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Synthesis of brain-targeted 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)-(*E*)-5-(2-iodovinyl)uracil coupled to a dihydropyridine ⇋ pyridinium salt redox chemical-delivery system

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ABSTRACT

1-(2-Deoxy-2-fluoro-β-D-ribofuranosyl-(*E*)-5-(2-iodovinyl)uracil (IVFRU) was coupled to a dihydropyridine ⇋ pyridinium salt redox chemical-delivery system (CDS) via a cleavable sugar-ester linkage as a site-directed approach to increase diffusion of the parent nucleoside into the central nervous system. Treatment of 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil with Bu^tMe_2SiCl in the presence of imidazole in DMF yielded the protected 5-*O*-*tert*-butyldimethylsilyl derivative. Subsequent reaction with nicotinoyl chloride hydrochloride in pyridine afforded 1-[5-*O*-tert-butyldimethylsilyl-2-deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-D-ribofuranosyl]uracil. Reaction with iodine monochloride in methanol simultaneously cleaved the silyl ether moiety and iodinated the uracil ring at the 5-position. Coupling with (*E*)-Bu_3Sn-CH=CH-$SiMe_3$ in the presence of $(Ph_3P)_2Pd_2(II)Cl_2$ in THF gave 1-[2-deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-trimethylsilylvinyl)uracil. Quaternization with iodomethane in acetone yielded the *N*-methylpyridinium iodide salt. Iodination of the reactive (*E*)-trimethylsilylvinyl moiety with iodine monochloride in acetonitrile and reduction of the quaternary pyridinium iodide salt with sodium dithionite in the presence of sodium hydrogen carbonate was carried out as a one-pot procedure to afford 1-[2-deoxy-2-fluoro-3-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-iodovinyl)uracil (IVFRU-CDS). This synthetic strategy is readily amenable to the high specfic-activity radioiodination of IVFRU.

INTRODUCTION

A number of pyrimidine nucleoside analogues that contain a fluorinated sugar moiety exhibit potent and selective activities. Incorporation of a fluorine substituent at the 2′-position of a variety of 5-substituted 2′-deoxyuridine derivatives has provided compounds which in many cases are selective substrates for phosphorylation by herpes simplex virus type-1 (HSV-1)-encoded thymidine kinase[1]. The (*E*)-5-(2-halovinyl)-2′-deoxyuridine class of compounds are among the most potent

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and selective agents that undergo selective phosphorylation by the viral-encoded enzyme[2]. However, rapid in vivo deglycosylation mediated by host nucleoside phosphorylases limits the clinical utility of this latter class of compounds[3]. (*E*)-5-(2-Iodovinyl)-2′-deoxyuridine (IVDU) is a unique member of this class, since γ-emmiting isotopes of iodine can be incorporated into the molecule that would allow external scintigraphic imaging of virus-infected tissue by single photon emission computed tomography (SPECT). The use of radiolabelled antiviral drugs for the diagnosis of herpes simplex encephalitis (HSE) has been proposed by Price et al.[4]. Quantitative autoradiographic mapping of HSE in rats using [^{14}C]-labelled 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (FMAU) suggested that the selective uptake of appropriately radiolabelled drugs that exploit viral thymidine kinase for their antiviral effect could be used in conjunction with clinical neuroimaging techniques to image infected regions of human brain, thereby providing a new approach for the diagnosis of HSE in man. It was found that [^{14}C]-FMAU was selectively taken up by infected brain cells and that the tracer can be used to map the distribution of the HSV-1 infection[5]. In an earlier study, IVDU was investigated as a potential diagnostic probe to aid in the diagnosis of HSE[6]. However, IVDU possesses a limited ability to traverse the blood–brain barrier (BBB) due to its low partition coefficient. In addition, the pharmacokinetics of IVDU are unfavorable for a putative radiopharmaceutical due to its rapid metabolism by phosphorylases[7]. It has been observed that the presence of an arabino fluoro substituent at the C-2 position of FMAU or 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine[8], and the C-2′-position of 2′,3′-dedeoxy-2′-fluoroadenosine[9] prevents deglycosylation while retaining anti-HSV-1 and anti-AIDS activity, respectively. Similar results have been reported for 5-alkenyl and 5-alkyl analogues of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil[10,11]. 1-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)-(*E*)-5-(2-iodovinyl)uracil (IVFRU) is a fluorinated analogue of IVDU that also retains the potent and selective antiviral properties of the parent nucleoside IVDU, yet is possesses a greatly enhanced resistance to phosphorolysis of the glycosyl bond[12]. For example, IVFRU exhibited comparable in vitro anti-HSV-1 activity (MIC_{50} = 0.01–0.1 μg/mL) to IVDU, its affinity for the murine erythrocyte nucleoside transporter system was greater than that of 2′-deoxyuridine, and it was selectively trapped within rabbit kidney cells (27.9 and 41.2% at 4 and 24 h, respectively) HSV-1 infected in vitro by thymidine kinase-positive (TK^+), but not within HSV (TK^-) or mock-infected cells, where uptake was less than 1%. Therefore, a lipophilic prodrug of IVFRU may circumvent the inherent limitations of radiolabelled IVDU encountered previously.

The dihydropyridine ⇋ pyridinium salt redox chemical-delivery system developed by Bodor et al. is one of the more promising methods for brain-directed drug delivery[13]. This approach involves the coupling of a lipophilic 1-methyl-1,4-dihydropyridyl promoiety to a drug entity via a cleavable ester or amide moiety. The prodrug may undergo enhanced CNS uptake due to its increased lipophilicity. The promoiety can then undergo oxidation, in a manner analogous to the NAD ⇋

NADH redox system, to a polar pyridinium salt which is trapped inside the brain due to the lipoidal nature of the BBB. The ester moiety can then undergo hydrolysis to release the active drug and the oxidized promoiety, trigonelline. This dihydropyridine ⇋ pyridinium salt redox chemical delivery approach has been applied to other polar nucleoside analogues[14–16] including IVDU[17] as a method to enhance CNS uptake of these agents. It was therefore expected that this chemical-delivery system coupled to IVFRU via a labile ester linkage could be a viable method to enhance the uptake of IVFRU into virus infected brain tissue.

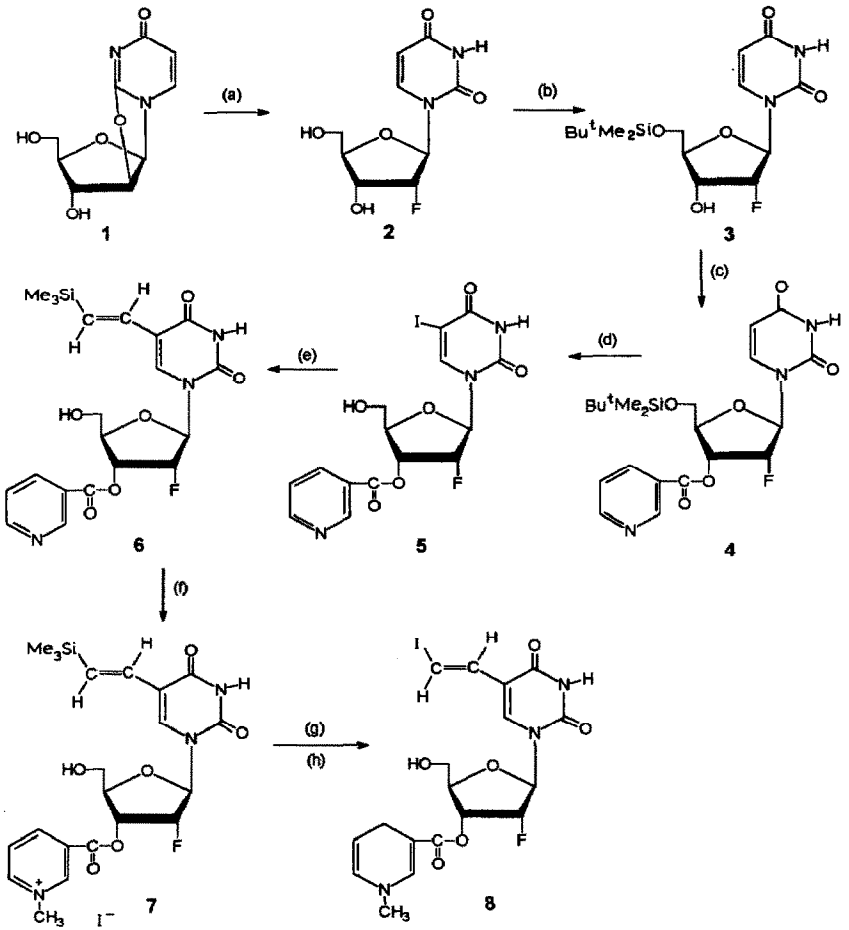
An important requirement in the design of our synthetic strategy was the development of a synthetic methodology that was suitable for the radiolabelled synthesis of a high specific-activity radioiodinated product. This high specific-activity requirement, which is typical of receptor imaging agents, is necessary for effective imaging of HSV-1 infected cells in the brains of individuals having herpes simplex encephalitis. We now describe the synthesis of 1-[2-deoxy-2-fluoro-3-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-iodovinyl)uracil (IVFRU-CDS, **8**) via methodology readily amenable to high specific-activity radioiodination with ^{123}I, an isotope suitable for SPECT imaging.

RESULTS AND DISCUSSION

The synthesis of IVFRU-CDS (**8**) was achieved using an eight-step synthetic sequence starting from commercially available O^2,2-anhydrouridine (**1**). 1-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)uracil (**2**) was prepared by reaction of **1** with HF in anhyd 1,4-dioxane as previously described[18]. The regiospecific reaction of **2** with tert-butylchlorodimethylsilane in the presence of imidazole in DMF gave 1-(5-*O*-tert-butyldimethylsilyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil (**3**, 67%). The 3-hydroxyl moiety of **3** was esterified with nicotinoyl chloride hydrochloride in pyridine to afford 1-[5-*O*-tert-butyldimethylsilyl-2-deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-D-ribofuranosyl]uracil (**4**, 73%).

The simultaneous cleavage of the silyl ether protecting group and C-5 iodination of the uracil ring were effected by treatment of **4** with iodine monochloride in methanol at reflux for 16 h afforded 1-[2-deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-D-ribofuranosyl]5-iodo-uracil (**5**, 41%). However, the mother liquor was found to contain appreciable amounts of the 5-iodo-6-methoxy-5,6-dihydro adduct which, on further heating, eliminated to give additional product (**5**). The ^1H NMR resonances and coupling constants for **5** were confirmed by selective decoupling experiments.

The 5-iodo nucleoside derivative (**5**) was then subjected to a $(Ph_3P)_2Pd(II)Cl_2$-catalyzed coupling reaction using (*E*)-Bu_3Sn-CH=CH-$SiMe_3$ in THF under Ar[19] to give 1-[2-deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-trimethylsilylvinyl)uracil (**6**, 50%), after recrystallization from EtOAc. The C-5 2-trimethylsilylvinyl substituent of **6** possessed the desired (*E*)-stereochemistry (J_{trans} 19 Hz). In contrast, recrystallization of **6** from MeOH induced isomerization



Scheme 1. Reagents: (a) HF, 1,4-dioxane; (b) Bu^tMe_2SiCl, imidazole, DMF; (c) nicotinoyl chloride·HCl, pyridine; (d) ICl, (e) (*E*)-Bu_3Sn-CH=CH-$SiMe_3$ $(Ph_3P)_2Pd(II)Cl_2$, THF; (f) MeI, acetone; (g) ICl, acetonitrile; (h) $Na_2S_2O_4$, $NaHCO_3$, H_2O–EtOAc.

to the (*Z*)-isomer, in accordance with a previous report[20]. Quaternization of **6** using an excess of iodomethane in acetone at reflux gave 1-[2-deoxy-2-fluoro-3-*O*-(1-methylpyridinium-3-carbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-trimethylsilylvinyl)-uracil iodide (**7**, 90%).

The reactive vinylsilane salt (**7**) was subjected to an iododemetallation reaction using iodine monochloride in MeCN, which proceeded rapidly with retention of the *E*-stereochemistry. Since the reactant (**7**) undergoes a slow isomerization to the (*Z*)-isomer in the MeCN solvent, iodine monochloride must be added immediately after dissolution of the salt (**7**). Reduction of the pyridinium salt was performed immediately using sodium dithionite in the presence of sodium hydrogencarbonate, employing a two phase water–EtOAc solvent-system. The residue from the EtOAc extract was chromatographed on a neutral alumina column since

silica gel column chromatography let to considerable decomposition. The title compound 1-[2-deoxy-2-fluoro-3-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-iodovinyl)uracil (IVFRU-CDS, **8**), obtained in this reaction, displayed a large *trans* coupling constant in the ^{1}H NMR spectrum for the iodovinyl protons, confirming the presence of the desired (*E*)-iodovinyl stereochemistry (J_{trans} 15 Hz). It was necessary to perform the iodination of **7** using ICl prior to reduction of the pyridinium salt to the 1,4-dihydropyridyl ring, since iodination of 1-[2-deoxy-2-fluoro-3-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-β-D-ribofuranosyl]-(*E*)-5-(2-trimethylsilylvinyl)uracil using ICl also resulted in the concomitant oxidation of the 1,4-dihydropyridyl ring to the pyridinium salt. The iododemetallation and reduction reactions were carried out using a one-pot sequence which is essential for the high specific-activity radiolabelled synthesis that is now underway.

EXPERIMENTAL

General methods.—Column chromatogrphy on silica gel was carried out using Merck 7734 silica gel (100–200 mesh) and on aluminum oxide with Camag 507-C neutral aluminum oxide. O^2,2-Anhydrouridine (**1**) was purchased fron the Aldrich Chemical Co. 1-(2-fluoro-2-deoxy-β-D-ribofuranosyl)uracil (**2**) was prepared using the literature procedure[18]. (*E*)-2-Tri-butylstannyl-1-trimethylsilylethene was prepared using a previously described method[21].

1-(5-O-tert-Butyldimethylsilyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil (**3**).—Imidazole (1.0 g, 14.69 mmol) and *tert*-butylchlorodimethylsilane (1.0 g, 6.63 mmol) were added to a solution of **2** (1.46 g, 5.93 mmol) in dry DMF (20 mL) and the reaction was allowed to proceed with stirring for 48 h at 25°C. Removal of the solvent in vacuo gave a residue which was purified by elution from a silica gel column using 96:4 $CHCl_3$–MeOH, as eluant to afford **3** (1.42 g, 67%) as a white solid, after recrystallization from MeOH; mp 58-60°C, ^{1}H NMR ($CDCl_3$): δ 0.13 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, Me_3C), 2.44 (br s, 1 H, 3-OH, exchanges with deuterium oxide), 3.88 (d, 1 H, J_{gem} 10.6 Hz, H-5′), 4.06–4.12 (m, 2 H, H-4, H-5″), 4.30–4.42 (m, 1 H, $J_{3,F}$ 18 Hz, H-3), 4.96 (dt, 1 H, $J_{2,F}$ 51, $J_{2,3}$ 4.3, $J_{1,2}$ 2.0 Hz, H-2), 5.70 (d, 1 H, $J_{5,6}$ 7.0 Hz, uracil H-5), 6.12 (dd, 1 H, $J_{1,F}$ 14.7, $J_{1,2}$ 2.0 Hz, H-1), 7.94 (d, 1 H, $J_{5,6}$ 7.0 Hz, uracil H-6), 8.86 (br s, 1 H, NH, exchanges with deuterium oxide). Anal. Calcd for $C_{15}H_{25}FN_2O_5Si.1/2H_2O$: C, 48.76; H, 7.11; N, 7.58. Found: C, 48.90; H, 7.03; N, 7.50.

1-[5-O-tert-Butyldimethylsilyl-2-deoxy-2-fluoro-3-O-(3-pyridylcarbonyl)-β-D-ribofuranosyl]uracil (**4**).—1-(5-*O*-*tert*-Butyldimethylsilyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil (**3**) (1.32 g, 3.65 mmol) was added to a solution of nicotinoyl chloride hydrochloride (1.24 g, 7.0 mmol) in dry pyridine (50 mL) and the reaction was allowed to proceed for 48 h at 25°C with stirring. Removal of the solvent in vacuo and purification of the residue obtained by elution from a silica gel column using 97:3 $CHCl_3$–MeOH as eluant afforded **4** (1.24 g, 73%), after recrystalliza-

tion from MeOH as a white solid; mp 212-214°C, ^{1}H NMR ($CDCl_3$): δ 0.13 (s, 6 H, $SiMe_2$), 0.93 (s, 9 H, Me_3C), 3.90 (d, 1 H, J_{gem} 10.6 Hz, H-5′), 4.12 (d, 1 H, J_{gem} 10.6 Hz, H-5″), 4.48 (d, 1 H, $J_{3,4}$ 5 Hz, H-4), 5.28 (ddd, 1 H, $J_{2,F}$ 51.0, $J_{2,3}$ 3.0, $J_{1,2}$ 2.7 Hz, H-2), 5.49 (ddd, 1 H, $J_{3,F}$ 13.7, $J_{3,4}$ 5.0, $J_{2,3}$ 3.0 Hz, H-3), 5.76 (d, 1 H, $J_{5,6}$ 7.0 Hz, uracil H-5), 6.25 (dd, 1 H, $J_{1,F}$ 14.0, $J_{1,2}$ 2.7 Hz, H-1), 7.46 (dd, 1 H, $J_{4,5}$ 8.0, $J_{5,6}$ 5.0 Hz, pyridine H-5), 7.90 (d, 1 H, $J_{5,6}$ 7.0 Hz, uracil H-6), 8.34 (ddd, 1 H, $J_{4,5}$ 8.0, $J_{2,4} = J_{4,6} = 1.6$ Hz, pyridine H-4), 8.46 (br s, 1 H, NH, exchanges with deuterium oxide), 8.86 (dd, 1 H, $J_{5,6}$ 5.0, $J_{4,6}$ 1.6 Hz, pyridine H-6), 9.27 (*d*, 1 H, $J_{2,4}$ 1.6 Hz, pyridine H-2). Anal. Calcd for $C_{21}H_{28}FN_3O_6Si$: C, 54.53; H, 5.46; N, 9.08. Found: C, 54.33; H, 5.85; N, 8.99.

*1-[2-Deoxy-2-fluoro-3-*O*-(3-pyridylcarbonyl)-β-*D*-ribofuranosyl]-5-iodouracil* (**5**). —Iodine monochloride (52 mg, 0.32 mmol) was added to a solution of **4** (0.12 g, 0.26 mmol) in MeOH (6 mL) and the mixture was stirred at reflux temperature for 24 h. Removal of the solvent in vacuo, purification of the residue obtained by elution from a silica gel column using 93:7 $CHCl_3$–MeOH as eluant and recrystallization of the product obtained from MeOH gave **5** (46 mg, 41%) as colorless crystals; mp 202-203°; ^{1}H NMR (CD_3OD): δ 3.84 (dd, 1 H, J_{gem} 12.2, $J_{4,5'}$ 2.3 Hz, H-5′), 4.00 (dd, 1 H, J_{gem} 12.2, $J_{4,5''}$ 1.8 Hz, H-5″), 4.48 (ddd, 1 H, $J_{3,4}$ 6.5, $J_{4,5'}$ 2.3, $J_{4,5''}$ 1.8 Hz, H-4), 5.59 (ddd, 1 H, $J_{2,F}$ 52.0, $J_{2,3}$ 4.5, $J_{1,2}$ 1.7 Hz, H-2), 5.64 (ddd, 1 H, $J_{3,F}$ 13.3, $J_{3,4}$ 6.5, $J_{2,3}$ 4.5 Hz, H-3), 6.12 (dd, 1 H, $J_{1,F}$ 19.8, $J_{1,2}$ 1.7 Hz, H-1), 7.64 (dd, 1 H, $J_{4,5}$ 7.5, $J_{5,6}$ 5.0 Hz, pyridine H-5), 8.45 (d, 1H, $J_{4,5}$ 7.5 Hz, pyridine H-4), 8.56 (s, 1 H, uracil H-6), 8.86 (d, 1 H, $J_{5,6}$ 5.0 Hz, pyridine H-6), 9.22 (s, 1 H, pyridine H-2); ^{19}F NMR (CD_3OD): δ 37.67 (ddd, 1 F, $J_{2,F}$ 52.0, $J_{1,F}$ 19.8, $J_{3,F}$ 13.3 Hz, F-2). Anal. Calcd for $C_{15}H_{13}FIN_3O_6$: C, 35.65; H, 2.60; N, 8.32. Found: C, 36.05; H, 2.45; N, 8.09.

1-[2-Deoxy-2-fluoro-3-O-(3-pyridylcarbonyl)-β-D-ribofuranosyl](E)-5-(2-trimethylsilylvinyl)uracil (**6**).—(*E*)-Bu_3Sn-CH=CH-$SiMe_3$ (41 mg, 0.106 mmol) was added to a solution of **5** (20 mg, 0.04 mmol) and $(Ph_3P)_2Pd(II)Cl_2$ (4 mg, 0.0057 mmol) in dry THF (30 mL) and the mixture was stirred at 50°C for 16 h under Ar. Removal of the solvent in vacuo and purification of the residue obtained by elution from a silica gel column using 19:1 $CHCl_3$–MeOH as eluant afforded **6** (9 mg, 50%) as colorless crystals, after recrystallization from EtOAc; mp 112–114°C; ^{1}H NMR ($CDCl_3$): δ 0.1 (s, 9 H, $SiMe_3$), 3.92 and 4.12 (two d, 1 H, J_{gem} 12.5 Hz, each, H-5), 4.45 (d, 1 H, $J_{3,4}$ 5.0 Hz, H-4), 5.58 (m, 1 H, $J_{2,F}$ 51 Hz, H-2), 5.68 (d, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 5.93 (dd, 1 H, $J_{1,F}$ 18.0, $J_{1,2}$ 2.0 Hz, H-1), 6.55 and 6.62 (two d, 1 H, J_{trans} 19 Hz, each, $CH = CHSiMe_3$), 7.44 (dd, 1 H, $J_{4,5}$ 8.0, $J_{5,6}$ 5.0 Hz, pyridine H-5), 7.78 (s, 1 H, uracil H-6), 8.32 (ddd, 1 H, $J_{4,5}$ 8.0, $J_{4,6} = J_{2,4} = 1.6$ Hz, pyridine H-4), 8.82 (dd, 1 H, $J_{5,6}$ 5.0, $J_{4,6}$ 1.6 Hz, pyridine H-6), 9.24 (d, 1 H, $J_{2,4}$ 2.0 Hz, pyridine H-2). Anal. Calcd for $C_{20}H_{24}FN_3O_6Si$: C, 53.44; H, 5.38; N, 9.35. Found: C, 53.11; H, 5.16; N, 9.03.

*1-[2-Deoxy-2-fluoro-3-*O*-(1-methylpyridinium-3-carbonyl)-β-*D*-ribofuranosyl]-(E)-5-(2-trimethylsilylvinyl)uracil iodide* (**7**).—Iodomethane (165 mg, 1.16 mmol) was added to a solution of **6** (26 mg, 0.058 mmol) in acetone (3 mL) and the

mixture was heated at reflux for 16 h. Removal of the solvent in vacuo and trituration of the residue obtained with ether (3 × 10 ml) gave the pyridinium salt (**7**, 31 mg, 90%) as yellow crystals; mp 172–174°C; ^{1}H NMR [$(CD_3)_2SO$]: δ 0.1 (s, 9 H, $SiMe_3$), 3.7–3.9 (m, 2 H, H-5), 4.44 (br s, 4 H, N-Me, H-4), 5.44 (t, 1 H, $J_{OH,5}$ 3 Hz, C-5 OH, exchanges with deuterium oxide), 5.55–5.58 (m, 1 H, H-3), 5.58–5.80 (m, 1 H, H-2), 6.12 (dd, 1 H, $J_{1,F}$ 17.0, $J_{1,2}$ 1.8 Hz, H-1), 6.60 (s, 2 H, CH = $CHSiMe_3$), 8.22 (s, 1 H, uracil H-6), 8.29 (dd, 1 H, $J_{4,5}$ 7.6, $J_{5,6}$ 5.0 Hz, pyridinium H-5), 9.06 (d, 1 H, $J_{4,6}$ 7.6 Hz, pyridinium H-4), 9.23 (d, 1 H, $J_{5,6}$ 5.0 Hz, pyridinium H-6), 9.66 (s, 1 H, pyridinium H-2), 11.62 (s, 1 H, NH, exchanges with deuterium oxide). Anal. Calcd for $C_{21}H_{27}FIN_3O_6Si$. 1/2 H_2O: C, 42.00; H, 4.71; N, 6.99. Found: C, 42.37; H, 4.57; N, 6.57.

*1-[2-Deoxy-2-fluoro-3-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-β-*D*-ribo-furanosyl]-(*E*)-5-(2-iodovinyl)uracil (IVFRU-CDS)* (**8**).—Iodine monochloride (1.7 mg, 0.01 mmol) was added to a solution of **7** (6 mg, 0.01 mmol) in MeCN (1 mL), immediately after its preparation, and the mixture was stirred at 25°C for 15 min. Removal of the solvent in vacuo gave the corresponding iodovinyl product as a yellow solid which was used immediately without purification. The iodovinyl product was dissolved in a two-phase solvent system comprised of water–EtOAc (1 mL each). Sodium dithionite (10 mg, 0.057 mmol) and $NaHCO_3$ (4 mg, 0.048 mmol) were added immediately, and the reaction was allowed to proceed at 25°C with stirring for 15 min. The EtOAc fraction was washed with water (1 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the product purified using a short column of neutral Al_2O_3. Elution with 9:1 $CHCl_3$–MeOH afforded **8** (3 mg, 59%) as a yellow solid, after recrystallization from MeOH; mp 131–133°C; ^{1}H NMR ($CDCl_3$): δ 3.02 (s, 3 H, N-Me), 3.11 (br s, 2 H, dihydropyridyl H-4), 3.86 and 4.10 (two d, 1 H, J_{gem} 12.5 Hz, each, H-5), 4.27 (d, 1 H, $J_{3,4}$ 7.5 Hz, H-4), 4.87 (dt, 1 H, $J_{5,6}$ 8.0, $J_{4,5}$ 3.8 Hz, dihydropyridyl H-5), 5.18 (m, 1 H, $J_{2,F}$ 51 Hz, H-2), 5.32 (m, 1 H, H-3), 5.68 (d, 1 H, $J_{5,6}$ 8.0 Hz, dihydropyridyl H-6), 6.05 (d, 1 H, $J_{1,F}$ 16 Hz, H-1), 7.06 (d, 1 H, J_{trans} 15 Hz, CH = CHI), 7.11 (s, 1 H, dihydropyridyl H-2), 7.40 (d, 1 H, J_{trans} 15 Hz, CH = CHI), 8.12 (s, 1 H, uracil H-6). Anal. Calcd for $C_{18}H_{19}FIN_3O_6$. H_2O: C, 40.24; H, 3.94; N, 7.82. Found: C, 40.52; H, 4.09; N, 7.61.

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