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Synthesis of Aza-*C*-disaccharides - a New Class of Sugar Mimics

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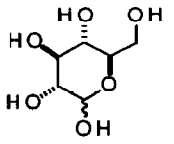
Abstract: Synthesis of a novel aza-*C*-disaccharide is described using a Suzuki coupling of the alkyl boron reagent **8** and vinyl bromide **7** as the key step.

Azasugars have attracted much interest due to their diverse structure and biological activity.[1] They have potential in the treatment of diabetes and other metabolic disorders,[2] cancer[3] and some viral diseases (notably human immunodeficiency virus (HIV)).[4]

The most widely recognized azasugars mirror the structure of the most common hexoses found in nature, *cf*, D-glucose (**1**) and 1-deoxynojirimycin (**2**), and are strong inhibitors of *exo*-glycosidases.[1, 5] The hepta-azasugar homologs that contain a hydroxymethyl substituent at the pseudo-anomeric carbon (*e.g.*, α-1-homo-nojirimycin (**3**)) display stronger selectivity for inhibition of α- *vs.* β-*exo*-glycosidases and *endo*-glycosidases.[2b,2c,6] Presumably the hydroxymethyl group mimics the second sugar unit of a disaccharide which results in a more efficient glycosidase inhibitor. A potent and selective glycosidase inhibitor and an antidiabetic drug candidate has been produced by carrying this anology one step further with the synthesis of MDL 25,637 (**4**) in which a second sugar is linked by a β-glycosidic bond.[2b,c] Such β-glycosides are generally more stable towards hydrolysis by pertinent mammalian enzymes.



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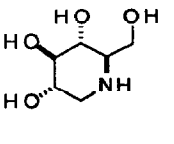

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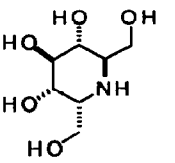

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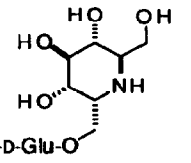


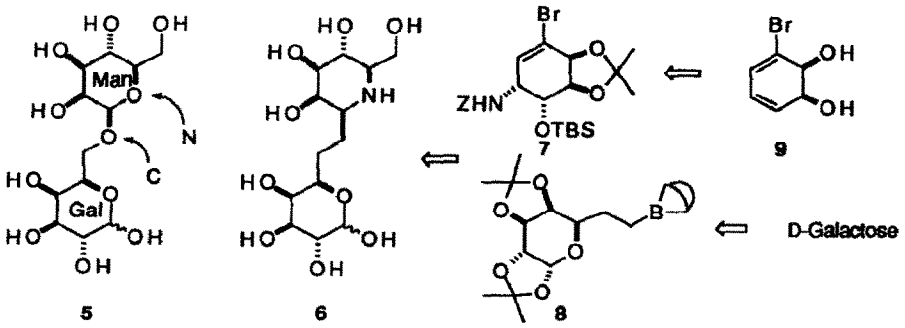
4 MDL 25.637

The synthesis of oligosaccharide analogues containing various glycoside-linked 1-deoxynojirimycins and related moieties at the reducing end have been reported.[7] The preparation of an azapyranosyl thioglycoside having the azasugar residue at the non-reducing end has also been described.[8]

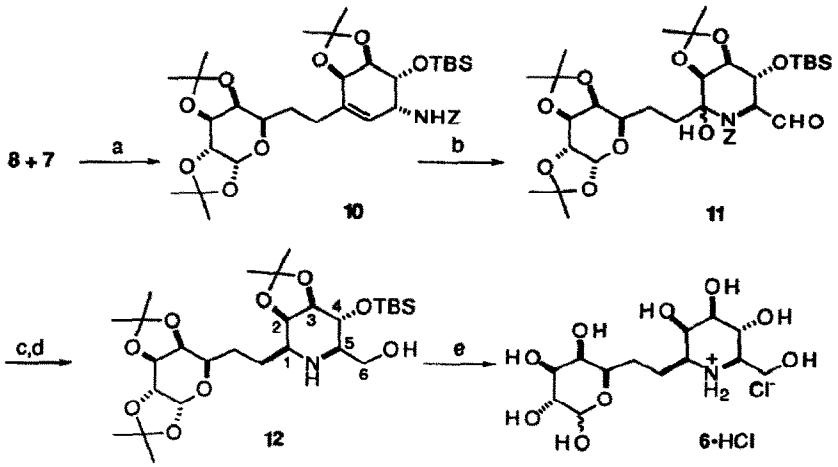
In this communication, we present a model synthesis of the aza-*C*-disaccharide **6** (Scheme I). This novel sugar mimic, fully resembling a parent disaccharide, 6-*O*-β-D-mannopyranosyl-D-galactose (**5**), should be inert towards acidic or enzymatic hydrolysis while preserving strong binding properties of the parent azasugar, 1-deoxy-*manno*-nojirimycin. Replacement of the glycosidic oxygen by a methylene unit should not significantly affect the conformation of the glycosidic linkage as illustrated by Kishi and coworkers.[9]

Vinyl bromide **7** was prepared according to Hudlicky's procedure[10] from enantiopure bromo diol **9**,[11] a product from microbial oxidation of bromobenzene. The alkyl boron reagent **8** was generated by hydroboration (1.5 eq of 9-BBN, THF, 4 h) of the corresponding olefin[12] derived in four steps from D-galactose. The key transformation was achieved using Suzuki coupling[13] of **7** and **8** in 80% yield. Ozonolysis followed by reductive work-up gave the keto-aldehyde, which existed predominatelly in the cyclic form **11** based on its ^{1}H NMR spectrum (Scheme II).

Scheme I



Scheme II[a]



[a]Reagents and conditions: a) $PdCl_2(dppf)$, DMF, K_3PO_4, rt (80%); b) O_3, MeOH:CH_2Cl_2 (1 : 1), -78 °C, then DMS 1 h; c) $NaBH_3CN$, MeOH, pH-4 buffer, rt ; d) H_2, Pd-C, MeOH (57 % from **10**); e) 1 *N* HCl, rt (95 %).

Chemoselective reduction of the aldehyde of **11** was achieved using sodium cyanoborohydride-HOAc/NaOAc buffer (borane-*t*-butyl amine complex in dichloromethane gave comparable results) (Scheme II). Hydrogenation of the resulting aminal gave the β-pseudo anomer **12** as a single diastereomer based on ^1H NMR (500 MHz) analysis of the crude product (57% isolated yield from the alkene **10**).[14] The relative sterochemistry of the pseudo-anomeric center was established on the coupling pattern as well strong NOE effect between H-1 and H-5 protons (Figure 1). Acidic deprotection of all blocking groups afforded the hydrochloride salt of **6** as an anomeric mixture in 95 % yield (α : β; 1 : 2).

An efficient method for the production of 1-6 linked aza-C-disaccharides has been developed. The scope and limitations of this methodology and the relevant biological activities of this new class of compounds will be reported in due course.

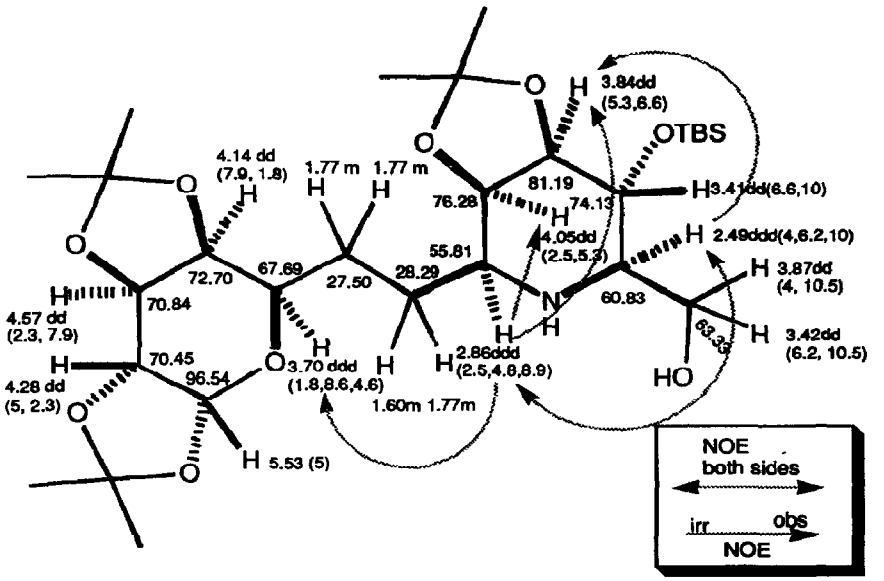


Figure 1. ^{1}H NMR data for compound **12**: Proton assignments by ^{1}H decoupling and DDR. Carbon assignments by HETCOR experiments. Relative stereochemistries by NOE experiments. All data obtained in $CDCl_3$ at 500 MHz.

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14. Selected Physical Data:

    10: $[\alpha]_D$ -57.5 (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.85 (s, 9 H), 1.31 (s, 3 H), 1.34 (s, 6 H), 1.36 (s, 3 H),1.46 (s, 3 H), 1.51 (s, 3 H), 1.67 (m, 1 H), 1.88 (m, 1 H), 2.16 (m, 1 H), 2.34 (m, 1 H), 3.71 (ddd, 1 H, J = 1.5, 4.2, 5.7 Hz), 4.09 (dd, 1 H, J = 1.8, 8.1 Hz), 4.18 (m, 2 H), 4.28 (dd, 1 H, J = 2.4, 5.4 Hz), 4.42 (d, 1 H, J = 4.8 Hz), 4.47 (d, 1 H, J = 8.7 Hz), 4.56 (dd, 1 H, J = 2.4, 8.1 Hz), 4.94 (d, 1 H, J = 9.6 Hz), 5.12 (s, 2 H), 5.30 (d, 1 H, J = 1.8 Hz), 5.53 (d, 1 H, J = 5.1 Hz), 7.40 (m,5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ –5.01, –4.78, 17.87, 24.32, 24.80, 25.66, 25.99, 26.16, 26.55, 27.72, 27.82, 28.83, 48.17, 66.56, 67.03, 69.93, 70.46, 70.91, 72.87, 73.44, 75.81, 96.46, 108.10, 108.88, 109.38, 122.11, 127.95, 128.38, 136.62, 137.70, 155.61.

    12: $[\alpha]_D$ -36.1 (*c* 2.5, CH_2Cl_2).

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