Bull. Korean Chem. Soc. 2009, Vol. 30, No. 12 2989
DOI 10.5012/bkcs.2009.30.12.2989

Selective Ring-opening Fluorination of Epoxide: An Efficient Synthesis of 2'-C-Fluoro-2'-C-methyl Carbocyclic Nucleosides

Lian Jin Liu,† Si Wouk Kim, Wonjae Lee, and Joon Hee Hong*

*BK21-Project Team, College of Pharmacy, Chosun University, Kwangju 501-759, Korea. *E-mail: hongjh@chosun.ac.kr*
†Department of Environmental Engineering, BK21 Team for Biohydrogen Production, Chosun University, Kwangju 501-759, Korea

Received September 5, 2009, Accepted October 16, 2009

An efficient synthetic route of novel 2'(α)-C-fluoro-2'(β)-C-methyl carbocyclic nucleoside analogues is described. The key fluorinated intermediate **7** was prepared from the epoxide intermediate **5** *via* selective ring-opening of epoxide. Coupling of **7** with nucleosidic bases under the Mitsunobu reactions followed by deprotection afforded the target carbocyclic nucleoside analogues. The synthesized compounds were evaluated as inhibitors of the hepatitis C virus (HCV) in Huh-7 cell line *in vitro*.

Key Words: Fluorohydrin, Carbocyclic nucleoside, Anti-HCV agent, Mitsunobu reaction

Introduction

The infection of hepatitis C virus (HCV)[1], accounts for many hepatitis cases worldwide and is also strongly associated with the development of cirrhosis and hepatocellular carcinoma. The current standard therapy for chronic HCV infection is interferon-α in combination with ribavirin, which is inadequate because of the low response rates as well as its side effects.[2]

The molecular virology of HCV has led to the identification of a number of antiviral molecular targets, including the NS5B RNA-dependent RNA polymerase. Inhibition of this enzyme inhibits HCV replication, making this enzyme a crucial target for new anti-HCV agents. Many nucleoside analogues have been evaluated as anti-HCV agents.[3] These nucleosides are incorporated into proviral RNA like a substrate after being converted to their corresponding triphosphates and act as chain terminators. Modification in the vicinity of the 2'-hydroxy of the ribose in natural ribonucleosides can produce effective RNA chain terminators.[4] For example replacement of the 2'-hydrogen of natural ribonucleosides with a methyl group yields compounds with excellent chain-terminating properties. Among them, 2'-C-methyladenosine[5] **1** and 2'-C-methylcytidine[6] **2** are potent anti-HCV agents in clinical trials (Figure 1). More recently, 2'-C-fluoro-2'-C-methylcytidine **3** was designed as a hepatitis C virus RNA-dependant RNA polymerase (HCV RdRp) inhibitor and showed better inhibitory activity in the HCV replicon assay than 2'-C-methylcytidine, with low cellular toxicity.

Carbocyclic nucleosides[7] are a group of compounds structurally analogous to natural and synthetic nucleosides in which the furanose oxygen has been replace by a methylene group. This replacement changes the furanose ring into a cyclopentane. The expected similarity in bond lengths and bond angles of the tetrahydrofuran and cyclopentane rings allows these analogues to behave as substrates or inhibitors of the enzymes in living cells. Therefore, the carbocyclic nucleosides possess a wide range of biological activities such as antiviral and antitumor effects.

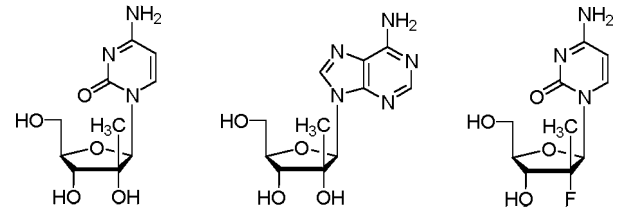
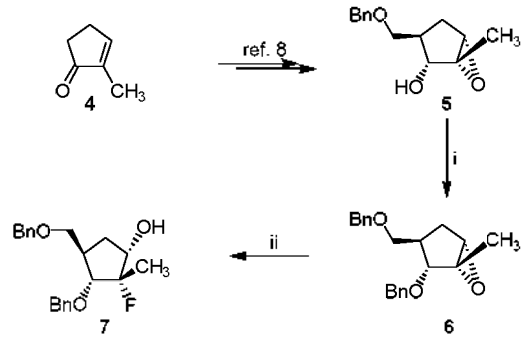


Figure 1. Structure of potent anti-HCV agents.



Scheme 1. Synthesis of fluorinated key intermediate **7**. Reagents: i) BnBr, NaH, DMF; ii) 47% HF, $(NH_4)_2SiF_6$, CsF

Based on this information, we designed fluorinated analogues of carbocyclic nucleosides as anti-HCV agents, focusing on the modification of the 2'-position of the potent 2'(β)-C methyl carbodine nucleosides. Geminal substitution at the 2'-position might impose favorable steric as well as electronic effect on the interaction with HCV polymerase.

As depicted in Scheme 1, we used the epoxide intermediate **5** as starting material, which could be readily synthesized *via* commercially available methylcyclopentenone **4** as described in a previous report.[8] First, the hydroxy functional group was masked with a benzyl group under the usual benzylation condi-

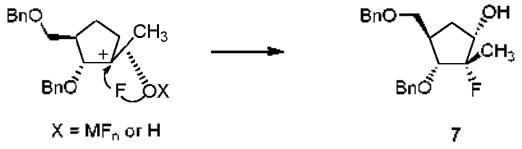
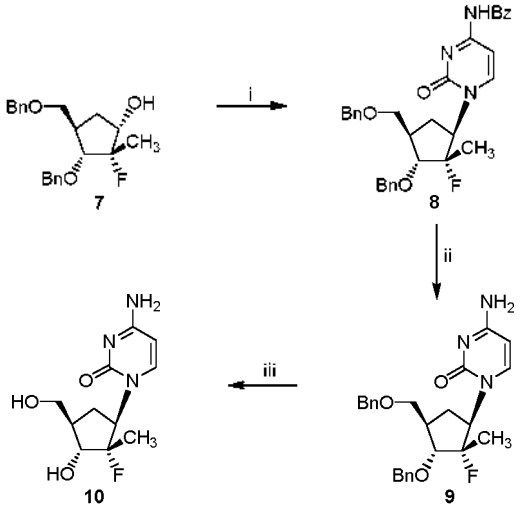


Figure 2. Possible intermediate for the formation of **7**.

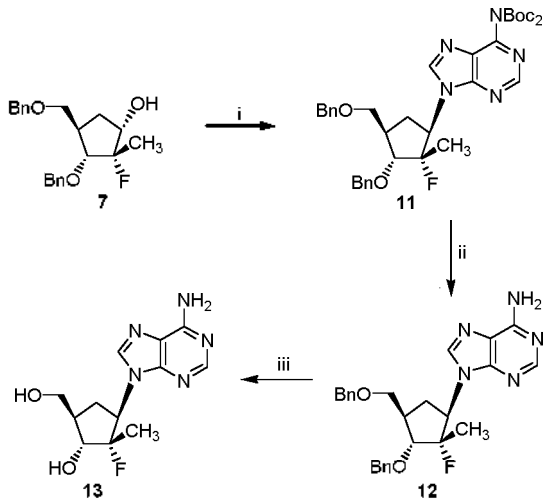


Scheme 2. Synthesis of target 2'-fluoro-cytidine analogue. Reagents: i) N^4-Bz-cytosine, PPh_3, DIAD; ii) NaOMe/MeOH; iii) $Pa(OH)_2$, cyclohexene, MeOH, reflux

tions (BnBr, NaH, DMF) to provide a fully protected intermediate **6**, which underwent a ring-opening fluorination reaction with hydrofluoric acid in the presence of silicon fluorides and additives to provide cis-fluorohydrin in good yield (Scheme 1).[9] The formation of the cis-isomer may be due to the hydrogen bonding and/or silyl ether formation as shown in Figure 2.

To synthesize the desired carbocyclic nucleoside analogues, the alcohol derivative was subjected to a Mitsunobu coupling condition, which is the most useful and common method for the direct substitution of the hydroxyl group with an inversion of the configuration.[10] First, N^4-benzoyl cytosine was treated with the protected fluorohydrin **7** in the presence of diisopropyl-azodicarboxylate (DIAD) and PPh_3 to give **8** in 68% yield (Scheme 2). The removal of N^4-benzoyl group of nucleoside analogue **8** was performed by sodium methoxide. Hydrogenolysis of the benzyl protecting group of **9** with a palladium hydroxide gave the target cytosine derivative **10**. For the synthesis of the adenine nucleoside analogue, similar reactions for the synthesis of the cytosine analogue were attempted. N^6-Bis-Boc-adenine[11] was similarly subjected to Mitsunobu coupling conditions (DIAD, PPh_3) to give adenine analogue **11** in a high yield, 93%. Two boc-protection groups of **11** were removed in trifluoric acetic acid (TFA) conditions to give **12**, which was finally transformed to target compound **13** through the debenzylation conditions as used for **10** (Scheme 3).

As shown in Figure 3, the relative stereochemistry was unambiguously confirmed on the basis of the NOE results between the proximal hydrogens. On irradiation of $C_2(CH_3)$-H, relatively weak NOE was observed at C_1-H (0.21%), compared to that of C_3-H (0.86%).



Scheme 3. Synthesis of target 2'-fluoro-adenosine analogue. Reagents: i) N^6-bis-Boc-adenine, PPh_3, DIAD, 0 °C; ii)TFA, DCE/MeOH, rt; iii) $Pa(OH)_2$, cyclohexene, MeOH, reflux

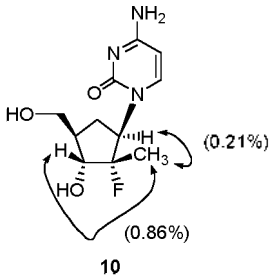


Figure 3. Possible intermediate for the formation of **7**.

Table 1. Anti-HCV activity of the newly synthesized compounds **10** and **13**

Compound No.	Anti-HCV EC_{50} (μg/mL)	Cytotoxicity CC_{50} (μg/mL)
10	18.2	32.1
13	> 50	> 50
2'-*C*-Me-Cyt	3.7	> 50

2'-*C*-Me-Cyt: 2'-*C*-Methylcytidine. EC_{50}(μg/mL): concentration required to inhibit 50% of the virus induced cytopathicity. CC_{50} (μg/mL): concentration required to reduce cell viability by 50%.

The synthesized compounds were tested for anti-HCV activity using an *in vitro* assay. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of an HCV replicon named NK-R2AN.[12] Cytosine analogue **10** weakly inhibited the replication of the replicon, NK-R2AN, in Huh-7 cells by 50% at 18.2 μM (Table 1).

In summary, the present ring-opening fluorination of epoxide using hydrofluoric acid offers a convenient procedure for the synthesis of cis-fluorhydrins. On the basis of potent anti-HCV activity of 2'-modified nucleosides, we have designed and synthesized 2'(α)-*C*-fluoro-2'(β)-*C*-methyl carbodine derivatives from 2-methyl cyclopentenone. The cytosine analogue **10** exhibited potent anti-HCV activity.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL JNM-AL300 Fourier transform; chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were performed under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene, and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(*rel*)-(1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-benzyloxymethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexane (6). To a solution of epoxide derivative **5** (2.1 g, 8.96 mmol) in dry DMF (20 mL) was slowly added NaH (258 mg, 10.75 mmol) at 0 °C. After 30 min, benzyl bromide (1.68 g, 9.85 mmol) was added, and the reaction mixture was stirred for 3 h at rt. The mixture was quenched by adding of saturated ammonium chloride (2 mL) and poured into water (30 mL). The mixture was extracted with ethyl acetate (30 m) two times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **6** (2.29 g, 79%) as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.29 (m, 10H), 4.59 (s, 2H), 4.53 (s, 2H), 3.98 (d, J = 7.0 Hz, 1H), 3.50 (dd, J = 5.4, 9.2 Hz, 1H), 3.34 (dd, J = 6.2, 9.2 Hz, 1H), 2.31 (m, 1H), 2.13 (m, 1H), 1.79 (dd, J = 6.3, 10.6 Hz, 1H), 1.64 (dd, J = 8.2, 10.5 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 139.2, 138.1, 128.3, 127.9, 127.1, 126.4, 79.4, 77.2, 74.2, 72.6, 68.8, 60.7, 41.3, 26.4, 14.3; MS (FAB+) *m/z* 325 $(M+H)^+$.

(*rel*)-(1*S*,2*S*,3*R*,4*S*)-3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentanol (7). To a mixture of $(NH_4)_2SiF_6$ (890 mg, 5.0 mmol), CsF (151.9 mg, 1.0 mmol) and epoxide (324 mg, 1.0 mmol) in 1,2-dichloroethane (10 mL) in polyethylene bottle was added 47% hydrofluoric acid (0.127 mL, 3.0 mmol) at 0 °C, and the mixture was stirred for 7 h at 0 °C. A saturated $NaHCO_3$ solution (10 mL) was slowly added and the whole mixture was extracted with diethyl ether (10 mL) two times. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give alcohol **7** (175 mg, 51%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.27 (m, 10H), 4.61 (s, 2H), 4.57 (s, 2H), 3.86 (ddd, J = 2.8, 6.2, 18.4 Hz, 1H), 3.57 (dd, J = 5.8, 9.0 Hz, 1H), 3.24 (dd, J = 5.8, 13.8 Hz, 1H), 2.29 (m, 1H), 1.76 (dd, J = 6.2, 10.4 Hz, 1H), 1.59 (dd, J = 8.4, 10.4 Hz, 1H), 1.28 (d, J = 21.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.2, 130.1, 128.4, 127.6, 127.0, 126.1, 102.8 (d, J = 181.2 Hz), 80.2 (d, J = 42.6 Hz), 76.1, 75.5, 73.2 (d, J = 18.8 Hz), 69.2, 38.8, 28.4, 14.1 (d, J = 24.5 Hz); Anal. Calcd. for $C_{21}H_{25}O_3$: C, 77.75; H, 7.46. Found: C, 77.82; H, 7.38; MS (FAB+) *m/z* 345 $(M+H)^+$; Anal. Calcd. for $C_{21}H_{25}FO_3$: C, 73.23; H, 7.32. Found: C, 73.29; H, 7.27.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) N^4-benzoyl cytosine (8). To a stirred solution of triphenylphosphine (561 mg, 2.14 mmol) in dry THF (8 mL) at 0 °C was added dropwise the diisopropyl azodicarboxylate (DIAD) (432 mg, 2.14 mmol) and the reaction mixture was stirred at this temperature for 30 min. After that, a solution of the alcohol **7** (368 mg, 1.07 mmol) in THF (8 mL) was added and the reaction mixture was stirred at 0 °C for 15 min. Then the cold bath was removed and the yellow solution was stirred for 30 min at room temperature. N^4-Benzoyl cytosine (460 mg, 2.14 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **8** (401 mg, 68%); mp 178 - 180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, J = 7.2 Hz, 1H), 7.92 (dd, J = 5.6, 8.6 Hz, 2H), 7.62 (d, J = 5.0 Hz, 2H), 7.38-7.26 (m, 11H), 5.60 (d, J = 7.2 Hz, 1H), 4.63 (s, 2H), 4.56 (s, 2H), 4.02 (dd, J = 5.8, 16.8 Hz, 1H), 3.54 (dd, J = 8.2, 12.0 Hz, 1H), 3.22 (ddd, J = 1.8, 6.2, 14.6 Hz, 1H), 2.30 (m, 1H), 1.85 (dd, J = 8.6, 10.8 Hz, 1H), 1.49 (dd, J = 6.2, 10.7 Hz, 1H), 1.32 (d, J = 22.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.38, 165.9, 157.8, 138.2, 136.2, 133.5, 132.9, 129.6, 128.1, 127.7, 127.1, 126.3, 101.9 (d, J = 181.8 Hz), 94.3, 81.5 (d, J = 44.1 Hz), 78.2, 76.2, 68.7, 55.5 (d, J = 16.8 Hz), 36.2, 25.2, 14.5 (d, J = 28.6 Hz); MS (FAB+) *m/z* 564 $(M+Na)^-$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) cytosine (9). To a stirred solution of compound **8** (324 mg, 0.6 mmol) in MeOH (8 mL), NaOMe (0.3 mL, 1 M solution in MeOH) was added at 0 °C under nitrogen and stirred overnight. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 3:1:0.2) to give compound **9** (233 mg, 89%) as a white solid: mp 169-171 °C; UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 7.2 Hz, 1H), 7.31-7.25 (m, 10H), 5.57 (d, J = 7.2 Hz, 1H), 4.64 (s, 2H), 4.57 (s, 2H), 4.06 (ddd, J = 2.8, 6.4, 18.8 Hz, 1H), 3.59 (dd, J = 8.2, 12.2 Hz, 1H), 3.27 (dd, J = 6.4, 14.4 Hz, 1H), 2.34 (m, 1H), 1.81 (dd, J = 8.4, 10.6 Hz, 1H), 1.39 (dd, J = 6.2, 10.6 Hz, 1H), 1.37 (d, J = 20.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.7, 156.5, 142.5, 137.8, 136.8, 134.2, 133.2, 129.4, 128.6, 127.9, 127.2, 126.9, 103.1 (d, J = 181.2 Hz), 94.9, 83.5 (d, J = 42.1 Hz), 79.0, 77.1, 68.4, 56.7 (d, J = 17.2 Hz), 35.8, 26.7, 14.2 (d, J = 27.8 Hz); MS (FAB+) *m/z* 438 $(M+H)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-1-(3-Hydroxy-4-hydroxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) cytosine (10). A solution of **9** (371 mg, 0.85 mmol) in MeOH (25 mL) was treated with palladium hydroxide (170 mg, 20% in activated charcoal) at 0 °C. Cyclohexene (10 mL) was added and the reaction mixture was refluxed overnight. The suspension was cooled down to room temperature, filtered over Celite, and the filtrates were concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 5:1) to give compound **10** (188 mg, 86%) as a white solid: mp 202 - 204 °C; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 7.87 (d, J = 7.2 Hz, 1H), 5.67 (d, J = 7.2 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.89 (t, J = 5.4 Hz, 1H,), 4.65 (s, 2H), 4.57 (s, 2H), 4.03 (dd,

J = 6.6, 18.6 Hz, 1H), 3.52 (dd, J = 8.0, 10.8 Hz, 1H), 3.31 (dd, J = 6.6, 14.8 Hz, 1H), 2.36 (m, 1H), 1.83 (dd, J = 8.6, 11.2 Hz, 1H), 1.39 (dd, J = 6.4, 11.2 Hz, 1H), 1.39 (d, J = 21.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, D_2O exchanged) δ 165.8, 156.3, 143.6, 101.9 (d, J = 182.0 Hz), 94.5, 84.1 (d, J = 40.8 Hz), 78.9, 76.3, 68.8, 55.8 (d, J = 16.8 Hz), 36.5, 25.3, 13.8 (d, J = 26.6 Hz); MS (FAB+) m/z 280 $(M+Na)^+$; Anal. Calcd. for $C_{11}H_{16}FN_3O_3$ (+0.5 MeOH): C, 50.54; H, 6.64; N, 16.38. Found: C, 50.46; H, 6.59; N, 16.32.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) N^6-bis-Boc-adenine (11). Nucleoside analogue **11** was synthesized from N^6-bis-Boc-protected adenine by the same procedure as described for the preparation of **8**: yield 93%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.82 (s, 1H), 7.97 (s, 1H), 7.32-7.24 (m, 10H), 4.66 (s, 2H), 4.58 (s, 2H), 4.07 (ddd, J = 2.0, 6.8, 15.6 Hz, 1H), 3.58 (dd, J = 8.4, 12.2 Hz, 1H), 3.38 (dd, J = 6.8, 15.2 Hz, 1H), 2.34 (m, 1H), 1.82 (dd, J = 8.8, 12.2 Hz, 1H), 1.54 (dd, J = 6.6, 12.2 Hz, 1H), 1.43 (s, 18H), 1.33 (d, J = 20.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 152.8, 152.1, 150.4, 142.4, 138.5, 137.5, 134.2, 133.6, 129.1, 128.2, 127.8, 127.2, 119.4, 104.9 (d, J = 182.2 Hz), 83.6, 79.5 (d, J = 40.8 Hz), 77.8, 76.1, 67.9, 54.3 (d, J = 17.6 Hz), 37.4, 27.5, 26.7, 14.1 (d, J = 26.4 Hz); MS (FAB+) m/z 684 $(M+Na)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) adenine (12). To a stirred solution of **11** (410 mg, 0.62 mmol) in $ClCH_2CH_2Cl$/MeOH = 1:1 (5 mL) was added dropwise trifluoric acid (2.6 g, 23.1 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 3:1:0.1) to give compound **12** (263 mg, 92%) as a white solid: mp 200 - 202 °C ; UV (MeOH) λ_{max} 259.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H), 8.28 (s, 1H), 7.36-7.28 (m, 10H), 4.61 (s, 2H), 4.52 (s, 2H), 4.01 (dd, J = 6.4, 15.8 Hz, 1H), 3.52 (dd, J = 8.6, 12.0 Hz, 1H), 3.40 (dd, J = 7.0, 15.8 Hz, 1H), 2.37 (m, 1H), 1.79 (dd, J = 8.6, 12.0 Hz, 1H), 1.56 (dd, J = 6.4, 12.1 Hz, 1H), 1.35 (d, J = 21.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.6, 152.2, 150.1, 149.4, 137.8, 136.4, 134.5, 132.2, 129.4, 128.1, 127.2, 119.6, 101.5 (d, J = 180.8 Hz), 80.1 (d, J = 44.3 Hz), 78.2, 76.5, 68.5, 56.7 (d, J = 18.8 Hz), 38.3, 27.1, 14.7 (d, J = 25.8 Hz); MS (FAB+) m/z 484 $(M+Na)^+$.

(*rel*)-(1*R*,2*S*,3*R*,4*S*)-9-(3-Hydroxy-4-hydroxymethyl-2-fluoro-2-methyl-cyclopentan-1-yl) adenine (13). Adenine analogue **13** was obtained by a similar procedure as described for the preparation of **10**: yield 84%; mp 216-219 °C ; UV (H_2O) λ_{max} 260. nm; ^{1}H NMR (300 MHz, DMSO-d_6, D_2O exchanged) δ 8.32 (s, 1H), 8.24 (s, 1H), 4.62 (s, 2H), 4.55 (s, 2H), 4.00 (dd, J = 6.2, 15.4 Hz, 1H), 3.51 (dd, J = 8.8, 12.2 Hz, 1H), 3.39 (dd, J = 7.2, 15.6 Hz, 1H), 2.35 (m, 1H), 1.80 (dd, J = 8.8, 12.0 Hz, 1H), 1.58 (dd, J = 6.6, 12.0 Hz, 1H), 1.37 (d, J = 21.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, D_2O exchanged) δ 155.7, 153.2, 150.2, 148.3, 120.0, 103.6 (d, J = 182.2 Hz), 81.2 (d, J = 44.6 Hz), 79.1, 75.2, 68.8, 55.3 (d, J = 20.2 Hz), 37.1, 26.7, 14.1 (d, J = 24.6 Hz); MS (FAB+) m/z 304 $(M+Na)^+$; Anal. Calcd. for $C_{12}H_{16}FN_5O_2$ (+1.0 H_2O): C, 48.15; H, 6.06; N, 23.40. Found: C, 48.19; H, 5.97; N, 23.36.

Acknowledgments. This work was supported by the Pioneer Research Program for Converging Technology of the Ministry of Education, Science and Technology, Republic of Korea (Grant No. M1071118001-08M1118-00110) (2008).

Reference

1. Tan, S. L.; Pause, A.; Shi, Y.; Sonenberg, N. *Nat. Rev. Drug Discovery* **2002**, *1*, 867-881.
2. Heathcote, E.; Shiffman, M.; Cooksley, W.; Dusheiko, G. M.; Lee, S. S.; Balart, L.; Reindollar, R.; Reddy, R. K.; Wright, T. L.; Lin, A.; Hoffman, J.; De Pamphilis, J. *N. Engl. J. Med.* **2000**, *343*, 1673-1680.
3. (a) Clark, J. L.; Hollecker, L.; Mason, J. C.; Stuyver, L. J.; Tharnish, P. M.; Lostia, S.; McBrayer, T. R.; Schinazi, R. F.; Watanabe, K. A.; Otto, M. J.; Furman, P. A.; Stec, W. J.; Patterson, S. E.; Pankiewicz, K. W. *J. Med. Chem.* **2005**, *48*, 5504-5508. (b) Smith, D. B. Kalayanov, G.; Sund, C.; Winqvist, A.; Pinho, P.; Maltseva, T.; Morisson, V.; Leveque, V.; Rajyaguru, S.; Le Pogam, S.; Najera, I.; Benkestock, K.; Zhou, X. X.; Maag. H.; Cammack, N.; Martin, J. A.; Swallow, S.; Johansson, N. G.; Klumpp, K.; Smith, M. *J. Med. Chem.* **2009**, *52*, 219-223; (c) Li, H.; Baik, Y. C.; Hong, J. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 1147-1151.
4. El Kouni, M. H. *Curr. Pharm. Des.* **2002**, *8*, 581-593.
5. Carrol, S. S.; Tomassini, J. E.; Bosserman, M.; Getty, K.; Stahlhut, M. W.; Eldrup, A. B.; Bhat, B.; Hall, D.; Simcoe, A. L.; LaFemina, R.; Rutkowski, C. A.; Wolanski, B.; Yang, Z.; Migliaccio, G.; De Francesco, R.; Kuo, L. C.; MacCross, M.; Olsen, D. B. *J. Biol. Chem.* **2003**, *278*, 11979-11984.
6. Eldrup, A. B.; Allerson, C. R.; Bennett, C. F.; Bera, S.; Bhat, B.; Bhat, N.; Bosserman, M. R.; Brooks, J.; Burlein, C.; Carrol, S. S.; Cook, P. D.; Getty, K. L.; MacCross, M.; McMasters, D. R.; Olsen, D. B.; Prakash, T. P.; Prhave, M.; Song, Q. L.; Tomassini, J. E.; Xia, J. *J. Med. Chem.* **2004**, *47*, 2283-2295.
7. (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623; (b) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768; (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670; (d) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229-9272; (e) Ariona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919-2036.
8. Gosselin, G.; Criffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2006**, *62*, 906-914.
9. Shimizu, M.; Nakahara, Y. *J. Fluorine Chem.* **1999**, *99*, 95-97.
10. Kitade, Y.; Ando, T.; Yamaguchi, T.; Hori, A.; Nakanishi, M.; Ueno, Y. *Bioorg. Med. Chem.* **2006**, *14*, 5578-5583.
11. Michel, B. Y.; Strazewski, P. *Tetrahedron* **2007**, *63*, 9836-9841.
12. Kim, H. J.; Sharon, A.; Bal, C.; Wang, J.; Allu, M.; Huang, Z.; Murray, M. G.; Bsaait, L.; Schinazi, R. F.; Korba, B.; Chu, C. K. *J. Med. Chem.* **2009**, *52*, 206-213.