Highly Stereoselective Synthesis of 2'-Deoxy-α-ribonucleosides and 2-Deoxy-α-C-ribofuranosides by Remote Stereocontrolled Glycosylation

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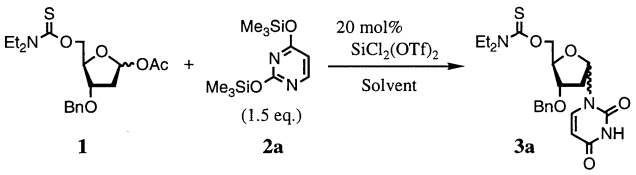
A new and efficient method for catalytic highly α-selective N- and C-glycosylations of 2-deoxyribose derivative with various trimethylsilylated nucleophiles was successfully developed by utilizing effective remote stereocontrol with 5-*O*-diethylthio carbamoyl directing group. Several 2'-deoxy-α-ribonucleosides and precursors of its C-analogues were prepared in good yields with high stereoselectivities.

In recent years, nucleosides and their C-analogues have been widely used as therapeutic agents for some intractable diseases such as cancer or AIDS because of their highly pharmacological potentials. Much attention therefore has been paid to develop a new and efficient method for the synthesis of these useful compounds.[1] However, stereoselective synthesis of 2'-deoxy-β-ribonucleosides is still a difficult problem due to the absence of C-2 substituent such as 2-*O*-acyl protecting group which are utilized for neighboring participation. In the previous papers, stereoselective synthesis of 2'-deoxy-β-ribonucleosides and 2-deoxy-β-C-ribofuranosides by use of 3-*O*-diethylthiocarbamoyl protected glycosyl donor were reported.[2,3] In these reactions, 3-*O*-thiocarbamoyl group was demonstrated as an excellent directing group for remote stereocontrol, and highly stereoselective N- and C-glycosylation reactions were performed. On the other hand, a stereoselective synthesis of 2'-deoxy-α-ribonucleosides is also a quite challenging problem because it is known to have wide pharmacological activities such as antitumor activity of 2'-deoxy-α-6-thioguanine[4] or cytostatic activity of 2'-deoxy-α-5-fluorocytosine[5] and so on. Further, 2'-deoxy-α-ribonucleosides are important precursors of oligo-2'-deoxy-α-ribonucleotides (α-oligo) as potent and nuclease resisitant agents for antisense therapy.[6] However, few reports are known for the stereoselective synthesis of these compounds including unexplored C-analogues.[5,7] Then, it was considered that β-side of anomeric position is selectively blocked by remote participation when the above mentioned thiocarbamoyl group was introduced to the 5-hydroxyl group located at β-side of 2-deoxyribose, and highly α-selective glycosylation would be achieved.[8] In this communication, we would like to report an efficient and practical method for the synthesis of 2'-deoxy-α-ribonucleosides and the precursors of its C-analogues on the basis of the above concept utilizing a stable 5-*O*-diethylthiocarbamoyl-protected glycosyl donor.

In the first place, the reaction of 2-deoxy-1-*O*-acetyl-3-*O*-benzyl-5-*O*-diethylthiocarbamoyl-D-ribofuranosides[9] **1** with trimethylsilylated uracil **2a** was tried in the presence of 20 mol% of dichlorobis(trifluoromethylsulfonyloxy)silane ($SiCl_2(OTf)_2$)[10] in benzene at 0 °C. The reaction proceeded smoothly and the corresponding 2'-deoxyribonucleoside **3a** was obtained in high yield (91%). As expected, this reaction preferentially gave the α-anomer and the ratio was α/β=85/15. This result indicated that β-side of the glycosyl donor is effectively blocked by the directing group and that this reaction proceeded under the remote stereocontrol of 5-*O*-thiocarbamoyl directing group. Next, effects of solvent and temperature were examined (Table 1) and the stereoselectivity lowered by increasing polarity of the solvent. The best selectivity was observed when the reaction was carried out in CCl_4 at 0 °C and the ratio reached α/β=89/11. It was found that the concentration of the substrate and the homogeneity of the solvent were very important in this reaction. When the reaction was carried out under lower concentration (0.010 mmol/ml) by adding the stock solution of trimethysilylated uracil in 1,2-dichloroethane to the CCl_4 solution of the catalyst, the stereoselectivity increased to α/β=91/9. This observation indicated the disadvantageous of entropically disfavorable 7-membered transition state under higher concentration in contrast to preferable 6-membered transition state in the reaction of 3-*O*-thiocarbamoyl glycosyl donor described in pervious papers.[2,3] Further, the best selectivity (α/β=93/7) was observed when the stock solution in CCl_4 was used under the same concentration. Several reactions of **1** with various trimethylsilylated bases were tried under the best condition (Table 2). In all cases, the corresponding 2'-deoxyribonucleosides were obtained in good yields with high α-selectivities.



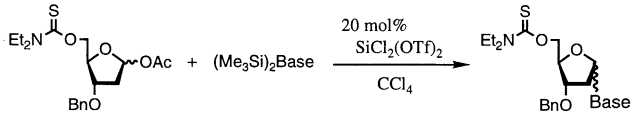
1 **2a** **3a**

Table 1. Effects of reaction conditions in N-glycosylation

Solvent[a]	Conc. (mmol/ml)[b]	Temp	Time (h)	Yield (%)	α / β
Benzene	0.020	0 °C	20	91	85 / 15
Toluene	0.020	0 °C	20	94	88 / 12
Fluorobenzene	0.020	0 °C	20	81	73 / 27
Mesitylene	0.020	0 °C	20	91	89 / 11
CH_2Cl_2	0.020	0 °C	20	83	69 / 31
$ClCH_2CH_2Cl$	0.020	0 °C	20	74	70 / 30
CCl_4	**0.020**	**0 °C**	**20**	**95**	**89 / 11**
CCl_4	0.020	-10 °C	20	36	88 / 12
CCl_4	0.020	room temp.	4	90	87 / 13
CCl_4	0.013	0 °C	20	96	90 / 10
CCl_4	0.010	0 °C	24	92	91 / 9
CCl_4[c]	**0.010**	**0 °C**	**27**	**95**	**93 / 7**

[a] The stock solution of **2a** in $ClCH_2CH_2Cl$ was added.
[b] The concentration was calculated based on the donor **1**.
[c] The stock solution of **2a** in CCl_4 was added.

Next, the reaction of **1** with 1-tert-butyl-dimethylsiloxy-1-benzyloxyethylene **4a** was tried in the presence of 100 mol% of chlorotris(trifluoromethylsulfonyloxy)silane ($SiCl(OTf)_3$)[10] in

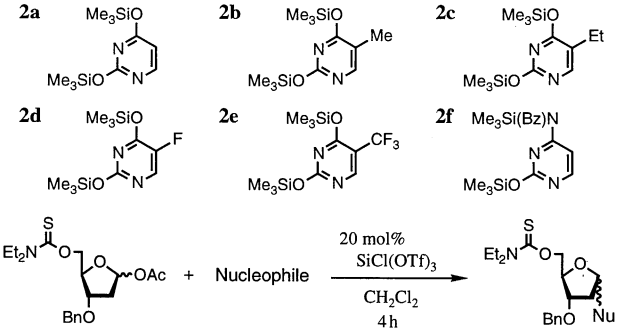


1 2 3

Table 2. Synthesis of 2-deoxy-α-ribonucleosides[a]

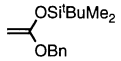
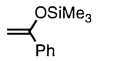
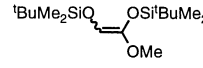
Base (eq.)			Temp	Time (h)	Yield (%)	α / β
Uracil	(1.5)	**2a**	0 °C	27	95	93 / 7
Thymine	(1.5)	**2b**	0 °C	27	93	89 / 11
5-Ethyluracil	(2.0)	**2c**	0 °C	24	94	86 / 14
5-Fluorouracil	(2.0)	**2d**	0 °C	30	92	89 / 11
5-Trifluoromethyluracil	(2.0)	**2e**	0 °C	40	78	92 / 8
N^4-Benzoylcytosine	(2.0)	**2f**	r.t.	50	70	91 / 9

[a] The stock solutions of **2** in CCl_4 were used.



1 4 5

Table 3. Synthesis of 2-deoxy-α-C-ribofuranosides

Nucleophile	(eq.)	Catalyst (mol%)	Temp	Yield (%)	α / β
 **4a**	(2.0)	100	-78 °C	trace	-
	(2.0)	100	0 °C	36	94 / 6
	(2.0)	100	r.t.	decomp.	-
	(2.0)	20	r.t.	78	92 / 8
	(3.0)	20	r.t.	86	92 / 8
	(4.0)	20	r.t.	94	91 / 9
 **4b**	(4.0)	20	r.t.	97	95 / 5
 **4c**	(3.0)	20	r.t.	89	86 / 14[a,b]

[a] The ratios of diastereomers were 62:38 (α-anomer) and 58:42 (β-anomer).
[b] The absolute configurations of diastereomers were not determined.

benzene at 0 °C in order to prepare 2-deoxy-α-C-ribofuranosides to be easily convertible to C-analogues of 2'-deoxy-α-ribonucleosides. The reaction, however, hardly proceeded and several reaction conditions concerning the amount of $SiCl(OTf)_3$ and temperature were examined (Table 3). As a result, the reaction smoothly proceeded at room temperture in the presence of catalytic amount of $SiCl(OTf)_3$ and the corresponding 2-deoxy-C-ribofuranoside **5a** was obtained in good yield with high α-selectivity. Interestingly, such a catalytic process was not achieved in the case of previously reported β-selective reaction. The yield of **5a** was improved by increasing amount of **4a** and reached 94% when four equivalents of **4a** were used. Several examples of the present C-glycosylation reaction with various silyl enol ethers are shown in Table 3. In every case, desired 2-deoxy-C-ribofuranosides were prepared in good yields with high α-selectivities.

The typical experimental procedure is as follows: to the stirred CCl_4 (10 ml) was added a stock solution of $SiCl_2(OTf)_2$ (0.1 M in toluene, 0.24 ml, 0.024 mmol) and cooled down to 0 °C. To the stirred mixture was successively added a stock solution of trimethysilylated uracil **2a** (1.0 M in CCl_4, 0.18 ml, 0.18 mmol) and a solution of 2-deoxy-1-*O*-acetyl-3-*O*-benzyl-5-*O*-diethylthiocarbamoyl-D-ribofuranosides **1** (45.8 mg, 0.120 mmol) in CCl_4 (2 ml). After the reaction mixture was stirred for 27 h at 0 °C, it was quenched by adding phosphate buffer solution (pH=7). By usual work-up and purification with preparative TLC (silica gel), 2'-deoxy-3'-*O*-benzyl-5'-*O*-diethylthiocarbamoyluridine **3a** (49.2 mg, 95% yield) was isolated. The ratio of the anomers was determined by ^{1}H-NMR and HPLC analysis. The thiocarbamoyl group of **3a** was readily removed to afford 5-hydroxyl derivative in 98% yield by the previously reported oxidation-hydrolysis procedure.[2]

Thus, a new and efficient method for catalytic stereoselective synthesis of 2'-deoxy-α-ribonucleosides and the precursors of its C-analogues was successfully developed.

Further investigation on synthesis of useful glycosides based on this remote stereocontrol strategy is now in progress.

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References and Notes

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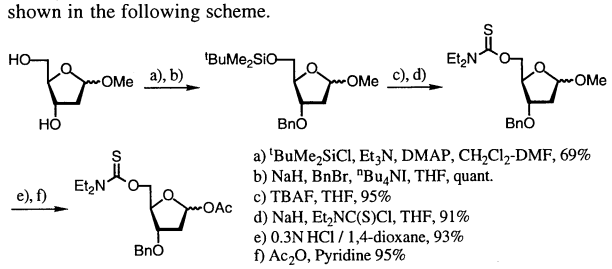
9 This glycosyl donor was prepared from methyl 2-deoxy-D-ribofuranoside shown in the following scheme.



10 Silyl triflates, $SiCl_2(OTf)_2$ and $SiCl(OTf)_3$, were prepared from $SiCl_4$ and two or three molar equivalents of AgOTf in toluene and stocked as this solution.

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.