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# Stereoselectivity in the Coupling Reaction between 2-Phenylthio-2,3-dideoxyribose and Silylated Pyrimidine Bases

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Coupling reaction between 2-α-phenylthio-2,3-dideoxyribose and silylated pyrimidine bases in the presence of $SnCl_4$ proceeded stereoselectively to give the β-anomers. These nucleosides were converted to 2',3'-dideoxy-2',3'-didehydro-nucleosides by oxidation followed by thermal elimination.

In recent years, nucleoside analogues have attracted much attention because of their biological activities. As they are a convenient starting point for the preparation of so many kinds of derivatives, the stereoselective coupling reaction between sugars and nucleic bases are useful. In general, the selectivities are low when there is no substituent group at 2-position of the sugar. On the other hand, it is also well known that the glycosidation reactions to form 1,2-trans configuration are highly stereoselective when the neighboring effect, for example acyloxonium ion intermediate, is expected. In connection with our studies to prepare 2'-deoxynucleosides utilizing stereoselective coupling reaction,[1] we have been interested in the 2-organothio group of the sugar because of its ability to cause the neighboring effect and because it is easy to remove. Here we report the stereo-selectivity in the coupling reaction with 2-phenylthiosugar.[2]

2-α-Phenylthio-2,3-dideoxyribose **1** was prepared as follows. γ-Lactone **3**, which had been conveniently prepared from levoglucosenone (**2**),[3] was phenysulfenylated.[4] Then, after reduction of the desired lactone **4** by DIBAL-H, it was acetylated. At first, the stereoselectivity was examined with silylated uracil (**5a**). The ratios of anomers were determined by $^1$H-NMR analysis after the purification with preparative TLC, and the assign-ment of anomers was finally made by converting to the known 2',3'-dideoxy-2',3'-didehydrouridine (*vide infra*).[5] These results were summarized in Table 1. The selectivity of this sugar cation, generated by trimethyl-silyl trifluoromethansulfonate (TMSOTf),[6] was in the ratio α : β =21:79 (entry 1). Higher selectivity was obtained when the reaction was conducted in more polar solvent, that is acetonitrile (entry 2). If phenylthio group caused the neighboring effect in forming the intermediate (**7a**),[7] the difference of selectivities may be explained because the formation of **7a** was not so rapid, and the longer lifetime of sugar cation in a polar solvent made a greater contribution of **7a**. On the other hand, the $SnCl_4$ catalyzed coupling reaction[8] proceeded with greater stereoselectively to give the ratio α : β =3:97 (entry 4). As the $SnCl_4$ can be expected to coordinate at the sulfur atom to form **7b**, the steric hindrance of this metal may, in this case, raise the β-selectivity. It seems interesting

Table 1. The coupling reactions between sugar **1** and silylated uracil (**5a**) in the presence of Lewis acids[a)]

| Entry | Catalyst(equiv.) | Solvent | Yield/%[b)] ($\alpha$ + $\beta$) | Stereoselectivity[c)] ($\alpha$ : $\beta$) |
|---|---|---|---|---|
| 1 | TMSOTf(0.2) | $ClCH_2CH_2Cl$ | 90 | 21 : 79 |
| 2 | TMSOTf(0.2) | $CH_3CN$ | 96 | 11 : 89 |
| 3 | $TiCl_4$(6.0) | $ClCH_2CH_2Cl$ | 65 | 15 : 85 |
| 4 | $SnCl_4$(6.0) | $ClCH_2CH_2Cl$ | 96 | 3 : 97 |
| 5[d)] | $SnCl_4$(1.8) | $ClCH_2CH_2Cl$ | 91 | 7 : 93 |

a) Coupling reactions were carried out under following conditions; 0.10 mmol scale, **1**:**5a**=1:5, in 2 ml solvent, room temperature.

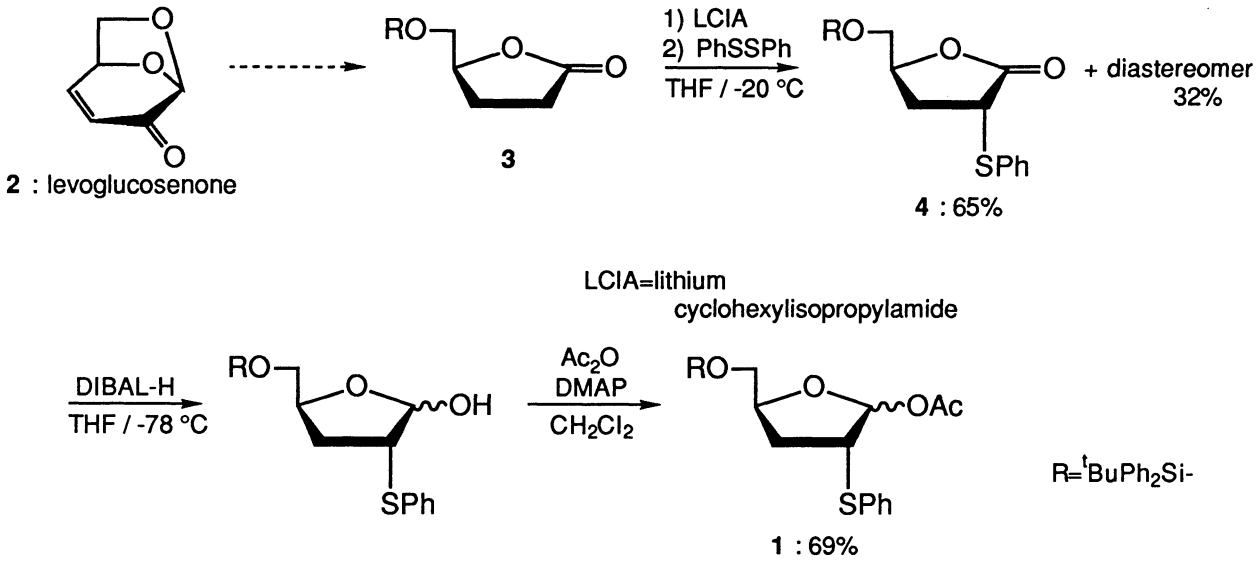
b) Isolated yields (preparative TLC).

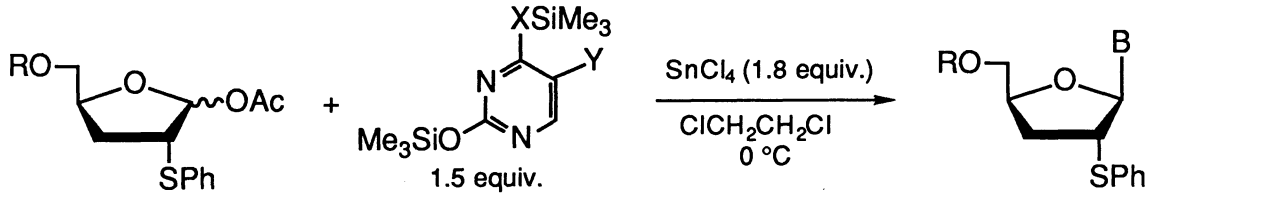
c) Determined by $^1$H-NMR.

d) Reaction conditions; 3.0 mmol scale, **1**:**5a**=1:1.5, in 20.5 ml solvent, 0 °C.

because, as reported by Nicolaou, the formation of the 2-phenylthiopyranose-$SnCl_4$ complex (like **7b**) prevented the formation of episulfonium ions (like **7a**), and changed the selectivity.[7)] Other pyrimidine bases were also subjected to these reaction conditions, and good stereoselectivities were similarly obtained (**6b**: yield 87% $\alpha$ : $\beta$=8:92; **6c**: yield 93% $\alpha$ : $\beta$=11:89).

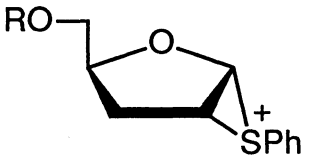
As the nucleosides **6** functionalized at 2'-position were obtained in good stereoselectivity, we turned our attention to converting them to 2',3'-dideoxy-2',3'-didehydronucleosides **8**, some of which are considered to be the next-generation anti-AIDS drugs.[9)] Oxidation of sulfides **6** to sulfoxides **9** was performed with 1.05 equivalent of mCPBA in methylene chloride at 0 °C. The crude sulfoxides **9** were subjected to the thermal elimination (reflux in xylene) in the presence of tributylamine or DBU to neutralize the generating sulfinic acid to



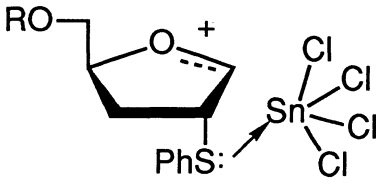



**1**
R=$^t$BuPh$_2$Si-

| | | |
|---|---|---|
| **5a** : X=O ; Y=H | 3.5 h | **6a** : B=U ; 91% ; α : β= 7 : 93 |
| **5b** : X=O ; Y=Me | 4 h | **6b** : B=T ; 87% ; α : β= 8 : 92 |
| **5c** : X=NAc ; Y=H | 4 h | **6c** : B=C$^{Ac}$ ; 93% ; α : β=11 : 89 |

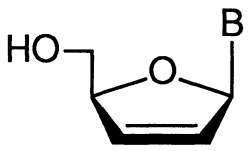



**7a**

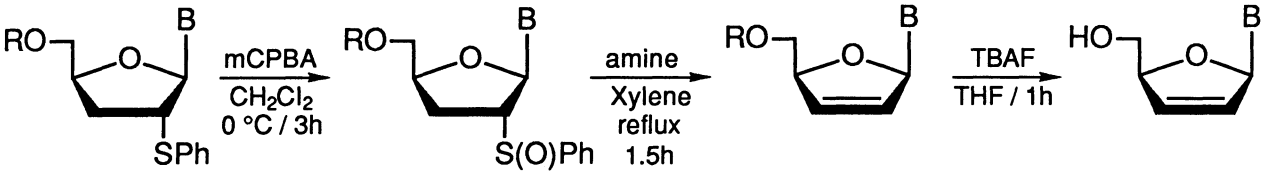



**7b**

give the protected 2',3'-dideoxy-2',3'-didehydronucleosides **10**. The moderate yield (56%) in the case of **9c** was caused by the instability of **9c** or **10c**, which was cleaved at the glycosyl bond to form the $^4$N-acetylcytosine. Deprotection with tetrabutylammonium fluoride gave the desired nucleosides **8**.[10]




**8**
2',3'-dideoxy-2',3'-didehydronucleoside




| | | | |
|---|---|---|---|
| **6a** : B=U | **9a** : B=U | **10a** : B=U ; 100% | **8a** : B=U ; 95% |
| **6b** : B=T | **9b** : B=T | **10b** : B=T ; 85% | **8b** : B=T ; 100% |
| **6c** : B=C$^{Ac}$ | **9c** : B=C$^{Ac}$ | **10c** : B=C$^{Ac}$ ; 56% | **8c** : B=C$^{Ac}$ ; 67% |

R=$^t$BuPh$_2$Si-

In conclusion, the coupling reaction between 2-phenythio-2,3-dideoxyribose and silylated pyrimidine bases proceeded stereoselectively when the reactions were catalyzed by $SnCl_4$. In these cases, the phenylthio-group was thought to be coordinated to $SnCl_4$, and to be blocked at its side. We also demonstrated that these

nucleosides, obtained by this coupling reaction, are versatile materials for the preparation of 2',3'-dideoxy-2',3'-didehydronucleosides. We are now investigating the conversions of these 2'-phenylthionucleosides to other useful ones.

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