GLYCOSIDATION OF GLYCOSYL PHOSPHORAMIDITES

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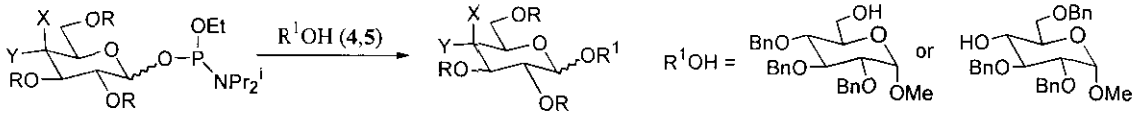
Abstract - A highly stereocontrolled 1,2-*trans* glycosidation reaction has been developed by using glycopyranosyl phosphoramidites as glycosyl donors in the presence of TMSOTf or $BF_3{\cdot}OEt_2$ as a promoter in a variety of solvents.

The increasing significance of glycosides and oligosaccharides as constituents in biologically active compounds has made stereocontrolled construction of the glycosidic linkage an important synthetic target. Recent studies have established that the leaving group of a glycosyl donor plays an important role in determining both stereoselectivities and yields of glycosidation reactions.[1] Among the various heteroatom-containing leaving groups available, trivalent-phosphorus glycosyl derivatives have been demonstrated to be effective donors in yielding stereocontrolled glycosidations.[2] Our interest stems from the fact that glycosyl phosphorous derivatives possess multiple substituents for effective phosphorus-based glycosyl donors. Advances made in this area could provide additional opportunities for glycosidation with a variety of glycosyl acceptors, [2,3] particularly relevant in solid-phase synthesis.[4]

We have reported an efficient procedure for the stereoselective construction of 2-deoxyglycosidic linkage by using 2-deoxyglycosyl *N,N*-diisopropylphosphoramidites as glycosyl donors. The phosphoroamidite derivatives appear to be excellent leaving groups of glycosyl donors. α-Couplings can be achieved in high stereoselectivity, even in the case of hindered alcohol acceptors.[3c] It is anticipated that the restoration of 2-alkoxy groups to donors may influence the yield and stereochemistry of glycosidation. We wish to report here an efficient procedure for the construction of 1,2-*trans* glycosidic linkage *via* glycopyranosyl *N,N*-diisopropylphosphoramidites[5] (**1-3**) with acceptor alcohols(**4-5**) in the presence of TMSOTf or $BF_3{\cdot}OEt_2$ as a promoter. The 6- or 4-unprotected glycosides (**4-5**) served as highly reactive and less reactive acceptor alcohols, respectively.

Table 1. Glycosidation of Glycophosphoramidites (**1-3**) with Glycoside Alcohols (**4,5**)



1: X=H, Y=OMe, R=Me; **2**: X=H, Y=OBn, R=Bn
3: X=OBn, Y=H, R=Bn

6-10 **4** **5**

entry	donor[a]	acceptor	promoter	solvent[b]	product	yield[c]	β:α[d]
1	**1**	**4**	TMSOTf	EtCN	**6**	92	99:1
2	**1**	**4**	TMSOTf	CH_2Cl_2	**6**	75	96:4
3	**1**	**4**	TMSOTf	Et_2O	**6**	92	95:5
4	**1**	**4**	$BF_3{\cdot}OEt_2$	EtCN	**6**	53	95:5
5	**1**	**4**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**6**	70	95:5
6	**1**	**4**	$BF_3{\cdot}OEt_2$	Et_2O	**6**	54	94:6
7	**2**	**4**	TMSOTf	EtCN	**7**	87	97:3
8	**3**	**4**	TMSOTf	EtCN	**8**	69	96:4
9	**2**	**5**	TMSOTf	EtCN	**9**	70	90:10
10	**3**	**5**	TMSOTf	EtCN	**10**	51	89:11
11	**3**	**5**	$BF_3{\cdot}OEt_2$	EtCN	**10**	92	91:9

[a] α:β=1:3. [b] Carried out at -78 °C with molar ratios of 1.5:1:1.5 (donor : acceptor : promoter). [c] Isolated yield. [d] determined by 200 MHz ^{1}H NMR (Gemini, Varian) and/or HPLC (column: adsorbosphere silica 5u, 4.6x250 mm; eluent: 15% ethyl acetate in cyclohexane; flow rate: 1.5 ml/min; detection: 250 nm).

Table 1 lists the preliminary results on glycosyl phosphoramidites (**1-3**) coupling with selected primary and secondary alcohols (**4-5**) to give disaccharides (**6-10**).[6] 1,2-*trans*-Selectivity was observed in the case of TMSOTf and $BF_3{\cdot}OEt_2$ promoted glycosidation. This selectivity was found to be independent of the anomeric composition of the donors (**1-3**).[3] Propionitrile appears to be the solvent of choice for achieving both high levels of β-selectivity and excellent yields. Glycosyl phosphoramidites, which possess comparable reactivity to that of phosphite compounds,[2h] allow for their coupling with glycosyl acceptors at low temperature. The complete formation of β-linkage of product (**6**) was found to be unusually independent of the solvent and promoter. Also of interest are the benzyl protected donors (**2-3**), that are reactive enough to allow coupling with the hindered secondary alcohol (**5**), despite the fact that glycosyl phosphoramidites (**1-3**) are less reactive towards glycosyl acceptors than the corresponding 2-deoxy

derivatives.[3c] The method described here demonstrates significant promise for wider applications in the use of glycopyranosyl phosphoramidites as glycosyl donors in glycosidation, wherein the use of either promoter $BF_3{\cdot}OEt_2$ or TMSOTf in several solvents allows for excellent β-selectivity in good yields.

Typical Procedure of Glycosidation: To a solution of glycosyl donor (0.2 mmol) and acceptor (0.14 mmol) in dry EtCN (5 mL) at -78°C was added TMSOTf (0.2 mmol), and the mixture was stirred for 4 h. The reaction was quenched with 5% aqueous $NaHCO_3$ solution. The resulting mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4 and then concentrated. The residue was applied to a silica gel column chromatography (ethyl acetate-petroleum ether: 35%-65%) to afford the corresponding disaccharide as a white solid.

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REFERENCES AND NOTES

1. For selected reviews, see: (a) S. J. Danishefsky and M. T. Bilodeau, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1380; (b) K. Toshima and K. Tatsuta, *Chem. Rev.*, 1993, **93**, 1503; (c) B. Fraser-Reid, U. E. Udodong, Z. Wu, H. Ottosson, J. R. Merritt, C. S. Rao, C. Roberts, and R. Madsen, *Synlett*, 1992, 927; (d) P. Sinay, *Pure Appl. Chem.*, 1991, **63**, 519.

2. (a) H. Kondo, Y. Ichikawa, and C.-H. Wong, *J. Am. Chem. Soc.*, 1992, **114**, 8748; (b) T. J. Martin and R. R. Schmidt, *Tetrahedron Lett.*, 1992, **33**, 6123; (c) Y. Watanabe, C. Nakamoto, and S. Ozaki, *Synlett*, 1993, 115; (d) M. M. Sim, H. Kondo, and C.-H. Wong, *J. Am. Chem. Soc.*, 1993, **115**, 2260; (e) T. Müller, R. Schneider, and R. R. Schmidt, *Tetrahedron Lett.*, 1994, **35**, 4763; (f) N. Falahatpisheh and G. A. Sulikowski, *Synlett*, 1994, 672; (g) Y. Watanabe, C. Nakamoto, T. Yamamoto, and S. Ozaki, *Tetrahedron*, 1994, **50**, 6523; (h) S. Hashimoto, K. Umeo, N. Watanabe, M. Nakajima, and S. Ikegami, *Tetrahedron Lett.*, 1995, **36**, 2251.

3. (a) M. Chen, K. Ravindran, D. W Landry, and K. Zhao, *Heterocycles,* 1997, **45**, 1247; (b) S. Pan, H. Li, B. Yu, F. Hong, and K. Zhao, *Tetrahedron Lett.,* 1997, **38**, 6139; (c) H. Li, M. Chen, and K. Zhao, *Tetrahedron Lett.*, 1997, **38**, 6143.

4. For recent works on polymer-supported carbohydrate synthesis, see: (a) R. Liang, L. Yan, J. Loebach, M. Ge, Y. Uozumi, K. Sekanina, N. Horan, J. Gildersleeve, C. Thompson, A. Smith, K. Biswas, W. C. Still, and D. Kahne, *Science,* 1996, **274**, 1520; (b) J. Hunt and W. Roush, *J. Am. Chem. Soc.*, 1996, **118**, 9998; (c) J. Rademann and R. R. Schmidt, *Tetrahedron Lett.*, 1996, **37**, 3989; (d) S. P. Douglas, D. M. Whitfield, and J. J. Krepinsky, *J. Am. Chem. Soc.*, 1995, **117**, 2116; (e) S. J. Danishefsky, K. F. McClure, J. T. Randolph, and R. B. Ruggeri, *Science,* 1993, **260**, 1307.

5. (a) Glycopyranosyl phosphoramidites (**1-3**) were readily prepared by condensation of 2,3,4,6-tetra-*O*-methylglucopyranose, 2,3,4,6-tetra-*O*-methylgalactopyranose, and 2,3,4,6-tetra-*O*-benzyl galactopyranose with ethoxy bis(diisopropylamine) phosphine (1.2 equiv) in the presence of diisopropylammonium tetrazolide (1.2 equiv, CH_2Cl_2, rt , 12 h); (b) W. Bannwarth and A. Trzeciak, *Helv. Chim. Acta,* 1987, **70**, 175.

6. Selected data of ^{1}H-NMR (200 MHz, $CDCl_3$): **6**: δ 4.22 (d, J = 7.32 Hz, 1H, β). **7**: δ 4.37 (d, J = 7.58 Hz, 1H, β). **8**: δ 4.32 (d, J = 7.70 Hz, 1H, β). **9**: δ 5.71 (d, J = 3.72 Hz, 1H, α), β-H is overlapped. **10**: δ 5.76 (d, J = 4.00 Hz, 1H, α), β-H is overlapped. Selected data of ^{13}C-NMR (50 MHz, $CDCl_3$): **6**: δ 98.55 (C-1, α), δ 104.05 (C-1', β). **7**: δ 98.59 (C-1, α), δ 104.34 (C-1', β). **8**: δ 98.45 (C-1, α), δ 104.76 (C-1', β).

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