

# Additive Pummerer Reaction of 3,5-O-(Di-tert-butyl)silylene-4-thiofuranoid Glycal: A High-Yield and $\beta$ -Selective Entry to 4'-Thioribonucleosides

Kazuhiro Haraguchi,\* Hiromitsu Matsui, Shin Takami, 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 December 04, 2008

B = uracil-1-yl, thymin-1-yl, N-Ac-cytosin-1-yl, 6-chloropurin-9-yl, 2-amino-6-chloro-purin-9-yl, thiophen-2-yl, furan-2-yl, 4-carbamoylthiazol-2-yl

Upon reacting 3,5-O-(di-tert-butyl)silylene-4-thiofuranoid glycal S-oxide (6) with Ac<sub>2</sub>O/TMSOAc/BF<sub>3</sub>·OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, the additive Pummerer reaction proceeded to furnish the corresponding 1,2-di-O-acetyl-4-thioribofuranose 7. Compound 7 serves as a highly  $\beta$ -selective glycosyl donor in the Vorbrüggen condensation carried out in the presence of TMSOTf. Thus, the 4-thio- $\beta$ -D-ribofuranosyl derivatives of uracil, thymine, N<sup>4</sup>-acetylcytosine, 6-chloropurine, and 2-amino-6-chloropurine were synthesized. The use of 7 can be extended to the  $\beta$ -selective synthesis of 4'-thio-C-ribonucleosides.

Nucleoside analogues are recognized as an important class of biologically active compounds, especially as antiviral and antitumor agents. The recent discovery that a simple replacement of the furanose ring-oxygen with a sulfur atom leads to promising antiviral or antitumor nucleosides, such as 4′-thiothymidine (1) and 2′-deoxy-4′-thiocytidine (2), has stimulated the synthesis of this class of nucleosides (Figure 1). $^{2-4}$  It has also been reported that 4′-thio-Cl-IB-MECA (4), a 4′-thioribonucleoside, exhibits a higher binding affinity to the human adenosine  $A_3$  receptor than the parent compound 3.5

Synthesis of these 4'-thionucleosides has been carried out based on either the Vorbrüggen condensation or Pummerer reaction. In one former example, 2,3,5-tri-*O*-acetyl-4-thioribo-

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

FIGURE 1. 2'-Deoxy-4'-thionucleosides and 4'-thioribonucleosides.

SCHEME 1. Synthesis of the  $\beta$ -Anomer of 2'-Deoxy-4'-thionucleosides on the Basis of Electrophilic Glycosidation with DTBS-4-thiofuranoid Glycal 5

furanosyl chloride was reacted with silylated uracil or 5-substituted uracils in the presence of  $Hg(OAc)_2$  to give the corresponding 4'-thiouridine derivatives with an anomeric ratio of  $\beta/\alpha=ca$ . 6/1, which contrasts to the usual ribofuranosyl cases that result in the exclusive formation of the  $\beta$ -anomer. Such lower  $\beta$ -selectivity observed in the synthesis of 4-thioribofuranosyl nucleosides has been explained by computational studies of model compounds that, due to inferior cationic character of the  $\alpha$ -thiocarbocation intermediate, neighboring group participation of the 2-acyloxy group does not function effectively. In the Pummerer glycosidation reaction,  $^{8-10}$  a significant improvement in the  $\beta$ -selectivity has been made, as reported by Matsuda et al., by employing 2-O-(2,4-dimethoxybenzoyl)-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol as a glycosyl donor.

We have previously reported the  $\beta$ -selective electrophilic glycosidation between the 3,5-O-(di-*tert*-butyl)silylene (DTBS)-protected 4-thiofuranoid glycal (5) and silylated nucleobases in the presence of phenylselenenyl chloride (Scheme 1). The glycosidation product **I** can readily be converted into the 2'-deoxy-4'-thionucleosides **II** by homolytic removal of the phenylseleno group. <sup>11,12</sup> In this paper, we describe a high yield and the  $\beta$ -selective synthesis of 4'-thionucleosides having the ribo-configuration, the outline of which is shown in Scheme 2.

<sup>(1)</sup> For a review, see: Nucleosides and Nucleotides as Antitumor and Antiviral Agents; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.

<sup>(2)</sup> Dyson, M. R.; Coe, P. L.; Walker, R. T. J. Med. Chem. 1991, 34, 2782–2786.

<sup>(3)</sup> Secrist, J. A., III; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361–2366.

<sup>(5)</sup> Jeong, L. S.; Jin, D. Z.; Kim, H. O.; Shin, D. H.; Moon, H. R.; Gunaga, P.; Chun, M. W.; Kim, Y.-C.; Meiman, N.; Gao, Z. C.; Jacobson, K. A. *J. Med. Chem.* **2003**, *46*, 3775–3777.

<sup>(6)</sup> Bobek, M.; Bloch, A.; Parthasarathy, R. J. Med. Chem. 1975, 18, 784–787.

<sup>(7)</sup> Naka, T.; Nishizono, N.; Minakawa, N.; Matsuda, A Tetrahedron Lett. 1999, 40, 6297–6300.

<sup>(8)</sup> Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. J. Am. Chem. Soc. 2000, 122, 7233–7243.

<sup>(9)</sup> In glycosidation with 1,2,3,5-tetra-O-acetyl-2- $\beta$ -methyl-4-thio ribofuranose, the respective 4'-thio- $\beta$ -ribonucleosides have been obtained stereoselectively Dukhan, D.; Bosc, E.; Peyronnet, J.; Storer, R.; Gosselin, G. *Nucleosides Nucleotides Nucleic Acids* **2005**, 24, 577–580.

<sup>(10)</sup> A practical synthesis of 4'-thioribonucleosides by Pummerer-type glycosidation has been recently reported: Yoshimura, Y.; Kuze, T.; Ueno, M.; Komiya, F.; Haraguchi, K.; Tanaka, H.; Kato, F.; Yamada, K.; Asami, K.; Kaneko, N.; Takahata, H. *Tetrahedron Lett.* **2006**, *47*, 591–594.

<sup>(11)</sup> Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713–3716.

<sup>(12)</sup> 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.

TABLE 1. Additive Pummerer Reaction of 6

entry	reaction conditions (equiv)	isolated yields (%)					
		7	8	9	10	11	6
1	Ac <sub>2</sub> O (5.0)/reflux	no reaction					
2	Ac <sub>2</sub> O (1.5)/TMSOTf (0.5)/rt	20	22	_	-	-	trace
3	Ac <sub>2</sub> O (3.0)/SnCl <sub>4</sub> (2.0)/rt	-	-	40	-	-	-
4	$Ac_2O (5.0)/BF_3 \cdot OEt_2 (5.0)/rt$	23	-	-	27	11	34
5	Ac <sub>2</sub> O (5.0)/BF <sub>3</sub> •OEt <sub>2</sub> (5.0)/TMSOAc (5.0)/rt	35	-	-	trace	trace	48
6	Ac <sub>2</sub> O (7.0)/BF <sub>3</sub> •OEt <sub>2</sub> (7.0)/TMSOAc (7.0)/rt	61	-	-	3	7	trace

## SCHEME 2. Synthetic Scheme for 4'-Thioribonucleosides from 4-Thiofuranoid Glycal

## SCHEME 3. Additive Pummerer Reaction of 4-Thiofuranoid Glycal S-Oxide 6

The first step of this approach is an additive Pummerer reaction<sup>13–15</sup> of the 4-thioglycal sulfoxide **III**, leading to the 4-thioribofuranose derivative **IV**.<sup>16</sup> The 4'-thioribonucleoside **V** can be obtained from **IV** by way of the Vorbrüggen method.

When the 4-thioglycal 5 was oxidized with m-CPBA at 0 °C, the corresponding sulfoxide 6 was obtained as a mixture of two diastereomers in 84% yield: 6a (major isomer)/6b (minor isomer) = 2.8/1 (Scheme 3). No reaction took place upon reacting 6 with Ac<sub>2</sub>O (5 equiv) in refluxing CH<sub>2</sub>Cl<sub>2</sub> (entry 1 in Table 1). As shown in entry 2, the presence of TMSOTf as a Lewis acid accelerated the additive Pummerer reaction to give the desired 1,2-di-O-acetyl-3,5-O-DTBS-4-thioribofuranose 7 in 20% yield as an anomeric mixture ( $\beta/\alpha = 12/1$ ). Additional products obtained in entry 2 were the 2'-O-triflates 8, which undoubtedly derived from TMSOTf. This observation led us to employ other Lewis acids. As shown in entry 3, the use of SnCl<sub>4</sub> resulted in cleavage of the cyclic silyl protecting group to give 9 as the sole product. In entry 4, when SnCl<sub>4</sub> was replaced with BF<sub>3</sub>•OEt<sub>2</sub> (5 equiv), there were formed three products, the desired 7 (23%) along with the partially desilylated products 10 (27%) and 11 (11%). When this BF<sub>3</sub>·OEt<sub>2</sub>-assisted reaction was carried out in the presence of TMSOAc (entry 5), the formation of 10 and 11 was suppressed to a trace amount, although a considerable amount of 6 was recovered. The highest yield of 7 (61%) was obtained by increasing the amounts of

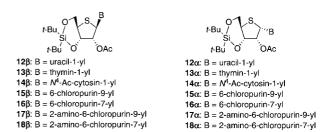


FIGURE 2. 4'-Thiopyrimidine- and purine-ribonucleosides.

TABLE 2. Vorbrüggen-Type Glycosidation between 7 and Nucleobase

entry	nucleobse	temp (°C)	products	isolated yield (%)	ratio of $\beta/\alpha$
1	uracil	60	$12\beta + 12\alpha$	93	22:1
2	thymine	80	$13\beta + 13\alpha$	93	22:1
3	$N^4$ -Ac-cytosine	60	$14\beta + 14\alpha$	91	23:1
4	6-Cl-purine	80	$15\beta + 15\alpha$	58	24:1
			$16\beta + 16\alpha$	21	23:1
5	2-NH <sub>2</sub> -6-Cl-purine	100	$17\beta + 17\alpha$	49	23:1
	•		$18\beta + 18\alpha$	22	13:1

<sup>&</sup>lt;sup>a</sup> The anomeric ratio was determined by comparison of integration of the proton at the base moiety.

the reagents (entry 6). To see if the stereochemistry of the sulfoxide has any influence on the yield of **7**, **6a** and **6b** were separately reacted under the conditions of entry 6, but no significant difference was seen: 59% yield from **6a** and 61% yield from **6b**.

With the glycosyl donor 7 in hand, its Vorbrüggen condensation with nucleobases was examined (Figure 2 and Table 2). When 7 was reacted with bis-O-TMS-uracil in the presence of TMSOTf in CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> at 50 °C for 24 h, the 4'-thiouridine derivative 12 was obtained in 93% yield in a highly  $\beta$ -selective manner (entry 1). The depicted structure of  $12\beta$  was determined on the basis of NOE experiment [H-1'/H-4' (2.5%), H-6/H-2' (2.5%), H-6/H-5'a (6.2%), 2'-O-COCH<sub>3</sub>/H-4' (0.6%)]. The  $\beta$ -stereochemistry of other 4'-thioribonucleosides (13 $\beta$ -18 $\beta$ ) was confirmed also by NOE experiments. The reaction of thymine and  $N^4$ -acetylcytosine also proceeded successfully both in terms of the yield and  $\beta$ -selectivity (entries 2 and 3). The use of 6-chloropurine (entry 4) maintained the high  $\beta$ -selectivity, although yield of the desired  $N^9$ - $\beta$ -4-thioriboside **15** $\beta$  decreased due to the formation of the  $N^7$ -isomer (16). The high  $\beta$ -selectivity was also the case for the formation of the  $N^9$ -isomer 17 of 2-amino-6-chloropurine (entry 5), but comparatively lower  $\beta$ -selectivity was observed in the formation of the  $N^7$ -isomer (18). At the moment, we do not have a clear explanation for this result.

<sup>(13)</sup> Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263–11304.

<sup>(14)</sup> Yamagiwa, S.; Sato, H.; Hoshi, N.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 570–583.

<sup>(15)</sup> Paquette, L. A.; Fabris, F.; Gallou, F.; Dong, S. J. Org. Chem. 2003, 68, 8625–8634.

<sup>(16)</sup> Sung, Z.-H.; Wang, B. J. Org. Chem. 2008, 73, 2462–2465.

<sup>(17)</sup> Of the two protons at the 5'-position, the one that appears at a higher field is designated as H-5'a, and the other as H-5'b, throughout the text and Experimental Section.

**JOC** Note

FIGURE 3. Intermediate VI and compound 19.

FIGURE 4. 4'-Thio-C-nucleosides  $20\beta$  and  $21\beta$ 

The above observed high  $\beta$ -selectivity, with the exception of the formation of 18, suggested that the 3,5-O-DTBSprotection may provide the incipient sulfonium ion VI with a favorable conformation for effective participation by the neighboring 2-acetoxy group. Inspection of a molecular model revealed that the 4-thiofuranose ring of VI is fixed as the 3-endo conformation as depicted in Figure 3, which accommodates the 2-acetoxy group in quasi-axial orientation. We assume that this 3-endo-fixed conformation would contribute to the observed uniformly high  $\beta$ -selectivity. It should be mentioned that the authors of ref 8 examined the reaction between the 3,5-O-cyclic silyl-protected 4-thioribofuranose 19 and silylated uracil in CH<sub>3</sub>CN in the presence of TMSOTf (Figure 3). Although this reaction gave the  $\beta$ -anomer of the respective glycosidated product stereoselectively, the yield was not satisfactory being only 35% even after 35 h with the recovery of 19 in 13% yield.

At this stage, we turned our attention to the synthesis of 4'-thio-C-nucleosides  $^{18-20}$  by employing 7. When 2-(tributyl-stannyl)thiophene was reacted with 7 in  $CH_2Cl_2$  in the presence of TMSOTf at 0 °C, the (thiophen-2-yl)nucleoside **20** was obtained in 79% yield with a ratio of  $\beta/\alpha=23/1$  (Figure 4). This C-glycosidation constitutes the first example for the  $\beta$ -selective synthesis of a 4'-thio-C-nucleoside. The reaction of 2-(tributylstannyl)furan under similar reaction conditions gave **21** in 61% yield again with a high  $\beta$ -selectivity ( $\beta/\alpha=24/1$ ).

The observed highly stereoselective *C*-glycosidation encouraged us to synthesize the 4'-thio-counterpart of tiazofurin, which is known as a synthetic *C*-nucleoside having antitumor activity.<sup>21</sup> However, when 4-bromo-2-(tributylstannyl)thiazole<sup>22</sup> was reacted with 7, a mixture of unknown products was formed. The reported synthetic route for tiazofurin has utilized a 1-*C*-cyanoribofuranose derivative as a key precursor.<sup>23</sup> The reaction of 7 with TMSCN/TMSOTf carried out in this context resulted in intramolecular cyclization of the 2-*O*-acetyl group to give the cyclic acetal **22a** (27%) and **22b** (10%) (Figure 5). An

FIGURE 5. Compounds 22–25.

#### SCHEME 4. Synthesis of 4'-Thiotiazofurin

apparent solution of this problem is to prepare a 2-*O*-silyl derivative corresponding to 7. Compound 7 was converted to the 1-phenylthio derivative **23** (87%) by reacting with (phenylthio)trimethylsilane in the presence of SnCl<sub>4</sub> (Figure 5). Deacetylation of **23** with NH<sub>3</sub>/MeOH and subsequent silylation gave **24** in 89% yield. The 2-*O*-TBDMS glycosyl donor **25** was obtained in 96% yield by acetolysis of **24** with Hg(OAc)<sub>2</sub>/AcOH.

Unexpectedly, the reactions of **25** with TMSCN by using several different Lewis acids (SnCl<sub>4</sub>, BF<sub>3</sub>•OEt<sub>2</sub>, TMSOTf, and EtAlCl<sub>2</sub>) all gave complex mixtures of products. In contrast to this, when the bromosugar **26**, prepared by reacting **25** with TMSBr, was reacted with Hg(CN)<sub>2</sub>, the desired 1-*C*-cyano derivative **27** was obtained in 63% overall yield as the sole product, the anomeric configuration of which was determined on the basis of NOE experiment: H-1/H-4 (0.9%) (Scheme 4). According to the published procedure, <sup>23</sup> **27** was reacted with cysteine ethyl ester to give the tiazolin derivative **28**, which subsequently was converted to the thiazole 4-carboxylic ethyl ester **29** by reacting with BrCCl<sub>3</sub>. Ammonolysis of **29** furnished the protected 4'-thiotiazofurin **30** in 87% overall yield from **27**. Deprotection of **30** with Bu<sub>4</sub>NF gave **31**.

In conclusion, we have prepared 1,2-di-O-acetyl-3,5-O-DTBS-4-thioribofuranose **7** by means of the additive Pummerer reaction of the glycal S-oxide **6**. The utility of **7** as a glycosyl donor for the  $\beta$ -selective synthesis of 4'-thioribonucleosides has been demonstrated by the preparation of 4'-thio analogues of pyrimidine-  $(12\beta-14\beta)$  and purine-ribonucleosides  $(15\beta)$  and  $17\beta$ ) based on the Vorbrüggen method. By reacting **7** with the 2-tributylstannyl derivatives of thiophene and furan in place of a nucleobase, the corresponding 4'-thio-C-ribonucleosides  $(20\beta)$  and  $(21\beta)$  were also synthesized, which constitutes the first example of a stereoselective synthesis of 4'-thio-C-nucleosides.

<sup>(18)</sup> Uenishi, J.; Sohma, A.; Yonemitsu, O. Chem. Lett. 1996, 595-596.

<sup>(19)</sup> Franchetti, P.; Marchetti, S.; Cappellacci, L.; Jayaram, H. N.; Yalowitz, J. A.; Goldstein, B. M.; Barascut, J.-L.; Dukhan, D.; Imbach, J.-M.; Grifantini, M. J. Med. Chem. 2000, 43, 1264–1270.

<sup>(20)</sup> Ulgar, V.; Lopez, O.; Maya, I.; Fernandez-Bolanos, J. G.; Bols, M. *Tetrahedron* **2003**, *59*, 2801–2809.

<sup>(21)</sup> Watanabe, K. A. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994: Vol. 3, pp 421–535. (22) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 9293–9296.

<sup>(23)</sup> Brown, R. S.; Dowden, J.; Moreau, C.; Potter, B. V. L. Tetrahedron Lett. 2002, 43, 6561–6562.

Synthesis of the 4'-thio-counterpart of tiazofurin (31) has also been carried out.

#### **Experimental Section**

Additive Pummerer Reaction of 6 with Ac<sub>2</sub>O/TMSOAc/ BF<sub>3</sub>·OEt<sub>2</sub>: Formation of 7, 10, and 11. To a CH<sub>2</sub>Cl<sub>2</sub> (25 mL) solution of **6** (1.15 g, 3.99 mmol) was added Ac<sub>2</sub>O (2.6 mL, 27.93 mmol), TMSOAc (4.2 mL, 27.93 mmol), and BF<sub>3</sub>•OEt<sub>2</sub> (3.5 mL, 27.93 mmol) at 0 °C under Ar atmosphere then the mixture was stirred overnight. The reaction mixture was partitioned between CHCl<sub>3</sub>/saturated aq NaHCO<sub>3</sub> and column chromatography (hexane/ AcOEt = 40/1-20/1) of the organic layer gave 7 (967.2 mg, 62%, solid,  $\beta$ -isomer/ $\alpha$ -isomer = 13:1), **10** (54.3 mg, 3%, syrup,  $\beta$ -isomer/ $\alpha$ -isomer = 13:1), and 11 (334.9 mg, 17%, syrup,  $\beta$ -isomer/ $\alpha$ -isomer = 4.9:1).

Physical data for 7 (β-anomer): m.p. 105–107 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.00 and 1.07 (18H, each as s, Si-t-Bu), 2.10 and 2.13 (6H, each as s, Ac), 3.66-3.73 (2H, m), 4.02 ( ${}^{1}$ H, t, J = J = 11.2Hz), 4.28-4.35 (2H, m), 5.47 (1H, d, J = 3.2 Hz), 5.70 (1H, s); NOE experiment: H-1/H-4 (1.7%) and H-2/H-3 (7.3%); <sup>13</sup>C NMR  $(CDCl_3)$   $\delta$  20.79, 20.86, 22.67, 26.91, 27.18, 44.61, 68.43, 78.55, 79.06, 169.30, 169.48. FAB-MS (m/z) 391  $(M^+ + H)$  and 331  $(M^+)$ OAc). Anal. Calcd for C<sub>17</sub>H<sub>30</sub>O<sub>6</sub>SSi: C, 52.28; H, 7.74. Found: C, 52.42; H, 7.89. Physical data for 7 (α-anomer): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.01 and 1.04 (18H, each as s, Si-t-Bu), 2.07 and 2.19 (6H, each as s, Ac), 3.91-3.99 (2H, m), 4.17 (1H, dd, J = 4.6 and J = 7.4Hz), 4.27 ( ${}^{1}$ H, dd, J = 3.2 and J = 10.8 Hz), 6.70 (1H, t, J = J =4.6 Hz), 6.21 (1H, d, J = 4.6 Hz); NOE experiment: H-1/H-2 (12%) and H-1/H-3 (4.8%);  $^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  20.12, 20.67, 22.74, 26.88, 27.16, 45.94, 72.73, 75.28, 78.69, 169.76, 169.88. FAB-MS (m/z) 391  $(M^+ + H)$  and 331  $(M^+ - OAc)$ . Anal. Calcd for C<sub>17</sub>H<sub>30</sub>O<sub>6</sub>SSi: C, 52.28; H, 7.74. Found: C, 52.56; H, 7.87.

Physical data for 10: <sup>1</sup>H NMR (CDCl<sub>3</sub>) ( $\beta$ -isomer)  $\delta$  1.05 and 1.06 (18H, each as s, Si-t-Bu), 2.07, 2.09, and 2.13 (9H, each as s), 3.64-3.69 (1H, m), 4.18 (1H, dd,  $J_{4,5a} = 7.2$  Hz and  $J_{5a,5b} =$ 11.6 Hz), 4.43 (1H, dd,  $J_{4,5b} = 5.6$  Hz and  $J_{5a,5b} = 11.4$  Hz), 4.59 (1H, dd,  $J_{2,3} = 5.6$  Hz and  $J_{3,4} = 8.8$  Hz), 5.41 (1H, dd,  $J_{1,2} = 3.2$ Hz and  $J_{2,3} = 3.6$  Hz), 5.81 (1H, d,  $J_{1,2} = 3.2$  Hz); ( $\alpha$ -isomer, selected data)  $\delta$  3.40–3.45 (1H, m), 4.52 (1H, dd,  $J_{4,5b} = 4.6$  Hz and  $J_{5a,5b} = 11.4$  Hz), 5.21 (1H, dd,  $J_{1,2} = 4.4$  Hz and  $J_{2,3} = 9.2$ Hz), 5.94 (1H, d,  $J_{1,2}$  = 4.4 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ (β-anomer) 20.1, 20.7, 20.9, 26.7, 26,8, 27,2, 29.7, 49.1, 64.9, 74.5, 77.9, 79.2, 169.7, 169.9, 170.4;  $\delta$  ( $\alpha$ -isomer, selected data) 26.8, 45.8, 65.5, 74.2, 76.1, 78.1, 170.4. FAB-MS (m/z) 393 (M<sup>+</sup> - OAc). Anal. Calcd for  $C_{19}H_{33}FO_7SSi^{-1}/_3AcOEt$ : C, 50.67; H, 7.46. Found: C, 51.02; H, 7.37.

Physical data for 11: <sup>1</sup>H NMR (CDCl<sub>3</sub>) ( $\beta$ -isomer)  $\delta$  1.07 and 1.08 (18H, s, Si-t-Bu), 2.10, 2.13 and 2.15 (12H, each as s), 3.68-3.73 (1H, m), 4.12 (1H, dd,  $J_{4,5a} = 7.6$  Hz and  $J_{5a,5b} = 11.6$ Hz), 4.51 (1H, dd,  $J_{4,5b} = 4.4$  Hz and  $J_{5a,5b} = 11.6$  Hz), 4.79 (1H, dd,  $J_{2,3} = 3.6$  Hz and  $J_{3,4} = 7.2$  Hz), 5.50 (1H, dd,  $J_{1,2} = 2.8$  Hz and  $J_{2,3} = 3.6$  Hz), 5.77 (1H, d,  $J_{1,2} = 2.8$  Hz); ( $\alpha$ -isomer)  $\delta$  1.09 and 1.11 (18H, each as s), 2.06, 2.08, 2.10, and 2.14 (12H, each as s), 3.79 (1H, dt, J = 2.0 Hz, J = 4.8 Hz, and J = 6.8 Hz), 410 (1H, dd,  $J_{4,5a} = 4.8$  Hz and  $J_{5a,5b} = 10.8$  Hz), 4.15 (1H, dd,  $J_{4,5b} =$ 6.8 Hz and  $J_{5a,5b} = 10.8$  Hz), 4.90 (1H, dd,  $J_{2,3} = 4.4$  Hz and  $J_{3,4}$ = 2.0 Hz), 5.28 (1H, dd,  $J_{1,2}$  = 5.6 Hz and  $J_{2,3}$  = 4.4 Hz), 6.24 (1H, d,  $J_{1,2} = 5.6$  Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  ( $\beta$ -anomer) 20.3, 20.5, 20.5, 20.7, 22.1, 26.8, 26.9, 48.6, 64.9, 72.4, 74.7, 77.3, 78.7, 169.3, 169.4, 169.5, 167.0;  $\delta$  ( $\alpha$ -anomer) 20.6, 20.6, 20.9, 21.3, 22.5, 27.0, 27.1, 27.2, 50.0, 64.9, 74.5, 76.2, 76.3, 169.6, 169.7, 170.1, 170.3. FAB-MS (m/z) 433 (M<sup>+</sup> – OAc). Anal. Calcd for C<sub>21</sub>H<sub>36</sub>O<sub>9</sub>SSi: C, 51.20; H, 7.37. Found: C, 51.41; H, 7.56.

1-[2-O-Acetyl-3,5-O-(di-tert-butylsilylene)-4-thio- $\beta$ , $\alpha$ -D-ribofuranosyl]uracil (12). To an CH<sub>3</sub>CN (3.5 mL) solution of bis-Otrimethylsilyluracil, prepared from uracil (90.8 mg, 0.81 mmol) and BSA (0.4 mL, 1.62 mmol), was added an CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL) solution of 7 (104.1 mg, 0.27 mmol) and TMSOTf (0.21 mL, 1.08 mmol) at 0 °C under Ar atmosphere and the mixture was stirred at 60 °C for 24 h. The reaction mixture was partitioned between CHCl<sub>3</sub>/ saturated ag NaHCO<sub>3</sub> and column chromatography (hexane/AcOEt = 3/1) of the organic layer gave 12 (111.7 mg, 93%,  $12\beta/12\alpha$  = 22:1) as a foam: UV (MeOH)  $\lambda_{\text{max}}$  264 nm ( $\epsilon$  10500),  $\lambda_{\text{min}}$  232 nm ( $\epsilon$  2400). <sup>1</sup>H NMR (CDCl<sub>3</sub>) (**12\beta**)  $\delta$  1.00 and 1.05 (18H, each as s), 2.15 (3H, s), 3.70–3.76 (1H, m), 4.12 (1H, dd,  $J_{4',5'a} = 10.4$ Hz and  $J_{5'a,5'b} = 11.2$  Hz), 4.27 (1H, dd,  $J_{2',3'} = 4.4$  Hz and  $J_{3',4'} =$ 10.0 Hz), 4.41 (1H, dd,  $J_{4',5'b} = 4.4$  Hz and  $J_{5'a,5'b} = 11.2$  Hz), 5.50 (1H, dd,  $J_{1',2'} = 0.8$  Hz and  $J_{2',3'} = 4.4$  Hz), 5.83 (1H, d,  $J_{5,6} = 8.2$ Hz), 5.96 (1H, d,  $J_{1',2'} = 0.8$  Hz), 7.61 (1H, d,  $J_{5.6} = 8.2$  Hz), 9.18 (1H, br); (12 $\alpha$ , selected data)  $\delta$  1.01 and 1.07 (18H, each as s), 2.12 (3H, s), 5.21 (1H, dd,  $J_{1',2'} = 7.2$  Hz and  $J_{2',3'} = 9.5$  Hz), 5.89 (1H, d,  $J_{5,6} = 8.2$  Hz), 6.11 (1H, d,  $J_{1',2'} = 7.2$  Hz), 7.86 (1H, d,  $J_{5.6} = 8.2 \text{ Hz}$ ). NOE experiment ( $\beta$ -isomer): H-1'/H-4' (1.2%), H-6/ H-2' (2.5%), H-6/H-5'a (6.2%), COCH<sub>3</sub>/H-4' (0.6%). <sup>13</sup>C NMR  $(CDCl_3) \delta (12\beta) 20.1, 20.8, 22.8, 26.8, 27.2, 27.3, 46.3, 63.6, 67.8,$ 79.4, 103.4, 140.3, 149.7, 162.0, 168.9. FAB-MS (*m/z*) 443 (M<sup>+</sup> + H). Anal. Calcd for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>SSi • <sup>1</sup>/<sub>4</sub>AcOEt: C, 51.70; H, 6.94; N, 6.02. Found: C, 51.98; H, 7.07; N, 5.83.

**Acknowledgment.** Financial support from the Japan Society for the Promotion of Science (KAKENHI No. 19590106 to K.H. and No. 17590094 to H.T.), the Research Foundation of Pharmaceutical Sciences (to K.H.), and the Japan Health Sciences Foundation (SA 14804 to H.T.) is gratefully acknowledged. The authors are also grateful to Ms. K. Shiohara and Y. Odanaka (Center for Instrumental Analysis, Showa University) for technical assistance with NMR, MS, and elemental analyses.

Supporting Information Available: Experimental procedures, full characterization, and copies of spectra for compounds 6−18 and 20−31. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802615H