Total Synthesis of (+)-α-Homonojirimycin

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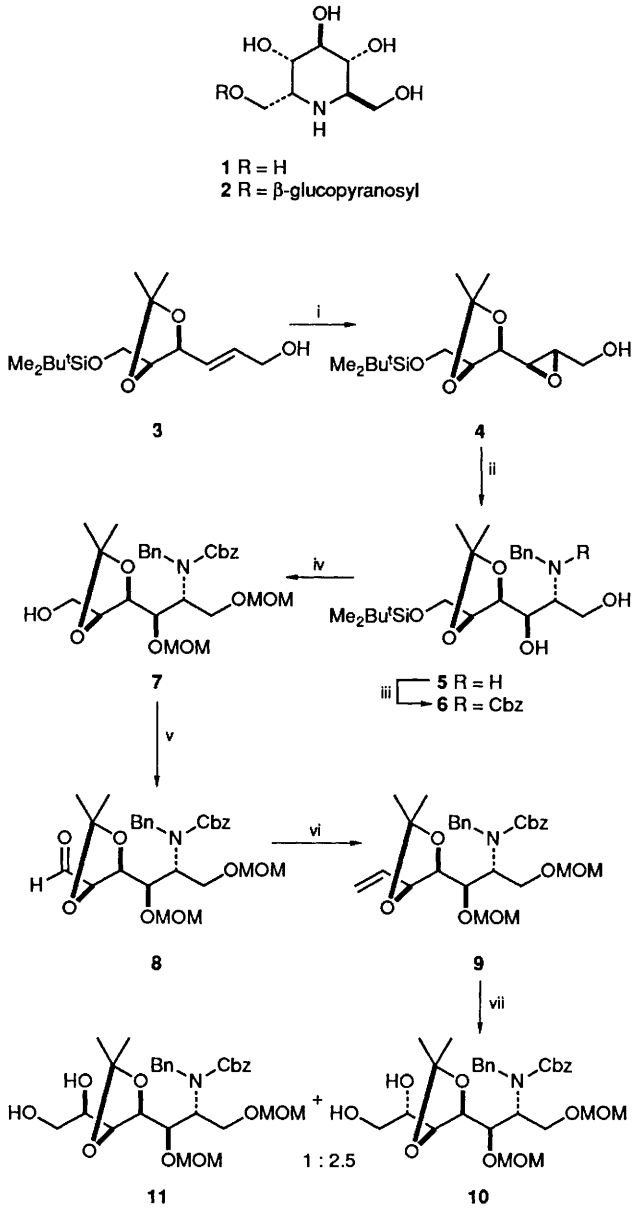
The total synthesis of (+)-α-homonojirimycin, the first example of a naturally occurring azaheptose, was achieved in 13 steps utilizing the allylic alcohol **3** as a non-carbohydrate chiral building block.

α-Homonojirimycin **1**, recently isolated from leaves of *Omphalea diandra*,[1] is the first example of a naturally occurring azapyranose analogue of a heptose.[2] It is a powerful α-glucosidase inhibitor and is expected to be a drug candidate for antidiabetic therapy. Indeed, MDL 25637 **2**, a novel compound designed as a prototype transition-state analogue, has been shown to possess potent inhibitory activity towards α-glucosidases.[3,4] Thus, in the course of preparing **2**, **1** has been obtained by chemical transformation of the natural azahexose nojirimycin.[5] However, there has so far been no report of the total synthesis of **1**.

Recent investigation from this laboratory has revealed that the chiral allylic alcohol **3** serves as a versatile, common chiral building block in the preparation of several naturally occurring azahexoses.[6] In this communication we describe our efforts, which resulted in the enantioselective total synthesis



Scheme 1 *Reagents*: i, (+)-DET, $Ti(OPr^i)_4$, TBHP (ref. 5*a*); ii, $Et_2AlNHCH_2Ph$, CH_2Cl_2; iii, $PhCH_2OCOCl$, aq. Na_2CO_3, CH_2Cl_2; iv, CH_3OCH_2Cl, $(Pr^i)_2NEt$, $CHCl_3$, then $(Bu^n)_4NF$, THF; v,$(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; vi, Ph_3PCH_3Br, Bu^nLi, THF; vii, *N*-methylmorpholine oxide, OsO_4, aq. Me_2CO.

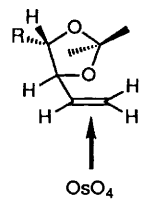
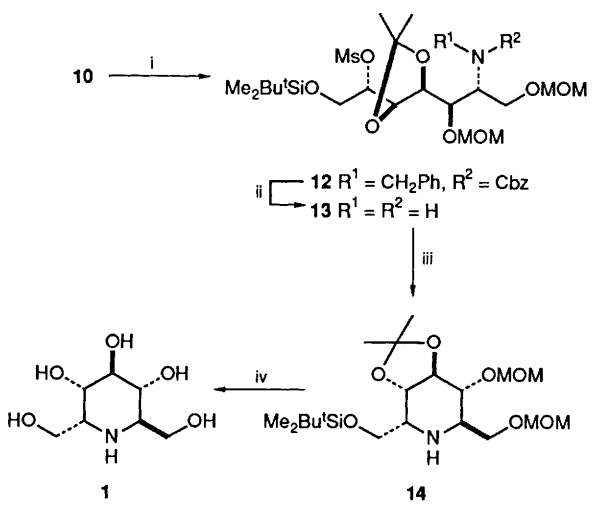


Fig. 1

of (+)-α-homonojirimycin **1** *via* a non-carbohydrate based approach utilizing **3**.

The allylic alcohol **3** was converted to the *syn* epoxide **4** by the Sharpless asymmetric epoxidation *via* the procedure previously reported.[6a] Regio- and stereo-selective ring opening of the epoxide was effected by using dialkylaluminium amide according to Overman's method.[7] Treatment of **4** with 1 equiv. of $Et_2AlNHCH_2Ph$ in CH_2Cl_2 at 0 °C resulted in the amino-alcohol **5**† as a single diastereoisomer in 70% yield (Scheme 1). The amino group of **5** was selectively protected with benzyl chloroformate (aq. Na_2CO_3, CH_2Cl_2) to afford the carbamate **6** (98% yield), which was then converted to **7** by methoxymethylation [2 equiv. of MOMCl and $(Pr^i)_2NEt$] followed by removal of the silyl group [$(Bu^n)_4NF$, THF] in 86% overall yield from **5**. Swern oxidation [$(COCl)_2$, Me_2SO, Et_3N] of **7** gave the aldehyde **8** (98% yield), which was transformed into the alkene **9** (84%) by the Wittig reaction (Ph_3PCH_3Br, Bu^nLi, THF). Hydroxylation of **9** using a catalytic quantity of osmium tetroxide with 2 equiv. of *N*-methylmorpholine oxide in aqueous acetone resulted in 2.5 : 1 diastereoselectivity in favour of the desired *anti*-product **10** (total yield of **10** and **11**: 90%). The observed *anti* preference for **10** can be rationalized by the transition-state conformation (Fig. 1) with the dioxolane alkyl group *anti* and the dioxolane oxygen inside. Addition of osmium to the alkene, thus, proceeds in accord with the inside alkoxy concept,[8] in which the electrophile adds *anti* to the alkyl group and inside to the alkoxy group in order to maximize σ_{C-C}/π overlap and minimize σ^*_{C-O}/π overlap.



Scheme 2 *Reagents*: i, Me_2Bu^tSiCl, imidazole, DMF, then MsCl, Et_3N, CH_2Cl_2; ii, H_2, $Pd(OH)_2$, MeOH; iii, Et_3N, MeOH, reflux; iv, conc. HCl, MeOH, reflux.

Compound **10** was converted to **12** *via* selective silylation of the primary alcohol function with t-butyldimethylsilyl chloride (imidazole, DMF), followed by mesylation under the standard conditions in 77% overall yield (Scheme 2). De-*N*-protection

† All new compounds gave spectral data (IR, ^1H and ^{13}C NMR, and mass spectra) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. *Selected data*: **5**: $[\alpha]_D^{26}$ +10.6° (*c* 0.8, $CHCl_3$). **6**: $[\alpha]_D^{27}$ −33.0° (*c* 0.8, $CHCl_3$). **7**: $[\alpha]_D^{29}$ −19.4° (*c* 0.1, $CHCl_3$). **8**: $[\alpha]_D^{26}$ −13.0° (*c* 0.7, $CHCl_3$). **9**: $[\alpha]_D^{27}$ −19.0° (*c* 1.1, $CHCl_3$). **10**: $[\alpha]_D^{26}$ −17.1° (*c* 0.3, $CHCl_3$). **11**: $[\alpha]_D^{22}$ −27.8° (*c* 0.9, $CHCl_3$). **12**: $[\alpha]_D^{26}$ −20.0° (*c* 0.3, $CHCl_3$). **14**: $[\alpha]_D^{25}$ +107.0° (*c* 0.6, $CHCl_3$). **1**: ^1H NMR (400 MHz, D_2O) δ(D_2O) 2.80 (1 H, ddd, *J* 9.5, 7.2, 2.9 Hz), 3.15 (1 H, dd, *J* 9.5, 9.4 Hz), 3.23 (1 H, dd, *J* 9.2, 6.2, 5.1 Hz), 3.44 (1 H, dd, *J* 9.5, 9.4 Hz), 3.52 (1 H, dd, *J* 11.4, 5.2 Hz), 3.69 (1 H, dd, *J* 9.5, 6.1 Hz), 3.74 (1 H, dd, *J* 10.5, 5.1 Hz), 3.77 (1 H, dd, *J* 10.5, 9.2 Hz), 3.85 (1 H, dd, *J* 11.4, 2.9 Hz); ^{13}C NMR (100.6 MHz, D_2O) δ (dioxane, δ 67.40) 54.89 (CH), 57.23 (CH_2), 57.69 (CH), 69.92 (CH_2), 72.43 (CH), 72.96 (CH), 75.19 (CH).

of **12** was carried out *via* hydrogenolysis over palladium hydroxide in methanol. At the conclusion of the reaction the catalyst was removed by filtration, and triethylamine was added to the filtrate containing **13**. The resulting mixture was refluxed to afford the cyclization product **14** in 81% yield from **12**. Finally, **14** was deprotected by treatment with HCl–MeOH at reflux. Application to an ion-exchange column (Dowex 1-X8) followed by lyophilization provided pure (+)-α-homonojirimycin **1** in 68% yield. Synthetic **1** had m.p. 205–207 °C (decomp.) and $[\alpha]_D^{27}$ +82.7° (*c* 0.8, H_2O) identical with those published for the natural product [m.p. 206–207 °C and $[\alpha]_D^{20}$ +88.2° (*c* 0.54, H_2O)][5] and showed spectra (^1H and ^{13}C NMR) identical with the corresponding authentic spectra of **1**.

The synthetic approach for the azaheptose presented here demonstrates synthetic versatility of the allylic alcohol **3** as a common chiral building block for the preparation of azapyranoses having inhibitory activity toward glycosidases.

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