One-Pot Sequential Stereoselective Synthesis of Trisaccharide (Glcβ1-6Glcβ1-6Glc) by Promotion of Trityl Tetrakis(pentafluorophenyl)borate Catalyst

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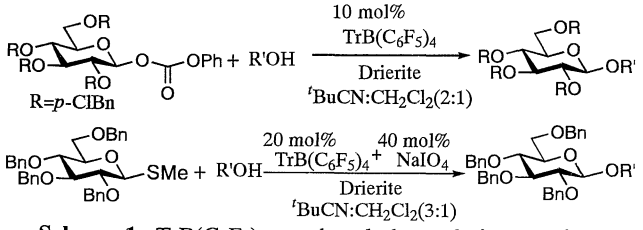
A one-pot synthesis of trisaccharides was successfully carried out by combination of two types of the trityl tetrakis(pentafluorophenyl)borate catalyzed stereoselective glycosylation reactions. Selective activation of a glycosyl phenyl carbonate in the presence of a thioglycoside allows two successive glycosyl coupling in one-pot manner to afford several protected trisaccharides, Glcβ1-6Glcβ1-6Glc, in good to high yields.

In these twenty years, various types of glycosyldonors and activators have been developed and useful glycosylation methods after classical Köenigs-Knorr type reactions[1] were reported. In addition, the development of new strategies and tactics in oligosaccharide synthesis is of growing importance, for example, armed-disarmed, two-stage activation, active-latent, orthogonal, one-pot multistep and solid-phase glycosylation reactions.[2]

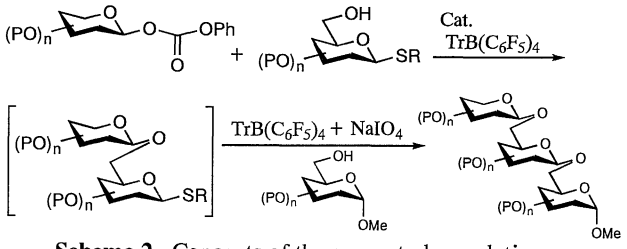
In order to develop a one-pot sequential glycosylation method, it is very important to choose most suitable combinations of glycosyldonors and related activating agents. Kahne reported[3] the one-pot glycosylation for the synthesis of Ciclamycin trisaccharide moiety to be carried out by tuning the reactivity of leaving groups, a sulfoxide. Takahashi and Chenault independently described the sequential one-pot glycosylation using the combination of other types of glycosyldonors such as glycosyl bromide and thioglycoside[4] or isopropenyl glycoside and *n*-pentenyl glycoside.[5] Also, Ley reported[6] the one-pot multistep glycosylation by utilizing their own protecting group strategy. In addition, programmable one-pot oligosaccharide synthesis was recently developed by Wong.[7]

Various stereoselective glycosylation reactions catalyzed by an active trityl salt, trityl tetrakis(pentafluorophenyl)borate [$TrB(C_6F_5)_4$], were recently reported from our laboratory. These reactions were successfully applied to several glycosyldonors such as 1-hydroxy sugar,[8] thioglycoside,[9] glycosyl fluoride[10] and glycosyl phenylcarbonate.[11] Among these reactions, the following two were picked up for one-pot synthesis of trisaccharides as shown in Scheme 1. The *p*-chlorobenzyl protected glycosyl phenylcarbonate reacted with various alcohols in the presence of trityl salt in mixed solvents containing pivalonitrile to afford β-glycosides stereoselectively. On the other hand, thioglycoside is activated by a catalytic amount of trityl salt



Scheme 1. $TrB(C_6F_6)_4$ catalyzed glycosylation reactions

in the coexistence of sodium periodate to afford the corresponding β-glycosides with high stereoselectivities. Then, the one-pot synthesis of trisaccharide was planned by utilizing the above reactions as shown in Scheme 2. In the first step, disaccharide (thioglycoside) was formed by treating thioglycoside with glycosyl phenylcarbonate in the presence of a catalytic amount of a trityl salt, and the following glycosylation with glycosylacceptor, methyl α-D-glucoside, successfully afforded trisaccharide in one-pot by a combined use of a trityl salt and sodium periodate.



Scheme 2. Concepts of the one-pot glycosylation

The first glycosylation step was examined by taking the reaction of 2,3,4,6-tetra-*O*-*p*-chlorobenzyl-β-D-glucopyranosyl phenylcarbonate (**1**) with several thioglycosides as shown in Table 1. Although the desired disaccharides were obtained in high yields with high β-selectivities, a considerable amount of 1,6-anhydro-β-D-glucoside derived from thioglycosides was formed when benzyl protected thioglycoside was used (Entry 1-3). In order to circumvent this problem, *p*-chlorobenzyl protected one was used because it was already shown that the stability of thioglycosidic linkage of the first *p*-chlorobenzyl protected acceptor increased remarkably.[12]

Next, the second glycosylation was examined. Although

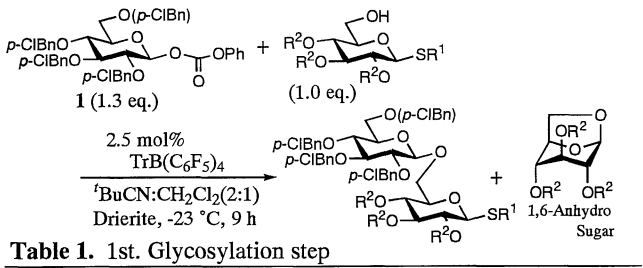


Table 1. 1st. Glycosylation step

Entry	R^1	R^2	Yield /%	α / β	Anhydro /%
1	Me	Bn	80	3 / 97	13
2	Et	Bn	89	3 / 97	9
3	Ph	Bn	88	3 / 97	5
4	Me	*p*-ClBn	85	2 / 98	12
5	**Et**	***p*-ClBn**	**94**	**2 / 98**	**6**
6	**Ph**	***p*-ClBn**	**97**	**2 / 98**	**0**

successful glycosylation of alcohols and several methyl α-D-glucosides was previously reported,[9] there still is room for application of the armed-disarmed protecting group strategy to the present glycosylation with thioglycosides. Actually, the $TrB(C_6F_5)_4$-$NaIO_4$ system was also applicable to the synthesis of disaccharides using thioglycosides based on the above glycosylation strategy as shown in Table 2. In addition, ethyl 1-thio-β-D-glycoside was used as a key component of this one-pot reaction due to the stability in the first glycosylation step and its rather high reactivity in the second step.

Finally, the one-pot sequential glycosylation was tried

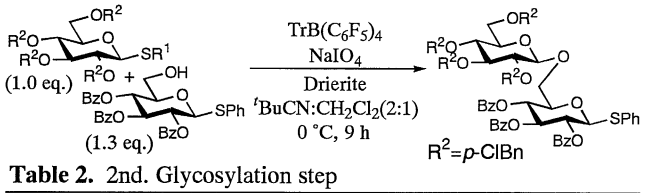


Table 2. 2nd. Glycosylation step

R^1	$TrB(C_6F_5)_4$ /mol%	$NaIO_4$ /mol%	Yield /%	α / β
Ph	20	105	77	14 / 86
Ph	30	105	82	9 / 91
Et	20	105	87	10 / 90
Et	**20**	**50**	**94**	**10 / 90**
Et	20	30	84	10 / 90

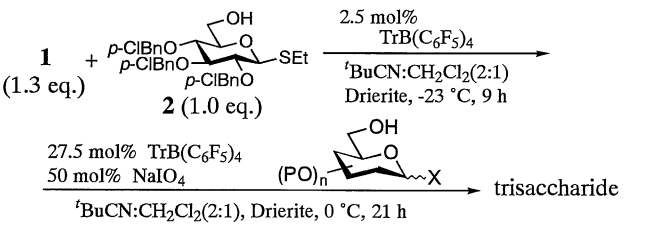
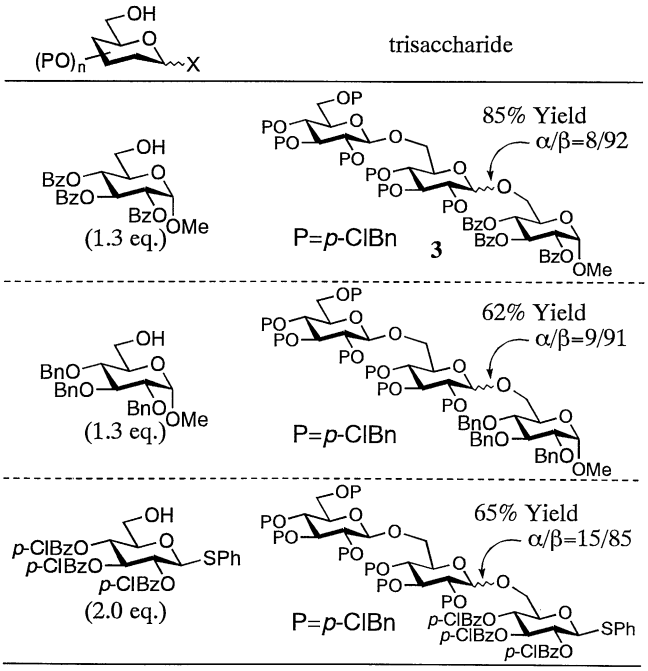


Table 3. One-pot synthesis of trisaccharides



based on the above experiments. In the first step, **1** was treated with ethyl 2,3,4-tri-*O*-*p*-chlorobenzyl-1-thio-β-D-glucopyranoside (**2**) in the presence of 2.5 mol% of $TrB(C_6F_5)_4$ in a mixed solvent (pivalonitrile:dichloromethane=2:1) for 9 h and then almost complete consumption of **2** was confirmed by TLC monitoring. Next, the second glycosylation of thus formed disaccharide with several glycosylacceptors was tried, and the desired protected trisaccharides were obtained stereoselectively in good to high yields by the combined use of a trityl salt (totally 30 mol%) and 50 mol% of sodium periodate in one-pot operation. It is noteworthy that the sequential rections were thoroughly carried out by using a catalytic amount of activators.

It is noted that a catalytic one-pot synthesis of trisaccharide was successfully carried out by using nearly equimolar amount of glycosyldonors and glycosylacceptors. Further study to apply this glycosylation method to more complicated oligosaccharide synthesis is now in progress.

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (2.5 mg, 0.0025 mmol) and Drierite (200 mg) in a mixed solvent (pivalonitrile:dichloromethane=2:1, 1.0 ml) was successively added **1** (103.8 mg, 0.13 mmol) and **2** (59.8 mg, 0.1 mmol) in the above mixed solvent (1.5 ml) at -23 °C. After the reaction mixture was stirred for 9 h at -23 °C, methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (65.9 mg, 0.13 mmol) and trityl tetrakis(pentafluorophenyl)borate (25.4 mg, 0.0275 mmol) in the above mixed solvent (1.5 ml) were successively added at -23 °C. After stirring the mixture for 15 min at 0 °C, sodium periodate (10.7 mg, 0.05 mmol) was added. The reaction mixture was stirred for additional 21 h at 0 °C and then it was quenched by adding saturated aqueous $NaHCO_3$ (10 ml) and 10% aqueous $Na_2S_2O_3$ (5 ml). The mixture was filtered through Celite and extracted with dichloromethane (3 times, each of 20 ml). The combined organic layer was washed with brine (5 ml) and dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to give the desired trisaccharide **3** (144.7 mg, 85%).

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