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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

Y- BnO	OBn OEt	TMSOTf, -78°C ROH (2-5)		R'O R'O R'O		OBN X07	\sim
1a : X=OBn, Y=H; 1b : X=H, Y=OBn			6-11	2: R'=Bn; 3:	R ⁱ =Bz	4	5 ⁶ –
entry	donor ^a	acceptor	solvent	product	yield ^b	α:β ^c	
1	1a	2	EtCN	6	82	98:2	
2	1a	2	CH ₂ Cl ₂	6	83	99:1	
3	1a	3	EtCN	7	77	96:4	
4	1a	3	CH ₂ Cl ₂	7	94	95:5	
5	1a	4	EtCN	8	82	94:6	
6	1a	4	CH ₂ Cl ₂	8	83	99:1	
7	1b	4	EtCN	9	82	94:6	
8	1b	4	CH ₂ Cl 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 ₂ Cl ₂	11	88	94:6	

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

^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/Et₃N (20:4:1)], the donors (**1a-b**) were obtained in the range of 75-85% yields, and could be stored at -10 $^{\circ}$ 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 (CH₂Cl₂ 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, CH₂Cl₂ 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 phosphoruscontaining 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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References and Notes:

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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, CDCl₃) and ¹³C (50 MHz, CDCl₃) 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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