7.5 Hz), 2.12 (1 H, m, H-3), 2.05 (3 H, s, OAc-Me), 1.64 (4 H, m), 1.40 (3 H, s, C-15 Me), 1.33 (3 H, d, J = 7.1 Hz, C-18 Me), 1.31 (2 H, m), 0.90 (3 H, d, J = 6.9 Hz, C-20 Me), 0.89 (3 H, t, J = 7.0 Hz). Compound 8 showed the following spectral characteristics: UV (MeOH) λ_{max} 237 nm (ϵ 6400); IR (CH_2Cl_2) 3580, 3050, 1780, 1730, 1370, 1240, 1170, 1015, 1000, 910 cm^{-1}; CIMS (NH_3), m/z (relative intensity) 503.5 (100) for $C_{28}H_{40}O_8$; HRMS (30 eV), m/z (relative intensity) 476.2810 (M^+ - CO, $C_{27}H_{40}O_7$, 11), 434.2681 (3), 360.1951 ($C_{21}H_{28}O_5$, 16), 176.0874 ($C_{11}H_{12}O_2$, 23), 166.0997 ($C_{10}H_{14}O_2$, 71), 124.0892 (81), 99.0812 (100); ^1H NMR (360 MHz, $CDCl_3$, 51 °C) δ 6.26 (1 H, d, J = 16.4 Hz, H-6), 5.76 (1 H, d, J = 16.4 Hz, H-7), 5.08 (1 H, dd, J = 7.6, 4.6 Hz, H-2), 5.00 (1 H, bs, H-16), 4.94 (1 H, bs, H-16), 4.87 (1 H, br t, J = 3.8 Hz, H-12), 4.26 (1 H, bs, H-9), 3.34 (1 H, t, J = 3.8 Hz, H-13), 2.81 (1 H, d, J = 3.8 Hz, H-14), 2.81 (1 H, q, J = 7.1 Hz, H-17), 2.32 (2 H, t, J = 7.3 Hz), 2.25 (1 H, m, H-3), 2.10 (3 H, s, OAc-Me), 1.95 (1 H, m, H-11), 1.84 (1 H, m, H-3), 1.63 (4 H, m), 1.32 (2 H, m), 1.31 (3 H, s, C-15 Me), 1.20 (3 H, d, J = 7.1 Hz, C-18 Me), 1.08 (3 H, d, J = 7.3 Hz, C-20 Me), 0.90 (3 H, t, J = 6.8 Hz). Product 9 showed the following spectral properties: UV (MeOH) λ_{max} 230 nm (ϵ 10500); IR (CH_2Cl_2) 3680, 3450-3400 br, 3050, 1780, 1735, 1370, 1185, 1070, 1035, 1000, 905 cm^{-1}; CIMS (NH_3), m/z (relative intensity), 424.2 ($M + NH_4^+$, 54), 406.5 (<1) for $C_{22}H_{30}O_7$; HRMS (20 eV), m/z (relative intensity) 378.2059 (M^+ - CO, $C_{21}H_{30}O_6$, 9), 336.1963 (5), 306.1472 ($C_{17}H_{28}O_5$, 32), 124.0890 (59), 109.0649 (59), 43.0194 (100); ^1H NMR (360 MHz, $CDCl_3$, 58 °C) δ 6.14 (1 H, d, J = 16.2 Hz, H-6), 5.83 (1 H, d, J = 16.2 Hz, H-7), 5.02 (1 H, m, H-2), 5.00 (1 H, bs, H-16), 4.97 (1 H, bs, H-16), 4.14 (1 H, d, J = 2.5 Hz, H-9), 3.87 (1 H, bs, H-12), 3.33 (1 H, dd, J = 4.2, 3.7 Hz, H-13), 2.95 (1 H, d, J = 3.7 Hz, H-14), 2.81 (1 H, ddd, J = 7.0 Hz, H-17), 2.41 (1 H, m, H-10), 2.11 (3 H, s, OAc-Me), 1.78 (1 H, m, H-11), 1.32 (3 H, s, C-15 Me), 1.18 (3 H, d, J = 7.0 Hz, C-18 Me), 1.03 (3 H, d, J = 7.5 Hz, C-20 Me). Following the identical procedure outlined above, solenolide A was refluxed for only 4 h. Upon workup, the product mixture was determined to be comprised of derivatives 7 (15.1 mg, 20% from 1) and 8 (32.5 mg, 43% from 1), with 31.0 mg (37%) of unreacted starting material remaining.

Conversion of Solenolide D (4) to Solenolide C (3). Following the same procedure described above, 15 mg (0.027 mmol) of compound 4 was refluxed in MeOH with 0.5 g of Zn/Cu couple for 4.5 h. Upon workup and HPLC purification, 12.5 mg (90% yield from 4) of a product, identical in all respects with solenolide C (3), was obtained.

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Synthesis of 2-Deoxy-2,2-difluoro-D-ribose and 2-Deoxy-2,2-difluoro-D-ribofuranosyl Nucleosides

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A program to synthesize fluorinated D-ribose and fluorinated nucleosides was initiated with hopes of finding compounds of potential value as anticancer and/or antiviral agents. Our approach is illustrated by a simple and stereocontrolled synthesis of 2-deoxy-2,2-difluoro-D-ribose. This was followed with the synthesis of a series of 1-(2-deoxy-2,2-difluororibofuranosyl)pyrimidine nucleosides. (*R*)-2,3-*O*-Isopropylideneglyceraldehyde was coupled with ethyl bromodifluoroacetate by using Reformatskii conditions to yield the carbon skeleton for the desired carbohydrate. Hydrolytic removal of the blocking groups with concomitant closure gave the γ-lactone 3. Reduction to the γ-lactol ultimately yielded 2-deoxy-2,2-difluoro-D-ribose (6). Functionalization of the difluoro carbohydrate with a leaving group at the anomeric position followed by displacement of the group with various pyrimidine bases yielded 1-(2-deoxy-2,2-difluororibofuranosyl)pyrimidine nucleosides.

The introduction of fluorine into a metabolite, such as a carbohydrate or a nucleoside, is a unique way of achieving distinctive modification with minimal disturbance of the overall stereochemistry. Replacing a hydrogen atom of the natural substrate with fluorine may alter the biochemical activity, producing a molecule that may inhibit one or more enzymes or be partly metabolized into an even more active substance. It has been argued that the van der Waals radii of the elements hydrogen (1.20 Å) and fluorine (1.35 Å) are sufficiently close to account for pseudosubstrate activity.[1]

A program was initiated to synthesize fluorinated D-ribose and fluorinated nucleosides with hopes of finding some unique biological activity. In recent years a renaissance of interest in the chemical synthesis of carbohydrates and functionalized nucleosides has occurred.[2] Our approach is illustrated by a simple and stereocontrolled synthesis of 2-deoxy-2,2-difluoro-D-ribose.[3] This was

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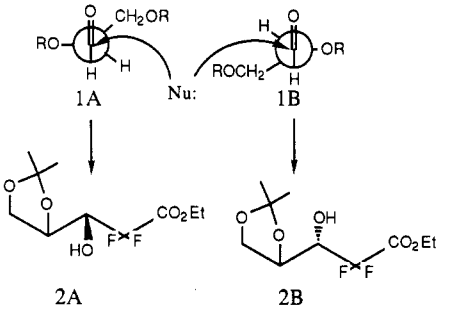
(2) For leading references, see: Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371-1373. Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515-3516. Minami, N.; Ko, S. S.; Kishi, Y. *Ibid.* **1982**, *104*, 1109-1110. Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981-1983. Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1981**, 1005-1008. Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Tetrahedron Lett.*, **1982**, *23*, 4143-4146. Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788-5789. Mukaiyama, T.; Yamada, T.; Suzuki, K. *Chem. Lett.* **1983**, 5-8. Watanabe, K. A.; Reichman, V.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21-24. Chwang, T. L.; Williams, R. D.; Schieber, J. E. *Tetrahedron Lett.* **1983**, *24*, 3183-3186.

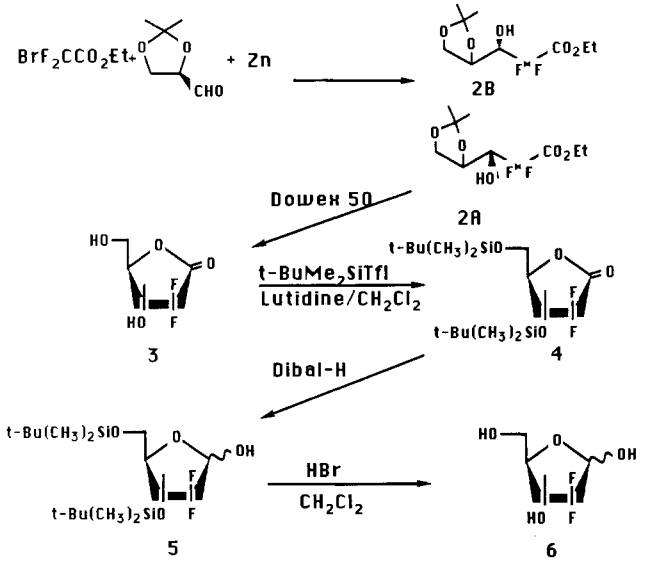
(3) While this publication was being written, an alternative synthesis of the title compound, 2-deoxy-2,2-difluoro-D-ribose, was published: Hanzawa, Y.; Inazawa, K.; Kon, A.; Aoki, H.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 659-662.

0022-3263/88/1953-2406$01.50/0

Scheme I



Scheme II

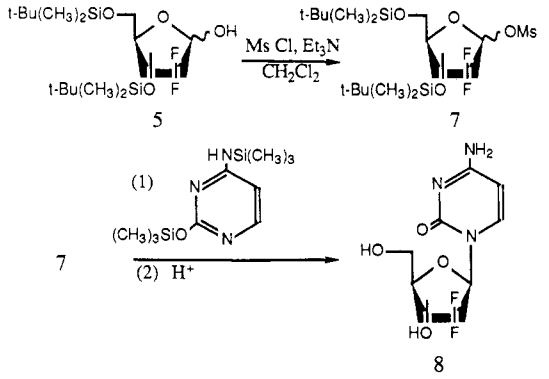


followed with the synthesis of a series of 1-(2-deoxy-2,2-difluororibofuranosyl)pyrimidines as part of our program in the design and synthesis of nucleosides of potential value as anticancer and/or antiviral agents.

(*R*)-2,3-*O*-Isopropylideneglyceraldehyde was prepared from D-mannitol by the method of Baer and Fischer.[4] Ethyl bromodifluoroacetate was prepared by the procedure described by Morel and Dawans,[5] or, more conveniently, it may be purchased.[6] The coupling, using standard Reformatskii conditions, i.e., activated Zn in ether/THF, afforded a 3:1 mixture of diasteromers **2A** and **2B**. These products were separated by HPLC (silica gel, methylene chloride with 0.5% methanol), giving **2A** in 65% yield.

The major and minor products from the reaction of the zinc enolate with the α-alkoxy aldehyde are those predicted from attack as illustrated in structures **1A** and **1B**. The transition state that is implied in structure **1A** amounts to application of Felkin's model for asymmetric induction;[7] i.e., the addition of a nucleophile to a carbonyl compound (bearing an α-asymmetric center) is anti to the large group (the one having the lowest energy σ^* C-2–x orbital). The theoretical work of Ahn supports the Felkin model.[8] This model is also supported experimentally by the work of Heathcock.[9]

Scheme III



The major isomer, **2A**, was subjected to hydrolytic removal of the isopropylidine group, with closure to the lactone **3** (94%). The lactone was silylated with *tert*-butyldimethylsilyl triflate[10] in lutidine to give the bis(*tert*-butyldimethylsilyl) derivative (**4**) in 92% yield. Reduction of this product with DIBAH gave the disilyl lactol **5** (79%) ($[\alpha]_D$ +25.1°). The optical rotation of the synthetic material was identical with that of the product reported by Kozikowski,[11] which he obtained by silylating authentic 2-deoxy-D-ribose. Removal of the silyl groups with HBr in methylene chloride yielded 2-deoxy-2,2-difluoro-D-ribose (**6**) in 79% yield.

Reaction of disilyl derivative **5** with methanesulfonyl chloride under standard conditions yielded the mesylate derivative **7** in 90% yield. Condensation of the mesylate **7** with trimethylsilylated cytosine, dichloroethane, and trimethylsilyl triflate at reflux for 15 h[12] afforded blocked nucleoside, which was deprotected by hydrolytic removal of protecting groups to give 2′-deoxy-2′,2′-difluorocytidine (**8**). The uridine nucleoside analogues were obtained by the same procedure, i.e., condensation of **7** with the corresponding trimethylsilylated uracils, e.g., **9**.

The procedure, involving condensation in dichloroethane in the presence of trimethylsilyl triflate, gave a 40% yield of the α-anomer and a 10% yield of the β-anomer after HPLC separation (C18/water). An alternative method, involving fusion of the protected sugar and a silylated pyrimidine, was reported to yield β-anomers as the predominant product.[13] In our hands this procedure gave a yield of 20% α and 5% β after separation of the anomers by HPLC (C18/water). Thus in both syntheses, the α/β ratio of the isolated compounds was about 4:1. The assignment of anomeric configuration was made by NMR spectra: the anomeric proton of the α-anomer was observed as a doublet of doublets with peak widths of 6 and 9Hz. The anomeric proton of the β-anomer appeared as an apparent triplet of peak width 8 Hz.[14] Confirmatory structural assignment was obtained from an X-ray crystal structure analysis of the anomers.

The presence of the electron-withdrawing difluoro substituents at C-2 should make dissociation of mesylate ion from the sugar more difficult. Consequently, condensation of the sugar mesylate with silylated bases should proceed

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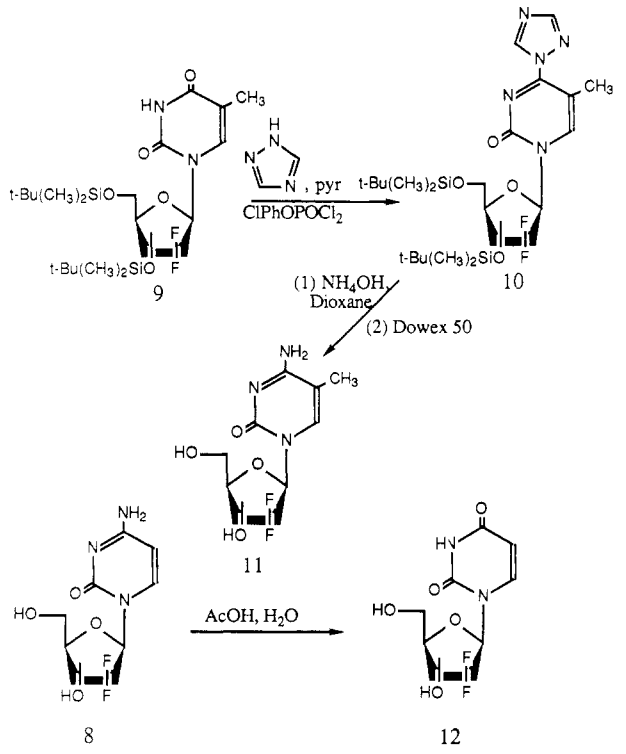
Scheme IV



in large measure by the S_N2 mechanism. The ^{13}C NMR spectra of the disilyl sugar **5** and disilyl mesylated sugar **7** indicate the α/β anomeric ratio at C-1 to be approximately 1:1; therefore the predominant formation of the α-nucleosides must involve facial differences of the sugar toward the nuclophile in an S_N1 type mechanism.

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-2′,2′-difluorothymidine (**9**) was treated with 1,2,4-triazole (3.0 mol equiv) and *p*-chlorophenyl phosphorodichloridate (1.5 mol equiv) in pyridine at room temperature for 3 days to give the intermediate **10**.[15] Subsequent treatment of **10** with aqueous ammonia in dioxane (1:3 (v/v)) yielded the protected deoxycytidine, which was deprotected by hydrolytic removal of the protecting groups to give **11**. 2′,2′-Difluorouridine (**12**) was prepared by hydrolytic deamination of the corresponding cytosine nucleoside (**8**).

The synthesis of 2′,2′-difluoro nucleosides can be extended to include other bases. Further synthetic and biochemical investigations to exploit these new leads are in progress.

Experimental Section

General Methods. All melting points are uncorrected and run on a Thomas-Hoover melting point apparatus. NMR spectra were measured with a Varian EM390, a Bruker WM250, or a General Electric QE300 using Me_4Si as the internal standard when appropriate and they are reported in δ. Infrared spectra were measured on a Nicolet 10DX FTIR spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were measured on a Varian MAT731 or V.G. ZAB-3F. Analyses were performed by MC 525, Lilly Research Laboratories, Indianapolis, IN.

Ethyl 2,2-Difluoro-3-hydroxy-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propionate (2A and 2B). To 24.9 g of activated zinc was added a small portion of a solution consisting of 77.3 g of ethyl bromodifluoroacetate and 55 g of 4-formyl-2,2-dimethyldioxolane in 129 mL of tetrahydrofuran and 129 mL of diethyl ether. Care was taken to exclude water from the reaction mixture. The solution began to reflux as soon as the first addition to the activated zinc was made. The remainder of the solution was added dropwise at a rate to maintain gentle reflux throughout the addition time of about 30 min. The mixture was then stirred under gentle relux for 30 min more. The reaction mixture was poured into 480 mL of 1 N hydrochloric acid and 480 g of ice, and the mixture was stirred until all of the ice had melted. The aqueous mixture was then extracted four times with 170-mL portions of diethyl ether, and the organic layers were combined and washed with 120 mL of saturated aqueous sodium chloride and with 120 mL of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated under vacuum to obtain 104 g of light yellow oil. The crude product was chromatographed on a 4-kg silica gel column, eluting with chloroform containing 0.5% methanol to separate the major 3(*R*)-hydroxy product (**2A**), from the minor 3(*S*)-hydroxy product (**2B**). The ratio of amounts of the two products was about 3:1; the minor product came off the column first. Evaporation of the fractions containing the 3(*R*)-hydroxy product (**2A**) provided 62 g (65%) in substantially pure form. Evaporation of the fractions containing the 3(*S*)-hydroxy product (**2B**) provided 20 g. **2A**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.2–1.47 (m, 9 H), 3.14 (d, J = 4.5 Hz, 1 H), 3.94–4.45 (m, 6 H). Anal. Calcd for $C_{10}H_{16}F_2O_5$: C, 47.24; H, 6.34; F, 14.95. Found: C, 47.00; H, 6.13; F, 14.92. **2B**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.5 (m, 9 H), 2.95 (d, J = 8 Hz, 1 H), 3.75–4.47 (m, 6 H).

2-Deoxy-2,2-difluoro-1-oxoribose (3). Fifty grams of the 3(*R*)-hydroxy product (**2A**) was dissolved in 500 mL of methanol and 250 mL of water, and 250 g of Dowex 50W-X12 resin was added. The mixture was stirred at ambient temperature for 4 days, and the mixture was then filtered through a pad of diatomaceous earth filter aid. The filtrate was evaporated to dryness under vacuum to obtain 31.0 g of the desired product, 94% yield. **3**: ^1H NMR (90 MHz, $CDCl_3$) δ 3.6–4.6 (series of multiplets, 4 H, 4.8 (bs, 2 H).

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-1-oxoribose (4). To 13 g of **3** was added 60 mL of dichloromethane, 22.5 mL of 2,6-lutidine, and 48.2 mL of ((trifluoromethanesulfonyl)oxy)-*tert*-butyldimethylsilane under nitrogen and mild cooling to keep the temperature below 25 °C. Within 15 min after the reagents were combined, the reaction became quite exothermic and the mixture became less viscous and easily stirred. The mixture was stirred overnight. The mixture was diluted with 150 mL of ethyl acetate and was washed successively with 40 mL of 1 N hydrochloric acid, 40 mL of saturated aqueous sodium bicarbonate, and 40 mL of saturated aqueous sodium chloride. It was then dried over magnesium sulfate and evaporated to dryness under vacuum to obtain 32.1 g of crude product, which was chromatographed on 260 g of 100-mesh silica gel, eluting with 10:1 (v/v) chloroform–diethyl ether. The fractions that contained the desired product were combined and evaporated under vacuum to obtain 12.3 g of pure product. Other fractions were combined and evaporated to obtain an additional 15.7 g of impure product, which was not further purified (92%). **4**: ^1H NMR (90 MHz, $CDCl_3$) δ 0.1–0.22 (m, 12 H), 0.83–0.98 (m, 18 H), 3.63–4.7 (series of multiplets, 4 H); IR (neat) 1820 cm^{-1}; MS m/e 339 (M – *tert*-butyl). Anal. Calcd for $C_{17}H_{34}F_2O_4Si_2$: C, 51.48; H, 8.64. Found: C, 51.75; H, 9.13.

3,5-Bis-*O*-(*tert*-Butyldimethylsilyl)-2-deoxy-2,2-difluororibose (5). A 10.3-g portion of **4** was dissolved in 120 mL of anhydrous toluene and cooled to −84 °C. To the solution was added 26 g of diisobutylaluminum hydride, added over a period of 20 min with constant stirring. The reaction mixture was held below −65 °C at all times. Two hours after the first addition of hydride, the reaction mixture was quenched with methanol at −20 °C and additional cold methanol was added until no more gas evolution occurred. The mixture was then allowed to warm slowly to ambient temperature and was washed with 100 mL of 0.1 N hydrochloric acid. The aqueous layer was then washed with 100 mL of diethyl ether and then three times with 50-mL portions of diethyl ether. The organic layers were combined, washed with 100 mL of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated under vacuum to dryness to obtain 8.2 g (79%) of the desired product in crude form. This material may be chromatographed, if necessary, on silica gel (25 g of silica gel/1 g of crude product) using 100% dichloromethane for elution. **5**: ^1H NMR (90 MHz, $CDCl_3$) δ 0.1–0.24 (m, 12 H), 0.85–1.0 (m, 18 H), 3.33–4.63 (series of multiplets, 5 H), 5.0–5.27

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(dd, 1 H); MS *m/e* 341 (M – *tert*-butyl); $[\alpha]^{25}_D$ +25.1° (*c* 1.3, MeOH). Anal. Calcd for $C_{17}H_{36}F_2O_4Si_2$: C, 51.22; H, 9.10. Found: C, 52.51; H, 9.43.

2-Deoxy-2,2-difluoro-D-ribose (6). A 3.0-g portion of **5** was dissolved in 50 mL of methylene chloride, and the mixture was then saturated with anhydrous hydrogen bromide. The reaction mixture was stirred at room temperature for 12 h. Evaporation to dryness under vacuum yielded 1.1 g of crude sugar. This crude product was dissolved in 25 mL of ethyl acetate and 25 mL of water. The organic layer was separated and washed with 25 mL of water. The combined aqueous layers were evaporated to dryness under reduced pressure, and the resulting residue was dissolved in ethyl acetate and dried over sodium sulfate. The mixture was filtered and the filtrate was evaporated under vacuum to a pale yellow oil that crystallized upon standing in the cold, yielding 1.0 g (79%) of **6**. **6**: ^{1}H NMR 300 MHz, D_2O) δ 3.63–4.2 (m, 4 H), 4.6–5.3 (m, 1 H); ^{13}C NMR (300 MHz, equilibrated in D_2O) δ 120.10, 120.04, 116.71, 113.41, 92.80, 92.51, 92.39, 92.10, 91.59, 91.16, 90.77, 69.59, 69.30, 69.04, 68.01, 67.84, 67.24, 66.96, 66.69, 65.39, 63.01; $[\alpha]^{26}_D$ –52° (*c* 1.3, H_2O) (lit.[16] –54°); IR (neat) 3461–3222 (br), 1098 (w), 822 (s) cm^{-1}; mp 125–131 °C; high-resolution mass spectrum, obsd 171.0474, calcd for M + 1, $C_5H_9O_4F_2$, 171.0469. Anal. Calcd for $C_5H_8O_4F_2$: C, 35.30; H, 4.74; F, 22.34. Found: C, 35.23; H, 5.03; F, 22.09.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-1-*O*-(methanesulfonyl)-2-deoxy-2,2-difluororibose (7). A 50-g portion of **5** was dissolved in 460 mL of anhydrous dichloromethane and 17.7 g of triethylamine. To the solution was added, with mild cooling, 11.6 mL of methanesulfonyl chloride. After 3 h of stirring under nitrogen at about 25 °C, the mixture was evaporated under vacuum, and the residue was taken up in 200 mL of ethyl acetate. The solution was extracted with 50 mL of saturated aqueous sodium bicarbonate and then successively with 50 mL of 1 N hydrochloric acid, 50 mL of water, and 50 mL of saturated aqueous sodium chloride. The organic solution was then dried over sodium sulfate and concentrated under vacuum to obtain 55 g (90%) of the desired product. **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.1–0.24 (m, 12 H), 0.85–1.0 (m, 18 H), 3.1 (apparent d, 3 H), 3.7–4.6 (series of multiplets, 4 H), 5.9 (apparent dd, 1 H); IR ($CDCl_3$) 2920, 2847, 1520, 1320 cm^{-1}; MS *m/e* 419, (M–*tert*-butyl).

1-(2-Oxo-4-amino-1,2-dihydropyrimidin-1-yl)-2-deoxy-2,2-difluororibose (8). To a solution of 47.3 g of **7** in 940 mL of dichloroethane under nitrogen was added 48 g of bis(trimethylsilyl)-*N*-acetylcytosine. To this mixture was added 39.23 g of ((trifluoromethanesulfonyl)oxy)trimethylsilane, and the resulting mixture was stirred under reflux for approximately 15 h. The reaction mixture was cooled to room temperature and 16 mL of methanol was added. The resulting solution was stirred for approximately 30 min and concentrated to about half of its original volume. The solution was cooled in ice, and the precipitated solid was collected by filtration. The filtrate was shaken one time with approximately 300 mL of 10% sodium bicarbonate and one time with 100 mL of brine. The organic layer was evaporated to dryness under vacuum at 45 °C and the residue was dissolved in 1.3 L of methanol saturated with ammonia. The resulting suspension was allowed to stir overnight at room temperature and the volatiles were removed under vacuum at 45 °C. The residue was dissolved in 275 mL of methanol and 100 g of BioRad ion-exchange resin (AG 50W-X8) was added. The suspension was stirred at room temperature overnight and the resin was collected by filtration. The resin was rinsed with 100 mL of methanol and suspended in 100 mL of methanol and 50 mL of concentrated ammonium hydroxide. The resin-containing suspension was stirred vigorously for 15 min and the resin was collected by filtration. This procedure was twice repeated with additional ammonia-saturated methanol. The basic methanolic fitrates were combined and evaporated at 45 °C under vacuum to provide 13.8 g of a solid. This material was chromatographed on a Waters Prep 500 C18 reverse-phase column with water as the eluent to provide 2.53 g of **8**. β-Anomer: ^{1}H NMR (250 MHz, D_2O and DMSO-d_6) δ 4.09 (dd, 1 H, $J_{4',5B'}$ = 4.3 Hz, J_{gem} = 13.2 Hz, 5B'-H), 4.24 (d, 1 H, $J_{4',5A'}$ = small, J_{gem} = 13.2 Hz, 5A'-H), 4.29 (m, 1 H, $J_{3',4'}$ = 8.6 Hz, 4'-H), 4.56 (m, 1 H, $J_{3,F}$ = 1.9 Hz, 3'-H), 6.33 (d, 1 H, $J_{5,6}$ = 7.6 Hz, 5-H), 6.50 (t, 1 H, $J_{1',F}$ = 8 Hz, 1'-H), 8.06 (d, 1 H, $J_{5,6}$ = 7.6 Hz, 6-H); ^{13}C NMR (250 MHz, D_2O and DMSO-d_6) δ 60.43 (C-5'), 70.38 (C-3'), 81.54 (C-4'), 85.44 (C-1'), 96.98 (C-5), 123.77 (C-2'), 142.53 (C-6), 157.37 (C-2), 167.04 (C-4). Anal. Calcd for $C_9H_{11}N_3O_4F_2{\cdot}2H_2O$: C, 36.12; H, 5.05; N, 14.04. Found: C, 36.47; H, 5.38; N, 13.91. Single-crystal X-ray analysis confirmed the structural assignment.

α-Anomer: ^{1}H NMR (250 MHz, D_2O) δ 3.93 (dd, 1 H, $J_{4',5B'}$ = 4.8 Hz, J_{gem} = 13.1 Hz, 5B'-H), 4.07 (apparent d, 1 H, $J_{4',5A'}$ = 2 Hz, J_{gem} = 13.1 Hz, 5A'-H), 4.50 (m, 1 H, $J_{3',4'}$ = 7.8 Hz, 4'-H), 4.66 (m, 1 H, $J_{3',F}$ = 10.9 Hz, 3'-H), 6.19 (d, 1 H, $J_{5,6}$ = 7.6 Hz, 5-H), 6.44 (dd, 1 H, $J_{1',F}$ = 6.0 and 9.1 Hz, 1'-H), 7.77 (d, 1 H, $J_{5,6}$ = 7.6 Hz, 6-H); ^{13}C NMR (250 MHz, D_2O) δ 60.96 (C-5'), 70.96 (C-3'), 84.36 (C-4'), 85.98 (C-1'), 96.88 (C-5), 123.37 (C-2'), 142.15 (C-6), 157.73 (C-2), 166.87 (C-4).

1-(5-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-deoxy-2,2-difluororibose (9). To 80.0 g of **7** under a nitrogen atmosphere was added 1.4 L of freshly distilled dichloroethane and 49.5 g of 5-methyl-2,4-bis((trimethylsilyl)oxy)pyrimidine. To this mixture was added 44.8 g of ((trifluoromethanesulfonyl)-oxy)trimethylsilane, and the reaction mixture was refluxed for approximately 3 h. The reaction mixture was stirred at room temperature overnight and 41.6 mL of methanol was added. The resulting mixture was stirred for approximately 30 min and the precipitated solid was collected by filtration. The filtrate was concentrated under vacuum at 45 °C to provide a dark oil, which was dissolved in 500 mL of methylene chloride saturated with anhydrous hydrogen bromide. The resulting suspension was stirred for approximately 3 h, after which the volatiles were removed under vacuum at 45 °C to provide a residue that was dissolved in 50 mL of water. This solution was chromatographed in 10-mL portions on a Waters Prep 500 C18 reverse-phase column using 9:1 (v/v) water/methanol as the eluent to provide 2.21 g of **9**.

β-Anomer: ^{1}H NMR (90 MHz, CD_3OD) δ 1.94 (s, 3 H, 5-Me), 3.83 (m, 3 H, 4'- and 5'-H), 4.35 (m, 1 H, 3'-H), 6.2 (t, 1 H, *J* = 8 Hz, 1'-H), 7.7 (s, 1 H, 6-H).

α-Anomer: ^{1}H NMR (90 MHz, CD_3OD) δ 1.83 (s, 3 H, 5-Me), 3.65 (m, 2 H, 5'-H), 4.2 (m, 1 H, 4'-H), 4.35 (m, 1 H, 3'-H), 6.25 (dd, 1 H, *J* = 6 and 9 Hz, 1'-H), 7.4 (s, 1 H, 6-H). Single-crystal X-ray analysis confirmed the structural assignment.

1-(5-Methyl-2-oxo-4-amino-1,2-dihydropyrimidin-1-yl)-2-deoxy-2,2-difluororibose (11). Preparation of **11** was by the method reported by Sung,[15] starting with **9**. **11**: ^{1}H NMR (90 MHz, CD_3OD) δ 1.94 (s, 3 H), 3.53–4.62 (m, 4 H), 4.75 (s, 4 H), 6.17 (t, *J* = 8 Hz, 1 H), 7.67 (s, 1 H); MS *m/e* 277 (M^+).

1-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-2-deoxy-2,2-difluororibose (12). A solution of 0.19 g of **8** in 16 mL of glacial acetic acid and 4 mL of water was refluxed for approximately 24 h. The reaction mixture was cooled to ambient temperature, and the volatiles were removed under vacuum at a temperature in the range of about 60 °C to about 70 °C. The residue was evaporated several times from 5 mL of toluene. The residue was dissolved in 12 mL of methanol, and the resulting solution was cooled in a salt/ice bath to approximately –15 °C. The solution was saturated with anhydrous ammonia and allowed to stir overnight at room temperature. The volatiles were evaporated under reduced pressure at 45 °C and the residue was suspended in 5 mL of hot water. The insoluble material was collected by filtration and the filtrate was chromatographed on a Whatman 50-cm Partisil ODS-3 reverse-phase column using 9:1 (v/v) water/methanol as the eluent to provide 0.05 g of the product containing a small trace of unreacted starting material. This unreacted starting material was removed by passing a solution of the product in approximately 5 mL of methylene chloride containing 10% methanol by volume through a Waters Silca Sep-Pak. The eluent was evaporated in vacuo at 45 °C to provide 0.036 g of **12**: ^{1}H NMR (300 MHz, D_2O) δ 3.83 (dd, 1 H, 5'-H), 3.98 (d, 1 H, 5'-H), 4.05 (m, 1 H, 4'-H), 4.35 (m, 1 H, 3'-H), 5.9 (d, 1 H, 5-H), 6.18 (t, 1 H, 1'-H), 7.75 (d, 1 H, 6-H); MS *m/e* 264 (M^+).

Registry No. **2A**, 95058-92-7; **2B**, 95058-93-8; **3**, 95058-77-8; **4**, 95058-78-9; **5**, 95058-79-0; **6**, 95058-90-5; **7**, 103882-89-9; β-**8**, 95058-81-4; α-**8**, 95058-85-8; β-**9**, 114184-77-9; α-**9**, 114184-78-0; **10**, 114184-79-1; **11**, 114248-22-5; **12**, 114248-23-6; BrF_2CCO_2Et, 667-27-6; (*R*)-4-formyl-2,2-dimethyldioxolane, 15186-48-8; bis(trimethylsilyl)-*N*-acetylcytosine, 18027-23-1; 5-methyl-2,4-bis((trimethylsilyl)oxy)pyridine, 7288-28-0.

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