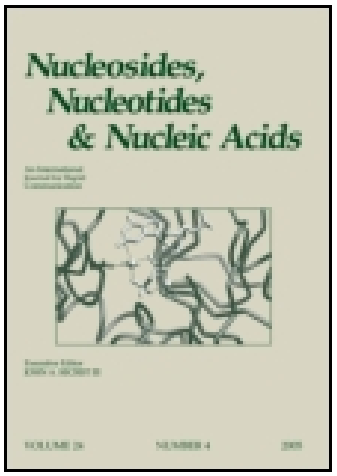

Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

Synthesis and Antiviral Activity of Apio Dideoxy Nucleosides with Azido or Amino Substituent

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Published online: 21 Aug 2006.

To cite this article: Lak Shin Jeong , Young A Lee , Hyung Ryong Moon & Moon Woo Chun (1998) Synthesis and Antiviral Activity of Apio Dideoxy Nucleosides with Azido or Amino Substituent, Nucleosides and Nucleotides, 17:8, 1473-1487, DOI: 10.1080/07328319808003481

To link to this article: http://dx.doi.org/10.1080/07328319808003481

NUCLEOSIDES & NUCLEOTIDES, 17(8), 1473-1487 (1998)

SYNTHESIS AND ANTIVIRAL ACTIVITY OF APIO DIDEOXY NUCLEOSIDES WITH AZIDO OR AMINO SUBSTITUENT

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ABSTRACT: Novel apio dideoxynucleosides with azido or amino substituent were synthesized starting from 1,3-dihydroxyacetone utilizing an acid-catalyzed 1,4-conjugated addition as a key step and evaluated for antiviral activity. Unfortunately, they were found to be neither active against HIV-1, HSV-1,2 and poliovirus nor toxic.

INTRODUCTION

3'-Azido-3'-deoxythymidine (AZT) is a nucleoside analogue and has been a drug of choice for acquired immunodeficiency syndrome (AIDS) although it exhibited many problems such as bone marrow toxicity and appearance of AZT-resistant strains.[1] Since then, a number of compounds have been synthesized and evaluated for anti-human immunodeficiency virus-1 (HIV-1) activity in order to find new anti-AIDS drugs to overcome side effects of AZT. Among them, four more nucleoside analogues (ddI, ddC, d4T and 3TC) have been approved by Food and Drug Administration (FDA) and are being clinically used for patients with AIDS and AIDS-related complex (ARC).[2-5] However, since these drugs also showed side effects (pancreatitis, peripheral neuropathy etc.) and resistance in patients receiving AIDS chemotherapy,[2-5] much more efforts

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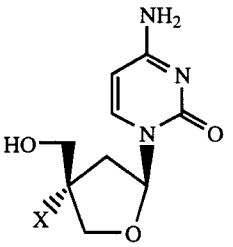
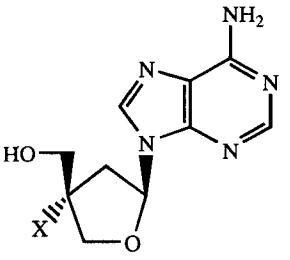
should be made to develop more potent and less toxic anti-AIDS drugs. So far, the introduction of electronegative atoms such as F and N_3 on the carbohydrate moiety has been the most common method[6,7] and various attempts have also been made through transposition of heteroatom, removal of heteroatom and addition of heteroatom on the carbohydrate moiety.[8-10]

Apio dideoxynucleosides which belong to novel class of nucleosides like 3TC in that oxygen of the furanose and C2-methylene were transposed, were reported to show anti-HIV activity and better profile about enzymatic deamination and glycosyl bond hydrolysis than 2',3'-dideoxynucleosides.[11] Among them, adenine analogue exhibited significant anti-HIV activity in MT-4 cells with no apparent toxicity.[12]



1a (X = N_3)
1b (X = NH_2)

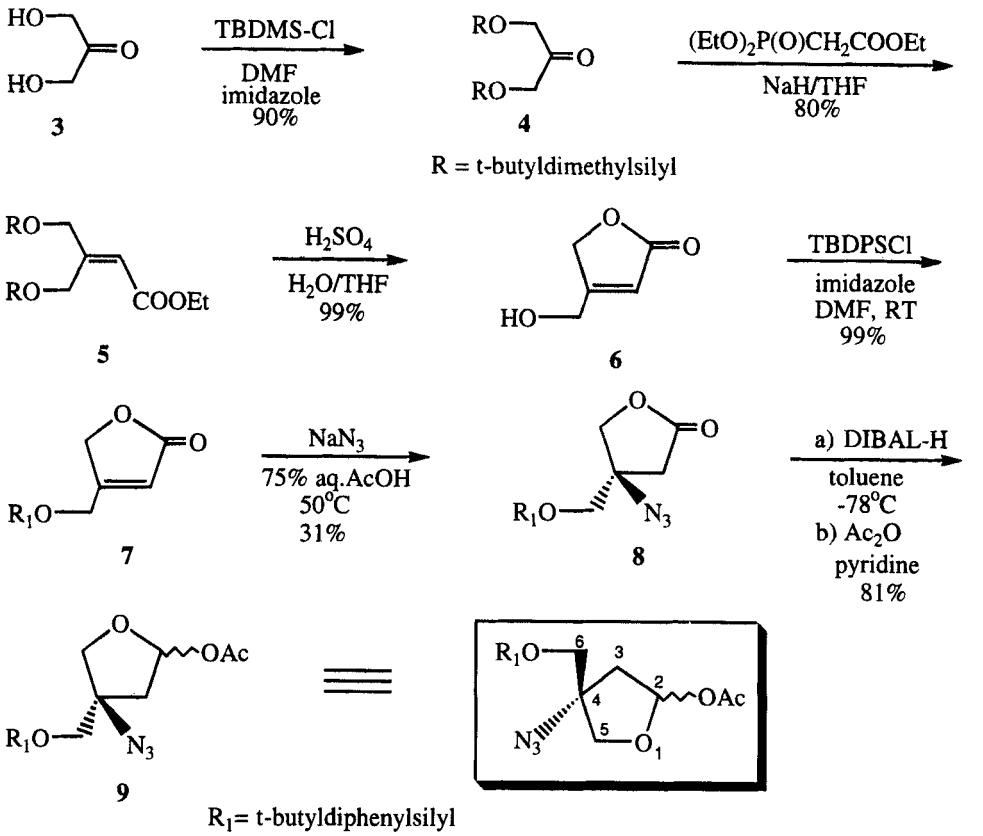


2a (X = N_3)
2b (X = NH_2)

As a part of our ongoing program to search for new anti-HIV nucleosides, we wanted to put azido or amino group into apio dideoxynucleosides since 4'-modified nucleosides had exhibited potent anti-HIV activity[13] and to compare their anti-HIV activity with that of parent nucleosides. Here, we wish to report the synthesis and antiviral activity of racemic apio dideoxynucleosides with azido or amino substituent utilizing an acid catalyzed 1,4-conjugated reaction.

RESULTS AND DISCUSSION

As seen in SCHEME 1, 1,3-dihydroxyacetone (**3**) was used as starting material for the synthesis of key intermediate **9**. 1,3-Dihydroxyacetone (**3**) was treated with t-butyldimethylsilyl chloride at room temperature for 48 h to give **4**. Horner-Emmons olefination of **4** afforded the α,β-unsaturated ester **5** in 80% yield. Lactonization of **5** with aqueous H_2SO_4 proceeded smoothly to give α,β-unsaturated lactone **6** in quantitative yield.[14]



SCHEME 1

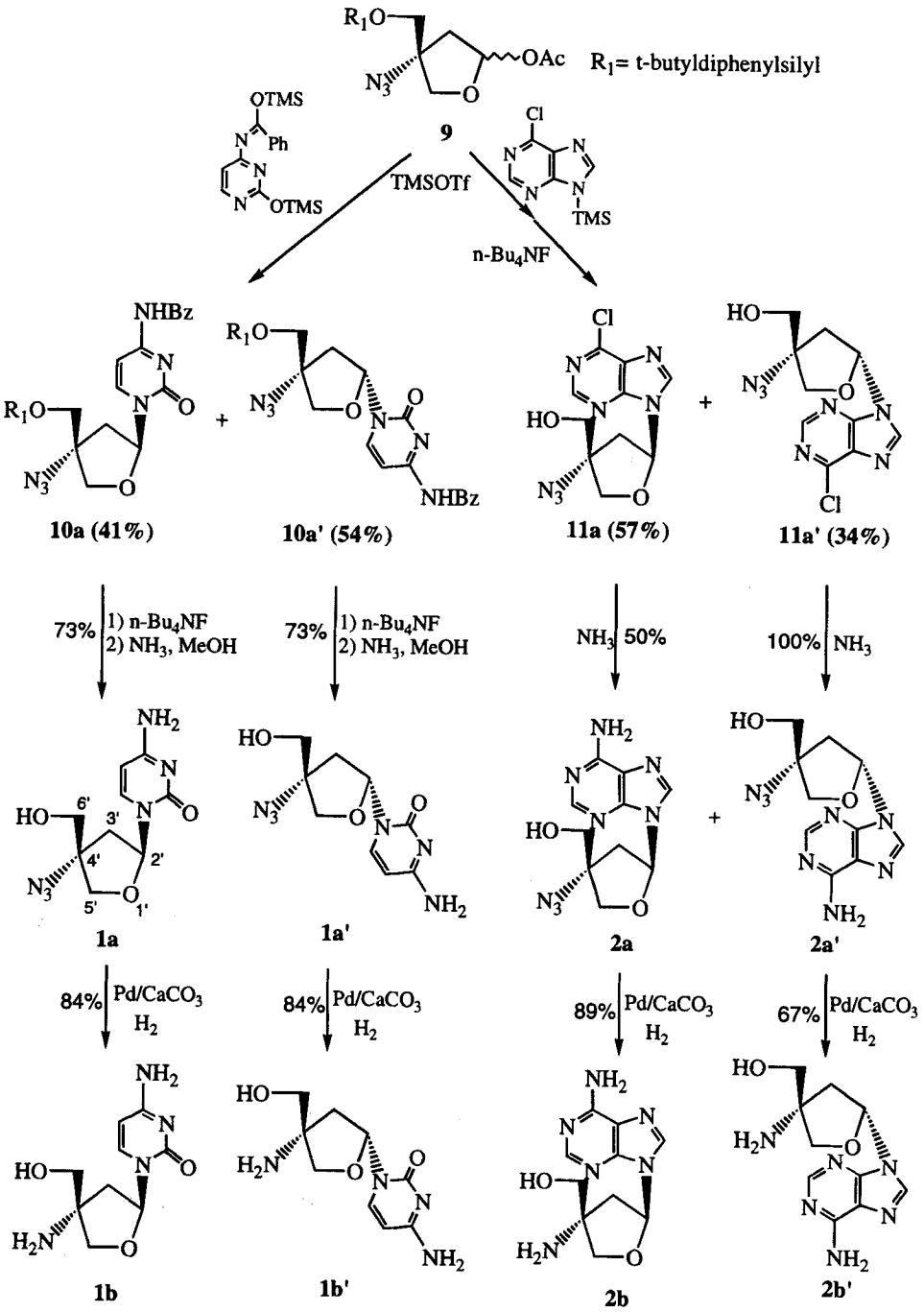
The primary hydroxyl group of **6** was protected with t-butyldiphenylsilyl group to afford the protected lactone **7**. Insertion of azido group into lactone **7** was achieved using an acid-catalyzed 1,4-conjugated addition described by Chu and his coworkers.[15] Treatment of **7** with sodium azide in DMF at high temperature or base-catalyzed 1,4-conjugated reaction ($TMSN_3$, NEt_3, 80 °C) or Lewis acid-catalyzed reaction ($BF_3{\cdot}Et_2O$ or TMSOTf) did not give any desired product, but reaction in aqueous acetic acid at 50 °C with large excess of sodium azide for 5 days gave the desired **8** as a sole product (31%) with recovered starting material **7** (25%).[15] Azido lactone **8** was reduced with diisobutylaluminum hydride (DIBAL-H) at -78 °C to give the lactol, which, without purification, was acetylated with acetic anhydride in pyridine to give the azido acetate **9**

(2:1 anomeric ratio determined by ^{1}H NMR) in 81% yield, which is ready for the condensation with bases.

Synthesis of the target nucleosides (**1** and **2**) is illustrated in SCHEME 2. The acetate **9** was condensed with silylated N^4-benzoylcytosine in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and seperated by silica gel column chromatography to give the protected nucleosides **10a** (41%) and **10a'** (54%). Assignments of each anomer were determined by ^{1}H NMR, which showed the typical coupling pattern reported in the literature.[16,17] The anomeric portion of **10a** showed the typical pseudotriplet indicating β-isomer, while that of **10a'** appeared as doublet of doublet indicating α-anomer. Another characteristic is that 6'-H's in **10a** shifted to more downfield than those in **10a'** due to the deshielding effect by cytosine. The anomeric configuration was also confirmed by NOE effect between 2'-H and 6'-H's which was observed in case of **10a'**. Desilylation of **10a** and **10a'** with n-tetrabutylammonium fluoride in THF followed by debenzoylation with methanolic ammonia afforded the final nucleosides **1a** (73%) and **1a'** (73%), respectively. The Azido group of **1a** and **1a'** was reduced using Pd on calcium carbonate (Lindlar's catalyst) to give the amino derivatives **1b** (84%) and **1b'** (84%), respectively.

Since condensation of N^6-benzoyladenine with acetate **9** resulted in very low yield, adenine analogues were synthesized from the condensation of acetate **9** with silylated 6-chloropurine. The acetate **9** was condensed with silylated 6-chloropurine in the presence of TMSOTf to give the protected nucleoside as an inseperable anomeric mixture, which was separated by silica gel column chromatography after treating with n-tetrabutylammonium fluoride to give cis-isomer **11a** (57%) and trans-isomer **11a'** (34%), respectively. Compounds **11a** and **11a'** were individually converted to **2a** (50%) and **2a'** (100%) by treating with methanolic ammonia at 90 °C. The anomeric configurations of **2a** and **2a'** were confirmed by the same methods used in the determination of those of **10a** and **10a'**. The azido groups of **2a** and **2a'** were also reduced using Pd on calcium carbonate to give the amino derivatives **2b** (89%) and **2b'** (67%), respectively.

Antiviral assays against HIV-1 in MT-4 cells, HSV-1 and HSV-2 in CCL81 cells and poliovirus in HeLa cells were performed on the azido and amino nucleosides (**1a-2b, 1a'-2b'**). It was found that the azido and amino nucleosides did neither exhibit



SCHEME 2

cytotoxicity nor antiviral activity up to 100 μg/mL. It is speculated that neither antiviral activity nor cytotoxicity is due to no conversion of the synthesized final nucleosides to their corresponding triphosphates by the viral or cellular kinase, resulting in no interaction with viral DNA polymerase or cellular DNA polymerase.

CONCLUSION

Novel apio dideoxy nucleosides with azido group (**1a-2a'**) were synthesized from the condensation of the key intermediate **9** with silylated N^4-benzoylcytosine or 6-chloropurine. The amino derivatives (**1b-2b'**) were also prepared from the azido derivatives (**1a-2a'**). It was found that azido and amino derivatives did not show any significant antiviral activity when tested against HIV-1, HSV-1,2 and poliovirus.

EXPERIMENTAL SECTION

Melting points were determined with a Buchi melting point B-545. Infrared (IR) spectra were measured with a Perkin-Elmer 1420 infrared spectrophotometer, ultraviolet spectra were recorded with a Beckman DU-68 spectrophotometer and ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX (250 or 300 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard; coupling constants are in hertz. Elemental analyses were performed by the general instrument laboratory of Ewha Womans University, Seoul, Korea. TLC was performed on Merck precoated $60F_{254}$ plates.. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck). All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to the reaction. For the convenience, the sugar numbering system of the azido acetate **9** was used for the ^1H NMR interpretation of the nucleoside analogues.

Bis(t-butyldimethylsilyloxy)acetone (4). To a solution of 1,3-dihydroxyacetone dimer (**3**) (2 g, 11 mmol) and imidazole (6.0 g, 28 mmol) in DMF was added a solution of t-butyldimethylsilyl chloride (8.28 g, 55 mmol) and the mixture was stirred at room temperature for 48 h. To this mixture was added water and the mixture was extracted with hexanes. The organic layer was washed with brine and dried (anhydrous $MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography

(Hx:EtOAc = 15:1) to give **4** (3.1 g, 90%) as a colorless syrup: R_f = 0.62 (Hx:EtOAc = 10:1); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 12 H, 4 x CH_3), 0.92 (s, 18 H, t-butyl), 4.41 (s, 4 H, 1-H and 3-H). Anal. Calcd for $C_{15}H_{34}O_3Si_2$: C, 56.60; H, 10.69. Found: C, 56.40; H, 10.81.

Ethyl 4-(t-butyldimethylsilyloxy)-3-[(t-butyldimethylsilyl)oxymethyl]-2-buten oate (5). To a suspension of sodium hydride (60% in mineral oil, 0.25 g, 6.3 mmol) in distilled THF was added dropwise triethyl phosphonoacetate (1.15 mL, 7.56 mmol) at 0 ℃ and the mixture was stirred at room temperature for 1 h. The ketone **4** (2.0 g, 6.3 mmol) was added to this mixture and the mixture was stirred for 30 min. The solution was neutralized with AcOH and stirred with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (Hx:EtOAc = 15:1) to give **5** (2.0 g, 80%) as a colorless syrup: R_f = 0.67 (Hx: EtOAc = 10:1); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H, CH_3 x 2), 0.13 (s, 6 H, CH_3 x 2), 0.93 (s, 9 H, t-butyl), 0.97 (s, 9 H, t-butyl), 1.31 (t, J = 7.1 Hz, 3 H, CH_3), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2), 4.46 (d, J = 0.9 Hz, 2 H, $SiOCH_2$), 4.90 (d, J = 0.8 Hz, 2 H, $SiOCH_2$), 6.00-6.02 (m, 1 H, 2-H). Anal. Calcd for $C_{19}H_{40}O_4Si_2$: C, 58.76; H, 10.31. Found: C, 56.52; H, 10.70.

4-Hydroxymethyl-3,4-didehydro-5*H*-furan-2-one[18] (6). To a solution of **5** (2.0 g, 5.16 mmol) in a mixture of H_2O and THF (1:1) was added concentrated H_2SO_4 (0.5 mL) and the mixture was stirred at room temperature overnight. After the removal of solvent, the residue was purified with flash silica gel column chromatography ($CHCl_3$:MeOH = 10:1) to give **6** (582 mg, 99%) as ivory solid whose spectral data were identical to those of the authentic material.

4-[(t-Butyldiphenylsilyl)oxymethyl]-3,4-didehydro-5*H*-furan-2-one (7). To a solution of **6** (582 mg, 5.1 mmol) and imidazole (1.04 g, 15.3 mmol) in DMF was added t-butyldiphenylsilyl chloride (1.51 mL, 5.61 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and H_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated, The residue was purified with flash silica gel column chromatography (Hx:EtOAc = 5:1) to give **7** (1.76 g 99%): mp 60 °C; 1H NMR ($CDCl_3$) δ 1.12 (s, 9 H, t-butyl), 4.59 (d, J = 1.5 Hz, 2 H, 6-H), 4.82 (d, J = 1.8 Hz, 2 H, 5-H), 6.06-6.08 (m, 1 H, 3-H), 7.30-7.69 (m, 10 H, Ar-H). Anal. Calcd for $C_{21}H_{24}O_3Si$: C, 71.59; H, 6.82. Found: C, 71.83; H, 6.90.

(±)-4-Azido-4-[(t-butyldiphenylsilyl)oxymethyl]-3*H*,5*H*-tetrahydrofuran-2-one (8). To a solution of **7** (1.76 g, 5.0 mmol) in glacial acetic acid (10 mL) and distilled water (2 mL) was added NaN_3 (1 g) and the reaction mixture was heated at 45 °C for 120 h. TLC (Hx:EtOAc = 4:1) of reacton mixture was performed and additional NaN_3 was added twice (1.0 g each) after stirring for 48 h and 96 h, respectively. After the removal of large part of solvent under vacuum, the residue was partitioned between CH_2Cl_2 and water. The organic layer was successively washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated to yield colorless syrup, which was purified by flash silica gel column chromatography (Hx:EtOAc = 9:1) to give **8** (618 mg, 31%) and recovered **7** (440 mg, 25%): R_f = 0.57 (Hx:EtOAc = 4:1); IR (KBr) 2120 (N_3), 1800 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.12 (s, 9 H, t-butyl), 2.61 (d, *J* = 17.7 Hz, 1 H, 3-H_a), 2.74 (d, *J* = 17.7 Hz, 1 H, 3-H_b), 3.80 (d, *J* = 10.7 Hz, 2 H, 6-H_a), 3.85 (d, *J* = 10.7 Hz, 2 H, 6-H_b), 4.27 (d, *J* = 10.2 Hz, 1 H, 5-H_a), 4.31 (d, *J* = 10.2 Hz, 1 H, 5-H_b), 7.42-7.69 (m, 10 H, Ar-H). Anal. Calcd for $C_{21}H_{25}N_3O_3Si{\cdot}0.1H_2O$: C, 62.56; H, 6.56; N, 10.43. Found: C, 62.51; H, 6.56; N, 10.41.

(±)-2-*O*-Acetoxy-4-azido-4-[(t-butyldiphenylsilyl)oxymethyl]-3*H*,5*H*-tetrahydr ofuran (9). To a solution of **8** (618 mg, 1.56 mmol) in anhydrous toluene (15 mL) at -78 ℃ was added DIBAL-H (1M solution in toluene, 1.87 mL, 1.87 mmol) and the mixture was stirred at -78 ℃ for 2 h. The reaction mixture was quenched with MeOH (2 mL) and $CHCl_3$ (5 mL) and stirred for 10 min at -78 ℃. To the reaction mixture were added a solution of sodium potassium tartrate and $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude lactol, without further purificaton, was dried under high vacuum for 1 h and acetylated by treatment with acetic anhydride (3.0 mL, 3.12 mmol) and pyridine (10 mL) at room temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified with flash silica gel column chromatography (Hx:EtOAc = 8:1) to give an anomeric mixture of **9** (576 mg, 81%) as pale pink syrup: R_f = 0.15 (Hx:EtOAc = 5:1); ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, t-butyl), 1.13 (s, 9 H, t-butyl), 2.08 (s, 3 H, $COCH_3$), 2.13-2.40 (m, 2 H, 3-H), 3.87 (dd, J = 7.3 and 10.5 Hz, 2

H, 5-H), 4.17 (q, J = 7.1 Hz, 2 H, 6-H), 6.43 (dd, J = 2.4 and J = 3.4 Hz, 1 H, 2-H), 7.41 -7.73 (m, 10 H, Ar-H). Anal. Calcd for $C_{23}H_{29}N_3O_4Si$: C, 62.02; H, 6.52; N, 10.79. Found: C, 62.03; H, 6.58; N, 10.55.

(±)-*cis*-1-[4-Azido-4-[(t-butyldiphenylsilyl)oxymethyl]-3*H*,5*H*-tetrahydrofuran-2-yl]-N^4-benzoylcytosine (10a) and (±)-*trans*-1-[4-Azido-4-[(t-butyldiphenylsilyl)oxymethyl]-3*H*,5*H*-tetrahydrofuran-2-yl]-N^4-benzoylcytosine (10a'). A suspension of N^4-benzoylcytosine (78.3 mg, 0.36 mmol) and ammonium sulfate (catalytic amount) in hexamethyldisilazane (HMDS, 6 mL) was heated at 140-150 ℃ until a clear solution was obtained. The reaction mixture was cooled to room temperature and HMDS was removed under reduced pressure under anhydrous conditions. To this residue was added a solution of **9** (106 mg, 0.24 mmol) in anhydrous 1,2-dichloroethane under nitrogen and the reaction mixture was cooled to 5 ℃. TMSOTf (0.07 mL, 0.36 mmol) was added and the mixture was allowed to stir at room temperature for 1 h under nitrogen. The reaction mixture was poured into CH_2Cl_2, neutralized with saturated $NaHCO_3$ solution and stirred for 10 min. The organic layers were seperated, washed once with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hx:EtOAc = 2:1 to 1:1) to give **10a** (58 mg, 41%) and **10a'** (76 mg, 54%). **10a**: R_f = 0.55 (Hx:EtOAC = 1:1); UV (MeOH) λ_{max} 301 nm; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9 H, t-butyl), 2.06-2.15 (m, 2 H, 3'-H), 3.74 (d, *J* = 10.7 Hz, 1 H, 6'-CH_a), 3.84 (d, *J* = 10.7 Hz, 1 H, 6'-CH_b), 4.12-4.20 (m, 2 H, 5'-H), 6.15 (t, *J* = 6.7 Hz, 1 H, 2'-H), 7.30-7.95 (m, 17 H, Ar-H, H-5, H-6). Anal. Calcd for $C_{32}H_{34}N_6O_4Si$: C, 64.65; H, 5.72; N, 14.14. Found: C, 64.87; H, 5.76; N, 14.43. **10a'**: R_f = 0.5 (Hx:EtOAc = 1:1); UV (MeOH) λ_{max} 301 nm; ^{1}H NMR($CDCl_3$) δ 1.12 (s, 9 H, t-butyl), 2.08 (m, 2 H, 3'-H), 3.83 (s, 2 H, 6'-H), 4.00 (d, *J* = 9.9 Hz, 1 H, 5'-CH_a), 4.30 (d, *J* = 9.9 Hz, 1 H, 5'-CH_b), 6.15-6.17 (m, 1 H, 2'-H), 7.29-7.69 (m, 16 H, Ar-H, H-5), 7.93 (d, *J* = 7.6 Hz, 1 H, H-6). Anal. Calcd for $C_{32}H_{34}N_6O_4Si$: C, 64.65; H, 5.72; N, 14.14. Found: C, 64.76; H, 5.76; N, 14.32.

(±)-*cis*-1-(4-Azido-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl)cytosine (1a). To a solution of **10a** (58 mg, 0.098 mmol) in THF was added n-tetrabutylammonium fluoride (1M solution in THF, 0.114 mL, 0.114 mmol) at 0 °C and

the mixture was stirred at 0 °C for 2 h. Solvent was removed under reduced pressure to give the residue, which was purified by flash silica gel column chromatography ($CHCl_3$:MeOH = 15:1) to give desilylated compound as a white solid, which was used directly for next reaction without identification; UV (MeOH) λ_{max} 301 nm. A solution of desilylated compound in methanolic ammonia (5 mL) was stirred at room temperature overnight. The reaction mixture was evaporated and the residue was recrystallized from MeOH/Ether to give **1a** (16 mg, 73%) as a white solid: R_f = 0.15 ($CHCl_3$:MeOH = 10:1); mp 218 ℃; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (DMSO-d_6) δ 2.19 (dd, J = 7.3, 13.9 Hz, 1 H, 3'-H_a), 2.44 (dd, J = 7.3, 13.9 Hz, 1 H, 3'-H_b), 3.79 (s, 2 H, 6'-H), 3.94 (d, J = 9.6 Hz, 1 H, 5'-CH_a), 4.21 (d, J = 9.6 Hz, 1 H, 5'-CH_b), 5.52 (br s, 1 H, OH), 5.82 (d, J = 7.4 Hz, 1 H, H-5), 6.15 (t, J = 7.3 Hz, 1 H, 2'-H), 7.24 (br s, 2 H, NH_2), 7.73 (d, J = 7.4 Hz, 1 H, H-6). Anal. Calcd for $C_9H_{12}N_6O_3$: C, 42.86; H, 4.76; N, 33.33. Found: C, 42.54; H, 4.96; N, 33.12.

(±)-*cis*-1-(4-Amino-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl)cytosine (1b). To a solution of **1a** (16 mg, 0.063 mmol) in methanol (3 mL) was added 5% Pd/$CaCO_3$ and the mixture was stirred at room temperature for 30 min under H_2. After the reaction mixture was checked by TLC, the reaction mixture was filtered through a Celite pad and washed with methanol. The solvent was evaporated and the residue was recrystallized from MeOH/Ether to give **1b** (12 mg, 84%): R_f = 0.08 ($CHCl_3$:MeOH = 5:1); mp 115 ℃; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (D_2O) δ 2.17 (dd, J = 6.9, 14.2 Hz, 1 H, 3'-H_a), 2.48 (dd, J = 6.9, 14.2 Hz, 1 H, 3'-H_b), 3.56 (d, J = 7.1 Hz, 1 H, 6'-CH_a), 3.62 (d, J = 7.1 Hz, 1 H, 6'-CH_b), 3.92 (d, J = 9.4 Hz, 1 H, 5'-CH_a), 4.14 (d, J = 9.4 Hz, 1 H, 5'-CH_b), 6.07 (d, J = 7.5 Hz, 1 H, H-5), 6.18 (t, J = 7.3 Hz, 1 H, 2'-H), 7.75 (d, J = 7.5 Hz, 1 H, H-6); ^{13}C NMR (DMSO-d_6) δ 165.8, 155.3, 141.7, 94.4, 87.1, 74.0, 73.0, 64.5, 39.9. Anal. Calcd for $C_9H_{14}N_4O_3 \cdot 0.1H_2O$: C, 47.41; H, 6.23; N, 24.58. Found: C, 47.56; H, 6.23; N, 24.63.

(±)-*trans*-1-(4-Azido-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl)cytosine (1a'). Compound **10a'** (76 mg, 0.13 mmol) was converted to **1a'** (16 mg, 73%) as a white solid according to the similar procedure used for the preparation of **1a**: R_f = 0.15 ($CHCl_3$:MeOH = 10:1); mp 165 ℃; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (DMSO-d_6) δ 2.13 (dd, J = 3.1, 14.4 Hz, 1 H, 3'-H_a), 2.57 (dd, J = 7.1, 14.4 Hz, 1 H, 3'-H_b), 3.69-3.81

(m, 2 H, 6'-H), 3.95 (d, J = 9.4 Hz, 1 H, 5'-H_a), 4.16 (d, J = 9.4 Hz, 1 H, 5'-H_b), 5.58 (t, J = 5.4 Hz, 1 H, OH), 5.84 (d, J = 7.4 Hz, 1 H, H-5), 6.06 (dd, J = 3.1, 14.4 Hz, 1 H, 2'-H), 7.18 (br s, 2 H, NH_2), 7.73 (d, J = 7.4 Hz, 1 H, H-6). Anal. Calcd for $C_9H_{12}N_6O_3$: C, 42.86; H, 4.76; N, 33.33. Found: C, 42.98; H, 4.36; N, 33.73.

(±)-*trans*-1-(4-Amino-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl)cytosine (1b'). Compound **1a'** (16 mg, 0.063 mmol) was converted to **1b'** (12 mg, 84%) as a white solid according to the similar procedure used for the preparation of **1b**: R_f = 0.08 ($CHCl_3$:MeOH = 5:1); mp 210 ℃; UV (MeOH) λ_{max} 272 nm; ^{1}H NMR (D_2O) δ 2.03 (dd, J = 6.1, 14.2 Hz, 1 H, 3'-H_a), 2.63 (dd, J = 7.2, 14.2 Hz, 1 H, 3'-H_b), 3.56 (d, J = 7.1 Hz, 1 H, 6'-H_a), 3.62 (d, J = 7.1 Hz, 1 H, 6'-H_b), 3.96 (d, J = 9.2 Hz, 1 H, 5'-H_a), 4.02 (d, J = 9.2 Hz, 1 H, 5'-H_b), 6.02 (dd, J = 6.1, 7.2 Hz, 1 H, 2'-H), 6.08 (d, J = 7.5 Hz, 1 H, H-5), 7.84 (d, J = 7.5 Hz, 1 H, H-6); ^{13}C NMR (DMSO-d_6) δ 166.0, 155.8, 140.9, 94.1, 86.9, 74.9, 71.2, 65.0, 39.8. Anal. Calcd for $C_9H_{14}N_4O_3$: C, 47.79; H, 6.19; N, 24.78. Found: C, 47.49; H, 6.24; N, 24.88.

(±)-*cis*-6-Chloro-9-[4-azido-3*H*,5*H*-tetrahydrofuran-2-yl]purine (11a) and (±)-*trans*-6-Chloro-9-[4-azido-3*H*,5*H*-tetrahydrofuran-2-yl]purine (11a'). A mixture of silylated 6-chloropurine (0.05 g, 0.35 mmol), prepared from ammonium sulfate (catalytic amount) and hexamethyldisilazane (HMDS, 6 mL), **9** (100 mg, 0.23 mmol) and TMSOTf (0.05 mL, 0.35 mmol) was converted to the protected 6-chloropurine derivative (111 mg, 88%) as an inseparable anomeric mixture according to the similar procedure used for the preparation of **10a** and **10a'**: R_f = 0.52 (Hx:EtOAc = 2:1). Anal. Calcd for $C_{26}H_{28}N_7O_2ClSi{\cdot}0.5H_2O$: C, 57.70; H, 5.33; N, 18.12. Found: C, 57.86; H, 5.45; N, 18.13. To a solution of the anomeric mixture (111 mg, 0.2 mmol) of the protected 6-chloropurine in THF (5 mL) was added n-tetrabutylammonium fluoride (1 M solution in THF, 0.11 mL, 0.11 mmol) at 0 ℃ and the mixture was stirred at 0 ℃ for 2 h. Solvent was removed under reduced pressure to give the residue, which was purified by flash silica gel column chromatography (Hx:EtOAc = 1:1) to give cis 6-chloropurine derivative **11a** (35 mg, 57%) and trans 6-chloropurine derivative **11a'** (21 mg, 34%). Compound **11a**: R_f = 0.28 (Hx:EtOAc = 1:1); ^{1}H NMR (DMSO-d_6) δ 2.70 (dd, J = 6.9, 14.3 Hz, 1 H, 3'-H_a), 2.97 (dd, J = 7.3, 14.3 Hz, 1 H, 3'-H_b), 3.96 (d, J = 4.9 Hz, 2 H, 6'-H), 4.07 (d, J = 9.6 Hz, 1 H, 5'-H_a), 4.38 (d, J = 9.6 Hz, 1 H, 5'-H_b), 5.64 (t, J

= 4.9 Hz, 1 H, OH), 6.61 (dd, J = 6.9, 7.3 Hz, 1 H, 2'-H), 8.67 (s, 1 H, H-2), 8.68 (s, 1 H, H-8). Compound **11a'**: R_f = 0.12 (Hx:EtOAc = 1:1); ^{1}H NMR (DMSO-d_6) δ 2.81-2.87 (m, 2 H, 3'-H), 3.82 (d, J = 5.4 Hz, 2 H, 6'-H), 4.10 (d, J = 9.4 Hz, 1 H, 5'-H_a), 4.26 (d, J = 9.4 Hz, 1 H, 5'-H_b), 5.68 (t, J = 4.9 Hz, 1 H, OH), 6.52 (t, J = 5.9 Hz, 1 H, 2'-H), 8.59 (s, 1 H, H-2), 8.65 (s, 1 H, H-8).

(±)-*cis*-9-[4-Azido-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl]adenine (2a). A solution of cis 6-chloropurine derivative (32 mg, 0.108 mmol) in methanolic ammonia (5 mL) was heated at 90 ℃ and stirred for 48 h. The solvent was removed under reduced pressure. The residue was purified with flash silica gel column chromatography ($CHCl_3$:MeOH = 10:1) and recrystallized from MeOH/ether to give **2a** (15.0 mg, 50%) as a white solid: R_f = 0.10 ($CHCl_3$:MeOH = 10:1); mp 179 ℃; UV (MeOH) λ_{max} 262 nm; ^{1}H NMR (DMSO-d_6) δ 2.64 (dd, J = 7.0, 14.2 Hz, 1 H, 3'-H_a), 2.97 (dd, J = 7.4, 14.2 Hz, 1 H, 3'-H_b), 3.96 (d, J = 5.3 Hz, 2 H, 6'-H), 4.04 (d, J = 9.6 Hz, 1 H, 5'-H_a), 4.36 (d, J = 9.6 Hz, 1 H, 5'-H_b), 5.61 (t, J = 5.3 Hz, 1 H, OH), 6.50 (q, J = 7.0, 7.4 Hz, 1 H, 2'-H), 7.39 (br s, 2 H, NH_2), 8.25 (s, 1 H, H-2), 8.43 (s, 1 H, H-8); ^{13}C NMR (DMSO-d_6) δ 156.1, 152.9, 149.2, 140.2, 119.4, 84.5, 74.2, 73.6, 64.5, 38.4. Anal. Calcd for $C_{10}H_{12}N_8O_2$: C, 43.48; H, 4.35; N, 40.58. Found: C, 43.88; H, 4.74; N, 40.98.

(±)-*trans*-9-[4-Azido-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl]adenine (2a'). A solution of trans 6-chloropurine derivative (21 mg, 0.071 mmol) in methanolic ammonia (5 mL) was heated at 90 ℃ and stirred for 48 h. The solvent was removed under reduced pressure. The residue was purified with flash silica gel column chromatography ($CHCl_3$:MeOH = 10:1) and recrystallized from MeOH/ether to give **2a'** (20.0 mg, 100%) as a white solid: R_f = 0.10 ($CHCl_3$:MeOH = 10:1); mp 203 ℃; UV (MeOH) λ_{max} 262 nm; ^{1}H NMR (DMSO-d_6) δ 2.77-2.80 (m, 2 H, 3'-H), 3.81 (d, J = 5.3 Hz, 2 H, 6'-H), 4.06 (d, J = 9.3 Hz, 1 H, 5'-H_a), 4.23 (d, J = 9.3 Hz, 1 H, 5'-H_b), 5.66 (t, J = 5.3 Hz, 1 H, OH), 6.41 (pseudo t, J = 5.3, 6.6 Hz, 1 H, 2'-H), 7.37 (br s, 2 H, NH_2), 8.24 (s, 1 H, H-2), 8.30 (s, 1 H, H-8); ^{13}C NMR (DMSO-d_6) δ 156.1, 153.1, 149.4, 139.6, 84.7, 73.9, 71.1, 65.0 39.8. Anal. Calcd for $C_{10}H_{12}N_8O_2$: C, 43.48; H, 4.35; N, 40.58. Found: C, 43.25; H, 4.56; N, 40.75.

(±)-*cis*-9-[4-Amino-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl]adenine (2b). Compound **2a** (15 mg, 0.054 mmol) was converted to **2b** (12 mg, 89%) according to the similar procedure for the preparation of **1b**: R_f = 0.09 ($CHCl_3$:MeOH = 5:1); mp 215 ℃; UV (MeOH) λ_{max} 262 nm; ^{1}H NMR (D_2O) δ 2.61 (dd, *J* = 6.8, 14.3 Hz, 1 H, 3'-H_a), 2.76 (dd, *J* = 6.8, 14.3 Hz, 1 H, 3'-H_b), 3.80 (s, 2 H, 6'-H), 3.96 (d, *J* = 9.5 Hz, 1 H, 5'-H_a), 4.10 (d, *J* = 9.5 Hz, 1 H, 5'-H_b), 6.54 (t, *J* = 6.8 Hz, 1 H, OH), 8.24 (s, 1 H, H-2), 8.34 (s, 1 H, H-8). Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.39; H, 4.84; N, 33.87. Found: C, 48.25; H, 4.57; N, 33.90.

(±)-*trans*-9-[4-Amino-4-hydroxymethyl-3*H*,5*H*-tetrahydrofuran-2-yl]adenine (2b'). Compound **2a'** (20 mg, 0.072 mmol) was converted to **2b'** (12 mg, 67%) according to the similar procedure for the preparation of **1b'**: R_f = 0.09 ($CHCl_3$:MeOH = 5:1); mp 240 ℃; UV (MeOH) λ_{max} 262 nm; ^{1}H NMR (D_2O) δ 2.54 (dd, *J* = 5.8, 14.5 Hz, 1 H, 3'-H_a), 2.77 (dd, *J* = 7.5, 14.5 Hz, 1 H, 3'-H_b), 3.56 (d, *J* = 7.1 Hz, 1 H, 6'-H_a), 3.62 (d, *J* = 7.1 Hz, 1 H, 6'-H_b), 3.70 (s, 2 H, 6'-H), 6.37 (pseudo t, *J* = 6.0, 7.3 Hz, 1 H, OH), 8.28 (s, 1 H, H-2), 8.34 (s, 1 H, H-8). Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.39; H, 4.84; N, 33.87. Found: C, 48.76; H, 4.93; N, 33.56.

ACKNOWLEDGMENT

This research was supported by alumni research fund of College of Pharmacy, Ewha Womans University. Authors thank Dr. Chong-Kyo Lee for the antiviral testing.

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Received 1/28/98
Accepted 3/11/98