Nucleic Acids Symposium Series No. 51 143–144
doi:10.1093/nass/nrm072

Additive Pummerer reaction of 3,5-*O*-(di-*t*-butylsilylene)-4-thio-furanoid glycal and stereoselective synthesis of β-anomer of 4'-thioribonucleosides

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ABSTRACT

Upon reacting 3,5-*O*-(di-*t*-butylsilylene) (DTBS)-4-thiofuranoid glycal *S*-oxide (7) with Ac_2O in the presence of TMSOAc and $BF_3{\cdot}OEt_2$, additive Pummerer reaction proceeded to furnish 1,2-di-*O*-acetyl-3,5-*O*-DTBS-4-thioribofuranose (8) in 61% yield. When 8 was reacted with bis-*O*-TMS-uracil and TMSOTf, 2'-*O*-acetyl-3',5'-*O*-DTBS-4'-thiouridine (13a) was obtained along with it's α-anomer (13b) in 93% yield (13a/13b = 22/1). This highly stereoselective glycosidation reaction was applicable to the synthesis of 14-17. The glycosyl donor 8 was also useful for the synthesis of 4'-thio-*C*-nucleoside 18 and 19. In contrast to the above results, treatment of 8 with TMSCN gave rise to the formation of the spiro derivative 20. To avoid this intramolecular cyclization, 2-*O*-TBDMS-protected 21 was prepared from 8. Bromination of 21 with TMSBr and substitution reaction of the resulting bromide 22 with $Hg(CN)_2$ gave 1'-*C*-cyanide 23.

INTRODUCTION

In 1991, it was reported that the simple replacement of the furanose ring-oxygen with a sulfur atom leads to promising antiviral or antitumor nucleosides such as 4'-thiothymidine (**1**) or 2'-deoxy-4'-thiocytidine (**2**) (Fig. 1). [1)]

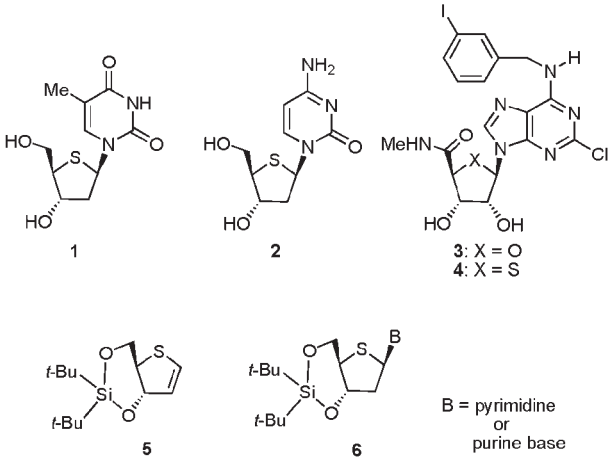

Fig. 1 4'-Thionucleosides.

Recently, it has also been reported that 4'-thio-Cl-IB-MECA (**4**) exhibited higher binding affinity to the human A_3 adenosine receptor than the parent compound **3**. [2)] These discovery has stimulated the synthesis of 4'-thionucleosides. The synthesis of these nucleosides has been carried out by way of Vorbrüggen-type or Pummerer-type glycosidation. A major drawback of these methods is the lack of β-stereoselectivity that is crucial for these 4'-thionucleosides to be active.

We have already reported a highly β-selective entry to 2'-deoxy-4'-thionucleoisides (**6**) based on an electrophilic glycosidation using **5** as a glycosyl donor. [3)] As a part of the study for 4-thiofuranoid glycal-based synthesis of 4'-thionucleosides, we present herein a novel synthesis of β-anomer of 4'-thioribonucleosides by glycosidation using 1,2-di-*O*-acetyl-3,5-*O*-DTBS-4-thioribofuranose, which is prepared by additive Pummerer reaction of 4-thiofuranoid glycal *S*-oxide .

RESULTS AND DISCUSSION

Reaction of **5** with *m*-CPBA gave the corresponding *S*-oxide **7** in 84% yield. When **7** was reacted with Ac_2O in the presence of TMSOTf, additive Pummerer reaction proceeded to furnish the target 1,2-di-*O*-acetyl-3,5-*O*-DTBS-4-thioribofuranose (**8**) in 20% yield along with 2-*O*-triflate (**9**, 22%). When this reaction was carried out using $SnCl_4$ as a Lewis acid, the desilylated **10** (52%) was the sole product. The use of $BF_3{\cdot}OEt_2$ gave **8** in 23% yield, together with **7** (34%), **11** (27%) and **12** (11%). On the other hand, **8** was obtained in 61% by reacting **7** with $Ac_2O/BF_3{\cdot}OEt_2$/TMSOAc: **11** (3%) and **12** (17%) were also formed.

With the glycosyl donor **8** in hand, we examined Vorbrüggen-type condensation with silylated nucleobase. When **8** was reacted with bis-*O*-TMS-uracil in the presence of TMSOTf in CH_2Cl_2 at 50 °C, the 4'-thiouridine derivative **13a** was formed in a highly stereoselective manner (93%, **13a/13b** = 22/1). Similarly, other pyrimidine nucleosides (**14** and **15**) and purine nucleosides (**16** and **17**) were obtained stereoselectively.

The above β-selective glycosidation using **8** was also used for the synthesis of *C*-nucleosides. Thus, the reaction

of **8** with 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan gave the corresponding 4'-thio-*C*-nucleosides **18** (79%, β-isomer/α-isomer = 23/1) and **19** (61%, β-isomer/α-isomer = 24/1). The reaction of **8** with TMSCN, however, gave a mixture of the spiro-derivatives **20a** and **20b** in 27% and 10%, respectively. To avoid this intramolecular cyclization, the 2-*O*-TBDMS-protected **21** was prepared. Compound **21** was then converted into the bromosugar **22**, which was subjected to the substitution reaction with $Hg(CN)_2$. This gave the 1-*C*-cyanide **23** in 63% yield from **21**. Synthesis of 4'-thiotiazofurin from **23** is now under investigation.

CONCLUSION

Additive Pummerer reaction of 4-thiofuranoid glycal *S*-oxide **7** with $Ac_2O/BF_3{\cdot}OEt_2$/TMSOAc gave 1,2-di-*O*-acetyl-3,5-*O*-DTBS-4-thioribofuranose (**8**) in 62% yield. The thiosugar **8** was found to be useful as a glycosyl donor for the synthesis of β-anomer of 4'-thioribonucleosides **13**-**17**. *C*-glycosidation of **8** also proceeded β-selectively to furnish the 4'-thio-*C*-nucleosides **18** and **19**. The 1-*C*-cyano derivative **23**, expected to serve as a precursor for the synthesis of 4'-thiotiazofurin, was prepared from the 2-*O*-TBDMS-4-thioribofuranose (**21**) to avoid intramolecular cyclization.

ACKNOWLEDGEMENT

Financial supports from Japan Society for the Promotion of Sciences (KAKENHI No. 19590106 to K. H.) are gratefully acknowledged.

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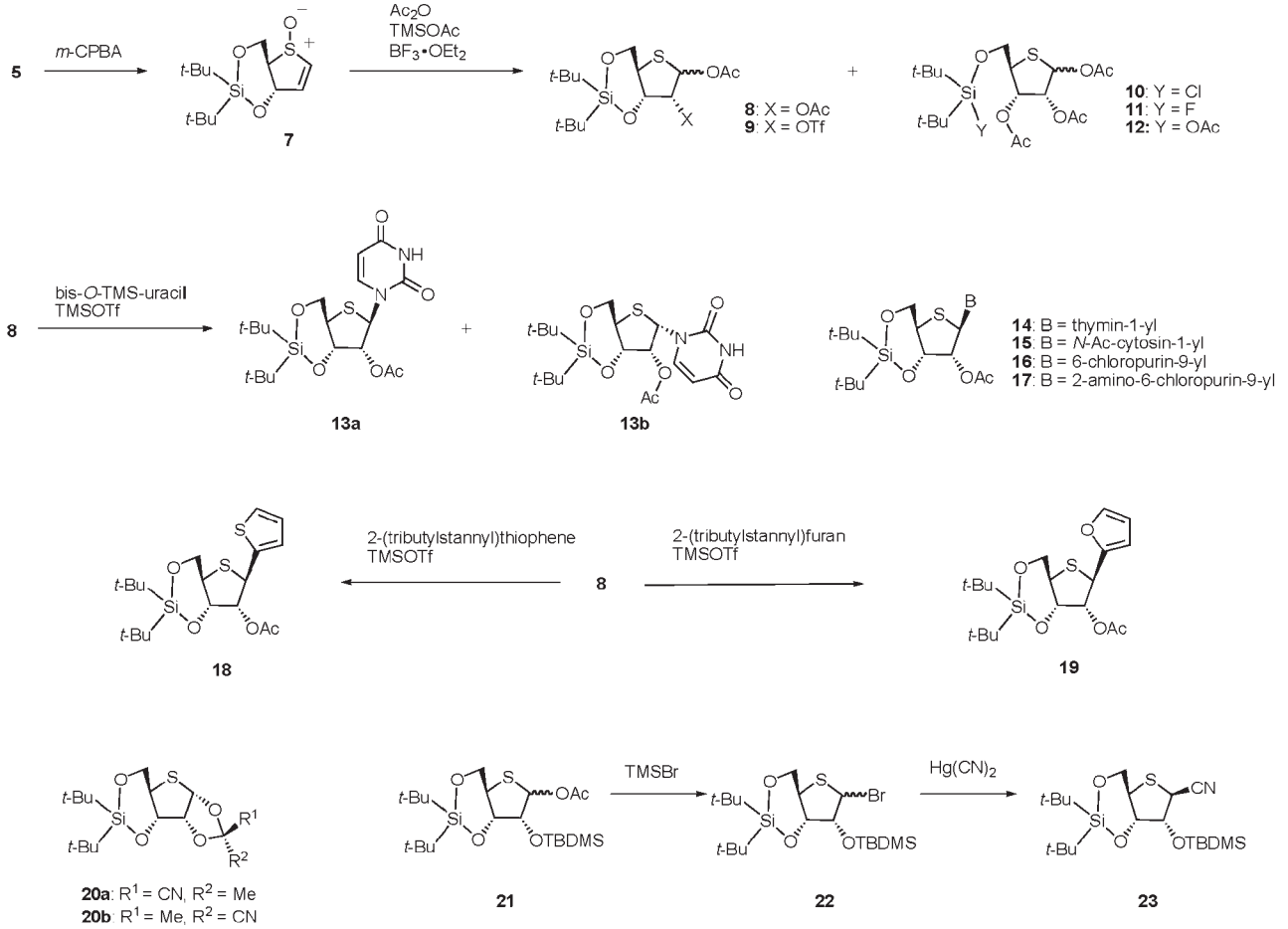

Scheme 1 Additive Pummerer reaction of **7** and synthesis of 4'-thioribonucleosides.