Synthesis of Brain-Targeted 5-Iodo-, 5-Vinyl- and (*E*)-5-(2-Iodovinyl)-2′-deoxyuridines Coupled to a Dihydropyridine ⇋ Pyridinium Salt Redox Chemical Delivery System

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5-Iodo-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15a**), 5-vinyl-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15b**) and (*E*)-5-(2-iodovinyl)-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15c**) were synthesized for future evaluation as lipophilic brain-selective antiviral agents for the treatment of herpes simplex encephalitis. Quaternization of the 3′-*O*-(3-pyridylcarbonyl) compounds **10-11** using iodomethane afforded the corresponding 1-methylpyridinium salts **12-13** which were reduced with sodium dithionite to yield the corresponding 3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl) compounds **14-15**.

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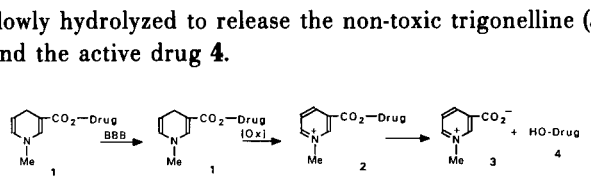
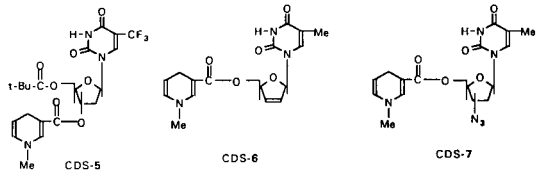
Introduction.

Herpes simplex virus type 1 (HSV-1) is one of the most common causes of fatal encephalitis (HSE) in humans [1]. Treatment of HSE requires early diagnosis and initiation of chemotherapy using potent antiviral drugs such as adenine arabinoside (Vidarabine^R) or acyclovir (Zovirax^R) before the patient goes into a coma [2]. Although acyclovir therapy reduces the mortality rate to 20-30%, some 30-40% of survivors are afflicted by subsequent neurologic deficits [3,4]. Polar pyrimidine nucleoside antiviral agents do not cross the blood-brain barrier (BBB) or cross to only a small extent. In an effort to overcome this problem, the potent antiviral agent (*E*)-5-(2-iodovinyl)-2′-deoxyuridine (**8c**, IVDU) was encapsulated in liposomes to increase its BBB penetration, but the uptake in brain was still too low to be clinically effective [5]. Bodor *et al.* [6] have demonstrated that drugs can be selectively delivered to the brain using a dihydropyridine ⇋ pyridinium salt redox chemical delivery system (CDS). A conceptual model which depicts this brain-selective CDS is illustrated below. When the CDS-**1** is administered, it localizes selectively in brain, as it readily crosses the BBB due to its high lipophilicity, relative to peripheral sites. The labile CDS-**1** is oxidized to the pyridinium salt **2** (NAD → NADH redox system) in the brain. In the brain, the BBB prevents egress of the polar species **2** which results in an elevated and sustained brain concentration. The *locked-in* salt **2** is then slowly hydrolyzed to release the non-toxic trigonelline (**3**) and the active drug **4**.



This type of dihydropyridine ⇋ pyridinium salt redox CDS is potentially useful for the selective delivery of the antiviral agent 5-trifluoromethyl-2′-deoxyuridine (CDS-**5**) [7], and the anti-HIV agents 2′,3′-didehydro-2′,3′-dideoxythymidine (CDS-**6**) [8] and 3′-azido-3′-deoxythymidine (CDS-**7**) [9] to the brain.



It was therefore of interest to develop methods for coupling the 1-methyl-1,4-dihydropyridyl-3-carbonyl moiety to the 3′-position of the antiviral agents 5-iodo- **8a**, 5-vinyl- **8b** and (**E**)-5-(2-iodovinyl)-2′-deoxyuridine (**8c**) [10]. This methodology would also be applicable to the synthesis of *no-carrier-added* [^{123}I]-labelled analogues ($t_{1/2}$ = 13.26 hours) for use as non-invasive radiopharmaceuticals for the imaging (SPECT, single photon emmision computed tomography) and diagnosis of HSE. We now report the synthesis of the 5-iodo- **15a**, 5-vinyl- **15b** and (*E*)-5-(2-iodovinyl)-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15c**) chemical delivery systems.

Chemistry.

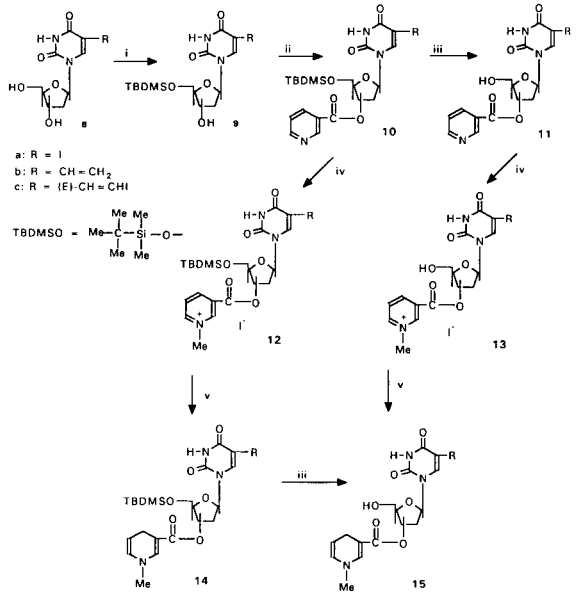
The regiospecific reaction of 5-iodo-, 5-vinyl- and (*E*)-5-(2-iodovinyl)-2′-deoxyuridines **8a-c** with *t*-butyldimethylsilyl chloride in the presence of imidazole afforded the respective 5′-*O*-*t*-butyldimethylsilyl (TBDMS) derivatives (**9a-c**) in 63-73% yields (see Scheme 1). The 5′-*O*-TBDMS protecting group was selected since it can be readily removed to regenerate the C-5′ hydroxyl group which is required for phosphorylation by viral kinases. Reaction of **9a-c** with nicotinoyl chloride hydrochloride in the presence of pyridine yielded the corresponding 5-iodo- **10a**, 5-vinyl- **10b** and (*E*)-5-(2-iodovinyl)-3′-*O*-(3-pyridylcarbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine (**10c**) in 43, 32 and 87% yields, respectively. Deprotection of **10a** and **10c** using *n*-$Bu_4N^+F^-$ afforded the corresponding derivatives **11a** and **11c** possessing a C-5′ hydroxyl group.

Quaternization of the nicotinoyl esters **10a-c**, **11a**, **11c** with iodomethane yielded the corresponding 1-methylpyridinium iodide salts **12a-c**, **13a**, **13c** in 64-96% yields. Reduction of the pyridinium salts **12a-c**, **13a**, **13c** using sodium dithionite under basic reaction conditions using a two-phase solvent system (water:ethyl acetate; 1:1, v/v) gave the corresponding 3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)- products **14a** (57%), **14b** (80%), **14c** (87%), **15a** (14%) and **15c** (44%). Superior yields were obtained in this reduction for those compounds possessing a 5'-*O*-TBDMS protecting group, **12a-c**, relative to compounds **13a** and **13c** possessing a free C-5' hydroxyl moiety. Deprotection of **14a-c** using *n*-$Bu_4N^+F^-$ yielded the respective 5-iodo- **15a** (47%), 5-vinyl- **15b** (80%) and (*E*)-5-(2-iodovinyl)-3'-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2'-deoxyuridine (**15c**, 37%).

A higher yield of the 5-iodo compound (**15a**) was obtained when the 5'-*O*-TBDMS protecting group was removed in the last step of the reaction sequence after the quaternization and reduction reactions, **10a** → **12a** → **14a** → **15a**; 22.2% overall yield, relative to the reaction sequence where deprotection was carried out prior to quaternization and reduction, **11a** → **13a** → **15a**; 13.4% overall yield. In contrast, the (*E*)-5-(2-iodovinyl) product **15c** was obtained in higher yield when deprotection was performed first, **10c** → **13c** → **15c**; 31.1% overall yield, relative to deprotection as the last reaction step **10c** → **12c** → **14c** → **15c**; 20.6% overall yield.

Purification of the 1-methyl-1,4-dihydropyridyl-3-carbonyl compounds **14** and **15** was carried out by neutral aluminum oxide column chromatography. The lower yields obtained using silica gel column chromatography may be due to acid catalyzed addition of water to the dihydropyridyl C_5-C_6 olefinic bond [11].

Scheme 1



Reagents: i, TBDMSCl, imidazole, DMF, 25 °C; ii, nicotinoyl chloride.HCl, pyridine, 25 °C; iii, n-$Bu_4N^+F^-$, THF, 25 °C; iv, MeI, acetone, reflux; v, $Na_2S_2O_3$, $NaHCO_3$, H_2O:EtOAc (1:1, v/v), 25 °C.

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H nmr, ^{13}C nmr) were determined for solutions in perdeuteriomethanol, deuteriochloroform or DMSO-d_6 with TMS as internal standard (^1H nmr) with a Bruker AM-300 spectrometer. The ^{13}C nmr spectra were determined using the J modulated spin echo technique where methyl and methine carbon resonances appear as positive peaks and methylene and quaternary carbon resonances appear as negative peaks. Silica gel column chromatography was carried out using Merck 7734 silica gel (60-200 μ particle size). Aluminum oxide chromatography was performed using Camag 507-C neutral aluminum oxide. 5-Iodo-2'-deoxyuridine (**8a**) was purchased from the Aldrich Chemical Co. 5-Vinyl-2'-deoxyuridine (**8b**) [12] and (*E*)-5-(2-iodovinyl)-2'-deoxyuridine (**8c**) [13] were prepared by using the literature methods.

5-Iodo-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**9a**).

Imidazole (0.9 g, 14.5 mmoles) and *t*-butyldimethylsilyl chloride (TBDMSCl) (0.9 g, 6 mmoles) were added to a solution of **8a** (2.0 g, 5.7 mmoles) in DMF (10 ml) and the reaction was allowed to proceed for 36 hours at 25° with stirring. Removal of the solvent *in vacuo* and elution of the product from a silica gel column using dichloromethane:methanol (95:5, v/v) as eluent afforded **9a** (1.95 g, 73%), mp 205-208° dec; ^1H nmr (DMSO-d_6): δ 0.1 (s, 6H, $SiMe_2$), 0.88 (s, 9H, Me_3C), 2.1 (m, 2H, H-2'), 3.78 (m, 2H, H-5'), 3.88 (m, 1H, H-4'), 4.18 (m, 1H, H-3'), 5.30 (d, $J_{CH,OH}$ = 4.5 Hz, 1H, C-3' OH, exchanges with deuterium oxide), 6.10 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 8.0 (s, 1H, H-6), 10.74 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{15}H_{25}IN_2O_5Si$: C, 38.46; H, 5.38; N, 5.98. Found: C, 38.77; H, 5.45; N, 6.16.

5-Vinyl-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**9b**).

Imidazole (0.42 g, 6.2 mmoles) and TBDMSCl (0.45 g, 3.0 mmoles) was added to a solution of **8b** (0.71 g, 2.81 mmoles) in DMF (10 ml) and the reaction was allowed to proceed with stirring for 30 hours. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using dichloromethane:methanol (97:3, v/v) as eluent yielded **9b** (0.65 g, 63%), mp 170-172° sublimes; ^1H nmr (DMSO-d_6): δ 0.1 (s, 6H, $SiMe_2$), 0.8 (s, 9H, Me_3C), 2.10 (m, 2H, H-2'), 4.72 (m, 3H, H-4', H-5'), 4.13 (m, 1H, H-3'), 5.10 (d, J_{cis} = 11 Hz of d, J_{gem} = 2.1 Hz, 1H, CH=C*H*H'), 5.24 (d, $J_{CH,OH}$ = 6 Hz, C-3' OH, exchanges with deuterium oxide), 5.92 (d, J_{trans} = 18 Hz of d, J_{gem} = 2.1 Hz, 1H, CH = CH*H'*), 6.10 (d, J = 6 Hz, of d, J = 6 Hz, 1H, H-1'), 6.28 (d, J_{trans} = 18 Hz of d, J_{cis} = 11 Hz, 1H, C*H* = CHH'), 7.66 (s, 1H, H-6), 11.42 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{17}H_{28}N_2O_5Si$: C, 55.40; H, 7.65; N, 7.60. Found: C, 55.10; H, 7.49; N, 7.57.

(*E*)-5-(2-Iodovinyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**9c**).

Imidazole (0.225 g, 3.6 mmoles) and TBDMSCl (0.225 g, 1.5 mmoles) was added to a solution of **8c** (0.57 g, 1.5 mmoles) in DMF (10 ml) and the reaction was allowed to proceed for 24

hours with stirring. An additional aliquot of TBDMSCl (0.338 g, 2.25 mmoles) was added to the reaction mixture and the reaction was allowed to proceed with stirring for 48 hours. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform:methanol (9:1, v/v) as eluent gave **9c** (0.55 g, 73%), mp 175-180° dec; ^{1}H nmr (DMSO-d_6): δ 0.1 (s, 6H, Me_2Si), 0.87 (s, 9H, Me_3C), 2.16 (m, 2H, H-2'), 3.80 (m, 3H, H-4', H-5'), 4.20 (m, 1H, H-3'), 5.30 (d, $J_{CH,OH}$ = 6 Hz, 1H, C-3' OH, exchanges with deuterium oxide), 6.12 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.1 (d, J_{trans} = 16 Hz, 1H, C*H* = CHI), 7.23 (d, J_{trans} = 16 Hz, 1H, CH = C*H*I), 7.78 (s, 1H, H-6), 11.60 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{17}H_{27}IN_2O_5Si \cdot H_2O$: C, 39.84; H, 5.70; N, 5.46. Found: C, 39.78; H, 5.29; N, 5.50.

5-Iodo-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**10a**).

Nicotinoyl chloride hydrochloride (1.42 g, 8.0 mmoles) was added to a solution of **9a** (1.9 g, 4.06 mmoles) in pyridine (50 ml) with stirring and the reaction was allowed to proceed for 48 hours at 25°. An additional aliquot of nicotinoyl chloride hydrochloride (0.35 g, 2.0 mmoles) was added and the reaction was allowed to continue for 24 hours. Removal of the solvent *in vacuo* and purification of the product by silica gel column chromatography using ethyl acetate:toluene (1:1, v/v) as eluent yielded **10a** (1.0 g, 43%), mp 210-215° dec; ^{1}H nmr (DMSO-d_6): δ 0.1 (s, 6H, Me_2Si), 0.88 (s, 9H, Me_3C), 2.32 and 2.52 (two m, 1H each, H-2'), 3.90 (m, 2H, H-5'), 4.30 (m, 1H, H-4'), 5.44 (m, 1H, H-3'), 6.21 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.58 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 8.05 (s, 1H, H-6), 8.33 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{4,6}$ = 1.6 Hz of d, $J_{2,4}$ = 1.6 Hz, 1H, pyridyl H-4), 8.82 (d, $J_{5,6}$ = 5.0 Hz of d, $J_{4,6}$ = 1.6 Hz, 1H, pyridyl H-6), 9.12 (d, $J_{2,4}$ = 1.6 Hz, 1H, pyridyl H-2), 11.77 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{21}H_{28}IN_3O_6Si$: C, 43.98; H, 4.92; N, 7.32. Found: C, 44.01; H, 4.93; N, 7.45.

5-Vinyl-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**10b**).

Nicotinoyl chloride hydrochloride (0.625 g, 3.5 mmoles) was added to an ice-chilled solution of **9b** (0.61 g, 1.65 mmoles) in pyridine (15 ml) with stirring which was continued for 30 minutes. The reaction mixture was allowed to warm to 25°, and the reaction mixture was stirred at 25° for 4 days. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using dichloromethane:methanol (98:2, v/v) as eluent afforded **10b** (0.25 g, 32%), mp 188-190° sublimes; ^{1}H nmr (deuteriochloroform): δ 0.18 (s, 6H, Me_2Si), 0.96 (s, 9H, Me_3C), 2.30 and 2.70 (two m, 1H each, H-2'), 4.05 (m, 2H, H-5'), 4.32 (m, 1H, H-4'), 5.30 (d, J_{cis} = 11 Hz, 1H, CH = C*H*H'), 5.58 (m, 1H, H-3'), 6.08 (d, J_{trans} = 18 Hz, 1H, CH = CH*H'*), 6.39 (d, J_{trans} = 18 Hz, of d, J_{cis} = 11 Hz, 1H, C*H* = CHH'), 6.47 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.48 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 7.80 (s, 1H, H-6), 8.34 (d, $J_{4,5}$ = 8.2 Hz, 1H, pyridyl H-4), 8.86 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.30 (s, 1H, pyridyl H-2), 9.45 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{23}H_{31}N_3O_6Si$: C, 58.32; H, 6.59; N, 8.87. Found: C, 57.93; H, 6.42; N, 8.84.

(*E*)-5-(2-Iodovinyl)-3'-*O*-(3-pyridylcarbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine (**10c**).

Nicotinoyl chloride hydrochloride (0.4 g, 2.24 mmoles) was added to a solution of **9c** (0.75 g, 1.5 mmoles) in pyridine (10 ml) and the mixture was stirred for 24 hours at 25°. An additional aliquot of nicotinoyl chloride hydrochloride (0.1 g, 0.56 mmole) was added and the reaction mixture was stirred for 5 hours at 25°. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform:methanol (99:1, v/v) as eluent yielded **10c** (0.78 g, 87%), mp 175° sublimes; ^{1}H nmr (DMSO-d_6): δ 0.11 (s, 6H, Me_2Si), 0.88 (s, 9H, Me_3C), 2.55 (m, 2H, H-2'), 3.92 (m, 2H, H-5'), 4.32 (m, 1H, H-4'), 5.48 (m, 1H, H-3'), 6.26 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.13 (d, J_{trans} = 15 Hz, 1H, C*H* = CHI), 7.28 (d, J_{trans} = 15 Hz, 1H, CH = C*H*I), 7.62 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 7.88 (s, 1H, H-6), 8.37 (d, $J_{4,5}$ = 8.2 Hz, 1H, pyridyl H-4), 8.85 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.16 (s, 1H, pyridyl H-2).

Anal. Calcd. for $C_{23}H_{30}IN_3O_6Si \cdot 0.5H_2O$: C, 45.39; H, 5.13; N, 6.90. Found: C, 45.06; H, 4.84; N, 6.84.

5-Iodo-3'-*O*-(3-pyridylcarbonyl)-2'-deoxyuridine (**11a**).

A solution of *n*-$Bu_4N^+F^-$ (1.5 ml of 1*M*) in THF was added to a solution of **10a** (0.30 g, 0.53 mmole) in THF (15 ml) and the reaction mixture was stirred for 90 minutes at 25°. Removal of the solvent *in vacuo* and purification of the product by elution from a silica gel column using chloroform:methanol (94:6, v/v) as eluent gave **11a** (0.195 g, 81%) as a colorless solid after recrystallization from acetone, mp 212-215° dec; ^{1}H nmr (DMSO-d_6): δ 2.48 (m, 2H, H-2'), 3.74 (m, 2H, H-5'), 4.24 (m, 1H, H-4'), 5.4 (t, J = 4.5 Hz, 1H, C-5' OH, exchanges with deuterium oxide), 5.52 (m, 1H, H-3'), 6.28 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.62 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 8.35 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{4,6}$ = 1.6 Hz of d, $J_{2,4}$ = 1.6 Hz, 1H, pyridyl H-4), 8.46 (s, 1H, H-6), 8.86 (d, $J_{5,6}$ = 5.0 Hz of d, $J_{4,6}$ = 1.6 Hz, 1H, pyridyl H-6), 9.18 (d, $J_{2,4}$ = 1.6 Hz, 1H, pyridyl H-2), 11.78 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{15}H_{14}IN_3O_6$: C, 39.23; H, 3.07; N, 9.15. Found: C, 39.28; H, 3.09; N, 9.31.

(*E*)-5-(2-Iodovinyl)-3'-*O*-(3-pyridylcarbonyl)-2'-deoxyuridine (**11c**).

A solution of *n*-$Bu_4N^+F^-$ (0.7 ml of 1*M*) in THF was added to a solution of **10c** (0.3 g, 0.5 mmole) in THF (10 ml) and the reaction was allowed to proceed with stirring for 3 hours at 25°. Removal of the solvent *in vacuo* and elution of the product from a silica gel column using chloroform:methanol (95:5, v/v) as eluent afforded **11c** (0.22 g, 90%), mp 205-210° dec; ^{1}H nmr (DMSO-d_6): δ 2.50 (m, 2H, H-2'), 3.74 (m, 2H, H-5'), 4.25 (m, 1H, H-4'), 5.32 (t, = 4.4 Hz, 1H, C-5' OH, exchanges with deuterium oxide), 5.52 (m, 1H, H-3'), 6.28 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1'), 7.14 (d, J_{trans} = 15 Hz, 1H, C*H* = CHI), 7.25 (d, J_{trans} = 15 Hz, 1H, CH = C*H*I), 7.60 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5). 8.12 (s, 1H, H-6), 8.36 (d, $J_{4,5}$ = 8.2 Hz, 1H, pyridyl H-4), 8.83 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.15 (s, 1H, pyridyl H-2), 11.65 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{17}H_{15}IN_3O_6 \cdot H_2O$: C, 40.65; H, 3.40; N, 8.36. Found: C, 40.38; H, 3.22; N, 8.11.

5-Substituted-3'-*O*-(1-methylpyridinium-3-carbonyl)-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyuridine Iodides **12a-c** and 5-Substituted-3'-*O*-(1-methylpyridinium-3-carbonyl)-2'-deoxyuridine Iodides **13a, 13c**. General Procedure A.

Iodomethane (100 mmoles) was added to a solution of the nicotinoate ester, **10a, 10b, 10c, 11a** or **11c** (5 mmoles) in acetone (50 ml) and the resulting solution was heated at reflux for 18 hours. After cooling to 25°, the yellow solid was filtered and washed

with acetone to afford **12a, 12b, 12c, 13a** or **13c**, respectively.

The physical and some spectral data for compounds **12-13** are presented below.

5-Iodo-3′-*O*-(1-methylpyridinium-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine Iodide (**12a**).

This compound was obtained in a yield of 83%, mp 203-208° dec.

Anal. Calcd. for $C_{22}H_{31}I_2N_3O_6Si \cdot H_2O$: C, 36.02; H, 4.53; N, 5.72. Found: C, 35.73; H, 4.58; N, 5.99.

5-Vinyl-3′-*O*-(1-methylpyridinium-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine Iodide (**12b**).

This compound was obtained in a yield of 74%, mp 205-208° dec.

Anal. Calcd. for $C_{24}H_{34}IN_3O_6Si \cdot H_2O$: C, 45.49; H, 5.72; N, 6.63. Found: C, 45.59; H, 5.61; N, 6.33.

(*E*)-5-(2-Iodovinyl)-3′-*O*-(1-methylpyridinium-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine Iodide (**12c**).

This compound was obtained in a yield of 64%, mp 218-222° dec; ^{1}H nmr (DMSO-d_6): δ 0.1 (s, 6H, Me_2Si), 0.89 (s, 9H, Me_3C), 2.56 (m, 2H, H-2′), 3.94 (m, 2H, H-5′), 4.38 (m, 1H, H-4′), 4.44 (s, 3H, N-Me), 5.52 (m, 1H, H-3′), 6.30 (J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 7.12 (d, J_{trans} = 15 Hz, 1H, C*H*=CHI), 7.27 (d, J_{trans} = 15 Hz, 1H, CH=C*H*I), 7.89 (s, 1H, H-6), 8.28 (d, $J_{4,5}$ = 8.2 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 9.05 (d, $J_{4,5}$ = 8.2 Hz, 1H, pyridyl H-4), 9.20 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.65 (s, 1H, pyridyl H-2), 11.68 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{24}H_{33}I_2N_3O_6Si$: C, 38.87; H, 4.48; N, 5.66. Found: C, 38.77; H, 4.70; N, 5.38.

5-Iodo-3′-*O*-(1-methylpyridinium-3-carbonyl)-2′-deoxyuridine Iodide (**13a**).

This compound was obtained in a yield of 96%, mp 215-220° dec; ^{1}H nmr (DMSO-d_6): δ 2.48 (m, 2H, H-2′), 3.70 (m, 2H, H-5′), 4.28 (m, 1H, H-4′), 4.41 (s, 3H, N-Me), 5.40 (s, 1H, C-5′ OH, exchanges with deuterium oxide), 5.54 (m, 1H, H-3′), 6.29 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 8.22 (d, $J_{4,5}$ = 8.0 Hz of d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-5), 8.41 (s, 1H, H-6), 8.98 (d, $J_{4,5}$ = 8.0 Hz, 1H, H-4), 9.14 (d, $J_{5,6}$ = 5.0 Hz, 1H, pyridyl H-6), 9.60 (s, 1H, pyridyl H-2).

Anal. Calcd. for $C_{16}H_{17}I_2N_3O_6$: C, 31.96; H, 2.85; N, 6.99. Found: C, 32.03; H, 2.87; N, 6.91.

(*E*)-5-(2-Iodovinyl)-3′-*O*-(1-methylpyridinium-3-carbonyl)-2′-deoxyuridine Iodide (**13c**).

This compound was obtained in a yield of 71%, mp 164-165° dec.

Anal. Calcd. for $C_{18}H_{19}I_2N_3O_6 \cdot 1.75H_2O$: C, 32.82; H, 3.43; N, 6.37. Found: C, 32.89; H, 3.80; N, 6.03.

5-Substituted-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridines **14a-c** and 5-Substituted-3′-*O*-(1-methyl-1,4-dihydropyridylcarbonyl)-2′-deoxyuridines **15a, 15c**. General Procedure B.

Sodium dithionite (5 mmoles) and sodium bicarbonate (5 mmoles) were added to a solution of the 1-methylpyridinium salt **12a, 12b, 12c, 13a** or **13c** in degassed water (20 ml) and ethyl acetate (20 ml) under a nitrogen atmosphere with stirring. The reaction was allowed to proceed with stirring at 25° until tlc indicated that the reaction was complete (2-5 hours). The two fractions were separated and the ethyl acetate fraction was washed with water prior to drying (sodium sulfate). Removal of the solvent *in vacuo* and elution of the product from a neutral aluminum oxide column using chloroform:methanol (90:10, v/v) as eluent afforded the respective 1-methyl-1,4-dihydropyridyl-3-carbonyl products **14a, 14b, 14c, 15a** and **15c** as yellow solids.

The physical and spectral data for compounds **14-15** are presented below.

5-Iodo-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine (**14a**).

This compound was obtained in a yield of 57%, mp 145-150° dec; ^{1}H nmr (DMSO-d_6): δ 0.12 (s, 6H, Me_2Si), 0.89 (s, 9H, Me_3C), 2.18 and 2.26 (two m, 1H each, H-2′), 2.96 (m, 5H, N-Me, dihydropyridyl H-4), 3.85 (m, 2H, H-5′), 4.06 (m, 1H, H-4′), 4.75 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ 3.7 Hz, 1H, dihydropyridyl H-5), 5.15 (m, 1H, H-3′), 5.86 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 6.12 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 7.14 (s, 1H, dihydropyridyl H-2), 8.02 (s, 1H, H-6).

Anal. Calcd. for $C_{22}H_{32}IN_3O_6Si \cdot 0.75H_2O$: C, 43.81; H, 5.59; N, 6.96. Found: C, 43.50; H, 5.38; N, 6.75.

5-Vinyl-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine (**14b**).

This compound was obtained in a yield of 80%, mp 135-140° dec; ^{1}H nmr (perdeuteriomethanol): δ 0.12 (s, 6H, Me_2Si), 0.92 (s, 9H, Me_3C), 2.26 and 2.46 (two m, 1H each, H-2′), 2.98 (s, 3H, N-Me), 3.04 (m, 2H, dihydropyridyl H-4), 3.98 (m, 2H, H-5′), 4.14 (m, 1H, H-4′), 4.83 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 3.7 Hz, 1H, dihydropyridyl H-5), 5.2 (d, J_{cis} = 11 Hz of d, J_{gem} = 2.0 Hz, 1H, CH=C*H*H′), 5.28 (m, 1H, H-3′), 5.78 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 5.98 (d, J_{trans} = 18 Hz of d, J_{gem} = 2.0 Hz, 1H, CH=CH*H*′), 6.24 (d, J = 6 Hz of d, J = 5.8 Hz, 1H, H-1′), 6.41 (d, J_{trans} = 18 Hz of d, J_{cis} = 11 Hz, 1H, C*H*=CHH′), 7.12 (s, 1H, dihydropyridyl H-2), 8.85 (s, 1H, H-6).

Anal. Calcd. for $C_{24}H_{35}N_3O_6Si \cdot 0.75H_2O$: C, 57.29; H, 7.31; N, 8.35. Found: C, 57.12; H, 7.15; N, 8.17.

(*E*)-5-(2-Iodovinyl)-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-5′-*O*-*t*-butyldimethylsilyl-2′-deoxyuridine (**14c**).

This compound was obtained in a yield of 87%, mp 110-115° dec; ^{1}H nmr (perdeuteriomethanol): δ 0.15 (s, 6H, Me_2Si), 0.95 (s, 9H, Me_3C), 2.23 and 2.50 (two m, 1H each, H-2′), 2.98 (s, 3H, N-Me), 3.05 (m, 2H, dihydropyridyl H-4), 3.98 (m, 2H, H-5′), 4.15 (m, 1H, H-4′), 4.82 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 3.7 Hz, 1H, dihydropyridyl H-5), 5.27 (m, 1H, H-3′), 5.78 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 6.24 (d, J = 6.0 Hz of d, J = 5.8 Hz, 1H, H-1′), 7.10 (d, J_{trans} = 15 Hz, 1H, C*H*=CHI), 7.15 (s, 1H, dihydropyridyl H-2), 7.32 (d, J_{trans} = 15 Hz, 1H, CH=C*H*I), 7.88 (s, 1H, H-6).

Anal. Calcd. for $C_{24}H_{34}IN_3O_6Si \cdot 1.5H_2O$: C, 44.86; H, 5.80; N, 6.53. Found: C, 44.83; H, 5.55; N, 6.71.

5-Iodo-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15a**).

This compound was obtained in a yield of 14%, mp 115-120°; ^{1}H nmr (DMSO-d_6): δ 2.27 (m, 2H, H-2′), 2.96 (m, 5H, N-Me, dihydropyridyl H-4), 3.65 (m, 2H, H-5′), 4.02 (m, 1H, H-4′), 4.75 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 3.5 Hz, 1H, dihydropyridyl H-5), 5.20 (m, 1H, H-3′), 5.31 (t, J = 6 Hz, 1H, C-5′ OH, exchanges with deuterium oxide), 5.88 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 6.18 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 7.16 (s, 1H, dihydro-

pyridyl H-2), 8.42 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{18}IN_3O_6 \cdot H_2O$: C, 38.96; H, 4.08. Found: C, 39.38; H, 4.51.

(*E*)-5-(2-Iodovinyl)-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15c**).

This compound was obtained in a yield of 44%, mp 165-168° dec; ^{1}H nmr (DMSO-d_6): δ 2.29 (m, 2H, H-2′), 2.98 (m, 5H, N-Me, dihydropyridyl H-4), 3.65 (m, 2H, H-5′), 4.02 (m, 1H, H-4′), 4.73 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 3.5 Hz, 1H, dihydropyridyl H-5), 5.20 (m, 1H, C-5′ OH, exchanges with deuterium oxide), 5.26 (m, 1H, H-3′), 5.86 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 6.18 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 7.12 (d, J_{trans} = 15 Hz, 1H, C*H*=CHI), 7.15 (s, 1H, dihydropyridyl H-2), 7.24 (d, J_{trans} = 15 Hz, 1H, CH=C*H*I), 8.09 (s, 1H, H-6), 11.60 (s, 1H, NH, exchanges with deuterium oxide).

Anal. Calcd. for $C_{18}H_{20}IN_3O_6 \cdot 0.75H_2O$: C, 41.99; H, 4.20; N, 8.16. Found: C, 41.91; H, 3.80; N, 8.13.

Synthesis of 5-iodo-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15a**) by Deprotection of **14a**.

A solution of *n*-$Bu_4N^+F^-$ (0.4 ml of 1*M*) in THF was added to a solution of **14a** (80 mg, 1.35 mmoles) in THF (8 ml) and the reaction was allowed to proceed with stirring for 1 hour at 25°. Removal of the solvent *in vacuo* and elution of the product from a neutral aluminum oxide column using chloroform:methanol (85:15, v/v) as eluent afforded **15a** as pale yellow crystals after recrystallization from methanol (26 mg, 47%). The mp and ^{1}H nmr spectrum for **15a** were identical to that of **15a** prepared using General Procedure B.

5-Vinyl-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15b**).

A solution of *n*-$Bu_4N^+F^-$ (0.1 ml of 1*M*) in THF was added to a solution of **14b** (15 mg, 0.03 mmole) and the reaction was allowed to proceed for 1 hour with stirring. Removal of the solvent and purification of the product by elution from a neutral aluminum oxide column using chloroform:methanol (80:20, v/v) as eluent yielded **15b** (9 mg, 80%) as yellow crystals after recrystallization from methanol, mp 100-105° sublimes; ^{1}H (perdeuteriomethanol): δ 2.38 (m, 2H, H-2′), 2.99 (s, 3H, N-Me), 3.06 (m, 2H, dihydropyridyl H-4), 3.84 (m, 2H, H-5′), 4.11 (m, 1H, H-4′), 4.82 (dt, $J_{5,6}$ = 8.0 Hz, $J_{4,5}$ = 3.5 Hz, 1H, dihydropyridyl H-5), 5.18 (d, J_{cis} = 11 Hz of d, J_{gem} = 2.0 Hz, 1H, CH=C*H*H′), 5.33 (m, 1H, H-3′), 5.78 (d, $J_{5,6}$ = 8.0 Hz, 1H, dihydropyridyl H-6), 5.96 (d, J_{trans} = 18 Hz of d, J_{gem} = 2.0 Hz, 1H, CH=CH*H*′), 6.32 (d, J = 6 Hz of d, J = 6 Hz, 1H, H-1′), 6.45 (d, J_{trans} = 18 Hz of d, J_{cis} = 11 Hz, 1H, C*H*=CHH′), 7.14 (s, 1H, dihydropyridyl H-2), 8.26 (s, 1H, H-6); ^{13}C nmr (perdeuteriomethanol): δ 22.58 (dihydropyridyl C-4), 39.11 (C-2′), 40.97 (N-Me), 62.96 (C-5′), 75.48 (C-3′), 86.73 (C-1′ or C-4′), 87.25 (C-4′ or C-1′), 96.18 (dihydropyridyl C-3), 105.95 (dihydropyridyl C-5), 113.95 (C-5), 115.35 (CH=*C*H_2), 129.24 (*C*H=CH$_2$), 130.38 (dihydropyridyl C-6), 138.74 (C-6), 145.15 (dihydropyridyl C-2), 151.80 (C-2), 164.38 (C-4), 169.10 (*C*O_2).

Anal. Calcd. for $C_{18}H_{21}N_3O_6 \cdot 1.75H_2O$: C, 53.13; H, 6.06; N, 10.32. Found: C, 53.27; H, 5.91; N, 10.68.

Synthesis of (*E*)-5-(2-Iodovinyl)-3′-*O*-(1-methyl-1,4-dihydropyridyl-3-carbonyl)-2′-deoxyuridine (**15c**) by Deprotection of **14c**.

A solution of *n*-$Bu_4N^+F^-$ (60 μl of 1*M*) in THF was added to a solution of **14c** (10 mg, 0.016 mmole) in THF (2 ml) and the reaction was allowed to proceed for 1 hour at 25°. Removal of the solvent *in vacuo* and purification of the product using neutral aluminum oxide column chromatography with chloroform:-methanol (90:10, v/v) as eluent afforded **15c** (3 mg, 37%) as yellow crystals after recrystallization from methanol. The mp and ^{1}H nmr spectrum for **15c** were identical to that of **15c** prepared using General Procedure B.

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