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Aglycon Mimicking: Glycoside Bond Cleavage Transition State Mimics based on Hydroxypyrrolidine Inhibitors.

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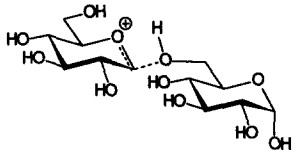
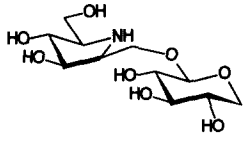
Abstract: β-L-xylopyranosides of a number of both known and new hydroxypyrrolidines were prepared.

In recent years much attention has been given to the development of selective glycosidase inhibitors, because such compounds have many interesting potential applications[1]. However, the attention has been directed mainly towards compounds that mimic a monosaccharide and thus often act as broadspectrum inhibitors. Little attention has been given to compounds that mimic both the glycon and the aglycon during glycoside cleavage, even though such compounds have a potential of much more specificity. Such compounds could also be useful as haptens for production of catalytic antibodies. We have recently been pursuing this goal in various ways, one of them being using known monosaccharide type glycosidase



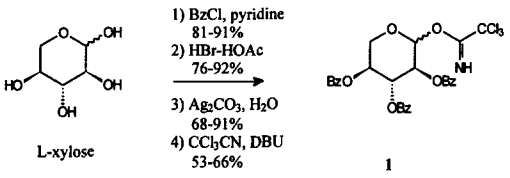


inhibitors and extending them to mimic the aglycon as well. Hydroxypyrrolidines are particularly interesting in this context because they are believed to resemble the glycon during glycoside cleavage quite well[2]. In this communication we describe an attempt of incorporating an aglycon mimic into a monosaccharide-type glycosidase inhibitor, such as a hydroxypyrrolidine, by simple O-glycosidation with a carefully selected, possibly unnatural, monosaccharide. Since modelling studies indicated that a L-xylopyranoside of a

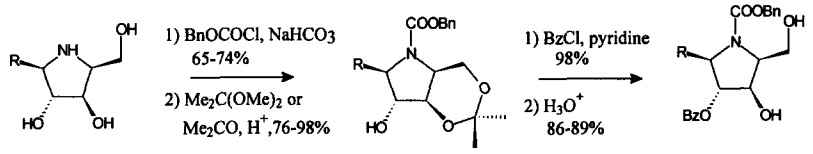
hydroxypyrrolidine would mimic cleavage of cellobiose quite well, we have chosen the synthesis of a number of L-xylopyranosides of hydroxypyrrolidine inhibitors.

RESULTS AND DISCUSSION

L-xylose and L-xylopyranosides are rare and nonaturally occuring compounds. We found that the best way to prepare L-xylose was from sorbitol, from which it can be prepared in three easy steps[3].



L-Xylose was then benzoylated in pyridine to the tetrabenzoate (mp 116-7 °C, $[\alpha]_D$ -146.5°[4]) in 81-91% yield, followed by treatment with HBr in acetic acid to give the 1-bromide (mp 134-6 °C, $[\alpha]_D$ -116.7°[5]) in 76-92% yield. Hydrolysis of the bromide gave the 1-hydroxysugar (mp 180-2 °C, $[\alpha]_D$ -23°[6]) in 68-91% yield, which finally was converted to a 53-68% yield of the trichloroacetimidate **1** (α:β 8:1, β: Mp 157-9 °C, $[\alpha]_D$ +33.1° (*c* 2.4, $CHCl_3$)) by using CCl_3CN and DBU.

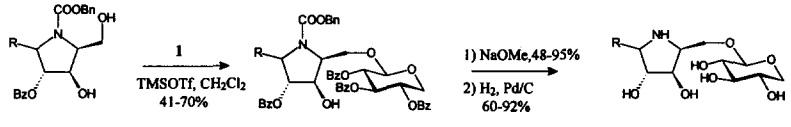


2, R=H
5, R=CH_2OH

3, R=H
6, R=CH_2OH

4, R=H
7, R=CH_2OBz

To achieve the desired regioselective glycosidation, the known hydroxypyrrolidines **2**[7] and **5**[8] were partially protected. Dissolving **2** in $NaHCO_3$-solution and treating with BnOCOCl gave the Cbz protected compound in 74% yield, which by reaction with 2,2-dimethoxypropane and HCl was converted to the acetonide **3** in 76% yield. Benzoylation and hydrolysis of the acetonide gave **4**. Similarly, **5** was converted to



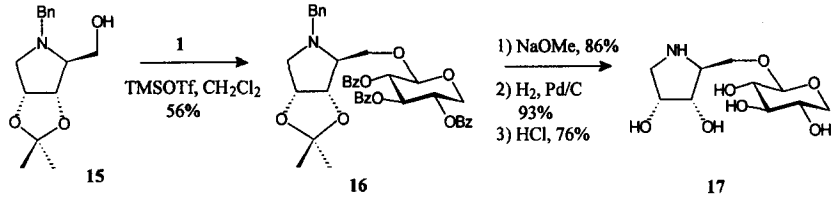
4, R=H
7, R=CH_2OBz, 5*R*
12, R=CH_2OBz, 5*S*

8, R=H
10, R=CH_2OBz, 5*R*
13, R=CH_2OBz, 5*S*

9, R=H
11, R=CH_2OH, 5*R*
14, R=CH_2OH, 5*S*

the dibenzoate **7**.

Selective glycosidation of **4**, **7** and **12**[9] with **1** in CH_2Cl_2 and TMSOTf as catalyst at room temperature proceeded smoothly to the β-L-xylosides **8**, **10** and **13** in 41%, 67% and 70% yield, respectively. Deprotection was performed by debenzoylation with NaOMe in methanol followed by hydrogenation (1 atm., Pd/C 5%, EtOH) to give the target compounds **9**, **11** and **14**[10].



15 **16** **17**

Furthermore the protected pyrrolidine **15**[11] was glycosylated using the same conditions to give the β-L-xyloside **16** in 56% yield. Debenzoylation using NaOMe in MeOH, followed by debenzylation by hydrogenation (1 atm., Pd/C 5%, EtOAc) and finally removal of the acetonide using HCl (1M, 25 °C, 3h) gave the glycoside **17**[10].

Screening of **9**, **11**, **14** and **17** gave the following preliminary K_i -values (mM) against α-glucosidase (Type 1 from bakers yeast, p-NO_2PhO-α-Glu as substrate, pH 6.8, 22 °C[12]) and β-glucosidase (from almonds, p-NO_2PhO-β-Glu as substrate, pH 6.8, 22 °C[12]): **9**: 0.60 & 3.18; **11**: 1.38 & 6.89; **14**: 2.05 & no inhibition; **17**: 0.96 & 0.58. These rather high K_i -values are very surprising and indicates a poor fit into these two enzymes catalytic pockets. Particularly the very high K_i -values of **11** compared with those of parent pyrrolidine **5**[8] (300-500 fold difference) are extremely intriguing, because one would expect a high tolerance for steric bulk in that end of the molecule, as both enzymes are fairly undemanding regarding the structure of the aglycon of their substrates. Therefore this seems to suggest that **5**, contrary to general belief, does not fit into enzyme in the expected manner and thus is a poor transitionstate analog. On the other hand **9** has somewhat lower K_i -values than its parent pyrrolidine **2**[7], indicating some of the expected fit in that case.

These new imino sugar derivatives described in this paper represents a novel attempt of preparing glycoside bond cleavage transition state analogues, where an unnatural sugar, L-xylose, has been used to mimic a glucose-aglycon. Preliminary inhibition studies suggests, however, that hydroxypyrrolidines might not be very good glycon mimics for this type of analogues. The concept can however readily be extended to other potential glycon mimics, such as other hydroxypiperidines or hydroxypiperidines, and further studies will explore these possibilities.

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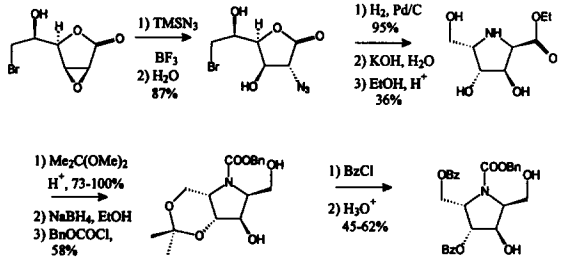
9. Protected iminoiditol **12** was prepared from a known and readily available α,β–epoxy-ω-bromolactone (Lundt, I.; Pedersen, C. *Synthesis* **1992** 669-672.) using the 9 step sequence shown right. Further details will be published later.



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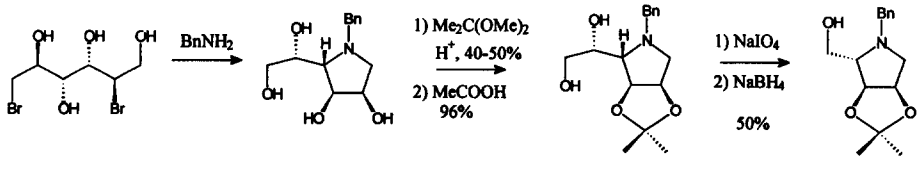
10. **9**: ^{13}C-NMR(D_2O) δ 104.1, 77.3, 77.1, 76.4, 73.8, 70.0, 69.1, 65.9, 60.3, 51.4; **9**,HCl: $[\alpha]_D$ -5.7° (*c* 1.0, H_2O); MS (CI, NH_3): m/z 266 (M + 1). **11**: ^{13}C-NMR(D_2O) δ 103.0, 75.6, 75.3, 74.3, 72.8, 69.0, 66.3, 65.0(2C), 61.1, 58.9; $[\alpha]_D$ +19.8° (*c* 0.5, H_2O); MS (CI, NH_3): m/z 296 (M + 1). **14**: ^{13}C-NMR(D_2O) δ 103.3, 76.9, 75.3, 75.1, 72.7, 69.0, 67.6, 65.0, 63.9, 61.7, 60.3; $[\alpha]_D$ +56.6° (*c* 1.0, H_2O); MS (CI, NH_3): m/z 296 (M + 1). **17**,HCl: ^{13}C-NMR(D_2O) δ 103.0, 75.5, 72.8, 71.2, 69.3, 69.1, 66.0, 65.1, 60.2, 49.8; $[\alpha]_D$ -7.7° (*c* 1.0, H_2O); MS (CI, NH_3): m/z 266 (M + 1).
11. Known iminoribitol **15** (Fleet, G. W. J.; Son, J. C.; Green, D. St. C.; Bello, I. C. di; Winchester, B. *Tetrahedron* **1988** *44* 2649-2655) was not prepared as previously described, but rather using a 5 step sequence, shown below, starting from known 2,6-dibromo-2,6-dideoxy-D-mannitol, which itself can be made from gluconolactone in 2 steps (Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res* **1981** *90* 7-16).



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