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# Stereoselective Synthesis of 1,2-trans-Ribofuranosides from 1-Hydroxy Sugars by the Use of [1,2-Benzenediolato(2-)-O,O']oxotitanium and Trifluoromethanesulfonic Anhydride

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A convenient method for stereoselective synthesis of 1,2-trans-ribofuranosides directly from 1-hydroxy sugars and alcohols or trimethylsilylated nucleophiles by the use of [1,2-benzenediolato(2-)-O,O']oxotitanium and trifluoromethanesulfonic anhydride is described.

Stereoselective glycosylation is one of the most important problems in carbohydrate chemistry and a large number of methods have been reported.1) In the previous paper,2) we have reported that the diphosphonium salt, prepared from tri-n-butylphosphine oxide and trifluoromethanesulfonic anhydride (triflic anhydride), is an effective reagent for stereoselective synthesis of 1,2-cis-ribofuranosides from 1-hydroxy sugars and alcohols or trimethylsilylated nucleophiles.

Recently, we have demonstrated that [1,2-benzenediolato(2-)-O,O']oxotitanium (1), having unprecedented and unique structure, behaves as an efficient Lewis acid catalyst in the Michael reaction of ketene silyl acetals with $\alpha,\beta$-unsaturated ketones3) and the aldol reaction of ketene silyl acetals with aldehydes,4) and [1,1'-bi-2-naphthalenediolato(2-)-O,O']oxotitanium is also an efficient chiral catalyst in the asymmetric aldol reaction.5) During continued investigation to develop a useful synthetic method based on a titanium oxide, it was postulated that an intermediate **2**, an active dehydrating reagent, would be generated from titanium oxide **1** and triflic anhydride similar to the case of using tri-n-butylphosphine oxide and triflic anhydride (see Scheme 1). In this communication, we would like to describe a convenient method for stereoselective glycosylation of 1-hydroxy sugar with alcohols or trimethylsilylated nucleophiles *via* the above mentioned intermediate.

In the first place, glycosylation reaction of 2,3,5-tri-O-benzyl-D-ribofuranose with cyclohexyl trimethylsilyl ether was tried using titanium oxide and triflic anhydride in the presence of diisopropylethylamine. After screening several titanium oxides (such as $^{i}Pr_2Ti=O$, $(PhO)_2Ti=O$, 1), it was found that the corresponding ribofuranoside was obtained in 95% yield ($\alpha / \beta$ = 12 / 88) when 1 was employed. Then, the effects of various bases and solvents on the above glycosylation reaction were further examined in order to achieve higher stereoselectivity and yield. Of several bases studied, the combined use of diisopropylethylamine and CsF gave the best result (see Table 1).

Concerning the effect of solvent, a better yield was achieved when the reaction was carried out in dichloromethane and a better stereoselectivity was attained in diethyl ether. While, the corresponding ribofuranoside was not obtained at all when acetonitrile was used (see Table 2).

In a similar manner, the reaction of 2,3,5-tri-O-benzyl-D-ribofuranose with several alcohols or trimethylsilylated nucleophiles afforded the corresponding 1,2-trans-ribofuranosides in high yields with good stereoselectivities (see Table 3).

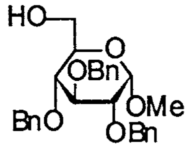
Table 1. Effect of Amines

| Amine | Yield / % | $\alpha/\beta$ |
|---|---|---|
| $^{i}Pr_2NEt$ | 95 | 12 / 88 |
| 2,6 - lutidine | 92 | 7 / 93 |
| CsF | 71 | 6 / 94 |
| 2,6 - lutidine + CsF | 93 | 6 / 94 |
| $^{i}Pr_2NEt$ + CsF | 95 | 5 / 95 |

Table 2. Effect of Solvents

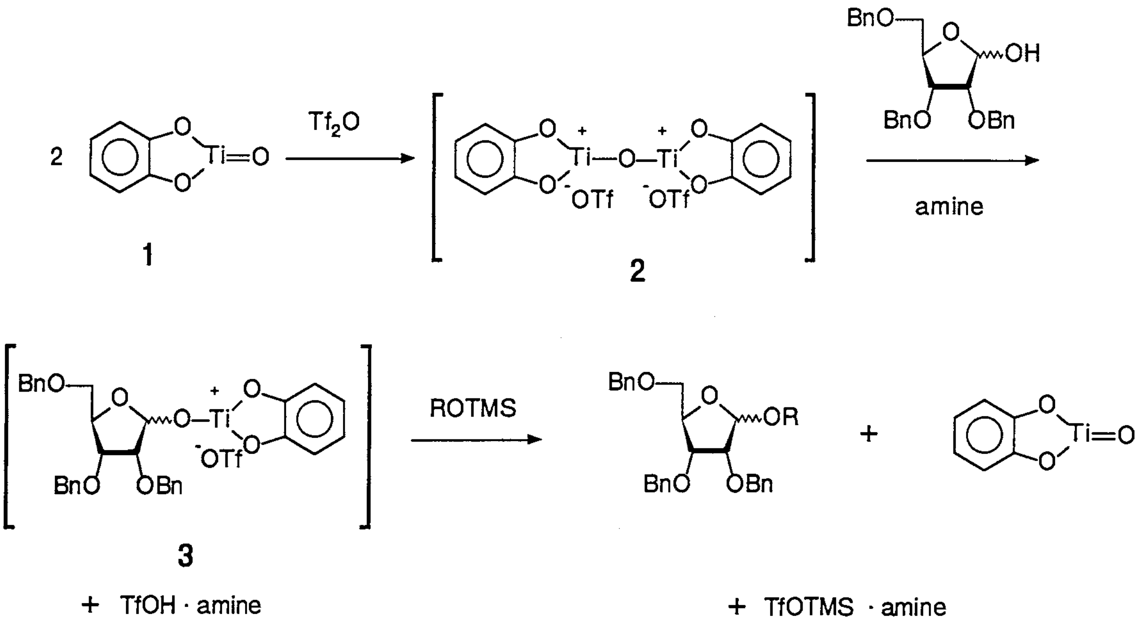
| Solvent | Yield / % | $\alpha/\beta$ |
|---|---|---|
| $CH_2Cl_2$ | 95 | 5 / 95 |
| Diethyl ether | 92 | 2 / 98 |
| Toluene | 92 | 3 / 97 |

Table 3. Synthesis of Ribofuranosides

| ROH or ROTMS | Yield / % | α/β |
|---|---|---|
| cyclohexanol | 95 | 5 / 95 |
| MeOTMS | 92 | 4 / 96 |
| 3β-cholestanyl-OTMS | 88 | 1 / 99 |
|  | 94 | 11 / 89 |

Contrary to the above results, when 3β-cholestanyl trimethylsilyl ether and 2,3,5-tri-O-benzyl-D-ribofuranose were allowed to react under the present conditions using triflic anhydride alone, the yield was very low.

The present reaction is assumed to proceed *via* the second intermediate 3 formed from 1-hydroxy sugar and 2 along with diisopropylethylammonium trifluoromethanesulfonate. The intermediate 3 in turn reacts with trimethylsilylated nucleophile to form the desired ribofuranoside accompanied with the elimination of 1 (see Scheme 1).



Scheme 1.

A typical experimental procedure is described for the reaction of 2,3,5-tri-O-benzyl-D-ribofuranose and cyclohexyl trimethylsilyl ether: To a solution of **1** (0.58 mmol) in dichloromethane (5 ml) was added dropwise a solution of triflic anhydride (0.26 mmol) in dichloromethane (2 ml) at 0 °C. After stirring for 1 h at 0 °C and 1 h at room temperature, CsF (100 mg) was added to the reaction mixture. A solution containing 2,3,5-tri-O-benzyl-D-ribofuranose (0.13 mmol) and diisopropylethylamine (0.13 mmol) in dichloromethane (2 ml) was added at -23 °C. Stirring was continued for 2 h, and then cyclohexyl trimethylsilyl ether (0.52 mmol) in dichloromethane (2 ml) was added dropwise. The solution was kept at 0 °C for 8 h and washed with aqueous sodium bicarbonate and dried over $MgSO_4$, and concentrated. The residue was purified by thin layer chromatography (silica gel) to give cyclohexyl 2,3,5-tri-O-benzyl-β-D-ribofuranoside (90%) and the corresponding α-anomer (5 %).

Thus, the combined use of [1,2-benzenediolato(2-)-O,O'] oxotitanium and triflic anhydride effectively promotes the stereoselective reaction of 1-hydroxy sugars with alcohols or trimethylsilylated nucleophiles to afford the corresponding 1,2-trans-ribofuranosides in high yields.

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