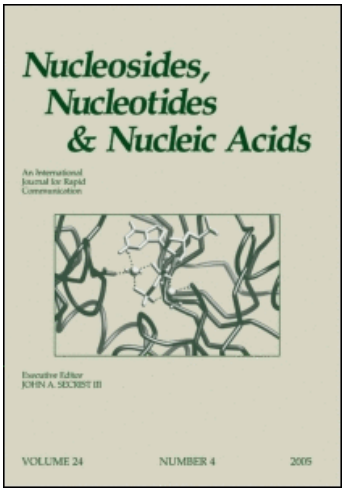

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Racemic Synthesis and Antiviral Evaluation of 4'(α)-Hydroxymethyl and 6'(α)-Methyl Substituted Apiosyl Nucleosides

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RACEMIC SYNTHESIS AND ANTIVIRAL EVALUATION OF 4′(α)-HYDROXYMETHYL AND 6′(α)-METHYL SUBSTITUTED APIOSYL NUCLEOSIDES

Aihong Kim and Joon Hee Hong □ *College of Pharmacy, Chosun University, Kwangju, Republic of Korea*

□ *This article reports the novel synthesis of substituted apiosyl nucleosides. The key apiosyl intermediate **9** was constructed by sequential ozonolysis, reductions, and acetylation from the ester derivative **6**. The nucleosides of uracil, thymine, cytosine, and adenine were synthesized using the glycosyl condensation procedure (silyated base and TMSOTf). The antiviral activities of the synthesized compounds against the HIV-1, HSV-1, HSV-2, and HCMV viruses were evaluated. The adenine derivative **26** showed weak anti-HIV activity ($EC_{50} = 10.1\ \mu g/ml$) without exhibiting any cytotoxicity up to a concentration of 100 μM.*

Keywords Antiviral agents; substituted apiosyl nucleoside; Ozonolysis

INTRODUCTION

Emerging drug-resistant viral strains in addition to the toxicity of various drugs are major problems in antiviral chemotherapy.[1] Therefore, there has been considerable research into the synthesis of structurally modified nucleosides. Recently, several branched-nucleosides[2] were synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4′(α)-*C*-cyanothymidine[3] (**1**), which has an additional branch at the 4′-position, was reported to show potent antiviral activity (Figure 1). More fundamental modifications of the pentofuranose moiety, such as isonucleosides and apionucleosides, were reported to be compatible with the antiviral activities. The apiosyl nucleosides[4] are a group of compounds that are structurally similar to natural nucleosides where the 4′-hydroxymethyl group of the classical nucleosides is moved to the C3′ position. Among this type of

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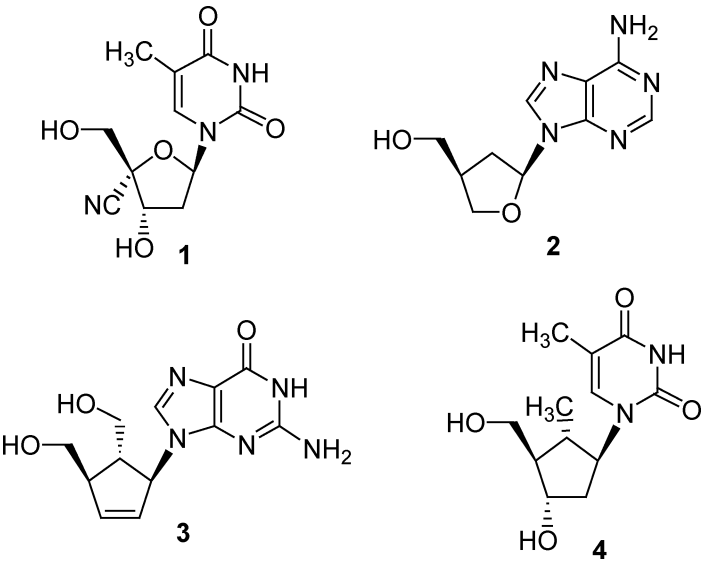


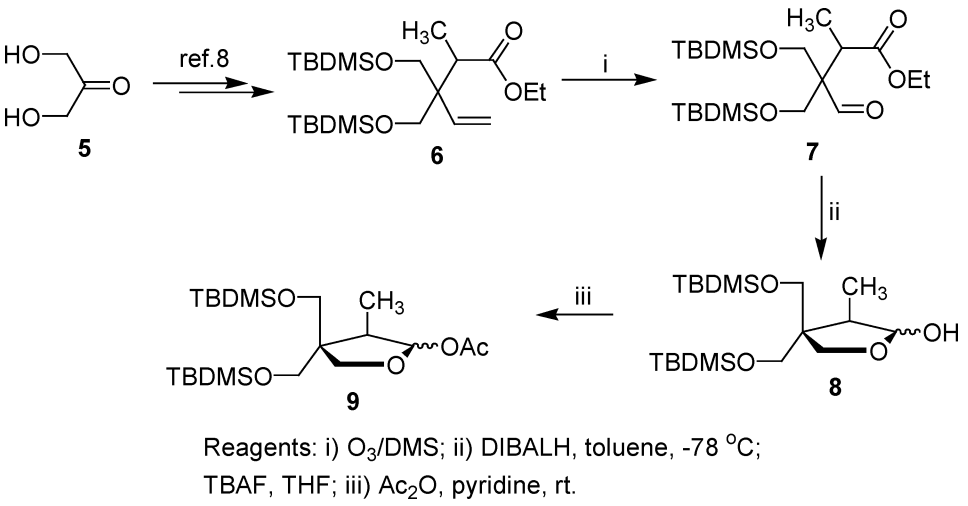
FIGURE 1 Synthesis rationale of target nucleotides

nucleoside, the adenine analogue (apio-ddA, **2**) was reported to show comparable anti-HIV activity to the parent 2′,3′-didieoxy adenosine.[5] Apio-ddA appears to possess the intrinsic metabolic advantages such as resistance to adenosine deaminase (ADA) and enhanced stability of glycosidic bond under acidic and enzymatic conditions compared to natural 2′,3′-dideoxynucleosides (ddNs) nucleosides.[6] Usually, ddNs have several drawbacks such as easy cleavage of their glycosidic bond under acidic conditions similar to a gastric environment and catabolism by ADA, adenosine-5′-monophosphate (AMP) deaminase, and purine nucleoside phosphorylase (PNP). Nevertheless, the systematic structure-activity relationship of apiodideoxy nucleosides is not completely understood. Therefore, more effort is needed to search this class of nucleosides for new antiviral agents. For example, the branched compounds synthesized, such as 6′(α)-hydroxymethylcarbovir **3**[7] and 6′(α)-methylcarbathymidine **4**[8] as potential antiviral and antitumor agents has encouraged the search for novel nucleosides in this class of compound (Figure 1).

Herein, we studied the synthetic procedure of novel substituted apiosyl nucleosides in an attempt to find new lead compounds with improved biological activity.

RESULTS AND DISCUSSION

The γ,δ-unsaturated ester derivative **6**, which was readily synthesized from 1,3-dihydroxy acetone using a previously reported method,[9] was

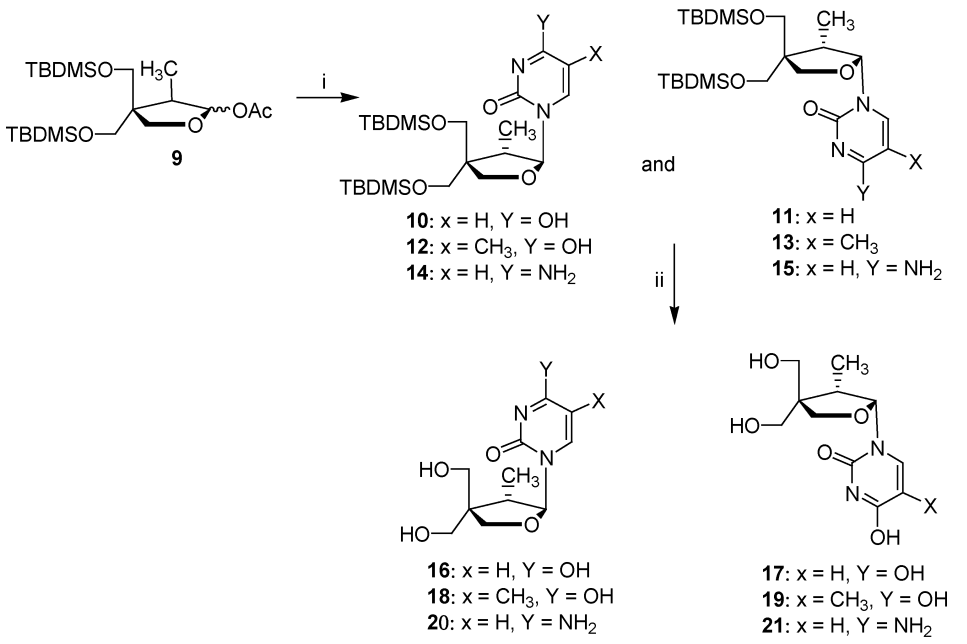


SCHEME 1 Synthesis of apiosyl acetate.

selected as the starting compound for the synthesis of the target nucleosides (Scheme 1).

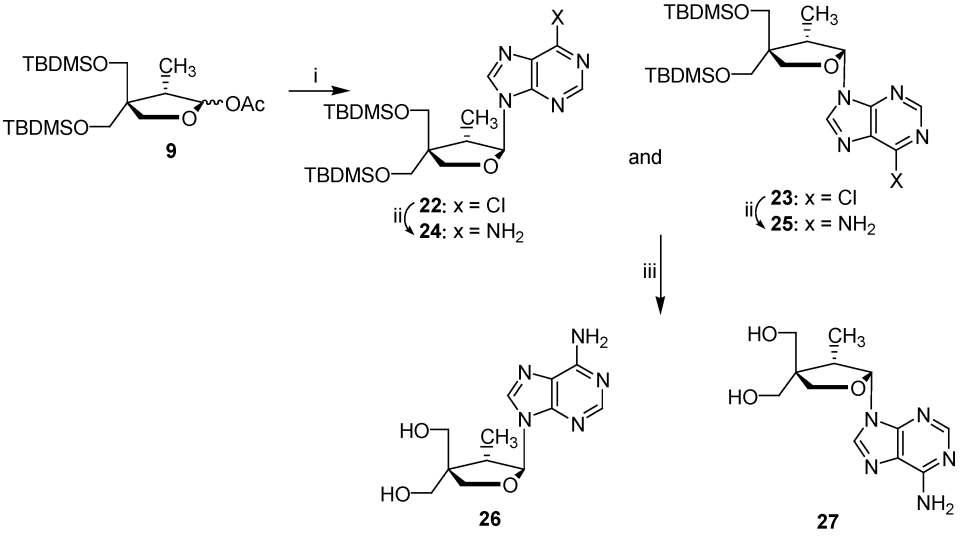
Ester **6** was treated with ozone in methylene chloride at −78°C, followed by the decomposition of the ozonide by dimethylsulfide (DMS) to give the aldehyde **7**. Compound **7** was subsequently reduced using DIBAL-H in toluene at −78°C to give the lactol **8** in 71% yield. The apiose lactol **8** was acetylated in pyridine to furnish the key intermediate **9** as the glycosyl donor (Scheme 1). The pyrimidine nucleosides were prepared by condensing compound **9** with the per-*O*-silylated bases of uracil, thymine and cytosine using trimethylsilyl trifluoromethanesulfonates (TMSOTf) as a catalyst in 1,2-dichloroethane (DCE) to give the protected nucleosides **10**∼**15** (Scheme 2). Actually, high stereoselectivity was not observed in any glycosidation reactions, which could be anticipated from the planar structures of oxonium ion. The deprotected pyrimidine nucleosides were synthesized from the corresponding nucleoside by a treatment with tetrabutylammonium fluoride (TBAF). The synthesis of the purine nucleoside was carried out by the condensation of compound **9** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give the protected 6-chloropurine derivatives **22** and **23**, respectively. These were then treated with ammonia in methanol in a steel bomb at 95–100°C followed by desilylation to give the final adenine nucleosides **26** and **27** (Scheme 3).

The stereochemical assignments of the synthesized compounds were carried out using ^{1}H NMR spectroscopy. A relatively strong cross peak (1.0%) between the proximal hydrogen atoms (anomeric H and CH_3) was found in the NOE spectrum for compound **10**. However, there were weak cross peaks (0.3%) in the spectrum of compound **11** (Figure 2). The



Reagents: i) (a) Bases (uracil, thynine, cytosine), HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated bases, TMSOTf, DCE; ii) TBAF, THF, rt.

SCHEME 2 Synthesis of dually branched pyrimidine nucleosides.



Reagents: i) (a) 6-chloropurine, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated 6-chloropurine, TMSOTf, DCE; ii) NH_3/MeOH, 95 ^oC-100^o C, overnight; iii) TBAF, THF.

SCHEME 3 Synthesis of dually branched purine nucleosides.

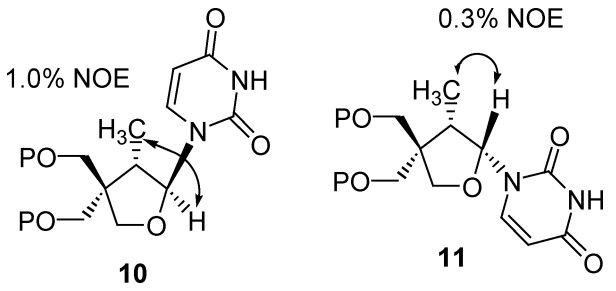


FIGURE 2 NOE result of uracil derivatives **10** and **11**.

stereochemistry of the other nucleoside analogues was determined in a similar manner based on the NOE data.

The antiviral evaluation of the synthesized compounds was performed against several viruses, HIV-1 (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169) (Table 1). However, the adenine derivative **26** showed weak antiviral activity against HIV-1 (EC_{50} = 10.1 μg/mL) without having any cytotoxicity up to a concentration of 100 μg/mL.

In summary, a novel method was developed for synthesizing substituted apiosyl analogues from 1,3-dihydroxyacetone. When the synthesized compounds were tested against several viruses such as the HIV-1, HSV-1, HSV-2, and HCMV, the adenine analogue **26** showed weak antiviral activity against HIV-1. Although we did not find excellent analogue of this class, the

TABLE 1 Antiviral activity of the synthesized compounds

	HIV-1 EC_{50} (μg/ml)	HSV-1 EC_{50} (μg/ml)	HSV-2 EC_{50} (μg/ml)	HCMV EC_{50} (μg/ml)	Cytotoxicity CC_{50} (μg/ml)
16	>100	66.3	>100	56.7	>100
17	>100	88.9	>100	>100	>100
18	37.1	>100	87.4	67.8	>90
19	>100	56.3	>100	>100	>100
20	76.9	>100	90.2	34.7	>100
21	27.2	>100	>100	>100	>100
26	**10.1**	32.6	>100	41.6	>100
27	37.5	78.4	>100	78.9	>100
AZT	0.008	ND	ND	ND	1.36
GCV	ND	ND	ND	1.3	>10
ACV	ND	0.25	ND	ND	>100

AZT: Azidothymidine; GCV: Ganciclovir; ACV: Acyclovir.

ND: Not Determined.

EC_{50} (μg/ml): Concentration required to inhibit 50% of the virus induced cytopathicity.

CC_{50} (μg/ml): Concentration required to reduce cell viability by 50%.

HCMV: Human cytomegalovirus.

information obtained in the present study will be useful for the development of novel nucleoside antiviral agents.

Experiments

All the chemicals were of reagent grade and were used as received without further purification. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer (Tokyo, Japan). The chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer (South Pasadena, CA, USA). The elemental analysis was performed using an Elemental Analyzer System (EA1112, ThermoFinnegan). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(±)-Ethyl-3,3′-bis-(t-butyldimethylsilyloxymethyl)-2-methyl-4-oxobutyrate (7): A solution of compound **6** (5.17 g, 12.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled to −78°C, and ozone gas was bubbled into the reaction mixture until a blue color had persisted for 5 minutes. The reaction mixture was then degassed with nitrogen, and methyl sulfide (4.4 mL, 60 mmol) was slowly added at −78°C. The mixture was stirred for 2 hours at room temperature under nitrogen. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:35) to give compound **7** (4.15 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.88–3.69 (m, 4H), 2.72 (q, J = 7.4 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 7.4 Hz, 3H), 0.86 (s, 18H), 0.02 (s, 12H); ^{13} C NMR ($CDCl_3$, 75 MHz) δ 204.36, 175.33, 64.54, 61.36, 55.32, 41.11, 25.81, 18.67, 14.10, 12.30, −5.65.

(*rel*)-(2*R* and 2 *S*,3 *S*)-4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-ol (8): A 1.5 M solution of DIBAL-H (7.5 mL, 11.2 mmol) in toluene was added dropwise to a solution of compound **7** (2.17 g, 5.03 mmol) in anhydrous toluene (40 mL) at −78°C under nitrogen. The mixture was then stirred for 15 minutes at −78°C. The reaction was quenched by MeOH (11 mL) and the temperature was elevated to room temperature. After stirring at room temperature for 2 hours, the resulting solid was removed by Celite filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **8** (1.29 g, 66%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.26 (m, 1H), 3.74–3.38 (m, 6H), 1.82 (m, 1H), 1.15 (dd, J = 12.8, 6.8 Hz, 3H), 0.87 (s, 9H), 0.82 (s, 9H),

0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 102.63, 73.29, 65.22, 63.04, 61.54, 52.42, 37.95, 34.10 25.74, 18.21, 12.88, 11.12, −5.68; Anal calc for $C_{19}H_{42}O_4Si_2$: C, 58.41; H, 10.84. Found: C, 58.20; H, 10.82.

(*rel*)-(2*R* and 2 *S*,3 *S*)-Acetic acid-[4,4-bis-(tert-butyldimethylsilanyloxymethyl) tetrahydrofuran-3-methyl-2-yl]ester (9): Ac_2O (0.71 g, 7.0 mmol) was slowly added to a solution of compound **8** (1.82 g, 4.67 mmol) in anhydrous pyridine (30 mL). The mixture was then stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure. The residue was extracted with EtOAc/H_2O, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **9** (1.67 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.13, 6.02 (s, s, 1H), 3.81 (d, J = 9.6 Hz, 1H), 3.77 (d. J = 9.6 Hz, 1H), 3.60 (d, J = 9.4 Hz, 1H), 3.50 (d, J = 9.4 Hz, 1H), 2.05, 2.00 (s, s, 3H), 1.11 (m, 1H), 1.01 (d, J = 6.9 Hz, 1H), 0.88 (s, 9H), 0.82 (s, 9H), 0.03 (s, 6), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 102.64, 95.45, 73.30, 73.09, 65.21, 63.06, 62.68, 52.45, 37.43, 25.81, 18.15, 12.91, 11.14, −5.65; Anal calc for $C_{21}H_{44}O_5Si_2$: C, 58.29; H, 10.25. Found: C, 58.51; H, 10.01.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-yl]uracil (10) and (*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl) tetrahydrofuran-3-methyl-2-yl]uracil (11): Uracil (150 mg, 1.33 mmol), anhydrous HMDS (15 mL), and a catalytic amount of ammonium sulfate were heated under reflux until a clear solution had formed, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (DCE). A solution of compound **9** (290 mg, 0.67 mmol) in dry DCE (7 mL) and TMSOTf (0.24 mL, 1.33 mmol) was added to this mixture. The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with 3 mL of saturated $NaHCO_3$ and stirred for 20 minutes. The resulting solid was filtered through a celite pad, and the filtrate was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compounds **10** (101 mg, 31%) and **11** (107 mg, 33%), respectively: Compound **10:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (br s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.17 (s, 1H), 5.65 (dd, J = 8.1, 2.4 Hz, 1H), 4.28 (t, J = 8.4 Hz, 1H), 3.79–3.61 (m, 3H), 3.52 (d, J = 10.8 Hz, 1H), 3.42 (d, J = 10.8 Hz, 1H), 2.45–2.36 (m, 1H), 1.05 (d, J = 8.7 Hz, 3H), 0.87 (s, 9H), 0.80 (s, 9H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13} C NMR ($CDCl_3$, 75 MHz) δ 165.14, 150.31, 141.44, 100.71, 75.48, 63.40, 62.24, 54.07, 36.46, 25.81, 18.28, 10.29, −5.69; Compound **11:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (br s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.11 (d, J = 4.8 Hz, 1H), 5.69 (d, J = 7.8 Hz, 1H), 4.21 (t, J = 8.4 Hz, 1H), 3.81 (d, J = 10.2 Hz, 1H), 3.75 (d, J = 10.2 Hz, 3.63 (d, J = 10.4 Hz, 1H), 3.48–3.32 (m, 2H), 2.42 (m, 1H), 1.03 (d, J = 8.6 Hz,

3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.32, 150.54, 140.76, 101.65, 74.22, 63.87, 62.06, 54.47, 37.61, 25.38, 18.58, 11.32, −5.49.

Compounds **12**, **13**, **14**, **15**, **22**, and **23** were prepared from the corresponding bases using a similar procedure as that described for synthesizing compounds **10** and **11**:

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-yl]thymine (12) and (*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl) tetrahydrofuran-3-methyl-2-yl]thymine (13): Compound **12:** yield 29%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (br s, 1H), 7.36 (s, 1H), 6.07 (s, 1H), 4.32 (t, J = 8.2 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 3.54 (m, 2H), 2.10 (m, 1H), 1.98 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.76, 151.54, 134.54, 107.76, 75.81, 64.29, 63.76, 55.65, 36.68, 25.54, 18.54, 12.21, 11.32, −5.65; Compound **13:** yield 28%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (br s, 1H), 7.31 (s, 1H), 6.05 (d, J = 5.4 Hz, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.65 (d, J = 11.4 Hz, 1H), 3.54 (m, 1H), 3.38 (d, J = 11.7 Hz, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.76, 151.54, 134.54, 107.76, 75.81, 64.29, 63.76, 55.65, 36.68, 25.54, 18.54, 12.21, 11.32, −5.65.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-yl]cytosine (14) and (*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl) tetrahydrofuran-3-methyl-2-yl]cytosine (15): Compound **14:** yield 19%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 7.5 Hz, 1H), 6.13 (s, 1H), 5.61 (d, J = 7.6 Hz, 1H), 4.28 (t, J = 7.5 Hz, 1H), 3.83–3.69 (m, 3H), 3.46 (dd, J = 14.4, 10.8 Hz, 1H), 2.54 (m, 1H), 1.12 (d, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.32, 156.43, 145.87, 93.44, 74.76, 63.69, 62.21, 54.55, 36.76, 25.61, 18.39, 11.02, −5.51; Compound **15:** yield 15%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, J = 7.6 Hz, 1H), 6.12 (d, J = 5.8 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 4.30 (t, J = 7.6 Hz, 1H), 3.87 (d, J = 10.2 Hz, 1H), 3.65 (m, 2H), 3.54 (d, J = 12.8 Hz, 1H), 3.45 (d, J = 12.7 Hz, 1H), 2.47 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.21, 156.67, 144.76, 94.65, 75.76, 64.71, 62.93, 54.50, 36.61, 25.54, 18.29, 11.32, −5.58.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] uracil (16): Tetrabutylammonium fluoride (0.99 mL, 1.0 M solution in THF) was added to a solution of **10** (160 mg, 0.33 mmol) in tetrahydrofurane (7 mL),at 0°C. The mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give compound **16** (64.3

mg, 76%): m.p. 157–159°C; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.21 (br s, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.08 (s, 1H), 5.57 (d, J = 7.6 Hz, 1H), 4.99 (t, J = 5.2 Hz, 1H), 4.80 (t, J = 5.2 Hz, 1H), 4.26 (t, J = 8.2 Hz, 1H), 3.82 (d, J = 10.0 Hz, 2H), 3.67–59 (m, 2H), 2.46 (m, 1H), 1.01 (d, J = 8.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.76, 151.43, 142.80, 102.49, 74.37, 64.10, 62.42, 53.42, 37.59, 10.95; Anal calc for $C_{11}H_{16}N_2O_5$(+0.7H_2O): C, 49.13; H, 6.52; N, 10.42. Found: C, 48.98; H, 6.41; N, 10.56.

Compounds **17**, **18**, **19**, **20**, **21**, **26**, and **27** were prepared from thymine using a similar procedure to that described for synthesizing compounds **10** and **11**:

(*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] uracil (17): yield 70%; m.p. 162–164°C; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.31 (br s, 1H), 7.27 (d, J = 7.4 Hz, 1H), 6.10 (d, J = 5.8 Hz, 1H), 5.55 (d, J = 7.6 Hz, 1H), 4.95 (t, J = 5.4 Hz, 1H), 4.82 (t, J = 5.2 Hz, 1H), 4.23 (t, J = 8.4 Hz, 1H), 3.80–3.71 (m, 2H), 3.63–51 (m, 3H), 2.44 (m, 1H), 1.00 (d, J = 8.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.21, 152.67, 143.51, 105.77, 75.71, 64.89, 61.62, 54.72, 36.70, 11.02; Anal calc for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.72; H, 6.36; N, 10.78.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] thymine (18): yield 80%; m.p. 161–163°C; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.50 (br s, 1H), 7.25 (s, 1H), 6.03 (s, 1H), 4.26 (d, J = 7.6 Hz, 1H), 3.80 (d, J = 6.8, 1H), 3.68–3.57 (m, 3H), 3.57 (d, J = 10.6 Hz, 1H), 2.43 (m, 1H), 1.31 (s, 3H), 1.04 (d, J = 9.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.62, 151.57, 138.61, 102.69, 73.32, 65.81, 63.38, 56.00, 36.62, 11.85, 10.76; Anal calc for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.21; H, 6.83; N, 10.48.

(*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] thymine (19): yield 76%; m.p. 154–156°C; UV (H_2O) λ_{max} 267.6 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.57 (br s, 1H), 7.24 (s, 1H), 6.11 (d, J = 5.4 Hz, 1H), 4.94 (br s, 1H), 4.85 (t, J = 5.4 Hz, 1H), 4.24 (t, J = 7.6 Hz, 1H), 3.89–3.78 (m, 3H), 3.59 (d, J = 10.2 Hz, 1H), 3.57 (d, J = 10.2 Hz, 1H), 2.48 (m, 1H), 1.34 (s, 3H), 1.01 (d, J = 10.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.69, 152.41, 137.69, 101.74, 74.69, 64.37, 62.18, 57.37, 37.72, 11.90, 10.97; Anal calc for $C_{12}H_{18}N_2O_5$(+0.5MeOH): C, 52.44; H, 7.04; N, 9.78. Found: C, 52.28; H, 6.92; N, 9.67.

(*rel*)-(2′*R*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] cytosine (20): yield 82%; m.p. 159–161°C; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.52 (d, J = 7.6 Hz, 1H), 5.99 (s, 1H), 5.71 (d, J = 7.6 Hz, 1H), 4.27 (t, J = 8.4 Hz, 1H), 3.87 (dd, J = 12.6, 6.8 Hz, 2H), 3.70 (d, J = 10.2 Hz, 1H), 3.62 (d, J = 10.0 Hz, 1H), 3.56 (d, J = 10.2 Hz, 1H), 2.38 (m, 1H), 0.98 (d, J = 9.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.26, 154.71, 143.82, 91.49, 74.32, 64.43, 62.29, 56.91, 36.30; Anal calc

for $C_{11}H_{17}N_3O_4(+1.0H_2O)$: C, 48.34; H, 7.00; N, 15.37. Found: C, 48.52; H, 6.86; N, 15.47.

(*rel*)-(2′*S*,3′*S*)-1-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] cytosine (21): yield 76%; m.p. 162–164°C; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.49 (d, $J = 7.6$ Hz, 1H), 6.05 (d, $J = 5.2$ Hz, 1H), 5.70 (d, $J = 7.6$ Hz, 1H), 5.02 (t, $J = 5.4$ Hz, 1H), 4.89 (t, $J = 5.4$ Hz, 1H), 4.20 (t, $J = 8.4$ Hz, 1H), 3.89 (dd, $J = 12.6$, 6.8 Hz, 2H), 3.71 (d, $J =$ 10.2 Hz, 1H), 3.60 (dd, $J = 13.4$, 6.8 Hz, 2H), 2.45 (m, 1H), 1.13 (d, $J =$ 10.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.62, 153.45, 142.21, 93.78, 75.63, 65.67, 63.79, 57.23, 37.02; Anal calc for $C_{11}H_{17}N_3O_4(+0.6MeOH)$: C, 50.75; H, 7.12; N, 15.31. Found: C, 50.60; H, 7.37; N, 15.46.

(*rel*)-(2′*R*,3′*S*)-6-Chloro-9-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)-tetrahydrofuran-3-methyl-2-yl]purine (22) and (*rel*)-(2′*S*,3′*S*)-6-Chloro-9-[4,4-Bis-(tert-butyldimethylsilanyl oxymethyl) tetrahydrofuran-3-methyl-2-yl]purine (23): Compound **22**: yield 28%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.92 (s, 1H), 8.36 (s, 1H), 5.96 (s, 1H), 4.29 (t, $J = 7.8$ Hz, 1H), 3.80 (m, 3H), 3.63 (d, $J = 10.0$ Hz, 1H), 3.46 (d, $J = 10.2$ Hz, 1H), 2.50 (m, 1H), 1.12 (d, $J = 7.4$ Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.98, 151.87, 147.31, 145.65, 131.65, 74.28, 65.43, 63.10, 55.74, 36.32, 25.64, 18.82, 11.06, −5.60; Compound **23**: yield 25%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (s, 1H), 8.20 (s, 1H), 5.99 (d, $J = 5.8$ Hz, 1H), 4.33 (t, $J = 7.6$ Hz, 1H), 3.89–3.78 (m, 3H), 3.58 (dd, $J = 14.8$, 6.8 Hz, 2H), 2.42 (m, 1H), 1.09 (d, $J = 7.6$ Hz, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.06 (s, 6H), 0.03 (s, 6H); ^{13} C NMR ($CDCl_3$, 75 MHz) δ 155.21, 152.54, 146.39, 144.78, 129.38, 73.44, 64.21, 62.78, 54.51, 36.82, 25.48, 18.56, 11.32, −5.66.

(*rel*)-(2′*R*,3′*S*)-9-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-yl]adenine (24): Adenine derivative **24** (135 mg, 0.256 mmol) was synthesized from compound **22** by treating it with saturated methanolic ammonia at 95–100°C in a steel bomb for 20 hours. After removing solvent, the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give compound **24** (100 mg, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 8.00 (s, 1H), 6.05 (s, 1H), 4.21 (t, $J = 8.8$ Hz, 1H), 3.82–3.74 (m, 3H), 3.63 (dd, $J = 13.6$, 9.6 Hz, 2H), 2.46 (m, 1H), 1.07 (d, $J = 9.8$ Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.65, 152.89, 150.61, 141.45, 119.62, 75.62, 64.61, 62.39, 56.42, 36.63, 25.53, 18.21, 11.07, −5.39.

(*rel*)-(2′*S*,3′*S*)-9-[4,4-Bis-(tert-butyldimethylsilanyloxymethyl)tetrahydrofuran-3-methyl-2-yl]adenine (25): Adenine derivative **25** was synthesized from compound **23** by the similar method to that described for synthesizing compound **24**: yield 75%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (s, 1H), 8.05 (s, 1H), 6.01 (d, $J = 5.8$ Hz, 1H), 4.15 (t, $J = 9.6$ Hz, 1H), 3.79 (dd, $J =$ 12.4, 8.6 Hz, 2H), 3.67–3.57 (m, 3H), 2.32 (m, 1H), 0.98 (d, $J = 9.6$ Hz,

3H), 0.86 (s, 9H), 0.80 (s, 9H), 0.04 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.43, 151.32, 149.48, 140.32, 118.31, 74.70, 65.31, 62.39, 55.42, 35.79, 25.41, 18.20, 10.82, −5.52.

(*rel*)-(2′*R*,3′*S*)-9-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] adenine (26): yield 73%; m.p.172–175°C; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 8.02 (s, 1H), 5.97 (s, 1H), 5.01 (t, J = 5.4 Hz, 1H), 4.92 (t, J = 5.4 Hz, 1H), 4.16 (t, J = 8.8 Hz, 1H), 3.79 (dd, J = 12.8, 8.6 Hz, 2H), 3.63 (d, J = 9.2 Hz, 1H), 3.52 (dd, J = 12.8, 9.4 Hz, 2H), 2.40 (m, 1H), 1.04 (d, J = 9.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.98, 151.37, 149.47, 141.21, 118.57, 74.17, 64.21, 61.89, 56.65, 36.32, 10.87; Anal calc for $C_{12}H_{17}N_5O_3$(+0.8MeOH): C, 50.42; H, 6.67; N, 22.97. Found: C, 50.56; H, 6.81; N, 22.96.

(*rel*)-(2′*S*,3′*S*)-9-[4,4-Bis-(hydroxymethyl)tetrahydrofuran-3-methyl-2-yl] adenine (27): yield 78%; m.p. 175–177°C; UV (H_2 O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.18 (s, 1H), 8.03 (s, 1H), 5.94 (dd, J = 5.6 Hz, 1H), 4.96 (t, J = 5.2 Hz, 1H), 4.89 (br s, 1H), 4.12 (t, J = 8.6 Hz, 1H), 3.84 (dd, J = 13.4, 8.2 Hz, 2H), 3.75–3.66 (m, 2H), 3.55 (d, J = 10.4 Hz, 1H), 2.44 (m, 1H), 1.01 (d, J = 9.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.43, 151.65, 147.41, 140.61, 118.50, 74.67, 65.52, 62.71, 57.44, 35.90, 10.88; Anal calc for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.83; H, 6.82; N, 16.59.

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