

Synthesis of Cyclopentanyl Carbocyclic 5-Fluorocytosine ((-)-5-Fluorocarbodine) Using a Facially Selective Hydrogenation Approach

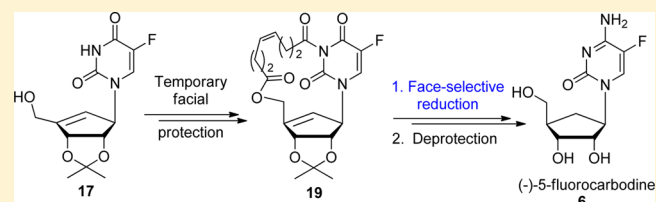
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S Supporting Information

ABSTRACT: An efficient synthetic route to biologically relevant (-)-5-fluorocarbodine **6** was developed. Direct coupling of N⁶-protected 5-fluorouracil **15** with cyclopentenyl intermediate **13**, followed by formation of a macrocycle between the base and the carbocyclic sugar moiety, via ring-closing metathesis, allowed for a facial selective hydrogenation of the sugar double bond to give, exclusively, the desired 4'- β stereoisomer.



Carbocyclic nucleosides, in which the furanose ring oxygen atom has been replaced by a carbon atom, are, in general, more chemically and enzymatically stable, and some of them have demonstrated interesting biological properties.¹ Thus, naturally occurring (-)-aristeromycin (**1**)² and (-)-neplanocin A (**2**)³ manifest cytotoxic and antiviral properties, while the drugs abacavir (**3**)⁴ and entecavir (**4**)⁵ are Food and Drug Administration (FDA) approved for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HBV), respectively (Figure 1).

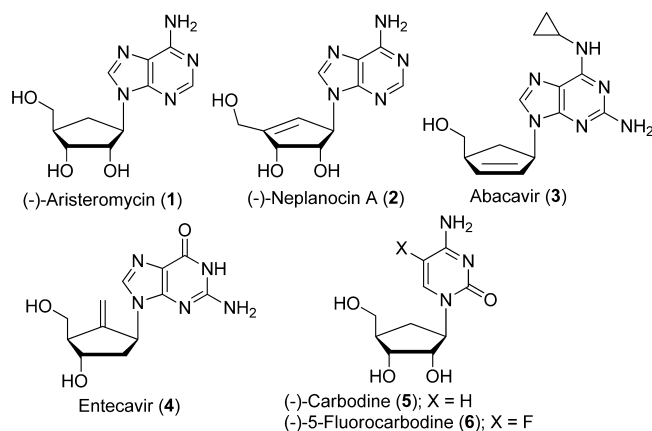


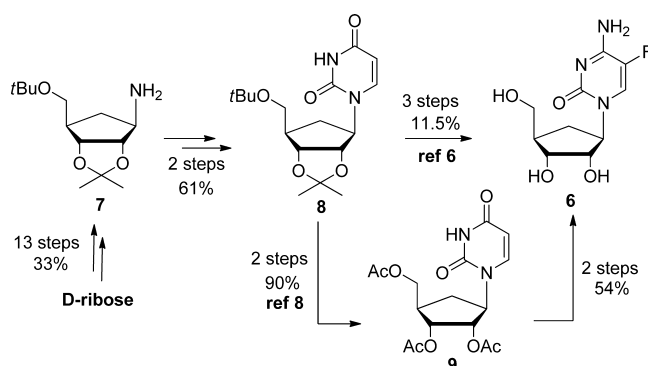
Figure 1. Structures of biologically relevant carbocyclic nucleosides.

The carbocyclic cytosine analogs (-)-carbodine (**5**) and (-)-5-fluorocarbodine (**6**) was reported to possess significant antitumor and antiviral activities. For instance, compound (**6**) showed selective submicromolar IC₅₀'s against a human T cell lymphoblast cell line and human B cell lymphoma cell line but also potent inhibition of HCV RNA replication (Δ Ct of 6 at 10 μ M in a Huh-7 cell based subgenomic replicon assay).⁶ In

addition, compounds (**5**) and (**6**) demonstrated selective activity against Venezuela equine encephalitis virus (VEEV)⁷ and various strains of H5N1 influenza.⁸

The most recently reported syntheses of (-)-carbodine (**5**) and (-)-5-fluorocarbodine (**6**) used a linear approach (Scheme 1) from known cyclopentenyl intermediate including stepwise

Scheme 1. Linear Approaches for the Synthesis of 5-Fluorocarbodine (**6**)



construction of the heterocyclic base. The key intermediate **7** was prepared from D-ribose in 13 steps by a sequence that used protecting/deprotection strategies, and each step required purification by column chromatography on silica gel. After the pyrimidine base was built, intermediate **8** was either converted, after a series of protection/deprotection, to its cytosine counterpart then fluorinated (ref 8) or directly fluorinated and then converted to its cytosine analogue (ref 6). Overall, both approaches are lengthy (18 and 19 steps) and

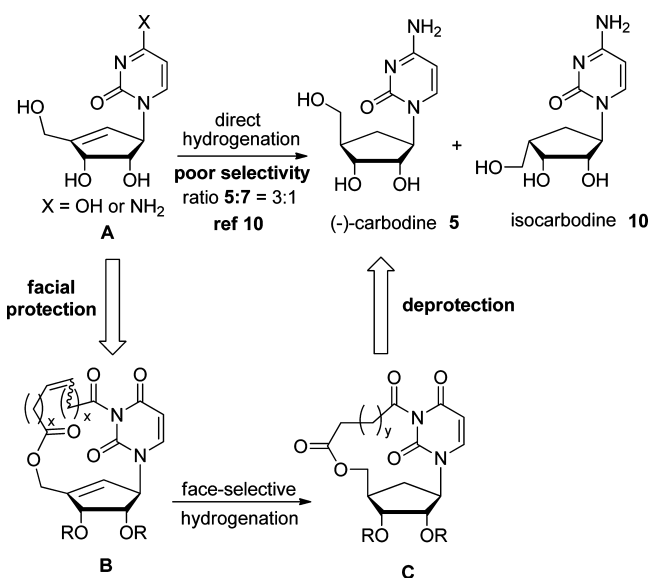
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resulted in the formation of (**6**) in an overall yield of 2⁶ and 10%.⁸

Preparation of (–)-carbodine (**5**) has also been achieved by either enzymatic hydrolysis⁹ or selective hydrogenation of cyclopentenyl cytosine.¹⁰ However, both of these methods resulted in poor overall yields and low selectivities. In the latter approach, the authors demonstrated that the use of diimide as a source of hydrogen was not completely diastereoselective and led to a mixture of **5**, along with isocarbodine (**10**) (Scheme 2).

Scheme 2. Facially Selective Hydrogenation

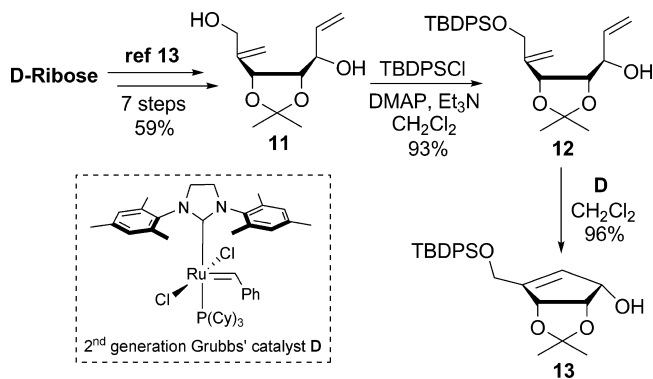


Furthermore, separation of the two isomers appeared problematic, and purification of enantiomerically pure **5** could only be achieved using semipreparative HPLC. With this last result in mind, we hypothesized that the introduction of a temporary sugar-base bridging group on compound **A** (Scheme 2; X = OH) would act as an umbrella, covering the β face of the cyclopentene and allow for selective α face hydrogenation. Furthermore, we envisioned a sequence to form a cyclic eight member linker using a ring-closing metathesis (RCM)¹¹ reaction that would connect the 5'-O of the sugar and 3-N of the uridine base as depicted in Scheme 2 compound **B**. Facial selectivity of the subsequent hydrogenation could also be rationalized by the calculated¹² increased ring strain of the macrocycle for β face hydrogenation that would ultimately lead to isocarbodine (**10**) formation.

In order to prepare 5-fluorocarbodine (**6**), the key cyclopentenol derivative **13** was synthesized in nine steps from D-ribose, using a slightly modified known methodology (Scheme 3).¹³ Thus, chiral intermediate **11** was selectively protected by treatment with TBDPSCI in the presence of DMAP to give compound **12**. Diene **12** was then cyclized via a ring-closing metathesis reaction in the presence of a catalytic amount of second-generation Grubbs' catalyst **D**, affording desired cyclopentenol **13**. Meanwhile, N3-benzoyl-5-fluorouracil **15** was prepared in two steps from 5-fluorouracil **14** (Scheme 4) by benzylation followed by selective deprotection using K₂CO₃ in dioxane.¹⁴

Coupling of chiral intermediate **13** with 3-N-Bz-5-F-uracil **15** under Mitsunobu conditions provided the desired N-alkylated derivative as a mixture with its O-alkylated isomer and DIAD byproducts (Scheme 4). The partially column purified mixture

Scheme 3. Preparation of Protected Sugar **13**



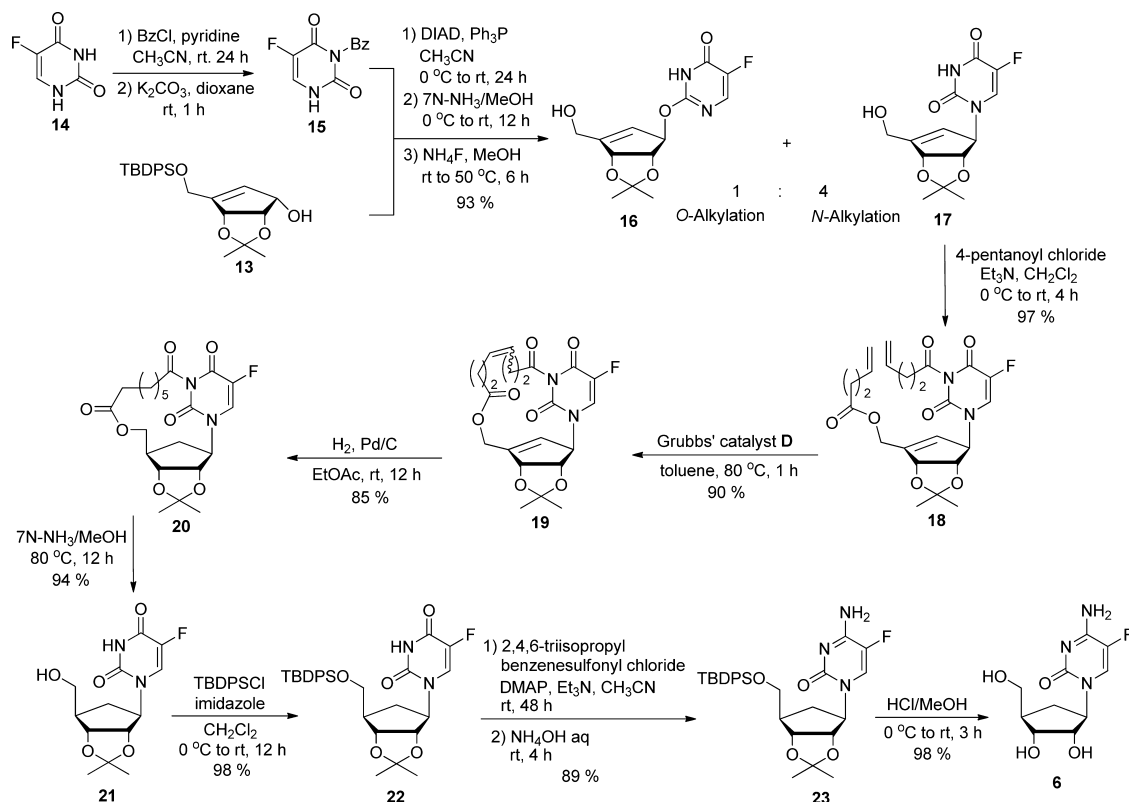
was directly deprotected by treatment with 7 N NH₃ in MeOH, followed by NH₄F in MeOH, to afford pure carbocyclic 5-fluorouridine derivative **17** along with pure O-alkylated compound **16** (ratio 4:1) in 93% yield over three steps. At this stage, introduction of pentenoyl moieties on both 5'-OH and 3-NH positions of compound **17** had to be optimized. While use of pyridine either alone or with DMAP or Et₃N gave the desired compound in low yields (the monoalkylated compound being predominant), the use of Et₃N in dichloromethane led to the nearly quantitative formation of dialkylated compound **18**. With intermediate **18** in hand, a ring-closing metathesis reaction to form the desired macrocycle **19** was investigated. Evaluation of solvents, catalyst loading, and reaction time was undertaken. The best results were obtained when compound **18** was treated with 2.0 mol % of second-generation Grubbs' catalyst **D** (Scheme 4) in toluene at 80 °C for 1 h.

As predicted, hydrogenation of unsaturated derivative **19** in the presence of Pd/C in EtOAc led to complete stereoselective formation of cyclopentane derivative **15** in 85% yield. The absolute stereochemistry of the final product was determined by ¹H NMR and 1D-NOE experiments on compound **21**, which was obtained after removal of the linker using NH₃ in MeOH. The NOE experiment showed an enhancement of the 4' proton when the 1' proton was irradiated, indicating that they reside on the same face of the sugar moiety. Finally, carbocyclic 5-F-uridine **21** was converted to its cytosine counterpart following a previously reported method.¹⁵ The primary alcohol in compound **21** was first protected using TBSCl. Compound **22** was then reacted with 2,4,6-triisopropylbenzenesulfonyl chloride followed by NH₄OH to give intermediate **23**. Final deprotection was achieved using HCl in MeOH providing the target 5-fluorocarbodine **6** in 98% isolated yield.

CONCLUSION

In summary, an efficient synthetic route to 5-fluorocarbodine **6** was developed utilizing a key α -face-selective hydrogenation driven by the introduction of a temporary macrocyclic tether. This approach represents a noteworthy improvement to the existing syntheses of biologically relevant compound **6** and allowed us to prepare **6** in 23% overall yield (compared with 2–10% yields from previous approaches) with no major purification problems nor use of special synthetic techniques. We are currently evaluating our umbrella approach's compatibility with other reactions to modify the olefin functionality and further explore the scope of this innovative methodology.

Scheme 4. Synthesis of 5-Fluorocarbodine 6



EXPERIMENTAL SECTION

General Considerations. Nuclear magnetic resonance (NMR) spectra (^1H , ^{13}C and ^{19}F) were recorded on a 400 MHz FT-NMR spectrometer at ambient temperature, with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), dt (doublet of triplets), or ddd (doublet of doublets of doublets). High-resolution mass spectra (HRMS) were recorded on a linear ion trap LTQ-FT mass spectrometer with electrospray ionization (ESI). Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel. Purifications were carried out by silica gel column chromatography (60 Å, 63–200 μm , or 40–75 μm).

(R)-1-((4R,5S)-5-(3-(tert-Butyldiphenylsilyloxy)prop-1-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (12). To a solution of compound 11 (4.0 g, 20.5 mmol) in 100 mL of anhydrous CH_2Cl_2 were added DMAP (0.2 g, 1.4 mmol), TBDPSCI (6.3 g, 24.6 mmol), and Et_3N (3.1 g, 30.8 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 12 h at room temperature and quenched with 5.0 mL of MeOH. The solution was adsorbed on silica gel and purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 2:1 v/v) to give compound 12 as a white foam (8.7 g, 19.1 mmol) in 93% yield: HRMS-ESI⁺ calcd for $\text{C}_{27}\text{H}_{37}\text{O}_4\text{Si}$ ($\text{M} + \text{H}^+$) 453.2462, found 453.2456; ^1H NMR (400 MHz, CDCl_3) δ 7.71–7.67 (m, 4H), 7.46–7.37 (m, 6H), 6.03–5.95 (m, 1H), 5.47 (dd, J = 13.2, 1.2 Hz, 2H), 5.32 (dt, J = 17.2, 1.2 Hz, 1H), 5.21 (dt, J = 10.4, 1.6 Hz, 1H), 4.65 (d, J = 5.6 Hz, 1H), 4.24 (s, 2H), 4.04–3.99 (m, 1H), 3.94 (dd, J = 8.8, 6.0 Hz, 1H), 2.63 (d, J = 3.2 Hz, 1H), 1.44 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 138.0, 135.9, 135.8, 132.9, 132.8, 130.2, 130.1, 128.1, 128.0, 116.2, 113.7, 108.2, 80.9, 77.6, 70.3, 66.2, 27.5, 27.0, 25.4, 19.4.

(3aS,4S,6aR)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (13). To a solution of compound 12 (8.2 g, 18.1 mmol) in 500 mL of anhydrous CH_2Cl_2 was added a solution of second Grubbs' catalyst (0.1 mol %, 0.02 g, 0.02 mmol) in 100 mL of anhydrous CH_2Cl_2 at

room temperature under argon atmosphere. After being stirred for 24 h, the reaction mixture was treated with 5.0 mL of DMSO, additionally stirred for 1 h at room temperature, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 1:1 v/v) to give compound 13 as a white foam (7.40 g, 17.43 mmol) in 96% yield: HRMS-ESI⁺ calcd for $\text{C}_{25}\text{H}_{33}\text{O}_4\text{Si}$ ($\text{M} + \text{H}^+$) 425.2149, found 425.2143; ^1H NMR (400 MHz, CDCl_3) δ 7.69–7.65 (m, 4H), 7.44–7.34 (m, 6H), 5.84 (d, J = 1.6 Hz, 1H), 4.86 (d, J = 5.6 Hz, 1H), 4.74 (t, J = 5.2 Hz, 1H), 4.56 (m, 1H), 4.38 (dd, J = 15.2, 20.0 Hz, 2H), 2.70 (d, J = 10.0 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.5, 135.7, 133.5, 129.9, 129.5, 127.9, 112.7, 83.0, 78.2, 73.5, 61.0, 27.8, 27.0, 26.9, 19.5.

N_3 -Benzoyl-5-fluorouracil (15). To a solution of 5-fluorouracil 14 (3.6 g, 27.3 mmol) in 50 mL of anhydrous CH_3CN were added BzCl (9.3 g, 68.2 mmol) and pyridine (10.8 g, 136.5 mmol) at 0 °C under N_2 atmosphere. The solution was stirred for 24 h at room temperature and concentrated under reduced pressure. The residue was dissolved in 200 mL of CH_2Cl_2 and then washed with cold water (50 mL \times 3) and concentrated under reduced pressure. The residue was redissolved in 50 mL of 1,4-dioxane and treated with aqueous K_2CO_3 (20 mL, 0.5 M in water solution) at 0 °C. After the solution was stirred for 30 min at room temperature, the pH was lowered to ca. 5.0 by careful addition of glacial acetic acid. The solution was concentrated in vacuo, and the residue was treated with a saturated solution of NaHCO_3 (100 mL). After the solution was stirred for 1 h, the white solid was filtered and washed with cold water (20 mL \times 5) then dried under vacuum for 48 h. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 1:1 to EtOAc) to give compound 15 as a white amorphous solid (5.6 g, 23.7 mmol) in 87% yield: MS-ESI⁺ m/z 235 ($\text{M} + \text{H}^+$); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.54 (br, 1H), 8.06 (d, J = 6.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.58 (dd, J = 8.4, 7.6 Hz, 2H).

5-Fluoro-2-(((3aS,4R,6aR)-6-(hydroxymethyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)oxy)pyrimidin-4(3H)-one (16) and 5-Fluoro-1-(((3aS,4R,6aR)-6-(hydroxymethyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d]

[1,3]dioxol-4-yl)pyrimidine-2,4(1H,3H)-dione (17). To a solution of Ph₃P (11.1 g, 42.4 mmol) in 150 mL of CH₃CN was added DIAD (8.6 g, 42.4 mmol) at 0 °C under N₂ atmosphere. After 30 min, to the reaction mixture were added a solution of compound **13** (7.2 g, 17.0 mmol) in 150 mL of CH₃CN and *N*-Bz-5-fluorouracil **15** (6.0 g, 25.4 mmol) at -78 °C. The reaction mixture was stirred for 24 h at room temperature and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1 to 1:1 v/v) to give a nonseparable mixture of *N*-*O*-alkylated products along with DIAD byproducts. This mixture was dissolved in 100 mL of MeOH and treated with 100 mL of 7 N NH₃ in MeOH at 0 °C. The solution was stirred for 12 h at room temperature and concentrated under reduced pressure. The residue was then directly treated with a solution of ammonium fluoride (1.6 g, 42.4 mmol) in 200 mL of MeOH at room temperature, and the solution was stirred at 50 °C for 6 h. After removal of the volatiles under vacuum, the residue was purified by silica gel column chromatography (hexane/EtOAc = 1:5 to EtOAc v/v) to give **16** as an off-white gum (0.94 g, 3.2 mmol) and **17** as an off-white gum (3.8 g, 12.6 mmol) in 93% yield over three steps. Compound **16**: MS-ESI⁺*m/z* 299 (M + H⁺); HRMS-ESI⁺calcd. for C₁₃H₁₆FN₂O₅ (M + H⁺) 299.1039, found 299.1035; ¹H NMR (400 MHz, CD₃OD) δ 7.77 (d, *J* = 3.2 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.72 (s, 1H), 5.19 (d, *J* = 5.6 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.24 (dd, *J* = 16.0, 10.8 Hz, 2H), 1.38 (s, 3H), 1.34 (s, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 154.7, 149.3, 146.8, 136.0, 123.7, 113.7, 87.3, 85.0, 84.4, 59.00, 27.8, 26.2. Compound **17**: MS-ESI⁺*m/z* 299 (M + H⁺); HRMS-ESI⁺calcd for C₁₃H₁₆FN₂O₅ (M + H⁺) 299.1038, found 299.1036; ¹H NMR (400 MHz, CD₃OD) δ 7.54 (d, *J* = 6.4 Hz, 1H), 5.60 (m, 1H), 5.36 (s, 1H), 5.24 (d, *J* = 6.0 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 1H), 4.29 (s, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 155.0, 151.5, 143.1, 140.8, 127.8, 122.6, 113.5, 85.6, 84.8, 68.9, 60.0, 27.7, 26.1; ¹⁹F NMR (376 MHz, CDCl₃) δ -169.69 (d, *J* = 6.0 Hz).

((3*aR*,6*R*,6*aS*)-6-(3-*But*-3-enoyl-5-fluoro-2,4-dioxo-3,4-dihydro-*pyrimidin*-1(2*H*)-yl)-2,2-dimethyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methyl But-3-enoate (18). To a solution of compound **17** (1.4 g, 4.7 mmol) in 40 mL of anhydrous CH₂Cl₂ were added Et₃N (2.4 g, 23.5 mmol) and 4-pentenoyl chloride (1.7 g, 14.1 mmol) at 0 °C under argon atmosphere. After being stirred for 4 h at room temperature, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1 to 1:1 v/v) to give a compound **18** as a white foam (2.1 g, 4.5 mmol) in 97% yield: MS-ESI⁺*m/z* 463 (M + H⁺); HRMS-ESI⁺calcd for C₂₃H₂₇FN₂O₇Na (M + Na⁺) 485.1705, found 485.1696; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 5.6 Hz, 1H), 5.90–5.78 (m, 2H), 5.57 (s, 1H), 5.39 (s, 1H), 5.21 (d, *J* = 5.6 Hz, 1H), 5.15–5.01 (m, 4H), 4.82 (q, *J* = 15.2 Hz, 2H), 4.59 (d, *J* = 5.6 Hz, 1H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.51 (m, 4H), 2.43 (m, 2H), 1.43 (s, 3H), 1.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 172.8, 158.7, 149.3, 148.0, 136.6, 135.6, 124.9, 122.9, 116.5, 116.1, 113.4, 94.6, 84.1, 83.5, 68.1, 60.9, 39.8, 33.4, 28.9, 27.5, 27.4, 25.9; ¹⁹F NMR (376 MHz, CDCl₃) δ -165.50 (d, *J* = 4.5 Hz).

Compound 19. To a solution of compound **18** (1.0 g, 2.16 mmol) in 500 mL of anhydrous toluene was added second-generation Grubbs' catalyst **D** (2.0 mol %, 0.037 g, 0.043 mmol) at room temperature under an argon atmosphere. After being stirred for 1 h at 80 °C, the reaction mixture was treated with 2.0 mL of DMSO at room temperature and additionally stirred for 1 h. The solution was concentrated under reduced pressure and then purified by silica gel column chromatography (hexane/EtOAc = 2:1 v/v) to give compound **19** as a white foam (0.85 g, 2.0 mmol) in 90% yield: MS-ESI⁺*m/z* 435 (M + H⁺); HRMS-ESI⁺calcd for C₂₁H₂₄FN₂O₇ (M + H⁺) 435.1562, found 435.1560; ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 5.2 Hz, 1H), 5.62 (s, 1H), 5.56–5.40 (m, 3H), 5.25 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 1H), 4.42 (s, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.07 (ddd, *J* = 18.0, 8.0, 2.4 Hz, 1H), 2.86 (ddd, *J* = 18.0, 10.4, 2.4 Hz, 1H), 2.60 (m, 1H), 2.50–2.30 (m, 3H), 2.28–2.15 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 172.7, 155.9, 146.9, 141.1, 138.7, 129.8, 129.1, 127.7, 125.5, 112.3,

84.5, 82.7, 74.9, 58.6, 39.4, 32.8, 27.4, 25.8; ¹⁹F NMR (376 MHz, CDCl₃) δ -165.63 (d, *J* = 6.0 Hz), -166.20 (d, *J* = 6.0 Hz).

Compound 20. To a solution of compound **19** (2.5 g, 5.8 mmol) in 100 mL of EtOAc was added Pd/C catalyst (10 wt %, 0.25 g). The solution was stirred for 12 h under H₂ atmosphere (1 atm) and then treated with Celite. After the solution was stirred for 30 min, the suspension was carefully filtered, and the filtrate concentrated under vacuum and then purified by silica gel column chromatography (hexane/EtOAc = 1:1 v/v) to give compound **20** as a white foam (2.1 g, 4.9 mmol) in 85% yield: MS-ESI⁺*m/z* 439 (M + H⁺); HRMS-ESI⁺calcd for C₂₁H₂₇FN₂O₇Cl (M + Cl⁻) 473.1496, found 473.1499; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 5.6 Hz, 1H), 5.00 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.88 (t, *J* = 5.6 Hz, 1H), 4.70 (d, *J* = 12.0, 1.2 Hz, 1H), 3.99 (dd, *J* = 12.0, 1.2 Hz, 1H), 3.91 (m, 1H), 2.95 (ddd, *J* = 16.0, 8.4, 3.2 Hz, 1H), 2.73 (ddd, *J* = 16.0, 9.6, 3.2 Hz, 1H), 2.55 (ddd, *J* = 16.0, 8.4, 5.2 Hz, 1H), 2.33–2.17 (m, 4H), 1.90 (m, 1H), 1.79 (s, 1H), 1.66–1.40 (m, 6H), 1.39–1.25 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 174.1, 147.6, 141.1, 138.7, 130.1, 129.8, 113.0, 94.6, 83.4, 80.3, 69.7, 61.0, 45.7, 40.1, 33.6, 31.2, 28.1, 27.1, 25.6, 24.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -166.59 (d, *J* = 4.5 Hz).

5-Fluoro-1-((3*aS*,4*R*,6*R*,6*aR*)-6-(hydroxymethyl)-2,2-dimethyltetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (21). A solution of compound **20** (2.0 g, 4.58 mmol) in 50 mL of MeOH was treated with 20 mL of 7 N NH₃ in MeOH at 0 °C in a sealed tube. After being stirred for 12 h at 80 °C, the solution was concentrated under reduced pressure and the residue was purified on a silica gel pad (CH₂Cl₂/MeOH = 30:1 to 10:1 v/v) to give compound **21** as a beige gum (1.3 g, 4.3 mmol) in 94% yield: MS-ESI⁺*m/z* 301 (M + H⁺); HRMS-ESI⁺calcd for C₁₃H₁₈FN₂O₅ (M + H⁺) 301.1194, found 301.1193; ¹H NMR (400 MHz, CDCl₃) δ 10.01 (br, 1H), 7.48 (d, *J* = 5.6 Hz, 1H), 4.77 (dd, *J* = 7.2, 5.6 Hz, 1H), 4.61 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.57 (m, 1H), 3.83 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.74 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.80 (br, 1H), 2.37–2.27 (m, 2H), 2.12–2.03 (m, 1H), 1.54 (s, 3H), 1.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.5, 157.2, 149.8, 141.9, 139.6, 127.9, 127.6, 113.2, 83.0, 81.4, 64.2, 63.3, 45.6, 32.0, 27.7, 25.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -169.67 (d, *J* = 6.0 Hz).

1-((3*aS*,4*R*,6*R*,6*aR*)-6-((*tert*-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (22). To a solution of compound **21** (1.3 g, 4.5 mmol) in 30 mL of anhydrous CH₂Cl₂ were added imidazole (0.74 g, 10.9 mmol) and TBDPSCI (1.7 g, 5.4 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was stirred for 12 h at room temperature and treated with 5.0 mL of MeOH. After being stirred for 1 h at room temperature, the solution was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/EtOAc = 2:1 to 1:4 v/v) to give compound **22** as an off white foam (2.3 g, 4.3 mmol) in 98% yield: MS-ESI⁺*m/z* 539 (M + H⁺); HRMS-ESI⁺calcd for C₂₉H₃₆FN₂O₅Si (M + H⁺) 539.2372, found 539.2368; ¹H NMR (400 MHz, CDCl₃) δ 9.78 (br, 1H), 7.66–7.62 (m, 4H), 7.40–7.36 (m, 6H), 7.23 (d, *J* = 5.6 Hz, 1H), 4.71 (m, 1H), 4.63 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.51 (dd, *J* = 7.2, 6.8 Hz, 1H), 3.79 (d, *J* = 5.2 Hz, 2H), 2.33 (m, 1H), 2.25 (m, 1H), 2.00 (q, *J* = 12.0 Hz, 1H), 1.53 (s, 3H), 1.29 (s, 3H), 1.09 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 157.2, 157.0, 149.7, 142.1, 139.7, 135.83, 135.78, 133.5, 133.4, 130.1, 128.0, 126.6, 126.3, 113.9, 82.8, 80.7, 64.3, 63.8, 45.2, 32.4, 27.8, 27.2, 25.5, 19.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -165.85 (d, *J* = 4.5 Hz).

4-Amino-1-((3*aS*,4*R*,6*R*,6*aR*)-6-((*tert*-butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-fluoropyrimidin-2(1*H*)-one (23). To a solution of compound **22** (2.2 g, 4.1 mmol) and DMAP (2.0 g, 16.4 mmol) in 50 mL of anhydrous CH₃CN were added 2,4,6-trisopropylbenzenesulfonyl chloride (3.1 g, 10.3 mmol) and Et₃N (1.7 g, 16.4 mmol) at room temperature under N₂ atmosphere. The reaction mixture was stirred for 48 h at room temperature and treated with 25 mL of 30% NH₄OH solution. After being stirred for 4 h at room temperature, the solution was poured into 150 mL of a cold water–CHCl₃ solution (1:2 v/v) and then extracted with CHCl₃ (30 mL × 3). The combined organic layers were washed with a saturated NH₄Cl aqueous solution (100

mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH = 10:1 v/v) to give compound **23** as a gum (2.0 g, 3.7 mmol) in 89% yield: MS-ESI⁺*m/z* 538 (M + H⁺); HRMS-ESI⁺ calcd for C₂₉H₃₇FN₃O₄Si (M + H⁺) 538.2532, found 538.2525; ¹H NMR (400 MHz, CDCl₃) δ 8.83, (br, 1H), 7.66–7.63 (m, 4H), 7.45–7.36 (m, 6H), 7.24 (d, *J* = 5.6 Hz, 1H), 5.60 (br, 1H), 4.80 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.52–4.44 (m, 2H), 3.82 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.74 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.33–2.25 (m, 2H), 2.16 (m, 1H), 1.50 (s, 3H), 1.26 (s, 3H), 1.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 154.6, 137.8, 135.8, 135.7, 135.4, 133.7, 133.6, 129.9, 128.4, 128.1, 127.9, 113.3, 83.0, 81.1, 66.1, 64.8, 46.2, 32.8, 27.8, 27.1, 25.5, 19.5; ¹⁹F NMR (376 MHz, CDCl₃) δ –169.48 (d, *J* = 7.5 Hz).

4-Amino-1-((1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-cyclopentyl)-5-fluoropyrimidin-2(1*H*)-one (6). A solution of compound **23** (2.5 g, 4.7 mmol) in 100 mL of MeOH was treated with 50 mL of HCl in MeOH at 0 °C. After being stirred for 3 h at room temperature, the acidic solution was concentrated under reduced pressure. The residue was dissolved in water (50 mL) and washed with EtOAc (20 mL × 5). The aqueous layer was concentrated under reduced pressure. The residue was dissolved in EtOH (10 mL), and the solution was concentrated under reduced pressure. After this process was repeated five times, the final residue was dried under vacuum for 72 h at room temperature to give pure compound **6** as a white amorphous solid (1.4 g, 4.6 mmol) as a HCl salt in 98% yield: MS-ESI⁺*m/z* 260 (M + H⁺); HRMS-ESI⁺ calcd for C₁₀H₁₃FN₃O₄ (M + H⁺) 260.1041, found 260.1039; ¹H NMR (400 MHz, CD₃OD) δ 8.35 (d, *J* = 7.2 Hz, 1H), 4.70 (q, *J* = 9.2 Hz, 1H), 4.12 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.85 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.53 (d, *J* = 5.2 Hz, 2H), 2.19 (m, 1H), 2.05 (m, 1H), 1.46 (m, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 154.65, 154.42, 148.52, 139.97, 137.78, 133.74, 133.46, 75.44, 73.49, 64.83, 64.53, 46.50, 28.67; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.75 (br, 1H), 9.14 (br, 1H), 8.53 (d, *J* = 7.2 Hz, 1H), 5.32 (br, 3H), 4.65 (q, *J* = 9.2 Hz, 1H), 4.01 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.72 (dd, *J* = 4.8, 2.4 Hz, 1H), 3.42 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.35 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.04 (m, 1H), 1.93 (m, 1H), 1.28 (m, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.1, 152.9, 147.8, 136.2, 133.9, 131.8, 131.5, 73.4, 71.2, 62.9, 61.8, 44.81, 27.8; ¹⁹F NMR (376 MHz, CD₃OD) δ –170.99 (d, *J* = 7.52 Hz).

■ ASSOCIATED CONTENT

📄 Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): Dr. Schinazi is the founder and a major shareholder of RFS Pharma, LLC. Emory received no funding from RFS Pharma, LLC to perform this work and vice versa.

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