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Stereoselective Synthesis of D(+)-erythro and L(-)-threo Sphingosines from Carbohydrates

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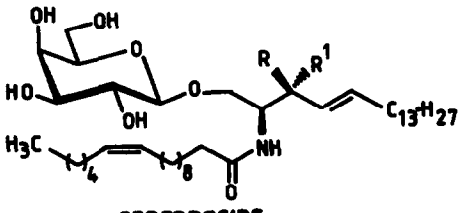
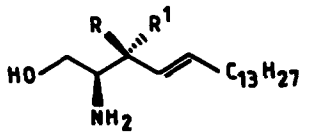
Keywords: D(+)-erythro and L(-)-threo sphingosines; base induced double elimination reaction; acetylenic alcohol

Abstract: Stereocontrolled syntheses of D(+)-erythro and L(-)-threo sphingosines are described starting from D-xylose and D-arabinose respectively through acetylenic intermediates **3** and **4**, obtained by base induced double elimination of the β-alkoxy chlorides **5** & **13**.

Glycosphingolipids belong to a broad class of biologically active compounds, a sub-class of which consists of the cerebrosides.[2] Cerebrosides, known to play an important role in the brain, have been shown to possess the structure I which has a long chain fatty acid attached to a sphingosine [(D)erythro in most cases] through an amide linkage which in turn is coupled to a hexose sugar, predominantly galactose[3]. Apart from being the backbone component of these cerebrosides, reports have also established[4] sphingosines to be the potent inhibitors of protein kinase C (PKC) in vitro and in vivo. Keeping in view the biological importance of sphingosines, it was envisaged to plan a stereoselective synthesis[5] for each of these diastereomers from the easily available carbohydrate precursors. We describe herein the stereo-selective synthesis of **1** and **2** from D-xylose and D-arabinose respectively using our recently developed acetylenic technology.[1]



CEREBROSIDE
I



1 R = H, R^1 = OH (D)-Erythro
2 R = OH, R^1 = H (L)-Threo

A retrosynthetic analysis (scheme 1) indicated that the formation of **1** and **2** could be visualised from **3** and **4** respectively by means of an acetylenic alkylation with the alkyl bromide as well as converting the hydroxyl to the amine function. **3** and **4** could be realized[1] using base induced double elimination of the β-alkoxy chlorides (**5** and **13**) as a key reaction, which in turn are easily accessible from the respective sugars.

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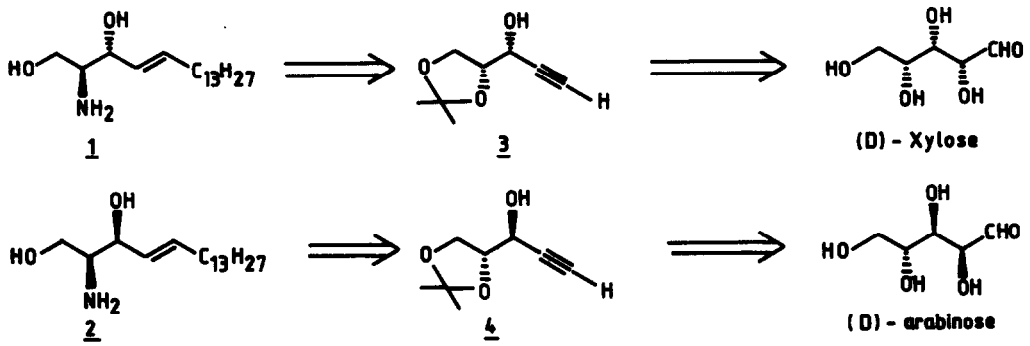
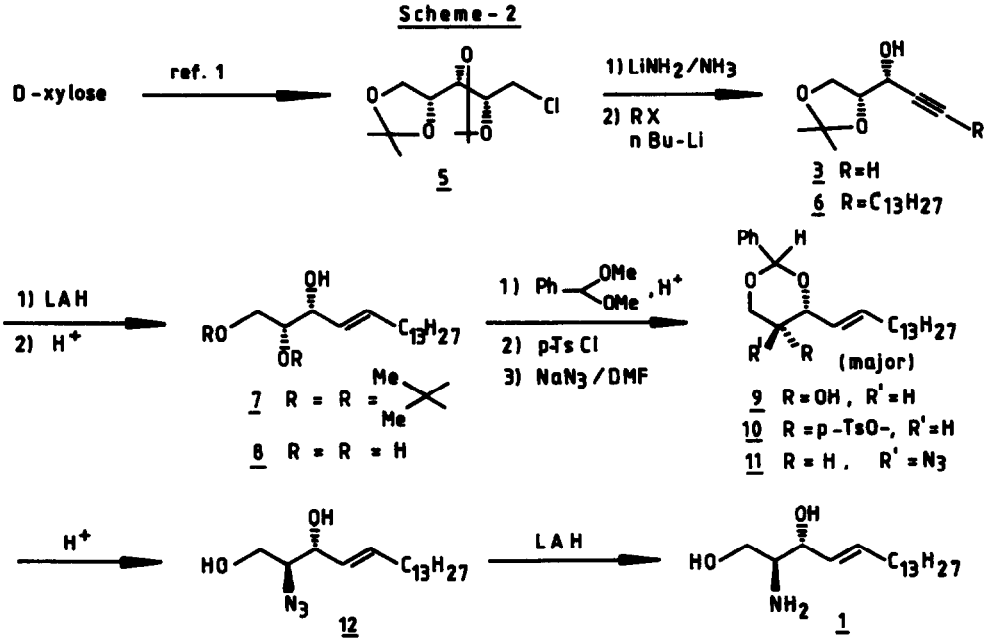
The C-2 and the C-3 centres of the sphingosines 1 and 2 can be correlated with the C-4 and C-3 centres of the respective sugars where the introduction of the amino group at C-4 of sugar in SN_2 fashion through tosylate incorporates the correct stereochemistry.

Scheme - 1



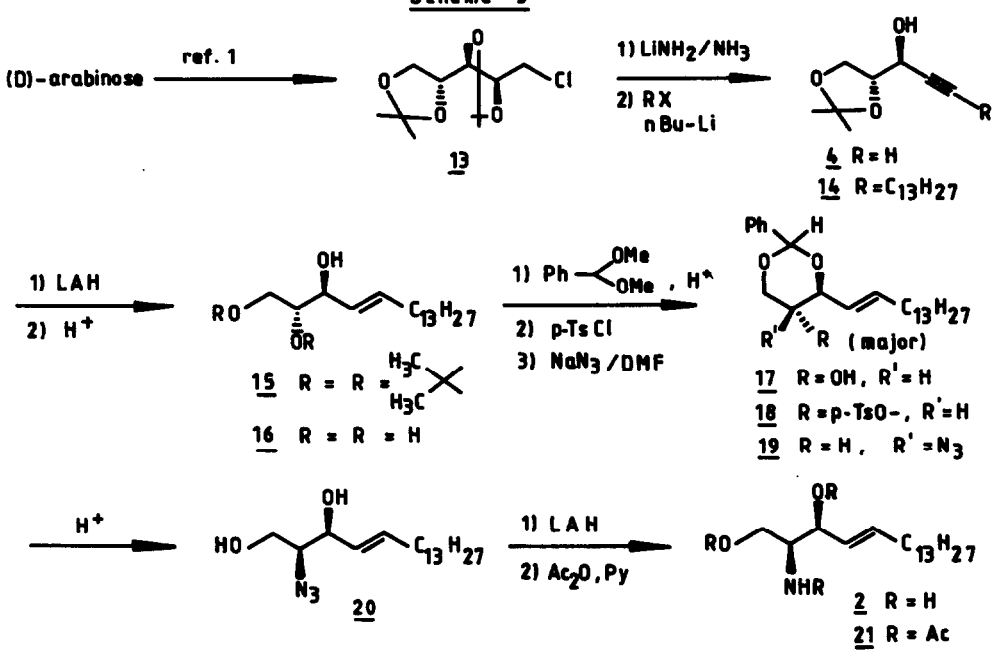
As per our synthetic plan (scheme 2), the chloro compound 5[6] was subjected to the key base induced double elimination reaction to give the acetylenic alcohol 3[7] (98%) which in turn was alkylated with 1-bromotridecane to obtain 6 (80%) $[\alpha]_D$ +11.0 (C 1.75, $CHCl_3$). Reduction of 6 with $LiAlH_4$ in THF gave the trans allylic alcohol 7[4,8] $[\alpha]_D$ +1.2 (C 1.25, $CHCl_3$) in high purity, which on treatment with

Scheme - 2



catalytic amount of p-TsA afforded the triol **8**. The benzylidene protection of **8** was effected in CH_2Cl_2 with benzaldehyde dimethyl acetal using catalytic amount of p-TsA to afford a mixture of 1,3[8]- and 1,2-benzylidene in 9:1 ratio. The desired major 1,3-benzylidene **9** was separated by silica gel column chromatography. Tosylation of **9** using p-TsCl in CH_2Cl_2 gave **10** which on treatment with NaN_3 in DMF gave the azide **11**[8] (80%) $[\alpha]_D$ -33.4 (C 0.7, $CHCl_3$). Removal of the benzylidene group in **11** with 3N HCl in THF afforded the azido diol **12**, which in turn was reduced with $LiAlH_4$ to realize D(+)-erythro sphingosine (m.p. 78.4°-80.8°C; $[\alpha]_D$ -2.72 (C 1.1, $CHCl_3$); lit[5h] m.p. 81-82°C, $[\alpha]_D$ -2.8° (C 1.0, $CHCl_3$).

Scheme -3



Similarly, L(-)-threo sphingosine **2** was prepared starting from D-arabinose using the same synthetic sequence in comparable yields. **2** was characterised as its triacetate derivative **21** (Ac_2O in pyridine), whose data was comparable with known compound (m.p. 41°C; lit[5h] m.p. 41-42°C; $[\alpha]_D$ +8.25 (C 0.8, $CHCl_3$), lit[5h] $[\alpha]_D$ +8.5 (C 1.0, $CHCl_3$).

In conclusion, here we have demonstrated a highly stereocontrolled synthesis of the D(+)-erythro and L(-)-threo sphingosines from the sugar precursors by a simple and operationally feasible acetylenic technology developed by us[1] which could be extended to the synthesis of other naturally occuring biologically active compounds.

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8. a) All new compounds gave expected spectral data; b) $[\alpha]_D$ in $CHCl_3$ and 200 MHz ^1H NMR (CCl_4-$CDCl_3$,1:1) of some selected compounds, **7**:δ5.81(dt,J=16,6.6 Hz,1H), 5.40(dd,J=16,7Hz,1H), 4.1-3.6(m,3H), 3.76-3.69(m,1H), 2.38(bs,1H,OH), **9** $[\alpha]_D$ +0.54(c 1.1):δ7.58-7.32(m,5H), 5.90-5.79(dt,J=15.5,6.4Hz,1H), 5.72-5.60 (m,1H), 5.7(1H,benzylidene H), 4.43(d,1H), 4.25(dd,J=12,2.5Hz,1H), 4.08(dd, J=1.2Hz,1H), 3.54(brs,1H), **11**:δ7.6-7.2(m,5H), 5.9(dt,J=12,6.4Hz,1H), 5.58(dd, J=6.5Hz,1H), 5.5(s,1H,benzylidene H), 4.35(dd,J_{gem}=9.5Hz,J=4.6Hz,1H), 4.23(dd, J=1.8Hz,1H), 4.06(dd,J=4.5Hz,1H), 3.49(ddd,1H), **15**:δ5.79(dd,J=15.8,7.48Hz,1H), 5.48(dd,J=15.8,6.03Hz,1H), 4.26(t,J=5.45Hz,1H), 4.11-4.02(m,1H), 4.01-3.86(m, 2H), **17** $[\alpha]_D$ -9.99(c 0.3):δ7.59-7.3(m,5H), 5.94(dt,J=15.5,7.4Hz,1H), 5.49-5.3 (dd,merged,1H), 5.52(s,1H,benzylidene H), 4.4-4.31(m,1H), 3.95(t,J=7.3Hz,1H), 3.7-3.56(m,2H), 2.25(brs,1H,OH).

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