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Synthesis of 1,7-Diamino-1,2,6,7-tetradeoxy-2,6-imino-D-*glycero*-D-*ido*-heptitol by Intramolecular Amination of Aziridine Ring

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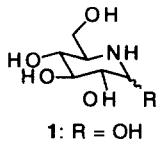
Abstract: A novel intramolecular 6-exo opening of a terminal Boc-protected aziridine ring by a strategically located amino group in the molecule enacted the crucial cyclisation to furnish the key intermediate **10** with requisite deoxyamino imino sugar framework leading to the stereoselective synthesis of 1,7-diamino-1,2,6,7-tetradeoxy-2,6-imino-D-*glycero*-D-*ido*-heptitol (**5**).

Azasugars and many of their unnatural congeners are gaining increasing importance in the emerging field of glycobiology specially as glycosidase and glycosyltransferase inhibitors.[1] Compounds like nojirimycin (**1**),[2] 1-deoxynojirimycin (**2**),[2] α-homonojirimycin (**3**),[3] and the corresponding 5-membered compound, 2,5-dideoxy-2,5-imino-D-mannitol (**4**),[4] are all powerful glycosidase inhibitors. As part of our studies directed toward the development of novel deoxyamino derivatives of "imino-C-glycosyl" sugars as glycosidase inhibitors we were interested to develop an efficient synthesis of 1,7-diamino-1,2,6,7-tetradeoxy-2,6-imino-D-*glycero*-D-*ido*-heptitol (**5**), the dideoxydiamino congener of α-homonojirimycin **3**, a new structural entity of its kind.



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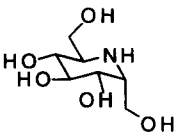
2: R = H



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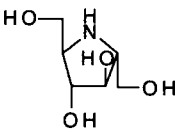

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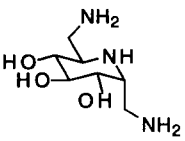


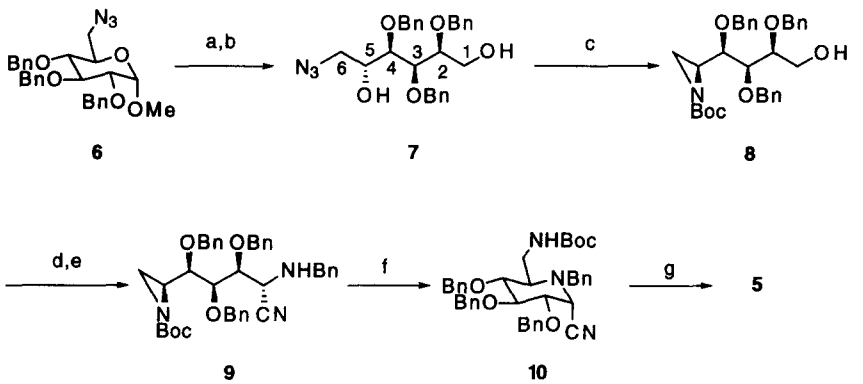
5

The title compound as well as its immediate precursor, the imino glycosyl cyanide **10**, can act as useful templates en route to various novel functional scaffolds like nojirimycin congeners and specially dipeptide isosteres which can be used to replace natural amino acids in peptides in the synthesis of imino sugar based carbopeptoids.[5]

Some recent syntheses of "imino-C-glycosyl" compounds involving reductive amination of unsaturated hexulose[6] and other ketose derivatives[7] followed by intramolecular amination of the double bond have led to mixture of diastereomers in both steps. Synthesis from bis-aziridine has also given mixture of 5- and 6-membered rings.[8]

Herein we report an efficient stereoselective synthesis of the title imino sugar by intramolecular 6-exo opening of a terminal aziridine ring with C_1 amino group of a suitably functionalised intermediate derived from methyl α-D-glucopyranoside. The salient features in this synthesis are: (i) novel intramolecular aziridine ring opening under very mild condition which is in contrary to earlier reports where Lewis acid catalysed aziridine ring opening has led to mixtures of products;[8] (ii) two S_N2-type stereoinversions at C_6 position, first during aziridine formation and later during its ring opening, which established the desired D-*glycero* configuration at C_6; (iii) complete diastereoselection in the Strecker synthesis of cyano amine leading exclusively to the D-*ido* configuration at C_2.

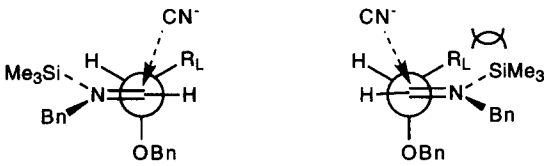
Our synthesis started with methyl 6-deoxy-6-azido-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **6** which was prepared from methyl α-D-glucopyranoside following reported procedures.[9] Acid hydrolysis of **6** with dil. HCl gave the intermediate lactol (82% yield) which was reduced with $NaBH_4$ to get the diol **7**[10] in 87% yield. When **7** was treated with Ph_3P in refluxing toluene under anhydrous conditions the terminal azido group displaced the adjacent hydroxyl leading to the formation of an aziridine ring which was protected in-situ with Boc_2O to get the intermediate **8**[10,11] in 85% yield. Presence of moisture in the reaction mixture gave reduced yield due to the formation of amino alcohol as side product. The aziridine formation followed S_N2 mechanism which executed the first inversion at C_5 position.



Scheme 1. a) dil. HCl, AcOH, 80-85° C; b) $NaBH_4$, MeOH, 0-25° C; c) Ph_3P, toluene, reflux, then Boc_2O, 25° C; d) DMP, pyridine, CH_2Cl_2, 25° C; e) $BnNH_2$, CH_2Cl_2, 0-25° C, then TMSCN, -78° C; f) DIPEA, EtOH, reflux; g) H_2, $Pd(OH)_2/C$, MeOH.

The next step was oxidation of the C_1 hydroxy to aldehyde. Most of the oxidizing agents led to the undesired opening of the aziridine ring. Finally the oxidation was successfully carried out with Dess-Martin periodinane (DMP)[12] (90% yield). Even SO_3-pyridine-Et_3N-DMSO system[13] was successful in this step. The resulting aldehyde was subjected to diastereoselective Strecker reaction. Reaction of the aldehyde with benzyl

amine gave the intermediate imine which on treatment with TMSCN gave the cyano amine **9**[10] as a single diastereomer in 92% yield. The stereochemistry of the newly generated centre was assigned *R* on the basis of nonchelate-controlled Felkin-Anh model[14] and earlier literature report.[15] Of the two possible transition state conformations **A** and **B**, where the nucleophilic attack takes place antiperiplanar to the α-benzyloxy group with the lowest σ* orbital energy occupying a position perpendicular to the carbonyl π-plane, conformer **A** is more favoured than **B** which has very significant steric interaction between the bulky substituent R_L and the imine nitrogen bonded to trimethylsilyl group. This led to selective *Re* face attack giving the *R*-cyanoamine.



A (Favoured) **B** (Disfavoured)

Having achieved the desired diastereoselectivity in the Strecker synthesis step, the stage was now set to try the crucial intramolecular amination of the aziridine ring. The purified cyano amine **9**[16] was taken in dry EtOH (0.005 M) and simple refluxing led to a facile intramolecular cyclisation with 6-exo opening of the aziridine ring by the C_1 amino group giving the desired imino sugar **10**.[16] The aziridine ring opening also followed S_N2 mechanism which brought about the anticipated second inversion at C_5 position (C_6 if cyanide carbon is numbered 1), necessary to get the desired D-*glycero* configuration of the cyclised product. Addition of a slight excess of base, *N,N*-diisopropylethyl amine (DIPEA), ensured a clean reaction and no other side product was formed. The mild reaction condition and the specificity observed in this step is noteworthy as it did not require any Lewis acid to catalyze aziridine ring opening.[8] This method will be useful in the synthesis of other structurally similar deoxyamino imino sugars.

The stereochemistry and conformation of the product **10** were confirmed by NMR and extensive decoupling studies. The C_6-H (cyanide carbon numbered 1) appeared at δ 2.76 as ddd with coupling constants of 9.4, 3.3 and 1.6 Hz. The two C_7 protons were at δ 3.82 (ddd, J = 14.5, 7.3 and 1.6 Hz) and 3.46 (ddd, J = 14.5, 3.3 and 3.3 Hz). The C_2-H came as a doublet (J = 5.2 Hz) at δ 3.68. The C_4 proton came as a triplet (J = 9.4 Hz) at δ 3.88. The C_5-H and C_3-H signals were multiplets centered around δ 3.42. The $^4C_1$ conformation of the sugar ring in **10** was evident from the above coupling constants of its ring protons. Finally, the glycosyl cyanide **10** was hydrogenated using $Pd(OH)_2$ on C (20%) in MeOH to get the target molecule **5**.[16]

In summary, a facile intramolecular aziridine ring opening paved the way to achieve stereoselective synthesis of a dideoxydiamino imino sugar **5**. Further studies on the syntheses of other imino sugars using this method, their uses as dipeptide isosteres, and biological evaluations are in progress.

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16. Cyanoamine **9**: R_f 0.5 (silica, 10% EtOAc in petroleum ether); $[\alpha]^{22}_D$: -55.1° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.15 (m, 20 H, aromatic), 4.98-4.53 (three ABq, 6 H, OCH_2Ph), 4.19 (dd, *J* = 8.5, 2.4 Hz, 1 H, C2-*H*), 3.92 and 3.35 (ABq, 2 H, NCH_2Ph), 3.84 (dd, *J* = 8.4, 2.4 Hz, 1 H, C3-*H*), 2.9 (d, *J* = 2.4 Hz, 1 H, C1-*H*), 2.72 (dd, *J* = 6.5, 2.4 Hz, 1 H, C4-*H*), 2.59 (ddd, *J* = 6.5, 6.5, 3.4 Hz, 1 H, C5-*H*), 1.9 (d, *J* = 6.4 Hz, 1 H, C6-*H*), 1.68 (d, *J* = 3.4 Hz, 1 H, C6-*H'*), 1.54 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.92, 138.17, 137.85, 137.59, 137.21, 128.98, 128.54, 128.37, 128.24, 128.11, 127.95, 127.85, 127.55, 118.8, 81.65, 80.36, 79.1, 76.68, 76.17, 75.26, 70.24, 51.29, 50.21, 38.76, 27.9, 26.39; IR (neat): ν_{max} 2925, 1720, 1450, 1310, 1175, 750, 700 cm^{-1}; MS (LSIMS): *m/e* 648 (M^+). HRMS (LSIMS): *m/e* 648.3461 ($C_{40}H_{45}N_3O_5$ requires 648.3437). Imino sugar **10**: R_f 0.5 (silica, 10% EtOAc in petroleum ether); $[\alpha]^{22}_D$: -17.8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.13 (m, 20 H, aromatic), 5.0-4.44 (three ABq and a m, 7 H, OCH_2Ph, N*H*Boc), 4.2 and 3.26 (ABq, 2 H, NCH_2Ph), 3.88 (t, *J* = 9.4 Hz, 1 H, C4-*H*), 3.82 (ddd, *J* = 14.5, 7.3, 1.6 Hz, 1 H, C7-*H*), 3.68 (d, *J* = 5.2 Hz, 1 H, C2-*H*), 3.46 (ddd, *J* = 14.5, 3.3, 3.3 Hz, 1 H, C7-*H'*), 3.45-3.4 (m, 2 H, C3-*H*, C5-*H*), 2.76 (ddd, *J* = 9.4, 3.3, 1.6 Hz, 1 H, C6-*H*), 1.42 (s, 9 H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.74, 138.42, 137.76, 137, 135.98, 128.99, 128.59, 128.52, 128.1, 127.97, 127.89, 127.76, 114.61, 83.81, 77.1, 76.92, 75.73, 75.64, 75.47, 73.09, 60.91, 54.26, 54.06, 28.38; IR (neat): ν_{max} 3425, 2900, 1720, 1500, 1450, 1370, 1175, 1100, 750, 700 cm^{-1}; MS (LSIMS): *m/e* 648 (M^+); HRMS (LSIMS): *m/e* 648.3438 ($C_{40}H_{45}N_3O_5$ requires 648.3437). Dideoxydiamino imino sugar **5**: $[\alpha]^{22}_D$: 18° (*c* 1, D_2O); ^1H NMR (D_2O, 400 MHz): δ 3.76 (d, *J* = 9.4 Hz, 1 H, C3-*H*), 3.7 (dt, *J* = 9.8, 6.5 Hz, 1 H, C6-*H*), 3.46 (t, *J* = 9.4 Hz, 1 H, C4-*H*), 3.34-2.74 (m, 5 H, C1-*H*, C2-*H*, C7-*H*), 3.19 (t, *J* = 9.6 Hz, 1 H, C5-*H*); MS (LSIMS): *m/e* 192 (M^++H, 96%), 185 (M^++Na-CH_2=NH, 100%), 175 (M^++H-NH_3, 42%).

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