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A Stereoselective Glycosidation Using Thioglycosides, Activation by Combination of *N*-Bromosuccinimide and Strong Acid Salts[1]

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Abstract : A stereoselective glycosidation with thioglycosides was effected under mild and neutral conditions by combined use of *N*-bromosuccinimide (NBS) and a catalytic amount of various strong acid salts. A combination of NBS with Ph_2IOTf, Bu_4NOTf, or Bu_4NClO_4 was advantageous for β-selective glucosidation with 2-*O*-acylated or 2-*O*-benzylated donors by virtue of either the neighboring group participation or the known solvent effect of nitrile, respectively. α-Selective glucosidation was effected by the use of a 2-*O*-benzylated donor in the presence of $LiClO_4$ or $LiNO_3$ as a catalyst in ether. Addition of silica gel to the reaction mixture increased both the α-selectivity and reaction rate.

INTRODUCTION

New effective procedures for stereoselective glycosidation under mild reaction conditions have been strongly required particularly for recent synthesis of complex carbohydrates. Thioglycosides have attracted much attention as versatile glycosyl donors since they are stable under conditions for a variety of chemical manipulations but can be activated with appropriate thiophilic reagents.[2] Recently, we reported that a hypervalent iodine reagent prepared from iodosobenzene (PhIO) and triflic anhydride (Tf_2O) effectively activates thioglycosides to promote facile β-glycosidation.[3] In the present study, we describe another novel method for stereoselective glycosidation with thioglycosides by combined use of *N*-bromosuccinimide (NBS) and strong acid salts, i.e., diphenyliodonium triflate (Ph_2IOTf), tetrabutylammonium triflate (Bu_4NOTf), tetrabutylammonium perchlorate (Bu_4NClO_4), lithium perchlorate ($LiClO_4$), and lithium nitrate ($LiNO_3$).

NBS itself can activate thioglycosides but has not been used in practical syntheses since the rate of glycosidation reaction with this reagent alone is not sufficiently high even for reactive, so-called "armed" thioglycosides.[2f] Recently, the use of *N*-iodosuccinimide (NIS) or NBS together with triflic acid (TfOH) proved to be very effective for activation of not only "armed" but also "disarmed" thioglycosides.[2h,i] This acceleration effect seems to be attributed to intermediary formation of a glycosyl triflate intermediate (or an ion pair of oxocarbenium cation and triflate anion) which reacts rapidly with a glycosyl acceptor. However, the use of TfOH renders the reaction medium strongly acidic, which causes problems in the reaction with acid-labile substrates. We anticipated that a similar but even better acceleration effect will be attained by using a neutral salt of strong acids such as triflates or perchlorates. The reaction is expected to proceed as shown in Fig. 1, the reaction medium being kept neutral throughout the process.

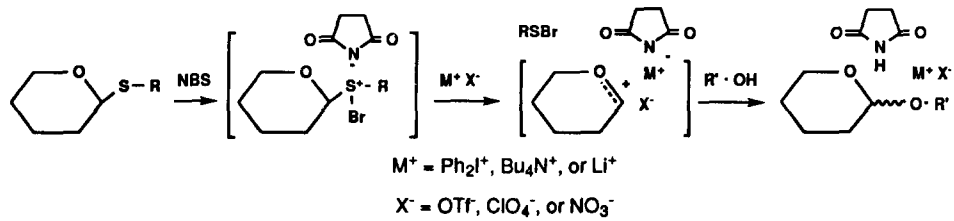
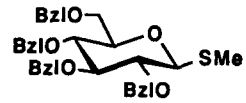


Fig. 1. A plausible reaction mechanism of the glycosidation by using NBS and strong acid salts.

donors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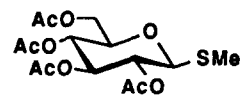
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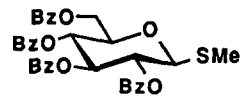
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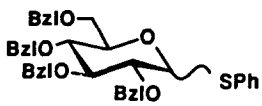
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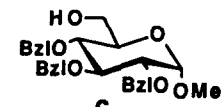
acceptors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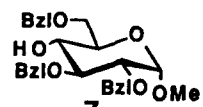
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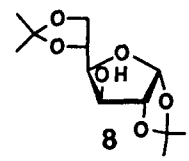
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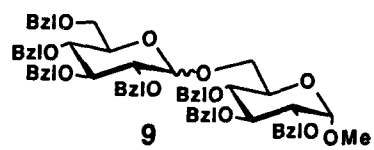
products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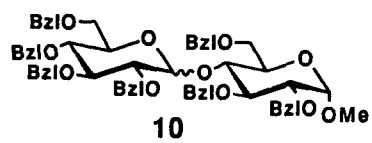
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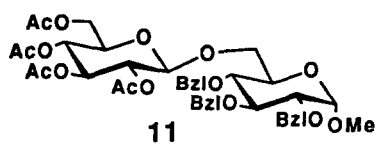
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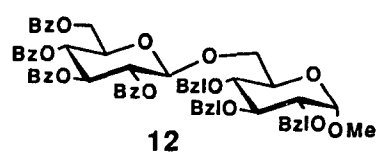
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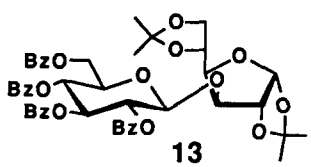
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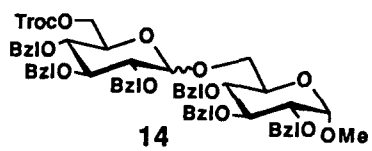
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RESULTS AND DISCUSSION

Glycosidation by this method was first examined with less expensive NBS as an activator and commercially available and crystalline salts, Ph_2IOTf, Bu_4NOTf, and Bu_4NClO_4 as catalysts. All these salts are soluble in organic solvents such as dichloromethane, dichloroethane, acetonitrile, and propionitrile usually employed for glycosidation. The reactions were carried out by use of 1.5 equiv. of NBS and 0.5 equiv. of a catalyst under N_2 atmosphere at -20 °C in either dichloroethane or acetonitrile. The results are summarized in Table 1.

Table 1. Reaction conditions and products in the glycosidation using NBS and either Ph_2IOTf or Bu_4NOTf as activating reagents for thioglycosides.

entry	D [a]	A [b]	D/A	additive	solvent	time [c]	P [d]	yield(%)	α : β [e]
1	**1**	**6**	1 / 0.8	Ph_2IOTf	CH_3CN	<1 min	**9**	90	1: 12
2	**1**	**6**	1 / 0.8	Bu_4NOTf	CH_3CN	<1 min	**9**	98	1: 13
3	**1**	**6**	1 / 0.8	Bu_4NClO_4	CH_3CN	<1 min	**9**	97	1: 12
4	**1**	**7**	1 / 1.1	Ph_2IOTf	CH_3CN	<1 min	**10**	92	1: 3.3
5	**1**	**7**	1 / 1.1	Bu_4NOTf	CH_3CN	<1 min	**10**	86	1: 2.1
6	**1**	**7**	1 / 1.2	Bu_4NClO_4	CH_3CN	<1 min	**10**	75	1: 5.5
7	**1**	**6**	1 / 1	Ph_2IOTf	$(CH_2Cl)_2$	<1 min	**9**	88	1: 0.8
8	**1**	**6**	1 / 1	Bu_4NOTf	$(CH_2Cl)_2$	<1 min	**9**	73	1: 1
9	**1**	**6**	1 / 0.8	Bu_4NClO_4	$(CH_2Cl)_2$	<1 min	**9**	97	1: 3
10	**1**	**7**	1 / 1.1	Ph_2IOTf	$(CH_2Cl)_2$	<1 min	**10**	85	1: 1.3
11	**1**	**7**	1 / 1.1	Bu_4NOTf	$(CH_2Cl)_2$	<1 min	**10**	87	1: 0.4
12	**1**	**7**	1 / 0.8	Bu_4NClO_4	$(CH_2Cl)_2$	30 min	**10**	81	1: 1.1
13	**2**	**6**	1 / 0.7	Bu_4NOTf	$(CH_2Cl)_2$	20 min	**11**	74	0 : 1
14	**3**	**6**	1 / 1.1	Bu_4NOTf	$(CH_2Cl)_2$	15 min	**12**	76	0 : 1
15	**3**	**8**	1 / 1	Bu_4NOTf	$(CH_2Cl)_2$	1.5 h	**13**	70	0 : 1

[a] D = donor. [b] A = acceptor. [c] The reaction time was estimated by TLC analysis on silica gel. [d] P = product. [e] The anomer ratios of compounds **9** and **10** were determined by comparison of the intensities of methyl signals in ^1H NMR, since the complete separation of the anomers was difficult by silica-gel column chromatography.

In fact, the reaction with NBS was remarkably accelerated by addition of these salts. Glycosidation of the free 6-OH group in acceptor **6** with 2,3,4,6-tetra-*O*-benzyl methyl thioglucoside **1** completed within a very short time as shown in Table 1, whereas the same reaction did not complete even after 2 h at room temperature by use of NBS alone. The glycosidation of **6** with **1** proceeded with high β-selectivity in acetonitrile via the known α-nitrilium kinetic intermediates in the case of the all onium salts examined (Table 1, entry 1-3).[2i,4] The β-orienting solvent effect of acetonitrile was reduced in the glucosidation of acceptor **7** possessing a more hindered 4-hydroxyl group (entry 4-6). In dichloroethane, the selectivity was low and varied depending on the salts used (entry 7-12).

By combination of NBS and Bu_4NOTf, the glycosidation with 2-*O*-acylated glucosyl donors **2** and **3** proceeded slightly slower but also quite smoothly under mild reaction conditions to give the corresponding 1,2-*trans*-β-glucoside in good yields (Table 1, entry 13-15). The isopropylidene group proved to be stable under the present neutral glycosidation conditions (entry 15). A remarkable difference was observed of the anion components of the salts on the course of the reaction: combination of NBS and Bu_4NClO_4 was not suitable for the activation of acylated donors **2** or **3** since considerable amounts of the orthoester derivatives were formed (data not shown).

As mentioned, 1,2-*trans*-β-glucosides were formed effectively by the present procedure with both 2-*O*-acylated and benzylated thioglycosides as donors and the combination of NBS with Ph_2IOTf, Bu_4NOTf, or Bu_4NClO_4 as activators.

The stereoselective formation of 1,2-*cis*-glycosides such as α-glucoside is generally rather difficult since no assisting effect such as participation of a neighboring group is available. The *in situ* anomerization method by using glycosyl bromide as a donor has been widely used for formation of α-glucosidic bonds.[5] Some of the other operationally different methods described for α-selective glucosidation seem to proceed via similar glycosyl halogenide intermediates prepared *in situ* from respective glycosyl donors,[2c, 6-8] but the low reaction rate in these methods have restricted their practical application.

In recent years various methods have been devised for rapid and selective α-glucosidation.[2g,4a,9-11] Since perchlorates were frequently used as a source of counter anion against oxocarbenium ion in these methods, we initially anticipated that α-selectivity of glycosidation may be increased by addition of perchloric acid salts in our present method as well. In the glycosidation reaction, however, not only counter anions against oxocarbenium ion but also cations in the reaction medium proved to manifest considerable influence on the stereoselectivity. We thus examined various strong acid salts and found the combined use of NBS with either $LiClO_4$ or $LiNO_3$ to be effective for selective α-glucosidation with thioglycosides. The details of the results are as follows.

Glycosidation was first examined of the same substrate **6** as above and thioglycoside **1** with NBS and various strong acid salts. The reaction was carried out by using 1.5 equiv. of NBS against the donor under N_2 atmosphere at -20 °C in ether.[12] The results are summarized in Table 2.[13] Generally speaking, the reaction in ether was remarkably accelerated by addition of salts which is highly soluble in ether, i.e., LiOTf, $LiClO_4$, $LiBF_4$, and $Mg(ClO_4)_2$. The acceleration effect was less significant with less soluble salts, i.e., Ph_2TOTf, Bu_4NOTf, KOTf, Bu_4NClO_4, $KClO_4$, $NaClO_4$, and $LiNO_3$. In the latter case of slow reaction, the yields of the disaccharide **9** were generally low because of the concomitant formation of the glycosyl bromide as a by-product. The same applied to sparingly soluble salts such as Bu_4NHSO_4, $MgSO_4$, and $CaSO_4$ (data not shown).

With regard to the anomeric selectivity, KOTf (entry 4) and Bu_4NClO_4 (entry 7) gave the highest α-selectivity among the triflates and perchlorates examined under the above conditions. However, the yields were not satisfactory owing to the formation of the glycosyl bromide as mentioned above. When the same reaction was carried out in other solvent systems, such as tetrahydrofuran (THF), THF-ether, and dichloroethane-ether, which dissolve Bu_4NClO_4 better, the reaction proceeded quite rapidly but stereoselectivity was almost completely lost (entry 8-10).

The glycosidation proceeded rapidly in the presence of 0.5 equiv. of $LiClO_4$ to give disaccharide **9** in a good yield (entry 13) although α-selectivity was not satisfactory. The reaction temperature (-50 °C, -30 °C, 20

°C) had no effect on the selectivity (data not shown). However, the use of lower amount of $LiClO_4$ (0.1 or 0.05 equiv.) remarkably improved the α-selectivity to give the desired α-glucoside **9** in good yields (entry 14,

Table 2. α-Selective glucosidation using NBS and strong acid salts as activating reagents for thioglucosides.

entry	D[a]	A[b]	D/A	additive (equiv.)	solvent	time[c]	P[d]	yield(%)	α : β[e]
1	**1**	**6**	1 / 0.8	none	ether	45 h	**9**	60	1 : 0.11
2	**1**	**6**	1 / 1	Ph_2IOTf (0.5)	ether	15 h	**9**	84	1: 0.17
3	**1**	**6**	1 / 0.8	Bu_4NOTf (0.5)	ether	5 h	**9**	61	1: 0.43
4	**1**	**6**	1 / 0.8	KOTf (0.5)	ether	7 h	**9**	65	1: 0.08
5	**1**	**6**	1 / 0.8	LiOTf (0.5)	ether	1 h	**9**	73	1: 0.39
6	**1**	**6**	1 / 0.8	LiOTf (0.04)	ether	4 h	**9**	68	1: 0.20
7	**1**	**6**	1 / 0.8	Bu_4NClO_4 (0.5)	ether	20 h	**9**	61	1 : 0.08
8	**1**	**6**	1 / 0.8	Bu_4NClO_4 (0.5)	THF	<1 min	**9**	84	1 : 1.1
9	**1**	**6**	1 / 0.8	Bu_4NClO_4 (0.5)	$(CH_2Cl)_2$:ether=1:1	<1 min	**9**	93	1 : 0.91
10	**1**	**6**	1 / 0.8	Bu_4NClO_4 (0.5)	THF:ether=2:3	<1 min	**9**	95	1 : 0.93
11	**1**	**6**	1 / 0.8	$KClO_4$ (0.5)	ether	2.5 h	**9**	49	1 : 0.25
12	**1**	**6**	1 / 0.8	$NaClO_4$ (0.5)	ether	14 h	**9**	68	1 : 0.15
13	**1**	**6**	1 / 0.8	$LiClO_4$ (0.5)	ether	3 min	**9**	92	1 : 0.40
14	**1**	**6**	1 / 0.8	$LiClO_4$ (0.1)	ether	12 min	**9**	88	1 : 0.12
15	**1**	**6**	1 / 0.8	$LiClO_4$ (0.05)	ether	2 h	**9**	99	1 : 0.11
16[f]	**1**	**6**	1 / 0.8	$LiClO_4$ (3.0)	ether	50 min	**9**	84	1 : 0.34
17	**1**	**6**	1 / 0.8	$Mg(ClO_4)_2$ (0.5)	ether	10 min	**9**	71	1 : 0.27
18	**1**	**6**	1 / 0.8	$LiNO_3$ (0.5)	ether	3.5 h	**9**	80	1 : 0.03
19	**1**	**6**	1 / 0.8	$LiNO_3$ (3.0)	ether	6 h	**9**	60	1 : 0.02
20	**1**	**6**	1 / 0.8	$LiBF_4$ (0.5)	ether	42 min	**9**	61	1 : 0.30
21	**1**	**7**	1 / 0.7	$LiClO_4$ (0.5)	ether	30 min	**10**	83	1 : 0.09
22	**1**	**7**	1 / 0.8	$LiClO_4$ (0.1)	ether	24 h	**10**	36	1 : 0.13
23	**1**	**7**	1 / 0.8	$LiNO_3$ (0.5)	ether	30 h	**10**	30	1 : 0.05
24	**4**	**6**	1 / 1	$LiClO_4$ (0.1)	ether	5.5 h	**9**	70	1 : 0
25	**5**	**6**	1 / 1	$LiClO_4$ (0.1)	ether	8 h	**14**	22	1 : 0

[a] D = donor. [b] A = acceptor. [c] The reaction time was estimated by TLC analysis on silica gel. [d] P = product. [e] The anomer ratios of compounds **9** and **10** were determined by comparison of the intensities of methyl signals in ^1H NMR, since the complete separation of the anomers was difficult by silica-gel column chromatography. [f] The reaction was carried out at 20 °C.

15). Under the latter conditions the reaction became slower but completed still within an acceptable period of time. By contrast, both reaction rate and selectivity decreased considerably when higher amount (3 equiv.) of $LiClO_4$ was used (entry 16). The mechanism responsible for these facts is not clear but the phenomena seem to

be typical of lithium cation rather than perchlorate. A similar, though less significant, tendency was observed with LiOTf (entry 5, 6), whereas anomeric selectivity did not change from the value given in Table 1 (entry 17) even when the amount of $Mg(ClO_4)_2$ was reduced (data not shown). Among the other salts examined as a catalyst, $LiNO_3$ gave disaccharide **9** with high α-selectivity in a good yield (entry 18). The reaction rate was decreased by use of excess $LiNO_3$ (3 equiv., entry 19) similarly to the case of $LiClO_4$.

The glycosidation of acceptor **7** possessing a more hindered 4-hydroxyl group also proceeded smoothly by use of *S*-methyl thioglycoside **1** as a donor and 0.5 equiv. of $LiClO_4$ as a catalyst to give disaccharide **10** with high α-selectivity (entry 21). On the other hand, the uses of 0.1 equiv. of $LiClO_4$ or 0.5 equiv. of $LiNO_3$ did not effectively promoted the glycosidation since a considerable amount of the glycosyl bromide was formed (entry 22, 23).

The combination of NBS and $LiClO_4$ (0.1 equiv.) efficiently activated less reactive phenyl thioglycoside **4** (α:β=2:1) to give disaccharide **9** with perfect α-selectivity (entry 24). However, the present method was not effective for the glycosidation with considerably less reactive phenyl thioglycoside **5** possessing 6-*O*-trichloroethoxycarbonyl (Troc) group as a donor, giving disaccharide **14** in a low yield and the corresponding glycosyl bromide as a major product (entry 25).[14]

Previously, we successfully applied a hypervalent iodine reagent prepared from PhIO and Tf_2O to the activation of thioglycosides.[3] In that work a dramatic enhancement of reaction rate was observed in the glycosidation with 2-*O*-acylated thioglycoside by addition of silica gel. The effect of silica gel was therefore examined in the present study. The reaction was carried out using *S*-methyl thioglycoside **1** and acceptor **6** (150 μmol) in ether (2 ml) in the presence of 200 mg of silica gel which was dried previously. In fact, both reaction rate and α-selectivity were remarkably increased by addition of silica gel in the reaction with NBS alone without additives (Table 3, entry 1 vs. Table 2, entry 1). The yield dropped, however, because of the formation of the glycosyl bromide: silica gel was found to enhance the glycosyl bromide formation rather than glycosidation.[15] Complete α-selectivity was obtained by addition of silica gel to the combination of NBS and KOTf, $LiClO_4$, or $LiNO_3$ (Table 3, entry 2, 4, 7) though the yields of the disaccharide remained around the range of 50-60 %. The yield was improved by employing higher ratio of the donor or longer reaction period, but under such conditions α-selectivity was partly lost (entry 3, 5, 6).[16] The reaction proceeded more slowly with lower amounts of silica gel (entry 8, 9), but addition of too much silica gel hindered stirring of the reaction mixture and decreased the selectivity (entry 10).

The reason is not known at moment why silica gel improves α-selectivity: heterogeneous reaction involving the solid surface of silica gel may bring about many complex factors. Furthermore, the ultimate active species of the present glycosidation reaction is not yet clear. We nevertheless expect further study with silica gel or other solid materials in combination with strong acid salts may lead to optimum reaction conditions which give higher yields of glycosides without loosing the anomeric selectivity.

Table 3. Enhancement of α-selectivity in glucosidation with thioglucoside and NBS by silica gel.[a]

entry	**1** / **6**	additive (equiv.)	silica gel (mg)[b]	time[c]	yield (%) of **9**	α : β[d]
1	1 / 0.8	none	200	50 min	44	1 : 0.02
2	1 / 0.8	KOTf (0.5)	200	2 h	51	1 : 0
3	1 / 0.6	KOTf (0.5)	200	2.5 h	82	1 : 0.06

4	1 / 0.8	$LiClO_4$	(0.05)	200	1 h	50	1 : 0
5	1 / 0.6	$LiClO_4$	(0.05)	200	3 h	62	1 : 0.01
6	1 / 0.7	$LiClO_4$	(0.05)	200	3 d [e]	91	1 : 0.07
7	1 / 0.7	$LiNO_3$	(0.5)	200	1 h	60	1 : 0
8	1 / 0.8	$LiNO_3$	(0.5)	50	1.5 h	51	1 : 0
9	1 / 0.8	$LiNO_3$	(0.5)	20	3.5 h	53	1 : 0
10	1 / 0.8	$LiNO_3$	(0.5)	1000	45 min	61	1 : 0.12

[a] The reaction was carried out using 150 μmol of **6** in ether (2.0 ml). [b] Merck Kieselgel 60 (0.040 - 0.063 mm). [c] The reaction time was estimated by TLC analysis on silica gel. [d] The anomer ratio was determined by comparison of the intensities of methyl signals of both anomers in ^1H NMR. [e] The reaction was continued after disappearance of thioglycoside **1** on TLC.

The present combinations of NBS and strong acid salts effectively promote glycosidation with thioglycosides under mild and neutral reaction conditions to give high yields of glycosides, providing one of the most practically useful method for the glycosidation. Both α- and β-anomers can be prepared from a single 2-*O*-benzylated donor by choosing appropriate combination of solvents and salts, i.e., β-selective glucosidation is effected by the use of Ph_2IOTf, Bu_4NOTf, or Bu_4NClO_4 in acetonitrile whereas α-selective glucosidation is effected by the use of $LiClO_4$ or $LiNO_3$ in ether. A combination of NBS with Bu_4NOTf effectively activates "disarmed" 2-*O*-acylated donors to give β-glucoside in good yields. The experimental procedure of the present glycosidation is quite simple and requires only commercially available crystalline, stable, and not hygroscopic reagents.

EXPERIMENTAL

All melting points are uncorrected. ^1H NMR spectra were measured on JEOL JNM-GSX 270, EX 270, or GX 500 spectrometers for $CDCl_3$ solutions unless otherwise noted. The chemical shifts are given in δ values with tetramethylsilane (TMS) as the internal standards. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Silica-gel column chromatography was carried out using Merck Kieselgel 60 (0.040 - 0.063 mm) at medium-pressure (2 - 4 kg cm^{-2}). Silica-gel TLC was carried out using Merck Kieselgel 60 F_{254}. Silica gel used for glycosidation was dried at 200 °C under reduced pressure overnight. Organic solutions were dried over $MgSO_4$ and evaporated *in vacuo*.

General Procedure for Glycosidation. To a solution of a thioglycoside (182 μmol) and an acceptor (151 μmol) in a dry solvent (2.0 ml) was added Molecular Sieves 4A (200 mg) under N_2 atmosphere. To the mixture were added NBS (271 μmol) and a salt (90 μmol) at -20 °C, and the mixture was stirred at -20 °C until the reaction was completed. Ethyl acetate and a saturated aqueous $NaHCO_3$ solution were added and Molecular Sieves 4A was removed by filtration. The organic layer was washed with brine, dried, and concentrated. The product was purified by silica-gel column chromatography.

Methyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (9). ^1H NMR, α-anomer: δ=4.98 (d, 1H, $J_{1',2'}$=3.36 Hz, H-1'), 4.55 (d, 1H, $J_{1,2}$=4.10 Hz, H-1), 3.53 (dd, 1H, $J_{2',1'}$=3.66 Hz, $J_{2',3'}$=9.15 Hz, H-2'), 3.43 (dd, 1H, $J_{2,1}$=4.10 Hz, $J_{2,3}$=9.46 Hz, H-2), 3.35 (s, 3H, OMe); β-anomer: δ=4.61 (d, 1H, $J_{1,2}$=3.50 Hz, H-1), 4.35 (d, 1H, $J_{1',2'}$=7.94 Hz, H-1'), 3.55-3.45 (H-2, H-2'), 3.32 (s, 1H, OMe). Found: C, 74.97; H, 6.70. Calcd for

$C_{62}H_{66}O_{11}$•0.34H_2O: C, 74.97; H, 6.77.

Methyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl-(1→4)-2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (10). ^{1}H NMR, α-anomer: δ=5.67 (d, 1H, $J_{1',2'}$=3.63 Hz, H-1'), 3,48 (dd, 1H, $J_{2',1'}$=3.63 Hz, $J_{2',3'}$=9.90 Hz, H-2'), 3.43 (dd, 1H, $J_{2,1}$=4.10 Hz, $J_{2,3}$=9.46 Hz, H-2), 3.38 (s, 3H, OMe); β-anomer δ=4.59 (d, 1H, $J_{1,2}$=2.64 Hz, H-1), 4.58 (d, 1H, $J_{1',2'}$=7.92 Hz, H-1'), 3.37 (s, 3H, OMe). Found: C, 74.89; H, 6.65. Calcd for $C_{62}H_{66}O_{11}$•0.4H_2O: C, 74.89; H, 6.77.

Methyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (11). $[\alpha]_D^{24}$ +8.73° (*c* 1.0, $CHCl_3$); ^{1}H NMR, δ=7.37-7.23 (m, 15H, Ph x 3), 5.17 (dd, 1H, $J_{3',4'}$=$J_{3',2'}$=9.24 Hz, H-3'), 5.14-5.00 (m, 2H, H-2', H-4'), 4.97 and 4.79 (each d, 2H, J_{gem}=11.05 Hz, $\underline{CH_2}$Ph), 4.85 and 4.53 (each d, 2H, J_{gem}=11.06 Hz, $\underline{CH_2}$Ph), 4.78 and 4.64 (each d, 2H, J_{gem}=12.20 Hz, $\underline{CH_2}$Ph), 4.58 (d, 1H, $J_{1,2}$=3.63 Hz, H-1), 4.51 (d, 1H, $J_{1',2'}$=7.59 Hz, H-1'), 4.23 (dd, 1H, $J_{6',5'}$=4.62 Hz, J_{gem}=12.21 Hz, H-6'), 4.11 (dd, 1H, $J_{6',5'}$=2.64 Hz, J_{gem}=12.21 Hz, H-6'), 4.05 (dd, 1H, $J_{6,5}$=1.64 Hz, J_{gem}=10.56 Hz, H-6), 3.97 (dd, 1H, $J_{3,2}$=$J_{3,4}$=9.57 Hz, H-3), 3.79-3.60 (m, 3H, H-5, H-5', H-6), 3.51 (dd, 1H, $J_{2,3}$=9.57 Hz, $J_{2,1}$=3.63 Hz, H-2), 3.45-3.37 (m, 1H, H-4), 3.36 (s, 3H, OMe), 2.09, 2.01, 1.99, and 1.95 (each s, 12H, Ac x 4). Found: C, 63.08; H, 6.27. Calcd for $C_{41}H_{50}O_{15}$: C, 63.47; H, 6.34.

Methyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (12). $[\alpha]_D^{21}$ +19.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR, δ=8.00-7.03 (m, 35H, Ph x 7), 5.88 (dd, 1H, $J_{3',4'}$=$J_{3',2'}$=9.57 Hz, H-3'), 5.66 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$=9.57 Hz, H-4'), 5.58 (dd, $J_{2',3'}$=9.57 Hz, $J_{2',1'}$=7.92 Hz, H-2'), 4.90-4.27 (m, 8H, $\underline{CH_2}$Ph x 3, H-6' x 2), 4.81 (d, 1H, $J_{1',2'}$=7.59 Hz, H-1'), 4.51 (d, 1H, $J_{1,2}$=3.63 Hz, H-1), 4.15-4.07 (m, 2H, H-6, H-5'), 3.88 (dd, 1H, $J_{3,2}$=$J_{3,4}$=9.24 Hz, H-3), 3.76-3.70 (m, 2H, H-5, H-6), 3.44-3.33 (m, 2H, H-2, H-4), 3.20 (s, 3H, OMe). Found: C, 70.97; H, 5.52. Calcd for $C_{63}H_{58}O_{15}$•0.6H_2O: C, 70.99; H, 5.60.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (13). $[\alpha]_D^{21}$ -16.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR, δ=8.08-7.18 (m, 20H, Ph x 4), 6.12 (d, 1H, $J_{1,2}$=5.18 Hz, H-1), 5.73 (d, 1H, $J_{1',2'}$=3.63 Hz, H-1'), 5.71 (dd, 1H, $J_{3,2}$=1.32 Hz, $J_{3,4}$=3,29 Hz, H-3), 5.42 (m, 1H, H-4), 4.83 (ddd, 1H, $J_{2,1}$=5.28 Hz, $J_{2,3}$=1.32 Hz, $J_{2,4}$=3.30 Hz, H-2), 4.51 (dd, 1H, $J_{6,5}$=2.64 Hz, $J_{6,6}$=12.2 Hz, H-6), 4.39-4.24 (m, 3H, H-6, H-5', H-6'), 4.11-4.03 (m, 3H, H-5, H-3, H-6'), 3.98 (d, 1H, $J_{2',3'}$=0.0 Hz, $J_{2'1'}$=3.63 Hz, H-2'), 3.92 (dd, 1H, $J_{4',3'}$=5.94 Hz, $J_{4',5'}$=8.58 Hz or vice versa, H-4'), 1.40, 1.35, 1.20, 1.15 (each s, 12H, Me x 4). Found: C, 64.83; H, 5.44. Calcd for $C_{46}H_{46}O_{15}$•0.6H_2O: C, 65.03; H, 5.60.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-trichloroethoxycarbonyl-D-glucopyranosyl-(1→6)-2,3,4-tetra-*O*-benzyl-α-D-glucopyranoside (14). Complete separation of α- and β-anomers was not possible by silica-gel column chromatography ($CHCl_3$-acetone = 200:1). ^{1}H NMR, α- anomer : δ=7.31-7.15 (m, 30H, Ph x 6), 4.94 (d, 1H, $J_{1',2'}$=3.96 Hz, H-1'), 4.54 (d, 1H, $J_{1,2}$=3.63 Hz, H-1), 4.98-4.54 (m, 14H, $\underline{CH_2}$Ph x 6 and CO$\underline{CH_2}$$CCl_3$), 4.31 (d, 2H, $J_{5,6'}$=3.30Hz, $J_{6',6'}$=0, H_2-6'), 3.98 (dd, 1H, $J_{3,2}$=$J_{3,4}$=9.24 Hz, H-3), 3.97 (dd, 1H, $J_{3',2'}$=$J_{3',4'}$=9.24 Hz, H-3'), 3.89-3.83 (ddd, 1H, $J_{5'6'}$=3.30 Hz, $J_{5',4'}$=9.24 Hz, H-5'), 3.81-3.68 (m, 3H, H-5, H_2-6), 3.63 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.24 Hz, H-4), 3.50 (dd, 1H, $J_{2',1'}$=3.96 Hz, $J_{2',3'}$=9.57 Hz, H-2'), 3.50 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$=9.57 Hz, H-4'), 3.43 (dd, 1H, $J_{2,1}$=3.63 Hz, $J_{2,3}$=9.56 Hz, H-2), 3.35 (s, 3H, OMe); β-anomer: δ=3.32 (s, 3H, OMe). Found: C, 63.36; H, 5.83. Calcd for $C_{58}H_{61}O_{13}Cl_3$•1.5H_2O: C, 63.36; H, 5.87.

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12. The plausible equatorial oxonium ion intermediates generally thought to favor the formation of an axial glycoside due to the reverse anomeric effect in an ether solution.[2g,4a,9a,10b-e]
13. The combination of NIS and $LiClO_4$ (0.5 equiv.) also promoted glycosidation of **6** with thioglycoside **1** in ether effectively to give corresponding disaccharide **9** in 72% yield, though the selectivity was not satisfactory ($\alpha:\beta = 1 : 0.57$).
14. We recently found that less reactive 6-*O*-Troc thioglycoside **5** was effectively activated by the use of

NBS-$AgClO_4$, PhIO-$SnCl_2$-$AgClO_4$, or PhIO-$SnCl_2$-$AgClO_4$ to give α-glucoside **14** with high selectivity by virtue of the influence of 6-*O*-Troc function, which was recently found in the glycosidation with glycosyl fluorides.[18] These results will be published soon elsewhere.

15. The corresponding glycosyl bromide was obtained quantitatively from thioglycoside **1** by the use of NBS and silica gel in the absence of glycosyl acceptor in ether at -20 °C for 40 min.
16. The stereoselectivity was not always reproducible from unknown reasons in the reaction with $LiClO_4$.
17. The glycosidation of **6** with the corresponding glycosyl bromide prepared *in situ* from **1** proceeded slowly in the presence of $LiClO_4$ (0.05 equiv.) and silica gel at -20 °C during 3 d to give disaccharide **9**: Yield 18% (α:β=1: 0.17). Therefore, the glycosidation with thioglycoside **1** using silica gel under the prolonged reaction conditions may proceed partly via the glycosyl bromide to give disaccharide **9** with lower α-selectivity.
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