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Scaffolded Bis-azasugars: A Dual Warhead Approach to Glycosidase Inhibition

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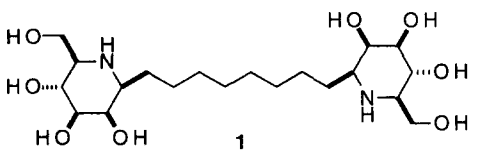
Abstract: Double Suzuki coupling was achieved with vinyl bromide **7**, synthesized from the bromobenzene microbial oxidation metabolite bromocyclohexadienediol **6** and α,ω-diborane coupling partners derived from the hydroboration of the corresponding diene. Ozonolysis and selective reduction protocols served to provide selectively the α/α or β/β tethered polyhydroxylated piperidine ring systems (bis-azabugars). The C_8 linked DMJ analogue **1** showed inhibitory activity against glycosidase enzymes.

Our laboratory has recently been involved in the synthesis of complex novel polyhydroxylated piperidine glycosidase inhibitors.[1] In an attempt to rationally design this type of inhibitor, the often dramatic differences in the physical and biological properties of tethered dimeric substrates and their parent monomeric counterparts attracted our attention.[2] With this observation in mind, we desired to investigate the synthesis of scaffolded polyhydroxylated piperidines. Further impetus for the synthesis of such compounds was derived from the propensity of proteins (or enzymes) to recognize clusters of sugar residues as a structural motif rather



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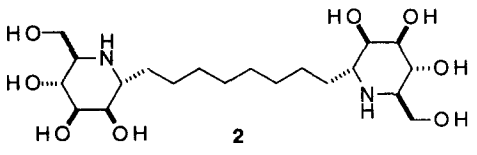

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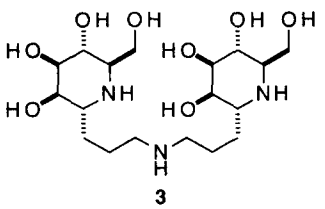

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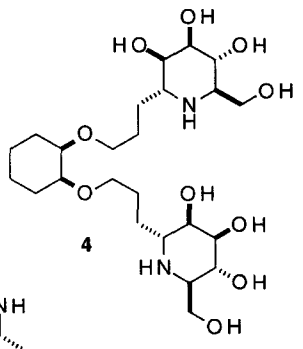

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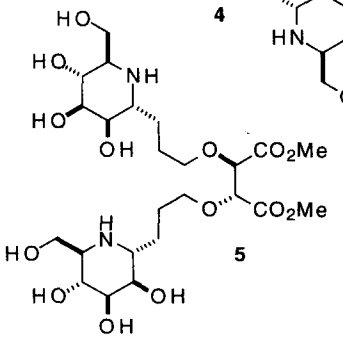

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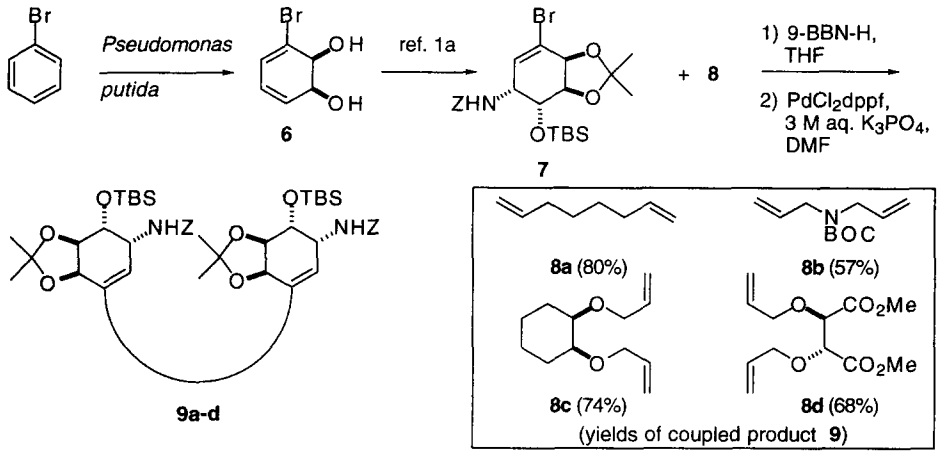
than individual monosaccharide units.[3] Our previously established *de novo* methodology for the synthesis of 1-*C*-substituted deoxymannojirimycin analogues appeared to be well suited for the construction of scaffolded azasugars.[1] We now wish to report the synthesis of five novel and diverse scaffolded bis-1,1'-*C*-linked azasugars (**1-5**). The bis-azasugars **1** and **2** consist of a simple tether containing eight methylene units, differing in the C^1 stereochemistry of the piperidine ring, while the bis-azasugars **3-5** contain more complex scaffolds. It was our desire to investigate a broad range of functionality and structural features in the scaffolding region of the substrates. The presence of heteroatoms, conformational rigidity, and stereochemistry in the scaffolds chosen for examples **3**, **4**, and **5** appeared to accomplish this goal for the first generation of compounds.

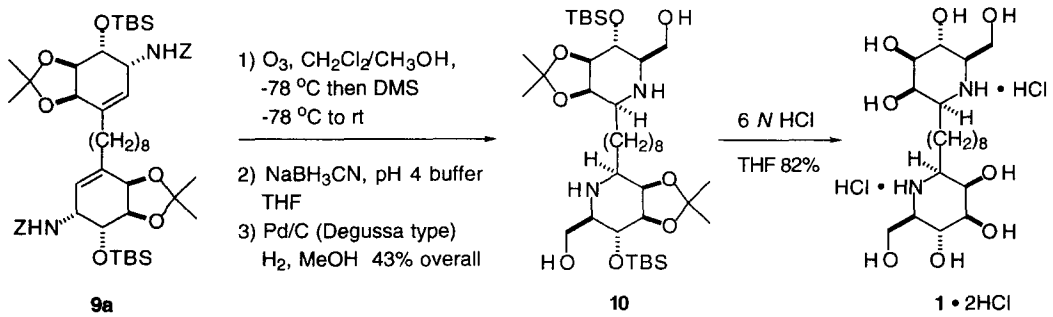
Our synthetic strategy centers on a double Suzuki cross-coupling[4] of vinyl bromide **7**[5], synthesized from the microbial oxidation metabolite bromodiol **6** derived from bromobenzene[6], and an α,ω-diboron transmetallation partner formed upon hydroboration of the corresponding terminal diene **8** (Scheme 1).

Scheme 1



Piperidine ring formation was initiated by cleavage of the trisubstituted olefin of **9a** with ozone followed by quenching with dimethyl sulfide (DMS) to provide the corresponding bis-keto-aldehyde. The aldehyde was reduced in the presence of the ketone moiety ($NaBH_3CN$, pH 4 buffer, THF) to give the bis-keto-alcohol. Cyclization was accomplished *via* an intramolecular reductive amination (Pd/C Degussa type, H_2, MeOH) to yield the protected β/β C_8 linked azasugar **10** in modest yield. The fully deprotected bis-azasugar was produced upon treatment with HCl (Scheme 2).

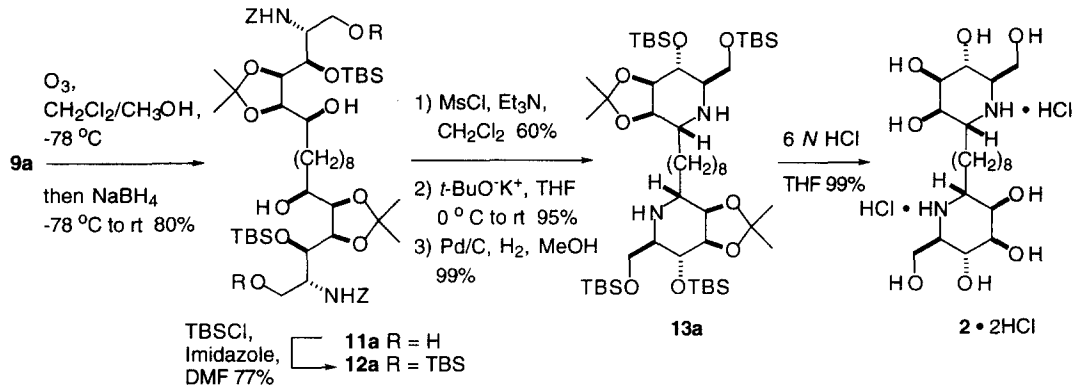
Scheme 2



The double reductive amination protocol gave satisfactory results with the non-functionalized scaffold example described above, but proved to be a capricious reaction sequence for the more complex scaffolds. At this point it was decided to investigate the more recent methodology developed to synthesize α-1-*C*-substituted deoxymannojirimycin systems.[1c,7]

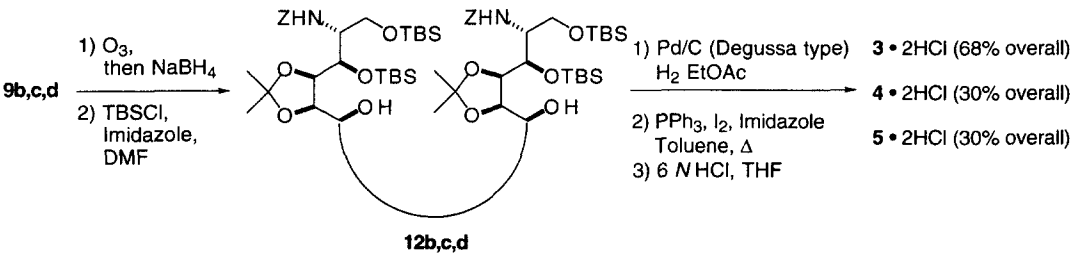
The diene **9a** was subjected to ozonolysis as above, but the ozonide was quenched with sodium borohydride to produce a single diastereomeric tetraol **11**. The primary alcohols were protected as their silyl ethers (TBSCl, imidazole, DMF). Mesylation of the remaining secondary alcohols (MsCl, Et_3N or Ms_2O, Pyridine, CH_2Cl_2) led to the requisite cyclization precursor which upon treatment with base (*t*-BuO^-K^+, THF) facilitated the S_N2 displacement of the mesylate by the tethered nitrogen to produce the desired α/α C_8 linked bis-azasugar. Hydrogenolysis of the Cbz carbamate provided diamine **13**. Treatment with HCl rendered the fully deprotected bis-azasugar **2** as its hydrochloride salt (Scheme 3).

Scheme 3



A similar protocol was employed for the remaining scaffolds to provide bis-azasugars **3-5**, but the mesylate ring closing sequence was circumvented using a more direct Mitsunobu strategy. The diol intermediates **12b-d** were subjected to hydrogenolysis conditions (Pd/C Degussa type, H_2, EtOAc) providing the corresponding bis-amino-alcohols. The removal of the carbamate nitrogen protecting group was crucial for the success of the Mitsunobu strategy. The intramolecular Mitsunobu cyclization depends on the nucleophilicity of the nitrogen lone pair, and hence the Cbz protected nitrogen was not sufficiently nucleophilic to facilitate displacement of the phosphonium intermediate. As expected, the lone pair on the free amine was found to be much more nucleophilic. The amino-alcohols underwent facile cyclization when subjected to the Mitsunobu conditions (PPh_3, I_2, imidazole, toluene, Δ) (Scheme 4).

Scheme 4



It should be noted that the Mitsunobu strategy required fewer chromatographic purifications than the mesylate protocol. This was crucial in the synthesis of scaffolded bis-azasugars **4** and **5** due to a lack of stability of the intermediates toward silica gel. The lowered yields of these substrates also reflect this observation.

Scaffolded bis-azasugar **1** (consisting of the β/β linkage) was screened against seven common glycosidases (amyloglucosidase, α-glucosidase (yeast), β-glucosidase, α-galactosidase, β-galactosidase, α-mannosidase, and β-mannosidase). Compound **1** was found to be active against two of the glycosidases. An IC_{50} of 20 μM was observed for amyloglucosidase. This was not surprising when compared to previous screening results of β-1-*C*-substituted deoxymannojirimycin analogues.[1a] Interestingly, substrate **1** was also found to inhibit α-mannosidase displaying an IC_{50} of 49 μM. Typically, C^1 substituted deoxymannojirimycin systems show little if any inhibition of mannosidase enzymes.[8]

In summary, a first generation of scaffolded azasugar glycosidase inhibitors has been introduced. The *de novo* synthetic methodology has been examined for several diverse scaffolds which address a broad range of structural features including heteroatom substitution, rigidity, and stereochemical bias. Biological evaluation showed unique and encouraging inhibitory activity against glycosidase enzymes. Further biological evaluation results will be reported in due course.

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