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Stereoselective Glycosylation Reaction Starting from 1-O-Trimethylsilyl Sugars by Using Diphenyltin Sulfide and a Catalytic Amount of Active Acidic Species

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1,2-trans-Ribofuranosides are stereoselectively synthesized from 1-O-trimethylsilyl ribofuranose and trimethylsilyl ethers in the presence of a catalytic amount of Me_3SiOTf using $Ph_2Sn{=}S$ as an additive, while 1,2-cis-ribofuranosides and 1,2-cis-glucopyranosides are prepared predominantly in the coexistence of $LiClO_4$ in the above reaction.

Recently, we have reported an efficient method for the stereoselecitve synthesis of 1,2-cis- and 1,2-trans-ribofuranosides directly from 1-hydroxy ribofuranose and silylated nucleophiles such as trimethylsilyl ethers and silylated sugars by the use of $Ph_2Sn{=}S$ and Tf_2O.[1] In the course of our investigation to clarify the mechanism of this reaction, it was found that 1-O-trimethylsilyl-D-ribofuranose was initially formed as an intermediate, which in turn reacted with the silyl ether to form the desired glycoside. According to the literature, the intermediate 1-O-trimethylsilyl sugars are easily prepared[2] and have already been employed as useful glycosyl donors;[3,4] as seen in the preparation of 1,2-trans- or 1,2-cis-glycosides by the reaction of 1-O-trimethylsilyl-2,3,4,6-tetra-O-acetyl-D-glucopyranose or 1-O-trimethylsilyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose with phenyl trimethylsilyl ethers or a t-butyldiphenylsilylated sugar. In these reports, however, nucleophiles were limited to phenyl trimethylsilyl ethers except for one case[4] where 1,2-trans-glycosides were obtained in high selectivities by utilizing the neighbouring effect of C-2 acetyl protective group while 1,2-cis-selectivities were not so high. These results led us to study on the development of a general stereoselective glycosylation reaction starting from 1-O-trimetylsilyl

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Dedicated to Professor Emeritus Osamu Shimamura of The University of Tokyo on the occasion on his 80th birthday.

sugars by the use of a catalytic amount of active acidic species.

In the first place, the reaction of 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-ribofuranose with cyclohexyl trimethylsilyl ether was tried by using 150 mol% of dipheyltin sulfide ($Ph_2Sn=S$) and 30 mol% of Me_3SiOTf, and the corresponding 1,2-trans-ribofuranoside was obtained in almost quantitative yield (quant., $\alpha/\beta=1/99$). Diphenyltin sulfide is proved to be an excellent additive in this reaction, while the corresponding glycosides were obtained in lower yields and lower selectivities when the reaction was carried out in the absence of $Ph_2Sn=S$. Furthermore, most of $Ph_2Sn=S$ could be recovered after the reaction has been completed (see experimental procedure).

Next, the amount of Me_3SiOTf was screened and it was made clear that 1,2-trans-ribofuranoside was given in high yield (quant., $\alpha/\beta=2/98$) even when 3 mol% of the triflate was employed. Similarly, the reaction using several other trimethylsilyl ethers was performed to afford the corresponding 1,2-trans-ribofuranosides in high yields with high stereoselectivities (see Table 1).

On the other hand, when the reaction was carried out in the coexistence of $LiClO_4$,[5] the corresponding 1,2-cis-ribofuranosides were stereoselectively obtained in high yields as summarized in Table 2.

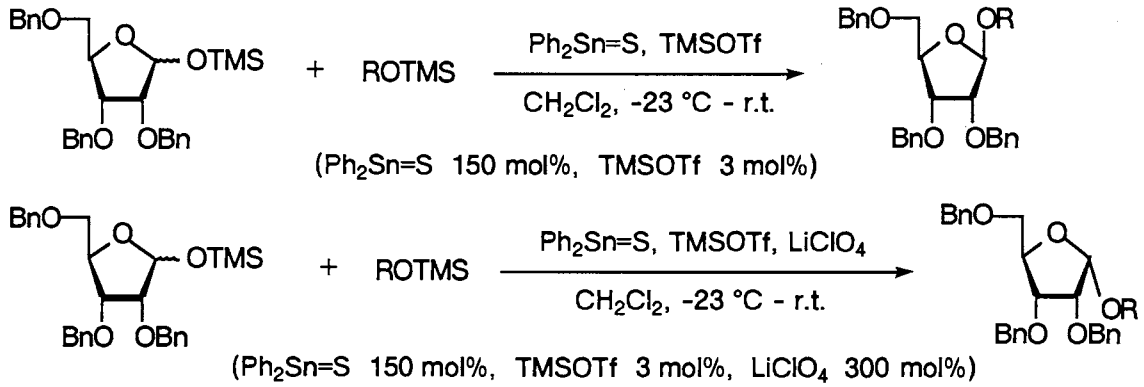


Table 1. Synthesis of 1,2-trans-Ribofuranosides

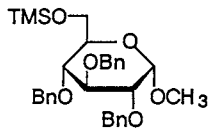
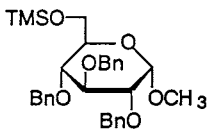
ROTMS	Yield / %	α / β
MeOTMS	quant.	1 / 99
CyclohexylOTMS	quant.	2 / 98
3β-CholestanylOTMS	98	1 / 99
^{t}BuOTMS	74	2 / 98
	98	5 / 95

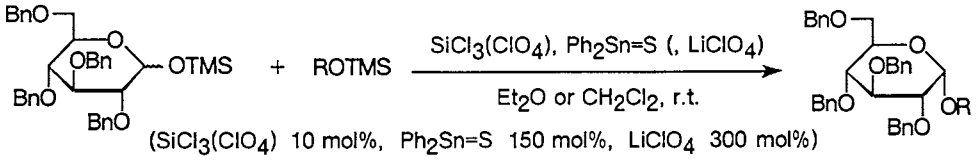
Table 2. Synthesis of 1,2-cis-Ribofuranosides

ROTMS	Yield / %	α / β
MeOTMS	quant.	95 / 5
CyclohexylOTMS	quant.	97 / 3
3β-CholestanylOTMS	96	99 / 1
^{t}BuOTMS	75	98 / 2
	quant.	95 / 5

Thus both 1,2-trans- and 1,2-cis-ribofuranosides can be stereoselectively prepared according to the present procedures.

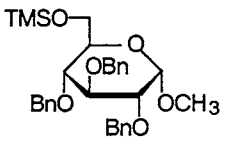
The followings are typical procedures for the preparation of both anomers of cyclohexyl-2,3,5-tri-O-benzyl-D-ribofuranosides. 1,2-trans-anomer: to a stirred solution of $Ph_2Sn{=}S$ (0.3 mmol), 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-ribofuranose (0.2 mmol) and cyclohexyl trimethylsilyl ether (0.3 mmol) in dichloromethane (7.0 ml) was added dropwise a solution of Me_3SiOTf (0.006 mmol) in dichloromethane at -23 °C, and the mixture was then warmed up to room temperature. After stirring for additional 2 h, Et_3N (0.5ml) was added to quench the reaction. Usual work up and separation by TLC afforded the corresponding 1,2-trans-anomer (98%) and 1,2-cis-anomer (2%). Ninety percent of $Ph_2Sn{=}S$ was recovered. 1,2-cis-anomer: to a stirred suspension of $Ph_2Sn{=}S$ (0.3 mmol), $LiClO_4$ (0.6 mmol), 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-ribofuranose (0.2 mmol) and cyclohexyl trimethylsilyl ether (0.3 mmol) in dichloromethane (7.0 ml) was added dropwise a solution of Me_3SiOTf (0.006 mmol) in dichloromethane at -23 °C, and the mixture was then warmed up to room temperature. After stirring for additional 2 h, Et_3N(0.5ml) was added to the reaction mixture. Usual work up and separation by TLC afforded the corresponding 1,2-cis-anomer (97%) and 1,2-trans-anomer (3%). Ninety percent of $Ph_2Sn{=}S$ was recovered.

The above procedure was further applied to the glycosylation reaction of 1-O-trimethylsilyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose with cyclohexyl trimethylsilyl ether, however, the corresponding 1,2-cis-glucopyranoside was obtained only in poor yield with low stereoselectivity. Then the effects of various active acidic species and solvents[6] were investigated in order to improve the yield and selectivity. When the reaction was carried out in diethyl ether by the use of an active catalyst generated from $SiCl_4$ and $AgClO_4$, the desired



($SiCl_3(ClO_4)$ 10 mol%, $Ph_2Sn{=}S$ 150 mol%, $LiClO_4$ 300 mol%)

Table 3. Synthesis of 1,2-cis-Glucopyranosides

ROTMS	Yield / %	α / β
CyclohexylOTMS	96	91 / 9
3β-CholestanylOTMS	quant.	83 / 17
	75	96 / 4

glucoside was obtained in high yield with high selectivity. In the case of employing a sterically hindered nucleophile such as 3β-cholestanyl trimethylsilyl ether, the yield of the corresponding 1,2-cis-glucopyranoside was poor. It was improved by adding $LiClO_4$ and using dichloromethane as a solvent instead of diethyl ether. The results of the present glycosylation reaction are summarized in Table 3.

A typical experimental procedure for the preparation of cyclohexyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside is as follows: to a stirred suspension of $AgClO_4$ (0.015 mmol, 10 mol%) and $Ph_2Sn{=}S$ (0.23 mmol) in ether (3.0 ml) was added a solution of $SiCl_4$ (0.015 mmol, 10 mol%) in toluene at room temperature. After stirring for 1h, an ethereal solution (2.0 ml) of 1-O-trimethylsilyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose (0.15 mmol) and cyclohexyl trimethylsilyl ether (0.22 mmol) was added to the mixture at room temperature. After stirring for additional 12 h, aqueous sodium bicarbonate was added. Usual work up and separation by TLC afforded the corresponding 1,2-cis-anomer (87.4%) and 1,2-trans-anomer (8.6%). Ninety three percent of $Ph_2Sn{=}S$ was recovered.

Thus, it is noted that highly stereoselective glycosylation was successfully carried out starting from 1-O-trimethylsilyl sugars and trimethylsilyl ethers by the use of $Ph_2Sn{=}S$ and a catalytic amount of active acidic species.

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