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Enantioselective synthesis of D-*ribo*-(2*S*,3*S*,4*R*)-C_{18}-phytosphingosine using double stereodifferentiation

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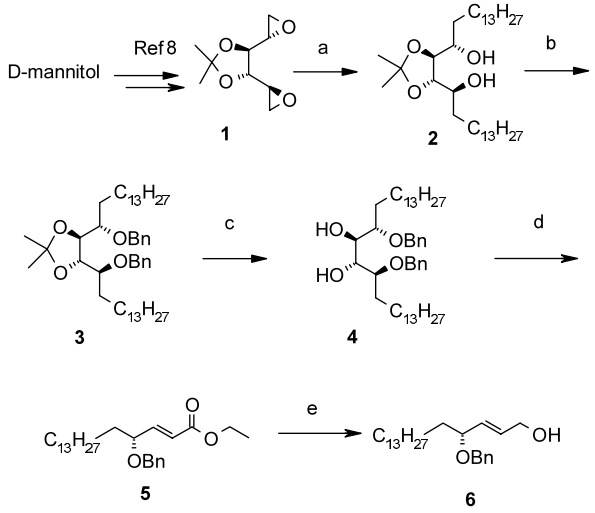
Abstract—An enantioselective synthesis of D-*ribo*-C_{18}-phytosphingosine as its tetraacetate derivative **10**, starting from D-mannitol and employing the Sharpless asymmetric dihydroxylation reaction on allylic alcohol **6** as the key step, is described.

Sphingolipids constitute a class of widely ranging natural products. Sphingosine, phytosphingosine and their biosynthetic precursor, sphinganine are long chain amino alcohols, generally possessing 18 or 20 carbon atoms. They are building blocks of sphingolipids such as sphingomyelins, glycosphingolipids, and phosphosphingolipids, which are important membrane constituents playing vital roles in cell regulation and signal transduction.[1]

Phytosphingosine was first detected in fungi,[2a] plants,[2b] yeasts[2c] and other microorganisms.[2d] Thus, it was found that its occurrence is not limited to plant tissues, but it is also present in mammalian tissues, for example in kidney,[3a–c] liver,[3d] uterus,[3e] intestine,[3f] skin,[3g,h] and blood plasma.[3i]

D-*ribo*-C_{18}-Phytosphingosine ((2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol) and its related C_{20}-homologue are widely distributed as amides of α-hydroxy long chain acids in plant sphingolipids.[4] Various methods for the synthesis of phytosphingosines either racemic[5] or enantiomerically enriched[6] have been described in literature. As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones[7a,b] and amino alcohols,[7c–f] the Sharpless asymmetric dihydroxylation was envisaged as a powerful tool to the chiral dihydroxy compounds offering considerable opportunity for synthetic manipulations. Herein we report a new and enantioselective synthesis of D-*ribo*-(2*S*,3*S*,4*R*)-C_{18}-phytosphingosine from D-mannitol and employing the Sharpless asymmetric dihydroxylation as a key step.

The allylic alcohol **6** is envisaged as a chiral building block from which D-*ribo*-C_{18}-phytosphingosine and related analogs can be synthesized. The synthesis of intermediate **6** starts from D-mannitol, an inexpensive



Scheme 1. *Reagents and conditions*: (a) *n*-$C_{13}H_{27}MgBr$, CuI, THF, 45°C to rt, 1 h, (86%); (b) BnBr, NaH, *n*-Bu_4NI, THF, rt, 4 h, (95%); (c) *p*-TSA, MeOH, rt, 32 h, (90%); (d) (i) $NaIO_4$ adsorbed on silica gel, DCM, rt, 30 min (95%); (ii) $(EtO)_2P(O)CH_2COOEt$, LiBr, Et_3N, THF, rt, overnight, (89%); (e) DIBAL-H, Et_2O, 0°C to rt, 2 h, (91%).

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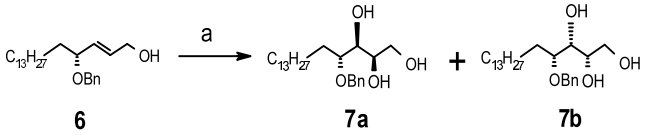
and readily available chiral pool material as illustrated in Scheme 1. D-Mannitol was first converted to diepoxide **1** following a literature procedure.[8]

The opening of diepoxide **1** was carried out regioselectively using tridecylmagnesium bromide in the presence of CuI to afford compound **2** in 86% yield having $[\alpha]_D^{20}=+21.33$ (c 0.36, $CHCl_3$). Protection of hydroxyl groups in **2** with benzyl bromide furnished the corresponding 2,5-*O*-dibenzylated product **3** in essentially quantitative yield which on subsequent deprotection of the isopropylidene group with a catalytic amount of *p*-TSA afforded compound **4** in excellent yield. Oxidative cleavage of **4** with $NaIO_4$ adsorbed on silica gel gave the corresponding aldehyde in 95% yield, which was subsequently treated with $(EtO)_2P(O)CH_2COOEt$ under the Wittig–Horner reaction conditions to afford the α,β-unsaturated ester **5** in 89% yield.

In the asymmetric dihydroxylation of an olefin, the stereoselective outcome of the reaction is affected by the presence of pre-existing chiral information in the substrate. With a view to exploiting the concept of double diastereoselection, the olefinic ester **5** was subjected to the Sharpless asymmetric dihydroxylation (SAD) conditions.[9] However, the reaction proceeded much more slowly with a poor diastereoselectivity probably as a consequence of the electron-withdrawing properties of the ester group.[9] While the Sharpless asymmetric dihydroxylation on the allylic alcohols with different long alkyl chains has been exploited to a large extent,[10] the reaction on allylic alcohols having chiral centers remains still unexplored. The enantioselectivity of an asymmetric dihydroxylation reaction can be modulated by the size of the allylic substituent and the configuration at the allylic position. Therefore, in order to explore the possibility of achieving a good diastereoselectivity, it was thought worthwhile to convert ester **5** into the allylic alcohol **6** for a SAD reaction. Thus, DIBAL-H reduction of ester **5** furnished the corresponding allyl alcohol **6**[11] in 91% yield which was then subjected to the Sharpless asymmetric dihydroxylation reaction (Scheme 2). The results of double diastereoselection are given in Table 1.

The dihydroxylation of allyl alcohol **6** under the Sharpless asymmetric dihydroxylation conditions using $(DHQD)_2PHAL$ ligand afforded the diastereomeric mixture **7a**:**7b** in a 9:1 ratio.[12] The stereochemical purity of **7a** was easily enriched to 90% by recrystallization twice from acetone. The compound **7a** was fully characterized by analytical and spectroscopic data.[11] The use of $(DHQ)_2$ PHAL ligand under similar conditions gave a diastereomeric ratio **7a**:**7b** (1:2). The high diastereoselectivity obtained in the former case could be regarded as a matched case where the chirality information of the reagent and the substrate probably act synergistically while the poor degree of diastereoselection observed in the latter case may be because of opposite influences of the chiral reagent and substrate (mismatched case). It should be mentioned here that the dihydroxylation of allylic alcohols and their derivatives using OsO_4 (stoichiometric or catalytic) and NMO is reported to give only poor to moderate diastereoselectivity.[13]

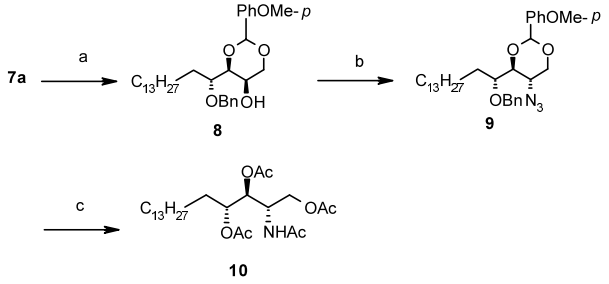
In order to achieve the synthesis of target compound **10** from **7a** (Scheme 3), we required the transformation of the hydroxy group into azide at the C-2 position. To this end protection of **7a** as *p*-methoxybenzylidene derivative was effected using 4-methoxybenzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TSA to afford a mixture of 1,3- and 1,2-benzylidene compounds in a 19:1 ratio. The desired major 1,3-benzylidene compound **8** was separated by silica gel column chromatography. Compound **8** was then converted into an *O*-mesylated derivative, which on treatment with sodium azide in DMF furnished the azide **9** with the desired stereochemistry at C-2. Deprotection of benzyl, cleavage of 1,3-benzylidene protecting group and reduction of azide to amine were carried in one-pot reaction by hydrogenation in the presence of 10% Pd/C in ethanol followed by acetylation to furnish **10** in 69% yield. The physical and spectroscopic data of **10** were in full agreement with the literature data.[6c]



Scheme 2. *Reagents and conditions*: (a) ligand, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0°C (89–92%).

Table 1. Double stereodifferentiation in AD reaction of **6**

Ligand	**7a**	**7b**	Yield (%)
$(DHQD)_2PHAL$	9	1	92
$(DHQ)_2PHAL$	1	2	89



Scheme 3. *Reagents and conditions*: (a) *p*-MeO-PhCH$(OMe)_2$, *p*-TSA, CH_2Cl_2, rt, overnight (70%); (b) (i) $MeSO_2Cl$, Et_3N, DMAP (Cat), CH_2Cl_2, rt, overnight; (ii) NaN_3, DMF, 80°C, 24 h (81%); (c) (i) Pd/C, H_2, EtOH; (ii) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 24 h (69%).

Conclusion

In summary, a highly enantioselective synthesis of D-*ribo*-C_{18}-phytosphingosine has been achieved from a readily available carbohydrate precursor by using the Sharpless asymmetric dihydroxylation procedure. The concept of double diastereoselection was employed for the first time on a chiral allylic alcohol in SAD reaction. The merits of this synthesis are high diastereoselectivity and high yielding reaction steps. The other isomer L-*lyxo*-C_{18}-phytosphingosine can be synthesized from *S*-diepoxide using the chiral ligand $(DHQ)_2PHAL$ in the dihydroxylation step and following the reaction sequence shown above.

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11. Spectroscopic data for selected compounds: Compound **6**: Colorless oil, $[\alpha]_D^{20}=+24.89$ (*c* 0.54, $CHCl_3$); IR (neat): ν_{max} 3372, 2924, 2853, 2450, 1464 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, $J=6$ Hz, 3H), 1.26 (m, 26H), 3.80 (dd, $J=6$, 8 Hz, 1H), 4.19 (d, $J=6$ Hz, 2H), 4.35 (d, $J=10$ Hz, 1H), 4.57 (d, $J=10$ Hz, 1H), 5.54 (m, 1H), 5.81 (dt, $J=6$, 16 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.07, 22.64, 25.36, 29.36, 29.66, 30.83, 31.90, 31.97, 35.65, 58.92, 63.00, 70.24, 127.36, 127.69, 128.31, 131.66, 132.61, 133.46, 138.12; MS (EI) *m*/*z* (%) 374 (M^+). Anal. calcd for $C_{25}H_{42}O_2$ (374.60): C, 80.15; H, 11.30. Found: C, 79.95; H, 11.31.
Compound **7a**: white solid (mp 77°C); $[\alpha]_D^{20}=-7.60$ (*c* 0.86, $CHCl_3$); IR: ν_{max} 3422, 2926, 1458, 1370, 1215, 765, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, $J=6$ Hz, 3H), 1.27–1.30 (m, 26H), 3.32 (br s, 3H), 3.65 (s, 2H), 3.75–3.80 (m, 2H), 3.95–4.10 (m, 1H), 4.62 (s, 2H), 7.34 (m, 5H); ^{13}C NMR (50 MHz $CDCl_3$): δ 14.03, 22.60, 25.17, 29.29, 29.62, 29.80, 30.57, 31.86, 65.02, 70.31, 72.77, 72.96, 76.38, 77.00, 77.66, 81.34, 127.80, 127.91 128.42, 138.13; MS (EI) *m*/*z* (%) 408 (M^+), 393 (M^+-15). Anal. calcd for $C_{25}H_{44}O_4$ (408.6): C, 73.48; H, 10.85. Found C, 73.21; H, 10.52.
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