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Catalytic Stereoselective Synthesis of 2-Amino-2-Deoxy-α-D-Glucopyranosides and Galactopyranosides

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In the presence of a catalyst generated from $SnCl_4$ and a silver salt, various 2-amino-2-deoxy-α-D-glucopyranosides or galactopyranosides are stereoselectively synthesized in good yields with high stereoselectivities through anomerization step starting from 1,3,4,6-tetra-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranose or galactopyranose and alkyl trimethylsilyl ethers, respectively.

2-Acetamido-2-deoxy-α-D-glycosides are very important fragments of glycoproteins and glycooligopeptides, therefore an establishment of efficient synthetic method for these glycosides is strongly desired.

Stereoselective formation of α-glycosidic linkages has been reported by way of various glycosylation methods.[1] However, there are some problems remained such as instability of the glycosyl donors, toxic character of the promoters, poor yields of the desired glycosides, and necessity of using more than stoichiometric amount of heavy metal activators such as silver salts or mercury salts. Furthermore, it is necessary to protect amino function at C-2 position for the type not to participate in the neighboring effect. Therefore, the preparation of both α- and β-anomers from a single glycosyl donor having acylamino group at C-2 position is considered to be a very difficult problem, and there are no examples to obtain both of these anomers in high yields from a single glycosyl donor using a catalytic amount of activator. In this communication, we would like to describe an efficient method for the highly stereoselective preparation of α-anomers starting from the same glycosyl donor previously employed in the preparation of β-anomers.

We have already reported a useful method for the preparation of 2-amino-2-deoxy-β-D-glucopyranosides and galactopyranosides starting from 1,3,4,6-tetra-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranose (**1**) or galactopyranose (**2**) and alkyl trimethylsilyl ethers by using a catalytic amount of $Sn(OTf)_2$.[2] During the course of the above experiment, α-anomers were obtained in considerable amounts when a catalyst (**3**) generated from $SnCl_4$ and $AgClO_4$[3] was used instead of $Sn(OTf)_2$. It was also observed that anomerized α-anomer was formed when the isolated β-anomer was treated under the above reaction conditions. Based on the results, glycosylation reaction of **1** with cyclohexyl trimethylsilyl ether was attempted using **3** as a catalyst, and it was observed that β-anomer was formed immediately when the substrates were added to the reaction system at room temperature, and initially formed β-anomer was gradually anomerized to α-anomer (see Table 1). The result would indicate that β-anomer, formed as a result of kinetic control, undergoes anomerization to the thermodynamically more stable α-anomer under the reaction conditions. After screening various solvents, it was found that the reaction rate of this anomerization was drastically increased when nitromethane was used as a

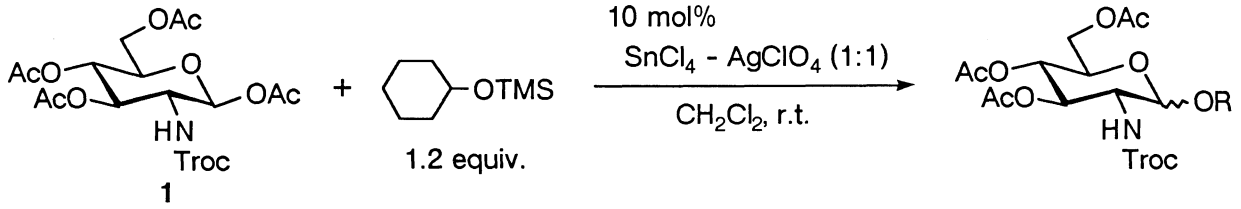


Table 1. Transition of anomerization

Entry	Time / m	Yield / %	α / β
1	1	>99	3 / 97
2	15	↑	58 / 42
3	30	↑	80 / 20
4	45	↑	92 / 8
5	60	↑	>99 / 1

solvent.

Next, effect of several silver salts was examined. Though the anomerization took place slowly, good result was also obtained when AgOTf or $AgSbF_6$ was used (see Table 2). Furthermore, the corresponding α-galactoside was also obtained in good yield with high stereoselectivity when the above procedure was applied to the glycosylation of **2** with cyclohexyl trimethylsilyl ether.

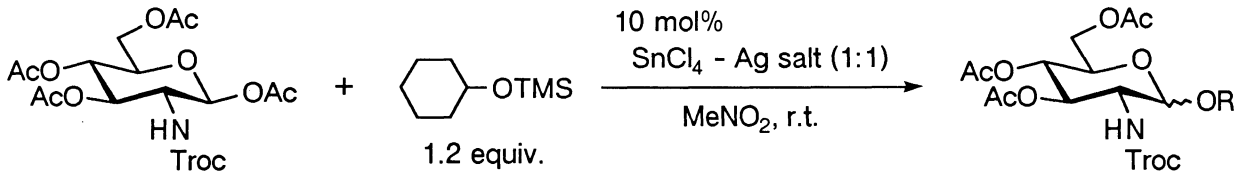
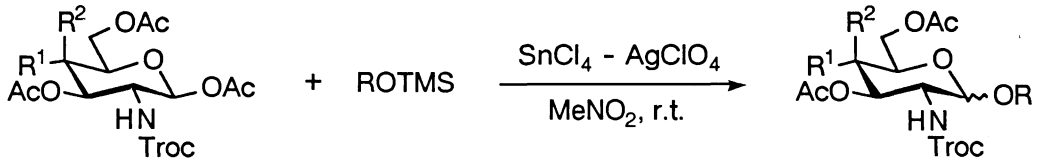


Table 2. Effect of silver salts

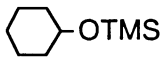
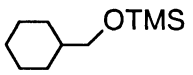
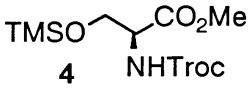
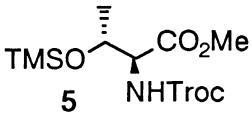
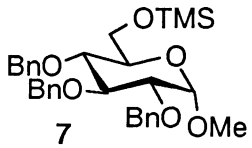
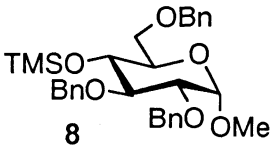
Entry	Ag salt	Time / h	Yield / %	α / β
1	$AgClO_4$	0.5	>99	>99 / 1
2	$AgSbF_6$	4	↑	↑
3	AgOTf	5	↑	99 / 1

Several examples of the present glycosylation reaction are demonstrated in Table 3. In every case including L-serine (**4**) and L-threonine (**5**) derivatives, the desired α-glucosides and galactosides were prepared in good yields with very high selectivities.[4] It is noted that the glycosylation reaction of **4** or **5** is an important preparative



1 : R^1 = OAc, R^2 = H
2 : R^1 = H, R^2 = OAc

Table 3. Synthesis of α-glycosides

				R^1 = OAc, R^2 = H		R^1 = H, R^2 = OAc	
Entry	ROTMS (1.2 equiv.)	Cat. / mol%	Time / h	Yield / %	α / β	Yield / %	α / β
1		10	1	>99	>99 / 1	>99	>99 / 1
2	↑	5	4	↑	↑	↑	↑
3		↑	3	↑	↑	↑	↑
4	3β-CholestanylOTMS	↑	5	98	99 / 1	99	99 / 1
5	 **4**	20	6	>99	>99 / 1	>99	>99 / 1
6	 **5**	↑	↑	97	99 / 1	98	↑
7	 **7**	10	1 min.	90	3 / 97	92	3 / 97
8	↑	↑	1	52	75 / 25	59	70 / 30
9 a)	↑	↑	10	97	1 / 99	97	1 / 99
10	 **8**	↑	5 min.	80	2 / 98	78	3 / 97
11	↑	↑	2	40	70 / 30	43	72 / 28
12 a)	↑	↑	10	86	1 / 99	83	1 / 99

a) The reaction was carried out at -15 °C.

method since the produced α-glycosides are the terminal components of the glycoproteins or glycooligopeptides. In our preceding paper, we reported the stereoselective glycosylation of 1-O-acetyl-2-azido-2-deoxy-3,4,6-tri-O-benzyl-D-galactopyranose (**6**) with **4** or **5** to afford the corresponding α-anomers,[5] but the preparation of **2** is more convenient compared with that of **6**. In addition, the present glycosylation method affords the desired α-galactosides in better yields. In the case when **7** or **8** was used as a glycosyl acceptor, the corresponding α-glycoside was produced predominantly in moderate yield via anomerization of initially formed (a few minutes) β-glycoside along with the unidentified complicated mixtures after being kept standing for a prolonged time. While, β-glycoside was obtained in high yield and the anomerized α-glycoside was formed only in trace amount when the reaction was carried out at lower temperature (-15 °C).

A typical experimental procedure for the preparation of cyclohexyl 3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranoside is as follows; a solution of $SnCl_4$ (0.01 mmol) in toluene (0.1 ml) was added to a solution of $AgClO_4$ (0.01 mmol) in nitromethane (2 ml) at room temperature, and the mixture was shielded from a light and stirred for 1 h. To this mixture was added a solution of **1** (0.2 mmol) and cyclohexyl trimethylsilyl ether (0.24 mmol) in nitromethane (2 ml) at room temperature. After stirring the mixture for 4 h, aqueous sodium hydrogen carbonate was added. Usual work up and separation by column chromatography on silica gel afforded α-anomer in more than 99% yield along with the very trace amount of β-anomer.

Thus, it is noted that suitable choice of catalyst and solvent enables the respective synthesis of 2-amino-2-deoxy-α- or β-D-glycosides with high selectivity from a single glycosyl donor having 2,2,2-trichloroethoxycarbonylamino group at C-2 position.

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2) T. Mukaiyama and K. Matsubara, *Chem. Lett.*, **1992**, 1755.

3) T. Mukaiyama, T. Takashima, M. Katsurada, and H. Aizawa, *Chem. Lett.*, **1991**, 533; T. Mukaiyama, M. Katsurada, and T. Takashima, *ibid.*, **1991**, 985.

4) The reaction is slow in the case when **4** or **5** was used as nucleophile probably because of the partial deactivation of the catalyst by coordinating to the substituents of amino acid derivatives.

5) K. Matsubara and T. Mukaiyama, *Chem. Lett.*, **1993**, 581.

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