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Diphosphonium Salts as Effective Reagents for Stereoselective Synthesis of 1,2-cis-Ribofuranosides

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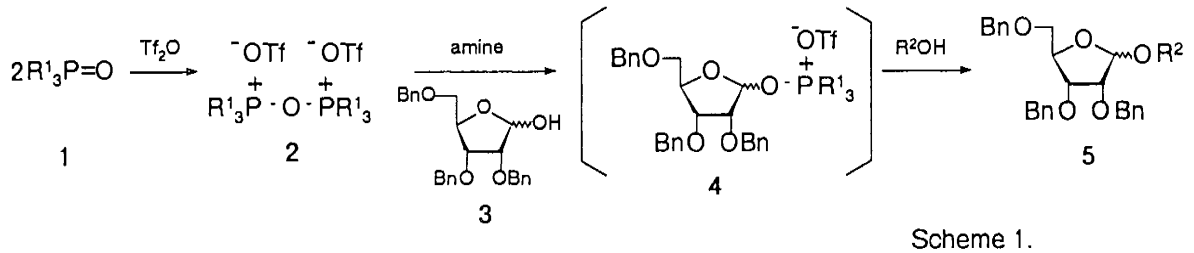
1,2-cis-Ribofuranosides are stereoselectively synthesized in high yields directly from 1-hydroxy sugars and alcohols or trimethylsilylated nucleophiles by the use of diphosphonium salts as a condensation reagent.

Stereoselective glycosylation is one of the most important problems in carbohydrate chemistry and recently several methods for stereoselective synthesis of glycopyranosides starting from glycopyranosyl phosphates or glycopyranosyl sulfoxide activated with trimethylsilyl trifluoromethanesulfonate or trifluoromethanesulfonic anhydride have been reported,[1] however, stereoselective synthesis of glycofuranosides, especially 1,2-cis-glycofuranosides, is known to be the most challenging problem.[2] Hendrickson reported that diphosphonium salts (Ph_3P^+-O-$^+PPh_3(^-OTf)_2$) is an effective dehydrating reagent[3] and it was recently reported from our laboratory that the phosphonium salts ($^nBu_3P^+$-O-$^+P^nBu_3(^-OTf)_2$) can be employed as effective catalysts of the aldol and Michael reactions between silyl enolate and carbonyl compounds.[4] The results led us to study on the glycosylation reaction based on the assumption that if the phosphonium salt (**4**) could be generated in situ from 1-hydroxy sugar and diphosphonium salts (**2**), **4** would behave as a reactive intermediate of glycosylation (Scheme 1). In this communication, we wish to report a convenient method for the synthesis of 1,2-cis-ribofuranosides directly from readily available 1-hydroxy sugars and alcohols by using diphosphonium salts (**2**) via the intermediate (**4**) as shown in the following equation.



Scheme 1.

Table 1. Effect of Diphosphonium Salts 2 [a)]

R^1	Yield / %	α / β
	49	82 / 18
	0	—
	14	86 / 14
-nBu	77	86 / 14
$-(CH_2)_{15}CH_3$	31	86 / 14

a) Solvent : CH_2Cl_2, amine : diisopropylethylamine.

Table 2. Effect of Solvents [a)]

Solvent	Yield / %	α / β
CH_2Cl_2	77	86 / 14
$CHCl_3$	79	86 / 14
$C_2H_4Cl_2$	79	86 / 14
CH_3CH_2CN	72	69 / 31
THF	58	53 / 47
P.E. / toluene	70	76 / 24

a) Diphosphonium salts:4 (R^1=Ph), amine : diisopropylethylamine.

In the first place, the reaction of the phosphonium intermediate (**4**, R^1=Ph), in situ generated by treating 2,3,5-tri-O-benzyl-D-ribofuranose (**3**) with diphosphonium salts (**2**,R^1=Ph) and diisopropylethylamine, and cyclohexanol was tried and the corresponding ribofuranoside with 1,2-cis configuration was predominantly obtained in 49% yield (α /β=82/18). Then, the above glycosylation reaction was further examined by using various diphosphonium salts, solvents and amines in order to achieve higher stereoselectivity and yield. The effect of substituents of the diphosphonium salts was examined (see Table 1) and it is noted that improvement of yield and stereoselectivity was attained when the reaction was carried out by the use of diphosphonium salts (R^1=^{n}Bu). Concerning the effect of solvents, better result was obtained when the reaction was carried out in dichloromethane, chloroform or 1,2-dichloroethane compared with that in tetrahydrofuran, propionitrile or petroleum ether/toluene (see Table 2). The effect of various amines was shown in Table 3 and it is noted that, by the addition of molecular sieve 4A(MS4A), the yield was dramatically improved. Thus, it was shown that the best result concerning both yield and stereoselectivity was attained when the present glycosylation reaction was carried out in 1,2-dichloroethane by using diphosphonium salts (**2**, R^1=^{n}Bu), diisopropylethylamine and MS4A.

In a similar manner, the reactions with several alcohols or trimethylsilylated nucleophiles afforded the corresponding 1,2-cis-ribofuranosides in high yields with good stereoselectivities (see Table 4).

The following is a typical procedure for the preparation of cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside: To a solution of tri-n-butylphosphine oxide (0.45 mmol) in 1,2-dichloroethane (2 ml) was added dropwise a solution of trifluoromethanesulfonic

Table 3. Effect of Amines [a)]

Amine	Yield / %	α / β
$^{i}Pr_2NEt$	79	86 / 14
TEA	42	86 / 14
	71	86 / 14
$^{i}Pr_2NEt$ + MS 4A	95	87 / 13

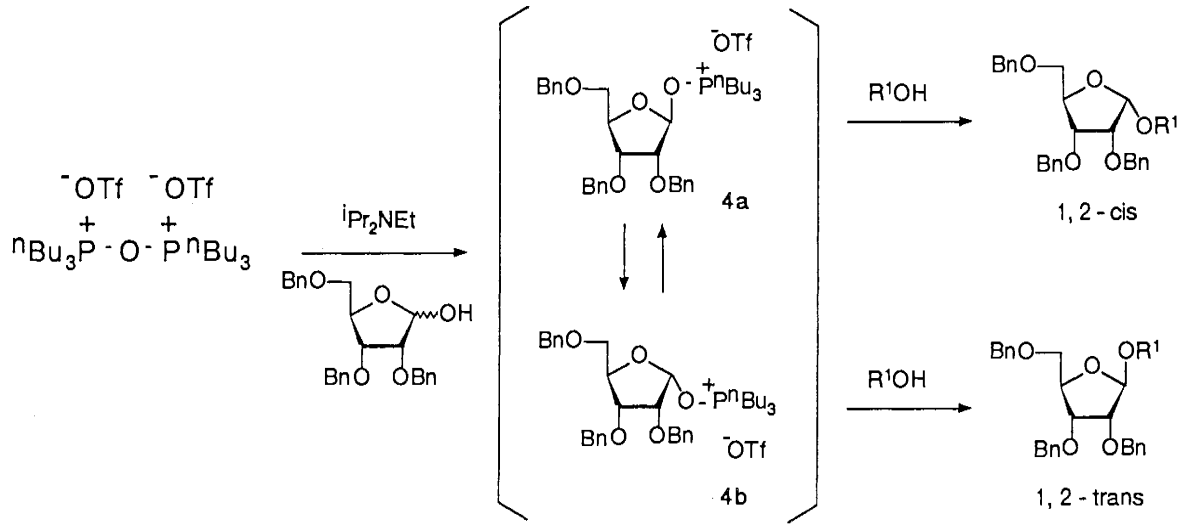
a) Diphosphonium salts : 2 (R^1=^{n}Bu), solvent : 1,2-dichloroethane.

anhydride (0.21 mmol) in 1,2-dichloroethane (1.5 ml) at 0 °C. After stirring for 30 min, MS4A (100 mg) and a solution containing 2,3,5-tri-O-benzyl-D-ribofuranose (0.1 mmol) and diisopropylethylamine (0.22 mmol) in 1,2-dichloroethane (2 ml) were added at the same temperature. Stirring was continued for 2 h, and then a solution of cyclohexanol (0.13 mmol) in 1,2-dichloroethane (2 ml) was added dropwise. After the reaction was completed , the solution was washed with aqueous sodium bicarbonate and dried over $MgSO_4$, and concentrated. The residue was applied onto TLC to give cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside (82.7%) and the corresponding β-anomer (12.3%).

Table 4. Synthesis of Ribofuranosides

R^2OH or R^2TMS	Yield / %	α / β
3β - cholestanol	75	86 / 14
2 - propanol	93	85 / 15
cyclohexanol	95	87 / 13
3β - cholestanyl - O - TMS	99	87 / 13
$TMSN_3$	97	82 / 18

It is interesting to mention that the ^{31}P NMR and ^{13}C NMR spectra of phosphonium intermediates (**4**, R^1=^{n}Bu) generated by the above experiment exhibits two isomers[5)] and the ratio of the intermediates (**4a** and **4b**) is about 1:1. Therefore, it is assumed that the stereoselective glycosylation depends on the difference in reactivities of two phosphonium intermediates (**4a** and **4b**). There would exist a rapid equilibrium between two intermediates (**4a** and **4b**), and β-anomer (**4a**) of the phosphonium intermediate would react much faster with alcohols resulting in the predominant formation of 1,2-cis-ribofuranosides (see Scheme 2). Further investigations concerning the reasons of stereoselectivity are now in progress.



Scheme 2.

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References

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2) We have already reported several useful methods concerning a stereoselective synthesis of 1,2-cis-ribofuranosides from 1-O-acyl-ribofuranoses or ribofuranosyl fluoride, see T. Mukaiyama, Y, Hashimoto, and S. Shoda, *Chem. Lett.*, **1983**, 935; T. Mukaiyama, S. Kobayashi, and S. Shoda, *ibid.*, **1984**, 907; T. Mukaiyama, T. Shimpuku, T. Takashima, and S. Kobayashi, *ibid.*,**1989**, 145.

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5) ^{31}P-NMR(CD_2Cl_2) 98.06 , 94.90; ^{13}C-NMR($CDCl_3$) 104.43 (C-1,d,$^2J_{C1P}$=9.18 Hz), 101.80 (C-1,d,$^2J_{C1P}$=9.43 Hz).

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