ORGANIC LETTERS

2004
Vol. 6, No. 16
2645−2648

Novel Stereoselective Entry to 2′-β-Carbon-Substituted 2′-Deoxy-4′-thionucleosides from 4-Thiofuranoid Glycals

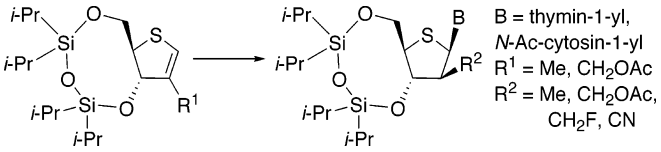
Kazuhiro Haraguchi,* Noriaki Shiina, Yuichi Yoshimura, Hisashi Shimada, Kyoko Hashimoto, and Hiromichi Tanaka

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

harakazu@pharm.showa-u.ac.jp

Received April 29, 2004

ABSTRACT



2′-β-Methyl- and 2′-β-hydroxymethyl-2′-deoxy-4′-thionucleosides have been synthesized through PhSeCl-mediated electrophilic glycosidation using 4-thiofuranoid glycals having carbon substituents at the C2-position as a glycosyl donor. Preparation of these glycals were carried out by means of the C2 lithiation of 1-chloro-4-thiofuranoid glycal with LTMP followed by the Birch reduction of the chlorine atom.

1-β-D-Arabinofuranosylcytosine (ara-C, **1**) is an antimetabolite under clinical use for the treatment of leukemia.[1] Despite its effectiveness, it has been pointed out that rapid deamination of **1** leads to inactive 1-β-D-arabinofuranosyluracil.[2] To overcome this drawback, a number of 2′-substituted arabinofuranosyl nucleosides, in which the 2′-hydroxyl group is replaced with other functional groups, have been evaluated for their effectiveness as antimetabolites. As a result of these studies, potent antitumor activity was found in 2′-β-carbon-substituted analogues such as SMDC (**2**), SFDC (**3**), and CNDAC (**4**).[3]

A recent discovery that the simple replacement of the furanose ring-oxygen of nucleosides with sulfur atom leads to promising antiviral and antitumor activities, e.g., 4′-thiothymidine (**5**) and 2′-deoxy-4′-thiocytidine (**6**),[4] has stimulated the synthesis of this class of nucleosides, especially those modified at the sugar moiety. There has been, however, only one report concerning the synthesis of 2′-β-carbon substituted 2′-deoxy-4′-thionucleosides.[5] As a part of our ongoing efforts toward the synthesis of 4′-thionucleosides,[6] we describe herein a novel stereoselective entry to 2′-β-carbon substituted analogues using 4-thiofuranoid glycals having a carbon substituent at the C2 position as a glycosyl donor.

We previously reported[6b] that the reaction between 4-thiofuranoid glycal **7** and silylated nucleobase in the presence

(1) Keating, M. J.; McCredie, K. B.; Bodey, G. P.; Smith, T. L.; Gehan, E.; Freidreich, E. J. *JAMA* **1982**, *248*, 2481−2486.

(2) (a) Prince, H. N.; Grumgerg, E.; Buck, M.; Cleeland, R. A. *Proc. Soc. Exp. Biol. Med.* **1969**, *130*, 1080−1086. (b) Ho, W. D. H. *Cancer. Res.* **1973**, *33*, 2816−2820. (c) Plunkett, W.; Gandhi, V. *Semin. Oncol.* **1993**, *20*, 50−63.

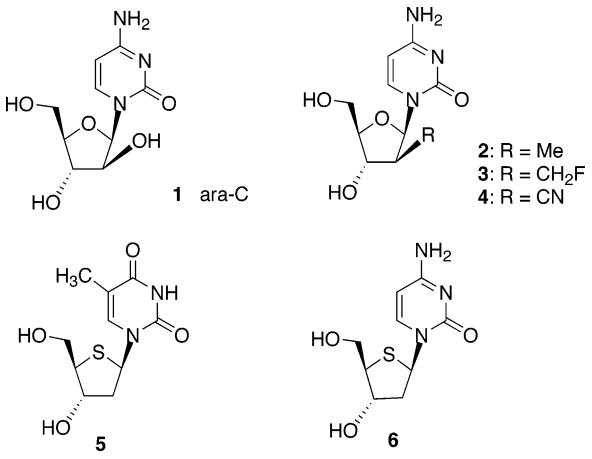
(3) (a) Matsuda, A. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 1−22. (b) Yoshimura, Y.; Saitoh, K.; Ashida, N.; Sakata, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 721−724.

(4) For a review, see: Yokoyama, M. *Synthesis* **2000**, 1637−1655.

(5) 2′-β-Methyl-2′-deoxy-4′-thiouridine and -thymidine have been synthesized by Vorbrüggen-type condensation. In this case, due to the steric hindrance exerted by the 2′-β-methyl substituent, the undesired α-anomers were obtained as the major products: Uenishi, J. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 186−195.

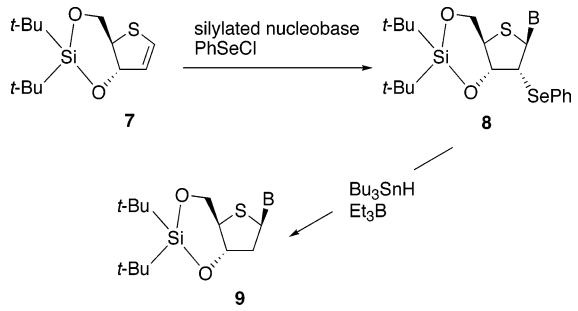
(6) (a) Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713−3716. (b) Haraguchi, K.; Takahashi, H.; Shiina, N.; Horii, C.; Yoshimura, Y.; Nishimura, A.; Sasakura, E.; Nakamura, K. T.; Tanaka, H. *J. Org. Chem.* **2002**, *67*, 5919−5927. (c) Haraguchi, K.; Takahashi, H.; Tanaka, H. *Tetrahedron Lett.* **2002**, *43*, 5657−5660.

10.1021/ol040035u CCC: $27.50
Published on Web 07/10/2004



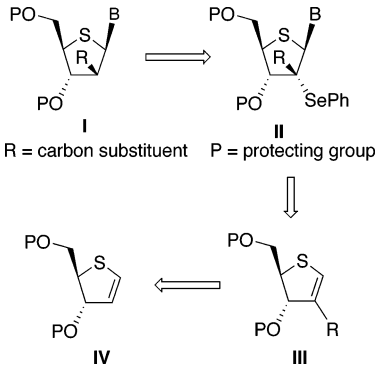
of phenylselenenyl chloride (PhSeCl) gave the β-anomer of 4′-thionucleosides **8** as shown in Scheme 1. Radical-mediated removal of the phenylseleno group in **8** allows ready access

Scheme 1



to 2′-deoxy-4′-thionucleosides (**9**). This method led us to propose the present synthetic plan shown in Scheme 2. Since

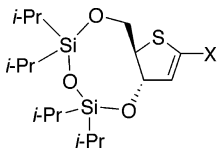
Scheme 2



the target molecules **I** can be prepared simply by removing the phenylseleno group from the glycosylated product (**II**), and since **II** would be prepared from appropriate C2-substituted 4-thioglycals (**III**) through PhSeCl-mediated electrophilic glycosidation, the major challenge was to construct the C−C bond at the C2-position of the starting material (**IV**).

We considered that generation of a C2-anion would be a suitable approach to construct C−C bonds, and thus, it was necessary to protect the more acidic H-1 in **IV**. For the protection of the C1-position, LDA lithiation (2.0 equiv, −70 °C, 15 min, in THF) of 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl) (TIPDS)-4-thiofuranoid glycal (**10**) was carried out by using electrophiles (2.0 equiv) such as Me_3SiCl, Bu_3SnCl, iodine, and $PhSO_2Cl$. Reflecting the fact that sulfur is the best α-activator through *d*-σ overlap, the C1-protected products **11**−**14** were obtained uniformly in good yields (Table 1).[7]

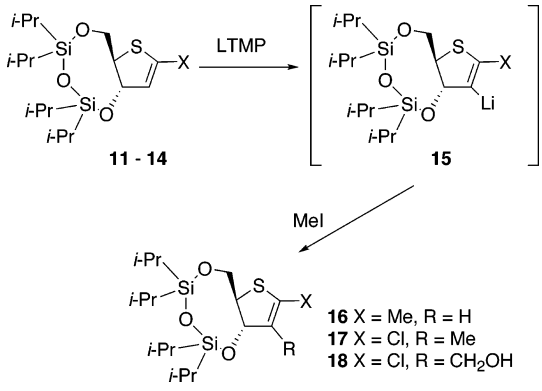
Table 1. Preparation of C1-Protected 4-Thiofuranoid Glycals (**11**−**14**)



entry	electrophile	product (isolated yield, %)
1	Me_3SiCl	**11** (82)
2	Bu_3SnCl	**12** (70)
3	I_2	**13** (84)
4	$PhSO_2Cl$	**14** (86)

Generation of the C2-anion of **11**−**14** was next examined with the more basic lithiating agent LTMP followed by quenching the lithiated species **15** with MeI (Scheme 3).

Scheme 3



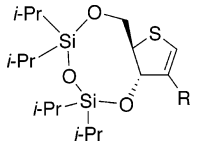
When **11** or **12** was used as a substrate, no reaction took place, presumably due to bulkiness of the C1-protecting group. In the case of **13**, exclusive halogen−lithium exchange reaction occurred to give the 1-methylglycal **16** (67%). In contrast to these results, the 1-chloroglycal **14** appeared to be a suitable substrate. Thus, LTMP lithiation (5 equiv, −70

(7) We expected that the use of 3,5-*O*-(di-*tert*-butylsilylene)-protected 4-thiofuranoid glycal **7** would give better stereoselectivity in the glycosidation step. However, the C1-chlorinated product derived from **7** was found to be unstable.

°C, 30 min, in THF) of **14** and successive methylation (10 equiv of MeI, −70 °C, 30 min) led to the isolation of the desired C2-methylated product (**17**) in 71% yield. When **15** was reacted with DMF and then treated with $NaBH_4$ in a one-pot manner, the 2-hydroxymethyl derivative **18** was isolated in 85% yield.

Alkali metal reduction was employed to remove the C1-chloro atom of **17** and **18**, and the results are summarized in Table 2. Upon reaction of **17** with lithium wire in THF, the dechlorinated product **19** was isolated in only 6% yield (entry 1). Although more reactive lithium dispersion improved the isolated yield of **19** to 36% yield, many unidentified byproducts were formed, along with the recovered starting material (entry 2). The Birch reduction of **17** was found to give the best result (entry 3). The reaction also works well for the 2-hydroxymethyl derivative **18**. After acetylation of the reaction mixture, **20** was isolated in 70% yield (entry 4).

Table 2. Dechlorination of Glycals **17** and **18**

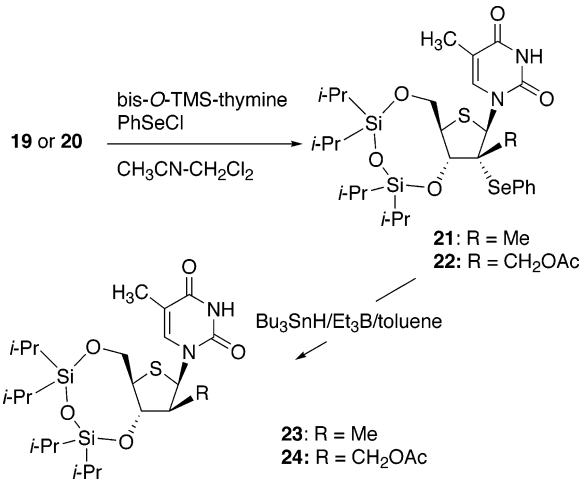


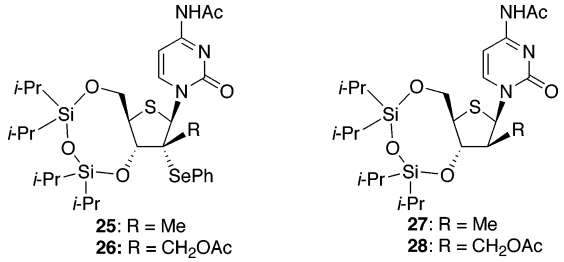
19: R = CH_3
20: R = CH_2OAc

entry	glycal	reaction conditions	products (isolated yields, %)
1	**17**	Li wire/THF/−70 °C/34 h	**19** (6), **17** (51)
2	**17**	Li dispersion/THF/−70 °C/ 3 h	**19** (36), **17** (13)
3	**17**	Na/liq NH_3−Et_2O/−80 °C/0.5 h	**19** (81)
4	**18**	(1) Na/liq NH_3−Et_2O/−80 °C/0.5 h (2) Ac_2O/*i*-Pr_2NEt/DMAP/CH_2Cl_2	**20** (70)

In Scheme 4 is shown electrophilic glycosidation of the above prepared glycals (**19** and **20**) and subsequent removal of the phenylseleno group (only the major diastereomers are depicted). When the 2-methylglycal **19** was reacted with silylated thymine in the presence of PhSeCl at 0 °C, a mixture of two diastereomers was obtained in 87% yield with a diastereomeric ratio of 27:1. A NOE experiment of the mixture confirmed overwhelmingly preferential formation of the desired β-anomer **21**. Under the same reaction conditions, the 2′-acetoxymethyl derivative **22** was prepared in 92% from **20** as a mixture (β/α = 21:1). Treatment of **21** with Bu_3-SnH in the presence of Et_3B in toluene at −70 °C gave the 4′-thiothymidine derivative **23** in quantitative yield. Similarly, **24** was obtained from **22** in almost quantitative yield. Synthesis of the corresponding 2′-deoxycytidine analogues is also feasible. Reactions of **19** and **20** with silylated *N*-acetylcytosine gave **25** (96%) and **26** (92%), respectively, with high stereoselectivity (**25**, β/α = 25/1; **26**, β/α = 23/1). Subsequent radical reduction gave 4′-thio-SMDC (**27**) and the 2′-β-acetoxymethyl-2′-deoxy-4′-thiocytidine derivative **28** in quantitative yields.

Scheme 4

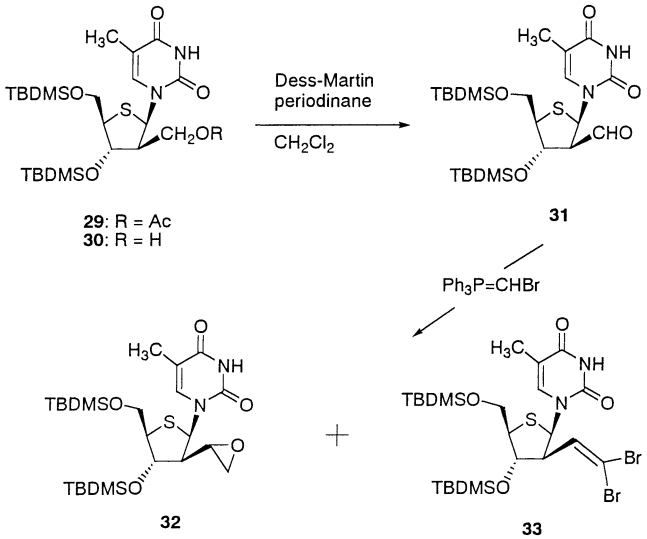




25: R = Me
26: R = CH_2OAc
27: R = Me
28: R = CH_2OAc

Some chemical transformations of the 2′-β-hydroxymethyl group were next explored starting from **24** (Scheme 5).

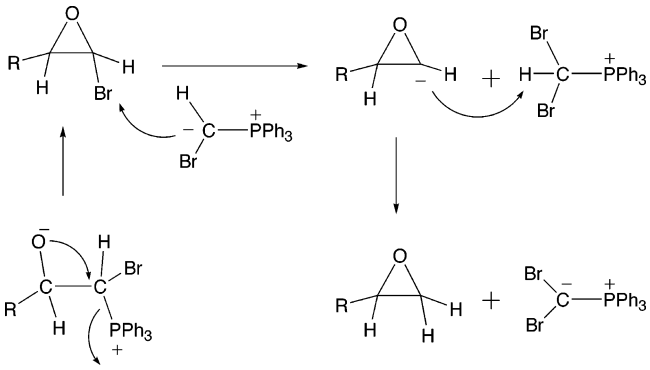
Scheme 5



Conventional NH_3/MeOH treatment of **24** did not effect deacetylation, probably due to encumbered accommodation of the acetyl group, while the use of NaOMe resulted in partial removal of the 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl) group. Therefore, the 3′,5′-bis-*O*-TBDMS-protected **29** was prepared from **24**, and it was converted to **30** by the treatment with NaOMe. Dess−Martin oxidation of **30** provided the formyl derivative **31** (93%).

As the first step toward the synthesis of the 2′-β-ethynyl derivative, reaction of **31** with 3.0 equiv of $Ph_3P{=}CHBr$[8] was carried out. Quite unexpectedly, this Wittig reagent gave the epoxide **32** (60%) as the major product. Careful examination of the reaction mixture revealed the presence of a small amount of an additional product. Its ^1H NMR and MS spectra showed that it was not the expected product but the dibromoolefin **33** (5%). When this reaction was conducted by using 6.0 equiv of the reagent, the yield of **33** increased to 32% at the expense of a lowered yield of **32** (33%). Although we do not have satisfactory explanation for the above two experimental results, it would be reasonable to assume that the epoxide formation could be accompanied by generation of the new Wittig reagent $Ph_3P{=}CBr_2$ as depicted in Scheme 6. Treatment of **33** with BuLi

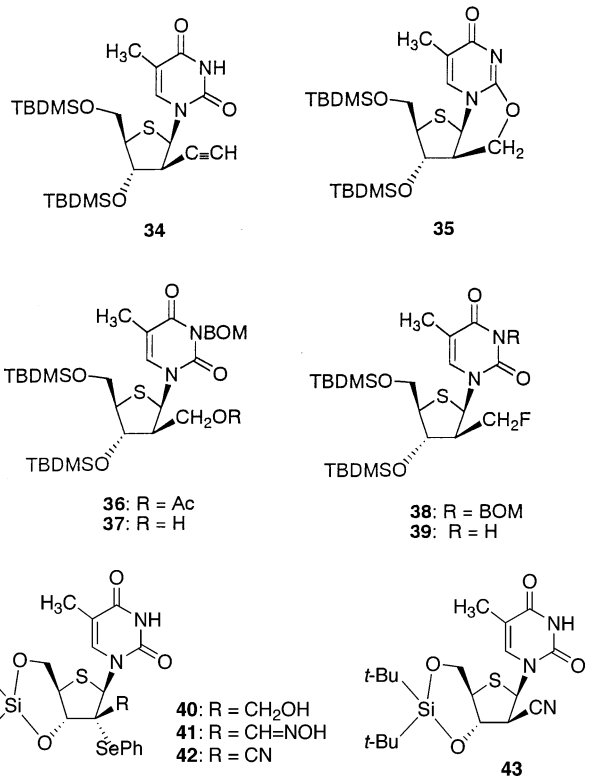
Scheme 6



(4.0 equiv) in THF at −30 °C gave the 2′-β-ethynyl-4′-thiothymidine derivative **34** in 56% yield.

Attempted fluorination of **30** by direct treatment with diethylaminosulfur trifluoride (DAST) gave the cyclonucleoside **35** as the sole product in 92% yield. To avoid this pathway, N^3-benzyloxymethyl (BOM)-protected **37** was prepared from **29** via **36** in a two step-sequence. Although no reaction was observed with DAST alone, addition of Na_2CO_3 accelerated the fluorination to give fluoromethylated **38** in 63% yield. Removal of the BOM group was carried out by hydrogenolysis with Pd-black to provide **39** in 69% yield.

Finally, synthesis of 2′-β-cyano-4′-thiothymidine **43** was explored. To prevent anticipated glycosyl bond cleavage caused by dissociation of the acidic 2′-hydrogen, the 2′-phenylseleno derivative **22** was used as the starting material. After deprotection of TIPDS and acetyl group in **22**, the resulting triol was converted to the 3′,5′-(di-*tert*-butylsilylene)-protected **40** in good yield. Dess−Martin oxidation of **40** gave the corresponding aldehyde, which was then reacted with hydroxylamine to give the oxime **41**. When the oxime **41** was mesylated with methanesulfonyl chloride in pyridine, spontaneous elimination took place to give the nitrile **42** in 97% yield. Tin radical-mediated removal of the phenylseleno group proceeded again stereoselectively to furnish the desired **43** in 72% yield.



In conclusion, we have developed a novel approach to the synthesis of 2′-β-carbon substituted 2′-deoxy-4′-thionucleosides. Biological evaluation of the corresponding parent nucleosides is under investigation.

Acknowledgment. Financial support from Japan Society for the Promotion of Science (KAKENHI No. 15590100 to K.H. and No. 15590020 to H.T.) and the Research Foundation of Pharmaceutical Sciences (to K.H.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full characterization for compounds **11**−**14** and **17**−**43**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL040035U

(8) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021−4024.