Nucleic Acid Related Compounds. 21. Direct Fluorination of Uracil and Cytosine Bases and Nucleosides Using Trifluoromethyl Hypofluorite. Mechanism, Stereochemistry, and Synthetic Applications[1,2]

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Abstract: Treatment of a methanolic solution of uracil (**1a**) or 1-methyluracil (**1b**) at −78 °C with trifluoromethyl hypofluorite (CF_3OF) in trichlorofluoromethane (Freon 11) at −78 °C resulted in rapid formation of (±)-*cis*-5-fluoro-6-methoxy-5,6-dihydrouracil (**2a**) (or the corresponding 1-methyl derivative **2b**) in high yield. The same compound (**2a**) was obtained by debromination of (±)-*r*-5-bromo-5-fluoro-*t*-6-methoxy-5,6-dihydrouracil (**5**). Adduct **5** was prepared by treatment of 5-fluorouracil (**3a**) with bromine in methanol (methyl hypobromite) or by reaction of 5-bromouracil (**4**) with trifluoromethyl hypofluorite in methanol. Adduct structures were compatible with ^1H and ^{19}F NMR data and a single-crystal x-ray analysis of **2b** confirmed stereochemical assignments. Evidence for a stereoelectronically selective mechanism for formation of cis fluoro to methoxy adducts was obtained using deuterium labeling. This effect is apparently operative with either cationic or anionic intermediates. Bases effect elimination of the elements of methanol from adducts **2a,b** to give 5-fluorouracil (**3a**) or 5-fluoro-1-methyluracil (**3b**) in ~90% overall yield from **1a** or **b**. Cytosine (**13**) was transformed into 5-fluorocytosine (**14**) in an analogous manner. A number of uracil and cytosine nucleosides (usually peracetylated) were subjected to this procedure to provide the corresponding 5-fluoro compounds. All nucleosides studied gave moderate to high product yields including uracil and cytosine ribonucleosides, 2′-deoxy-D-*erythro*-pentofuranosides (2′-deoxyribonucleosides), arabinosides, 2′- and/or 3′-*O*-methylribonucleosides, and the intact 1-β-D-arabinofuranosyluracil-$O^2 \rightarrow$2′-anhydronucleoside (**10**). Resolved ^{19}F and ^1H NMR parameters and certain mass spectral fragmentation trends are noted, and biochemical rationale for the biological evaluation of sugar-methylated 5-fluoropyrimidine nucleosides are discussed. The facile acetylation of nucleosides using 4-*N*,*N*-dimethylaminopyridine as catalyst is described. A reassignment of 5-fluorouracil photohydrate stereochemistry is suggested.

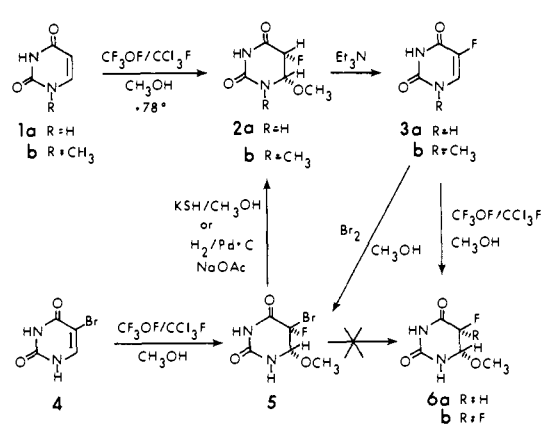
Prior to the initiation of our studies,[6] all reported syntheses of 5-fluoropyrimidine bases, nucleosides, and nucleotides had involved de novo construction of the base from small aliphatic precursors involving the preformed fluorine–carbon bond of the highly toxic ethyl fluoroacetate.[7,8] Transformation of the 4-keto group of 5-fluorouracil compounds to give the 4-amino function of analogous cytosine products involved thiation followed by amination,[8c,h,k] chlorination–amination,[7a,8g,l] or chlorination and displacement of chloro by alkoxyl with subsequent amination of the alkoxy derivative.[8e-g,j] We now wish to report mechanistic, stereochemical, and synthetic details of a convenient two-stage procedure for the direct fluorination of uracil and cytosine bases, nucleosides, and nucleotides[9] to give the corresponding 5-fluoropyrimidine compounds in moderate to high yields.

The biological activity and clinical uses of 5-fluorouracil and related compounds have been studied extensively and several reviews are available.[7b,10] A covalent complex of 5-fluoro-2′-deoxyuridylate and 5,10-methylenetetrahydrofolate with thymidylate synthetase[11] has been discovered recently.[12,13] This coupled with the recent finding of Holý et al.[14] that 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimidin-2-one 5′-phosphate (a 4-deoxyuracil 2′-deoxynucleotide with no dissociable proton on the base) is a strong *competitive* inhibitor of thymidylate synthetase would appear to obviate a previously considered pK_a binding criterion.[15] Appreciable incorporation of 5-fluorouracil into RNA (but not into DNA) has also been observed.[7b,16] Honjo and coworkers reported that 2′-*O*-and 3′-*O*-methyluridine[17] were unaffected by phosphorylase and hydrolase enzymes which rapidly cleave uridine to give uracil. Therefore, the synthesis of 2′- and 3′-*O*-methyl ethers of 5-fluoropyrimidine nucleosides as potential cytotoxic agents (RNA incorporation or enzyme inhibitors) of enhanced metabolic stability[18] was of interest.

Trifluoromethyl hypofluorite (CF_3OF) was synthesized by Cady and coworkers, and addition of this electrophilic reagent to a few unsaturated organic compounds was explored.[19] Barton et al. reported its use in fluorination of activated olefins and aromatic rings in 1968 and studied the reaction extensively in the steroid area.[20] In 1969 the reagent was also reported to add to unsaturated carbohydrates.[21] Our previous attempts to introduce fluorine into the uracil ring using fluoride nucleophiles with (±)-1-methyl-5-bromo-6-methoxy-5,6-dihydrouracil[22] (the adduct of 1-methyluracil with methyl hypobromite) gave 5-bromo-1-methyluracil by elimination of the elements of methanol from the adduct.[6a] Attention was then turned to investigation of analogous adduct formation–elimination using trifluoromethyl hypofluorite.

Treatment of a solution of uracil (**1a**) or 1-methyluracil[23] (**1b**) (Scheme I) in methanol at −78 °C with trifluoromethyl hypofluorite in fluorotrichloromethane (Freon 11) at −78 °C (*caution*)[24] resulted in rapid loss of uv absorption at 260 nm.

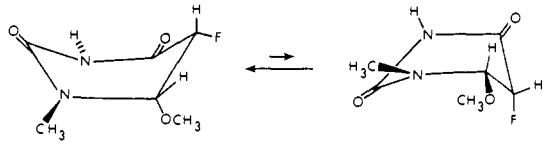
Scheme I



Removal of excess reagent and evaporation of solvents gave colorless adduct **2**. Treatment of **2** with triethylamine in aqueous methanol gave 5-fluorouracil[7a] (**3a**) or 1-methyl-5-fluorouracil[8g,23b] (**3b**) in over 90% overall yields from **1**.

^{1}H NMR spectra of the crude adducts (**2**) were sharp and indicated the presence of only one geometric isomer. Thus, the addition proceeded with apparently complete stereoselectivity as well as regiospecificity. A three-proton singlet at δ 3.30 was indicative of a methoxyl group. This indicated that solvent had been incorporated at C-6 rather than trifluoromethoxyl and this initially unexpected result was corroborated by the absence of a peak corresponding to trifluoromethyl in the ^{19}F NMR spectra. Elemental analyses as well as mass spectroscopy were in accord with 5-fluoro-6-methoxy-5,6-dihydrouracil (**2a**) or its 1-methyl derivative (**2b**) as the structures of the adducts.

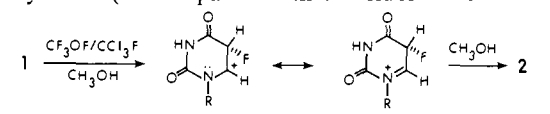
^{1}H and ^{19}F NMR spin coupling parameters of these adducts indicated H-6 to H-5, F-5 dihedral angles of intermediate magnitude (~60°) (see Experimental Section). Treatment of 5-fluorouracil (**3a**) under identical reaction conditions gave (±)-5,5-difluoro-6-methoxy-5,6-dihydrouracil (**6b**). Evaluations of cis and trans coupling constants are compatible with conformer i (F-5 replacing H-5 for **6b**) but not with "ring-flipped" conformer ii for all three adducts (**2a**, **2b**, and **6b**) in solution. The relative vicinal coupling magnitudes would be expected to be reversed for the corresponding trans adducts of **2a** and **2b**. However, configurational assignments based on such intermediate coupling values involving only the one obtained diastereomer of such a highly electronegatively substituted system would be capricious.[25] Therefore, a single-crystal x-ray analysis of **2b** was determined which conclusively established the cis stereochemistry of the adducts.[26] The solid-state conformation corresponds closely to that of i, which was derived by examination of Dreiding molecular models.



i ii

The apparently complete stereoselectivity in the formation of **2** from **1** using CF_3OF/CH_3OH is very interesting. Barton[20d] had considered the possibility of cyclic addition or "intimate" ion pair mechanisms to explain the cis addition of trifluoromethoxyl and fluoro groups to olefinic systems using CF_3OF/CCl_3F–$CHCl_3$. He noted that methanol added in "large (molecular) excess"[20d] did not compete successfully with trifluoromethoxyl in the halocarbon solvents used. In the present methanolic solutions, unique incorporation of solvent methoxyl occurs at the 6 position of the pyrimidine ring in exclusively cis orientation to the 5-fluoro group. A moderately high stereoselectivity for cis adduct formation in methoxyfluoro adducts of *cis*- and *trans*-stilbene has since been noted using CF_3OF in methanolic solution.[27a] Merritt had noted methoxyfluoro adducts with complete Markownikoff regiospecificity but no stereoselectivity upon treatment of *cis*- or *trans*-propenylbenzene with fluorine in methanol.[27b] A number of recent publications have discussed the favorable gauche interaction of certain highly electronegatively substituted systems.[28] This has been suggested to provide a possible stereoelectronic basis for the cis or trans electrophilically initiated addition of XY molecules to an olefin.[28a]

Electrophilic attack by positive fluorine at C-5 of the pyrimidine ring would give the α-stabilized cation iii. The added stability of iii (as compared with the fluorocarbon cations



iii

previously noted[27]) would provide a longer lifetime of the intermediate thus allowing the "tight" or "intimate" counterion to be replaced by solvent. There is no exchange of fluorine between CF_3OF and solvent methanol observed (NMR) at low temperature.[29] Bond formation of C-6 with solvent oxygen leading to a "late transition state" would now be expected to proceed with energetically favorable[28] cisoid (gauche) stereochemistry to produce **2**. Treatment of 5-bromouracil (**4**) under the same conditions (CF_3OF/CCl_3F/MeOH) gave the same adduct (**5**) as was obtained by addition of methyl hypobromite to 5-fluorouracil (**3a**). This is in accord with the parallel directing effects of (1) gauche orientation[28a] of methoxy and fluoro, (2) trans electronic orientation of methoxy and bromo,[28a] and (3) steric repulsion of bromo and methoxyl[8i] which would result in stereoselective formation of **5** from either precursor.

Duschinsky, Fox, and coworkers had prepared a number of 5-fluoro-5,6-dihydrouracil adducts by addition of hypohalites[30] to 5-fluorouracil (**3a**).[8i,31a] Treatment of **3a** with bromine in methanol gave the described product **5** with comparable properties.[8i] Adduct **5** was previously assigned the trans (5-bromo to 6-methoxy) structure. This is compatible with the $J_{H\text{-}6\text{-}F\text{-}5} \simeq 0.7$ Hz observed by us which is indicative of a trans H-6 to F-5 configuration. Debromination of **5** by catalytic hydrogenolysis or by treatment with potassium hydrosulfide had been suggested to proceed with inversion to give trans adduct **6a**.[8i]

Debromination of **5** was repeated by us using both the hydrosulfide and hydrogenolytic conditions described. The 5-fluoro-6-methoxy-5,6-dihydrouracil adduct obtained from the two reactions corresponded to that reported[8i] and had the same melting and mixture melting point behavior as well as superimposable ir spectra after recrystallization. The total collected crude reaction products had identical sharply resolved NMR spectra. Thus, complete stereoselectivity of adduct formation was again indicated. Identical correspondence of these properties with those of the above conclusively established cis adduct **2a** was also found. Therefore, the previous tentative assignment[8i] of trans adduct structure **6a** is incorrect and must be reassigned the cis configuration **2a**.

Hydrogenolysis of **5** in the presence of sodium acetate produces cis adduct **2a** with retention of fluoro to methoxy configuration (in addition to ~30% of **3a**). The function of the acetate buffer is obscure. Gordon, Duschinsky, and coworkers[31a] and Duschinsky, Fox, and coworkers[8i] found that hydrogenolysis of **5** (or its 6-hydroxy analogue) in the absence of acetate led to essentially complete generation of 5-fluorouracil (**3a**), whereas addition of acetate resulted in the 5,6-dihydro adduct (**2a**) plus ~30% of **3a** (by uv spectroscopy). These authors had suggested that in the unbuffered, acidic medium, hydrogenolysis proceeded with retention of cis fluoro to methoxy (or hydroxy) configuration. They proposed[8i,31a] that trans elimination of 5-H and 6-OCH_3 (or 6-OH) then occurred readily.[31b] In the presence of sodium acetate, hydrogenolysis with inversion of configuration was proposed[8i,31a] to give **6a** (or its 6-hydroxy analogue) whose cis arrangement of 5-H and 6-OCH_3 (or 6-OH), it was rationalized, would be relatively stable toward elimination to produce 5-fluorouracil (**3a**). The identical 5-fluoro-6-hydroxy adduct was produced photochemically,[31a] and the absence of intramolecular infrared spectroscopic effects in the analogous 1,3-dimethyl-5-fluorouracil photohydrate noted by Shugar et al.[31c] was quoted as support for a trans 5-fluoro to 6-hydroxy orientation. However, this suggestion was later retracted by Shugar.[31d]

These experimental hydrogenolyses[8i] were repeated in this laboratory. In unbuffered methanolic solution, hydrogenolysis of **5** gave **3a** in over 90% yield (uv). In the presence of sodium acetate, triethylammonium bicarbonate, or barium carbonate, ~30–50% (uv) of **3a** was produced plus **2a** as the only spec-

troscopically visible (^{1}H NMR) saturated adduct. That **3a** did not arise from the cis adduct **2a** by simple acid-catalyzed elimination of methanol during hydrogenolysis (formation of HBr) was convincingly demonstrated by control experiments. In the first series, individual 1-mmol samples of **5** were hydrogenolyzed in the absence of acetate. To one was then added sodium acetate plus a 1-mmol sample of **2a**; **2a** without sodium acetate was added to the second. These mixtures were again subjected to the hydrogenolytic conditions, processed, and evaluated by ultraviolet spectroscopy. The two results were essentially identical (~0.9 mmol of **3a**, *total*, produced). Therefore the presence of HBr in the unbuffered second solution did not cause elimination from the added adduct **2a** to give further **3a**. The second series of experiments involved hydrogenolyses of (a) 1 mmol of **5**, no buffer; (b) 1 mmol of **5** plus 1 mmol of **2a**, no buffer; and (c) 1 mmol of **5** plus 1 mmol of **2a** plus 1 mmol of NaOAc. Ultraviolet analysis indicated ~0.3 mmol of **3a** produced in c, and ~0.9 mmol of **3a** produced in *both* a and b. Therefore, buffered hydrogenolysis of **5** clearly produces the cis adduct **2a** exclusively with *retention* rather than the previously suggested[8i] **6a** by inversion. However, **2a** is not an intermediate in the path from **5** to **3a** in the absence of buffer and the mechanism[8i,31a,b] of that "catalytic elimination" remains unclear.

The two resolved (undoubtedly cis fluoro to methoxy) diastereomeric 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-bromo-5-fluoro-6-methoxy-5,6-dihydrouracil adducts formed by addition of methyl hypobromite to 2′-deoxyuridine were reported to give the two corresponding optically active 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil [presumably (+)- and (−)-cis fluoro to hydroxy) enantiomers upon treatment with fuming nitric acid.[8i] A synthetic mixture of these antipodes was identical with the racemate produced by the addition of hypobromous acid to 5-fluorouracil. Hydrogenolysis of this racemate in the presence of sodium acetate gave 5-fluoro-6-hydroxy-5,6-dihydrouracil identical with the product of photohydration. The reported proton–proton and proton–fluorine coupling constants of this photohydrate[31a] are closely similar to those found by us for cis adduct **2a** (see the Experimental Section). As noted above, the enantiomerically distinct 5-bromo-5-fluoro-6-hydroxyuracil adducts were obtained by nitric acid oxidation of the corresponding resolved 6-methoxy nucleosides.[8i] Buffered hydrogenolysis of this racemic 6-hydroxy adduct (under conditions which are shown to proceed with retention of configuration of **5** → **2a** in the present study) gave a racemate identical with the photolysis product (whose ^{1}H NMR coupling parameters are similar to those of **2a**). It is therefore reasonable to propose that the structure of the photohydrate is (±)-*cis*-5-fluoro-6-hydroxy-5,6-dihydrouracil rather than the previously assumed[31a] trans adduct.

Bardos had suggested an unexplained double displacement involving disulfide formation to rationalize "the observed retention of configuration"[22b] in the Duschinsky et al. adduct **2a** formed by thiolate reduction of **5**. (Note that *inversion* of configuration was invoked in the tentative trans assignment made by Duschinsky et al. in the original reference.[8i])

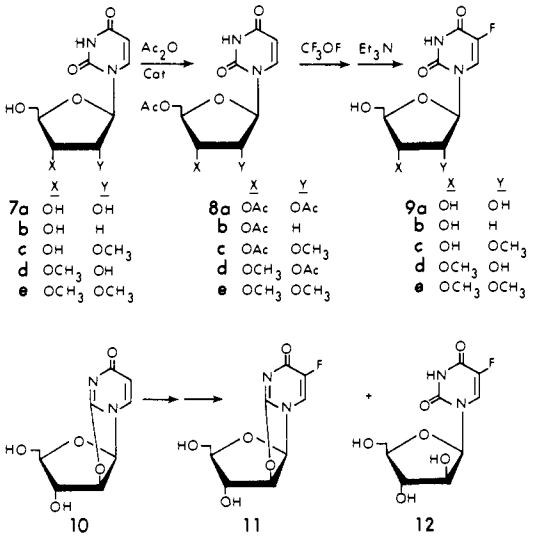
However, nucleophilic attack of hydrosulfide on bromine (or electron transfer processes) would give the 5-carbanion iv. Alternatively, SN2-type displacement of bromide by hydrosulfide would give v, and a second hydrosulfide attack on the thiol sulfur of v would give the same stabilized α-fluoroenolate anion iv plus disulfide. Selective proton capture by iv would give the stereoelectronically favored[28] cis adduct **2a** whereas expulsion of methoxide anion from iv would give enone **3a**.

In order to investigate this postulate experimentally, adduct **2a** was treated under the basic conditions (Et_3N–MeOH–H_2O, 10:45:45) used to effect elimination of the elements of methanol to produce 5-fluorouracil (**3a**). The reaction was interrupted by quenching with an acidic resin, and recovered adduct (**2a**) was investigated by ^{19}F and ^{1}H NMR spectroscopy. When **2a** was treated for 11 min in a deuterated solvent mixture, 70% of **3a** (by uv spectroscopy) was produced and the remaining (presumably 30%) 5-deuterio-5-fluoro adduct (**2a**, ^{2}H-5) had ^{1}H and ^{19}F NMR spectra essentially equivalent to that of **2a** except for lack of geminal 5-F and vicinal 6-H coupling with 5-D. A sample of **2a** (^{2}H-5, prepared by catalytic deuterolysis of **5**) was subjected to the same basic solution–acidic resin quenching procedure employing protium solvents. Approximately 28% of **3a** was generated during the equivalent time (11.5 min). The sole remaining saturated product which was spectroscopically visible had ^{1}H and ^{19}F NMR spectra identical with those of **2a** (^{1}H-5). These experiments demonstrate that reversible enolate formation is rapid relative to elimination of methoxide from iv, and also that proton (deuteron) capture by iv occurs stereoselectively to produce the more thermodynamically stable cis adduct **2a.** Pitman[32a,b] and Sander[32c] and their coworkers have very recently reported kinetic investigations on dehalogenation of 5-halouracils with bisulfite. Analogous reversible enolate formation with subsequent elimination of bisulfite or methoxyl was invoked[32] although the prior studies of Duschinsky, Fox, and coworkers[8i] were apparently overlooked.[32b] Precedent for nucleophilic attack on halogen at C-5 and sulfur attack at sulfur bonded to C-5 may be noted in these and other recent papers.[33a-c] In addition, the somewhat analogous α,α-dibromomalonamide serves as a source of positive bromine in reaction with phosphites.[33d]

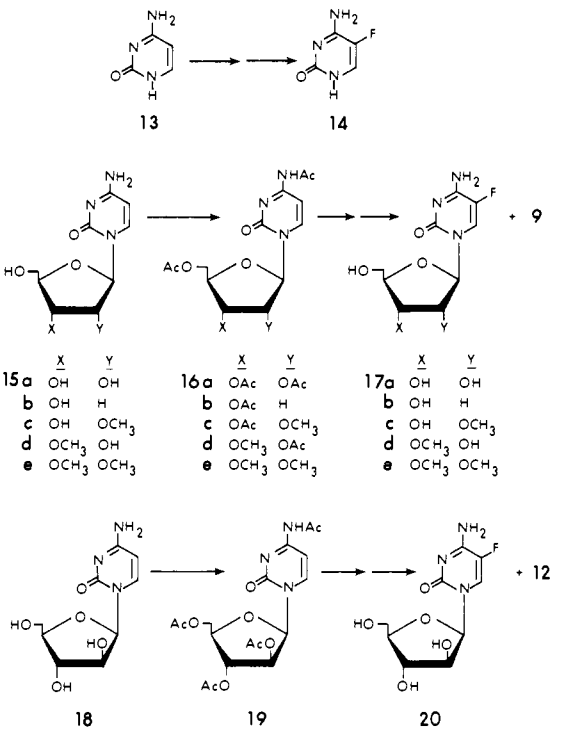
Shortly after our preliminary reports of this convenient and high-yield procedure for direct introduction of fluorine into preformed uracil[6a] and cytosine[6b] systems appeared, Barton and coworkers described the fluorination of uracil using elemental fluorine or trifluoromethyl hypofluorite in aqueous media. An analogous 5-fluoro-6-hydroxy-5,6-dihydrouracil adduct of undetermined stereochemistry was isolated.[34a] Similar fluorination of other simple pyrimidines has since been noted,[34b] but the sublimation technique used for isolation of these heterocycles is not applicable to nucleosides. German authors have investigated direct fluorination of uracil using electrochemical techniques,[35a] a fluorine–pyridine complex,[35b] and elemental fluorine in water or acetic acid.[35c,d] Hydrolysis of glycosyl linkages presented a problem when reaction with uracil nucleosides was investigated.[35b,c] Russian workers have also reported fluorination of uracil using elemental fluorine[36a] or xenon difluoride (~10% yield of 5-fluorouracil).[36b] The use of trifluoromethyl hypofluorite in organic solvents as presently outlined is experimentally convenient, proceeds in moderate to high yields, and is amenable to sensitive and nonvolatile glycosides. Reports[37] employing this procedure[6] to synthesize 5-fluoropyrimidine derivatives of biochemical and medicinal interest have appeared.

Treatment of a chloroform solution of 2′,3′,5′-tri-*O*-acetyluridine[38] (**8a**) (Scheme II) at −78 °C with CF_3OF in CCl_3F at −78 °C caused rapid loss of uv absorption at 260 nm. The resulting adduct was predictably less stable[8i] and was not isolated. Excess reagent was removed by bubbling nitrogen through the solution to avoid overfluorination[34] of any re-

Scheme II



Scheme III



generated 5,6-double bond, and solvents were evaporated. Treatment of the adduct residue with triethylamine in aqueous methanol at room temperature effected elimination to generate the chromophore with concomitant deblocking of the sugar to give 5-fluorouridine[8b] (**9a**) in 80% yield. An analogous reaction of uridine (**7a**) in methanolic solution was found to give **9a** in 50% yield with no serious attempt to optimize conditions. Similar treatment of 3′,5′-di-*O*-acetyl-2′-deoxyuridine[39] (**8b**) (see the Experimental Section for an improved[6a] preparation) gave 5-fluoro-2′-deoxyuridine[8a] (**9b**) in 55% yield. This reaction appears to be sensitive to temperature and light and care must be exercised to avoid decomposition during adduct treatment.

In order to explore new 5-fluorouridine compounds with potentially enhanced metabolic stability[17,18] (vide supra), 3′,5′-di-*O*-acetyl-2′-*O*-methyluridine (**8c**), 2′,5′-di-*O*-acetyl-3′-*O*-methyluridine (**8d**), and 5′-*O*-acetyl-2′,3′-di-*O*-methyluridine (**8e**) (obtained by acetylation of the now readily available sugar-methylated nucleosides[40]) were treated by this two-stage in situ process to provide 2′-*O*-methyl-5-fluorouridine (**9c**), 3′-*O*-methyl-5-fluorouridine (**9d**), and 2′,3′-di-*O*-methyl-5-fluorouridine (**9e**) in good yields. In order to explore the generality of this procedure further, a methanolic solution of 1-β-D-arabinofuranosyluracil-$O^2 \rightarrow$2′-anhydronucleoside (**10**) (2,2′-anhydro-1-β-D-arabinofuranosyluracil)[41] was treated under the usual conditions. Decomposition of the resulting adduct gave 5-fluoro-1-β-D-arabinofuranosyluracil-$O^2 \rightarrow$2′-anhydronucleoside[8b] (**11**) in ~60% yield plus ~20% of 5-fluoro-1-β-D-arabinofuranosyluracil[8b] (**12**). In view of the known hydrolytic lability of the $O^2 \rightarrow$2′-anhydronucleoside linkage,[42] it is interesting that the majority of the anhydronucleoside survived intact and demonstrates the mildness of this procedure. The marked contrast between the former multistep preparation[8b] of **11** and **12** and this direct conversion is also apparent.

Attention was next focused on the cytosine ring (Scheme III) since previous indirect conversions from the corresponding 5-fluorouracil compounds (vide supra) were sometimes rather laborious.[8a,c,e-h,j-l] Treatment of cytosine (**13**) with CF_3OF under the usual conditions effected loss of the uv chromophore. The resulting adduct appeared to be less stable than in the uracil case as noted previously[8i] and no serious effort was made to isolate it. Treatment with triethylamine in aqueous methanol gave 5-fluorocytosine[7a] (**14**) in 85% yield. The adducts in the cytosine system were susceptible to deamination. Varying quantities of the corresponding 5-fluorouracil compound were usually observed depending on the basic reaction conditions employed for adduct decomposition. Whereas the concomitant formation of uracil derivatives is undesirable if only the pure cytosine compound is wanted, the two pyrimidine system derivatives always exhibit markedly different chromatographic behavior and are, therefore, easily separated. Since closely related cytosine nucleoside precursors with minor differences in the sugar portion are amenable to facile separation using anion exchange chromatography[43] (whereas the corresponding uracil nucleosides are not unless derivatized[44]), this provides convenient access into both systems simultaneously. This is advantageous for biological evaluation of new compounds since the two bases usually show divergent activities.[10] Treatment of cytidine adducts with dimethylamine in dried absolute ethanol gave the 5-fluorocytidine compounds with no observed (TLC) formation of the related 5-fluorouridine.

Cytidine (**15a**), 2′-deoxycytidine (**15b**), 2′-*O*-methylcytidine[40] (**15c**), 3′-*O*-methylcytidine[40] (**15d**), and 2′,3′-di-*O*-methylcytidine[40b,45] (**15e**) were N^4,per-O-acetylated. Chloroform solutions of these completely blocked derivatives were treated with CF_3OF/CCl_3F. After removal of excess reagent and solvents, the dried adducts were subjected to aqueous elimination conditions which effected concomitant deblocking. The 5-fluorocytosine nucleosides (**17a–e**) were produced along with varying amounts of the corresponding 5-fluorouracil products (**9a–e**) in high combined overall yields (see the Experimental Section). Inexplicably, the adduct from the di-*O*-methyl product (**16e**) was extremely susceptible to deamination and only minor amounts of **17e** were obtained along with good yields of **9e** when elimination deblocking was allowed to proceed to completion in the usual manner. Use of dimethylamine in absolute ethanol circumvented this problem and **17e** was obtained in 87– yield as the only observed (TLC) product. Analogous treatment of cytidine gave **17a** in 88% yield with no **9a** observed. Cytidine (**15a**) in methanolic solution was subjected directly to the two-stage procedure to yield 55% of 5-fluorocytidine[8c] (**17a**) plus 5-fluorouridine (**9a**).

Significant antiviral activity as well as antileukemia activity has been observed[46] with 5-fluoro-1-β-D-arabinofuranosylcytosine[8h] (**20**). Treatment of N^4,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetraacetyl-1-β-D-arabinofuranosylcytosine[47] (**19**) under the usual con-

Table I. ^1H and ^{19}F NMR Data for "Aromatic" 5-Fluoropyrimidines and Nucleosides

Compd (solv)[a]	F-5[b] ($^5J_{F\text{-}5\text{-}H\text{-}1'}$)[c]	H-6[d] ($J_{H\text{-}6\text{-}F\text{-}5}$)[e]	H-1'[d] ($J_{H\text{-}1'\text{-}H\text{-}2'}$)[c]	CH_3[f]
3a (A)	171 (d)	7.74 (6)		
3b (A)	170 (d)	8.16 (7)		3.30
9a (B)	166 (dd, 1.6)	8.37 (6.5)	6.17 (dd, 4.2)	
9b (B)	166 (dd, 1.6)	8.31 (6.6)	6.52 (td, 6.5)	
9c (A)	168 (dd, 1.8)	8.44 (7.5)	5.94 (dd, 4.2)	3.50
9d (C)	168 (dd, 2.0)	8.26 (6.5)	5.86 (dd, 4)	3.48
9e (B)	166 (dd, 1.5)	8.39 (6.4)	6.12 (dd, 3.9)	3.66 (3'), 3.74 (2')
11 (B)	131 (d)	8.26 (4)	6.70 (d, 6.4)	
12 (A)	169 (dd, 1.8)	7.98 (7.2)	5.97 (dd, 4.4)	
14 (A)	171 (d)	7.57 (6.4)		
17a (B)	166 (dd, 1.6)	8.60 (6.6)	6.00 (dd, 3.3)	
17b (B)	165 (dd, 1.8)	7.92 (6.6)	6.14 (ddd, 8 + 6)	
17c (B)	165 (dd, 1.6)	8.17 (6.5)	6.02 (dd, 3.6)	3.67
17d (C)	169 (dd, 1.6)	8.32 (6.4)	5.80 (dd, 3.2)	3.47
17e (A)	168 (dd, ~1.6)	8.80 (7.3)	5.74 (t, ~1.6)	3.32 (3'), 3.46 (2')
20 (B)	167 (dd, 1.6)	8.50 (6.6)	6.31 (dd, 4.7)	

[a] Solvents: A, $(CD_3)_2SO$; B, D_2O; C, CD_3OD. [b] ^{19}F chemical shifts, parts per million upfield from external CCl_3F. [c] Peak multiplicity and coupling in hertz. [d] ^1H chemical shifts, parts per million downfield from Me_4Si. [e] All doublets, coupling in hertz. [f] All singlets.

Table II. Ultraviolet Absorption Data[a]

	H^+		OH^-	
Compd	λ_{max}[b] (ϵ)	λ_{min}[b] (ϵ)	λ_{max}[b] (ϵ)	λ_{min}[b] (ϵ)
3a	266 (7000)	232 (1600)	280 (5200)	248 (2300)
3b	273 (8300)	236 (1200)	271 (6100)	248 (3200)
9a	268 (9100)	234 (2300)	268 (7300)	249 (5400)
9b	268 (8400)	234 (1900)	268 (6600)	249 (4600)
9c	269 (10 500)	234 (3100)	267 (9000)	249 (7300)
9d	269 (8300)	235 (1800)	269 (6400)	250 (4600)
9e	268 (9200)	234 (2400)	267 (9500)	245 (6000)
14	285 (8900)	246 (1300)	292 (7600)	251 (1000)
17a	289 (11 000)	248 (1800)	281 (7900)	259 (5400)
17b	291 (12 600)	250 (1900)	281 (8800)	259 (6300)
17c	290 (13 600)	248 (2600)	280 (10 700)	260 (7000)
17d	290 (13 300)	249 (1900)	279 (10 700)	260 (6800)
17e	289 (11 000)	248 (1900)	280 (8200)	258 (5900)
20	290 (11 700)	248 (1700)	282 (8100)	257 (4100)

[a] See the Experimental Section for conditions. [b] Wavelength in nanometers.

ditions gave **20** in 83% yield (as the hydrochloride). Again this yield from commercially available cytosine arabinoside (**18**, 1-β-D-arabinofuranosylcytosine) may be contrasted with multistep procedures to **20** available previously.[8h,j]

It was found that addition of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine[48] to a stirred suspension of nucleoside in acetic anhydride provided rapid and clean peracetylation. Reactions proceed smoothly to completion making processing and purification convenient. Products often crystallize readily or are chromatographically homogeneous and can be used directly. Colored by-products frequently observed using the usual acetic anhydride/pyridine solution are avoided. In this manner crystalline 3',5'-di-*O*-acetyl-2'-deoxyuridine (**8b**) was obtained directly in over 90% yield[6a] without recourse to chromatography.[39]

Sugar anomeric and base ^1H NMR parameters of these compounds are in general agreement with published values. The long-range coupling ($^5J_{F\text{-}5\text{-}H\text{-}1'} \simeq 1.5\text{-}2.0$ Hz) noted by Keller[8j] and investigated by Fox and coworkers[49] was present in all of these nucleosides except the rigid *syn*-anhydronucleoside **11**, as noted previously.[49] The $^4J_{F\text{-}5\text{-}H\text{-}3}$ coupling observed in saturated adduct **2b** is of the same general magnitude as the $^4J_{H\text{-}5\text{-}H\text{-}3}$ noted by Moffatt in uridine derivatives.[50]

Mass spectral fragmentation trends are compatible with the assigned structures. As noted previously[40a] with other pairs of pyrimidine 2'-*O*- and 3'-*O*-methylnucleosides, the 2' isomer undergoes presumed loss of the elements of methanol to give a significant M − 32 peak. This peak is essentially absent in the 3'-*O*-monomethyl compounds and provides a readily observed check on isomeric identity.[40a]

No attempt was made to systematically optimize reaction conditions and the indicated yields have been found to be readily attainable when repeated by others in this laboratory. These procedures provide convenient access into 5-fluoropyrimidine nucleosides with modified sugar moieties and it might be noted that chemical synthesis of the biologically potent 5-fluoropolyoxins[8n] should proceed readily by this route.

Experimental Section

General Procedures. Melting points were determined on Fisher-Johns or Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on Varian 56/60, HA-100, Brüker 90, or Perkin-Elmer R-32 spectrometers. Me_4Si (usually as internal standard) was used for all ^1H spectra and CCl_3F was employed as the external standard for ^{19}F NMR determinations. Optical rotations were determined using a Perkin-Elmer Model 141 polarimeter with a 10-cm 1-ml micro cell. For uv spectra, accurately weighed samples were dissolved in MeOH, H_2O, or a mixture and diluted to 10 ml with the more solubilizing solvent. A 1-ml sample of this stock solution was diluted to 10 ml with

0.1 N HCl (H^+), 0.1 N NaOH (OH^-), or other solvent listed and spectra were recorded on Cary 14 or 15 instruments. Mass spectra were determined by the mass spectroscopy laboratory of this department on AEI MS-2, MS-9, or MS-50 instruments at 70 eV using a direct probe for sample introduction. Elemental analyses were determined by the microanalytical laboratory of this department or Schwarzkopf Microanalytical laboratory, Woodside, N.Y. Evaporations were effected using Büchler rotating evaporators under aspirator or mechanical oil pump vacuum at 40 °C or lower. Thin-layer chromatography (TLC) was performed using Eastman Kodak chromatogram sheets (silica gel 13181 with 6060 indicator or cellulose 13254 with 6065 indicator). Column chromatography was effected using J. T. Baker 3405 silica gel unless otherwise specified. Trifluoromethyl hypofluorite was purchased from PCR Inc., Gainesville, Fla. Analytical values within ±0.4% of theory are indicated by the symbol of the element analyzed.

General Fluorination and Elimination Procedures. The compound to be fluorinated was dissolved in a volume of the appropriate solvent(s) (contained in a round-bottomed flask equipped with a magnetic stir-bar) such that solubility at low temperature was retained. This solution was cooled to −78 °C. Excess (usually approximately two- to fourfold) CF_3OF was dissolved in CCl_3F [precooled to −78 °C (dry ice) or −98 °C (MeOH/N_2 (liquid))] by slow addition of the gas through a spurge tube (the CF_3OF cylinder was continuously weighed on a Sartorious electric balance). The CF_3OF/CCl_3F solution at −78 or −98 °C was slowly added to the magnetically stirred solution of substrate at −78 °C in an efficient fume hood. *Caution.*[24] Progress of the reaction was monitored periodically by uv spectroscopy (disappearance of the characteristic chromophore of the uracil, ~260 nm, or cytosine, ~270 nm, ring upon adduct formation). After disappearance (or minimization) of the uv absorption, stirring was continued for ~5 min. Nitrogen gas was bubbled through the solution to remove excess CF_3OF at −78 °C and the solution was allowed to warm to room temperature. Solvents were evaporated under reduced pressure and adducts were usually dried in vacuo for several hours.

The 5-fluoropyrimidine products were obtained from these adducts by stirring at room temperature with Et_3N-MeOH-H_2O (10:45:45) in an open flask or with Me_2NH in dried absolute EtOH in a pressure vessel. Evaporation of volatiles gave the crude products which were processed further as required.

(±)-*r*-5-Bromo-5-fluoro-*t*-6-methoxy-5,6-dihydrouracil (5). Method A. A 0.57-g portion of 5-fluorouracil (**3a**) was treated with bromine in methanol as described[8i] to yield 0.84 g (79%) of **5**: mp 214–216 °C dec (lit.[8i] mp 214–215 °C dec); ^1H NMR (Me_2SO-d_6) δ 3.37 (s, 3, OCH_3), 5.02 (d of d, $J_{H\text{-}6\text{-}H\text{-}1}$ = 5.1 Hz, $J_{H\text{-}6\text{-}F\text{-}5} \simeq$ 0.7 Hz, 1, H-6), 9.16 (br, 1 H-1), 11.04 (br, 1, H-3); (Me_2SO-d_6-D_2O) δ 5.02 (d, $J_{H\text{-}6\text{-}F\text{-}5} \simeq$ 0.7 Hz, 1, H-6); ^{19}F (Me_2SO-d_6) δ 139 (s, 1, F-5); mass spectrum *m/e* 240, 242 (M^+).

Method B. A 0.57-g (0.003 mol) sample of 5-bromouracil (4) in 300 ml of MeOH at −78 °C was treated with 0.62 g (0.006 mol) of CF_3OF in 25 ml of CCl_3F at −98 °C by the general fluorination procedure. The residue was crystallized from EtOAc to give 0.65 g (90%) of **5** which had identical melting point, mixture melting point (213–214 °C), ir (KBr), ^1H and ^{19}F NMR, and mass spectra with those of the product of method A.

(±)-*cis*-5-Fluoro-6-methoxy-5,6-dihydrouracil (2a). Method A. A solution of 0.336 g (0.003 mol) of uracil (**1a**) in 375 ml of MeOH at −78 °C was treated with 1 g (0.0096 mol) of CF_3OF in 40 ml of CCl_3F at −78 °C by the general fluorination procedure. The white solid obtained was dissolved in hot water and 0.44 g (91%) of **2a** crystallized upon cooling. Crystalline **2a** had mp 196–198 °C (with gas evolution to form 5-fluorouracil which then melted at 284 °C dec); ^1H NMR (Me_2SO-d_6) δ 3.30 (s, 3, OCH_3), 4.70 (d of d of d, $J_{H\text{-}6\text{-}H\text{-}5}$ = 4.0 Hz, $J_{H\text{-}6\text{-}F\text{-}5}$ = 2.2 Hz, $J_{H\text{-}6\text{-}H\text{-}1}$ = 5.0 Hz, 1, H-6), 5.44 (d of d, $J_{H\text{-}5\text{-}F\text{-}5(gem)}$ = 45.5 Hz, $J_{H\text{-}5\text{-}H\text{-}6}$ = 4.0 Hz, 1, H-5); ^{19}F NMR (Me_2SO-d_6-D_2O) δ 208 (d of d, $J_{F\text{-}5\text{-}H\text{-}5(gem)}$ = 45.5 Hz, $J_{F\text{-}5\text{-}H\text{-}6}$ = 2.2 Hz, 1, F-5); mass spectrum *m/e* 162 (M^+), 131 (M − 31 [OCH_3]), 130 (M − 32 [CH_3OH]), 119 (M − 43 [HNCO]), 87 (M − 32 − 43). Anal. ($C_5H_7FN_2O_3$) C, H, F, N.

Method B. A 0.2-g portion of **5** was treated with KSH/MeOH as described[8i] to yield 0.075 g (56%) of **2a**, mp 195–198 °C (with gas evolution to form **3a** which then melted at ~285 °C dec). Mixture melting point, ir (KBr), ^1H and ^{19}F NMR, and mass spectra of the samples prepared by methods A and B were identical. This experiment was repeated and the initial crude product was found to have NMR spectral parameters corresponding to those of **2a** as the *sole* dihydro adduct.

Method C. Catalytic hydrogenation of **5** was effected as described.[8i] In the absence of buffer, essentially quantitative formation of **3a** was observed (by uv). An isolated yield of ~25% of **2a** was obtained using the NaOAc-buffer conditions.[8i] This crystalline sample was found to be identical with the material prepared by methods A and B by the criteria listed under B. Again, NMR spectral examination of the crude hydrogenation mixture showed **2a** as the *sole* dihydro adduct (with ~32% accompanying formation of **3a**, by uv).

(±)-*cis*-5-Deuterio-5-fluoro-6-methoxy-5,6-dihydrouracil (2a, ^{2}H-5). A 0.22-g (1.6 mmol) sample of NaOAc·$3H_2O$ was dissolved in ~1 ml of D_2O and evaporated to dryness. This was repeated two additional times and 0.35 g (1.45 mmol) of **5** was added. Three successive additions of ~1 ml of CH_3OD followed by evaporation to dryness gave a stiff white solid glass which was dissolved in 3.5 ml of CH_3OD. A 70-mg portion of 10% Pd/C catalyst (predeuterated by stirring for 40 min in D_2O under 85 psi of D_2) was added and atmospheric deuteration (32.7 ml of D_2(STP), ~1 equiv) was complete in 30 min. The filtered solution was evaporated to give a residue which contained ~52% of **3a** (by uv). A portion of this residue was chromatographed (Whatman No. 2 paper, descending) using EtOH-H_2O (85:15). The homogeneous band running faster (R_f ~0.75) than **3a** (R_f ~0.5) (detection by exposing a narrow strip cut from the edge of the paper to ammonia and visualization of the resulting **3a** under 2537-Å light) was eluted using MeOH-H_2O (1:1). The eluate was evaporated, and the residue dissolved in MeOH, filtered, and evaporated to yield 33 mg of pure title compound (TLC, silica, MeOAc): ^1H NMR (Me_2SO-d_6) δ 3.29 (s, 3, OCH_3), 4.70 (m, 1, H-6; d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 2.2 Hz upon D_2O exchange), 8.78 (br, 1, H-1); mass spectrum *m/e* 163 (no peak observed at 162 amu). The mass spectrum of the crude material had *m/e* 163 as the highest peak and no *m/e* 162 peak was present.

Reaction of 2a, ^{1}H-5 with Triethylamine/Methanol-d_1/Deuterium Oxide. A 20-mg sample of **2a**, ^{1}H-5 was dissolved in 1 ml of CH_3OD in a centrifuge tube and 1 ml of D_2O was added. Dry Et_3N (20 μl) was added and the solution was stirred for 11 min at room temperature. A 3-ml portion of Amberlite IRC-50 (D^+) was added; the mixture was shaken until neutral (~4 min) and then centrifuged. The resin was washed with 5 × 2 ml of MeOH-H_2O (1:1) and the pooled supernatant fraction was evaporated. The crude residue contained an ~70% yield (by uv) of **3a**. The ^1H NMR spectrum of the crude residue [δ 4.72 (d of d, $J_{H\text{-}6\text{-}F\text{-}5}$ = 2.3 Hz, $J_{H\text{-}6\text{-}H\text{-}1}$ = 4.8 Hz, 1, H-6)] was essentially identical with that of **2a**, ^{2}H-5 prepared above in the adduct spectral region and no additional peaks (except for **3a**) were observed.

Reaction of 2a, ^{2}H-5 with Triethylamine/Methanol/Water. A 19-mg sample of **2a**, ^{2}H-5 was treated with 1 ml of MeOH, 1 ml of H_2O, and 20 μl of Et_3N for 11.5 min, quenched with ~5 ml of Amberlite IRC-50 (H^+) (neutralization complete in ~1 min), and processed as the protio adduct reaction above. Uv analysis indicated ~28% yield of **3a** and ^1H NMR analysis showed **2a**, ^{1}H-5 as the *sole* saturated adduct (integration of H-5 vs. H-6 demonstrated complete exchange for protium): δ 4.70 (m, 1, H-6; $J_{H\text{-}6\text{-}F\text{-}5}$ = 2.0 Hz upon D_2O exchange), 5.43 (d of d, $J_{H\text{-}5\text{-}F\text{-}5}$ = 46 Hz, $J_{H\text{-}5\text{-}H\text{-}6}$ = 4.0 Hz, 1, H-5).

(±)-5,5-Difluoro-6-methoxy-5,6-dihydrouracil (6b). A stirred solution of 0.2 g (1.5 mmol) of **3a** in 150 ml of MeOH at −78 °C was treated with 1 g (~10 mmol) of CF_3OF in 10 ml of CCl_3F at −98 °C by the general fluorination procedure. One-third of the crude residue (homogeneous by TLC, silica, glass slide, MeOAc, detection by spraying with 5% H_2SO_4 in EtOH and charring) was used directly for ^1H and ^{19}F NMR. Crystallization of the remaining two-thirds from Et_2O with diffusion of pentane[51] gave 126 mg (68%) of **6b**: mp 203–204 °C (lit.[34b] mp 201–202 °C); ^1H NMR (Me_2SO-d_6) δ 3.38 (s, 3, OCH_3), 4.89 (d of d of d, $J_{H\text{-}6\text{-}F\text{-}5'}$ = 6.05 Hz, $J_{H\text{-}6\text{-}F\text{-}5}$ = 2.1 Hz, $J_{H\text{-}6\text{-}H\text{-}1}$ = 4.8 Hz, 1, H-6), 9.19 (br, 1, H-1), 11.28 (br, 1, H-3); ^{19}F NMR (Me_2SO-d_6) δ 112 (d of d, $J_{F\text{-}5'\text{-}F\text{-}5}$ = 274 Hz, $J_{F\text{-}5'\text{-}H\text{-}6}$ = 6 Hz, 1, F-5'), 131 (d of d, $J_{F\text{-}5\text{-}F\text{-}5'}$ = 274 Hz, $J_{F\text{-}5\text{-}H\text{-}6}$ = 2 Hz, 1, F-5); mass spectrum calcd for M^+: 180.03465; found: *m/e* 180.03471. Anal. ($C_5H_6F_2N_2O_3$) C, H, F, N.

(±)-*cis*-5-Fluoro-6-methoxy-1-methyl-5,6-dihydrouracil (2b). A solution of 0.37 g (0.0029 mol) of 1-methyluracil[23] (**1b**) in 100 ml of MeOH at −78 °C was treated with a solution of 1 g (0.0096 mol) of CF_3OF in 40 ml of CCl_3F at −78 °C as described above for the conversion of **1a** → **2a**. The product was crystallized from MeOH/H_2O to yield 0.48 g (92%) of **2b**: mp 162–168 °C dec; ^1H NMR (Me_2SO-

d_6) δ 3.06 (s, 3, N-1 CH_3), 3.43 (s, 3, OCH_3), 5.03 (d of d, $J_{H\cdot6-H\cdot5}$ = 4.0 Hz, $J_{H\cdot6-F\cdot5}$ = 2.5 Hz, 1, H-6), 5.39 (d of d, $J_{H\cdot5-F\cdot5(gem)}$ = 46 Hz, $J_{H\cdot5-H\cdot6}$ = 4.0 Hz, 1, H-5); ^{19}F NMR (Me_2SO-d_6) δ 209 (d of t, $J_{F\cdot5-H\cdot5(gem)}$ = 46 Hz, $J_{F\cdot5-H\cdot6} \simeq 2$ Hz, $J_{F\cdot5-H\cdot3} \simeq 1$ Hz, 1, F-5); mass spectrum *m/e* 176 (M^+), 145 (M − 31 [OCH_3]), 144 (M − 32 [CH_3OH]), 133 (M − 43 [HNCO]), 102 (M − 31 − 43). Anal. ($C_6H_9FN_2O_3$) C, H, F, N.

5-Fluorouracil (3a). A 0.38-g (0.0034 mol) sample of **1a** in 350 ml of MeOH was treated with 1 g (0.0096 mol) of CF_3OF in 45 ml of CCl_3F according to the general fluorination and elimination procedures. The residue was triturated with 2 ml of H_2O and then recrystallized from H_2O. The colorless crystals were filtered and dried at 0.1 mmHg for 24 h at room temperature over P_2O_5 to give 0.4 g (91%) of **3a,** mp 284–286 °C dec (lit.[7a] mp 282–283 °C dec). Anal. ($C_4H_3FN_2O_2$) C, H, F, N.

5-Fluoro-1-methyluracil (3b). A solution of 0.378 g (0.003 mol) of **1b** in 300 ml of MeOH was treated with 1 g (0.0096 mol) of CF_3OF in 30 ml of CCl_3F at −78 °C according to the conversion of **1a** → **3a.** Crystalline **3b** (0.39 g, 90%) had mp 258–260 °C (lit.[23b] mp 236 °C subl.); mass spectrum calcd for M^+: 144.0335; found: *m/e* 144.0343. Anal. ($C_5H_5FN_2O_2$) C, H, F, N.

5-Fluorouridine (9a). Method A. A solution of 3.7 g (0.01 mol) of 2′,3′,5′-tri-*O*-acetyluridine[38] (**8a**) in 150 ml of $CHCl_3$ was treated with 1.6 g (0.015 mol) of CF_3OF in 30 ml of CCl_3F according to the general fluorination and elimination procedures. The residue was stirred with 6 ml of Dowex 50-X8 (H^+) resin in 50 ml of MeOH for 10 min and filtered, and the resin was washed thoroughly with MeOH. Evaporation of solvent and coevaporation of the residue with three 20-ml portions of EtOH–EtOAc–$PhCH_3$ (1:1:2) gave 2.7 g of dry solid. Crystallization of this material from 22 ml of absolute EtOH gave 2.14 g (82%) (in two crops) of **9a:** mp 181–182 °C (an isomorphic form with mp 151–154 °C is sometimes obtained which can be converted to the mp 181–182 °C form by warming the solution and recooling) (lit.[8b] mp 180–182, 184–185 °C); $[\alpha]^{26}D$ 16.5° (*c* 1.1, H_2O); mass spectrum calcd for M^+: 262.0601; found: *m/e* 262.0617. Anal. ($C_9H_{11}FN_2O_6$) C, H, F, N.

Method B. A solution of 1.22 g (0.005 mol) of uridine (**7a**) in 500 ml of MeOH was treated with 1 g (0.0096 mol) of CF_3OF in CCl_3F according to the general fluorination procedure. The reaction was processed analogously to method A above to give 0.62 g (47%) of **9a,** mp 148–154 °C. Recrystallization of this material from EtOH gave **9a,** mp 180–182 °C, which was identical with the product from method A. Anal. C, H, N.

3′,5′-Di-*O*-acetyl-2′-deoxyuridine (8b). To 12 ml of Ac_2O was added 1.03 g (0.0045 mol) of **7b** and 25 mg of 4-*N,N*-dimethylaminopyridine and the mixture was stirred for 24 h at room temperature. TLC showed complete reaction. The solution was evaporated in vacuo at 35 °C and the residue was coevaporated with three 25-ml portions of EtOH. The resulting colorless solid was crystallized from 18 ml of H_2O to give 1.23 g (88%) of **8b:** mp 108–109 °C (lit.[39] mp 107–110 °C); $[\alpha]^{25}D$ 15.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 6, 3′- and 5′-$COCH_3$), 2.16–2.57 (m, 2, H-2′, H-2″), 4.35 (m, 3, H-4′, H-5′, H-5″), 5.14–5.38 (m, 1, H-3′), 5.80 (d, $J_{H\cdot5-H\cdot6}$ = 8.0 Hz, 1, H-5), 6.30 (d of d, $J_{H\cdot1'-H\cdot2',H\cdot2''}$ = 8 and 6 Hz, 1, H-1′), 7.52 (d, $J_{H\cdot6-H\cdot5}$ = 8.0 Hz, 1, H-6). Anal. ($C_{13}H_{16}N_2O_7$) C, H, N.

5-Fluoro-2′-deoxyuridine (9b). A solution of 0.624 g (0.002 mol) of **8b** in 15 ml of $CHCl_3$ was treated with 0.9 g (0.0087 mol) of CF_3OF in 10 ml of CCl_3F according to the general fluorination procedure. The flask was protected from light (aluminum foil) while evaporation of solvents was conducted at below 30 °C. Decomposition of the adduct sometimes occurred to give a purple coloration during evaporation and high vacuum drying. The adduct was treated as in the conversion of **8a** → **9a** and recrystallization of the product from absolute EtOH gave 0.27 g (55%) of **9b:** mp 149–150 °C (lit.[8a] mp 150–151 °C); $[\alpha]^{26}D$ 36° (*c* 1.1, H_2O); mass spectrum calcd for M^+: 246.0652; found: *m/e* 246.0662. Anal. ($C_9H_{11}FN_2O_5$) C, H, F, N.

3′,5′-Di-*O*-acetyl-2′-*O*-methyluridine (8c). A suspension of 0.51 g (0.002 mol) of **7c**[40a] in 8 ml of Ac_2O was stirred with 10 mg of 4-*N,N*-dimethylaminopyridine for 3 h at room temperature. The solution was evaporated to dryness and coevaporated with 2 × 40 ml of MeOH. The residue crystallized upon addition of 2 ml of H_2O. This material was recrystallized from water to yield 0.54 g (80%) of **8c:** mp 69–70 °C; uv (H_2O) max 260 nm (ε 10 900), min 229.5 nm (ε 2700); ^{1}H NMR ($CDCl_3$) δ 2.12, 2.14 (s, s; 3, 3; 3′ and 5′-$OCOCH_3$), 3.50 (s, 3, OCH_3), 5.83 (d, $J_{H\cdot5-H\cdot6}$ = 8 Hz, 1, H-5), 5.96 (d, $J_{H\cdot1'-H\cdot2'}$ = 3.5 Hz, 1, H-1′), 7.57 (d, $J_{H\cdot6-H\cdot5}$ = 8 Hz, 1, H-6); mass spectrum *m/e* 342 (M^+). Anal. ($C_{14}H_{18}N_2O_8$) C, H, N.

5-Fluoro-2′-*O*-methyluridine (9c). A solution of 0.48 g (0.0014 mol) of **8c** in 50 ml of $CHCl_3$ was treated with 0.9 g (0.0087 mol) of CF_3OF in 20 ml of CCl_3F by the general fluorination procedure. The adduct was treated as in the conversion of **8a** → **9a** and after removal of Et_3N with resin, thick layer chromatography (MeOH–$CHCl_3$, 15:85, silica gel) was used to obtain the pure product band. This material was eluted and then crystallized from EtOH/EtOAc to give 0.30 g (78%) of needles of **9c:** mp 145–147 °C; $[\alpha]^{22}D$ 51.2° (*c* 1, MeOH); mass spectrum *m/e* 276 (M^+), 244 (M − 32 [MeOH]). Anal. ($C_{10}H_{13}FN_2O_6$) C, H, F, N.

5′-*O*-Acetyl-2′,3′-di-*O*-methyluridine (8e). A suspension of 0.10 g (0.00037 mol) of **7e**[40b] and 10 mg of 4-*N,N*-dimethylaminopyridine in 10 ml of Ac_2O was stirred for 6 h at room temperature. The solution was evaporated, the residue coevaporated twice with MeOH, and 2 ml of H_2O was added to the gummy residue. Crystallization occurred after a few minutes stirring with a spatula and the resulting fine needles were recrystallized from H_2O/EtOH to give 0.093 g of **8e** (70% as the solvate): mp 120–124 °C; uv (H_2O) 264 nm (ε 9800), min 232 nm (ε 1800); ^{1}H NMR (Me_2SO-d_6) δ 2.12 (s, 3, $COCH_3$), 3.38 (s, 3, 3′-OCH_3), 3.46 (s, 3, 2′-OCH_3) 5.82 (d, $J_{H\cdot1'-H\cdot2'}$ = 2.5 Hz, 1, H-1′), 5.92 (d, $J_{H\cdot5-H\cdot6}$ = 8 Hz, 1, H-5), 7.80 (d, $J_{H\cdot6-H\cdot5}$ = 8 Hz, 1, H-6) (the presence of 1 mol of EtOH was observed in this spectrum); mass spectrum *m/e* 314 (M^+), 282 (M − 32 [CH_3OH]). Anal. ($C_{13}H_{18}N_2O_7 \cdot C_2H_5OH$) C, H, N.

5-Fluoro-2′,3′-di-*O*-methyluridine (9e). A solution of 0.10 g (0.00028 mol) of **8e**·EtOH in 45 ml of MeOH was treated with 0.3 g (0.0029 mol) of CF_3OF in 10 ml of CCl_3F according to the general fluorination procedure. After processing the adduct as in the conversion of **8a** → **9a** and thick layer chromatography (EtOAc–*n*-PrOH–H_2O, 4:1:2, upper phase on silica gel), a pure gum was obtained which was dissolved in 5 ml of MeOH and precipitated by addition of dry Et_2O. The resulting white solid (0.054 g, 67%) **9e** had mp 78–79 °C; $[\alpha]^{22}D$ 68° (*c* 1, MeOH); mass spectrum *m/e* 290 (M^+), 258 (M − 32 [CH_3OH]). Anal. ($C_{11}H_{15}FN_2O_6$) C, H, F, N.

5-Fluoro-1-β-D-arabinofuranosyluracil-*O*^{2}→2′-anhydronucleoside [2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorouracil] (11) and 5-Fluoro-1-β-D-arabinofuranosyluracil (12). A solution of 1.7 g (0.0075 mol) of **10**[41] in 750 ml of MeOH was treated with 3.3 g (0.032 mol) of CF_3OF in 60 ml of CCl_3F according to the general fluorination and elimination procedures. The resulting crystalline mass was recrystallized from absolute EtOH to give 1.05 g (57%) of colorless platelets of **11:** mp 195–196 °C (lit.[8b] mp 196–197 °C); $[\alpha]^{22}D$ −57° (*c* 0.09, MeOH); uv (H_2O) max 254, 222.5 nm (ε 8500, 7100), min 234, 215 nm (ε 4900, 5900); mass spectrum *m/e* 244 (M^+). Anal. ($C_9H_9FN_2O_5$) C, H, F, N.

The mother liquor was concentrated and subjected to thick-layer chromatography (EtOAC–*n*-PrOH–H_2O, 4:1:2, upper phase, silica gel) to give an additional 0.10 g (5.5%) of **11** plus 0.34 g (17%) of **12** (recrystallized from EtOH): mp 187–189 °C (lit.[8b] mp 187–188 °C); uv (H_2O) max 270 nm (ε 9000), min 233.5 nm (ε 1450); mass spectrum calcd for M^+: 262.0601; found: *m/e* 262.0596.

5-Fluorocytosine (14). A solution of 0.444 g (0.004 mol) of **13** in 350 ml of MeOH was treated with 0.9 g (0.0087 mol) of CF_3OF in 40 ml of CCl_3F according to the general fluorination procedure and by the elimination procedure for 8 h. The resulting colorless solid (0.44 g, 85%) was crystallized from EtOH to give **14** (as the 0.25 solvate): mp 300–302 °C dec (lit.[7a] mp 295–297 °C dec); mass spectrum calcd for M^+: 129.0338; found: *m/e* 129.0340. Anal. ($C_4H_4FN_3O \cdot 0.25C_2H_5OH$) C, H, F, N. The presence of 0.25 M EtOH was verified in the ^{1}H NMR spectrum.

5-Fluorocytidine (17a). Method A. A solution of 1.22 g (0.005 mol) of **15a** in 400 ml of MeOH was treated with 0.9 g (0.0087 mol) of CF_3OF in 75 ml of CCl_3F according to the general fluorination procedure only. The residue was allowed to stand overnight at room temperature under high vacuum and was then dissolved in 50 ml of absolute EtOH. A 25-ml portion of 1 N HCl in absolute EtOH was added and the solution was allowed to stand at room temperature overnight. Evaporation of this solution and trituration of the resulting amorphous glass with 25 ml of absolute EtOH gave 0.4 g of solid. The mother liquor was concentrated and cooled to provide an additional 0.4 g of **17a**·HCl. The two crops (0.8 g, 54%) had mp 175–178 °C dec. Recrystallization of this material from EtOH gave **17a**·HCl: mp 174–176 °C dec (lit.[8c] mp ca. 170 °C dec); $[\alpha]^{23}D$ 45.5° (*c* 1.1, H_2O); mass spectrum calcd for M^+: 261.0761; found: *m/e* 261.0761. Anal. ($C_9H_{12}FN_3O_5 \cdot HCl$) C, H, Cl, N.

In another experiment, column chromatography was used ($MeOH-CHCl_3$, 1:9, silica gel) to separate **17a** (52%) from an undetermined quantity of 5-fluorouridine (**9a**).

Method B. A solution of 158 mg (0.384 mmol) of **16a**[52] in 24 ml of dry tetrahydrofuran (THF) was cooled to −78 °C and treated with 625 mg (6 mmol) of CF_3OF in 5 ml of CCl_3F at −98 °C according to the general fluorination procedure. The residue was dissolved in 3 ml of dry EtOH and 0.43 ml of dry Me_2NH was added. The resulting solution was allowed to stand for 2 days at room temperature in a Parr pressure vessel and was then evaporated. The pure (TLC) product was dissolved in 10 ml of 98% EtOH and 2.5 ml of HCl/EtOH (saturated at room temperature) was added. Evaporation and treatment of the residue with ~8 ml of dry EtOH gave a mixture which was placed in a desiccator containing Et_2O[51] for 3 h. The mixture was then cooled to −15 °C and filtered to give 100 mg (88%) of **17a**·HCl: mp 173–177 °C dec; mass spectrum calcd for M^+: 261.0761; found: *m/e* 261.0760; ^1H and ^{19}F NMR and mass spectra and TLC were identical with those of material prepared by method A.

5-Fluoro-2′-deoxycytidine (17b). A mixture of 0.114 g (0.0005 mol) of **15b**, 0.45 ml (0.49 g, 0.0048 mol) of Ac_2O, and 4.5 ml of dry pyridine was stirred for 4.5 h at room temperature. TLC ($MeOH-CHCl_3$, 1:9) showed complete reaction. The solution was evaporated in vacuo at 30 °C; the residue was coevaporated with $EtOH-PhCH_3$ and then partitioned between $CHCl_3$ and H_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to dryness. After drying the residue over P_2O_5 at 0.01 mmHg, 0.175 g (99%) of $O^{3'},O^{5'},N^4$-triacetyl-2′-deoxycytidine (**16b**) was obtained as a glass which did not crystallize. This product had: uv (H^+) max 307, 239 nm (ϵ/ϵ 1.5), min 267, 226 nm (ϵ/ϵ 0.43), (OH^-) max 270 nm, min 250 nm ($\epsilon_{max}/\epsilon_{min}$ 1.3) (hydrolysis of the N^4-acetyl function occurred in the 0.1 N NaOH); ^1H NMR ($CDCl_3$) δ 2.12 (s, 6, 3′- and 5′-$OCOCH_3$), 2.32 (s, 3, N-4 $COCH_3$), 2.60–3.05 (m, 2, H-2′, H-2″), 4.41 (m, 3, H-4′, H-5′, H-5″), 5.28 (m, 1, H-3′), 6.30 (d of d, $J_{H\text{-}1'\text{-}H\cdot2',H\cdot2''}$ = 8 and 6 Hz, 1, H-1′), 7.56 (d, $J_{H\cdot5\text{-}H\cdot6}$ = 7.5 Hz, 1, H-5), 8.12 (d, $J_{H\cdot6\text{-}H\cdot5}$ = 7.5 Hz, 1, H-6); mass spectrum *m/e* 353 (M^+).

A solution of 0.71 g (0.002 mol) of **16b** in 350 ml of $CHCl_3$ was treated with 0.6 g (0.0058 mol) of CF_3OF in 25 ml of CCl_3F according to the general fluorination and elimination procedures. The residue was dissolved in a minimum volume of MeOH and applied to a dry-packed column (1.8 × 55 cm) of silica gel (Mallinckrodt pH 4). After drying, the column was developed with EtOAc-*n*-PrOH-H_2O (4:1:2, upper phase). Fractions 16–45 were combined and evaporated to dryness, and the residue was crystallized from EtOH to give 0.113 g (23%) of **9b**, mp 148–150 °C (identified by mixture melting point and spectral comparison with a sample prepared above).

Fractions 46–155 were uv transparent and were discarded. The following fractions were combined and evaporated, and the residue crystallized from EtOH to give 0.34 g (69%) of **17b**: mp 198–200 °C (lit.[8c] mp 195–196.5 °C); $[\alpha]^{26}D$ 68.7° (*c* 1, H_2O); mass spectrum calcd for M^+: 245.0812; found: *m/e* 245.0806. Anal. ($C_9H_{12}FN_3O_4$) C, H, F, N.

2′-*O*-Methyl-$O^{3'},O^{5'},N^4$-triacetylcytidine (16c). A 0.15-g (0.00058 mol) portion of **15c**[40] was stirred in 5 ml of Ac_2O and 3 ml of pyridine for 20 h at room temperature. TLC indicated complete reaction. The solution was evaporated and the residue was coevaporated several times with MeOH/EtOAc. The resulting solid was purified by passage through a short column of silica gel in EtOH. Upon evaporation of EtOH, the compound crystallized giving 0.20 g (90%) of **16c**: mp 119–120 °C; uv (H_2O) max 299.5, 247, 213 nm (ϵ 11 300, 21 700, 23 000), min 271.5, 226, 201 nm (ϵ 6200, 6900, 9700); ^1H NMR (CD_3OD) δ 2.14 (s, 6, 3′- and 5′-$OCOCH_3$), 2.22 (s, 3, N-4 $COCH_3$), 3.54 (s, 3, 2′-OCH_3), 5.97 (d, $J_{H\cdot1'\text{-}H\cdot2'}$ = 2 Hz, 1, H-1′), 7.48 (d, $J_{H\cdot5\text{-}H\cdot6}$ = 6.5 Hz, 1, H-5), 8.20 (d, $J_{H\cdot6\text{-}H\cdot5}$ = 6.5 Hz, 1, H-6); mass spectrum *m/e* 383 (M^+), 351 ($M - 32$ [CH_3OH]). Anal. ($C_{16}H_{21}N_3O_8$) C, H, N.

5-Fluoro-2′-*O*-methylcytidine (17c) and 5-Fluoro-2′-*O*-methyluridine (9c). A solution of 1.08 g (0.0028 mol) of **16c** in 300 ml of MeOH was treated with 1.9 g (0.018 mol) of CF_3OF in 20 ml of CCl_3F according to the general fluorination and elimination procedures. Increasing conversion of **17c** → **9c** occurs with increasing time (after 30 h, only **9c** is present). After 8 h, the solution was evaporated and processed analogously to that in the above conversion of **16b** → **17b** using a column of J. T. Baker 3405 silica gel with $MeOH-CHCl_3$ (1:9) for elution. Evaporation of pooled fractions and recrystallization of the residue from EtOH/EtOAc gave 0.32 g (41%) of **9c**, mp 144–147 °C (which was identical by comparison with a sample of **9c** prepared above). Upon concentration of the appropriately combined fractions to near dryness, 0.37 g (48%) of **17c** crystallized as hard colorless needles: mp 249–250 °C; $[\alpha]^{22}D$ 98.5° (*c* 0.95, MeOH); mass spectrum *m/e* 275 (M^+), 243 ($M - 32$ [CH_3OH]). Anal. ($C_{10}H_{14}FN_3O_5$) C, H, F, N.

5-Fluoro-3′-*O*-methylcytidine (17d) and 5-Fluoro-3′-*O*-methyluridine (9d). A 0.56-g (0.0022 mol) portion of **15d**[40] in 5 ml of Ac_2O and 3 ml of pyridine was stirred for 15 h at room temperature. Evaporation of the solution gave a gum which was coevaporated with MeOH several times to give 0.76 g (91%) of $O^{2'},O^{5'},N^4$-triacetyl-3′-*O*-methylcytidine (**16d**) as a fluffy white solid which did not crystallize. This product had uv (H_2O) max 299.5, 247, 213 nm, min 271.5, 226, 201 nm; ^1H NMR (CD_3OD) δ 2.10, 2.13 (s, s; 3, 3; 2′- and 5′-$OCOCH_3$), 2.17 (s, 3, N-4 $COCH_3$), 3.35 (s, 3, 3′-OCH_3), 3.9–4.4 (m, 4, H-5′, H-5″, H-4′, H-3′), 5.54 (d of d, $J_{H\cdot2'\text{-}H\cdot3'}$ = 3 Hz, $J_{H\cdot2'\text{-}H\cdot1'}$ = 2.1 Hz, 1, H-2′), 5.86 (d, $J_{H\text{-}1'\text{-}H\cdot2'}$ = 2.1 Hz, 1, H-1′), 7.39 (d, $J_{H\cdot5\text{-}H\cdot6}$ = 7.2 Hz, 1, H-5), 8.10 (d, $J_{H\cdot6\text{-}H\cdot5}$ = 7.2 Hz, 1, H-6); mass spectrum *m/e* 383 (M^+).

A solution of 0.75 g (0.002 mol) of **16d** in 35 ml of MeOH was treated with 1 g (0.0096 mol) of CF_3OF in 10 ml of CCl_3F according to the general fluorination and elimination procedures and was processed as in the above conversion of **16c** → **17c** + **9c**. Evaporation of appropriate fractions gave 0.3 g (56%) of chromatographically homogeneous **9d**. This product was recrystallized with difficulty from MeOH/EtOAc to give 0.18 g (33%) of **9d**: mp 170–171 °C; $[\alpha]^{22}D$ 29.3° (*c* 1, MeOH); mass spectrum *m/e* 276 (M^+). Anal. ($C_{10}H_{13}FN_2O_6$) C, H, F, N. This product was identical with a small sample prepared by fluorination of 2′,5′-di-*O*-acetyl-3′-*O*-methyluridine[40a] (**8d**) analogously to the above conversion of **8c** → **9c**.

Evaporation of the later appropriate fractions from the above column separation gave a solid which was readily crystallized from $MeOH/CHCl_3$ to yield 0.11 g (20%) of **17d**: mp 108–111 °C; $[\alpha]^{22}D$ 52.7° (c 1.1, MeOH); mass spectrum *m/e* 275 (M^+). Anal. ($C_{10}H_{14}FN_3O_5$) C, H, F, N.

***O*^5',*N*^4-Diacetyl-2′,3′-di-*O*-methylcytidine (16e).** A solution of 0.31 g (0.0011 mol) of **15e**[40b,45] [prepared by the general procedure of Shugar[45] and purified by column chromatography on J. T. Baker 3405 silica gel using $MeOH-CHCl_3$ (8:92) followed by crystallization from PhH/EtOH to give **15e**, mp 105–108 °C, in 45% overall yield from crystalline 5′-*O*-tritylcytidine] and 10 mg of 4-*N*,*N*-dimethylaminopyridine in 10 ml of Ac_2O was allowed to stand for 10 h at room temperature. Evaporation of the solution to dryness in vacuo and coevaporation of the residue with three 15-ml portions of MeOH gave a crystalline solid. This material was recrystallized from MeOH to give 0.32 g (82%) of **16e**: mp 189–190 °C; uv (H_2O) max 297, 247, 214 nm (ϵ 9200, 18 000, 19 700), min 271, 226, 200 (ϵ 2900, 4200, 14 500); ^1H NMR ($CDCl_3$) δ 2.18 (s, 3, 5′-$OCOCH_3$), 2.34 (s, 3, N-4 $COCH_3$), 3.39 (s, 3, 3′-OCH_3), 3.75 (s, 3, 2′-OCH_3), 5.92 (s, 1, H-1′), 7.48 (d, $J_{H\cdot5\text{-}H\cdot6}$ = 7 Hz, 1, H-5), 8.18 (d, $J_{H\cdot6\text{-}H\cdot5}$ = 7 Hz, 1, H-6); mass spectrum *m/e* 355 (M^+), 323 ($M - 32$ [CH_3OH]). Anal. ($C_{15}H_{21}N_3O_7$) C, H, N.

5-Fluoro-2′,3′-di-*O*-methylcytidine (17e) and 5-Fluoro-2′,3′-di-*O*-methyluridine (9e). Method A. A solution of 0.76 g (0.0021 mol) of **16e** in 25 ml of MeOH was treated with 0.8 g (0.0077 mol) of CF_3OF in 10 ml of CCl_3F according to the general fluorination procedure. The adduct residue was stirred with 10 ml of triethylamine solution for 2 h and this solution was processed similarly to that in the above conversion of **16c** → **17c** + **9c**. Evaporation of appropriate fractions gave 0.35 g (57%) of 5-fluoro-2′,3′-di-*O*-methyluridine (**9e**) (identified by TLC and spectroscopic comparison with an above sample prepared by fluorination of **8e**).

Evaporation of the appropriate later fractions gave 0.08 g (13%) of crystalline 5-fluoro-2′,3′-di-*O*-methylcytidine (**17e**).

Method B. A solution of 0.37 g (0.001 mol) of **16e** in 60 ml of dry THF at −78 °C was treated with 1 g (9.6 mmol) of CF_3OF in 10 ml of CCl_3F at −98 °C by the general fluorination procedure. The residue was treated with ~15 ml of CH_2Cl_2 and reevaporated to give a solid foam which was dissolved in ~8 ml of dry EtOH. This solution was treated with ~0.55 ml of dry Me_2NH and sealed in a Parr pressure vessel for 2.5 days at room temperature. Evaporation followed by addition of 5 ml of EtOH plus 2 ml of HCl/EtOH (saturated at room temperature) and evaporation and finally addition and evaporation of MeOH gave a stiff white solid foam. This material was dissolved in ~15 ml of EtOH and allowed to stand at room temperature for ~18 h in a desiccator containing Et_2O.[51] Filtration gave 0.3 g (87%) of

17e·HCl, mp 171–175 °C dec. Recrystallization of a small sample from 98% EtOH (with diffusion of Et_2O[51]) gave crystalline **17e**·HCl: mp 175–180°C dec; $[\alpha]^{23}D$ 116.6° (*c* 0.99, MeOH); mass spectrum *m/e* 289 (M^+, free base). Anal. ($C_{11}H_{16}FN_3O_5$·HCl) C, H, Cl, F, N.

5-Fluoro-1-β-D-arabinofuranosylcytosine[8h,j] (**20**). A solution of 0.235 g (0.00057 mol) of $O^{2'},O^{3'},O^{5'},N^4$-tetraacetyl-1-β-D-arabinofuranosylcytosine (**19**) (prepared in near quantitative yield by acetylation of **18** according to the general procedure of Goodman[47]) in 50 ml of $CHCl_3$ was treated with 0.2 g (0.0019 mol) of CF_3OF in 15 ml of CCl_3F according to the general fluorination and elimination procedures and processed as in **8a** → **9a** described above. The combined filtrate was evaporated to yield 0.023 g (15%) of 5-fluoro-1-β-D-arabinofuranosyluracil (**12**) (identified by TLC and spectroscopic comparison with a sample obtained in the above fluorination of **10**).

The resin was then washed with 1 N HCl in EtOH (~25 ml) until the filtrate was uv transparent. Evaporation of the combined filtrate gave 0.14 g (82%) of crystalline 5-fluoro-1-β-D-arabinofuranosylcytosine (**20**) hydrochloride which was recrystallized from EtOH to give needles of **20**·HCl: mp 178–180 °C; $[\alpha]^{23}D$ 141° (*c* 1, H_2O); mass spectrum calcd for M^+ ($C_9H_{12}FN_3O_5$): 261.0761; found: *m/e* 261.0756. Anal. ($C_9H_{12}FN_3O_5$·HCl) C, H, N.

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References and Notes

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(24) *Caution:* Trifluoromethyl hypofluorite (CF_3OF) is toxic and is a strong oxidizing agent. We have experienced no difficulties over a period of 6 years involving well over 100 individual experiments executed by five different persons employing additions of CF_3OF in CCl_3F at −78 or −98 °C to cold (usually −78 °C) solutions of pyrimidine compounds in chloroform, tetrahydrofuran, methanol, or aqueous mixtures. However, we have been informed of violent explosions occurring upon direct introduction of gaseous CF_3OF into methanol. CF_3OF is a pseudohalogen of F_2, and direct addition to alcohols or other readily oxidizable solutions especially at room temperature *should not be attempted.* A well-ventilated fume hood should always be used for transfers and evaporations.

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