# NUCLEOSIDE SYNTHESIS FROM FURANOID GLYCALS

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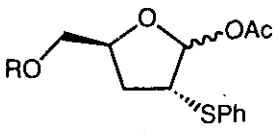
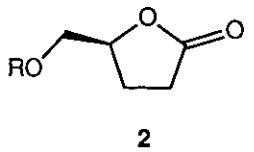
Abstract --- Reaction of furanoid glycals with PhSCl afforded 1-chlorosugars, which were used for condensation reaction with silylated uracil in the presence of $SnCl_4$. These two reactions proceeded in a highly stereoselective manner.

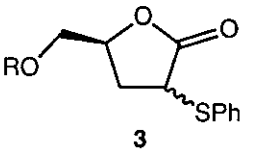
2',3'-Dideoxynucleosides and 2',3'-didehydro-2',3'-dideoxynucleosides are known to be active compounds against HIV, which causes AIDS.[1] To prepare these nucleosides, we have focused on the stereoselective condensation reaction between sugars and nucleic bases, since this reaction can be used to synthesize a wide variety of structurally related compounds.[2-5] In the course of this study, we have clarified the effect of the phenylthio group on sugar C-2 as a stereocontrolling element.[3,4] The condensation reaction between 2-α-phenylthio-2,3-dideoxyribose (**1**) and silylated pyrimidine bases in the presence of $SnCl_4$ as a catalyst afforded the anomeric mixture of nucleosides in a ratio of $\alpha : \beta = 1 : 9$. The phenylthio group on the sugar moiety was used as a hand hold to introduce the carbon-carbon double bond of 2',3'-didehydro-2',3'-dideoxynucleosides. This method, however, has a serious disadvantage. The stereoselectivity of the phenylsulfenylation of γ-lactone




**1**

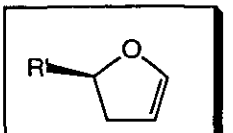



**2**




**3**

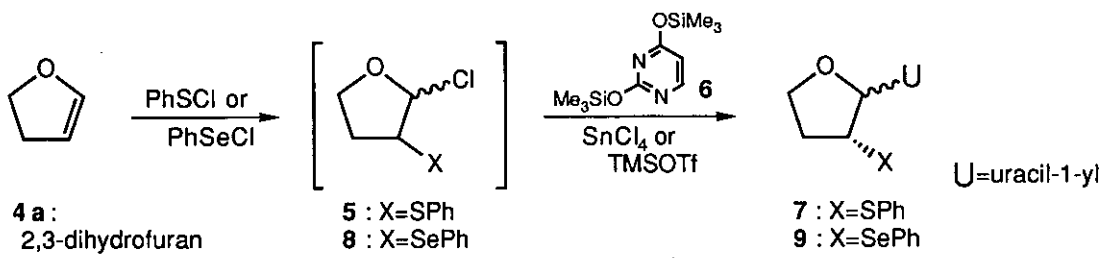
R=*tert*-$BuPh_2Si$-




**4a** : R'=H
**4b** : R'=$ROCH_2$-

(2) to **3**, which is the starting material for **1**, is rather low (*trans* : *cis* = 2 : 1).[3,4,6] In recent years, there have been reported some instances in which the electrophilic sulfenylation reaction of glycals was used directly for the *O*-glycosylation reaction.[7] In this paper, we report a novel and stereoselective condensation reaction between silylated uracil and furanoid glycals (**4**) by the aid of benzenesulfenyl chloride (PhSCl).[8]

There have been two reports concerning the reaction of furanoid glycals with PhSCl used for the carbon-carbon bond formation.[9] In both cases, the existence of chlorotetrahydrofuran (similar to **5**) was assumed. As **5** could be considered the equivalent of 2-phenylthio sugar (**1**), we at first examined the condensation reaction between **5** and silylated uracil (**6**). After 2,3-dihydrofuran (**4a**) was treated with PhSCl at -50°C for 30 min to generate **5** *in situ*,[9b] **5** was subjected to reaction with **6** in the presence of $SnCl_4$ as a catalyst at 0°C for 2 h. The condensation products (**7**) were isolated in the ratio of *trans* : *cis* = 99 : 1 in 80% yield (Scheme 1). Although we have not determined the diastereomeric ratio of **5**, *trans* isomer is thought to be the major isomer when the reaction mechanism is taken into account. It was also supported that the condensation reaction without $SnCl_4$ proceeded to give **7** in the ratio of *trans* : *cis* = 15 : 85 (82% yield), under which conditions 1-chlorosugars react with **6** in $S_N2$ mode.[2,10]




**4a**: 2,3-dihydrofuran

**5** : X=SPh
**8** : X=SePh

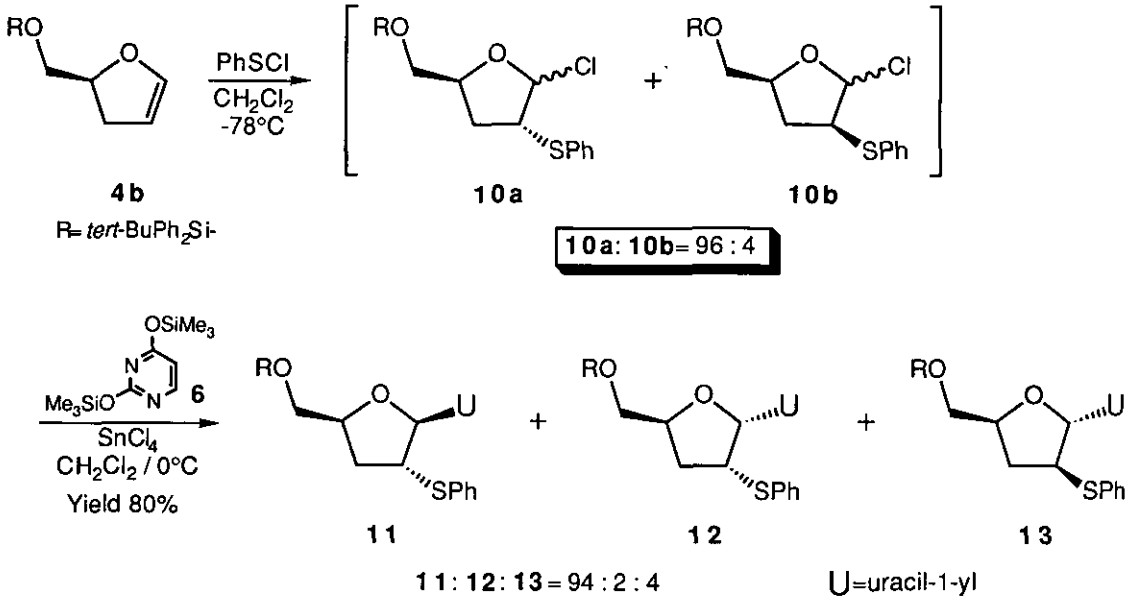
**7** : X=SPh
**9** : X=SePh

**Scheme 1.**

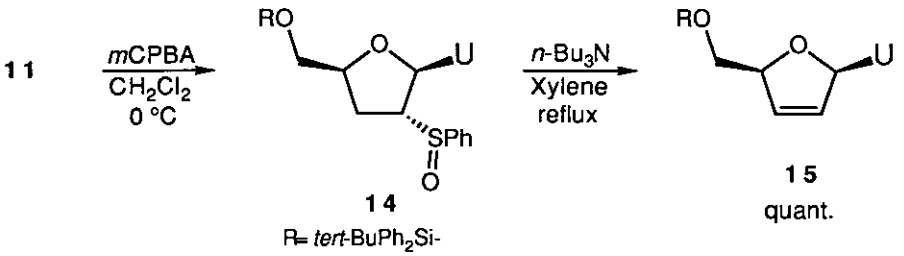
**4a** was also reported to react with PhSeCl to yield **8**.[9a] We examined the condensation reaction of **8** with **6** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) or $SnCl_4$ as a catalyst, since the phenylselenyl group on sugar C-2 was useful as the stereocontrolling element.[5] In the reaction with **8**, better stereoselectivity was achieved in the presence of $SnCl_4$ (*trans* : *cis* = 98 : 2) than with TMSOTf (*trans* : *cis* = 85 : 15). In both cases, however, the yields of the condensation products (**9**) were not as good (up to 38%) as those for

the reaction with PhSCl. This results could be attributed to the more radical character of PhSeCl than PhSCl, which caused the various side reactions.[7c]

As a new route for nucleosides from **4a** was at hand, we turned our attention to the stereoselectivity of the reaction with the substituted glycal (**4b**).[11] The condensation reaction between silylated uracil (**6**) and substituted 1-chlorosugar (**10**),[12] which was prepared *in situ* from **4b** and PhSCl, was performed under the same conditions as those for **4a**. Three stereoisomers (**11** - **13**) were obtained, as indicated in Scheme 2. The ratio was determined by hplc, and the stereochemistry of each was determined by comparison with the samples previously prepared from **1** and its β-phenylthio isomer.[3] It was pointed out by the ratio of **11** to **12** that stereo-selectivity in the condensation reaction between **10a** and **6** was as much high as that with 1-chlorosugar (**5**) derived from **4a** ($\alpha : \beta = 2 : 98$). It was also revealed that electrophilic addition of PhSCl to **4b** proceeded unexpectedly in a highly stereoselective manner (**10a** : **10b** = 96 : 4) when the ratio of **13** was compared to the sum of those of **11** and **12**. The latter selectivity was not strongly affected by the reaction temperature. In fact, the mixture of **11** - **13** was obtained in similar ratio when the addition step of PhSCl was carried out at 0°C (**11** : **12** : **13** = 94 : 3 : 3).




**Scheme 2.**




**Scheme 3.**

After purification with hplc, β-nucleoside (**11**) was converted to protected 2',3'-didehydro-2',3'-dideoxyuridine (**15**) by oxidation with *m*CPBA followed by thermal elimination of benzenesulfenic acid (Scheme 3).[3,4] In conclusion, a novel and stereoselective route for the 2-phenylthionucleosides was established. In this route, a key step is the electrophilic addition of PhSCl to furanoid glycals. Condensation reaction with other nucleic bases is now underway.

REFERENCES AND NOTES

1. H. Mitsuya and S. Broder, Proc. Natl. Acad. Sci. USA, 1986, 83, 1911; J. Balzarini, G.-J. Kang, H. Dalal, P. Herdwijn, E. De Clercq, S. Broder, and D. G. Johns, Mol. Pharmacol., 1987, 32, 162; T. S. Lin, R. F. Schinazi, M. S. Chen, E. K.-Thomas, and W. H. Prusoff, Biochem. Pharmacol., 1987, 36, 311; Y. Hamamoto, H. Nakashima, T. Matsui, A. Matsuda, T. Ueda, and N. Yamamoto, Antimicrob. Agents Chemother., 1987, 31, 907; T. S. Lin, R. F. Schinazi, and W. H. Prusoff, Biochem. Pharmacol., 1987, 36, 2713.
2. H. Kawakami, T. Ebata, K. Koshi, K. Matsumoto, H. Matsushita, Y. Naoi, and K. Itoh, Heterocycles, 1990, 31, 2041.
3. H. Kawakami, T. Ebata, K. Koshi, H. Matsushita, Y. Naoi, and K. Itoh, Chem. Lett., 1990, 1459; H. Kawakami, T. Ebata, K. Koshi, K. Matsumoto, H. Matsushita, Y. Naoi, and K. Itoh, Heterocycles, 1991, 32, 2451.
4. L. J. Wilson and D. Liotta, Tetrahedron Lett., 1990, 31, 1815.
5. C. K. Chu, J. R. Babu, J. W. Beach, S. K. Ahn, H. Huang, L. S. Jeong, and S. J. Lee, J. Org. Chem., 1990, 55, 1418; C. K. Chu, J. W. Beach, J. R. Babu, L. S. Jeong, H. K. Jeong, S. K. Ahn, Q. Islam, S.

J. Lee, and Y. Chen, Nucleosides, Nucleotides, 1991, 10, 423; J. W. Beach, H. O. Kim, L. S. Jeong, S. Nampalli, Q. Islam, S. K. Ahn, J. R. Babu, and C. K. Chu, J. Org. Chem., 1992, 57, 3887.

6. L. J. Wilson and D. Liotta, J. Org. Chem., 1992, 57, 1948.
7. (a) Y. Itoh and T. Ogawa, Tetrahedron Lett., 1987, 28, 2723; (b) R. Preuss and R. R. Schmidt, Synthesis, 1988, 694; (c) Y. Itoh and T. Ogawa, Tetrahedron, 1990, 46, 89; (d) G. Jaurand, J.-M. Beau, and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 1981, 572; G. Grewal, N. Kaila, and R. W. Franck, J. Org. Chem., 1992, 57, 2084.
8. Similar approach from furanoid glycal was reported very recently; C. U. Kim and P. F. Misco, Tetrahedron Lett., 1992, 33, 5733.
9. (a) R. P. Alexander and I. Paterson, Tetrahedron Lett., 1983, 24, 5911; (b) M. A. Ibragimov, M. I. Lazareva, and W. A. Smit, Synthesis, 1985, 880.
10. A. J. Hubbard, A. J. Jones, and R. T. Walker, Nucleic Acids Res., 1984, 12, 6827.
11. A. Takle and P. Kocienski, Tetrahedron, 1990, 46, 4503.
12. The numbering system in this paper is based on that for the sugar system, except for 2,3-dihydrofuran (**4a**).

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