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A tethered aminohydroxylation route to L-*arabino*-[2*R*,3*S*,4*R*] and L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosines

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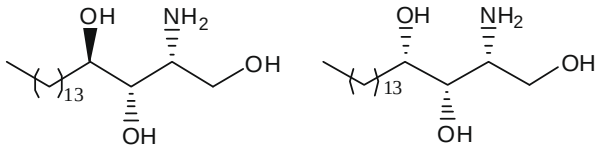
ABSTRACT

A concise and highly efficient synthesis of L-*arabino*-[2*R*,3*S*,4*R*] and L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosines has been achieved. The synthetic strategy features the Sharpless kinetic resolution and tethered aminohydroxylation as the key steps.

Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast, and in some prokaryotic organisms and viruses.[1] They exhibit a wide range of biological activities such as cell proliferation, differentiation, adhesion, and signal transduction.[2] Phytosphingosine exists in nature as one of the molecular species of sphingolipids in microorganisms, plants, and many mammalian tissues such as brain, hair, intestine,[3] uterus,[4] liver,[5] skin,[6] kidney,[7] and in blood plasma[8] (Fig. 1). It was first isolated from mushrooms in 1911[9] and its structure was elucidated by Oda[10a] and by Carter et al.[10b] In addition to its structural function as long-chain base of sphingolipids in membranes, phytosphingosine is a potential heat stress signal in yeast cells[11a,b] and some of its derivatives exhibit important physiological activity. α- and β-galactosyl and glucosylphytoceramids are highly potent against tumors.[11c]

Most synthetic studies have been focused primarily on the preparation of *ribo*-phytosphingosines, the stereochemistry of the C-2 position being either derived from the chiral pool materials, particularly serine, or by asymmetric synthesis.[12] Although several procedures of the target compound have already been reported, most of these methods suffer either from large number of steps, low yields or from low stereo- or regioselectivity. Therefore, a practical, concise expeditious, and high yield synthesis of the target molecule is still desirable. The tethered aminohydroxylation[13] has recently emerged as a powerful method of preparing vicinal amino alcohols in a regio- and stereoselective manner. This method overcomes the problem of low regioselectivity mainly encountered during the asymmetric aminohydroxylation,[14] a recent discovery of Sharpless to introduce amine and alcohol functionality in a single step in enantio- and stereoselective way. As a part of our research interest in asymmetric synthesis of bioactive molecules such as lactones[15] and amino alcohols,[16] we became interested in developing a new and highly concise route to phytosphingosine. Herein we report a highly efficient synthesis of L-*arabino*- and L-*xylo*-phytosphingosines employing Sharpless kinetic resolution and tethered aminohydroxylation as the key steps.

As illustrated in Scheme 1, the synthesis of L-*arabino*-[2*R*,3*S*,4*R*]-C_{18}-phytosphingosine started from commercially available pentadecanol **3**. Compound **3** was oxidized using DMSO-pivaloyl



1 L-*arabino*-[2*R*,3*S*,4*R*]-C_{18}-Phytosphingosine

2 L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-Phytosphingosine

Figure 1. Structures of L-*arabino*-[2*R*,3*S*,4*R*]- and L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-Phytosphingosines.

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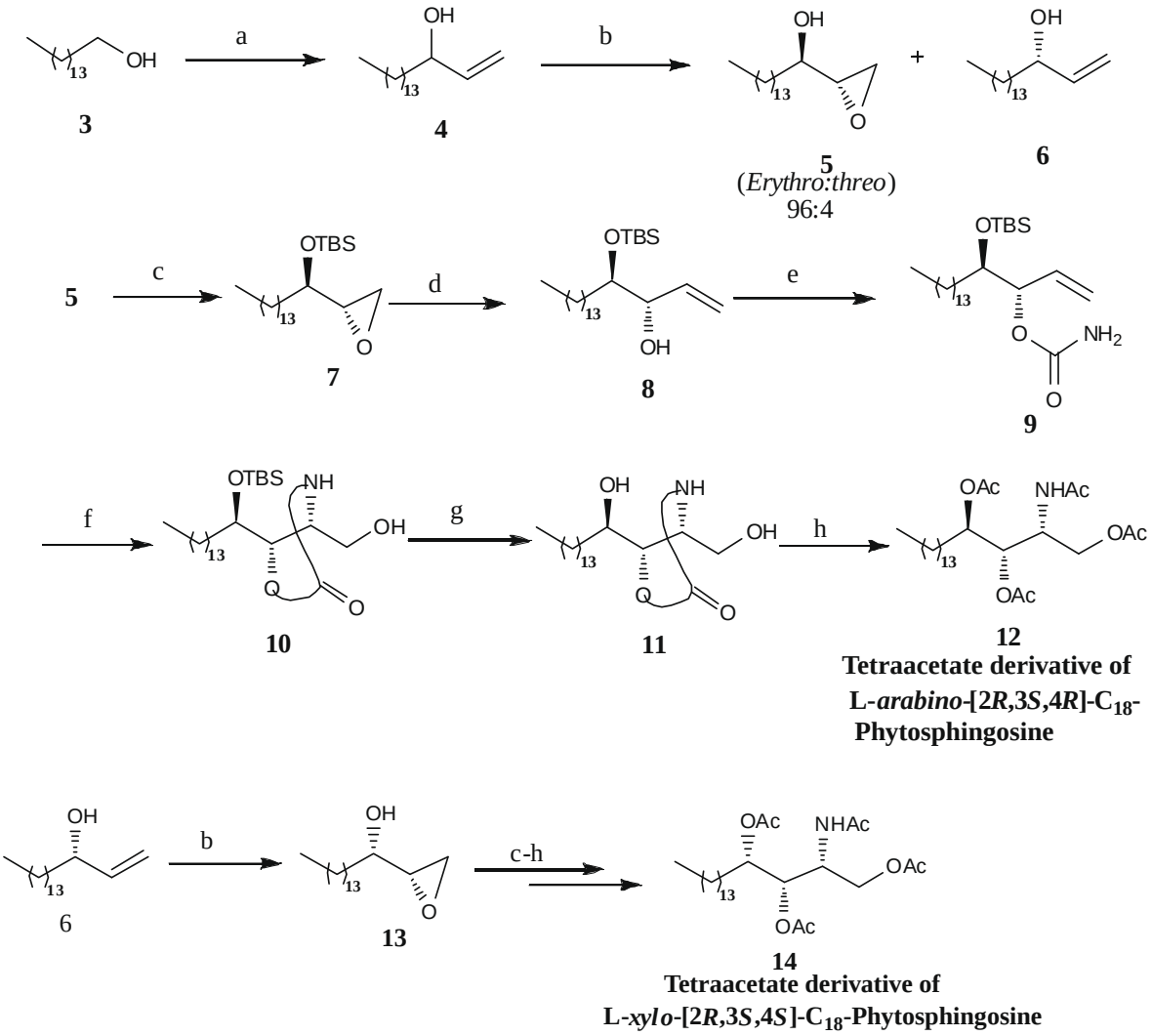

Scheme 1. *Reagents and conditions*: (a) (i) pivaloyl chloride, DMSO, Et_3 N, -78 °C; (ii) vinyl bromide, Mg, −78 °C, 2 h, 88%; (b) (−)-DIPT, Ti(O-^{i}Pr)$_4$, TBHP, dry DCM, molecular sieves, 3 Å, −20 °C, 4 days, 49% for **5** and 46% for **6**; (c) TBS-OTf, 2,6-lutidine, dry CH_2Cl_2, 15 min, −10 °C, 90%; (d) $(CH_3)_3S^+I^-$, *n*-BuLi, −20 °C, 75% (e) $Cl_3CCONCO$, K_2CO_3, CH_2Cl_2:CH_3OH (1.5:1), 4 h, 90%; (f) NaOH, *t*-BuOCl, $^i Pr_2EtN$, potassium osmate, 2.5 h, 66%; (g) TsOH (Cat.), MeOH (h) (i) K_2CO_3, methanol, rt, 6 h; (ii) Ac_2O, pyridine, DMAP (cat), overnight, 82%.

chloride[17] to give the aldehyde, which on Grignard reaction with vinyl magnesium bromide furnished the allylic alcohol **4** in 88% yield. The treatment of **4** with titanium tetraisopropoxide and *tert*-butylhydroperoxide in the presence of (−)-DIPT under Sharpless asymmetric kinetic resolution conditions[18] provided the epoxy alcohol **5** and chiral allylic alcohol **6**[19] in 46% yield and 97% ee (determined from the corresponding Mosher's ester). The epoxide **5** was found to be a mixture of *erythro* and *threo* (96:4) which was subsequently converted into their silyl derivatives by treatment with TBSOTf in the presence 2,6-lutidine. The required *erythro* isomer **7**[20] could easily be separated by column chromatography in 90% yield. Epoxide **7** was treated with excess of dimethylsulfonium methylide[21] (generated from trimethylsulfonium iodide and *n*-BuLi) to furnish the allylic alcohol **8** in 75% yield. Alcohol **8** was then reacted with trichloroacetyl isocyanate in CH_2Cl_2 to give the corresponding isocyanate which on treatment with aq. K_2CO_3 and methanol furnished the carbamate **9** in 90% yield. The carbamate was converted into the oxazolidinone derivative **10** by a tethered aminohydroxylation protocol[13] using *tert*-butyl hypochlorite as the oxidant, potassium osmate, NaOH, diisopropylethylamine, and propanol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **10**[22] in 66% yield with complete regio- and excellent diastereoselectivity (*syn:anti* 12:1, determined from ^{1}H NMR). The diastereomeric mixture could easily be separated by column chromatography. The key step in the tethered aminohydroxylation as depicted in Figure 2 is the intramolecular addition of the RN═Os═O fragment across the alkene leading to *syn* or *anti* relative stereochemistry.[13] In the conformation **A**, due to the presence of hydrogen in the inside allylic position, the intramolecular approach of active osmium species to alkene would be favored thus leading to the major *syn*-product. The presence of bulky group (R in **B**) may hinder the approach of the active osmium species to the alkene and thus the reaction via conformation **B** leading to the *anti*- product is disfavored.

The compound **10** was desilylated using p-TSA and methanol to give the alcohol **11** in 78% yield, which on hydrolysis with K_2CO_3 in methanol furnished the crude aminoalcohol. Subsequent acylation using Ac_2O in the presence of pyridine and catalytic amount of DMAP produced the tetraacetate derivative of phytosphingosine **12**[23] in 82% yield.

For the synthesis of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine, the allylic alcohol **6** obtained by the chiral resolution of **4** was subjected to Sharpless asymmetric epoxidation to give the epoxide **13** in 75% yield as a single diastereomer, which was converted into the tetraacetate derivative of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingo-

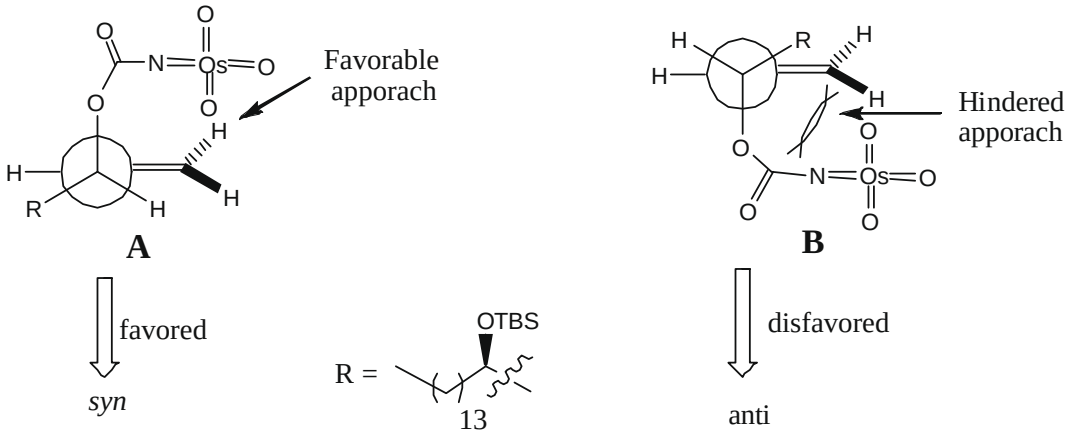

Figure 2. Proposed transition states for the syn/anti selectivity observed during the TA reaction.

sine **14** following the same sequence of reactions as described for **12** (Scheme 1).The physical and spectroscopic data of **14** were in accordance with those described in literature.[12b]

In conclusion, we have achieved a concise synthesis of both L-*arabino*- and L-*xylo*-phytosphingosines using tethered aminohydroxylation and Sharpless kinetic resolution as the key steps and as a source of chirality. The tethered aminohydroxylation was used to introduce the amino functionality in a highly diastereoselective manner. The generality of the method shown has significant potential of its further extension to the other isomers of phytosphingosine and related analogues. Currently studies are in progress to this direction.

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19. *Spectral data of* **6**: mp = 46 °C. $[\alpha]_D^{25}$ +2.38 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.89 (t, *J* = 6.1 Hz, 3H), 1.26 (m, 24H), 1.54 (m, 2H), 1.69 (br s, 1H), 4.11 (m, 1H), 5.08–5.26 (m, 2H), 5.78–5.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0, 22.6, 25.3, 25.7, 29.3, 29.6, 31.8, 32.6, 36.9, 62.6, 73.0, 114.2, 141.3; Anal. Calcd for $C_{17}H_{34}O$ (254.45): C, 80.24; H, 13.47. Found: C, 79.95; H, 13.73.
20. *Spectral data of* **7**: $[\alpha]_D^{25}$ −4.1 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.12 (s, 3H), 0.84–0.93 (m, 12H), 1.26 (s, 24 H), 1.49–1.53 (m, 2H), 2.55 (q, *J* = 2.72, 5.12, 1H), 2.75–2.83 (m, 1H), 2.87–2.97 (m, 1H), 3.19–3.33 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.9, −4.4, 14.0, 18.1, 22.6, 24.8, 25.2, 25.6, 25.7, 25.9, 29.3, 29.5, 29.6, 29.7, 31.9, 35.2, 44.7, 54.6, 71.2; Anal. Calcd for $C_{23}H_{48}O_2Si$ (384.71): C, 71.81; H, 12.58. Found. C, 71.65; H, 12.73.
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22. *Spectral data of* **10**: $[\alpha]_D^{25}$ +28.47 (*c* 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.88–0.91 (m, 12H), 1.26 (m, 24 H), 1.39–1.41 (m, 2H), 3.42–3.6 (m, 1H), 3.65–3.8 (m, 1H), 3.85–4 (m, 2H), 4.32 (m, 1H), 6.55 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.6, −4.4, 14.0, 17.9, 22.6, 24.9, 25.7, 29.3, 29.6, 31.8, 32.8, 54.3, 63.8, 71.9, 80.3, 160.3; Anal. Calcd for $C_{25}H_{51}NO_4Si$ (457.76): C, 65.59; H, 11.23; N, 3.06. Found. C, 65.35; H, 11.48; N, 3.36.
23. Spectral data of **12**: mp = 48 °C; $[\alpha]_D^{20}$ −25.95 (*c* 1.5, $CHCl_3$); lit.[12d] $[\alpha]_D^{20}$ −25.1 (*c* 1.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): 0.86 (t, *J* = 6 Hz, 3H), 1.2–1.3 (m, 24 H), 1.55 (m, 2H), 2.03 (s, 3H), 2.04 (s, 6H), 2.07 (s, 3H), 3.95–4.05(m, 2H), 4.5 (m, 1H), 5.02–5.18 (m, 2H), 5.92 (d, *J* = 10 Hz, 1H) .^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6, 21.2, 21.4, 23.6, 25.5, 30.1, 32.4, 33.9, 47.5, 63.5, 71.4, 72.4, 170.3, 170.6, 170.7, 171.1.