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An Extremely Mild and Stereocontrolled Construction of 1,2-*trans*-β-Glycosidic Linkages Capitalizing on Benzyl-Protected Glycopyranosyl Diethyl Phosphites as Glycosyl Donors

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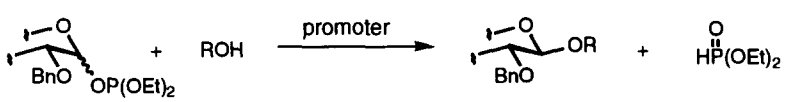
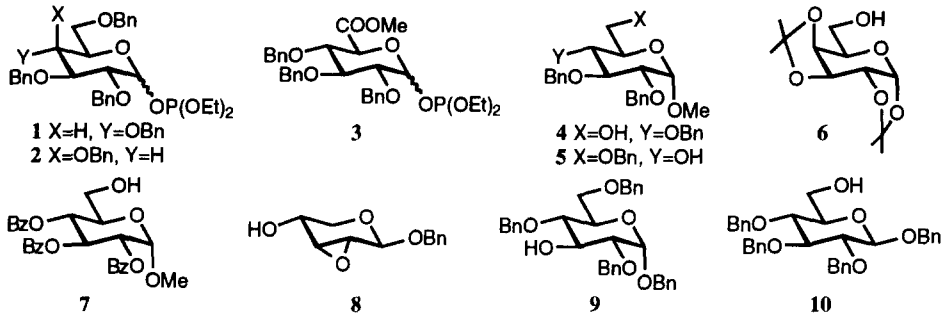
Abstract: *A highly stereocontrolled 1,2-trans-β-glycosidation reaction without neighboring group participation has been developed by using benzyl-protected glycopyranosyl diethyl phosphites as glycosyl donors and boron trifluoride etherate as a promoter. The present method exhibits the highest level of 1,2-trans-β-selectivity known to date for glycosidations with a non-participating group on O-2.*

The rapidly growing significance of glycosides and oligosaccharides as constituents of biologically important compounds such as antitumor antibiotics, glycolipids, and glycoproteins has sparked considerable interest in the rational design and development of stereocontrolled glycosidation reactions, wherein the leaving group of glycosyl donors is becoming recognized as one of the most dominant parameters responsible for the stereoselectivity and yield of glycosidation reactions.[1] One of the current topics in this area is the emergence of glycosyl phosphites,[2-6] the effectiveness of which has been demonstrated not only by high-yield and α-selective sialylation[2a,3a,b] using sialyl phosphite as a donor and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter but also by the first total synthesis of paeoniflorin[5] including $ZnCl_2$-$AgClO_4$ promoted glucosylation of an extremely acid-sensitive aglycone as the final crucial step. In this context, of particular interest are the following facts: (1) Glycosidation of the sialyl dibenzyl phosphite is far superior to that of the corresponding dibenzyl phosphate in terms of both chemical yield and stereocontrol.[3a,b] (2) To our surprise, glycosidations of benzyl-protected glucopyranosyl phosphites, the authorized probe for new glycosidation reactions, exhibit only moderate stereoselectivities in view of the currently required levels.[4,5] As part of a program to develop novel and efficient glycosidation methods capitalizing on the phosphorus-containing leaving groups,[7,8] our interest has been centered on an investigation of the scope and utility of glycosidations with the benzyl-protected glycosyl phosphites from aldohexoses and uronates through comparison with those of the glycosyl phosphates previously developed.[7a] We now wish to report that coupling of benzyl-protected glycopyranosyl diethyl phosphites with a variety of acceptor alcohols can be effected by the aid of boron trifluoride etherate (BF_3·OEt_2) as a promoter even at -78 °C to exhibit the highest 1,2-*trans*-β-selectivity known to date for glycosidations with a non-participating group on *O*-2, whereas no glycosidation was observed with the phosphates under such conditions.





Benzyl-protected glycopyranosyl diethyl phosphites **1**-**3**[9-11] were readily prepared by condensation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and -D-galactopyranose, and methyl 2,3,4-tri-*O*-benzyl-D-gluco-pyranuronate with diethyl phosphorochloridite (1.2 equiv) in the presence of triethylamine (2.5 equiv) (CH_2Cl_2, -78 °C, 0.5 h), wherein the α:β ratio of the products **1**-**3**[12] was found to be highly dependent on an anomeric composition of the starting pyranoses.

We first examined glycosidation of **1** (α:β=90:10 or 61:39) in three different types of solvents (CH_2Cl_2, Et_2O or EtCN) with 6- or 4-unprotected glycosides **4** or **5** (1.1 equiv each) as highly reactive and less reactive acceptor alcohols, respectively, wherein TMSOTf or $BF_3{\cdot}OEt_2$ was employed as a promoter.[13] Some representative results are summarized in Table 1, from which several features have been noted.

1,2-*trans*-β-selectivities observed with TMSOTf-promoted glycosylation of **4** or **5** in each solvent,[14] which were irrespective of the anomeric composition of the donor **1**, exceeded or matched those obtained with the corresponding phosphates.[7a,15,16] Somewhat surprisingly, $BF_3{\cdot}OEt_2$-promoted glycosidation of **1** (α:β=90:10) with **4** or **5** proceeded smoothly even at -78 °C to exhibit the highest 1,2-*trans*-β-selectivities known to date,[17] whereas no glycosidation below 0 °C was observed with the phosphates. In this regard, it is particularly noteworthy that virtually complete β-selectivities with **4** were independent of the solvent as well as the anomeric composition of the donor.[18] In stark contrast, the β-selectivities with **5** in dichloromethane or ether diminished with a decrease in a proportion of α- to β-anomer of the donor,[18] though the selectivities in propionitrile were still independent of the anomeric composition of the donor.[19] Consequently, it appears that

Table 1. Glycosidation of Glucopyranosyl Diethyl Phosphite **1** with Glycoside Alcohols **4**, **5**[a]

TMSOTf as promoter					$BF_3{\cdot}OEt_2$ as promoter				
entry	acceptor	solvent	yield,[b,c] %	α : β[c,d]	entry	acceptor	solvent	yield,[b,c] %	α : β[c,d]
1[e]	4	CH_2Cl_2	78 (87)	6:94 (7:93)	7	4	CH_2Cl_2	97 (97)	1:99 (2:98)
2[e]	4	EtCN	78 (73)	2:98 (2:98)	8	4	EtCN	88 (82)	1:99 (1:99)
3[e]	4	Et_2O	86 (94)	6:94 (7:93)	9	4	Et_2O	91 (88)	1:99 (2:98)
4	5	CH_2Cl_2	83 (84)	32:68 (33:67)	10	5	CH_2Cl_2	68 (64)	3:97 (17:83)
5	5	EtCN	65 (75)	17:83 (19:81)	11	5	EtCN	44 (49)	4:96 (4:96)
6	5	Et_2O	68 (74)	38:62 (31:69)	12	5	Et_2O	40 (37)	6:94 (14:86)

[a] General procedure: the promoter (0.14 mmol) was added to a mixture of the donor **1** (0.14 mmol) and acceptor (0.15 mmol) in solvent (2 ml) at -78°C, and the reaction was performed at the same temperature for 0.5 h with TMSOTf and 1 h with $BF_3{\cdot}OEt_2$ under argon atmosphere. In the case of the reaction with $BF_3{\cdot}OEt_2$, pulverized 4Å molecular sieves (100 mg) was added to the reaction mixture in advance. The product was isolated by extractive work up and subsequent chromatography on silica gel. [b] Isolated yield. The spectroscopic data of the product are consistent with those of the authentic sample previously reported.[7a,c] [c] Values and those in parentheses were obtained starting with the phosphite **1** of α:β ratio of 90:10 and 61:39, respectively. [d] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 x 250 mm; eluent, 15% THF in hexane; flow rate, 1.5 mL/min). [e] The reaction was performed with 0.2 equiv of TMSOTf.

propionitrile is the solvent of choice for allowing exceptionally high 1,2-*trans*-β-selectivities, but our efforts to improve the chemical yields met with little success. Taken together with these results, it has been suggested that BF_3·OEt_2-promoted glycosidation of the benzyl-protected glycopyranosyl diethyl phosphites coupled with the use of dichloromethane as the solvent is likely to be of much wider applicability than TMSOTf-promoted glycosidation of the corresponding phosphites or phosphates, provided that the donor with the highest α:β ratio possible can be efficiently secured.

To demonstrate an applicability of the present method, we explored the glycosidation of **1** (α:β=90:10), **2** (α:β=98:2), and **3** (α:β=97:3) with a range of acceptor alcohols featured by the presence of the acid-labile groups as well as different reactivities. The examples listed in Table 2 document the mildness and generality of this simple method of glycosidation. Furthermore, it should be emphasized here again that the 1,2-*trans*-β-selectivities observed in each case are the highest on record in glycosidations with a non-participating group on *O*-2.[7a,8a]

Table 2. BF_3·OEt_2-Promoted 1,2-*trans*-Glycosidation of Glycopyranosyl Phosphites **1**-**3**[a,b]

entry	donor	acceptor	temp, °C	time, h	yield,[c] %	α : β[d]
1	**1**	**6**	-78	1	92[e]	1:99
2	**1**	**7**	-78	1	91[e]	2:98
3	**1**	**8**	-78	1	96	1:99
4	**1**	**9**	-78	1	71	2:98
5	**2**	**6**	-78	1	83[f]	1:99
6	**2**	**10**	-78	1	86	2:98
7	**3**	**4**	-65[g]	3	67	1:99
8	**3**	**8**	-65[g]	0.5	83[e]	1:99

[a] The reaction was carried out on 0.2 mmol scale. [b] Donor/acceptor/BF_3·OEt_2 molar ratio=1.0/1.1/1.0. [c] Isolated yield. The spectroscopic data of the product are consistent with those of the authentic sample previously reported,[7a,c] except in entries 2, 5 and 8. [d] The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 x 250 mm; eluent, 15~20% ethyl acetate in hexane or 15~20% THF in hexane; flow rate, 1.5 mL/min). [e] $[\alpha]_D^{25}$ (*c*, $CHCl_3$) : -29.0° (0.93) in entry 1; +39.8° (1.01) in entry 2; -12.0° (1.12) in entry 8. Chemical shift (δ ppm) in ^{13}C NMR (100.4 MHz) spectrum for the anomeric center newly formed: 104.4 in entry 1; 104.0 in entry 2; 103.3 in entry 8. [f] The reported specific rotation value[7a] should be revised to $[\alpha]_D^{25}$ -39.3° (*c* 2.26, $CHCl_3$). [g] The limit temperature to allow the smooth reaction.

In conclusion, we have demonstrated the effectiveness of benzyl-protected glycopyranosyl diethyl phosphites from aldohexoses and uronates as glycosyl donors, wherein BF_3·OEt_2 is proven to be the promoter of choice for allowing virtually complete β-selectivities with the fundamental but hitherto difficult category of glycosyl phosphites. Further extension of the present method to the construction of carbohydrate-containing natural products and oligosaccharides is in progress.

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9. The donor **1** of α:β ratio of 90:10 and 61:39 was originated from the corresponding glucopyranose (α:β=90:10) prepared by the literature method (Schmidt, O. T.; Auer, T.; Schmadel, H. *Chem. Ber.* **1960**, *93*, 556) and the anomerized one (α:β=56:44) obtained by treatment with cat. TsOH in aq. THF, respectively.
10. The donor **2** of α:β ratio of 98:2 was obtained by flash chromatography of **2** with 54:46 ratio, which was originated from the corresponding galactopyranose (α:β=55:45) prepared by the literature procedure (Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639).
11. The donor **3** of α:β ratio of 97:3 was originated from the corresponding methyl glucopyranuronate (α:β=97:3) prepared by the literature method (van Boeckel, C. A. A.; Delbressine, L. P. C.; Kaspersen, F. M. *Rec. Trav. Chim. Pays-Bas* **1985**, *104*, 259).
12. The anomeric ratio of the phosphites **1-3** was determined by 202.5 MHz ^{31}P NMR using 85% H_3PO_4 as an external standard. **1**, δ_P=140.3 (α), 141.0 (β); **2**, δ_P=140.8 (α), 140.5 (β); **3**, δ_P=140.6 (α), 140.8 (β).
13. With TMSOTf, 0.2 equiv of the reagent was enough to allow the smooth glycosylation of **4** in each solvent at -78 °C, but an about stoichiometric amount of the reagent was required for that of **5** under otherwise similar conditions. With BF_3·OEt_2, an about stoichiometric amount of the reagent was required to complete the glycosylation of both **4** and **5** within 1 h.
14. Quite recently, Wong and co-workers reported that TMSOTf-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dibenzyl phosphite with **4** (CH_2Cl_2, -78 °C, 1 h) led exclusively to the formation of the 1,2-*trans*-linked disaccharide.[3c]
15. TMSOTf (1.5 equiv)-promoted glycosidation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl diethyl phosphate with **4** or **5** gave the results summarized in the table, wherein the temperature indicates the limit one to allow the smooth reaction. The phosphite **1** was found to exhibit much higher reactivities than the corresponding phosphate.

acceptor	solvent	temp, °C	time, h	yield, %	α : β
4	CH_2Cl_2	-45	1	70	20:80
4	EtCN	-60	3	89	4:96
4	Et_2O	-78	1	92	11:89
5	CH_2Cl_2	-45	1	62	48:52
5	EtCN	-60	5	75	16:84
5	Et_2O	-70	3	77	47:53

16. As is the case with TMSOTf-promoted glycosidation of the phosphates, the present glycosidation is assumed to proceed through the intermediacy of the thermodynamically more stable α-D-glycopyranosyl triflate (or its tight α-ion pair) or α-D-glycopyranosyl-nitrilium ion associated with triflate as a gegenion when propionitrile is used as a solvent followed by the back side attack of acceptor alcohols on this intermediate.
17. When the present reaction was performed in dichloromethane above -78 °C, the following selectivities were obtained. The α:β ratio with **4**: 2:98 at -50 °C; 3:97 at -30 °C. The α:β ratio with **5**: 8:92 at -50 °C; 11:89 at -30 °C. Thus, the temperature effect was found to be more pronounced with **5** than with **4**; the lower the reaction temperature, the higher the selectivities.
18. The explanation of 1,2-*trans*-β-selectivities observed with BF_3·OEt_2-promoted glycosidations of the phosphite **1** with **4** or **5** remains presently to be open, except when propionitrile was used as the solvent.[19]
19. The intermediacy of α-nitrilium ion[1d,8a,20] by use of propionitrile as the solvent is manifested by exceptionally high order of β-selectivity with **5**.
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