80%) of **3** as a white solid; mp 214.0–214.8 °C; $[\alpha]^{25}_D$ −6.6° (*c* 0.64, $CHCl_3$/MeOH 1:1); R_f 0.45 ($CHCl_3$/MeOH/H_2O/HOAc 65:25:4:1); ^1H NMR ($CDCl_3$/CD_3OD 1:1) δ 0.88 (t, 3H, J = 6.4 Hz), 1.22–1.35 (m, 24H), 1.60 (m, 2H), 1.89 (m, 2H), 2.06 (m, 2H), 3.47 (m, 1H), 3.68 (m, 1H), 3.79 (m, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD 1:1) δ 14.3, 23.1, 23.4, 23.8, 26.1, 29.8, 30.1, 30.2, 32.4, 34.0, 56.7 (d, J_{CP} = 13.0 Hz), 70.6, 71.5; ^{31}P NMR ($CDCl_3$/CD_3OD 1:1) δ 27.9; HR-MS (FAB, MNa$^+$) *m/z* calcd for $C_{19}H_{42}NO_5PNa^+$ 418.2693, found 418.2712.

Acknowledgment. This work was supported in part by USPHS Grant HL16660.

Supporting Information Available: General experimental information, preparation of compounds **7** and **8**, and copies of ^1H and ^{13}C NMR spectra for compounds **2**, **3**, **7**–**11**, **13**, **14**, **16**, **17**, **19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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