Stereoselective synthesis of 2′-β-carbon-substituted 2′-deoxy-4′-thioribonucleosides from 4-thiofuranoid glycal

Kazuhiro Haraguchi, Noriaki Shiina, Yuichi Yoshimura, Hisashi Shimada, Kyoko Hashimoto and Hiromichi Tanaka
School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

ABSTRACT
The 4-thiofuranoid glycal 6 was converted into 1-chlorinated derivative 7 through LDA lithiation. When 7 was treated with LTMP, successful C-2 lithiation occurred, and subsequent treatment of the lithiated species with MeI gave 8. Dechlorination of 8 with Na/liq.NH3 yielded the 2-methyl glycal 9. Glycosidation of 9 with silylated thymine was mediated with PhSeCl as an electrophile, and gave the β-isomer 10 stereoselectively. Removal of the 2′-phenylselenyl group of 10 was effected with tributyltin radical, and subsequent deprotection furnished the target 2′-β-methyl 4′-thiothymidine (11). In a similar manner, the corresponding cytosine analogue 12 could also be synthesized.

INTRODUCTION
2′-β-Carbon-substituted 2′-deoxynucleosides have been attracted much attention due to potent antitumor activity of SMDC (1), SFDC (2) and CNDAC (3). It has also been known that replacement of the furanose ring oxygen of nucleosides with a sulfur atom often leads to promising nucleoside antimetabolites, as evidenced by the discovery of potent antiviral and antitumor activities of 4′-thiothymidine (4) and 2′-deoxy-4′-thiocytidine (5). Through several publications, we have demonstrated that 4-thiofuranoid glycols serve as efficient glycosyl donor for stereoselective synthesis of 4′-thionucleosides. As a part of this program, we carried out the synthesis of 2′-β-carbon-substituted 2′-deoxy-4′-thioribonucleoside, the results of which are presented here.

RESULTS AND DISCUSSION
Our synthetic plan starting from 4-thiofuranoid glycal IV is shown in Scheme 1. The desired 4′-thionucleoside I would be obtained from II by tin radical-mediated removal of the 2′-phenylseleno group. Nucleoside II would result from PhSeCl-mediated glycosidation using the 2-carbon-substituted glycal III. We first examined the preparation of III based on lithiation chemistry. Acidic character of H-1 of IV requires protection of the 1-position. Thus, 3,5-O-TIPDS-4-thiofuranoid glycal (6) was transformed into the 1-chloro derivative 7 (86%) by LDA lithiation followed by treatment with PhSO2Cl. When 7 was treated with LTMP, lithiation of the 2-position was feasible. Upon reacting the 2-lithiated species with MeI, 8 was obtained in 71% yield. Dechlorination of 8 was carried out by Birch reduction (Na/liq.NH3) to yield the 2-methyl-4-thiofuranoid glycal (9) in 81% yield. Compound 9 underwent glycosidation when reacted with silylated thymine in the presence of PhSeCl, forming the desired β-isomer of 4′-thiothymidine nucleoside (10) stereoselectively in 87% yield. Removal of the 2′-phenylseleno group of 10 by reacting with tributyltin radical was followed by desilylation to furnish 2′-β-methyl-4′-thiothymidine (11) in quantitative...
yield. The synthesis of 2'-deoxy-2'-β-methyl-4'-thiocytidine (12) was carried out in a similar manner.

REFERENCES


ACKNOWLEDGEMENT

Financial supports from JSPS (KAKENHI, No. 15590100 to K. H. and No. 15590020 to H. T.) and the Research Foundation for Pharmaceutical Sciences (to K. H.) are gratefully acknowledged.