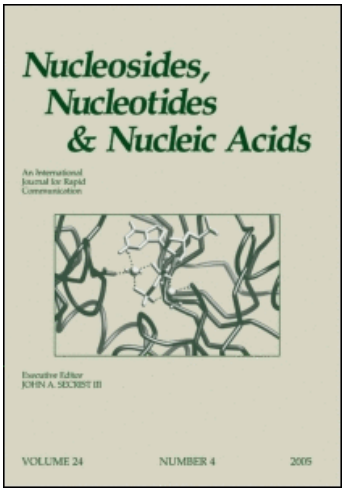

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Synthesis of *N,N*-Dialkylaniline-2'-deoxyuridine Conjugates for DNA-Mediated Electron Transfer Studies

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SYNTHESIS OF *N,N*-DIALKYLANILINE-2'-DEOXYURIDINE CONJUGATES FOR DNA-MEDIATED ELECTRON TRANSFER STUDIES

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ABSTRACT. Syntheses of two analogs of deoxyuridine with *N,N*-dialkylaniline chromophores are reported. 5-[3-(N-methylphenylamino)propanoyl]-2'-deoxyuridine (**1**) and 5-[2-(4-*N,N*-dimethylaminophenyl)ethyl)]-2'-deoxyuridine (**2**) are prepared by palladium-mediated coupling. Preparation of **2** was facilitated by *in situ* transient O^4-trimethylsilyl protection during alkynylation which suppressed secondary cyclization of the coupling adduct.

INTRODUCTION

In recent years a number of measurements of DNA-mediated electron transfer (ET) have been reported, and this work has also been reviewed several times.[1-3] Understanding of DNA-mediated ET is growing,[4-12] but it is still unclear whether the distance dependence of ET in DNA is always strong or can under some circumstances be quite shallow.[13-20] Recent studies by Giese *et al.*[4,5] and by Schuster *et al.*[21] examine the distance dependence of cation migration in DNA indirectly from strand-cleavage assays and provide important information concerning the distance dependence of cation tunneling and hole hopping. At the same time these and related investigations[12,16,22] underscore the need for direct rate measurements of charge migration in DNA.

One of our interests in DNA-mediated ET concerns developing a system for examining electron migration from a photoproduced 2'-deoxyuridine anion ($dU^{\bullet-}$) to covalently attached electron acceptors.[23] These experiments are designed to measure directly the kinetics of electron migration in DNA by means of laser-flash transient absorbance (TA) spectroscopy. To understand structural influences on $dU^{\bullet-}$ photoproduction in DNA, we have synthesized and studied the photophysics of intramolecular ET in a family of pyrenyl-dU nucleosides.[24-27] This work shows that indeed photoinduced electron transfer readily occurs (≤30 ps) in these

nucleotides to form the pyrene$^{\bullet+}$/dU$^{\bullet-}$ ET product and that this ET product can live as long as 430 ps.[26]

Measurement of electron migration in DNA over extended distances requires trapping an excess electron on deoxyuridine long enough to allow it time to travel to other DNA sites. The competing reaction, of course, is back ET between the photooxidized pyrenyl ligand (pyrene$^{\bullet+}$) and the initially reduced deoxyuridine nucleoside (dU$^{\bullet-}$). One way of accomplishing this would be to make the covalent linker that joins the pyrenyl and deoxyuridine subunits of the right length and composition. This would allow the photoinduced charge separation event (formation of pyrene$^{\bullet+}$/dU$^{\bullet-}$) to be ca. 99% efficient and the back (or reverse) ET reaction to be slow enough to allow the electron on the reduced deoxyuridine to transfer to other DNA sites. However, another anion trapping approach that is likely to be both practical and successful would use an attached secondary electron donor to reduce the pyrene$^{\bullet+}$ species and thus lengthen the lifetime of the associated dU$^{\bullet-}$ anion.

With these considerations in mind, we present in this paper the syntheses two *N,N*-dimethylaniline-deoxyuridine (DMA-dU) conjugates. *N,N*-dimethylaniline (DMA) chromophores are reversible electron donors that also produce a strong, sharp absorbance feature near 470 nm upon oxidation.[28] Tethered close to a pyrenyl-dU site on a DNA duplex, a DMA residue can readily reduce photogenerated pyrene$^{\bullet+}$ and thus prolong the lifetime of an associated dU$^{\bullet-}$ radical. The free nucleoside forms of these two conjugates are shown in Figure 1: **1** employs an acyl linker between a methyl of DMA and the deoxyuridine-C5 position, while **2** employs an ethylene linker to connect the *para*-position of DMA and the same deoxyuridine site.

RESULTS AND DISCUSSION

Stille-type palladium coupling affords a quick route to functionalized nucleosides via 5-propenoyl (acryloyl) modified uracils. Subsequent Michael addition to the α,β-unsaturated enone furnishes a modular route to a variety of functionalized thymidines, and it is known that amines will undergo conjugate addition to propenoyl groups on compounds such as **5** and **8** (see Scheme 1).[29,30] Thus exposing a propenoyldeoxyuridine to excess secondary amine in a dry dimethyl formamide (DMF) solution is expected to form the corresponding 3-(dialkylamino)propionyl-dU compounds. For our purposes, *N*-methylaniline (NMA) was used to form adducts with 5'-*O*-dimethoxytrityl- (DMT) and 5',3'-*bis*-*tert*-butyldimethylsilyl- (TBDMS) protected 5-propenoyl-2'-deoxyuridine (**5** and **8**). The propenoyl compounds may be prepared by the reported method,[31] although we used slightly different concentrations for this coupling (see Experimental).

Scheme 1 shows the synthesis of **6** and its corresponding free nucleoside **1**. We investigated two different glycone protection approaches to the synthesis of **6**, as it is key to incorporating **1** into DNA. In particular TBDMS protection was investigated as an alternative to using solely DMT protection. After first protecting **3**, the propenoyl compounds **5** and **8** were prepared by "PdL_3" mediated cross-coupling of iododeoxyuridine to tributylvinyltin. In each case, the propenoyl compound was isolated adequately pure by treating the crude reaction mixture with

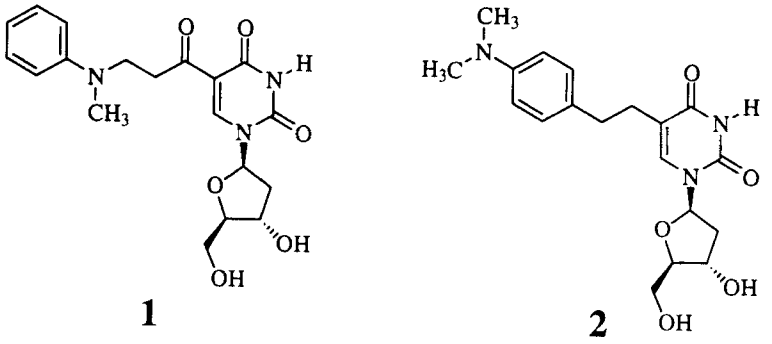


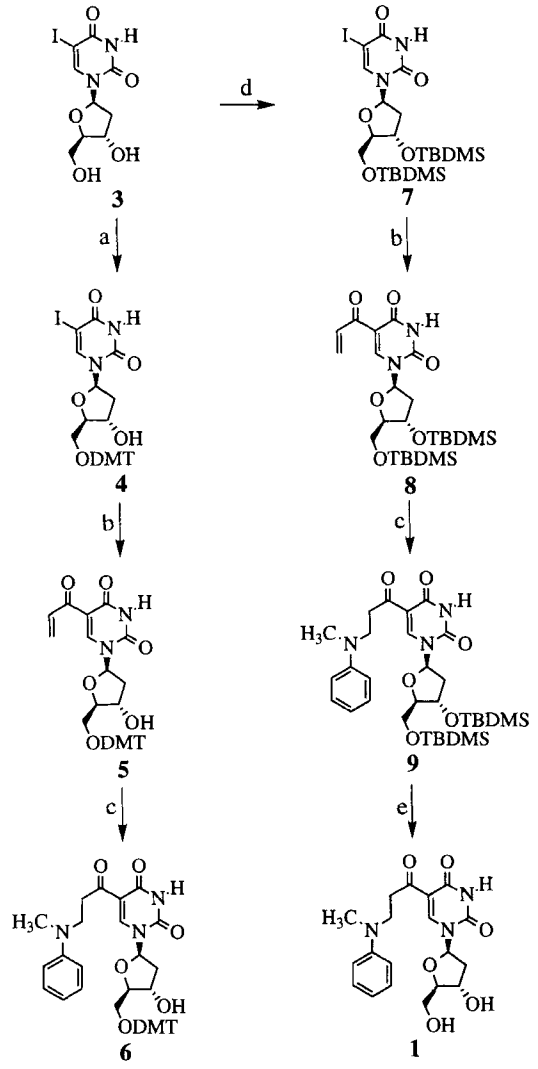
Figure 1. Structural drawings of DMA-dU conjugates **1** and **2**.

flash-silica pad filtration. Each propenoyl compound was then treated with NMA in DMF at ambient temperature overnight, and the conjugate addition product was isolated by flash chromatography. In this way, **6** and **9** were produced in 73.4% and 44.5% yields, respectively, in two steps from the corresponding protected iodo-nucleosides **4** and **7**.

Compound **1** was prepared by deprotecting **9** with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF). Preparing **6** by tritylation of **1** was successful, but problematic as other components of the reaction mixture could not be removed by available chromatographic methods. Additionally this synthetic route to **6** requires two additional steps starting from **3** compared to proceeding through compounds **4** and **5**. Thus there is no advantage to synthesizing **6** via TBDMS-protected precursors. However, the syntheses of compounds **8** and **9** are useful for preparing compound **1**.

Computational studies of pyrenyl-dU nucleoside conjugates in which the pyrenyl-moiety is joined to the uracil-C5 position via a cross-conjugated carbonyl group as in **1** reveal distinct disadvantages for this type of linkage with regard to intramolecular ET reactions.[26,27,32] Experimentally these disadvantages manifest themselves in a wide range of rates for ET-induced emission quenching.[24-27] Clearly conjugates such as **1** with five rotatable bonds between the phenyl and uracil groups will have many conformers both as a free nucleoside and when incorporated into a DNA duplex. While wide variations of electronic properties among conformers of **1** may not be a problem in some studies of DNA-mediated ET, it is likely that such variations will at times be undesirable. Thus we investigated other linkages between the uracil C5-position and a DMA moiety.

Palladium-mediated alkynylation of 5-iodouracils is appealing since the coupling provides the option to produce both deoxyuridine conjugates with an alkyne linkage and precursors to alkyl-linked conjugates via reduction of the alkyne groups. Numerous examples of Sonogashira-type



a: DMTCl, pyridine, r.t.; b: $Pd(OAc)_2$, CuI, PPh_3, vinyltributyltin, CO (50 psig), THF, 70 °C; c: NMA, DMF, r. t.; d: TBDMSCl, imidazole, DMF; e: TBAF, THF.

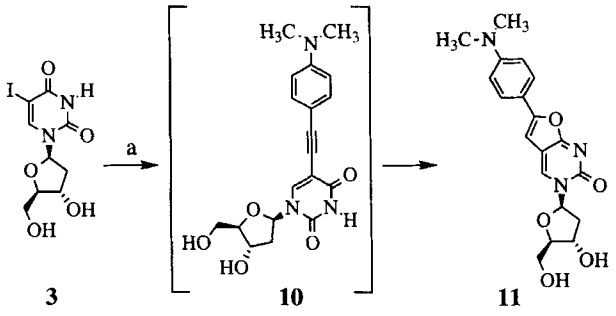
Scheme 1.

coupling reactions of 5-iodouracils are present in the literature (see below). It is also known that a competing cyclization reaction converts the desired 5-(alkynyl)-uracil into a furopyrimidinone, presumably by a copper-mediated reaction of the uracil-C4 carbonyl and the distal acetylenic carbon. Optimal alkynylation conditions use DMF as solvent and triethylamine (Et_3N) as an acid scavenger. Under these conditions even unprotected nucleosides undergo successful Sonogashira coupling (see below).

Coupling of 4-ethynyl-*N,N*-dimethylaminobenzene (EDMA) and **3** was first attempted under conditions analogous to those used with free nucleosides (see Scheme 2). Compound **10** was the anticipated product under conditions designed to suppress cyclization,[33,34] but the sole recognizable product isolated from the reaction mixture was consistent with furopyrimidinone **11**. Speculating that the reaction might improve in another solvent, the reaction was repeated twice in THF with either **7** (see Scheme 3) or 5',3'-*bis*-*O*-acetyl-5-iododeoxyuridine replacing **1** for reasons of nucleoside solubility. Attempting the coupling reactions with these changes produced in each case product mixtures from which no products consistent with either coupling or cyclization could be isolated.

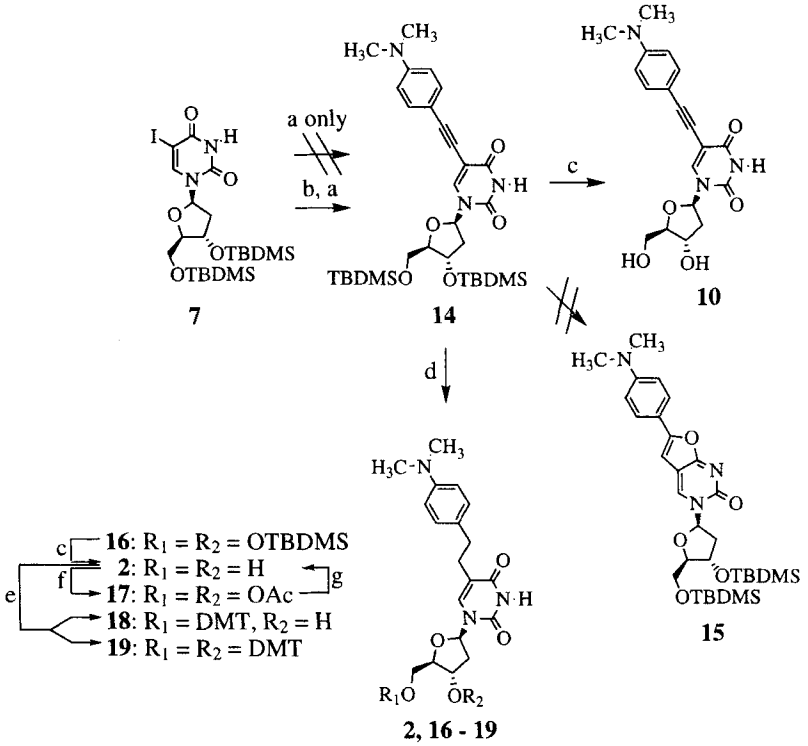
Although compound **11** in Scheme 2 is a reasonable product from Sonogashira-type alkynylation reactions of nucleosides, it is not usually found when coupling in DMF. Reaction conditions can be adjusted to produce the furopyrimidinone adduct either as a byproduct [33,35-37] or as the dominant product.[38] In addition, certain alkynylation products have been treated with CuI in Et_3N/methanol (MeOH) to induce cyclization as a second independent step.[35,36,38] Recently palladium-on-carbon was used to form exclusively the furopyrimidinone cycloadduct from 5-halouracils and terminal acetylenes.[39,40] A surprising aspect of the attempts to form **10** and **14** (see Schemes 2 and 3) is that EDMA coupling products are not found under conditions similar to those that produce coupling as the dominant (or even exclusive) product with ethynylarenes,[35,36,41,42] metal-complexed ethynylheteroarenes,[43] propargylic metal complexes[44,45] and other 1-alkynes.[33,34,37,46-51] Possibly preference for the furopyrimidinone cycloadduct is due to a more electron-rich alkyne product in the cases of **10** and **14** than in other instances.

Reasoning that the C4-carbonyl was essential for cyclization but unnecessary for coupling, we sought to suppress the cyclization reaction through transient protection of the uracil ring with an O^4-trimethylsilyl group. O^4-Silyl uracils appear several times in the literature. Uses include persilylation of nucleosides and nucleotides for mass spectrometry,[52,53] palladium-mediated cross-coupling of 5-halouracils to aryl lithiums or aryl zincs,[54,55] photochemical addition of arenes[55,56] and alkenes,[57] and the exchange of TMS for the CHF_2 group.[58-60] In none of these reports is the silyl-group used to prevent reaction of the C4-carbonyl. Thus **14** was synthesized in one pot as shown in Scheme 3 by silylating with chlorotrimethylsilane (TMSCl) and hexamethyldisilazane (HMDS), removing excess silylating agents under vacuum, and then performing the coupling reaction. Presumably **12**, which was not isolated, gave rise to compound **13** (see Figure 2) which could not cyclize to the furopyrimidinone adduct **15**. Rather **13** hydrolyzed during work-up to produce **14**. The trimethylsilyl-group (TMS) was especially convenient since it afforded one-pot *in situ* protection and spontaneous deprotection during



a: PdL_4, CuI, Et_3N, DMF, EDMA.

Scheme 2.



a: PdL_4, CuI, Et_3N, THF, EDMA; b: HMDS, TMSCl, 80 °C; c: TBAF, THF; d: Pd/C, H_2, MeOH; e: DMTCl, pyridine; f: Ac_2O, pyridine; g: 30% NH_4OH (aq).

Scheme 3.

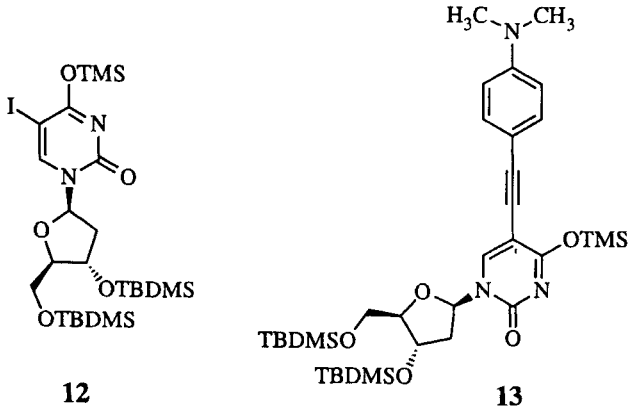


Figure 2. Structural drawings of two O^4-TMS-protected nucleosides likely present in the one-pot silylation and alkynylation of **7** with EDMA (see Scheme 3).

work-up. To the best of our knowledge, this is the first report of silylating the deoxyuridine O^4-position to suppress unwanted cycloadduct formation under Sonogashira coupling conditions.

Compound **14** was recrystallized in high purity after pad filtration and chromatography. Treating **14** with TBAF produced **10**; however due to purification difficulties, synthesis of **2** based on **10** was not pursued further. Therefore compound **14** was hydrogenated in the presence of hydrogen and palladium-on-carbon (Pd/C) to reduce the alkyne group. Compound **16** was then desilylated using TBAF to give **2**. Chromatographic separation of **2** from tetrabutylammonium salts formed in the desilylation step proceeded without difficulty for small-scale syntheses (94% yield). Tritylation of **2** forms both **18** (55.5%) and the *bis*-tritylated compound **19** (21.7%).[61]

While the isolation of **2** was readily achieved on a small scale, preparative scale reaction mixtures proved difficult to purify. For these larger scale preparations of **2**, the nucleoside and tetrabutylammonium salts co-eluted during silica gel chromatography. Thus TBDMS removal with TBAF was followed by peracetylation in excess pyridine/acetic anhydride (Ac_2O). The resulting *bis*-acetate **17** was readily purified by silica gel chromatography. Finally **18** was produced from **17** in one pot by deprotection, which formed **2**, followed by tritylation.

CONCLUSION

The synthesis of **1** utilizes 5-propenoyldeoxyuridine to attach the DMA chromphore via its exocyclic nitrogen to C5 of deoxyuridine. The resulting nucleoside conjugate has three linking atoms between the DMA-nitrogen and the uracil subunit. This new conjugate has considerable freedom to position its DMA subunit external to an attached duplex and close to the pyrenyl group of a neighboring pyrenyl-dU nucleotide. The synthesis of **2** proceeds via palladium-mediated coupling of an alkyne attached to the *para*-position of DMA to link this chromophore

to the C5 of deoxyuridine. Mild reduction of the alkyne results in a nucleoside conjugate with two saturated carbons linking the DMA and uracil subunits. The shorter linker and *para*-DMA attachment point in **2** produce a conjugate with much less freedom of motion between its DMA and uracil subunits than **1**. Depending on the duplex substitution site available in a given DNA-mediated ET experiment, the reduced conformational freedom of conjugate **2** may provide desirable control in positioning DMA with respect to other redox active groups.

The two DMA-dU conjugates reported here provide important options in the placement of a secondary electron donor along a DNA duplex in order to reduce a nearby photogenerated pyene$^{+\bullet}$ species and thus lengthen the lifetime of an associated dU$^{\bullet-}$ anion: DMA/**pyrene**$^{+\bullet}$/dU$^{\bullet-}$ → **DMA**$^{+\bullet}$/pyrene/dU$^{\bullet-}$. These new conjugates are likely to make photochemical trapping of a uracil anion in DNA both practical and successful; thereby permitting study of anion migration in DNA duplexes.

EXPERIMENTAL

General Considerations. Where organometallic reagents or 4,4'-dimethoxytrityl chloride (DMTCl) were involved, a Vacuum Atmospheres M040-2 glove-box pressurized with dry nitrogen was used. All other reactions were carried out on the benchtop under dry nitrogen. Chromatography employed a Biotage Flash® system using KP-Sil® prepackaged cartridges. The silica gel used for pad filtrations or in the concentration of crude reaction mixtures was Whatman® flash silica (80Å pore, 230-400 mesh). Tetrakistriphenylphosphinepalladium(0) (PdL_4) was prepared according to the literature[62] and stored in a glove-box freezer. 4-Ethynyl-*N,N*-dimethylaniline (EDMA) was prepared by adaptation of a literature procedure,[63] purified by vacuum transfer, and stored in a glove-box freezer. Tetrahydrofuran (THF) was dried by distillation from benzophenone ketyl and stored under nitrogen. Toluene was dried by distillation from benzophenone ketyl and stored over activated 4 Å molecular sieves pending use. *N,N*-dimethylformamide (DMF), triethylamine (Et_3N), pyridine, and *N*-methylaniline (NMA) were dried by distillation from CaH_2, and stored under nitrogen. Methanol (MeOH) was dried by distillation from magnesium turnings under nitrogen. Copper and palladium salts were obtained from Strem Chemicals. 5-Iodo-2'-deoxyuridine (**3**) obtained from Aldrich was used as received. Other reagents and solvents came from common suppliers and were usually used without further purification. Mass spectrometry was performed at the Georgia Institute of Technology. NMR spectra were obtained from 300 MHz and 600 MHz spectrometers located at Georgia State University.

5'-*O*-Dimethoxytrityl-5-[3-(N-methylphenylamoino)propanoyl]-2'-deoxyuridine (6). In an inert atmosphere glove-box, a Pyrex® bomb equipped with Teflon® vacuum stopcocks and a pressure equalizing addition funnel was charged with **4** (467 mg, 0.711 mmol), copper(I) iodide (65mg, 0.34 mmol), palladium(II) acetate ($Pd(OAc)_2$) (26mg, 0.12 mmol), triphenylphosphine (86mg, 0.33 mmol) and THF (25mL, freshly distilled) in the reaction chamber, and with THF (25mL, freshly distilled) in the addition funnel. After removing the apparatus from the box, tributylvinyltin (360 μL, 1.23 mmol) was added to the addition funnel by syringe through a 6"

18-gauge needle. The syringe was flushed into the vessel supplying excess tin reagent. The apparatus was charged with CO to 50 psig, placed in a 70°C oil bath, and stirred with gradual addition of the tin/THF solution. When the reaction mixture's color discharged and metal residue coated the glass, the bomb was opened, and the contents washed out with acetone. The crude material was concentrated to dryness, then dissolved in a small amount of chloroform. The choloroform solution was transferred to a pad of silica gel in a 60 mL sintered glass Büchner funnel. The pad was washed with 150 mL $CHCl_3$ followed by 300 mL of ethyl acetate (EtOAc). *In vacuo* concentration of the EtOAc eluate yielded **5** sufficiently pure to perform the conjugate addition. Dried compound **5** (404 mg) was dissolved in DMF (17.3 mL) in a 50 mL flask. NMA (750 μL, 6.91 mmol) was added, and the reaction mixture was stirred under nitrogen overnight at room temperature (~14 h). DMF and remaining NMA were removed *in vacuo* with warming by a water bath (<70 °C). Final purification was achieved with chromatography by stepwise elution ($CHCl_3$, 25% EtOAc in $CHCl_3$, 50% EtOAc in $CHCl_3$; $CHCl_3$ was first neutralized with basic alumina). The product (**6**) was a yellow oil (219 mg, 0.317 mmol, 44.5% yield from **4**). **6**: ^{1}H NMR (300 MHz; $CDCl_3$) δ: 2.19 (~p, 1H, J_{ave}= 6.7 Hz), 2.52 (ddd, 1H, J = 2.8, 5.8, 13.7 Hz), 2.87 (s, 3H), 3.18 (~q, 2H, J_{ave} = 6.3 Hz), 3.37 (m, 2H), 3.60 (t, 2H, J = 6.958 Hz), 3.74 (s, 6H), 4.08 (~q, 1H, J_{ave} = 3.5), 4.33 (~p, 1H, J = 2.7 Hz), 6.14 (~t, 1H, J_{ave} = 6.5 Hz), 6.60 (arom., 3H), 6.82 (arom., 4H), 7.26 (arom., 11H), 8.47 (s, 1H), 9.66 (s, br, 1H). ^{13}C{^{1}H} (75 MHz; $CDCl_3$) δ: 38.08, 39.49, 41.08, 47.66, 55.13, 63.50, 72.45, 86.54, 86.78, 86.84, 112.28, 112.37, 113.18, 116.30, 126.88, 127.87, 127.91, 129.08, 130.01, 135.40, 135.47, 144.45, 146.44, 148.76, 149.65, 158.48, 161.06, 194.78.[64] HRMS *m/z* (FAB) for $C_{40}H_{42}N_3O_8$ (MH^+): calc'd 692.2972, found 692.2949.

5',3'-Bis-*O*-*tert*-butyldimethylsilyl-5-[3-(N-methylphenylamino)propanoyl]-2'-deoxyuridine (9). In an inert atmosphere glove-box, a Pyrex® bomb equipped with Teflon® vacuum stopcocks and a pressure equalizing addition funnel was charged with **7** (647 mg, 1.11 mmol), copper(I) iodide (63mg, 0.33 mmol), palladium(II) acetate (27mg, 0.120 mmol), triphenylphosphine (88mg, 0.34 mmol) and THF (20mL, freshly distilled) in the reaction chamber, and with THF (25mL, freshly distilled) in the addition funnel. After removing the apparatus from the box, tributylvinyltin (360 μL, 1.23 mmol) was added to the addition funnel by syringe and a 6" 18-gauge needle. The syringe was also flushed into the vessel. The apparatus was charged with CO to 50 psig, placed in a 70°C oil bath, and stirred with gradual addition of the tin/THF solution. When the reaction mixture's color discharged and metal residue coated the glass, the bomb was opened, and the contents washed out with acetone. The crude material was concentrated to dryness and then dissolved in a small amount of chloroform. The choloroform solution was transferred to a pad of silica gel in a 60 mL sintered glass Büchner funnel. The pad was washed with 150 mL $CHCl_3$ and then with 150 mL 25% EtOAc in $CHCl_3$. Concentration of the EtOAc/$CHCl_3$ eluate *in vacuo* gave **8** of sufficient purity to perform the conjugate addition. The dried compound **8** (574 mg) was dissolved in DMF (29 mL) in a 50 mL flask. NMA (1.22 mL, 11.2 mmol) was added, and the reaction mixture was stirred under nitrogen overnight at room temperature (~14 h). DMF and remaining NMA were removed *in vacuo* with warming by a water bath (<70°C). Final purification was achieved with

chromatography (KP-Sil® Flash-40M® using 1:1 chloroform/hexanes for pre-elution and first eluate, followed by neat chloroform, and then by 5% EtOAc in $CHCl_3$). The product **9** was a yellow solid (504 mg, 0.815 mmol, 73.4% yield from **7**). **9**: ^{1}H NMR (300MHz; $CDCl_3$) δ: 0.09 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 2.04 (ddd, *J* = 5.7, 7.6, 13.3 Hz; 1H), 2.41 (ddd, *J* = 2.1, 5.7, 13.3 Hz, 1H), 2.96 (s, 3H), 3.27 (dt, *J* = 1.2, 7.0 Hz; 2H), 3.70 (t, *J* = 7.1 Hz, 2H), 3.78 (dd, *J* = 3.1, 11.4 Hz, 1H), 3.84 (dd, *J* = 3.4, 11.4 Hz, 1H), 4.05 (dt, *J* = 2.3, 2.8 Hz, 1H), 4.42 (dt, *J* = 2.4, 5.6 Hz, 1H), 6.22 (dd, *J* = 7.6, 5.7, 1H), 6.71 (m, 3H), 7.21 (m, 2H) 8.55 (s,1H), 9.11 (s, 1H). ^{13}C{^{1}H} (75 MHz; $CDCl_3$) δ: -5.65, -5.51, -4.86, -4.71, 17.99, 18.38, 25.72, 25.93, 38.16, 39.62, 42.05, 47.84, 63.07, 72.80, 86.89, 88.92, 112.38, 112.44, 116.36, 129.124, 146.76, 148.85, 149.44, 160.97, 194.91. HRMS *m/z* (EI) $C_{31}H_{51}N_3O_6Si_2$ (M^+): calc'd 617.3318, found 617.3300.

5-[3-(N-Methylphenylamino)propanoyl]-2'-deoxyuridine (1). Compound **9** (372mg, 0.602 mmol) was dissolved in THF (11.0 mL, freshly distilled), tetra-*n*-butylammonium fluoride (TBAF, 1.5 mL, 1M in THF, 1.51 mmol) was added, and the mixture was stirred for 4 h under nitrogen. Dry flash-silica gel, MeOH, and Et_3N were added and the mixture concentrated to dryness. The product was purified by chromatography on a KP-Sil® Flash-12M® column using stepwise elution with $CHCl_3$/MeOH (neat $CHCl_3$, 5% MeOH in $CHCl_3$, and 10% MeOH in $CHCl_3$). Upon removal of the eluant *in vacuo*, **1** was obtained as a yellow oil (234 mg, 0.601 mmol, 71% yield). **1**: ^{1}H NMR (300 MHz; acetone-d_6) δ: 2.29 (m, 2H, $H_{2'\alpha/\beta}$), 2.87 (s, 3H, CH_3), 3.17 (t, *J*= 7.2 Hz, CH_2), 3.63 (t, *J*= 7.2 Hz, 2H CH_2), 3.78 (~t, *J*= 3.2 Hz, 2H, $H_{5'\alpha/\beta}$), 4.00 (q, *J* = 3.2 Hz, 1H, $H_{4'}$), 4.47 (dt, *J* = 5.7, 3.2 Hz, 1H, $H_{5'}$), 6.22 (t, *J* = 6.7 Hz, 6.5 Hz, 1H, $H_{1'}$), 6.56 (arom., 1H), 6.70 (arom., 2H), 7.11 (arom., 2H), 8.81 (s, 1H, H_6). The imide proton was not observed due to rapid exchange with the solvent. ^{13}C{^{1}H} (75 MHz; acetone-d_6) δ: 38.26, 39.77, 41.82, 48.38, 62.49, 71.99, 87.10, 89.11, 112.91, 113.08, 116.80, 129.76, 148.08, 149.86, 150.53, 162.00, 195.72. HRMS *m/z* (FAB) for $C_{19}H_{24}N_3O_6$(MH^+): calc'd 390.1665, found 390.1684.

3-(2'-Deoxy-β-D-ribofuranosyl)-6-(4-dimethylaminophenyl)furo-[2,3-*d*]-pyrimidin-2-one (11). In a glove box, **3** (122 mg, 0.344 mmol), EDMA (83 mg, 0.572 mmol), CuI (7 mg, 0.037 mmol), PdL_4 (18 mg, 0.016 mmol), Et_3N (200 μL) and DMF (1 mL) were combined in a vial with a Teflon®-backed silicone rubber seal. The vial was sealed and heated to 60 °C in an oil bath for 2-3 h. After *in vacuo* concentration, the mixture was chromatographed using 0-20% methanol in methylene chloride on silica gel. **11** was isolated in low yield (<20%). **11**: ^{1}H NMR (300 MHz; DMSO-d_6) δ: 2.07 (dt, *J* = 6.1, 13.4 Hz; 1H), 2.38 (ddd, *J* = 4.3, 6.1, 13.4 Hz; 1H), 2.97 (s, 6H), 3.66 (m, 2H), 3.91 (dt, *J* = 3.54, 3.66 Hz; 1H), 4.24 (dq, *J* = 4.1, 9.6 Hz; 1H), 5.16 (t, *J* = 5.2 Hz, 1H), 5.29 (d, *J* = 4.3 Hz, 1H), 6.19 (t, *J* = 6.1 Hz, 1H), 6.78 (AA', *J* = 9.0 Hz, 2H), 6.90 (s, 1H), 7.62 (BB', *J* = 9.0 Hz, 2H), 8.68 (s, 1H).

5',3'-*Bis*-*O*-*tert*-butyldimethylsilyl-5-[2-(4-*N*,*N*-dimethylaminophenyl)ethynyl)]-2'-deoxyuridine (14). Compound **7** (2.120g, 3.64 mmol) was combined with hexamethyldisilazane (HMDS, 13.0 mL, 61.6 mmol) and chlorotrimethylsilane (TMSCl, 2.0 mL, 15.8 mmol) in a flask and refluxed under nitrogen for 1.5-2 h. The flask was then equipped with a vacuum stopcock

adapter and placed on a vacuum manifold to remove HMDS and TMSCl *in vacuo* with heating from a water bath (<80 °C). The residue was then dissolved in dry toluene added via a cannula. After *in vacuo* concentration to a syrup, the flask was transferred to a glovebox where PdL_4 (219 mg, 0.190 mmol), Et_3N (2mL), THF (8mL), CuI (79 mg, 0.414 mmol) and EDMA (585mg, 4.03 mmol) were added. The flask was closed with a septum. Upon removal from the box, the flask was placed in a 60 °C oil bath and the contents stirred for 2 h. Almost immediately fine crystals formed in the reaction mixture. After removal from the oil bath, the flask was opened and the contents dried and applied to the top of a pad of Whatman® flash silica in a Flash-40S® column barrel using minimal amounts of CH_2Cl_2. The pad was washed with benzene followed by EtOAc. The washings were combined, concentrated, and chromatographed (Flash-40M® using 12.5% EtOAc in $CHCl_3$ followed by 5% MeOH in benzene) giving **14** in a mixture of other compounds. **14** was recrystallized from benzene/hexanes.[65] The crystals were collected by vacuum filtration, washed with hexanes, and dried *in vacuo* to give **14** as yellow crystals (1.335 g, 2.225 mmol, 61.2% yield). **14**: ^1H and ^{13}C NMR showed insignificant contamination, and the compound was used without further purification in hydrogenation reactions. ^1H NMR (300 MHz; $CDCl_3$) δ: 0.08 (s, 3H), 0.09 (s, 3H), 0.14 (s, 3H), 0.159 (s, 3H), 0.90 (s, 9H), 0.92 (s,9H), 2.06 (ddd; J = 5.9, 7.6, 13.2 Hz; 1H, $H_{2'}$), 2.32 (ddd; J = 2.6, 5.8, 13.2 Hz; 1H, $H_{2'}$), 2.98 (s, 6H), 3.77 (dd; J = 2.3, 11.4 Hz; 1H, $H_{5'}$), 3.91 (dd; J = 2.3, 11.4 Hz; 1H, $H_{5'}$), 3.99 (~q, J = 2.3 Hz, 1H, $H_{4'}$), 4.43 (dt; J = 2.5, 5.7; 1H, $H_{3'}$), 6.33 (dd; J = 5.7, 7.6 Hz, 1H, $H_{1'}$), 6.62 (AA', 2H), 7.37 (BB', 2H), 7.98 (s, 1H, H_6), 8.67 (s, 1H, H_{imide}). $^{13}C\{^1H\}$ (75 MHz; $CDCl_3$) δ: -5.55, -5.26, -4.87, -4.67, 17.99, 18.41, 25.72, 26.00, 40.14, 41.89, 62.95, 72.43, 78.02, 85.67, 88.29, 95.19, 101.22, 109.46, 111.57, 132.84, 140.91, 149.17, 150.15, 161.48. HRMS *m/z* (EI) for $C_{31}H_{49}N_3O_5Si_2$ (M^+): calc'd 599.3213, found 599.3195.

5-[2-(4-*N,N*-Dimethylaminophenyl)ethynyl)]-2'-deoxyuridine (10). **10** was prepared from **14** in the same manner that **2** was prepared from **16**. **10**: ^1H NMR (300 MHz; DMSO-d_6) δ: 2.14 (m, 2H), 2.92 (s, 6H), 3.60 (m, 2H), 3.80 (~q, 1H, J_{ave} = 3.1 Hz), 4.25 (~p, 1H, J_{ave} = 4.1 Hz), 5.14 (t, 1H, J = 6.6 Hz), 5.26 (d, 1H, J = 4.2 Hz), 6.13 (~t, 1H, J = 6.6 Hz), 6.68 (AA', 2H), 7.26 (BB', 2H), 8.24 (s,1H), 11.63 (s,br, 1H). $^{13}C\{^1H\}$ (75 MHz; DMSO-d_6) δ: 39.72, 54.94, 60.97, 70.13, 79.79, 84.67, 87.57, 93.26, 99.22, 108.59, 111.84, 132.28, 142.57, 149.48, 150.05, 161.64. HRMS *m/z* (FAB) for $C_{19}H_{22}N_3O_5$ (MH^+): calc'd 372.1559, found 372.1532.

5',3'-Bis-*O*-*tert*-butyldimethylsilyl-5-[2-(4-*N,N*-dimethylaminophenyl)ethyl)]-2'-deoxyuridine (16). Compound **14** (854 mg, 1.42 mmol) and palladium-on-carbon (10% Pd, 396 mg) were placed in a 250-mL Fisher-Porter® pressure bottle. The bottle was flushed with nitrogen before dry MeOH (30 mL) was added. The vessel was then sealed, flushed and charged with hydrogen (~40 psig), and stirred for 2 d at ambient temperature. The reaction mixture was filtered, washed with benzene and chloroform, and concentrated with a rotovap; the product was recrystallized using benzene/hexanes. The solid was filtered and dried *in vacuo* to give **16** as an off-white solid (688 mg, 1.14 mmol, 80.2% yield). **16**: ^1H NMR (600 MHz; $CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.099 (s, 3H), 0.102 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 1.80 (ddd, 1H; J = 6.0, 7.9, 13.5 Hz), 2.16 (ddd, 1H; J = 1.9, 5.6, 13.2 Hz), 2.49 (ddd, 1H, J = 6.8, 8.8, 13.9 Hz), 2.63

(ddd, 1H, J = 5.8, 8.4, 13.9 Hz), 2.73 (m, 2H), 2.90 (s, 6H), 3.72 (m, 2H), 3.89 (~q, 1H, J = 2.7 Hz), 4.34 (~dt, 1H, J = 2.9, 5.8 Hz), 6.30 (dd, 1H, J = 5.8, 8.3 Hz), 6.68 (AA', 2H), 7.02 (BB', 2H), 7.13 (s, 1H), 9.06 (s, br, 1H). $^{13}C\{^1H\}$ (75 MHz; $CDCl_3$) δ: -5.58, -5.41, -5.01, -4.84, 17.83, 18.23, 25.60, 25.72, 25.82, 29.55, 33.69, 40.70, 62.80, 72.09, 84.38, 87.42, 112.81, 114.23, 129.09, 129.19, 135.61, 148.90, 150.52, 163.61. HRMS *m/z* (FAB) for $C_{31}H_{54}N_3O_5Si_2$ (MH^+): calc'd 604.3602, found 604.3639.

5-[2-(4-*N*,*N*-Dimethylaminophenyl)ethyl)]-2'-deoxyuridine (2). Compound **16** (279 mg, 0.462 mmol) was dissolved in THF (14 mL) and TBAF (2.0 mL, 1.0 M solution in THF, 2.0 mmol) was added. After stirring for 2 h at ambient temperature, the reaction mixture was concentrated with a rotovap. The residue was then chromatographed (Flash-40M®) using neat EtOAc followed by 5% MeOH in methylene chloride for the mobile phase. Upon removal of the solvent *in vacuo*, **2** was a yellow solid (163 mg, 0.434 mmol, 94.0% yield). **2**: ^1H NMR (300 MHz; DMSO-d_6) δ: 1.95 (m, 2H), 2.49 (m, 4H but overlaps DMSO-d_5), 2.82 (s, 6H), 3.51 (m, 2H), 3.73 (~q, 1H, J = 3.1 Hz), 4.17 (m, 1H), 5.02 (t, 1H, J = 4.9 Hz), 5.21 (d, 1H, J = 4.2 Hz), 6.13 (~t, 1H, J = 6.9 Hz), 6.64 (AA', 2H), 6.97 (BB', 2H), 7.52 (s, 1H), 11.27 (s, 1H). $^{13}C\{^1H\}$ (75 MHz; DMSO-d_6) δ: 28.45, 32.94, 40.40, 61.32, 70.44, 83.76, 87.28, 112.66, 112.92 128.81, 136.46, 148.89, 150.28, 163.34.[66] HRMS *m/z* (FAB) for $C_{19}H_{26}N_3O_5$ (MH^+): calc'd 376.1872, found 376.1907.

5'-*O*-Dimethoxytrityl-5-[2-(4-*N*,*N*-dimethylaminophenyl)ethyl)]-2'-deoxyuridine (18) & 3',5'-*bis*-*O*-Dimethoxytrityl-5-[2-(4-*N*,*N*-dimethylaminophenyl)ethyl)]-2'-deoxyuridine (19). Water was removed from compound **2** (994 mg, 2.65 mmol) by coevaporation with several portions of dry pyridine. DMTCl (1.077 g, 3.18 mmol) was added to **2** in a glovebox. Upon removal from the box, the mixture was dissolved in pyridine (6.6 mL) while cooled by an ice bath and allowed to warm to ambient temperature overnight in the bath. MeOH was added to quench the reaction, and the mixture was concentrated *in vacuo*. The crude material was chromatographed (Flash-40M® passivated and loaded with 0.25% Et_3N in $CHCl_3$; elution with 0.25% Et_3N/2.5% EtOH/25%EtOAc in $CHCl_3$) giving three fractions comprised of impure **19** (high R_f fraction), a mixture of **18** and **19** (intermediate R_f fraction), and pure **18** (low R_f fraction). The high and intermediate R_f fractions were separately re-chromatographed each with different conditions[67] to give pure **18** and **19**. After combining appropriate fractions and *in vacuo* solvent removal, compound **18** (923 mg, 1.36 mmol, 55.5%) was a yellow solid and compound **19** (565 mg, 0.669 mmol, 21.7%) was a yellow oil. **18**: ^1H NMR (300 MHz; $CDCl_3$) δ: 1.97 (dt, J = 6.0, 13.3 Hz; 1H), 2.08 (dt, J = 7.8, 13.3 Hz; 1H), 2.29 (dt; J = 5.9, 13.4 Hz; 1H), 2.51 (m, 3H), 2.80 (s, 6H), 3.26 (ddd, J = 4, 10.3, 20.6 Hz; 2H), 3.75 (s, 6H), 3.84 (dt, J = 5.5, 5.7 Hz; 1H), 3.97 (dt, J = 3.7, 4.5 Hz, 1H), 6.29 (t, J = 6.0 Hz, 1H), 6.59 (AA', J = 8.6 Hz, 2H), 6.75 (BB', J = 8.6 Hz, 2H), 6.82 (AA', J = 9.0 Hz, 4H), 6.94 (s, 1H), 7.33 (m, 9H), 9.32 (s, br, 1H). $^{13}C\{^1H\}$ (75 MHz; $CDCl_3$) δ: 29.00, 33.52, 40.67, 41.09, 55.18, 63.93, 71.23, 84.49, 84.97, 86.57, 113.21, 113.54, 113.76, 127.03, 127.93, 128.13, 129.38, 130.02, 130.26, 135.55, 135.59, 136.05, 144.38, 149.07, 150.24, 158.60, 163.32.[68] HRMS *m/z* (FAB) for $C_{40}H_{43}N_3O_7$ (MH^+): calc'd 677.3101, found 677.3184 (average[69]). **19**: HRMS *m/z* (FAB) for $C_{61}H_{61}N_3O_9$ (M^+): calc'd 979.4408, found 979.4476. Connectivities were verified by COSY.

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64. Two different ^{13}C NMR data sets from **6** were reviewed for these assignments. In both sets 28 ^{13}C resonances were observed instead of the expected 27, possibly the result of diastereotopic arrangement of subgroups within the DMT group.

65. Alternately, flash chromatography performed by loading crude material in neat chloroform followed by elution with 17% EtOAc in chloroform may be used to isolate **14**.

66. Only 14 ^{13}C resonances were observed in DMSO-d_6 instead of the expected 16. The septet produced by the solvent is probably obscuring one resonance, while another is likely coincident with some other analyte resonance. Unfortunately solubility severely limits the number of NMR solvents that can be used to study this nucleoside.

67. The high R_f fraction containing impure **19** was re-chromatographed using a stepwise elution as follows: 1%, 2%, and 5% EtOH in 0.3% Et_3N/CH_2Cl_2. The intermediate R_f fraction containing **18** and **19** was re-chromatographed using stepwise elution as follows: 0.3% Et_3N/25% EtOAc in $CHCl_3$, 0.3% Et_3N/1% EtOH/25% EtOAc in $CHCl_3$, 0.3% Et_3N/2% EtOH/25% EtOAc in $CHCl_3$, and finally 0.3% Et_3N/5% EtOH in CH_2Cl_2.

68. Three different ^{13}C NMR data sets were reviewed for these assignments. Consistently 27 ^{13}C resonances were observed instead of the expected 26, possibly the result of diastereotopic arrangement of subgroups within the DMT group.

69. The reported mass is the average of three separate measurements with the following values: 677.3279, 677.3312, 677.2961.

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