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AMIDINE PSEUDODISACCHARIDES

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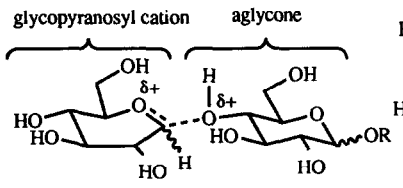
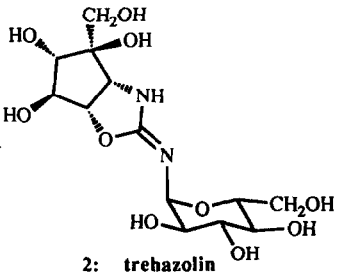
Key words: glycosidase inhibitors, transition state mimics, Vilsmeier activation, glucopyranosyl cation, amidine stability

Abstract: *The synthesis of several aminoglucopyranose-based amidine pseudodisaccharides is described. They may serve as glycosidase inhibitors by virtue of structural similarities to both the reducing and non-reducing pyranose units involved in glycolysis.*

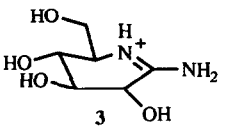
Many glycosidases are thought to catalyze the cleavage of the glycosyl bond by protonating the interpyranosidic oxygen atom and stabilizing the developing glycopyranosyl cation (see **1**).[1] Likewise, a variety of inhibitors of these enzymes may function by mimicking the charge and/or shape of the cation or a transition state leading to it.[2] However, less consideration has been given to mimics of the "aglycone," which also interacts with the glycosidase.[3] Recent developments in the design and evaluation of amidine-based inhibitors[4,5] such as **3** and the simpler (hypothetical[6]) version **4** led us to the belief that amidine containing *pseudodisaccharides* represent improved inhibitors that might bind in both the "glycopyranosyl" and the aglycone sites. This idea receives support in the structures of the naturally-occurring pseudodisaccharide trehalase inhibitor trehazolin[7] (**2**) and the valienamine-based pseudo-oligosaccharides,[8] which all possess a basic nitrogen at the interpyranosidic position. Here we report the synthesis of some first generation amidine pseudodisaccharides that model structural aspects of both portions of **1**.



1: stylized glycosidase transition state



2: trehazolin



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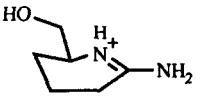
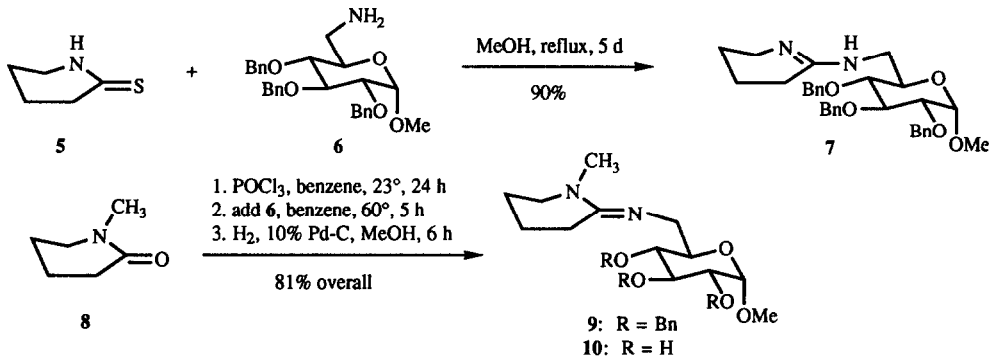
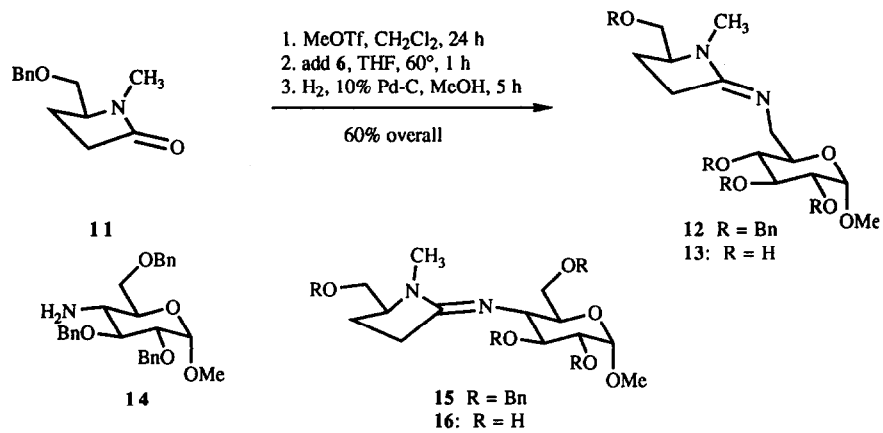


4

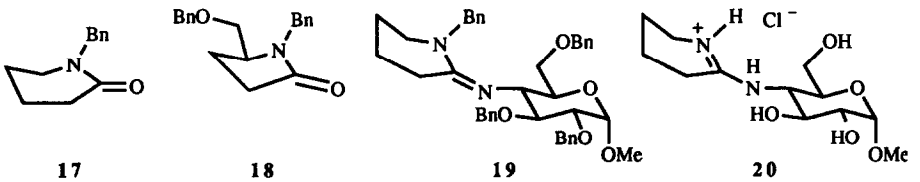
Coupling[4] of δ-valerothiolactam **5**[9] and benzyl-protected 6-aminoglucoside **6**[10] gave the protected (1→6)-linked amidine pseudodisaccharide **7** in good yield. The structure of **7** is confirmed by its IR, ^{1}H NMR, and ^{13}C NMR , and mass spectra (the amidine carbon resonance at δ 165.6 is diagnostic).[11] However **7**, like **3**, was not stable when stored as the free base. Therefore the N-methyl analogue **9** was prepared by a Vilsmeier procedure[12] as shown. The intermediate chloroiminium species derived from lactam **8** coupled smoothly with **6** to give **9** as a single, presumably *E*, isomer. Not only was **9** stable and chromatographable as the free base, it also could be deprotected by hydrogenolysis in nearly quantitative yield to give **10** (δ 164.6, D_2O), the first stable amidine pseudodisaccharide.



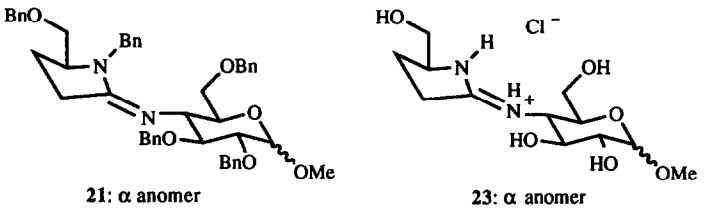
To bring the glycopyranosyl portion of **10** closer to **4**, 5*S*-(benzyloxy)methyl-1-methylpyrrolidin-2-one[13] (**11**) was coupled with **6** following activation with methyl triflate[14] to afford protected amidine **12**. Hydrogenolysis gave the amidine pseudodisaccharide **13** in high yield. Both **12** (δ 168.8, $CDCl_3$) and **13** (δ 169.7, D_2O) were obtained as a mixture (~5:3) of geometric isomers.[15] Further refinement of the amidine pseudodisaccharide was achieved by switching the aglycone portion to a 4-amino-4-deoxy-glucopyranoside. Thus amino sugar **14**[16] was coupled with **11** by using Vilsmeier activation as for **9** (80%). The protected amidine **15** was obtained, and this was deprotected as before (99%) to afford the (1→4)-linked pseudodisaccharide **16** (one isomer,[15] δ 170.2)



Whereas the addition of an N-methyl group in **10** had greatly increased the stability of the 6-aminoglucopyranoside-based amidine, the use of the bulkier 4-aminoglucopyranoside **14** as the coupling partner was viewed as now allowing a removable amidine N-substituent. Thus N-benzyl lactams **17** and **18**[17] were coupled with **14** by using Vilsmeier activation to give amidines **19** (60%) and **21** (75%), respectively. Hydrogenolysis in the presence of HCl gave the corresponding deprotected amidinium products **20** (97%, δ 165.8, D_2O) and **23** (91%, δ 164.8, 167.7). The β-anomer of **14**[18] was likewise coupled with **18** to give the β-anomers **22** (53%) and its deprotected version, **24** (99%, δ 164.8, 167.6). Products **21** - **24** were obtained as isomeric mixtures[15] (~5:2), but could be characterized by ^{13}C NMR and FAB-MS. Hydrochlorides **23** and **24** can be chromatographed on Iatrobeads®,[19] and are stable for days at room temperature and in D_2O solution.



17 18 19 20



21: α anomer
22: β anomer
23: α anomer
24: β anomer

The amidine pseudodisaccharides mimic several aspects of **1** to varying degrees. Hydrogen bond donor and acceptor sites are available in the form of hydroxyls on the aglycone portions, and there is evidence from studies of other inhibitors that filling the aglycone pocket might improve inhibitor binding.[3,8,20] In principal one could also tune the specificity of inhibition by adjusting the aglycone part to match the natural substrate. With respect to the glycopyranosyl part, the amidine substructure mimics the developing sp^2 hybridization of the pyranosyl ring oxygen.[1,2,4] Because the C_1 and the exocyclic amidine nitrogen are also sp^2-hybridized, the aglycone of the amidine pseudodisaccharides is situated approximately in the plane of the glycopyranosyl part, which resembles more closely its location in β-glycoside substrates than in α-glycosides.[2,21] Additionally, the O-C_1-O-$C_{(4'\text{-or-}6')}$ dihedral angle for the amidines is limited to values of about 0° or 180°, whereas the O-C_1-O-$C_{4'}$ angle of **1** does not have this constraint. The highly basic amidines will be protonated at physiological pH, and the resulting amidinium species mimic the charge distribution in **1** (see **23** and **24**),[4] although they are thereby not capable of accepting a proton from a side-chain carboxylic acid in the enzyme active site as the natural substrates are alleged to do.[1,2] The hydroxylmethyl substituent present in the glycopyranosyl portions of **13**, **16**, **23**, and **24** provides an additional potential binding site that is thought to be important for some glycosidases.[1,6] There is also some indication that five-membered nitrogen heterocycles offer an improved conformational match to the glycopyranosyl cation as compared to the corresponding six-membered pseudosugars.[22] The ability to incorporate a ring nitrogen substituent (here methyl) has proven beneficial in cases of certain inhibitors,[6,8] and may be an important option for the amidines. Finally, and most obviously, the amidines prepared to date lack the ring hydroxyls at C_2, C_3, and C_4 of **3**. Fully hydroxylated pseudodisaccharides are more challenging synthetic targets, but resemble **1** more closely. Thus the synthesis of more elaborate models of **1** is of continuing interest. The enzyme binding and inhibitory properties of amidines **10**, **13**, **16**, **20**, **23**, and **24** are currently being evaluated, and will be reported elsewhere.

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