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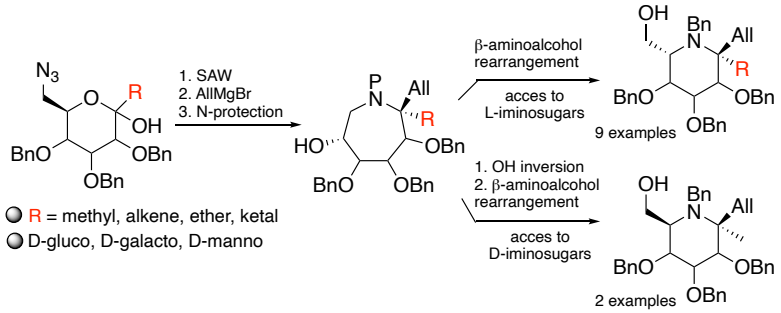
Supporting Information Placeholder



ABSTRACT: We report the synthesis of iminosugar *C,C*-glycosides starting from 6-azido-ketopyranoses. Their Staudinger-azaWittig-mediated cyclization provided bicyclic *N,O*-acetals which were stereoselectively opened with AllMgBr to afford β-hydroxyazepanes with a quaternary carbon α to the nitrogen. Their ring contraction via a β-aminoalcohol rearrangement produced the six-membered L-iminosugars with two functional handles at the pseudoanomeric position. Inversion of the free OH at the azepane level furnished the D-iminosugars.

Naturally occurring six-membered 1-deoxyiminosugars[1] constitute one of the most promising class of glycomimetics as therapeutic candidates.[2,3] They have been extensively used as non-covalent probes to decipher the mechanism of glycosidases by virtue of their mimicry of the oxocarbenium character of the enzyme transition state.[4] Their potential has been translated into approved medicines to treat diabetes[5] and rare diseases.[6] In the search for other therapeutic candidates, mimicking the aglycon moiety of the enzymatic substrate with the introduction of a pseudo-anomeric substituent has been pursued, leading to a vast array of so-called iminosugar *C*-glycosides.[7] Within this family, introduction of an extra carbon substituent at the pseudoanomeric position to yield iminosugar *C,C*-glycosides (Figure 1a) is worth investigating as it might lead to new potent and selective glycosidase inhibitors. The scarce examples reported in the literature emphasize the difficulty to predict the impact of the quaternarization of the carbon adjacent to the nitrogen in polyhydroxylated piperidines on their glycosidase inhibition profile. Indeed, this structural modification either abolished inhibition of the parent iminosugar[8] or led to improved inhibitory potency.[9,10] To the best of our knowledge, there are only two reports, respectively using a chemoenzymatic route (Wong)[11] and an allylic azide rearrangement (Murphy),[12] of six-membered iminosugars displaying a complete hydroxyl pattern (Figure 1a). In sharp contrast with the broad palette of methods allowing access to iminosugar *C*-glycosides,[13] and sugar *C,C*-glycosides,[14,15,16] syntheses of iminosugar *C,C*-glycosides are scarce illustrating the challenging introduction of a quaternary carbon atom alpha to a nitrogen atom.[17,18,19] Indeed, a vast array of so called C-branched iminosugars has been reported[20] in which a quaternary carbon at C-2, C-3 or C-4 positions has been built. When the C-1 position is involved, the iminosugars usually lack one hydroxyl group of the parent sugar and/or display two identical pseudoanomeric appendages.[10,21]

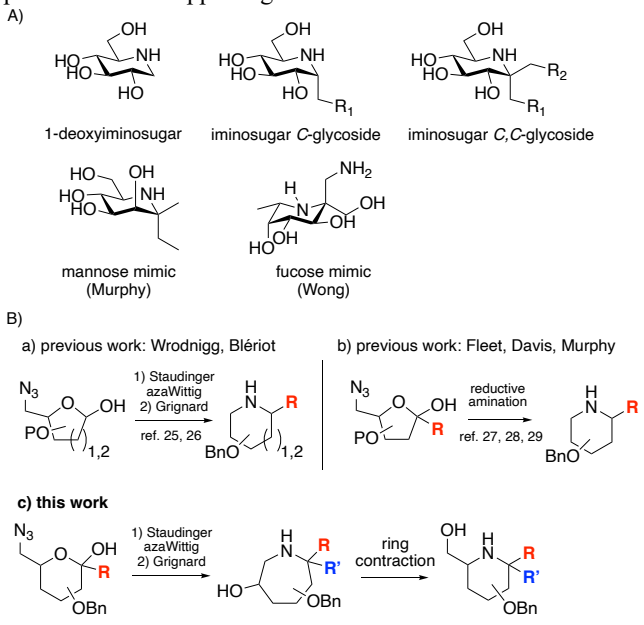
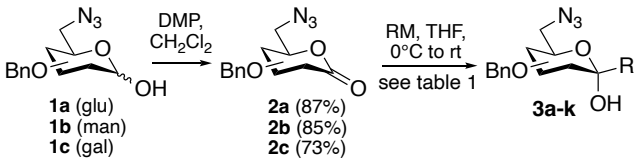
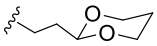
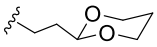


Figure 1. A) General structures of a 1-deoxyiminosugar, iminosugar *C*-glycoside and iminosugar *C,C*-glycoside and iminosugar *C,C*-glycosides with a full sugar hydroxyl pattern in the literature; B) a) and b) Synthetic routes previously developed from 6-azidolactols to iminosugar *C*-glycosides; C) Strategy explored herein to access iminosugar C,C-glycosides.

In this context, we were interested in developing a robust route to original iminosugar *C,C*-glycosides that would enable the stereo-controlled introduction of two distinct substituents that could be further decorated independently after their installation on the iminosugar core. We hypothesized that, if these two substituents allow subsequent chemical diversification, such scaffold would constitute an attractive platform to target glycosyl transferases considering the ternary nature of their positively charged transition state,[22,23] a feature that has been mimicked by bisubstrate inhibitors.[24] Azidolactols have been useful precursors to access iminosugar *C*-glycosides either through a Staudinger-AzaWittig / Grignard (SAWG) sequence[25,26] or through the reductive amination of a 6-azidoketosugar (Figure 1B).[27,28,29] We postulated that applying the SAWG sequence to a 6-azidoketosugar should give access to a seven-membered iminosugar *C,C*-glycoside, which upon β-aminoalcohol rearrangement would furnish the corresponding piperidine (Figure 1C). We anticipated that the sequential introduction of the two pseudoanomeric substituents should take place with high stereocontrol according to previous results obtained during the synthesis of iminosugar *C*-glycosides.[26] To examine the scope of this approach, known azidolactols with a respective D-gluco,[30] D-manno[31] and D-galacto[32] configuration **1a–c** were synthesized in 5 to 6 steps following literature procedures and were further oxidized with Dess-Martin periodinane to furnish the corresponding 6-azidolactones **2a**–**c** in good yields (73-87%). Their reaction with a range of commercially or easily available organolithium and Grignard reagents bearing diverse carbon chains (methyl, vinyl, allyl, homoallyl, alkyne, propargyl) or masked functions (silyl ether, methoxymethyl ether, ketal) yielded the corresponding 6-azido-ketopyranoses **3a–k** in moderate to excellent yields (41-98%) (Table 1). Regarding the anomeric configuration of 6-azidoketopyranoses **3**, the closely related C-5 benzyloxymethyl derivatives,[33,34] have been reported to exist predominantly as α-anomers (>90%). To elucidate the anomeric stereochemistry of compounds **3** (that does not impact their subsequent chemical transformation), we performed their indepth NMR analyses (HMBC, J resolved-HMBC, NOESY) and found that all compounds adopt predominantly an α-configuration except mannose derivative **3b** for which we could not conclude about its anomeric configuration according to NMR experiments (see Supporting Information).

Table 1. Synthesis of 6-azido ketopyranoses **3a–k**

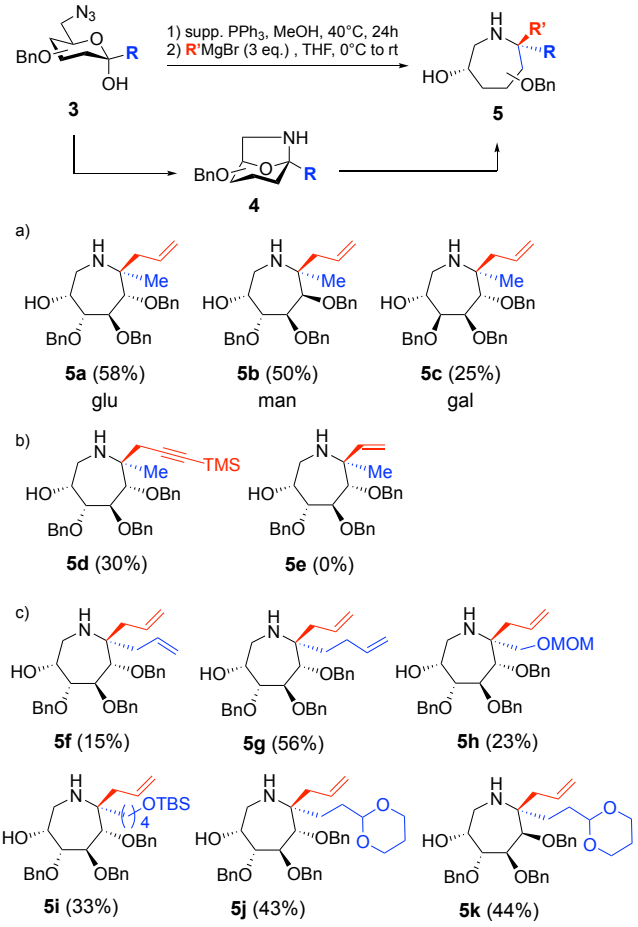


Entry	**2**	R	**3**	yield (%)
1	2a	Methyl	3a	90
2	2b	Methyl	3b	68
3	2c	Methyl	3c	84
4	2a	Vinyl	3d	69
6	2a	propargyl TMS	3e	65
7	2a	allyl	3f	98
9	2a	homoallyl	3g	85
10	2a	CH_2OMOM	3h	41
11	2a	$(CH_2)_4OTBS$	3i	85
12	2a		3j	92
13	2b		3k	70

The SAW-mediated cyclisation of azidolactols **3a–k** followed by the nucleophilic opening of the resulting bicyclic hemiaminal was then examined. The D-gluco configured ketopyranose **3a** bearing an anomeric methyl group was used as a model compound and AllMgBr selected as the nucleophile of choice based on our previous experience with bicyclic hemiaminals[26] and the possibility to convert the allyl group into other functional groups.[35,36,37] Solvent and phosphine screening identified methanol and supported PPh_3 as the best combination for the SAW step, providing the bicyclic hemiaminal **4a** in 70% yield (see Table S1). Opening of **4a** with AllMgBr afforded the α,α-disubstituted azepane **5a** in 65% yield (45% yield over two steps). This transformation reached 58% yield when the hemiaminal **4a** was not isolated. This two steps sequence was then applied to the D-manno- and D-galacto-configured azidolactols **3b** and **3c** to afford the azepanes **5b** and **5c** in satisfactory (50%) and low (25%) yield over two steps respectively (Scheme 1a). The poor yield obtained for **5c** was tentatively attributed to a steric clash between the axial 4-OH and the 1,6 bridge of the bicyclic hemiaminal. Addition of other unsaturated organometallic reagents on hemiaminal **4a** was also evaluated. Use of silylated propargyl magnesium bromide produced azepane **5d** in modest 30% yield while treatment with vinyl magnesium bromide failed to provide the corresponding azepane **5e** (Scheme 1b). This sequence, using AllMgBr as nucleophile, was then applied to ketopyranoses **3d–k** bearing a functional group at the anomeric position. Compounds **3d** and **3e** with a vinyl and propargyl aglycon moiety respectively failed to generate the corresponding bicyclic hemiaminals. The other ketopyranoses **3f–k** were successfully converted to the corresponding α,α-disubstituted azepanes **5f–k** in modest (15%) to good (56%) yields over two steps (Scheme 1c). Importantly, all compounds were obtained as single stereoisomers but the stereochemistry of the quaternarized centre could not be determined by NMR at this stage because of the inherent ring flexibility of the polyhydroxylated azepane.[38] These seven-membered iminosugar *C,C*-glycosides are of interest not only as glycosidase inhibitors once deprotected but also because they can be used to access piperidines through ring contraction. Their ring contraction exploiting a β-aminoalcohol rearrangement,[39] which requires installation of an electron donating group on the nitrogen, was scrutinized next (Scheme 2). *N*-benzylation was performed under phase transfer conditions (BnBr, $KHCO_3$, KI, $AcOEt/H_2O$) to provide the *N*-benzyl azepanes **6a–d** and **6g–k** (see Supporting Information) in moderate (41%) to very good (87%) yield depending on the steric hindrance caused by the two pseudoanomeric substituents. Their skeletal rearrangement was then achieved with trifluoroacetic anhydride (TFAA) and triethylamine in toluene at 120°C, producing a transient fused piperidine-aziridinium ion intermediate that was opened at the

methylene carbon by the released carboxylate, affording the corresponding six-membered L-iminosugars **7a–d** and **7g–k** in a stereo-retentive manner in moderate (33%) to good yields (70%) after ester hydrolysis.

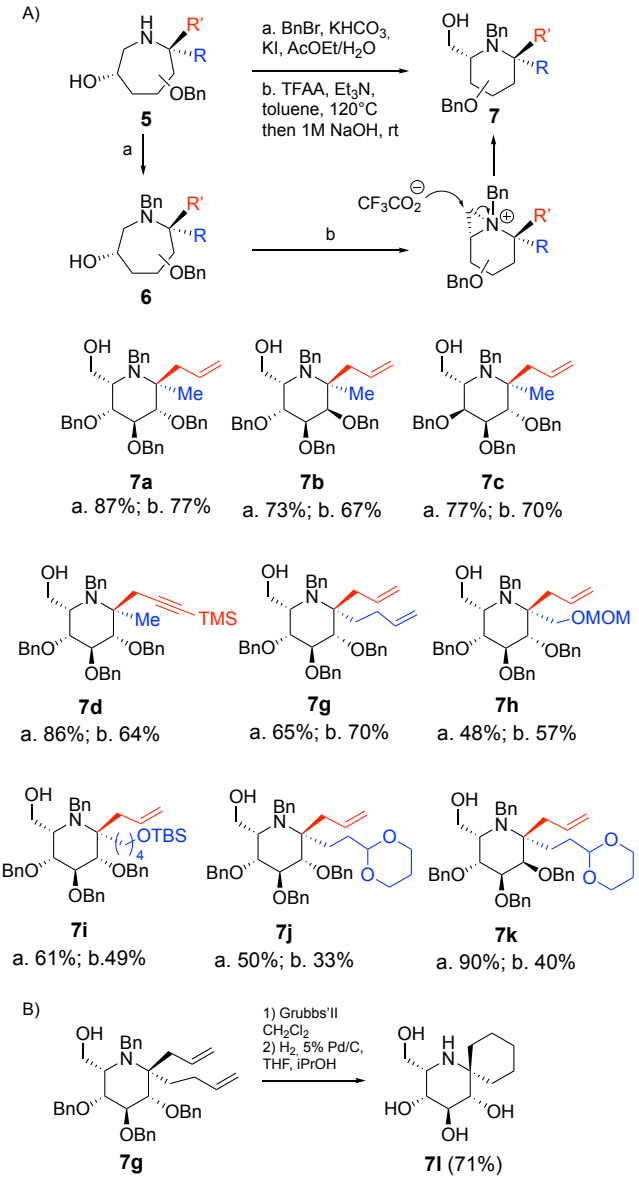
Scheme 1. Synthesis of α,α-disubstituted azepanes 5a–k



The stereochemistry of the quaternary pseudoanomeric position in the piperidine derivatives was firmly established by extensive NMR analysis (See Supporting Information) and then deduced for the azepane precursors. In all compounds, the allyl group is pointing above the piperidine ring, suggesting an attack of the seven-membered imine by AllMgBr from the upper side of the azepane ring. A combination of stereoelectronic and torsional effects, observed for related monosubstituted seven-membered oxocarbenium ions and taking place at the seven-membered iminium level, could explain this stereochemical outcome.[40] To rapidly illustrate the synthetic potential of an iminosugar bearing two functional handles at the pseudoanomeric position, the ring closing metathesis of piperidine **7g** followed by hydrogenolysis was performed to afford the spirocyclohexyl iminosugar **7l** in 71% yield, a type of scaffold scarce in the literature.[41]

Importantly, epimerization of the free OH in azepane **5** followed by ring contraction should pave the way to D-iminosugars *C,C*-glycosides (Scheme 3). Accordingly, azepane **5a** was protected as its benzyl carbamate **8a** (80% yield) and next submitted to Mitsunobu conditions followed by hydrogenolysis to remove the Cbz group that took place with concomitant reduction of the allylic moiety. The resulting azepane **9a** was obtained in 51% yield over three steps and its structure was firmly established by X-ray crystallography, confirming the inversion of the free OH group and the stereochemistry at C-1 position.

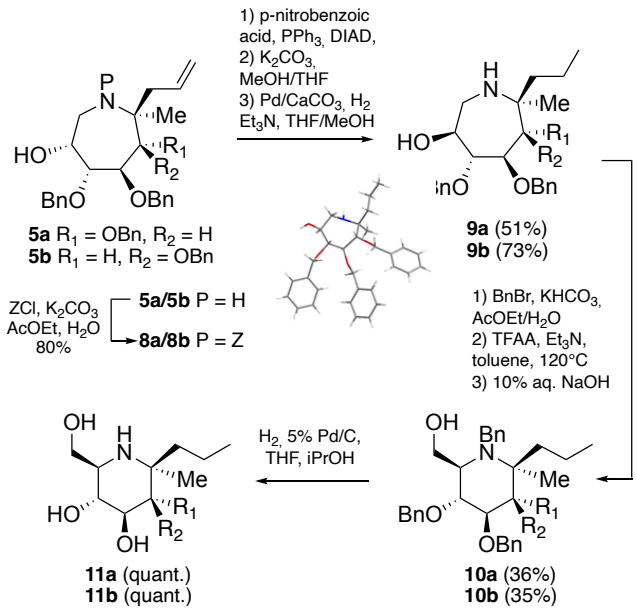
Scheme 2. A) Access to protected α,α-disubstituted six-membered L-iminosugars 7a–d and 7g–k; B) Synthesis of spirocyclohexyl L-iminosugar 7l



Ring contraction of compound **9a** was achieved next via *N*-benzylation followed by free OH activation with TFAA to afford the protected piperidine **10a** in 36% over three steps. Final hydrogenolysis furnished the known α,α-methyl, propyl 1-deoxynojirimycin **11a** (quantitative yield), a compound that was obtained as a mixture of anomeric diastereoisomers by Murphy.[12] To exemplify this route, the same sequence was applied to azepane **5b** to furnish the D-manno-configured iminosugar **11b** via the carbamate **8b** (80%), the amine **9b** (73%) and the piperidine **10b** (35%).

In conclusion, we have disclosed the synthesis of six-membered L-iminosugars quaternarized at the pseudoanomeric position. The strategy developed herein, compatible with D-gluco and D-manno-configured starting monosaccharides, allows the stereocontrolled stepwise introduction of two pseudoanomeric substituents. The observed stereochemical outcome is rationalized on the basis of structural and stereoelectronic considerations that have been invoked for related seven-membered oxocarbenium ions. Some of these substituents could be further derivatized to increase the structural diversity at the C-1 position as illustrated by the synthesis of spirocyclic compound **12**. Finally, inversion of the free OH at the azepane level gives access to the epimeric D-iminosugar *C,C*-glycosides.

Scheme 3. Synthesis of α,α-disubstituted D-iminosugars 11a and 11b and X-ray structure of compound 9a



Supporting Information

Experimental procedures, characterization data for compounds **1–11**, copies of ^{1}H, NOESY and ^{13}C NMR spectra for compounds **1–11**; X-ray crystallography of compound **9a** (CCDC 2122405).

Notes

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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