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An efficient synthesis of D-*ribo*- and L-*lyxo*-phytosphingosine from D-tartaric acid

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Abstract—The preparations of D-*ribo*- and L-*lyxo*-phytosphingosines (**1**, **2**) are described. Chelation-controlled addition of tetradecylmagnesium bromide to pentylidene-protected D-threitol aldehyde **6** afforded the key intermediate tetrol **7**, providing the desired L-*lyxo* stereochemistry of phytosphingosine. Inversion at C4 of intermediate **7** provided the D-*ribo* stereochemistry.

D-*ribo*-Phytosphingosine (4D-hydroxysphinganine, PHS, **1**, Fig. 1) consists of a long-chain base (an aliphatic chain, predominantly octadecyl) with a 2-amino-1,3,4-triol head group. It is broadly distributed in fungal, plant, and animal sphingolipids, where it forms the backbone of various glycosphingolipids.[1] In addition to its structural role in membranes, D-*ribo*-PHS (**1**) has been implicated in the regulation of cellular growth; for example, PHS is involved in the heat stress response of yeast cells[2] and induction of apoptosis in some cancer cells.[3] Amide-linked derivatives of PHS, which constitute ~30% of the total ceramide content of the outer layer of the epidermis (stratum corneum), are important components of the lipid architecture that make up the water permeability barrier of human skin.[4] PHS also forms the backbone of (a) the marine glycolipid KRN7000, a ligand of natural killer cells (a unique class of T lymphocytes that produce cytokines and have many potential therapeutic applications in disease settings),[5] and (b) the glycosylphosphatidylinositol (GPI) of the membrane-anchored proteins in yeast.[6]

The biological significance of PHS has intensified the interest in this lipid as a synthetic target.[7] We report here the preparation of **1** and one of its diastereomers, L-*lyxo*-PHS (**2**), from D-threose synthon **6**[8] via reaction with tetradecylmagnesium bromide. The route also provides a convenient access to the corresponding 2-azido-3,4-*O*-dibenzyl intermediates **3** and **4**, which are useful galactosyl acceptors in the preparation of galactosylphytoceramides.[9]

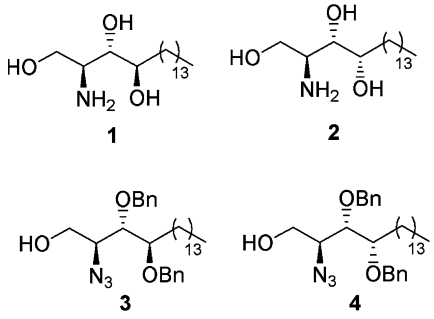

Figure 1. Structures of D-*ribo*-PHS (**1**), L-*lyxo*-PHS (**2**), and their corresponding 2-azido-3,4-*O*-dibenzyl intermediates **3** and **4**, respectively.

Scheme 1 illustrates the retrosynthetic analysis for our syntheses of D-*ribo*- and L-*lyxo*-PHS (**1** and **2**, respectively) starting with readily available D-(−)-tartaric acid (**5**). The key step is the addition of the long aliphatic chain to aldehyde **6** under stereocontrolled conditions, which was accomplished by a chelation-controlled Grignard reaction. After the 4*S*-hydroxy group was protected as a benzyl ether, the acetal of the tetrol was released to form a 1,2-diol. Regioselective azidation at C2 was accomplished with inversion of configuration, affording azido alcohol **4**. Reduction of the azido group and removal of the *O*-benzyl groups of **4** in a one-pot

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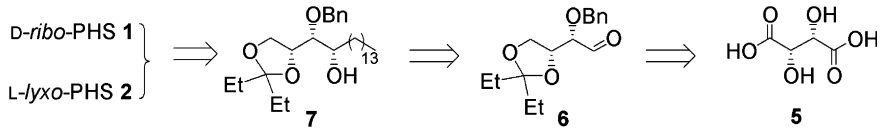


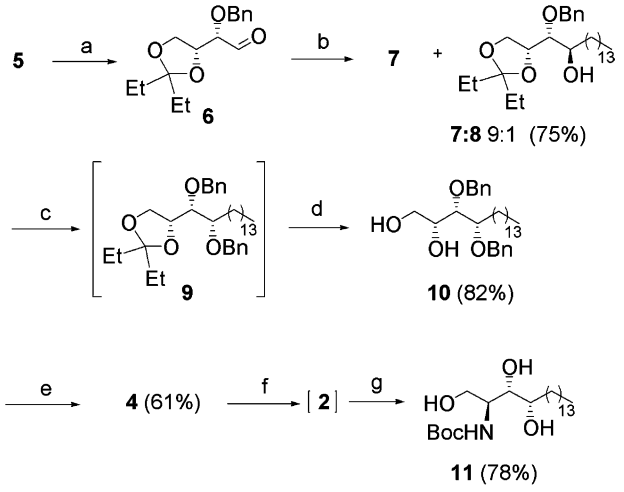
Scheme 1. Retrosynthetic plan.

reaction gave target **2**, which was characterized as its *N*-Boc derivative **11**. For the synthesis of **1**, the requisite *R* configuration at C4 was obtained by inversion of intermediate **7** using the Mitsunobu reaction.

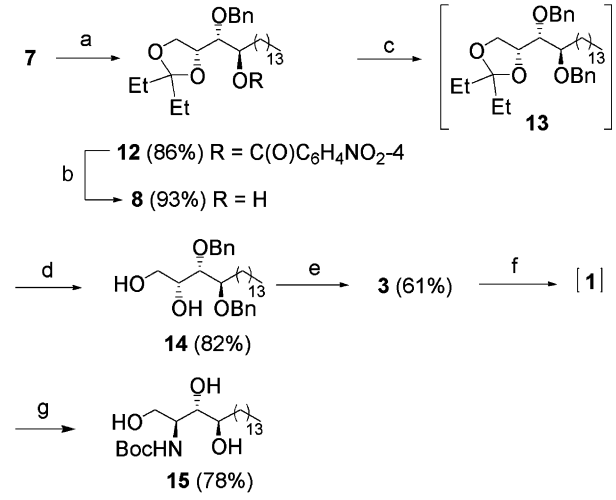
Scheme 2 outlines the synthesis of **2** from D-tartaric acid (**5**). Aldehyde **6** was prepared from D-tartaric acid as reported previously.[8] Reaction of aldehyde **6** with tetradecylmagnesium bromide in Et_2O at 0 °C gave a 9:1 mixture of compounds **7** and **8**.[10] The diastereoselectivity of the Grignard addition is markedly higher than that of the reaction between aldehyde **6** and tetradecynyllithium in Et_2O at −20 °C in the presence of $ZnBr_2$, which (as we reported previously) furnished the 2*R*,3*R*,4*S* and 2*R*,3*R*,4*R* diastereomers in a 3:1 ratio.[8] Thus Grignard addition afforded the chelation-controlled product **7**,[11] which was obtained in 68% yield after purification by column chromatography (elution with hexane/EtOAc 3:1). The configuration at C4 was confirmed when **7** was finally converted to L-*lyxo*-PHS (**2**). After the hydroxy group of **7** was protected as a benzyl ether (BnBr, NaH, catalytic *n*-Bu_4NBr (TBAB)), selective deprotection of **9** with 5% H_2SO_4 provided 1,2-diol **10**[12] in 82% yield for the two steps. Diol **10** was converted to azido alcohol **4** in a one-pot reaction.[13] 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 together with silylation of the primary hydroxyl group. Hydrolysis of the silyl ether with *n*-Bu_4NF (TBAF) provided azido alcohol **4** in 61% yield. Simultaneous reduction of the azido group and hydrogenolysis of the benzyl groups in the presence of Pearlman's catalyst ($Pd(OH)_2$/C) gave **2**, whose amino group was protected as carbamate **11** for ease of isolation[14] (78% yield for the two steps).

Scheme 3 outlines the synthesis of **1** from alcohol **7**. The configuration at C4 of compound **7** was inverted by Mitsunobu reaction (*p*-nitrobenzoic acid, DIAD, PPh_3). Hydrolysis of benzoate ester **12**[15] with NaOMe in methanol gave alcohol **8** (80% overall yield for the two steps). As in the preparation of **2** (Scheme 2), the C4 hydroxy group was protected as a benzyl ether and the acetonide was opened by treatment with H_2SO_4. After the secondary hydroxy group of diol **14**[16] was converted to an azido group,[17] the azido group was reduced and the *O*-benzyl groups were deprotected to give product **1**. The amino group of **1** was protected as a *N*-Boc group to give **15**[18] (78% yield for two steps).

In summary, short routes to L-*lyxo*-PHS (**2**) and D-*ribo*-PHS (**1**) via D-threitol acetal derivative **6** are reported here. Coupling of tetradecylmagnesium bromide with aldehyde **6** gave a mixture of alcohols **7** and **8** in a 9:1 ratio. 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**). For the synthesis of D-*ribo*-PHS (**1**), a Mitsunobu reaction was used to invert the requisite configuration of the third chiral center.



Scheme 2. Synthesis of *N*-Boc-L-*lyxo*-phytosphingosine (**11**). Reagents and conditions: (a) Ref. 8; (b) $C_{14}H_{29}Br$, Mg, $BrCH_2CH_2Br$, Et_2O; (c) BnBr, NaH, THF; (d) 5% H_2SO_4, MeOH; (e) (i) PPh_3, DIAD, CH_2Cl_2, 0 °C, (ii) $TMSN_3$, 0 °C–rt, (iii) TBAF, THF; (f) $Pd(OH)_2$/C, H_2, MeOH; (g) Boc_2O, Et_3N, dioxane/H_2O.



Scheme 3. Synthesis of *N*-Boc-D-*ribo*-phytosphingosine (**15**). Reagents and conditions: (a) DIAD, PPh_3, *p*-nitrobenzoic acid, CH_2Cl_2; (b) NaOMe, MeOH; (c) BnBr, NaH, THF; (d) 5% H_2SO_4, MeOH; (e) (i) PPh_3, DIAD, CH_2Cl_2, 0 °C, (ii) $TMSN_3$, 0 °C–rt, (iii) TBAF, THF; (f) $Pd(OH)_2$/C, H_2, MeOH; (g) Boc_2O, Et_3N, dioxane/H_2O.

Acknowledgements

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10. Experimental details for the addition of aldehyde **6** to $C_{14}H_{29}MgBr$ and the isolation of **7** and **8**: To a solution of aldehyde **6** (1.39 g, 5.0 mmol) in 50 mL of Et_2O at 0 °C was quickly added freshly prepared $C_{14}H_{29}MgBr$ (15 mmol) in 50 mL of Et_2O. The reaction mixture was stirred at 0 °C for 3 h, then warmed to room temperature and stirred overnight. The reaction mixture was quenched by adding 50 mL of water, the organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed by vacuum evaporation. The residue was purified by chromatography (hexane/EtOAc 3:1) to give 1.61 g of **7** (68%) as a colorless oil: R_f 0.54 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ +18.6 (*c* 2.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86–0.95 (m, 9H), 1.25–1.35 (m, 24H), 1.62–1.72 (m, 6H), 1.82 (s, 1H), 3.31 (m, 1H), 3.39 (m, 1H), 3.62 (dd, 1H, J = 8.0, 0.4 Hz), 4.08 (dd, 1H, J = 8.0, 6.4 Hz), 4.40 (m, 1H), 4.67 (d, 1H, J = 11.2 Hz), 4.92 (d, 1H, J = 11.2 Hz), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.12, 8.31, 14.1, 22.7, 25.9, 29.3, 29.6, 29.7, 31.9, 34.8, 68.2, 72.1, 74.1, 78.3, 81.2, 113.2, 127.8, 128.3, 128.4, 138.4. Also obtained was 168 mg of **8** (7%): R_f 0.58 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ +17.0 (*c* 0.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86–0.94 (m, 9H), 1.25–1.35 (m, 24H), 1.48–1.70 (m, 6H), 2.48 (m, 1H), 3.42 (m, 1H), 3.65 (m, 1H), 3.75 (m, 1H), 3.99 (m, 1H), 4.30 (m, 1H), 4.66 (d, 1H, J = 11.2 Hz), 4.76 (d, 1H, J = 11.2 Hz), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.14, 8.31, 14.1, 22.7, 25.9, 29.3, 29.6, 29.7, 31.9, 33.1, 66.4, 72.1, 74.1, 78.3, 81.3, 113.1, 127.4, 127.8, 128.3, 138.4.
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12. Data for (−)-**10**: R_f 0.24 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −11.6 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.33–1.71 (m, 26H), 2.60 (s, 2H), 3.49 (m, 1H), 3.60 (m, 3H), 3.78 (m, 1H), 4.56 (m, 3H), 4.71 (d, 1H, J = 11.2 Hz), 7.28–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 26.0, 29.4, 29.6, 30.4, 32.0, 64.3, 71.3, 72.9, 74.2, 77.3, 79.6, 127.8, 128.0, 128.1, 128.2, 128.5, 128.6, 137.9, 138.0.
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14. Data for (−)-**11**: R_f 0.29 (hexane/EtOAc 1:1); mp 129.5–131.2 °C; $[\alpha]_D^{25}$ −7.9 (*c* 0.35, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.33–1.71 (m, 33H), 1.62 (m, 2H), 3.32 (m, 1H), 3.51 (m, 1H), 3.72 (m, 1H), 4.06 (m, 1H), 5.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 28.3, 29.4, 29.6, 32.0, 53.5, 61.9, 69.7, 72.8, 80.4, 157.3.
15. Data for (−)-**12**: R_f 0.69 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −15.0 (*c* 1.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86–0.93 (m, 9H), 1.23–1.55 (m, 24H), 1.60–1.69 (m, 6H), 3.67 (m, 1H), 3.77 (m, 1H), 4.01 (m, 1H), 4.25 (m, 1H), 4.75 (d, 1H, J = 11.2 Hz), 4.79 (d, 1H, J = 11.2 Hz), 5.04 (m, 1H), 7.26–7.37 (m, 5H), 8.14 (d, 2H, J = 7.2 Hz), 8.29 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 8.14, 8.23, 14.1, 22.7, 25.7, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 66.7, 73.9, 76.2, 77.6, 80.7, 113.4, 123.5, 127.7, 128.1, 128.3, 130.8, 135.5, 138.2, 150.6, 164.2.
16. Data for (−)-**14**: R_f 0.24 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −9.8 (*c* 1.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.33–1.71 (m, 26H), 2.51 (s, 1H), 3.34 (m, 1H), 3.53 (m, 1H), 3.65 (m, 3H), 3.87 (m, 1H), 4.54 (m, 2H), 4.63 (d, 1H, J = 11.2 Hz), 4.71 (d, 1H, J = 11.2 Hz), 7.28–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 25.6, 29.4, 29.6, 30.8, 31.9, 63.7, 71.4, 72.7, 73.6, 77.4, 79.7, 127.8, 128.0, 128.1, 128.2, 128.5, 128.6, 137.9, 138.0.
17. Data for azido alcohol (−)-**3**: R_f 0.58 (hexane/EtOAc 3:1); $[\alpha]_D^{25}$ −3.71 (*c* 4.15, $CHCl_3$); R_f 0.70 (hexane/EtOAc 3:1);

^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.33–1.51 (m, 24H), 1.60 (m, 2H), 2.61 (m, 1H), 3.63 (m, 3H), 3.78 (m, 1H), 3.87 (m, 1H), 4.59 (m, 2H), 4.67 (m, 2H), 7.28–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.5, 29.4, 29.6, 30.2, 31.9, 62.2, 63.1, 72.5, 73.6, 79.1, 80.4, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 137.7, 138.2.

18. Data for (+)-**15**: R_f 0.29 (hexane/EtOAc 1:1); mp 89.2–90.4 °C; $[\alpha]_D^{25}$ +7.5 (c 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.16–1.78 (m, 35H), 3.64 (m, 3H), 3.82 (m, 2H), 4.09 (m, 1H), 4.16 (m, 1H), 4.44 (m, 1H), 5.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 28.3, 29.4, 29.6, 29.7, 31.9, 52.6, 61.7, 73.0, 75.6, 79.9, 156.3.