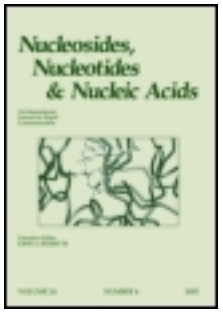


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# Synthesis of 2′-Fluoro and 2′,4′-Dimethyl Pyrimidine C-Nucleoside Analogues as Potential Anti-HCV Agents

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# SYNTHESIS OF 2′-FLUORO AND 2′,4′-DIMETHYL PYRIMIDINE *C*-NUCLEOSIDE ANALOGUES AS POTENTIAL ANTI-HCV AGENTS

**Lian Jin Liu and Joon Hee Hong**
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□ *Stereoselective synthesis of novel 2′-fluoro and 2′,4′-dimethyl carbocyclic pyrimidine* C-*nucleoside analogues using selective fluorination of an epoxide opening reaction is described. The key fluorinated intermediate* **7** *was prepared from the epoxide intermediate* **5** *via selective ring opening of the epoxide. Synthesis of isonucleosidic bases through the mesylate* **7** *and final deprotection provided the target carbocyclic pyrimidine* C-*nucleoside analogues. The synthesized compounds* **15** *and* **18** *were evaluated as inhibitors of the hepatitis C virus (HCV) in the Huh-7 cell line in vitro.*

**Keywords** Carbocyclic *C*-nucleoside; cis-fluorohydrin; anti-HCV agent; Krapcho's procedure

## INTRODUCTION

Carbocyclic *C*-nucleoside[1] is a unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a *C-C* bond instead of the *C-N* bond of the carbocyclic nucleosides. *C*-Nucleosides have received considerable attention due to their chemical stability and interesting biological activities of naturally occurring compounds such as isocytidine,[2] thiazofurin,[3] and 9-deazaadenosine.[4] Few examples of carbocyclic *C*-nucleosides[5] have been synthesized, probably due to difficulties in synthesis.

Hepatitis C virus (HCV) infection[6] accounts for many hepatitis cases worldwide and is also strongly associated with the development of cirrhosis and hepatocellular carcinoma. The current standard therapy for chronic HCV infection is interferon-$\alpha$ in combination with ribavirin, which is inadequate because of the low response rates as well as its side effects.[7]

The molecular virology of HCV has led to the identification of a number of antiviral molecular targets, including the NS5B RNA-dependent RNA polymerase. Inhibition of this enzyme prevents HCV replication, making

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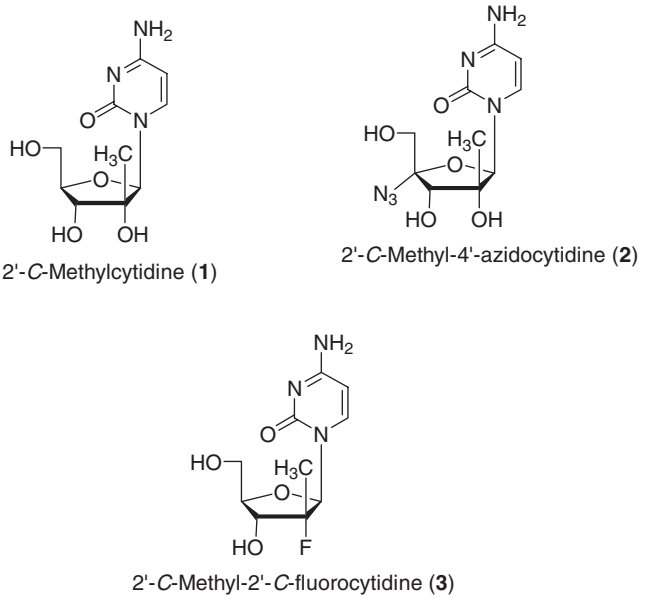
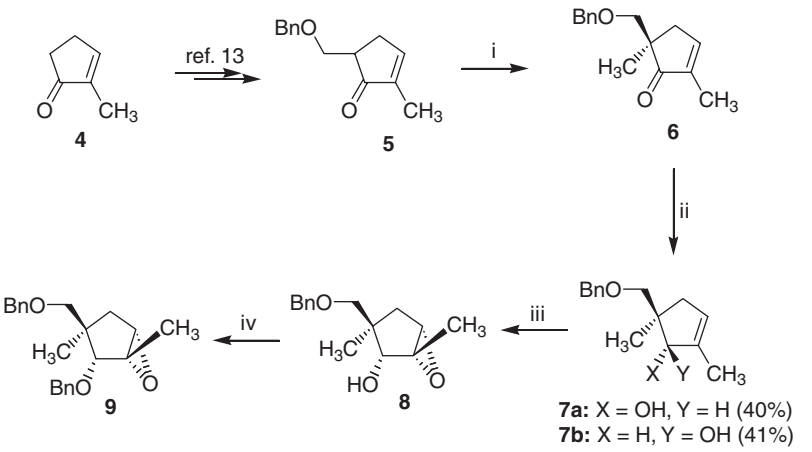



**FIGURE 1** Structure of potent anti-HCV agents.

this enzyme a crucial target for new anti-HCV agents. Many nucleoside analogues have been evaluated as anti-HCV agents.[8] These nucleosides are incorporated into viral RNA like a substrate after being converted to their corresponding triphosphates, and act as chain terminators. Modification in the vicinity of the 2′-hydroxy of the ribose in natural ribonucleosides can produce effective RNA chain terminators.[9] For example, replacement of the 2′-hydrogen of natural ribonucleosides with a methyl group yields compounds with excellent chain-terminating properties. 2′-*C*-Methylcytidine[10] **1** and 2′-*C*-methyl-4'-azidocytidine[11] **2** are potent anti-HCV agents (Figure 1). More recently, 2′-*C*-fluoro-2′-*C*-methylcytidine[12] **3** was designed as a hepatitis C virus RNA-dependant RNA polymerase (HCV RdRp) inhibitor and showed better inhibitory activity in the HCV replicon assay than 2′-*C*-methylcytidine, with low cellular toxicity.

Based on these branched pyrimidine nucleoside analogues, we designed fluorinated analogues of carbocyclic *C*-nucleosides as anti-HCV agents, focusing on the modifications of the 2′ and 4′-positions of the potent 2′($\beta$)-*C* methyl carbodine nucleosides. Substitution at the 2′-position and further modification of the 4′-position might impose favorable steric as well as electronic effects on the interaction with HCV polymerase.

As depicted in Scheme 1, we used the benzyloxymethylated cyclopentenone intermediate **6** as starting material, which could be readily synthesized via commercially available methylcyclopentenone **4** as described in a previous report.[13] An attempt was made to methylate the enone derivative **5** using a typical enolate alkylation procedure (LiHMDS/$CH_3I$) to




**SCHEME 1** Synthesis of fluorinated epoxide intermediate **9**. Reagents: i) LiHMDS, $CH_3I$, THF, −78°C; ii) $NaBH_4$, $CeCI_3{\cdot}7H_2O$, MeOH, 0°C; iii) m-CPBA, $CH_2CI_2$; iv) BnBr, NaH, DMF.

produce **6**, which was subjected to Luche's reduction conditions[14] ($NaBH_4$, $CeCl_3{\cdot}7H_2O$), to provide enol derivatives **7a** and **7b** without stereoselectivity. The correct configuration for these compounds could readily be assigned through the NOE comparisons between proximal protons in the cyclopentenol structures. On irradiation of $C_5(CH_3)$-H, relatively weak NOE was observed at $C_1$-H (0.6%) of **7a**, compared to that of **7b** (1.2%; Figure 2).

The allylic alcohol **7a** was subjected to stereoselective epoxidation conditions (*m*-CPBA, $NaHCO_3$, $CH_2Cl_2$) to give epoxide derivative **8** as the only product. The hydroxy functional group of **8** was protected with another benzyl group under normal benzylation conditions (BnBr, NaH, DMF) to provide a fully protected intermediate **9**, which underwent a ring-opening fluorination reaction with hydrofluoric acid in the presence of silicon fluorides and additives to provide cis-fluorohydrin in good yield using the reported procedure.[15] For the synthesis of target fluorinated carbocyclic pyrimidine *C*-nucleosides, we utilized the key intermediate **11** prepared from methanesulfonylation of **10** with MsCl and TEA in anhydrous $CH_2Cl_2$. The mesylate intermediate **11** was alkylated with diethyl malonate by nucleophilic $S_N2$ substitution conditions to give **12** with chiral inversion. Decarboethoxylation of **12** using Krapcho's condition (LiCl, DMSO, $H_2O$) gave fluoroester derivative **13**. The isocytosine base was built by sequential treatment of **13**

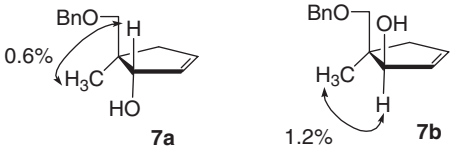
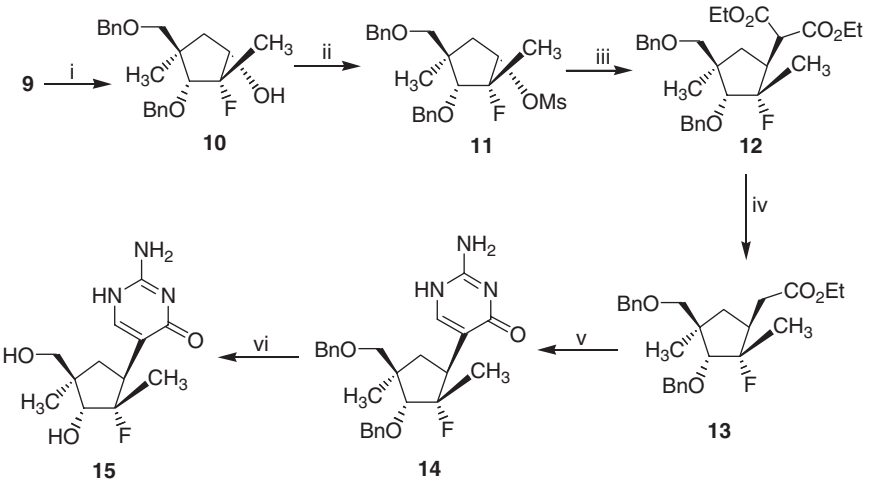



**FIGURE 2** NOE differences of isomers **7a** & **7b**.

with lithium diisopropylamide (LDA), ethyl formate, and guanidine carbonate in the presence of sodium ethoxide in ethanol to provide carbocyclic isocytidine analogue **14**. Debenzylation of **14** with palladium black[16] in 5% formic acid afforded **15** in good yield (Scheme 2).

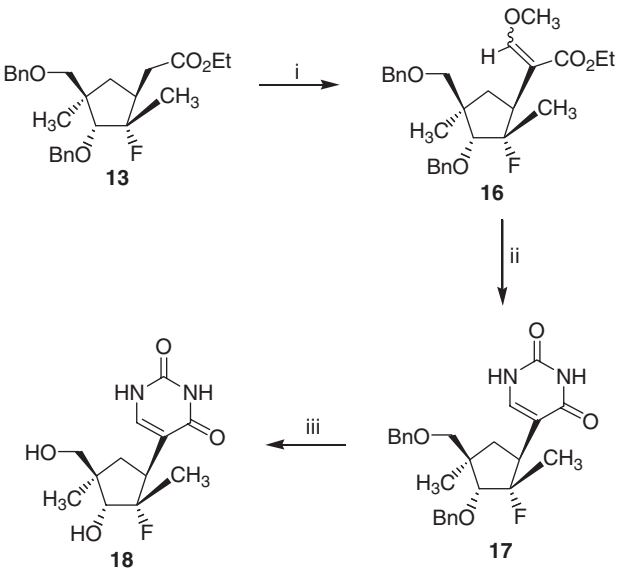



**SCHEME 2** Synthesis of target 2′-fluorinated isocytosine nucleoside analogue. Reagents: i) 47% HF, $(NH_4)_2SiF_6$, CsF; ii) MsCI, TEA, $CH_2CI_2$; iii) NaH, $CH_2(CO_2Et)_2$, THF; iv) LiCI, DMSO; v) (a) LDA/THF, HCOEt; (b) $H_2NC(=NH)NH_2$.carbonate, NaOEt/EtOH; vi) Pd black, 5% $HCO_2H$ in MeOH, reflux overnight.

Under similar conditions, synthesis of the carbocyclic isouridine analogue **18** was prepared from the same intermediate **13** as describe for isocytidine.[17] Generation of enolate with lithium diisopropylamide in THF and formylation with ethyl formate gave the corresponding anion, which was methylated with iodomethane in DMF to give the methyl enol ether derivative **16**. Treatment of **16** with urea in the presence of potassium *tert*-butoxide in THF provided isouridine analogue **17**. Debenzylation was performed by a similar procedure as described for **15** to provide the target isouridine derivative **18** (Scheme 3).

The synthesized compounds were tested for anti-HCV activity using an in vitro assay composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of an HCV replicon named NK-R2AN.[18] But unlike 2′-fluoro-2′-*C*-methylcytidine, tested compounds **15** and **18** demonstrated no activity or cytotoxicity in the HCV assay.

In summary, the present ring-opening fluorination of epoxide using hydrofluoric acid offers a convenient procedure for the synthesis of *cis*-fluorhydrins. On the basis of potent anti-HCV activity of 2′-modified nucleosides, we have designed and synthesized 2′-fluoro-2′,4′-dimethyl pyrimidine *C*-nucleoside derivatives. Also, the synthesis of other analogues (A,G,T) is in progress and will be reported elsewhere.




**SCHEME 3** Synthesis of target 2′-flourinated isouracil nucleoside analogue. Reagents: i) (a) LDA/THF, HCOEt; (b) MeI, DMF; ii) $NH_2CONH_2$, t-BuOK, THF; iii) Pd black, 5% $HCO_2H$ in MeOH, reflux overnight.



## EXPERIMENTAL

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL JNM-AL300 Fourier transform; chemical shifts are reported in parts per million ($\delta$) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). Ultraviolet (UV) spectra were obtained on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Thin layer chromatography (TLC) was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were performed under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene, and pyridine were obtained by distillation from $CaH_2$. Dry tetrahydrofuran (THF) was obtained by distillation from Na and benzophenone immediately prior to use.

**(±)-5-Benzyloxymethyl-2,5-dimethyl-cyclopent-2-enone (6):** To a stirred solution of lithium hexamethyldisilazane (LiHMDS, 10.32 mL, 1.0 M solution in THF) in tetrahydrofuran (25 mL), a solution of compound **5** (1.116 g, 5.16 mmol) in tetrahydrofuran (8 mL) was added at –78°C. After stirring for 1.5 hours at the same temperature, the reaction temperature was elevated to –20°C and stirred for an additional 1 hour at the same temperature. Iodomethane (1.1 g, 7.74 mmol) was then added to this mixture at –78°C and stirred for 3 hours. The mixture was warmed to –20°C and the mixture was stirred for an additional 2 hours. The reaction was quenched

with addition of a saturated ammonium chloride solution (8.0 mL). The resulting mixture was warmed to room temperature, poured into water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (EtOAc/hexane, 1:25) to give compound **6** (927 mg, 78%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.35–7.30 (m, 5H), 6.98 (m, 1H), 4.54 (s, 2H), 4.53 (s, 2H), 3.51 (d, $J = 6.2$ Hz, 1H), 3.42 (d, $J = 6.2$ Hz, 1H), 1.98–1.94 (m, 2H), 1.77 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.3, 152.3, 140.1, 137.9, 128.3, 127.9, 127.1, 126.4, 74.4, 72.2, 58.8, 30.2, 12.3, 10.4; Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.32; H, 7.96.

**(*rel*)-(1*S*,5*S*)-5-Benzyloxymethyl-2,5-dimethyl-cyclopent-2-enol (7a) and (*rel*)-(1*R*,5*S*)-5-benzyloxymethyl-2,5-dimethyl-cyclopent-2-enol (7b):** $CeCl_3 \cdot 7H_2O$ (6.26 g, 16.8 mmol) was added to a solution of 6 (2.54 g, 11.04 mmol) in MeOH (65 mL) at 0°C and stirred for 30 minutes. Then, $NaBH_4$ (832 mg, 22.0 mmol) was carefully added to the mixture and stirred for 3 hours at room temperature. The reaction mixture was quenched by addition of acetic acid (3.6 mL) and concentrated under reduced pressure. The resulting residue was dissolved in $H_2O$ (120 mL) and extracted with EtOAc (120 mL) two times. The organic layer was sequentially washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (EtOAc/hexane, 1:15) to give compounds 7a (1.02 g, 40%) and 7b (1.05 g, 41%) as syrups, respectively: data for 7a; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36 (m, 5H), 5.47 (m, 1H), 4.59 (s, 2H), 4.01 (s, 1H), 3.43 (d, $J = 6.6$ Hz, 1H), 3.39 (d, $J = 6.6$ Hz, 1H), 2.39–2.24 (m, 2H), 1.69 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.6, 137.9, 127.6, 127.1, 126.9, 125.4, 85.3, 76.2, 73.1, 51.8, 34.2, 13.4, 10.7; Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.53; data for 7b; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.34 (m, 5H), 5.50 (m, 1H), 4.58 (s, 2H), 4.12 (s, 1H), 3.42 (dd, $J = 10.2$, 4.8 Hz, 2H), 2.38–2.26 (m, 2H), 1.59 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.9, 138.0, 127.5, 127.0, 126.4, 125.2, 86.1, 77.0, 72.2, 52.2, 35.8, 14.7, 11.1; Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.66; H, 8.70.

**(*rel*)-(1*S*,2*R*,3*R*,5*S*)-3-Benzyloxymethyl-1,3-dimethyl-6-oxa-bicyclo[3.1.0] hexan-2-ol (8):** m-Chloroperbenzoic acid (3.64 g, 15.6 mmol, 77% purity) was added to a solution of **7a** (2.78 g, 11.96 mmol) in anhydrous $CH_2Cl_2$ (58 mL) at 0°C. The solution was stirred at 0°C for 1 hours and stirred for additional 2 hours at room temperature. A saturated $NaHCO_3$ solution (120 mL) was added to the reaction mixture and extracted with EtOAc (120 mL) two times. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (EtOAc/hexane, 1:10) to give compound **8** (2.46 g, 83%) as an oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.37–7.35 (m, 5H), 4.57 (s, 2H), 3.99 (s, 1H), 3.47 (d, $J = 7.2$ Hz, 1H), 3.34 (d, $J = 7.3$ Hz, 1H), 3.12 (m, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 1.52 (s, 3H), 1.18 (s, 3H); $^{13}$C

NMR ($CDCl_3$) $\delta$ 137.8, 127.6, 127.2, 126.7, 83.3, 76.7, 75.3, 66.2, 60.1, 28.7, 24.2, 17.2, 14.2; Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.05.

**(*rel*)-(1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-benzyloxymethyl-1,3-dimethyl-6-oxa-bicyclo[3.1.0]hexane (9)**: NaH (312 mg, 13.0 mmol) was slowly added to a solution of epoxide derivative **8** (2.49 g, 10.75 mmol) in dry DMF (30 mL) at 0°C. After 30 minutes, benzyl bromide (2.02 g, 11.82 mmol) was added, and the reaction mixture was stirred for 4 hours at room temperature. The mixture was quenched by adding saturated ammonium chloride (2.5 mL) and concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (100 mL) two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give **9** (2.73 g, 75%) as a syrup. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.34 (m, 10H), 4.63 (s, 2H), 4.60 (s, 2H), 3.41 (d, $J$ = 7.0 Hz, 1H), 3.32 (d, $J$ = 7.1 Hz, 1H), 3.21 (s, 1H), 2.61 (m, 1H), 1.66–1.54 (m, 2H), 1.38 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 137.8, 137.6, 127.9, 127.5, 127.1, 126.8, 126.6, 89.8, 78.2, 76.5, 74.2, 65.9, 59.4, 28.7, 23.6, 18.0, 13.6; Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 77.94; H, 7.68.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentanol (10)**: 47% Hydrofluoric acid (0.154 mL, 3.6 mmol) was added to a mixture of $(NH_4)_2SiF_6$ (1.06 g, 6.0 mmol), CsF (182 mg, 1.2 mmol), and epoxide **9** (406 mg, 1.2 mmol) in 1,2-dichloroethane (15 mL) at 0°C, and the mixture was stirred for 5 hours at the same temperature. A saturated $NaHCO_3$ solution (40 mL) was slowly added and the whole mixture was extracted with diethyl ether (70 mL) two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give alcohol **10** (193 mg, 45%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.37–7.31 (m, 10H), 4.67 (s, 2H), 4.61 (s, 2H), 3.69 (ddd, $J$ = 3.2, 6.4, 18.6 Hz, 1H), 3.48 (d, $J$ = 20.2 Hz, 1H), 3.21 (dd, $J$ = 8.6, 12.4 Hz, 2H), 1.71 (dd, $J$ = 6.4, 12.0 Hz, 1H), 1.61 (dd, $J$ = 8.6, 12.0 Hz, 1H), 1.38 (d, $J$ = 20.6 Hz, 3H), 1.15 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 138.1, 137.8, 128.7, 127.9, 127.5, 127.1, 126.7, 126.2, 103.2 (d, $J$ = 184.4 Hz), 86.4 (d, $J$ = 21.2 Hz), 77.1, 74.8, 74.1, 72.4 (d, $J$ = 20.2 Hz), 28.8, 26.4, 15.4 (d, $J$ = 22.8 Hz), 13.4; Anal. Calcd. for $C_{22}H_{27}FO_3$: C, 73.72; H, 7.59. Found: C, 73.62; H, 7.63.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-Methanesulfonic acid-3-benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentanyl ester (11)**: MsCl (0.59 g, 5.15 mmol) was added to a solution of the alcohol **10** (1.68 g, 4.68 mmol) and triethylamine (1.5 mL) in anhydrous $CH_2Cl_2$ (40 mL) at 0°C. The mixture was stirred for 5 hours at room temperature, and quenched by a saturated $NaHCO_3$

solution (1.0 mL). The mixture was poured into excess cold water (100 mL) and extracted with EtOAc (100 mL) two times. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give mesylate **11** (1.59 g, 78%) as a syrup: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.32 (m, 10H), 5.12 (ddd, $J$ = 3.3, 6.8, 19.2 Hz, 1H), 4.70 (s, 2H), 4.63 (s, 2H), 3.54 (d, $J$ = 19.8 Hz, 1H), 3.33 (dd, $J$ = 8.2, 12.2 Hz, 2H), 3.01 (s, 3H), 1.73 (dd, $J$ = 6.2, 12.2 Hz, 1H), 1.63 (dd, $J$ = 8.4, 12.1 Hz, 1H), 1.34 (d, $J$ = 20.2 Hz, 3H), 1.14 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 138.0, 137.7, 128.5, 128.0, 127.8, 127.4, 126.9, 126.4, 98.1 (d, $J$ = 182.8 Hz), 85.2 (d, $J$ = 21.8 Hz), 78.1, 76.8, 75.1, 68.8 (d, $J$ = 19.4 Hz), 37.4, 29.4, 25.6, 15.7 (d, $J$ = 21.4 Hz), 12.1.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-2-[3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentanyl] malonic acid diethyl ester (12):** Diethyl malonate (4.5 g, 28.12 mmol) in THF (60 mL) was added to a solution of NaH (0.45 g, 18.75 mmol) in THF (50 mL) under a nitrogen atmosphere at 0°C and stirred for 1.5 hours at room temperature. Mesylate **11** (3.32 g, 7.6 mmol) in THF (50 mL) was slowly added to the reaction mixture and stirred overnight at room temperature. The mixture was quenched by the addition of water (150 mL) and extracted with ethyl acetate (150 mL) twice. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **12** (2.62 g, 69%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.31 (m, 10H), 4.73 (s, 2H), 4.69 (s, 2H), 4.14 (m, 4H), 3.35 (dd, $J$ = 8.0, 12.4 Hz, 2H), 3.19 (d, $J$ = 5.8 Hz, 1H), 3.12–3.08 (m, 2H), 1.49 (d, $J$ = 20.2 Hz, 3H), 1.39–1.30 (m, 8H), 1.16 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.4, 170.1, 138.1, 137.9, 128.9, 128.6, 128.1, 127.8, 127.4, 126.9, 96.2 (d, $J$ = 185.2 Hz), 89.4 (d, $J$ = 20.4 Hz), 77.4, 76.6, 75.1, 68.8 (d, $J$ = 21.4 Hz), 60.3, 43.2, 30.2, 28.8 (d, $J$ = 23.2 Hz, 1H), 21.3, 17.3 (d, $J$ = 20.4 Hz), 15.3, 13.2; Anal. Calcd. for $C_{29}H_{37}FO_6$: C, 69.58; H, 7.45. Found: C, 69.50; H, 7.39.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-[3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentanyl] acetic acid ethyl ester (13):** LiCl (470 mg, 11.1 mmol) and $H_2O$ (2 drops) were added to a solution of **12** (1.85 g, 3.7 mmol) in DMSO (10 mL). The mixture was stirred overnight at 170°C. After cooling to room temperature, the reaction mixture was poured into $H_2O$ (80 mL) and extracted with diethyl ether (80 mL) two times. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **13** (1.2 g, 76%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.33 (m, 10H), 4.70 (s, 2H), 4.67 (s, 2H), 4.12 (q, $J$ = 7.2 Hz, 2H), 3.18–3.09 (m, 3H), 2.44–2.36 (m, 1H), 2.17 (dd, $J$ = 7.4, 12.6 Hz, 2H), 1.46 (d, $J$ = 19.2 Hz, 3H), 1.37–1.29 (m, 2H), 1.24 (t, $J$ = 7.2 Hz, 3H), 1.14 (s, 3H); $^{13}$C NMR

($CDCl_3$) $\delta$ 171.1, 137.9, 127.5, 128.8, 128.4, 128.1, 127.7, 127.3, 126.5, 98.6 (d, $J$ = 187.6 Hz), 90.8 (d, $J$ = 20.0 Hz), 76.8, 75.2, 73.4, 60.1 32.6 ($J$ = 19.8 Hz), 29.3, 28.1, 24.5, 17.5 ($J$ = 23.6 Hz), 15.2, 12.5; Anal. Calcd. for $C_{26}H_{33}FO_4$: C, 72.87; H, 7.76. Found: C, 72.93; H, 7.82.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentan-1-yl) isocytosine (14):** A solution of **13** (1.36 g, 3.18 mmol in THF 20 mL) was slowly added to a solution of lithium diisopropylamide (4.8 mL, 1 M in hexane) in THF (12 mL) at –78°C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1.5 hours and ethyl formate (0.933 mg, 12.6 mmol) was added to the mixture and stirred overnight at room temperature. The mixture was poured into saturated $NH_4Cl$ solution (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness to obtain a crude residue. The residue was dissolved in absolute ethanol (10 mL). To a solution of guanidine carbonate (1.62 g, 9.0 mmol) in EtOH (20 mL), EtONa/EtOH (21% solution, 3.88 mL, 12.0 mmol) was added and stirred for 2 hours. To this mixture, the above-obtained residue in ethanol (10 mL) was added and refluxed overnight. The mixture was filtered, concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.1) to give **14** (847 mg, 59%) as a white solid: m.p. 143–145°C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 10.88 (br s, 1H), 7.37–7.33 (m, 10H), 7.21 (s, 1H), 6.49 (br s, 2H), 4.75 (s, 2H), 4.69 (s, 2H), 3.35 (d, $J$ = 8.2 Hz, 1H), 3.21 (d, $J$ = 8.2 Hz, 1H), 3.11 (d, $J$ = 19.0 Hz, 1H), 2.57 (ddd, $J$ = 3.4, 8.2, 18.8 Hz, 1H), 1.51–1.40 (m, 5H), 1.16 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.5, 155.2, 138.7, 138.3, 134.7, 127.9, 127.6, 115.3, 95,4 ($J$ = 184.4 Hz), 89.6 ($J$ = 19.8 Hz), 77.3, 75.7, 36.7 ($J$ = 20.6 Hz), 29.4, 22.1, 18.1 ($J$ = 21.8 Hz), 14.2; Anal. Calcd. for $C_{26}H_{30}FN_3O_3$: C, 69.16; H, 6.70; N, 9.31. Found: C, 69.20; H, 6.61; N, 9.25.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-1-(3-Hydroxy-4-hydroxymethyl-2-fluoro-2,4-dimethyl-cyclopentan-1-yl) isocytosine (15):** Pd black (98% Pd, 10 mg, catalytic amount) was added to a stirred solution of **14** (115 mg, 0.254 mmol) in 5% formic acid in MeOH (20 mL), and the reaction mixture was refluxed overnight. The mixture was filtered through a Celite pad and washed with MeOH several times. After solvent evaporation, the residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH, 5:1) to give **15** (56 mg, 82%) as a white solid: m.p. 198–200°C; UV ($H_2O$) $\lambda_{max}$ 289.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 12.43 (s, 1H), 8.29 (br s, 2H), 7.33 (s, 1H), 5.07 (d, $J$ = 4.6 Hz, 1H), 4.90 (t, $J$ = 5.0 Hz, 1H), 3.53–3.41 (m, 3H), 2.52 (ddd, $J$ = 3.6, 8.4, 19.2 Hz, 1H), 1.49–1.39 (m, 5H), 1.13 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 161.3, 153.1, 146.2, 134.7, 116.5, 96.7 ($J$ = 179.8 Hz), 85.2 ($J$ = 21.2 Hz), 35.6 ($J$ = 21.2 Hz), 33.3, 22.6, 17.2 ($J$ = 24.2 Hz), 13.2; Anal. Calcd. for $C_{12}H_{18}FN_3O_3$(+1.0 MeOH): C, 51.47; H, 7.31; N, 13.85. Found: C, 51.53; H, 7.33; N, 13.79.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentan-1-yl) 3-methoxy-acrylic acid ethyl ester (16):** A solution of 13 (1.35 g, 3.156 mmol) in THF (25 mL) was added to a solution of lithium diisopropylamide (LDA, 2M in hexane, 2.352 mL) in THF (13 mL) at –78°C under nitrogen atmosphere. The mixture was stirred at the same temperature for 1 hour and then ethyl formate (933 mg, 12.6 mmol) was added. After being stirred at −78°C for an additional 1.5 hours, the mixture was warmed up to room temperature and stirred overnight. The resulting mixture was evaporated to dryness and the residue was dissolved in dry DMF (10.0 mL) and iodomethane (1.34 g, 9.48 mmol) was added slowly to the mixture under a nitrogen atmosphere. After being stirred for 5 hours at room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (100 mL) twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give 16 (920 mg, 62%) as a colorless syrup: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.36–7.33 (m, 11H), 4.69 (s, 2H), 4.63 (s, 2H), 4.13 (q, $J$ = 7.2 Hz, 2H), 3.35–3.27 (m, 5H), 3.12 (d, $J$ = 19.0 Hz, 1H), 1H), 2.49 (dd, $J$ = 6.2, 18.8 Hz, 1H), 1.51–1.45 (m, 4H), 1.34 (d, $J$ = 8.0 Hz, 1H), 1.24 (t, $J$ = 7.2 Hz, 3H), 1.13 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.8, 154.2, 138.2, 137.6, 127.9, 127.2, 126.3, 110.2, 95.4 ($J$ = 181.8 Hz), 90.4 ($J$ = 22.1 Hz), 77.8, 73.6, 54.6, 61.7, 34.2 ($J$ = 20.2 Hz), 29.2, 18.3 ($J$ = 24.2 Hz), 14.1, 12.7; Anal. Calcd. for $C_{28}H_{35}FO_5$: C, 71.47; H, 7.50. Found: C, 71.53; H, 7.47.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-1-(3-Benzyloxy-4-benzyloxymethyl-2-fluoro-2,4-dimethyl-cyclopentan-1-yl) isouracil (17):** A mixture of urea (240 mg, 3.996 mmol) and KO$^t$Bu (443 mg, 3.996 mmol) in THF (15 mL) was stirred for 1.5 hours at room temperature and then **16** (937 mg, 1.992 mmol) in THF (15 mL) was added to the mixture under anhydrous conditions. The mixture was refluxed overnight and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **17** (297 mg, 33%) as a white solid: m.p. 165–167°C; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 11.16 (br s, 1H), 10.75 (br s, 1H), 7.35–7.32 (m, 10H), 6.96 (s, 1H), 4.70 (s, 2H), 4.64 (s, 2H), 3.40 (d, $J$ = 8.8 Hz, 1H), 3.31 (d, $J$ = 8.9 Hz, 1H), 3.14 (d, $J$ = 19.4 Hz, 1H), 2.51 (dd, $J$ = 6.8, 19.8 Hz, 1H), 1.53–1.42 (m, 5H), 1.17 (d, $J$ = 19.2 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.5, 151.4, 143.9, 137.5, 128.9, 127.5, 126.3, 110.2, 95.2 ($J$ = 182.8 Hz), 90.2, 89.9 ($J$ = 19.8 Hz), 77.3, 75.2, 73.8, 35.3 ($J$ = 20.0 Hz), 29.3, 21.2, 17.3 ($J$ = 21.8 Hz), 14.3; Anal. Calcd. for $C_{26}H_{29}FN_2O_4$: C, 69.01; H, 6.46; N, 6.19. Found: C, 69.09; H, 6.40; N, 6.23.

**(*rel*)-(1*S*,2*S*,3*R*,4*S*)-1-(3-Hydroxy-4-hydroxymethyl-2-fluoro-2,4-dimethyl-cyclopentan-1-yl) isouracil (18):** Isouridine derivative **18** was prepared from **17** using a similar procedure described for **15**: yield 88%; m.p. 208–210°C: UV ($H_2O$) $\lambda_{max}$ 262.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 11.13 (br s,

1H), 10.73 (br s, 1H), 7.03 (s, 1H), 5.19 (d, $J = 4.6$ Hz, 1H), 4.86 (t, $J = 4.4$ Hz, 1H), 3.60–3.53 (m, 2H), 3.43 (d, $J = 9.5$ Hz, 1H), 2.51 (ddd, $J = 3.2$, 8.9, 19.6 Hz, 1H), 1.51–1.42 (m, 3H), 1.15 (d, $J = 19.2$ Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 165.0, 151.2, 147.3, 114.8, 97.2 ($J = 184.4$ Hz), 85.6 ($J = 21.0$ Hz), 68.2, 35.2 ($J = 18.8$ Hz), 32.7, 21.3, 17.1 ($J = 23.1$ Hz), 13.8; Anal. Calcd. for $C_{12}H_{17}FN_2O_4$ (+ 1.0 $H_2O$): C, 49.65; H, 6.59; N, 9.65. Found: C, 49.73; H, 6.63; N, 9.70.

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