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An Efficient Method for the Stereoselective Synthesis of 1,2-*cis*- and 1,2-*trans*-Ribofuranosides from 1-Hydroxy Ribofuranose by the Use of Diphenyltin Sulfide and Trifluoromethanesulfonic Anhydride

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1,2-trans-Ribofuranosides are stereoselectively synthesized in high yields directly from 1-hydroxy ribofuranose and trimethylsilylated nucleophiles by the use of diphenyltin sulfide and trifluoromethanesulfonic anhydride. Even further, in the coexistence of lithium perchlorate, 1,2-cis-ribofuranosides are prepared predominantly in high yields.

Recently we have reported that the active dehydrating reagent, generated from [1,2-benzenediolato(2-)-O,O']oxotitanium and trifluoromethanesulfonic anhydride (triflic anhydride), is effective for the stereoselective synthesis of 1,2-trans-ribofuranosides from 1-hydroxy ribofuranose and alcohols or trimethylsilylated nucleophiles.1) The result prompted us to search for a more effective metal oxide in order to achieve higher yield and stereoselectivity in the above glycosylation.

In this communication, we would like to describe an efficient method for the highly stereoselective synthesis of 1,2-trans- and 1,2-cis-ribofuranosides just starting from 1-hydroxy ribofuranose and alcohols or trimethylsilylated nucleophiles by the combined use of diphenyltin sulfide and triflic anhydride.

In the first place, glycosylation reaction of 2,3,5-tri-O-benzyl-D-ribofuranose with cyclohexyl trimethylsilyl ether was tried by using several Sn(IV) oxides (such as $Ph_2Sn=O$2) and $^nBu_2Sn=O$3)) or Sn(IV) sulfides (such as $Ph_2Sn=S$2) and $^nBu_2Sn=S$2)) together with triflic anhydride in the presence of diisopropylethylamine. It was found there that the corresponding 1,2-trans-ribofuranoside was obtained in 93% yield ($\alpha/\beta=2/98$) when $Ph_2Sn=S$ was employed. After screening various bases and solvents, the use of CsF, an acid capture, in ether or toluene gave the best result (yield 99%, $\alpha/\beta=1/99$). Similarly, the reaction using several trimethylsilylated nucleophiles afforded the corresponding 1,2-trans-ribofuranosides in high yields with high stereoselectivities (see Table 1).

In the next place, the above mentioned reaction was further studied in the coexistence of several additives in order to perform the stereoselective 1,2-cis-glycosylation reaction. Then, it was found that when the glycosylation reaction of 2,3,5-tri-O-benzyl-D-ribofuranose with cyclohexanol was carried out in the coexistence of lithium perchlorate under the above reaction condition, the corresponding 1,2-cis-ribofuranoside was obtained in 75% yield (α/β=64/36). Both yield and stereoselectivity were improved by further examination of the reaction conditions as bases and solvents. Finally, the best result (yield 99%, α/β=99/1) was attained when the reaction was carried out in dichloromethane by using lithium perchlorate, an additive, and CsF, a base. Similarly, various 1,2-cis-ribofuranosides were successfully synthesized under the above mentioned reaction conditions (see Table 2).

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

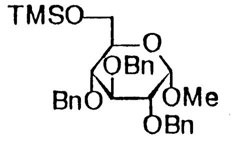
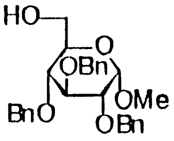
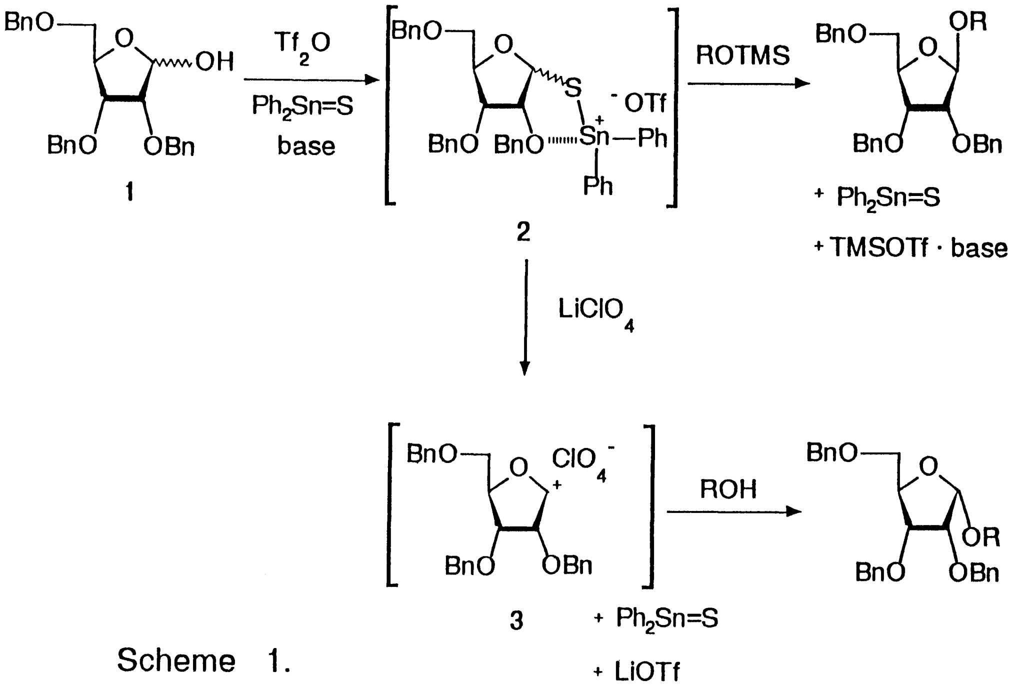
ROTMS	Yield / %	α/β
MeOTMS	98	1 / 99
Cyclohexyl-OTMS	quant.	1 / 99
3β-Cholestanyl-OTMS	95	1 / 99
	98	10 / 90

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

ROH	Yield / %	α/β
MeOH	quant.	99 / 1
Cyclohexanol	quant.	99 / 1
3β-Cholestanol	91	99 / 1
	98	99 / 1

The following is a typical procedure for the preparation of cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside; to a stirred suspension of diphenyltin sulfide (0.30 mmol), lithium perchlorate (3 mmol) and CsF (3 mmol) in dichloromethane (6.0 ml) was added dropwise a solution of triflic anhydride (0.24 mmol) in dichloromethane (1.5 ml) at 0 °C. After being stirred for 2 h, a dichloromethane (1.5 ml) solution of 2,3,5-tri-O-benzyl-D-ribofuranose (0.20 mmol) was added at -23 °C. After stirred for additional 1 h, a solution of cyclohexanol (0.40 mmol) in dichloromethane (1.5 ml) was added and then warmed to room temperature. After completion of the reaction, triethylamine was added to the reaction mixture. And then, usual work up and separation by TLC afforded cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside (99%) and the corresponding β-anomer (trace amount) along with recovery of diphenyltin sulfide (85%).

At present, the reaction is assumed to proceed *via* the intermediate **2**, initially generated from **1** by the application of diphenyltin sulfide and triflic anhydride. Since α-side of the anomeric center in the intermediate **2** is blocked by the internal chelation between positively charged Sn(IV) atom and oxygen atom located at 2-position of ribofuranose, trimethylsilylated nucleophiles would exclusively approach from β-side to form 1,2-trans-ribofuranosides accompanied with the elimination of diphenyltin sulfide. On the other hand, in the coexistence of lithium perchlorate, the second intermediate **3** would be formed from **2** and lithium perchlorate along with diphenyltin sulfide and lithium triflate. In the intermediate **3**, β-side of the anomeric center is blocked by the perchlorate anion and the anomeric carbon is attacked from α-side by alcohols to form 1,2-cis-ribofuranosides stereoselectively (see Scheme 1).



Scheme 1.

Thus, the combined use of diphenyltin sulfide and triflic anhydride effectively promotes the stereoselective formation of 1,2-trans-ribofuranosides in high yields directly from 1-hydroxy ribofuranose and trimethylsilylated nucleophiles. Even further, 1,2-cis-ribofuranosides are obtained predominantly in high yields by the addition of lithium perchlorate to the above reaction system.

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References

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2) These compounds were prepared by the Reichle method; W. T. Reichle, *J. Poly. Sci.*, **49**, 521 (1961); W. T. Reichle, *J. Org. Chem.*, **26**, 4634 (1961).

3) This compound is commercially available.

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