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Supplementary Material for:

The Synthesis of Novel Nucleic Acid Mimics *via* the Stereoselective Intermolecular Radical Coupling of 3′-Iodo Nucleosides and Formaldoximes

Balkrishen Bhat,* Eric E. Swayze, Patrick Wheeler, Stuart Dimock,

Michel Perbost† and Yogesh S. Sanghvi

Isis Pharmaceuticals, Medicinal Chemistry Department,

2292 Faraday Avenue, Carlsbad, CA 92008

Experimental Section

2′,3′-Dideoxy-3′-iodo-5-methyl-5′-*O*-(triphenylmethyl)cytidine (6c). To 1,2,4-triazole (2.38 g, 34.4 mmol) in dry MeCN (30 mL) under argon at 0 °C was added $POCl_3$ (0.75 mL, 8 mmol) dropwise with vigorous stirring. Et_3N (5.56 mL, 40 mmol) was added dropwise over 0.5 h, and the thick suspension was stirred at 0 °C for an additional 0.5 h. 3′-Deoxy-3′-iodo-5′-*O*-(triphenylmethyl)thymidine 1.19 g (2.0 mmol) was added in one portion, and the mixture allowed to warm to rt over 3 h. The mixture was then cooled to 0 °C, and Et_3N (5.5 mL) and water (0.55 mL) were added, the mixture allowed to warm to room temperature with stirring, then concentrated to a small volume. The residue was partitioned between EtOAc (50 mL) and 5% $NaHCO_3$ (50 mL), and the organic layer washed with 5% $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), brine, then dried ($MgSO_4$) and concentrated to a foam, which was azeotroped with toluene, then CH_2Cl_2. This material was dissolved in dry 1,4-dioxane (25 mL), saturated with anhydrous NH_3 at rt, then stirred at rt under a balloon filled with anhydrous NH_3 overnight. The solvent was removed, and the residue dissolved in EtOAc (25 mL), washed with 5% $NaHCO_3$ (2 x 25 mL), brine, then dried ($MgSO_4$) and concentrated to a foam: R_f 0.46 (10%

MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.50-7.20 (m, 15H), 6.09 (t, *J*=4.8 Hz, 1H), 4.43 (dd, 1H), 4.26 (m, 1H), 3.56 (m, 2H), 2.84 (m, 2H), 1.43 (s, 3H). Anal. Calcd for $C_{29}H_{28}N_3O_3I$: C, 58.69; H, 4.76; N, 7.08. Found: C, 58.81; H, 4.92; N, 6.76.

3′-*O*-*tert*-Butyldiphenylsilyl-5′-*O*- (methyleneimino)thymidine (7a). 5′-*O*-Amino-3′-*O*-*tert*-butyldiphenylsilyl-thymidine[1] (5.0 g, 10 mmol) was suspended in EtOAc/MeOH (25 mL + 25 mL), formaldehyde (20 % w/w aqueous, 1.60 mL, 10.5 mmol) was added, and the mixture stirred 1 h at rt. The solution was concentrated, then chromatographed (50% EtOAc/hexane) to afford 4.79 g (94%) of **7a**: mp 166-167 °C; R_f 0.51 (% 50% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.62 (m, 4H), 7.45 (m, 6H), 7.29 (s, 1H), 6.90 (d, 2H), 6.42 (m, 2H), 4.44 (m, 1H), 4.10 (m, 2H), 3.78 (dd, 1H), 2.35 (ddd, 1H), 1.85 (s, 3H), 1.82 (m, 1H), 1.09 (s, 9H). Anal. Calcd for $C_{27}H_{33}N_3O_5Si$: C, 63.88; H, 6.55; N, 8.28. Found: C, 63.77; H, 6.50; N, 8.20.

3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxy-5′-*O*-phthalimidoadenosine. To 5′-*O*-phthalimido-2′-deoxyadenosine[2] 0.40 g (1 mmol) and imidazole (0.18 g, 2.6 mmol) in dry DMF (5 mL) was added *tert*-butyldiphenylsilyl chloride (0.31 mL, 1.2 mmol), and the reaction mixture was stirred at rt for 18 h. The solution was partitioned between water (50 mL) and EtOAc (25 mL), the organic layer washed with water (2 x 25 mL) and brine, then dried ($MgSO_4$) and concentrated to afford 0.60 g (94%) of crude product (containing only traces of silyl by-products), which could be used directly for the next step. A portion of material so obtained was chromatographed (0 to 10% MeOH/CH_2Cl_2) to provide an analytical sample: R_f 0.46 (10% MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.30 (s, 2H), 7.85-7.60 (m, 8H), 7.40 (m, 6H), 6.57 (t, *J*=6.9 Hz, 1H), 5.73 (s, 2H), 4.83 (m, 1H), 4.28 (m, 1H), 4.08 (dd, 1H), 3.94 (dd, 1H), 2.60 (m, 2H), 1.13 (s, 9H). Anal. Calcd for $C_{34}H_{34}N_6O_5Si \cdot 0.5\ H_2O$: C, 63.43; H, 5.48; N, 13.05. Found: C, 63.24; H, 5.29; N, 13.03.

3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxy-5′-*O*-(methyleneimino)adenosine (7b). 3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxy-5′-*O*-phthalimidoadenosine (1.05 g, 1.65 mmol) was dissolved in CH_2Cl_2 (17 mL), cooled to 0 °C, and methylhydrazine (0.11 mL, 1.98 mmol) was added dropwise. The mixture was stirred at 0 °C for 0.5 h, filtered, and the solid washed twice with cold CH_2Cl_2. The combined filtrates were diluted with toluene (6 mL), then concentrated and combined with an additional portion (0.95 g, 1.88 mmol) of 5′-*O*-amino-3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxyadenosine prepared in a similar manner. This solid was suspended in EtOAc/MeOH (17 mL + 17 mL), formaldehyde (20 % w/w aqueous, 0.53 mL, 3.53 mmol) was added, and the mixture stirred 1 h at 40 °C. The solution was concentrated, then chromatographed (80% EtOAc/hexane to 5% MeOH in 80% EtOAc/hexane) to afford 1.33 g (73%) of **7b**: R_f 0.47 (5% MeOH in 80% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.93 (s, 1H), 7.65 (m, 4H), 7.41 (m, 6H), 6.88 (d, *J*=7.9 Hz, 1H), 6.50 (t, *J*=6.6 Hz, 1H), 6.35 (d, *J*=7.9 Hz, 1H), 5.70 (s, 2H), 4.65 (dd, 1H), 4.28 (dd, 1H), 4.15 (dd, 1H), 3.92 (dd, 1H), 2.51 (m, 2H), 1.11 (s, 9H). Anal. Calcd for $C_{27}H_{32}N_6O_3Si$: C, 62.77; H, 6.24; N, 16.27. Found: C, 62.77; H, 6.11; N, 15.94.

3′-*O*-*tert*-Butyldiphenylsilyl-2′-deoxy-2-*N*-(dimethylamino)methylene-5′-*O*- (methyleneimino)guanosine (7c). This material was prepared from 2′-deoxyguanosine according to the general procedures described for the 2′-*O*-methyl series in 61% overall yield: R_f 0.38 (10% MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 11.34 (s, 1H), 8.49 (s, 1H), 7.91 (s, 1H), 7.62 (m, 4H), 7.42 (m, 6H), 6.94 (d, *J*=7.5 Hz, 1H), 6.52 (d, *J*=7.5 Hz, 1H), 6.34 (dd, *J*=6.1, 8.2 Hz, 1H), 4.57 (m, 1H), 4.17 (dd, 1H), 4.55 (dd, 1H), 3.96 (dd, 1H), 3.08 (s, 3H), 3.01 (s, 3H), 2.71 (m, 1H), 2.24 (m, 1H), 1.05 (s, 9H). Anal. Calcd for $C_{30}H_{37}N_7O_4Si \cdot 0.25\ H_2O$: C, 60.84; H, 6.38; N, 16.55. Found: C, 60.80; H, 6.49; N, 16.46.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(triphenylmethyl)thymidylyl-(3′→5′)-3′-*O*-(*tert*-

butyldiphenylsilyl)thymidine (9a). Method 1: From 0.59 g (1.0 mmol) of 3′-deoxy-3′-iodo-5′-*O*-(triphenylmethyl)thymidine (**6a**) and 1.52 g (3.0 mmol) of 3′-*O*-*tert*-butyldiphenylsilyl-5′-*O*-(methyleneimino)thymidine (**7a**) according to the general procedure was obtained unreacted oxime (0.84 g, 75% of unreacted material) upon elution of the column with 50% EtOAc/hexane, and 0.80 g (82%) of the dimer **9a** upon elution with 10% MeOH/CH_2Cl_2. **Method 2:** From the 3′-iodide (713 mg, 1.2 mmol), oxime (508 mg, 1.0 mmol), and bis(trimethystannyl)benzopinacolate (2.08 g, 3.0 mmol) according to the general procedure was obtained 789 mg (81%, based on oxime) of **9a** after chromatography as described for method 1. **Method 3:** A solution of Bu_3SnH (0.19 mL, 0.7 mmol) and AIBN (30 mg, 0.18 mmol) in degassed benzene (0.50 mL) was added via syringe pump to a solution of the 3′-iodide (297 mg, 0.50 mmol) and the oxime (762 mg, 1.5 mmol) in degassed benzene (5 mL) over 24 h at 80 °C. The mixture was cooled, treated with EtOAc/KF as described in the general procedure, then chromatographed as described for method 1 to yield 623 mg of unreacted oxime (88% of unreacted material), 66 mg (28%) of 3′-deoxy-5′-(triphenylmethyl)thymidine, and 232 mg (48%) of **9a**. Dimeric material obtained by each method was identical, and gave the following data: R_f 0.30 (70% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.46 (s, 1H), 7.65-7.05 (m, 27H), 6.32 (t, *J*=6.8, 1H), 6.10 (t, *J*=5.5, 1H), 5.30 (t, 1H), 4.26 (m, 1H), 4.03 (m, 1H), 3.82 (m, 1H), 3.49 (m, 2H), 3.35 (m, 2H), 2.77 (m, 2H), 2.53 (m, 1H), 2.33 (m, 1H), 2.21 (m, 2H), 1.83 (m, 1H), 1.78 (s, 3H), 1.51 (s, 3H), 1.07 (s, 9H). Anal. Calcd for $C_{56}H_{61}N_5O_9Si$: C, 68.90; H, 6.30; N, 7.17. Found: C, 68.61; H, 6.31; N, 7.10.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(*tert*-butyldiphenylsilyl)thymidylyl-(3′→5′)-3′-*O*-(*tert*-butyldiphenylsilyl)thymidine (9b). From 0.59 g (1.0 mmol) of 5′-*O*-*tert*-butyldiphenylsilyl-3′-deoxy-3′-iodo-thymidine (**6b**) and 1.52 g (3.0 mmol) of 3′-*O*-*tert*-butyldiphenylsilyl-5′-*O*-(methyleneimino)thymidine (**7a**) according to the general

procedure was obtained unreacted oxime (1.10 g, 99% of unreacted material) upon elution of the column with 50% EtOAc/hexane, and 0.78 g (81%) of **9b** upon elution with 10% MeOH/1:1 EtOAc/hexane: R_f 0.36 (10% MeOH/1:1 EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ 8.58 (bs, 2H), 7.66 (m, 8H), 7.41 (m, 13H), 7.18 (s, 1H), 6.34 (t, *J*=6.8, 1H), 6.10 (t, *J*=6.1, 1H), 5.34 (t, 1H), 4.28 (m, 1H), 4.10-3.25 (m, 5H), 2.82 (m, 2H), 2.58-2.10 (m, 3H), 1.88 (m, 1H), 1.82 (s, 3H), 1.63 (s, 3H), 1.07 (s, 18H). Anal. Calcd for $C_{53}H_{65}N_5O_9Si_2 \cdot H_2O$: C, 64.28; H, 6.82; N, 7.07. Found: C, 64.08; H, 6.81; N, 6.95.

3′-De(oxyphosphinico)-2′-deoxy-5-methyl-3′-(methyleneimino)-5′-*O*-(triphenylmethyl)cytidylyl-(3′→5′)-3′-*O*-(*tert*-butyldiphenylsilyl)thymidine (9c). From 297 mg (0.5 mmol) of **6c** and 760 mg (1.5 mmol) of **7a** according to the general procedure was obtained unreacted oxime (0.59 g, 97% of unreacted material) upon elution of the column with 50% EtOAc/hexane, and 0.29 g (58%) of **9c** upon elution with 7% MeOH/CH_2Cl_2: R_f 0.30 (7% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.70-7.20 (m, 25H), 7.16 (s, 1H), 6.31 (dd, *J*=6.0, 7.5 Hz, 1H), 6.10 (t, *J*=6.8 Hz, 1H), 5.25 (bs, 1H), 4.26 (m, 1H), 4.00 (m, 1H), 3.85 (m, 1H), 3.51 (m, 2H), 3.24 (m, 2H), 2.76 (m, 2H), 2.50-2.20 (m, 4H), 1.80 (m, 1H), 1.76 (s, 3H), 1.50 (s, 3H), 1.07 (s, 9H). Anal. Calcd for $C_{56}H_{62}N_6O_8Si \cdot 0.5\ H_2O \cdot 0.15$ EtOAc (EtOAc evident in ^{1}H NMR): C, 68.16; H, 6.49; N, 8.43. Found: C, 68.41; H, 6.31; N, 8.06.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(triphenylmethyl)thymidylyl-(3′→5′)-3′-*O*-(*tert*-butyldiphenylsilyl)-2′-deoxyguanosine (9e). From 297 mg (0.5 mmol) of **6b** and 880 mg (1.5 mmol) of **7c** according to the general procedure was obtained a mixture of products after elution of the column with 20% MeOH/CH_2Cl_2. TLC analysis of this mixture (10% MeOH/CH_2Cl_2, 3 developments) indicated the presence of four major nucleosidic products, presumably resulting from partial loss of the dimethylformamidine protecting group. The mixture was dissolved in 1,4-dioxane (5 mL), concentrated aqueous ammonia (5 mL) was added, and the mixture was stirred at 55 °C in a sealed vessel for 2 h. The resulting clear solution was

cooled in an ice bath, and the solvent removed in vacuo. The solid residue was triturated with EtOAc (25 mL, 1h at 40 °C, with stirring), filtered, washed with EtOAc, and dried to provide 0.54 g of 3′-*O*-*tert*-butyldiphenylsilyl-2′-deoxy-5′-*O*- (methyleneimino)guanosine (81% based on unreacted oxime). This material could be converted back to the dimethylformamidine protected starting material in nearly quantitative yield.[3] The combined filtrates were concentrated and chromatographed (5% MeOH in 7:3 MeCN/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide an additional 80 mg of the deblocked oxime (8%, total recovery 91%), and 230 mg (46%) of **9e**: R_f 0.63 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 12.13 (s, 1H), 9.67 (s, 1H), 7.70-7.60 (m, 5H), 7.57 (s, 1H), 7.45-7.10 (m, 21H), 6.24 (t, *J*=6.5 Hz, 1H), 6.12 (bs, 2H), 6.02 (t, *J*=5.2 Hz, 1H), 5.68 (bs, 1H), 4.49 (m, 1H), 4.09 (m, 1H), 3.81 (m, 1H), 3.48 (m, 3H), 3.19 (m, 1H), 2.72 (m, 2H), 2.48 (m, 3H), 2.12 (m, 2H), 1.48 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.25, 158.85, 153.49, 151.25, 150.52, 143.44, 143.33, 136.36, 135.77, 135.72, 133.22, 133.07, 130.06, 128.64, 127.94, 127.86, 127.27, 117.46, 110.41, 87.05, 86.00, 85.35, 84.26, 83.28, 77.21, 73.71, 73.40, 63.92, 53.24, 40.11, 37.47, 36.99, 26.88,19.07, 12.08. Anal. Calcd for $C_{59}H_{64}N_8O_8Si$: C, 67.18; H, 6.04; N, 11.19. Found: C, 67.57; H, 6.00; N, 11.23.

6-*N*-[1-(Dimethylamino)ethylene]-2′-*O*-methyladenosine (10c) 2′-*O*-methyladenosine (**10b**, 5.0 g, 17.8 mmol) was dried over P_2O_5 at 40 °C for 24h. It was then azeotroped with anhydrous pyridine (20mL x 2) and the residue dried under reduced pressure for 1.5 h. After taking up in anhydrous MeOH (20 mL), dimethylacetamide dimethylacetal (8.48 g, 63.6 mmol) was added, and the reaction mixture was stirred at room temperature for 36 h. It was concentrated to an oil, dissolved in EtOAc (100 mL) and washed with water (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. It was purified by column chromatography on silica gel (5-7% MeOH/CH_2Cl_2) to provide 5.6 g (90%) of **10c** as a colorless foam: ^{1}H NMR(DMSO-d_6) δ 8.50 (s, 1H), 8.45 (s,1H) 6.07 (d, *J*=5.3, 1H), 5.32(bs, 2H, D_2O exchangeable), 4.43-

4.28 (m, 2H), 4.01-3.99 (m, 1H), 3.80-3.55 (m, 3H), 3.33 (s, 3H), 3.12 (s, 6H), 2.07 (s, 3H); MS (FAB+) *m/e* 351 (M+H). Anal. Calcd for $C_{15}H_{22}N_6O_4.0.25\ H_2O$: C, 50.77; H, 6.39; N, 23.68. Found: C, 50.58; H, 6.50; N, 23.38.

2-*N*-Isobutyryl-2′-*O*-methylguanosine (10e). Dried **10d** (5.0 g, 16.8 mmol) was azeotroped with anhydrous pyridine (30 mL). After dissolving the residue in anhydrous pyridine (80 mL), TMSCl (14.0 mL, 110 mmol) was added and the reaction mixture was allowed to stir at room temperature for 17 h. To this was added isobutyryl chloride (9.35 g, 89.5 mmol) and the stirring was continued for an additional 5 h. It was quenched with water (20 mL) and cooled to 0 °C. To this was added NH_4OH (25 mL). It was stirred at this temperature for 30 m, and the separated solid was removed by filtration, then washed with hexane (3 x 20 mL). The mother liquor was concentrated to a small volume, water (15 mL) and EtOAc (30 mL) were added, and the residue and left overnight at rt. The precipitate was filtered and the combined solid was recrystallized from CH_3CN to give 4.1 g (68%) of a colorless solid: ^{1}H NMR (DMSO-d_6) δ 12.05 (s, 1H); 11.70 (s, 1H); 8.28 (s, 1H); 5.82 (d, *J*=6.02 Hz, 1H), 4.29-4.22 (m, 2H), 3.90-3.88 (m, 1H), 3.55-3.50 (m, 2H); 3.27 (s, 3H), 2.77 (m, 1H); 1.06-1.03 (d, 6H); MS (FAB+) *m/e* 368 (M+H). Anal. Calcd for $C_{15}H_{21}N_5O_6{\bullet}H_2O$: C, 46.75; H, 6.02; N, 18.17. Found: C, 46.90; H, 6.13; N, 18.52.

2-*N*-(Dimethylamino)methylene-2′-*O*-methylguanosine (10f). A mixture of dry 2′-*O*-methylguanosine (5.0 g, 16.8 mmol), *N,N*′-dimethylformamide diethylacetal (9.87 g, 67 mmol) in anhydrous MeOH (100mL) was stirred at room temperature for 24 h., when the TLC (10%MeOH/CH_2Cl_2) indicated the reaction was complete. Solvent was removed under reduced pressure and the light brown syrup was azeotroped with acetonitrile (3x20 mL). Finally, trituration of the residue with CH_3CN (50 ml) furnished a solid which was filtered and dried. The mother liquor was concentrated to a smaller volume and left overnight to furnish additional solid which was filtered. The total yield of **10f** was 5.7 g (96%): mp 198-201 °C; ^{1}HNMR (DMSO-d_6) δ 11.36 (s, 1H),

8.53 (s, 1H), 8.08 (s, 1H), 5.90 (d, *J*=5.86 Hz, 1H), 5.25 (d, *J*=4.90 Hz, 1 H), 5.0-5.2 (m, 1H), 4.1-4.4 (m, 2H), 3.8-4.0 (m, 1H), 3.4-3.7 (m, 2H), 3.31 (s, 3H), 3.14 (s, 3H), 3.02 (s, 3H); MS (FAB+) *m/e* 351 (M+H). Anal. Calcd for $C_{14}H_{20}N_6O_5.0.5\ H_2O$: C, 46.53; H, 5.86; N, 23.26. Found: C, 46.18; H, 5.93; N, 23.07.

5′-*O*-(4,4′-Dimethoxytriphenylmethyl)-6-*N*-[1-(dimethylamino)ethylene]-2′-*O*-methyladenosine (11b). A solution of **10c** (6.0 g, 17.16 mmol), DMTCl (7.1 g, 21 mmol and DMAP (0.7 g, 5.7 mmol) in anhydrous pyridine (50 mL) was stirred at room temperature for 4 h. It was poured into ice water (100 mL) and extracted with EtOAc (150 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel using 5-7% MeOH-CH_2Cl_2 gave 7.5 g (67.5%) of **11b** as a light yellow foam: ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.08 (s, 1H), 7.45-7.19 (m, 9H), 6.82-6.78 (m, 4H), 6.19 (d, *J*=4Hz,1H), 4.52-4.41 (m, 2H), 4.26-4.18 (m, 1H), 3.77-3.70 (m, 8H), 3.55 (s, 3H), 3.20-3.14 (bs, 6H), 2.15 (s, 3H); MS (FAB+) *m/e* 653 (M+H). Anal. Calcd for $C_{36}H_{40}N_6O_6.\ 0.5\ H_2O$: C, 65.34; H, 6.24; N, 12.70. Found: C, 65.37; H, 6.20; N, 12.35.

5′-*O*-(4,4′-Dimethoxytriphenylmethyl)-2-*N*-isobutyryl-2′-*O*-methylguanosine (11c). A solution of **10e** (2.12 g, 5.01 mmol) in anhydrous pyridine (20 mL) was azeotroped under reduced pressure. It was re-dissolved in anhydrous pyridine (18 mL) and after adding DMTCl (2.11 g, 6.2 mmol) and DMAP (9.21 g, 1.7 mmol), the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was poured into cold water (60 mL) and it was extracted with EtOAc (2 x 60 mL). The organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure at 35 °C. The residual oil thus obtained was purified by column chromatography using 3-7% MeOH/CH_2Cl_2 (trace of Et_3N, 5 drops/L). Appropriate fractions were collected and concentrated which after drying overnight under reduced pressure furnished 2.94 g (82%) **11c** as a light yellow foam: ^{1}H NMR (DMSO-d_6) δ 12.13 (s, 1H), 11.65 (s, 1H), 8.18 (s, 1H, 7.39-7.23 (m, 9H), 6.88-6.82 (m, 4H), 5.99 (d, *J*=6 Hz, 1H), 5.30

(d, *J*=6 Hz, 1H), 4.41-4.31 (m, 2H), 4.09-4.06 (m, 1H), 3.74 (s, 6H), 3.42 (s, 3H), 3.31-3.20 (m, 2H), 2.84-2.66 (m, 1H), 1.16-1.13 (m, 6H); MS (FAB$^+$) *m/e* 670 (M+H). Anal. Calcd for $C_{36}H_{39}N_5O_8 \cdot 0.5\ H_2O$: C, 63.71; H, 5.94; N, 10.32. Found: C, 63.84; H, 6.10; N, 10.13.

5′-*O*-(4,4′-Dimethoxytriphenylmethyl)-2-*N*-(dimethylamino)methylene-2′-*O*-methylguanosine (11d). A mixture of **10f** (3.0 g, 8.2 mmol) DMTCl (3.46 g, 12.2 mmol) and DMAP (0.35 g, 2.86 mmol) in anhydrous pyridine (20 mL) was stirred at room temperature for 5 h, at which point TLC (10% MeOH/CH_2Cl_2) on silica gel indicated the reaction was complete. It was poured into cold water (100 mL) and extracted with EtOAc (2 x 60 mL). The Organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography using 3-5% MeOH/CH_2Cl_2 (Et_3N, 5 drop/L) and after concentrating the appropriate fractions followed by drying under high vacuum gave 3.5 g (63%) of **11d** as a light yellow foam: ^{1}H NMR (DMSO-d_6) δ 11.42 (s, 1H), 8.52 (s, 1H), 7.96 (s, 1H), 7.39-7.22 (m, 9H), 6.88-6.83 (m, 4H), 5.98 (d, *J*=4 Hz, 1H), 5.31 (d, *J*=5.7 Hz, 1H), 4.40-4.27 (m, 2H), 4.15-3.95 (m, 1H), 3.91 (bs, 2H), 3.74 (s, 6H), 3.39 (s, 3H), 3.11 (s, 3H), 3.04 (s, 3H); MS (FAB$^+$) *m/e* 655 (M+H). Anal. Calcd. for $C_{35}H_{38}N_6O_7 \cdot 1.5\ H_2O$: C, 61.66; H, 6.06; N, 12.33. Found: C, 61.95; H, 5.81; 12.19.

5′-*O*-*tert*-Butyldiphenylsilyl-2′-*O*-methyl-5-methyluridine (11e). A solution of **10a** (2 g, 7.34 mmol), *tert*-butyldiphenylsilyl chloride (1.73 g, 6.29 mmol) and DMAP (0.01 g, 0.15 mmol) in anhydrous pyridine (7 mL) was stirred for 18 h. After the reactions was complete, it was concentrated to a smaller volume and diluted with EtOAc (50 mL), washed with water (2 x 10 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by column chromatography using 2-5% MeOH/CH_2Cl_2. Appropriate fractions were pooled and concentrated to give 3.0 g (80%) of **11e** as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 11.44 (s, 1H), 7.70-7.42 (m, 10H), 5.95 (d, *J*=6 Hz, 1H), 5.30 (bs, 1H), 4.28 (bs, 1H), 3.98-3.80 (m, 3H), 3.39 (s,

3H), 1.48 (s, 3H), 1.06 (s, 9H),; MS (FAB+) *m/e* 511 (M+H). Anal. Calcd for $C_{27}H_{34}N_2O_6Si$: C, 63.51; H, 6.71; N, 5.49. Found: C, 63.20; H, 6.69; N, 5.42.

5′-*O*-(*tert*-Butyldiphenylsilyl)-2′-*O*-methyladenosine (11f) A mixture of dried **10b** (5.0 g, 17.8 mmol), TBDPSCl (6.10 g, 22.2 mmol) and DMAP (0.4 mmol) in anhydrous pyridine (15 mL) was stirred at room temperature for 15 h when TLC (10% MeOH/CH_2Cl_2) indicated the completion of the reaction. The reaction mixture was concentrated, taken up in EtOAc (100 mL) and washed with water (2 x 20 mL). The organic layer was concentrated, and residue purified by flash chromatography (5-7% MeOH/CH_2Cl_2) to give 8 g (86%) of the desired 5′-protected analog as colorless foam: ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 8.11 (s, 1H), 7.65-7.34 (m, 10H), 6.07 (d, *J*=4 Hz, 1H), 5.36 (d, *J*=6 Hz, 1H), 4.55-4.41 (m, 2H), 4.10-3.75 (m, 3H), 3.37 (s, 3H); MS (FAB+) *m/e* 520 (M+H). Anal. Calcd for $C_{27}H_{33}N_5O_4Si$: C, 62.40; H, 6.40; N, 13.48. Found: C, 62.62; H, 6.49; N, 13.23.

6-*N*-[1-(Dimethylamino)ethylene]-5′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyladenosine (11g). A solution of **10c** (1 g, 2.8 mmol), TBDPSCl (1.1 g, 4 mmol) and DMAP (0.020 g, 0.3 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature for 15 h. The solution was concentrated to a smaller volume and taken up in EtOAc (30 mL) and washed with water (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. It was flash chromatographed on silica gel using 80:18:2, CH_2Cl_2:CH_3COCH_3:MeOH mixture as the eluent. The product fractions were concentrated to a colorless foam to yield 1.2 g (72%) of **11g**: ^{1}H NMR (DMSO-d_6) δ 8.39 (s, 1H), 8.37 (s, 1H), 7.64-7.36 (m, 10H), 6.10 (d, *J*=4 Hz, 1H), 5.38 (d, *J*=4 Hz, 1H), 4.52-4.47 (m, 2H), 4.10-3.75 (m, 1H), 3.38 (s, 3H), 3.12 (bs, 6H), 2.05 (s, 3H), 0.99 (s, 9H).

5′-*O*-*tert*-Butyldiphenylsilyl-6-*N*-(dimethylamino)methylene-2′-*O*-methyladenosine (11h) A solution of **11f** (5.0 g, 9.6 mmol) and *N,N′*-dimethylformamide diethylacetal (4.0 g, 27.7 mmol) in anhydrous MeOH (25 mL) was

allowed to stir at room temperature for 15 h. After concentrating, it was taken up in EtOAc (100 mL) and washed with water (2 x 20 mL), and the organic layer separated, then dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified over silica gel to afford desired nucleoside 5.32 g (96%) as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 8.91 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 7.65-7.32 (m, 10H), 6.11 (d, *J*=6 Hz, 1H), 5.39 (d, *J*=6 Hz, 1H), 4.57-4.44 (m, 2H), 4.09-3.70 (m, 3H), 3.37 (s, 2H), 3.21 (2, 3H), 3.14 (s, 3H), 1.00 (s, 9H); MS (FAB$^+$) *m/e* 575 (M+H). Anal. Calcd for $C_{30}H_{38}N_6O_4Si$: C, 62.69; H, 6.66; N, 14.62. Found: C, 62.31; H, 6.75; N, 14.71.

5′-*O*-tert-Butyldiphenylsilyl-2′-*O*-methylguanosine (11i). A suspension of 2′-*O*-methylguanosine (5.0 g, 16.8 mmol), TBDPSCl (5.8 g, 21.5 mmol) and DMAP (0.05 g, 0.4 mmol) in anhydrous pyridine (15 mL) was stirred at room temperature for 20 h, at which time the reaction was complete. After concentrated to a small volume, water was added to the reaction mixture, and when colorless solid separated, it was collected by filtration, washed thoroughly with water (2 x 20 mL) and ether (3 x 20 mL) respectively. The solid nucleoside analog (**11i**) was dried under reduced pressure to yield 8.1 g (89%) of **11i**: ^{1}H NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.84 (s,1H), 7.66-7.37 (m, 10 H), 6.51 (bs, 2H), 5.85 (d, *J*=6 Hz, 1H), 5.33 (d, *J*=6 Hz, 1H), 4,41-4.36 (m, 1H), 4.20-4.16 (m, 1H), 4.02-3.70 (m, 2H), 3.37 (s, 3H); MS (FAB$^+$) *m/e* 536 (M+H). Anal. Calcd for $C_{27}H_{33}N_5O_5Si$•0.25 H_2O: C, 60.04; H, 6.25; N, 12.96. Found: C, 60.29; H, 6.33; N, 12.64.

5′-*O*-(*tert*-Butyldiphenylsilyl)-2-*N*-(dimethylamino)methylene-2′-*O*-methylguanosine (11j). A solution of **11i** (6.0 g, 11.2 mmol) and *N,N′*-dimethylformamide diethylacetal (4.72 g, 32.06 mmol in anhydrous MeOH (25 mL) was stirred at room temperature for 18 h. After removing the solvent under reduced pressure, the residue was dissolved in EtOAc (100 mL) and washed with water (2 x 20 mL). The organic layer was concentrated and the residual oil purified by column chromatography using 3-6% MeOH/CH_2Cl_2. The product fractions were concentrated and dried to yield

6.17g (93%) of a colorless foam: ^{1}H NMR (DMSO-d_6) δ 11.40 (s, 1H), 8.53 (s, 1H), 7.98 (s, 1H), 7.65-7.39 (m, 10H), 5.98 (d, *J*=6.0 Hz, 1H), 5.38 (d, 1H), 4.45-3.70 (m, 5H), 3.39 (s, 3H), 3.11 (s, 3H), 3.03 (s, 3H), 1.01 (s, 9H); MS (FAB$^+$) *m/e* 591 (M+H). Anal. Calcd for $C_{30}H_{38}N_6O_5Si$•0.25 H_2O: C, 60.53; H, 6.52; N, 14.12. Found: C, 60.80; H, 6.53; N, 13.75.

3′-Deoxy-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-6-*N*-[1-(dimethylamino)ethylene]-3′-iodo-2′-*O*-methyladenosine (12b). From **11b** (5 g, 7.6 mmol) according to general procedure A was obtained 3.1 g (60%) of **12b** after chromatography (20% acetone in CH_2Cl_2) and precipitation by ether-hexane mixture: ^{1}H NMR (DMSO-d_6) d 8.43 (s, 1H), 8.14 (s, 1H), 7.45-7.22 (m, 9H), 6.90-6.86 (m, 4H), 4.86-4.72 (m, 2H), 3.97 (m, 1H), 3.73-3.62 (s, 6H), 3.44-3.39 (m,5H), 3.10 (s, 6H), 1.23 (s, 3H); MS (FAB$^+$) *m/e* 763 (M+H). Anal. Calcd for $C_{36}H_{39}N_6O_5I$•0.5 H_2O: C, 56.04; H, 5.22; N, 10.89. Found: C, 56.20; H, 5.62; N, 10.69.

3′-Deoxy-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2-*N*-(dimethylamino)methylene-3′-iodo-2′-*O*-methylguanosine (12d). This compound was prepared by the general procedure A from 1.0 g (1.5 mmol) of **11d** after chromatography using 30% acetone/Ch_2Cl_2 as the eluent to give 0.61 g (52%) of **12d**: ^{1}H NMR (DMSOd_6) δ 11.44 (s, 1H), 8.58 (s, 1H), 7.85 (s, 1H), 7.44-7.24 (m, 9H), 6.89 (d, *J*=8 Hz, 4H), 5.91 (d, *J*=2.8 Hz,1H), 4.89-4.87 (m,1H), 4.73-4.71 (m, 1H), 3.90 (bs, 1H), 3.75 (s, 6H), 3.46 (s, 3H), 3.40-3.35 (m, 2H), 3.12 (s, 3H), 3.04 (s, 3H). mass spectrum (FAB) m/z 765 (MH^+). Anal. Calcd for $C_{35}H_{37}N_6O_6I$•0.5 MeOH: C, 54.62; H, 5.04; N, 10.77. Found: C, 55.01; H, 5.17; N, 10.51.

3′-Deoxy-3′-iodo-2′-*O*-methyl-5-methyluridine (12h). A mixture of **12a** (0.580 g, 0.847 mmol) and 1,1,1,3,3,3-hexafluoroisopropanol (5 mL) was stirred for 4 h. The solvent was removed under reduced pressure with a good trap and the residue was purified by flash chromatography using a mixture of 80:18:2 CH_2Cl_2:acetone:MeOH as the eluent. Appropriate fractions were combined and concentrated to give 0.250 g (77%) of

12h as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 7.72 (d, *J*=2 Hz, 1H), 5.73 (d, *J*=3.6 Hz, 1H), 5.21-5.10 (m, 1H), 4.66-4.62 (m, 1H), 4.40-4.37 (m, 1H),3.72-3.5 (m, 3H), 3.40 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.68, 150.25, 136.19, 109.34, 90.74, 88.37, 79.88, 66.15, 57.56, 26.91, 12.39; MS (FAB$^+$) *m/e* 383 (M+H). Anal. Calcd for $C_{11}H_{15}N_2O_5I$•0.25 H_2O: C, 34.17; H, 4.04; N, 7.24. Found: C, 34.55, H,3.92; N, 6.92.

3′-Deoxy-6-*N*-[1-(dimethylamino)ethylene]-3′-iodo-2′-*O*-methyladenosine (12i). A similar procedure described for the preparation of compound**12h** gave from 0.225 g (0 .29 mmol) of **12b**, 0.110 g (80%) of **12i** as a colorless compound: ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1H), 8.40 (s, 1H), 5.95 (bs, 1H), 5.30-5.27 (m,1H), 4.82-4.80 (m, 1H), 4.77-4.75 (m, 1H), 3.81-3.60 (m, 3H), 3.40 (s, 3H), 3.15 (s, 6H), 2.03 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.20, 159.98, 152.44, 150.35, 140.36, 125.54, 90.42, 87.57, 80.44, 66.20, 57.75, 25.88, 17.07.; MS (FAB$^+$) *m/e* 461 (M+H). Anal. Calcd for $C_{15}H_{21}N_6O_3I$: C, 39.14; H, 4.60; N, 18.26. Found: C, 39.18; H, 4.58; N, 18.01.

3′-Deoxy-3′-iodo-2-*N*-isobutyryl-2′-O-methylguanosine (12j). A solution **11c** (0.20g ,0.25mmol) was stirred with hexafluoroisopropanol (2ml) for 6 h and the reaction was worked up as in case of **12h** to afford 0.095g, (78%) of **12j** as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 12.17 (s, 1H), 11.64 (s, 1H), 5.79 (bs ,1H), 5.18 (bs, 1H), 4.80-4.68 (m, 2H), 3.40 (s, 3H), 3.26 (s, 3H), 3.80-3.53 (m, 3H), 2.8-2.70 (m, 1H), 1.05 (bs,6H); ^{13}C NMR (DMSO-d_6) δ 180.21, 154.78, 148.43, 137.34, 120.13, 91.01, 87.28, 80.55, 66.05, 57.85, 34.73, 26.31, 18.88, 18.83; MS (FAB$^+$) *m/e* 478 (M+H). Anal. Calcd for $C_{15}H_{20}N_5O_5I$: C, 37.74; H, 4.50; N, 14.20. Found: C, 37.34; H, 4.34; N, 14.06.

3′-*tert* -Butyldiphenylsilyl-2′-*O*-methyl-5′-*O* -phthalimido-5-methyluridine (14a). From **13a** (5.5 g, 13.2 mmol) according to general procedure C was obtained crude **14a** in essentially quantitative yield, along with silyl by-products.

Purification on a short silica gel column (0 to 3% MeOH/CH_2Cl_2) gave 8.0 g (93%) of **14a**: R_f 0.48 (1:1 CH_2Cl_2/EtOAc). ^{1}H NMR (DMSO-d_6) δ 11.37 (s, 1H), 7.86 (s, 4H), 7.5-7.7 (m, 5H), 7.3-7.4 (m, 6H), 5.97 (d, J=5.82 Hz, 1H), 4.1-4.5 (m, 4H), 3.08 (s, 3H), 1.75 (s, 3H), 1.04 (s, 9H). Anal. Calcd for $C_{35}H_{37}N_3O_8Si$: C, 61.57; H, 5.90; N, 6.15. Found: C, 61.60; H, 5.93; N, 6.46.

3′-*tert*-Butyldiphenylsilyl-2′-*O*-methyl-5′-*O* -phthalimidoadenosine (14b). From **13b** (5.0 g, 11.7 mmol) according to general procedure C was obtained crude **13b** in essentially quantitative yield, along with silyl by-products. Purification on a short silica gel column (80:15:5 EtOAc/hexane/MeOH).gave 7.3 g (93%) of pure **14b**: R_f 0.57 (10% MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 8.37 (s, 1H), 8.07 (s, 1H), 7.82 (s, 4H), 7.5-7.8 (m, 4H), 7.2-7.5 (m, 6H), 6.14 (d, J=5.75 Hz, 1H), 4.6-4.8 (m, 1H), 4.2-4.4 (m, 3H), 3.9-4.2 (m, 1H), 3.34 (br s, 1H), 3.08 (s, 3H), 1.06 (s, 9H); HRMS (FAB$^+$, CsI/NBA) calcd for $C_{35}H_{36}N_6O_6Si$ 797.1520, found 797.1535. Anal. Calcd for $C_{35}H_{36}N_6O_6Si$•0.5 H_2O: C, 62.39; H, 5.53; N, 12.47. Found: C, 62.53; H, 5.32; N, 12.44.

3′-*O*-*tert*-Butyldiphenylsilyl-2′-*O*-methyl-5′-*O*- (methyleneimino)-5-methyluridine (15a). 2′-*O*-Methyl-5′-*O*-phthalimido-5-methyluridine (2.90 g, 6.95 mmol) and imidazole (2.13 g, 31.3 mmole) were dissolved in dry DMF (35 mL) under an inert atmosphere, and TBDPSCl (2.71 mL, 10.42 mmol) was added. The reaction was stirred at room temperature for 48 h, then poured into EtOAc (100 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL), dried ($MgSO_4$), and concentrated. The crude material was dissolved in dry CH_2Cl_2 (70 mL), and methylhydrazine (0.44 mL, 8.34 mmole) was added dropwise at 0 °C. After 1 h, the mixture was filtered, and the filtrates washed well with CH_2Cl_2. Toluene (35 mL) was added to the combined filtrates, and the solution concentrated, then azeotroped with toluene. The residue was dissolved in EtOAc/MeOH (50 mL + 50 mL), formaldehyde (20 % w/w aqueous, 1.05 mL, 7.0 mmol) was added, and the mixture stirred 1 h at rt. The

solution was concentrated, then chromatographed (20% to 50% EtOAc/hexane, 4.5 x 15 cm) to provide 3.43 g (92%) of **15a** as a large foam: R_f 0.53 (50% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.44 (bs, 1H), 7.73-7.30 (m, 10H), 7.25 (s, 1H), 6.89 (d, *J*=7.9 Hz, 1H), 6.44 (d, *J*=7.9 Hz, 1H), 5.90 (d, *J*=2.3 Hz, 1H), 4.50-4.05 (m, 3H), 3.33 (s, 3H), 3.18 (m, 1H), 1.80 (s, 3H), 1.11 (s, 9H). Anal. Calcd for $C_{28}H_{35}N_3O_6Si$: C, 62.55; H, 6.56; N, 7.81. Found: C, 62.47; H, 6.46; N, 7.66.

3′-*O*-*tert*-Butyldiphenylsilyl-4-*N*-benzoyl-2′-*O*-methyl-5′-*O*-(methyleneimino)-5-methylcytidine (15b). To 1,2,4-triazole (11.88 g, 172.0 mmol) in dry MeCN (75 mL) under argon at 0 °C was added $POCl_3$ (3.73 mL, 40 mmol) in MeCN (25 mL) dropwise with vigorous stirring. Et_3N (27.9 mL, 200 mmol) was added dropwise over 0.5 h, and the thick suspension was stirred at 0 °C for an additional 0.5 h. A solution of **15a** (5.40 g, 10.0 mmol) in MeCN (50 mL) was then added dropwise over 0.5 h, and the mixture allowed to warm to rt over 3 h. The mixture was then cooled to 0 °C, and Et_3N (28 mL) and water (2.8 mL) were added, the mixture allowed to warm to room temperature with stirring, then concentrated to a small volume. The residue was partitioned between EtOAc (200 mL) and 5% $NaHCO_3$ (100 mL), and the organic layer washed with 5% $NaHCO_3$ (2 x 200 mL), water (3 x 200 mL), and brine, then dried ($MgSO_4$) and concentrated. The resulting foam was azeotroped with dry toluene (2 x 100 mL) to provide the triazolide in essentially quantitative yield, which was used immediately for the next step: R_f 0.28 (50% EtOAc/hexane). In a separate reaction vessel, sodium hydride (60% w/w, 1.60 g, 40 mmol) was added portionwise to benzamide (4.85 g, 40 mmol) in dry 1,4-dioxane (100 mL), and the resulting mixture stirred for 1h at rt. This suspension was then added *via* cannula to a solution of the triazolide obtained above in dry 1,4-dioxane (100 mL), and the mixture stirred at rt for 3 h. AcOH (2.25 mL, 40 mmol) was added, and the mixture diluted with EtOAc (100 mL) and hexane (100 mL), then washed with 5% $NaHCO_3$, water, dried ($MgSO_4$), concentrated, and chromatographed (0 to 30% EtOAc/hexane) to provide 5.16 g (80%) of **15b**: R_f 0.71

(30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 13.26 (s, 1H), 8.31 (d, 2H), 7.75-7.25 (m, 14H), 6.91 (d, *J*=7.9 Hz, 1H), 6.47 (d, *J*=7.9 Hz, 1H), 5.90 (d, *J*=1.9 Hz, 1H), 4.50 (dd, 1H), 4.31 (m, 1H), 4.20 (dd, 1H), 4.11 (dd, 1H), 3.36 (s, 3H), 3.20 (dd, 1H), 1.99 (d, *J*=1.0 Hz, 3H), 1.10 (s, 9H). Anal. Calcd for $C_{35}H_{40}N_4O_6Si$: C, 65.60; H, 6.29; N, 8.74. Found: C, 65.25; H, 6.34; N, 8.42.

3′-*O*-*tert*-Butyldiphenylsilyl-2′-*O*-methyl-5′-*O*- (methyleneimino)-5-methylcytidine (15c). The triazolide (38 g, 64 mmol) obtained from the procedure given for **15b** was dissolved in dry 1,4-dioxane (200 mL), cooled on ice, and ca 20 mL of condensed anhydrous NH_3 was added. The was allowed to warm to rt over 2h, with stirring, and then concentrated to a syrup, which was dissolved in CH_2Cl_2 (500 mL) washed with water, dried ($MgSO_4$), concentrated, and chromatographed (0 to 5% MeOH/CH_2Cl_2) to provide 26.6 g (77%) of **15c**: R_f 0.27 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 4H), 7.45-7.25 (m, 7H), 6.84 (d, *J*=8.1 Hz, 1H), 6.42 (d, *J*=8.1 Hz, 1H), 5.88 (s, 1H), 4.53 (dd, 1H), 4.32 (m, 1H), 4.23 (dd, 1H), 4.00 (dd, 1H), 3.46 (s, 3H), 3.24 (dd, 1H), 1.74 (s, 3H), 1.08 (s, 9H). Anal. Calcd for $C_{28}H_{36}N_4O_5Si$: C, 62.66; H, 6.76; N, 10.44. Found: C, 62.26; H, 6.53; N, 10.23.

3′-*tert*-Butyldiphenylsilyl-2′-*O*-methyl-5′-*O* -(methyleneimino)adenosine (15d). From **14b** (2.0 g,3.0 mmol) according to general procedure D was obtained 1.3 g (79%) of **15d** after chromatography (70:27:3 EtOAc/hexane/MeOH): R_f 0.43 (10% MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 8.29 (s, 1H), 8.10 (s, 1H), 7.6-7.8 (m, 4H), 7.2-7.5 (m, 6H), 6.14 (d, *J*=5.75 Hz, 1H), 4.6-4.8 (m, 1H), 4.2-4.4 (m, 3H), 3.9-4.2 (m, 1H), 3.34 (br s, 1H), 3.08 (s, 3H), 1.06 (s, 9H). Anal. Calcd for $C_{28}H_{34}N_6O_4Si$: C, 61.52; H, 6.27; N, 15.37. Found: C, 61.21; H, 6.19; N, 15.18.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2′-*O*-methyl-5-methyluridylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methyluridine (16a). 3′-Deoxy-5′-*O*-(4,4′-

dimethoxytrityl)-3′-iodo-2′-*O*-methyl-5-methyluridine (343 mg, 0.50 mmol) and 3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5′-*O*-(methyleneimino)-5-methyluridine (807 mg, 1.50 mmol) were combined, azeotroped with dry benzene (5 mL), dissolved in dry benzene (2.5 mL), degassed (argon, 0.5 h), and heated to 80 °C in an oil bath. A degassed (argon, 0.5 h) solution of bis(trimethystannyl)benzopinacolate (484 mg, 0.70 mmol) in dry benzene (3.5 mL) was then added via syringe pump over 24 h (145 μL/h flow rate). The solution was stirred at 80 °C for an additional 16 h, allowed to cool, diluted with EtOAc (30 mL) and 10% aqueous KF (10 mL), and stirred vigorously for 24 h. The organic layer was dried ($MgSO_4$), concentrated, dissolved in the minimum amount of CH_2Cl_2, and applied to a column of silica (3.5 x 15 cm). Elution with 20% EtOAc/hexane (5 column volumes) provided tin by-products and benzophenone; with 50% EtOAc/hexane (20 column volumes) provided unreacted oxime (0.60 g, >90% of unreacted material), followed by minor side products; and elution with 10% MeOH/CH_2Cl_2 afforded the hydroxylamino linked dimer **16a** (0.39 g, 70%, based on starting iodide): R_f 0.37 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.79 (bs, 1H), 8.60 (bs, 1H), 7.83 (s, 1H), 7.70-7.20 (m, 19H), 7.16 (s, 1H), 6.83 (m, 4H), 5.91 (s, 1H), 5.82 (d, *J*=2.3 Hz, 1H), 5.46 (bs, 1H), 1.70 (s, 3H), 1.38 (s, 3H), 1.09 (s, 9H), and other protons. Anal. Calcd for $C_{60}H_{69}N_5O_{13}Si•H_2O$: C, 64.67; H, 6.42; N, 6.28. Found: C, 64.61; H, 6.24; N, 6.13.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2′-*O*-methyl-5′-methyluridylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methylcytidine (16b). A solution of **12a** (0.310 g, 0.5 mmol) and **15c** (0.810 g, 1.5 mmol) in benzene was treated with **8** (0.483 g, 0.7 mmol) in degassed benzene (5 mL) *via* a syringe pump as described for **16a**. The crude residue was purified by flash chromatography using 5-10% MeOH in CH_2Cl_2 as the eluent to furnish 0.385 g (75%) of **16b** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 7.68-7.26 (m, 24H), 5.91 (bs, 1H), 5.84 (bs, 1H), 5.58 (s, 1H), 4.30-3.20 (m, 16H), 3.10-2.75 (m, 2H), 1.71 (s, 3H), 1.47 (s, 3H), 1.09-1.06 (m,18H); MS (FAB$^+$) *m/e* 1031

(M+H). Anal. Calcd for $C_{55}H_{70}N_6O_{10}Si_2$: C, 64.05; H, 6.84; N, 8.15. Found: C, 63.65; H, 6.91; N, 8.24.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-6-*N*-[1-(dimethylamino)ethylene]-2′-*O*-methyl-adenosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methyluridine (16c) A mixture of **12b** (1.09 g, 1.5 mmol) and **15a** (2.4 g, 4.5 mmol in degassed benzene (8 mL) was treated with **8** (1.5 g, 2.1 mmol) in degassed benzene (10 mL) *via* a syringe pump as described for **16a.** The crude residue was purified by flash chromatography using CH_2Cl_2/EtOAc/MeOH (80:17:3) as the eluent to furnish 0.91 g (52%) of **16c** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.17 (s, 1H), 7.68-7.17(m, 20H), 6.82-6.77 (m, 4H), 6.22 (bs 1H), 5.80 (bs, 1H), 5.45 (m, 1H), 4.50-2.50 (m, 31H), 2.14 (s, 3H), 1.70 (s, 3H), 1.06 (S, 9H); MS (FAB$^+$) *m/e* 1174 (M+H). Anal. Calcd for $C_{64}H_{75}N_9O_{11}Si$•MeOH: C, 64.71; H, 6.60; N,10.45. Found: C, 65.00; H, 6.57; N, 10.18.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2-*N*-isobutyryl-2′-*O*-methyl-guanosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methyluridine (16d) A mixture of **12c** (2.0 g, 2.5 mmol) and **15a** (4.3 g, 8.0) mmol in degassed benzene was treated with **8** (2.73 g, 3.8 mmol) in degassed benzene *via* a syringe pump as described for **16a.** The crude residue was purified by flash chromatography using the usual conditions, then treated with DMTCl in pyridine in presence of DMAP for 12 h, and finally re-purified to give 1.2 g (40%) of **16d** as a light yellow foam: ^{1}H NMR (DMSO-*d*$_6$) δ 12.13 (s, 1H), 11.55 (s, 1H), 11.33 (s, 1H), 8.04 (s, 1H), 7.65-7.16 (m, 19H), 6.81-6.77 (m, 4H), 6.55 (m, 1H), 5.99 (bs, 1H), 5.84 (d, *J*=6 Hz, 1H), 4.3-4.04 (m, 4H), 3.68-2.57 (m, 23H), 1.63 (s, 3H), 1.14-0.99 (m, 15H); MS (FAB$^+$) *m/e* 1191 (M+H). Anal. Calcd for $C_{64}H_{74}N_8O_{13}Si$•0.5 H_2O: C, 64.04; H, 6.30; N, 9.33. Found: C, 63.78; H, 6.35; N, 9.13.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2-*N*-isobutyryl-2′-*O*-methyl-guanosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methylcytidine (16e). A mixture of **12c** (0.250 g, 0.32 mmol) and **15c** (0.44 g, 0.82 mmol) mmol in degassed benzene (2 mL) was treated with **8** (0.354 g, 0.5 mmol) in benzene (2.5 mL) *via* a syringe pump as described for **16a.** The crude residue was purified by column chromatography on silica gel using EtOAc-hexane-MeOH (70:15:15) as the eluent. Appropriate fractions were combined and concentrated to give 0.211 g (55%) of **16e** as a colorless foam,: ^{1}H NMR (DMSO-*d6*) δ 12.16 (s, 1H), 11.6 (s, 1H), 8.08 (s, 1H) 7.66-7.17 (m, 19H), 7.00-6.66 (m, 6H), 6.06-5.85 (m, 3H), 4.45-3.00 (m, 26H), 1.72 (s, 3H), 1.25-0.87 (m, 15H); MS (FAB$^+$) *m/e* 1191 (M+H). Anal. Calcd for $C_{64}H_{74}N_8O_{13}Si•H_2O•0.5\ CH_3CN$: C, 63.47; H, 6.35; N, 9.68. Found: C, 63.27; H, 6.54; N, 10.04.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2-*N*-isobutyryl-2′-*O*-methyl-guanosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyladenosine (16f). A mixture of **12c** (0.076 g, 0.08 mmol), **15d** (0.160 g, 0.3 mmol) and **8** (0.107 g, 0.1 mmol) in degassed benzene (1.5 mL) was reacted according to general procedure E, then purified by chromatography (60:30:5-10% EtOAc/hexane/MeOH) to furnish 0.035 g (35%) of **16f** as a colorless foam: ^{1}H NMR (DMSO-*d6*) δ 12.20 (s, 1H), 11.60 (s, 1H), 8.29 (s, 1H), 7.71-7.15 (m, 20H), 6.83-6.77 (m, 4H), 6.53(bs, 1H), 6.05-6.00 (m, 2H), 4.45-2.80 (m, 27H), 1.16-1.03 (m, 15H); MS (FAB$^+$) *m/e* 1201 (M+H); HRMS (FAB$^+$, CsI/NBA) calcd for $C_{64}H_{13}N_{11}O_{11}Si+Cs^+$ 1332.4315, found 1332.4328.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-6-*N*-[1-(dimethylamino)ethylene]-2′-*O*-methyl-adenosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyladenosine (16g). A mixture of **12b** (0.107 g, 0.14 mmol), **15d** (0.230 g, 0.42 mmol) and **8** (0.153 g, 0.22 mmol) in degassed benzene (1mL) was reacted according to general

procedure E, then purified by chromatography (70:20:10 EtOAc/hexane/MeOH) to furnish 0.065 g (40%) of **16g** as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.30 (s, 2H), 7.69-7.16 (m, 21H), 6.80-6.76 (m, 4H), 6.52-6.46 (m, 1H), 6.19 (bs, 1H), 6.01 (d, *J*=6Hz, 1H), 4.60-4.00 (m, 6H), 3.67 (s, 6H), 3.63-2.70 (m, 18H), 1.25 (s,3H), 1.02 (s, 9H); MS (FAB$^+$) *m/e* 1183 (M+H). Anal. Calcd for $C_{64}H_{74}N_{12}O_9Si$•EtOAc: C, 65.05; H, 6.58; N, 13.39. Found: C, 65.26; H, 6.71; N, 13.60.

3′-De(oxyphosphinico)-3′-(methyleneimino)-5′-*O*-(*tert*-butyldiphenylsilyl)-6-*N*-(dimethylamino)methylene-2′-*O*-methyl-adenosylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyladenosine (16i). A mixture of **12f** (0.427 g, 0.6 mmol) and **15d** (1.0 g, 1.82 mmol) and **8** (0.631 g, 0.91 mmol) were reacted according to general procedure E, then purified by column chromatography using 3-7% MeOH/CH_2Cl_2 to give 0.203 g (30%) of **16i** as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 8.91 (s, 1H), 8.44 (s, 1H), 8.42 (s, 1H), 8.34 (s, 1H), 8.06(s, 1H), 7.69-32 (m, 22H), 6.54 (bs 1H), 6.32 (bs, 1H), 5.94 (d, *J*=5.4 Hz, 1H), 4.60-3.50 (m, 12H), 3.34 (s, 6H), 3.17 (s, 3H), 3.13-2.9 (m, 5H), 1.02 (s, 9H), 0.92 (s, 9H). mass spectrum (FAB) m/z 1105 (MH$^+$). Anal. Calcd for $C_{58}H_{72}N_{12}O_7Si_2$: C, 63.02; H, 6.56; N, 15.20. Found: C, 62.73; H, 6.31; N, 14.89.

3′-De(oxyphosphinico)-3′-(methyleneimino)-2′-*O*-methyl-5-methyluridylyl-(3′→5′)-3′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-methyl-5-methyluridine (16l). A mixture of **12h** (0.215 g, 0.446 mmol), **15a** (0.720 g,1.34 mmol) and **8** (0.450 g, 0.65 mmol) was reacted according to general procedure E, then chromatographed (5-10% MeOH in 2:1 EtOAc/Hexane) to afford 0.270 g (68%) of **16l**: ^{1}H NMR (DMSO-d_6) δ 11.38 (s, 1H), 11.37 (s, 1H), 8.00-7.45 (m, 12H), 6.59 (m, 1H), 5.93 (d, *J*=4 Hz, 1H), 5.74 (bs, 1H), 5.25 (bs, 1H), 4.30-2.7 (m, 18H), 1.74 (s, 6H), 1.05 (s, 9H). Anal. Calcd for $C_{39}H_{51}N_5O_{11}Si$•0.25 H_2O: C, 58.67; H, 6.50; N, 8.77. Found: C, 58.50; H, 6.53; N, 8.72.

3′-*N*-(Benzyloxyamino)methyl-3′-deoxy-5′-*O*-(4,4′-dimethoxytriphenylmethyl)-2′-*O*-methyl-5-methyluridine (18). A mixture of **12a** (2.0 g, 3.22 mmol), *O*-benzyl formaldoxime **17** (1.3 g, 9.61 mmol) and **8** (3.3 g, 4.83 mmol) was reacted according to general procedure E, then purified by flash chromatography using 60% EtOAc/hexane as the eluent to give 0.805 g (40%) of **18a** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 8.66 (s, 1H), 7.71-7.26 (m, 16H), 5.86 (bs, 1H), 5.72 (bs, 1H), 4.61 (bs, 2H), 4.20-3.67 (m, 3H), 3.50 (s, 3H), 3.12-2.49 (m, 3H), 1.49 (s, 3H), 1.11 (s, 9H); MS (FAB$^+$) *m/e* 630 (M+H). Anal. Calcd for $C_{35}H_{43}N_3O_6Si$•0.25 H_2O: C, 66.27; H, 6.91; N, 6.62. Found: C, 66.14; H, 6.81; N, 6.31.

References For Supplementary Material

*Author to whom correspondence should be addressed.

†Current address: Hewlett-Packard, 3500 Deer Creek Rd. 25-45, Palo Alto, CA 94304

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