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SYNTHESIS OF 4'-THIOPURINE NUCLEOSIDES USING HYPERVALENT IODINE COMPOUNDS

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Abstract – The reaction of a silylated purine base with thiofuranoid using phenyl iodosyl bis(trifluoroacetate) gave 4'-thio purine nucleosides.

INTRODUCTION

Nucleoside analogues are recognized as an important class of biologically active compounds, especially as antiviral and antitumor agents. Therefore, many nucleoside derivatives have been synthesized and their biological activities have been evaluated. Among these, thionucleosides are attractive compounds that contain sulfur either in the nucleobase or the sugar moiety.[1] 4'-Thionucleosides, in which the furanose ring oxygen is replaced by a sulfur atom, have been studied extensively over the past 10 years because a number of 4'-thionucleoside analogs have emerged as potent antiviral agents. Importantly, these analogs have good metabolic stability against phosphorylase enzymes[2] that cleave the glycosidic bond of nucleosides.

We recently reported a novel method for synthesizing 4'-thio pyrimidine nucleosides based on the condensation of thiofuranoid and silylated nucleobases in the presence of a hypervalent iodine compound.[3] In this paper, the application of this approach to the synthesis of purine 4'-thionucleosides **1**-**2** is described (Figure 1). These thionucleosides **1** are expected to act as inhibitors of an *S*-adenosyl-L-homocysteine hydrolase, which has emerged as a target enzyme for the molecular design of antiviral agents.[4]

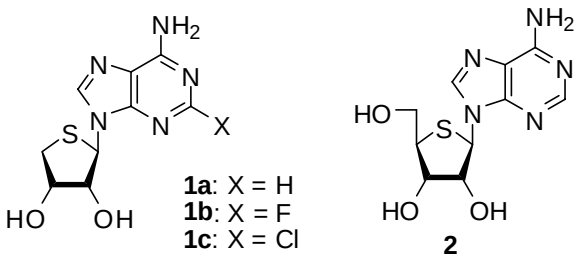
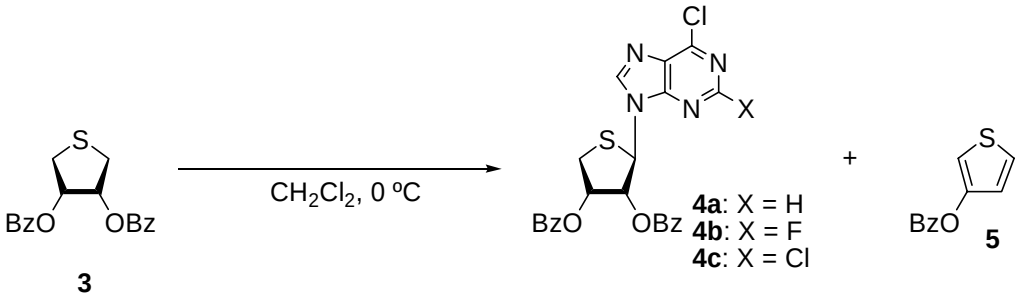


Figure 1. Structures of target compounds

RESULTS AND DISCUSSION

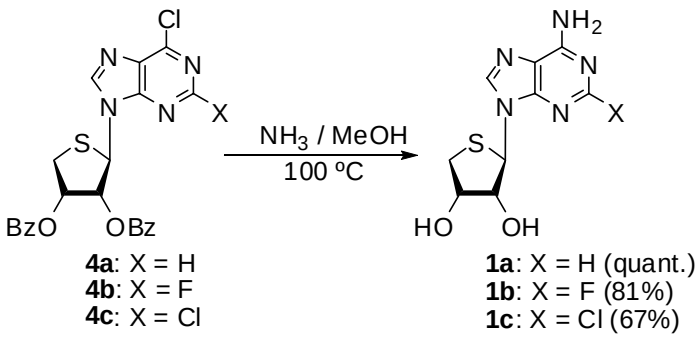
First, the coupling reaction of **3** with purine in the presence of a hypervalent iodine compound was examined under various conditions (Table 1). When 6-chloropurine was treated with **3** under conditions similar to those used for the synthesis of 4'-thio pyrimidine nucleosides,[3] the desired **4a** was not obtained; instead, thiophene derivative **5** was produced due to the low nucleophilicity of the purine base. Using phenyl iodosyl bis(trifluoroacetate) (PIFA) instead of iodosobenzene, the desired **4a** was obtained in 35% yield along with the *N*-7 stereoisomer (24%). The nucleobases 2,6-dichloropurine and 2-fluoro-6-chloropurine similarly reacted with **3** to give products **4b** and **4c**, respectively. In the case of 2,6-dichloropurine, the product **4c** was obtained in 72% yield.

Table 1. Coupling reaction of **3** with purine base.



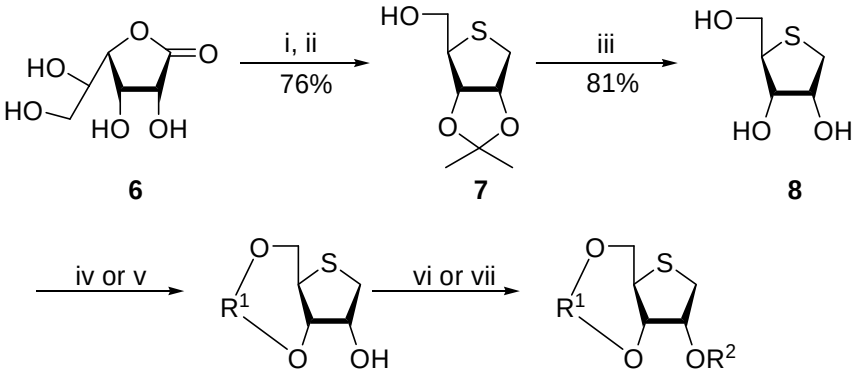
entry	base	condition	yield of **4** (%)	ratio (β:α)
1	6-chloropurine	PhI=O (1.5 eq), TMSOTf (10 eq), Et_3N (10 eq)	-	-
2	6-chloropurine	PIFA (1.5 eq), TMSOTf (10 eq), Et_3N (10 eq)	35	5:1
3	2-fluoro-6-chloropurine	PIFA (1.5 eq), TMSOTf (10 eq), Et_3N (10 eq)	36	3:1
4	2,6-dichloropurine	PIFA (1.5 eq), TMSOTf (10 eq), Et_3N (10 eq)	72	15:1

The target compounds **1a-c** were obtained by treating **4a-c** with methanolic ammonia in a steel container at 100 °C (Scheme 1).



Scheme 1

Next, the synthesis of 4'-thioadenosine (**2**)[5] was examined. Thiofuranoids **10a-d** were prepared as shown in Scheme 2. 1,4-Anhydro-2,3-isopropylidene-4-thio-D-ribitol (**7**), prepared from D-glulono-γ-lactone (**6**) by a modification of the method of Jeong *et al.*[6], was treated with 80% acetic acid under reflux to give 1,4-anhydro-4-thio-D-ribitol (**8)** in 81% yield. The 3- and 5-hydroxy groups of **8** were first protected with silyl groups, and the resulting silylated compounds **9** were then reacted with acyl chloride to give **10**.



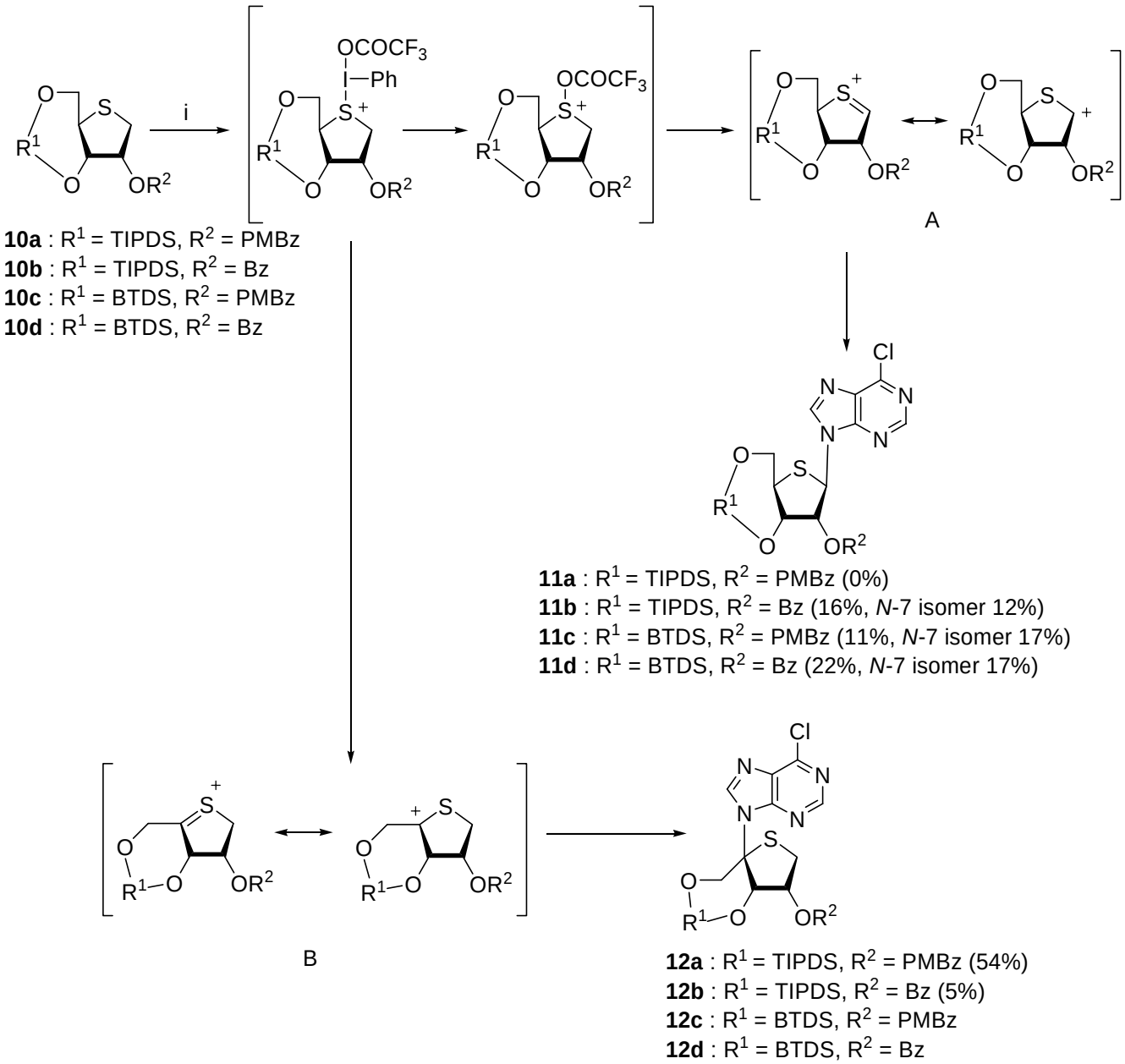
Scheme 2. *Reagents and conditions*: i) $Pb(OAc)_2$, EtOAc, 0 ºC; ii) $NaBH_4$, MeOH; iii) 80% AcOH, reflux; iv) TIPDSCl, pyridine; v) $BTDSCl_2$, DMAP, DMF; vi) PMBzCl, pyridine; vii) BzCl, pyridine.

Surprisingly, treatment of **10a** with 6-chloropurine under the conditions used for the synthesis of **4** afforded regioisomer **12a** in 54% yield, but the desired nucleoside **11a** was not obtained (Scheme 3). The structure of **12a** was determined by ^{1}H-NMR spectroscopy, an NOE experiment and FAB-HRMS. In contrast to the case of the pyrimidine reported in a previous paper,[3] this result indicates that the reaction progresses via the more stable tertiary cation intermediate **B** which is generated by elimination of a proton at the 4-position on the thiofuranose ring. The generated thionium cation **B** is attacked by a nucleobase from the β-face to give only the β-anomer **12a**.

The desired nucleoside was obtained using **10b**, which possesses benzoyl instead of *p*-methoxybenzoyl protecting groups on the 2-hydroxy groups. The acidity of the 1-position of **10b** is increased, as benzoyl is a more electron-withdrawing group than *p*-methoxybenzoyl. Consequently, the thionium cation **A** is generated by elimination of a proton at the 1-position of **10b**. The silylated 6-chloropurine then attacks the generated **A** to afford **11b**. This result suggests that the acidity of the α hydrogen adjacent to a sulfur atom affects the regioselectivity of a reaction.

When the 1,4-hydroxyl groups were protected by DTBS (di-*tert*-butyl-silylene) instead of TIPDS (tetraisopropyldisiloxanane-1,3-diyl), regardless of the protective group on the 2-hydroxyl group, the desired nucleoside **11c-d** was obtained regioselectively along with the *N*-7 stereoisomer. In a manner

similar to the Pummerer reaction, regiochemistry is controlled by steric hindrance due to the bulkiness of the protecting group, the DTBS group being more bulky than TIPDS. Therefore, elimination of a proton will occur at the less hindered 1-position in preference to the 4-position on the thiofuranose ring to generate thionium cation **A**. The generated **A** coupled with silylated 6-chloropurine to give **11c-d**.



10a : R^1 = TIPDS, R^2 = PMBz
10b : R^1 = TIPDS, R^2 = Bz
10c : R^1 = BTDS, R^2 = PMBz
10d : R^1 = BTDS, R^2 = Bz

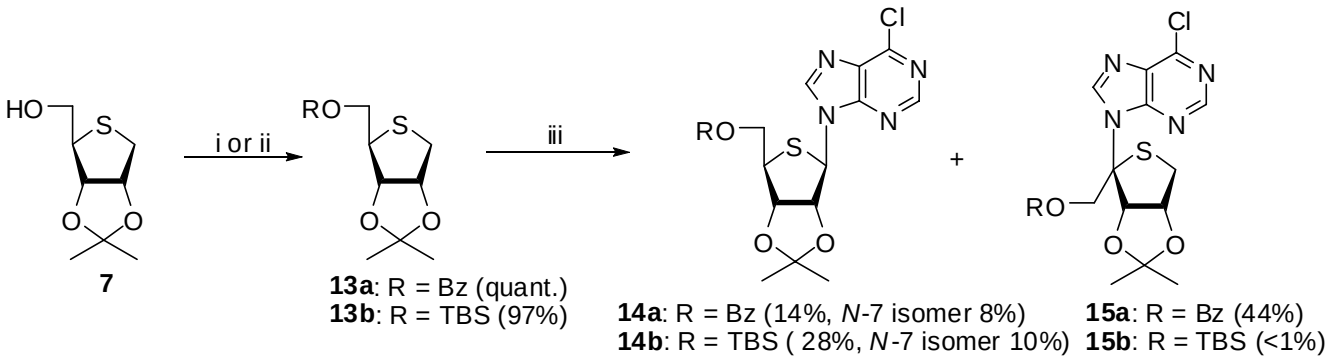
11a : R^1 = TIPDS, R^2 = PMBz (0%)
11b : R^1 = TIPDS, R^2 = Bz (16%, *N*-7 isomer 12%)
11c : R^1 = BTDS, R^2 = PMBz (11%, *N*-7 isomer 17%)
11d : R^1 = BTDS, R^2 = Bz (22%, *N*-7 isomer 17%)

12a : R^1 = TIPDS, R^2 = PMBz (54%)
12b : R^1 = TIPDS, R^2 = Bz (5%)
12c : R^1 = BTDS, R^2 = PMBz
12d : R^1 = BTDS, R^2 = Bz

Scheme 3. *Reagents and conditions*: i) 6-chloropurine, TMSOTf, Et_3N, PIFA, CH_2Cl_2.

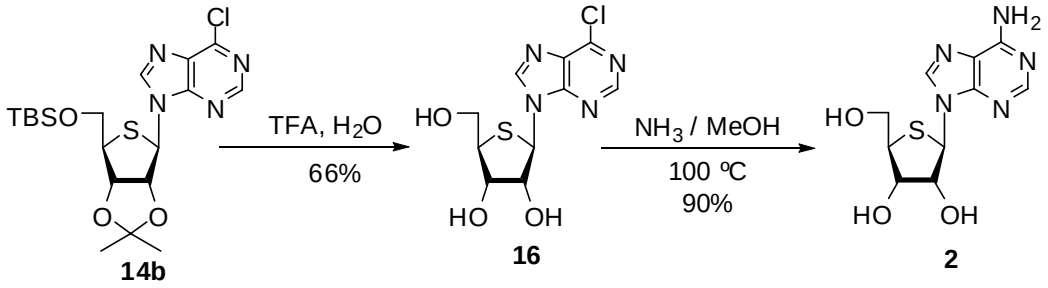
Different protecting groups on the hydroxyl groups in the sugar moiety clearly affected regioselectivity; therefore, the regioselectivity of the reaction was examined using the 2,3-*O*-acetonides **13a-b** (Scheme 4). When the 5-hydroxyl group was protected with a benzoyl group, a condensation reaction occurred at the 4-position of **13a** to give **15a** (44%) as the main product. In contrast, when the 5-hydroxyl group was protected with TBS (*tert*-butyldimethylsilyl), a condensation reaction occurred at the 1-position of **13b** to

give **14b** (25%) along with the *N*-7 stereoisomer (10%). These results also indicate that the acidity of the α hydrogen adjacent to the sulfur atom affects the regioselectivity of the reaction.



Scheme 4. *Reagents and conditions*: i) TBSCl, imidazol, DMF; ii) BzCl, pyridine; iii) 6-chloropurine, TMSOTf, Et_3N, PIFA, CH_2Cl_2.

Finally, 4'-thioadenosine (**2**) was obtained in 59% yield by treatment of **14b** with TFA and then with methanolic ammonia in a steel container at 100 °C (Scheme 5).



Scheme 5

As described, the 4'-thio purine nucleosides were synthesized by a condensation of thiofuranoid and silylated nucleobase in the presence of a phenyl iodosyl bis(trifluoroacetate), and the regioselectivity of this reaction was clarified. Increasing the acidity of the 1-position hydrogen or protecting the 3, 5-hydroxyl groups with bulky DTBS favored the condensate at the 1-position as the major product. This method will provide a convenient tool for the synthesis of 4'-thio purine nucleosides. Further investigations using this approach are in progress.

EXPERIMENTAL

All melting points were determined on a Yamato melting point apparatus (model MP-2) and are uncorrected. NMR spectra were recorded on a JEOL JNM-LA-300 and JEOL JNM-ECA-500

spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS (0.0 ppm) as internal standard, and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Coupling constants, *J*, are given in Hz. MS spectra were obtained on a JEOL JMS-HX110 and JEOL JMS-700TZ. TLC was done on Merck Silica gel 60 F_{254} plates. Column chromatography was conducted using silica gel (Merck, Silica gel 60, 70-230 mesh).

(*2R, *3R**, *4S**)-6-Chloro-9-(3,4-di-*O*-benzoylthiolan-3,4-diol-2-yl)-9*H*-purine (4a).** To a suspension of 6-chrolopurine (94 mg, 0.60 mmol) in dry CH_2Cl_2 (2 mL) were added Et_3N (84 μL, 0.60 mmol) and TMSOTf (271 μL, 1.50 mmol) at rt under a nitrogen atmosphere. After the mixture had been stirred for 1 h, a clear solution was obtained. A solution of **3** (50 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (97 mg, 0.23 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (126 μL, 0.90 mmol) was added to the reaction mixture. After the mixture had been stirred for 24 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (1 : 1), to give **4a** (25 mg, 35%) as a colorless foam. MS (FAB) *m/z* 481 (MH^+). HRMS (FAB) calcd for $C_{23}H_{18}ClN_4O_4S$ (MH^+): 481.0737, found: 481.0733. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1 H), 8.54 (s, 1 H), 8.06-7.36 (m, 10 H), 6.52 (d, 1 H, *J* = 6.6 Hz), 6.23 (dd, 1 H, *J* = 3.4 and 6.6 Hz), 6.14 (m, 1 H), 3.97 (dd, 1 H, *J* = 4.0 and 12.0 Hz), 3.40 (dd, 1 H, *J* = 3.4 and 12.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 165.0, 152.2, 151.7, 151.5, 143.9, 133.8, 133.7, 132.4, 129.8, 129.0, 128.6, 128.5, 128.3, 78.4, 73.3, 61.4, 33.1.

(*2R, *3R**, *4S**)-6-Chloro-2-fluoro-9-(3,4-di-*O*-benzoylthiolan-3,4-diol-2-yl)-9*H*-purine (4b).** This compound was prepared using 6-chloro-2-fluoropurine (104 mg, 0.60 mmol) by the procedure described for the preparation of **4a**. Yellow foam product, 28 mg (36%). MS (FAB) *m/z* 499 (MH^+). HRMS (FAB) calcd for $C_{23}H_{17}ClFN_4O_4S$ (MH^+): 499.0643, found: 499.0640. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.50 (s, 1 H), 8.07-7.29 (m, 10 H), 6.45 (d, 1 H, *J* = 5.7 Hz), 6.13-6.10 (m, 2 H), 3.96 (dd, 1 H, *J* = 4.6 and 12.0 Hz), 3.39 (dd, 1 H, *J* = 2.9 and 12.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 165.2, 157.3 (d, *J* = 219.4 Hz), 153.6 (d, *J* = 16.7 Hz), 153.3 (d, *J* = 17.9 Hz), 144.6, 134.0, 133.9, 131.1, 129.9, 129.1, 128.8, 128.7, 128.2, 78.7, 73.4, 61.5, 33.4.

(*2R, *3R**, *4S**)-2,6-Dichloro-9-(3,4-di-*O*-benzoylthiolan-3,4-diol-2-yl)-9*H*-purine (4c).** This compound was prepared using 2,6-dichloropurine (113 mg, 0.60 mmol) by the procedure described for the preparation of **4a**. Colorless foam product, 55 mg (72%). MS (FAB) *m/z* 515 (MH^+). HRMS (FAB)

calcd for $C_{23}H_{17}Cl_2N_4O_4S$ (MH^+): 515.0347, found: 515.0363. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.53 (s, 1 H), 8.08-7.30 (m, 10 H), 6.49 (d, 1 H, *J* = 6.9 Hz), 6.13 (dd, 1 H, *J* = 4.0 and 6.9 Hz), 6.05 (m, 1 H), 3.96 (dd, 1 H, *J* = 4.6 and 12.0 Hz), 3.39 (dd, 1 H, *J* = 3.4 and 12.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.4, 165.1, 153.3, 153.0, 152.2, 144.4, 133.9, 133.8, 131.4, 129.9, 128.9, 128.6, 128.1, 79.0, 73.3, 61.4, 33.4.

(*2R, *3R**, *4S**)-9-(Thiolan-3,4-diol-2-yl)-9*H*-adenine (1a).** A solution of **4a** (173 mg, 0.34 mmol) in methanolic ammonia (saturated at 0 ºC, 10 mL) was heated for 24 h at 100 ºC in a steel container. The solvent was removed *in vacuo*, and the residue was purified on silica gel column, eluted with $CHCl_3$-EtOH (5 : 1), to give **1a** (86 mg, 99%) as colorless crystals, mp 247-249 ºC. MS (FAB) m/z 254 (MH^+). HRMS (FAB) calcd for $C_9H_{12}N_5O_2S$ (MH^+): 254.0712, found: 254.7716. Anal. Calcd for $C_9H_{11}N_5O_2S{\cdot}0.2H_2O$: C, 42.08; H, 4.47; N, 27.26. Found: C, 42.05; H, 4.41; N, 27.10. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.38 (s, 1 H), 8.11 (s, 1 H), 7.22 (s, 2 H), 5.86 (d, 1 H, *J* = 6.8 Hz), 5.49 (d, 1 H, *J* = 6.3 Hz), 5.31 (d, 1 H, *J* = 4.0 Hz), 4.64 (m, 1 H), 4.32 (m, 1 H), 3.37 (dd, 1 H, *J* = 4.0 and 10.3 Hz), 2.76 (dd, 1 H, *J* = 2.9 and 10.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 156.6, 153.0, 150.4, 140.4, 119.5, 78.8, 72.8, 62.0, 34.9.

(*2R, *3R**, *4S**)-2-Fluoro-9-(thiolan-3,4-diol-2-yl)-9*H*-adenine (1b).** This compound was prepared from **4b** (137 mg, 0.27mmol) by the procedure described for the preparation of **1a**. Colorless crystals, 59 mg (81%). mp 213 ºC (decomp). MS (FAB) *m/z* 272 (MH^+). HRMS (FAB) calcd for $C_9H_{11}FN_5O_2S$ (MH^+): 272.0617, found: 272.0614. Anal. Calcd for $C_9H_{10}FN_5O_2S$: C, 39.85; H, 3.72; N, 25.82. Found: C, 39.76; H, 3.83; N, 25.60. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.43 (s, 1 H), 7.77 (s, 2 H), 5.76 (d, 1 H, *J* = 7.4 Hz), 5.54 (d, 1 H, *J* = 5.7 Hz), 5.35 (d, 1 H, *J* = 2.9 Hz), 4.56 (m, 1 H), 4.30 (m, 1 H), 3.37 (dd, 1 H, *J* = 3.4 and 10.9 Hz), 2.76 (dd, 1 H, *J* = 2.3 and 10.9 Hz).

(*2R, *3R**, *4S**)-2-Chloro-9-(thiolan-3,4-diol-2-yl)-9*H*-adenine (1c).** This compound was prepared from **4c** (30 mg, 0.06 mmol) by the procedure described for the preparation of **1a**. Colorless crystals, 11 mg (67%). mp 234-236 ºC. MS (FAB) *m/z* 288 (MH^+). HRMS (FAB) calcd for $C_9H_{11}ClN_5O_2S$ (MH^+): 288.0322, found: 288.0333. Anal. Calcd for $C_9H_{10}ClN_5O_2S{\cdot}0.6MeOH$: C, 37.56; H, 4.07; N, 22.82. Found: C, 37.26; H, 4.01; N, 22.89. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.43 (s, 1 H), 7.77 (s, 2 H), 5.77 (d, 1 H, *J* = 7.4 Hz), 5.53 (d, 1 H, *J* = 6.3 Hz), 5.34 (d, 1 H, *J* = 4.0 Hz), 4.56 (m, 1 H), 4.30 (dd, 1 H, *J* = 2.9 and 2.9 Hz), 3.37 (dd, 1 H, *J* = 4.0 and 10.9 Hz), 2.76 (dd, 1 H, *J* = 2.3 and 10.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 157.3, 153.7, 151.6, 140.9, 118.5, 79.1, 72.7, 61.9, 35.0.

1,4-Anhydro-2,3-*O*-isopropylidene-4-thio-D-ribitol (7). To a solution of **6** (100 mg, 0.45 mmol) in AcOEt (2 mL) was added $Pb(OAc)_4$ (219 mg, 0.51 mmol) at 0 ºC and the reaction mixture was stirred for 15 min. The mixture was filtered through a silica gel, washed with hexane-AcOEt (1 : 1), and dried *in vacuo*. The residue was dissolved in MeOH (10 mL), and $NaBH_4$ (19 mg, 0.5 mmol) was added to the mixture at 0 ºC. After stirring for 30 min, the reaction was quenched by addition of acetic acid, and the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt and then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (1 : 1), to give **7** (64 mg, 76%) as a colorless syrup. MS (EI) *m/z* 190 (M^+). HRMS (EI) calcd for $C_8H_{14}O_3S$ (M^+): 190.0663, found: 190.0674. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.92 (ddd, 1H, *J* = 1.7, 5.1 and 5.3 Hz), 4.70 (dd, 1 H, *J* = 1.1 and 5.7), 3.61 (m, 2 H), 3.46 (dd, 1 H, *J* = 6.2 and 6.4 Hz), 3.10 (dd, 1 H, *J* = 5.0 and 12.8 Hz), 2.92 (dd, 1 H, *J* = 1.7 and 12.8 Hz), 2.04 (dd, 1 H, *J* = 5.3 and 7.2 Hz), 1.53 (s, 3 H), 1.33 (s, 3 H).

1,4-Anhydro-4-thio-D-ribitol (8). A solution of **7** (600 mg, 3.2 mmol) in 80% acetic acid (20 mL) was refluxed with stirring for 5 h. After the solvent was removed *in vacuo*, the residue was purified on silica gel column, eluted with $CHCl_3$-EtOH (5 : 1), to give **8** (389 mg, 81%) as a colorless syrup. MS (FAB) *m/z* 151 (MH^+). HRMS (FAB) calcd for $C_5H_{11}O_3S$ (MH^+): 151.0430, found: 151.0431. Anal. Calcd for $C_5H_{10}O_3S$: C, 39.98; H, 6.71; N, 21.23. Found: C, 39.88; H, 6.55; N, 21.38. ^{1}H NMR (300 MHz, CD_3OD) δ: 4.21 (ddd, 1 H, *J* = 3.6, 5.1 and 5.3 Hz), 3.93 (dd, 1 H, *J* = 3.6 and 5.6 Hz), 3.70 (dd, 1 H, *J* = 5.9 and 11.2 Hz), 3.53 (dd, 1 H, *J* = 6.5 and 11.2 Hz), 3.32 (m, 1 H), 2.90 (dd, 1 H, *J* = 5.1 and 10.8 Hz), 2.73 (dd, 1 H, *J* = 5.3 and 10.8 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 77.7, 75.8, 65.4, 52.6, 33.4.

1,4-Anhydro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (9a). To a solution of **8** (201 mg, 1.3 mmol) in dry pyridine (5 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (377 μL, 1.2 mmol) at 0 ºC under a nitrogen atmosphere, and the mixture was stirred at rt for 68 h. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (5 : 1), to give **9a** (357 mg, 70%) as a colorless syrup. MS (FAB) *m/z* 393 (MH^+). HRMS (FAB) calcd for $C_{17}H_{37}O_4SSi_2$ (MH^+): 393.1951, found: 393.1972. Anal. Calcd for $C_{17}H_{36}O_4SSi_2$: C, 51.99; H, 9.24; S, 8.17. Found: C, 51.76; H, 9.00; S, 8.26. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.33 (m, 1 H), 4.23 (dd, 1 H, *J* = 3.9 and 8.3Hz), 4.04 (dd, 1 H, *J* = 3.3 and 12.4 Hz), 3.90 (dd, 1 H, *J* = 4.7 and 12.4 Hz), 3.50 (ddd, 1 H, *J* = 3.3, 4.7 and 8.3 Hz), 3.03 (ddd, 1 H, *J* = 1.5, 4.7 and 12.1 Hz), 2.84 (dd, 1 H, *J* = 1.6 and 12.1 Hz),

2.64 (m, 1 H), 1.09-0.95 (m, 28 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 77.5, 74.4, 61.0, 49.2, 32.4, 17.4, 17.3, 17.2, 17.1, 13.4, 13.3, 12.7, 12.6.

1,4-Anhydro-3,5-*O*-(di-*tert*-butylsilylene)-4-thio-D-ribitol (9b). To a solution of **8** (201 mg, 1.3 mmol) in dry DMF (5 mL) was added di-*tert*-butylsilyl-bis-(trifluoromethanesulfonate) (377 μL, 1.2 mmol) and DMAP (849 mg, 6.7 mmol) at 0 ºC under a nitrogen atmosphere, and the mixture was stirred at rt for 24 h. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (4 : 1), to give **9b** (288 mg, 76%) as a colorless syrup. MS (FAB) *m/z* 291 (MH^+). HRMS (FAB) calcd for $C_{13}H_{27}O_3SSi$ (MH^+): 291.1450, found: 291.1460. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.42 (dd, 1 H, *J* = 4.0 and 4.6 Hz), 4.33 (dd, 1 H, *J* = 4.6 and 9.7), 4.03-3.96 (m, 2 H), 3.63 (m, 1 H), 3.06 (dd, 1 H, *J* = 4.0 and 12.6 Hz), 2.89 (d, 1 H, *J* = 12.6 Hz), 2.33 (s, 1 H), 1.05 (s, 9 H), 1.01 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 83.2, 72.6, 68.6, 43.9, 32.6, 27.3, 27.2, 22.7, 20.1.

1,4-Anhydro-2-*O*-(*p*-methoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (10a). To a solution of **9a** (730 mg, 1.9 mmol) in dry pyridine (35 mL) was added *p*-methoxybenzoyl chloride (650 μL, 3.8 mmol) at 0 ºC under a nitrogen atmosphere, and the mixture was stirred at rt for 12 h. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (15 : 1), to give **10a** (980 mg, 98%) as a colorless syrup. MS (FAB) *m/z* 527 (MH^+). HRMS (FAB) calcd for $C_{25}H_{43}O_6SSi_2$ (MH^+): 527.2241, found: 527.2305. Anal. Calcd for $C_{25}H_{43}O_6SSi_2$: C, 56.99; H, 8.04; S, 6.09. Found: C, 56.90; H, 8.00; S, 6.04. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05-8.00 (m, 2 H), 6.95-6.90 (m, 2 H), 5.73 (dd, 1 H, *J* = 3.8 and 4.5 Hz), 4.34 (dd, 1 H, *J* = 3.8 and 9.5 Hz), 4.10 (dd, 1 H, *J* = 3.0 and 12.4 Hz), 3.96 (dd, 1 H, *J* = 3.2 and 12.4 Hz), 3.86 (s, 3 H), 3.66 (ddd, 1 H, *J* = 3.0, 3.2 and 9.5 Hz), 3.23 (dd, 1 H, *J* = 4.5 and 12.5 Hz), 2.90 (d, 1 H, *J* = 12.5 Hz), 1.11-0.87 (m, 28 H).

1,4-Anhydro-2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (10b). This compound was prepared from **9a** (301 mg, 0.8 mmol) and benzoyl chloride (111 μL, 1.0 mmol) by the procedure described for the preparation of **10a**. Colorless syrup product, 347 mg (90%). MS (FAB) *m/z* 497 (MH^+). HRMS (FAB) calcd for $C_{24}H_{41}O_5SSi_2$ (MH^+): 497.2213, found: 497.2213. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07-8.05 (m, 2 H), 7.58-7.43 (m, 3 H), 5.76 (dd, 1 H, *J* = 3.4 and 4.6 Hz),

4.35 (dd, 1 H, *J* = 3.4 and 9.7 Hz), 4.09 (dd, 1 H, *J* = 2.9 and 12.6 Hz), 3.96 (dd, 1 H, *J* = 2.9 and 12.6 Hz), 3.66 (ddd, 1 H, *J* = 2.9, 2.9 and 9.7 Hz), 3.24 (dd, 1 H, *J* = 4.6 and 12.6 Hz), 2.90 (d, 1 H, *J* = 12.6 Hz), 1.11-0.83 (m, 28 H).

1,4-Anhydro-2-*O*-(*p*-methoxybenzoyl)-3,5-*O*-(di-*tert*-butylsilylene)-4-thio-D-ribitol (10c). This compound was prepared from **9b** (663 mg, 2.28 mmol) and *p*-methoxybenzoyl chloride (364 μL, 3.42 mmol) by the procedure described for the preparation of **10a**. Colorless foam product, 651 mg (67%). MS (FAB) *m/z* 425 (MH^+). HRMS (FAB) calcd for $C_{21}H_{33}O_5SSi$ (MH^+): 425.1818, found: 425.1828. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.04-8.02 (m, 2 H), 6.93-6.89 (m, 2 H), 5.75 (t, 1 H, *J* = 4.0 Hz), 4.36 (dd, 1 H, *J* = 4.6 and 9.7 Hz), 4.19 (dd, 1 H, *J* = 4.0 and 9.7 Hz), 4.03 (dd, 1 H, *J* = 9.7 and 12.1 Hz), 3.86 (s, 3 H), 3.81 (ddd, 1 H, *J* = 4.6, 9.7 and 12.1 Hz), 3.24 (dd, 1 H, *J* = 4.0 and 13.2 Hz), 2.95 (d, 1 H, *J* = 13.2 Hz), 1.03 (s, 9 H), 0.90 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.5, 163.6, 131.9, 122.4, 113.6, 81.7, 74.4, 69.0, 55.5, 44.7, 31.8, 27.4, 27.0, 22.9, 20.0.

1,4-Anhydro-2-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilylene)-4-thio-D-ribitol (10d). This compound was prepared from **9b** (241 mg, 0.80 mmol) and benzoyl chloride (139 μL, 1.20 mmol) by the procedure described for the preparation of **10a**. Colorless foam product, 278 mg (88%). mp 101-102 ºC. MS (FAB) *m/z* 395 (MH^+). HRMS (FAB) calcd for $C_{20}H_{31}O_4SSi$ (MH^+): 395.1712, found: 395.1709. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.06-8.08 (m, 2 H), 7.58-7.42 (m, 3 H), 5.80 (t, 1 H, *J* = 4.0 Hz), 4.37 (dd, 1 H, *J* = 4.0 and 10.3 Hz), 4.21 (dd, 1 H, *J* = 4.0 and 9.7 Hz), 4.04 (dd, 1 H, *J* = 10.3 and 10.9 Hz), 3.82 (ddd, 1 H, *J* = 4.0, 9.7 and 10.9 Hz), 3.26 (dd, 1 H, *J* = 4.0 and 13.2 Hz), 2.96 (d, 1 H, *J* = 13.2 Hz), 1.04 (s, 9 H), 0.89 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 133.2, 130.0, 129.8, 128.3, 81.6, 74.7, 68.9, 44.6, 31.7, 27.3, 26.9, 22.8, 19.9.

6-Chloro-9-[2-*O*-(*p*-methoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)4-thio-β-L-lyxofuranos-4-yl]-9*H*-purine (12a). To a suspension of 6-chrolopurine (62 mg, 0.40 mmol) in dry CH_2Cl_2 (2 mL) were added Et_3N (56 μL, 0.40 mmol) and TMSOTf (145 μL, 0.80 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **10a** (107 mg, 0.20 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (129 mg, 0.30 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (56 μL, 0.40 mmol) was added to the reaction mixture. After the mixture had been stirred for 24 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with

hexane-AcOEt (5 : 1), to give **12a** (76 mg, 54%) as a yellow syrup. MS (FAB) *m/z* 679 (MH^+). HRMS (FAB) calcd for $C_{30}H_{44}ClN_4O_6SSi_2$ (MH^+): 679.2209, found: 679.2183. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.73 (s, 1 H), 8.66 (s, 1 H), 8.02-7.99 (m, 2 H), 6.95-6.92 (m, 2 H), 6.25 (d, 1 H, *J* = 2.4 Hz), 5.38 (ddd, 1 H, *J* = 2.6, 6.8 and 8.3 Hz), 4.40 (m, 2 H), 3.89 (s, 3 H), 3.52 (dd, 1 H, *J* = 8.8 and 10.7 Hz), 3.21 (dd, 1 H, *J* = 6.8 and 8.8 Hz), 1.16-0.78 (m, 28 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.9, 163.9, 152.2, 144.3, 132.5, 131.9, 121.3, 113.9, 113.7, 80.3, 75.5, 71.6, 64.2, 55.5, 30.5, 17.4, 17.3, 17.2, 17.1, 17.0, 16.9, 16.8, 13.3, 13.0, 12.8, 12.7.

6-Chloro-9-[2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)4-thio-β-D-ribofuranos-1-yl]-9*H*-purine (11b) and 6-chloro-9-[2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane- 1,3-diyl)-4-thio-β-L-lyxofuranos-4-yl]-9*H*-purine (12b). To a suspension of 6-chrolopurine (90 mg, 0.58 mmol) in dry CH_2Cl_2 (3 mL) were added Et_3N (82 μL, 0.58 mmol) and TMSOTf (265 μL, 1.46 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **10b** (70 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (92 mg, 0.22 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (82 μL, 0.58 mmol) was added to the reaction mixture. After the mixture had been stirred for 96 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by MPLC (hexane : AcOEt = 1 : 1) to give **11b** (16 mg, 16%) as a yellow foam, *N*-7 isomer of **11b** (11 mg, 12%) as a yellow foam and **12b** (5 mg, 5%) as a yellow foam. **11b**: MS (FAB) *m/z* 649 (MH^+). HRMS (ESI) calcd for $C_{29}H_{41}ClN_4O_5SSi_2Na$ (MNa^+): 671.1922, found: 671.1913. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1 H), 8.62 (s, 1 H), 8.10-7.47 (m, 5 H), 6.09 (s, 1 H), 5.86 (d, 1 H, J = 3.4 Hz), 4.93 (dd, 1 H, J = 3.4 and 9.7 Hz), 4.21 (dd, 1 H, J = 3.4 and 12.6 Hz), 4.12 (d, 1 H, J = 12.6 Hz), 3.88 (d, 1 H, J = 9.7 Hz), 1.24-0.87 (m, 28 H). *N*-7 isomer of **11b**: MS (FAB) *m/z*: 649 (MH^+). HRMS (ESI) calcd for $C_{29}H_{41}ClN_4O_5SSi_2Na$ (MNa^+): 671.2123, found: 671.2390. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.17 (s, 1 H), 8.92 (s, 1 H), 8.10-7.48 (m, 5 H), 6.46 (s, 1 H), 5.88 (d, 1 H, *J* = 3.4 Hz), 4.64 (dd, 1 H, *J* = 3.4 and 9.7 Hz), 4.20 (dd, 1 H, *J* = 2.9 and 12.6 Hz), 4.14 (d, 1 H, *J* = 12.6 Hz), 3.85 (dd, 1 H, *J* = 1.7 and 9.7 Hz), 1.24-0.81 (m, 28 H). **12b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1 H), 8.63 (s, 1 H), 8.10-7.48 (m, 5 H), 6.29 (d, 1 H, *J* = 2.3 Hz), 5.39 (m, 1 H), 4.43 (d, 1 H, *J* = 11.7 Hz), 4.31 (d, 1 H, *J* = 11.7 Hz), 3.52 (dd, 1 H, *J* = 8.6 and 10.9 Hz), 3.23 (dd, 1 H, *J* = 6.9 and 8.9 Hz), 1.20-0.80 (m, 28 H).

6-Chloro-9-[2-*O*-(*p*-methoxybenzoyl)-3,5-*O*-(di-*tert*-butylsilylene)-4-thio-β-D-ribofuranos-1-yl]-9*H*-purine (11c). To a suspension of 6-chrolopurine (90 mg, 0.58 mmol) in dry CH_2Cl_2 (3 mL) were added

Et_3N (85 μL, 0.60 mmol) and TMSOTf (272 μL, 1.50 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **10c** (64 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (96 mg, 0.23 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (85 μL, 0.60 mmol) was added to the reaction mixture. After the mixture had been stirred for 96 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was by MPLC (hexane : AcOEt = 1 : 1) to give **11c** (9 mg, 11%) as a yellow foam and *N*-7 isomer of **11c** (15 mg, 17%) as a yellow foam. **11c**: MS (FAB) *m/z* 577 (MH^+). HRMS (FAB) calcd for $C_{26}H_{35}ClN_4O_5SSi$ (MH^+): 557.1708, found: 557.1705. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.77 (s, 1 H), 8.37 (s, 1 H), 8.06 (d, 2 H, *J* = 9.2 Hz), 6.95 (d, 2 H, *J* = 9.2 Hz), 6.10 (s, 1 H), 5.83 (d, 1 H, *J* = 4.0 Hz), 5.16 (dd, 1 H, *J* = 4.0 and 10.3 Hz), 4.49 (dd, 1 H, *J* = 4.6 and 10.3 Hz), 4.31 (dd, 1 H, *J* = 10.3 and 10.9 Hz), 4.01 (ddd, 1 H, *J* = 4.6, 10.3 and 10.9 Hz), 3.89 (s, 3 H), 1.08 (s, 9 H), 0.93 (s, 9 H). *N*-7 isomer of **11c**: MS (FAB) *m/z* 577 (MH^+). HRMS (FAB) calcd for $C_{26}H_{34}ClN_4O_5SSi$ (MH^+): 557.1708, found: 557.1705. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.92 (s, 1 H), 8.89 (s, 1 H), 8.06 (d, 2 H, *J* = 8.6 Hz), 6.96 (d, 2 H, *J* = 8.6 Hz), 6.53 (s, 1 H), 5.95 (d, 1 H, *J* = 3.4 Hz), 4.52 (dd, 1 H, *J* = 4.6 and 10.3 Hz), 4.47 (dd, 1 H, *J* = 3.4 and 10.3 Hz), 4.24 (t, 1 H, *J* = 10.9 Hz), 3.98 (ddd, 1 H, *J* = 4.6, 10.3 and 10.9 Hz), 3.89 (s, 3 H), 1.01 (s, 9 H), 0.81 (s, 9 H).

6-Chloro-9-[2-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilylene)-4-thio-β-D-ribofuranos-1-yl]-9*H*-purine (11d). To a suspension of 6-chrolopurine (90 mg, 0.58 mmol) in dry CH_2Cl_2 (3 mL) were added Et_3N (85 μL, 0.60 mmol) and TMSOTf (272 μL, 1.50 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **10d** (50 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (84 mg, 0.20 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (85 μL, 0.60 mmol) was added to the reaction mixture. After the mixture had been stirred for 96 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by MPLC (hexane : AcOEt = 1 : 1) to give **11d** (16 mg, 22%) as a yellow foam and *N*-7 isomer of **11d** (12 mg, 17%) as a yellow foam. **11d**: MS (FAB) *m/z* 547 (MH^+). HRMS (FAB) calcd for $C_{25}H_{32}ClN_4O_4SSi$ (MH^+): 547.1602, found: 547.1603. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.77 (s, 1 H), 8.37 (s, 1 H), 8.12-8.10 (m, 2 H), 7.64-7.47 (m, 3 H), 6.10 (s, 1 H), 5.87 (d, 1 H, *J* = 3.7 Hz), 5.16 (dd, 1 H, *J* = 3.7 and 10.3 Hz), 4.49 (dd, 1 H, *J* = 4.6 and 10.3 Hz), 4.30 (dd, 1 H, *J* = 10.3 and 10.9 Hz), 4.07 (ddd, 1 H, *J* = 4.6, 10.3 and 10.9 Hz), 1.08 (s, 9 H), 0.91 (s, 9 H). *N*-7 isomer of

11d: MS (FAB) *m/z* 547 (MH^+). HRMS (FAB) calcd for $C_{25}H_{32}ClN_4O_4SSi$ (MH^+): 547.1602, found: 547.1596. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.92 (s, 1 H), 8.90 (s, 1 H), 8.11-7.48 (m, 5 H), 6.55 (s, 1 H), 5.98 (d, 1 H, *J* = 4.0 Hz), 4.52 (dd, 1 H, *J* = 4.0 and 10.9 Hz), 4.48 (dd, 1 H, *J* = 4.0 and 10.3 Hz), 4.25 (t, 1 H, *J* = 10.9 Hz), 3.99 (ddd, 1 H, *J* = 4.6, 10.3 and 10.9 Hz), 1.01 (s, 9 H), 0.79 (s, 9 H).

1,4-Anhydro-5-*O*-benzoyl-2,3-*O*-isopropyridene-4-thio-D-ribitol (13a). To a solution of **7** (1.1 g, 5.5 mmol) in dry pyridine (40 mL) was added benzoyl chloride (922 μL, 8.3 mmol) at 0 ºC under a nitrogen atmosphere, and the mixture was stirred at rt for 12 h. The reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (1 : 1), to give **13a** (1.6 g, 99%) as a colorless solid. mp 35-37 ºC. MS (FAB) *m/z* 295 (MH^+). HRMS (FAB) calcd for $C_{15}H_{19}O_4S$ (MH^+): 295.1004, found: 295.1000. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06-8.02 (m, 2 H), 7.61-7.43 (m, 3 H), 4.98 (ddd, 1 H, *J* = 1.3, 4.8 and 5.7 Hz), 4.80 (dd, 1 H, *J* = 1.1 and 5.7 Hz), 4.42 (dd, 1 H, *J* = 6.1 and 11.6 Hz), 4.32 (dd, 1 H, *J* = 8.1 and 11.6 Hz), 3.64 (ddd, 1 H, *J* = 1.1, 1.6 and 8.1 Hz), 3.18 (dd, 1 H, *J* = 4.8 and 13.0 Hz), 2.96 (dd, 1 H, *J* = 1.3 and 13.0 Hz), 1.54 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.2, 133.2, 129.7, 129.6, 128.4, 111.3, 85.7, 83.5, 65.2, 52.5, 37.7, 26.5, 24.7.

1,4-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropyridene-4-thio-D-ribitol (13b). To a solution of **7** (500 mg, 2.6 mmol) and imidazol (481 mg, 6.5 mmol) in dry DMF (20 mL) was added *tert*-butyldimethylsilyl chloride (579 mg, 3.9 mmol) at 0 ºC under a nitrogen atmosphere, and the mixture was stirred at rt for 4 h. The reaction was quenched by addition of ice, and the mixture was partitioned between Et_2O and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on silica gel column, eluted with hexane-AcOEt (1 : 1), to give **13b** (771 mg, 97%) as a colorless syrup. MS (FAB) *m/z* 305 (MH^+). HRMS (FAB) calcd for $C_{14}H_{29}O_3SSi$ (MH^+): 305.1607, found: 305.1627. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.83 (ddd, 1 H, *J* = 1.3, 4.8 and 5.8 Hz), 4.73 (dd, 1 H, *J* = 0.9 and 5.8 Hz), 3.73 (dd, 1 H, *J* = 4.6 and 10.5 Hz), 3.53 (dd, 1 H, *J* = 6.4 and 10.5 Hz), 3.27 (ddd, 1 H, *J* = 0.9, 4.6 and 6.4 Hz), 3.10 (dd, 1 H, *J* = 4.8 and 12.5 Hz), 2.78 (dd, 1 H, *J* = 1.3 and 12.5 Hz), 1.46 (s, 3 H), 1.26 (s, 3 H), 0.83 (s, 9 H), 0.00 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.7, 86.2, 84.0, 65.8, 55.6, 38.5, 26.6, 25.9, 24.6, 18.3, -5.4.

6-Chloro-9-(5-*O*-benzoyl-2,3-*O*-isopropyridene-4-thio-β-D-ribofuranos-1-yl)-9*H*-purine (14a) and 6-Chloro-9-(5-*O*-benzoyl-2,3-*O*-isopropyridene-4-thio-β-L-lyxofuranos-4-yl)-9*H*-purine (15a). To a suspension of 6-chrolopurine (465 mg, 3.0 mmol) in dry CH_2Cl_2 (15 mL) were added Et_3N (423 μL, 3.0

mmol) and TMSOTf (1.36 mL, 7.5 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **13a** (222 mg, 0.75 mmol) in dry CH_2Cl_2 (10 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (480 mg, 1.2 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (636 μL, 4.5 mmol) was added to the reaction mixture. After the mixture had been stirred for 48 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by MPLC (hexane : AcOEt = 1 : 1) to give **14a** (47 mg, 14%) as a yellow foam, *N*-7 isomer of **14a** (27 mg, 8%) as a yellow foam and **15a** (148 mg, 44 %) as a yellow foam. **14a**: MS (FAB) *m/z* 447 (MH^+). HRMS (FAB) calcd for $C_{20}H_{20}ClN_4O_4S$ (MH^+): 447.0894, found: 447.0884. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.80 (s, 1 H), 8.41 (s, 1 H), 7.90-7.34 (m, 5 H), 6.10 (d, 1 H, *J* = 1.7 Hz), 5.49 (dd, 1 H, *J* = 1.7 and 5.5 Hz), 5.16 (dd, 1 H, *J* = 1.9 and 5.5 Hz), 4.75 (dd, 1 H, *J* = 6.8 and 11.6 Hz), 4.53 (dd, 1 H, *J* = 6.2 and 11.6 Hz), 4.10 (ddd, 1 H, *J* = 1.9, 6.2 and 6.8 Hz), 1.66 (s, 3 H), 1.40 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.0, 152.2, 151.6, 151.3, 144.2, 133.6, 132.8, 129.6, 129.2, 128.5, 113.1, 89.4, 85.8, 68.8, 65.6, 54.1, 27.4, 25.3. *N*-7 isomer of **14a**: MS (FAB) *m/z* 447 (MH^+). HRMS (FAB) calcd for $C_{20}H_{20}ClN_4O_4S$ (MH^+): 447.0894, found: 447.0891. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.89 (s, 1 H), 8.84 (s, 1 H), 8.00-7.42 (m, 5 H), 6.59 (d, 1 H, *J* = 2.2 Hz), 5.13 (dd, 1 H, *J* = 2.2 and 5.7 Hz), 4.99 (dd, 1 H, *J* = 2.9 and 5.7 Hz), 4.61 (dd, 1 H, *J* = 7.4 and 11.5 Hz), 4.51 (dd, 1 H, *J* = 6.9 and 11.5 Hz), 4.07 (ddd, 1 H, *J* = 2.9, 6.9 and 7.4 Hz), 1.64 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 162.6, 153.0, 147.1, 143.4, 133.8, 129.8, 129.1, 128.7, 122.6, 113.5, 90.2, 84.9, 68.8, 65.1, 53.4, 27.3, 25.2. **15a**: MS (FAB) *m/z* 447 (MH^+). HRMS (FAB) calcd for $C_{20}H_{20}ClN_4O_4S$ (MH^+): 447.0894, found: 447.0889. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.89 (s, 1 H), 8.78 (s, 1 H), 7.78-7.35 (m, 5 H), 6.04 (d, 1 H, *J* = 5.3 Hz), 5.49 (d, 1 H, *J* = 12.1 Hz), 5.02 (dd, 1 H, *J* = 3.9 and 5.3 Hz), 4.93 (d, 1 H, *J* = 12.1 Hz), 3.24 (d, 1 H, *J* = 13.5 Hz), 3.11 (dd, 1 H, *J* = 3.9 and 13.5 Hz), 1.66 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 151.8, 151.6, 145.9, 134.0, 133.5, 129.6, 128.8, 128.6, 112.5, 86.4, 84.6, 83.7, 66.3, 37.9, 26.1, 24.9.

6-Chloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropyridene-4-thio-β-D-ribofuranos-1-yl]-9*H*-purine (14b). To a suspension of 6-chrolopurine (1.53 g, 9.9 mmol) in dry CH_2Cl_2 (70 mL) were added Et_3N (1.39 mL, 9.9 mmol) and TMSOTf (4.48 mL, 24.7 mmol) at 0 ºC under a nitrogen atmosphere. After the mixture had been stirred for 1 h at rt, a clear solution was obtained. A solution of **13b** (1.13 g, 3.7 mmol) in dry CH_2Cl_2 (30 mL) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (2.34 g, 5.6 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (2.09 mL, 14.8 mmol) was added to the reaction mixture. After the mixture had been stirred for 72 h, the reaction was quenched by addition of ice, and the mixture was partitioned between AcOEt and water. The

organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by MPLC (hexane : AcOEt = 1 : 1) to give **14b** (474 mg, 28%) as a yellow foam and *N*-7 isomer of **14b** (166 mg, 10%) as a yellow foam. **14b**: MS (FAB) *m/z* 457 (MH^+). HRMS (FAB) calcd for $C_{19}H_{30}ClN_4O_3SSi$ (MH^+): 457.1496, found: 457.1490. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.79 (s, 1 H), 8.63 (s, 1 H), 6.11 (d, 1 H, *J* = 2.2 Hz), 5.15 (dd, 1 H, *J* = 2.2 and 5.3 Hz), 4.91 (dd, 1 H, *J* = 1.8 and 5.3 Hz), 3.91 (d, 2 H, *J* = 5.1 Hz), 3.83 (dd, 1 H, *J* = 1.8 and 5.1 Hz), 1.65 (s, 3 H), 1.31 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.00 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.2, 151.6, 151.3, 144.7, 132.6, 112.6, 90.2, 85.6, 68.5, 65.3, 57.0, 27.5, 26.0, 25.2, -5.2. *N*-7 isomer of **14b**: MS (FAB) *m/z* 457 (MH^+). HRMS (FAB) calcd for $C_{19}H_{30}ClN_4O_3SSi$ (MH^+): 457.1496, found: 457.1494. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.10 (s, 1 H), 8.89 (s, 1 H), 6.58 (d, 1 H, *J* = 2.2 Hz), 4.92 (dd, 1 H, *J* = 2.2 and 5.1 Hz), 4.89 (dd, 1 H, *J* = 2.0 and 5.1 Hz), 3.94-3.72 (m, 3 H), 1.64 (s, 3 H), 1.35 (s, 3 H), 0.92 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.7, 152.7, 148.2, 143.1, 121.5, 112.6, 91.2, 85.2, 69.3, 65.1, 56.5, 27.5, 26.1, 25.3, 18.6, -5.1.

6-Chloro-9-(4-thio-β-D-ribofuranos-1-yl)-9*H*-purine (16). To a solution of **14b** (55 mg, 0.12 mmol) in THF (5 mL) was added trifluoroacetic acid (4.5 mL) and water (0.5 mL) at rt, and the mixture was stirred for 18 h. The solvent was removed *in vacuo*, and the residue was purified on silica gel column, eluted with $CHCl_3$-MeOH (3 : 1), to give **16** (24 mg, 66%) as a colorless foam. MS (FAB) *m/z* 303 (MH^+). HRMS (FAB) calcd for $C_{10}H_{12}ClN_4O_3S$ (MH^+): 303.0319, found: 303.0320. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.01 (s, 1 H), 8.78 (s, 1 H), 5.94 (d, 1 H, *J* = 6.3 Hz), 5.62 (d, 1 H, *J* = 6.3 Hz), 5.36 (d, 1 H, *J* = 4.6 Hz), 5.18 (dd, 1 H, *J* = 5.2 and 5.7 Hz), 4.67 (m, 1 H), 4.19 (m, 1 H), 3.79 (m, 1 H), 3.62 (m, 1 H), 3.31 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 152.5, 152.2, 149.7, 147.1, 131.9, 77.6, 73.6, 63.6, 62.6, 54.1.

4´-Thioadenosine (2). A solution of **16** (24 mg, 0.08 mmol) in methanolic ammonia (saturated at 0 ºC, 10 mL) was heated for 24 h at 100 ºC in a steel container. The solvent was removed *in vacuo*, and the residue was purified on silica gel column, eluted with $CHCl_3$-MeOH (3 : 1), to give **2** (20 mg, 90%) as a colorless solid, mp 253-256 ºC. MS (FAB) m/z 284 (MH^+). HRMS (FAB) calcd for $C_{10}H_{14}N_5O_3S$ (MH^+): 284.0818, found: 284.0813. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.46 (s, 1 H), 8.16 (s, 1 H), 7.28 (br s, 2 H), 5.87 (d, 1 H, *J* = 6.6 Hz), 5.56 (d, 1 H, *J* = 6.3 Hz), 5.34 (d, 1 H, *J* = 4.6 Hz), 5.23 (dd, 1 H, *J* = 5.2 and 5.7 Hz), 4.68 (ddd, 1 H, *J* = 3.4, 6.3 and 6.6 Hz), 4.22 (dt, 1 H, *J* = 3.4 and 4.6 Hz), 3.81 (ddd, 1 H, *J* = 5.2, 6.3 and 11.5 Hz), 3.65 (dd, 1 H, *J* = 5.7 and 11.5 Hz), 3.35 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 156.6, 153.0, 150.3, 140.4, 119.6, 77.5, 73.8, 63.8, 61.8, 53.8.

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