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Stereoselective Synthesis of 1,2-cis-Arabinofuranosides Using a New Titanium Catalyst [#]

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In the presence of catalytic amounts of [1,2-benzenediolato(2-)-O,O']oxotitanium and trimethylsilyl triflate, 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose stereoselectively reacts with various trimethylsilyl ethers to afford the corresponding 1,2-cis-arabinofuranosides in high yields.

Arabinofuranosides having the axial hydroxy group at 2-position are often observed in nature as a variety of natural resources produced by plants or microorganism.$^{1)}$ Because of the steric repulsion between the axial substituent and aglycones, 1,2-cis-arabinofuranosides (β-arabinofuranosides) are quite easily isomerized to thermodynamically stable 1,2-trans-arabinofuranosides (α-arabinofuranosides) under the usual glycosylation reaction conditions. Therefore, the synthesis of 1,2-cis-arabinofuranosides (β-arabinofuranosides) is known as one of the most challenging tasks in carbohydrate chemistry and only a few examples were reported. In 1983, V. Dourtoglow et al. reported the synthesis of 1,2-cis-arabinofuranosides via the alkoxyiminium salt intermediate prepared from 2,3,5-tri-O-benzyl-D-arabinofuranose by using DMF and $COCl_2$.$^{2)}$ It was also found in our laboratory that 1-fluoro-L-arabinofuranose reacted with an alcohol to give the corresponding arabinofuranoside in good β-selectivity ($\alpha/\beta=1/4$).$^{3)}$

In this communication, we would like to describe a convenient method for the stereoselective synthesis of 1,2-cis-arabinofuranosides starting from 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**) and trimethylsilyl ethers using a new titanium catalyst generated from [1,2-benzenediolato(2-)-O,O']oxotitanium (**2**) and trimethylsilyl triflate (TMSOTf, **3**).

Recently, an efficient method for the synthesis of 1,2-cis- or 1,2-trans-ribofuranosides starting from 1-hydroxy sugar has been reported from our laboratory by using [1,2-benzenediolato(2-)-O,O']oxotitanium (**2**) and Tf_2O in the presence of bases.$^{4)}$ This procedure was then applied to the arabinose system; namely, in the presence of **2**, Tf_2O, CsF, and Hünig base, 2,3,5-tri-O-benzyl-D-arabinofuranose$^{5)}$ was treated with cyclohexyl trimethylsilyl ether (**4**). The reaction proceeded smoothly at 0 °C to give the corresponding arabinofuranoside in quantitative yield, however, the selectivity was low ($\alpha/\beta=49/51$).

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

In the course of our investigations to clarify the mechanism of the above glycosylation reaction, the dynamic ^{1}H-NMR experiment was performed, which suggested that the 1-hydroxy sugar was immediately converted to the corresponding 1-O-trimethylsilyl sugar under the reaction conditions and that this 1-O-trimethylsilyl sugar in turn reacted with a trimethylsilyl ether to afford the corresponding glycoside. At this stage, 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**),6) prepared according to the standard procedure (TMSCl, Et_3N, rt, 12 h; 92% yield), was employed as a starting material in order to simplify the reaction system.

In the presence of [1,2-benzenediolato(2-)-O,O']oxotitanium (**2**),7) TMSOTf, and CsF, 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**) was treated with cyclohexyl trimethylsilyl ether (**4**) at r.t. to give the corresponding arabinofuranoside in 32% yield (α/β=63/37). Cesium fluoride employed in the above reaction was used on consideration that it would work as a base and suppress the isomerization of 1,2-cis-arabinosides to 1,2-trans-arabinosides.4) However, after careful examinations of the reaction system, it was made clear that trimethylsilyl fluoride was generated in situ from CsF and TMSOTf and that it accelerated the isomerization of the produced 1,2-cis-arabinosides to the 1,2-trans-arabinosides.

The reaction was then carried out in the absence of CsF. 1-O-Trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**) was treated with cyclohexyl trimethylsilyl ether (**4**) in the presence of [1,2-benzenediolato(2-)-O,O']oxotitanium (**2**) and TMSOTf in dichloromethane at 0 °C. The reaction proceeded smoothly under the conditions to give the corresponding 1,2-cis-arabinofuranoside in 76% yield (α/β=18/82). The yield and the selectivity were improved when the reaction was carried out at -23 °C (90%yield, α/β=9/91).

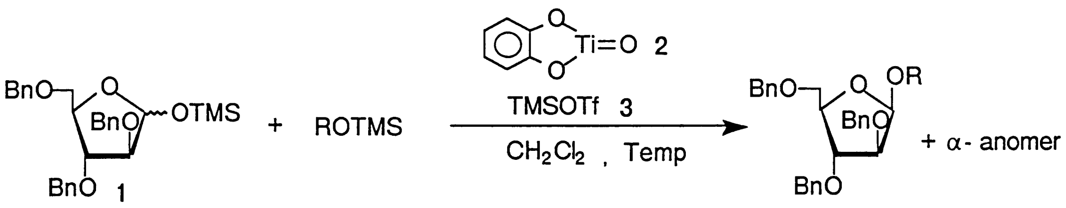
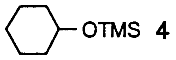
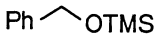
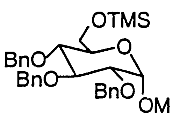


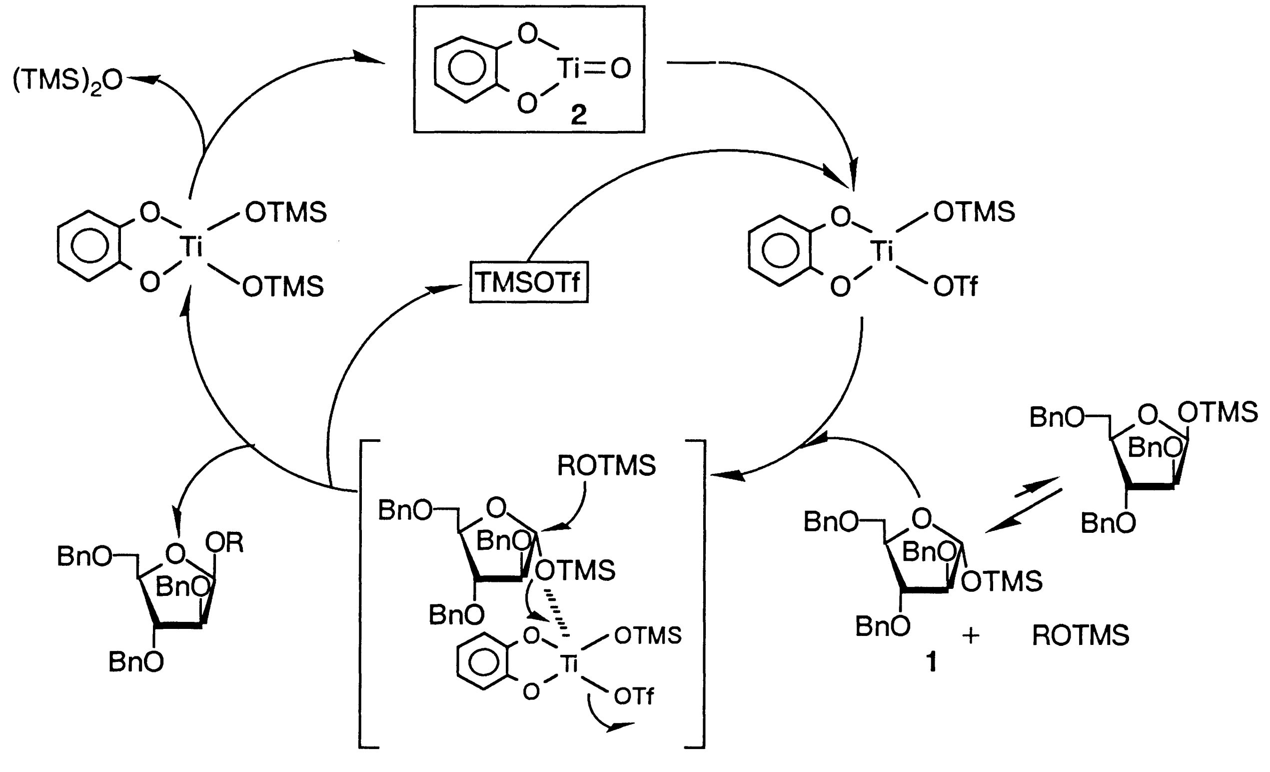
Table 1. Synthesis of β-Arabinofuranosides Using a New Titanium Catalyst

Entry	ROTMS	2 (equiv.)	3 (equiv.)	Temp / °C	Yield / %	α / β
1		2.0	1.0	0	76	18/82
2		2.0	1.0	-23	90	9/91
3		0.8	0.4	-15	77	10/90
4		0.4	0.2	0	62	14/86
5		0.8	0.4	-23	93	10/90
6		0.4	0.2	-23	96	13/87
7		0.2	0.1	-23	91	10/90
8		0.8	0.4	-23	92	8/92
9		0.8	0.4	-23	84	8/92
10	3β - Cholestanyl OTMS	0.8	0.4	0	96	13/87

Next, in order to realize high efficiency, the reaction was carried out by using *catalytic amounts of the titanium oxide 2 and TMSOTf*. In the presence of 40 mol% of titanium oxide 2 and 20 mol% of TMSOTf, the reaction proceeded smoothly at 0 °C to produce the corresponding arabinoside in 62% yield with rather high β-selectivity (α/β=14/86).[8] Several examples of the present glycosylation reaction are shown in Table 1, and in every case the corresponding 1,2-cis-arabinofuranosides are obtained in high yields with high selectivities.

A typical experimental procedure is described for the reaction of 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (**1**, α/β=75/25) with benzyl trimethylsilyl ether; 1 M dichloromethane solution of TMSOTf (0.01 mmol) was added to the titanium oxide **2** (0.02 mmol) in dichloromethane (5 ml) at r.t., and the mixture was cooled down to -23 °C. To this mixture was successively added dropwise a dichloromethane solution (2 ml) of benzyl trimethylsilyl ether (0.3 mmol) and 1-O-trimethylsilyl-D-arabinofuranose **1** (0.1 mmol) in dichloromethane (2 ml). The solution was kept at -23 °C, and after the reaction was completed (checked by TLC), triethylamine (2 ml) was added to quench the reaction. Then, sat. aqueous sodium hydrogen carbonate was added to the mixture and insoluble materials were filtrated. After usual work up, the corresponding 1,2-cis-arabinofuranoside and 1,2-trans-anomer were obtained in 82% and 9% yields, respectively.

The present reaction may be explained by assuming the catalytic cycle as shown in Scheme 1. The starting material, a mixture of α- and β-forms of 1-O-trimethylsilyl-2,3,5-tri-O-benzyl-D-arabinofuranose (α/β=75/25), is at equilibrium under the reaction conditions, and an active species generated from titanium oxide 2 and TMSOTf, preferentially interacts with α-trimethylsiloxy group at anomeric carbon rather than with β-trimethyl-



Scheme 1. The catalytic cycle.

siloxy group owing to the steric repulsion with the benzyloxy group at C-2 position. A trimethylsilyl ether attacks this anomeric center from β-side via S_N2 process to give the corresponding β-anomer with the regeneration of TMSOTf and the titanium oxide.

Thus, highly 1,2-cis-selective glycosylation reaction of arabinofuranose is successfully carried out starting from 1-O-trimethylsilyl-D-arabinofuranose **1** by using catalytic amounts of titanium oxide **2** and TMSOTf. It should be noted that no isomerization from 1,2-cis-arabinosides to thermodynamically stable 1,2-trans-arabinosides occurred under the present reaction conditions owing to the formation of the above active catalyst which minimized the existing acidic species, while the rapid isomerization was observed when typical Lewis acids such as $TiCl_4$, $SnCl_4$, BF_3OEt_2, and TMSOTf were used alone.

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7) **2** was an efficient catalyst in the aldol and Michael reactions. See, T. Mukaiyama and R. Hara, *Chem. Lett.*, **1989**, 1171; R. Hara and T. Mukaiyama, *ibid.*, **1989**, 1909.
8) The reaction proceeded very slowly at -23 °C under these conditions.

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