Pergamon

Tetrahedron Letters 39 (1998) 3713–3716

TETRAHEDRON LETTERS

Electrophilic Addition to 4-Thio Furanoid Glycal: a Highly Stereoselective Entry to 2'-Deoxy-4'-Thio Pyrimidine Nucleosides

Kazuhiro Haraguchi, Ayako Nishikawa, Eiko Sasakura, Hiromichi Tanaka,* Kazuo T. Nakamura, and Tadashi Miyasaka

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

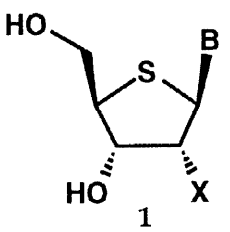
Received 6 February 1998; revised 2 March 1998; accepted 6 March 1998

Abstract: 4-Thio furanoid glycals with different types of *O*-silyl protection have been prepared from benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside. Face-selectivity for PhSeCl- or *N*-iodosuccimide-initiated addition of a pyrimidine base to the thioglycal was found to be controlled by *O*-silyl protecting groups. Using the thioglycal protected with a 3,5-*O*-di-*t*-butylsilyl group, a highly stereoselective synthesis of β-2'-deoxy-4'-thio pyrimidine nucleosides has been accomplished.

Keywords: Thiosugars; Glycals; Nucleosides; Addition reactions

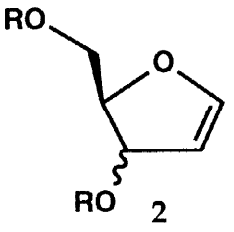
4'-Thionucleosides (**1**), in which the furanose ring oxygen is replaced by a sulfur atom, have attracted much attention due to their potent and broad-spectrum antiviral activities.[1] The synthesis of these nucleosides has so far been carried out based on Vorbrüggen-type condensation between an appropriate 4-thiosugar and a silylated nucleobase.[2] However, a major drawback of this method is lack of β-stereoselectivity. Thus, in the synthesis of 2'-deoxy-4'-thionucleoside, the undesired α-isomer was obtained as a major product in many cases.[1i] Even in the case of 4-thioribofuranoside, where neighbouring group participation by its acyloxy group at the 2-position can be expected, the β-anomer is formed in only a slight excess.[1k]

Nucleosides have also been synthesized by electrophilic reagent-mediated reactions starting from glycals **2**, in which high β-stereoselectivity is observed in some cases.[3, 4] In contrast to this, such approach has not been investigated for the synthesis of 4'-thionucleoside. In this context, we intended to examine the potential of 4-thio furanoid glycal **3** for stereoselective synthesis of 4'-thionucleoside. In this communication, we describe the preparation of **3** and face-selective electrophilic addition to it controlled by silyl protecting groups. This constitutes the first β-selective synthetic method for 2'-deoxy-4'-thio pyrimidine nucleoside.



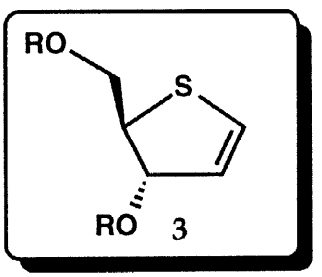
1

B= nucleobase
X= OH or H



2

R= protecting group

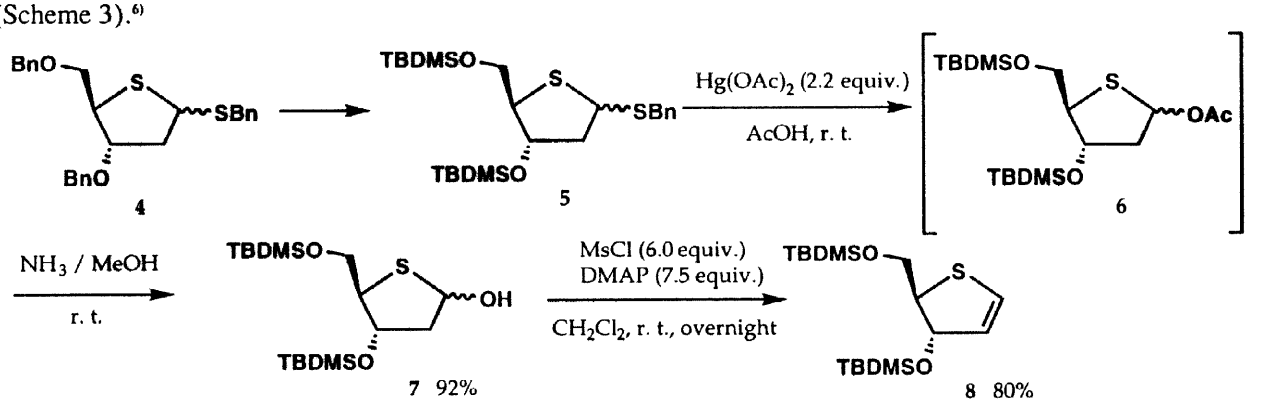


3

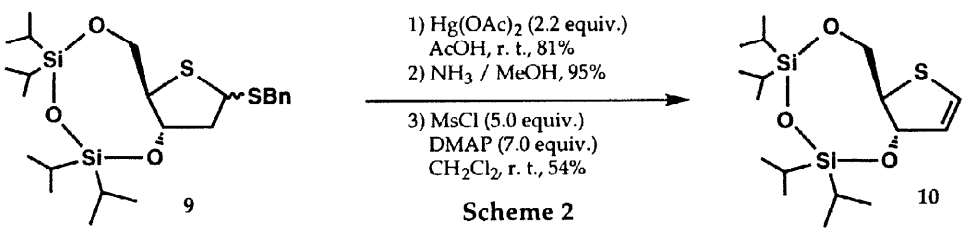
R= protecting group

0040-4039/98/$19.00
PII: S0040-4039(98)00543-7

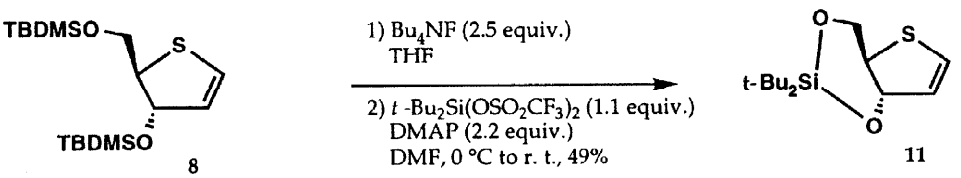
First of all, we examined preparation of 3,5-bis-*O*-(*t*-butyldimethylsilyl)-4-thio furanoid glycal **8**. After screening of starting materials, 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside **4**[5] was found to be a suitable sugar. As shown in Scheme 1, the thiosugar **4** was transformed to the corresponding *O*-(*t*-butyldimethylsilyl) derivative **5** through debenzylation with BBr_3 and silylation. The dithioacetal moiety of **5** was subjected to acetolysis with $Hg(OAc)_2$. Because a reagent-derived by-product could not be separated from **6** by silica gel column chromatography, we isolated as a hemithioacetal **7** in pure form in 92% overall yield from **5**. We next examined the dehydration of **7**. The hemithioacetal **7** was treated with MsCl (DMAP/CH_2Cl_2/r.t.). Under the conditions, the desired elimination reaction occurred in one flask to give 3,5-bis-*O*-(*t*-butyldimethylsilyl)-4-thio furanoid glycal **8** in 80% yield as a syrup. By following the same reaction sequence, 3,5,-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-4-thio furanoid glycal **10** was prepared from **9** (Scheme 2).[6] On the other hand, 3,5-*O*-di-*t*-butylsilyl-4-thio furanoid glycal **11** could not be obtained by the same method, because acetolysis of the corresponding dithioacetal gave an unidentified product. Therefore, **11** was prepared from **8** through desilylation and silylation with di-*t*-butylsilyl bis(trifluoromethanesulfonate) (Scheme 3).[6]



Scheme 1



Scheme 2

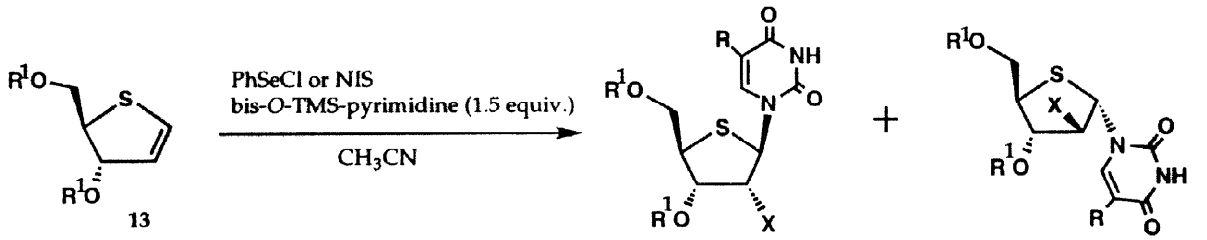


Scheme 3

Next, we examined electrophilic addition to the thioglycals (Scheme 4 and Table 1). Thus, PhSeCl was added to a solution of TBDMS-protected glycal **8** in CH_3CN in the presence of bis-*O*-trimethylsilyluracil to give a mixture of stereoisomers **12**β and **12**α in a 4 : 1 ratio as shown in entry 1. Compound **12**β was converted to the acetate **17**β and X-ray crystallographic analysis of **17**β confirmed the stereochemistry of **12**β.[7] Compound **12**α was also transformed into acetate **17**α and its stereochemistry was confirmed based on its nOe experiment. In the case of **10**, the ratio of α-face attack by the electrophilic reagent increased and the

desired β-2'-deoxy-4'-thionucleoside **13β** was obtained in a ratio of 18 : 1 (entry 2). As shown in entry 3, DTBS-protected glycal **11** gave β-anomer **14β** as the sole product in 88% yield.[8] Using **11** as a substrate, thymine nucleoside **15β** was also obtained in 62% yield stereoselectively. Instead of PhSeCl as an electrophile, NIS also worked well to give 2'-deoxy-2'-iodo derivative **16β** in 73% (entry 5).[9]

The 4'-thionucleosides involved in the present study can be further transformed to biologically useful derivatives. For example, **15β** was treated with tributyltin hydride to afford protected 4'-thiothymidine **18** which possesses activity against herpes virus (Scheme 5).[10]



13

8: R^1 = *t*-butyldimethylsilyl(TBDMS)
10: R^1 = 1,1,3,3,-tetraisopropyldisiloxan -1,3,-diyl(TIPDS)
11: R^1 = di-*t*-butylsilyl(DTBS)

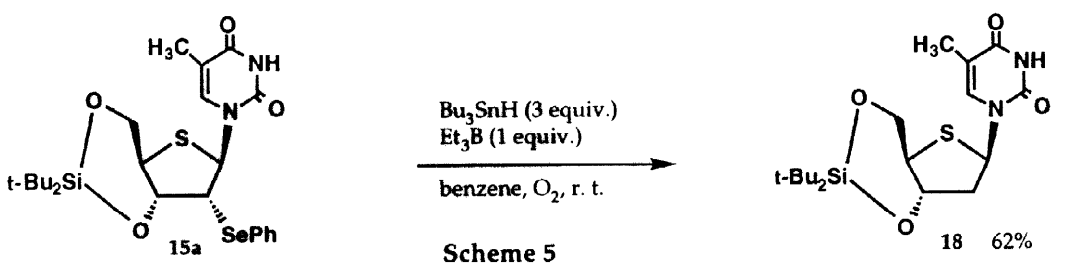
12β: R^1 = TBDMS (X= SePh) **12α**: R^1 = TBDMS (X= SePh)
13β: R^1 = TIPDS (X= SePh) **13α**: R^1 = TIPDS (X= SePh)
14β: R^1 = DTBS (X= SePh)
15β: R^1 = DTBS (X= SePh)
16β: R^1 = DTBS (X= I)
17β: R^1 = Ac, R= H **17α**: R^1 = Ac, R= H

Scheme 4

Table 1. Electrophilic addition to 4-thio furanoid glycals.

Entry	Glycal	Electrophile (equiv.)	bis-*O*-TMS-pyrimidine	R	Products (Isolated yield)	Product ratio [a]
1	8	PhSeCl (1.5)	uracil	H	12β and 12α (88%)	4 : 1
2	10	PhSeCl (1.5)	uracil	H	13β and 13α (87%)	18 : 1
3	11	PhSeCl (1.5)	uracil	H	14β (88%)	-
4	11	PhSeCl (2.3)	thymine	CH_3	15β (62%)	-
5	11	NIS (1.5)	uracil	H	16β (73%)	-

a) The ratio was determined by ^{1}H NMR spectroscopy.



15a **18** 62%

Scheme 5

In summary, we have developed a method for stereoselective synthesis of β-2'-deoxy-4'-thio pyrimidine nucleosides by means of face-selective electrophilic addition to 4-thio furanoid glycal. Further applications of this method, involving reactions with other nucleobases and chemical transformation into ribo- and arabino-type derivatives, are now underway.

Acknowledgement. Financial support from the Ministry of Education, Science, Sports and Culture (Grant-in-Aid No. 09771922 to K.H.) is gratefully acknowledged. The authors are grateful to Professor R. T. Walker for supply of **4**.

REFERENCES AND NOTES

1) (a) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782-2786. (b) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Chem. Soc., Chem. Commun.* **1991**, 741-743. (c) Secrist III, J. A.; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361-2366. (d) Uenishi, J.; Motoyama, M.; Nishiyama, Y.; Wakabayashi, S. *J. Chem Soc., Chem. Commun.* **1991**, 1421-1422. (e) Bellon, L.; Barascut, J.-I.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 1467-1479. (f) Huang, B.; Hui Y. *Nucleosides Nucleotides* **1993**, *12*, 139-147. (g) Uenishi, J.; Motoyama, M.; Takahashi, K. *Tetrahedron Asymm.* **1994**, *5*, 101-106. (h) Uenishi, J.; Takahashi, K.; Motoyama, M.; Akashi, H.; Sasakai, T. *Nucleosides Nucleotides* **1994**, *13*, 1347-1361. (i) Tiwari, K. N.; Secrist III, J. A.; Montgomery, J. A. *Nucleosides Nucleotides* **1994**, *13*, 1819-1828. (j) Leydier, C.; Bellon, L.; Barascut, J.-L.; Deydier, J.; Maury, G.; Pelicano, H.; El Alaoui, M. A.; Imbach, J.-L. *Nucleosides Nucleotides* **1994**, *13*, 2035-2050. (k) Secrist III, J. A.; Parker, W. B.; Tiwari, K. N.; Messini, L.; Shaddix, S. C.; Rose, L. M.; Bennett, L. L. Jr; Montgomery, J. A. *Nucleosides Nucleotides* **1995**, *14*, 675-686. (l)Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822-833. (m) Selwood, D. L.; Carter, K.; Young, R. J.; Jandu, K. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 991-994. (n) Hancox, E. L.; Walker, R. T. *Nucleosides Nucleotides* **1996**, *15*, 135-148. (o) Uenishi, J. *J. Synth. Org. Chem., Japan* **1997**, *55*, 186-195. (p) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *61*, 3140-3152.

2) (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255. (b) Vorbrüggen, H.; Hofle, G. *Chem. Ber.* **1981**, *114*, 1256-1268.

3) For a review of synthetic chemistry of glycals:Collins, P. M.; Ferrier, R. J. *Monosaccharides, Their Chemistry and Their Roles in Natural Products.* Chichester, U. K: John Wiley & Sons, 1995; pp. 317-326.

4) Díaz, Y.; El-Langhdach, A.; Castillón, S. *Tetrahedron* **1997**, *53*, 10921-10938.

5) Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carbohydrate Res.* **1991**, *216*, 237-248.

6) The yields of the elimination step in Scheme 2 and *O*-silylation in Scheme 3 were not optimized.

7) The atomic coordinates for **17**β are available on request from the Cambridge Crystallographic Data Centre, University of Chemical Laboratory, Lensfield Road, Cambridge CB21EW, UK.

8) Similar protecting group-controlled stereoselective reactions have been observed in electrophilic addition to 1',2'-unsaturated uracil nucleosides. (a) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656-662. (b) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Matsumoto, K.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 3867-3870. These face-selective electrophilic additions controlled by the silyl protecting groups can be accounted for as follows. In the case of TBDMS-protected glycal **8**, 3-*O*-TBDMS group shields the α-face of the double bond. On the other hand, in the case of cyclic silyl protected glycals such as **10** or **11**, the shielding of the α-face weakened. These steric environments lead to preferential α-face attack of the electrophilic reagent to increase the ratio of β-anomer / α-anomer, in the reaction of **10** and **11**. In particular, in the case of **11**, one of the two *t*-butyl groups, which is located in β-axial configuration, inhibits the approach of the reagent to the β-face to afford β-nucleoside as the sole product.

9) The overall yields of the 2'-deoxy-4'-thionucleosides by this method were comparable to or better than that of the methods previously reported.