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An Efficient and Diastereoselective Synthesis of PSI-6130: A Clinically Efficacious Inhibitor of HCV NS5B Polymerase

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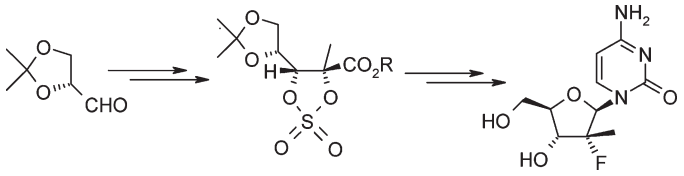

R7128 is the prodrug of 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine (PSI-6130), a potent and selective inhibitor of HCV NS5B polymerase. Currently, R7128 is in clinical trials for the treatment of HCV infection. To support clinical development efforts, we needed an efficient and scalable synthesis of PSI-6130. We describe an improved, diastereoselective synthetic route starting with protected D-glyceraldehyde. No chiral reagents or catalysts were used to produce the three new contiguous stereocenters. Introduction of fluorine at the C-2 tertiary carbon was accomplished in a highly regio- and stereoselective manner through nucleophilic substitution on a cyclic sulfate. Scale-limiting chromatographic purifications were eliminated through the use of crystalline intermediates.

Introduction

It is estimated that 130 million people[1] worldwide are infected with the Hepatitis C virus (HCV). Chronic infection greatly increases the risk of hepatic carcinoma.[2] In the United States, there are estimated to be 3.9 million people infected with HCV and 8 000−10 000 annual deaths attributed to HCV infection.[3] The current standard of care, pegylated interferon and ribavirin, produces viral response rates in only 50% of the patients infected with the genotype 1 virus.[4] Clearly, there is an unmet medical need for more effective therapies.

Over the last several years, ribonucleoside analogues with a 2′-*C*-methyl substituent have been identified as potent and selective inhibitors[5] of NS5B polymerase of the HCV replication complex. Clark et al.[6] disclosed the synthesis and biological activity of a fluorinated cytidine analogue, 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine (PSI-6130, **1**, Figure 1). On the basis of its superior profile, PSI-6130 was selected for clinical development. Currently its diisobutyryl prodrug (R7128, **2**) is in phase IIb clinical trials for Hepatitis C. R7128 has demonstrated antiviral activity in genotype 1 nonresponders with 14 day monotherapy.[7] In combination with the standard of care over 28 days, treatment with R7128 led to undetectable viral levels in 88% of genotype 1 naive patients and 90% undetectable viral levels in genotype 2 and 3 nonresponder patients.[7] R7128 is the first direct acting

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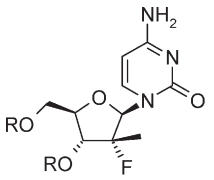


1, R = H, PSI-6130
2, R = $(CH_3)_2CHC(=O)$, R7128

FIGURE 1. Structures of PSI-6130 and R7128.

antiviral to demonstrate potent activity in the clinic against both genotype 2 and 3 virus.

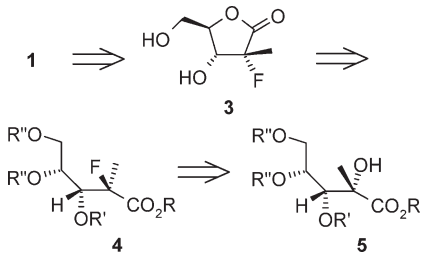
Although structure **1** appears as a close analogue of the natural ribonucleoside cytidine, it presented a synthetic challenge to functionalize stereoselectively the C-2′ position to generate a quaternary center having 2′-*C*-methyl and 2′-fluoro substituents. The discovery synthesis[6] converted cytidine to its 2′-*C*-methyl arabinoside analogue in six steps by using standard methods. Nucleophilic fluorination of the C-2′ tertiary alcohol with (diethylamino)sulfur trifluoride (DAST) did result in inversion of configuration to give the desired stereochemistry, but not surprisingly, the yield was low due to the formation of elimination and hydrolysis byproduct. Difficult chromatographic separation of the mixture limited the scale as well. An alternative synthesis of **1** from D-xylose proceeded via benzoyl protected 2-deoxy-2-fluoro-2-*C*-methyl-ribonolactol, using again a low-yielding DAST conversion of the tertiary alcohol, followed by coupling with the cytosine base to give the benzoylated cytidine precursor of **1**.[8] More recently, Mayes and Moussa disclosed[9] a synthesis of the sugar moiety by converting 3,4-*O*-isopropylidene-2-*C*-methyl-D-arabinono-1,5-lactone to its corresponding triflate, followed by fluoride displacement with tris(dimethylamino)sulfur trimethylsilyl difluoride (TASF) and deprotection to the six-membered-ring 1, 5-ribonolactone. This was subsequently converted to the five-membered-ring 1,4-ribonolactone. From a process chemistry standpoint, all of these routes have major limitations. Most notably, the key fluorination step comes too late in each of the synthetic schemes. This low-yielding step is done on advanced and therefore more expensive intermediates and the fluorinating agent, DAST, is hazardous to use on scale. Undesirable multiple chromatographic separations are required in the sequences and overall yields are low.

To produce enough material for preclinical and early clinical development, we needed a new, efficient, and scalable route that provided crystalline intermediates for purification. Retrosynthetically, we desired a convergent synthesis that would couple a fully elaborated sugar unit with the requisite base (Scheme 1).

Results and Discussion

The key intermediate needed was ribonolactone **3**. We envisioned[10] introduction of the C-2 fluorine functionality via stereoselective displacement of an activated hydroxyl group on an acyclic intermediate (**5**) to form **4**. Aparicio,

SCHEME 1. Retrosynthetic Analysis of PSI-6130



Cubero, and Olea[11] described the synthesis of ethyl 4,5-*O*-isopropylidine-2-*C*-methyl-DL-arabinoate via osmium tetraoxide mediated dihydroxylation of a pentenoate precursor that met our needs. In their earlier synthesis of the pentenoate,[12] they used a Knoevenagel−Doebner condensation on isopropylidene protected D-glyceraldehyde. The alkaline conditions led to racemization of the stereocenter. A Wittig reaction with an isolated ylide did not lead to any racemization. They also observed high selectivity for the desired *E* geometric isomer under their reaction conditions.

Proceeding forward with our synthesis of the ribonolactone intermediate (Scheme 2), commercially available isopropylidine protected D-glyceraldehyde (**6**) can be made economically on scale by symmetrical oxidative cleavage of the diisopropylidine derivative of D-mannitol.[13,14] Treating **6** with commercially available (carbethoxyethylidene)triphenylmethylphosphorane gave the desired chiral pentenoate ester (**7**) in 79% crude yield (ratio *E*/*Z* 97:3 by NMR). The mixture was carried on to the next step without further purification

Osmium tetraoxide can approach the double bond of the pentenoate from either face and therefore create two diastereomers for each of the geometric isomers. Cubero[11] observed that treating purified geometric DL isomers with catalytic osmium tetraoxide and potassium chlorate resulted in roughly equal facial selectivity for the *Z*-isomer and 2:1 for desired arabinoate from the *E*-isomer. In our early work, we used Sharpless AD-mix-β catalyst[15] to direct the attack to the desired face and create the correct stereochemistry in 91% yield after chromatography. While this worked well, we wanted to avoid using an expensive catalyst early in the synthesis. Even without using a chiral catalyst, the reaction on allylic alcohol derivatives should mostly occur on the face opposite to the pre-existing hydroxyl or alkoxyl groups.[16] After trying several oxidative conditions, we found that *tert*-butyl hydroperoxide with catalytic osmium tetraoxide in an tetraethylammonium acetate buffer[17] worked exceptionally

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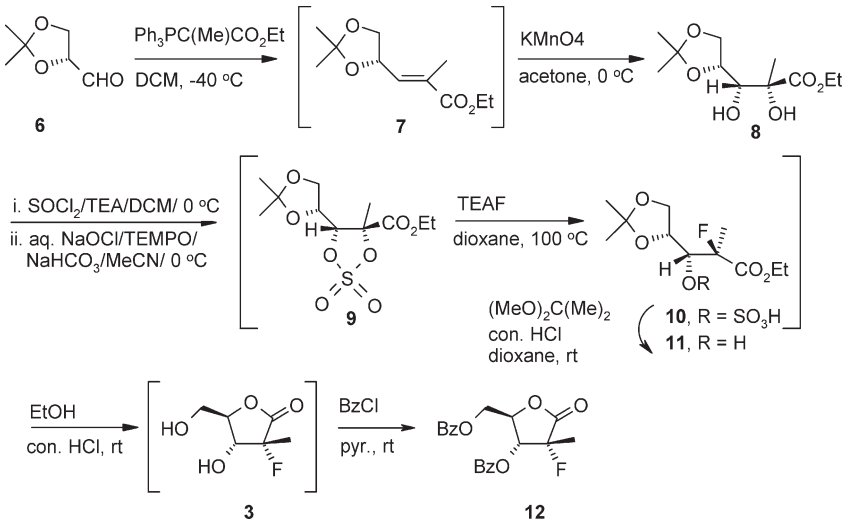
SCHEME 2. Synthesis of Protected Ribonolactone



well. The desired pure diol (**8**) was isolated in 87% yield after chromatography. Due to the hazardous nature of osmium tetraoxide, we also explored using permanganate salts for the dihydroxylation. Typically, permanganate dihydroxylations are performed in alkaline conditions to suppress overoxidation. Due to the presence of an ester in our substrate, we wanted to minimize exposure to strong base. We tried conditions described by Hazra[18] using tetradecyltrimethylammonium permanganate (TDTAP), which included 0.1 equiv of potassium hydroxide. This produced **8** in an 8:1 mixture in 71% yield. The reaction also worked without the addition of the base and gave a similar ratio and yield. Potassium permanganate with 18-crown-6 ether[19] in dichloromethane gave a 6:1 mixture in 94% yield. We found the most practical conditions to be potassium permanganate in acetone with or without 10% triethylamine to give a 12:1 ratio. After an aqueous workup, the solid residue was recrystallized to give the pure D-isomer diol **8** in 67% yield from the crude alkene mixture without any chromatography.

With the diol ester **8** in hand, our first approach[10] was to selectively benzoylate the secondary C-3 hydroxyl (71%) and then use a DAST fluorination of the C-2 tertiary alcohol (68%). The acyclic ester could then be cyclized to form the desired ribonolactone (58%). Alternatively, the acyclic ester could be first cyclized with acid to form the arabinolactone, then selectively dibenzoylated on the C-3,5 (55% two-step yield) and finally treated with DAST (51%) to afford the same ribonolactone. Although these routes were an improvement over the D-xylose route, we observed that the yields of the DAST mediated fluorinations fell as the scale increased and there were still multiple chromatographic separations required. Consequently, we searched for alternative scalable fluorination methods that could be used with **8**. Gao and Sharpless[20] reported efficiently opening cyclic sulfates of 1,2 diols with nucleophiles including fluoride. Interestingly, opening cyclic sulfates from diols derived from α,β-unsaturated esters resulted in a high selectivity for the α-position. Furthermore, Avenoza[21] et al. observed that a cyclic sulfate substituted with an ester and methyl on the α-carbon and unsubstituted on the β-carbon was opened by azide at the more hindered α-position in a 4.5:1 ratio over the β-position. These observations led us to try this approach on **8**.[22]

Although the cyclic sulfate **9** could be made directly with sulfuryl chloride or 1,1′-sulfonyldiimidazole, we found higher and more reproducible yields using the two-step method of first making the cyclic sulfite with thionyl chloride and then further oxidizing to the cyclic sulfate with catalytic ruthenium trichloride and sodium periodate[20] or with catalytic TEMPO and sodium hypochlorite. After an aqueous workup, **9** could be used without further purification. We explored a number of nucleophilic fluorinating reagents and conditions. In the tetraalkylammonium fluoride series, tetrabutylammonium fluoride led to some hydrolysis of the ester. Tetramethylammonium fluoride worked well, but solubility limited the reaction concentration. Tetraethylammonium fluoride hydrate in acetonitrile or dioxane worked best in the series. No fluorinated C-3 regioisomer could be observed by ^{1}H NMR of the crude product **10**. The reaction mixture was used directly in the next step.

Hydrolysis of a sulfate ester in the presence of an ester and acetonide was reported by Kim and Sharpless[23] using catalytic concentrated sulfuric acid and 0.5 to 1.0 equiv of water in THF. In our case, the reaction did not proceed to completion. We could perform a global deprotection and lactonization by adding Dowex 50Wx2−200 resin to give directly crude lactone **3**, but the resulting product mixture required chromatographic separation. We found that hydrolysis of the sulfate could be accomplished while maintaining the acetonide by treating the crude reaction mixture with concentrated hydrochloric acid in 2,2-dimethoxypropane. After an aqueous wash that removed most of the impurities, the resulting acyclic product **11** was dissolved in ethanol and treated with concentrated hydrochloric acid. Upon concentration, the lactone product **3** presented as a white solid in 67% yield from the diol **8**. This was benzoylated in pyridine and then diluted with water to give **12** as a solid in 70% yield.

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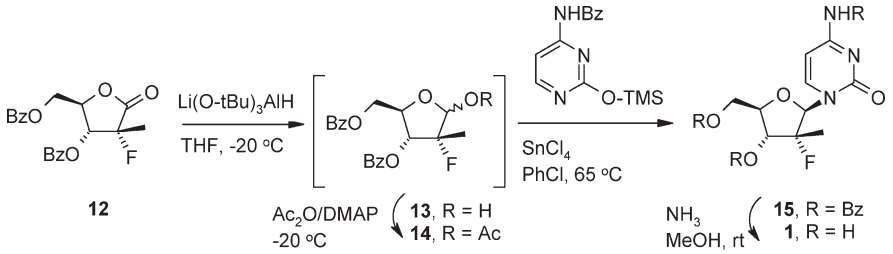
SCHEME 3. Synthesis of PSI-6130



There was some yield loss due to hydrolysis during the isolation. Structure **12** could also be isolated chromatographically in 91% yield.

Reduction of ribonolactone **12** to the ribonolactol **13** (Scheme 3) required a hindered reducing reagent to minimize over-reduction to the acyclic 1,4-diol. Titration with lithium tri-*tert*-butoxyaluminum hydride maximized production of **13** in a 2:1 β/α anomeric ratio. Clark reported coupling the 1-*O*-benzoyl derivative of **13** with silylated N^4-benzoylcytosine using stannic chloride catalyst in acetonitrile to give an even mixture of anomers. After screening a number of coupling conditions and reagents, improved results were obtained by the coupling the 1-*O*-acetate of ribonolactol (**14**) and changing the solvent and temperature to chlorobenzene at 65 °C to give a 4:1 ratio of the β/α anomers. A possible explanation for the increased β selectivity in the nonpolar chlorobenzene solvent is enhanced coordination of the tin catalyst with the C-2 fluoro and C-1 chloro on the α-face and thus favoring attack from the β-face. The β/α anomeric ratio of **14** had no influence on the anomeric ratio of the subsequent nucleosides under the Lewis acid mediated coupling conditions. For the process run, the crude lactol **13** was converted to **14** and used directly for coupling to form **15**. After filtering off the tin salts, the pure β-anomer crystallized out of a methanolic solution of the reaction mixture in 29% yield from protected lactone **12**. Deprotection of **12** to the target nucleoside could be readily accomplished in methanolic ammonia to give the product PSI-6130 (**1**) as a pure solid in 88% yield. The resulting product was identical in all respects with the discovery synthesis product.

Conclusion

In summary, we developed an efficient, diastereoselective, and scalable synthesis of the nucleoside HCV NS5B inhibitor, PSI-6130. We started from a protected three-carbon synthon with a single chiral center and created three additional contiguous chiral centers without the use of chiral reagents or catalysts. For the key C-2′ fluorinated quaternary center, we used a nucleophilic fluoride reagent to open a cyclic sulfate in a highly regio- and stereoselective manner. There were three solid intermediates that could be isolated after multiple steps: diol **8** (53%), protected lactone **12** (47%), and protected product **15** (29%). No chromatography was used throughout the process to produce pure final product **1** in 6.4% overall yield from (carbethoxyethylidene)triphenylmethylphosphorane. Further process development of this route led to the multikilogram clinical material production route[24] with the most notable improvement atz the glycosylation step (59%) and an overall yield over 20%.

Experimental Section

(2*S*,3*R*)-Ethyl 3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydroxy-2-methylpropanoate (8). (Carbethoxyethylidene)triphenylmethylphosphorane (66.2 g, 182.6 mmol) was dissolved in anhydrous dichloromethane (250 mL) and the solution was cooled to −40 °C with stirring under a nitrogen atmosphere. (*R*)-(+)-2,2-Dimethyl-1,3-dioxolane-4-carboxaldehyde (**6**, 25.0 g, 192.3 mmol) was dissolved in anhydrous dichloromethane (100 mL) and added to the reaction solution over 20 min at −40 °C. The stirred reaction mixture was allowed to warm to ambient temperature for 17 h. The mixture was concentrated under reduced pressure to dryness and the residue was suspended in *tert*-butyl methyl ether (200 mL). The suspension was filtered to remove triphenylphosphine oxide and the filtrate was concentrated under reduced pressure to afford 25.8 g of crude alkene (**7**) in 97:3 *E*/*Z* ratio by H NMR consistent with literature values.[12] The crude alkene **7** (15.0 g, 70.1 mmol) was dissolved in acetone (700 mL) at 0−5 °C. Potassium permanganate (13.24 g, 83.8 mmol) was added in one portion. After being stirred at 0−5 °C for 5 h, the reaction was quenched by the addition of saturated aq sodium sulfite (150 mL). After 30 min, a colorless suspension formed. The solid was removed by filtration and washed with ethyl acetate (200 mL). The filtrate was extracted with ethyl acetate (3 × 75 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a white solid reside as a 12:1 mixture of diol isomers by NMR. The residue was dissolved in warm ethyl acetate (30 mL). Hexanes (120 mL) was added slowly to form a precipitate. The solid was collected by filtration, washed with hexanes (2 × 50 mL), and dried under vacuum (0.2 mmHg, ambient temperature, 24 h) to give 11.2 g of white crystalline solid **8** (11.2 g, 53% from the phosphorane) as a single isomer by NMR, mp 75.0−75.5 °C. Optical rotation $[\alpha]^{25}_{D}$ +37.8 (*c* 0.50, EtOH). ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.23 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.28 (s, 3H, 2-CH_3), 3.66 (dd, 1H, J=7.4 Hz, 3-H), 3.80−3.89 (m, 2H, 5-H), 4.05 (dt, 2H, J=7.2 and 2 Hz, CH_2CH_3), 4.11 (q, 1H, J=6.4 Hz, 4-H), 4.90 (s, 1H, 2-OH), 5.09 (d, 1H, J = 7.4 Hz, 3-OH). ^{13}C NMR (DMSO-d_6) δ 14.73, 22.74, 26.23, 27.11, 61.00, 66.51, 75.44, 75.48, 77.35, 108.52, 175.33. IR (neat, cm^{-1}) 3271.45, 2984.72, 1724.80, 1456.12, 1370.25, 1292.13, 1254.14, 1207.58, 1141.85, 1043.18, 954.12, 895.63, 844.93. HR-MS calcd for $C_{11}H_{20}NaO_6$ (M + Na) 271.1160, obsd 271.1152.

((2*R*,3*R*,4*R*)-3-(Benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl Benzoate (12) [Common Name: 3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribono-γ-lactone]. To a stirred solution of diol **8** (7.2 g, 29.0 mmol) in anhydrous dichloromethane (80 mL) and triethylamine (12.1 mL, 87.1 mmol) at 0 °C was slowly added thionyl chloride (3.2 mL, 43.8 mmol). After 15 min, the reaction was diluted with dichloromethane (100 mL) and washed with cold water (2 × 50 mL) and brine (50 mL). The organic layer was concentrated under reduced pressure to roughly one-third the volume and

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then diluted with acetonitrile (100 mL). The solution was cooled to 0 °C and then TEMPO catalyst (44 mg) was added. A sodium hypochlorite solution (10−13% available chlorine, 79 mL) was added and the reaction was stirred vigorously at 0 °C for 20 min and then at ambient temperature for 1 h. The upper organic layer was separated and dried over sodium sulfate, filtered, concentrated under reduced pressure, coevaporated with dichloromethane (2 × 50 mL), and dried (0.2 mmHg, ambient temperature, 17 h) to 8.2 g of crude cyclic sulfate (**9**). In turn, this was dissolved in anhydrous dioxane (100 mL). Tetraethylammonium fluoride hydrate (6.5 g, 37 mmol) was added and the mixture was heated to 100 °C for 1 h and then cooled to ambient temperature. 2,2-Dimethoxypropane (100 mL), followed by conc. aq hydrochloric acid (6 mL) were added and the mixture was stirred for 3 h at ambient temperature. The reaction was diluted with ethyl acetate (100 mL) and then washed with cold saturated aq sodium bicarbonate (2×50 mL) and brine (2×50 mL). The combined aqueous layer was back-extracted with ethyl acetate (50 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude acyclic **11** as a semisolid (5.1 g). This was dissolved in reagent ethanol (50 mL) and conc. aq hydrochloric acid (1 mL). The resulting solution was stirred at ambient temperature for 15 h and then concentrated under reduced pressure followed by coevaporations with toluene (5 × 15 mL) to give the unprotected lactone **3** as a white solid (3.2 g). Compound **3** was combined with other lots made in a similar way for a total of 15.0 g (91.5 mmol). This was dissolved in anhydrous pyridine (150 mL). Benzoyl chloride (42 mL, 362.16 mmol) was added slowly over 5 min at 0−5 °C. The resulting reaction mixture was stirred at ambient temperature for 25 min, then water was added (50 mL) and the mixture was stirred for 5 min to form a suspension. The precipitated product was collected by filtration. The filter cake was suspended in cold water (200 mL), and the solid was collected. This was repeated three times followed in the last run by washing a minimal amount of methanol. The filter cake was dried (0.2 mmHg, ambient temperature, 17 h) to give **12** as a white solid (24.0 g, 70% from **3**, 47% from **8**), mp 137.2−137.8 °C. Optical rotation $[\alpha]^{25}{}_{D}$ +131 (*c* 0.50, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 1.68 (d, 3H, J = 24.2 Hz, CH_3), 4.62−4.74 (m, 2H, H-5, 5′), 5.11−5.15 (m, 1H, H-4), 5.76 (dd, 1H, J = 7.0, 18.4 Hz, H-3), 7.46 (m, 2H, *m*-Ar), 7.55 (m, 2H, *m*-Ar), 7.62 (m, 1H, *p*-Ar), 7.70 (m, 1H, *p*-Ar), 7.93 (m, 2H, *o*-Ar), 8.06 (m, 2H, *p*-Ar), 8.08 (m, 2H, Ar). ^{13}C NMR (DMSO-d_6) δ 18.69 (d, J = 24.3 Hz), 63.90, 72.53 (d, J = 7.0 Hz), 78.30, 92.38 (d, J = 183.5 Hz), 128.95, 129.43, 129.59, 129.67, 130.00, 133.36, 134.32, 134.81, 165.47, 165.94, 170.24 (d, J = 21.4 Hz). IR (neat, cm^{-1}) 1724.96, 1454.88, 1370.30, 1291.90, 1207.60, 1140.99, 1069.90, 1043.33, 953.48, 845.22. HR-MS calcd for $C_{20}H_{17}O_6FLi$ 1(M + Li) 379.1169, obsd 379.1151.

(2*R*,3*R*,4*R*,5*R*)-5-(4-Benzamido-2-oxopyrimidin-1(2*H*)-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl Benzoate (15) [Common Names: 3′,5′-*O*-*N*^{4}-Tribenzoyl-2′-deoxy-2′-fluoro-2′-*C*-methylcytidine and 1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranosyl)-*N*^{4}-benzoylcytosine]. Protected lactone **12** (23.0 g, 61.8 mmol) was dissolved in anhydrous tetrahydrofuran (500 mL) and the solution was cooled to −20 °C under a nitrogen atmosphere. Lithium tri-*tert*-butylaluminum hydride (1.0 M in THF, 75 mL, 75 mmol) was added in over 15 min with stirring while maintaining the temperature at −20 °C. After 5 h, based on TLC, an additional amount of the hydride (10 mL) was added. After 1.5 h more, the reaction was complete to give lactol **13**. To the reaction mixture were added DMAP (7.5 g, 62 mmol) and acetic anhydride (58.1 g, 569 mmol) and the reaction was stirred at −20 °C for 2 h. The reaction was diluted with ethyl acetate (400 mL) and water (200 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layer was washed with water (3×150 mL) and brine (150 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and coevaporated with toluene (2×100 mL) to give the crude acetate **14** as clear brown oil. The oil was poured onto a plug of silica gel (50 g) in a sintered glass Buchner funnel and eluted with 20% ethyl acetate in hexanes until all the acetate was recovered. The solution of the acetate **14** was concentrated under reduced pressure to a colorless, thick oil (32 g) in roughly 2:1 β/α anomers as determined by NMR in DMSO-d_6. Silylated base was prepared by heating to reflux a suspension of *N*-benzoylcytosine (19.39 g, 90.14 mol) and ammonium sulfate (300 mg) in hexamethyldisilazane (200 mL) for 6 h and concentrating the resulting solution by vacuum distillation under aspiration, followed by drying under vacuum (0.2 mmHg) for 2 h at ambient temperature. The oily residue was dissolved in chlorobenzene (250 mL). To this solution was added a portion (25.0 g) of the semipurified acetate **14** and neat tin(IV) chloride (31 mL, 265 mmol). After stirring under a nitrogen atmosphere for 2 h at ambient temperature, the reaction was heated to 60−70 °C for 19 h. The reaction mixture was cooled to 0 °C and solid sodium bicarbonate (96 g, 1.14 mol) and ethyl acetate (500 mL) were added. To the stirred solution was slowly added water (20 mL) (**caution**: vigorous evolution of carbon dioxide). After the mixture was stirred for 30 min at ambient temperature, the suspension was filtered and the collected solid was washed with ethyl acetate (200 mL). The filtrate was washed with water and brine (2×250 mL each), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a pale yellow-brown solid. Methanol (250 mL) was added and the mixture was heated under reflux for 30 min thencooled to ambient temperature, and the resulting precipitate was collected by filtration, washed with methanol (2 × 30 mL), and dried (0.2 mmHg, 24 h, ambient temperature) to give **15** as a white solid (8.0 g, 29% from lactone **12**), mp 240−241 °C. ^{1}H NMR ($CDCl_3$) δ 1.47 (d, 3H, J = 22.3 Hz, CH_3), 4.63 (dd, 1H, J = 2.8, 12.7 Hz, H-5′), 4.72 (d, 1H, J = 9.4 Hz, H-4′), 4.87 (d, 1H, J = 12.7 Hz, H-5″), 5.55 (br dd, 1H, 8.4, 20.9 Hz, H-3′), 6.50 (br d, 1H, J = 16.8 Hz, H-1′), 7.41−7.55 (m, 7H, Ar and H-5), 7.61−7.69 (m, 3H, Ar), 7.88 (d, 1H, J = 6.8 Hz, H-6), 8.06−8.10 (m, 5H, Ar), 8.65 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 17.19 (d, J = 25.8 Hz), 61.75 (s), 71.88 (s), 90.20 (br s), 96.98 (br s), 100.08 (d, J = 197 Hz), 127.51, 128.34, 128.65, 128.83, 129.14, 128.37, 129.54, 130.12, 132.80, 133.38, 133.78, 134.02, 143.80 (br s), 154.30, 157.50, 162.51, 165.43, 165.95. IR (neat, cm^{-1}) 1726.99, 1485.04, 1314.13, 1254.93, 1090.94, 1024.45, 708.53. HR-MS calcd for $C_{31}H_{27}FN_3O_7$ (M + H) 572.1838, found 572.1828.

4-Amino-1-((2*R*,3*R*,4*R*,5*R*)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one (1) [Common Names: 2′-Deoxy-2′-fluoro-2′-*C*-methylcytidine and 1-(2-Deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranosyl)cytosine]. Protected nucleoside **15** (16.7 g, 30.8 mmol) was suspended in methanolic ammonia (7 M, 750 mL). The mixture was stirred at atmospheric pressure at ambient temperature for 12 h, then concentrated under reduced pressure to a yellow solid. Tetrahydrofuran (400 mL) was added and the suspension was heated under reflux with stirring for 30 min and then allowed to cool to ambient temperature. The resulting solid was collected by filtration, washed with methanol (2× 100 mL), and dried (0.2 mmHg, 24 h, ambient temperature) to give 6.7 g of **1** (88% from 15) as an off-white powder, mp 218−219 °C. Optical rotation $[\alpha]^{25}{}_{D}$ +128.6 (0.50, water). TLC and spectral data matched the authentic standard.[6] ^{1}H NMR (DMSO-d_6) δ 1.15 (d, 3H, J = 22.5 Hz, CH_3), 3.62 (m, 1H, H-5′), 3.78 (m, 3H, H-3′, H-4′, H-5″), 5.20 (br s, 1H,

3′-OH), 5.56 (d, 1H, $J = 4.8$ Hz, 5′-OH), 5.72 (d, 1 H, $J = 7.6$ Hz, H-5), 6.08 (d, $J = 19.2$ Hz, H-1′), 7.26 (s, 2H, NH_2), 7.86 (d, 1H, $J = 7.4$ Hz., H-6). ^{13}C NMR (DMSO-d_6) δ 17.08 (d, $J = 25.8$ Hz), 59.19 (s), 71.21 (d, $J = 17.6$ Hz), 81.95 (s), 89.17 (d, $J = 40.5$ Hz), 94.96 (s), 100.85 (s), 102.65 (s), 140.95 (s), 155.86 (s), 166.21 (s). IR (neat, cm^{-1}) 3218.64, 1610.93, 1496.63, 1397.15, 1283.51, 1192.45, 1045.18, 1028.91, 842.98, 789.67, 706.70. LR-MS m/z 259. HPLC purity at 254 nm 99.9%.

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Supporting Information Available: General analytical methods and copies of ^1H and ^{13}C NMR spectra for compounds **8**, **12**, **15**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.