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Synthesis of Novel (2*R*,4*R*)- and (2*S*,4*S*)-*iso* Dideoxynucleosides with Exocyclic Methylene as Potential Antiviral Agents[1]

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Abstract—Novel (2*R*,4*R*)- and (2*S*,4*S*)-*iso* dideoxynucleosides with exocyclic methylene have been designed and synthesized, based on the lead BMS-200475 (**3**) which exhibited potent anti-HBV activity. For the synthesis of D types of (2*R*,4*R*)-nucleosides, L-xylose was converted to the key intermediate **14**. The intermediate **14** was converted to the uracil derivative **4a** and the cytosine derivative **4b**. Compound **14** was also converted to the purine derivatives such as adenine derivative **4c**, hypoxanthine derivative **4d**, and guanine derivative **4e**. The corresponding L types of (2*S*,4*S*)-enantiomers were more efficiently synthesized from the commercially available 1,2-isopropylidene-D-xylose (**20**) than the synthetic method used in the synthesis of (2*R*,4*R*)-nucleosides. The key intermediate **25** was converted to the pyrimidine analogues **5a** and **5b** and the purine derivatives **5c**, **5d**, and **5e** using the similar method used in the preparation of **4c**, **4d**, and **4e**. The synthesized final (2*R*,4*R*)- and (2*S*,4*S*)-nucleosides were tested against several viruses such as HIV-1, HSV-1, HSV-2, HCMV and HBV. (2*R*,4*R*)-Adenine analogue **4c** exhibited potent anti-HBV activity ($EC_{50} = 1.5\ \mu M$ in 2.2.15 cells) among compounds tested, while (2*R*,4*R*)-uracil derivative **4a** was the most active against HCMV among compounds tested and (2*R*,4*R*)-adenine derivative **4c** was found to be moderately active against the same virus. However, the corresponding (2*S*,4*S*)-isomers were found to be totally inactive against all tested viruses. Both (2*R*,4*R*)-adenine derivative **4c** and (2*S*,4*S*)-adenine analogue **5c** were totally resistant to the adenosine deaminase like *iso*-ddA (**1**). From the molecular modeling study the hydroxymethyl side chains of BMS-200475 (**3**) and **4c** were almost overlapped, indicating that **4c** may be suitable for phosphorylation by cellular kinases like the lead **3**, but some discrepancy between two bases was observed, indicating why **4c** is less potent against HBV than **3**. It is concluded that discovery of (2*R*,4*R*)-adenine analogue **4c** as potent anti-HBV agent suggested that the sugar moiety of this series can be regarded as a novel template for the development of new anti-HBV agent and oxygen atom can be acted as a bioisostere of C–OH.

Introduction

Iso dideoxynucleosides[2–6] belong to unique nucleosides in that furanose oxygen was moved to the C3 position, among which adenine analogue (*iso*-ddA, **1**)[2,4] and guanine analogue (*iso*-ddG, **2**)[4] exhibited potent anti-HIV activity comparable to 2′,3′-dideoxyadenosine (ddA) and 2′,3′-dideoxyguanosine (ddG), respectively. Besides potent anti-HIV activity, this class of nucleosides also possess chemical and metabolic advantages such as glycosyl bond stabilization and resistance to the adenosine deaminase, which 2′,3′-dideoxynucleosides do not have (Fig. 1).[2–4]

Recently, D- and L-carbocyclic nucleosides with exocyclic methylene in place of furanose oxygen were synthesized and evaluated for antiviral activities, among which D-guanine derivative (BMS-200475, **3**) was very active against hepatitis B virus (HBV) and was 100 times more potent than clinically available drug, lamivudine.[7]

Based on these findings and bioisosteric concept, it was of great interest to design and synthesize D types of (2*R*,4*R*)-*iso* dideoxynucleosides **4** substituted with exocyclic methylene from the lead **3** because C–OH was known to serve as a bioisostere of oxygen as in the case of 1,3-dioxolanyl nucleosides.[8] It was also interesting to synthesize their L types of the corresponding (2*S*,4*S*)-enantiomers **5** for comparison of their antiviral activity since many L-nucleosides[9] were found to be more potent than the corresponding D-nucleosides. Here, we report

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the full accounts of synthesis and antiviral activity of novel (2*R*,4*R*)- and (2*S*,4*S*)-*iso* dideoxynucleosides with exocyclic methylene.

Results and Discussion

Chemistry

Our synthetic plan to the desired (2*R*,4*R*)- and (2*S*,4*S*)-*iso* dideoxynucleosides is to synthesize the glycosyl donor from a chiral template, carbohydrate precursor and then to condense with nucleosidic bases. Synthesis of the key D-glycosyl donor **14** from L-xylose is shown in Scheme 1.

L-Xylose (**6**) was converted to compound **7** in three steps.[10] Methylation of **6** at the anomeric position with 0.5% methanolic HCl, treatment of the triol with $CuSO_4$ and *p*-TsOH in acetone, and benzylation at the C2 position with benzyl bromide afforded **7** (85% from **6**). Hydrolysis of the 3,5-acetonide in **7** with 70% acetic acid gave the diol **8** in quantitative yield. Selective benzylation of **8** was achieved using well-known organotin chemistry[11] to give **9** in 99% yield. To remove the methoxy group at the anomeric position, compound **9** was first refluxed with hexamethyldisilazane (HMDS) to protect the C3-position in situ to the trimethylsilyl (TMS) ether and then without purification, treated with triethylsilane in the presence of TMSOTf at room temperature for 2 h to give **10** in 80% yield after the purification by silica gel column chromatography.[12] This procedure was proved to be more efficient than the following method: benzoylation of **9** followed by treatment of the resulting benzoate with triethylsilane and TMSOTf and then debenzoylation to give the same product **10** (61% from **9**). Oxidation of **10** with DMSO and acetic anhydride produced ketone **11** (80%). Wittig reaction to convert the ketone **11** to the olefin **12** was found to be greatly affected by the base used in the reaction. When **11** was treated with methyl triphenylphosphonium bromide in the presence of NaH or *n*-BuLi, extensive decomposition on TLC was observed with low yield (30–40%) of the desired product. However, addition of *t*-amyl alcohol in the presence of NaH and methyl triphenylphosphonium bromide to the reaction mixture resulted in high yield (92%) of **12**.[13] Debenzylation of **12** with boron trichloride in methylene chloride at −78 °C gave the diol **13** which was selectively silylated with TBDPSCl to yield the key intermediate **14**.

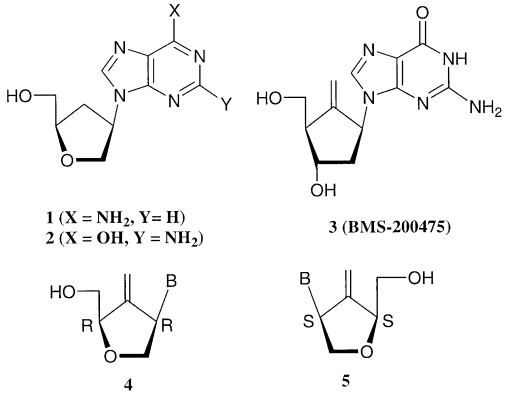
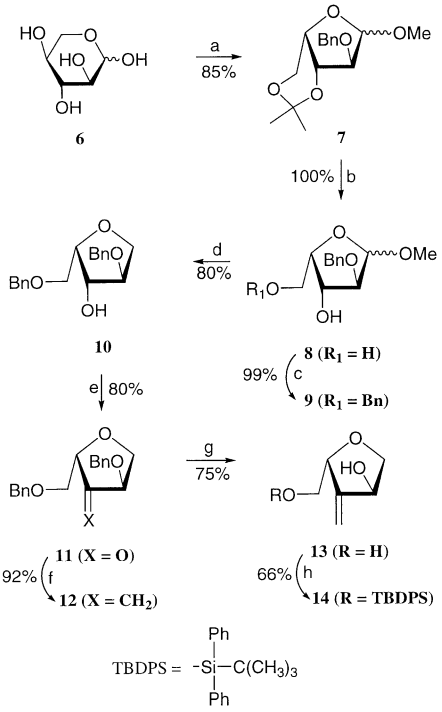


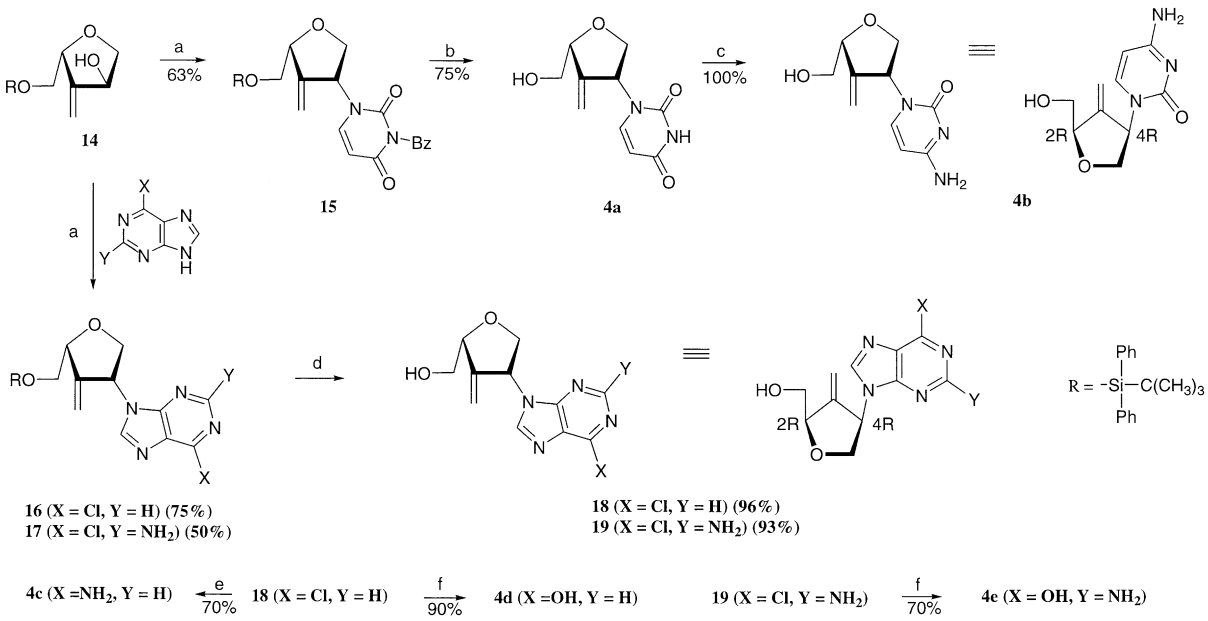
Figure 1. Rationale to the design of the target nucleosides.

Synthesis of the desired D-nucleosides from D-allylic alcohol **14** was achieved by the Mitsunobu reaction[14] and is well shown in Scheme 2.

Condensation of **14** with N^3-benzoyluracil under the standard Mitsunobu conditions afforded the protected uracil derivative **15** (63%) with concommitant formation of *O*-glycosylated product (10%). The regioisomers was easily confirmed by the comparison of the UV literature data.[14] Debenzoylation of **15** with sodium methoxide in methanol followed by desilylation with tetra-*n*-butylammonium fluoride produced the final D-uracil derivative **4a**. The stereochemistry of the C2′ position in compound **4a** was confirmed by NOESY experiment, proving that Mitsunobu condensation of the allylic alcohol was proceeded in pure S_N2 reaction, not S_N1 or S_N2' reaction.[15] For the preparation of the cytosine derivative **4b**, compound **4a** was treated with acetic anhydride in pyridine to protect the hydroxyl group followed by treatment of the acetate with 1,2,4-triazole and phosphorous oxytrichloride in triethyl amine to give the triazole derivative. Without purification, triazole derivative was treated with ammonium hydroxide in dioxane followed by deacetylation with methanolic ammonia to give the final D-cytosine derivative **4b**. For the synthesis of the D-purine derivatives, D-glycosyl donor **14** was condensed with 6-chloropurine and 2-amino-6-chloropurine under the same Mitsunobu



Scheme 1. Reagents: a) (i) HCl, MeOH, rt. (ii) CH_3COCH_3, *p*-TsOH, $CuSO_4$. (iii) BnBr, NaH, *n*-Bu_4NI. b) 70% AcOH, 60 °C. c) (i) *n*-Bu_2SnO, toluene, reflux. (ii) *n*-Bu_4NBr, BnBr, 100 °C. d) (i) HMDS, reflux. (ii) Et_3SiH, TMSOTf, rt. e) DMSO, Ac_2O, rt. f) Ph_3PCH_3Br, NaH, t-amyl alcohol, 0 °C. g) BCl_3, CH_2Cl_2, −78 °C. h) TBDPSCl, imidazole, DMF, 0 °C.



Scheme 2. Reagents: a) N^3-benzoyluracil or 2-amino-6-chloropurine, PPh_3, DEAD, THF, −10 °C. b,c) NaOMe, MeOH, 0 °C. d) (i) Ac_2O, pyridine, rt. (ii) $POCl_3$, 1,2,4-triazole, Et_3N, rt. (iii) NH_4OH, dioxane, rt. (iv) NaOMe, MeOH, 0 °C. c) *n*-Bu_4NF, THF, 0 °C. e) NH_3/MeOH, 100 °C. f) 1 N NaOH, reflux.

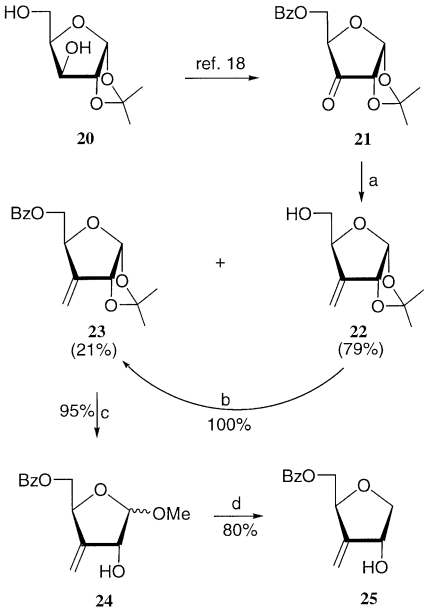
conditions[14] to give D-6-chloropurine analogue **16** (75%) and D-2-amino-6-chloropurine analogue **17** (50%), respectively. In case of 6-chloropurine, N^7-isomer was not formed during the Mitsunobu reaction, while 2-amino-6-chloropurine condensation produced the N^7-substituted product (5%), in which UV of N^9-isomer was appeared at 308 nm, while that of N^7-isomer was shown at 323 nm.[16] Desilylation of **16** with tetra-*n*-butylammonium fluoride gave D-6-chloropurine derivative **18**. Compound **18** was converted to the D-adenine analogue **4c** and the D-hypoxanthine analogue **4d** by treating **18** with methanolic ammonia at 100 °C and refluxing with 1 N NaOH, respectively. The D-guanine derivative **4e** was obtained by refluxing **19** obtained from the desilylation of **17**, with 1 N NaOH.

The corresponding (2*S*,4*S*)-enantiomers of the synthesized (2*R*,4*R*)-nucleosides could be more efficiently synthesized starting from commercially available 1,2-isopropylidene-D-xylose (**20**) than the method used in the preparation of (2*R*,4*R*)-nucleosides.[17]

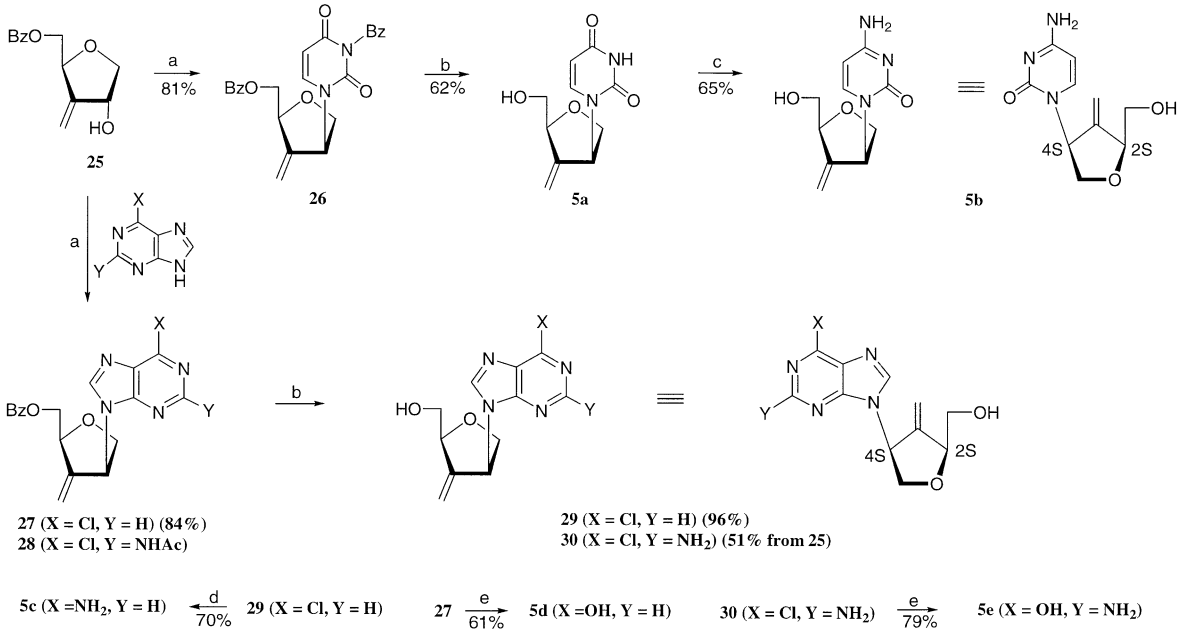
As shown in Scheme 3, 1,2-isopropylidene-D-xylose (**20**) was converted to the ketone **21** according to the known procedure.[18] Wittig reaction of **21** with methyl triphenylphosphonium bromide, *t*-amyl alcohol and NaH was smoothly proceeded to yield the desired olefin **23** with the debenzoylated olefin **22** which could be rebenzoylated to **23** in quantitative yield. Acid-catalyzed hydrolysis (95%) of 1,2-acetonide of **23** followed by anomeric demethoxylation[12] (80%) of the resulting methoxide **24** gave the key intermediate **25** in very good yield. This method was proved much better than that used in Scheme 1 in terms of total steps and overall yield.

Synthesis of the (2*S*,4*S*)-nucleosides from the intermediate **25** was achieved according to the similar procedure used in Scheme 2 and is depicted in Scheme 4.

Condensation of **25** with N^3-benzoyluracil under the Mitsunobu conditions gave the protected nucleoside **26** which was debenzoylated with sodium methoxide to afford the final L-uracil derivative **5a**. The final L-cytosine derivative **5b** was obtained from **5a** using the same method used in Scheme 2. Mitsunobu condensation of **25** with 6-chloropurine and 2-acetamido-6-chloropurine yielded the protected nucleosides **27** and **28**, respectively. After deblocking of **27** and **28** with sodium methoxide, L-6-chloropurine derivative **29** and L-2-amino-6-chloropurine derivative **30** were obtained, respectively. Treatment of compound **29** with methanolic ammonia at 100 °C afforded the adenine derivative



Scheme 3. Reagents: a) Ph_3PCH_3Br, NaH, *t*-amyl alcohol, 0 °C. b) BzCl, pyridine, rt. c) 1% HCl, MeOH, rt. d) (i) HMDS, $(NH_4)_2SO_4$. (ii) Et_3SiH,TMSOTf, rt.



Scheme 4. Reagents: a) N^3-benzoyluracil or 2-acetamido-6-chloropurine, PPh_3, DEAD, THF, −10 °C. b) NaOMe, MeOH, 0 °C. c) (i) Ac_2O, pyridine, rt. (ii) $POCl_3$, 1,2,4-triazole, Et_3N, rt. (iii) NH_4OH, dioxane, rt. (iv) NaOMe, MeOH, 0 °C. d) NH_3/MeOH, 100 °C. e) 1 N NaOH, reflux.

5c. L-Hypoxanthine analogue **5d** was directly obtained from the protected nucleoside **27** by refluxing it with 1 N NaOH. Similarly, L-2-amino-6-chloropurine **30** was transformed to the L-guanine derivative **5e**.

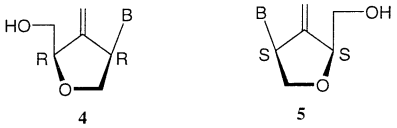
Antiviral activity

All synthesized (2*R*,4*R*)- and (2*S*,4*S*)-nucleosides were tested against several viruses such as HIV-1 (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL81 cells), HCMV (AD-169) and HBV (2.2.15 cells). None of the final nucleosides was found to be active against HIV-1, HSV-1 and HSV-2 up to 100 μg/mL, but many nucleosides exhibited weak to potent antiviral activities against HCMV and HBV as shown in Table 1.

D-Adenine analogue **4c** exhibited the most potent anti-HBV activity among compounds tested although it was less potent than the control, lamivudine. To the best of our knowledge, since none of the *iso* dideoxynucleosides was reported to show anti-HBV activity so far, compound **4c** is the first example to show anti-HBV activity in this type of nucleosides. No anti-HIV activity of **4c** unlike *iso*-ddA might be explained by the fact that HIV-1 prefers flexible conformation of *iso*-ddA like 2′,3′-dideoxynucleosides to the rigid conformation of **4c**. D-Uracil derivative **4a** was the most potent against HCMV among tested and D-adenine derivative **4c** was found to be moderately active against the same virus. It is interesting to note that (2*R*,4*R*)-isomers exhibited potent antiviral activities, while the corresponding (2*S*,4*S*)-isomers were found to be totally inactive against all tested viruses, indicating that only (2*R*,4*R*)-derivatives might be phosphorylated by cellular kinases. We also examined the affinity to the adenosine deaminase for the adenine derivatives **4c** and **5c**. They were found to be resistant to adenosine deaminase like *iso*-ddA (**1**).[2–4] We have done the molecular modeling study[19] to understand why **4c** is active against HBV and less active than BMS-200475.

As seen in Figure 2, we superimposed the lead **3** with (2*R*,4*R*)-adenine analogue **4c** to find out whether hydroxymethyl side chains of both compounds overlap well. As expected, two compounds were well overlapped and their hydroxymethyl side chains were almost coincident, which may be suitable for phosphorylation by cellular kinases, but their bases did not match perfectly and the value of the root mean square deviation between two structures is 0.11 Å, which may explain lower anti-HBV activity of compound **4c** than that of the lead **3**. The anti-HBV activity of compound **4c** may

Table 1. Anti-HCMV and anti-HBV activities of the synthesized D- and L-nucleosides



	HCMV[a] EC_{50} (μg/mL)	HBV[b] EC_{50} (μM)	Cytotoxiciy CC_{50} (μg/mL)
D-Uracil (**4a**)	10.6	> 10	> 100
D-Cytosine (**4b**)	> 100	> 10	> 100
D-Adenine (**4c**)	33.3	1.5	> 100
D-Hypoxanthine (**4d**)	> 100	> 10	> 100
D-Guanine (**4e**)	> 100	> 10	> 100
L-Uracil (**5a**)	> 100	> 10	> 100
L-Cytosine (**5b**)	> 100	> 10	> 100
L-Adenine (**5c**)	> 100	> 10	> 100
L-Hypoxanthine (**5d**)	> 100	> 10	> 100
L-Guanine (**5e**)	> 100	> 10	> 100
Ganciclovir	0.74	ND	> 100
Lamivudine	ND	0.05	> 100

[a]AD-169 infected cells.
[b]2.2.15 cells.

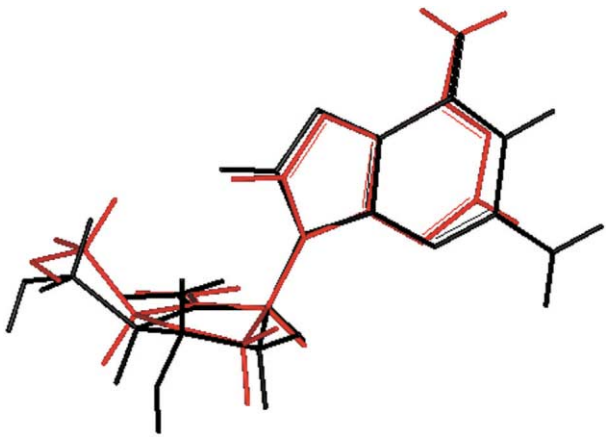


Figure 2. Superimposition of two structures obtained through computer aided molecular modeling calculations (black; BMS-200475, red; compound **4c**).

be also attributed to the rigid sugar conformation endowed by exocyclic double bond as in the case of BMS-200475. To our best knowledge, since none of the *iso* dideoxynucleosides was reported to show anti-HBV activity so far, compound **4c** is the first example to show anti-HBV activity in this type of nucleosides. No anti-HIV activity of **4c** unlike *iso*-ddA might be explained by the fact that HIV-1 prefers flexible conformation of *iso*-ddA like 2′,3′-dideoxynucleosides to the rigid conformation of **4c**.

Conclusion

In summary, we have completed the synthesis and structure–activity relationship study of (2*R*,4*R*)- and (2*S*,4*S*)-*iso* dideoxynucleosides with exocyclic methylene as antiviral agents. Although we could not find excellent antiviral agents, when compared to the control compounds, several compounds including (2*R*,4*R*)-adenine analogue **4c** exhibited significant antiviral activities, indicating that the sugar moiety of this series can be regarded as a novel template for the development of new antiviral agents and oxygen atom can be acted as a bioisostere of C–OH.

Experimental

Ultra violet (UV) spectra were recorded on a Beckman DU-68 spectrophotometer and ^{1}H and ^{13}C spectra were recorded on Varian-400 (250 and 100 MHz) spectrometer, respectively, using $CDCl_3$ or DMSO-d_6 and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. FAB mass spectra were recorded on Jeol HX 110 spectrometer. Elemental analyses were performed at the general instrument laboratory of Ewha Womans University, 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.

2-*O*-Benzyl-1-*O*-methyl-3,5-*O*-isopropylidene-α,β-L-xylofuranoside (7). To a stirred solution of L-xylose (10 g, 66.61 mmol) in anhydrous methanol (46 mL) was added acetyl chloride (0.31 mL) dropwise at ambient temperature under nitrogen and the reaction mixture was stirred overnight at ambient temperature under nitrogen. The reaction mixture was neutralized with silver nitrate and filtrated through a Celite pad. The filtrate was evaporated to dryness to give a crude mixture of 1-methyl-α,β-L-xylose as a sticky oil, which, without purification, was treated with *p*-TsOH·H_2O (508 mg, 2.67 mmol) and anhydrous copper(II) sulfate (205 g, 1.286 mol) in anhydrous acetone (60 mL) at ambient temperature under nitrogen. The reaction mixture was stirred overnight at ambient temperature under nitrogen. The solid was removed by filtration and the filtrate was neutralized with ammonia water and evaporated. The residue was extracted with methylene chloride, washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 4:1) to give methyl-3,5-*O*-isopropylidene-α,β-L-xylofuranoside (13.6 g, 100%) as a yellow oil. To a stirred solution of methyl-3,5-*O*-isopropylidene-α,β-L-xylofuranoside (6 g, 29.38 mmol) in dry THF (50 mL) were added NaH (1.76 g, 60% in oil, 44.07 mmol) and BnBr (4.19 mL, 35.26 mmol), followed by *n*-Bu_4NI (1.1 g, 2.94 mmol) at ice bath under nitrogen and the reaction mixture was stirred for 2 h at ambient temperature under nitrogen. The reaction mixture was neutralized with acetic acid, extracted with EtOAc, washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 7:1 to 4:1 to 2:1) to give **7** (7.35 g, 85.0%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H, α isomer CH_3), 1.36 (s, 3H, α isomer CH_3), 1.38 (s, 3H, β isomer CH_3), 1.39 (s, 3H, β isomer CH_3), 3.42 (s, 3H, β isomer OCH_3), 3.46 (s, 3H, α isomer OCH_3), 3.76–4.00 (m, 3H, α and β isomer 2-H and 5-H), 4.15–4.19 (m, 1H, α and β isomer 4-H), 4.24 (d, 1H, J = 4.0 Hz, β isomer 3-H), 4.29 (dd, 1H, J = 2.4 Hz, J = 4.4 Hz, α isomer 3-H), 4.61 (d, 2H, J = 1.2 Hz, β isomer benzylic H), 4.66 (d, 2H, J = 6.0 Hz, α isomer benzylic H), 4.98 (s, 1H, β isomer 1-H), 5.01 (d, 1H, J = 4.4 Hz, α isomer 1-H), 7.29–7.39 (m, 5H, α and β isomer Ph). Anal. calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.29; H, 7.77.

2-*O*-Benzyl-1-*O*-methyl-α,β-L-xylofuranoside (8). A solution of **7** (5.9 g, 16.99 mmol) in 70% acetic acid (25 mL) was stirred for 1 h at 60 °C. The reaction mixture was evaporated and the residue was further dried by coevaporating with toluene and ethanol. The residue was purified by flash silica gel column chromatography (chloroform/methanol = 100:1 to 50:1) to give **8** (5.10 g, 100%) as a yellow oil, which was subjected to the next reaction.

2,5-Di-*O*-benzyl-1-*O*-methyl-α,β-L-xylofuranoside (9). To a stirred solution of **8** (3 g, 11.80 mmol) in toluene (50 mL) was added *n*-Bu_2SnO (4.41 g, 17.70 mmol) and the reaction mixture was heated for 5 h at 140–150 °C under nitrogen. After the oil bath was cooled to 90–100 °C, *n*-Bu_4NBr (1.90 g, 5.90 mmol) and BnBr

(2.22 mL, 17.70 mmol) were added to the reaction mixture. The whole mixture was heated overnight at 90–100 °C under nitrogen. The solvent was evaporated and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 3:1) to give **9** (4.01 g, 99.0%) as a yellow oil.

α-Isomer. ^{1}H NMR ($CDCl_3$) δ 3.04 (d, 1H, J = 9.8 Hz, OH), 3.33 (s, 3H, OCH_3), 3.68 (dd, 1H, J = 6.2, 10.4 Hz, 5-H_a), 3.82 (dd, 1H, J = 4.9, 10.4 Hz, 5-H_b), 3.92 (s, 1H, 2-H), 4.20 (m, 1H, 4-H), 4.60 (dd, 1H, J = 4.8, 10.7 Hz, 3-H), 4.63–4.57 (m, 4H, benzylic H), 4.93 (s, 1H, 1-H), 7.34–7.24 (m, 10H, 2×Ph). Anal. calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.78; H, 7.18.

β-Isomer. 3.08 (d, 1H, J = 7.6 Hz, OH), 3.38 (s, 3H, OCH_3), 3.72 (d, 2H, J = 3.8 Hz, 5-H), 3.87 (dd, 1H, J = 4.3, 6.3 Hz, 2-H), 4.11 (m, 1H, 4-H), 4.28 (dd, 1H, J = 3.7, 7.6 Hz, 3-H), 4.60–4.49 (m, 4H, benzylic H), 4.79 (d, 1H, J = 4.3, 1-H), 7.35–7.25 (m, 10H, 2×Ph). Anal. calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.45; H, 7.42.

1,4-Anhydro-2,5-di-*O*-benzyl-L-xylitol (10). Method A. To a stirred solution of **9** (3.7 g, 10.74 mmol) in pyridine (40 mL) was added benzoyl chloride (1.87 mL, 16.12 mmol) dropwise at ambient temperature under nitrogen and the reaction mixture was stirred for 2 h at ambient temperature under nitrogen. The reaction mixture was quenched with methanol and evaporated. The residue was dissolved in methylene chloride and the organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 7:1 to 5:1) to give methyl-3-*O*-benzoyl-2,5-di-*O*-benzyl-α,β-L-xylofuranoside (3.60 g, 75.0%) as a white oil. To a stirred solution of methyl-3-*O*-benzoyl-2,5-di-*O*-benzyl-α,β- L-xylofuranoside (200 mg, 0.44 mmol) in anhydrous methylene chloride (10 mL) was added triethylsilane (0.36 mL, 2.22 mmol) followed by slowly adding trimethylsilyl trifluoromethansulfonate (0.44 mL, 2.22 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 3 h at ambient temperature under nitrogen. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with methylene chloride. The organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 5:1) to give 1,4-anhydro-3-*O*-benzoyl-2,5-di-*O*-benzyl-L-xylitol (180 mg, 96.0%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 3.76 (d, 2H, J = 5.9 Hz, 5-H), 3.87 (dd, 1H, J = 2.4, 10.0 Hz, 1-H_a), 4.16 (dd, 1H, J = 1.7, 5.3 Hz, 2-H), 4.26 (dd, 1H, J = 5.4, 10.0 Hz, 1-H_b), 4.46 (d, 1H, J = 11.9 Hz, benzylic H_c), 4.43 (m, 1H, 4-H), 4.59 (d, 1H, J = 11.9 Hz, benzylic H_d), 4.66 (d, 1H, J = 11.9 Hz, benzylic H_b), 4.84 (d, 1H, J = 11.9 Hz, benzylic H_a), 5.58 (d, 1H, J = 3.7 Hz, 3-H), 8.00–7.18 (m, 15H, 3×Ph).

To a stirred solution of 1,4-anhydro-3-*O*-benzoyl-2,5-di-*O*-benzyl-L-xylitol (170 mg, 0.41 mmol) in methanol (10 mL) was added NaOMe (1 M solution in MeOH, 0.08 mL, 0.08 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 2 h at 0 °C under nitrogen. The reaction mixture was neutralized with acetic acid and evaporated. The residue was dissolved in methylene chloride and the organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 2:1) to give **10** (110 mg, 85%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 3.48 (d, 1H, J = 3.9 Hz, OH), 3.83 (dd, 1H, J = 2.2, 9.8 Hz, 1-H_a), 3.89 (d, 2H, J = 4.9 Hz, 5-H), 4.03 (m, 1H, 2-H), 4.12 (q, 1H, J = 3.9 Hz, 3-H), 4.22 (dd, 1H, J = 4.9, 9.8 Hz, 1-H_b), 4.35 (m, 1H, 4-H), 4.53–4.67 (m, 4H, benzylic H), 7.27–7.39 (m, 10H, 2×Ph). Anal. calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.86; H, 6.97.

Method B. A mixture of **9** (1 g, 2.90 mmol) and ammonium sulfate (catalytic amount) in HMDS (2 mL) was refluxed for 1 h under nitrogen. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under anhydrous conditions. The residue was dissolved in anhydrous methylene chloride (15 mL) and triethylsilane (2.32 mL, 14.50 mmol) was added to this solution followed by adding slowly trimethylsilyl trifluoromethansulfonate (2.62 mL, 14.50 mmol) at ambient temperature under nitrogen. After the mixture was stirred for 2 h at ambient temperature under nitrogen, it was poured into saturated $NaHCO_3$ solution and stirred for 30 min. The mixture was extracted with methylene chloride and the organic layer was washed with brine and water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 2:1) to give **10** (730 mg, 80.0%) as a white oil.

1,4-Anhydro-2,5-di-*O*-benzyl-L-xylofurano-3-ulose (11). To a stirred solution of **10** (250 mg, 0.8 mmol) in DMSO (2 mL) was added Ac_2O (2 mL, 22.3 mmol) dropwise at ambient temperature under nitrogen and the reaction mixture was stirred for 9 h at ambient temperature under nitrogen. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ether, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 5:1) to give **11** (200 mg, 80.0%) as a white oil, which was subjected to the next reaction.

1,4-Anhydro-2,5-di-*O*-benzyl-3-deoxy-3-*C*-methylene-L-xylitol (12). Method A. To a stirred suspension of methyl triphenylphosphonium bromide (1.27 g, 3.56 mmol) in dry THF (10 mL) was added *n*-BuLi (1.6 M solution in hexane, 2.62 mL, 4.19 mmol) at 0 °C under nitrogen and followed by dropwise addition of a solution of **11** (654 mg, 2.09 mmol) in dry THF (3 mL) through cannula for 30 min at 0 °C under nitrogen. The mixture was stirred for 30 min at ambient temperature under nitrogen. Ether was added to the mixture to precipitate out triphenylphosphine oxide and the mixture was filtered off. The filtrate was evaporated and the

residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 5:1) to give **12** (200 mg, 32.0%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 3.53 (dd, 1H, J = 5.9, 10.4 Hz, 5-H_a), 3.59 (dd, 1H, J = 3.8, 10.4 Hz, 5-H_b), 3.82 (dd, 1H, J = 4.3, 9.5 Hz, 1-H_a), 4.04 (dd, 1H, J = 5.2 Hz, J = 9.5 Hz, 1-H_b), 4.37 (m, 1H, 2-H), 4.50 (d, 1H, J = 11.9 Hz, benzylic H_a), 4.58 (s, 2H, benzylic H_c and H_d), 4.63 (d, 1H, J = 11.9 Hz, benzylic H_b), 4.68 (m, 1H, 4-H), 5.17 (m, 1H, vinylic H_a), 5.34 (m, 1H, vinylic H_b), 7.22–7.34 (m, 10H, 2×Ph). Anal. calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.79; H, 6.75.

Method B. To a stirred suspension of methyl triphenylphosphonium bromide (2.19 g, 6.13 mmol) and *t*-amyl alcohol (0.73 mL, 6.68 mmol) in dry THF (18 mL) was added NaH (160 mg, 60% in oil, 6.68 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 2 h at ambient temperature under nitrogen. To this yellow phosphrous ylide was added a solution of **11** (580 mg, 1.86 mmol) in dry THF (3 mL) dropwise through cannula at 0 °C under nitrogen. After the mixture was stirred for 30 min at ambient temperature under nitrogen, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAC. The organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 7:1) to give **12** (510 mg, 92.0%) as a white oil.

1,4-Anhydro-3-deoxy-3-*C*-methylene-L-xylitol (13). To a stirred solution of **12** (200 mg, 0.67 mmol) in anhydrous methylene chloride (10 mL) was added boron trichloride (2.68 mL, 1 M solution in methylene chloride, 2.68 mmol) at −78 °C under nitrogen and the reaction mixture was stirred for 30 min at −78 °C under nitrogen. The reaction mixture was quenched with methanol, neutralized with pyridine, and evaporated to dryness. The residue was purified by flash silica gel column chromatography (chloroform/methanol = 10:1) to give **13** (60 mg, 75.0%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 2.31 (br s, 2H, 2×OH), 3.59–3.77 (m, 3H, 1-H_a and 5-H), 4.14 (dd, 1H, J = 5.4, 9.3 Hz, 1-H_b), 4.57–4.67 (m, 2H, 2-H and 4-H), 5.17 (m, 1H, vinylic H_a), 5.43 (m, 1H, vinylic H_b). Anal. calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74; N. Found: C, 55.16; H, 7.86.

1,4-Anhydro-5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-methylene-L-xylitol (14). To a stirred solution of **13** (60 mg, 0.51 mmol) and imidazole (104 mg, 1.53 mmol) in DMF (5 mL) was added *t*-butyldiphenylsilyl chloride (0.13 mL, 0.61 mmol) dropwise at 0 °C under nitrogen and the reaction mixture was stirred for 1 h at 0 °C under nitrogen. The reaction mixture was quenched with water at 0 °C and extracted with EtOAC. The organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 2:1) to give **14** (120 mg, 66.0%) as a white oil: ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H, *tert*-butyl), 1.76 (d, 1H, J = 5.9 Hz, OH, D_2O exchangeable), 3.64–3.72 (m, 3H, 1-H_a and 5-H), 4.12 (dd, 1H, J = 5.4, 9.3 Hz, 1-H_b), 4.61–4.63 (m, 2H, 2-H and 4-H), 5.11 (m, 1H, vinylic H_a), 5.36 (m, 1H, vinylic H_b), 7.34–7.43 (m, 6H, Ph), 7.65–7.70 (m, 4H, Ph). Anal. calcd for $C_{22}H_2O_3$: C, 71.70; H, 7.66. Found: C, 71.98; H, 7.35.

(2*R*,4*R*)-3-Benzoyl-1-(2-*tert*-butyldiphenylsilyloxymethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2,4-dione (15). To a stirred solution of **14** (250 mg, 0.70 mmol), N^3-benzoyluracil (421 mg, 1.61 mmol), and triphenyl phosphine (552 mg, 2.10 mmol) in dry THF (11 mL) was added diethyl azodicarboxylate (0.33 mL, 2.10 mmol) dropwise at −10 °C under nitrogen and the reaction mixture was stirred for 1 h at −10 °C under nitrogen. The solvent was evaporated and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 7:2) to give **15** (270 mg, 63.0%) as a white oil and *O*-glycosylated product (40 mg, 10.0%) as a white oil: UV (MeOH) λ_{max} 271 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9 H, *t*-butyl), 4.21–3.94 (m, 4H, 5′-H and 1′-H), 4.46 (m, 1H, 4′-H), 5.39 (m, 1H, vinylic H_a), 5.47 (m, 1H, vinylic H_b), 5.49 (d, 1H, J = 7.4 Hz, H-5), 5.67 (m, 1H, 2′-H), 7.53 (d, 1H, J = 7.4 Hz, H-6), 7.98–7.45 (m, 15H, 3×Ph). Anal. calcd for $C_{33}H_{34}N_2O_5Si$: C, 69.94; H, 6.05; N, 4.94. Found: C, 70.34; H, 6.42; N, 4.89.

(2*R*,4*R*)-6-Chloro-9-(2-*tert*-butyldiphenylsilyloxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (16). The intermediate **14** (40 mg, 0.11 mmol) was converted to compound **16** (hexanes/EtOAc = 3:1, 40 mg, 75.0%) as a white oil under the same Mitsunobu conditions used in the synthesis of compound **15**: UV (MeOH) λ_{max} 264 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H, *tert*-butyl), 3.94 (d, 2H, J = 4.7 Hz, 5′-H), 4.23 (d, 2H, J = 5.4 Hz, 1′-H), 4.59 (m, 1 H, 4′-H), 5.33 (m, 2H, vinylic H), 5.72 (m, 1H, 2′-H), 7.35–7.47 (m, 6H, Ph), 7.60–7.71 (m, 4H, Ph), 8.25 (s, 1H, H-2), 8.73 (s, 1H, H-8). Anal. calcd for $C_{27}H_{29}ClN_4O_2Si$: C, 64.21; H, 5.79; N, 11.09. Found: C, 64.05; H, 5.99; N, 11.49.

(2*R*,4*R*)-2-Amino-6-chloro-9-(2-*tert*-butyldiphenylsilyloxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (17). The intermediate **14** (30 mg, 0.08 mmol) was converted to compound **17** (hexanes/EtOAc = 2:1, 20 mg, 50.0%) as a white oil under the same Mitsunobu conditions used in the synthesis of compound **15**: UV (MeOH) λ_{max} 308 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H, *tert*-butyl), 3.94 (m, 2H, 5′-H), 4.16 (dd, 1H, J = 4.6, 9.9 Hz, 1′-H_a), 4.23 (dd, 1H, J = 6.2, 9.9 Hz, 1′-H_b), 4.62 (m, 1H, 4′-H), 5.17 (br s, 2H, NH_2), 5.27 (m, 1H, vinylic H_a), 5.32 (m, 1H, vinylic H_b), 5.52 (m, 1H, 2′-H), 7.39–7.50 (m, 6H, Ph), 7.71–7.75 (m, 4H, Ph), 7.88 (s, 1H, H-8). Anal. calcd for $C_{27}H_{30}ClN_5O_2Si$: C, 62.35; H, 5.81; N, 13.47. Found: C, 62.76; H, 5.45; N, 13.21.

(2*R*,4*R*)-6-Chloro-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (18). To a stirred solution of **16** (100 mg, 0.20 mmol) in THF (5 mL) was added tetra *n*-butylammonium fluoride (1 M solution in THF, 0.24 mL, 0.24 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 30 min at 0 °C under nitrogen. The solvent was evaporated and the residue was purified by flash silica gel column chromatography

(chloroform/methanol = 10:1) to give **18** (50 mg, 96.0%) as a white sticky oil: UV (MeOH) λ_{max} 265 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 2.29 (d, 1H, J = 4.3 Hz, OH), 4.00 (dd, 1H, J = 3.8, 12.2 Hz, 5′-H_a), 4.12 (br d, 1H, J = 12.2 Hz, 5′-H_b), 4.34 (pseudo t, 2H, J = 4.3, 10.3 Hz, 1′-H), 4.68 (m, 1H, 4′-H), 5.31 (m, 1H, vinylic H_a), 5.40 (m, 1H, vinylic H_b), 5.68 (m, 1H, 2′-H), 8.20 (s, 1H, H-2), 8.56 (s, 1H, H-8). Anal. calcd for $C_{11}H_{12}ClN_4O_2$: C, 49.54; H, 4.16; N, 21.01. Found: C, 49.15; H, 4.48; N, 21.32.

(2*R*,4*R*)-2-Amino-6-chloro-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (19). Compound **17** (80 mg, 0.15 mmol) was converted to compound **19** (chloroform/methanol = 10:1, 40 mg, 93.0%) as a white sticky oil: UV (MeOH) λ_{max} 310 nm (pH 7); ^{1}H NMR (CD_3OD) δ 3.85 (dd, 1H, J = 7.9, 12.3 Hz, 5′-H_a), 3.91 (dd, 1H, J = 9.1, 12.3 Hz, 5′-H_b), 4.15 (dd, 1H, J = 5.9, 10.1 Hz, 1′-H_a), 4.25 (dd, 1H, J = 3.2, 10.1 Hz, 1′-H_b), 4.51 (m, 1H, 4′-H), 5.37 (m, 2H, vinylic H), 5.57 (m, 1H, 2′-H), 8.26 (s, 1H, H-8). Anal. calcd for $C_{11}H_{12}ClN_5O_2$: C, 46.90; H, 4.29; N, 24.86. Found: C, 46.91; H, 4.48; N, 24.99.

(2*R*,4*R*)-1-(2-Hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2,4-dione (4a). To a stirred solution of **15** (250 mg, 0.41 mmol) in methanol (10 mL) was added NaOMe (1.0 M solution in MeOH, 0.49 mL, 0.49 mmol) dropwise at 0 °C under nitrogen and the reaction mixture was stirred for 2 h at 0 °C under nitrogen. The reaction mixture was neutralized with acetic acid and evaporated. The residue was dissolved in methylene chloride, and the organic layer was washed with water and brine, dried with anhydrous $MgSO_4$ and evaporated. To a stirred solution of this crude debenzoylated product in THF (6 mL) was added tetra *n*-butylammonium fluoride (1.0 M solution in THF, 0.49 mL, 0.49 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 4 h at 0 °C under nitrogen. The mixture was evaporated and the residue was purified by flash silica gel column chromatography (chloroform/methanol = 10:1) to give **4a** (80 mg, 75.0%) as a white solid which was crystallized from ether: MS (FAB) m/z 225 (MH^+); mp 176.5 °C (methanol/ether); UV (H_2O) λ_{max} 266 nm (ε 12,490) (pH 7); 265 nm (ε 12,090) (pH 2); 264 nm (ε 9240) (pH 11); $[\alpha]_D^{25}$ −18.5° (c 0.13); ^{1}H NMR (DMSO-d_6) δ 3.67 (dd, 1H, J = 4.0, 12.0 Hz, 5′-H_a), 3.73 (dd, 1H, J = 2.4, 12.0 Hz, 5′-H_b), 3.88 (dd, 1H, J = 4.0, 9.6 Hz, 1′-H_a), 3.98 (dd, 1H, J = 6.8, 9.6 Hz, 1′-H_b), 4.32 (m, 1H, 4′-H), 5.03 (br s, 1H, OH), 5.23 (m, 1H, vinylic H_a), 5.32 (m, 1H, vinylic H_b), 5.45 (m, 1H, 2′-H), 5.57 (d, 1H, J = 7.6 Hz, H-5), 7.74 (d, 1H, J = 7.6 Hz, H-6), 11.32 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 57.65, 63.28, 71.09, 81.88, 102.35, 111.64, 143.22, 148.07, 151.97, 163.87. Anal. calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.32; H, 5.68; N, 12.10.

(2R,4R)-4-Amino-1-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2-one (4b). To a stirred solution of **4a** (35 mg, 0.13 mmol) in pyridine (1 mL) was added acetic anhydride (0.05 mL) at ambient temperature under nitrogen and the reaction mixture was stirred for 3 h at ambient temperature under nitrogen. The solvent was evaporated to give the crude acetylated product. To a stirred mixture of 1,2,4-triazole (108 mg, 1.56 mmol), phosphorus oxytrichloride (0.12 mL, 1.30 mmol) in dry acetonitrile (2 mL) was added triethylamine (0.18 mL, 1.30 mmol) followed by dropwise addition of a solution of crude acetylated product in acetonitrile at ambient temperature under nitrogen and the whole mixture was stirred overnight at ambient temperature under nitrogen. The reaction mixture was quenched with water and triethylamine and evaporated. The residue was dissolved in methylene chloride and the organic layer was washed with water, dried with anhydrous $MgSO_4$ and evaporated to give the triazole intermediate. This triazole intermediate was treated with dioxane (1.16 mL) and ammonium hydroxide (0.39 mL) and stirred overnight at ambient temperature. The reaction mixture was evaporated and the residue was dissolved in methanol (3 mL) followed by treatment with NaOMe (1.0 M solution in MeOH, 0.16 mL, 0.16 mmol). The mixture was stirred for 4 h at ambient temperature under nitrogen. The reaction mixture was neutralized with acetic acid and evaporated. The residue was purified by flash silica gel column chromatography (chloroform/methanol = 8:1) to give **4b** (35 mg, 100%) as white solid which was crystallized from ether: MS (FAB) m/z 224 (MH^+); UV (H_2O) λ_{max} 273 nm (ε 7170) (pH 7); 282 nm (ε 9800) (pH 2); 273 nm (ε 6940) (pH 11); $[\alpha]_D^{25}$ +9.2° (c 0.13); ^{1}H NMR (DMSO-d_6) δ 3.66 (dd, 1H, J = 4.4, 11.6 Hz, 5′-H_a), 3.71 (dd, 1H, J = 3.6, 11.6 Hz, 5′-H_b), 3.78 (dd, 1H, J = 4.4, 9.6 Hz, 1′-H_a), 3.96 (dd, 1H, J = 7.2, 9.6 Hz, 1′-H_b), 4.32 (m, 1H, 4′-H), 5.01 (br s, 1H, OH), 5.11 (m, 1H, vinylic H_a), 5.28 (m, 1H, vinylic H_b), 5.51 (m, 1H, 2′-H), 5.68 (d, 1H, J = 7.6 Hz, H-5), 7.08 (br d, 2H, J = 40.8 Hz, NH_2), 7.58 (d, 1 H, J = 7.6 Hz, H-6); ^{13}C NMR (DMSO-d_6) δ 58.43, 63.43, 71.68, 82.04, 94.63, 110.89, 143.65, 149.04, 156.59, 166.05. Anal. calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.81; H, 5.93; N, 18.77.

(2*R*,4*R*)-6-Amino-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (4c). A solution of **18** (50 mg, 0.20 mmol in methanolic ammonia (6 mL) was stirred at 100 °C for 2 days. The solvent was evaporated and the residue was purified by flash silica gel column chromatography (chloroform/methanol = 10:1) to give **4c** (33 mg, 70%) as a white solid which was crystallized from ether: MS (FAB) m/z 248 (MH^+); mp 251.5 °C (methanol/ether); UV (H_2O) λ_{max} 260 nm (ε 17,430) (pH 7); 259 nm (ε 17,050) (pH 2); 260 nm (ε 17,120) (pH 11); $[\alpha]_D^{25}$ +16.7° (c 0.12); ^{1}H NMR (DMSO-d_6) δ 3.73 (m, 2H, 5′-H), 4.11 (dd, 1H, J = 6.0, 9.6 Hz, 1′-H_a), 4.15 (dd, 1H, J = 4.4, 9.6 Hz, 1′-H_b), 4.44 (m, 1H, 4′-H), 5.07 (t, 1H, J = 5.6 Hz, OH), 5.15 (m, 1H, vinylic H_a), 5.30 (m, 1H, vinylic H_b), 5.56 (t, 1H, J = 4.8 Hz, 2′-H), 7.26 (br s, 2H, NH_2), 8.15 (s, 1H, H-2), 8.16 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6) δ 57.09, 63.56, 71.41, 82.08, 111.41, 119.22, 139.86, 148.43, 150.00, 153.10, 156.64. Anal. calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.83; H, 5.38; N, 28.11.

(2*R*,4*R*)-9-(2-Hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1,9-dihydro-purine-6-one (4d). A solution of **18** (20 mg, 0.08 mmol) in 1 N sodium hydroxide solution (2 mL) was refluxed for 1 h. The reaction mixture was

neutralized with 1 N hydrochloride and evaporated. The residue was dissolved in methanol and NaCl salt was filtrated off. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (chloroform/methanol = 8:1) to give **4d** (17 mg, 90%) as a white solid which was crystallized from ether: MS (FAB) *m*/*z* 237 (MH^+); mp 232.3 °C (methanol/ether); UV (H_2O) λ_{max} 248 nm (ε 13,770) (pH 7); 247 nm (ε 13,280) (pH 2); 253 nm (ε 13,820) (pH 11); $[\alpha]_D^{25}$ −35.4° (*c* 0.13); ^{1}H NMR (DMSO-d_6) δ), 3.72 (d, 2H, *J* = 4.0 Hz, 5′-H), 4.12 (pseudo t, 2H, *J* = 4.0, 6.0 Hz, 1′-H), 4.42 (m, 1H, 4′-H), 4.77 (t, 1H, *J* = 3.6 Hz, OH), 5.18 (m, 1H, vinylic H_b), 5.32 (m, 1H, vinylic H_a), 5.54 (t, 1H, *J* = 4.8 Hz, 2′-H), 8.06 (s, 1H, H-2), 8.07 (s, 1H, H-8), 11.52 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 57.41, 71.58, 82.10, 89.45, 111.77, 126.01, 129.75, 139.22, 146.36, 148.25, 157.37. Anal. calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 52.98; H, 5.17; N, 22.18.

(2*R*,4*R*)-2-Amino-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1,9-dihydro-purine-6-one (4e). A solution of **19** (40 mg, 0.14 mmol) in 1 N sodium hydroxide solution (2 mL) was refluxed for 1 h. The reaction mixture was neutralized with 1 N hydrochloride and evaporated. The residue was dissolved in methanol and NaCl salt was filtrated off. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (chloroform/methanol = 5:1) to give **4e** (25 mg, 70%) as a white solid which was crystallized from ether: MS (FAB) *m*/*z* 264 (MH^+); mp 269.4 °C (methanol/ether); UV (H_2O) λ_{max} 252 nm (ε 10,770) (pH 7); 252 nm (ε 10,460) (pH 2); 265 nm (ε 8770) (pH 11); $[\alpha]_D^{25}$ −43.6° (*c* 0.11); ^{1}H NMR (DMSO-d_6) δ 3.70 (pseudo t, 2H, *J* = 5.6, 10.0 Hz, 5′-H), 4.04 (pseudo t, 2H, *J* = 2.8, 6.8 Hz, 1′-H), 4.39 (m, 1H, 4′-H), 5.03 (t, 1H, *J* = 5.6 Hz, OH), 5.15 (m, 1H, vinylic H_b), 5.29 (m, 2H, 2′-H and vinylic H_a), 6.59 (br s, 2H, NH_2), 7.69 (s, 1H, H-8), 10.67 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 56.64, 63.52, 71.58, 82.03, 111.38, 116.89, 136.08, 148.49, 151.77, 154.30, 157.39. Anal. calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 50.45; H, 4.76; N, 26.24.

5-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methylene-α-D-xylofuranose (23). To a stirred solution of methyl triphenylphosphonium bromide (26.8 g, 80.16 mmol) and *t*-amyl alcohol (9.58 mL, 87.45 mmol) in dry THF (100 mL) was added NaH (60% in oil, 3.50 g, 87.45 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 2 h at ambient temperature under nitrogen. To the yellow ylide was added a solution of **21** (7.1 g, 24.29 mmol) in dry THF (5 mL) at 0 °C under nitrogen and the mixture was stirred for 1 h at 0 °C under nitrogen. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water, dried with $MgSO_4$, and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 5:1) to give **22** (3.4 g, 79.4%) as an oil and **23** (1.4 g, 20.7%) as an oil. Compound **22** was converted to compound **23** in quantitative yield by treating with benzoyl chloride (2.79 mL, 20.05 mmol) in pyridine (10 mL) at ambient temperature under nitrogen: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 4.40 (dd, 1H, *J* = 5.5, 11.9 Hz, 5-H_a), 4.55 (dd, 1H, *J* = 3.4, 11.9 Hz, 5-H_b), 4.96 (dd, 1H, *J* = 0.9, 4.0 Hz, 2-H), 5.08 (m, 1H, 4-H), 5.30 (m, 1H, vinylic H_a), 5.52 (m, 1H, vinylic H_b), 5.93 (d, 1H, *J* = 4.0 Hz, 1-H), 7.41–8.06 (m, 5H, Ph). Anal. calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.38; H, 6.47.

5-*O*-Benzoyl-1-*O*-methyl-3-deoxy-3-*C*-methylene-D-xylofuranoside (24). To a stirred solution of **23** (2.9 g, 10.35 mmol) in anhydrous methanol (15 mL) was added acetyl chloride (0.2 mL) equivalent to 1% HCl at ambient temprerature under nitrogen and the reaction mixture was stirred for 6 h at ambient temperature under nitrogen. The reaction mixture was neutralized with pyridine and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 2:1) to give **24** (2.5 g, 95%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.38 (br s, 1H, α and β isomer OH), 3.43 (s, 3H, β isomer OCH_3), 3.49 (s, 3H, α isomer OCH_3), 4.34–4.60 (m, 3H, β isomer 2-H, and α and β isomer 5-H), 4.62 (m, α isomer 2-H), 4.86 (m, 1H, α isomer 4-H), 4.94 (s, 1H, β isomer 1-H), 5.01 (d, 1H, *J* = 4.6 Hz, α isomer 1-H), 5.06 (m, 1H, β isomer 4-H), 5.28 (m, 1H, α isomer vinylic H_a), 5.36 (m, 1H, β isomer vinylic H_a), 5.46 (m, 1H, α isomer vinylic H_b), 5.56 (m, 1H, β isomer vinylic H_b), 7.44–8.13 (m, 5H, α and β isomer Ph). Anal. calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.33; H, 6.50.

1,4-Anhydro-5-*O*-benzoyl-3-deoxy-3-*C*-methylene-D-erythro-pentitol (25). A mixture of **24** (3.6 g, 14.20 mmol) and $(NH_4)_2SO_4$ (0.2 g, 1.42 mmol) in HMDS (5 mL) was refluxed for 2 h under nitrogen. The reaction mixture was cooled to ambient temperature and HMDS was evaporated with the exclusion of moisture. To a stirred solution of the silylated residue in anhydrous methylene chloride (15 mL) were added Et_3SiH (11.3 mL, 70.96 mmol) and TMSOTf (12.8 mL, 70.96 mmol) at ambient temperature under nitrogen and the reaction mixture was stirred for 2 h at ambient temperature under nitrogen and poured into saturated $NaHCO_3$ solution with vigorously stirring. The whole mixture was extracted with methylene chloride and the organic layer was washed with water, dried with $MgSO_4$, and evaporated. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 1:1) to give **25** (2.5 g, 80%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.95 (d, *J* = 5.0 Hz, OH), 3.75 (dd, 1H, *J* = 5.2, 9.5 Hz, 1-H_a), 4.22 (dd, 1H, *J* = 5.7, 9.5 Hz, 1-H_b), 4.41 (dd, 1H, *J* = 6.0, 11.9 Hz, 5-H_a), 4.48 (dd, 1H, *J* = 3.6, 9.5 Hz, 1-H_b), 4.73 (m, 1H, 2-H), 4.72 (m, 1H, 4-H), 5.30 (m, 1H, vinylic H_a), 5.49 (m, 1H, vinylic H_b), 7.45–8.10 (m, 5H, Ph). Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.34; H, 6.35.

(2*S*,4*S*)-3-Benzoyl-1-(2-benzoylmethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2,4-dione (26). To a stirred solution of **25** (300 mg, 1.35 mmol), N^3-benzoyluracil (705 mg, 2.70 mmol), and triphenyl phosphine (1.06 g, 4.05 mmol) in dry THF (12 mL) was added diethylazodicarboxylate (0.64 mL, 4.05 mmol) slowly at

−10 °C under nitrogen and the reaction mixture was stirred for 1 h at −10 to 5 °C under nitrogen. The solvent was evaporated and the residue was purified by flash silica gel column chromatography (hexanes/EtOAc = 3:2) to give **26** (505 mg, 80.5%) as a colorless oil contaminated with impurities, which was subjected to the next reaction.

(2*S*,4*S*)-1-(2-Hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2,4-dione (5a). To a stirred solution of impure **26** (505 mg, 1.09 mmol) in MeOH (8 mL) was added NaOMe (1 M solution in MeOH, 2.60 mL, 2.60 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 1 h at 0 °C under nitrogen. The reaction mixture was neutralized with acetic acid and evaporated. The residue was purified by flash silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give **5a** (199 mg, 61.5%) as a white solid which was crystallized from ether, whose spectral data was identical to those of **4a** except optical rotation: $[\alpha]_D^{25}$ +18.1° (*c* 0.11). Anal. calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.43; H, 5.79; N, 12.26.

(2*S*,4*S*)-4-Amino-1-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1*H*-pyrimidine-2-one (5b). Compound **5a** (55 mg, 0.20 mmol) was converted to compound **5b** ($CHCl_3$/MeOH = 8:1, 35 mg, 65%) as a white solid which was crystallized from ether according to the same procedure used in the synthesis of **4b**, whose spectral data was identical to those of **4b** except optical rotation: $[\alpha]_D^{25}$ −9.6° (*c* 0.12). Anal. calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 54.12; H, 5.86; N, 17.98.

(2S,4S)-6-Chloro-9-(2-benzoylmethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (27). The intermediate **25** (300 mg, 1.35 mmol) was converted to compound **27** (hexanes/EtOAc = 1:1, 408 mg, 84.3%) as a white solid under the same Mitsunobu conditions used in the synthesis of compound **26**: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 4.34 (dd, 1H, *J* = 5.8, 10.4 Hz, 1′-H_a), 4.43 (dd, 1H, *J* = 3.4, 10.4 Hz, 1′-H_b), 4.71 (pseudo t, 2H, *J* = 1.8, 3.8 Hz, 5′-H), 4.91 (m, 1H, 4′-H), 5.50 (m, 2H, vinylic H), 5.82 (m, 1H, 2′-H), 7.46–8.04 (m, 5H, Ph), 8.33 (s, 1H, H-2), 8.79 (s, 1H, H-8). Anal. calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.32; H, 4.37; N, 15.10.

(2*S*,4*S*)-2-Acetamido-6-chloro-9-(2-benzoylmethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (28). The intermediate **25** (300 mg, 1.35 mmol) was converted to the impure **28** (chloroform/methanol = 20:1, 300 mg) under the same Mitsunobu conditions used in the synthesis of compound **26**.

(2*S*,4*S*)-6-Chloro-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (29). To a stirred solution of **27** (220 mg, 0.61 mmol) in MeOH (8 mL) was added NaOMe (1 M solution in MeOH, 0.74 mL, 0.74 mmol) at 0 °C under nitrogen and the reaction mixture was stirred for 1 h at 0 °C under nitrogen. The reaction mixture was neutralized with acetic acid and evaporated. The residue was purified by flash silica gel column chromatography ($CHCl_3$: MeOH = 20:1) to give **29** (148 mg, 96%) as a sticky oil: UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 2.29 (d, 1H, *J* = 4.3 Hz, OH), 4.00 (dd, 1H, *J* = 3.8, 12.2 Hz, 5′-H_a), 4.12 (br d, 1H, *J* = 12.2 Hz, 5′-H_b), 4.34 (pseudo t, 2H, *J* = 4.3, 10.3 Hz, 1′-H), 4.68 (m, 1H, 4′-H), 5.31 (m, 1H, vinylic H_a), 5.40 (m, 1H, vinylic H_b), 5.68 (m, 1H, 2′-H), 8.20 (s, 1H, H-2), 8.56 (s, 1H, H-8). Anal. calcd for $C_{11}H_{12}ClN_4O_2$: C, 49.54; H, 4.16; N, 21.01. Found: C, 49.34; H, 4.56; N, 21.11.

(2*S*,4*S*)-2-Amino-6-chloro-9-(2-benzoylmethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (30). The impure **28** (300 mg) was converted to compound **30** (chloroform/methanol = 10:1, 187 mg, 51% from **25**) using the same conditions used in the synthesis of compound **29** as white sticky oil: UV (MeOH) λ_{max} 309 nm; ^{1}H NMR (CD_3OD) δ 3.85 (dd, 1H, *J* = 7.9, 12.3 Hz, 5′-H_a), 3.91 (dd, 1H, *J* = 9.1, 12.3 Hz, 5′-H_b), 4.15 (dd, 1H, *J* = 5.9 Hz, *J* = 10.1 Hz, 1′-H_a), 4.25 (dd, 1H, *J* = 3.2, 10.1 Hz, 1′-H_b), 4.51 (m, 1H, 4′-H), 5.37 (m, 2H, vinylic H), 5.57 (m, 1H, 2′-H), 8.26 (s, 1H, H-8). Anal. calcd for $C_{11}H_{12}ClN_5O_2$: C, 46.90; H, 4.29; N, 24.86. Found: C, 46.76; H, 4.31; N, 24.75.

(2*S*,4*S*)-6-Amino-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-9*H*-purine (5c). Compound **29** (30 mg, 0.12 mmol) was converted to compound **5c** ($CHCl_3$/MeOH = 10:1, 20 mg, 70%) as a white solid which was crystallized from ether according to the same procedure used in the synthesis of **4c**, whose spectral data was identical to those of **4c** except optical rotation: $[\alpha]_D^{25}$ −15.9° (*c* 0.15). Anal. calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.22; H, 5.16; N, 28.76.

(2*S*,4*S*)-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1,9-dihydropurine-6-one (5d). Compound **27** (100 mg, 0.28 mmol) was refluxed with 1 N NaOH to give **5d** ($CHCl_3$: MeOH = 8:1, 40 mg, 61%) as a white solid, which was crystallized from ether, whose spectral data was identical to those of **4d** except optical rotation: $[\alpha]_D^{25}$ +35.6° (*c* 0.14). Anal. calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.62; H, 4.85; N, 22.44.

(2*S*,4*S*)-2-Amino-9-(2-hydroxymethyl-3-methylene-tetrahydrofuran-4-yl)-1,9-dihydropurine-6-one (5e). Compound **30** (178 mg, 0.66 mmol) was converted to compound **5e** ($CHCl_3$/MeOH = 8:1, 139 mg, 79%) as a white solid which was crystallized from ether according to the same procedure used in the synthesis of **4e**, whose spectral data was identical to those of **4e** except optical rotation: $[\alpha]_D^{25}$ +44.8° (*c* 0.15). Anal. calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 50.59; H, 5.12; N, 26.85.

Antiviral assays

Anti-HCMV assay. Anti-HCMV activity was measured as published previously.[20]

Anti-HBV assay. Cell culture and chemical treatment. The HepG2 2.2.15 cell line was cultured according to Korba's protocol[21] with the following procedural

modifications. The cell line was maintained in DMEM medium (Gibco BRL #430-2200) containing 10% fetal bovine serum (FBS, Gibco BRL #16000-028), 1% ABAM and 200 ug/mL G418 (Sigma, #G-9516). Cells were routinely checked for resistance to G418.[22]

For the anti-HBV assay, cells were seeded into 96-well tissue culture plates at approximately 1×10(exp4)/well and grown to confluence. When cells become confluent, medium was changed with fresh one containing 2% FBS. During the 10 day treatment period, the culture medium was replaced with fresh one containing test chemicals at a 2 days interval. Immediately prior to the first dose of test chemical (day 0), and after 2, 4, 6, 8, and 10 days of treatment, culture media were collected and stored at −70 °C for HBV DNA analysis.

Estimation of inhibitory effect against HBV replication by real-time PCR. The HBV gene from nucleotide 2001 to 2319 was amplified using the forward (HBV2001: 5′-CGCCTCAGCTCTGTATCG-3′) and the reverse (HBV2319: 5′-GATAGGGGCATT-TGGTGGTC-3′) primers. These primers are conserved in all strains of HBV. The fluorescent probe (5′-FAM-CCTCACCATACTGCACTCAGGCAA-BHQ-3′) was designed against a conserved region of the HBV polymerase genome, and was synthesized by Biosearch Technologies, Inc. (Novato, CA, USA). The components for PCR included the following: 50 mM Tris, pH 8.5; 3.5 mM $MgCl_2$; 200 nM concentrations of each PCR primer; 300 nM of the probe primer; 250 uM concentrations of each deoxynucleoside triphosphate; and 0.4 unit of Taq polymerase. Alternatively, the fluorescent probe was replaced with Sybr green 1 at a final concentration of 1:20,000. Conditions for cycling were 95 °C for 1 min, followed by 40 cycles of 95 °C for 15 s, 55 °C for 30 s, and 85 °C for 15 s. PCR was done with Rotor-Gene 2000 Real-time Cycler (Corbett Research, Australia). Following amplification, real-time data acquisition and analysis are performed by the Real-time Analysis Software provided by manufacturer. Once the threshold was chosen by the software automatically, the point at which the amplification plot crossed the threshold was defined as the threshhold cycle (Ct). The Ct represents the threshold of sequence detection and is also dependent on the starting quantity of HBV DNA. The Ct values for a 5-fold dilution series of plasmid DNA containing HBV genome were plotted to yield a standard curve for each experiment. Also amplifications without templates and/or polymerase were included as negative controls.

Determination of cytotoxicity

After 10 days of the chemical treatment, 30 uL/well of MTT (Thiazolyl Blue Tetrazolium Bromide, Amresco, #0793-5G) solution (7.5 ug/mL) was added to each well and 96-well plates were incubated at 37 °C for 2 h. After incubation finished, the media were discarded, and an isopropanol solution containing 10% Triton X-100 and 0.4% c-HCl was added to dissolve the precipitate dye in amount of 120 uL/well. After shaking for 2 h, absorbance at 540 nm was measured with an Elisa Reader (Molecular Devices E09013).

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