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A convenient synthesis of novel aza-*C*-disaccharide analogues

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ABSTRACT

Novel aza-*C*-disaccharide analogues have been conveniently synthesized by using the isoxazoline-linked *C*-disaccharide derivatives as the intermediates. Firstly, the C=N of isoxazoline was reduced to C–N by using DIBAL-H as reducing agent, then followed by the tandem multi-step reactions through catalytic hydrogenation with $Pd(OH)_2/C$ involving debenzylated, reductive cleavage of the N–O, condensation–cyclization of the aldehyde and the in situ generated amine group to form imine C=N and then C=N hydrogenation to form C–N, thus providing a practical and new access to the synthesis of novel aza-*C*-disaccharide analogues.

Azasugar (iminosugar) is a kind of carbohydrate mimics which has remarkable biological properties, and some aza-disaccharides exhibit excellent selective glycosidase inhibition.[1] In order to overcome the instability of the *O*-glycosides moiety toward acidic or enzymatic hydrolysis, design and synthesis of novel stabile aza-*C*-disaccharides is very important for the development of glycosidase inhibitors which have high activity and selectivity. Aza-*C*-disaccharide (imino-*C*-disaccharide), which has the combined property of azasugar and *C*-glycoside, is expected to be inert toward acidic or enzymatic hydrolysis while still possessing strong binding properties of the parent azasugar. Therefore, these sugar mimics may have improved effectiveness and selectivity compared with that of the well known azasugar inhibitors.[1] Since the first example of this class of sugar mimics has been prepared by Johnson and co-workers[2] applying the Suzuki reaction, several synthetic approaches toward this class of compounds have been reported, the main synthetic strategy was to form C–C bond by various reactions of sugar with azasugar, such as reductive amination,[2–4] Suzuki coupling,[5,6] Wittig condensation,[7] and cycloaddition to nitrones.[8–13] In recent years, 1,3-dipolar cycloaddition reaction has been widely used in the synthesis of carbohydrate derivatives including nitrogen atom.[14,15] We have reported some synthesis of functionalized *C*-glycoside derivatives via the 1,3-dipolar cycloaddition[16–20] of sugar-derived alkenes to nitrone or nitrile oxides. Herein, we use the 1,3-dipolar cycloaddition of α-allyl-*C*-glycoside with sugar-derived nitrile oxide to build the structure of *C*-disaccharide, and introduce nitrogen atom at the same time, and then use reduction and catalytic hydrogenation, the isoxazoline C=N—O reduction, condensation, reduction again to obtain the novel aza-*C*-disaccharide analogues.

The synthesis of aza-C-disaccharide analogues: The isoxazoline-linked pseudo disaccharide derivatives ((5*S*)-3-(benzyl 2,3-*O*-isopropylidene-4-*C*-5-deoxy-D-lyxofuranosidyl)isoxazoline-5-yl) methyl 2,3,4,6-tetra-*O*-benzyl-α-*C*-D-glucopyranoside (**1a**) and its 5*R* diastereoisomer (**1b**) were prepared via the 1,3-dipolar cycloaddition of allyl 2,3,4,6-tetra-*O*-benzyl-α-*C*-D-glycopyranose with sugar-derived nitrile oxides using glucose and mannose as starting materials following the reported procedures[20] (Scheme 1).

The synthesis of aza-*C*-disaccharide derivatives was explored from compound **1a** as shown in Scheme 1. We attempted to obtain the target molecule using one pot multi-step tandem reaction, debenzylation, C=N double bond reduced to C–N bond, N–O bond cleavage to form amine, and then reductive amination directly by $Pd(OH)_2/C$ catalytic hydrogenation of **1a**, but only obtained the isoxazoline-linked pseudo disaccharide derivative. And after several reducing agents[21–25] $LiAlH_4$, Raney Ni, Zn/AcOH, etc., have been explored, we did not succeed in N–O bond cleavage in **1a**. So we applied the indirect method, that is to reduce the C=N double bond to C–N bond using DIBAL-H as reducing agent to get the intermediate **2a**, and then obtain the aza-*C*-disaccharide derivatives **3a** using tandem multi-step reactions involving debenzylation, N–O bond cleavage to form amine, and then intramolecular condensation–cyclization of the aldehyde and the in situ generated amine group to form imine C=N and then C=N hydrogenation to form C–N, etc., four steps reaction by $Pd(OH)_2/C$ catalytic hydrogenation. To

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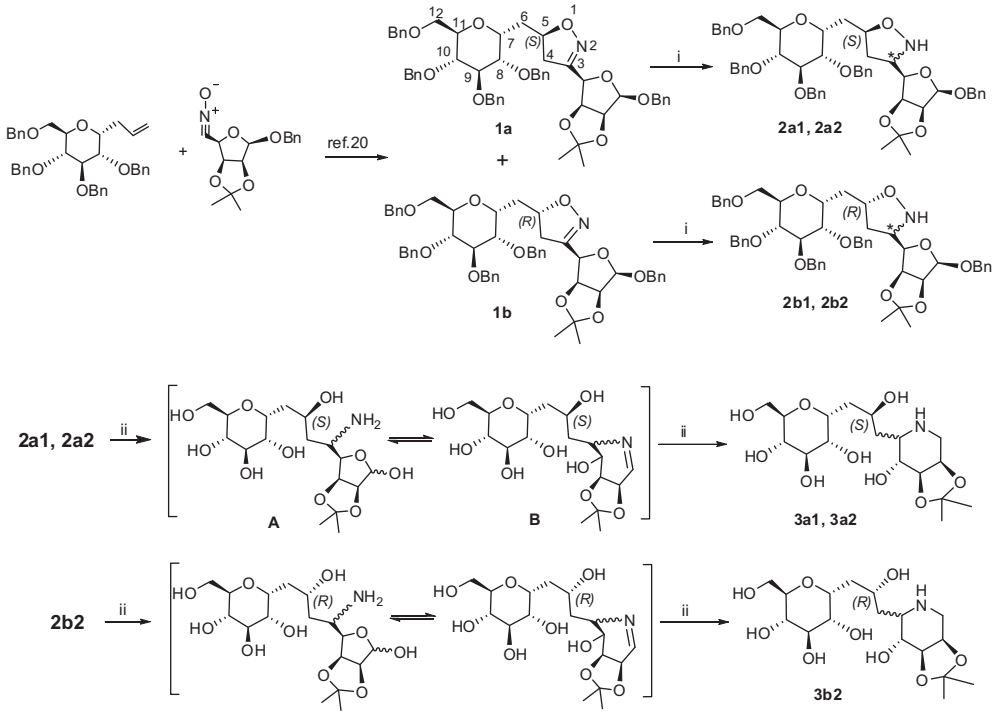

Scheme 1. Reagents and conditions: (i) DIBAL-H (in cyclohexane), CH_2Cl_2, −5 to −10 °C, 15 min; (ii) MeOH–HCl (c_{HCl} = 0.5%), $Pd(OH)_2/C$, H_2, rt, 12 h.

do so compound **1a** was dissolved in CH_2Cl_2, then cooled to −5 to −10 °C under N_2 atmosphere, the solution of DIBAL-H in cyclohexane was added dropwise, and the mixture was stirred 15 min. to afford two diastereomers, after using column chromatography to obtain the compounds **2a1** (24.0%) and **2a2** (72.0%). Following the above procedure, the compounds **2b1** (9.7%) and **2b2** (87.3%) were afforded from **1b** in the high yield, almost quantitation. Then the isoxazolidine-linked pseudo disaccharide derivative **2a1** was dissolved in MeOH–HCl (c_{HCl} = 0.5%), a catalytic amount of $Pd(OH)_2/C$ was added. The mixture was stirred under H_2 atmosphere for 12 h to afford the corresponding aza-*C*-disaccharide derivative **3a1** in high yield (62%). Under the same condition, the one-pot reaction of the isoxazolidine-linked pseudo disaccharide derivatives **2a2** and **2b2** was carried out to afford the corresponding aza-*C*-disaccharide derivatives **3a2** (61%) and **3b2** (64%).

*The structures of compounds **2** and **3***: The structures of **1a** and **1b** have been confirmed using single-crystal X-ray crystallography and ^{1}H NMR, ^{13}CNMR at C-5[20], in which C-5 adopted the *S* (**1a**) and *R* (**1b**) configuration. The structure of compounds **2** and **3** were determined by analyses of their spectral data of ^{1}H NMR, ^{13}C NMR, 2D (H–H, C–H) COSY, and NOESY, MS. As shown in Figure 1, the NOESY correlations between H_3–H_5 in **2a2** supported the *R*-form of C-3. Consequently, its diastereomer **2a1** should be in *S* configuration at the corresponding C-3, which was identical to the observation in the NOESY of **2a1**. Similarly, the *S*-configuration of **2b2** and *R*-configuration of **2b1** at C-3 could also be assigned on the basis of the NOE correlations between H_3–H_5. The corresponding carbons (C-6′) in compounds **3** (Fig. 2) possessed the same configuration with the corresponding **2** because the configuration of the carbons was in retention during the synthetic process as shown in Scheme 1.

In summary, using the isoxazoline-linked pseudo disaccharide derivatives which were synthesized via the 1,3-dipolar cycloaddition of allyl *C*-glucoside derivative with sugar-derived nitrile oxide as the starting material, we hydrogenated the C=N double bond with DIBAL-H to obtain the isoxazolidine-linked pseudo disaccharide derivatives in high yields, then following the catalytic hydrogenation by $Pd(OH)_2/C$ in MeOH–HCl (c_{HCl} = 0.5%), we finished the four step reactions in one pot in high yield, and obtained the aza-*C*-disaccharide analogues, provided a efficient and convenient method to synthesize the aza-*C*-disaccharide analogues. The synthesis and biological activity study of aza-*C*-disaccharide and aza-*C*-glycoside derivatives by using the isoxazoline-linked disaccharide and glycoside derivatives which were prepared via the 1,3-dipolar cycloaddition of sugar-derived nitrile oxides with sugar or nonsugar derived alkenes as intermediate are underway.

1. Experimental

1.1. General methods

^{1}H NMR, ^{13}C NMR spectra were measured on a RT-NMR Bruker AVANCE 400 (400 MHz) spectrometer using tetramethylsilane (Me_4Si) as the internal standard. High-resolution mass spectra

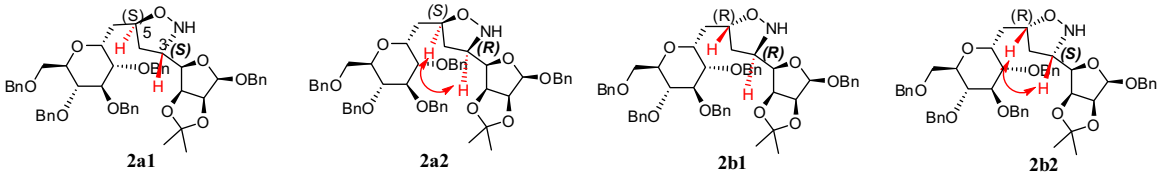

Figure 1. NOESY of compound **2**.