Reaction and Stereochemistry of C-Glycosidation in 2-Deoxy-4-Thioribofuranoside

Jun'ichi Uenishi,* Atsushi Sohma, and Osamu Yonemitsu
Department of Chemistry, Faculty of Science, Okayama University of Science, Ridaicho, Okayama 700

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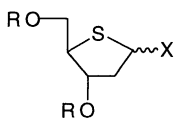
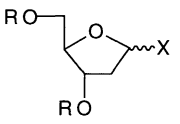
$SnCl_4$ mediated C-glycosidation reactions of ethyl 2-deoxy-4-thioribofuranoside with silylated nucleophiles were described. α-Anomer was the major product formed in the reactions. The stereochemical course was found to be similar to that of ethyl 2-deoxyribofuranoside.

Glycosidation of sugar is one of the most important reactions in nucleoside and carbohydrate chemistry. The reaction products have been utilized for clinical medicines and also biological agents, including *anti*-cancer and *anti*-viral drugs, glycosidase inhibitors and so on. A vast number of glycosidation reactions in nucleoside syntheses[1] and oligosaccharide syntheses[2] have appeared. Nucleosides containing sulfur atom in the nucleic base part or in the sugar part have been reported.[3] Among them, sulfur nucleosides replacing the oxygen atom by a sulfur atom in the furanose ring have been prepared, and found to show potent *anti*-viral and *anti*-tumor activities.[4] These sulfur nucleosides were prepared by glycosidation reaction of thiosugars with silylated pyrimidine or purine bases. Although C-glycosidation has been well documented,[5] that for sulfur analogues has never been studied. In this letter, we report the first C-glycosidation reaction of 2-deoxy-4-thioribofuranoside, and compare its stereochemistry with that of 2-deoxyribofuranoside.

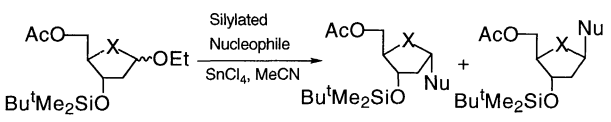


2-Deoxy-4-thioribose



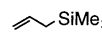
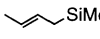
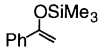
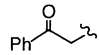
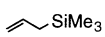
2-Deoxyribose

Ethyl 5-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-2-deoxy-4-thio-D-*erythro*-pentofuranoside (**1**)[6] and ethyl 5-*O*-acetyl-3-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-*erythro*-pentofuranoside (**2**)[7] were used for this study. The reactions of **1** and **2** with silylated nucleophiles such as trimethyl-silyl enol ethers, allyltrimethyl-silanes and trimethylsilyl cyanide were examined, which were carried out in anhydrous acetonitrile at room temperature in the presence of $SnCl_4$.[8]



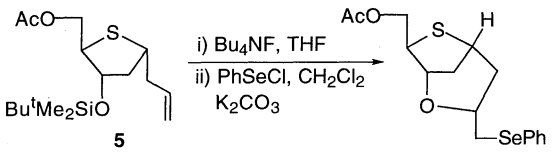
1 : X : S
2 : X : O

Table 1. Chemical Yields and Isomeric Rations in C-Glycosidation Reactions for **1** and **2**.

Entry	Substrate	Nucleophile	Product[a]	Nu	Yield (%)	Ratio (α:β)[b]
1	**1**		**3**[c]		65	1.1 : 1
2	**1**		**4**		79	4.4 : 1
3	**1**		**5**		84	100 : 0
4	**1**		**6**[c]		69	100 : 0
5	**1**	Me_3SiCN	**7**	NC	89	8 : 1
6	**2**		**8**[c]		76	1.3 : 1
7	**2**		**9**		75	4.8 : 1
8	**2**		**10**		85	100 : 0
9	**2**	Me_3SiCN	**11**	NC	84	2: 1

[a] All the reactions were carried out at rt under an Ar atmoshere.
[b] The ratio was determined by ^{1}H-NMR.
[c] The stereochemistry at branched chain has not assigned but its nmr indicated a single diastereomer.

The reaction of trimethylsilyl enol ether of cyclohexanone with **1** gave the corresponding 2-cyclohexanone derivative **3** in 65% yield (entry 1). In this case, the stereoselectivity was poor at a 1.1:1 ratio. However, the reaction of trimethylsilyl enol ether of acetophenone afforded the preferred formation of the α-anomer[9] in the ratio of 4.4:1 in 79% yield (entry 2). An allylated product **5**[10] was obtained as a single stereoisomer by the reaction of **1** with allylsilane (entry 3). The α-configuration of **5** was confirmed by the selenium induced ring formation. Thus, deprotection of *tert*-butyldimethylsilyl (TBDMS) ether in **5** followed by treatment with phenylselenenyl chloride gave a tetrahydropyran.



The reaction with crotylsilane also gave 3-butenyl derivative **6** as a single isomer (entry 4). As for the stereochemistry in the reaction with allylsilanes, the attack occurred perfectly from the α-side. Introduction of a cyano group was performed by the reaction of trimethylsilyl cyanide with high stereoselectivity (8:1) in 89% yield (entry 5). These results are summarized in Table 1, together with those of **2**. Surprisingly, the yields and stereochemistries for the reaction of **2** in entries 6~8 were quite similar to those obtained in **1** (entries 1~3). However, in the reaction of **1** with trimethylsilyl cyanide, the α-cyanide was obtained with lower selectivity.

As the reactions most probably proceed through a cyclic thionium or an oxoniun intermediate, they are not stereospecific but stereoselective. In fact, starting reactions from either α- or β-isomer of **1**, the stereochemical outcomes of the above C-glycosidation were the same. Although the conformations of the thionium and oxonium intermediates generated from **1** and **2** would be quite different due to the C-S-C and the C-O-C bond lengths and angles, there were few stereochemical differences observed in the C-glycosidation reactions. The bulky TBDMS group at C-3 plays a minor role concerning the stereocontrol, because its replacement by an acetyl group brought little change in its stereoselectivity.[11] Due to the lack of neighboring effect, stereocontrol of glycosidation in 2-deoxy sugars is generally difficult except a few cases.[12] It usually provided a slight preference of α-anomer,[1] and the favorable formation of α-anomer was also observed in the cases of 2,3-dideoxyribose derivatives.[13]

In summary, C-glycosidation of 2-deoxy-4-thioribofuranoside occurred in good yield with moderate to exclusively high selectivity. Inherent selectivity of α-preference for **1** as well as **2** is quite interesting, and the result would be valuable in synthesis for C-nucleoside of pseudo sugars.

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References and Notes

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7 This compound was derived from 2-deoxyribose in 3 steps by the standard method.

8 Typical experiment: To a mixture of **1** or **2** (0.6 mmol) and silylated nucleophile (0.9~1.1 mmol) in anhydrous acetonitrile was added $SnCl_4$ (0.9 mmol) at -30℃, and the mixture was stirred at the same temperature for 15 to 30 min. Aqueous work up with sodium bicarbonate, extraction with ether, and purification by silica gel column chromatography gave compound **3~11**.

9 Stereochemistry of the product was determined by NOE experiment in ^{1}H NMR.

10 **5** ; Colorless oil, $[\alpha]_D^{24}$ +107° (*c* 1.0, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, m), 5.10~5.03 (2H, m), 4.18 (1H, dd, J = 11.2 and 6.4 Hz), 4.17 (1H, ddd, J = 7.3, 6.0 and 5.0 Hz), 4.02 (1H, dd, J = 11.2 and 6.8 Hz) 3.46 (1H, ddd, J = 6.8, 6.4 and 6.0 Hz), 3.38 (1H, quint, J = 7.1 Hz), 2.48 (1H, m), 2.38 (1H, m), 2.21 (1H, ddd, J = 12.6, 7.1 and 5.0 Hz), 2.05 (3H, s), 1.80 (1H, ddd, J = 12.6, 7.3 and 7.2 Hz), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.7, 136.1, 116.7, 76.9, 65.9, 53.0, 43.5, 42.6, 42.1, 25.7, 20.8, 17.9, -4.7, -5.0; IR (neat) 1746 cm^{-1}; MS (FAB-Low) *m/z* 331 (M^++1); MS (FAB-High) *m/z* calcd for $C_{16}H_{30}O_3SSi$: 331.1764. Found: 331.1758.

11 Poor selectivity was reported for glycosidation in 2-deoxy 3-*tert*-butyldiphenylsilyloxy derivative; see T.-F. Yang, L. P. Kotra, Q. Teng, F. N. M. Naguib, J.-P. Sommadossi, M. el Kouni, and C. K. Chu, *Tetrahedron Lett.*, **36**, 983 (1995).

12 A few excellent stereocontrols in glycodsidation reaction were reported. Remote sterocontrol by the protecting group of the C-3 α-hydroxy function, see Y. Ichikawa, H. Kubota, K. Fujita, T. Okauchi, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **62**, 845 (1989); Lewis acid coordinated stereo control, see W.-B. Choi, L. J. Wilson, S. Yeola, D. C. Liotta, and R. F. Schinazi, *J. Am. Chem. Soc.*, **113**, 9377 (1991).

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