

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

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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.

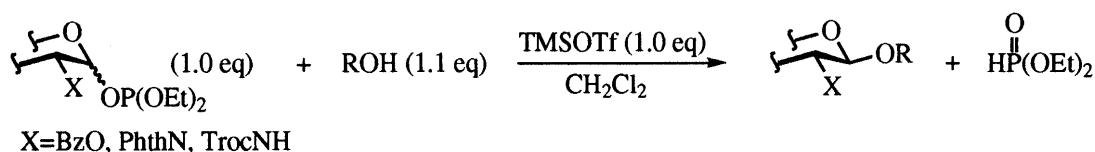
KEY WORDS glycosidation; 1,2-*trans*-glycosidic linkage; neighboring group participation; glycosyl phosphite

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 sialylation^{3a,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 (BF₃·OEt₂) 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 (CH₂Cl₂, -78 °C, 0.5 h).⁷⁾ In the presence of BF₃·OEt₂ (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

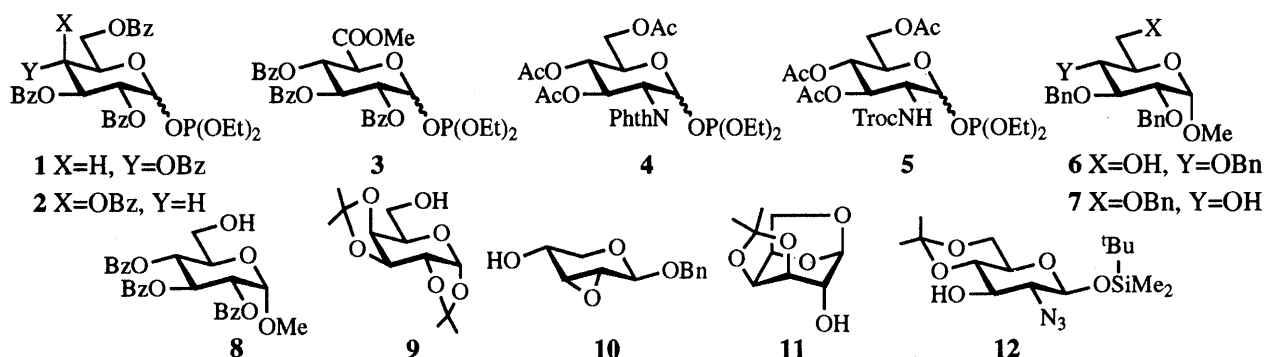
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Table 1. TMSOTf-Mediated 1,2-*trans*-Glycosidation of Glycopyranosyl Diethyl Phosphites **1-5**^{a)} with Alcohols **6-12**^{b)}



Entry	Donor	Acceptor	Temp, °C	Time, h	Yield, ^{c)} %	NMR data ^{d)}		
						δ ¹ H ^{e)}	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 ³¹P NMR in CDCl₃ at 109 MHz using 85% H₃PO₄ 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 CH₂Cl₂ (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 CDCl₃ at 500 MHz. f) In CDCl₃ at 68 MHz.



the orthoester,¹²⁾ and 24% of the orthoester-type phosphonate¹²⁾ 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 BF₃·OEt₂ 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.

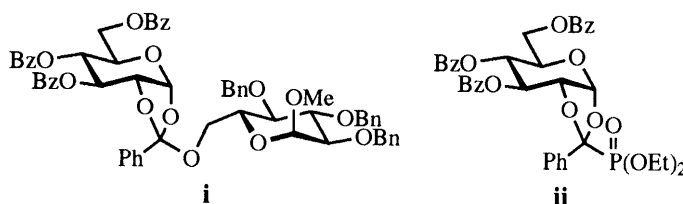
With the superiority of a benzoyl group over an acetyl group manifested, we then explored the applicability of this method to the construction of 1,2-*trans*- β -glycosidic linkages from a range of glycosyl phosphites **1-5**, derived from 1-unprotected derivatives of D-glucopyranose,¹³⁾ D-galactopyranose,¹³⁾ D-glucuronic acid¹⁴⁾ 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 phthalimido¹⁷⁾ and trichloroethyl carbamate¹⁸⁾ 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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