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Convenient construction of a variety of glycosidic linkages using a universal glucosyl donor

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Abstract—This letter deals with the concept of constructing four types (*cis*-α, *trans*-α, *cis*-β, and *trans*-β) of glycosidic linkages using a universal glucosyl donor. The selectively protected universal glucosyl donor **8** was synthesized in 36% yield from D-glucose (eight steps). The donor **8** undergoes glycosidation with a primary carbohydrate alcohol **7** to give disaccharide **9** having a 1,2-*cis*-α-glycosidic linkage in 90% yield. The construction of the corresponding 1,2-*trans*-α-glycosidic linkage was performed in 68% yield (three steps) from **9**. A similar glycosidation of the 2-*O*-(*N*-phenylcarbamoyl)-glucosyl donor **6** derived from **8** with **7** gave disaccharide **11** having a 1,2-*trans*-β-glycosidic linkage in 75% yield. The construction of the corresponding 1,2-*cis*-β-linkage was performed in 53% yield (three steps) from **11**.

The simple, efficient and selective synthesis of oligosaccharides is one of the central problems in carbohydrate chemistry.[1] The so-called Koenigs–Knorr glycosidation[2] has been an essential synthesis for a very long time. Recently, many studies have been devoted to searching for the 'non-Koenigs–Knorr' activation of the anomeric center. The trichloroacetimidate glycosidation[3] has been frequently used for the practical and selective syntheses of complex oligosaccharides and glycoconjugates. Thioglycosides are also attracting attention on donors along this line[4] and for these stabilities. Usually, the anomeric and steric effects, as well as the neighboring group participation, result in the stereocontrolled glycosidation, for example, 1,2-*trans*-α, and -β-linkages are effectively achieved by the neighboring group (such as acyloxy) participation at *C*-2.[5] Contrary to the 1,2-*trans*-α-linkage, construction of a 1,2-*cis*-β-linkage is not easy[6] by the effects mentioned above. Therefore, we have been developing an indirect method for constructing the 1,2-*cis*-β-linkage including a S_N2 displacement reaction at *C*-2[7] of the suitably protected glycosyl donor for synthesizing the naturally occurring oligosaccharides. In these syntheses, the appropriate donor and reaction conditions are selected for each purpose.

In this letter, we describe the concept of constructing four different types of glycosidic linkages by the use of a multipurpose glucosyl donor. Our concept consists of the neighboring group participation of the *N*-phenylcarbamoyl (Car) group and S_N2 displacement reaction at *C*-2. Thus, the Car group, stable from pH 1 to pH 12, has not been used for the protection of the hydroxyl group, because of the difficulties with its unmasking procedure. However, our research group has developed a novel unmasking procedure[8] without affecting the acyl, silyl, methoxymethyl, benzylidene acetal, and isopropylidene acetal protecting groups. At this stage, the Car group is of a particular value for the synthesis of complex oligosaccharides, which necessitates the delicate chemical differentiation of a variety of protecting groups under mild conditions. On the other hand, Nakagawa et al. reported that the stereoselective α-glycosidation with a donor having 6-*O*-Car[9] suggested that the stereoselectivity is at least partly controlled by the neighboring group participation of the Car group at *C*-6. We have now examined the ability of the neighboring group participation of Car group at *C*-2 and *C*-6 for the first time. The results of the glycosidation are shown in Table 1.

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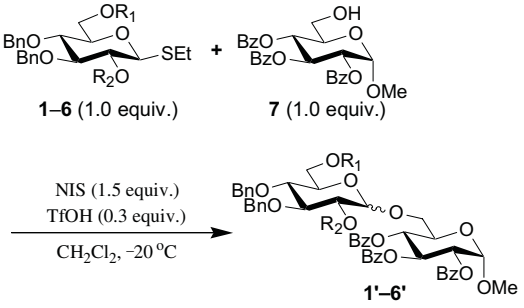
Table 1. Glycosidation of donors **1**–**6** with acceptor **7**

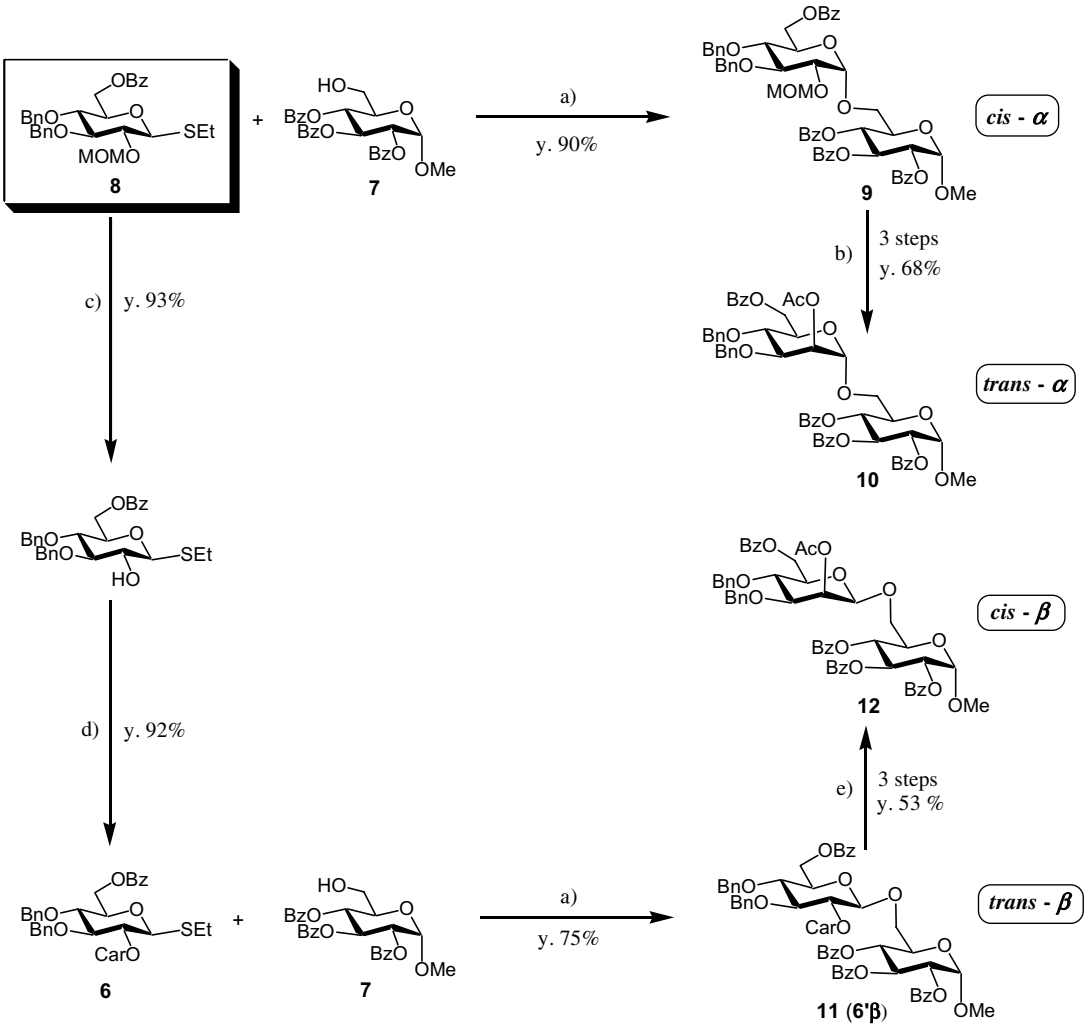
Entry	Donor: R_1, R_2	Product yield (%)[a]	α/β[b]
1	**1**: Bn, Bn	**1′**: 97	4:1
2	**2**: Bz, Bn	**2′**: 90	6:1
3	**3**: Car, Bz	**3′**: 93	6:1
4	**4**: Bn, Bz	**4′**: 98	1:8
5	**5**: Bn, Car	**5′**: 93	1:8
6	**6**: Bz, Car	**6′**: 87	1:6

[a] Based on donors **1**–**6**.
[b] Determined by ^{1}H NMR spectrum.



Scheme 1. Glycosidation of donors **1**–**6** with acceptor **7**.

Donors **1**–**6** and acceptor **7** were synthesized in the usual manner. The ability of the neighboring group participation of Car at *O*-6 was newly examined and compared with that of Car at *O*-2 for the reaction of donors **1**–**6** with acceptor **7** (Scheme 1 and Table 1). The reaction of **1** and **7** in the presence of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) in dichloromethane at −20 °C gave the corresponding disaccharide **1′** (α/β = 4:1) in 97% yield. The ratios of α/β were determined by ^{1}H NMR spectra in this study. Under similar reaction conditions, the reaction of **2** and **3** gave the corresponding disaccharide **2′** (α/β = 6:1) and **3′** (α/β = 6:1) in good yields, respectively. In entry 1, the stereoselectivity seems to be mainly controlled by the anomeric effect. In entries 2 and 3, the ratio of the *cis*-α disaccharide increased compared with that of entry 1. These results suggest that the contribution of a certain neighboring group participation of the Car group at *O*-6 is the same as the benzoyl (Bz) group. Under similar reaction conditions, the reaction of **4** and **5** gave the corresponding disaccha-



Scheme 2. Reagents and conditions: (a) NIS, TfOH/CH_2Cl_2, −20 °C; (b) [i] 70% AcOH aq; [ii] Tf_2O, Py/CH_2Cl_2; [iii] CsOAc, 18-crown-6/toluene, ultrasonication; (c) 70% AcOH aq; (d) PhNCO/Py; (e) [i] *n*-Bu_4NNO_2, Ac_2O, Py, 0–40 °C; [ii] Tf_2O, Py/CH_2Cl_2; [iii] CsOAc, 18-crown-6/toluene.

ride **4′** (α/β = 1:8) and **5′** (α/β = 1:8) in good yields, respectively. The result of entry 5 also shows that the contribution of a certain neighboring group participation of the Car group at *O*-2 seems to be the same as the Bz group (entry 4). The result of entry 6 suggests that the neighboring group participation at the *O*-6 Bz group reduces the β selectivity caused by that of the *O*-2 Car group.

Considering these results, a universal glucosyl donor **8** was designed and synthesized in 36% yield from D-glucose in the usual manner.[10] Especially, the 2-*O* protecting group is to be distinguished from the other protecting groups by considering its selective deprotection. Our concept for constructing four types of glycosidic linkages using **8** was examined as shown in Scheme 2. The reaction of acceptor **7** and donor **8** in the presence of molecular sieves 4A in dichloromethane, NIS (1.5 equiv) then TfOH (0.3 equiv) at −20 °C gave the corresponding *cis*-α disaccharide **9**.[11] The ratio of α/β was 15:1. The deprotection of the methoxymethyl (MOM) group of disaccharide **9** in 70% aq acetic acid solution gave the corresponding 2-OH *cis*-α disaccharide quantitatively. Then, trifluoromethanesulfonation of 2-OH derivative with trifluoromethanesulfonic anhydride (1.5 equiv) and pyridine (5.0 equiv) and subsequently S_N2 reaction with cesium acetate (2.0 equiv) and 18-crown-6 ether (2.0 equiv) gave *trans*-α disaccharide **10**[11] in 73% yield.[7] The total yield of the reaction from **9** into **10** was 68% (three steps).

The other donor **6** producing a β-linkage was synthesized from **8** in two steps as follows.[10] The hydrolysis of **8** in 70% aq acetic acid gave the corresponding 2-OH derivative in 93% yield. The reaction of the 2-OH derivative with phenylisocyanate (1.5 equiv) in pyridine gave the corresponding 2-*O*-Car derivative **6** in 92% yield.[10] For a similar treatment of the reaction of **7** with **8**, the reaction of donor **7** and acceptor **6** gave the corresponding *trans*-β disaccharide **11** (**6′**β),[11] which was purified on a column of silica gel, in 75% yield.[10] The α/β ratio was 1:6. The deprotection of the Car group of **11** with tetra-*n*-butylammonium nitrite (4.0 equiv) and acetic anhydride (1.5, 1.2, and 1.0 equiv) in pyridine[8] gave the corresponding 2-OH *trans*-β disaccharide in 73% yield. In a similar reaction of **9** into **10**, the 2-OH *trans*-β disaccharide was quantitatively converted into the corresponding 2-*O*-trifluoromethanesulfonate, and subsequently S_N2 reaction with cesium acetate (2.0 equiv) and 18-crown-6 ether (2.0 equiv) gave *cis*-β disaccharide **12**[11] in 73% yield.[7,10] The total yield of the reaction from **11** into **12** was 53% (three steps).

In this letter, an example is described for constructing four types of glycosidic linkages using a stable donor (2-*O*-MOM or 2-*O*-Car), which can be synthesized in a large quantity and stored for a long time. The MOM group acts like the ether-type protecting group, which is easily cleaved. The convenient interconversion between the MOM and the Car groups without affecting the other protecting groups seems to have wide applications, for example, introducing an N_3 group or deoxynation at *C*-2.[7] Therefore, we consider that this concept may be useful for the synthesis of a variety of oligosaccharides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.109.

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10. For experimental procedure and their physical data, see Supplementary data at doi:10.1016/j.tetlet.2005.08.109.
11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **9**, **10**, **11**, and **12**.
Compound **9**: δ 7.99–7.23 (30H, m, Ph*H*), 6.13 (1H, dd, $J_{2',3'} = 9.8$ Hz, $J_{3',4'} = 9.5$ Hz, H-3′), 5.63 (1H, dd, $J_{4',5'} = 10.7$ Hz, H-4′), 5.22 (1H, dd, $J_{1',2'} = 3.7$ Hz, H-2′), 5.21 (1H, d, H-1′), 5.02 (1H, d, $J_{1,2} = 3.7$ Hz, H-1), 5.02, 4.86 (2H, each d, $J_{AB} = 11.0$ Hz, Ph–CH_2–), 4.91, 4.60 (2H, each d, $J_{AB} = 10.7$ Hz, Ph–CH_2–), 4.46 (1H, dd, $J_{5',6a} = 2.1$ Hz, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.35 (1H, dd, $J_{5,6b} = 11.6$ Hz, H-6b), 4.25 (1H, ddd, $J_{5',6a'} = 6.4$ Hz, $J_{5',6b'} = 2.1$ Hz, H-5′), 3.96 (1H, ddd, $J_{4,5} = 10.1$ Hz, H-5), 3.92 (1H, dd, $J_{6a',6b'} = 11.6$ Hz, H-6a′), 3.82 (1H, dd, $J_{2,3} = 9.2$ Hz, $J_{3,4} = 8.9$ Hz, H-3), 3.67–3.75 (2H, m, H-2,

H-6b′), 3.58 (1H, dd, H-4), 3.44 (3H, s, –OCH_3), 2.60 (1H, br s, –OH).

Compound **10**: δ 8.02–7.23 (30H, m, PhH), 6.14 (1H, dd, $J_{2',3'} = 9.8$ Hz, $J_{3',4'} = 9.8$ Hz, H-3′), 5.75 (1H, dd, $J_{1,2} = 0.9$ Hz, $J_{2,3} = 2.7$ Hz, H-2), 5.39 (1H, dd, $J_{4',5'} = 9.8$ Hz, H-4′), 5.23 (1H, dd, $J_{1',2'} = 3.7$ Hz, H-2′), 5.20 (1H, d, H-1′), 4.91, 4.59 (2H, each d, $J_{AB} = 10.7$ Hz, Ph–CH_2–), 4.79, 4.57 (2H, each d, $J_{AB} = 11.0$ Hz, Ph–CH_2–), 4.63 (1H, d, H-1), 4.59 (1H, dd, $J_{5,6a} = 2.1$ Hz, $J_{6a,6b} = 11.6$ Hz, H-6a), 4.44 (1H, dd, $J_{5,6b} = 5.5$ Hz, H-6b), 4.24 (1H, ddd, $J_{5',6a'} = 1.8$ Hz, $J_{5',6b'} = 7.6$ Hz H-5′), 4.07 (1H, dd, $J_{6a',6b'} = 11.3$ Hz, H-6a′), 3.82 (1H, dd, $J_{3,4} = 9.2$ Hz $J_{4,5} = 9.5$ Hz, H-4), 3.73 (1H, dd, H-3), 3.69 (1H, dd, H-6b′), 3.61 (1H, ddd, H-5), 3.43 (3H, s, –OCH_3),2.19 (3H, s, –OCOCH_3).

Compound **11**: δ 8.00–7.05 (36H, m, PhH, –NH–), 6.05 (1H, dd, $J_{2',3'} = 9.5$ Hz, $J_{3',4'} = 9.5$ Hz, H-3′), 5.49 (1H, dd, $J_{4',5'} = 9.8$ Hz, H-4′), 5.13 (1H, dd, $J_{1',2'} = 3.0$ Hz, H-2′), 5.10 (1H, d, H-1′), 5.01 (1H, dd, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 9.5$ Hz, H-2), 4.86, 4.59 (2H, each d, $J_{AB} = 10.7$ Hz, Ph–CH_2–), 4.82, 4.77 (2H, each d, $J_{AB} = 11.3$ Hz, Ph–CH_2–), 4.54 (1H, dd, $J_{5,6a} = 2.1$ Hz, $J_{6a,6b} = 11.9$ Hz, H-6a), 4.43 (1H, dd, $J_{5,6b} = 4.3$ Hz, H-6b), 4.39 (1H, d, H-1), 4.21 (1H, ddd, $J_{5',6a'} = 1.8$ Hz, $J_{5,6b'} = 5.2$ Hz, H-6a′), 4.17 (1H, dd, $J_{6a',6b'} = 10.9$ Hz, H-6a′) , 3.79 (1H, dd, $J_{3,4} = 8.9$ Hz, $J_{4,5} = 8.9$ Hz, H-4), 3.71 (1H, dd, H-3), 3.61 (1H, ddd, H-5), 3.59 (1H, dd, H-6b′), 3.27 (3H, s, –OCH_3).

Compound **12**: δ 8.05–7.27 (30H, m, PhH), 6.12 (1H, dd, $J_{2',3'} = 9.6$ Hz, $J_{3',4'} = 9.6$ Hz, H-3′), 5.61 (1H, dd, $J_{1,2} = 0.8$ Hz, $J_{2,3} = 1.1$ Hz, H-2), 5.43 (1H, dd, $J_{4',5'} = 9.6$ Hz, H-4′), 5.23 (1H, dd, $J_{1',2'} = 3.5$ Hz, H-2′), 5.18 (1H, d, H-1′), 4.98, 4.72 (2H, each d, $J_{AB} = 10.9$ Hz, Ph–CH_2–), 4.85, 4.66 (2H, each d, $J_{AB} = 11.0$ Hz, Ph–CH_2–), 4.63 (1H, d, H-1) 4.61 (1H, dd, $J_{5,6a} = 4.8$ Hz, $J_{6a,6b} = 12.1$ Hz, H-6a), 4.41 (1H, dd, $J_{5,6b} = 9.8$ Hz, H-6b), 4.18 (1H, ddd, $J_{5',6a'} = 3.6$ Hz, $J_{5',6b'} = 7.6$ Hz, H-5′), 4.07 (1H, dd, $J_{6a',6b'} = 11.8$ Hz, H-6a′), 3.79 (1H, dd, $J_{3,4} = 9.2$ Hz, $J_{4,5} = 9.2$ Hz, H-4), 3.74 (1H, dd, H-3), 3.70 (1H, dd, H-6b′), 3.63 (1H, ddd, H-5), 3.44 (3H, s, –OCH_3), 2.23 (3H, s, –OCOCH_3).