Stereocontrolled synthesis of fully functionalized D-glucosamine monosaccharides *via* a domino nitro-Michael/Henry reaction†

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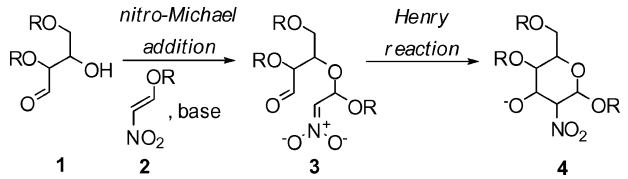
A diastereoselective domino nitro-Michael/Henry reaction involving a β-hydroxyaldehyde and a nitroalkene provides direct access to fully functionalized D-glucosamine monosaccharides.

2-Aminosugars constitute the most abundant class of naturally occurring monosaccharides in mammalian carbohydrates,[1] including glycosaminoglycans, glycoproteins and GPI anchors.[2] Efficient stereoselective preparation of 2-aminosugars has been a major focus in preparative carbohydrate chemistry.[3] Mostly based on modification of glycals by electrophilic reagents, these methodologies, however, suffer from several drawbacks, such as low stereoselectivity and incompatibility with common protecting groups.

Nitroalkenes are very useful electrophiles due to their reactivity towards various nucleophiles and the versatility of the nitro group as precursor for other functional groups.[4] Additionally, nitroolefins are well suited for domino processes, allowing for one-pot assembly of structurally complex cyclic molecules from simpler acyclic precursors.[5] As a part of our ongoing studies towards the *de novo* synthesis of carbohydrate building blocks[6] we report a concise route to D-glucosamines *via* a novel domino nitro-Michael/Henry reaction (Scheme 1).[7]

We anticipated that the base-mediated nucleophilic conjugate addition of β-hydroxyaldehyde **1** to nitroalkene **2**, followed by an intramolecular Henry reaction between the intermediary formed nitronate **3** and the aldehyde should yield the nitropyranoside **4**. The synthetic utility of 2-nitropyranosides as precursors for β-selective glycosyl donors has been reported by Schmidt and co-workers.[8] In addition, we envisaged the subsequent conversion of 2-nitropyranoside **4** into the corresponding 2-aminosugar building block by reduction of the nitro group and anomeric substitution.

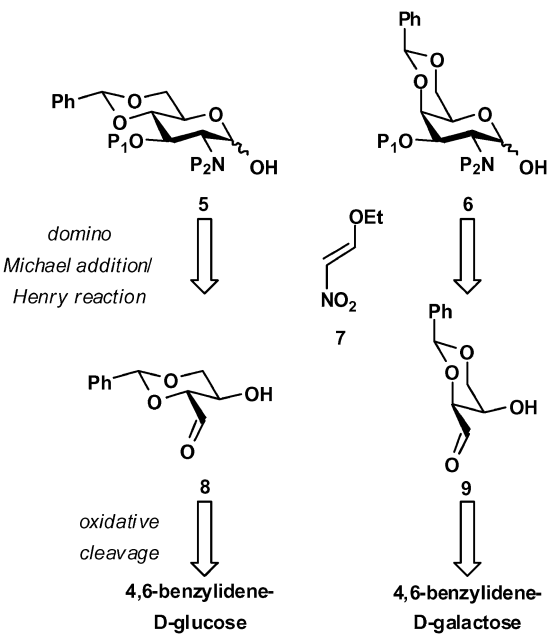
Our retrosynthetic considerations for selectively protected D-glucosamine **5** as well as D-galactosamine **6** are depicted in Scheme 2. Hydroxyaldehydes **8** and **9** can be prepared in one step from corresponding 4,6-benzylidene-D-glucose and 4,6-benzylidene-D-galactose by oxidative cleavage with sodium periodate.[9] Push-pull-substituted 2-ethoxy nitroalkene **7** has



Scheme 1 Proposed domino nitro-Michael/Henry reaction to form 2-nitropyranoside **4**.

previously been shown to be a valuable Michael acceptor[10] and can easily be prepared in two steps starting from nitromethane, DMF and ethyl orthoformate.

In order to investigate the Henry reaction with aldehydes **8** and **9**, trials with nitromethane as the nucleophile under various basic conditions were performed (Scheme 3). Treating an excess of nitromethane with sodium methoxide in methanol at room temperature before adding the erythrose **8** resulted in smooth formation of two diastereomeric addition products **10** and **11** in 2.6 : 1 ratio and a total yield of 82%. A crystal structure of *allo*-configured diastereomer **10** simplified the structural assignment. In contrast, the addition of nitromethane to threose **9** delivered an inseparable mixture of both diastereomers **12** and **13** in only 18% yield.



Scheme 2 Retrosynthetic analysis of D-glucosamine and D-galactosamine building blocks **5** and **6**.

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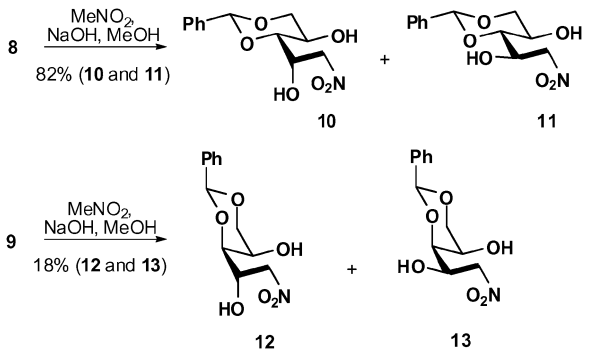


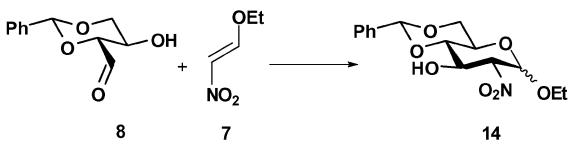
Scheme 3 Henry reaction between β-**8** and **9** and nitromethane.

Next, the domino nitro-Michael/Henry reaction between hydroxyaldehyde **8** and nitroalkene **7** was investigated. The results of a series of reactions using different bases are summarized in Table 1.

Applying the same reaction conditions (entry 1) used in the Henry reaction with nitromethane, even after prolonged reaction times no conversion was observed. Only the starting material was isolated after testing tertiary amine bases in THF (entries 2 and 3). Considering that every step of this domino process is in principle reversible, we next tried to trap the potentially formed nitronate intermediate **3** with TBSCl.[11] In this case, only silylation of alcohol **8** was observed. Stronger bases were explored next. With NaH, 2-nitropyranoside **14** was isolated as an α/β-mixture (entry 5). Even though the product was obtained only in moderate yield (32%), only the *gluco*-configured isomer out of four possible stereoisomers was formed. The crystal structure of α-**14** is shown in Fig. 1. While NaHMDS as base furnished the same product in slightly higher yield, reaction with KHMDS resulted in the formation of a complex and inseparable mixture of diastereomers. Gratifyingly, when LiHMDS was employed as base, only α-**14** was isolated in a very good yield of 83% (Entry 8). Thus, only one of eight possible stereoisomers was formed under these reaction conditions.

With the optimized protocol in hand, this reaction was also applied to threose **9**. Again an inseparable mixture of different diastereomers was formed. Further attempts to optimize this transformation did neither result in improved selectivity nor yield.

Table 1 Domino nitro-Michael/Henry reaction to afford 2-nitropyranoside **14**



Entry	Reagent	Solvent	*T*/°C	r.t./h	Yield
1	NaOMe	MeOH	rt	—	n.r.
2	Et_3N	THF	rt	—	n.r.
3	NEt(*i*Pr$_2$)	THF	rt	—	n.r.
4	Et_3N, TBSCl	THF	rt	—	n.r.
5	NaH	THF	0 to rt	72	32% of **14** (α : β, 1 : 1)
6	NaHMDS	THF	−78 to 0	3	41% of **14** (α : β, 1 : 1)
7	KHMDS	THF	−78 to 0	3	Complex mixture
8	LiHMDS	THF	−78 to 0	3	83% of **14** (only α)

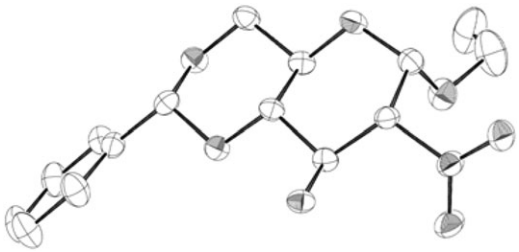


Fig. 1 ORTEP plot (50% ellipsoid probability) of ethyl 4,6-*O*-benzylidene-2-deoxy-2-nitro-α-D-glucopyranoside (α-**14**). Hydrogen atoms are omitted for the sake of clarity.

According to frontier orbital considerations we assume that the most reactive conformation of the acyclic nitronate intermediate is that of the C–O bond adjacent to the carbonyl group adopting an almost perpendicular position. Such a conformation would lower the LUMO by efficient overlap of the π* orbital of the aldehyde with the low-lying σ* orbital of the adjacent C–O bond. Keeping in mind that coordinating lithium cations are present in the reaction mixture, chair-like transition states are plausible as shown in Fig. 2. We suppose that the energetically most favorable transition state is TS_1 with the substituents of the six-membered structure in an almost equatorial arrangement (Fig. 2). TS_1 leads to the observed product. The other two possible transition states TS_2 and TS_3 leading to non-observed diastereomers show a less favorable axial-equatorial arrangement of the substituents. A fourth transition structure (not shown) would have both substituents in an axial position; chelation with lithium would thus not be possible.

A comparable transition state to TS_1, leading from threose to the D-galactosamine motif, would force the aldehyde moiety in line with the adjacent C–O bond. In such a case, the LUMO energy cannot be decreased, thus, the reactivity of the carbonyl is not increased. This unfavorable stereoelectronic effect may account for the poor selectivity and the low yield observed in the case of galactosamine.

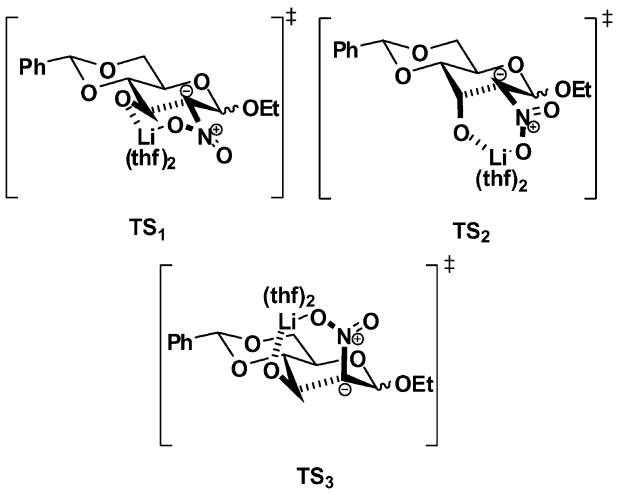
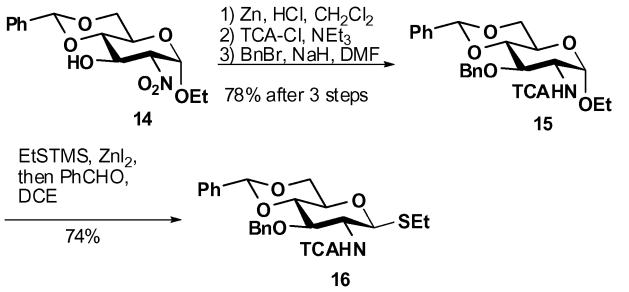


Fig. 2 Potential transition states TS_1–TS_3 for the reaction of nitronate with the carbonyl.



Scheme 4 Conversion of ethyl 2-nitropyranoside **14** into thioglycoside **16**.

In order to demonstrate the utility of 2-nitropyranoside α-**14** as a valuable intermediate for the preparation of glycosylating agents (Scheme 4), the 2-nitro group was reduced with zinc dust/HCl and the amine was chemoselectively protected as a trichloroacetamide in 81% yield after 2 steps. The free hydroxyl was masked as a benzyl ether to provide the fully protected D-glucosamine **15**. After considerable screening, the ethyl glycoside was efficiently converted into the corresponding ethyl thioglycoside **16** in 74% yield using thioethyl-trimethylsilane and ZnI_2 in dichloroethane.[12] Benzaldehyde was added during the reaction to replace the partially cleaved benzylidene acetal.[13]

In conclusion, we report the development and first application of a new type of domino reactions between a β-hydroxy aldehyde and 2-ethoxy nitroalkene. The nitro-Michael/Henry reaction between readily accessible 2-ethoxy nitroalkene **7** and β-hydroxy aldehyde **8** yielded the "*gluco*"-configured ethyl 2-nitropyranoside **14** upon treatment with LiHMDS in high yield and excellent diastereoselectivity. We assume that this transformation proceeds *via* a cyclic six-membered transition state, with lithium chelation between nitronate and alkoxide intermediates as the determining factor for stereoselectivity. The nitropyranoside was subsequently converted to a differentially protected glucosamine thioglycoside upon reduction of the nitro group and efficient exchange of the anomeric group.

Current efforts in our group are directed at the expansion of the substrate scope of this transformation to access further members of the family of 2-aminosugars as well as its unnatural analogues.

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