

Selected Paper

Glycosyl Phosphonium Halide as a Reactive Intermediate in Highly α-Selective Glycosylation

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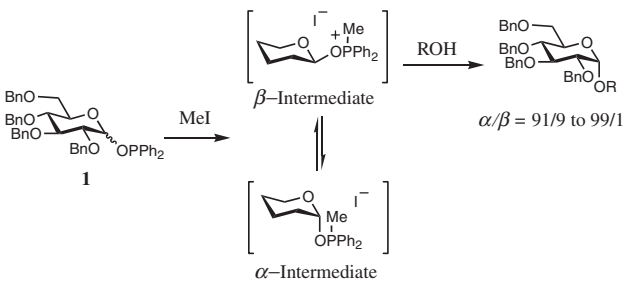
Highly α-selective glycosylations of several glycosyl acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide (**4**) proceeded smoothly in the presence of tri(1-pyrrolidino)phosphine oxide in CH_2Cl_2 at room temperature or in refluxing $CHCl_3$ via glycosyl phosphonium bromide intermediates and the corresponding disaccharides were afforded in good yields with high selectivities. Further, the one-pot glycosylation starting from glycosyl acetate using iodotrimethylsilane and phosphine oxide also proceeded efficiently in CH_2Cl_2 at room temperature to give the corresponding disaccharides, although this one-pot synthesis of α-glycoside via in situ anomerization procedure is considered difficult because glycosyl halide reacts with trimethylsilyl acetate easily to regenerate glycosyl acetate, a starting glycosyl donor.

To develop a new method for the stereoselective glycosylation is one of the most important and fundamental topics in carbohydrate chemistry.[1] 1,2-cis-Glycosylation is less successful than 1,2-trans-glycosylation since the substituent at C-2 that does not participate in neighboring effect, for example *O*-benzyl ether, must be chosen. Secondly, S_N2 reaction at anomeric center of an unstable β-glucosyl bromide is quite difficult.[2] Lemieux and co-workers showed that the reaction of α-pyranosyl bromide with bromide ion produced highly reactive β-pyranosyl bromide, which in turn reacted with an acceptor much faster than the α-one, and consequently α-glycoside was formed predominantly.[3] This method is generally called in situ anomerization method and is employed frequently in the formation of α-glycosyl linkage[4] when galactose and fucose are employed as donors, although it is less effective in the case when glucose is used. The above glycosyl bromide is generally prepared from glycosyl acetate and trialkylsilyl bromide, though its isolation is often difficult.[5] To isolate glycosyl bromide is necessary for the in situ anomerization method because an undesired reverse reaction of forming glycosyl acetate takes place in the subsequent glycosylation reaction when the above mixture is used without purification.[6] Thus, the one-pot synthesis of α-glycoside starting from glycosyl acetate involving in situ anomerization procedure has long been considered difficult.

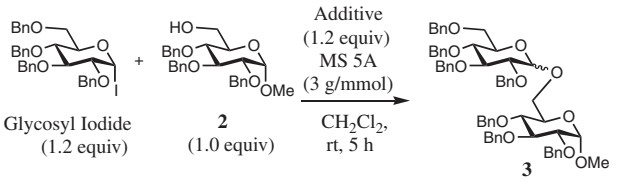
Recently, successful α-stereoselective glycosylation of glycosyl acceptors using glycosyl diphenylphosphinite **1**, a glycosyl donor, and iodomethane, a promoter, was reported from our laboratory (Scheme 1).[7]

It is considered that this glycosylation proceeds via glycosyl phosphonium iodide intermediates formed by the reaction of glycosyl diphenylphosphinite and iodomethane, as was explained in the previous experiment result that phosphine oxide promoted the reaction of glycosyl iodide and **2** and the corresponding disaccharide **3** was formed in α-selective manner



Scheme 1. Glycosylation of glycosyl acceptor with donor **1** and iodomethane.

Table 1. Effect of Additives on Glycosylation of Acceptor **2** with Glycosyl Iodide



Entry	Additive	Yield/% (α/β)[a)]
1	—	47 (71.3/28.7)
2	n-Bu_4NI/(i-$Pr)_2NEt$	42 (92.2/7.8)
3	$Ph_2P(=O)Me$	**86 (94.2/5.8)**

a) The α/β ratios were determined by HPLC analysis.

(Table 1).[7] It is also noted that this system of using phosphine oxide was more effective to promote the glycosylation than the n-Bu_4NI/(i-$Pr)_2NEt$ system of Lemieux's in situ anomerization process.

In order to maximize this interesting character of a glycosyl phosphonium halide, we studied in detail glycosylations using glycosyl halides by the promotion of phosphine oxide. Further,

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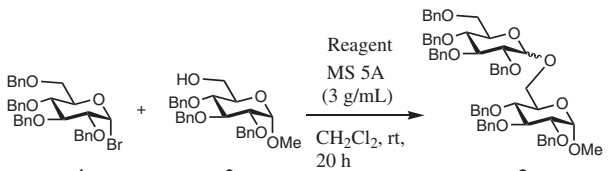
the one-pot glycosylation of several acceptors using glycosyl acetate and iodotrimethylsilane in the presence of phosphine oxide was studied in order to establish a more useful glycosylation method.

In this paper, we would like to report on highly α-selective glycosylation of several acceptors with glycosyl bromide in the presence of phosphine oxide as a promoter. Further, a one-pot glycosylation via glycosyl phosphonium iodide by using glycosyl acetate, iodotrimethylsilane, and triphenylphosphine oxide is also described.

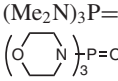
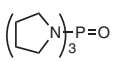
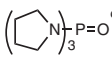
Results and Discussion

Glycosylation by Using Glycosyl Bromide by the Promotion of Phosphine Oxide. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl bromide (**4**) was selected for a glycosyl donor since the bromide **4** was more stable than the corresponding glycosyl iodide. It is easily prepared by the reaction of glycosyl acetate with bromotrimethylsilane in $CHCl_3$, followed by evaporation of solvent and TMSOAc.[5a] In the first place, glycosylations of the acceptor **2** were tried with glycosyl bromide **4** in the presence of several promoters and molecular sieves 5A[8] in dichloromethane at room temperature (Table 2). The glycosylation was promoted effectively by using phosphine oxides such as diphenylmethylphosphine oxide, tributylphosphine oxide, or triphenylphosphine oxide; the desired **3** was afforded in good yields with high stereoselectivities in all cases (Table 2, Entry 1–4). While yields and stereoselectivities of reactions promoted by triphenylphosphine sulfide or triphenyl phosphate were low (Table 2, Entry 5, 6), the corresponding disaccharides were obtained in a highly α-selective manner when phosphoric acid triamide derivatives were used (Table 2, Entries 7–10). Finally, it was found that tri(1-pyrrolidino)phosphine oxide[9] was the most effective promoter: it afforded **3** in 92% yield (Table 2, Entry 10, $\alpha/\beta = 94.3/5.7$). The stereoselectivity of **3** increased as the amount of reagent increased (Table 2, Entry 11, $\alpha/\beta = 95.6/4.4$), although the α-selectivity remained low if the reaction was performed according to Lemieux's procedure (Table 2, Entry 12, $\alpha/\beta = 89.5/10.5$).

Table 2. Glycosylations of Acceptor **2** with Glycosyl Bromide **4** in the Presence of Various Reagents

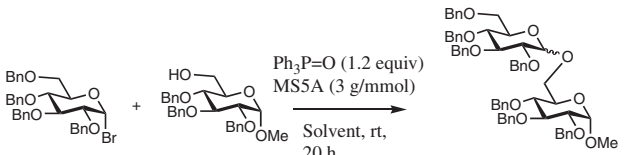


4 **2** **3**

Entry	**1**/equiv	Reagent[b)]	Yield/%	α/β[a)]
1	1.0	$Ph_2P(=O)Me$	72	93.8/6.2
2	1.2	$Ph_2P(=O)Me$	86	94.0/6.0
3	1.2	$Bu_3P=O$	86	93.1/6.9
4	1.2	$Ph_3P=O$	84	94.5/5.5
5	1.2	$Ph_3P=S$	10	79.7/20.3
6	1.2	$(PhO)_3P=O$	6	75.4/24.6
7	1.0	$(Me_2N)_3P=O$	74	94.3/5.7
8	1.2	$(Me_2N)_3P=O$	89	93.8/6.2
9	1.2		64	93.0/7.0
10	1.2		**92**	**94.3/5.7**
11	1.5		**95**	**95.6/4.4**
12	1.2	$Et_4NBr/(i\text{-}Pr)_2NEt$	84	89.5/10.5

a) The α/β ratios were determined by HPLC analysis. b) The same equivalent to **4** was used. c) 3.0 equivalent of reagent was used.

Table 3. Glycosylation of **2** with Glycosyl Bromide **4** in the Presence of Triphenylphosphine Oxide in Various Solvent



4 (1.2 equiv) **2** (1.0 equiv) **3**

Entry	Solvent	Yield/%	α/β[a)]
1	THF	60	92.3/7.7
2	$i\text{-}Pr_2O$	44	95.1/4.9
3	DME	35	95.8/4.2
4	CH_3CN	69	87.5/12.5
5	Toluene	51	92.0/8.0
6	EtOAc	52	90.3/9.7
7	Acetone	39	89.1/10.9
8	DMF	69	81.9/18.1
9	CH_3NO_2	77	84.6/15.4
10	$CHCl_3$	72	92.1/7.9
11	CH_2Cl_2	**84**	**94.5/5.5**

a) The α/β ratios were determined by HPLC analysis.

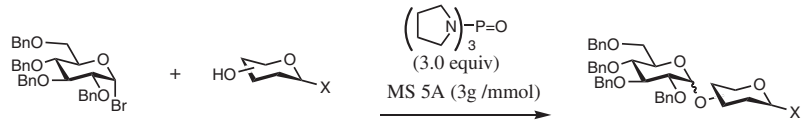
Next, the effect of solvents was examined (Table 3). In ethers such as THF, $i\text{-}Pr_2O$, or DME, the desired **3** was produced in moderate yields with high stereoselectivities (Table 3, Entries 1–3). The reaction in dichloromethane solvent afforded **3** in high yield with high stereoselectivity (Table 3, Entry 11), while the stereoselectivities were low when other typical organic solvents were used (Table 3, Entries 4–10).

Next, glycosylations of various acceptors with glycosyl bromide **4** in the presence of tri(1-pyrrolidino)phosphine oxide were tried (Table 4). Each reaction proceeded efficiently in dichloromethane at room temperature and afforded the corresponding disaccharides in good to high yields with high α-selectivities even when an acid-labile glycosyl fluoride[10] was used as an acceptor (Table 4, Condition a). The reactions were highly accelerated in refluxing chloroform, but their stereoselectivities became slightly lower (Table 4, Condition b).

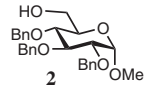
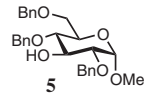
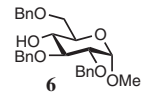
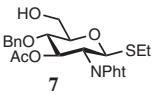
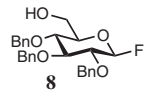
Thus, the glycosylation using glycosyl bromide could be successfully carried out by the promotion of phosphine oxide and various α-disaccharides were afforded in high yields with high α-selectivities.

Glycosylation via a Glycosyl Phosphonium Iodide Intermediate Generated from Glycosyl Acetate. In order to establish a more useful glycosylation reaction, we tried a one-pot in situ anomerization procedure starting from glycosyl acetate in the co-existence of iodotrimethylsilane and phosphine oxide even though the one-pot synthesis of α-glycoside via the in situ anomerization procedure was not successful, as shown in several reports.

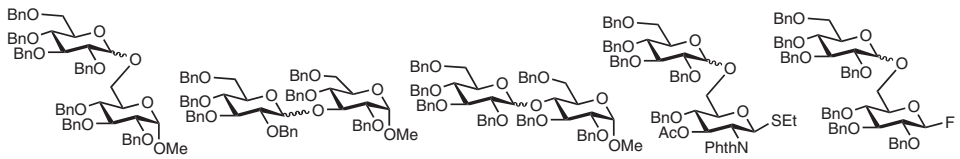
Table 4. Glycosylation of Various Acceptors with Donor **4** by the Promotion of Tri(1-pyrrolidino)-phosphine Oxide



Donor **4** (1.5 equiv) Acceptor (1.0 equiv) Disaccharide

Entry	Acceptor	Product	Condition[a)]	Time/h	Yield/%	α/β
1	 **2**	**3**	a	20	95	95.6/4.4[b)]
2			b	3	94	94.7/5.3[b)]
3	 **5**	**9**	a	72	91	97.2/2.8[b)]
4			b	5	83	95.6/4.4[b)]
5	 **6**	**10**	a	96	83	98.3/1.7[b)]
6			b	5	66	95.8/4.2[b)]
7	 **7**	**11**	a	40	88	95.0/5.0[b)]
8			b	3	87	91.5/8.5[b)]
9	 **8**	**12**	a	24	88	95.5/4.5[c)]
10			b	3	76	93.3/6.7[c)]

a) Condition a: CH_2Cl_2, rt; b: $CHCl_3$, reflux. b) The α/β ratios were determined by HPLC analysis. c) The α/β ratios were determined by isolated yields of both isomers. d) 3.0 equiv of **4** was used.

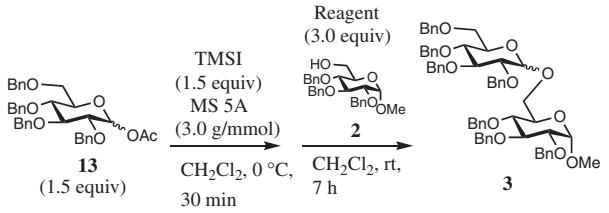


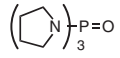
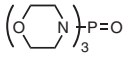
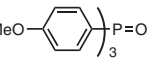
3 **9** **10** **11** **12**

In the first place, glycosylations of acceptor **2** with glycosyl iodide generated from glycosyl acetate **13** and iodotrimethylsilane in the presence of several promoters were tried in dichloromethane at room temperature (Table 5). When phosphoric acid triamide derivatives were used, the desired disaccharides were obtained in moderate yields with high stereoselectivities (Table 5, Entries 1–3). When trialkylphosphine oxides were used, the corresponding disaccharides were effectively formed in a highly α-selective manner (Table 5, Entries 6–9), although yields and stereoselectivities of those promoted by triphenylphosphine sulfide and phenyl diphenylphosphinite, respectively, remained low (Table 5, Entries 4, 5). It is thus noted that triphenylphosphine oxide excellently promoted the glycosylation to afford the corresponding disaccharide in high yield with high selectivity (Table 5, Entry 9). In the absence of phosphine oxide, however, the stereoselectivity was not controlled well (Table 5, Entry 10), and also **3** was afforded in low yield with lower selectivity when bromotrimethylsilane, a milder promoter than iodotrimethylsilane, was used (Table 5, Entry 11). In the case when tetrabutylammonium iodide was used as a promoter in the co-existence of *N*,*N*-diisopropylethylamine, a starting material, namely glycosyl acetate **13**, was recovered by the reverse reaction between glycosyl iodide and trimethylsilyl acetate (Table 5, Entry 12). It is remarkable to note that the glycosyl acetate formed by this reverse reaction was not obtained if phosphine oxide was used as a promoter.

Next, the effect of the molar ratio of **13**, iodotrimethylsilane and triphenylphosphine oxide was studied (Table 6). The desired disaccharide was obtained in 86% yield with high α-selectivity ($\alpha/\beta = 96.1/3.9$) when 1.5 equivalents each of **13** and iodotrimethylsilane and 3.0 equivalents of triphenylphosphine oxide were used (Table 6, Entry 3). When an excess amount of triphenylphosphine oxide was used, the glycosyl phosphonium iodide intermediate was stabilized by coordination of the phosphine oxide and the yield of the disaccharide decreased (Table 6, Entry 4). On the other hand, the glycosylation was accelerated and **3** was obtained in 95% yield when double amounts of **13**, iodotrimethylsilane and triphenylphos-

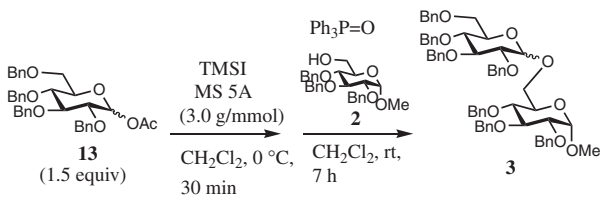
Table 5. Glycosylations of Acceptor **2**, with Glycosyl Acetate **13** via Glycosyl Phosphonium Iodide Using Various Reagents



Entry	Reagent	Yield/%	α/β[a]
1		61	94.1/5.9
2	$(Me_2N)_3P{=}O$	69	94.3/5.7
3		61	95.9/4.1
4	$Ph_3P{=}S$	58	71.2/22.8
5	$Ph_2P(=O)OPh$	56	95.2/4.1
6	n-$Bu_3P{=}O$	72	95.0/5.0
7	$Ph_2P(=O)Me$	73	95.4/4.6
8		69	94.8/5.2
9	$Ph_3P{=}O$	**89**	**96.1/3.9**
10	—	59	68.4/31.6
11	$Ph_3P{=}O$[b]	8	93.1/6.9
12	n-$Bu_4NI/(i\text{-}Pr)_2NEt$	19	91.6/8.4

a) The α/β ratios were determined by HPLC analysis. b) TMSBr was used instead of TMSI.

Table 6. Optimization of the Molar Ratios of **13**, TMSI, and $Ph_3P{=}O$



Entry	TMSI/equiv	$Ph_3P{=}O$/equiv	Yield/%	α/β[a]
1	1.5	0.1	51	86.9/13.1
2	1.5	1.5	63	95.0/5.0
3	1.5	3.0	**86**	**96.1/3.9**
4	1.5	6.0	73	96.0/4.0
5[b]	3.0	3.0	82	94.6/5.4
6[b]	3.0	6.0	**95**	**94.5/5.5**

a) The α/β ratios were determined by HPLC analysis. b) 3.0 equiv of **13** was used.

phine oxide were used (Table 6, Entry 6).

Next, glycosylations of the acceptors with glucosyl acetate **13** or galactosyl acetate **14** using iodotrimethylsilane and triphenylphosphine oxide were tried (Table 7). Each reaction proceeded efficiently in dichloromethane at room temperature and afforded the corresponding disaccharides in high yields with high α-selectivities, as expected. In the case of using less reactive acceptors such as **5** and **6**, however, 3.0 equivalents each of the donor and iodotrimethylsilane and 6.0 equivalents of triphenylphosphine oxide were needed for completion of the reactions (Table 7, Entries 2–5, 8, 9).

Thus, the glycosylations using glycosyl phosphonium iodide generated from the corresponding glycosyl acetate, i.e., an easily accessible and manageable glycosyl donor, proceeded successfully in CH_2Cl_2 at room temperature. In this reaction, the glycosyl acetate regenerated by the reaction of glycosyl halide and trimethylsilyl acetate formed by the one-pot in situ anomerization procedure was not obtained. The result causes the present one-pot glycosylation to proceed effectively.

Mechanism

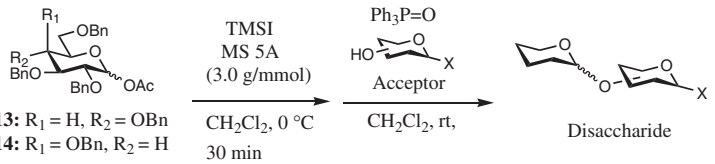
The glycosylation of **2** with **13** using $Ph_3P{=}O$–TMSI adduct was tried in order to show the reason why the reverse reaction did not take place in this one-pot in situ anomerization procedure.[11] Interestingly, the desired **3** was obtained in 54% yield along with the recovery of **13** (Table 8, Entry 1). On the other hand, the disaccharide **3** was not obtained in the case when n-Bu_4NI/i-Pr_2NEt system was employed in place of $Ph_3P{=}O$ in the above-mentioned reaction (Table 8, Entry 2). This result indicates that $Ph_3P{=}O$–TMSI adduct is reactive enough to promote the formation of glycosyl phosphonium iodide from the glycosyl acetate, although the acetate is formed by the reverse reaction in general.

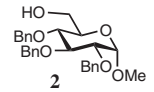
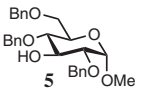
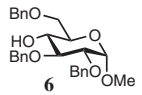
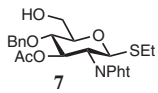
The glycosyl phosphonium iodide was not detected by ^1H NMR study of the reaction mixture of glycosyl iodide and triphenylphosphine oxide in $CDCl_3$. This indicates that very small amounts of glycosyl phosphonium iodide existed in equilibrium with a mixture of glycosyl iodide and phosphine oxide. The proposed reaction mechanism is illustrated below (Scheme 2). The reactive intermediate, glycosyl phosphonium iodide **20**, is formed from the corresponding glycosyl iodide **19** and phosphine oxide. A glycosyl acceptor in turn reacts dominantly with highly-reactive **β-20** to afford **α-21** while less-reactive **α-20** epimerizes to the above more reactive **β-20**, which also affords **α-21**. There is an alternative pathway to convert glycosyl acetate **18** directly into glycosyl phosphonium iodide **20** by the promotion of $Ph_3P{=}O$–TMSI adduct, though the glycosyl iodide **19** is generally converted to **18** by the reverse reaction. In addition, hydrogen iodide, a co-product, is rapidly neutralized by phosphine oxide to form a $Ph_3P{=}O$–HI adduct (**22**);[12] therefore, the present glycosylation proceeds smoothly under almost neutral condition.

Conclusion

The glycosylations of various acceptors with glycosyl halides such as glycosyl bromide and glycosyl iodide are effectively promoted by phosphine oxide to afford the corresponding α-disaccharides in good yields with high selectivities. In the case of one-pot glycosylation using glycosyl acetate and iodotrimethylsilane, the glycosyl acetate is converted directly into glycosyl phosphonium iodide when $Ph_3P{=}O$–TMSI adduct, a promoter to activate glycosyl acetate, is generated, and consequently, the present one-pot glycosylation proceeded effectively. This method is considered practical in the syntheses of complex oligosaccharides because the glycosyl acetate, the glycosyl donor, is easy to access and handle, and the reaction always gives α-disaccharide with quite high selectivity.

Table 7. Glycosylation of Various Acceptors with Donor **13** or **14** via Glycosyl Phosphonium Iodide Using TMSI and $Ph_3P{=}O$



Entry	Donor	Acceptor	Product	Condition[a)]	Time/h	Yield/%	α/β[b)]
1	**13**	 **2**	**3**	a	7	89	96.1/3.9
2		 **5**	**9**	a	24	72	98.3/1.7
3				b	24	91	97.4/2.6
4		 **6**	**10**	a	24	52	98.7/1.3
5				b	34	80	98.9/1.1
6		 **7**	**11**	a	21	85	94.9/5.1
7	**14**	**2**	**15**	a	7	93	96.6/3.4
8		**5**	**16**	a	34	94	93.1/6.9
9		**6**	**17**	b	34	91	96.3/3.7

a) Condition a: **13** or **14** (1.5 equiv), $Ph_3P{=}O$ (3.0 equiv), TMSI (1.5 equiv); b: **13** or **14** (3.0 equiv), $Ph_3P{=}O$ (6.0 equiv), TMSI (3.0 equiv). b) The α/β ratios were determined by HPLC analysis.

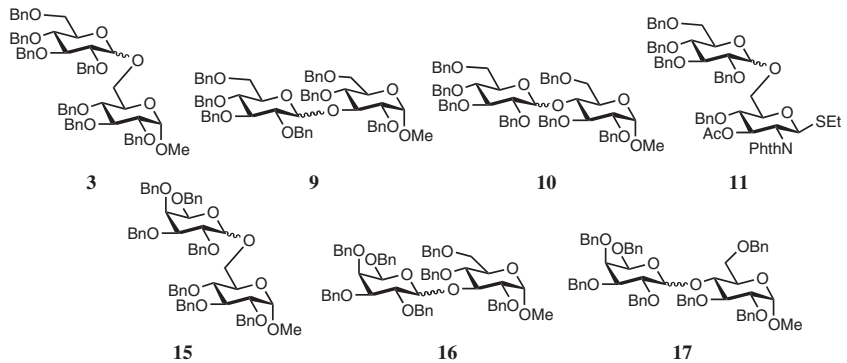
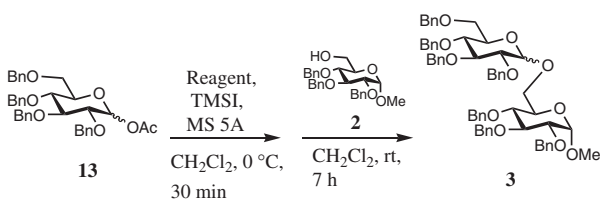


Table 8. Glycosylation of **2** with **13** Promoted by $Ph_3P{=}O$–TMSI Adduct[a)]

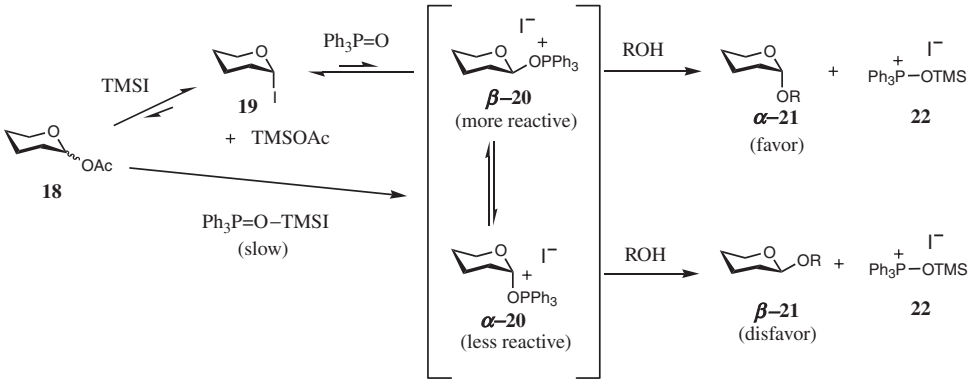


Entry	Reagent	Yield/%	α/β[b)]
1	n-Bu_4NI/i-Pr_2NEt	N.R.	—
2	$Ph_3P{=}O$	54[c)]	94.9/5.1

a) Reaction condition: **13** (1.5 equiv), Reagent (3.0 equiv), TMSI (1.5 equiv), MS 5A (3.0 g/mL). b) The α/β ratios were determined by HPLC analysis. c) **13** was recovered in 46% yield.

Experimental

General. All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Infrared spectra were recorded on a Perkin Elmer Spectrum One infrared spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270L (270 MHz) or JEOL JNM-LA500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a JEOL JNM EX270L (68 MHz) or a JEOL JNM-LA500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane, with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0 ppm). ^{31}P NMR spectra were recorded on a JEOL JNM EX270L (108 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative



Scheme 2. Reaction mechanism of glycosylation with glycosyl acetate by the promotion of TMSI and $Ph_3P{=}O$ via glycosyl phosphonium iodide.

to trimethylphosphite in $CDCl_3$ as the external standard (δ 140.0 ppm). High-resolution mass spectra were recorded on a Micromass Q-TOF2 instrument [ESI positive, 0.01 M (1 M = 1 mol dm^{-3}) $AcONH_4$ in H_2O/MeCN]. High-performance liquid chromatography (HPLC) was carried out using a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. Optical rotations were recorded on a Jasco-P-1020 polarimeter. Analytical TLC was done on precoated (0.25 mm) silica gel 60 F_{254} plates (E. Merck). Thin-layer chromatography was performed on Wakogel B-5F. Column chromatography was performed on Silica gel 60 (Merck).

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. All reagents were purchased from Tokyo Kasei Kogyo, Kokusan Chemical, Kanto Chemical, Aldrich, or Fluka and were used without further purification, unless otherwise noted. CH_2Cl_2 was distilled from P_2O_5 and then from CaH_2 and was stored over molecular sieves 4A. Toluene and CH_3CN were distilled from P_2O_5 and stored over molecular sieves 4A. DMF was distilled from CaH_2 under reduced pressure (pre-dried over P_2O_5) and stored over molecular sieves 4A. Dehydrated DME, IPE, $CHCl_3$, THF, and Et_2O were purchased from Kanto Chemical. Dehydrated EtOAc and acetone were purchased from Kokusan Chemical. Powdered and pre-dried (at 200 °C/133 Pa, 6 h) molecular sieves 5A (MS 5A) was used in glycosylation reactions.

Glycosylation Using Glycosyl Bromide and Phosphine Oxide (General Procedure). To a stirred suspension of MS 5A (240 mg), **4** (0.12 mmol), and glycosyl acceptor (0.08 mmol) in CH_2Cl_2 (0.8 mL) was added tri(1-pyrrolidino)phosphine oxide (0.24 mmol) at room temperature. After the completion of glycosylation reaction was confirmed by monitoring TLC, the reaction mixture was diluted with EtOAc and filtered through Celite. After having been dried over $MgSO_4$, filtered, and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the corresponding disaccharide. The α to β ratios for **3**, **9**, **10**, and **11** were determined by HPLC analysis and the ratio for **16** was determined by isolation of both isomers according to published conditions.

Glycosylation Using Glycosyl Acetate, Iodotrimethylsilane, and Phosphine Oxide (General Procedure). To a stirred suspension of MS 5A (240 mg) and glycosyl acetate (0.12 mmol) in CH_2Cl_2 (1.2 mL) was added iodotrimethylsilane (0.12 mmol) at 0 °C. After stirring for 30 min, $Ph_3P{=}O$ (0.24 mmol) and glycosyl acceptor (0.08 mmol) were added in turn. The reaction mixture was stirred at room temperature until the completion of glycosylation reaction was confirmed by monitoring TLC, diluted with EtOAc, filtered through Celite, and evaporated. The resulting residue was purified by preparative TLC (silica gel) to give the corresponding disaccharide. The α to β ratios were determined by HPLC analysis.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (3): The α/β ratio was determined by HPLC analysis[13] (Shodex SIL-5B, ϕ4.6 × 250 mm^2; *n*-hexane/ethyl acetate = 4/1; 1.0 mL/min; 254 nm; α-isomer, 14.3 min; β-isomer, 12.5 min).

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (9): The α/β ratio was determined by HPLC analysis[13] (Shodex SIL-5B, ϕ4.6 × 250 mm^2; *n*-hexane/ethyl acetate = 4/1; 1.0 mL/min; 254 nm; α-isomer, 10.4 min; β-isomer, 11.9 min).

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (10): The α/β ratio was determined by HPLC analysis[13] (YMC J'sphere ODS M80, ϕ4.6 × 250 mm^2; MeOH/H_2O = 4/1; 1.0 mL/min; 254 nm; α-isomer, 14.6 min; β-isomer, 16.1 min).

Ethyl 3-*O*-Acetyl-4-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (11): The α/β ratio was determined by HPLC analysis[13] (Shodex SIL-5B, ϕ4.6 × 250 mm^2; *n*-hexane/ethyl acetate = 4/1; 1.0 mL/min; 254 nm; α-isomer, 21.8 min; β-isomer, 19.4 min).

2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranosyl fluoride (12): The α/β ratio was determined by isolated yields of both isomers.[14]

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (15): The α/β ratio was determined by HPLC analysis[13] (Shodex SIL-5B, ϕ4.6 × 250 mm^2; *n*-hexane/ethyl acetate = 4/1; 1.0 mL/min; 254 nm; α-isomer, 11.0 min; β-isomer, 12.8 min).

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (16): The α/β ratio was determined by HPLC analysis[15] (GL Sciences Intersil SIL, ϕ4.6 × 250 mm^2; *n*-hexane/ethyl acetate = 4/1; 1.0 mL/min; 254 nm; α-isomer, 8.3 min; β-isomer, 9.6 min).

16α: Colorless oil; $[\alpha]_D^{20}$ +53.3 (*c* 1.00, $CHCl_3$); IR (Neat) 2907, 2867, 1606, 1586, 1496, 1454, 1363, 1208, 1156, 1133, 1096, 1055, 1028, 912, 735, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.50–3.76 (m, 6H), 3.95–3.97 (m, 1H), 4.01 (dd, *J* = 10.2, 2.6 Hz, 1H), 4.07 (dd, *J* = 10.2, 3.7 Hz, 1H), 4.24 (dd, *J* = 9.5, 8.2 Hz, 1H), 4.33 (d, *J* = 11.3 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* =

11.9 Hz, 1H), 4.44–4.51 (m, 1H), 4.48 (d, $J = 4.0$ Hz, 1H, H-1), 4.50 (d, $J = 4.6$ Hz, 1H), 4.57, (d, $J = 11.6$ Hz, 1H), 4.58 (d, $J = 11.9$ Hz, 1H), 4.64, (d, $J = 11.9$ Hz, 1H), 4.68–4.76 (m, 4H), 4.90, (d, $J = 11.6$ Hz, 1H), 4.94 (d, $J = 11.2$ Hz, 1H), 5.59 (d, $J = 3.7$ Hz, 1H, H-1′), 6.98–7.01 (m, 2H), 7.11–7.33 (m, 33H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 54.92, 68.50, 68.85, 69.02, 69.49, 72.61, 73.11, 73.34, 73.49, 73.70, 73.79, 74.85, 75.20, 76.03, 76.29, 78.57, 79.12, 79.29, 97.76 (C-1), 97.85 (C-1′), 127.14, 127.26, 127.33, 127.44, 127.48, 127.66, 127.89, 127.91, 128.07, 128.12, 128.17, 128.22, 128.24, 128.26, 128.33, 128.36, 128.39, 137.92, 138.29, 138.34, 138.38, 138.43, 138.72, 138.82; HRMS m/z calcd for $C_{62}H_{70}NO_{11}$ $[M + NH_4]^+$ 1004.4943, found 1004.4948.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (17): The α/β ratio was determined by HPLC analysis[13] (DAICEL Chiralcel OD-H, $\phi 4.6 \times 250$ mm^2; *n*-hexane/2-propanol = 10/1; 1.0 mL/min; 254 nm; α-isomer, 13.4 min; β-isomer, 25.5 min).

Mechanistic Study of the Glycosylation with Glycosyl Acetate Promoted by Ph_3P=O–TMSI Adduct: To a stirred suspension of MS 5A (240 mg), Ph_3P=O (0.67 g, 0.24 mmol), and iodotrimethylsilane (17.1 μL, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added **13** (0.070 g, 0.12 mmol) at 0 °C. After stirring for 30 min, **2** (0.037 g, 0.08 mmol) was added and the resulting mixture was stirred for 7 h at room temperature, diluted with EtOAc, filtered through Celite and evaporated. The resulting residue was purified by preparative TLC (silica gel) to give **3** (0.042 g, 0.043 mmol, 54%, $\alpha/\beta = 94.9/5.1$).

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