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Stereoselective entry to 1′-*C*-branched 4′-thionucleosides from 4-thiofuranoid glycal: synthesis of 4′-thioangustmycin C

Kazuhiro Haraguchi,* Haruhiko Takahashi and Hiromichi Tanaka

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

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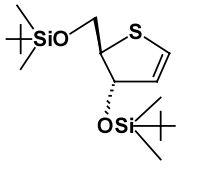
Abstract—A stereoselective synthetic method for the synthesis of novel 1′-*C*-carbon-substituted 4′-thionucleosides has been developed. The present method consists of the following steps: (1) preparation of the 1-*C*-carbon-substituted 4-thiofuranoid glycals based on lithiation, and (2) NIS- or PhSeCl-initiated stereoselective glycosidation to these 1-substituted glycals. This synthetic sequence enabled us to synthesize the 4′-thio analogue of antitumor antibiotic angustmycin C.

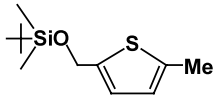
The discovery that the simple replacement of the furanose ring-oxygen with sulfur atom leads to promising antiviral or antitumor nucleosides, such as 4′-thiothymidine (**1**) and 4′-thio-2′-deoxycytidine (**2**),[1] has stimulated the synthesis of this class of nucleosides, especially those modified at the sugar moiety.[2–4] A major drawback of commonly adopted synthetic methods for these 4′-thionucleosides is the lack of β-stereoselectivity[5] that is crucial for their activities. We have recently reported a highly β-selective synthetic method for pyrimidine 2′-deoxy-4′-thionucleosides based on an electrophilic glycosidation to 4-thiofuranoid glycal.[6]

The present study was motivated by the occurrence of an antitumor nucleoside antibiotic angustmycin C (**3**) which is structurally unique in being branched at the anomeric position. We describe herein (1) preparation of the 1-*C*-carbon-substituted 4-thiofuranoid glycals based on lithiation, (2) stereoselective electrophilic glycosidation to these 1-substituted glycals, and (3) the synthesis of 4′-thioangustmycin C (**4**)[7] as an application of the present strategy.[8]

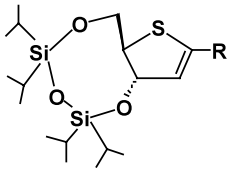
Two types of the 4-thiofuranoid glycals **5** and **6**, prepared in our previous study,[6] were used as substrates for the introduction of carbon-substituents to the 1-position based on lithiation.[9] Although the 3,5-bis-*O*-TBDMS (*tert*-butyldimethylsilyl) glycal (**5**) underwent successful lithiation with BuLi (1.2 equiv.) as evidenced by deuteration (96%), reaction of the lithiated species with MeI (5 equiv.) resulted in the sole formation of the aromatized product **7** (92%). On the other hand, when the 3,5-*O*-TIPDS (tetraisopropyldisiloxane-1,3-diyl)-



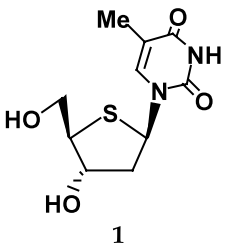
5



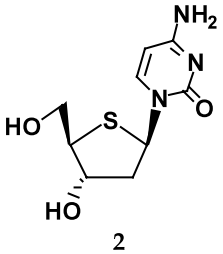
7 (92%)



6 R=H
8 R= Me (73%)
9 R= $CH_2OTBDMS$ (69%)
10 R= $CH{=}CHCO_2Me$ (85%)
11 R= I (87%)
12 R= C≡CTMS (89%)



1



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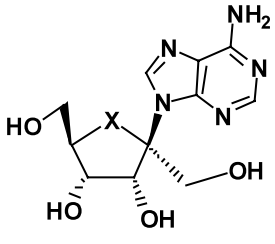

3 X = O
4 X = S

Keywords: nucleosides; glycals; glycosidation; antibiotics.

* Corresponding author. Tel.: 81-3-3784-8187; fax: 81-3-3784-8252; e-mail: harakazu@showa-u.ac.jp

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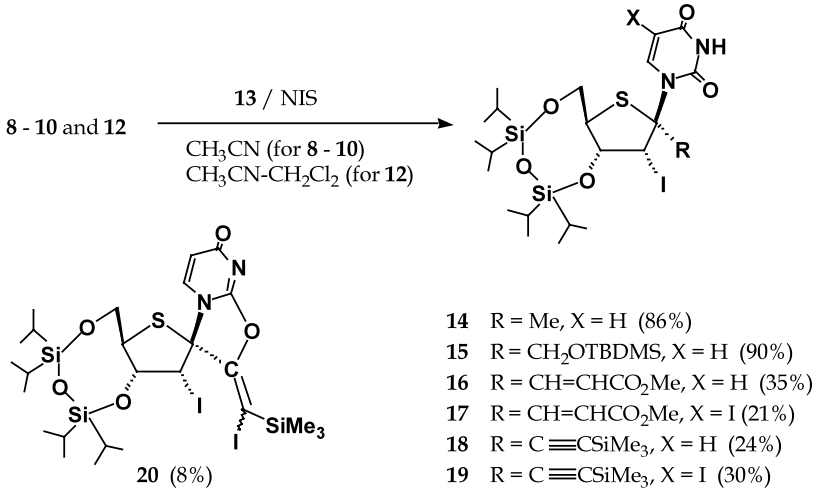
glycal (**6**) was lithiated with LDA (5 equiv.) and then treated with MeI (10 equiv.), the expected product **8** was obtained in good yield (isolated yields are given in parentheses). The 1-silyloxymethyl and 1-methoxycarbonylethenyl derivatives (**9** and **10**) were prepared by reacting DMF (6 equiv.) as an electrophile followed by either reduction with $NaBH_4$ and subsequent silylation or the Wittig reaction. Introduction of an ethynyl group was carried out by cross-coupling reaction[10] between the 1-iodo derivative (**11**), prepared by reacting the lithiated species with iodine, and (trimethylsilyl)acetylene in the presence of $(Ph_3P)_2PdCl_2$/CuI in DMF to give **12**.

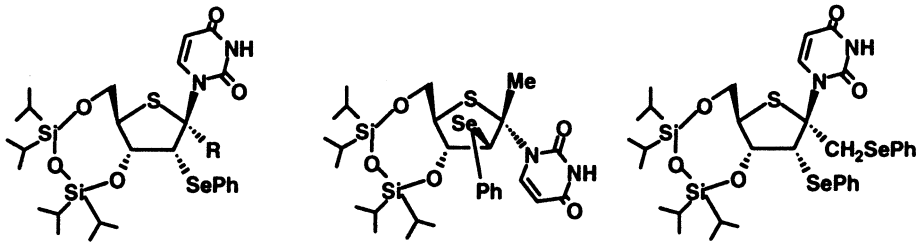
Electrophilic glycosidation between the 1-substituted TIPDS-glycals (**8**–**10** and **12**) as glycosyl donors and bis-*O*-(trimethylsilyl)uracil (**13**) as a nucleobase was examined first by using NIS (*N*-iodosuccimide) as an electrophile (Scheme 1). When **8** was treated with NIS (1.5 equiv.) in the presence of **13** (1.5 equiv.) in CH_3CN at 0°C, a high yield of the desired β-anomer **14** was observed as the exclusive product (isolated yields are given in parentheses). This was also the case for the 1-silyloxymethyl glycal (**9**), forming **15** exclusively in high yield.[6a] Unlike **8** and **9**, it is conceivable that electrophilicity of the glycal double bond of **10** and **12** is reduced due to the conjugation of a multiple bond. In fact, under the above reaction conditions, these glycosyl donors were recovered unchanged and the formation of 5-iodouracil was confirmed by TLC analysis of the reaction mixtures. Quite unexpectedly, however, upon conducting these reactions at a much lower temperature of −40°C, the β-4′-thionucleosides **16** and **18** were obtained along with their 5-iodo derivatives (**17** and **19**). In the reaction of **12**, the cyclized by-product **20** was also formed. Stereochemistry of these glycosylated products (**14–16**, and **18**) was determined based on NOE experiment, wherein correlations between H-3′/H-6 (2–3%) and H-2′/H-3′ (9–10%) were observed.

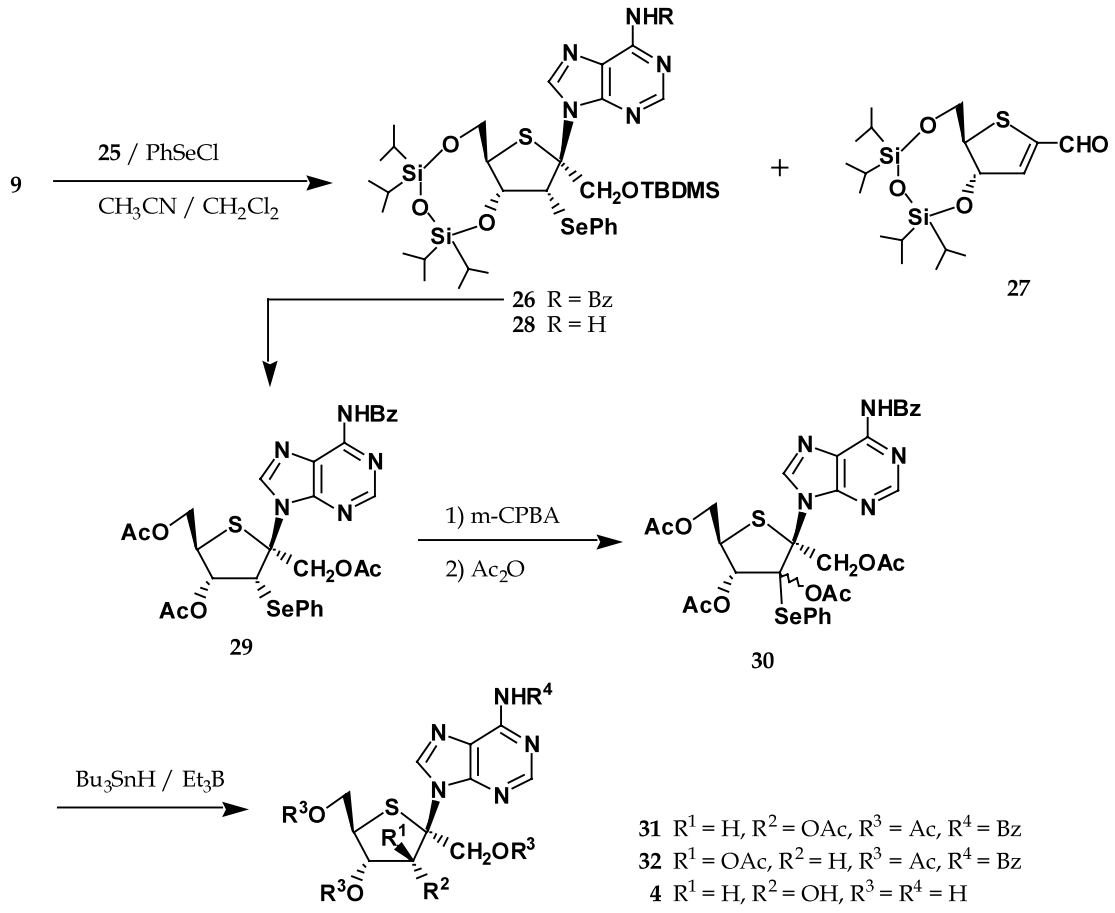
We next examined the use of PhSeCl as an electrophile in the reactions of the glycals **8** and **9**, because the synthesis of 4′-thioangustmycin C **4** requires the 2′-down hydroxyl group to be introduced, which could be done by means of a seleno-Pummerer reaction.[11] When **8** was reacted at −40°C with PhSeCl (1.5 equiv.) in the presence of **13** (1.5 equiv.) in CH_3CN, a mixture of the two anomers (**21**/**22** = 15/1) was obtained in 62% yield together with a by-product **23** (8%). Compound **23** had apparently resulted from methyl-proton abstraction of the initially formed 1,2-episeleniranium ion followed by electrophilic glycosidation to the *exo*-methylene intermediate. The reaction of **9**, on the other hand, gave solely the β-anomer **24** in 49% yield.

Finally, as shown in Scheme 2, the synthesis of 4′-thioangustmycin C (**4**) was investigated. The glycosidation reaction between **9** and bis(trimethylsilyl)-N^6-benzoyladenine (**25**) was carried out at −40°C to give the β-anomer **26** (40%) exclusively, although the by-product **27**[12] was also formed in 34% yield. The depicted regiochemistry of **26** was confirmed by UV spectroscopy after converting to **28**.[13] The stereochemistry of **26** came from the following NOE data: H-2′/H-8 (1%), H-2′/H-2 (1%), and H-2′/H-3′ (7%). Desilylation (Bu_4NF/THF) of **26** followed by acetylation (Ac_2O/iPr_2NEt/DMAP/CH_2Cl_2)



Scheme 1.





Scheme 2.

gave the tri-*O*-acetyl derivative **29** in 90% yield. For selective oxidation of **29** at the selenium atom, its reaction with *m*-CPBA was performed at −70°C. After extract workup, the resulting selenoxide was subjected to the seleno-Pummerer reaction (10 equiv. of Ac_2O/CH_2Cl_2, at room temperature overnight). This gave the monoselenoacetal **30** in 96% yield as a mixture of two epimers. Removal of the 2′-phenylselenenyl group of **30** was achieved by the radical reaction using Bu_3SnH (2 equiv.)/Et_3B. Stereochemical outcome of this reaction (ratio of **31**/**32**) was found to be highly dependent on the reaction temperature. Thus, at room temperature in benzene, **31** having the right 2′-configuration was obtained only in 46% yield (**32**, 22%).[14] At −20°C in toluene, the yield of **31** increased to 67% (**32**, 21%). At −70°C in toluene, a highest yield of 74% was attained for **31**, while the yield of **32** decreased to 8%. The target molecule **4** was obtained in 72% yield simply by deprotecting **31** with NH_3/MeOH.

In conclusion, we have developed a method for the β-selective preparation of novel 4′-thionucleosides branched at the anomeric position based on electrophilic glycosidation to the 1-carbon-substituted TIPDS-4-thiofuranoid glycals. As exemplified in our previous study,[6] the pyrimidine derivatives of 2′-iodo-4′-thionucleoside shown in Scheme 1 could be transformed not only to 2′-deoxy analogues but also to those having ribo- and arabino- configurations based on the cyclonucleoside chemistry. The present synthesis of 4′-thioangustmycin C (**4**) also suggests that similar transformations would be feasible even in the cases of purine counterparts. We are currently evaluating the biological activity of 4′-thioangustmycin C.

Acknowledgements

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