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New Access to Aza-*C*-disaccharides by Cycloadditions of Pyrroline *N*-Oxides to Glycals

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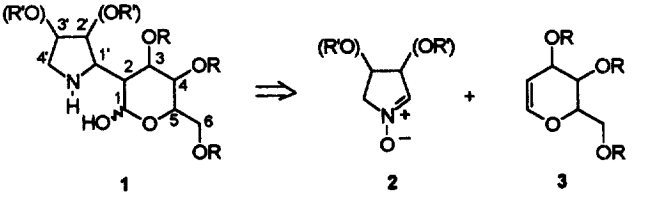
Abstract: A novel, highly stereoselective intermolecular cycloaddition reaction of simple and enantiopure cyclic nitrones to glucose and galactose-derived 1,2-glycals offers a direct access to a new class of pseudoaza-C-disaccharides with isoxazolidine structure, potential glycosidase inhibitors. The synthesis of new (1→2)-linked aza-disaccharides is accomplished by simple reductive ring-opening of the isoxazolidine. © 1997 Elsevier Science Ltd.

Polyhydroxylated pyrrolidines and piperidines (azasugars) have great potential as antibacterial, antitumor and antiviral agents[1] since their inhibitory activity towards glycosidases[2] interferes with the biosynthesis of glycoproteins, which are responsible for intercellular recognition processes.[3] Since glycosidases display high specificity towards oligosaccharides having only subtle structural differences, incorporation of a peculiar sugar moiety may improve the enzyme-selectivity, in addition to the efficiency, of inhibitors.[4] In this context, azasugars linked to common sugars by a non-hydrolyzable *C*-link (aza-*C*-disaccharides) are valuable synthetic targets as new selective glycosidase inhibitors. Syntheses of a pseudoazadisaccharide, of (1→1)-, (1→3)-, (1→4)- and (1→6)-*C*-linked azadisaccharides have been recently accomplished by several groups.[4,5]

We recently reported the synthesis of the potent dihydroxylated indolizidine glycosidase inhibitor, lentiginosine,[6] by 1,3-dipolar cycloaddition of a *trans*-3,4-dihydroxy pyrroline *N*-oxide. Therefore, we envisaged a straightforward assembly of the skeleton of a new (1→2)-linked aza-disaccharide **1**, having a hydroxylated aza-sugar moiety, via the cycloaddition of enantiomerically pure pyrroline *N*-oxides **2** to appropriate glycals **3** (scheme 1).

Scheme 1



1 **2** **3**

Nitrone cycloadditions to glycals have no precedent in the literature, with the exception of a single example of an intramolecular cycloaddition *en route* to the synthesis of chiral tetrahydrofurans.[7] Intermolecular cycloaddition to glycals are limited to a nitrile oxide[8] or particular enophile systems in [2+2][9] or hetero-Diels-Alder cycloadditions.[10]

We report here the results of novel intermolecular cycloaddition reactions of simple and enantiopure nitrones to glucose and galactose-derived 1,2-glycals. Transformations of the adducts are also addressed, including the isoxazolidine ring-opening to a new (1→2)-linked aza-disaccharide.

The cycloaddition reactions were performed at high temperature (100 °C, toluene as solvent), using an excess of glycal (Table 1).[11] These conditions were necessary for complete conversion of the nitrones. Nitrone **4** (entry 1) was not reactive under these conditions, but also the more reactive pyrroline *N*-oxide (**5**) gave only very low yield of cycloadduct **10**, probably due to nitrone decomposition. Good yields were obtained with pyrrolidine-derived hydroxylated nitrones **6**[12] and **7**.[13] The lower yield of galactal **9**, compared to glucal **8**, cannot be rationalized at this stage.

The cycloaddition step proceeds with essentially complete regio- and stereoselectivity. Only traces of minor cycloaddition products were in some cases detected in the crude reaction mixtures, but it was not possible to isolate them. As reported for other examples of cycloadditions on 1,2-glycals,[9a,10c] the stereoselectivity is controlled by the pseudoequatorial group on C(3), thus favoring the nitrone approach *exo* to the less hindered *bottom* face (Fig. 1). D-Tartaric acid derived nitrone (3*R*,4*R*)-**6** gave with this approach a "matched" interaction with glucal **8**, being able to approach to the *bottom* face of glucal *anti* to the vicinal *O-tert*-butyl group in the *exo* orientation.[6,13]

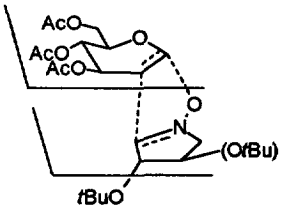


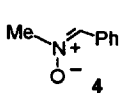
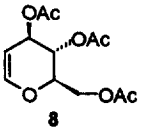
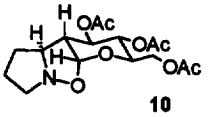
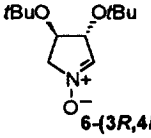
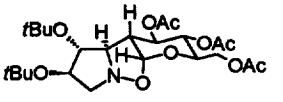
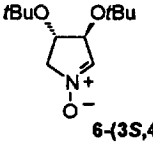
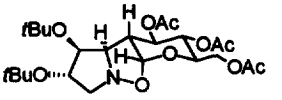
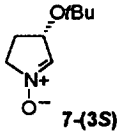
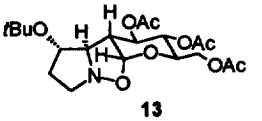
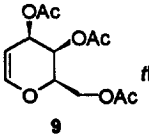
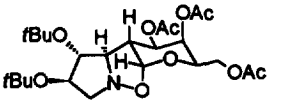
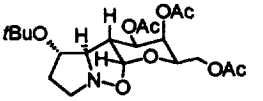
Figure 1. Bottom-exo-anti approach for the cycloaddition of nitrones **6**-(3*R*, 4*R*) and **7**-(3*S*) to glucal **8**.

However, no trace of the *top-exo* adduct (*anti*) has been detected in the reaction mixture from the enantiomeric (3*S*,4*S*)-**6**, the product **12** still deriving from a *bottom-exo* approach which occurs *syn* with respect to the vicinal *O-tert*-butyl group. This "mismatched" interaction is responsible for the lower reactivity and reaction yield. The stereochemistry of the cycloaddition products, as well as the "chair" conformation of the sugar moiety, has been confirmed by ^{1}H-NMR coupling constants and by COSY and NOESY experiments.

Cycloadducts can readily afford aza-*C*-disaccharides by simple transformations.[11] An example using compound **11** which contains the *trans*-dihydroxy moiety on the azasugar part, is reported in Scheme 2. The protecting groups on both the sugar portion and the isoxazolidine ring were removed in high yields. The pentahydroxylated isoxazolidine **17** is stable to acid and base catalyzed hydrolysis, and can be viewed as a non-reducing disaccharide unit particularly promising for glycosidase inhibitor activity, as it contains all the features of a disaccharide frozen in a stable isoxazolidine ring. Reductive ring-opening of the isoxazolidine with

cleavage of the N-O bond ($H_2/Pd(OH)_2$) afforded an anomeric mixture of the new (1→2)-linked aza-disaccharide **18**, which showed low stability when left in water solution for long periods.

Table 1. Cycloadditions of Nitrones **4-7** to Glycals **8-9**.[a]

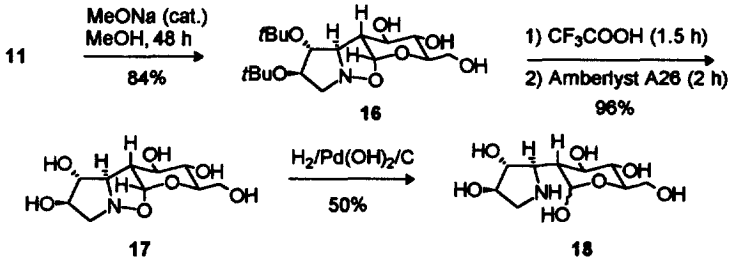
Nitrone	Glycal	Adduct	Reaction time	Yield (%)
 **4**	 **8**	n.r.[b]	13 d	n.r.
 **5**	**8**	 **10**	40 min[c]	12
 **6-(3*R*,4*R*)**	**8**	 **11**	3 d	61
 **6-(3*S*,4*S*)**	**8**	 **12**	11 d	33
 **7-(3*S*)**	**8**	 **13**	4 d	68
6-(3*R*,4*R*)	 **9**	 **14**	3 d	26
7-(3*S*)	**9**	 **15**	7 d	30

a) Reactions conditions: 3 eq of glycals, toluene, 100 °C.

b) n. r. = no reaction.

c) 1.5 eq of nitrone **5**, mesitylene, 152 °C.

Scheme 2



In conclusion, the results described in this communication show the potential of the present approach for the synthesis of a broad new class of aza-*C*-disaccharides, candidates for glycosidase inhibitory activity, by cycloaddition of polyhydroxylated cyclic nitrones to glycals.

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