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AN EXTREMELY MILD AND GENERAL METHOD FOR THE CONSTRUCTION OF 1,2-*TRANS*-β-GLYCOSIDIC LINKAGES *VIA* GLYCOPYRANOSYL DIETHYL PHOSPHITES WITH PARTICIPATING GROUPS AT C-2

Shun-ichi HASHIMOTO,*[a] Ai SANO,[a] Kazuhiro UMEO,[a] Makoto NAKAJIMA,[a] and Shiro IKEGAMI[b]

Faculty of Pharmaceutical Sciences, Hokkaido University,[a] Sapporo 060, Japan and Faculty of Pharmaceutical Sciences, Teikyo University,[b] Sagamiko, Kanagawa 199-01, Japan

A highly efficient 1,2-*trans*-β-glycosidation reaction has been developed by using glycopyranosyl diethyl phosphites bearing participating groups such as benzoate, phthalimido, or trichloroethyl carbamate groups at C-2 as glycosyl donors and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter.

KEY WORDS glycosidation; 1,2-*trans*-glycosidic linkage; neighboring group participation; glycosyl phosphite

Due to the rapidly recognized biological significance of saccharide residues of carbohydrate-containing biomolecules, the design and development of stereocontrolled glycosidation reactions1) are of growing importance not only in carbohydrate chemistry but also in medicinal chemistry.2) One of the current topics in this area is the emergence of glycosyl phosphites as a new family of glycosyl donors,3-6) whose effectiveness has been demonstrated well by high-yield and α-selective sialylation3a,4a,b) using sialyl phosphite as a donor and TMSOTf as a promoter. As yet another advantage of glycosyl phosphites, we recently reported that glycosidations of benzyl-protected glycopyranosyl diethyl phosphites with a variety of acceptor alcohols could be effected with the aid of boron trifluoride etherate ($BF_3 \cdot OEt_2$) as a promoter at -78 °C to exhibit the highest 1,2-*trans*-β-selectivity known to date for glycosidations without neighboring group participation.7) On the other hand, Wong and his collaborators reported discouraging results for the glycosidation of glycosyl phosphites bearing a participating acetate group at C-2,4c) which have led us to explore the applicability of glycosyl phosphites to the most reliable glycosidation method, dating back to 1901.8) Herein we wish to report that TMSOTf-mediated glycosidation of glycosyl phosphites bearing participating groups such as benzoate, phthalimido, or trichloroethyl carbamate groups at C-2 constitutes an extremely mild and general method for the stereocontrolled construction of 1,2-*trans*-β-glycosidic linkages.

There have recently been reported an increasing number of unsuccessful examples of glycosidations with acetate group at C-2,9) wherein major by-products are an anomeric mixture of glycosides deacetylated on O-2 and orthoesters. Hence, acetate is being replaced by benzoyl10) or pivaloyl11) groups at the cost of an easy and selective deprotection. We thus set out to explore glycosidation of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl diethyl phosphite **1**, readily prepared by condensation of the corresponding glycopyranose with diethyl phosphorochloridite in the presence of triethylamine (CH_2Cl_2, -78 °C, 0.5 h).7) In the presence of $BF_3 \cdot OEt_2$ (1.0 eq), a promoter of choice in the previous studies, glycosidation of **1** with **6** in dichloromethane proceeded at -30 °C to give the desired disaccharide in 33% yield, along with 10% of the 1-hydroxy compound derived from **1**, 7% of

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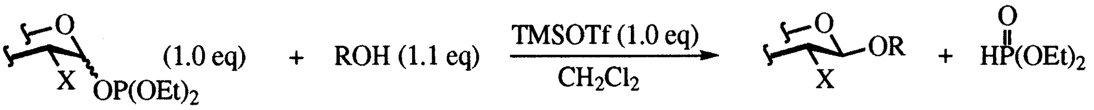
* To whom correspondence should be addressed.

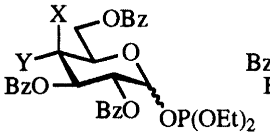
Table 1. TMSOTf- Mediated 1,2-*trans*-Glycosidation of Glycopyranosyl Diethyl Phosphites **1**-**5**[a] with Alcohols **6**-**12**[b]



X=BzO, PhthN, TrocNH

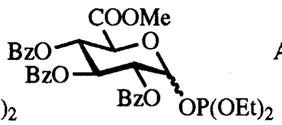
Entry	Donor	Acceptor	Temp, °C	Time, h	Yield,[c] %	NMR data[d] δ ^1H[e]	NMR data[d] δ ^{13}C[f]	$[\alpha]_D^{25}$/°(c, $CHCl_3$)
1	**1**	**6**	-50	1	90	4.81	101.3	+20.9 (1.16)
2	**1**	**7**	-50	1	95	4.80	100.4	-3.1 (1.75)
3	**1**	**8**	-50	2	94	4.99	101.7	+44.4 (1.09)
4	**2**	**9**	-50	1	93	5.02	101.7	+40.6 (1.04)
5	**2**	**10**	-50	1	87	5.22	101.1	+84.3 (1.04)
6	**3**	**6**	-30	1	63	4.83	101.2	+10.1 (1.02)
7	**3**	**10**	-30	1	71	5.27	99.8	-5.9 (1.14)
8	**4**	**11**	-78	1	92	5.60	97.6	-3.2 (1.01)
9	**4**	**12**	-78	1	79	5.42	98.9	-7.5 (1.02)
10	**5**	**9**	-65	1	99	4.81	101.0	-36.2 (1.04)
11	**5**	**12**	-65	1	84	4.92	100.5	-6.0 (1.06)

a) The anomeric ratio of the phosphites **1**-**5** was determined by ^{31}P NMR in $CDCl_3$ at 109 MHz using 85% H_3PO_4 as an external standard: **1**, 80:20; **2**, 98:2; **3**, 89:11; **4**, 97:3; **5**, 91:9. *b*) TMSOTf (0.14 mmol) was added to a mixture of the donor (0.14 mmol) and acceptor (0.15 mmol) in CH_2Cl_2 (2 ml) at the indicated temperature under argon atmosphere. The mixture was quenched with triethylamine (0.2 ml), and the product was isolated by extractive workup and subsequent chromatography on silica gel. *c*) Isolated yield. *d*) Chemical shifts (δ ppm) for the anomeric centers newly formed. *e*) In $CDCl_3$ at 500 MHz. *f*) In $CDCl_3$ at 68 MHz.



1 X=H, Y=OBz

2 X=OBz, Y=H



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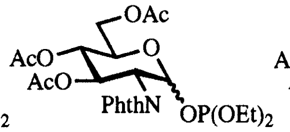

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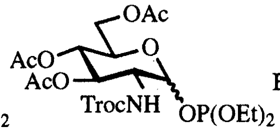

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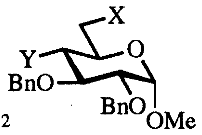
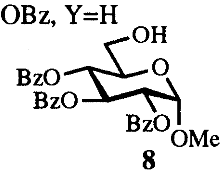


6 X=OH, Y=OBn

7 X=OBn, Y=OH



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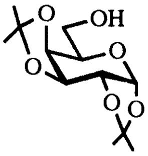

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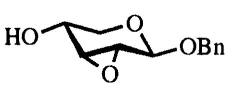

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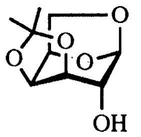

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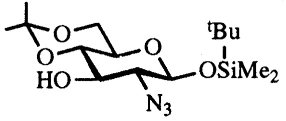

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the orthoester,[12] and 24% of the orthoester-type phosphonate[12] described by Wong,[4c] whose composition could not be changed by raising the temperature to room temperature. On this disappointing result, we then switched the promoter from $BF_3 \cdot OEt_2$ to TMSOTf. In stark contrast to the observation by Wong,[4c] we were pleased to find that TMSOTf (1.0 eq)-mediated glycosidation of **1** with **6** in dichloromethane proceeded smoothly at -50 °C to afford the 1,2-*trans*-β-disaccharide as the sole product in 90% yield, with no trace of the foregoing by-products being detected.

With the superiority of a benzoyl group over an acetyl group manifested, we then explored the applicability of this method to the construction of 1,2-*trans*-β-glycosidic linkages from a range of glycosyl phosphites **1**-**5**, derived from 1-unprotected derivatives of D-glucopyranose,[13] D-galactopyranose,[13] D-glucuronic acid[14] and D-glucosamine,[15,16] and acceptor alcohols with different reactivities. Some representative results are summarized in Table 1. As seen from the table, TMSOTf-mediated glycosidations were found to offer an efficient and stereocontrolled procedure for 1,2-*trans*-β-disaccharides, wherein acceptor alcohols bearing the acid-labile groups such as epoxy, acetal, or *O-t*-butyldimethylsilyl groups were safely glycosylated. As expected, the phthalimido[17] and trichloroethyl carbamate[18] groups as well as the benzoyl group worked well as C-2 stereodirecting substituents, demonstrating the potentiality of the present method to the synthesis of glycolipids, glycoproteins, and aminoglycoside antibiotics.[19]

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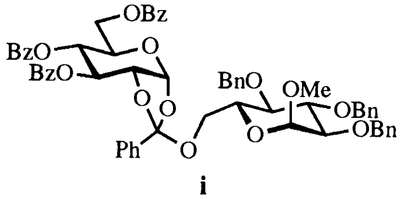
REFERENCES AND NOTES

1) For recent reviews, see: Toshima K., Tatsuta K., *Chem. Rev.*, **93**, 1503-1531 (1993); Schmidt R. R., Kinzy W., *Adv. Carbohydr. Chem. Biochem.*, **50**, 21-123 (1994).
2) Ogura H., Hasegawa A., Suami T. (eds.), "Carbohydrates-Synthetic Methods and Applications in Medicinal Chemistry," Kodansha Ltd., Tokyo, 1992; Kováč P. (ed.), "Synthetic Oligosaccharides," ACS Symposium Series No. 560, American Chemical Society, Washington, D.C., 1993.
3) *a*) Martin T. J., Schmidt R. R., *Tetrahedron Lett.*, **33**, 6123-6126 (1992); *b*) Müller T., Schneider R., Schmidt R. R., *ibid.*, **35**, 4763-4766 (1994).
4) *a*) Kondo H., Ichikawa Y., Wong C.-H., *J. Am. Chem. Soc.*, **114**, 8748-8750 (1992); *b*) Sim M. M., Kondo H., Wong C.-H., *ibid.*, **115**, 2260-2267 (1993); *c*) Kondo H., Aoki S., Ichikawa Y., Halcomb R. L., Ritzen H., Wong C.-H., *J. Org. Chem.*, **59**, 864-877 (1994).
5) Watanabe Y., Nakamoto C., Ozaki S., *Synlett*, **1993**, 115-116; Watanabe Y., Nakamoto C., Yamamoto T., Ozaki S., *Tetrahedron*, **50**, 6523-6536 (1994).
6) Corey E. J., Wu Y.-J., *J. Am. Chem. Soc.*, **115**, 8871-8872 (1993).
7) Hashimoto S., Umeo K., Sano A., Watanabe N., Nakajima M., Ikegami S., *Tetrahedron Lett.*, **36**, 2251-2254 (1995).
8) Igarashi K., *Adv. Carbohydr. Chem. Biochem.*, **34**, 243-283 (1977).
9) Banoub J., Bundle D. R., *Can. J. Chem.*, **57**, 2091-2097 (1979); Garegg P. J., Konradsson P., Kvarnstrom I., Norberg T., Svensson S. C. T., Wigilius B., *Acta Chem. Scand.*, **B39**, 569-577 (1985); Ziegler T., Kováč P., Glaudemans C. P. J., *Liebigs Ann. Chem.*, **1990**, 613-615.
10) Garegg P. J., Norberg T., *Acta Chem. Scand.*, **B33**, 116-118 (1979); Fügedi P., Garegg P. J., *Carbohydr. Res.*, **149**, C9-C12 (1986).
11) Kunz H., Harreus A., *Liebigs Ann. Chem.*, **1982**, 41-48; Sato S., Nunomura S., Nakano T., Ito Y., Ogawa T., *Tetrahedron Lett.*, **29**, 4097-4100 (1988); Nicolaou K. C., Caulfield T. J., Kataoka H., *Carbohydr. Res.*, **202**, 177-191 (1990).
12) The structures of the orthoester **i** and the orthoester-type phosphonate **ii** are shown below.



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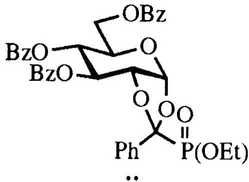

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13) Fiandor J., García-López M. T., de las Heras F. G., Méndez-Castrillón P. P., *Synthesis*, **1985**, 1121-1123.
14) Its derivative was prepared from the corresponding glycosyl bromide. Zorbach W. W., Valiaveedan G. D., *J. Org. Chem.*, **29**, 2462-2463 (1964).
15) For the phthalimido derivative, see: Grundler G., Schmidt R. R., *Carbohydr. Res.*, **135**, 203-218 (1985).
16) For the trichloroethyl carbamate derivative, see: Paulsen H., Helpap B., *Carbohydr. Res.*, **216**, 289-313 (1991)
17) Sato S., Ito Y., Ogawa T., *Tetrahedron Lett.*, **29**, 5267-5270 (1988); Mootoo D. R., Fraser-Reid B., *ibid.*, **30**, 2363-2366 (1989).
18) Boullanger P., Jouineau M., Bouammali B., Lafont D., Descotes G., *Carbohydr. Res.*, **202**, 151-164 (1990); Matsubara K., Mukaiyama T., *Chem. Lett.*, **1993**, 2145-2148.
19) Banoub J., Boullanger P., Lafont D., *Chem. Rev.*, **92**, 1167-1195 (1992).

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