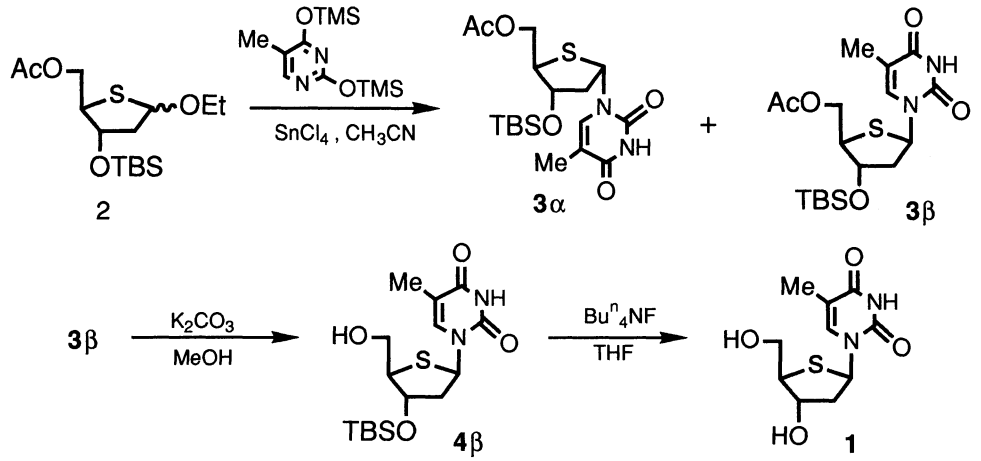
CHEMISTRY LETTERS, pp. 255-256, 1993.

Synthesis and X-Ray Structure of 4'-Thiothymidine

Jun'ichi UENISHI, * Keiji TAKAHASHI, Mitsuhiro MOTOYAMA, and Haruo AKASHI†
Department of Chemistry, Okayama University of Science, Ridaicho Okayama 700
† Analytical Center, Okayama University of Science, Ridaicho Okayama 700

4'-Thiothymidine was synthesized by $SnCl_4$ mediated coupling of 5-O-acetyl-3-O-*tert*-butyldimethylsilyl-2-deoxy-4-thio-D-erythro-pentofuranoside with 2,4-bis(trimethylsilyl)thymine and the structure was determined by X-ray analysis.

A great deal of efforts have been made in finding a new selective and potent nucleic *anti*-metabolite, particularly for the treatment of certain viral infections including AIDS.[1] Among them, 2'-deoxyribonucleoside analogues have shown promising activities for such a chemotherapy. 4'-Thia analogue in which the furanose ring oxygen atom of 2'-deoxyribonucleosides is replaced by sulfur atom is one of the candidates and of our current interests. Recently, synthetic methods for 4'-thio-2'-deoxyribonucleoside have developed by us[2] and other groups.[3] In this letter, we would like to describe synthesis and crystal structure of 4'-thiothymidine (**1**) which has revealed the first solid state conformation of 4'-thio-2'-deoxyribonucleoside.



An anomeric mixtures of protected 4'-thiothymidine (**3**) was isolated in 88% yield by the reaction of 4-thio-2-deoxyfuranose (**2**) and bistrimethylsilylthymine (2 equiv.) in the presence of $SnCl_4$ (1.2 equiv.) at 0 °C in CH_3CN. The stereo isomeric ratio was 1.9:1 (α : β) and they are separable by column chromatography on silica gel. The acetyl group of **3β** was removed by potassium carbonate catalyzed hydrolysis in methanol to give **4β** in 93% yield. Deprotection of the silyl ether was carried out by treatment of Bu^n_4NF in THF to lead **1** in 95% yield. The crystalline **1** was subjected to X-ray analysis[4] whose ortep view was shown in Fig. 1. In recognition of 5'-hydroxy group for monophosphorylation by virus kinase and inhibition of reverse

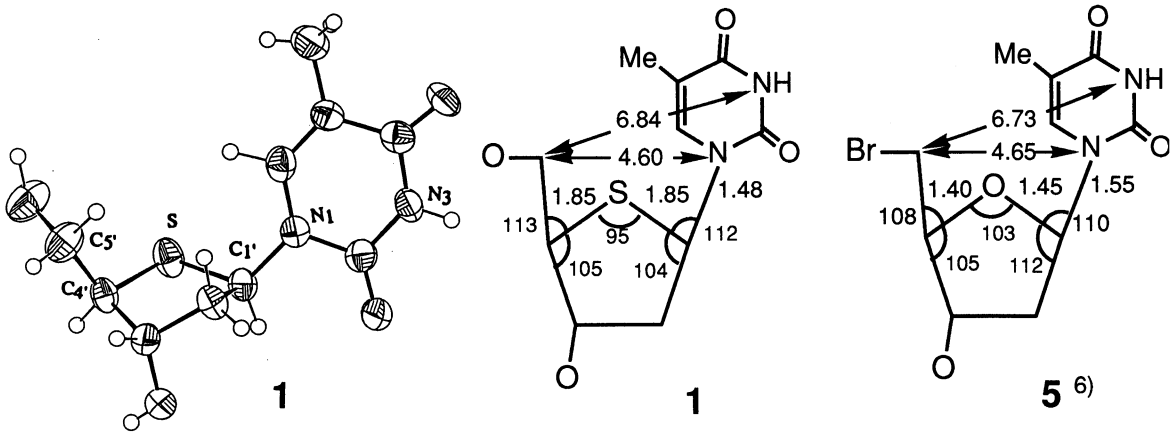


Fig. 1. Ortep drawing of **1** and selected bond lengths (Å) and angles (°) in compounds **1** and **5** .[6)]

transcriptase, the conformation of nucleoside is very important.[5)] In comparison of the crystal structures in **1** and 5'-bromothymidine (**5**) reported by Huber,[6)] the sugar moieties are quite different. In the 4'-thia analogue, the two C_1'-S and S-C_4' bonds are 1.85 Å which are much longer than the corresponding C-O bonds in **5**. The angle of C_1'-S-C_4' was determined to be 95°. While, the distances between C_5' carbon in sugar part and two nitrogen atoms on pyrimidine ring are quite closed, for example, N_1-C_5' is 4.60 Å in **1** and 4.65 Å in **5** and N_3-C_5' is 6.84 Å in **1** and 6.73 Å in **5**. This fact indicates that in the molecule of **1,** the key atoms such as 5'-carbon and two nitrogens on pyrimidine ring locate in resemble positions to those of the corresponding 2'-deoxyuridine analogues.

This work was supported by Grant-in-Aid for Scientific Research on Priority Area No. 03242104 for Ministry of Education, Science and Culture, Japan.

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4) Crystal data of **1**: C10H14N2O4S, F.W.=258.30, mp 209-210 °C. Monoclinic, *P*21, *a*=12.104(7), *b*=5.182 (4), *c*= 9.254(5) Å, *β*=93.17(5) °,*V*=579.5(7) Å3, *Z*= 2, *D*c=1.48 g cm-3, *μ*(Mo *K*α)=2.34 cm-1. *R*= 0.069, *R*w=0.061, for total 1404 reflections with |Fo| ≥5.0σ(Fo)(2θ max=55°).

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(Received October 21, 1992)