SUPPORTING INFORMATION

Facile Deprotection of O-Cbz-Protected Nucleosides by Hydrogenolysis: An Alternative to O-Benzyl Ether-Protected Nucleosides.

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General Experimental Information:

Solvents were distilled from potassium benzophenone ketyl (THF, Et₂O) or calcium hydride (CH₃CN, DCM, HMPA and pyridine) under an atmosphere of dry N₂. In the procedures below, NaCl and NaHCO₃ refer to saturated aqueous solutions. Flash column chromatography was performed with 60Å 230-400 mesh silica gel. Compound **7**,¹ **10**,² **12**¹ and **21**¹ were synthesized according to literature protocols. ¹H and ¹³C spectra were recorded at 400 and 100 MHz or 300 and 75 MHz, respectively. Fourier-transformed infrared spectra were recorded as neat liquids or as thin films (obtained from the evaporation of chloroform). The method used to obtain high-resolution mass spectra (FAB, EI or CI) are indicated.

Supplementary figures to illustrate text discussion:

Figure 1. Comparison of the 400 MHz ^1H NMR spectra for the ureido-proton region of: uridine **6** (A), a mixture of uridines **6** and **4** (B), and reduced uridine **4** (C).

Figure 2. Comparison of the 400 MHz ^1H -NMR spectra of uridine **6** (A), mixture of uridines **6** and **4** (B), and reduced uridine **4** (C).

Synthetic Procedures:

***N*₃,2',3'-Tris-benzyl-uridine (1).** Nucleoside **23** (2.312 g, 3.676 mmol) was dissolved in THF (15 ml), cooled to 0 °C and TBAF (5 ml, 5.000 mmol) was added dropwise. After stirring the reaction for five minutes, H₂O (10 ml) was added. All volatiles were removed using a rotary evaporator. The syrup obtained was dissolved in EtOAc and washed with NaHCO₃. The organic phase was collected, dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography (Et₂O) giving **1** (1.783 g, 3.465 mmol) as a solid. Yield = 94%.

¹H NMR (400 MHz, CDCl₃): δ= 7.50-7.24 (m, 16 H), 5.75 (d, *J* = 3.6 Hz, 1 H), 5.69 (d, *J* = 8.1 Hz, 1 H), 5.08 (A of AB, *J* = 13.7 Hz, 1 H), 5.03 (B of AB, *J* = 13.7 Hz, 1 H), 4.76 (A of AB, *J* = 12.1 Hz, 1 H), 4.66 (B of AB, *J* = 12.1 Hz, 1 H), 4.56 (A of AB, *J* = 11.7 Hz, 1 H), 4.41 (B of AB, *J* = 11.7 Hz, 1 H), 4.25 (m, 2 H), 4.05 (t, *J* = 5.6 Hz, 1 H), 3.96 (m, 1 H), 3.71 (m, 1 H), 2.43 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ= 162.72, 150.89, 139.52, 137.59, 137.43, 136.74, 129.36, 128.67, 128.65, 128.62, 128.58, 128.26, 128.21, 127.98, 127.87, 101.94, 92.02, 93.30, 78.35, 74.87, 72.56, 72.20, 61.38, 44.24; IR (film): ν = 3470, 3085, 3066, 3039, 2914, 2360, 1700, 1653, 1454, 1394, 1265, 1109 cm⁻¹; HRMS (CI) *m/z* calcd. for C₁₅H₂₇N₂O₆Si (MH⁺): 515.21821, found; 515.21838.

***N*₃-Benzyl-uridine (2).** Nucleoside **1** (200 mg, 0.3886 mmol) was dissolved in 3:1 EtOAc: EtOH (2.1 ml) and Pearlman's catalyst was added (40 mg, 0.1g catalyst/ mmol nucleoside). The heterogeneous mixture was stirred 12 hours under an atmosphere of H₂ (balloon). The mixture was filtered through Celite 545 with EtOH and the filtrate concentrated using a rotary

evaporator. The product was isolated by silica gel chromatography (10% MeOH/ DCM) giving **2** (129 mg, 0.3886 mmol) as a solid. Yield = Quantitative.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 8.01 (d, J = 7.8 Hz, 1 H), 7.32-7.23 (m, 5 H), 5.83 (m, 2 H), 5.43 (d, J = 5.0 Hz, 1 H), 5.14 (t, J = 4.8 Hz, 1 H), 5.11 (d, J = 5.0 Hz, 1 H), 4.99 (A of AB, J = 14.7 Hz, 1 H), 4.97 (B of AB, J = 14.7 Hz, 1 H), 4.04 (m, 1 H), 3.98 (m, 1 H), 3.86 (m, 1 H), 3.65 (m, 1 H), 3.56 (m, 1 H) (t, J = 5.6 Hz, 1 H), 3.96 (m, 1 H), 3.71 (m, 1 H), 2.43 (m, 1 H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ = 161.97, 150.93, 139.51, 137.06, 128.36, 127.65, 127.21, 100.97, 88.94, 84.83, 73.76, 69.64, 60.64, 43.46; IR (film): ν = 3415, 3090, 3058, 3031, 2930, 1700, 1652, 1495, 1456, 1394, 1346, 1266, 1100 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_6$ (M^+): 334.11649, found; 334.11646.

2',3'-Benzylidene-uridine (3). Uridine (500 mg, 2.048 mmol) and benzaldehyde dimethylacetal (1.537 ml, 10.24 mmol) were dissolved in dry acetonitrile (14 ml) and cooled to 0 °C. Phosphorous oxychloride (0.38 ml, 4.095 mmol) was added dropwise and the reaction stirred for one hour at 0 °C. The reaction was poured into NaHCO_3 (40 ml) and stirred for 90 minutes at 0 °C. The mixture was filtered, and the precipitate washed with cold Et_2O . The precipitate was collected and dried under vacuum to constant mass. The precipitate was then stirred with methanol and filtered. The filtrate was evaporated to dryness giving **3** (209 mg, 0.6289 mmol) as a solid. Yield = 31%.

(The product was obtained as an inseparable mixture of diastereomers: dr = 80:20. The identity was confirmed by HRMS.)

HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_6$ ($\text{M}^+ - \text{H}$): 331.09301, found; 331.09279.

C₅,C₆-Tetrahydro-uridine (4). Benzylidene **3** (38 mg, 0.1144 mmol) was dissolved in EtOH (1.5 ml) and 10% Pd/C (10 mg) added. The heterogeneous solution was stirred 48 hours under

an atmosphere of H₂ (balloon). The reaction was filtered through Celite 545 with MeOH. The filtrate was concentrated using a rotary evaporator and the product isolated by silica gel chromatography (20% MeOH/ DCM) giving **4** (22 mg, 0.08863 mmol) as a solid. Yield = 78%. ¹H NMR (400 MHz, DMSO-*d*₆): δ= 10.23 (br s, 1 H), 5.67 (d, *J* = 6.4 Hz, 1 H), 5.10 (d, *J* = 5.0 Hz, 1 H), 4.96 (d, *J* = 3.7 Hz, 1 H), 4.82 (t, *J* = 5.5 Hz, 1 H), 3.95 (m, 1 H), 3.86 (m, 1 H), 3.67 (m, 1 H), 3.54-3.27 (m, 4 H), 2.50 (m, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ= 170.46, 153.07, 87.18, 83.50, 70.36, 70.29, 61.49, 35.59, 30.83; IR (film): ν = 3586, 3402, 3178, 2933, 2873, 2259, 2130, 1695, 1487, 1452, 1380, 1337, 1216, 1126, 1025 cm⁻¹; HRMS (EI) *m/z* calcd. for C₉H₁₅N₂O₆ (MH⁺): 247.09301, found; 247.09307.

(5)

2',3'-Dicarbobenzyloxy-uridine (5). Uridine **11** (2.847 g, 4.543 mmol) was dissolved in THF (18 ml) and cooled to 0 °C. Triethylamine trihydrofluoride (5 ml, 30.67 mmol) was added dropwise and the solution stirred at RT. After 48 hours all volatiles were removed using a rotary evaporator. The resultant liquid was dissolved in EtOAc and washed twice with NaHCO₃. The organic phase was collected, dried (Na₂SO₄) and all volatiles removed using a rotary evaporator. The product was isolated by silica gel chromatography (5% MeOH/ DCM) giving **5** (2.276 g, 4.441 mmol) as a solid. Yield = 98%.

¹H NMR (400 MHz, CDCl₃): δ= 9.36 (br s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.33-7.26 (m, 10 H), 5.93 (d, *J* = 5.9 Hz, 1 H), 5.75 (d, *J* = 8.2 Hz, 1 H), 5.57 (t, *J* = 5.9 Hz, 1 H), 5.47 (t, *J* = 3.2 Hz, 1 H), 5.14-5.07 (m, 4 H), 4.26 (s, 1 H), 3.92 (A of AB, *J*_{AB} = 11.9 Hz, 1 H), 3.82 (B of AB, *J*_{AB} = 11.9 Hz, 1 H), 3.41 (br s, 1 H), (s, 2 H), 4.17 (m, 1 H), 3.90 (m, 2 H), 3.08 (br s, 1 H), 2.54-2.40 (m, 2 H), 1.89 (d, *J* = 0.9 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ= 163.45, 154.32, 154.02, 150.51, 141.72, 134.71, 134.62, 128.87, 128.78, 128.74, 128.66, 128.55, 103.29, 89.05, 83.31, 75.70, 74.33, 70.74, 70.54, 61.78; IR (film): ν = 3443, 3179, 3064, 3031, 2957, 2360, 2341, 1757, 1700, 1680, 1457, 1387, 1266, 1099, 1016 cm⁻¹; HRMS (CI) *m/z* calcd. for C₂₅H₂₅N₂O₁₀ (MH⁺): 513.15092, found 513.14972.

General procedure for the carbomaoylation of 5'-TBS-protected nucleosides:

A 0.35 M DCM solution of the appropriate 5'-TBS-protected nucleoside and DMAP were cooled to 0 °C. Benzyl chloroformate was added dropwise and the suspension stirred at RT. After three days, the solution was diluted with DCM and extracted with 2 M HCl. The organic phase was collected, dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography using the solvent system indicated.

5'-O-tert-Butyldimethylsilyl-3'-carbobenzyloxy-thymidine (8). Quantities: nucleoside **7** (250 mg, 2.104 mmol), DMAP (257 mg, 2.104 mmol), benzyl chloroformate (0.15 ml, 1.052 mmol). Eluent = 5% EtOH/ DCM gives **8** (315 mg, 0.6637 mmol) as a solid. Yield = 95%.

¹H NMR (400 MHz, CDCl₃): δ= 9.11 (br s, 1 H), 7.51 (s, 1 H), 7.39-7.36 (m, 5 H), 6.37 (dd, *J* = 9.2 Hz, 5.0 Hz, 1 H), 5.17 (s, 3 H), 4.19 (s, 1 H), 3.91, (m, 2 H), 2.49 (m, 1 H), 2.12 (m, 1 H), 1.92 (s, 3 H), 0.92 (s, 9 H), 0.13 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ= 164.19, 154.58, 160.62, 135.04, 134.85, 128.77, 128.42, 111.25, 85.06, 84.75, 78.94, 70.10, 63.72, 38.21, 26.00, 18.39, 12.61, -5.31, -5.44; IR (film): ν = 3198, 3062, 3035, 2953, 2929, 2852, 2360, 2342, 1744, 1695, 1260, 1202, 1128, 1069 cm⁻¹ HRMS (EI) *m/z* calcd. for C₂₀H₂₅N₂O₇Si (M⁺ - C₄H₉): 433.14310, found 433.14328.

5'-O-tert-Butyldimethylsilyl-2',3'-dicarbobenzyloxy-uridine (11). Quantities: nucleoside **10** (1.485 g, 4.143 mmol), DMAP (1.518 g, 12.43 mmol), benzyl chloroformate (1.749 ml, 12.43 mmol). Eluent = 10% Acetone/ DCM gives **11** (2.421 g, 3.861 mmol) as a solid. Yield = 93%.

¹H NMR (400 MHz, CDCl₃): δ= 9.34 (br s, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.34-7.30 (m, 10 H), 6.27 (d, *J* = 5.5 Hz, 1 H), 5.71 (d, *J* = 8.2 Hz, 1 H), 5.29-5.24 (m, 2 H), 5.14-5.06 (m, 4 H), 4.26 (m, 1 H), 3.93 (A of ABX, *J*_{AB} = 11.4, *J*_{AX} = 1.6 Hz, 1 H), 3.80 (B of ABX, *J*_{BA} = 11.4, *J*_{BX} = 1.6 Hz, 1 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ= 163.25,

154.22, 153.93, 150.38, 139.53, 134.73, 134.67, 128.83, 128.75, 128.67, 128.49, 103.18, 85.66, 82.90, 76.64, 74.30, 70.56, 70.48, 62.79, 25.97, 18.43, -5.49; IR (film): ν = 3187, 3068, 3039, 2955, 2930, 2360, 1756, 1695, 1456, 1385, 1265, 1121 cm^{-1} ; HRMS (CI) m/z calcd. for $\text{C}_{31}\text{H}_{39}\text{N}_2\text{O}_{10}\text{Si}$ (MH^+): 627.23740, found 627.23627.

5'-*O*-tert-Butyldimethylsilyl-2',3',*N*₄-tris-carbobenzyloxy-cytidine (13). Quantities: nucleoside **12** (1.432 g, 3.995 mmol), DMAP (4.392 g, 35.95 mmol), benzyl chloroformate (2.5 ml, 17.98 mmol). Eluent = 10% Acetone/ DCM gives **13** (2.193 g, 2.882 mmol) as a solid. Yield = 72%.

^1H NMR (400 MHz, CDCl_3): δ = 8.33 (d, J = 7.1 Hz, 1 H), 8.06 (br s, 1 H), 7.40-7.23 (m, 15 H), 6.29 (d, J = 3.7 Hz, 1 H), 5.40 (t, J = 4.1 Hz, 1 H), 5.32 (t, J = 5.3 Hz, 1 H), 5.23 (m, 2 H), 5.15-5.07 (m, 4 H), 5.35 (d, J = 5.5 Hz, 1 H), 4.07 (A of AB, J_{AB} = 11.3 Hz, 1 H), 3.82 (B of AB, J_{AB} = 11.3 Hz, 1 H), 0.96 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 162.66, 154.70, 153.96, 153.85, 152.38, 144.07, 135.09, 134.74, 134.70, 128.75, 128.67, 128.61, 128.49, 128.39, 95.20, 87.83, 82.04, 72.77, 70.42, 67.99, 65.11, 61.58, 25.94, 18.40, -5.50, -5.55; IR (film): ν = 3288, 3101, 3066, 3039, 2954, 2930, 2857, 2360, 1757, 1676, 1629, 1558, 1499, 1456, 1384, 1267, 1233, 1198, 1131 cm^{-1} ; HRMS (CI) m/z calcd. for $\text{C}_{39}\text{H}_{46}\text{N}_3\text{O}_{11}\text{Si}$ (MH^+): 760.29016, found 760.29102.

5'-*O*-tert-Butyldimethylsilyl-2',3',*N*₄-tris-carbobenzyloxy-adenosine (16). Adenosine (3.000 g, 11.23 mmol) was dissolved in pyridine (50 ml) and cooled to 0 °C. TBS-Cl (1.861 g, 12.35 mmol) was added and the solution stirred for 4 days at RT. All volatiles were removed under high-vacuum and resulting residue was dissolved in EtOAc and washed with NaHCO_3 . The organic phase was collected and dried (Na_2SO_4) and evaporated to dryness. The resulting solid

was suspended in DCM (90 ml) and DMAP (8.232 g, 67.38 mmol) was added. After cooling to 0 °C, benzyl chloroformate (5.37 ml, 38.18 mmol) was added dropwise and the suspension was stirred at RT. After three days, the solution was diluted with DCM and extracted with 2 M HCl. The organic phase was collected, dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography (10% Acetone/ DCM) giving **16** (3.913 g, 6.022 mmol) as a solid. Yield = 54%.

¹H NMR (400 MHz, CDCl₃): δ= 8.31 (s, 1 H), 8.13 (s, 1 H), 7.36-7.30 (m, 10 H), 6.33 (d, *J* = 6.0 Hz, 1 H), 6.24 (br, s, 2 H), 5.83 (t, *J* = 6.0 Hz, 1 H), 5.54 (dd, *J* = 5.0, 3.2 Hz, 1 H), 5.17-5.04 (m, 4 H), 4.36 (m, 1 H), 3.98 (A of ABX, *J*_{AB} = 11.4, *J*_{AX} = 2.7 Hz, 1 H), 3.86 (B of ABX, *J*_{BA} = 11.4, *J*_{BX} = 2.8 Hz, 1 H), 0.93 (s, 9 H), 0.12 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ= 155.82, 154.26, 153.81, 153.49, 150.09, 138.65, 134.79, 134.60, 128.74, 128.66, 128.48, 119.91, 85.00, 83.13, 76.94, 74.61, 70.53, 70.39, 62.81, 26.01, 18.49, -5.35, -5.41; IR (film): ν = 3370, 3299, 3158, 3039, 2953, 2926, 2867, 2360, 2341, 1762, 1700, 1653, 1617, 1457, 1276, 1130, 1090, 1048 cm⁻¹; HRMS (CI) *m/z* calcd. for C₃₂H₃₉N₅O₈Si (M⁺): 649.25679, found 649.2

General procedure for the desilylation of 5'-TBS-carbamoylated nucleosides:

A 0.25 M THF solution of the appropriate 5'-TBS- carbamoylated nucleoside was cooled to 0 °C. Triethylamine trihydrofluoride was added dropwise and the solution stirred at room temperature. After 48 hours all volatiles are removed using a rotary evaporator. The resultant liquid was dissolved in EtOAc and washed twice with NaHCO₃. The organic phase was collected, dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography using the solvent system indicated.

3'-Carbobenzyloxy-thymidine (9). Quantities: nucleoside **8** (3.616 g, 7.374 mmol), triethylamine trihydrofluoride (5 ml, 30.67 mmol). Eluent = 5% EtOH/ CHCl₃ gives **9** (2.746 g, 7.300 mmol) as a solid. Yield = 99%.

^1H NMR (400 MHz, CDCl_3): δ = 9.30 (br s, 1 H), 7.46 (d, J = 0.8 Hz, 1 H), 7.38-7.35 (m, 5 H), 6.18 (dd, J = 8.2, 6.0 Hz, 1 H), 5.31-5.29 (m, 1 H), 5.17 (s, 2 H), 4.17 (m, 1 H), 3.90 (m, 2 H), 3.08 (br s, 1 H), 2.54-2.40 (m, 2 H), 1.89 (d, J = 0.9 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 164.09, 154.64, 150.64, 136.91, 134.83, 128.93, 128.86, 128.58, 111.48, 86.77, 85.07, 78.46, 70.30, 62.69, 37.21, 12.67; IR (film): ν = 3447, 3194, 3070, 3035, 2949, 2930, 2360, 1735, 1700, 1684, 1472, 1385, 1266, 1198, 1102, 1062 cm^{-1} ; HRMS (EI) m/z calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_7$ (MH^+): 377.13488, found 377.13419.

2',3',*N*₄-tris-carbobenzyloxy-cytidine (14). Quantities: nucleoside **13** (2.185 g, 2.872 mmol), triethylamine trihydrofluoride (3 ml, 18.40 mmol). Eluent = 5% MeOH/ DCM gives **14** (1.842 g, 2.849 mmol) as a solid. Yield = 99%.

^1H NMR (400 MHz, CDCl_3): δ = 8.16 (br s, 1 H), 8.07 (d, J = 7.3 Hz, 1 H), 7.37-7.26 (m, 15 H), 5.87 (d, J = 4.6 Hz, 1 H), 5.73 (t, J = 4.6 Hz, 1 H), 5.52 (t, J = 5.0 Hz, 1 H), 5.18 (m, 2 H), 5.11-5.04 (m, 4 H), 4.28 (m, 1 H), 4.13 (br s, 1 H), 3.97 (A of AB, J_{AB} = 11.2 Hz, 1 H), 3.81 (B of AB, J_{AB} = 11.2 Hz, 1 H), 0.96 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 163.10, 155.38, 154.29, 153.91, 152.44, 146.50, 135.09, 134.76, 128.81, 128.75, 128.69, 128.57, 128.54, 128.51, 96.01, 91.21, 83.68, 76.34, 74.05, 70.54, 70.45, 68.13, 61.22; IR (film): ν = 3311, 3093, 3066, 3035, 2957, 2354, 1751, 1653, 1558, 1498, 1456, 1384, 1267, 1225, 1194. 1100 cm^{-1} ; HRMS (ESI): m/z calcd. for $\text{C}_{33}\text{H}_{32}\text{N}_3\text{O}_{11}$ (MH^+): 646.20368, found 646.20422.

2',3'-Bis-carbobenzyloxy-adenosine (17). Quantities: nucleoside **16** (3.913 g, 6.022 mmol), triethylamine trihydrofluoride (2.5 ml, 15.34 mmol). Eluent = 5% EtOH/ CHCl_3 gives **17** (3.064 g, 5.721 mmol) as a solid. Yield = 95%.

^1H NMR (400 MHz, CDCl_3): δ = 8.30 (s, 1 H), 7.75 (s, 1 H), 7.35-7.26 (m, 10 H), 6.18 (br s, 2 H), 6.04 (A of AB, J_{AB} = 8.5 Hz, 1 H), 6.02 (B of AB, J_{AB} = 8.5 Hz, 1 H), 5.65 (d, J = 4.1 Hz, 1 H), 5.15 (A of AB, J_{AB} = 12.4 Hz, 1 H), 5.13 (B of AB, J_{AB} = 12.4 Hz, 1 H), 5.09 (A of AB, J_{AB} = 11.9 Hz, 1 H), 5.04 (B of AB, J_{AB} = 11.9 Hz, 1 H), 4.44 (s, 1 H), 3.98 (A of AB, J_{AB} = 13.0 Hz, 1 H), 3.84 (B of AB, J_{AB} = 13.0 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.15, 154.29, 153.55, 152.75, 148.64, 140.53, 134.79, 134.55, 128.95, 128.76, 128.61, 121.34, 88.07, 86.17, 76.25, 75.66, 70.76, 70.51, 62.83; IR (film): ν = 3442, 3331, 3177, 3065, 3034, 2360, 2341, 1756, 1647, 1600, 1456, 1387, 1277, 1100, 1016 cm^{-1} ; HRMS (ESI): m/z calcd. for $\text{C}_{26}\text{H}_{26}\text{N}_8\text{O}_5$ (MH^+): 536.17814, found 536.17816.

(1R, 2S, 5R)-(-)-O-Benzyl menthol (18). (1R, 2S, 5R)-(-)-Menthol (2.000 g, 12.79 mmol) was dissolved in DCM (43 ml) and the solution cooled to 0 °C. Benzyl trichloroacetamide (2.85 ml, 15.35 mmol) was added slowly followed by the dropwise addition of trifluoromethanesulfonic acid (0.1 ml, 1.279 mmol). The reaction was stirred overnight at RT. After cooling the reaction to 0 °C, the precipitate was filtered and the filtrate concentrated using a rotary evaporator. The product was isolated by silica gel chromatography (3:1 Hexanes: Et_2O) giving **18** (3.151 g, 12.79 mmol) as a liquid. Yield = Quantitative.

^1H NMR (400 MHz, CDCl_3): δ = 7.37-7.27 (m, 5 H), 4.67 (A of AB, J_{AB} = 11.4 Hz, 1 H), 4.41 (B of AB, J_{AB} = 11.4 Hz, 1 H), 3.18 (td, J = 10.5 Hz, J = 4.1 Hz, 1 H), 2.31 (m, 1 H), 2.21 (m, 1 H), 1.65 (m, 3 H), 1.33 (m, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 7.3 Hz, 3 H), 0.71 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 139.28, 128.46, 128.04, 127.58, 78.87, 70.60, 48.48, 40.47, 34.75, 31.75, 25.67, 23.38, 22.57, 21.22, 16.20; IR (film): ν = 3085, 3064, 3029, 2954, 2922, 2868, 1497, 1454, 1385, 1369, 1344, 1110, 1069, 1029 cm^{-1} ; HRMS (EI): m/z calcd. for $\text{C}_{17}\text{H}_{27}\text{O}$ (MH^+): 247.20564, found 247.20512.

2'-Deoxy-3',5'-bis(*O*-*tert*-butyldimethylsilyl)-adenosine (19). To a stirring suspension of 2'-deoxy adenosine monohydrate (1.762 mg, 6.543 mmol) and powdered 4 Å molecular sieves (65 mg, 0.01g/mmol) in pyridine (25 ml) was added TBSCl (4.931 g, 3.273 mmol) and DMAP (79 mg, 0.6543 mmol). After stirring for 3 days, the precipitate was filtered and all volatiles were removed using a high-vacrotary evaporator. The syrup obtained was dissolved in EtOAc and washed with 2 M HCl. The organic phase was dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography (10% MeOH/DCM) giving **19** (1.902 g, 3.821 mmol) as a solid. Yield = 58%.

¹H NMR (400 MHz, CDCl₃): δ= 8.34 (s, 1 H), 8.13 (s, 1 H), 6.45 (t, *J* = 6.4 Hz, 1 H), 5.93 (br s, 2 H), 4.60 (m, 1 H), 4.01 (m, 1 H), 4.14 (A of ABX, *J*_{AB} = 11.4 Hz, *J*_{AX} = 3.9 Hz, 1 H), 3.19 (B of ABX, *J*_{BA} = 11.4 Hz, *J*_{BX} = 3.2 Hz, 1 H), 2.62 (m, 1 H), 2.42 (m, 1 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.09 (s, 6 H), 0.08 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ= 155.66, 153.12, 149.74, 139.15, 120.15, 88.03, 84.47, 72.03, 69.93, 41.50, 26.14, 25.92, 18.60, 18.17, -4.49, -4.64, -5.20, -5.31; IR (film): ν = 3327, 3171, 2955, 2929, 2885, 2858, 2360, 1646, 1599, 1472, 1362, 1331, 1301, 1254, 1111, 1069 cm⁻¹; HRMS (EI): *m/z* calcd. for C₂₂H₄₁N₅O₃Si₂ (M⁺): 479.27479, found; 479.27621.

N₆-Acetyl-2'-deoxy-3',5'-bis(*O*-*tert*-butyldimethylsilyl)-adenosine (20). Nucleoside **19** (1.762 mg, 6.543 mmol) was dissolved in pyridine (7 ml) and cooled to 0 °C. Acetyl chloride (0.46 ml, 6.528 mmol) was added dropwise and the solution stirred at RT for 1 hour. The reaction was quenched by cooling to 0 °C, adding NH₄OH (7 ml) and stirring at RT for 30 min. All volatiles

were removed using a high-vac rotary evaporator. The syrup obtained was dissolved in EtOAc and washed with NaHCO₃. The organic phase was dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography (10% Acetone/DCM) giving **20** (300 mg, 0.5557 mmol) as a solid. Yield = 43%.

¹H NMR (400 MHz, CDCl₃): δ = 9.22 (s, 1 H), 8.66 (s, 1 H), 8.34 (s, 1 H), 6.47 (t, *J* = 6.4 Hz, 1 H), 4.60 (m, 1 H), 4.01 (m, 1 H), 3.85 (A of ABX, *J*_{AB} = 11.0 Hz, *J*_{AX} = 4.2 Hz, 1 H), 3.75 (B of ABX, *J*_{BA} = 11.0 Hz, *J*_{BX} = 2.9 Hz, 1 H), 2.65 (m, 1 H), 2.59 (s, 3 H), 2.44 (m, 1 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 170.84, 152.33, 151.03, 149.33, 141.75, 122.35, 88.18, 84.75, 72.00, 62.85, 41.32, 26.06, 25.88, 25.82, 18.52, 18.13, -4.53, -4.67, -5.29, -5.37; IR (film): ν = 3238, 3194, 3128, 3058, 3019, 2955, 2930, 2886, 2858, 2365, 1704, 1610, 1585, 1471, 1373, 1299, 1283, 1258, 1109 cm⁻¹; HRMS (EI): *m/z* calcd. for C₂₃H₄₀N₅O₄Si₂ (M⁺ - CH₃): 506.26080, found; 506.26188.

N₃, 2', 3'-Tris-benzyl-5'-(O-tert-butylidimethylsilyl)-uridine (23). Nucleoside **10** (1.781 g, 4.968 mmol) was dissolved in dry DMF (25 ml) and cooled to 0 °C. Sodium hydride (60% in oil dispersion, 795 mg, 19.87 mmol) was added slowly and the solution stirred until cessation of bubbling (10 min). Benzyl chloride (2.287 ml, 19.87 mmol) and TBAI (184 mg, 0.4968 mmol) were added and the reaction stirred 12 hrs at RT. The reaction was cooled to 0 °C and quenched by the addition of NH₄Cl (10 ml). All volatiles were removed using a high-vac rotary evaporator. The syrup obtained was dissolved in EtOAc and washed with H₂O. The organic phase was collected, dried (Na₂SO₄) and all volatiles were removed using a rotary evaporator. The product was isolated by silica gel chromatography (1:1 Et₂O: Hexanes) giving **23** (2.316 g, 3.683 mmol) as a solid. Yield = 74%.

¹H NMR (400 MHz, CDCl₃): δ = 8.08 (d, *J* = 8.1 Hz, 1 H), 7.61-7.25 (m, 15 H), 6.13 (s, 1 H), 5.71 (d, *J* = 8.1 Hz, 1 H), 5.21 (A of AB, *J* = 13.8 Hz, 1 H), 5.18 (B of AB, *J* = 13.8 Hz, 1 H), 4.91 (A of AB, *J* = 12.5 Hz, 1 H), 4.89 (B of AB, *J* = 12.5 Hz, 1 H), 4.40 (A of AB, *J* = 11.4 Hz, 1 H), 4.33 (m, 1 H), 4.29 (B of AB, *J* = 11.4 Hz, 1 H), 4.12 (A of AB, *J* = 11.9 Hz, 1 H), 4.01

(m, 1 H), 3.94 (m, 1 H), 3.84 (B of AB, $J = 11.9$ Hz, 1 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 162.74, 150.81, 137.88, 137.25, 136.90, 129.33, 128.99, 128.52, 128.17, 128.04, 127.81, 127.77, 101.43, 88.84, 82.41, 78.41, 73.59, 72.22, 71.18, 60.91, 44.07, 25.97, 18.49, -5.43, -5.56$; IR (film): $\nu = 3090, 3065, 3033, 2928, 2360, 2340, 2248, 1701, 1677, 1654, 1497, 1457, 1395, 1350, 1261, 1215, 1128\text{ cm}^{-1}$; HRMS (CI): m/z calcd. for $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_6\text{Si}$ ($\text{M}^+ - \text{C}_4\text{H}_9$): 571.22644, found; 571.22558.

Figure 3. 400 MHz ^1H NMR Spectrum of compound 1.

Figure 4. 100 MHz ^{13}C NMR Spectrum of compound **1**.

Figure 5. 400 MHz ^1H NMR Spectrum of compound **2**.

Figure 6. 100 MHz ^{13}C NMR Spectrum of compound **2**.

Figure 7. 400 MHz ^1H NMR Spectrum of compound 4.

Figure 8. 100 MHz ^{13}C NMR Spectrum of compound 4.

Figure 9. 400 MHz ^1H NMR Spectrum of compound **5**.

Figure 10. 100 MHz ^{13}C NMR Spectrum of compound **5**.

Figure 11. 400 MHz ^1H NMR Spectrum of compound **8**.

Figure 13. 400 MHz ^1H NMR Spectrum of compound **9**.

Figure 16. 100 MHz ^{13}C NMR Spectrum of compound **11**.

Figure 17. 400 MHz ^1H NMR Spectrum of compound **13**.

Figure 19. 400 MHz ^1H NMR Spectrum of compound **14**.

Figure 20. 100 MHz ^{13}C NMR Spectrum of compound **14**.

Figure 21. 400 MHz ^1H NMR Spectrum of compound **16**.

Figure 23. 400 MHz ^1H NMR Spectrum of compound **17**.

Figure 24. 100 MHz ^{13}C NMR Spectrum of compound **17**.

Figure 25. 400 MHz ^1H NMR Spectrum of compound **18**.

Figure 26. 100 MHz ^{13}C NMR Spectrum of compound **18**.

Figure 28. 100 MHz ^{13}C NMR Spectrum of compound **19**.

Figure 29. 400 MHz ^1H NMR Spectrum of compound **20**.

Figure 30. 100 MHz ^{13}C NMR Spectrum of compound **20**.

Reference

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