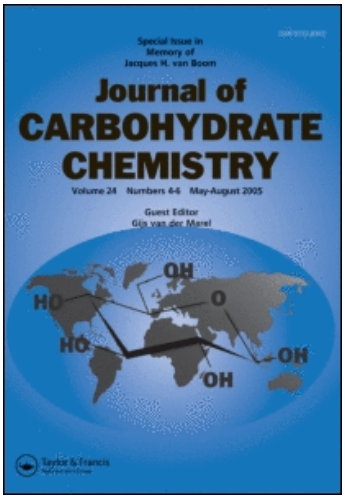

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Synthesis of 2-Deoxy-2-Fluoro-2-*C*-Methyl-D-Ribofuranoses

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Synthesis of 2-Deoxy-2-Fluoro-2-*C*-Methyl-D-Ribofuranoses

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The synthesis of methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside and the conversion to the corresponding 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose and 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose is reported. The key synthetic step is the fluorination of the tertiary center of methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside to provide methyl

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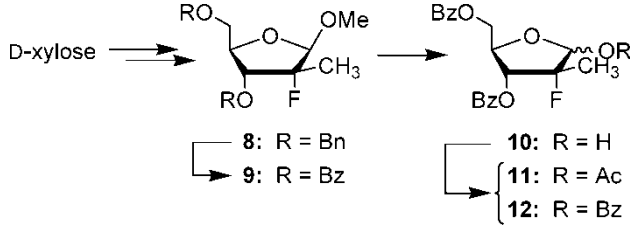
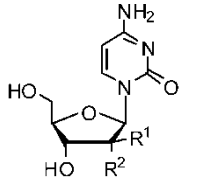
3,5-di-*O*-benzyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside.



Keywords Synthesis, Ribofuranoses, Fluorination, Oligonucleotides

Nucleoside analogs containing 2′-modifications are important not only as chemotherapeutic agents, but also as tools for studying the structure and function of oligonucleotides (Fig. 1). The synthesis of 2′,2′-difluorocytidine (**1**) was first reported in 1988 and, in 1996, this compound received FDA approval for the treatment of metastatic pancreas cancer.[1] 2′-Deoxy-2′-fluorocytidine (**2**) has shown in vitro activity against both DNA[2] and RNA viruses.[3,4] (2′*S*)-2′-Deoxy-2′-*C*-methylcytidine (SMDC) (**3**) demonstrated very potent in vitro cytotoxicity against several leukemia cancer cell lines[5] and has been used for studying the mechanism of the group II intron ribozyme due to its conformational similarity to RNA.[6] Several 2′-*C*-methylnucleosides, such as 2′-*C*-methylcytidine (**4**), have proven effective at inhibiting HCV RNA replication in vitro and the 3′-*O*-L-valinyl ester of **4** (NM283, valopicitabine) is currently in phase 2b clinical trials.[7] Additionally, 2′-*C*-methylribonucleosides have been utilized to varying degrees as biological probes for studying RNA and ribozyme function.[8]

Recently, the synthesis of 2′-deoxy-2′-fluoro-2′-C-methylcytidine was described starting from N^4-benzoyl-(2-*C*-methyl-3,5-di-O-benzoyl-β-D-arabinofuranosyl)cytosine.[9] While such a linear synthetic approach has the



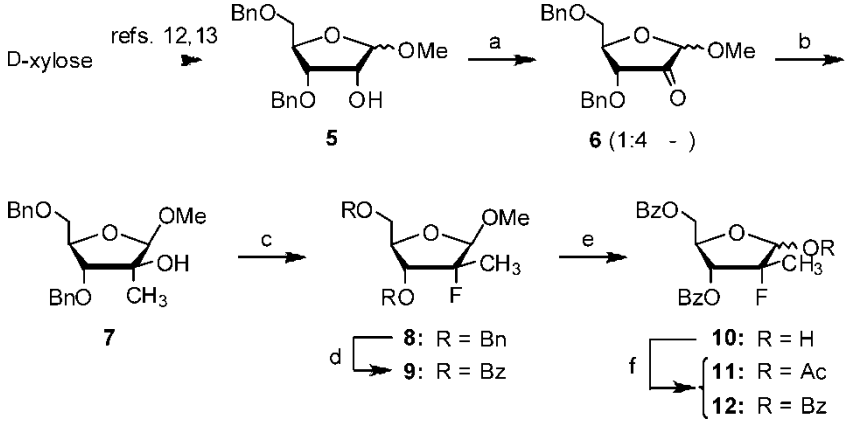
1: $R^1 = R^2 = F$
2: $R^1 = H$, $R^2 = F$
3: $R^1 = CH_3$, $R^2 = H$
4: $R^1 = CH_3$, $R^2 = OH$

Figure 1: Structures of several 2′-modified nucleosides.

advantage of avoiding the glycosylation reaction to a nucleobase, it does not provide the opportunity to prepare a wide variety of base-modified nucleoside analogs. In this regard, a more convenient approach to the preparation of these compounds is a convergent approach in which a protected 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose is prepared first and then used to glycosylate a variety of nucleobases. The synthesis of methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (**9**) and its conversion to 1-*O*-acetyl-3, 5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (**11**) and 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (**12**) is reported herein.

The major synthetic challenge for the synthesis of the 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranoses (**8**–**12**) is the stereoselective introduction of the fluorine atom at the 2-position. In the initial synthetic planning, the number of literature examples describing the nucleophilic fluorination of tertiary alcohols, particularly those desiring stereospecificity, were scarce. Of the few literature examples that describe the nucleophilic fluorination of tertiary alcohols, both inversion[10] and retention of configuration[11] were reported. For the synthesis of methyl 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (**8**), it was reasoned that the carbohydrate starting material, methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside (**7**), would not only serve to introduce the fluorine in the ribose configuration, but also minimize the number of stereocenters requiring assembly.

Methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside (**7**) was prepared in nine steps starting from D-xylose (Sch. 1). The intermediate methyl 3,5-di-*O*-benzyl-D-ribofuranoside (**5**) was obtained as an inseparable 1:4 α-β mixture by essentially the same procedure described by Ritzmann et al.[12] A few minor changes from the procedure of Ritzmann allowed for the preparation of



Scheme 1: Reagents and conditions: (a) TEMPO, NaOCl, 0°C; (b) MeLi, Et_2O, −78°C; (c) DAST, CH_2Cl_2, rt; (d) (i) Pd/C, cyclohexene, reflux, (ii) BzCl, pyridine; (e) ~80% HCO_2H, 60–70°C; (f) Ac_2O or BzCl, TEA, CH_2Cl_2.

compound **5** using no column chromatography. For example, a 4-chlorobenzoyl protecting group was used to protect the 5-hydroxyl group rather than the methoxycarbonyl group used by Ritzmann and a catalytic TEMPO oxidation was found more effective than a ruthenium tetraoxide oxidation.[13] Additionally, the same catalytic TEMPO oxidiation was successful for the conversion of **5** to **6**; however, a slightly larger excess of TEMPO and sodium hypochlorite was required.

The majority of the synthetic efforts for introducing 2-*C* alkyl groups on carbohydrates have focused on the addition of the alkyl group from the β-face of the furanose ring.[14–17] However, since the anomeric mixture of ketone **6** consisted of $\sim$80% of the desired β-anomer, it was anticipated that methyl lithium addition should proceed from the α face of the furanose ring to provide **7** as the major product. Accordingly, treating the anomeric mixture of 2-ketone (**6**) with methyl lithium at -78°C provided a reaction mixture from which the desired methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside (**7**) was isolated in 78.3%. The identification and isolation of the minor diastereomers from the crude reaction mixture was difficult due to the presence of the α-anomer. Therefore, the stereoselectivity for the β-anomer was not determined. The structure of **7** was supported by nuclear Overhauser enhancement (NOE) ^{1}H NMR difference spectroscopy (Fig. 2). Irradiation of the 2-*C*-CH_3 resonance (s, δ 1.40) resulted in large enhancements of H-4 (m, δ 4.03), H-1 (s, δ 4.48), and the diastereotopic benzyl methine protons (d, δ 4.83).

Treating **7** with DAST in CH_2Cl_2 provided a complex reaction mixture from which methyl 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (**8**) was isolated in 20% yield. The regiochemistry and the stereochemistry of the fluorination was determined by ^{1}H and ^{13}C NMR. Since several rearrangements have been reported in the DAST fluorination of pentofuranoses, it was necessary to ensure that the fluorination had proceeded regioselectively.[18,19] Analysis of the ^{1}H and ^{13}C NMR spectra revealed the anticipated ^{19}F couplings arising from a C-2 fluorinated product. The three ^{19}F, ^{1}H couplings that were evident in the ^{1}H NMR spectrum of compound **8** were a doublet at δ 1.43 (2-CH_3), a doublet of doublets at δ 3.87 (H-3), and a doublet at δ 4.72 (H-1). The four observed ^{13}C multiplicties arising from ^{19}F coupling were a doublet at δ 17.0 (2-CH_3), a doublet at δ 81.1 (C-3), a doublet at δ 99.7 (C-2), and a

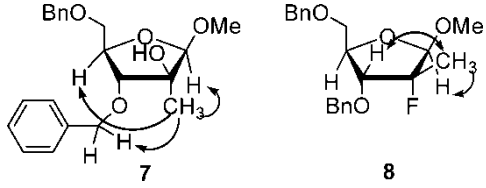


Figure 2: ^{1}H NMR NOE correlations of compounds **7** and **8**.

doublet at δ 106.7 (C-1). Additionally, the presence of the C-2 fluorine was further supported by the significant low-field shift in the C-2 ^{13}C resonance due to an α effect (δ 99.7 for **8** vs. δ 79.5 for **7**).[20] The stereochemistry of the DAST fluorination was determined by NOE ^{1}H NMR difference spectroscopy (Fig. 2). For compound **8**, relatively large NOEs were observed between the 2-CH_3 and H-3 and, to a lesser extent, between the 2-CH_3 and H-1.

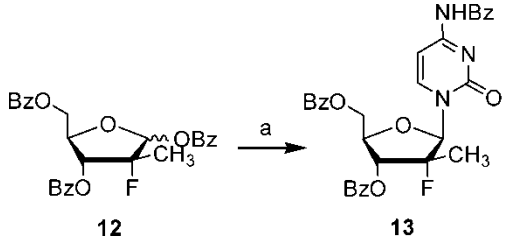
The benzyl protecting groups of **8** were removed using transfer hydrogenolysis (Pd/C, cyclohexene) and replaced with benzoyl protecting groups to provide methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (**9**). Formic acid cleavage of furanoside **9** at 60 to 70°C provided **10** that was acylated to provide anomeric mixtures of 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (**11**) and 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (**12**) in 85.6% and 88.7% yield, respectively (Sch. 2).

Vorbrüggen condensation of **12** with silylated N^4-benzoylcytosine was achieved as described by Harry-O'kuru et al.[15,17] Condensation of **12** with the preformed bis(trimethylsilyl)N^4-benzoylcytosine in acetonitrile/$SnCl_4$ at 50 to 55°C provided **13** in 70% yield as an ~1:1 α-β mixture. The pure β-anomer was isolated in 37% yield from the crude anomeric mixture by silica gel chromatography. The structure of the β-anomer obtained from the glycosylation was identical to the N^4-benzoyl-1-(3′,5′-di-*O*-benzoyl-2′-fluoro-2′-*C*-methyl)cytidine (**13**) prepared by the linear approach.[9]

In summary, the synthesis of the novel carbohydrate building blocks needed for making a variety of base modified 2′-fluoronucleosides is described. This approach should provide numerous diverse 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose nucleosides for HCV structure-activity relationship studies in addition to mechanistic studies related to RNA.

EXPERIMENTAL

All reagents and anhydrous solvents were purchased from Aldrich or Acros and were used as received. ^{1}H, ^{19}F, and ^{13}C NMR spectra were obtained with a Varian Unity Plus 400 spectrometer at 400, 376, and 100 MHz, respectively.



12 13

Scheme 2: Reagents and conditions: (a) bis(trimethylsilyl)N^4-benzoylcytosine, $SnCl_4$, MeCN, 50–55°C, 4 h.

^{1}H and ^{13}C NMR chemical shifts are reported as δ (ppm) downfield with respect to an internal standard of tetramethylsilane, while ^{19}F chemical shifts are reported downfield from an external standard of hexafluorobenzene. Atlantic Microlab, Inc. of Norcross, GA provided the elemental analysis.

Methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside (7). Compound **6** (7.70 g, 22.5 mmol) was dissolved in anhydrous diethyl ether and cooled to −78°C. To this solution was added MeLi (30 mL, 1.6 M in diethyl ether) dropwise over 5 min. After the reaction was complete, the mixture was treated cautiously with ammonium chloride (1M, 65 mL) and the mixture was warmed to rt and stirred for 1 h. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated to dryness. Silica gel chromatography eluting with 1:4 EtOAc-hexanes followed by crystallization from diethyl ether-hexanes afforded pure **7** (6.31 g, 78.3%). mp 48.0–50.5°C. ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H, 2-CH_3), 2.93 (s, 1H, OH), 3.40 (s, 3H, OCH_3), 3.49 (dd, 1H, $J = 6.9$, 10.3 Hz, H-5), 3.57 (dd, 1H, $J = 3.9$, 10.3 Hz, H-5a), 3.83 (d, 1H, $J = 7.3$ Hz, H-3), 4.03 (m, 1H, H-4), 4.48 (s, 1H, H-1), 4.58 (m, 3H, OCH_2Ph), 4.83 (d, 1H, $J = 11.6$ Hz, OCH_2Ph), 7.30–7.35 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ 18.4, 55.4, 72.2, 73.4, 79.5, 80.2, 84.7, 107.4, 127.7, 127.8, 127.83, 128.5, 138.2, 138.3. Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.25; H, 7.18.

Methyl 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (8). Compound **7** (3.50 g, 9.76 mmol) was dissolved in CH_2Cl_2 (40.0 mL) and treated with DAST (4.0 mL, 30.3 mmol) at rt under argon. The solution was stirred at rt overnight. The so-obtained mixture was poured into sat $NaHCO_3$ (100 mL) and washed with sat $NaHCO_3$ (1 × 15 mL) until gas evolution ceased. The organic layer was then washed with water (1 × 25 mL). Silica gel chromatography (1:5 EtOAc-hexanes) gave **8** (0.671 g, 19.3%) that was sufficiently pure for the next step. An analytical sample was obtained by further silica gel chromatography. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, 3H, $J = 22.8$ Hz, 2-CH_3), 3.35 (s, 3H, OCH_3), 3.49 (dd, 1H, $J = 5.4$, 10.5 Hz, H-5), 3.55 (dd, 1H, $J = 4.1$, 10.5 Hz, H-5a), 3.87 (dd, 1H, $J = 7.5$, 23.5 Hz, H-3), 4.26 (m, 1H, H-4), 4.56 (d, 2H, $J = 6.9$ Hz, OCH_2Ph), 4.66 (d, 2H, $J = 8.2$ Hz, OCH_2Ph), 4.72 (d, 1H, $J = 10.8$ Hz, H-1), 7.29–7.36 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$): δ 17.0 (d, $J = 24.4$ Hz), 55.1, 71.0, 73.3, 73.7, 80.2, 81.1 (d, $J = 15.5$ Hz), 99.7 (d, $J = 179.3$ Hz), 106.7 (d, $J = 32.5$ Hz), 127.7, 128.0, 128.2, 128.3, 128.5, 128.6, 137.7, 138.2. ^{19}F NMR ($CDCl_3$): δ −3.3 (m, 1F). Anal. Calcd. for $C_{21}H_{25}FO_4$: C, 69.98; H, 6.99. Found: C, 70.03; H, 7.04.

Methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (9). Compound **8** (0.39 g, 1.1 mmol) was dissolved in 1:2 EtOH-EtOAc and treated with Pd/C (∼0.1 g) and cyclohexene (∼1 mL). The mixture was

heated under reflux overnight and then filtered through celite. The solvent was removed in vacuo and the residue was dissolved in pyridine (5.0 mL). To this solution was added benzoyl chloride (0.22 mL, 1.83 mmol) and the mixture was stirred at rt overnight. The pyridine was removed in vacuo and the residue was partitioned between CH_2Cl_2 and satd $NaHCO_3$ (10.0 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solution was concentrated to dryness. Column chromatography eluting with 1:5 EtOAc-hexanes provided pure **9** (0.350 g, 83.3% for 2 steps). ^{1}H NMR ($CDCl_3$): δ 1.53 (d, 3H, $J = 22.4$ Hz, 2-CH_3), 3.39 (s, 3H, OCH_3), 4.46 (dd, 1H, $J = 4.7$, 11.6 Hz, H-5), 4.58 (m, 1H, H-4), 4.65 (dd, 1H, $J = 3.9$, 11.6 Hz, H-5a), 4.87 (d, 1H, $J = 9.8$ Hz, H-1), 5.64 (dd, 2H, $J = 7.8$, 24.1 Hz, H-3), 7.37 (app t, 2H, $J = 9.8$ Hz, Ph), 7.47 (app t, 2H, Ph), 7.53 (app t, 1H, $J = 7.3$ Hz, Ph), 7.61 (app t, 1H, Ph), 8.02 (d, 2H, $J = 8.3$ Hz, Ph), 8.10 (d, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 16.6 (d, $J = 23.5$ Hz), 55.3, 64.7, 75.0 (d, $J = 14.3$ Hz), 78.0, 99.7 (d, $J = 180.1$ Hz), 106.8 (d, $J = 31.8$ Hz), 128.3, 128.5, 128.9, 129.0, 129.7, 129.8, 130.0, 130.6, 133.0, 133.7, 134.6, 165.8, 166.1. ^{19}F NMR ($CDCl_3$): δ -2.65 (m, 1F). Anal. Calcd. for $C_{21}H_{21}FO_6$: C, 64.94; H, 5.45. Found: C, 64.87; H, 5.32.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (10). Compound **9** (0.540 g, 1.39 mmol) was dissolved in formic acid (25.0 mL, 95–98%) and diluted with water (5.0 mL). The resulting solution was heated at 60–70°C for 2 days whereby TLC (1:3 EtOAc-hexanes) showed starting material (R_f 0.6) in addition to single, more polar component (R_f 0.4). The solvent was removed in vacuo, coevaporated with toluene (4× 5 mL), and chromatographed on silica gel using a gradient of 1:8 to 1:4 EtOAc-hexanes to provide an anomeric mixture of **10** as a syrup (0.271 g, 52.1%). ^{1}H NMR ($CDCl_3$): δ 1.58 (d, 3H, $J = 22.6$ Hz, 2-CH_3), 1.59 (d, 1H, $J = 22.8$ Hz, 2-CH_3), 3.45 (s, 1.3H, OH), 4.42–4.69 (m, 4H, H-5, H-4, H-1), 5.28 (m, 0.3H, H-4), 5.34 (dd, 1H, $J = 2.8$, 9.6 Hz, H-5a), 5.41 (dd, 0.3H, $J = 8.2$, 19.0 Hz, H-3), 5.65 (dd, 1H, $J = 7.4$, 23.4 Hz, H-3), 7.34–7.39 (m, 3H, Ph), 7.44–7.54 (m, 4H, Ph), 7.60–7.63 (m, 1H, Ph), 7.97–8.02 (m, 3H, Ph), 8.08–8.11 (m, 3H, Ph). Anal. Calcd. for $C_{20}H_{19}FO_6 \cdot 0.1H_2O$: C, 63.86; H, 5.14. Found: C, 63.89; H, 5.30.

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (11). A solution of **10** (0.042 g, 0.112 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was treated sequentially with TEA (0.02 mL, 0.157 mmol) and Ac_2O (0.014 mL, 0.146 mmol). After stirring overnight at rt, the solvent was removed in vacuo and the residue was purified by column chromatography eluting with a gradient of 1:20 to 1:10 EtOAc-hexanes. Compound **11** was isolated as a colorless syrup (0.040 g, 85.6%) containing a 4:1 α-β mixture. ^{1}H NMR ($CDCl_3$): δ 1.53 (d, 3H, $J = 22.3$ Hz, 2-CH_3), 1.72 (d, $J = 22.4$ Hz, 12H, 2-CH_3), 1.98 (s, 3H, $COCH_3$), 2.19 (s, 12H, $COCH_3$), 4.44 (dd, 1H, $J = 4.4$,

12.0 Hz, H-5), 4.56 (dd, 4H, $J = 4.8$, 12.3 Hz, H-5a), 4.63–4.72 (m, 5H, H-5, H-4), 4.73–4.79 (m, 4H, H-5a, H-4), 5.27 (app t, 4H, $J = 5.9$, 11.7 Hz, H-3), 5.69 (dd, 1H, $J = 8.2$, 23.7 Hz, H-3), 6.19 (d, 4H, $J = 2.0$ Hz, H-1), 6.23 (d, 1H, $J = 9.7$ Hz, H-1), 7.35–7.50 (m, 20H, Ph), 7.52–7.63 (m, 10H, Ph), 8.02 (d, 10H, $J = 7.5$ Hz, Ph), 8.09 (d, 10H, $J = 7.5$ Hz, Ph). ^{13}C ($CDCl_3$): δ 16.58 (d, $J = 23.8$ Hz), 21.0, 21.1, 22.05 (d, $J = 25.4$ Hz), 22.8, 73.8 (d, $J = 14.8$ Hz), 74.2 (d, $J = 15.7$ Hz), 78.8, 80.5, 94.4 (d, $J = 206.7$ Hz), 98.5, (d, $J = 35.1$ Hz), 98.3 (d, 1H, $J = 18.4$ Hz), 98.2, 98.3, 98.4, 98.7, 128.4, 128.6, 128.65, 128.7, 129.0, 129.5, 129.8, 130.0, 130.2, 133.3, 133.4, 133.8, 134.0, 165.8, 166.2, 169.7. ^{19}F NMR ($CDCl_3$): δ −4.89 (m, α anomer), −2.90 (m, β anomer). Anal. Calcd. for $C_{22}H_{21}FO_7$: C, 63.46; H, 5.08. Found: C, 63.56; H, 5.04.

1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranose (12). This compound was prepared and purified by the same method described for **11** except that benzoyl chloride was used as the acylating agent. Starting with compound **10** (0.202 g, 0.540 mmol) provided **12** as a syrup (0.229 g, 88.7%). ^{1}H NMR ($CDCl_3$): δ 1.79 (d, 3H, $J = 22.4$ Hz, 2-CH_3), 4.62 (dd, 1H, $J = 4.8$, 12.4 Hz, H-5), 4.73 (dd, 1H, $J = 3.6$, 12.4 Hz, H-5a), 4.85 (m, 1H, H-4), 5.34 (dd, 1H, $J = 4.0$, 5.2 Hz, H-3), 6.42 (s, 1H, H-1), 7.41–7.48 (m, 6H, Ph), 7.55–7.63 (m, 3H, Ph), 8.02–8.05 (m, 2H, Ph), 8.11–8.14 (m, 4H, Ph). Anal. Calcd. for $C_{27}H_{23}FO_7$: C, 67.78; H, 4.85. Found: C, 67.59; H, 4.81.

N^4-Benzoyl-1-(3′,5′-di-*O*-benzoyl-2′-fluoro-2′-*C*-methyl)cytidine (13). Compounds **13-β** and **13-α** were prepared following known literature methods.[15,17] N^4 benzoylcytosine (0.150 g, 0.69 mmol) was silylated as previously described and treated with a solution of **12** (0.22 g, 0.46 mmol) in anhydrous MeCN (5 mL) with stirring under argon.[8] Stannic chloride (0.12 mL, 0.85 mmol) was added slowly and the resulting solution was placed in an oil bath maintained at 50–55°C for 4 h. The crude reaction was diluted with EtOAc (10 mL) and quenched with saturated $NaHCO_3$ (25.0 mL). The organic layer was separated, washed with brine (10.0 mL), dried (Na_2SO_4), and concentrated to dryness. Analysis of the crude reaction mixture by ^{1}H NMR indicated a 1:1 α-β mixture that was purified by silica gel chromatography eluting with 1:1 EtOAc-hexanes to afford compound **13-β** (0.097 g, 37.0%) as a white solid. Further elution gave compound **13-α** (0.088 g, 33.0%) as a clear glass. Analytical samples were obtained by crystallization from the indicated solvents. The ^{1}H NMR of compound **13-β** was identical to that obtained by the linear approach starting from cytidine.

N^4-Benzoyl-1-(3′,5′-di-*O*-benzoyl-2′-fluoro-2′-*C*-methyl)cytidine (13-α) (α anomer). mp 174–175°C (CH_2Cl_2-hexanes), ^{1}H NMR ($CDCl_3$): δ 1.67 (d, 3H, $J = 24.4$ Hz, 2′-CH_3), 4.54 (dd, 1H, $J = 4.2$, 12.2 Hz, H-5′), 4.75 (dd,

1H, $J = 3.4$, 12.2 Hz, H-5a′), 4.83–4.86 (m, 1H, H-4′), 5.75 (dd, 1H, $J = 9.2$, 22.4 Hz, H-3′), 6.62 (d, 1H, $J = 19.2$ Hz, H-1′), 7.39–7.63 (m, 9H, Ph), 7.90 (m, 3H, Ph), 8.00 (d, 2H, $J = 8.4$ Hz, Ph), 8.08 (d, 2H, $J = 8.8$ Hz, Ph), 8.71 (bs, 1H, NHPh). Anal. Calcd. for $C_{31}H_{26}FN_3O_7$: C, 65.14; H, 4.59; N, 7.35. Found: C, 65.10; H, 4.55; N, 7.25.

N^4-Benzoyl-1-(3′,5′-di-*O*-benzoyl-2′-fluoro-2′-*C*-methyl)cytidine (13-β) (β anomer). mp 239–241°C (CH_2Cl_2-hexanes), lit mp 241°C (CH_2Cl_2-hexanes).[9] Anal. Calcd. for $C_{31}H_{26}FN_3O_7$: C, 65.14; H, 4.59; N, 7.35. Found: C, 65.20; H, 4.63; N, 7.34.

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