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Additive Pummerer Reaction of 3,5-*O*-(Di-*tert*-butyl)silylene-4-thiofuranoid Glycal: A High-Yield and β-Selective Entry to 4′-Thioribonucleosides

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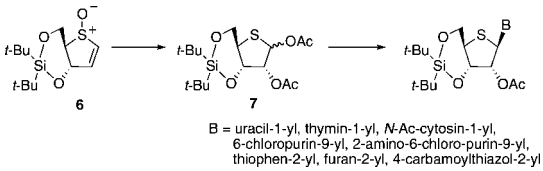


Upon reacting 3,5-*O*-(di-*tert*-butyl)silylene-4-thiofuranoid glycal *S*-oxide (**6**) with Ac_2O/TMSOAc/$BF_3 \cdot OEt_2$ in CH_2Cl_2, the additive Pummerer reaction proceeded to furnish the corresponding 1,2-di-*O*-acetyl-4-thioribofuranose **7**. Compound **7** serves as a highly β-selective glycosyl donor in the Vorbrüggen condensation carried out in the presence of TMSOTf. Thus, the 4-thio-β-D-ribofuranosyl derivatives of uracil, thymine, N^4-acetylcytosine, 6-chloropurine, and 2-amino-6-chloropurine were synthesized. The use of **7** can be extended to the β-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.[1] 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-thioribofuranosyl 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 β/α = ca. 6/1,[6] which contrasts to the usual ribofuranosyl cases that result in the exclusive formation of the β-anomer. Such lower β-selectivity observed in the synthesis of 4-thioribofuranosyl nucleosides has been explained by computational studies of model compounds[7] that, due to inferior cationic character of the α-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 β-selectivity has been made, as reported by Matsuda et al.,[8] 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.

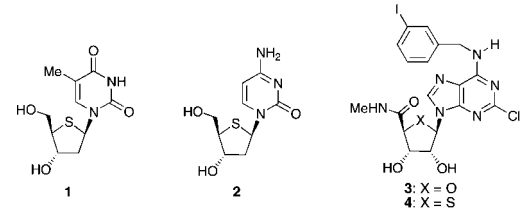
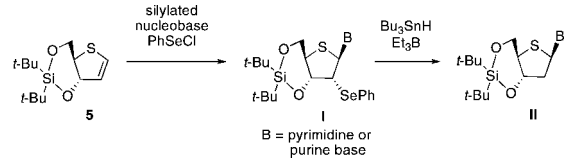


FIGURE 1. 2′-Deoxy-4′-thionucleosides and 4′-thioribonucleosides.

SCHEME 1. Synthesis of the β-Anomer of 2′-Deoxy-4′-thionucleosides on the Basis of Electrophilic Glycosidation with DTBS-4-thiofuranoid Glycal 5



We have previously reported the β-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.[11,12] In this paper, we describe a high yield and the β-selective synthesis of 4′-thionucleosides having the ribo-configuration, the outline of which is shown in Scheme 2.

(1) For a review, see: *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993.
(2) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782–2786.
(3) Secrist, J. A., III; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361–2366.
(4) For a review, see: Yokoyama, M. *Synthesis*, **2000**, 1637−1655.
(5) 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.
(6) Bobek, M.; Bloch, A.; Parthasarathy, R. *J. Med. Chem.* **1975**, *18*, 784–787.
(7) Naka, T.; Nishizono, N.; Minakawa, N.; Matsuda, A *Tetrahedron Lett.* **1999**, *40*, 6297–6300.
(8) Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 7233–7243.
(9) In glycosidation with 1,2,3,5-tetra-*O*-acetyl-2-β-methyl-4-thio ribofuranose, the respective 4′-thio-β-ribonucleosides have been obtained stereoselectively Dukhan, D.; Bosc, E.; Peyronnet, J.; Storer, R.; Gosselin, G. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 577–580.
(10) 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.
(11) Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713–3716.
(12) 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.

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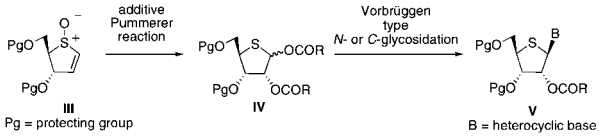
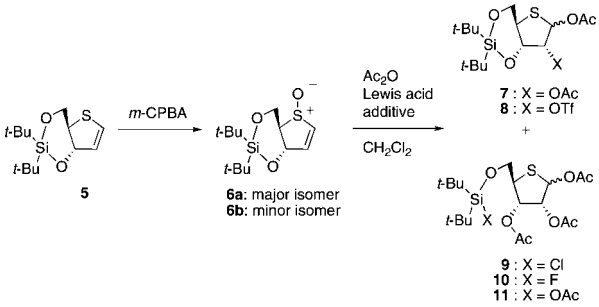
TABLE 1. Additive Pummerer Reaction of 6

entry	reaction conditions (equiv)	isolated yields (%) 7	8	9	10	11	6
1	Ac_2O (5.0)/reflux	no reaction					
2	Ac_2O (1.5)/TMSOTf (0.5)/rt	20	22	-	-	-	trace
3	Ac_2O (3.0)/$SnCl_4$ (2.0)/rt	-	-	40	-	-	-
4	Ac_2O (5.0)/$BF_3 \cdot OEt_2$ (5.0)/rt	23	-	-	27	11	34
5	Ac_2O (5.0)/$BF_3 \cdot OEt_2$ (5.0)/TMSOAc (5.0)/rt	35	-	-	trace	trace	48
6	Ac_2O (7.0)/$BF_3 \cdot OEt_2$ (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[13−15] of the 4-thioglycal sulfoxide **III**, leading to the 4-thioribofuranose derivative **IV**.[16] 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_2O (5 equiv) in refluxing CH_2Cl_2 (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 (β/α = 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 $SnCl_4$ resulted in cleavage of the cyclic silyl protecting group to give **9** as the sole product. In entry 4, when $SnCl_4$ was replaced with $BF_3 \cdot OEt_2$ (5 equiv), there were formed three products, the desired **7** (23%) along with the partially desilylated products **10** (27%) and **11** (11%). When this $BF_3 \cdot OEt_2$-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 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**.

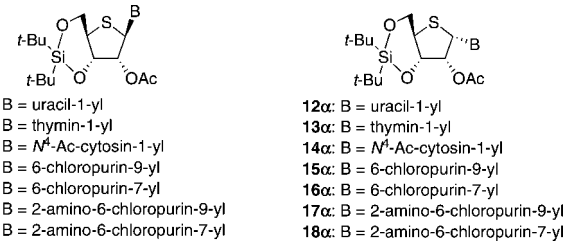


FIGURE 2. 4′-Thiopyrimidine- and purine-ribonucleosides.

TABLE 2. Vorbrüggen-Type Glycosidation between 7 and Nucleobase

entry	nucleobse	temp (°C)	products	isolated yield (%)	ratio of β/α
1	uracil	60	**12β** + **12α**	93	22:1
2	thymine	80	**13β** + **13α**	93	22:1
3	N^4-Ac-cytosine	60	**14β** + **14α**	91	23:1
4	6-Cl-purine	80	**15β** + **15α**	58	24:1
			16β + **16α**	21	23:1
5	2-NH_2-6-Cl-purine	100	**17β** + **17α**	49	23:1
			18β + **18α**	22	13:1

[a] The anomeric ratio was determined by comparison of integration of the proton at the base moiety.

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_3CN/CH_2Cl_2 at 50 °C for 24 h, the 4′-thiouridine derivative **12** was obtained in 93% yield in a highly β-selective manner (entry 1). The depicted structure of **12β** 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*-$COCH_3$/H-4′ (0.6%)].[17] The β-stereochemistry of other 4′-thioribonucleosides (**13β**−**18β**) was confirmed also by NOE experiments. The reaction of thymine and N^4-acetylcytosine also proceeded successfully both in terms of the yield and β-selectivity (entries 2 and 3). The use of 6-chloropurine (entry 4) maintained the high β-selectivity, although yield of the desired N^9-β-4-thioriboside **15β** decreased due to the formation of the N^7-isomer (**16**). The high β-selectivity was also the case for the formation of the N^9-isomer **17** of 2-amino-6-chloropurine (entry 5), but comparatively lower β-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.

(13) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263–11304.
(14) Yamagiwa, S.; Sato, H.; Hoshi, N.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 570−583.
(15) Paquette, L. A.; Fabris, F.; Gallou, F.; Dong, S. *J. Org. Chem.* **2003**, *68*, 8625–8634.
(16) Sung, Z.-H.; Wang, B. *J. Org. Chem.* **2008**, *73*, 2462–2465.

(17) 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.

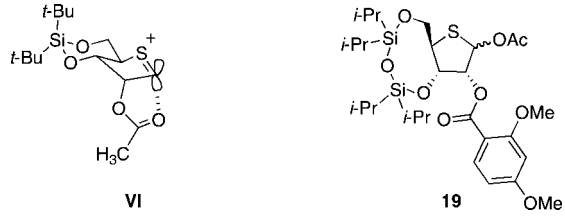


FIGURE 3. Intermediate VI and compound **19**.

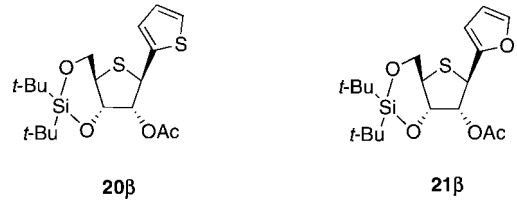


FIGURE 4. 4′-Thio-*C*-nucleosides **20*β*** and **21*β***

The above observed high β-selectivity, with the exception of the formation of **18**, suggested that the 3,5-*O*-DTBS-protection 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 β-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_3CN in the presence of TMSOTf (Figure 3). Although this reaction gave the β-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-(tributylstannyl)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 β/α = 23/1 (Figure 4). This *C*-glycosidation constitutes the first example for the β-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 β-selectivity (β/α = 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.[21] However, when 4-bromo-2-(tributylstannyl)thiazole[22] 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.[23] 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

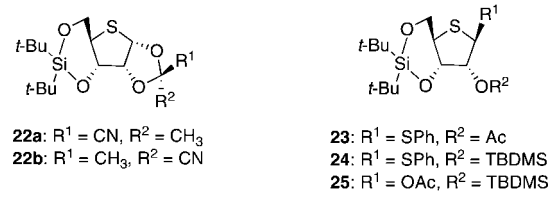
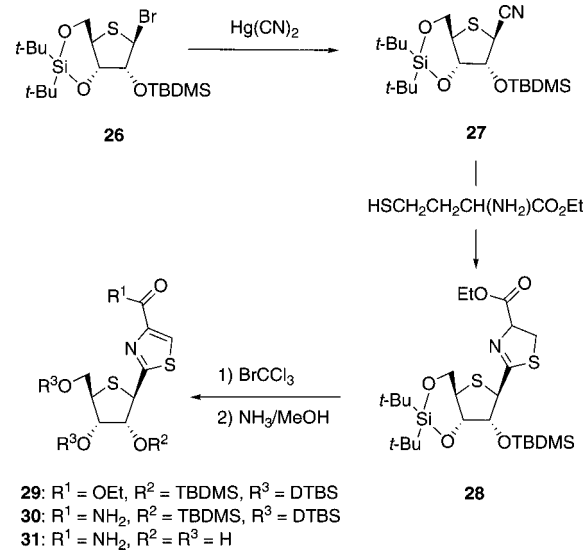


FIGURE 5. Compounds **22**−**25**.

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 $SnCl_4$ (Figure 5). Deacetylation of **23** with NH_3/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 $Hg(OAc)_2$/AcOH.

Unexpectedly, the reactions of **25** with TMSCN by using several different Lewis acids ($SnCl_4$, $BF_3 \cdot OEt_2$, TMSOTf, and $EtAlCl_2$) all gave complex mixtures of products. In contrast to this, when the bromosugar **26**, prepared by reacting **25** with TMSBr, was reacted with $Hg(CN)_2$, 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,[23] **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 $BrCCl_3$. Ammonolysis of **29** furnished the protected 4′-thiotiazofurin **30** in 87% overall yield from **27**. Deprotection of **30** with Bu_4NF 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 β-selective synthesis of 4′-thioribonucleosides has been demonstrated by the preparation of 4′-thio analogues of pyrimidine- (**12*β***−**14*β***) and purine-ribonucleosides (**15*β*** and **17*β***) 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*β*** and **21*β***) were also synthesized, which constitutes the first example of a stereoselective synthesis of 4′-thio-*C*-nucleosides.

(18) Uenishi, J.; Sohma, A.; Yonemitsu, O. *Chem. Lett.* **1996**, 595−596.
(19) 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.
(20) Ulgar, V.; Lopez, O.; Maya, I.; Fernandez-Bolanos, J. G.; Bols, M. *Tetrahedron* **2003**, *59*, 2801–2809.
(21) 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.
(23) 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_2O/TMSOAc/BF_3·OEt_2: Formation of 7, 10, and 11. To a CH_2Cl_2 (25 mL) solution of **6** (1.15 g, 3.99 mmol) was added Ac_2O (2.6 mL, 27.93 mmol), TMSOAc (4.2 mL, 27.93 mmol), and BF_3·OEt_2 (3.5 mL, 27.93 mmol) at 0 °C under Ar atmosphere then the mixture was stirred overnight. The reaction mixture was partitioned between $CHCl_3$/saturated aq $NaHCO_3$ and column chromatography (hexane/AcOEt = 40/1−20/1) of the organic layer gave **7** (967.2 mg, 62%, solid, β-isomer/α-isomer = 13:1), **10** (54.3 mg, 3%, syrup, β-isomer/α-isomer = 13:1), and **11** (334.9 mg, 17%, syrup, β-isomer/α-isomer = 4.9:1).

Physical data for **7** (β-anomer): m.p. 105−107 °C. ^{1}H NMR ($CDCl_3$) δ 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, $J = J = 11.2$ Hz), 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%); ^{13}C NMR ($CDCl_3$) δ 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 $C_{17}H_{30}O_6SSi$: C, 52.28; H, 7.74. Found: C, 52.42; H, 7.89. Physical data for **7** (α-anomer): ^{1}H NMR ($CDCl_3$) 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 $J = 7.4$ Hz), 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 ($CDCl_3$) δ 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 $C_{17}H_{30}O_6SSi$: C, 52.28; H, 7.74. Found: C, 52.56; H, 7.87.

Physical data for **10**: ^{1}H NMR ($CDCl_3$) (β-isomer) δ 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); (α-isomer, selected data) δ 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). ^{13}C NMR ($CDCl_3$) 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; δ (α-isomer, selected data) 26.8, 45.8, 65.5, 74.2, 76.1, 78.1, 170.4. FAB-MS (*m/z*) 393 ($M^+ - OAc$). Anal. Calcd for $C_{19}H_{33}FO_7SSi$·$^1/_3$AcOEt: C, 50.67; H, 7.46. Found: C, 51.02; H, 7.37.

Physical data for **11**: ^{1}H NMR ($CDCl_3$) (β-isomer) δ 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); (α-isomer) δ 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). ^{13}C NMR ($CDCl_3$) δ (β-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; δ (α-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 ($M^+ - OAc$). Anal. Calcd for $C_{21}H_{36}O_9SSi$: 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-β,α-D-ribofuranosyl]uracil (12). To an CH_3CN (3.5 mL) solution of bis-*O*-trimethylsilyluracil, prepared from uracil (90.8 mg, 0.81 mmol) and BSA (0.4 mL, 1.62 mmol), was added an CH_2Cl_2 (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 $CHCl_3$/saturated aq $NaHCO_3$ and column chromatography (hexane/AcOEt = 3/1) of the organic layer gave **12** (111.7 mg, 93%, **12β/12α** = 22:1) as a foam: UV (MeOH) λ_{max} 264 nm (ϵ 10500), λ_{min} 232 nm (ϵ 2400). ^{1}H NMR ($CDCl_3$) (**12β**) δ 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); (**12α**, selected data) δ 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, $J_{5,6} = 8.2$ Hz). NOE experiment (β-isomer): H-1′/H-4′ (1.2%), H-6/H-2′ (2.5%), H-6/H-5′a (6.2%), CO*CH*$_3$/H-4′ (0.6%). ^{13}C NMR ($CDCl_3$) δ (**12β**) 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 ($M^+ + H$). Anal. Calcd for $C_{19}H_{30}N_2O_6SSi$·$^1/_4$AcOEt: C, 51.70; H, 6.94; N, 6.02. Found: C, 51.98; H, 7.07; N, 5.83.

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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.

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