were combined, and the solvent was evaporated. The residue was dissolved in a 1:1 mixture of water-dioxane, filtered, and lyophilized to give $N^{6'}$-(benzyloxycarbonyl)-$N^{2'}$-[(*S*)-γ-[(benzyloxycarbonyl)amino]-α-hydroxybutyryl]nebramine (1.06 g, 79% yield).

$N^{6'}$-(Benzyloxycarbonyl)-$N^{2'}$-[(*S*)-γ-[(benzyloxycarbonyl)-amino]-α-hydroxybutyryl]nebramine (975 mg) was dissolved in a mixture of dioxane (20 mL), water (20 mL), and glacial acetic acid (1 mL). Palladium on charcoal (5%, 270 mg) was added and the mixture was hydrogenated at 40 psi overnight at ambient temperature. The palladium catalyst was removed by filtration and the filtrate was concentrated under reduced pressure and then loaded onto a column of 200 mL of Bio-Rex 70 (ammonium hydroxide cycle, pH 8.6). After first eluting with a gradient of 0.005 N ammonium hydroxide (2 L) and 0.4 N ammonium hydroxide (3 L), the desired product was eluted with 0.5 N ammonium hydroxide. The fractions containing the desired product were combined and lyophilized to yield $N^{2'}$-[(*S*)-γ-amino-α-hydroxybutyryl]nebramine (**40**) (397 mg, 70% yield).

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Registry No. 1, 12772-35-9; 2, 36441-41-5; 3, 26098-04-4; 4, 25876-10-2; 5, 37517-28-5; 6, 32986-56-4; 7, 1403-66-3; 8, 25876-11-3; 9, 4696-76-8; 10, 32385-11-8; 11, 56391-56-1; 12, 7542-37-2; 13, 1404-04-2; 14, 57-92-1; 15, 34493-98-6; 16, 56276-26-7; 17, 36019-37-1; 18, 68743-79-3; 19, 55779-06-1; 20, 37321-09-8; 21, 59-01-8; 22, 25546-65-0; 23, 1695-77-8; 24, 31282-04-9; 25, 60407-80-9; 26, 124-20-9; 27, 52932-64-6; 28, 60-54-8; 29, 56-75-7; 30, 2037-48-1; 31, 99237-10-2; 32, 50721-31-8; 33, 71472-01-0; 34, 67117-30-0; 35, 104995-33-7; 36, 105018-30-2; 37, 104995-34-8; 38, 34051-04-2; 39, 52945-48-9; 40, 82472-95-5; 41, 82473-01-6; 42, 89194-90-1; 43, 82472-91-1; 44, 82473-03-8; 45, 58617-24-6; DHS, 128-46-1.

Synthesis and Antitumor Activity of Fluorine-Substituted 4-Amino-2(1*H*)-pyridinones and Their Nucleosides. 3-Deazacytosines

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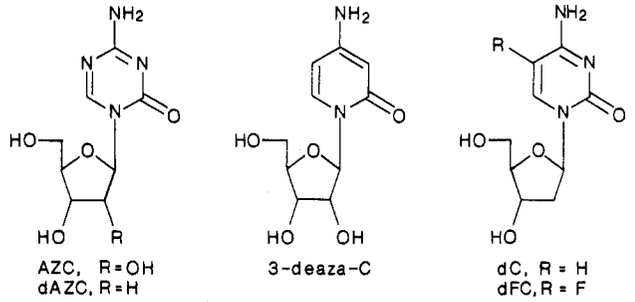
Novel fluorine-substituted deaza analogues of 5-azacytidine (AZC) and 5-aza-2′-deoxycytidine (dAZC) (3-deazacytosines) have been synthesized and tested for antitumor activity. Thus, 4-amino-3,5-difluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**16**), 4-amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**17**), 4-amino-5-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**18**), 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone (**25**), 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3-fluoro-2(1*H*)-pyridinone (**26**), 4-amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone (**27**), and 4-amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3-fluoro-2(1*H*)-pyridinone (**28**) were prepared by standard glycosylation procedures. Requisite heterocycle 4-amino-3,5-difluoro-2(1*H*)-pyridinone (**6**) was prepared in five steps from pentafluoropyridine (**1**). Other requisite fluoro heterocycles, 4-amino-3-fluoro-2(1*H*)-pyridinone (**7**) and 4-amino-5-fluoro-2(1*H*)-pyridinone (**8**), were obtained from a bis-defluorination of 4-amino-3,5,6-trifluoro-2(1*H*)-pyridinone (**3**) with hydrazine. Acetylation of **17** provided 4-amino-3-fluoro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (**29**). Structure proof of target nucleosides and heterocyclic compounds was provided by X-ray diffraction, ^{19}F and ^{1}H NMR, and UV. The ID_{50} values of fluorine-substituted 3-deazacytosines and 3-deazacytidines were greater than 1×10^{-5} M in L1210 lymphoid leukemia cells in culture. Nucleoside **17** and its tri- and tetraacetates were the most active compounds with ID_{50} values of 1.07×10^{-5}, 1.23×10^{-5}, and 1.25×10^{-5} M, respectively. The target nucleosides and intermediate heterocycles were inactive against P388 and L1210 lymphocytic leukemia in mice, except nucleoside **17** (NSC-378066) and its triacetate **29** (NSC-382021). Nucleoside **17** exhibited confirmed DN2 activity (% T/C 169–230) at five dose levels (25–300 mg/kg). Prodrug **29** exhibited similarly confirmed L1210 in vivo activity.

5-Azacytidine[1] (AZC) and 5-aza-2′-deoxycytidine (dAZC) are toxic to cells in culture[2,3] and are effective antileukemic agents in humans.[4,5] Furthermore, the properties of cytotoxicity and anticancer activity may not be related,[6] and thus they may be noncytotoxic anticancer agents.[7] At low, sublethal concentrations, the major biochemical effect of AZC and dAZC is rapid inhibition of DNA methylation, caused by irreversible inactivation of DNA-cytosine methyltransferase.[8] At these concentrations, AZC and dAZC induce a variety of undifferentiated cells to differentiate, presumably by inhibition of DNA methylation.[8,9] It is noteworthy that the activity of dAZC against L1210 leukemia in mice correlates well with its inhibition of DNA



† Present address: Eastman Kodak Company, Life Sciences Division, Rochester, NY 14650.

(1) Abbreviations used are as follows: AZC, 5-azacytidine; dAZC, 2′-deoxy-5-azacytidine; 3-deaza-C, 3-deazacytidine; dC, 2′-deoxycytidine; *ara*-C, 1-β-D-arabinofuranosylcytosine; dFC, 2′-deoxy-5-fluorocytidine; FC, 5-fluorocytidine; DAU, 3-deazauridine; NCI, National Cancer Institute.

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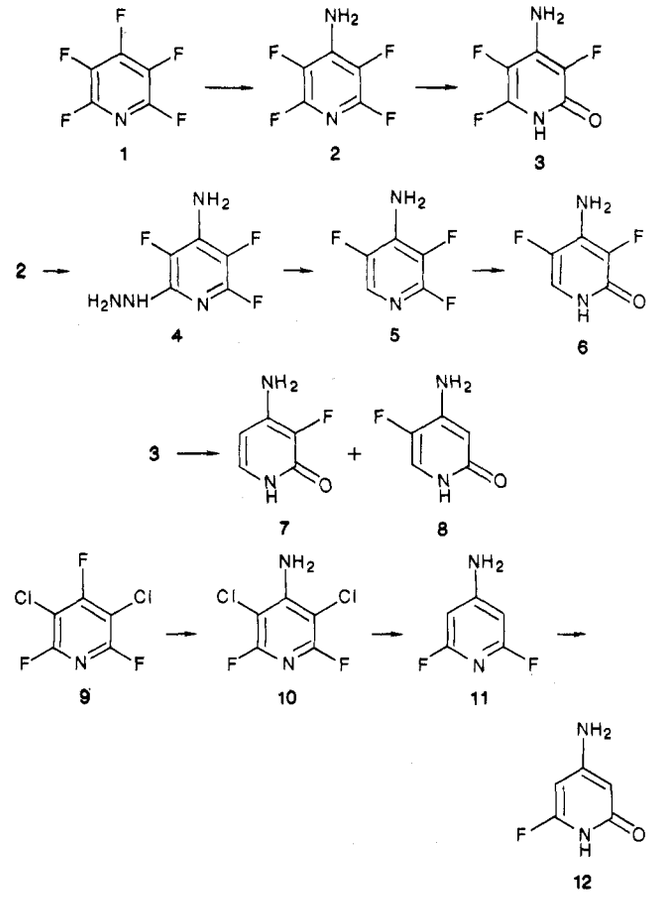
methylation.[10] Moreover, dAZC and AZC have been shown not to be potent inhibitors of DNA synthesis in L1210 cells whereas *ara*-C, also an analogue of cytidine and structurally similar to dAZC and AZC, is a potent inhibitor of L1210 DNA synthesis but does not inhibit DNA-cytosine methyltransferase.[3] Although it has not been definitely proven, the above facts have led to the hypothesis that AZC and dAZC exert their anticancer activity by inhibiting DNA-cytosine methyltransferase, thus allowing genes previously not expressed to be expressed, thereby inducing cancer cells to differentiate into normal cells.[10]

We have recently become interested in noncytotoxic approaches to cancer chemotherapy and have begun a program to improve upon AZC and dAZC as anticancer agents. Although AZC and dAZC are effective antileukemic agents, AZC, at least, is ineffective against solid tumors in humans.[11] Another disadvantage of AZC and dAZC is their chemical instability. Both exist in aqueous solution in equilibria with their respective triazine ring-opened products, which gradually and irreversibly react further with water to yield inactive compounds.[12] This has led to problems in their clinical formulation. Finally, both compounds are enzymatically unstable, with the major degradative pathway being deamination.[13]

The degree of electrophilicity of the 6-position of dAZC and AZC is of paramount importance to their reactivity, both the chemical instability and enzyme inhibition. The strong electron withdrawing effect of the ring nitrogen in the 5-azacytosine ring system enhances covalent hydration at its 6-position and subsequent ring opening and loss of antitumor effects. On the other hand, the mode of DNA-cytosine methyltransferase inhibition of dAZC and AZC is thought to involve the covalent bonding of a sulfhydryl group of the enzyme to the 6-position of the DNA incorporated 5-azacytosine ring system.[14] Thus, we have sought to modify the electrophilicity of AZC and dAZC without significantly changing their cytosine ring systems in an effort to broaden their spectrum of anticancer activity. We note that enzyme–substrate binding sites may be affected by electron density at certain areas in the substrate and that 3-deazacytidine (3-deaza-C, which itself is toxic to cells in culture but has no reported in vivo antitumor activity) is not deaminated by cell-free extracts of *Escherichia coli*[15] and appears to be chemically stable.[16] Furthermore, our structure modifications were guided by the success in placing fluorine atoms in molecules, particularly that of fluorouracil,[17] and the report that conversion of 2′-deoxycytidine (dC) to its 5-fluoro analogue (dFC) resulted in a compound that inhibits DNA-cytosine methyltransferase and induces differentiation.[9] Thus, we suggest that the exchange of an aromatic ring nitrogen atom with a fluorine-substituted aromatic carbon atom will affect the electrophilicity of dAZC and AZC without causing significant steric changes. Toward this end, we have synthesized a series of fluorine-substituted 4-amino-2(1*H*)-pyridinones and their 1-β-D-ribofuranosyl and 1-(2′-deoxyribofuranosyl) derivatives. the target compounds may be viewed as 3,5-dideaza-AZC (or dAZC) analogues or 3-deazacytosines with fluorine atoms placed at the deaza positions.

Scheme I



The synthesis but not biological activity of one of our target compounds, 4-amino-5-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**18**), has been previously reported by Nesnow and Heidelberger.[18]

Chemistry

The fluorine-substituted 4-amino-2(1*H*)-pyridinones were synthesized from commercially available pentafluoropyridine (**1**) or 3,5-dichloro-2,4,6-trifluoropyridine (**9**), as illustrated in Scheme I. Treatment of **1** with ammonium hydroxide gave 2,3,5,6-tetrafluoro-4-pyridinamine (**2**).[19] Reaction of **2** with aqueous sodium hydroxide gave 4-amino-3,5,6-trifluoro-2(1*H*)-pyridinone (**3**). The ^{19}F NMR spectrum of **3**, with one downfield (F-6) and two upfield (F-3 and F-5) multiplets, agreed well with that predicted from the literature.[19-22] and definitely established the structure of **3** as shown.

Reaction of **2** with hydrazine gave 2,3,5-trifluoro-6-hydrazino-4-pyridinamine (**4**), which was treated with

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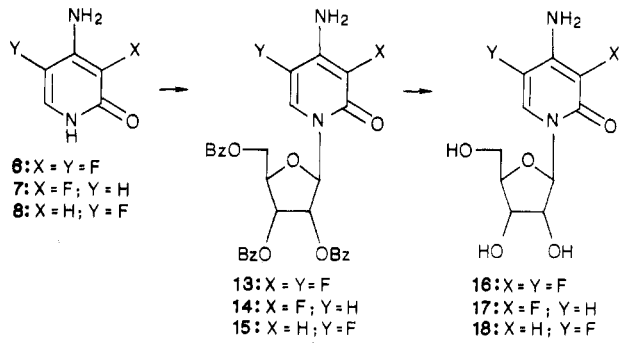
Scheme II



copper(II) sulfate to give 2,3,5-trifluoro-4-pyridinamine (**5**). Hydrolysis of **5** gave 4-amino-3,5-difluoro-2(1*H*)-pyridinone (**6**). The structures of **4**–**6** were clearly established by their ^{19}F NMR spectra, with fluorines in the 2- and 6-positions appearing considerably downfield from those in the 3- and 5-positions.

Heterocycle **3** was treated with hydrazine in an attempt to obtain its 6-hydrazino derivative, which would then have been reduced to give **6**. This reaction, however, gave two unexpected products, 4-amino-3-fluoro-2(1*H*)-pyridinone (**7**, major) and 4-amino-5-fluoro-2(1*H*)-pyridinone (**8**, minor). The structure of **7** was unequivocally proven by an X-ray diffraction of a subsequent derivative, 4-amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**17**). The structure of **8** was unequivocally proven by conversion to its hydrochloride salt and comparison of its spectral properties with reported values.[18] The ^{19}H and ^{1}H NMR spectra of **7** and **8** were consistent with their structures. This defluorination by hydrazine to give the otherwise difficultly accessible **7** and **8**, while unexpected, is not without precedent.[23]

Reaction of 3,5-dichloro-2,4,6-trifluoropyridine (**9**) with ammonium hydroxide gave 3,5-dichloro-2,6-difluoro-4-pyridinamine (**10**).[20] Catalytic reduction of **10** gave 2,6-difluoro-4-pyridinamine (**11**), which upon hydrolysis yielded 4-amino-6-fluoro-2(1*H*)-pyridinone (**12**).

Treatment of heterocycles **6**–**8** with excess hexamethyldisilazane and a catalytic amount of ammonium sulfate gave the trimethylsilyl derivatives, which were treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane with tin(IV) chloride as catalyst[24] to give tribenzoyl-protected **13**–**15** (Scheme II). Subsequent deblocking with sodium methoxide gave target nucleosides **16**–**18**. The structure of **17** was unequivocally established by X-ray diffraction.[25] The structure of **18** was established by comparison of its spectral properties with reported values.[18] Although a discrepancy exists in the melting points (203–205 °C vs. 92–94 °C), the very good agreement between the UV and ^{1}H NMR spectra leaves no doubt that the compound reported here is that obtained previously. Further support for the structure of **18** comes from the similarity of the ^{1}H NMR spectrum of **18** to that of **17**. Long-range coupling between the anomeric proton and F-5 was observed in the ^{1}H NMR spectrum of **18**, as has been noted in fluorinated pyrimidine nucleosides.[26]

(23) For example, bromomalonic esters are debrominated by hydrazine (Gallus, H. P.; Macbeth, A. K. *J. Chem. Soc.* **1937**, 1810) and 5-chloro-2-pyridinamine is dechlorinated by hydrazine with palladium on charcoal as a catalyst (Mosby, W. L. *Chem. Ind. (London)* **1959**, 1348).
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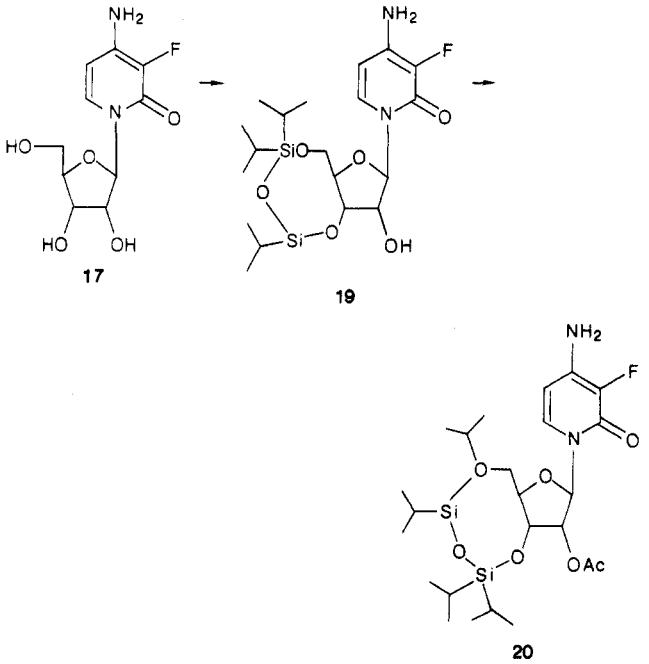
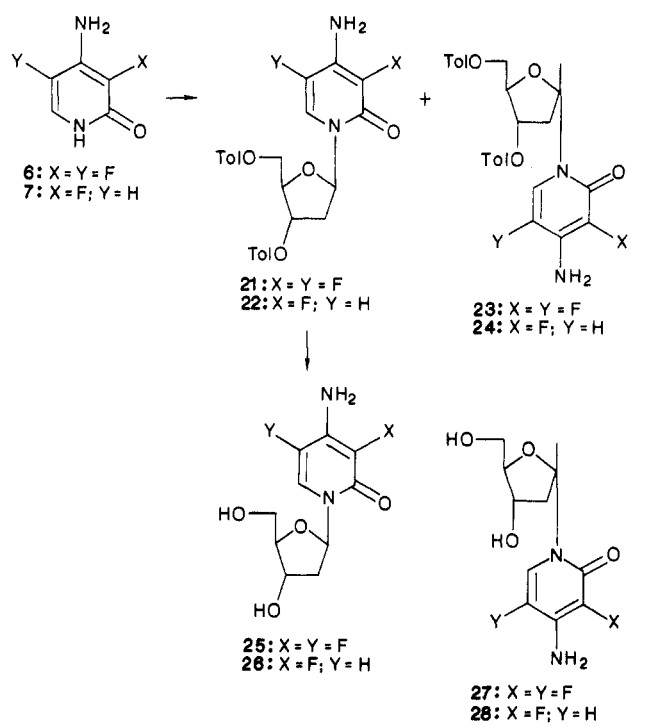
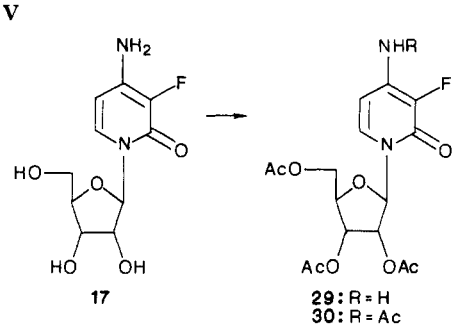
Scheme III



Scheme IV



Scheme V



The ^{1}H NMR spectrum 4-amino-3,5-difluoro-1-β-D-ribofuranosyl-2-(1*H*)-pyridinone (**16**) was very similar to that of **17** and **18**. Long-range coupling between the anomeric

Table I. Activity of 4-Amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**17**) and 4-Amino-3-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (**29**) against L1210 Lymphoid Leukemia in Mice[a]

compound	mg/kg inj	NET log[b] kill[10]		BWD[c]		% T/C[d]	
17 (NSC-378066)	300	5.37	ND[g]	−4.7	ND	230	ND
	200	3.91	4.86[f]	−4.8	−3.4[f]	208	208[f]
	100	2.93	5.54	−3.0	−1.3	193	216
	50	2.20	3.01	−1.7	−1.1	182	185
	25	1.30	0.78	−1.0	−1.0	169	157[d]
	12.5	ND	−0.97	ND	−0.5	ND	136
29 (NSC-382021)	400	3.59	ND	−5.0	ND	205	ND
	200	2.43	3.34[f]	−2.3	−1.9[f]	189[e]	186[f]
	100	0.49	3.68	−2.0	−0.7	161	190
	50	−1.94	2.01	−1.0	0.4	127	168
	25	−2.25	−1.09	−1.0	0.1	113	129
	12.5	−2.22	−2.25	−2.0	−0.4	115	109

[a] CD_2F_1 mice in groups of six were inoculated ip with 1×10^5 cells of L1210 lymphoid leukemia. Treatment (ip) was initiated 24 h after tumor inoculation and continued once-a-day for 5 days. [b] Difference between estimated tumor burdens before the first and just after the last treatment. This value is based on the observed doubling time for the tumor in that test and the median survival after the last treatment.[36] It includes an estimate of the regrowth of the tumor cell population between treatments. It is calculated by subtracting the life span of the control mice (*C*) and the treatment days (Rx) from the life span of the control mice (*T*) and this divided by 3.32 times and doubling time (Td) of the L1210 tumor cells. Thus, net cell kill of **17** (100 mg/kg dose on days 2–6) = (*T* − *C* − Rx)/3.32Td = (18.0 − 8.3 − 4)/3.32(0.31) = 5.54. A net cell kill of zero indicates the tumor cells are equal to the original inoculum, 10^5, after therapy. A positive net cell kill indicates less than original 10^5 inoculum of tumor cells are left after therapy and a negative net cell kill implies that the tumor actually grew ($>10^5$) during the course of therapy.[36] [c] Mean weight change (days 5 minus 1) of the treated mice minus the mean weight change of the control mice. [d] (Mean survival time of treated mice in days/mean survival time of control mice) × 100. % T/C > 125 indicates significant activity (Decision Network I activity). Decision Network 2 activity is a % T/C ≥ 150. No cures were recorded for either compound at any dose level. [e] A toxic death was recorded at this dose level and it is excluded from the % T/C calculation. [f] Confirmation data shown in this column. [g] Not determined.

proton and F-5 was also oberved in **16**.

Attempted ribosylation of **3** and **12** using tin(IV) chloride as catalyst and 1,2-dichloroethane is solvent, as well as using trimethylsilyl trifluoromethanesulfonate as catalyst and acetonitrile as solvent,[27] resulted in complex mixtures that did not yield isolable products. The failure to ribosylate these heterocycles was ascribed to the presence of the very electronegative fluorine atom adjacent to the desired site of ribosylation. The difficulty in ribosylating 6-substituted 2(1*H*)-pyridinones has previously been noted.[28]

The synthesis of 2′-deoxy derivatives of **16** and **17** was first pursued according to the general procedure of Robins et al.[29] (Scheme III). Protection of the 3′,5′-hydroxyls of **17** gave 4-amino-3-fluoro-1-[3,5-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-ribofuranosyl]-2-(1*H*)-pyridinone (**19**). It is noteworthy that in the ^1H NMR spectrum of **19** the anomeric proton appeared as a singlet, thus confirming the β configuration according to the criterion of Robins et al.[30] However, subsequent reaction of **19** with phenyl chlorothionocarbonate did not give an isolable product. Attempted acetylation of the 4-amino group of **19** to prevent possible complications from its reaction with phenyl chlorothionocarbonate resulted instead in acetylation of the 2′-hydroxyl to give **20**. In more traditional nucleoside chemistry, the trimethylsilyl derivative of **6** was treated with 1-chloro-2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranose[31] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSTf) to give protected nucleosides **21** and **23**. These were separated and deblocked to give target deoxynucleosides 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone and 4-amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone, **25** and **27**, respectively. The site of deoxyribosylation was assigned to be N-1 by the similarity of the UV spectra of **25** and **27** with that of **16**. The β-isomer **25** exhibited the characteristic[32] triplet with a peak width of 14 Hz for the anomeric proton and the α-isomer **27** a quartet with a peak width of ~10 Hz. Similar deoxyribosylation of heterocycle **7** gave protected nucleosides **22** and **24**, which were separated and deblocked to give target deoxynucleosides 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3-fluoro-2-(1*H*)-pyridinone and 4-amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3-fluoro-2(1*H*)-pyridinone, **26** and **28**, respectively. The site of deoxyribosylation was assigned to be on N-1 by the similarity of the UV spectra of **26** and **28** with that of **17**. The β-isomer **26** exhibited a doublet of doublets[33] with a peak width of 13.6 Hz for the anomeric proton, while the α-isomer **28** exhibited a doublet of doublets with a peak width of 10.7 Hz.

Acetylated compounds 4-amino-3-fluoro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-(1*H*)-pyridinone (**29**) and 4-(acetylamino)-3-fluoro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (**30**) were synthesized as prodrugs of **17** by usual acetylation procedures.

Biology

Target nucleosides and their parent heterocycles were tested for their ability to inhibit the growth of L1210 lymphoid leukemia cells in culture by the method of Baguley and Nash.[34] The ID_{50} value, the concentration required to inhibit the growth rate of the control cells by 50%, for the heterocyclic bases **3**–**8**, **11**, and **12** fell within the range (2.60–4.71) × 10^{-5} M. The target nucleosides **16**,

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18, and **25–28** were inactive (<50% inhibition) when tested at 10 μg/mL ($ID_{50} > 1 \times 10^{-4}$ M). The IC_{50} values for compound **17** and its triacetyl derivative **29** and tetraacetyl derivative **30** were 1.07×10^{-5}, 1.23×10^{-5}, and 1.25×10^{-5} M, respectively. For comparison, the IC_{50} values for 3-deaza-C, AZC, and dAZC were 1.78×10^{-5}, 4.09×10^{-7}, and 3.93×10^{-7} M, respectively.

Heterocycles **3–8** and **12** were then tested against P388 lymphocytic leukemia in mice under the auspices of the National Cancer Institute (NCI) by standard NCI protocol.[35] All were inactive (% T/C < 125). Nucleosides **16–18** and **25–29** were tested against L1210 lymphoid leukemia in mice under the auspices of the NCI by standard NCI protocol.[35] Compounds **16**, **18**, and **25–28** were inactive (% T/C < 125). Compound **17** displayed confirmed Decision Network 2 activity (% T/C ≥ 150) at five dose levels, starting at 25 to 300 mg/kg with a corresponding % T/C range of 169–230 (Table I). Very moderate toxicity, as noted by body weight difference (BWD, −1.7 to −1.0), occurred at doses below 100 mg/kg. Net cell kill ranged from 1.3 to 5.54 at dose levels of 25 to 100 mg/kg. All mice survived treatment except one as noted in Table I. Prodrug **29** exhibited confirmed L1210 in vivo activity similar to that of *17*. The net cell kill of 5.54 for **17** at 100 mg/kg indicates, according to theoretical calculations of Schabel et al.,[36] that less than 10 cancer cells remained after therapy. Thus, nucleoside **17**, administered with this regimen, was essentially curative.

Discussion

Nucleoside **17** exhibited excellent in vivo L1210 antitumor activity as determined by net cell kill, toxicity, and % ILS of the mice. Furthermore, the triacetyl-blocked nucleoside **29** exhibited similar but less potent activity than that of **17** and thus likely serves as a prodrug to **17**. Whether **17** (and **29**) exerts its cytotoxicity by inhibition of DNA-cytosine methyltransferase after metabolism to the 2′-deoxy 5′-triphosphate and incorporation into DNA, like the 5-azacytosines dAZC and AZC, cannot be determined by the antitumor data accumulated thus far. However, some observations concerning this question can be made.

It is disconcerting that the 2′-deoxy derivative of **17**, compound **26**, did not exhibit in vitro or in vivo antitumor activity analogous to dAZC activity with respect to AZC activity. It is possible that whereas the ribonucleoside **17** can be metabolized and incorporated into DNA and subsequently inhibit DNA-cytosine methyltransferase, the necessary deoxypyrimidine nucleoside kinases may not phosphorylate deoxyribonucleoside **26**.

We have postulated that the electron-withdrawing effect of the ring-nitrogen atoms in the 3- and 5-positions of dAZC and AZC might be approximated by replacement with ring-carbon atoms bearing fluorine atoms. Thus, it is also disconcerting that the 3,5-difluoropyridinone nucleoside **16** and its 2′-deoxy derivative **25** did not exhibit in vitro or in vivo antitumor activity. In this regard, the ring systems of tribenzoyl-protected nucleosides **13–15** were stable to standard sodium methoxide deprotecting conditions whereas dAZC and AZC suffered ring-opening degradation from initial nucleophilic attack at their electron-deficient 6-positions.[12,37] Therefore, the 6-position of the fluorine-substituted pyridinone nucleosides may not be sufficiently activated by the fluorine atoms in the 3- and 5-positions for attack of the DNA-cytosine methyltransferase sulfhydryl group. We note that, in parallel studies[38] of 3-deaza-3-fluoro-5-azacytosines (reverse pyrimidines) as potential DNA-cytosine methyltransferase inhibitors, standard sodium methoxide deprotecting conditions affected ring opening.

Finally, nucleoside **17** may not exert its antitumor activity in a manner similar to dAZC and AZC; it may have an action similar to a structurally related cytosine-type nucleoside such as 5-fluorocytidine (FC), arabinofuranosylcytosine (*ara*-C), or 3-deazauridine (DAU). In this regard, we note that whereas dAZC, AZC, *ara*-C, dFC, and FC exhibited in vitro L1210 ID_{50} values in the range of 10^{-7} to 10^{-10} and DAU of 10^{-6}, nucleoside **17** was much less active in L1210 cells with an ID_{50} value of 10^{-5}. Furthermore, of this group of cytosine-type nucleosides, only dAZC and AZC exhibited significantly better in vivo L1210 antitumor activity than nucleoside **17**. *ara*-C, dFC, FC, and DAU had % ILS values less than 161. Thus, an interesting question can be posed. Does the insignificant in vitro L1210 antitumor activity of nucleoside **17** yet excellent in vivo L1210 antitumor activity suggest some type of noncytotoxic antitumor activity? Biochemical studies to determine the mode of action of nucleoside **17** have been initiated and further evaluations of nucleoside **17** against a panel of tumors and as an agent that may inhibit DNA-cytosine methyltransferase and induce cellular differentiation are in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were determined on a Finnigan 4000 mass spectrometer with a INCOS 2300 data system using direct introduction, electron impact at 70 eV and 150 °C. ^{1}H NMR spectra were determined at 90 MHz on a Varian EM-390, at 100 MHz on an IBM WP100SY, at 200 MHz on a Varian XL-200, or at 300 MHz on a Varian XL-300 in Me_2SO-d_6 with tetramethylsilane as an internal standard. The presence of exchangeable protons was confirmed by the addition of deuterium oxide. ^{19}F NMR spectra were determined at 282 MHz on a Varian XL-300 with $CFCl_3$ as an external standard. Chemical shifts are recorded in ppm from the reference, with absorptions downfield from the reference being positive and those upfield negative.

Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter with a 10-cm, 1-mL microcell. UV spectra were determined on a Cary C118 UV–vis spectrophotometer. All compounds had infrared spectra (potassium bromide) consistent with their structure as determined on a Nicolet 205X FT/IR. Elemental analyses were determined by the microanalytical laboratory of this department. TLC was performed with E. Merck silica gel 60 F-254 precoated glass plates (0.25 mm). Flash column chromatography was effected with E. Merck silica gel, 230–450 mesh. Concentrations were performed on a Büchi rotary evaporator at ≤45 °C (20 torr).

2,3,5,6-Tetrafluoro-4-pyridinamine (2). This compound was prepared from pentafluoropyridine (1) according to Chambers et al.:[19] mp 80–82 °C (lit.[19] mp 85–86 °C); ^{19}F NMR δ −96.03 (m, F-2), −163.23 (m, F-3) [lit.[19] ^{19}F NMR δ −95.72 (F-2), −165.94 (F-3)]; MS, *m/e* 166 (M^+).

4-Amino-3,5,6-trifluoro-2(1*H*)-pyridinone (3). A suspension of 16.26 g (97.9 mmol) of **2** in 350 mL of 1 N NaOH was heated under reflux for 6 h. Small amounts of ether were used to wash down the starting material that sublimed into the condenser. The solution was cooled and acidified with concentrated HCl. The solid was collected by filtration and dissolved in EtOAc. The solution was filtered to remove a small amount of solid and then concentrated to give 12.8 g of material. Recrystallization from

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toluene gave 11.83 g (73.7%) of **3** as shiny, off-white needles: mp 199–201 °C; ^{1}H NMR (90 MHz) δ 6.56 (s, 2, NH_2), 11.07 (s, 1, NH); ^{19}F NMR δ −96.16 (m, F-6), −162.52 (m, F-3 or -5), −170.06 (m, F-5 or -3); MS, *m/e* 164 (M^+). Anal. ($C_5H_3F_3N_2O$) C, H, F, N.

2,3,5-Trifluoro-6-hydrazino-4-pyridinamine (4). A solution of 10.0 g (60.2 mmol) of **2** and 40 mL of anhydrous hydrazine in 400 mL of EtOH was heated under reflux for 24 h. The solution was cooled and filtered to remove a small amount of white solid. The filtrate was concentrated to give a solid. Recrystallization from EtOH gave 7.67 g (69.5%) of **4** as a dark tan solid: mp 189–191 °C; ^{1}H NMR (200 MHz) δ 3.89 (s, 2, NH_2, exchangeable), 6.35 (s, 2, NH_2, exchangeable), 7.37 (s, 1, NH, exchangeable); ^{19}F NMR δ −98.13 (m, F-6), −165.02 (m, F-3 or -5), −175.93 (m, F-5 or -3); MS, *m/e* 178 (M^+). Anal. ($C_5H_5F_3N_4$) C, H. N.

2,3,5-Trifluoro-4-pyridinamine (5). To a suspension of 17.06 g (96 mmol) of **4** in 50 mL of distilled H_2O cooled in an ice bath was added a solution of 88.5 g (560 mmol) of $CuSO_4$ in a minimum amount of distilled H_2O. The temperature was not allowed to exceed 25 °C during the addition. Gas was evolved and the suspension became dark green. The suspension was stirred at room temperature 48 h and diluted with EtOAc. The mixture was filtered to remove a small amount of black solid. The layers were separated, and the H_2O layer was extracted with EtOAc. The EtOAc extracts were combined, dried ($MgSO_4$), and concentrated to give 11.77 g of a red solid. This was dissolved in MeOH and treated with 50 g of flash silica gel, and the MeOH was evaporated. The resulting powder was applied to a column of 800 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2 gave 7.89 g (56%) of **5** as shiny, white crystals: mp 103–105 °C; ^{1}H NMR (100 MHz) δ 6.93 (s, 2, NH_2), 7.72 (d of d, $J_{H\text{-}6\text{-}F\text{-}5,F\text{-}2 or F\text{-}3} < 3$, < 3 Hz, 1, H-6); ^{19}F NMR δ −93.70 (m, F-2), −148.83 (m, F-3 or -5), −162.02 (m, F-5 or -3); MS, *m/e* 148 (M^+). Anal. ($C_5H_3F_3N_2$) C, H, N.

4-Amino-3,5-difluoro-2(1*H*)-pyridinone (6). A suspension of 6.75 g (45.6 mmol) of **5** in 290 mL of 2 N NaOH was heated under reflux for 24 h. Small amounts of ether were used to wash down the starting material that sublimed into the condenser. The solution was cooled and acidified with 48 mL of concentrated HCl. A white solid precipitated. The suspension was concentrated by coevaporating with EtOH. To the residue was added MeOH, and the suspension was heated to boiling and filtered to remove the inorganic material. The filtrate was treated with 25 g of flash silica gel. Evaporation of the MeOH gave a powder, which was applied to a column of 200 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (10:1) gave a solid, which was recrystallized from H_2O to give 5.47 g (82.1%) of **6** as a light beige solid: mp 240–242 °C; ^{1}H NMR (100 MHz) δ 6.35 (s, 2, NH_2, exchangeable), 7.25 (d of d, $J_{H\text{-}6\text{-}F\text{-}5,F\text{-}3}$ = 6, 2 Hz, 1, H-6), 10.92 (br s, 1, NH, exchangeable); ^{19}F NMR δ −164.88 (m, F-3 or -5), −165.14 (m, F-5 or -3); MS, *m/e* 146 (M^+). Anal. ($C_5H_4F_2N_2O$) C, H, N.

4-Amino-3-fluoro-2(1*H*)-pyridinone (7) and 4-Amino-5-fluoro-2(1*H*)-pyridinone (8). A solution of 1.6 g (10 mmol) of **3** in 50 mL of EtOH was treated with 3.2 mL (100 mmol) of anhydrous N_2H_4. The resulting suspension was heated under reflux for 48 h. Another 3.2 mL (100 mmol) of anhydrous N_2H_4 was added to the solution and heating under reflux was continued another 24 h. The resulting suspension was filtered to remove a white solid, which was discarded. The filtrate was concentrated to give 1.65 g of a gold oil. The oil was dissolved in MeOH, and the solution was filtered to remove a small amount of solid. To the solution was added 6 g of flash silica gel, and the MeOH was evaporated. The resulting powder was applied to a column of 200 g of flash silica gel packed in CH_2Cl_2/MeOH (4:1). Flash chromatography with the same solvent gave 1.06 g of material. This material was dissolved in MeOH and treated with 5 g of flash silica gel, and the MeOH was evaporated. The resulting powder was applied to a column of 100 g of flash silica gel packed in CH_3CN/H_2O (10:1). Flash chromatography with the same solvent gave two products. Fractions containing the first product were concentrated to give 0.8 g of material. This material was dissolved in MeOH, and the solution was filtered. Evaporation of the MeOH gave 700 mg (55%) of **7** as a tan solid: mp 222–226 °C; ^{1}H NMR (100 MHz) δ 5.75 (t, $J_{H\text{-}5\text{-}H\text{-}6,F\text{-}3}$ = 7 Hz, 1, H-5), 6.03 (s, 2, NH_2, exchangeable), 6.88 (d, $J_{H\text{-}6\text{-}H\text{-}5}$ = 7 Hz, 1, H-6), 10.85 (br s, 1, NH, exchangeable); ^{19}F NMR δ −169.30 (d, $J_{F\text{-}3\text{-}H\text{-}5}$ = 6.4 Hz, F-3); MS, *m/e* 128 (M^+). Anal. ($C_5H_5FN_2O$) C, H, N.

Fractions containing the second product were concentrated to give 100 mg (8%) of **8** as a beige solid. The analytical sample of **8** was obtained in a larger scale experiment by recrystallization from EtOH–ether: mp 230–232 °C; ^{1}H NMR (100 MHz) δ 5.32 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 9 Hz, 1, H-3), 6.28 (s, 2, NH_2, exchangeable), 7.27 (d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 7 Hz, 1, H-6), 10.32 (br s, 1, NH, exchangeable); ^{19}F NMR δ −163.22 (t, $J_{F\text{-}5\text{-}H\text{-}3,H\text{-}6}$ = 7.0 Hz, F-5); MS, *m/e* 128 (M^+). Anal. $C_5H_5FN_2O{\cdot}0.1H_2O$) C, H, N, H_2O.

4-Amino-5-fluoro-2(1*H*)-pyridinone Hydrochloride. To 300 mg (2 mmol) of **8** was added 30 mL of concentrated HCl. The solution was concentrated, coevaporating with EtOH to give a solid. The solid was dissolved in a small amount of MeOH and ether was added to precipitate a gum, which crystallized on stirring. Filtration gave 350 mg (90%) of **8**·HCl as a beige solid: mp 202–205 °C (lit.[18] mp 201–205 °C); UV (0.1 N HCl) max 257 nm (ϵ 13 300), (MeOH) max 258 nm (ϵ 11 700), (1 N NaOH) max 288 nm (ϵ 3740) [lit.[18] UV (0.1 N HCl) max 260 nm (ϵ 15 476), (MeOH) max 258 nm, 275 nm (sh), (1 N NaOH) max 288 nm]; ^{1}H NMR (100 MHz) δ 6.43 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 8 Hz, 1, H-3), 7.90 (s, 2, NH_2, exchangeable), 8.03 (d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 6 Hz, 1, H-6) [lit.[18] ^{1}H NMR (Me_2SO-d_6) δ 6.54 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 7.5 Hz, 1, H-3), 8.05 (d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 5.8 Hz, 1, H-6)]. Anal. ($C_5H_5FN_2O{\cdot}1.0HCl{\cdot}0.1H_2O$) C, H, N, Cl^-, H_2O.

3,5-Dichloro-2,6-difluoro-4-pyridinamine (10). The compound was prepared from 3,5-dichloro-2,4,6-trifluoropyridine (**9**) according to Chambers et al.:[20] mp 107–110 °C (lit.[20] mp 112–113 °C); ^{19}F NMR δ −73.41 (s, F-2) (lit.[20] ^{19}F NMR δ −75.600); MS, *m/e* 198 (M^+). Anal. ($C_5H_2Cl_2F_2N_2$) C, H, N.

2,6-Difluoro-4-pyridinamine (11). A solution of 12.2 g (61.3 mmol) of **10** and 17 mL (130 mmol) of Et_3N in 120 mL of MeOH was treated with 1 g of 20% Pd/C and H_2 at an initial pressure of 52 psi for 3 days. The reaction was treated with an additional 1 g of 20% Pd/C and repressurized to 52 psi two times during its course. The catalyst was filtered, and the filtrate was concentrated. The residue was partitioned between ether and H_2O. The ether layer was dried ($MgSO_4$) and concentrated to give 7.92 g of material. This was dissolved in MeOH and the solution was treated with 50 g flash silical gel. The MeOH was evaporated to give a powder, which was applied to a column of 600 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2 gave 7.39 g (92.6%) of **11** as a fluffy white solid: mp 125–127 °C (lit.[21] mp 124–125 °C); ^{1}H NMR (100 MHz) δ 6.03 (s, 2, H-3 and H-5), 6.88 (s, 2, NH_2, exchangeable); ^{19}F NMR δ −69.33 (s, F-2) (lit.[21] ^{19}F NMR δ −68.7); MS, *m/e* 130 (M^+). Anal. ($C_5H_4F_2N_2$) C, H, N.

4-Amino-6-fluoro-2(1*H*)-pyridinone (12). A suspension of 4.94 g (38 mmol) of **11** in 250 mL of 1 N NaOH was heated under reflux 24 h. The resulting solution was cooled and acidified with 21 mL of concentrated HCl. The suspension was extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a solid. Recrystallization from toluene–EtOAc gave 3.60 g (74.1%) of **12** as a dull cream solid: mp 176–178 °C; ^{1}H NMR (100 MHz) δ 5.60 (s, 2, H-3 and H-5), 6.20 (s, 2, NH_2, exchangeable), 10.30 (s, 1, NH, exchangeable); ^{19}F NMR δ −74.39 (s, F-6); MS, *m/e* 128 (M^+). Anal. ($C_5H_5FN_2O$) C, H, N.

4-Amino-3-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (14). A suspension of 1.00 g (7.8 mmol) of **7** and 5 mg of $(NH_4)_2SO_4$ in 100 mL of hexamethyldisilazane (HMDS) was heated under reflux for 24 h. The solution was concentrated to give a yellow oil, which was dissolved in 100 mL of 1,2-dichloroethane. This solution was cooled in an ice bath with 4.33 g (8.6 mmol) and first treated with a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and 50 mL of 1,2-dichloroethane and then with 1.1 mL (9.4 mmol) of $SnCl_4$. The resulting yellow solution was stirred 30 min cold, followed by 24 h at room temperature, and then poured into an ice-saturated $NaHCO_3$ solution. The solution was treated with EtOAc, and the mixture was filtered through Celite. The aqueous layer was separated and extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and concentrated to give 4.68 g of yellow foam. The yellow foam was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 250 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (50:1) gave 3.49 (78.3%) of **14** as a white foam: ^{1}H NMR (100 MHz) δ

4.50–4.83 (m, 3, H-5′, H-5″, H-4′), 5.77–6.07 (m, 3, H-2′, H-3′, H-5), 6.28 (d, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 3 Hz, 1, H-1′), 6.43 (s, 2, NH_2, exchangeable), 7.33–8.10 (m, 16, Ph and H-6). Anal. ($C_{31}H_{25}FN_2O_8$) H, N; C: calcd, 65.03; found, 64.57.

4-Amino-3,5-difluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (13). Ribosylation of 1.00 g (6.85 mmol) of **6** analogous to the preparation of **14** gave 4.48 g of crude material. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 250 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (100:1) gave 3.64 g (90.1%) of **13** as a white foam: ^{1}H NMR (200 MHz) δ 4.64–4.74 (m, 3, H-5′, H-5″, H-4′), 5.92 (m, 2, H-2′, H-3′), 6.30 (d, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 3.4 Hz, 1, H-1′), 6.71 (s, 2, NH_2, exchangeable), 7.38–8.02 (m, 16, Ph and H-6); ^{19}F NMR δ −159.13 (m, F-3 or -5), 161.65 (m, F-5 or -3). Anal. ($C_{31}H_{24}F_2N_2O_8$) C, H, N.

4-Amino-5-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (15). Ribosylation of 1.51 g (11.8 mmol) of **8** in the manner described above gave 7.47 g of crude material. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 250 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (50:1) gave 4.37 g (64.6%) of **15** as a white foam: ^{1}H NMR (200 MHz) δ 4.63–4.73 (m, 3, H-5, H-5″, H-4′), 5.34 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 8.7 Hz, 1, H-3), 5.9 (m, 2, H-2′, H-3′), 6.24 (d, $J_{H\text{-}1'\text{-}H'\text{-}2'}$ = 3.4 Hz, 1, H-1′), 6.60 (s, 2, NH_2, exchangeable), 7.38–8.02 (m, 16, Ph and H-6). Anal. ($C_{31}H_{25}FN_2O_8$) C, H, N.

4-Amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (17). A solution of 2.21 g (3.86 mmol) of **14** in 42.5 mL (4.25 mmol) of 0.1 N $NaOCH_3$ was stirred at room temperature for 24 h. MeOH-washed IRC-50 (H^+) ion exchange resin was added to the solution. The suspension was stirred until neutral (pH paper). The resin was filtered, washed with MeOH, and discarded. The filtrate was concentrated to give a semisolid, which was triturated in ether to give 1.0 g of material. This was combined with 550 mg of material obtained from another experiment using 1.19 g of **14**. The resulting 1.55 g of material was dissolved in MeOH, and the solution was treated with 25 g of flash silica gel. Evaporation of the MeOH gave a powder, which was applied to a column of 200 g of flash silica gel packed in CH_2Cl_2/MeOH (4:1). Flash chromatography with the same solvent gave 0.91 g of material. Recrystallization from MeOH gave 600 mg (39%) of **17** as a white solid: mp 234–236 °C; $[\alpha]^{22}_D$ +8.4° (*c* 1.02, H_2O); UV (0.1 N HCl) max 255, 274 nm (ε 8400, 7000), (MeOH) max 255, 279 nm (ε 6500, 5500), (1 N NaOH) max 255, 278 nm (ε 8900, 6800); ^{1}H NMR (200 MHz) δ 3.45–3.97 (m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 5.0 (m, 2, OH (2), exchangeable), 5.26 (d, 1, OH, exchangeable), 5.82 (t, $J_{H\text{-}5\text{-}H\text{-}6,F\text{-}3}$ = 7.6 Hz, 1, H-5), 5.94 (d, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 3.9 Hz, 1, H-1′), 6.17 (s, 2, NH_2, exchangeable), 7.43 (d, $J_{H\text{-}6\text{-}H\text{-}5}$ = 7.7 Hz, 1, H-6); ^{19}F NMR δ −167.89 (d, $J_{F\text{-}3\text{-}H\text{-}5}$ = 7.6 Hz, F-3); MS, *m/e* 260 (4%, M^+). Anal. ($C_{10}H_{13}FN_2O_5$) C, H, N.

4-Amino-3,5-difluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (16). Deprotection of 3.64 g (6.17 mmol) of **13** according to the manner described above gave crude material. This was dissolved in MeOH and treated with 7 g of flash silica gel. Evaporation of the MeOH gave a powder, which was applied to a column of 100 g of flash silica gel packed in CH_2Cl_2/MeOH (4:1). Flash chromatography with the same solvent gave 1.27 g of material, which was triturated in ether and then recrystallized from EtOH to give 700 mg (40%) of **16** as a white solid: mp 175–177 °C; $[\alpha]^{22}_D$ +24.2° (*c* 1.05, H_2O); UV (0.1 N HCl) max 257, 280 nm (ε 10 500, 6100), (MeOH) max 258, 284 nm (ε 10 100, 5600), (1 N NaOH) max 258, 282 nm (ε 12 000, 6700); ^{1}H NMR (300 MHz) δ 3.56–4.01 (m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 5.04 (d, 1, OH, exchangeable), 5.22 (t, 1, OH, exchangeable), 5.37 (d, 1, OH, exchangeable), 6.00 (d of d, $J_{H\text{-}1'\text{-}H\text{-}2',F\text{-}5}$ = 3.8, 1.4 Hz, 1, H-1′), 6.53 (s, 2, NH_2, exchangeable), 7.92 (d of d, $J_{H\text{-}6\text{-}F\text{-}5,F\text{-}3}$ = 7.8, 1.6 Hz, 1, H-6); ^{19}F NMR δ −162.32 (m, F-3 or -5), −164.13 (m, F-5 or -3); MS, *m/e* 279 (9%, $M^+ + 1$). Anal. ($C_{10}H_{12}F_2N_2O_5$) C, H, N.

4-Amino-5-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (18). Deprotection of 4.37 g (7.63 mmol) of **15** according to the manner described above gave 710 mg (36%) of **18** as a fluffy white solid. Recrystallization from EtOH: mp 203–205 °C (lit.[18] mp 92–94 °C); $[\alpha]^{22}_D$ +21.5° (*c* 1.17, H_2O); UV (0.1 N HCl) max 263 nm (ε 14 900), (MeOH) max 263, 287 (sh) nm (ε 10 500, 5300), (1.0 N NaOH) max 263, 286 (sh) nm, (ε 11 200, 5900) [lit.[18] UV (0.1 N HCl) max 264 nm, (MeOH) max 264, 287 (sh) nm (ε 11 450, 6300) (1.0 N NaOH) max 262, 288 (sh) nm]; ^{1}H NMR (200 MHz) δ 3.48–3.97 (m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 4.95 (d, 1, OH, exchangeable), 5.15 (t, 1, OH, exchangeable), 5.27 (m, 1, OH, exchangeable), 5.30 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 8.8 Hz, 1, H-3), 5.88 (d of d, $J_{H\text{-}1'\text{-}H\text{-}2',F\text{-}5}$ = 3.9, 1.6 Hz, 1, H-1′), 6.38 (s, 2, NH_2 exchangeable), 7.87 (d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 8.3 Hz, 1, H-6) [lit.[18] ^{1}H NMR (Me_2SO-d_6) δ 5.66 (d, $J_{H\text{-}3\text{-}F\text{-}5}$ = 8.0 Hz, 1, H-3), 6.05 (s, 1, H-1′), 7.86 (d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 7.8 Hz, 1, H-6)]; ^{19}F NMR δ −163.46 (t, $J_{F\text{-}5\text{-}H\text{-}3,H\text{-}6}$ = 8.1 Hz, F-5); MS, *m/e* 260 (3%, M^+). Anal. ($C_{10}H_{13}FN_2O_5$) C, H, N.

4-Amino-3-fluoro-1-[3,5-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-ribofuranosyl]-2(1*H*)-pyridinone (19). A solution of 1.00 g (3.84 mmol) of **17** in 50 mL of pyridine, cooled by an ice bath, was treated with 1.34 mL (3.84 mmol) of 1,3-dichloro-1,1,3,3-tetrakis(1-methylethyl)disiloxane. The solution was stirred at room temperature for 24 h and concentrated. The residue was partitioned between H_2O and EtOAc. The EtOAc layer was washed successively with cold 1 N HCl (2 × 50 mL), H_2O, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give 1.98 g of a gum. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 100 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (100:1) gave 1.30 g (67.4%) of **19** as a white foam: ^{1}H NMR (200 MHz) δ 0.89–1.03 (m, 28, isopropyl), 3.85–4.10 (m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 5.64 (d, 1, 2′-OH, exchangeable), 5.74 (s, 1, H-1′), 5.81 (t, $J_{H\text{-}5\text{-}H\text{-}6,F\text{-}3}$ = 7.5 Hz, 1, H-5), 6.20 (s, 2, NH_2, exchangeable), 7.34 (d, $J_{H\text{-}6\text{-}H\text{-}5}$ = 7.5 Hz, 1, H-6); MS, *m/e* 502 (16%, M^+). Anal. ($C_{22}H_{39}FN_2O_6Si_2$) C, H, N.

1-[2-*O*-Acetyl-3,5-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-ribofuranosyl]-4-amino-3-fluoro-2-(1*H*)-pyridinone (20). A solution of 500 mg (1.0 mmol) of **19** in 10 mL of pyridine, cooled by an ice bath, was treated with 0.10 mL (1.0 mmol) of Ac_2O. The solution was stirred at room temperature for 24 h. Another 0.10 mL of Ac_2O was added, and the solution was heated at 60 °C for 24 h. The solution was concentrated, and the residue was partitioned between H_2O and EtOAc. The EtOAc layer was washed successively with cold 1 N HCl (2 × 50 mL), H_2O, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give 520 mg of a foam. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 100 g of flash silica gel packed in CH_2Cl_2. Flash chromatography using CH_2Cl_2/MeOH (100:1) gave 470 mg (87%) of **20** as a light yellow foam: ^{1}H NMR (200 MHz) δ 0.90–1.03 (m, 28, isopropyl), 2.06 (s, 3, $COCH_3$), 3.85–4.06 (m, 3, H-4′, H-5′, H-5″), 4.48 (d of d, $J_{H\text{-}3'\text{-}H\text{-}4',H\text{-}2'}$ = 8.7, 5.6 Hz, 1, H-3′), 5.32 (d of d, $J_{H\text{-}2'\text{-}H\text{-}3',H\text{-}1'}$ = 5.6, 1.0 Hz, 1, H-2′), 5.84 (d, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 1.2 Hz, 1, H-1′), 5.86 (t, $J_{H\text{-}5\text{-}H\text{-}6,F\text{-}3}$ = 7.5 Hz, 1, H-5), 6.30 (s, 2, NH_2, exchangeable), 7.27 (d, $J_{H\text{-}6\text{-}H\text{-}5}$ = 7.8 Hz, 1, H-6). Anal. ($C_{24}H_{41}FN_2O_7Si_2$) C, H, N.

4-Amino-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-3,5-difluoro-2(1*H*)-pyridinone (21) and 4-Amino-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl]-3,5-difluoro-2(1*H*)-pyridinone (23). Deoxyribosylation of 3.68 g (2.52 mmol) as described above gave 12.0 g of crude material. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 800 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with EtOAc/CH_2Cl_2 (3:1) provided two products. Fractions containing the faster moving product were concentrated to give 2.19 (17.4%) of **21** as a white foam: $[\alpha]^{22}_D$ −21.6° (*c* 1.05, MeOH); UV (0.1 N HCl) max 242 nm (ε 2000), (MeOH) max 242, 280 nm (ε 37 200, 6800); ^{1}H NMR (300 MHz) δ 2.40 (s, 3, CH_3), 2.42 (s, 3, CH_3), 2.49–2.59 (m, 2, H-2′, H-2″), 4.52–4.63, 5.59 (2 m, 4, H-3′, H-4′, H-5′, H-5″), 6.52 (t, $J_{H\text{-}1'\text{-}H\text{-}2',H\text{-}2''}$ = 6.7 Hz, peak width 13.5 Hz, 1, H-1′), 6.62 (s, 2, NH_2), 7.35 (d of d, 4, Ph), 7.58 (d of d, $J_{H\text{-}6\text{-}F\text{-}5,F\text{-}3}$ = 7.4, 1.5 Hz, 1, H-6), 7.90 (d of d, 4, Ph). Anal. ($C_{26}H_{24}F_2N_2O_6$) C, H, N.

Intermediate fractions were concentrated to give 7.58 g (60.6%) of a mixture of **21** and **23** as a white foam.

Fractions containing the slower moving product were concentrated to give 0.44 g (3.5%) of **23** as a white foam: $[\alpha]^{22}_D$ −49.2° (*c* 1.01, MeOH); UV (0.1 N HCl) max 244 nm (2500), (MeOH) max 242, 280 nm (ε 34 700, 6500); ^{1}H NMR (100 MHz) δ 2.37 (s, 3, CH_3), 2.38 (s, 3, CH_3), 2.4, 2.9 (2 m, 2, H-2′, H-2″), 4.45, 5.13, 5.53 (3 m, 4, H-3′, H-4′, H-5′, H-5″), 6.35 (d, $J_{H\text{-}1'\text{-}H\text{-}2'}$ = 6 Hz, peak width 6 Hz, 1, H-1′), 6.53 (s, 2, NH_2), 7.33, 7.83 (2 m, 9, Ph and H-6). Anal. ($C_{26}H_{24}F_2N_2O_6$) C, H, N.

4-Amino-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-3-fluoro-2(1*H*)-pyridinone (22) and 4-Amino-1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl]-3-fluoro-2(1*H*)-pyridinone (24). A suspension of 6.40 g (50 mmol) of **7** and a catalytic amount of $(NH_4)_2SO_4$ in 250 mL of HMDS was heated under reflux for 24 h. The solution was concentrated to give a yellow oil, which was treated with 500 ml of 1,2-dichloroethane and 19.44 g (50 mmol) of 1-chloro-2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranose. The solution was cooled to −25 °C by a dry ice/IPA bath. To the resulting suspension was added a solution of 2.4 mL (130 mmol) of trimethylsilyl trifluoromethanesulfonate in 100 mL of 1,2-dichloroethane during 30 min such that the temperature did not exceed −25 °C. The suspension was allowed to reach room temperature, becoming a solution, and was stirred for 24 h. The solution was poured into an ice-saturated $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers werre separated, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and concentrated to give 24.0 g of a yellow foam. The foam was dissolved in CH_2Cl_2 and applied to a column of 1 kg of flash silica gel packed in CH_2Cl_2. Flash chromatography, initially with CH_2Cl_2/EtOAc (10:1) and gradually increasing the polarity to CH_2Cl_2/EtOAc (2:1), provided two products. Fractions containing the faster moving product were concentrated to give 5.10 g (21.3%) of **22** as a white foam. Intermediate fractions were concentrated to give 9.66 g (40.3%) of a mixture of **22** and **24** as a white foam. Fractions containing the slower moving product were concentrated to give 5.08 g (21.2%) of **24** as a white foam.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone (25). Deprotection of 2.00 g (4.01 mmol) of **21** as described gave 680 mg (65%) of **25** as a light yellow solid. Recrystallization from EtOH: mp 191–193 °C; $[\alpha]^{22}_D$ +52.9° (*c* 1.06, H_2O); UV (0.1 N HCl) max 256, 280 nm (ε 9900, 5900), (MeOH) max 257, 286 nm (ε 9600, 5700), (1 N NaOH) max 256, 282 nm (ε 10 400, 6200); ^{1}H NMR (100 MHz) δ 1.80–2.27 (m, 2, H-2′, H-2″), 3.60, 3.80, 4.20 (3 m, 4, H-3′, H-4′, H-5′, H-5″), 5.10 (t, $J_{5'\text{-OH-H-5}',\text{H-5}''}$ = 5 Hz, 1, 5′-OH, exchangeable), 5.25 (d, $J_{3'\text{-OH-H-3}'}$ = 5 Hz, 1, 3′-OH, exchangeable), 6.37 (t, $J_{\text{H-1}'\text{-H-2}',\text{H-2}''}$ = 7 Hz, peak width 14 Hz, 1, H-1′), 6.52 (s, 2, NH_2, exchangeable), 7.82 (d of d, $J_{\text{H-6-F-5,F-3}}$ = 9, 2 Hz, 1, H-6); ^{19}F NMR δ −163.05 (m, F-3 or -5), −165.58 (m, F-5 or -3); MS, *m/e* 262 (6%, M^+). Anal. ($C_{10}H_{12}F_2N_2O_4$) C, H. N.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3-fluoro-2(1*H*)-pyridinone (26). deprotection of 5.80 g (12 mmol) of **22** as described above gave 920 mg (31%) of **26** as a cream solid. Recrystallization (two times) from EtOH: mp 168–170 °C; $[\alpha]^{22}_D$ +41.7° (c 1.03, H_2O), UV (0.1 N HCl) max 254, 274 nm (ε 8100, 6800), (MeOH) max 254, 280 nm (ε 7300, 6400), (1 N NaOH) max 252, 278 nm (ε 8900, 7300); ^{1}H NMR (200 MHz) δ 1.87–2.18 (m, 2, H-2′, H-2″), 3.5, 3.8, 4.2 (3 m, 4, H-3′, H-4′, H-5′, H-5″), 4.5 (br s, 2, 3′-OH, 5′-OH, exchangeable), 5.88 (t, $J_{\text{H-5-F-3,H-6}}$ = 7.5 Hz, 1, H-5), 6.17 (br s, 2, NH_2, exchangeable), 6.63 (d of d, $J_{\text{H-1}'\text{-H-2}',\text{H-2}''}$ = 7.4, 6.2 Hz, peak width 13.6 Hz, 1, H-1′), 7.45 (d of d, $J_{\text{H-6-H-5,F-3}}$ = 7.7, 1.2 Hz, 1, H-6); ^{19}F NMR δ −157.42 (d, $J_{\text{F-3-H-5}}$ = 7.2 Hz, F-3); MS, *m/e* 244 (3%, M^+). Anal. ($C_{10}H_{13}FN_2O_4 \cdot 0.15H_2O$) C, H. N, H_2O.

4-Amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3,5-difluoro-2(1*H*)-pyridinone (27). Deprotection of 2.69 g (5.4 mmol) of **23** as described above gave 810 mg (57%) of **27** as a light cream solid. Recrystallization from EtOH: mp 177–179 °C; $[\alpha]^{22}_D$ +25.0° (*c* 0.85, DMF); UV (0.1 N HCl) max 255, 277 nm (ε 10 200, 6100), (MeOH) max 257, 285 nm (ε 9500, 5500), (1 N, NaOH) max 255, 282 nm (ε 10 300, 6100); ^{1}H NMR (200 MHz) δ 1.8, 2.6 (2 m, 2, H-2′, H-2″), 3.4, 4.2 (2 m, 4, H-3′, H-4′, H-5′, H-5″), 4.86 (t, 1, 5′-OH, exchangeable), 5.31 (d, 1, 3′-OH, exchangeable), 6.33 (distorted d of d, $J_{\text{H-1}'\text{-H-2}',\text{H-2}''}$ = 7.3, ~ 3 Hz, width ~ 10 Hz, 1, H-1′), 6.47 (s, 2, NH_2, exchangeable), 7.73 (d of d, $J_{\text{H-6-F-5,F-3}}$ = 7.8, 1.6 Hz, H-6); ^{19}F NMR δ −163.70 (m, F-3 or -5), −165.34 (m, F-5 or -3); MS, 262 (6%, M^+). Anal. ($C_{10}H_{12}F_2N_2O_4$) C, H. N.

4-Amino-1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-3-fluoro-2(1*H*)-pyridinone (28). Deprotection of 5.08 g (11 mmol) of **24** gave 750 mg (29%) of **28** as white solid. Recrystallization from EtOH: mp 161–163 °C; $[\alpha]^{22}_D$ −11.8° (*c* 1.11, H_2O); UV (0.1 N HCl) max 252, 275 nm (ε 6800, 5700), (MeOH) max 252, 278 nm (ε 7200, 6300), (1 N NaOH) max 252, 277 nm (7900, 6500); ^{1}H NMR (200 MHz) δ 1.8, 2.5 (2 m, 2, H-2′, H-2″), 3.4, 4.1 (2 m, 4, H-3′, H-4′, H-5′, H-5″), 4.82 (t, 1, 5′-OH, exchangeable), 5.20 (d, 1, 3′-OH, exchangeable), 5.83 (t, $J_{\text{H-5-H-6,F-3}}$ = 7.6 Hz, 1, H-5), 6.10 (s, 2, NH_2, exchangeable), 6.23 (d of d, $J_{\text{H-1}',\text{H-2}',\text{H-2}''}$ = 7.6, 3.0 Hz, peak width 10.7 Hz, 1, H-1′), 7.42 (d, $J_{\text{H-6-H-5}}$ = 7.5 Hz, 1, H-6); ^{19}F NMR δ −161.10 (d, $J_{\text{F-3-H-5}}$ = 7.3 Hz, F-3); MS, *m/e* 244 (8%, M^+). Anal. ($C_{10}H_{13}FN_2O_4$ C, H. N.

4-Amino-3-fluoro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (29). To a solution of 1.00 g (3.84 mmol) of **17** in 20 mL of pyridine, cooled by an ice bath, was added dropwise 1.20 mL (12.7 mmol) of Ac_2O. The solution was stirred at room temperature for 24 h and then concentrated, coevaporating with toluene. The residue was combined with that from an experiment using 500 mg (1.9 mmol) of **17** as starting material. The residues were dissolved in EtOAc, and the solution was washed with H_2O and then brine, dried ($MgSO_4$), and concentrated to give 1.63 g of a gum. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 100 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (50:1) gave 1.49 g (67.1%) of **29** as an off-white foam: $[\alpha]^{22}_D$ +16.8° (*c* 1.09, MeOH); UV (0.1 N HCl) max 254, 280 nm (ε 6700, 5800), (MeOH) max 255, 283 nm (ε 6900, 6200), (1 N NaOH) max 255, 280 nm (ε 7500, 5800); ^{1}H NMR (100 MHz) δ 2.03, 2.07 (2 s, 9, 3 $COCH_3$), 4.25, 5.40 (2 m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 5.92 (t, $J_{\text{H-5-H-6,F-3}}$ = 8 Hz, 1, H-5), 6.07 (d, $J_{\text{H-1}'\text{-H-2}'}$ = 4 Hz, 1, H-1′), 6.38 (s, 2, NH_2), 7.28 (d, $J_{\text{H-6-H-5}}$ = 8 Hz, 1, H-6); MS, *m/e* 386 (24%, M^+). Anal. ($C_{16}H_{19}FN_2O_8$) C, H. N.

4-(Acetylamino)-3-fluoro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone (30). A suspension of 500 mg (1.92 mmol) of **17** and 20 mg (catalytic amount) of 4-(dimethylamino)pyridine in 10 mL of Ac_2O was heated on a steam bath for 3 h. The resulting solution was concentrated, coevaporating with EtOH and toluene. The residue was dissolved in EtOAc, and the solution was washed with H_2O and then brine, dried ($MgSO_4$), and concentrated to give 680 mg of a gum. This was dissolved in a minimum amount of CH_2Cl_2 and applied to a column of 100 g of flash silica gel packed in CH_2Cl_2. Flash chromatography with CH_2Cl_2/MeOH (50:1) gave 330 mg (40%) of **30** as a white foam: $[\alpha]^{22}_D$ +21.1° (*c* 0.53, MeOH); ^{1}H NMR (200 MHz) δ 2.03, 2.06, 2.11 (4 s, 12, 4 $COCH_3$), 4.31, 5.40 (2 m, 5, H-2′, H-3′, H-4′, H-5′, H-5″), 6.10 (d, $J_{\text{H-1}'\text{-H-2}'}$ = 4.3 Hz, 1, H-1′), 7.18 (d of d, *J* = 7.7, 6.7 Hz, 1, H-5), 7.51 (d of d, $J_{\text{H-6-H-5,F-3}}$ = 8.1, 1.5 Hz, 1, H-6), 10.12 (s, 1, NH); MS, *m/e* 428 (7%, M^+). Anal. ($C_{18}H_{21}FN_2O_9 \cdot 0.3H_2O$) C, H. N, H_2O.

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