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Stereoselective Synthesis of α-Glycosyl Phosphites and Phosphoramidites via *O*-Selective Glycosylation of *H*-Phosphonate Derivatives

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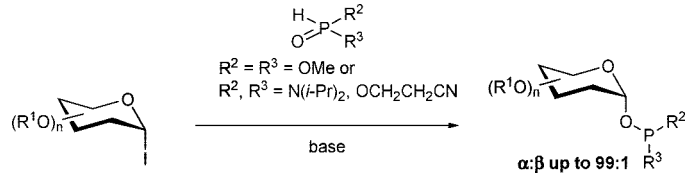
ABSTRACT



A highly stereo- and chemoselective glycosylation of *H*-phosphonate derivatives with glycosyl iodides was discovered as a reverse reaction of the formation of a glycosyl iodide from a glycosyl phosphite and I^- under mild acidic conditions. Further study on the unique reaction showed that the reaction provided various α-glycosyl phosphites and phosphoramidites in a highly stereoselective manner with complete *O*-selectivity.

Glycosyl phosphates are the repeating units of phosphoglycans, which are widely distributed in nature as the constituents of cell-wall or capsule of bacteria and yeasts, glycocalyx of a protozoan parasite *Leishmania*, etc.[1] Since these phosphoglycans often work as virulence factors of pathogenic bacteria, etc., their structures and functions have been extensively studied. Chemically synthesized fragments of the phosphoglycans and their analogues are indispensable tools for these studies and their therapeutic applications have also been studied continuously.[2]

Since the glycosyl phosphate units consisting of the phosphoglycans have the α-anomeric configuration in most cases, α-glycosyl phosphate derivatives are required as building blocks to construct α-glycosyl phosphate diester intersaccharide linkages via condensation reactions.[2b] Currently, glycosyl *H*-phosphonate monoesters are employed as building blocks because their α-isomers, especially those having a 2-*O*- or *N*-acyl group, can be synthesized with relative ease,[2b,3] though they have some drawbacks, such as the instability of *H*-phosphonate diester intermediates.[1a,3a,b] Several methods have been reported for the synthesis of α-glycosyl phosphate triesters, but it is difficult to use them as the building blocks via partial deprotection of their phosphate moiety and following condensation due to their chemical instability. Therefore, their applications are mostly limited to those as glycosyl donors.[2b,4] Only a very limited number of other building blocks are available (e.g., α-D-Man, α-D-GlcNAc 1-phosphoramidites), which can be ste-

(1) (a) Hansson, J.; Oscarson, S. *Curr. Org. Chem.* **2000**, *4*, 535–564. (b) Weintraub, A. *Carbohydr. Res.* **2003**, *338*, 2539–2547. (c) Naderer, T.; Vince, J. E.; McConville, M. J. *Curr. Mol. Med.* **2004**, *4*, 649–665.

(2) (a) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077–3092. (b) Nikolaev, A. V.; Botvinko, I. V.; Ross, A. J. *Carbohydr. Res.* **2007**, *342*, 297–344.

(3) (a) Westerduin, P.; Veeneman, G. H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1986**, *27*, 6271–6274. (b) Berkin, A.; Coxon, B.; Pozsgay, V. *Chem. Eur. J.* **2002**, *8*, 4424–4433. (c) Ruhela, D.; Vishwakarma, R. A. *J. Org. Chem.* **2003**, *68*, 4446–4456. (d) Higson, A. P.; Ross, A. J.; Tsvetkov, Y. E.; Routier, F. H.; Sizova, O. V.; Ferguson, M. A. J.; Nikolaev, A. V. *Chem. Eur. J.* **2005**, *11*, 2019–2030.

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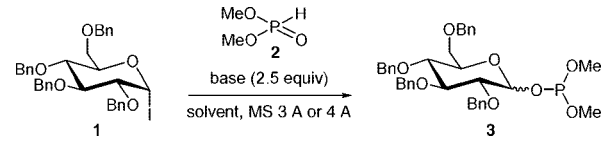
reoselectively synthesized by using the stereoelectronic effect of 2-*O*- or *N*-acyl protecting groups.[3a,5]

On the other hand, while studying the chemistry of glycosyl iodides,[6] we found that an α-D-glucosyl iodide **1**[6b] underwent a unique *O*-selective glycosylation with dimethyl *H*-phosphonate (**2**) in a highly α-selective manner (Table 1).[7] Further investigation showed that the new reaction provided various α-glycosyl phosphites and phosphoramidites including potential building blocks for phosphoglycans, which are otherwise difficult to obtain (e.g., α-D-Glc, α-D-Gal 1-phosphoramidites). The results of this study are described in this paper.

The reaction was carried out as follows: The α-D-glucosyl iodide **1** was allowed to react with dimethyl *H*-phosphonate **2** in the presence of 1,8-bis(dimethylamino)naphthalene (DMAN) to give the corresponding glucosyl phosphite **3** (Table 1). The reaction was monitored by TLC and quenched when **1** was completely consumed. Stereoselectivity of the reaction was determined by ^{31}P NMR analysis of crude **3**,[8] which was then converted into the corresponding glycosyl boranophosphate triester **4** by treatment with BH_3·THF and isolated by silica gel column chromatography. As we have recently reported,[9] glycosyl boranophosphate triesters are superior in chemical stability to the corresponding glycosyl phosphites and phosphates and can be used as building blocks to synthesize glycosyl phosphate-containing molecules through deprotection of the boranophosphate moiety and condensation, whereas such applications are difficult for the glycosyl phosphites.

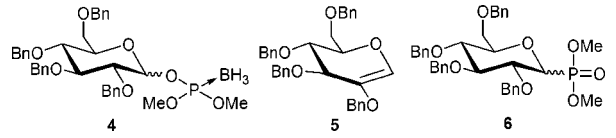
Increasing the amount of **2** accelerated the reaction and improved the yield of the final product **4**. The stereoselectivity of the reaction was also slightly improved (entries 1, 2, and 4). Glycosyl iodide **1** decomposed very slowly into **5**;[6] this resulted in low yields when the reaction of **1** with **2** was slow (entries 1 and 2). In contrast, decomposition of **1** was suppressed at 0 °C or in less-polar solvents (toluene, dioxane), though an extended reaction time was required (entries 3, 8, and 9). *N*,*N*-Diisopropylethylamine (DIPEA) gave similar results to DMAN (entries 4 and 5), whereas weaker bases resulted in lower yields and stereoselectivity (entries 6 and 7). This is due to the isomerization of the resultant **3** and the reverse reaction to regenerate **1** in mild acidic media, especially in the case of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).[7] It should be noted that the glycosyl iodide **1** immediately decomposed into **5** when a strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used in the reactions (data not shown). In entries 1, 2, 6, and 7, a *P*-glycoside **6**[10] was also observed as a major byproduct, which was not observed under appropriate conditions (entries 3−5 and 8−10). The reaction was accelerated as the polarity of the solvent increased, but the stereoselectivity was slightly reduced (entries 4 and 8−10).

Table 1. Synthesis of α-D-Glucosyl Phosphite **3** from α-D-Glucosyl Iodide **1** and Dimethyl *H*-Phosphonate **2**[a,b]



entry	equiv of **2**	reaction conditions	α:β[c]	% of yield[d]
1	1.1	DMAN, MeCN, 25 °C, 48 h	89:11	41
2	3	DMAN, MeCN, 25 °C, 8 h	91:9	71
3	3	DMAN, MeCN, 0 °C, 24 h	93:7	93
4	10	DMAN, MeCN, 25 °C, 2 h	93:7	82
5	10	DIPEA, MeCN, 25 °C, 2 h	92:8	79
6	10	K_2CO_3, MeCN, 25 °C, 30 h	88:12	34
7	10	DTBMP, MeCN, 25 °C, 48 h	79:21	28
8	10	DMAN, toluene, 25 °C, 65 h	98:2	83
9	10	DMAN, dioxane, 25 °C, 75 h	95:5	71
10	10	DMAN, DMF, 25 °C, 15 min	92:8	76

[a] MS 3 A was used for MeCN and MS 4 A was used for the other solvents. [b] The glucosyl phosphite **3** was converted into the corresponding boranophosphate triester **4** by treatment with BH_3·THF at rt for 15 min and isolated. [c] Anomeric ratios of **3** (^{31}P NMR). [d] Isolated yields of **4**.



Next, the reaction was applied to other glycosyl iodides **7**−**9**[6] (Table 2, entries 1−3). When 2,3,4,6-tetra-*O*-acetyl glycosyl iodide **7** was used, only ca. 50% of **7** was converted into the desired glycosyl phosphite with poor stereoselectivity (entry 1). ^{1}H NMR analysis of the reaction revealed that neighboring group participation of the 2-*O*-acyl group occurred to generate some rather stable 1,2-cyclic intermediates, resulting in a lower reaction rate and stereoselectivity. In contrast, the reaction was applicable to per-*O*-benzyl glycosyl iodides **8** and **9**, though the stereoselectivity was modest in the case of the mannosyl iodide **9** (entries 2 and 3).

It is noteworthy that the *O*-selective glycosylation occurred not only with dimethyl *H*-phosphonate **2** but also with an *H*-phosphonamidate derivative **11**,[11] yielding glycosyl phosphoramidites **14**−**16**[5] from the glycosyl iodides **1**, **8**, and **10**[6] (Table 2, entries 4−6) with good stereoselectivity and

(4) (a) Schmidt, R. R.; Gaden, H.; Jatzke, H. *Tetrahedron Lett.* **1990**, *31*, 327–330. (b) Sabesan, S.; Neira, S. *Carbohydr. Res.* **1992**, *223*, 169–185. (c) Garcia, B. A.; Gin, D. Y. *Org. Lett.* **2000**, *2*, 2135–2138. (d) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554. (e) Ravidà, A.; Liu, X.; Kovacs, L.; Seeberger, P. H. *Org. Lett.* **2006**, *8*, 1815–1818.

(5) (a) Westerduin, P.; Veeneman, G. H.; Marugg, J. E.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1986**, *27*, 1211–1214. (b) Majumdar, D.; Elsayed, G. A.; Buskas, T.; Boons, G.-J. *J. Org. Chem.* **2005**, *70*, 1691–1697.

(6) (a) Thiem, J.; Mayer, B. *Chem. Ber.* **1980**, *113*, 3075–3085. (b) Hadd, M. J.; Gervey, J. *Carbohydr. Res.* **1999**, *320*, 61–69. (c) Mukhopadhyay, B.; Kartha, K. P. R.; Russell, D. A.; Field, R. A. *J. Org. Chem.* **2004**, *69*, 7758–7760.

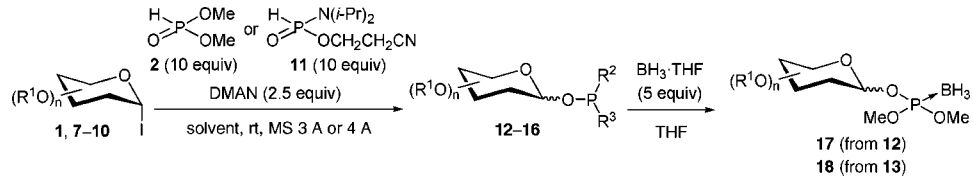
(7) We found the reaction as a reverse reaction of the generation of **1** from a glycosyl phosphite and I^- under mild acidic conditions. Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260. Details are given in the Supporting Information.

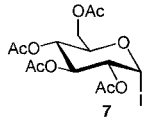
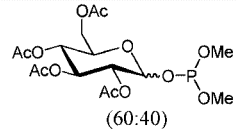
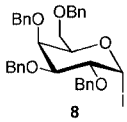
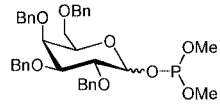
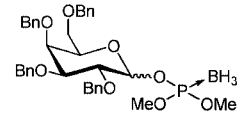
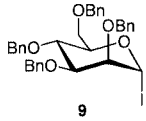
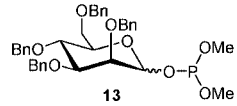
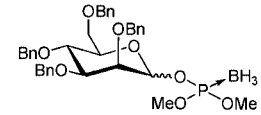
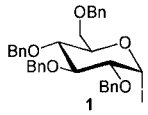
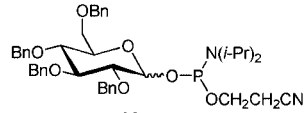
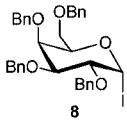
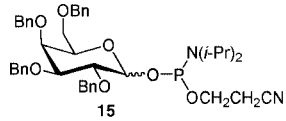
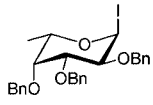
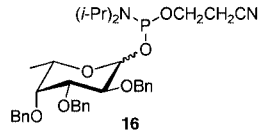
(8) Watanabe, Y.; Nakamoto, C.; Yamamoto, T.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523–6536.

(9) Matsumura, F.; Oka, N.; Wada, T. *Org. Lett.* **2008**, *10*, 1557–1560.

(10) Meuwly, R.; Vasella, A. *Helv. Chim. Acta* **1986**, *76*, 25–34.

Table 2. Synthesis of Glycosyl Phosphites **12** and **13** and Phosphoramidites **14**−**16**[a]



entry	starting materials		conditions	ratio of crude **12–16** (α:β)[b]	isolated product[c]
1	 **7**	**2**	MeCN, 12 h	 (60:40)	not isolated
2	 **8**	**2**	MeCN, 2 h	 **12** (91:9)	 **17** (78%, 91:9)
3	 **9**	**2**	MeCN, 24 h	 **13** (75:25)	 **18** (62%, 75:25)
4	 **1**	**11**	toluene, 48 h	 **14** (97:3)	**14** (73%, 99:1)
5	 **8**	**11**	toluene, 48 h	 **15** (90:10)	**15** (82%, 97:3)
6	 **10**	**11**	toluene, 18 h	 **16** (87:13)	**16** (82%, 92:8)

[a] MS 3 A was used for MeCN. MS 4 A was used for the other solvents. [b] Anomeric ratios of glycosyl phosphites **12**−**16** (^{31}P NMR). [c] Isolated yields and anomeric ratios (α:*β*, determined by ^{31}P NMR) of **14**−**18** are given in parentheses. The glycosyl boranophosphates **17** and **18** were derived from **12** and **13**, respectively.

complete *O*-selectivity. Since the *β*-isomers of **14**−**16** were more prone to decomposition on silica gel, highly α-enriched **14**−**16** were obtained after a simple silica gel column chromatography.

Thus, the study demonstrated that glycosyl iodides underwent an *O*-selective glycosylation with *H*-phosphonate derivatives to give the corresponding α-glycosyl phosphites and phosphoramidites in a highly stereoselective manner. Since the resultant α-glycosyl phosphoramidites and boranophosphate triesters derived from the glycosyl phosphites are potentially useful as building blocks of phosphoglycans and are otherwise difficult to synthesize, the method developed in this study should expand the availability of chemically synthesized phosphoglycans and their analogues.

In addition, it is important to note that it is not only a unique reaction of glycosyl iodides, but also an unprecedented *O*-selective reaction of *H*-phosphonate derivatives. It is well-known that the reactions of *H*-phosphonate diesters with *C*-electrophiles are almost exclusively *P*-selective.[12] Therefore, the elucidation of the reaction mechanism will provide new insights into the chemistry of *H*-phosphonate derivatives. Although further

(11) Ahmadibeni, Y.; Parang, K. *Org. Lett.* **2005**, *7*, 5589–5592.

investigation is necessary for full clarification of the reaction mechanism, the data obtained in this study indicate that it proceeds via the nucleophilic attack of the lone pair on the P═O: function to the highly reactive β-glycosyl iodides, which are in equilibrium with the dominating α-isomers.[13] Further studies on the mechanism as well as on the applications of the reaction are in progress.

(12) (a) Soborovskii, L. Z.; Baina, N. F. *J. Gen. Chem. USSR* **1959**, *29*, 1115–1117. (b) Seela, F.; Kretschmer, U. *J. Org. Chem.* **1991**, *56*, 3861–3869. (c) Waschbüsch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Synthesis* **1997**, 727–743. (d) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2005**, 29–49.

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Supporting Information Available: Experimental details and characterizing data, including ^{1}H, ^{13}C and ^{31}P spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See the Supporting information.