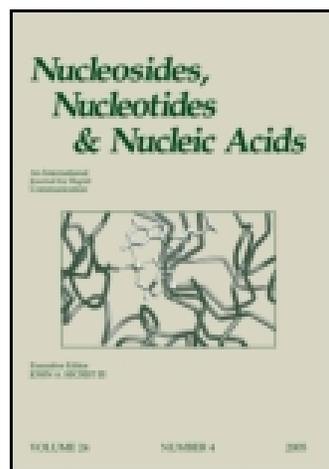


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SYNTHESIS OF 5-(PYRIDINYL AND PYRIDINIUMYL)-2'-DEOXYURIDINE NUCLEOSIDES: REVERSIBLE ELECTRON TRAPS FOR DNA

Samir T. Gaballah^a & Thomas L. Netzel^a

^a Department of Chemistry, Georgia State University, Atlanta, GA, 30303, U.S.A.

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**SYNTHESIS OF 5-(PYRIDINYL
AND PYRIDINIUMYL)-2'-DEOXYURIDINE
NUCLEOSIDES: REVERSIBLE ELECTRON
TRAPS FOR DNA**

Samir T. Gaballah and Thomas L. Netzel*

Department of Chemistry, Georgia State University,
Atlanta, GA 30303

ABSTRACT

The desire to produce reversible electron traps for direct, room temperature studies of excess electron transport in DNA duplexes and hairpins motivated our efforts first to link pyridines to 2'-deoxyuridine (pyridinyl-dU) and then to convert these new conjugates into pyridiniumyl-dU nucleosides. Base sensitivity studies presented here rule out general use of bipyridinediiumyl compounds, but show that pyridiniumyl compounds are suitable for use under the strand cleavage and base deprotection procedures required for automated solid-phase oligonucleotide synthesis. This paper presents the synthesis of four 5'-O-DMT-protected 5-(*N*-methylpyridiniumyl)-dU conjugates using either ethynyl or ethylenyl linkers to join the pyridiniumyl and dU subunits.

*Corresponding author. Fax: (404) 651-3129; E-mail: tnetzel@gsu.edu

INTRODUCTION

Interest in the mechanisms and possible lessening of radiation damage to deoxyribonucleic acid (DNA) in biological systems has prompted a number of studies of charge transport in model DNA systems.^[1] The vast majority of these studies focused on the mechanisms of hole transport.^[2–35] A few recent ones using naturally occurring DNA with added intercalating electron acceptors have studied excess electron transport at low temperatures.^[36–38] Importantly a recent study of photoinduced excess electron transfer in DNA at room temperature implies that excess electrons can hop over distances as large as 24 Å to reductively repair thymine dimers.^[39] The timescale for this biologically desirable electron transport is, however, unknown as the dynamics of this process have not yet been directly observed. Even for the case of hole transport in DNA duplexes at room temperature there are only a small number of direct observations of elementary electron transfer reactions and no direct observations of the dynamics of hole transport.^[7,8,10,11,29–31,40,41]

We desired to advance real-time studies of excess electron transport in DNA by creating additional electron trapping nucleosides that can be incorporated into DNA duplexes and that offer a range of trap depths (ease of reduction). To this end we sought to link pyridines to 2'-deoxyuridine (pyridinyl-dU) and then to convert these new conjugates into pyridiniumyl-dU nucleosides. By analogy to 4,4'-bipyridinedium (methyl viologen),^[42,43] we reasoned that pyridiniumyl-dU nucleoside conjugates could function as reversible electron acceptors when incorporated into DNA duplexes. Importantly, pyridinyl radicals are known to have intense absorbances in the near-UV and moderately strong absorbances in the visible spectral regions.^[44,45] Thus pyridiniumyl-dU nucleosides should serve as good indicators of excess electron trapping in kinetics studies of electron transport in DNA. Our prior work on the synthesis 5-(2,2'-bipyridinediumyl)-dU conjugates alerted us to the necessity of testing the stability of quaternized aromatic heterocycles toward bases commonly used in the base deprotection and strand cleavage reactions that follow automated DNA synthesis.^[46] As will be discussed below, bipyridinediumyl-dU nucleosides are base sensitive, but pyridiniumyl-dU nucleosides are not.

To date our work in the area of nucleoside conjugate chemistry has produced a number of pyrenyl-dU (Py-dU) conjugates that are capable of photoinjecting an excess electron into a DNA π -stack.^[47–51] In these conjugates the lowest electronic, excited singlet-state of pyrene reduces the attached uracil in less than 30 ps, and in methanol the resulting primary electron transfer (ET) product, $\text{Py}^{\bullet+}/\text{dU}^{\bullet-}$, lives from 6 ps to 2.1 ns depending upon the type of linker that joins the pyrenyl and uracil subunits. To further increase the lifetime of a photogenerated uracil anion in a DNA duplex, we have also synthesized several dimethylanilino-dU conjugates

(DMA-dU) to serve as secondary electron donors.^[52] In duplexes labeled with both Py-dU and DMA-dU, secondary ET from DMA to $\text{Py}^{\bullet+}/\text{dU}^{\bullet-}$ should produce the $\text{DMA}^{\bullet+}/\text{Py}/\text{dU}^{\bullet-}$ ET product that is expected to live significantly longer than $\text{Py}^{\bullet+}/\text{dU}^{\bullet-}$. Thus the time is right to develop electron-trapping nucleoside conjugates. In addition to the syntheses of four pyridinyl-dU nucleosides, this paper also reports the synthesis of four pyridinium-dU nucleoside traps.

Our approach to constructing electron-trapping nucleoside conjugates focused initially on nitrogen-containing aromatic heterocycles as a class of compounds in which imine nitrogen atoms could be quaternized to give π -electron-deficient heterocycles. *N,N'*-Dimethyl-4,4'-bipyridinediium (MV^{2+}), *N,N'*-polymethylene-2,2'-bipyridinediium (**2,2'-BpyEt**²⁺ and **2,2'-BpyPr**²⁺), and *N*-methylpyridinium (MP^+) salts were thus candidates for attachment to dU (see Fig. 1 for structures). The base sensitivity studies presented below ruled out general use of bipyridinediium compounds, but showed that pyridinium compounds were not base sensitive. Importantly MP^+ showed remarkable stability towards a variety of basic conditions used during phosphoramidite creation and strand cleavage following automated oligonucleotide synthesis. Additionally, MP^+ could be attached to dU at a number of pyridinyl positions, and could also be substituted prior to attachment to vary its reduction potential.^[44,53–55]

A straightforward way of positioning an electron trap in the DNA major groove is to attach covalently an easily reducible subunit to the 5-position of uridine. Based on reduction potential considerations alone, either uridine or cytidine could be used as the reducible nucleoside in an electron trapping conjugate: these two nucleosides are the easiest of naturally occurring nucleosides to reduce, and they have the same reduction potential.^[56–58] However, uridine is simpler to modify, and the anion radical of uridine is not protonated in DNA while that of cytidine is.^[59–64] Thus other factors remaining the same, excess electron hopping from a reduced uridine should proceed more rapidly than from a reduced cytidine. In addition to locating the electron trap in the major groove, it is also important to provide strong electronic coupling between the trapping subunit and the initially reduced uracil base in the nucleoside conjugate. Thus both ethynyl and ethylenyl linkers are of interest in this context. This paper reports the

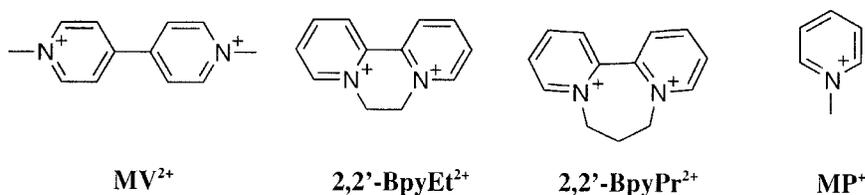
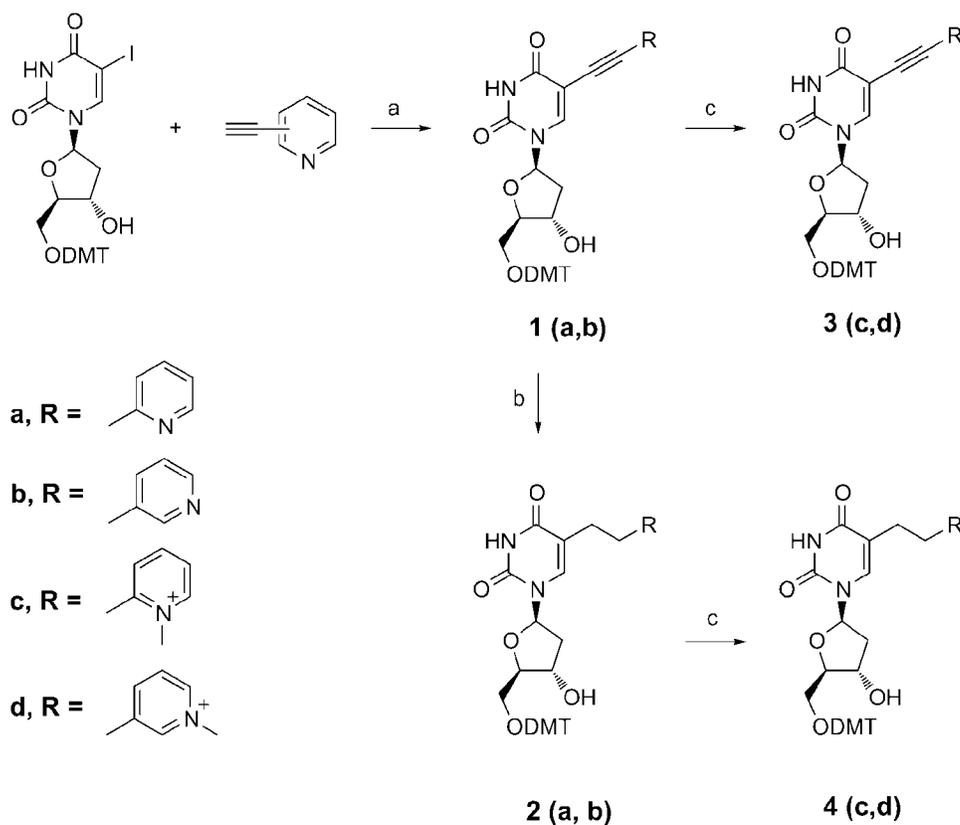


Figure 1. Structural drawings of four electron-trap candidates.

synthesis of four pyridiniumyl-dU nucleoside conjugates: 2- and 3-pyridiniumyl subunits attached with both ethynyl and ethylenyl linkers to C5-uracil (see Sch. 1). The ethylenyl linked pyridiniumyl-dU conjugates are formed via selective hydrogenation of the corresponding ethynyl-linked conjugates. To our knowledge no pyridiniumyl-dU conjugates have been made previously and among the precursor pyridinyl-dU conjugates only 3',5'-*O*-di-trimethylsilyl-5-(2-ethynylpyridinyl)-2'-deoxyuridine has been synthesized previously.^[65] Also in that prior work, the starting 2-ethynylpyridine was first lithiated and then transformed into 2-ethynylpyridylzinc before PdL₂ (or nickel) catalyzed coupling to 3',5'-*O*-di-trimethylsilyl-dU. This work presents a shorter synthetic route with a higher yield to either protected or unprotected 5-(2- and 3-ethynylpyridinyl)-dU compounds. A related pyridiniumyl-dG covalent adduct has been reported in work on an α,ω -diether linked di(1-methyl-2-pyridiniumaldehyde) bifunctional compound that inhibits growth of cultured tumor cells.^[66] At room temperature the di(pyridiniumaldehyde) reagent associates with the outside of a self-complementary



Scheme 1. (a) PdL₄, CuI, Et₃N, THF; (b) H₂ (50 psi), Pd/C, MeOH; (c) MeI, MeCN, 50°C.

DNA decamer mainly at the central 5'-CpG-3' site. At 38°C the exocyclic amino group of this central dG forms a covalent bond with one of the di(pyridiniumaldehyde)'s carbonyl groups. The resulting reversible, covalent adduct has not been isolated.

In this paper, we present the synthesis of four 5'-*O*-DMT-protected 5-(*N*-methylpyridinium)-dU conjugates as precursors to phosphoramidites that can be incorporated into DNA strands via automated synthesis. To create these conjugates, we connected 2- and 3-ethynylpyridines to the 5-position of 5'-*O*-DMT-dU using Pd(0) cross-coupling chemistry.^[67] This was followed when desired by heterogeneous catalytic reduction of the alkyne linkers.^[68] Lastly, we selectively quaternized the pyridinyl nitrogen atoms of both the ethynyl- and the ethylenyl-linked, DMT-protected dU conjugates.

RESULTS AND DISCUSSION

To produce nucleoside conjugates that can function as traps for excess electrons in DNA duplexes, we decided to join electron deficient moieties to dU as discussed above. After this was accomplished, the DMT-protected nucleoside traps would be ready to be phosphorylated and incorporated into DNA strands. During the course of DNA strand synthesis, bases would be used in capping, deprotection, and strand cleavage reactions.^[69,70] Since the electron-deficient centers in the nucleoside traps could possibly be attacked by nucleophiles during these reactions, we tested the chemical stability of several potential electron trapping moieties against bases used in DNA synthesis. Based on the base-stability results presented below, we selected the trapping moieties to be used as labels in nucleoside conjugate traps.

Model Salt Stability in 0.05 M K₂CO₃/Methanol (MeOH). Solutions of MV², 2,2'-BpyEt²⁺, and 2,2'-BpyPr²⁺ in 0.05 M K₂CO₃/MeOH⁷¹ (by vol.) turned bright yellow immediately after addition of the test salt and progressively darkened until they became light red after two h of stirring at room temperature. (Solutions of these compounds in MeOH, however, remained pale yellow.) After this time TLC showed a mobile organic spot (R_f about 0.65) in 2% MeOH (by vol.) in dichloromethane. After continued stirring overnight, the solution became dark red and no organic spot was seen on the TLC plate. In contrast for MP⁺ under the same conditions, color, TLC, and ¹H NMR showed no changes compared to solution of the salt in MeOH.

Model Salt Stability in 10% Diethyl Amine/MeOH. Solutions of the salts of MV², 2,2'-BpyEt²⁺, and 2,2'-BpyPr²⁺ in 10% diethyl amine in MeOH (by vol.) showed a rapid color change from yellow to red over a 1 m time period. After 2 h TLC showed a mobile organic spot (R_f about 0.5) in

2% MeOH (by vol.) in dichloromethane. The same results were observed for solutions of the salts in 60% diethyl amine in MeOH except that the organic spots in TLC were smaller. As above MP^+ under the same conditions showed no changes in color, TLC behavior, or ^1H NMR signal compared to a solution of the salt in MeOH.

Model Salt Stability in 10% 2,6-Lutidine/Dimethylsulfoxide (DMSO).

Solutions of the salts of MV^{2+} , $2,2'\text{-BpyEt}^{2+}$, and $2,2'\text{-BpyPr}^{2+}$ in 10% 2,6-Lutidine (by vol.) in DMSO showed an immediate change in color from yellow to yellowish-green and turned dark green after 2 h. TLC analysis in water and MeOH (1:1 by vol.) showed that ca. half of the initial amount of BpyPr^{2+} was still present after stirring for 2 h along with two mobile organic spots. For solutions of MV^{2+} and $2,2'\text{-BpyEt}^{2+}$, however, TLC analysis showed complete loss of the initial material after stirring for 2 h. After continuous stirring overnight, all three solutions became dark red, and TLC analysis showed complete loss of the initial dications. However, as in the previous tests, MP^+ under the same conditions showed no change in color, TLC behavior, or ^1H NMR signal compared to a solution of the salt in MeOH.

Clearly the three bipyridinediiumyl compounds MV^{2+} , $2,2'\text{-BpyEt}^{2+}$, and $2,2'\text{-BpyPr}^{2+}$ are not stable in the presence of the above bases, and thus will not survive DNA base deprotection and strand cleavage reactions. In contrast the MP^+ cation survived the above tests of base stability and thus, with respect to basic reagents, is compatible with automated solid-phase oligonucleotide synthesis. Based on these results, we decided invest our time to synthesize four *N*-methylpyridiniumyl-dU conjugates.

Syntheses of N-Methylpyridiniumyl-dU Conjugates. Syntheses of *N*-methylpyridiniumyl-dU conjugates were achieved as described in Sch. 1. Initially (not shown) 5'-*O*-(4,4'-dimethoxytrityl)-5-iodo-2'-deoxyuridine was synthesized according to a published procedure,^[72] then it was cross-coupled to 2-ethynyl pyridine using Sonogashira⁶⁷ PdL_4 catalytic chemistry to afford **1a** in 70% yield.^[73-75] The same Pd(0) cross-coupling approach, produced **1b** in low yield (<28%). Because an active Pd-catalyst can be generated in situ from PdL_2Cl_2 and CuI and this procedure may facilitate alkynylation of a palladium(II) intermediate,^[76] we ran the reaction to produce **1b** with PdL_2Cl_2 and CuI instead of PdL_4 and thereby increased its yield to 69%. Heterogeneous catalytic hydrogenation^[68] of **1a** and **1b** in dry MeOH using H_2 (50 psi) over 10% Pd/C was performed by stirring at room temperature in a sealed glass vessel. The glass vessel was sealed with either stainless steel or brass fittings and topped with a pressure gauge. Before adding the reactants (**1a** and **1b**), the Pd/C-catalyst in MeOH was activated by pressurizing the hydrogenation vessel with hydrogen (50 psi) and stirring the slurry for

15–20 m. After complete consumption of the reactants, the hydrogenation reaction afforded **2a** and **2b** in yields, respectively, of 71 and 93%.

Compounds **1** and **2** quaternized readily in dry acetonitrile containing freshly distilled iodomethane to give, respectively, compounds **3** and **4** in yields of ranging from 54 to 72%.

EXPERIMENTAL

General Procedures

5-Iodo-2'-deoxyuridine (IdU), 2- and 3-ethynylpyridines, iodomethane, and 4,4'-dimethoxytrityl chloride (DMTCl) were obtained from Aldrich Chemicals and were used after drying. Dichlorodi(triphenylphosphine) palladium(II) (PdL_2Cl_2) and copper(I) iodide (CuI) were obtained from Strem Chemicals and used without further purification. Tetrakis-(triphenylphosphine)palladium(0) (PdL_4) was prepared according to the literature and stored in a glove-box freezer (-33°C).^[77] The following solvents were dried and redistilled in continuous circulation distillation apparatus: tetrahydrofuran (THF, dried with benzophenone/ Na^0), triethylamine (Et_3N , dried with CaH_2), *N,N*-dimethylformamide (DMF, dried with CaH_2), and MeOH (dried with Mg turnings). PdL_4 and DMTCl were handled in a Vacuum AtmospheresTM M040-2 glove box that was pressurized with dry nitrogen gas. All other reactions were carried out on the benchtop under a dry nitrogen atmosphere. Chromatography was carried out on a Biotage Flash-40TM system using either prepackaged KP-SilTM cartridges, or Flash-40TM cartridge housings repacked with WhatmanTM flash silica (80 Å pore, 230–400 mesh). WhatmanTM flash silica was also used for pad filtrations and dry powder sample loading for silica gel chromatography. Mass spectrometry was performed at the Georgia Institute of Technology. ^1H and ^{13}C NMR spectra were recorded at GSU on a Varian Unity+300 spectrometer operating, respectively, at 300- and 75-MHz frequencies.

Stability Studies of Model Electron Traps in Basic Solutions. To 10 mg each of MV^{2+} , **2,2'-BpyEt²⁺**, **2,2'-BpyPr²⁺**, and MP^+ (dried over a vacuum manifold), 10 mL of 0.05 M $\text{K}_2\text{CO}_3/\text{MeOH}$ (or 10% diethyl amine/MeOH or 10% 2,6-lutidine/DMSO, v/v) was added under a nitrogen atmosphere, and the solutions were allowed to stir overnight. Reaction progress was monitored with NaBr-treated TLC plates^[78] every 30 m for 3 h and after overnight stirring.

5'-O-(4,4'-Dimethoxytrityl)-5-(pyridin-2-yl-ethynyl)-2'-deoxyuridine, 1a.

To a solution of 5'-O-(4,4'-dimethoxytrityl)-5-iodo-2'-deoxyuridine (650 mg, 1.00 mmol), PdL_4 (57 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and Et_3N

(275 μ L, 2.00 mmol) in DMF (5 mL) was added 2-ethynylpyridine (352 mL, 3.00 mmol) in a glove box. The reaction mixture was stirred at 50–60°C for 30–50 min. After drying in vacuo, the solid was applied to a column packed with silica gel or purified by flash chromatography. In both cases the adsorbent was pretreated with 1% pyridine or Et₃N (by vol.) in dichloromethane. Purification using flash chromatography on silica gel with the following elutions, 50% hexane (by vol.) in dichloromethane, dichloromethane, and 1% MeOH (by vol.) in dichloromethane, gave 445 mg (70% yield) of **1a**. ¹H NMR (CDCl₃, 300 MHz) δ : 2.41–2.62 (2 H, m, H_{2' α} /H_{2' β}), 3.31–3.46 (2 H, m, H_{5' α} /H_{5' β}), 3.67 (6 H, s, DMT-(OCH₃)₂), 4.10 (1 H, m, H_{4'}), 4.16 (1H, br, OH_{3'}), 4.58 (1 H, m, H_{3'}), 6.33 (1 H, t, J = 6.3 Hz, H_{1'}), 6.76 (4 H, d, J = 7.7 Hz, Ar), 7.04–7.33 (9 H, m, Ar), 7.38–7.43 (3 H, m, pyridine), 8.23 (1 H, s, H₆), 8.47 (1 H, d, J = 4.0 Hz, pyridine), 9.80 (1 H, br, H_{N3}). ¹³C NMR (CDCl₃, 75 MHz) δ : 41.25, 55.13, 63.57, 71.10, 81.29, 85.88, 86.10, 86.67, 92.10, 99.03, 113.20, 122.76, 126.81, 127.53, 127.88, 129.92, 130.00, 135.57, 135.67, 136.09, 142.44, 144.04, 144.64, 149.27, 149.31, 158.45, 161.18. HRMS (FAB) m/z for C₃₇H₃₄N₃O₇ (M + H)⁺: calc'd. 632.2396, found 632.2407.

2-[5'-O-(4,4'-dimethoxytrityl)-2'-deoxyuridine-5-yl-ethynyl]-N-methylpyridinium iodide, 3c. In a Schlenk-like flask, **1a** (100 mg, 0.16 mmol) was co-evaporated 3 times with dry THF at 5×10^{-4} torr. The Schlenk-like flask was then brought inside a glove box, charged with 6 mL of dry acetonitrile and 300 μ L of freshly distilled iodomethane. The solution was degassed 3 times at 5×10^{-4} torr. The solution was stirred overnight at 50°C in vacuo. The acetonitrile solution was removed in vacuo, and the greenish-yellow solid was washed several times with hexane, dichloromethane, and acetone and purified by repeated precipitations with hexane to afford 65 mg of **3c** (56% yield). ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 2.23–2.42 (2 H, m, H_{2' α} /H_{2' β}), 3.14–3.26 (3 H, m, H_{5' α} /H_{5' β} /H_{4'}), 3.63 (3 H, s, DMT-OCH₃), 3.64 (3 H, s, DMT-OCH₃), 3.97 (3 H, s, CH₃), 4.33 (1 H, m, H_{3'}), 5.38 (1 H, d, J = 4.8 Hz, OH_{3'}), 6.10 (1 H, t, J = 6.0 Hz, H_{1'}), 6.86–6.82 (4 H, m, Ar), 7.44–7.10 (10 H, m, Ar), 7.98 (1 H, t, J = 6.3 Hz, pyridinium), 8.39 (1 H, t, J = 8.4 Hz, pyridinium), 8.48 (1 H, s, H₆), 8.95 (1 H, d, J = 6.3 Hz, pyridinium), 12.05 (1 H, br, H_{N3}). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ : 46.55, 55.05, 55.07, 69.51, 79.20, 83.73, 85.87, 86.05, 95.15, 100.38, 113.32, 126.20, 127.61, 128.00, 129.64, 129.72, 130.18, 135.44, 135.51, 136.73, 144.43, 144.76, 146.94, 147.09, 149.11, 158.07, 158.11, 161.01. HRMS (FAB) m/z for C₃₈H₃₆N₃O₇⁺(M⁺): calc'd. 646.2553, found 646.2527.

5'-O-(4,4'-Dimethoxytrityl)-5-(pyridin-2-yl-ethylenyl)-2'-deoxyuridine, 2a.

Dry **1a** (280 mg, 0.44 mmol) was dissolved in 60 mL of dry MeOH and added to 30 mL MeOH solution containing 150 mg of 10% Pd/C previously activated by stirring under H₂ (50 psi) for 20 m at room temperature. The reaction mixture

was further stirred under H₂ (50 psi) at room temperature until complete consumption of the starting materials (18 h). The solution was then filtered, reduced in volume to 0.5 mL, and purified on a silica gel column or by flash chromatography. In both cases the adsorbent was pretreated with 1% pyridine or Et₃N (by vol.) in dichloromethane. Eluting with hexane, 50% hexane (by vol.) in dichloromethane, and 1.5%–3.5% MeOH (by vol.) in dichloromethane afforded a yellow foam of **2a** (198 mg, 71% yield). ¹H NMR (CDCl₃, 300 MHz) δ: 2.13 (1 H, m, H_{2'β}), 2.23–2.34 (2 H, m, CH₂), 2.42 (1 H, m, H_{2'α}), 2.67–2.82 (2 H, m, CH₂), 3.20–3.36 (2 H, m, H_{5'α}/H_{5'β}) 3.60 (6 H, s, DMT-(OCH₃)₂), 3.96 (1 H, m, H_{4'}), 4.16 (1 H, br, OH_{3'}), 4.45 (1 H, m, H_{3'}), 6.30 (1 H, t, *J* = 6.5 Hz, H_{1'}), 6.66–6.71 (5 H, m, Ar), 6.91–7.38 (12 H, m, Ar), 8.34 (1 H, d, *J* = 4.2 Hz, pyridine), 10.12 (1 H, s, H_{N3}). ¹³C NMR (CDCl₃, 75 MHz) δ: 27.02, 36.51, 40.25, 55.17, 63.70, 72.01, 84.33, 85.43, 86.64, 113.19, 114.35, 121.17, 123.08, 126.99, 127.91, 128.10, 130.03, 135.51, 136.23, 136.41, 144.43, 148.82, 150.35, 158.57, 160.59, 163.20. HRMS (FAB) *m/z* for C₃₇H₃₈N₃O₇ (M + H)⁺: calc'd. 636.2709, found 636.2824.

2-[5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine-5-yl-ethylenyl]-N-methylpyridinium Iodide, 4c. In a Schlenk-like flask, **2a** (191 mg, 0.30 mmol) was co-evaporated 3 times with dry THF at 5 × 10⁻⁴ torr. The Schlenk-like flask was then brought inside a glove box, charged with 6 mL of dry acetonitrile containing 280 μL of freshly distilled iodomethane. The solution was freeze/pump (5 × 10⁻⁴ torr)/thaw degassed 3 times and stirred overnight at 50°C in vacuo. The acetonitrile solution was removed in vacuo, and the greenish-yellow solid was washed several times with hexane, dichloromethane, and acetone. Finally the solid was purified by repeated precipitations with hexane to afford 125 mg (54% yield). ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 2.15–2.42 (4 H, m, H_{2'α}/H_{2'β}/CH₂), 2.82–3.04 (2 H, m, CH₂), 3.12 (1 H, m, H_{5'β}), 3.25 (1 H, m, H_{5'α}), 3.67 (6 H, s, DMT-(OCH₃)₂), 3.86 (1 H, m, H_{4'}), 4.05 (3 H, s, CH₃), 4.32 (1 H, m, H_{3'}), 5.34 (1 H, d, *J* = 4.8 Hz, OH_{3'}), 6.20 (1 H, t, *J* = 6.6 Hz, H_{1'}), 6.85 (4 H, dd, *J* = 2.7, 9.1 Hz, Ar), 7.13–7.38 (9 H, m, Ar), 7.56 (1 H, d, *J* = 7.5 Hz, pyridinium), 7.67 (1 H, s, H₆), 7.91 (1 H, t, *J* = 6.4 Hz, pyridinium), 8.39 (1 H, t, *J* = 7.5 Hz, pyridinium), 8.89 (1 H, d, *J* = 7.2 Hz, pyridinium), 11.50 (1 H, s, H_{N3}). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 24.07, 31.57, 44.91, 55.06, 63.51, 70.21, 83.97, 85.42, 85.67, 111.14, 113.22, 125.41, 126.81, 127.58, 127.74, 127.90, 129.74, 135.35, 137.66, 144.60, 145.01, 146.56, 150.19, 156.88, 158.09, 163.31. HRMS (FAB) *m/z* for C₃₈H₄₀N₃O₇⁺ (M⁺): calc'd. 650.2866, found 650.2920.

5'-O-(4,4'-Dimethoxytrityl)-5-(pyridin-3-yl-ethynyl)-2'-deoxyuridine, 1b.

To a solution of 5-*O*-(4,4'-dimethoxytrityl)-5-iodo-2'-deoxyuridine (650 mg, 1.00 mmol), PdL₂Cl₂ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and Et₃N (300 μL, 2.00 mmol) in DMF (6 mL) was added 3-ethynylpyridine (356 μL, 3.00 mmol) in a glove box. The reaction mixture was stirred at 50–60°C for

30–50 m. After drying in vacuo, the solid was applied to a column packed with silica gel or purified by flash chromatography. In both cases the adsorbent was pretreated with 1% pyridine or Et₃N (by vol.) in dichloromethane. Purification by flash chromatography on silica gel using the following elutions, 50% (by vol.) hexane in dichloromethane, dichloromethane, and 1% MeOH (by vol.) in dichloromethane, gave **1b** (437 mg, 69% yield). ¹H NMR (CDCl₃, 300 MHz) δ: 2.34 (1 H, m, H_{2'β}), 2.58 (1 H, m, H_{2'α}), 3.28 (1 H, m, H_{5'β}), 3.46 (1 H, m, H_{5'α}), 3.65 (3 H, s, DMT-OCH₃), 3.66 (3 H, s, DMT-OCH₃), 4.15 (1 H, m, H_{4'}), 4.58 (1 H, m, H_{3'}), 5.40 (1 H, d, *J* = 4.0 Hz, OH_{3'}), 6.39 (1 H, t, *J* = 6.0 Hz, H_{1'}), 6.76 (4 H, dd, *J* = 2.2, 9.0 Hz, Ar), 7.00–7.44 (11 H, m, Ar), 8.20, (1 H, s, H₆), 8.34 (1 H, s, pyridine), 8.39 (1 H, d, *J* = 3.6 Hz, pyridine), 10.07 (1 H br, H_{N3}). ¹³C NMR (CDCl₃, 75 MHz) δ: 41.81, 55.16, 63.38, 72.26, 83.17, 85.84, 86.75, 87.14, 90.27, 99.92, 113.32, 119.61, 122.58, 127.06, 127.84, 128.05, 129.87, 135.38, 135.47, 138.56, 142.88, 144.36, 148.38, 148.98, 151.95, 158.61, 160.98. HRMS (FAB) *m/z* for C₃₇H₃₄N₃O₇ (M + H)⁺: calc'd. 632.2396, found 632.2425.

3-[5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine-5-yl-ethynyl]-N-methyl-pyridinium Iodide, 3d. In a Schlenk-like flask, **1b** (75 mg, 0.11 mmol) was co-evaporated 3 times with dry THF at 5 × 10⁻⁴ torr. The Schlenk-like flask was then brought inside a glove box, charged with 4 mL of dry acetonitrile containing 110 μL of freshly distilled methyl iodide. The solution was freeze/pump (2 × 10⁻⁴ torr)/thaw degassed 3 times. The solution was stirred for 20 h at 60°C in vacuo. The acetonitrile solution was removed in vacuo, and the greenish-yellow oily material was washed several times with hexane, dichloromethane, and acetone. Finally the solid was purified by repeated precipitations with hexane to afford 60 mg of **3d** (69% yield). ¹H NMR (DMSO-*d*₆, 300 MHz) δ: 2.28–2.36 (2 H, m, H_{2'α}/H_{2'β}), 3.28–3.13 (2 H, m, H_{5'α}/H_{5'β}), 3.66 (3 H, s, DMT-OCH₃), 3.67 (3 H, s, DMT-OCH₃), 3.95 (1 H, m, H_{4'}), 4.24 (3 H, s, CH₃), 4.32 (1 H, m, H_{3'}), 5.35 (1 H, d, *J* = 4.6 Hz, OH_{3'}), 6.12 (1 H, t, *J* = 6.3 Hz, H_{1'}), 6.83 (4 H, d, *J* = 8.7 Hz, Ar), 7.11–7.42 (9 H, m, Ar), 7.71 (1 H, d, *J* = 8.8 Hz, pyridinium), 7.95 (1 H, t, *J* = 7.0 Hz, pyridinium), 8.36 (1 H, s, H₆), 8.73 (1 H, s, pyridinium), 8.87 (1 H, d, *J* = 6.1 Hz, pyridinium), 11.89 (1 H, s, H_{N3}). ¹³C NMR (DMSO-*d*₆, 75 MHz) δ: 48.11, 55.02, 69.84, 78.51, 78.95, 79.40, 84.94, 85.91, 86.01, 89.88, 96.44, 113.25, 122.56, 126.76, 127.29, 127.50, 127.94, 129.58, 129.64, 135.45, 135.51, 144.85, 145.34, 146.69, 149.16, 158.06, 161.01. HRMS (FAB) *m/z* for C₃₈H₃₆N₃O₇⁺ (M⁺): calc'd. 646.2553, found 646.2556.

5'-O-(4,4'-Dimethoxytrityl)-5-(pyridin-3-yl-ethylenyl)-2'-deoxyuridine, 2b. Dry **1b** (320 mg, 0.50 mmol) was dissolved in 220 mL of dry MeOH and added to 30 mL MeOH solution containing 200 mg of 10% Pd/C previously activated by stirring under H₂ (50 psi) for 20 m at room temperature. The reaction mixture was then stirred under H₂ (50 psi) at room temperature until the

starting materials were completely consumed (18 h). The solution was filtered and solvent was removed in vacuo to afford a yellow foam of **2b** (300 mg, 93% yield). ^1H NMR (CDCl_3 , 300 MHz) δ : 1.84 (1 H, m, $\text{H}_{2'\beta}$), 2.00–2.32 (2 H, m, CH_2), 2.36–2.46 (2 H, m, CH_2), 2.63 (1 H, m, $\text{H}_{2'\alpha}$), 2.95 (1 H, br, $\text{OH}_{3'}$), 3.33 (1 H, dd, $J=2.0, 10.4$ Hz, $\text{H}_{5'\beta}$), 3.53 (1 H, dd, $J=2.8, 10.5$ Hz, $\text{H}_{5'\alpha}$), 3.71 (6 H, s, $\text{DMT}-(\text{OCH}_3)_2$), 4.06 (1 H, m, $\text{H}_{4'}$), 4.53 (1 H, m, $\text{H}_{3'}$), 6.43 (1 H, t, $J=6.4$ Hz, $\text{H}_{1'}$), 6.76–6.80 (4 H, m, Ar), 7.04–7.40 (11 H, m, Ar), 7.53 (1 H, s, H_6), 8.02 (1 H, s, pyridine), 8.34 (1 H, d, $J=4.8$ Hz, pyridine), 9.03 (1 H, br, H_{N_3}). ^{13}C NMR (CDCl_3 , 75 MHz) δ : 28.59, 31.81, 41.02, 55.20, 63.46, 72.30, 84.66, 86.15, 86.81, 99.93, 113.25, 114.09, 123.15, 127.24, 128.00, 128.23, 130.03, 130.13, 135.20, 135.36, 135.96, 136.33, 144.08, 147.13, 149.60, 150.23, 158.69, 158.72, 163.13. HRMS (FAB) m/z for $\text{C}_{37}\text{H}_{38}\text{N}_3\text{O}_7$ ($\text{M} + \text{H}$) $^+$: calc'd. 636.2709, found 636.2670.

3-[5'-O-(4,4'-Dimethoxytrityl)-2'-deoxyuridine-5-yl-ethylenyl]-N-methylpyridiniumyl Iodide, 4d. In a Schlenk-like flask, **2b** (74 mg, 0.11 mmol) was co-evaporated 3 times with dry THF at 5×10^{-4} torr. The flask was then brought inside a glove box and charged with 5 mL of dry acetonitrile containing 110 μL of freshly distilled iodomethane. The solution was freeze/pump (2×10^{-4} torr)/thaw degassed 3 times and stirred for 10 h at 70°C in vacuo. The acetonitrile solvent was removed in vacuo, and the greenish-yellow solid was washed several times with hexane, dichloromethane, and acetone. Finally the solid was purified by repeated precipitations with hexane to afford 65 mg of **4d** (72% yield). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 2.10–2.37 (4 H, m, $\text{H}_{2'\alpha}/\text{H}_{2'\beta}/\text{CH}_2$), 2.57–2.81 (2 H, m, CH_2), 3.12–3.27 (2 H, m, $\text{H}_{5'\alpha}/\text{H}_{5'\beta}$), 3.68 (6 H, s, $\text{DMT}-(\text{OCH}_3)_2$), 3.87 (1 H, m, $\text{H}_{4'}$), 4.26 (3 H, s, CH_3), 4.30 (1 H, m, $\text{H}_{3'}$), 5.31, (1 H, d, $J=3.9$, $\text{OH}_{3'}$), 6.18 (1 H, t, $J=6.5$ Hz, $\text{H}_{1'}$), 6.86, (4 H, d, $J=8.1$ Hz, Ar), 7.38–7.18 (9 H, s, Ar), 7.55 (1 H, s, H_6), 7.93–7.99 (2 H, m, pyridinium), 8.68 (1 H, s, pyridinium), 8.80 (1 H, d, $J=4.2$ Hz, pyridinium), 11.43 (1 H, s, H_{N_3}). ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ : 26.78, 31.00, 47.75, 55.07, 63.64, 70.33, 83.98, 85.42, 85.68, 111.99, 113.22, 126.83, 127.05, 127.71, 127.90, 129.68, 129.73, 135.37, 137.06, 141.21, 143.17, 144.24, 144.52, 144.62, 150.18, 158.08, 158.10, 163.20. HRMS (FAB) m/z for $\text{C}_{38}\text{H}_{40}\text{N}_3\text{O}_7^+$ (M^+): calc'd. 650.2866, found 650.2871.

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