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A concise route to phytosphingosine from lyxose

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Abstract—Phytosphingosine was synthesized from the commercially available D-2,3-*O*-isopropylidene-D-lyxofuranose in 28% overall yield by a six-step procedure. This procedure is expedient and flexible for introduction of other lipid moieties on the phytosphingosine structure to make a variety of derivatives that can support the further exploration of their related biological functions. © 2003 Published by Elsevier Science Ltd.

The biomembrane components sphingophospholipids and glycosphingolipids are of physiologically importance in cell proliferation, differentiation, adhesion, neuronal repair, and signal transduction.[1–3] A sphingolipid consists of an hydrophilic head (e.g. saccharide or phosphate) and a lipophilic tail (e.g. ceramide). α-Galactosyl ceramide (α-GalCer), a glycolipid originally extracted from marine sponge *Agelas mauritinu*,[4] has been recently shown to recognize and bind with CD1d molecules on an antigen-presenting cell surface.[5] Such an interaction presents the sugar moiety of the antigen to a receptor on natural killer T-cells (NKT cells) to activate the immune system.[6] The structure of α-GalCer incorporates a phytosphingosine (**1**) type ceramide and galactose with α glycosidic linkage.

Many methods for the synthesis of phytosphingosine have been developed by using amino acids,[7] carbohydrates[8] and other chiral building blocks[9] as the precursors. However, most of the methods require multistep reactions (more than 10 steps) that resulted in low total yields (less than 10%). As a continuing effort in seeking new glycolipids of immune stimulators, we thus explored a concise and efficient method for the synthesis of phytosphingosine. The starting material D-lyxose is an inexpensive sugar[10] that possesses all the required chiral centers found in phytosphingosine. The retrosynthetic plan of phytosphingosine is depicted in Figure 1. Given these advantages, the amino group can be introduced by an S_N2 replacement at the C4 position of lyxose, and the lipid chain can be introduced by Wittig olefination at the C1 position.

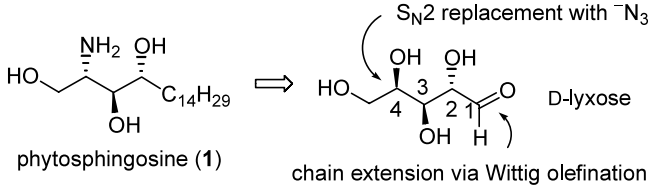

Figure 1. Retrosynthesis of phytosphingosine from D-lyxose.

The synthetic procedures, reagents and conditions are outlined in Scheme 1. Selective protection of 2,3 dihydroxyl groups of lyxose[11] using 2,2-dimethoxypropane was followed by treatment with trityl chloride to give compound **2** (71% yield). The subsequent condensation with a Wittig reagent $C_{13}H_{27}PPh_3Br$ (**3**) in the presence of lithium hexamethyldisilazide (LHMDS) afforded alkene **4** (93% yield).[12] The *E*/*Z* ratio of **4** was determined to be 2:1 by ^1H NMR analysis. The double bond of **4** was reduced by catalytic hydrogenation to give **5** (91% yield).[13] Compound **5** was sequentially treated with trifluoromethanesulfonic anhydride (Tf_2O) and tetramethylguanidinium azide (TMGA)[14] to produce the azido compound **6** (73% yield)[15] with inversion of the reacting carbon center. The acetal and trityl protecting groups in **6** were removed by an acid-catalyzed hydrolysis, and the azide group was reduced by Staudinger reaction[16] using Ph_3P/H_2O to give the desired product **1** as white solid. Thus, D-*ribo*-C_{18}-phytosphingosine **1**[17] was synthesized from D-2,3-*O*-isopropylidene-D-lyxofuranose in 28% overall yield by this six-step procedure. This method was further simplified by using Tf_2O/TMGA to convert alcohol **4** into azido compound **7** (84% yield).[18] After meticulous studies, we found a way

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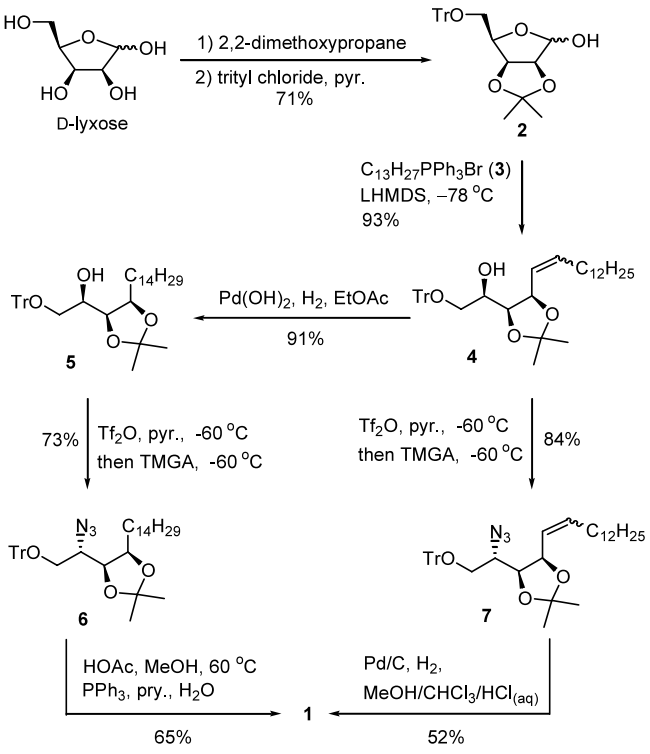

Scheme 1. Synthesis of phytosphingosine from D-lyxose.

to remove the acetal and trityl groups and simultaneously reduce the azide and double bond of **7** in a one-pot procedure. Thus, a solution of **7** in $CHCl_3$/$MeOH/HCl_{(aq)}$ (2/2/1) was treated with a catalytic amount of $Pd(OH)_2$ under an atmosphere of hydrogen for 15 h at room temperature to give phytosphingosine **1** in 52% yield.

In conclusion, we have devised a very efficient method for the synthesis of phytosphingosine by using the inexpensive starting material D-lyxose (2,3-*O*-isopropylidene-D-lyxofuranose is also the relatively inexpensive starting material). This method only requires six steps (from 2,3-*O*-isopropylidene-D-lyxofuranose) to give phytosphingosine in 28% overall yield. To our knowledge, this method is so far the shortest and relatively high-yielding route for a potential large-scale synthesis of phytosphingosine. By using different Wittig reagents, our method can also be modified to prepare a variety of sphingosine analogs.

Acknowledgements

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13. Selective data for compound **5**: $[\alpha]_D^{26}=-3.7$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J=6.0$ Hz, 3H), 1.26 (br, 24H), 1.35 (s, 3H), 1.35–1.50 (m, 1H overlapped with s at 1.45 ppm, 3H), 1.55–1.72 (m, 1H), 2.33 (d, $J=6.0$ Hz, 1H), 3.13–3.25 (m, 2H), 3.65–3.76 (m, 1H), 4.00–4.16 (m, 2H), 7.15–7.35 (m 9H), 7.35–7.50 (m, 6H).
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