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Hybrid sugars as glycosidase inhibitors en route to 2-deoxy-2-amino *C*-glycosyl amino acids

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Abstract—Sugar-azasugar hybrid molecules made up of D-galactose with nojirimycin-δ-lactam and pyrrolidine analogues are synthesized using intramolecular cyclization as a key step from 2-nitro galactal and found to be glycosidase inhibitors. Further, some of the intermediate compounds are converted into 2-deoxy-2-amino *C*-glycosyl glycines and *C*-glycosyl alanines.

Polyhydroxylated pyrrolidine and piperidine alkaloids have attracted considerable attention due to their ability to inhibit glycosidases.[1a] A variety of analogues of these compounds have been synthesized and identified as important therapeutic targets with applications in the treatment of influenza,[2] cancer,[3] AIDS[4] and diabetes.[5] In the design and synthesis of analogues[1b] resembling transition states that are involved during glycoside hydrolysis, work has focussed on the synthesis of molecules, which mimic the assumed charge, whilst other work has focussed on imitating the geometry of the transition state. Thus, the transition-state analogues resemble a flattened heterocyclic ring through sp^2 hybridization at the anomeric carbon and mimic a distorted half-chair conformation. Several groups have tried to introduce new inhibitors, which exist in the half-chair conformation. In this direction amidines,[6] amidoximes,[7] hexono δ-lactams,[8] imidazoles,[9] triazoles[10] and tetrazoles[11] have been synthesized and evaluated as glycosidase inhibitors. Due to the emerging importance of hybrid molecules[12] and our recent report of hybrid sugars (D-galactose with deoxynojirimycin[13]) as glycosidase inhibitors it is of interest to prepare a hybrid of transition-state analogues possessing a sugar unit. In this letter, we report the syntheses of the hybrids of 3-deoxynojirimycin δ-lactam and 1,4-dideoxy-1,4-imino-D-lyxitol and L-ribitol with D-galactose as potential glycosidase inhibitors. These are expected to mimic the transition state in terms of geometry.

Thus, the synthesis started with 2-deoxy-2-amino allyl-*C*-glycoside **1**, which was obtained from 3,4,6-tri-*O*-benzyl-2-nitrogalactal, by reaction with allylzinc bromide at −60 °C as earlier reported[13] by us. Dihydroxylation of **1** with OsO_4 and NMO gave the corresponding diols in a 1:1 ratio as an inseparable mixture (Scheme 1). However, protection of the primary hydroxyl group with a trityl group permitted the separation of the diastereomers **2a** and **2b** by SiO_2 column chromatography. After separation, the trityl groups in **2a** and **2b** were cleaved with 1% HCl in $CHCl_3$ and a subsequent selective oxidation of the primary alcohol with TEMPO gave the corresponding α-hydroxy acid, which was esterified using diazomethane to afford δ-nitro-α-hydroxy esters **3a** and **3b**, respectively. Reduction of the nitro group with Zn–HCl in THF–AcOH followed by aqueous basic work-up (aq $NaHCO_3$) gave bicyclic lactams **4a** and **4b** whose ^1H NMR and NOESY spectra[14] were used to assign the stereochemistry. Thus, proton H-3 of compound **4a** appeared as a doublet of doublet ($J = 11.7$ and 6.6 Hz) indicating that it was axially oriented coupling to one axial and one equatorial proton.

Disappearance of the peaks at 1738 and 1552 cm^{-1} and the appearance of a lactam peak at 1668 cm^{-1} in the IR spectrum confirmed the cyclization. Likewise, lactam **4b** was found to possess the configuration as shown in Scheme 1. Attempts to debenzylate lactams **4a** and **4b** using 10% palladium on activated carbon in MeOH containing HCl were unsuccessful. On the other hand, hydrogenolysis of **4a** and **4b** using 10% palladium on activated carbon in CH_3COOH gave the desired

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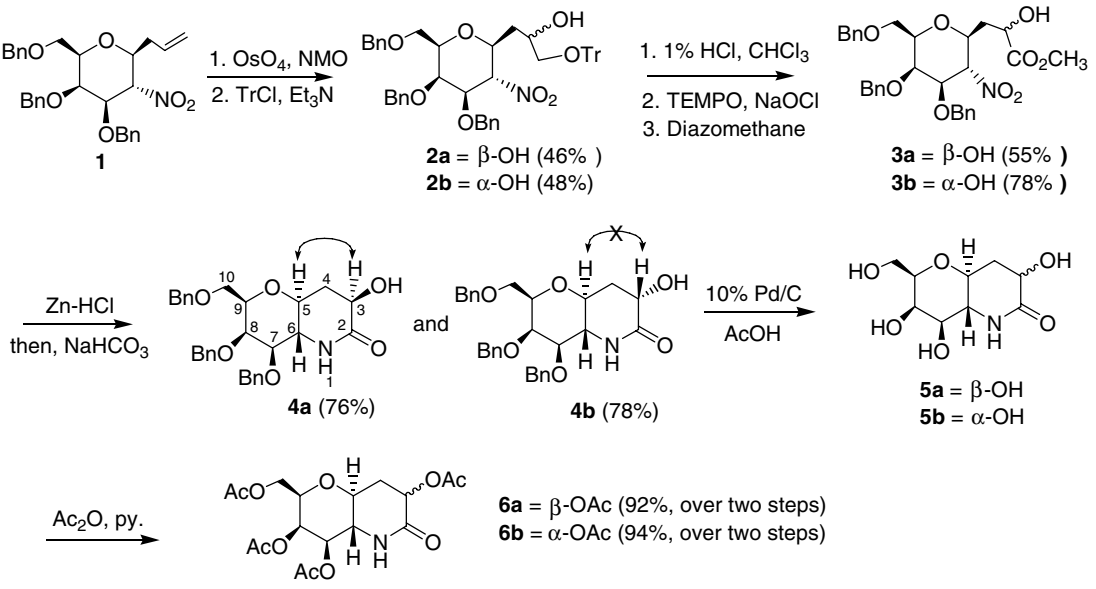
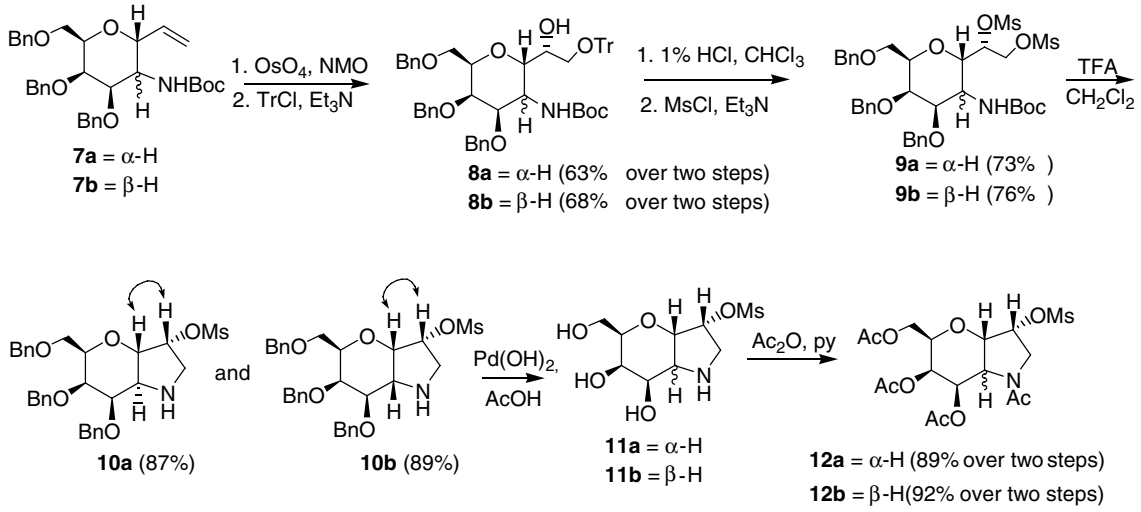


Scheme 1.

tetrahydroxy lactams **5a** and **5b** in 95% and 98% yield, respectively, which were characterized as the corresponding acetyl derivatives **6a** and **6b**.

For the synthesis of hybrid pyrrolidine analogues with D-galactose, we employed 2-deoxy-2-amino-*C*-vinyl glycosides **7a** and **7b** as the starting materials (Scheme 2), which were earlier prepared by us[13] from 3,4,6-tri-*O*-benzyl-2-nitrogalactal. Dihydroxylation of **7a** and **7b** with OsO_4 and NMO followed by trityl protection of the primary hydroxyl group with trityl chloride and triethylamine gave in each case a mixture of diastereomers in a 3:1 ratio. The formation of the major *erythro* isomer **8a** or **8b** is in agreement with Kishi's empirical rule[15a,b] for the dihydroxylation of allylic ethers due to preferential approach[15c] of OsO_4 from the face opposite to that of the allylic ring oxygen bond. Detritylation of compounds **8a** and **8b** with 1% HCl in $CHCl_3$ at 0 °C followed by mesylation of the diols with MsCl and triethylamine gave dimesylates **9a** and **9b**, respectively. Deprotection of the NHBoc group of each of these compounds using trifluoroacetic acid in dichloromethane furnished **10a** and **10b** in 87% and 89% yields, respectively. The presence of a singlet at δ 3.01 for the –OMs group and the absence of the Boc group signal at δ 1.40 in the ^{1}H NMR spectrum of **10a** suggested that cyclization to the pyrrolidine analogue may have taken place. This was further confirmed from its mass spectrum, which showed the presence of a peak at *m*/*z* 576 $[M+Na]^+$. Likewise, the structure of compound **10b** was confirmed. The stereochemical assignments were made on the basis of ^{1}H NMR and NOESY experiments.[14] Hydrogenolysis of **10a** and **10b** with 10% palladium hydroxide on activated carbon gave the hybrid



Scheme 2.

derivatives of L-ribitol and D-lyxitol, **11a** and **11b**, respectively, which were characterized as their acetyl derivatives **12a** and **12b** (Scheme 2).

The hybrid molecules **5a**, **5b**, **11a** and **11b** were then evaluated against a range of commercially available glycosidases, namely, α-glucosidase (rice), β-glucosidase (almonds), α-galactosidase (coffee beans) and β-galactosidase (bovine). The IC_{50} values obtained are summarized in Table 1. D-Mannonolactam **5b** showed inhibition towards only α-glucosidase and D-gluconolactam **5a** showed inhibition towards β-galactosidase only.

The hybrid of L-ribitol, that is, **11a** was found to be specific towards galactosidases and was not active towards glucosidases. On the other hand, **11b** inhibited all the enzymes tested apart from α-glucosidase. Although the inhibition was moderate, it was expected that structure modification would lead to improved inhibition.

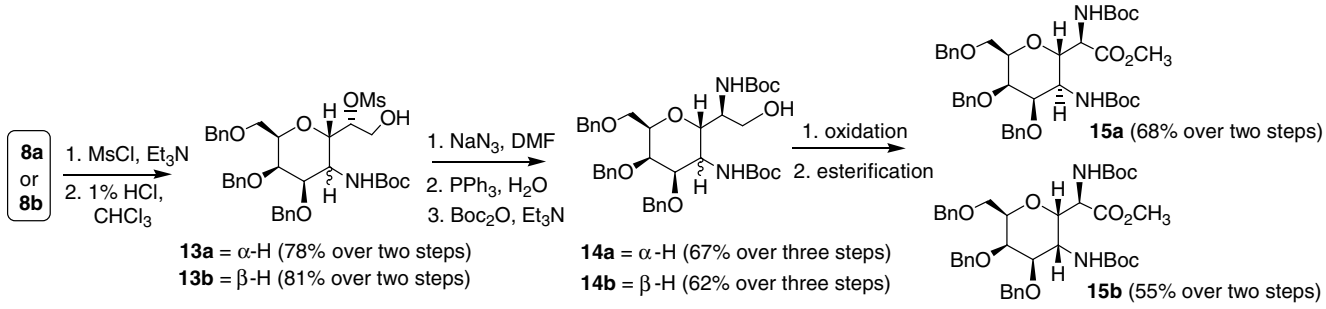
Table 1. IC_{50} (mM) for compounds **5a**, **5b**, **11a** and **11b**

Enzyme	5a	5b	11a	11b
α-Glucosidase (rice)	NI	3.3	NI	NI
β-Glucosidase (almonds)	NI	NI	NI	9.4
α-Galactosidase (coffee beans)	NI	NI	7.8	9.8
β-Galactosidase (bovine)	25.4	NI	18.2	5.1

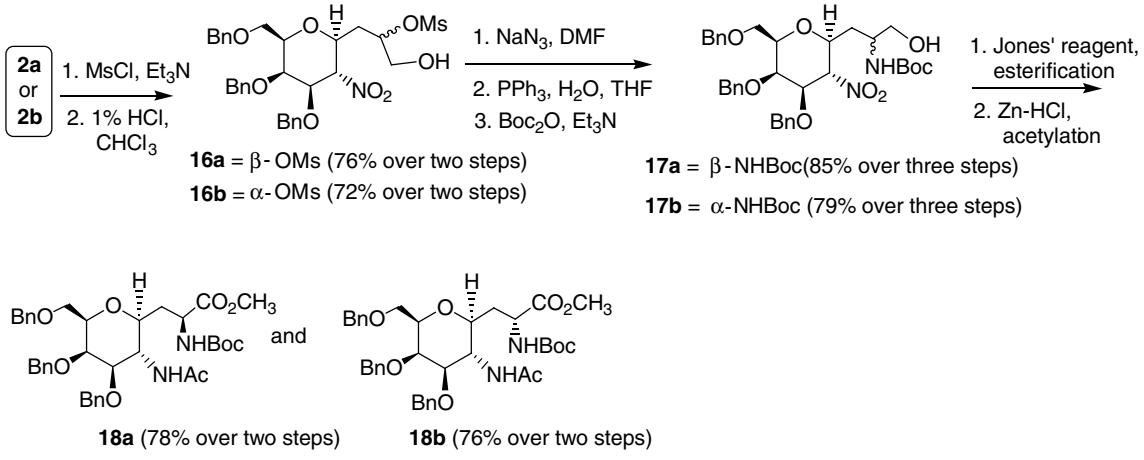
NI = no inhibition.

The growing interest in using artificial glycopeptides[16] over their natural counterparts, which are of low metabolic and chemical stability, and our current interest[17] in *C*-glycosyl amino acids led us to synthesize 2-deoxy-2-amino-*C*-glycosyl glycines and 2-deoxy-2-amino-*C*-glycosyl alanines, respectively, from compounds **8** and **2** by converting the secondary alcohol into an amine and the primary alcohol into an acid. Glycosyl amino acids with an additional amino group at C-2, that is, 2-deoxy-2-amino-*C*-glycosyl amino acids[18] would be attractive synthons for constructing artificial glycopeptides as an additional amino group can be utilized to construct the branched oligomeric peptides.[19]

Thus, compounds **8a** and **8b** were treated with MsCl and triethylamine followed by detritylation with 1% HCl in $CHCl_3$ leading to mesylates **13a** and **13b**, respectively. Replacement of the mesylate groups with an azide moiety gave the corresponding azides, via S_N2 substitution,[20] whose reduction with Ph_3P–H_2O followed by protection of the amino functionality as NHBoc gave alcohols **14a** and **14b**. Finally, the oxidation of the primary alcohols **14a** (under Jones' conditions) and **14b** (with TEMPO) gave the carboxylic acids, which were then esterified with diazomethane to give 2-deoxy-2-amino *C*-glycosyl glycines **15a** and **15b**, respectively. The stereochemistry of the newly generated chiral centres in these amino acids was established based on the ^1H NMR and NOESY spectral data[14] of the corresponding bicyclic derivatives **10a** and **10b** (Schemes 2 and 3).



Scheme 3.



Scheme 4.

For the synthesis of 2-deoxy-2-amino-*C*-glycosyl alanines **18a** and **18b** (Scheme 4), we treated compounds **2a** and **2b** with MsCl and triethylamine followed by detritylation, which gave alcohols **16a** and **16b**. Replacement of the mesylate group by azide, reduction of the azido group followed by protection as NHBoc gave amino alcohols **17a** and **17b**[20] in 85% and 79% yields, respectively. Oxidation of **17a** and **17b** using Jones' reagent gave the corresponding acids, which were esterified using diazomethane. Finally, reduction of the nitro group with zinc–hydrochloric acid in tetrahydrofuran-acetic acid to the amine and subsequent protection as the acetates gave the 2-deoxy-2-amino-*C*-glycosyl alanines **18a** and **18b** in 78% and 76% yields, respectively. The stereochemistry of the *C*-glycosyl alanines **18a** and **18b** was confirmed by analyzing the spectra[14] of the corresponding bicyclic derivatives **4a** and **4b** (Scheme 1).

In summary, this letter describes the first example of the synthesis of the hybrids of nojirimycin δ-lactam and pyrrolidine with D-galactose and their evaluation against a variety of enzymes, which has shown them to be a new class of glycosidase inhibitors. Although the enzyme inhibition activity is moderate, it may be possible to improve the same by appropriately changing the structural features of these molecules. Work in this direction is being pursued. Additionally, 2-deoxy-2-amino-*C*-glycosyl glycines and alanines have been synthesized using a general strategy. This new class of amino acids can be useful in modifying the properties of certain oligopeptides by virtue of the presence of a stable C-glycosidic linkage at C-1 and an additional amino group at C-2.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedures and ^{1}H and ^{13}C NMR spectra of the compounds synthesized) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.024.

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19. For sugar diamino acids see: Sicherl, F.; Wittmann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 2096.
20. Compounds **14a** and **17b**, obtained from mesylates **13a** and **16b** by reacting with NaN_3, were converted to the corresponding cyclic compounds **19** and **20** (see the Supplementary data), respectively, whose spectral data

(this data is abstracted from the Ph.D. thesis of Dr. K. Jayakanthan, Ph.D. thesis entitled 'Synthesis of unnatural glycosamino acids and glycosidase inhibitors' April 2006, Indian Institute of Technology, Kanpur) and NOE experiments clearly indicated that the azide displacements had taken place via S_N2 substitution confirming the stereochemistry as shown in **14a** and **17b**. Based on this information we infer that the stereochemistry in compounds **14b** and **17a** is also as shown, that is, via S_N2 displacement.