A Concise Enantioselective Synthesis of *N*-Morpholinosphingosines from D-Aspartic Acid

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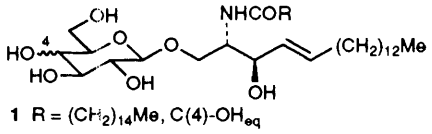
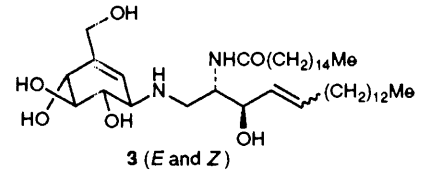
D-Aspartic acid, by *N*-tosylation, anhydride formation, reduction, α-hydroxylation and iodo-esterification, gives ethyl (2*R*,3*R*)-3-[(*N*-tosyl)amino]-2-hydroxy-4-iodobutyrate which, by treatment with morpholine, silylation, DIBAH reduction, Wittig reaction and deprotection, gives the *N*-morpholinosphingosine **13** in an overall yield of 27%.

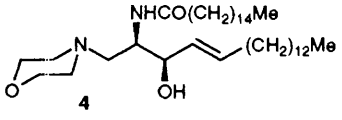
Glycosphingolipids, exemplified by glucosylceramide (GlcCer, **1**) and cerebroside (**2**), are constituents of cell walls and membranes where they play diverse roles in processes such as cell growth, cell differentiation and the immune response.[1] Glycosphingolipids (GSL) are biosynthesized by the coupling of UDP-glucose (UDP = uridine diphosphate) and an *N*-acylsphingosine when catalysed by GlcCer-synthase; or Cer:UDP-glc glucosyltransferase.[2] Inhibitors of this latter enzyme have valuable potential as anti-tumour agents since cancer cells produce high concentrations of GSL.[3] Consequently, the synthesis of stable structural analogues of **1** as transition state mimics has attracted intense attention.[4] Two recent reports[5,6] have described the *E* and *Z* carbocyclic amino analogues **3** and the *N*-morpholinodeoxyceramide **4**. These compounds powerfully inhibit GlcCer-synthase and glucocerebrosidase. Significantly, the more effective of the pair was the unnatural *Z*-isomer of **3**. Equally significant was the fact that **4**, the unnatural isomer having the 2*R*,3*R* configuration, was the most potent of the four possible stereoisomers. From these findings, we conclude that there is a need for a versatile, preferably short, method for preparing variously substituted sphingosines of both the *erythro* and *threo* configurations. We now report that 3-(*N*-tosyl)amino-4-butanolide **6**, thanks to its regio- and diastereoselective potential, provides the basis for such a method.[7]



1 R = $(CH_2)_{14}Me$, C(4)-OH_{eq}
2 R = $(CH_2)_7CH{=}CH(CH_2)_7Me$ (*cis*), C(4)-OH_{ax}



3 (*E* and *Z*)



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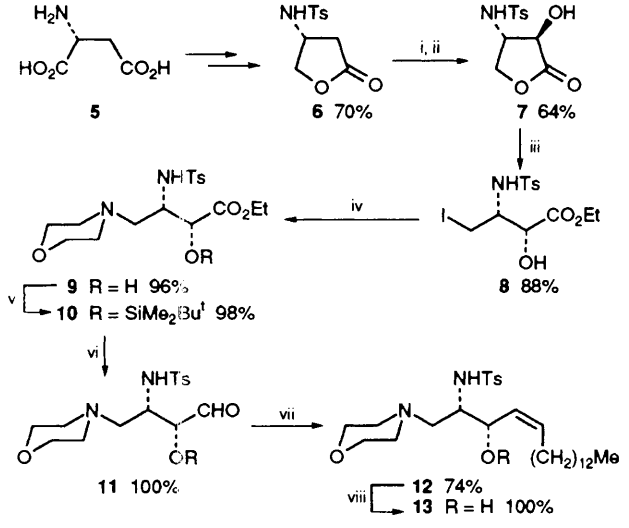

5 **6** 70% **7** 64% **8** 88% **9** R = H 96% **10** R = $SiMe_2{}^tBu$ 98% **11** 100% **12** 74% **13** R = H 100%

Scheme 1 *Reagents and conditions*: i, NaHMDS, THF; ii, 2-phenylsulfonyl-3-phenyloxaziridine, −78 °C, 2 h; iii, Me_3SiI, EtOH, CH_2Cl_2, 22 °C, 5.5 h; iv, morpholine, CH_2Cl_2, 22 °C; v, TBDMSOTf, 2,6-lutidine, CH_2Cl_2; vi, DIBAH, PhMe, −78 °C, 3 h; vii, $C_{14}H_{29}P^+Ph_3Br^-$, NaHMDS, THF, −78 to 20 °C; viii, Bu_4NF, THF, 22 °C, 2 h

By way of illustration we describe the synthesis of the unnatural *N*-morpholinosphingosine **13** (Scheme 1). The required chirality was installed at the outset by converting D-aspartic acid **5**, by *N*-tosylation, anhydride formation and regioselective reduction, to the crucial building block (3*R*)-3-[(*N*-tosyl)amino]-4-butanolide **6**.† Next, treatment of **6** with sodium hexamethyldisilazide (NaHMDS) and racemic *trans*-2-phenylsulfonyl-3-phenyloxaziridine[8,9] afforded solely the *trans*-α-hydroxylactone **7**. Opening to the desired key intermediate **8**‡ was effected by the reaction of **7** with trimethylsilyl iodide (TMSI) in methylene chloride containing a little ethanol.[10] Nucleophilic substitution by morpholine proceeded smoothly to give **9**. Protection of the hydroxy group as its *tert*-butyldimethylsilyl derivative **10** was efficient (98% yield) and permitted quantitative reduction with diisobutylaluminium hydride (DIBAH) to the aldehyde **11**. Olefination of the latter with the Wittig reagent,[11] generated from tetradecyltriphenylphosphonium bromide and NaHMDS in THF, gave exclusively the *Z*-olefin **12**.§ Deprotection with tetrabutylammonium fluoride in THF was quantitative and afforded the alcohol **13**. The *E*-isomer, admixed with **12** (ratio 1:4), was obtained by conducting the Wittig reaction under thermodynamic conditions, namely by using lithium diisopropylamide (LDA) in THF at 87 °C in the presence of lithium bromide.

In conclusion, the present method makes a complete range of GlcCer-synthase inhibitors available from inexpensive chiral aspartic acid in a few simple operations.

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Footnotes

† The configurational purity of **6** was confirmed by comparing its ^1H NMR spectrum with that of its 3*S* enantiomer taken at 200 MHz in the presence of chiral shift reagent [Eu(hfc)$_3$] in $CDCl_3$ as solvent. The $[\alpha]_D^{20}$ value of **6** was determined as +15.5 (*c* 1.0, EtOH).

‡ *Selected data* for **8**: mp 89–91°; $[\alpha]_D^{25}$ −43.3 (*c* 0.55, AcOEt); ^1H NMR (400 MHz, $CDCl_3$; all *J* in Hz): δ 7.66 Cd, *J* 8, 2H), 7.25 (d, *J* 8, 2H), 5.14 (d, *J* 12, 1H), 4.57 (s, 1H), 4.06 (qd, *J* 4, 1H), 3.84 (m, 1H), 3.74 (qd, *J* 8, 1H), 3.23 (m, 1H), 3.19 (m, 2H), 2.36 (s, 3H), 1.11 (t, *J* 8, 3H).

§ *Selected spectroscopic data* for **12**: ^1H NMR (200 MHz, $CDCl_3$; all *J* in Hz): δ 7.74 (d, *J* 8.1, 2H), 7.28 (d, *J* 8.1, 2H), 5.19 (dt, *J* 11.0, 7.3, 1H), 5.07 (dd, *J* 11.0, 8.5, 1H), 4.90 (brs, 1H), 4.88 (dd, *J* 8.5, 1.3, 1H),

3.55 (t, *J* 4.4, 4H), 3.16 (m, 1H), 2.50 (dd, *J* 12.3, 8.2, 1H), 2.43 (s, 3H), 2.35 (m, 2H), 2.25 (dd, *J* 12.3, 6.8, 1H), 2.19 (m, 2H), 2.01, (m, 2H), 1.3–1.2 (m, 22H), 0.88 (t, *J* 7.0, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). The *E*-isomer corresponding to **12** displayed similar chemical shifts except for the olefinic protons which appeared at δ 5.62 (dtd, *J* 15.2, 6.6, 1.4, 1H), 5.53 (dtd, *J* 15.2, 6.7, 1.0, 1H).

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