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STEREOSELECTIVE LINKAGES OF 2-DEOXYGLYCOSIDES WITH HINDERED ACCEPTORS

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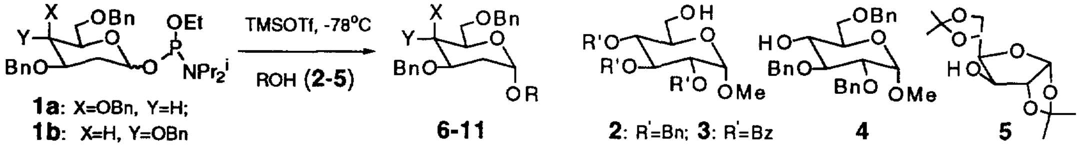
Abstract: The use of 2-deoxyglycosyl phosphoramidites as glycosyl donors allows the construction of 2-deoxyglycosidic linkages in high yield and excellent α-stereoselectivity. © 1997 Elsevier Science Ltd.

We have developed an approach employing the Staudinger reaction of phenyl azide with glycosyl phosphites or phosphoramidites for preparing a range of glycosyl donors.[1] These donors are versatile, as they allow the attachment of multiple variable substituents on the phosphorus for the potential construction of diversified glycosidic bonds.[2] Herein, we report the preliminary studies of using 2-deoxyglycosyl phosphoramidites as glycosyl donors for their stereoselective coupling with hindered glycosyl acceptors.[3]

Table. Glycosidation of 2-deoxyglycosyl phosphoramidites **1** with acceptors **2-5**.



1a: X=OBn, Y=H;
1b: X=H, Y=OBn

6-11

2: R'=Bn; **3**: R'=Bz

4

5

entry	donor[a]	acceptor	solvent	product	yield[b]	α:β[c]
1	**1a**	**2**	EtCN	**6**	82	98:2
2	**1a**	**2**	CH_2Cl_2	**6**	83	99:1
3	**1a**	**3**	EtCN	**7**	77	96:4
4	**1a**	**3**	CH_2Cl_2	**7**	94	95:5
5	**1a**	**4**	EtCN	**8**	82	94:6
6	**1a**	**4**	CH_2Cl_2	**8**	83	99:1
7	**1b**	**4**	EtCN	**9**	82	94:6
8	**1b**	**4**	CH_2Cl_2	**9**	83	96:4
9	**1a**	**5**	EtCN	**10**	81	98:2
10	**1b**	**5**	EtCN	**11**	84	91:9
11	**1b**	**5**	CH_2Cl_2	**11**	88	94:6

[a] Anomeric composition of **1a**: α only, **1b**: α : β = 1.6:1. [b] Isolated yields are based on the acceptors used. Glycosidation conditions: the reaction was conducted at -78 °C with donor/acceptor/promoter molar ratios = 1.5/1.0/1.5; typical reaction times were 1-3 h. [c] The ratios were determined by 200 MHz ^1H NMR (Gemini, Varian) and HPLC (column, adsorbosphere silica 5u, 4.6 x 250 mm; eluent, 20% ethyl acetate in hexanes; flow rate, 1.5 ml/min; detection, 254 nm).

The desired 2-deoxyglycosyl donors, 3,4,6-tri-*O*-benzyl-2-deoxy-glucopyranosyl and galactopyranosyl *N,N*-diisopropyl phosphoramidites (**1a-b**), were readily prepared by treatment of the corresponding pyranoses[4a] with ethoxy bis(diisopropylamino)phosphite (1.2 equiv.) in the presence of diisopropylammonium tetrazolide (1.5 equiv. CH_2Cl_2, rt, 12h).[4b] After silica-gel column chromatography [petroleum ether/ethyl acetate/Et_3N (20:4:1)], the donors (**1a-b**) were obtained in the range of 75-85% yields, and could be stored at -10 °C for months without any detectable deterioration.

In our preliminary survey of the glycosidation conditions, the acceptors (**2-5**) ranging from primary to hindered alcohols, two solvents (CH_2Cl_2 and EtCN) and a catalyst (TMSOTf) defined the reaction parameters. The glycosidation of donors (**1a-b**) proceeded smoothly to efficient formation of glycoside linkages to disaccharides (**6-11**) in good yield. As summarized in the table, the stereochemical outcome of the glycosidation, which is independent of the anomeric configuration of the donors, appears to be under kinetic control.[5] Of the two solvents, CH_2Cl_2 appears to promote higher α-selectivity than EtCN. In general, the α-selectivity was observed from both galactosyl compound (**1a**) and glucosyl derivative (**1b**).[6,7] Particularly important feature of this method is the high α-selectivity observed even with hindered alcohols (**4-5**) in comparison with other phosphorus-containing donors. The examples listed in the table document the considerable scope and versatility of this method.

In summary, we have demonstrated the effectiveness of *N,N*-diisopropyl phosphoramidites as 2-deoxyglycosyl donors in the construction of α-glycosidic bonds. Further extension of this work to include steroidal alcohols and anthracyclines is currently in progress.

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3. For selected examples of 2-deoxyglycosidation, see: (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236.
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6. The α-isomers gave a doublet with $J_{1,2ax}$ between 2-4 Hz, see references 2c-d, 3b and 7.
7. Selected data of ^1H (200 MHz, $CDCl_3$) and ^{13}C (50 MHz, $CDCl_3$) NMR for **1** and **6-11**. **1a**: δ_H 5.05 (dd, J = 2.5 Hz, J_{HP} = 9.4 Hz, 1H, α); **1b**: δ_H: 5.45 (dd, J = 2.5 Hz, J_{HP} = 9.1 Hz, 1H, α); **6**: δ_H: 4.97 (d, J = 3.4 Hz, 1H, α); δ_C: 101.3 (C-1, α), 98.62 (C-1', α); **7**: δ_H: 5.02 (d, J = 2.8 Hz, 1H, α); δ_C: 98.64 (C-1), 97.54 (C-1', α); **8**: δ_H: 5.49 (d, J = 2.9 Hz, 1H, α); δ_C: 100.2 (C-1), 98.32 (C-1', α); **9**: δ_H: 5.45 (d, J = 2.5 Hz, 1H, α); δ_C: 99.93 (C-1), 98.28 (C-1', α); **10**: δ_H: 5.83 (d, J = 3.6 Hz, 1H, H-1', α), 5.24 (d, J = 2.7 Hz, 1H, α); δ_C: 105.8 (C-1, α), 99.99 (C-1', α); **11**: δ_H: 5.83 (d, J = 3.6 Hz, 1H, H-1', α); 5.25 (d, J = 2.3 Hz, 1H, α); δ_C: 105.8 (C-1), 99.22 (C-1', α).

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