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1,2-*cis*-α-GLUCOSIDE FORMATION FROM A 2-BENZYLOXY-CARBONYLAMINO-2-DEOXY-α-D-GLUCOPYRANOSYL ACETATE DERIVATIVE BY AN ACTIVATING SYSTEM THAT USED A COMBINATION OF YTTERBIUM(III) TRIFLATE AND A CATALYTIC BORON TRIFLUORIDE DIETHYL ETHERATE COMPLEX

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Abstract – We investigated a glucoside formation reaction that utilized a 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl acetate donor derivative and various types of alcohol acceptors. The reaction was promoted by an activating system that used a combination of ytterbium(III) triflate and a catalytic boron trifluoride diethyl etherate complex, and it gave the corresponding 1,2-*cis*-α-glucopyranosides with high stereoselectivity. This glucoside reaction is a new and useful method for producing α-glucopyranoside derivatives from 2-amino-2-deoxy-D-glucopyranose.

Some natural products of gastric mucins,[1] lipopolysaccharides of bacteria,[2] and tunicamycin,[3] such as *O*-glycans, have α-glucoside derivatives from 2-amino-2-deoxy-D-glucopyranose ($GlcNH_2$). It is important in synthetic carbohydrate chemistry that stereoselective 1,2-*cis*-α-glucopyranoside reactions are developed using appropriately *N*-protected glucosyl donor derivatives from $GlcNH_2$. It is known that classical glucosidation methods using donor derivatives with weak neighboring participation groups such as *p*-methoxybenzylideneamino, dinitroanilino, or trifluoroacetamido groups at the C-2 position of $GlcNH_2$ produce 1,2-*cis*-α-glucopyranosides with poor stereoselectivities.[4] Some 1,2-*cis*-α-glucopyranosidation reactions using 2,3-*trans*-oxazolidinone donor derivatives, which need multi-step preparation processes to form $GlcNH_2$, have been recently reported.[5] However, no report has been published on practical α-glucosidation reactions using donor derivatives whose C-2 amino functions are protected by commonly used *N*-protecting groups.

The benzyloxycarbonyl (Cbz) group can be used as a convenient carbamate-type *N*-protecting group in organic chemistry. However, the Cbz group has been rarely used as the *N*-protecting group of the glucosyl donor derivatives from $GlcNH_2$.[6] Although *N*-Cbz-protected donor derivatives lead to the production of 1,2-*trans*-β-glucopyranosides due to the neighboring participation effect, the yields of the produced glucosides are heavily dependent on the species of acceptor alcohol used. When low reactive acceptor alcohols are used, *N*-Cbz-protected donor derivatives are easily converted into stable glucosyl 1,2-cyclocarbonated derivatives (i.e., oxazolidones) as shown in Figure 1 (i),[7] and the desired glucosides are not produced.[8] Thus, the *N*-Cbz protection strategy of $GlcNH_2$ has not been suitable for constructing 1,2-*cis*-α-glucopyranosidic linkages. Though the glucosidation reactions using other carbamate-type protected donors from $GlcNH_2$ have been reported, they are β-selective.[9]

We have recently reported that an activation system using a combination of ytterbium(III) triflate ($Yb(OTf)_3$) and a catalytic boron trifluoride diethyl etherate complex ($BF_3{\cdot}OEt_2$) successfully promotes the glucosidation reaction of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl acetate (**1**), as shown in Figure 1 (ii), with the acceptor alcohols and produces the corresponding D-glucopyranosides.[10] This glucosidation reaction was characterized by the production of certain amounts of 1,2-*cis*-α-glucosides in spite of **1** having a neighboring group participation of the *N*-acetyl group at the C-2 position. In particular, the 1,2-*cis*-α-glucosides were obtained with high stereoselectivity when aryl alcohols were used as glucosyl acceptors. It is generally known that glucosyl donor derivatives with *N*-acetyl groups are converted into oxazoline derivatives as glycosyl intermediates, and 1,2-*trans*-β-glucosides are formed through the S_N2-like nucleophilic substitution of an alcohol to oxazoline derivatives (or oxazolinium cation intermediates). Therefore, our above-mentioned glycosidation method seems to involve a different pathway because it does not generate oxazoline intermediates; rather, it seems as though the activating system promotes an α-glucoside formation reaction using the glucosyl donor derivatives of $GlcNH_2$ even when their C-2 position is protected with a group that has a neighboring group participation.

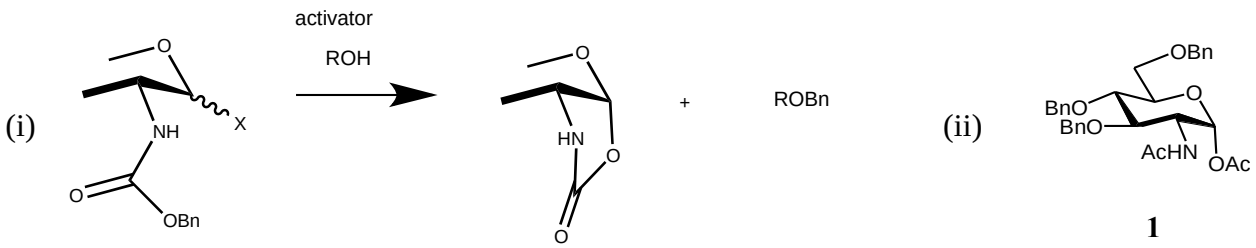
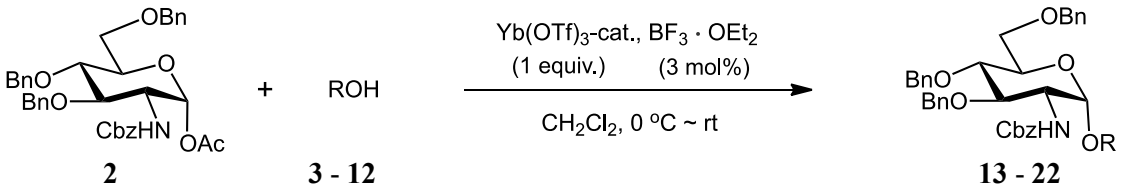


Figure 1. (i) Side reaction using the glucosyl donors with a *N*-Cbz group; (ii) The donor from $GlcNH_2$ used in our former research

Our next intention was to develop the glucosidation method using an *N*-Cbz-protected donor derivative from $GlcNH_2$. We anticipated that an activating system using a combination of $Yb(OTf)_3$ and a catalytic $BF_3{\cdot}OEt_2$ would have the potential to promote the formation of glucopyranoside from an *N*-Cbz-protected donor derivative because the activating system would suppress the neighboring group participation of the *N*-Cbz protecting group and prevent the production of a 1,2-oxazolidone derivative. We were also interested in the steric and electronic effects of the *N*-Cbz protecting group of the glucosyl donor because these might influence the stereoselectivity of the α-glucosidation reaction. In this study, we describe the detailed glucopyranoside reaction from 3,4,6-tri-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosyl acetate (**2**) promoted by the activating system using a combination of $Yb(OTf)_3$ and catalytic $BF_3{\cdot}OEt_2$; in addition, we focus on the stereoselectivity of the α-glucosidation reaction.

Compound **2** was readily prepared from 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyanose hydrochloride[11] via two steps. The first step involved the introduction of the Cbz group into the amino function using Cbz-succinimide in pyridine-DMF, and the second step comprised the acetylation of an anomeric hydroxy group using Ac_2O-pyridine.

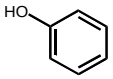
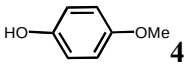
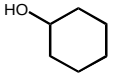
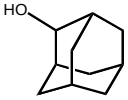
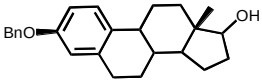
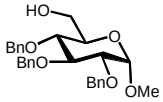
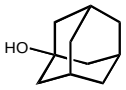
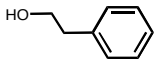
First, the glucoside formation from **2** was investigated with aryl alcohols such as phenol (**3**) and 4-methoxyphenol (**4**) used as the glucosyl acceptors under the same glucosidation reaction conditions for **1**, as shown in Scheme 1. The reaction using the activating system that combined $Yb(OTf)_3$ (1 equiv.) with $BF_3{\cdot}OEt_2$ (0.03 equiv.) in CH_2Cl_2 overnight at room temperature gave the desired aryl glucosides (**13** and **14**) in 64% yields with α-stereoselectivities. The reaction using only $Yb(OTf)_3$ (1 equiv.) with no use of $BF_3{\cdot}OEt_2$ did not proceed at all. The observation corresponded to that of our former research using the donor **1**. Therefore, the combination of $Yb(OTf)_3$ and $BF_3{\cdot}OEt_2$ was also useful for the activation of **2**. The stereochemistry at the anomeric positions of **13** and **14** were determined via the *J* values of their H-1 protons. The corresponding aryl β-glucosides and the predicted by-product, the 1,2-oxazolidone derivative (**23**), were not detected in the reaction products by ^{1}H-NMR spectroscopy. Thus, compound **2** was smoothly converted into aryl α-glucosides with high stereoselectivity. The specificity of this reaction was similar to that of **1**. These results strongly suggest that the glucosyl cyclic oxocarbenium cation intermediate based on the neighboring group participation effect of the carbonyl group on the *N*-Cbz protecting group was not generated from **2**.



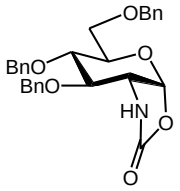
2 **3 - 12** **13 - 22**

Scheme 1. The glucosidation reaction using **2**

Table 1. Glucosidation of **2** with various types of alcohols using an activating system that utilizes a combination of $Yb(OTf)_3$ and catalytic $BF_3{\cdot}OEt_2$

Entry[a]	Acceptor	Glucoside	Yield/%	H-1/ppm, *J* value/Hz[b] Produced α/β isomer ratio	Our former result using **1**[c] Yield/%, α/β Isomer ratio
1	 **3**	**13**	64	5.55, 2.8 α only	67, α only
2	 **4**	**14**	64	5.42, 2.8 α only	84, α only
3	 **5**	**15**	71	4.91, 2.8 α only	–
4	 **6**	**16**	73	4.96, 3.5 α only	68, 53/47
5	 **7**	**17**	73	4.98, 3.5 α only	71, 31/69
6	 **8**[12]	**18**	72	4.84, 3.4 α only	–
7	 **9**	**19**	50	4.79, 3.4 α only	37, 35/65
8	 **10**	**20**	57	5.23, 3.5 α only	–
9	 **11**	**21**	41	4.66, 2.8 88/12	86, 51/49
10	*n*-octanol **12**	**22**	75	4.79, 2.8 48/52	–

a) Molar Ratio: **2**: Acceptor: $Yb(OTf)_3$: $BF_3{\cdot}OEt_2$ = 1.2: 1: 1: 0.03. b) Each of the reactions using **2** produced a single isomer (Entries 1-8). The glucosidic linkages were determined as an α by ^{1}H-NMR spectroscopy. c) Our previously reported results using **1** are shown for comparison with the results using **2**. See Ref. 10.



Predicted by-product **23**

Second, the glucoside formation from **2** was examined using some alcohols (**5**–**10**) under the same reaction conditions. These reactions also stereoselectively produced the corresponding α-glucosides (**15**–**20**) in satisfactory yields without producing the corresponding β-glucosides or **23**. Comparing these results with that of our former research in which the glucosidation of **1** with **6** or **7** gave the corresponding glucoside with an anomeric mixture of α/β = 53/47 and 31/69, respectively, we found that the existence of the *N*-Cbz group of **2** seemed to make a significant contribution to the appearance of higher α-stereoselectivities during the glucosidation reactions. The reaction using the sugar alcohol (**9**) also gave α-glucoside in a 50% yield as a single isomer. Moreover, even the reaction using the bulky alcohol (**10**) smoothly afforded only α-glucoside in a 57% yield. However, we found that the reaction using the simple primary acceptor alcohol (**11** or **12**) gave the glucoside (**21** or **22**) with an anomeric mixture of α/β = 88/12 or 48/52, respectively. The less sterically hindered primary alcohols seemed to reduce the α-glucosidation stereoselectivity. These results are presented in Table 1.[13]

Figure 3 shows the proposed glucosyl intermediate, which is an oxocarbenium ion 2,3-bridged by a Yb metal. The formation of this metal complex can reduce the Lewis basicity of the carbonyl function on the Cbz group and keep **2** from being converted into a 1,2-cyclocarbonated derivative. Considering the molecular structure of the metal complexated oxocarbenium ion, the phenyl group on the Cbz group sterically existed at the β-face, and thus prevented the attack of the acceptor alcohol from the β-face. Consequently, the desired α-glucosidation reaction proceeded with high stereoselectivities in our glucosylation system.

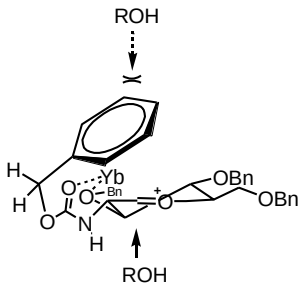


Figure 2. Proposed glucosyl intermediate

In conclusion, we found that an activating system using a combination of $Yb(OTf)_3$ and a catalytic boron $BF_3 \cdot OEt_2$ stereoselectively promoted the α-glucoside formation reaction of the glucosyl donor **2** with an *N*-Cbz group from $GlcNH_2$. This α-glucosidation system is very useful for the construction of α-glucoside derivatives from $GlcNH_2$.

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13. Typical glucosidation procedure: $Yb(OTf)_3$ (89.7 mg, 0.14 mmol) was added to a solution of **2** (110.0 mg, 0.18 mmol), **3** (13.0 mg, 0.14 mmol), and $BF_3 \cdot OEt_2$ (0.5 μL, 0.004 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting mixture was stirred for 5 h 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 = 1/1) to give **13** (58.2 mg, 64%). White amorphous powder: $[\alpha]_D^{25}$ +107 (*c*2.6, $CHCl_3$); ^{1}H-NMR δ 3.61 (1H, d, *J* = 11.0 Hz, H_a-6), 3.75 (1H, dd, *J* = 2.1 Hz, *J* = 11.0 Hz, H_b-6), 3.88 (3H, m, H-3, H-4, H-5), 4.21 (1H, dt, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2), 4.44 (1H, d, *J* = 11.7 Hz, CH_2Ph), 4.54 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.61 (1H, d, *J* = 11.7 Hz, CH_2Ph), 4.74 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.82 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.87 (1H, d, *J* = 11.7 Hz, CH_2Ph), 4.92 (1H, d, *J* = 9.6 Hz, NH), 5.02 (1H, d, *J* = 11.6 Hz, Cbz), 5.13 (1H, d, *J* = 12.4 Hz, Cbz), 5.55 (1H, d, *J* = 2.8 Hz, H-1), 7.00-7.30 (25H, m, Ph); ^{13}C-NMR δ 54.7 (C-2), 67.0 (Cbz), 68.2 (C-6), 71.5 (C-5), 73.4 (CH_2Ph), 75.0 (CH_2Ph), 75.2 (CH_2Ph), 77.9 (C-4), 80.7 (C-3), 96.7 (C-1), 116.5 (Ph), 122.6 (Ph), 127.6-129.5 (Ph), 136.2-138.2 (Ph), 155.9 (C=O), 156.2 (Ph). HRMS (ESI): *m/z* calcd for $C_{41}H_{41}NO_7 \cdot Na^+$: 682.2775; found: 682.2794.