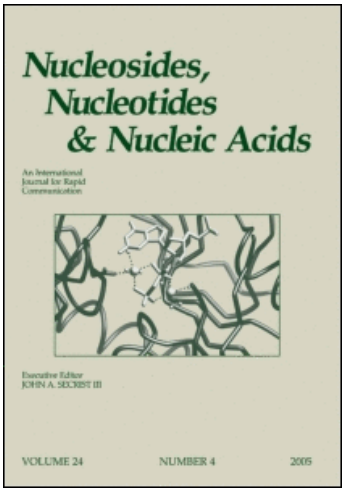

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4-Thiofuranoid Glycals: Versatile Synthons for Stereoselective Synthesis of 4'-Thionucleosides

Kazuhiro Haraguchi[a]; Haruhiko Takahashi[a]; Hiromichi Tanaka[a]
[a] School of Pharmaceutical Sciences, Showa University, Shinagawa-ku, Tokyo, Japan

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4-Thiofuranoid Glycals: Versatile Synthons for Stereoselective Synthesis of 4′-Thionucleosides

Kazuhiro Haraguchi,* Haruhiko Takahashi, and Hiromichi Tanaka

School of Pharmaceutical Sciences, Showa University, Shinagawa-ku, Tokyo, Japan

ABSTRACT

β-anomers of 4′-thionucleosides have been synthesized stereoselectively, through PhSeCl- or *N*-iodosuccimide (NIS)-initiated electrophilic glycosidation to 3,5-*O*-(di-*t*-butylsilylene)-4-thiofuranoid glycal (**1**). This synthetic method has been applied to the synthesis of those analogues branched at the anomeric position using 1-*C*-carbon-substituted 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-4-thiofuranoid glycals (**11**–**14**) prepared based on lithiation of **10**.

Key Words: Glycal; 4′-Thionucleoside; Glycosidation; Stereoselective.

INTRODUCTION

4′-Thionucleosides, in which the furanose ring oxygen is replaced by a sulfur atom, have been emerged as promising nucleoside antimetabolites, since the discovery of potent antiviral and antitumor activities of 4′-thiothymidine and 2′-deoxy-4′-thiocytidine.[1] The synthesis of 4′-thionucleosides has mostly been carried out

*Correspondence: Kazuhiro Haraguchi, Showa University, School of Pharmaceutical Sciences, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan; Fax: +81 33 784 8252; E-mail: harakazu@pharm.showa-u.ac.jp.

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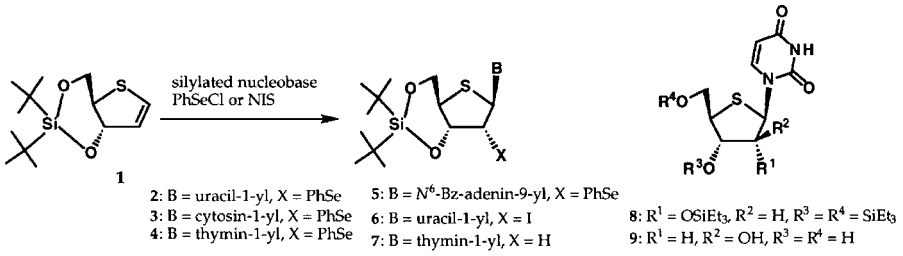
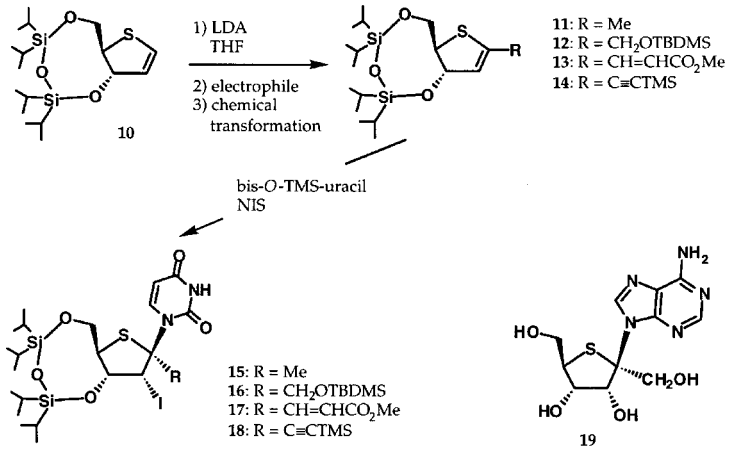


Scheme 1.

employing the Vorbrüggen-type condensation between an appropriate 4-thiopentofuranose and a silylated nucleobase. A major drawback commonly seen in this method is the lack of the desired β-stereoselectivity. In this paper, we describe a novel method for the stereoselective synthesis of 4′-thionucleosides through electrophilic glycosidation to 4-thiofuranoid glycal.[2] Also reported here is an extension of the above chemistry to the synthesis of 4′-thionucleoside analogues branched at the anomeric position.[3]

RESULTS AND DISCUSSION

When PhSeCl was reacted with 3,5-*O*-(di-*t*-butylsilylene)-4-thiofuranoid glycal (**1**) in the presence of silylated nucleobases (uracil, thymine, N^4-acetylcytosine and N^6-benzoyladenine) in CH_3CN at 0°C, the reaction went to completion to give the respective β-anomers of 2′-deoxy-2′-phenylseleno-4′-thionucleosides (**2**–**5**) as a single stereoisomer (Sch. 1). This glycosidation also proceeded efficiently by using NIS as an electrophile to furnish the corresponding 2′-deoxy-2′-iodo derivative (**6**). Tributyltin radical-mediated removal of phenylseleno group of **4** gave 4′-thiothymidine (**7**).



Scheme 2.

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4′-Thiouridine derivative (**8**) and 1-(4-thioarabinofuranosyl)uracil (**9**) were obtained from **6** via O^2,2′-cyclonucleoside.

3,5-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-4-thiofuranoid glycal (**10**) was transformed into 1-*C*-carbon-substituted glycals (**11**–**14**) using lithiation chemistry (Sch. 2). NIS-initiated electrophilic glycosidation between **11**–**14** and bis-*O*-TMS-uracil proceeded stereoselectively, giving anomerically branched analogues (**15-18**). This method enabled us to synthesize the 4′-thio analogue of antitumor nucleoside antibiotic angustmycin C (**19**).

REFERENCES

1. Synthesis of biological activity of thionucleosides. Synthesis **2000**, 1637–1655.
2. Haraguchi, K.; Takahashi, H.; Shiina, N.; Horii, C.; Yoshimura, Y.; Nishikawa, A.; Sasakura, E.; Nakamura, K.T.; Tanaka, H. Stereoselective synthesis of the β-anomer of 4′-thionucleosides based on electrophilic glycosidation to 4-thiofuranoid glycal. J. Org. Chem. **2002**, *67*, 5919–5927.
3. Haraguchi, K.; Takahashi, H.; Tanaka, H. Streoselective entry to 1′-*C*-branced 4′-thionucleosides from 4-thiofuranoid glycal: Synthesis of 4′-thioangustmycin C. Tetrahedron Lett. **2002**, *43*, 5657–5660.

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