An Efficient Synthesis of Exo-*N*-carbamoyl Nucleosides: Application to the Synthesis of Phosphoramidate Prodrugs

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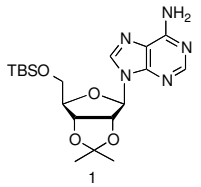
Supporting Information

General Experimental Information

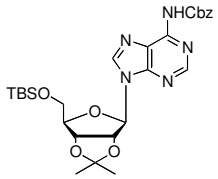
Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C and ^{31}P) were recorded on a Varian Unity Plus 400 MHz Fourier transform spectrometer at ambient temperature, with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), or ddd (doublet of doublets of doublets). Low-resolution mass spectra (MS) were measured on a time-of-flight (TOF) mass spectrometry with electrospray ionization (ESI). High-resolution mass spectra (HRMS) were recorded on a Micromass Autospec high-resolution mass spectrometer with ESI. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel. Purifications were carried out on silica gel column chromatography (60 A, 63- 200 μm, or 40-75 μm).



1

9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (1)

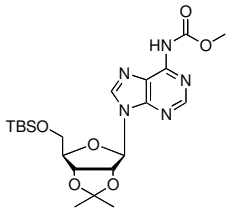
To a solution of adenosine (5.0 g, 18.70 mmol) in 150 mL of acetone was treated with perchloroic acid (0.50 mL, 70% in water) at 0 °C for 1 h and then room temperature for 6 h. The resulting solution was neutralized with $NaHCO_3$ at 0 °C and the resulting white solid removed by filtration. The filtrate was concentrated under reduced pressure and purified by silica gel column to give acetonide (5.48 g, 17.77 mmol) in 95% yield. To a solution of 2',3'-*O*-isopropylidene adenosine (5.0 g, 16.22 mmol) in 100 mL of CH_2Cl_2 was added *t*-butyldimethylsilyl chloride (TBDMSCl, 3.67 g, 24.33 mmol) and imidazole (3.31 g, 48.66 mmol) at 0 ºC under N_2 atmosphere. The reaction mixture was stirred at room temperature for 12 h and treated with methanol (8.0 mL). After stirring for 30 min, the solvent was removed under reduced pressure. The residue was purified on silica gel column chromatography (EtOAc:hexane = 1:10 to 4:1 v/v) to give compound **1** (6.56 g, 15.57 mmol) in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38(s, 1H), 8.05 (s, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 5.66 (br, 2H), 5.27 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.95 (dd, *J* = 2.6, 6.0 Hz, 1H), 4.43 (q, *J* = 2.4 Hz, 1H), 3.88 (dd, *J* = 3.6, 10.8 Hz, 1H), 3.77(dd, *J* = 4.4, 10.8 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.4, 139.5, 114.3, 91.8, 87.6, 85.2, 81.7, 63.8, 27.4, 26.1, 25.6, 18.5, -5.2, -5.3; MS-ESI$^+$ *m/z* 422 ($M+H^+$).



Benzyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2a)

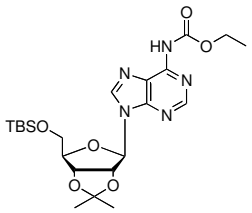
To a solution of compound **1** (0.10 g, 0.24 mmol) in 10 mL of CH_2Cl_2 was added benzyl chlorofomate (0.16 g, 0.96 mmol) and *N*-methyl imidazole (0.16 g, 1.92 mmol) at 0 °C under N_2 atmosphere. After stirring for 12 h at room temperature, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:hexane = 1:4 to 1:1 v/v) to give compound **2a** (0.12 g, 0.22 mmol) in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.65 (s, 1H), 8.19 (s, 1H), 7.45-7.34 (m,

5H), 6.18 (d, *J* = 2.4 Hz, 1H), 5.30 (s, 2H), 5.26 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.94 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.47 (q, *J* = 4.0 Hz, 1H), 3.87 (dd, *J* = 4.0, 11.2 Hz, 1H), 3.76 (dd, *J* = 4.0, 11.2 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 3H), 0.80 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.0, 150.8, 149.5, 141.7, 135.6, 128.9, 128.8, 128.7, 122.6,114.3, 92.2, 87.8, 85.3, 81.7, 68.0, 63.8, 37.3, 27.4, 26.0, 25.6, 18.5, -5.3, -5.4; MS-ESI$^+$ *m/z* 556 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{27}H_{38}N_5O_6Si$ (M+H$^+$) 556.2598, found 556.2599.



Methyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2b)

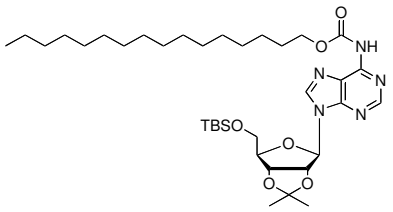
Compound **2b** was prepared using the same procedure as for compound **2a**: 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.79 (s, 1H), 8.23 (s, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.27 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.93 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.47 (q, *J* = 3.6 Hz, 1H), 3.88 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.87 (s, 3H), 3.75 (dd, *J* = 3.6, 11.6 Hz, 1H), 1.63 (s, 3H), 1.40 (s, 3H), 0.79 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.9, 150.9, 149.6, 141.6, 122.6, 114.3, 92.2, 87.7, 85.2, 81.7, 63.8, 53.2, 27.4, 26.0, 25.5, 18.4, -5.3, -5.4; MS-ESI$^+$ *m/z* 480 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{21}H_{34}N_5O_6Si$ (M+H$^+$) 480.2281, found 480.2286.



Ethyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2c)

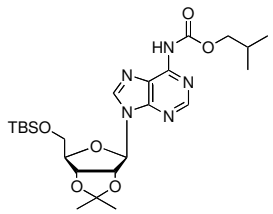
Compound **2c** was prepared using the same procedure as for compound **2a**: 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.73 (s, 1H), 8.22 (s, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.26 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.93 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.46 (q, *J* = 3.6 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.88 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.76 (dd, *J* = 3.6, 11.2 Hz, 1H), 1.63 (s, 3H), 1.40 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.3, 150.8, 149.7, 141.5, 122.6, 114.3, 92.2,

87.7, 85.3, 81.7, 63.8, 62.3, 27.4, 26.6, 25.5, 18.4, 14.6, -5.3, -5.4; MS-ESI$^+$ *m/z* 494 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{22}H_{36}N_5O_6Si$ (M+H$^+$) 494.2437, found 494.2443.



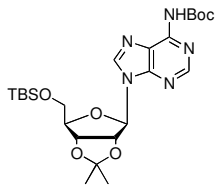
Hexadecyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2d)

Compound **2d** was prepared using the same procedure as for compound **2a**: 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.58 (s, 1H), 8.22 (s, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.26 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.93 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.46 (q, *J* = 3.6 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.88 (dd, *J* = 4.0, 11.2 Hz, 1H), 3.76 (dd, *J* = 4.0, 11.2 Hz, 1H), 1.72-1.64 (m, 2H), 1.63 (s, 3H), 1.40 (s, 3H), 1.37-1.19 (m, 26H), 0.86 (t, *J* = 10.8 Hz, 3H), 0.80 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.3, 150.8, 149.7, 141.5, 122.5, 114.3, 92.2, 87.7, 85.3, 81.7, 66.4, 63.8, 39.3, 32.1, 29.86, 29.82, 29.75, 27.69, 29.53, 29.41, 28.88, 27.38, 25.97, 25.5, 22.9, 18.5, 14.3, -5.3, -5.4; MS-ESI$^+$ *m/z* 690 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{36}H_{64}N_5O_6Si$ (M+H$^+$) 690.4638, found 690.4634.



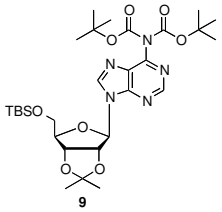
Isobutyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2e)

Compound **2e** was prepared using the same procedure as for compound **2a**: 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.78 (s, 1H), 8.22 (s, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.24 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.92 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.45 (q, *J* = 4.0 Hz, 1H), 4.02 (d, *J* = 7.2 Hz, 2H), 3.86 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.75 (dd, *J* = 3.6, 11.2 Hz, 1H), 1.98 (m, 1H), 1.61 (s, 3H), 1.38 (s, 3H), 0.94 (dd, *J* = 1.6, 7.2 Hz, 6H), 0.78 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.4, 150.8, 149.7, 141.5, 122.5, 114.3, 92.1, 87.6, 85.2, 81.6, 72.2, 63.7, 27.9, 27.3, 25.9, 25.5, 19.2, 18.4, -5.4, -5.5; MS-ESI$^+$ *m/z* 522 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{24}H_{40}N_5O_6Si$ (M+H$^+$) 522.2749, found 522.2756.



***tert*-Butyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2f)**

Compound **2f** was prepared using the same procedure as for compound **2a**: 14% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 5.26 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.93 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.47 (q, *J* = 3.6 Hz, 1H), 3.89 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.76 (dd, *J* = 3.6, 11.6 Hz, 1H), 1.64 (s, 3H), 1.55 (s, 9H), 1.41 (s, 3H), 0.82 (s, 9H), -0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 150.5, 150.0, 149.8, 141.2, 122.2, 114.4, 92.2, 87.7, 85.3, 82.4, 81.7, 63.8, 28.3, 27.4, 26.0, 25.5, 18.5, -5.3, -5.4; MS-ESI$^+$ *m/z* 522 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{24}H_{40}N_5O_6Si$ (M+H$^+$) 522.2751, found 522.2756.



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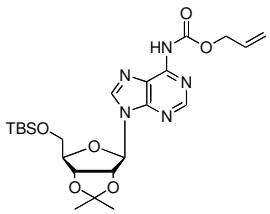
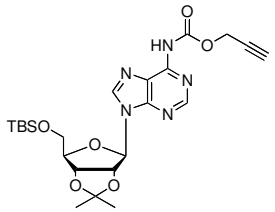
***N*^{6}, *N*'^{6}-*Bis*-*tert*-butyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (9)**

Yield was 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.36 (s, 1H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.23 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.96 (dd, *J* = 2.4, 6.4 Hz, 1H), 4.47 (q, *J* = 3.6 Hz, 1H), 3.91 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.80 (dd, *J* = 3.6, 11.2 Hz, 1H), 1.66 (s, 3H), 1.45 (s, 18H), 1.41 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.8, 152.4, 150.5, 143.5, 129.6, 114.4, 91.8, 87.5, 85.3, 83.9, 81.6, 63.7, 28.0, 27.4, 26.1, 25.5, 18.5, -5.2, -5.3; MS-ESI$^+$ *m/z* 622 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{29}H_{48}N_5O_8Si$ (M+H$^+$) 622.3276, found 622.3280.



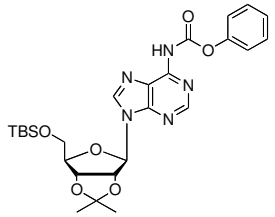
Allyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2g)

Compound **2g** was prepared using the same procedure as for compound **2a**: 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.79 (s, 1H), 8.23 (s, 1H), 6.19 (d, *J* = 2.8 Hz, 1H), 6.01-5.94 (m, 1H), 5.38 (ddd, *J* = 1.6, 2.8, 17.6 Hz, 1H), 5.28-5.25 (m, 2H), 4.93 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.75 (td, *J* = 1.2, 6.0 Hz, 2H), 4.46 (q, *J* = 4.0 Hz, 1H), 3.87 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.75 (dd, *J* = 3.6, 11.2 Hz, 1H), 1.62 (s, 3H), 1.39 (s, 3H), 0.78 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.1, 150.9, 149.6, 141.7, 131.9, 122.6, 119.2, 114.3, 92.2, 87.7, 85.2, 81.7, 66.8, 63.7, 27.4, 25.9, 25.5, 18.4, -5.3, -5.4; MS-ESI$^+$ *m/z* 506 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{23}H_{36}N_5O_6Si$ (M+H$^+$) 506.2436, found 506.2443.



Prop-2-yn-1-yl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2h)

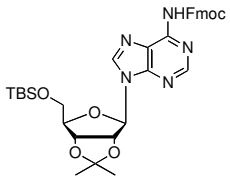
Compound **2h** was prepared using the same procedure as for compound **2a**: 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.81 (s, 1H), 8.28 (s, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.28 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.93 (dd, *J* = 2.0, 6.0 Hz, 1H), 4.86 (dd, *J* = 2.4, 3.6 Hz, 2H), 4.46 (q, *J* = 4.0 Hz, 1H), 3.87 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.75 (dd, *J* = 3.6, 11.6 Hz, 1H), 2.54 (t, *J* = 2.4 Hz, 1H), 1.62 (s, 3H), 1.39 (s, 3H), 0.77 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.0, 150.5, 149.4, 142.1, 122.7, 114.3, 92.2, 87.7, 85.1, 81.7, 77.4, 75.9, 63.7, 53.6, 27.3, 25.9, 25.5, 18.40, -5.3, -5.4; MS-ESI$^+$ *m/z* 504 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{23}H_{34}N_5O_6Si$ (M+H$^+$) 504.2283, found 504.2286.



Phenyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2i)

Compound **2i** was prepared using the same procedure as for compound **2a**: 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.89 (s, 1H), 8.34 (s, 1H), 7.46-7.42 (m, 2H), 7.32-7.29 (m, 3H), 6.28 (d, *J* = 2.4 Hz,

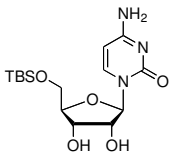
1H), 5.32 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.99 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.53 (q, *J* = 3.6 Hz, 1H), 3.94 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.82 (dd, *J* = 3.6, 11.6 Hz, 1H), 1.69 (s, 3H), 1.46 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.1, 150.5, 149.3, 141.9, 129.6, 126.1, 122.9, 121.7, 114.4, 92.3, 87.8, 85.4, 81.7, 63.8, 27.4, 26.0, 25.5, 18.5, -5.3, -5.4; MS-ESI$^+$ *m/z* 542 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{26}H_{36}N_5O_6Si$ (M+H$^+$) 542.2440, found 542.2443.



(9*H*-Fluoren-9-yl)methyl (9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)carbamate (2j)

Compound **2j** was prepared using the same procedure as for compound **2a**: yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.67 (dd, *J* = 7.2, 6.0 Hz, 2H), 7.42 (dd, *J* = 7.2, 7.6 Hz, 2H), 7.35-7.33 (m, 2H), 6.22 (d, *J* = 2.8 Hz, 1H), 5.26 (dd, *J* = 2.4, 6.0 Hz, 1H), 4.95 (dd, *J* = 2.0, 6.0 Hz, 2H), 4.64 (m, 2H), 4.49 (q, *J* = 3.6 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 1H), 3.90 (dd, *J* = 4.0, 11.6 Hz, 1H), 3.78 (dd, *J* = 4.0, 11.6 Hz, 1H), 1.66 (s, 3H), 1.42 (s, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.1, 150.9, 149.4, 143.7, 141.6, 128.1, 127.4, 125.3, 122.5, 120.3, 114.3, 92.3, 87.8, 85.4, 81.7, 68.0, 63.8, 47.1, 27.4, 26.0, 25.6, 18.5, -5.2, -5.3; MS-ESI$^+$ *m/z* 644 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{34}H_{42}N_5O_6Si$ (M+H$^+$) 644.2915, found 644.2917.

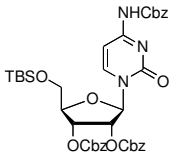
Data for tri-Cbz protected C and di-Cbz protected U when reacted with 7 in the presence of *t*-BuMgCl.[i]



5'-*O*-*tert*-Butyldimethylsilyl cytosine, Step 1

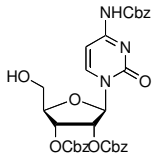
To a solution of cytidine (1.20 g, 4.93 mmol) in 20 mL of anhydrous pyridine was added imidazole (1.34 g, 19.72 mmol) and TBSCl (1.49 g, 9.86 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 12 h and then treated with methanol (1.0 mL). After stirring at room temperature for

1 h, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 25:1 to 10:1 v/v) to give the title compound (1.69 g, 4.73 mmol) in 96% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, *J* = 7.6 Hz, 1H), 1H), 5.87 (d, *J* = 2.4 Hz, 1H), 5.85 (d, *J* = 7.6 Hz, 1H), 4.14 (dd, *J* = 5.2, 10.0, Hz, 1H), 4.07-4.06 (m, 2H), 4.04 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.86 (dd, *J* = 2.4, 11.6 Hz, 1H), 0.95 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.7, 158.5, 142.8, 95.8, 91.9, 85.4, 76.9, 70.2, 63.1, 26.6, 19.5, -5.2, -5.3; MS-ESI$^+$ *m/z* 358 (M+H$^+$).



5'-*O-tert*-Butyldimethylsilyl-2',3'-*O*-*N*^{4}-tris-benzyloxycarbonyl cytosine,[ii] Step 2

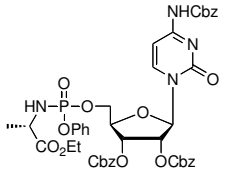
To a solution of compound from above (2.68 g, 7.50 mmol) in 50 mL of anhydrous CH_2Cl_2 was added CbzCl (4.76 mL, 33.74 mmol) and NMI (5.50 g, 45.0 mmol) at 0 ºC under N_2 atmosphere. After stirring for 12 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and then washed with cold 0.5 M HCl aqueous solution (50 mL), water (50 mL) and brine (50 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on silica gel column chromatography (EtOAc:hexane = 1:10 to 1:1 v/v) to give the title compound (5.53 g, 7.28 mmol) in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.87 (br, 1H), 7.38-7.30 (m, 15H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.36 (t, *J* = 4.0 Hz, 1H), 5.29 (t, *J* = 5.6 Hz, 1H), 5.22 (s, 2H), 5.13-5.05 (m, 4H), 4.33 (d, *J* = 5.6 Hz, 1H), 4.05 (d, *J* = 10.8 Hz, 1H), 3.79 (dd, *J* = 2.0, 12.0 Hz, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 154.8, 154.1, 153.9, 152.4, 144.2, 135.1, 134.80, 134.77, 128.87, 128.77, 128.71, 128.60, 128.50, 128.47, 95.2, 87.9, 82.1, 72.8, 70.53, 70.51, 68.1, 61.6, 26.0, 18.5, -5.3, -5.5; MS-ESI$^+$ *m/z* 760 (M+H$^+$).



2',3'-*O*-*N*^{4}-tris-benzyloxycarbonyl cytosine, Step 3

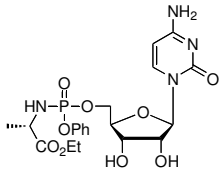
To a solution of compound from above (4.50 g, 5.92 mmol) in 20 mL of anhydrous THF was added triethylamine trihydrofluoride (Et_3N-3HF, 6.0 mL, 36.81 mmol) at 0 ºC under N_2 atmosphere. The solution was stirred for 24 h at room temperature and all volatiles were removed by using rotary evaporator. The

residue was dissolved in EtOAc (100 mL) and washed with cold saturated $NaHCO_3$ (30 mL x 2), and brine (30 mL). The resulting solution was dried over Na_2SO_4 for 3 h and filtered. The filtrate was adsorbed on silica gel and purified by silica gel column chromatography (CH_2Cl_2: MeOH = 40:1 to 20:1 v/v) to give the title compound (3.75 g, 5.80 mmol) in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.66 (br, 1H), 7.39-7.26 (m, 16H), 5.80-5.75 (m, 2H), 5.51 (t, *J* = 4.8 Hz, 1H), 5.21 (s, 2H), 5.13-5.07 (m, 4H), 4.33 (m, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 3.80 (m, 1H), 3.60 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 155.2, 154.3, 153.9, 152.4, 146.8, 135.0, 134.8, 128.94, 128.89, 128.83, 128.79, 128.68, 128.64, 95.9, 92.3, 83.8, 75.9, 73.9, 70.7, 70.6, 68.3, 61.5, 47.9; MS-ESI$^+$ *m/z* 646 (M+H$^+$).



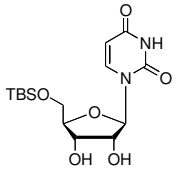
5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl-2',3'-*O*-*N*^{4}-tris-benzyloxycarbonyl cytosine, Step 4

To a solution of compound from above (0.50 g, 0.78 mmol) in 10 mL of anhydrous THF was added *t*-BuMgCl (1.94 mL, 1.94 mmol, 1.0 M in THF) over 10 min at -78 ºC under argon atmosphere. After stirring for 30 min at -78 ºC, to the reaction mixture was added a solution of compound **7** (0.46 g, 1.56 mmol) in 10 mL of anhydrous THF. The resulting solution was maintained for 3 h at -78 ºC and then warmed to room temperature. After stirred for 6 h at room temperature, the solution was treated with saturated NH_4Cl at 0 ºC and then poured into EtOAc (100 mL) and washed with cold NH_4Cl (30 mL), cold water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (CH_2Cl_2:MeOH = 20:1 to 10:1 v/v) to give the title compound (0.66 g, 0.73 mmol) in 94% yield (the ratio of diastereomers = 1:1 by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br, 1H), 7.89 (d, *J* = 7.6 Hz, 0.5H), 7.75 (d, *J* = 7.6 Hz, 0.5H), 7.37-7.21 (m, 23H), 7.14-7.07 (m, 2H), 6.09-6.08 (m, 1H), 5.39-5.30 (m, 2H), 5.19 (br, 2H), 5.14-5.02 (m, 5H), 4.52-4.25 (m, 4H), 4.17-3.98 (m, 4H), 1.38 (d, *J* = 6.8 Hz, 1.5H), 1.35 (d, *J* = 6.8 Hz, 1.5H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (m), 162.9 (d), 154.7, 154.0, 153.9 (d), 152.4 (d), 150.6 (d), 144.4 (d), 135.2, 134.7, 130.0, 129.9, 129.8, 128.82, 128.78, 128.73, 128.69, 128.53, 128.51, 128.49, 128.4, 125.3 (d), 120.2 (m), 95.7, 89.2 (d), 80.1 (m), 76.7 (d), 72.7 (d), 70.5, 68.0, 64.9 (d), 61.7, 50.5 (m), 20.9 (d), 14.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.22, 3.06; MS-ESI$^+$ *m/z* 901 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{44}H_{45}N_4O_{15}NaP$ (M+Na$^+$) 923.2530, found 923.2525.



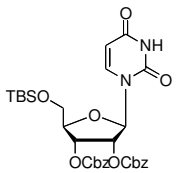
5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl cytosine, Step 5

To a solution of compound from above (0.37 g, 0.41 mmol) in 10 mL of EtOAc-EtOH (1:1 v/v) was added Pd/C (0.02 g, 10% Pd on activated carbon) at room temperature. The mixture was stirred for 3 h under an atmosphere of H_2 (1 atm, balloon) and then treated with celite (0.1 g) and stirred for 30 min. The suspension was filtered and washed with MeOH (10 mL x 3). The collected solution was concentrated under the reduced pressure and the residue was purified on silica gel column chromatography (MeOH: EtOAc = 1:10 v/v) to give the titlecompound (0.20 g, 0.40 mmol) in 98% yield (the ratio of diastereomers = 1:1 by ^{1}H NMR). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75-7.67 (m, 1H), 7.36-7.31 (m, 2H), 7.24-7.13 (m, 3H), 5.88-5.79 (m, 3H), 4.46-4.26 (m, 2H), 4.18-4.06 (m, 3H), 4.06-4.02 (m, 1H), 3.94-3.85 (m, 1H), 1.33-1.28 (m, 3), 1.24-1.24-1.14 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.1 (m), 167.7, 158.6 (m), 152.2 (m), 142.5 (m), 131.0 (d), 130.3, 126.4, 124.0, 121.6 (d), 121.5 (m), 96.5 (d), 92.1 (d), 83.6 (m), 76.1 (d), 70.8 (d), 67.2 (m), 62.5, 51.8 (d), 20.6 (m), 14.6; ^{31}P NMR (162 MHz, CD_3OD) δ 4.89, 4.74; MS-ESI$^+$ *m/z* 499 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{20}H_{27}N_4O_9NaP$ (M+Na$^+$) 521.1403, found 521.1408.



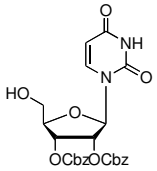
5'-*O-tert*-Butyldimethylsilyl uridine[i]

The title compound was prepared using the same procedure as the C analog above (Step 1): yield 97%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, *J* = 8.0 Hz, 1H), 5.91 (d, *J* = 3.2 Hz, 1H), 5.64 (d, *J* = 8.0 Hz, 1H), 4.17-4.12 (m, 2H), 4.07-4.05 (m, 1H), 4.00 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.86 (dd, *J* = 2.0, 11.6 Hz, 1H), 0.96 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.2, 152.4, 142.3, 102.6, 90.6, 86.1, 76.4, 71.0, 63.7, 26.6, 19.4, -5.2, -5.3; MS-ESI$^+$ *m/z* 359 (M+H$^+$).



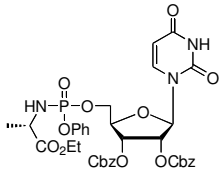
5'-*O-tert*-Butyldimethylsilyl-2',3'-*O*-bis-benzyloxycarbonyl uridine[ii]

The title compound was prepared using the same procedure as the C analog above (Step 2): yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.36-7.31 (m, 10H), 6.28 (d, *J* = 4.8 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.31-5.26 (m, 3H), 5.16-5.09 (m, 4H), 4.29 (q, *J* = 1.6 Hz, 1H), 3.95 (dd, *J* = 2.0, 11.6 Hz, 1H), 3.82 (dd, *J* = 2.0, 11.6 Hz, 1H), 0.94 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 154.3, 153.9, 150.4, 139.6, 134.74, 134.68, 128.88, 128.80, 128.72, 128.57, 128.55, 103.2, 85.7, 82.9, 74.3, 70.6, 70.5, 62.8, 26.0, 18.5, -5.5; MS-ESI$^+$ *m/z* 627 (M+H$^+$).



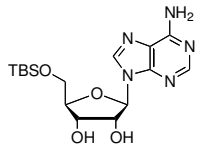
2',3'-*O*-Bis-benzyloxycarbonyl uridine

The title compound was prepared using the same procedure as C analog above (Step 3): yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.35-7.30 (m, 10H), 5.96 (d, *J* = 6.0 Hz, 1H), 5.74 (d, *J* = 8.0 Hz, 1H), 5.54 (dd, *J* = 5.2, 6.0 Hz, 1H), 5.45 (dd, *J* = 3.6, 5.2 Hz, 1H), 5.12-5.05 (m, 4H), 4.25 (d, *J* = 2.4 Hz, 1H), 3.89 (d, *J* = 12.0 Hz, 1H), 3.80 (m, 1H), 3.69 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 154.3, 154.0, 150.6, 141.7, 134.7, 134.6, 128.85, 128.77, 128.72, 128.66, 128.55, 103.3, 88.6, 83.3, 75.8, 74.4, 70.7, 70.5, 61.7; MS-ESI$^+$ *m/z* 513 (M+H$^+$).



5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl-2',3'-*O*-bis-benzyloxycarbonyl uridine

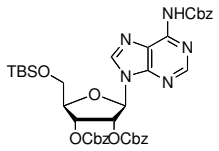
The title compound was prepared using the same procedure as the C analog above (Step 4): yield 97% (the ratio of diastereomers = 3:2 by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65-9.58 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 0.6H), 7.35-7.22 (m, 14.4H), 7.16-7.11 (m, 1H), 6.11-6.08 (m, 1H), 5.73 (d, *J* = 8.0 Hz, 0.6H), 5.54 (d, *J* = 8.0 Hz, 0.4H), 5.43-5.38 (m, 1H), 5.29-2.60 (m, 1H), 5.19-5.06 (m, 5H), 4.46-4.31 (m, 3H), 4.26-4.10 (m, 3H), 4.08-3.95 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 7.2 Hz, 2H), 1.25-1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.75 (m), 163.29 (d), 154.01 (m), 150.48 (m), 139.87 (d), 134.64, 130.04 (d), 128.85, 128.76, 128.72, 128.57, 128.53, 128.51, 125.37 (d), 120.29 (m), 103.55 (d), 86.64 (d), 80.37 (m), 75.64 (d), 73.17 (d), 70.62 (d), 65.37 (m), 61.81, 50.48 (d), 21.00 (m), 14.21; ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.07, 3.02; MS-ESI$^+$ *m/z* 768 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{36}H_{38}N_3O_{14}NaP$ (M+Na$^+$) 790.2001, found 790.1997.



3a

5'-*O-tert*-Butyldimethylsilyl adenosine (3a)

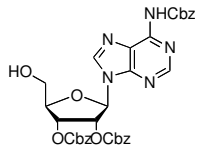
Compound **3a** was prepared using the same procedure as the C analog above (Step 1): yield 94%; ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.13 (s, 1H), 5.99 (d, *J* = 4.0 Hz, 1H), 4.49 (t, *J* = 4.8 Hz, 1H), 4.30 (t, *J* = 4.8 Hz, 1H), 4.06 (m, 1H), 3.94 (dd, *J* = 3.2, 11.6 Hz, 1H), 3.81 (dd, *J* = 3.2, 11.6 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.4, 154.1, 150.6, 140.8, 120.5, 90.2, 86.4, 76.5, 71.4, 63.9, 26.6, 19.5, -5.1, -5.2; MS-ESI$^+$ *m/z* 382 (M+H$^+$).



4a

5'-*O-tert*-Butyldimethylsilyl-2',3'-*O*-*N*^{6}-tris-benzyloxycarbonyl adenosine (4a)

Compound **4a** was prepared using the same procedure as the C analog above (Step 2): yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.29 (s, 1H), 8.26 (br, 1H), 7.45-7.28 (m, 15H), 6.36 (d, *J* = 6.4 Hz, 1H), 5.80 (dd, *J* = 5.2, 6.4 Hz, 1H), 5.51 (dd, *J* = 3.2, 5.2 Hz, 1H), 5.30 (s, 2H), 5.13 (dd, *J* = 12.0, 14.0 Hz, 2H), 5.07 (dd, *J* = 11.6, 20.4 Hz, 2H), 4.39 (q, *J* = 2.8 Hz, 1H), 3.98 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.86 (dd, *J* = 2.8, 11.6 Hz, 1H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 153.8, 153.4, 151.43, 150.9, 149.5, 141.0, 135.6, 134.8, 134.6, 128.96, 128.86, 128.80, 128.77, 128.63, 122.3, 85.3, 83.5, 77.1, 74.7, 70.7, 70.6, 68.0, 62.9, 26.1, 18.6, -5.2, -5.3; MS-ESI$^+$ *m/z* 784 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{40}H_{46}N_5O_{10}Si$ (M+H$^+$) 784.3024, found 784.3022.

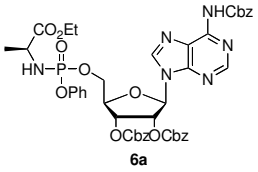


5a

2',3'-*O*-*N*^{6}-tris-benzyloxycarbonyl adenosine (5a)

Compound **5a** was prepared using the same procedure as the C analog above (Step 3): yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (br, 1H), 8.75 (s, 1H), 7.84 (s, 1H), 7.43-7.26 (m, 15H), 6.15 (dd, *J* = 2.4, 11.6 Hz, 1H), 5.99 (dd, *J* = 5.2, 8.0 Hz, 1H), 5.85 (d, *J* = 8.0 Hz, 1H), 5.63 (d, *J* = 5.2 Hz, 1H), 5.28 (dd, *J* = 12.0,

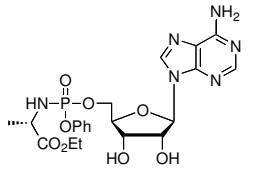
16.8 Hz, 2H), 5.15 (s, 2H), 5.04 (dd, *J* = 12.0, 23.2 Hz, 2H), 4.44 (s, 1H), 3.98 (dd, *J* = 2.4, 11.2 Hz, 1H), 3.84 (dt, *J* = 1.6, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 153.4, 152.7, 151.0, 150.6, 150.2, 143.1, 135.3, 134.7, 134.4, 129.1, 129.0, 128.9, 128.8, 128.6, 123.7, 88.0, 86.1, 76.1, 75.5, 70.8, 70.5, 68.2, 62.8; MS-ESI$^+$ *m/z* 670 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{34}H_{32}N_5O_{10}$ (M+H$^+$) 670.2161, found 670.2157.



6a

5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl-2',3'-*O*-*N*^{6}-tris-benzyloxycarbonyl adenosine (6a)

Compound **6a** was prepared using the same procedure as the C analog above (Step 4): yield 96% (the ratio of diastereomers = 2:1 by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74-8.71 (s, 1H), 8.55-8.53 (s, 1H), 8.13-8.05 (s, 1H), 7.45-7.09 (m, 20H), 6.19 (d, *J* = 5.6 Hz, 1H), 5.96-5.88 (t, *J* = 5.6 Hz, 1H), 5.67 (t, *J* = 4.8 Hz, 1H), 5.29 (s, 2H), 5.14-5.13 (s, 2H), 5.11-5.03 (m, 2H), 4.47-4.34 (m, 3H), 4.15-3.97 (m, 3H), 3.86-3.77 (m, 1H), 1.92 (s, 1H), 1.35-1.25 (d, *J* = 7.2 Hz, 3H), 1.22-1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (m), 153.9 (d), 153.3, 151.1 (d), 149.7 (d), 144.1 (d), 135.5, 134.6 (d), 129.9, 129.0, 128.9, 128.85, 128.80, 128.7, 125.3, 122.6 (d), 120.3 (m), 85.9, 81.0 (m), 75.8 (d), 73.6 (d), 70.8 (d), 68.0, 65.4 (m), 61.8 (d), 50.4, 21.2 (m), 14.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.00, 2.96; MS-ESI$^+$ *m/z* 925 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{45}H_{46}N_6O_{14}P$ (M+H$^+$) 925.2818, found 925.2817.

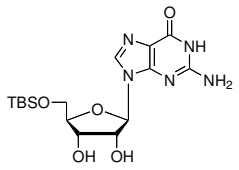


8a

5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl adenosine (8a)

Compound **8a** was prepared using the same procedure as the C analog above (Step 5): yield 94% (the ratio of diastereomers = 1:1 by ^{1}H NMR). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25-8.16 (m, 2H), 7.31-7.28 (m, 2H), 7.20-7.11 (m, 3H), 6.02 (t, *J* = 4.8 Hz, 1H), 4.66-4.61 (m, 1H), 4.45-4.30 (m, 3H), 4.29-4.23 (m, 1H), 4.09-4.01 (m, 2H), 3.91-3.08 (m, 1H), 1.27-1.20 (m, 3H), 1.18-1.13 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ175.09, 157.45, 154.12, 152.22, 150.78, 141.15, 130.91, 130.09, 126.32, 121.53, 121.51, 120.57, 90.04,

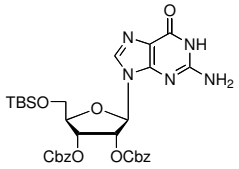
84.50, 75.52, 71.68, 67.40, 62.49, 51.67, 20.55, 14.58; ^{31}P NMR (162 MHz, CD_3OD) δ 4.93, 4.78; MS-ESI$^+$ *m/z* 523 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{21}H_{27}N_6O_8NaP$ (M+Na$^+$) 545.1517, found 545.1515.



3b

5'-*O-tert*-Butyldimethylsilyl guanosine (3b)

To a solution of guanosine (1.0 g, 3.53 mmol) in 5.0 mL of anhydrous DMSO and 20 mL of CH_2Cl_2 was added DMAP (0.04 g, 0.35 mmol), TBSCl (1.07 g, 7.06 mmol) and Et_3N (0.79 g, 7.77 mmol) at room temperature under N_2 atmosphere. After stirring for 24 h, the solution was treated with 10 mL of MeOH and stirred for 3 h at room temperature and was concentrated. The residue was adsorbed on silica gel and purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1 to 5:1 v/v) to give compound **3b** (1.22 g, 3.07 mmol) in 87% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (br, 1H), 7.81 (s, 1H), 6.53 (br, 2H), 5.66 (d, *J* = 5.6 Hz, 1H), 5.46 (d, *J* = 5.6 Hz, 1H), 5.15 (d, *J* = 4.8 Hz, 1H), 4.29 (q, *J* = 4.8 Hz, 1H), 4.04 (q, *J* = 4.8 Hz, 1H), 3.85 (q, *J* = 4.0 Hz, 1H), 3.76 (dd, *J* = 4.0, 11.2 Hz, 1H), 3.67 (dd, *J* = 4.0, 11.2 Hz, 1H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.8, 153.8, 151.4, 134.9, 116.6, 86.2, 84.3, 73.9, 67.0, 63.0, 25.9, 18.1, -5.3, -5.4; MS-ESI$^+$ *m/z* 398 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{16}H_{27}N_5O_5Si$ (M+H$^+$) 398.1855, found 398.1854.

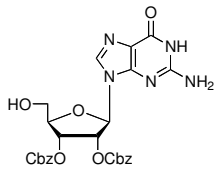


4b

5'-*O-tert*-Butyldimethylsilyl-2',3'-*O*-bis-benzyloxycarbonyl-guanosine (4b)

Compound **4b** was prepared using the same procedure as the C analog above (Step 2): yield 89%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.85 (s, 1H), 7.36-7.29 (m, 10H), 6.56 (br, 2H), 5.99 (d, *J* = 6.8 Hz, 1H), 5.67 (dd, *J* = 5.2, 7.2 Hz, 1H), 5.40 (dd, *J* = 2.4, 5.2 Hz, 1H), 5.18-5.07 (m, 4H), 4.30 (q, *J* = 3.6 Hz, 1H), 3.87 (d, *J* = 3.6 Hz, 2H), 0.89 (s, 9H), 0.09 (3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 154.1, 153.5, 153.1, 151.3, 135.0, 134.8, 134.3, 128.61, 128.55, 128.49, 128.37, 128.20, 116.5, 82.9, 82.4,

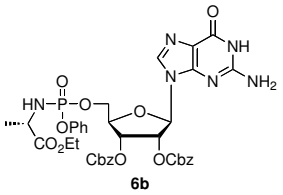
76.1, 74.6, 69.9, 69.6, 62.8, 25.8, 18.0, -5.5, -5.6; MS-ESI$^+$ *m/z* 666 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{32}H_{40}N_5O_9Si$ (M+H$^+$) 666.2601, found 666.2603.



5b

2',3'-*O*-Bis-benzyloxycarbonyl guanosine (5b)

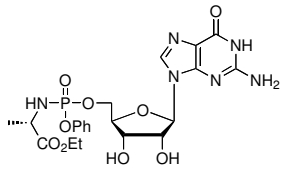
Compound **5b** was prepared using the same procedure as the C analog above (Step 3): yield 95%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (br, 1H), 7.99 (s, 1H), 7.35-7.29 (m, 10H), 6.58 (br, 2H), 5.99 (d, *J* = 7.2 Hz, 1H), 5.72 (dd, *J* = 4.8, 7.2 Hz, 1H), 5.47 (t, *J* = 5.6 Hz, 1H), 5.42 (dd, *J* = 2.0, 5.2 Hz, 1H), 5.18-5.06 (m, 4H), 4.26 (dd, *J* = 3.2, 5.2 Hz, 1H), 3.68 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 154.0, 153.6, 153.1, 151.2, 135.2, 135.0, 134.8, 128.6, 128.53, 128.49, 128.37, 128.19, 116.6, 83.11, 83.07, 76.1, 75.1, 69.8, 69.6, 60.9; MS-ESI$^+$ *m/z* 552 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{26}H_{26}N_5O_9$ (M+H$^+$) 552.1726, found 552.1725.



6b

5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl-2',3'-*O*-bis-benzyloxycarbonyl guanosine (6b)

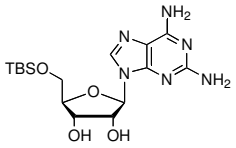
Compound **6b** was prepared using the same procedure as the C analog above (Step 4): yield 93% (the ratio of diastereomers = 1:1.2 by ^{1}H NMR); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (br, 1H), 7.91-7.86 (s, 1H), 7.37-7.14 (m, 15H), 6.55 (br, 2H), 6.20-6.11 (m, 1H), 6.05-6.02 (m, 1H), 5.77-5.70 (m, 1H), 5.55-5.53 (m, 1H), 5.19-5.07 (m, 4H), 4.49-4.22 (m, 3H), 4.06-3.90 (m, 2H), 3.89-3.79 (m, 1H), 3.37 (s, 1H), 1.23-1.19 (m, 3H), 1.14-1.10 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.6 (m), 158.1, 154.3 (d), 154.0, 151.7, 150.8 (d), 136.9 (d), 135.2 (d), 129.6, 129.5, 128.5128.3, 128.2, 125.1 (d), 120.2 (d), 116.7 (d), 85.7 (d), 80.5 (d), 76.0 (d), 73.9 (d), 70.2 (d), 65.5 (d), 61.2, 50.3 (d), 29.6 (d), 19.2 (m), 13.3; ^{31}P NMR (162 MHz, CD_3OD) δ 4.96, 4.82; MS-ESI$^+$ *m/z* 807 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{37}H_{40}N_6O_{13}P$ (M+H$^+$) 807.2399, found 807.2399.



8b

5'-*O*-[Phenyl-(ethoxy-L-alaninyl)]phosphoryl guanosine (8b)

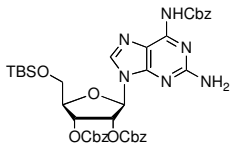
Compound **8b** was prepared using the same procedure as the C analog above (Step 5): yield 96% (the ratio of diastereomers = 1:1 by ^{31}P NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (br, 1H), 7.84 (s, 1H), 7.38-7.14 (m, 5H), 6.57 (br, 2H), 6.11-6.02 (m, 1H), 5.76-5.71 (m, 1H), 5.56 (m, 1H), 5.37-5.33 (m, 1H), 4.43-4.39 (m, 1H), 4.24-3.98 (m, 6H), 3.80 (m, 1H), 1.23-1.18 (m, 3H), 1.15-1.10 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 173.2, 156.8, 153.9, 151.5, 150.7, 135.3, 129.96, 124.6, 120.2, 116.7, 86.3, 82.5, 73.2, 70.2, 66.0, 60.6, 49.8, 19.7 (m), 14.0; ^{31}P NMR (162 MHz, DMSO-d_6) δ 4.66, 4.65; MS-ESI$^+$ *m/z* 539 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{21}H_{27}N_6O_9NaP$ (M+Na$^+$) 561.1468, found 561.1469.



3c

(2*R*,3*S*,4*R*,5*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(2,6-diamino-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (3c)

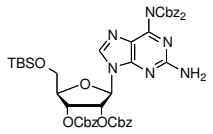
Compound **3c** was prepared using the same procedure as for compound **3b**: yield 95%; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 5.78 (d, *J* = 4.4 Hz, 1H), 4.31 (t, *J* = 4.4 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 1H), 3.97 (m, 1H), 3.83 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.72 (dd, *J* = 2.8, 11.6 Hz, 1H), 0.78 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.1, 157.7, 152.8, 137.5, 114.4, 89.5, 86.3, 76.6, 71.5, 64.0, 26.6, 19.5, -5.1, -5.2; MS-ESI$^+$ *m/z* 397 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{16}H_{29}N_6O_4Si$ (M+H$^+$) 397.2013, found 397.2014.



4c

Benzyl (2-amino-9-((2*R*,3*R*,4*R*,5*R*)-3,4-bis(((benzyloxy)carbonyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-9*H*-purin-6-yl)carbamate (4c)

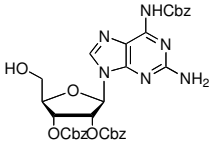
Compound **4c** was prepared using the same procedure as the C analog above (Step 2): yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br, 1H), 7.91 (s, 1H), 7.40-7.31 (m, 15H), 6.15 (d, *J* = 6.0 Hz, 1H), 5.78 (dd, *J* = 5.2, 6.4 Hz, 1H), 5.54 (dd, *J* = 3.2, 4.8 Hz, 1H), 5.14 (br, 2H), 5.13 (s, 2H), 5.10 (d, *J* = 1.6 Hz, 2H), 5.07 (dd, *J* = 12.0, 23.6 Hz, 2H), 4.30 (q, *J* = 2.8 Hz, 1H), 3.91 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.83 (dd, *J* = 2.8, 11.6 Hz, 1H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 154.3, 153.8, 153.6, 151.3, 150.1, 138.0, 135.6, 134.8, 134.6, 128.82, 128.79, 128.74, 128.67, 128.65, 128.55, 128.50, 116.5, 84.4, 82.9, 76.6, 74.6, 70.5, 70.4, 67.6, 62.8, 26.0, 18.5, -5.3, -5.4; MS-ESI$^+$ *m/z* 799 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{40}H_{47}N_6O_{10}Si$ (M+H$^+$) 799.3134, found 799.3131.



10

Compound 10

Yield was 5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 8.38-7.23 (m, 20H), 6.21 (d, *J* = 6.4 Hz, 1H), 5.75 (d, *J* = 5.2, 6.4 Hz, 1H), 5.54 (dd, *J* = 2.8, 5.2 Hz, 1H), 5.26 (s, 2H), 5.25 (s, 2H), 5.15-5.09 (m, 4H), 4.95 (br, 2H), 4.34 (q, *J* = 2.4 Hz, 1H), 3.92 (dd, *J* = 2.4, 11.6 Hz, 1H), 3.85 (dd, *J* = 2.4, 11.6 Hz, 1H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 155.7, 154.4, 153.8, 153.5, 151.8, 150.0, 140.4, 135.1, 134.8, 134.7, 129.0, 128.96, 128.90, 128.83, 128.72, 128.63, 128.44, 128.23, 123.6, 84.4, 83.3, 76.7, 74.9, 70.7, 70.6, 69.2, 63.1, 47.9, 26.2, 18.6, -5.2, -5.3; MS-ESI$^+$ *m/z* 933 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{48}H_{53}N_6O_{12}Si$ (M+H$^+$) 933.3514, found 933.3499.

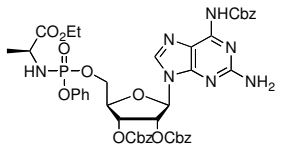


5c

Benzyl (2-amino-9-((2*R*,3*R*,4*R*,5*R*)-3,4-bis(((benzyloxy)carbonyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9*H*-purin-6-yl)carbamate (5c)

Compound **5c** was prepared using the same procedure as the C analog above (Step 3): yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (br, 1H), 7.49 (s, 1H), 7.35-7.24 (m, 15H), 6.62 (d, *J* = 11.2 Hz, 1H), 5.98 (dd, *J* = 4.8, 7.6 Hz, 1H), 5.77 (d, *J* = 7.6 Hz, 1H), 5.63 (d, *J* = 4.8 Hz, 1H), 5.43 (br, 2H), 5.18 (dd, *J* = 12.0, 20.8 Hz, 2H), 5.11 (d, *J* = 1.2 Hz, 2H), 5.05 (dd, *J* = 12.0, 27.2 Hz, 2H), 4.37 (s, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.77 (t, *J* =11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 154.2, 153.6, 151.8, 151.2, 150.9, 139.9,

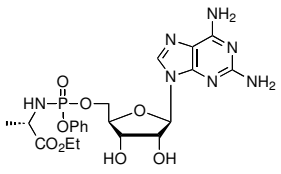
135.5, 134.7, 134.5, 128.82, 128.79, 128.73, 128.67, 128.63, 128.53, 128.50, 117.3, 87.4, 85.4, 76.0, 75.1, 70.6, 70.3, 67.6, 62.6; MS-ESI$^+$ *m/z* 685 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{34}H_{33}N_6O_{10}$ (M+H$^+$) 685.2268, found 685.2266.



6c

(2*S*)-Ethyl 2-(((((2*R*,3*R*,4*R*,5*R*)-5-(2-amino-6-(((benzyloxy)carbonyl)amino)-9*H*-purin-9-yl)-3,4-bis(((benzyloxy)carbonyl)oxy)tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (6c)

Compound **6c** was prepared using the same procedure as the C analog above (Step 4): yield 95% (the ratio of diastereomers = 6:4 by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.24 (s, 1H), 7.64-7.60 (s, 1H), 7.42-7.10 (m, 20H), 6.07-5.98 (t, *J* = 5.6 Hz, 1H), 5.95-5.92 (d, *J* = 5.6 Hz, 1H), 5.77-5.69 (t, *J* = 4.8 Hz, 1H), 5.41-5.34 (s, 2H), 5.24 (s, 2H), 5.12 (s, 2H), 5.10-5.04 (m, 2H), 4.59-4.54 (m, 1H), 4.45-4.40 (m, 1H), 4.39-4.31 (m, 1H), 4.15-3.77 (m, 4H), 2.10 (br, 1H), 1.32-1.24 (d, *J* = 7.2 Hz, 3H), 1.20-1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (m), 160.1, 154.1, 153.7 (d), 153.1 (d), 151.2, 150.5 (d), 150.2 (d), 139.1 (d), 135.7, 134.6 (d), 129.9, 128.88, 128.78, 128.72, 128.66, 128.59, 128.56, 125.2 (d), 120.5 (d), 120.2 (d), 116.9 (d), 86.1 (d), 80.6 (m), 77.4, 75.4 (d), 73.9 (d), 70.6 (d), 67.6 (d), 65.4 (m), 61.6 (d), 50.3 (d), 21.0 (m), 14.2 (d); ^{31}P NMR (162 MHz, $CDCl_3$) δ 3.49, 3.20; MS-ESI$^+$ *m/z* 940 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{45}H_{47}N_7O_{14}$ (M+H$^+$) 940.2930, found 940.2927.



8c

(2*S*)-Ethyl 2-(((((2*R*,3*S*,4*R*,5*R*)-5-(2,6-diamino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (8c)

Compound **8c** was prepared using the same procedure as the C analog above (Step 5): yield 96% (the ratio of diastereomers = 1:1 by ^{1}H NMR); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.38-7.32 (m, 2H), 7.22-7.14 (m, 3H), 6.75 (br, 2H), 6.09-6.01 (m, 1H), 5.83 (br, 2H), 5.76 (t, *J* = 6.0 Hz, 1H), 5.53 (br, 1H), 5.33 (br, 1H), 4.50 (t, *J* = 5.2 Hz, 1H), 4.30-4.24 (m, 1H), 4.20-3.97 (m, 5H), 3.86-3.76 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.15-1.10 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2 (m), 160.3, 156.2, 152.0, 150.7, 135.7,

129.6, 124.6, 120.2, 113.3, 86.4, 82.3, 72.9, 70.3, 66.0, 60.6, 49.8, 19.7 (m), 14.0; ^{31}P NMR (162 MHz, DMSO-d_6) δ 4.67, 4.63; MS-ESI$^+$ *m/z* 538 (M+H$^+$); HRMS-ESI$^+$: *m/z* calcd. for $C_{21}H_{29}N_7O_8P$ (M+H$^+$) 538.1808, found 538.1809.

(i) Cho, J. H.; Amblard, F.; Coats, S. J.; Schinazi, R. F. *Tetrahedron* **2011**, *67*, 5487-5493.
(ii) Johnson II, D. C.; Widlanski, T. S. *Org. Lett*. **2004**, *6*, 4643-4646.