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An Efficient Construction of 1,2-*trans*-β-Glycosidic Linkages Capitalizing on Glycopyranosyl *N,N,N',N'*-Tetramethylphosphoroamidates as Shelf-Stable Glycosyl Donors†

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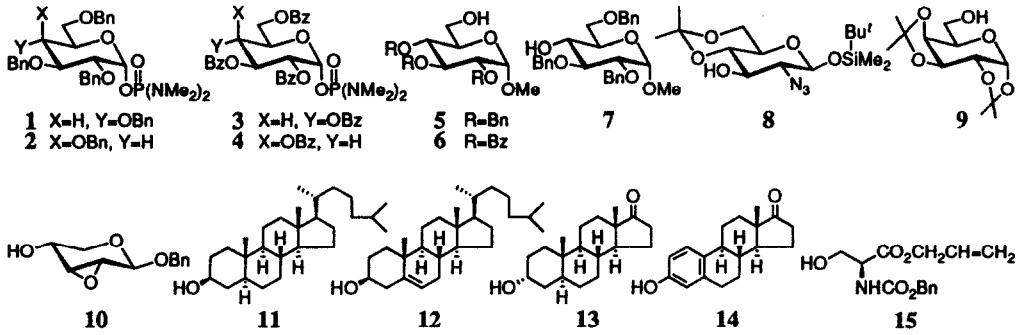
Abstract: A highly stereocontrolled 1,2-trans-β-glycosidation reaction with or without neighbouring group participation has been developed by using benzyl- or benzoyl-protected glycopyranosyl N,N,N',N'-tetramethylphosphoroamidates as shelf-stable glycosyl donors in the presence of trimethylsilyl trifluoromethanesulfonate or boron trifluoride etherate. Several notable features of the present method not observed with the diphenyl phosphate method are also described.

An increase in the biological significance of saccharide moieties of carbohydrate-containing biomolecules has generated considerable interest in the rational design and implementation of stereocontrolled glycosidation reactions.[1,2] Our interest in this area centered on the design of the leaving groups of glycosyl donors coupled with their activation without resorting to precious, explosive, or toxic heavy-metal salts as promoters. In an effort to capitalize on the phosphorus-containing leaving groups, we have recently devised new glycosyl donors incorporating diphenyl phosphate, diphenylphosphinimidate, or phosphorodiamidimidothioate as leaving groups, the glycosidations of which constitute mild and efficient methods for the highly stereocontrolled construction of 1,2-*trans*-β- and 1,2-*cis*-α-glycosidic linkages.[3] With respect to the diphenyl phosphate method[3a] with a non-participating group on *O*-2, although this method offers advantages of allowing extremely rapid glycosidation with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at -78 °C as well as the highest 1,2-*trans*-β-selectivity known to date, relatively poor shelf-stabilities of the benzyl-protected glycopyranosyl diphenyl phosphates precluded its wider application. Thus, we directed our efforts to the development of the more shelf-stable glycopyranosyl phosphates with similar reactivities and stereoselectivities in glycosidation reactions. After a number of variations of substituents on the phosphorus atom of a phosphate group, we now wish to report an efficient procedure for the stereocontrolled construction of 1,2-*trans*-β-glycosidic linkage *via* benzyl- or benzoyl-protected glycopyranosyl *N,N,N',N'*-tetramethylphosphoroamidates, which fulfills the above requirements.

Benzyl-protected glycopyranosyl *N,N,N',N'*-tetramethylphosphoroamidates **1** and **2** were readily prepared by condensation of the 1-*O*-lithium salts of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and -D-galactopyranose with bis(dimethylamino)phosphorochloridate (5:1 THF-HMPA, -30°C, 2 h).[4] The shelf-stability of **1** was examined through methanolysis (0.015 M, 23 °C), which led to the formation of 12% of methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside after 30 days. A comparison with $t_{1/2}$=45 min for the corresponding diphenyl phosphate further confirmed the excellent stability of **1**. Somewhat surprisingly in the light of this result, it was found that coupling of the phosphoroamidates **1** and **2** (1.05 equiv) with a variety of glycoside alcohols (1.0 equiv) in propionitrile in the presence of TMSOTf (1.8 equiv) at -78 °C proceeded to

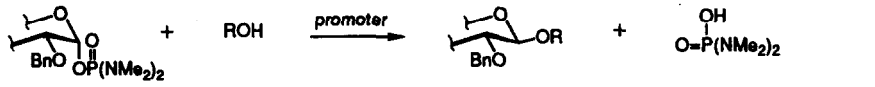
†This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.



completion within 0.5 h to afford the 1,2-*trans*-β-linked disaccharides with high degrees of stereoselectivity and in high yields (entries 1, 3, 5, 6, and 8 in Table 1). It has now been demonstrated that the phosphoroamidates with excellent shelf-lives exhibit reactivities and stereoselectivities comparable to those of the corresponding diphenyl phosphates in TMSOTf-promoted glycosidation. It is also worthy of note that the alcohols bearing the acid-sensitive groups were safely glycosylated (entries 5, 6, and 8). The glycosidation of the β-anomers of **1** and **2** under the foregoing conditions showed that the stereochemical outcome and the yield of this glycosidation were irrespective of the anomeric configuration of the donors, as observed with that of the corresponding diphenyl phosphates. Among the solvents screened, propionitrile proved to be the best choice for allowing high levels of 1,2-*trans*-β-selectivity. By switching to dichloromethane, β-selectivities dropped sharply except for glucosylation of the primary alcohols[5] (entries 2, 4, 7, and 9). The significant effect of the nitrile solvents on stereoselectivities of glycosidation with benzyl-protected glycopyranosyl donors in favor of the predominant formation of β-glycosides is well documented.[2e,2r,6] In this regard, it is of particular interest to mention that Ratcliffe and Fraser-Reid,[7] Schmidt *et al.*,[8] and Sinaÿ[1d] have recently proposed the intermediacy of α-D-glycopyranosyl-nitrilium ion, based on the results obtained by glucosylation of 2-chlorobenzoic acid in acetonitrile.[7,9] Thus, we examined the glycosidation of **1** with 2-chlorobenzoic acid in acetonitrile or propionitrile in the presence of TMSOTf at -40 and -78 °C, respectively.[10] However, the reactions led to the exclusive formation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-(2-chlorobenzoyl)-D-glucopyranose with the α:β ratios of 68:32 and 36:64, respectively, with no trace of the α-*N*-glucosides being detected. These findings, taken together with the result with glucosylation of the primary alcohols in dichloromethane, suggest that the formation of an α-nitrilium intermediate, if any, might not be necessarily responsible for high β-selectivity in this glycosidation. Consequently, while the mechanistic basis for the remarkable effect of propionitrile is presently unclear,[11,12] the present glycosidation reaction apparently proceeds through the intermediacy of the thermodynamically more stable tight α-ion pair consisting of oxocarbenium ion and phosphoroamidate-TMSOTf complex followed by the backside attack of acceptor alcohols on this intermediate.

An additional feature of the phosphoroamidates is the fact that they can be activated by boron trifluoride etherate at -10 °C, whereas glycosidation of the corresponding diphenyl phosphates are promoted by this reagent at 10 °C to give an anomeric mixture of products. On this positive note, we focused our attention on glycosylation of steroidal alcohols, which proved to be acceptors inappropriate to TMSOTf-promoted glycosidation due mainly to the poor solubility of them in propionitrile below -50 °C, the limit temperature allowing for high β-selectivity. We now found that condensation of the phosphoroamidates **1** and **2** (1.05 equiv) with steroidal alcohols (1.0 equiv) in dichloromethane in the presence of boron trifluoride etherate (1.8

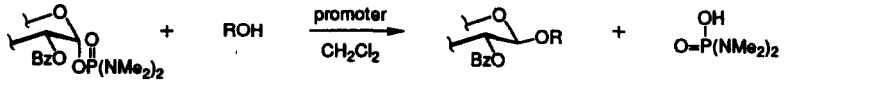
Table 1. 1,2-*trans*-Glycosidation of Benzyl-Protected Glycopyranosyl *N,N,N',N'*-Tetramethylphosphoroamidates **1** and **2**[a,b,c]



entry	donor	acceptor	promoter	solvent	temp, °C	time, h	yield,[d,e] %	α : β[f]
1	**1**	**5**	TMSOTf	EtCN	-78	0.5	93	4:96
2	**1**	**5**	TMSOTf	CH_2Cl_2	-78	0.5	84	4:96
3	**1**	**7**	TMSOTf	EtCN	-78	0.5	89	11:89
4	**1**	**7**	TMSOTf	CH_2Cl_2	-78	0.5	81	32:68
5	**1**	**8**	TMSOTf	EtCN	-78	0.5	75	8:92
6	**2**	**9**	TMSOTf	EtCN	-78	0.5	90	6:94
7	**2**	**9**	TMSOTf	CH_2Cl_2	-78	0.5	87	36:64
8	**2**	**10**	TMSOTf	EtCN	-78	0.5	86	8:92[g]
9	**2**	**10**	TMSOTf	CH_2Cl_2	-78	0.5	82	57:43
10	**1**	**11**	BF_3·OEt_2	CH_2Cl_2	-10	6	73	10:90
11	**1**	**12**	BF_3·OEt_2	CH_2Cl_2	-10	6	70	9:91
12	**2**	**13**	BF_3·OEt_2	CH_2Cl_2	-10	5	76	13:87

[a]The reaction was carried out on 0.1 mmol scale in the manner reported in ref. 3c. [b]Donor/acceptor/TMSOTf molar ratio=1.05/1.0/1.8. [c]Donor/acceptor/BF_3·OEt_2 molar ratio=1.05/1.0/1.8. [d]Isolated total yield based on the acceptor alcohol used. [e]The spectroscopic data of the product are consistent with those of the authentic sample previously reported,[3a,b] except in entries 8 and 9. [f]The ratio was determined by HPLC (column, Zorbax® Sil, 4.6 x 250 mm; eluent, 5~13% ethyl acetate in hexane or 9~13% THF in hexane; flow rate, 1.5 mL/min; detection, 254 nm). [g]Chemical shift in ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum for the anomeric center newly formed: δ 96.8 (α-anomer) and 103.6 (β-anomer).

Table 2. 1,2-*trans*-Glycosidation of Benzoyl-Protected Glycopyranosyl *N,N,N',N'*-Tetramethylphosphoroamidates **3** and **4**[a,b,c]



entry	donor	acceptor	promoter	temp, °C	time, h	yield,[d] %
1	**3**	**7**	TMSOTf	0	2	81
2	**3**	**14**	TMSOTf	0	2	72
3	**4**	**10**	TMSOTf	0	1.5	82
4	**4**	**12**	TMSOTf	0	2	80[e]
5	**3**	**6**	BF_3·OEt_2	15	4	86
6	**4**	**15**	BF_3·OEt_2	15	5	81[f]

[a]The reaction was carried out on 0.1 mmol scale in the manner reported in ref. 3a and 3b. [b]Donor/acceptor/TMSOTf/1,1,3,3-tetramethylurea molar ratio=1.05/1.0/1.7/1.5. [c]Donor/acceptor/BF_3·OEt_2 molar ratio=1.05/1.0/2.5. [d]The spectroscopic data of the product are consistent with those of the authentic sample previously reported,[3a] except in entries 4 and 6. [e]$[\alpha]_D^{23}$ +78.7° (*c* 1.09, $CHCl_3$). [f]$[\alpha]_D^{23}$ +71.9° (*c* 1.11, $CHCl_3$).

equiv) and pulverized 4Å molecular sieves at -10 °C led to the predominant formation of 1,2-*trans*-β-linked steroidal glycosides (entries 10-12 in Table 1). It is of particular interest that the glycosidation of the corresponding β-anomers under the foregoing conditions gave essentially the same yields and stereoselectivities as that of **1** or **2**, unlike the diphenylphosphinimidate method previously developed.[3c] These results can be accounted for by rapid anomerization of β- to α-anomers (within 5 min at -10 °C) prior to glycosidation, suggesting the mechanism *via* the backside attack of alcohols on the thermodynamically more stable tight α-ion pair consisting of oxocarbenium ion and phosphoroamidate-boron trifluoride complex.

Finally, it is worth noting that the reaction works well with benzoyl-protected glycopyranosyl *N,N,N',N'*-tetramethylphosphoroamidates **3** and **4**. Thus, glycosidation of **3** or **4** led to the exclusive formation of 1,2-*trans*-linked glycosides or disaccharides with the aid of TMSOTf or boron trifluoride etherate as promoters, as might be anticipated from the anchimeric assistance by *O*-2 benzoyl group. The examples listed in Table 2 document the considerable scope and versatility of this simple method of glycosidation. It should be emphasized here again that the present glycosidation can be promoted by boron trifluoride etherate which is not capable of activating the corresponding diphenyl phosphates even at 23 °C.

In summary, we have demonstrated the effectiveness of glycopyranosyl *N,N,N',N'*-tetramethylphosphoroamidates as glycosyl donors. Further extension of the present method endowed with several salient features to the construction of carbohydrate-containing natural products and oligosaccharides is in progress.[13]

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4. The following procedure for the preparation of the phosphoroamidate **1** is representative. To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (α:β=94:6, 2 g, 3.70 mmol) in THF (30 mL) was added *n*-butyllithium (1.59 M in hexane, 2.44 mL) at -78 °C under argon atmosphere. After 15 min, a solution of bis(dimethylamino)phosphorochloridate (644 mg, 3.77 mmol) in HMPA (6 mL) was added at this temperature, and then the bath temperature was raised to -30 °C over 0.5 h. The reaction mixture was stirred at this temperature for 2 h, and then treated with ice followed by stirring at 0 °C for 15 min. The mixture was poured into an ice-cold, two-layer mixture of ether (20 mL) and satd. $NaHCO_3$ solution-brine (1:1, 20 mL), and the whole was extracted with ethyl acetate (80 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 3:2:1 ether-ethyl acetate-hexane) to give **1** (1.85 g, 74%) as a colorless oil and its β-anomer (240 mg, 9.6%) as white needles. **1**: $[\alpha]_D^{23}$ +62.3° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.93 (dd, J=3.4, 8.5 Hz, H-1). Its β-anomer: mp 93-94 °C (hexane); $[\alpha]_D^{23}$ +19.4° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.17 (t, J=7.5 Hz, H-1). The α:β ratio of the product was found to be independent of an anomeric composition of the starting pyranose.
5. Glucosylation of the primary alcohol **9** in propionitrile or dichloromethane gave the corresponding glucoside with the α:β ratios of 3:97 and 10:90, respectively.
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10. No reaction occurred at 23 °C in the absence of TMSOTf.
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12. For an alternative mechanism, see: Noyori, R.; Hayashi, M.; Hashimoto, S. In *Organosilicon and Bioorganosilicon Chemistry*; Sakurai, H., Ed.; Ellis Horwood Limited: Chichester, 1985; pp 213-218.

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