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α-GLUCOSIDE FORMATION FROM 2-DEOXY-2-(2,2,2-TRICHLORO-ETHOXYCARBOXAMIDO)-α-D-GLUCOPYRANOSYL ACETATE USING AN ACTIVATING SYSTEM THAT USED A COMBINATION OF YTTERBIUM(III) TRIFLATE AND A CATALYTIC BORON TRIFLUORIDE DIETHYL ETHERATE COMPLEX

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Abstract – This study describes the formation of α-glucoside from 3,4,6-tri-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarboxamido)-α-D-glucopyranosyl acetate using an activating system that used a combination of ytterbium(III) triflate and a catalytic boron trifluoride diethyl etherate complex. This glucoside formation using various types of alcohol acceptors proceeded with high α-stereoselectivity. The novel glucoside method employed in this study is a useful technique for producing 2-amino-2-deoxy-α-D-glucopyranoside derivatives because a 2,2,2-trichloroethoxycarbonyl group from an *N*-protecting group is easily removable.

In synthetic carbohydrate chemistry, the development of methods for forming α-glucoside from 2-amino-2-deoxy-D-glucopyranose ($GlcNH_2$) derivatives has received an increasing level of attention because certain natural substances, such as gastric mucins,[1] lipopolysaccharides of bacteria,[2] and tunicamycin[3] contain α-glucopyranoside units of the $GlcNH_2$ unit as sugar components. The enzymes that attach 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) to threonine/serine in some peptides via α-linkage have been also discovered.[4] $GlcNH_2$ donor derivatives with an *N*-neighboring participation

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Dedicated to Professor Dr. Tohru Fukuyama on his 70th Birthday

group at the C-2 position have been generally converted into β-glucopyranosides during glucosidation reactions, whereas glucoside reactions using $GlcNH_2$ donor derivatives with a weak *N*-neighboring participation group at the C-2 position, such as *p*-methoxybenzylideneamino, dinitroanilino, or trifluoroacetamido groups, provided α-glucopyranosides with relatively poor stereoselectivities.[5] Recently research groups have reported the formation of α-glucoside from 2,3-*trans*-oxazolidinone donor derivatives, which were prepared from $GlcNH_2$ through multi-step reaction processes.[6]

Our research focuses on the development of a convenient α-glucoside formation method using $GlcNH_2$ donor derivatives with a commonly-used *N*-neighboring participation group at C-2 because there are no published reports on practical α-glucoside methods using such glucosyl donor derivatives. We then reported on the formation of α-glucoside from the $GlcNH_2$ donor derivative (**1** or **2**) with the neighboring participation group of an *N*-acetyl (Ac) or *N*-benzyloxycarbonyl (Cbz) group at the C-2 position, as shown in Figure 1(i). The glucoside formations were characterized using an activation system[7] that used a combination of ytterbium(III) triflate ($Yb(OTf)_3$) and a catalytic boron trifluoride diethyl etherate complex ($BF_3 \cdot OEt_2$). The glucoside reactions between **1** and general alcohol acceptors produced certain amounts of α-glucopyranosides, although the α-glucopyranosides were highly stereoselective only when phenols were used as glucosyl acceptors.[8] Furthermore, the glucoside reactions between **2** and various kinds of alcohol acceptors including phenols produced α-glucopyranosides with high stereoselectivities.[9] Thus, the reactions using **2** were likely to show higher α-stereoselectivity than those using **1**.

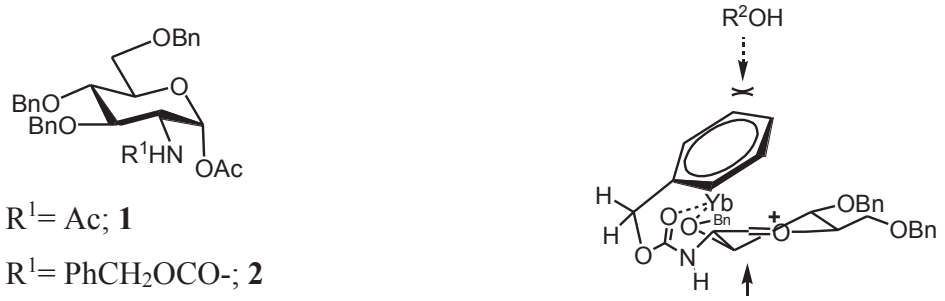


Figure 1. (i) Glucosyl donors used in former research; (ii) Our proposed oxocarbenium ion 2,3-bridged by an Yb metal as the glucosyl intermediate from **2**

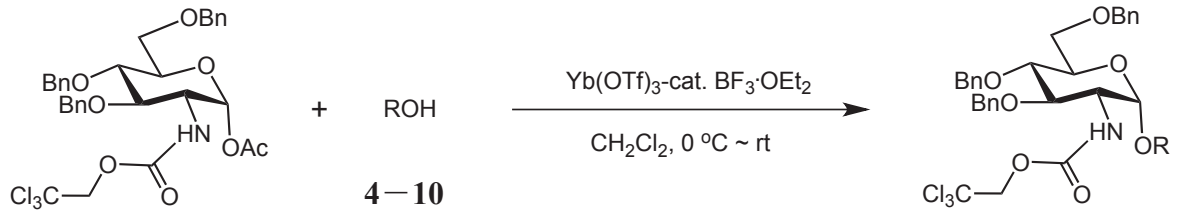
The above results suggested that the glucoside reactions using **1** or **2** did not proceed via a glucosyl 1,2-cyclic oxocarbenium cation intermediate formed by the neighboring group participation effect of the Ac or Cbz group. We were then able to predict the glucosyl cation intermediates during glucosidation reactions using **1** or **2** as follows. The complex of an Yb metal and **1** (or **2**) through the carbonyl function of the *N*-protecting group might be formed as a glycosyl cation intermediate. The formation of the Yb

metal complex can reduce the Lewis basicity of the carbonyl function affecting the neighboring group participation. Figure 1(ii) shows our proposed oxocarbenium ion 2,3-bridged by an Yb metal as the glucosyl intermediate from **2**. Considering the molecular structure of the metal-complexed oxocarbenium ion **2**, the phenyl group on the Cbz group sterically existed at the β-face, which prevented the acceptor alcohols from attacking at the β-face. Because the *N*-Cbz group was bulkier than the *N*-Ac group, the glucoside formation from **2** would proceed with higher α-stereoselectivity than that associated with **1**.

The above speculation suggested a tendency of α-glucoside formation from a $GlcNH_2$ donor derivative with another bulky *N*-neighboring participation group, which we sought to confirm. The 2,2,2-trichloroethoxycarbonyl (Troc) group, which is a commonly-used bulky *N*-neighboring participation group, has been frequently used for the amino protection of $GlcNH_2$ donor derivative for β-glucopyranosidation.[10] We then decided to investigate the formation of α-glucopyranoside from a $GlcNH_2$ donor derivative with an *N*-Troc group using the activation system that combined $Yb(OTf)_3$ with a catalytic $BF_3{\cdot}OEt_2$.

As part of our ongoing study of α-glucoside formations from $GlcNH_2$ donor derivatives with an *N*-neighboring participation group, this paper focuses on the formation of glucoside between 3,4,6-tri-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarboxamido)-α-D-glucopyranosyl acetate (**3**) and various alcohols in the presence of $Yb(OTf)_3$ and a catalytic $BF_3{\cdot}OEt_2$, in addition to the associated α-stereoselectivity.

Compound **3** was readily prepared in 84% yield from 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose·hydrochloride[11] via a two-step process. The first step involved the introduction of the Troc group into the amino function using 2,2,2-trichloroethoxycarbonyl chloride and $NaHCO_3$ in THF-H_2O, and the second step comprised the acetylation of an anomeric hydroxyl group using Ac_2O-pyridine.



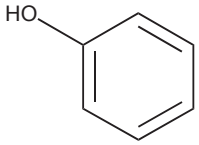
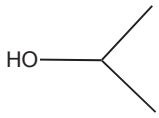
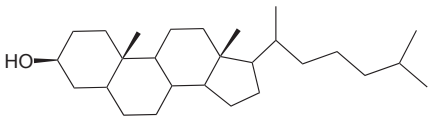
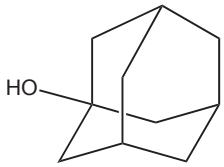
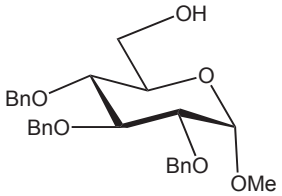
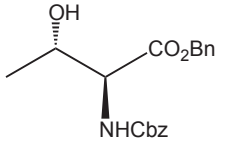
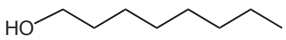
3 **11－17**

Scheme 1

First, the glucoside formation from **3** was investigated using phenol (**4**) as the glucosyl acceptor under the same glucosidation reaction conditions for **1** or **2**, as depicted in Scheme 1. The reaction was performed at

room temperature in the presence of $Yb(OTf)_3$ (1 equiv.) and $BF_3{\cdot}OEt_2$ (0.03 equiv.) in CH_2Cl_2 for 5 h, and it afforded the desired α-phenyl glucosides **11** in 77% yield with high stereoselectivity, as shown in Table 1. The α-stereochemistry at the anomeric positions of **11** was determined via the *J* values of the H-1 proton (*J* = 2.8 Hz). Production of the corresponding phenyl β-glucopyranoside was not confirmed by our experiments. Thus, as compound **3** was highly stereoselectively converted into phenyl α-glucosides, the glucosidation stereospecificity of **3** was similar to that obtained using **1** or **2**.

Table 1. Glucoside reactions of **3** with various types of alcohols in the presence of $Yb(OTf)_3$ and catalytic $BF_3{\cdot}OEt_2$

Entry[a)]	Glucoside Acceptor	Glucoside	Yield/ %[b)]	H-1/ ppm, *J* value/ Hz
1	 **4**	**11**	77	5.55, 2.8 (α only)
2	 **5**	**12**	84	4.94, 3.5 (α only)
3	 **6**	**13**	81	4.97, 4.1 (α only)
4	 **7**	**14**	52	5.25, 4.1 (α only)
5	 **8**	**15**	63	4.89, 4.2 (α only)
6	 **9**	**16**	57[c)]	4.82, 3.5 (α only)
7	 **10**	**17**	88[d)]	4.83, 2.8 (α/β= 1/3)

a) Molar ratio: **2**: Acceptor: $Yb(OTf)_3$: $BF_3{\cdot}OEt_2$= 1.2: 1: 1: 0.03; reaction time: 5 h~overnight. b) 3,4,6-Tri-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarboxamido)-D-glucopyranose which was hydrolyzed from **3** was formed as a by-product. c) A small amount of unidentified product was produced. d) The glucoside was obtained as anomeric mixture.

The glucoside formations from **3** were then examined using several alcohols **5**–**9** under the same reaction conditions. These glucoside formations also occurred to stereoselectively produce the corresponding α-glucopyranosides **12**–**16** without producing the corresponding β-glucopyranosides. The reactions using **5** and **6** produced the α-glucosides in relatively high yields of 84% and 81%, respectively. Even the reaction using the bulky tertiary alcohol **7** smoothly afforded only α-glucoside in 52% yield. The sugar alcohol **8** and amino acid **9** also worked as the glucosyl acceptors for α-glucopyranosidation to provide satisfactory yields. However, the reaction using primary alcohol **10** afforded glucoside **17** in 88% yield with an α/β ratio of 1/3. The poor α-stereoselectivity was observed using the less hindered alcohol **10**. This result was quite corresponded to our former one using **2** and **10**. The α-stereochemistry at the anomeric positions of the produced glucosides (**12**–**17**) was determined via the *J* values of the H-1 protons (J = 2.8–4.2 Hz). These results are also presented in Table 1.[12]

The glucosidation α-stereoselectivity of **3** for these alcohol acceptors were similar to those of **2**. Therefore, we assumed that donor derivative **3** similarly formed an oxocarbenium ion 2,3-bridged by an Yb metal as the glucosyl intermediate, whose *N*-Troc group played a part in preventing the alcohol acceptors from attacking at the β-face, as shown in Figure 2.

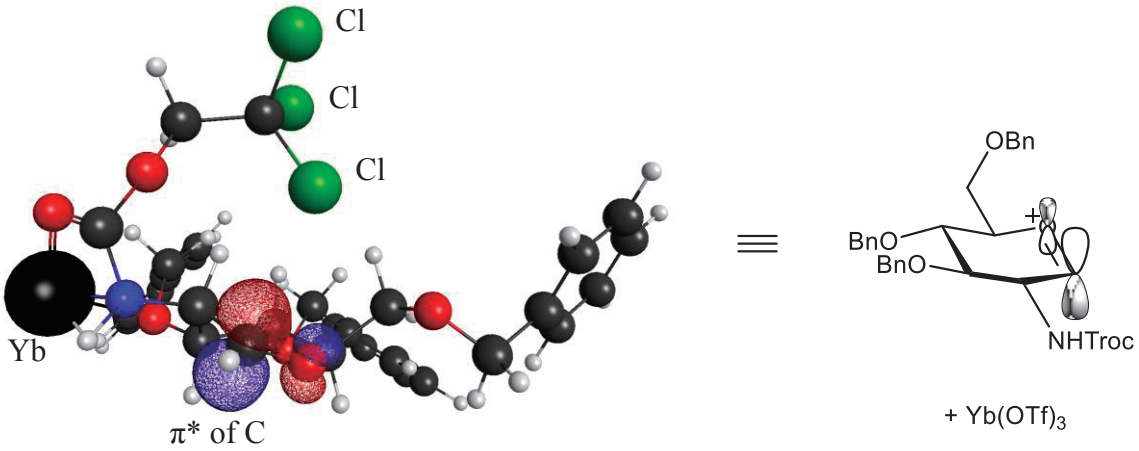


Figure 2. Proposed oxocarbenium form with π* orbital ($Yb(OTf)_3$ was simplified as Yb)

In conclusion, the activating system using a combination of $Yb(OTf)_3$ and a catalytic amount of $BF_3 \cdot OEt_2$ stereoselectively promoted the formation of α-glucoside between the *N*-Troc-group-protected glucosyl donor **3** and various acceptor alcohols (**4**–**9**). The reactivity and stereoselectivity of **3** during the glucoside reaction were similar to those of **2**. This formation of α-glucoside is promising for the synthesis of α-glucoside derivatives from $GlcNH_2$.

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12. Typical glucosidation procedure: $Yb(OTf)_3$ (125.8 mg, 0.2 mmol) was added to a solution of **3**

(173.7 mg, 0.26 mmol), **5** (15.4 μL, 0.2 mmol), and $BF_3 \cdot OEt_2$ (0.8 μL, 0.006 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction was then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and a saturated aqueous NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified using preparative silica-gel TLC (EtOAc/hexane = 1/2) to give **12** (113.3 mg, 84%). **12**: White amorphous powder: $[\alpha]_D^{25}$ +66 (*c* 5.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$ 600 MHz) δ: 1.13 (3H, d, *J* = 5.5 Hz, CH_3), 1.20 (3H, d, *J* = 6.2 Hz, CH_3), 3.66 (1H, d, *J* = 9.7 Hz, H_a-6), 3.70-3.75 (2H, m, H-3, H-4), 3.77 (1H, dd, *J* = 4.1 Hz, *J* = 11.0 Hz, H_b-6), 3.85-3.87 (1H, m, H-5), 3.89 (1H, m, CH), 3.99 (1H, dt, *J* = 3.4 Hz, *J* = 9.7 Hz, H-2), 4.47-4.85 (7H, m, CH_2Ph, $CH_aH_bCCl_3$), 4.94 (1H, d, *J* = 3.5 Hz, H-1), 5.03 (1H, d, *J* = 9.6 Hz, $CH_aH_bCCl_3$), 7.14-7.34 (15H, m, Ph); ^{13}C-NMR ($CDCl_3$ 150 MHz) δ: 21.4 (CH_3), 23.2 (CH_3), 55.1 (C-2), 68.4 (C-6), 69.9 (CH), 70.8 (C-5), 73.4, 74.5, 75.0, 75.2 (CH_2Ph, CH_2CCl_3), 78.3 (C-4), 80.7 (C-3), 95.8 (C-1), 97.1 (CCl_3), 127.6-138.2 (Ph), 154.1 (C=O); HRMS (ESI): *m/z* calcd for $C_{33}H_{38}Cl_3NO_7 \cdot Na^+$: 688.1606; found: 688.1580.