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# Stereoselective Synthesis of β-2-Deoxyribonucleosides from 1-O-Acetyl-3-O-[2-(methylsulfinyl)ethyl]-2-deoxyribose

Tatsuo OKAUCHI, Hideki KUBOTA, and Koichi NARASAKA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

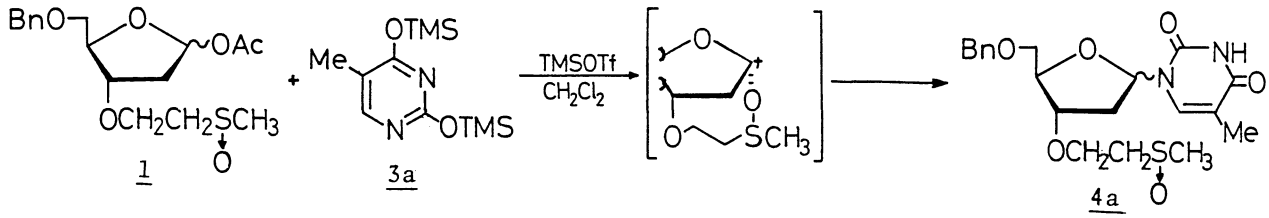
β-2-Deoxyribonucleosides are prepared stereoselectively from 1-O-acetyl-5-O-benzyl-3-O-[2-(methylsulfinyl)ethyl]-2-deoxy-D-erythro-pentofuranose by the reaction with the silyl or zinc derivatives of nucleoside bases in the presence of trimethylsilyl trifluoromethanesulfonate.

Since most of ribonucleosides and 2-deoxyribonucleosides exist as β-isomers in the nature, stereoselective preparation of β-nucleosides is a fundamental problem in the synthesis of nucleoside derivatives. For chemical synthesis of β-ribonucleosides, the Vorbrüggen's method has been widely employed and the β-selectivity is controlled by the neighboring group participation of 2-O-acyl group to the cation at 1-position generated by the acid activation of the leaving group.[1)]

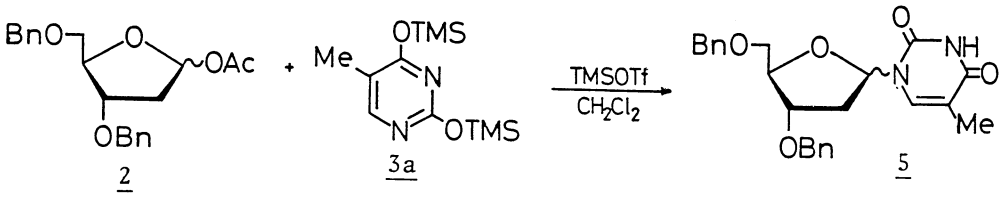
On the other hand, such a participation from 2-O-group is not applied to the glycosylation of 2-deoxyribose derivatives. Only the modified Hilbert-Johnson method has been known as a stereoselective method for preparation of 2-deoxyribonucleosides, in which $S_N2$ type replacement proceeds between an α-1-chloro-2-deoxyribose and the silylated pyrimidine[2)] or purine derivatives.[3)] But the utility of this procedure is limited, because the stereoselective preparation of the starting material, α-1-halo-3,5-O-diaroyl-2-deoxyribose, is indispensable in this method. Accordingly, the stereoselective method for the preparation of β-2-deoxyribonucleosides still remains to be developed. We previously reported the β-C-glycosylation of 1-acetoxy-2-deoxyribose derivatives with silyl enol ethers or ketene silyl acetals by using the remote interaction of α-3-O-[2-(methylsulfinyl) ethyl] group to the cation at 1-position generated by the activation with a Lewis acid.[4)] It is considered that the above participation would be also suitable to control the stereochemistry of β-2-deoxyribonucleoside formation. Furthermore, the separation of α and β anomers of the starting 1-acetoxy-2-deoxyribose derivative would not be required because this reaction maybe proceeds via $S_N1$ pathway.

First the reaction of 1-O-acetyl-2-deoxyribose derivatives having 3-O-[2-(methylsulfinyl)ethyl] group **1**[4b)] or 3-O-benzyl group **2** with the silylated thimine **3a**[5)] was examined in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[1b)] (Eq. 1). The reaction proceeded at -23 °C to yield the corresponding nucleosides **4a** and **5**, and higher β-selectivity was observed by the use of **1** as compared with **2**. These results would indicate that the interaction of 3-O-[2-

(methylsulfinyl)ethyl] group to the cation at 1-position from the α-side realizes the good β-selectivity, while the 3-O-benzyl group does not.



Yield 89% α:β=11:89 (1)



Yield 54% α:β=40:60

In this reaction, the choice of the Lewis acids exhibited a large influence on the β-selectivity. TMSOTf was found to give the β-nucleoside β-4a in good selectivity among various Lewis acids such as triphenylmethylium tetrafluoroborate, boron trifluoride etherate, and tin tetrachloride.

Subsequently reactions of 1 and some silylated pyrimidine derivatives,[5] 3a-d and 6, were tried in the presence of TMSOTf (Eq. 2). As shown in Table 1, the urasil derivatives 3a-d could react at -23 °C to give the β-nucleosides 4a-d in good selectivity. The more basic silylated cytosine derivative 6 is less reactive presumably due to the complex formation with TMSOTf[6] and reacts with 1a at 0 °C.

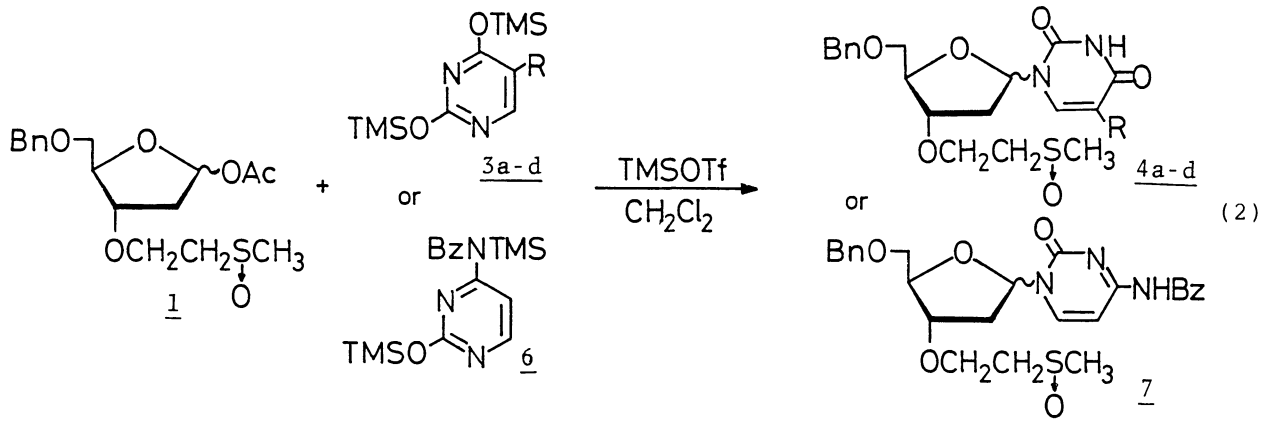


Table 1. The reaction of 1 with pyrimidime bases

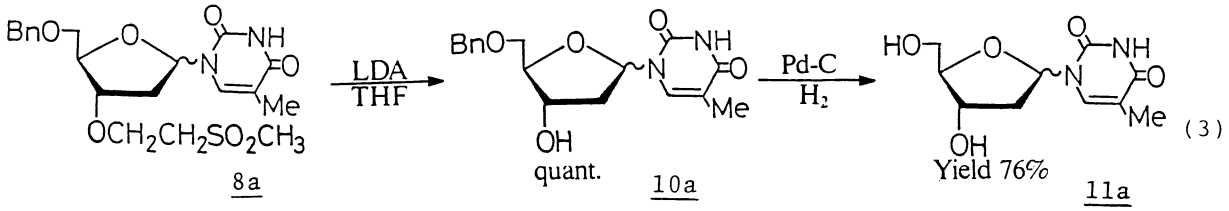
| 3 or 6 | Temp/°C | Yield/% | α : β |
|---|---|---|---|
| 3a (R=Me) | -23 | 89 | 11:89 |
| 3b (R=H) | -23 | 90 | 18:82 |
| 3c (R=F) | -23 | 91 | 16:84 |
| 3d (R=$NO_2$) | -23 | 71 | 11:89 |
| 6 | 0 | 89 | 25:75 |

The typical experimental procedure is as follows: To a dichloromethane (3 ml) solution of silylated pyrimidine base 3a (59 mg, 0.23 mmol) and the 1-acetoxy-

2-deoxyribose 1 (62.3 mg, 0.17 mmol) was added slowly a dichloromethne (1.5 ml) solution of TMSOTf (77 mg, 0.35 mmol) at -23 °C and was stirred for 1.5 h. By usual work-up and purificatoin with preparative TLC (silica gel), the corresponding nucleoside derivative 4a was isolated(65.5 mg, 89% yield).

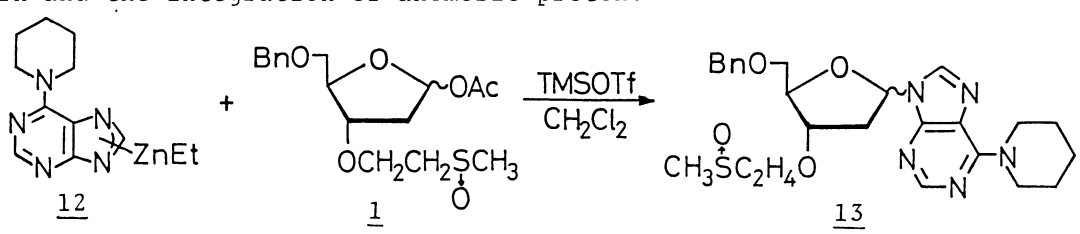
The ratio of α- and β-isomers was determined as follows. As the each glycosylation product 4a-d and 7 has four diastereomers due to the two chiral centers of the anomeric position and the sulfoxide, the sulfoxides 4a-d and 7 were oxidized to the corresponding sulfones 8a-d and 9 with $H_2O_2$-$(NH_4)_6Mo_7O_{24}$[7] or $NaIO_4$-$RuCl_3$.[8] For each major product, the $^1$H-NMR signal of the anomeric proton appears as a pseudotriplet which means the major product to be the β-isomer. The anomeric $^1$H signals of all the minor isomers appear as a double doublet.[9] Then the α/β ratio was determined by the integration of signals of the anomeric or the sulfonylmethyl protons.

In order to confirm the position of the glycosylation concerning pyrimidine base (1- or 3-position), the substituents of 3′- and 5′-hydroxyl groups of 8a were removed to afford thimidine 11a as shown in Eq. 3. As the $^1$H-NMR spectrum of the deprotected nucleoside 11a is identical with that of the authentic thimidine, the glycosylation apparently proceeds on 1-position of thimine base. The analogy of the $^1$H-NMR spectra of the product 8a-d and 9 suggests that the reaction occurs at 1-position of the pyrimidine bases.[10]




8a 10a 11a (3)

In contrast with the primidine bases, the silylated 6-piperidinopurine[11] did not react with 1 under the above reaction conditions. In order to increase the nucleophilicity of the base, the purine base was converted to the zinc salt 12. To a dichlorometnane (1 ml) suspension of 6-piperidinopurine (62 mg, 0.31 mmol) and Molecular Sieves 4A (70 mg) was added slowly a 1 mol/l hexane solution of diethylzinc (0.28 ml) at room temperature and the mixture was stirred for 1 h. This suspension was treated with 1 (59 mg, 0.165 mmol) and TMSOTf(90 mg, 0.41 mmol) at -23 °C for 17 h to yield the desired purine nucleoside 13 in 78% yield with the ratio of 23/77 (α/β) as shown in Eq. 4. The purine nucleoside 13 was oxdized to the corresponding sulfone with $NaIO_4$-$RuCl_3$. Then, the anomeric configuration and the ratio of the α and β isomers were determined by the coupling pattern and the integration of anomeric proton.[12]




12 1 13 (4)

As mentioned, the β-selective 2-deoxyribonucleoside synthesis was achieved by using the remote neighboring effect of 2-(methylsulfinyl)ethyl group on the 3-hydroxyl group. By this method, various β-nucleosides are prepared in good selectivity without the separation of anomeric isomers of the 1-acetoxy-2-deoxyribose.

References

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10) In $^{1}$H-NMR spectra of the sulfone derivatives 8a-d and 9 from 4a-d and 7, 1-α-protons appear at δ 8a, 6.32 ppm; 8b, 6.28 ppm; 8c, 6.28 ppm; 8d, 6.17 ppm; 9, 6.24 ppm. If the glycosylation occurred at 3-position of the primidine base, the chemical shift of the anomeric proton would shift downfield up to 1 ppm.[13]
11) The silylated purine was prepared as follows. The purine was heated under reflux in hexamethyldisilazane with a catalytic amount of ammonium sulfate until a clear solution was achieved. Then, the solvent was removed in vacuo and the residue was used without further purification. 6-Piperidinopurine was prepared from hypoxanthine according to the literature.[14]
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