A New Efficient Method for Stereoselective Synthesis of 2-Deoxy-C-ribofuranosides

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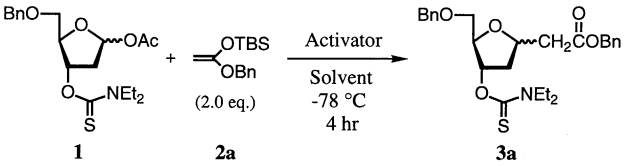
Stereoselective C-glycosylation of 2-deoxyribose derivatives having 3-*O*-thiocarbamoyl directing group with carbon nucleophiles was successfully carried out by using $SiCl(OTf)_3$ as an activator. Several 2-deoxy-β-C-ribofuranosides which can be easily converted to 2'-deoxy-C-nucleosides were obtained in good yields with high stereoselectivities.

Since pseudouridine was discovered from calf-liver-derived tRNA in 1957,[1] C-nucleosides, a series of compounds having β-ribofuranosyl moiety linked to a carbon atom of a heterocyclic ring, have attracted great interest in chemical and biological areas. Several natural or synthetic C-nucleosides exhibited novel pharmacological potential as anticancer, antiviral and other activities.[2] In addition, a number of naturally occuring or artifical bioactive 2'-deoxyribonucleosides were also known and 2'-deoxy analogues of C-nucleoside which have not yet been discovered in nature are expected to have new therapeutic activities for some intractable diseases such as AIDS. Synthetic approaches to 2'-deoxy-C-nucleosides are generally classified into four main types:[3] (1) construction of the heterocycle moiety on C-1 of a suitably functionalized 2-deoxyribose derivative; (2) construction of 2-deoxyribose on an appropriately substituted non-sugar heterocycle; (3) direct substitution of a suitably C-1-functionalized 2-deoxyribose derivative by a metallated heterocycle and (4) stepwise formation of a 2'-deoxyribose derivative from a ribofuranosyl-C-nucleoside. Of these approaches, (1) is recognized as the most useful one because many types of 2'-deoxy-C-nucleosides are synthesized from a common intermediate. However, stereoselective C-glycosylation of 2-deoxyribose derivative is difficult because of the abscence of C-2 substituent which is generally utilized in the stereocontrolled glycosylation by neighboring participation. Therefore, it has been strongly desired to develop a new efficient synthetic method for the stereoselective C-glycosylation. In the previous paper, highly stereoselective synthesis of 2-deoxyribonucleosides from 2-deoxy-1-*O*-acetyl-3-*O*-diethylthiocarbamoyl-5-*O*-benzyl-D-ribofuranosides, which is a readily-prepared and stable glycosyl donor, was reported.[4] In the above reaction, the α-side of glycosyl donor was efficiently blocked by the 3-*O*-thiocarbamoyl group during the reaction and a highly stereocontrolled glycosylation was achieved.[5] In this communication, we would like to describe the C-glycosylation reaction of the above glycosyl donor with carbon nucleophiles forming synthetic precursors of novel 2'-deoxy-C-nucleosides.

In the first place, the reaction of 2-deoxy-1-*O*-acetyl-3-*O*-diethylthiocarbamoyl-5-*O*-benzyl-D-ribofuranosides **1** with 1-tert-butyldimethylsiloxy-1-benzyloxyethylene **2a** was tried in the presence of several kinds of Lewis acids (Table 1). The reaction proceeded to yield the corresponding 2-deoxy-C-ribofuranoside **3a** with high β-selectivity at -78 °C when one equivalent of chlorotris(trifluoromethylsulfonyloxy)silane ($SiCl(OTf)_3$)[6] was used as an activator. Interestingly, however, similar titanium(IV) or tin(IV) derivatives were quite ineffective. Next, the effect of solvent was examined (Table 2) and a remarkable solvent effect on yield and stereoselectivity was observed when dichloro methane was used. Based on the results, the reaction of the donor with ketene silyl acetal derived from benzyl protected glycolic acid ester was tried under the optimum condition in C-glycosylation (Table 3). The reaction proceeded smoothly to give the desired product in high yield, but with low stereoselectivity. No improvement in stereoselectivity was observed when *tert*-butyl dimethylsilyl group, a bulkier and less interactive group toward Lewis acid, was employed for protection instead of benzyl group. Finally, ketene silyl acetals having other ester or silyl substituent were examined and the best result was obtained when (*E*)-1-*tert*-butyldimethylsiloxy-2-trimethylsiloxy-2-methoxyethylene **2f** was used. This reaction product is readily convertible to corresponding α-ketoester which is a useful precursor of several novel C-nucleosides. Several examples of the present C-glycosylation reaction with other carbon nucleophiles are shown in Table 4. Silyl enol ethers derived from ketones **2g-h** also reacted to give the corresponding 2-deoxy-C-ribofuranosides **3g-h** in high yields with good stereoselectivities. Interestingly, a revarsal of stereoselectivities in two cases was observed depending on whether allyltrimethylsilane **2i** or allyltributyltin **2j** was used as a nucleophile.



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

Table 1. Effect of activator

Activator	(mol%)	Solvent	Yield / %	α / β
$SnCl_2(OTf)_2$	(100)		9	28 / 72
$TiCl_2(OTf)_2$	(100)		5	25 / 75
$SiCl_2(OTf)_2$	(100)		86	23 / 77
$SiCl_2(OTf)_2$	(200)	CH_2Cl_2	82	10 / 90
$SiCl(OTf)_3$	(50)		86	19 / 81
$SiCl(OTf)_3$	**(100)**		**89**	**4 / 96**
$SiCl(OTf)_3$	(200)		81	2 / 98

Table 2. Effect of solvent

Activator	(mol%)	Solvent	Yield / %	α / β
$SiCl(OTf)_3$	(100)	toluene	64	20 / 80
		CH_2Cl_2	**89**	**4 / 96**
		$EtNO_2$	54	33 / 67
		Et_2O	21	15 / 85
		EtCN	59	31 / 69

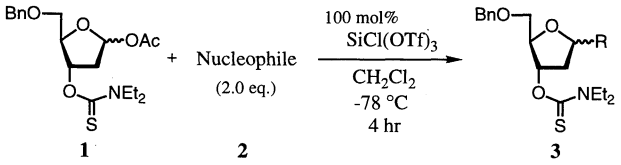


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Table 3. Reactions with several ketene silyl acetals

Nucleophile	(E / Z)	Product[a]	R	Yield / %	α / β
BnO, OTBS, OMe **2b**	(6 / 94)	**3b**	OBn, OMe	99	25 / 75
TBSO, OTBS, OMe **2c**	(5 / 95)	**3c**	OTBS, OMe	89	23 / 77
TBSO, OTBS, OMe **2d**	(87 / 13)	**3c**	OTBS, OMe	92	23 / 78
TBSO, OTMS, O^{t}Bu **2e**	(88 / 12)	**3e**	OTBS, O^{t}Bu	72	21 / 79
TBSO, OTMS, OMe **2f**	(94 / 6)	**3c**	OTBS, OMe	**94**	**14 / 86**

[a] The ratio of diastereomers was about 1:1 in all cases.

Table 4. Reactions with several nucleophiles

Nucleophile	Product	R	Yield / %	α / β
OTMS, Me **2g**	**3g**	Me	87	19 / 81
OTMS, Ph **2h**	**3h**	Ph	95	24 / 76
TMS **2i**	**3i**		52	79 / 21
Bu_3Sn **2j**	**3i**		59	19 / 81

The thiocarbamate group of thus formed 2-deoxy-C-ribofuranosides was readily removed in high yield by the previously described oxidation-hydrolysis procedure[4] (Table 5).

The typical experimental procedure is as follows: to a stirred solution of 2-deoxy-1-*O*-acetyl-3-*O*-diethylthiocarbamoyl-5-*O*-benzyl-D-ribofuranosides **1** (45.8 mg, 0.120 mmol) and 1-benzyloxy-1-trimethylsiloxyethylene **2a** (63.5 mg, 0.240 mmol) in dichloromethane (7 ml) was successively added a toluene solution of chlorotris(trifluoromethylsulfonyloxy)silane[6] (0.3 M, 0.400 ml, 0.120 mmol) at -78 °C. After the reaction mixture was stirred for 4 hours, it was quenched by adding saturated aqueous sodium hydrogen carbonate. By usual work-up and purification with preparative TLC (silica gel), 1,2-dideoxy-1-benzyloxy carbonylmethyl-3-*O*-diethylthiocarbamoyl-5-*O*-benzyl-D-ribofuranosides **3a** (50.5 mg, 89% yield) was isolated. The ratio of the anomers was determined by ^{1}H-NMR analysis.

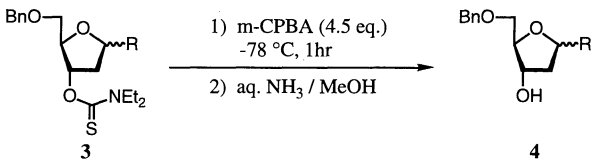

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Table 5. Removal of 3-*O*-thiocarbamoyl group

Substrate	R	Yield / %
3a	OBn	97
3c	OTBS, OMe	96
3h	Ph	91

Thus, a new efficient method for stereoselective synthesis of 2-Deoxy-C-ribofuranosides was successfully developed.

Further investigation on synthesis of valuable 2'-deoxy-C-nucleoside based on this new strategy is now in progress.

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References and Notes

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6 The stock solution of chlorotris(trifluoromethylsulfonyloxy) silane was prepared from $SiCl_4$ and three equivalent of AgOTf in toluene.