The Stereoselective Synthesis of 4′-β-Thioribonucleosides via the Pummerer Reaction†

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Received February 14, 2000

Abstract: An efficient stereoselective synthesis of 4′-β-thioribonucleosides **14**, **15**, **27**, and **30** using the Pummerer reaction as the key step is described. The Pummerer reaction of 1,4-anhydro-2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-sulfinyl-D-ribitol (*R*-**10**:*S*-**10** = 2.7:1) in the presence of silylated uracil afforded the desired β-anomer of the 4′-thiouridine derivative **11** in 66% yield without formation of its α-anomer. The reaction with *R*-**10** gave **11** in 87% yield, while the one with *S*-**10** resulted in a 27% decrease of the desired product **11** along with a 22% yield of 3,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-3-hydroxy-2-hydroxymethylthiophene (**12**). A likely explanation for the observed difference in the reaction of *R*-**10** and *S*-**10** is that the reaction proceeds via an E2 type pathway, which prefers anti elimination. Thus, *R*-**10** would preferentially afford the α-thiocarbocation intermediate **21** via an E2 anti elimination under the reaction conditions. The resulting **21** would be expected to react with silylated uracil stereoselectively to give **11** in good yield. However, formation of the more stable tertiary α-thiocarbocation intermediate **23**, which would prefer to give **12** and/or to decompose, would compete with the formation of the desired **21** in the reaction with *S*-**10**. Consequently, this argument would explain the low yields of the desired product **11** and the poor mass balance in the reaction with *S*-**10**. When the sulfoxide **10** (*R*-**10**:*S*-**10** = >16:1) prepared by oxidation of **9** with ozone was used for the Pummerer reaction, the desired **11** was obtained in 80% yield. Compound **11** was converted to 4′-β-thiouridine (**14**) by treatment of **11** with ammonium fluoride, followed by methanolic ammonia. Similarly, 4′-β-thiocytidine (**15**) was prepared when silylated N^4-acetylcytosine was used in the Pummerer reaction. For the Pummerer reactions with purine bases, 6-chloropurine and 2-amino-6-chloropurine were found to be the most suitable. When the reactions were conducted in a mixture of acetonitrile and 1,2-dichloroethane at room temperature, followed by reflux, the desired products **25** and **28** were obtained in 65% and 56% yields, respectively. These compounds were then converted to 4′-β-thioadenosine (**27**) and 4′-β-thioguanosine (**30**) under the usual conditions. This is therefore the first time that the stereoselective synthesis of 4′-β-thioribonucleosides has been performed using the neighboring group participation of the Pummerer reaction.

Introduction

Nucleoside antimetabolites occupy a pivotal position in the search for effective anticancer and antiviral agents. Hence, much attention has been focused on efforts to synthesize and evaluate new nucleoside analogues. For example, 4′-thionucleosides, in which the furanose ring oxygen is replaced by a sulfur atom, have been studied extensively over the past 10 years because of their potent biological activity.[1] In 1964, 4′-thioadenosine was synthesized as the first example of this class of compounds by Reist et al.[2] Although further examples were reported,[3] studies in this area declined due to unfavorable results of biological evaluation and difficulty in devising an efficient and large scale preparation of the requisite 4′-thiosugars. The next significant attempts to synthesize 4′-thionucleosides were initiated independently by Dyson et al.[1a] with *E*-5-(2-bromovinyl)-4′-thio-2′-deoxyuridine (4′-thioBVDU) and by Secrist et al.[1b] with their report of 2′-deoxy-4′-thiopyrimidine nucleosides. Although the parent compound, i.e., *E*-5-(2-bromovinyl)-2′-deoxyuridine (BVDU),[4] is known to be a potent and selective inhibitor of herpes simplex virus type-1 and varicella zoster virus, BVDU is rapidly metabolized to the inactive *E*-5-(2-bromovinyl)uracil and 2-deoxyribose 1-phosphate by pyrimidine nucleoside phos-

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† This paper constitutes Part 198 of Nucleosides and Nucleotides. Part 197: Abe, H.; Shuto, S.; Matsuda, A. *J. Org. Chem.* In press.

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(3) For examples, see; (a) Reist, E. J.; Fisher, L. V.; Goodman, L. *J. Org. Chem.* **1968**, *33*, 189−192. (b) Bobek, M.; Whistler, R. L.; Bloch, A. *J. Med. Chem.* **1970**, *13*, 411−413. (c) Ritchie, R. G. S.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1973**, 686−687. (d) Bobek, M.; Bloch, A.; Parthasarathy, R.; Whistler, R. L. *J. Med. Chem.* **1975**, *18*, 784−787. (e) Pickering, M. V.; Witkowski, J. T.; Robins, R. K. *J. Med. Chem.* **1976**, *19*, 841−842.

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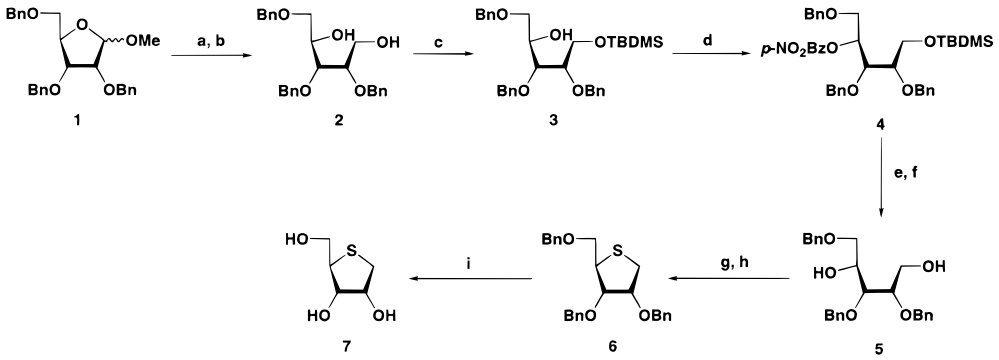
10.1021/ja000541o CCC: $19.00
Published on Web 07/14/2000

Scheme 1[a]



[a] Reagents: (a) 4 N HCl, dioxane, 100 °C; (b) $NaBH_4$, MeOH; (c) TBDMSCl, imidazole, DMF; (d) *p*-nitrobenzoic acid, diisopropyl azodicarboxylate, PPh_3, THF; (e) NaOMe, MeOH; (f) TBAF, THF; (g) methanesulfonyl chloride, pyridine; (h) Na_2S, DMF, 100 °C; (i) BCl_3, CH_2Cl_2, <−90 °C.

phorylase.[5] In contrast, 4′-thioBVDU is resistant to pyrimidine nucleoside phosphorylase, and showed a higher chemotherapeutic index than BVDU.[1a,6] Also the significant cytotoxicity arising from replacement of the furanose ring oxygen in the naturally occurring pyrimidine 2′-deoxyribonucleosides with a sulfur atom reported by Secrist et al. attracted the interest of medicinal chemists. These intriguing reports revived interest in the synthesis and evaluation of 4′-thionucleosides, including the replacement of the furanose ring oxygen in biologically active nucleosides with a sulfur atom and investigation of their L-isomers.[1,7] Moreover, 4′-thionucleosides could be used as antisense components, because oligonucleotides containing 4′-thioribonucleosides showed high nuclease resistance and thermal stability.[8]

The desired 4′-thionucleosides have generally been synthesized by classical thioglycosidation of the corresponding thiosugars and nucleobases. As an alternative method, we[1e,9] and others[10] developed the Pummerer reaction in order to condense a nucleobase and a sulfoxide. However, despite numerous attempts to synthesize 4′-thionucleoside analogues, little attention was paid to the stereoselectivity of the resulting 4′-thionucleosides.[11] Surprisingly, the stereocontrol in the thioglycosidation is unsatisfactory even with the assistance of the neighboring *C*-2 acetoxy group, unlike the normal glycosidation between a ribofuranose derivative and a nucleobase.[3d,7b] Thus far, there have been no systematic studies on the correlation between the stereoselectivity and the neighboring group effect on an adjacent acyloxy group. Based on these considerations, we envisioned the stereoselective synthesis of 4′-*β*-thioribonucleosides, which would be useful as ribonucleoside units for not only sugar-modified 4′-thionucleosides synthesis but also functionalized RNA molecule synthesis.

As part of our program, we recently reported the stereoselective coupling of thymine with *meso*-thiolane-3,4-diol-1-oxide derivative via the Pummerer reaction.[12] We indicated that the α-thiocarbocation intermediates were less susceptible to neighboring group effects than those of oxocarbocations. Consequently, the stereoselective coupling was achieved by the introduction of 2,4-dimethoxybenzoyl groups to the hydroxyl groups of *meso*-thiolane-3,4-diol-1-oxide to give (2*R**,3*R**,4*S**)-1-[3,4-di-*O*-(2,4-dimethoxybenzoyl)thiolane-3,4-diol-2-yl]thymine.

Herein, we describe the efficient and stereoselective synthesis of 4′-*β*-thioribonucleosides, based on our preliminary investigations using the Pummerer reaction. During our studies, we found that a large difference exists between each diastereomer of the starting sulfoxides in the Pummerer reaction. We also provide some explanations for the observed differences from a mechanistic point of view.

Results and Discussion

Preparation of the 4′-Thiosugar Portion. To conduct the Pummerer reaction, 1,4-anhydro-4-thio-D-ribitol (**7**) is needed. Although Althenbach et al. have reported the synthesis of **7** from achiral thiophene-2-carboxylic acid,[13] the method does not provide **7** efficiently because the strategy consists of enzymatic resolution and long reaction times for oxidation of the double bond. Thus, an alternative method was necessary for large-scale preparation. Among the efforts to synthesize the 4′-thioribofuranose derivatives, the synthetic tactics involving two consecutive S_N2 reactions of D-ribose reported by Dyson et al.[14] and Leydier et al.[15] seemed most promising. Accordingly, compound **7** was prepared as shown in Scheme 1. Methyl 2,3,5-

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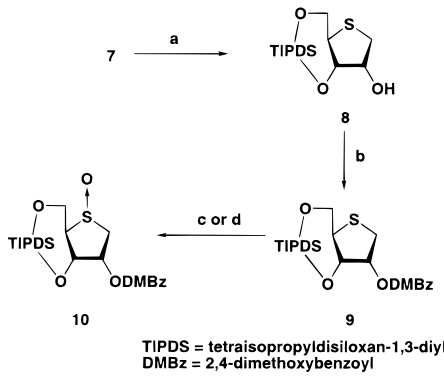
tri-*O*-benzyl-D-ribofuranoside (**1**) was synthesized from commercially available D-ribose using the Barker and Fletcher procedure.[16] Acidic methanolysis of **1**, followed by reduction of the resulting lactol derivative with sodium borohydride, gave diol **2** in 87% yield. After the selective protection of the primary hydroxyl group of **2** with *tert*-butyldimethylsilyl chloride, **3** was converted to the L-lyxose derivative **4** by the Mitsunobu reaction using *p*-nitrobenzoic acid. Deprotection of the *p*-nitrobenzoyl and *tert*-butyldimethylsilyl groups was performed by treatment of **4** with NaOMe, followed by tetrabutylammonium fluoride (TBAF) to give the diol **5** in 81% yield. Reaction of **5** with methanesulfonyl chloride in pyridine gave the dimesylate, which was treated with sodium sulfide in DMF to give **6** in 84% yield. When the tribenzylated derivative **6** was treated with boron trichloride in dichloromethane at −78 °C, the usual conditions for debenzylation of 4′-thiosugar derivatives,[1e,7b] the reaction gave a complex mixture, with the desired **7** being isolated in poor yield. The reaction was thus carried out at −98 °C and quenched by addition of MeOH below −90 °C. As a result, **7** was obtained in 79% yield. Control of the temperature is critical and quenching the reaction above −90 °C resulted in a reduced isolated yield of **7**.[17] Consequently, **7** was obtained in 29% yield by an 11-step synthesis from inexpensive D-ribose.

To achieve the stereoselective synthesis of 4′-β-thioribonucleosides, introduction of the 2,4-dimethoxybenzoyl group on the hydroxyl group at the 2-position was necessary for the Pummerer reaction.[12] Compared to reaction with the *meso*-thiolane-3,4-diol-1-oxide derivative described in the Introduction, control of not only the stereoselectivity (at the anomeric position), but also the regioselectivity (at the anomeric position or the 4-position), is required. The regioselectivity of the Pummerer reaction is likely to depend on the acidity of the α-proton.[18] In addition, steric hindrance may also affect stereoselectivity.[19] Hence, electron-donating and sterically hindering protecting groups would be preferable as protecting groups of the hydroxyl groups at the 3- and 5-positions to avoid formation of the regioisomer. Accordingly, **7** was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine to give **8**, which was subsequently converted to **9** (79% and 99%, respectively). Oxidation of **9** by *m*-chloroperoxybenzoic acid (*m*-CPBA) gave the desired sulfoxide **10** in 82% yield as a diastereomeric mixture (*R*/*S* = 2.7:1) (Scheme 2). The configurations of each diastereomer, *R*-**10** and *S*-**10** (Figure 1), were assigned through a study of solvent- and Eu(dpm)$_3$-induced shifts in their ^{1}H NMR spectra as reported by Folli et al.[20] After separation of the diastereomers, assignment of proton signals, especially the Ha and Hb protons of each compound, was based on two-dimensional NMR and nOe experiments. In the major isomer, the Ha signal was observed at 3.57 ppm in $CDCl_3$ while the Hb signal was observed upfield at 2.89 ppm. Unlike the major isomer, in the minor isomer, the Ha signal was observed at 3.05 ppm, which appeared farther upfield than the Hb signal (3.70 ppm). Since a greater deshielding is expected for the proton at the α-position closer to the sulfinyl oxygen atom, the configuration of the major isomer was assigned as *R*, while *S* was assigned for the minor isomer. Further evidence was obtained by a comparison of the downfield shifts of the Ha and Hb signals in the presence of increasing amounts of Eu(dmp)$_3$. As shown in Figure 2, a larger downfield shift of the Ha signal of *S*-**10**, which is situated in a *cis*-orientation relative to the sulfinyl oxygen, was observed on increasing the concentration of the shift reagent while the opposite effect was observed in the major isomer, and consequently, its configuration was assigned as *R* (data not shown).

Scheme 2[a]



[a] Reagents: (a) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine; (b) 2,4-dimethoxybenzoyl chloride, pyridine; (c) *m*-CPBA, CH_2Cl_2, −40 °C; (d) O_3, CH_2Cl_2, −78 °C.

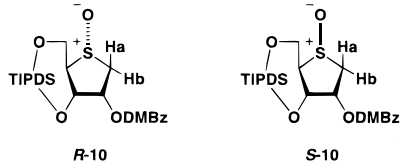


Figure 1. Structures of *R*-**10** and *S*-**10**.

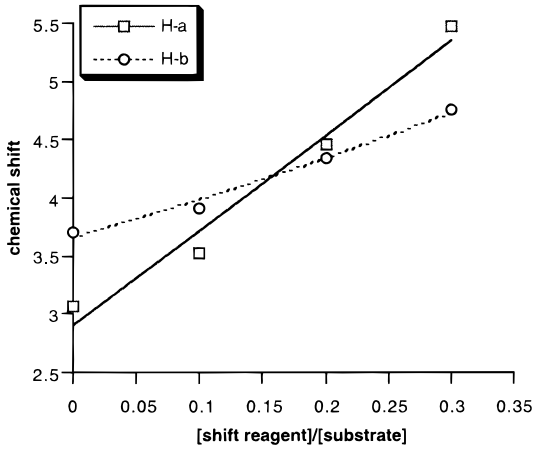


Figure 2. Chemical shifts of Ha and Hb of *S*-**10** in $CDCl_3$, as a function of concentration of Eu(dpm)$_3$.

Synthesis of 4′-β-Thioribopyrimidine Nucleosides. In a previous report,[12] we achieved the β-selective coupling of thymine with *meso*-3,4-di-*O*-(2,4-dimethoxybenzoyl)thiolane-3,4-diol-1-oxide using the Pummerer reaction. The optimized conditions were used for the reaction of **10** with the silylated uracil. Accordingly, a solution of the silylated uracil in a mixture of toluene−CH_2Cl_2 containing an excess amount of triethylamine and trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added to a solution of **10** (*R*/*S* = 2.7:1) in CH_2Cl_2 at 0 °C. The reaction proceeded immediately, and the desired 4′-β-

(16) Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605−4609.

(17) Hancox et al. also reported the importance of maintaining low temperature throughout the debenzylation reaction and during the quenching process. In our reaction with boron trichloride, the quenching of the reaction by adding MeOH is an extremely exothermic process. This may contribute to forming a bicyclic episulfonium intermediate, which gives a complex mixture, but not the desired product; see: Hancox, E. L.; Walker, R. T. *Nucleosides Nucleotides* **1996**, *15*, 135−148.

(18) For examples, see: (a) Johnson, C. R.; Sharp, J. C.; Phillips, W. G. *Tetrahedron Lett.* **1967**, 5299−5302. (b) Davenport, D. A.; Moss, D. B.; Rhodes, J. E.; Walsh, J. A. *J. Org. Chem.* **1969**, *34*, 3353−3359.

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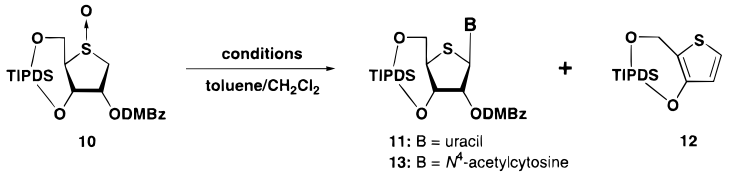
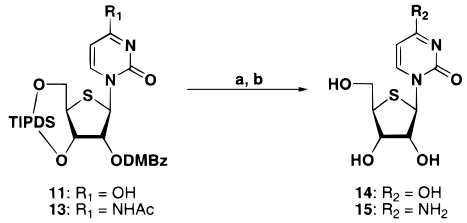
Table 1. The Pummerer Reaction of **10** with Pyrimidine Bases



entry	*R*/*S* ratio of **10**	nucleobase	conditions	**11** or **13** (%)	**12** (%)
1	2.7:1	uracil	TMSOTf (8 equiv), Et_3N (8 equiv), 0 °C	52	7
2	2.7:1	uracil	TMSOTf (8 equiv), Et_3N (8 equiv), rt	57	8
3	2.7:1	uracil	TMSOTf (8 equiv), Et_3N (4 equiv), followed by Et_3N (4 equiv), rt	66	9
4	*R* only	uracil	TMSOTf (8 equiv), Et_3N (4 equiv), followed by Et_3N (4 equiv), rt	87	0
5	*S* only	uracil	TMSOTf (8 equiv), Et_3N (4 equiv), followed by Et_3N (4 equiv), rt	27	22
6	>16:1	uracil	TMSOTf (8 equiv), Et_3N (4 equiv), followed by Et_3N (4 equiv), rt	80	trace
7	>16:1	N^4-acetylcytosine	TMSOTf (8 equiv), Et_3N (2 equiv), followed by Et_3N (6 equiv), rt	75	trace

Scheme 3[a]

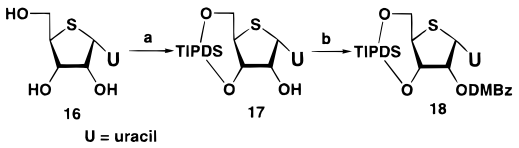


[a] Reagents: (a) NH_4F, MeOH, reflux; (b) NH_3/MeOH.

thiouridine derivative **11** was obtained stereoselectively in 52% yield, along with a 7% yield of the thiophene derivative **12** (Table 1, entry 1). When the reaction was run at room temperature, **11** was obtained in 57% yield (entry 2). As described in the previous communication, formation of the thiophene derivative **12** was caused by the presence of triethylamine. Accordingly, the reaction was carried out by adding triethylamine in two portions as shown in entry 3 (see the Experimental Section). Although formation of the unfavorable **12** was not suppressed, the yield of **11** was increased to 66%. Further changing conditions such as solvent, base, and reaction temperature did not improve the overall reaction. During the course of our investigations, we found that a large difference in reactivity existed between each diastereomer, i.e., *R*-**10** and *S*-**10**. Surprisingly, when the separated *R*-**10** was subjected to the Pummerer reaction, **11** was obtained in 87% yield (entry 4). Furthermore, none of the undesired product **12** was observed. In contrast, the reaction with *S*-**10** gave **11** in only 27% yield, along with a 22% yield of **12** (entry 5). As can be readily seen from these results, *R*-**10** is much more suitable for the Pummerer reaction to give **11** than *S*-**10**. Hence, we examined the oxidation of **9** with the idea of improving the *R*-selectivity. When **9** was treated with ozone in CH_2Cl_2 at −78 °C, the sulfoxide **10** was obtained in 82% yield with >16:1 *R*/*S* ratio (see the Experimental Section). The Pummerer reaction using **10** (*R*/*S* = >16:1) with the silylated uracil gave **11** in 80% yield with only a trace amount of **12** (entry 6). For the synthesis of the 4′-*β*-thiocytidine derivative **13**, the optimal results were obtained when the reaction was conducted with the silylated N^4-acetylcytosine, as shown in entry 7. The 4′-*β*-thiouridine (**14**) and the 4′-*β*-thiocytidine (**15**) were obtained by treatment of **11** and **13** with ammonium fluoride in MeOH under reflux, followed by methanolic ammonia, respectively (Scheme 3). The structures of **14** and **15** were confirmed by comparison of the analytical data with those reported by Imbach et al.[15,21]

In all of our attempts, none of the 4′-α-thiouridine derivative **18** or its cytidine derivative was detected in the Pummerer reaction. To confirm the absence of the α-isomer, compound **18** was prepared using an alternative method (Scheme 4). The 4′-α-thiouridine (**16**) was prepared according to the method reported by Bellon et al.[21] After protection of the hydroxyl groups at the 3′- and 5′-position by a TIPDS group to give **17**, introduction of a 2,4-dimethoxybenzoyl group on the remaining hydroxyl group was examined. When **17** was treated with 2,4-dimethoxybenzoyl chloride in pyridine at room temperature, none of the desired **18** was obtained due to steric hindrance. However, when the reaction was carried out in the presence of triethylamine and DMAP in acetonitrile under reflux conditions, compound **18** was obtained in 39% yield. Although both **11** and **18** showed almost the same R_f values on TLC analysis, characteristic differences were observed in the ^1H NMR spectra. For example, the anomeric proton signal of **11** was observed at 6.00 ppm as a singlet arising from the predominance of the C-3′-endo conformation, whereas that of **18** was observed at 6.52 ppm as a doublet. No proton signals corresponding to **18** were observed in compound **11** obtained from the Pummerer reaction. Furthermore, the other possible regioisomers, having a thioglycosidic linkage at the 4′-position, were not obtained either. These results therefore imply that the stereoselective and regioselective coupling of the sulfoxide **10** with pyrimidines was achieved via the Pummerer reaction.

Scheme 4[a]

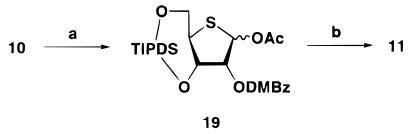


[a] Reagents: (a) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine; (b) 2,4-dimethoxybenzoyl chloride, Et_3N, DMAP, CH_3CN, reflux.

We were next interested in determining if there was a difference between the Pummerer reaction and the classical thioglycosidation. Both reactions are thought to proceed via α-thiocarbocation intermediates, although the mechanism of their formation differs in each. Thus, similar stereoselectivity would be expected with the assistance of the 2,4-dimethoxybenzoyl group even in the classical thioglycosidation. As shown in Scheme 5, we examined the thioglycosidation of the silylated uracil with the 1-acetoxy derivative **19**. Compound **10** was converted into **19** by treatment with acetic anhydride. Interestingly, the neighboring group assistance of the 2,4-dimethoxybenzoyl group was not affected and the reaction gave **19** as a diastereomeric mixture (α:*β* = 1:1), which was then subjected

(21) Bellon, L.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 1467−1479.

Scheme 5[a]



[a] Reagents: (a) Ac_2O, 110 °C; (b) uracil, *N*,O-bis(trimethylsilyl)-acetamide, TMSOTf, CH_3CN.

to thioglycosidation conditions. According to the method reported by Bellon et al.,[21] **19** was treated with the silylated uracil in acetonitrile in the presence of TMSOTf. However, the starting material **19** was not consumed even after 39 h, and the desired product **11** was obtained in only 35% yield along with a 13% yield of **19**. Although the stereochemistry of the resulting **11** was β-selective as expected, the isolated yield was not satisfactory. When subjected to the same conditions, the reaction between 2,3,5-tri-*O*-benzyl-1-*O*-acetyl-4-thio-D-ribofuranose and the silylated uracil gave the 4′-thiouridine derivative in 74% yield.[21] However, the product was an α/β mixture. These results may be explained in terms of the so-called armed−disarmed principle reported by Fraser-Reid et al.[22] It is well known that the glycosyl acceptors possessing an ether type of protecting group on the C-2 hydroxyl group are much more reactive than those possessing an ester type of protecting group. The same differences would be expected in the case of 4-thiosugar derivatives. No improvement was observed even using the Vorbrüggen method.[23] Although further attempts with other Lewis acids, solvents, and leaving groups at the C-1 position have not been conducted, it can be concluded that the Pummerer reaction is an efficient alternative method of synthesizing 4′-β-thioribopyrimidine nucleosides stereoselectively.

Considerations of the Differences in Chemical Reactivity between the Two Diastereomeric Sulfoxides. As described in the previous communication,[12] the Pummerer reactions between each diastereomer of the *meso*-3,4-di-*O*-(2,4-dimethoxybenzoyl)thiolane-3,4-diol-1-oxides, that is, between the *cis*- and *trans*-sulfoxides and the silylated thymine, resulted in similar products distribution. In contrast, striking differences were observed between *R*-**10** and *S*-**10** in a similar Pummerer reaction. Thus, the Pummerer reaction with *R*-**10** gave the desired **11** in good yield while the reaction with *S*-**10** gave **11** in only 27% yield along with a 22% yield of the undesired thiophene **12**. Moreover, the mass balance of the reaction with *S*-**10** was poor. It was presumed that these observed chemical reactivity differences would arise from differences in the ease of formation of the α-thiocarbocation intermediates, which would afford the desired compound **11** from each diastereoisomer.

To date, numerous investigations have been carried out to clarify the mechanism of the Pummerer reaction.[24] Depending on the structures of the starting sulfoxides, both E1cb and E2 type pathways are known to give the α-thiocarbocation intermediates from sulfoxides. The differences in our reaction can be explained if the formation of the α-thiocarbocation intermediates occurs via the E2 type pathway. As illustrated in Scheme 6, trimethylsilylation of the sulfoxide by TMSOTf is the initial step of the Pummerer reaction, and this process is expected to occur immediately in both *R*-**10** and *S*-**10** to give **20** and **22**, respectively. It appears that the definitive differences should exist in the subsequent E2 elimination step to give the α-thiocarbocation intermediates. In the E2 elimination, it is well known that anti elimination is greatly favored over syn elimination. This tendency is also maintained in the Pummerer reaction and has been demonstrated by Oae et al.[25] and Kita et al.[26] in the reaction of conformationally rigid cyclic sulfoxides, that is, deuterated 1-thiadecalin 1-oxides. In the silylated sulfoxide **20**, there is a single proton, i.e., H-1β, which has an anti orientation with the leaving group to give the α-thiocarbocation intermediate **21** predominantly via an E2 elimination (path a). The resulting intermediate **21** is expected to react with a silylated nucleobase with neighboring group participation to give 4′-β-thioribonucleoside **11** in good yield. In contrast, two properly positioned protons for E2 anti elimination, i.e., H-1α and H-4, are present in the silylated sulfoxide **22**. Consequently, formation of the more stable tertiary cation intermediate **23** via path b would compete with the formation of the desired **21**. Since **23** is thought to be less reactive than **21** toward attack by a silylated nucleobase due to steric hindrance, **23** would prefer to give the thiophene **12** and/or to decompose, but not give possible regioisomers, which have a thioglycosidic linkage at the 4′-position. This would explain the low yields of the desired **11** and the poor mass balance of the Pummerer reaction with *S*-**10**. *R*-**10** and *S*-**10** differ from the six-membered cyclic sulfoxides such as 1-thiadecalin 1-oxides, in that they are rather perturbational molecules, and it is difficult to estimate the exact dihedral angles between the hydrogen atoms and the leaving group for E2 elimination. In addition, the cyclic protecting group of the hydroxyl groups at the 3- and 5-position of **10**, which forces the sugar pucker mode to the C-3-endo conformation,[27] may also be a contributing factor in explaining the differences; however, the considerations as illustrated in Scheme 6 would be one of the explanations of the observed chemical reactivity differences.

We further examined the molecular orbital theoretical argument for the above hypothesis. Fukui and Fujimoto have demonstrated good parallelism between the reactivity of hydrogen atoms and the frontier electron density of the LUMO in E2 eliminations.[28] Thus, a hydrogen atom which possesses a larger frontier electron density of the LUMO is expected to participate in E2 elimination. Based on these considerations, the electron density of the LUMO at each hydrogen atom (H-1α,β and H-4) of the intermediates **20** and **22** was calculated.[29] As can be seen in Figure 3, the resulting electron densities agree well with the experimental results in the Pummerer reaction. In the intermediate **20**, the H-1β possesses a much larger frontier electron density of the LUMO than H-1α and H-4, implying that elimination of H-1β is preferable to elimination of H-1α and H-4, as we had speculated. In contrast,

(22) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1988**, *110*, 5583−5584.

(23) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber*. **1981**, *114*, 1234−1255.

(24) Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 909−947 and references therein.

(25) Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 270−279.

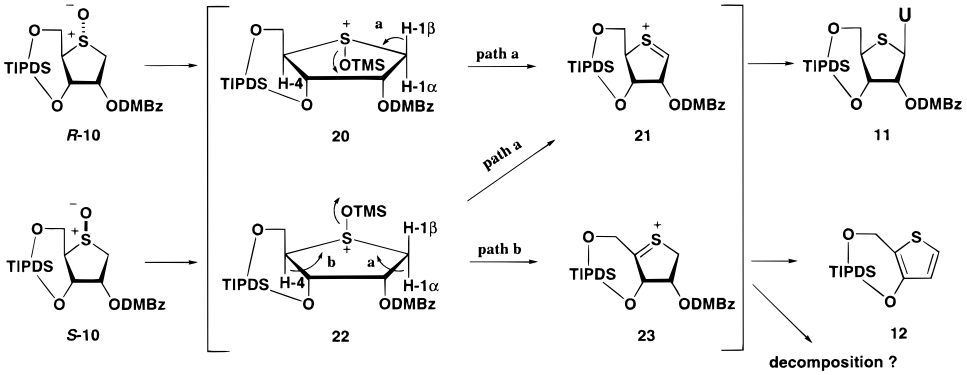
(26) Kita, Y.; Shibata, N.; Yoshida, N.; Kawano, N.; Fujimori, C.; Yoshikawa, N.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2829−2834.

(27) The sugar pucker modes of *R*-**10** and *S*-**10** were predicted from the coupling constants of $J_{1\alpha,2}$ and $J_{3,4}$ which were the same as for the ribose. The coupling constants of $J_{1\alpha,2}$ and $J_{3,4}$ of *R*-**10** were 0 and 12.0 Hz, and those of *S*-**10** were 0.9 and 10.3 Hz, respectively. Consequently, the sugar pucker modes of *R*-**10** and *S*-**10** were both estimated to be preferentially C-3-endo conformations.

(28) (a) Fukui, K.; Fujimoto, H. *Tetrahedron Lett*. **1965**, 4303−4307. (b) Fukui, K.; Fujimoto, H. *Frontier Orbitals and Reaction Path*; World Scientific: Singapore, 1997; pp 171−202.

(29) The preoptimal geometries of the intermediates **20** and **22** were calculated by MM2 methods. The final optimal conformations and a coefficient of the LUMO at each hydrogen atom were obtained by PM3 methods. The frontier electron density was calculated from 2 times the square of the coefficient of the LUMO.

Scheme 6



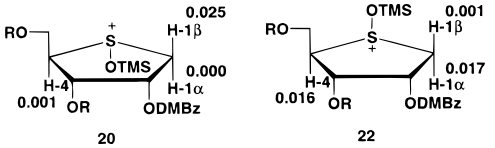


Figure 3. Frontier electron densities of LUMO in **20** and **22**.

a larger frontier electron density of the LUMO was observed at H-1α as well as at H-4, implying that E2 elimination of these protons takes place in preference to that of H-1*β* in the intermediate **22**. It appears that the observed chemical reactivity differences between the two diastereomeric sulfoxides would also be explained by these calculations.

Synthesis of 4′-*β*-Thioribopurine Nucleosides. In contrast to reactions with pyrimidine bases, those with purine bases are somewhat more complex due to the possible formation of regioisomers, i.e., N-3, N-7, and the desired N-9 isomers. In the usual glycosidation conditions using Lewis acids, the N-3 and N-7 isomers, which are kinetically controlled products, are known to rearrange subsequently to the thermodynamically most stable N-9 isomer.[30] Accordingly, the Pummerer reaction was conducted in the presence of various purine bases.[31] Among the nucleobases examined, the reaction with 6-chloropurine gave the simplest result; i.e., two separable compounds were obtained in 43% and 3% yields, respectively (Table 2, entry 1). Since the anomeric proton signals in both compounds were observed at 6.41 ppm (major) and 6.07 ppm (minor) as singlets, the stereochemistries at the anomeric positions were considered to be the *β* configuration.[32] In the glycosidation with 6-chloropurine, the N-7 isomer is generally formed along with the N-9 isomer,[33] and these isomers are typically differentiated by ^{1}H NMR by the characteristic downfield shifts for the H-1′ and nucleobase proton signals of the N-7 isomer relative to those of the N-9 isomer.[33b] Based on this information, the major product was assigned as the N-7 isomer **24**, while the minor was the desired N-9 isomer **25**.[34] Since the kinetic N-7 isomer is expected to rearrange into the N-9 isomer, the reaction conditions were further investigated. Interestingly, rearrangement of **24** into the desired **25** was observed on TLC analysis when the Pummerer reaction was conducted first at room temperature then under reflux conditions. Accordingly, **25** was obtained in 65% yield under the conditions shown in entry 4. Conversion of **25** into 4′-*β*-thioadenosine (**27**) by treatment with TBAF, followed by ethanolic ammmonia,[35] gave **27** in good yield (Scheme 7). The structure of **27** was confirmed by comparison of the analytical data with those of reported by Leyder et al.[15]

The synthesis of 4′-*β*-thioguanosine (**30**) was achieved as shown in Scheme 8. The Pummerer reaction of **10** with 2-amino-6-chloropurine gave the desired N-9 isomer **28** in 56% yield when the reaction was conducted under reflux conditions.[36] The structure of **28** was deduced from its UV spectrum, which was similar to the spectra of the N-9 glycosyl isomers of 2-amino-6-chloropurine[37] but not those of the N-7 isomers.[36] The resulting **28** was then deprotected by TBAF to give **29** quantitatively. Conversion of **29** into 4′-*β*-thioguanosine (**30**) was done by treatment with 2-mercaptoethanol at room temperature, followed by sodium methoxide under reflux conditions to give **30** in 55% yield. The UV spectrum of **30** in H_2O showed two absorption maxima at 284 and 253 nm, which are identical with those of guanosine. In addition, the *β* configuration of **30** was confirmed by NOE experiment. Thus, the expected NOEs were observed at H-1′ (3.5%) and H-2′ (6.0%) upon irradiation of H-8.

In conclusion, we have developed a multigram synthesis of the thiosugar **7** via the Mitsunobu reaction from inexpensive D-ribose. Using the sulfoxide **10** prepared from **7**, the first stereoselective synthesis of 4′-*β*-thiouridine, -cytidine, -adenosine, and -guanosine was accomplished with the assistance of neighboring group participation using the Pummerer reaction. Since thioglycosidation of **19**, which has a 2,4-dimethoxybenzoyl group on the C-2 hydroxyl group, was unsuccessful, the Pummerer reaction was shown as to be an efficient alternative

(30) (a) Vorbrüggen, H.; Hofle, G. *Chem. Ber*. **1981**, *114*, 1256−1268. (b) Boryski, J. *Nucleosides Nucleotides* **1996**, *15*, 771−791.

(31) Adenine, hypoxanthine, and N^6-benzoyladenine were also used in place of 6-chloropurine. The Pummerer reactions in the presence of both adenine and hypoxanthine gave complex mixtures, while the reaction with N^6-benzoyladenine gave the coupling product in 66% yield as a mixture of regioisomers, which probably correspond to N-3, N-7, and the desired N-9 isomers. However, the resulting mixture was inseparable, and the N-9 isomer was not obtained preferentially under any conditions.

(32) The assignment of the configuration at the anomeric carbon as α or *β* has been often based on the splitting pattern of H-1′. In the ribonucleosides possessing 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl group on their 3′- and 5′-hydroxyl groups, a somewhat broad singlet is generally observed for the *β* isomer, while a doublet is observed for the α isomer. In comparison with those of **11** and **18**, the same tendency appeared to be maintained in the 4′-thioribonucleoside analogues.

(33) (a) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc*. **1984**, *106*, 6379−6382. (b) Hildebrand, C.; Wright, G. E. *J. Org. Chem*. **1992**, *57*, 1808−1813.

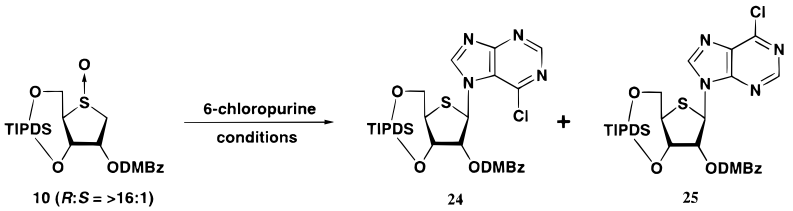
(34) The proton signals of the nucleobase and H-1′ were observed at 8.76 and 8.59 ppm (H-2 and H-8) and 6.07 ppm (H-1′) for N-9 isomer **25**, while those of **24** were observed at 9.11 and 8.88 ppm (H-2 and H-8) and 6.41 pp (H-1′), respectively.

(35) When **26** was treated with methanolic ammonia, a 6-methoxypurine derivative was observed along with the 4′-thioadenosine (**27**).

(36) When the Pummerer reaction was carried out in a mixture of toluene−CH_2Cl_2 at room temperature, the N-7 isomer was obtained in 58% yield preferentially. The UV spectrum of the N-7 isomer in MeOH showed absorption maxima at 325, 294, and 256 nm. Among them, the maximum at 325 nm is characteristic of the N-7 glycosyl isomers of 2-amino-6-chloropurine; see: Hanna, N. B.; Ramasamy, K.; Robins, R. K.; Revankar, G. R. *J. Heterocycl. Chem*. **1988**, *25*, 1899−1903.

(37) The UV spectrum of **28** in MeOH showed absorption maxima at 315 (shoulder), 298, and 256 nm; see ref 36.

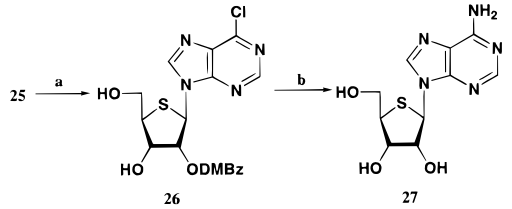
Table 2. The Pummerer Reaction of **10** with 6-Chloropurine



10 (*R*:*S* = >16:1) 24 25

entry	6-chloropurine (equiv)	conditions	yield of **24** (%)	yield of **25** (%)
1	2	TMSOTf (8 equiv), Et_3N (4 equiv), then Et_3N (4 equiv), toluene−CH_2Cl_2, rt	43	3
2	4	TMSOTf (8 equiv), Et_3N (4 equiv), then Et_3N (4 equiv), toluene−CH_2Cl_2, rt	46	9
3	4	TMSOTf (8 equiv), Et_3N (4 equiv), then Et_3N (4 equiv), toluene−$ClCH_2CH_2Cl$, rt then 83 °C	trace	42
4	4	TMSOTf (8 equiv), Et_3N (4 equiv), then Et_3N (4 equiv), CH_3CN−$ClCH_2CH_2Cl$, rt then 83 °C	trace	65

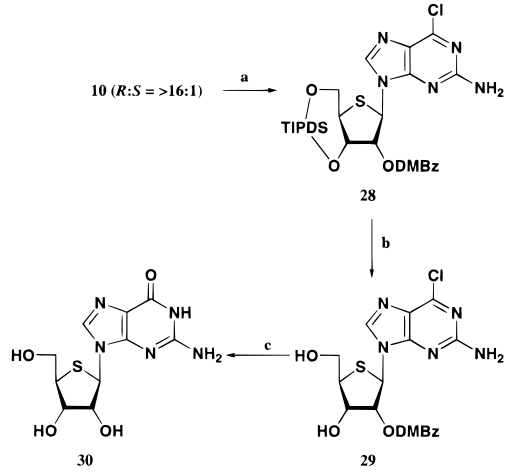
Scheme 7[a]



26 27

[a] Reagents: (a) TBAF, AcOH, THF; (b) NH_3/EtOH.

Scheme 8[a]



28 30 29

[a] Reagents: (a) 2-amino-6-chloropurine, TMSOTf, Et_3N, CH_3CN−$ClCH_2CH_2Cl$, room temperature then 83 °C; (b) TBAF, AcOH, THF; (c) 2-mercaptoethanol, NaOMe, MeOH, reflux.

method for synthesizing 4′- β-thioribonucleosides stereoselectively. In addition, we demonstrated the striking differences between *R*-**10** and *S*-**10** in the Pummerer reaction. The differences in E2 elimination behavior to give α-thiocarbocation intermediates from *R*-**10** and *S*-**10** was postulated as one of the possible interpretations for the observed chemical reactivity differences. This should be one of the best methods to date for producing 4′-β-thioribonucleosides.

Experimental Section

General Methods. Physical data were measured as follows. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on 270, 400, or 500 MHz and 67.5, 100, or 125 MHz instruments in $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. Assignment of ^1H signals was based on two-dimensional NMR and NOE experiments. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70−230 mesh).

2,3,5-Tri-*O*-benzyl-D-ribitol (2). To a solution of **1**[16] (101.3 g, 0.23 mol) in 1,4-dioxane (800 mL) was added 4 N aqueous HCl (800 mL), and the whole was heated under reflux. The reaction mixture was partitioned between ether and saturated aqueous $NaHCO_3$. The separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in MeOH (1.0 L), and sodium borohydride (35.3 g, 0.93 mol) was added at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was concentrated in vacuo, and the residue was coevaporated with MeOH. The residue was purified by a silica gel column, eluted with hexane/AcOEt (1:1), to give **2** (85.4 g, 87% as a colorless oil): FAB-LRMS *m*/*z* 423 (MH^+, 12.4%); ^1H NMR (270 MHz, $CDCl_3$) δ 7.35−7.20 (m, 15 H), 4.73−4.48 (m, 6 H), 3.98−3.56 (m, 7 H), 2.98 (br s, 1 H), 2.61 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.81, 137.78, 137.64, 128.34, 128.31, 128.28, 127.93, 127.78, 127.73, 127.69, 79.24, 79.17, 73.89, 73.34, 71.89, 70.94, 60.88. Anal. Calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.76; H, 7.20.

2,3,5-Tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-ribitol (3). A mixture of **2** (20.0 g, 47 mmol), imidazole (14.2 g, 208 mmol), and TBDMSCl (7.9 g, 52 mmol) in dry DMF (200 mL) was stirred at 0 °C for 30 min. The reaction was quenched by addition of ice, and the reaction mixture was partitioned between ether and H_2O. The separated organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (20:1−5:1), to give **3** (24.7 g, 97% as a colorless oil): FAB-LRMS *m*/*z* 537 (MH^+, 1.4%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−6.34 (m, 15 H), 4.74−4.50 (m, 6 H), 4.02−3.60 (m, 7 H), 2.93 (br s, 1 H), 0.83 (s, 9 H), −0.01 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.47, 138.16, 128.36, 128.31, 128.29, 127.95, 127.82, 127.73, 127.64, 127.58, 127.54, 80.69, 78.93, 73.65, 73.35, 72.66, 71.25, 71.08, 62.57, 25.91, 18.27, −5.41. Anal. Calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26. Found: C, 71.55; H, 8.27.

2,3,5-Tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-4-*O*-*p*-nitrobenzoyl-L-lyxitol (4). A solution of **3** (21.2 g, 39.5 mmol) in THF (150 mL) containing *p*-nitrobenzoic acid (13.2 g, 79 mmol) and triphenylphosphine (20.7 g, 79 mmol) was cooled to 0 °C, and a THF solution of diisopropyl azodicarboxylate (15.5 mL, 79 mmol in 100 mL) was added to the mixture over 3 h. After being stirred for 12 h at room temperature, the reaction mixture was partitioned between ether and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (50:1−10:1), to give **4**

(22.6 g, 83% as a yellow oil): FAB-LRMS *m*/*z* 686 (MH^+, 20.9%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.15−8.03 (m, 4 H), 7.27−7.11 (m, 15 H), 5.64 (dd, 1 H, J = 5.1, 9.5 Hz), 4.72−4.39 (m, 6 H), 4.04−3.57 (m, 6 H), 0.84 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.08, 150.40, 138.22, 138.10, 137.78, 135.76, 130.82, 128.34, 128.28, 128.22, 127.87, 127.80, 127.69, 127.66, 127.52, 79.17, 76.59, 74.18, 73.41, 73.14, 72.43, 68.42, 61.64, 25.88, 18.21, −5.40, −5.46. Anal. Calcd for $C_{39}H_{47}NO_8Si$: C, 68.30; H, 6.91; N, 2.04. Found: C, 68.12; H, 6.95; N, 2.12.

2,3,5-Tri-*O*-benzyl-L-lyxitol (5). To a solution of **4** (103 g, 150 mmol) in MeOH (300 mL) was added NaOMe (28% solution, 2 mL), and the whole was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between ether and H_2O. The separated organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was suspended in ether, and insoluble materials were filtered off. The filtrate was concentrated in vacuo, and the residue was dissolved in THF (300 mL). To the solution was added TBAF (1 M in THF, 150 mL, 150 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between ether and H_2O, and the separated organic layer was washed with brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (5:1−4:1), to give **5** (51.5 g, 81% as a colorless oil): FAB-LRMS *m*/*z* 423 (MH^+, 35.4%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37−7.25 (m, 15 H), 4.75−4.44 (m, 6 H), 4.00−3.43 (m, 7 H), 2.59 (br s, 1 H), 2.27 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.88, 137.79, 128.39, 128.31, 128.11, 127.81, 127.76, 127.66, 79.59, 77.09, 74.23, 73.29, 72.29, 71.20, 69.65, 60.44. Anal. Calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.81; H, 7.19.

1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-ribitol (6). To a solution of **5** (51.5 g, 121 mmol) in dry pyridine (300 mL) was added methanesulfonyl chloride (28.0 mL, 363 mmol) at 0 °C. After the mixture was stirred for 2 h at the same temperature, the reaction was quenched by addition of ice. The reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was coevaporated several times with toluene. The residue was dissolved in dry DMF (500 mL), and sodium sulfide nonahydrate (32.0 g, 133 mmol) was added to the solution. The mixture was heated at 100 °C for 2 h. After being cooled to room temperature, the mixture was diluted with ether and washed with H_2O (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (10:1), to give **6** (43.2 g, 84% as a colorless oil): FAB-LRMS *m*/*z* 421 (MH^+, 19.3%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32−7.22 (m, 15 H), 4.65−4.44 (m, 6 H), 4.02 (ddd, 1 H, J = 6.9, 5.6, 3.6 Hz), 3.95 (dd, 1 H, J = 3.6, 4.3 Hz), 3.67 (m, 1 H), 3.48 (m, 2 H), 3.03 (dd, 1 H, J = 6.9, 10.6 Hz), 2.88 (dd, 1 H, J = 5.6, 10.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.88, 137.84, 137.82, 128.20, 128.15, 127.77, 127.54, 127.47, 80.82, 79.48, 72.93, 71.79, 71.71, 71.68, 47.07, 30.61. Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.15; H, 6.75.

1,4-Anhydro-4-thio-D-ribitol (7). A solution of **6** (7.0 g, 17 mmol) in dry CH_2Cl_2 (100 mL) was cooled to −98 °C, and 1 M BCl_3 in CH_2Cl_2 (100 mL, 100 mmol) was added over 2 h. After the solution was stirred at the same temperature for 1 h, MeOH (100 mL) was added to the reaction mixture under −90 °C. The solvent was removed in vacuo, and the residue was purified by a silica gel column, eluted with hexane/AcOEt (5:1−4:1), to give **7** (2.0 g, 79% as a yellow oil): FAB-LRMS *m*/*z* 151 (MH^+, 12.5%); ^{1}H NMR (270 MHz, CD_3OD) δ 4.12 (ddd, 1 H, J = 5.0, 5.3, 3.6 Hz), 3.85 (dd, 1 H, J = 3.6, 5.6 Hz), 3.63 (dd, 1 H, J = 5.9, 11.2 Hz), 3.46 (dd, 1 H, J = 6.3, 11.2 Hz), 3.25 (ddd, 1 H, J = 5.6, 5.9, 6.3 Hz), 2.82 (dd, 1 H, J = 5.0, 10.9 Hz), 2.65 (dd, 1 H, J = 5.3, 10.9 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 77.73, 75.85, 65.46, 52.68, 33.46. Anal. Calcd for $C_5H_{10}O_3S$: C, 39.99; H, 6.71. Found: C, 39.85; H, 6.59.

1,4-Anhydro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (8). To a solution of **7** (1.54 g, 10.3 mmol) in dry pyridine (20 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (3.6 mL, 11.0 mmol) at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was coevaporated with toluene. The residue was purified by a silica gel column, eluted with hexane/AcOEt (50:1), to give **8** (3.2 g, 79% as a colorless oil): FAB-LRMS *m*/*z* 393 (MH^+, 14.6%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.33 (ddd, 1 H, J = 1.6, 0.8, 4.0 Hz), 4.24 (dd, 1 H, J = 4.0, 8.3 Hz), 4.05 (dd, 1 H, J = 3.2, 12.3 Hz), 3.92 (dd, 1 H, J = 4.4, 12.3 Hz), 3.50 (ddd, 1 H, J = 8.3, 3.2, 4.4 Hz), 3.04 (dd, 1 H, J = 1.6, 12.3 Hz), 2.86 (dd, 1 H, 0.8, 12.3 Hz), 2.67 (s, 1 H), 1.12−1.05 (m, 28 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 77.58, 74.39, 61.08, 49.24, 32.36, 17.34, 17.25, 17.06, 13.37, 13.25, 12.69, 12.65. Anal. Calcd for $C_{17}H_{36}O_4SSi_2$: C, 52.00; H, 9.24. Found: C, 52.00; H, 9.06.

1,4-Anhydro-2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (9). To a solution of **8** (2.8 g, 7.2 mmol) in dry pyridine (35 mL) was added 2,4-dimethoxybenzoyl chloride (2.9 g, 14.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was coevaporated with toluene. The residue was purified by a silica gel column, eluted with hexane/AcOEt (10:1−5:1), to give **9** (3.9 g, 99% as a colorless oil): FAB-LRMS *m*/*z* 557 (MH^+, 6.7%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.88 (d, 1 H J = 9.5 Hz), 6.49 (m, 2 H), 5.71 (dd, 1 H, J = 4.8, 4.0 Hz), 4.33 (dd, 1 H, J = 4.0, 9.5 Hz), 4.11 (dd, 1 H, J = 2.8, 12.3 Hz), 3.96 (dd, 1 H, J = 3.2, 12.3 Hz), 3.88, 3.85 (each s, each 3 H,), 3.66 (ddd, 1 H, J = 9.5, 2.8, 3.2 Hz), 3.21 (dd, 1 H, J = 4.8, 12.7 Hz), 2.89 (d, 1 H, J = 12.7 Hz), 1.13−0.96 (m, 28 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.42, 164.12, 161.38, 133.74, 112.38, 104.36, 98.82, 75.58, 74.92, 59.67, 55.91, 55.44, 49.61, 31.08, 17.44, 17.37, 17.34, 17.31, 17.27, 17.07, 13.45, 13.35, 12.78, 12.75. Anal. Calcd for $C_{26}H_{44}O_7SSi_2$: C, 56.08; H, 7.96. Found: C, 55.99; H, 7.99.

1,4-Anhydro-2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-sulfinyl-D-ribitol (10). Method A. To a solution of **9** (978 mg, 1.76 mmol) in dry CH_2Cl_2 (10 mL) was added *m*-CPBA (328 mg, 1.90 mmol) at −40 °C, and the mixture was stirred at the same temperature for 30 min. The reaction was quenched by addition of saturated aqueous sodium thiosulfate, and the reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (1:1), to give **10** as a mixture of diastereomers (743 mg, 82%; *R*/*S* = 1:2.7). Separation of *R*-**10** and *S*-**10** was performed by preparative TLC, developed with benzene/AcOEt (3:1).

Physical data for *R*-**10** (a colorless oil): FAB-LRMS *m*/*z* 573 (MH^+, 10.4%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, 1 H, Ar, J = 8.3 Hz), 6.49 (m, 2 H, Ar), 5.79 (dd, 1 H, H-2, $J_{2,1\beta}$ = 5.4, $J_{2,3}$ = 3.6 Hz), 4.59 (d, 1 H, H-5a, $J_{5a,5b}$ = 12.8 Hz), 4.22 (dd, 1 H, H-5b, $J_{5b\ 4}$ = 2.8, $J_{5b,5a}$ = 12.8 Hz), 4.12 (dd, 1 H, H-3, $J_{3,2}$ = 3.6, $J_{3,4}$ = 12.0 Hz), 3.88, 3.86 (each s, each 3 H, MeO), 3.57 (dd, 1 H, H-1β, $J_{1\beta,2}$ = 5.4, $J_{1\beta,1\alpha}$ = 15.5 Hz), 3.49 (dd, 1 H, H-4, $J_{4,3}$ = 12.0, $J_{4,5b}$ = 2.8 Hz), 2.89 (d, 1 H, H-1α, $J_{1\alpha,1\beta}$ = 15.5 Hz), 1.11−0.94 (m, 28 H, TIPDS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.47, 164.14, 161.62, 133.99, 111.70, 104.52, 98.80, 77.20, 72.54, 72.40, 67.89, 55.80, 55.36, 54.28, 17.22, 17.14, 17.08, 17.03, 17.00, 16.84, 16.82, 13.28, 13.04, 12.55, 12.51 Anal. Calcd for $C_{26}H_{44}O_8SSi_2 \cdot 0.5\ H_2O$: C, 53.67; H, 7.80. Found: C, 53.35; H, 7.53.

Physical data for *S*-**10** (a colorless oil): FAB-LRMS *m*/*z* 573 (MH^+, 29.2%); FAB−HRMS Calcd for $C_{26}H_{44}O_8SSi_2$ (MH^+) 573.2373. Found 573.2392. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 1 H, Ar, J = 9.3 Hz), 6.44 (m, 2 H, Ar), 5.96 (ddd, 1 H, H-2, $J_{2,1\beta}$ = 5.4, $J_{2,1\alpha}$ = 0.9, $J_{2,3}$ = 3.9 Hz), 5.36 (dd, 1 H, H-3, $J_{3,2}$ = 3.9, $J_{3,4}$ = 10.3 Hz), 4.49 (dd, 1 H, H-5a, $J_{5a,4}$ = 3.6, $J_{5a,5b}$ = 12.8 Hz), 4.43 (dd, 1 H, H-5b, $J_{5b,4}$ = 4.6, $J_{5b,5a}$ = 12.8 Hz), 3.83, 3.82 (each s, each 3 H, MeO), 3.70 (dd, 1 H, H-1α, $J_{1\alpha,2}$ = 0.9, $J_{1\alpha,1\beta}$ = 15.0 Hz), 3.05 (dd, 1 H, H-1β, $J_{1\beta,2}$ = 5.4, $J_{1\beta,1\alpha}$ = 15.0 Hz), 3.01 (ddd, 1 H, H-4, $J_{4,3}$ = 10.3, $J_{4,5b}$ = 3.6, $J_{4,5b}$ = 4.6 Hz), 1.08−0.87 (m, 28 H, TIPDS); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 164.55, 164.12, 161.48, 133.81, 111.70, 104.56, 98.87, 74.95, 72.58, 62.28, 58.51, 55.85, 54.45, 17.30, 17.26, 17.23, 17.20, 17.15, 16.95, 16.88, 13.09, 12.97, 12.68. Anal. Calcd for $C_{26}H_{44}O_8SSi_2 \cdot 0.5\ H_2O$: C, 53.67; H, 7.80. Found: C, 53.35; H, 7.53.

Method B. Ozone was bubbled through a solution of **9** (2.1 g, 3.8 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After 30 min, N_2 gas was bubbled through the solution to remove excess ozone. The reaction mixture was allowed to warm to room temperature and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (1:1), to give **10** as a mixture of diastereomers (1.8 g, 82%; *R*/*S* = >16:1).

1-[2-*O*-(2,4-Dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-β-D-ribofuranosyl]uracil (11) (Entry 6). To a suspension of uracil (35 mg, 0.31 mmol) in dry toluene (2 mL) was added triethylamine (87 μL, 0.62 mmol) and TMSOTf (241 μL, 1.25 mmol), and the mixture was stirred at room temperature until two-phase clear solution was obtained. Dry CH_2Cl_2 (1 mL) was added to the above solution, which gave a one-phase clear solution, and the whole was added to a solution of **10** (100 mg, 0.18 mmol, *R*/*S* = >16:1) in dry CH_2Cl_2 (1 mL) dropwise over 15 min via a cannula. An additional amount of triethylamine (87 μL, 0.16 mmol) in dry toluene (0.5 mL) was added dropwise to the reaction mixture to initiate the Pummerer reaction. After the mixture was stirred for 5 min at room temperature, the reaction was quenched by addition of ice, and the reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (5:1−1:1), to give **11** (84 mg, 80% as a white foam): FAB-LRMS *m*/*z* 667 (MH^+, 6.5%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (br s, 1 H, NH), 8.15 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 7.85 (d, 1 H, Ar, J = 8.6 Hz), 6.50 (m, 2 H, Ar), 6.00 (s, 1 H, H-1′), 5.74 (d, 1 H, H-5, $J_{5,6}$ = 8.1 Hz), 5.61 (d, 1 H, H-2′, $J_{2',3'}$ = 3.7 Hz), 4.45 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.7, $J_{3',4'}$ = 9.5 Hz), 4.16 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 2.7, $J_{5'a,4'}$ = 12.7 Hz), 4.07 (d, 1 H, H-5′b, $J_{5'b,5'a}$ = 12.7 Hz), 3.87, 3.86 (each s, each 3 H, MeO), 3.73 (dd, 1 H, H-4′, $J_{4',3'}$ = 9.5, $J_{4',5'a}$ = 2.7 Hz), 1.15−0.90 (m, 28 H, TIPDS); ^{13}C NMR (68 MHz, $CDCl_3$) δ 164.51, 163.45, 162.73, 161.61, 150.01, 140.86, 133.93, 111.82, 104.64, 102.25, 99.01, 77.68, 71.45, 62.70, 58.03, 55.94, 55.49, 50.93, 17.45, 17.33, 17.25, 17.02, 16.84, 13.32, 13.14, 12.55. Anal. Calcd for $C_{30}H_{46}N_2O_9SSi_2$: C, 54.03; H, 6.95; N, 4.20. Found: C, 54.03; H, 6.90; N, 4.11.

Physical data for **3,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-3-hydroxy-2-hydroxymethylthiophene (12)**: FAB-LRMS *m*/*z* 372 (MH^+, 31.3%); FAB−HRMS calcd for $C_{17}H_{33}O_3SSi_2$ (MH^+) 372.1611, found 373.1672; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10 (d, 1 H, J = 5.3 Hz), 6.66 (d, 1 H, J = 5.3 Hz), 4.74 (s, 2 H), 1.25−0.75 (m, 28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.24, 122.86, 122.25, 122.03, 55.03, 16.89, 16.87, 16.67, 16.62, 13.00, 12.78.

***N*^{4}-Acetyl-1-[2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-β-D-ribofuranosyl]cytosine (13).** In the similar manner as described for **11**, the Pummerer reaction of **10** (88 mg, 0.15 mmol, *R*/*S* = >16:1) with *N*^{4}-acetylcytosine (47 mg, 0.31 mmol) using trietylamine (43 μL, 0.31 mmol, and an additional 129 μL, 0.92 mmol) and TMSOTf (238 μL, 1.23 mmol) gave **13** (82 mg, 75% as a yellow solid): FAB-LRMS *m*/*z* 708 (MH^+, 2.1%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (br s, 1 H), 8.57 (d, 1 H, J = 7.6 Hz), 7.82 (d, 1 H, J = 8.7 Hz), 7.41 (d, 1 H, J = 7.6 Hz), 6.46 (m, 2 H), 6.07 (s, 1 H), 5.66 (d, 1 H, J = 3.7 Hz), 4.40 (dd, 1 H, J = 3.7, 9.5 Hz), 4.14 (dd, 1 H, J = 3.0, 12.8 Hz), 4.06 (d, 1 H, J = 12.8 Hz), 3.83 (s, 6 H), 3.74 (dd, 1 H, J = 9.5, 3.0 Hz), 2.24 (s, 3 H), 1.14−0.87 (m, 28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.48, 164.30, 163.22, 163.02, 161.41, 155.21, 145.74, 133.82, 112.08, 104.54, 98.94, 96.95, 77.44, 71.20, 64.31, 58.08, 55.88, 55.40, 50.68, 24.82, 17.40, 17.31, 17.29, 17.26, 16.96, 16.95, 16.81, 16.79, 13.27, 13.07, 12.48. Anal. Calcd for $C_{32}H_{49}N_3O_9SSi_2 \cdot 0.25H_2O$: C, 53.94; H, 7.00; N, 5.90. Found: C, 54.20; H, 7.08; N, 5.43.

1-(4-Thio-β-D-ribofuranosyl)uracil (14). A solution of **11** (460 mg, 0.69 mmol) in MeOH (10 mL) containing ammonium fluoride (510 mg, 13.8 mmol) was heated under reflux for 12 h. The solvent was removed in vacuo, and the residue was dissolved in methanolic ammonia (saturated at 0 °C, 20 mL). The reaction mixture was kept for 24 h at room temperature, and the solvent was removed in vacuo. The residue was purified by a silica gel column, eluted with 25% MeOH in $CHCl_3$, to give **14** (152 mg, 85% as a pale brown foam, crystallized from EtOH): mp 195−196 °C (lit.[21] mp 195−196 °C); FAB-LRMS *m*/*z* 261 (MH^+, 8.3%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (br s, 1 H, NH), 7.98 (d, 1 H, H-6, $J_{6,5}$ = 8.2 Hz), 5.88 (d, 1 H, H-1′, $J_{1',2'}$ = 7.4 Hz), 5.68 (d, 1 H, H-5, $J_{5,6}$ = 8.2 Hz), 5.46 (d, 1 H, 2′-OH, $J_{2'OH,2'}$ = 6.1 Hz), 5.24 (d, 1 H, 3′-OH, $J_{3'-OH,3'}$ = 4.2 Hz), 5.16 (t, 1 H, 5′-OH, $J_{5'-OH,5'}$ = 5.3 Hz), 4.13 (ddd, 1 H, H-2′, $J_{2',2'-OH}$ = 6.1, $J_{2',1'}$ = 7.4, $J_{2',3'}$ = 3.5 Hz), 4.00 (ddd, 1 H, H-3′, $J_{3',3'-OH}$ = 4.2, $J_{3',2'}$ = 3.5, $J_{3',4'}$ = 3.0 Hz), 3.61 (ddd, 1 H, H-5′a, $J_{5'a,5'-OH}$ = 5.3, $J_{5'a,4'}$ = 6.6, $J_{5'a,5'b}$ = 11.4 Hz), 3.53 (ddd, 1 H, H-5′b, $J_{5'b,5'-OH}$ = 5.3, $J_{5'b,4'}$ = 5.4, $J_{5'b,5'a}$ = 11.4 Hz), 3.18 (ddd, 1 H, H-4′, $J_{4',3'}$ = 3.0, $J_{4',5'a}$ = 6.6, $J_{4',5'b}$ = 5.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.03, 151.16, 141.60, 102.25, 76.43, 73.11, 63.24, 62.39, 53.12.

1-(4-Thio-β-D-ribofuranosyl)cytosine (15). In a manner similar to that described for **14**, **13** (324 mg, 0.46 mmol) was treated with ammonium fluoride, followed by methanolic ammonia to give **15** (75 mg, 63% as a pale brown foam): FAB-LRMS *m*/*z* 260 (MH^+, 63.5%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, 1 H, H-6, $J_{6,5}$ = 7.5 Hz), 7.12 (d, 2 H, NH_2), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 6.6 Hz), 5.78 (d, 1 H, H-5, $J_{5,6}$ = 7.5 Hz), 5.30 (d, 1 H, 2′-OH, $J_{2'OH,2'}$ = 6.1 Hz), 5.14 (d, 1 H, 3′-OH, $J_{3'-OH,3'}$ = 4.2 Hz), 5.10 (t, 1 H, 5′-OH, $J_{5'-OH,5'}$ = 5.1 Hz), 4.04 (ddd, 1 H, H-2′, $J_{2',2'-OH}$ = 6.1, $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 3.6 Hz), 3.96 (ddd, 1 H, H-3′, $J_{3',3'-OH}$ = 4.2, $J_{3',2'}$ = 3.6, $J_{3',4'}$ = 3.7 Hz), 3.61 (ddd, 1 H, H-5′a, $J_{5'a,5'-OH}$ = 5.1, $J_{5'a,4'}$ = 6.3, $J_{5'a,5'b}$ = 11.3 Hz), 3.53 (ddd, 1 H, H-5′b, $J_{5'b,5'-OH}$ = 5.1, $J_{5'b,4'}$ = 5.6, $J_{5'b,5'a}$ = 11.3 Hz), 3.19 (ddd, 1 H, H-4′, $J_{4',3'}$ = 3.7, $J_{4',5'a}$ = 6.3, $J_{4',5'b}$ = 5.6 Hz). Anal. Calcd for $C_9H_{13}N_3O_4S \cdot 0.8$MeOH: C, 41.31; H, 5.73; N, 14.75. Found: C, 41.05; H, 5.35 N, 14.67.

1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-4-thio-α-D-ribofuranosyl]uracil (17). In the same manner as described for **8**, **16** (7 mg, 0.03 mmol) was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (40 μL, 0.1 mmol) to give **17** (10 mg, 67% as a white solid): FAB-LRMS *m*/*z* 503 (MH^+, 42.7%); FAB−HRMS calcd for $C_{21}H_{39}N_2O_6SSi_2$ (MH^+) 503.2067, found 503.2049; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.90 (br s, 1 H, NH), 7.98 (d, 1H, H-6, $J_{6,5}$ = 8.3 Hz), 6.32 (d, 1 H, H-1′, $J_{1',2'}$ = 4.9 Hz), 5.70 (d, 1 H, H-5, $J_{5,6}$ = 8.3 Hz), 4.49 (dd, 1 H, H-2′, $J_{2',1'}$ = 4.9, $J_{2',3'}$ = 3.7 Hz), 4.32 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.4, $J_{3',4'}$ = 9.5 Hz), 4.10 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 3.0, $J_{5'a,5'b}$ = 12.9 Hz), 3.95 (dd, 1 H, H-5′b, $J_{5'b,4'}$ = 2.0, $J_{5'b,5'a}$ = 12.9 Hz), 3.81 (ddd, 1 H, H-4′, $J_{4',3'}$ = 9.5, $J_{4',5'a}$ = 3.0, $J_{4',5'b}$ = 2.0 Hz), 3.04 (br s, 1 H, 2′-OH), 1.11−1.05 (m, 28 H, TIPDS).

1-[2-*O*-(2,4-Dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α-D-ribofuranosyl]uracil (18). To a solution of **17** (10 mg, 0.02 mmol) in dry CH_3CN (2 mL) were added 2,4-dimethoxybenzoyl chloride (11 mg, 0.06 mmol), triethylamine (10 μL, 0.06 mmol), and DMAP (23 mg, 0.19 mmol), and the mixture was heated under reflux for 12 h. The reaction was quenched by addition of ice, and the reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (1:1), to give **18** (5 mg, 39% as a white solid): FAB-LRMS *m*/*z* 667 (MH^+, 14.8%); FAB−HRMS calcd for $C_{30}H_{47}N_2O_9SSi_2$ (MH^+) 667.2540, found 667.2522; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, 1 H, NH), 7.87 (d, 1H, H-6, $J_{6,5}$ = 8.3 Hz), 7.79 (d, 1 H, Ar, J = 8.6 Hz), 6.52 (d, 1 H, H-1′, $J_{1',2'}$ = 4.9 Hz), 6.48 (m, 2 H, Ar), 5.85 (dd, 1 H, H-2′, $J_{2',1'}$ = 4.9, $J_{2',3'}$ = 3.4 Hz), 5.46 (dd, 1 H, H-5, $J_{5,6}$ = 8.3, $J_{5,1'}$ = 2.3 Hz), 4.44 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.4, $J_{3',4'}$ = 9.6 Hz), 4.15 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 2.7, $J_{5'a,5'b}$ = 12.7 Hz), 3.98 (dd, 1 H, H-5′b, $J_{5'b,4'}$ = 1.7, $J_{5'b,5'a}$ = 12.7 Hz), 3.95 (ddd, 1 H, H-4′, $J_{4',3'}$ = 9.6, $J_{4',5'a}$ = 2.7, $J_{4',5'b}$ = 1.7 Hz), 1.14−0.95 (m, 28 H, TIPDS).

2-*O*-(2,4-Dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-1-*O*-acetyl-4-thio-D-ribofuranose (19). A solution of **10** (210 mg, 0.36 mmol) in Ac_2O (10 mL) was heated at 110 °C for 6 h. The reaction was quenched by addition of H_2O, and the mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by

brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (7:1), to give **19** (93 mg, 41% as a colorless oil): FAB-LRMS *m*/*z* 555 ($M^+ - OAc$, 6.0%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.86 (d, 0.5 H, J = 8.6 Hz), 7.82 (d, 0.5 H, J = 9.2 Hz), 6.48 (m, 2 H), 5.77 (s, 0.5 H), 5.62 (d, 0.5 H, J = 3.3 Hz), 5.57 (m, 0.5 H), 4.63 (dd, 0.5 H, J = 3.3, 9.8 Hz), 4.58 (m, 1H), 4.15−4.06 (m, 1.5 H), 3.88, 3.87, 3.86, 3.85 (each s, each 1.5 H), 3.66 (m, 0.5 H), 3.26 (dd, 0.5 H, J = 9.2, 10.6 Hz), 3.09 (dd, 0.5 H, 6.6, 9.2 Hz), 2.07, 2.05 (each s, each 1.5 H), 1.13−0.98 (m, 28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.33, 169.22, 164.59, 164.53, 164.15, 161.75, 161.72, 133.97, 133.74, 111.87, 111.74, 104.66, 104.36, 99.01, 98.82, 96.97, 78.92, 77.58, 74.90, 72.41, 61.19, 59.26, 55.97, 55.86, 55.49, 49.77, 30.44, 21.90, 20.86, 17.45, 17.32, 17.29, 17.25, 17.22, 17.19, 17.16, 17.03, 13.48, 13.36, 13.07, 13.00, 12.77, 12.72, 12.46.

6-Chloro-9-[2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-*β*-D-ribofuranosyl]-9*H*-purine (25). To a suspension of 6-chloropurine (70 mg, 0.46 mmol) in a mixture of dry CH_3CN (2 mL) and 1,2-dichloroethane (1 mL) were added triethylamine (65 μL, 0.46 mmol) and TMSOTf (180 μL, 0.93 mmol), and the mixture was stirred at room temperature until the solution was clear. The resulting solution was added to a solution of **10** (67 mg, 0.12 mmol, R/S = >16:1) in dry 1,2-dichloroethane (1 mL) dropwise over 15 min via a cannula. An additional amount of triethylamine (65 μL, 0.46 mmol) in dry 1,2-dichloroethane (0.5 mL) was added dropwise to the reaction mixture to initiate the Pummerer reaction. After being stirred at room temperature for 5 min, the reaction mixture was heated at 83 °C for 24 h. The reaction was quenched by addition of ice, and the reaction mixture was partitioned between AcOEt and H_2O. The separated organic layer was washed with saturated aqueous $NaHCO_3$ (three times), followed by brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by a silica gel column, eluted with hexane/AcOEt (5:1−1:1), to give **25** (53 mg, 65% as a yellow solid): FAB-LRMS *m*/*z* 709 (MH^+, 1.0%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76, 8.59 (each s, each 1 H, H-2 and 8), 7.93 (d, 1 H, Ar, J = 8.8 Hz), 5.96 (m, 2 H, Ar), 6.07 (s, 1 H, H-1′), 5.84 (d, 1 H, H-2′, $J_{2',3'}$ = 3.9 Hz), 4.96 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.9, $J_{3',4'}$ = 9.8 Hz), 4.56 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 12.9 Hz), 4.12 (d, 1 H, H-5′b, $J_{5'b,5'a}$ = 12.9 Hz), 3.90, 3.88 (each s, each 3 H, MeO × 2), 3.86 (dd, 1 H, H-4′, $J_{4',3'}$ = 9.8, $J_{4',5'a}$ = 2.9 Hz), 1.16−0.89 (m, 28 H, TIPDS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.64, 163.59, 161.69, 152.07, 151.18, 151.10, 144.24, 134.02, 132.17, 111.24, 104.63, 98.88, 77.87, 72.22, 60.65, 58.10, 55.98, 55.56, 51.36, 17.52, 17.43, 17.12, 17.08, 16.98, 13.36, 13.24, 13.08, 12.65. Anal. Calcd for $C_{31}H_{46}N_4O_7SSi_2Cl$: C, 52.49; H, 6.39; N, 7.90. Found: C, 52.38; H, 6.40; N, 7.56.

^{1}H NMR data for **6-chloro-7-[2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-*β*-D-ribofuranosyl]-9*H*-purine (24):** ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.11, 8.88 (each s, each 1 H, H-2 and 8), 7.82 (d, 1 H, Ar, J = 8.4 Hz), 6.45 (m, 2 H, Ar), 6.41 (s, 1 H, H-1′), 5.83 (d, 1 H, H-2′, $J_{2',3'}$ = 3.2 Hz), 4.60 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.2, $J_{3',4'}$ = 9.2 Hz), 4.19 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 3.2, $J_{5'a,5'b}$ = 13.0 Hz), 4.10 (d, 1 H, H-5′b, $J_{5'b,5'a}$ = 13.0 Hz), 3.86, 3.84 (each s, each 3 H, MeO × 2), 3.82 (m, 1 H, H-4′), 1.17−0.87 (m, 28 H, TIPDS).

6-Chloro-9-[2-*O*-(2,4-dimethoxybenzoyl)-4-thio-*β*-D-ribofuranosyl]-9*H*-purine (26). To a solution of **25** (52 mg, 0.07 mmol) in THF (2 mL) containing AcOH (9 μL, 0.15 mmol) was added TBAF (1 M in THF, 150 μL, 0.15 mmol). The mixture was stirred at room temperature for 10 min. The solvent was removed in vacuo, and the residue was purified by a silica gel column, eluted with acetone, to give **26** (34 mg, 99% as a white solid): FAB-LRMS *m*/*z* 467 (MH^+, 22.7%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81, 8.34 (each s, each 1 H, H-2 and 8), 7.73 (d, 1 H, Ar, J = 8.6 Hz), 6.50 (m, 2 H, Ar), 6.27 (d, 1 H, H-1′, $J_{1',2'}$ = 6.3 Hz), 6.23 (dd, 1 H, H-2′, $J_{2',1'}$ = 6.3, $J_{2',3'}$ = 9.8 Hz), 4.81 (dd, 1 H, H-3′, $J_{3',2'}$ = 9.8, $J_{3',4'}$ = 3.7 Hz), 4.27 (m, 1 H, 5′-OH), 4.15 (m, 1 H, H-5′a, $J_{5'a,4'}$ = 3.2, $J_{5'a,5'b}$ = 12.0 Hz), 4.01 (m, 1 H, H-5′b, $J_{5'b,4'}$ = 2.9, $J_{5'b,5'a}$ = 12.0 Hz), 3.88, 3.85 (each s, each 3 H, MeO × 2), 3.79 (ddd, 1 H, H-4′, $J_{4',3'}$ = 3.7, $J_{4',5'a}$ = 3.2, $J_{4',5'b}$ = 2.9 Hz), 3.20 (d, 1 H, 3′-OH, $J_{3'-OH,3'}$ = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.00, 164.40, 160.80, 151.69, 151.44, 150.88, 144.95, 134.37, 132.86, 110.34, 105.07, 99.01, 79.67, 77.12, 75.30, 63.53, 56.06, 55.59, 54.34. Anal. Calcd for $C_{19}H_{19}N_4O_6SCl$: C, 48.87; H, 4.10; N, 12.00. Found: C, 48.54; H, 4.10; N, 11.76.

9-(4-Thio-*β*-D-ribofuranosyl)adenine (27). A solution of **26** (37 mg, 0.08 mmol) in ethanolic ammonia (saturated at 0 °C, 5 mL) was heated for 24 h at 100 °C in a steel container. The solvent was removed in vacuo, and the residue was purified by a silica gel column, eluted with 25% MeOH in $CHCl_3$, to give **27** (18 mg, 83%, crystallized from MeOH−H_2O): mp 254−256 °C (lit.[15] mp 246−248 °C); FAB-LRMS *m*/*z* 285 (MH^+, 33.3%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42, 8.12 (each s, each 1 H, H-2 and 8), 7.27 (br s, 2 H, NH_2), 6.59 (d, 1 H, H-1′, $J_{1',2'}$ = 6.6 Hz), 5.57 (d, 1 H, 2′-OH, $J_{2'OH,2'}$ = 6.1 Hz), 5.35 (d, 1 H, 3′-OH, $J_{3'-OH,3'}$ = 4.6 Hz), 5.23 (t, 1 H, 5′-OH, $J_{5'-OH,5'}$ = 5.6 Hz), 4.63 (ddd, 1 H, H-2′, $J_{2',2'-OH}$ = 6.1, $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 3.4 Hz), 4.17 (ddd, 1 H, H-3′, $J_{3',3'-OH}$ = 4.6, $J_{3',2'}$ = 3.4, $J_{3',4'}$ = 3.4 Hz), 3.76 (ddd, 1 H, H-5′a, $J_{5'a,5'-OH}$ = 5.6, $J_{5'a,4'}$ = 6.6, $J_{5'a,5'b}$ = 11.2 Hz), 3.59 (ddd, 1 H, H-5′b, $J_{5'b,5'-OH}$ = 5.6, $J_{5'b,4'}$ = 5.9, $J_{5'b,5'a}$ = 11.2 Hz), 3.29 (ddd, 1 H, H-4′, $J_{4',3'}$ = 3.4, $J_{4',5'a}$ = 6.6, $J_{4',5'b}$ = 5.9 Hz). Anal. Calcd for $C_{10}H_{13}N_5O_3S\cdot0.6H_2O$: C, 40.84; H, 4.87; N, 23.81. Found: C, 41.01; H, 4.86; N, 23.45.

2-Amino-6-chloro-9-[2-*O*-(2,4-dimethoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-*β*-D-ribofuranosyl]-9*H*-purine (28). In the same manner as described for **25**, the Pummerer reaction of **10** (179 mg, 0.31 mmol, R/S = >16:1) with 2-amino-6-chloropurine (106 mg, 0.62 mmol) gave **28** (127 mg, 56% as a white solid): FAB-LRMS *m*/*z* 724 (MH^+, 0.3%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1 H, H-8), 7.87 (d, 1 H, Ar, J = 8.4 Hz), 6.49 (m, 2 H, Ar), 5.84 (s, 1 H, H-1′), 5.77 (d, 1 H, H-2′, $J_{2',3'}$ = 3.6 Hz), 5.29 (br s, 2 H, NH_2), 4.71 (dd, 1 H, H-3′, $J_{3',2'}$ = 3.6, $J_{3',4'}$ = 9.5 Hz), 4.17 (dd, 1 H, H-5′a, $J_{5'a,4'}$ = 2.9, $J_{5'a,5'b}$ = 12.6 Hz), 4.08 (d, 1 H, H-5′b, $J_{5'b,5'a}$ = 12.6 Hz), 3.87, 3.84 (each s, each 3 H, MeO × 2), 3.79 (m, 1 H, H-4′), 1.13−0.86 (m, 28 H, TIPDS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.70, 163.55, 161.72, 159.19, 153.27, 151.45, 140.79, 134.01, 125.57, 111.52, 104.73, 99.00, 77.83, 72.39, 59.59, 58.26, 55.99, 55.52, 50.93, 17.45, 17.34, 17.04, 17.02, 16.87, 13.35, 13.18, 13.05, 12.59. Anal. Calcd for $C_{31}H_{46}N_5O_7SSi_2Cl$: C, 51.33; H, 6.53; N, 9.65. Found: C, 51.45; H, 6.52; N, 9.23.

2-Amino-6-chloro-9-[2-*O*-(2,4-dimethoxybenzoyl)-4-thio-*β*-D-ribofuranosyl]-9*H*-purine (29). In the same manner as described for **26**, treatment of **28** (127 mg, 0.18 mmol) with TBAF (1 M in THF, 350 μL, 0.35 mmol) gave **29** (84 mg, 99% as a white solid): FAB-LRMS *m*/*z* 482 (MH^+, 2.5%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1 H, H-8), 7.66 (d, 1 H, Ar, J = 9.3 Hz), 7.04 (br s, 2 H, NH_2), 6.54 (m, 2 H, Ar), 6.14 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 5.75 (m, 2 H, H-2′ and 3′-OH), 5.32 (br s, 1 H, 5′-OH), 4.57 (m, 1 H, H-3′), 3.86 (m, 1 H, H-5′a), 3.79 (s, 3 H, MeO), 3.72 (m, 1 H, H-5′b), 3.64 (s, 3 H, MeO), 3.43 (m, 1 H, H-4′); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.17, 163.36, 160.90, 159.70, 153.99, 149.50, 141.63, 133.40, 123.24, 110.73, 105.33, 98.74, 78.37, 71.22, 62.95, 58.67, 55.69, 55.64, 54.32. Anal. Calcd for $C_{19}H_{20}N_5O_6SCl\cdot0.5H_2O$: C, 46.49; H, 4.31; N, 14.27. Found: C, 46.64; H, 4.19; N, 14.11.

9-(4-Thio-*β*-D-ribofuranosyl)guanine (30). A solution of **29** (80 mg, 0.17 mmol) in MeOH (10 mL) containing 2-mercaptoethanol (47 μL, 0.66 mmol) and NaOMe (28% solution, 130 μL) was heated under reflux for 24 h. The reaction mixture was neutralized with 1 N HCl, and the solution was concentrated in vacuo. The residue was dissolved in H_2O, and the aqueous layer was washed with AcOEt. The aqueous layer was concentrated in vacuo, and the residue was crystallized from H_2O to give **30** (28 mg, 55% as pale brown crystals): mp 240 °C dec; FAB-LRMS *m*/*z* 300 (MH^+, 8.3%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (br s, 1 H, NH), 8.02 (s, 1 H, H-8), 6.50 (br s, 2 H, NH_2), 5.65 (d, 1 H, H-1′, $J_{1',2'}$ = 6.8 Hz), 5.48 (d, 1 H, 2′-OH, $J_{2'OH,2'}$ = 5.6 Hz), 5.28 (m, 1 H, 3′-OH), 5.15 (t, 1 H, 5′-OH, $J_{5'-OH,5'}$ = 5.4 Hz), 4.46 (ddd, 1 H, H-2′, $J_{2',2'-OH}$ = 5.6, $J_{2',1'}$ = 6.8, $J_{2',3'}$ = 3.4 Hz), 4.15 (m, 1 H, H-3′), 3.72 (ddd, 1 H, H-5′a, $J_{5'a,5'-OH}$ = 5.4, $J_{5'a,4'}$ = 7.1, $J_{5'a,5'b}$ = 11.4 Hz), 3.53 (ddd, 1 H, H-5′b, $J_{5'b,5'-OH}$ = 5.4, $J_{5'b,4'}$ = 5.9, $J_{5'b,5'a}$ = 11.4 Hz), 3.24 (m, 1 H, H-4′); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.61, 153.39, 151.53, 135.84, 116.40, 76.99, 73.03, 63.18, 60.16, 52.96. Anal. Calcd for $C_{10}H_{13}N_5O_4S\cdot0.5H_2O$: C, 38.90; H, 4.58; N, 22.71. Found: C, 39.28; H, 4.47; N, 22.82.

Acknowledgment. This investigation was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports, and Culture of Japan. We thank Ms. H. Matsumoto and Ms. A. Maeda (Center for Instrumental Analysis, Hokkaido University) for elemental analysis. We also thank Ms. S. Oka and Ms. N. Hazama (Center for Instrumental Analysis, Hokkaido University) for measurement of mass spectra.

JA000541O