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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*-iodosuccinimide (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*-(tetraisopropylidisiloxane-1,3-diyl)-4-thiofuranoid glycals (**11–14**) prepared based on lithiation of **10**.

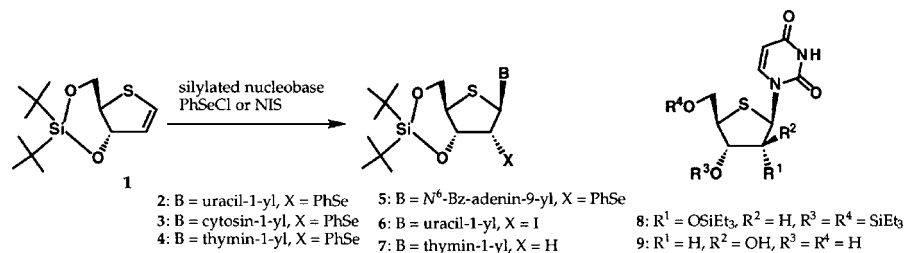
Key Words: Glycal; 4'-Thionucleoside; Glycosidation; Stereoselective.

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.



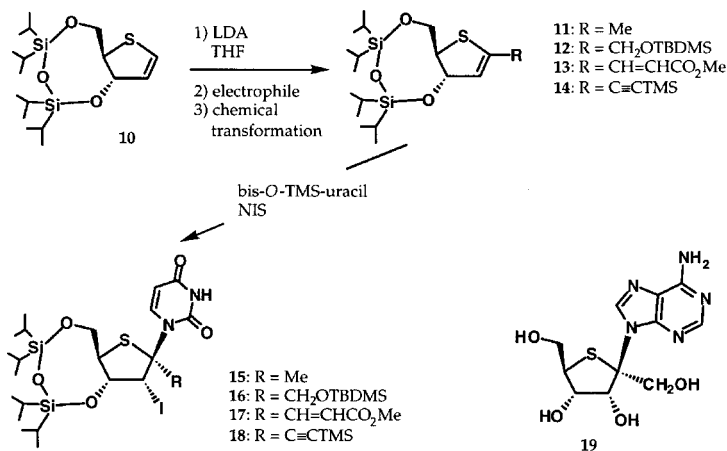


Scheme 1.

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 glycol.^[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 glycol (**1**) in the presence of silylated nucleobases (uracil, thymine, *N*⁴-acetylcytosine and *N*⁶-benzoyladenine) in CH₃CN 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.

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

3,5-*O*-(Tetraisopropylidisiloxane-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**).

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