SYNTHESES OF 1,3-DIOXOLANYL AND CARBOCYCLIC NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGNETS

by

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(Under the Direction of CHUNG K. CHU)

ABSTRACT

The focus of this thesis is on the asymmetric synthesis of dioxolane and various novel carbocyclic nucleoside analogues with antiviral activity.

Enantiomerically pure 5-alkyluracil-1,3-dioxolane nucleoside analogues were synthesized by palladium mediated cross-Stille coupling reaction from L-gulono-γ-lactone in 17 steps.

The synthetic methodology of enantiomerically pure key intermediates for carbocyclic nucleosides, D- and L-2-cyclopentenone, were developed by ring-closing metathesis reaction from D-ribose in 8 steps, which were utilized to synthesize D-cyclopetenyl and cyclopentyl nucleosides. Among them, D-cyclopetenyl adenine, cytosine and 5-F-cytosine analogues were found to be active against orthopox virus including smallpox, monkeypox, and cowpox virus.

Enantiomerically pure D-2'-fluoro-2',3'-dideoxy-2',3'-didehydro and D-3'-fluoro-2',3'-dideoxy-2',3'-didehydro carbocyclic nucleosides were synthesized using epoxide ring opening reduction from D-ribose in 24 and 23 steps, respectively.

INDEX WORDS: 1,3-Dioxolanyl Nucleoside, Carbocyclic Nucleoside, D and L-Cyclopentenone.

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I would like to dedicate this thesis to my family. My parents in Korea and son, Mingue Jin and wife, Kammy Kim, have been giving me continuous love, encouragement and care. Without them, it would be impossible for me to finish this thesis.

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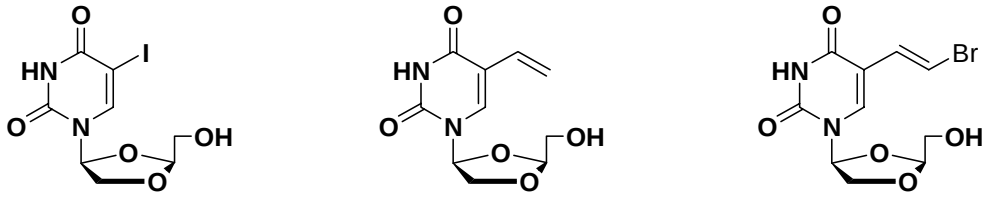
CHAPTER 1

SYNTHESIS OF L-β-5-TRANS-ACRYLIC & PENTADIENE-1,3-DIOXOLANY URACIL NUCLEOSIDES

Introduction

The anti-HIV activity of (±)-dioxolanylthymidine has been reported by Belleau et al.,[1] and the asymmetric synthesis of its D and L-dioxolane nucleoside analogues was published by Chu et al.[2] and Kim et al.[3] Recently, Lin et al.[4] reported β-L-5-iodouridine dioxolane **1** showed selective anti-Epstein Barr virus (EBV) activity (EC_{50} = 0.033 μM). EBV is associated with oral hairy leukoplakia in AIDS patients, and a new EBV-related virus, human herpes type 8, has been identified to be responsible for Kaposi's sarcomna.[5-8] Several nucleoside analogues have been shown to be effective against EBV replication in cell culture including DHPG,[9] D-FIAU,[10] ACV,[11] D-FMAU.[12] However, their clinical application was limited by their lack of potency and side effects.[13] Therefore, the discovery and development of new drugs for the treatment and prevention of EBV-associated malignancies are highly desirable. More recently, Choi et al.[14] reported 5-vinyluridine dioxolane **2** and 5-bromovinyluridine dioxolane **3** showed potent antiviral activity against EBV. Herein we reported the extensive synthesis of 5-*trans*-acrylic and 5-*trans*-pentadiene dioxolane analogues.

Figure 1. β-L-Dioxolane Nucleoside Active against Epstein Barr virus

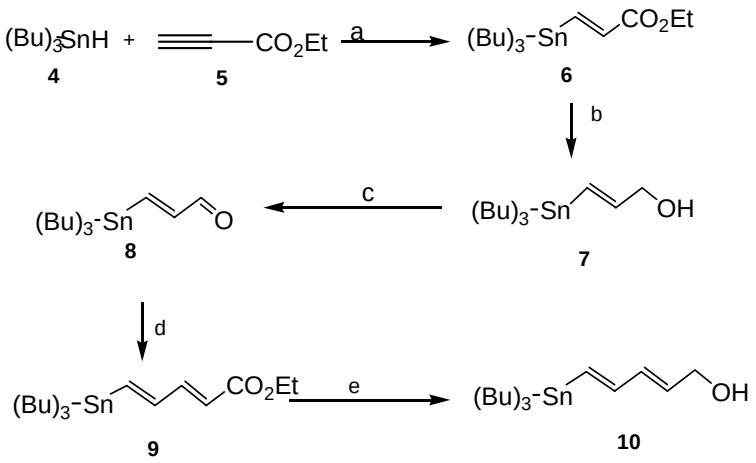


Chemistry

The synthesis of the new L-5-*trans*-acrylic-1,3-dioxolane ethyl ester nucleosides and L-5-*trans*-pentadiene-1,3-dioxolanyl ethyl ester nucleosides were prepared from 5-I-OddU **12** which was synthesized by our previously published method from L-gulono-γ-lactone **11**. The *trans*-3-(tri-

butylstannyl) acrylic ethyl ester **6** was obtained by using AIBN as a radical source. *Trans*-3-(tributylstannyl) propenol **7** was synthesized by Dibal-reduction of *trans*-3-(Tri-butylstannyl) acrylic ethyl ester **6**. This alcohol was oxidized with tetrapropylammonium perruthenate (TPAP) and 4-methylmorphorine N-oxide (NMO) as a co-oxidant mildely to give the aldehyde **8**.[15]

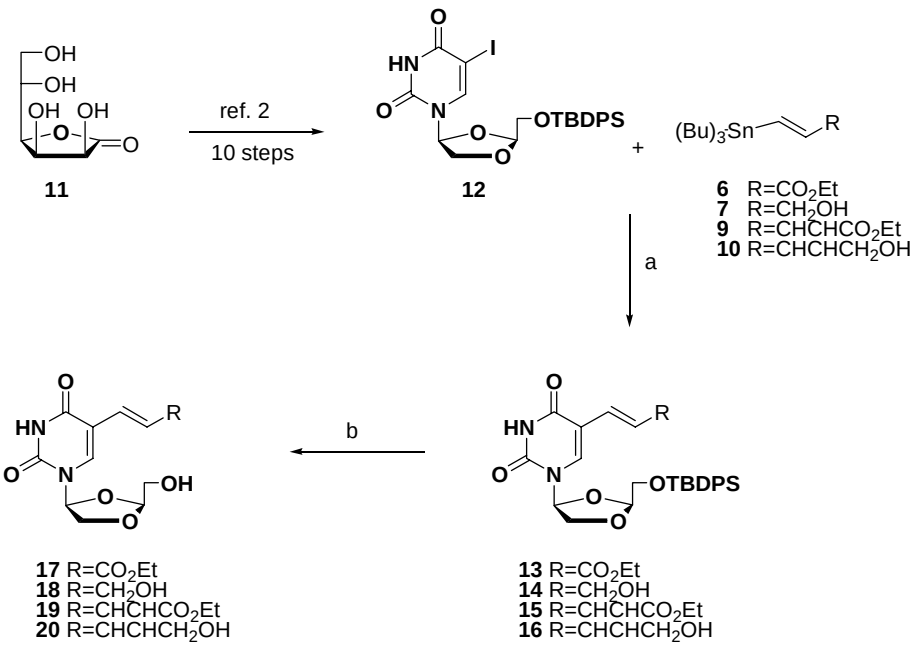
Scheme 1. Synthesis of *Trans*-tributylstannyl Acrylic and Pentadiene



Reagents and conditions: (a) AIBN; (b) Dibla-H, toluene, -78 ^{o}C; (C) tetrapropylammonium perruthenate, 4-methylmorphorine N-oxide, CH_2Cl_2; (d) triethyl phosphonoacetate, THF, -78 ^{o}C; (e) Dibla-H, toluene, -78 ^{o}C.

The aldehyde **8** was reacted with triethyl phosphonoacetate to give *trans*-tributylstannyl-pentadiene ethylester **9**. (Scheme1) The 5-I-OddU **12** was coupled with each prepared organotin reagents **6, 7, 9, 10** in separate reactions, and catalytic amount of tri-2-furylphophine (TFP) and tri(dibenzylidine acetone)dipalladium (Pd_2dba_3) in N-methyl-pyrollidinone to give the four protected L-dioxolanyl nucleosides **13-16** respectively.[16-18] These protected nucleosides were deprotected by 1M solution of tetrabutyl ammonium fluoride (TBAF) in THF and purified by an appropriate method to give the four enantiomerically pure β-L-dioxolanyluracil derivatives **17-20**. (Scheme 2)

Scheme 2. Synthesis of D-dioxolnayl Nuclosides



Reagents and conditions: (a) tri-2-furylphophine, tri(dibenzylidineacetone)dipalladium, N-methyl-pyrollidinone; (b) tetrabutylammonium fluoride, THF.

Experimental Sections

General methods. Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Bruker 400 Fourier transform spectrometer; chemical shifts are reported in parts per million(δ), and signals are quoted as s(singlet), d(doublet), t(triplet), q(quartet), m (multiplet), and dd(double of doublets). UV spectra were obtained on a beckman DU-7 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analysis was performed by Atlantic Micolab, Inc., Norcross, GA. Dry dichloromethane, acetonitrile, pyridine were obtained by distillation from CaH2 prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

Table 1. Elemental Analysis

Compound No.	Formula	Calcd.	Found
7	$C_{15}H_{32}OSn$	C, 51.90; H, 9.29	C, 52.11; H, 9.03
8	$C_{15}H_{30}OSn$	C, 52.47; H, 8.81	C, 52.31; H, 8.60
9	$C_{19}H_{36}O_2Sn$	C, 54.96; H, 8.74	C, 54.99; H, 8.99
10	$C_{17}H_{34}OSn$	C, 54.72; H, 9.18	C, 55.01; H, 9.31
13	$C_{29}H_{34}N_2O_7Si_1$	C, 63.25; H, 6.22; N, 5.09	C, 63.54; H, 6.46; N, 5.00
14	$C_{27}H_{32}N_2O_6Si_1$	C, 63.76; H, 6.34; N, 5.51	C, 63.65; H, 6.56; N, 5.80
15	$C_{31}H_{36}N_2O_6Si_1$	C, 64.56; H, 6.29; N, 4.86	C, 64.78; H, 6.64; N, 4.81
16	$C_{29}H_{34}N_2O_6Si_1$	C, 65.14; H, 6.41; N, 5.24	C, 65.22; H, 6.56; N, 5.58
17	$C_{13}H_{16}N_2O_7$	C, 50.00; H, 5.16; N, 8.97	C, 50.25; H, 5.21; N, 9.15
18	$C_{11}H_{14}N_2O_6$	C, 48.89; H, 5.22; N, 10.37	C, 49.01; H, 5.13; N, 10.60
19	$C_{15}H_{18}N_2O_7$	C, 53.25; H, 5.36; N, 8.28	C, 53.34; H, 5.61; N, 8.52
20	$C_{13}H_{16}N_2O_6$	C, 52.70; H, 5.44; N, 9.46	C, 52.57; H, 5.76; N, 9.32

3-Tributylstannyl-2-propeneol (7)

A solution of **6** (4.4g, 0.011mol) in toluene(50mL) was cooled to –78 ^{o}C and Dibal-H (13.6mL, 1.0M solution in Hexane) was added to the solution dropwise. After 30min stirring at the same

temperature, MeOH(5mL) was added to quench and then allowed to reach to room temperature. Saturated sodium potassium tartrate solution was added and filtered over a celite pad. The clear bi-phase solution was extracted with EtOAc (200mL x 3) and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (3% EtOAc in hexane) to give **7** (3.0g, 77.4%) as a colorless syrup.

^{1}H-NMR ($CDCl_3$) δ 6.68 (m, 1H), 6.07 (d, 1H, *J* = 12.8Hz), 4.11 (t, 2H, *J* = 5.6Hz), 1.50 (m, 6H), 1.31(m, 6H), 0.90 (m, 15H); Anal. Calcd for $C_{15}H_{32}OSn$: C, 51.90; H, 9.29. Found: C, 52.11; H, 9.03.

3-Tributylstannyl-2-propene aldehyde (8)

A mixture of **7** (2.2g, 0.0064mol), 4Å molecular sieve (1g), NMO (820mg, 0.007mol) and TPAP (22mg, 0.064mmol) was stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (2% EtOAc in Hexane) to give **8** (1.1g, 50.2%) as a colorless syrup.

^{1}H-NMR ($CDCl_3$) δ 9.50 (d, 1H, *J* = 6.9Hz), 7.71 (d, 1H, *J* = 13.0Hz), 6.97 (dd, 1H, *J* = 13.0 and 6.9Hz), 1.50 (m, 6H), 1.31(m, 6H), 0.90 (m, 15H); Anal. Calcd for $C_{15}H_{30}OSn$: C, 52.47; H, 8.81. Found: C, 52.31; H, 8.60.

3-Tributylstannylpentadiene ethylester (9)

A solution of triethyl phosphonoacetate (974mg, 4.346mmol) in anhydrous THF (10mL) was cooled to –78 ^oC and treated with n-BuLi (2.7mL, 1.6M solution in hexane). After being stirred for 10 min at the same temperature, **8** (1.0g, 2.898mmol) in anhydrous THF (3mL) was added and stirred for another 30 min at –78 ^oC. The reaction mixture was warmed to room temperature

and stirred for 12h. MeOH (5mL) was added to quench the reaction and the reaction mixture was concentrated in a vacuo. The residue was purified by silica gel column chromatography (1% EtOAc in hexane) to give **9** (1.18g, 98.3%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 7.16 (m, 2H), 6.71 (d, 1H, *J* = 11.9Hz), 5.87 (d,1H, *J* = 14.3Hz), 4.20 (q, 2H, *J* = 7.1Hz), 1.50 (m, 6H), 1.31(m, 9H), 0.90 (m, 15H); Anal. Calcd for $C_{19}H_{36}O_2Sn$: C, 54.96; H, 8.74. Found: C, 54.99; H, 8.99.

3-Tributylstannylpentadienol (10)

A solution of **9** (410mg, 0.987mmol) in toluene (10mL) was cooled to –78 ^oC and treated with Dibal-H (3.0mL, 1.0M solution in hexane) dropwise. After being stirred for 30 min at the same temperature, MeOH (2mL) was added to quench and then warmed to room temperature. Saturated sodium potassium tartrate solution was added and filtered over the celite pad (5 cm). The clean bi-phase solution was extracted with EtOAc (50mL x 2) and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (3% EtOAc in hexane) to give **10** (3.0g, 77.4%) as a colorless syrup.

^{1}H- NMR ($CDCl_3$) δ 7.05 (dd, 1H, *J* = 12.5 and 10.6Hz), 6.15 (m, 2H), 5.85 (m,1H), 4.22 (s, 2H), 1.50 (m, 6H), 1.33(m, 6H), 0.90 (m, 15H); Anal. Calcd for $C_{17}H_{34}OSn$: C, 54.72; H, 9.18. Found: C, 55.01; H, 9.31.

(2S,4S)-1[[2-[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-propeneuracil-ethyl carboxylate (13)

A solution of **6** (437mg, 1.129mmol) and 5-I-OddU **12** (500mg, 0.864mmol) in NMP (10mL) was treated with catalytic amounts of TFP (8mg, 0.035mmol) and Pd_2dba_3(8mg, 0.009mmol).

After being stirred at 55°C for 12h, the reaction mixture was purified by silica gel column chromatography (30% EtOAc in hexane) to give **13** (285mg, 60.0%) as a colorless oil.

UV (H_2O) λ_{max} 263nm (ε = 8030), 312nm (ε = 6780) pH 11.0, 227nm (ε = 14700), 263nm (ε = 8310), 319nm (ε = 6830) pH 7.0, 227nm (ε = 13500) 264nm (ε =7100), 320nm (ε = 5940) pH 2.0; $[\alpha]^{25}_{D}$ –22.6 ; ^{1}H-NMR ($CDCl_3$) δ 9.06 (s, 1H, H-6), 8.24 (bs, 1H, NH, D_2O exchangeable), 7.65 (m, 4H, ar), 7.37 (m, 6H, ar), 6.78 (d, 1H, *J* = 12.9Hz, vinyl), 6.33 (dd, 1H, *J* = 5.8 and 1.7Hz, H-4'), 5.83 (d, 1H, *J* = 12.9Hz, vinyl), 5.15 (t, 1H, *J* = 3.9Hz, H-2'), 4.29 (dd, 1H, *J* = 10,2 and 1.8Hz, H-5_b'), 4.18 (dd, 1H, *J* = 10.3 and 5.8Hz, H-5_a'), 4.05 (t, 2H, *J* = 3.9Hz, H-2"), 3.83(q, 2H, *J* = 7.1Hz, ethyl) 1.12 (t, 3H, *J* = 7.1Hz, ethyl), 1.03 (s, 9H, *t*-butyl); Anal. Calcd for $C_{29}H_{34}N_2O_7Si_1$: C, 63.25; H, 6.22; N, 5.09. Found: C, 63.54; H, 6.46; N, 5.00.

(2S, 4S)-1[(2-*tert*-Butyldiphenylsilyloxymethyl)-1,3-dioxolan-4-yl]-5-(2-propenol)-uracil (14)

A solution of **7** (720mg, 2.074mmol) and 5-I-OddU **12** (600mg, 1.037mmol) in NMP (10mL) was treated with catalytic amounts of TFP (4 mol%, 10mg, 0.004mmol) and Pd_2dba_3 (1 mol %, 10mg, 0.001mmol). After being stirred at 55 °C for 12h, the reaction mixture was purified by silica gel column chromatography (30% EtOAc in hexane) to give **14** (330mg, 62.5%) as a yellowish foam.

UV (in MeOH) λ_{max} 282nm (ε = 8240); $[\alpha]^{25}_{D}$ –12.5 ; ^{1}H-NMR ($CDCl_3$) δ 8.64 (bs, 1H, NH, D_2O exchangeable), 7.67 (m, 4H, ar), 7.45 (s, 1H, H-6), 7.42 (m, 6H, ar), 6.34 (dd, 1H, *J* = 4.7 and 2.6Hz, H-4'), 6.07 (d, 1H, *J* = 11.5Hz, vinyl), 5.82 (m, 1H, vinyl), 5.11 (t, 1H, *J* = 3.8Hz, H-2'), 4.18 (s, 2H, H-5'), 3.92 (d, 2H, *J* = 3.8Hz, H-2"), 3.88(s, 2H, allylic), 1.05 (s, 9H, *t*-butyl). ; Anal. Calcd for $C_{27}H_{32}N_2O_6Si_1$: C, 63.76; H, 6.34; N, 5.51. Found: C, 63.65; H, 6.56; N, 5.80.

(2S, 4S)-1[[2-[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(2,4-pentadiene) uracil-ethyl carboxylate (15)

A solution of **8** (610mg, 1.469mmol) and 5-I-OddU **12** (655mg, 1.132mmol) in NMP (10mL) was treated with catalytic amounts of TFP (10mg, 0.043mmol) and Pd_2dba_3 (10mg, 0.011mmol). After being stirred at 55 ^oC for 12h, the reaction mixture was purified by silica gel column chromatography (30% EtOAc in hexane) to give **15** (642mg, 98.4%) as a colorless foam.

UV (H_2O) λ_{max} 323nm (ε = 12450) pH 11.0, 335nm (ε = 13710) pH 7.0, 228nm (ε = 14940), 338nm (ε = 10580) pH 2.0; $[\alpha]^{25}_D$ –15.6; ^{1}H-NMR ($CDCl_3$) δ 8.54 (bs, 1H, NH, D_2O exchangeable), 7.61 (m, 4H, ar), 7.51 (s, 1H, H-6), 7.37 (m, 6H, ar), 6.34 (m, 2H, diene), 6.24 (t, 1H, *J* = 11.5Hz, diene), 5.87 (d, 1H, *J* = 15.3Hz, diene), 5.07 (t, 1H, *J* = 3.4Hz, H-2'), 4.29 (d, 1H, *J* = 10.3Hz, H-5_b'), 4.18 (dd, 1H, *J* = 10.3 and 5.8Hz, H-5_a'), 4.05 (q, 2H, *J* = 7.1, ethyl), 3.92(dd, 1H, *J* = 11.8 and 3.4Hz, H-2_b"), 3.86 (dd, 1H, *J* = 11.8 and 3.6Hz, H-2_a") 1.21 (t, 3H, *J* = 7.1Hz, ethyl), 1.00 (s, 9H, *t*-butyl); Anal. Calcd for $C_{31}H_{36}N_2O_6Si_1$: C, 64.56; H, 6.29; N, 4.86. Found: C, 64.78; H, 6.64; N, 4.81.

(2S, 4S)-1[[2-[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(2,4-pentadiene-ol)-uracil (16)

A solution of **9** (360mg, 0.965mmol) and 5-I-OddU **12** (430mg, 0.743mmol) in NMP (10mL) was treated with catalytic amounts of TFP (7mg, 0.003mmol) and Pd_2dba_3 (7mg, 0.001mmol). After stirring at 55 ^oC for 12h, the reaction mixture was purified by silica gel column chromatography (45% EtOAc in hexane) to give **16** (275mg, 69.5%) as a yellowish foam.

UV (H_2O) λ_{max} 247nm (ε = 11200), pH 11.0, 246nm (ε = 10890), pH 7.0, 248nm (ε = 9870), pH 2.0; $[\alpha]^{25}_D$ –13.2; ^{1}H-NMR ($CDCl_3$) δ 8.94 (bs, 1H, NH, D_2O exchangeable), 7.66 (m, 4H, ar),

7.43 (s, 1H, H-6), 7.40 (m, 6H, ar), 6.38 (m, 2H, diene), 6.21 (t, 1H, *J* = 11.3Hz, diene), 6.00 (d, 1H, *J* = 10.8Hz, diene), 5.86 (t, 1H, *J* = 4.8Hz, H-2'), 5.05 (t, 1H, *J* = 4.0Hz, OH, D_2O exchangeable), 4.19 (dd, 1H, *J* = 10.3 and 1.7Hz, H-5_b'), 4.12 (dd, 1H, *J* = 10.4 and 4.8Hz, H-5_a'), 3.99(bs, 2H, pentane CH_2), 3.89 (m, 2H, H-2"), 1.09 (s, 9H, *t*-butyl); Anal. Calcd for $C_{29}H_{34}N_2O_6Si_1$: C, 65.14; H, 6.41; N, 5.24. Found: C, 65.22; H, 6.56; N, 5.58.

(2S,4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-propeneuracil-ethyl carboxylate (17)

TBAF (0.6mL, 1.0M solution in THF) was added to a suspension of **12** (165mg, 0.303mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. The resulting solution was concentrated *in vacuo*. EtOH (5mL) was added to the residue and precipitate was filtered and the filter cake was recrystalized from EtOH to give **17** (53mg, 48.0%) as a white solid.

mp 158~160 ^oC ; UV (H_2O) λ_{max} 264nm (ε = 12450), 302nm (ε = 9760), pH 11.0, 265nm (ε = 11410), 291nm (ε = 11800), pH 7.0, 265nm (ε = 10590) 292nm (ε =11220) ; $[\alpha]^{25}_D$ +3.7 ; ^{1}H-NMR (DMSO-d_6) δ 9.59 (s, 1H, H-6), 8.99 (s, 1H, NH, D_2O exchangeable), 7.01 (d, 1H, *J* = 13.2Hz, vinyl), 6.30 (dd, 1H, *J* = 5.5 and 1.7Hz, H-4'), 5.93 (d, 1H, *J* = 13.2Hz, vinyl), 5.12 (t, 1H, *J* = 2.5Hz, H-2'), 4.34 (dd, 1H, *J* = 10,2 and 1.8Hz, H-5_b'), 4.25 (dd, 1H, *J* = 10.2 and 5.6Hz, H-5_a'), 4.18 (q, 2H, *J* = 7.1Hz, ethyl), 3.94(m, 2H, H-2"), 3.21(t, 1H, *J* = 7.1Hz, OH, D_2O exchangeable), 1.30 (t, 3H, *J* = 7.2Hz, ethyl); Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 50.25; H, 5.21; N, 9.15.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(2-propenol)uracil (18)

TBAF (0.6mL, 1.0M solution in THF) was added to a solution of **14** (215mg, 0.423mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. The resulting yellowish solution was

concentrated *in vacuo*. EtOH (5mL) was added to the residue and precipitate was filtered. The filtered cake was recrystalized from EtOH to give **18** (84mg, 72.4%) as a white solid.

mp 198-200 ^{o}C ; UV (H_2O) λ_{max} 276nm (ε = 5800), pH 11.0, 228nm (ε = 9940), 280nm (ε = 7110), pH 7.0, 229nm (ε = 9500), 280nm (ε = 6980) pH 2.0; $[\alpha]^{25}_{D}$ –178.7 (c 0.49 in DMF) ; ^{1}H-NMR (DMSO-d_6) δ 11.50 (s, 1H, NH, D_2O exchangeable), 7.62 (s, 1H, H-6), 6.25 (d, 1H, *J* = 5.4Hz, H-4'), 6.09 (d, 1H, *J* = 11.8Hz, vinyl), 5.73 (m, 1H, vinyl), 5.21 (t, 1H, *J* = 5.8Hz, OH, D_2O exchangeable), 4.90 (m, 2H, H-2' and OH , D2O exchangeable), 4.29 (d, 1H, *J* = 10.0Hz, H-5_b'), 4.08 (m, 2H, H-5_a' and allylic), 3.64(dd, 2H, *J* = 5.7 and 2.3 Hz, H-2). ; Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 49.01; H, 5.13; N, 10.60.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(2,4-pentadiene)uracil-ethyl carboxylate (19)

TBAF (0.8mL, 1.0M solution in THF) was added to a suspension of **15** (300mg, 0.520mmol) in CH_3CN (5mL) and stirred at room temperature for 1hr. The resulting clear solution was concentrated *in vacuo*. EtOH (5mL) and hexane (5mL) were added to the residue and precipitate was filtered. The filtered cake was recrystalized from EtOH to give **19** (135mg, 76.7%) as a white solid.

mp 190-192 ^{o}C ; UV (H_2O) λ_{max} 314nm (ε = 13880), pH 11.0, 247nm (ε = 11420), 295nm (ε = 14800), pH 7.0, 248nm (ε = 10240), 296nm(ε =14220), pH 2.0 ; $[\alpha]^{25}_{D}$ +71.5 ; ^{1}H-NMR ($CDCl_3$) δ 8.66 (s, 1H, NH, D_2O exchangeable), 8.36 (s, 1H, H-6), 7.70(dd, 1H, *J* = 15.3 and 12.2Hz, diene), 6.62 (d, 1H, *J* = 11.6Hz, diene), 6.35 (m, 2H, H-4' and diene), 6.05 (d, 1H, *J* = 15.2Hz, diene), 5.07 (s, 1H, OH, D_2O exchangeable), 4.25 (m, 4H, H-5' and ethyl), 3.98 (m, 2H, H-2'),

1.31 (t, 3H, *J* = 7.1Hz, ethyl); Anal. Calcd for $C_{15}H_{18}N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.34; H, 5.61; N, 8.52.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(2,4-pentandiene-ol)uracil (20)

TBAF (0.8mL, 1.0M solution in THF) was added to the solution of **16** (270mg, 0.505mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. The resulting yellowish solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5% MeOH in CH_2Cl_2) and recrystalized from EtOH to give **20** (75mg, 50.1%) as a white solid.

mp 178-180 ^oC ; UV (H_2O) λ_{max} 250nm (ε = 12300), pH 11.0, 247nm (ε = 13760), pH 7.0, 248nm (ε = 13500), pH 2.0; $[\alpha]^{25}_D$ 15.2 (c 0.53 in MeOH) ; ^{1}H-NMR (DMSO-d_6) δ 11.53 (s, 1H, NH, D_2O exchangeable), 7.72 (s, 1H, H-6), 6.54 (d, 1H, *J* = 12.4Hz, diene), 6.26 (m, 2H, diene), 5.98 (m, 2H, H-4' and diene), 5.17 (t, 1H, *J* = 5.8Hz, OH, D2O exchangeable), 4.92 (s, 1H, OH , D_2O exchangeable), 4.86 (t, 1H, *J* = 4.6Hz, H-2'), 4.30 (d, 1H, *J* = 10.0Hz, H-5_b'), 4.19 (dd, 1H, J = 10.0 and 5.7Hz, H-5_a'), 4.01(m, 2H, H-2"), 3.61 (bs, 2H, pentane CH_2); Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.57; H, 5.76; N, 9.32.

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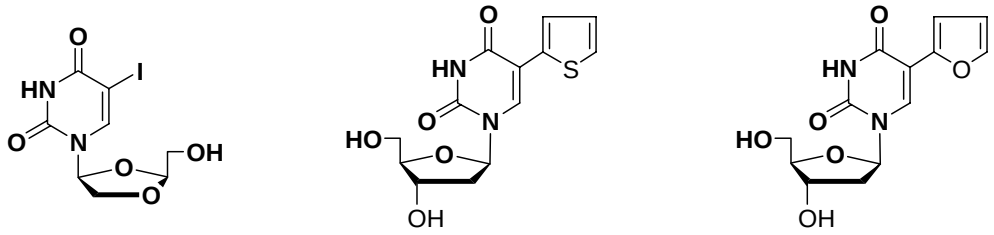
CHAPTER 2

SYNTHESIS OF L-β-5-FURAN-2-YL & THIEN-2-YL-1,3-DIOXOLANYL URACIL NUCLEOSIDES

Introduction

Recently, we reported a series of 1,3-dioxolanyluracil analogues, prepared from the dioxolane intermediates, L-5-Iodo-1,3-dioxolanyluracil **21**, which had potent and selective antiviral activity against EBV replication.[19] Interestingly, the Structure-Activity Relationships showed the decreasing potency, depending on the 5 position (I > Br > Cl > F). Several publications dealing with the uridine synthesis with unsaturated substituents in the 5-position have appeared. The coupling of 5-Iodo-2'-deoxyuridine with alkenylstanneous was reported by Crisp et. al.[20] By using these methods, aromatic rings like furanyl and thienyl rings were also introduced in the 5-position of 2'-deoxyuridine by P. Wigerinck.[21] Among the synthesized 2'-deoxynucleosides, 5-thieny-2-yl analog **2**2 and 5-furan-2-yl analog 2**3** showed potent antiviral activities against various viruses.[21,22] Recent advances in carbon-carbon coupling chemistry using palladium as a transition metal catalyst and tetraorganotin reagents have offered a number of powerful synthetic possibilities to nucleoside chemists.[23,24] The effect of changing the palladium ligands on the rates of typical Stille cross-coupling reactions was studied. Tri-2-furylphophine (TFP) was utilized as the new ligand in the palladium-catalyzed coupling reactions.[24] Herein, we have reported the syntheses of several other L-5-aromatic substituted-1,3-dioxolanuracil analogues with TFP as a ligand in the Stille reaction from key dioxolaneintermediates as potential antiviral agents.

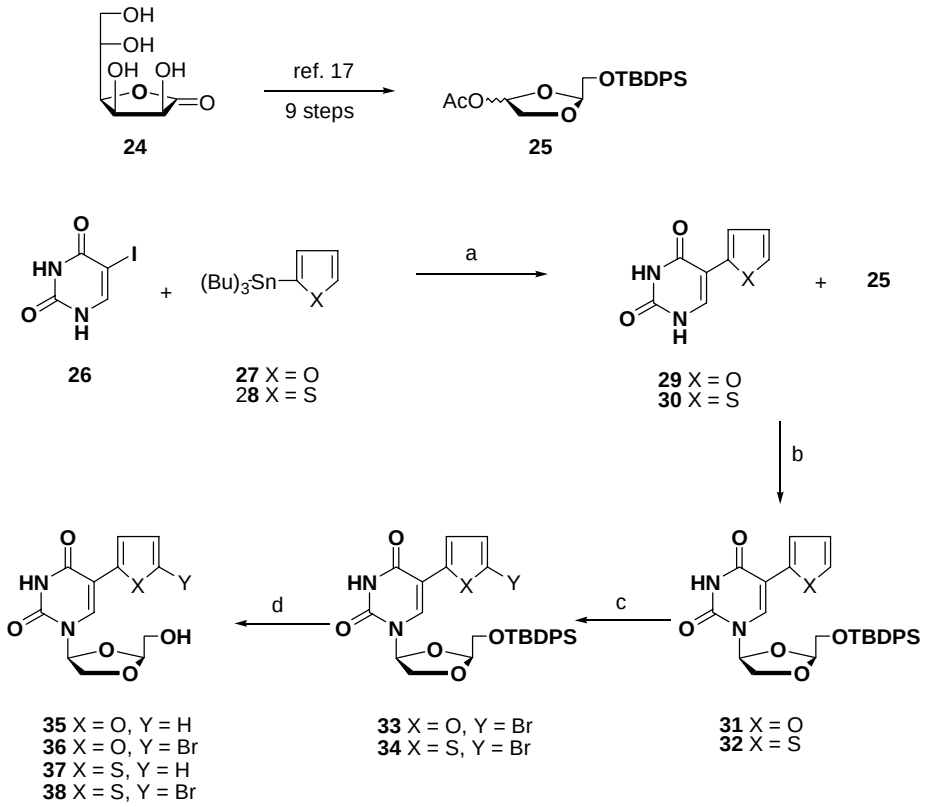
Figure 2. Nucleosides Biologically Active against HSV and EBV



Chemistry

The new L-5-furanyl-1,3-dioxolanyl nucleosides and L-5-thienyl-1,3-dioxolanyl nucleosides were prepared from the key intermediate 2**5** which was synthesized from L-gulono-γ-lactone 2**4** according to our previously published method.[25] The key intermediate acetate 2**5** was coupled with 5-substituted uracil prepared previously with 5-Iodouracil and catalytic amounts of tri-2-furylphophine (TFP) and tri(dibenzylidine acetone)dipalladium (Pd_2dba_3) in N-methyl-pyrollidinone to give protected L-dioxolanyl nucleosides, **31** and **32**.

Scheme 3. Synthesis of 5-Furanyl and 5-Thienyl-1,3-dioxolane Nucleosides



Reagents and conditions: (a) tri-2-furylphophine, tri(dibenzylidineacetone)dipalladium, N-methyl-pyrollidinone; (b) TBDMSOTf, 2,4,6-collidine, TMSI; (c) bromine, carbontetrachloride; (d) tetrabutylammonium fluoride, THF.

Then the protected nucleosides were treated carefully with an equivalent of bromine to give 5-mono bromine substituted nucleosides (**33** and **34**).[26] These protected nucleosides were deprotected using 1M solution of tetrabutylammonium fluoride in THF and purified by appropriate method to give enantiomerically pure β-L-(2S, 4S)-dioxolanyluracil derivatives (**35-38**) (Scheme 3).

Table 2. Elemental Analysis

Compd. No.	Formula	Calcd.	Found
31	$C_{28}H_{30}N_2O_6Si_1$	C, 64.67; H, 5.83; N, 5.40.	C, 64.39; H, 5.99; N, 5.50.
32	$C_{28}H_{30}N_2O_6S_1Si_1$	C, 62.90; H, 5.66; N, 5.24.	C, 63.10; H, 5.64; N, 5.30.
33	$C_{28}H_{29}N_2O_6Br_1Si_1$	C, 56.28; H, 4.89; N, 4.69.	C, 55.97; H, 6.65; N, 4.81.
34	$C_{28}H_{29}N_2O_5Br_1S_1Si_1$	C, 54.81; H, 4.76; N, 4.57.	C, 54.59; H, 4.87; N, 4.76
35	$C_{12}H_{12}N_2O_6$	C, 51.43; H, 4.32; N, 10.00	C, 51.54; H, 6.71; N, 10.32
36	$C_{12}H_{11}N_2O_4Br_1$	C, 40.13; H, 3.09; N, 7.80.	C, 40.43; H, 3.18; N, 7.80.
37	$C_{12}H_{12}N_2O_5S_1$	C, 48.64; H, 4.08; N, 9.45.	C, 48.91; H, 4.12; N, 9.34.
38	$C_{12}H_{11}N_2O_5Br_1S_1$	C, 38.41; H, 2.96; N, 7.47.	C, 38.77; H, 3.12; N, 7.80.

Experimental Section

General methods. Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Bruker 400 Fourier transform spectrometer; chemical shifts are reported in parts per million(δ), and signals are quoted as s (singlet), d(doublet), t(triplet), q(quartet), m (multiplet), and dd(double of doublets). UV spectra were obtained on a beckman DU-7 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Elemental analysis was performed by Atlantic Micolab, Inc., Norcross, GA. Dry dichloromethane, acetonitrile, pyridine were obtained by distillation from CaH2 prior to use. Dry THF was obtyaioned by distillation from Na and benzophenone when the solution became purple.

5-(Furan-2-yl)-uracil (29)

A solution of 5-Iodouracil (3g, 0.0126mol), catalytic amounts of TFP (4 mol %, 117mg) and Pd_2dba_3 (1 mol%, 117mg) in NMP (15mL) was treated with 2-(Tributylstannyl)furan and stirred at room temperature for 12h. The resulting reaction mixture was purified by silica gel column chromatography (4% MeOH in CH2Cl2) to give **9** (1.95g, 86.9%) as a gray solid. mp 310-312 ^oC ; UV (MeOH) λ_{max} 249nm, 316nm ; ^{1}H-NMR (DMSO-d_6) δ 11.64 (bs, 1H, NH, D_2O exchangeable), 11.20 (bs, 1H, NH, D_2O exchangeable), 7.70 (s, 1H, H-6), 7.62 (s, 1H, H-5'), 6.81 (d, 1H, *J* = 3.1Hz, H-3'), 6.50 (t, 1H, J =1.4 Hz, H-4')

5-(Thien-2-yl)-uracil (30)

A solution of 5-Iodouracil **26** (3g, 12.6mol), catalytic amounts of TFP (1 mol%, 117mg) and Pd_2dba_3 (1 mol%, 117mg) in NMP (15mL) was treated with 2-(tributylstannyl)thiophene (4.8mL,

0.0152nol) and stirred at room temperature for 12h. The resulting reaction mixture was purified by silica gel column chromatography (4% MeOH in CH_2Cl_2) and recrystalize from dichloromethane to give **30** (1.37g, 55.9%) as a yellowish solid.

mp 285-287 ^oC dec. ; UV (MeOH) λ_{max} 260nm, 312nm ; 1H-NMR (DMSO-d_6) δ 11.44 (s, 1H, NH, D_2O exchangeable), 11.29 (s, 1H, NH, D_2O exchangeable), 7.98 (s, 1H, H-6), 7.47 (s, 1H, H-5'), 7.41 (d, 1H, *J* = 3.1 Hz, H-3'), 7.03 (s, 1H, H-4').

(2S, 4S)-1[[2-[(tert-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(furan-2-yl)uracil (31)

A suspension of 2**9** (1.0g, 0.006mol) in dichloromethane (25mL) was treated with tert-butyldimethylsilyloxytriflate (2.9mL, 0.013mol) and 2,4,6-collidine (1.7mL, 0.013mol). After being stirred at room temperature for 30 min, dioloxane 2**5** (2.4g, 0.06mol) in dichloromethane (10mL) and trimethylsilane iodine (0.88mL, 0.0061mol) were added to the resulting clear solution and stirred at room temperature for an additional 1h. The reaction mixture was neutralized with saturated $Na_2S_2O_3$ and extracted with dichloromethane (50mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (30% EtOAc in Hexane) to give **31** (1.55g, 53.2%) as a white solid.

mp 315-316 ^oC ; UV (H_2O) λ_{max} 253nm (ε = 12420), 314nm (ε = 7960), pH 11.0, 253nm (ε = 13500), pH 7.0, 328nm (ε = 8920), pH 2.0; $[\alpha]^{25}_D$ -35.3 ; ^{1}H-NMR ($CDCl_3$) δ 9.18 (bs, 1H, NH, D_2O exchangeable), 7.82 (s, 1H, H-6), 7.61 (m, 4H, ar), 7.28 (m, 6H, ar), 7.00 (s, 1H, H-5"), 6.93 (d, 1H, *J* = 3.26 Hz, H-3"), 6.30 (m, 2H, H-4' and H-4"), 5.10 (t, 1H, *J* = 3.8 Hz, H-2'), 4.18 (dd, 1H, *J* = 10,2 and 1.5 Hz, H-5_b'), 4.14 (dd, 1H, *J* = 10.2 and 5.4 Hz, H-5_a'), 3.90 (dd, 2H,

J = 16.8 and 3.8 Hz, H-2"), 0.97 (s, 9H, *t*-butyl); Anal. Calcd for $C_{28}H_{30}N_2O_6Si_1$: C, 64.67; H, 5.83; N, 5.40. Found: C, 64.39; H, 5.99; N, 5.50.

(2S, 4S)-1[[2-[(tert-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(thien-2-yl)uracil (32)

A suspension of **30** (1.0g, 0.005mol) in dichloromethane (25mL) was treated with TBDMSOTf (2.7mL, 0.013mol) and 2,4,6-collidine (1.6mL, 0.013mol). After being stirred at room temperature for 30 min, dioxolane intermediate **25** (2.1g, 0.006mol) was added in dichloromethane (10mL) and TMSI (0.9mL, 0.006mol) to the resulting clear solution and stirred at the same temperature for an additional 1h. The reaction mixture was neutralized with saturated $Na_2S_2O_3$ and extracted with dichloromethane (50mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (30% EtOAc in hexane) to give **32** (1.41g, 51.3%) as a white-off solid.

mp 113-115 ^oC ; UV (H_2O) λ_{max} 264nm (ε = 14730), 324nm (ε = 7100) pH 11.0, (MeOH) 260nm **(**ε = 10750), 316nm **(**ε = 8980) ; $[\alpha]^{25}_D$ –21.4, ^{1}H-NMR ($CDCl_3$) δ 8.71 (bs, 1H, NH, D_2O exchangeable), 7.70 (s, 1H, H-6), 7.67 (m, 4H, ar), 7.37 (m, 6H, ar), 7.22 (d, 1H, *J* = 5.1 and 1.0 Hz, H-5"), 7.15 (dd, 1H, *J* = 3.2 and 0.9 Hz, H-3"), 6.92 (dd, 1H, *J* = 5.1 and 3.7 Hz, H-4"), 6.36 (dd, 1H, *J* = 5.2 and 1.6 Hz, H-4'), 5.17 (t, 1H, *J* = 4.0 Hz, H-2'), 4.25 (dd, 1H, *J* = 10,2 and 1.6 Hz, H-5_b'), 4.20 (dd, 1H, *J* = 10.3 and 5.4 Hz, H-5_a'), 3.96 (dd, 1H, *J* = 11.4 and 4.0 Hz, H-2_b"), 3.90 (dd, 1H, *J* = 11.4 and 4.1 Hz, H2_a"), 0.97 (s, 9H, *t*-butyl); Anal. Calcd for $C_{28}H_{30}N_2O_6S_1Si_1$: C, 62.90; H, 5.66; N, 5.24. Found: C, 63.10; H, 5.64; N, 5.30.

(2S, 4S)-1[[2-[(tert-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(5-bromofuran-2-yl)uracil (33)

A solution of **31** (200mg, 0.3347mmol) in dichloromethane (5mL) was treated with Br_2 in tetrachlorocarbon (2mL) and stirred at room temperature for 4h. The resulting mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (20% EtOAC in hexane) to obtain **33** (185mg, 80.3%) as a colorless syrup.

UV (H_2O) λ_{max} 255nm (ε = 9290), 320nm (ε = 6380) pH 11.0, 224 (ε = 15800), 257 (ε = 9300), 329nm (ε = 6850) pH7.0, 224nm (ε = 14700), 258nm (ε = 9200), 329nm (ε = 6820) pH 2.0 ; $[\alpha]^{25}_D$ –48.3 ; ^{1}H-NMR ($CDCl_3$) δ 8.61 (bs, 1H, NH, D_2O exchangeable), 7.77 (s, 1H, H-6), 7.67 (m, 4H, ar), 7.33 (m, 6H, ar), 6.95 (d, 1H, *J* = 3.4 Hz, H-3"), 6.34 (dd, 1H, *J* = 5.2 and 1.7 Hz, H-5"), 6.32 (d, 1H, *J* = 3.4 Hz, H-4"), 5.15 (t, 1H, *J* = 4.0 Hz, H-2'), 4.24 (dd, 1H, *J* = 10.3 and 1.6 Hz, H-5_b'), 4.20 (dd, 1H, *J* = 10.3 and 5.4 Hz, H-5_a'), 4.00 (dd, 1H, *J* = 11.4 and 3.9 Hz, H-2_b"), 3.95 (dd,1H, *J* = 15.4 and 5.4 Hz, H-2_a"), 1.05 (s, 9H, *t*-butyl); Anal. Calcd for $C_{28}H_{29}N_2O_6Br_1Si_1$: C, 56.28; H, 4.89; N, 4.69. Found: C, 55.97; H, 6.65; N, 4.81.

(2S, 4S)-1[[2-[(tert-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-4-yl]-5-(5-bromothien-2-yl)uracil (34)

A solution of **32** (400mg, 0.748mmol) in dichloromethane (10mL) was treated with Br_2 (118mg, 0.748mmol) in tetrachlorocarbon (2mL) and stirred at room temperature for 4h. The resulting mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (20% EtOAC in Hexane) following with crystalization from dichloromethane and hexane to obtain **34** (310mg, 67.7%) as a white solid. mp 61~63 ^oC ; UV (MeOH) λ_{max} 266nm (ε = 7650), 325nm (ε = 9800) ; $[\alpha]^{25}_D$ –21.9 ; ^{1}H-NMR ($CDCl_3$) δ 9.24(bs, 1H, NH, D_2O exchangeable), 7.66 (m, 5H, H-6 and ar), 7.38 (m, 6H, ar), 6.80(d, 1H, *J* = 4.0 Hz, H-3"), 6.75 (d, 1H, *J* = 4.0 Hz, H-4"), 6.35 (d, 1H, *J* = 4.6 Hz, H-4'), 5.18 (t, 1H, *J* = 3.9 Hz, H-2'), 4.25 (d, 1H,

J = 10.2 Hz, H-5_b'), 4.20 (dd, 1H, *J* = 10.3 and 5.3 Hz, H-5_a'), 3.96 (dd, 1H, *J* = 11.5 and 3.8 Hz, H-2 $_b$"), 3.91 (dd, 1H, *J* = 11.5 and 4.0 Hz, H-2 $_a$"), 1.04 (s, 9H, *t*-butyl); Anal. Calcd for $C_{28}H_{29}N_2O_5Br_1S_1Si_1$: C, 54.81; H, 4.76; N, 4.57. Found: C, 54.59; H, 4.87; N, 4.76.

(2S, 4S)-1-[2-Hydroxymethyl-1,3-dioxolan-4-yl]-5-(furan-2-yl)uracil (35)

1M solution of tetrabutylammonium fluoride (0.6mL, 1.0M solution in THF) was added to the suspension of **31** (200mg, 0.38mmol) in CH_3CN (5mL) and stirred at room temperature for 3h. EtOH (5mL) was added to the resulting clear solution, the precipitate was filtered and recrystalized from EtOH to give **35** (96mg, 88.0%) as a white solid.

mp 240-241 ^oC ; UV (H_2O) λ_{max} 257nm (ε = 12990), 303nm(ε = 8530), pH 11.0, 247(ε = 12760), 314(ε = 8720), pH 7.0, 248nm(ε = 12179), 313(ε = 10200), pH 2.0 ; $[\alpha]^{25}_D$ +7.4 ; ^{1}H-NMR (DMSO-d_6) δ 11.69 (s, 1H, NH, D_2O exchangeable), 8.50 (s, 1H, H-6), 7.64 (s, 1H, H-5"), 6.86 (d, 1H, *J* = 2.6 Hz, H-3"), 6.52 (t, 1H, *J* = 1.3 Hz, H-4"), 6.27 (d, 1H, *J* = 5.5 Hz, H-4"), 5.25 (t, 1H, *J* =6.0 Hz, OH, D_2O exchangeable), 4.99 (s, 1H, H-2'), 4.37 (d, 1H, *J* = 9.9 Hz, H-5_b'), 4.11 (dd, 1H, *J* = 9.9 and 5.3 Hz, H-5_a'), 3.67 (d, 2H, *J* = 5.6 Hz, H-2") ; Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.54; H, 6.71; N, 10.32.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(5-bromofuran-2-yl)uraci l(36)

1M solution of tetrabutyl ammonium fluoride (0.4mL, 1.0M solution in THF) was added to the suspension of **33** (160mg, 0.27mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. EtOH (5mL) and hexane (3mL) were added to the resulting clear solution, the precipitate was filtered and recrystalized from EtOH to give **36** (53mg, 70.7%) as a white solid.

mp 139-140 ^{o}C ; UV (H_2O) λ_{max} 263nm (ε = 14900), 308nm (ε = 9740) pH 11.0, 258 (ε = 14330), 319 (ε = 10140) pH7.0, 258nm (ε = 14440), 319 (ε = 10400) pH2.0 ; $[\alpha]^{25}_{D}$ +3.0 ; ^{1}H-NMR (DMSO-d_6) δ 11.74 (s, 1H, NH, D_2O exchangeable), 8.29 (s, 1H, H-6), 6.83 (d, 1H, *J* = 3.1 Hz, H-3"), 6.61 (d, 1H, *J* = 3.2 Hz, H-4"), 6.29 (d, 1H, *J* = 4.9 Hz, H-4'), 5.27(t, 1H, *J* =5.8 Hz, OH, D_2O exchangeable), 4.96 (s, 1H, H-2'), 4.36 (d, 1H, *J* = 10.0 Hz, H-5_b'), 4.09 (dd, 1H, *J* = 15.4 and 5.4 Hz, H-5_a'), 3.67 (d, 2H, *J* = 5.7 Hz, H-2"); Anal. Calcd for $C_{12}H_{11}N_2O_4Br_1$: C, 40.13; H, 3.09; N, 7.80. Found: C, 40.43; H, 3.18; N, 7.80.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(thien-2-yl)uracil (37)

1M solution of tetrabutylammonium fluoride (0.6mL, 1.0M solution in THF) was added to the suspension of **32** (200mg, 0.37mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. EtOH (5mL) was added to the resulting clear solution, the precipitate was filtered and recrystallized from EtOH to give **37** (93mg, 88.0%) as a white solid.

mp 182-184 ^{o}C ; UV (H_2O) λ_{max} 260nm (ε = 9450), 312nm (ε = 7630) pH 11.0, 267 (ε = 10670), 304 (ε = 8300) pH 7.0, 250nm (ε = 9590), 312 (ε = 7460) pH 2.0 ; $[\alpha]^{25}_{D}$ –2.1 ; 1-H-NMR (DMSO-d_6) δ 11.73 (s, 1H, NH, D_2O exchangeable), 8.68 (s, 1H, H-6), 7.46 (d, 1H, *J* = 5.1 Hz, H-5"), 7.39 (d, 1H, *J* = 3.6 Hz, H-3"), 7.05 (dd, 1H, *J* = 5.1 and 3.6 Hz, H-4"), 6.30 (d, 1H, *J* = 5.4 Hz, H-4'), 5.53 (t, 1H, *J* =5.4 Hz, OH, D_2O exchangeable), 4.98 (s, 1H, H-2'), 4.38 (d, 1H, *J* = 9.8 Hz, H-5_b'), 4.11 (dd, 1H, *J* = 9.4 and 5.7 Hz, H-5_a'), 3.74 (d, 2H, *J* = 4.6 Hz, H-2"); Anal. Calcd for $C_{12}H_{12}N_2O_5S_1$: C, 48.64; H, 4.08; N, 9.45. Found: C, 48.91; H, 4.12; N, 9.34.

(2S, 4S)-1-[2-(Hydroxymethyl)-1,3-dioxolan-4-yl]-5-(5-bromothien-2-yl)uracil (38)

1M solution of tetrabutylammonium fluoride (0.4mL, 1.0M solution in THF) was added to the suspension of **34** (150mg, 0.244mmol) in CH_3CN (5mL) and stirred at room temperature for 1h. EtOH (5mL) and hexane(3mL) was added to the resulting clear solution, the precipitate was filtered and recrystalized by EtOH to give 18 (51mg, 55.6%) as a white solid.

mp 165~167^{0}C dec. ; UV (H_2O) λ_{max} 281nm (ε = 12420), 316nm (ε = 13080) pH 11.0, 274 (ε = 11330), 322 (ε = 11100) pH 7.0, 274nm (ε = 12590), 320nm (ε = 12670) pH 2.0 ; $[\alpha]^{25}_D$ +0.8 ; ^{1}H-NMR (DMSO-d_6) δ 11.84 (s, 1H, NH, D_2O exchangeable), 8.76 (s, 1H, H-6), 7.19 (d, 1H, *J* = 3.9 Hz, H-3"), 7.15 (d, 1H, *J* = 3.9 Hz, H-4"), 6.27 (d, 1H, *J* = 4.9 Hz, H-4'), 5.60(t, 1H, *J* =4.4 Hz, OH, D_2O exchangeable), 4.97 (s, 1H, H-2'), 4.38 (d, 1H, *J* = 9.8 Hz, H-5_b'), 4.11 (dd, 1H, *J* = 9.7 and 5.8 Hz, H-5_a'), 3.76 (d, 2H, *J* = 5.5 Hz, H-2"); Anal. Calcd for $C_{12}H_{11}N_2O_5Br_1S_1$: C, 38.41; H, 2.96; N, 7.47. Found: C, 38.77; H, 3.12; N, 7.80.

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CHAPER 3

PRACTICAL SYNTHESIS OF D- & L-2-CYCLOPENTENONE AND THEIR UTILITY FOR THE SYNTEHSIS OF CARBOCYCLIC ANTIVIRAL NUCLEOSIDES AGAINST ORTHOPOXVIRUSES (SMALLPOX, MONKEYPOX AND COWPOXVIRUS)[1]

[1] Jin, Y. H., Liu, P., Wang, J., Baker, R., Huggins, J. and Chu, C. K. 2003. *J. Org. Chem. 68*(23). 9012-9018.

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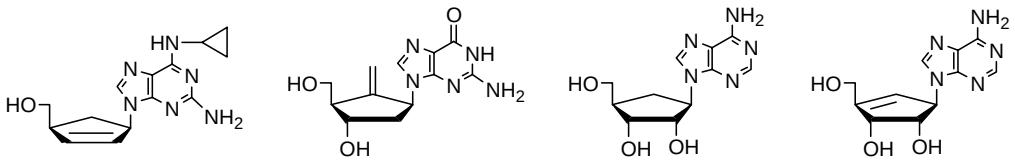
Abstract

Highly efficient and practical methodology for the syntheses of D- and L-4,5-*O*-isopropylidene-2-cyclopentenone (**47** and **60**), versatile intermediates for the synthesis of carbocyclic nucleosides, have been developed *via* a ring closing metathesis reaction from D-ribose in 8 steps. The utility of D- and L-4,5-*O*-isopropylidene-2-cyclopentenone are demonstrated by their application for the preparation of D-cyclopentyl-6-azauridine **50** and D-cyclopentenyl-5-halo-cytosine nucleosides (**71**, **72** and **73**) using Mitsunobu reaction to introduce pyrimidine bases as potential antiviral agents. Preliminary antiviral activity against orthopoxviruses (Smallpox, Monkeypox and Cowpoxvirus) of the synthesized nucleosides are described.

Introduction

Nucleosides have played a major role in the treatment of viral infectious diseases such as human immunodeficiency virus, hepatitis B virus and various herpes viruses infections. Recently, much attention has been focused on carbocyclic nucleosides, as a synthetic carbocyclic nucleoside such as abacavir[27] has been approved by the Food and Drug Administration as an anti-HIV agent. A carbocyclic nucleoside with exocyclic double bond, entecavir,[28] is also currently undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infection (Figure 3). Furthermore, carbocyclic nucleosides have recently been reported as antiviral agents against Smallpox and Monkeypox virus as well as West Nile virus,[29] which are related to bioterrorism-related organisms, and therapeutic agents against these organisms are critically needed as part of national biodefense strategies. In view of these interesting antiviral activities demonstrated by the carbocyclic nucleosides, an efficient preparative synthetic methodology is critically needed for additional exploration of this important class of compounds.

Figure 3. Biologically Active Carbocyclic Nucleosides



Abacavir Entecavir Aristeromycin Neplanocin A

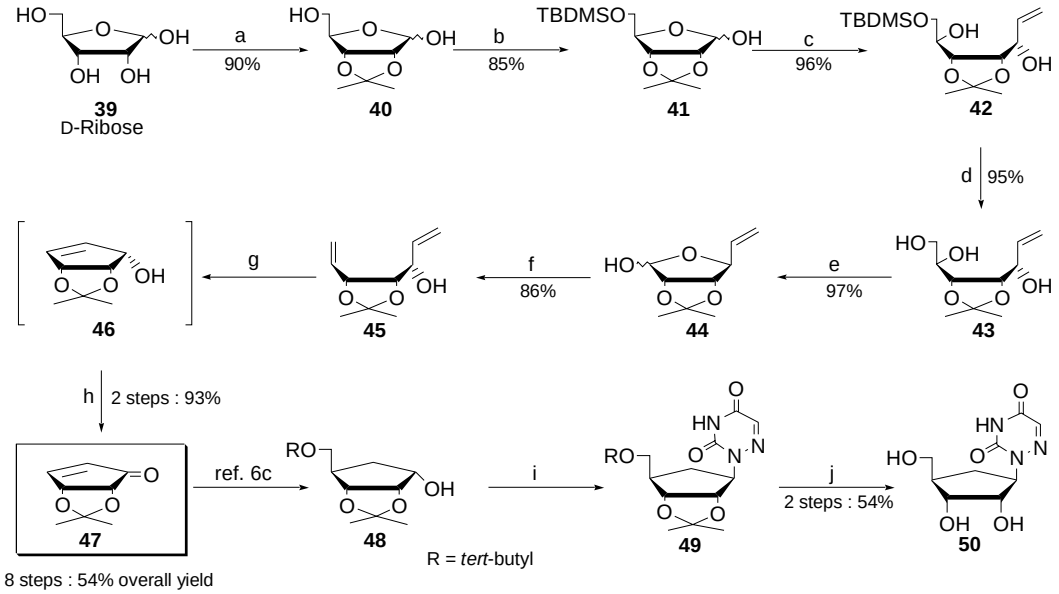
Previously, the synthesis of enantiomerically pure D- and L-aristeromycin[30] and neplanocin A[31] have been developed in our laboratory.[32] However, the overall availability of optically active carbocyclic nucleosides has been limited due to the lack of a methodology for a preparative scale preparation of the key intermediate such as D-2-cyclopentenone. D- and L-2-cyclopentenone (**47** and **60**) have been previously prepared from D-ribose,[33] D-lyxose[34] and D-isoascorbic acid[35] with low and inconsistent yields. Therefore, efficient and practical synthetic methodologies for

optically pure D- and L-2-cyclopentenone are highly desirable. Recently, we reported preliminary results of an efficient and practical synthetic methodology of D- and L-2-cyclopentenone[36] as well as antiviral activities of several cyclopentenyl nucleosides as a communication.[29b] Among the synthesized nucleosides, adenine, cytosine and 5-fluorocytosine analogues were found to be active against HIV, West-Nile virus and orthopoxviruses including Smallpoxvirus.[29] Additionally, Morrey et al. reported that 6-azauridine was found to be a potent antiviral agent against West-Nile virus.[37] Therefore, herein we report the full accounts of further improved preparative scale synthesis for the D- and L-2-cyclopentenone (**47** and **60**) over the previously reported method[29b,36] as well as additional exploration of carbocyclic 5-halo-cyclopentenylpyrimidines and the 6-carbocyclic azauridine derivative as potential antiviral agents.

Results and Discussion

D-Ribose **39** was converted to the isopropylidene-protected derivative **40** with 2,2-dimethoxypropane in the presence of catalytic amount of *p*-toluenesulfonic acid in 90 % yield, followed by silylation of primarily hydroxyl group using *t*-butyldimethylsilyl chloride to give lactol **41** in 85% yield (Scheme 4). Compound **41** was reacted with vinylmagnesium bromide to obtain a ring-opened olefine **42** in quantitative yield as a single stereoisomer. The stereoselectivity is probably due to the steric as well as the electronic effect of the isopropylidene group, which prevents the coordination of vinyl magnesium bromide at the α site. To introduce another olefinic moiety, deprotection of the silyl group was accomplished by using 1 M solution of TBAF in THF followed by an oxidative cleavage of the vicinal diol with sodium periodate to give a lactol **44** in 92% yield. The lactol **44** was subjected to the Wittig reaction using NaH, DMSO and methyltriphenylphosphonium bromide to give a diene **45** in 86% yield.[35]

Scheme 4. Synthesis of D-2-Cyclopentenone and D-Cyclopentyl-6-azauridine



[a] Reagents and conditions: (a) 2,2-Dimethoxypropane, *p*-Toluenesulfonic acid, acetone, 0 ^{o}C to rt, 1 hr; (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 hr; (c) Vinylymagnesium bromide, anhydrous THF, -78 ^{o}C to rt, 1 hr; (d) TBAF, THF, rt, 1 hr; (e) $NaIO_4$, H_2O, rt,1 hr; (f) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0 ^{o}C to reflux, 3 hr; (g) Grubbs' catalyst, anhydrous CH_2Cl_2, 24 ^{o}C, 4 hr; (h) Pyridinium dichromate, 4 Å molecular sieve, AcOH, CH_2Cl_2, rt, 12 hr; (i) 6-azauracil, PPh_3, DIAD, -78 ^{o}C to rt, 3 days, (j) 6 N HCl, MeOH, rt, 12 hr.

The ring closing metathesis reaction was carried out using Grubbs' catalyst to obtain D-cyclopentenol **46**. It was found that the metathesis reaction was affected by the reaction temperature. Although the diene **45** was converted to ring-closed cyclopentenol **46** at 17 ^{o}C with 1 mole % Grubbs' catalyst for 24 hr, the reaction was completed within 4 hr at 25 ^{o}C with the same amounts of catalyst. However, since the ring-closed cyclopentenol **46** was highly volatile, the desired key intermediate D-2-cyclopentenone **47** was directly obtained by oxidation of the secondary alcohol under PDC oxidation conditions without isolation of the cyclopentenol **46** in 54% overall yield from D-Ribose. D-2-Cyclopentenone **47** can also be obtained from D-ribonolactone using intramolecular Horner-Emmons reaction[33] as well as from D-isoascorbic acid using ring closing metathesis reaction.[35] However, these synthetic methods are problematic

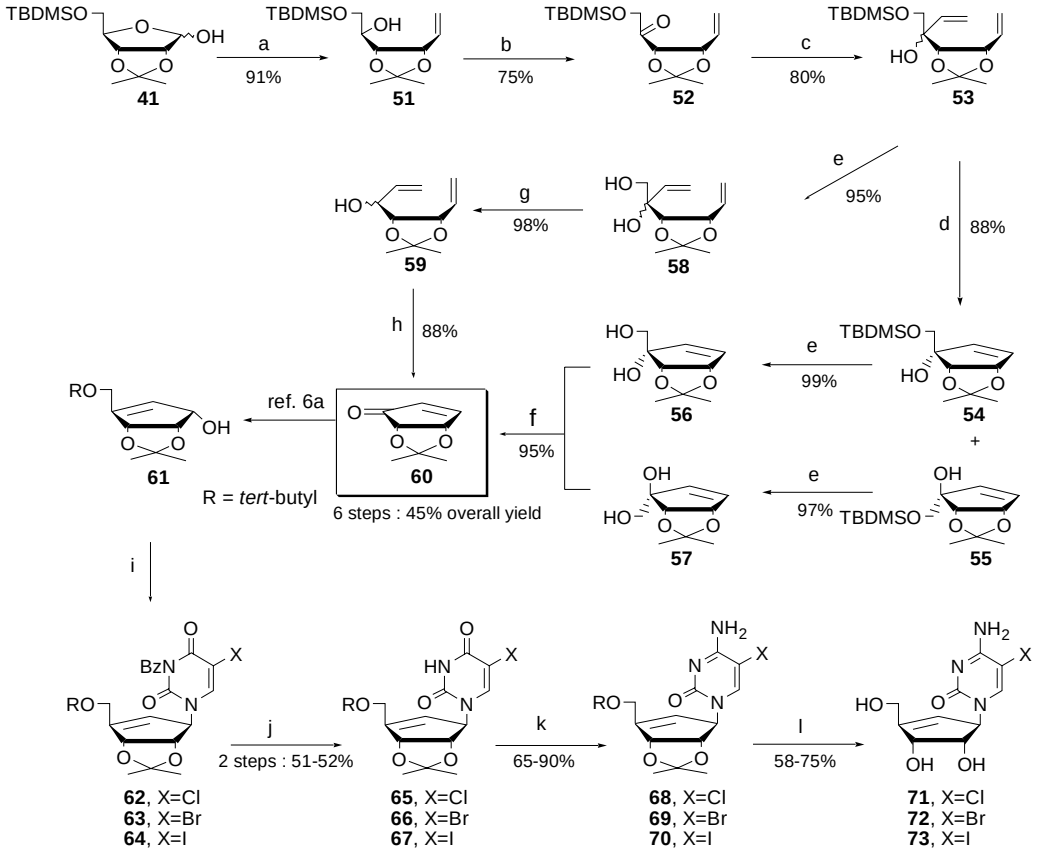
for a large scale preparation due to extreme sensitivity to the reaction conditions as well as difficulties of controlling stereoselective oxidation and reduction steps, which lower the overall yields. In our synthetic methodology, most reaction conditions are mild and give excellent yields for the D-2-cyclopentenone **47** up to 10g scale.

An efficient preparative methodology in hand, it was of interest to synthesize cyclopentyl-6-azauridine, in which D-2-cyclopentenone **47** was converted to an additional product **48** by our previously reported method.[32] As observed previously,[38] Mitsunobu reaction of pyrimidines is more difficult and problematic than that of purines, both in terms of protecting group strategies as well as *N*- vs. *O*-alkylation. However, upon introduction of the third nitrogen into the pyrimidine ring, the acidity of its adjacent N^1 atom is greatly increased, thus favorable to the regioselective N^1-substitution with respect to the N^3- or *O*-alkylation. This allows us to condense 6-azauracil with **48** to obtain the desired nucleoside **49** under the Mitsunobu conditions. The major problem in direct coupling of the sugar moiety **48** with 6-azauracil would be to discriminate N^1, N^3 and *O*-substituted products. We found that the best method for distinguishing these structures was ^{13}C NMR spectra. In the ^{13}C NMR spectrum of the carbocyclic 6-azauridine derivative **49**, C-1' appeared at 57.39 (in MeOH-d_4), which was assigned to be the *N*-substituted rather than *O*-substituted product. It is noteworthy to mention that the chemical shift of the C-1' resonance signal in the ^{13}C NMR spectrum (in DMSO-d_6) of 1-(2,3-dihydroxypropyl)-6-azauracil is at 53.63 ppm,[39] and the chemical shift of C-1' resonance signal in the ^{13}C NMR (in $CDCl_3$) of *O*- alkylated derivatives of uracil and thymine are >67 ppm.[40] Evidence for the regioselectivity of N^1- instead of N^3-substituted compound was provided by the comparison of ^{13}C NMR data of compound **50** with that of 6-azauridine. The heterocyclic base peaks of **50** (157.4, 149.8 and 135.1 ppm) were similar to those of 6-azauridine (158.5, 149.5 and 137.3

ppm),[41] clearly indicating that it was N^1-substituted compound. Furthermore, the UV spectrum of **50** (257.5 nm in pH 7) was similar to that of 6-azauridine (253 nm in pH 9).[42] The antiviral activity of synthesized β-D-cyclopentyl-6-azauridine **50** was evaluated against West Nile virus. But it did not show any significant antiviral activity against this virus.

In order to develop an efficient preparative synthetic method for L-2-cyclopentenone **22**, the protected D-ribose **41** was converted to an olefin **51** by the Wittig reaction using NaH, DMSO

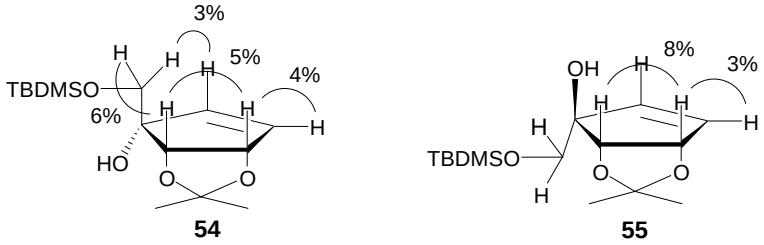
Scheme 5. Synthesis of L-2-Cyclopentenone and D-Cyclopentenyl Nucleosides



[a] Reagents and conditions: (a) NaH, DMSO, methyltriphenylphosphonium bromide, THF, 0 ^oC to reflux, 3 hr; (b) Dicyclohexyl carbodiimide, DMSO, pyridine, trifluoroacetic acid, toluene, rt, 4hr; (c) Vinylmagnesium bromide, anhydrous THF, -78 ^oC to rt, 1 hr; (d) 5% Grubbs' catalyst, anhydrous CH_2Cl_2, reflux, 24 hr; (e) TBAF,THF, rt, 1 hr; (f) $NaIO_4$, H_2O, rt, 0.5 hr; (g) i) $NaIO_4$, H_2O/CH_2Cl_2 (1:2), 0 ^oC to rt, 0.5 hr, ii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ^oC, 0.5 hr; (h) Grubbs' catalyst, anhydrous CH_2Cl_2, 24 ^oC, 4 hr and then pyridinium dichromate, 4 Å molecular sieve, AcOH, CH_2Cl_2, rt, 12 hr; (i) PPh_3, DEAD, N^3-benzoyl-5-chlorouracil (for **28**), N^3-benzoyl-5-bromouracil (for **29**), N^3-benzoyl-5-iodouracil (for **30**), rt, 17 hr; (j) sat. NH_3 in MeOH, 0 ^oC, 4 hr; (k) 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP, Et_3N, MeCN, 0 ^oC to rt, 24 hr then 30% NH_4OH, rt, 5 hr; (l) CF_3CO_2H/H_2O (2:1), 50 ^oC, 3 hr.

and methyltriphenylphosphonium bromide in refluxing THF in 91% yield (Scheme 5). The oxidation of the secondary hydroxyl group of **51** was highly affected by the oxidation conditions. Oxidation with pyridinium chlorochromate as an oxidizing agent provided ketone **52** in 53% yield. Although Swern oxidation with DMSO, oxalyl chloride and triethylamine in dichloromethane gave ketone **52** in 70% yield, the yield was dramatically decreased to 15% in the large scale (10g scale). However, a milder oxidation condition, Moffatt oxidation with dicyclohexyl carbodiimide, DMSO, pyridine and trifluoroacetic acid in toluene, was successfully carried out to obtain ketone **52** in 75% yield in a 30g scale. A grignard reaction was then performed on **52** to introduce another olefin with vinylmagnesium bromide in anhydrous THF to give an inseparable diastereomeric mixture of dienes **53** in 80% yield. The diene **53** was converted to a cyclopentene moiety by ring closing metathesis reaction using 5% Grubbs catalyst at refluxing condition in anhydrous CH_2Cl_2 as a separable diastereomeric mixture of α and β cyclopentanol **54** and **55** (**54**/**55** ratio = 1/10) in 88% yield. The α and β isomers were assigned by ^{1}H NMR and NOE spectroscopy (Figure 4). We investigated the reaction with several other protecting groups to improve the ratio (**54**/**55**) without success.

Figure 4. NOE relationships of **54** and **55**

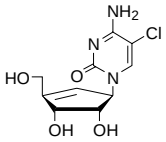
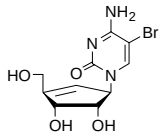
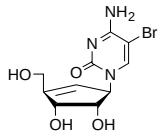
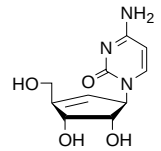


Removal of the primary hydroxyl protecting group using 1M solution of TBAF in THF gave diols **56** and **57**. Oxidative cleavage with sodium periodate afforded the L-2-cylopentenone **60** in 95% yield which served as the key intermediate for D-cyclopentenyl nucleosides. However, the

ring closing metathesis reaction for the synthesis of L-2-cyclopentenone **60** required harsh conditions in comparison to that of D-2-cycloentenone **47**, which might be due to the steric hindrance of the quaternary carbon adjacent to the vinyl group. An alternative route was developed to generate a diene alcohol **59** which was efficiently converted to the L-2-cycloentenone **60**. Deprotection of the silyl group using TBAF gave diol **58** in 95% yield. Oxidative cleavage of the vicinal diol using sodium periodate followed by reduction of ketone using sodium borohydride and cerium(III) chloride heptahydrate provided an alcohol **21** in 98% yield. The L-2-cycloentenone **60** was obtained from **59** by the same procedure for D-2-cyclopentenone **47,** giving 34% overall yield from D-Ribose. D-Cyclopentenyl alcohol **61** was synthesized by the previously reported method from L-2-cycloentenone **60**.[32a] Coupling of **61** with the appropriate protected 5-halouracils was accomplished under the standard Mitsunobu coupling conditions using N^3-benzoyl-5-halouracils, DEAD and Ph_3P in THF followed by removal of the benzoyl group using saturated methanolic ammonia. The conversion of uracil analogues to cytosine analogues was carried out by the treatment of 2,4,6-triisopropylbenzenesulfonyl chloride, DMAP and NEt_3 in CH_3CN to give **68**-**70** in 65-90% yield. Deprotection of *tert*-butyl and isopropylidene groups was carried out with CF_3COOH/H_2O (2:1, v/v) solution at 50-60 ^{0}C to give β-D-cyclopetenyl-5-halocytosine nucleosides 71-**73** in 58-75% yield. β-D-cyclopetenyl-cytosine nucleoside **74** was previously synthesized in our laboratory and it has shown to have significant anti-orthopox virus activities.[29b] It is of interest to evaluate the antiviral activity of its 5-halo-cytosine analogues for the structural activity relationship study. The anti-orthopox virus activities of the synthesized β-D-cyclopetenyl-5-halocytosine nucleosides were evaluated and the results are summarized in Table 3.

It was found that β-D-cyclopentenyl-5-iodocytidine **73** showed significant anti-monkeypox

Table 3. Anti-orthopox Virus Activity of Cyclopentenyl-5-halo-cytosine Nucleosides[a]

compd	Anti-orthopox Virus (EC_{50}, μg/mL)				
	VAR-BSH	VAR-7124	MPX	CPX	VAC
 **71**	22.8	>100	ND	21.1	>100
 **72**	100	>100	>100	100	>100
 **73**	10.4	>100	3.7	8.7	10.8
 **74**	0.03[3b]	0.08	0.1	0.06	0.12

[a]VAR-BSH (variola major strain Bangladesh 1975); VAR-7124 (variola major strain 7124); MPX (monkeypox strain Zaire); CPX (cowpox strain Brighton); VAC (vaccinia strain Copenhagen); ND : not determined.

virus, anti-cowpox virus, anti-smallpox virus and anti-vaccinia virus acitivities. β-D-Cyclopentenyl-5-chlorocytidine **71** exhibited moderate anti-smallpox virus and anti-cowpox

virus activities. However, β-D-Cyclopentenyl-5-bromocytidine **72** did not display any significant antiviral activity against orthopox viruses.

In summary, we have developed an efficient and practical synthetic method for D- and L-2-cyclopentenone (**47** and **60**) as key intermediates for the synthesis of various carbocyclic nucleosides in a preparative scale (>10g scale). From these intermediates we synthesized enantimerically pure D-cyclopentyl-6-azauridine and several D-cyclopentenyl-5-halo-cytidine nucleosides, which demonstrated interesting anti-orthopoxvirus activity.

Experimental Section

(4*R*, 5*S*)-(+)-1-{4-[2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl]-2,2-dimethyl-[1,3]dioxolan-5-yl}-(*S*)-2-propen-1-ol (42) A solution of **43** (91 g 0.30 mol) in dry tetrahydrofuran (1000 mL) was cooled to –78 ^{o}C and vinylmagnesium bromide (1M solution in tetrahydrofuran, 890 mL, 0.89 mol) was added dropwise at -60 ^{o}C. After addition was completed, the reaction mixture was allowed to stir at room temperature for 1 hr. Upon recooling the resulting clear brown mixture to –78 ^{o}C, sat. NH_4Cl solution (1000 mL) was added dropwise to quench and the resulting solution was extracted with EtOAc (1500 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1:20), giving compound **42** (94 g, 96%) as colorless oil. $[\alpha]^{23}_{D}$ +6.86^{o} (C 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (m, 2H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.35 (bs, OH, D_2O exchangeable, 1H), 4.31 (bs, 1H), 4.07 (m, 2H), 3.86 (m, 2H), 3.65 (dd, *J* = 6.7 and 9.9 Hz, 1H), 3.36 (bs, OH, D_2O exchangeable, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ137.3, 115.9, 108.6, 80.6, 76.5, 69.6, 69.2, 64.1, 27.9, 25.7, 25.3, -5.5. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70. Found: C, 58.13; H, 9.80.

(4*R*, 5*S*)-(-)-1-[4-(1,2-dihydroxyethyl)-2,2-dimethyl-[1,3]dioxolan-5-yl]-(*S*)-2-propen-1-ol (43) Tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 333 mL, 333 mmol) was added to a solution of **42 (**107 g, 322 mmol) in tetrahydrofuran (1000 mL) and stirred at room temperature for 1 hr. The resulting brown mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 2:1), giving compound **43** (66 g, 95%) as a white crystal. mp 72.4-73.9 ^oC. $[\alpha]^{23}_D$ -31.33^o (C 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.40 (dd, *J* = 0.8 and 17.2 Hz, 1H), 5.31 (dd, *J* = 0.8 and 10.5 Hz, 1H), 4.34 (t, *J* = 8.1 Hz, 1H), 4.16 (dd, *J* = 5.4 and 9.4 Hz, 1H), 4.06 (dd, *J* = 5.4 and 9.2 Hz, 1H), 3.95-3.87 (m, 1H D_2O exchangeable, 3H), 2.15 (bs, OH, D_2O exchangeable, 1H), 1.40 (s, 3H), 1.34(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 117.1, 80.0, 77.8, 69.3, 64.6, 28.0, 25.4. Anal. Calcd for $C_{10}H_{18}O_5$•0.03hexane: C, 55.37; H, 8.41. Found: C, 55.60; H, 8.31.

(1*S*, 2*S*, 3*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (44) A solution of triol **43** (38.9 g, 178.2 mmol) in H_2O (400 mL) was cooled to 0 ^oC and $NaIO_4$ (57.2 g, 26.7 mmol) was added portionwise. After being stirred at room temperature for 1 hr, the reaction mixture was extracted with EtOAc (500 mL x 3) and the extracts were dried over $MgSO_4$, filtered, and concentrated to dryness in reduced pressure. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1:10), giving compound **44 (**32.4 g, 97%) as a colorless oil. ^1H NMR spectral data was identical to the literature.[35] ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9,

134.4, 117.3, 117.0, 114.3, 112.5, 103.0, 102.9, 96.2, 88.5, 86.6, 84.7, 80.5, 79.0, 26.4, 26.2, 25.0. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05 H, 7.58. Found: C, 58.38; H, 7.74.

(1*S*, 2*S*, 3*R*)-(-)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-(*S*)-2-propen-1-ol (45) A suspension of NaH (9.9 g, 0.248 mol, 60% dispersion in mineral oil) in tetrahydrofuran (1000 mL) was cooled to 0 ^oC and then added by DMSO (29.3 mL, 0.413 mol). After being stirred at room temperature for 0.5 hr, the resulting white suspension mixture was cooled to 0 ^oC and treated with methyltriphenylphosphonium bromide (88.6 g, 0.248 mol). The reaction mixture was stirred at room temperature for 1 hr and then recooled to 0 ^oC. A solution of lactol **44** (30.8 g, 0.165 mol) in tetrahydrofuran (300 mL) was added to the resulting reaction mixture at 0 ^oC. After being heated at reflux for 3 hr, the reaction mixture was cooled to room temperature. Diethyl ether (1000 mL) was added to the reaction mixture, and washed with H_2O (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1:10), giving compound **45** (26.2 g, 86%) as a colorless oil. All the spectral data were identical to the literature.[35]

(4*R*, 5*R*)-(-)-4,5-*O*-Isopropylidene-2-cyclopentenone (47) To a 500 mL round bottom flask filled with the Grubbs' catalyst (670 mg, 1 mol%, flushed with N_2 three times), a solution of the diene **45** (15.1g, 81.3 mmol) in anhydrous CH_2Cl_2 (300 mL) was added. After being stirred at 24 ^oC for 4 hr, 4Å molecular sieve (30 g), pyridinium dichromate (35.3 g, 162.1 mmol) and acetic acid (0.23 mL, 5 mol%) were added to the resulting dark brown mixture. The reaction mixture was stirred at the same temperature for 12 hr and filtered over a silica gel pad (~15 cm) with

EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:10), giving **47** (11.4 g, 93%) as a white crystal. mp 68.5-70.3 ^{o}C. $[\alpha]^{23}_{D}$ -69.3^{o} (C 0.60, $CHCl_3$) [reported:[35] mp 68.6-70.1 ^{o}C. $[\alpha]_D$ – 70.4^{o} (C 0.92, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 2.4, 6.0 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 5.28 (dd, *J* = 2.4, 5.6 Hz, 1H), 4.47 (d, *J* = 5.6 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ159.6, 134.6, 115.4, 78.6, 76.5, 27.4, 26.1. Anal. Calcd for $C_{10}H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.15; H, 6.52.

(1'*R*, 2'*S*, 3'*R*, 4'*R*)-1-[2,3-Dihdroxy-4-(hydroxymethyl)cyclopet-1-yl]-6-azauracil (50) 6-azauracil (170 mg, 1.5 mmol) and alcohol **48** (245 mg, 1.0 mmol) were dried in vacuo for 3 hr at 50 ^{o}C. Anhydrous THF (10 mL) was added and cooled to –78 ^{o}C. DIAD (0.5 mL, 2.5 mmol) was added dropwise to a solution of triphenylphosphine (660 mg, 2.5 mmol) in THF (15 mL) at 0 ^{o}C. The DIAD and Ph_3P complex was stirred for 10 min before being added to the mixture of 6-azauracil and cyclopentanol **10** at –78 ^{o}C. The reaction was stirred at the same temperature for 1 hr and allowed to reach room temperature. After being stirred for three days at room temperature, the clear amber solution was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:10), giving compound **49** which was contaminated by reduced DIAD and used in the next reaction without further purification. The crude compound **49** was dissolved in methanol (5 mL) and then added dropwise by 6N hydrochloric acid (5 mL). After being stirred for 12 hr at room temperature, the solvent was evaporated in diminished pressure and the residue was purified by column chromatography on a silica gel (CH_2Cl_2 : MeOH = 20:1 to 10:1), giving carbocyclic 6-azauridine **50** (128 mg, 54%) as a white solid. mp 278-279 ^{o}C. $[\alpha]^{23}_{D}$ -3.26^{o} (*c* 0.61, MeOH). UV (H_2O) λ_{max} 257.5 nm (3,459,

pH 2), 257.5 nm (4,548, pH 7), 300 nm (3,110, pH 11). ^{1}H NMR (CD_3OD, 500 MHz) δ 7.34 (s, 1H), 5.14-5.09 (m, 1H), 4.58 (t, J = 6.0 Hz, 1H), 4.04 (t, J = 6.0 Hz, 1H), 3.74 – 3.71 (m, 1H), 3.76–3.54 (m,1H), 2.15–2.12 (m,1H), 2.04–1.99 (m,1H), 1.89–1.82 (m, 1H). ^{13}C NMR (CD_3OD, 125 MHz) δ157.4, 149.8, 135.1, 72.5, 72.1, 63.6, 57.4, 45.9, 25.6. MS (ESI) *m/z*: 242 (M^+ - 1), 266 (M^+ + Na), 282 (M^{-+} + K). Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.56; H, 5.54; N, 17.18.

(4*R*, 5*S*)-(-)-1-(2,2-Dimethl-5-vinyl[1,3]dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy)-1-(*R*)-ethane-1-ol (51) Compound **41** (62.1g, 204 mmol) was converted to compound **51** (56.1 g, 91%) using the same procedure as for **45**. $[\alpha]^{23}_{D}$ -9.97^{o} (C 0.39, MeOH). ^{1}H NMR spectral was identical to the literature.[43] ^{13}C NMR (100 MHz, $CDCl_3$) δ134.2, 117.6, 108.7, 78.8, 77.4, 69.6, 64.3, 27.8, 25.4, 18.3, -5.4, -5.5. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.53; H, 10.04.

(4*R*, 5*S*)-(-)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-2-(*tert*-butyldimethylsilyloxy) ethan-1-one (52) To a solution of alcohol **51** (31.0 g, 0.10 mol), dicyclohexyl carbodiimide (42.0 g, 0.21 mol), DMSO (18.1 mL, 0.25 mol) and pyridine (17.2 mL, 0.10 mol) in toluene (500 mL), trifluoroacetic acid (8.3 mL, 0.10 mol) was added dropwise at 0 ^{o}C for 10 min. After being stirred at room temperature for 10 hr, the resulting suspension mixture was filtered through a celite pad. The filtrate was washed with H_2O, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:30) to give a crude compound contaminated by reduced DCC which was dissolved in hexane. The precipitate was filtered off and the filtrate was concentrated

in vacuo. The residue was repurified by column chromatography on a silica gel (EtOAc : hexane = 1:30), giving ketone **52** (23.4 g, 75%). $[\alpha]^{23}_{D}$ -20.34^{o} (C 0.70, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.66 (m, 1H), 5.41 (d, *J* = 16.6 Hz, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.92-4.87 (m, 2H), 4.47 (d, *J* = 18.9 Hz, 1H), 4.22 (d, *J* = 18.9 Hz, 1H), 1.61 (s, 3H), 1.40 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ132.7, 118.9, 81.9, 78.2, 68.6, 31.4, 27.0, 25.8, 24.9, 22.6, 13.7, -5.5. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.92; H, 9.17.

(4*R*, 5*S*)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-1-(*tert*-butyldimethylsilyloxymethyl)-2-propen-1-ol (53) Compound **52** (20.1 g 67.1 mmol) was converted to inseparable diastereomers **53** (17.0 g, 80%) using the same procedure as for **42**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14-5.88 (m, 2H), 5.43-5.14 (m, 4H), 4.66 (t, *J* = 7.1 Hz, 0.9H), 4.54 (t, *J* = 6.6 Hz, 0.1H), 4.38 (d, *J* = 6.4 Hz, 0.1H), 4.29 (d, *J* = 6.9 Hz, 0.9H), 2.77 (s, OH, D_2O exchangeable, 0.9H), 2.51 (s, OH, D_2O exchangeable, 0.1H), 1.53 (s, 0.3H), 1.51 (s, 2.7H), 1.38 (s, 0.3H), 1.36 (s, 2.7H), 0.89 (s, 8.1H), 0.87 (s, 0.9H), 0.05 (s, 5.4H), 0.03 (s, 0.6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ138.1, 138.0, 135.7, 135.3, 117.6, 117.1, 115.8, 115.7, 108.2, 107.9, 79.3, 78.6, 78.3, 75.1, 76.7, 75.1, 74.8, 68.2, 68.0, 27.7, 27.3, 25.8, 25.8, 25.4, 24.9, 18.3, 18.2, -5.4, -5.5. Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.05; H, 9.76.

(1*R*, 4*S*, 5*S*)-(+)-4,5-*O*-Isopropylidene-1-(*tert*-butyldimethylsilyloxymethyl)-2-cyclopenten-1-ol (54) and its Epimer (55) To a 500 mL round bottom flask filled with the Grubbs' catalyst (1.25 g, 5 mol%, flushed with N_2 three times), a solution of the diene **53** (10.0g, 30.4 mmol) in anhydrous CH_2Cl_2 (300 mL) was added. After being heated at reflux for 24 hr, the resulting dark brown mixture was concentrated *in vacuo* and the residue was purified by column

chromatography on a silica gel (EtOAc : hexane = 1:10) to give β–cyclopentenol **55** (7.3 g, 80%) and its α-epimer **54** (729 mg, 8%). Compound **55**: $[\alpha]^{23}_{D}$ +55.97° (C 0.37, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, *J* = 5.7 Hz, 1H), 5.74 (d, *J* = 5.7 Hz, 1H), 5.31 (d, *J* = 5.3 Hz, 1H), 4.47 (d, *J* = 5.4 Hz, 1H), 3.92 (d, *J* = 9.9 Hz, 1H), 3.62 (d, *J* = 9.9 Hz, 1H), 3.22 (s, OH, D_2O exchangeable, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 135.2, 135.0, 112.1, 84.8, 84.7, 65.0, 27.5, 26.0, 25.9, 18.4, -5.4. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.05; H, 9.48. Compound **54**: $[\alpha]^{24}_{D}$ +72.04° (C 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 5.7 Hz, 1H), 5.66 (d, *J* = 5.7 Hz, 1H), 5.00 (d, *J* = 5.3 Hz, 1H), 4.47 (d, *J* = 5.2 Hz, 1H), 3.69 (ddd, *J* = 1.5, 9.7 and 38.7 Hz, 2H), 3.12 (s, OH, D_2O exchangeable, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 133.2, 112.4, 84.1, 82.5, 80.8, 67.0, 27.9, 26.8, 25.8, -5.5. Anal. Calcd for $C_{15}H_{29}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.10; H, 9.39.

(1*R*, 4*S*, 5*S*)-(+)-4,5-*O*-Isopropylidene-1-hydroxymethyl-2-cyclopenten-1-ol (56) and its Epimer (57) α-cyclopentenol **54** (5.0 g, 17.2 mmol) and β-cyclopentenol **55** (150 mg, 0.49 mmol) was converted to cyclopentenediol **56** (3.9g, 99%) and **57** (90 mg, 97%), respectively, using the same procedure as for compound **43**. Compound **54**: mp 103-104 °C. $[\alpha]^{23}_{D}$ +104.12° (C 0.28, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 1.6 and 5.8 Hz, 1H), 5.64 (d, *J* = 5.8 Hz, 1H), 5.25 (d, *J* = 5.8 Hz, 1H), 4.49 (d, *J* = 5.8 Hz, 1H), 3.84 (dd, *J* = 4.2 and 11.4 Hz, 1H), 3.56 (dd, *J* = 8.7 and 11.2 Hz, 1H), 2.89 (s, OH, D_2O exchangeable, 1H), 2.32 (dd, , *J* = 4.7 and 8.6 Hz, OH, D_2O exchangeable, 1H), 1.38 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 135.1, 112.9, 86.3, 84.4, 65.8, 27.1, 25.4. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.06; H, 7.61. Compound **55**: $[\alpha]^{23}_{D}$ +88.18° (C 0.27, MeOH). ^{1}H NMR (400

MHz, $CDCl_3$) δ 5.95 (dd, *J* = 1.7 and 5.8 Hz, 1H), 5.72 (d, *J* = 5.8 Hz, 1H), 5.07 (d, *J* = 5.5 Hz, 1H), 4.61 (d, *J* = 5.6 Hz, 1H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.31 (bs, OH, D_2O exchangeable, 1H), 3.26 (d, *J* = 11.5 Hz, 1H), 2.13 (bs, OH, D_2O exchangeable, 1H), 1.46 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ136.4, 133.6, 112.8, 83.4, 82.6, 79.1, 66.4, 27.7, 26.5. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.10; H, 7.63.

(4*R*, 5*S*)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-1-(hydroxymethyl)-2-propen-1-ol (58) Compound **53** (28.5g, 86.7 mol) was converted to diastereomers **58** (17.6g, 95%) as a colorless oil using the same procedure as for compound **43**. ^1H NMR (500 MHz, $CDCl_3$) δ 6.17-6.10 (m, 2H), 5.86-5.80 (m, 0.3H), 5.47-5.20 (m, 5.2H), 4.70 (t, *J* = 6.0 Hz, 1H), 4.62 (t, *J* = 5.6Hz, 0.3H), 4.32 (t, *J* = 5.6 Hz, 1H), 3.76 (d, *J* = 9.2Hz, 0.3H), 3.69 (d, *J* = 8.8Hz, 1H), 3.45 (d, *J* = 8.4 Hz, 1H), 2.88 (s, OH, D_2O exchangeable, 0.2H), 2.59 (s, OH, D_2O exchangeable, 1H), 2.25 (s, OH, D_2O exchangeable, 1H), 1.53 (s, 3H), 1.39(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.6, 135.5, 135.1, 119.5, 118.5, 117.1, 116.8, 108.8, 108.7, 81.7, 79.6, 79.4, 76.2, 75.3, 69.2, 67.6, 27.6, 27.3, 25.5, 25.0. Anal. Calcd for $C_{11}H_{18}O_4$: C, 59.85; H, 8.24. Found: C, 59.91; H, 8.21.

(4*R*, 5*S*)-1-(2,2-Dimethyl-5-vinyl[1,3]dioxolan-4-yl)-2-propen-1-ol (59) To a solution of diol **58** (13.4 g, 63.1 mmol) in CH_2Cl_2 (200 ml) and H_2O (100 ml), $NaIO_4$ (16.2 g, 75.8 mmol) was added at 0 ^oC and stirred at room temperature for 35 min. The organic phase was separated and water phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. After the residue was dissolved in MeOH (200 ml) and cooled to 0 ^oC, $CeCl_3 \cdot 7H_2O$(19.0 g, 51.0 mmol) was added and stirred at 0 ^oC for 10 min. Sodium borohydride (2.38 g, 63.1 mmol) was then added portionwise. The reaction was stirred at

0 ^{o}C for 30 min and a solution of (EtOAc : hexane = 1:1) was added. After filtering off the precipitate, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on a silica gel (EtOAc : hexane = 10:1) to give alcohol **59** (11.4 g, 98%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04-6.00 (m, 1H), 5.88-5.82 (m, 1H), 5.41-5.23 (m, 4H), 4.63-4.60 (m, 1H), 4.14-4.08 (m, 2H), 2.38-2.36 (m, OH, D_2O exchangeable, 1H), 1.55 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 134.1, 119.7, 117.3, 109.0, 80.8, 79.2, 70.8, 27.6, 25.2. Anal. Calcd for $C_{10}H_{16}O_3 \cdot$ 0.15 CH_2Cl_2: C, 61.89; H, 8.34. Found: C, 61.83; H, 8.41.

(4*S*, 5*S*)-(+)-4,5-*O*-Isopropylidene-2-cyclopentenone (60) Compound **59** (11.4 g, 61.8 mmol) was converted to compound **60** (8.3 g, 88%) using the same procedure as for compound **47**. mp 68.1-69.4 ^{o}C. $[\alpha]^{23}_{D}$ +69.1^{o} (C 0.77, $CHCl_3$). [reported:[9] mp 68.7-69.8 ^{o}C. $[\alpha]_{D}$ +69.1^{o} (C 1.98, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 2.0 and 5.8 Hz, 1H), 6.17 (d, *J* = 5.9 Hz, 1H), 5.23 (dd, *J* = 2.3 and 5.4 Hz, 1H), 4.42 (d, *J* = 5.4 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ159.6, 134.6, 115.4, 78.6, 76.5, 27.4, 26.1. Anal. Calcd for $C_{10}H_{10}O_3$: C, 62,33; H, 6.54. Found: C, 62.20; H, 6.48.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-chlorouracil (65) To a solution of N^3-benzoyl-5-chlorouracil (0.75 g, 3.18 mmol), Ph_3P (1.06 g, 4.22 mmol) and **61** (0.51 g, 2.12 mmol) in anhydrous THF was added a solution of diethylazodicarboxylate (0.73 g, 4.22 mmol) in anhydrous THF at 0 ^{o}C under N_2 atmosphere. The mixture was stirred for 15 hr at room temperature and solvent was removed in vacuo. The resulting residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:4)

to give **62** (0.92 g) as a crude white solid which was used in the next reaction without further purification. The crude **62** (0.92 g) was dissolved in saturated methanolic ammonia solution (20 mL) at 5 ^{o}C and stirred for 3 hr at room temperature. The solvent was evaporated under vacuum, and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:1), giving compound **65** (397 mg, 51%) as a white solid. mp 170-172 ^{o}C. $[\alpha]^{24}_{D}$ -55.27^{o} (c 0.57, $CHCl_3$). UV (MeOH) λ_{max} 280 nm. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (br s, 1H), 7.44 (s, 1H), 5.78 (s, 1H), 5.62 (s, 1H), 5.38 (d, J = 5.76 Hz, 1H), 4.74 (d, J = 5.81 Hz, 1H), 4.32 (dd, J = 7.48 Hz, J = 15.04 Hz, 2H), 1.57 (s, 3H), 1.50 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.0, 149.5, 138.0, 120.9, 112.8, 108.9, 84.4, 83.4, 74.0, 68.0, 58.9, 27.4, 27.2, 25.7. MS: *m/z* 371 (M+1), 373 (M+3). Anal. Calcd for $C_{17}H_{23}ClN_2O_5$: C, 55.06; H, 6.25; N, 7.55. Found: C, 55.06; H, 6.26; N, 7.51.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-bromouracil (66). Compound **66** was prepared using the same procedure as for compound **65**. Yield: 52 %. mp 196-198 ^{o}C. $[\alpha]^{23}_{D}$ –54.60^{o} (c 0.88, $CHCl_3$). UV (MeOH) λ_{max} 282 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 7.28 (s, 1H), 5.59 (s, 1H), 5.42 (s, 1H), 5.19 (d, J = 5.78 Hz, 1H), 4.55 (d, J = 5.82 Hz, 1H), 4.14 (dd, J = 16.12 Hz, J = 21.68 Hz, 2H), 1.43 (s, 3H), 1.34 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.3, 150.3, 141.0, 121.3, 113.2, 97.0, 84.8, 83.8, 77.1, 74.4, 59.3, 30.7, 27.8, 27.6, 26.2. MS: *m/z* 415 (M+1), 417 (M+3). Anal. Calcd for $C_{17}H_{23}BrN_2O_5$: C, 49.17; H, 5.58; N, 6.75 Found: C, 49.59; H, 5.79; N, 6.52.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-(Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-iodouracil (67) Compound **67** was prepared using the same procedure as for compound **65**. Yield: 52 %. mp 198-200 ^{o}C. $[\alpha]^{23}_{D}$ –86.87^{o} (c 0.57, MeOH). UV (MeOH) λ_{max} 289 nm. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 7.37 (s, 1H), 5.59 (s, 1H), 5.39 (s, 1H), 5.21 (d, J = 5.74 Hz, 1H), 4.56 (d, J = 5.81 Hz, 1H), 4.14 (dd, J = 15.44 Hz, J = 21.44 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.37, 153.18, 150.63, 146.14, 121.37, 113.18, 108.78, 84.36, 83.84, 74.43, 68.49, 59.31, 27.84, 27.62, 26.17. MS: *m/z* 463 (M+1). Anal. Calcd for $C_{17}H_{23}IN_2O_5$: C, 44.17; H, 5.01; N, 6.06 Found: C, 44.21; H, 5.12; N, 5.97.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-chlorocytosine (68) A mixture of **65** (0.21 g, 5.61 mmol), 2,2-dimethylaminopyridine (0.14 g, 1.12 mmol), triethylamine (0.17 mL, 1.68 mmol), and 2,4,6-triisopropylbenzene sulfonyl chloride (0.51 g, 1.68 mmol) in anhydrous CH_3CN (15 mL) was stirred at room temperature for 36 hr. After an addition of 28% NH_4OH (15 mL), the mixture was stirred at room temperature for 5 hr. Solvent was coevaporated with ethanol under reduced pressure. The residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 3:100) to give **68** (0.13 g, 65 %) as a white solid. mp 178-180 ^oC. $[\alpha]^{23}_D$ -38.37^o (c 0.54, $CHCl_3$). UV (MeOH) λ_{max} 290 nm. ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.58 (s, 1H), 5.41 (s, 1H), 5.14 (d, J = 5.69 Hz, 1H), 4.52 (d, J = 5.78 Hz, 1H), 4.12 (dd, J = 15.01 Hz, J = 23.02 Hz, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 154.7, 152.2, 139.9, 121.5, 112.4, 99.8, 84.5, 83.4, 73.8, 68.7, 58.9, 27.4, 25.8. MS: *m/z* 370 (M+1), 372 (M+3). Anal. Calcd for $C_{17}H_{24}ClN_3O_4 \bullet 0.2H_2O$: C, 54.68; H, 6.59; N, 11.24 Found: C, 54.64; H, 6.55; N, 10.94.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Isopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-bromocytosine (69) Compound **69** was prepared using the same procedure as for compound **68**.

Yield: 90 %, mp 194-196 ^{o}C. $[\alpha]^{22}_{D}$ –62.63^{o} (c 0.56, MeOH). UV (MeOH) λ_{max} 291 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 5.59 (s, 1H), 5.43 (s, 1H), 5.16 (d, J = 5.70 Hz, 1H), 4.55 (d, J = 5.78 Hz, 1H), 4.14 (dd, J = 15.10 Hz, J = 23.00 Hz, 2H), 1.42 (s, 3H), 1.31 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ162.3, 155.0, 152.0, 142.3, 121.5, 112.3, 87.1, 84.5, 83.3, 73.8, 68.9, 58.9, 29.6, 27.4, 27.2, 25.8. MS: *m/z* 414 (M+1), 416 (M+3). Anal. Calcd for $C_{17}H_{24}BrN_3O_4$•0.4hexane: C, 51.92; H, 6.65; N, 9.36 Found: C, 52.92; H, 6.65; N, 9.36.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-sopropylenedioxy)-4-(*tert*-butoxymethyl)-4-cyclopenten-1-yl]-5-iodocytosine (70) Compound **70** was prepared using the same procedure as for compound **68**. Yield: 65 %, mp 200-202 ^{o}C. $[\alpha]^{25}_{D}$ –82.24^{o} (c 0.46, MeOH). UV (MeOH) λ_{max} 296 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 5.59 (s, 1H), 5.47 (s, 1H), 5.16 (d, J = 5.71 Hz, 1H), 4.54 (d, J = 5.75 Hz, 1H), 4.13 (dd, J = 15.17 Hz, J = 22.50 Hz, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 152.5, 148.4, 122.0, 112.8, 85.0, 83.8, 74.3, 69.4, 59.9, 28.9, 27.7, 26.2. MS: *m/z* 462 (M+1). Anal. Calcd for $C_{17}H_{24}IN_3O_4$: C, 44.26; H, 5.24; N, 9.11; Found: C, 44.35; H, 5.37; N, 8.93.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-chlorocytosine (71) Compound **68** (0.15 g, 0.42 mmol) was dissolved in 30 mL of CF_3COOH/H_2O (2:1, v/v) and heated at 50 ^{o}C for 5 hr. The solvent was removed under vacuum, and the residue was coevaporated twice with ethanol (20 mL) under vacuum. The resulting residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:5), giving compound **71** (90 mg, 75%) as a white solid (recrytallized from MeOH and diethyl ether). mp 194-196 ^{o}C. $[\alpha]^{25}_{D}$ – 96.40^{o} (c 0.13, MeOH). UV (H_2O) λ_{max} 299.5 nm (ε 12106, pH 2), 289.0 nm (ε 8143, pH 7.4),

290.0 nm (ε 7504, pH 11). ^{1}H NMR (400 MHz, MeOH-d_4) δ 5.70 (s, 1H), 5.47 (bs, 1H), 4.53 (d, J = 5.26 Hz, 1H), 4.27 (dd, J = 15.27 Hz, J = 17.72 Hz, 2H), 4.05 (t, J = 5.59 Hz, 1H). ^{13}C NMR (100 MHz, MeOH-d_4) δ163.7, 152.7, 142.4, 125.9, 102.6, 79.0, 74.6, 69.9, 60.7. MS: *m/z* 274 (M+1), 276 (M+3). Anal. Calcd for $C_{17}H_{24}ClN_3O_4$: C, 43.89; H, 4.42; N, 15.35; Found: C, 43.81; H, 4.51; N, 15.18.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-bromocytosine (72) Compound **72** was prepared using the same procedure as for compound **71**. Yield: 58 %. mp 236-238 ^{o}C. $[\alpha]^{28}_{D}$ –116.27^{o} (c 0.49, H_2O). UV (H_2O) λ_{max} 303 nm (ε 11949, pH 2), 291.0 nm (ε 9711, pH 7.4), 291.0 nm (ε 9658, pH 11). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.62 (s, 1H), 5.49 (s, 1H), 5.32 (br s, 1H), 4.31 (d, J = 5.64 Hz, 1H), 4.03 (dd, J = 15.20 Hz, J = 17.62 Hz, 2H), 3.89 (t, J = 5.31 Hz, 1H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 162.2, 156.1, 152.1, 143.5, 124.1, 75.3, 72.2, 67.2, 59.0. MS: *m/z* 318 (M+1), 320 (M+3). Anal. Calcd for $C_{17}H_{24}BrN_3O_4$: C, 37.75; H, 3.80; N, 13.21; Found: C, 37.63; H, 3.95; N, 12.97.

(1'*S*, 2'*R*, 3'*S*)-(-)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl]-5-iodocytosine (72) Compound **72** was prepared using the same procedure as for compound **70**. Yield: 63 %. mp 210-212 ^{o}C. $[\alpha]^{29}_{D}$ –127.90^{o} (c 0.46, H_2O). UV (H_2O) λ_{max} 312.0 nm (ε 13418, pH 2), 295.5 nm (ε 7576, pH 7.4), 297.0 nm (ε 8739, pH 11). ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.63 (s, 1H), 5.48 (s, 1H), 5.31 (br s, 1H), 4.30 (d, J = 5.56 Hz, 1H), 4.04 (dd, J = 15.27 Hz, J = 17.72 Hz, 2H), 3.87 (t, J = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6 + D_2O) δ 167.8, 159.5, 155.1, 152.8, 128.3, 81.1, 76.5, 71.1, 62.9, 60.6. MS: *m/z* 366 (M+1). Anal. Calcd for $C_{17}H_{24}IN_3O_4$: C, 32.89; H, 3.31; N, 11.51; Found: C, 33.14; H, 3.34; N, 11.27.

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CHAPER 4

ASYMMETRIC SYNTHESIS OF D-2'-FLUORO-2',3'-DIDEOXY-2',3'-DIDEHYDRO CARBOCYCLIC NUCLEOSIDES AND THEIR ANTIVIRAL ACTIVITY AGAINST HIV

Introduction

Nucleosides have continued to play a major role in the chemotherapy of human immunodeficiency virus the last two decades. To date, seven nucleoside analogs have been received the approval for the treatment of HIV infection by FDA.[44] The currently used highly active antiretroviral therapy (HAART),[45,46] mostly combination of two nucleoside reverse transcriptase inhibitors and a protease inhibitor or a non nucleoside reverse transcriptase inhibitor, has led to a substantial decrease in the frequency of opportunistic infections among HIV-infected individuals, along with a significant reduction in their mortality rate. However, undesired side toxicities[47,48] and emergence of resistant viral strains[49,50] have been the main limitations of nucleosides analogs. This led to an extensive structural modifications of current agents to develop more efficient and less cytotoxic antiviral agent.

Since six of the anti-HIV nucleosides (AZT, ddI, ddC, d4T, 3TC and abacavir) could be classified as a 2',3'-dideoxy nucleosides, and d4T and abacavir are also considered as 2',3'-dideoxy-2',3'-didehydro nucleosides. They may act as inhibitors of viral DNA polymerase or chain terminators of growing viral DNA produced by HIV reverse transcriptase. In addition, substitution of an electronegative fluorine atom at 2' position is known to stabilize the glycosidic bond as well as affect the electronic environment in regard to the hydrogen bond acceptor.[51,52]

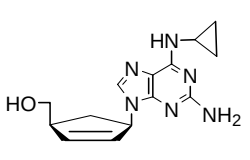
On the basis of these aspects, previously, we have extensively explored the structure-activity relationship studies with a series of D- and L-2'-fluoro-2',3'-dideoxy-2',3'-didehydro nucleosides and D- and L-2'-fluoro-2',3'-dideoxy-2',3'-didehydro-4'-thio nucleosides (Figure 5).[53-56] Among them, L-2'-fluoro-2',3'-dideoxy-2',3'-didehydrocytosine, 5-fluorocytosine and adenine analogs showed potent anti-HIV (EC_{50} 0.51, 0.17, and 1.5 μM, respectively) activities in human peripheral blood mononuclear (PBM) cells and anti-HBV (EC_{50} 0.18, 0.225, and 1.7 μM,

respectively) activities in 2.2.15 cells without significant cytotoxicities.[54] D-2'-fluoro-2',3'-dideoxy-2',3'-didehydro-5-fluorocytosine and adenine analogs also exhibited potent anti-HIV (EC_{50} 0.82 and 4.4 μM, respectively) activities in PBM cell without significant cytotoxicities.[53]

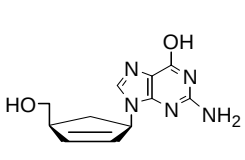
On the other hand, carbocyclic nucleosides have received much attention. Since some of them have interesting antiviral and antitumor activities.[57,58] The approval of abacavir against HIV infection has been the milestone of the carbocyclic nucleosides of clinical usefulness.[59,60] Recently, we reported an efficient and practical synthetic methodology for D and L-cyclopent-2-enone, key intermediates for carbocyclic nucleosides, as well as the antiviral activities of cyclopentenyl nucleosides.[61-63] Among the synthesized nucleosides, adenine, cytosine and 5-fluorocytosine analogs were found to be active against HIV, West-Nile virus and orthopoxviruses including smallpoxvirus.

Therefore, it is of interest to synthesize the carbocyclic 2'-fluoro-2',3'-dideoxy-2',3'-didehydro nucleosides. Previously, Kaneko et al. reported the racemic synthesis of carbocyclcic 2'-fluoro-2',3'-dideoxy-2',3'-didehydro guanosine analog using linear build-up of heterocyclic guanosine base.[64] Herein we report the synthesis of enantiomerically pure carbocyclic 2'-fluoro-2',3'-dideoxy-2',3'-didehydro nucleosides using the ring-opening reduction of expoxide **3** as a key step, followed by oxidation, fluorination, elimination and direct condensation of heterocyclic base under Mitsunobu coupling reaction [65,66] as well as their antiviral activity against HIV.

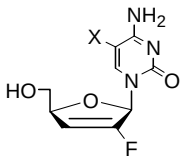
Figure 5. 2',3'-Dideoxy-2',3'-didehydro Nucleosides Active against HIV



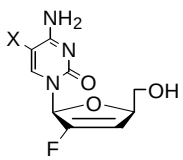
Abacavir



Carbovir



X=H, D-2'-F-d4C
X=F, D-2'-F-d4FC

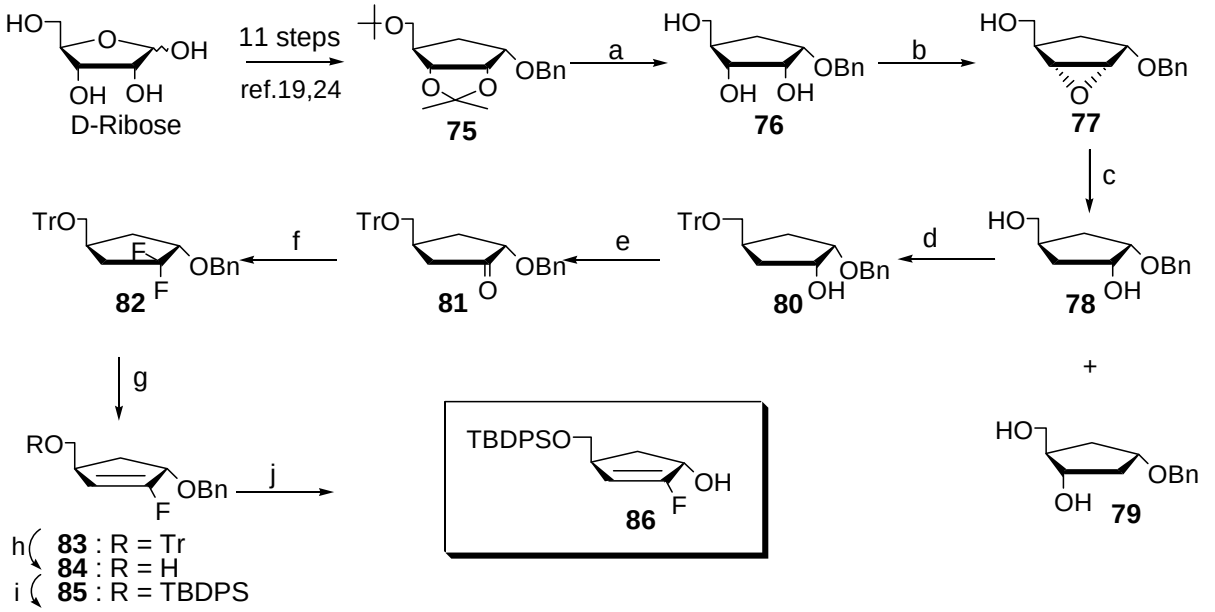


X=H, L-2'-F-d4C
X=F, L-2'-F-d4FC

Chemistry

For the synthesis of carbocyclic 2'-fluro-2',3'-dideoxy-2',3'-didehydro nucleosides, we utilized the fully protected enantiomeically pure cyclopentane **75**, previously prepared in 14 steps from D-ribose (Scheme 6).[62,67] The acidic labile protecting groups, isopropylidine and *tert*-butyl were selectively cleaved by refluxing in a 6N-HCl and methanol solution to give a triol **76** which was treated with 1-bromocarbonyl-methylethylacetate at –30 °C and potassium carbonate to provide an epoxide **77** in 79% yield.[68,69]

Scheme 6. Synthesis of 1-Fluoro-3-(*O-tert*-butyldiphenylsilyloxymethyl)-5-hydroxyl-cyclopentene

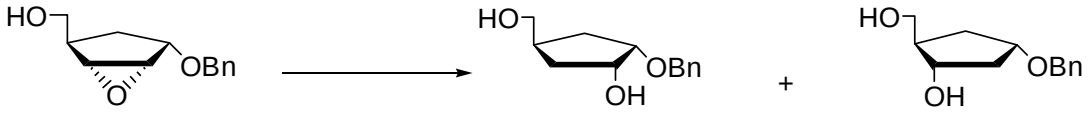


Reagents and conditions: (a) 6N HCl, H_2O; (b) AIBBr, CH_3CN and then K_2CO_3; (C) LAH, anhydrous THF ; (d) TrCl, pyridine; (e) PDC, AcOH, CH_2Cl_2; (f) DAST, anhydrous CH_2Cl_2; (g) K^{t}OBu, THF; (h) 3N HCl, MeOH; (i) TBDPSCl, imidazole, CH_2Cl_2; (j) Na, NH_3

Extensive investigation of epoxide ring-opening reaction with several reducing agents was conducted to optimize the ratio of 2- vs 3-hydroxyl compound. Ring-opening reduction with lithium aluminum hydride (LAH), diisobutyl aluminum hydride (Dibal-H) and lithium tri-*tert*-

butoxy aluminum hydride predominantly gave a 2-hydroxyl isomer **78** as shown in Figure 6. Although reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) provided solely the 2-hydroxyl isomer **78**, which probably due to the coordination of aluminum with 6-hydroxyl group, the yield was lower (54%) than that of reduction by lithium aluminum hydride (68%). A primary alcohol was selectively protected by the trityl group in 81% yield, followed by oxidation of the secondary alcohol to give a ketone **81**, in 70% yield. Treatment of the carbonyl group with diethylaminosulfur trifluoride (DAST) in methylenechloride gave a difluorinated **82** in 76% yield which was subjected to the elimination reaction with potassium *tert*-butoxide in THF at 50 °C to afford a vinyl **83**, in 97% yield. The acidic hydrolysis was conducted to selectively remove the trityl protecting group, followed by the silylation and debenzylation using sodium in liquid ammnonia at –78 °C to give a key intermediate vinyl alcohol **86**, in 64 % yield in 3 steps.

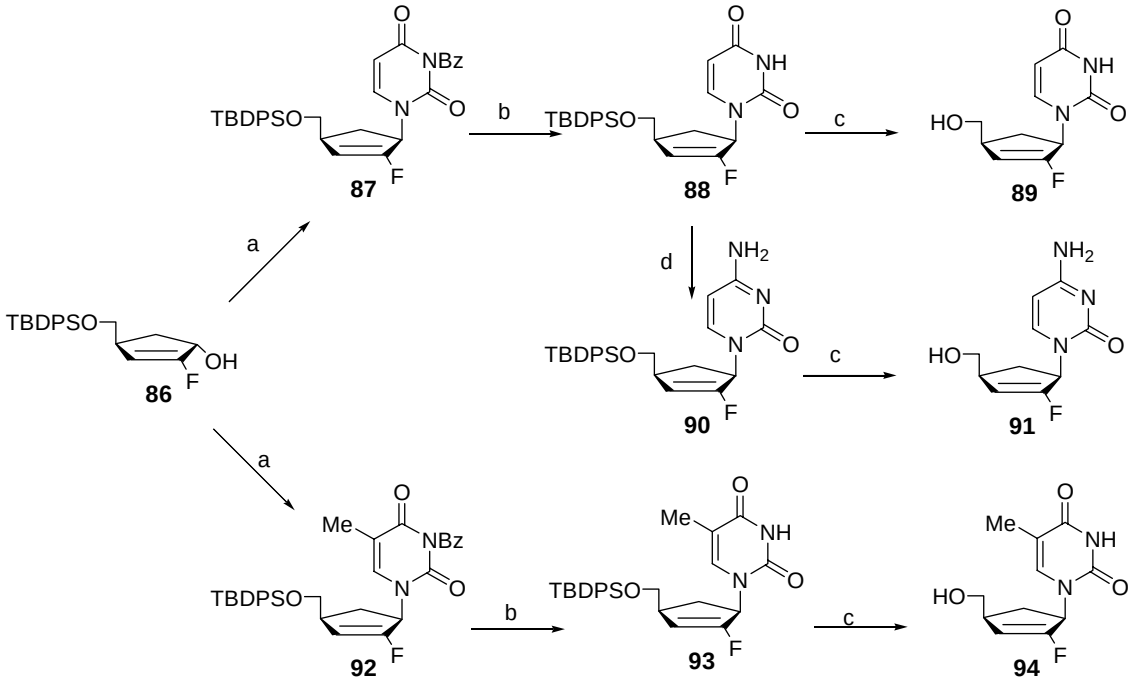
Figure 6. Investigation of Epoxide **77** Ring-opening Reaction



Reducing agent	78:79 ratio	yield
LAH	4.3:1	89%
Dibal-H	3.9:1	63%
Red-Al	1:0	52%
LiAl(*t*-butoxy)$_3$	1:0	5%

As shown in scheme 7, coupling of **86** with appropriately blocked pyrimidine bases was carried out under Mitsunobu condition[65] to obtain the nucleoside analogues. For the syntheses of uridine and thymidine analogs, **86** was treated with N^3-benzoyluracil and N^3-benzoylthymine in the presence of triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran at room temperature to give **87** and **92** as crude compounds, which was contaminated with the reduced diisopropyl azodicarboxylate. Treatment of **87** and **92** with methanolic ammonia provided debenzoylated **88** and **93** in 41% and 54% yield with two steps, respectively. For the synthesis of a cytidine analog, the uridine analog **88** was subjected to the ammonolysis using 2,4,6-triisopropylbenzenesulfonyl chloride, 4-dimethylamino pyridine and triethylamine in acetonitrile to give **90** in 65% yield.[61]

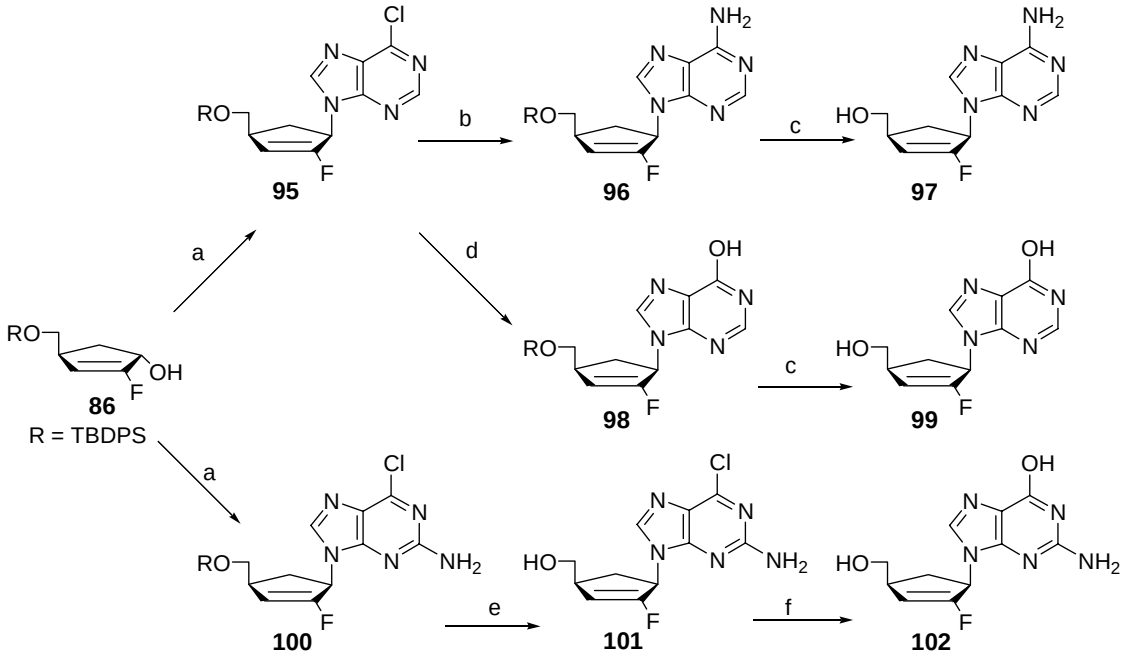
Scheme 7. Synthesis of D-2'-Fluoro-2',3'-dideoxy-2',3'-didehydro Carbocyclic Pyrimidine Nucleosides



Reagents and conditions: (a) DIAD, Ph_3P, N3-benzoyluracil for **87**, N3-benzoylthymine for **92**; (b) NH_3, MeOH; (c) 3N HCl, MeOH; (d) TIDPSCl, Et_3N, DMAP, acetonitrile and then NH_4OH.

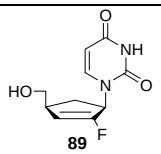
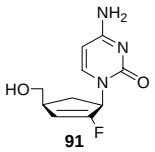
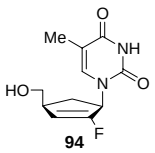
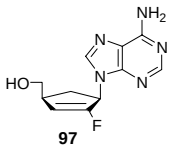
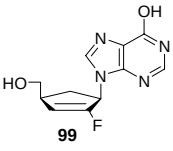
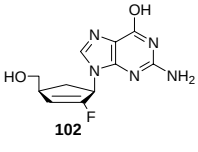
Uridine, cytidine and thymidine analogs **89**, **91** and **94** were obtained by deprotection of the silyl group using 3N-HCl in 88% - 92% yield. The purine analogs were also prepared with the similar procedure. Coupling of **86** with 6-chloropurine under Mitsunobu condition gave a 6-chloropurine analog **95** in 60% yield (Scheme 8). Treatment of **95** with saturated ammonia in methanol in a steel bomb at 110 °C provided an adenine moiety **96** in 62% yield and the deprotection of silyl group gave an adenine analog **97** in 93% yield. In order to synthesize the inosine analog, the 6-chloropurine analog **98** was treated with 2-mercaptoethanol and sodium methoxide in refluxing methanol and then the silyl group was removed under acidic condition to give an inosine analog **99** in 64% yield with two steps.

Scheme 8. Synthesis of D-2'-Fluoro-2',3'-dideoxy-2',3'-didehydro Carbocyclic Purine Nucleosides



Reagents and conditions: (a) DIAD, Ph_3P, 6-chloropurine for **95**, 6-chloro-2-aminopurine for **100**; (b) NH_3, MeOH, steal bomb, 110 ^oC; (C) 3N HCl, MeOH; (d) mercaptoethanol, NaOMe, MeOH; (e) TBAF, THF; (f) HCO_2H, 80 ^oC and then NH_4OH, MeOH.

Table 4. Antiviral Activity of Carbocyclic 2'-Fluoro-2',3'- dideoxy-2',3'- didehydro Nucleosides against HIV

Comounds	Anti-viral activity (EC_{50}, μM)	Cytotoxicity (IC_{50}, μM)		
	HIV	PBM	CEM	Vero
 **89**	>100	>100	>100	>100
 **91**	>100	>100	>100	>100
 **94**	>100	>100	>100	>100
 **97**	72.8	>100	>100	>100
 **99**	>100	>100	>100	>100
 **102**	37.8	>100	>100	>100

However, the synthesis of the guanine analog was more complicated in terms of Mitsunobu condition, which was affected by solvent and reaction temperature. Although treatment of **86** with 2-amino-6-chloropurine in the presence of triphenylphosphine and diisopropyl

azodicarboxylate in tetrahydrofuran or dimethylformamide at 0 °C failed to provide a 2-amino-6-chlorpurine analog **100**, it was obtained in tetrhydrofuran and 1,4-dioxane co-solvent at –78 °C. The removal of silyl group using tetrabutylammonium fluoride gave **101** in 40% yield with 2 steps. The guanine analog **102** was obtained by treatment of **101** with formic acid at 80 °C and 28 % ammonium hydroxide solution in 84% yield.

Antiviral Activity

The synthesized nucleosides were tested for their antiviral activities against HIV as well as their cytotoxicity. Anti-HIV activity of the synthesized nucleosides was evaluated in human peripheral blood mononuclear (PBM) cells infected with HIV. The results were summarized in Table 4. It was found that among the synthesized carbocyclic 2'-fluoro-2',3'-dideoxy-2',3'-didehydro nucleosides, guanine **102** and adenine **99** analogs exhibited moderate antiviral activity (EC_{50} 37.8 and 72.8 μM, respectively) without significant cytotoxicity (IC_{50} >100) in PBM, CEM and Vero cells. However, pyrimidine and inosine analogs (**89**, **91**, **94** and **99**) did not show any significant antiviral activity.

In summary, we have developed an asymmetric synthetic methodology for 2'-fluoro-2',3'-dideoxy-2',3'-didehydro carbocyclic nucleosides and evaluated their anti-HIV activities.

Experimental Section

General Methods. Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Bruker 400 Fourier transform spectrometer; chemical shifts are reported in parts per million(δ), and signals are quoted as s (singlet),

Table 5. Elemental Analysis

Compd. No.	Formula	Calcd.	Found
76	$C_{12}H_{18}O_4$	C, 65.53; H, 7.61	C, 65.42; H, 7.54
77	$C_{12}H_{16}O_3$	C, 70.89; H, 7.32	C, 70.45; H, 7.29
78	$C_{12}H_{18}O_3$	C, 70.24; H, 8.16	C, 69.98; H, 8.24
79	$C_{12}H_{18}O_3$	C, 70.24; H, 8.16	C, 70.58; H, 8.33
80	$C_{31}H_{32}O_3$	C, 82.73; H, 6.94	C, 82.86; H, 7.22
81	$C_{31}H_{30}O_3$	C, 83.09; H, 6.54	C, 82.84; H, 6.61
82	$C_{31}H_{30}O_2F_2$	C, 79.32; H, 6.24	C, 79.36; H, 6.34
83	$C_{31}H_{30}O_2F_1$	C, 82.73; H, 6.29	C, 82.89; H, 6.44
84	$C_{13}H_{15}O_2F_1 \cdot 0.3CH_2Cl_2$	C, 69.96; H, 6.87	C, 69.83; H, 6.87
85	$C_{29}H_{35}O_2F_1Si_1$	C, 75.61; H, 7.22	C, 75.58; H, 7.22
86	$C_{22}H_{27}O_2F_1Si_1$	C, 71.31; H, 7.34	C, 71.32; H, 7.44
88	$C_{26}H_{29}N_2O_4F_1Si_1 \cdot 0.7H_2O$	C, 65.44; H, 6.42; N, 5.87	C, 65.39; H, 6.41; N, 5.88
89	$C_{10}H_{11}N_2O_3F_1 \cdot 0.2H_2O$	C, 52.26; H, 5.00; N, 12.09	C, 52.24; H, 5.09; N, 11.96
90	$C_{26}H_{30}N_2O_2F_1Si_1$	C, 67.36; H, 6.52; N, 9.06	C, 67.27; H, 6.57; N, 8.97
91	$C_{10}H_{12}N_3O_2F_1$	C, 45.90; H, 5.01; N, 16.06	C, 45.86; H, 4.97; N, 16.00
93	$C_{27}H_{31}N_2O_4F_1Si_1$	C, 67.75; H, 6.53; N, 5.85	C, 67.92; H, 6.64; N, 5.80

Table 5. Continued

Compd. No.	Formula	Calcd.	Found
94	$C_{11}H_{13}N_2O_3F_1$	C, 55.00; H, 5.45; N, 11.66	C, 54.71; H, 5.40; N, 11.39
96	$C_{27}H_{30}N_5O_1F_1Si_1 \cdot 0.7H_2O$	C, 64.83; H, 6.33; N, 14.00	C, 64.95; H, 6.25; N, 13.98
97	$C_{11}H_{12}N_5O_1F_1 \cdot HCl$	C, 46.24; H, 4.59; N, 24.51	C, 46.35; H, 4.59; N, 24.44
98	$C_{27}H_{39}N_4O_2F_1Si_1 \cdot 0.6H_2O$	C, 64.93; H, 6.09; N, 11.22	C, 65.02; H, 6.07; N, 10.94
99	$C_{11}H_{12}N_4O_2F_1 \cdot 0.6H_2O$	C, 50.61; H, 4.71; N, 21.46	C, 50.29; H, 4.74; N, 21.45
101	$C_{11}H_{11}N_5O_1FCl \cdot 0.3MeOH$	C, 46.31; H, 4.16; N, 23.96	C, 46.35; H, 4.14; N, 23.65
102	$C_{11}H_{12}N_5O_2F_1 \cdot 1.6H_2O$	C, 44.93; H, 4.62; N, 23.14	C, 45.01; H, 4.68; N, 23.11

d(doublet), t(triplet), q(quartet), m(multiplet), and dd(double of doublets). Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplate 25TLC plates purchased from Analtech Co. Column chromatogaphy was performed using silica gel (60 Å, 32-63 μM Sorbent Technologies). Elemental analysis was performed by Atlantic Micolab, Inc., Norcross, GA**.** Anhydrous solvents were purchased from Aldrich Co.

(1*S*, 2*R*, 3*R*, 4*S*)-(+)- (+)-1-*O*-Benzyloxy-2,3-dihydroxyl-4-hydroxymethyl-cyclopentane (76)

A solution of fully protected cyclopentane **75** (29.9 g, 89.4 mol) in MeOH (150 mL) was treated with 3N HCl (150 mL). After refluxed for 4 h, the clear resulting brown mixture concentrated *in vacuo* with ethanol (100 mL x 2) and the residue was purified by silica gel column chromatography (MeOH : CH_2Cl_2 = 1:20) to afford **76** (15.7 g, 73.7%) as a white-off solid. mp :

115.7-116.9 °C $[\alpha]_D$ +11.37° (C 0.71, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.38-7.24 (m, 5H), 4.55 (dd, *J* = 11.9 and 35.1 Hz, 1H), 4.00 (t, *J* = 3.9 Hz, 1H), 3.85 (dt, , *J* = 3.7 and 7.4 Hz, 1H), 3.72 (dd, , *J* = 4.2 and 7.6 Hz, 1H), 3.60 (dd, *J* = 4.6 and 10.7 Hz, 2H), 3.50 (dd, *J* = 6.1 and 10.7 Hz, 2H), 2.23 (m, 1H), 2.00 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 137.8, 128.8, 128.3, 128.0, 78.7, 75.8, 72.9 (d, *J* = 11.8 Hz), 72.1, 65.1 (d, *J* = 11.4 Hz), 45.9, 30.1, 0.2. Anal. Calcd for $C_{12}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.42; H, 7.54.

(1*S*, 2*R*, 3*R*, 4*S*)-(+)-(-)-1-*O*-Benzyloxy-2,3-anhydro-4-hydroxymethyl-cyclopentane (77) To a solution of triol **76** (15.7 g, 65.9 mmol) in anhydrous acetonitrile (200 mL) was cooled to –30 °C and then treated with 1-bromocarbonyl-methylethylacetate (24.2 mL, 164.7 mmol). After being stirred at room temperature for 1 h, H_2O (150 mL) and EtOAc (150 mL) were added to the resulting mixture and the organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in methanol (200 mL). Potassium *t*-butoxide (36.4 g, 263.6 mmol) was added and reacted for 12 h at room temperature. The reaction mixture was filtered over celite pad (~5 cm) and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (100 mL), dried over $MgSO_4$ and filtered. The residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:3 to 1:1) to give **77** (11.5 g, 79.3 %) as a colorless oil. $[\alpha]_D$ –54.06° (C 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.39-7.27 (m, 5H), 4.63 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 1H), 3.61 (dd, , *J* = 5.3 and 10.6 Hz, 1H), 3.52 (m, 2H), 3.45 (d, *J* = 2.6 Hz, 1H), 2.52 (q, *J* = 6.7 Hz, 1H), 1.76 (dd, , *J* = 8.1 and 13.2 Hz, 1H), 2.00 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ137.5, 128.7, 128.0, 127.9, 79.2, 71.9, 64.0, 57.7, 56.7, 41.1, 28.5. Anal. Calcd for $C_{12}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.45; H, 7.29.

(1*S*, 2*R*, 4*S*)-(-)-1-*O*-Benzyloxy-2-hydroxyl-4-hydroxymethyl-cyclopentane (78) and its isomer (79) To a solution of epoxide **77** (10.0 g, 45.4 mmol) in anhydrous THF (150 mL) at –78 ^{o}C, was slowly added dropwise Lithium aluminum hydride (5.4g, 136.2 mmol). After addition of LAH, the reaction mixture was warmed to reach room temperature and stirred for 4 h. Celite (20 g) was added to the reaction mixture and iced H_2O (150 mL) was added dropwise to slowly quench the reaction. The slurry was filtered over celite pad (~10 cm) and the filtrate was extracted with ethyl acetate (100 mL x 4). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:2) to give **78** (6.9 g, 68.6 %) as a colorless oil and **79** (1.5 g, 14.8%) as a colorless oil. Compound **78** : $[\alpha]_D$ –6.08^{o} (C 0.38, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.56 (dd, , *J* = 11.7 and 29.3 Hz, 2H), 4.17 (bs, 1H), 3.90 (m, 1H), 3.48 (m, 2H), 2.60 (bs, 1H), 2.49 (m, 1H), 1.97-1.87 (m, 2H), 1.66 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.0, 128.5, 127.8, 127.7, 81.0, 72.3, 71.6, 66.9, 36.8, 34.3, 31.1. Anal. Calcd for $C_{12}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.24. compound **79** : $[\alpha]_D$ +6.00^{o} (C 0.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.48 (s, 2H), 4.03 (m, 2H), 3.71 (dd, , *J* = 5.5 and 10.4 Hz, 1H), 3.53 (dd, , *J* = 8.0 and 10.4 Hz, 1H), 2.34 (m, 1H), 2.09 (m, 2H), 1.92 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.2, 128.4, 127.6, 78.9, 76.1, 70.6, 65.4, 48.7, 40.8, 33.4. Anal. Calcd for $C_{12}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.58; H, 8.33.

(1*S*, 2*R*, 4*S*)-(-)-1-*O*-Benzyloxy-2-hydroxyl-4-(*O*-trityl-oxymethyl)-cyclopentane (80) A mixture of diol **78** (7.27 g, 32.7 mmol) and trityl chloride (10.0 g, 32.7 mmol) in pyridine (100 mL) was refluxed for 4h. The reaction mixture was concentrated *in vacuo* and the residue was

dissolved in ethyl acetate (200 mL), washed with water and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:30) to give **80** (15.1 g, 99.4 %) as a colorless oil. $[\alpha]_D$ – 11.18^o (C 0.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.12 (m, 20H), 4.47 (dd, , *J* = 11.8 and 29.0 Hz, 2H), 4.07 (bs, 1H), 3.81 (dd, *J* = 6.6 and 10.7 Hz, 1H), 2.86 (m, 2H), 2.54 (m, 1H), 2.45 (d, , *J* = 3.6 Hz, 1H), 1.86 (m, 2H), 1.55 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 144.3, 128.7, 128.5, 127.8, 127.7, 126.9, 81.0, 72.4, 71.6, 67.2, 35.1 (d, *J* = 19.8 Hz), 31.8. Anal. Calcd for $C_{31}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.86; H, 7.22.

(2*S*, 4*S*)-(-)-2-*O*-Benzyloxy-4-(*O*-trityl-oxymethyl)-cyclopentan-1-one (81) To a solution of alcohol **80** (15.1 g, 32.5 mmol) in anhydrous CH_2Cl_2 (250 mL), 4Å molecular sieve (15 g), pyridinium dichromate (24.5 g, 65.0 mmol) and acetic acid (0.7 mL, 0.05 mol%) were added respectively. After being stirred at room temperature for 12 h, the resulting brown slurry mixture was filtered over silica gel pad (~15 cm) with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:50 to 1:20) to give ketone **81** (12.2 g, 81.3 %) as a colorless oil. $[\alpha]_D$ –27.05^o (C 0.14, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.24 (m, 20H), 4.82 (d, , *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 3.91 (t, *J* = 6.6, 1H), 3.13 (m, 2H), 2.70 (m, 1H), 2.53 (dd, , *J* = 8.8 and 19.0 Hz, 1H), 2.17 (dd, *J* = 6.0 and 18.6 Hz, 1H), 2.09-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 216.0, 143.9, 86.7, 78.3, 71.9, 66.4, 39.6, 33.6, 32.6. Anal. Calcd for $C_{31}H_{30}O_3$: C, 83.09; H, 6.54. Found: C, 82.84; H, 6.61.

(2*S*, 4*S*)-(-)-1-Difluoro-2-*O*-benzyloxy-4-(*O*-trityl-oxymethyl)-cyclopentane (82) To a solution of ketone **81** (11.2 g, 24.2 mmol) in anhydrous CH_2Cl_2 (100 mL), diethyl aminosulfur trifluoride (14.8 mL, 121.5 mmol) was added at room temperature. After being stirred at room temperature for 4 h, the reaction mixture was poured to a sat. $NaHCO_3$ (150 mL) solution and extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:100) to give difluorinated compound **82** (10.0 g, 85.5 %) as a colorless oil. $[\alpha]_D$ –12.95^o (C 0.16, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.27 (m, 20H), 4.84 (d, , *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 3.94 (m, 1H), 3.05 (m, 2H), 2.64 (m, 1H), 2.40 (m, 1H), 2.04-1.94 (m, 2H), 1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 217.5, 144.1, 138.3, 128.9, 128.7, 128.0, 128.0, 127.8, 127.3, 86.8, 74.9, 70.8, 62.3, 46.7, 45.8, 33.1. Anal. Calcd for $C_{31}H_{30}O_2F_2$: C, 79.32; H, 6.24. Found: C, 79.36; H, 6.34.

(3*S*, 5*S*)-(-)-1-Fluoro-3-(*O*-trityl-oxymethyl)-5-*O*-benzyloxy-cyclopent-1-ene (83) To a solution of compound **82** (10.9 g, 22.5 mmol) in anhydrous tetrahydrofuran (150 mL), potassium *tert*-butoxide (13.3 g, 112.5 mmol) was added at room temperature. After being stirred at 50 $^\circ$C for 28 h, (the completion of reaction was monitored by NMR.) H_2O (150 mL) was added to the resulting dark brown mixture and extracted with ethyl acetate (150 mL x 2). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:30) to give vinyl compound **83** (9.1 g, 87.5 %) as a colorless oil. $[\alpha]_D$ –74.99^o (C 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.24 (m, 20H), 5.40 (s, 1H), 4.62 (dd, *J* = 11.7 and 20.7 Hz, 2H), 4.54 (d, *J* = 5.67 Hz, 1H), 3.09 (m, 2H), 2.97 (t, *J* = 7.33 Hz, 1H), 2.08 (dd, *J* = 8.1 and 13.9 Hz, 1H),

1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 144.5, 129.1, 128.8, 128.2, 128.0, 127.4, 110.2 (d, *J* = 8.9 Hz), 78.6 (d, *J* = 20.9 Hz), 71.5, 67.7, 38.9 (d, *J* = 7.7 Hz), 33.1 (d, *J* = 7.8 Hz). Anal. Calcd for $C_{31}H_{30}O_2F_1$: C, 82.73; H, 6.29. Found: C, 82.89; H, 6.44.

(3*S*, 5*S*)-(-)-1-Fluoro-3-hydroxymethyl-5-*O*-benzyloxy-cyclopent-1-ene (84) To a solution of vinyl **83** (1.0 g, 2.15 mmol) in tetrahydrofuran (15 mL), 6N HCl (4 mL) solution and methanol (4 mL) were added at room temperature. After being heated at 50 °C for 5 h, the resulting mixture was cooled to 0 °C and neutralized by 1N NaOH solution. After evaporation of half volume, the residue was extracted with ethyl acetate (50 mL x 2). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:10 to 1:5) to give alcohol **84** (429 mg, 89.7 %) as a colorless oil. $[\alpha]_D$ = -154.82° (C 0.76, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 5.28 (s, 1H), 4.61 (dd, *J* = 13.0 and 24.7 Hz, 2H), 4.57 (bs, 1H), 3.58 (dd, *J* = 5.5 and 10.5 Hz, 1H), 3.51 (dd, *J* = 5.8 and 10.5 Hz, 1H), 2.97 (m, 1H), 2.04 (m, 2H), 1.37 (t, *J* = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.3, 128.7, 128.0, 128.0, 108.8 (d, *J* = 7.3 Hz), 78.4 (d, *J* = 16.8 Hz), 71.5, 66.6 (d, *J* = 2.7 Hz), 40.6 (d, *J* = 5.7 Hz), 32.4 (d, *J* = 5.7 Hz). Anal. Calcd for $C_{13}H_{15}O_2F_1 \cdot 0.3CH_2Cl_2$: C, 69.96; H, 6.87. Found: C, 69.83; H, 6.87.

(3*S*, 5*S*)-(-)-1-Fluoro-3-(*O*-*tert*-butyldiphenylsilyloxymethyl)-5-*O*-benzyloxy-cyclopent-1-ene (85) To a solution of vinyl alcohol **84** (3.0 g, 13.5 mmol) in CH_2Cl_2 (50 mL), *tert*-butyldiphenylsilane chloride (3.9 mL, 14.8 mmol) and imidazole (1.38 g, 20.2 mmol) were added at room temperature. After being stirred at room temperature for 1 h, H_2O (150 mL) was added to the resulting white suspension mixture and the organic layer was dried over $MgSO_4$ and

filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:100) to give **85** (6.2 g, 99 %) as a colorless oil. $[\alpha]_D$ –74.99 ° (C 0.79, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 4H), 7.40-7.34 (m, 11H), 5.29 (s, 1H), 4.61 (dd, *J* = 131.7 and 22.1 Hz, 2H), 4.55 (bs, 1H), 3.52 (m, 2H), 2.97 (bs, 1H), 1.99 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.2, 160.9, 138.2, 135.6 (d, *J* = 8.4 Hz), 129.7 (d, *J* = 2.2 Hz), 128.4, 127.8, 127.8, 127.7, 127.7, 109.5 (d, *J* = 6.8 Hz), 78.3 (d, *J* = 16.4 Hz), 71.1, 67.5 (d, *J* = 2.7 Hz), 40.4 (d, *J* = 5.7 Hz), 32.2 (d, *J* = 5.7 Hz), 26.8, 19.2. Anal. Calcd for $C_{29}H_{35}O_2F_1Si_1$: C, 75.61; H, 7.22. Found: C, 75.58; H, 7.22.

(3*S*, 5*S*)-(-)-1-Fluoro-3-(*O*-*tert*-butyldiphenylsilyloxymethyl)-5-hydroxyl-cyclopent-1-ene (86) Liquid ammonia (20 mL) was trapped in three neck round bottom flask (50 mL) at –78 °C and then sodium (825 mg, 35.8 mmol) was added slowly. To a resulting dark blue solution, a solution of **85** (660 mg, 1.43 mmol) in 1,4-dioxane (3 mL) was added dropwise at –78 °C for 5min. After being stirred at the same temperature for 10 min, dichloromehtane (50 mL) was added slowly to the reaction mixture and then the brown resulting mixture was poured into iced water (50 mL). (caution!! Remaining sodium causes flames.) The mixture was extracted with dichloromethane (50 mL x 2). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:5) to give vinyl alcohol **86** (380 mg, 71.7%) as a colorless oil. $[\alpha]_D$ –90.52 ° (C 0.47, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.42-7.36 (m, 6H), 5.23 (s, 1H), 4.79 (bs, 1H), 3.55 (m, 2H), 2.96 (bs, 1H), 2.12 (m, 2H), 1.91 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.2, 161.4, 155.2, 135.8 (d, *J* = 4.5 Hz), 133.8 (d, *J* = 9.1 Hz), 130.0 (d, *J* = 2.3 Hz), 127.9, 108.5 (d, *J* = 8.4 Hz), 72.1 (d, *J* = 22.9 Hz), 71.9, 67.6 (d, *J* =

3.0 Hz), 40.4 (d, *J* = 7.6 Hz), 34.9 (d, *J* = 6.8 Hz), 27.0, 19.5. Anal. Calcd for $C_{22}H_{27}O_2F_1Si_1$: C, 71.31; H, 7.34. Found: C, 71.32; H, 7.44.

(1'*R*, 4'*S*)-(-)-1-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6-(*O*-*tert*-butyldiphenylsilyloxy methyl)-cyclopent-2-enyl]uracil (88) A solution of vinyl alcohol **86** (1.0g, 2.70 mmol), tripheyl phosphine (2.83 g, 10.80 mmol) and N^3-benzyoluracil (1.17 g, 5.40 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C and then a solution of diisopropyl azodicaroxylate (2.17 g, 10.80 mmol) was added dropwise. The reaction mixture was slowly allowed to warm to room temperature and stirred for 12 h. The yellowish resulting mixture was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:10) to give **87** (750 mg) as a crude product, which was used for the next reaction without further purification. The crude **87** (700 mg) was treated with methanolic ammonia and stirred at room temperature for 12 h. After the reaction mixture was concentrated *in vacuo*, the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:5) to give **88** (530 mg, 41% from **86**) as a white foam. $[\alpha]^{23}_D$ –14.76° (C 0.41, $CHCl_3$); UV (MeOH) λ_{max} 263.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.62 (d, *J* = 6.8 Hz, 4H), 7.48-7.37 (m, 6H), 7.45 (s, 1H), 5.70 (bs, 1H), 5.46 (s, 1H), 5.30 (s, 1H), 3.73 (dd, *J* = 4.4 and 10.0 Hz,1H), 3.60 (dd, *J* = 3.6 and 9.2 Hz, 1H), 2.86 (bs, 1H), 2.72-2.64 (m, 1H), 1.61 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 163.0, 157.8, 155.0, 151.1, 140.5, 135.8, 133.4 (d, *J* = 12.2 Hz), 130.2 (d, *J* = 3.0 Hz), 128.1 (d, *J* = 3.0 Hz), 112.5 (d, *J* = 7.6 Hz), 103.3, 66.3, 56.8 (d, *J* = 21.3 Hz), 53.7, 39.8 (d, *J* = 6.1 Hz), 31.4, 27.2, 19.6; Anal. Calcd for $C_{26}H_{29}N_2O_4F_1Si_1 \cdot 0.7H_2O$: C, 65.44; H, 6.42; N, 5.87. Found: C, 65.39; H, 6.41; N, 5.88.

(1'*R*, 4'*S*)-(-)-1-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-cyclopent-2-enyl]uracil (89) To a solution of **88** (130 mg, 0.27 mmol) in methanol (5 mL), 3N HCl (5 mL) was added at room temperature. After being stirred at room temperature for 1 h, the resulting mixture was co-evaporated with ethanol and the residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:15) to give **89** (45 mg, 68%) as a white foam. $[\alpha]_D$ –9.73° (C 0.56, MeOH); UV (H_2O) λ_{max} 264.5 nm (ε 11145, pH 2), 264.5 nm (ε 8932, pH 7), 264.5 nm (ε 13131, pH 11); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (bs, 1H), 7.58 dd, *J* = 1.5 and 8.0 Hz, 1H), 5.74 (d, *J* = 7.5 Hz, 1H),5.66 (m, 1H), 5.48 (t, *J* = 2.0 Hz, 1H), 3.77 (m, 1H), 3.62 (m, 1H), 2.89 (m, 1H), 2.74 (dt, *J* = 9.0 and 14.5 Hz, 1H), 1.96 (t, *J* = 4.5 Hz, 1H), 1.72 (dt, *J* = 5.0, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 163.4 (d, *J* = 10.4 Hz), 151.2 (d, *J* = 5.6 Hz), 142.1, 140.7, 112.7, 111.4, 103.7, 102.2, 78.3, 64.6, 57.7; MS : *m/z* 227 (M+1); Anal. Calcd for $C_{10}H_{11}N_2O_3F_1 \cdot 0.2H_2O$: C, 52.26; H, 5.00; N, 12.09. Found: C, 52.24; H, 5.09; N, 11.96.

(1'*R*, 4'*S*)-(-)-1-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6-(*O*-*tert*-butyldiphenylsilyloxy methyl)-cyclopent-2-enyl]cytosine (90) To a solution of uracil derivative **88** (120 mg, 0.26 mmol) in anhydrous acetonitrile (5 mL), 2,4,6-triisopropyl benzenesulfonyl chloride (156 mg, 0.52 mmol), 4-(dimethylamino)pyridine (32 mg, 0.26 mmol) and triethylamine (0.15 mL, 1.04 mmol) were added respectively at 0 °C. After being stirred at room temperature for 12 h, 28% solution of ammonium hydroxide (5 mL) was added to the resulting brown mixture solution and stirred at room temperature for another 12 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:30) to give **90** (100 mg, 83%) as a colorless oil. $[\alpha]_D$ –45.68° (C 0.76, $CHCl_3$); UV (MeOH) λ_{max} 272.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.23 (m, 10H), 6.96 (s, 1H), 5.80 (s, 1H), 5.57 (d, *J* =

6.5 Hz, 1H), 5.42 (s, 1H), 4.32 (quintet, *J* = 6.5 Hz, 1H), 3.65 (dd, *J* = 5.0and 10.0 Hz, 1H), 3.50 (dd, *J* = 5.5 and 11.0 Hz, 1H), 2.81-2.68 (m, 2H), 1.45 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.1, 158.4, 156.1, 142.1, 135.6, 133.3 (d, *J* = 22.9 Hz), 129.9, 127.8 (d, *J* = 5.3 Hz), 112.0 (d, *J* = 7.6 Hz), 94.4, 66.4, 57.4 (d, *J* = 20.0 Hz), 39.6 (d, *J* = 6.8 Hz), 32.2, 27.0 (d, *J* = 6.5 Hz), 22.0, 19.3, 0.0; Anal. Calcd for $C_{26}H_{30}N_2O_2F_1Si_1$: C, 67.36; H, 6.52; N, 9.06. Found: C, 67.27; H, 6.57; N, 8.97.

(1'*R*, 4'*S*)-(-)-2-*O*-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-cyclopent-2-enyl]cytosine (91) Compound **90** (100 mg, 0.22 mmol) was converted to the cytosine derivative **91** (45 mg, 92 %) as a white solid using same procedure as for **89**. mp : dec. at 185-187 ^{o}C $[\alpha]^{24}_{D}$ –36.92 $^{\circ}$ (C 0.64, MeOH); UV (H_2O) λ_{max} 281.5 nm (ε 9661, pH 2), 272.5 nm (ε 13881, pH 7), 272.0 nm (ε 16461, pH 11); ^{1}H NMR (500 MHz, MeOH-d_4) δ7.80 (d, *J* = 7.0 Hz, 1H), 6.00 (d, *J* = 6.5 Hz, 1H), 5.71 (bs, 1H), 5.54 (s, 1H), 3.62 (dd, *J* = 4.5 and 11.5 Hz, 1H), 3.50 (dd, *J* = 1.5, 4.5 and 11.5 Hz, 1H), 2.84 (bs, 1H), 2.72 (dt, *J* = 9.5 and 14.0 Hz, 1H), 1.61 (dt, *J* = 4.5 and 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.1, 158.2, 155.4, 142.8, 112.3 (d, *J* = 9.5 Hz), 64.0, 58.0 (d, *J* = 27.6 Hz), 53.6, 39.9 (d, , *J* = 6.6 Hz), 31.7; MS : *m/z* 227 (M+); Anal. Calcd for $C_{10}H_{12}N_3O_2F_1$: C, 45.90; H, 5.01; N, 16.06. Found: C, 45.86; H, 4.97; N, 16.00.

(1'*R*, 4'*S*)-(-)-1-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6-(*O*-*tert*-butyldiphenylsilyloxy methyl)-cyclopent-2-enyl]thymine (93) Compound **86** (400 mg, 1.08 mmol) was converted to **93** (243 mg, 46% from **90**) as a white foam using same procedure as for **86**. $[\alpha]_D$ –24.72^{o} (C 0.61, $CHCl_3$); UV (MeOH)λ_{max} 267.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.63-7.26 (m, 10H), 6.99 (s, 1H), 5.69 (bs, 1H), 5.47 (s, 1H), 3.68 (dd, *J* = 4.4 and 10.8 Hz,1H), 3.60 (dd, *J*

= 4.8 and 10.4 Hz, 1H), 2.85 (bs, 1H), 2.64 (m, 1H), 1.77 (s, 3H), 1.26 (s, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 231.7, 185.3, 163.6, 159.4, 135.8, 134.6, 133.4, 130.3, 128.1, 112.0, 98.2, 83.4, 41.5, 27.1, 19.6, 12.7, 11.5; Anal. Calcd for $C_{27}H_{31}N_2O_4F_1Si_1$: C, 67.75; H, 6.53; N, 5.85. Found: C, 67.92; H, 6.64; N, 5.80.

(1'*R*, 4'*S*)-(+)-1-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-cyclopent-2-enyl]thymine (94) Compound **93** (225 mg, 0.46 mmol) was converted to the thymine derivative **94** (104 mg, 88 %) as a white foam using same procedure as for **86**. $[\alpha]_D$ +28.19^o (C 0.76, $CHCl_3$); UV (H_2O) λ_{max} 269.0 nm (ε 5678, pH 2), 271.0 nm (ε 6971, pH 7), 279.0 nm (ε 6911, pH 11); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (bs, 1H), 7.36 (s, 1H), 5.66 (bs, 1H), 5.48 (s, 1H), 3.77 (dd, *J* = 4.0 and 10.4 Hz, 1H), 3.64 (dd, *J* = 2.8 and 10.4 Hz, 1H), 2.88 (bs, 1H), 2.73 (m, 1H), 2.23 (bs, 1H), 1.91 (s, 3H), 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.1, 151.4, 137.1, 111.8 (d, *J* = 8.4 Hz), 91.4, 64.8, 57.0 (d, *J* = 21.4 Hz), 39.7 (d, *J* = 6.1 Hz), 31.1, 12.8; MS : *m/z* 241 (M+1); Anal. Calcd for $C_{11}H_{13}N_2O_3F_1$: C, 55.00; H, 5.45; N, 11.66. Found: C, 54.71; H, 5.40; N, 11.39.

(1'*R*, 4'*S*)-(-)-9-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6-(*O*-*tert*-butyldiphenylsilyloxy methyl)-cyclopent-2-enyl]adenine (96) A solution of vinyl alcohol **86** (700 mg, 1.89 mmol), tripheyl phosphine (990 mg, 3.78 mmol) and 6-chloropurine (613 mg, 3.96 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C and then a solution of diisopropyl azodicaroxylate (760 mg, 3.78 mmol) was added dropwise. The reaction mixture was slowly allowed to warm to room temperature and stirred for 12 h. The yellowish resulting mixture was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:10) to give **95** (570 mg) as a crude product, which was used for the next reaction without

further purification. The crude **95** (220 mg) was treated with methanolic ammonia and heated in a steel bomb at 100 °C for 24 h. After the reaction mixture was concentrated *in vacuo*, the residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:20) to give **96** (335 mg, 36 % from **86**) as a colorless oil. $[\alpha]^{24}_D$ +2.18^o (C 0.40, $CHCl_3$); UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.63-7.35 (m, 10H), 5.68 (bs, 1H), 5.66 (bs, 1H), 5.55 (t, *J* = 2.0 Hz, 2H), 3.66 (dd, *J* = 2.5 and 6.0 Hz, 1H), 2.97 (bs, 1H), 2.84 (dt, *J* = 9.0 and 14.5 Hz, 1H), 1.81 (dt, *J* = 8.0 and 14.0 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 155.7 (d, *J* = 14.8 Hz), 153.3, 150.3, 138.6, 135.8, 133.4 (d, *J* = 4.4 Hz), 130.1, 128.0, 111.5 (d, *J* = 8.1 Hz), 67.1, 55.3 (d, *J* = 21.4 Hz), 40.4 (d, *J* = 6.3 Hz), 33.3 (d, *J* = 4.8 Hz), 27.1, 19.5, 0.2; Anal. Calcd for $C_{27}H_{30}N_5O_1F_1Si_1 \cdot 0.7H_2O$: C, 64.83; H, 6.33; N, 14.00. Found: C, 64.95; H, 6.25; N, 13.98.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6'-hydroxymethyl-cyclopent -2-enyl]adenine (97) Compound **96** (180 mg, 0.37 mmol) was converted to adenine derivative **97** (85 mg, 93 %) as a white solid using same procedure as for **89**. $[\alpha]^{23}_D$ +76.49^o (C 0.30, MeOH); mp = 218-220 ^{o}C; UV (H_2O) λ_{max} 258.0 nm (ε 11106, pH 2), 260.5 nm (ε 8708, pH 7), 260.5 nm (ε 10234, pH 11); ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.53 (s, 1H), 8.42 (s, 1H), 5.85 (bs, 1H), 5.60 (s, 1H), 3.69 (dd, *J* = 3.5 and 11.0 Hz, 1H), 3.60 (dd, *J* = 7.5 and 14.0 Hz, 1H), 2.96 (bs, 1H), 2.92 (d, *J* = 12.5 Hz, 1H), 2.00 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.7, 154.9, 150.5, 149.02, 144.1 (d, *J* = 3.9 Hz), 143.0, 118.8, 111.5 (d, *J* = 10.5 Hz), 64.1, 56.5 (d, *J* = 26.6 Hz), 40.5 (d, *J* = 7.2 Hz), 32.3 (d, *J* = 6.8 Hz), 17.2; MS : *m/z* 250 (M+1); Anal. Calcd for $C_{11}H_{12}N_5O_1F_1 \cdot HCl$: C, 46.24; H, 4.59; N, 24.51. Found: C, 46.35; H, 4.59; N, 24.44.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6-(*O*-*tert*-butyldiphenylsilyloxy methyl)-cyclopent-2-enyl]inosine (98) To a solution of 6-chloropurine analog **96** (240 mg, 0.47 mmol) in methanol (10 mL), 2-mercaptoethanol (130 mg, 1.65 mmol) and sodium methoxide (94 mg, 1.65 mmol) were added at room temperature. After being refluxed for 12 h, the reaction mixture was neutralized with acetic acid and concentrated *in vacuo*. The residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:50) to give **98** (180 mg, 78%) as a colorless oil. $[\alpha]_D$ +22.28° (C 1.65, $CHCl_3$); UV (MeOH) λ_{max} 220.5 and 249.5 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.16 (bs, 1H), 7.77 (s, 1H), 7.66-7.37 (m, 10H), 5.65 (m, 1H), 5.45 (t, *J* = 2.0 Hz, 2H), 3.68 (d, *J* = 6.5 Hz, 2H), 2.98 (d, *J* = 5.5 Hz, 1H), 2.87 (m, 1H), 1.82 (dt, *J* = 6.0 and 14.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.6, 155.4, 149.3, 145.1, 138.4, 135.8, 133.4, 130,2, 128.1, 124.9, 111.5, 67.1, 55.8 (d, *J* = 21.3 Hz), 40.4, 33.4, 27.1, 19.5; Anal. Calcd for $C_{27}H_{39}N_4O_2F_1Si_1 \cdot 0.6H_2O$: C, 64.93; H, 6.09; N, 11.22. Found: C, 65.02; H, 6.07; N, 10.94.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6'-hydroxymethyl-cyclopent -2-enyl]inosine (99) Compound **98** (180 mg, 0.37 mmol) was converted to a inosine derivative **99** (85 mg, 93 %) as a white solid using same procedure as for **89**. $[\alpha]^{23}_D$ +157.06° (C 0.22, MeOH); mp = 195-197 °C; UV (H_2O) λ_{max} 249.0 nm (ε 11354, pH 2), 248.5 nm (ε 15927, pH 7), 254.0 nm (ε 12152, pH 11); ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.15 (s, 1H), 8.07 (s, 1H), 5.78 (m, 1H), 5.67 (s, 1H), 3.67 (dd, *J* = 4.5 and 10.5 Hz, 1H), 3.60 (ddd, *J* = 1.5, 5.0 and 11.0 Hz, 1H), 2.95-2.85 (m, 2H), 1.97 (dt, *J* = 5.90 and 13.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.7, 154.9, 150.5, 149.0, 144.1 (d, *J* = 3.9 Hz), 143.0, 118.8, 111.5 (d, *J* = 10.5 Hz), 64.1, 56.5 (d, *J*

= 26.6 Hz), 40.5 (d, *J* = 7.6 Hz), 32.3 (d, *J* = 5.8 Hz), 17.2; MS : *m/z* 251 (M+); Anal. Calcd for $C_{11}H_{12}N_4O_2F_1 \cdot 0.6H_2O$: C, 50.61; H, 4.71; N, 21.46. Found: C, 50.29; H, 4.74; N, 21.45.

(1'*R*, 4'*S*)-(+)-2-Amino-6-chloro-9-[2',3'-dideoxy-2',3'-didehydro-2'-fluoro-6-hydroxy methyl-cyclopent-2-enyl]purine (101) A solution of tripheylphosphine (1.25 g, 4.75 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C and then treated with a solution of diisopropyl azodicaroxylate (956 mg, 4.75 mmol) in anhydrous 1,4-dioxane (2 mL) slowly. The resulting suspension was stirred at 0 °C for 30 min and then cooled to –78 °C. A solution of vinyl alcohol **86** (440 mg, 1.19 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise, followed by the addition of 2-amino-6-chloropurine (806 mg, 4.75 mmol). The reaction mixture was slowly allowed to warm to room temperature and stirred for 6 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:4) to give **100** (970 mg) as a crude product, which was used for the next reaction without further purification. The crude **100** (970 mg) was dissolved in tetrahydrofuran (10 mL) and then treated with a 1.0M solution of tetrabutylammonium fluoride in tetrahydrofuran. After being stirred at room temperature for 3 h, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:40) to give **101** (135 mg, 40 % from **86**) as a white foam. $[\alpha]_D$ +9.76° (C 1.09, MeOH); UV (MeOH) λ_{max} 247.0 and 309.0 nm; ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.26 (d, *j* = 1.0 Hz, 1H), 5.68 (m, 1H), 5.53 (t, *J* = 2.0 Hz, 2H), 3.72 (m, 1H), 3.63 (ddd, *J* = 2.0, 6.0 and 14.0 Hz, 1H), 2.96 (m, 1H), 2.87 (dt, *J* = 11.5 and 17.5 Hz, 1H), 1.99 (ddt, *J* = 1.5, 6.8 and 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.2, 158.1, 155.3, 153.7, 150.2, 141.5, 123.6, 110.6 (d, *J* = 10.5 Hz), 64.0 (d, *J* = 2.9 Hz), 55.4 (d, *J* = 26.8 Hz), 40.2 (d, *J*

= 8.6 Hz), 31.6 (d, *J* = 6.8 Hz); Anal. Calcd for $C_{11}H_{11}N_5O_1F_1Cl_1 \cdot 0.3MeOH$: C, 46.31; H, 4.16; N, 23.96. Found: C, 46.35; H, 4.14; N, 23.65.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-2'-fluoro-6'-hydroxymethyl-cyclopent -2-enyl]guanine (102) A mixture of **101** (95 mg, 0.33 mmol) and formic acid (4 mL) was heated at 90 °C for 2 h and then concentrated *in vacuo*. The residue was dissoloved in methanol (4 mL) and treated with a 28 % solution of ammonium hydroxide (1 mL). After being stirred at room temperature for 2 h, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:30) to give **102** (15.5 g, 85%) as a white solid. $[\alpha]_D$ +23.13° (C 0.45, MeOH); mp = dec. at 252 °C, ; UV (H_2O) λ_{max} 253.5 nm (ε 1259.2, pH 2), 252.5 nm (ε 12600, pH 7), 252.0 nm (ε 12779, pH 11); ms : 266 (M+1) and 288 (M+Na); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.50 (bs, 2H), 5.53 (s, 1H), 5.39 (bs, 1H), 4.83 (bs, 1H), 3.45 (m, 2H), 2.76 (d, *J* = 4.0 Hz, 1H), 2.67 (dt, *J* = 4.5 and 14.0 Hz, 1H), 1.74 (dt, *J* = 4.5 and 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.5, 157.2, 155.7, 154.1, 151.6, 135.6, 117.0, 111.1 (d, *J* = 9.5 Hz), 64.4, 54.4 (d, *J* = 27.6 Hz), 32.6; MS : *m/z* 266 (M+); Anal. Calcd for $C_{11}H_{12}N_5O_2F_1 \cdot 1.6H_2O$: C, 44.93; H, 4.62; N, 23.14. Found: C, 45.01; H, 4.68; N, 23.11.

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CHAPTER 5

ASYMMETRIC SYNTHESIS OF D-3'-FLUORO-2',3'-DIDEOXY-2',3'-DIDEHYDRO CARBOCYCLIC NUCLEOSIDES

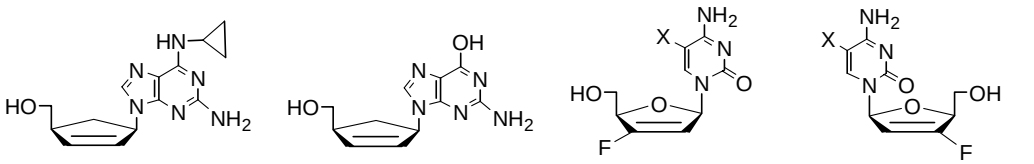
Introduction

During the last decade, nucleosides have continued to play a major role in the chemotherapy of HIV and HBV. To date, eight nucleoside analogs have received approval for the treatment of HIV infection by FDA.[70] The currently used highly active antiretroviral therapy (HAART),[71,72] has led to a substantial decrease in the frequency of opportunistic infections among HIV-infected individuals, along with a significant reduction in their mortality rate. However, undesired side toxicities[73,74] and emergency of resistant viral strains[75,76] during long-term therapy have been the main limitations of nucleosides analogs. This led to an extensive structural modification of some currently active agents to develop more efficient and less cytotoxic antiviral agent.

Since six of the anti-HIV nucleosides (AZT, ddI, ddC, d4T, 3TC and abacavir) could be classified as a 2',3'-dideoxy nucleosides, and particularly, d4T and abacavir was considered as 2',3'-dideoxy-2',3'-didehydro nucleosides. In addition, substitution of electronegative fluorine atom at 2' and 3' position was known to stabilize the glycosidic bond as well as affect the electronic environment in regard to the hydrogen bond acceptor.[77,78]

On the basis of these aspects, previously, we have extensively explored the structure-activity relationship study with a series of D- and L-3'-fluoro-2',3'-dideoxy-2',3'-didehydronucleosides (Figure 7).[79-81]

Figure 7. 2',3'-Dideoxy-2',3'-didehydro Nucleosides Active against HIV



Abacavir Carbovir X=H, D-2'-F-d4C X=F, D-2'-F-d4FC X=H, L-2'-F-d4C X=F, L-2'-F-d4FC

Among them, L-3'-fluoro-2',3'-dideoxy-2',3'-didehydrocytosine analog showed potent anti-HIV (EC_{50} 0.03 mM in PBM cells) with little or no significant cytotoxicities.[80]

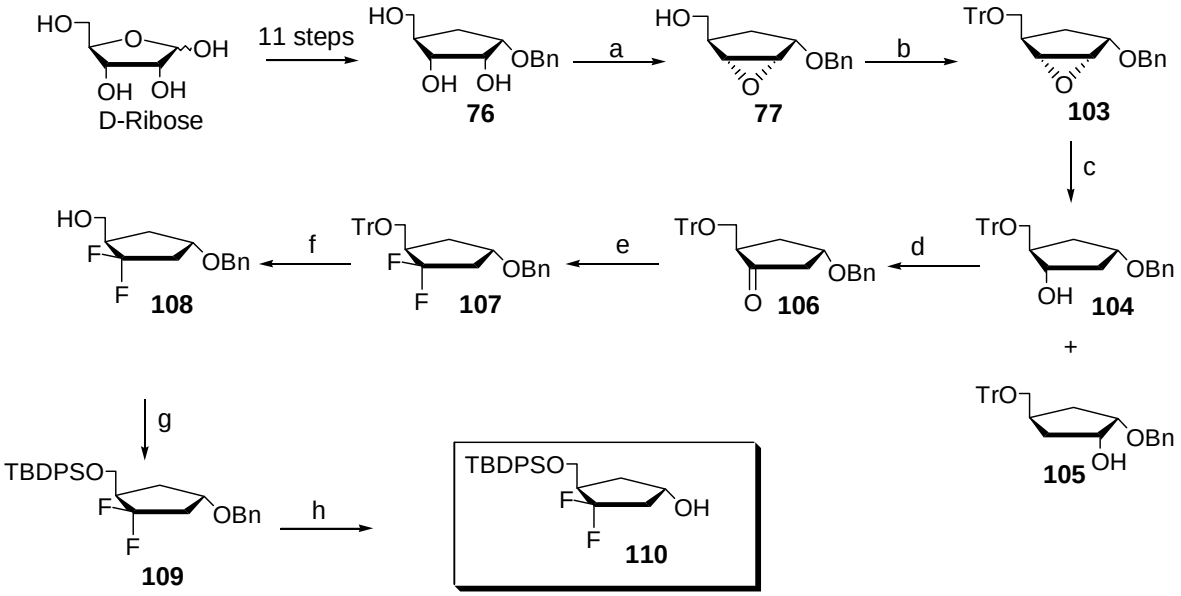
On the other hand, carbocyclic nucleosides have received much attention, some of them have interesting antiviral and antitumor activities.[82,83] The approval of abacavir against HIV infection has shown the clinical usefulness of carbocyclic nucleosides.[84,85] Recently, we have reported an efficient and practical synthetic methodology of D and L-cyclopent-2-enone, key intermediates for carbocyclic nucleosides, as well as the antiviral activities of cyclopentenyl nucleosides. Among the synthesized nucleosides, adenine, cytosine and 5-fluorocytosine analogs were found to be active against HIV, West-Nile virus and orthopoxviruses including smallpoxvirus.[86-88]

Therefore, it is of interest to synthesize the carbocyclic D-3'-fluoro-2',3'-dideoxy-2',3'-didehydronucleosides. Herein we report the synthesis of enantiomerically pure carbocyclic D-3'-fluoro-2',3'-dideoxy-2',3'-didehydronucleosides using the ring-opening reduction of expoxide **103** as a key step, followed by oxidation, fluorination and direct condensation of heterocyclic base under Mitsunobu coupling reactions.[89,90]

Chemistry

For the synthesis of carbocyclic 3'-fluro-2',3'-dideoxy-2',3'-didehydro nucleosides, we utilized enantiomeically pure cyclopentane **76**, which was previously prepared in 14 steps from D-ribose (Scheme 9).[88,91] The acidic labile isopropylidine and *tert*-butyl groups were cleaved by refluxing in a 6N HCl and methanol solution and treatment with 1-bromocarbonyl-methylethylacetate at –30 $^{\circ}$C and potassium carbonate to provide an epoxide **103** in 79% yield.[92,93] Extensive investigation of epoxide ring-opening reaction was conducted to optimize the regioisomeric ratio of 2- vs 3-hydroxyl compound. (Figure 8.)

Scheme 9. Synthesis of 1,1-difluoro-3-(*O*-*tert*-butyldiphenylsilyloxymethyl)-5-hydroxyl Cyclopentene

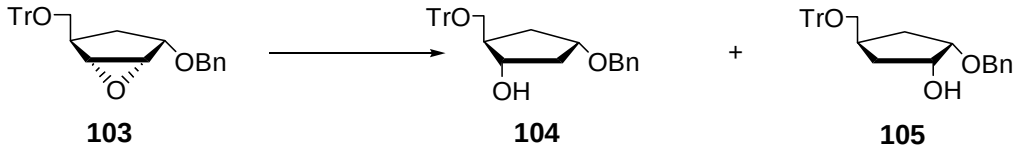


0Reagents and conditions: (a) a-AIBBr, CH_3CN and then K_2CO_3, MeOH; (b) TrCl, pyridine, C) LAH, anhydrous THF ; (d) PDC, AcOH, CH_2Cl_2; (e) DAST; (f) 6N HCl, MeOH, THF; (g) TBDPSCl, imidazole, CH_2Cl_2; (h) 10% Pd-C, MeOH, H_2.

Interestingly 3-hydroxyl compound **104** could be provided as a major compound with trityl protection. Extensive investigation was performed to optimize the selective ring-opening reduction with lithium aluminum hydride (LAH), diisobutyl aluminum hydride (Dibal-H), lithium tri-*tert*-butoxy aluminum hydride and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al). Reduction with Dibal-H, Red-Al, lithium tri-*tert*-butoxyaluminum hydride did not provide ring opening compound. However ring-opening reduction using LAH predominantly provided 3'-hydroxyl isomer **104** (**104**/**105** ratio = 5.1/1) in 88% yield, due to the steric hindrance of trityl group. PDC oxidation of the secondary alcohol was performed to give a ketone **106** in 78% yield. In contrast to the difluorination of 2'-ketone which was smoothly completed with 5 equvalents of DAST in CH_2Cl_2, harsh condition (20 equivalent of DAST

without solvent at 40 ^{o}C for 20 h was required to obtain a 3'-diflurinated compound **107** in 80% yield.

Figure 8. Investigation of Epoxide **103** Ring-opening Reaction



103 **104** **105**

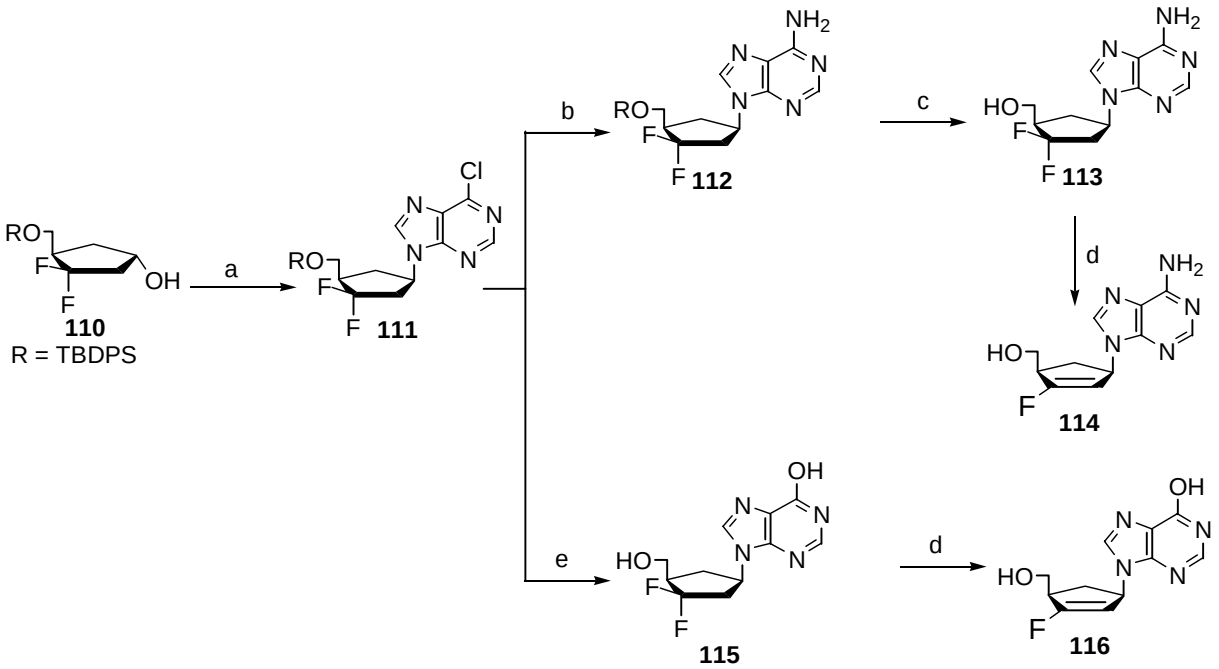
Reducing agent	**104 : 105 ratio**	**yield**
LAH	5.1 : 1	88%
Dibal-H	-	0%
Red-Al	-	0%
LiAl(*t*-butoxy)$_3$	-	0%

Eliminations using potassium *tert*-butoxide in THF, DMF and 1,4-dioxane were conducted to obtain olefin moiety without success, therefore, the double bond was generated after condensation of the base moiety. Removal of trityl primary hydroxyl protecting group under acidic conditions using 80% acetic acid and MeOH followed by silylation with TBDPSCl and imidazole to obtain a silyl protected compound **109** in 51% two step yield . Hydogenation with 10% Pd on activated carbon afforded an alcohol **110** in 75% yield which was ready to directly condense with purine and pyrimidine bases under Mitsunobu reaction.

As shown in scheme 10, coupling of **110** with 6-chloropurine was carried out under Mitsunobu condition[15] to obtain the adenine and inosine analogues. For the syntheses of adenine analog, **110** was treated with 6-chloropurine in the presence of triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran at room temperature to give **111** as crude compounds, which

was contaminated with the reduced diisopropyl azodicarboxylate. Treatment of **111** with saturated methanolic ammonia in a steel bomb at 110 °C provided a adenine moiety **112** in 62% yield followed by the deprotection of silyl group to give an difluorinate analog **113** in 93% yield. Elimination reaction using potassium t-butoxide was carried out to generated olefin moiety to give adenine analog **114** in 47% yield.

Scheme 10. Synthesis of D-3'-Fluoro-2',3'-dideoxy-2',3'-didehydro Carbocyclic Purine Nucleosides



Reagents and conditions: (a) DIAD, Ph_3P, 6-Chloropurine; (b) NH_3, MeOH, steal bomb, 110 ^oC; (C) 3N HCl, MeOH; (d) potassium *t*-butoxide, THF; (e) HCO_2H, 80 ^oC and then NH_4OH, MeOH.

Table 6. Elemental Analysis

Compd. No.	Formula	Calcd.	Found
77	$C_{12}H_{16}O_3$	C, 70.89; H, 7.32	C, 70.45; H, 7.29.
103	$C_{32}H_{30}O_3$	C, 83.09; H, 6.54	C, 82.93; H, 6.57.
104	$C_{32}H_{32}O_3$	C, 82.73; H, 6.94.	C, 82.52; H, 6.90
105	$C_{32}H_{32}O_3$	C, 82.73; H, 6.94.	C, 82.86; H, 7.22.
106	$C_{32}H_{30}O_3$	C, 83.09; H, 6.54.	C, 82.84; H, 6.61
107	$C_{32}H_{30}O_2F_2$	C, 79.32; H, 6.24.	C, 79.30; H, 6.32.
108	$C_{13}H_{16}O_2F_2$	C, 64.45; H, 6.66.	C, 64.26; H, 6.74
109	$C_{29}H_{35}O_2F_1Si_1$	C, 72.46; H, 7.13.	C, 72.44; H, 7.29
110	$C_{22}H_{28}O_2F_2Si_1$	C, 67.66; H, 7.23.	C, 67.62; H, 7.47
112	$C_{27}H_{31}OF_2Si_1$	C, 63.88; H, 6.16; N, 13.80	C, 63.96; H, 6.38; N, 14.01.
113	$C_{11}H_{13}N_5OF_2$	C, 49.07; H, 4.87; N, 26.01	C, 49.15; H, 4.77; N, 26.29
114	$C_{11}H_{12}N_5OF_1$	C, 53.01; H, 4.85; N, 28.10	C, 53.31; H, 4.59; N, 28.44.
115	$C_{11}H_{12}N_4O_2F_2$	C, 48.89; H, 4.48; N, 20.73	C, 49.10; H, 4.51; N, 20.99.
116	$C_{11}H_{11}N_4O_2F_1$	C, 52.80; H, 4.43; N, 22.39	C, 52.99; H, 4.74; N, 22.45.

In order to synthesize the inosine analog, the 6-chloropurine analog **111** was treated with 80% acetic acid and MeOH to give an inosine analog **115** in 75% yield which was subjected to the

elimination reaction by potassium *t*-butoxide in THF and 1,4-dioxane to provide inosine analog **116** in 54% yield.

Experimental Section

General Methods. Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Bruker 400 Fourier transform spectrometer; chemical shifts are reported in parts per million(δ), and signals are quoted as s (singlet), d(doublet), t(triplet), q(quartet), m(multiplet), and dd(double of doublets). Optical rotations were measured on a JASCO DIP-370 digital polarimeter. TLC was performed on Uniplate 25TLC plates purchased from Analtech Co. Column chromatogaphy was performed using silica gel (60 Å, 32-63μ Sorbent Technologies). Elemental analysis was performed by Atlantic Micolab, Inc., Norcross, GA**.** Anhydrous solvents were purchased from Aldrich Co.

(1*S*, 2*R*, 3*R*, 4*S*)-(+)-(-)-1-*O*-Benzyloxy-2,3-anhydro-4-hydroxymethyl-cyclopentane (77) To a solution of triol **76** (15.7 g, 65.9 mmol) in anhydrous acetonitrile (200 mL) was cooled to –30 ^{o}C and then treated with 1-bromocarbonyl-methylethylacetate (24.2 mL, 164.7 mmol). After being stirred at room temperature for 1 h, H_2O (150 mL) and EtOAc (150 mL) were added to the resulting mixture and the organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in methanol (200 mL). Potassium *t*-butoxide (36.4 g, 263.6 mmol) was added and reacted for 12 h at room temperature. The reaction mixture was filtered over celite pad (~5 cm) and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (100 mL), dried over $MgSO_4$ and filtered. The residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:3 to

1:1) to give **77** (11.5 g, 79.3 %) as a colorless oil. $[\alpha]_D$ –54.06° (C 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.39-7.27 (m, 5H), 4.63 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 1H), 3.61 (dd, , *J* = 5.3 and 10.6 Hz, 1H), 3.52 (m, 2H), 3.45 (d, *J* = 2.6 Hz, 1H), 2.52 (q, *J* = 6.7 Hz, 1H), 1.76 (dd, , *J* = 8.1 and 13.2 Hz, 1H), 2.00 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 137.5, 128.7, 128.0, 127.9, 79.2, 71.9, 64.0, 57.7, 56.7, 41.1, 28.5. Anal. Calcd for $C_{12}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.45; H, 7.29.

(1*S*, 2*R*, 3*R*, 4*S*)-(+)-(-)-1-*O*-Benzyloxy-2,3-anhydro-4-(*O*-triphenylmethyl-oxymethyl)-cyclopentane (103) To a solution of epoxide **77** (12.5 g, 56.7 mmol) in pyridine (100 mL), TrCl was added and heated at 55 °C for 10h. After evaporation in vacuo, the residue was dissolved in CH_2Cl_2 (200mL) and washed with H_2O (150 mL) and brine (150mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:30 to 1:20) to give **103** (17.8 g, 65.3 %) as a white-off solid: mp 85-87 °C; $[\alpha]^{25}_D$ –42.1° (C 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.21 (m, 15H), 4.59 (s, 2H), 4.17 (dt, *J* = 1.5 and 8.5 Hz, 1H), 3.54 (dd, , *J* = 1.5 and 3.0 Hz, 1H), 3.45 (d, *J* = 2.5 Hz, 1H), 3.14 (dd, *J* = 4.5 and 9.0 Hz, 1H), 2.97 (dd, *J* = 6.5 and 9.5 Hz, 1H), 2.57 (dd, , *J* = 6.0 and 14.0 Hz, 1H), 1.64 (dd, *J* = 8.0 and 13.0 Hz, 1H), 1.57 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.1, 138.5, 128.9, 128.7, 128.1, 128.0, 127.9, 127.3, 87.0, 79.2, 71.9, 64.4, 58.1, 56.9, 39.3, 28.9. Anal. Calcd for $C_{32}H_{30}O_3$: C, 83.09; H, 6.54. Found: C, 82.93; H, 6.57.

(1*S*, 2*R*, 4*S*)-(-)-1-*O*-Benzyloxy-3-hydroxyl-4-(*O*-triphenylmethyl-oxymethyl)-cyclopentane (104) and its isomer (105) To a solution of epoxide **103** (17.8 g, 38.5 mmol) in anhydrous THF

(200 mL) at –78 ^{o}C, was slowly dropped 1.0M solution of lithium aluminum hydride in THF (154 mL, 154.0 mmol). After addition of LAH, the reaction mixture was allowed to reach room temperature and stirred for 12 h. Celite (20 g) was added to the reaction mixture and ice-water (150 mL) was added dropwise to slowly quench the reaction. The slurry was filtered over celite pad (~10 cm) and the filtrate was extracted with ethyl acetate (100 mL x 2). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:20) to obtain **104** (11.4 g, 56.2 %) as a colorless oil and **105** (2.3 g, 12.9%) as a colorless oil. Compound **104** : $[\alpha]^{24}_{D}$ –16.92^{o} (C 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29(m, 5H), 4.56 (dd, , *J* = 11.7 and 29.3 Hz, 2H), 4.17 (bs, 1H), 3.90 (m, 1H), 3.48 (m, 2H), 2.60 (bs, 1H), 2.49 (m, 1H), 1.97-1.87 (m, 2H), 1.66 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.0, 128.5, 127.8, 127.7, 81.0, 72.3, 71.6, 66.9, 36.8, 34.3, 31.1. Anal. Calcd for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.52; H, 6.90. compound **105** : $[\alpha]_{D}$ –11.18^{o} (C 0.30, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.12 (m, 20H), 4.47 (dd, , *J* = 11.8 and 29.0 Hz, 2H), 4.07 (bs, 1H), 3.81 (dd, *J* = 6.6 and 10.7 Hz, 1H), 2.86 (m, 2H), 2.54 (m, 1H), 2.45 (d, , *J* = 3.6 Hz, 1H), 1.86 (m, 2H), 1.55 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 144.3, 128.7, 128.5, 127.8, 127.7, 126.9, 81.0, 72.4, 71.6, 67.2, 35.1 (d, *J* = 19.8 Hz), 31.8. Anal. Calcd for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 82.86; H, 7.22.

(2*S*, 4*S*)-(-)-2-*O*-Benzyloxy-4-(*O*-triphenylmethyloxymethyl)-cyclopentan-1-one (106) To a solution of alcohol **104** (11.4 g, 24.5 mmol) in anhydrous CH_2Cl_2 (200 mL), 4Å molecular sieve (11.4 g), pyridinium dichromate (22.0 g, 59.0 mmol) and acetic acid (0.2 mL, 0.05 mol%) were added respectively. After being stirred at room temperature for 24 h, the resulting brown slurry

mixture was filtered over silica gel pad (~15 cm) with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : Hexane = 1:15 to 1:10) to give ketone **106** (9.3 g, 82.3 %) as a white solid: mp 109-110 ^{o}C $[\alpha]^{23}_{D}$ 58.66^{o} (C 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.21 (m, 20H), 4.52 (s, 2H), 4.33 (t, *J* = 5.0 Hz, 1H), 3.47 (dd, *J* = 5.0 and 9.0 Hz, 1H), 3.20 (dd, *J* = 4.0 and 9.0 Hz, 2H), 2.64 (m, 1H), 2.57-2.38 (m, 3H), 2.13 (ddd, *J* = 4.5, 10.0 and 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 217.5, 144.1, 138.3, 128.9, 128.7, 128.0, 127.9, 127.8, 127.2, 86.8, 75.0, 70.8, 62.3, 46.7, 45.8, 33.1. Anal. Calcd for $C_{32}H_{30}O_3$: C, 83.09; H, 6.54. Found: C, 82.84; H, 6.61.

(2*S*, 4*S*)-(-)-1,1-Difluoro-3-*O*-benzyloxy-5-(*O*-trityloxymethyl)-cyclopentane (107) A mixture of ketone **106** (9.3 g, 20.1 mmol) and diethyl aminosulfur trifluoride (52.7 mL, 402 mmol) was heated at 40 ^{o}C for 20h and diluted with CH_2Cl_2 (100 mL). The mixture was drop-wised into iced sat. $NaHCO_3$ solution and the organic layer was separated, washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:100) to give difluorinated compound **107** (7.78 g, 79.8 %) as a brown oil. $[\alpha]_D$ –6.13^{o} (C 1.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (m, 20H), 4.84 (d, , *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 3.94 (m, 1H), 3.05 (m, 2H), 2.64 (m, 1H), 2.40 (m, 1H), 2.04-1.94 (m, 2H), 1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 217.5, 144.1, 138.3, 128.9, 128.7, 128.0, 128.0, 127.8, 127.3, 86.8, 74.9, 70.8, 62.3, 46.7, 45.8, 33.1. Anal. Calcd for $C_{32}H_{30}O_2F_2$: C, 79.32; H, 6.24. Found: C, 79.30; H, 6.32.

(2*S*, 4*S*)-(-)-1,1-Difluoro-3-*O*-benzyloxy-5-hydroxymethyl-cyclopentane (108) A solution of compound **107** (2.5 g, 5.38 mmol) in 80% acetic acid (10 mL) and MeOH (10 mL) was refluxed

for 36h. The dark brown resulting mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:10) to give compound **108** (640 mg, 57.9 %) as a yellowish oil. $[\alpha]^{27}_{D}$ +6.24^{o} (C 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27(m, 5H), 4.48 (s, 2H), 4.09 (bs, 1H), 3.83-3.76 (m, 2H), 2.78-2.66 (m, 1H), 2.46-2.37 (m, 2H), 2.15 (dd, *J* = 8.5 and 14.0 Hz, 1H), 1.85 (ddd, *J* = 2.5, 6.0 and 17.0 Hz 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.9, 128.5, 127.8, 127.6, 75.0, 70.7, 60.4 (d, *J* = 8.1 Hz), 46.2 (t, *J* = 22.5 Hz), 43.0 (t, *J* = 23.8 Hz), 32.9 (d, *J* = 6.1 Hz); MS (ESI) *m/z* 223 (M+1). Anal. Calcd for $C_{13}H_{16}O_2F_2$: C, 64.45; H, 6.66. Found: C, 64.26; H, 6.74.

(2*S*, 4*S*)-(-)-1,1-Difluoro-3-*O*-benzyloxy-5-(*O*-*tert*-butyldiphenylsilyloxymethyl)-cyclopentane (109) To a solution of alcohol **108** (580 mg, 2.61 mmol) in CH_2Cl_2 (10 mL), *tert*-butyldiphenylsilane chloride (0.76 mL, 2.87 mmol) and imidazole (267 mg, 3.92 mmol) were added at room temperature. After being stirred at room temperature for 1 h, H_2O (10 mL) was added to the resulting white suspension mixture and the organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:100) to give **109** (1.10 g, 88.0 %) as a colorless oil. $[\alpha]_D$ +6.03 $^{\circ}$ (C 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.44-7.27 (m, 11H), 4.46 (s, 2H), 4.10 (bs, 1H), 3.83 (dd, *J* = 6.0 and 11.0 Hz, 1H), 3.70 (dd, *J* = 6.5 and 11.0 Hz, 1H), 2.73 (m, 1H), 2.46-2.28 (m, 2H), 2.20-2.14 (m, 1H), 1.85 (ddd, *J* = 6.0, 10.0 and 15.5 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.1, 135.7, 133.5 (d, *J* = 6.1 Hz), 130.8, 129.8 (d, *J* = 1.5 Hz), 128.5, 127.8, 127.8, 127.7, 127.7, 75.1, 70.8, 61.5 (d, *J* = 7.1 Hz), 46.5 (t, *J* = 21.5 Hz), 43.0 (t, *J* = 24.3 Hz), 33.8 (d, *J* = 5.3 Hz), 26.8, 19.3. Anal. Calcd for $C_{29}H_{35}O_2F_1Si_1$: C, 72.46; H, 7.13. Found: C, 72.44; H, 7.29.

(3*S*, 5*S*)-(-)-1,1-Difluoro-5-(*O*-*tert*-butyldiphenylsilyloxymethyl)-3-hydroxy-cyclopentane (110) To a solution of compound **109** (103 mg, 0.21 mmol) in MeOH (10 mL), 10% Pd on activated carbon (100 mg) was added at room temperature. After being stirred at room temperature under H_2 gas for 24 h, resulting mixture was filtered over celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:5) to give compound **110** (62 mg, 74.7 %) as a colorless oil. $[\alpha]^{24}_{D}$ +14.97 ° (C 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.66 (m, 4H), 7.45-7.37 (m, 11H), 4.44 (bs, 1H), 3.80 (dd, *J* = 5.0 and 10.5 Hz, 1H), 3.72 (dd, *J* = 6.0 and 10.5 Hz, 1H), 2.75 (m, 1H), 2.45 (m, 1H), 2.20 (q, *J* = 14.0 Hz 1H), 2.02-1.98 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 135.6, 133.3 (d, *J* = 3.9 Hz), 133.2, 131.2, 129.8 (d, *J* = 1.4 Hz), 129.1, 127.8 (d, *J* = 1.4 Hz), 68.8, 61.5, 46.4 (t, *J* = 21.4 Hz), 46.0 (t, *J* = 28.1 Hz), 37.1 (d, *J* = 5.3 Hz), 26.8, 19.3. Anal. Calcd for $C_{22}H_{28}O_2F_2Si_1$: C, 67.66; H, 7.23. Found: C, 67.62; H, 7.47.

(1'*R*, 4'*S*)-(-)-9-[2',3'-Dideoxy-3',3'-difluoro-6-(*O*-*tert*-butyldiphenylsilyloxymethyl)-cyclopent-2-enyl]adenine (112) A solution of tripheyl phosphine (1.34 g, 5.11 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to 0 °C and then a solution of diisopropyl azodicarboxylate (1.03 g, 5.11 mmol) in anhydrous 1,4-dioxane (5 mL) was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 30 min and then white suspension mixture was cooled to -78 °C. A solution of alcohol **110** (500 mg, 1.28 mmol) in anhydrous THF (10 mL) and 6-chloropurine (790 mg, 5.11 mmol) were added respectively. The reaction mixture was slowly allowed to warm to room temperature and stirred for 24 h. The yellowish resulting mixture was concentrated *in vacuo* and the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:10) to give **111** (1.30 g) as a crude product contaminated with

reduced diisopropylazodicarboxylate, which was used for the next reaction without further purification. The crude **111** (500 mg) was treated with methanolic ammonia and stirred at room temperature for 36 h. After the reaction mixture was concentrated *in vacuo*, the residue was purified by column chromatography on a silica gel (EtOAc : hexane = 1:5 to CH_2Cl_2 : MeOH = 50 : 1) to give **112** (240 mg, 96.1% from **110**) as a white foam. $[\alpha]^{24}_D$ –11.28° (C 2.21, $CHCl_3$); UV (MeOH) λ_{max} 259.0 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.84 (s, 1H), 7.68-7.65 (m, 4H), 7.47-7.37 (m, 6H), 5.92 (bs, 2H), 5.08 (quintet, *J* = 8.5 Hz, 1H), 3.95 (dd, *J* = 5.0 and 10.0 Hz, 1H), 3.89 (dd, *J* = 6.0 and 11.0 Hz,1H), 2.85 (m, 1H), 2.73-2.56 (m, 3H), 2.25 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.6, 153.0, 150.1, 135.6 (d, *J* = 6.6 Hz), 133.1 (d, *J* = 4.4 Hz), 129.9, 127.8 (d, *J* = 1.5 Hz), 119.9, 61.1 (d, *J* = 7.6 Hz), 49.7, 47.4 (t, *J* = 23.4 Hz), 42.1 (t, *J* = 25.2 Hz), 33.7, 26.8, 19.3; Anal. Calcd for $C_{27}H_{31}OF_2Si_1$: C, 63.88; H, 6.16; N, 13.80 Found: C, 63.96; H, 6.38; N, 14.01.

(1'*R*, 4'*S*)-(-)-9-[2',3'-Dideoxy-3',3'-difluoro-6hydroxymethyl-cyclopent-2-enyl]adenine (113) A solution of **112** (110 mg, 0.27 mmol) in anhydrous THF (5 mL) was treated with 1M solution of TBAF and stirred at room temperature for 1 h. After concentration *in vacuo*, the residue was purified by the residue was purified by column chromatography on a silica gel ($CHCl_3$: MeOH = 12 : 1) to give **113** (55 mg, 94.3 %) as a white solid. $[\alpha]^{22}_D$ –9.50° (C 0.33, $CHCl_3$); UV (MeOH) λ_{max} 260 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.24 (s, 1H), 5.12 (m, 1H), 3.99 (dd, *J* = 5.5 and 11.5 Hz, 1H), 3.85 (dd, *J* = 6.0 and 11.0 Hz,1H), 2.85 (m, 2H), 2.65 (m, 2H), 2.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.9, 152.3, 149.3, 139.5, 130.9, 128.9 (d, *J* = 3.9 Hz), 119.0, 78.1, 59.2 (t, *J* = 5.8 Hz), 50.3, 41.1 (t, *J* = 25.7 Hz), 32.9; Anal. Calcd for $C_{11}H_{13}OF_2N5$: C, 49.07; H, 4.87; N, 26.01 Found: C, 49.15; H, 4.77; N, 26.29.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-3'-fluoro-6'-hydroxymethyl-cyclopent-2-enyl]adenine (114) A solution of compound **113** (45 mg, 0.17 mmol) in anhydrous THF (5 mL) and anhydrous 1,4-dioxane (5 mL) was treated with potassium *t*-butoxide (60 mg, 0.51 mmol) and refluxed for 12 h. After the reaction mixture was concentrated *in vacuo*, the residue was purified by column chromatography on a silica gel (CH_2Cl_2 : MeOH = 12 : 1) to give **114** (20 mg, 48.0%) as a white solid. $[\alpha]^{23}_D$ +8.90 (C 0.21, MeOH); mp = 218-220 ^oC; UV (H_2O) λ_{max} 260.0 nm (ε 10925, pH 2), 261.0 nm (ε 10807, pH 7), 261.0 nm (ε 11780, pH 11); ^1H NMR (500 MHz, MeOH-d_4) δ 8.31 (s, 1H), 8.24 (s, 1H), 5.66 (bs, 1H), 5.44 (s, 1H), 3.88 (dd, *J* = 3.5 and 11.0 Hz, 1H), 3.62 (dd, *J* = 3.0 and 11.0 Hz, 1H), 3.05 (bs, 1H), 2.98 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.4, 165.1, 155.9, 152.1, 103.2 (d, *J* = 14.3 Hz), 60.0, 53.9 (t, *J* = 12.9 Hz), 48.4, 43.2 (d, *J* = 18.6 Hz), 32.2 (d, *J* = 5.8 Hz), 29.4; MS : *m/z* 250 (M+1); Anal. Calcd for $C_{11}H_{12}N_5O_1F_1$: C, 53.01; H, 4.85; N, 28.10. Found: C, 53.31; H, 4.59; N, 28.44.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-3,3'-fluoro-cyclopent-2-enyl]inosine (115) To a solution of 6-chloropurine analog **111** (70 mg, 0.24 mmol) in formic acid (3 mL, 1.65 mmol) was heated at 90 ^oC for 2 h and then reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) and treated with NH_4OH (1 mL). After being stirred at room temperature for 2 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on a silica gel (MeOH : CH_2Cl_2 = 1:10) to give **115** (49 mg, 75%) as a white solid. $[\alpha]^{23}_D$ +9.97 (C 0.45, MeOH); mp = 227 ^oC; UV (MeOH) λ_{max} 247.0 nm; ^1H NMR (500 MHz, MeOH-d_4) δ 8.25 (s, 1H), 8.09 (s, 1H), 5.14 (m, 1H), 3.90 (dd, *J* = 6.0 and 11.5 Hz, 1H), 3.79 (dd, *J* = 5.5 and 11.0 Hz, 1H), 2.82 (m, 1H), 2.65 (m, 1H), 2.32 (dd, *J* = 10.0 and 22.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.6, 145.1, 139.1, 130.8, 128.8 (d, *J* = 3.4 Hz),

126.8, 124.3, 59.0 (dd, *J* = 2.4 and 8.0 Hz), 50.7, 41.3 (t, *J* = 25.9 Hz), 33.1 (t, *J* = 4.8 Hz), 29.3; Anal. Calcd for $C_{11}H_{12}N_4O_2F_2$: C, 48.89; H, 4.48; N, 20.73. Found: C, 49.10; H, 4.51; N, 20.99.

(1'*R*, 4'*S*)-(+)-9-[2',3'-Dideoxy-2',3'-didehydro-3'-fluoro-6'-hydroxymethyl-cyclopent-2-enyl]inosine (116) Compound **115** (44 mg, 0.16 mmol) was converted to a inosine analog **116** (22 mg, 54.3 %) as a colorless oil using same procedure as for **114**. $[\alpha]^{23}_D$ + (C 1.51, MeOH); mp = 254-256 ^oC; UV (H_2O) λ_{max} 249.0 nm (ε 10354, pH 2), 248.5 nm (ε 13925, pH 7), 254.0 nm (ε 10142, pH 11); ^1H NMR (500 MHz, MeOH-d_4) δ 8.12 (s, 1H), 7.94 (s, 1H), 5.55 (m, 1H), 5.29 (s, 1H), 3.73 (dd, *J* = 4.0 and 11.5 Hz, 1H), 3.49 (dd, *J* = 3.5 and 11.0 Hz, 1H), 3.21 (quintet, *J* = 1.5 Hz, 1H), 2.91 (bs, 1H), 2.84 (dd, *J* = 9.0 and 13.5 Hz, 1H), 1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.5, 165.2, 157.6, 145.1, 139.1, 103.1 (d, *J* = 14.8 Hz), 59.9, 54.1 (d, *J* = 12.9 Hz), 48.5, 43.2 (d, *J* = 19.1 Hz), 32.3 (d, *J* = 5.8 Hz); Anal. Calcd for $C_{11}H_{11}N_4O_2F_1$: C, 52.80; H, 4.43; N, 22.39. Found: C, 52.99; H, 4.74; N, 22.45.

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