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Glycosyl Sulfates as Glycosyl Donors

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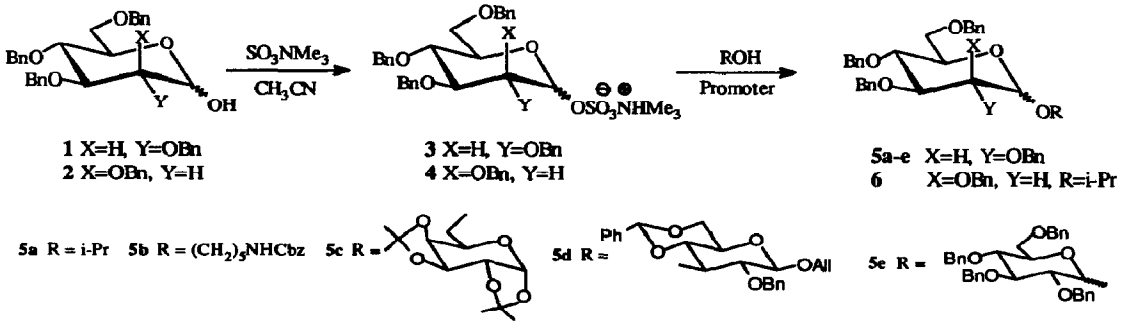
Abstract: Glycosyl sulfates are easily synthesised from tetrabenzyl pyranoses; their reaction with various acceptors promoted by Lewis acids affords glycosides and disaccharides as α,β mixtures.

Simple, efficient, and selective synthesis of oligosaccharides is a central problem in carbohydrate chemistry. The Koenigs-Knorr glycosylation, based on the use of glycosyl halides as glycosyl donors, has by and large been the essential synthesis for a very long period of time. Recently many efforts have been devoted to the search for a "non Koenigs-Knorr" activation of the anomeric centre.[1] Among many others, 1-*O*-sulfonyl derivatives as glycosyl donors were widely described by Schuerch's group, but their use was quite limited.[2]

During our studies on *O*-sulfated oligosaccharides, we found that 1-*O*-sulfated derivatives are easily available and can act as glycosyl donors in the synthesis of glycosides. In particular, we synthesised the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl sulfate **3** by treatment of the corresponding pyranose **1** with $SO_3 \cdot NMe_3$ complex. The reaction was clean and easy to perform and furnished the expected 1-*O*-sulfate **3** in a good yield as a 3:1 mixture of α,β anomers. The anomeric sulfates can be separated by flash chromatography (1:1 dichloromethane - acetone) and stored for several weeks as triethylammonium salts obtained by washing their chloroform solution with triethylammonium hydrogen carbonate buffer. Furthermore, they can be used without any purification; in fact, the crude products react readily with several alcohols in CH_2Cl_2, using $BF_3 \cdot OEt_2$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf) as acid promoter, to give α,β mixtures of glycosides and disaccharides in fair to good yields.



In preliminary experiments we did not find significant variations in the glycosylation stereoselectivity starting from either α or β glycosyl sulfate. We therefore used the anomeric mixture of glycosyl donors in all the experiments.

Our results are summarized in Table 1: interestingly, they show some analogies with those reported by Sinaÿ *et al.*[3]. In fact, in every case a stoichiometric amount of acid promoter was necessary and TMSOTf gave better results compared to $BF_3{\cdot}OEt_2$. The comparison of the anomeric ratios of glycosyl sulfates and glycosylation products suggests that the more reactive alcohols (Cbz-5-amino-1-pentanol, 6-OH of sugar) react mainly with inversion, whereas the amount of α anomer increases with more hindered alcohols (entries 6,7,8). Worthy of note is the good result obtained in the synthesis of trehaloses. In fact, coupling of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl sulfate with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose as glycosyl acceptor (entry 8) afforded the trehaloses in 96% overall yield, with β,α being the predominant isomer (β,α:α,α:β,β = 8:4:3).[4] Finally, only the 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl sulfate **4** from 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose was obtained. Treatment of **4** with *i*Pr-OH and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 gave the expected glycosides in 49% yield (based on **2**) and in α:β ratio of 5:1.

In a typical procedure, a mixture of **1** (1 g, 1.85 mmol) and freshly purified[5] $SO_3{\cdot}NMe_3$ complex (9.25 mmol, 5 eq.) in dry acetonitrile was stirred at reflux for 36-48 hours and then cooled to room temperature and concentrated to dryness. The residue was dissolved in chloroform, washed with water and the combined organic phases were dried (Na_2SO_4) and rotoevaporated to give 1.3 g (100%) of the almost pure product **3** (α:β = 3:1). To a cooled (0°C), stirred mixture of a portion of the so obtained crude glycosyl sulfate (120 mg, 0.176 mmol), glycosyl acceptor (1.2 eq.), activated 4Å powdered molecular sieves (200 mg) and dry dichloromethane (8 ml) the promoter (1 eq.) was added. Stirring was continued for an additional 30 min. at 0°C, then the mixture was allowed to warm to room temperature until the disappearance of glycosyl sulfate (1-2 hours). Addition of a saturated solution of $NaHCO_3$, usual workup and flash chromatography gave the products.

In conclusion, glycosyl sulfates offer a new and simple way for the activation of the anomeric position. Work is in progress to investigate the solvent effect on the α:β ratio and to extend the procedure to other glycosyl donors.

Table 1 : Glycosylation of glucosyl sulfate as glucosyl donor.

Entry	Product	Promoter[a]	Yield, %[b]	α:β ratio
1	**5a**	$BF_3{\cdot}Et_2O$	49	3:1
2	**5b**	$BF_3{\cdot}Et_2O$	25	1:1
3	**5b**	TMSOTf	72	1:1
4	**5c**	$BF_3{\cdot}Et_2O$	52	1:1
5	**5c**	TMSOTf	67	1:1
6	**5d**	$BF_3{\cdot}Et_2O$	19	4:1
7	**5d**	TMSOTf	48	4:1
8	**5e**	$BF_3{\cdot}Et_2O$	96	8:4:3[c]

[a] freshly distilled.
[b] Yields calculated on tetrabenzyl pyranose.
[c] β,α:α,α:β,β ratio.

References and notes

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2. Eby, R.; Schuerch, C. *Carbohydr. Res.* **1982**, *102*, 131-138 and references cited therein.
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4. Spectroscopic data of known compounds were in full agreement with literature values. All new compounds gave correct analytical and spectroscopic data. Selected ^{1}H-NMR data: **3α**: δ 5.92 (d, 1 H, $J_{1,2}$ = 3.65 Hz, H-1); **3β**: δ 5.35 (d, 1 H, $J_{1,2}$ = 7.80 Hz, H-1); **4α**: δ 6.08 (s, 1H, H-1).
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