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Double stereodifferentiation in asymmetric dihydroxylation: application to the first diastereoselective synthesis of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine

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Abstract

The first diastereoselective synthesis of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine (**1**) has been achieved by double stereodifferentiation of enantiomerically enriched terminal olefin **14** using $(DHQD)_2$–PHAL ligand in an asymmetric dihydroxylation with a diastereomeric ratio of 83:17. This phytosphingosine was fully characterized by the physical and spectral data of the corresponding tetraacetate **21**. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric dihydroxylation; double stereodifferentiation; diastereoselective synthesis; sphingolipids; phytosphingosines.

Although known for more than 100 years, the finding that defects in sphingolipid metabolism leads to several inherited human diseases and that sphingolipids are involved in essentially all aspects of cell regulation have led to an explosion of interest in sphingolipids;[1] namely sphingomyelins, gangliosides, cerebrosides and other complex cellular lipid homologues. These have long-chain bases as the backbone, i.e. sphingosine, dihydrosphingosine and phytosphingosine which are important membrane components playing vital roles in cell regulation and signal transduction.[2] Due to their varied biological activities, a great deal of effort has been made towards the synthesis of sphingolipids.

Of the eight C_{18}-phytosphingosine isomers belonging to *ribo*-, *arabino*-, *xylo*-,and *lyxo*-series, most synthetic studies have been focused primarily on the preparation of *ribo*- or *arabino*-phytosphingosines, the stereochemistry of the C-2 position being either derived from the chiral pool materials or by asymmetric synthesis.[3] To our knowledge, only seven syntheses of *lyxo*- or *xylo*-phytosphingosines either racemic[4] or enantiomerically enriched[5] have been

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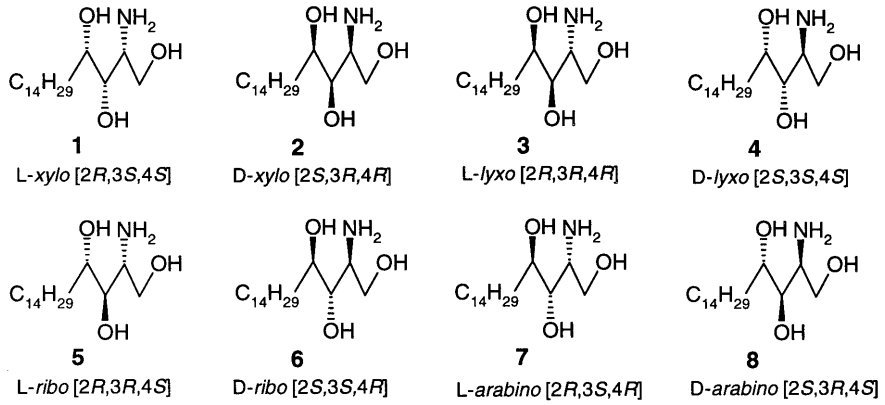
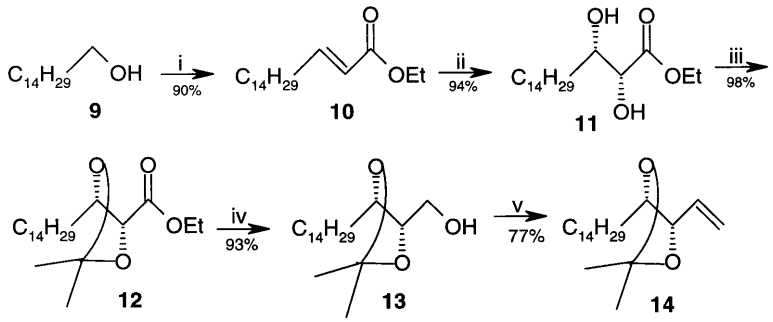
described to date. As part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[6a,b] and amino alcohols,[6c,d] Sharpless asymmetric dihydroxylation and subsequent transformation of the diols formed *via* cyclic sulfites/sulfates were envisaged as powerful tools offering considerable opportunities for synthetic manipulations. Herein we report the first diastereoselective synthesis of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **1** by employing the Sharpless asymmetric dihydroxylation as the source of chirality.



The enantiomerically enriched terminal olefin **14** was prepared following the reaction steps as shown in Scheme 1. The commercially available pentadecanol **9** was oxidized to the aldehyde and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane to give the Wittig product **10**. The dihydroxylation of olefin **10** under the Sharpless asymmetric dihydroxylation conditions[7] gave the diol **11** in 94% yield and 99% ee[8] ($[\alpha]_D^{20}$ −10.13, $c=1$, $CHCl_3$). The dihydroxy protection as acetonide **12** followed by lithium aluminum hydride reduction of the ester gave compound **13** in excellent yield. The primary alcohol was oxidized to the aldehyde under the normal Swern oxidation conditions which on subsequent Wittig reaction furnished the olefin **14**.

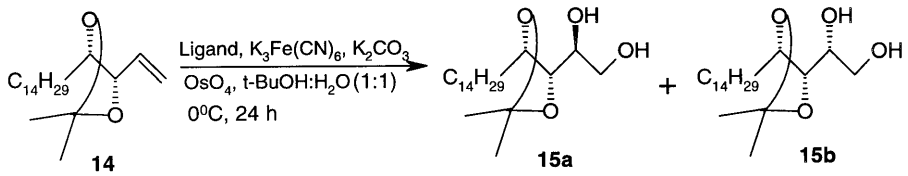


Scheme 1. Reagents and conditions: (i) (a) P_2O_5, DMSO, CH_2Cl_2, Et_3N, 0°C. (b) $Ph_3P{=}CHCO_2Et$, THF, reflux, 12 h; (ii) $(DHQ)_2$–PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O [1:1], 24 h., 0°C; (iii) 2,2-DMP, $(CH_3)_2CO$, PTSA, rt, overnight; (iv) $LiAlH_4$, Et_2O, 0°C to rt, overnight; (v) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C. (b) $Ph_3P^+CH_3I^-$, NaHMDS, THF, 0°C to rt, 12 h

The concept of double diastereoselection[9] was introduced for ever-increasing demand of higher selectivity in stereoselective reactions. In asymmetric dihydroxylation of olefins also, the stereoselective outcome of the reaction gets affected by the presence of pre-existing chiral information in the substrate.

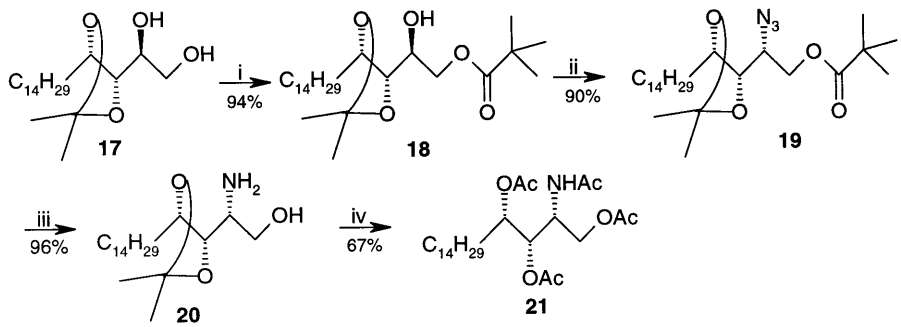
With a view to exploiting the concept of double diastereoselection, the olefin **14** was subjected to the Sharpless asymmetric dihydroxylation conditions. The results of double stereodifferentiation are given in Table 1.

Table 1
Double stereodifferentiation in AD reaction of **14**[10]



Ligand	**15a**	**15b**	Yield	Diastereomeric mixture
$(DHQ)_2$–PHAL	1	2	89%	**16** ($[\alpha]_D^{20}$ −17.3, $c=1$, $CHCl_3$)
$(DHQD)_2$–PHAL	5	1	92%	**17** ($[\alpha]_D^{20}$ −19.5, $c=1$, $CHCl_3$)

Thus, the diastereomeric ratio of **15a:15b** in the case of $(DHQ)_2$-PHAL ligand was 1:2 whereas a considerable enhancement in the diastereomeric ratio of **15a:15b** (5:1) was observed with the use of $(DHQD)_2$–PHAL ligand (Table 1). The poor diastereoselectivity observed in the former case may be because of opposite influences of the chiral reagent and substrate (mismatched case) while the latter could be regarded as matched case where the chirality information of the reagent and the substrate probably act synergistically and therefore, a high degree of diastereoselection was obtained. Mixture **17** was then converted into L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **1** as its tetraacetate derivative **21** as shown in Scheme 2.



Scheme 2. Reagents and conditions: (i) Pivaloyl chloride, pyr, CH_2Cl_2, 0°C to rt, overnight; (ii) (a) $MeSO_2Cl$, pyr, DMAP(cat.), CH_2Cl_2, 60°C, overnight. (b) LiN_3, DMF, 80°C, 12 h; (iii) $LiAlH_4$, Et_2O, 0°C to rt, overnight; (iv) (a) 6 N HCl, MeOH, rt, overnight. (b) Ac_2O, pyr, DMAP(cat.), CH_2Cl_2, rt, 12 h

Protection of the primary hydroxyl group of **17** was carried out using pivaloyl chloride and pyridine at 0°C to give **18**. The C-2 hydroxy was then converted into the azido functionality through mesylation followed by the nucleophilic displacement with LiN_3 to give **19** with inversion of configuration at C-2. The protection of the primary hydroxyl group as a pivaloate was advantageous over other protecting groups since both pivaloate deprotection and azide reduction could be accomplished together under the same conditions. Thus the lithium aluminum hydride reduction of **19** gave the amino alcohol **20** in excellent yield. Deprotection of the

acetonide was effected with 6N HCl in MeOH to give the hydrochloride salt of (2*R*,3*S*,4*S*)-2-amino-1,3,4-trihydroxyoctadecane. This was subsequently acetylated using Ac_2O, pyridine and catalytic amount of DMAP to give the tetraacetate **21** of L-*xylo*-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **1** (66% de) in 30% overall yield.

Similarly compound **16** was converted into the tetraacetate of D-*lyxo*-(2*S*,3*S*,4*S*)-C_{18}-phytosphingosine **4** (33% de) in 26% overall yield.

In conclusion, the first diastereoselective synthesis of the L-*xylo* isomer of phytosphingosine has been achieved through double stereodifferentiation using the Sharpless asymmetric dihydroxylation. The synthetic strategy described here has significant potential for further extension to the syntheses of other *lyxo*- and *xylo*- isomers simply by changing the ligand and also to the *arabino*- and *ribo*- isomers by employing the *cis* olefin for step 2 (Scheme 1). Currently, studies are in progress in this direction.

Acknowledgements

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