Amide-Linked Ribonucleoside Dimers Derived from 5′-Amino-5′-deoxy- and 3′-(Carboxymethyl)-3′-deoxynucleoside Precursors[1]

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Treatment of *tert*-butyldimethylsilyl (TBDMS) derivatives of 3′-keto(adenosine or uridine) with [(ethoxycarbonyl)methylene]triphenylphosphorane gave exocyclic alkenes that underwent stereoselective hydrogenation to give 3′-deoxy-3′-[(ethoxycarbonyl)methyl](Ado or Urd) analogues. Saponification provided the 3′-(carboxymethyl)-3′-deoxy(Ado and Urd) derivatives **37** and **38**. Treatment of **37** or **38** with DCC and 5′-amino-2′,3′-bis-*O*-TBDMS-5′-deoxynucleosides gave the amide-linked dimers (74−82%). Activation of **37** or **38** with 4-nitrophenol/DCC, and direct coupling of the 4-nitrophenyl esters with 5′-amino-5′-deoxy(Ado or Urd) in pyridine also produced amide dimers efficiently (65−70%). Analogous activation of a 5′-*O*-DMT-protected carboxylate, and its coupling with 5′-amino-5′-deoxy-2′-*O*-methyladenosine gave the amide dimer in good yield (74%). Coupling (DCC) of a 5′-azido-2′-*O*-TBDMS-3′-(carboxymethyl)-3′,5′-dideoxyuridine intermediate with 5′-amino-5′-deoxynucleosides gave amide-linked dimers (72−78%) that can serve as masked (azide reduction) 5′-amino dimers for analogous synthesis of extended amide-linked oligomers.

Introduction

Major research efforts have been focused on synthesis of modified oligomers for antisense applications.[2] Oligonucleotide analogues have been designed to have desirable properties, including (1) increased cellular permeability, (2) resistance to nucleolytic degradation, and (3) increased affinity for target nucleic acids. Sugar and base modifications have been examined,[3] but the primary target has been modification of the phosphodiester backbone. Serious limitations of phosphodiesters as antisense therapeutics are their low membrane permeability (negative charge density) and their high susceptibility to nucleolytic degradation. A number of phosphodiester replacements have been examined,[2,4] and analogues containing modified linkages have exhibited promising properties in vitro and in vivo. Problems with bioavailability and/or sequence-nonspecific side effects stimulate continued research in this area.[5]

We[6] and others[7,8] became interested in amide-linked oligonucleotide analogues for potential antisense applications. The Novartis group[7] have shown that oligomers containing amide-linked 2′-deoxynucleoside analogues exhibited increased duplex stability (0.4−0.9 °C/dimer) and resistance to degradation by (endo and exo)nucleases. Additional enhancements of duplex stability observed with oligomers containing amide-linked dimers with 2′-*O*-methyl substituents on both sugar rings were attributed to increased population of the 3′-endo (ribo-like) furanose conformation range.[7e] NMR and molecular modeling studies were consistent with similar trends observed with oligonucleotides with analogous 2′-substituents.[9]

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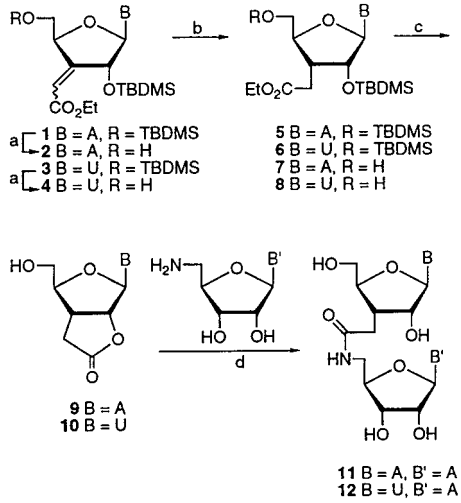
Scheme 1[a]



[a] Key: (a) TFA/H_2O (9:1)/0 °C; (b) H_2/Pd−C; (c) TBAF/THF; (d) 2-Pyridone/DMF/70 °C.

We have communicated[10] synthesis of the γ-butyrolactone-fused (3.3.0) nucleosides **9** and **10** and their application for the preparation of amide-linked ribonucleoside dimers (Scheme 1) that were expected to have a favorable 3′-endo conformational bias,[7e,9] resistance to nucleases, and enhanced membrane permeability (no backbone charge).[11] We had hoped that the lactones would be readily susceptible to ring opening with 5′-amino-5′-deoxynucleosides by analogy with model reactions.[6,12] However, **9** and **10** proved to be unreactive with 5′-amino-5′-deoxyadenosine at ambient temperature under a number of reaction conditions, including addition of several acylation promoters. Effective lactone opening (65−83%) was achieved only at elevated temperatures (70 °C/DMF/24 h) with excess aminonucleoside (5 equiv) and 2-pyridone (2 equiv) as a promoter. We now report an alternative approach that employs ester saponification, carboxylate activation, and stoichiometric coupling with aminonucleosides to provide efficient conversions of **5**, **6**, and **8** to a number of amide-linked ribonucleoside dimers and intermediates suitable for further elongation.

Results and Discussion

Treatment of 2′,5′-bis-*O*-TBDMS-3′-keto(uridine or adenosine)[13] with [(ethoxycarbonyl)methylene]triphenylphosphorane in refluxing CH_2Cl_2 gave adducts **1**[14] or **3**[6] (80−96%). Stereoselective reduction[10,14] of **3** (10% Pd−C/MeOH) gave **6**, whose ribo configuration was indicated by difference NOE (6% enhancement of the H3′ resonance upon irradiation of H2′) and corroborated by conversion to lactone **10**. This two-step sequence (Wittig olefination and stereoselective hydrogenation) provides a valuable alternative to free-radical coupling methods[15] used for the preparation of 3′-substituted 2′,3′-dideoxynucleosides.[7,8] Monomers prepared by free-radical methods are obtained with high α-facial diastereoselectivity at C3′ from 5′-*O*-protected 2′-deoxynucleosides. However, analogous treatment of 2′,5′-di-*O*-protected ribonucleosides resulted in coupling at the opposite (β) face to give contaminating[15f] or predominant[7e] formation of xylofuranosyl products. The sequence we have employed provides efficient access to 3′-(carboxymethyl)-3′-deoxy compounds with the desired ribo configuration. The Novartis group[7f] has recently reported adoption of our approach[10] for the stereoselective preparation of the ribo monomers.

Treatment of **1** or **3** with TFA/H_2O (9:1, 0 °C)[16] effected clean O5′ desilylation to give **2** (90%) or **4** (84%), respectively. Hydrogenation of **2** or **4** gave **7** or **8** (80−98%). Hydrogenation of the adenine analogues **1** and **2** required more forcing conditions [150% (w/w) catalyst, 30−35 psi, 4 days) than the uracil derivatives **3** and **4** [5−40% (w/w) catalyst, 5−10 psi, 1−2 days]. Partial saturation of the 5,6-double bond of uracil sometimes occurred with **3** and **4** (≤10%, dependent on the catalyst batch), but this could be avoided by adjustments of H_2 pressure, catalyst ratio, and reaction time. Desilylation (TBAF/THF) of **5** or **7** gave **9** (72 or 83%, respectively), and parallel treatment of **6** or **8** gave **10** (85 and 93%, respectively). Treatment of **9** or **10** with 5′-amino-5′-deoxy(Ado or Urd) under various conditions failed to give amide-linked dimers. However, **9** or **10** reacted with 5′-amino-5′-deoxyAdo (5 equiv) in the presence of 2-pyridone (2 equiv) in DMF (70 °C, 24−30 h) to give **11** (65%) or **12** (83%), respectively. Low reactivity of nucleoside fused-lactones with isobutylamine has been noted previously.[17]

We next examined coupling reactions of 4-nitrophenyl esters, and condensation of carboxylates (DCC), with aminonucleosides. Protection of 5′-azido-5′-deoxy[Ado (**13**) or Urd (**14**)] (TBDMSCl/imidazole/pyridine) and azide reduction (1,3-propanedithiol) gave the 5′-amino-5′-deoxy derivatives **17** (51%) or **18** (62%) (Scheme 2). Silylation of 2′-*O*-methyl[Ado (**19**) or 5-methylUrd (**20**)] gave **21** or **22**, which were selectively deprotected (O5′), converted to the 5′-chloro-5′-deoxy derivatives **23** or **24**, and treated with lithium or sodium azide to give **25** or **26**. Deprotection of **25** or **26** (TBAF/THF) gave **27** or **28**, which were hydrogenolyzed (10% Pd−C/EtOH) to give **29** or **30**. Benzoylation of **31** gave **32** (96%), and selective deprotection (O5′) gave **33** (81%). The limited solubility of **32** in TFA/H_2O required the use of a cosolvent (CH_2Cl_2). The 5′-*O*-TBDMS linkage is more stable in CH_2Cl_2/TFA/H_2O (20:9:1) than in TFA/H_2O (9:1), and longer reaction times at ambient temperature (extremely slow at 0 °C) were required to effect complete cleavage. Treatment of **33** with $SOCl_2$/pyridine overnight at ambient temperature gave **34** (70%), which was stirred with LiN_3/DMF/110 °C to give **35**. $SnCl_2$/MeOH effected clean (TLC) reduction

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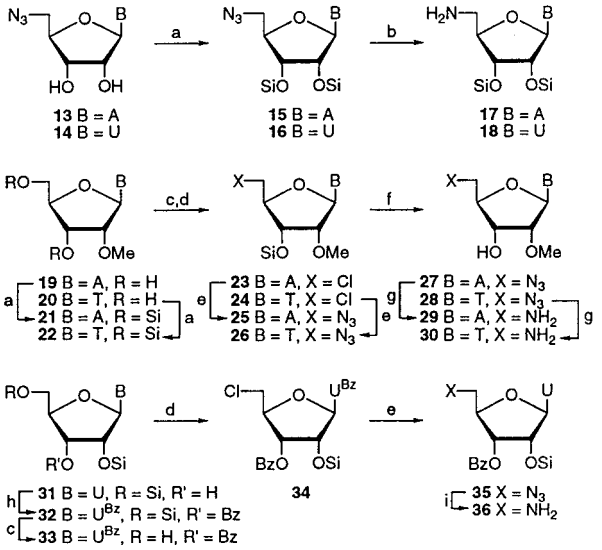
Scheme 2[a]



A = adenin-9-yl, T = thymin-1-yl, U = uracil-1-yl, U^{Bz} = 3-benzoyluracil-1-yl, Si = *tert*-butyldimethylsilyl.

[a] Key: (a) TBDMSCl/imidazole/pyridine; (b) $HS(CH_2)_3SH/Et_3N$; (c) TFA/H_2O (9:1)/0 °C; (d) ($SOCl_2$ or MsCl)/pyridine; (e) (NaN_3 or LiN_3)/DMF/110 °C; (f) Bu_4NF/THF; (g) H_2/Pd−C; (h) BzCl/pyridine; (i) $SnCl_2 \cdot 2H_2O$/MeOH.

of **35** to **36** (52%), whereas certain other methods for conversion of azides to amines (H_2/Pd−C, 1,3-propanedithiol, $Ph_3P/NH_3/H_2O$/dioxane) gave mixtures.

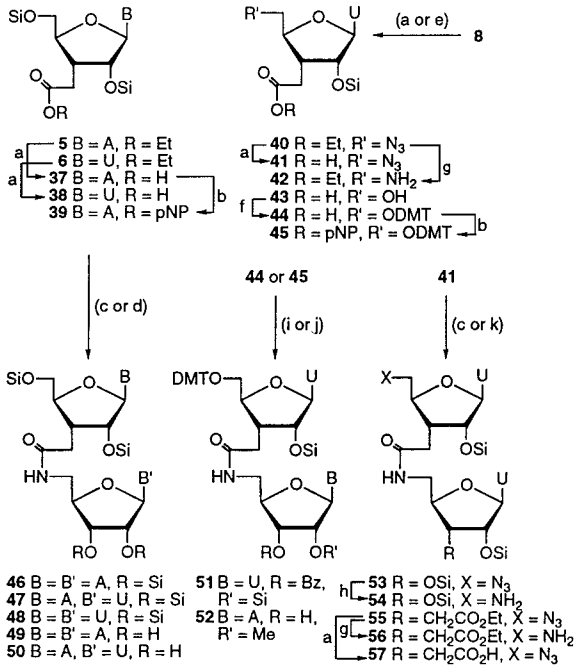
Saponification of **5** or **6** ($NaOH/H_2O$/MeOH) gave the 3′-(carboxymethyl) derivatives **37** (73%) or **38** (88%), respectively (Scheme 3). Analogous treatment of **8** or **40** gave **43** (66%) or **41** (77%), respectively. Stoichiometric DCC-mediated condensation of **37** or **38** with **17** or **18** generated the amide-linked dimers **46**−**48** (74−82%), and analogous coupling of **41** with **18** (0.9 equiv) or **42** (1.1 equiv) gave dimers **53** (78%) or **55** (72%).

Block incorporation of amide dimers into oligonucleotides via automated synthesizer technology requires appropriate protection, and the DMT group at O5′ is used extensively. Treatment of **43** with DMTCl/pyridine gave **44** (62%), which was subjected to DCC-mediated condensation with **36** to give **51** (71%). Active ester **45** [prepared (61%) from **44**/4-nitrophenol/DCC] was treated with **29** (1.2 equiv)/THF/EtOH to give **52** (74%) and **39** [prepared (72%) from **37**/4-nitrophenol/DCC] was treated with 5′-amino-5′-deoxy(Ado or Urd) to give dimers **49** (65%) or **50** (70%), respectively. Thus, standard protecting group manipulation is compatible with the present amide−dimer chemistry. Dimers **53**−**57** were prepared to explore the potential of this approach for synthesis of amide oligomers. Key intermediate **55** underwent saponification to give **57** (64%). Treatment of **55** with 1,3-propanedithiol/EtOH gave **56** (71%), and hydrogenation of **53** (H_2/10% Pd−C/THF) proceeded without incident to give **54** (63%).

Conclusions

Free radical-mediated coupling procedures with 2′,5′-di-O-protected nucleosides have resulted in contaminating[15f] or preferential[7e] attack at the β face to give xylofuranosyl products, whereas the present Wittig olefination of 3′-keto-2′,5′-bis-*O*-TBDMS nucleosides and stereoselective[10,14] hydrogenation provides efficient access

Scheme 3[a]



A = adenin-9-yl, U = uracil-1-yl, Si = *tert*-butyldimethylsilyl.

[a] Key: (a) (i) $NaOH/H_2O$, (ii) HCl/H_2O; (b) 4-nitrophenol/DCC; (c) (**17** or **18**)/DCC/CH_2Cl_2; (d) 5′-amino-5′-deoxy(Ado or Urd)/EtOH; (e) (i) MsCl/pyridine/CH_2Cl_2, (ii) NaN_3/DMF/110 °C; (f) DMTCl/Et_3N/pyridine; (g) $HS(CH_2)_3SH/Et_3N$; (h) H_2/Pd−C; (i) **36**/DCC/CH_2Cl_2; (j) **29**/EtOH; (k) **42**/DCC/CH_2Cl_2.

to 3′-deoxy-3′-(carboxymethyl)ribonucleoside derivatives. The 3′-deoxy-3′-[(ethoxycarbonyl)methyl](Ado and Urd) compounds **5**−**8** have been employed for synthesis of amide-linked ribonucleoside dimers. Derivatives **5**−**8** were saponified to give 3′-(carboxymethyl)-3′-deoxy(Ado or Urd) intermediates, which were condensed (DCC) with protected 5′-amino-5′-deoxynucleosides to give amide dimers in good yields. Conversion of the carboxymethyl intermediates into active esters (4-nitrophenol/DCC) allowed their coupling with unprotected 5′-amino-5′-deoxynucleosides to give amide dimers with free hydroxyl groups. No problems were encountered with chemistry involved with the use of dimethoxytrityl (DMT) and other standard protecting groups.

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. ^1H (200 or 500 MHz) and ^{13}C (50 MHz) NMR spectra were determined with solutions in (Me_4Si)/$CDCl_3$ unless otherwise noted. Observed ("apparent") multiplicities are noted with quotation marks for ^1H NMR peaks that should exhibit more complex splitting patterns. Mass spectra (MS and HRMS) were obtained with electron impact (EI, 20 eV), chemical ionization (CI, isobutane), or fast-atom bombardment (FAB, NaOAc/thioglycerol or thioglycerol matrix) techniques. Reagent chemicals were used, and solvents were dried by reflux and distillation from standard drying agents under N_2. TLC was performed on Merck kieselgel 60-F_{254} sheets, and Merck kieselgel 60 (230−400 mesh) was used for flash chromatography.[18] "Solvent system A (SSA)" for chromatography is the separated organic phase of EtOAc/*i*-PrOH/H_2O (4:1:2). Elemental analyses were determined by M−H−W Laborato-

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ries, Phoenix, AZ. Compounds **1**,[19] **5**,[14] **13**,[20] **14**,[21] **19**,[22] **20**,[22] and **31**[23] were prepared as described.

General procedures A−F were performed with quantities and other conditions specified for the individual compounds. **Procedure A (Desilylation of O5′).** TFA/H_2O was added to a cold flask (ice/H_2O bath) containing the silyl ether, and the solution was stirred at ∼0 °C until the desilylation was complete (TLC). Volatiles were evaporated quickly at ≤17 °C (to minimize further solvolysis reactions). The residue was partitioned, and the aqueous layer was extracted. The combined organic phase was washed (H_2O, brine) and dried ($MgSO_4$). Filtration, evaporation of volatiles, and chromatography of the residue gave the product. **Procedure B (Hydrogenation of Alkenes).** A mixture of the compound, 10% Pd−C, and H_2 in a solvent was shaken (Parr apparatus) at ambient temperature. The mixture was filtered (with Celite), and the filter cake was washed with solvent. Volatiles were evaporated from the combined filtrate to give the product. **Procedure C (Chemical Reduction of Azides).** Et_3N and 1,3-propanedithiol were added to a stirred, deoxygenated (N_2) solution of the azide in a solvent. Stirring was continued at ambient temperature (under N_2) until reduction was complete (TLC). Volatiles were evaporated, and the residue was chromatographed to give the product. **Procedure D (Saponification of Esters)**. Solid NaOH was added to a stirred solution of the compound in an aqueous solvent mixture, and stirring was continued at ambient temperature until saponification was complete (TLC). The solution was concentrated under reduced pressure, and the resulting aqueous solution was cooled (∼0 °C) and carefully acidified to pH ∼2−4 (HCl/H_2O). The suspension was immediately partitioned (EtOAc/brine), and the organic layer was dried ($MgSO_4$) and filtered. Volatiles were evaporated, and the residue was chromatographed to give the product. **Procedure E [DCC-Mediated Condensation of 3′-(Carboxymethyl)-3′-deoxy- and 5′-Amino-5′-deoxynucleoside Components].** A solution of the protected 3′-(carboxymethyl)-3′-deoxy- and 5′-amino-5′-deoxynucleoside components and DCC in dried CH_2Cl_2 was stirred overnight at ambient temperature (under N_2). When coupling was complete (TLC), the suspension was filtered (with Celite), the filter cake was washed (CH_2Cl_2), and the combined filtrate was evaporated. The residue was chromatographed to give the amide product. **Procedure F (Condensation of 3′-[[(4-Nitrophenoxy)carbonyl]methyl]-3′-deoxy- and 5′-Amino-5′-deoxynucleoside Components).** A solution of the protected 3′-(carboxymethyl)-3′-deoxynucleoside 4-nitrophenyl ester and 5′-amino-5′-deoxynucleoside components in a solvent was stirred at ambient temperature (coupling progress was monitored by TLC). Volatiles were evaporated, and the residue was chromatographed to give the amide product.

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methylene]adenosine (2). Procedure A [**1** (5.00 g, 8.87 mmol), TFA/H_2O (9:1, 80 mL), ∼20 min, partitioned (EtOAc//NaCl/H_2O), aqueous layer extracted (EtOAc, 2×), chromatography (EtOAc/hexanes, 7:3)] gave **2** (3.58 g, 90%) as a solid foam: ^{1}H NMR δ 8.35 (s, 1H), 7.85 (s, 1H), 6.45 (br s, 2H), 5.92 ("t", J = 2.1 Hz, 1H), 5.60−5.50 (m, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.10 (dd, J = 11.8, 1.6 Hz, 1H), 3.99 (dd, J = 12.0, 1.6 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.80 (s, 9H), −0.09 (s, 3H), −0.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.1, 158.6, 155.9, 152.2, 148.6, 140.7, 121.0, 114.2, 90.1, 81.9, 75.0, 63.8, 60.6, 25.5, 17.7, 14.2, −4.9, −5.9; MS (FAB) m/z 450.2180 (MH^+ [$C_{20}H_{32}N_5O_5Si$] = 450.2173).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methylene]uridine (3). A solution of 2′,5′-bis-*O*-TBDMS-3′-ketouridine[13] (619 mg, 1.32 mmol) and Ph_3PCHCO_2-Et (550 mg, 1.58 mmol) in CH_2Cl_2 (25 mL) was refluxed for 16 h. Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2) to give **3** (689 mg, 96%) as a solid foam: ^{1}H NMR δ 9.39 (br s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 5.98 (d, J = 7.7 Hz, 1H), 5.88 ("t", J = 2.2 Hz, 1H), 5.76 (dd, J = 8.1, 1.6 Hz, 1H), 5.36−5.32 (m, 1H), 4.68 (dt, J = 7.6, 2.0 Hz, 1H), 4.28−4.13 (m, 3H), 3.92 (dd, J = 11.1, 2.0 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.88 (br s, 18H), 0.05, 0.03, 0.02, −0.08 (4 × s, 4 × 3H); ^{13}C NMR δ 165.1, 162.9, 159.2, 150.5, 139.8, 113.9, 103.2, 85.6, 80.0, 76.9, 64.5, 60.6, 25.8, 25.5, 18.3, 17.8, 14.2, −4.9, −5.1, −5.6; MS (FAB) m/z 541.2773 (MH^+ [$C_{25}H_{45}N_2O_7Si_2$] = 541.2765). Anal. Calcd for $C_{25}H_{44}N_2O_7Si_2$: C, 55.52; H, 8.20; N, 5.18. Found: C, 55.69; H, 8.00; N, 5.09.

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methylene]uridine (4). Procedure A [**3** (3.00 g, 5.55 mmol), TFA/H_2O (9:1, 60 mL), partitioned (EtOAc//NaCl/H_2O), aqueous layer extracted (EtOAc, 2×), chromatography (30 → 70% EtOAc/hexanes)] gave **4** (1.99 g, 84%) as a solid foam: ^{1}H NMR δ 9.81 (br s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 5.89 ("t", J = 2.2 Hz, 1H), 5.82 (d, J = 8.1 Hz, 1H), 5.49 (d, J = 7.9 Hz, 1H), 5.36 (br s, 1H), 5.12 ("d", J = 7.8 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.11−4.04 (m, 1H), 3.90 (dd, J = 11.7, 1.8 Hz, 1H), 3.25 (br s, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), −0.08 (s, 3H); ^{13}C NMR δ 165.1, 163.4, 158.7, 150.6, 142.3, 114.5, 103.2, 90.4, 80.3, 74.3, 63.4, 60.6, 25.5, 17.7, 14.1, −4.9, −5.1; MS (FAB) m/z 427.1916 (MH^+ [$C_{19}H_{31}N_2O_7Si$] = 427.1901). Anal. Calcd for $C_{19}H_{30}N_2O_7Si$: C, 53.50; H, 7.09; N, 6.57. Found: C, 53.36; H, 7.23; N, 6.42.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methyl]uridine (6). Procedure B [**3** (100 mg, 0.185 mmol), 10% Pd−C (39 mg), H_2 (5−10 psi), dried MeOH (15 mL), 38 h] gave **6** (94 mg, 94%) as a solid foam: ^{1}H NMR δ 8.55 (br s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 5.71 (s, 1H), 5.61 (dd, J = 8.3, 1.5 Hz, 1H), 4.43 (d, J = 3.7 Hz, 1H), 4.19−3.99 (m, 4H), 3.70 (dd, J = 12.0, 1.6 Hz, 1H), 2.69−2.50 (m, 2H), 2.22 ("d", J = 12.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.23 (s, 3H), 0.11 (br s, 6H), 0.07 (s, 3H); ^{13}C NMR δ 171.6, 163.3, 150.1, 140.4, 101.2, 91.3, 84.4, 69.1, 61.3, 60.7, 37.0, 29.1, 25.9, 25.8, 18.4, 18.1, 14.2, −4.5, −5.5, −5.6, −5.7; MS (FAB) m/z 543.2927 (MH^+ [$C_{25}H_{47}N_2O_7Si_2$] = 543.2922). Anal. Calcd for $C_{25}H_{46}N_2O_7Si_2$: C, 55.32; H, 8.54; N, 5.16. Found: C, 55.10; H, 8.23; N, 5.07.

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methyl]adenosine (7). Procedure B [**2** (100 mg, 0.222 mmol), 10% Pd−C (0.150 g), H_2 (30−35 psi), dried MeOH, 4 days] gave **7** (80 mg, 80%) as a solid foam: ^{1}H NMR δ 8.31 (s, 1H), 8.26 (s, 1H), 6.80 (br s, 2H), 5.81 (d, J = 3.7 Hz, 1H), 4.91 (dd, J = 5.6, 4.7 Hz, 1H), 4.06−4.22 (m, 4H), 3.75 (dd, J = 12.2, 1.6 Hz, 1H), 3.10−2.96 (m, 1H), 2.74 (dd, J = 17.3, 6.4 Hz, 1H), 2.25 (dd, J = 17.5, 8.1 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.85 (s, 9H), −0.05 (s, 3H), −0.12 (s, 3H); ^{13}C NMR δ 172.3, 153.9, 149.6, 148.2, 141.1, 120.0, 91.8, 85.8, 76.2, 62.3, 60.9, 38.0, 31.0, 25.6, 17.9, 14.2, −5.1, −5.4; MS (FAB) m/z 452.2330 (MH^+ [$C_{20}H_{34}N_5O_5Si$] = 452.2329). Anal. Calcd for $C_{20}H_{33}N_5O_5Si$: C, 53.19; H, 7.37; N, 15.51. Found: C, 53.08; H, 7.15; N, 14.95.

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-3′-[(ethoxycarbonyl)methyl]uridine (8). Procedure B [**4** (65 mg, 0.15 mmol), 10% Pd−C (15 mg), H_2 (5 psi), dried MeOH (10 mL), 2 days] gave **8** (63 mg, 98%) as a solid foam: ^{1}H NMR δ 9.53 (br s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 5.70 (dd, J = 8.3, 2.2 Hz, 1H), 5.65 (s, 1H), 4.39 (d, J = 3.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.10−4.05 (m, 2H), 3.70 ("d", J = 13.6 Hz, 1H), 3.23 (br s, 1H), 2.64 (dd, J = 16.1, 4.9 Hz, 1H), 2.57−2.43 (m, 1H), 2.37 (dd, J = 15.9, 6.5 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.25 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 173.1, 164.3, 150.5, 140.9, 101.4, 91.8, 85.5, 78.8, 61.4, 60.8, 36.7, 30.1, 26.0, 18.2, 14.4, −4.2, −5.3; MS (FAB) m/z 429.2067 (MH^+ [$C_{19}H_{33}N_2O_7Si$] = 429.2057). Anal. Calcd for $C_{19}H_{32}N_2O_7Si$: C, 53.25; H, 7.53; N, 6.54. Found: C, 53.13; H, 7.46; N, 6.43.

3′-(Carboxymethyl)-3′-deoxyadenosine-2′,3′-lactone (9). TBAF/THF (1.0 M; 1.27 mL, 1.27 mmol) was added to a solution of **7** (452 mg, 1.00 mmol) in THF (11 mL), and stirring was continued for 16 h at ambient temperature. Silica gel (3 g) was added, volatiles were evaporated, and the loaded

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adsorbent was added to a flash column. Chromatography (3 → 5% MeOH/CH_2Cl_2) gave a solid that was triturated with MeOH to give **9** (243 mg, 83%) with mp 233−236 °C dec: ^{1}H NMR (DMSO-d_6) δ 8.35 (s, 1H), 8.16 (s, 1H), 7.36 (s, 2H), 6.27 (d, J = 1.5 Hz, 1H), 5.48 (dd, J = 7.0, 1.4 Hz, 1H), 5.06 (t, J = 5.7 Hz, 1H), 4.01−3.95 (m, 1H), 3.63−3.56 (m, 1H), 3.20−3.00 (m, 1H), 2.95 (dd, J = 18.0, 8.5 Hz, 1H), 2.54 (dd, J = 18.1, 1.3 Hz, 1H; solvent-peak overlap); ^{13}C NMR (DMSO-d_6) δ 176.0, 156.4, 153.1, 149.0, 139.8, 119.3, 88.2, 87.3, 86.6, 84.6, 61.9, 32.3; MS (FAB) m/z 292.1040 (MH^+ [$C_{12}H_{14}N_5O_4$] = 292.1046).

3′-(Carboxymethyl)-3′-deoxyuridine-2′,3′-lactone (10). TBAF/THF (1.0 M; 0.39 mL, 0.39 mmol) was added to a solution of **8** (150 mg, 0.350 mmol) in THF (4 mL), and stirring was continued for 24 h at ambient temperature. Evaporation of volatiles gave a residue that was washed (EtOAc, 4×) and chromatographed (3 → 5% MeOH/CH_2Cl_2) to give **10** (87 mg, 93%) as a solid foam: ^{1}H NMR (DMSO-d_6) δ 11.42 (br s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 5.91 (d, J = 1.3 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.15 (dd, J = 7.1, 1.4 Hz, 1H), 5.07 ("d", J = 5.3 Hz, 1H), 3.90−3.82 (m, 1H), 3.70−3.54 (m, 2H), 3.11 ("q", J = 8.0 Hz, 1H), 2.84 (dd, J = 18.0, 8.6 Hz, 1H), 2.45 ("d", J = 18.5 Hz, 1H; solvent-peak overlap); ^{13}C NMR (DMSO-d_6) δ 175.6, 163.2, 150.2, 141.6, 101.8, 89.93, 89.87, 87.2, 85.8, 60.8, 31.7; MS (CI) m/z 268.0682 (M^+ [$C_{11}H_{12}N_2O_6$] = 268.0695). Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.24; H, 4.77; N, 10.54.

3′-Deoxy-3′-[[*N*-(5′-deoxyadenosin-5′-yl)carboxamido]-methyl]adenosine (11). A stirred solution of **9** (25 mg, 0.086 mmol), 5′-amino-5′-deoxyAdo (114 mg, 0.428 mmol), and 2-pyridone (16 mg, 0.17 mmol) in DMF (2 mL) was heated for 24 h at 70 °C. TLC indicated conversion to a less polar product (R_f ~0.5; SSA). Volatiles were evaporated, the residue was suspended in MeOH, silica gel (~1 g) was added, and the mixture was added to a flash column. Chromatography (SSA) gave **11** (31 mg, 65%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.41 (s, 1H), 8.34 (t, J = 5.8 Hz, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.31 (br s, 2H), 7.26 (br s, 2H), 5.89 (d, J = 1.5 Hz, 1H), 5.83 (d, J = 6.5 Hz, 1H), 5.81 (d, J = 4.5 Hz, 1H), 5.39 (d, J = 6.5 Hz, 1H), 5.20 (d, J = 4.5 Hz, 1H), 5.14 (t, J = 5.8 Hz, 1H), 4.67 ("q", J = 6.0 Hz, 1H), 4.45 (dt, J = 5.0, 1.8 Hz, 1H), 4.03 (dd, J = 8.0, 5.0 Hz, 1H), 3.95−3.93 (m, 2H), 3.73 (ddd, J = 12.5, 5.5, 2.5 Hz, 1H), 3.53 (ddd, J = 12.3, 6.0, 3.8 Hz, 1H), 3.44−3.34 (m, 2H), 2.74−2.67 (m, 1H), 2.53 (dd, J = 16.0, 8.5 Hz, 1H), 2.28 (dd, J = 15.5, 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.2, 156.1, 155.9, 152.4, 152.3, 149.1, 148.7, 140.2, 138.7, 119.4, 119.0, 90.1, 87.8, 84.5, 83.5, 75.5, 72.5, 71.1, 61.1, 30.9; MS (FAB) m/z 558.2184 (MH^+ [$C_{22}H_{28}N_{11}O_7$] = 558.2173).

3′-Deoxy-3′-[[*N*-(5′-deoxyadenosin-5′-yl)carboxamido]-methyl]uridine (12). A solution of **10** (14 mg, 0.052 mmol), 5′-amino-5′-deoxyAdo (69 mg, 0.26 mmol), and 2-pyridone (10 mg, 0.10 mmol) in DMF (1.5 mL) was stirred for 30 h at 70 °C. Workup and chromatography (as described for **9** → **11**) gave **12** (23 mg, 83%): ^{1}H NMR (DMSO-d_6/D_2O, 500 MHz) δ 8.33 (s, 1H), 8.22 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 5.87 (d, J = 6.5 Hz, 1H), 5.67 (d, J = 6.0 Hz, 1H), 5.64 (d, J = 7.0 Hz, 1H), 4.67 (dd, J = 6.4, 5.4 Hz, 1H), 4.17 ("d", J = 5.0 Hz, 1H), 4.08−4.03 (m, 2H), 3.93−3.88 (m, 2H), 3.77 (dd, J = 12.7, 2.0 Hz, 1H), 3.48 (dd, J = 12.7, 3.4 Hz, 1H), 3.44 (dd, J = 14.2, 5.4 Hz, 1H), 3.37 (dd, J = 14.1, 4.5 Hz, 1H), 2.46−2.34 (m, 1H), 2.20 (dd, J = 14.9, 5.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.4, 164.5, 156.4, 153.2, 151.0, 149.6, 141.3, 141.2, 119.8, 101.4, 91.5, 88.5, 85.0, 84.1, 76.3, 73.2, 71.6, 63.0, 60.7, 31.2, 25.7; MS (FAB) m/z 535.1904 (MH^+ [$C_{21}H_{27}N_8O_9$] = 535.1901).

5′-Azido-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyadenosine (15). A solution of **13** (408 mg, 1.40 mmol), TBDMSCl (742 mg, 4.92 mmol), and imidazole (344 mg, 5.05 mmol) in dried pyridine (6 mL) was heated for 8 h at 70 °C (under N_2). The mixture was poured into $NaHCO_3$/H_2O and extracted ($CHCl_3$, 3×). The combined organic phase was dried (Na_2SO_4) and filtered. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 7:3) to give **15** as a white solid (445 mg, 61%): mp 208−210 °C; ^{1}H NMR δ 8.36 (s, 1H), 8.01 (s, 1H), 5.89 (d, J = 4.2 Hz, 1H), 5.56 (br s, 2H), 4.94 (t, J = 4.3 Hz, 1H), 4.33 (t, J = 4.3 Hz, 1H), 4.25−4.15 (m, 1H), 3.72 (d, J = 4.8 Hz, 2H), 0.93 (br s, 9H), 0.83 (br s, 9H), 0.12, 0.11, −0.01, −0.18 (4 × s, 4 × 3H); ^{13}C NMR δ 156.0, 152.9, 149.5, 140.0, 120.5, 89.8, 82.8, 74.2, 72.3, 51.5, 25.7, 25.6, 17.9, 17.7, −4.6, −4.9, −5.0, −5.1; MS (FAB) m/z 521.2826 (MH^+ [$C_{22}H_{41}N_8O_3Si_2$] = 521.2840). Anal. Calcd for $C_{22}H_{40}N_8O_3Si_2$: C, 50.74; H, 7.74; N, 21.52. Found: C, 50.86; H, 7.84; N, 21.70.

5′-Azido-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridine (16). A solution of **14** (2.82 g, 10.5 mmol), TBDMSCl (6.4 g, 43 mmol), and imidazole (3.4 g, 50 mmol) in dried pyridine (30 mL) was stirred for 24 h at ambient temperature (under N_2). Volatiles were evaporated, and the residue was partitioned ($NaHCO_3$/H_2O//$CHCl_3$). The aqueous layer was extracted ($CHCl_3$, 2×), and the combined organic phase was dried (Na_2SO_4) and filtered. Volatiles were evaporated to give a solid foam (4.7 g, 90%; ~95% ^{1}H NMR purity): ^{1}H NMR δ 8.83 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 5.77 (d, J = 8.2 Hz, 1H), 5.67 (d, J = 2.8 Hz, 1H), 4.21−4.13 (m, 2H), 3.99−3.93 (m, 1H), 3.87−3.81 (m, 1H), 3.61 (dd, J = 13.6, 3.2 Hz, 1H), 0.91 (br s, 9H), 0.89 (br s, 9H), 0.12 (s, 3H), 0.09 (s, 9H); ^{13}C NMR δ 163.5, 150.2, 140.3, 102.2, 91.0, 81.2, 75.0, 71.1, 50.9, 25.71, 25.68, 17.94, 17.89, −4.4, −4.6, −5.0, −5.1; MS (FAB) m/z 498.2575 (MH^+ [$C_{21}H_{40}N_5O_5Si_2$] = 498.2568).

5′-Amino-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyadenosine (17). Procedure C [Et_3N (0.8 mL), 1,3-propanedithiol (0.80 mL, 0.86 g, 8.0 mmol), **15** (294 mg, 0.564 mmol), THF/EtOH (1:1, 2 mL), 36 h, chromatography (SSA)] gave **17** (249 mg, 84%) with mp 205−208 °C dec: ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 8.12 (s, 1H), 7.30 (s, 2H), 5.86 (d, J = 7.0 Hz, 1H), 4.97 (dd, J = 7.0, 4.6 Hz, 1H), 4.34 (d, J = 4.2 Hz, 1H), 4.00−3.92 (m, 1H), 3.47 (br s, 2H), 2.98−2.92 (m, 2H), 0.90 (br s, 9H), 0.67 (br s, 9H), 0.11, 0.09, −0.13, −0.50 (4 × s, 4 × 3H); ^{13}C NMR (DMSO-d_6) δ 156.3, 152.6, 149.4, 140.8, 119.7, 87.4, 86.3, 73.5, 73.0, 42.8, 25.7, 25.4, 17.8, 17.4, −4.7, −4.8, −5.8; MS (FAB) m/z 495.2921 (MH^+ [$C_{22}H_{43}N_6O_3Si_2$] = 495.2935). Anal. Calcd for $C_{22}H_{42}N_6O_3Si_2 \cdot 2H_2O$: C, 49.36; H, 8.76; N, 15.70. Found: C, 49.20; H, 8.11; N; 15.81.

5′-Amino-2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridine (18). Procedure C [Et_3N (0.3 mL), 1,3-propanedithiol (0.30 mL, 0.32 g, 3.0 mmol), **16** (250 mg, 0.502 mmol), EtOH (2 mL), 18 h, chromatography (MeOH/CH_2Cl_2, 1:9)] gave **18** (164 mg, 69%) as a white solid: mp ~198 °C dec; ^{1}H NMR (300 MHz) δ 7.85 (d, J = 8.1 Hz, 1H), 5.73 (d, J = 8.1 Hz, 1H), 5.69 (d, J = 3.6 Hz, 1H), 4.25 ("t", J = 3.9 Hz, 1H), 4.07−4.02 (m, 1H), 3.96 (dd, J = 5.6, 4.4 Hz, 1H), 3.10 (dd, J = 14.0, 3.6 Hz, 1H), 2.90 (dd, J = 13.4, 5.0 Hz, 1H), 0.92 (br s, 9H), 0.91 (br s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.086 (s, 3H); ^{13}C NMR δ 163.5, 150.2, 141.2, 102.0, 91.3, 84.7, 75.2, 71.7, 42.4, 25.8, 25.7, 18.0, 17.9, −4.4, −4.7, −4.9; MS (FAB) m/z 472.2675 (MH^+ [$C_{21}H_{42}N_3O_5Si_2$] = 472.2663). Anal. Calcd for $C_{21}H_{41}N_3O_5Si_2$: C, 53.47; H, 8.76; N, 8.91. Found: C, 53.79; H, 8.61; N, 9.02.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-methyladenosine (21). A solution of **19** (500 mg, 1.78 mmol), TBDMSCl (590 mg, 3.91 mmol), and imidazole (400 mg, 5.88 mmol) in dried pyridine (5 mL) was stirred for 8 h at 65 °C (under N_2). TBDMSCl (178 mg, 1.18 mmol) was added, and stirring was continued until reaction was complete (TLC, 4 h). Volatiles were evaporated, and the residue was partitioned ($NaHCO_3$/H_2O//$CHCl_3$). The aqueous layer was extracted ($CHCl_3$, 2×), and the combined organic phase was washed (brine), dried (Na_2SO_4), and filtered. Volatiles were evaporated, and the residue was chromatographed (EtOAc) to give **21** (846 mg, 93%) with mp 100−103 °C: ^{1}H NMR δ 8.35 (s, 1H), 8.19 (s, 1H), 6.15 (d, J = 3.6 Hz, 1H), 5.70 (br s, 2H), 4.54 (t, J = 4.9 Hz, 1H), 4.19−4.08 (m, 2H), 4.01 (dd, J = 11.4, 3.2 Hz, 1H), 3.78 (dd, J = 11.2, 2.4 Hz, 1H), 3.49 (s, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.11 (s, 12H); ^{13}C NMR δ 156.0, 152.9, 149.3, 138.8, 119.9, 86.4, 84.5, 83.6, 69.4, 61.5, 58.2, 25.7, 25.5, 18.1, 17.8, −4.9, −5.2, −5.7, −5.8; MS (FAB) m/z 510.2930 (MH^+ [$C_{23}H_{44}N_5O_4Si_2$] = 510.2932). Anal. Calcd for $C_{23}H_{43}N_5O_4Si_2$: C, 54.19; H, 8.50; N, 13.74. Found: C, 54.37; H, 8.40; N, 13.90.

3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-*O*-methyl-5-methyluridine (22). A solution of **20** (200 mg, 0.735 mmol), TBDMSCl (277 mg, 1.84 mmol), and imidazole (165 mg, 2.42

mmol) in dried pyridine (2 mL) was stirred for 5.5 h at 70 °C (under N_2). Volatiles were evaporated, and the residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The organic phase was dried (Na_2SO_4) and filtered, and volatiles were evaporated. The residue was chromatographed (EtOAc/hexanes, 7:3) to give **22** (340 mg, 92%): ^{1}H NMR δ 8.29 (br s, 1H), 7.48 (d, J = 1.4 Hz, 1H), 6.01 (d, J = 4.4 Hz, 1H), 4.25 (t, J = 5.1 Hz, 1H), 4.02−3.93 (m, 2H), 3.76 (dd, J = 11.8, 2.2 Hz, 1H), 3.66 ("t", J = 4.7 Hz, 1H), 3.46 (s, 3H), 1.92 (d, J = 1.0 Hz, 3H), 0.95 (s, 9H), 0.91, (s, 9H), 0.134, 0.127, 0.11, 0.09 (4 × s, 4 × 3H); ^{13}C NMR δ 164.4, 150.5, 135.3, 110.6, 87.0, 84.2, 83.5, 69.1, 61.5, 58.0, 25.8, 25.5, 18.3, 17.9, 12.3, −4.9, −5.1, −5.5, −5.7; MS (CI) m/z 501.2805 (MH^+ [$C_{23}H_{45}N_2O_6Si_2$] = 501.2816).

3′-*O*-(*tert*-Butyldimethylsilyl)-5′-chloro-5′-deoxy-2′-*O*-methyladenosine (23). Procedure A [**21** (831 mg, 1.63 mmol), TFA/H_2O (9:1, 4 mL), ∼45 min, partitioned ($NaHCO_3/H_2O//CH_2Cl_2$), aqueous layer extracted (CH_2Cl_2, 2×), combined organic dried (Na_2SO_4), chromatography (5 → 10% MeOH/CH_2Cl_2)] gave 3′-*O*-TBDMS-2′-*O*-methylAdo (383 mg, 60%): ^{1}H NMR (500 MHz) δ 8.35 (s, 1H), 7.89 (s, 1H), 6.81 (dd, J = 11.8, 1.8 Hz, 1H), 5.87 (d, J = 8.0 Hz, 1H), 5.79 (br s, 2H), 4.62 (dd, J = 7.5, 4.5 Hz, 1H), 4.58 (d, J = 4.0 Hz, 1H), 4.21 (s, 1H), 3.95 (dt, J = 13.0, 1.6 Hz, 1H), 3.72 (dd, J = 12.8, 1.5 Hz, 1H), 3.26 (s, 3H), 0.94 (br s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR δ 156.4, 152.2, 148.3, 140.7, 121.0, 89.4, 89.3, 82.1, 71.3, 62.6, 58.1, 25.5, 17.9, −4.9, −5.1; MS (FAB) m/z 396.2082 (MH^+ [$C_{17}H_{30}N_5O_4Si$] = 396.2067). Anal. Calcd for $C_{17}H_{29}N_5O_5Si$: C, 51.62; H, 7.39; N, 17.71. Found: C, 51.85; H, 7.15; N, 17.84.

This material (368 mg, 0.930 mmol) was dissolved in dried pyridine, and volatiles were evaporated (∼5 mL, 2×). The residue was dissolved in dried pyridine (4 mL) and cooled (0 °C) under N_2. $SOCl_2/CH_2Cl_2$ (2.0 M; 1.6 mL, 3.2 mmol) was added, and stirring was continued at ambient temperature until reaction was complete (TLC, ∼20 h). Volatiles were evaporated, and the residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The combined organic phase was dried (Na_2SO_4) and filtered, and volatiles were evaporated. Chromatography (5 → 8% MeOH/CH_2Cl_2) gave **23** (278 mg, 72%): ^{1}H NMR δ 8.35 (s, 1H), 8.05 (s, 1H), 6.05 (d, J = 4.2 Hz, 1H), 5.56 (s, 2H), 4.59 (t, J = 4.8 Hz, 1H), 4.52 (t, J = 4.5 Hz, 1H), 4.32−4.05 (m, 1H), 4.01 (dd, J = 11.8, 5.8 Hz, 1H), 3.72 (dd, J = 12.0, 4.0 Hz, 1H), 3.47 (s, 3H), 0.94 (br s, 9H), 0.15 (s, 6H); ^{13}C NMR δ 156.0, 153.0, 149.4, 139.7, 120.4, 87.7, 83.4, 82.0, 70.9, 58.5, 43.5, 25.6, 18.0, −4.9, −5.0; MS (FAB) m/z 414.1739 (MH^+ [$C_{17}H_{29}{}^{35}ClN_5O_3Si$] = 414.1728).

3′-*O*-(*tert*-Butyldimethylsilyl)-5′-chloro-5′-deoxy-2′-*O*-methyl-5-methyluridine (24). Procedure A [**22** (270 mg, 0.540 mmol), TFA/H_2O (9:1, 5 mL), ∼15 min, partitioned ($NaHCO_3/H_2O//CH_2Cl_2$), aqueous layer extracted (CH_2Cl_2, 2×) and combined organic dried (Na_2SO_4), chromatography (EtOAc/hexanes, 7:3)] gave 3′-*O*-TBDMS-2′-*O*-methyl-5-methylUrd (150 mg, 72%): ^{1}H NMR δ 8.26 (br s, 1H), 7.36 (d, J = 1.2 Hz, 1H), 5.54 (d, J = 5.0 Hz, 1H), 4.39 (t, J = 4.8 Hz, 1H), 4.13−4.03 (m, 2H), 4.00−3.92 (m, 1H), 3.78−3.68 (m, 1H), 3.67 (s, 3H), 2.92 (dd, J = 7.9, 3.1 Hz, 1H), 1.92 (d, J = 1.4 Hz, 3H), 0.92 (br s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 164.2, 150.5, 138.5, 110.8, 91.8, 85.8, 81.9, 69.8, 61.3, 58.3, 25.6, 18.0, 12.3, −4.9, −5.0; MS (CI) m/z 387.1938 (MH^+ [$C_{17}H_{31}N_2O_6Si$] = 387.1951).

This material (90 mg, 0.23 mmol), dried pyridine (3 mL), and MsCl (0.15 mL, 0.22 g, 1.9 mmol) were added to a dried flask, and the solution was stirred for 6 h at 90 °C (under N_2). Volatiles were evaporated, the residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$), and the aqueous layer was extracted (CH_2Cl_2, 2×). The combined organic phase was dried (Na_2SO_4) and filtered. Volatiles were evaporated, and the residue was chromatographed (40 → 50% EtOAc/hexanes) to give **24** (78 mg, 84%): ^{1}H NMR δ 8.74 (br s, 1H), 7.55 (d, J = 1.2 Hz, 1H), 5.84 (d, J = 2.8 Hz, 1H), 4.23 ("d", J = 2.6 Hz, 2H), 4.00 (dd, J = 13.1, 1.9 Hz, 1H), 3.80−3.72 (m, 2H), 3.53 (s, 3H), 1.93 (d, J = 1.0 Hz, 3H), 0.92 (br s, 9H), 0.13 (s, 6H); ^{13}C NMR δ 164.3, 150.3, 135.9, 110.8, 89.0, 83.0, 81.6, 70.1, 58.4, 43.7, 25.5, 17.9, 12.5, −4.8, −5.1; MS (CI) m/z 405.1598 (MH^+ [$C_{17}H_{30}{}^{35}ClN_2O_5Si$] = 405.1613).

5′-Azido-3′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-2′-*O*-methyladenosine (25). A solution of **23** (117 mg, 0.283 mmol) and NaN_3 (73 mg, 1.1 mmol) in dried DMF (2 mL) was stirred for 5 h at 105 °C. Volatiles were evaporated, and the residue was chromatographed (5 → 8% MeOH/CH_2Cl_2) to give **25** (117 mg, 98%): ^{1}H NMR (500 MHz) δ 8.36 (s, 1H), 8.04 (s, 1H), 6.05 (d, J = 3.5 Hz, 1H), 5.54 (s, 2H), 4.57 (t, J = 5.5 Hz, 1H), 4.40 (t, J = 4.5 Hz, 1H), 4.18 (dd, J = 10.0, 4.5 Hz, 1H), 3.74 (dd, J = 13.0, 4.0 Hz, 1H), 3.59 (dd, J = 13.5, 4.5 Hz, 1H), 3.49 (s, 3H), 0.94 (br s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR δ 155.9, 153.1, 149.4, 139.5, 120.3, 87.6, 82.50, 82.46, 70.9, 58.6, 51.2, 25.6, 18.0, −4.8, −5.1; MS (FAB) m/z 421.2142 (MH^+ [$C_{17}H_{29}N_8O_3Si$] = 421.2132).

5′-Azido-3′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-2′-*O*-methyl-5-methyluridine (26). A solution of **24** (78 mg, 0.19 mmol) and LiN_3 (40 mg, 0.82 mmol) in dried DMF (2.0 mL) was stirred for 4 h at 110 °C (under N_2). Volatiles were evaporated, the residue was partitioned (EtOAc//$NaHCO_3$/H_2O), and the aqueous layer was extracted (EtOAc, 2×). The combined organic phase was dried (Na_2SO_4) and filtered, and volatiles were evaporated. Chromatography of the residue (EtOAc/hexanes, 1:1) gave **26** (75 mg, 96%): ^{1}H NMR δ 8.71 (br s, 1H), 7.44 (d, J = 1.2 Hz, 1H), 5.82 (d, J = 2.2 Hz, 1H), 4.16 (dd, J = 7.2, 5.2 Hz, 1H), 4.06 (dt, J = 7.2, 3.0 Hz, 1H), 3.83 (dd, J = 13.5, 3.0 Hz, 1H), 3.71 (dd, J = 5.1, 2.5 Hz, 1H), 3.55 (dd, J = 13.5, 3.0 Hz, 1H), 3.52 (s, 3H), 1.95 (d, J = 1.4 Hz, 3H), 0.91 (br s, 9H), 0.11 (br s, 6H); ^{13}C NMR δ 164.3, 150.3, 135.8, 111.0, 89.1, 83.1, 81.3, 70.0, 58.4, 50.7, 25.5, 18.0, 12.6, −4.8, −5.1; MS (CI) m/z 412.2003 (MH^+ [$C_{17}H_{30}N_5O_5Si$] = 412.2016).

5′-Azido-5′-deoxy-2′-*O*-methyladenosine (27). TBAF/THF (1.0 M; 0.100 mL, 0.100 mmol) was added to a solution of **25** (25 mg, 0.059 mmol) in THF (0.5 mL), and stirring was continued for 2 h. Volatiles were evaporated, and the residue was chromatographed (10% MeOH/CH_2Cl_2) to give **27** (16 mg, 88%): ^{1}H NMR (DMSO-d_6) δ 8.38 (s, 1H), 8.16 (s, 1H), 7.35 (br s, 2H), 6.03 (d, J = 5.4 Hz, 1H), 5.49 (br s, 1H), 4.53 (t, J = 5.1 Hz, 1H), 4.38 (t, J = 4.3 Hz, 1H), 4.05 (ddd, J = 6.8, 3.7, 3.6 Hz, 1H), 3.70 (dd, J = 13.1, 6.9 Hz, 1H), 3.53 (dd, J = 13.0, 3.6 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 156.3, 152.9, 149.4, 140.0, 119.3, 85.7, 83.6, 81.6, 69.5, 57.7, 51.6; MS (FAB) m/z 307.1264 (MH^+ [$C_{11}H_{15}N_8O_3$] = 307.1267).

5′-Azido-5′-deoxy-2′-*O*-methyl-5-methyluridine (28). TBAF/THF (1.0 M; 0.250 mL, 0.250 mmol) was added to a solution of **26** (75 mg, 0.18 mmol) in THF (1.0 mL), and stirring was continued for 3 h. MeOH (4 mL) and Dowex 1-X2 ($^-$OH) resin were added, and the suspension was stirred until the supernatant was UV transparent. The mixture was filtered, the resin was washed (MeOH, 4×, AcOH/MeOH), and the combined filtrate was evaporated to give **28** (50 mg, 93%): ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 7.51 (d, J = 1.0 Hz, 1H), 5.84 (d, J = 5.0 Hz, 1H), 5.34 (d, J = 6.0 Hz, 1H), 4.09 (dd, J = 10.8, 6.0 Hz, 1H), 3.94−3.86 (m, 2H), 3.58 (d, J = 4.8 Hz, 2H), 3.31 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.9, 150.7, 136.5, 110.1, 86.9, 82.5, 81.2, 69.2, 57.7, 51.6, 12.1; MS (FAB) m/z 298.1168 (MH^+ [$C_{11}H_{16}N_5O_5$] = 298.1151).

5′-Amino-5′-deoxy-2′-*O*-methyladenosine (29). Procedure B [**27** (380 mg, 1.24 mmol), 10% Pd−C (102 mg), H_2 (30 psi), EtOH (20 mL), overnight, filter cake washed (EtOH, dilute NH_3/H_2O), recrystallized (EtOH)] gave **29** (300 mg, 86%): mp 200−202 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (s, 1H), 8.16 (s, 1H), 7.36 (br s, 2H), 5.98 (d, J = 6.2 Hz, 1H), 5.27 (br s, 3H), 4.47 (dd, J = 6.0, 5.2 Hz, 1H), 4.35 (dd, J = 4.6, 3.4 Hz, 1H), 3.88 ("q", J = 3.9 Hz, 1H), 3.30 (s, 3H), 2.84 (dd, J = 13.4, 4.6 Hz, 1H), 2.74 (dd, J = 13.2, 5.0 Hz, 1H), 1.70 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 156.3, 152.9, 149.5, 140.2, 119.4, 86.9, 85.4, 82.0, 69.2, 57.5, 43.8; MS (FAB) m/z 303.1164 (MNa^+ [$C_{11}H_{16}N_6O_3Na$] = 303.1182. Anal. Calcd for $C_{11}H_{16}N_6O_3$: C, 47.14; H, 5.75; N, 29.98. Found: C, 47.32; H, 5.54; N, 30.21.

5′-Amino-5′-deoxy-2′-*O*-methyl-5-methyluridine (30). Procedure B [**28** (174 mg, 0.585 mmol), 10% Pd−C (83 mg), H_2 (30 psi), EtOH (25 mL), overnight, filter cake washed (EtOH, dilute NH_3/H_2O), recrystallized (EtOH)] gave **30** (135 mg, 85%): mp 140−143 °C; ^{1}H NMR (DMSO-d_6) δ 7.76 (s, 1H), 5.82 (d, J = 5.4 Hz, 1H), 5.26 (br s, 4H), 4.11 ("t", J = 4.5 Hz,

1H), 3.84 ("t", J = 5.2 Hz, 1H), 3.74 ("d", J = 4.2 Hz, 1H), 3.33 (s, 3H), 2.78 (br s, 2H), 1.78 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.0, 150.9, 136.7, 109.9, 86.0, 82.0, 69.0, 57.6, 43.0, 12.2; MS (FAB) m/z 316.0903 {($MNa_2 - H)^+$ [$C_{11}H_{16}N_3O_5Na_2$] = 316.0885}.

1-[3-*O*-Benzoyl-2,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-3-*N*-(benzoyl)uracil (32). Benzoyl chloride (1.0 mL, 1.2 g, 8.6 mmol) was added to a solution of **31** (1.03 g, 2.18 mmol) in dried pyridine (5 mL), and the solution was stirred overnight at ambient temperature (under N_2). EtOAc and $NaHCO_3/H_2O$ were added, and the aqueous layer was extracted (EtOAc, 2×). The combined organic phase was dried (Na_2SO_4) and filtered. Volatiles were evaporated, and the residue was chromatographed (10 → 20% EtOAc/hexanes) to give **32** (1.42 g, 96%): ^{1}H NMR δ 8.10−7.95 (m, 5H), 7.66−7.41 (m, 6H), 6.17 (d, J = 5.9 Hz, 1H), 5.86 (d, J = 8.0 Hz, 1H), 5.40 (dd, J = 4.9, 3.1 Hz, 1H), 4.50 (t, J = 5.3 Hz, 1H), 4.39 (d, J = 2.6 Hz, 1H), 4.05 (dd, J = 12.1, 2.0 Hz, 1H), 3.92 (d, J = 11.8 Hz, 1H), 0.98 (s, 9H), 0.74 (s, 9H), 0.17 (s, 6H), 0.05 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 168.4, 165.6, 162.0, 149.3, 139.6, 135.0, 133.5, 131.4, 130.4, 129.7, 129.2, 129.0, 128.4, 128.3, 102.6, 88.3, 83.1, 74.8, 72.9, 62.9, 25.9, 25.3, 18.3, 17.7, −5.18, −5.23, −5.6; MS (FAB) m/z 681.3020 (MH^+ [$C_{35}H_{49}N_2O_8Si_2$] = 681.3027).

1-[3-*O*-Benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-3-*N*-(benzoyl)uracil (33). Procedure A [**32** (1.42 g, 2.09 mmol), CH_2Cl_2/TFA/H_2O (20:9:1, 15 mL), ambient temperature, 45 min, volatiles evaporated, chromatography (40 → 60% EtOAc/hexanes)] gave **33** (949 mg, 81%): ^{1}H NMR δ 8.09−7.86 (m, 5H), 7.71−7.42 (m, 6H), 5.90 (d, J = 8.2 Hz, 1H), 5.83 (d, J = 5.5 Hz, 1H), 5.46 (dd, J = 4.9, 3.8 Hz, 1H), 4.74 (t, J = 5.3 Hz, 1H), 4.38 (m, 1H), 4.06−3.82 (m, 2H), 2.80 ("t", J = 4.9 Hz, 1H), 0.79 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 168.4, 165.8, 162.1, 149.4, 141.2, 135.2, 133.5, 131.2, 130.4, 129.7, 129.2, 129.1, 128.4, 102.5, 90.9, 83.1, 73.6, 72.7, 61.6, 25.4, 17.7, −5.16, −5.24; MS (FAB) m/z 567.2147 (MH^+ [$C_{29}H_{35}N_2O_8Si$] = 567.2163).

1-[3-*O*-Benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-5-chloro-5-deoxy-β-D-ribofuranosyl]-3-*N*-(benzoyl)uracil (34). $SOCl_2$/CH_2Cl_2 (2.0 M; 2.2 mL, 4.4 mmol) was added to a stirred solution of **33** (700 mg, 1.24 mmol) in dried pyridine (14 mL) at 0 °C (under N_2), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, the residue was partitioned (EtOAc//$NaHCO_3/H_2O$), and the organic layer was washed ($NaHCO_3/H_2O$ and brine), dried (Na_2SO_4), and filtered. Volatiles were evaporated, and the residue was chromatographed (40% EtOAc/hexanes) to give **34** (505 mg, 70%): ^{1}H NMR δ 8.10 (d, J = 7.2 Hz, 2H), 7.96 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.68−7.27 (m, 6H), 6.13 (d, J = 6.2 Hz, 1H), 5.97 (d, J = 8.2 Hz, 1H), 5.37 (dd, J = 5.4, 3.4 Hz, 1H), 4.60−4.51 (m, 2H), 3.97 (d, J = 2.8 Hz, 2H), 0.77 (br s, 9H), 0.07 (s, 3H), −0.02 (s, 3H); ^{13}C NMR δ 168.3, 165.7, 161.8, 149.4, 139.3, 135.2, 133.8, 131.4, 130.5, 129.88, 129.17, 129.0, 128.6, 103.3, 88.5, 81.0, 73.7, 72.7, 44.8, 25.3, 17.7, −5.3; MS (FAB) m/z 585.1807 (MH^+ [$C_{29}H_{34}{}^{35}ClN_2O_7Si$] = 585.1824).

5′-Azido-3′-*O*-benzoyl-2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridine (35). A stirred solution of **34** (342 mg, 0.584 mmol) and LiN_3 (144 mg, 2.94 mmol) in dried DMF (3 mL) was heated for 2 h at 110 °C. Volatiles were evaporated (∼60 °C), and the residue was chromatographed (30 → 40% EtOAc/hexanes) to give **35** (231 mg, 81%): ^{1}H NMR δ 8.08 (br s, 1H), 8.07 (d, J = 7.6 Hz, 2H) 7.62−7.43 (m, 4H), 6.00 (d, J = 5.4 Hz, 1H), 5.84 (d, J = 7.2 Hz, 1H), 5.25 (t, J = 4.9 Hz, 1H), 4.50−4.40 (m, 2H), 3.86 (dd, J = 13.2, 2.6 Hz, 1H), 3.75 (dd, J = 13.2, 3.0 Hz, 1H), 0.76 (br s, 9H), 0.027 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 165.8, 163.1, 150.4, 139.7, 133.7, 129.9, 129.0, 128.6, 103.3, 89.5, 80.1, 73.5, 72.3, 51.9, 25.3, 17.7, −5.2, −5.4; MS (FAB) m/z 488.1964 (MH^+ [$C_{22}H_{30}N_5O_6Si$] = 488.1965).

5′-Amino-3′-*O*-benzoyl-2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridine (36). $SnCl_2 \cdot 2H_2O$ (190 mg, 0.842 mmol) was added to a cold (∼0 °C) solution of **35** (98 mg, 0.20 mmol) in MeOH (5 mL), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, and the residue was chromatographed (10% MeOH/CH_2Cl_2) to give **36** (48 mg, 52%): ^{1}H NMR δ 8.07 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.2 Hz, 1H), 7.64−7.56 (m, 1H), 7.49−7.42 (m, 2H), 5.90 (d, J = 4.0 Hz, 1H), 5.78 (d, J = 7.8 Hz, 1H), 5.29 (br s, 1H), 4.60 (br s, 1H), 4.34 (br s, 1H), 3.40−2.5 (br s, 4H), 0.77 (s, 9H), 0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR δ 165.9, 163.4, 150.4, 140.9, 133.5, 129.9, 129.3, 128.5, 102.7, 90.8, 73.8, 72.3, 29.6, 25.4, 17.7−5.2, −5.3; MS (FAB) m/z 462.2051 (MH^+ [$C_{22}H_{32}N_3O_6Si$] = 462.2060.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxyadenosine (37). Procedure D [NaOH (500 mg, 12.5 mmol), **5** (200 mg, 0.353 mmol), MeOH/H_2O (9:1, 10 mL), 3 h, pH ∼2 (0.5 M HCl/H_2O), (EtOAc/brine), chromatography (3% MeOH/$CHCl_3$)] gave **37** (139 mg, 73%) as a solid foam: ^{1}H NMR (DMSO-d_6) δ 12.4 (br s, 1H), 8.35 (s, 1H), 8.14 (s, 1H), 7.33 (br s, 2H), 5.92 (s, 1H), 4.58 (d, J = 4.6 Hz, 1H), 4.03−3.96 (m, 2H), 3.78 (dd, J = 11.3, 2.2 Hz, 1H), 2.75−2.60 (m, 1H), 2.50−2.36 (m, 2H), 0.88 (s, 18H), 0.13 (s, 3H), 0.08 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 173.6, 156.2, 152.8, 148.9, 138.1, 119.2, 89.9, 83.8, 77.5, 62.3, 37.6, 29.4, 25.9, 25.7, 18.1, 17.7, −4.7, −5.5, −5.58, −5.63; MS (FAB) m/z 538.2870 (MH^+ [$C_{24}H_{44}N_5O_5Si_2$] = 538.2881). Anal. Calcd for $C_{24}H_{43}N_5O_5Si_2$: C, 53.60; H, 8.06; N, 13.02. Found: C, 53.39; H, 7.85; N, 12.78.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxyuridine (38). Procedure D [NaOH (529 mg, 13.2 mmol), **6** (306 mg, 0.564 mmol), MeOH/THF/H_2O (4:2:1, 3.5 mL), 1 h, pH ∼2 (0.5 M HCl/H_2O), (EtOAc/brine), chromatography (EtOAc)] gave **38** (256 mg, 88%) as a solid foam: ^{1}H NMR (500 MHz) δ 8.91 (br s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 5.72 (s, 1H), 5.66 (d, J = 9.0 Hz, 1H), 4.45 (d, J = 4.5 Hz, 1H), 4.17−4.13 (m, 2H), 4.05 (d, J = 10.5 Hz, 1H), 3.72 (d, J = 11.0 Hz, 1H), 2.70 (dd, J = 16.8, 10.3 Hz, 1H), 2.55−2.52 (m, 1H), 2.30 (dd, J = 16.8, 4.3 Hz, 1H), 0.93 (s, 9H), 0.92 (s, 9H), 0.25 (s, 3H), 0.13 (s, 6H), 0.12 (s, 3H); ^{13}C NMR δ 176.9, 164.9, 150.6, 141.0, 101.2, 91.4, 84.5, 61.1, 36.7, 28.9, 25.8, 25.7, 18.3, 17.9, −4.6, −5.7, −5.9; MS (FAB) m/z 515.2597 (MH^+ [$C_{23}H_{43}N_2O_7Si_2$] = 515.2609).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[(4-nitrophenoxy)carbonyl]methyl]adenosine (39). A solution of **37** (500 mg, 0.930 mmol), 4-nitrophenol (190 mg, 1.37 mmol), DCC (280 mg, 1.36 mmol), and 1-hydroxybenzotriazole (63 mg, 0.47 mmol) in dried DMF (10 mL) was stirred for 36 h at ambient temperature (under N_2). Volatiles were evaporated, and the residue was suspended (CH_2Cl_2) and filtered (Celite). The filter cake was washed (CH_2Cl_2), and the combined filtrate was evaporated. The residue was chromatographed (30 → 50% EtOAc/hexanes) to give **39** (441 mg, 72%): ^{1}H NMR δ 8.37 (s, 1H), 8.32 (s, 1H), 8.26 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 9.3 Hz, 2H), 6.20 (br s, 2H), 6.06 (s, 1H), 4.77 (d, J = 4.0 Hz, 1H), 4.21−4.10 (m, 2H), 3.84 ("dd", J = 9.4, 2.4 Hz, 1H), 3.09−2.84 (m, 2H), 2.70 (dd, J = 15.9, 2.8 Hz, 1H), 0.95 (br s, 18H), 0.24, 0.15, 0.14, 0.08 (4 × s, 4 × 3H); ^{13}C NMR δ 169.9, 155.4, 154.1, 149.4, 149.3, 145.9, 140.6, 131.8, 125.8, 122.6, 120.2, 91.4, 84.7, 69.6, 62.7, 38.4, 30.1, 26.5, 26.3, 19.0, 18.5, 1.5, −3.9, −4.8, −5.0; MS (FAB) m/z 659.3046 (MH^+ [$C_{30}H_{47}N_6O_7Si_2$] = 659.3045).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]uridine (40). Method A. MsCl (0.10 mL, 148 mg, 1.29 mmol) was added to a cold (∼0 °C) solution of **8** (295 mg, 0.688 mmol) in dried pyridine (2 mL) and stirred for 3 h at ∼0 °C (under N_2). Volatiles were evaporated, and the residue was chromatographed (5% MeOH/CH_2Cl_2) to give 2′-*O*-TBDMS-3′-deoxy-3′-[(ethoxycarbonyl)-methyl]-5′-*O*-methanesulfonylUrd (289 mg, 83%) as a white solid: mp 120−123 °C; ^{1}H NMR δ 8.40 (br s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 5.74 (dd, J = 8.2, 2.3 Hz, 1H), 5.69 (s, 1H), 4.60 (dd, J = 11.7, 1.9 Hz, 1H), 4.50 (d, J = 4.0 Hz, 1H), 4.40 (dd, J = 11.9, 3.4 Hz, 1H), 4.27−4.22 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.10 (s, 3H), 2.68−2.60 (m, 1H), 2.50−2.35 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.21 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 171.4, 163.7, 150.3, 139.3, 101.7, 92.0, 81.3, 77.1, 67.4, 60.9, 38.3, 37.6, 29.2, 25.6, 17.9, 14.0, −4.5, −5.8; MS (FAB) m/z 507.1824 (MH^+ [$C_{20}H_{35}N_2O_9SSi$] = 507.1833).

A solution of this material (260 mg, 0.513 mmol) and LiN_3 (92 mg, 1.9 mmol) in dried DMF (2 mL) was stirred for 5.5 h at 97 °C (under N_2). Volatiles were evaporated, the residue

was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$), and the aqueous layer was extracted (CH_2Cl_2, 2×). The combined organic phase was dried (Na_2SO_4), volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:1) to give **40** (214 mg, 92%) as a solid foam: ^{1}H NMR (300 MHz) δ 9.19 (br s, 1 H), 7.77 (d, J = 8.1 Hz, 1 H), 5.76 (d, J = 8.4 Hz, 1 H), 5.71 (s, 1 H), 4.45 (d, J = 4.5 Hz, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.11 (dd, J = 6.6, 3.3 Hz, 1H), 3.87 (dd, J = 13.7, 2.9 Hz, 1H), 3.59 (dd, J = 13.7, 3.8 Hz, 1H), 2.64 (dd, J = 16.7, 8.3 Hz, 1H), 2.47−2.38 (m, 1H), 2.31 (dd, J = 16.8, 5.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.21 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz) δ 171.8, 163.5, 150.4, 139.7, 102.2, 91.9, 82.1, 77.7, 61.2, 51.8, 39.6, 29.8, 26.0, 18.2, 14.4, −4.3, −5.4; MS (FAB) m/z 454.2123 (MH^+ $[C_{19}H_{32}N_5O_6Si]$ = 454.2122).

Method B. A solution of **8** (108 mg, 0.252 mmol), I_2 (83 mg, 0.33 mmol), and Ph_3P (86 mg, 0.33 mmol) in dried pyridine (2 mL) was stirred for 12 h at ambient temperature. Volatiles were evaporated, the residue was partitioned ($NaHCO_3/H_2O//CHCl_3$), and the organic phase was washed ($Na_2S_2O_3/H_2O$) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 2:1) to give 2′-*O*-TBDMS-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]-5′-iodoUrd (101 mg, 74%) as a glass: ^{1}H NMR (300 MHz) δ 9.50 (br s, 1H), 7.70 (d, J = 8.4 Hz, 1H), 5.77 (d, J = 8.1 Hz, 1H), 5.73 (d, J = 1.5 Hz, 1H), 4.53 (dd, J = 5.1, 1.5 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.79 (ddd, J = 8.8, 5.6, 3.2 Hz, 1H), 3.60 (dd, J = 11.6, 3.2 Hz, 1H), 3.36 (dd, J = 11.4, 5.4 Hz, 1H), 2.63 (dd, J = 16.8, 8.4 Hz, 1H), 2.35 (dd, J = 16.4, 5.6 Hz, 1H), 2.30−2.25 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz) δ 171.8, 163.7, 150.4, 140.3, 102.4, 91.6, 81.7, 77.7, 61.2, 44.3, 29.9, 25.9, 18.1, 14.3, 7.2, −4.4, −5.6; MS (FAB) m/z 539.1073 (MH^+ $[C_{19}H_{32}IN_2O_6Si]$ = 539.1074).

A solution of this material (101 mg, 0.188 mmol) and NaN_3 (37 mg, 0.57 mmol) in dried DMF (3.5 mL) was stirred for 24 h at 65 °C. Volatiles were evaporated (∼60 °C), the residue was partitioned (EtOAc//$NaHCO_3/H_2O$), and the organic layer was washed ($NaHCO_3/H_2O$) and dried (Na_2SO_4). Volatiles were evaporated to give **40** (85 mg, 99%) as a solid foam (∼95%, ^{1}H NMR).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-(carboxymethyl)-3′,5′-dideoxyuridine (41). Procedure D [NaOH (43 mg, 1.1 mmol), **40** (85 mg, 0.19 mmol), MeOH/H_2O (4:1, 2.1 mL), 3 h, pH ∼4 (4% HCl/H_2O)]. The precipitate was filtered, washed (cold H_2O), and dried (vacuum) to give **41** (62 mg, 77%): ^{1}H NMR (300 MHz) δ 9.86 (br s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 5.80 (d, J = 8.1 Hz, 1H), 5.68 (s, 1 H), 4.48 (d, J = 4.5 Hz, 1H), 4.14 (dt, J = 9.9, 2.9 Hz, 1H), 3.89 (dd, J = 13.4, 2.6 Hz, 1H), 3.61 (dd, J = 14.0, 3.5 Hz, 1H), 2.68 (dd, J = 16.4, 8.3 Hz, 1H), 2.49−2.43 (m, 1H), 2.36 (dd, J = 16.5, 4.8 Hz, 1H), 0.91 (s, 9H), 0.20 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz) δ 176.3, 164.4, 150.5, 140.4, 102.1, 92.4, 82.2, 77.6, 51.7, 39.6, 29.9, 26.0, 18.2, −4.3, −5.4; MS (FAB) m/z 448.1610 (MNa^+ $[C_{17}H_{27}N_5O_6SiNa]$ = 448.1628).

5′-Amino-2′-*O*-(*tert*-butyldimethylsilyl)-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]uridine (42). Procedure C [Et_3N (0.95 mL), 1,3-propanedithiol (0.94 mL, 1.0 g, 9.4 mmol), **40** (708 mg, 1.56 mmol), dried EtOH (28 mL), 12 h, chromatography (MeOH/CH_2Cl_2, 1:9)] gave **42** (512 mg, 77%): ^{1}H NMR (300 MHz) δ 8.28 (d, J = 8.1 Hz, 1H), 5.71 (s, 1H), 5.70 (d, J = 8.1 Hz, 1H), 4.41 (d, J = 3.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.03 (d, J = 8.4 Hz, 1H), 3.14 (br s, 1H), 2.91 (br s, 1H), 2.64 (dd, J = 16.5, 7.2 Hz, 1H), 2.43−2.35 (m, 1H), 2.31 (dd, J = 16.0, 5.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz) δ 172.3, 164.0, 150.5, 140.8, 101.7, 92.1, 85.1, 78.4, 61.1, 39.2, 29.9, 26.0, 18.2, 14.4, −4.2, −5.4; MS (FAB) m/z 428.2233 (MH^+ $[C_{19}H_{34}N_3O_6Si]$ = 428.2217).

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxyuridine (43). Procedure D [NaOH (640 mg, 16.0 mmol), **8** (774 mg, 1.81 mmol), MeOH/H_2O (5:1, 60 mL), 5 h, pH ∼2 (0.5 M HCl/H_2O), chromatography (MeOH/CH_2Cl_2, 1:9) gave **43** (480 mg, 66%): ^{1}H NMR (Me_2CO-d_6) δ 10.04 (br s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 5.69 (s, 1H), 5.54 (d, J = 8.2 Hz, 1H), 4.52 (br s, 1H), 4.06−4.00 (m, 2H), 3.82 (d, J = 12.4 Hz, 1H), 3.50−3.31 (m, 1H), 3.00−2.81 (br s, 1H), 2.71−2.42 (m, 2H), 0.92 (br s, 9H), 0.25 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (Me_2CO-d_6) δ 174.1, 164.3, 151.6, 150.6, 141.5, 101.4, 92.3, 85.8, 79.1, 60.8, 38.0, 26.3, 18.7, −4.1, −5.4; MS (FAB) m/z 401.1762 (MH^+ $[C_{17}H_{29}N_2O_7Si]$ = 401.1744).

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-(carboxymethyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)uridine Triethylammonium Salt (44). Dried pyridine (1.0 mL), dried Et_3N (0.10 mL), DMTCl (120 mg, 0.354 mmol), and **43** (70 mg, 0.18 mmol) were added to a flame-dried flask, and the solution was stirred for 4 h at ambient temperature (under N_2). Volatiles were evaporated, the residue was chromatographed (Et_3N/MeOH/CH_2Cl_2, 1:5:95), and the product was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The aqueous layer was extracted (CH_2Cl_2, 3×), and the combined organic phase was dried (Na_2SO_4). Volatiles were evaporated to give **44** (90 mg, 62%): ^{1}H NMR δ 8.33 (br s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.44−7.21 (m, 9H), 6.83 (d, J = 8.6 Hz, 4H), 5.70 (s, 1H), 5.25 (d, J = 8.2 Hz, 1H), 4.55 (d, J = 3.0 Hz, 1H), 4.10 (d, J = 9.4 Hz, 1H), 3.78 (s, 6H), 3.60 (d, J = 11.0 Hz, 1H), 3.31 (dd, J = 11.0, 3.3 Hz, 1H), 2.94 (q, J = 7.3 Hz, 6H), 2.57−2.37 (m, 2H), 2.08−2.00 (m, 1H), 1.20 (t, J = 7.3 Hz, 9H), 0.88 (br s, 9H), 0.22 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ 176.2, 163.9, 158.6, 150.2, 144.5, 140.7, 135.4, 135.2, 130.1, 128.1, 127.9, 127.0, 113.2, 101.1, 92.0, 86.7, 83.5, 61.7, 55.1, 45.2, 38.5, 30.1, 25.7, 17.9, 8.4, −4.7, −5.7; MS (FAB) m/z 702.2971 [$(M - Et_3N)^+$ $[C_{38}H_{46}N_2O_9Si]$ = 702.2973].

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-3′-[[(4-nitrophenoxy)carbonyl]methyl]uridine (45). A solution of **44** (50 mg, 0.062 mmol), 4-nitrophenol (10 mg, 0.072 mmol), and DCC (15 mg, 0.073 mmol) in dried CH_2Cl_2 (1.0 mL) was stirred overnight at ambient temperature (under N_2). The suspension was filtered (Celite), volatiles were evaporated, and the residue was chromatographed (EtOAc/CH_2Cl_2, 1:9) to give **45** (31 mg, 61%): ^{1}H NMR δ 8.28 (d, J = 9.2 Hz, 2H), 8.24 (d, J = 8.4 Hz, 1H), 7.91 (br s, 1H), 7.51−7.18 (m, 12H), 6.84 (dd, J = 8.9, 2.3 Hz, 4H), 5.77 (s, 1H), 5.31 (dd, J = 8.1, 2.5 Hz, 1H), 4.47 (d, J = 3.8 Hz, 1H), 4.14−4.08 (m, 1H), 3.90 ("d", J = 12.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.35 ("d", J = 13.4 Hz, 1H), 2.84−2.62 (m, 1H), 2.13 (m, 1H), 0.90 (br s, 9H), 0.25 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 169.3, 163.5, 158.8, 155.0, 150.3, 145.4, 144.3, 140.2, 135.1, 134.9, 130.2, 128.1, 127.2, 125.3, 122.1, 113.3, 101.6, 91.5, 87.3, 83.2, 77.4, 60.8, 55.2, 37.6, 29.6, 27.3, 25.7, 17.9, −4.5, −5.8; MS (FAB) m/z 824.3220 (MH^+ $[C_{44}H_{50}N_3O_{11}Si]$ = 824.3215).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[*N*-(2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyadenosin-5′-yl)-carboxamido]methyl]adenosine (46). Procedure E [**17** (100 mg, 0.202 mmol), **37** (110 mg, 0.204 mmol), DCC (50.0 mg, 0.241 mmol), dried CH_2Cl_2 (1.0 mL), chromatography (MeOH/CH_2Cl_2, 1:9)] gave **46** (168 mg, 82%): ^{1}H NMR (500 MHz) δ 8.56 (br s, 1H), 8.40, 8.37, 8.36, 7.85 (4 × s, 4 × 1H), 6.07 (d, J = 2.5 Hz, 1H), 5.75 (d, J = 8.0 Hz, 1H), 5.74 (br s, 2H), 5.56 (br s, 2H), 4.90 (dd, J = 7.8, 5.3 Hz, 1H), 4.83 (dd, J = 5.0, 2.0 Hz, 1H), 4.28 (s, 1H), 4.21 (d, J = 7.5 Hz, 1H), 4.10 (d, J = 5.0 Hz, 2H), 4.08 (dd, J = 11.5, 2.0 Hz, 1H), 3.80 (dd, J = 11.8, 2.8 Hz, 1H), 3.27 (d, J = 14.5 Hz, 1H), 2.97−2.89 (m, 1H), 2.72 (dd, J = 15.5, 6.0 Hz, 1H), 2.44 (dd, J = 15.0, 8.0 Hz, 1H), 0.94 (s, 18H), 0.87, 0.75, 0.14 (3 × s, 3 × 9H), 0.12, 0.11, 0.04, −0.16, −0.57 (5 × s, 5 × 3H); ^{13}C NMR δ 171.5, 156.5, 155.6, 152.9, 152.5, 149.6, 148.9, 141.2, 138.9, 121.3, 119.7, 90.2, 90.0, 86.3, 85.1, 78.4, 73.4, 73.1, 63.7, 40.8, 38.9, 32.5, 25.9, 25.7, 25.6, 25.4, 18.4, 17.8, 17.6, −4.7, −4.8, −5.0, −5.2, −5.5, −5.8; MS (FAB) m/z 1014.5621 (MH^+ $[C_{46}H_{84}N_{11}O_7Si_4]$ = 1014.5632). Anal. Calcd for $C_{46}H_{83}N_{11}O_7Si_4$: C, 54.46; H, 8.25; N, 15.19. Found: C, 54.37; H, 8.41; N, 15.05.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[*N*-(2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridin-5′-yl)carboxamido]methyl]adenosine (47). Procedure E [**18** (46 mg, 0.098 mmol), **37** (53 mg, 0.099 mmol), DCC (25 mg, 0.12 mmol), dried CH_2Cl_2 (0.5 mL), chromatography (EtOAc/hexanes, 7:3)] gave **47** (73 mg, 75%): ^{1}H NMR (500 MHz) δ 10.75, 8.54, 8.46 (3 × s, 3 × 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.12 (m, 1H), 6.19 (d, J = 2.0 Hz, 1H), 5.82 (br s, 2H), 5.73 (dd, J = 7.8, 2.3 Hz, 1H), 5.10 (d, J = 7.0 Hz, 1H), 4.83 (dd, J = 7.5, 5.0 Hz, 1H), 4.46 (dd, J = 4.3, 2.3 Hz, 1H), 4.14 (dt, J = 8.0, 2.5 Hz, 1H), 4.11−4.09 (m, 1H), 4.07 (dd, J = 12.0, 2.5 Hz, 1H), 3.90 (dd, J =

5.0, 1.5 Hz, 1H), 3.83−3.78 (m, 2H), 3.26 (dt, J = 14.5, 3.1 Hz, 1H), 2.88 (ddd, J = 15.5, 7.5, 5.0 Hz, 1H), 2.57 (dd, J = 15.5, 8.0 Hz, 1H), 2.49 (dd, J = 15.5, 8.0 Hz, 1H), 0.97, 0.91, 0.88, 0.87 (4 × s, 4 × 9H), 0.17, 0.16, 0.14 (3 × s, 3 × 3H), 0.09 (s, 6H), 0.04, 0.01, −0.01 (3 × s, 3 × 3H); ^{13}C NMR (75 MHz) δ 171.2, 163.6, 163.6, 155.5, 153.0, 150.9, 149.5, 143.9, 139.4, 119.4, 102.7, 96.2, 89.4, 84.9, 84.3, 78.0, 73.3, 71.8, 63.3, 41.0, 38.3, 32.5, 29.7, 26.1, 25.8, 25.7, 18.6, 18.0, 17.9, −4.6, −4.7, −4.8, −5.29, −5.33; MS (FAB) m/z 991.5354 (MH$^+$ [$C_{45}H_{83}N_8O_9Si_4$] = 991.5360). Anal. Calcd for $C_{45}H_{82}N_8O_9Si_4$: C, 54.51; H, 8.34; N, 11.30. Found: C, 54.46; H, 8.08; N, 10.96.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[*N*-(2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridin-5′-yl)carboxamido]methyl]uridine (48). Procedure E [**38** (80 mg, 0.16 mmol), **18** (80 mg, 0.17 mmol), DCC (64 mg, 0.31 mmol), dried CH_2Cl_2 (0.8 mL), chromatography (40 → 70% EtOAc/hexanes)] gave **48** (115 mg, 74%): ^{1}H NMR (500 MHz) δ 8.88 (br s, 1H), 8.66 (br s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.91 (dd, J = 6.7, 4.2 Hz, 1H), 5.80 (d, J = 2.5 Hz, 1H), 5.75 (d, J = 7.5 Hz, 1H), 5.65 (d, J = 8.5 Hz, 1H), 5.24 (d, J = 6.0 Hz, 1H), 4.68 (dd, J = 6.0, 5.0 Hz, 1H), 4.44 (dd, J = 5.3, 2.3 Hz, 1H), 4.12−4.10 (m, 1H), 4.07−4.03 (m, 2H), 3.92 (dd, J = 5.0, 3.0 Hz, 1H), 3.71 (dd, J = 12.3, 1.8 Hz, 1H), 3.62 (quint, J = 6.9 Hz, 1H), 3.40 (dt, J = 14.3, 3.6 Hz, 1H), 2.65−2.62 (m, 1H), 2.53 (dd, J = 15.4, 7.6 Hz, 1H), 2.26 (dd, J = 15.4, 7.1 Hz, 1H), 0.93, 0.90, 0.89, 0.86 (4 × s, 4 × 9H), 0.16 (s, 3H), 0.11 (s, 6H), 0.08 (s, 6H), 0.07, 0.04, −0.02 (3 × s, 3 × 3H); ^{13}C NMR δ 171.3, 164.0, 163.5, 150.6, 150.5, 143.7, 140.7, 128.3, 102.5, 101.4, 95.6, 90.5, 84.5, 73.1, 72.2, 62.3, 41.1, 37.8, 31.4, 25.8, 25.70, 25.65, 25.6, 18.3, 17.91, 17.85, 17.8, −4.65, −4.72, −4.8, −4.9, −5.0, −5.5, −5.7, −5.8; MS (FAB) m/z 968.5101 (MH$^+$ [$C_{44}H_{82}N_5O_{11}Si_4$] = 968.5088). Anal. Calcd for $C_{44}H_{81}N_5O_{11}Si_4$: C, 54.57; H, 8.43; N, 7.23. Found: C, 54.62; H, 8.18; N, 7.08.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[*N*-(5′-deoxyadenosin-5′-yl)carboxamido]methyl]adenosine (49). Procedure F [**39** (100 mg, 0.152 mmol), 5′-amino-5′-deoxyAdo (40 mg, 0.15 mmol), pyridine (5 mL), 4 days, chromatography (SSA)] gave **49** (77 mg, 65%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.39 (s, 1H), 8.37 (s, 1H), 8.31 (t, J = 4 Hz, 1H), 8.21 (s, 1H), 8.20 (s, 1H), 7.36 (br s, 4H), 5.95 (d, J = 2.0 Hz, 1H), 5.89 (d, J = 6.5 Hz, 1H), 5.48 (d, J = 5.5 Hz, 1H), 5.29 (d, J = 4.0 Hz, 1H), 4.73 (d, J = 5.5 Hz, 1H), 4.65 (dd, J = 5.0, 1.5 Hz, 1H), 4.39 (d, J = 4.0 Hz, 1H), 4.11−3.98 (m, 4H), 3.81−3.79, 3.53−3.42, 2.82−2.74 (3 × m, 3 × 1H), 2.49 (dd, J = 16.8, 7.2 Hz, 1H; overlap with solvent peaks), 2.30 (dd, J = 16.8, 6.3 Hz, 1H), 0.93 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.11 (s, 6H), 0.10 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.5, 156.1, 156.0, 152.6, 152.4, 149.2, 148.8, 140.2, 137.9, 119.4, 118.9, 89.3, 87.9, 84.0, 83.2, 77.6, 72.6, 71.3, 62.8, 37.8, 30.5, 25.8, 25.6, 18.1, 17.6, −4.9, −5.5; MS (FAB) m/z 786.3919 (MH$^+$ [$C_{34}H_{56}N_{11}O_7Si_2$] = 786.3903).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-[[*N*-(5′-deoxyuridin-5′-yl)carboxamido]methyl]adenosine (50). Procedure F [**39** (10 mg, 0.015 mmol), 5′-amino-5′-deoxyUrd (4 mg, 0.02 mmol), pyridine (0.5 mL), 3 days, chromatography (SSA)] gave **50** (8 mg, 70%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.39, 8.38, 8.20 (3 × s, 3 × 1H), 8.15 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.35 (s, 2H), 5.95 (d, J = 2.0 Hz, 1H), 5.77 (d, J = 5.5 Hz, 1H), 5.66 (d, J = 8.5 Hz, 1H), 5.42 (d, J = 5.5 Hz, 1H), 5.17 (d, J = 5.5 Hz, 1H), 4.66 (dd, J = 5.0, 1.5 Hz, 1H), 4.11 (dd, J = 10.8, 5.3 Hz, 1H), 4.05−4.02 (m, 2H), 3.87 (dd, J = 10.0, 5.0 Hz, 1H), 3.84−3.78 (m, 2H), 3.52−3.49, 3.23−3.19, 2.80−2.77 (3 × m, 3 × 1H), 2.48 (dd, J = 16.0, 8.0 Hz, 1H), 2.30 (dd, J = 15.8, 6.3 Hz, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 6H), 0.11 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.5, 162.9, 156.0, 152.5, 150.6, 148.8, 141.3, 137.9, 118.9, 101.9, 89.3, 88.4, 83.9, 82.2, 77.6, 72.4, 70.9, 62.8, 41.2, 37.8, 30.5, 25.8, 25.6, 18.1, 17.6, −4.9, −5.5; MS (FAB) m/z 763.3649 (MH$^+$ [$C_{33}H_{55}N_8O_9Si_2$] = 763.3631).

3′-[[*N*-(3′-*O*-Benzoyl-2′-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridin-5′-yl)carboxamido]methyl]-2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-(4,4′-dimethoxytrityl)-3′-deoxyuridine (51). Procedure E [**44** (88 mg, 0.11 mmol), **36** (48 mg, 0.10 mmol), DCC (40 mg, 0.19 mmol), dried CH_2Cl_2 (0.9 mL), chromatography (50 → 60% EtOAc/hexanes)] gave **51** (81 mg, 71%): ^{1}H NMR δ 8.50 (s, 1H), 8.20−8.13 (m, 2H), 8.04 ("d", J= 7.2 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.49−7.17 (m, 12H), 6.85 ("d", J = 6.2 Hz, 4H), 6.73 (br s, 1H), 5.77 (s, 1H), 5.75 (d, J = 8.0 Hz, 1H), 5.36−5.21 (m, 3H), 4.90 (t, J = 5.7 Hz, 1H), 4.60 ("d", J = 3.8 Hz, 1H), 4.39 (m, 1H), 4.08 ("d", J = 8.6 Hz, 1H), 3.80 (s, 6H), 3.69−3.63 (m, 1H), 3.39 (d, J = 14.8 Hz, 1H), 3.22 (d, J = 10.2 Hz, 1H), 2.79−2.61 (m, 1H), 2.53−2.41 (m, 1H), 2.10−2.00 (m, 2H), 0.88 (s, 9H), 0.72 (s, 9H), 0.23, 0.09, −0.04, −0.05 (4 × s, 4 × 3H); ^{13}C NMR δ 171.2, 165.5, 163.7, 163.0, 158.7, 158.6, 150.4, 150.3, 144.4, 142.9, 140.6, 135.3, 135.0, 133.5, 130.3, 130.2, 129.8, 129.2, 128.5, 128.1, 128.0, 127.1, 113.3, 102.9, 101.4, 95.5, 91.3, 86.9, 83.3, 80.9, 73.1, 71.5, 61.7, 55.2, 41.1, 38.3, 30.6, 25.7, 25.3, 17.9, 17.6, −4.7, −5.3, −5.3, −5.6; MS (FAB) m/z 1168.4785 (MNa$^+$ [$C_{60}H_{75}N_5O_{14}Si_2Na$] = 1168.4747).

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-3′-[[*N*-(2′-*O*-methyl-5′-deoxyadenosin-5′-yl)carboxamido]methyl]uridine (52). Procedure F [**45** (29 mg, 0.035 mmol)/THF/EtOH (1:1, 2.0 mL), **29** (12 mg, 0.043 mmol)/EtOH (1.8 mL), 5 days, preparative TLC (Et_3N/MeOH/CH_2Cl_2, 0.5:10:90)] gave **52** (25 mg, 74%): ^{1}H NMR (500 MHz) δ 9.31 (br s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.92 (m, 1H), 7.91 (s, 1H), 7.41 (dd, J = 7.0, 1.5 Hz, 2H), 7.32−7.22 (m, 7H), 6.82 (dd, J = 6.8, 1.8 Hz, 2H), 6.80 (dd, J = 7.5, 2.0 Hz, 2H), 6.06 (br s, 2H), 5.84 (d, J = 6.5 Hz, 1H), 5.79 (s, 1H), 5.27 (d, J = 8.0 Hz, 1H), 4.58−4.56 (m, 2H), 4.31 (m, 2H), 4.09 (d, J = 10.0 Hz, 1H), 3.97 (ddd, J = 14.5, 8.3, 3.0 Hz, 1H), 3.77 (dd, J = 12.0, 2.0 Hz, 1H), 3.73, 3.71, 3.32 (3 × s, 3 × 3H), 3.32−3.27 (m, 2H), 2.80−2.75 (m, 2H), 2.57 (dd, J = 16.0, 8.5 Hz, 1H), 1.94 (dd, J = 16.0, 4.5 Hz, 1H), 0.84 (br s, 9H), 0.22 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 171.1, 164.2, 158.7, 156.3, 152.8, 150.9, 149.0, 144.4, 141.0, 140.7, 135.3, 135.1, 130.4, 130.2, 128.2, 128.0, 127.1, 120.7, 113.3, 101.8, 91.3, 88.7, 87.1, 84.7, 83.5, 81.4, 78.0, 70.6, 61.5, 58.8, 55.1, 41.1, 38.0, 30.6, 25.7, 17.9, −4.8, −5.3; MS (FAB) m/z 987.4097 (MNa$^+$ [$C_{49}H_{60}N_8O_{11}SiNa$] = 987.4049).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-[[*N*-(2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridin-5′-yl)carboxamido]methyl]-3′,5′-dideoxyuridine (53). Procedure E [**41** (225 mg, 0.529 mmol), **18** (223 mg, 0.473 mmol), DCC (118 mg, 0.572 mmol), dried CH_2Cl_2 (2.2 mL), chromatography (2.5 → 5% MeOH/CH_2Cl_2)] gave **53** (324 mg, 78%): ^{1}H NMR (300 MHz) δ 9.11 (br s, 1H), 8.93 (br s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 6.9, 3.6 Hz, 1H), 5.76 (s, 1H), 5.74 (t, J = 2.0 Hz, 2H), 5.21 (d, J = 6.6 Hz, 1H), 4.74 (dd, J = 6.6, 5.1 Hz, 1H), 4.40 (dd, J = 4.7, 1.7 Hz, 1H), 4.18−4.14 (m, 2H), 3.95 (dd, J = 4.8, 2.1 Hz, 1H), 3.81 (dd, J = 13.5, 2.7 Hz, 1H), 3.72−3.61 (m, 2H), 3.39 (dt, J = 13.8, 3.2 Hz, 1H), 2.59−2.49 (m, 2H), 2.34 (dd, J = 17.0, 9.5 Hz, 1H), 0.92, 0.91, 0.86 (3 × s, 3 × 9H), 0.19, 0.10, 0.096, 0.09, 0.04, −0.02 (6 × s, 6 × 3H); ^{13}C NMR (75 MHz) δ 171.4, 163.3, 162.9, 150.7, 150.5, 144.7, 139.9, 102.9, 102.4, 97.0, 91.2, 85.3, 82.6, 78.1, 73.5, 71.8, 52.7, 41.4, 40.1, 32.4, 26.04, 25.99, 25.9, 18.3, 18.1, −4.3, −4.4, −4.7, −5.1; MS (FAB) m/z 901.4114 (MNa$^+$ [$C_{38}H_{66}N_8O_{10}Si_3Na$] = 901.4107).

5′-Amino-2′-*O*-(*tert*-butyldimethylsilyl)-3′-[[*N*-(2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxyuridin-5′-yl)carboxamido]methyl]-3′,5′-dideoxyuridine (54). Procedure B [**53** (25 mg, 0.028 mmol), 10% Pd−C (5 mg), H_2 (5 psi), dried THF (5 mL), 8 h, chromatography (SSA)] gave **54** (15 mg, 63%): ^{1}H NMR (500 MHz) δ 8.30, 7.30, 7.24 (3 × br s, 3 × 1H), 5.76 (d, J = 7.0 Hz, 1H), 5.69 (d, J = 6.5 Hz, 1H), 5.63 (s, 1H), 5.21 (s, 1H), 4.71 (br s, 1H), 4.41 (br s, 1H), 4.12 (br s, 2H), 3.95 (br s, 1H), 3.72 (m, 1H), 3.34 (d, J = 12.5 Hz, 1H), 3.18 (m, 1H), 2.97 (br s, 1H), 2.55 (br s, 1H), 2.53 (d, J = 15.5 Hz, 1H), 2.33 (m, 1H), 0.92, 0.91, 0.85 (3 × br s, 3 × 9H), 0.19 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz) δ 172.0, 164.3, 163.8, 150.9, 150.7, 144.3, 141.7, 102.8, 101.8, 95.8, 92.4, 85.0, 84.3, 78.5, 73.3, 72.3, 42.6, 41.4, 39.9, 32.1, 30.4, 29.9, 26.04, 25.97, 25.9, 18.2, 18.2, 18.1, −4.30, −4.32, −4.4, −4.5, −4.7, −5.1; MS (FAB) m/z 853.4390 (MH$^+$ [$C_{38}H_{69}N_6O_{10}Si_3$] = 853.4386).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-[[*N*-(2′-*O*-(*tert*-butyldimethylsilyl)-3′,5′-dideoxy-3′-[(ethoxycarbonyl)-

methyl]uridin-5′-yl)carboxamido]methyl]-3′,5′-dideoxyuridine (55). Procedure E [**41** (447 mg, 1.05 mmol), **42** (494 mg, 1.16 mmol), DCC (237 mg, 1.15 mmol), dried CH_2Cl_2 (4.5 mL), chromatography (EtOAc/hexanes, 7:3)] gave **55** (630 mg, 72%): ^{1}H NMR (500 MHz) δ 8.84 (br s, 1H), 8.81 (br s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 6.54 (t, J = 5.8 Hz, 1H), 5.76 (dd, J = 8.3, 1.8 Hz, 1H), 5.73 (dd, J = 7.5, 2.0 Hz, 1H), 5.71 (d, J = 1.5 Hz, 1H), 5.49 (d, J = 1.0 Hz, 1H), 4.58 (d, J = 4.0 Hz, 1H), 4.46 (d, J = 2.5 Hz, 1H), 4.16−4.13 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 4.08−4.04 (m, 1H), 3.83 (dd, J = 13.3, 2.8 Hz, 1H), 3.76 (ddd, J = 14.5, 6.0, 2.5 Hz, 1H), 3.63 (dd, J = 13.5, 4.0 Hz, 1H), 3.37−3.32 (m, 1H), 2.65 (dd, J = 16.3, 7.8 Hz, 1H), 2.58−2.50 (m, 2H), 2.44−2.36 (m, 2H), 2.27 (dd, J = 14.3, 5.8 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.19, 0.12, 0.08, 0.05 (4 × s, 4 × 3H); ^{13}C NMR (75 MHz) δ 172.2, 171.3, 163.2, 163.0, 150.5, 150.2, 141.2, 139.9, 102.5, 102.4, 100.2, 95.3, 91.6, 82.6, 82.5, 77.9, 77.0, 61.2, 52.4, 41.5, 40.8, 40.2, 34.2, 32.1, 30.0, 26.0, 25.9, 18.3, 18.2, 14.4, −4.3, −5.2, −5.3; MS (FAB) m/z 857.3678 (MNa^+ $[C_{36}H_{58}N_8O_{11}Si_2Na]$ = 857.3662).

5′-Amino-2′-*O*-(*tert*-butyldimethylsilyl)-3′-[[*N*-(2′-*O*-(*tert*-butyldimethylsilyl)-3′,5′-dideoxy-3′-[(ethoxycarbonyl)methyl]uridin-5′-yl)carboxamido]methyl]-3′,5′-dideoxyuridine (56). Procedure C [Et_3N (0.3 mL), 1,3-propanedithiol (0.276 mL, 297 mg, 2.75 mmol), **55** (380 mg, 0.455 mmol), dried EtOH (8.6 mL), 12 h, chromatography (SSA)] gave **56** (260 mg, 71%): ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.79 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 5.70 (d, J = 2.5 Hz, 1H), 5.69 (d, J = 3.0 Hz, 1H), 5.68 (s, 1H), 5.61 (d, J = 1.0 Hz, 1H), 4.56−4.54 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 4.05−3.98 (m, 2H), 3.52 (dd, J = 15.0, 3.5 Hz, 1H), 3.47 (dd, J = 14.8, 6.8 Hz, 1H), 3.05 (dd, J = 13.8, 2.8 Hz, 1H), 2.94 (dd, J = 13.8, 7.8 Hz, 1H), 2.62 (dd, J = 17.0, 10.0 Hz, 1H), 2.59 (dd, J = 15.0, 6.5 Hz, 1H), 2.51 (dd, J = 17.8, 4.3 Hz, 1H), 2.39−2.30 (m, 2H), 2.23 (ddd, J = 14.8, 10.0, 4.8 Hz, 1H), 1.24 (t, J = 7.5 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.16, 0.15, 0.08, 0.05 (4 × s, 4 × 3H); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 174.1, 173.7, 166.4, 152.22, 152.17, 142.6, 142.4, 102.5, 102.4, 94.2, 93.9, 85.1, 84.1, 79.1, 78.6, 62.0, 44.5, 42.5, 42.1, 32.2, 30.6, 26.6, 26.5, 19.08, 19.05, 14.7, −4.0, −4.1, −4.9, −5.3; MS (FAB) m/z 809.3954 (MH^+ $[C_{36}H_{61}N_6O_{11}Si_2]$ = 809.3937).

5′-Azido-2′-*O*-(*tert*-butyldimethylsilyl)-3′-[[*N*-(2′-*O*-(*tert*-butyldimethylsilyl)-3′,5′-dideoxy-3′-(carboxymethyl)uridin-5′-yl)carboxamido]methyl]-3′,5′-dideoxyuridine (57). Procedure D [NaOH (109 mg, 2.73 mmol), **55** (380 mg, 0.455 mmol), MeOH/H_2O (9:1, 11 mL), 8 h, pH ∼4 (4% HCl/H_2O), volatiles evaporated, MeOH added, NaCl filtered, filtrate evaporated, residue chromatographed (MeOH/CH_2Cl_2, 1:9)] gave **57** (235 mg, 64%): ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.87 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 5.72 (d, J = 8.5 Hz, 1H), 5.71 (s, 1H), 5.70 (d, J = 7.5 Hz, 1H), 5.62 (s, 1H), 4.56 (d, J = 5.0 Hz, 1H), 4.50 (dd, J = 5.3, 1.3 Hz, 1H), 4.12−4.07 (m, 1H), 4.02 (ddd, J = 10.5, 7.8, 2.8 Hz, 1H), 3.76 (dd, J = 13.5, 3.0 Hz, 1H), 3.63 (dd, J = 13.8, 4.8 Hz, 1H), 3.56 (dd, J = 14.5, 2.5 Hz, 1H), 3.46 (dd, J = 14.3, 7.8 Hz, 1H), 2.59 (dd, J = 17.0, 9.5 Hz, 1H), 2.56 (dd, J = 15.8, 8.0 Hz, 1H), 2.50−2.44 (m, 2H), 2.33 (dd, J = 15.5, 6.0 Hz, 1H), 2.20 (ddd, J = 14.6, 9.9, 4.9 Hz, 1H), 0.91 (s, 18H), 0.17 (s, 3H), 0.16 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 173.9, 166.5, 166.4, 152.2, 142.4, 142.1, 102.5, 102.3, 93.9, 93.1, 84.7, 83.9, 79.1, 53.2, 43.3, 43.0, 41.3, 33.2, 32.2, 26.6, 19.1, −4.1, −4.86, −4.92; MS (FAB) m/z 829.3344 (MNa^+ $[C_{34}H_{54}N_8O_{11}Si_2Na]$ = 829.3349).

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Supporting Information Available: Copies of ^{1}H NMR spectra for **2**, **9**, **11**, **12**, **16**, **22**−**28**, **30**, **32**, **33**−**36**, **38**−**45**, and **49**−**57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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