Facile functionalization at the C4 position of pyrimidine nucleosides *via* amide group activation with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and biological evaluations of the products

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TABLE OF CONTENTS

General Experimental Considerations

Reactions were conducted in screw-cap glass vials with Teflon-lined caps. Thin layer chromatography was performed on 200 μm aluminum-foil-backed silica gel plates. Column chromatography was performed using 200–300 mesh silica gel. In some cases the silica gel column had to be flushed twice with 5% Et_3N in hexanes before loading the crude material in order to neutralize silica gel (see details under the compound headings). THF was distilled from $LiAlH_4$ and then from Na prior to use. CH_3CN and 1,2-dimethoxyethane (DME) were distilled from CaH_2. All other reagents were used as received from commercial suppliers. ^1H NMR spectra were obtained at 500 MHz and are referenced to the residual protonated solvent resonance. ^{13}C NMR spectra were obtained at 125 MHz and are referenced to the solvent resonance. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are in hertz (Hz). Standard abbreviations are used to designate resonance multiplicities.

General Procedures

*Step 1 of two-step procedure (synthesis of **4**, **9**, and **10**)*

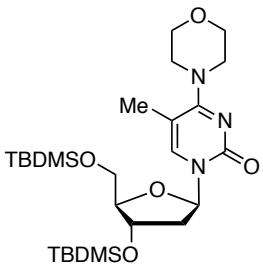
To a 0.424 M solution of the nucleoside derivative (**2:** 0.212 mmol, **7:** 0.219 mmol, **8:** 0.262 mmol) in THF, BOP (2 equiv.) and DBU (2 equiv.) were added, and the mixture was stirred at room temperature for 30 min.

*Step 2 for aliphatic amines (synthesis of **6**, **11a–f**, **12a–d**, **13a–d**)*

To the reaction mixture from step 1, the appropriate amine (4 equiv.) was added and the reaction mixture was stirred at room temperature until consumption of the corresponding benzotriazolyl intermediate (**4**, **9** or **10**) occurred. The mixture was diluted with EtOAc (25 mL) and washed with deionized water (3 x 50 mL) followed by brine (15 mL). The organic

layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings below).

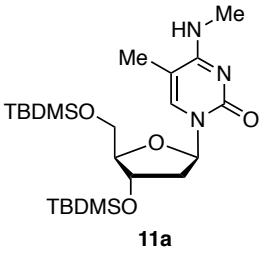
1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-4-(morpholin-4-yl)-5-methyl-2(*1H*)-pyrimidinone (6)



6

Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes and EtOAc gave compound **6** (86.9 mg, 76%) as a sticky, white solid. R_f (SiO_2/EtOAc) = 0.32. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.66 (s, 1H, H-6), 6.29 (t, J = 6.7 Hz, 1H, H-1'), 4.50 (dt, J = 2.8, 5.8 Hz, 1H, H-3'), 3.96 (app q, J_{app} ~ 3.2 Hz, 1H, H-4'), 3.90 (dd, J = 3.7, 11.3 Hz, 1H, H-5'), 3.86 (dd, J = 3.6, 11.4 Hz, 1H, H-5'), 3.70–3.66 (m, 4H, morpholinyl-CH_2), 3.65–3.61 (m, 4H, morpholinyl-CH_2), 2.30 (ddd, J = 2.9, 5.9, 13.3 Hz, 1H, H-2'), 2.15 (m, 4H, Me, and H-2'), 0.92 and 0.91 (2s, 18H, *t*-Bu), 0.13 and 0.12 (2s, 6H, SiMe), 0.11 and 0.10 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 166.9, 156.5, 142.2, 104.8, 88.7, 86.4, 73.3, 67.1, 63.8, 48.3, 42.0, 26.3, 26.1, 18.9, 18.5, 18.0, –4.5, –4.7, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{26}H_{49}N_3O_5Si_2Na$ $[M + Na]^+$: 562.3103, found 562.3107.

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*N*,5-dimethyl-2'-deoxycytidine (11a)

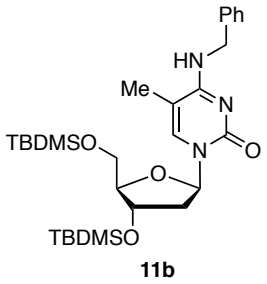


11a

Chromatography on a silica gel column by sequential elution with EtOAc and 1% MeOH in EtOAc, gave compound **11a** (85.8 mg, 84%) as a white solid. R_f (SiO_2/EtOAc) = 0.17. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 1H, H-6), 6.38 (t, J = 6.5 Hz, 1H, H-1'), 5.25 (br s, 1H, NH), 4.36 (dt, J = 3.3, 6.4 Hz, 1H, H-3'), 3.90–3.87 (m, 2H, H-4' and H-5'), 3.77–3.74 (m, 1H, H-5'), 3.06 (d, J = 4.7 Hz, 3H, NMe), 2.39 (ddd, J = 3.7, 6.1, 13.3 Hz, 1H, H-2'), 1.97 (dt, J = 6.6, 13.3 Hz,

1H, H-2'), 1.88 (s, 3H, Me), 0.92 and 0.88 (2s, 18H, *t*-Bu), 0.10 and 0.09 (2s, 6H, SiMe), 0.06 and 0.05 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 156.4, 136.5, 102.1, 87.6, 85.7, 71.9, 62.9, 42.1, 28.4, 26.1, 25.9, 18.5, 18.1, 13.3, –4.5, –4.7, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{23}H_{45}N_3O_4Si_2Na$ $[M + Na]^+$: 506.2841, found 506.2844**.**

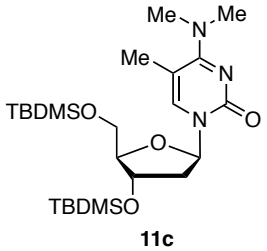
_N_-Benzyl-3',5'-di-_O_-(_t_-butyldimethylsilyl)-5-methyl-2'-deoxycytidine (11b)



11b

Chromatography on a silica gel column by elution with 50% EtOAc in hexanes gave compound **11b** (85.7 mg, 72%) as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.24. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.54 (s, 1H, H-6), 7.36 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.28 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.21 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.06–6.98 (m, 1H, NH), 6.35 (dd, *J* = 6.0, 7.7 Hz, 1H, H-1'), 4.70–4.68 (m, 2H, NCH_2), 4.50 (dt, *J* = 2.8, 5.7 Hz, 1H, H-3'), 3.92 (app q, $J_{app} \sim$ 3.1 Hz, 1H, H-4'), 3.90–3.84 (m, 2H, H-5'), 2.24 (ddd, *J* = 2.7, 5.8, 13.1 Hz, 1H, H-2'), 2.08–2.04 (m, 1H, H-2'), 1.99 (s, 3H, Me), 0.95 and 0.92 (2s, 18H, *t*-Bu), 0.15 and 0.14 (2s, 6H, SiMe), 0.13 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 164.1, 156.1, 140.6, 137.9, 128.9, 128.6, 127.5, 102.6, 88.3, 86.1, 73.6, 64.0, 44.6, 42.0, 26.4, 26.2, 18.9, 18.6, 13.6, –4.4, –4.6, –5.1, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{29}H_{49}N_3O_4Si_2Na$ $[M + Na]^+$: 582.3154, found 582.3156.

3',5'-Di-_O_-(_t_-butyldimethylsilyl)-_N_,_N_,5-trimethyl-2'-deoxycytidine (11c)

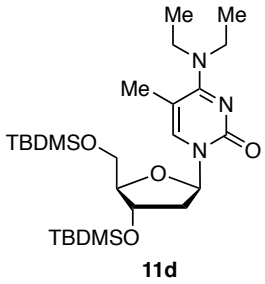


11c

Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes and EtOAc gave compound **11c** (79.9 mg, 76%) as a viscous, colorless liquid. R_f (SiO_2/EtOAc) = 0.35. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H, H-6), 6.34 (t, *J* = 6.4 Hz, 1H, H-1'), 4.35 (dt, *J* = 3.3, 6.4 Hz, 1H, H-3'), 3.90-3.86 (m, 2H, H-4' and H-5'), 3.75 (dd, *J* = 2.5, 11.1 Hz, 1H, H-5'), 3.13 (s, 6H, NMe_2), 2.37 (ddd, *J* = 3.8, 5.9, 13.3 Hz, 1H, H-2'), 2.13 (s, 3H, Me), 1.95 (dt,

J = 6.6, 13.3 Hz, 1H, H-2'), 0.91 and 0.87 (2s, 18H, *t*-Bu), 0.10 and 0.09 (2s, 6H, SiMe), 0.05 and 0.04 (2s, 6H, SiMe). HRMS (ESI/TOF) *m/z* calculated for $C_{24}H_{47}N_3O_4Si_2Na$ $[M + Na]^+$: 520.2997, found 520.2974. The ^1H NMR spectrum matches that of the material reported (H. Yamada, K. Tanabe, T. Ito, S.-I. Nishimoto, *Chem. Eur. J.*, 2008, **14**, 10453–10461).

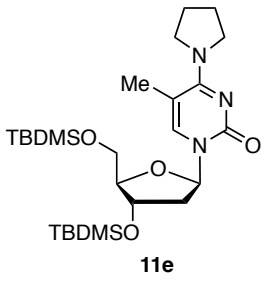
3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*N*,*N*-diethyl-5-methyl-2'-deoxycytidine (11d)



11d

Chromatography on a silica gel column by sequential elution with 25% EtOAc in hexanes and 50% EtOAc in hexanes gave compound **11d** (86.9 mg, 78%) as a viscous, colorless liquid. R_f (SiO_2/50% EtOAc in hexanes) = 0.24. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (s, 1H, H-6), 6.35 (t, *J* = 6.5 Hz, 1H, H-1'), 4.37 (dt, *J* = 3.2, 6.3 Hz, 1H, H-3'), 3.90–3.86 (m, 2H, H-4' and H-5'), 3.76 (dd, *J* = 2.0, 11.2 Hz, 1H, H-5'), 3.60–3.52 (m, 4H, NCH_2), 2.38 (ddd, *J* = 3.8, 5.7, 13.2 Hz, 1H, H-2'), 2.13 (s, 3H, Me), 1.99 (dt, *J* = 6.7, 13.3 Hz, 1H, H-2'), 1.20 (t, *J* = 7.0 Hz, 6H, Me), 0.92 and 0.88 (2s, 18H, *t*-Bu), 0.10 (s, 6H, SiMe), 0.06 and 0.05 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 155.4, 140.7, 102.2, 87.7, 85.8, 71.9, 62.9, 43.8, 42.2, 26.2, 26.0, 19.0, 18.6, 18.2, 14.0, –4.3, –4.7, –5.1, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{26}H_{52}N_3O_4Si_2$ $[M + H]^+$: 526.3491, found 526.3499.

1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-5-methyl-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (11e)

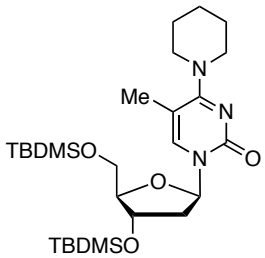


11e

Chromatography on a silica gel column by sequential elution with 40% EtOAc in hexanes and 75% EtOAc in hexanes gave compound **11e** (83.5 mg, 75%) as a viscous, colorless liquid. R_f (SiO_2/EtOAc) = 0.48. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H, H-6), 6.26 (t, *J* = 6.5 Hz, 1H, H-1'), 4.33 (dt, *J* = 3.1, 6.1 Hz, 1H, H-3'), 3.86 (app q, $J_{app} \sim 2.9$ Hz, 1H, H-4'), 3.82 (dd, *J* =

2.8, 11.3 Hz, 1H, H-5'), 3.73–3.71 (m, 5H, H-5' and $N(CH_2)_2$), 2.27 (ddd, *J* = 3.5, 6.0, 13.3 Hz, 1H, H-2'), 2.16 (s, 3H, Me), 1.95 (dt, *J* = 6.7, 13.4 Hz, 1H, H-2'), 1.92–1.84 (m, 4H, CH_2), 0.89 and 0.84 (2s, 18H, *t*-Bu), 0.07 and 0.06 (2s, 6H, SiMe), 0.03 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 163.4, 155.1, 140.1, 102.6, 88.2, 85.9, 73.6, 64.0, 49.7, 41.9, 26.3, 26.2, 25.9 (br), 18.9, 18.6, 18.2, –4.5, –4.6, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{26}H_{49}N_3O_4Si_2Na$ $[M + Na]^+$: 546.3154, found 546.3159.

1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-5-methyl-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (11f)

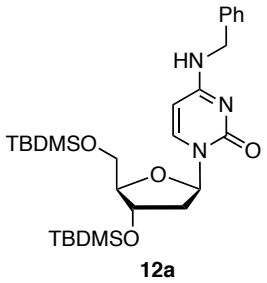


11f

Chromatography on a silica gel column by sequential elution with 25% EtOAc in hexanes and 50% EtOAc in hexanes gave compound **11f** (85.8 mg, 75%) as a viscous, colorless liquid. R_f (SiO_2/50% EtOAc in hexanes) = 0.28. ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (s, 1H, H-6), 6.35 (t, *J* = 6.5 Hz, 1H, H-1'), 4.36 (dt, *J* = 3.3, 6.4 Hz, 1H, H-3'), 3.92–3.86 (m, 2H, H-4' and H-5'), 3.75 (dd, *J* = 1.8, 10.7 Hz, 1H, H-5'), 3.55–3.50 (br m, 4H, NCH_2), 2.39 (ddd, *J* = 3.9, 6.1, 13.3 Hz, 1H, H-2'), 2.06 (s, 3H, Me), 1.99 (dt, *J* = 6.6, 13.3 Hz, 1H, H-2'), 1.69-1.58 (br m, 6H, $(CH_2)_3$), 0.92 and 0.88 (2s, 18H, *t*-Bu), 0.10 and 0.09 (2s, 6H, SiMe), 0.06 and 0.05 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 155.6, 140.8, 103.4, 87.6, 85.8, 71.7, 62.8, 48.4, 42.1, 26.2, 26.1, 25.9, 24.6, 18.5, 18.2, 18.1, –4.4, –4.8, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{27}H_{51}N_3O_4Si_2Na$ $[M + Na]^+$: 560.3310, found 560.3315.

***N*-benzyl-3',5'-Di-*O*-(*t*-butyldimethylsilyl)-2'-deoxycytidine (12a)**

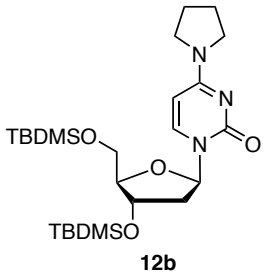
Chromatography on a silica gel column by sequential elution with 25% EtOAc in hexanes and 60% EtOAc in hexanes gave compound **12a** (93.6 mg, 78%) as a viscous, colorless



12a

liquid. R_f (SiO_2/50% EtOAc in hexanes) = 0.20. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.83 (d, J = 7.5 Hz, 1H, H-6), 7.36 (d, J = 7.2 Hz, 2H, Ar-H), 7.31 (t, J = 7.5 Hz, 2H, Ar-H), 7.24 (t, J = 7.2 Hz, 1H, Ar-H), 7.18–7.17 (br t, J = 6.0 Hz, 1H, NH), 6.30 (t, J = 6.3 Hz, 1H, H-1'), 5.83 (d, J = 7.5 Hz, 1H, H-5), 4.63–4.60 (m, 2H, NCH_2), 4.52 (dt, J = 3.7, 6.0 Hz, 1H, H-3'), 3.92–3.89 (m, 2H, H-4' and H-5'), 3.87–3.84 (m, 1H, H-2'), 2.30 (ddd, J = 4.2, 6.1, 13.2 Hz, 1H, H-2'), 2.11 (dt, J = 6.5, 13.1 Hz, 1H, H-2'), 0.94 and 0.92 (2s, 18H, *t*-Bu), 0.13 (s, 12H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 164.7, 156.4, 140.5, 140.0, 129.1, 128.6, 127.7, 95.5, 88.0, 86.2, 72.5, 63.4, 44.6, 42.2, 26.3, 26.2, 18.9, 18.5, –4.4, –4.6, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{47}N_3O_4Si_2Na$ $[M + Na]^+$: 568.2997, found 568.2996.

1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (12b)

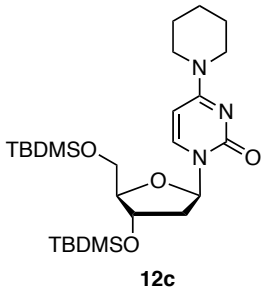


12b

Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes and EtOAc, gave compound **12b** (79.7 mg, 71%) as a white solid. R_f (SiO_2/EtOAc) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.6 Hz, 1H, H-6), 6.30 (t, J = 5.7 Hz, 1H, H-1'), 5.60 (d, J = 7.6 Hz, 1H, H-5), 4.36 (app q, J_{app} ~ 5.7 Hz, 1H, H-3'), 3.91 (dd, J = 2.4, 11.3 Hz, 1H, H-5'), 3.86 (dt, J = 2.4, 4.9 Hz, 1H, H-4'), 3.75 (dd, J = 2.2, 11.3 Hz, 1H, H-5'), 3.66 (t, J = 6.8 Hz, 2H, NC<u>H</u>H), 3.38 (t, J = 6.8 Hz, 2H, NCH<u>H</u>), 2.40 (dt, J = 6.4, 13.1 Hz, 1H, H-2'), 2.11–2.06 (m, 1H, H-2'), 2.04–1.97 (m, 2H, CH_2), 1.96–1.87 (m, 2H, CH_2), 0.92 and 0.86 (2s, 18H, *t*-Bu), 0.10 and 0.09 (2s, 6H, SiMe), 0.04 and 0.03 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 162.3, 155.7, 141.2, 93.0, 88.2, 86.3, 72.8, 63.6, 47.3, 42.3, 26.4, 26.2, 25.3, 18.9, 18.6, –4.4,

–4.6, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{25}H_{47}N_3O_4Si_2Na$ $[M + Na]^+$: 532.2997, found 532.2994.

1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (12c)

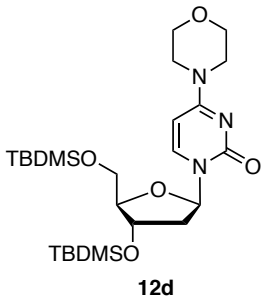


12c

Chromatography on a silica gel column by sequential elution with 30% EtOAc in hexanes and 60% EtOAc in hexanes, gave compound **12c** (86.4 mg, 75%) as a white solid. R_f (SiO_2/100% EtOAc) = 0.57. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.91 (d, *J* = 7.8 Hz, 1H, H-6), 6.30 (t, *J* = 6.4 Hz, 1H, H-1'), 6.28 (d, *J* = 7.8 Hz, 1H, H-5), 4.52 (dt, *J* = 3.2, 6.1 Hz, 1H, H-3'), 3.94–3.88 (m, 3H, H-4' and H-5'), 3.85 (dd, *J* = 2.9, 11.2 Hz, 1H, H-5'), 3.81–3.49 (br m, 4H, NCH_2), 2.30 (ddd, *J* = 3.9, 6.0, 13.2 Hz, 1H, H-2'), 2.21 (dt, *J* = 6.5, 13.2 Hz, 1H, H-2'), 1.71–1.64 (m, 2H, CH_2), 1.59–1.51 (br m, 4H, CH_2), 0.93 and 0.91 (2s, 18H, *t*-Bu), 0.13 (s, 6H, SiMe), 0.12 and 0.11 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): *δ* 163.1, 156.7, 141.7, 92.4, 88.3, 86.3, 72.8, 63.6, 47.0 (br), 45.2 (br), 42.2, 26.6 (br), 26.3, 26.1, 25.1, 18.9, 18.5, –4.5, –4.6, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{26}H_{49}N_3O_4Si_2Na$ $[M + Na]^+$: 546.3154, found 546.3159.

1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (12d)

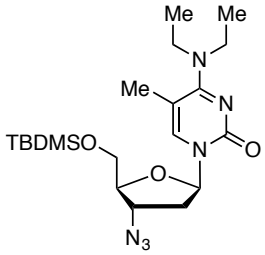
Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes followed by EtOAc, gave compound **12d** (87.5 mg, 76%) as a colorless liquid. R_f (SiO_2/EtOAc) = 0.48. ^{1}H NMR (500 MHz, acetone-d_6): *δ* 7.93 (d, *J* = 7.8 Hz, 1H, H-6), 6.27 (t, *J* = 6.3 Hz, 1H, H-1'), 6.01 (d, *J* = 7.8 Hz, 1H, H-5), 4.51 (dt, *J* = 3.5, 5.7 Hz, 1H, H-3'), 3.93–3.89 (m, 2H, H-4' and H-5'), 3.85 (dd, *J* = 2.4, 10.8 Hz, 1H, H-5'), 3.66 (br s, 8H, $O(CH_2)_2$ and



12d

N(CH_2)$_2$), 2.31 (ddd, *J* = 4.1, 6.0, 13.2 Hz, 1H, H-2'), 2.18 (dt, *J* = 6.5, 13.1 Hz, 1H, H-2'), 0.94 and 0.92 (2s, 18H, *t*-Bu), 0.13 and 0.12 (2s, 12H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0, 155.3, 142.1, 91.2, 88.3, 86.4, 72.8, 67.1, 63.6, 45.2 (br), 42.4, 26.4, 26.2, 18.9, 18.6, –4.4, –4.6, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{25}H_{47}N_3O_5Si_2Na$ [M + Na]$^+$: 548.2946, found 548.2950.

3'-Azido-5'-*O*-(*t*-butyldimethylsilyl)-*N*,*N*-diethyl-5-methyl-2',3'-dideoxycytidine (13a)

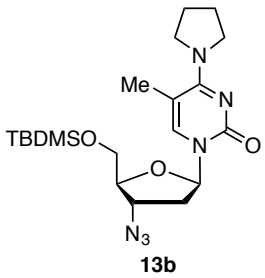


13a

Chromatography on a silica gel column by sequential elution with 25% EtOAc in hexanes and 75% EtOAc in hexanes gave compound **13a** (65.4 mg, 57%) as colorless, viscous liquid. R_f (SiO_2/EtOAc) = 0.35. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.52 (s, 1H, H-6), 6.18 (t, *J* = 6.5 Hz, 1H, H-1'), 4.43 (dt, *J* = 3.8, 7.3 Hz, 1H, H-3'), 4.00–3.94 (m, 2H, H-4' and H-5'), 3.92 (dd, *J* = 3.4, 11.1 Hz, 1H, H-5'), 3.58 (q, *J* = 7.0 Hz, 4H, NCH_2), 2.43 (ddd, *J* = 4.6, 6.1, 13.6 Hz, 1H, H-2'), 2.34 (dt, *J* = 6.9, 13.7 Hz, 1H, H-2'), 2.19 (s, 3H, Me), 1.19 (t, *J* = 7.0 Hz, 6H, Me), 0.94 (s, 9H, *t*-Bu), 0.15 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 165.0, 155.2, 141.6, 102.7, 86.1, 85.2, 64.0, 62.1, 44.2, 38.6, 26.3, 18.9, 18.8, 14.0, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{20}H_{36}N_6O_3SiNa$ [M + Na]$^+$: 459.2510, found 459.2519.

1-(3-Azido-5-*O*-(*t*-butyldimethylsilyl)-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (13b)

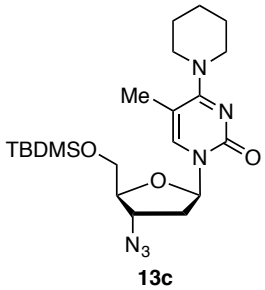
Chromatography on a silica gel column using EtOAc gave compound **13b** (60.4 mg, 53%) as a viscous, colorless liquid. R_f (SiO_2/EtOAc) = 0.27. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.43 (s, 1H, H-6), 6.19 (t, *J* = 6.6 Hz, 1H, H-1'), 4.42 (dt, *J* = 3.8, 7.4 Hz, 1H, H-3'), 3.97–3.90 (m, 3H, H-4', H-5', and H-5'), 3.73–3.63 (br m, 4H, NCH_2), 2.39 (ddd, *J* = 4.4, 6.3, 13.6 Hz, 1H, H-2'),



13b

2.30 (dt, *J* = 6.9, 13.7 Hz, 1H, H-2'), 2.20 (d, *J* = 0.9 Hz, 3H, Me), 1.93-1.85 (m, 4H, CH_2), 0.94 (s, 9H, *t*-Bu), 0.15 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 163.6, 154.9, 140.2, 102.7, 85.9, 85.0, 64.1, 62.1, 49.8, 38.5, 26.3, 25.9 (br), 18.9, 18.2, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{20}H_{34}N_6O_3SiNa$ [M + Na]$^+$: 457.2354, found 457.2365.

1-(3-Azido-5-*O*-(*t*-butyldimethylsilyl)-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (13c)

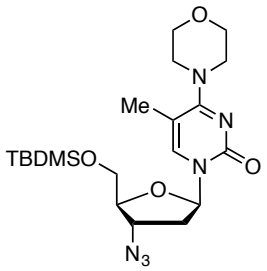


13c

Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes and EtOAc gave compound **13c** (74.1 mg, 63%) as a colorless, viscous liquid. R_f (SiO_2/EtOAc) = 0.55. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.57 (d, *J* = 0.7 Hz, 1H, H-6), 6.16 (t, *J* = 6.5 Hz, 1H, H-1'), 4.43 (dt, *J* = 4.1, 7.2 Hz, 1H, H-3'), 4.00–3.95 (m, 2H, H-4' and H-5'), 3.92 (dd, *J* = 3.3, 11.2 Hz, 1H, H-5), 3.51 (t, *J* = 5.2 Hz, 4H, NCH_2), 2.44 (ddd, *J* = 4.5, 6.3, 13.7 Hz, 1H, H-2'), 2.33 (dt, *J* = 6.9, 13.7 Hz, 1H, H-2'), 2.10 (d, *J* = 0.7 Hz, 3H, Me), 1.70–1.64 (m, 2H, CH_2), 1.64–1.58 (m, 4H, CH_2), 0.94 (s, 9H, *t*-Bu), 0.15 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 167.4, 155.1, 141.9, 103.6, 86.2, 85.2, 64.0, 62.0, 48.8, 38.7, 26.7, 26.3, 25.3, 18.9, 18.0, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{21}H_{36}N_6O_3SiNa$ [M + Na]$^+$: 471.2510, found 471.2506.

1-(3-Azido-5-*O*-(*t*-butyldimethylsilyl)-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (13d)

Chromatography on a silica gel column by sequential elution with 50% EtOAc in hexanes and EtOAc, gave compound **13d** (67.3 mg, 57%) as a colorless liquid. R_f (SiO_2/EtOAc) = 0.27. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.62 (s, 1H, H-6), 6.15 (t, *J* = 6.4 Hz, 1H, H-1'), 4.43



13d

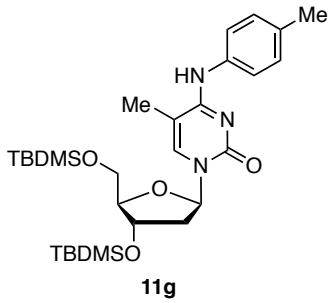
(dt, *J* = 4.3, 7.1 Hz, 1H, H-3'), 4.01 (app q, J_{app} ~ 3.7 Hz, 1H, H-4'), 3.97 (dd, *J* = 3.5, 11.3 Hz, 1H, H-5'), 3.93 (dd, *J* = 3.4, 11.3 Hz, 1H, H-5), 3.73–3.65 (m, 4H, morpholinyl–CH_2), 3.62–3.52 (m, 4H, morpholinyl–CH_2), 2.47 (ddd, *J* = 4.5, 6.3, 13.7 Hz, 1H, H-2'), 2.34 (dt, *J* = 6.9, 13.7 Hz, 1H, H-2'), 2.11 (s, 3H, Me), 0.94 (s, 9H, *t*-Bu), 0.15 (s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 167.5, 155.0, 142.3, 103.5, 86.4, 85.4, 67.3, 64.0, 62.0, 48.4, 38.7, 26.3, 18.9, 17.8, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{20}H_{34}N_6O_4SiNa$ [M + Na]$^+$: 473.2303, found 473.2302.

*Step 2 for p-toluidine (synthesis of **11g** and **12e**)*

The reaction mixture from step 1 was evaporated on a rotary evaporator and dried under high vacuum for 10 min. The residual material was dissolved in EtOH (2 mL), *p*-toluidine (2 equiv.) and iPr_2NEt (2 equiv.) were added, and the mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings below).

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-5-methyl-*N*-(*p*-tolyl)-2'-deoxycytidine (11g)

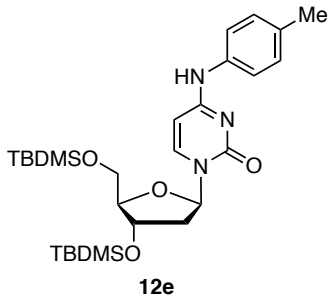
Chromatography on a silica gel column by sequential elution with 15% EtOAc in hexanes and 40% EtOAc in hexanes, gave compound **11g** (73.6 mg, 62%) as a light-brown solid. R_f (SiO_2/25% EtOAc in hexanes) = 0.14. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (br s, 3H, H-6, Ar-H), 7.36 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.67–6.40 (m, 1H, NH), 6.34 (t, *J* = 6.4 Hz, 1H, H-1'), 4.37 (dt, *J* = 3.3, 6.3 Hz, 1H, H-3'), 3.92–3.89 (m, 2H, H-4' and H-5'), 3.77 (dd, *J* = 2.3, 11.2 Hz, 1H,



11g

H-5'), 2.42 (br s, 1H, H-2'), 2.33 (s, 3H, ArMe), 2.03–1.98 (m, 4H, H-2', Me), 0.93 and 0.89 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 6H, SiMe), 0.07 and 0.06 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 155.6, 137.9, 135.8, 134.1, 129.6, 121.9, 102.2, 87.7, 86.0, 71.8, 62.9, 42.1, 26.1, 25.9, 21.0, 18.6, 18.2, 13.8, –4.4, –4.7, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{29}H_{50}N_3O_4Si_2$ $[M + H]^+$: 560.3334, found 560.3311.

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*N*-(*p*-tolyl)-2'-deoxycytidine (12e)



12e

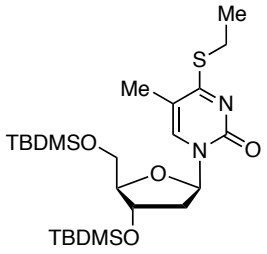
Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and 40% EtOAc in hexanes gave compound **12e** (74.1 mg, 64%), as a light-brown solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.24. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46–8.08 (br, 1H, NH), 8.19 (d, *J* = 7.4 Hz, 1H, H-6), 7.52–7.22 (br m, 2H, Ar-H), 7.22–7.11 (m, 2H, Ar-H), 6.32–6.27 (m, 1H, H-1'), 5.88 (d, *J* = 7.4 Hz, 1H, H–5), 4.41–4.34 (m, 1H, H-3'), 3.94–3.87 (m, 2H, H-4' and H-5'), 3.77 (d, *J* = 11.5 Hz, 1H, H-5'), 2.49–2.40 (m, 1H, H-2'), 2.34 (s, 3H, ArMe), 2.16-2.08 (m, H-2), 0.90 and 0.88 (2s, 18H, *t*-Bu), 0.09 (s, 6H, SiMe), 0.06 (s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9 (br), 155.8 (br), 141.7 (br), 135.3 (br), 130.0, 124.1 (br), 92.1 (br), 87.5, 86.2, 70.4, 62.1, 42.3, 26.1, 25.9, 21.1, 18.5, 18.1, –4.4, –4.8, –5.3, –5.4. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{48}N_3O_4Si_2$ $[M + H]^+$: 546.3178, found 546.3173.

*Step 2 for thiols (synthesis of **11h** and **11i**)*

The reaction mixture from step 1 was evaporated on a rotary evaporator and dried under high vacuum for 10 min. The residual material was dissolved in dry DME (2 mL), the appropriate thiol (0.425 mmol, 2 equiv.) and Cs_2CO_3 (138.1 mg, 0.425 mmol, 2 equiv.) were

added, and the mixture was stirred at room temperature until consumption of **9** occurred. The reaction mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a neutralized silica gel column using a suitable eluting solvent (see individual compound headings below and the General Experimental Considerations).

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*S*^{4}-ethyl-4-thiothymidine (11h)

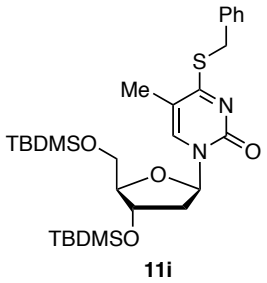


11h

Chromatography on a neutralized silica gel column by sequential elution with 5% EtOAc in hexanes and 10% EtOAc in hexanes gave compound **11h** (74.4 mg, 68%) as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.75. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.73 (d, J = 0.4 Hz, 1H, H-6), 6.20 (t, J = 6.6 Hz, 1H, H-1'), 4.52 (dt, J = 2.9, 5.8 Hz, 1H, H-3'), 4.02 (app q, J_{app} ~ 3.1 Hz, 1H, H-4'), 3.93 (dd, J = 3.6, 11.4 Hz, 1H, H-5'), 3.89 (dd, J = 3.3, 11.4 Hz, 1H, H-5'), 3.15 (q, J = 7.4 Hz, 2H, SCH_2) 2.43 (ddd, J = 3.0, 5.9, 13.3 Hz, 1H, H-2'), 2.15 (ddd, J = 6.1, 7.2, 13.3 Hz, 1H, H-2'), 1.99 (d, J = 0.6 Hz, 3H, Me), 1.31 (t, J = 7.3 Hz, 3H, Me), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.14 (2s, 6H, SiMe), 0.13 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 177.6, 153.5, 138.4, 111.2, 88.9, 87.3, 73.3, 63.7, 42.5, 26.3, 26.2, 24.3, 18.9, 18.5, 14.5, 14.3, –4.5, –4.7, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{24}H_{46}N_2O_4SSi_2Na$ $[M + Na]^+$: 537.2609, found 537.2611.

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*S*^{4}-benzyl-4-thiothymidine (11i)

Chromatography on a neutralized silica gel column by sequential elution with 5% EtOAc in hexanes, 7% EtOAc in hexanes, and 10% EtOAc in hexanes gave compound **11i** (85.6 mg, 70%) as a white solid. R_f (SiO_2/25% EtOAc in hexanes) = 0.57. ^{1}H NMR (500 MHz, acetone-



11i

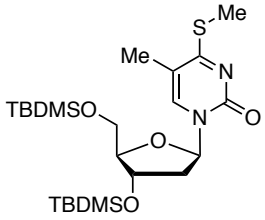
d_6): δ 7.77 (s, 1H, H-6), 7.46 (d, J = 7.2 Hz, 2H, Ar-H), 7.31 (t, J = 7.4 Hz, 2H, Ar-H), 7.25 (t, J = 7.3 Hz, 1H, Ar-H), 6.23 (t, J = 6.6 Hz, 1H, H-1'), 4.53 (dt, J = 2.9, 5.8 Hz, 1H, H-3'), 4.45 (s, 2H, SCH_2), 4.03 (app q, J_{app} ~ 3.2 Hz, 1H, H-4'), 3.94 (dd, J = 3.6, 11.4 Hz, 1H, H-5'), 3.89 (dd, J = 3.3, 11.4 Hz, 1H, H-5'), 2.45 (ddd, J = 3.1, 5.9, 13.3 Hz, 1H, H-2'), 2.17 (ddd, J = 6.2, 7.1, 13.3 Hz, 1H, H-2'), 1.99 (s, 3H, Me), 0.93 (2s, 18H, *t*-Bu), 0.14 (2s, 12H, SiMe). ^{13}C NMR (125 MHz, acetone-d_6): δ 177.1, 153.5, 138.9, 138.3, 130.1, 129.3, 128.0, 111.1, 89.1, 87.5, 73.4, 63.8, 42.5, 34.1, 26.3, 26.2, 18.9, 18.5, 14.3, –4.4, –4.6, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{29}H_{48}N_2O_4SSi_2Na$ $[M + Na]^+$: 599.2766, found 599.2764.

*Step 2 for NaSMe (synthesis of **11j**)*

The reaction mixture from step 1 was evaporated on a rotary evaporator and dried under high vacuum for 10 min. The residual material was dissolved in dry DMSO (1 mL) and NaSMe (29.7 mg, 2 equiv.) was added, and the mixture and stirred at 50 °C for 2 h. The reaction mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified on a neutralized silica gel column by sequential elution with 10% EtOAc in hexanes, 15% EtOAc in hexanes, 20% EtOAc in hexanes, and 50% EtOAc in hexanes to give: **18** (6.5 mg, 5%) as an off-white solid, **11j** (52.4 mg, 49%) as a colorless, viscous oil, and **17** (15.4 mg, 12%) as an off-white solid.

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*S*^{4}-methyl-4-thiothymidine (11j)

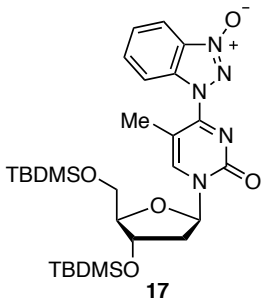
R_f (SiO_2/50% EtOAc in hexanes) = 0.67. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1H, H-6), 6.27 (t, J = 6.3 Hz, 1H, H-1'), 4.36 (dt, J = 3.6, 6.4 Hz, 1H, H-3'), 3.96 (app q, J_{app} ~ 3.0 Hz, 1H, H-4'),



11j

3.91 (dd, *J* = 2.6, 11.4 Hz, 1H, H-5'), 3.77 (dd, *J* = 2.5, 11.4 Hz, 1H, H-5'), 2.56 (s, 3H, SMe), 2.51 (ddd, *J* = 4.0, 6.2, 13.4 Hz, 1H, H-2'), 2.04-1.99 (m, 4H, H-2', Me), 0.91 and 0.89 (2s, 18H, *t*-Bu), 0.11 and 0.10 (2s, 6H, SiMe), 0.07 and 0.06 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 154.0, 136.9, 111.7, 88.2, 86.8, 71.6, 62.7, 42.5, 26.1, 26.0, 18.6, 18.2, 14.5, 13.3, –4.3, –4.7, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{23}H_{45}N_2O_4SSi_2$ [M + H]$^+$: 501.2633, found 501.2631.

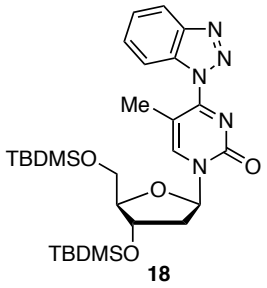
1-(3,5-Di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-5-methyl-4-(3-oxido-1*H*-benzotriazol-1-yl)-2(*1H*)-pyrimidinone (17)



17

R_f (SiO_2/50% EtOAc in hexanes) = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 8.6 Hz, 1H, Ar-H), 8.19 (s, 1H, H-6), 8.02 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.75 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.55 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.30 (t, *J* = 6.3 Hz, 1H, H-1'), 4.40 (dt, *J* = 3.1, 6.1 Hz, 1H, H-3'), 4.07 (app q, J_{app} ~ 2.8 Hz, 1H, H-4'), 3.95 (dd, *J* = 2.5, 11.5 Hz, 1H, H-5'), 3.80 (dd, *J* = 2.4, 11.5 Hz, 1H, H-5'), 2.64 (ddd, *J* = 3.6, 6.1, 13.5 Hz, 1H, H-2'), 2.50 (s, 3H, Me), 2.09 (dt, *J* = 6.5, 13.3 Hz, 1H, H-2'), 0.91 and 0.90 (2s, 18H, *t*-Bu), 0.12 and 0.11 (2s, 6H, SiMe), 0.09 and 0.08 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 154.0, 146.0, 133.9, 132.5, 131.9, 126.8, 118.6, 115.3, 105.3, 89.0, 87.9, 72.0, 62.9, 42.8, 26.1, 25.9, 18.6, 18.4, 18.2, –4.3, –4.7, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{46}N_5O_5Si_2$ [M + H]$^+$: 588.3032, found 588.3032.

4-(1*H*-Benzotriazol-1-yl)-1-(3,5-di-*O*-(*t*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl)-5-methyl-2(*1H*)-pyrimidinone (18)



18

R_f (SiO_2/20% EtOAc in hexanes) = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H, H-6), 8.07 (d, J = 8.4 Hz, 1H, Ar-H), 7.52 (t, J = 7.5 Hz, 1H, Ar-H), 7.44–7.40 (m, 2H, Ar-H), 6.19 (t, J = 6.2 Hz, 1H, H-1'), 4.38 (dt, J = 3.4, 6.3 Hz, 1H, H-3'), 4.00 (app q, J_{app} ~ 2.9 Hz, 1H, H-4'), 3.96 (dd, J = 2.2, 11.5 Hz, 1H, H-5'), 3.80 (dd, J = 2.0, 11.5 Hz, 1H, H-5'), 2.51 (ddd, J = 4.1, 6.0, 13.4 Hz, 1H, H-2'), 2.28 (s, 3H, Me), 2.02 (dt, J = 6.4, 13.2 Hz, 1H, H-2'), 0.96 and 0.88 (2s, 18H, *t*-Bu), 0.16 and 0.14 (2s, 6H, SiMe), 0.07 (s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 154.0, 144.1, 143.8, 129.1, 128.9, 125.0, 120.8, 108.9, 100.7, 88.6, 87.6, 71.6, 62.7, 42.7, 26.2, 26.0, 18.7, 18.2, 12.2, –4.3, –4.7, –5.1. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{46}N_5O_5Si_2$ $[M + H]^+$: 588.3032, found 588.3018.

*One-step procedure for aliphatic amines (synthesis of **6**, **11a–f**, **12a–d**, **13a–d**)*

To a 0.424 M solution of the nucleoside derivative (**2:** 0.212 mmol, **7:** 0.219 mmol, **8:** 0.262 mmol) in THF, BOP (2 equiv.) and DBU (2 equiv.) were added, and the mixture was stirred at room temperature for 5 min. Then an *appropriate amine* (4 equiv.) was added to the mixture and the stirring was continued at room temperature until the consumption of the starting material was observed. The mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings above).

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*N*,5-dimethyl-2'-deoxycytidine (11a)

Chromatography on a silica gel column by sequential elution with EtOAc and 1% MeOH in EtOAc gave compound **11a** (92.6 mg, 90%) as a white solid, and the starting material **2** (7 mg, 7%).

*One-step procedure for reaction with p-toluidine (synthesis of **11g** and **12e**)*

To a solution of the nucleoside derivative (**2:** 0.212 mmol, **7:** 0.219 mmol) in dry CH_3CN (2 mL), BOP (2 equiv.) and DBU (4 equiv.) were added, and the mixture was stirred at room temperature for 5 min. Then *p*-toluidine (2 equiv.) was added and the mixture was stirred at 50 °C for 16 h. The mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaaporated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings above).

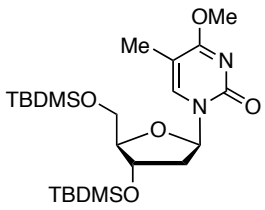
*One-step procedure for reactions with thiols (synthesis of **11i–j**)*

To a solution of nucleoside derivative **2** (100 mg, 0.212 mmol, 1 equiv.) in dry DME (2 mL), BOP (188 mg, 0.425 mmol, 2 mol equiv) and DBU (127 µL, 0.850 mmol, 4 mol equiv) were added, and the mixture was stirred at room temperature for 5 min. Then an *appropriate thiol* (0.425 mmol, 2 equiv.) was added to the mixture and the stirring was continued at room temperature for 3 h. The reaction mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a neutralized silica gel column using a suitable eluting solvent (see individual compound headings above).

*Procedure for reactions with methyl and cyclohexyl alcohols (synthesis of **14a**, **14b**, and **15**)*

The reaction mixture from step 1 was evaporated on a rotary evaporator and dried under high vacuum for 10 min. The residual material was dissolved in the appropriate alcohol (20 equiv.) and DBU (2 equiv.) was added, and the mixture was stirred at room temperature until consumption of the corresponding benzotriazolyl ether intermediate was observed. The reaction mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings below).

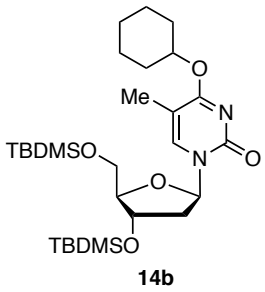
3',5'-Di-*O*-(*t*-butyldimethylsilyl)-O^4-methylthymidine (14a)



14a

Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and 40% EtOAc in hexanes gave compound **14a** (93.4 mg, 91%) as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.56. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H, H-6), 6.28 (t, J = 6.4 Hz, 1H, H-1'), 4.32 (dt, J = 3.3, 6.3 Hz, 1H, H-3'), 3.91 (s, 3H, OMe), 3.88 (app q, J_{app} ~ 2.8 Hz, 1H, H-4'), 3.84 (dd, J = 2.5, 11.4 Hz, 1H, H-5'), 3.71 (dd, J = 2.3, 11.3 Hz, 1H, H-5'), 2.39 (ddd, J = 3.7, 6.1, 13.3 Hz, 1H, H-2'), 1.94 (dt, J = 6.6, 13.3 Hz, 1H, H-2'), 1.87 (s, 3H, Me), 0.86 and 0.82 (2s, 18H, *t*-Bu), 0.05 and 0.04 (2s, 6H, SiMe), 0.01 and 0.00 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 155.9, 139.4, 104.2, 87.9, 86.3, 71.7, 62.6, 54.5, 42.2, 25.9, 25.8, 18.4, 18.0, 12.3, –4.6, –4.9, –5.3, –5.4. HRMS (ESI/TOF) *m/z* calculated for $C_{23}H_{45}N_2O_5Si_2$ [M + H]$^+$: 485.2862, found 485.2863.

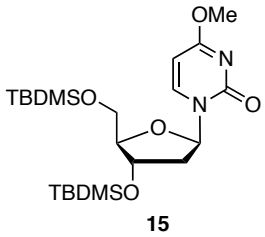
3',5'-Di-*O*-(*t*-butyldimethylsilyl)-O^4-(cyclohex-1-yl)thymidine (14b)



14b

Chromatography on a silica gel column by elution with 20% EtOAc in hexanes gave compound **14b** (80.0 mg, 88%) as a colorless liquid. R_f (SiO_2/20% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H, H-6), 6.38 (t, J = 6.4 Hz, 1H, H-1'), 5.35–5.28 (m, 1H, OCH), 4.37 (dt, J = 3.3, 6.5 Hz, 1H, H-3'), 3.93 (app q, J_{app} ~ 2.9 Hz, 1H, H-4'), 3.89 (dd, J = 2.6, 11.3 Hz, H-5'), 3.76 (dd, J = 2.4, 11.3 Hz, H-5'), 2.44 (ddd, J = 3.7, 6.2, 13.3 Hz, 1H, H-2'), 1.99 (dt, J = 6.6, 13.3 Hz, 1H, H-2'), 1.96–1.86 (m, 5H, Me, and cyclohexyl-H), 1.77–1.67 (m, 2H, cyclohexyl-H), 1.58–1.48 (m, 2H, cyclohexyl-H), 1.47–1.38 (m, 2H, cyclohexyl-H), 1.36–1.23 (m, 2H, cyclohexyl-H), 0.92 and 0.88 (2s, 18H, *t*-Bu), 0.11 and 0.09 (2s, 6H, SiMe), 0.06 and 0.05 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 156.4, 139.3, 105.1, 87.9, 86.3, 74.4, 71.7, 62.8, 42.4, 31.6, 26.1, 26.0, 25.7, 23.7, 18.6, 18.2, 12.7, –4.4, –4.7, –5.1, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{52}N_2O_5Si_2Na$ $[M + Na]^+$: 575.3307, found 575.3309.

3',5'-Di-*O*-(*t*-butyldimethylsilyl)-*O*^{4}-methyl-2'-deoxyuridine (15)



15

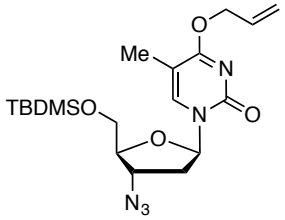
Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and 40% EtOAc in hexanes gave compound **15** (88.0 mg, 85%) as a colorless, viscous liquid. R_f (SiO_2/50% EtOAc in hexanes) = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, J = 7.4 Hz, 1H, H-6), 6.24 (dd, J = 4.8, 6.4 Hz, 1H, H-1'), 5.81 (d, J = 7.4 Hz, 1H, H-5), 4.35 (app q, J_{app} ~ 5.7 Hz, 1H, H-3'), 3.94–3.91 (m, 4H, H-5', OMe), 3.89 (dt, J = 2.3, 4.8 Hz, 1H, H-4'), 3.75 (dd, J = 1.9, 11.4 Hz, 1H, H-5'), 2.45 (dt, J = 6.5, 13.2 Hz, 1H, H-2'), 2.09 (ddd, J = 4.8, 6.4, 13.4 Hz, 1H, H-2'), 0.89 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*-Bu), 0.08 and 0.07 (2s, 6H, SiMe), 0.03 and 0.02 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 156.0, 143.0, 95.2, 87.6, 86.6, 70.0, 61.9,

54.5, 42.4, 26.0, 25.9, 18.5, 18.1, –4.4, –4.8, –5.3, –5.4. HRMS (ESI/TOF) *m/z* calculated for $C_{22}H_{42}N_2O_5Si_2Na$ $[M + Na]^+$: 493.2524, found 493.2524.

*Procedure for reactions with allyl and benzyl alcohols (synthesis of **16a** and **16b**)*

To the reaction mixture from step 1, the appropriate alcohol (0.525 mmol, 2 equiv.), and DBU (0.525 mmol, 2 mol equiv) were added, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with EtOAc (25 mL), washed with deionized water (3 x 50 mL), and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on a silica gel column using a suitable eluting solvent (see individual compound headings below).

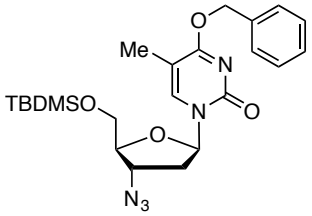
O^4-Allyl-3'-azido-5'-*O*-*t*-butyldimethylsilyl-2',3'-dideoxythymidine (16a)



16a

Chromatography on a silica gel column eluted with 30% EtOAc in hexanes gave compound **16a** (61.6 mg, 56%) as a colorless liquid. R_f (SiO_2/20% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H, H-6), 6.21 (t, J = 6.0 Hz, 1H, H-1'), 6.04 (ddt, J = 5.7, 11.0, 16.9 Hz, 1H, =CH), 5.38 (dd, J = 1.0, 17.2 Hz, 1H, $=CH_{trans}$), 5.26 (dd, J = 0.7, 10.5 Hz, 1H, $=CH_{cis}$), 4.89 (d, J = 5.4 Hz, 2H, OCH_2), 4.43 (app q, J = 5.9 Hz, 1H, H-3'), 4.00–3.96 (m, 2H, H-4' and H-5'), 3.81 (dd, J = 2.7, 11.7 Hz, 1H, H-5'), 2.62 (dt, J = 5.9, 13.7 Hz, 1H, H-2'), 2.24 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 1.96 (s, 3H, Me), 0.92 (s, 9H, *t*-Bu), 0.12 and 0.11 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 155.8, 139.4, 132.3, 118.3, 104.5, 86.3, 84.9, 67.9, 62.7, 60.0, 39.0, 26.0, 18.5, 12.5, –5.2, –5.3. HRMS (ESI/TOF) *m/z* calculated for $C_{19}H_{31}N_5O_4SiNa$ $[M + Na]^+$: 444.2038, found 444.2038.

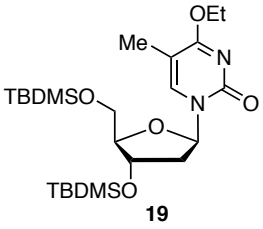
3'-Azido- *O*^{4}-benzyl-5'-*O*-*t*-butyldimethylsilyl-2',3'-dideoxythymidine (16b)



16b

Chromatography on a silica gel column eluted with 30% EtOAc in hexanes gave compound **16b** (105.0 mg, 85%) as a colorless liquid. R_f (SiO_2/40% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, H-6), 7.42 (d, J = 6.9 Hz, 2H, Ar-H), 7.38 (t, J = 7.2 Hz, 2H, Ar-H), 7.33 (t, J = 7.1 Hz, 1H, Ar-H), 6.23 (t, J = 6.0 Hz, 1H, H-1'), 5.44 (ABq, $\Delta\Upsilon_{AB}$ = 11.9 Hz, J_{AB} = 12.7 Hz, 2H, OCH_2), 4.20–4.17 (m, 1H, H-3'), 4.01–3.96 (m, 2H, H-4' and H-5'), 3.81 (dd, J = 2.9, 12.2 Hz, 1H, H-5'), 2.63 (dt, J = 5.8, 13.7 Hz, 1H, H-2'), 2.25 (ddd, J = 6.2, 7.1, 13.5 Hz, 1H, H-2'), 1.97 (s, 3H, Me), 0.92 (s, 9H, *t*-Bu), 0.13 and 0.12 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 155.9, 139.5, 136.1, 128.7, 128.4, 128.2, 104.6, 86.3, 85.0, 69.0, 62.7, 60.0, 39.1, 26.1, 18.6, 12.6, –5.1, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{23}H_{33}N_5O_4SiNa$ $[M + Na]^+$: 494.2194, found 494.2194.

Undesired 3',5'-di-*O*-(*t*-butyldimethylsilyl)-*O*^{4}-ethylthymidine (19) obtained in a reaction with NaSMe



19

To a solution of the nucleoside derivative **2** (100 mg, 0.212 mmol, 1 equiv.) in THF (0.5 mL), BOP (187.5 mg, 0.424 mmol, 2 mol equiv) and DBU (64 µL, 0.424 mmol, 2 mol equiv) were added, and the mixture was stirred at room temperature for 30 min. The mixture was evaporated on a rotary evaporator and dried under high vacuum for 10 min. The residual material was then dissolved in dry EtOH (1 mL), NaSMe (59.4 mg, 0.848 mmol, 4 equiv.) was added, and the mixture was stirred at room temperature for 12 h. The mixture was evaporated and the crude material was loaded onto a silica gel column. Sequential elution with 15% hexanes in EtOAc and 30% hexanes in EtOAc gave compound **19** (77.5 mg, 73%)

as a colorless, viscous liquid. R_f (SiO_2/50% EtOAc in hexanes) = 0.68. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H, H-6), 6.32 (t, J = 6.4 Hz, 1H, H-1'), 4.42 (t, J = 7.1 Hz, 2H, OCH_2), 4.35 (dt, J = 3.3, 6.3 Hz, 1H, H-3'), 3.91 (app q, J_{app} ~ 2.8 Hz, 1H, H-4'), 3.88 (dd, J = 2.6, 11.3 Hz, 1H, H-5'), 3.74 (dd, J = 2.5, 11.3 Hz, 1H, H-5'), 2.42 (ddd, J = 3.7, 6.1, 13.3 Hz, 1H, H-2'), 1.97 (dt, J = 6.6, 13.3 Hz, 1H, H-2'), 1.90 (s, 3H, Me), 1.33 (q, J = 7.1 Hz, 3H, Me), 0.89 and 0.86 (2s, 18H, *t*-Bu), 0.09 and 0.08 (2s, 6H, SiMe), 0.04 and 0.03 (2s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 156.1, 139.4, 104.5, 88.0, 86.4, 71.8, 63.3, 62.8, 42.4, 26.0, 25.9, 18.5, 18.2, 14.4, 12.5, –4.4, –4.7, –5.2. HRMS (ESI/TOF) *m/z* calculated for $C_{24}H_{46}N_2O_5Si_2Na$ $[M + Na]^+$: 521.2837, found 521.2858.

General procedure for the evaluation of various products formed with BOP from two commercial suppliers

To a solution of **2** (100.0 mg, 0.212 mmol, 1 equiv.) in dry THF (0.5 mL), BOP (188.0 mg, 0.424 mmol, 2 equiv.) and DBU were added, and the mixture was stirred at room temperature for a certain period of time.

Table 4: reactions with BOP from supplier 1 (Chem-Impex)

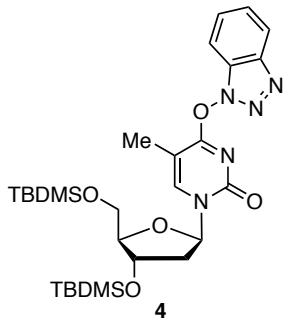
Conditions 1. DBU (64 μL, 0.424 mmol, 2 equiv.) was used. The reaction mixture was stirred for 0.5 h and then evaporated. Chromatography through a plug of neutralized silica gel by initial elution with 15% EtOAc in hexanes gave compound **18** (1.0 mg, 1%) as a white solid. Subsequent elution with 25% EtOAc in hexanes gave a mixture of compounds **4** (39.1 mg, 31%) and **2** (14.1 mg, 14%) as a white, sticky solid. Further elution with 50% EtOAc in hexanes gave compound **17** (21.9 mg, 18%) as a white solid. Yields of **4** and **2** were calculated on the basis of the integration in the ^{1}H NMR spectrum of the mixture.

Conditions 2. DBU (64 μL, 0.424 mmol, 2 equiv.) was used. The reaction mixture was stirred for 24 h and then evaporated. Chromatography through a plug of neutralized silica gel by initial elution with 30% EtOAc in hexanes gave a mixture of compounds **18** (12.0 mg, 10%) and **4** (39.1 mg, 31%) as a white solid. Subsequent elution with 50% EtOAc in hexanes gave compound **17** (39.4 mg, 32%) as a white solid. Yields of **18** and **4** were calculated on the basis of the integration in the ^{1}H NMR spectrum of the mixture.

Table 4: reactions with BOP from supplier 2 (Sigma-Aldrich)

Conditions 1. DBU (64 μL, 0.424 mmol, 2 equiv.) was used. The reaction mixture was stirred for 0.5 h and then evaporated. Chromatography through a plug of neutralized silica gel by initial elution with 30% EtOAc in hexanes gave compound **4** (73.0 mg, 59%) as a white solid. Subsequent elution with 50% EtOAc in hexanes gave compound **17** (29.3 mg, 23%) as a white solid.

***O*^{4}-(1*H*-Benzotriazol-1-yl)-3',5'-di-*O*-(*t*-butyldimethylsilyl)thymidine (4)**



4

R_f (SiO_2/20% EtOAc in hexanes) = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H, H-6), 8.07 (d, J = 8.4 Hz, 1H, Ar-H), 7.52 (t, J = 7.5 Hz, 1H, Ar-H), 7.44–7.40 (m, 2H, Ar-H), 6.19 (t, J = 6.2 Hz, 1H, H-1'), 4.38 (dt, J = 3.4, 6.3 Hz, 1H, H-3'), 4.00 (app q, J_{app} ~ 2.9 Hz, 1H, H-4'), 3.96 (dd, J = 2.2, 11.5 Hz, 1H, H-5'), 3.80 (dd, J = 2.0, 11.5 Hz, 1H, H-5'), 2.51 (ddd, J = 4.1, 6.0, 13.4 Hz, 1H, H-2'), 2.28 (s, 3H, Me), 2.02 (dt, J = 6.4, 13.2 Hz, 1H, H-2'), 0.96 and 0.88 (2s, 18H, *t*-Bu), 0.16 and 0.14 (2s, 6H, SiMe), 0.07 (s, 6H, SiMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 154.0, 144.1, 143.8, 129.1, 128.9, 125.0, 120.8, 108.9, 100.7, 88.6,

87.6, 71.6, 62.7, 42.7, 26.2, 26.0, 18.7, 18.2, 12.2, –4.3, –4.7, –5.1. HRMS (ESI/TOF) *m/z* calculated for $C_{28}H_{46}N_5O_5Si_2$ $[M + H]^+$: 588.3032, found 588.3018.

Conditions 2. DBU (64 μL, 0.424 mmol, 2 equiv.) was used. The reaction mixture was stirred for 24 h and then evaporated. Chromatography through a plug of neutralized silica gel by initial elution with 30% EtOAc in hexanes gave a mixture of compounds **18** (4.2 mg, 3%) and **4** (27.0 mg, 22%) as a white solid. Subsequent elution with 50% EtOAc in hexanes gave compound **17** (57.4 mg, 46%) as a white solid. Yields of **18** and **4** were calculated on the basis of the integration in ^{1}H NMR spectrum of the mixture.

Conditions 3. DBU (127 μL, 0.424 mmol, 4 equiv.) was used. The reaction was stirred for 24 h and then evaporated. Chromatography through a plug of neutralized silica gel by initial elution with 30% EtOAc in hexanes gave a mixture of compounds **18** (31.4 mg, 26%) as a white solid. Subsequent elution with 50% EtOAc in hexanes gave compound **17** (10.5 mg, 8%) as a white solid.

Procedure for the deoxygenation of 17 to 18 with $B_2(OH)_4$

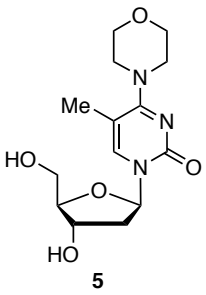
To a solution of *N*-oxide **17** (20 mg, 0.034 mmol, 1 mol equiv) in dry MeCN (0.2 mL) $B_2(OH)_4$ (3.7 mg, 0.041 mmol, 1.2 equiv.) was added, and the mixture was stirred at 60 °C for 2 h. The mixture was then evaporated and the crude material was purified on a silica gel column eluted with 30% EtOAc in hexanes to give compound **18** (18.8 mg, 97%) as a white solid.

Procedure for desilylation reactions

Method A *(with n-Bu_4NF/THF for synthesis of **5**, **20b–i**, **21a–d**, **22a–d**, **23b**, **25a–b**)*

To a 0.115 M solution of the appropriate nucleoside (1 equiv.) in dry THF, *n*-Bu_4NF (1 M solution in THF, 2.4 equiv.) was added, and the mixture was stirred at room temperature for 20 min. The mixture was evaporated and the crude material was purified by chromatography on a short silica gel column using a suitable eluting solvent (see individual compound headings below)

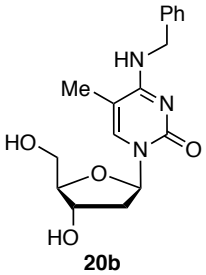
1-(2-Deoxy-β-D-ribofuranosyl)-5-methyl-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (5)



5

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **5** (83.4 mg, 96%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.18. ^{1}H NMR (500 MHz, CD_3OD): δ 7.98 (s, 1H, H-6), 6.26 (t, J = 6.4 Hz, 1H, H-1'), 4.41 (dt, J = 3.7, 6.4 Hz, 1H, H-3'), 3.96 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.85 (dd, J = 3.1, 12.1 Hz, 1H, H-5'), 3.78–3.75 (m, 5H, morpholinyl–CH_2 and H-5'), 3.72–3.70 (m, 4H, morpholinyl–CH_2), 2.39 (ddd, J = 4.0, 6.1, 13.5 Hz, 1H, H-2'), 2.21–2.14 (m, 4H, Me and H-2'). ^{13}C NMR (125 MHz, CD_3OD): δ 167.4, 157.5, 143.6, 105.8, 88.9, 87.6, 71.8, 67.8, 62.6, 48.8, 42.1, 17.9. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{21}N_3O_5Na$ $[M + Na]^+$: 334.1373, found 334.1366.

***N*-Benzyl-5-methyl-2'-deoxycytidine (20b)**

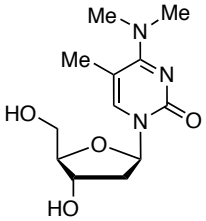


20b

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **20b** (54.2 mg, 92%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.24. ^{1}H NMR (500 MHz, CD_3OD): δ 7.82 (s, 1H, H-6), 7.35 (d, J = 7.1 Hz, 2H, Ar-H), 7.31 (t, J = 7.5 Hz, 2H, Ar-H), 7.23 (t, J = 7.2 Hz, 1H, Ar-H), 6.30 (t, J = 6.5 Hz, 1H, H-1'), 4.71 (s, 2H, CH_2), 4.40 (dt, J = 3.3, 6.4 Hz, 1H, H-3'), 3.94 (app q, J_{app} ~ 3.4 Hz, 1H, H-4'), 3.84 (dd, J = 3.1, 12.1 Hz, 1H, H-5'), 3.76 (dd, J = 3.8, 12.1 Hz, 1H, H-5'), 2.34 (ddd, J = 3.8, 5.9, 13.5 Hz, 1H, H-2'), 2.17 (dt, J = 6.7,

13.5 Hz, 1H, H-2'), 2.00 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 164.9, 158.6, 140.3, 138.9, 129.3, 128.6, 128.0, 104.9, 88.7, 87.3, 72.0, 62.8, 45.1, 41.9, 13.2. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{21}N_3O_4Na$ [M + Na]$^+$: 354.1424, found 354.1440.

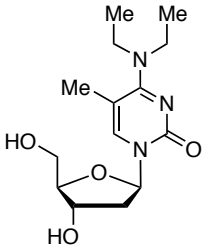
N,N,5-Trimethyl-2'-deoxycytidine (20c)



20c

Chromatography on a silica gel column by sequential elution with EtOAc and 20% MeOH in EtOAc gave compound **20c** (51.5 mg, 96%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.10. ^{1}H NMR (500 MHz, CD_3OD): δ 7.81 (s, 1H, H-6), 6.23 (t, *J* = 6.5 Hz, 1H, H-1'), 4.38 (dt, *J* = 3.4, 6.5 Hz, 1H, H-3'), 3.92 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.81 (dd, *J* = 3.2, 12.0 Hz, 1H, H-5'), 3.73 (dd, *J* = 3.7, 12.0 Hz, 1H, H-5'), 3.21 (s, 6H, NMe_2), 2.32 (ddd, *J* = 3.8, 6.1, 13.5 Hz, 1H, H-2'), 2.25 (s, 3H, Me), 2.15 (dt, *J* = 6.7, 13.5 Hz, 1H, H-2'). ^{13}C NMR (125 MHz, CD_3OD): δ 166.9, 157.4, 142.3, 105.2, 88.8, 87.3, 71.9, 62.7, 41.9, 40.6, 18.7. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{19}N_3O_4Na$ [M + Na]$^+$: 292.1268, found 292.1272.

N,N-Diethyl-5-methyl-2'-deoxycytidine (20d)

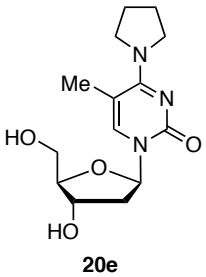


20d

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **20d** (81.1 mg, 96%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.20. ^{1}H NMR (500 MHz, CD_3OD): δ 7.83 (s, 1H, H-6), 6.26 (t, *J* = 6.5 Hz, 1H, H-1'), 4.41 (dt, *J* = 3.4, 6.5 Hz, 1H, H-3'), 3.95 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.84 (dd, *J* = 3.1, 12.0 Hz, 1H, H-5'), 3.76 (dd, *J* = 3.7, 12.0 Hz, 1H, H-5'), 3.66 (q, *J* = 7.0 Hz, 4H, NCH_2), 2.35 (ddd, *J* = 3.8, 6.1, 13.5 Hz, 1H, H-2'), 2.25 (s, 3H, Me), 2.19 (dt, *J* = 6.7, 13.5 Hz, 1H, H-2'), 1.26 (t, *J* = 7.0 Hz, 6H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 165.1, 157.4, 142.6, 104.8, 88.8, 87.3, 71.9, 62.7, 45.0,

41.9, 18.7, 14.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{23}N_3O_4Na$ $[M + Na]^+$: 320.1581, found 320.1568.

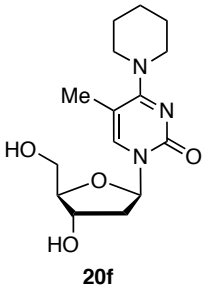
1-(2-Deoxy-β-D-ribofuranosyl)-5-methyl-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (20e)



20e

Chromatography on a silica gel column by sequential elution with EtOAc and 20% MeOH in EtOAc gave compound **20e** (54.6 mg, 97%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.12. ^{1}H NMR (500 MHz, CD_3OD): δ 7.75 (s, 1H, H-6), 6.24 (t, J = 6.6 Hz, 1H, H-1'), 4.38 (dt, J = 3.4, 6.5 Hz, 1H, H-3'), 3.91 (app q, J_{app} ~ 3.4 Hz, 1H, H-4'), 3.81 (dd, J = 3.1, 12.0 Hz, 1H, H-5'), 3.78-3.72 (m, 5H, H-5' and NCH_2), 2.30 (ddd, J = 3.8, 6.1, 13.5 Hz, 1H, H-2'), 2.25 (s, 3H, Me), 2.17–2.12 (m, 1H, H-2'), 1.93 (br s, 4H, $(CH_2)_2$). ^{13}C NMR (125 MHz, CD_3OD): δ 163.9, 157.6, 141.2, 105.2, 88.7, 87.2, 72.0, 62.8, 50.6, 41.9, 26.1, 18.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{21}N_3O_4Na$ $[M + Na]^+$: 318.1424, found 318.1403.

1-(2-Deoxy-β-D-ribofuranosyl)-5-methyl-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (20f)

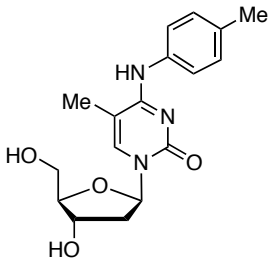


20f

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc, gave compound **20f** (53.9 mg, 94%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.20. ^{1}H NMR (500 MHz, CD_3OD): δ 7.90 (s, 1H, H-6), 6.26 (t, J = 6.5 Hz, 1H, H-1'), 4.41 (dt, J = 3.5, 6.6 Hz, 1H, H-3'), 3.95 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.85 (dd, J = 3.2, 12.1 Hz, 1H, H-5'), 3.76 (dd, J = 3.7, 12.1 Hz, 1H, H-5'), 3.68–3.64 (m, 4H, NCH_2), 2.37 (ddd, J = 3.9, 6.1, 13.5 Hz, 1H, H-2'), 2.21–2.15 (m, 4H, Me and H-2'), 1.77–1.72 (m, 2H, CH_2), 1.71–1.66 (m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 167.2, 153.8, 143.1, 105.9, 88.9, 87.4, 71.9, 62.7, 49.4, 42.0, 27.3, 25.5,

18.2. HRMS (ESI/TOF) *m/z* calculated for $C_{15}H_{23}N_3O_4Na$ $[M + Na]^+$: 332.1581, found 332.1584.

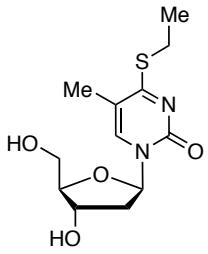
5-Methyl-*N*-(*p*-tolyl)-2'-deoxycytidine (20g)



20g

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **20g** (83.2 mg, 94%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.30. ^{1}H NMR (500 MHz, CD_3OD): δ 7.90 (s, 1H, H-6), 7.52 (d, J = 8.3 Hz, 2H, Ar-H), 7.12 (d, J = 8.2 Hz, 2H, Ar-H), 6.26 (t, J = 6.5 Hz, 1H, H-1'), 4.38 (dt, J = 3.4, 6.6 Hz, 1H, H-3'), 3.93 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.83 (dd, J = 3.2, 12.1 Hz, 1H, H-5'), 3.74 (dd, J = 3.8, 12.1 Hz, 1H, H-5'), 2.34 (ddd, J = 3.9, 6.1, 13.5 Hz, 1H, H-2'), 2.30 (s, 3H, Me), 2.19 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 2.08 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 163.5, 158.3, 139.8, 136.9, 135.6, 130.0, 124.5, 105.5, 88.8, 87.5, 71.9, 62.7, 42.0, 21.0, 13.6. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{22}N_3O_4$ $[M + H]^+$: 332.1605, found 332.1604.

***S*^{4}-Ethyl-4-thiothymidine (20h)**

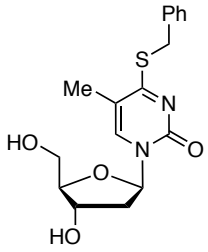


20h

Chromatography on a neutralized silica gel column by sequential elution with EtOAc and 5% MeOH in EtOAc gave compound **20h** (58.7 mg, 70%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.36. ^{1}H NMR (500 MHz, CD_3OD): δ 8.09 (s, 1H, H-6), 6.20 (t, J = 6.2 Hz, 1H, H-1'), 4.38 (dt, J = 3.6, 6.6 Hz, 1H, H-3'), 3.98 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.85 (dd, J = 2.9, 12.2 Hz, 1H, H-5'), 3.75 (dd, J = 3.6, 12.2 Hz, 1H, H-5'), 3.20 (q, J = 7.4 Hz, 2H, SCH_2), 2.46 (ddd, J = 4.5, 6.0, 13.6 Hz, 1H, H-2'), 2.16 (dt, J = 6.6, 13.4 Hz, 1H, H-2'), 2.04 (s, 3H, Me), 1.35 (t, J = 7.4 Hz, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 179.9, 156.0, 139.4, 114.2, 89.3, 88.3, 71.5,

62.4, 42.4, 25.1, 14.5, 14.2. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{18}N_2O_4SNa$ $[M + Na]^+$: 309.0879, found 309.0866.

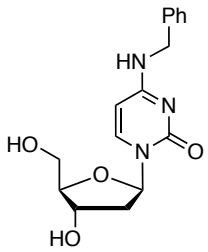
S^4-Benzyl-4-thiothymidine (20i)



20i

Chromatography on neutralized silica gel column by sequential elution with EtOAc and 5% MeOH in EtOAc, gave compound **20i** (95.7 mg, 79%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.37. ^{1}H NMR (500 MHz, CD_3OD): δ 8.13 (s, 1H, H-6), 7.42 (d, J = 7.9 Hz, 2H, Ar-H), 7.30 (t, J = 7.3 Hz, 2H, Ar-H), 7.24 (t, J = 7.1 Hz, 1H, Ar-H), 6.22 (t, J = 6.2 Hz, 1H, H-1'), 4.47 (s, 2H, SCH_2), 4.38 (dt, J = 4.0, 5.7 Hz, 1H, H-3'), 3.98 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.85 (dd, J = 3.0, 12.2 Hz, 1H, H-5'), 3.75 (dd, J = 3.7, 12.2 Hz, 1H, H-5'), 2.48 (ddd, J = 4.4, 6.2, 13.6 Hz, 1H, H-2'), 2.18 (dt, J = 6.6, 13.4 Hz, 1H, H-2'), 2.04 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 179.1, 155.9, 139.8, 138.3, 130.3, 129.6, 128.4, 113.9, 89.2, 88.3, 71.5, 62.3, 42.4, 34.7, 14.1. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{20}N_2O_4SNa$ $[M + Na]^+$: 371.1036, found 371.1035.

***N*-Benzyl-2'-deoxycytidine (21a)**

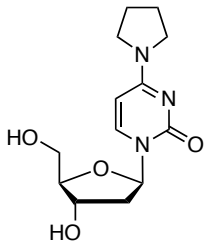


21a

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **21a** (53.6 mg, 92%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.24. ^{1}H NMR (500 MHz, CD_3OD): δ 7.91 (d, J = 7.5 Hz, 1H, H-6), 7.34–7.28 (m, 4H, Ar-H), 7.25–7.22 (m, 1H, Ar-H), 6.27 (t, J = 6.5 Hz, 1H, H-1'), 5.90 (d, J = 7.5 Hz, 1H, H-5), 4.59–4.56 (m, 2H, NCH_2), 4.36 (dt, J = 3.3, 6.4 Hz, 1H, H-3'), 3.93 (app q, J_{app} ~ 3.6 Hz, 1H, H-4'), 3.78 (dd, J = 3.3, 12.0 Hz, 1H, H-5'), 3.72 (dd, J = 3.9, 12.0 Hz, 1H, H-5'), 2.34 (ddd, J = 3.7, 6.1, 13.5 Hz, 1H, H-2'), 2.13 (dt, J = 6.7, 13.5 Hz, 1H, H-2'). ^{13}C NMR (125 MHz, CD_3OD): δ 165.4, 158.7,

141.3, 139.7, 129.5, 128.8, 128.3, 96.9, 88.8, 87.5, 72.1, 62.8, 45.2, 41.9. HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{19}N_3O_4Na$ $[M + Na]^+$: 340.1268, found 340.1265.

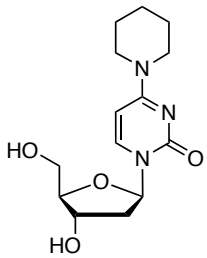
1-(2-Deoxy-β-D-ribofuranosyl)-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (21b)



21b

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **21b** (72.1 mg, 87%) as a white solid. R_f (SiO_2/20% MeOH in EtOAc) = 0.22. ^{1}H NMR (500 MHz, CD_3OD): δ 8.01 (d, J = 7.6 Hz, 1H, H-6), 6.26 (t, J = 6.5 Hz, 1H, H-1'), 5.96 (d, J = 7.7 Hz, 1H, H-5), 4.36 (dt, J = 3.3, 6.4 Hz, 1H, H-3'), 3.93 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.79 (dd, J = 3.2, 12.0 Hz, 1H, H-5'), 3.72 (dd, J = 3.8, 12.0 Hz, 1H, H-5'), 3.56 (t, J = 6.8 Hz, 2H, NC<u>H</u>H), 3.46 (t, J = 6.8 Hz, 2H, NCH<u>H</u>), 2.35 (ddd, J = 4.0, 5.9, 13.5 Hz, 1H, H-2'), 2.03 (dt, J = 6.6, 13.4 Hz, 1H, H-2'), 2.03 (quint, J = 6.7 Hz, 2H, CH_2), 1.95 (quint, J = 6.7 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 162.8, 158.0, 142.0, 95.0, 88.8, 87.5, 72.0, 62.8, 48.2, 48.1, 42.1, 26.5, 25.7. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{19}N_3O_4Na$ $[M + Na]^+$: 304.1268, found 304.1272.

1-(2-Deoxy-β-D-ribofuranosyl)-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (21c)

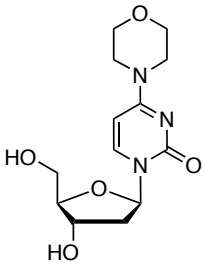


21c

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **21c** (52.1 mg, 90%) as a white solid. R_f (SiO_2/20% MeOH in EtOAc) = 0.17. ^{1}H NMR (500 MHz, CD_3OD): δ 8.00 (d, J = 7.9 Hz, 1H, H-6), 6.24 (t, J = 6.5 Hz, 1H, H-1'), 6.21 (d, J = 7.9 Hz, 1H, H-5), 4.36 (dt, J = 3.4, 6.5 Hz, 1H, H-3'), 3.93 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.89–3.69 (m, 2H, NC<u>H</u>H), 3.79 (dd, J = 3.3, 12.0 Hz, 1H, H-5'), 3.72 (dd, J = 3.7, 12.1 Hz, 1H, H-5'), 3.67–3.55 (m, 2H, NCH<u>H</u>), 2.35 (ddd, J = 3.8, 6.1, 13.5 Hz, 1H, H-2'), 2.35 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 1.76–1.69 (m, 2H, CH_2), 1.65–1.57 (m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ

163.8, 158.3 (br), 142.5, 93.6, 88.8, 87.5, 72.1, 62.8, 47.8 (br), 47.8 (br), 42.0, 27.0 (br), 25.5. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{21}N_3O_4Na$ $[M + Na]^+$: 318.1424, found 318.1449.

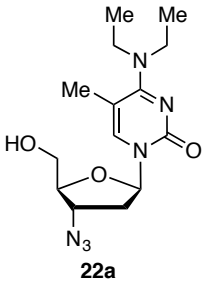
1-(2-Deoxy-β-D-ribofuranosyl)-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (21d)



21d

Chromatography on a silica gel column by sequential elution with EtOAc followed by 15% MeOH in EtOAc gave compound **21d** (54.2 mg, 93%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.12. ^{1}H NMR (500 MHz, CD_3OD): δ 8.08 (d, J = 7.8 Hz, 1H, H-6), 6.24 (t, J = 6.4 Hz, 1H, H-1'), 6.20 (d, J = 7.8 Hz, 1H, H-5), 4.36 (dt, J = 3.4, 6.4 Hz, 1H, H-3'), 3.94 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.79 (dd, J = 3.3, 12.0 Hz, 1H, H-5'), 3.74–3.55 (m, 9H, H-5' and morpholinyl–CH_2), 2.37 (ddd, J = 3.9, 6.1, 13.5 Hz, 1H, H-2'), 2.14 (dt, J = 6.7, 13.4 Hz, 1H, H-2'). ^{13}C NMR (125 MHz, CD_3OD): δ 164.5, 158.1, 143.0, 93.3, 88.9, 87.7, 72.0, 67.5, 62.7, 46.6 (br), 45.1 (br), 42.1. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{19}N_3O_5Na$ $[M + Na]^+$: 320.1217, found 320.1213.

3'-Azido-*N,N*-diethyl-5-methyl-2',3'-dideoxycytidine (22a)

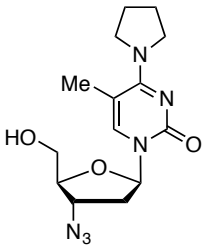


22a

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **22a** (71.0 mg, 96%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.59. ^{1}H NMR (500 MHz, CD_3OD): δ 7.80 (s, 1H, H-6), 6.13 (t, J = 6.2 Hz, 1H, H-1'), 4.32 (app q, J_{app} ~ 6.1 Hz, 1H, H-3'), 3.92 (dt, J = 3.2, 4.9 Hz, 1H, H-4'), 3.86 (dd, J = 3.1, 12.2 Hz, 1H, H-5'), 3.75 (dd, J = 3.2, 12.2 Hz, 1H, H-5'), 3.63 (q, J = 7.0 Hz, 4H, NCH_2), 2.44 (dt, J = 6.4, 13.2 Hz, 1H, H-2'), 2.36 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 2.22 (s, 3H, Me), 1.23 (t, J = 7.0 Hz, 6H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 165.2, 157.3, 142.5, 104.8, 87.0, 86.2, 62.3, 61.4,

45.0, 39.0, 18.7, 14.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{22}N_6O_3Na$ $[M + Na]^+$: 345.1646, found 345.1646.

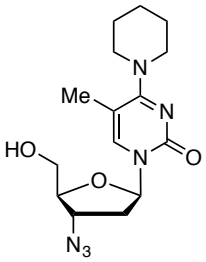
1-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (22b)



22b

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **22b** (71.5 mg, 97%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.20. ^{1}H NMR (500 MHz, CD_3OD): δ 7.75 (s, 1H, H-6), 6.13 (t, J = 6.2 Hz, 1H, H-1'), 4.32 (app q, J_{app} ~ 6.0 Hz, 1H, H-3'), 3.91 (app q, J_{app} ~ 3.9 Hz, 1H, H-4'), 3.85 (dd, J = 3.1, 12.2 Hz, 1H, H-5'), 3.76–3.66 (m, 5H, H-5' and NCH_2), 2.41 (dt, J = 6.3, 13.1 Hz, 1H, H-2'), 2.36 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 2.24 (s, 3H, Me), 1.92 (br s, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 163.2, 157.4, 141.0, 105.2, 86.9, 86.1, 62.4, 61.5, 50.6 (br), 38.9, 26.2 (br), 18.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{21}N_6O_3$ $[M + H]^+$: 321.1670, found 321.1663.

1-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (22c)

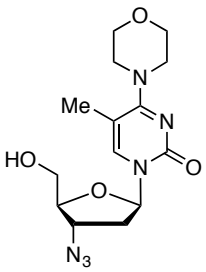


22c

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **22c** (122.1 mg, 99%) as an off-white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.60. ^{1}H NMR (500 MHz, CD_3OD): δ 7.87 (s, 1H, H-6), 6.13 (t, J = 6.1 Hz, 1H, H-1'), 4.32 (app q, J_{app} ~ 6.1 Hz, 1H, H-3'), 3.93 (dt, J = 2.8, 5.3 Hz, 1H, H-4'), 3.86 (dd, J = 3.0, 12.2 Hz, 1H, H-5'), 3.75 (dd, J = 3.2, 12.2 Hz, 1H, H-5'), 3.66–3.60 (m, 4H, NCH_2), 2.45 (dt, J = 6.4, 13.2 Hz, 1H, H-2'), 2.35 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 2.15 (s, 3H, Me), 1.75–1.68 (m, 2H, CH_2), 1.68–1.61(m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 167.2, 157.5, 142.9, 105.9, 87.1, 86.3, 62.3, 61.3,

49.4, 39.1, 27.3, 25.5, 18.2. HRMS (ESI/TOF) *m/z* calculated for $C_{15}H_{22}N_6O_3Na$ $[M + Na]^+$: 357.1646, found 357.1670.

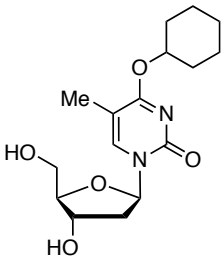
1-(3-Azido-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (22d)



22d

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **22d** (73.2 mg, 98%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.23. ^{1}H NMR (500 MHz, CD_3OD): δ 7.96 (s, 1H, H-6), 6.13 (t, *J* = 6.0 Hz, 1H, H-1'), 4.32 (app q, J_{app} ~ 6.2 Hz, 1H, H-3'), 3.94 (dt, *J* = 2.9, 5.4 Hz, 1H, H-4'), 3.87 (dd, *J* = 3.1, 12.2 Hz, 1H, H-5'), 3.77-3.73 (m, 5H, H-5', and morpholinyl–CH_2), 3.71–3.68 (m, 4H, morpholinyl–CH_2), 2.47 (dt, *J* = 6.5, 13.3 Hz, 1H, H-2'), 2.37 (dt, *J* = 6.6, 13.5 Hz, 1H, H-2'), 2.15 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 167.0, 156.9, 143.6, 105.8, 87.3, 86.4, 67.8, 62.1, 61.1, 48.9, 39.1, 17.9. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{20}N_6O_4Na$ $[M + Na]^+$: 359.1438, found 359.1434.

***O*^{4}-(Cyclohex-1-yl)thymidine (23b)**

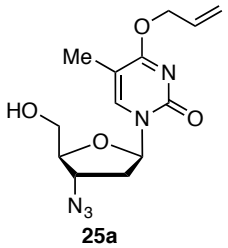


23b

Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and EtOAc gave compound **23b** (33.1 mg, 89%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.58. ^{1}H NMR (500 MHz, CD_3OD): *δ* 8.11 (d, *J* = 0.9 Hz, 1H, H-6), 6.24 (t, *J* = 6.4 Hz, 1H, H-1'), 5.18 (m, 1H, OCH), 4.38 (dt, *J* = 3.9, 6.3 Hz, 1H, H-3'), 3.95 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.83 (dd, *J* = 3.1, 12.1 Hz, 1H, H-5'), 3.74 (dd, *J* = 3.7, 12.1 Hz, 1H, H-5'), 2.40 (ddd, *J* = 4.0, 6.1, 13.6 Hz, 1H, H-2'), 2.19–2.11 (m, 1H, H-2'), 2.00–1.91 (m, 2H, cyclohexyl-H), 1.96 (s, 3H, Me), 1.82–1.73 (m, 2H, cyclohexyl-H), 1.62–1.52 (m, 3H, cyclohexyl-H), 1.50–1.30 (m, 3H, cyclohexyl-H). ^{13}C NMR (125 MHz, CD_3OD): *δ* 171.6, 158.4, 141.9, 107.0, 89.1, 87.9,

76.3, 71.7, 62.5, 42.2, 32.4, 32.3, 26.5, 24.6, 12.2. HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{24}N_2O_5Na$ $[M + Na]^+$: 347.1577, found 347.1578.

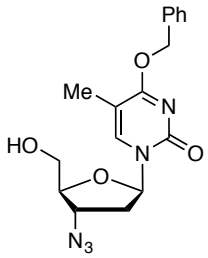
O^4-Allyl-3'-azido-2',3'-dideoxythymidine (25a)



25a

Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and EtOAc gave compound **25a** (45.0 mg, 90%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.77. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H, H-6), 6.05–5.97 (m, 2H, H-1'and =CH), 5.36 (d, J = 17.2 Hz, 1H, $=CH_{trans}$), 5.25 (d, J = 10.5 Hz, 1H, $=CH_{cis}$), 4.86 (d, J = 5.5 Hz, 2H, OCH_2), 4.39 (app q, J_{app} ~ 5.7 Hz, 1H, H-3'), 4.03–3.95 (m, 2H, H-4' and H-5'), 3.83 (d, J = 11.1 Hz, 1H, H-5'), 3.72 (br s, 1H, OH), 2.56 (dt, J = 6.6, 13.4 Hz, 1H, H-2'), 2.46 (dt, J = 6.3, 13.2 Hz, 1H, H-2'), 1.95 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 156.1, 141.3, 132.1, 118.5, 105.3, 88.4, 85.3, 68.0, 61.9, 59.9, 38.1, 12.4. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{17}N_5O_4Na$ $[M + Na]^+$: 330.1173, found 330.1177.

3'-Azido-O^4-benzyl-2',3'-dideoxythymidine (25b)



25b

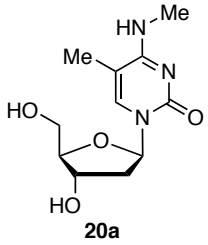
Chromatography on a silica gel column by sequential elution with 20% EtOAc in hexanes and EtOAc gave compound **25b** (35.1 mg, 93%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.80. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, H-6), 7.40 (d, J = 6.9 Hz, 2H, Ar-H), 7.37 (t, J = 7.2 Hz, 2H, Ar-H), 7.34–7.31 (m, 1H, Ar-H), 6.05 (t, J = 5.9 Hz, 1H, H-1'), 5.41 (s, 2H, OCH_2), 4.40 (app q, J_{app} ~ 5.6 Hz, 1H, H-3'), 4.04–3.97 (m, 2H, H-4', and H-5'), 3.83 (d, J = 10.2 Hz, 1H, H-5'), 3.61–3.47 (br, 1H, OH), 2.60 (dt, J = 6.5, 13.2 Hz, 1H, H-2'), 2.47 (dt, J = 6.4, 13.2 Hz, 1H, H-2'), 1.96 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 156.1, 141.4,

135.9, 128.7, 128.4, 128.2, 105.3, 88.3, 85.3, 69.0, 61.8, 59.9, 39.1, 12.4. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{20}N_5O_4$ $[M + H]^+$: 358.1510, found 358.1510.

Method B *(with KF for synthesis of **20a** and **21e**)*

To a 0.096 M solution of the appropriate nucleoside (1 equiv.) in dry MeOH, KF (4 equiv.) was added, and the mixture was stirred at 80 °C for 12 h. The mixture was evaporated and the crude material was purified through a short silica gel column by elution with suitable solvent system (see individual compound headings below).

***N*,5-Dimethyl-2'-deoxycytidine (20a)**

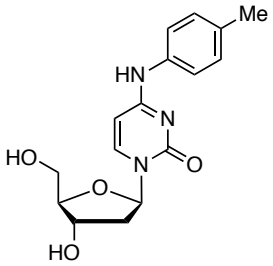


20a

Chromatography on a silica gel column by sequential elution with EtOAc and 20% MeOH in EtOAc gave compound **20a** (35.4 mg, 89%) as a white solid. R_f (SiO_2/20% MeOH in EtOAc) = 0.16. ^{1}H NMR (500 MHz, CD_3OD): δ 7.73 (s, 1H, H-6), 6.28 (t, J = 6.6 Hz, 1H, H-1'), 4.37 (dt, J = 3.4, 6.5 Hz, 1H, H-3'), 3.91 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.80 (dd, J = 3.2, 12.0 Hz, 1H, H-5'), 3.73 (dd, J = 3.8, 12.1 Hz, 1H, H-5'), 2.94 (s, 3H, NMe), 2.30 (ddd, J = 3.7, 6.1, 13.5 Hz, 1H, H-2'), 2.13 (dt, J = 6.7, 13.5 Hz, 1H, H-2'), 1.93 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 165.4, 158.6, 138.3, 105.0, 88.7, 87.2, 72.0, 62.8, 41.9, 28.3, 13.1. HRMS (ESI/TOF) *m/z* calculated for $C_{11}H_{17}N_3O_4Na$ $[M + Na]^+$: 278.1111, found 278.1123.

***N*-(*p*-Tolyl)-2'-deoxycytidine (21e)**

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **21e** (42.9 mg, 87%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.40. ^{1}H NMR (500 MHz, CD_3OD): δ 8.05 (d, J = 7.5 Hz, 1H, H-6), 7.60 (br s, 2H, Ar-H), 7.14 (d, J = 7.3 Hz, 2H, Ar-H), 6.27 (t, J = 6.5 Hz, 1H, H-1'), 6.03 (d, J = 7.5 Hz, 1H, H-5), 4.37 (dt, J =



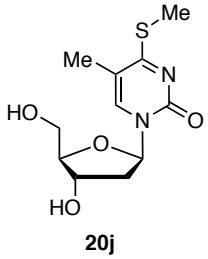
21e

3.4, 6.5 Hz, 1H, H-3'), 3.95 (app q, J_{app} ~ 3.6 Hz, 1H, H-4'), 3.80 (dd, *J* = 3.3, 12.0 Hz, 1H, H-5'), 3.73 (dd, *J* = 3.9, 12.1 Hz, 1H, H-5'), 2.39 (ddd, *J* = 3.8, 6.1, 13.6 Hz, 1H, H-2'), 2.31 (s, 3H, Me), 2.16 (dt, *J* = 6.7, 13.5 Hz, 1H, H-2'). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.62 (br s, 1H, NH), 7.93 (d, *J* = 7.5 Hz, 1H, H-6), 7.63 (br s, 2H, Ar–H), 7.13 (d, *J* = 8.2 Hz, 2H, Ar–H), 6.17 (t, *J* = 6.6 Hz, 1H, H-1'), 5.97 (d, *J* = 7.4 Hz, 1H, H-5), 5.22 (d, *J* = 4.2 Hz, 1H, OH), 4.99 (t, *J* = 5.2 Hz, 1H, OH), 4.24–4.18 (m, 1H, H-3'), 3.79 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.62–3.51 (m, 2H, H-5' and H-5'), 2.26 (s, 3H, Me), 2.16 (ddd, *J* = 3.3, 5.8, 13.2 Hz, 1H, H-2'), 1.97 (dt, *J* = 6.6, 13.3 Hz, 1H, H-2'). HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{20}N_3O_4$ $[M + H]^+$: 318.1448, found 318.1443. The ^{1}H NMR spectrum matches that of the material as reported (Q. Dai, C. Ran, R. G. Harvey, *Tetrahedron*, 2006**, 62**, 1764–1771.

Method C *(with TASF for synthesis of **20j**, **23a**, and **24**)*

To a 0.095 M solution of appropriate nucleoside (1 mol equiv) in dry MeCN at 0 °C, a 1.515 M solution of TASF in dry MeCN (5 mol equiv) was added dropwise and stirred at 0 °C for 1 h. Then the reaction mixture was allowed to stir at room temperature for 16 h. The crude material was concentrated and purified over a short plug silica gel column by eluting with suitable solvent system (see individual compound headings below).

***S*^{4}-Methyl-4-thiothymidine (20j)**

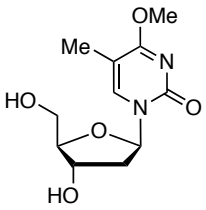


20j

The crude material after desilylation was quickly filtered through a short silica plug plug using 10% MeOH in EtOAc. The filtrate was evaporated and washed with EtOAc followed by 2% MeOH in EtOAc to obtain compound **20j** (18.3 mg, 68%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.49. ^{1}H NMR (500 MHz, CD_3OD): *δ* 8.10 (s, 1H, H-6), 6.21 (t, *J* = 6.2 Hz, 1H, H-1'),

4.39 (dt, *J* = 4.1, 6.1 Hz, 1H, H-3'), 3.99 (app q, J_{app} ~ 3.5 Hz, 1H, H-4'), 3.85 (dd, *J* = 3.0, 12.1 Hz, 1H, H-5'), 3.76 (dd, *J* = 3.7, 12.1 Hz, 1H, H-5'), 2.54 (s, 3H, SCH_3), 2.46 (ddd, *J* = 4.4, 6.1, 13.6 Hz, 1H, H-2'), 2.17 (dt, *J* = 6.6, 13.4 Hz, 1H, H-2'), 2.10 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 180.3, 156.0, 139.2, 114.1, 89.3, 88.2, 71.6, 62.4, 42.4, 14.1, 13.0. HRMS (ESI/TOF) *m/z* calculated for $C_{11}H_{16}N_2O_4SNa$ $[M + Na]^+$: 295.0723, found 295.0716.

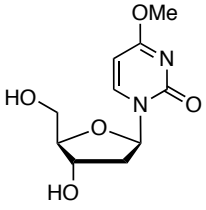
O^4-Methylthymidine (23a)



23a

Chromatography on a silica gel column by sequential elution with EtOAc and 10% MeOH in EtOAc gave compound **23a** (25.3 mg, 96%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.37. ^1H NMR (500 MHz, CD_3OD): δ 8.13 (s, 1H, H-6), 6.24 (t, *J* = 6.4 Hz, 1H, H-1'), 4.38 (dt, *J* = 3.8, 6.3 Hz, 1H, H-3'), 3.97–3.94 (m, 4H, H-4' and OCH_3), 3.84 (dd, *J* = 3.1, 12.1 Hz, 1H, H-5'), 3.75 (dd, *J* = 3.7, 12.1 Hz, 1H, H-5'), 2.41 (ddd, *J* = 4.1, 6.2, 13.6 Hz, 1H, H-2'), 2.15 (dt, *J* = 6.6, 13.4 Hz, 1H, H-2'), 1.97 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 172.5, 158.2, 142.0, 106.6, 89.1, 87.9, 71.7, 62.5, 55.1, 42.2, 12.1. HRMS (ESI/TOF) *m/z* calculated for $C_{11}H_{16}N_2O_5Na$ $[M + Na]^+$: 279.0951, found 279.0948.

O^4-Methyl-2'-deoxyuridine (24)



24

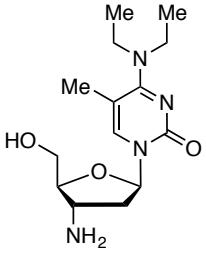
Chromatography on a silica gel column by sequential elution with EtOAc and 20% MeOH in EtOAc gave compound **24** (23.7 mg, 95%) as a white solid. R_f (SiO_2/10% MeOH in EtOAc) = 0.20. ^1H NMR (500 MHz, CD_3OD): δ 8.31 (d, *J* = 7.4 Hz, 1H, H-6), 6.23 (t, *J* = 6.3 Hz, 1H, H-1'), 6.07 (d, *J* = 7.4 Hz, 1H, H-5), 4.37 (dt, *J* = 3.8, 6.2 Hz, 1H, H-3'), 3.98 (app q, J_{app} ~ 3.6 Hz, 1H, H-4'), 3.92 (s, 3H, OCH_3), 3.81 (dd, *J* = 3.2, 12.1 Hz, 1H, H-5'), 3.74 (dd, *J* = 3.8, 12.1 Hz, 1H, H-5'), 2.45 (ddd, *J* = 4.0, 6.1, 13.6 Hz, 1H, H-2'), 2.15 (dt, *J* = 6.6, 13.4 Hz, 1H, H-2'). ^{13}C NMR (125 MHz, CD_3OD):

δ 173.7, 158.2, 145.0, 97.0, 89.2, 88.3, 71.8, 62.5, 54.9, 42.3. HRMS (ESI/TOF) *m/z* calculated for $C_{10}H_{14}N_2O_5Na$ $[M + Na]^+$: 265.0795, found 265.0805.

General Procedure For Reduction of 3'-Azido nucleosides To Amines (synthesis of 26a–d)

To a solution of the AZT derivative (0.131 mmol, 1equiv.) in dry MeOH (0.6 mL) in a 4 mL vial, 5% Pd/C (27.5 mg) was added. The reaction vial was placed in a two-necked flask to which a hydrogen balloon was attached with via a gas inlet adapter with a Teflon stopcock at one neck and the other neck was stoppered with a rubber septum. The flask was connected to a vacuum line via a needle inserted through the septum. The flask was degassed and filled with H_2 gas via the balloon, and this process was repeated three times. Finally, the reaction was allowed to proceed for 1 h at room temperature under a balloon filled with hydrogen gas. The reaction mixture was filtered through a short plug of Celite and the residue was washed with methanol. The filtrate was evaporated under reduced pressure and washed with EtOAc followed by 5% MeOH in EtOAc. The resulting solid was dried under high vacuum. All the products are very polar materials.

3'-Amino-*N,N*-diethyl-5-methyl-2',3'-dideoxycytidine (26a)

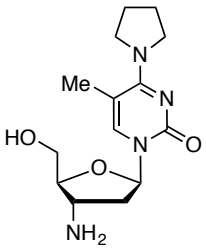


26a

Compound **26a** (38.4 mg, 99%) was obtained as a light-yellow solid. R_f (SiO_2/MeOH) = 0.34. ^{1}H NMR (500 MHz, CD_3OD): δ 7.90 (s, 1H, H-6), 6.12 (t, *J* = 5.4 Hz, 1H, H-1'), 3.89 (dd, *J* = 2.4, 12.2 Hz, 1H, H-5'), 3.79 (dd, *J* = 3.2, 12.2 Hz, 1H, H-5'), 3.72 (dt, *J* = 3.2, 6.7 Hz, 1H, H-4'), 3.62 (q, *J* = 7.0 Hz, 4H, NCH_2), 3.50 (app q, J_{app} ~ 7.4 Hz, 1H, H-3'), 2.26–2.22 (m, 5H, H-2', H-2', and Me), 1.22 (t, *J* = 7.0 Hz, 6H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 165.2, 157.4, 142.7, 104.4, 88.8, 86.7, 61.8,

51.0, 45.0, 42.7, 18.2, 14.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{25}N_4O_3$ $[M + H]^+$: 297.1921, found 297.1916.

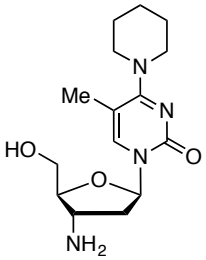
1-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(piperidin-1-yl)-2(*1H*)-pyrimidinone (26b)



26b

Compound **26b** (37.5 mg, 97%) was obtained as a light-yellow solid. R_f (SiO_2/MeOH) = 0.23. ^{1}H NMR (500 MHz, CD_3OD): δ 7.84 (s, 1H, H-6), 6.12 (t, J = 5.5 Hz, 1H, H-1'), 3.89 (dd, J = 2.6, 12.2 Hz, 1H, H-5'), 3.80–3.69 (m, 6H, H-4', H-5', and NCH_2), 3.49 (app q, J_{app} ~ 7.4 Hz, 1H, H-3'), 2.28–2.20 (m, 5H, H-2', H-2', and Me), 1.96-1.90 (m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 164.0, 157.5, 141.2, 104.8, 88.8, 86.6, 61.9, 51.1, 50.5, 42.6, 26.2, 18.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{22}N_4O_3Na$ $[M + Na]^+$: 317.1584, found 317.1598.

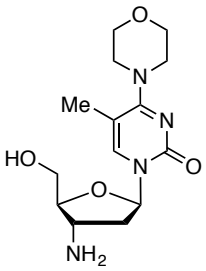
1-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(pyrrolidin-1-yl)-2(*1H*)-pyrimidinone (26c)



26c

Compound **26c** (39.9 mg, 99%) was obtained as a white solid. R_f (SiO_2/MeOH) = 0.31. ^{1}H NMR (500 MHz, CD_3OD): δ 7.98 (s, 1H, H-6), 6.12 (t, J = 5.3 Hz, 1H, H-1'), 3.90 (dd, J = 2.6, 12.3 Hz, 1H, H-5'), 3.80 (dd, J = 3.3, 12.3 Hz, 1H, H-5'), 3.72 (dt, J = 3.2, 6.7 Hz, 1H, H-4'), 3.65–3.58 (m, 4H, NCH_2), 3.49 (app q, J_{app} ~ 7.5 Hz, 1H, H-3'), 2.27–2.22 (m, 2H, H-2' and H-2'), 2.14 (s, 3H, Me), 1.74–1.68 (m, 2H, CH_2), 1.68-1.61(m, 4H, CH_2). ^{13}C NMR (125 MHz, CD_3OD): δ 167.3, 157.6, 143.1, 105.5, 88.9, 86.8, 61.7, 50.9, 49.4, 42.7, 27.3, 25.5, 18.2. HRMS (ESI/TOF) *m/z* calculated for $C_{15}H_{24}N_4O_3Na$ $[M + Na]^+$: 331.1741, found 331.1744.

1-(3-Amino-2,3-dideoxy-β-D-ribofuranosyl)-5-methyl-4-(morpholin-4-yl)-2(*1H*)-pyrimidinone (26d)



26d

Compound **26d** (39 mg, 96%) was obtained as a light-yellow solid. R_f (SiO_2/MeOH) = 0.17. ^{1}H NMR (500 MHz, CD_3OD): δ 8.07 (s, 1H, H-6), 6.11 (t, J = 5.2 Hz, 1H, H-1'), 3.91 (dd, J = 2.3, 12.3 Hz, 1H, H-5'), 3.80 (dd, J = 3.2, 12.3 Hz, 1H, H-5'), 3.76–3.71 (m, 5H, H-4', morpholinyl-CH_2), 3.70–3.65 (m, 4H, morpholinyl-CH_2), 3.49 (app q, J_{app} ~ 7.5 Hz, 1H, H-3'), 2.31-2.21 (m, 2H, H-2' and H-2'), 2.14 (s, 3H, Me). ^{13}C NMR (125 MHz, CD_3OD): δ 167.4, 157.4, 143.6, 105.4, 89.0, 87.0, 67.8, 61.6, 50.8, 48.7, 42.7, 17.9. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{23}N_4O_4$ $[M + H]^+$: 311.1714, found 311.1712.

Antiviral activity assays

The synthesized compounds were evaluated against different herpesviruses, including herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK–) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strain G, varicella-zoster virus (VZV) strain Oka, TK– VZV strain 07-1, human cytomegalovirus (HCMV) strains AD-169 and Davis as well as feline herpes virus (FHV), the poxvirus vaccinia virus (Lederle strain), parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, respiratory syncytial virus (RSV), feline coronavirus (FIPV) and influenza A virus subtypes H1N1 (A/PR/8), H3N2 (A/HK/7/87) and influenza B virus (B/HK/5/72), and human immune deficiency virus (HIV-1 and HIV-2). The antiviral assays, other than HIV, were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey kidney cells (Vero), human epithelial cervix carcinoma cells (HeLa), Crandell-Rees feline kidney cells (CRFK), or Madin

Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation (VZV) was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathicity or viral plaque formation by 50%. Cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology.

Cytostatic activity against immortalized cell lines

Murine leukemia (L1210), human T-lymphocyte (CEM), human cervix carcinoma (HeLa), and immortalized human dermal microvascular endothelial cells (HMEC-1) were suspended at 300,000–500,000 cells/mL of culture medium, and 100 µL of a cell suspension was added to 100 µL of an appropriate dilution of the test compounds in 200 µL-wells of 96-well microtiter plates. After incubation at 37 °C for two (L1210), three (CEM) or four (HeLa) days, the cell number was determined using a Coulter counter. The IC_{50} was defined as the compound concentration required to inhibit cell proliferation by 50%.