Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

Divergent Synthesis of 5-Substituted Pyrimidine 2'-Deoxynucleosides and Their Incorporation into Oligodeoxynucleotides for the Survey of Uracil DNA Glycosylases

Ai Tran[†], Song Zheng[†], Dawanna S. White[†], Alyson M. Curry[†], Yana Cen[‡,#,*]

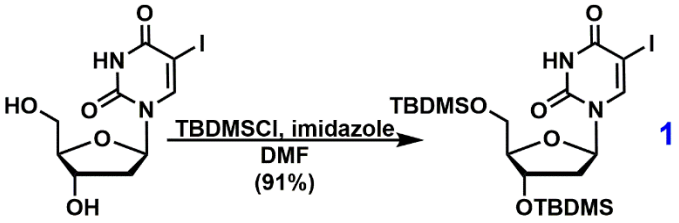
[†]*Department of Pharmaceutical Sciences, Albany College of Pharmacy and Health Sciences, Colchester, VT 05446*

[‡]*Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond, VA 23219*

[#]*Institute for Structural Biology, Drug Discovery and Development, Virginia Commonwealth University, Richmond, VA 23219*

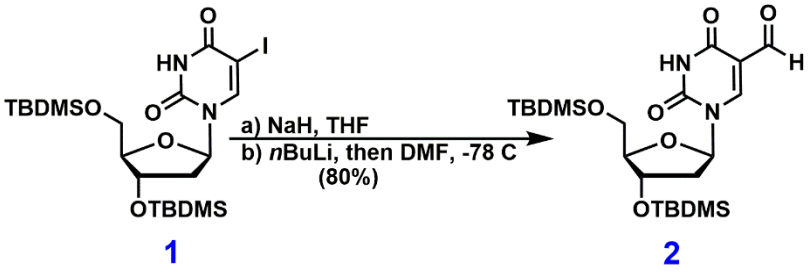
[*]Correspondence: ceny2@vcu.edu, phone: 804-828-7405

Synthesis of 1



To a solution of 5-iodo-2'-deoxyuridine (1 g, 2.82 mmol) in 10 mL of DMF were added TBDMSCl (1.275 g, 8.46 mmol) and imidazole (861 mg, 12.66 mmol). The reaction mixture was stirred at r.t. until completion. Solvent was evaporated *in vacuo*. Residue was redissolved in ethyl acetate, washed with water, sat. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (hexanes:ethyl acete 4:1) to afford **1**[1] (1.49 g, 2.56 mmol, 91% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 8.07 (s, 1H), 6.25 (t, *J* = 6.4 Hz, 1H), 4.38 (m, 1H), 3.97 (m, 1H), 3.86 (m, 1H), 3.74 (m, 1H), 2.28 (m, 1H), 1.96 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H), 0.13 (s, 6H), 0.06 (s, 6H). HRMS (*m/z*): calculated for $C_{21}H_{40}IN_2O_5Si_2$ (M+H): 583.1515; found: 583.1523.

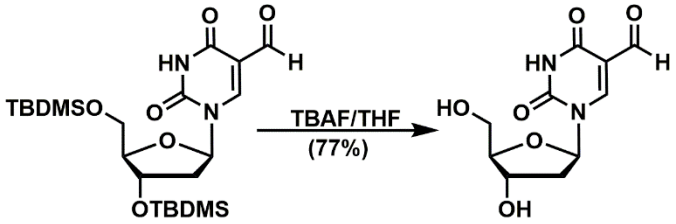
Synthesis of 2



To a solution of **1** (420 mg, 0.722 mmol) in 3 mL of THF was added NaH (26 mg, 1.083 mmol) at r.t. The solution was stirred for another 30 min before it was cooled down to -78°C and *n*BuLi (1.35 mL, 2.17 mmol) was added. After 15 min, DMF (316 mg, 4.332 mmol) was then added dropwise. The reaction mixture was kept at -78°C for another hour before it was quenched with the addition of NH_4Cl solution. Organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (hexanes:ethyl acete 5:1) to afford **2**[2] (280 mg, 0.579 mmol, 80% yield) as a white foam. ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 10.18 (s), 9.93 (s), 8.47 (s), 6.16 (t, *J* = 6.1 Hz, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 3.82, (d, *J* = 11.4 Hz, 1H), 3.71 (d, *J* = 11.4 Hz, 1H), 2.39 (m, 1H), 1.98 (m, 1H), 0.82 (s, 18H), 0.017~0.036 (stack, 12H). HRMS (*m/z*): calculated for $C_{22}H_{41}N_2O_6Si_2$ (M+H): 485.7475; found: 485.7476.

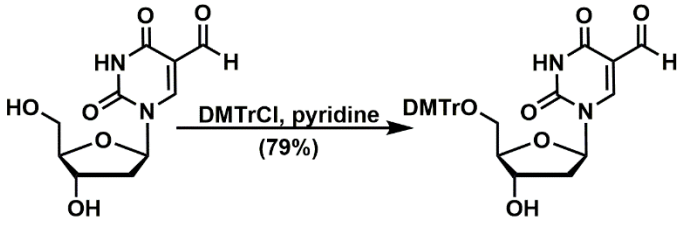
Synthesis of 3 (5-formyl-2'-deoxyuridine)



2 **3**

To a solution of **2** (340 mg, 0.70 mmol) in 1 mL of THF was added TBAF (1 M in THF, 1.75 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 8~10% methanol) to afford **3**[2] (138 mg, 0.54 mmol, 77% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ: 9.76 (s. 1H), 8.71 (s, 1H), 6.09, (t, *J* = 6.3 Hz, 1H), 5.27 (br, 1H), 5.11 (br, 1H), 4.23 (dd, *J* = 4.2, 8.9 Hz, 1H), 3.85 (dd, *J* = 3.5, 6.9 Hz, 1H), 3.62 (m, 2H), 2.21 (m, 2H). HRMS (*m/z*): calculated for $C_{10}H_{13}N_2O_6$ (M+H): 257.0768; found: 257.0772.

Synthesis of 4

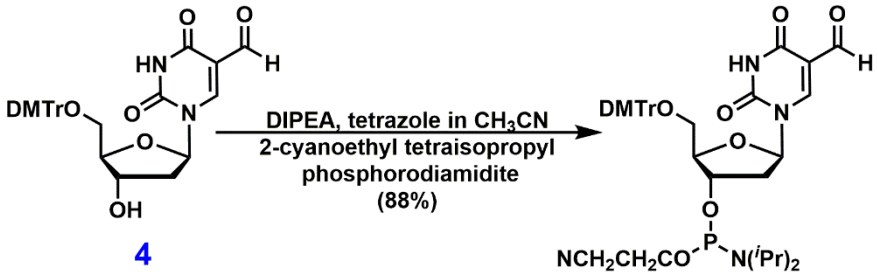


3 **4**

Compound **3** (138 mg, 0.54 mmol) was co-evaporated with dry pyridine (3 x 3 mL) and dissolved in dry pyridine (5 mL). 4,4'-Dimethoxytrityl chloride (220 mg, 0.648 mmol) was added

and the reaction mixture was stirred at r.t. for overnight. MeOH (1 mL) was added and the reaction mixture was stirred for an additional 10 min, and then evaporated to dryness. The residue was redissolved in CH_2Cl_2, washed with water, sat. $NaHCO_3$, and dried over Na_2SO_4. Crude product was purified by column chromatography (CH_2Cl_2 with 2% methanol) to afford **4** (238 mg, 0.43 mmol, 79% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.65 (s, 1H), 8.42 (s, 1H), 7.24 (m, 2H), 7.22 (m, 7H), 6.80 (dd, *J* = 0.84, 9 Hz, 4H), 6.15 (t, *J* = 6.6 Hz, 1H), 4.42 (m, 1H), 4.10 (m, 1H), 3.73 (s, 6H), 3.38 (m, 2H), 2.59 (m, 1H), 2.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.3, 161.6, 158. 6, 149.3, 145.8, 144.3, 135.4, 135.3, 130.0, 127.9, 127.0, 113.3, 111.1, 87.06, 87.00, 86.8, 72.4, 63.4, 55.2, 41.5. HRMS (*m/z*): calculated for $C_{31}H_{31}N_2O_8$ (M+H): 559.2075; found: 559.2078.

Synthesis of 5-fodU-CE phosphoramidite

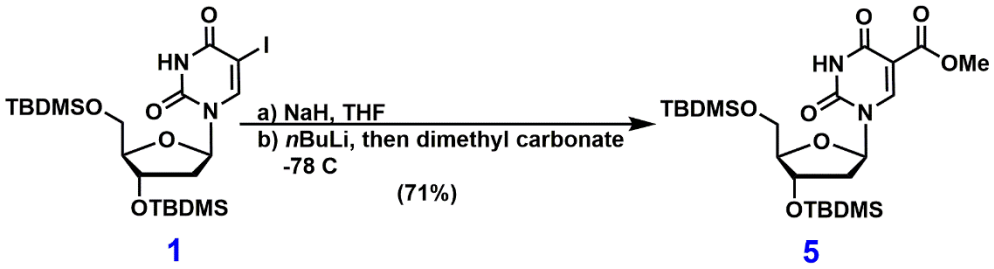


4 **5-fodU-CE phosphoramidite**

To a solution of **4** (40 mg, 0.072 mmol) in 1 mL of anhydrous CH_3CN were added diisopropylethylamine (28 mg, 0.215 mmol), tetrazole in CH_3CN (0.24 mL, 0.108 mmol) and 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphordiamidite (33 mg, 0.108 mmol). The reaction was kept at r.t. and monitored by TLC. Ten minutes later, precipitate appeared. Upon completion, the reaction was quenched with the addition of 0.5 mL of absolute ethanol. Reaction was diluted with ethyl acetate with 1% triethylamine, washed with 5% $NaHCO_3$, water, brine, and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 2% methanol and 1% triethylamine) to afford 5-fodU-CE

phosphoramidite (48 mg, 0.063 mmol, 88% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.64 (d, J = 3.34 Hz, 1H), 8.46 (s, 0.53H), 8.42 (s, 0.47H), 7.99 (s, 1H), 7.21 (m, 10H), 6.81 (m, 4H), 6.14 (m, 1H), 5.86 (s, 1H), 4.49 (m, 1H), 4.15 (m, 1H), 3.76 (s, 6H), 3.61 (m, 8H), 2.72 (m, 2H), 2.58 (m, 1H), 2.42 (m, 1H), 1.23 (m, 12H). ^{13}C NMR (75 MHz, CD_3OD) δ: 187.5, 163.7, 160.4, 151.1, 149.0, 146.2, 137.1, 136.9, 131.53, 131.50, 129.4, 129.0, 128.1, 114.4, 112.2, 88.9, 88.8, 88.3, 72.7, 64.8, 55.9, 55.0, 41.7, 26.7, 26.4, 19.4, 19.0. ^{31}P NMR (120 MHz, $CDCl_3$) δ: 149.2, 148.8. HRMS (*m/z*): calculated for $C_{40}H_{48}N_4O_9P$ (M+H): 759.3153; found: 759.3158.

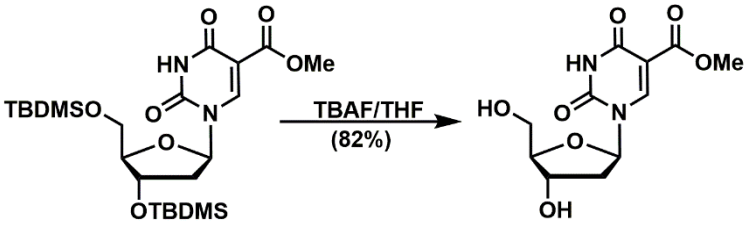
Synthesis of 5



1 **5**

To a solution of **1** (0.6 g, 1.03 mmol) in 4 mL of THF was added NaH (37 mg, 1.55 mmol) at r.t. The solution was stirred for another 30 min before it was cooled down to -78°C and *n*BuLi (1.93 mL, 3.09 mmol) was added. After 15 min, dimethyl carbonate (556 mg, 6.18 mmol) was then added dropwise. The reaction mixture was kept at -78°C for another hour before it was quenched with the addition of NH_4Cl solution. Organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (hexanes:ethyl acetate 3:1) to afford **5**[1] (375 mg, 0.73 mmol, 71% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.37 (broad, 1H), 8.48 (s, 1H), 6.15 (t, *J* = 6.2 Hz, 1H), 4.36 (m, 1H), 4.25 (m, 2H), 3.99 (m, 1H), 3.70 (s, 3H), 2.39 (m, 1H), 2.03 (m, 1H), 0.85 (s, 9H), 0.83 (s, 9H), 0.04 (s, 12H). HRMS (*m/z*): calculated for $C_{23}H_{43}N_2O_7Si_2$ (M+H): 515.2603; found: 515.2609.

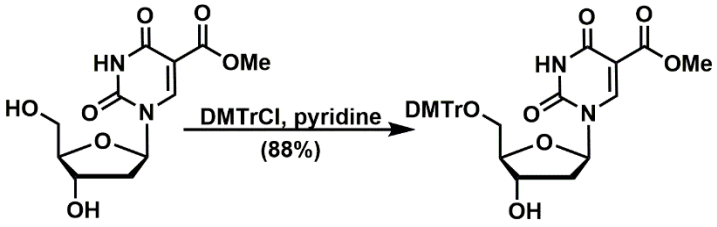
Synthesis of 6



5 **6**

To a solution of **5** (375 mg, 0.73 mmol) in 1 mL of THF was added TBAF (1 M in THF, 1.825 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 8% methanol) to afford **6**[3] (171 mg, 0.60 mmol, 82% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ: 8.81 (s, 1H), 6.08 (t, *J* = 6.3 Hz, 1H), 5.23 (br, 1H), 5.03 (br, 1H), 4.23 (m, 1H), 3.83 (m, 1H), 3.68 (s, 3H), 3.58 (m, 2H), 2.20 (m, 2H). HRMS (*m/z*): calculated for $C_{11}H_{15}N_2O_7$ (M+H): 287.0874; found: 287.0871.

Synthesis of 7

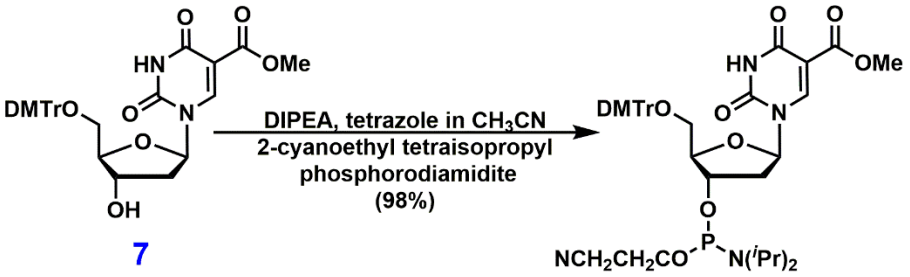


6 **7**

To a solution of **6** (250 mg, 0.874 mmol) in 20 mL of anhydrous pyridine was added 4,4'-dimethoxytrityl chloride (355 mg, 1.049 mmol) under argon atmosphere. The mixture was stirred overnight at room temperature before it was quenched with the addition of 1 mL of methanol. Solvent was evaporated under reduced pressure. The residue was redissolved in CH_2Cl_2, washed with 5% $NaHCO_3$, water, brine and dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (CH_2Cl_2 with 3% methanol) to afford **7**[4] (450 mg, 0.765 mmol, 88% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 8.61 (s,

1H), 7.51 (m, 2H), 7.31 (m, 7H), 6.88 (m, 4H), 6.24 (t, *J* = 6.8 Hz, 1H), 4.47 (m, 1H), 4.11 (m, 1H), 3.79 (s, 6H), 3.42 (dd, *J* = 3.3, 10.5 Hz, 1H), 3.33 (dd, *J* = 4.3, 10.5 Hz, 1H), 3.31 (s, 3H), 2.37 (m, 2H). HRMS (*m/z*): calculated for $C_{32}H_{33}N_2O_9$ (M+H): 589.2181; found: 589.2189.

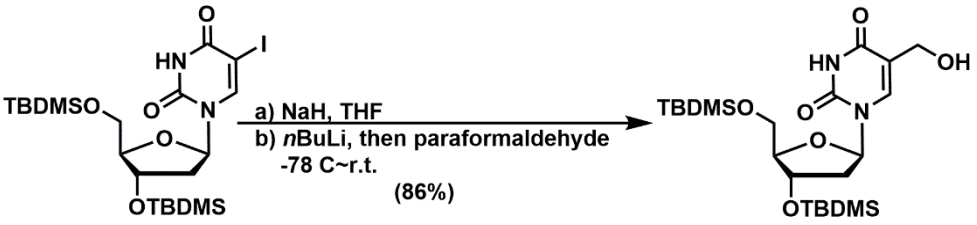
Synthesis of 5-cadU-CE phosphoramidite



7 **5-cadU-CE phosphoramidite**

To a solution of **7** (80 mg, 0.136 mmol) in 2 mL of anhydrous CH_3CN were added diisopropylethylamine (53 mg, 0.408 mmol), tetrazole in CH_3CN (0.45 mL, 0.204 mmol) and 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphordiamidite (61 mg, 0.204 mmol). The reaction was kept at room temperature and monitored by TLC. Ten minutes later, a white precipitate appeared. Upon completion, the reaction was quenched with the addition of 0.5 mL of absolute ethanol. Reaction was diluted with ethyl acetate with 1% triethylamine, washed with 5% $NaHCO_3$, water, brine, and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, crude product was purified by column chromatography (CH_2Cl_2 with 1.5% methanol and 1% triethylamine) to afford 5-cadU-CE phosphoramidite[4] (105 mg, 0.133 mmol, 98% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.69 (s, 0.52H), 8.65 (s, 0.48H), 7.39 (m, 2H), 7.23 (m, 7H), 6.79 (m, 4H), 6.22 (m, 1H), 4.48 (m, 1H), 4.20 (m, 1H), 3.74 (s, 6H), 3.54 (m, 5H), 3.21 (m, 1H), 3.18 (s, 1.5H), 3.17 (s, 1.5H), 2.72 (m, 2H), 2.57 (m, 1H), 2.22 (m, 1H), 1.23 (m, 12H). ^{31}P NMR (120 MHz, $CDCl_3$) δ: 149.2, 148.6. HRMS (*m/z*): calculated for $C_{41}H_{50}N_4O_{10}P$ (M+H): 789.3259; found: 789.3264.

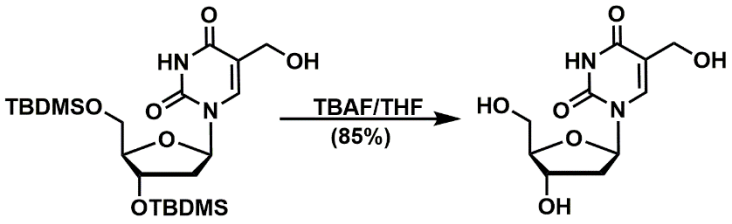
Synthesis of 8



1 **8**

To a solution of **1** (0.4 g, 0.687 mmol) in 3 mL of THF was added NaH (25 mg, 1.03 mmol) at r.t. The solution was stirred for another 30 min before it was cooled down to -78°C and *n*BuLi (1.29 mL, 2.06 mmol) was added. After 15 min, paraformaldehyde (124 mg, 4.12 mmol) was added. The reaction mixture was then allowed to slowly warm to r.t. and stir overnight before it was quenched with the addition of NH_4Cl solution. Organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (hexanes:ethyl acetate 3:1) to afford **8** (287 mg, 0.59 mmol, 86% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.68 (s, 1H), 6.25 (dd, *J* = 5.9, 7.9 Hz, 1H), 4.48 (m, 1H), 4.31 (d, *J* = 0.6 Hz, 2H), 3.92 (m, 1H), 3.80 (m, 2H), 2.20 (m, 1H), 2.15 (m, 1H), 0.93 (s, 9H), 0.92 (s, 9H), 0.12 (s, 12H). ^{13}C NMR (75 MHz, CD_3OD) δ: 165.1, 152.3, 138.7, 115.5, 89.4, 86.6, 74.1, 64.4, 58.0, 41.7, 26.7, 26.4, 19.4, 19.0, -4.3, -4.4, -5.05, -5.12. HRMS (*m/z*): calculated for $C_{22}H_{43}N_2O_6Si_2$ (M+H): 487.2654; found: 487.2655.

Synthesis of 9



8 **9**

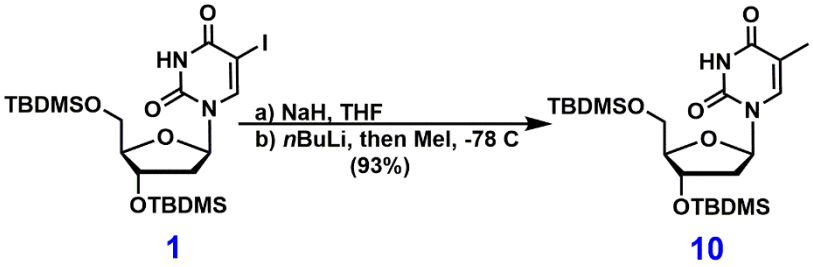
To a solution of **8** (87 mg, 0.18 mmol) in 1 mL of THF was added TBAF (1 M in THF, 0.45 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was

removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 15% methanol) to afford **9**[5] (39 mg, 0.151 mmol, 85% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.96 (s, 1H), 6.29 (t, *J* = 7.0 Hz, 1H), 4.40 (m, 1H), 4.32 (s, 2H), 3.91 (m, 1H), 3.75 (m, 2H), 2.25 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ: 165.3, 152.4, 139.6, 115.4, 89.0, 86.6, 72.4, 63.0, 58.1, 41.4. HRMS (*m/z*): calculated for $C_{10}H_{15}N_2O_6$ (M+H): 259.0925; found: 259.0928.

Synthesis of 5-hmdU-CE phosphoramidite

5-hmdU-CE phosphoramidite was synthesized as described previously.[5]

Synthesis of 10

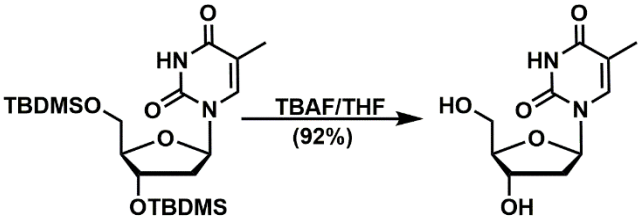


1 **10**

To a solution of **1** (1.49 g, 2.56 mmol) in 10 mL of THF was added NaH (92 mg, 3.84 mmol) at r.t. The solution was stirred for another 30 min before it was cooled down to -78°C and *n*BuLi (4.8 mL, 7.68 mmol) was added. After 15 min, methyliodide (1.86 g, 12.8 mmol) was then added dropwise. The reaction mixture was kept at -78°C for another hour before it was quenched with the addition of NH_4Cl solution. Organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed *in vacuo*. Crude product was purified by column chromatography (hexanes:ethyl acetate 3:1) to afford **10**[6] (1.12, 2.38 mmol, 93% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.45 (s, 1H), 6.31 (t, *J* = 6.3 Hz, 1H), 4.39 (m, 1H), 3.92 (m, 1H), 3.85 (d, *J* = 11.6 Hz, 1H), 3.74 (d, *J* = 11.6 Hz, 1H), 2.23 (m, 1H), 1.99 (m, 1H), 1.75 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.06 (s, 6H). HRMS (*m/z*): calculated for $C_{22}H_{43}N_2O_5Si_2$

(M+H): 471.2705; found: 471.2707.

Synthesis of 11



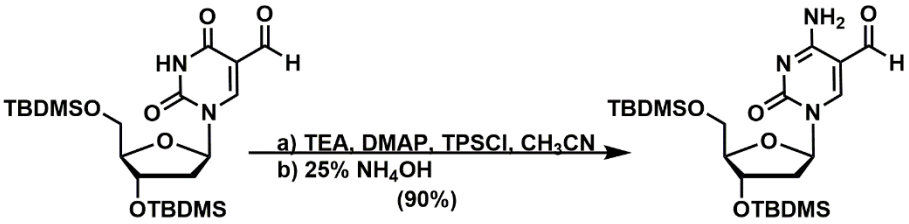
10 **11**

To a solution of **10** (638 mg, 1.36 mmol) in 2 mL of THF was added TBAF (1 M in THF, 3.4 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 8~10% methanol) to afford **11**[7] (303 mg, 1.25 mmol, 92% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.80 (d, *J* = 1.1 Hz, 1H), 6.27 (t, *J* = 6.9 Hz, 1H), 4.38 (m, 1H), 3.89 (m, 1H), 3.75 (m, 2H), 2.21 (m, 2H), 1.87 (d, *J* = 1.1 Hz, 3H). HRMS (*m/z*): calculated for $C_{10}H_{15}N_2O_5$ (M+H): 243.0975; found: 243.0979.

Synthesis of dT-CE phosphoramidite

dT-CE phosphoramidite was synthesized as described previously.[8]

Synthesis of 12

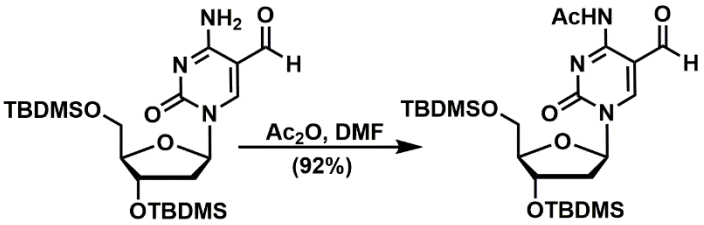


2 **12**

To a solution of **2** (212 mg, 0.44 mmol) in CH_3CN (7 mL) were added TEA (141 mg, 1.39 mmol), DMAP (164 mg, 1.35 mmol) and TPSCl (409 mg, 1.35 mmol). The reaction was stirred at r.t. for 21 h before NH_4OH (25%, 10 mL) was added. The reaction was kept stirring at r.t. for

another 1.5 h. Solvent was removed under vacuum. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate 3 times. Combined organic layer was washed with 5% $NaHCO_3$, brine and dried over Na_2SO_4. Crude product was purified by column chromatography (CH_2Cl_2 with 5% methanol) to afford **12**[9] (191 mg, 0.395 mmol, 90% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ: 9.56 (s, 1H), 8.62 (s, 1H), 6.14 (t, *J* = 6.5 Hz, 1H), 4.46 (m, 1H), 4.10 (m, 1H), 3.90 (m, 2H), 2.55 (m, 1H), 2. 15 (m, 1H), 0.93 (s, 9H), 0.90 (s, 9H), 0.131 (s, 3H), 0.125 (s, 3H), 0.11 (s, 6H). HRMS (*m/z*): calculated for $C_{22}H_{42}N_3O_5Si_2$ (M+H): 484.2658; found: 484.2663.

Synthesis of 13



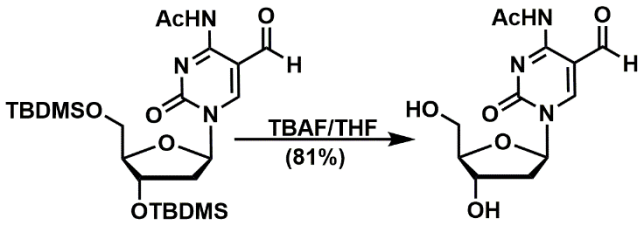
12 **13**

To a solution of **12** (60 mg, 0.124 mmol) in 1 mL of DMF was added Ac_2O (15.2 mg, 0.15 mmol). The reaction mixture was stirred at r.t. overnight. MeOH (0.5 mL) was added to quench the reaction. After the mixture was stirred for additional 15 min, the solvents were removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2 with 2~4% methanol) to afford **13**[10] (60 mg, 0.114 mmol, 92% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 9.58 (s, 1H), 8.83 (s, 1H), 6.15 (t, *J* = 6.7 Hz, 1H), 4.47 (m, 1H), 4.15 (m, 1H), 3.93 (m, 2H), 2.63 (m, 1H), 2.59 (s, 3H), 2.22 (m, 1H), 0.93 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H), 0.11 (s, 6H). HRMS (*m/z*): calculated for $C_{24}H_{44}N_3O_6Si_2$ (M+H): 526.2763; found: 526.2766.

Synthesis of 14

To a solution of **13** (28 mg, 0.053 mmol) in 0.5 mL of THF was added TBAF (1 M in THF,

0.133 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 10% methanol) to afford **14**[10] (13 mg, 0.043 mmol, 81% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 9.58 (s, 1H), 9.06 (s, 1H), 6.23 (t, *J* = 5.9 Hz, 1H), 4.44 (m, 1H), 4.06 (m, 1H), 3.95 (dd, *J* = 3.0, 12.1 Hz, 1H), 3.82 (dd, *J* = 3.5, 12.1 Hz, 1H), 2.49 (m, 1H), 2.39 (s, 3H), 2.29 (m, 1H). HRMS (*m/z*): calculated for $C_{12}H_{16}N_3O_6$ (M+H): 298.1034; found: 298.1038.

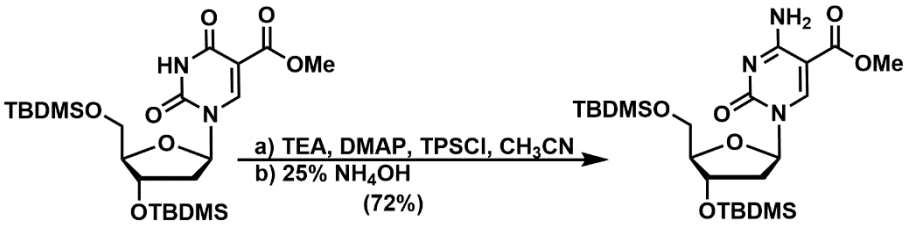


13 **14**

Synthesis of 5-fodC-CE phosphoramidite

5-fodC-CE phosphoramidite was synthesized as described previously.[10]

Synthesis of 15

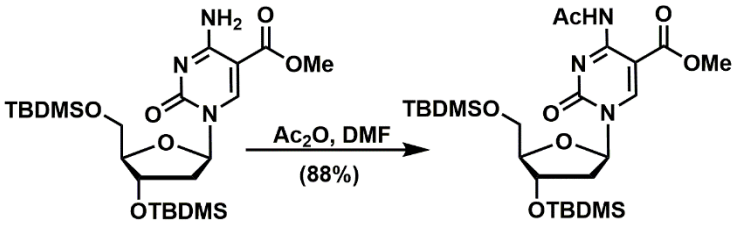


5 **15**

To a solution of **5** (258 mg, 0.50 mmol) in CH_3CN (7.7 mL) were added TEA (157 mg, 1.55 mmol), DMAP (183 mg, 1.50 mmol) and TPSCl (454 mg, 1.50 mmol). The reaction was stirred at r.t. for 21 h before NH_4OH (25%, 11 mL) was added. The reaction was kept stirring at r.t. for another 1.5 h. Solvent was removed under vacuum. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate 3 times. Combined organic layer was washed with sat. $NaHCO_3$, brine and dried over Na_2SO_4. Crude product was purified

by column chromatography (CH_2Cl_2 with 2~4% methanol) to afford **15**[11] (185 mg, 0.36 mmol, 72% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.65 (s, 1H), 6.09 (dd, *J* = 5.9, 7.4 Hz, 1H), 4.45 (m, 1H), 4.12 (m, 1H), 3.84 (m, 2H), 3.66 (s, 3H), 2.56 (m, 1H), 2.09 (m, 1H), 0.93 (s, 9H), 0.87 (s, 9H), 0.133 (s, 3H), 0.125 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). HRMS (*m/z*): calculated for $C_{23}H_{44}N_3O_6Si_2$ (M+H): 514.2763; found: 514.2760.

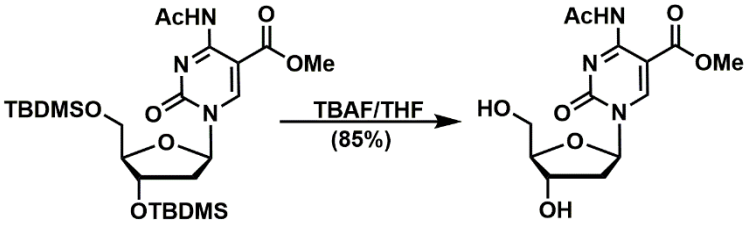
Synthesis of 16



15 **16**

To a solution of **15** (185 mg, 0.36 mmol) in 2.3 mL of DMF was added Ac_2O (44 mg, 0.432 mmol). The reaction mixture was stirred at r.t. overnight. MeOH (0.5 mL) was added to quench the reaction. After the mixture was stirred for additional 15 min, the solvents were removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 10% methanol) to afford **16**[11] (176 mg, 0.317 mmol, 88% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.80 (s, 1H), 6.07 (dd, *J* = 6.1, 7.2 Hz, 1H), 4.46 (m, 1H), 4.17 (m, 1H), 3.85 (m, 2H), 3.78 (s, 3H), 2.65 (m, 1H), 2.53 (s, 3H), 2.17 (m, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). HRMS (*m/z*): calculated for $C_{25}H_{46}N_3O_7Si_2$ (M+H): 556.2869; found: 556.2875.

Synthesis of 17



16 **17**

To a solution of **16** (176 mg, 0.317 mmol) in 0.5 mL of THF was added TBAF (1 M in THF, 0.793 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 10% methanol) to afford **17**[10] (88 mg, 0.269 mmol, 85% yield) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.63 (s, 1H), 9.22 (s, 1H), 0.04 (t, J = 5.7 Hz, 1H), 4.23 (m, 1H), 3.90 (m, 1H), 3.78 (s, 3H), 3.63 (m, 2H), 2.41 (s, 3H), 2.35 (m, 1H), 2.13 (m, 1H). HRMS (*m/z*): calculated for $C_{13}H_{18}N_3O_7$ (M+H): 328.1139; found: 328.1144.

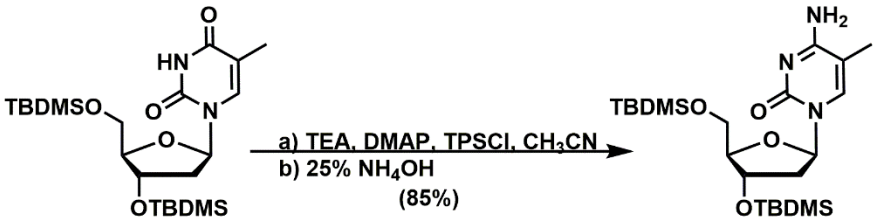
Synthesis of 5-cadC-CE phosphoramidite

5-cadC-CE phosphoramidite was synthesized as described previously.[10]

Synthesis of 5-hmdC-CE phosphoramidite

5-hmdC-CE phosphoramidite was synthesized as described previously.[12]

Synthesis of 18

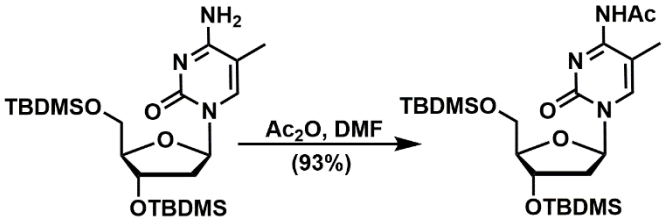


10 **18**

To a solution of **10** (600 mg, 1.276 mmol) in CH_3CN (15 mL) were added TEA (407 mg, 4.02 mmol), DMAP (478 mg, 3.919 mmol) and TPSCl (1.16 g, 3.919 mmol). The reaction was stirred at r.t. for 21 h before NH_4OH (25%, 15 mL) was added. The reaction was kept stirring at r.t. for another 1.5 h. Solvent was removed under vacuum. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate 3 times. Combined organic layer was washed with 5% $NaHCO_3$, brine and dried over Na_2SO_4. Crude product was purified by column chromatography (CH_2Cl_2 with 5% methanol) to afford **18** (509 mg, 1.09 mmol,

85% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 6.1 (t, *J* = 6.6 Hz, 1H), 4.35 (m, 1H), 4.01 (m, 1H), 3.88 (dd, *J* = 2.5, 11.6 Hz, 1H), 3.74 (dd, *J* = 2.5, 11.6 Hz, 1H), 2.57 (m, 1H), 1.97 (m, 1H), 1.88 (s, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). HRMS (*m/z*): calculated for $C_{22}H_{44}N_3O_4Si_2$ (M+H): 470.2865; found: 470.2867.

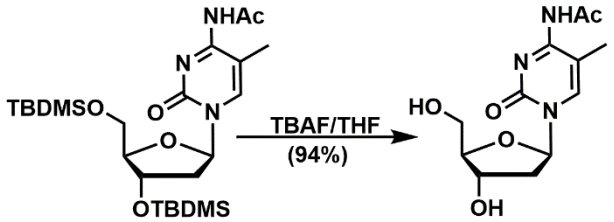
Synthesis of 19



18 **19**

To a solution of **18** (250 mg, 0.533 mmol) in 2 mL of DMF was added Ac_2O (66 mg, 0.645 mmol). The reaction mixture was stirred at r.t. overnight. MeOH (1 mL) was added to quench the reaction. After the mixture was stirred for additional 15 min, the solvents were removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2 with 2% methanol) to afford **19** (253 mg, 0.496 mmol, 93% yield) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 6.15 (t, *J* = 6.4 Hz, 1H), 4.34 (m, 1H), 4.04 (m, 1H), 3.90 (m, 1H), 3.74 (m, 1H), 2.63 (m, 1H), 2.30 (s, 3H), 2.06 (m, 1H), 1.89 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H). HRMS (*m/z*): calculated for $C_{24}H_{46}N_3O_5Si_2$ (M+H): 512.2971; found: 512.2976.

Synthesis of 20



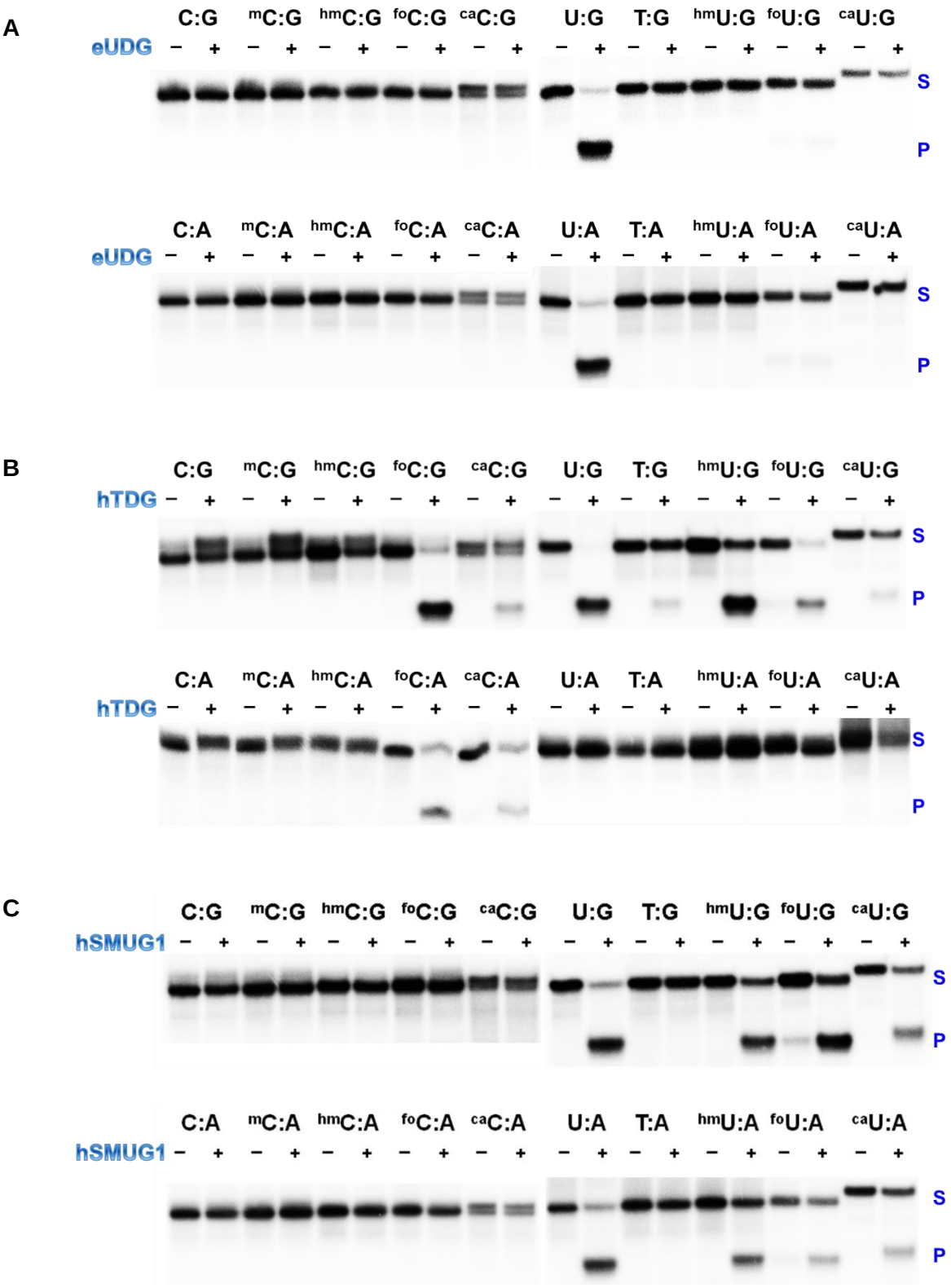
19 **20**

To a solution of **19** (250 mg, 0.489 mmol) in 1 mL of THF was added TBAF (1 M in THF, 1.22 mmol). The reaction was kept at r.t. and monitored by TLC. Upon completion (about 1h), solvent was removed under reduced pressure. Crude product was purified by column chromatography (CH_2Cl_2 with 10% methanol) to afford **20** (130 mg, 0.46 mmol, 94% yield) as a white foam. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.95 (d, *J* = 1.1 Hz, 1H), 6.29 (t, *J* = 6.2 Hz, 1H), 4.38 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 2.38 (s, 3H), 2.24 (m, 2H), 1.92 (d, *J* = 1.1 Hz, 3H). HRMS (*m/z*): calculated for $C_{12}H_{18}N_3O_5$ (M+H): 284.1241; found: 284.1242.

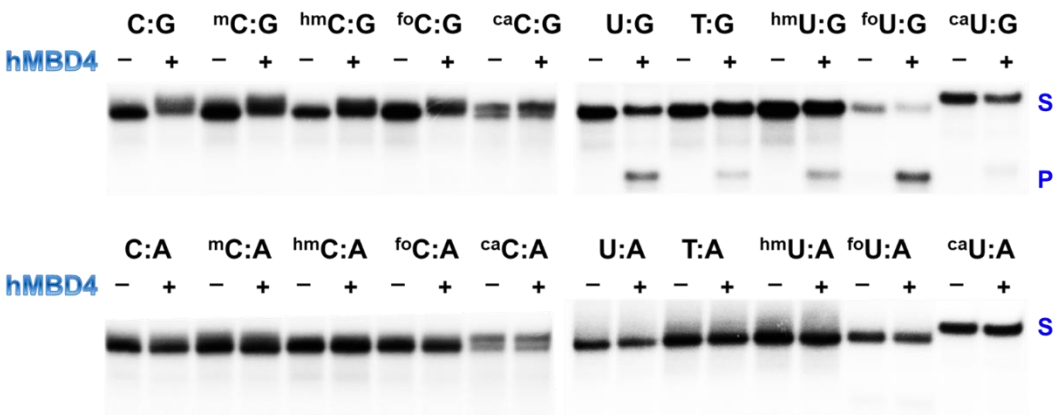
Synthesis of 5-mdC-CE phosphoramidite

5-mdC-CE phosphoramidite was synthesized as described previously.[13]

Figure S1. Substrate selectivity of recombinant eUDG (A), hTDG (B), hSMUG1 (C) and hMBD4 (D).



D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foC:G
caC:G
U:G
T:G
hmU:G
foU:G
caU:G
hMBD4
– + – + – + – + – + – + – + – + – + – +
S
P
C:A
mC:A
hmC:A
foC:A
caC:A
U:A
T:A
hmU:A
foU:A
caU:A
hMBD4
– + – + – + – + – + – + – + – + – + – +
S

Figure S2. DNA glycosylase activity in HeLa (A), U87 (B) and hES (C) cell extracts.

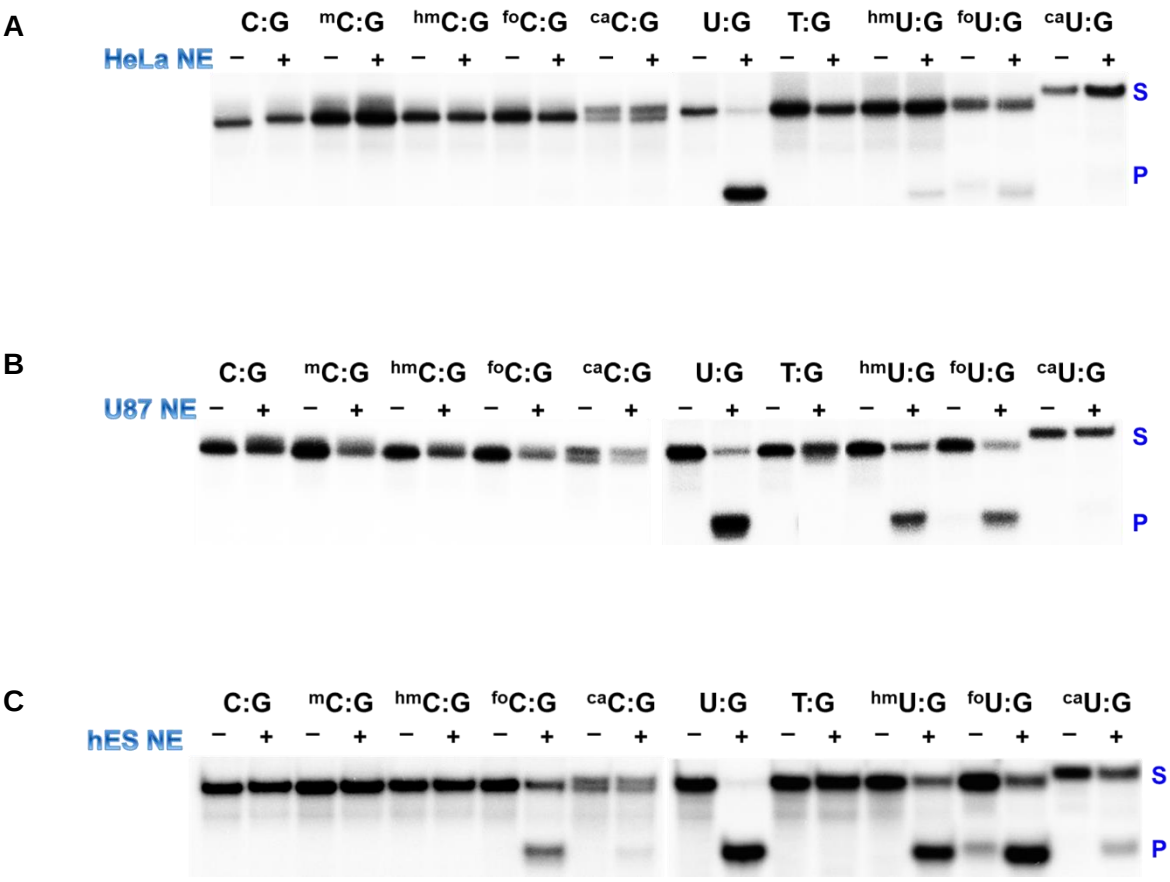
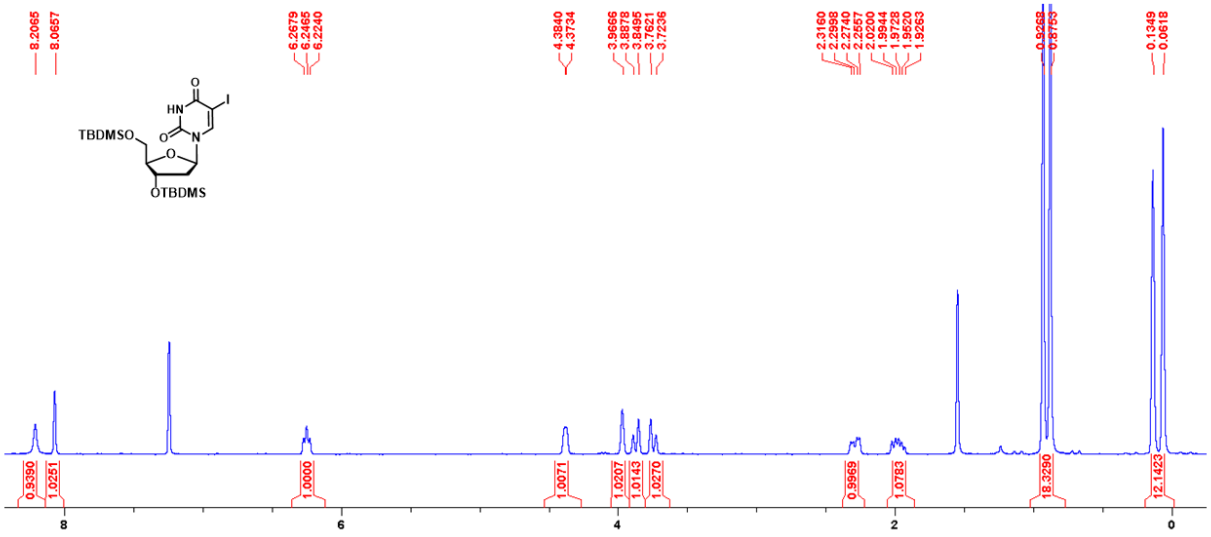


Table S1. Sequence, theoretical mass and experimentally determined mass for ODNs used in the current study.

Name	Sequence	$[M+H]^+$ (expected)	$[M+H]^+$ (detected)
24mer-C	5'-GGCTATCGTGGCCGGCCACGACGG-3'	7396.8150	7397.1624
24mer-mC	5'-GGCTATCGTGGC^{m}CGGCCACGACGG-3'	7410.8422	7410.8543
24mer-hmC	5'-GGCTATCGTGGC^{hm}CGGCCACGACGG-3'	7426.8409	7426.9180
24mer-foC	5'-GGCTATCGTGGC^{fo}CGGCCACGACGG-3'	7424.8252	7425.3954
24mer-caC	5'-GGCTATCGTGGC^{ca}CGGCCACGACGG-3'	7440.8236	7440.9183
24mer-U	5'-GGCTATCGTGGCUGGCCACGACGG-3'	7397.7990	7398.7812
24mer-T	5'-GGCTATCGTGGCTGGCCACGACGG-3'	7411.8260	7413.2112
24mer-hmU	5'-GGCTATCGTGGC^{hm}UGGCCACGACGG-3'	7427.8249	7427.9502
24mer-foU	5'-GGCTATCGTGGC^{fo}UGGCCACGACGG-3'	7425.8089	7425.9761
24mer-caU	5'-GGCTATCGTGGC^{ca}UGGCCACGACGG-3'	7441.8078	7441.9971
Complementary-G	5'-CCGTGGTCGCCGGCCACGATAGCC-3'	7316.7933	7316.8995
Complementary-A	5'-CCGTCGTGGCCGACCACGATAGCC-3'	7300.7934	7300.9025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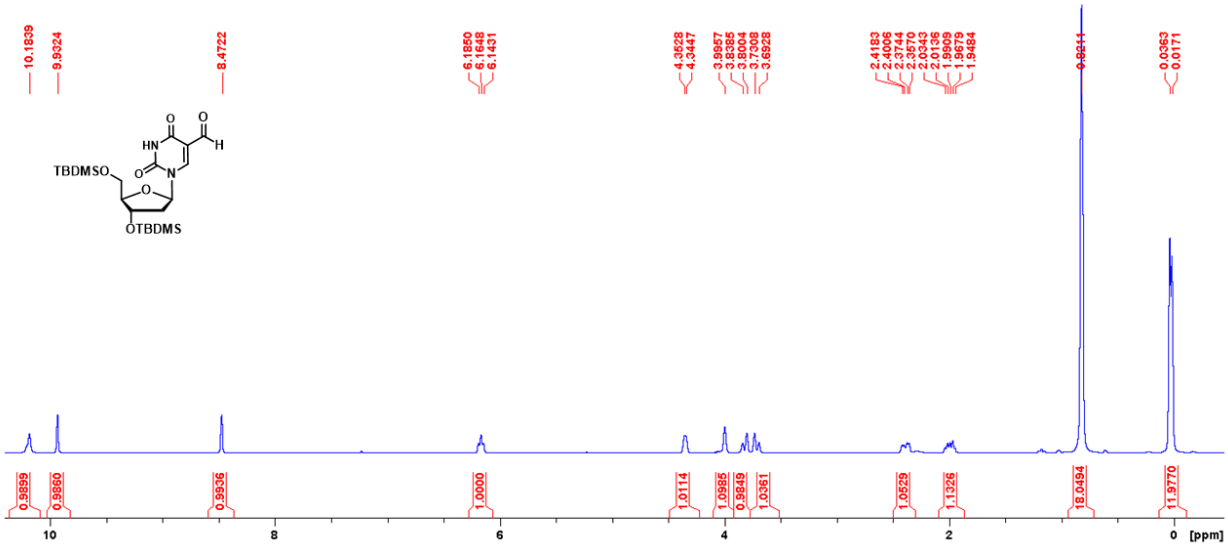
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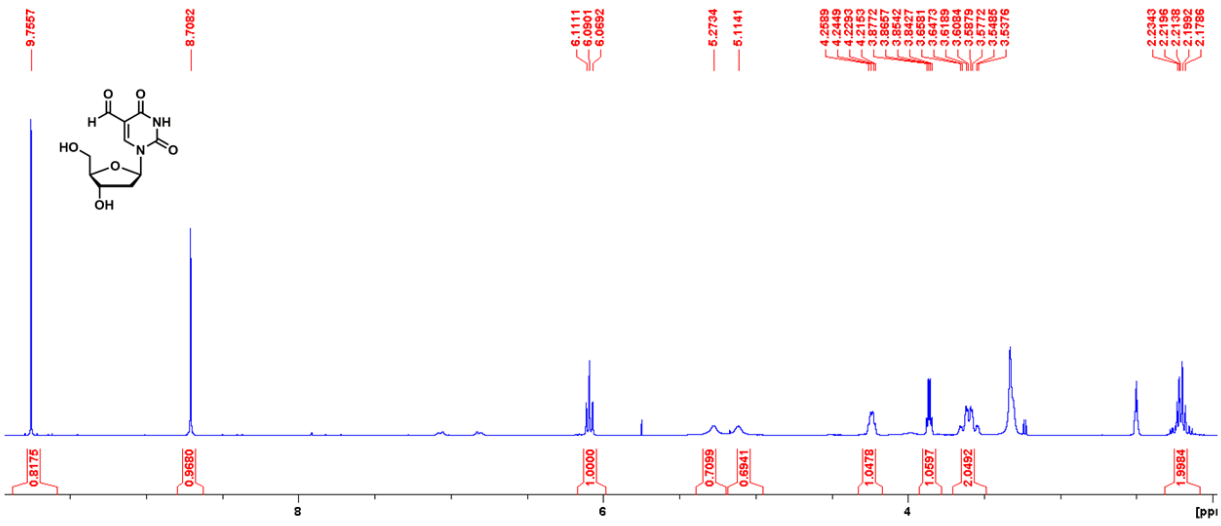
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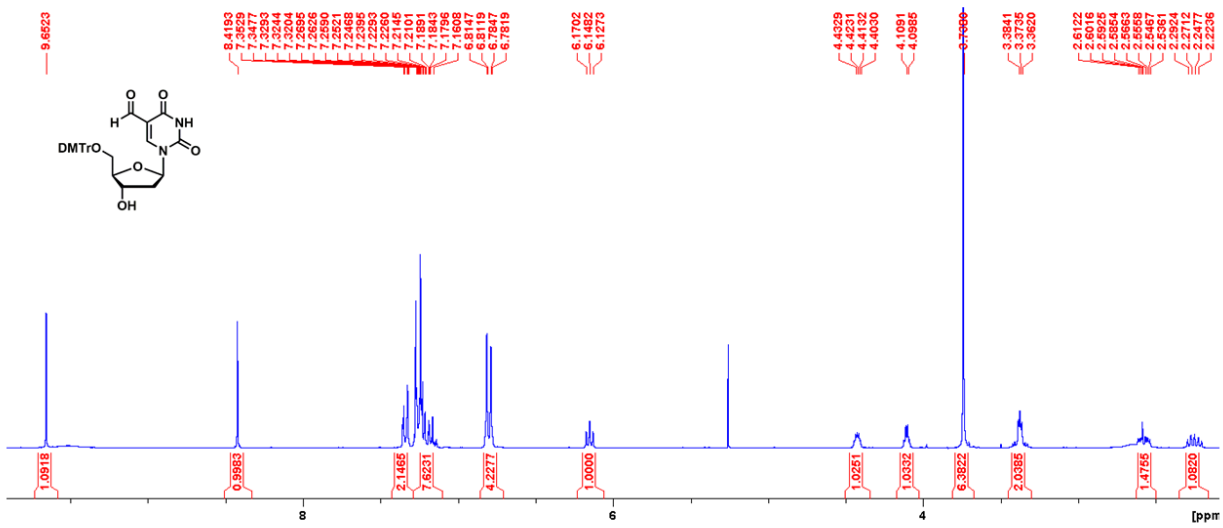
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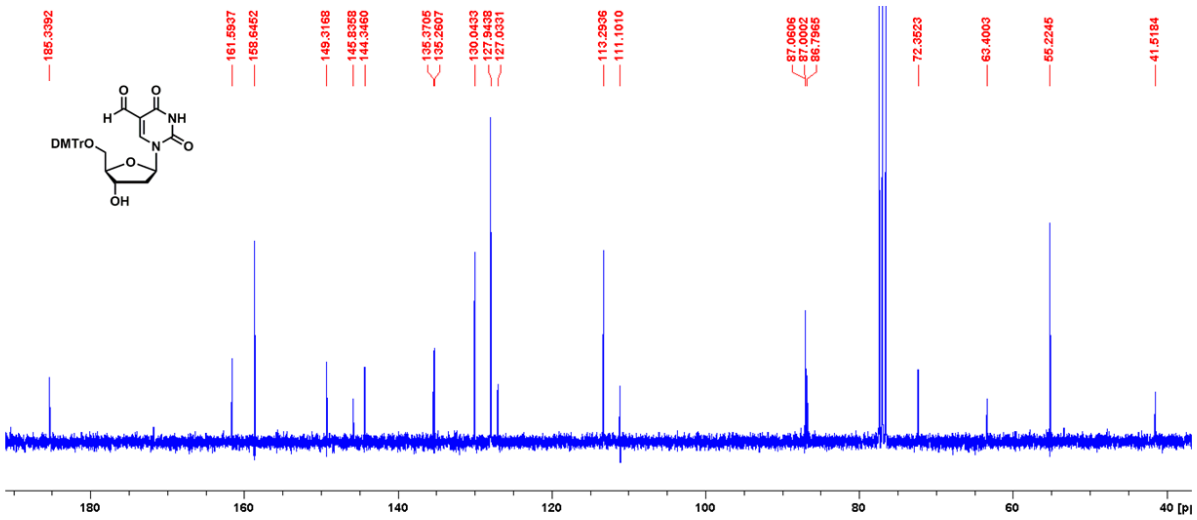
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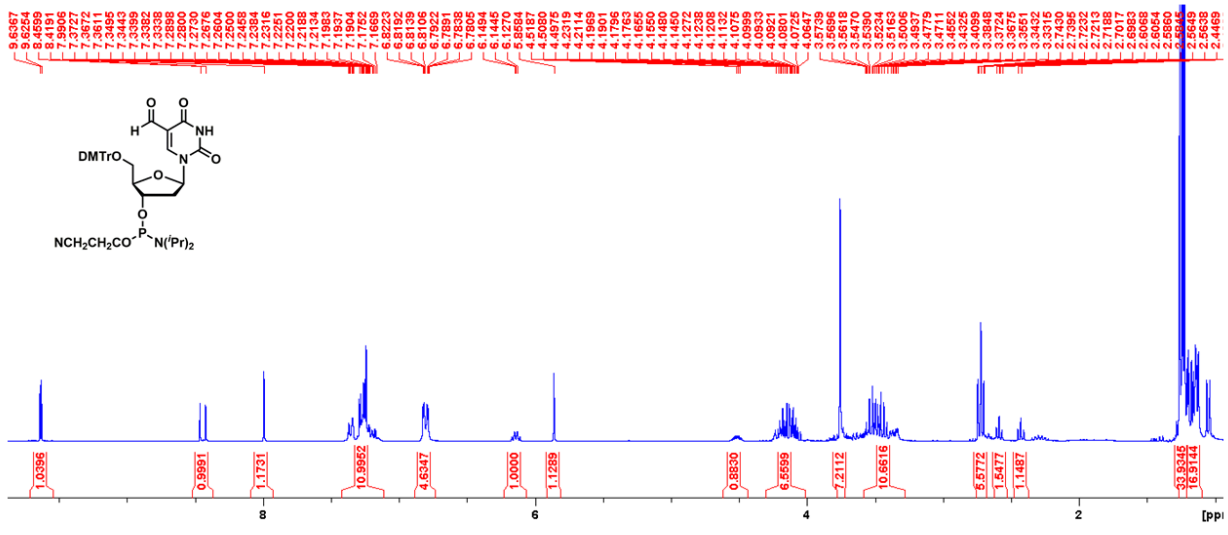
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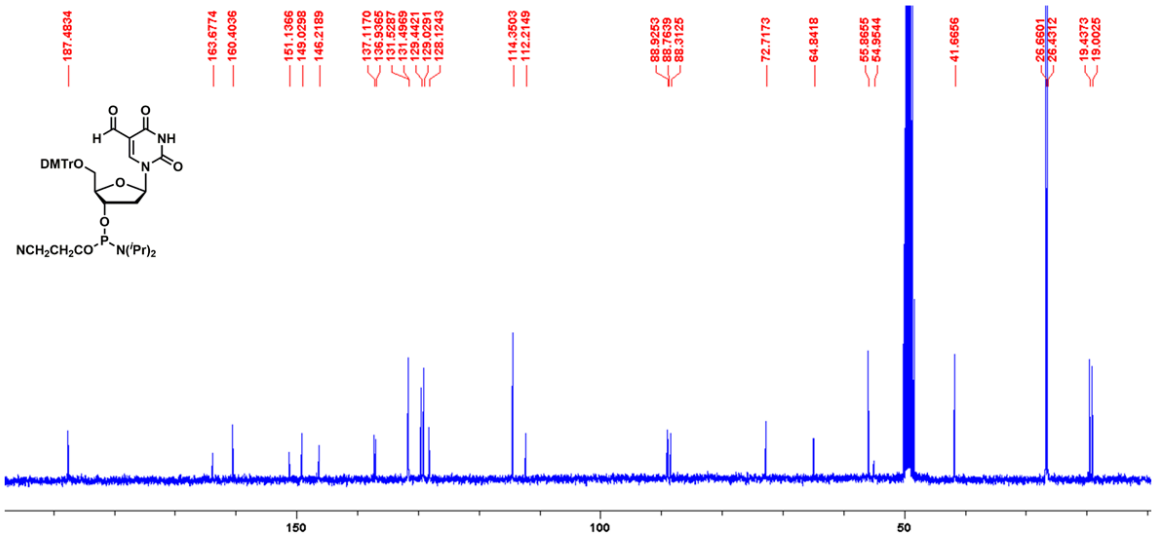
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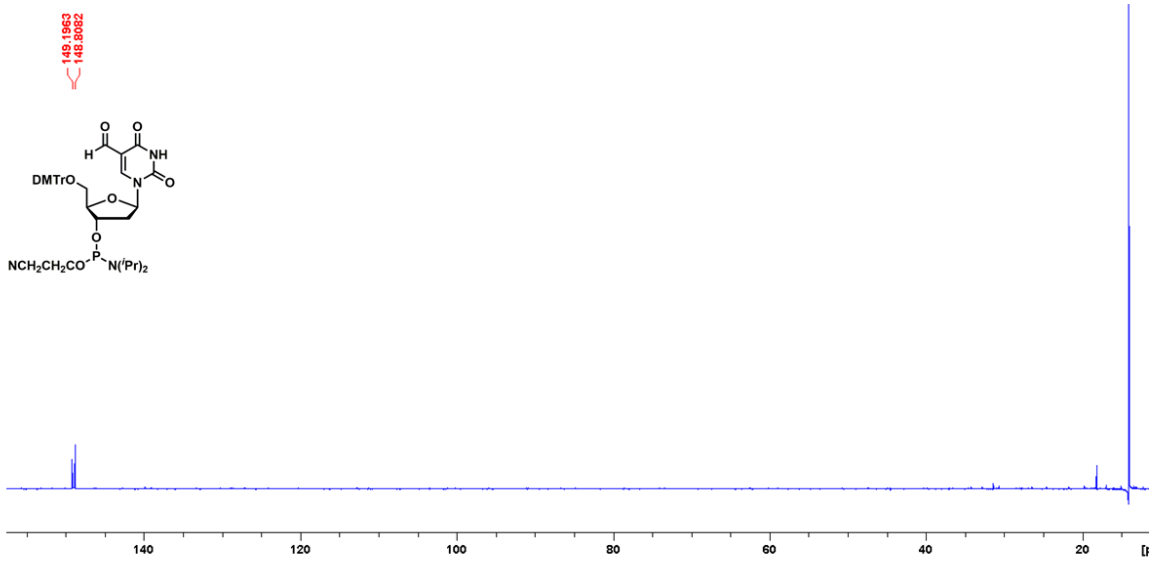
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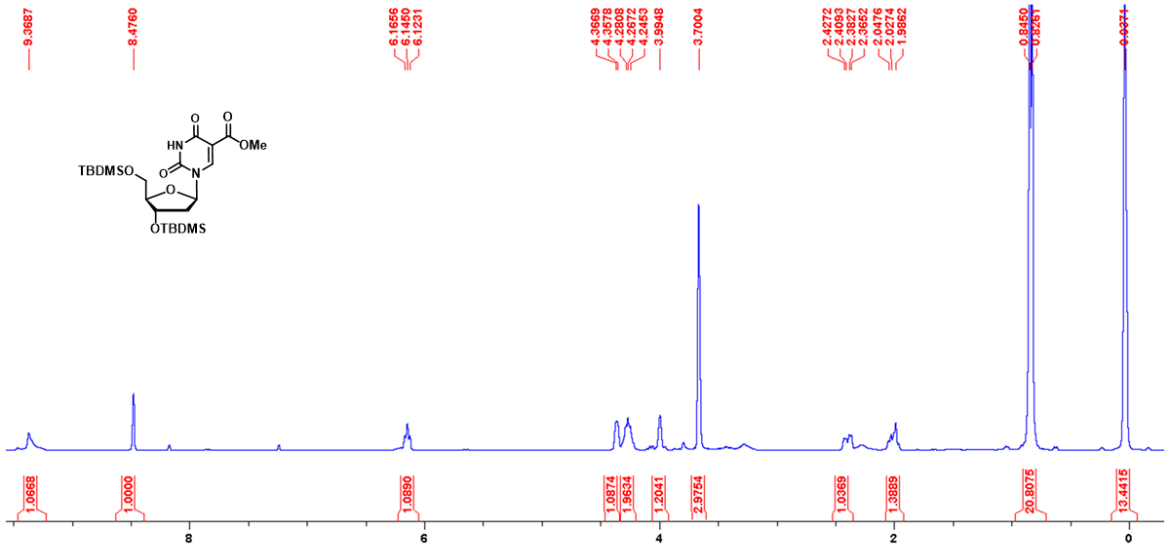
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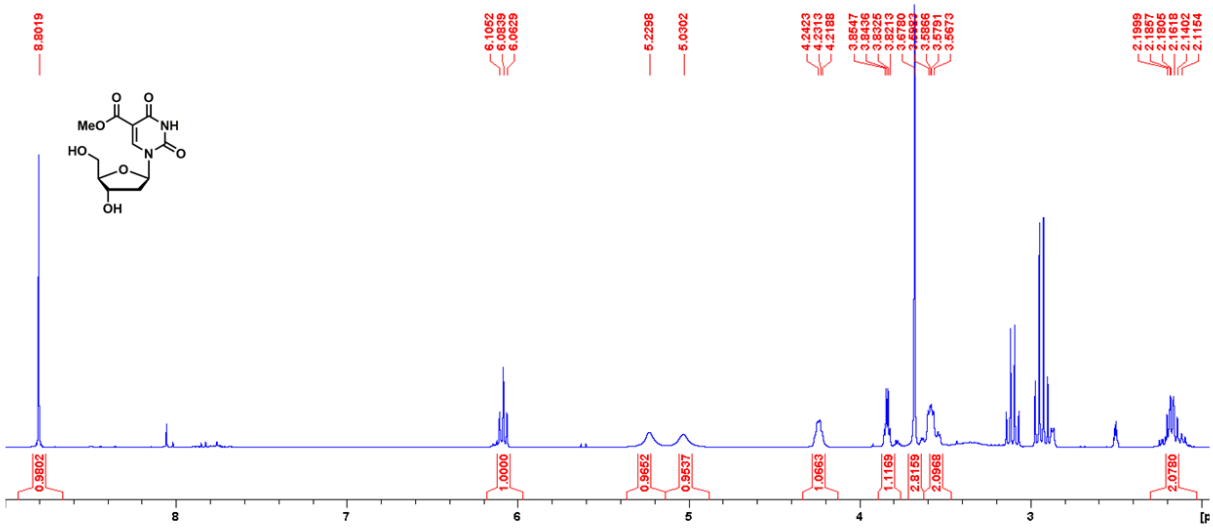
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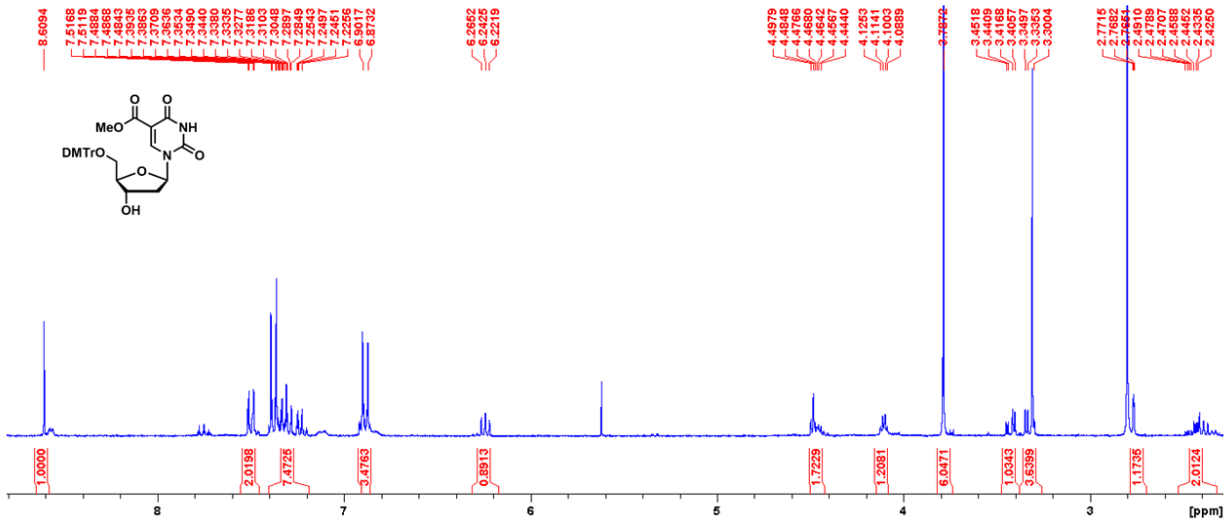
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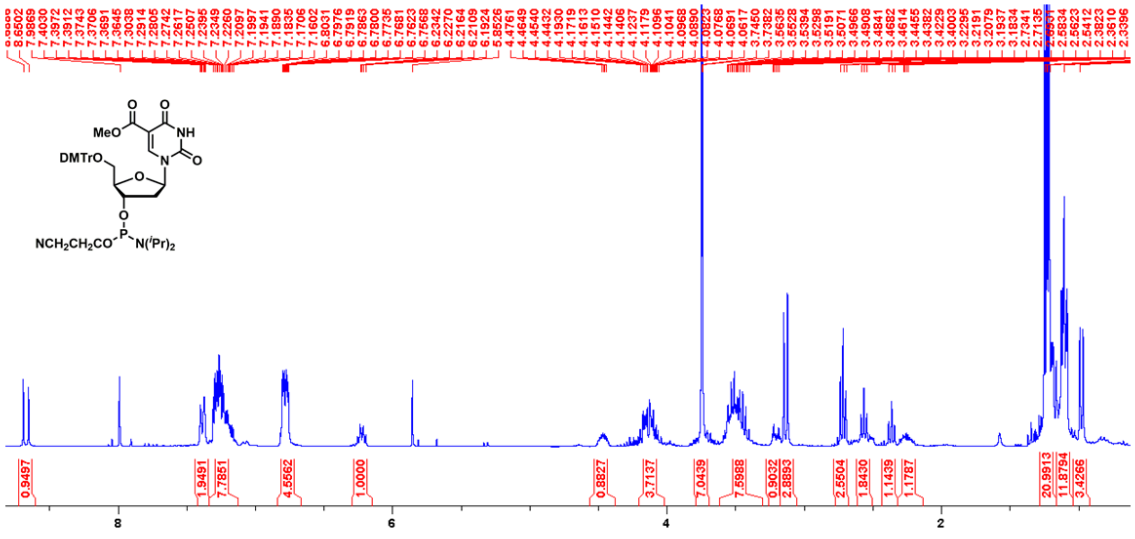
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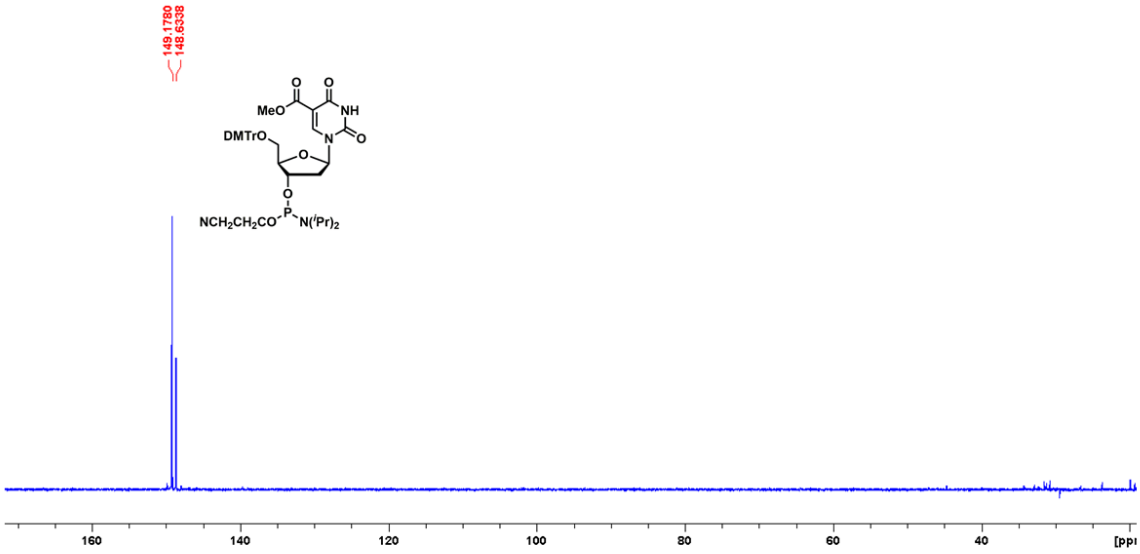
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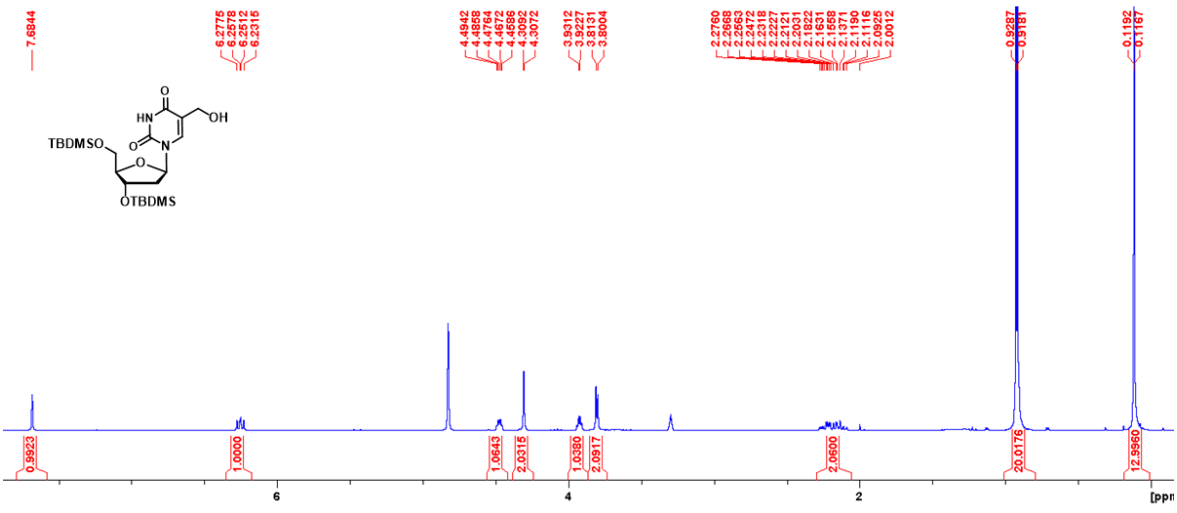
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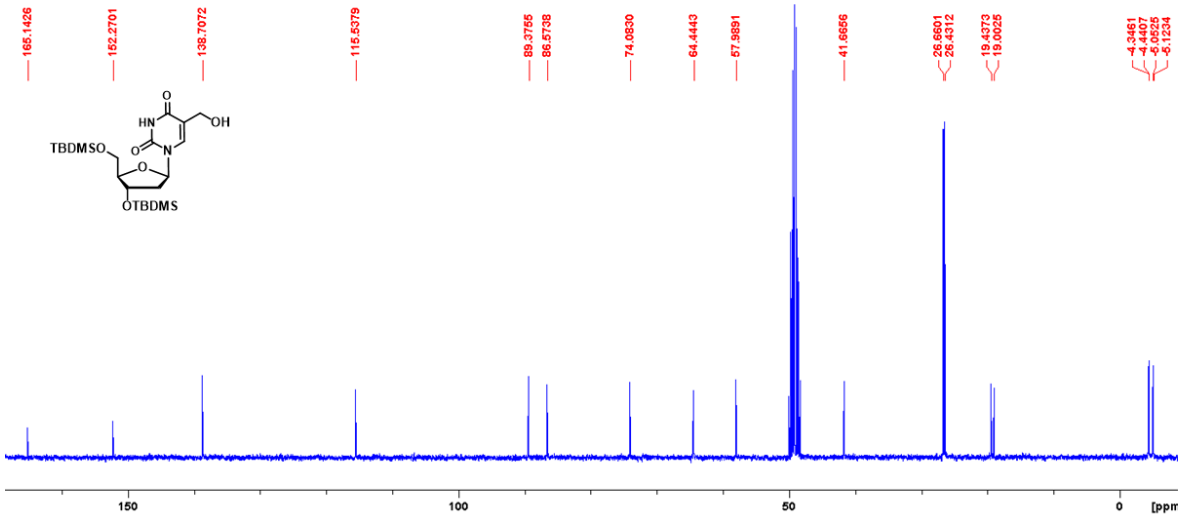
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19.4373
19.0025
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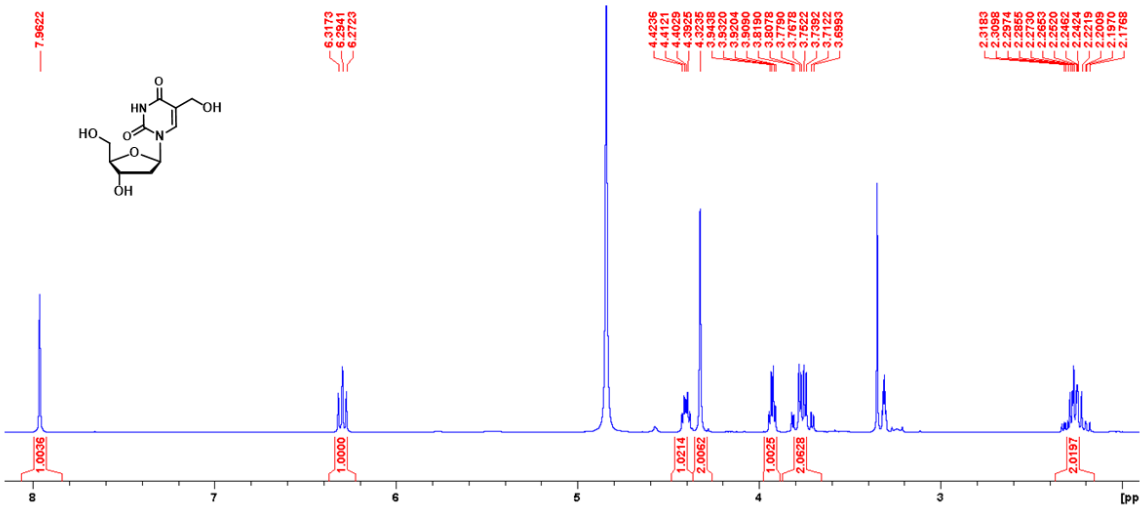
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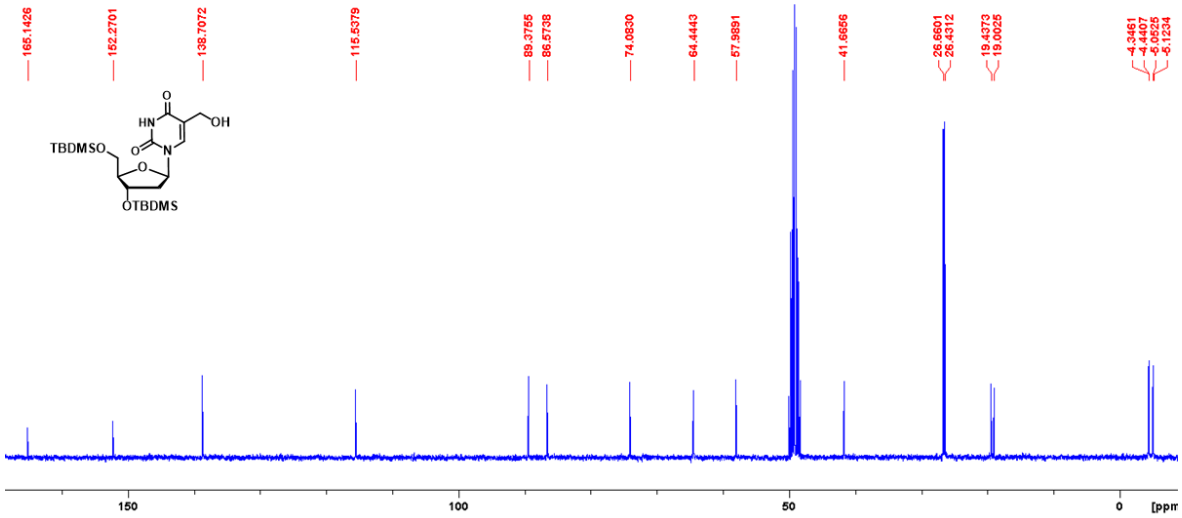
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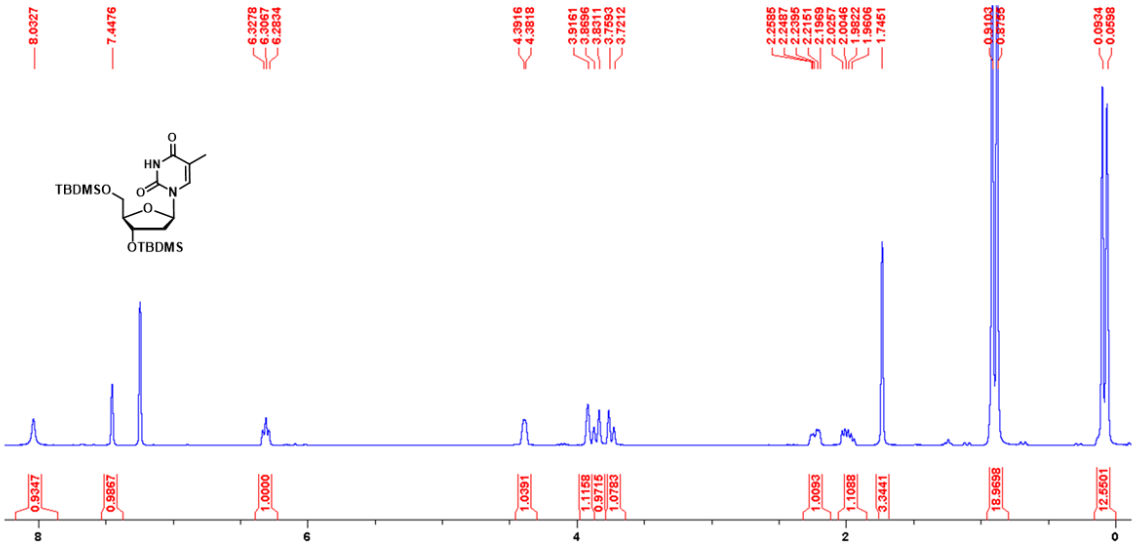
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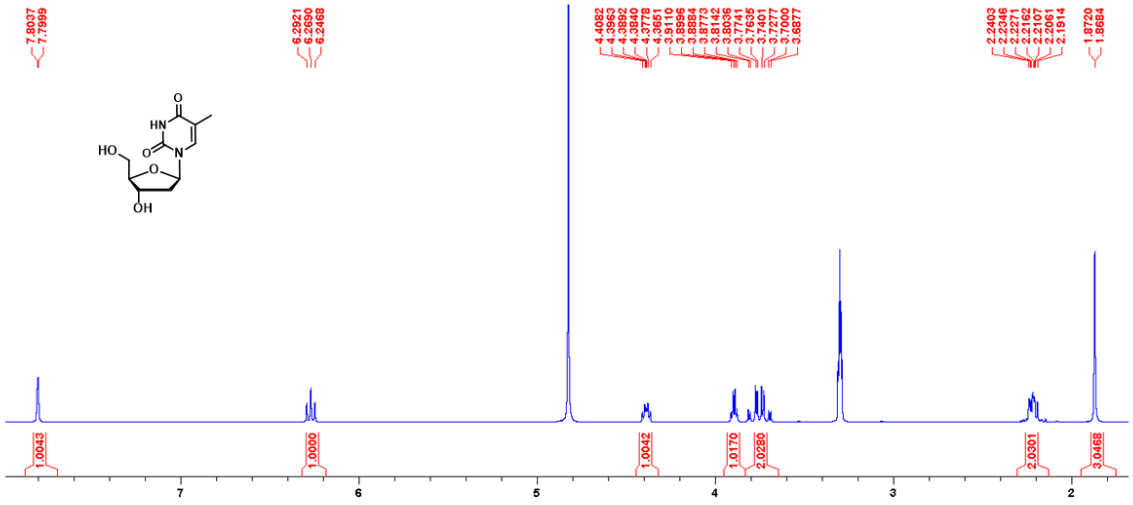
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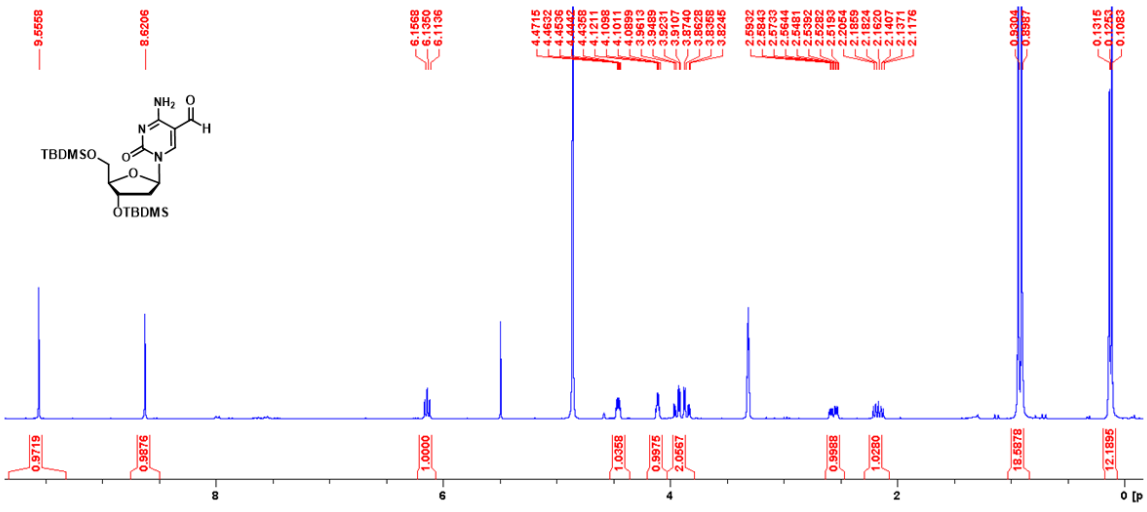
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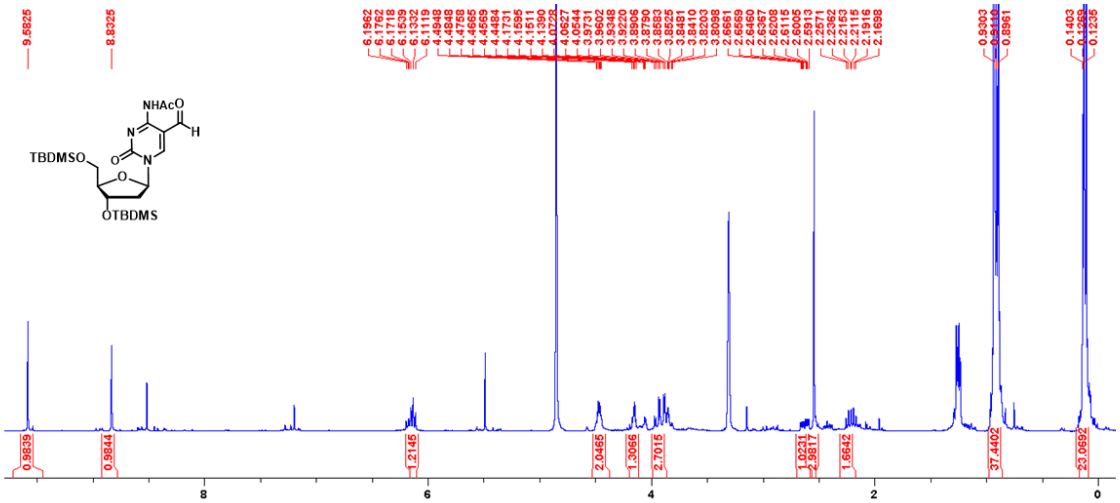
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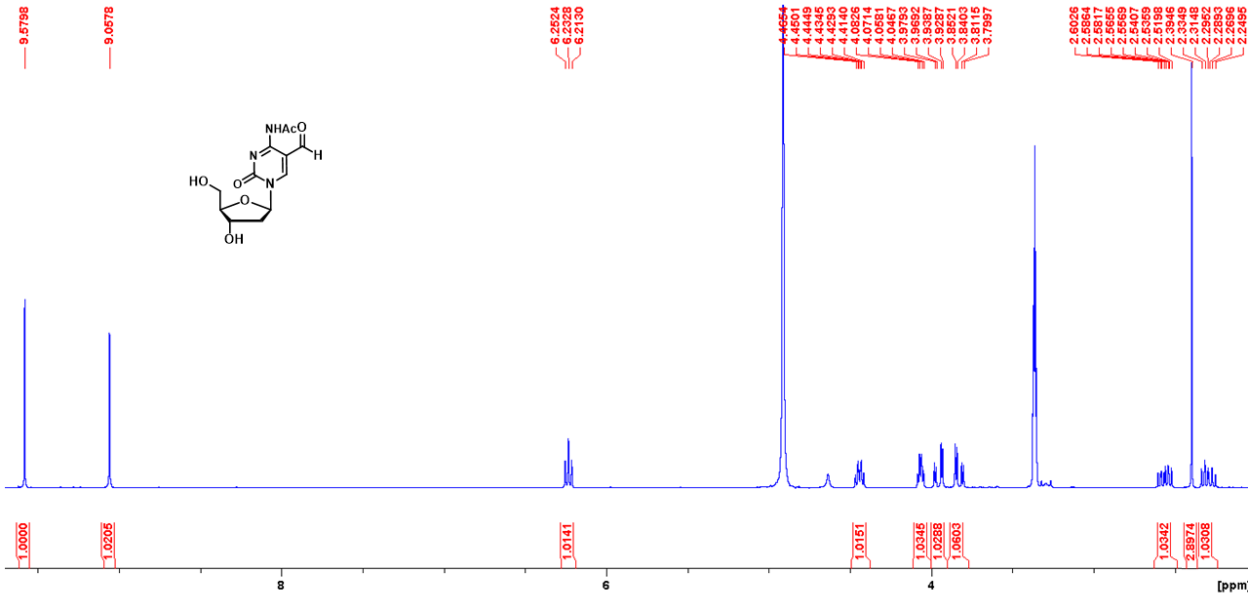
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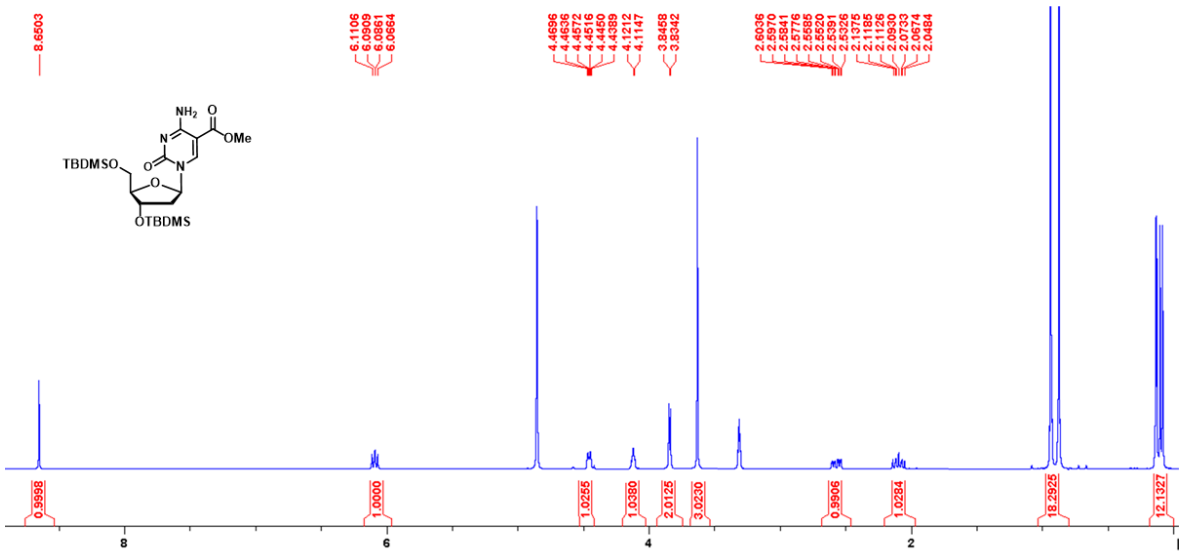
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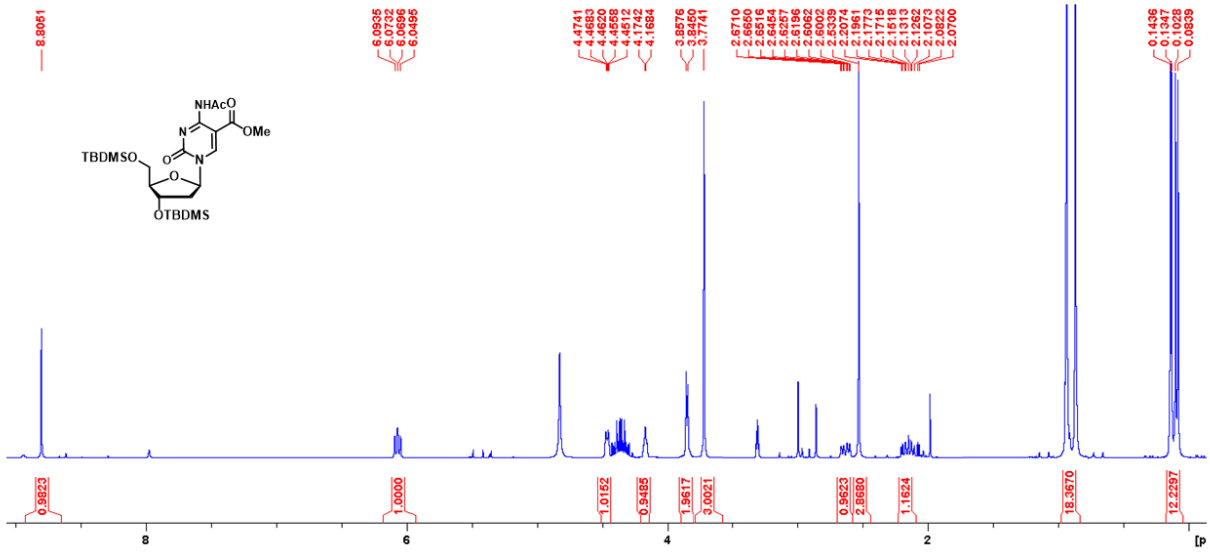
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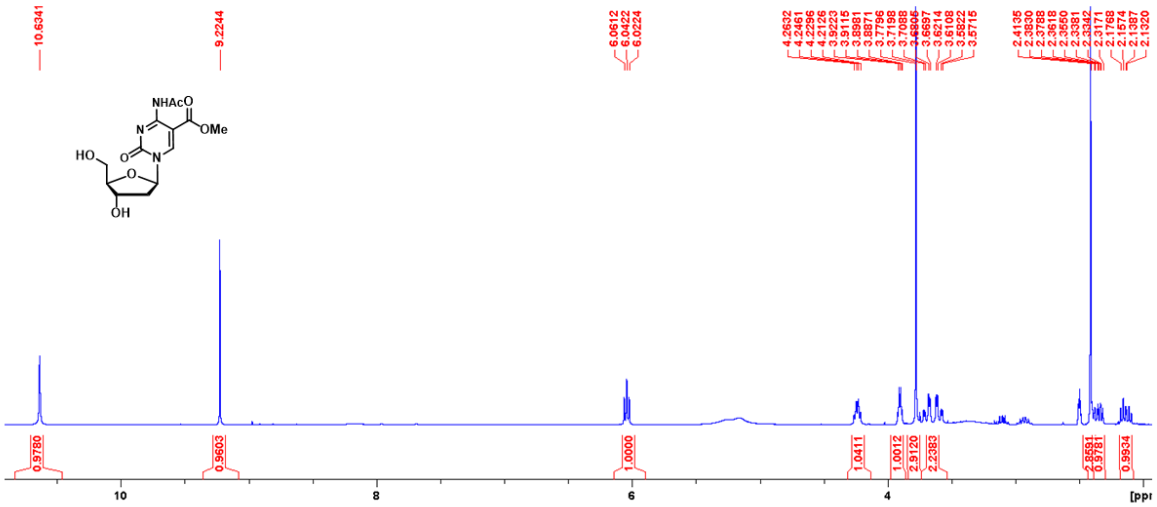
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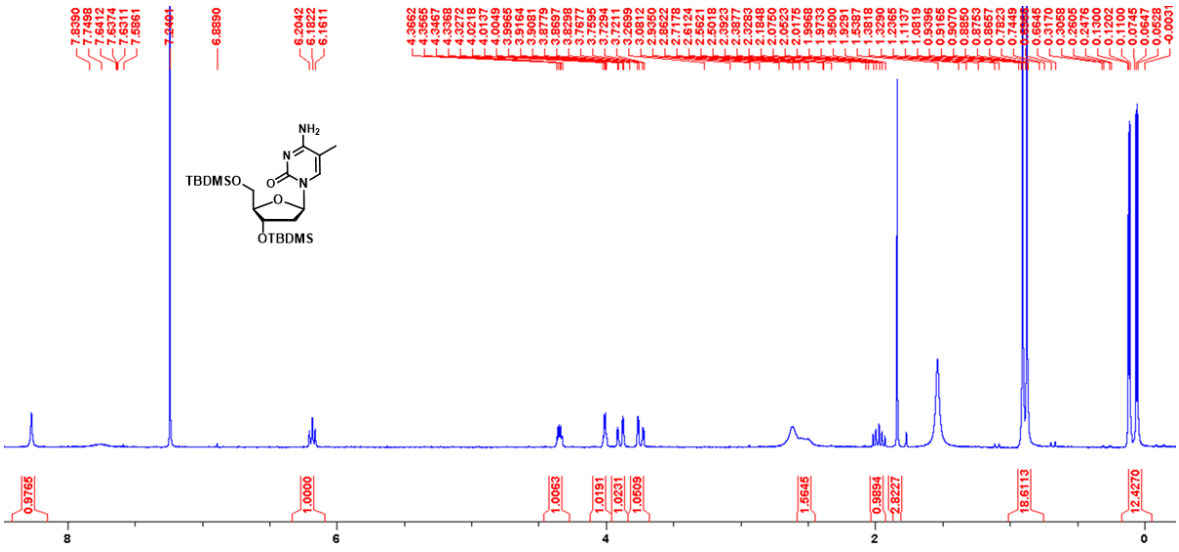
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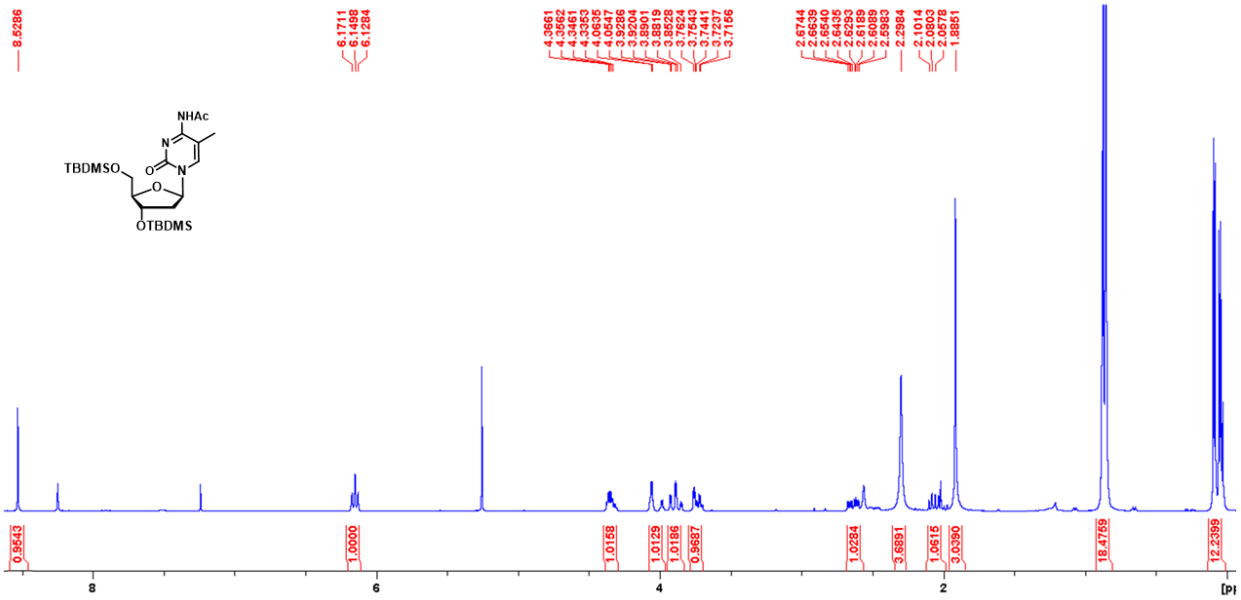
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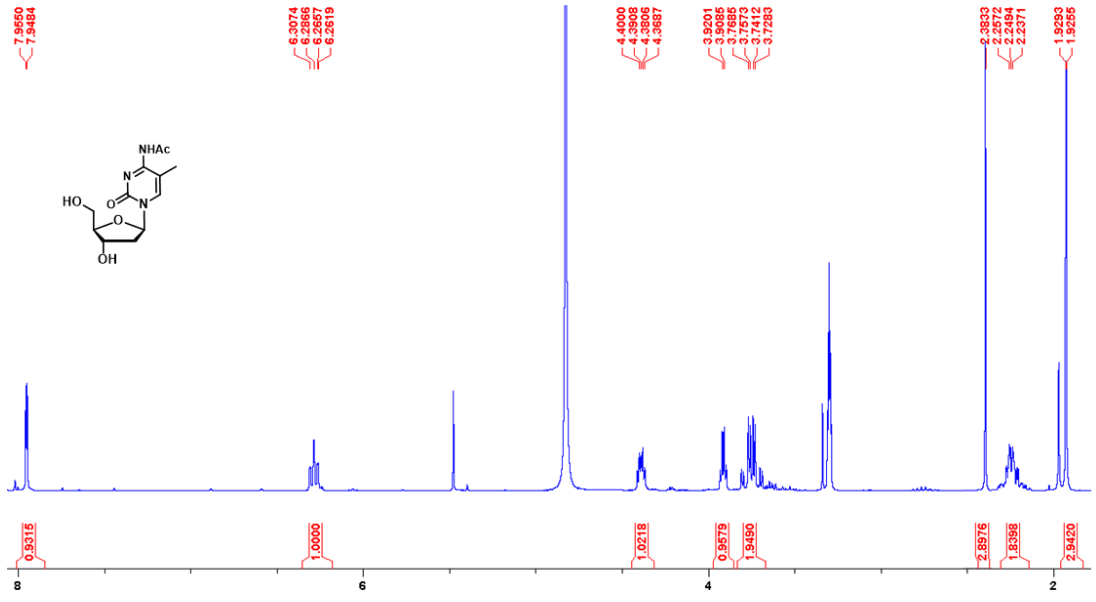
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Reference

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