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Carbohydrate mimics: analogues of aza-di-(or tri-)saccharides

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Abstract—Four enantiopure pseudo-aza-di-(or tri-)saccharides have been synthesized by aminocyclization of a C_2-symmetrical D-*manno*-bis-epoxide either with a primary amine having a polyhydroxylated tetrahydrofuran skeleton or with a polyhydroxylated piperidine or azepan.

Carbohydrates play a critical role in biological events such as intercellular communication and cell-mediated processes. Thus, inhibitors of glycosidases or glycosyltransferases involved in these processes may find therapeutic applications to treat various diseases such as diabetes,[1] cancer[2] and viral infections.[3] Enzymatic hydrolysis of a glycosidic bond is assumed to proceed via a general acid–base catalysis. Monosaccharide analogues with nitrogen in place of the oxygen are potent glycosidase inhibitors because protonation at physiological pH allows them to mimic the oxycarbenium ion-like transition state.[4,5] Furthermore, since the aglycon part of the glycoside plays an important role in achieving selectivity towards different glycosidases, pseudo-disaccharides or pseudo-sugars containing an aglycon part are worth considering.[6,7]

With the goal of developing new routes to carbohydrate mimics as potential drugs or pharmacological tools, our ongoing program is directed towards the synthesis of

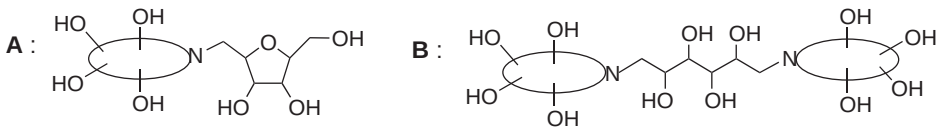

Figure 1.

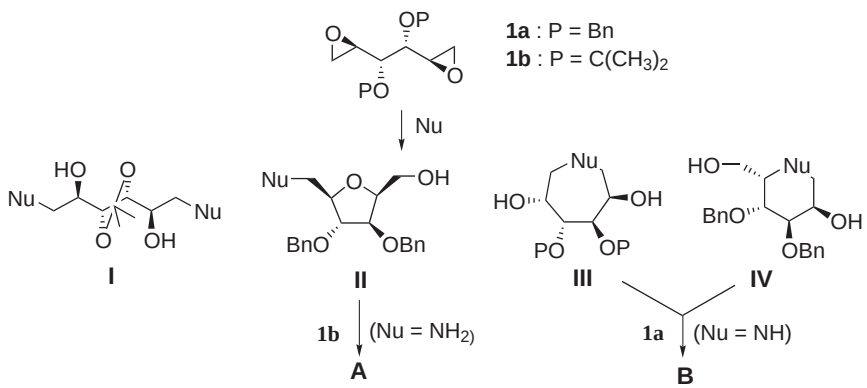

Figure 2.

Keywords: glycosidases; pseudo-azasaccharide; bis-epoxide; polycyclic heterocyclic compounds.

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enantiopure aza-di-(or tri-)saccharides from C_2-symmetrical bis-epoxides derived from D-mannitol (Fig. 1).

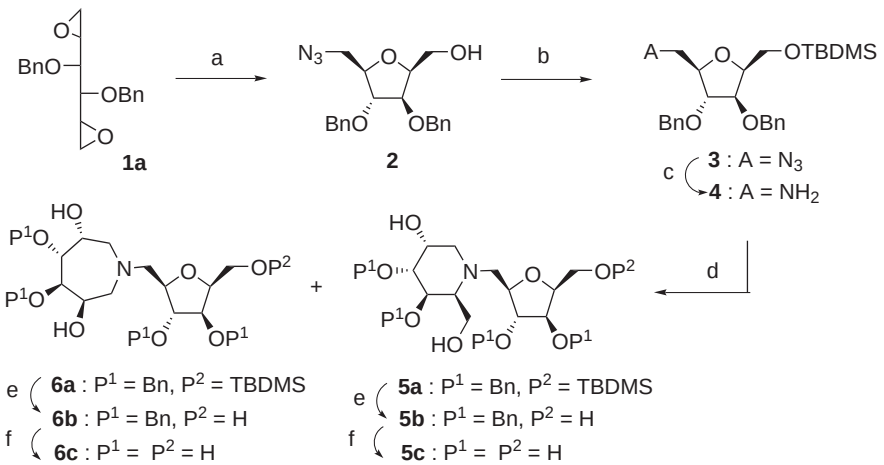
In previous papers, we have reported the regiospecific opening of a C_2-symmetric D-*manno* or L-*ido*-bis-epoxide by various nucleophiles to afford iminosugars, thiosugars, guanidinosugars and aminothiazolinosugars.[8] Nucleophilic opening of bis-epoxide **1** depends on different factors, such as the nature of the nucleophile or the 3,4-*O*-protecting groups of the bis-epoxide, and the experimental conditions (Fig. 2).

After nucleophilic opening of the first epoxide moiety at the least substituted site, three different evolutions can occur.[8] Opening of the other epoxide by a second equivalent of nucleophile leads to the C_2-symmetric acyclic compound **I**. *O*-Cyclization according to a *5-exo-tet* process gives mainly the tetrahydrofuran compound **II**. *Nu*-Cyclization, after acid–base reaction between the alkoxide and the introduced nucleophile, leads to a seven- and a six-membered ring **III** and **IV**, according to the regioselectivity of the second epoxide opening.

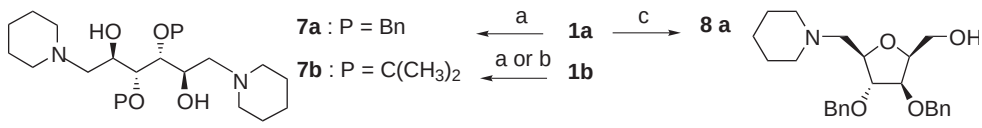
In order to obtain pseudo-azadi-(or tri-)saccharides **A** and **B**, respectively, our synthetic strategy involves the aminocyclization of bis-epoxide **1**, on the one hand with a primary amine having a polyhydroxylated tetrahydrofuran skeleton derived from **II** (Nu = NH_2) and on the other hand with a secondary heterocyclic amine having an azepan or a piperidine skeleton derived from **III** and **IV**, respectively (Nu = NH).

Pseudo-azadisaccharides were obtained according to Scheme 1.[9] Azidomethyl-tetrahydrofuran formation was initiated by opening of the 3,4-di-*O*-benzyl D-*manno* bis-epoxide **1a** with sodium azide in the presence of silica gel (95% yield).[10] Protection of the primary alcohol function of **2** into the *tert*-butyldimethylsilyl ether followed by selective heterogeneous catalytic hydrogenation led to the aminomethyl-tetrahydrofuran **4** (95% overall yield). Aminocyclization of a second bis-epoxide **1a**, with the primary amine **4** cleanly occurred in methanol affording a mixture of bicycles *N*-methylfurano-piperidine **5a** and *N*-methylfurano-azepan **6a**, which could be separated by flash chromatography (30 and 40%, respectively, for **5a** and **6a**).[11] Subsequent desilylation (nBu_4NF, THF) led to **5b** and **6b** in 80 and 85% yields, respectively. After removal of all benzyl protecting groups by hydrogenolysis in the presence of palladium black in acetic acid, the desired azadisaccharides with an *N*-methylfurano-piperidine **5c** or azepan **6c** skeleton were isolated at its acetate salt after purification by flash chromatography (80 and 85% yields, respectively).

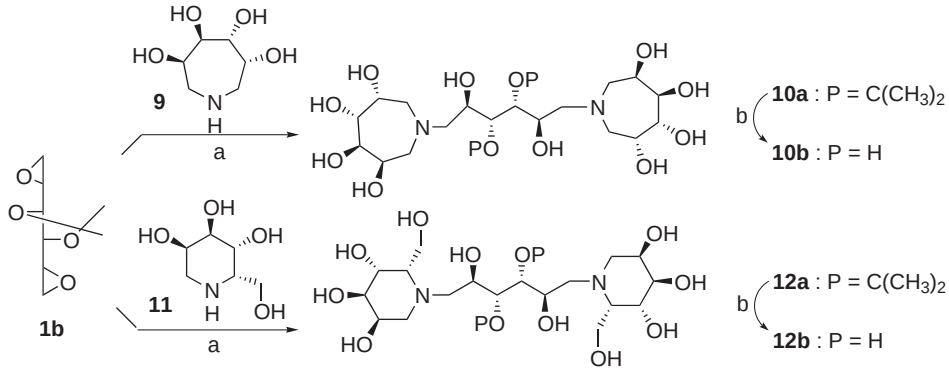
The second strategy to afford pseudo-azatrisaccharides **B** involves the bis-epoxide opening with a sterically hindered heterocyclic amine. We initially investigated



Scheme 1. Reagents and conditions: (a) NaN_3, SiO_2, CH_3CN, Δ, 48 h; (b) TBDMSCl, imidazole, DMF, 15 h; (c) H_2, Pd black, EtOAc; (d) **1a**, CH_3OH, 8 days; (e) Bu_4NF, THF; (f) H_2, Pd black, CH_3CO_2H.



Scheme 2. Reagents and conditions: (a) neat piperidine, 20°C, 4 days, 80% of **7a** or 90% of **7b** (b) piperidine (2 equiv.), MeOH, 20°C, 90% of **7b**; (c) piperidine, 2 equiv., CH_3CN, Δ, 85% of **8a**.



Scheme 3. Reagents and conditions: (a) **9** or **11**, 2 equiv. in MeOH, 12 h, 20°C; 75%, or 95% for **10a** or **12a**, respectively; (b) CF_3CO_2H/H_2O 4/1, 20°C, 70%, or 80% for **10b** or **12b**, respectively.

the reactivity of piperidine towards the 3,4-di-*O*-benzyl and 3,4-*O*-isopropylidene-D-*manno*-bis-epoxide, **1a** and **1b**, respectively (Scheme 2).[9]

Nucleophilic opening of the 3,4-*O*-dibenzyl-D-*manno*-bis-epoxide **1a** in neat piperidine at room temperature led cleanly to the acyclic C_2-symmetric compounds **7a** (80%). On the other hand, treatment of the same bis-epoxide **1a** with two equivalents of piperidine in refluxing acetonitrile afforded the piperidinomethyl-tetrahydrofuran **8a** (85%). In this case, only the *O*-cyclization occurred by a 5-*exo*-*tet* process (no tetrahydropyran has been isolated after flash chromatography). These results interestingly proved that experimental conditions could modify the course of the reaction. Furthermore, the more rigid 3,4-*O*-isopropylidene bis-epoxide **1b** afforded the acyclic compound **7b** (90%), whatever the experimental conditions were (piperidine as solvent or 2 equiv. of piperidine in methanol). In connection with these results leading to acyclic C_2-symmetrical compounds, we looked at the opening reaction of the 3,4-*O*-acetonide-D-*manno*-bis-epoxide **1b** by the polyhydroxylated azepan **9** and piperidine **11** (Scheme 3). Each of these heterocyclic secondary amines **9** and **11**[8] cleanly reacted with the 3,4-*O*-isopropylidene-D-*manno*-bis-epoxide **1b** in methanol at room temperature to afford **10a** (75%) or **12a** (95%). Subsequent treatment with aqueous trifluoroacetic acid at room temperature and purification by flash chromatography gave access to the pseudo-azatrisaccharide **10b** (70%) or **12b** (80%).

In summary, we have synthesized four potential inhibitors of glycosidases, pseudo-azadisaccharides **A** and pseudo-azatrisaccharides **B**. Glycosidase inhibitory evaluations are currently underway and will be reported in due course. Synthesis of pseudo-azatrisaccharides could also be achieved following the described strategy for pseudo-azadisaccharides **A** according to a recursive process, which involves transformation of the primary hydroxy group into a primary amine.

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11. In the absence of the silyl protecting group of the primary alcohol function, the *N*-amino cyclization also occurs in similar yield, but we were unable to separate the corresponding bicycles **5a** and **6a** for which $P^2 = H$ by flash chromatography.