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1,3-Dipolar cycloaddition of *exo*-methylenesugars with nitrone: approach to new amino-*C*-ketosyl disaccharides[☆]

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Abstract—Stereoselective 1,3-dipolar cycloadditions of *exo*-methylenesugars **1a**–**c** to a sugar nitrone **2** were carried out with refluxing a toluene solution and afforded the corresponding cycloadducts, ketosyl spiro-isoxazolidine disaccharides **3a** and **4a**–**c**. Followed by reductive cleavage of the N–O bond of the isoxazolidine ring with the treatment of Zn–AcOH–Ac_2O or with catalytic hydrogenation ($Pd(OH)_2/C$), the cycloadduct **3a** could be readily converted into a novel amino-*C*-disaccharide possessing a ketose form, providing an access to novel amino-*C*-ketosyl disaccharides.

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The understanding of the fundamental roles of carbohydrates and glycoconjugates in numerous biological processes has prompted considerable interest in the development of potential carbohydrate-based therapeutic agents in recent years.[1] As one of the most important carbohydrate mimics, *C*-glycosides have attracted great attention due to their stability to chemical and enzymatic hydrolysis of the glycosidic linkage. Consequently, a number of methodologies for the preparation of *C*-glycosides, for instance, using anomeric anions, cations, radicals, and carbenes as the intermediates of the preparation have been extensively investigated.[2,3] Recently, 1,3-dipolar cycloaddition reactions have also been found application in the synthesis of such compounds.[4] Although *exo*-methylenesugars have been successfully used for the preparation of *C*-glycosides,[5] very few of examples on the utilization of 1,3-dipolar cycloaddition of *exo*-methylenesugars to the synthesis of *C*-glycosides, especially *C*-disaccharides have been reported.[6,7]

In the previous study,[7] we described a diastereoselective 1,3-dipolar cycloaddition of *exo*-methylenesugars with nitrones under the catalysis of a Lewis acid, and the conversion of the resulted ketosyl spiro-isoxazolidine to a novel *C*-glycosyl amino acid possessing a ketose form. As a continuation of our research work on the syntheses of ketosyl *C*-glycosides using *exo*-methylenesugars as the precursor, we wish to report in this letter the 1,3-dipolar cycloaddition of *exo*-methylenesugars to a sugar nitrone affording spiro-isoxazolidine disaccharides, and followed by a reductive ring opening to give novel amino-*C*-ketosyl-disaccharides as shown in Schemes 1–3.

The 1,3-dipolar cycloadditions of *exo*-methylenesugars **1a** were performed with nitrone **2**[8] by refluxing a toluene solution to provide the corresponding cycloadducts, ketosyl spiro-isoxazolidine **3a** and **4a** in the yields of 17.4% and 52.1%, respectively, (Scheme 1).[11,12] It should be noted that the cycloaddition of **1a** and **2** underwent diastereoselectively and afforded only two anomeric isomers **3a** and **4a** possessing *R*-configuration on C-6, which is similar to the previous report.[7] Under the same conditions the cycloadditions of the galactose and mannose derivatives **1b** and **1c** to nitrone **2** were carried out, but only *O*-β-anomeric isomers **4b** (53.2%) and **4c** (50.7%) were obtained in these two cases (Scheme 1).[12]

It should be mentioned that Lewis acids, such as $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $AlClEt_2$, were found not to be efficient to this reaction as catalysts at room temperature, although it has been recently reported that some of such Lewis acids could efficiently promote the 1,3-dipolar cycloadditions of some nitrones and

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Keywords: Cycloaddition; Nitrone; Disaccharide.

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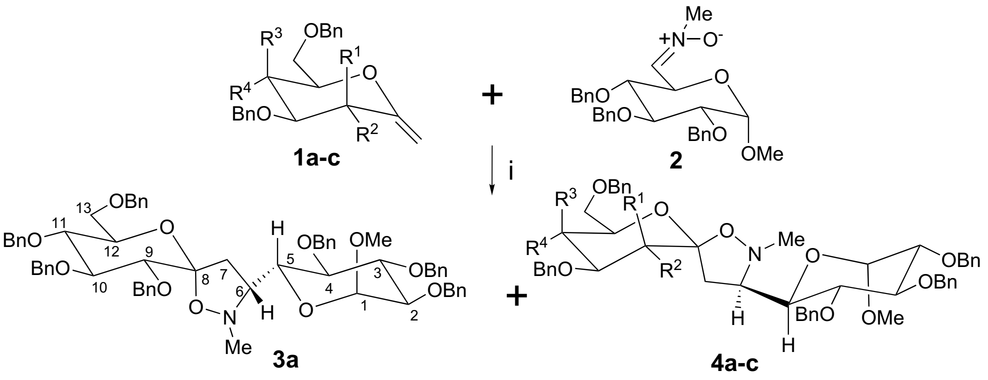
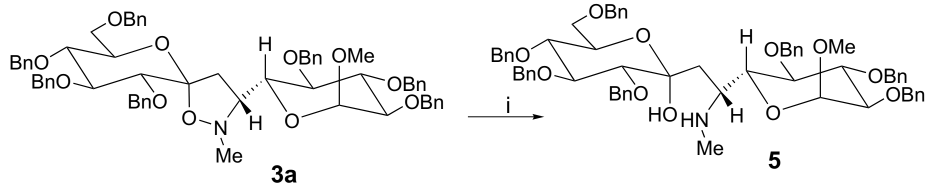
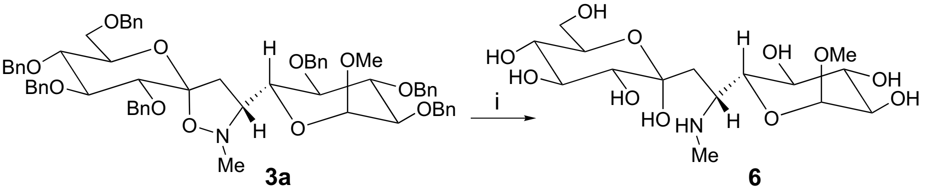


	R^1	R^2	R^3	R^4	**3**: % yield	**4**: % yield
a (Glc)	H	BnO	H	BnO	17.4	52.1
b (Gal)	H	BnO	BnO	H	-	53.2
c (Man)	BnO	H	H	BnO	-	50.7

Scheme 1. Reaction conditions: (i) toluene, reflux.



Scheme 2. Reaction conditions: (i) Zn, AcOH, Ac_2O, rt.



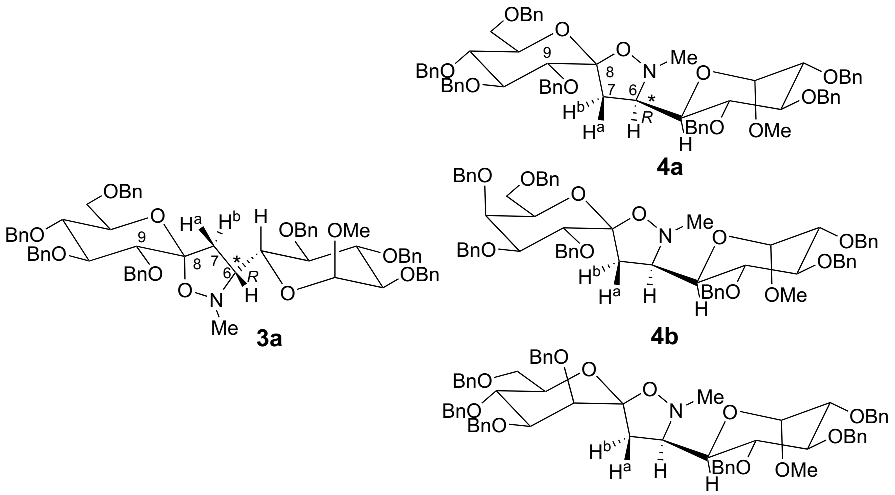
Scheme 3. Reaction conditions: (i) $Pd(OH)_2/C$, H_2, MeOH.

electron-rich alkene such as, enolic compounds in stereoselective way. [9] This inverse electron-demand 1,3-dipolar cycloaddition carried out thermally would proceed in the different stereochemical manner as compared with the glycosylation and afforded the β-anomers stereoselectively.

The structures and configurations of compounds **3a**, **4a–c**, **5**, and **6** were determined by the analyses of their spectral data of ^{1}H NMR, ^{13}C NMR, 2D (H–H, C–H) COSY, and NOESY experiments (See Fig. 1, Table 1 and Ref. 12). It has been reported that in the ^{13}C NMR spectra of *C*-glycosides,[10] *C*-ketosides,[5h] and *C*-spiroketosides[5i,7] the signals of α-anomeric carbons appeared in upper field than those of β-anomeric carbons. With comparison of the chemical shifts of the anomeric carbons in compounds **A** and **B** (Fig. 2) reported previously,[7] the configurations of the anomeric carbons (C-8) in compounds **3a** and **4a–c** were assigned.

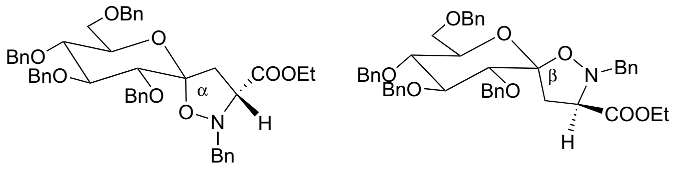
The relative orientation of the substituents on the isoxazolidine ring was established from the NOE observations between H^7 and H^6, H^7 and H^9 (Table 1) as exemplified by the analyses of compounds **3a**, **4a–c** in Figure 1. It was found that in the cycloadducts **3a** and **4a–c** the chiral carbons (C-6) in the isoxazolidine ring possessed *R*-configuration. The NOE experiment results also supported the above assignments on the anomeric configurations (Fig. 1).

With the cycloadducts in hands, we turned our attention to approaching to the synthesis of amino-*C*-ketosyl disaccharides by reductively opening the isoxazolidine ring. As shown in Scheme 2, cycloadduct **3a** can be readily converted into the ring-opened amino-*C*-ketosyl disaccharide **5** in yield of 65.1% upon exposure to activated zinc powder in AcOH–Ac_2O solution at room temperature (Scheme 2). More directly, the cleavage of the O–N bond, and the debenzylation were accom-



4c

Figure 1. NOE analyses of the compounds **3a**, **4a**–**c**.



A ($\delta_{\alpha\text{-C}}$ = 105.41 ppm) **B** ($\delta_{\beta\text{-C}}$ = 107.96 ppm)

Figure 2. Chemical shifts of the anomeric carbons in ^{13}C NMR.[7]

Table 1. Selected NOE data and chemical shifts of the anomeric carbons (C-8) in ^{13}C NMR spectra of spiro-isoxazolidines **3a** and **4a**–**c**

	3a	4a	4b	4c
$H^{7a} \rightarrow H^9$	0.72%	0.47%	0.21%	1.36%
$H^{7a} \rightarrow H^{7b}$	9.17%	8.22%	5.07%	2.21%
$H^{7a} \rightarrow H^6$	3.38%	2.11%	1.80%	2.18%
$H^{7b} \rightarrow H^9$	0.30%	0%	0%	0%
$H^{7b} \rightarrow H^{7a}$	5.26%	1.98%	1.68%	5.41%
$H^{7b} \rightarrow H^6$	2.02%	3.71%	2.74%	3.61%
$\delta_{\text{C-8}}$ (ppm)	104.33	107.60	108.30	108.41

plished in the one step reaction of catalytic hydrogenation ($Pd(OH)_2/C$), and a novel amino-*C*-ketosyl disaccharide **6** was afforded in 51.6% yield (Scheme 3). The spectral data of compounds **5** and **6** were identical with the proposed structure.[12]

In summary, we have described a stereoselective synthesis of a new kind of ketosyl spiro-isoxazolidinic disaccharides using the 1,3-dipolar cycloaddition of *exo*-methylenesugars and a sugar nitrone. The conversion of the cycloadducts into a novel amino-ketosyl *C*-disaccharides was achieved by reductive cleavage of the O–N bound using the combination of Zn–AcOH–Ac_2O or the catalytic hydrogenation.

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12. Physical and spectral data of the new compounds (**3a**, **4a–c**, **5**, **6**) are compiled in Supplementary data.