CHEMISTRY LETTERS, pp. 1187-1190, 1993.

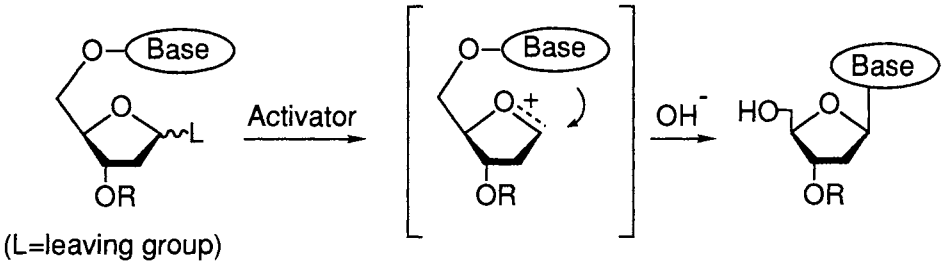
Stereocontrolled Synthesis of β-D-2'-Deoxyribonucleosides by Intramolecular Glycosylation

Keiko SUJINO and Hideyuki SUGIMURA*
The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo 173

Intramolecular glycosylation of phenyl 2-deoxy-5-*O*-(2-pyridyl)- and 2-deoxy-5-*O*-(4-methoxy-2-pyrimidyl)-1-thio-D-ribofuranoside by activation with dimethyl(methylthio)sulfonium tetrafluoroborate followed by hydrolysis gave the corresponding β-2'-deoxyribonucleoside derivatives in good yields.

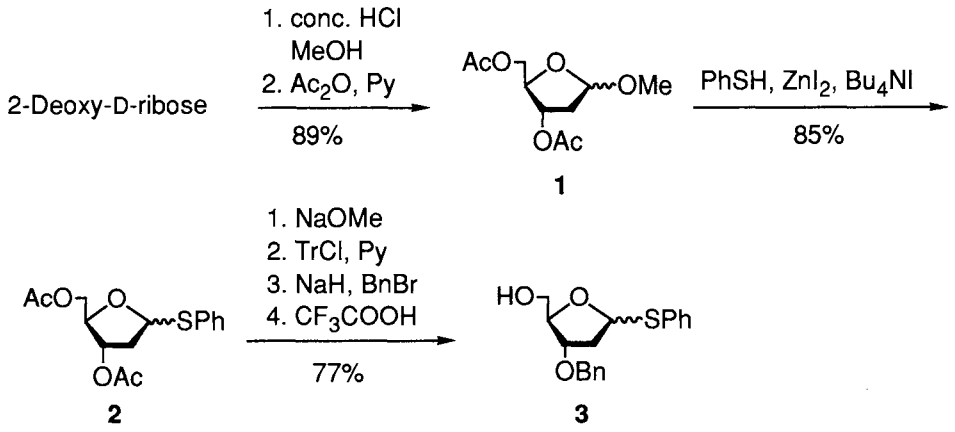
Since sugar modified β-2'-deoxyribonucleosides are expected to exhibit clinically important biological activities (e. g. 3'-azido-3'-deoxythymidine and 2',3'-dideoxy-3'-fluoro nucleosides),[1] many efforts have been made on the development of synthetic methods for these derivatives. The condensation of a sugar moiety and a nucleoside base is one of the most simple ways to construct the skeleton of nucleoside derivatives. However, the Vorbrüggen reaction, most commonly used for coupling sugar and nucleoside base, employing 2-deoxy sugars usually results in the formation of both α and β anomers.[2] Although the SN2 type reaction using 1-chloro-2-deoxy-3,5-di-*O*-toluoyl-α-D-ribofuranose provides a selective route to β-2'-deoxynucleosides,[3] the applicability of this procedure to other modified 2-deoxy sugars is limited because the corresponding α-chloro sugars are not always obtained selectively.

As part of our continuing efforts to develop a general method for β-selective formation of 2'-deoxynucleosides,[4] we planned the glycosylation of the nucleoside base utilizing the C-4 configuration of the glycosyl donor. Scheme 1 illustrates our intramolecular glycosylation strategy, which originated from a recently introduced concept for stereocontrolled glycosylation by several research groups.[5] Namely, the nucleoside base is initially introduced at the 5-position of the glycosyl donor. After activation of the anomeric position, the nucleoside base will be delivered to the resulting oxonium ion from the β-face to produce the β-*N*-glycoside solely. Although there have been some reports concerning the intramolecular *N*-glycosylation reaction,[6] they seem not to be suitable for the direct synthesis of β-D-2'-deoxyribonucleosides. A recent publication regarding a similar approach by Jung and Castro[7] prompted us to report our preliminary findings.



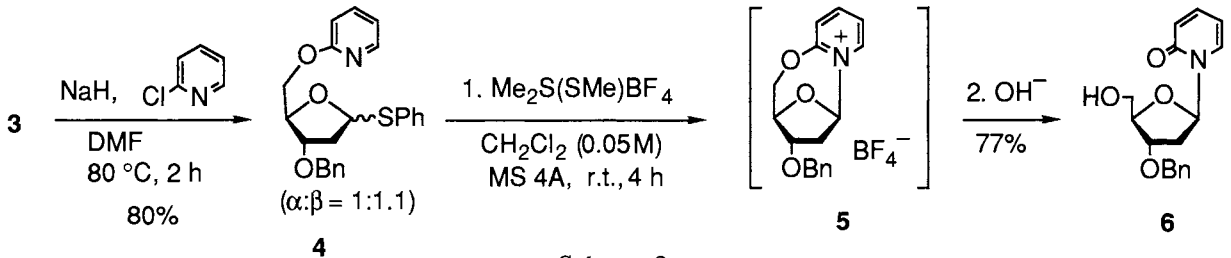
Scheme 1.

We have already revealed that thioglycosides are efficient glycosyl donors in several situations of nucleoside synthesis.[4, 8] In addition, they are easily prepared from the corresponding methyl glycosides, stable under a variety of protection and deprotection conditions, and capable of selective activation at the anomeric carbon under mild conditions. Therefore, we chose thioglycoside **3** as a substrate of the intramolecular glycosylation and prepared it as follows (Scheme 2). 2-Deoxy-D-ribose was transformed to the methyl glycoside **1** in good yield in the usual manner. Then the phenylthio group was introduced at the anomeric position by a modification of Hanessian's method.[9] After deacetylation of **2**, the hydroxy group at C-3 was selectively benzylated in three steps to afford **3** in totally good yield.



Scheme 2.

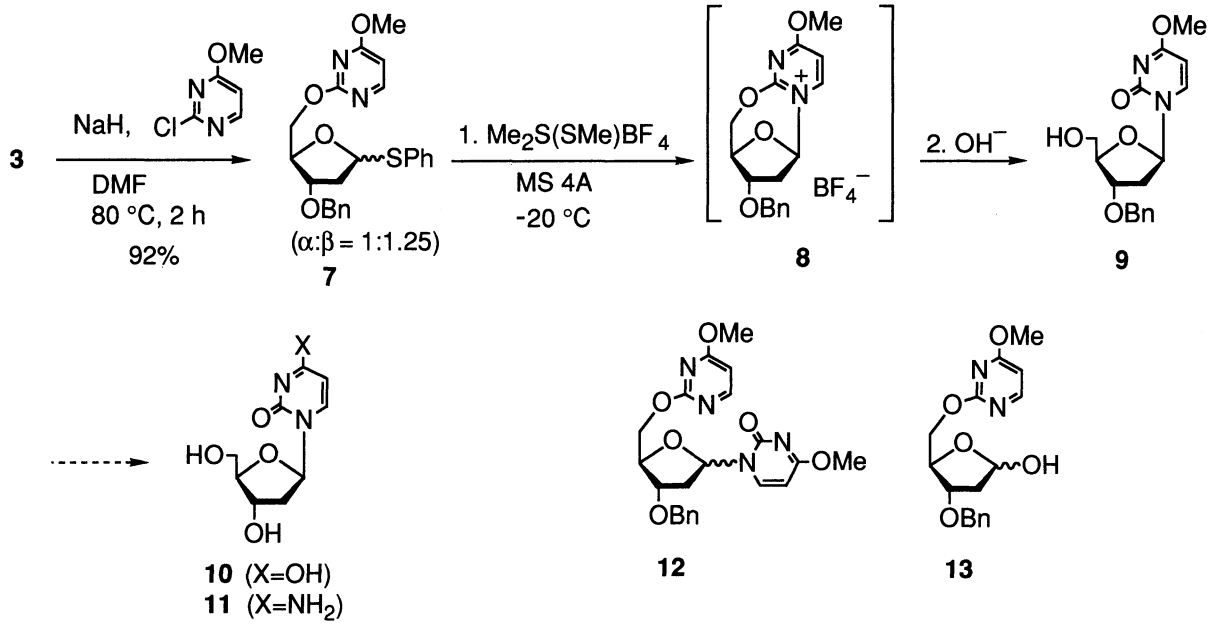
Intramolecular *N*-glycosylation was initially investigated using 2-chloropyridine as a model reaction (Scheme 3). The introduction of the 2-pyridyl group at the 5-position of thioglycoside **3** was achieved using sodium hydride and 2-chloropyridine in DMF to give **4** in 80% yield. Activation of **4** with 1.1 equiv. of *N*-bromosuccinimide at -20 °C to r.t. in dichrolomethane followed by basic hydrolysis led to formation of many unidentified products. A solution to this problem was found by using sulfonium ion as the activator. When **4** was treated with 1.1 equiv. of dimethyl(methylthio)sulfonium tetrafluoroborate in dichloromethane at r.t. in the presence of MS 4A, a fine precipitate, probably the pyridinium salt **5**, was observed. After stirring for 4 h, a saturated aqueous solution of sodium carbonate was added to the reaction mixture and stirring was continued overnight to provide β-*N*-glycoside **6**[10] in 77% yield.



Scheme 3.

Next, we applied this methodology to the synthesis of pyrimidine nucleosides (Scheme 4). 2-Chloro-4-methoxypyrimidine, which was prepared from 2, 4-dichloropyrimidine by a reported procedure[11] in 90% yield, was allowed to react with **3** in the same manner as described above, affording **7** in 92% yield. Then **7**

was treated with 1.1 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate under several reaction conditions as summarized in Table 1. Under conditions similar to those described in the reaction of **4**, the desired β-nucleoside **9**[12] was obtained in only moderate yield due to by-products **12** and **13** (entry 1). Although the formation of **12** was suppressed by lowering the concentration, the yield of **13** was increased (entry 2). This problem was overcome by the use of acetonitrile as solvent instead of dichloromethane. Furthermore, by performing the hydrolysis with 1M NaOH the yield of **9** was improved to 82% (entry 4). Product **9** can be easily transformed to the 2'-deoxyuridine **10** or 2'-deoxycytidine **11** by removal of the 3'-*O*-benzyl group and hydrolysis or ammonolysis of the 4-methoxy group respectively.[12]



Scheme 4.

Table 1. Synthesis of **9** from **7**

Entry	Reaction Conditions		Hydrolysis Conditions	Yields/%		
	Solvent (Concentration/M)	Time		**9**	**12**	**13**
1	CH_2Cl_2 (0.05)	195 min	sat. Na_2CO_3, r.t., overnight	47	13	15
2	CH_2Cl_2 (0.004)	5 h	sat. Na_2CO_3, r.t., overnight	48	trace	33
3	CH_3CN (0.004)	5 h	sat. Na_2CO_3, r.t., overnight	71	trace	5
4	CH_3CN (0.004)	5 h	1M NaOH, 0 °C, 2.5 h	82	trace	4

M=mol·dm^{-3}

In conclusion, an efficient method for the stereocontrolled synthesis of β-2'-deoxyribonucleosides derivatives utilizing intramolecular *N*-glycosylation reaction was described. The application of this methodology to the synthesis of β-2', 3'-dideoxynucleosides and some base modified β-2'-deoxynucleosides are now in progress in our laboratory and will be published in due course.

We are deeply grateful to professor Teruaki Mukaiyama, Science University of Tokyo, for many helpful discussions.

References

1) For recent reviews: E. DeClercq, *J. Antimicrob. Chemother.*, **23** Suppl. A, 35 (1989); G. D. Diana, D. Pevear, and D. C. Young, *Ann. Rep. Med. Chem.*, **24**, 129 (1989); E. DeClercq, *Antiviral Res.*, **12**, 1 (1989); E. DeClercq, *Trends Pharm. Sci.*, **11**, 198 (1990); D. W. Norbeck, *Ann. Rep. Med. Chem.*, **25**, 149 (1990).

2) H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.* **114**, 1234 (1981).

3) H. Aoyama, *Bull. Chem. Soc. Jpn.*, **60**, 2073 (1987); Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, *J. Am. Chem. Soc.*, **106**, 6379 (1984).

4) H. Sugimura, K. Sujino, and K. Osumi, *Tetrahedron Lett.*, **33**, 2515 (1992); K. Sujino and H. Sugimura, *Synlett*, **1992**, 553.

5) F. Barresi and O. Hindsgaul, *J. Am. Chem. Soc.*, **113**, 9376 (1991); G. Stork and G. Kim, *J. Am. Chem. Soc.*, **114**, 1087 (1992); M. Bols, *J. Chem. Soc., Chem. Commun.*, **1992**, 913; F. Barresi and O. Hindsgaul, *Synlett*, **1992**, 759.

6) L.-Y. Hsu, D. S. Wise, L. S. Kucera, J. C. Drach, and L. B. Townsend, *J. Org. Chem.*, **57**, 3354 (1992); Y. Yoshimura, A. Matsuda, and T. Ueda, *Chem. Pham. Bull.*, **37**, 660 (1989); T. Ueda, A. Matsuda, Y. Yoshimura, and K. Takenuki, *Nucleosides & Nucleotides*, **8**, 743 (1989); Y. Mizuno, C. Kaneko, and Y. Oikawa, *J. Org. Chem.*, **39**, 1440 (1974); H. I. E. Subbagh, L.-J. Ping, and E. Abushanab, *Nucleosides & Nucleotides* **11**, 603 (1992).

7) M. E. Jung and C. Castro, *J. Org. Chem.*, **58**, 807 (1993).

8) H. Sugimura, K. Osumi, T. Yamazaki, and T. Yamaya, *Tetrahedron Lett.*, **32**, 1813 (1991); H. Sugimura, I. Muramoto, T. Nakamura, and K. Osumi, *Chem. Lett.*, **1993**, 169.

9) S. Hanessian and Y. Guindon, *Carbohydr. Res.*, **86**, C3 (1980).

10) ^{1}H NMR(400 MHz) data ($CDCl_3$): δ=2.48-2.59(m, 2H), 3.35(br, 1H), 3.76(d, 1H, *J*=9.8 Hz), 3.95(d, 1H, *J*=11.7 Hz), 4.24(dd, 1H, *J*=2.9, 6.4 Hz), 4.34(ddd, 1H, *J*=2.9, 3.4, 6.4 Hz), 4.52(d, 1H, *J*=11.7 Hz), 4.59(d, 1H, *J*=11.7 Hz), 6.19(t, 1H, *J*=6.5 Hz), 6.22(dt, 1H, *J*=6.5, 6.5, 0.86 Hz), 6.53(d, 1H, *J*=9.3 Hz), 7.26-7.38(m, 6H), 7.55(d, 1H, *J*=6.8 Hz).

11) A. R. Katritzky, G. Baykunt, S. Rachwal, M. Szafran, K. C. Caster, and J. Eyler, *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1499.

12) ^{1}H NMR(400 MHz) data ($CDCl_3$): δ=2.32(dd, 1H, *J*=6.3, 13.7 Hz), 2.58(ddd, 1H, J=3.2, 6.1, 13.7 Hz), 3.54(br, 1H), 3.75(dd, 1H, *J*=10.0, 20.3 Hz), 3.92(d, 3H, *J*=2.4 Hz), 3.93(dd, 1H, *J*=6.4, 19.0 Hz), 4.21(dd, 1H, *J*=2.9, 5.9 Hz), 4.29(dt, 1H, *J*=3.1, 3.1, 6.1 Hz), 4.49(d, 1H, *J*=11.7 Hz), 4.57(d, 1H, *J*=11.7 Hz), 5.91(d, 1H, *J*=7.3 Hz), 6.16(t, 1H, *J*=6.6 Hz), 7.26-7.36(m, 5H), 8.00(t, 1H, *J*=6.8 Hz).

13) For example: A. Matsuda, K. Takenuki, T. Sasaki, and T. Ueda, *J. Med. Chem.*, **34**, 234 (1991).

(Recieved April 16, 1993)