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2'-Deoxy-2'-Alkoxylaminouridines: Novel 2'-Substituted Uridines Prepared by Intramolecular Nucleophilic Ring Opening of 2,2'-*O*-Anhydrouridines

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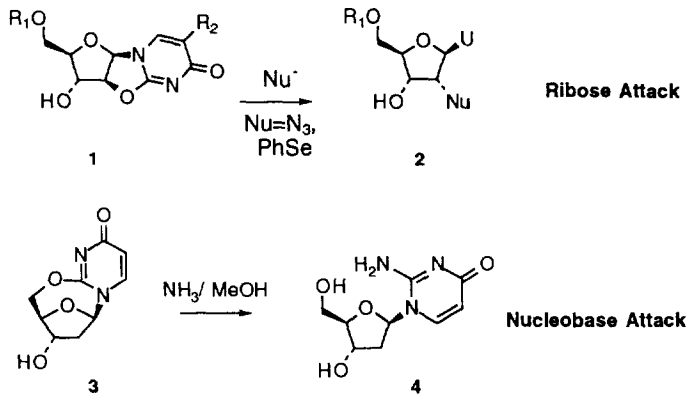
Abstract: Natural and unnatural modified nucleosides and nucleotides play important roles in biology, medicine, and as biomedical research tools. Reported herein is an application of synthetic methodology developed for the stereo- and regiospecific introduction of structural modifications at the 2'-position of uridine nucleosides. A novel class of modified nucleosides, 2'-alkoxylamino-2'-deoxy uridines, are prepared by intramolecular nucleophilic addition of a 3'-tethered alkoxycarbamate nucleophile to the 2'-position with concomitant opening of a 2,2'-anhydrouridine.

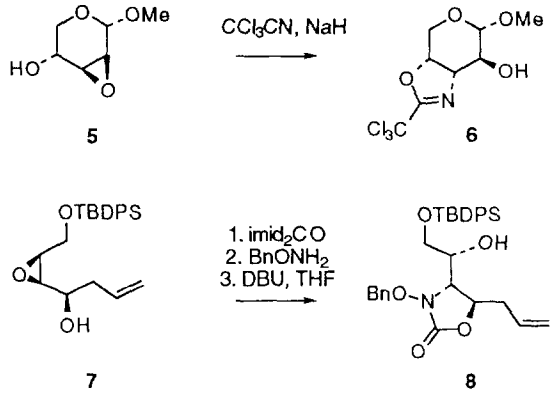
INTRODUCTION

Natural and unnatural modified nucleosides and nucleoside analogues play important roles in biology, medicine, and as biomedical research tools.[1] 5'-Triphosphate derivatives of modified nucleosides are potential precursors to chemically modified oligonucleotides prepared by *in vitro* enzymatic synthesis. Eckstein and coworkers have shown that 2'-amino-2'-deoxypyrimidine triphosphates (2'-NH_2 UTP and 2'-NH_2 CTP) are substrates for T7 RNA polymerase[2] and these triphosphates have been employed in the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process.[3] In these SELEX process examples, T7 RNA polymerase catalyzed the incorporation of 2'-NH_2 UTP and 2'-NH_2 CTP into pools of 10^{14}-10^{15} single-stranded oligonucleotides containing 30-40 nucleotide random regions from which families of high affinity oligonucleotide antagonists to human chorionic gonadotropin, basic fibroblast growth factor, and vascular endothelial growth factor were identified. By "front-loading" SELEX in this way, 2'-aminopyrimidine substituted oligonucleotides were evolved which exhibited substantially enhanced stability toward serum endonuclease degradation relative to the comparable sequences prepared with unmodified UTPs.



Scheme 1: ***The Two Modes of Nucleophilic Addition to Anhydrouridines***

We recently described a versatile synthetic methodology for preparing uridine derivatives modified at the 2'-position by an intramolecular nucleophilic derivatization of 2, 2'-*O*-anhydrouridine derivatives and report herein a detailed account of an application of this methodology that enables the preparation of structurally novel and diverse 2'-deoxy uridine derivatives substituted by 2'-(*O*-alkyl)hydroxylamines.[4] These nucleosides are precursors to modified oligonucleotides prepared by either enzymatic or automated synthesis.[5]



Scheme 2: ***Hydroxyl Directed Nucleophilic Heterocycle Opening***

Background.

Anhydronucleosides have served as versatile precursors to modified nucleosides.[6] Several 2,2'-anhydrouridine derivatives of general structure **1** (Scheme 1) are readily prepared and have served as key

intermediates in the preparation of ribose-modified uridine nucleosides, including 2'-azido-[6a,b] and 2'-phenylseleno-2'-deoxyuridines[6c] such as **2**. Nucleophilic addition to anhydropyrimidines at the 2 position of the nucleobase is also known and the tendency of amine nucleophiles toward C2 attack has been exploited in the preparation of isocytidine derivative **4** from 2'-deoxy-2,5'-anhydrouridine **3**.[7,8]

The use of a hydroxy tether to direct regioselective nucleophilic opening of a heterocycle is a well established strategy, particularly in the area of epoxy alcohol substitution.[9] Representative examples are shown in Scheme 2. Jacobson reports trichloroacetimidate opening of carbohydrate epoxide **5** under basic conditions,[9a] while Roush[9b] stereospecifically introduced nitrogen functionality adjacent to a hydroxy group by intramolecular nucleophilic epoxide opening via a hydroxy-tethered alkoxy cabamate. Many other examples might alternatively have been cited.[9c-h]

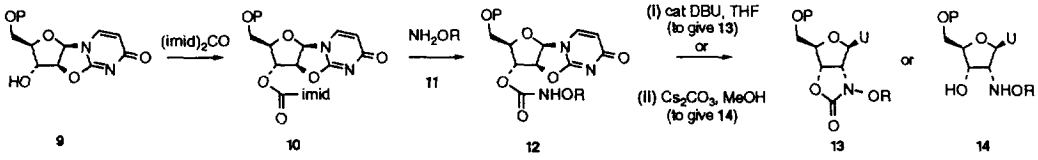
As discussed above, selective addition of amine nucleophiles to the 2-position of the nucleobase represents a problem in the synthesis of 2'-amine substituted ribouridines. Our methodology offers a useful and general solution to the regio- and stereoselective functionalization of the 2'-position by tethering latent amine nucleophiles to the 3'-OH and effecting intramolecular nucleophilic substitution of the 2'-position. By employing *O*-substituted hydroxylamines in the sequence, novel 2'-substituted nucleosides not readily available by other approaches[10] are prepared with good to excellent overall efficiency.

RESULTS AND DISCUSSION

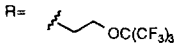
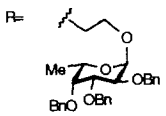
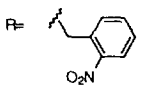
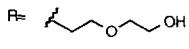
Our studies began with the preparation of 5'-*O*-protected anhydrouridine derivatives **9** (P=TBDPS, DMT; see Table). The TBDPS anhydrouridine derivative was easily prepared on a 50 gram scale and was purified by crystallization, while we found it most convenient to simply use the 5'-*O*-DMT substrate crude, directly from the tritylation reaction mixture. Elaboration of the 3'-hydroxyl as the carbonyl imidazole (with 1.05 equiv carbonyl diimidazole) resulted in conversion to the activated intermediate **10**. The acyl imidiazole intermediate was treated with hydroxylamines **11a-g** in either the free base or the hydrochloride salt forms to yield the alkoxycarbamate derivatized anhydrouridines **12a-g**. While examples of the alkoxycarbamate intermediates **12** were isolated and characterized, we found their formation to be quite efficient and often simply carried out a solvent exchange and directly subjected the crude substrates to the cyclization conditions without further purification.

Intramolecular nucleophilic addition to the 2'-position was carried out under two complementary reaction conditions. Treatment of **12a-12g** with catalytic DBU facilitated efficient, regioselective nucleophilic attack at the 2'-position, displacing the O2 leaving group. The resulting bicyclic uridine derivatives **13a-13g** were formed in good to excellent overall yields (Table). Alternatively, upon treatment of alkoxy carbamates **12a** and **12b** with Cs_2CO_3 in MeOH, initial coversion to the corresponding bicyclic products **13a** and **13b** occurred, followed by *in situ* cleavage of the 2',3'-carbonyl to afford **14a** and **14b**.

Table: ***2'-Alkoxylaminouridines Prepared by Intramolecular Ring Opening***



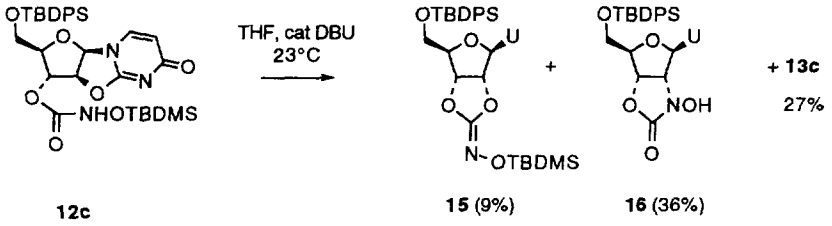
9 10 12 13 14

entry (P)	hydroxylamine 11	12 (yield)	reaction conditions	13 (yield)	14 (yield)
1 (P=TBDPS)	R= Bn (11a)	12a (93%)	i	13a (88%)	
2 (P=TBDPS)	R= Bn (11a)	12a (not isolated)	ii		14a (79%)
3 (P=TBDPS)	R= Me[a] (11b)	12b (93%)	i	13b (87%)	
4 (P=TBDPS)	11b	12b (93%)	ii		14b (68%)
5 (P=TBDPS)	R= TBDMS (11c)	12c (73%)	i	13c (27%)	
6 (P=TBDPS)	R=  11d [a,b]	12d (not isolated)	i	13d (80%)	
7 (P=TBDPS)	R=  11e [b]	12e (73%)	i	13e (89%)	
8 (P=TBDPS)	R=  11f [b]	12f (not isolated)	i	13f (62%)	
9 (P=DMT)	R=  11g [b]	12g (68%)	i	13g (75%)	

Footnotes: (a) used as the HCl salt (b) see experimental section for synthesis

The regioselectivity of the intramolecular nucleophilic attack was impressive. Only in the case of *O*-TBDMS substrate **12c** were any products resulting from 2'-nucleophilic attack by the carbonyl oxygen isolated (Scheme 3). Compared to the other less hindered *O*-alkyl substituted substrates, one might rationalize a steric destablization by the TBDMS group of the transition state for 2'-attack by the nitrogen which leads to the

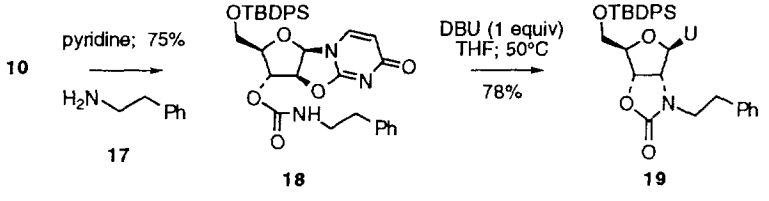
formation of minor amounts of **15** by the alternate pathway of carbonyl oxygen attack. Significant amounts of the desilylated product **16** were also formed, contributing to the low yield (27%) of **13c**.



Scheme 3

Intramolecular Nucleophilic Attack by a 3'-Carbamate Nucleophile.

We were interested in evaluating a comparable synthetic pathway wherein a 2'-N-alkylamino substituent was introduced. Phenethylamine (**17**) was employed in the substitution of imidazole intermediate **10** and, as predicted,[11] was substantially less reactive than the isosteric $BnONH_2$ (Scheme 4). Furthermore, elevated temperatures were required (compared to room temperature for the alkoxycarbamate substrate **12a**) to effect the isomerization of phenethyl carbamate **18** to uridine derivative **19**. This sequence establishes the viability of introducing 2'-alkylamino functionality by the intramolecular nucleophilic anhydronucleoside ring opening strategy which complements the above 2'-alkoxyaminouridine preparation.



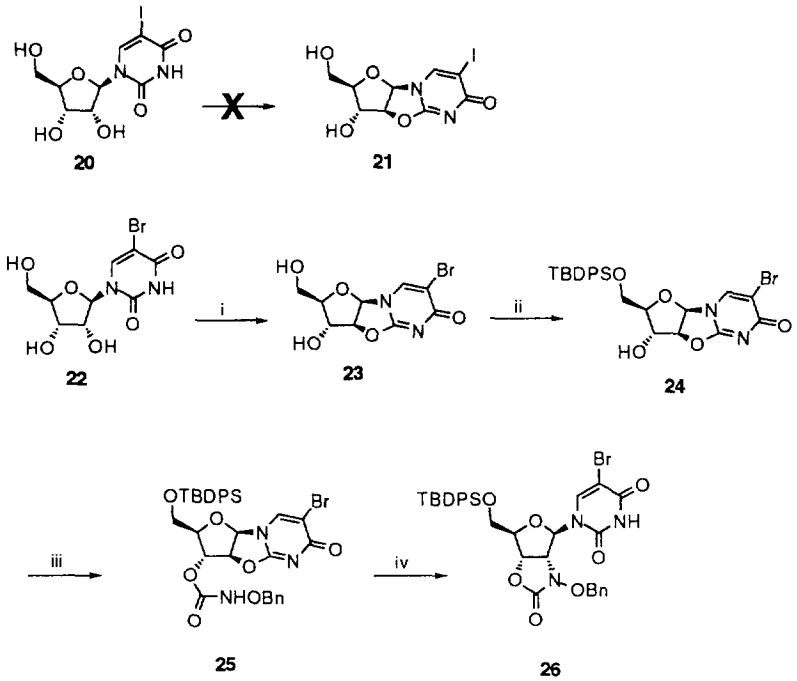
Scheme 4: ***Intramolecular Opening by a 3'-Carbamate***

Intramolecular Nucleophilic Opening of 5-Bromoanhydrouridine.

A 2'-benzyloxyamino-5-bromouridine derivative has been prepared by the intramolecular nucleophilic displacement methodology. 5-Halouridine nucleosides are important monomers for biophysical research involving photocrosslinking of oligonucleotides and proteins[12] and also represent versatile synthetic precursors to modified nucleosides and oligonucleotides via Pd(0)-catalyzed cross coupling with acetylenes,[13] and vinyl and aryl stannanes.[14] We sought to expand the scope of our methodology to the preparation of members of this useful class of nucleosides.

Our attempts to prepare 5-iodoanhydrouridine **21** were thwarted by the instability of 5-iodouridine **20** under the fairly harsh reaction conditions required for the dehydration leading to anhydronucleoside

formation,[15] therefore we focused our efforts on the 5-bromo derivative. 5-Bromo-2,2'-anhydrouridine **23** (Scheme 5) was prepared in 79% yield from 5-bromouridine **22** upon treatment with diphenylcarbonate and $NaHCO_3$ in DMF at 110°C. 5'-*O*-Silylation of **23** under standard conditions (TBDPSCl, pyridine) gave 5'-*O*-



Reagents and Conditions (i) $(C_6H_5O)_2CO$, $NaHCO_3$, DMF, 110°C; 71% (ii) TBDPSCl, pyridine; 40% (iii) CDI, pyridine, then $BnONH_2$ (iv)10 mole% DBU, THF; 64%.

Scheme 5: *5-Bromoanhydrouridine Opening*

TBDPS derivative **24** in 40% yield. 2'-Benzyloxyamine derivative **26** was prepared from compound **24** upon treatment with carbonyldiimidazole and $BnONH_2$, followed by catalytic DBU in THF in 64% overall yield. The alkoxycarbamate derivative **25** was qualitatively observed to be more reactive to intramolecular nucleophilic opening than its 5-unsubstituted analogue **12a**, as evidenced by the appearance of detectable amounts of cyclization product **26** in preparations of the anhydrouridine intermediate **25**. For this reason, isolated yields of **25** were fairly low, and more efficient overall yields of **26** were realized by simply subjecting crude **25** to the cyclization conditions.

CONCLUSION

We have developed versatile synthetic methods for the preparation structurally novel and diverse uridine nucleoside analogues. Studies establishing the scope of the synthetic method and the utility of the nucleosides prepared in this manner in biochemical systems are ongoing.

EXPERIMENTAL SECTION

5'-*O*-*tert*-Butyldiphenylsilyl-2,2'-anhydrouridine (9; P=TBDPS): To a stirred slurry of 35 g (0.15 mol) of 2,2'-anhydrouridine (**1**)[6a] in 300 mL of anyhdrous pyridine and 135 mL anhydrous DMF was added 40.1 mL (0.15 mol) of *tert*-butylchlorodiphenylsilane dropwise via syringe over 5 min. Upon stirring overnight, all solids went into solution and the reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in 800 mL CH_2Cl_2 and the cloudy solution washed with 1.2 L of saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The residue was recrystallized from EtOAc to give 45 g (63%) of product as a white chalk. Concentration of the mother liquor afforded an additional 4.8 g (6.5%) of crystalline product. **9 (P=TBDPS):** UV λmax (EtOH) 248.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.51 (m, 4H), 7.48-7.30 (m, 7H), 6.17 (d, *J* = 5.8 Hz, H1'), 6.00 (d, *J* = 7.5 Hz, H5), 5.41 (dd, *J* = 5.9, 1.8 Hz, H2'), 5.26 (d, *J* = 4.8 Hz, OH), 4.61 (m, H3'), 4.26 (dd, *J* = 10.0, 5.2 Hz, H4'), 3.62 (dd, *J* = 11.4, 5.1 Hz, H5'), 3.55 (dd, *J* = 11.4, 6.1 Hz, H5'), 0.98 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d6) δ 172.24, 160.68, 137.9, 136.0, 135.9, 133.6, 133.4, 130.9, 128.9, 109.6, 90.2, 89.4, 87.9, 74.7, 63.2, 60.3, 26.8, 19.1; Low resolution MS m/e for $C_{25}H_{29}N_2O_5Si$ ($M+1^+$)calcd 465.3, found 465.2 (M+1; 10%).

5'-*O*-(4,4'-Dimethoxytrityl)-2,2'-anhydro-1-(β-D arabinofuranosyl)uracil (9; P=DMT): A suspension of 10.1 g (0.045 mol) of 2,2'-*O*-anhydrouridine,[6a] 17.5 g (0.049 mol) of dimethoxytrityl chloride, and catalytic DMAP (~50 mg) in 100 mL of pyridine was stirred 16 h at ambient temperature. The mixture was concentrated *in vacuo* and the residue was disolved in dichloromethane and water. The organic phase was washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting foam was purified on silica gel eluting with 0-20% methanol/ ethyl acetate to afford 13.3 g (56%) of the product as a foam. **9 (P=DMT):** ^{1}H NMR (300 MHz, DMSO-*d6*) 7.96 (d, *J* = 7.4, H6), 6.84, 7.16, 7.28 (m, 13H), 6.33 (d, *J* = 5.6 Hz, H1'), 5.96 (d, *J* = 4.4 Hz, 3'-OH), 5.89 (d,*J* = 7.4 Hz, H5), 5.21 (d, *J* = 5.7 Hz,H2'), 4.31(m,H4'), 4.22 (m,H3'), 3.73 (s,3H,OCH_3), 2.81 and 2.85 (ABX, 2H ,*Jab* = 10.2 Hz, *Jax* = 4.2 Hz,*Jbx* = 1 Hz); *Anal.* Calcd for $C_{30}H_{28}N_2O_7$ /0.5 H_2O: C, 67.03; H, 5.43; N, 5.21. Found: C, 67.02; H, 5.55 ; N, 4.99.

Hydroxylamine Syntheses: Hydroxylamines **11d-g** were prepared from N-hydroxyphthalimde via alkylation with the appropriate alkyl halide or tosylate, followed by hydrazinolysis.[17] General Procedures A and B, respectively, describe these steps.

General Procedure A: N-Hydroxyphthalimide Alkylation: To a stirred solution of 1 mmol of N-hydroxyphthalimide in 50-100 mL of DMF was added 1 mmol of base (either NaOAc or DBU). To this dark red solution was added 1 mmol of an alkyl halide or tosylate. The reaction mixture was heated to 80°C for 16 h, during which time it became pale yellow. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc. The organic phase was washed with saturated $NaHCO_3$ solution until the aqueous phase was colorless, then dried over Na_2SO_4, and concentrated. The crude products were purified by silica gel chromatography or used directly without further purification.

N-*o*-Nitrobenzyloxyphthalimide: Prepared in ca. 80% yield from 7.56 g (0.046 mol) of N-hydroxyphthalimide, 3.80 g (0.046 mmol) of NaOAc, and 10.0 g (0.046 mol) of *o*-nitrobenzylbromide. The crude material contained approximately 7% of an impurity tentatively assigned as *o*-nitrobenzylacetate and was used without further purification. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.13 (d, J=1.2 Hz, 1H), 7.92-7.77 (m, 6H), 7.70-7.64 (m, 1H), 5.55 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 164.0, 148.9, 135.6, 134.6, 132.1, 130.9, 130.7, 129.2, 125.6, 124.0, 75.8.

N-2-(2-Hydroxyethoxy)ethoxyphthalimide: Prepared from 11.18 g (0.069 mol) of N-hydroxyphthalimide, 10.2 mL (0.069 mol) of DBU, and 17.84 g (0.069 mol) of di(ethylene glycol) *p*-toluenesulfonate. This material was purified by silica gel chromatography (eluting with hexanes, then 70% EtOAc/ hexanes) to afford 8.9 g (52%) as a white solid. mp 100-101°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.79 (m, 2H), 7.76-7.68 (m, 2H), 4.38-4.35 (m, 2H), 3.86-3.80 (m, 2H), 3.68-3.39 (m, 4H), 2.53 (br t, J=5.5 Hz, 1H).^{13}C NMR (75 MHz, DMSO-d6) δ 168.4, 140.0, 133.9, 128.5, 81.9, 77.6, 73.9, 65.3; *Anal.* Calcd for $C_{12}H_{13}NO_5$: C, 57.36; H, 5.21; N, 5.56. Found: C, 57.21; H, 5.41; N, 5.53.

General Procedure B: Hydrazinolysis of N-Alkoxyphthalimides to give Hydroxylamines 11d-g: To a stirred solution of 1 mmol of the phthalimide derivative in EtOH or dichloromethane was added ca. 1 mmol of hydrazine hydrate. A white solid precipitated and the mixture was stirred 1 h. The solids were filtered and the filtrate was dried over Na_2SO_4 and concentrated. If solids result, these are washed with dichloromethane and filtered. The filtrate was concentrated and the crude hydroxylamine derivatives were either converted to the corresponding HCl salt, purified by silica gel chromatography, or used directly without further purification.

N-2-Perfluoro-*tert*-butyloxyethoxylamine hydrochloride (11d): Prepared from 4.6 g (10.8 mmol) of N-2-perfluoro-*tert*-butyloxyethoxyphthalimide[16] in 30 mL of dichloromethane and 0.92 mL of hydrazine hydrate. A dichloromethane solution of crude **11d** was treated with concentrated HCl to afford 2.5 g (70%) of **11d•HCl**. ^{1}H NMR (300Mz; DMSO-*d6*) δ 4.33 (br d). *Anal.* Calcd for $C_6H_7NO_2F_9Cl$: C, 21.73; H, 2.13; N, 4.22. Found: C, 21.31; H, 2.29 ; N, 4.92.

N-2-α-(2,3,4-Tri-*O*-benzyl-L-fucopyranosyloxy)ethoxylamine (11e): Prepared from 2.22 g (3.56 mmol) of N-2-(α-2,3,4-tri-*O*-benzyl-L-fucopyranosyloxy)ethoxyphthalimide[18] and 0.2 mL (ca. 3.5 mmol) of hydrazine hydrate in 30 mL of 95% EtOH and 5 mL of dichloromethane. The crude product **11e** (1.7 g; 97%) was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 15H), 5.43 (br hump), 4.89 (d, J=11.5 Hz, 1H), 4.88-4.71 (overlapping benzyllic protons and H1, 5H), 4.65 (d, *J* = 11.43 Hz, 1H), 4.04 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.98-3.67 (m, 5H), 1.11 (d, *J* = 6.6 Hz, 3H).

***o*-Nitrobenzyloxylamine hydrochloride (11f•HCl):** Prepared from 12.92 g (0.043 mol) of N-*o*-nitrobenzyloxylphthalimide and 2.45 mL of hydrazine hydrate in EtOH. This intermediate was isolated as the HCl salt. **11f•HCl:** ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.19 (bs, 2H), 8.15-8.12 (m, 1H), 7.87-7.81 (m, 1H), 7.73-7.65 (m, 2H), 5.41 (s, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 135.1, 130.8, 130.3, 125.6, 72.3. *Anal.* Calcd for $C_4H_{11}O_3N$ (**11f**): C, 50.00; H, 4.80; N, 16.66. Found: C, 49.90; H, 4.93; N, 16.61.

2-(2-Hydroxyethoxy)ethoxylamine (11g): Prepared in 72% yield from 1.67 g of N-2-(2-hydroxyethoxy)ethoxyphthalimide and 4.6 mL of hydrazine hydrate in 50 mL of MeOH. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 5.98 (br s, 2H), 4.60, (t, *J* = 5.2 Hz, 1H), 3.64-3.61 (m, 2H), 3.53-3.50 (m, 2H), 3.48-3.45 (m, 2H), 3.41-3.38 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d6) δ 79.4, 77.6, 73.9, 65.5; *Anal.* Calcd for $C_4H_{11}O_3N$: C, 39.66; H, 9.15; N, 11.56. Found: C, 39.51; H, 9.23; N, 11.46.

General Procedure C: Conversion of anhydrouridine derivatives 9 to alkoxycarbamates 12: To a stirred solution of 1 mmol of **9** in 10 mL of pyridine was added 1.05 mmol of 1,1' carbonyldiimidazole. After conversion of **9** to **10** (as determined by ^{1}H NMR analysis of concentrated aliquots, generally 2-20 h), 1.1-1.6 mmol of hydroxylamine **11** was added. After conversion of **10** to **12** (by ^{1}H NMR analysis, generally 2-20 h), the mixture was concentrated *in vacuo* and the residue either purified by silica gel column chromatography (eluting with MeOH/ EtOAc gradients from 0-20% unless otherwise specified) or used directly without purification in General Procedures D or E (*vida infra*). Signals characteristic of the acyl imidazole intermediate **10; P=TBDPS**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, *J* = 5.7 Hz, H1'), 5.98 (d, *J* = 7.5 Hz, H5), 5.73 (br d, *J* = 2.1 Hz, H3'), 5.55 (br d, *J* = 5.7 Hz, H2'), 4.51 (m, *J* = 6.5, 2.2 Hz, H4'), 3.68 (dd, *J* = 11.3, 6.0 Hz, H5'), 3.56 (dd, *J* = 11.3, 7.1 Hz, H5').

General Procedure D: Conversion of alkoxycarbamate anhydrouridine derivatives 12 to uridine derivatives 13: To a stirred, 23 °C solution of 1 mmol of the alkoxycarbamate anhydrouridine **12** in 10 mL of THF was added 0.1 mmol of DBU. The mixture was stirred until complete conversion to the higher Rf product **13** was observed (by TLC analysis), then concentrated *in vacuo*. The crude residue was dissolved in EtOAc and the organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The crude residue was purfied by flash silica gel chromatography (typically eluting with EtOAc/ hexanes gradients from 10-100%).

General Procedure E: Conversion of alkoxycarbamate anhydrouridine derivatives 12 to uridine derivatives 14: To a stirred, 23 °C solution of 1 mmol of the alkoxycarbamate anhydrouridine **12** in 10 mL of MeOH was added 2 mmol of Cs_2CO_3. The mixture was stirred until complete conversion to the higher Rf product was observed (by TLC analysis), then concentrated *in vacuo*. The crude residue was dissolved in EtOAc and the organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. The crude residue was purfied by flash silica gel chromatography (typically eluting with EtOAc/ hexanes gradients from 10-100%).

3'-*O*-(Benzyloxyamino)carbonyl-5'-*O*-*tert*-butyldiphenylsilyl-2,2'-*O*-anhydrouridine (12a): Prepared from 10 g (21.5 mmol) of **9; P=TBDPS** and 2.9 g (23.58 mmol) of **11a** according to General procedure C in 93% yield. Data for **12a**: mp 107.2-108.8 °C; UV λmax (EtOH) 248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (br s, NH), 7.55 (m, 4H), 7.41-7.25 (m, 11H), 7.26 (s, 1H), 7.25 (d, *J* = 7.6 Hz, H6), 6.12 (d, *J* = 5.7 Hz, H1'), 5.93 (d, *J* = 7.5 Hz, H5), 5.43 (br d, *J* = 2.0 Hz, H3'), 5.29 (br d, *J* = 5.6 Hz, H2'), 4.88 (s, 2H, OCH$_2$Ph), 4.32 (dt, *J* = 6.3, 2.1 Hz, H4'), 3.51 (dd, *J* = 11.3, 6.3 Hz, H5'), 3.50 (dd, *J* = 11.2, 6.4 Hz, H5'), 1.01 (s, 9H). *Anal.* Calcd for $C_{33}H_{35}O_7N_3Si$: C, 64.58; H, 5.75; N, 6.85. Found: C, 63.94; H, 5.81; N, 6.85.

5'-*O*-*tert*-Butyldiphenylsilyl-3'-*O*-(methoxyamino)carbonyl-2,2'-*O*-anhydrouridine (12b): Prepared from 0.85 g (1.83 mmol) of **9; P=TBDPS** and 0.17 g (2.04 mmol) of **11b** according to General Procedure C in 93% yield. Data for **12b:** mp 161.4-163.1 °C. UV λmax (EtOH) 248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.57-7.52 (m, 4H), 7.37-7.30 (m, 7H), 6.28 (d, *J* = 5.6 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 5.45-5.42 (overlapping signals, 2H), 4.36 (dt, *J* = 5.9, 2.7 Hz, 1H), 3.72 (s, 3H), 3.56 (d, *J* = 5.9 Hz, 2H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 159.5,. 155.6, 135.4, 135.1, 132.78, 132.4, 128.0, 127.9, 127.8, 110.0, 90.1, 87.0, 64.6, 62.8, 26.7, 19.1. *Anal.* Calcd for $C_{27}H_{31}O_7N_3Si$: C, 60.30; H, 5.81; N, 7.82. Found: C, 59.70; H, 5.70; N, 7.59.

3'-*O*-(*t*-Butyldimethylsilyloxylamino)carbonyl-5'-*O*-*tert*-butyldiphenylsilyl-2,2'-*O*-anhydrouridine (12c): Prepared from 5.0 g (11 mmol) of **9; P=TBDPS** and 2.97 g (19.9 mmol) of **11c** according to General Procedure C in 73% yield. Data for **12c:** UV λmax (EtOH) 251; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.46 (br s, NH), 7.93 (d, *J* = 7.5 Hz, H6), 7.55-7.31 (m, 10H), 6.38 (d, *J* = 5.7 Hz, H1'), 5.89 (d, *J* = 7.5 Hz, H5), 5.28 (d, *J* = 5.7 Hz, H2'), 5.40 (d, *J* = 3.2 Hz, H3'), 4.35 (m, H4'), 3.59 (dd, *J* = 11.3, 5.3 Hz, H5'), 3.50 (dd, *J* = 11.3, 6.4 Hz, H5'), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); *Anal.* Calc'd for $C_{32}H_{43}N_3O_7Si_2$: C, 60.27; H, 6.79; N, 6.59. Found: C, 59.16; H, 6.89; N, 6.63.

Fucosylanhydrouridine 12e: Prepared from 1.6 g (3.46 mmol) of **9; P=TBDPS** and 1.7 g (3.63 mmol) of **11e** according to General procedure C in 73% yield: Data for **12e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 7.62 (m, 4H), 7.48-7.35 (m, 20H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.85 (br d, *J* = 4.9 Hz, 1H), 5.43 (br s, 1H), 5.13 (br d, *J* = 5.3 Hz, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.94 (d, *J* = 11.7

Hz, 1H), 4.94 (d, *J* = 3.7 Hz, 1H), 4.84 (s, 2H), 4.82 (d, *J* = 10.5 Hz, 1H), 4.74 (d, *J* = 11.5 Hz, 1H), 4.27-3.95 (m, 7H), 3.82-3.79 (m, 2H), 3.56 (d, *J* = 6.2 Hz, 2H), 1.23 (d, J=6.5 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 159.1, 154.5, 138.5, 138.2, 137.8, 135.4, 135.3, 134.4, 132.4, 129.9, 128.4-127.1 (overlapping signals), 110.2, 99.0, 89.8, 86.5, 79.7, 76.0, 75.1, 74.9, 73.8, 72.9, 68.6, 66.8, 62.6, 26.6, 19.0, 16.6. *Anal.* Calcd for $C_{55}H_{61}N_3O_{12}Si$: C, 67.10; H, 6.25; N, 4.27. Found: C, 66.62; H, 6.26; N, 4.79.

5'-*O*-(4,4'-Dimethoxytrityl)-3'-*O*-[2-(2-hydroxyethoxy)ethoxyamino]carbonyl-2,2'-*O*-anhydrouridine (12g): Prepared in ca. 90% purity from 0.93 g (2 mmol) of **9; P=DMT** and 0.56 g (3.2 mmol) of **11g** according to General procedure C in 68% yield. This product was purified by silica gel column eluting with MeOH/ dichloromethane/ triethylamine (3:96:1 then 10:89:1): UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.29-7.20 (m, 18H), 6.80 (d, *J* = 7.5 Hz, 4H), 6.18 (d, *J* = 5.6 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 5.35 (br s, 2H), 4.86 (br t, *J* = 6.2 Hz, 1H), 4.86 (br t, *J* = 6.2 Hz, 1H), 4.09-4.06 (m, 2H), 3.79 (s, 6H), 3.79-3.74 (m, 4H), 3.65-3.63 (m, 2H), 3.04 (dd, *J* = 6.9, 2.1 Hz, 2H). Low resolution MS m/e calcd for $C_{35}H_{38}N_3O_{11}$ (M+1+) 676.8, found 676.6 (100%).

2'-Benzyloxyamino-5'-*O*-*tert*-butyldiphenylsilyl-2'-*N*, 3'-*O*-carbonyl-2'-deoxyuridine (13a): Prepared in 88% yield from 0.49 g (0.8 mmol) of **12a** according to General procedure D. Data for **13a**: UV λmax (EtOH) 257.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (br s, NH), 7.68-7.56 (m, 4H), 7.49-7.32 (m, 11H), 6.78 (d, *J* = 8.1 Hz, H6), 5.43 (dd, *J* = 8.1, 1.9 Hz, H5 [w/ D_2O this signal was observed as a doublet, *J* = 8.1]), 5.16 (d, *J* = 2.1 Hz, H1'), 5.09 (dd, *J* = 8.1, 5.0 Hz, H3'), 5.08 (d, *J* = 11.6 Hz, OCH_2Ph), 5.02 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.23 (dd, *J* = 8.1, 2.1 Hz, H2'), 4.18 (q, *J* = 4.7 Hz, H4'), 3.91 (dd, *J* = 11.3, 4.2 Hz, H5'), 3.81 (dd, *J* = 11.4, 4.5 Hz, H5'), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 158.1, 150.4, 142.7, 136.5, 136.3, 136.1, 133.4, 133.0, 130.8, 130.0, 129.7, 128.6, 103.2, 92.1, 86.6, 78.7, 76.4, 67.7, 63.5, 26.9, 19.3.*Anal.* Calcd for $C_{33}H_{35}O_7N_3Si$: C, 64.58; H, 5.75; N, 6.85. Found: C, 64.78; H, 5.88; N, 7.18.

5'-*O*-*tert*-Butyldiphenylsilyl-2'-*N*, 3'-*O*-carbonyl-2'-deoxy-2'-methoxyaminouridine (13b): Prepared in 87% yield from 6.5 mmol of **12b** according to General procedure D. Data for **13b**, X=CO UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.65-7.62 (m, 4H), 7.49-7.40 (m, 6H), 6.04 (br s, 1H), 5.61 (br d, *J* = 9.0 Hz, 1H), 5.16 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.88 (d, *J* = 8.5 Hz, 1H), 4.25 (q, *J* = 5.5 Hz, 1H), 3.99-3.89 (m, 2H), 3.83 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 158.1, 150.4, 142.7, 136.4, 136.2, 136.0, 133.4, 133.0, 130.8, 130.7, 130.0, 129.7, 128.5, 103.2, 92.1, 86.6, 67.7, 63.5, 53.7, 26.9, 19.2. Low resolution MS m/e calcd for $C_{27}H_{32}N_3O_7Si$ (M+1+) 538.4, found 538.2 (2%).

2'-(*tert*-Butyldimethyl)silyloxylamino-5'-*O*-*tert*-butyldiphenylsilyl-2'-*N*, 3'-*O*-carbonyl-2'-deoxyuridine (13c): Prepared in 27% yield from 3.0 g (4.7 mmol) of **12c** according to General procedure

D. Data for **13c**, X=CO: mp 94-96°C; UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, DMSO-d6) δ 11.52 (s, 1H), 7.68-7.61 (m, 5H), 7.49-7.41 (m, 6H), 6.11 (d, *J* = 4.6 Hz, 1H), 5.53 (d, *J* = 8.0 Hz, 1H), 5.19 (dd, *J* = 7.8, 3.7 Hz, 1H), 4.69 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.29 (q, *J* = 4.7 Hz, 1H), 3.91-3.86 (m, 2H), 1.01 (s, 9H), 0.85 (s, 9H), 0.138 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 164.3, 158.0, 150.3, 141.9, 136.2, 136.0, 133.5, 133.0, 132.7, 130.9, 130.8, 128.7, 128.6, 103.7, 90.6, 86.1, 76.5, 67.6, 63.6, 27.0, 25.7, 19.3, 17.8, 0.5; *Anal.* Calc'd for $C_{32}H_{43}N_3O_7Si_2$: C, 60.27; H, 6.79; N, 6.59. Found: C, 59.11; H, 6.66; N, 6.33. Also isolated from the reaction mixture were regioisomer **15** in 9% yield and the desilylated product **16** in 36% yield: Data for **15**: ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.46 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.63-7.59 (m, 4H), 7.47-7.36 (m, 6H), 5.98 (br s, 1H), 5.74 (br d, *J* = 6.7 Hz, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 5.39 (dd, *J* = 6.6, 4.35 Hz, 1H), 4.27 (q, *J* = 5.3 Hz, 1H), 3.92 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.83 (dd, *J* = 10.7, 6.8 Hz, 1H), 0.98 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 164.2, 160.4, 150.7, 143.5, 136.3, 136.1, 133.5, 133.2, 130.7, 128.5, 128.4, 103.6, 94.6, 87.1, 86.5, 81.8, 63.8, 26.8, 26.3, 19.2, 18.4, -5.5; *Anal.* Calc'd for $C_{32}H_{43}N_3O_7Si_2$: C, 60.27; H, 6.79; N, 6.59. Found: C, 59.39; H, 6.93; N, 6.28. Data for de-TBDMS product **16:** mp 219-220°C; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.53 (s, 1H), 10.25 (s, 1H), 7.65-7.59 (m, 5H), 7.47-7.36 (m, 6H), 5.90 (br s, 1H), 5.52 (d, 7.95H), 5.17 (dd, *J* = 8.07, 5.55 Hz, 1H), 4.69 (br d, 8.8H), 4.19 (q, *J* = 5.3 Hz, 1H), 3.92-3.83 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d6) δ 164.1, 157.1, 151.0, 143.9, 135.9, 135.8, 133.5, 133.2, 130.7, 128.7, 128.6, 102.7, 91.3, 86.5, 79.6, 67.9, 64.0, 26.7, 18.9; *Anal.* Calc'd for $C_{26}H_{29}N_3O_7Si$: C, 59.64; H, 5.58; N, 8.02. Found: C, 59.41; H, 5.61; N, 7.85.

5'-*O*-(t-Butyldiphenylsilyl)-2'-*N*, 3'-*O*-carbonyl-2'-deoxy-2'-[*O*-(2-perfluoro-*tert*-butyloxyethyl)]hydroxylaminouridine (13d): Prepared in 80% yield from 2.88 g (6.2 mmol) of **9; P=TBDPS** and 2.46 g (7.42 mmol) of **11d•HCl** according to General procedures C then D. UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, CDCl3) δ 7.64-7.60 (m, 4H), 7.44-7.37 (m, 7H), 6.02 (d, *J* = 2.0 Hz, 1H), 5.53 (d, *J* = 8.1 Hz, 1H), 5.20 (dd, *J* = 8.4, 5.3 Hz, 1H), 4.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.43-4.24 (m, 5H), 4.10 (m, 1H), 4.04 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.91 (dd, *J* = 11.6, 3.9 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 162.8, 160.3, 149.7, 140.4, 135.5, 135.3, 132.6, 132.0, 130.2, 130.1, 128.0, 127.9, 120.2 (q, J=291 Hz), 103.2, 90.7, 85.9, 79.5 (m), 75.2, 74.8, 67.7, 67.6, 62.7, 26.8, 19.3; Low resolution MS m/e calc'd for $C_{32}H_{33}N_3O_8F_9Si$ ($M+1^+$): 786.7; Found 786.4 (18%).

Fucosyluridine 13e: Prepared from 330 mg (0.34 mmol) of **12e** in 89% yield according to General procedure D. Data for **13e:** UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, CDCl3) δ 7.61-7.57 (m, 4H), 7.38-7.15 (m, 21H), 6.09 (br s, 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 5.13 (dd, *J* = 8.2, 5.9 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 3.7 Hz, 1H), 4.73-4.62 (overlapping benzyllic signals, 5H), 4.46 (br d, *J* = 8.5 Hz, 1H), 4.31 (m, 2H), 4.24 (m, 1H), 4.05 (dd, J=10.1, 3.6 Hz, 1H), 3.97-3.81 (m, 5H), 3.68 (br d, *J* = 2.1 Hz, 1H), 3.60 (dd, *J* = 11.6, 4.4 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 163.2, 156.8, 149.7, 149.6, 141.6, 138.6, 138.4, 138.1, 135.4, 135.3, 132.7, 132.2, 130.0, 128.3-123.7 (several overlapping signals), 123.7, 102.6, 97.6, 90.3, 85.8, 79.2, 76.5, 75.0, 74.8, 74.6,

73.4, 73.0, 68.1, 66.5, 65.6, 62.5, 26.7, 19.2, 16.6. *Anal.* Calcd for $C_{55}H_{63}N_3O_{13}Si$ (**13e**+H_2O): C, 65.90; H, 6.34; N, 4.20. Found: C, 66.87; H, 6.46; N, 4.02.

5'-*O*-*tert*-Butyldiphenylsilyl-2'-deoxy-2'-*N*, 3'-*O*-carbonyl-2'-(*o*-nitrobenzyloxy)-aminouridine (13f): Prepared in 62% yield from 5.0 g (10.78 mmol) of **9; P=TBDPS** and 1.99 g (11.86 mmol) of **11f** according to General procedures C and D. UV λmax (EtOH) 257; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 11.45 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.78-7.76 (m, 2H), 7.65-7.60 (m, 6H), 7.48-7.39 (m, 6H), 5.99 (d, *J* = 1.7 Hz, 1H), 5.57 (d, *J* = 8.0 Hz, 1H), 5.43 (dd, *J* = 12.5, 9.8 Hz, 2H), 5.15 (dd, *J* = 8.2, 5.4 Hz, 1H), 4.87 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.25 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.94-3.82 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 164.0, 156.8, 151.0, 150.5, 148.7, 143.9, 135.8, 135.8, 134.6, 133.4, 133.2, 131.6, 130.9, 130.7, 128.7, 128.6, 125.5, 102.5, 91.6, 85.8, 77.6, 74.0, 65.6, 63.9, 26.6, 18.8. *Anal.* Calcd for $C_{33}H_{33}N_4O_9Si$: C, 60.26; H, 5.06; N, 8.52. Found: C, 60.16; H, 5.39; N, 8.65.

5'-*O*-(4,4'-Dimethoxytrityl)-2'-*N*, 3'-*O*-carbonyl-2'-[2-(2-hydroxyethoxy)ethoxyamino]-uridine (13g): Prepared in 75% overall yield from 5 mmol of **9; P=DMT** and 0.91 g (7.5 mmol) of **11g** according to General Procedures C and D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (br s, 1), 7.63 (d, *J* = 8.1 Hz, 1H), 7.35-7.24 (m, 11H), 6.83 (d, *J* = 8.6 Hz, 4H), 6.19 (d, *J* = 1.5 Hz, 1H), 5.46 (d, *J* = 8.1 Hz, 1H), 5.18 (dd, *J* = 8.2, 5.6 Hz, 1H), 4.60 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.33-4.29 (m, 3H), 3.79 (s, 6H), 3.79-3.71 (m, 4H), 3.62-3.57 (m, 2H), 3.57-3.52 (m, 2H), 2.58 (q, *J* = 7.2 Hz, TEA), 1.04 (t, *J* = 7.2 Hz, TEA). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 158.7, 156.8, 150.2, 144.1, 141.1, 135.1, 134.9, 130.1, 130.0, 128.0, 127.2, 113.7, 113.3, 103.1, 90.0, 87.0, 85.1, 75.9, 75.2, 72.5, 68.4, 67.7, 62.2, 61.4, 55.2, 45.9; Low resolution MS m/e calcd for $C_{35}H_{38}N_3O_{11}$ (M+1+) 676.8, found 676.4 (55%).

2'-Benzyloxyamino-5'-*O*-*tert*-butyldiphenylsilyl-2'-deoxyuridine (14a): Prepared in 79% yield from 0.4 g (0.65 mmol) of **12a** and 0.49 g (1.5 mmol) of Cs_2CO_3. Data for **14a:** UV λmax (EtOH) 263; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.66-7.64 (m, 4H), 7.47-7.27 (m, 11H), 5.99 (d, *J* = 7.0 Hz, 1H), 5.49 (d, *J* = 8.0 Hz, 1H), 4.71 (m, 2H), 4.30 (br d, *J* = 2.7 Hz, 1H), 4.14 (br s, 1H), 3.80 (br d, *J* = 12.0 Hz, 1H), 3.63 (br d, *J* = 12.1 Hz, 1H), 3.63 (br t, 1H), 3.19 (s, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 150.9, 139.8, 136.7, 135.6, 135.3, 132.6, 132.0, 130.1, 128.8, 128.5, 128.3, 128.0, 102.7, 86.8, 85.4, 70.5, 68.5, 64.0, 27.0, 19.3; Low resolution MS m/e calc'd for $C_{32}H_{37}N_3O_6Si$ ($M+1^+$): 588.4; Found 588.2 (23%).

5'-*O*-*tert*-Butyldiphenylsilyl-2'-deoxy-2'-methoxyaminouridine (14b): Prepared in 68% yield from 0.85 g (1.6 mmol) of **12b** and 1.05 g (3.2 mmol) of Cs_2CO_3 according to General procedure E. Data for **14b:** UV λmax (EtOH) 263; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.65-7.61 (m, 4H), 7.44-7.38 (m, 6H), 6.42 (d, *J* = 5.22 Hz, 1H), 6.01 (d, *J* = 6.7 Hz, 1H), 5.48 (d, *J* = 8.1 Hz, 1H), 4.39 (dd, *J* = 5.5, 2.7 Hz, 1H), 4.15 (br d, *J* = 2.4 Hz, 1H), 3.99 (dd, *J* = 11.8, 2.2 Hz, 1H), 3.83 (dd, *J* = 11.8, 2.4 Hz, 1H), 3.72 (q, *J* = 5.6 Hz, 1H), 3.60 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3,

150.9, 139.8, 135.6, 135.3, 132.6, 132.0, 130.2, 130.1, 128.0, 102.6, 86.8, 85.5, 70.4, 68.1, 64.0, 62.3, 26.9, 19.3. *Anal.* Calcd for $C_{26}H_{33}O_6N_3Si$: C, 61.00; H, 6.50; N, 8.21. Found: C, 60.70; H, 6.22; N, 8.21.

5'-*O*-*tert*-Butyldiphenylsilyl-3'-*O*-(*N*-phenethylamino)carbonyl-2,2'-*O*-anhydrouridine (18): To a stirred solution of 3.0 g (6.5 mmol) of **9** (P=TBDPS) in 30 mL of pyridine was added 1.56 g (9.7 mmol) of carbonyldiimidazole. The mixture was stirred overnight, then 1.2 mL (9.7 mmol) of phenethylamine was added. After 72 h, the reaction mixture was concentrated *in vacuo* to afford a tan paste. This residue was dissolved in EtOAc and the organic phase was washed with 0.5N HCl, water, and brine, dried over Na_2SO_4 and concentrated. The product was recrystallized from EtOAc to afford 3.0 g (75%) of **18** as a white solid. UV λmax (EtOH) 248; ^{1}H NMR (300 MHz, DMSO-*d6*, measured at 313 K) δ 7.90 (d, *J* = 7.4 Hz, 1H), 7.56-7.54 (m, 4H), 7.46-7.38 (m, 6H), 7.29-7.19 (m, 5H), 6.38 (d, *J* = 5.6 Hz, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 5.45 (d, *J* = 5.5 Hz, 1H), 5.34 (br s, 1H), 4.31 (br m, 1H), 3.61 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.51 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.32-3.25 (m, 2H), 2.77 (br t, *J* = 7.2 Hz, 2H), 0.95 (s, 9H); *Anal.* Calcd for $C_{34}H_{37}N_3O_6Si$: C, 66.75; H, 6.09; N, 6.86. Found: C, 66.67; H, 5.97; N, 6.81.

5'-*O*-*tert*-Butyldiphenylsilyl-2'-*N*,3'-*O*-carbonyl-2'-deoxy-2'-(N-phenethyl)aminouridine (19): To a stirred solution of 0.61 g (1 mmol) of **18** in 5 mL of THF was added 0.05 mL of DBU (0.3 mmol) and the mixture was heated to reflux. After 48 h, the reaction was diluted with EtOAc and the organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified on a column of 150 mL of silica gel (eluting with 10% hexane in EtOAc). The product was recrystallized from hexane/ EtOAc to afford 476 mg (78%) of the product as a white solid. mp 159-160 °C; UV λmax (EtOH) 260; ^{1}H NMR (300 MHz, DMSO-*d6*, measured at 313 K) δ 11.42 (s, 1H), 7.65-7.59 (m, 5H), 7.48-7.40 (m, 6H), 7.30-7.19 (m, 5H), 5.92 (d, *J* = 1.9 Hz, 1H), 5.53 (d, *J* = 8.0 Hz, 1H), 5.02 (dd, *J* = 8.6, 5.0 Hz, 1H), 4.49 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.21 (dd, *J* = 9.7, 4.8 Hz, 1H), 4.00-3.88 (m, 2H), 3.71-3.61 (m, 1H), 3.53-3.44 (m, 1H), 2.94-2.78 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, DMSO-*d6*, measured at 313 K) δ 163.0, 155.9, 150.2, 141.3, 138.6, 135.1, 135.0, 132.7, 132.5, 129.9, 128.5, 128.4, 127.9, 127.8, 126.3, 102.0, 90.5, 85.8, 75.9, 64.3, 63.4, 44.2, 32.8, 26.6, 18.8. *Anal.* Calcd for $C_{34}H_{37}N_3O_6Si$: C, 66.75; H, 6.09; N, 6.86. Found: C, 66.46; H, 5.92; N, 6.67.

5-Bromo-2,2'-anhydrouridine (23): A solution of 1.0 g (3 mmol) of 5-bromouridine (**22**) in DMF was treated with 0.73 g (3.4 mmol) of diphenylcarbonate and the mixture was heated to 80°C. After 5 minutes, 25 mg (0.28 mmol) of $NaHCO_3$ was added. After 2 h, TLC indicated complete conversion of **3** and the reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to afford a tan oil. This residue was dissolved in methanol and the solution refluxed for 2-3 h. The crude residue was adsorbed on silica gel and purified by flashing through a column of silica gel eluting with MeOH/ dichloromethane (2:8). Concentration of the fractions containing product gave 0.65 g (71%) of **23** as a white foam. UV λmax (EtOH) 266; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.48 (s, 1H, H6), 6.31 (d, *J* = 5.8 Hz, 1H, H1'), 5.89 (d, *J* = 4.4 Hz, 1H), 5.23

(d, J = 5.8 Hz, 1H, H2'), 5.00 (t, J = 5.1 Hz, 1H), 4.40 (d, J = 4.0 Hz, 1H), 4.13-4.11 (m, 1H), 3.31-3.27 (m, 2H), 3.18 (d, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 166.4, 160.0, 137.4, 106.3, 91.1, 90.5, 90.3, 75.5, 61.4; Low resolution MS m/e calc'd for $C_9H_9BrN_2O$ (M+): 304.0; Found 304.8.

5-Bromo-5'-*O*-*tert*-butyldiphenylsilyl-2,2'-*O*-anhydrouridine (24): To a stirred solution of 7.0 g (23 mmol) of **23** in 20 mL of pyridine was added 6.6 mL (25.3 mmol) of TBDPSCl. The mixture was stirred at ambient temperature overnight, then concentrated *in vacuo*. The crude oil residue was dissolved in CH_2Cl_2 and washed with 0.5 N HCl solution (twice), water, and brine. The crude residue was combined with another batch prepared in the same manner from 6.8 g (22.3 mmol) of **23** and 6.4 mL (24.5 mmol) of TBDPSCl, adsorbed on silica gel and purified by flashing through a column of silica gel eluting with hexanes/ EtOAc (8:2) then EtOAc. Concentration of the product containing fractions gave 9.93 g (40%) of **24** as a white solid. An analytical sample was prepared by recrystallization from boiling methanol. Data for **24**: mp 160-162°C; UV λmax (EtOH) 266; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.59 (s, 1H), 7.54-7.40 (m, 10H), 6.33 (d, J = 5.8 Hz, 1H), 6.04 (d, J = 4.8 Hz, 1H), 5.31 (d, J = 5.5 Hz, 1H), 4.44 (br d, 1H), 4.21 (m, 1H), 3.63 (dd, J = 11.7, 4.4 Hz, 1H), 3.46 (dd, J = 11.4, 6.6 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.2, 159.5, 137.4, 135.5, 135.4, 133.1, 132.9, 130.5, 128.5, 106.8, 90.4, 90.1, 88.0, 74.5, 63.2, 27.0, 19.3; Low resolution MS m/e calc'd for $C_{31}H_{43}BrSiO_5N_3$ (M+Et_3NH^+): 644.3; Found 644.1. *Anal.* Calc'd for $C_{25}H_{27}BrN_2O_5Si$: C, 55.25; H, 5.00; N, 5.16. Found: C, 55.02; H, 5.10; N, 5.11.

5-Bromo-3'-*O*-benzyloxylaminocarbonyl-5'-*O*-*tert*-butyldiphenylsilyl-2,2'-*O*-anhydrouridine (25): To a stirred solution of 0.28 g (0.5 mmol) of **24** in 2 mL of pyridine was added 0.09 g (0.53 mmol) of CDI. The mixture was stirred overnight, then 0.07 g (0.55 mmol) of **11a** was added. After 3 days, the mixture was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution, water, and brine, then concentrated *in vacuo*. The crude residue was adsorbed on silica gel and purified by flashing through a column of silica gel eluting with EtOAc. Concentration of the product containing fractions gave 0.165 g (51%) of **25** as a white foam. UV λmax (EtOH) 227, 263; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.89 (br s, 1H), 8.61 (s, 1H), 7.55-7.39 (m, 15H), 6.39 (d, J = 5.6 Hz, 1H), 5.55 (d, J = 6.0 Hz, 1H), 5.39 (d, J = 3.0 Hz, 1H), 4.81 (s, 2H), 4.39 (m, 1H), 3.66 (dd, J = 11.9, 4.5 Hz, 1H), 3.48 (dd, J = 11.5, 6.4 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 136.2, 135.5, 132.9, 130.6, 130.5, 129.5, 128.9, 128.5, 106.5, 90.1, 87.8, 85.7, 76.6, 63.0, 26.9, 19.3.

5-Bromo-2'-benzyloxylamino-5'-*O*-*tert*-butyldiphenylsilyl-2'-*N*,3'-*O*-carbonyl-2'-deoxyuridine (26): To a stirred solution of 0.75 g (1.17 mmol) of **24** in 10 mL of pyridine was added 0.39 g (2.4 mmol) of CDI in 3 portions over 4 h. The mixture was stirred 16 h, then 0.3 g (2.4 mmol) of $BnONH_2$ (**11a**) was added. The mixture was stirred 16 h then was concentrated *in vacuo*. The residue was disolved in 10 mL of THF and treated with one drop of DBU. After stirring 24 h, the mixture was concentrated to 5 mL and applied to a column of silica gel. The product was eluted using hexanes, then 10-20-

30-40% EtOAc in hexanes. Concentration of the product containing fractions gave 520 mg (64%) of **26** as a white foam. UV λmax (EtOH) 272; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.77-7.26 (m, 15H), 6.67 (s, 1H), 4.95 (m, 3H), 4.68 (d, 2.1H), 4.16 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.10 (q, 5H), 3.82 (dd, *J* = 11.3, 4.8 Hz, 1H), 3.69 (dd, *J* = 11.2, 5.4 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 157.5, 148.6, 141.6, 136.3, 135.6, 135.5, 132.7, 132.6, 130.2, 130.1, 129.6, 129.3, 127.9, 127.8, 97.3, 93.0, 86.5, 78.4, 76.5, 67.2, 63.3, 26.9, 19.3. *Anal.* Calc'd for $C_{33}H_{33}BrN_3O_7Si$: C, 57.30; H, 4.81; N, 6.08. Found: C, 57.57; H, 4.83; N, 5.90.

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β-1-O-Acetyl-2,3,4-tri-O-benzyl-L-fucopyranose: To a stirred solution of 8.0 g (18.4 mmol) of 2,3,4-tri-O-benzyl-L-fucopyranose (Pfanstiehl) in 20 mL of CH_2Cl_2 and 10 mL of triethylamine was added 10 mL of acetic anhydride. After 2 h, 50-75 mL of $NaHCO_3$ solution was added to the reaction

mixture. After 45 min, the mixture was diluted with EtOAc and the organic phase was washed with $NaHCO_3$ solution, 10% KH_2PO_4 solution, and $NaHCO_3$ solution, then dried over Na_2CO_3 and concentrated. The crude residue was purified by filtration through a pad of 300 mL of silica gel (eluting with 0-75% EtOAc in hexanes) to give 8.34 grams (97%) of a mixture of α- and β-acetates (1: <10 α:β). Data for major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.27 (m, 15H), 5.50 (d, J = 7.9 Hz, 1H), 4.88-4.57 (overlapping signals, 6H), 3.80-3.74 (m, 3H), 3.64 (dd, J = 9.6, 8.1 Hz, 1H), 2.02 (s, 3H), 1.12 (d, J = 6.3 Hz, 3H). *Anal.* Calcd for $C_{29}H_{32}O_6$; C, 73.07; H, 6.77. Found: C, 72.82; H, 6.77.

N-(2-α-(2,3,4-tri-O-benzyl-L-fucopyranosyloxy)ethoxy)phthalimide: To a stirred, -78°C solution of 8.34 g (17.9 mmol) of β-1-O-acetyl-2,3,4-tri-O-benzyl-L-fucopyranose and 4.45 g (21.6 mmol) of N-(2-hydroxyethyloxy)phthalimide[16] in 125 mL of dichloromethane over 4Å molecular sieves was added 1 mL (5.17 mmol) of TMSOTf. The mixture was allowed to warm to ambient temp and was treated with $NaHCO_3$ solution. This mixture was decanted into a separatory funnel and the sieves washed with dichloromethane. The organic phase was separated and aqueous phase was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude glycosidation product was determined to be approximately 2/3 of the desired α-anomer (by ^1H NMR) and this was separated from the remainder of the uncharacterized products by chromatography on a column of 1.5 L of silica gel eluting with EtOAc/ hexanes (0-35%) to give 3.2 grams (29%) of the α-glycoside as a clear wax, along with 3.0 grams of mixed fractions comprised of ca. 50% of the α-anomer. Data for α-anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H), 7.71-7.69 (m, 2H), 7.38-7.25 (m, 15H), 4.97 (d, J = 11.6 Hz, 1H), 4.89 (d, J = 3.5 Hz, 1H, H1), 4.74 (d, J = 14.8 Hz, 1H), 4.73 (s, 2H), 4.65 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.50-4.37 (m, 2H), 4.11-3.75 (m, 5H), 3.68 (br d, J = 1.9 Hz, 1H), 1.12 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 139.0, 138.7, 138.6, 134.3, 128.9, 128.3-128.0 (several overlapping signals), 127.5, 127.3, 123.4, 97.8, 79.3, 77.8, 77.2, 76.2, 74.7, 73.3, 72.9, 66.5, 65.6, 16.6. *Anal.* Calcd for $C_{37}H_{37}O_8N$; C, 71.23; H, 5.98; N, 2.25. Found: C, 70.96; H, 6.09; N, 2.22.

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