

Total Synthesis of (+)- α -Homonojirimycin

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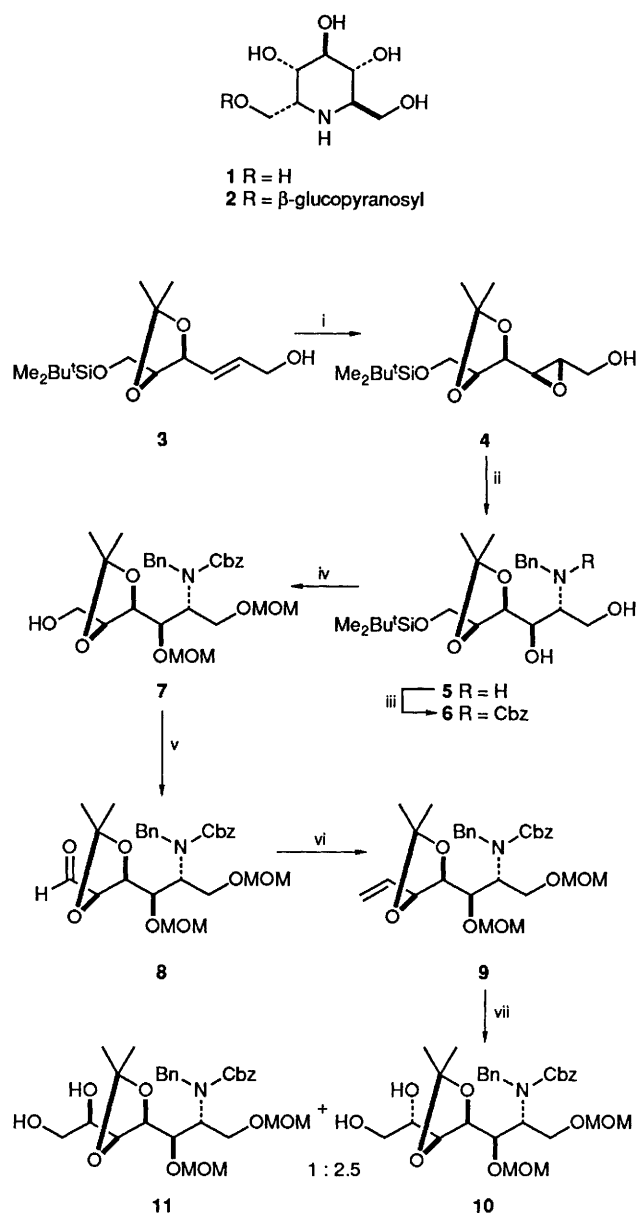
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The total synthesis of (+)- α -homonojirimycin, the first example of a naturally occurring azaheptose, was achieved in 13 steps utilizing the allylic alcohol **3** as a non-carbohydrate chiral building block.

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 25 637 **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, $\text{Ti}(\text{OPr})_4$, TBHP (ref. 5a); ii, $\text{Et}_2\text{AlNHCH}_2\text{Ph}$, CH_2Cl_2 ; iii, $\text{PhCH}_2\text{OCOC}_2\text{H}_5$, aq. Na_2CO_3 , CH_2Cl_2 ; iv, $\text{CH}_3\text{OCH}_2\text{Cl}$, $(\text{Pr})_2\text{NEt}$, CHCl_3 , then $(\text{Bu}^n)_4\text{NF}$, THF; v, $(\text{COCl})_2$, Me_2SO , Et_3N , CH_2Cl_2 ; vi, $\text{Ph}_3\text{PCH}_3\text{Br}$, Bu^nLi , THF; vii, *N*-methylmorpholine oxide, OsO_4 , aq. Me_2CO .

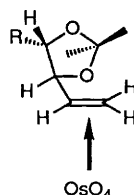
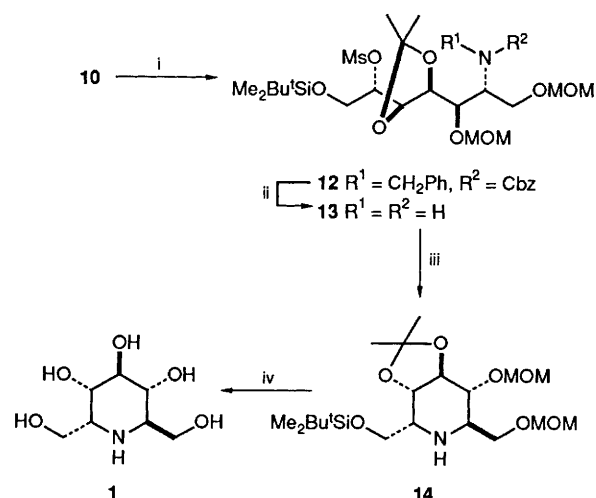


Fig. 1

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 open-



Scheme 2 Reagents: i, $\text{Me}_2\text{Bu}^t\text{SiCl}$, imidazole, DMF, then MsCl , Et_3N , CH_2Cl_2 ; ii, H_2 , $\text{Pd}(\text{OH})_2$, MeOH ; iii, Et_3N , MeOH , reflux; iv, conc. HCl , MeOH , reflux.

ing of the epoxide was effected by using dialkylaluminium amide according to Overman's method.⁷ Treatment of **4** with 1 equiv. of $\text{Et}_2\text{AlNHCH}_2\text{Ph}$ 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 $(\text{Pr})_2\text{NEt}$] followed by removal of the silyl group [$(\text{Bu}^n)_4\text{NF}$, THF] in 86% overall yield from **5**. Swern oxidation [$(\text{COCl})_2$, Me_2SO , Et_3N] of **7** gave the aldehyde **8** (98% yield), which was transformed into the alkene **9** (84%) by the Wittig reaction ($\text{Ph}_3\text{PCH}_3\text{Br}$, 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 $\sigma_{\text{C}-\text{C}}/\pi$ overlap and minimize $\sigma_{\text{C}-\text{O}}/\pi$ overlap.

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**: $[\alpha]_{\text{D}}^{26} +10.6^\circ$ (c 0.8, CHCl_3). **6**: $[\alpha]_{\text{D}}^{27} -33.0^\circ$ (c 0.8, CHCl_3). **7**: $[\alpha]_{\text{D}}^{29} -19.4^\circ$ (c 0.1, CHCl_3). **8**: $[\alpha]_{\text{D}}^{26} -13.0^\circ$ (c 0.7, CHCl_3). **9**: $[\alpha]_{\text{D}}^{27} -19.0^\circ$ (c 1.1, CHCl_3). **10**: $[\alpha]_{\text{D}}^{26} -17.1^\circ$ (c 0.3, CHCl_3). **11**: $[\alpha]_{\text{D}}^{22} -27.8^\circ$ (c 0.9, CHCl_3). **12**: $[\alpha]_{\text{D}}^{26} -20.0^\circ$ (c 0.3, CHCl_3). **14**: $[\alpha]_{\text{D}}^{25} +107.0^\circ$ (c 0.6, CHCl_3). **1**: ^1H NMR (400 MHz, D_2O) $\delta(\text{D}_2\text{O})$ 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 $[\alpha]_D^{27} +82.7^\circ$ (c 0.8, H₂O) identical with those published for the natural product [m.p. 206–207 °C and $[\alpha]_D^{20} +88.2^\circ$ (c 0.54, H₂O)]⁵ and showed spectra (¹H and ¹³C 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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