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Stereoselective Preparation of β-C-Glycosides from 2-Deoxyribose Utilizing Neighboring Participation by 3-O-Methylsulfinylethyl Group

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Acid catalyzed reaction of 2-deoxy-3-O-methylsulfinylethyl-ribofuranosyl acetate with silyl enol ethers proceeded stereoselectively, resulting in the predominant formation of the corresponding β-C-glycosides.

Much attention has been devoted to various types of nucleosides because of their antitumor and/or antiviral activities.[1] In the synthesis of these nucleoside derivatives, β-selective glycosylation method of ribose or 2-deoxyribose derivatives is required. The synthesis of β-glycosides from ribose derivatives has been attained stereoselectively by utilizing a neighboring group participation from 2-acyl group.[2] As such a participation from 2-O-protecting group cannot be expected in the case of 2-deoxyribose,[3] only the S_N2 displacement of 2-deoxy-3,5-di-O-toluoyl-α-D-erythro-pentofuranosyl chloride by basic nucleophiles has afforded successful results in the preparation of β-glycosides.[4] To achieve a stereoselective method for the preparation of C-glycosides of 2-deoxyribose, we have examined C-glycoside formation by the use of neighboring participation from a 3-O-substituent.

As a model reaction, we chose the C-glycosylation of 3-O-substituted 1-O-acetyl-5-O-benzyl-2-deoxy-D-erythro-pentofuranose (3-substituted 1-O-acetyl-2-deoxyribose, **1**) with the silyl enol ether of acetophenone **2** in the presence of a Lewis acid such as trityl perchlorate,[5] $SnCl_4$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf).[6] The reaction of 3-O-benzyl derivative **1a**, which is not expected to cause neighboring participation, gave α- and β-C-glycosides with high selectivity for the α-C-glycoside (**3aα**:**3aβ** = 82:18). To attain good stereoselectivity for the β-C-glycoside, the glycosylation of various 3-O-substituted 2-deoxyriboses **1b-f** was examined in detail with the expectation that the 3-O-substituent could regulate the stereoselection by the formation of a cyclic stabilized cationic intermediate. Among a variety of 3-substituents such as an ether, esters and sulfides, the alkylthioethyl group was found to afford the promising results. That is, the treatment of the 3-O-methylthioethyl derivative **1d** with the silyl enol ether **2** in the presence of $SnCl_4$ in dichloromethane at -78 °C gave the corresponding C-glycoside **3d** in 46% yield in the ratio of α:β = 42:58. When bulkier sulfides such as ethylsulfide and t-butylsulfide were used instead of

methylsulfide, less β-stereoselectivity was observed.

Next, the methylsulfide **1d** was converted to the corresponding sulfoxide **1g** by the consideration that the participation by the sulfinyl group should occur more efficiently with respect to the electronic and steric effects. The sulfoxide **1g** reacted with the silyl enol ether **2** to afford the β-C-glycoside predominantly (**3gα**:**3gβ** = 32:68) in an excellent yield. These results are summarized in Table 1.

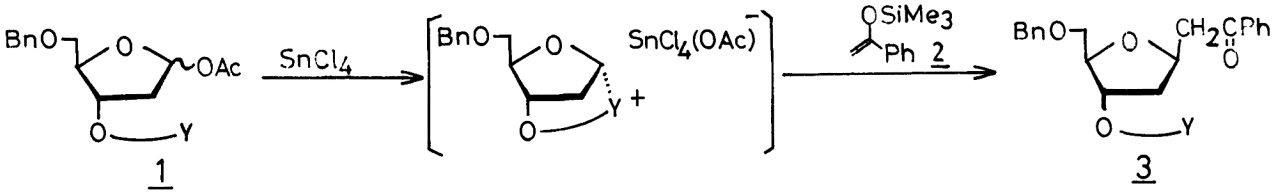
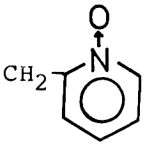


Table 1. The reaction of various 3-substituted 2-deoxyribose **1** with **2**[a)]

	Y	Yield of 3/%	3α : 3β[7)]
1a	CH_2Ph[b)]	95	82 : 18
1b	$CH_2OCH_2CH_2OMe$	83	75 : 25
1c	CH_2SMe[c)]	56	82 : 18
1d	CH_2CH_2SMe	46	42 : 58
1e	$CH_2CH_2S^tBu$	44	68 : 32
1f		87	49 : 51
1g	$CH_2CH_2S(O)Me$[d)]	92	32 : 68

a) The reaction was carried out in the presence of **2** (1.2 mol equiv.) and $SnCl_4$ (1.2 mol equiv.) at -78 °C.
b) The reaction was carried out at -45 °C.
c) Trityl perchlorate was used as a Lewis acid.
d) Yield and ratio were determined after the conversion of the products into the corresponding sulfones.

As the 3-O-methylsulfinylethyl group was found to realize good β-selectivity, the reactions of **1g** with silyl enol ethers **4A,B** and ketene silyl acetals **4C,D** were examined. The products were converted to the corresponding sulfones **5** to

determine the isomer ratio and the stereochemistry, and the results are listed in Table 2. Useful synthetic intermediates such as **5C,D** for the synthesis of various C-nucleosides[8] were prepared with high β-selectivity (ca. α:β = 1:9) by the reaction of **1g** with ketene silyl acetals which are generally better nucleophiles as compared with silyl enol ethers.

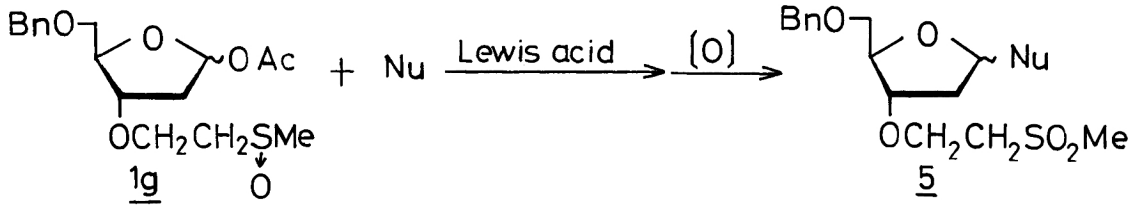
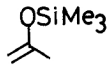
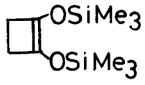
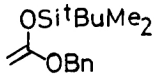
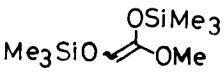


Table 2. The reaction of **1g** with silyl nucleophiles **4A-D**

	Nucleophile	Lewis acid	Yield of 5/%	5α : 5β
4A		$SnCl_4$	82	22 : 78
4B		$SnCl_4$	76	32 : 68[a]
4C		TMSOTf	86	9 : 91[9]
4D		TMSOTf	91	11 : 89

a) The structure of each stereoisomer was not determined absolutely, but by analogy with other results.

A typical experimental procedure is as follows: A dichloromethane (2 mL) solution of TMSOTf (0.80 mmol) was added slowly to a dichloromethane (10 mL) solution of **1g** (0.53 mmol) and **4C** (0.67 mmol) at -78 °C, and the mixture was stirred for 12 h at this temperature. The reaction was quenched by addition of pH 7 buffer and the mixture was extracted with dichloromethane. After purification by column chromatography on silica gel (hexane:ethyl acetate:methanol = 3:5:1, volume ratio), the products were oxidized at room temperature in methanol (10 mL) by the addition of 10% H_2O_2 (10 mL) and ammonium molybdate(VI) tetrahydrate (0.08 mmol). The reaction mixture was extracted with dichloromethane and purified by column chromatography on silica gel (ethyl acetate:hexane = 2:1, volume ratio) to afford a mixture of α- and β-C-glycosides **5C** in 86% yield (α:β = 9:91).

Thus, by using the neighboring group participation of methylsulfinylethyl group on the 3-hydroxyl group, stereoselective β-C-glycosylation of 2-deoxyribose

was achieved, and these results suggest that the neighboring effect from the 3-O-position has the possibility to control the stereochemistry efficiently in the glycosylation of 2-deoxyribose.

References

1) Reviews: S. Hanessian and A. G. Pernet, Adv. Carbohydr. Chem. Biochem., 33, 111 (1976); U. Hacksell and G. D. Daves, Jr., "The Chemistry and Biochemistry of C-Nucleosides and C-Arylglycosides," in "Progress in Medicinal Chemistry," ed by G. P. Ellis and G. B. West, Elsevier Science Publishers, B. V. (1985), Vol.22.

2) For example: U. Niedballa and H. Vorbruggen, J. Org. Chem., 39, 3654 (1974); T. Ogawa, A. G. Pernet, and S. Hanessian, Tetrahedron Lett., 1973, 3547; Y. S. Yokoyama, M. H. R. Elmoghayar, and I. Kuwajima, ibid., 23, 2673 (1982).

3) W. Wierenga and H. I. Skulnick, Carbohydr. Res., 90, 41 (1981).

4) A. Kolb, T. H. Dinh, and J. Igolen, Bull. Soc. Chim. Fr., 1973, 3447; Z. Kazimierczuk, H. B. Cotton, G. R. Revankar, and R. K. Robins, J. Am. Chem. Soc., 106, 6379 (1984).

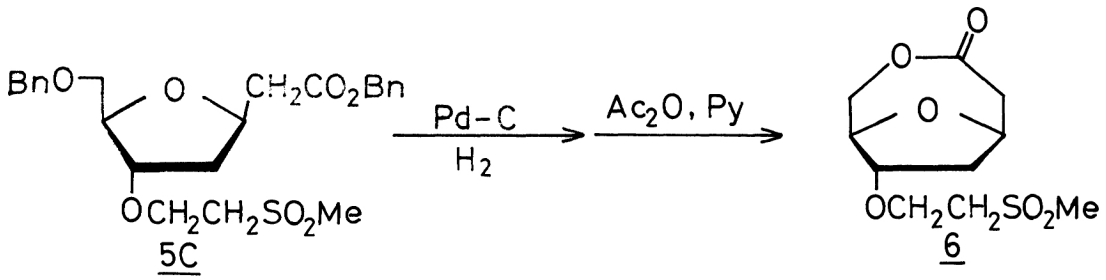
5) T. Mukaiyama, S. Kobayashi, and S. Shoda, Chem. Lett., 1984, 1529.

6) Each Lewis acid exhibited almost the same stereoselectivity in the glycosylation reaction.

7) The ratio of α- and β-glycosides 3 was determined by the comparison of their 400 MHz and 270 MHz ^{1}H NMR spectra with those of the glycosides 5C. In fact, all of the product in Table 1 and 5C show the characteristic patterns of H-2 and H-2′ protons in the ^{1}H-NMR. The NMR signals of H-2 and H-2′ are as follows; α-isomer δ=2.13-2.28 (ddd, J=1.3-1.9, 5.3-5.9, 13.0-13.8 Hz), 1.69-1.72 (ddd, J=6.1-6.5, 9.6-10.8, 13.0-13.8 Hz), β-isomer δ=2.35-2.51 (td, J=6.5-6.9, 13.0-13.8 Hz), 1.80-1.84 (ddd, J=4.0-4.4, 5.5-5.9, 13.0-13.8 Hz).

8) C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, J. Org. Chem., 41, 2793 (1976); G. Just and M. Lin, Can. J. Chem., 55, 2993 (1977).

9) The major isomer 5C was converted to the lactone 6 by hydrogenation and successive treatment with acetic anhydride-pyridine, and the stereochemistry of 5C was determined as the β-isomer.



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