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Synthesis of 1,2-*trans*-2-Acetamido-2-deoxyhomoiminosugars

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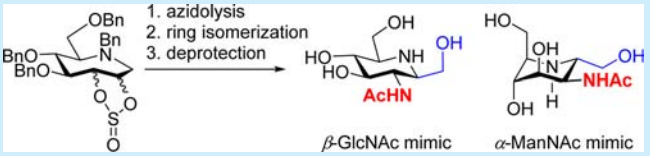
Supporting Information

ABSTRACT: The first synthesis of 1,2-*trans*-homoiminosugars devised as mimics of β-D-GlcNAc and α-D-ManNAc is described. Key steps include a regioselective azidolysis of a cyclic sulfite and a β-amino alcohol skeletal rearrangement applied to a polyhydroxylated azepane. The β-D-GlcNAc derivative has been coupled to serine to deliver an iminosugar *C*-amino acid. The two homoiminosugars demonstrate moderate glycosidase inhibition.



Glycosidase inhibitors are enjoying much interest as they find applications in an increasing number of therapies.[1] Hexosaminidases that trim *N*-acetyl-β-D-glucosamine (GlcNAc) from glycoconjugates are of high therapeutic interest, being involved in several human pathologies including allergy,[2] osteoarthritis,[3] Parkinson's[4] and Alzheimer's[5] diseases. Iminosugars, i.e. sugars analogues in which the endocyclic oxygen has been replaced by nitrogen, constitute the most promising class of glycosidase inhibitors. Among the most potent β-hexosaminidase inhibitors, we can mention the naturally occurring pochonicine (**1**),[6] siastatin B (**2**),[7] nagstatin (**3**),[8] the synthetic pyrrolidines LABNAc (**4**),[9] ADMDP-acetamide (**5**),[10] polyhydroxylated proline amide **6**,[11] azepane (**7**),[12] and piperidines such as IFGNAc (**8**),[13] DNJNAc (**9**),[14] and DGJNAc (**10**)[15] (Figure 1). Introduction of structural diversity in compounds **9** and **10**, to possibly increase their potency and selectivity, have mainly focused on the functionalization of the endocyclic nitrogen,[16] the ring hydroxyl groups,[17] or the acetamido group.[18] Introduction of a stereochemically defined and chemically stable pseudoanomeric substituent *cis* to the C-2 substituent of the piperidine ring has been achieved and could constitute a promising alternative.[19] We would like to report herein, and in parallel to our previous paper, a synthetic strategy allowing access to the complementary 1,2-*trans* homo-2-acetamido-1,2-dideoxy iminosugars, illustrated by the synthesis of β-homo-2-acetamido-1,2-dideoxynojirimycin (β-HNJNAc, **11**) and α-homo-2-acetamido-1,2-dideoxy-mannojirimycin (α-HMJNAc, **12**) (Figure 1).

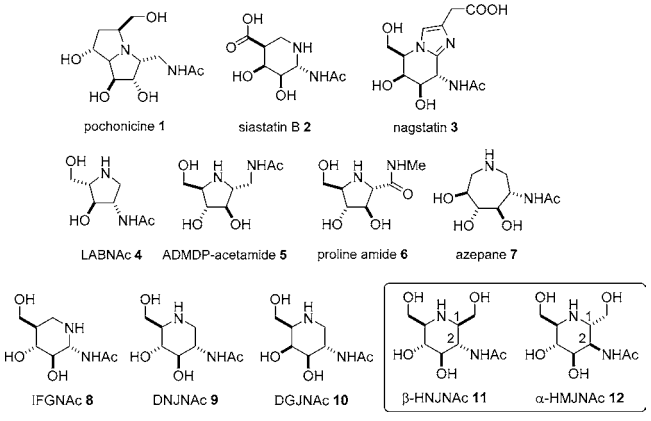


Figure 1. Structure of iminosugars **1**−**12**.

The ring isomerization of seven-membered polyhydroxylated azacycles constitutes one strategy among many others to generate new or known piperidine iminosugars.[20] This transformation, based on a β-aminoalcohol rearrangement,[21] requires a free alcohol at the β position and exploits the anchimeric assistance of the nitrogen. Access to 1,2-*trans* 2-acetamido-2-deoxy-homoiminosugars using this approach requires the preliminary *trans* introduction of OH and N_3 functionalities at the respective β and γ positions of the azepane ring. Epoxide azidolysis appears to be a suitable route toward this goal. Epoxidation of known azacycloheptene **13** (see our previous paper) was thus studied (Scheme 1). While *m*-CPBA-, oxone-, or H_2O_2-mediated oxidation gave disappointing results, the procedure developed by Shi[22] furnished the 3*R*,4*R* epoxide **14** in an acceptable 54% yield. The stereochemistry of the oxirane ring in **14** was established by comparing the ^{1}H NMR coupling constants for the protons H-3, H-4, and H-5 that matched those obtained for the

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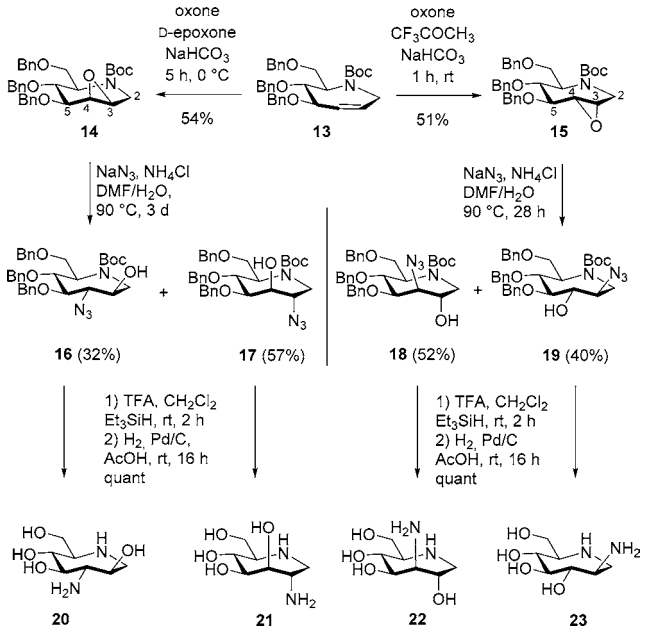
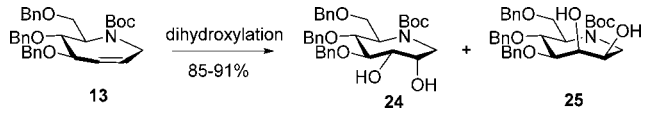
Scheme 1. Synthesis of Azido Alcohols 16−19



corresponding *N*-Cbz epoxide derivative.[24] Additionally, a NOESY experiment supported a *cis* relationship for the H-4 and H-5 protons. In parallel, oxirane-mediated epoxidation using CF_3COCH_3 furnished the diastereomeric 3*S*,4*S* epoxide **15** (51%) along with epoxide **14** (29%). Azidolysis of **14** using NaN_3 and NH_4Cl in DMF/H_2O at 90 °C afforded the required *trans* azido alcohol **16** as the minor product (32%) along with its regioisomer **17** (57%). Similar treatment of epoxide **15** furnished the azido alcohol **18** (52%) along with its regioisomer **19** (40%). Because of the presence of rotamers, the stereochemistry of azido alcohols **16**−**19** was difficult to elucidate by NMR. Their firm structure assignment was achieved via their deprotection with TFA followed by hydrogenolysis (H_2, Pd/C, AcOH) to give the known tetrahydroxylated aminoazepanes **20**−**23**, the ^{1}H NMR data for which were in good agreement with the literature.[23b] The observed regioselectivities for the azidolysis step are similar to those reported in the case of a *N*-Cbz protecting group.[23] While the well-established Fürst−Plattner principle[24] of *trans* diaxial epoxide ring-opening usually furnishes major diastereoisomers in the case of piperidines,[25] the azepane ring flexibility can be invoked here to explain the lack of regiocontrol during azidolysis. On the basis of the disappointing results above (17% yield for azido alcohol **16** and 26% yield for azido alcohol **18** from compound **13**), we concluded that a second round of optimization would be necessary to achieve synthetically useful yields. We anticipated that protection of the corresponding 3,4-*cis* diols as their cyclic sulfites[26] could provide the synthetic equivalent of an epoxide, possibly allowing the regioselective introduction of an azide at the γ position. To this end, several asymmetric dihydroxylation conditions were applied to **13** in order to improve the modest level of diastereoselectivity obtained in the case of OsO_4-mediated dihydroxylation (Table 1).

The best conversion and diastereoselectivities were obtained with the modified Sharpless asymmetric dihydroxylation (SAD) method[27] using AD-mix α and β, respectively, with 0.2 equiv of ligand (entries 4 and 7) that afforded the bottom-face diol **24** and the top-face diol **25** in 65% and 58% yields, respectively. As

Table 1. Dihydroxylation of Azacycloheptene 13

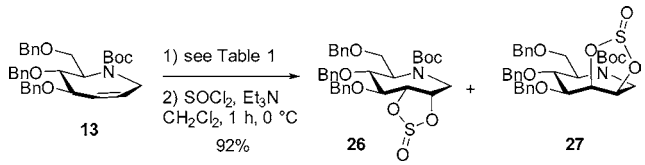


entry	conditions	24:25 ratio[a]
1	OsO_4, acetone/H_2O	2:1
2	α-AD-mix, *t*-BuOH/H_2O	1.5:1
3	modified SAD, 0.05 equiv of ligand **I**,[b] *t*-BuOH/H_2O	2.5:1
4	modified SAD, 0.2 equiv of ligand **I**,[b] *t*BuOH/H_2O	**2.9:1**
5	β-AD-mix, *t*-BuOH/H_2O	1:1.4
6	modified SAD, 0.05 equiv of ligand **II**,[b] *t*-BuOH/H_2O	1:1.5
7	modified SAD, 0.2 equiv of ligand **II**,[b] *t*-BuOH/H_2O	**1:1.9**

[a]The ratio of diols **24**/**25** was determined by ^{1}H NMR by integrating the protons of the Boc group. [b]Ligand **I** = [$(DHQ)_2PHAL$]; ligand **II** = [$(DHQD)_2PHAL$].

these diols were found to be difficult to separate on a large scale, the mixture of diols obtained after dihydroxylation was directly treated with thionyl chloride and Et_3N to furnish the separable sulfites **26** and **27** in an excellent 92% yield (Scheme 2). Because of the presence of a stereogenic sulfur atom, **26** and **27** were both obtained as a mixture of diastereoisomers that were not separated and directly used in the next step.

Scheme 2. Synthesis of Cyclic Sulfites 26 and 27



With the synthesis of β-HNJNAc (**11**) in mind, we took advantage of the cyclic sulfite **27** to study its azidolysis (Scheme 3).[28] Treatment of **27** with LiN_3 (20% solution in water) at 130 °C provided the desired azido alcohol **16** (57%). A significant amount of diol **25** (25%) was also recovered probably arising from cyclic sulfite hydrolysis. Switching to neat NaN_3 at 130 °C furnished the required azido alcohol **16** in 80% yield (42% from **13**) along with its regioisomer **17** (9%). Removal of the Boc group in **16** with TFA followed by N-benzylation furnished the *N*-benzyl azepane **28** (82% over two steps), which was characterized by a large coupling constant between the *trans* H-3 and H-4 protons (J = 9.5 Hz) and NOE contacts between H-3 and H-5 and between H-4 and H-6. The β-amino alcohol rearrangement of **28** under Mitsunobu conditions proved unsatisfactory, affording the piperidine **29** in low yield. Use of TFAA[29] was beneficial as it furnished piperidine **29** in excellent yield (93%) after ester hydrolysis. For this transformation, we propose a mechanism (Scheme 4) in which the free alcohol in **28** is activated as its trifluoroacetate ester **30** and displaced by the endocyclic nitrogen, generating a fused piperidine−aziridinium ion **31**. The released trifluoroacetate ion then attacks the methylene carbon of the aziridinium ion and displaces the ammonium group to furnish the piperidine **29** after ester hydrolysis. ^{1}H NMR analysis of **29** ($J_{1,2}$ = 10.0 Hz, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz) confirmed its β-D-*gluco* configuration. Conversion of the azide functionality into an acetamide under standard conditions (PPh_3, THF/H_2O then Ac_2O, py) gave the crystalline diacetylated derivative **32** (61%), the crystal

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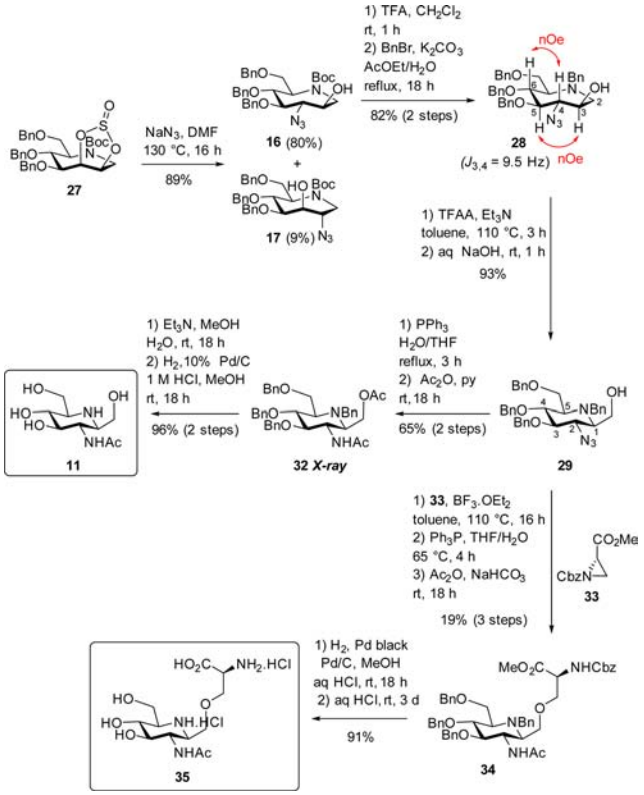
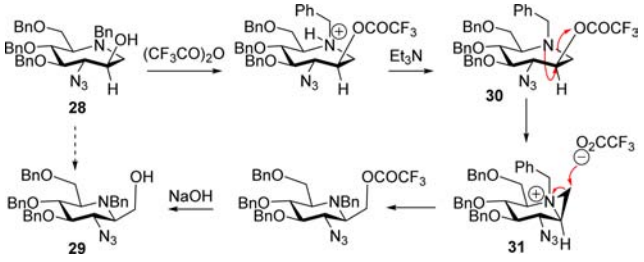
Scheme 3. Synthesis of β-HNJNAc 11 and Conjugate 35



Scheme 4. Proposed Mechanism for the Formation of Piperidine 29 from 28



structure of which was solved (Figure 2). O-Deacetylation with Et_3N in MeOH followed by hydrogenolysis under mild acidic conditions furnished the target β-HNJNAc **11** (Scheme 3).[30] To demonstrate the potential of these derivatives as "iminosugar *C*-glycosyl donors", homoiminosugar **29** was coupled to the serine precursor **33**[31] to yield the corresponding iminosugar amino acid precursor **34** after functional group interconversion from azide to acetamide. Hydrogenolysis followed by ester hydrolysis provided the homoiminosugar amino acid **35** (Scheme 3).

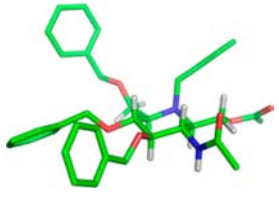
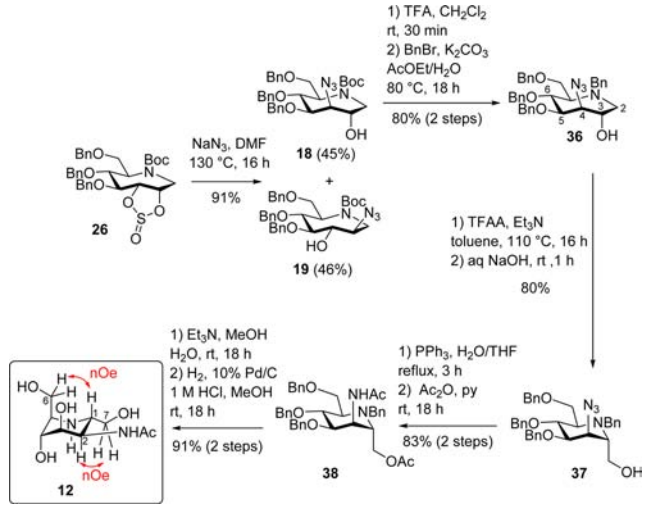


Figure 2. X-ray crystallography of compound **32** (CCDC 1015486).

To further exemplify our methodology, we synthesized a mannose analogue, namely the α-homo-2-acetamido-1,2-dideoxymannojirimycin (α-HMJNAc, **12**). Azidolysis of the cyclic sulfite **26** under the conditions depicted above furnished the azido alcohol **18** in 45% yield (27% from **13**) along with its regioisomer **19** (46%). Replacement of the Boc group by the electron-donating benzyl group yielded azepane **36**, as characterized by a small coupling constant between the *cis* H-4 and H-5 protons (J = 1.5 Hz) and a correlation in the COSY spectrum between H-3 and the free OH. Treatment of **36** with TFAA in toluene at 110 °C yielded the piperidine **37** in 80% yield after ester hydrolysis. Introduction of the acetamide group in **37** uneventfully provided piperidine **38** in 83% yield. O-Deacetylation followed by hydrogenolysis under mild acidic conditions yielded the target α-HMJNAc **12**. The *trans* relationship between the NHAc function and the pseudoanomeric CH_2OH group is confirmed by a NOESY cross-correlation between H-2 and H-7 (Scheme 5). NMR analysis indicated that, in CD_3OD, β-HNJNAc (**11**) adopts a β-glucose-like $^4C_1$-type conformation ($J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 8.8 Hz, $J_{4,5}$ = 9.7 Hz) and α-HMJNAc (**12**) an inverted $^1C_4$ chair ($J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 3.5 Hz and H-6/H-1 NOESY cross-correlation).

Scheme 5. Synthesis of α-HMJNAc 12



The β-HNJNAc (**11**) and α-HMJNAc (**12**) were assayed on a panel of β-*N*-acetylhexosaminidases from human placenta, bovine kidney, HL-60, Jack bean, and *Aspergillus oryzae* and α-*N*-acetylgalactosaminidase from chicken liver (Table 2). Surprisingly, β-HNJNAc (**11**) is only a moderate inhibitor of

Table 2. Concentration (in μM) of Iminosugars 11 and 12 Giving 50% Inhibition of Various Glycosidases (IC_{50})

enzyme	11	12
β-*N*-acetylhexosaminidase		
human placenta	72	302
bovine kidney	65	624
HL-60	88	394
Jack bean	41	95
Aspergillus oryzae	NI[a]	NI
α-*N*-acetylgalactosaminidase chicken liver	NI	NI

[a]NI: no inhibition (less than 50% inhibition at 1000 μM).

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β-*N*-acetylhexosaminidases. As expected, α-HMJNAc (**12**), which displays a different configuration for two hydroxyl groups compared to the parent *gluco*-configured substrate, is a poor inhibitor of these enzymes.

In summary, the first synthesis of 1,2-*trans* homoiminosugars derived from GlcNAc and ManNAc bearing a pseudoanomeric CH_2OH group is reported exploiting a β-amino alcohol rearrangement applied to a seven-membered iminosugar. Use of a cyclic sulfite derivative as an epoxide equivalent and its azidolysis proved beneficial to access the azepane precursor necessary for the ring-contraction step. This work has produced novel structures that could be used as probes in the field of β-*N*-acetylhexosaminidases.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR spectra, and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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