A Facile Synthesis of Phytosphingosine from Diisopropylidene- d -mannofuranose

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A Facile Synthesis of Phytosphingosine from Diisopropylidene-D-mannofuranose

Hsin-Yi Chiu, Der-Lii M. Tzou,*
Laxmikant Narhari Patkar, and Chun-Cheng Lin*

Institute of Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan

cclin@chem.sinica.edu.tw

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Abstract: In the present study, an efficient method with a high overall yield for preparing phytosphingosine and an analogue was developed. Starting with commercially available 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose, a variety of lipid moieties were incorporated to obtain phytosphingosine and an analogue. Through an eight-step manipulation, phytosphingosine was obtained with an overall yield of 57%.

Sphingolipids and glycosphingolipids are important elements of plasma membranes[1]and are physiologically important for cell proliferation, differentiation, adhesion, neuronal repair, and signal transduction.[2] Phytosphingosine **1**, one of the major long-chain components of glycosphingolipids, typically consists of an 18-carbon chain (in a few cases a 20-carbon chain) that incorporates a 2-amino-1,3,4-triol moiety at one end. Phytosphingosine itself is a bioactive lipid,[3] and its glycosylated derivatives display promising antitumor[4]and antivirus[5] activity. Recently, the α-galactosylphytoceramide[6] and an analogue[7] were shown to modulate different immune responses. Consequently, since phytosphingosine and its derivatives are only available in a limited amount from natural sources, there is a continuing interest in developing efficient methods for their synthesis.[8−10]

There are many methods for synthesizing phytosphingosines reported in the literature. Most of these methods are based on a chiral pool strategy that usually employs carbohydrate[8]- or amino acid[9]-derived starting materials, and very few are based on asymmetric synthesis.[10] The chiral pool approach appears attractive because most of the chiral centers required in the final product are already present at the outset. There is also a high degree of stereocontrol in subsequent synthetic manipulations. However, this method suffers the drawback of being a multistep synthesis with a poor overall yield (<20%).[8−10]

The key to cost-effective and efficient synthesis is the choice of a proper starting material that requires minimal protection−deprotection steps, a high level of stereocontrol, and a minimal number of steps required. We recently disclosed such a synthesis of **1**, which required only six steps with an overall yield of 28%[11] starting from D-lyxofuranose. In the present study, we report a convenient and concise route for the synthesis of D-ribo-phytosphingosine **1** with an almost 2-fold increase in overall yield to 57% starting with the readily available 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose.

Our choice of starting material was dictated by the type of reactions we planned to use in the synthesis of phytosphingosine **1**. The retrosynthetic analysis is shown in Figure 1. Our plan involved a starting material **2** with the proper stereochemistry at the *gem*-diol part, a hydroxyl group at position 4 that could be replaced with azide, and an aldehyde function for introducing the lipid chain by Wittig olefination. The Wittig olefination confers versatility to this route by giving access to analogues of phytosphingosine **1**. With this in mind, 2,3;5,6-di-*O*-

(1) (a) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532−1568. (b) Kaufer, J. M.; Hakomori, S. *Handbook of Lipids Research*: *Sphingolipid Biochemistry*; Kanfer, J. N., Hakomori, S., Eds.; Plenum Press: New York, 1983; Vol. 3 pp 1−150.

(2) (a) Chang, Y.-T.; Choi, J.; Ding, S.; Prieschl, E. E.; Baumruker, T.; Lee, J.-M.; Chung, S.-K.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1856−1857. (b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075−1091. (c) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771−2784. (d) Turinsky, J.; Nagel, G. W. *Biochem. Biophys. Res. Commun.* **1992**, *188*, 358−364. (e) Honda, M.; Ueda, Y.; Sugiyama, S.; Komori, T. *Chem. Pharm. Bull.* **1991**, *39*, 1385−1391. (f) Merrill, A. H., Jr.; Nimkar, S.; Menaldino, D.; Hannun, Y. A.; Loomis, C.; Bell, R. M.; Tyagi, S. R.; Lambeth, J. D.; Stevens, V. L.; Hunter, R.; Liotta, D. C. *Biochemistry* **1989**, *28*, 3138−3145. (g) Dharmawardhane, S.; Rubinstein, B.; Stern, A. I. *Plant Physiol.* **1989**, *89*, 1345−1350.

(3) (a) Zanolari, B.; Friant, S.; Funato, K.; Sütterlin, C.; Stevenson, B. J.; Riezman, H. *EMBO J.* **2000**, *19*, 2824−2833. (b) Schneiter, R. *BioEssays* **1999**, *21*, 1004−1010. (c) Wells, G. B.; Dickson, R. C.; Lester, R. L. *J. Bio. Chem.* **1998**, *273*, 7235−7243.

(4) Kobayashi, E.; Motoki, K.; Yamaguchi, Y.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Bioorg. Med. Chem.* **1996**, *4*, 615−619.

(5) Gonzalez-Aseguinolaza, G.; Kaer, L. V.; Bergmann, C. C.; Wilson, J. M.; Schmieg, J.; Kronenberg, M.; Nakayama, T.; Taniguchi, M.; Koezuka, Y.; Tsuji, M. J. *Exp. Med.* **2002**, *195*, 617−624.

(6) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* **1997**, *278*, 1626−1629.

(7) Miyamoto, K.; Miyake, S.; Yamamura, T. *Nature* **2001**, *413*, 531−534.

(8) (a) Plettenburg, O.; Bodmer-Narkevitch, V.; Wong, C.-H. *J. Org. Chem.* **2002**, *67*, 4559−4564. (b) Luo, S.-Y.; Thopate, S. R.; Hsu, C.-Y.; Hung, S.-C. *Tetrahedron Lett.* **2002**, *43*, 4889−4892. (c) Figueroa-Pérez, S.; Schmidt, R. R. *Carbohydr. Res.* **2000**, *328*, 95−102. (d) Graziani, A.; Passacantelli, P.; Piancatelli, G.; Tani, S. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3921−3937. (e) Murakami, T.; Taguchi, K. *Tetrahedron* **1999**, *55*, 989−1004. (f) Li, Y.-L.; Mao, X.-H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1559−1563. (g) Matsumoto, K.; Ebata, T.; Matsushita, H. *Carbohydr. Res.* **1995**, *279*, 93−106. (h) Wild, R.; Schmidt, R. R. *Tetrahedron*: *Asymmetry* **1994**, *5*, 2195−2208. (i) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett.* **1994**, *35*, 745−748.

(9) (a) Ndakala, A. J.; Hashemzadeh, M.; So, R. C.; Howell, A. R. *Org. Lett.* **2002**, *4*, 1719−1722. (b) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538−3541. (c) Takikawa, H.; Muto, S.-E.; Mori, K. *Tetrahedron* **1998**, *54*, 3141−3150. (d) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657−10670. (e) Shimizu, M.; Wakioka, I.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 6027−6030. (f) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2113-2116. (g) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439−1446. (h) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1990**, 1069−1078.

(10) (a) Ayad, T.; Génisson, Y.; Verdu, A.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **2003**, *44*, 579−582. (b) Lee, H.-K.; Kim, E.-K.; Pak, C.-S. *Tetrahedron Lett.* **2002**, *43*, 9641−9644. (c) Nakamura, T.; Shiozaki, M. *Tetrahedron* **2001**, *57*, 9087−9092. (d) Martin, C.; Prünck, W.; Bortoloussi, M.; Bloch, R. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1585−1592. (e) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7618−7626. (f) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309−10312. (g) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643−13658. (h) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **1999**, *40*, 9063−9064. (i) Li, S.; Pang, J.; Wilson, W. K.; Schroepfer, G. J., Jr. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1697−1707. (j) Wee, A. G. H.; Tang, F. *Tetrahedron Lett.* **1996**, *37*, 6677−6680. (k) Lin, G.-Q.; Shi, Z.-C. *Tetrahedron* **1996**, *52*, 2187−2192. (l) Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 9573−9576.

(11) Lin, C.-C.; Fan, G.-T.; Fang, J.-M. *Tetrahedron Lett.* In press.

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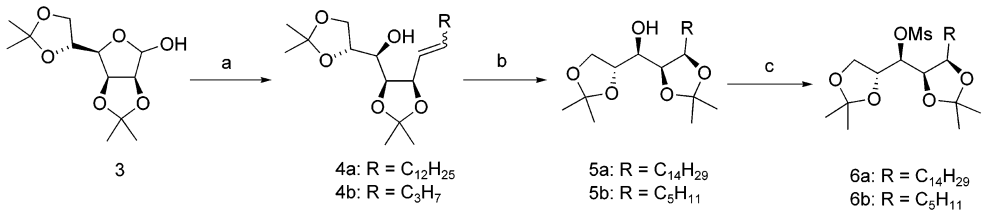
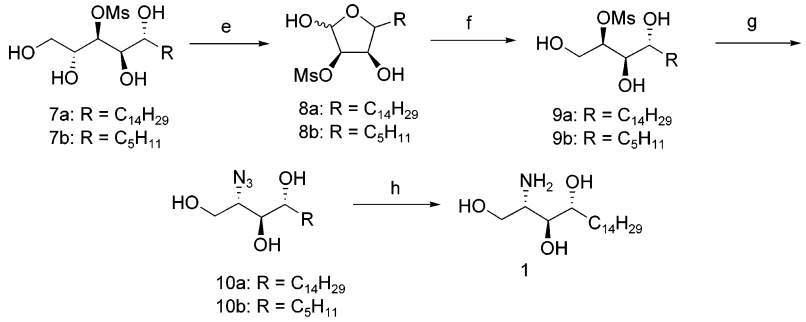
SCHEME 1[a]



[a] Reagents and conditions: (a) LHMDS, $C_{13}H_{27}P^{+}Ph_3Br^{-}$, THF, 0 °C to room temperature, overnight, 98%; (b) H_2, 5% Pd/C, EtOAc, rt, 3 h, 94%; (c) MsCl, pyridine, 0 °C to room temperature, overnight, 96%.

SCHEME 2[a]



[a] Reagents and conditions: (e) $NaIO_4/H_2O$, THF, 0−4 °C, 1 day, 90%; (f) $NaBH_4$, MeOH, 0 °C, 1.5 h, quantitative; (g) TMGA, DMF, 50 °C, 2 day, 84%; (h) H_2, 10% Pd/C, MeOH, rt, 2 day, 94%.

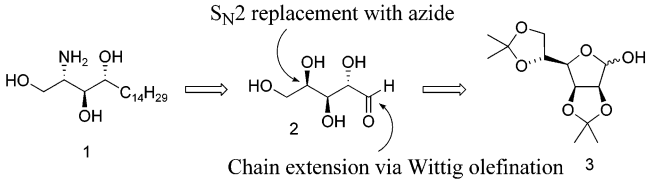
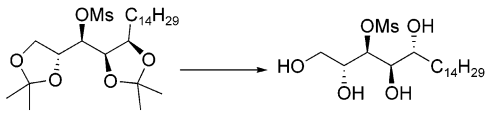


FIGURE 1. Retrosynthesis of phytosphingosine from a D-mannofuranose derivative.

isopropylidene-D-mannofuranose **3** appeared to be a very attractive starting material due to its commercial availability, and after truncation of the hydroxymethylene group at position 6, it met all of the requirements described aboved. The synthesis of **1** is illustrated in Scheme 1. Olefination of **3** with the Wittig reagent derived from $C_{13}H_{27}P^{+}Ph_3Br^{-}$ in the presence of lithium hexamethyldisilazide (LHMDS) afforded an unseparable mixture of alkenes **4a*E*** and ***Z*** (ratio of 1:2) in 98% yield.[12] Hydrogenation of the double bond of **4a** followed by mesylation[13] gave compound **6a** in high yield (90% for two steps). It should be noted that attempts to replace the C-3 hydroxy group in **4a** or **5a** by using tetramethylguanidium azide (TMGA)[8c] as the soluble azide ion donor and Tf_2O in pyridine resulted in a low yield of the desired product.

After meticulous investigation of the deprotection of the acetal groups in **6a**, as shown in Table 1, we found that hydrochloric acid in methanol[14] was the condition of choice to lead to the tetraol derivative **7a** (91%). Cleaving the hydroxylmethylene arm with sodium periodate[15] gave **8a** as an anomeric mixture in a ratio of 1:2 (α:*β*) in 90% yield, as shown in Scheme 2. The mixture was reduced with sodium borohydride[16] to furnish triol **9a** in a quantitative yield. Finally, the *O*-mesyl group in triol **9a** was replaced by azide in an S_N2 reaction by treatment with TMGA to afford azido triol **10a** in 84% yield and with inversion at the azide bearing carbon.[8c] The multiplet of H-2 of **10a** in the ^1H NMR spectrum was strongly shifted upfield (4.93 to 3.92 ppm), and the signal of C-2 in the ^{13}C NMR was also shifted from 84.1 to 76.1 ppm, indicating the replacement of the mesylate group by an azide group. The change of optical rotation was also in agreement with literature data showing the inversion of C-2 configuration.[8c] Azido triol **10a** is a very versatile intermediate with the possibility of transforming its azido function into amino, isothiocyanate,[17] and

TABLE 1.



procedure	yield (%)
(a) 60% AcOH, rt, 1 day	15
(b) acetone/H_2O (9/1), DDQ, rt, 1 day	61
(c) 5% CBr_4 in MeOH, *hν* 30 mins, rt, 1 h	63
(d) MeOH/H_2O, 2 equiv of oxone, rt, 1 day	85
(e) 1 N HCl, MeOH/H_2O, rt, 1 day	20
(f) concd HCl, MeOH, 0 °C, 1 day	91

(12) Harcken, C.; Martin, S. F. *Org. Lett.* **2001**, *3*, 3591−3593.
(13) Ohlsson, J.; Magnusson, G. *Carbohydr. Res.* **2001**, *331*, 91−94.
(14) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239−10252.
(15) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M.; Petit, P. *Tetrahedron Lett.* **1992**, *33*, 3637−3640.
(16) Beauhaire, J.; Ducrot, P.-H. *Synth. Commun.* **1998**, *28*, 2443−2456.
(17) (a) García-Moreno, M. I.; Díaz-Pérez, P.; Benito, J. M.; Ortiz Mellet, C.; Defaye, J.; García Fernández, J. M. *Carbohydr. Res.* **2002**, *337*, 2329−2334. (b) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1−65.

other functional groups. Finally, hydrogenation of **10a** completed the synthesis of D-ribo-phytosphingosine in 94% yield. The ^{1}H NMR data of **1** were identical with those published in the literature.[8e] Thus starting with 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose **3**, phytosphingosine **1** was synthesized in eight steps with an overall yield of 57%. To our knowledge this is the highest overall yield obtained for phytosphingosine from commercially available starting material. The versatility of this method was established by the synthesis of **10b**, a C_5H_{11} lipid chain analogue of **10a**, with an overall yield of 50%.

In conclusion, we have developed a short and highly efficient synthesis of D-ribo-phytosphingosine by using simple reactions and starting with commercially available 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose. The generality of this high-yield method was proven by the synthesis of the short-chain phytosphingosine analogue **10b**. This method provides easy access to the synthesis of chain-modified phytosphingosines.

Experimental Section

(2*R*,3*R*,4*R*,5*R*)-3-Hydroxy-1,2;4,5-di-*O*-isopropylidene-6-nonadecene (4a). To a mixture of $C_{13}H_{27}$ $P^+Ph_3Br^-$ (4.04 g, 7.68 mmol) in dried THF (40 mL) under Ar at 0 °C was added 7.8 mL of LHMDS (1.0 M THF solution). The reaction was stirred at 0 °C for 90 min. The anion solution was then added to a solution of 2,3;5,6-di-*O*-isopropylidene-D-mannofuranose in dried THF (20 mL) with LHMDS (3.9 mL, 1.0 M THF solution) under Ar at 0 °C and stirred at 0 °C for 90 min**.** The mixture was further stirred at 0 °C for 2 h and then at room temperature for 1 day. The mixture was quenched with MeOH, extracted with EtOAc, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography with EtOAc/hexane (1:8) to give **4a*E*** and **4a*Z*** as a mixture (1.61 g, 3.77 mmol, 98%), *E*/*Z* 1/2. R_f 0.15 (1:8 EtOAc/hexane). For **4a*E***: $[\alpha]^{26}_D$ −19.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.82 (m, 1 H), 5.75−5.70 (m, 1 H), 4.69 (t, 1 H, J = 7.6 Hz), 4.33 (dd, 1 H, J = 7.6, 0.8 Hz), 4.10 (m, 1 H), 4.02 (m, 2 H), 3.47 (m, 1 H), 2.22 (d, OH, J = 8 Hz), 2.06 (m, 2 H), 1.53 (s, 3 H), 1.41−1.27 (m, 29 H), 0.89 (t, 1 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 125.3, 109.5, 108.5, 79.3, 76.8, 76.3, 70.9, 67.2, 32.6, 32.1, 29.9−22.9, 14.3; HRMS (FAB, M − H$^+$) calcd for $C_{25}H_{45}O_5$ 425.3267, found 425.3263. For **4a*Z***: $[\alpha]^{26}_D$ −56.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−5.65 (m, 2 H), 5.09 (t, 1 H, J = 7.6 Hz), 4.37 (d, 1 H, J = 7.6 Hz), 4.12−3.99 (m, 3 H), 3.44 (t, 1 H, J = 8 Hz), 2.17 (d, OH, J = 8 Hz), 2.13−2.02 (m, 2 H), 1.69−1.27 (m, 32 H), 0.90 (t, 1 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 125.5, 109.5, 108.5, 76.7, 76.2, 73.6, 70.9, 67.2, 32.1, 29.9−22.9, 14.3; HRMS (FAB, M − H$^+$) calcd for $C_{25}H_{45}O_5$ 425.3267, found 425.3263.

(2*R*,3*R*,4*R*,5*R*)-3-Hydroxy-1,2;4,5-di-*O*-isopropylidene-6-decene (4b). The synthetic procedure was the same as that described in the synthesis of **4a**. R_f 0.38 (1:3 EtOAc/hexane). For **4b*E***: $[\alpha]^{27}_D$ −9.5 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.81 (m, 1 H), 5.76−5.70 (m, 1 H), 4.69 (t, 1 H, J = 7.6 Hz), 4.33 (dd, 1 H, J = 7.6, 1.6 Hz), 4.12−4.05 (m, 1 H), 4.03−3.99 (m, 2 H), 3.49−3.45 (m, 1 H), 3.22 (d, OH, J = 8 Hz), 2.12−2.05 (m, 2 H), 1.52 (s, 3 H), 1.48−1.42 (m, 2 H), 1.40−1.38 (m, 6 H), 1.37−1.35 (m, 3 H), 0.92 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 125.4, 109.2, 108.2, 79.1, 76.6, 76.1, 70.7, 67.0, 34.4, 26.8, 26.6, 25.3, 24.4, 22.1, 13.6; HRMS (FAB, M − H$^+$) calcd for $C_{16}H_{27}O_5$ 299.1859, found 299.1859. For **4b*Z***: $[\alpha]^{27}_D$ −137.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77−5.67 (m, 2 H), 5.10 (t, 3 H, J = 7.6 Hz), 4.38 (dd, 1 H, J = 7.6,0.8 Hz), 4.12−4.07 (m, 1 H), 4.03−3.98 (m, 2 H), 3.44 (t, 1 H, J = 8 Hz), 2.17 (dd, OH, J = 8.4 Hz), 2.13−2.01 (m, 2 H), 1.53 (s, 3 H), 1.48−1.35 (m, 8 H), 1.35 (s, 3 H), 0.92 (t, 3 H, J = 7.2 Hz);^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 125.6, 109.2, 108.3, 76.5, 76.0, 73.4, 70.7, 67.0, 29.9, 26.8, 26.6, 25.3, 24.4, 22.7, 13.7; HRMS (FAB, M − H$^+$) calcd for $C_{16}H_{27}O_5$ 299.1859, found 299.1860.

(2*R*,3*R*,4*R*,5*R*)-3-Hydroxy-1,2;4,5-di-*O*-isopropylidene-nonadecane (5a). A mixture of **4a*E*** and **4a*Z*** (976 mg, 2.34 mmol) and 5% Pd/C (100 mg) in EtOAc (20 mL) was stirred under a H_2 atmosphere at room temperature for 3 h. The mixture was filtered and concentrated, and the residue was purified by column chromatography with EtOAc/hexane (1:8) to give compound **5a** (927 mg, 2.16 mmol, 94%). R_f 0.30 (1:6 EtOAc/hexane); $[\alpha]^{26}_D$ −12.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28−4.21 (m, 2 H), 4.13−4.09 (m, 1 H), 4.05−4.00 (m, 2 H), 3.50 (t, 1 H, J = 7.6 Hz), 2.20 (d, OH, J = 7.6 Hz), 1.84−1.27 (m, 38 H), 0.89 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.4, 107.9, 77.7, 77.4, 77.1, 76.8, 76.3, 70.9, 67.3, 32.1, 30.0−22.9, 14.3; HRMS (FAB, M + H$^+$) calcd for $C_{25}H_{49}O_5$ 429.3580, found 429.3575.

(2*R*,3*R*,4*R*,5*R*)-3-Hydroxy-1,2;4,5-di-*O*-isopropylidene-decane (5b). The synthetic procedure was the same as that described in the synthesis of **5a**. R_f 0.30 (1:6 EtOAc/hexane); $[\alpha]^{27}_D$ −18.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29−4.21 (m, 2 H), 4.14−4.09 (m, 1 H), 4.05−4.01 (m, 2 H), 3.50 (td, 1 H, J = 7.2, 0.8 Hz), 2.20 (dd, 1 H, J = 7.6 Hz), 1.84−1.79 (m, 1 H), 1.68−1.60 (m, 1 H), 1.50 (s, 3 H), 1.41−1.31 (m, 15 H), 0.92−0.89 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.4, 108.0, 77.8, 76.4, 76.3, 71.0, 67.3, 32.0, 30.0, 27.1, 27.0, 26.9, 25.5, 24.9, 22.8, 14.2; HRMS (FAB, M + H$^+$) calcd for $C_{16}H_{31}O_5$ 303.2172, found 303.2178.

(2*R*,3*R*,4*R*,5*R*)-3-*O*-Methanesulfonyl-1,2;4,5-di-*O*-isopropylidene-3-nonadecanol (6a). To a solution of compound **5a** (600 mg, 1.4 mmol) in anhydrous pyridine (13 mL) was added MsCl (0.325 mL, 4.2 mmol) at 0 °C, and the solution was stirred at 0 °C to room temperature overnight. The reaction mixture was quenched with MeOH and extracted with EtOAc. After drying with $MgSO_4$, the solvent was concentrated and the resulting residue was purified by column chromatography with EtOAc/hexane (1:6) to give compound **6a** (683 mg, 1.35 mmol, 96%). R_f 0.25 (1:6 EtOAc/hexane); $[\alpha]^{26}_D$ +9.6 (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (t, 1 H, J = 6 Hz), 4.22−4.15 (m, 4 H), 4.09−4.03 (m, 1 H), 3.13 (s, 3 H), 1.68−1.27 (m, 36 H), 0.90 (t, 3 H, J = 3.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.2, 108.8, 79.6, 77.6, 77.1, 75.0, 66.7, 39.8, 32.1, 29.9−22.9, 14.4; HRMS (FAB, M + H$^+$) calcd for $C_{26}H_{51}O_7S$ 507.3356, found 507.3365.

(2*R*,3*R*,4*R*,5*R*)-3-*O*-Methanesulfonyl-1,2;4,5-di-*O*-isopropylidene-3-decanol (6b). The synthetic procedure was the same as that described in the synthesis of **6a**. R_f 0.13 (1:8 EtOAc/hexane); $[\alpha]^{27}_D$ +20.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (t, 1 H, J = 6 Hz), 4.21−4.14 (m, 4 H), 4.07−4.05 (m, 1 H), 3.12 (s, 3 H), 1.70−1.50 (m, 4 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 1.36−1.26 (m, 10 H), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.2, 108.8, 79.6, 77.6, 77.1, 75.1, 66.8, 39.8, 31.8, 29.5, 27.7, 26.3, 26.2, 25.9, 25.4, 22.7, 14.2; HRMS (FAB, M − H$^+$) calcd for $C_{17}H_{31}O_7S$ 379.1790, found 379.1796.

(2*R*,3*R*,4*R*,5*R*)-3-*O*-Methanesulfonyl-1,2,3,4,5-nonadecanepentol (7a). To a solution of compound **6a** (390 mg, 0.77 mmol) in MeOH (2.7 mL) was added HCl (0.39 mL, 4.12 mmol) dropwise at 0 °C and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography with MeOH/EtOAc/hexane (1:10:10) to give compound **7a** (300 mg, 0.70 mmol, 91%). R_f 0.25 (1:10:10 MeOH/EtOAc/hexane); $[\alpha]^{28}_D$ +16.3 (*c* 0.5, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.00 (dd, 1 H, J = 6, 1.2 Hz), 4.01−3.97 (m, 1 H), 3.82−3.78 (m, 1 H), 3.68−3.61 (m, 2 H), 3.57−3.52 (m, 1 H), 3.21−3.20 (m, 3 H), 1.86−1.81 (m, 1 H), 1.58−1.56 (m, 1 H), 1.39−1.29 (m, 24 H), 0.92−0.88 (m, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 82.5, 74.4, 73.1, 71.3, 64.0, 38.8, 34.9, 33.2, 31.1−23.9, 14.6; HRMS (FAB, M + H$^+$) calcd for $C_{20}H_{43}O_7S$ 427.2730, found 427.2729.

(2*R*,3*R*,4*R*,5*R*)-3-*O*-Methanesulfonyl-1,2,3,4,5-decanepentol (7b). The synthetic procedure was the same as that described in the synthesis of **7a**. R_f 0.12 (1:10:10 MeOH/EtOAc/hexane); $[\alpha]^{28}_D$ +25.3 (*c* 0.5, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.00 (dd, 1 H, J = 6, 1.6 Hz), 4.01−3.97 (m, 1 H), 3.82−3.78 (m, 1 H),

3.68−3.61 (m, 2 H), 3.57−3.52 (m, 1 H), 3.20 (s, 3 H), 1.86−1.81 (m, 1 H), 1.60−1.56 (br, 1 H), 1.43−1.34 (br, 6 H), 0.92 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 82.6, 74.4, 73.1, 71.3, 64.1, 38.9, 34.9, 33.3, 26.2, 23.9, 14.6; HRMS (FAB, M + H^+) calcd for $C_{11}H_{25}O_7S$ 301.1321, found 301.1316.

2-*O*-Methanesulfonyl-5-*C*-tridecyl-5-deoxy-D-ribofuranose (8a). To a solution of compound **7a** (100 mg, 0.23 mmol) in THF (2.3 mL) was added a solution of $NaIO_4$ (50 mg, 0.23 mmol) in H_2O (2.3 mL) at 0 °C and the mixture was stirred at 0 °C for 1 day. The solvent was evaporated and the resulting residue was purified by column chromatography with EtOAc/CH_2Cl_2 (1:3) to give compound **8a** as anomeric mixture (83 mg, 0.21 mmol, 90%), α/β = 1/2. R_f 0.25 (1:3 EtOAc/CH_2Cl_2); For the α isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 5.49 (s, 1 H), 4.70−4.68 (m, 1 H), 4.11−4.08 (m, 1 H), 3.66−3.60 (m, 1 H), 1.72−1.22 (m, 26 H), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 95.1, 85.7, 81.8, 77.6, 38.8, 36.5, 34.3−23.9, 14.6; HRMS (FAB, M^+ − OH) calcd for $C_{19}H_{37}O_5S$ 377.2362, found 377.2354. For the β isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 5.30 (m, 1 H), 4.72 (dd, 1 H, J = 4.4, 2 Hz), 3.97 (td, 1 H, J = 7.6, 4.4 Hz), 3.86−3.83 (m, 1 H), 1.72−1.22 (m, 26 H), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 100.5, 92.6, 82.8, 80.7, 38.6, 34.3−23.9, 14.6; HRMS (FAB, M^+ − OH) calcd for $C_{19}H_{37}O_5S$ 377.2362, found 377.2354.

3-*O*-Methanesulfonyl-5-*C*-butyl-5-deoxy-D-ribofuranose (8b). The synthetic procedure was the same as that described in the synthesis of **8a**. R_f 0.20 (1:3 EtOAc/CH_2Cl_2). For the α isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 5.30 (m, 1 H), 4.70−4.68 (m, 1 H), 4.10 (t, 1 H, J = 7.2 Hz), 3.66−3.61 (m, 1 H), 3.16 (s, 3 H), 1.72−1.28 (br, 8 H), 0.92 (m, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 95.1, 85.7, 81.7, 77.6, 38.8, 36.4, 33.0, 26.5, 23.7, 14.5; HRMS (FAB, M + Na^+) calcd for $C_{10}H_{20}O_6SNa$ 291.0878, found 291.0885. For the β isomer: ^{1}H NMR (400 MHz, CD_3OD) δ 5.30 (s, 1 H), 4.73−4.71 (m, 1 H), 4.00−3.95 (td, 1 H, J = 7.6, 4.4 Hz), 3.85 (dd, 1 H, J = 7.2, 4 Hz), 3.16 (s, 3 H), 1.72−1.28 (br, 8 H), 0.92 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.5, 92.5, 82.8, 80.6, 38.6, 34.2, 33.0, 26.6, 23.7, 14.5; HRMS (FAB, M + Na^+) calcd for $C_{10}H_{20}O_6SNa$ 291.0878, found 291.0885.

(2*R*,3*R*,4*R*)-2-*O*-Methanesulfonyl-1,2,3,4-octadecanetetrol (9a).[8c] To a solution of compound **8a** (85 mg, 0.22 mmol) in dried MeOH (3 mL) was added $NaBH_4$ (4 mg, 0.11 mmol) at 0 °C and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with 10% aqueous hydrochloric acid, and the resulting solution was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give compound **9a** (88 mg, 0.22 mmol, quantitative). R_f 0.15 (1:1 EtOAc/CH_2Cl_2); $[\alpha]^{24}_D$ +13.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 4.93 (td, 1 H, J = 6.4, 2 Hz), 3.89−3.79 (m, 2 H), 3.58−3.48 (m, 2 H), 3.18−3.17 (m, 3 H), 1.83−1.78 (br, 1 H), 1.57−1.55 (br, 1 H), 1.44−1.22 (m, 24 H), 0.90 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 83.9, 74.2, 71.4, 62.7, 38.7, 34.8, 33.2, 31.1−23.9, 14.5; HRMS (FAB, M + H^+) calcd for $C_{19}H_{41}O_6S$ 397.2624, found 397.2624.

(2*R*,3*R*,4*R*)-2-*O*-Methanesulfonyl-1,2,3,4-nonanetetrol (9b). The synthetic procedure was the same as that described in the synthesis of **9a**. R_f 0.15 (1:1 EtOAc/CH_2Cl_2); $[\alpha]^{24}_D$ +11.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 4.93 (td, 1 H, J = 5.6, 2 Hz), 3.89−3.79 (m, 2 H), 3.58−3.48 (m, 2 H), 3.17 (s, 3 H), 1.83−1.78 (m, 1 H), 1.59−1.55 (br, 1 H), 1.44−1.28 (br, 6 H), 0.94−0.91 (m, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 84.0, 74.1, 71.4, 62.7, 38.8, 34.7, 33.2, 26.2, 23.8, 14.5; HRMS (FAB, M + H^+) calcd for $C_{10}H_{23}O_6S$ 271.1215, found 271.1216.

(2*S*,3*S*,4*R*)-2-Azido-1,3,4-octadecanetriol (10a).[8c] Compound **9a** (60 mg, 0.15 mmol) was stirred with tetramethylguanidinium azide (120 mg, 0.76 mmol) in dried DMF (0.5 mL) at 50 °C for 2 days. The solution was concentrated and the residue was purified by column chromatography with EtOAc/hexane (1:1) to give compound **10a** (43 mg, 0.13 mmol, 84%). R_f 0.38 (1:10:10 MeOH/EtOAc/hexane); $[\alpha]^{26}_D$ +3.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 3.92 (dd, 1 H, J = 11.6, 3.2 Hz), 3.78−3.73 (m, 1 H), 3.62−3.52 (m, 3 H), 1.68−1.65 (br, 1 H), 1.54−1.41 (br, 1 H), 1.38−1.24 (m, 24 H), 0.90 (t, 3 H, J = 7.2); ^{13}C NMR (125 MHz, CD_3OD) δ 76.1, 73.0, 66.9, 62.6, 34.0, 33.2, 30.9−23.9, 14.6; HRMS (FAB, M + H^+) calcd for $C_{18}H_{38}O_3N_3$ 344.2913, found 344.2910.

(2*S*,3*S*,4*R*)-2-Azido-1,3,4-nonanetriol (10b). The synthetic procedure was the same as that described in the synthesis of **10a**. R_f 0.35 (1:10:10 MeOH/EtOAc/hexane); $[\alpha]^{27}_D$ +3.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 3.92 (dd, 1 H, J = 11.6, 3.6 Hz), 3.79−3.74 (m, 1 H), 3.61−3.53 (m, 3 H), 1.72−1.48 (br, 2 H), 1.46−1.20 (br, 6 H), 0.93 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 76.2, 73.1, 66.8, 62.7, 34.0, 33.2, 26.5, 23.8, 14.5; HRMS (FAB, M + H^+) calcd for $C_9H_{20}N_3O_3$ 218.1505, found 218.1508.

(2*S*,3*S*,4*R*)-2-Amino-1,3,4-octadecanetriol (D-*ribo*-Phytosphingosine) (1).[8e] Compound **10a** (20 mg, 0.058 mmol) and 10% Pd/C (20 mg) in dried MeOH (1 mL) was stirred under a H_2 atmosphere at room temperature for 2 days. The mixture was filtered and concentrated and the resulting residue was evaporated in vacuo to give compound **1** (17 mg, 0.054 mmol, 94%). R_f 0.30 (1:10:10 MeOH/EtOAc/hexane); $[\alpha]^{24}_D$ +7.9 (*c* 1.0, C_5H_5N); ^{1}H NMR (400 MHz, pridine-d_5/D_2O) δ 4.32 (br, 1 H), 4.22 (dd, 1 H, J = 9.3, 6.1 Hz), 4.19 (m, 1 H), 3.97 (t, 1 H, J = 7.1 Hz), 3.52 (br, 1 H), 2.16−2.30 (m, 1 H), 1.78−1.95 (m, 2 H), 1.66 (m, 1 H), 1.37 (m, 1 H), 1.21 (br, 21 H), 0.83 (t, 3 H, J = 6.7 Hz).

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Supporting Information Available: General considerations of the Experimental Section and ^{1}H and ^{13}C spectra of compounds **4**∼**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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