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Development of a highly α-selective galactopyranosyl donor based on a rational design

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ABSTRACT

A galactosyl donor was rationally designed based on protecting group-stereoselectivity study. This donor was prepared and tested in a series of glycosylation reaction. Excellent α-selectivity was observed in the test reactions.

Carbohydrates are important biopolymers playing pivotal roles in many cellular processes.[1] Glycomics, the comprehensive study of all glycan structures, has become an increasingly interesting research field for both life science and bio-medical research.[2,3] At the same time, chemical synthesis provides one of the major means to access large quantity of carbohydrate compounds in homogenous and structurally defined form.[4,5] However, synthesis of oligosaccharides is much more challenging than synthesis of other types of biopolymers (like peptides and nucleotides), largely due to the difficulties in controlling the stereoselectivity and regioselectivity. The control of the stereochemistry (which is not present in cases of peptide linkages and nucleotide linkages) is especially difficult because of the complexity of the contributing factors to the stereoselectivity, including the configuration of the glycosyl donor,[6–11] the structure of the leaving group,[12] the reaction conditions, the reactivity of the glycosyl acceptor,[13,14] and the protecting groups on the donor. Protecting groups, in particular, have a profound influence on the stereoselectivity of donors.[15–21] Neighboring group participation, for example, has been one of the most powerful strategies for the stereoselective synthesis of 1,2-*trans* glycosidic linkages. On the other hand, development of an efficient method to synthesize 1,2-*cis* glycosidic linkages is difficult due to the lack of neighboring group participating. α-Galactosidic linkage, for example, has been an interesting research target due to its wide presence in biologically interesting oligosaccharides.[22–25] Our group is particularly interested in the influence of remote protecting groups on the stereoselectivity of glycosyl donors. Here we report our recent discovery of a highly α-selective Gal donor based on a rational design of protecting groups.

Our group recently reported a correlation between α-selectivity and acyl protecting group at 3- and 4-positions of 2-azido-2-deoxygalactose ($GalN_3$) donors.[26] The observation was that acyl groups at 3- and 4-positions of $GalN_3$ donors promote the α-selectivity. At the same time, acetyl group at 6-position seems to have little or even adverse effect. Based on this discovery, we rationally designed a highly α-selective $GalN_3$ donor and successfully applied in the synthesis of Tn antigen and *O*-glycan core 7 derivatives.[27] The mechanism we proposed to explain this remote protecting group effect is shown in Scheme 1. If the glycosylation reaction takes a S_N1-like pathway, oxocarbenium ion (like A and B in Scheme 1) should be the key intermediate in the reaction. There are two likely conformations for the galactose oxocarbenium ions, $^4H_3$ (A) and $^3H_4$ (B). When nucleophile reacts with the oxocarbenium ion, it tends to attack the anomeric carbon through pseudoaxial direction. This attack can happen from either top-face or bottom-face to afford products of different stereochemistry. For $^4H_3$ oxocarbenium ion (A), bottom attack to give α-product is more favorable than the top attack (β-product), because the bottom attack goes through a chair-like transition state instead of a twist-boat transition state when attack from the top face. For $^3H_4$ oxocarbenium ion (B), the situation is opposite: attack from the top face to afford the β-product is more favorable. This is why both anomers are often observed in glycosylations. When the acetyl groups are present at 3- and 4-position, the carbonyl oxygen can approach the anomeric carbon to form the participation intermediate. In case of $^4H_3$ oxocarbenium ion, 4-acetyl can participate to form an intermediate like C; in case of $^3H_4$ oxocarbenium ion, 3-acetyl can participate to form the intermediate D. In both participating intermediates, the

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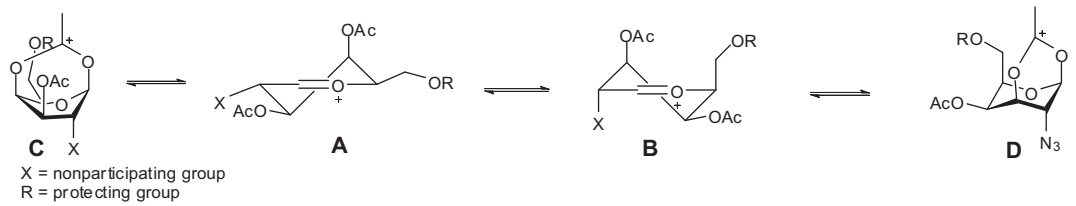
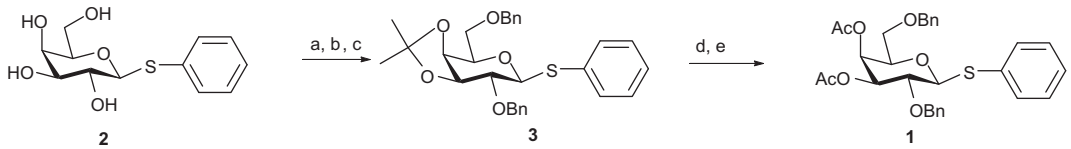
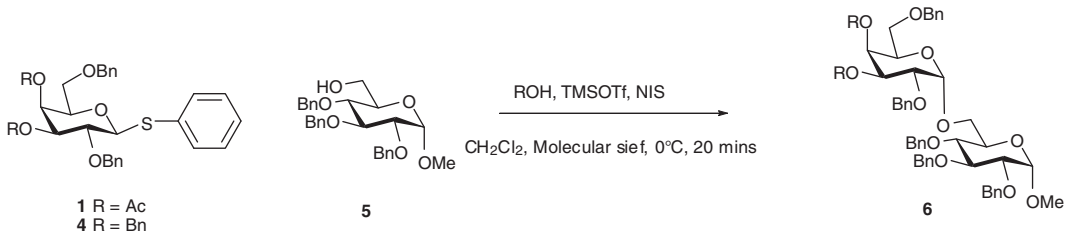


Scheme 1. Mechanism of the remote protecting group directing effect.



(a) 2,2-dimethoxypropane, CSA; (b) MeOH/H_2O (10 : 1), heat; (c)BnBr, NaH, DMF, 88% three steps; (d) 80% HOAc, 90 °C; (e) Ac_2O, Et_3N, DCM, DMAP, 70% two steps

Scheme 2. Preparation of donor **1**.



Scheme 3. Glycosylation reaction with acceptor **5**.

top-face of the anomeric carbon is covered and the nucleophile can only approach from the bottom-face to afford α product.

Since galactose (Gal) has very similar configurations to $GalN_3$ monosaccharides, it is reasonable to believe that the α-directing effect of acetyl groups observed in $GalN_3$ donors is also valid for Gal donors. Based on this hypothesis, we designed a Gal donor (compound **1**) that has the following pattern of the protecting group: acetyl groups at 3- and 4-positions and benzyl groups at 2- and 6-positions. The rationale is that the benzyl group at 2-position would avoid the neighboring group participation; the acetyl groups at 3- and 4-positions would favor the α-selectivity through the mechanism proposed in Scheme 1; the benzyl group at the 6-position would avoid possible adverse effect of acetyl group. This donor can be readily prepared from known thioglycoside **2** in five steps (Scheme 2). Compound **2** was first protected with isopropylidene in two steps by following literature procedure.[28] The crude product was benzylated to afford compound **3**, which was then treated under acidic conditions to remove the isopropylidene protecting group.[29] An acetylation reaction would therefore afford the desired compound **1**. Surprisingly, this donor has never been prepared before. The only similar donor identified through literature search is an ethyl thiogalactoside with same protecting pattern, but no detailed study of the stereoselectivity was reported.[30]

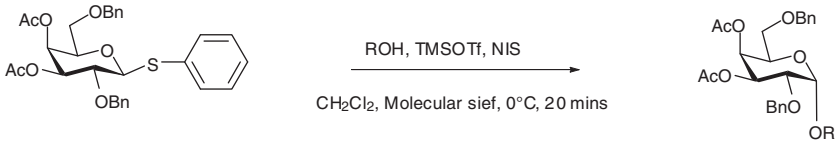
This new donor was then compared with a commonly tetrabenzyl protected donor **4** in glycosylation reactions with a common acceptor **5** (Scheme 3). The reactions are carried out using NIS/TMSOTf as promoter, DCM as solvent at 0 °C. In the test reactions, donor **1** showed excellent stereoselectivity with only α-product isolated. The ^1H NMR spectra of compound **6** showed a doublet at δ 5.02 for anomeric proton with $J_{1,2}$ = 4.0 Hz which confirm the α-stereochemistry in the dissacharide **6**. Donor **4**, on the other hand, showed no stereoselectivity and afforded a 1:1 mixture of anomers. These results demonstrated the superior stereoselectivity of donor **1** compared to donor **4**.

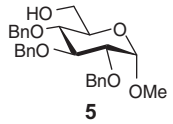
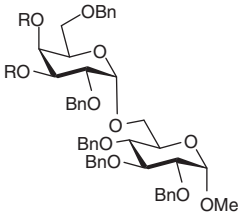
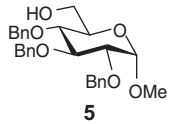
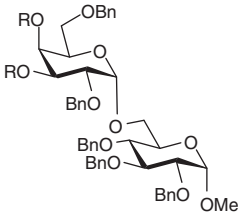
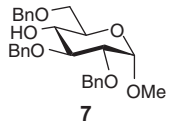
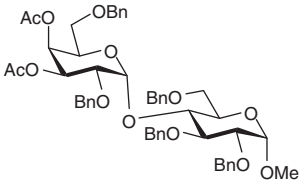
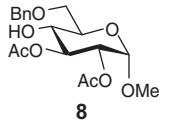
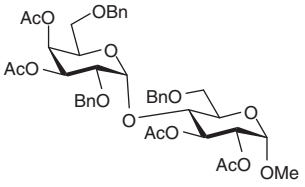
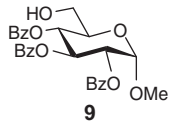
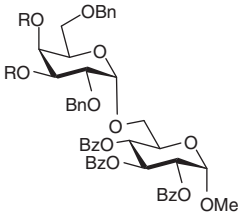
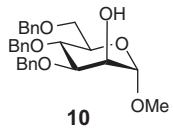
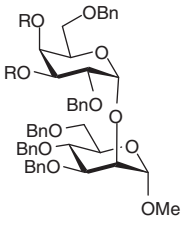
This donor was then further tested with a number of other glycosyl acceptors. These acceptors were carefully chosen to represent some of the commonly used acceptors (Table 1). Representative acceptors include primary alcohol (**5** and **9**), secondary equatorial alcohol (**7** and **8**), secondary axial alcohol (**10**), primary alcohol with electron-withdrawing protecting groups (**9**), and secondary alcohol with electron withdrawing protecting groups (**8**). All the reactions were carried out under the same conditions. Donor **1** show excellent stereoselectivity in the test reactions, only α-products were isolated in all the reactions (Table 1). These results further demonstrated that donor **1** is a donor with high α-selectivity. Further application of using this donor in preparation of biologically interesting α-galactosyl epitope containing molecules is underway.

In conclusion, a rationally designed galactose donor was prepared and tested in glycosylation reactions with a series of glycosyl acceptors. Excellent α-selectivity was observed in all test reactions. Superior stereoselectivity was also observed comparing with tetrabenzyl protected galactose donor. This research not only provides a new highly stereoselectivity donor for future synthesis of complex oligosaccharides, but also demonstrates that the rational design of glycosyl donor is a powerful approach to achieve highly efficient and selectivity glycosylation reactions.

Typical procedure for the glycosylation reactions: Donor (0.11 mmol, 1.1 equiv) and acceptor (0.1 mmol, 1 equiv) were dissolved in anhydrous dichloromethane (2 mL). Flame-dried molecular sieve was added. The mixture was stirred at room temperature for 30 min and then cooled to 0 °C in ice bath. NIS (0.11 mmol, 1.1 equiv) and TMSOTf

Table 1
Glycosylation results of donor **1**



Entry	R-OH	Products	Yield[a] (%)	α:β[b]
1	 **5**		95	α Only
2	 **5**		60	1:1
3	 **7**		95	α Only
4	 **8**		95	α Only
5	 **9**		68	α Only
6	 **10**		97	α Only

[a] Isolated yield.
[b] Determined by NMR.

(5 μL) was added. After 30–60 min, the reaction was quenched with triethylamine (20 μL) and purified by chromatograph.

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