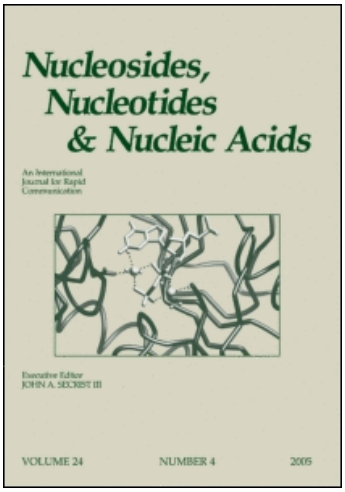

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Synthesis and Antiviral Activities of 5-Substituted 1-(2-Deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)uracilst

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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF 5-SUBSTITUTED 1-(2-DEOXY-2-*C*-METHYLENE-4-THIO-β-D-*ERTYTHRO*-PENTOFURANOSYL)URACILS†

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ABSTRACT: Various 5-substituted 1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)uracils (4'-thioDMDUs) were synthesized from D-glucose *via* sila-Pummerer-type glycosylation. All of the β-anomers of 5-substituted 4'-thioDMDU, except the 5-hydroxyethyl derivative, showed potent anti-HSV-1 activity (ED_{50} = 0.016-0.096 μg/mL). 5-Ethyl- and 5-iodo-4'-thioDMDUs were also active against HSV-2 (ED_{50} = 0.17 and 0.86 μg/mL, respectively). 5-Bromovinyl-4'-thioDMDU was particularly active against VZV (ED_{50} = 0.013 μg/mL).

INTRODUCTION

In 1986, a new 2'-modified nucleoside, 2'-deoxy-2'-*C*-methylenecytidine (DMDC, **1**, Chart 1), was synthesized,[1] and its potent antineoplastic property has been reported.[1,2] While DMDC also has potent anti-herpesvirus activity, its potent cytotoxicity has made it difficult to use as an antiviral agent.[3] 2'-*C*-

† This paper is dedicated to the memory of late Professor Tsujiaki Hata, who deceased on September 7, 1996.

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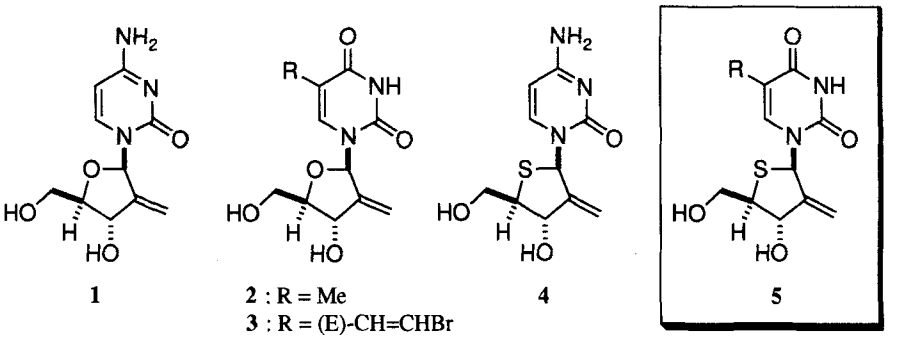


Chart 1

Methylenethymidine (DMDT, **2**), a thymidine congener of DMDC, retains its anti-herpesvirus activity, but is also relatively cytotoxic.[3] In an attempt to enhance antiviral activity and reduce cytotoxicity, we previously synthesized various 5-substituted-2'-deoxy-2'-*C*-methyleneuridines (DMDUs). Although 5-bromovinyl (BV)-DMDU **3** was relatively less cytotoxic and active against herpes simplex virus type 1 (HSV-1), its efficacy against varicella zoster virus (VZV) was less than 1/100 of that of the parental sorivudine (5-bromovinylarabinosyluracil, BVAU).[3]

We recently used a new method to synthesize 2'-modified 4'-thionucleosides, such as 1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)cytosine (4'-thio-DMDC, **4**), a 4'-thio counterpart of DMDC, and other derivatives.[4] 4'-Thionucleosides have been the subject of research[5] for the development of antiviral agents ever since the reports of Walker[6] and Secrist.[7] Since both 2'-*C*-methylene-substitution and 4'-thio-replacement should potentiate the antiviral activities of the corresponding nucleosides, 5-substituted-2'-deoxy-2'-*C*-methylene-4'-thiouridines may be promising antiviral agents. As part of our continuing program concerning the synthesis of new types of 4'-thionucleosides, we describe here the synthesis and antiviral effects of 5-substituted-1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)uracils (4'-thioDMDUs) **5**.

RESULTS AND DISCUSSION

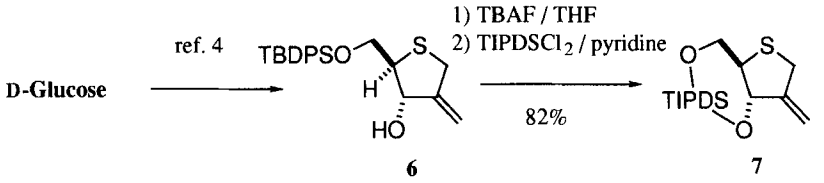
Chemistry. We have previously reported a novel synthesis of 4'-thioDMDC using sila-Pummerer-type glycosylation reaction as a key step.[4] This new glycosylation reaction of the sulfoxide of 1,4-anhydro-5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-*C*-methylene-4-thio-*erythro*-pentofuranose (**6**) with persilylated N^4-acetylcytosine efficiently gave the corresponding 4'-thionucleoside. However the desired β-anomer of

4'-thioDMDC was only a minor component.[4] We first tried to improve the β-selectivity of the sila-Pummerer glycosylation reaction using various protected 4-thiosugar portions. After several attempts, we found that the reaction between 1,4-anhydro-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-2-*C*-methylene-4-thio-*erythro*-pentitol *S*-oxide (**8**) and persilylated N^4-acetylcytosine somewhat improved the β-selectivity of 4'-thioDMDC formation (data not shown). We applied similar conditions to the synthesis of 5-substituted-4'-thioDMDU.

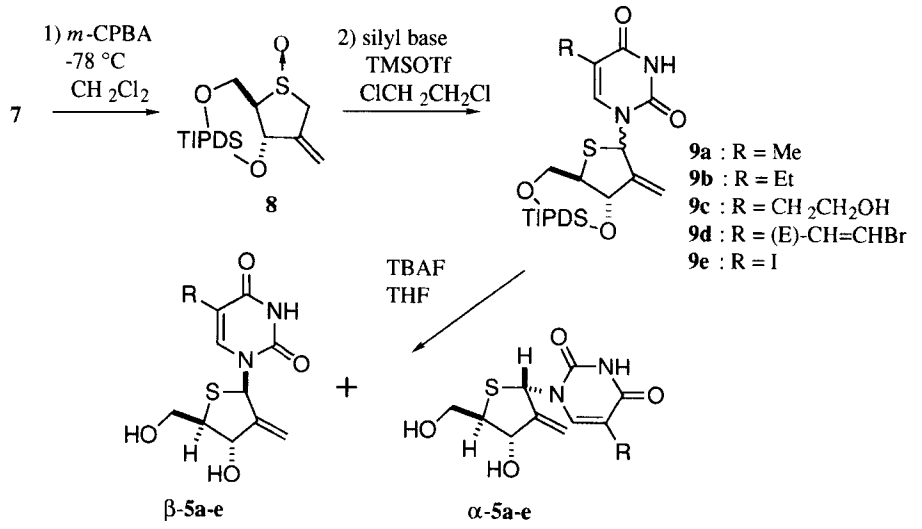
Oxidation of 1,4-anhydro-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-2-*C*-methylene-4-thio-D-*erythro*-pentitol (**7**), which was easily derived from **6** in 2 steps (Scheme 1), gave the corresponding sulfoxide **8**. The sila-Pummerer glycosylation reaction of **8** with pertrimethysilylated thymine catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave an anomeric mixture of the protected 1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)thymine (4'-thioDMDT, **9a**, Scheme 2). Deprotection of **9a** by treatment with tetrabutylammonium fluoride (TBAF) gave the free nucleoside **5a** in 51% yield from **9a**. The ratio of the resulting α- and β-anomers was 1.5 : 1 (Table 1). Similarly, the reaction of **8** with 5-ethyl- and 5-hydroxyethyluracil[8] gave the corresponding 4'-thionucleosides **9b** and **9c**, respectively (α/β = 1.5-1.7).

In contrast, the same reaction using uracils with electron-withdrawing substituents at the 5-position, such as 5-(*E*)-bromovinyl and 5-iodo, gave little of the products (**9d** and **9e**) and very low β-selectivity (Table 1). A plausible explanation for this outcome is that introduction of the electron-withdrawing substituents at the 5-position reduced their basicity and the nucleophilicity of the N-1 position. The decrease in basicity should be particularly important: from a mechanistic consideration of this reaction, absorption of α-proton of the sulfoxide should be rate-limiting. To verify our hypothesis, we re-examined the reaction in the presence of triethylamine. As a result, both the yield and β-selectivity were improved in the reactions with 5-bromovinyl- and 5-iodouracils. Deprotection of these compounds was achieved by treatment with TBAF in THF to give 5-BV- (**5d**) and 5-iodo-4'-thioDMDUs (**5e**).

Chlorination of the hydroxyethyl moiety of **5c** by treatment with triphenylphosphine and carbon tetrachloride[9] gave α- and β-5-chloroethyl-4'-thioDMDU (**5f**) in yields of 43 and 21%, respectively (Scheme 3). Mixtures of the α- and β-anomers of 5-methyl- (**5a**), 5-ethyl- (**5b**), and 5-chloroethyl-4'-thioDMDU (**5f**) were separated by HPLC. 5-Bromovinyl- and 5-iodo- derivatives could be separated into each of the anomers by silica gel column chromatography before deprotection. On the other hand, it was difficult to separate the anomers of 5-hydroxyethyl-4'-thioDMDU (**5c**) by HPLC. Fortunately, fractional crystallization of the mixture gave partially purified α- and β-anomers of **5c**. Therefore, the biological activities of α- and β-**5c** were evaluated using



Scheme 1

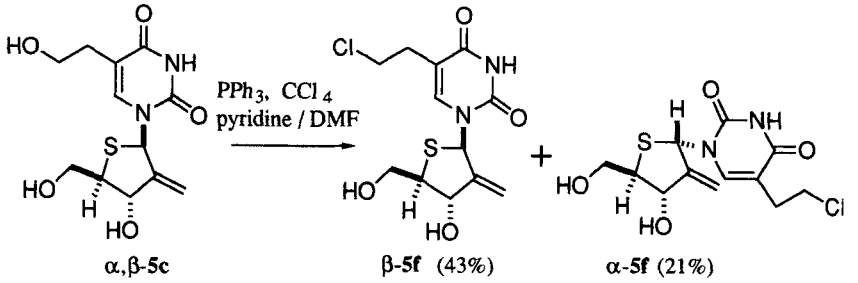


Scheme 2

TABLE 1: Summary of the Pummerer-type Glycosylation Reaction

Comp	R	Yield (%)[a]	α / β[c]
9a	Me	56	1.5
9b	Et	28	1.7
9c	CH_2CH_2OH	56	1.6
9d	CH=CHBr	23	2.7
9d	CH=CHBr	55[b]	1.5
9e	I	9	13[d]
9e	I	27[b]	1.5

[a]Isolated yields. [b]Addition of 0.6 eq. triethylamine. [c]Determined by HPLC analysis of the deprotected compounds. [d]Determined by ^1H NMR of the product.



Scheme 3

these partially purified derivatives. The stereochemistry at the anomeric carbon of the separated 4'-thioDMDU derivatives, except 5-chloroethyl **5f**, was confirmed by NOE experiments (see Experimental Section).

Antiviral Effects. Antiviral activities and cytotoxicities of 5-substituted-4'-thioDMDU derivatives are summarized in Table 2. The antivral activities of these compounds were determined by plaque reduction assay as described previously.[3,10] The cytotoxicities were evaluated as anti-proliferative activities against the cell lines CCRF-HSB-2, human T-cell leukemia cells[10,11] and KB, human solid tumor cells,[11] *in vitro*. Most of the α- and β-5-substituted 4'-thioDMDUs were not cytotoxic against either CCRF-HSB-2 or KB cells. However, α-5-chloroethyl (α-**5f**) and α- and β-BV-4'-thioDMDUs (**5d**) exhibited weak cytotoxicities against CCRF-HSB-2. None of the compounds showed any cytotoxicity against KB cells.

All of the β-anomers of 5-substituted 4'-thioDMDU, except the 5-hydroxyethyl derivative **5c**, had significant anti-HSV-1 activity which was greater than that of acyclovir. The ineffectiveness of 5-hydroxyethyl-4'-thioDMDU (**5c**), a synthetic intermediate of 5-chloroethyl-4'-thioDMDU (**5f**), was predictable because its parental 5-hydroxyethyl-2'-deoxyuridine is known to be inactive.[9] 5-Ethyl and 5-iodo derivatives (β-**5b** and β-**5e**) were as active as acyclovir against HSV-2. 5-BV-4'-thioDMDU (β-**5d**) also had potent anti-HSV-1 activity, but was inactive against HSV-2. 4'-ThioDMDT (β-**5a**) exhibited antiviral profiles similar to those of DMDT. Note that 4'-thioDMDT (β-**5a**) had no cytotoxicity against CCRF-HSB-2 while DMDT inhibited the growth of the same cell line. Thus, replacement of the 4'-oxygen by sulfur is effective for separating antiviral activity from cytotoxicity in DMDT.

The above-mentioned 4'-thionucleosides, except 5-ethyl and 5-hydroxyethyl derivatives (β-**5b** and β-**5c**), also had potent anti-VZV activity. The prominent activity of 5-BV-4'-thioDMDU (β-**5d**) is particularly noteworthy. 5-BV-4'-thioDMDU (β-**5d**)

TABLE 2: Antiviral Activities and Cytotoxicitiy of 5-Substituted-4'-thioDMDU

Compd No.	R	Antiviral Activities ED_{50} (μg/mL)				Anti-cell proliferative Activities IC_{50} (μg/mL)	
		HSV-1	HSV-2	VZV	HCMV	CCRF-HSB-2	KB
α-**5a**	Me	>10	>10	>50	>50	>100	>100
β-**5a**	Me	0.074	2.24	4.8	>50	>100	>100
α-**5b**	Et	>10	>10	>50	>50	>100	>100
β-**5b**	Et	0.039	0.17	>50	>50	>100	>100
α-**5c**	C_2H_4OH	>10	>10	>50	>50	>100	>100
β-**5c**	C_2H_4OH	>10	>10	>50	>50	>100	>100
α-**5d**	CH=CHBr	>10	>10	>50	>50	64.2	>100
β-**5d**	CH=CHBr	0.016	>10	0.013	>50	94.1	>100
α-**5e**	I	>10	>10	>50	>50	>100	>100
β-**5e**	I	0.073	0.86	2.67	>50	>100	>100
α-**5f**	C_2H_4Cl	>10	>10	44.9	>50	73.1	>100
β-**5f**	C_2H_4Cl	0.096	4.54	0.52	>50	>100	>100
DMDT		1.48	3.9	10.3	18.3	8.5	ND[a]
BVDMDU[b]		0.32	100	0.13	>50	>100	>100
BVAU[c]		0.036	62	0.0013	>50	>100	>100
4'-thioBVAU[c]		0.82	57.6	0.20	>50	>100	>100
Acyclovir		0.26	0.56	1.8	11	>100	>100

[a]ND: Not determined, [b]Data from ref 3. [c]Data from ref 10.

had a 15-fold greater effect on VZV than 4'-thioBVAU, but was 10 times less active than BVAU. In addition, 5-BV-4'-thioDMDU (β-**5d**) was 10 times more potent than its 4'-oxy counterpart, 5-BVDMDU. This suggests that replacement of the 4'-oxygen of 5-BVDMDU with a sulfur atom greatly improves its antiviral property. In contrast, none of the 4'-thioDMDU derivatives, that we tested, including 4'-thioDMDT (β-**5a**) showed any activity against HCMV, although the 4'-oxy congener, DMDT, was active against HCMV.[3] DMDT, as described above, was highly cytotoxic to CCRF-HSB-2. Thus, the anti-HCMV effect of DMDT should relate with its potent cytotoxicity; i.e., monophosphorylation of DMDT could be catalyzed by host thymidine kinase, which can no longer recognize 4'-thioDMDT as a substrate. As a result, 4'-thioDMDT would have lost both its cytotoxicity and anti-HCMV activity.

In summary, we have synthesized various 5-substituted-4'-thioDMDU derivatives from D-glucose *via* the sila-Pummerer-type glycosylation. The β-anomers of these compounds possess potent anti-HSV-1 activity, and some also have anti-HSV-2 activity. Although none of the compounds revealed anti-HCMV activity, 5-BV-4'-thioDMDU was particularly active against VZV. It is noteworthy that replacement of the 4'-oxygen of DMDT with sulfur decreased its cytotoxic effect.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz 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.

1,4-Anhydro-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-deoxy-2-*C*-methylene-4-thio-D-*erythro*-pentitol (7). Tetrabutylammonium fluoride (TBAF) (50 mL of 1 M THF solution, 50 mmol) was added to a solution of 1,4-anhydro-5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-2-*C*-methylene-4-thio-D-*erythro*-pentitol **6**[4] (9.6 g, 25 mmol) in THF (100 mL), and stirred at room temperature for 20 min. The solvent was evaporated, and the residue was purified on column chromatography over silica gel (2% MeOH in $CHCl_3$) to give 1,4-anhydro-2-deoxy-2-*C*-methylene-4-thio-D-*erythro*-pentitol (4.0 g, quant. syrup). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSCl, 12 mL, 37.5 mmol) was added to a solution of 1,4-anhydro-2-deoxy-2-*C*-methylene-4-thio-D-*erythro*-pentitol (4.0 g, 25 mmol) in pyridine (100 mL) at 0 °C, and the mixture was stirred for 2 h. TIPDSCl (3.0 mL, 12.5 mmol) was added further to the mixture, and the whole was stirred for 1.5 h. After the reaction was quenched with water, the solvent was removed under reduced pressure. The residue was partitioned between AcOEt and water, and the organic phase was washed with brine, then dried (Na_2SO_4). The filtrate was concentrated, and the residue was purified on a silica gel column (1% AcOEt in hexane), giving **7** (8.0 g, 82%). **Data for 7**: ^{1}H NMR ($CDCl_3$) δ 5.21 (1H, t, 2-CH_2a, J = 1.0 Hz), 4.99 (1H, t, 2-CH_2b, J = 1.0 Hz), 4.58 (1H, d, H-3, J = 9.3 Hz), 4.10 (1H, dd, H-5a, J = 2.9, 12.2 Hz), 3.90 (1H, dd, H-5b, J = 3.4, 12.7 Hz), 3.54 (1H, dd, H-1a, J = 1.5, 13.7 Hz), 3.42 (1H, dd, H-1b, J = 1.0, 13.7 Hz), 3.10 (1H, dt, H-4, J = 3.2, 9.3 Hz), 0.99-1.22 (28H, m, 3,5-*O*-TIPDS); FAB-MS *m*/*z* 389 (M^++H).

5-Methyl-1-(2-deoxy-2-*C*-methylene-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-9a). To a solution of **7** (8.0 g, 20.6 mmol) in dichloromethane (200 mL) was added dropwise a solution of *m*-chloroperoxybenzoic acid (80%, 4.4 g 20.6 mmol) in dichloromethane (75 mL) at -78 °C. The mixture was stirred at the same temperature for 45 min. The reaction was

quenched with saturated sodium bicarbonate solution and the whole was extracted with $CHCl_3$ (× 2). The organic phase was washed with 10% sodium thiosulfate solution, saturated sodium bicarbonate (× 2), brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give crude **8** (10.5 g, quant.). A suspension of thymine (488 mg, 3.9 mmol) and ammonium sulfate (10 mg) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (15 mL, 71 mmol) was heated at reflux overnight. The resulting clear solution was evaporated to remove all volatiles, and the remaining clear syrup of the persilylated thymine was taken up in 1,2-dichloroethane (10 mL). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (240 μL, 1.2 mmol) and **8** (477 mg, 1.2 mmol) were added to the solution. The mixture was stirred at 0 °C overnight. The reaction was quenched with saturated sodium bicarbonate solution. The precipitates were removed by Celite filtration. The filtrate was diluted with $CHCl_3$, washed with water and brine, and dried (Na_2SO_4). After concentration, the residue was purified on a silica gel column (15-50% AcOEt in hexane) to afford α,β-**9a** (352 mg, 56%, α/β = 1.5, foam). **Data for α,β-9a**: ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, s, 3-NH), 8.27 (1H, s, 3-NH), 7.42 (1H, d, H-6, J = 1.0 Hz), 7.13 (1H, d, H-6, J = 1.5 Hz), 6.74 (1H, s, H-1'), 6.52 (1H, d, H-1', J = 1.0 Hz), 5.44-5.49 (3H, m, 2'-CH_2), 4.88 (1H, t, 2'-CH_2, J = 2.2 Hz), 4.79 (1H, dd, H-3', J = 1.5, 9.3 Hz), 4.65 (1H, dd, H-3', J = 1.0, 8.8 Hz), 4.15-4.20 (2H, m, H-5'a), 3.92-3.96 (2H, m, H-5'b), 3.28-3.31 (1H, m, H-4'), 3.14-3.17 (1H, m, H-4'), 1.94 (3H, d, 5-CH_3, J = 1.5 Hz), 1.88 (3H, 5-CH_3, J = 1.0 Hz), 0.97-1.14 (56H, m, 3',5'-*O*-TIPDS); MS *m/z* 513 (M^++H).

5-Methyl-1-(2-deoxy-2-*C*-methylene-4-thio-α and β-D-*erythro*-pentofuranosyl)-uracil (α,β-5a). A TBAF solution (1.1 mL of 1 M THF solution, 1.1 mmol) was added to a solution of α,β-**9a** (290 mg, 0.57 mmol) in THF (10 mL), and the mixture was stirred for 20 min. After the solvent was removed under reduced pressure, the residue was purified on a silica gel column (3-6% MeOH in $CHCl_3$) to afford α,β-**5a** (165 mg) as a colorless syrup. An anomeric mixture of α- and β-**5a** were separated by HPLC (YMC-Pack SIL-06, 20×250 mm, YMC Co., Ltd. Japan, 4% MeOH in $CHCl_3$, flow-rate: 9.9 mL/min). Crystallization of each anomer from MeOH gave analytically pure α-**5a** (84 mg, 55%) and β-**5a** (56 mg, 36%), respectively. **Data for α-5a**: mp 192-194 °C: UV(H_2O)λ_{max} 271nm; ^{1}H NMR (DMSO-d_6) δ 11.38 (1H, br s, 3-NH), 7.45 (1H, d, H-6, J = 1.4 Hz), 6.53 (1H, s, H-1'), 5.84 (1H, d, 3'-OH, J = 5.9 Hz), 5.36 (1H, t, 2'-CH_2a, J = 2.0 Hz), 4.99 (1H, t, 5'-OH, J = 4.9 Hz), 4.94 (1H, t, 2'-CH_2b, J = 2.0 Hz), 4.27 (1H, br t, H-3', J = 6.6 Hz), 3.83-3.86 (1H, m, H-5'a), 3.44-3.48 (2H, m, H-4', 5'b), 1.79 (3H, d, 5-CH_3, J = 1.0 Hz); FAB-MS *m/z* 271 (M^++H). Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.77; H, 5.56; N, 10.07. **Data for β-5a**: mp 179-180 °C: UV(H_2O)λ_{max} 270nm; ^{1}H NMR (DMSO-d_6) δ 11.40 (1H, br

s, 3-NH), 7.44 (1H, d, H-6, J = 1.5 Hz), 6.59 (1H, s, H-1'), 5.63 (1H, d, 3'-OH, J = 4.9 Hz), 5.35 (1H, s, 2'-CH_2a), 5.13 (1H, t, 5'-OH, J = 5.4 Hz), 5.03 (1H, s, 2'-CH_2b), 4.56 (1H, br t, H-3', J = 4.6 Hz), 3.60-3.63 (1H, m, H-5'a), 3.53-3.58 (1H, m, H-5'b), 3.16-3.17 (1H, m, H-4'), 1.79 (3H, s, 5-CH_3); NOE, irradiate H-6, observe H-3' (5.4%); irradiate H-1', observe H-4' (1.7%); FAB-MS m/z 271 (M^++H). Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.68; H, 5.22; N, 10.50.

5-Ethyl-1-(2-deoxy-2-*C*-methylene-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-9b). From **8** (620 mg, 1.5 mmol), α,β-**9b** were obtained as described in the synthesis of α,β-**9a**. The residue was purified on a silica gel column (15-50% AcOEt in hexane) to afford α,β-**9b** (225 mg, 28%) as a colorless syrup. An anomeric mixture of **9b** were separated by HPLC (YMC-Pack SIL-06, 20×250 mm, YMC Co., Ltd. Japan, $CHCl_3$, flow-rate: 9.0 mL/min), and α-**9b** (91 mg, 11%) and β-**9b** (85 mg, 11%, d.e. = 74%; judged from HPLC) were obtained as a colorless syrup. **Data for α-9b**: ^{1}H NMR ($CDCl_3$) δ 8.81 (1H, s, 3-NH), 7.09 (1H, s, H-6), 6.75 (1H, s, H-1'), 5.45 (1H, t, 2'-CH_{2a}, J = 2.4 Hz), 4.87 (1H, t, 2'-CH_2, J = 2.2 Hz), 4.65 (1H, d, H-3', J = 9.8 Hz), 4.17 (1H, dd, H-5'a, J =2.9, 12.7 Hz), 3.95 (1H, dd, H-5'b, J = 2.5, 12.7 Hz), 3.31-3.27 (1H, m, H-4'), 2.38 (2H, dd, 5-$\underline{CH_2}CH_3$, J = 7.3, 14.7 Hz), 0.90-1.16 (31H, m, 5-$CH_2\underline{CH_3}$, 3',5'-*O*-TIPDS); FAB-Mass m/z 527 (M^++H). **Data for β-9b**: ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, s, 3-NH), 7.34 (1H, s, H-6), 6.57 (1H, d, H-1', J = 1.0 Hz), 5.45 (1H, d, 2'-CH_{2a}, J = 1.4 Hz), 5.44 (1H, t, 2'-CH_{2b}, J = 1.2 Hz), 4.80 (1H, dd, H-3', J = 1.7, 9.5 Hz), 4.17 (1H, dd, H-5'a, J = 2.9, 12.7 Hz), 3.95 (1H, dd, H-5'b, J = 2.0, 12.7 Hz), 3.14-3.17 (1H, m, H-4'), 2.31 (2H, dd, 5-$\underline{CH_2}CH_3$, J = 7.3, 14.7 Hz), 1.02-1.13 (31H, m, 5-$CH_2\underline{CH_3}$, 3',5'-*O*-TIPDS); FAB-Mass m/z 527 (M^++H).

5-Ethyl-1-(2-deoxy-2-*C*-methylene-4-thio-α-D-*erythro*-pentofuranosyl)uracil (α-5b). Compound α-**9b** (72 mg, 0.14 mmol) was deblocked as described in the synthesis of α,β-**5a**. The residue was purified on a silica gel column (5% MeOH in $CHCl_3$), and crystallization of the residue from MeOH gave α-**5b** (34 mg, 88%) . **Data for α-5b**: mp 156-158 °C: UV(H_2O)λ_{max} 270nm; ^{1}H NMR (DMSO-d_6) δ 11.36 (1H, br s, 3-NH), 7.43 (1H, s, H-6), 6.53 (1H, s, H-1'), 5.85 (1H, d, 3'-OH, J = 5.9 Hz), 5.37 (1H, d, 2'-CH_2a, J = 2.0 Hz), 5.02 (1H, t, 5'-OH, J = 5.1 Hz), 4.96 (1H, br s, 2'-CH_2b), 4.30 (1H, br s, H-3'), 3.79-3.81 (1H, m, H-5'a), 3.42-3.47 (2H, m, H-4', 5'b), 2.23 (2H, q, -$\underline{CH_2}CH_3$, J = 7.3 Hz), 1.02 (3H, t, 5-$CH_2\underline{CH_3}$, J = 7.6 Hz); FAB-MS m/z 285 (M^++H). Anal. Calcd. for $C_{12}H_{16}N_2O_4S$•0.25H_2O: C, 49.90; H, 5.76; N, 9.70. Found: C, 49.91; H, 5.75; N, 9.36.

5-Ethyl-1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)uracil (β-5b). Compound β-**5b** (72 mg, 0.14 mmol, d.e.= 74%) was obtained by the method

described above. After silica gel column chromatography, the residue was further purified by HPLC (silica gel, 5% MeOH in $CHCl_3$) to give α-**5b** (13 mg, 28%, crystallized from MeOH) and β-**5b** (28 mg, 62%, foam). **Data for β-5b**: UV(H_2O)λ_{max} 270nm; ^{1}H NMR (DMSO-d_6) δ 11.38 (1H, br s, 3-NH), 7.77 (1H, s, H-6), 6.59 (1H, s, H-1'), 5.65 (1H, d, 3'-OH, J = 4.9 Hz), 5.34 (1H, s, 2'-CH_2a), 5.17 (1H, t, 5'-OH, J = 5.1 Hz), 5.02 (1H, br s, 2'-CH_2b), 4.54 (1H, br t, H-3' J = 4.6 Hz), 3.54-3.60 (2H, m, H-5'a, b), 3.13-3.21 (1H, m, H-4'), 2.21 (2H, q, -$\underline{CH_2}CH_3$, J = 7.6 Hz), 1.00 (3H, t, 5-$CH_2\underline{CH_3}$, J = 7.3 Hz); NOE, irradiate H-6, observe H-3' (6.4%); irradiate H-4', observe H-1' (2.1%); FAB-MS m/z 285 (M^++H). Anal. Calcd. for $C_{12}H_{16}N_2O_4S$•0.7H_2O: C, 48.54; H, 5.91; N, 9.43. Found: C, 48.80; H, 6.04; N, 9.03.

5-(2-Hydroxyethyl)-1-(2-deoxy-2-*C*-methylene-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-9c). From **8** (490 mg, 1.2 mmol), α,β-**9c** were obtained as described in the synthesis of α,β-**9a**. The residue was purified on a silica gel column (2% MeOH in $CHCl_3$) to afford α,β-**9c** (365 mg, 56%, α/β = 1.5, foam). **Data for α,β-9c**: ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, br s, 3-NH), 8.20 (1H, br s, 3-NH), 7.52 (1H, s, H-6), 7.25 (1H, s, H-6), 6.73 (1H, s, H-1'), 6.54 (1H, d, H-1', J = 1.5 Hz), 5.46-5.50 (3H, m, 2'-CH_2), 4.89 (1H, t, 2'-CH_2, J = 2.2 Hz), 4.78 (1H, d, H-3', J = 8.3 Hz), 4.64 (1H, d, H-3', J = 10.0 Hz), 4.15-4.19 (1H, m, H-5'a), 3.91-3.97 (1H, m, H-5'a), 3.72-3.79 (2H, m, H-5'b), 3.28-3.31 (1H, m, H-4'), 3.15-3.18 (1H, m, H-4'), 2.60-2.63 (4H, m, 5-$\underline{CH_2}CH_2OH$), 2.50-2.56 (4H, m, 5-$CH_2\underline{CH_2}OH$), 2.41 (1H, br t, 5-$CH_2CH_2\underline{OH}$), 2.29 (1H, br t, 5-$CH_2CH_2\underline{OH}$), 1.00-1.13 (56H, m, 3', 5'-*O*-TIPDS); FAB-MS m/z 543 (M^++H).

5-(2-Hydroxyethyl)-1-(2-deoxy-2-*C*-methylene-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-5c). Compound α,β-**9c** (222 mg, 0.40 mmol) was deblocked as described in the synthesis of α,β-**5a** The residue was purified on a silica gel column (5-9% MeOH in $CHCl_3$). Crystallization of the residue from acetone gave α-**5c** (35 mg, 29%, d.e.= 88%; judged from HPLC). After the filtrate was concentrated, β-**5c** was obtained as a crystalline form (19 mg, 16%, d.e. = 71%). **Data for α-5c**: mp 178-180 °C; UV(H_2O)λ_{max} 271nm; ^{1}H NMR (DMSO-d_6) δ 11.37 (1H, br s, 3-NH), 7.43 (1H, s, H-6), 6.53 (1H, s, H-1'), 5.83 (1H, d, 3'-OH, J = 5.9 Hz), 5.36 (1H, d, 2'-CH_2a, J = 2.0 Hz), 5.03 (1H, br t, 5'-OH, J = 5.1 Hz), 4.95 (1H, t, 2'-CH_2b, J = 2.0 Hz), 4.55 (1H, t, 5-$C_2H_4\underline{OH}$, J = 5.4 Hz), 4.28 (1H, br s, H-3'), 3.82-3.86 (1H, m, H-5'a), 3.40-3.49 (4H, m, 5-$CH_2\underline{CH_2}OH$, H-4', 5'b), 2.36 (2H, t, 5- $\underline{CH_2}CH_2OH$, J = 6.3 Hz); NOE, irradiate H-3', observe H-1' (4.3%); FAB-MS m/z 301 (M^++H). Anal. Calcd. for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 47.77; H, 5.32; N, 9.30. **Data for β-5c**: mp 137-138 °C; UV(H_2O)λ_{max} 271nm; ^{1}H NMR (DMSO-d_6) δ 11.39 (1H, br s, 3-NH), 7.43 (1H, s, H-6), 6.59 (1H, s, H-1'), 5.65 (1H, d, 3'-OH, J = 5.4 Hz), 5.35 (1H, s, 2'-CH_2a),

5.14 (1H, t, 5'-OH, J = 5.4 Hz), 5.05 (1H, s, 2'-CH_2b), 4.54 (2H, t, 5-CH_2CH_2OH J = 4.6 Hz), 3.54-3.62 (2H, m, H-5'a,b), 3.41-3.49 (2H, m, 5-CH_2CH_2OH), 3.15-3.18 (1H, m, H-4'), 2.36 (2H, dd, 5- CH_2CH_2OH, J = 6.8, 7.2 Hz); FAB-MS m/z 301 (M^++H). Anal. Calcd. for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33. Found: C, 48.03; H, 5.56; N, 9.27.

5-(*E*)-(2-Bromovinyl)-1-(2-deoxy-2-*C*-methylene-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-9d). Bistrimethylsilyl acetamide (0.93 mL, 3.76 mmol) was added to a suspension of 5-bromovinyluracil (408 mg, 1.88 mmol) in 1,2-dichloroethane (10 mL). The mixture was kept under reflux for 3.5 h. After the resulted solution was cooled to room temperature, a solution of **8** (272 mg, 0.6 mmol) in 1,2-dichloroethane (3 mL) and triethylamine (60 μL, 0.43 mmol) were added to this solution. Then, TMSOTf (120 μL, 0.62 mmol) was added dropwise to the solution at 0°, and the mixture was stirred at 0 °C overnight. The reaction was quenched with saturated sodium bicarbonate solution, and the precipitated materials were removed by Celite filtration. The filtrate was diluted with $CHCl_3$, and washed with water and brine, then dried (Na_2SO_4). After the solvent was evaporated, the residue was purified on a silica gel column (6-9% AcOEt in hexane) to give α-**9d** (124 mg, 33% crystallized from hexane-AcOEt) and β-**9d** (85 mg, 22.4%, foam). **Data for α-9d**: mp 96-98 °C; ^{1}H NMR ($CDCl_3$) δ 8.69 (1H, s, 3-NH), 7.43 (1H, d, 5-CH=CH-Br, J = 13.2 Hz), 7.29 (1H, s, H-6), 6.74 (1H, s, H-1'), 6.73 (1H, d, 5-CH=CH-Br, J = 13.7 Hz), 5.49 (1H, t, 2'-CH_2a, J = 2.4 Hz), 4.88 (1H, t, 2'-CH_2b, J = 2.4 Hz), 4.65 (1H, dd, H-3', J = 1.0, 9.8 Hz), 4.18 (1H, dd, H-5'a, J = 2.9, 12.7 Hz), 3.94 (1H, dd, H-5'b, J = 2.4, 12.7 Hz), 3.28-3.31 (1H, m, H-4'), 0.88-1.16 (28H, m, 3',5'-*O*-TIPDS); FAB-MS: m/z 603 (M^++H), 605 (M^++H). Anal. Calcd. for $C_{24}H_{39}BrN_2O_5SSi_2$•0.25$H_2O$: C, 47.39; H, 6.55; N, 4.61. Found : C, 47.19; H, 6.50; N, 4.49. **Data for β-9d**: ^{1}H NMR ($CDCl_3$) δ 8.42 (1H, s, 3-NH), 7.69 (1H, s, H-6), 7.39 (1H, d, 5-CH=CH-Br, J = 13.7 Hz), 6.58 (1H, d, 5-CH=CH-Br, J = 13.7 Hz), 6.52 (1H, s, H-1'), 5.49 (2H, s, 2'-CH_2), 4.75 (1H, d, H-3', J = 9.8 Hz), 4.17 (1H, dd, H-5'a, J = 3.2, 12.9 Hz), 3.97 (1H, dd, H-5'b, J = 1.5, 12.7 Hz), 3.17 (1H, br d, H-4', J = 9.8 Hz), 0.88-1.16 (28H, m, 3',5'-*O*-TIPDS); FAB-MS: m/z 603 (M^++H), 605 (M^++H).

5-(*E*)-(2-Bromovinyl)-1-(2-deoxy-2-*C*-methylene-4-thio-α-D-*erythro*-pentofuranosyl)uracil (α-5d). Compound α-**9d** (106 mg, 0.18 mmol) was deblocked as described in the synthesis of α,β-**5a**. The residue was purified on a silica gel column (3-5% MeOH in $CHCl_3$), and crystallization of the residue from MeOH gave α-**5d** (58 mg, 92%). **Data for α-5d**: mp 192-193 °C (dec.): UV(H_2O)λ_{max} 251nm, 296nm; ^{1}H NMR (DMSO-d_6) δ 11.67 (1H, br s, 3-NH), 7.89 (1H, s, H-6), 7.30 (1H, d, 5-CH=CHBr, J = 13.7 Hz), 6.98 (1H, d, 5-CH=CHBr, J = 13.7 Hz), 6.53 (1H, s, H-1'), 5.84 (1H, br d, 3'-

OH, J = 5.9 Hz), 5.36 (1H, t, 2'-CH_2a, J = 2.0 Hz), 4.99-5.02 (2H, m, 2-CH_2b, 5'-OH), 4.26-4.30 (1H, m, H-3'), 3.84-3.89 (1H, m, H-5'a), 3.53-3.58 (1H, m, H-4'), 3.43-3.49 (1H, m, H-5'b); NOE, irradiate H-3', observe H-1' (4.5%); FAB-MS *m/z* 361 (M^++H), 363 (M^++H). Anal. Calcd for $C_{12}H_{13}BrN_2O_4S$: C, 39.90; H, 3.63; N, 7.76. Found: C, 39.97; H, 3.64; N, 7.39.

5-Bromovinyl-1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl)-uracil (β-5d). Compound β-**5d** (45 mg, 95.5%) was obtained by the method described above. **Data for β-5d**: mp 145-147 °C (crystallized from MeOH); UV(H_2O)λ_{max} 297nm, 251nm; ^{1}H NMR (DMSO-d_6) δ 11.69 (1H, br s, 3-NH), 7.89 (1H, s, H-6), 7.30 (1H, d, 5-CH=CHBr, J = 13.7 Hz), 7.00 (1H, d, 5-CH=CHBr, J = 13.7 Hz), 6.57 (1H, s, H-1'), 5.65 (1H, d, 3'-OH, J = 5.4 Hz), 5.36 (1H, s, 2'-CH_2a), 5.17 (1H, br t, 5'-OH), 5.12 (1H, s, 2'-CH_2b), 4.57 (1H, br t, H-3', J = 4.9 Hz), 3.69-3.71 (1H, m, H-5'a), 3.57-3.61 (1H, m, H-5'b), 3.17-3.20 (1H, m, H-4'); FAB-MS *m/z* 361 (M^++H), 363 (M^++H). Anal. Calcd. for $C_{12}H_{13}BrN_2O_4S$: C, 39.90; H, 3.63; N, 7.76. Found: C, 39.79; H, 3.73; N, 7.65.

5-Iodo-1-(2-deoxy-2-*C*-methylene-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-9e). From **8** (490 mg, 1.2 mmol), α,β-**9e** were obtained as described in the synthesis of α,β-**9d**. The residue was purified on a silica gel column (17-50% AcOEt in hexane) to give α-**9e** (259 mg, 16%, crystallized from hexane-AcOEt) and β-**9e** (185 mg, 11%, crystallized from hexane-AcOEt). **Data for α-9e**: mp 92-94 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, s, 3-NH), 7.74 (1H, s, H-6), 6.69 (1H, s, H-1'), 5.51 (1H, t, 2'-CH_2a, J = 2.4 Hz), 4.91 (1H, t, 2'-CH_2b, J = 2.4 Hz), 4.65 (1H, d, H-3', J = 9.7 Hz), 4.18 (1H, dd, H-5'a, J = 2.9, 12.7 Hz), 3.94 (1H, dd, H-5'b, J = 2.2, 12.9 Hz), 3.30-3.33 (1H, m, H-4'), 1.00-1.13 (28H, m, 3',5'-*O*-TIPDS); FAB-MS *m/z* 625 (M^++H). Anal. Calcd. for $C_{22}H_{37}IN_2O_5SSi_2 \cdot 1.5H_2O$: C, 40.55; H, 6.19; N, 4.30. Found : C, 40.37; H, 5.82; N, 4.26. **Data for β-9e**: mp 106-107 °C ; ^{1}H NMR ($CDCl_3$) δ 8.52 (1H, s, 3-NH), 8.00 (1H, s, H-6), 6.44 (1H, d, H-1', J = 1.0 Hz), 5.55 (1H, t, 2'-CH_2a, J = 1.2 Hz), 5.49 (1H, t, 2'-CH_2b, J = 1.2 Hz), 4.74 (1H, dd, H-3', J = 1.5, 9.8 Hz), 4.14-4.19 (1H, m, H-5'a), 3.95 (1H, dd, H-5'b, J = 1.5, 12.7 Hz), 3.14-3.17 (1H, m, H-4'), 0.99-1.18 (28H, m, 3',5'-*O*-TIPDS); FAB-MS *m/z* 625 (M^++H). Anal. Calcd. for $C_{22}H_{37}IN_2O_5SSi_2$: C, 42.30; H, 5.97; N, 4.48. Found : C, 42.41; H, 6.05; N, 4.42.

5-Iodo-1-(2-deoxy-2-*C*-methylene-4-thio-α-D-*erythro*-pentofuranosyl)uracil (α-5e). Compound α-**9e** (180 mg, 0.29 mmol) was deblocked as described in the synthesis of α,β-**5a**. The residue was purified on a silica gel column (13% MeOH in $CHCl_3$), and crystallization of the residue from MeOH gave α-**5e** (106 mg, 96%). **Data for α-5e**: mp 184-185 °C (dec.); UV(H_2O)λ_{max} 290nm; ^{1}H NMR (DMSO-d_6) δ 11.77 (1H, br s, 3-

NH), 8.08 (1H, s, H-6), 6.46 (1H, s, H-1'), 5.84 (1H, br d, 3'-OH, J = 5.9 Hz), 5.40 (1H, s, 2'-CH_2a), 5.11 (1H, s, 2'-CH_2b), 5.02 (1H, t, 5'-OH, J = 5.1 Hz), 4.32 (1H, br t, H-3', J = 6.4 Hz), 3.68-3.72 (1H, m, H-5'a), 3.37-3.49 (2H, m, H-4', 5'b); NOE, irradiate H-3', observe H-1' (3.1%); FAB-MS *m/z* 383 (M^++H). Anal. Calcd. for $C_{10}H_{11}IN_2O_4S$: C, 31.43; H, 2.90; N, 7.33. Found: C, 31.45; H, 2.77; N, 7.38.

5-Iodo-1-(2-deoxy-2-*C*-methylene-4-thio-β-D-*erythro*-pentofuranosyl) uracil (β-5e). Compound β-**5e** (88 mg, 86%) was obtained by the method described above. **Data for β-5e**: mp 152-153 °C: UV(H_2O)λ_{max} 291nm; ^{1}H NMR (DMSO-d_6) δ 11.78 (1H, br s, 3-NH), 8.10 (1H, s, H-6), 6.50 (1H, s, H-1'), 5.67 (1H, d, 3'-OH, J = 4.9 Hz), 5.34 (1H, s, 2'-CH_2a), 5.25 (1H, t, 5'-OH, J = 5.3 Hz), 5.11 (1H, s, 2'-CH_2b), 4.53 (1H, br t, H-3', J = 4.9 Hz), 3.57-3.60 (2H, m, H-5'a,b), 3.16-3.17 (1H, m, H-4'); FAB-MS *m/z* 383 (M^++H). Anal. Calcd. for $C_{10}H_{11}IN_2O_4S$: C, 31.43; H, 2.90; N, 7.33. Found: C, 31.42; H, 2.95; N, 7.30.

5-Chloroethyl-1-(2-deoxy-2-*C*-methylene-4-thio-α and β-D-*erythro*-pentofuranosyl)uracil (α,β-5f). Triphenylphosphine (312 mg, 1.18 mmol) was added to a solution of α,β-**5c** (180 mg, 0.59 mmol) in DMF (10 mL). The mixture was stirred for 20 min, then, pyridine (172 μL, 2.12 mmol) and carbon tetrachloride (86 μL, 0.89 mmol) were added. The mixture was stirred at room temperature overnight. Triphenylphosphine (187 mg, 0.71 mmol), carbon tetrachloride (52 μL, 0.16 mmol), and pyridine (104 μL, 1.28 mmol) were added further to the mixture. After stirring at room temperature overnight, the reaction was quenched with 1-butanol. The solvents were removed under reduced pressure. The residue was purified on a silica gel column (5% MeOH in $CHCl_3$). The anomeric mixture was purified by HPLC (YMC-Pack SIL-06, 20×250 mm, YMC Co., Ltd. Japan, hexane:dichloromethane:ethanol = 10:20:3, flow-rate: 9.0 mL/min) to give α-**5f** (82 mg, 43%, crystallized from MeOH) and β-**5f** (40 mg, 21%, crystallized from MeOH). **Data for α-5f**: mp 92-94 °C: UV(H_2O)λ_{max} 288nm; ^{1}H NMR (DMSO-d_6) δ 11.52 (1H, br s, 3-NH), 7.59 (1H, s, H-6), 6.53 (1H, s, H-1'), 5.85 (1H, d, 3'-OH, J = 5.9 Hz), 5.36 (1H, t, 2'-CH_2a, J = 2.2 Hz), 5.02 (1H, t, 5'-OH, J = 4.4 Hz), 4.93 (1H, t, 2'-CH_2b, J = 2.0 Hz), 4.28 (1H, br t, H-3', J = 6.6 Hz), 3.84-3.87 (1H, m, H-5'a), 3.67-3.72 (2H, m, 5-$CH_2\underline{CH_2}Cl$), 3.46-3.51 (2H, m, H-4', 5'b), 2.69 (2H, t, 5- $\underline{CH_2}CH_2Cl$, J = 6.8 Hz); FAB-MS *m/z* 319 (M^++H). Anal. Calcd. for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.74; N, 8.79. Found: C, 45.44; H, 4.79; N, 8.63. **Data for β-5f**: mp 104-105 °C: UV(H_2O)λ_{max} 270nm; ^{1}H NMR (DMSO-d_6) δ 11.54 (1H, br s, 3-NH), 7.58 (1H, s, H-6), 6.58 (1H, s, H-1'), 5.67 (1H, d, 3'-OH, J = 5.4 Hz), 5.36 (1H, s, 2'-CH_2a), 5.16 (1H, t, 5'-OH, J = 5.6 Hz), 5.05 (1H, s, 2'-CH_2b), 4.56 (1H, br t, H-3'), 3.66-3.71 (2H, m, 5-$CH_2\underline{CH_2}Cl$), 3.60-3.64 (2H, m, H-5'a), 3.52-3.57 (1H, m, H-5'b), 3.14-3.19 (1H, m, H-4'), 2.70 (2H, dt, 5- $CH_2\underline{CH_2}Cl$, J = 7.1, 21.5 Hz);

FAB-MS *m/z* 319 (M^++H). Anal. Calcd for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.74; N, 8.79. Found: C, 44.97; H, 4.76; N, 8.56.

Antiviral Assays. HEL cells and the following virus strains were used: HSV-1 VR-3 strain, HSV-2 MS strain, VZV Oka strain, and HCMV AD 169 strain. Antiviral activities against these herpesviruses were determined by the plaque reduction assay as described earlier.[3,10]

Cell Growth Inhibition Assays. Anti-cell proliferative activities against CCRF-HSB-2 and KB-cells were assayed by the method described earlier. Anti-cell proliferative activity of the test compounds against CCRF-HSB-2 were evaluated by MTT method.[10,12] Cell growth inhibition against KB cells were assessed by dye uptake method.[11,13]

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