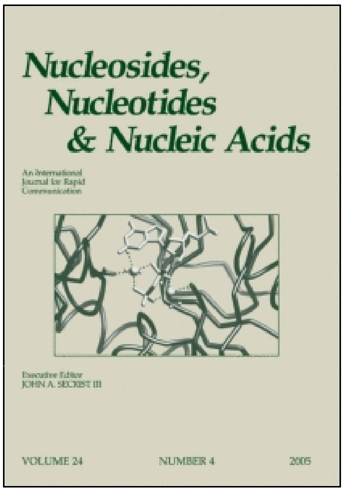

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Synthesis and Antiviral Evaluation of Novel 4'-Hydroxymethyl Branched Apiosyl Nucleosides

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SYNTHESIS AND ANTIVIRAL EVALUATION OF NOVEL 4′-HYDROXYMETHYL BRANCHED APIOSYL NUCLEOSIDES

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□ *Novel 4′-hydroxymethyl branched apiosyl nucleosides were synthesized in this study. The introduction of a hydroxymethyl group in the 4′-position was accomplished by a [3,3]-sigmatropic rearrangement. Apiosyl sugar moiety was constructed by sequential ozonolysis and reductions. The natural bases (uracil, thymine, cytosine, and adenine) were efficiently coupled by a classical glycosyl condensation procedure (persilyated base and TMSOTf). The antiviral activities of the synthesized compounds were evaluated against HIV-1, HSV-1, HSV-2, and HCMV. Compound* ***18*** *displayed moderate anti-HCMV activity ($EC_{50} = 20.1\ \mu g/mL$) without exhibiting any cytotoxicity up to $100\ \mu M$.*

Keywords Antiviral agents; Branched nucleoside; Apiosyl nucleoside; Claisen rearrangement; Ozonolysis

INTRODUCTION

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of nucleoside chemists for a several decades. In particular, since the emergence of the HIV pandemic, extensive efforts have been concentrated on various modifications in the sugar moiety of nucleosides, resulting in FDA approved anti-HIV agents such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] and abacavir.[6] However, side effects and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents. It is now clear that judicious combination therapy is the optimum way to improve the survival of patients infected with HIV-1. Therefore, the development of structurally new nucleoside derivatives, which have potent antiviral activities and low toxicity as well as novel resistant profiles, are urgently needed to provide better choices for combination chemotherapy. Recently, the compounds synthesized (Figure 1), 4′-cyanothymidine **1**,[7] 4′-azidothymidine **2**,[8] and 4′-hydroxymethythymidine **3**[9] are of particular interest as they represent a new

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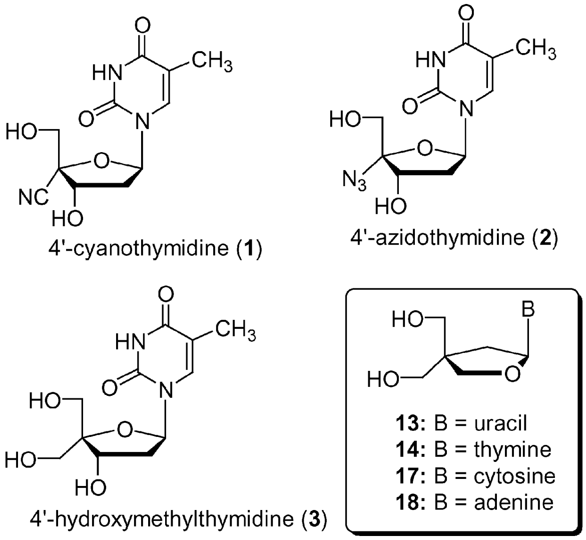
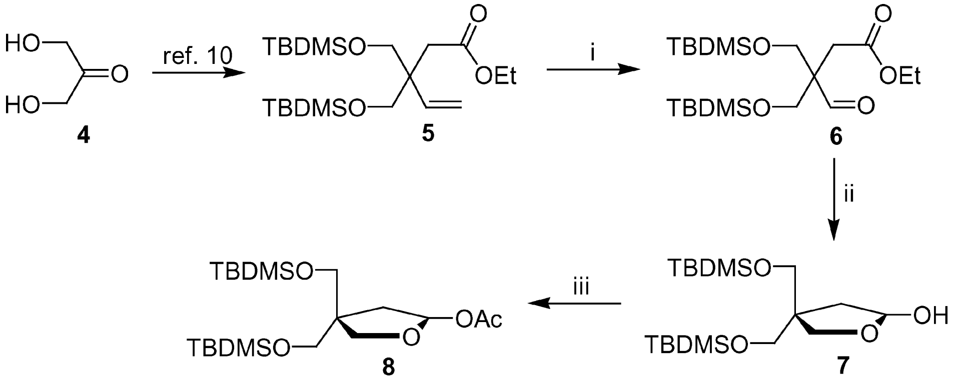


FIGURE 1 Structures of potent 4′-branched nucleosides, and target nucleosides.

class of compounds and exhibit significant biological activity. Furthermore, more fundamental modifications of the pentofuranose moiety, such as isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities. In attempts to find new lead compounds with improved biological activity, we have synthesized novel 4′-hydroxymethyl branched apionucleosides. Previously, we reported an efficient synthetic method[10] of producing quaternary carbon useful for target molecules using the Claisen rearrangement reaction.

RESULTS AND DISCUSSION

As shown in Scheme 1, the γ,δ-unsaturated ester derivative **5**, which was readily synthesized from 1,3-dihydroxy acetone by a previously reported method[10] (Scheme 1), was selected as the starting compound for the synthesis of the 4′-hydroxymethyl branched apiosyl nucleosides. Ester **5** was treated with ozone in methylene chloride at −78°C, followed by decomposition of the ozonide by dimethylsulfide (DMS) to give the aldehyde **6** and subsequently reduced using DIBAL-H in toluene at −78°C to give lactol **7** in 71% yield. The apiose lactol **7** was acetylated in pyridine to furnish the key intermediate **8** as glycosyl donor (Scheme 1). For the preparation of the uracil and thymine nucleosides, compound **8** was condensed with corresponding per-*O*-silylated bases using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the catalyst in 1,2-dichloroethane (DCE) to give protected nucleosides **9** and **10**, respectively. Cytosine nucleoside **17** was prepared from the corresponding N^4-benzoyl cytosine nucleoside analogue **11**, which was prepared



[a]Reagents: i) O_3, dimethylsulfide, CH_2Cl_2, -78 °C; ii) Dibal-H, toluene, -78 °C; iii) Ac_2O, pyridine, rt.

SCHEME 1 Synthesis of apiosyl acetate.

from corresponding N^4-benzoyl cytosine in a similar method described for **9** and **10**. The synthesis of adenine nucleoside was carried out by condensation of compound **8** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivative **12**, which was treated with ammonia in methanol in a steel bomb at 90–100°C followed by desilylation to give final nucleoside **18** (Scheme 2).

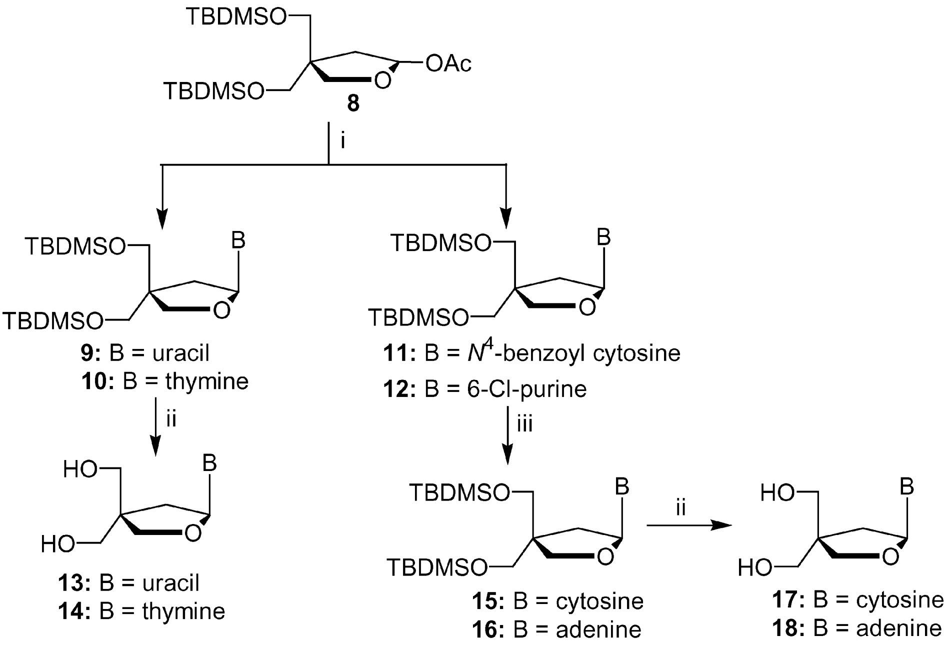
The synthesized compounds **13**, **14**, **17**, and **18** were tested against several viruses such as HIV (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169, Davis cells). All the compounds synthesized showed neither excellent antiviral activity nor any cytotoxicity when tested up to 100 μg/mL. However, the adenine analogue **18** did show moderate antiviral activity against HIV-1 (Table 1), indicating that this virus might allow the sugar moiety for phosphorylation as well as for DNA polymerase, which is different from other viruses.

In summary, a novel synthetic method for 4′-branched apiosyl nucleosides from a simple 1,3-dihydroxy acetone derivative was developed. When

TABLE 1 The Antiviral Activities of the Synthesized Compounds

Compound	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HSV-2 EC_{50} (μg/mL)	HCMV EC_{50} (μg/mL)	Cytotoxicity IC_{50} (μg/mL)
13	>100	>100	>100	>100	>100
14	51.0	>100	>100	>100	>100
17	>100	>100	>100	>100	>100
18	**20.1**	>100	>100	>100	>100
AZT	0.0008	ND	ND	ND	2.01
Ganciclovir	ND	1.9	1.9	ND	>10
Ribavirin	ND	ND	ND	10.5	300.00

ND: Not determined.



[a]Reagents: i) (a) Bases, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) persilylated bases, TMSOTF; ii) TBAF, THF; iii) (a) for **15**: NH_3/MeOH, rt, overnight; (b) for **16**: NH_3/MeOH, steel bomb, 90-100 °C, overnight.

SCHEME 2 Synthesis of target apiosyl nucleosides.

the synthesized compounds were tested against several viruses such as HIV-1, HSV-1, HSV-2, and HCMV, only the adenosine analogue **18** exhibited weak antiviral activity against the HIV-1. The lack of antiviral activity of these racemic compounds is presumably associated with their unfavorable conformations for the phosphorylation step occurring during the nucleotide activation process. However, the information obtained in the present study will be useful for the development of a novel apiosyl nucleoside. Studies toward this end and to clarify the mechanism are underway.

EXPERIMENTAL

All the chemicals were of reagent grade and were used 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. 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. The elemental analyses were performed using an Elemental Analyzer System (EA1112). 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)-4-oxobutyrate (6). A solution of compound **5** (10 g, 23.9 mmol) in anhydrous CH_2Cl_2 (200 mL) was cooled down to −78°C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 min. The reaction mixture was degassed with nitrogen, and methyl sulfide (8.7 mL, 119 mmol) was slowly added at −78°C. The mixture was stirred for 2 h at rt under nitrogen. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **6** (8.7 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.66 (s, 1H), 4.05 (q, $J = 7.2$ Hz, 2H), 3.84–3.64 (m, 4H), 2.36 (s, 2H), 1.19 (t, $J = 7.2$ Hz, 3H), 0.83 (s, 18H), 0.06 (s, 6H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.41, 171.06, 65.40, 60.22, 55.11, 25.48, 18.22, 14.10, −5.72.

(±)-4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-ol (7). To a solution of compound **6** (4.5 g, 10.7 mmol) in anhydrous toluene (100 mL), 1.5 M solution of DIBAL-H (14.9 mL, 22.47 mmol) in toluene was added dropwise at −78°C under nitrogen, and the mixture was then stirred for 20 min at −78°C. The reaction mixture was quenched by MeOH (23 mL), and the temperature was elevated to rt. After stirring at rt for 2 h, 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 **7** (2.86 g, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.24 (dd, $J = 9.3, 4.5$ Hz, 1H), 3.73 (d, $J = 9.3$ Hz, 1H), 3.66 (d, $J = 9.3$ Hz, 1H), 3.54 (dd, $J = 14.4, 9.3$ Hz, 2H), 1.77 (dd, $J = 13.5, 5.1$ Hz, 1H), 1.62 (d, $J = 13.5$ Hz, 1H), 0.81 (s, 9H), 0.75 (s, 9H), 0.04 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ98.63, 70.38, 67.08, 66.39, 49.30, 40.87, 25.83, 18.13, −5.62; Anal calc for $C_{18}H_{40}O_4Si_2$: C, 57.39; H, 10.70. Found: C, 57.55; H, 10.54.

(±)-Acetic Acid 4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl Ester (8). To a solution of compound **7** (3.5 g, 9.34 mmol) in anhydrous pyridine (50 mL), Ac_2O (1.42 g, 14.0 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene. 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, 1:15) to give compound **8** (3.5 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (d, $J = 5.4$ Hz, 1H), 3.72 (s, 2H), 3.59 (s, 2H), 3.46 (dd, $J = 13.5$, 9.6 Hz, 2H), 1.98 (s, 3H), 1.93 (dd, $J = 14.1$, 6.0 Hz, 1H), 1.82 (d, $J = 14.1$ Hz, 1H), 0.84 (s, 9H), 0.82 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.41, 99.62, 73.17, 64.27, 63.78, 49.95, 37.34, 25.64, 21.36, 18.22, −5.61; Anal calc for $C_{20}H_{42}O_5Si_2$: C, 57.37; H, 10.11. Found: C, 57.52; H, 10.20.

(±)-1-[4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl]-uracil (9). Uracil (300 mg, 2.67 mmol), anhydrous HMDS (20 mL), and a catalytic amount of ammonium sulfate were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (DCE). To this mixture, a solution of **8** (559 mg, 1.335 mmol) in dry DCE (10 mL) and TMSOTf (0.48 mL, 2.67 mmol) was added, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with 5 mL of saturated $NaHCO_3$ and stirred for 10 min. 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, 2:1) to give compound **9** (414 mg, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (br s, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 6.00 (t, $J = 5.4$ Hz, 1H), 5.67 (d, $J = 7.8$ Hz, 1H), 4.07 (dd, $J = 13.5$, 6.6 Hz, 2H), 3.89 (d, $J = 8.7$ Hz, 1H), 3.78 (d, $J = 8.7$ Hz, 1H), 3.49 (d, $J =$ 7.5 Hz, 2H), 2.25 (dd, $J = 14.1$, 6.6 Hz, 1H), 1.83 (dd, $J = 14.4$, 5.4 Hz, 1H), 0.82 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.02, 151.78, 141.49, 102,25, 86.83, 72.90, 64.65, 63.93, 50.91, 37.30, 25.79, 18.23, −5.57; Anal calc for $C_{22}H_{42}N_2O_5Si_2$: C, 56.13; H, 8.99; N, 5.95. Found: C, 56.30; H, 8.78; N, 5.82.

(±)-1-[4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl] Thymine (10). Compound **10** was prepared from thymine using the similar method as described for **9**: yield 56%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (br s, 1H), 7.48 (s, 1H), 6.02 (t, $J = 7.5$ Hz, 1H), 4.20 (dd, $J = 8.4$, 3.9 Hz, 1H), 3.91 (dd, $J = 13.5$, 6.8 Hz, 1H), 3.85 (d, $J = 8.7$ Hz, 1H), 3.76 (d, $J = 8.7$ Hz, 1H), 3.54 (d, $J = 12.9$ Hz, 1H), 3.44 (d, $J = 12.9$ Hz, 1H), 2.17 (dd, $J = 13.5$, 6.4 Hz, 1H), 1.80 (dd, $J = 14.0$, 5.6 Hz, 1H), 1.26 (s, 3H), 0.88 (s, 18H), 0.04 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.44, 151.48, 135.79, 106.98, 89.11, 72.44, 64.29, 63.42, 50.62, 36.74, 25.53, 17.95, 12.48, −5.89; Anal calc for $C_{23}H_{44}N_2O_5Si_2$: C, 56.98; H, 9.15; N, 5.78. Found: C, 56.82; H, 9.30; N, 5.82.

(±)-N^4-Benzoyl-1-[4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl]cytosine (11). Compound **11** was prepared from N^4-benzoyl cytosine using the method as described for **9**: yield 65%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97–7.54 (m, 7H), 5.99 (s, 1H), 4.16 (dd, *J* = 10.5, 6.9 Hz, 2H), 3.81 (dd, *J* = 13.5, 6.8 Hz, 2H), 3.66 (dd, *J* = 14.0, 8.7 Hz, 2H), 2.23 (d, *J* = 7.2 Hz, 1H), 2.10 (s, 1H), 0.89 (s, 9H), 0.76 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.02, 161.79, 133.06, 128.98, 127.53, 69.12, 64.73, 62.59, 54.85, 30.16, 25,77, 18.12, −5.55; Anal calc for $C_{29}H_{47}N_3O_5Si_2$: C, 60.69; H, 8.26; N, 7.32. Found: C, 60.49; H, 8.08; N, 7.21.

(±)-6-Chloro-9-[4,4-*bis*-(*tert*-butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl]purine (12). Compound **12** was prepared from 6-Cl-purine using the similar method as described for **9**: yield 60%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 8.04 (s, 1H), 6.02 (s, 1H), 4.04 (dd, *J* = 14.4, 6.6 Hz, 2H), 3.66 (dd, *J* = 16.2, 10.2 Hz, 2H), 3.34 (d, *J* = 10.5 Hz, 1H), 3.22 (d, *J* = 10.5 Hz, 1H), 2.11 (d, *J* = 8.1 Hz, 1H), 1.93 (s, 1H), 0.80 (s, 9H), 0.56 (s, 9H), 0.05 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.75, 152.67, 148.44, 147.89, 129.54, 69.17, 63.64, 62.24, 55.11, 29.55, 25.65, 18.21, 18.02, −5.44, −5.99; Anal calc for $C_{23}H_{41}ClN_4O_3Si_2$: C, 53.83; H, 8.05; N, 10.92. Found: C, 53.78; H, 8.15; N, 10.80.

(±)-1-(4,4-*bis*-Hydroxymethyltetrahydrofuran-2-yl)uracil (13). To a solution of **9** (180 mg, 0.382 mmol) in tetrahydrofurane (10 mL), tetrabutylammonium fluoride (1.15 mL, 1.0 M solution in THF) was added at 0°C. The mixture was stirred for 6 h at rt, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:5) to give compound **13** (66 mg, 72%): mp 168–169°C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.23 (br s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 6.01 (t, *J* = 6.6 Hz, 1H), 5.65 (d, *J* = 8.0 Hz, 1H) 4.97 (t, *J* = 5.4 Hz, 1H), 4.76 (t, *J* = 5.6 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.77 (d, *J* = 9.3 Hz, 1H), 3.52 (m, 4H), 2.27 (dd, *J* = 14.4, 6.9 Hz, 1H), 1.82 (dd, *J* = 14.4, 6.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.34, 153.45, 140.67, 99.31, 78.22, 72.97, 65.25, 64.12, 51.78, 30.21; Anal calc for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.77; H, 5.81; N, 11.40.

(±)-1-(4,4-*bis*-Hydroxymethyltetrahydrofuran-2-yl)thymine (14). Compound **14** was synthesized from **10** with use of similar procedure as described for **13**: yield 78%; mp 166–168°C; UV (H_2O) λ_{max} 265.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.45 (br s, 1H), 7.23 (s, 1H), 6.00 (t, *J* = 7.2 Hz, 1H), 4.12 (d, *J* = 7.8 Hz, 1H), 3.93 (dd, *J* = 6.8, 1H), 3.88 (d, *J* = 8.6 Hz, 1H), 3.72 (d, *J* = 8.6 Hz, 1H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.31 (d, *J* = 13.5 Hz, 1H), 2.15 (dd, *J* = 12.5, 6.8 Hz, 1H), 1.82 (dd, *J* = 12.0, 5.4 Hz, 1H), 1.26 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.76, 151.51, 135.12, 103.34, 89.11, 74.12, 64.67, 62.98, 49.87, 35.76, 11.87; Anal calc for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.79; H, 6.09; N, 10.78.

(±)-1-[4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl) tetrahydrofuran-2-yl]cytosine (15). Compound **11** (200 mg, 0.348 mmol) was treated with saturated methanolic ammonia overnight at rt. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give compound **15** (140 mg, 86%): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, $J = 7.5$ Hz, 1H), 5.90 (s, 1H), 5.72 (d, $J = 7.5$ Hz, 1H), 4.27 (dd, $J = 14.7, 9.0$ Hz, 1H), 4.06 (dd, $J = 14.7, 6.6$ Hz, 1H), 3.80 (d, $J = 9.9$ Hz, 1H), 3.73 (d, $J = 9.9$ Hz, 1H), 3.65 (d, $J = 10.2$ Hz, 1H), 3.56 (d, $J = 10.2$ Hz, 1H), 2.13 (m, 2H), 0.94 (s, 9H), 0.87 (s, 9H), 0.12 (d, $J = 6.0$ Hz, 6H), 0.01 (d, $J = 7.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.50, 156.12, 142.55, 93.14, 90.49, 68.76, 64.94, 62.70, 54.40, 30.78, 25.81, 18.14, −5.67; Anal calc for $C_{22}H_{43}N_3O_4Si_2$: C, 56.25; H, 9.23; N, 8.94. Found: C, 56.11; H, 9.13; N, 8.81.

(±)-9-[4,4-*bis*-(*tert*-Butyldimethylsilanyloxymethyl)tetrahydrofuran-2-yl]adenine (16). Compound **12** (150 mg, 0.29 mmol) was treated with saturated methanolic ammonia for 15 h at 90–100°C in a steel bomb. After removal of the solvent, the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:10) to give compound **16** (101 mg, 70%): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.73 (s, 1H), 5.91 (s, 1H), 4.37 (dd, $J = 14.0, 8.1$ Hz, 1H), 4.02 (dd, $J = 14.2, 7.8$ Hz, 1H), 3.71 (d, $J = 9.6$ Hz, 1H), 3.63 (d, $J = 9.6$ Hz, 1H), 3.34 (d, $J = 10.2$ Hz, 1H), 3.23 (d, $J = 10.2$ Hz, 1H), 2.07 (m, 2H), 0.89 (s, 9H), 0.52 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.45, 152.81, 140.44, 88.99, 68.99, 63.01, 61.95, 55.01, 29.61, 25.83, 18.21, −5.56, −6.01; Anal calc for $C_{23}H_{43}N_5O_3Si_2$: C, 55.94; H, 8.78; N, 14.18. Found: C, 55.81; H, 8.60; N, 14.02.

(±)-1-(4,4-*bis*-Hydroxymethyltetrahydrofuran-2-yl)cytosine (17). Compound **17** was prepared from **15** by the similar method as described for **13**: yield 56%; mp 171–173°C; UV (H_2O) λ_{max} 270.5 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, $J = 7.5$ Hz, 1H), 7.21 (br d, 2H), 5.77 (d, $J = 8.7$ Hz, 1H), 5.73 (d, $J = 7.5$ Hz, 1H), 4.92 (t, $J = 5.6$ Hz, 1H), 4.64 (t, $J = 5.7$ Hz, 1H), 4.20 (dd, $J = 14.1, 6.6$ Hz, 1H), 3.90 (dd, $J = 15.9, 8.1$ Hz, 1H), 3.27 (d, $J = 10.2$ Hz, 1H), 3.21 (d, $J = 10.2$ Hz, 1H), 3.16 (d, $J = 11.1$, 1H), 3.13 (d, $J = 11.1$ Hz, 1H), 1.86 (d, $J = 6.9$ Hz, 1H), 1.81 (d, $J = 12.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.65, 156.12, 141.80, 93.63, 67.77, 62.84, 60,55, 54.91, 54.03, 29.94; Anal calc for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.52; H, 6.38; N, 17.29.

(±)-9-(4,4-*bis*-Hydroxymethyltetrahydrofuran-2-yl)adenine (18). Compound **18** was synthesized from **16** using the similar procedure as described for **13**: yield 60%; mp 180–183°C; UV (H_2O) λ_{max} 260.0 nm; ^1H NMR

(DMSO-d_6, 300 MHz) δ 8.41 (s, 1H), 8.25 (s, 1H), 7.35 (br s, 2H), 6.01 (s, 1H), 5.01 (t, J= 5.8 Hz, 1H), 4.78 (t, J = 5.8 Hz, 1H), 4.21 (dd, J= 13.5, 8.2 Hz, 2H), 3.81 (d, J= 9.2 Hz, 1H), 3.60 (d, J= 9.2 Hz, 1H), 3.24 (d, J= 10.4 Hz, 1H), 3.19 (d, J= 10.2 Hz, 1H), 2.01 (s, 1H), 1.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.61, 152.78, 140.12, 87.34, 69.76, 63.12, 61.67, 54.67, 30.21; Anal calc for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.72; H, 5.55; N, 26.19.

REFERENCES

1. Furman, P.A.; Fyfe, J.A.; St. Clair, M.H.; Weinhold, K.; Rideout, J.L.; Freeman, G.A.; Nusinoff-Lehrman, S.; Bolognesi, D.P.; Broder, S.; Mitsuya, H.; Barry, D.W. Phosphorylation of 3′-azido-3′-deoxythymidine and selective interaction of the 5′-triphosphate with human immunodeficiency virus reverse transcriptase. Proc. Natl. Acad. Sci. U.S.A. **1986**, 83, 8333–8337.
2. Yarchoan, R.; Thomas, R.V.; Allain, J.-P.; McAtee, N.; Dubinsky, R.; Mitsuya, H.; Lawley, T.J.; Safai, B.; Myers, C.E.; Perno, C.F.; Klecker, R.W.; Wills, R.J.; Fischl, M.A.; McNeely, M.C.; Pluda, J.M.; Leuther, M.; Collins, J.M.; Broder, S. The phase I studies of 2′,3′-dideoxycytidine in human immunodeficiency virus infection as single agent and alternating with zidovudine (AZT). Lancet **1988**, 1, 76–81.
3. Yarchoan, R.; Mitsuya, H.; Thomas, R.V.; Pluda, J.M.; Hartman, N.R.; Perno, C.F.; Marczyk, K.S.; Allain, J.-P.; Johns, D.G.; Broder, S. In vivo activity against HIV and favorable toxicity profile of 2′,3′-dideoxyinosine. Science **1989**, 245, 412–415.
4. Lin, T.-S.; Schinazi, R.F.; Prusoff, W.H. Potent and selective in vitro activity of 3′-deoxy thymidine-2′-ene(3′-deoxy-2′,3′dideoxydehydrothymidine) against human immunodeficiency virus. Biochem. Pharmacol. **1987**, 36, 2713–2718.
5. Schinazi, R.F.; Chu, C.K.; Peck, A.; McMillan, A.; Mathis, R. Cannon, D.; Jeong, L.S.; Beach, J.W.; Choi, W.B.; Yeola, S.; Liotta, D.C. Activities of the four optical isomers of 2′,3′-dideoxy-3′-thiacytidine (BCH-189) against human immunodeficiency virus type I in human lymphocytes. Antimicrob. Agents Chemother. **1992**, 36, 672–676.
6. Daluge, S.M.; Good, S.S.; Faletto, M.B.; Miller, W.H.; St. Clair, M.H.; Boone, L.R.; Tisdale, M.; Parry, N.R.; Reardon, J.E.; Dornsife, R.E.; Averett, D.R.; Krenitsky, T.A. A novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. Antimicrob. Agents Chemother. **1997**, 41, 1082–1093.
7. O-Yang, C.; Wu, H.Y.; Fraser-Smith, E.B.; Walker, K.A.M. Synthesis of 4′-cyanothymidine and analogs as potent inhibitors of HIV. Tetrahedron Lett. **1992**, 33, 37–40.
8. Maag, H.; Rydzewski, R.M.; McRoberts, M.J.; Crowford-Ruth, D.; Verheyden, J.P.; Prisbe, E.J. Synthesis and anti-HIV activity of 4′-azido and 4′-methoxynucleosides. J. Med. Chem. **1992**, 35, 1440–1451.
9. O-Yang, C.; Kurz, W.; Eugui, E.M.; McRoberts, M.J.; Verheyden, J.P.; Kurz, L.J.; Walker, K.A.M. 4′-Substituted nucleosides as inhibitors of HIV: An unusual oxetane derivative. Tetrahedron Lett. **1992**, 33, 41–44.
10. Ko, O.H.; Hong, J.H. Efficient synthesis of novel carbocyclic nucleosides via sequential Claisen rearrangement and ring-closing metathesis. Tetrahedron Lett. **2002**, 43, 6399–6402.