Synthesis of a new potent α-fucosidase inhibitor

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Enantiomerically pure (3*S*,4*R*,5*R*)-3,4-dihydroxy-5-methylpiperidine was prepared from L-arabinose and found to be a potent human placenta α-fucosidase inhibitor.

Recently we discovered that the 1-azamonosaccharide isofagomine **1**, a D-glucose derivative with a nitrogen in place of the anomeric carbon, is a potent inhibitor of glucosidases.[1] Perhaps even more significant, **1** is also an important building block that can be elaborated at the nitrogen to create more selective inhibitors such as **2**, which has a K_i of 6.3×10^{-8} M on glucoamylase.[2] Other 1-azamonosaccharides have also been found to be potent glycosidase inhibitors.[3,4] From this information we conceived the idea that the L-fucose analogue of **1**, compound **3**, might inhibit α-fucosidase. L-Fucose **4** is a very common and important sugar in glycoproteins and glycans, and the ability to inhibit α-fucosidase and create highly selective α-fucosidase inhibitors could be very valuable in the treatment of a number of diseases, *e.g.* AIDS[5] and cancer,[6] where affecting glycoprotein processing is crucial. Here we report the enantiospecific synthesis of the new compound (3*S*,4*R*,5*R*)-3,4-dihydroxy-5-methylpiperidine **3**, a potent and selective α-fucosidase inhibitor.

The enantioselective synthesis of **3** was not straightforward, as the compound is carbohydrate-like but contains a branched carbon-chain that had to be synthesised in a stereoselective fashion. Obviously no elements of the synthesis of **1** could be used as the stereochemistry of the two compounds were entirely different.

Our synthetic plan relied on the information that the β-face of benzyl 3,4-*O*-isopropylidene-β-L-*erythro*-pent-2-ulopyranoside **5** was the less hindered side, shown by the fact that methyllithium adds selectively from the β-side[7] (Fig. 1). We could therefore expect that the known alkene **6**[8] would be stereoselectively hydrogenated from the β-side giving the required α-methyl group.

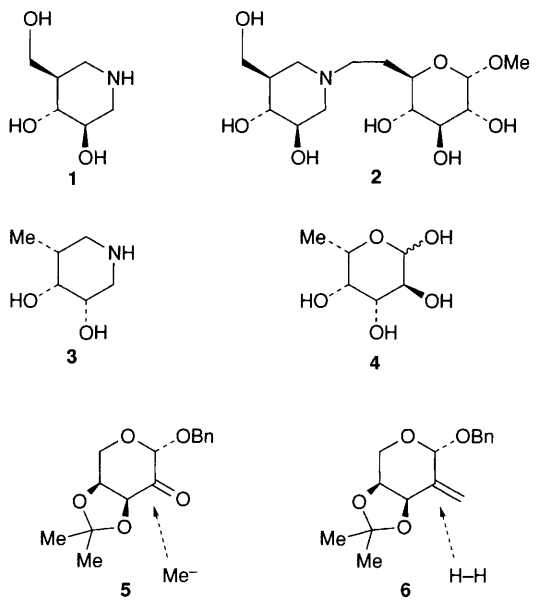
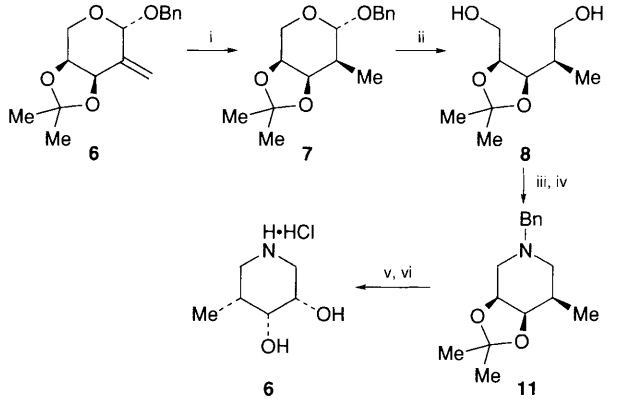


Fig. 1

Alkene **6** was prepared in 4 steps from L-arabinose, essentially as described previously.[7–8] Hydrogenation of **6** in EtOAc with 1 atm of H_2 over 5% palladium on carbon as catalyst, with NH_3 present (20 °C, 18 h, [**7**] = 33 mM, [NH_3] = 0.13 M, Pd–C 3.6 mg ml^{-1}) to avoid debenzylation, gave the hoped-for stereoselective formation of **7** in 95–97% yield‡ (Scheme 1). The stereochemistry at C-2 was confirmed from the ^1H NMR spectrum, where a large coupling of 7.5 Hz between H-1 and H-2 was observed, showing that these protons were diaxial. Subsequent reduction of **7** using 8 equiv. of sodium in $MeOCH_2CH_2OMe$–liquid ammonia (1 : 6) gave directly diol **8** in 51% yield (−78 °C, 3 h, [**7**] = 0.05 M). When less sodium or no co-solvent was used, mixtures of **8** and the intermediate of the reaction, the hemiacetal **9**, were obtained.§ Ditosylation of **8** using 2.5 equiv. of toluene-*p*-sulfonyl chloride (TsCl) in pyridine (5 °C, 21 h, [**8**] = 0.24 M, [TsCl] = 1.2 M) gave **10** in 62% yield. Reaction of **10** with excess neat benzylamine at 40 °C for 2 days ([**10**] = 0.1 M), as described for other carbohydrate ditosylates,[9] gave piperidine **11** in 76% yield. Reaction of **11** with aqueous TFA ([**11**] = 0.05 M) for 1.5 h at 25 °C removed the acetonide. Finally, hydrogenation of the product in 1 M HCl solution under 1 atm of H_2 with 10% Pd–C as catalyst (20 °C, [S] = 0.03 M, Pd–C 10 mg ml^{-1}) for 3 days gave **3** in 69% yield.¶

Piperidine **3** was tested for inhibition of α-fucosidase from human placenta catalysing the hydrolysis of 4-nitrophenyl α-L-fucopyranoside at 26 °C.‖ At pH 7.5, **3** showed competitive inhibition of the enzyme with a dissociation constant K_i of 6.4 μM. Inhibition of **3** was selective, as α-glucosidase from baker's yeast and β-galactosidase from *E. Coli* were unaffected by the compound in concentrations below 1 mM, while the K_i *versus* β-glucosidase from almonds was 121 μM.

In conclusion, we have synthesised a new, potent and selective human α-fucosidase inhibitor. It will be interesting to investigate the anti-viral and anti-tumor activity of **3**. Future work will also explore the fascinating possibilities of modifying



Scheme 1 *Reagents and conditions*: i, H_2 (1 atm), Pd–C, NH_3, 95–97%; ii, Na (8 equiv.) NH_3, 81%; iii, TsCl (2.5 equiv.), pyridine, 62%; iv, $BnNH_2$, 76%; V, TFA–H_2O; vi, H_2, Pd–C, 1 M HCl, 69% from **11**

3 at the anomeric nitrogen to create selective inhibitors for some of the highly substrate-specific fucosidases.

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Footnotes

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‡ *Selected data* for **7**: $[\alpha]_D^{22}$ −104.6 (*c* 0.7, $CHCl_3$); *m/z* (EI) 278 (M^+). For **8**: $[\alpha]_D^{22}$ −60.9 (*c* 1.00, $CHCl_3$); *m/z* (CI) 208 (M + NH_4^+). For **9**: mp 55–57 °C; $[\alpha]_D^{22}$ 42.4 (*c* 4.2, $CHCl_3$); *m/z* (CI) 189 (M + H^+). For **10**: $[\alpha]_D^{22}$ −16.5 (*c* 1.14, $CHCl_3$); *m/z* (CI) 516 (M + NH_4^+). For **11**: $[\alpha]_D^{22}$ −25.3 (*c* 0.1, $CHCl_3$); *m/z* (EI) 261 (M^+).

§ These mixtures could be converted to pure **8** with $NaBH_4$ in EtOH.

¶ *Selected data* for **3**: $[\alpha]_D^{25}$ −6.3 (*c* 0.75, H_2O); *m/z* (EI) 131 (M^+); ^1H NMR (D_2O): δ 3.8–3.95 (m, 2 H, H-3 and H-4), 3.2 (dd, 1 H, *J* 3 and 11 Hz), 3.0 (dd, 1 H, *J* 4 and 12.5 Hz), 2.9 (t, 1 H, *J* 11 Hz), 2.7 (t, 1 H, *J* 12.5 Hz), 2.0 (m, 1 H, H-5), 0.9 (d, 3 H, *J* 6.5 Hz, Me); ^{13}C NMR (D_2O): δ 72.2 and 68.7 (C-3 and C-4), 45.8 and 44.4 (C-2 and C-6), 34.4 (C-5), 16.5 (C-5′).

‖ The assay was performed as follows: Samples were prepared by mixing 1 ml sodium phosphate buffer (pH 7.5), 0.2 to 0.8 ml of a 5 mM solution of 4-nitrophenyl α-L-fucopyranoside in water, 10 μl of a 9 mM solution of **6** (or nothing) and distilled water to a total volume of 1.9 ml. Reaction was started by adding 0.1 ml of a 0.04 unit ml^{-1} solution of α-fucosidase from human placenta (EC 3.2.1.51, Sigma F-6151) and was followed for 10 min at 26 °C by measuring absorbance at 400 nm. Initial velocities were calculated from the slopes and used to construct a Lineveawer–Burk plot from which K_ms and, subsequently, K_i were obtained.

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