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Synthesis and Biological Activities of 2′-Deoxy-2′-fluoro-4′-thioarabinofuranosylpyrimidine and -Purine Nucleosides

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Abstract—As part of our ongoing investigation of the synthesis of biologically interesting 2′-modified-4′-thionucleosides, we synthesized 2′-deoxy-2′-fluoro-4′-thioarabinofuranosylpyrimidine and -purine nucleosides, and evaluated their antiviral and antitumor activities. In the pyrimidine series, β-anomers of 5-ethyluracil, 5-iodouracil, 5-chloroethyluracil, and 5-iodocytosine derivatives showed potent and selective anti-HSV-1 and HSV-2 activities in vitro. In the purine series, guanine and 2,6-diaminopurine derivatives showed prominent antiviral activities with slight cytotoxicity. On the other hand, the 5-fluorocytosine derivative (5F-4′-thioFAC) showed potent antitumor activity against both leukemia and solid tumor. Its antitumor spectrum against 14 human solid tumor and one leukemic cell lines was compared with that of 4′-thioFAC. The results showed that 5F-4′-thioFAC had an antitumor spectrum similar to that of 4′-thioFAC. However, 5F-4′-thioFAC was about 10 times less active than 4′-thioFAC.

Introduction

Ever since Secrist[1] and Walker[2] independently reported the antiviral activities of 2′-deoxy-4′-thionucleosides **1**, 4′-thionucleosides have been recognized as a novel and important class of antiviral agents. In addition, the potent antitumor activities of 4′-thiothymidine[1] and 2-chloro-2′-deoxy-4′-thioadenosine[3] were reported by Secrist, and the cytotoxicity of 2′-deoxy-4′-thionucleosides was reported by Uenishi.[4] These reports suggest that 4′-thionucleosides can also be considered promising antitumor candidates. Akin to the usual '4′-oxy' nucleoside antimetabolites, these 4′-thionucleoside analogues should be phosphorylated by kinases coded by virus or host cells, and the resulting triphosphate derivatives should inhibit replicating enzymes. In this metabolic activation process, the controlling step is the first phosphorylation of free nucleosides, at which point they are converted to the corresponding monophosphate derivatives. The 2′-modified nucleoside analogues, such as arabino[5] and 2′-fluoroarabino nucleosides,[6,7] which comprise an important category of antiviral agents, can also pass this barrier. Thus, 2′-modified 4′-thionucleosides seem to be promising as potential antiviral and antitumor agents. Previously, we synthesized 4′-thioarabinonucleosides **2**[8] and 2′-deoxy-2′-methylene-4′-thionucleosides **3**,[9] and found that both **2** and **3** had potent antiviral activities. The 5-substituted uracil derivatives of both **2** and **3** are active against herpes simplex virus (HSV) type 1.[8,9] Purine derivatives of **3** have shown broad antiviral activities against HSV-1, HSV-2, and human cytomegalovirus (HCMV).[8] However, the latter was relatively cytotoxic.[8] More recently, we developed a novel synthetic route to 2-fluoro-4-thioarabinose, which was successfully converted to 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine (4′-thioFAC, **4**).[10] 4′-Thio FAC **4** was highly effective against various human solid tumor cell lines in vitro, and has shown prominent antineoplastic activities in vivo.[10,11] Based on these results, together with the fact that 2′-deoxy-2′-fluoroarabino nucleosides **5** have potent antiviral activity,[6,7] as mentioned above, 2′-deoxy-2′-fluoro-4′-thioarabino nucleosides **6** should be potential antiviral and antineoplastic agents. In this report, we describe the synthesis of various pyrimidine and purine analogues of 2′-deoxy-2′-fluoro-4′-thioarabino nucleosides **6** and their biological activities, including their antiviral[12] and antineoplastic activities. Some structure–activity relationships of these compounds are also discussed.

Results and Discussion

Chemistry

At the beginning of this project, we synthesized various 5-substituted pyrimidine derivatives, since such analogues

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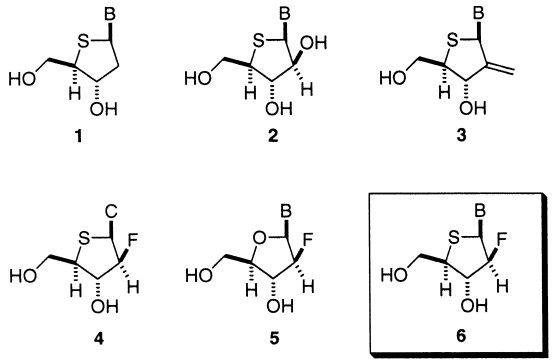
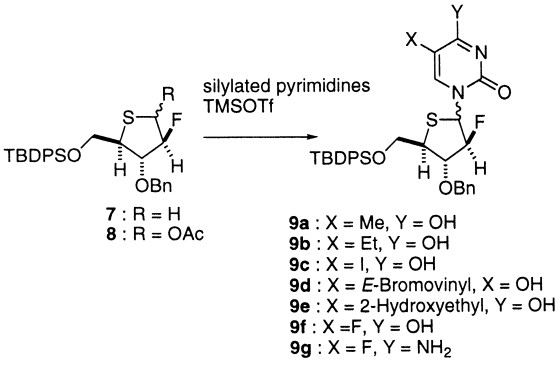


Chart 1.

often possess potent anti-HSV-1 activities.[5,8,9] As we reported previously, 1,4-anhydro-2-deoxy-2-fluoro-4-thio-D-arabitol **7** was obtained from D-glucose in 12 steps.[10] The glycosylation reaction of various pyrimidine bases with 1-acetate **8**, which was prepared by the Pummerer rearrangement of the corresponding sulfoxide of **7**,[10] gave 2-fluoro-4′-thionucleosides **9** (Scheme 1). The results are summarized in Table 1. The chemical yields of **9** from **8** were fair, and the ratio of the α- and β-anomers was roughly 2:1. These results are consistent with that of the previous synthesis of 4′-thioFAC **4**.[10] In the case of 5-fluorocytidine derivative **9g**, the glycosylation reaction was performed with 5-fluorocytosine itself, not the corresponding N^4-acetyl derivative. In our previous synthesis of 4′-thioDMDC and its analogues **3**, we synthesized 5-fluoro-4′-thioDMDC, in which the glycosylation reaction of silylated N^4-acetyl-5-fluorocytosine gave none of the desired product.[13] Therefore, it was synthesized by the direct coupling of 5-fluorocytosine and the 4-thiosugar portion. For this reason, we chose the direct coupling of 5-fluorocytosine with **8** for the synthesis of **9g**. A thymidine derivative **9a** was debenzylated by BCl_3, followed by desilylation, to give an anomeric mixture of free nucleosides, which were separated by HPLC to give α-**6a** and β-**6a**. In a similar manner, deprotection of 5-fluorocytidine derivative **9g** gave α-**6g** and β-**6g**. (Scheme 2).



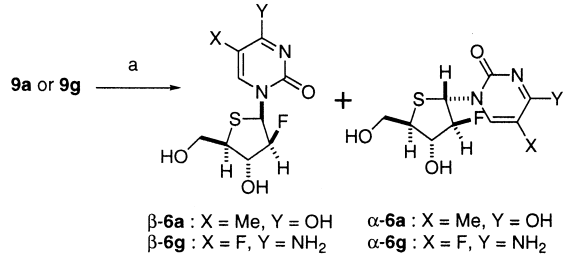
Scheme 1.

Table 1. Summary of the glycosylation reaction of various pyrimidines with **8**

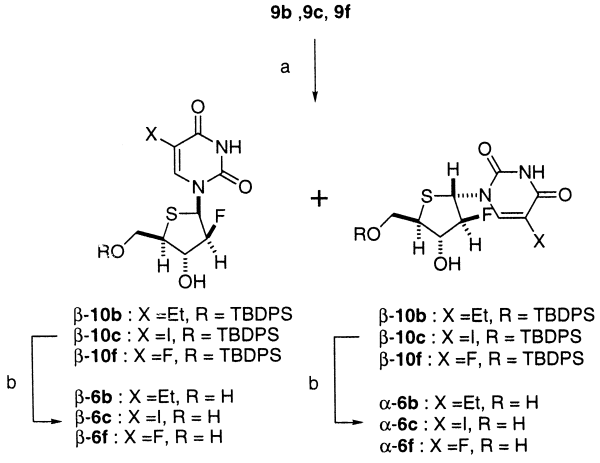
Run	X	Y	Products no.	Yields[a] (%)	α/β ratio[b]
1	Me	OH	**9a**	79	2.4
2	Et	OH	**9b**	68	2.2
3	I	OH	**9c**	78	1.9
4	*E*-Bromovinyl	OH	**9d**	75	2.2
5	2-Hydroxyethyl	OH	**9e**	71	1.9
6	F	OH	**9f**	79	2.1
7	F	NH_2	**9g**	70	2.4

[a]Isolated yields.
[b]The ratios of the α- and β-anomers were determined by ^1H NMR.

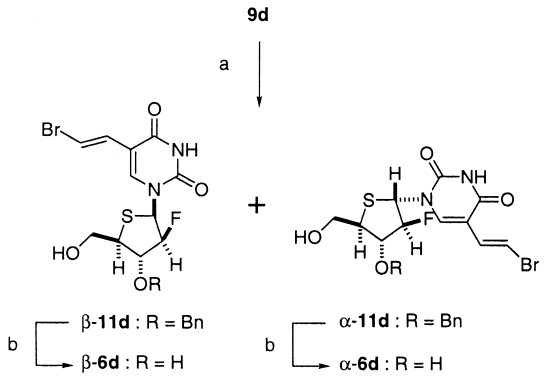
As shown in Scheme 3, debenzylation of 5-ethyl **9b**, 5-iodo **9c**, and 5-fluoro **9f** derivatives gave compounds **10b**, **10c** and **10f**, the α- and β-anomers of which were easily separated by silica gel column chromatography. The separated α- and β-anomers of **10b**, **10c** and **10f** were desilylated by treatment with NH_4F to give α- and β-anomers of **6b**, **6c** and **6f**, respectively. (Scheme 3) On the other hand, the 5-bromovinyl derivative **9d** was first desilylated to give α- and β-**11d**, which were separable by silica gel column chromatography. α- and β-**11d** were debenzylated to give α- and β-**6d**, respectively. (Scheme 4) The 5-hydroxyethyl derivative **9e**, which was an intermediate for the preparation of a 5-chloroethyl derivative **6e**, was debenzylated to give diol **12e**. The relatively polar derivative **12e** was silylated once by a *tert*-butyldimethylsilyl group at the primary hydroxyl group. After separation by the silica gel column chromatography, the resulting α- and β-**13e** were treated



Scheme 2. Conditions: for **6a**, (a) (i) TBAF, THF; (ii) BCl_3, CH_2Cl_2, −78 °C; (iii) HPLC separation. For **6g**, (a) (i) BBr_3, CH_2Cl_2, −78 °C; (ii) $NH_4F{\cdot}HF$, MeOH; (iii) HPLC separation.



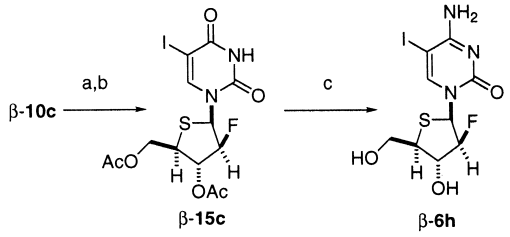
Scheme 3. Conditions: (a) (i) BBr_3, CH_2Cl_2, −78 °C; (ii) silica gel column; (b) $NH_4F{\cdot}HF$, MeOH.



Scheme 4. Conditions: (a) (i) BCl_3, CH_2Cl_2, −78 °C; (ii) silica gel column; (b) TBAF, THF.

with NH_4F to give α- and β-**14e**, respectively. The β-anomer of **14e** was chlorinated at the primary hydroxyl group of the base moiety by treatment with CCl_4, PPh_3, and pyridine[9] to give the 5-chloroethyl derivative β-**6e** in a good yield. (Scheme 5).

As a final target of the pyrimidine derivatives, we selected a 5-iodocytidine derivative **6h**, the 4′-oxy counterpart, of which, FIAC, is a well-known antiviral agent.[7] The β-anomer of 5-iodouracil derivative **10c** was deprotected and re-protected by an acetyl group to give diacetate β-**15c**. Treatment of diacetate β-**15c** with triisopropylbenzenesulfonyl chloride (TPSCl), followed by ammonolysis of the resulting 4-TPS and acetyl groups, gave the 5-iodocytidine derivative β-**6h**. (Scheme 6).

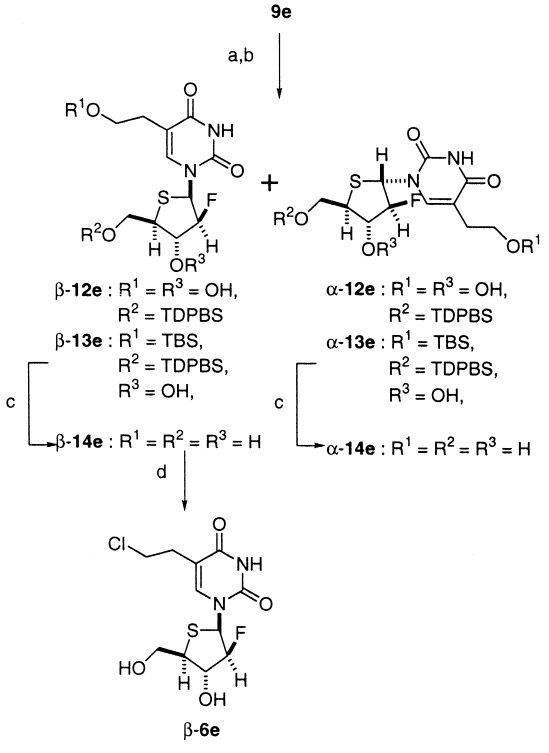


Scheme 6. Conditions: (a) TBAF, THF; (b) Ac_2O, DMAP; (c) TPSCl, DMAP, CH_3CN, then NH_4OH.

Purine analogues of 2′-deoxy-2′-fluoro-4′-thioarabino nucleosides are interesting potential antitumor and antiviral agents. 4′-ThioaraG has been shown to have potent antiherpesvirus activities and is highly cytotoxic.[8] Among the usual 4′-oxy derivatives, 2-chloro-2′-deoxyadenosine is known to have potent cytotoxicity,[14] and 2-fluoroadenine arabinoside monophosphate, fludarabine phosphate, is an antileukemic drug.[14,15] The 4′-thio analogue of the former compound has already been reported,[3] as mentioned above. Therefore, adding to the usual 2′-deoxy-2′-fluoro-4′-thioarabino nucleosides of adenine, guanine, and 2,6-diaminopurine (DAP), we synthesized 2-chloro and 2-fluoroadenine derivatives.

To prepare the adenine derivative, we first investigated the glycosylation reaction of adenine, N^6-benzoyladenine, and 6-chloropurine with 1-acetate **8**. The coupling reaction of persilylated 6-chloropurine with **8** in the presence of stannic chloride as a Lewis acid gave N^9-glycosylated product in 27% yield, accompanied by N^7-glycosylated product in 58% yield. The ratio of the α- and β-anomers was about 2:1 (data not shown). The same reaction using intact N^6-benzoyladenine resulted in the formation of an inseparable mixture of the desired products and structurally unknown compounds. The reaction of intact adenine with **8** in the presence of excess TMS triflate gave the desired N^9-glycosylated product **16i** in 23% yield, along with the N^7-glycosylated product in 38% yield. In this case, the ratio of the α- and β-anomers (α:β = 0.7:1) was slightly better than that in the reaction of 6-chloropurine. Similarly, the same reaction of 2,6-diaminopurine with **8** gave N^9-glycosylated product **16j** in 39% yield (α:β = 1:1). None of the N^7-glycosylated product was observed in the reaction mixture of 2,6-diaminopurine with **8**. In the previous synthesis of 4′-thioarabinonucleosides, the glycosylation reaction of purine bases, such as adenine and 2,6-diaminopurine, gave N^9-glycosylated products selectively.[8] Similarly, the coupling reaction of 2,6-diamino- and 2,6-dichloropurine (vide infra) with **8** resulted in the selective formation of N^9-adducts, while the reaction of 6-monosubstituted purine (adenine and 6-chloropurine) gave a mixture of N^9/N^7-adducts. The reason why the reaction of adenine and 6-chloropurine with **8** produced predominantly N^7-adducts is not yet clear.

Deblocking of the protecting group of **16i** gave a mixture of α- and β-anomers, which was separated by ODS column chromatography to give adenine derivative α- and β-**6i**. The α- and β-anomers of diaminopurine derivative **6j** were also obtained by the same procedure.



Scheme 5. Conditions: (a) BBr_3, CH_2Cl_2, −78 °C; (b) (i) TBDMSCl, pyridine; (ii) silica gel column; (c) NH_4F·HF, MeOH; (d) PPh_3, CCl_4, pyridine, DMF.

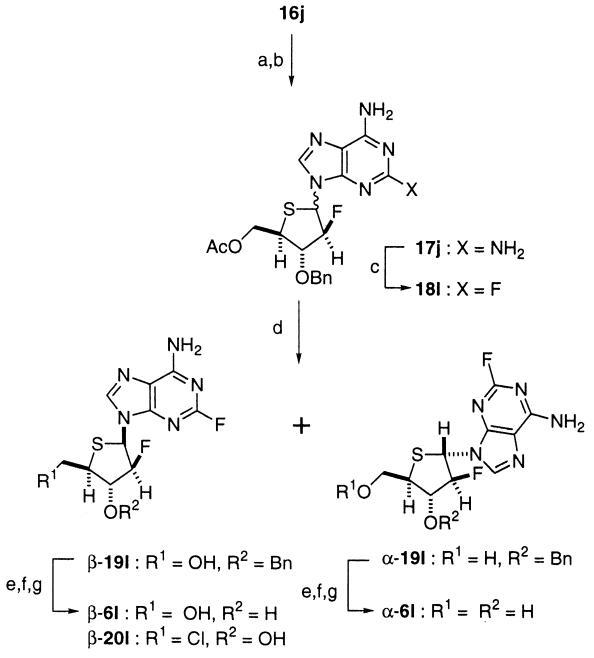
Treatment of the mixture of the α- and β-anomers of **6i** with adenosine deaminase led to the selective hydrolysis of the 6-amino group of β-**6i**. Thus, the resulting β-anomer of guanine derivative **6k** and unreacted α-diamino derivative **6j** could be separated by simple ODS column chromatography (Scheme 7).

As in the previous report,[16] the 2-fluoroadenine derivative was synthesized from the diaminopurine derivative **16j**. The anomeric mixture of diamino derivative **16j** was desilylated and re-protected by an acetyl group to give **17j**, which was treated with *tert*-butyl nitrite and 60% HF-pyridine to give 2-fluoro derivative **18l** in 58% yield, along with a 2,6-difluoro derivative (20% yield). Deacetylation of **18l** gave a mixture of α- and β-**19l**, which could be separated by silica gel column chromatography. The resulting α-**19l** was transiently protected by a TMS group to facilitate increased solubility in an organic solvent, and then debenzylated by BCl_3, followed by treatment with NH_4OH/MeOH, to give α-**6l** in 76% yield. On the other hand, the same reaction with β-**19l** led to the desired β-**6l** (56%) and a 5′-chlorinated product β-**20l** (36%) (Scheme 8).

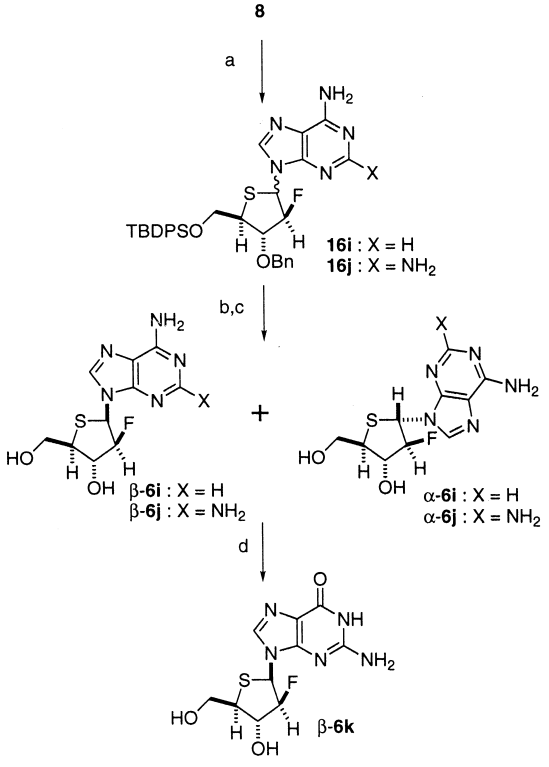
Finally, we synthesized a 2-chloroadenine derivative. The glycosylation reaction of intact 2,6-dichloropurine with **8** in the presence of TMS triflate selectively gave a N^9-adduct **21m** in 69% yield (α:β = 1.5:1). The same reaction with stannic chloride, instead of TMS triflate, resulted in a decreased yield of **21m** (16%, α:β = 1.4:1, data not shown). After debenzylation, the α- and β-anomers of **22m** separated by silica gel column chromatography were treated with NH_3/EtOH, followed by desilylation, to give the α- and β-anomers of 2-chloroadenine derivatives **6m**, respectively (Scheme 9).

Biological activities

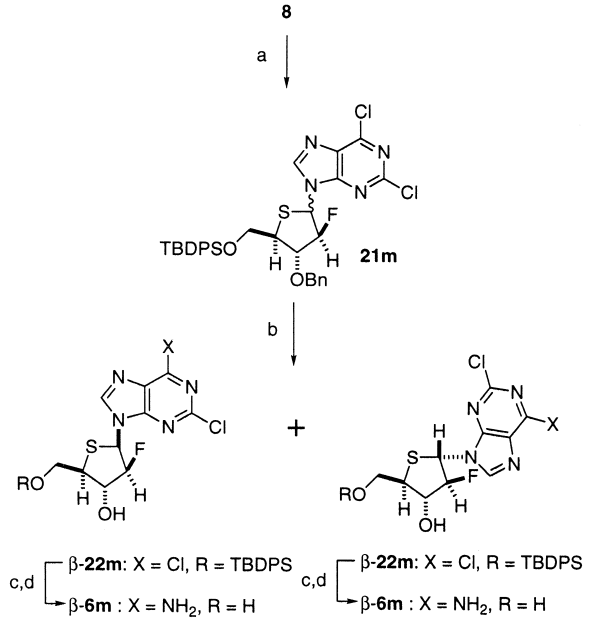
The biological activities of 2′-deoxy-2′-fluoro-4′-thio-arabino nucleosides were evaluated as follows: as a preliminary evaluation of antiviral activity, anti-HSV-1



Scheme 8. Conditions: (a) NH_4F·HF, DMF; (b) Ac_2O, Et_3N, CH_3CN; (c) *t*-butyl nitrite, 60% HF-pyridine, 0 °C; (d) NH_4OH, MeOH, then ODS column; (e) TMSCl, CH_2Cl_2, then BCl_3, −78 °C.



Scheme 7. Conditions: (a) adenine or 2,6-DAP, TMSOTf, CH_3CN; (b) BCl_3, CH_2Cl_2, −78 °C; (c) NH_4F·HF, DMF, then ODS column; (d) adenosine deaminase, Tris–HCl buffer.



Scheme 9. Conditions: (a) 2,6-dichloropurine, TMSOTf, CH_3CN, 0 °C; (b) BCl_3, CH_2Cl_2, −78 °C, then silica gel column; (c) NH_3, EtOH, 80 °C; (d) NH_4F·HF, DMF.

and-2 activities were determined by the cytopathic effect (CPE) inhibition method.[17] Antineoplastic activities against human T-cell leukemia, CCRF-HSB-2, and solid tumor, KB cells, were also evaluated. The former was determined by MTT assay,[8] and the latter was determined by the dye uptake method,[17] as previously reported. The results with the pyrimidine series are summarized in Table 2, and those with the purine series are shown in Table 3. Most of the β-anomers of 2′-deoxy-2′-fluoro-4′-thioarabinosylpyrimidine nucleosides showed potent and selective anti-HSV-1 activities, except for the 5-fluorouracil derivative β-**6f** and the 5-hydroxyethyluracil derivative β-**14e**. Among them, the 5-ethyluracil derivative β-**6b**, the 5-iodouracil derivative β-**6c**, and the 5-iodocytosine derivative β-**6g** also showed potent anti-HSV-2 activities. Of these three analogues, the antiviral profile of the 5-ethyluracil derivative β-**6b** is noteworthy. While the 5-iodouracil derivative β-**6c** and the 5-iodocytosine derivative β-**6g** showed weak cytotoxicity, the 5-ethyluracil derivative β-**6b** did not show any cytotoxicity up to 100 μg/mL. Although the thymine derivative β-**6a**, the 5-bromovinyluracil derivative β-**6d**, and the 5-chloroethyl derivative β-**6e** showed potent anti-HSV-1 activity, their anti-HSV-2 activities were relatively weak. None of the α-anomers of pyrimidine derivatives showed any antiviral activities, except for 5-ethyluracil derivative α-**6b**, due to contamination by the β-anomer (2.5%, estimated from HPLC analysis).

The purine derivatives also had potent antiviral activities. The adenine derivative β-**6i**, 2-fluoroadenine β-**6l**, and 2-chloroadenine β-**6m** had moderate anti-HSV-1 and-2 activities. On the other hand, the guanine derivative β-**6k** and 2,6-diaminopurine derivative β-**6j** showed prominent antiviral activities against both HSV-1 and-2, with moderate cytotoxicity against both CCRF-HSB-2

Table 2. Biological activities of 2′-deoxy-2′-fluoro-4′-thioarabinosyl pyrimidine nucleosides

Compound no.	Base	Antiviral activities ED_{50} (μg/mL)		Antineoplastic activities IC_{50} (μg/mL)	
		HSV-1[a,e]	HSV-2[b,e]	CCRF-HSB-2[c]	KB[d]
β-**6a**	Thymine	0.32	3.2	0.49	> 100
β-**6b**	5-Ethyluracil	0.012	0.11	> 100	> 100
β-**6c**	5-Iodouracil	0.037	0.32	78	48
β-**6d**	5-*E*-Bromovinyluracil	0.32	9.0	> 100	> 100
β-**6e**	5-Chloroethyluracil	0.11	3.0	> 100	> 100
β-**6f**	5-Fluorouracil	> 27	> 27	> 100	63
β-**6h**	5-Iodocytosine	0.037	0.32	38	44
β-**14e**	5-Hydroxyethyluracil	27	> 27	> 100	> 100
α-**6a**	Thymine	> 27	> 27	> 100	ND[f]
α-**6b**	5-Ethyluracil	1.0	27	> 100	> 100
α-**6c**	5-Iodouracil	> 27	> 27	> 100	96
α-**6d**	5-*E*-Bromovinyluracil	> 27	> 27	> 100	> 100
α-**6f**	5-Fluorouracil	> 27	> 27	> 100	> 100
α-**14e**	5-Hydroxyethyluracil	> 27	> 27	> 100	> 100
	Acyclovir	0.32	0.32	> 100	ND

[a]VR strain.
[b]HSV-2 MS strain.
[c]MTT assay.
[d]Dye uptake method.
[e]CPE inhibition assay.
[f]ND, not determined.

Table 3. Biological activities of 2′-deoxy-2′-fluoro-4′-thioarabinosyl purine nucleosides

Compound no.	Base	Antiviral activities IC_{50} (μg/mL)		Antineoplastic activities ED_{50} (μg/mL)	
		HSV-1[a,e]	HSV-2[b,e]	CCRF-HSB-2[c]	KB[d]
β-**6i**	Adenine	3.0	9.0	54	35
β-**6j**	2,6-Diaminopurine	0.0041	0.037	2.1	14
β-**6k**	Guanine	0.0041	0.037	3.6	9.8
β-**6l**	2-Fluoroadenine	9.0	3.0	4.0	35
β-**6m**	2-Chloroadenine	1.0	9.0	50	36
α-**6i**	Adenine	> 27	> 27	> 100	69
α-**6j**	2,6-Diaminopurine	9.0	> 27	> 100	30
α-**6l**	2-Fluoroadenine	> 27	> 27	54	54
α-**6m**	2-Chloroadenine	> 27	> 27	> 100	82
	Acyclovir	0.32	0.32	> 100	ND[f]

[a]VR strain.
[b]HSV-2 MS strain.
[c]MTT assay.
[d]Dye uptake method.
[e]CPE inhibition assay.
[f]ND, not determined.

and KB cells. The finding that the guanine and 2,6-diaminopurine derivatives showed potent antiherpes virus activities and moderate cytotoxicity is consistent with previous results regarding purine 4′-thioarabinonucleosides.[8] This, as well as the result that the 2,6-diaminopurine derivative could be a substrate of adenosine deaminase, as mentioned above, suggests that the generated triphosphate analogue of guanine derivative β-**6k** should be an active metabolite of both β-**6l** and β-**6k**. This result also suggests that replacement of the 2′-hydroxyl group of 4′-thioarabinonucleosides with a fluorine atom does not affect the antiviral activities of 4′-thioarabinonucleosides. This substitution reduced the cytotoxicity of 2′-deoxy-2′-fluoro-4′-thioarabinonucleosides to one tenth of that of 4′-thioarabinonucleosides. As with the pyrimidine derivatives, none of the α-anomers of purine derivatives showed antiherpes virus activity except for 2,6-diaminopurine derivative α-**6j**. The weak activity of α-**6j** was due to contamination by the β-anomer (0.2%, estimated from HPLC analysis), as in the case of the 5-ethyl derivative α-**6b**. On the other hand, several α-anomers of purine derivatives showed weak inhibitory activities against KB cells, and this could not be explained by contamination by the corresponding β-anomers.

2-Fluoroadenine β-**6l** and 2-chloroadenine β-**6m**, which were designed as potential antitumor agents, showed little or no activity against both CCRF-HSB-2 and KB cells. In contrast to these purine derivatives, 5-fluoro-4′-thioFAC (5-F-4′-thioFAC, β-**6g**) had potent antitumor activities against both CCRF-HSB-2 and KB cells. Thus, to evaluate the potency of β-**6g**, its antitumor spectrum was compared with those of araC and 4′-thioFAC, **4**. The antitumor activities of araC, 4′-thioFAC 4, and 5-F-4′-thioFAC β-**6g** against 15 different human solid and leukemic cell lines, including the two cell lines mentioned above, were tested, and the results are summarized in Table 4. All three compounds showed similar antitumor spectra. This strongly suggests that these analogues should be phosphorylated by deoxycytidine kinase, and the resulting dCTP analogues should inhibit replicating enzymes such as DNA polymerase. Of the three compounds tested, only 4′-thioFAC **4** showed potent antitumor activities against all of the stomach and colon cancer cell lines tested. 4′-ThioFAC **4** also showed prominent activities against small cell lung carcinoma (SCLC), QG-90, soft tissue tumor, HT-1080, and KB cells, but was almost inactive against non-small cell lung carcinoma (NSCLC). Similarly, 5-F-4′-thioFAC β-**6g** showed potent activities against two stomach cancer cells and two colon cancer cells. β-**6g** was slightly more active than araC, but almost ten times less active than 4′-thioFAC **4**.

Table 4. Comparison of antitumor spectra of araC, 4′-thioFAC, and 5F-4′-thioFAC

Cell lines	Origin	IC_{50} (μg/mL)[a]		
		araC	4′-thio FAC **4**	5F-4′-thio FAC β-**6g**
MKN-45	Stomach	1.5	0.057	0.23
MKN-28		0.13	0.035	0.20
KATO-III		9.2	0.60	51
NUGC-4		2.6	0.17	2.9
Colo320DM	Colon	0.027	0.025	0.033
HCT-15		> 100	1.3	80
SW-48		0.27	0.018	0.11
PANC-1	Pancreas	> 100	> 100	> 100
PC-8	Lung (NSCLC)	> 100	> 100	> 100
PC-9		> 100	> 100	> 100
Lu-65		1.3	17	38
QG-90	Lung (SCLC)	10	0.26	4.4
HT-1080	Soft tissue	3.0	0.28	4.9
KB	Head and neck	0.21	0.067	0.14
CCRF-HSB-2	Leukemia	0.056	0.086	0.080

[a]Antineoplastic activities against the cell lines listed were determined by MTT assay.

Before starting the synthesis of 5-F-4′-thioFAC β-**6g**, we expected that its metabolite's 5-fluorouracil derivative would act like 5-fluoro-2′-deoxyuridine. However, the results did not meet our expectation because the 5-fluorouracil derivative β-**6f**, which should be generated by an enzymatic deamination of β-**6g**, was almost inactive against both leukemic and solid tumors. Based on previous observations that both 2′-fluoroarabinonucleosides and 4′-thionucleosides were resistant to hydrolysis of the glycosidic bond catalyzed by nucleoside phosphorylase,[18,19] 2′-fluoro-4′-thioarabinonucleosides should be resistant to enzymatic deglycosylation. This ruled out the possibility that the 5-fluorouracil derivative β-**6f** and 5-F-4′-thioFAC β-**6g** act as prodrugs of 5-fluorouracil. Therefore, 5-F-4′-thioFAC β-**6g** behaved as a deoxycytidine antimetabolite and exhibited antitumor properties similar to those of araC and 4′-thioFAC.

In conclusion, we have synthesized 2′-deoxy-2′-fluoro-4′-thioarabinofuranosylpyrimidine and-purine nucleosides as potential antiviral and antitumor agents. Biological evaluation of the compounds synthesized showed that β-anomers of 5-ethyluracil, 5-iodouracil, 5-chloroethyluracil, and 5-iodocytosine derivatives had potent and selective anti-HSV-1 and HSV-2 activities in vitro. While guanine and 2,6-diaminopurine derivatives also showed prominent antiviral activities, they were slightly cytotoxic. In addition, 5-F-4′-thioFAC showed potent antitumor activities against both leukemia and solid tumor. The antitumor spectrum of 5-F-4′-thioFAC was similar to those of araC and 4′-thioFAC. However, the introduction of a 5-fluoro group at the 5-position of 4′-thioFAC caused a slight decrease in antitumor activity.

Experimental

General

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz (^{1}H) and at 100 MHz (^{13}C) using $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Mass spectra were obtained by fast atom bombardment (FAB) mode. Silica gel for chromatography was Merck Kieselgel 60.

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-methyluracil (9a). A CH_3CN suspension (5 mL) of thymine (76.0 mg, 0.60 mmol) and BSA (0.175 mL, 1.32 mmol) was kept

under reflux for 4 h. After the solution was allowed to cool to room temperature, a CH_3CN solution (2 mL) of **8** (108 mg, 0.20 mmol) and $SnCl_4$ (0.40 mL of 1 M CH_2Cl_2 solution, 0.40 mmol) was added at 0 °C under Ar atmosphere. The mixture was stirred at room temperature for 1.5 h and then kept under reflux for 3.5 h. After allowed to cool to room temperature, the mixture was quenched with saturated $NaHCO_3$. After filtration through a pad of Celite, the filtrate was extracted with $CHCl_3 \times 3$. The organic phase was washed with brine and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (25% AcOEt in hexane) to give **9a** ($\alpha/\beta = 2.4/1$) (96 mg, 79%) as a foam: UV λ_{max} (MeOH) 266 nm; ^{1}H MMR ($CDCl_3$) δ 8.24 (0.29H, br s, D_2O exchangeable), 8.20 (0.71H, br s, D_2O exchangeable), 7.62–7.70 (4H, m), 7.59 (0.71H, d, $J = 1.0$ Hz), 7.55 (0.29H, d, $J = 1.0$ Hz), 7.17–7.50 (11H, m), 6.56 (0.29H, dd, $J = 22.5$, 4.4 Hz), 6.31 (0.71H, dd, $J = 16.6$, 2.9 Hz), 5.08 (0.71H, dt, $J = 47.9$, 2.9 Hz), 5.03 (0.29H, dt, $J = 51.0$, 3.0 Hz), 4.64 (0.29H, d, $J = 11.2$ Hz), 4.60 (0.29H, d, $J = 11.7$ Hz), 4.59 (0.71H, d, $J = 11.7$ Hz), 4.56 (0.71H, d, $J = 11.2$ Hz), 4.39 (0.71H, dt, $J = 11.2$, 3.4 Hz), 4.35 (0.29H, dt, $J = 10.8$, 2.9 Hz), 3.60–3.91 (3H, m), 1.85 (0.87H, d, $J = 1.0$ Hz), 1.73 (2.13H, d, $J = 1.5$ Hz), 1.08 (6.39H, s), 1.07 (2.61H, s); FAB–MS m/z 605 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-ethyluracil (9b). From **8** (780 mg, 1.45 mmol), **9b** was obtained as described in the synthesis of **9a**. The residue was purified by column chromatography over silica gel (25% AcOEt in hexane) to give **9b** ($\alpha/\beta = 2.2/1$) (609 mg, 68%) as a foam: UV λ_{max} (MeOH) 266 nm; ^{1}H NMR ($CDCl_3$) δ 7.98 (0.31H, br s, D_2O exchangeable) 7.95 (0.69H, br s, D_2O exchangeable), 7.55–7.69 (5H, m), 7.18–7.50 (11H, m), 6.57 (0.31H, dd, $J = 23.0$, 4.4 Hz), 6.31 (0.69H, dd, $J = 17.1$, 2.4 Hz), 5.08 (0.69H, dt, $J = 48.3$, 2.9 Hz), 5.04 (0.31H, ddd, $J = 50.6$, 3.7, 2.9 Hz), 4.64 (0.31H, d, $J = 11.6$ Hz), 4.60 (0.31H, d, $J = 11.1$ Hz), 4.59 (1.38H, s), 4.39 (0.69H, dt, $J = 11.7$, 2.9 Hz), 4.34 (0.31H, dt, $J = 10.3$, 2.4 Hz), 3.62–3.90 (3H, m), 2.12–2.32 (2H, m), 1.07 (6.21H, s), 1.06 (2.79H, s), 1.04 (0.93H, t, $J = 7.3$ Hz), 0.96 (2.07H, t, $J = 7.3$ Hz); FAB–MS m/z 619 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-iodouracil (9c). From **8** (427 mg, 0.794 mmol), **9c** was obtained as described in the synthesis of **9a**. The residue was purified by column chromatography over silica gel (25% AcOEt in hexane) to give **9c** ($\alpha/\beta = 1.9/1$) (443 mg, 78%) as a foam: UV λ_{max} (MeOH) 289 nm; ^{1}H NMR ($CDCl_3$) δ 8.32 (0.34H, br s, D_2O exchangeable), 8.27 (1H, s, D_2O exchangeable), 8.13 (0.66H, br s), 7.60–7.69 (4H, m), 7.21–7.50 (11H, m), 6.52 (0.34H, dd, $J = 23.0$, 3.9 Hz), 6.22 (0.66H, dd, $J = 15.1$, 2.0 Hz), 5.06 (0.66H, dt, $J = 46.9$, 1.7 Hz), 5.01 (0.34H, dt, $J = 51.2$, 2.3 Hz), 4.64 (0.34H, d, $J = 11.2$ Hz), 4.63 (0.66H, d, $J = 11.2$ Hz), 4.57 (0.34H, d, $J = 11.7$ Hz), 4.53 (0.66H, d, $J = 11.7$ Hz), 4.42 (0.66H, dt, $J = 11.2$, 1.8 Hz), 4.34 (0.34H, dt, $J = 10.0$, 1.8 Hz), 3.73–3.97 (2H, m), 3.64–3.72 (1H, m), 1.08 (3.06H, s), 1.07 (5.94H, s); FAB–MS m/z 717 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-(*E*)-(2-bromovinyl)uracil (9d). From **8** (128 mg, 0.237 mmol), **9d** was obtained as described in the synthesis of **9a**. The residue was purified by column chromatography over silica gel (17% AcOEt in hexane) to give **9d** ($\alpha/\beta = 2.2/1$) (124 mg, 75%) as a foam: UV λ_{max} (MeOH) 295, 251 nm; ^{1}H NMR ($CDCl_3$) δ 8.11 (0.31H, br s, D_2O exchangeable), 8.05 (0.69H, br s, D_2O exchangeable), 7.78 (0.69H, s), 7.62–7.67 (4.31H, m), 7.16–7.52 (12H, m), 6.56 (0.31H, dd, $J = 21.5$, 3.9 Hz), 6.55 (0.31H, d, $J = 14.2$ Hz), 6.31 (0.69H, dd, $J = 16.1$, 2.0 Hz), 6.30 (0.69H, d, $J = 14.2$ Hz), 5.07 (0.69H, dt, $J = 46.9$, 1.8 Hz), 5.03 (0.31H, dt, $J = 50.3$, 3.4 Hz), 4.63 (0.31H, d, $J = 12.2$ Hz), 4.60 (0.31H, d, $J = 11.2$ Hz), 4.59 (0.69H, d, $J = 10.3$ Hz), 4.52 (0.69H, d, $J = 11.2$ Hz), 4.45 (0.69H, dt, $J = 10.7$, 1.9 Hz), 4.33 (0.31H, dt, $J = 10.3$, 2.4 Hz), 3.65–3.97 (3H, m), 1.09 (6.21H, s), 1.08 (2.79H, s); FAB–MS m/z 695, 697 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-(2-hydroxyethyl)uracil (9e). From **8** (258 mg, 0.48 mmol), **9e** was obtained as described in the synthesis of **9a**. The residue was purified by column chromatography over silica gel (60% AcOEt in hexane) to give **9e** ($\alpha/\beta = 1.9/1$) (216 mg, 71%) as a foam: UV λ_{max} (MeOH) 267 nm; ^{1}H NMR ($CDCl_3$) δ 8.11 (0.34H, br s, D_2O exchangeable), 8.08 (0.66H, br s, D_2O exchangeable), 7.73 (0.66H, s), 7.57–7.69 (4.34H, m), 7.18–7.49 (11H, m), 6.55 (0.34H, dd, $J = 22.2$, 4.5 Hz), 6.29 (0.66H, dd, $J = 16.6$, 2.4 Hz), 5.09 (0.66H, dt, $J = 47.4$, 2.4 Hz), 5.04 (0.34H, dt, $J = 50.8$, 3.3 Hz), 4.64 (0.34H, d, $J = 12.5$ Hz), 4.60 (0.34H, d, $J = 11.7$ Hz), 4.59 (0.69H, d, $J = 11.7$ Hz), 4.55 (0.66H, dt, $J = 11.2$ Hz), 4.40 (0.66H, dt, $J = 11.2$, 2.4 Hz), 4.34 (0.34H, dt, $J = 10.1$, 2.2 Hz), 3.62–3.93 (3.68H, m), 3.56 (1.32H, q, $J = 5.9$ Hz), 2.49 (0.68H, m, D_2O exchangeable), 2.36 (1.32H, t, $J = 5.9$ Hz), 2.10 (0.34H, t, $J = 5.4$ Hz, D_2O exchangeable), 2.07 (0.66H, t, $J = 5.9$ Hz, D_2O exchangeable), 1.07 (5.94H, s), 1.06 (3.06H, s); FAB–MS m/z 635 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-fluorouracil (9f). From **8** (769 mg, 1.43 mmol), **9f** was obtained as described in the synthesis of **9a**. The residue was purified by column chromatography over silica gel (25% AcOEt in hexane) to give **9f** ($\alpha/\beta = 2.1/1$) (687 mg, 79%) as a foam: UV λ_{max} (MeOH) 271 nm; ^{1}H NMR ($CDCl_3$) δ 8.26 (0.32H, br s, D_2O exchangeable), 8.22 (0.68H, br s, D_2O exchangeable), 8.00 (0.68H, d, $J = 6.8$ Hz), 7.89 (0.32H, dd, $J = 6.4$, 2.0 Hz), 7.60–7.67 (4H, m), 7.15–7.49 (11H, m), 6.51 (0.32H, ddd, $J = 20.9$, 3.7, 0.9 Hz), 6.24 (0.68H, d, $J = 15.1$ Hz), 5.05 (0.68H, dt, $J = 47.4$, 2.4 Hz), 5.04 (0.32H, dt, $J = 51.3$, 3.9 Hz), 4.64 (1H, d, $J = 11.2$ Hz), 4.53 (1H, d, $J = 11.7$ Hz), 4.40 (0.68H, dt, $J = 10.7$, 2.4 Hz), 4.34 (0.32H, dt, $J = 10.3$, 3.4 Hz), 3.60–3.94 (3H, m), 1.08 (2.88H, s), 1.07 (6.12H, s); FAB–MS m/z 609 ($M^+ + H$).

1-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-D-*arabino*-pentofuranosyl)-5-fluorocytosine (9g). From **8** (764 mg, 1.42 mmol), **9g** was obtained as described in the synthesis of **9a**. The residue was purified

by column chromatography over silica gel (5% MeOH in $CHCl_3$) to give **9g** ($\alpha/\beta = 2.4/1$) (605 mg, 70%) as a foam: UV λ_{max} (MeOH) 285, 244 nm, λ_{max} (MeOH, H^+) 295 nm; ^1H NMR ($CDCl_3$) δ 8.02 (0.71H, d, $J = 6.8$ Hz), 7.91 (0.29H, dd, $J = 6.8$, 2.0 Hz), 7.60–7.68 (4H, m), 7.12–7.48 (11H, m), 6.70 (0.29H, ddd, $J = 22.4$, 3.7, 1.9 Hz), 6.65 (1H, br s, D_2O exchangeable), 6.32 (0.71H, d, $J = 14.7$ Hz), 5.35 (1H, br s, D_2O exchangeable), 5.14 (0.71H, d, $J = 46.4$ Hz), 5.10 (0.29H, dt, $J = 49.8$, 3.4 Hz), 4.61 (0.58H, s), 4.56 (1H, d, $J = 11.7$ Hz), 4.47 (0.71H, d, $J = 11.7$ Hz), 4.39 (0.71H, d, $J = 10.7$ Hz), 4.36 (0.29H, dt, $J = 10.7$, 2.4 Hz), 3.61–3.94 (3H, m), 1.07 (9H, s); FAB–MS m/z 608 ($M^+ + H$).

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-methyluracil (α, β-6a). To a THF solution (23 mL) of **9a** (662 mg, 1.10 mmol) was added TBAF (1.20 mL of 1 M THF solution, 1.20 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. The solvent was removed under reduced pressure, and the residue was passed through a short silica gel column (5% MeOH in $CHCl_3$) to give crude desilylated product (421 mg).

To a CH_2Cl_2 solution (8 mL) of crude desilylated product was added dropwise BCl_3 (5.50 mL of 1 M CH_2Cl_2 solution, 5.50 mmol) at −78 °C under Ar atmosphere, and the mixture was stirred for 3 h at −45 °C. After addition of MeOH (7 mL)–CH_2Cl_2 solution (7 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure, and the residue was co-distilled with MeOH×4. The residue was purified by column chromatography over silica gel (9% MeOH in $CHCl_3$), and the anomers were separated by HPLC (Wakosil-II 5C18 HG-perp., 20×250 mm, Wako Pure Chemicals Industries, Ltd., Japan; 5% EtOH in H_2O, flow rate 9.9 mL/min; retention time α 31 min, β 34 min) to give α-**6a** (149 mg, 49%) and β-**6a** (71 mg, 23%). Data for α-**6a**: mp 179–181 °C (crystallized from H_2O); UV λ_{max} (H_2O) 269 nm; ^1H NMR (DMSO-d_6) δ 11.4 (1H, br s, D_2O exchangeable), 7.92 (1H, s), 6.09 (1H, dd, $J = 17.6$, 6.8 Hz), 6.01 (1H, d, $J = 4.9$ Hz, D_2O exchangeable), 5.12 (1H, dt, $J = 52.7$, 6.8 Hz), 5.04 (1H, t, $J = 5.4$ Hz, D_2O exchangeable), 4.03–4.14 (1H, m), 3.81 (1H, dt, $J = 10.8$, 4.4 Hz), 3.59–3.66 (1H, m), 3.43 (1H, ddd, $J = 10.8$, 7.8, 5.9 Hz), 1.81 (3H, s); FAB–MS m/z 277 ($M^+ + H$). Anal. calcd for $C_{10}H_{13}FN_2O_4S \cdot 0.35$-MeOH: C, 43.24; H, 5.05; N, 9.74. Found: C, 42.96; H, 4.91; N, 10.04. Data for β-**6a**: UV λ_{max} (H_2O) 270 nm; ^1H NMR (DMSO-d_6) δ 11.4 (1H, br s, D_2O exchangeable), 8.08 (1H, s), 6.24 (1H, dd, $J = 8.8$, 5.9 Hz), 5.92 (1H, br s, D_2O exchangeable), 5.43 (1H, br s, D_2O exchangeable), 5.00 (1H, dt, $J = 50.8$, 6.3 Hz), 4.18–4.28 (1H, m), 3.71 (2H, br s), 3.17 (1H, dt, $J = 5.4$, 4.9 Hz), 1.79 (3H, s); FAB–MS m/z 277 ($M^+ + H$). Anal. calcd for $C_{10}H_{13}FN_2O_4S \cdot 0.5H_2O$: C, 42.10; H, 4.95; N, 9.82. Found: C, 42.15; H, 5.05; N, 9.74.

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-fluorocytosine (α, β-6g). To a CH_2Cl_2 solution (7 mL) of **9g** (466 mg, 0.786 mmol) was added dropwise BBr_3 (0.22 mL, 2.30 mmol) at −78 °C under Ar atomsphere, and the mixture was stirred for 2 h at the same temperature. After addition of MeOH (6 mL)-saturated $NaHCO_3$ (6 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The whole was extracted with $CHCl_3$, and the organic phase was washed with brine. After dryness (Na_2SO_4), the filtrate was concentrated under reduced pressure.

To a MeOH solution (16 mL) of the residue was added $NH_4F \cdot HF$ (568 mg, 9.98 mmol) at room temperature, and the mixture was stirred at the same temperature for 2.5 days. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography over silica gel (20% MeOH in $CHCl_3$), and the anomers were separated by HPLC (Wakosil-II 5C18 HG-prep., 20×250 mm, Wako Pure Chemicals Industries, Ltd., Japan; 2.5% CH_3CN in H_2O, flow rate 9.9 mL/min; retention time α 41 min, β 48 min) to give α-**6g** (98 mg, 46%) and β-**6g** (40.0 mg, 19%). Data for α-**6g**: UV λ_{max} (H_2O) 282, 239 nm, λ_{max} (H_2O, H^+) 290 nm; ^1H NMR (DMSO-d_6) δ 8.27 (1H, d, $J = 7.3$ Hz), 7.90 (1H, br, D_2O exchangeable), 7.64 (1H, br s, D_2O exchangeable), 6.12 (1H, ddd, $J = 16.6$ 5.4, 1.5 Hz), 5.95 (1H, d, $J = 3.9$ Hz, D_2O exchangeable), 5.10 (1H, dt, $J = 51.3$, 5.9 Hz), 5.04 (1H, t, $J = 5.1$ Hz, D_2O exchangeable), 4.06–4.16 (1H, m), 3.75 (1H, dt, $J = 10.7$, 5.1 Hz), 3.63 (1H, ddd, $J = 7.3$, 6.8, 5.4 Hz), 3.44 (1H, ddd, $J = 10.7$, 7.8, 5.1 Hz); FAB–MS m/z 280 ($M^+ + H$). Anal. calcd for $C_9H_{11}F_2N_3O_3S \cdot 0.25$EtOH: C, 39.24; H, 4.33; N, 14.45. Found: C, 39.22; H, 4.00; N, 14.40. Data for β-**6g**: mp 210–215 °C (dec, crystallized from H_2O); UV λ_{max} (H_2O) 283, 239 nm, λ_{max} (H_2O, H^+) 291 nm; ^1H NMR (DMSO-d_6) δ 8.33 (1H, d, $J = 7.3$ Hz), 7.88 (1H, br s, D_2O exchangeable), 7.64 (1H, br s, D_2O exchangeable), 6.32 (1H, ddd, $J = 11.3$, 5.6, 1.5 Hz), 5.88 (1H, d, $J = 4.9$ Hz, D_2O exchangeable), 5.40 (1H, d, $J = 5.1$ Hz, D_2O exchangeable), 4.96 (1H, dt, $J = 51.3$, 6.1 Hz), 4.25 (1H, dq, $J = 18.1$, 5.9 Hz), 3.72 (2H, t, $J = 5.4$ Hz), 3.18 (1H, q, $J = 5.4$ Hz); FAB–MS m/z 280 ($M^+ + H$). Anal. calcd for $C_9H_{11}F_2N_3O_3S \cdot 0.25$EtOH: C, 39.24; H, 4.33; N, 14.45. Found: C, 39.01; H, 4.21; N, 14.62.

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-ethyluracil (α, β-6b). To a CH_2Cl_2 solution (8 mL) of **9b** (491 mg, 0.794 mmol) was added dropwise BBr_3 (0.23 mL, 2.38 mmol) at −78 °C under Ar atmosphere, and the mixture was stirred for 1.5 h at the same temperature. After addition of MeOH (5 mL)–saturated $NaHCO_3$ (10 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The whole was extracted with $CHCl_3$×2, and the organic phase was washed with brine. After dryness (Na_2SO_4), the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel [hexane:AcOEt:EtOH(20:10:1)], and the anomers were separated by flash silica gel column (33% AcOEt in hexane) to give α-**10b** (234 mg, 56%) and β-**10b** (124 mg, 30%).

From α-**10b** (282 mg, 0.534 mmol) and β-**10b** (124 mg, 0.235 mmol), α-**6b** and β-**6b** were obtained as described in the synthesis of **6g**. The each residue was purified by

column chromatography over silica gel (9% MeOH in $CHCl_3$) to give α-**6b** (148 mg, 96%) and β-**6b** (50 mg, 73%). Data for α-**6b**: UV λ_{max} (H_2O) 270 nm; ^1H NMR (DMSO-d_6) δ 11.41 (1H, br s, D_2O exchangeable), 7.85 (1H, s), 6.10 (1H, dd, $J=17.6$, 6.4 Hz), 6.02 (1H, br s, D_2O exchangeable), 5.16 (1H, dt, $J=52.3$, 6.8 Hz), 5.05 (1H, br s, D_2O exchangeable), 4.06–4.15 (1H, m), 3.79 (1H, dt, $J=11.2$, 4.4 Hz), 3.63 (1H, dt, $J=7.3$, 5.4 Hz), 3.38–3.47 (1H, m), 2.25 (2H, q, $J=7.3$ Hz), 1.05 (3H, t, $J=7.3$ Hz); FAB–MS m/z 291 ($M^+ + H$). Anal. calcd for $C_{11}H_{15}FN_2O_4S$: C, 45.51; H, 5.21; N, 9.65. Found: C, 45.30; H, 4.91; N, 9.52. Data for β-**6b**: mp 173–175 °C (crystallized from CH_3CN); UV λ_{max} (H_2O) 270 nm; ^1H NMR (DMSO-d_6) δ 11.37 (1H, br s, D_2O exchangeable), 8.04 (1H, s), 6.24 (1H, dd, $J=7.8$, 5.9 Hz), 5.89 (1H, d, $J=5.4$ Hz, D_2O exchangeable), 5.42 (1H, t, $J=5.4$ Hz, D_2O exchangeable), 5.01 (1H, ddd, $J=50.8$, 7.3, 5.9 Hz), 4.23 (1H, ddt, $J=12.7$, 6.3, 5.4 Hz), 3.70 (2H, t, $J=4.9$ Hz), 3.16 (1H, dt, $J=6.4$, 4.9 Hz), 2.23 (2H, q, $J=7.3$ Hz), 1.04 (3H, t, $J=7.3$ Hz); FAB–MS m/z 291 ($M^+ + H$). Anal. calcd for $C_{11}H_{15}FN_2O_4S$: C, 45.51; H, 5.21; N, 9.65. Found: C, 45.34; H, 5.10; N, 9.62.

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-iodouracil (α, β-6c). From **9c** (409 mg, 0.571 mmol), **10c** was obtained as described in the synthesis of **10b**. The anomers were separated by column chromatography over silica gel (33% AcOEt in hexane) to give α-**10c** (229 mg, 64%) and β-**10c** (102 mg, 29%).

From α-**10c** (266 mg, 0.425 mmol) and β-**10c** (111 mg, 0.177 mmol), α-**6c** and β-**6c** were obtained as described in the synthesis of **6g**. The residue was purified by column chromatography over silica gel (9% MeOH in $CHCl_3$) to give α-**6c** (137 mg, 83%) and β-**6c** (58 mg, 84%). Data for α-**6c**: UV λ_{max} (H_2O) 291 nm; ^1H NMR (DMSO-d_6) δ 11.79 (1H, br s, D_2O exchangeable), 8.47 (1H, s), 6.06 (1H, dd, $J=18.1$, 5.4 Hz), 5.98 (1H, $J=4.9$ Hz, D_2O exchangeable), 5.18 (1H, dt, $J=51.8$, 5.4 Hz), 5.06 (1H, $J=5.4$ Hz, D_2O exchangeable), 4.15 (1H, ddt, $J=12.7$, 6.4, 4.9 Hz), 3.75 (1H, dt, $J=10.7$, 4.9 Hz), 3.68 (1H, dt, $J=7.3$, 5.9 Hz), 3.41 (1H, ddd, $J=10.7$, 7.4, 6.4 Hz); FAB–MS m/z 389 ($M^+ + H$). Anal. calcd for $C_9H_{10}FIN_2O_4S$: C, 27.85; H, 2.60; N, 7.22. Found: C, 27.87; H, 2.37; N, 6.83. Data for β-**6c**: UV λ_{max} (H_2O) 291 nm; ^1H NMR (DMSO-d_6) δ 11.79(1H, br s, D_2O exchangeable), 8.76 (1H, s), 6.17 (1H, dd, $J=7.3$, 6.3 Hz), 5.94 (1H, d, $J=5.4$ Hz, D_2O exchangeable), 5.56 (1H, t, $J=5.4$ Hz, D_2O exchangeable), 5.02 (1H, ddd, $J=50.8$, 7.3, 5.9 Hz), 4.18 (1H, ddt, $J=12.7$, 6.4, 5.4 Hz), 3.62–3.73 (2H, m), 3.16 (1H, dt, $J=6.4$, 4.4 Hz); FAB–MS m/z 389 ($M^+ + H$). Anal. calcd for $C_9H_{10}FIN_2O_4S \cdot 0.25EtOH$: C, 28.55; H, 2.90; N, 7.01. Found: C, 28.41; H, 2.57; N, 6.98.

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-fluorouracil (α, β-6f). From **9f** (560 mg, 0.921 mmol), **10f** was obtained as described in the synthesis of **10b**. The anomers were separated by flash silica gel column (40% AcOEt in hexane) to give α-**10f** (329 mg, 69%) and β-**10f** (151 mg, 31%).

From α-**10f** (318 mg, 0.614 mmol) and β-**10f** (151 mg, 0.292 mmol), α-**6f** and β-**6f** were obtained as described in the synthesis of **6g**. The residue was purified by column chromatography over silica gel (9% MeOH in $CHCl_3$) to give α-**6f** (134 mg, 78%) and β-**6f** (63 mg, 77%). Data for α-**6f**: mp 184–186 °C (crystallized from MeOH); UV λ_{max} (H_2O) 271 nm; ^1H NMR (DMSO-d_6) δ 11.95 (1H, br s, D_2O exchangeable), 8.39 (1H, d, $J=7.3$ Hz), 6.03 (1H, dd, $J=17.1$, 5.4 Hz), 6.01 (1H, $J=4.9$ Hz, D_2O exchangeable), 5.13 (1H, dt, $J=51.8$, 6.4 Hz), 5.05 (1H, $J=4.9$ Hz, D_2O exchangeable), 4.13 (1H, ddt, $J=13.2$, 6.8, 4.9 Hz), 3.76 (1H, dt, $J=10.8$, 4.9 Hz), 3.65 (1H, dt, $J=7.3$, 4.9 Hz), 3.42 (1H, ddd, $J=10.7$, 7.8, 5.9 Hz); FAB–MS m/z 281 ($M^+ + H$). Anal. calcd for $C_9H_{10}F_2N_2O_4S$: C, 38.57; H, 3.60; N, 10.00. Found: C, 38.89; H, 3.28; N, 9.64. Data for β-**6f**: mp 189–191 °C (crystallized from MeOH); UV λ_{max} (H_2O) 271 nm; ^1H NMR (DMSO-d_6) δ 11.95 (1H, br s, D_2O exchangeable), 8.60 (1H, d, $J=7.3$ Hz), 6.19 (1H, t, $J=5.9$ Hz), 5.93 (1H, d, $J=5.4$ Hz, D_2O exchangeable), 5.50 (1H, t, $J=4.9$ Hz, D_2O exchangeable), 5.03 (1H, dt, $J=50.3$, 6.4 Hz), 4.22 (1H, ddt, $J=12.7$, 6.4, 5.4 Hz), 3.63–3.77 (2H, m), 3.16 (1H, dt, $J=6.4$, 4.4 Hz); FAB–MS m/z 281 ($M^+ + H$). Anal. calcd for $C_9H_{10}F_2N_2O_4S$: C, 38.57; H, 3.60; N, 10.00. Found: C, 38.80; H, 3.44; N, 9.74.

(*E*)-5-(2-Bromovinyl)-1-(2-deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)uracil (α, β-6d). From **9d** (740 mg, 1.08 mmol), **11d** was obtained as described in the synthesis of **6a**. The anomers were separated by flash silica gel column (33% AcOEt in hexane) to give α-**11d** (230 mg, 47%) and β-**11d** (151 mg, 31%).

From α-**11d** (214 mg, 0.468 mmol) and β-**11d** (147 mg, 0.322 mmol), α-**6d** and β-**6d** were obtained as described in the synthesis of **6a**. The each residue was purified by column chromatography over silica gel (9% MeOH in $CHCl_3$) to give α-**6d** (114 mg, 66%) and β-**6d** (80 mg, 68%). Data for α-**6d**: mp 223–228 °C (dec, crystallized from MeOH); UV λ_{max} (H_2O) 296, 252 nm; ^1H NMR (DMSO-d_6) δ 11.70 (1H, br s, D_2O exchangeable), 8.30 (1H, s), 7.32 (1H, d, $J=13.7$ Hz), 6.92 (1H, d, $J=13.7$ Hz), 6.10 (1H, dd, $J=16.6$, 6.4 Hz), 6.03 (1H, d, $J=4.9$ Hz, D_2O exchangeable), 5.12 (1H, dt, $J=52.3$, 6.4 Hz), 5.07 (1H, t, $J=5.4$ Hz, D_2O exchangeable), 4.06–4.17 (1H, m), 3.82 (1H, dt, $J=10.8$, 4.4 Hz), 3.63–3.70 (1H, m), 3.43 (1H, ddd, $J=10.8$, 7.8, 5.9 Hz); FAB–MS m/z 367, 369 ($M^+ + H$). Anal. calcd for $C_{11}H_{12}BrFN_2O_4S$: C, 35.98; H, 3.29; N, 7.63. Found: C, 36.26; H, 3.16; N, 7.53. Data for β-**6d**: mp 178–181 °C (crystallized from MeOH); UV λ_{max} (H_2O) 294, 251 nm; ^1H NMR (DMSO-d_6) δ 11.70 (1H, br s, D_2O exchangeable), 8.52 (1H, s), 7.27 (1H, d, $J=13.2$ Hz), 6.89 (1H, d, $J=13.2$ Hz), 6.23 (1H, t, $J=6.4$ Hz), 5.92 (1H, d, $J=5.4$ Hz, D_2O exchangeable), 5.53 (1H, t, $J=5.2$ Hz, D_2O exchangeable), 5.04 (1H, ddd, $J=49.2$, 7.8, 6.4 Hz), 4.17–4.28 (1H, ddd, m), 3.16 (1H, dt, $J=6.8$, 4.4 Hz), 3.71–3.79 (2H, m); FAB–MS m/z 367, 369 ($M^+ + H$). Anal. calcd for $C_{11}H_{12}BrFN_2O_4S \cdot 0.3EtOH$: C, 36.57; H, 3.65; N, 7.35. Found: C, 36.97; H, 3.34; N, 7.32.

5-(2-*O*-*tert*-Butyldimethylsilyloxyethyl)-1-(5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-3-hydroxy-4-thio-α(and β)-D-*arabino*-pentofuranosyl)uracil (α, β-13e). To a CH_2Cl_2 solution (11 mL) of **9e** (684 mg, 1.08 mmol) was added

dropwise BBr_3 (0.31 mL, 3.24 mmol) at −78 °C under Ar atmosphere, and the mixture was stirred for 2 h at the same temperature. After addition of MeOH (7 mL)-saturated $NaHCO_3$ (14 mL) to the mixture at the same temperature, the solution was allowed to warm to room temperature. The whole was extracted with $CHCl_3$×2, and the organic phase was washed with brine. After dryness (Na_2SO_4), the filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (4 mL), and TBDMSCl (425 mg, 1.62 mmol) was added to the solution at room temperature. The mixture was stirred for 2.5 h at the same temperature under Ar atmosphere. After addition of H_2O, the whole was extracted with AcOEt×3. The organic phase was washed with H_2O and then dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel [hexane:AcOEt:EtOH(20:10:1)], and the anomers were separated by a flash silica gel column (30% AcOEt in hexane) to give α-**13e** (359 mg, 51%) and β-**13e** (172 mg, 24%). **Data for α-13e**: ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, br s, D_2O exchangeable), 7.63–7.71 (4H, m), 7.38–7.50 (6H, m), 6.18 (1H, dd, J = 17.1, 6.4 Hz), 4.97 (1H, dt, J = 52.3, 6.8 Hz), 4.35–4.45 (1H, m), 3.67–3.91 (4H, m), 2.83 (1H, d, J = 3.4 Hz, D_2O exchangeable), 2.55 (2H, t, J = 5.9 Hz), 1.08 (9H, s), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); FAB–MS m/z 659 (M^+ + H). Data for β-**13e**: ^{1}H NMR ($CDCl_3$) δ 8.12 (1H, br s, D_2O exchangeable), 7.62–7.73 (4H, m), 7.57 (1H, s), 7.38–7.50 (6H, m), 6.51 (1H, dd, J = 15.6, 5.4 Hz), 4.99 (1H, dt, J = 50.8, 4.9 Hz), 4.49–4.59 (1H, m), 3.95 (1H, t, J = 9.8 Hz), 3.85 (1H, ddd, J = 10.7, 6.4, 1.6 Hz), 3.73 (1H, dt, J = 9.9, 5.9 Hz), 3.70 (1H, dt, J = 9.9, 5.9 Hz), 3.43–3.49 (1H, m), 2.47 (2H, t, J = 5.9 Hz), 2.37 (1H, d, J = 3.9 Hz, D_2O exchangeable), 1.09 (9H, s), 0.82 (9H, s), 0.0 (3H, s), −0.03 (3H, s); FAB–MS m/z 659 (M^+ + H).

1-(2-Deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-5-(2-hydroxyethyl)uracil (α, β-14e). From α-**13e** (403 mg, 0.612 mmol) and β-**13e** (185 mg, 0.281 mmol), α-**14e** and β-**14e** were obtained as described in the synthesis of **6g**. The residue was purified by column chromatography over silica gel (20% MeOH in $CHCl_3$) to give α-**14e** (166 mg, 89%) and β-**14e** (79 mg, 91%). Data for α-**14e**: mp 146–147 °C (crystallized from MeOH); UV λ_{max} (H_2O) 269 nm; ^{1}H NMR (DMSO-d_6) δ 11.41 (1H, br s, D_2O exchangeable), 7.85 (1H, s), 6.09 (1H, dd, J = 17.1, 6.4 Hz), 6.00 (1H, br d, D_2O exchangeable), 5.11 (1H, dt, J = 52.7, 6.4 Hz), 5.04 (1H, d, J = 5.4 Hz, D_2O exchangeable), 4.58 (1H, t, J = 5.4 Hz, D_2O exchangeable), 4.03–4.14 (1H, m), 3.81 (1H, dt, J = 10.7, 4.4 Hz), 3.62 (1H, dt, J = 7.3, 4.4 Hz), 3.48 (2H, dt, J = 6.4, 5.9 Hz), 3.38–3.44 (1H, m), 2.39 (2H, t, J = 6.4 Hz); FAB–MS m/z 307 (M^+ + H). Anal. calcd for $C_{11}H_{15}FN_2O_5S$: C, 43.13; H, 4.94; N, 9.15. Found: C, 43.15; H, 4.82; N, 8.94. Data for β-**14e**: mp 203–205 °C (crystallized from MeOH); UV λ_{max} (H_2O) 270 nm; ^{1}H NMR (DMSO-d_6) δ 11.40 (1H, br s, D_2O exchangeable), 8.02 (1H, s), 6.24 (1H, dd, J = 9.3, 5.9 Hz), 5.91 (1H, d, J = 5.4 Hz, D_2O exchangeable), 5.38 (1H, t, J = 5.4 Hz, D_2O exchangeable), 5.00 (1H, dt, J = 50.3, 6.3 Hz), 4.58 (1H, t, J = 5.4 Hz, D_2O exchangeable), 4.21 (1H, ddt, J = 12.7, 6.3, 5.4 Hz), 3.74 (1H, dt, J = 11.2, 4.9 Hz), 3.66 (1H, dt, J = 11.7, 5.9 Hz), 3.43–3.51 (2H, m), 3.17 (1H, dt, J = 5.9, 5.4 Hz), 2.37 (2H, t, J = 6.8 Hz); FAB–MS m/z 307 (M^+ + H). Anal. calcd for $C_{11}H_{15}FN_2O_5S \cdot 0.75H_2O$: C, 41.31; H, 5.20; N, 8.76. Found: C, 41.34; H, 4.94; N, 8.41.

5-(2-Chloroethyl)-1-(2-deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)uracil (β-6e). A DMF solution (3 mL) of β-**14e** (59.0 mg, 0.193 mmol) and Ph_3P (152 mg, 0.579 mmol) was stirred at room temperature for 20 min under Ar atmosphere, followed by addition of a pyridine solution (93.0 μL) of CCl_4 (47.0 μl, 0.483 mmol). The mixture was stirred at room temperature for 20 h. After *n*-BuOH (90.0 μL) was added, the mixture was stirred for 20 min. The solvent was removed under reduced pressure, and the residue was codistilled with toluene×2. The residue was passed through a short silica gel column (5% MeOH in $CHCl_3$) to give crude β-**6e**, which was purified by reversed-phase ODS column chromatography (Wakosil 40C18, 10% CH_3CN in H_2O) to give β-**6e** (30 mg, 48%): mp 145–147 °C (crystallized from H_2O); UV λ_{max} (H_2O) 270 nm; ^{1}H NMR (DMSO-d_6) δ 11.52 (1H, br s, D_2O exchangeable), 8.19 (1H, s), 6.23 (1H, dd, J = 7.8, 5.9 Hz), 5.91 (1H, d, J = 5.4 Hz, D_2O exchangeable), 5.41 (1H, t, J = 4.9 Hz), 5.02 (1H, dt, J = 49.8, 5.9 Hz), 4.24 (1H, ddt, J = 12.7, 5.9, 5.4 Hz), 3.66-3.76 (4H, m), 3.17 (1H, dt, J = 5.9, 5.4 Hz), 2.72 (1H, dt, J = 14.2, 7.3 Hz), 2.65 (1H, dt, J = 14.2, 7.3 Hz); FAB–MS m/z 325 (M^+ + H). Anal. calcd for $C_{11}H_{14}ClFN_2O_4S$: C, 40.68; H, 4.35; N, 8.63. Found: C, 40.93; H, 4.20; N, 8.52.

1-(3,5-Di-*O*-acetyl-2-deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)-5-iodouracil (β-15c). To a THF solution (5 mL) of β-**10c** (159 mg, 0.254 mmol) was added TBAF (0.30 mL of 1 M TBAF solution, 0.30 mmol) in THF at room temperature, and the mixture was stirred for 30 min at the same temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in pyridine (10 mL). To the solution was added Ac_2O (0.16 mL, 1.7 mmol) and DMAP (4.8 mg), and the mixture was stirred for 2.5 h at room temperature under Ar atmosphere. After H_2O was added, the solution was stirred for 15 min. The solvent was removed under reduced pressure, and the residue was partitioned between AcOEt and H_2O. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (50% AcOEt in hexane) to give β-**15c** (109 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, br s, D_2O exchangeable), 8.23 (1H, d, J = 2.4 Hz), 6.58 (1H, dd, J = 23.4, 3.9 Hz), 5.50 (1H, dt, J = 9.8, 2.0 Hz), 5.07 (1H, ddd, J = 49.3, 3.4, 2.4 Hz), 4.45 (1H, ddd, J = 11.2, 6.8, 2.4 Hz), 4.28 (1H, ddd, J = 11.7, 8.8, 1.5 Hz), 3.73 (1H, dd, J = 8.3, 6.8 Hz), 2.16 (3H, s), 2.15 (3H, s); FAB–MS m/z 473 (M^+ + H).

1-(2-Deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)-5-iodocytosine (β-6h). To a CH_3CN solution (3 mL) of β-**15c** (45.0 mg, 95.3 μmol), TPSCl (57.0 mg, 0.191 mmol) and DMAP (23.0 mg, 0.191 mmol) was added Et_3N (26.0 μL, 0.191 mmol) at 0 °C under Ar atmosphere. After the mixture was stirred for 8.5 h at room temperature, concentrated NH_4OH (1.6 mL) was added at

0 °C. The solution was stirred at room temperature for 21 h, followed by evaporation of the solvent under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O, and H_2O phase was wased with $CHCl_3 \times 1$ and then concentrated under reduced pressure. The residue was co-distilled with EtOH×2 and passed through a short silica gel column (9% MeOH in $CHCl_3$) to give crude β-**6h**, which was purified by reversed-phase ODS column chromatography (Wakosil 40C18, 5% CH_3CN in H_2O) to give β-**6h** (16 mg, 43%): mp 206–210 °C (dec, crystallized from H_2O); UV λ_{max} (H_2O) 297 nm, λ_{max} (H_2O, H^+) 311 nm; ^1H NMR (DMSO-d_6) δ 8.53 (1H, s, 6-H), 7.94 (1H, br s, D_2O exchangeable), 6.74 (1H, br s, D_2O exchangeable), 6.33 (1H, dd, $J = 10.7$, 5.4 Hz), 5.89 (1H, d, $J = 5.4$ Hz, D_2O exchangeable), 5.47 (1H, t, $J = 4.9$ Hz, D_2O exchangeable), 4.96 (1H, dt, $J = 50.8$, 5.9 Hz), 4.22 (1H, ddt, $J = 11.7$, 5.9, 5.4 Hz), 3.66 (2H, t, $J = 4.9$ Hz), 3.19 (1H, dt, $J = 5.4$, 4.9 Hz); FAB–MS m/z 388 ($M^+ + H$). Anal. calcd for $C_9H_{11}FIN_3O_3S$: C, 27.92; H, 2.86; N, 10.85. Found: C, 27.74; H, 2.97; N, 10.64.

9-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)adenine (16i). To a mixture of **8** (1.60 g, 3.0 mmol), adenine (0.77 g, 5.7 mmol), and 4A molecular sieves (2.70 g) in CH_3CN (26 mL) was added TMSOTf (2.20 mL, 11.4 mmol) and stirred at 0 °C for 0.5 h. The reaction was quenched with saturated $NaHCO_3$. The whole was extracted with $CHCl_3$, and the organic phase was washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified on column chromatography over silica gel (4.2×22 cm; 1% MeOH in $CHCl_3$) to give α,β-**16i** (0.44 g, 23%, $\alpha/\beta = 0.7$) as an amorphous foam: UV λ_{max} (MeOH) 260 nm; ^1H NMR ($CDCl_3$) δ 8.37 (0.42H, s), 8.35 (0.58H, s), 8.21 (0.42H, s), 8.19 (0.58H, d, $J = 2.4$ Hz), 7.69–7.64 (4H, m), 7.48–7.14 (11H, m), 6.54 (0.58H, dd, $J = 4.4$, 19.1 Hz), 6.25 (0.42H, dd, $J = 3.4$, 15.1 Hz), 5.61 (2H, br s, D_2O exchangeable), 5.39 (0.42H, dt, $J = 3.4$, 48.3 Hz), 5.12 (0.58H, dt, $J = 4.4$, 50.8 Hz), 4.64 (1.16H, s), 4.59 (0.42H, d, $J = 11.7$ Hz), 4.55 (0.42H, d, $J = 11.7$ Hz), 4.50–4.41 (1H, m), 4.06–4.02 (0.42H, m), 3.99–3.94 (0.58H, m), 3.88–3.83 (1H, m), 3.78–3.69 (1H, m), 1.09 (5.22H, s), 1.07 (3.78H, s), FAB MS m/z 614 ($M^+ + H$).

9-(2-Deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)adenine (6i). To a solution of α,β-**16i** (290 mg, 0.47 mmol, $\alpha/\beta = 0.7$) in CH_2Cl_2 (9 mL) was added slowly a solution of BCl_3 (2.4 mL of a 1 M CH_2Cl_2 solution, 2.4 mmol) at −78 °C under argon. After being stirred at 0 °C for 0.5 h, the reaction was quenched by addition of MeOH (2.5 mL) at −78 °C. The mixture was allowed to warm to room temperature. The solvent was removed and co-evaporated with MeOH (×3) under reduced pressure. The residue was dissolved in DMF (10 mL). To the solution was added $NH_4F{\cdot}HF$ (320 mg, 5.64 mmol) and stirred at room temperature overnight. After concentration, the residue was purified by column chromatography over silica gel (2.3×15 cm; 1–10% MeOH in $CHCl_3$) to give α,β-**6i** (87 mg, 65%, $\alpha/\beta = 0.56$, estimated by HPLC) as a white solid. Then, α- and β-isomers were separated by reverse-phased ODS column chromatography (YMC·GEL ODS-AQ 120-S50, 1.5×19 cm; 0–3% EtOH in H_2O). The unseparable fractions were collected, concentrated, and rechromatographed (×2) to give β-**6i** (28 mg, 21%), α-**6i** (19 mg, 14%) and unseparable α,β-**6i** (12 mg, 9%). Data for α-**6i**: mp 197–200 °C (crystallized from H_2O); UV λ_{max} (MeOH) 260 nm; ^1H NMR (DMSO-d_6) δ 8.42 (1H, s), 8.16 (1H, s), 7.34 (2H, br s, D_2O exchangeable), 6.18 (1H, dd, $J = 6.8$, 17.1 Hz), 6.09 (1H, d, $J = 5.4$ Hz, D_2O exchangeable), 5.64 (1H, dt, $J = 6.8$, 52.7 Hz), 5.07 (1H, t, $J = 4.9$ Hz, D_2O exchangeable), 4.20–4.15 (1H, m), 3.87–3.82 (1H, m), 3.73 (1H, dt, $J = 4.4$, 7.8 Hz), 3.49–3.43 (1H, m); FAB–MS m/z 286 ($M^+ + H$). Anal. calcd for $C_{10}H_{12}FN_5O_2S{\cdot}0.75H_2O$: C, 40.20; H, 4.55; N, 23.44. Found: C, 40.33; H, 4.52; N, 20.41. Data for β-**6i**: mp 151–153 °C (crystallized from MeOH); UV λ_{max} (MeOH) 261 nm; ^1H NMR (DMSO-d_6) δ 8.50 (1H, s), 8.14 (1H, s), 7.31 (2H, br s, D_2O exchangeable), 6.23 (1H, t, $J = 5.9$ Hz), 5.96 (1H, d, $J = 5.9$ Hz, D_2O exchangeable), 5.35 (1H, t, $J = 5.4$ Hz, D_2O exchangeable), 5.13 (1H, ddd, $J = 5.9$, 7.8 and 50.8 Hz), 4.46–4.42 (1H, m), 3.83–3.75 (2H, m), 3.28–3.24 (1H, m); FAB–MS m/z 286 ($M^+ + H$). Anal. calcd for $C_{10}H_{12}FN_5O_2S{\cdot}0.5$-MeOH: C, 41.85; H, 4.68; N, 23.24. Found: C, 41.67; H, 4.68; N, 23.00.

9-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)-2,6-diaminopurine (16j). To a mixture of **8** (1.80 g, 3.35 mmol), 2,6-diaminopurine (0.96 g, 6.37 mmol), and 4 Å molecular sieves (3.0 g) in CH_3CN (24 mL) was added TMSOTf (2.50 mL, 12.7 mmol) at 0 °C and stirred at room temperature for 1 h. The reaction was quenched with saturated $NaHCO_3$. The whole was extracted with $CHCl_3$, and the organic phase was washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified on column chromatography over silica gel (4.2×22 cm; 1% MeOH in $CHCl_3$) to give α,β-**16j** (0.83 g, 39%, $\alpha/\beta = 1.0$) as an amorphous foam: UV λ_{max} (MeOH) 282, 260 nm; ^1H NMR ($CDCl_3$) δ 7.91 (0.5H, s), 7.90 (0.5H, d, $J = 2.4$ Hz), 7.68–7.65 (4H, m), 7.47–7.17 (11H, m), 6.35 (0.5H, dd, $J = 3.9$, 19.5 Hz), 6.08 (0.5H, dd, $J = 3.4$, 16.1 Hz), 5.39 (0.5H, dt, $J = 3.4$, 48.8 Hz), 5.40 (2H, br s, D_2O exchangeable), 5.38 (2H, br s, D_2O exchangeable), 5.08 (0.5H, dt, $J = 3.9$, 50.3 Hz), 4.73 (1H, d, $J = 6.8$ Hz), 4.62 (1H, d, $J = 21.5$ Hz), 4.46 (0.5H, dt, $J = 3.4$, 9.8 Hz), 4.41 (0.5H, dt, $J = 3.9$, 12.2 Hz), 4.01–3.92 (1H, m), 3.85–3.81 (1H, m), 3.76–3.67 (1H, m), 1.08 (4.5H, s), 1.07 (4.5H, s), FAB MS m/z 629 ($M^+ + H$).

9-(2-Deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)-2,6-diaminopurine (6j). To a solution of α,β-**16j** (815 mg, 1.3 mmol, $\alpha/\beta = 1.0$) in CH_2Cl_2 (26 mL) was added slowly a solution of BCl_3 (6.5 mL of a 1 M CH_2Cl_2 solution, 6.5 mmol) at −78 °C under argon. After being stirred at 0 °C for 1 h, the reaction was quenched by addition of MeOH (6 mL) at −78 °C. The mixture was allowed to warm to room temperature and neutralized by addition of saturated $NaHCO_3$. The solvent was removed and co-evaporated with MeOH (×3) under reduced pressure. The residue was dissolved in DMF (28 mL). To the solution was added $NH_4{\cdot}HF$ (890 mg, 15.6 mmol) and stirred at room temperature overnight. After concentration, residue was purified by column

chromatography over silica gel (2.2×18 cm; 2–20% MeOH in $CHCl_3$) to give α,β-**6j** (306 mg, 78%, α/β = 0.8, estimated by HPLC) as a white solid. Then, α- and β-isomer (67 mg) were separated by reverse-phased ODS column chromatography (YMC·GEL ODS-AQ 120-S50, 1.5×15 cm; 0–1.5% CH_3CN in H_2O). The unseparable fractions were collected, concentrated, and rechromatographed to give β-**6j** (28.4 mg) and α-**6j** (26.7 mg). Data for α-**6j**: mp 193–195 °C (crystallized from H_2O); UV λ_{max} (MeOH) 283, 260 nm; ^{1}H NMR (DMSO-d_6) δ 8.05 (1H, s), 6.76 (2H, br s, D_2O exchangeable), 6.07 (1H, d, J = 5.4 Hz, D_2O exchangeable), 5.97 (1H, dd, J = 6.8, 16.1 Hz), 5.87 (2H, br s, D_2O exchangeable), 5.55 (1H, dt, J = 6.8, 52.2 Hz), 5.05 (1H, t, J = 5.9 Hz, D_2O exchangeable), 4.18–4.14 (1H, m), 3.84–3.79 (1H, m), 3.69 (1H, dt, J = 4.4, 7.3 Hz), 3.50–3.44 (1H, m); FAB–MS m/z 301 (M^+ + H). Anal. calcd for $C_{10}H_{13}FN_6O_2S$: C, 39.99; H, 4.36; N, 27.98. Found: C, 39.71; H, 4.48; N, 27.79. Data for β-**6j**: mp 183–185 °C (crystallized from H_2O); UV λ_{max} (MeOH) 282, 260 nm; ^{1}H NMR (DMSO-d_6) δ 8.04 (1H, s), 6.75 (2H, br s, D_2O exchangeable), 6.06 (1H, dd, J = 5.9, 9.3 Hz), 5.97 (1H, d, J = 5.4 Hz, D_2O exchangeable), 5.87 (2H, br s, D_2O exchangeable), 5.32 (1H, br s, D_2O exchangeable), 5.07 (1H, dt, J = 5.9, 49.8 Hz), 4.45–4.41 (1H, m), 3.81–3.69 (2H, m), 3.28–3.24 (1H, m); FAB–MS m/z 301 (M^+ + H). Anal. calcd for $C_{10}H_{13}FN_6O_2S{\cdot}0.5H_2O$: C, 38.83; H, 4.56; N, 27.17. Found: C, 38.65; H, 4.32; N, 27.30.

9-(2-Deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)-guanine (β-6k). A solution of α,β-**6j** (114 mg, 0.38 mmol, α/β = 0.64) and adenosine deaminase (0.43 mL, 100 units) in Tris–HCl buffer (25 mL, pH 7.0) was stirred at room temperature for 6 h. The mixture was purified by reverse-phased ODS column chromatography (YMC·GEL ODS-AQ 120-S50, 1.5×19 cm; 0–2% CH_3CN in H_2O) to give β-**6k** (48 mg, 42%) as a white solid: mp 248–255 °C (dec) (crystallized from H_2O); UV λ_{max} (MeOH) 258 nM; ^{1}H NMR (DMSO-d_6) δ 10.64 (1H, br s, D_2O exchangeable), 8.08 (1H, s), 6.52 (2H, br s, D_2O exchangeable), 5.99–5.96 (2H, m, D_2O exchangeable for 3′-OH), 5.32 (1H, t, J = 5.4 Hz, D_2O exchangeable), 5.07 (1H, ddd, J = 5.9, 7.3 and 50.8 Hz), 4.39–4.35 (1H, m), 3.80–3.68 (2H, m), 3.26–3.21 (1H, m); FAB–MS m/z 302 (M^+ + H). Anal. calcd for $C_{10}H_{12}FN_5O_3S{\cdot}1.0H_2O$: C, 37.61; H, 4.42; N, 21.93. Found: C, 37.87; H, 4.39; N, 21.77.

9-(5-*O*-Acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)-2,6-diaminopurine (17j). A mixture of α,β-**16j** (686 mg, 1.09 mmol, α/β = 1.0) and $NH_4F{\cdot}HF$ (756 mg, 13.1 mmol) in DMF (24 mL) was stirred at room temperature overnight. After concentration, the residue was passed through a short silica gel column. The eluate with 5% MeOH in $CHCl_3$ was collected and concentrated. The residue was dissolved in CH_3CN (21 mL). To the solution was added Ac_2O (0.19 mL, 2.02 mmol) and Et_3N (0.3 mL, 2.21 mmol), and stirred at room temperature overnight. The reaction was quenched by addition of MeOH (5.0 mL) and the mixture was stirred at room temperature for 0.5 h. After the solvents were removed under reduced pressure, the concentrated residue was purified by column chromatography over silica gel (1.5×23 cm; 0–10% MeOH in $CHCl_3$) to give α,β-**17j** (393 mg, 86%) as an amorphous foam: ^{1}H NMR ($CDCl_3$) δ 7.96 (0.52H, d, J = 2.0 Hz), 7.91 (0.48H, s), 7.41–7.24 (5H, m), 6.34 (0.52H, dd, J = 3.9, 18.6 Hz), 6.09 (0.48H, dd, J = 3.4, 16.1 Hz), 6.05–5.75 (2H, br, D_2O exchangeable), 5.43 (0.48H, dt, J = 3.4, 48.8 Hz), 5.14 (0.52H, dt, J = 3.9, 50.3 Hz), 5.10–4.85 (2H, br, D_2O exchangeable), 4.70 (0.52H, d, J = 11.7 Hz), 4.65 (0.52H, d, J = 11.7 Hz), 4.63 (0.48H, d, J = 11.7 Hz), 4.59 (0.48H, d, J = 11.7 Hz), 4.40–4.16 (3H, m), 4.14–4.06 (0.48H, m), 3.77–3.70 (0.52H, m), 2.05 (1.56H, s), 2.04 (1.44H, s); FAB MS m/z 433 (M^+ + H).

9-(5-*O*-Acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-4-thio-α(and β)- D-*arabino*-pentofuranosyl)-2-fluoroadenine (18l). *t*-Butyl nitrite (0.13 mL, 1.06 mmol) was added dropwise to a solution of α,β-**17j** (327 mg, 0.76 mmol) in 60% HF-pyridine (4.3 mL) at 0 °C. After the solution was stirred at the same temperature for 0.5 h, the reaction was quenched by addition of ice-water. The mixture was extracted with $CHCl_3$ (×2). The organic phase was washed with water and brine, then dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography over silica gel (1.5×17 cm; 0–2% MeOH in $CHCl_3$) to give α,β-**18l** (230 mg, 58%) as an amorphous foam: UV λ_{max} (MeOH) 262 nm; ^{1}H NMR ($CDCl_3$) δ 8.19 (0.52H, d, J = 2.4 Hz), 8.16 (0.48H, s), 7.42–7.21 (5H, m), 6.44 (0.52H, dd, J = 3.9, 18.6 Hz), 6.30–6.00 (2H, br, D_2O exchangeable), 6.19 (0.48H, dd, J = 3.4, 15.1 Hz), 5.38 (0.48H, dt, J = 3.4, 47.9 Hz), 5.14 (0.52H, dt, J = 3.9, 50.3 Hz), 4.70 (0.52 -H, d, J = 12.2 Hz), 4.65 (0.52H, d, J = 12.2 Hz), 4.60 (0.96H, s), 4.38–4.06 (3.48H, m), 3.80–3.71 (0.52H, m), 2.05 (1.44H, s), 2.04 (1.56H, s); FAB MS m/z 436 (M^+ + H).

9-(3-*O*-Benzyl-2-deoxy-2-fluoro-4-thio-α-(and β)-D-*arabino*-pentofuranosyl)-2-fluoroadenine (19l). To a solution of α,β-**18l** (206 mg, 0.47 mmol) in MeOH (7.0 mL) was added concentrated NH_4OH (5.0 mL) and stirred at room temperature for 4 h. After the solvents were evaporated under reduced pressure, the concentrated residue was purified by reverse-phased ODS column chromatography (Wakosil 40C18, 1.5×18 cm; 0–25% CH_3CN in H_2O) to give α-**19l** (76.1 mg, 41%) and β-**19l** (84.4 mg, 46%) as a white solid, respectively. Data for β-**19l**: UV λ_{max} (MeOH) 262 nm; ^{1}H NMR (DMSO-d_6) δ 8.49 (1H, s), 8.05–7.75 (2H, br, D_2O exchangeable), 7.39–7.29 (5H, m), 6.14 (1H, dd, J = 5.4, 8.3 Hz), 5.46 (1H, dt, J = 5.4, 49.8 Hz), 5.44 (1H, t, J = 4.9 Hz, D_2O exchangeable), 4.68 (2H, s), 4.57–4.51 (1H, m), 4.83–4.74 (2H, m), 3.49 (1H, q, J = 5.9 Hz); FAB–MS m/z 394 (M^+ + H). **Data for α-19l**: UV λ_{max} (MeOH) 262 nm; ^{1}H NMR (DMSO-d_6) δ 8.38 (1H, s), 8.04–7.78 (2H, br, D_2O exchangeable), 7.37–7.28 (5H, m), 6.16 (1H, dd, J = 5.4, 15.6 Hz), 5.77 (1H, dt, J = 5.4, 50.8 Hz), 5.24 (1H, t, J = 5.4 Hz, D_2O exchangeable), 4.68 (1H, d, J = 11.7 Hz), 4.64 (1H, d, J = 11.7 Hz), 4.38–4.31 (1H, m), 3.92 (1H, q, J = 6.4 Hz), 3.78–3.73 (1H, m), 3.56-3.46 (1H, m); FAB–MS m/z 394 (M^+ + H).

9-(2-Deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)-2-fluoroadenine (β-6l). To a suspension of β-**19l** (79 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was added TMSCl

(80 μL, 0.63 mmol) under argon, and stirred at room temperature for 10 min. A solution of BCl_3 (1.0 mL, of a 1 M solution, 1.0 mmol) was added slowly to the mixture at −78 °C. After being stirred at room temperature for 1 h, the reaction was quenched by addition of MeOH (2.0 mL) at −78 °C. The mixture was allowed to warm to room temperature, and then concentrated NH_4OH (2.0 mL) was added. After concentration, the residue was purified by column chromatography over silica gel (1.0×15 cm; 2–20% MeOH in $CHCl_3$) to give β-**6l** (34 mg, 56%) and **β-20l** (21 mg, 36%) as a white solid, respectively. Data for β-**6l**: mp 210–212 °C (crystallized from MeOH–H_2O); UV λ_{max} (MeOH) 262 nm; ^{1}H NMR (DMSO-d_6) δ 8.51 (1H, s), 7.87 (2H, br s, D_2O exchangeable), 6.10 (1H, t, J = 5.9 Hz), 5.97 (1H, br s, D_2O exchangeable), 5.35 (1H, br t, J = 4.9 Hz, D_2O exchangeable), 5.16 (1H, ddd, J = 5.9, 7.8 and 50.3 Hz), 4.44–4.37 (1H, m), 3.84–3.77 (2H, m), 3.27–3.23 (1H, m); FAB–MS m/z 304 (M^+ + H). Anal. calcd for $C_{10}H_{11}F_2N_5O_2S{\cdot}0.25H_2O$: C, 39.02; H, 3.77; N, 22.75. Found: C, 38.89; H, 3.71; N, 22.57. Data for β-**20l**: UV λ_{max} (MeOH) 263 nm; ^{1}H NMR (DMSO-d_6) δ 8.37 (1H, d, J = 1.5 Hz), 8.05–7.74 (2H, br, D_2O exchangeable), 6.26–6.22 (2H, m, D_2O exchangeable (1H)), 5.20 (1H, dt, J = 5.9, 49.3 Hz), 4.54–4.50 (1H, m), 4.17–4.09 (2H, m), 3.55 (1H, q, J = 6.4 Hz); FAB–MS m/z 322 (M^+ + H). Anal. calcd for $C_{10}H_{10}ClF_2N_5OS{\cdot}0.2H_2O$: C, 36.92; H, 3.22; N, 21.53. Found: C, 36.85; H, 3.51; N, 21.30.

9-(2-Deoxy-2-fluoro-4-thio-α-D-*arabino*-pentofuranosyl)-2-fluoroadenine (α-6l). Compound α-**19l** (69 mg, 0.17 mmol) was converted as described for the synthesis of β-**6l** to give α-**6l** (39 mg, 76%) as a white solid: mp 265–267 °C (dec) (crystallized from H_2O-MeOH); UV λ_{max} (MeOH) 262 nm; ^{1}H NMR (DMSO-d_6) δ 8.42 (1H, s), 7.90 (2H, br s, D_2O exchangeable), 6.10 (1H, dd, J = 6.8, 16.6 Hz), 6.09 (1H, br s, D_2O exchangeable), 5.54 (1H, dt, J = 6.8, 52.7 Hz), 5.09 (1H, t, J = 5.4 Hz, D_2O exchangeable), 4.22–4.14 (1H, m), 3.88–3.83 (1H, m), 3.75–3.70 (1H, m), 3.50–3.43 (1H, m); FAB–MS m/z 304 (M^+ + H). Anal. calcd for $C_{10}H_{11}F_2N_5O_2S$: C, 39.60; H, 3.66; N, 23.09. Found: C, 39.67; H, 3.51; N, 22.83.

9-(3-*O*-Benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-α(and β)-D-*arabino*-pentofuranosyl)-2,6-dichloropurine (21m). To a mixture of **8** (440 mg, 0.82 mmol), 2,6-dichloropurine (304 mg, 1.56 mmol), and 4A molecular sieves (730 mg) in CH_3CN (6.0 mL) was added TMSOTf (0.56 mL, 2.90 mmol) at 0 °C and stirred at 60 °C for 5 h. The reaction was quenched with saturated $NaHCO_3$. The whole was extracted with $CHCl_3$, and the organic phase was washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified on column chromatography over silica gel (2.2×17 cm; 10% AcOEt in *n*-hexane) to give α,β-**21m** (370 mg, 68%, α/β = 1.5) as a colorless oil: UV λ_{max} (MeOH) 274, 223 nm; ^{1}H NMR ($CDCl_3$) δ 8.55 (0.6H, s), 8.46 (0.4H, d, J = 2.4 Hz), 7.68–7.64 (4H, m), 7.49–7.09 (11H, m), 6.51 (0.4H, dd, J = 4.4, 17.6 Hz), 6.26 (0.6H, dd, J = 2.4, 14.2 Hz), 5.25 (0.6H, dt, J = 2.4, 47.4 Hz), 5.11 (0.4H, dt, J = 4.4, 50.8 Hz), 4.66 (0.4H, d, J = 11.7 Hz), 4.62 (0.4H, d, J = 11.7 Hz), 4.60 (0.6H, d, J = 11.7 Hz), 4.49 (0.6H, d, J = 11.7 Hz), 4.50–4.45 (1H, m), 4.08–4.04 (0.6H, m), 3.98-3.93 (0.4H, m), 3.89–3.81 (1H, m), 3.77–3.72 (1H, m), 1.09 (3.6H, s), 1.08 (5.4H, s), FAB MS m/z 667, 669 (M^+ + H).

9-(5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-2-fluoro-4-thio-α (and β)-D-*arabino*-pentofuranosyl)-2,6-dichloropurine (22m). To a solution of α,β-**21m** (360 mg, 0.54 mmol, α/β = 1.5) in CH_2Cl_2 (11 mL) was added slowly a solution of BCl_3 (2.7 mL of a 1 M CH_2Cl_2 solution, 2.7 mL) at −78 °C under argon. After being stirred at room temperature for 0.5 h, the reaction was quenched by addition of MeOH (1.0 mL) at −78 °C. The mixture was allowed to warm to room temperature and neutralized by addition of saturated $NaHCO_3$. The solvent was removed and co-evaporated with MeOH (×3) under reduced pressure. The residue was purified column chromatography over silica gel (1.5×23 cm; 0–1% MeOH in $CHCl_3$) to give less polar β-**22m** (121.7 mg, 39%) and more polar α-**22m** (184 mg, 59%) as an amorphous foam, respectively. Data for β-**22m**: ^{1}H NMR ($CDCl_3$) δ 8.46 (1H, s), 7.70–7.68 (4H, m), 7.50–7.41 (6H, m), 6.41 (1H, dd, J = 5.4, 10.3 Hz), 5.10 (1H, dt, J = 5.4, 50.3 Hz), 4.69–4.63 (1H, m), 4.05 (1H, dd, J = 6.8, 9.3 Hz), 3.96 (1H, dd, J = 6.4, 9.3 Hz), 3.58–3.54 (1H, m), 2.70–2.40 (1H, br, D_2O exchangeable), 1.12 (9H, s); FAB–MS m/z 577, 579 (M^+ + H). Data for α-**22m**: ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, s), 7.69–7.66 (4H, m), 7.49–7.40 (6H, m), 6.21 (1H, dd, J = 4.4, 15.6 Hz), 5.31 (1H, dt, J = 4.4, 49.8 Hz), 4.68–4.62 (1H, m), 3.99–3.81 (3H, m), 3.04 (1H, d, J = 4.4 Hz, D_2O exchangeable), 1.09 (9H, s); FAB–MS m/z 577, 579 (M^+ + H).

9-(2-Deoxy-2-fluoro-4-thio-β-D-*arabino*-pentofuranosyl)-2 - chloroadenine (β - 6m). Compound β-**22m** (115 mg, 0.2 mmol) was dissolved in saturated ethanolic ammonia (20 mL) and heated at 80 °C in sealed tube for 7 h. After cooling, the solvent was removed under reduced pressure and the residue was dissolved in DMF (5.0 mL). To the solution was added $NH_4F{\cdot}HF$ (137 mg, 2.4 mmol) and stirred at room temperature overnight. After concentration, the residue was purified by column chromatography over silica gel (1.0×14 cm; 0–10% MeOH in $CHCl_3$) to give β-**6m** (50.9 mg, 80%) as a white solid: mp 151–153 °C (crystallized from H_2O); UV λ_{max} (MeOH) 265 nm; ^{1}H NMR (DMSO-d_6) δ 8.55 (1H, s), 7.86 (2H, br s, D_2O exchangeable), 6.14 (1H, t, J = 5.9 Hz), 5.97 (1H, d, J = 5.9 Hz, D_2O exchangeable), 5.35 (1H, t, J = 4.9 Hz, D_2O exchangeable), 5.16 (1H, ddd, J = 5.9, 7.8 and 50.3 Hz), 4.43–4.39 (1H, m), 3.85–3.78 (2H, m), 3.27–3.23 (1H, m); FAB–MS m/z 320, 322 (M^+ + H). Anal. calcd for $C_{10}H_{11}ClFN_5O_2S{\cdot}0.5H_2O$: C, 36.53; H, 3.68; N, 21.30. Found: C, 36.36; H, 3.68; N, 21.26.

9-(2-Deoxy-2-fluoro-4-thio-α-D-*arabino*-pentofuranosyl)-2-chloroadenine (α-6m). Compound α-**22m** (178 mg, 0.31 mmol) was converted as described for the synthesis of β-**6m** to give α-**6m** (75 mg, 76%) as a white solid: mp 217–219 °C (crystallized from H_2O); UV λ_{max} (MeOH) 266 nm; ^{1}H NMR (DMSO-d_6) δ 8.49 (1H, s), 7.89 (2H, br s, D_2O exchangeable), 6.13 (1H, dd, J = 6.8, 16.1 Hz), 6.10 (1H, d, J = 5.4 Hz, D_2O exchangeable), 5.54 (1H, dt, J = 6.8, 52.3 Hz), 5.10 (1H, t, J = 5.4 Hz, D_2O exchangeable), 4.23–4.19 (1H, m), 3.88–3.83 (1H, m), 3.74–3.70

(1H, m), 3.69–3.45 (1H, m); FAB–MS *m*/*z* 320, 322 ($M^+ + H$). Anal. calcd for $C_{10}H_{11}ClFN_5O_2S$: C, 37.56; H, 3.47; N, 21.90. Found: C, 37.31; H, 3.49; N, 22.11.

Antiviral assays

HEL cells and the following virus strains were used: HSV-1 VR-strain and HSV-2 MS strain. Antiviral activities against these herpes viruses were determined by the CPE inhibition method as described earlier.[17]

Cytotoxicity test

Antineoplastic activities against leukemic (CCRF-HSB-2) and solid tumor cell lines were assayed by the MTT method as described previously,[8,17] except KB-cells. Cytotoxicity against KB-cells was determined by the dye uptake method.[17]

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