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A convenient and highly stereoselective approach for α-galactosylation performed by galactopyranosyl dibenzyl phosphite with remote participating groups

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Abstract—By using 4- and 6-acyl remote group participation, a galactosyl phosphite donor exhibits exceptionally high α-anomeric selectivity for primary and secondary hydroxyl acceptors. It was observed that temperature played an important factor in glycosylation. The higher α-selectivities were obtained at higher reaction temperatures.

Although numerous complex carbohydrates occur in nature,[1,2] saccharide structures and functions have been minimally studied, mainly due to the difficulty of synthesizing oligosaccharides.[3–7] The synthesis of 1,2-*cis* α-glycosides and β-mannopyranosides,[8] for example, still represents a significant challenge. Since many carbohydrate antigens, such as α-galactosyl ceramide (Galα1-Ceramide, α-GalCer),[9] α-Gal epitope (Galα(1→3)Gal), and P^k antigen (Galα(1→4)Gal), contain a 1,2-*cis*-α-galactosyl glycosidic bond, the development of new and more efficient methods to synthesize 1,2-*cis* glycosidic bonds is of current interest.

It has been shown[6,10–12] that protecting groups on sugars affect the reaction rate and stereochemical outcome of glycosylation. Although highly α-selective galactosylation using a thiol galactosyl donor with remote electron-donating group participation at C-4 has been reported,[13,14] a complicated solvent system was needed to ensure good selectivities.[13] In addition, enhanced α-selectivity in galactosylation was achieved by employing the 6-*O*-acetyl participation strategy and phosphite leaving group.[15] In certain cases, glycopyranosyl phosphites also showed better α-selectivity in glycosylation,[16,17] but using commercially unavailable 2,6-di-*tert*-butylpyridinium iodide (DTBPI) as the promotor. As part of our continuing efforts in the synthesis of carbohydrate antigens as killer T-cell activators, we found that the 2,3-*O*-dibenzyl-4,6-*O*-dibenzoyl galactosyl phosphite donor **1** (Fig. 1) served as an excellent α-selective galactosyl donor under standard glycosylation reaction conditions. Compound **1** contains 4- and 6-acyl groups which may exhibit remote group participation, through the intermediates shown in Fig. 2, resulting in high α-anomeric selectivity.

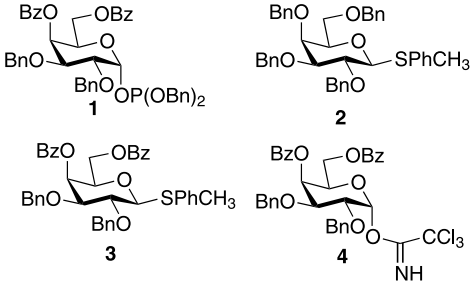

Figure 1. Galactosyl donors used in this study.

Since aryl thiol glycosides are commonly used as α selective donors, we first examined glycosylation of acceptor **5** using **2** (Fig. 3). The reaction gave a good yield but low selectivity (Table 1, entry 2). In order to increase the α-selectivity, we introduced the remote group participation strategy and changed the protecting groups of the 4- and 6-hydroxyl groups of **2** to the benzoyl group (derivative **3**). Consequently, the replacement showed a significant improvement of α-selectivity from α:β=2:1 to 9:1 (entry 3). To investigate further whether the leaving group at the anomeric center would influence the α-selectivity, the thiocresol group of **3** was replaced by trichloroimidate and dibenzyl phosphite to give **4** and **1**, respectively. Surprisingly, coupling of an

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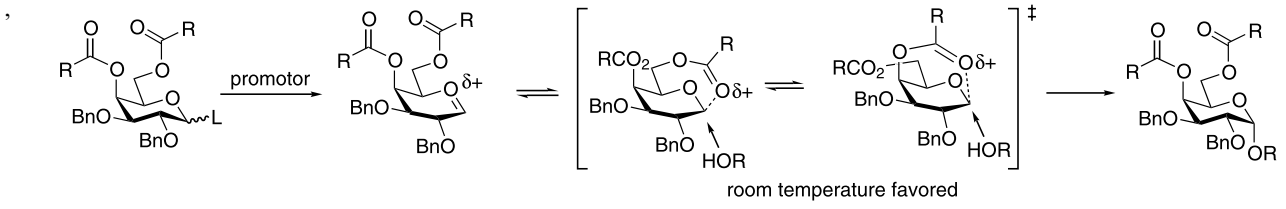

Figure 2. Proposed 4- and 6-acyl remote participation.

α/β mixture (α:β = 6:1) of the phosphite donor **1** with **5** gave only the α-glycosylation product (entry 1), while using the imidate donor **4** (the α form) gave a mixture of products (α:β = 1:10, entry 4). The results of entries 1 and 4 showed that the glycosylation mechanism of phosphite donor **1** was S_N1 like while that of imidate donor **4** was more S_N2 like. These results encouraged us to investigate further the scope and limitation of phosphite donor **1** using a number of acceptors (Fig. 3).

As shown in Table 1, for secondary hydroxyl acceptors, phosphite donor **1** provided excellent α-selectivities (entries 5–9). It is worth pointing out that the 3-OH is more reactive than the 4-OH in the galactose case, thus we obtained disaccharide **18** in high yield and selectivity. However, when primary hydroxyl acceptors were used, the α-selectivity decreased, except with acceptor **5** (entries 1, and 10–12). The good α-selectivity of the primary acceptor **5** may be a result of an anomeric effect together with the π–π interaction between the 2-Bn of **1** and the Fmoc of **5** resulting in a nucleophilic approach from the α-face to give an α-glycosidic bond. This phenomenon has also been observed in the cases of fucosylation of tribenzyl fucosyl phosphite with Fmoc-Thr-OBzl.[15,18] It should be noted that all the above mentioned glycosylations were performed at −15°C except those of entries 11 and 12. Interestingly, the selectivity of the galactosylation using donor **1** was temperature dependent. The higher α-selectivities were obtained at higher reaction temperatures. The temperature effect of entry 11 implied that the nucleophilic addition to the phosphite donor becomes more like kinetic control at low reaction temperatures (−78°C), resulting in inversion of the reaction center for the major product. When the temperature is increased, the remote group participating effect is enhanced and thus gives better α-selectivity. The temperature effect was further demonstrated by running the glycosylation at

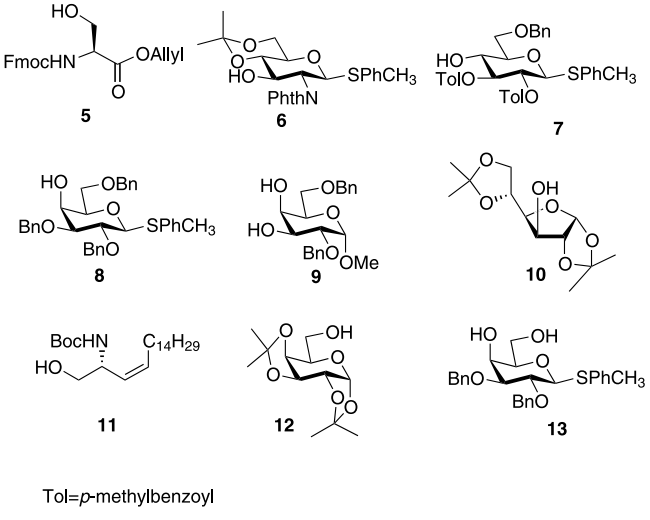

Figure 3. Glycosylation acceptors used in this study.

Table 1. [a]

Entry	Donor	Aceptor	Product (Yield, α:β)
1	**1**	**5**	**14** 95% (α only)
2	**2**	**5**	**14** 93% (2:1)
3	**3**	**5**	**14** 89% (9:1)
4	**4**	**5**	**14** 89% (1:10)
5	**1**	**6**	**15** 73% (α only)
6	**1**	**7**	**16** 62% (α only)
7	**1**	**8**	**17** 76% (α only)
8	**1**	**9**	**18** 84% (11:1)
9	**1**	**10**	**19** 71% (9:1)
10	**1**	**11**	**20** 80% (8:1)
11	**1**	**12**	**21** 85% (6.2:1, 0°C) (6:1, -15°C) (1:2, -78°C)
12	**1**	**13**	**22** 74% (5:1, -15°C) (12:1, rt)

[a] Tol=*p*-methylbenzoyl

room temperature as shown in entry 12. In comparison with the −15°C reaction, the α-selectivity at room temperature is significantly increased. Since the thiocresol leaving group is present on the disaccharides **15**–**17**[19] and **21**, they can serve as disaccharide donors for the next glycosylation. Compound **17** was obtained in excellent α-selectivity and could be used as a synthon of P^k and Globo H antigens. Compounds **20** and **14**[19] can be used as precursors for the synthesis of NK T cell activators, α-GalCer[9,20,21] and its analogs.

In brief, we have demonstrated that galactosyl phosphite **1** is an excellent donor for α-galactosylation. Its superior selectivity may be due to 4- and 6-acyl group participation and π–π interaction between the acceptor and the donor. Glycosylation with this donor for the synthesis of NK T cell activators is underway.

General procedure for glycosylation

A mixed solution of **1** (1.33 g, 1.63 mmol) and **5** (0.55 g, 1.48 mmol) in CH_2Cl_2 (20 mL) in the presence of molecular sieves (2.4 g) was stirred at rt for 30 min, and then cooled to −15°C for another 30 min. TfOH (25.9 μL, 0.30 mmol) was added, and the mixture was stirred at −15°C under argon. After the acceptor disappeared on TLC, the mixture was filtered; the filtrate was concentrated and the residue was partitioned between ethyl acetate and $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and concentrated. The resulting residue was checked by NMR to determine the ratio of α and β anomers, and purified on a silica gel column to give 95% yield of the product.

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