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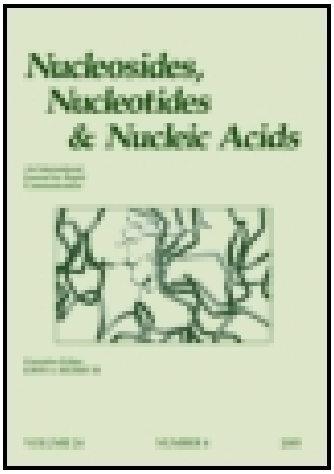

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Synthesis of Amide-Linked [(3′)CH_2CO-NH(5′)] Nucleoside Analogues of Small Oligonucleotides

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(1&2), 69–86 (2000)

SYNTHESIS OF AMIDE-LINKED [(3')CH_2CO–NH(5')] NUCLEOSIDE ANALOGUES OF SMALL OLIGONUCLEOTIDES[§,1]

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ABSTRACT: We report syntheses of new amide-linked (di–penta)nucleoside analogues of antisense oligonucleotide components. Solution-phase coupling of 3'-(carboxymethyl)-3'-deoxy- and 5'-amino-5'-deoxynucleoside derivatives provides amide dimers. Activated [3'-(carboxymethyl)-3'-deoxy] units with a 5'-azido-5'-deoxy function provide "masked" 5'-amino-5'-deoxy residues for chain extension, and a 5'-*O*-DMT-protected unit provides the 5'-terminus for attachment to a phosphodiester linkage.

Modulation of the expression of genetic messages into coded proteins is an area of intense interest. Antisense and other related therapeutic strategies have concentrated on the development of oligonucleotide mimics with resistance to nuclease cleavage, potent affinity for complementary oligonucleotide sequences, and pharmacokinetic accessibility to target cells. Initial antisense analogue approaches focused on changes at phosphorus on modified phosphodiester backbones. More recent modifications include carbon–heteroatom linkages without phosphorus, and this field has been reviewed extensively.[2]

We were interested in amide-linked nucleoside analogues of phosphodiesters,[3] and the Novartis group has described studies which confirm the potent affinity of nucleoside amide-dimer units for complementary oligonucleotide sequences.[4] We reported syntheses of 3'-(carboxymethyl)-3'-deoxynucleosides from nucleosides[3b,c] and carbohydrates.[3d] However, coupling of derived lactones with 5'-amino-5'-deoxynucleosides did not occur readily.[3b,c] We now describe mild and efficient couplings of 5'-amino and activated 3'-carboxylate derivatives which provide dimer–pentamer amide-linked oligonucleosides.

[§]This paper is dedicated to happy memories of Gertrude B. Elion.

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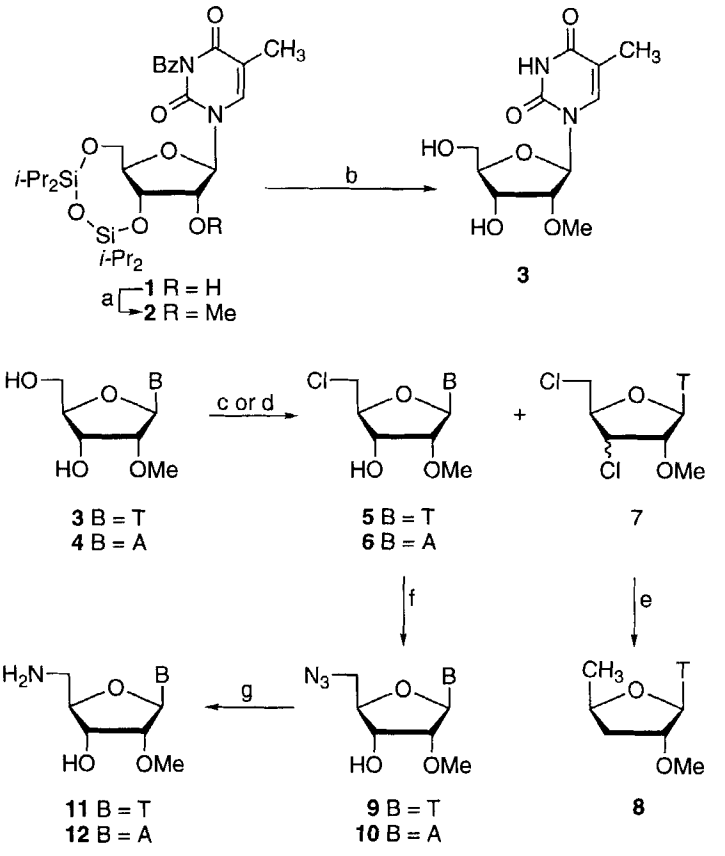
RESULTS AND DISCUSSION

Our targets for the 2'-*O*-methyl 3'-terminal units were the 5'-amino-5'-deoxy-2'-*O*-methylnucleosides **11** and **12** (Scheme 1). Known derivative[5] **1** was methylated to give **2** as described[6] (MeI/Ag_2O) for its uridine analogue. Debenzoylation (NaOMe/MeOH) of **2** and desilylation (NH_4F/MeOH)[7] gave 2'-*O*-methyl-5-methyluridine[8] (**3**). Chlorination of **3** with $SOCl_2$/HMPA[9] gave the 5'-chloro derivative **5** and diastereomeric byproducts **7**. NMR spectra of **7** indicated two closely related compounds, and mass spectra verified the presence of two chlorine atoms. Dechlorination of **7** with Bu_4SnH/AIBN gave a single product, 3',5'-dideoxy-2'-*O*-methyl-5-methyluridine (**8**), in harmony with the assignment of **7** epimers. Treatment[10] of **3** with Ph_3P/CCl_4 gave the desired 5'-chloro derivative **5** without detected formation of the 3',5'-dichloro byproducts. Chlorination of 2'-*O*-methyladenosine[11] (**4**) with $SOCl_2$/HMPA[9] gave **6** cleanly. Azide displacement with **5** or

Scheme 1[a]

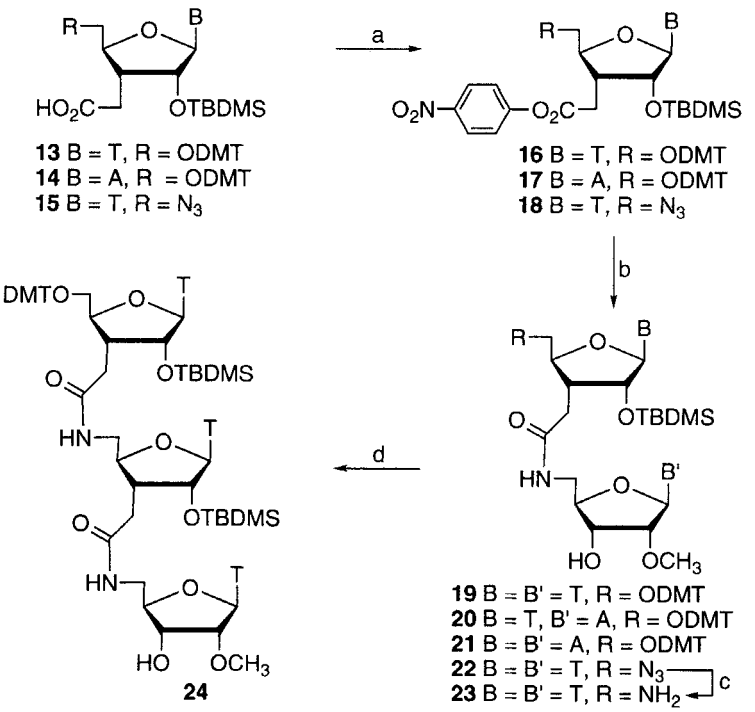


[a] (a) MeI/Ag_2O/toluene. (b) (i) NaOMe/MeOH; (ii) NH_4F/MeOH/Δ. (c) $SOCl_2$/HMPA. (d) CCl_4/PPh_3/DMF. (e) Bu_3SnH/AIBN/toluene/Δ. (f) NaN_3/DMF/Δ. (g) H_2/Pd–C/EtOH.

6 (NaN_3/DMF/Δ) occurred without incident to give the 5'-azido-5'-deoxy products **9** or **10**, respectively. Catalytic hydrogenolysis of **9** or **10** as described[3b,c] gave the 5'-amino-5'-deoxynucleosides **11** or **12**, respectively.

Treatment[12] of the protected 3'-carboxylates[3c] **13** or **15** (Scheme 2) and 5'-amine **11** with DCC in DMF or pyridine generated minor quantities of the amide-linked dimers plus unknown byproducts. Active esters **16** and **18** were prepared[13] from **13** and **15**, respectively, with 4-nitrophenol/DCC/1-hydroxybenzotriazole/DMF. As anticipated, the 5'-amines **11** or **12** coupled with the active ester **16** in ethanol solution at ambient temperature[13a] to give amide dimers **19** (74%) or **20** (75%), respectively. Active ester **17** was generated from **14** (4-nitrophenol/DCC/CH_2Cl_2) and coupled directly with **12** to give the A–A dimer **21** (77%). Analogous coupling of **11** and **18** gave **22** (71%), which was subjected to catalytic hydrogenolysis to give the 5'-terminal amino dimer **23**. Treatment of **23** with **16** in EtOH at ambient temperature gave trimer **24** (65%).

Scheme 2[a]



[a] (a) 4-Nitrophenol/DCC. (b) (**11** or **12**)/EtOH. (c) H_2/Pd–C/EtOH. (d) **16**/EtOH.

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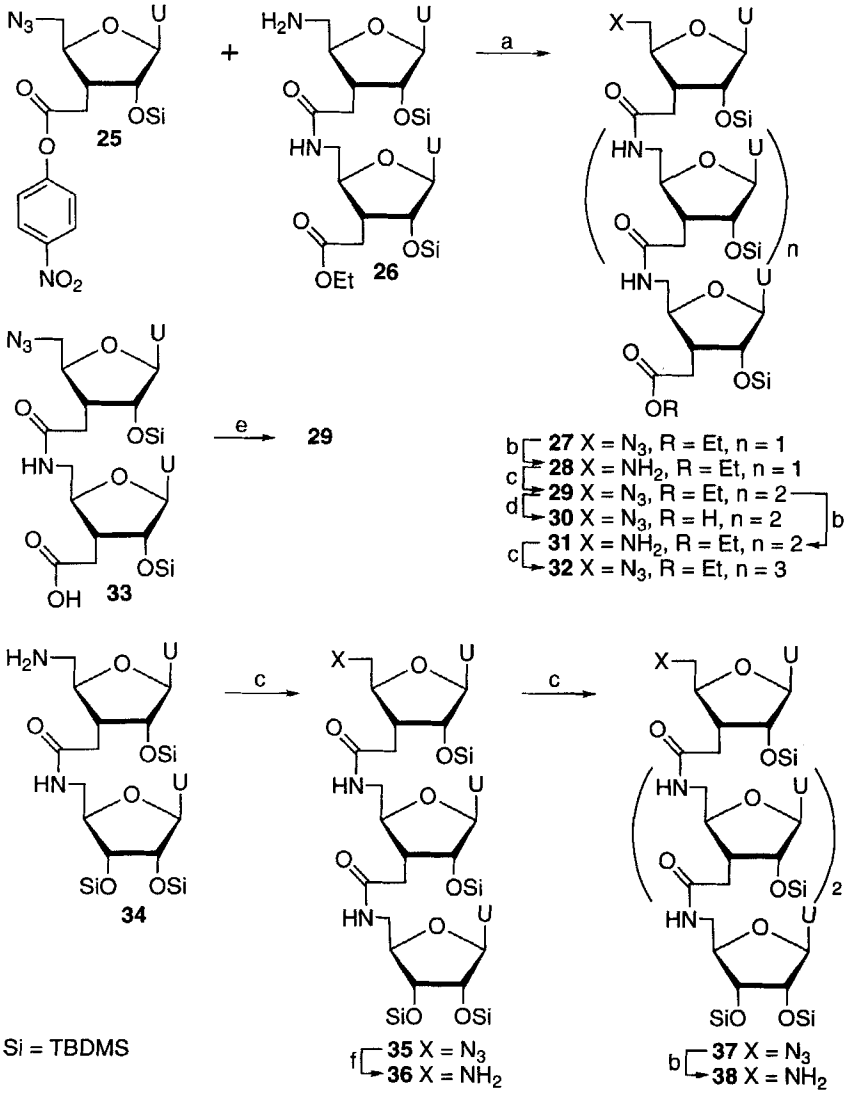
Ester **25** (Scheme 3) was generated from 5'-azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(carboxymethyl)-3',5'-dideoxyuridine.[3c] Coupling of **25** and dimer **26**[3c] (diglyme/65 °C) gave trimer **27** (84%). Catalytic hydrogenolysis of the azido group was sluggish and incomplete under the usual conditions. Treatment of **27** with 1,3-propanedithiol and Et_3N in deoxygenated ethanol provided clean conversion to the 5'-terminal amine **28** (92%). Treatment of **28** with **25** (diglyme/65 °C) gave tetramer **29** (92%). Alternative ambient

Scheme 3[a]



[a] (a) Diglyme/65 °C. (b) $HS(CH_2)_3SH$/EtOH. (c) **25**/(diglyme/65 °C or CH_2Cl_2/ambient). (d) NaOH/MeOH/H_2O. (e) **26**/DCC/dioxane. (f) H_2/Pd–C/THF.

temperature coupling of dimers **26** and **33**[3c] with DCC/dioxane gave **29** (61%). Saponification of the 3'-terminal ester of **29** ($NaOH/MeOH/H_2O$) gave the carboxylate **30** (69%), and reduction of the 5'-terminal azido group of **29** (1,3-propanedithiol/Et_3N/EtOH) gave amino tetramer **31** (74%). Coupling of **31** with **25** (diglyme/65 °C) gave pentamer **32** (75%).

The 5'-amino dimer **34**[3c] (with 2',3'-bis-*O*-TBDMS protection at the 3'-terminal) was coupled with **25** in CH_2Cl_2 at ambient temperature to give trimer **35** (61%), which underwent catalytic hydrogenolysis of the azido group to give **36** (72%). Coupling of **36** with **25** (CH_2Cl_2/ambient temperature) gave tetramer **37** (49%), which also was prepared (60%) by condensation of dimers **33**[3c] and **34**[3c] (DCC/CH_2Cl_2). Treatment of **37** with 1,3-propanedithiol/Et_3N/EtOH resulted in clean reduction of the 5'-azido group to give amine **38** (75%), but attempted catalytic hydrogenolysis was sluggish and incomplete.

SUMMARY AND CONCLUSIONS

Condensation reactions between protected 3'-(carboxymethyl)-3'-deoxynucleoside 4-nitrophenyl esters and 5'-amino-5'-deoxynucleosides take place at ambient temperature in ethanol or at 65 °C in diglyme to give amide linked dimers (~75%). The DCC-mediated coupling of protected 5'-amino-5'-deoxynucleoside and 3'-(carboxymethyl) units provides an alternative method. The use of 5'-azido-5'-deoxy-3'-(carboxymethyl) monomers allows successive reduction of the 5'-(azido → amino) group and coupling with another activated 3'-(carboxymethyl) unit. This methodology provides access to amide-linked oligomer analogues of oligonucleotides by well-established procedures of peptide synthesis, and is readily ameanable to solid-phase techniques as well as the solution sequences demonstrated in this study. Catalytic hydrogenolysis of the azide moiety was effective with the smaller molecules, and in one case with a tetramer. Chemical reduction with 1,3-propanedithiol in the presence of triethylamine was more effective with most larger molecules. These routes make synthesis of oligomers with 2'-*O*-methylribonucleoside monomers readily available, whereas prior approaches that employed free radical-mediated coupling for generation of the 3'-(carboxymethyl) subunits[2i,4b,d] produced mixtures of the xylo and ribo epimers. Our condensation reactions with 5'-*O*-(dimethoxytrityl) and 2',3'-bis-*O*-(*tert*-butyldimethylsilyl) protection at the 5' and 3' termini demonstrate compatibility with standard oligonucleotide synthesizer technology. Incorporation of dimer (or larger) units into "gapmer" oligonucleotides should proceed without difficulty.

EXPERIMENTAL SECTION

Uncorrected melting points were determined with a capillary tube apparatus. NMR spectra were determined with solutions in Me_4Si/Me_2SO-d_6 at 200 or 300 MHz (^1H) or 50

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or 75 MHz (^{13}C) unless otherwise specified. Proton signals designated "ex" underwent exchange with D_2O, but not all NMR spectral solutions were subjected to D_2O exchange. High resolution mass spectra (MS) were determined under FAB conditions with a matrix of NaOAc/thioglygerol unless otherwise specified. Solvents were dried by distillation from CaH_2, except THF (Na/benzophenone) and CH_2Cl_2 (P_4O_{10}). Silica gel TLC plates were visualized under 254 nm light, and silica gel (200–400 mesh) was used for flash column chromatography. "Solvent A" for chromatography is the separated organic phase of EtOAc/*i*-PrOH/H_2O (4:1:2). "HOBT" is 1-hydroxybenzotriazole. Compounds (**11**, **12**, **26**, **33**, **34**)[3c] and (**13–15**)[3d] were prepared as described previously.

3-*N*-Benzoyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2'-*O*-methyl-5-methyluridine (2). A suspension of 3-*N*-benzoyl-3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-5-methyluridine[5] (**1**; 810 mg, 1.34 mmol), CH_3I (6 mL), and Ag_2O (2.5 g) in dried toluene (40 mL) was stirred (under Ar) and protected from light for 2 days.[6] CH_3I (2 mL) and Ag_2O (0.8 g) were added, and stirring was continued for 4 days (nearly all of **1** was methylated, TLC). The mixture was filtered (sintered glass), and volatiles were evaporated. The residue was chromatographed (EtOAc/hexanes, 1:4) to give **2** (640 mg, 77%) as a glass: ^1H NMR δ 7.99–7.57 (m, 6H), 5.64 (s, 1H), 4.29 (dd, *J* = 4.8, 9.1 Hz, 1H), 4.19 (d, *J* = 12.7 Hz, 1H), 3.99–3.89 (m, 3H), 3.46 (s, 3H), 1.83 (d, *J* = 1.0 Hz, 3H), 1.06–0.99 (m, 28H); ^{13}C NMR δ 169.5, 162.5, 148.5, 136.0, 135.5, 131.1, 130.4, 129.5, 108.7, 88.9, 82.3, 81.0, 68.7, 59.4, 58.6, 17.3, 17.23, 17.15, 17.1, 17.0, 16.9, 16.8, 12.8, 12.38, 12.37, 12.2, 11.9; MS *m/z* 641.2687 (MNa^+ [$C_{30}H_{46}N_2O_8Si_2Na$] = 641.2690).

2'-*O*-Methyl-5-methyluridine (3). A solution of **2** (600 mg, 0.992 mmol) in NaOMe/MeOH (chip of Na/70 mL) was stirred for 4 days (TLC showed 2 products, partial disiloxane ring cleavage), and then was neutralized (solid CO_2). NH_4F (400 mg, 10.8 mmol) was added,[7] and the mixture was refluxed (2 days, TLC showed conversion to a more polar product). The mixture was filtered, and volatiles were evaporated. The residue was chromatographed (MeOH/CH_2Cl_2, 1.8:20) and the product was recrystallized (MeOH) to give **3** (220 mg, 83%) with mp 192–195 °C (Lit.[8] mp 194–195 °C).

5'-Chloro-5'-deoxy-2'-*O*-methyl-5-methyluridine (5) and 1-[3,5-Dichloro-3,5-dideoxy-2-*O*-methyl-β-D-(ribo/xylo)furanosyl]-5-methyluracil (7). Method A.[9] $SOCl_2$ (0.75 mL, 1.2 g, 10 mmol) was added by syringe to a stirred solution of **3** (500 mg, 1.84 mmol) in HMPA (5 mL), and stirring was continued overnight (TLC, MeOH/CH_2Cl_2, 1:10, showed 2 less polar products). Standard extraction workup (CH_2Cl_2/brine), evaporation of volatiles, and short-path distillation of HMPA gave a residue that was chromatographed (MeOH/CH_2Cl_2, 0.7:20) to give **7** (162 mg, 30%; xylo/ribo, ~8:1): ^1H NMR (major isomer) δ 11.47 (br s, 1H, ex), 7.43 (q, *J* = 1.2 Hz,

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1H), 5.80 ("d," J = 2.6 Hz, 1H), 4.73 (dd, J = 1.0, 3.8 Hz, 1H), 4.44 ("dt", J = 4.0, 6.2, 6.2 Hz, 1H), 4.17 (dd, J = 1.2, 2.4 Hz, 1H), 3.92 (dd, J = 1.6, 6.0 Hz, 2H), 3.40 (s, 3H), 1.79 (d, J = 1.2 Hz, 3H); ^{13}C NMR (major isomer) δ 162.7, 149.3, 134.4, 108.8, 89.0, 87.7, 79.2, 58.9, 56.7, 41.1, 11.2; MS *m/z* 331.0225 (MNa^+ $[C_{11}H_{14}{}^{35}Cl_2N_2O_4Na]$ = 331.0228).

Further elution and recrystallization (CH_2Cl_2/Et_2O) gave **5** (305 mg, 57%) with mp 145–146 °C: ^{1}H NMR δ 11.40 (br s, 1H, ex), 7.49 (d, J = 1.0 Hz, 1H), 5.85 (d, J = 5.8 Hz, 1H), 5.42 (d, J = 6.0 Hz, 1H, ex), 4.11 ("dd", J = 5.6, 9.8 Hz, 1H), 4.01–3.76 (m, 4H), 3.33 (s, 3H), 1.77 (d, J = 0.8 Hz, 3H); ^{13}C NMR δ 162.7, 149.6, 135.1, 109.1, 85.3, 82.1, 79.9, 68.3, 56.5, 43.6, 11.0; MS (FAB, thioglycerol) *m/z* 291.0736 (MH^+ $[C_{11}H_{16}{}^{35}ClN_2O_5]$ = 291.0748.

Method B.[10] A solution of **3** (70 mg, 0.26 mmol), Ph_3P (100 mg, 0.381 mmol), and CCl_4 (300 μL, 478 mg, 3.11 mmol) in DMF (5 mL) was stirred (under Ar) for 24 h (nearly all of **3** was converted to **5**, TLC). Volatiles were evaporated, and xylene was added and evaporated to remove residual DMF. Chromatography ($MeOH/CH_2Cl_2$, 0.7:20) gave **5** (55 mg, 73%).

1-(3,5-Dideoxy-2-*O*-methyl-β-D-*erythro*-pentofuranosyl)-5-methyluracil (8). Bu_3SnH (520 μL, 560 mg, 1.92 mmol) and AIBN (33 mg, 0.20 mmol) in toluene (15 mL) were added dropwise (2 h) to a stirred solution of **7** (120 mg, 0.390 mmol) in toluene (20 mL) at 90 °C (TLC, $MeOH/CH_2Cl_2$, 0.7:20, showed a more polar product). Volatiles were evaporated, the residue was chromatographed ($MeOH/CH_2Cl_2$, 0.6:20), and recrystallization (CH_2Cl_2/Et_2O) gave **8** (68 mg, 73%) with mp 124–125 °C: ^{1}H NMR δ 11.36 (s, 1H, ex), 7.32 (d, J = 1.2 Hz, 1H), 5.73 (d, J = 1.8 Hz, 1H), 4.19 (hep, J = 5.5 Hz, 1H), 3.95 (d, J = 6.0 Hz, 1H), 3.29 (s, 3H), 2.04 (dd, J = 5.2, 13.6 Hz, 1H), 1.81 (d, J = 1.2 Hz, 3H), 1.73 (dd, J = 6.2, 13.4 Hz, partial overlap), 1.32 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 163.3, 149.7, 135.5, 109.1, 89.2, 84.6, 75.1, 56.1, 37.2, 19.3, 11.6; MS *m/z* 241.1183 (MH^+ $[C_{11}H_{17}N_2O_4]$ = 241.1188).

5'-Chloro-5'-deoxy-2'-*O*-methyladenosine (6). $SOCl_2$ (0.90 mL, 1.5 g, 12 mmol) and 2'-*O*-MeAdo[11] (**4**; 600 mg, 2.14 mmol) in HMPA (12 mL) was treated as described for **3** → **5** [workup after 16 h, recrystallization (H_2O)] to give **6** (390 mg, 62%) with mp 171–172 °C: ^{1}H NMR δ 8.37, 8.16 (2 × s, 2 × 1H), 7.37 (br s, 2H, ex), 6.04 (d, J = 5.6 Hz, 1H), 5.56 (d, J = 5.6 Hz, 1H, ex), 4.55 (t, J = 5.4 Hz, 1H), 4.41 ("dt", J = 4.0, 4.0, 5.2 Hz, 1H), 4.14–4.07 (m, 1H), 3.95 (dd, J = 5.6, 11.4 Hz, 1H), 3.84 (dd, J = 6.4, 11.4 Hz, 1H), 3.33 (s, 3H); ^{13}C NMR δ 156.3, 153.0, 149.4, 139.8, 119.3, 85.6, 84.3, 81.4, 69.7, 57.7, 44.7; MS *m/z* 300.0868 (MH^+ $[C_{11}H_{15}{}^{35}ClN_5O_3]$ = 300.0863).

5'-Azido-5'-deoxy-2'-*O*-methyl-5-methyluridine[3c] **(9).** A solution of **5** (360 mg, 1.24 mmol) and NaN_3 (1.21 g, 18.6 mmol) in DMF (30 mL) was stirred for 2 h at 90–100 °C (TLC showed the conversion of **5** → **9** with similar R_f values, but **9** chars intensely upon spraying with 5% H_2SO_4/EtOH and heating). Extraction workup and chromatography ($MeOH/CH_2Cl_2$, 0.8:20) gave **9**[3c] (242 mg, 66%).

5'-Azido-5'-deoxy-2'-*O*-methyladenosine[3c] **(10).** A solution of **6** (390 mg, 1.30 mmol) and NaN_3 (1.27 g, 19.5 mmol) in DMF (35 mL) was stirred for 8 h at ~100 °C (TLC showed no formation of cyclonucleoside byproducts, but **6** and **10** had equal R_f values). Volatiles were evaporated, and the residue (in a minimum volume of MeOH) was applied to a silica gel column. Elution ($MeOH/CH_2Cl_2$, 1.5:20) gave **10**.[3c]

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxy-3'-{[(4-nitrophenoxy)carbonyl]methyl}-5'-*O*-dimethoxytrityl-5-methyluridine (16). A mixture of **13** (240 mg of the Et_3N salt, 0.293 mmol), DCC (91 mg, 0.44 mmol), HOBT (20 mg, 0.15 mmol), 4-nitrophenol (61 mg, 0.44 mmol), and DMF (10 mL) was stirred for 2 days and then partitioned (CH_2Cl_2/brine). The organic layer was washed ($NaHCO_3/H_2O$) and dried ($MgSO_4$), and volatiles were evaporated. Xylene was added and evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 0.25:20 containing ~0.5% Et_3N) to give **16** (155 mg, 63%): ^1H NMR δ 11.40 (s, 1H, ex), 8.27 (d, J = 9.4 Hz, 2H), 7.56 (s, 1H), 7.40–7.22 (m, 13H), 6.85 (d, J = 9.0 Hz, 2H), 5.66 (d, J = 2.4 Hz, 1H), 4.54 (dd, J = 2.6, 5.1 Hz, 1H), 4.15–4.05 (m, 1H), 3.68 (s, 6H), 3.55–3.42 (m, 1H), 3.39–3.25 (m, H_2O signal overlap), 2.82–2.57 (m, 3H), 1.37 (s, 3H), 0.84 (s, 9H), 0.07, 0.00 (2 × s, 2 × 3H); ^{13}C NMR (125 MHz) δ 169.6, 163.6, 158.18, 158.16, 154.9, 150.4, 145.0, 144.6, 135.23, 135.17, 135.15, 129.8, 127.9, 127.6, 126.8, 125.2, 122.8, 113.2, 109.2, 90.2, 86.0, 82.0, 76.1, 63.2, 55.0, 30.1, 25.6, 25.3, 17.7, 11.8, –4.8, –5.6; MS m/z 860.3151 (MNa^+ $[C_{45}H_{51}N_3O_{11}SiNa]$ = 860.3191.

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-{[(4-nitrophenoxy)carbonyl]methyl}-5-methyluridine (18). A mixture of **15** (380 mg of the Et_3N salt, 0.703 mmol), DCC (220 mg, 1.06 mmol), HOBT (48 mg, 0.35 mmol), 4-nitrophenol (147 mg, 1.06 mmol), and DMF (30 mL) was stirred overnight. Workup (as described for **13** → **16**) and chromatography ($MeOH/CH_2Cl_2$, 0.25:20) gave **18** (300 mg, 76%): ^1H NMR δ 11.43 (s, 1H, ex), 8.33 (d, J = 9.4 Hz, 2H), 7.59 (d, J = 1.0 Hz, 1H), 7.42 (d, J = 9.4 Hz, 2H), 5.69 (d, J = 2.4 Hz, 1H), 4.52 (dd, J = 2.2, 5.4 Hz, 1H), 4.13–4.06 (m, 1H), 3.83 (dd, J = 2.6, 13.8 Hz, 1H), 3.70 (dd, J = 5.2, 13.4 Hz, 1H), 2.88 (d, J = 5.8 Hz, 2H), 2.69–2.58 (m, 1H), 1.81 (s, 3H), 0.88 (s, 9H), 0.07, 0.00 (2 × s, 2 × 3H); ^{13}C NMR (125 MHz) δ 169.9, 163.7, 155.0, 150.4, 145.0, 135.9, 125.4, 122.9, 109.5, 90.8, 81.1, 75.8, 51.5, 29.7, 25.62, 25.59, 17.7, 12.2, –4.8, –5.6; MS m/z 583.1927 (MNa^+ $[C_{24}H_{32}N_6O_8SiNa]$ = 583.1949.

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2'-*O*-(*tert*-Butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3'-deoxy-5'-*O*-(dimethoxytrityl)-5-methyluridinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyl-5-methyluridine (19). A solution of **11** (20 mg, 0.074 mmol) and **16** (62 mg, 0.074 mmol) in EtOH (4 mL) was stirred for 4 days. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1.3:20 containing ~0.5% Et_3N) to give **19** (53 mg, 74%): ^1H NMR δ 11.38 (s, 2H, ex), 8.08 (t, J = 5.4 Hz, 1H, ex), 7.55, 7.49 (2 × d, J ~1Hz, 2 × 1H), 7.40–6.87 (m, 13H), 5.80 (d, J = 5.8 Hz, 1H), 5.64 (d, J = 2.4 Hz, 1H), 5.21 (d, J = 6.0 Hz, 1H, ex), 4.48–4.42 (m, 1H), 4.02–3.92 (m, 2H), 3.73 (s, 6H), 3.44–3.12 (m) and 3.30 (s) (9H), 2.67 (quin, J = 5.8 Hz, 1H), 2.37 (dd, J = 7.3, 16.3 Hz, 1H), 2.04 (dd, J = 6.3, 16.3 Hz, 1H), 1.77, 1.32 (2 × s, 2 × 3H), 0.83 (s, 9H), 0.07, 0.00 (2 × s, 2 × 3H); MS *m/z* 992.4105 (MNa^+ $[C_{50}H_{63}N_5O_{13}SiNa]$ = 992.4089.

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3'-deoxy-5'-*O*-(dimethoxytrityl)-5-methyluridinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyladenosine (20). A solution of **12** (12 mg, 0.043 mmol) and **16** (30 mg, 0.036 mmol) in EtOH (1 mL) was stirred for 3 days. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:9 containing ~0.5% Et_3N). The residue was partitioned ($EtOAc//NaHCO_3/H_2O$) and the organic phase was dried (Na_2SO_4). Volatiles were evaporated to give **20** (26 mg, 75%): ^1H NMR ($CDCl_3$) δ 10.82 (br s, 1H), 8.20 (s, 1H), 8.01 ("d", J = 7.0 Hz, 1H), 7.98, 7.75 (2 × s, 2 × 1H), 7.45–7.19 (m, 9H), 6.80 (dd, J = 1.5, 8.9 Hz, 4H), 6.66 (br s, 2H), 5.89 (s, 1H), 5.85 (d, J = 7.4 Hz, 1H), 4.64–4.55, 4.34–4.25 (2 × m, 2 × 2H), 4.14 (d, J = 7.4 Hz, 1H), 4.05–3.90 (m, 1H), 3.73, 3.72, 3.32 (3 × s, 3 × 3H), 3.32–3.22 (m, 1H, overlap with the singlet at δ 3.32), 3.00–2.88, 2.74–2.56, 2.17–1.96 (3 × m, 3 × 2H), 1.37 (s, 3H), 0.82 (br s, 9H), 0.17, 0.05 (2 × s, 2 × 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 164.7, 158.7, 156.4, 152.9, 151.1, 149.0, 144.4, 140.9, 135.9, 135.5, 135.4, 130.34, 130.25, 128.3, 128.0, 127.2, 120.7, 113.3, 110.6, 106.3, 90.7, 88.6, 86.8, 84.7, 83.3, 81.5, 77.3, 70.6, 63.0, 58.9, 55.2, 46.1, 41.1, 38.9, 31.5, 25.7, 18.0, 11.8, –4.7, –5.3; MS *m/z* 1001.4194 (MNa^+ $[C_{50}H_{62}N_8O_{11}SiNa]$ = 1001.4205).

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3'-deoxy-5'-*O*-(dimethoxytrityl)adenosinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyl-adenosine (21). A solution of **14** (24 mg, 0.029 mmol), 4-nitrophenol (6 mg, 0.04 mmol), and DCC (9 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was stirred for 24 h. Volatiles were evaporated to give 2'-*O*-TBDMS-3'-deoxy-3'-{[(4-nitrophenoxy)carbonyl]-methyl}-5'-*O*-DMT-adenosine (**17**). This material was dissolved in EtOH (1 mL), a solution of **12** (10 mg, 0.036 mmol) in EtOH (2 mL) was added, and stirring was continued for 3 days. Volatiles were evaporated, and the residue was chromatographed (5 → 10% $MeOH/CH_2Cl_2$ containing ~0.5% Et_3N). Volatiles were evaporated, and the residue was

partitioned (EtOAc//$NaHCO_3/H_2O$). The organic phase was dried (Na_2SO_4), and volatiles were evaporated to give **21** (22 mg, 77%): ^{1}H NMR δ 8.36 (s, 1H), 8.26 (br s, 1H, ex), 8.20, 8.13, 8.12 (3 × s, 3 × 1H), 7.36–7.20 (m, 13H), 6.82 (dd, *J* = 5.0, 11.8 Hz, 4H), 5.95 (d, *J* = 6.6 Hz, 1H), 5.90 (d, *J* = 1.0 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H, ex), 4.87–4.82, 4.48–4.42, 4.25–4.16, 4.08–4.02, 3.98–3.90 (5 × m, 5 × 1H), 3.69 (s, 6H), 3.26 (s, 3H), 2.90–2.80 (m, 2H), 2.40–2.36 (m, 1H), 2.20–2.02 (m, 2H), 0.78 (br s, 9H), –0.02, –0.07 (2 × s, 2 × 3H); ^{13}C NMR δ 170.6, 162.4, 158.1, 156.6, 156.3, 156.2, 152.8, 149.2, 144.9, 140.3, 138.5, 135.6, 129.8, 127.9, 126.8, 119.2, 113.2, 89.6, 85.9, 85.7, 83.9, 82.7, 81.4, 76.8, 69.7, 69.1, 63.9, 57.5, 55.0, 35.8, 30.7, 25.6, 17.6, –5.0, –5.6; MS *m/z* 1010.4302 (MNa^+ [$C_{50}H_{61}N_{11}O_9SiNa$] = 1010.4321).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxy-5-methyluridinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyl-5-methyluridine (22). A solution of **11** (120 mg, 0.442 mmol) and **18** (202 mg, 0.360 mmol) in EtOH (18 mL) was stirred for 3 days. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1.3:20) to give **22** (178 mg, 71%): ^{1}H NMR δ 11.40 (s, 2H, ex), 8.18 (t, *J* = 5.5 Hz, 1H, ex), 7.57, 7.52 (2 × d, *J* = 1.2 Hz, 2 × 1H), 5.83 (d, *J* = 5.6 Hz, 1H), 5.65 (d, *J* = 2.6 Hz, 1H), 5.25 (d, *J* = 5.6 Hz, 1H, ex), 4.41 (dd, *J* = 2.1, 6.5 Hz, 1H), 4.08–3.74 (m, 4H), 3.67 (d, *J* = 3.4 Hz, 2H), 3.56–3.16 (m) overlap with 3.35 (s) and H_2O signal, 2.56–2.24 (m, partial overlap with the Me_2SO-d_6 signals), 1.81 (s, 3H), 0.85 (s, 9H), 0.05, 0.00 (2 × s, 2 × 3H); ^{13}C NMR (125 MHz) δ 170.5, 163.6, 150.4, 150.3, 136.3, 135.5, 109.8, 109.3, 90.1, 86.3, 82.4, 81.6, 81.2, 76.3, 69.7, 57.5, 52.0, 41.0, 30.9, 25.58, 25.56, 17.6, 12.0, 11.9, –5.1, –5.6; MS (FAB) *m/z* 715.2843 (MNa^+ [$C_{29}H_{44}N_8O_{10}SiNa$] = 715.2847.

5'-Amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxy-5-methyluridinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyl-5-methyluridine (23). A suspension of **22** (22 mg, 0.032 mmol) and 10% Pd–C (5 mg) in EtOH (12 mL) was hydrogentated (28 psi) overnight in a Parr shaking apparatus (TLC showed a minor amount of **22**). The mixture was filtered (with Celite), volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:4; followed by $MeOH/CH_2Cl_2$ containing ~4% of 28% NH_3/H_2O) to give **23** (14 mg, 66%): ^{1}H NMR δ 8.32 (s, 1H), 8.18 (t, *J* = 5.0 Hz, 1H), 7.52 (s, 1H), 5.82 (d, *J* = 5.8 Hz, 1H), 5.56 (d, *J* = ~1 Hz, 1H), 4.31 (d, *J* = 3.8 Hz, 1H), 4.02 (t, *J* = 4.8 Hz, 1H), 3.85 (t, *J* = 5.5 Hz) partial overlap with 3.83–3.72 (m, 3H total), 4.46 ("dt", *J* = 5.3, 5.3, 14.0 Hz, 1H), 3.33 (s) partial overlap with 3.33–3.14 (m, 4H total), 2.91 (d, *J* = 12.4 Hz, 1H), 2.73 (d, *J* = 12.0 Hz, 1H), 2.47–2.38, 2.31–2.15 (2 × m, 2 × 3H), 1.79, 1.77 (2 × s, 2 × 3H), 0.84 (s, 9H), 0.08, 0.00 (2 × s, 2 × 3H); ^{13}C NMR (125 MHz) δ 171.0, 163.8, 163.6, 150.5, 150.4, 136.6, 136.4, 109.9, 108.4, 89.8, 86.3, 84.5, 82.6, 81.2, 77.8, 69.7, 57.51,

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57.49, 42.1, 41.0, 38.2, 30.8, 25.7, 17.7, 12.1, 12.0, –4.8, –5.5; MS *m/z* 689.2943 (MNa^+ [$C_{29}H_{46}N_6O_{10}SiNa$] = 689.2942.

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3'-deoxy-5'-*O*-(dimethoxytrityl)-5-methyluridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxy-5-methyluridinyl-(3'→5')-5'-amino-5'-deoxy-2'-*O*-methyl-5-methyluridine (24). A solution of **16** (27 mg, 0.032 mmol) and **23** (13 mg, 0.020 mmol) in EtOH (6 mL) was stirred for 4 days. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1.2:20 containing ~0.5% Et_3N) to give **24** (18 mg, 65%): ^1H NMR (500 MHz, $CDCl_3$) δ 9.68, 8.54, 8.06 (3 × s, 3 × 1H), 7.67 (d, *J* = 1.0 Hz, 1H), 7.46 (d, *J* = 15.0 Hz, 2H), 7.33–7.22 (m, 6H), 7.13, 6.99 (2 × s, 2 × 1H), 6.85–6.82 (m, 5H), 6.36 (t, *J* = 5.3 Hz, 1H), 5.81 (d, *J* = 2.5 Hz, 1H), 5.62 (s, 1H), 5.22 (d, *J* = 4.5 Hz, 1H), 4.61 (dd, *J* = 2.0, 5.0 Hz, 1H), 4.49 (d, *J* = 5.5 Hz, 1H), 4.39 (t, *J* = 5.8 Hz, 1H), 4.23–4.20, 4.13–4.10, 3.99–3.94 (3 × m, 3 × 2H), 3.79, 3.78 (2 × s, 2 × 3H), 3.73 (ddd, *J* = 3.5, 7.5, 14.0 Hz, 1H), 3.57 (dd, *J* = 2.0, 11.0 Hz, 1H), 3.50 (m, 3H), 3.39 (dt, *J* = 3.0, 14.0 Hz, 1H), 3.24 (dd, *J* = 3.5, 11.0 Hz, 1H), 3.20–3.13 (m, 2H), 2.86 (d, *J* = 5.0 Hz, 1H), 2.81–2.75 (m, 1H), 2.61 (dd, = 7.8, 15.3 Hz, 1H), 2.39 (dd, *J* = 9.0, 15.5 Hz, 1H), 2.29 (dd, *J* = 4.5, 15.0 Hz, 1H), 2.14 (dd, *J* = 4.0, 15.5 Hz, 1H), 1.92, 1.90, 1.41 (3 × s, 3 × 3H), 0.91, 0.89 (2 × s, 2 × 9H), 0.20, 0.17, 0.14, 0.06 (4 × s, 4 × 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 171.3, 164.1, 163.6, 163.5, 158.7, 150.74, 150.65, 150.2, 144.3, 138.5, 135.7, 135.6, 135.4, 135.3, 130.19, 130.16, 129.1, 128.2 128.0, 127.1, 113.3, 113.1, 111.7, 110.6, 110.4, 93.6, 93.1, 90.9, 86.7, 83.2, 82.8, 82.6, 81.0, 77.1, 70.5, 63.1, 58.9, 55.2, 46.1, 42.2, 42.1, 41.0, 39.3, 31.4, 31.2, 25.83, 25.80, 18.1, 18.0, 12.6, 12.4, 11.9, –4.4, –4.6, –5.3, –5.5; MS *m/z* 1387.5941 (MNa^+ [$C_{68}H_{92}N_8O_{18}Si_2Na$] = 1387.5966.

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-{[(4-nitrophenoxy)carbonyl]methyl}uridine (25). DCC (176 mg, 0.853 mmol), 4-nitrophenol (117 mg, 0.842 mmol), and 5'-azido-2'-*O*-TBDMS-3'-(carboxymethyl)-3',5'-dideoxyuridine[3c] (301 mg, 0.707 mmol) in dried CH_2Cl_2 (12 mL) was stirred (under Ar) for 12 h. The mixture was filtered (with Celite), and volatiles were evaporated. The residue was chromatographed (EtOAc/hexanes, 3:7) to give **25** (260 mg, 67%): ^1H NMR ($CDCl_3$) δ 8.80 (br s, 1H), 8.29 (d, *J* = 9.0 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 5.77 (d, *J* = 8.1 Hz, 1H), 5.74 (s, 1H), 4.53 (d, *J* = 4.8 Hz, 1H), 4.19 (dt, *J* = 3.0, 9.6 Hz, 1H), 3.93 (dd, *J* = 3.0, 13.5 Hz, 1H), 3.65 (dd, *J* = 3.5, 13.7 Hz, 1H), 2.97 (dd, *J* = 8.9, 17.6 Hz, 1H), 2.65 (dd, *J* = 5.3, 17.6 Hz, 1H), 2.60–2.50 (m, 1H), 0.93 (s, 9H), 0.22, 0.10 (2 × s, 2 × 3 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 163.1, 155.1, 150.2, 139.7, 125.6, 122.4, 102.4, 100.2, 92.1, 81.8, 77.5, 51.7, 39.4, 30.0, 26.0, 18.3, –4.2, –5.3; MS *m/z* 569.1797 (MNa^+ [$C_{23}H_{30}N_6O_8SiNa$] = 569.1792).

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5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]uridine (27). A solution of **25** (35 mg, 0.064 mmol) and **26** (40 mg, 0.049 mmol) in dried diglyme (1.0 mL) was stirred (under N_2) for 32 h at 65 °C. Volatiles were evaporated, and the residue was chromatographed (5 → 10% MeOH/CH_2Cl_2) to give **27** (50 mg, 84%): ^{1}H NMR (Me_2CO-d_6, 500 MHz) δ 10.10, 10.09, 10.07 (3 × br s, 3 × 1H), 7.85, 7.80 (2 × d, J = 8.0 Hz, 2 × 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.65, 7.60 (2 × t, J = 6.0 Hz, 2 × 1H), 5.76 (d, J = 1.5 Hz, 1H), 5.67 (d, J = 8.5 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.64, 5.63 (2 × s, 2 × 1H), 5.59 (d, J = 8.5 Hz, 1H), 4.62–4.58 (m, 3H), 4.18 ("quin", J = 4.4 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 4.05–4.03 (m, 2H), 3.80 (dd, J = 3.0, 13.5 Hz, 1H), 3.77 (dd, J = 4.8, 13.3 Hz, 1H), 3.73 (ddd, J = 3.0, 6.3, 14.3 Hz, 1H), 3.63 (ddd, J = 3.0, 5.5, 14.5 Hz, 1H), 3.58–3.52, 3.44–3.39 (2 × m, 2 × 1H), 2.65–2.54 (m, 5H), 2.50 (dd, J = 6.0, 16.0 Hz, 1H), 2.46 (dd, J = 6.0, 15.0 Hz, 1H), 2.30 ("sep", J = 4.8 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H), 0.920, 0.915, 0.910 (3 × br s, 3 × 9H), 0.20 (s, 9H), 0.18, 0.11, 0.08 (3 × s, 3 × 3H); ^{13}C NMR (Me_2CO-d_6) δ 172.7, 172.2, 164.0, 151.6, 141.3, 141.1, 140.9, 102.6, 102.4, 102.3, 93.5, 93.2, 92.5, 84.3, 83.9, 83.6, 79.0, 78.5, 61.1, 53.3, 42.0, 41.9, 41.5, 41.4, 41.3, 32.0, 31.6, 31.1, 26.44, 26.42, 26.3, 18.7, 14.6, –4.07, –4.16, –4.24; MS *m/z* 1238.5369 (MNa^+ [$C_{53}H_{85}N_{11}O_{16}Si_3Na$] = 1238.5381).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]uridine (29). Method A. Et_3N (1.0 mL, 0.72 g, 7.2 mmol) and 1,3-propanedithiol (1.0 mL, 1.1 g, 1.0 mmol) were added to a stirred solution of **27** (500 mg, 0.411 mmol) in deoxygenated EtOH (20 mL), and stirring was continued (under N_2) for 16 h. Volatiles were evaporated, and the residue was chromatographed (10 → 20% MeOH/CH_2Cl_2) to give **28** (457 mg, 92%) with MS *m/z* 1212.5479 (MNa^+ [$C_{53}H_{87}N_9O_6Si_3Na$] = 1212.5476. A solution of **25** (280 mg, 0.512 mmol) and **28** (457 mg, 0.384 mmol) in diglyme (10 mL) was stirred (under N_2) for 24 h at 65 °C. Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:9) to give **29** (562 mg, 92%).

Method B. DCC (28 mg, 0.14 mmol) was added to a stirred solution of **26** (108 mg, 0.133 mmol) and **33** (98 mg, 0.12 mmol) in dioxane (6 mL) (under Ar), and stirring was

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continued for 48 h. The mixture was filtered (with Celite), volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:9) to give **29** (118 mg, 61%): ^1H NMR (MeOH-d_4, 500 MHz) δ 7.87 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 5.73–5.68 (m, 4.5H), 5.62 (d, J = 1.0 Hz, 1H), 5.61 (s, 2H), 5.48 (s, 0.5H), 4.53 (dd, J = 5.3, 7.8 Hz, 3H), 4.49 (dd, J = 1.3, 5.3 Hz, 1H), 4.11 (q, J = 7.5 Hz, 2H), 4.12–4.09 (m, 1H), 4.05 (dd, J = 2.5, 10.0 Hz, 1H), 4.03 (dd, J = 2.5, 7.0 Hz, 1H), 3.99 (dd, J = 3.8, 6.8 Hz, 1H), 3.76 (dd, J = 3.0, 13.5 Hz, 1H), 3.63 (dd, J = 5.0, 13.5 Hz, 1H), 3.58 (dd, J = 2.8, 14.3 Hz, 1H), 3.52 (dd, J = 2.8, 14.5 Hz, 1H), 3.50–3.48 (m, 2H), 3.40 (dd, J = 8.3, 13.8 Hz, 1H), 3.37 (dd, J = 8.5, 14.0 Hz, 1H), 3.34 (s, 1H), 2.61 (dd, J = 10.0, 17.5 Hz, 1H), 2.58 (dd, J = 10.0, 16.5 Hz, 1H), 2.57–2.55 (m, 1H), 2.54–2.51 (m, 2H), 2.50–2.46 (m, 1H), 2.40 ("t", J = 5.3 Hz, 1H), 2.37 ("t", J = 5.5 Hz, 1H), 2.33 (dd, J = 6.3, 15.3 Hz, 1H), 2.26–2.17 (m, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.908, 0.905, 0.898, 0.895 (4 × s, 4 × 9H), 0.16 (s, 12H), 0.08, 0.069, 0.066, 0.05 (4 × s, 4 × 3H); ^{13}C NMR (MeOH-d_4) δ 174.1, 173.92, 173.87, 173.7, 166.5, 166.4, 152.2, 142.32, 142.25, 142.1, 102.6, 102.5, 94.1, 93.9, 93.8, 93.1, 84.3, 84.1, 84.0, 79.2, 79.1, 78.7, 62.0, 53.3, 43.0, 42.8, 42.52, 42.50, 42.4, 42.1, 41.3, 32.3, 32.0, 31.9, 31.0, 30.9, 30.8, 30.6, 26.61, 26.58, 26.5, 19.11, 19.07, 14.7, –4.01, –4.02, –4.1, –4.90, –4.95, –4.97, –5.3; MS *m/z* 1619.7068 (MNa^+ $[C_{70}H_{112}N_{14}O_{21}Si_4Na]$ = 1619.7101).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(carboxymethyl)-3',5'-dideoxyuridine (30). NaOH (10 mg, 0.25 mmol) was added to a solution of **29** (62 mg, 0.039 mmol) in $MeOH/H_2O$ (9:1, 1 mL), and stirring was continued for 24 h. Volatiles were evaporated to a small volume, and this solution was cooled (ice/H_2O). HCl/H_2O (4%) was added (to pH 4–6), volatiles were evaporated, and the residue was chromatographed (solvent A) to give **30** (42 mg, 69%): ^1H NMR (MeOH-d_4, 500 MHz) δ 7.88, 7.80 (2 × d, J = 8.0 Hz, 2 × 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 5.74–5.69 (m, 5H), 5.62 (s, 2H), 5.61 (s, 1H), 4.55 (dd, J = 4.8, 10.3 Hz, 3H), 4.50 (dd, J = 1.0, 5.0 Hz, 1H), 4.14–4.10 (m, 1H), 4.07 (dd, J = 2.5, 10.5 Hz, 1H), 4.03 (dd, J = 2.5, 10.0 Hz, 1H), 4.00 (dd, J = 3.8, 6.3 Hz, 1H), 3.77 (dd, J = 2.5, 14.0 Hz, 1H), 3.64 (dd, J = 4.5, 14.0 Hz, 1H), 3.60 (dd, J = 2.3, 14.8 Hz, 1H), 3.55–3.52 (m, 3H), 3.41 (dd, J = 8.5, 14.0 Hz, 1H), 3.39 (dd, J = 8.3, 14.8 Hz, 1H), 2.57 (dd, J = 8.5, 16.0 Hz, 1H), 2.56 (dd, J = 7.8, 14.8 Hz, 1H), 2.53–2.48 (m, 2H), 2.44–2.38 (m, 1H), 2.42 ("t", J = 5.8 Hz, 1H), 2.37 (dd, J = 6.0, 13.5 Hz, 1H), 2.35 (dd, J = 6.0, 15.5

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Hz, 1H), 2.28–2.19 (m, 3H), 0.92 (s, 9H), 0.915 (s, 18H), 0.91 (s, 9H), 0.17 (s, 12H), 0.09, 0.08 (2 × s, 2 × 6H); ^{13}C NMR (MeOH-d_4) δ 174.1, 174.0, 173.92, 173.87, 166.4, 152.1, 143.4, 142.3, 142.1, 102.5, 102.41, 102.36, 101.55, 101.53, 94.0, 93.8, 93.7, 93.1, 90.2, 84.3, 84.2, 84.0, 79.2, 79.1, 78.8, 53.3, 43.0, 42.9, 42.7, 42.4, 41.3, 32.3, 32.0, 30.9, 30.8, 26.61, 26.58, 26.56, 19.11, 19.08, –4.0, –4.07, –4.12, –4.9, –4.96, –4.97, –5.2; MS *m/z* 1591.6763 (MNa^+ [$C_{68}H_{108}N_{14}O_{21}Si_4Na$] = 1591.6788).

5'-Amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]uridine (31). Et_3N (23 μL, 16 mg, 0.16 mmol) and 1,3-propanedithiol (23 μL, 24 mg, 0.23 mmol) were added to a solution of **29** (60 mg, 0.038 mmol) in deoxygenated (Ar, 30 min) EtOH, and stirring was continued for 48 hours. Volatiles were evaporated, and the residue was chromatographed (solvent A) to give **31** (44 mg, 74%): ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.811 (d, J = 8.0 Hz, 1H), 7.810 (d, J = 7.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 5.72 (d, J = 8.5 Hz, 1H), 5.71 (d, J = 8.5 Hz, 2H), 5.694 (s, 1H), 5.686 (d, J = 8.0 Hz, 1H), 5.62 (d, J = 1.0 Hz, 1H), 5.61, 5.60 (2 × s, 2 × 1H), 4.59 (dd, J = 1.3, 5.3 Hz, 1H), 4.56–4.54 (m, 3H), 4.14–4.12 (m, 1H), 4.12 (q, J = 7.0 Hz, 2H), 4.05 (dd, J = 2.8, 10.3 Hz, 1H), 4.049–4.035 (m, 1H), 4.01 (dd, J = 5.5, 10.0 Hz, 1H), 3.64–3.57 (m, 1H), 3.54–3.50 (m, 3H), 3.43 (dd, J = 8.3, 14.8 Hz, 2H), 3.21 ("d", J = 12.5 Hz, 1H), 3.12–3.08 (m, 1H), 2.65–2.53, 2.50–2.35 (2 × m, 2 × 4H), 2.29–2.19 (m, 3H), 1.24 (t, J = 7.3 Hz, 3H), 0.92, 0.91, 0.908, 0.903, 0.17 (5 × s, 5 × 9H), 0.15, 0.09 (2 × s, 2 × 3H), 0.08 (s, 6H), 0.06 (s, 3H); ^{13}C NMR (MeOH-d_4) δ 174.1, 174.0, 173.9, 173.8, 173.7, 166.48, 166.45, 166.4, 166.3, 152.18, 152.15, 152.1, 142.8, 142.38, 142.35, 142.3, 102.7, 102.5, 102.3, 101.5, 94.4, 94.0, 93.9, 93.7, 84.42, 84.38, 84.1, 83.6, 79.14, 79.06, 78.8, 78.7, 62.0, 44.1, 42.8, 42.54, 42.52, 42.4, 42.1, 32.3, 32.25, 32.0, 30.6, 26.62, 26.56, 26.5, 19.10, 19.07, 14.7, –4.0, –4.1, –4.9, –5.0, –5.2; MS *m/z* 1595.7358 (MH_2Na^+ [$C_{70}H_{116}N_{12}O_{21}Si_4Na$] = 1595.7353).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3',5'-dideoxy-3'-[(ethoxycarbonyl)methyl]uridine (32). A solution of **31** (161 mg, 0.101 mmol) and **25** (80 mg, 0.15 mmol) in dried diglyme (3 mL) was stirred (under N_2)

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for 28 h at 65 °C. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:9) to give **32** (150 mg, 75%): ^1H NMR (Me_2CO-d_6, 500 MHz) δ 10.19 (br s, 2H), 10.14 (br s, 1H), 10.11 (br s, 2H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.68–7.63 (m, 4H), 5.75 (d, *J* = 1.5 Hz, 1H), 5.69–5.60 (m, 7H), 4.61–4.57 (m, 5H), 4.20–4.18 (m, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 4.08–4.03 (m, 3H), 3.81–3.75 (m, 2H), 3.74–3.72, 3.71–3.69, 3.68–3.66, 3.65–3.64, 3.63–3.61 (5 × m, 5 × 1H), 3.58–3.50, 3.47–3.43 (2 × m, 2 × 3H), 2.68–2.56 (m, 6H), 2.54–2.42, 2.40–2.28 (2 × m, 2 × 4H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.91 (br s, 45H), 0.20 (s, 12H), 0.192, 0.187 (2 × s, 2 × 3H), 0.124, 0.115 (2 × s, 2 × 3H), 0.111 (s, 6H); ^{13}C NMR (Me_2CO-d_6) δ 172.7, 172.6, 172.3, 164.3, 151.5, 141.2, 102.5, 102.3, 93.3, 93.0, 92.5, 84.3, 83.8, 83.7, 79.0, 78.4, 72.7, 71.1, 61.1, 58.9, 53.3, 42.2, 41.6, 41.4, 41.2, 32.2, 31.8, 26.53, 26.48, 26.4, 18.8, 18.7, 14.7, –3.95, –3.99, –4.1, –4.87, –4.93, –5.0, –5.3; MS *m/z* 2000.8848 (MNa^+ [$C_{87}H_{139}N_{17}O_{26}Si_5Na$] = 2000.8821).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2',3'-bis-*O*-(*tert*-butyldimethylsilyl)uridine (35). A solution of **25** (58 mg, 0.11 mmol) and **34** (100 mg, 0.117 mmol) in dried CH_2Cl_2 was stirred (under N_2) for 4 days. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:9) to give **35** (85 mg, 61%): ^1H NMR ($CDCl_3$) δ 10.06 (br s, 1H), 9.01 (br s, 1H), 8.38 (br s, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.70 (br s, 1H), 5.81 (s, 1H), 5.80–5.78 (m, 1H), 5.76 (dd, *J* = 2.0, 8.3 Hz, 1H), 5.71 (dd, *J* = 2.1, 8.1 Hz, 1 H), 5.63 (s, 1H), 4.85 (dd, *J* = 5.4, 6.9 Hz, 1H), 4.53 (d, *J* = 4.5 Hz, 1H), 4.47 (dd, *J* = 2.4, 5.4 Hz, 1H), 4.25–4.22 (m, 1H), 4.18–4.01 (m, 2H), 3.97 (dd, *J* = 2.1, 5.1 Hz, 1H), 3.82 (dd, *J* = 2.7, 13.5 Hz, 1H), 3.80–3.74 (m, 1H), 3.64 (dd, *J* = 3.6, 13.8 Hz, 1H), 3.28–3.18 (m, 2H), 2.66–2.49 (m, 3H), 2.38 (dd, *J* = 5.1, 15.6 Hz, 1H), 2.33 (dd, *J* = 4.5, 15.0 Hz, 1H), 2.13–2.01, 1.96–1.90, 1.78–1.72 (3 × m, 3 × 1H), 0.93, 0.92, 0.91, 0.87 (4 × s, 4 × 9H), 0.22, 0.19, 0.15, 0.09, 0.08, 0.07, 0.04, –0.03 (8 × s, 8 × 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 171.6, 163.7, 163.2, 151.2, 150.8, 150.3, 144.9, 140.1, 103.2, 102.5, 101.1, 100.2, 97.4, 93.5, 91.1, 85.5, 83.5, 82.1, 73.5, 71.5, 52.6, 42.4, 41.2, 40.3, 32.1, 31.1, 26.1, 26.01, 25.98, 25.96, 18.3, 18.23, 18.19, 18.1, –4.2, –4.29, –4.32, –4.4, –4.7, –5.1, –5.2; MS *m/z* 1282.5813 (MNa^+ [$C_{55}H_{93}N_{11}O_{15}Si_4Na$] = 1282.5827).

5'-Amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2',3'-bis-*O*-(*tert*-butyldimethylsilyl)uridine (36). A mixture of **35** (85 mg, 0.067 mmol) and 10%

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Pd–C (12 mg) in dried THF (17 mL) was hydrogenolyzed (5 psi) with a Parr shaking apparatus for 12 h and then filtered (with Celite). Volatiles were evaporated, and the residue was chromatographed (solvent A) to give **36** (60 mg, 72%): ^{1}H NMR (500 MHz) δ 8.21 (m, 2H), 8.14 (br s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 5.77 (d, J = 6.5 Hz, 1H), 5.65, 5.60, 5.59 (3 × d, J = 8.0 Hz, 3 × 1H), 5.57 (d, J = 1.0 Hz, 1H), 5.53 (d, J = 1.5 Hz, 1H), 4.41 (d, J = 6.0 Hz, 1H), 4.36 (d, J = 3.5 Hz, 1H), 4.29 (dd, J = 4.5, 6.5 Hz, 1H), 4.02 (dd, J = 2.3, 4.8 Hz, 1H), 3.90–3.83 (m, 2H), 3.80 (dt, J = 2.0, 6.5 Hz, 1H), 3.60–3.58 (m, 1H), 2.97 (d, J = 12.5 Hz, 1H), 2.88–2.82 (m, 1H), 2.35–2.32 (m, 3H), 2.31–2.25 (m, 2H), 2.17–2.12 (m, 1H), 0.86, 0.843, 0.837, 0.80 (4 × s, 4 × 9H), 0.09, 0.07, 0.05, 0.04 (4 × s, 4 × 3H), 0.00 (s, 9H), –0.07 (s, 3H); ^{13}C NMR (Me_2CO-d_6) δ 172.1, 171.6, 163.8, 163.7, 163.5, 151.6, 151.5, 151.3, 142.5, 142.3, 142.2, 140.9, 103.0, 102.0, 101.5, 93.0, 92.4, 90.1, 85.1, 84.4, 79.2, 79.1, 75.0, 74.2, 51.0, 47.4, 42.2, 41.91, 41.88, 40.23, 40.21, 32.0, 31.7, 26.4, 26.3, 18.77, 18.74, 18.70, 18.6, –4.1, –4.16, –4.20, –4.3, –4.5, –5.01, –5.04; MS *m/z* 1256.5914 (MNa^+ [$C_{55}H_{95}N_9O_{15}Si_4Na$] = 1256.5922).

5'-Azido-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2',3'-bis-*O*-(*tert*-butyldimethylsilyl)uridine (37). Method A. A solution of **25** (30 mg, 0.055 mmol) and **36** (60 mg, 0.049 mmol) in dried CH_2Cl_2 (5 mL) was stirred (under Ar) for 5 days. Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 1:9) to give **37** (39 mg, 49%).

Method B. DCC (26 mg, 0.12 mmol) was added to a solution of **33** (91 mg, 0.11 mmol) and **34** (106 mg, 0.124 mmol) in dried CH_2Cl_2 (3 mL) (under Ar), and stirring was continued for 12 h. The mixture was filtered (with Celite), and volatiles were evaporated. The residue was chromatographed (MeOH/CH_2Cl_2, 1:9) to give **37** (111 mg, 60%): ^{1}H NMR (Me_2CO-d_6, 500 MHz) δ 10.19 (br s, 1H), 10.13 (br s, 3H), 7.85, 7.78, 7.76 (3 × d, J = 8.0 Hz, 3 × 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.69 ("t", J = 6.0 Hz, 1H), 7.62–7.61 (m, 2H), 5.86 (d, J = 6.5 Hz, 1H), 5.76 (d, J = 1.5 Hz, 1H), 5.68 (d, J = 8.5 Hz, 1H), 5.66, 5.65 (2 × d, J = 8.0 Hz, 2 × 1H), 5.64 (s, 1H), 5.62 (d, J = 1.0 Hz, 1H), 5.60 (d, J = 8.5 Hz, 1H), 4.60–4.57 (m, 3H), 4.48 (dd, J = 4.5, 5.8 Hz, 1H), 4.19–4.16 (m, 2H), 4.07–4.03 (m, 3H), 3.78 (d, J = 4.5 Hz, 2H), 3.73–3.68 (m, 2H), 3.54 ("t", J = 5.8 Hz, 2H), 3.48–3.38 (m, 2H), 2.66–2.56 (m, 4H), 2.51 (dd, J = 5.3, 16.3 Hz, 1H), 2.46 (dd, J = 6.3, 15.3 Hz, 1H), 2.43 (dd, J = 5.8, 15.8 Hz, 1H), 2.36–2.32 (m, 2H), 0.93, 0.92, 0.91, 0.909, 0.89 (5 × s, 5 × 9H), 0.20 (s, 6H), 0.19, 0.14, 0.13 (3 × s, 3 × 3H), 0.12 (s, 6H), 0.10, 0.096, 0.06 (3 × s, 3 × 3H); ^{1}H NMR (MeOH-d_4) δ 7.87, 7.80 (2 × d, J = 8.1 Hz, 2 × 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 5.84 (d,

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J = 6.3 Hz, 1H), 5.76–5.69 (m, 5H), 5.63, 5.62 (2 × s, 2 × 1H), 4.55–4.50 (m, 3H), 4.37 (dd, J = 4.8, 5.7 Hz, 1H), 4.13–4.09 (m, 1H), 4.04–4.00 (m, 4H), 3.77 (dd, J = 2.1, 13.5 Hz, 1H), 3.63 (dd, J = 3.6, 13.2 Hz, 1H), 3.57–3.55, 3.51–3.50 (2 × m, 2 × 1H), 3.47–3.35, 2.60–2.53 (2 × m, 2 × 4H), 2.44–2.32 (m, 3H), 2.25–2.17 (m, 2H), 0.93, 0.92, 0.915, 0.91, 0.88, 0.17 (6 × s, 6 × 9H), 0.13, 0.12, 0.09 (3 × s, 3 × 3H), 0.08 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (Me_2CO-d_6) δ 172.23, 172.19, 172.1, 163.8, 163.7, 163.6, 151.7, 151.5, 142.3, 141.0, 140.8, 103.0, 102.5, 102.3, 102.2, 101.0, 93.1, 93.0, 92.5, 90.5, 85.0, 84.23, 84.16, 83.7, 78.94, 78.91, 78.89, 75.0, 74.3, 53.3, 42.4, 42.1, 42.0, 41.9, 41.8, 41.3, 32.2, 32.1, 32.0, 31.7, 26.48, 26.46, 26.42, 26.39, 26.3, 18.8, 18.7, 18.6, –4.0, –4.12, –4.14, –4.19, –4.20, –4.3, –4.4, –4.9, –5.02, –5.04; MS m/z 1663.7570 (MNa^+ [$C_{72}H_{120}N_{14}O_{20}Si_5Na$] = 1663.7548).

5'-Amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2'-*O*-(*tert*-butyldimethylsilyl)-3'-(*N*-carbonylmethyl)-3',5'-dideoxyuridinyl-(3'→5')-5'-amino-2',3'-bis-*O*-(*tert*-butyldimethylsilyl)uridine (38). Et_3N (17 μL, 12 mg, 0.12 mmol) and 1,3-propanedithiol (17 μL, 18 mg, 0.17 mmol) were added to a deoxygenated (Ar, 30 min) solution of **37** (46 mg, 0.028 mmol) in EtOH (5 mL), and stirring was continued for 48 h. Volatiles were evaporated, and the residue was chromatographed (solvent A) to give **38** (34 mg, 75%): ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.78 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 6.5 Hz, 1H), 5.74–5.68 (m, 5H), 5.61 (d, J = 1.5 Hz, 1H), 5.60 (d, J = 1.0 Hz, 1H), 4.55 (dd, J = 1.5, 5.5 Hz, 1H), 4.53, 4.50 (2 × d, J = 5.0 Hz, 2 × 1H), 4.36 (dd, J = 4.5, 6.5 Hz, 1H), 4.07–3.99 (m, 5H), 3.55–3.47 (m, 2H), 3.45–3.37 (m, 4H), 3.09 (dd, J = 2.5, 13.5 Hz, 1H), 2.98 (dd, J = 8.0, 14.0 Hz, 1H), 2.59 (dd, J = 6.5, 16.0 Hz, 1H), 2.56–2.52 (m, 2H), 2.43–2.35 (m, 2H), 2.35 (dd, J = 5.8, 16.3 Hz, 1H), 2.32 (dd, J = 6.5, 16.0 Hz, 1H), 2.26–2.18 (m, 2H), 0.92, 0.91, 0.903, 0.901, 0.87 (5 × s, 5 × 9H), 0.15 (s, 6H), 0.14, 0.12, 0.11, 0.08 (4 × s, 4 × 3H), 0.07 (s, 6H), 0.065, 0.01 (2 × s, 2 × 3H); ^{13}C NMR (MeOH-d_4) δ 173.91, 173.85, 166.48, 166.46, 166.3, 166.1, 152.5, 152.19, 152.15, 152.09, 143.5, 142.8, 142.4, 142.3, 103.4, 102.7, 102.4, 102.3, 94.4, 94.0, 93.7, 90.9, 85.6, 84.4, 84.3, 83.7, 79.1, 79.0, 78.9, 75.4, 74.7, 44.1, 42.9, 42.8, 42.5, 42.4, 42.3, 32.3, 32.2, 32.00, 31.96, 26.62, 26.60, 26.56, 26.50, 19.1, 19.0, –3.97, –4.03, –4.08, –4.13, –4.2, –4.4, –4.9, –5.0; MS m/z 1637.7673 (MNa^+ [$C_{72}H_{122}N_{12}O_{20}Si_5Na$] = 1637.7642).

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