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Access to Ring-Expanded Analogues of 2-Amino Sugars

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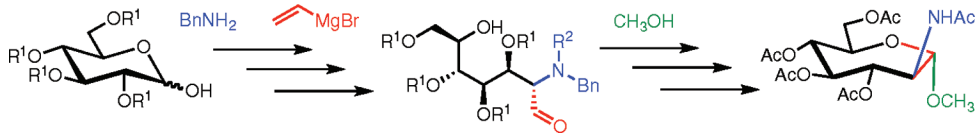
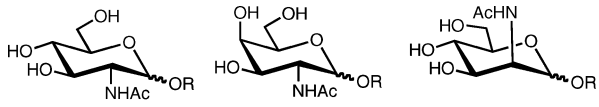
ABSTRACT



Ring-expanded 2-*N*-acetylamino sugar analogs of D-glucose, D-galactose, and D-mannose have been prepared by a new synthetic route. Aspects of the highly substituted α-amino aldehyde intermediates made them central to the approach. First, they were accessed via diastereoselective addition of a vinyl Grignard onto protected glycosyl amines. Also, the sterics of the bis-protected amine favored the formation of only one glycoside anomer. The new analogues reported here should prove useful in the development of tools to investigate the role of 2-amino sugars in biology.

Carbohydrates that incorporate at least one 2-amino sugar residue make up an important facet of glycobiology. The diversity of examples ranges from small molecule natural products[1] to glycans,[2] glycolipids,[3] and glycoproteins.[4] Functions mediated by these carbohydrates are similarly broad and include antibiotic activity, biosynthesis, metabolism, and cell−cell signaling. Among the most common 2-amino sugars are the N-acetylated gluco- (GlcNAc), galacto- (GalNAc), and manno- (ManNAc) hexoses (**1**−**3**). Analogues of 2-amino sugars have been utilized to explore numerous aspects of glycobiology[5] and also in the development of new drugs.[6]



1 **2** **3**

Our group has focused on the synthesis[7] and characterization[8] of ring-expanded carbohydrates. Homologation of six-membered ring pyranoses to seven-membered ring septanoses is akin to the homologation of purine and pyrimidine nucleosides to their benzo-fused analogues[9] or of α-amino acids to β-amino acids.[10] Syntheses of septanose carbohydrates to date have most commonly involved functionalization of ring-expanded glycals (oxepines).[11] Here we describe a synthetic route for the preparation of 2-*N*-acetylamino septanosides derived from D-glucose, D-galactose, and D-mannose. Oxepines do not serve as intermediates in the synthesis; rather, the expanded ring is formed via an

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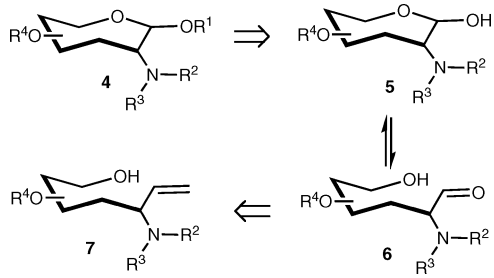
addition−cyclization sequence. A detailed consideration of the synthesis has provided insight into the factors that contribute to cyclization of these molecules. Importantly, the new analogues reported here should prove to be useful in the development of tools to investigate the role of 2-amino sugars in biology.

The strategy employed for the synthesis of the 2-amino sugar analogues is shown in Scheme 1. Cyclization of a

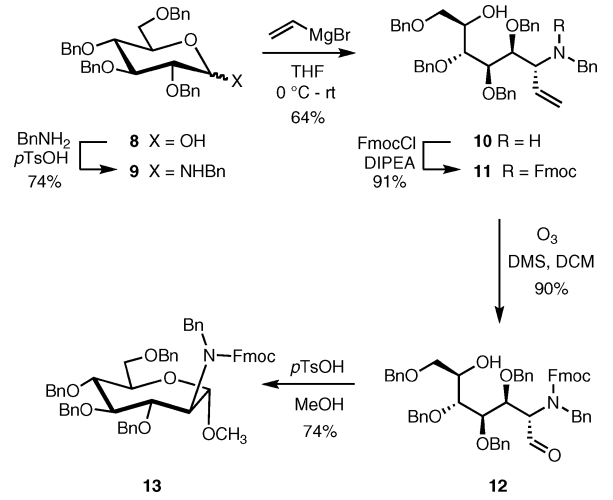
Scheme 1. 2-Amino Septanoside Retrosynthetic Analysis



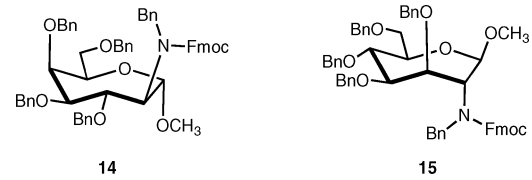
protected hydroxy aldehyde such as **6** and subsequent glycosylation to form **4** were the central features of the approach. Formation of **7** via stereoselective addition of a vinyl Grignard onto a D-glucosyl amine (**9**) was precedented[12] and provided confidence that the glycosyl amines prepared from D-galactose and D-mannose would react in a predictable way (vida infra). Ozonolysis of **7** to give **6** seemed equally likely. It was critical that hemiacetal **5** be an energetically favorable intermediate in the sequence. Reaction of related α-silyloxy and α-hydro aldehydes[13] (in place of α-amino aldehyde **6**) in acidic methanol provided only the acyclic dimethyl acetal or a mixture of cyclic and acyclic products. We wanted to know whether, under the same conditions, **6** would deliver glycoside **4**. In short, the route would allow us to investigate the role of the α-substituent in the cyclization reaction and also would provide the desired analogues.

The preparation of protected methyl 2-amino septanoside **13** from **8** illustrates the synthetic route (Scheme 2).[14] Formation of glycosyl amine **9** and subsequent diastereoselective addition of a vinyl Grignard followed literature conditions[12] giving **10** in 47% yield (two steps). Syntheses where acetyl or Cbz groups were used to protect the allyl amine proved problematic during deprotection; instead, amine **10** was protected as its Fmoc carbamate, giving **11** (91%). Ozonolyis of the alkene in **11** provided hydroxy aldehyde **12** (90%). Analysis of the NMR spectra of **12** indicated that both the aldehyde and hemiacetal forms were populated; this was also true for the hydroxy aldehydes

Scheme 2. Synthesis of 2-Amino Septanoside **13**



prepared from D-galactose and D-mannose.[15] Cyclization of **12** in an acidic methanol solution furnished the protected methyl α-2-amino septanoside **13** in 74% yield. Overall, the five-step process gave a combined yield of 29% or an average of 79% yield per step. The same sequence of transformations was used to prepare **14** and **15** in 38% and 26% overall yields, respectively.



For each case we investigated, one diastereomer of the allyl amine was selectively obtained in the Grignard addition.[16] In turn, each allyl amine delivered a single septanoside meaning that only one anomer was formed. We ascribed the selective glycoside formation to the steric bulk associated with the bis-protected amine at C2. Such a model would require that glycosylation went through a cyclic oxonium ion derived from a hemiacetal (**5**). Preference for a cyclic (methyl septanoside) rather than an acyclic (dimethyl acetal) pathway was likely based on the stability of the products. By considering together the absolute stereochemistry at C2 as predicted by the Cram-chelate model and the *trans*-1,2 nature of the methyl septanosides based on the bulk of the amino substituents,[17] we proposed structures **13**−**15** as the products of our synthetic route. Both the ^{1}H and ^{13}C NMR spectra of **13**−**15** proved complicated. Specifically, ^{1}H spectra were essentially uninterpretable, and the ^{13}C spectra

(12) (a) Cipolla, L.; Lay, L.; Nicotra, F.; Pangrazio, C.; Panza, L. *Tetrahderon* **1995**, *51*, 4679. (b) Cipolla, L.; Fernandes, M. R.; Gregori, M.; Airoldi, C.; Nicotra, F. *Carbohydr. Res.* **2007**, *342*, 1813.

(13) Castro, S.; Peczuh, M. W. *J. Org. Chem.* **2005**, *70*, 3312.

(14) The Supporting Information contains schemes for the syntheses of **14** and **15**.

(15) The product of Fmoc removal from **12** was a cyclic hemiacetal that gave simplified NMR spectra. See Supporting Information.

(16) For D-glucosyl amine (**9**) and D-galactosyl amine (**9-Gal**), only one diastereomer was formed and isolated. For D-mannosyl amine (**9-Mann**), a 4:1 ratio of diastereomers was observed, but only the major isomer was isolated. See Supporting Information for details.

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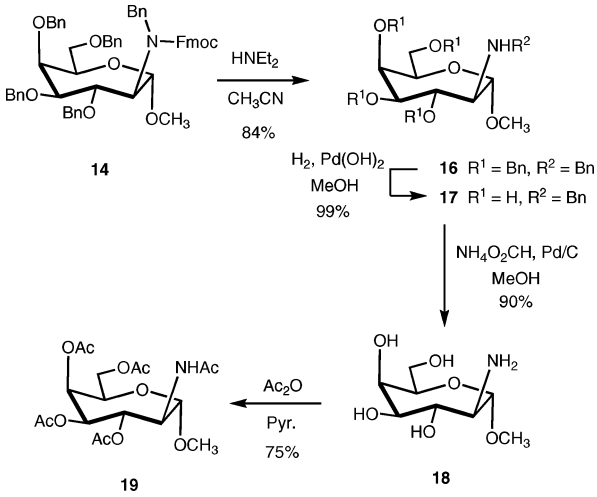
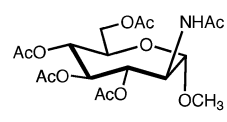
were characterized by a proliferation of each carbon signal into multiple signals. Restricted rotation of the C−N bond of the bis-substituted amino group was responsible for this effect.[18]

To test our rationale for the complicated NMR spectra and also to prepare more relevant derivatives, we proceeded with the stepwise deprotection of methyl septanosides **13**−**15**. For clarity, the deprotection sequence is shown only for D-galactose derived septanoside **14** (Scheme 3).[19] The Fmoc

Scheme 3. Formation of 2-*N*-Acetylamino Septanoside **19**



carbamate was first removed under standard conditions[12b] to give **16** (84%). In the absence of the Fmoc group, the NMR spectra of the per-benzylated systems (e.g., **16**) simplified considerably and allowed for standard interpretation. A two-step debenzylation sequence, the first to remove the benzylic groups from oxygen and the second to remove the benzylic group from the nitrogen, provided methyl α-2-amino septanoside **18** in 89% yield over two steps. ^3J Coupling constant analysis on **18** proved the stereochemical assignment at C1 and C2. Specifically, $^3J_{H1,H2}$ (7.6 Hz) and $^3J_{H2,H3}$ (10.0 Hz) indicated an *anti* relationship between H1 and H2 as well as between H2 and H3. Peracetylation of **18** then provided methyl α-2-*N*-acetylamino septanoside **19** in 75% yield (56% overall). The same sequence applied to **13** and **15** provided **20** and **21** in 54% and 42% yields.



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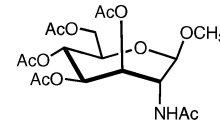

21

We have demonstrated a rapid and efficient route to 2-amino septanosides from protected pyranoses. The steric bulk of the bis-substituted amine at C2 of the hydroxy aldehyde directed both cyclization and formation of a single glycosidic linkage. The new ring-expanded sugar analogues should serve as valuable tools in glycobiology. They can be used as novel substrates in metabolic pathways or inhibitors of glycosyl transferases and glycosidases. Similarly, they may be used to assess the specificity of lectins in a number of biological contexts. A key challenge that we are currently addressing is the ability to attach other relevant aglycones in place of a methyl group which will broaden the utility of the analogues.

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Supporting Information Available: Additional synthetic schemes, experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The Supporting Information contains schemes for the syntheses of **20** and **21**.