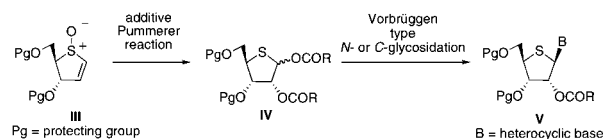
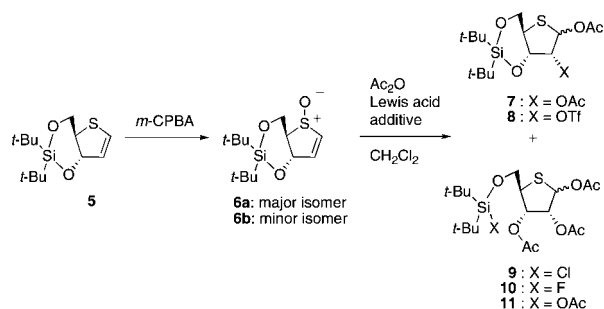


TABLE 1. Additive Pummerer Reaction of **6**

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

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

SCHEME 3. Additive Pummerer Reaction of 4-Thiofuranoid Glycol S-Oxide **6**

The first step of this approach is an additive Pummerer reaction^{13–15} of the 4-thioglycol 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-thioglycol **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 Ac₂O (5 equiv) in refluxing CH₂Cl₂ (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 SnCl₄ resulted in cleavage of the cyclic silyl protecting group to give **9** as the sole product. In entry 4, when SnCl₄ was replaced with BF₃·OEt₂ (5 equiv), there were formed three products, the desired **7** (23%) along with the partially desilylated products **10** (27%) and **11** (11%). When this BF₃·OEt₂-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

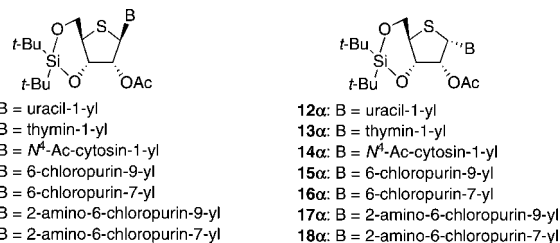


FIGURE 2. 4'-Thiopyrimidine- and purine-ribonucleosides.

TABLE 2. Vorbrüggen-Type Glycosidation between **7** and Nucleobase

entry	nucleobase	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.

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 CH₃CN/CH₂Cl₂ 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*-COCH₃/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 N⁴-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 N⁹-β-4-thioriboside **15β** decreased due to the formation of the N⁷-isomer (**16**). The high β-selectivity was also the case for the formation of the N⁹-isomer **17** of 2-amino-6-chloropurine (entry 5), but comparatively lower β-selectivity was observed in the formation of the N⁷-isomer (**18**). At the moment, we do not have a clear explanation for this result.

(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.

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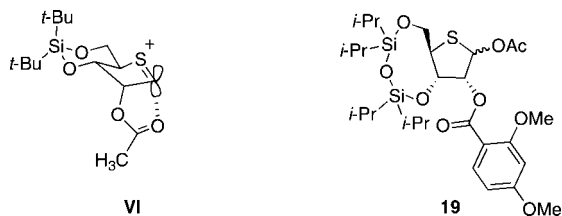
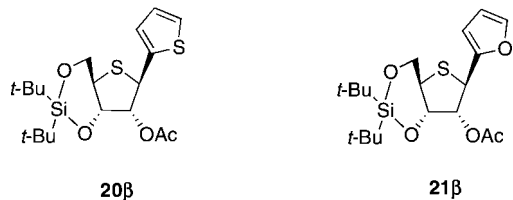


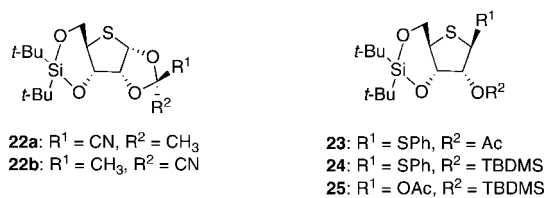
FIGURE 3. Intermediate VI and compound 19.

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

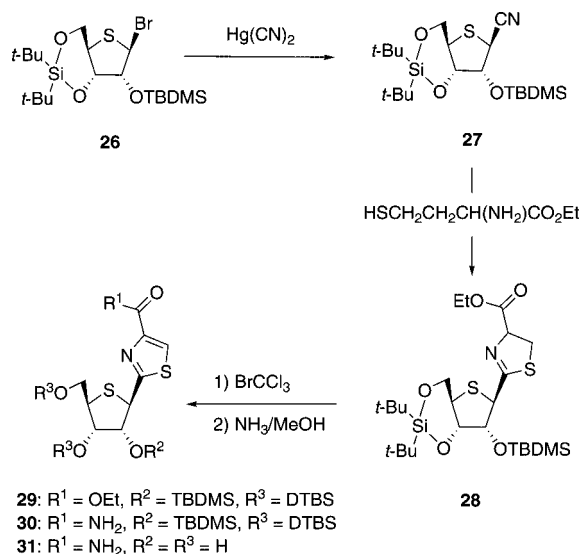
The above observed high β -selectivity, with the exception of the formation of **18**, suggested that the 3,5-*O*-DTBS-protection may provide the incipient sulfonium ion **VI** with a favorable conformation for effective participation by the neighboring 2-acetoxy group. Inspection of a molecular model 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 CH₃CN 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 CH₂Cl₂ 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 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 ($\beta/\alpha = 24/1$).

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.²¹ However, when 4-bromo-2-(tributylstannyl)thiazole²² 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 SnCl₄ (Figure 5). Deacetylation of **23** with NH₃/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 (SnCl₄, BF₃·OEt₂, TMSOTf, and EtAlCl₂) 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 thiazolin derivative **28**, which subsequently was converted to the thiazole 4-carboxylic ethyl ester **29** by reacting with BrCCl₃. Ammonolysis of **29** furnished the protected 4'-thiotiazofurin **30** in 87% overall yield from **27**. Deprotection of **30** with Bu₄NF 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- (**12β–14β**) and purine-ribonucleosides (**15β** and **17β**) 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 (**20β** and **21β**) were also synthesized, which constitutes the first example of a stereoselective synthesis of 4'-thio-*C*-nucleosides.

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

Experimental Section

Additive Pummerer Reaction of 6 with Ac₂O/TMSOAc/BF₃·OEt₂: Formation of 7, 10, and 11. To a CH₂Cl₂ (25 mL) solution of **6** (1.15 g, 3.99 mmol) was added Ac₂O (2.6 mL, 27.93 mmol), TMSOAc (4.2 mL, 27.93 mmol), and BF₃·OEt₂ (3.5 mL, 27.93 mmol) at 0 °C under Ar atmosphere then the mixture was stirred overnight. The reaction mixture was partitioned between CHCl₃/saturated aq NaHCO₃ 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. ¹H NMR (CDCl₃) 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 (1H, t, *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%); ¹³C NMR (CDCl₃) 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 C₁₇H₃₀O₆SSi: C, 52.28; H, 7.74. Found: C, 52.42; H, 7.89. Physical data for **7** (α-anomer): ¹H NMR (CDCl₃) 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 (1H, dd, *J* = 3.2 and *J* = 10.8 Hz), 6.70 (1H, t, *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%); ¹³C NMR (CDCl₃) 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 C₁₇H₃₀O₆SSi: C, 52.28; H, 7.74. Found: C, 52.56; H, 7.87.

Physical data for **10**: ¹H NMR (CDCl₃) (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). ¹³C NMR (CDCl₃) 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 C₁₉H₃₃FO₇SSi·1/3 AcOEt: C, 50.67; H, 7.46. Found: C, 51.02; H, 7.37.

Physical data for **11**: ¹H NMR (CDCl₃) (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), 4.10 (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). ¹³C NMR (CDCl₃) 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 C₂₁H₃₆O₉SSi: 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 a CH₃CN (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 a CH₂Cl₂ (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 CHCl₃/saturated aq NaHCO₃ 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). ¹H NMR (CDCl₃) (**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%), COCH₃/H-4' (0.6%). ¹³C NMR (CDCl₃) 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 C₁₉H₃₀N₂O₆SSi·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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