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Synthesis of α-L-Threose Nucleoside Phosphonates via Regioselective Sugar Protection

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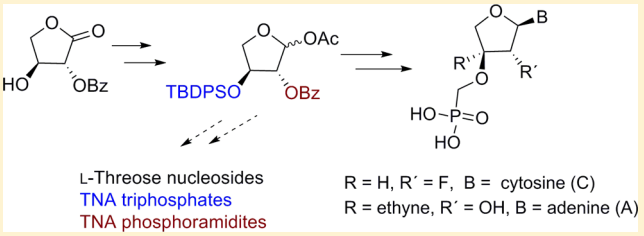
Supporting Information

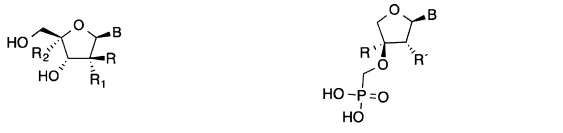
ABSTRACT: A new synthesis route to α-L-threose nucleoside phosphonates via 2-*O* and 3-*O* selectively protected L-threose is developed. The key intermediates 2-*O*-benzoyl-L-threonolactone and 1-*O*-acetyl-2-*O*-benzoyl-3-*O*-*t*-butyldiphenylsilyl-L-threofuranose were functionalized to synthesize 2′-deoxy-2′-fluoro- and 3′-*C*-ethynyl L-threose 3′-*O*-phosphonate nucleosides. The key intermediates developed are important intermediates for the synthesis of new L-threose-based nucleoside analogues, TNA phosphoramidites, and TNA triphosphates.



INTRODUCTION

The modification of the nucleobase and/or sugar moiety of a natural nucleoside is an obvious choice for developing new antiviral compounds, and threose-based nucleosides could serve this purpose.[1−4] Moreover, (3′,2′)-α-L-threose nucleic acid (TNA) is a possible RNA progenitor because of the chemical simplicity of threose relative to that of ribose and the ability of TNA to form thermally stable duplexes with DNA and RNA that are comparable to those of natural nucleic acid associations.[5] α-L-Threose nucleosides have been synthesized and assembled chemically[5,6] to generate TNA; recently, all four threo-nucleoside triphosphates (tNTPs) were successfully assembled into TNA oligomers with high fidelity by DNA polymerases.[7−9] There are convincing reasons to develop new efficient routes for the synthesis of L-threose nucleosides and to try to discover new α-L-threose nucleoside analogues that can target viral polymerase as a triphosphate.[10−15]

Recently, we have demonstrated that the L-2′-deoxythreose nucleoside phosphonates PMDTA (**5**, EC_{50} = 2.5 μM) and PMDTT (**6**) selectively inhibit HIV without affecting normal cell proliferation (Figure 1).[10] The 4′-*C*-ethynyl substitution of natural nucleosides (e.g., **4**) has a beneficial effect on anti-HIV activity.[16] This has generated our interest in synthesizing the 3′-*C*-ethynyl analogue of PMTA (**8**). Furthermore, 2′-deoxy-2′-fluoro nucleosides were found to possess interesting biological properties because fluorine mimics both H or OH to some extent.[17] In particular, the cytosine-based 2′-deoxy-2′-fluoro-threose phosphonate (**7**) analogue is an attractive target because several bioactive nucleosides are cytosine nucleosides[4,18] with a 2′-mono or 2′,2′-difluoro modification (e.g., **1**−**3**), with the latter showing potent inhibition of HCV replication. 2′-Fluoro-2′-methyl-substituted nucleosides have become leading compounds in the development of an anti-HCV therapy, and these analogues are currently being investigated under phase II and III clinical trials.[4] Herein, we describe an easy chemical synthesis route to develop new α-L-threose nucleoside analogues via differentially protected 2-*O*- and 3-*O*-L-threose (**17**, Scheme 2).



1 : R = F, R_1 = H: F-araC (L1210)
2 : R = F, R_1 = F: Gemcitabine
3 : R = CH_3, R_1 = F: PSI-6130
} R_2 = H, B = cytosine

4 : R = R_1 = H, R_2 = ethyne, B = adenine: 4′EdA

5 : R = H; R′ = H, B = adenine (A) : PMDTA
6 : R = H; R′ = H, B = thymine (T) : PMDTT
7 : R = H, R′ = F, B = cytosine (C)
8 : R = ethyne, R′ = OH, B = A

Figure 1. Structures of biologically active nucleoside analogues (**1**−**6**) and current L-threose nucleoside phosphonate targets (**7**, **8**).

RESULTS AND DISCUSION

Our initial synthesis plan for the synthesis of **7** is shown in Scheme 1. Eschenmoser et al.[6] have described an efficient strategy for the synthesis of compounds **9** and **10**. The stereoselective Vorbrüggen glycosylation of silylated nucleobases requires the availability of 1-*O*- and 2-*O*-acylated sugars. To fulfill this requirement, the synthesis of the PMDT analogue was accomplished via multistep protection, deprotection, and reprotection procedures to obtain compound **14**[10] via **11** and **12** (Scheme 1). For the nucleophilic fluorination at the 2′ position, the epimerization of the 2′-hydroxyl group in threose to an erythrose is needed, which was successfully accomplished via Dess−Martin periodinane (DMP) oxidation followed by sodium borohydride reduction to afford compound **15**.

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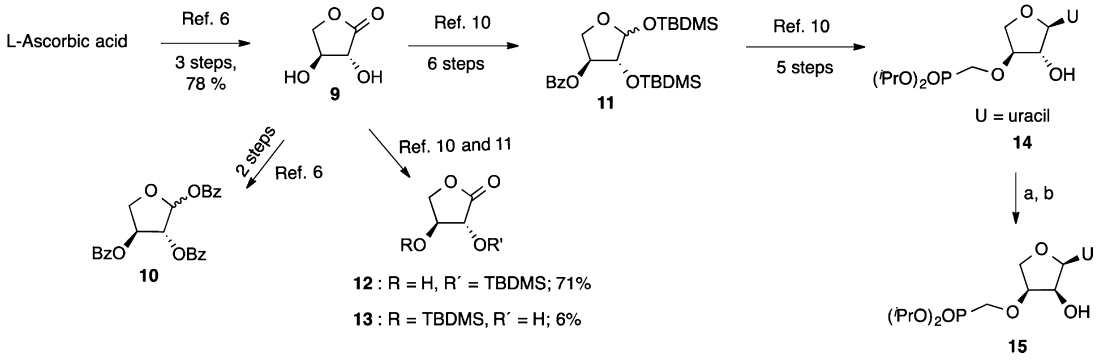
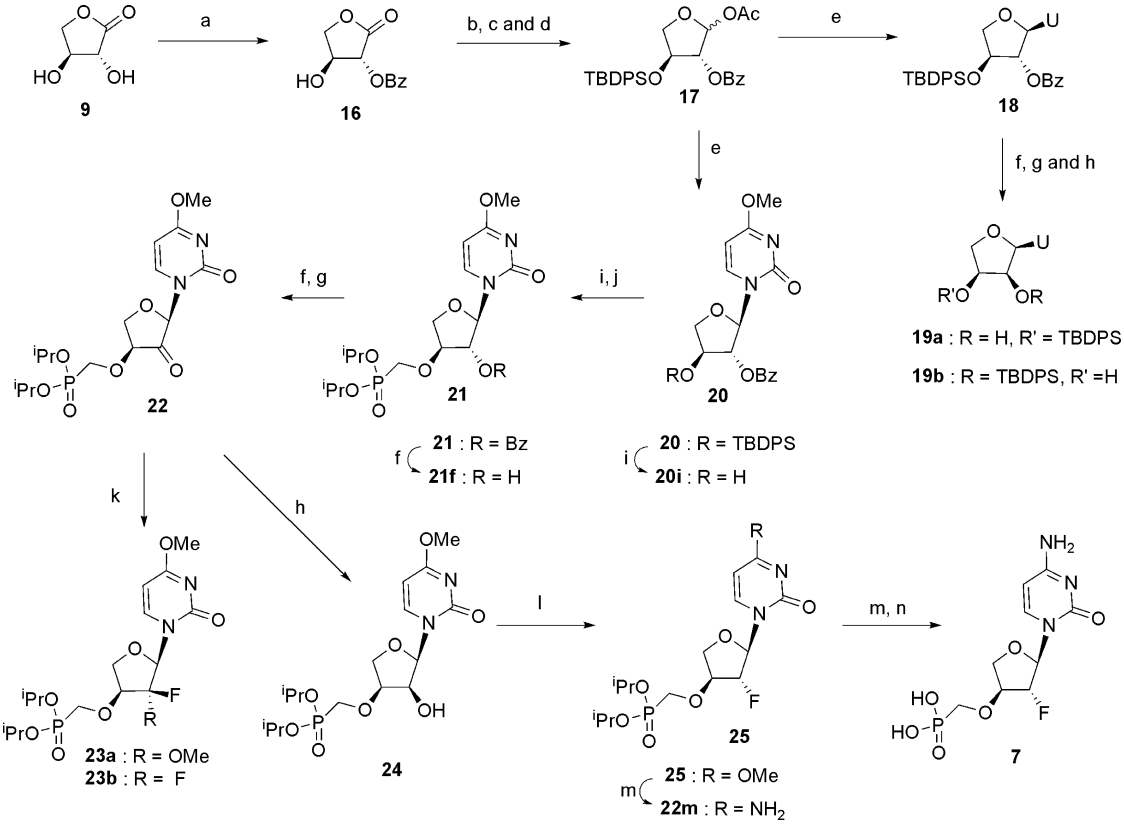
Scheme 1. Previous Synthesis Strategies for α-L-Threose Nucleosides and Our Initial Synthesis Work toward the Target Compound 7 via 15.[a]



[a]Reagents and conditions: (a) DMP (15% in CH_2Cl_2), 0 °C to rt, 1 h, 98% and (b) $NaBH_4$, MeOH, 1 h, 0 °C to rt, 80%. Note that the attempts to form the anhydro from **14** were unsuccessful.

Scheme 2. Synthesis of 2′-Deoxy-2′-fluoro L-Threose Analogue[a]



[a]Reagents and conditions: (a) benzoyl chloride (1 equiv), imidazole (Im, 2 equiv), CH_3CN, −5 °C to rt, 8 h, 95%; (b) TBDPSCl, cat. DMAP, Im (2 equiv), 0 °C to rt, 10 h, 98%; (c) DIBAL-H (1.2 M in toluene, 2 equiv), dry THF, −70 to −60 °C, 3 h, 94%; (d) acetic anhydride, Et_3N, dry CH_2Cl_2, 0 °C to rt, 8 h, 92%; (e) O^4-methyluracil or uracil, *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 2 equiv), TMSOTf (3 equiv), 60 °C, 2.5 h, 82−88%; (f) LiOH, H_2O/MeOH, rt, 1 h, 83%; (g) DMP (15% in CH_2Cl_2), 0 °C to rt, 1 h, 98%; (h) $NaBH_4$, MeOH, 1 h, 0 °C to rt, 80%; (i) TBAF (1 M in THF), 0 °C to rt or $Et_3N{\cdot}3HF$, 15 h, 0 °C to rt, 84−90%; (j) NaH, CH_3CN, −5 to −10 °C, $(^iPrO)_2POCH_2OTf$, 45 min, 85%; (k) DAST, Py-HF, CH_2Cl_2, −5 °C to rt, 12 h, 29% of **23a**; (l) DAST (4 equiv), $Et_3N{\cdot}HF$ (0.05 equiv), CH_2Cl_2, −10 °C to rt, 10 h, 46%; (m) sat. NH_3 in MeOH, 60 °C, 6 h, 81%; and (n) TMSBr, Et_3N, rt, 30 h, 71%.

This synthesis approach is cumbersome, and we have investigated ways to shorten this synthesis pathway. All of the effort to 3-*O*-phosphonomethylate **12** in the presence of hindered bases (e.g., 2,6-di-*tert*-butyl-4-methylpyridine, Hünig's base) as well as the Lewis acid-catalyzed benzylation of the 3′-hydroxyl group with benzyl trichloroacetimidate were unsuccessful.[19] However, the regioselective benzoylation of L-threonolactone (**9**) was successful. The addition of benzoyl chloride to a solution of **9** and imidazole in acetonitrile at −5 °C to room temperature (rt) for 8 h furnished **16** exclusively in excellent yield (95%, Scheme 2). Compound **16** was silylated at the 3′-hydroxyl group with TBDPSCl (98%) followed by the DIBAL-H-mediated reduction of the lactone to the lactol and acetylation, affording key intermediate **18** in 87% yield.

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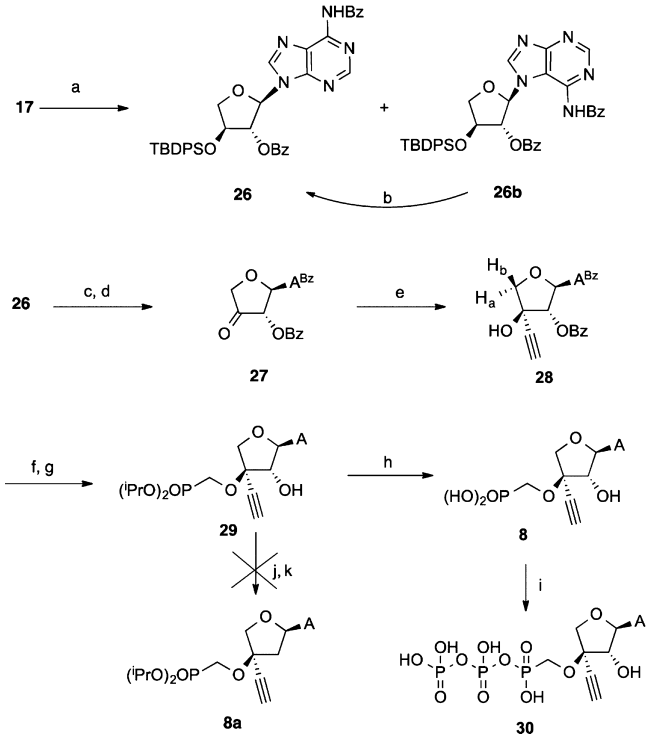
The Vorbrüggen glycosylation of silylated uracil using trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 60 °C in acetonitrile furnished **18** in 80% yield. Unfortunately, the 2′-*O*-debenzoylation of **18** and the oxidation followed by reduction of the 2′-hydroxy function resulted in the formation of a mixture of **19a** and **19b** resulting from TBDPS migration under reducing conditions. Alternatively, compound **17** was glycosylated with O^4-methyluracil to obtain **20** in 82% yield. Several reaction conditions were tested for the sodium hydride-mediated 3′-*O*-phosphomethylation of desilylated compound **20** with diisopropylphosphonomethyl triflate to avoid undesired side reactions resulting from the presence of the 2′-*O*-benzoyl moiety. The addition of 1 equiv of sodium hydride to a equimolar mixture of desilylated compound **20** and diisopropylphosphonomethyl triflate in acetonitrile at −5 to −10 °C for 45 min afforded 3′-phonsphonomethylated **21** in 85% yield. Compound **24** could readily be prepared by the functional-group manipulation of **21** in a manner similar to the one described for the conversion of **14** to **15** (64% over three steps). The difluorination of 2′-keto nucleoside **22** was attempted under various reaction conditions with diethylaminosulfur trifluoride (DAST) and morpholinodifluorosulfinium tetraborate[20] (XtalFluoro-M) with or without a promoter, such as $Et_3N{\cdot}3HF$, Py-HF, or DBU. Required difluoro compound **23b** could not be obtained. Under DAST and Py-HF-DBU conditions, only a trace of required compound **23b** was formed. All of the efforts to improve the yields failed in our hands. TLC of the reaction mixture showed the formation of a second product that, however, disappeared to starting material after an aqueous sat. $NaHCO_3$ workup. Thus, the reaction mixture was purified (elution with 98:2 CH_2Cl_2/MeOH) without a previous reaction workup to afford **23a** in 29% yield. The configuration of 2′-OMe in **23a** was confirmed by HMBC analysis.

The fluorination of **24** was carried out with DAST and $Et_3N{\cdot}3HF$ as a promoter from −10 °C to rt to furnish 2′-fluorinated nucleoside **25** in 46% yield. The smooth conversion of the O^4-methyluracil moiety to a cytosine base was achieved by treatment of **25** with sat. methanolic ammonia at 60 °C to obtain analogue **25m** in 81% yield. The final trimethylsilyl bromide-mediated hydrolysis of the diisopropylesters furnished the target cytosyl nucleoside phosphonate **7**.

To synthesize the 3′-*C*-ethynyl analogue of PMTA (**8**), silylated N^6-benzoyladenine was glycosylated with **17** using TMSOTf as a Lewis acid catalyst to give a mixture of **26** and **26b** (1.7:1, Scheme 3). N^7 isomer **26b** was isomerized to N^9 isomer **26** under acidic conditions. N^7 nucleoside **26b** was refluxed in toluene in the presence of *p*-toluenesulfonic acid to furnish **26** in 45% yield.[21] The TBDPS group was removed by treatment with TBAF in THF, and the oxidation of the 3′-hydroxyl with DMP provided ketone **27**. The ethynyl group was introduced using ethynylmagnesium bromide in the presence of $CeCl_3$ in THF at −78 °C. As expected, the addition reaction showed no selectivity, yielding 3′-ethynyl nucleoside **28** and its epimer as a 1:1 mixture that can be separated by silica gel chromatography. The configuration of both epimers was confirmed by 2D-NMR experiments. In the ROESY measurement, a cross peak was observed between 3′-OH and 4′-H_b (**28**) and 4′-H_a (epimer), respectively. The phosphonate function was introduced using diisopropylphosphonomethyl triflate and NaH in THF at −15 °C. The benzoyl group was removed with ammonia in methanol, and the hydrolysis of the phosphonate ester function of **29** was carried out with TMSI in the presence of HMDS at 0 °C to furnish the 3′-ethynyl analogue of PMTA (**8**). Diphosphate-phosphonate **30** was prepared by the reaction with pyrophosphate, following a literature procedure.[22,23]

Scheme 3. Synthesis of the 3′-Ethynyl Analogue of PMTA[a]



[a]Reagents and conditions: (a) N^6-benzoyladenine, *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 2 equiv), TMSOTf (1 equiv), 70 °C, 12 h, 65%; (b) *p*-TSA, toluene, reflux; (c) TBAF (1 M in THF), 0 °C to rt, 78%; (d) DMP (15% in CH_2Cl_2), 0 °C to rt, 1 h then rt, 10 h, 97%; (e) $CeCl_3$, ethynylmagnesium bromide (0.5 M in THF), dry THF, −78 °C, 6 h, 32%; (f) NaH, CH_3CN, −10 °C, $(^iPrO)_2POCH_2OTf$, 1 h, 88%; (g) sat. NH_3 in MeOH, 24 h, rt, 86%; (h) TMSI, HMDS, 0 °C, 2 h, 60%; (i) Bu_3N, *N*,*N*-carbonyldiimidazole, tris(*tetra*-butylammonium)hydrogen pyrophosphate, DMF, 16 h, 31%; (j) phenyl chloroformate, DMAP, CH_3CN, rt, 2 h, 91%; and (k) Bu_3SnH, AIBN, toluene, 75 °C.

Biellmann et al. described a modified Barton−McCombie reaction for the 2′-deoxygenation of 3′-C-ethynyl nucleoside analogues.[24] However, in our hands the attempts to 2′-deoxygenate compound **29** were not successful. When we followed Biellmann's method no reaction had taken place. Under standard conditions, a complex mixture of byproducts was obtained.

CONCLUSION

An efficient synthesis route to L-threose nucleoside analogues is developed. Key intermediates 2-*O*-benzoyl-L-threonolactone (**16**) and 1-*O*-acetyl-2-*O*-benzoyl-3-*O*-*tert*-butyldiphenylsilyl-L-threofuranose (**17**) were functionalized to obtain the 2′-deoxy-2′-fluoro and 3′-*C*-ethynyl (PMTA) L-threose 3′-*O*-phosphonate nucleosides (**7** and **8**) and diphosphate-phosphonate compound **30**. Unfortunately, none of the synthesized compounds showed either any significant in vitro activity against HIV, HCV, and RSV or cytotoxicity at concentrations up to 100 μM. Diphosphate-phosphonate compound **30** did not inhibit HCV polymerase (IC_{50} > 200 μM) and was not incorporated into mtRNA. Nevertheless, key intermediate **17** is

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an important synthon for the synthesis of new L-threose-base nucleoside analogues. Until now,[25] a mixture of 2′-*O*-DMTr- and 3′-*O*-DMTr-protected L-threose nucleosides needed to be separated[6] to obtain TNA phosphoramidite and TNA triphosphate for the construction of TNA oligomers. The accessibility of intermediates such as **16** and **17** allows for a more straightforward synthesis of TNA monomers.

EXPERIMENTAL SECTION

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a 300 (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz; ^{31}P NMR, 121 MHz) or 500 MHz (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz) spectrometer. Two-dimensional NMRs (H−COSY, NOESY, ROESY, HSQC, and HMBC) were used for the assignment of all of the intermediate and final compounds. The specific optical rotation was measured at 589 nm, and *c* is given in g/100 mL. The mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer. The column chromatographic separations were carried out by gradient elution with a suitable combination of two or three solvents and silica gel (100−200 mesh or 230−400 mesh). The solvents for the reactions were distilled prior to use (THF and toluene from Na/benzophenone; CH_2Cl_2 and CH_3CN from CaH_2; Et_3N and pyridine from KOH).

1′*α*-(Uracil-1-yl)-3′-*O*-diisopropylphosphonomethyl-L-erythrose (15). Following the procedure described for **24**, the 2′-hydroxyl moiety in compound **18** was epimerized to **15**. ^{1}H NMR (acetone-d_6, 500 MHz): δ 11.25 (s, 1H, NH), 7.67 (d, J = 8.0 Hz, 1H, H6), 5.99 (d, J = 5.8 Hz, 1H, H1′), 5.56 (d, J = 5.3 Hz, 1H, OH), 5.47 (dd, J = 8.1, 2.2 Hz, 1H, H5), 4.62 [m, 2H, P(OC*H*(CH$_3$)$_2$)$_2$], 4.15 (q, J = 5.2 Hz, 1H, H-2′), 3.97 (dd, J = 9.4, 4.4 Hz, 1H, H4a′), 3.95 (dd, J = 13.9, 8.3 Hz, 1H, PCH$_a$), 3.88 (dd, J = 13.9 Hz, 9.1 Hz, 1H, PCH$_b$), 3.83 (dd, J = 9.4, 4.8 Hz, 1H, H4b′), 1.25 [m, 12H, P(OCH(C*H*$_3$)$_2$)$_2$]. ^{13}C NMR (acetone-d_6, 125 MHz): δ 163.3 (C4), 150.8 (C2), 143.3 (C6), 100.0 (C5), 84.1 (C1′), 79.5 (d, $^2J_{P,C}$ = 11.9 Hz, C3′), 70.4 and 70.4 (CH(CH$_3$)$_2$), 69.4 (C2′), 68.9 (C4′), 64.2 (PCH$_2$, $^1J_{P,C}$ = 165.5 Hz), 23.8 and 23.9 [P(OCH(CH$_3$)$_2$)$_2$]. HRMS (ESI+): [M + Na]$^+$ calcd for $C_{15}H_{25}N_2O_8PNa$, 415.1246; found, 415.1240.

2-*O*-Benzoyl-L-threonolactone (16). To a solution of L-threonolactone (**9**, 11.20 g, 95 mmol) and imidazole (12.91 g, 190 mmol) in dry acetonitrile at 0 to −5 °C, benzoyl chloride (11.02 mL, 95 mmol) was slowly added over a period of 10 min. The reaction mixture was stirred at rt for 8 h. The acetonitrile was removed under reduced pressure, the residue was taken up into 150 mL of ethyl ether, and 100 mL of water was added. The resulting mixture was sequentially washed with 2 × 100 mL of ice-cold 1 M HCl soln., 100 mL of water, 100 mL of sat. $NaHCO_3$ soln., and 100 mL of sat. aq. NaCl soln. The organic layer was dried over $MgSO_4$ and concentrated to obtain the crude product. The residue was purified by column chromatography (9:1 to 7:3, hexane/EtOAc; R_f = 0.4, 6:1 hexane/EtOAc) to obtain **16** (20 g, 90 mmol, 95% yield). $[\alpha]_D^{20}$ −21.5 (c = 0.065, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 7.4 Hz, 2H, Ph), 7.73 (t, J = 7.4 Hz, 1H, Ph), 7.60 (t, J = 7.9 Hz, 2H, Ph), 6.9 (d, J = 4.9 Hz, 1H, 3′-OH), 5.74 (d, J = 8.0 Hz, 1H, H2′), 4.75 (ddd, J = 5.21, 8.0 Hz, 1H, H3′), 4.55 (appt t, J = 8.3 Hz, 1H, H4a′), 4.10 (appt, J = 8.3 Hz, 1H, H4b′). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0 (C1′), 165.7 (CO), 135.0 (Ph), 130.5 (Ph), 129.9 (Ph), 129.4 (Ph), 76.0 (C2′), 70.6 (C4′ and C3′). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{11}H_{10}O_5Na$, 245.0421; found, 245.0414.

2-*O*-Benzoyl-3-*O*-*tert*-butyldiphenylsilyl-L-threonolactone (16b). To a solution of lactone (**16**, 25.7 g, 116 mmol), cat. DMAP (0.1 g), and imidazole (15.75 g, 231 mmol) in dry acetonitrile at 0 °C, *tert*-butyldiphenylchlorosilane (29.7 mL, 116 mmol) was added dropwise. The reaction mixture was allowed to stir at rt for 10 h. The acetonitrile was removed under reduced pressure, the residue was taken up into 400 mL of ethyl ether, and 200 mL of water was added. The resulting mixture was sequentially washed with 2 × 200 mL of ice-cold 1 M HCl soln., 200 mL of water, 100 mL of sat. $NaHCO_3$ soln., and 100 mL of sat. aq. NaCl soln. The organic layer was dried over $MgSO_4$ and concentrated to obtain the crude product. The residue was purified by column chromatography (95:5 hexane/EtOAc; R_f = 0.4) to obtain **16b** (52.2 g, 113 mmol, 98% yield). $[\alpha]_D^{20}$ −20.2 (c = 0.47, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.89 (m, 15H, Ph), 6.05 (d, J = 7.8 Hz, 1H, H2′), 4.95 (dd, J = 7.8, 16.8 Hz, 1H, H3′), 4.35 (appt t, J = 7.8 Hz, 1H, H4a′), 4.27 (appt t, J = 8.2 Hz, 1H, H4b′), 0.97 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (C1′), 165.4 (PhCO), 136.0, 135.9, 135.4, 135.0, 133.0, 132.6, 131.1, 130.9, 130.4, 129.7, 129.0, 128.9, 128.9, 128.7, 128.3, 75.8 (C2′), 72.5 (C3′), 69.7 (C4′), 27.3 (CH$_3$), 19.5 (C(CH$_3$)$_3$). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{27}H_{28}O_5SiNa$, 483.1598; found, 483.1581.

2-*O*-Benzoyl-3-*O*-*tert*-butyldiphenylsilyl-L-threofuranose (16c). To a solution of **16b** (27.7 g, 60.1 mmol) in 350 mL of dry THF at −78 °C, a 1.2 M DIBAL-H (100 mL, 120 mmol) solution in toluene was added dropwise via cannula. The mixture was stirred at −78 to −60 °C for 3 h (the starting material was consumed in 3 h). The reaction was quenched by the dropwise addition of 15 mL of MeOH at −78 °C. The cooling bath was removed, the reaction mixture was diluted with EtOAc, 300 mL of a sat. aq. sodium potassium tartrate solution was added, and the mixture was stirred vigorously for 2 h. The reaction mixture was filtered, and the organic phase was washed with water and sat. NaCl solution and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and coevaporated with 2 × 200 mL of toluene. This crude residue was passed through a short silica column (1:1 EtOAc/hexane) to obtain **16c** as a diastereomeric mixture at anomeric position (26 g, 56.2 mmol, 94% yield). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{27}H_{30}O_5SiNa$, 485.1755; found, 485.1740.

1-*O*-Acetyl-2-*O*-benzoyl-3-*O*-*tert*-butyldiphenylsilyl-L-threofuranose (17). To a solution of lactol **16c** (26.0 g, 56.2 mmol) and triethylamine (39 mL, 281 mmol) in 200 mL of dry dichloromethane at 0 °C was added acetic anhydride (10.6 mL, 112 mmol) dropwise. The reaction mixture was stirred at rt for 8 h and given a water and brine wash. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to obtain the crude product. The residue was purified by column chromatography (95:5 EtOAc/hexane; R_f = 0.15) to obtain **17** as a diastereomeric mixture at anomeric position (26 g, 51.5 mmol, 92% yield). C1′ *β*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 7.1 Hz, 2H, Bz-H), 7.68−7.63 (m, 4H, Ph-H), 7.56 (t, J = 7.5 Hz, 1H, Bz-H), 7.43−7.30 (m, 8H, Ph-H, Bz-H), 6.17 (s, 1H, H1′), 5.43 (d, J = 1.9 Hz, 1H, H2′), 4.50 (dt, J = 2.0, 5.2 Hz, 1H, H3′), 4.06−3.96 (m, 2H, H4′), 2.18 (s, 3H, C*H*$_3$CO), 1.10 ((s, 9H, C(CH$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 165.3, 135.9, 135.8, 133.6, 133.3, 132.8, 130.2, 130.2, 130.0, 129.9, 128.6, 128.1, 128.03, 100.0, 83.5, 75.9, 75.0, 26.9, 21.3, 19.3. HRMS: [M + Na]$^+$ calcd for $C_{29}H_{32}O_6SiNa$, 527.1860; found, 527.1863. C1′ *α*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 7.1 Hz, 2H, Bz-H), 7.67−7.56 (m, 4H, Ph-H), 7.45 (t, J = 7.5 Hz, 1H, Bz-H), 7.43−7.25 (m, 8H, Ph-H, Bz-H), 6.50 (d, J = 4.5 Hz, 1H, H1′), 5.44 (t, J = 5.3 Hz, 1H, H2′), 4.75 (q, J = 6.0 Hz, 1H, H3′), 3.95 (dd, J = 6.5, 9.3 Hz, 1H, H4′), 3.77 (dd, J = 4.7, 9.3 Hz, 1H, H4′), 1.87 (s, 3H, C*H*$_3$CO), 1.06 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 165.5, 135.8, 133.5, 133.3, 132.8, 130.3, 130.1, 129.9, 129.3, 128.5, 128.1, 127.9, 94.5, 79.4, 74.3, 72.5, 26.9, 21.0, 19.2. HRMS (ESI+): [M + Na]$^+$ calcd for $C_{29}H_{32}O_6SiNa$, 527.1860; found, 527.1859.

1′*α*-(Uracil-1-yl)-2′-*O*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-L-threose (18). Following the procedure described for **20**, compound **18** was obtained in 87% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (dd, J = 1.2, 8.4 Hz, 2H, Ph), 7.90 (d, J = 8.1 Hz, 1H, H6), 7.60−7.64 (m, 4H, Ph), 7.54−7.58 (m, 1H, Ph), 7.34−7.48 (m, 8H, Ph), 6.10 (d, J = 1.5 Hz, 1H, H1′), 5.76 (dd, J = 2.0, 8.1 Hz, 1H, H5), 5.46 (d, J = 1.0 Hz, 1H, H2′), 4.40 (dt, J = 1.0, 3.4 Hz, 1H, H3′), 4.12 (bd, J = 10.4 Hz, 1H, H4a′), 3.94 (dd, J = 3.4, 10.4 Hz, 1H, H4′), 1.10 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2 (C4), 162.0 (PhCO), 149.7 (C3), 140.4 (C6), 135.40, 135.38, 133.3, 132.1, 131.3, 130.3, 129.5, 128.4, 128.1, 127.8, 127.7, 100.1 (C5), 89.5 (C1′), 82.1 (C2′), 75.5 (C4′), 75.4 (C3′), 26.5 (CH$_3$), 18.7 [SiC(CH$_3$)$_3$]. HRMS (ESI+): [M + Na]$^+$ calcd for $C_{31}H_{32}N_2O_6SiNa$, 579.1922; found, 579.1890.

1′*α*-(Uracil-1-yl)-3′-*O*-*tert*-butyldiphenylsilyl-L-threose (18f). To a solution of compound **18** (1.0 g, 1.790 mmol) in 6 mL of methanol was added a LiOH (0.107 g, 4.47 mmol) solution in 3 mL of

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water, and the reaction mixture was stirred at rt for 2 h. The solvent was removed, and the residue was subjected to column chromatography (elution with 1:1 hexane/EtOAc; R_f = 0.5, 1:1 hexane/EtOAc) to obtain compound **18f** (0.7 g, 15.40 mmol, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (dd, J = 8.0 Hz, 1H, H6), 7.52−7.61 (m, 4H, Ph), 7.33−7.48 (m, 6H, Ph), 5.74 (d, J = 8 Hz, 1H, H5), 5.72 (s, 1H, H1′), 4.35 (s, 1H, H2′), 4.27 (d, J = 2.7, 1H, H3′), 4.09−4.17 (m, 2H, H4), 1.02 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0 (C4), 151.0 (C2), 140.7 (C6), 135.66, 135.57, 132.58, 132.41, 130.20, 130.16, 127.9, 100.5 (C5), 94.0 (C1′), 81.4 (C2′), 76.9 (C3′), 77.5 (C4′), 26.8 (CH_3), 19.0 (SiC(CH_3)$_3$). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{24}H_{28}N_2O_5SiNa$, 475.1660; found, 475.1657.

A Dess−Martin oxidation reaction of compound **18f** in CH_2Cl_2 (2 h, rt) followed by the sodium borohydride-mediated reduction of the ketone resulted in mixture **19a** and **19b** (6:4).

Diisopropylphosphonomethyl Trifluoromethanesulfonate. To a solution of (hydroxymethyl)diisopropylphosphonate (2.9 g, 14.78 mmol) in 50 mL of dry diethyl ether at −78 °C was added a solution of 2.5 M *n*-BuLi (6.12 mL, 15.29 mmol). This reaction mixture was allowed to stir at this temperature for 5 min, and trifluoromethanesulfonyl chloride (1.628 mL, 15.29 mmol) was added dropwise over 5 min. The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched with sat. NH_4Cl. The organic layer was given a wash with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure at rt to obtain diisopropylphosphonomethyl triflate (4.77 g, 14.53 mmol, 98% yield). The crude product was pure, without any traces of phosphonate dimer or any other reactant. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35−1.40 (m, 12H, POCH(CH_3)$_2$), 4.55 (d, $^1J_{P,H}$ = 8.97 Hz, 2H, PCH_2), 4.82 (sept, J = 6.21 Hz, 2H, POCH(CH_3)$_2$). ^{31}P NMR ($CDCl_3$, 125 MHz): δ 10.01.

1′α-(O^4-Methyluracil-1-yl)-2′-*O*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-L-threose (20). A solution of **17** (12.88 g, 25.5 mmol) and O^4-methyluracil (3.22 g, 25.5 mmol) in 120 mL of dry acetonitrile was treated with BSA (13.94 mL, 56.2 mmol) and stirred at 60 °C for 30 min. TMSOTf (13.86 mL, 77 mmol) was added, and the heating was continued of another 2 h, after which time the Vorbrüggen glycosylation was found to be complete. The reaction mixture was cooled to rt, diluted with 200 mL of EtOAc, and poured into 100 mL of a 10% $NaHCO_3$ solution with stirring. The organic layer was separated and washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The oily residue was purified by column chromatography (6:4 hexane/EtOAc; R_f = 0.4) to obtain light-yellow low-melting solid **20** (12 g, 21.03 mmol, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 7.5, Hz 1H, H6), 7.96 (dd, J = 1.9, 8.2 Hz, 2H, Ph), 7.51−7.64 (m, 4H, Ph), 7.51−7.56 (m, 1H, Ph), 7.34−7.46 (m, 8H, Ph), 6.22 (d, J = 1.0 Hz, 1H, H1′), 5.92 (d, J = 7.5 Hz, 1H, H5), 5.60 (d, J = 1.0 Hz, 1H, H2′), 4.36 (dt, J = 1.0, 3.5 Hz, 1H, H3′), 4.12 (d, J = 9.9 Hz, 1H, H4′), 4.00 (dd, J = 3.5, 10.2 Hz, 1H, H4′), 3.98 (s, 3H, CH_3O), 1.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0 (C2′), 164.5 (PhCO), 155.9 (C3), 143.4 (C6), 135.9, 135.8, 133.5, 132.7, 131.8, 130.34, 130.32, 130.0, 129.2, 128.5, 128.4, 128.1, 128.0, 95.5 (C5), 91.0 (C1′), 82.2 (C2′), 76.4 (C4′), 75.9 (C3′), 54.6 (OMe), 26.7 (CH_3), 19.1 (SiC(CH_3)$_3$). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{32}H_{34}N_2O_6SiNa$, 593.2078; found, 593.2076.

1′α-(O^4-Methyluracil-1-yl)-2′-*O*-benzoyl-L-threose (20i). To a solution of compound **20** (0.330 g, 0.578 mmol) in 10 mL of THF at 0 °C was added tetra-*n*-butylammonium fluoride (0.578 mL, 0.578 mmol) dropwise. The reaction mixture was stirred in an ice bath for 1 h and found to be complete (i.e., clean reaction). The solvent was removed and purified by column chromatography with 1:1 hexane/EtoAc followed by 100% EtOAc to obtain **20i** (0.162 g, 0.487 mmol, 84% yield). Note that the deprotection of TBDPS with triethylamine trihydrofluoride (2 equiv) in dichloromethane for 15 h at rt gave **20i** in 90% yield. $[\alpha]_D^{20}$ −34.5 (c = 0.185, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (dd, J = 1.5, 8.4 Hz, 2H, Ph), 7.60−7.64 (m, 2H, H6 and Ph), 7.46−7.50 (appt t, J = 7.8 Hz, 2H, Ph), 5.98 (d, J = 7.5 Hz, 1H, H5), 5.65 (d, J = 1.8 Hz, 1H, H1′), 5.47 (s, 1H, H2′), 4.54 (m, 1H, H3′), 4.30 (bd, J = 10.0 Hz, 1H, H4a′), 4.24 (dd, J = 4.3, 10.0 Hz, 1H, H4b′), 3.99 (s, 3H, CH_3O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4 (C2), 166.2 (PhCO), 155.8 (C4), 145.6 (C6), 145.6, 133.8, 129.9, 128.6, 96.2 (C5), 96.1 (C1′), 84.1 (C2′), 76.1 (C3′), 75.1 (C4′), 55.2 (CH_3O). HRMS (ESI+): [M + Na]$^+$ calcd for $C_{16}H_{16}N_2O_6Na$, 355.0906; found, 355.0898.

1′α-(O^4-Methyluracil-1-yl)-2′-*O*-benzoyl-3′-*O*-diisopropylphosphonomethyl-L-threose (21). To a solution of **20i** (3.20 g, 9.63 mmol) in dry acetonitrile (10 mL) was added triflate diisopropylphosphonomethanol (6.32 g, 19.26 mmol). The reaction mixture was cooled to 5−10 °C (ice−salt bath) under argon before the addition of NaH (0.463 g, 11.56 mmol, 60% suspension). After 45 min of stirring at 0 °C, the reaction was quenched with 5 mL of EtOAc containing 0.1 mL of acetic acid. The content was further diluted with 20 mL of EtOAc, and 10 mL of water was added, the mixture was stirred well, extracted, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (3% MeOH in CH_2Cl_2) afforded product **21** as a colorless liquid (4.2 g, 8.23 mmol, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 7.4 Hz, 2H, Ph), 7.61 (d, J = 7.6 Hz, 1H, H6), 7.62 (t, J = 7.6 Hz, 1H, Ph), 7.48 (t, J = 7.6 Hz, 2H, Ph), 6.35 (s, 1H, H1′), 5.95 (d, J = 7.6 Hz, 1H, H5), 5.46 (s, 1H, H2′), 4.66−4.80 (m, 2H, CH(CH_3)$_3$), 4.46 (bd, J = 9.17 Hz, 1H, H4a′), 4.24−4.29 (m, 2H, H4b′ and H3), 3.98 (s, 3H), 3.93 (dd, J = 9.17, 13.6 Hz, 1H, PCH_a), 3.87 (dd, J = 9.17, 13.6 Hz, 1H, PCH_b), 1.30−1.35 (m, 12H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.7 (C2), 164.9 (PhCO), 155.4 (C4), 142.8 (C6), 135.3, 129.6, 128.5, 128.2, 95.2 (C5), 90.2 (C1′), 83.1 (C3′, $^3J_{P,C}$ = 10.4 Hz), 79.4 (C2′), 73.6 (C4′), 71.0 (CH(CH_3)$_2$, $^2J_{P,C}$ = 6.4 Hz), 70.9 (CH(CH_3)$_2$, $^2J_{P,C}$ = 6.4 Hz), 64.1 (PCH_2, $^1J_{P,C}$ = 169.3 Hz), 54.1 (OMe), 23.6 [CH(CH_3)$_2$]. ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.9. HRMS (ESI+): [M + H]$^+$ calcd for $C_{23}H_{32}N_2O_9P$, 511.1840; found, 511.1847.

1′α-(O^4-Methyluracil-1-yl)-3′-*O*-diisopropylphosphonomethyl-L-threose (21f). A solution of **21** (4.70 g, 9.21 mmol) in 10 mL of acetonitrile was treated with LiOH (0.220 g, 9.21 mmol) in 4 mL of water and 10 mL of MeOH. The reaction mixture was stirred at rt. The reaction was found to be complete in 1 h, and the reaction mixture was neutralized with acetic acid. The solvent was removed and purified by column chromatography (elution with 7% MeOH in CH_2Cl_2; R_f = 0.2, 5% MeOH in CH_2Cl_2) to obtain **21f** as a colorless solid (3.11 g, 7.65 mmol, 83% yield). $[\alpha]_D^{20}$ +33.3 (c = 0.045 CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 7.6 Hz, 1H, H6), 5.92 (d, J = 7.6 Hz, 1H, H5), 5.75 (d, J = 1.3 Hz, 1H, H1′), 4.61−4.85 (m, 2H, CH(CH_3)$_2$), 4.22−4.37 (m, 3H, H3′ and H4′), 4.09 (s, 1H, H2′), 3.90 (s, 3H, CH_3O), 3.68 (d, J = 8.7 Hz, 1H, PCH_2), 1.15−1.42 (m, 12H, P[CH(CH_3)$_2$]$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1 (C2), 156.6 (C4), 143.1 (C6), 95.1 (C5), 94.2 (C1′), 85.6 (C3′, $^3J_{P,C}$ = 11.2 Hz), 79.0 (C2′), 73.6 (C4′), 71.3 (CH(CH_3)$_2$, $^2J_{P,C}$ = 4.7 Hz), 71.2 (CH(CH_3)$_2$, $^2J_{P,C}$ = 4.7 Hz), 64.2 (PCH_2, $^1J_{P,C}$ = 169.3 Hz), 54.4 (OMe), 24.0 (CH(CH_3)$_2$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.3. HRMS (ESI+): [M + Na]$^+$ calcd for $C_{16}H_{27}N_2O_8PNa$, 429.1403; found, 429.1408.

(1′α,2′*S*)-1′-(O^4-Methyluracil-1-yl)-2′-fluoro-2′-*O*-methyl-3′-*O*-diisopropylphosphonomethyl-L-threose (23a). A solution of **22** (0.033 g, 0.082 mmol) in dry CH_2Cl_2 was cooled in an ice−salt bath to maintain temperature from −5 to −10 °C. To this was added (diethylamino)sulfur trifluoride (0.219 mL, 1.632 mmol) and Py-HF (0.809 mg, 8.16 μmol) as a solution in 1 mL of dry CH_2Cl_2. The reaction mixture was allowed to stir at rt for 12 h. The volatiles were removed under reduced pressure to obtain a crude oil. This residue was purified by silica gel flash column chromatography (98:2 CH_2Cl_2/MeOH) to obtain **23a** as a light-yellow liquid (0.01 g, 0.023 mmol, 29% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 7.6 Hz, 1H, H6), 6.44 (d, $^2J_{FH}$ = 16.4 Hz, 1H, H1′), 5.86 (d, J = 7.6 Hz, 1H, H5), 4.70−4.81 (m, 2H, CH(CH_3)$_2$), 4.33 (d, J = 11.5 Hz, 1H, H4a′), 4.14 (dd, J = 2.4, 7.9 Hz, 1H, H3′,), 4.00−4.07 (m, 1H, H4b′), 3.97 (s, 3H, OCH_3), 3.86 (d, J = 9.0 Hz, 2H, PCH_2), 3.52 (s, 3H, 2′-OCH_3), 1.30−1.38 (m, 12 H, P[CH(CH_3)$_2$]$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4 (C2), 155.8 (C4), 144.9 (C6), 119.0 (C2′, $^1J_{F,C}$ = 227.2 Hz), 95.3 (C5), 86.6 (C1′, $^2J_{F,C}$ = 48.6), 82.3 (C3′, $^3J_{P,C}$ = 11.1 Hz, $^2J_{F,C}$ = 43.1), 71.1 and 71.0 (CH(CH_3)$_2$, $^2J_{P,C}$ = 6.4 Hz), 69.1 (C4′), 64.1 (PCH_2, $^1J_{P,C}$ = 171.0 Hz), 54.1 (OCH_3), 53.27 (2′-OCH_3, $^2J_{F,C}$ = 4.5 Hz), 29.6 (CH(CH_3)$_2$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.6. HRMS

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(ESI+): $[M + Na]^+$ calcd for $C_{17}H_{28}FN_2O_8PNa$, 461.1465; found, 461.1457.

1′α-(*O*⁴-Methyluracil-1-yl)-3′-*O*-diisopropylphosphonomethyl-L-erythrose (24). A solution of **21f** (0.129 g, 0.317 mmol) in 1 mL of dichloromethane was treated with a 15% solution of Dess−Martin periodinane (DMP) in CH_2Cl_2 (1.8 mL, 0.635 mmol). A drop of water was added to accelerate the reaction, and the reaction was completed in 1 h. The reaction mixture was diluted with diethyl ether and filtered off. The organic solvent was removed under reduced pressure to obtain crude keto **22** (R_f = 0.4, 7% MeOH in CH_2Cl_2). HRMS (ESI+): $[M + H]^+$ calcd for $C_{16}H_{26}N_2O_8$, 405.1421; found, 405.1386.

Crude ketone **22** was taken up in 2 mL of methanol and treated with sodium borohydride (0.635 mmol, 0.024g) at 0 °C. The reaction mixture was stirred at rt for 1 h, quenched by the dropwise addition of brine solution (1 mL), and stirred at rt for 30 min. The reaction mixture was diluted in 20 mL of CH_2Cl_2 and washed with 5 mL of water and 5 mL of brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography (elution with 7% MeOH in CH_2Cl_2; R_f = 0.3) to obtain **24** (0.1 g, 0.247 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6, Hz 1H, H6), 6.20 (d, *J* = 3.4 Hz, 1H′), 5.91 (d, *J* = 7.6 Hz, 1H, H5), 4.61−4.83 (m, 2H, C*H*$(CH_3)_2$), 4.60 (t, *J* = 3.9 Hz, 1H, H2′), 4.20−4.32 (m, 1H, H3′), 4.11 (d, *J* = 5.8 Hz, 2H, H4′), 3.90−4.00 (m, CH_3O and PCH_a), 3.77 (dd, *J* = 8.6, 14.1 Hz, 1H, PCH_a,) 1.18−1.45 (m, 12H, P[CH(CH_3)$_2$]$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6 (C2), 156.2 (C4), 144.1 (C6), 94.3 (C5), 86.7 (C1′), 81.1 (C3′, $^3J_{P,C}$ = 7.6 Hz), 71.5 (*C*H$(CH_3)_2$, $^2J_{P,C}$ = 6.9 Hz), 71.3 (*C*H$(CH_3)_2$, $^2J_{P,C}$ = 6.9 Hz), 69.4 (C4′), 69.30 (C2′), 65.3 (P*C*H$_2$, $^1J_{P,C}$ = 169.0 Hz), 54.4 (CH_3O), 23.7 (CH(*C*H$_3$)$_2$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.3. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{16}H_{27}N_2O_8PNa$, 429.1403; found, 429.1408.

(1′α,2′*R*)-1′-(*O*⁴-Methyluracil-1-yl)-2′-deoxy-2′-fluoro-3′-*O*-diisopropylphosphono-methyl-L-threose (25). A solution of **24** (0.111 g, 0.273 mmol) in 1 mL of dry CH_2Cl_2 at −10 °C was treated with diethylaminosulfur trifluoride (DAST) (0.147 mL, 1.093 mmol). The reaction mixture was allowed to warm to rt and was stirred for 10 h. The resulting solution was then carefully poured into an ice-cold sat. solution of sodium bicarbonate (5 mL) and extracted with diethyl ether (4 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to a crude oil that was purified by silica gel flash column chromatography (elution with 3% MeOH in CH_2Cl_2; R_f = 0.3) to obtain **25** as a light-yellow liquid (0.051 g, 0.125 mmol, 45.7% yield). Note that the reaction yield is poor if the reaction begins at rt or 0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.6 Hz, 1H, H6), 6.10 (d, $^2J_{FH}$ = 17.1 Hz, 1H, H1′), 5.89 (d, *J* = 7.6 Hz, 1H, H5), 5.14 (d, $^1J_{FH}$ = 47.8 Hz, 1H, H2′), 4.62−4.76 (m, 2H, C*H*$(CH_3)_2$), 4.45 (d, *J* = 10.3 Hz, 1H, H4a′), 4.25−4.32 (m, 2H, H4b′ and H3′), 3.95 (s, 3H, CH_3O), 3.69 (d, *J* = 1.48, 8.69 Hz, 2H, PCH_2), 1.27−1.32 (m, 12H, P[CH(CH_3)$_2$]$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1 (C2), 155.8 (C4), 142.7 (C6), 95.5 (C2′, $^1J_{F,C}$ = 186.2 Hz), 95.2 (C5), 90.8 (C1′, $^2J_{F,C}$ = 36.5 Hz), 82.3 (C3′, $^3J_{P,C}$ = 9.6 Hz, $^2J_{F,C}$ = 26.9 Hz), 73.7 (C4′), 71.4 (*C*H$(CH_3)_2$, $^2J_{P,C}$ = 4.6 Hz), 64.5 (P*C*H$_2$, $^1J_{P,C}$ = 169.0 Hz), 54.4 (OCH_3), 29.6 (CH(*C*H$_3$)$_2$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.5. HRMS (ESI+): $[M + Na]^+$ calcd for $C_{16}H_{26}FN_2O_7PNa$, 431.1360; found, 431.1365.

(1′α,2′*R*)-1′-(Cytosin-1-yl)-2′-deoxy-2′-fluoro-3′-*O*-diisopropylphosphonomethyl-L-threose (25m). Compound **25** (0.051 g, 0.125 mmol) was taken up in 2 mL of sat. ammonia in methanol and refluxed for 6 h. The volatiles were removed and purified by column chromatography (elution with 7% MeOH in CH_2Cl_2; R_f = 0.2) to obtain compound **25m** (0.04 g, 0.102 mmol, 81% yield) as a light-yellow liquid. ^{1}H NMR (500 MHz, MeOD): δ 7.65 (d, *J* = 7.6 Hz, 1H, H6), 5.99 (d, $^1J_{F,H}$ = 18.3 Hz, 1H, H1), 5.89 (d, *J* = 7.6 Hz, 1H, H5), 5.16 (d, $^1J_{F,H}$ = 47.8 Hz, 1H, H2), 4.62−4.73 (m, 2H, C*H*$(CH_3)_2$), 4.50 (d, *J* = 10.9 Hz, 1H, H4a′), 4.35 (dd, *J* = 3.6, 11.2 Hz, 1H, H4b′), 4.25 (ddd, *J* = 10.9, 3.6, 2.1 Hz, 1H, H3′), 3.95 (dd, *J* = 9.7, 13.6 Hz, 1H, PCH_a), 3.88 (dd, *J* = 9.7, 13.6 Hz, 1H, PCH_b), 1.28−1.34 (m, 12H, P[CH(CH_3)$_2$]$_2$). ^{13}C NMR (125 MHz, MeOD): δ 165.3 (C2), 155.1 (C4), 141.3 (C6), 95.4 (C2′, $^1J_{F,C}$ = 181.0 Hz), 93.4 (C5), 90.3 (C1′, $^2J_{F,C}$ = 36.1 Hz), 82.3 (C3′, $^3J_{P,C}$ = 10.8 Hz, $^2J_{F,C}$ = 28.7, Hz), 73.1 (C4′), 71.1 (*C*H$(CH_3)_2$, $^2J_{P,C}$ = 7.4 Hz), 64.2 (P*C*H$_2$, $^1J_{P,C}$ = 169.0 Hz), 23.7 [*C*H$(CH_3)_2$]. ^{31}P NMR (121 MHz, MeOD): δ 17.6. HRMS (ESI+): $[M + H]^+$ calcd for $C_{15}H_{26}FN_3O_6P^-$, 394.1538; found, 394.1555.

(1′α,2′*R*)-1′-(Cytosin-1-yl)-2′-deoxy-2′-fluoro-3′-*O*-phosphonomethyl-L-threose (7). A solution of **25m** (5.00 mg, 0.014 mmol) and triethylamine (0.019 mL, 0.137 mmol) in 2 mL of dry CH_2Cl_2 was treated with bromotrimethylsilane (0.018 mL, 0.137 mmol) at rt for 30 h. The reaction was quenched with 1 M TEAB solution, and the reaction mixture was concentrated to dryness. The residue was purified by flash column chromatography (50:25:3 CH_2Cl_2/MeOH/1 M TEAB) to obtain target compound **7** (3 mg, 9.70 μmol, 70.9% yield) as an off-white solid. ^{1}H NMR (500 MHz, MeOD): δ 7.76 (d, *J* = 7.6 Hz, 1H, H6), 6.08 (d, $^1J_{F,H}$ = 20.5 Hz, 1H, H1′), 6.02 (d, *J* = 7.6 Hz, 1H, H5), 5.22 (d, $^1J_{F,H}$ = 47.8 Hz, 1H, H2), 4.50 (d, *J* = 11.2 Hz, 1H, H4a′), 4.39 (bd, *J* = 12.8, 1H, H3′), 4.19 (bd, *J* = 11.2 Hz, 1H, H4b′), 3.47 (bd, *J* = 8.6 Hz, 2H, PCH_2). ^{13}C NMR (125 MHz, MeOD): δ 166.0 (C2), 157.1 (C4), 142.0 (C6), 96.1 (C2′, $^1J_{F,C}$ = 181.6 Hz), 95.8 (C5), 89.7 (C1′, $^2J_{F,C}$ = 39.0 Hz), 81.3 (C3′, $^3J_{P,C}$ = 9.0 Hz, $^2J_{F,C}$ = 27.0 Hz), 72.9 (C4′), 66.6 (P*C*H$_2$, $^1J_{P,C}$ = 152.4 Hz). ^{31}P NMR (121 MHz, MeOD): δ 13.4. HRMS (ESI-): $[M - H]^-$ calcd for $C_9H_{12}FN_3O_6P^-$, 308.0453; found, 308.0450.

1′α-(*N*⁶-Benzoyladenin-9-yl)-2′-*O*-benzoyl-3′-*O*-*tert*-butyldiphenylsilyl-L-threose (26). To a solution of N^6-benzyladenine (3.98 g, 16.7 mmol) in CH_3CN (80 mL) was added BSA (8.14 mL, 33.3 mmol), and the mixture was stirred for 20 min at rt. To the mixture, a solution of **17** in CH_3CN (10 mL) was added. After cooling to 0 °C, TMSOTf (3.01 mL, 16.7 mmol) was added dropwise, and the reaction mixture was stirred for 1 h at rt and held at 70 °C overnight. The reaction mixture was poured into a mixture of CH_2Cl_2 and sat. $NaHCO_3$ solution (5:1 v/v). The CH_2Cl_2 layer was removed, and the water layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (CH_2Cl_2/MeOH 50:1) on silica gel to afford **26** (2.71 g, 51%) and **26b** (1.71 g, 30%) as a light-yellow foam.

N^7 to N^9 isomerization was carried out as follows. To a solution of **26b** (1.71 g, 2.50 mmol) in toluene (25 mL), a catalytic amount of *p*-TsOH-H_2O (48 mg, 0.25 mmol) was added and the mixture was held at 130 °C overnight. After the volatiles were removed, the residue was diluted with CH_2Cl_2 and washed with a sat. $NaHCO_3$ solution. The CH_2Cl_2 layer was removed, and the water layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4. After the solvent was removed, the residue was purified by column chromatography (CH_2Cl_2/MeOH 50:1) on silica gel to afford **26** (0.77 g, 45%) as a light-yellow foam. $[\alpha]_D^{20}$ −115.4 (*c* = 0.42 CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.17 (s, 1H, NH), 8.84 (s, 1H, H2), 8.55 (s, 1H, H8), 8.04 (d, *J* = 7.1 Hz, 2H, Bz-H), 7.95 (d, *J* = 7.1 Hz, 2H, Bz-H), 7.66−7.29 (m, 16H, Ph-H, Bz-H), 6.37 (d, *J* = 1.4 Hz, 1H, H1′), 5.94 (s, 1H, H2′), 4.60−4.57 (m, 1H, H3′), 4.22 (dd, *J* = 2.3, 10.0 Hz, 1H, H4′), 4.11 (dd, *J* = 4.4, 10.0 Hz, 1H, H4′), 1.03 (s, 9H, C$(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 164.7, 153.1, 151.8, 149.7, 141.8, 135.9, 135.8, 134.0, 133.9, 132.9, 132.6, 131.9, 130.5, 130.4, 130.1, 129.0, 128.8, 128.7, 128.2, 128.1, 128.0, 123.2, 88.5, 82.8, 76.3, 75.8, 27.0, 19.1. HRMS: $[M + H]^+$ calcd for $C_{39}H_{38}N_5O_5Si$, 684.2637; found, 684.2642.

1′α-(*N*⁶-Benzoyladenin-9-yl)-2′-*O*-benzoyl-L-threose (26c). To a solution of **26** (4.3 g, 6.29 mmol) in THF (65 mL) were added a 1 M solution of TBAF in THF (7.55 mL, 7.55 mmol) and AcOH (0.5 mL), and the solution was stirred for 2 h at rt. After removing the volatiles, the residue was diluted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. After evaporation, the crude residue was purified by silica gel chromatography (40:1 CH_2Cl_2/MeOH) to afford **26c** (2.18 g, 78%) as a white foam. $[\alpha]_D^{20}$ −75.2 (*c* = 0.34 CH_2Cl_2). ^{1}H NMR (300 MHz, MeOD): δ 8.68 (s, 1H, H2), 8.66 (s, 1H, H8), 8.08−8.02 (m, 4H, Bz-H), 7.64−7.45 (m, 6H, Bz-H), 6.44 (d, *J* = 1.1 Hz, 1H, H1′), 5.68 (s, 1H, H2′), 4.59 (s, 1H, H3′), 4.35 (br s, 2H, H4′). ^{13}C NMR (75 MHz, MeOD): δ 166.7, 153.2,

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152.9, 151.2, 144.7, 135.0, 134.9, 133.9, 130.8, 130.3, 129.7, 129.4, 124.9, 90.0, 84.0, 77.0, 75.0. HRMS: $[M + H]^+$ calcd for $C_{23}H_{20}N_5O_5$, 446.1459; found, 446.1459.

1′α-(*N*⁶-Benzoyladenin-9-yl)-2′-*O*-benzoyl-3′-oxo-L-threose (27). Under argon, to **26c** (1.87 g, 4.2 mmol) was added a solution of Dess−Martin periodinane (15% in CH_2Cl_2, 13.4 mL, 6.3 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was stirred overnight at rt (a white solid formed). To the reaction mixture, a solution of sat. aqueous sodium thiosulfate and sat. aqueous $NaHCO_3$ (1:1, 100 mL) was added, and the mixture was stirred for 20 min at rt. After separation, the organic layer was brined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude product **27** (1.8 g, 97%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H, NH), 8.79 (s, 1H, H2), 8.20 (s, 1H, H8), 8.04 (d, *J* = 7.2 Hz, 4H, Bz-H), 7.66−7.44 (m, 6H, Bz-H), 6.46 (d, *J* = 5.5 Hz, 1H, H1′), 6.18 (d, *J* = 5.5 Hz, 1H, H2′), 4.76 (d, *J* = 16.9 Hz, 1H, H4a′), 4.58 (d, *J* = 16.9 Hz, 1H, H4b′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 165.5, 165.0, 152.9, 151.9, 150.1, 142.3, 134.3, 133.5, 132.9, 130.2, 128.9, 128.7, 128.1, 127.7, 123.8, 86.3, 73.9, 72.0. HRMS: $[M + H]^+$ calcd for $C_{23}H_{18}N_5O_5$, 444.1302; found, 444.1307.

(1′α,3′*S*)-1′-(*N*⁶-Benzoyladenin-9-yl)-2′-*O*-benzoyl-3′-ethynyl-L-threose (28). A suspension of anhydrous $CeCl_3$ (5.10 g, 20.7 mmol) in THF (80 mL) under argon was stirred overnight. The solution was cooled to −78 °C. Ethynylmagnesium bromide (0.5 M in THF, 40.6 mL, 20.3 mmol) was added over 20 min. The suspension was stirred at −78 °C for 1.5 h. A solution of **27** (1.8 g, 4.06 mmol) in THF (10 mL) was added over 10 min and stirred at −78 °C for 4 h. The reaction was quenched with sat. NH_4Cl (10 mL). After being allowed to warm to rt, the reaction mixture was filtered and extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (60:1 CH_2Cl_2/MeOH) to afford **28** (0.61 g, 32%) as a white foam. ^{1}H NMR (500 MHz, DMSO): δ 11.24 (s, 1H, NH), 8.76 (s, 1H, H2), 8.59 (s, 1H, H8), 8.09−8.05 (m, 4H, Bz-H), 7.73 (tt, *J* = 1.3, 7.5 Hz, 1H, Bz-H), 7.66 (tt, *J* = 1.2, 7.4 Hz, 1H, Bz-H), 7.59 (t, *J* = 8.1 Hz, 2H, Bz-H), 7.56 (t, *J* = 8.0 Hz, 2H, Bz-H), 7.00 (s, 1H, OH), 6.47 (d, *J* = 2.2 Hz, 1H, H1′), 5.88 (d, *J* = 1.9 Hz, 1H, H2′), 4.48 (d, *J* = 9.1 Hz, 1H, H4a′), 4.27 (d, *J* = 9.1 Hz, 1H, H4b′), 3.70 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 164.3, 151.9, 151.8, 150.5, 142.7, 134.1, 133.4, 132.5, 129.7, 129.0, 128.5, 125.5, 87.9, 81.2, 78.5, 78.2, 73.4. HRMS: $[M + H]^+$ calcd for $C_{25}H_{20}N_5O_5$, 470.1459; found, 470.1458.

(1′α,3′*S*)-1′-(*N*⁶-Benzoyladenin-9-yl)-2′-*O*-benzoyl-3′-ethynyl-3′-*O*-(diisopropylphosphonomethyl)-L-threose (28f). To a solution of **28** (0.60 g, 1.28 mmol) and diisopropylphosphonomethyl trifluoromethanesulfonate (0.42 g, 1.28 mmol) in dry THF was added NaH (60% in oil, 0.13 g, 3.3 mmol) at −15 °C. The reaction mixture was stirred at −15 °C for 1 h. The reaction was quenched with sat. NH_4Cl (5 mL) and concentrated. The residue was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (50:1 CH_2Cl_2/MeOH) to afford **28f** (0.73 g, 88%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.33 (s, 1H, NH), 8.70 (s, 1H, H2), 8.66 (s, 1H, H8), 8.01 (d, *J* = 7.1 Hz, 2H, Bz-H), 7.95 (d, *J* = 7.1 Hz, 2H, Bz-H), 7.55−7.48 (m, 2H, Bz-H), 7.44−7.38 (m, 4H, Bz-H), 6.47 (d, *J* = 2.1 Hz, 1H, H1′), 5.79 (s, 1H, H2′), 4.77−4.70 (m, 2H, $CH(CH_3)_2$), 4.54 (d, *J* = 10.5 Hz, 1H, H4a′), 4.17 (d, *J* = 10.5 Hz, 1H, H4b′), 4.01−3.96 (m, 2H, PCH_2), 2.71 (s, 1H, CH), 1.31−1.26 (m, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 164.6, 152.9, 151.6, 149.6, 142.5, 133.9, 132.6, 130.0, 128.8, 128.6, 127.9, 122.6, 87.9, 82.6 (d, $^3J_{P,C}$ = 15.5 Hz), 80.9, 80.5, 75.4, 74.3, 71.7 (d, $^2J_{P,C}$ = 6.5 Hz), 60.5 (d, $^1J_{P,C}$ = 170.8), 24.1 (d, *J* = 4.2 Hz), 24.0 (d, $^3J_{P,C}$ = 5.5 Hz). ^{31}P NMR (125 MHz, $CDCl_3$, 25 °C): δ 17.7. HRMS: $[M + H]^+$ calcd for $C_{32}H_{35}N_5O_8P_1$, 648.2218; found, 648.2218.

(1′α,3′*S*)-1′-(*N*⁶-Benzoyladenin-9-yl)-3′-ethynyl-3′-*O*-(diisopropylphosphonomethyl)-L-threose (29). A solution of **28f** (0.6 g, 0.93 mmol) in 7 N NH_3 in MeOH (5 mL) was stirred at rt for 24 h. After removing the volatiles, the crude residue was purified by chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to afford **29** (0.35 g, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, H2), 8.23 (s, 1H, H8), 7.29 (s, 2H, NH_2), 6.19 (s, 1H, H1′), 4.79−4.69 (m, 2H, $CH(CH_3)_2$), 4.53 (s, 1H, H2′), 4.47 (d, *J* = 9.9 Hz, 1H, H4a′), 4.18 (d, *J* = 9.9 Hz, 1H, H4b′), 3.95 (quint, *J* = 9.9 Hz, 2H, PCH_2), 2.93 (s, 1H, CH), 1.34−1.24 (m, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 152.9, 149.1, 140.0, 119.4, 90.6, 83.8 (d, $^3J_{P,C}$ = 13.9 Hz), 80.6, 80.4, 76.4, 74.4, 71.9 (d, $^2J_{P,C}$ = 3.5 Hz), 71.8 (d, $^2J_{P,C}$ = 2.8 Hz), 60.4 (d, $^1J_{P,C}$ = 171.4 Hz), 24.2 (d, $^3J_{P,C}$ = 3.5 Hz), 24.1 (d, $^3J_{P,C}$ = 4.4 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 18.4. HRMS: $[M + H]^+$ calcd for $C_{18}H_{27}N_5O_6P_1$, 440.1693; found, 440.1687.

(1′α,3′*S*)-1′-(Adenin-9-yl)-3′-ethynyl-3′-*O*-(phosphonomethyl)-L-threose (8). Compound **29** (0.15 g, 0.34 mmol) in dry CH_2Cl_2 (2 mL) was treated with HMDS (1.07 mL, 5.12 mmol), and TMSI (0.29 mL, 2.05 mmol) was added dropwise under stirring at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with 1 M TEAB (1 mL). The mixture was concentrated, and the residue was purified by RP-HPLC running a gradient of CH_3CN in 0.1 M TEAB buffer solution to afford **8** (0.115 g, 60%, triethylamine salt) as a white solid. $[\alpha]_D^{20}$ −65.9 (*c* = 0.22 H_2O). ^{1}H NMR (300 MHz, D_2O): δ 8.41 (s, 1H, H2), 8.07 (s, 1H, H8), 6.04 (s, 1H, H1′), 4.68 (s, 1H, H2′), 4.58 (d, *J* = 10.0 Hz, 1H, H4a′), 4.21 (d, *J* = 10.0 Hz, 1H, H4b′), 3.74 (d, *J* = 10.5 Hz, 2H, PCH_2), 3.27 (s, 1H, CH). ^{13}C NMR (75 MHz, D_2O): δ 154.9, 152.2, 148.1, 140.5, 117.8, 88.9, 82.4 ($CH(CH_3)_2$, $^3J_{P,C}$ = 13.8 Hz), 80.4, 79.2, 75.8, 74.3, 61.7 (PCH_2, $^1J_{P,C}$ = 154.6 Hz). ^{31}P NMR (121 MHz, D_2O): δ 14.1. HRMS: $[M - H]^-$ calcd for $C_{12}H_{13}N_5O_6P$, 354.0609; found, 354.0613.

(1′α,3′*S*)-1′-(Adenin-9-yl)-3′-ethynyl-3′-*O*-(diphosphate-phosphonomethyl)-L-threose (30). Compound **8** (70 mg, 0.13 mmol) was dissolved in anhydrous DMF (1 mL), and Bu_3N (0.09 mL, 0.38 mmol) was added. The mixture was concentrated in vacuo, redissolved in anhydrous DMF (1 mL), and treated with *N*,*N*-carbonyldiimidazole (0.2 g, 1.25 mmol). The mixture was stirred for 30 min and tris(tetrabutylammonium) hydrogen pyrophosphate (0.9 g, 1.0 mmol) in DMF (1 mL) was added. The mixture was stirred overnight. Excess aqueous ammonia (25% in water, 2 mL) was added, and the mixture was concentrated by lyophilization. The residue was purified by RP-HPLC running a gradient of CH_3CN in 0.1 M TEAB buffer solution to afford **30** (0.02 g, 31%) as a white solid. ^{1}H NMR (500 MHz, D_2O): δ 8.37 (s, 1H, H2), 8.06 (s, 1H, H8), 5.97 (d, *J* = 3.3 Hz, 1H, H1′), 4.60 (s, 1H, H2′), 4.45 (d, *J* = 10.0 Hz, 1H, H4a′), 4.07 (d, *J* = 10.0 Hz, 1H, H4b′), 3.87 (d, *J* = 10.5 Hz, 2H, PCH_2), 3.12 (s, 1H, CH). ^{13}C NMR (125 MHz, D_2O): δ 155.3, 152.4, 148.5, 140.5, 118.1, 88.7, 82.5 (d, $^3J_{P,C}$ = 15.4 Hz), 80.9, 79.2, 74.8, 74.3, 61.2 (d, $^1J_{P,C}$ = 165.7 Hz). ^{31}P NMR (200 MHz, D_2O): δ 7.5 (d, *J* = 24 Hz, P_α), −7.3 (br s, P_γ), −22.2 (t, *J* = 21 Hz, P_β). HRMS: $[M - H]^-$ calcd for $C_{12}H_{16}N_5O_{12}P_3$, 513.9935; found, 513.9933.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR data for compounds **7**, **8**, **15**−**21**, and **23**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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