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Synthesis and Biological Activity of a Series of Methylene-Expanded Oxetanocin Nucleoside Analogues

Michael E. Jung[1,*], **Akemi Toyota**[1], **Erik de Clercq**[2], and **Jan Balzarini**[2]

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095-1569, USA
[2] Rega Institute, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Summary. A series of methylene-expanded oxetanocin nucleoside analogues, *e.g.* analogues of **2** and the known antiviral nucleosides *AZT*, *FLT*, and *ddC* (**3**) were prepared by a very direct route beginning with the readily available (*S*)-glycidol **4** and proceeding *via* the dihydrofuran-3-methanols **9a**,**b**. Biological testing of these modified nucleosides indicates that they are non-cytotoxic compounds with generally weak antiviral activity. However, the guanosine analogue **2G** showed pronounced activity *vs*. herpes simplex virus type 1 (HSV-1) in cell culture and was HSV-1-encoded thymidine kinase dependent. This compound is therefore an interesting new lead structure for the development of new anti-HSV agents.

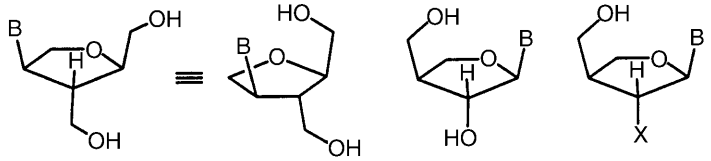
Keywords. Nucleoside synthesis; Anhydro nucleosides; Cyclic stereocontrol; Alkoxyepoxide chemistry; Antiviral evaluation; Anti-HSV-1 activity.

Introduction

In the search for ever more potent and selective agents for antiviral therapy, scientists have turned more and more towards modified nucleosides since many such compounds have quite good antiviral activity [1]. In the last several years, nucleosides with abnormal structures, *e.g. L*-nucleosides, isonucleosides, α-nucleosides, oxetanocins, cyclopropyl nucleosides, acyclic nucleosides, *etc*. have been shown to be very useful antiviral agents [2]. For quite some time now we have been interested in the synthesis of potentially antiviral modified nucleosides of several different structural classes and have developed some new efficient synthetic methods for their preparation [3]. For example, we have published a general synthesis of several methylene-expanded oxetanocin isonucleosides (**1**) in which a methylene group was inserted between the ring oxygen and the carbon bearing the base. One of these – the thymidine analogue **1a** – showed moderate anti-HIV activity in the anti-HIV drug testing system of the National Cancer Institute ($IC_{50} > 2 \times 10^{-4}\,M$, $EC_{50} = 8 \times 10^{-7}\,M$, $TI_{50} > 250$) [3g]. Recently, we have reported on a very efficient synthesis of a different class of methylene-expanded oxetanocin analogues

* Corresponding author. E-mail: jung@chem.ucla.edu

(**2**) in which the methylene group is inserted between the oxygen and the carbon bearing the hydroxymethyl group [4]. We have also described the synthesis of several modified nucleosides in this class containing azido, fluoro, or hydrido groups in place of the secondary hydroxyl (**3**) [4]. We now report the full details of this synthesis and the results of the testing of these new modified nucleosides, which identified the guanosine analogue **2G** as an interesting new lead structure for an anti-herpes agent.

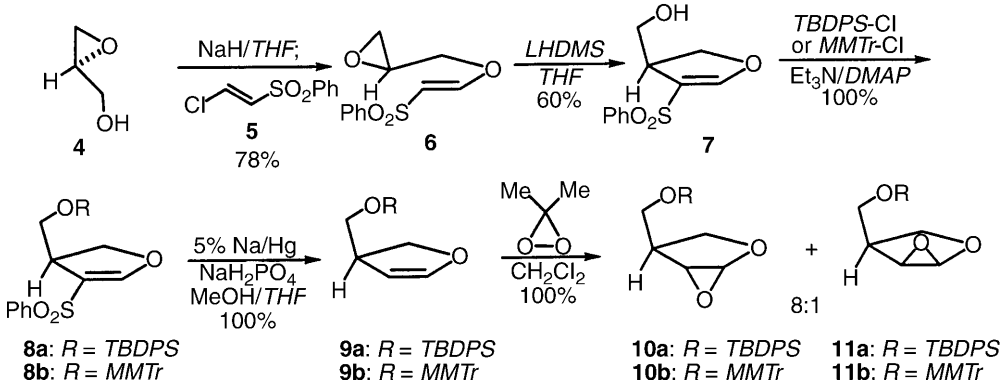


1 (**1a**: *B* = *Th*) **2** **3**

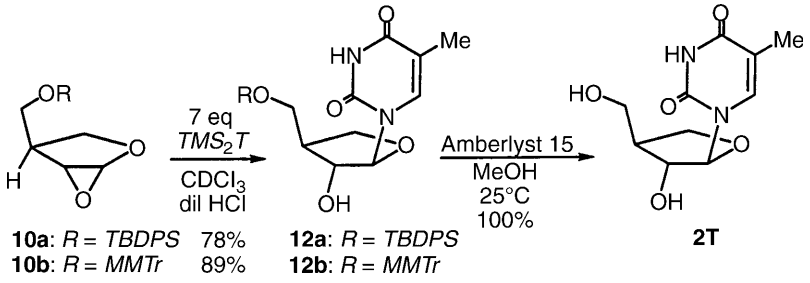
Results and Discussion

Synthesis

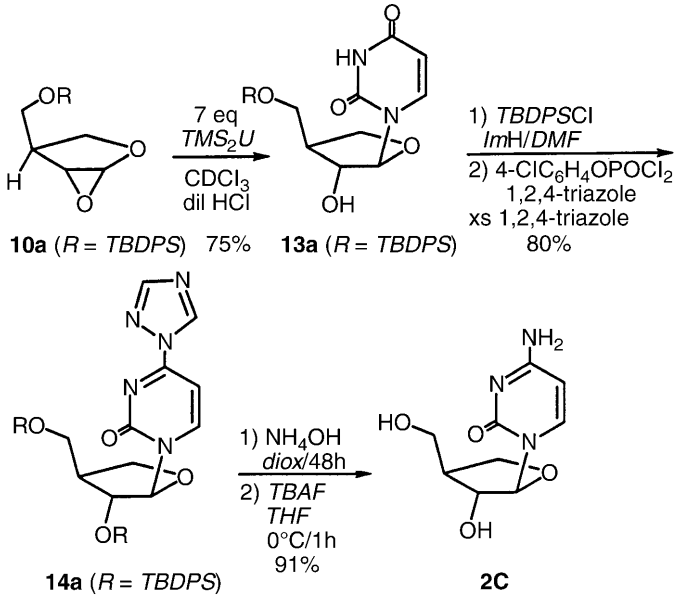
Our *de novo* synthesis of these important modified nucleosides uses a novel approach in which all of the asymmetry required is derived from the inexpensive precursor (*S*)-glycidol (**4**). *Sharpless* asymmetric epoxidation of allyl alcohol using *D*-(+)-*DIPT* and cumyl hydroperoxide afforded (*S*)-glycidol **4** in 43% yield and > 90% *ee* [5] (Scheme 1). This compound has been prepared in very large scale by an industrial application of this process [6]. Treatment of the anion of **4** with 2-chloroethenyl phenyl sulfone (**5**; prepared in three steps and 82% overall yield from 1,1,2-trichloroethane [7]) afforded the addition-elimination product **6** in 78% yield [7]. Treatment of **6** with *LHMDS* gave in 60% yield the cyclized product **7**, the alcohol function of which was protected as either the *tert*-butyldiphenylsilyl (*TBDPS*) or monomethoxytrityl (*MMTr*) ether, **8a**,**b**, in quantitative yield. Sodium amalgam reduction gave the desired enol ethers **9a**,**b** also quantitatively. Epoxidation with dimethyl dioxirane gave the epoxides **10a**,**b** as the major isomers in an 8:1 ratio with the opposite diastereomers **11a**,**b** in quantitative yield. These two key



Scheme 1

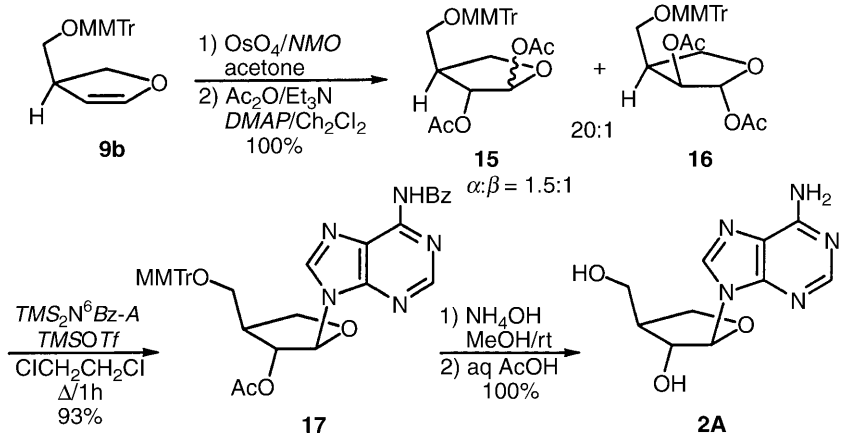


Scheme 2

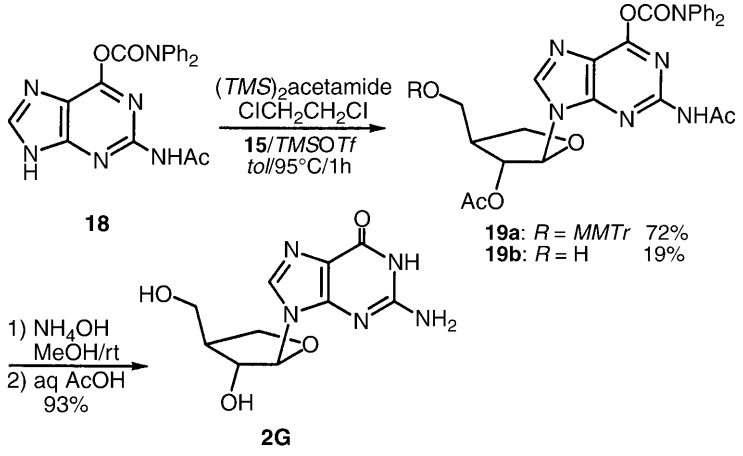


Scheme 3

compounds were then converted into the desired modified nucleosides as shown in Schemes 2–5. Both of the ethers **10a**,**b** could be opened with excess *bis*-silylated thymine to give in good yields the protected nucleoside analogues **12a**,**b**, the latter of which could be hydrolyzed to give **2T** in quantitative yield (Scheme 2). The cytidine analogue **2C** could also be prepared by treatment of the epoxide **10a** with excess *bis*-silylated uracil to give the protected nucleoside analogue **13a** in 75% yield (Scheme 3). Protection of the secondary alcohol as the *TBDPS* ether and conversion of the amide into the triazole afforded the *bis*-silyl ether triazole **14a** in 80% yield. Final conversion to the cytosine ring and deprotection of both silyl ethers gave the cytidine analogue **2C** in 91% yield. The purine analogues were prepared by a different route, again starting with the enol ether **9b** (Scheme 4). Dihydroxylation using catalytic amounts of osmium tetroxide and *NMO* followed by acetylation gave a quantitative yield of a 20:1 ratio of the two isomeric diacetates **15**, as a 1.5:1 mixture of α and β anomers, and **16** as only the α-anomer. Reaction of this mixture with the N^6-benzoyl *bis*-silylated adenine in the presence of trimethylsilyl triflate (*TMSOTf*) afforded in 93% yield the desired β anomer **17** which was debenzoylated and then deprotected to give the adenosine analogue **2A**.



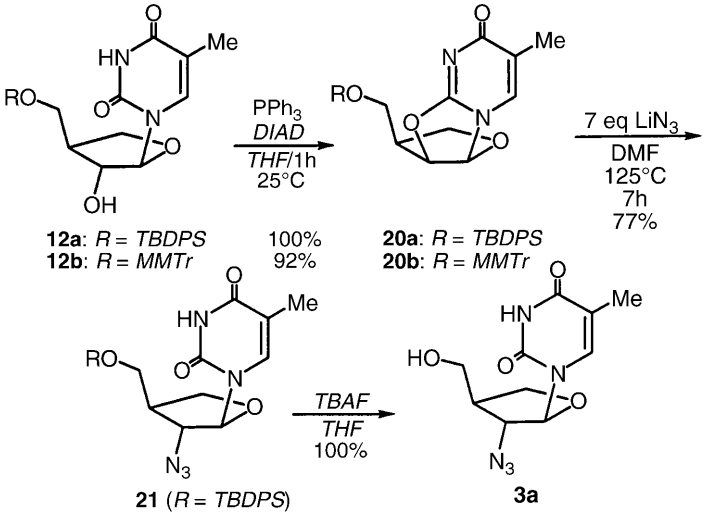
Scheme 4



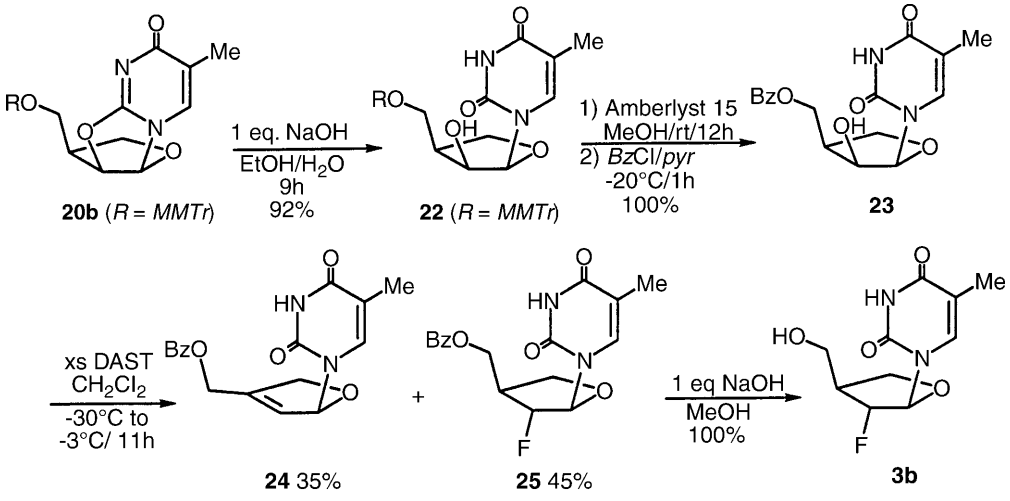
Scheme 5

Finally, a similar route afforded the guanosine analogue (Scheme 5). Thus, the known carbamate **18** (prepared in two steps from guanine by acetylation followed by O-acylation with diphenylcarbamoyl chloride [8]) was *bis*-silylated using *bis*-(trimethylsilyl)-acetamide and then treated with the diacetate **15** and *TMSOTf* to give a mixture of the *MMTr* ether and the alcohol **19a**,**b** in yields of 72% and 19%, respectively. These compounds were both treated with ammonium hydroxide; then, the protecting groups were removed to give the guanosine analogue **2G**.

In addition to the simple analogues of the natural nucleosides, we also wished to prepare several analogues which resembled more closely well-known antiviral agents such as *AZT*, *FLT*, *ddC*, *etc*. Therefore, we decided to prepare compounds **3a**–**c** in which azido, fluoro, and hydrido groups replace the secondary hydroxyl group of the appropriate nucleosides. The syntheses of these compounds are shown in Schemes 6–8. Thus, an internal *Mitsunobu* reaction on the two protected thymidine analogues **12a**,**b** using diisopropyl azodicarboxylate (*DIAD*) afforded the 1′,2′-anhydronucleosides **20a**,**b** in excellent yield. Opening of the silyl ether

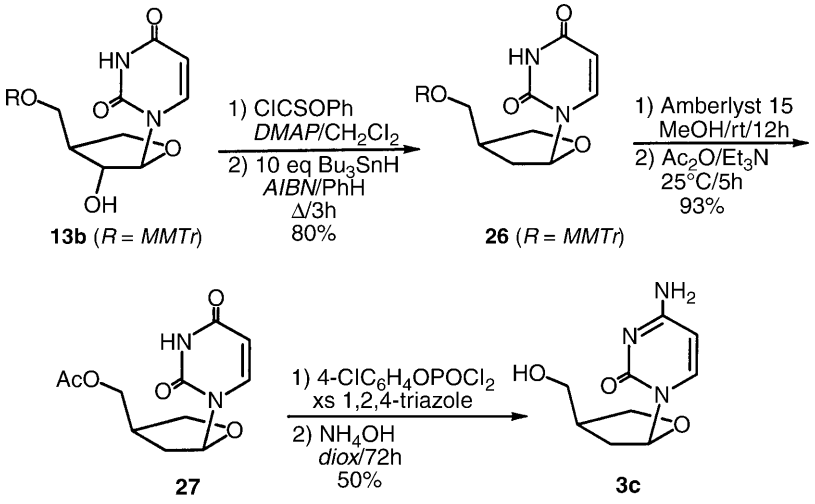


Scheme 6



Scheme 7

20a with excess lithium azide in *DMF* at 125°C furnished the azidothymidine **21** in 77% yield along with 17% recovered starting material. Cleavage the *TBDPS* protecting group afforded the desired *AZT* analogue **3a** quantitatively. The preparation of the fluoro analogue was somewhat more difficult since we were unable to achieve a clean opening of the 1′,2′-anhydronucleoside with fluoride ion (*e.g.* by using the method of *Green* and *Blum* [9]). Therefore, we had to use a longer but more certain route (Scheme 7). Basic hydrolysis of the anhydro nucleoside **20b** afforded the secondary alcohol of retained stereochemistry **22** in 92% yield. The protecting group on the primary alcohol was exchanged for a benzoate in two steps to give the alcohol **23**. Treatment of **23** with excess *DAST* gave 45% of the inverted fluoride **25** along with 33% of the elimination product **24**. The desired nucleoside



Scheme 8

analogue of *FLT* (**3b**) was then prepared in quantitative yield by basic hydrolysis of the benzoate of **25**.

The final target, the *ddC* analogue **3c**, was prepared as shown in Scheme 8. The monomethoxytrityl ether of the uridine analogue **13b** was deoxygenated by a *Barton–McCombie* procedure [10], *i.e.* by formation of the phenyl thionocarbonate and treatment with excess tributylstannane to give the deoxygenated compound **26** in 80% yield for the two steps. Exchange of the trityl protecting group for an acetate was effected in two steps and 93% yield to give the acetate **27**. Final transformation of the uridine to the cytidine *via* the standard triazole procedure gave the desired *ddC* analogue **3c** in 50% yield.

Testing

The synthetic modified nucleosides **2T**, **2C**, **2A**, **2G**, **3a**, and **3b** were subjected to extensive cytotoxicity and antiviral screening. In addition, some well known standard antiviral agents were also used as controls. The results of the testing is shown in Tables 1–3.

Table 1 gives the cytotoxicity and antiviral activity of the compounds in E_6SM cell cultures. Five viruses were included in the study: Herpes Simplex Virus type 1 (HSV-1), Herpes Simplex Virus type 2 (HSV-2), Vaccinia Virus, Vesicular Stomatitis Virus, and Thymidine Kinase-deficient Herpes Simplex Virus type 1 (HSV-1/TK$^-$ KOS-ACV^R). As Table 1 shows, only two of the synthetic compounds showed activity in these screens, the thymidine and guanosine analogues **2T** and **2G**, with the guanosine analogue being preferably active *vs.* HSV-1 and fivefold less so *vs.* HSV-2. Compound **2G** is inactive against the thymidine kinase deficient HSV-1 strain, implying that it must be phosphorylated by the virus-encoded thymidine kinase before showing antiviral activity. Even though this compound has significantly lower activity than BVDU, acyclovir (ACV), or

Table 1. Cytotoxicity and antiviral activity in E_6SM cell cultures

Compound	Minimum cytotoxic concentration[a] ($\mu g/cm^3$)	Minimum inhibitory concentration[b] ($\mu g/cm^3$)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus 2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK^-KOS ACV^R
2T	>400	9.6	>400	>400	>400	240
3a	≥ 400	>80	>80	>80	>80	240
3b	≥ 400	>80	>80	240	>80	240
2C	>400	240	>400	240	>400	240
2A	≥ 400	>80	>80	240	>80	240
2G	≥ 400	1.9	9.6	240	>400	240
BVDU	400	0.001	>80	0.026	>80	>80
Ribavirin	>400	240	240	48	48	240
ACV	400	0.077	0.128	>80	>80	48
GCV	>100	0.001	0.032	>100	>100	0.48

[a] Required to cause a microscopically detectable alteration of normal cell morphology; [b] required to reduce virus-induced cytopathogenicity by 50%

Table 2. Cytotoxicity and antiviral activity in Vero cell cultures

Compound	Minimum cytotoxic concentration[a] ($\mu g/cm^3$)	Minimum inhibitory concentration[b] ($\mu g/cm^3$)				
		Parainfluenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
2T	400	>80	>80	>80	>80	>80
3a	400	>80	>80	>80	>80	>80
3b	400	>80	>80	>80	>80	>80
2C	400	>80	>80	>80	>80	>80
2A	400	>80	>80	>80	>80	>80
2G	≥ 80	>16	>16	>16	>16	>16
BVDU	>400	>400	>400	>400	>400	>400
(S)-DHPA	≥ 400	400	48	>80	>80	>80
Ribavirin	>400	80	80	400	80	16

[a] Required to cause a microscopically detectable alteration of normal cell morphology; [b] required to reduce virus-induced cytopathogenicity by 50%

ganciclovir (GCV), its activity *vs.* HSV-1 is potent and selective enough to postulate that certain derivatives might have increased activity and perhaps be useful anti-herpes agents.

Table 2 lists the cytotoxicity and antiviral activity of the compounds in Vero cell cultures. Five RNA viruses were used: Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus. As Table 2 shows, all of the synthetic compounds were inactive in these evaluations at subtoxic

Table 3. Cytotoxicity and antiviral activity in HeLa cell cultures

Compound	Minimum cytotoxic concentration[a] ($\mu g/cm^3$)	Minimum inhibitory concentration[b] ($\mu g/cm^3$)		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
2T	400	>80	>80	>80
3a	400	>80	>80	>80
3b	400	>80	>80	>80
2C	400	>80	>80	>80
2A	400	>80	>80	>80
2G	400	>80	>80	>80
BVDU	≥ 400	>80	>80	>80
(*S*)-*DHPA*	≥ 400	>240	>400	>400
Ribavirin	≥ 400	9.6	240	16

[a] Required to cause a microscopically detectable alteration of normal cell morphology; [b] required to reduce a virus-induced cytopathogenicity by 50%

concentrations ($80\,\mu g/cm^3$ for **2G** and $\sim 400\,\mu g/cm^3$ for the other compounds). Also, the known standard antiviral agents (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), the (*S*)-enantiomer of 9-(2,3-dihydroxypropyl)-adenine (*DHPA*), and ribavirin were not markedly inhibitory.

Table 3 gives the cytotoxicity and antiviral activity of the compounds in HeLa cell cultures. As expected, these compounds show no activity *vs.* the *RNA* viruses Vesicular Stomatitis Virus, Coxsackie Virus B4, and Respiratory Syncytial Virus, as is the case also for the reference compounds *BVDU* and (*S*)-*DHPA*. Ribavirin showed modest antiviral activity.

Thus, the testing results indicate that four of the synthetic nucleoside analogues – **2C**, **2A**, **3a**, and **3b** – are inactive in all antiviral test systems. The thymidine analogue **2T** has weak antiviral activity *vs.* HSV-1. However, the major finding of the testing is that the guanosine analogue **2G** is reasonably active (*MIC* = 1.9–$9.6\,\mu g/cm^3$) *vs.* HSV-1 and HSV-2 with some selectivity *vs.* HSV-1 in E_6SM cell cultures. None of the compounds proved inhibitory against human immunodeficiency virus type 1 (HIV-1) (strain III_B) and type 2 (HIV-2) (strain ROD) in CEM cell cultures (data not shown). These data indicate that the compounds, particularly the fluoro- and azido-substituted **2T** derivatives, were not efficiently recognized by cellular nucleos(t)ide kinases and/or are not inhibitory against HIV-reverse transcriptase, the antiviral target for the triphosphates of AZT and FLT.

Conclusions

Efficient *de novo* syntheses of a series of methylene-expanded oxetanocin nucleoside analogues – **2C**, **2A**, **2T**, **2G**, **3a**, **3b**, and **3c** – beginning with (*S*)-glycidol **4** are reported. Evaluation of these compounds in cell cultures indicates that the guanosine analogue **2G** is reasonably inhibitory against herpes simplex virus. This compound is an interesting new lead structure for the development of new anti-HSV agents.

Experimental

(R)-2-((2-Phenylsulfonyl)-ethenyloxymethyl)-oxirane (**6**; $C_{11}H_{12}O_4S$)

To a stirred suspension of sodium hydride (60% in oil dispersion, 465 mg, 10.7 mmol) in *THF* (5.5 cm^3), a solution of (*S*)-glycidol (**4** [5]; 660 mg, 8.91 mmol) in *THF* (5.5 cm^3) was added at −23°C, and the mixture was stirred for 30 min at the same temperature. To the mixture was added a solution of (*E*)-chlorovinyl phenyl sulfone (**5** [7]; 2.16 g, 10.7 mmol) in *THF* (11 cm^3), and the stirred mixture was gradually warmed to 0°C over 1 h. After the reaction was quenched with sat. aq. NH_4Cl (11 cm^3), the mixture was extracted with diethyl ether (3 × 15 cm^3) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the epoxy vinyl ether **6** (1.68 g, 78%).

$[\alpha]_D^{23} = -12.0°$ ($c = 0.6$, $CHCl_3$); IR (neat): $\nu = 3200$, 1636, 1615, 1450, 1306, 1217, 1144, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.64$ (1H, dd, $J = 4.8$ and 2.6 Hz), 2.84 (1H, dd, $J = 4.8$ and 4.3 Hz), 3.22 (1H, m), 3.72 (1H, dd, $J = 11.6$ and 6.1 Hz), 4.17 (1H, dd, $J = 11.6$ and 2.5 Hz), 5.77 (1H, d, $J = 12.2$ Hz), 7.50 (2H, m), 7.57 (1H, d, $J = 12.2$ Hz), 7.57 (1H, m), 7.85 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.16$ (CH of epoxy), 49.25 (CH_2 of epoxy), 72.32 (CH_2O-vinyl), 107.80 (CHS), 126.93 (2C of Ph), 129.21 (2C of Ph), 132.94 (1C of Ph), 142.24 (C-S), 160.36 (vinyl CH–O) ppm.

(3S)-4-Phenylsulfonyl-2,3-dihydrofuran-3-methanol (**7**; $C_{11}H_{12}O_4S$)

To a solution of **6** (1.17 g, 4.87 mmol) in *THF* (28 cm^3), *LHMDS* (1 *M* in hexane, 5.75 cm^3) was added at −78°C, and the stirred mixture was gradually warmed to 0°C over 30 min. After the reaction was quenched with sat. aq. $(NH_4)_2SO_4$ (23 cm^3), the mixture was extracted with AcOEt (3 × 15 cm^3) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the dihydrofuran **7** (697 mg, 60%).

$[\alpha]_D^{20} = +48.0°$ ($c = 1.6$, $CDCl_3$); IR (neat): $\nu = 3522$, 1605, 1447, 1304, 1125, 1073, 1038, 727, 688 cm^{-1}; (400 MHz, ^{1}H NMR, $CDCl_3$): $\delta = 2.64$ (1H, t, $J = 7$ Hz, OH), 3.16 (1H, m), 3.68 (1H, ddd, $J = 11.6$, 7 and 5.1 Hz), 3.77 (1H, ddd, $J = 11.7$, 7 and 4.2 Hz), 4.49 (1H, dd, $J = 9.6$ and 7.3 Hz), 4.66 (1H, dd, $J = 10.7$ and 9.6 Hz), 7.34 (1H, d, $J = 1.4$ Hz), 7.56 (2H, m), 7.64 (1H, m), 7.92 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.02$ (C4), 62.94 (CH_2OH), 77.42 (C5), 117.93 (C3), 127.21 (C3′ and C5′ of Ph), 129.39 (C2′ and C6′ of Ph), 133.41 (C4′ of Ph), 140.55 (C1′ of Ph), 159.53 (C2) ppm.

(3R)-3-(((4-Methoxyphenyl)-diphenylmethoxy)-methyl)-4-phenylsulfonyl-2,3-dihydrofuran (**8b**; $C_{31}H_{28}O_5S$)

To a solution of **7** (256 mg, 1.07 mmol) in CH_2Cl_2 (2.5 cm^3), triethylamine (0.19 cm^3, 1.4 mmol), *DMAP* (11 mg, 0.09 mmol), and 4-monomethoxy-trityl chloride (416 mg, 1.30 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 2 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 (3 × 15 cm^3) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 3:1) to give the monomethoxytrityl ether **8b** (548 mg, 100%).

$[\alpha]_D^{23} = +57.6°$ ($c = 0.5$, $CHCl_3$); IR (neat): $\nu = 1607$, 1510, 1447, 1306, 1252, 1144, 1073, 1034, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.95$ (1H, dd, $J = 9.4$ and 9.4 Hz), 3.23 (1H, m), 3.37 (1H, dd, $J = 9.4$ and 3.8 Hz), 3.81 (3H, s), 4.53 (1H, dd, $J = 9.6$ and 6 Hz), 4.65 (1H, dd, $J = 9.6$ and 9.6 Hz), 6.82 (2H, ddd, $J = 9.0$, 3.1 and 2.1 Hz), 7.18 (2H, ddd, $J = 9.0$, 3.1 and 2.1 Hz), 7.25–7.35 (10H, m), 7.32 (1H, d, $J = 1.4$ Hz), 7.42 (2H, m), 7.57 (1H, m), 7.71 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 42.07$ (C4), 55.26 (OCH_3), 64.21 (CH_2OH), 78.68 (C5), 86.64 (CAr_3), 113.13 (*ortho*-C × 2 of MeOAr), 118.00 (C3), 126.98 (Tr), 127.02 (Tr), 127.27 (C3′ and C5′ of PhS),

127.85 (2C of *Tr*), 127.87 (2C of *Tr*), 128.26 (2C of *Tr*), 128.32 (2C of *Tr*), 129.10 (C2′ and C6′ of PhS), 130.31 (2C of Tr), 132.95 (C4′ of PhS), 135.29 (*para*-C of MeOAr), 141.32 (C1′ of Ph), 144.12 (*meta*-C of MeOAr), 144.23 (*meta*-C of MeOAr), 158.63 (C–OMe), 158.79 (C2) ppm.

(3R)-3-(((4-Methoxyphenyl)-diphenylmethoxy)-methyl)-2,3-dihydrofuran (**9b**; $C_{25}H_{24}O_3$)

To a solution of **8b** (264 mg, 0.515 mmol) in MeOH (3.6 cm^3) *THF* (0.72 cm^3), $NaH_2PO_4 \cdot H_2O$ (808 mg, 5.86 mmol) and 5% Na–Hg (1.43 g, 3.11 mmol) were added at −25°C, and the stirred mixture was gradually warmed to +5°C over 45 min. After the mixture was extracted with hexane (3 × 10 cm^3) and hexane:ether = 5:1 (10 cm^3), the combined extracts were dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:ether = 5:1) to give the dihydrofuran **9b** (192 mg, 100%).

$[\alpha]_D^{23} = -61.0°$ ($c = 0.6$, $CHCl_3$); IR (neat): $\nu = 2950$, 1609, 1510, 1491, 1447, 1300, 1252, 1181, 1138, 1067, 1034, 831, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.00$ (1H, dd, $J = 8.5$ and 8.5 Hz), 3.16 (1H, dd, $J = 8.5$ and 5.6 Hz), 3.30 (1H, m), 3.81 (3H, s), 4.16 (1H, dd, $J = 9.5$ and 6.3 Hz), 4.40 (1H, dd, $J = 9.5$ and 9.5 Hz), 4.94 (1H, dd, $J = 2.5$ and 2.5 Hz), 6.36 (1H, dd, $J = 2.5$ and 2.2 Hz), 6.86 (2H, ddd, $J = 8.9$, 3.1 and 2.1 Hz), 7.18 (2H, ddd, $J = 9.0$, 3.1 and 2.1 Hz), 7.2–7.4 (8H, m), 7.47 (4H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 43.17$ (C4), 55.24 (OCH_3), 66.53 (CH_2OH), 73.13 (C5), 86.08 (CAr_3), 101.45 (C3), 113.09 (*ortho*-C × 2 of MeOAr), 126.88 (2C of Ph), 127.82 (4C of Ph), 128.46 (2C of Ph), 128.47 (2C of Ph), 130.40 (2C of Ph), 135.82 (*para*-C of MeOAr), 144.60 (*meta*-C of MeOAr), 144.70 (*meta*-C of MeOAr), 146.86 (C2), 158.55 (C–OMe) ppm.

5-Methyl-1-((1R,2R,3S)-tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**12b**; $C_{30}H_{30}N_2O_6$)

To a solution of **9b** (104 mg, 0.28 mmol) in CH_2Cl_2 (4 cm^3), dimethyl dioxirane (*ca.* 0.1 *M* solution in acetone, 3.5 cm^3) was added at −78°C, and the stirred mixture was gradually warmed to 0°C over 1 h. After removal of the solvent, the residue (the epoxide **10b**) was coevaporated with C_6H_6 and dissolved in $CDCl_3$ (1.5 cm^3). To the solution of the epoxide **10b** was added a solution of *bis*-silylated thymine (457 mg, 1.69 mmol) in $CDCl_3$ (0.2 cm^3), and the mixture was stirred at room temperature for 36 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1, 1:1, 1:2) to give the silyl ether (122 mg, 71%) and the alcohol **12b** (17 mg, 12%).

Silyl ether of **12b**: $[\alpha]_D^{20} = -2.4°$ ($c = 1.0$, $CDCl_3$); IR (neat): $\nu = 2957$, 1690, 1510, 1464, 1449, 1254, 1181, 1111, 1074, 872, 843, 706 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.03$ (9H, s), 1.77 (3H, s), 2.60 (1H, m), 3.10 (2H, d, $J = 6.4$ Hz), 3.80 (3H, s), 4.06 (1H, dd, $J = 9$ and 5.7 Hz), 4.35 (1H, m), 4.35 (1H, m), 5.62 (1H, d, $J = 3.8$ Hz), 6.82 (2H, m), 6.99 (1H, d, $J = 1$ Hz), 7.2–7.45 (12H, m), 8.26 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 0.04$ (*TMS*), 12.49 (5-Me), 47.32 (C3′), 55.24 (OCH_3), 62.51 (C4′), 71.25 (C2′), 77.47 (C5′), 86.55 (CAr_3), 93.02 (C1′), 110.69 (C5), 113.22 (*ortho*-C × 2 of MeOAr), 127.15 (2C of Ph), 127.94 (4C of Ph), 128.32 (4C of Ph), 130.25 (2C of Ph), 135.15 (C4), 135.46 (*para*-C of MeOAr), 144.03 (*meta*-C of MeOAr), 144.11 (*meta*-C of MeOAr), 150.63 (C6), 158.70 (C–OMe), 164.33 (C2) ppm.

To a solution of the above silyl ether (122 mg, 0.20 mmol) in MeOH (1.4 cm^3)/*THF* (0.6 cm^3), 1 *N* aq. HCl (0.002 cm^3) in MeOH (1 cm^3) was added at 0°C, and the stirred mixture was gradually warmed to room temperature over 30 min. After the reaction was neutralized with 1 *N* aq. NaOH (0.002 cm^3), the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the alcohol **12b** (103 mg, 100%).

$[\alpha]_D^{20} = +11.8°$ ($c = 1.0$, $CDCl_3$); IR (neat): $\nu = 3401$, 1694, 1510, 1468, 1252, 1181, 1089, 1034, 911, 831, 729 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.84$ (3H, s), 2.72 (1H, m), 3.11 (1H, dd, $J = 9.1$ and 7.3 Hz), 3.24 (1H, dd, $J = 9.1$ Hz and 5.8 Hz), 3.78 (3H, s), 3.97 (1H, dd, $J = 8.7$ and

7.7 Hz), 4.15 (1H, m), 4.36 (1H, dd, $J = 8.7$ and 7.7 Hz), 5.57 (1H, d, $J = 3.5$ Hz), 6.81 (2H, m), 7.16 (1H, d, $J = 1.1$ Hz), 7.2–7.45 (12H, m), 9.31 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.49$ (5-Me), 46.49 (C3′), 55.23 (OCH_3), 62.02 (C4′), 71.71 (C2′), 79.12 (C5′), 86.44 (CAr_3), 94.22 (C1′), 110.62 (C5), 113.17 (*ortho*-C × 2 of MeOAr), 127.05 (2C of Ph), 127.90 (4C of Ph), 128.29 (4C of Ph), 130.24 (2C of Ph), 134.55 (*para*-C of MeOAr), 135.25 (C4), 144.10 (*meta*-C of MeOAr), 144.20 (*meta*-C of MeOAr), 151.47 (C6), 158.62 (C–OMe), 164.25 (C2) ppm.

5-Methyl-1-((1R,2R,3S)-tetrahydro-2-hydroxy-3-hydroxymethyl-1-furanyl)-2,4 (1H,3H)-pyrimidinedione (**2T**; $C_{10}H_{14}N_2O_4$)

To a solution of **12b** (39 mg, 0.076 mmol) in MeOH (0.8 cm^3), Amberlyst 15-H (18 mg) was added at room temperature, and the mixture was stirred for 14 h. After filtration, the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (AcOEt:MeOH = 10:1) to give the thymidine analogue **2T** (19 mg, 100%).

$[\alpha]_D^{20} = -9.5°$ ($c = 0.4$, MeOH); IR (neat): $\nu = 3386$, 1696, 1480, 1267, 1100, 1070 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CD_3OD = 20:1): $\delta = 1.86$ (3H, d, $J = 0.9$ Hz), 2.48 (1H, m), 3.63 (2H, d, $J = 5.7$ Hz), 3.96 (1H, dd, $J = 8.7$ Hz and 8.3 Hz), 4.17 (1H, dd, $J = 6.6$ and 4.4 Hz), 4.23 (1H, dd, $J = 8.4$ and 8.3 Hz), 5.56 (1H, d, $J = 4.4$ Hz), 7.24 (1H, d, $J = 1.1$ Hz) ppm; ^{13}C NMR (50 MHz, CD_3OD): $\delta = 10.92$ (5-Me), 48.05 (C3′), 60.22 (C4′), 70.02 (C2′), 75.45 (C5′), 92.04 (C1′), 110.20 (C5), 136.91 (C4), 151.33 (C6), 165.01 (C2).

(3R)-3-((((1,1-Dimethylethyl)-diphenyl)-silyloxy)-methyl)-4-phenylsulfonyl-2,3-dihydrofuran (**8a**; $C_{27}H_{30}O_4SSi$)

To a solution of **7** (198 mg, 0.82 mmol) in CH_2Cl_2 (1.9 cm^3), triethylamine (0.14 cm^3, 1.0 mmol), *DMAP* (5 mg, 0.04 mmol), and *tert*-butyldiphenyl-silyl chloride (*TBDPS*Cl; 0.25 cm^3, 0.96 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 20 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 (3 × 12 cm^3) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 10:1) to give the *TBDPS* ether (376 mg, 96%).

$[\alpha]_D^{22} = +38.9°$ ($c = 0.55$, $CHCl_3$); IR (neat): $\nu = 2934$, 2860, 1605, 1472, 1447, 1429, 1316, 1306, 1144, 1113, 1034, 727, 704, 606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ (9H, s), 3.18 (1H, m), 3.57 (1H, dd, $J = 10.3$ and 8.3 Hz), 3.76 (1H, dd, $J = 10.3$ and 3.8 Hz), 4.59 (1H, dd, $J = 9.7$ and 9.7 Hz), 4.69 (1H, dd, $J = 9.6$ and 5.5 Hz), 6.82 (2H, ddd, $J = 9.0$, 3.1 and 2.1 Hz), 7.31 (1H, d, $J = 1.3$ Hz), 7.35–7.5 (8H, m), 7.5–7.6 (5H, m), 7.7–7.75 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.22$ (*t*-Bu), 26.84 (*t*-Bu), 43.91 (C4), 64.08 (CH_2OSi), 78.11 (C5), 117.92 (C3), 127.16 (C3′ and C5′ of PhS), 127.76 (Ph), 127.80 (Ph), 129.12 (C2′ and C6′ of PhS), 129.82 (Ph), 129.86 (Ph), 132.93 (Ph), 133.07 (C4′ of PhS), 133.26 (Ph), 135.57 (Ph), 141.45 (C1′ of Ph), 158.96 (C2) ppm.

5-Methyl-1-((1R,2R,3R)-tetrahydro-2-hydroxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**12a**; $C_{26}H_{32}N_2O_5Si$)

To a solution of **8a** (94.0 mg, 0.195 mmol) in MeOH (1.4 cm^3)/*THF* (0.28 cm^3), $NaH_2PO_4 \cdot H_2O$ (298 mg, 2.16 mmol) and 5% Na–Hg (528 mg, 1.15 mmol) were added at −30°C, and the stirred mixture was gradually warmed to +5°C over 1 h. After the mixture was extracted with hexane (3 × 5 cm^3), the combined extracts were dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:ether = 10:1) to give the dihydrofuran **9a** (66.0 mg, 100%).

To a solution of **9a** (66.0 mg, 0.195 mmol) in CH_2Cl_2 (2.8 cm^3), dimethyldioxirane (*ca.* 0.1 *M* solution in acetone, 2.3 cm^3) was added at −78°C, and the stirred mixture was gradually warmed to 0°C over 35 min. After removal of the solvent, the residue (the epoxide **10a**) was coevaporated with C_6H_6 and dissolved in $CHCl_3$ (0.8 cm^3). To the solution of **10a**, *bis*-silylated thymine (281 mg, 1.04 mmol) in $CDCl_3$ (0.2 cm^3) was added, and the mixture was stirred at room temperature for 36 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 5:1, 5:2, 1:1) to give the trimethylsilyl ether of **12a** (76 mg, 71%) and the alcohol **12a** (7 mg, 7%).

Trimethylsilyl ether of **12a**: $[\alpha]_D^{20} = +14.0°$ ($c = 1.0$, $CDCl_3$); IR (neat): $\nu = 2959$, 1690, 1472, 1429, 1391, 1265, 1254, 1113, 845, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (9H, s), 1.08 (9H, s), 1.86 (3H, s), 2.49 (1H, ddd, $J = 6$, 6 and 5.2 Hz), 3.61 (1H, dd, $J = 10.5$ and 5.2 Hz), 3.68 (1H, dd, $J = 10.5$ Hz and 6 Hz), 4.08 (1H, dd, $J = 8.8$ and 7 Hz), 4.20 (1H, dd, $J = 8.8$ and 8.5 Hz), 4.41 (1H, dd, $J = 6$ and 4.6 Hz), 5.72 (1H, d, $J = 4.6$ Hz), 7.07 (1H, s), 7.35–7.5 (6H, m), 7.55–7.7 (4 H, m), 8.06 (1H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.01$ (*TMS*), 12.53 (5-Me), 19.28 (*t*-Bu), 26.90 (*t*-Bu), 48.74 (C3′), 61.56 (C4′), 70.07 (C2′), 76.12 (C5′), 92.16 (C1′), 111.02 (C5), 127.85, 127.90, 129.98, 130.04, 132.82, 132.95, 135.47, 135.49 (Ph), 135.52 (C4), 150.55 (C6), 163.94 (C2) ppm.

To a solution of the above trimethylsilyl ether (127 mg, 0.23 mmol) in MeOH (3 cm^3)/*THF* (0.6 cm^3), 1 *N* aq. HCl (0.003 cm^3) in MeOH (1 cm^3) was added at 0°C, and the stirred mixture was gradually warmed to room temperature over 30 min. After the reaction was neutralized with 1 *N* aq. NaOH (0.003 cm^3), the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography (hexane:AcOEt = 1:1) to give the alcohol **12a** (111 mg, 100%).

$[\alpha]_D^{20} = +9.7°$ ($c = 0.5$, $CDCl_3$); IR (neat): $\nu = 3407$, 2932, 1694, 1472, 1429, 1265, 1113, 739, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (9H, s), 1.91 (3H, d, $J = 1.2$ Hz), 2.62 (1H, m), 3.75 (1H, dd, $J = 10.5$ and 5.5 Hz), 3.78 (1H, dd, $J = 10.5$ Hz and 4.6 Hz), 4.03 (1H, dd, $J = 8.5$ and 8 Hz), 4.18 (1H, dd, $J = 7$ and 4.1 Hz), 4.28 (1H, dd, $J = 8.5$ and 8 Hz), 5.54 (1H, d, $J = 4.1$ Hz), 7.26 (1H, s), 7.35–7.5 (6H, m), 7.55–7.7 (4 H, m), 8.66 (1H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.57$ (5-Me), 19.29 (*t*-Bu), 26.84 (*t*-Bu), 48.05 (C3′), 61.46 (C4′), 70.62 (C2′), 77.98 (C5′), 93.62 (C1′), 110.69 (C5), 127.84 (Ph), 129.90 (Ph), 129.92 (Ph), 133.04 (Ph), 134.71 (C4), 135.50 (Ph), 135.53 (Ph), 151.65 (C6), 164.24 (C2) ppm.

2,2′-Anhydro-5-methyl-1-((1R,2S,3R)-tetrahydro-2-hydroxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**20a**; $C_{26}H_{30}N_2O_4Si$)

To a solution of **12a** (104 mg, 0.216 mmol) and triphenyl phosphine (90 mg, 0.34 mmol) in *THF* (1.5 cm^3), *DIAD* (0.07 cm^3, 0.34 mmol) was added at room temperature, and the mixture was stirred for 1 h. After removal of the solvent, the residue was purified by flash chromatography (hexane: AcOEt = 2:1, 1:1, 1:2; AcOEt) to give the anhydrothymidine **20a** (97 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (9H, s), 1.99 (3H, d, $J = 1.3$ Hz), 2.68 (1H, m), 3.44 (1H, dd, $J = 11.6$ and 9.3 Hz), 3.79 (1H, dd, $J = 10.5$ Hz and 7.2 Hz), 4.03 (1H, dd, $J = 10.5$ and 7.4 Hz), 4.17 (1H, dd, $J = 9.3$ and 7.2 Hz), 5.33 (1H, dd, $J = 5.2$ and 5.2 Hz), 6.07 (1H, d, $J = 5.2$ Hz), 7.19 (1H, d, $J = 1.3$ Hz), 7.35–7.45 (6H, m), 7.6–7.7 (4 H, m) ppm.

5-Methyl-1-((1R,2R,3R)-tetrahydro-2-azido-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**21**; $C_{26}H_{31}N_5O_3Si$)

To a solution of **20a** (95 mg, 0.20 mmol) in *DMF* (1.6 cm^3), LiN_3 (70 mg, 1.4 mmol) was added at room temperature, and the mixture was stirred at 125–130°C for 7 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1, AcOEt, AcOEt:MeOH = 10:1) to give the azide **21** (75 mg, 72%), the desilylated compound (3 mg, 5%), and starting material (16 mg, 17%).

$[\alpha]_D^{20} = +2.3°$ ($c = 1.2$, $CDCl_3$); IR (neat): $\nu = 2932$, 2108, 1694, 1472, 1429, 1265, 1113, 741, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.07$ (9H, s), 1.89 (3H, d, $J = 0.9$ Hz), 2.54 (1H, m), 3.68 (1H, dd, $J = 10.6$ and 5.1 Hz), 3.77 (1H, dd, $J = 10.6$ Hz and 5.1 Hz), 4.08 (1H, dd, $J = 9$ and 7.6 Hz), 4.17 (1H, dd, $J = 9$ and 7.7 Hz), 4.17 (1H, dd, $J = 4$ and 4 Hz), 5.77 (1H, d, $J = 4.9$ Hz), 7.07 (1H, d, $J = 1.2$ Hz), 7.35–7.5 (6H, m), 7.55–7.7 (4 H, m), 8.79 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.63$ (5-Me), 19.30 (*t*-Bu), 26.87 (*t*-Bu), 47.02 (C3′), 61.27 (C4′), 66.51 (C2′), 70.04 (C5′), 91.04 (C1′), 111.48 (C5), 127.00 (Ph), 130.17 (Ph), 132.82 (Ph), 132.66 (Ph), 134.63 (C4), 135.50 (Ph), 151 (C6), 163 (C2) ppm.

5-Methyl-1-((1R,2R,3S)-tetrahydro-2-azido-3-hydroxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**3a**; $C_{10}H_{13}N_5O_3$)

To a solution of **21** (77 mg, 0.15 mmol) in *THF* (0.8 cm^3), *TBAF* (1 *M* in *THF*, 0.15 cm^3) was added at 0°C, and the mixture was stirred at the same temperature for 1 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1, AcOEt) to give the *AZT* analogue **3a** (42 mg, 100%).

$[\alpha]_D^{20} = -11.5°$ ($c = 2$, $CDCl_3$); IR (neat): $\nu = 3450$, 2957, 2108, 1694, 1470, 1267, 1115, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.92$ (3H, d, $J = 0.9$ Hz), 2.56 (1H, m), 3.75 (1H, dd, $J = 11$ and 5.6 Hz), 3.85 (1H, dd, $J = 11$ Hz and 5.1 Hz), 4.13 (1H, dd, $J = 8.5$ and 7.2 Hz), 4.23 (1H, dd, $J = 8.5$ and 8.5 Hz), 4.44 (1H, dd, $J = 5.8$ and 4.3 Hz), 5.61 (1H, d, $J = 4.3$ Hz), 7.18 (1H, d, $J = 1.2$ Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.49$ (5-Me), 47.30 (C3′), 60.53 (C4′), 66.86 (C2′), 70.94 (C5′), 93.32 (C1′), 110.67 (C5), 136.47 (C4), 150.82 (C6), 164.42 (C2) ppm.

2,2′-Anhydro-5-Methyl-1-((1R,2S,3R)-tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**20b**; $C_{30}H_{28}N_2O_5$)

To a solution of **12b** (101 mg, 0.197 mmol) and triphenyl phosphine (78 mg, 0.29 mmol) in *THF* (1.5 cm^3), *DIAD* (0.06 cm^3, 0.30 mmol) was added at room temperature, and the mixture was stirred for 1.5 h. After removal of the solvent, the residue was purified by flash chromatography (hexane: AcOEt = 2:1, 1:1, 1:2, AcOEt, AcOEt:MeOH = 10:1) to give the anhydro thymidine **12b** (90 mg, 92%).

IR (neat): $\nu = 1649$, 1561, 1509, 1483, 1449, 1288, 1252, 1229, 1181, 1132, 1080, 1034, 980, 833, 733, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.97$ (3H, d, $J = 0.9$ Hz), 2.63 (1H, m), 3.29 (1H, dd, $J = 9.5$ and 7.6 Hz), 3.41 (1H, dd, $J = 11.45$ Hz and 9.2 Hz), 3.54 (1H, dd, $J = 9.5$ and 6.7 Hz), 3.80 (3H, s), 4.24 (1H, dd, $J = 9.2$ and 7.1 Hz), 5.33 (1H, dd, $J = 5.2$ and 5.2 Hz), 6.07 (1H, d, $J = 5.1$ Hz), 6.84 (2H, m), 7.18 (1H, d, $J = 1.3$ Hz), 7.2–7.45 (12H, m) ppm.

5-Methyl-1-((1R,2S,3S)-tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**22**; $C_{30}H_{30}N_2O_6$)

To a solution of **20b** (89 mg, 0.18 mmol) in EtOH (4.3 cm^3)/H_2O (2.1 cm^3), 1 *N* aq. NaOH (0.43 cm^3) was added at room temperature, and the mixture was stirred at the same temperature for 9 h. After the reaction was neutralized with 1 *N* aq. HCl (0.43 cm^3), the mixture was extracted with AcOEt and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the alcohol **22** (85 mg, 92%).

IR (neat): $\nu = 3384$, 2928, 1698, 1667, 1510, 1478, 1279, 1252, 1181, 1057, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.83$ (3H, s), 2.76 (1H, m), 3.22 (1H, dd, $J = 9$ and 6.4 Hz), 3.52 (1H, dd, $J = 9$ Hz and 7.6 Hz), 3.78 (3H, s), 3.88 (1H, dd, $J = 11.1$ and 7.7 Hz), 4.09 (1H, m), 4.78 (1H, m), 6.06 (1H, d, $J = 2.3$ Hz), 6.82 (2H, m), 7.2–7.5 (13H, m), 10.39 (1H, br) ppm.

5-Methyl-1-((1R,2S,3S)-tetrahydro-2-hydroxy-3-hydroxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione ($C_{10}H_{14}N_2O_5$)

To a solution of **22** (93 mg, 0.18 mmol) in MeOH (1.8 cm^3), Amberlyst 15-H (28 mg) was added at room temperature, and the mixture was stirred for 12 h. After filtration, the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (AcOEt:MeOH = 10:1) to give the diol (44 mg, 100%).

^{1}H NMR (200 MHz, $CDCl_3$:CD_3OD = 20:1): $\delta = 1.89$ (3H, d, $J = 0.8$ Hz), 2.53 (1H, m), 3.67 (2H, d, $J = 5.8$ Hz), 3.97 (1H, dd, $J = 8.7$ Hz and 8.5 Hz), 4.18 (1H, dd, $J = 6.7$ and 4.4 Hz), 4.26 (1H, dd, $J = 8.5$ and 8.3 Hz), 5.55 (1H, d, $J = 4.4$ Hz), 7.26 (1H, s) ppm.

5-Methyl-1-((1R,2S,3S)-tetrahydro-2-hydroxy-3-benzoyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**23**; $C_{17}H_{18}N_2O_6$)

To a solution of the above diol (44 mg, 0.18 mmol) in CH_2Cl_2 (2.1 cm^3)/pyridine (0.8 cm^3), benzoyl chloride (0.07 cm^3, 0.60 mmol) was added at -40°C, and the stirred mixture was gradually warmed to -5°C over 2 h. After the reaction was quenched with MeOH (0.3 cm^3, 10 mmol) the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the benzoate **23** (59 mg, 95%).

$[\alpha]_D^{20} = +61.7°$ ($c = 0.3$, $CDCl_3$); IR (neat): $\nu = 3362$, 2924, 1694, 1665, 1480, 1275, 1144, 1113 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.79$ (3H, s), 2.89 (1H, m), 4.09 (1H, dd, $J = 10.9$ and 7.8 Hz), 4.22 (1H, dd, $J = 7.9$ Hz and 7.8 Hz), 4.47 (1H, dd, $J = 11.1$ and 6.8 Hz), 4.69 (1H, dd, $J = 11.1$ and 7.6 Hz), 4.86 (1H, m), 6.04 (1H, d, $J = 2.5$ Hz), 7.37 (1H, s), 7.4–7.65 (3H, m), 8–8.1 (2H, m), 10.64 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 12.27$ (5-Me), 44 (C3′), 61.59 (C4′), 71 (C2′), 89.08 (C5′), 100 (C1′), 108.25 (C5), 128.41 (2C of Ph), 129.59 (2C of Ph), 129.75 (Ph), 133.22 (Ph), 138.52 (C4), 152 (C6), 166 (COPh), 166.74 (C2) ppm.

5-Methyl-1-((1R,2R,3S)-tetrahydro-3-benzoyloxymethyl-2-fluoro-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**25**; $C_{17}H_{17}FN_2O_5$)

To a solution of **23** (58 mg, 0.17 mmol) in CH_2Cl_2 (2.5 cm^3), DAST (0.60 cm^3, 4.5 mmol) was added at -30°C, and the stirred mixture was gradually warmed to -10°C over 2 h and stirred at -10°C ~ 3°C for 17 h. After the reaction was quenched with 2 *N* aq. NaOH (5 cm^3)/sat. aq. $NaHCO_3$, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1, 1:1, 1:2) to give the fluoride **25** (25 mg, 45%), the dehydrated product **24** (19 mg, 35%) and starting material **23** (7 mg, 12%).

25: $[\alpha]_D^{20} = +22°$ ($c = 0.4$, $CDCl_3$); IR (neat): $\nu = 1694$, 1468, 1453, 1275, 1115, 1110, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.89$ (3H, d, $J = 1.2$ Hz), 3.09 (1H, dm, $J = 27$ Hz), 4.20 (1H, dd, $J = 9$ and 7.1 Hz), 4.39 (1H, dd, $J = 9$ Hz and 8.2 Hz), 4.49 (1H, dd, $J = 11.5$ and 6.7 Hz), 4.52 (1H, dd, $J = 11.5$ and 7.0 Hz), 5.50 (1H, ddd, $J = 54$, 4 and 3 Hz), 5.70 (1H, dd, $J = 18$ and 3 Hz), 7.10 (1H, d, $J = 1.2$ Hz), 7.44 (2H, m), 7.58 (1H, m), 8.01 (2H, m), 8.50 (1H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.41$ (5-Me), 45.24 (d, $J = 86$ Hz, C3′), 62.52 (d, $J = 17$ Hz, C4′), 71.49 (d, $J = 13.5$ Hz, C5′), 94.40 (d, $J = 147$ Hz, C1′), 96.85 (d, $J = 738$ Hz, C2′), 111.35 (C5), 128.53 (2C of Ph), 129.43 (Ph), 129.65 (2C of Ph), 133.43 (Ph), 137.16 (C4), 150.51(C6), 164.03 (COPh), 166.23 (C2) ppm.

24: IR (neat): $\nu = 1694$, 1470, 1453, 1275, 1256, 1111, 1061, 714 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.92$ (3H, d, $J = 0.9$ Hz), 4.75 (1H, dm, $J = 14$ Hz), 4.91 (1H, dm, $J = 14$ Hz), 5.08 (2H, s), 5.82 (1H, d, $J = 1.5$ Hz), 6.93 (1H, d, $J = 1.4$ Hz), 7.04 (1H, m), 7.44 (2H, m), 7.58 (1H, m), 8.06 (2H, m), 8.35 (1H, br) ppm.

5-Methyl-1-((1R,2R,3S)-tetrahydro-3-hydroxymethyl-2-fluoro-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**3b**; $C_{10}H_{13}FN_2O_4$)

To a solution of **25** (20.5 mg, 0.0588 mmol) in MeOH (0.4 cm^3), 1 *N* aq. NaOH (0.07 cm^3) was added at room temperature, and the mixture was stirred at the same temperature for 30 min. After removal of the solvent, the residue was purified by flash chromatography (AcOEt) to give the fluoro nucleoside **3b** (14 mg, 100%).

$[\alpha]_D^{20} = -16^\circ$ ($c = 0.4$, $CDCl_3$); IR (neat): $\nu = 3389$, 2928, 1692, 1470, 1269, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.91$ (3H, d, $J = 1.1$ Hz), 2.66 (1H, br), 2.79 (1H, dm, $J = 28.5$ Hz), 3.81 (1H, dd, $J = 11$ and 5.5 Hz), 3.88 (1H, dd, $J = 11$ Hz and 5 Hz), 4.17 (1H, dd, $J = 9$ and 6 Hz), 4.32 (1H, dd, $J = 9$ and 8.2 Hz), 5.50 (1H, ddd, $J = 54$, 3.2 and 2.6 Hz), 5.67 (1H, dd, $J = 19$ and 2.6 Hz), 7.17 (1H, d, $J = 1.2$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.42$ (5-Me), 47.48 (d, $J = 82$ Hz, C3′), 60.57 (d, $J = 25$ Hz, C4′), 71.57 (d, $J = 10$ Hz, C5′), 94.43 (d, $J = 151$ Hz, C1′), 97.40 (d, $J = 722$ Hz, C2′), 110.60 (C5), 137.51 (C4), 150.93 (C6), 164.45 (C2) ppm.

1-((1R,2R,3R)-Tetrahydro-2-hydroxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**13a**; $C_{25}H_{30}N_2O_5Si$)

To a solution of **10a** (138 mg, 0.39 mmol) in $CDCl_3$ (1.6 cm^3), *bis*-silylated uracil (705 mg, 2.75 mmol) in $CDCl_3$ (0.4 cm^3) was added, and the mixture was stirred at room temperature for 36 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 3:1, 2:1, 1:1) to give the trimethylsilyl ether of **13a** (113 mg, 54%) and the alcohol **13a** (12 mg, 7%).

Trimethylsilyl ether of **13a**: $[\alpha]_D^{20} = +20.0^\circ$ ($c = 0.70$, $CHCl_3$); IR (neat): $\nu = 3054$, 2957, 1686, 1460, 1429, 1383, 1265, 1254, 1113, 843, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.07$ (9H, s), 1.07 (9H, s), 2.52 (1H, m), 3.60 (2H, d, $J = 6.1$ Hz), 4.07 (1H, dd, $J = 8.7$ and 6.2 Hz), 4.24 (1H, dd, $J = 8.7$ and 8 Hz), 4.40 (1H, dd, $J = 4.7$ and 4 Hz), 5.60 (1H, dd, $J = 8.1$ and 2.3 Hz), 5.67 (1H, d, $J = 4$ Hz), 7.21 (1H, $J = 8.1$ Hz), 7.3–7.5 (6H, m), 7.55–7.65 (4 H, m), 8.14 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 0.02$ (*TMS*), 19.25 (*t*-Bu), 26.89 (*t*-Bu), 49.09 (C3′), 61.93 (C4′), 70.67 (C2′), 76.74 (C5′), 93.09 (C1′), 102.34 (C5), 127.88, 127.93, 130.02, 130.07, 132.78, 132.91, 135.51, 135.56 (Ph), 139.73 (C4), 150.50 (C6), 163.72 (C2) ppm.

To a solution of the above silyl ether (108 mg, 0.200 mmol) in MeOH (2 cm^3)/*THF* (0.5 cm^3), 1 *N* aq. HCl (0.002 cm^3) in MeOH (0.6 cm^3) was added at 0°C, and the stirred mixture was gradually warmed to room temperature over 30 min. After the reaction was neutralized with 1 *N* aq. NaOH (0.002 cm^3), the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give the alcohol **13a** (93 mg, 100%).

$[\alpha]_D^{20} = +24.9^\circ$ ($c = 0.43$, $CHCl_3$); IR (neat): $\nu = 1696$, 1472, 1429, 1267, 1113, 741, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.03$ (9H, s), 2.62 (1H, m), 3.67 (1H, dd, $J = 10.5$ and 6.4 Hz), 3.77 (1H, dd, $J = 10.5$ Hz and 4.9 Hz), 3.91 (1H, br s), 4.04 (1H, dd, $J = 8.7$ and 8.5 Hz), 4.18 (1H, ddd, $J = 6.2$, 3.6 and 3 Hz), 4.28 (1H, dd, $J = 8.5$ and 8 Hz), 5.57 (1H, d, $J = 3.6$ Hz), 5.67 (1H, d, $J = 8.2$ Hz), 7.3–7.5 (7H, m), 7.55–7.7 (4 H, m), 9.63 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.29$ (*t*-Bu), 26.87 (*t*-Bu), 48.27 (C3′), 61.65 (C4′), 71.00 (C2′), 78.27 (C5′), 94.21 (C1′), 102.20 (C5), 127.81 (Ph), 129.96 (Ph), 129.98 (Ph), 133.04 (Ph), 135.52 (Ph), 135.56 (Ph), 138.92 (C4), 151.65 (C6), 163.99 (C2) ppm.

1-((1R,2R,3R)-Tetrahydro-2-(1,1-dimethylethyldiphenyl)-silyloxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2,4(1H,3H)-pyrimidinedione ($C_{41}H_{48}N_2O_5Si_2$)

To a solution of **13a** (74 mg, 0.16 mmol) in *DMF* (0.8 cm^3), imidazole (56 mg, 0.82 mmol) and *TBDPS*Cl (0.11 cm^3, 0.42 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 23 h. After the reaction was quenched with H_2O, the mixture was extracted

with Et_2O ($3 \times 6\,cm^3$) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 3:1) to give the *bis*-silyl ether (71.5 mg, 81%).

$[\alpha]_D^{22} = +57.6°$ ($c = 0.25$, $CHCl_3$); IR (neat): $\nu = 2920, 2861, 1696, 1472, 1429, 1250, 1113, 824, 741, 702, 613\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (9H, s), 1.01 (9H, s), 2.64 (1H, m), 3.45 (1H, dd, $J = 10.4$ and 7.1 Hz), 3.53 (1H, dd, $J = 10.4$ and 4.2 Hz), 4.02 (1H, dd, $J = 9$ and 6.3 Hz), 4.18 (1H, dd, $J = 9$ and 8.0 Hz), 4.30 (1H, dd, $J = 5.5$ and 5 Hz), 5.26 (1H, dd, $J = 8.1$ and 2.4 Hz), 5.85 (1H, d, $J = 5$ Hz), 6.74 (1H, d, $J = 8$ Hz), 7.25–7.6 (20H, m), 8.1 (1H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.04$ and 19.21 (*t*-Bu), 26.79 and 26.85 (*t*-Bu), 49.09 (C3′), 62.61 (C4′), 70.16 (C2′), 76.78 (C5′), 92.40 (C1′), 102.51 (C5), 127.80, 127.83, 127.99, 129.89, 129.95, 130.05, 130.20, 132.14, 132.92, 133.03, 133.05, 135.51, 135.70, 135.83 (Ph), 140.19 (C4), 150.13 (C6), 163.20 (C2) ppm.

1-((1R,2R,3R)-Tetrahydro-2-(1,1-dimethylethyldiphenyl)-silyloxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-4-(1,2,4-triazol-1-yl)-2(1H)-pyrimidinone (**14a**; $C_{43}H_{49}N_5O_4Si_2$)

To a solution of the above *bis*-silyl ether (19 mg, 0.027 mmol) in pyridine ($0.5\,cm^3$), 4-chlorophenyl dichlorophosphate ($0.020\,cm^3$, 0.12 mmol) and 1,2,4-triazole (37 mg, 0.54 mmol) were added at 0°C, and the mixture was stirred at room temperature for 28 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 ($3 \times 5\,cm^3$) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:1) to give the triazolyl nucleoside **14a** (19 mg, 93%).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.94$ (9H, s), 1.08 (9H, s), 2.57 (1H, m), 3.10 (1H, dd, $J = 8.7$ and 8.7 Hz), 3.20 (1H, m), 4.23 (1H, m), 4.4 (2H, m), 5.93 (1H, d, $J = 2.6$ Hz), 6.53 (1H, d, $J = 7.2$ Hz), 7.25–7.6 (21H, m), 8.12 (1H, s), 9.21 (1H, s) ppm.

4-Amino-1-((1R,2R,3R)-tetrahydro-2-(1,1-dimethylethyldiphenyl)-silyloxy-3-(1,1-dimethylethyldiphenyl)-silyloxymethyl-1-furanyl)-2(1H)-pyrimidinone ($C_{41}H_{49}N_3O_4Si_2$)

To a solution of **14a** (58 mg, 0.077 mmol) in dioxane ($1.7\,cm^3$), sat. aq. NH_3 ($0.85\,cm^3$) was added, and the mixture was stirred at room temperature for 3 days. After removal of the solvent, the residue was purified by flash chromatography ($CHCl_3$:MeOH = 20:1) to give the protected cytidine (50 mg, 93%).

$[\alpha]_D^{23} = +72.7°$ ($c = 0.22$, $CHCl_3$); IR (neat): $\nu = 3300, 2932, 2859, 1634, 1487, 1474, 1428, 1250, 1113, 741, 702, 613\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (9H, s), 1.02 (9H, s), 2.56 (1H, m), 3.23 (1H, dd, $J = 10.2$ and 8.7 Hz), 3.34 (1H, dd, $J = 10.2$ and 4.9 Hz), 4.10 (1H, dd, $J = 8.9$ and 5.6 Hz), 4.24 (1H, dd, $J = 8.9$ and 7.7 Hz), 4.29 (1H, dd, $J = 4.5$ and 4 Hz), 5.27 (1H, d, $J = 7.4$ Hz), 5.90 (1H, d, $J = 4$ Hz), 6.87 (1H, d, $J = 7.4$ Hz), 7.2–7.6 (20H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.10$ and 19.15 (*t*-Bu), 26.81 and 26.85 (*t*-Bu), 49.65 (C3′), 62.89 (C4′), 70.77 (C2′), 77.57 (C5′), 94.27 (C1′), 94.88 (C5), 127.74, 127.83, 129.74, 129.79, 129.87, 132.47, 133.17, 133.19, 133.39, 135.50, 135.70, 135.85 (Ph), 141.26 (C4), 155.82 (C6), 165.62 (C2) ppm.

4-Amino-1-((1R,2R,3S)-tetrahydro-2-hydroxy-3-hydroxymethyl-1-furanyl)-2(1H)-pyrimidinone (**2C**; $C_9H_{13}N_3O_4$)

To a solution of the above protected cytidine (56 mg, 0.079 mmol) in C_6H_6 ($0.8\,cm^3$), Amberlite A26 F^- (226 mg) was added, and the mixture was stirred under reflux for 6 h. After the resin was filtered off, washed with C_6H_6, Et_2O, and AcOEt, and extracted with MeOH, the MeOH extract was evaporated *in vacuo*. The residue was purified by flash chromatography ($CHCl_3$:MeOH = 10:1) to give the cytidine analogue **2C** (17 mg, 94%).

$[\alpha]_D^{20} = +65.6^\circ$ ($c = 0.13$, $CHCl_3$:$CH_3OH = 5{:}1$); IR (neat): $\nu = 3347$, 2928, 2859, 1653, 1526, 1491, 1289, 1111, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$:$CD_3OD = 5{:}1$): $\delta = 2.45$ (1H, m), 3.48 (1H, dd, $J = 11.2$ and 7.0 Hz), 3.60 (1H, dd, $J = 11.2$ and 5.1 Hz), 3.94 (1H, dd, $J = 8.6$ and 8.2 Hz), 4.03 (1H, dd, $J = 5.8$ and 3.8 Hz), 4.25 (1H, dd, $J = 8.6$ and 7.9 Hz), 5.50 (1H, d, $J = 3.5$ Hz), 5.77 (1H, d, $J = 7$ Hz), 7.51 (1H, d, $J = 7$ Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): $\delta = 48.65$ (C3′), 60.41 (C4′), 70.64 (C2′), 77.09 (C5′), 94.21 (C1′), 94.51 (C5), 141.17 (C4), 157.39 (C6), 166.32 (C2) ppm.

1-((1R,2R,3S)-Tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**13b**; $C_{29}H_{28}N_2O_6$)

To a solution of **10b** (89 mg, 0.23 mmol) in $CDCl_3$ (0.95 cm^3), a solution of *bis*-silylated uracil (450 mg, 1.75 mmol) in $CDCl_3$ (0.24 cm^3) was added, and the mixture was stirred at room temperature for 36 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1, 1:1, 1:2) to give the silyl ether of **13b** (84 mg, 64%) and the alcohol **13b** (13 mg, 11%).

Trimethylsilyl ether of **13b**: $[\alpha]_D^{20} = +7.2^\circ$ ($c = 1.0$, $CHCl_3$); IR (neat): $\nu = 2930$, 1684, 1609, 1510, 1449, 1254, 1181, 1107, 1071, 1034, 843, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.07$ (9H, s), 2.61 (1H, m), 3.06 (2H, m), 3.81 (3H, s), 4.04 (1H, dd, $J = 9$ and 5.1 Hz), 4.32 (1H, dd, $J = 3.2$ and 3.2 Hz), 4.36 (1H, dd, $J = 9$ and 9 Hz), 5.48 (1H, dd, $J = 8.2$ and 2.2 Hz), 5.90 (1H, d, $J = 3.2$ Hz), 6.83 (2H, m), 7.09 (1H, d, $J = 8.2$ Hz), 7.2–7.45 (12H, m), 8.51 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 0.01$ (*TMS*), 47.45 (C3′), 55.28 (OCH_3), 62.33 (C4′), 71.62 (C2′), 77.81 (C5′), 86.59 (CAr_3), 93.66 (C1′), 102.08 (C5), 113.24 (*ortho*-C × 2 of MeOAr), 127.14 (2C of Ph), 127.96 (4C of Ph), 128.27 (4C of Ph), 130.23 (2C of Ph), 135.05 (C4), 135.58 (*para*-C of MeOAr), 143.91 (*meta*-C of MeOAr), 144.04 (*meta*-C of MeOAr), 150.29 (C6), 158.71 (C–OMe), 163.55 (C2) ppm.

To a solution of the above silyl ether (86 mg, 0.15 mmol) in MeOH (1.3 cm^3)/*THF* (0.5 cm^3), 1 *N* aq. HCl (0.001 cm^3) in MeOH (0.7 cm^3) was added at 0°C, and the stirred mixture was gradually warmed to room temperature over 30 min. After neutralization with 1 *N* aq. NaOH (0.001 cm^3), the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography (hexane: AcOEt = 1:4) to give the alcohol **13b** (75 mg, 100%).

$[\alpha]_D^{20} = +26.5^\circ$ ($c = 0.4$, $CHCl_3$); IR (neat): $\nu = 3393$, 1694, 1609, 1510, 1464, 1449, 1265, 1254, 1181, 1088, 1034, 833, 737, 708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.72$ (1H, m), 3.09 (1H, dd, $J = 9.2$ and 7.5 Hz), 3.27 (1H, dd, $J = 9.2$ Hz and 5.7 Hz), 3.64 (1H, br s), 3.79 (3H, s), 3.95 (1H, dd, $J = 8.7$ and 8.2 Hz), 4.10 (1H, m), 4.35 (1H, dd, $J = 8.7$ and 7.5 Hz), 5.52 (1H, d, $J = 3.5$ Hz), 5.64 (1H, d, $J = 8.0$ Hz), 6.82 (2H, m), 7.2–7.4 (13H, m), 8.87 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 46.49$ (C3′), 55.26 (OCH_3), 61.83 (C4′), 71.96 (C2′), 79.17 (C5′), 86.48 (CAr_3), 94.62 (C1′), 102.10 (C5), 113.21 (*ortho*-C × 2 of MeOAr), 127.07 (2C of Ph), 127.95 (4C of Ph), 128.26 (4C of Ph), 130.28 (2C of Ph), 135.17 (*para*-C of MeOAr), 138.71 (C4), 144.02 (*meta*-C of MeOAr), 144.21 (*meta*-C of MeOAr), 151.46 (C6), 158.66 (C–OMe), 163.84 (C2) ppm.

1-((1R,3S)-Tetrahydro-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-2,4(1H,3H)-pyrimidinedione (**26**; $C_{29}H_{28}N_2O_5$)

To a solution of **13b** (55 mg, 0.11 mmol) in CH_2Cl_2 (3.2 cm^3) *DMAP* (50 mg, 0.41 mmol) and phenyl chlorothionoformate (0.03 cm^3, 0.22 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 3 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:1) to give the thionoformate (63 mg, 90%).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.94$ (1H, m), 3.30 (1H, dd, $J = 9.4$ and 6.5 Hz), 3.41 (1H, dd, $J = 9.4$ Hz and 6.1 Hz), 3.79 (3H, s), 4.17 (1H, dd, $J = 9$ and 5.6 Hz), 4.29 (1H, dd, $J = 9$ and 7.8 Hz), 5.52 (1H, dd, $J = 8.1$ and 2.2 Hz), 5.84 (1H, dd, $J = 4$ and 4 Hz), 5.97 (1H, d, $J = 4$ Hz), 6.84 (2H, m), 7.05–7.5 (18H, m), 8.53 (1H, br) ppm.

Argon gas was bubbled through a solution of the above thionoformate (58 mg, 0.091 mmol) in C_6H_6 (1.5 cm^3) for 20 min. *AIBN* (16 mg, 0.095 mmol) and Bu_3SnH (0.24 cm^3, 0.87 mmol) were added to the mixture, and the mixture was stirred under reflux for 3 h. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:1) to give the deoxygenated product **26** (43 mg, 97%).

$[\alpha]_D^{20} = +29.5°$ ($c = 0.6$, $CHCl_3$); IR (neat): $\nu = 2924$, 1686, 1609, 1510, 1462, 1449, 1265, 1252, 1181, 1074, 1034, 710, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.70$ (1H, m), 2.61 (1H, m), 2.74 (1H, m), 3.05 (1H, dd, $J = 9$ and 6.8 Hz), 3.18 (1H, dd, $J = 9$ Hz and 5.9 Hz), 3.81 (3H, s), 3.90 (1H, dd, $J = 8.5$ and 6.6 Hz), 4.13 (1H, dd, $J = 8.5$ and 7.2 Hz), 5.58 (1H, dd, $J = 8.2$ and 2.2 Hz), 5.97 (1H, dd, $J = 6$ and 6 Hz), 6.82 (2H, m), 7.2–7.45 (13H, m), 8.17 (1H, br) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 35.80$ (C3′), 38.92 (C2′), 55.26 (OCH_3), 63.75 (C4′), 71.96 (C5′), 86.44 (CAr_3), 86.96 (C1′), 102.14 (C5), 113.19 (*ortho*-C × 2 of MeOAr), 127.08 (2C of Ph), 127.93 (4C of Ph), 128.27 (4C of Ph), 130.29 (2C of Ph), 135.22 (*para*-C of MeOAr), 139.03 (C4), 144.12 (*meta*-C of MeOAr), 144.21 (*meta*-C of MeOAr), 150.24 (C6), 158.67 (C–OMe), 163.19 (C2) ppm.

4-Amino-1-((1R,2R,3S)-tetrahydro-3-hydroxymethyl-1-furanyl)-2(1H)-pyrimidinone
(**3c**; $C_9H_{13}N_3O_3$)

To a solution of **26** (32.5 mg, 0.67 mmol) in MeOH (1.0 cm^3), Amberlyst 15-H (11 mg) was added at room temperature, and the mixture was stirred for 4 h. After filtration, the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (AcOEt:MeOH = 10:1) to give the alcohol (14 mg, 100%).

^1H NMR (200 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 1.77$ (1H, m), 2.56 (2H, m), 3.56 (1H, dd, $J = 10.9$ and 6.1 Hz), 3.62 (1H, dd, $J = 10.9$ Hz and 5.3 Hz), 3.91 (1H, dd, $J = 8.6$ and 6.8 Hz), 4.09 (1H, dd, $J = 8.6$ and 8 Hz), 5.69 (1H, d, $J = 8.2$ Hz), 5.95 (1H, dd, $J = 6.2$ and 6.2 Hz), 7.49 (1H, d, $J = 8.2$ Hz) ppm.

To a solution of the above alcohol (13 mg, 0.061 mmol) in CH_2Cl_2 (0.77 cm^3), Ac_2O (0.008 cm^3, 0.09 mmol), NEt_3 (0.013 cm^3, 0.093 mmol), and *DMAP* (1 mg, 0.008 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 5 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (AcOEt) to give the acetate **27** (14.5 mg, 93%).

IR (neat): $\nu = 2926$, 1690, 1464, 1379, 1273, 1242, 1038, 814 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.72$ (1H, m), 2.07 (3H, s), 2.73 (2H, m), 3.87 (1H, dd, $J = 8.8$ and 7.2 Hz), 4.12 (3H, m), 5.77 (1H, dd, $J = 8.2$ and 2 Hz), 5.98 (1H, dd, $J = 6.4$ and 6.4 Hz), 7.42 (1H, d, $J = 8.2$ Hz), 8.79 (1H, br) ppm.

To a solution of **27** (14.5 mg, 0.057 mmol) in pyridine (0.6 cm^3) 4-chlorophenyl dichlorophosphate (0.03 cm^3, 0.18 mmol) and 1,2,4-triazole (44 mg, 0.64 mmol) were added at 0°C, and the mixture was stirred at room temperature for 25 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 (3 × 5 cm^3) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography ($CHCl_3$:MeOH = 20:1) to give the triazolyl nucleoside (11 mg, 63%).

^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.80$ (1H, ddd, $J = 13.5$, 7.2 and 6 Hz), 2.04 (3H, s), 2.82 (1H, m), 3.01 (1H, ddd, $J = 13.5$, 8.2 and 6 Hz), 3.95 (1H, dd, $J = 8.8$ and 7.0 Hz), 4.03 (2H, m), 4.26 (1H, dd, $J = 8.8$ and 7.4 Hz), 6.01 (1H, dd, $J = 6.1$ and 5.7 Hz), 6.09 (1H, d, $J = 7.2$ Hz), 8.12 (1H, s), 8.19 (1H, d, $J = 7.2$ Hz), 9.27 (1H, s) ppm.

To a solution of the above triazolyl nucleoside (11 mg, 0.036 mmol) in dioxane (0.8 cm^3), sat. aq. NH_3 (0.4 cm^3) was added, and the mixture was stirred at room temperature for 3 days. After removal of the solvent, the residue was purified by flash chromatography ($CHCl_3$:MeOH = 20:1) to give the *ddC* analogue **3c** (6 mg, 80%).

$[\alpha]_D^{23} = +95°$ ($c = 0.35$, $CHCl_3$); IR (neat): $\nu = 3343$, 2924, 1653, 1609, 1528, 1489, 1287, 1115, 1053, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 1.64$ (1H, m), 2.57 (2H, m), 3.45

(1H, dd, $J = 10.8$ and 6.5 Hz), 3.52 (1H, dd, $J = 10.8$ Hz and 5.2 Hz), 3.87 (1H, dd, $J = 8.5$ and 7.1 Hz), 4.09 (1H, dd, $J = 8.5$ and 7.5 Hz), 5.72 (1H, d, $J = 7.5$ Hz), 5.88 (1H, dd, $J = 6.3$ and 5.8 Hz), 7.52 (1H, d, $J = 7.5$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$:$CD_3OD = 10{:}1$): $\delta = 35.82$ (C3′), 40.84 (C2′), 62.62 (C4′), 71.55 (C5′), 88.18 (C1′), 94.30 (C5), 140.32 (C4), 156.4 (C6), 165.73 (C2) ppm.

(1RS,2R,3S)-Tetrahydro-1,2-bis-acetoxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-furan (**15**; $C_{29}H_{30}O_7$)

To a solution of the dihydrofuran **9b** (150 mg, 0.40 mmol) in acetone (2 cm^3), OsO_4/*t*-BuOH solution (0.16 cm^3, prepared from OsO_4 (60 mg, 0.24 mmol), *t*-BuOH (6 cm^3), and 30% H_2O_2 (1 drop)) and 4-methylmorpholine N-oxide (*NMO*, 50% in H_2O, 0.20 cm^3, 1.0 mmol) were added at 0°C, and the mixture was stirred at the same temperature for 1.5 h. After the reaction was quenched with sat. aq. NH_4Cl, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:2) to give a mixture of the 1,2-diols (165 mg, 100%). To a solution of this diol mixture (165 mg, 0.406 mmol) in CH_2Cl_2 (1.6 cm^3), NEt_3 (0.41 cm^3, 2.9 mmol), Ac_2O (0.17 cm^3, 1.4 mmol), and *DMAP* (3 mg, 0.025 mmol) were added at room temperature, and the mixture was stirred at the same temperature for 22 h. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 2:1) to give the diacetates **15** and **16** (199 mg, 100%) as a 12:8:1 mixture of (1*R*,2*R*,3*S*)-, (1*S*,2*R*,3*S*)-, and (1*R*,2*S*,3*S*)-isomers.

IR (neat): $\nu = 2932$, 1748, 1609, 1510, 1449, 1372, 1300, 1250, 1221, 1181, 1078, 1032, 961, 833, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): (1*R*,2*R*,3*S*)-**15**: $\delta = 2.04$ (3H, s), 2.08 (3H, s), 2.78 (1H, m), 3.18 (1H, dd, $J = 9.2$ and 6.4 Hz), 3.34 (1H, dd, $J = 9.2$ and 6.9 Hz), 3.80 (3H, s), 3.8 (1H, m), 4.23 (1H, dd, $J = 8.7$ and 6.7 Hz), 5.04 (1H, dd, $J = 8.8$ and 4.2 Hz), 6.33 (1H, d, $J = 4.2$ Hz), 6.85 (2H, m), 7.2–7.45 (12H, m) ppm; (1*R*,2*R*,3*S*)-**15**: $\delta = 1.91$ (3H, s), 2.09 (3H, s), 2.61 (1H, m), 3.24 (2H, m), 3.79 (3H, s), 3.8 (1H, m), 4.28 (1H, dd, $J = 8.6$ and 7.9 Hz), 5.15 (1H, d, $J = 2.5$ Hz), 6.09 (1H, s), 6.85 (2H, m), 7.2–7.45 (12H, m) ppm; (1*R*,2*S*,3*S*)-**15**: $\delta = 1.87$ (3H, s), 2.09 (3H, s), 2.78 (1H, m), 3.24 (2H, m), 3.79 (3H, s), 3.8 (1H, m), 4.28 (1H, dd, $J = 8.6$ and 7.9 Hz), 5.35 (1H, d, $J = 4.8$ Hz), 6.07 (1H, s), 6.85 (2H, m), 7.2–7.45 (12H, m) ppm.

6-N-Benzoyl-9-((1R,2R,3S)-tetrahydro-2-acetoxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-9H-adenine (**17**; $C_{39}H_{35}N_5O_6$)

To a suspension of 6-benzoyl-adenine (25 mg, 0.10 mmol) in 1,2-dichloroethane (1 cm^3), N,O-*bis*-(trimethylsilyl)-acetamide (0.080 cm^3, 0.32 mmol) was added, and the mixture was stirred under reflux for 15 min. To the above solution, a mixture of **15** and **16** (21 mg, 0.034 mmol) in 1,2-dichloroethane (0.2 cm^3) and trimethylsilyl triflate (*TMSOTf*, 0.065 cm^3) were added, and the mixture was stirred under reflux for 1 h. After the reaction was neutralized with aq. $KHCO_3$, the mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (AcOEt) to give the acetate **17** (21 mg, 93%) and the detritylated product (1.5 mg, 4%).

$[\alpha]_D^{23} = -2°$ ($c = 0.1$, $CHCl_3$); IR (neat): $\nu = 1744$, 1701, 1611, 1582, 1510, 1456, 1250, 1181, 1074, 1034, 812, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.09$ (3H, s), 2.87 (1H, m), 3.42 (1H, dd, $J = 9$ and 7.5 Hz), 3.46 (1H, dd, $J = 9$ and 6.3 Hz), 3.79 (3H, s), 4.26 (1H, dd, $J = 8.8$ and 8.4 Hz), 4.36 (1H, dd, $J = 8.8$ and 7.8 Hz), 5.84 (1H, dd, $J = 5.8$ and 3.6 Hz), 6.01 (1H, d, $J = 3.6$ Hz), 6.83 (2H, m), 7.2–7.35 (8H, m), 7.42 (4H, m), 7.53 (2H, t, $J = 7.5$ Hz), 7.61 (1H, d, $J = 7.5$ Hz), 7.98 (1H, s), 8.02 (1H, d, 7.5 Hz), 8.64 (1H, s), 8.95 (1H, br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.74$ (CH_3CO), 45.82 (C3′), 55.27 (OCH_3), 61.54 (C4′), 71.69 (C2′), 78.97 (C5′), 86.67 (CAr_3), 90.28 (C1′), 113.20 (*ortho*-C × 2 of MeOAr), 124(C5), 127.09 (2C of Ph), 127.87 (2C of *Bz*), 127.92 (4C of Ph), 128.32 and 128.35 (4C of Ph), 128.85 (2C of *Bz*), 130.26 (2C of Ph), 132.74 (1C of *Bz*), 134

(1C of *Bz*), 135.28 (*para*-C of MeOAr), 141.86 (C8), 144.12 (2 × *meta* C of MeOAr), 149.5 (C4), 151.3 (C6), 152.68 (C2), 158.67 (C–OMe), 164.66 (PhCO), 170.27 (COMe) ppm.

9-((1R,2R,3S)-Tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-9H-adenine ($C_{30}H_{29}N_5O_4$)

To a solution of **17** (40.0 mg, 0.0597 mmol) in MeOH (3.2 cm^3), sat. aq. NH_3 (2.2 cm^3) was added, and the mixture was stirred at room temperature for 24 h. After removal of the solvent, the residue was purified by flash chromatography (AcOEt:MeOH = 20:1) to give the monomethoxytrityl ether (31.5 mg, 100%).

$[\alpha]_D^{23.5} = +8.8°$ ($c = 0.16$, $CHCl_3$); IR (neat): $\nu = 3335$, 3187, 2930, 1653, 1605, 1576, 1510, 1447, 1418, 1300, 1252, 1181, 1088, 1034, 831, 797, 729, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.88$ (1H, m), 3.20 (1H, dd, $J = 9$ and 7.6 Hz), 3.46 (1H, dd, $J = 9$ and 4.8 Hz), 3.79 (3H, s), 4.08 (1H, dd, $J = 9.2$ and 9.1 Hz), 4.45 (1H, dd, $J = 8.3$ and 6.5 Hz), 4.45 (1H, m), 5.51 (1H, br), 5.68 (2H, br s), 5.75 (1H, d, $J = 5.6$ Hz), 6.82 (2H, m), 7.2–7.45 (12H, m), 7.94 (1H, s), 8.27 (1H, s) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 46.08$ (C3′), 55.23 (OCH_3), 62.38 (C4′), 71.84 (C2′), 77.99 (C5′), 86.48 (CAr_3), 92.68 (C1′), 113.17 (*ortho*-C × 2 of MeOAr), 120 (C5), 127.01 (2C of Ph), 127.89 (4C of Ph), 128.31 (4C of Ph), 130.29 (2C of Ph), 135.32 (*para*-C of MeOAr), 138.34 (C8), 144.15 and 144.24 (2 × *meta*-C of MeOAr), 149.12 (C4), 152.51 (C6), 155.60 (C2), 158.61 (C–OMe) ppm.

9-((1R,2R,3S)-Tetrahydro-2-hydroxy-3-(hydroxymethyl)-1-furanyl)-9H-adenine (**2A**; $C_{10}H_{13}N_5O_3$)

To the above monomethoxytrityl ether (12.0 mg, 0.023 mmol), AcOH (0.64 cm^3) and H_2O (0.16 cm^3) were added, and the mixture was stirred at room temperature for 5 h. After removal of the solvent, the residue was coevaporated with toluene and purified by flash chromatography ($CHCl_3$:MeOH = 5:1) to give the adenosine analogue **2A** (6 mg, 100%).

$[\alpha]_D^{20} = -21.6°$ ($c = 0.25$, $CHCl_3$); IR (neat): $\nu = 3335$, 3187, 2924, 1651, 1605, 1576, 1478, 1420, 1061 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 2.57$ (1H, m), 3.65 (2H, d, $J = 5.8$ Hz), 4.11 (1H, dd, $J = 9$ and 8 Hz), 4.30 (1H, dd, $J = 9$ and 8 Hz), 4.54 (1H, dd, $J = 6$ and 4.4 Hz), 5.77 (1H, d, $J = 4.4$ Hz), 7.96 (1H, s), 8.18 (1H, s) ppm; ^{13}C NMR (50 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 52.55$ (C3′), 64.48 (C4′), 74.71 (C2′), 80.93 (C5′), 96.10 (C1′), 123 (C5), 143.09 (C8), 153 (C4), 156.42 (C6), 159.59 (C2) ppm.

2-N-Acetyl-6-O-diphenylcarbamoyl-9-((1R,2R,3S)-tetrahydro-2-acetoxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-9H-guanine (**19a**; $C_{47}H_{42}N_6O_7$)

To a suspension of 2-N-acetyl-6-O-diphenylcarbamoylguanine **18** (40 mg, 0.10 mmol) in 1,2-dichloroethane (1 cm^3), N,O-*bis*-(trimethylsilyl)-acetamide (0.080 cm^3, 0.32 mmol) was added, and the mixture was stirred under reflux for 15 min. After removal of the solvent, the residue was dissolved in toluene (0.5 cm^3). To the solution, a mixture of diacetates **15** and **16** (19 mg, 0.039 mmol) in toluene (0.5 cm^3) and trimethylsilyl triflate (*TMSOTf*, 0.065 cm^3) were added, and the mixture was stirred at 90°C (bath temperature). After neutralization with aq. $KHCO_3$, the mixture was extracted with AcOEt and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (hexane:AcOEt = 1:2, AcOEt:MeOH = 30:1) to give the acetate **19a** (23 mg, 72%) and the detritylated product (4 mg, 19%).

$[\alpha]_D^{23} = +6°$ ($c = 0.13$, $CHCl_3$); IR (neat): $\nu = 3310$, 2900, 1748, 1622, 1590, 1510, 1493, 1449, 1412, 1372, 1298, 1231, 1183, 1063, 1034, 984, 758, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.07$ (3H, s), 2.44 (3H, s), 2.79 (1H, m), 3.29 (1H, dd, $J = 9.7$ and 4 Hz), 3.32 (1H, dd, $J = 9.7$ and 3.5 Hz), 3.77 (3H, s), 4.17 (1H, dd, $J = 8.8$ and 7.9 Hz), 4.31 (1H, dd, $J = 8.8$ and 7.9 Hz), 5.75

(1H, dd, $J = 5.5$ and 3.6 Hz), 5.93 (1H, d, $J = 3.6$ Hz), 6.81 (2H, m), 7.2–7.55 (22H, m), 7.78 (1H, br s), 7.87 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.74$ (CH_3COO), 25.09 (CH_3CON), 45.71 (C3′), 55.24 (OCH_3), 61.67 (C4′), 71.23 (C2′), 78.61 (C5′), 86.74 (CAr_3), 89.93 (C1′), 113.25 (*ortho*-C × 2 of MeOAr), 121.27 (C5), 127.15 (2C of *Tr*), 127.94 (4C of *Tr*), 128.23 and 128.25 (4C of Ph), 129.24 (Ph), 130.20 (2C of *Tr*), 135.14 (*para*-C of MeOAr), 142.16 (C8), 143.98 (Ph), 144.04 (Ph), 150.28 (C4), 152.02 (C2), 154.45 (C6), 156.23 (OCON), 158.70 (C–OMe), 169.97 ($NCOCH_3$) ppm.

9-((1R,2R,3S)-Tetrahydro-2-hydroxy-3-(((4-methoxyphenyl)-diphenylmethoxy)-methyl)-1-furanyl)-9H-guanine ($C_{30}H_{29}N_5O_5$)

To a solution of the above acetate (54 mg, 0.066 mmol) in MeOH (5.9 cm^3), sat. aq. NH_3 (2 cm^3) was added, and the mixture was stirred at room temperature for 66 h. After removal of the solvent, the residue was purified by flash chromatography (AcOEt:MeOH = 10:1) to give the monomethoxytrityl ether (33 mg, 93%).

$[\alpha]_D^{22} = +72^\circ$ ($c = 0.15$, $CHCl_3$); IR (neat): $\nu = 3337$, 3179, 2922, 1694, 1636, 1607, 1534, 1509, 1489, 1447, 1368, 1250, 1177, 1034, 779, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 2.70$ (1H, m), 3.11 (1H, dd, $J = 9$ and 8 Hz), 3.29 (1H, dd, $J = 8$ and 6 Hz), 3.73 (3H, s), 3.99 (1H, dd, $J = 8.8$ and 8.8 Hz), 4.31 (1H, dd, $J = 8.8$ and 8.8 Hz), 4.35 (1H, dd, $J = 7$ and 4.5 Hz), 5.57 (1H, d, $J = 4.5$ Hz), 6.77 (2H, m), 7.1–7.55 (13H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD = 10:1): $\delta = 50.43$ (C3′), 59.08 (OCH_3), 66.34 (C4′), 75.28 (C2′), 81.26 (C5′), 90.35 (CAr_3), 95.33 (C1′), 117.04 (*ortho*-C × 2 of MeOAr), 120.8 (C5), 130.90 (2C of *Tr*), 131.75 (4C of *Tr*), 132.19 (4C of Ph), 134.15 (2C of *Tr*), 139.26 (*para*-C of MeOAr), 139.5 (C8), 148.04 and 148.12 (2 × *meta*-C of MeOAr), 154.9 (C4), 157.32 (C2), 162.2 (C6), 162.45 (C–OMe) ppm.

9-((1R,2R,3S)-Tetrahydro-2-hydroxy-3-hydroxymethyl-1-furanyl)-9H-guanine (**2G**; $C_{10}H_{13}N_5O_4$)

To the above monomethoxytrityl ether (18.0 mg, 0.033 mmol), AcOH (0.92 cm^3) and water (0.23 cm^3) were added, and the mixture was stirred at room temperature for 6 h. After removal of the solvent, the residue was coevaporated with toluene and washed with Et_2O and AcOEt to give the guanosine analogue **2G** (9 mg, 100%).

$[\alpha]_D^{22} = -23^\circ$ ($c = 0.06$, MeOH); IR (neat): $\nu = 3341$, 3127, 1696, 1603, 1534, 1485, 1364, 1250, 1180, 1044, 781 cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 2.33$ (1H, m), 3.51 (1H, ddd, $J = 11$, 7.6 and 5.5 Hz), 3.61 (1H, ddd, $J = 11$, 5 and 4.8 Hz), 3.92 (1H, dd, $J = 8.8$ and 8.2 Hz), 4.02 (1H, dd, $J = 8.2$ and 8.2 Hz), 4.39 (1H, ddd, $J = 7.5$, 5.5 and 5.5 Hz, C2′–H), 4.72 (1H, dd, $J = 5.5$ and 5 Hz, C5′–OH), 5.537 (1H, d, $J = 5.5$ Hz), 5.542 (1H, d, $J = 5.5$ Hz), 6.41 (2H, br s), 7.83 (1H, s), 10.57 (1H, br s) ppm.

Antiviral assays

The antiviral assays, other than HIV, were based on inhibition of virus-induced cytopathicity in either E_6SM (herpes simplex virus type 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, vesicular stomatitis virus and thymidine kinase-deficient HSV-1 (KOS-ACV^R)), Vero (parainfluenza-3, reovirus-1, Sindbis, Coxsackie B4, Punta Toro virus), or HeLa (Vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytial virus) cell cultures. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus, 1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures. After a 1 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (400, 200, 100, ... μg/cm^3) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. The methodology of the anti-HIV assays was as follows: human CEM ($\sim 3 \times 10^5$ cells · cm^{-3}) cells were infected with $CCID_{50}$

(HIV) (III_B) or HIV-2 (ROD)/cm^3 and seeded in 200 cm^3 wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37°C, HIV-induced CEM giant cell formation was examined microscopically.

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