NUCLEOSIDE SYNTHESIS FROM FURANOID GLYCALS

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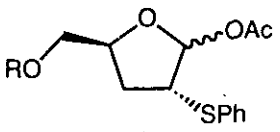
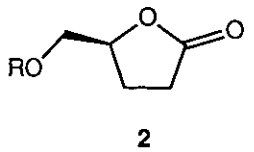
Abstract --- Reaction of furanoid glycals with PhSCl afforded 1-chlorosugars, which were used for condensation reaction with silylated uracil in the presence of $SnCl_4$. These two reactions proceeded in a highly stereoselective manner.

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



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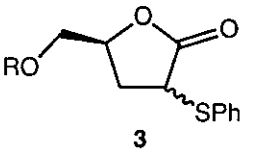
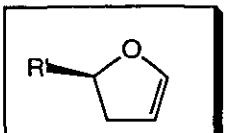


3

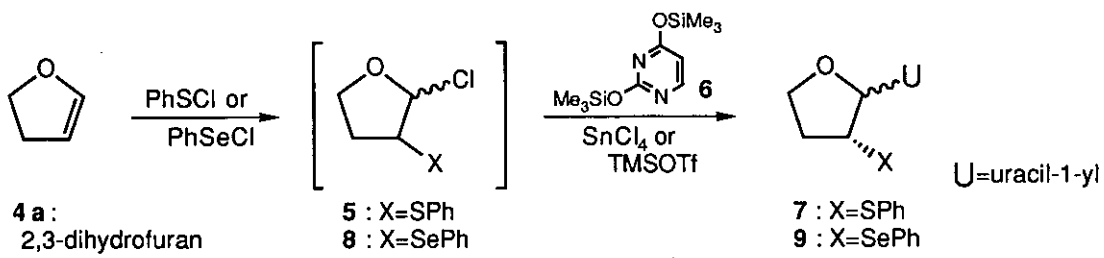
R=*tert*-$BuPh_2Si$-



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

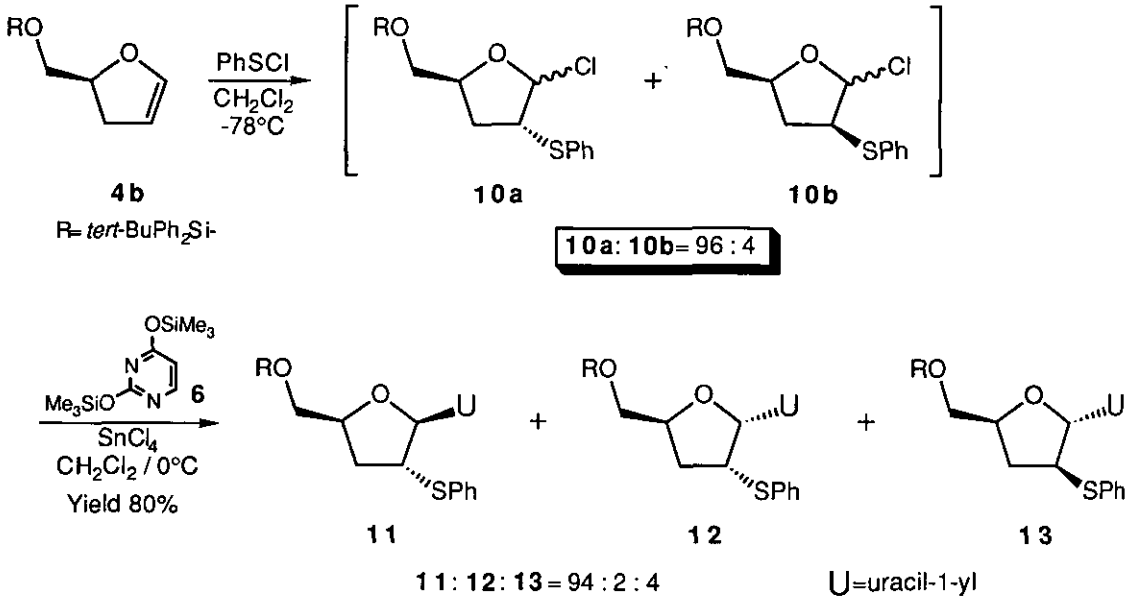
7 : X=SPh
9 : X=SePh

Scheme 1.

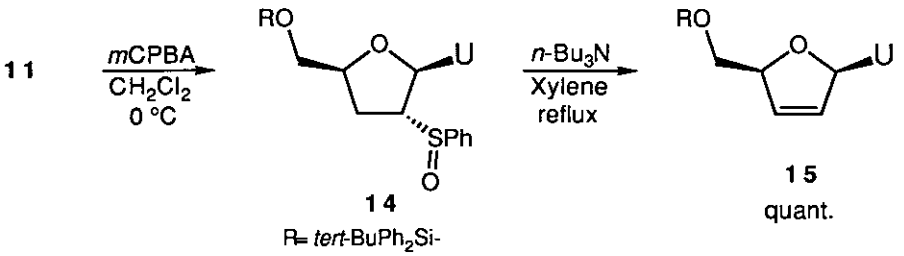
4a was also reported to react with PhSeCl to yield **8**.[9a] We examined the condensation reaction of **8** with **6** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) or $SnCl_4$ as a catalyst, since the phenylselenyl group on sugar C-2 was useful as the stereocontrolling element.[5] 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.

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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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