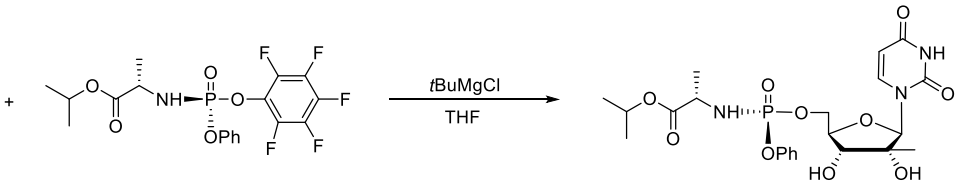
Supplemental Material

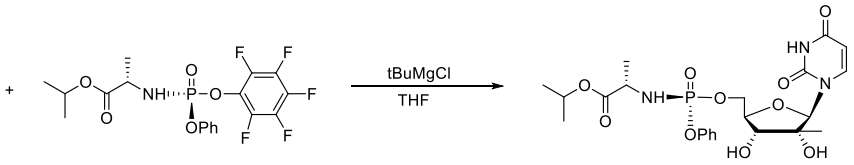
Synthesis of compounds 14 and 15:

Anhydrous solvents were purchased from Aldrich Chemical Company, Inc. (Milwaukee). Reagents were purchased from commercial sources. Unless noted otherwise, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. ^{1}H, ^{13}C and ^{31}P NMR spectra were taken on a Bruker Ascend^{TM} 400 spectrometer at rt, and reported in ppm downfield from internal tetramethylsilane (for ^{1}H-NMR). NMR processing was performed with MestReNova version 10.0.2-15465. Deuterium exchange and decoupling experiments were utilized to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), bs (broad singlet), m (multiplet). All J-values are in Hz and calculated by Mnova or MestReNova programs. Mass spectra were determined on a Micromass Platform LC spectrometer using electrospray ionization. Column chromatography was performed on Combiflash R_f 200.

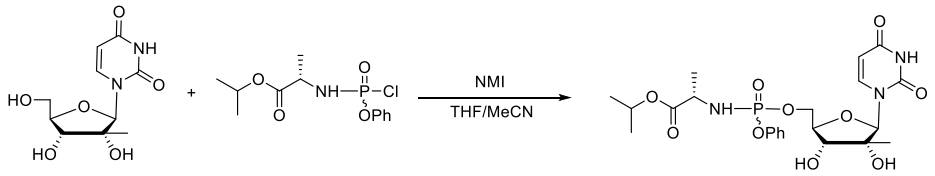


To a solution of 2'-methyluridine **A** (50 mg, 0.19 mmol) in THF (1.5 mL) was added a solution of tert-butyl magnesium chloride (3 M in THF, 0.20 mL, 0.6 mmol) at 0 °C. After being stirred at room temperature for 30 min, a solution of phosphoramidate **B** (105 mg, 0.23 mmol) in THF (0.5 mL) was added at room temperature. The reaction mixture was then stirred at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3), washed with brine and dried over sodium sulfate. After removal of the volatiles

solvent under reduced pressure, the residue was purified by column chromatography (0 to 8% methanol in dichloromethane) to give **11** (56 mg, 56%).
^{1}H NMR (400 MHz, MeOD) δ 7.48 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 2H), 7.05 (ddd, *J* = 16.8, 9.0, 1.0 Hz, 2H), 7.00 (td, *J* = 7.5, 0.9 Hz, 1H), 5.76 (s, 1H), 5.41 (d, *J* = 8.1 Hz, 1H), 4.75 (dt, *J* = 12.6, 6.3 Hz, 1H), 4.30 (ddd, *J* = 11.7, 5.8, 1.9 Hz, 1H), 4.17 (ddd, *J* = 11.8, 5.9, 3.6 Hz, 1H), 4.09 – 3.86 (m, 1H), 3.71 (dd, *J* = 10.0, 7.1 Hz, 1H), 3.60 (d, *J* = 9.3 Hz, 1H), 1.14 (dd, *J* = 7.1, 0.7 Hz, 3H), 1.01 (dd, *J* = 6.3, 1.0 Hz, 6H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 174.34 (d, *J* = 5.7 Hz), 165.81 (s), 152.43 – 151.96 (m), 141.96 (s), 130.87 (s), 126.21 (s), 121.32 (d, *J* = 4.9 Hz), 102.79 (s), 93.54 (s), 81.55 (d, *J* = 8.1 Hz), 79.57 (s), 73.98 (s), 70.17 (s), 66.28 (d, *J* = 5.3 Hz), 51.64 (s), 21.92 (d, *J* = 9.0 Hz), 20.64 (d, *J* = 6.2 Hz), 20.19 (s); ^{31}P NMR (162 MHz, MeOD) δ 3.80 (s); LCMS: 528.2 $(M+1)^{+}$.

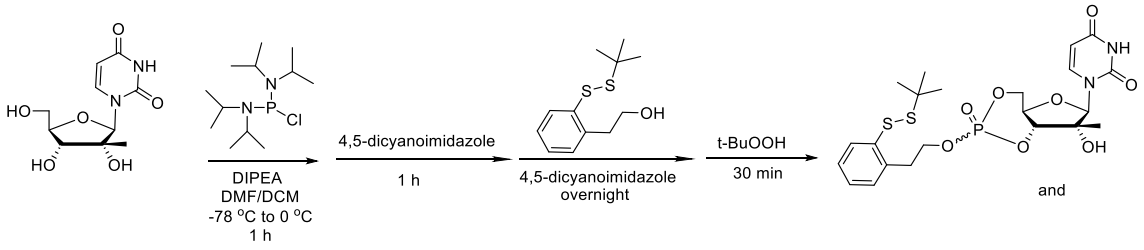


To a solution of **A** (50 mg, 0.19 mmol) in THF (1.5 mL) was added a solution of tert-butyl magnesium chloride (3 M in THF, 0.20 mL, 0.6 mmol) at 0 °C. After being stirred at room temperature for 30 min, a solution of phosphoramidate **C** (60 mg, 0.13 mmol) in THF (1.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with water and extracted with ethyl acetate (30 mL × 3), washed with brine and dried over sodium sulfate. After removal of the volatiles solvent under reduced pressure, the residue was purified by column chromatography (0 to 8% methanol in dichloromethane) to give **12** (2 mg, 2 %).
^{1}H NMR (400 MHz, MeOD) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.34 – 7.15 (m, 3H), 5.98 (s, 1H), 5.64 (d, *J* = 8.1 Hz, 1H), 5.11 – 4.96 (m, 1H), 4.69 – 4.52 (m, 1H), 4.43 – 4.37 (m, 1H), 4.11 (dd, *J* = 9.2, 2.2 Hz, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 3.79 (d, *J* = 9.2 Hz, 1H), 1.37 – 1.23 (m, 9H), 1.14 (d, *J* = 8.3 Hz, 3H); ^{31}P NMR (162 MHz, MeOD) δ 3.92 (s); LCMS: 528.3 $(M+1)^{+}$.



To a solution of 2'-methyluridine **A** (50.0 mg, 0.19 mmol) and chlorophosphoramidate **D** (118 mg, 0.38 mmol) in anhydrous THF (1 mL) and acetonitrile (1 mL) was added *N*-methylimidazole (31.2 mg, 0.38 mmol) at room temperature. The reaction mixture was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3), washed with brine and dried over sodium sulfate. After removal of the volatils under reduced pressure, the residue was purified by column chromatography (0 to 8% methanol in dichloromethane) to give **13** (75.1 mg, 75%) as a 1/1 Rp/Sp mixture.

^{1}H NMR (400 MHz, MeOD) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.38 (m, 2H), 7.30 – 7.12 (m, 3H), 5.98 (s, 0.5H), 5.97 (s, 0.5H), 5.64 (d, *J* = 8.1 Hz, 1H), 5.61 (d, *J* = 8.1 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.54 (m, 1H), 4.43 – 4.34 (m, 1H), 4.15 – 4.05 (m, 1H), 3.97 – 3.84 (m, 1H), 3.80 (m, 1H), 1.33 (m, 3H), 1.25 – 1.19 (m, 6H), 1.16 (s, 1.5H), 1.13 (s, 1.5H); ^{13}C NMR (101 MHz, MeOD) δ 174.62, 174.58, 174.37, 174.31, 165.80, 152.27, 152.25, 152.16, 152.10, 141.96, 141.76, 130.89, 130.87, 126.23, 121.34, 121.29, 121.25, 102.84, 102.79, 93.54, 93.32, 81.59, 81.50, 79.66, 79.57, 74.00, 73.68, 70.20, 70.18, 66.31, 66.26, 65.78, 65.73, 51.81, 51.80, 51.64, 51.63, 21.98, 21.97, 21.90, 21.88, 20.67, 20.61, 20.42, 20.35, 20.18; ^{31}P NMR (162 MHz, MeOD) δ 3.91 (s), 3.79 (s); LC/MS: 528.3 $(M+1)^{+}$.



A solution of bis-(*N,N*-diisopropylamino)-chlorophosphine (270 mg, 1.0 mmol) and 4Å MS (5 counts) in dry DCM (0.5 mL) was added dropwise to a solution of **A** (260

mg, 1.0 mmol) and DIPEA (190 □L, 1.1 mmol) in dry DMF (2 mL) and 4Å MS (6 counts) at -78 °C. The reaction mixture was warmed to room temperature and stirred at room temperature for 1 h. A solution of 4,5-dicyanoimidazole (110 mg, 1.0 mmol) in DMF (0.5 mL) was added, and the mixture was stirred at room temperature for 1 h. The solution of alcohol **E** (240 mg, 1.0 mmol) and 4,5-dicyanoimidazole (110 mg, 1.0 mmol) in DMF (1 mL) was added, and the mixture was stirred overnight. A solution of *t*-butyl hydroperoxide (0.2 mL, 5-6 M in decane) was then added and the mixture was stirred for 30 min. The reaction mixture was extracted with ethyl acetate (150 mL) and water (50 mL). The organic phase was washed with brine (30 mL) and dried over sodium sulfate. After removal of the volatiles solvent under reduced pressure, the residue was purified by column chromatography (0 to 8% methanol in dichloromethane) to give the more polar isomer **14** (24.9 mg, 4.6 %) and the less polar isomer **15** (53.2 mg, 9.8%).

14: ^{1}H NMR (400 MHz, MeOD) δ 7.89 – 7.77 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.10 (m, 3H), 6.09 (s, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 4.54 (dd, *J* = 13.3, 4.2 Hz, 2H), 4.41 (dd, *J* = 14.4, 7.1 Hz, 3H), 4.31 (d, *J* = 9.7 Hz, 1H), 3.29 – 3.25 (m, 2H), 1.30 (s, 9H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 165.51 (s), 152.15 (s), 141.47 (s), 138.80 (s), 136.26 (s), 131.76 (s), 129.55 (s), 128.74 (s), 128.02 (s), 103.42 (s), 95.66 (s), 83.43 (s), 77.68 (d, *J* = 7.1 Hz), 71.83 – 70.56 (m), 70.56 – 70.19 (m), 69.63 (d, *J* = 6.8 Hz), 50.12 (s), 35.04 (d, *J* = 7.2 Hz), 30.21 (s), 19.78 (s); ^{31}P NMR (162 MHz, MeOD) δ -4.16 (s); HRMS: $(M-1)^-$ 543.1025, found 543.1034.

15: ^{1}H NMR (400 MHz, MeOD) δ 7.88 – 7.82 (m, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.32– 7.19 (m, 1H), 7.25 – 7.20 (m, 2H), 6.04 (s, 1H), 5.84 (d, *J* = 7.9 Hz, 1H), 4.58 (dd, *J* = 21.5, 5.6 Hz, 1H), 4.40 (q, *J* = 6.5 Hz, 2H), 4.28 – 4.16 (m, 2H), 3.83 (d, *J* = 8.3 Hz, 1H), 3.34 (d, *J* = 5.7 Hz, 2H), 1.29 (s, 9H), 1.15 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 165.43 (s), 152.00 (s), 141.00 (s), 139.01 (s), 136.81 (s), 131.63 (s), 129.52 (s), 128.91 (s), 128.22 (s), 103.59 (s), 95.61 (s), 84.49 (s), 77.53 (d, *J* = 7.6 Hz), 72.63 – 70.19 (m), 69.05 (s), 50.32 (s), 34.90 (d, *J* = 7.1 Hz), 30.18 (s), 19.94 (s); ^{31}P NMR (162 MHz, MeOD) δ -5.81 (s); HRMS: $(M-1)^-$ 543.1025, found 543.1032.