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Synthesis of 1,2-*cis*-Homoiminosugars Derived from GlcNAc and GalNAc Exploiting a β-Amino Alcohol Skeletal Rearrangement

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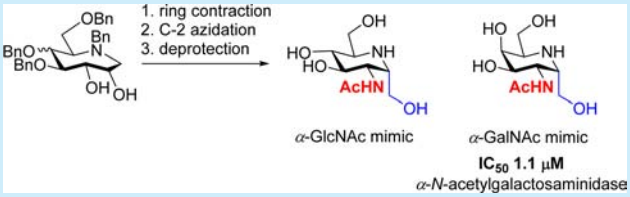
Supporting Information

ABSTRACT: The synthesis of 1,2-*cis*-homoiminosugars bearing an NHAc group at the C-2 position is described. The key step to prepare these α-D-GlcNAc and α-D-GalNAc mimics utilizes a β-amino alcohol skeletal rearrangement applied to an azepane precursor. This strategy also allows access to naturally occurring α-HGJ and α-HNJ. The α-D-GlcNAc-configured iminosugar was coupled to a glucoside acceptor to yield a novel pseudodisaccharide. Preliminary glycosidase inhibition evaluation indicates that the α-D-GalNAc-configured homoiminosugar is a potent and selective α-*N*-acetylgalactosaminidase inhibitor.



Iminoalditols rank among the most powerful glycosidase inhibitors. The most well-known representative, 1-deoxynojirimycin (**1**, DNJ), is found in two approved medicines.[1] Nature has overcome the absence of pseudoanomeric information in DNJ and the instability of the hemiaminal in the related molecule nojirimycin (**2**, NJ)[2] by producing homonojirimycins (**3**, HNJ)[3] that carry an extra pseudoanomeric CH_2OH group (Figure 1). This functionality not only improves

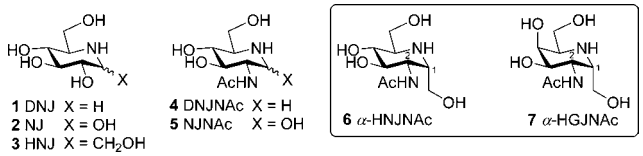


Figure 1. Structure of NJ, DNJ, HNJ, DNJNAc, NJNAc, and target iminosugars α-HNJNAc and α-HGJNAc.

the glucosidase inhibition profile of the parent iminosugar but also allows the introduction of aglycon moieties to generate chemically stable iminoglycoconjugates with promising biological activities.[4] Many synthetic routes to these highly substituted piperidines have been reported, covering most of the important monosaccharides.[5] There is one notable exception that has stood the test of time until very recently,[6] that is the homologues of the GlcNAc-derived iminosugars DNJNAc (**4**) and NJNAc (**5**).[7] We disclose herein a general synthetic strategy allowing access to α-homo-2-acetamido-1,2-dideoxynojirimycin (α-HNJNAc, **6**) and α-homo-2-acetamido-1,2-dideoxy-galactonojirimycin (**7**, α-HGJNAc).

Our groups and others[8] have exploited the ring isomerization of seven-membered polyhydroxylated azacycles to generate new or known piperidine iminosugars. This transformation, based on a β-amino alcohol rearrangement,[9] requires a free alcohol at the β-position and proceeds via a double S_N2 mechanism. We have previously used this process to access homoglyconojirimycins[10] and iminosugar *C*-glycosides.[11] Applying this strategy to a *cis* β,γ-dihydroxyazepane bearing an electron-donating group on the endocyclic nitrogen followed by the introduction of an azido group at C-2 could pave the way to the GlcNAc-derived 1,2-*cis* homoiminosugars. To this end, a stereoselective route to a D-arabino-like azacycloheptene was developed. Commercially available D-arabinofuranose derivative **8**[12] was olefinated and the resulting free alcohol inverted using Mitsunobu conditions to provide alcohol **9** after ester hydrolysis (66% over three steps). Esterification with triflic anhydride, followed by nucleophilic displacement with allylamine, produced the corresponding iminodiene that was protected as its *tert*-butyl carbamate to give diene **10** (66% over three steps). Ring-closing metathesis with Grubbs' first-generation catalyst in 1,2-dichloroethane at reflux afforded azacycloheptene **11** (85%). According to our

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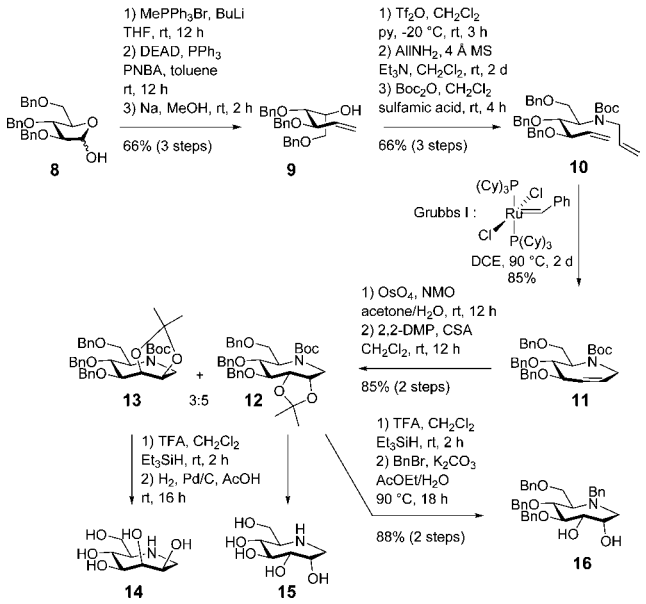
strategy, access to α-HNJNAc requires the preparation of the β,γ-dihydroxyazepane. Dihydroxylation of **11** with OsO_4 proceeded with a facial diastereoselectivity (5:3 ratio) similar to that observed for azepanes bearing a *N*-Cbz group.[13] As the separation of these diols proved to be difficult on a large scale, they were converted into the separable isopropylidene acetals **12** and **13**. Because of the presence of rotamers, the elucidation of the stereochemistry of acetals **12** and **13** and corresponding diols was difficult by NMR. This was achieved through the full deprotection of **12** and **13** to give the known pentahydroxylated azepanes **15** and **14**, respectively.[13] Removal of both the isopropylidene and Boc groups in **12** with TFA, followed by N-benzylation, gave the *N*-benzyl diol **16** (88% over two steps) ready for ring contraction (Scheme 1).

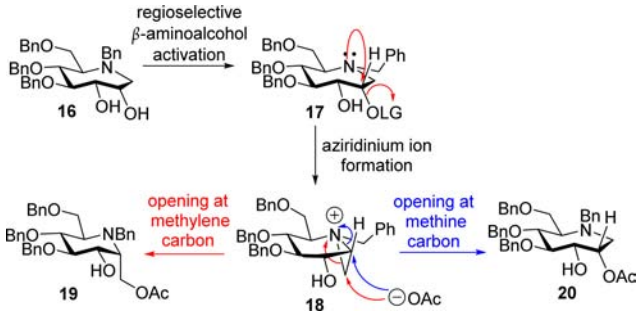
Scheme 1. Synthesis of Protected Azepanes 12 and 13



We have previously exploited the superior reactivity of the β-OH group over its γ-counterpart in syn β,γ-dihydroxyazepanes in order to achieve its selective protection.[10a] As a consequence, under β-amino alcohol rearrangement conditions, we expected the β-OH in **16** to be selectively activated and displaced by the endocyclic nitrogen to generate a transient fused piperidine–aziridinium ion **18**. Opening of the aziridinium ion by the acetate at the methylene carbon should provide the corresponding piperidine **19**. The acetylated azepane **20** resulting from attack of the aziridinium ring at the methine carbon could also be observed (Scheme 2).

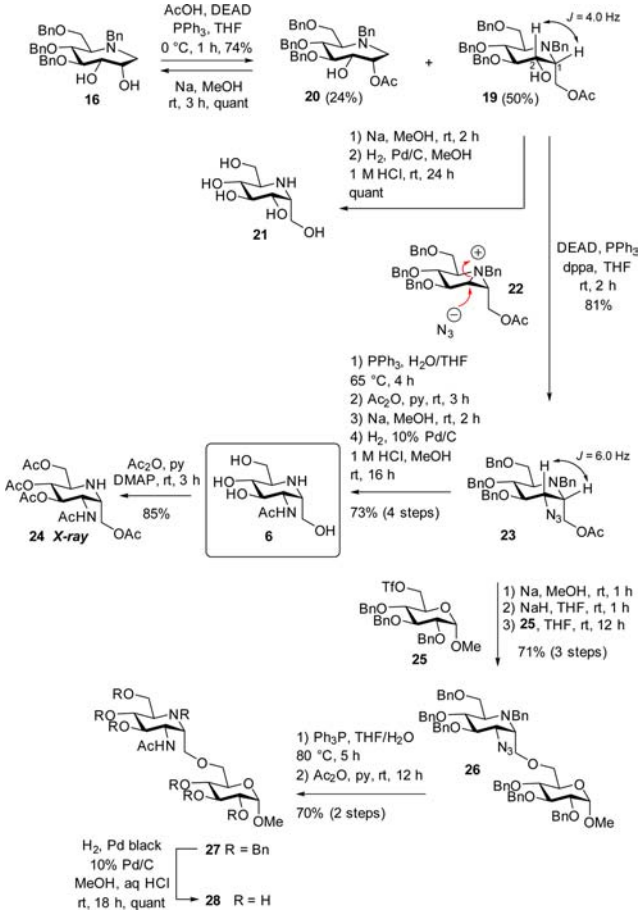
Satisfyingly, when diol **16** was treated with a small excess of AcOH, PPh_3, and DEAD in THF at 0 °C, the piperidine **19** was isolated in 50% yield along with azepane **20** (24%). Piperidine **19** displayed a small coupling constant ($J_{1,2}$ = 4.0 Hz) in agreement with a 1,2-*cis* relationship for the piperidine ring. To further confirm its structure, piperidine **19** was fully deprotected by deacetylation, followed by hydrogenolysis, to give the naturally occurring α-homonojirimycin (α-HNJ) **21**,[14] the ^{1}H NMR data for which agreed perfectly with that reported in the literature. The structure of azepane **20** was supported by the production of dihydroxyazepane **16** following its deacetylation with NaOMe in MeOH. Protection of the pseudoanomeric alcohol in **19** as methyl ester was exploited to investigate the azidation at the C-2 position. We relied on the hypothesis that nucleophilic

Scheme 2. Proposed Mechanism for the Ring Contraction of Azepane 16 Leading to Piperidine 19 and Azepane 20



displacement of the free OH at C-2 should also involve the anchimeric assistance of the endocyclic nitrogen to generate the transient bicycle **22** (Scheme 3). This bicycle would then be

Scheme 3. Synthesis of α-HNJNAc 6 and Pseudodisaccharide 28



attacked at the C-2 position, providing the thermodynamically stable six-membered ring. When piperidine **19** was treated with diphenyl phosphoryl azide (dppa), DEAD, and PPh_3 in THF, the 2-azidopiperidine **23**, displaying an α-D-gluco configuration according to the ^{1}H NMR coupling constants ($J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 10.1 Hz), was obtained in 81% yield. Conversion of the azido group into an acetamide (PPh_3 in THF/water then Ac_2O/py) followed by O-deacetylation and hydrogenolysis furnished the target α-HNJNAc **6** (73% over four steps) (Scheme 3). The

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structure of **6** was further confirmed by X-ray crystallography of the corresponding per-*O*-acetylated derivative **24** (Figure 2).

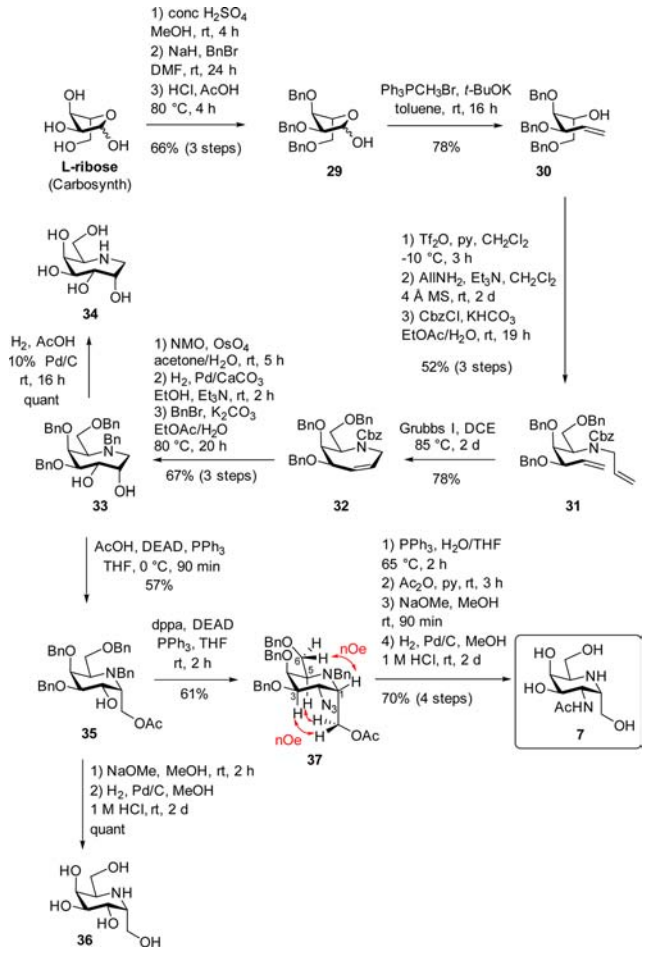
Figure 2. X-ray crystallography of iminosugar **24** (CCDC 1023880).

The main synthetic advantage of this new class of inhibitors over previously reported iminosugars that mimic GlcNAc is their ability to incorporate aglycons at the pseudoanomeric position to form chemically stable iminoglycoconjugates. We examined this capacity through the synthesis of a pseudodisaccharide. The anchimeric assistance of the endocyclic amine associated with the sensitivity of the acetamide to basic conditions required a specific coupling strategy. It should involve an aglycon partner bearing a leaving group and a nucleophilic homominosugar derivative bearing an azido group as a masked NHAc functionality. Piperidine **23** was O-deacetylated with sodium methoxide and treated with the known activated sugar **25**[15] to furnish the protected pseudodisaccharide **26** (71% over three steps). Subsequent generation of the acetamide group as described above (70% yield) provided compound **27** that was further hydrogenolyzed to afford the α-1,6-pseudodisaccharide **28** (Scheme 3).

Encouraged by these results, we used our strategy to access the α-homo-2-acetamido-1,2-dideoxygalactonojirimycin (α-HGJNAc), a GalNAc analogue that could interfere with human α-*N*-acetyl-D-galactosaminidase (α-GalNAcase) involved in Shindler–Kanzaki disease.[16] Starting from L-ribose (Carbosynth), glycosylation in methanol followed by perbenzylation and selective anomeric deprotection furnished furanose **29** (66% over three steps). Wittig olefination under classical conditions proved problematic[17] and needed optimization. While BuLi gave poor yields, the use of *t*-BuOK (2.5 equiv) in toluene at reflux provided alkene **30** in 78% yield. Introduction of allylamine as described above produced the corresponding diene that was protected as its benzyl carbamate to afford compound **31** (52% over three steps). Ring-closing metathesis gave the azacycloheptene **32** (78% yield) that furnished the required dihydroxyazepane **33** (67% over three steps) upon dihydroxylation (OsO_4, NMO) and protecting group interconversion. The stereochemistry of **33** was firmly established through its full deprotection to yield the known pentahydroxylated azepane **34**[18] (Scheme 4).

Application of the optimized ring-contraction conditions to diol **33** generated the desired piperidine **35** (57% yield). As the ^{1}H NMR spectrum of **35** contained broad signals that could not be easily assigned, the structure of **35** was established by achieving its full deprotection. It cleanly provided the known α-homogalactonojirimycin (α-HGJ, **36**), the spectroscopic data for which agreed perfectly with that reported in the literature.[19] The parallel introduction of an azido group at the C-2 position of piperidine **35** with dppa, DEAD, and PPh_3 furnished the azidopiperidine **37** in 61% yield while also retaining an α-D-*galacto* configuration as confirmed by the NOE effects observed between H-3 and the pseudoanomeric methylene group, H-5 and the pseudoanomeric methylene group, and H-1 and H-6, respectively. Final acetamide installation at C-2 and protecting

Scheme 4. Synthesis of α-HGJNAc 7



group removal afforded the target α-HGJNAc (**7**) (Scheme 4). Both α-HNJNAc (**6**) and α-HGJNAc (**7**) adopt a $^4C_1$ conformation in CD_3OD as illustrated by the key coupling constants ($J_{1,2}$ = 5.6 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 8.3 Hz, $J_{4,5}$ = 9.3 Hz for α-HNJNAc (**6**) and $J_{1,2}$ = 5.9 Hz, $J_{2,3}$ = 10.9 Hz, $J_{3,4}$ = 2.1 Hz for α-HGJNAc (**7**)). The α-HNJNAc (**6**), α-HGJNAc (**7**), and pseudodisaccharide **28** 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 1).

While pseudodisaccharide **28** is a poor inhibitor of these enzymes, α-HNJNAc (**6**) is a moderate inhibitor of β-*N*-acetylhexosaminidases, displaying two digit IC_{50}. The α-

Table 1. Concentration (in μM) of Iminosugars 6, 7, and 28 Giving 50% Inhibition of Various Glycosidases (IC_{50})

enzyme	**6**	**7**	**28**
β-*N*-acetylhexosaminidase			
human placenta	56	46	269
bovine kidney	67	36	310
HL-60	265	52	416
Jack bean	48	22	917
Aspergillus oryzae	NI	ND	NI
α-*N*-acetylgalactosaminidase chicken liver	NI	**1.1**	567

NI: no inhibition (less than 50% inhibition at 1 mM). ND: Not determined.

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HGJNAc (7) is a potent and rather selective α-*N*-acetylgalactosaminidase inhibitor (IC_{50} 1.1 μM).

In summary, the synthesis of 1,2-*cis* homoiminosugars derived from GlcNAc and GalNAc bearing an α configuration for the pseudoanomeric CH_2OH group has been achieved by exploiting a β-aminoalcohol rearrangement applied to a seven-membered iminosugar. This strategy also allows access to naturally occurring α-HGJ and α-HNJ. These derivatives can be coupled to various aglycon moieties and a pseudodisaccharide incorporating the α-HNJNAc has been obtained. These molecules increase the array of homoiminosugars available for biologists that could be used as probes to decipher the conformational itineraries and mechanisms of glycosidases.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, and X-ray crystallographic 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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