Supporting Information

Direct Synthesis of Aryloxy Phosphonamidate Nucleotide Prodrugs Using the Cross Metathesis Associated by Ultrasonic Irradiation

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Experimental section

1. General experimental information

All the reagents were commercially available from Sigma Aldrich, Thermo Fisher Scientific, (Waltham, MA), or TCI (Tokyo, Japan) chemical companies and used without further purification unless indicated otherwise. Nuclear magnetic resonance (NMR) spectra (\(^1\)H, \(^{13}\)C and \(^{31}\)P) were recorded on an Agilent MR 400 DD2 instrument, Bruker Avance NEO 600 MHz and Bruker Avance III \(^{100}\) HD 500 MHz with tetramethylsilane (TMS) as an internal standard. The splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (double of doublets) and dt (double of triplets). Mass spectra were recorded with an HRMS (Thermo Fisher Scientific, Q EXACTIVE Orbitrap and Bruker, Compact Qq-TOF). Thin layer-chromatography (TLC) was performed on TLC Silica gel 60, F254 (layer thickness 0.2 mm; Merck, Darmstadt, Germany) aluminum backed silica gel plates and visualized by ultralight (UV) light (254 nm) or staining with potassium permanganate stain. Chromatographic purification was carried out using silica gel 60 (200 mesh, SK-Chemical).
2. Abbreviations

(Boc)$_2$O: Di-tert-butyl dicarbonate

Boc: tert-Butyloxycarbonyl

BSA: Bis(trimethylsilyl)acetamide

Bz: Benzoyl

DMAP: 4-Dimethylaminopyridine

DMF: Dimethyl formamide

Et$_3$N: Triethylamine

EtOAc: Ethyl acetate

GlyOEt: Glycine ethyl ester

IBX: 2-Iodoxybenzoic acid

L-Ala-OEt: L-Alanine ethyl ester

L-PheOEt: L-Phenylalanine ethyl ester

MeCN: Acetonitrile

MeOH: Methyl alcohol

n-BuLi: n-Butyllithium

NaOMe: Sodium methoxide

Pd/C: Palladium on carbon

Ph$_3$PCH$_2$Br: Methyltriphenylphosphonium bromide

TBAF: Tetra-n-butylammonium fluoride

TBDPSCI: tert-Butyl(chloro)diphenyl silane

TBSCI: tert-Butyldimethylsilyl chloride

TBSOTf: tert-Butyldimethylsilyl trifluoromethanesulfonate

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TMSOTf: Trimethylsilyl trifluoromethanesulfonate
3. Synthetic procedures

3.1. Investigation of cross metathesis (CM) reaction

3.1.1. Synthesis of compound 2

\[(R)-1-((4R,5S)-5-((tert-Butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (2)\] 

According to the reported procedures, a suspension of D-Ribose (10.0 g, 66.60 mmol) and conc. H$_2$SO$_4$ (0.65 g, 6.66 mmol) in 250 mL of acetone was stirred for 24 h at room temperature. The reaction mixture was neutralized with NaHCO$_3$ and the solid was filtered out. The filtrate was adsorbed on silica gel and purified by silica gel column chromatography (CH$_2$Cl$_2$:MeOH = 15:1 to 10:1 v/v) to give 2,3-O-isopropylidene-D-ribose as a mixture of $\alpha$- and $\beta$-isomers (11.90 g, 62.61 mmol) in 94% yield. To a solution of 2,3-O-isopropylidene-D-ribose (11.90 g, 62.61 mmol) in 150 mL of anhydrous CH$_2$Cl$_2$ were added TBDPSCl (19.79 g, 72.00 mmol) and imidazole (10.22 g, 150.26 mmol) at 0 ℃ under argon atmosphere. After being stirred for 24 h at room temperature, the reaction mixture was adsorbed on silica gel and purified by silica gel column chromatography (hexane:EtOAc = 20:1 v/v) to give 5-O-TBDPS-2,3-O-isopropylidene-D-ribose (22.54 g, 52.59 mmol) in 84% yield. To a solution of 5-O-TBDPS-2,3-O-isopropylidene-D-ribose (22.54 g, 52.59 mmol) in 250 mL of anhydrous THF was added vinylmagnesium bromide (210 mmol, 1.0 M in THF) at -78 ℃ under argon atmosphere. After being stirred for 1 h at the same temperature, the reaction mixture was stirred for 6 h at room temperature. The resulting solution was poured into ether-sat. NH$_4$Cl solution (600 mL, 3:1 v/v) and extracted with diethyl ether (200 mL x 3). The combined organic layer was washed with brine (200 mL) and dried over Na$_2$SO$_4$. The solid was filtered out, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 30:1 to 10:1 v/v) to give a compound 2 (21.37 g, 46.90 mmol) in 89% yield as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90-7.56 (m, 4H), 7.53-7.31 (m, 6H), 6.04 (m, 1H), 5.53-5.35 (m, 1H), 5.30-5.21 (m, 1H), 4.36 (dd, $J = 9.3$ Hz, 5.3 Hz, 1H), 4.16-4.08 (m, 1H), 4.04 (dd, $J = 9.2$ Hz, 5.4 Hz, 1H), 3.95-3.87 (m, 2H), 3.83-3.72 (m, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.08 (s, 9H).
3.1.2. Synthesis of vinylphosphonate/amidate analogs (3a and 3c-f)

Scheme 1. Synthesis of vinylphosphonate/amidate analogs

\[
\begin{align*}
\text{HO-} & \quad \text{P} & \quad \text{OH} \\
& \quad \text{a)} \quad (\text{COCl})_2, \text{DMF, CH}_2\text{Cl}_2, 0 \degree \text{C then rt, 3 h} \\
& \quad \text{b)} \quad \text{MeOH for 3a, L-amino ethyl esters for 3c-e, PhOH, L-AlaOEt for 3f, CH}_2\text{Cl}_2, \text{Et}_3\text{N, -78 \degree C, 6 h} \\
20 & \quad \rightarrow & \quad 3a, 3c-f \\
\end{align*}
\]

Yield: 70-90%

\[3a: R = \text{OMe (90%)}, \quad 3c: R = \text{GlyOEt (90%)} \]
\[3d: R = \text{L-AlaOEt (88%)}, \quad 3e: R = \text{L-PheOEt (70%)} \]
\[3f: R = \text{PhO, L-AlaOEt (70%)} \]

Dimethyl vinylphosphonate (3a)\textsuperscript{52}

To a solution of vinyl phosphonic acid (20) (5.0 g, 46.28 mmol) in 80 mL of anhydrous CH\textsubscript{2}Cl\textsubscript{2} were added oxalyl chloride (14.68 g, 115.70 mmol) and catalytic amount of DMF at 0 \degree C. After being stirred for 3 h at the room temperature, the turbid solution was cooled to -78 \degree C. The reaction mixture were added anhydrous MeOH (5.6 mL) and Et\textsubscript{3}N (13.80 g, 101.80 mmol) at -78 \degree C for 30 min. After being stirred for 6 h at the same temperature, the resulting solution was poured into iced ether, washed with aqueous 2% HCl solution. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc) to give a compound 3a (5.67 g, 41.65 mmol) in 90% yield as a colorless liquid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 6.34-5.81 (m, 6H), 3.73-3.58 (m, 6H).

Diethyl 2,2'-((vinylphosphoryl)bis(azanediyl))diacetate (3c)

To a solution of vinyl phosphonic acid (20) (0.68 g, 6.35 mmol) in 10 mL of anhydrous CH\textsubscript{2}Cl\textsubscript{2} were added oxalyl chloride (1.74 g, 14.3 mmol) and catalytic amount of DMF 0 \degree C. After being stirred for 3 h at the room temperature, the turbid solution was cooled to -78 \degree C. The reaction mixture was added glycine ethyl ester (2 g, 14.3 mmol) and triethylamine (3.3 g, 33.3 mmol) at -78 \degree C for 30 min. After being stirred for 6 h at the same temperature, the resulting solution was poured into iced ether, washed with aqueous 2% HCl solution. The organic layer was dried
over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:MeOH = 10:1 v/v) to give a compound 3c (1.6 g, 5.71 mmol) in 90% yield as a colorless liquid.

1H NMR (400 MHz, CDCl₃) δ 6.19-5.71 (m, 3H), 4.02 (q, J = 7.2 Hz, 4H), 3.66-3.52 (m, 4H), 3.49-3.40 (m, 2H), 1.10 (t, J = 7.1 Hz, 6H).

13C NMR (100 MHz, CDCl₃) δ 171.6, 171.5, 133.7, 130.4, 128.9, 61.1, 41.6, 41.5, 14.0.

31P NMR (202 MHz, CDCl₃) δ 18.86. HRMS (ESI) m/z: [M + Na]+ Calcd for C₁₀H₁₉N₂NaO₅P 301.0924; Found 301.0925.

**Diethyl 2,2'-(vinylphosphoryl)bis(azanediyl)(2R,2'R)-dipropionate (3d)**

Compound 3d was prepared with the same procedure as compound 3c (1.74 g, 5.68 mmol) in 88% yield as a colorless liquid. 1H NMR (400 MHz, CDCl₃) δ 6.26-5.92 (m, 3H), 4.16-4.09 (m, 4H), 4.03-3.97 (m, 1H), 3.94-3.87 (m, 1H), 3.16-3.04 (m, 2H), 1.36-1.34 (m, 6H), 1.25-1.19 (m, 6H).

13C NMR (100 MHz, CDCl₃) δ 174.4, 174.3, 133.8, 131.1, 129.6, 61.2, 48.9, 48.6, 21.6, 21.4, 14.1, 14.0. 31P NMR (202 MHz, CDCl₃) δ 15.99. HRMS (ESI) m/z: [M + Na]+ Calcd for C₁₂H₂₃N₂NaO₅P 329.1237; Found 329.1241.

**Diethyl 2,2'-(vinylphosphoryl)bis(azanediyl)(2R,2'R)-bis(3-phenylpropanoate) (3e)**

Compound 3e was prepared with the same procedure as compound 3c (1.11 g, 2.42 mmol) in 70% yield as a colorless liquid.

1H NMR (400 MHz, CDCl₃) δ 7.29-7.18 (m, 6H), 7.10 (m, 4H), 6.10-5.63 (m, 3H), 4.10 (q, J = 7.0 Hz, 6H), 3.15-2.82 (m, 4H), 1.39-0.82 (m, 6H).

13C NMR (100 MHz, CDCl₃) δ 173.0, 172.9, 172.9, 172.8, 136.3, 136.1, 133.8, 133.8, 129.6, 129.6, 128.4, 126.9, 126.9, 61.2, 61.2, 54.2, 53.9, 41.0, 41.0, 40.7, 40.6, 14.1, 14.0. 31P NMR (202 MHz, CDCl₃) δ 15.98. HRMS (ESI) m/z: [M + Na]+ Calcd for C₂₄H₃₅N₂NaO₅P 481.1863; Found 481.1868.
Ethyl (phenoxy(vinyl)phosphoryl)-D-alaninate (3f) as a mixture of Rp-/Sp-isomers (~1:1)

Compound 3f was prepared with the same procedure as compound 3c (2.43 g, 8.57 mmol) in 70% yield as a white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.40-6.91\) (m, 5H), 6.39-5.78 (m, 3H), 4.16-4.01 (m, 2H), 4.02-3.92 (m, 1H), 3.68 (dt, \(J = 25.7\) Hz, 10.1 Hz, 1H), 2.63 (br, 1H), 1.27 (t, \(J = 7.3\) Hz, 3H), 1.23-1.13 (m, 3H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 173.8, 173.7, 173.5, 173.5, 150.4, 150.3, 150.3, 150.2, 134.0, 134.0, 129.4, 129.4, 129.1, 129.0, 127.3, 127.3, 124.5, 124.4, 120.7, 120.5, 120.5, 120.4, 61.2, 61.1, 49.3, 49.3, 49.2, 21.1, 21.0, 21.0, 20.9, 13.9. \(^3\)P NMR (202 MHz, CDCl\(_3\)) \(\delta 17.30, 16.76\). HRMS (ESI) \(m/z\): [M + Na]\(^+\) Calcd for C\(_{13}\)H\(_{18}\)NNaO\(_4\)P 306.0866; Found 306.0867.

3.1.3. Cross metathesis reaction

Diethyl \(((R)-4-((4R,5S)-5-((R)-2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxybut-2-en-1-yl)phosphonate (4b)

To a solution of compound 2 (0.14 g, 0.30 mmol) in 3 mL of anhydrous CH\(_2\)Cl\(_2\) were added diethyl allylphophonate (3b) (0.23 g, 1.20 mmol) and added Hoveyda-Grubbs catalyst 2\(^{nd}\) generation (6 mg, 3 mol%) at room temperature. After being stirred for 24 h at 40 °C using an oil bath, the reaction mixture was adsorbed on a silica gel to purified by silica gel column chromatography (CH\(_2\)Cl\(_2\):EtOAc = 2:1 to EtOAc:MeOH = 10:1 v/v) to give a compound 4b (65.5 mg, 0.10 mmol) in 36% yield as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.85-7.54\) (m, 4H), 7.49-7.35 (m, 6H), 6.04-5.85 (m, 1H), 5.73-5.51 (m, 1H), 5.22 (br, 1H), 4.54 (t, \(J = 8.6\) Hz, 1H), 4.33 (dd, \(J = 9.5\)Hz, 5.4 Hz, 1H), 4.18 (dd, \(J = 9.0\) Hz, 5.4 Hz, 1H), 4.18-4.04 (m, 4H), 3.95 (dd, \(J = 10.7\) Hz, 2.2 Hz, 2H), 3.84 (dd, \(J = 10.7\) Hz, 5.5 Hz, 1H), 2.92-2.80 (m, 1H), 2.69-2.57 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.08 (s, 9H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 135.7, 135.6, 135.6, 133.5, 133.4, 129.6, 129.5, 127.6, 127.5, 121.0, 120.9, 108.5, 79.6, 69.5, 65.5, 64.8, 64.7, 62.8, 62.8, 62.3, 62.3, 29.7, 28.0, 26.8, 26.6, 25.4, 25.2, 19.3, 16.4, 16.4, 16.3. HRMS (ESI) \(m/z\): [M + Na]\(^+\) Calcd for C\(_{31}\)H\(_{43}\)NaO\(_8\)PSi 629.2670; Found 629.2673.
3.2. Investigation of CM reaction using ultrasonic irradiation (6a-b)

3.2.1. Synthesis of compound 5

\[
\text{(3aS,6aS,6aS)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (5)} \quad \text{S3}
\]

According to the reported procedures S3, to a solution of compound 2 (10.0 g, 22.59 mmol) in 100 mL of MeOH was added ammonium fluoride (4.18 g, 112.96) at 0 °C. After being stirred for 12 h at 50 °C using an oil bath, the resulting solution was diluted with EtOAc and washed with brine. The organic layer was concentrated under reduced pressure, and the residue was dissolved in dioxane/H\textsubscript{2}O (1:1 v/v). The reaction mixture was treated with NaIO\textsubscript{4} (5.62 g, 26.27 mmol) at 0 °C. After being stirred for 6 h at the room temperature, the reaction mixture was diluted with 400 mL of EtOAc and washed with brine (100 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1 to 1:2 v/v) to give compound 5 (0.57 g, 3.06 mmol) as a mixture of α- and β-isomers in 62% yield for 2 steps as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 6.08-5.90 (m, 1H), 5.91-5.73 (m, 0.3H), 5.48 (d, \( J = 2.9 \) Hz, 1H), 5.38 (d, \( J = 17.4 \) Hz, 0.2H), 5.28 (d, \( J = 17.2 \) Hz, 1H), 5.22 (d, \( J = 10.5 \) Hz, 0.2H), 5.16 (d, \( J = 10.4 \) Hz, 1H), 4.73-4.62 (m, 3H), 4.58 (s, 0.2H), 4.57-4.51 (m, 0.2H), 3.41 (s, 0.2H), 3.25-3.02 (m, 0.2H), 1.57 (s, 0.6H), 1.49 (d, \( J = 2.7 \) Hz, 3H), 1.38 (s, 0.6H), 1.31 (d, \( J = 2.7 \) Hz, 3H). \textsuperscript{1}H NMR (The ratio of α-/β- isomers was determined by \textsuperscript{1}H NMR.)

3.2.2. Cross metathesis reaction

(6a)

\[
\text{(6aS,6aS)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (5)} \quad \text{S3}
\]
Dimethyl((E)-2-((3aS,4S,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinyl)phosphonate (6a)

To a solution of compound 5 (0.10 g, 0.53 mmol) and 3a (0.15 g, 1.07 mmol) in 5 mL of anhydrous CH₂Cl₂ was added three times of 1 mol% of Hoveyda-Grubbs catalyst 2nd generation (3.36 mg, 5.30 Mmol, three times, each 2 h) and then irradiated at 50 °C using a sonicator. The reaction mixture was cooled to room temperature and adsorbed on a silica gel to purified by silica gel column chromatography (CH₂Cl₂:EtOAc = 2:1 to EtOAc : MeOH = 10:1 v/v) to give a compound 6a (0.12 g, 0.39 mmol) as E-/Z- isomers in 73% yield as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ 6.90 (m, 1H), 6.73 (m, 0.5H), 6.07-5.88 (m, 1.5H), 5.52 (s, 1H), 5.30 (dd, J = 10.1 Hz, 3.9 Hz, 0.5H), 4.89 (br, 1H), 4.77-4.66 (m, 0.5H), 4.64-4.60 (m, 1.5H), 4.58 (dd, J = 6.4 Hz, 3.9 Hz, 0.5H), 3.71 (m, 9H), 1.57 (s, 1.5H), 1.48 (s, 3H), 1.37 (s, 1.5H), 1.31 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 152.8, 152.7, 149.0, 149.0, 117.6, 116.6, 115.7, 115.1, 114.6, 112.5, 102.9, 96.6, 86.9, 86.5, 85.8, 84.0, 84.0, 83.0, 83.0, 80.1, 79.9, 78.8, 52.6, 52.5, 52.5, 52.5, 52.4, 26.4, 26.1, 24.9, 24.9.

31P NMR (202 MHz, CDCl₃) δ 20.66, 20.06. HRMS (ESI) m/z: [M + Na]+ Calcd for C₁₁H₁₉NaO₇P 317.0761; Found 317.0764. E-/Z- isomer 0.5: 1 (The ratio of E-/Z- isomers was determined by 1H NMR.)

Diethyl ((Z)-3-((3aS,4S,6aS)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)allyl)phosphonate (6b)

Compound 6b was prepared with the same procedure as compound 6a (0.15 g, 0.44 mmol) in 93% yield as a colorless oil. 1H NMR (400 MHz, CDCl₃) δ 5.94-5.79 (m, 1H), 5.80-5.73 (m, 0.15H), 5.68 (t, J = 7.4 Hz, 1H), 5.45 (s, 1H), 5.28 (dd, J = 10.2 Hz, 3.7 Hz, 0.2H), 4.75-4.60 (m, 2H), 4.60-4.51 (m, 0.5H), 4.19-3.99 (m, 6H), 2.57 (dd, J = 21.9 Hz, 7.2 Hz, 2H), 1.56 (s, 0.6H), 1.48 (s, 3H), 1.37 (s, 0.7H), 1.33-1.28 (m, 9H), 1.25 (t, J = 6.8 Hz, 3H). 13C NMR (100 MHz, CDCl₃) δ 135.5, 135.3, 131.6, 131.5, 122.4, 122.3, 122.3, 122.1, 114.4, 112.3, 102.2, 96.1, 87.5, 87.5, 86.2, 84.7, 83.8, 83.8, 80.0, 80.0, 79.1, 62.1, 62.0, 62.0, 62.0, 61.9, 30.9, 30.8, 29.5, 29.5, 26.5, 25.0, 24.9, 16.4, 16.4. 31P NMR (202 MHz, CDCl₃) δ 26.98, 26.49. HRMS (ESI) m/z: [M + Na]+ Calcd for C₁₄H₂₅NaO₇P 359.1230; Found 359.1234. E-/Z- isomer 0.15:1 (The ratio of E-/Z- isomers was determined by 1H NMR.)

3.3. Synthesis of L-nucleoside dimethyl phosphonates (9a-e)

3.3.1. Synthesis of compound 7
According to reported procedures\textsuperscript{4,5}, to a solution of compound 6a (5.37 g, 18.25 mmol) in 20 mL of MeOH was added 30 mL of hydrogen chloride solution (15 mmol, 0.5 M in MeOH) at 0 °C. After being stirred for 12 h at the room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH\textsubscript{2}Cl\textsubscript{2}:MeOH = 30:1 to 20:1 v/v) to give a 5-dimethylphosphonyl furanose derivative in quantitative yield. To a solution of the phosphonate derivative in 200 mL of anhydrous CH\textsubscript{2}Cl\textsubscript{2} were added Et\textsubscript{3}N (5.54 g, 54.75 mmol) and benzoyl chloride (6.15 g, 43.80 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 24 h at room temperature and treated with 10 mL of MeOH. After being stirred for 30 min at the same temperature, the resulting solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1 to 1:2 v/v) to give a 2,3-dibenzyldimethylphosphonate furanose derivative (7.73 g, 16.24 mmol) in 89% yield. To a solution of the dibenzyl derivative (7.37 g, 16.24 mmol) in 30 mL of acetic anhydride were added 18 mL of acetic acid and conc. H\textsubscript{2}SO\textsubscript{4} (0.16 g, 1.62 mmol) at 0 °C. After being stirred for 12 h at the room temperature, the reaction mixture was poured into cold saturated aqueous NaHCO\textsubscript{3} solution (50 mL) and neutralized with NaHCO\textsubscript{3}. The resulting solution was extracted with diethyl ether (100 mL x 3) and the combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}. After filtered out excess of Na\textsubscript{2}SO\textsubscript{4}, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 15:1 to 3:1 v/v) to give an 1-O-acetyl furanose derivative in quantitative yield. To a solution of the acetyl derivative (8.19 g, 16.24 mmol) in 50 mL of EtOAc was added 10 wt% of Pd/C (0.82 g). After being stirred for 18 h under H\textsubscript{2} (1 atm) atmosphere, 1.0 g of celite was added to the reaction mixture and stirred for 30 min. After filtered out of the solid, the filtrate was concentrated under reduced pressure to give a compound 7 (7.97 g, 15.75 mmol) as a mixture of α- and β-isomers in 97% yield as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.29-7.74 (m, 8H), 7.69-7.17 (m, 10H), 6.60 (d, J = 4.1 Hz, 0.6H), 6.36 (d, J = 1.1 Hz, 1H), 6.13-5.87 (m, 0.4H), 5.83-5.73 (m, 0.4H), 5.68 (d, J = 4.9 Hz, 1H), 5.67-5.57 (m, 0.4H), 5.57-5.49 (m, 1H), 5.49-5.42 (m, 1H), 5.32-5.19 (m, 0.4H), 4.55-4.34 (m, 1.7H), 3.74 (dd, J = 10.8 Hz, 6.3 Hz, 9H), 3.66-3.60 (m, 1.5H), 3.58 (d, J = 10.4 Hz, 1H), 3.41 (d, J = 34.7 Hz, 1.2H), 2.14 (s, 3H), 2.10 (s, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 169.5, 169.2, 165.5, 165.3, 165.0, 164.9, 133.6, 133.5, 133.5, 133.5, 133.4, 129.8, 129.7, 129.6, 129.6, 128.6, 128.4, 128.4, 128.4, 128.4, 98.3, 95.9, 95.2, 93.9, 83.5, 83.3, 81.9, 81.7, 75.3, 73.8, 72.5, 70.7, 52.5, 52.4, 52.4, 52.4, 52.3, 27.2, 27.1, 26.7, 26.6, 26.4, 21.4, 21.3, 21.1, 21.0, 19.9, 19.9. \textsuperscript{31}P NMR (202 MHz, CDCl\textsubscript{3}) δ 33.48, 33.20. HRMS (ESI) m/z: [M + Na]\textsuperscript{+} Calcd for C\textsubscript{24}H\textsubscript{27}NaO\textsubscript{10}P 529.1234; Found 529.1236
3.3.2. Coupling reaction

![Chemical structure](image)

**Dimethyl (2-((2S,3R,4S,5S)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl)phosphonate (9a)**

To a solution of \(N^\text{6}-\text{benzoyladenine (8a)} (0.06 \text{ g}, 0.24 \text{ mmol})\) in 4 mL of anhydrous MeCN was added BSA (0.06 g, 0.29 mmol). After being stirred for 1 h, a solution of compound 7 (0.10 mg, 0.20 mmol) in 3 mL of anhydrous MeCN and SnCl\(_4\) (0.13 g, 0.50 mmol) were added to the reaction mixture at -10 °C. The reaction mixture was stirred at the room temperature under nitrogen atmosphere. After being stirred for 24 h at the same temperature, the resulting solution was poured into saturated aqueous NaHCO\(_3\) solution at 0 °C and then extracted with EtOAc. The combined organic layer was dried over Na\(_2\)SO\(_4\). After filtered out the excess of Na\(_2\)SO\(_4\), the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH\(_2\)Cl\(_2\):MeOH = 50:1 to 10:1 v/v) to give a adenosine dimethyl phosphonate. To a solution of the adenosine derivative (0.09 g, 0.13 mmol) in 3 mL of MeOH was added K\(_2\)CO\(_3\) (0.08 g, 0.06 mmol) at -10 °C. After being stirred for 12 h at room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH\(_2\)Cl\(_2\):MeOH = 10:1 to 5:1 v/v) to give a compound 9a (0.05 g, 0.12 mmol) in 61% yield for 2 steps as a white solid. \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 8.22 (d, \(J = 15.1 \text{ Hz}, 2\text{H})\), 5.94 (d, \(J = 4.8 \text{ Hz}, 1\text{H})\), 4.79 (t, \(J = 5.1 \text{ Hz}, 1\text{H})\), 4.22 (t, \(J = 5.2 \text{ Hz}, 1\text{H})\), 4.03 (q, \(J = 5.8 \text{ Hz}, 2\text{H})\), 3.72 (d, \(J = 10.9 \text{ Hz}, 6\text{H})\), 2.12-1.93 (m, 4\text{H})\). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 157.3, 153.9, 150.6, 141.7, 129.2, 90.5, 84.9, 74.8, 53.2, 30.7, 27.1, 21.7, 20.2. \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 33.59. HRMS (ESI) \(m/z\): [M + H]\(^+\) Calcd for C\(_{13}\)H\(_{21}\)N\(_5\)O\(_6\)P 374.1224; Found 374.12247.

**Dimethyl (2-((2S,3R,4S,5S)-5-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl)phosphonate (9b)**
To a solution of N2-Ac-N6-DPC-guanosine (8b) (0.09 g, 0.24 mmol) in 4 mL of anhydrous MeCN was added BSA (0.06 g, 0.30 mmol). After being stirred for 1 h, a solution of compound 7 (0.10 g, 0.20 mmol) in 3 mL of anhydrous MeCN and SnCl4 (0.13 g, 0.50 mmol) were added to the reaction mixture at -10 °C. The reaction mixture was stirred at room temperature under nitrogen atmosphere. After being stirred for 2 h at the room temperature, the resulting solution was poured into saturated aqueous NaHCO3 solution at 0 °C and then extracted with EtOAc. The combined organic layer was dried over Na2SO4. After filtered out the excess of Na2SO4, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH2Cl2:MeOH = 50:1 to 10:1 v/v) to give a guanosine dimethyl phosphonate. To a solution of guanosine derivative (0.01 g, 0.17 mmol) in 3 mL of MeOH was added 0.2 mL of NaOMe (0.19 mmol, 5.4 M in MeOH) 0 °C. After being stirred for 12 h at the room temperature, the solvent was removed under reduced pressure. The residue was dissolved in small amounts of MeOH and treated with CH2Cl2. The precipitate was filtered and washed with CH2Cl2. The white solid was dried over under vacuum to give a compound 9b (0.06 g, 0.12 mmol) in 60% yield for 2 steps. 1H NMR (400 MHz, D2O) δ 7.79 (s, 1H), 5.72 (d, J = 5.5 Hz, 1H), 4.72 (t, J = 5.5 Hz, 1H), 4.15 (t, J = 4.7 Hz, 1H), 3.99 (d, J = 5.1 Hz, 1H), 3.59 (d, J = 10.9 Hz, 6H), 3.39 (d, J = 9.6 Hz, 2H), 1.91-1.85 (m, 4H). 13C NMR (100 MHz, D2O) δ 152.6, 116.5, 87.5, 83.9, 72.8, 72.7, 53.0, 52.9, 25.1, 19.4, 18.0. 31P NMR (202 MHz, CDCl3) δ 35.93. HRMS (ESI) m/z: [M + H]+ Calcd for C13H20N5O7P 390.1173; Found 390.1170.

Dimethyl (2-((2S,3R,4S,5S)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl)phosphonate (9c)

Compound 9c was prepared with the same procedure as compound 9b (0.04 g, 0.11 mmol) in 74% yield as a white solid. 1H NMR (400 MHz, CD3OD) δ 7.65 (d, J = 7.5 Hz, 1H), 5.99 (br, 1H), 5.76 (d, J = 3.2 Hz, 1H), 4.17 (dd, J = 5.2 Hz, 3.3 Hz, 1H), 3.96-3.83 (m, 2H), 3.76 (d, J = 10.8 Hz, 6H), 2.08-1.89 (m, 4H). 13C NMR (100 MHz, CD3OD) δ 143.4, 94.0, 84.0, 83.8, 75.5, 74.5, 30.4, 27.0, 27.0, 26.0, 21.9, 20.4. 31P NMR (202 MHz, CDCl3) δ 33.43. HRMS (ESI) m/z: [M + H]+ Calcd for C12H20N3O7P 350.11116; Found 350.11139.
Dimethyl (2-((2S,3R,4S,5S)-3,4-dihydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)ethyl)phosphonate (9d)

Compound 9d was prepared with the same procedure as compound 9a (0.03 g, 0.08 mmol) in 73% yield as a white solid. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.38 (d, $J = 1.3$ Hz, 1H), 5.75 (d, $J = 4.5$ Hz, 1H), 4.24 (dd, $J = 5.9$ Hz, 4.5 Hz, 1H), 3.94 (t, $J = 5.8$ Hz, 1H), 3.87-3.84 (m, 1H), 3.75 (d, $J = 10.9$ Hz, 6H), 2.03-1.92 (m, 4H), 1.89 (d, $J = 1.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 164.9, 150.9, 137.2, 110.4, 90.6, 82.6, 73.0, 51.8, 51.8, 25.7, 20.3, 18.9, 10.9. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 33.45. HRMS (ESI) $m/z$: [M + H]$^+$ Calcd for C$_{13}$H$_{21}$N$_2$O$_8$P 365.11083; Found 365.11047.

Dimethyl (2-((2S,3R,4S,5S)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl)phosphonate (9e)

Compound 9e was prepared with the same procedure as compound 9a (0.12 g, 0.34 mmol) in 82% yield as a white solid. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.35 (d, $J = 7.7$ Hz, 1H), 6.23 (d, $J = 2.5$ Hz, 1H), 5.63 (d, $J = 7.6$ Hz, 1H), 4.53 (dd, $J = 6.4$ Hz, 2.5 Hz, 1H), 4.29 (d, $J = 7.7$ Hz, 1H), 3.73 (d, $J = 10.8$ Hz, 6H), 2.08-1.79 (m, 4H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 164.1, 151.2, 140.9, 100.1, 88.1, 81.7, 72.2, 51.7, 24.8, 24.8, 19.9, 18.5. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 33.98. HRMS (ESI) $m/z$: [M + H]$^+$ Calcd for C$_{12}$H$_{19}$N$_2$O$_8$P 351.09518; Found 351.09531.

3.4. Synthesis of phosphonate D-ribofuranosyl analogs (11a-f)

3.4.1. Synthesis of compound 10
(3aR,6R,6aR)-4-(Benzyloxy)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (10)\textsuperscript{85}

To a solution of D-Ribose (1) (5.0 g, 33.3 mmol) in 250 mL of acetone were added benzyl alcohol (36.01 g, 330.04 mmol) and conc. H₂SO₄ (0.03 g, 0.33 mmol) at 0 °C. The reaction mixture was heated to 70 °C using an oil bath and allowed to stir for 6 h. The reaction mixture was cooled to room temperature and neutralized with Et₃N until pH 6. The acetone was removed under reduced pressure and the residue was dissolved in EtOAc. The solution was washed with brine (100 mL x 3). The organic layer was concentrated under reduced pressure and the benzyl alcohol was removed under high vacuum. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1 to 50:1 v/v) to give a 1-O-Benzyl-2,3-O-isopropylidene-D-ribose derivative (4.66 g, 16.65 mmol) in 50% yield. To a solution of 1-O-Benzyl-2,3-O-isopropylidene-D-ribose derivative (4.66 g, 16.65 mmol) in 100 mL of anhydrous MeCN was added IBX (9.32 g, 33.31 mmol). After being stirred for 12 h at 80 °C using an oil bath, the resulting solution was cooled to room temperature and diluted with EtOAC (200 mL). After filtered out of the excess solid, the filtrate was concentrated under reduced pressure. The aldehyde residue was used the next step without further any purification. To a suspension of Ph₃PCH₃Br (23.79 g, 66.61 mmol) in 100 mL of THF was added 39.5 mL of n-BuLi (63.27 mmol, 1.6 M in hexane) at 0 °C under N₂ atmosphere. After 30 min, a solution of aldehyde derivative in 150 mL of THF was added to the reaction mixture at -10 °C and then stirred for 4 h at the room temperature. The resulting solution was treated with 20 mL of MeOH, and poured into ether-water solution (360 mL, 3:1 v/v). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (100 mL × 2). The combined organic layer was washed with brine (50 mL × 2) and dried over MgSO₄. After filtered out the excess of solid, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 100:1 to 60:1 v/v) to give a compound 10 (3.31 g, 11.98 mmol) in 72% yield as a colorless oil. \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.40-7.24 (m, 4H), 5.97 (m, 1H), 5.31 (d, \(J = 17.2\) Hz, 1H), 5.18 (d, \(J = 9.3\) Hz, 2H), 4.80-4.72 (m, 2H), 4.71-4.61 (m, 2H), 4.48 (d, \(J = 11.8\) Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H).

3.4.2. Cross metathesis reaction

Dimethyl \(\text{(2-((3aR,4R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-}\)
yl)vinyl)phosphonate (11a)

Compound 11a was prepared with the same procedure as compound 6a (1.17 g, 3.04 mmol) in 70% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.25 (m, 5H), 6.88-6.77 (m, 1H), 5.96-5.86 (m, 1H), 5.21 (s, 1H), 4.80-4.75 (m, 1H), 4.72-4.68 (m, 3H), 4.50 (d, $J$ = 11.7 Hz, 1H), 3.67-3.61 (m, 6H), 1.48 (s, 3H), 1.30 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.9, 136.7, 128.4, 128.1, 118.4, 118.4, 116.5, 112.8, 107.7, 87.0, 85.3, 83.8, 69.5, 52.4, 52.3, 26.4, 24.9.  $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 15.53, 17.77, 19.58, 21.28. HRMS (ESI) $m/z$: [M + Na]$^+$. Calcd for C$_{18}$H$_{25}$NaO$_7$P 407.1230; Found 407.1229.

Diethyl (3-((3a$R$,4$R$,6a$R$)-6-(benzyl oxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)allyl)phosphonate (11b)

Compound 11b was prepared with the same procedure as compound 6a (1.93 g, 4.52 mmol) in 90% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.24 (m, 5H), 5.73-5.68 (m, 1H), 5.14 (s, 1H), 4.70 (d, $J$ = 3.8 Hz, 1H), 4.69-4.64 (m, 2H), 4.62 (dd, $J$ = 6.0 Hz, 1.0 Hz, 1H), 4.45 (d, $J$ = 11.7 Hz, 1H), 4.13-4.01 (m, 4H), 2.57 (dd, $J$ = 6.5 Hz, 4.8 Hz, 1H), 2.51 (dd, $J$ = 6.0 Hz, 4.5 Hz, 1H), 1.46 (s, 3H), 1.34-1.29 (m, 5H), 1.28 (s, 3H), 1.27 (d, $J$ = 1.7 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.1, 134.7, 128.4, 128.1, 123.1, 112.3, 107.0, 87.8, 85.6, 84.5, 68.7, 61.9, 61.8, 31.0, 29.6, 26.4, 24.9, 16.4, 16.4. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 24.44, 24.50. HRMS (ESI) $m/z$: [M + Na]$^+$. Calcd for C$_{21}$H$_{31}$NaO$_7$P 449.1700; Found 449.1703.

Diethyl 2,2'-(((2-((3a$R$,4$R$,6a$R$)-6-(benzyl oxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinyl)phosphoryl)bis(azanediyl))diacetate (11c)

Compound 11c was prepared with the same procedure as compound 6a (0.72 g, 1.36 mmol) in 54% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.27 (m, 5H), 6.77 (m, 1H), 6.01 (m, 1H), 5.20 (s, 1H), 4.79 (dt,
$J = 3.2$ Hz, 1.5 Hz, 1H), 4.78-4.64 (m, 3H), 4.52 (d, $J = 11.9$ Hz, 1H), 4.20-4.13 (m, 4H), 3.78-3.46 (m, 4H), 3.02 (dt, $J = 11.3$ Hz, 6.4 Hz, 1H), 2.94 (dt, $J = 13.4$ Hz, 6.6 Hz, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.27-1.24 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 171.4, 149.0, 136.9, 128.5, 127.9, 112.7, 107.6, 87.3, 87.0, 85.3, 83.9, 69.1, 61.4, 61.3, 60.3, 41.7, 41.7, 29.6, 29.3, 26.4, 24.9, 21.0, 14.1, -0.07. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 2.52, 15.93, 27.23. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{24}$H$_{35}$N$_2$NaO$_9$P 549.1972; Found 549.1974.

Diethyl 2,2'-(((2-((3aR,4R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinyl)phosphoryl)bis(azanediyl))(2S,2'S)-dipropionate (11d)

Compound 11d was prepared with the same procedure as compound 6a (0.88 g, 1.58 mmol) in 33% yield as a colorless oil. $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 7.42-7.16 (m, 5H), 6.70 (m, 1H), 6.22-6.11 (m, 1H), 6.10-5.95 (m, 1H), 5.14 (s, 1H), 4.78-4.71 (m, 3H), 4.66 (d, $J = 5.8$ Hz, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.20-4.03 (m, 4H), 3.93-3.75 (m, 2H), 3.66 (dd, $J = 13.5$ Hz, 11.4 Hz, 1H), 1.43 (s, 3H), 1.29 (s, 3H), 1.28-1.17 (m, 12H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 174.3, 174.3, 174.3, 174.2, 148.1, 148.1, 137.1, 128.1, 127.9, 127.4, 123.9, 122.3, 112.4, 107.8, 87.4, 87.2, 85.3, 84.0, 84.0, 69.0, 60.8, 60.8, 25.3, 23.7, 13.0, 13.0. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 15.87, 16.39, 20.73, 21.22. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{26}$H$_{39}$N$_2$NaO$_9$P 577.2285; Found 577.2283.

Diethyl 2,2'-(((2-((3aR,4R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinyl)phosphoryl)bis(azanediyl))(2S,2'S)-bis(3-phenylpropanoate) (11e)

Compound 11e was prepared with the same procedure as compound 6a in trace yield as a colorless oil. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{38}$H$_{47}$N$_2$NaO$_9$P 729.2931; Found 729.2933. (Checked by Mass spectrometer)
Ethyl ((2-((3aR,4R,6aR)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinyl)(phenoxy)phosphoryl)-L-alaninate (11f)

Compound 11f was prepared with the same procedure as compound 6a (0.58 g, 1.09 mmol) in 60% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.21 (m, 7H), 7.16-7.10 (m, 3H), 6.93-6.70 (m, 1H), 6.19-5.97 (m, 1H), 5.20 (s, 1H), 4.81-4.76 (m, 1H), 4.75-4.59 (m, 3H), 4.51-4.42 (m, 1H), 4.11 (m, 2H), 4.02-3.90 (m, 1H), 3.35 (dt, $J$ = 19.9 Hz, 10.2 Hz, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 1.28-1.16 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.5, 150.1, 149.3, 136.7, 129.5, 128.5, 128.1, 127.9, 124.7, 122.1, 121.9, 120.7, 120.4, 120.2, 112.7, 107.6, 87.0, 85.3, 83.9, 69.3, 61.4, 49.4, 26.4, 24.9, 21.2, 14.0. $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 14.30, 14.68, 17.80. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for C$_{27}$H$_{34}$NNaO$_8$P 554.1914; Found 554.1916.

3.5. Synthesis of 5'-vinyl nucleoside derivatives (15a-d) with method A and B

3.5.1. Method A

1-((2R,3R,4R,5R)-3,4-bis((tert-Butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (13a) S7

According to the reported procedures S7, to a solution of uridine (5.0 g, 20.47 mmol) in 100 mL of anhydrous DMF were added TBSCI (12.34 g, 81.9 mmol), and imidazole (8.36 g, 122.85 mmol) at 0 °C. After being stirred for 24 h at the room temperature, the reaction mixture was poured into cold water and extracted with diethyl ether (150 mL x 3). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The residue was dissolved in 160 mL of THF and treated with 60 mL of TFA/H$_2$O (1:2 v/v) solution at 0 °C. After being stirred for 6 h at the same temperature, the reaction mixture was neutralized with saturated aqueous NaHCO$_3$ solution until pH 6 and diluted with dichloromethane (300 mL). After separation, the aqueous layer was extracted
with dichloromethane (100 mL x 3). The combined organic layer was washed with brine and dried over Na₂SO₄. After filtered out of the solid, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH = 200:1 to 50:1 v/v) to give a compound 13a (7.74 g, 16.37 mmol) in 80% yield as a white solid. 1H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 5.73 (dd, J = 2.0 Hz, 6.4 Hz, 1H), 5.48 (d, J = 5.2 Hz, 1H), 4.54 (t, J = 5.2 Hz, 4.8 Hz, 1H), 4.17 (t, J = 4.0 Hz, 4.4 Hz, 1H), 4.09 (m, 1H), 3.95 (dd, J = 2.0 Hz, 10.4 Hz, 1H), 3.73 (dd, J = 2.0 Hz, 10.4 Hz, 1H), 2.75 (br, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.08 (d, J = 2.4 Hz, 6H), 0.05 (s, 3H), 0.03 (s, 3H).

13a

1H NMR (400 MHz, CDCl₃) δ 9.33 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 5.95-5.87 (m, 1H), 5.76 (dd, J = 2.0 Hz, 6.4 Hz, 1H), 5.68 (d, J = 2.4 Hz, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.36 (d, J = 10.4 Hz, 1H), 4.49 (t, J = 6.4 Hz, 6.8 Hz, 1H), 4.19 (dd, J = 2.8 Hz, 2.4 Hz, 1H), 3.78 (dd, J = 4.0 Hz, 2.8 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 163.4, 150.0, 139.7, 134.7, 119.2, 102.1, 91.5, 84.1, 75.3, 75.1, 25.8, 25.7, 18.0, 18.0, -4.1, -4.5, -4.6, -4.8.

To a solution of compound 13a (5.0 g, 10.57 mmol) in 100 mL of anhydrous MeCN was added IBX (5.90 g, 21.15 mmol) and then stirred for 12 h at 80 °C using an oil bath, The reaction mixture was cooled to 0 °C, and diluted with 200 mL of EtOAc. The precipitate was filtered out, and the filtrate was concentrated under reduced pressure. The residue was used in the next step without any further purification. To a suspension of Ph₃PCH₃Br (15.11 g, 42.30 mmol) in 80 mL of THF was added 25.2 mL of n-BuLi (40.19 mmol, 1.6 M in hexane) at 0 °C under N₂ atmosphere. After 30 min, a solution of aldehyde derivative in 150 mL of anhydrous THF was added to the reaction mixture at -78 °C and then stirred for 4 h at the room temperature. The resulting solution was treated with 20 mL of MeOH, and poured into ether-water solution (360 mL, 3:1 v/v). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (100 mL × 2). The combined organic layer was washed with brine (50 mL × 2) and dried over MgSO₄. After filtered out the solid, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 to 1:1 v/v) to give a compound 14a (3.96 g, 8.46 mmol) in 80% yield as a white solid. 1H NMR (400 MHz, CDCl₃) δ 9.33 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 5.95-5.87 (m, 1H), 5.76 (dd, J = 2.0 Hz, 6.4 Hz, 1H), 5.68 (d, J = 2.4 Hz, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.36 (d, J = 10.4 Hz, 1H), 4.49 (t, J = 6.4 Hz, 6.8 Hz, 1H), 4.19 (dd, J = 2.8 Hz, 2.4 Hz, 1H), 3.78 (dd, J = 4.0 Hz, 2.8 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 163.4, 150.0, 139.7, 134.7, 119.2, 102.1, 91.5, 84.1, 75.3, 75.1, 25.8, 25.7, 18.0, 18.0, -4.1, -4.5, -4.6, -4.8.
**tert-Butyl 3-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (15a)**

To a solution of compound 14a (1.10 g, 2.34 mmol) in 50 mL of THF were added Boc$_2$O (0.61 g, 2.81 mmol) and DMAP (0.03 g, 0.23 mmol) at 0 ℃. After being stirred for 12 h at room temperature, the reaction mixture was adsorbed on a silica gel and then purified by silica gel column chromatography (hexane:EtOAc = 10:1 to 5:1 v/v) to give a compound 15a (1.28 g, 2.25 mmol) in ~80% yield as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, $J$ = 8.0 Hz, 1H), 5.94-5.85 (m, 1H), 5.76-5.74 (m, 2H), 5.44 (d, $J$ = 17.2 Hz, 1H), 5.34 (d, $J$ = 10.4 Hz, 1H), 4.47 (dd, $J$ = 5.2 Hz, 1.6 Hz, 1H), 4.14 (t, $J$ = 4 Hz, 1H), 3.79 (dd, $J$ = 4.4 Hz, 4.0 Hz, 1H), 1.59 (s, 9H), 0.88 (s, 18H), 0.08-0.05 (m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.3, 148.1, 147.6, 138.8, 134.7, 119.0, 101.8, 90.9, 86.7, 84.6, 75.2, 27.4, 25.8, 25.7, 18.0, 17.9, -4.2, -4.6, -4.6, -4.7. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{27}$H$_{48}$N$_2$NaO$_7$Si$_2$: 591.2892; Found 591.2886.

**N-(1-((2R,3R,4R,5R)-3,4-bis((tert-Butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)benzamide (13b)**

Compound 13b was prepared with the same procedure as compound 13a (4.77 g, 8.28 mmol) in 75% yield as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.82 (br, 1H), 8.19 (d, $J$ = 7.6 Hz, 1H), 7.88 (d, $J$ = 7.2 Hz, 2H), 7.61 (t, $J$ = 7.2 Hz, 7.6 Hz, 1H), 7.50 (t, $J$ = 8.0 Hz, 7.2 Hz, 3H), 5.51 (d, $J$ = 4.4 Hz, 1H), 4.68 (t, $J$ = 4.0 Hz, 4.4 Hz, 1H), 4.20-4.41 (m, 2H), 4.03 (d, $J$ = 12.0 Hz, 1H), 3.8-3.72 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 9H), 0.05 (s, 3H).
Compound 14b was prepared with the same procedure as compound 14a (1.10 g, 1.92 mmol) in 75% yield as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.91 (br, 1H), 7.96-7.89 (m, 3H), 7.62 (t, $J$ = 7.6 Hz, 1H), 7.52 (t, $J$ = 8.0 Hz, 7.2 Hz, 3H), 5.99-5.90 (m, 1H), 5.70 (s, 1H), 5.54 (d, $J$ = 17.2 Hz, 1H), 5.42 (d, $J$ = 10.4 Hz, 1H), 4.60 (t, $J$ = 8.4 Hz, 6.8 Hz, 1H), 4.26 (d, $J$ = 3.2 Hz, 1H), 3.69 (dd, $J$ = 4.0 Hz, 4.4 Hz, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.26 (s, 3H), 0.14 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 162.3, 143.8, 134.6, 133.1, 129.0, 127.6, 119.7, 92.7, 83.4, 75.7, 74.6, 25.8, 25.8, 25.7, 25.7, 18.0, -4.1, -4.2, -4.6, -5.1. HRMS (ESI) $m/z$: [M + Na]$^+$. Calcd for C$_{29}$H$_{45}$N$_3$NaO$_5$Si$_2$: 594.2790; Found 594.2794.

5'-Vinyl-N$^4,N^4$-bisBoc-cytidine derivative (15b)

To a solution of compound 14b (3.12 g, 5.45 mmol) in 40 mL of MeOH was added 0.1 mL of NaOMe (0.54 mmol, 5.4 M in MeOH) at 0 °C. After being stirred for 6 h at room temperature, the reaction mixture was adsorbed on a silica gel and purified by silica gel column chromatography (CH$_2$Cl$_2$:MeOH = 20:1 v/v) to give a 2,3-O-diTBS-5'-vinyl cytidine derivative (2.39 g, 5.14 mmol) in 94% yield. To a solution of 5'-vinyl cytidine derivative (2.39 g, 5.14 mmol) in 50 mL of anhydrous THF were added (Boc)$_2$O (3.34 g, 15.32 mmol) and DMAP (0.31 g, 2.55 mmol) and then stirred for 12 h at room temperature. The reaction mixture was adsorbed on a silica gel and purified by silica gel column chromatography (hexane:EtOAc = 10:1 v/v) to give a compound 15b (3.07 g, 4.59 mmol) in 75% yield as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J$ = 7.6 Hz, 1H), 7.07 (d, $J$ = 7.6 Hz, 1H), 5.95-5.86 (m, 1H), 5.62 (s, 1H), 5.51 (d, $J$ = 16.8 Hz, 1H), 5.38 (d, $J$ = 10.8 Hz, 1H), 4.58 (t, $J$ = 7.2 Hz, 8.4 Hz, 1H), 4.25 (d, $J$ = 4.0 Hz, 1H), 3.63 (dd, $J$ = 3.6 Hz, 5.2 Hz, 1H), 1.55 (s, 18H), 0.92 (s, 9H), 0.85 (s, 9H), 0.27
(s, 3H), 0.13 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 162.4, 154.1, 149.5, 142.7, 134.6, 119.6, 95.9, 93.0, 84.9, 83.1, 75.4, 74.4, 27.7, 25.8, 25.8, 18.0, -4.0, -4.1, -4.7, -5.0. HRMS (ESI) m/z: [M + Na]^+ Calcd for C₃₂H₅₇N₃NaO₈Si₂ 690.3576; Found 690.3578.

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N-(9-((2R,3R,4R,5R)-3,4-bis((tert-Butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (13c) 87

Compound 13c was prepared with the same procedure as compound 13a (3.88 g, 6.46 mmol) in 80% yield as a white solid. 1H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.06-8.02 (m, 3H), 7.63 (t, J = 7.2 Hz, 7.6 Hz, 1H), 7.55 (t, J = 8.0 Hz, 7.2 Hz, 2H), 5.87 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 4.8 Hz, 4.4 Hz, 1H), 4.35 (d, J = 4.4 Hz, 1H), 4.19 (s, 1H), 3.98 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 13.2 Hz, 1H), 0.95 (s, 9H), 0.74 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), -0.13 (s, 3H), -0.16 (s, 3H).

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N-(9-((2R,3R,4R,5R)-3,4-bis((tert-Butyldimethylsilyl)oxy)-5-vinyltetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (14c) 89

Compound 14c was prepared with the same procedure as compound 14a (0.99 g, 1.66 mmol) in 80% yield as a white solid. 1H NMR (400 MHz, CDCl₃) δ 9.36 (br, 1H), 8.74 (s, 1H), 8.08 (s, 1H), 8.00 (d, J = 6.8 Hz, 2H), 7.56 (t, J = 4.8 Hz, 7.6 Hz, 2H), 6.14-6.05 (m, 1H), 5.96 (d, J = 4.4 Hz, 1H), 5.43 (d, J = 17.2 Hz, 1H), 5.31 (d, J = 10.8 Hz, 1H), 4.88 (t, J = 4.4 Hz, 1H), 4.52-4.49 (m, 1H), 4.14 (t, J = 4.4 Hz, 1H), 0.90 (s, 9H), 0.80 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H), -0.18 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 152.4, 151.4, 149.6, 142.2, 135.3, 133.6, 132.7, 128.7, 127.9, 124.0, 118.6, 89.8, 85.8, 76.0, 74.5, 25.8, 25.6, 18.0, 17.8, -4.3, -4.5, -4.6, -4.9
**3.5.2. Method B**

(3R,4R,5R)-5-Vinyltetrahydrofuran-2,3,4-triyl triacetate (16) \(^{S4,S5}\)

According to the reported procedures \(^{S4,S5}\), to a solution of D-Ribose (8.0 g, 53.28 mmol) in 200 mL of MeOH was added H₂SO₄ (0.52 g, 5.32 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was neutralized with NaHCO₃ at 0 °C until pH 6 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH = 10:1 v/v) to give a 1-O-methyl-D-ribose (8.22 g, 50.08 mmol) in 94% yield. To a solution of 1-O-methyl-D-ribofuranose derivative (8.22 g, 50.08 mmol) in 150 mL of anhydrous DMF were added TBSCl (30.18 g, 200.29 mmol) and imidazole (23.86 g, 350.51 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was diluted with diethyl ether (600 mL) and washed with H₂O (100 mL x 2). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in 200 mL of THF/H₂O (4:1 v/v) and treated with TFA (2.85 g, 25.03 mmol) at 0 °C. After being stirred for 8 h at the same temperature, the reaction mixture was treated with NaHCO₃ at 0 °C until pH 6 and extracted with diethyl ether (150 mL x 3). The organic layer was dried over Na₂SO₄. After filtered out of excess solid, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 to 3:1 v/v) to give a 1-O-methyl-2,3-O-diTBS-D-ribose derivative in 85% yield. To a solution of 1-O-methyl-2,3-O-diTBS-D-ribose derivative (10 g, 25.46 mmol) in 150 mL of anhydrous
MeCN was added IBX (14.26 g, 50.93 mmol). After being stirred for 6 h at 80 °C using an oil bath, the reaction mixture was cooled to 0 °C and diluted with EtOAc (200 mL). After filtered out of the excess solid, the filtrate was concentrated under reduced pressure to give an aldehyde derivative. The aldehyde was used the next step without any further purification. To a suspension of Ph₃PCH₃Br (36.38 g, 101.86 mmol) in 200 mL of THF was added 60.4 mL of n-BuLi (96.77 mmol, 1.6 M in hexane) at 0 °C under N₂ atmosphere. After 30 min, a solution of the aldehyde derivative in 200 mL of THF was added to the reaction mixture at -10 °C and then stirred for 4 h at the room temperature. The resulting solution was treated with 20 mL of MeOH, and then poured into ether-water solution (360 mL, 3:1 v/v). The organic layer was separated, and the aqueous layer was extracted with ether (200 mL × 2). The combined organic layer was washed with brine (80 mL × 2) and dried over MgSO₄. After filtered out the solid, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 25:1 to 5:1 v/v) to give a 5-vinyl-D-ribose derivative (7.91 g, 20.37 mmol) in 80% yield. To a solution of 5-vinyl-D-ribose derivative (3.0 g, 7.71 mmol) in 20 mL of anhydrous CH₂Cl₂ were added acetic acid (4.63 g, 77.18 mmol), acetic anhydride (3.93 g, 38.59 mmol) and H₂SO₄ (0.07 g, 0.71 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was neutralized with saturated aqueous NaHCO₃ solution until pH 7 and extracted with diethyl ether (100 mL x 2). The organic layer was dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:EtOAc = 10:1 to 2:1 v/v) to give a compound 16 as a mixture of α- / β-isomers (1.93 g, 7.10 mmol) in 92% yield as a colorless oil. α-form: ¹H NMR (400 MHz, CDCl₃) δ 6.39 (d, J = 4.8 Hz, 1H), 5.87-5.79 (m, 1H), 5.39 (dt, J = 1.2 Hz, 1.6 Hz, 1H), 5.28-5.18 (m, 2H), 5.06 (dd, J = 3.6 Hz, 3.2 Hz, 1H), 4.65 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H). ¹³C NMR (400 MHz, CDCl₃) δ 169.9, 169.6, 169.2, 133.6, 117.9, 93.6, 83.3, 72.5, 69.4, 20.9, 20.5, 20.2, β-form: ¹H NMR (400 MHz, CDCl₃) δ 6.10 (d, J = 1.6 Hz, 1H), 5.83-5.75 (m, 1H), 5.32 (dt, J = 1.2 Hz, 1.6 Hz, 1H), 5.26 (m, 1H), 5.21-5.15 (m, 2H), 4.52-4.49 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H). ¹³C NMR (400 MHz, CDCl₃) δ 169.6, 169.3, 169.1, 134.9, 118.7, 97.9, 82.2, 74.1, 73.7, 20.9, 20.4, 20.4

![Image of chemical structure](image)

(2R,3R,4R,5R)-2-(2-Acetamido-6-((diphenylcarbamoyl)oxy)-9H-purin-9-yl)-5-vinyltetrahydrofuran-3,4-diyl diacetate (18)
A suspension of compound 17 (1.45 g, 3.74 mmol) in 20 mL of anhydrous MeCN was added BSA (1.52 g, 7.49 mmol) at room temperature. After being stirred for 30 min at 80 °C using an oil bath, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 10 mL of anhydrous toluene, a solution of compound 16 (0.85 g, 3.12 mmol) in 30 mL of anhydrous toluene was added to the mixture followed by addition of TMSOTf (0.83 g, 3.74 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at 80 °C using an oil bath, and then treated with 5 mL of saturated aqueous NaHCO₃ solution at 0 °C. The resulting solution was extracted with EtOAc and washed with brine (30 mL). The organic layer was dried over Na₂SO₄ and filtered. The filtrate was purified by silica gel column chromatography (CH₂Cl₂:MeOH = 30:1 to 20:1 v/v) to give a compound 18 (1.36 g, 2.24 mmol) in 72% yield as a white solid.

1H NMR (400 MHz, CDCl₃) δ 8.21 (s 1H), 8.01 (s, 1H), 7.42-7.32 (m, 8H), 7.23-7.21 (m, 2H), 6.08-5.99 (m, 2H), 5.96 (t, J = 5.2 Hz, 1H), 5.45 (dt, J = 1.2 Hz, 1.6 Hz, 1H), 5.35 (dt, J = 1.2 Hz, 1H), 4.62-4.61 (m, 1H), 2.48 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H).

13C NMR (100 MHz, CDCl₃) δ 169.5, 169.3, 156.3, 154.4, 152.3, 150.2, 142.6, 133.4, 129.2, 121.4, 119.6, 86.6, 82.8, 73.3, 72.5, 25.1, 20.5, 20.4. HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₃₀H₂₈N₆NaO₁₈ 623.1861; Found 623.1867.

To a solution of compound 18 (0.54 g, 0.89 mmol) in 8 mL of MeOH was added 0.01 mL of NaOMe (0.05 mmol, 5.4 M in MeOH) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was treated with aqueous 1 N HCl solution until pH 6 and concentrated under reduced pressure. The residue was dissolved in 4 mL of anhydrous CH₂Cl₂, and pyridine (0.28 g, 3.59 mmol) and TBSOTf (0.42 g, 1.58 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was adsorbed on a silica gel and purified by silica gel column chromatography (hexane:EtOAc = 5:1 to 3:1 v/v) to give a compound 15d (0.48 g, 6.47 mmol) in 47% yield for 2 steps as a white solid.

1H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 7.98 (br, 1H), 7.43-7.34 (m, 8H), 7.27-7.23 (m, 2H), 6.16-6.07 (m, 1H), 5.94 (d, J = 4.8 Hz, 1H), 5.43 (d, J = 17.2 Hz, 1H), 5.33 (d, J = 10.8 Hz, 1H), 4.76 (br, 1H), 4.51-4.48 (m, 1H), 4.08 (t, J = 4.0 Hz, 1H), 2.53 (s, 3H), 0.93 (s, 9H), 0.80 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), -0.01 (s, 3H), -0.20 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 156.2, 154.5, 151.9, 150.2, 142.8, 135.2, 129.2, 118.5, 89.1, 85.8, 75.9, 74.5, 25.8, 25.6, 25.1, 18.0, 17.8, -4.3, -4.4, -4.6, -4.9. HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₃₈H₄₂N₆NaO₂₆Si₂ 767.3379; Found 767.3382.
3.6. Synthesis of phosphonamidate nucleotide prodrugs (19a-d)

*tert*-Butyl-3-((2R,3R,4R,5R)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((S)-1-ethoxy-1-oxopropan-2-yl)amino)(phenoxy)phosphoryl)vinyl)tetrahydrofuran-2-yl)-2,6-dioxo-3,6-dihydropyrimidine-1(2H)-carboxylate (19a) as a mixture of *E/-Z*-and *Rp/-Sp*-isomers

To a solution of compound 15a (0.15 g, 0.26 mmol) and 3f (0.15 g, 0.52 mmol) in 5 mL of anhydrous CH$_2$Cl$_2$ was added three times of 3 mol% of Hoveyda-Grubbs catalyst 2nd generation (4.95 mg, 0.0079 mmol, four times, each 2 h) and then irradiated at 50 °C using a sonicator. The reaction mixture was cooled to room temperature and adsorbed on a silica gel then, purified by silica gel column chromatography (hexane:EtOAc = 3:1 to 1:1 v/v) to give a compound 19a (0.18 g, 0.21 mmol) as a mixture of *E/-Z*-isomers in 82% yield as a white solid. The ratio of *E/-Z*-isomers was ~1:1 by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.25 (m, 7H), 7.20-7.18 (m, 4H), 7.13-7.09 (m, 2H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.91-6.74 (m, 3H), 6.21-6.11 (m, 2H), 5.79-5.76 (m, 3H), 5.66 (d, $J = 8.4$ Hz, 1H), 4.52 (br, 2H), 4.13-4.05 (m, 6H), 4.02-3.96 (m, 2H), 3.81 (t, $J = 4.4$ Hz, 2H), 3.68 (t, $J = 10.0$ Hz, 1H), 3.58 (t, $J = 10.0$ Hz, 1H, 1.56 (d, $J = 2.0$ Hz, 18H), 1.33 (t, $J = 7.2$ Hz, 7H), 1.22 (t, $J = 7.2$ Hz, 1H), 0.87-0.84 (m, 6H), 0.05-0.02 (m, 24H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.8, 173.7, 173.5, 173.4, 160.2, 160.1, 150.2, 148.2, 148.2, 147.4, 147.4, 146.8, 146.7, 146.3, 146.2, 139.2, 139.0, 129.7, 129.7, 129.9, 124.9, 124.4, 122.6, 122.2, 120.8, 120.5, 120.5, 120.4, 120.4, 119.5, 115.4, 102.3, 103.2, 90.5, 90.5, 86.7, 86.7, 83.9, 83.8, 83.6, 74.4, 74.7, 74.4, 74.4, 61.5, 61.5, 49.6, 49.4, 49.4, 27.4, 25.7, 25.6, 21.5, 21.4, 21.1, 21.0, 17.9, 17.8, 17.8, 14.0, -4.4, -4.4, -4.7, -4.7. $^{31}$P NMR (243 MHz, CDCl$_3$) $\delta$ 20.47, 19.93, 17.03, 16.19. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for C$_{38}$H$_{62}$N$_3$NaO$_{11}$PSi$_2$ 846.3553; Found 846.3554.
Ethyl-((2-((2R,3R,4R,5R)-5-(4,4-bis((tert-butoxycarbonyl)amino)-2-oxopyrimidin-1(2H)-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)vinyl)(phenoxy)phosphoryl)-L-alaninate (19b) as a mixture of E-/Z- and Rp-/Sp-isomers

Compound 19b was prepared with the same procedure as compound 19a (0.21 g, 0.22 mmol) as a mixture of E-/Z-isomers in 77% yield as a white solid. The ratio of E-/Z-isomers was ~1:0.8 by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 0.8H), 7.34-7.25 (m, 4H), 7.22-7.09 (m, 7H), 7.03 (d, $J = 3.6$ Hz, 1H), 4.19 (d, $J = 3.6$ Hz, 1H), 4.17-4.09 (m, 4.3H), 4.03-3.97 (m, 1H), 3.69 (dd, $J = 3.6$ Hz, 5.2 Hz, 1H), 3.63 (dd, $J = 3.6$ Hz, 4.0 Hz, 0.8H), 3.52 (t, $J = 10.0$ Hz, 1H), 3.42 (t, $J = 10.4$ Hz, 0.8H), 1.54 (d, $J = 1.2$ Hz, 3H), 1.34-1.30 (m, 5.6H), 1.25-1.20 (m, 7H), 0.9-0.8 (m, 32H), 0.25 (s, 5.2H), 0.11 (d, $J = 2.8$ Hz, 5.2H), 0.01 (br, 11H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 173.9, 173.6, 173.5, 162.5, 162.4, 154.1, 154.0, 150.3, 150.2, 149.4, 146.9, 146.8, 146.3, 146.2, 129.7, 129.2, 124.9, 124.8, 122.8, 122.4, 121.0, 120.7, 120.5, 120.4, 120.3, 119.4, 115.5, 96.4, 96.2, 93.0, 92.9, 85.0, 81.9, 81.8, 81.7, 81.6, 75.4, 75.3, 74.2, 74.1, 61.6, 49.6, 49.5, 49.5, 29.2, 27.6, 25.8, 21.6, 21.6, 21.2, 21.1, 18.0, 14.0, 14.0, -4.1, -4.2, -4.8, -4.8, -5.0. $^{31}$P NMR (243 MHz, CDCl$_3$) $\delta$ 16.65, 15.57. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for C$_{43}$H$_{71}$N$_4$O$_{12}$P$_2$Si$_9$ 945.4237; Found 945.4245.

Ethyl-((2-((2R,3R,4R,5R)-5-(6,6-bis((tert-butoxycarbonyl)amino)-9H-purin-9-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)vinyl)(phenoxy)phosphoryl)-L-alaninate (19c) as a mixture of E-/Z- and Rp-/Sp-isomers

Compound 19c was prepared with the same procedure as compound 19a (0.17 g, 0.17 mmol) as a mixture of E-/Z-isomers in 68% yield as a white solid. The ratio of E-/Z-isomers was ~2:1 by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.86 (s, 0.45H), 8.78 (s, 1H), 8.16 (s, 0.45H), 8.04 (s, 1H), 7.33-7.27 (m, 6H), 7.19-7.11 (m, 2.4H), 7.07-6.94 (m, 1.5H), 6.39-6.25 (m, 1.5H), 6.02 (d, $J = 5.6$ Hz, 1.5H), 4.91 (t, $J = 4.0$ Hz, 5.6 Hz, 0.45H), 4.83 (t, $J = 4.0$ Hz, 6.0 Hz, 1H), 4.64 (br, 1.5H), 4.19-4.00 (m, 6H), 3.55 (t, $J = 10.0$ Hz, 0.5H), 3.43 (t, $J = 10.0$ Hz, 1H), 1.43 (s, 27H), 1.37 (d, $J = 7.2$ Hz, 1.8H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.23-1.17 (m, 5H), 0.93 (d, $J = 1.6$ Hz, 13H), 0.76 (d, $J = 4.8$ Hz, 13H), 0.10 (d, $J = 3.2$ Hz, 9H), -0.05 (s, 1.5H), -0.07 (s, 3H), -0.33 (s, 1.5 H), -0.38 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 173.8, 173.4, 152.8, 152.1, 152.0, 150.6, 150.6, 150.4, 150.3, 150.3, 147.7, 146.6, 144.2, 144.1, 129.7, 129.6, 124.8, 124.7, 122.4, 122.0, 120.6, 120.6, 120.5, 120.5, 120.3, 89.4, 89.3, 84.9, 84.7, 83.7, 77.3, 77.0, 76.7, 75.5, 75.3, 75.3, 75.4, 61.6, 61.4, 49.5, 49.4, 49.4, 27.7, 25.7, 25.5, 25.5, 21.5, 21.5.
P NMR (243 MHz, CDCl$_3$) $\delta$ 17.17, 16.68. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{44}$H$_{71}$N$_6$NaO$_{11}$PSi$_2$ 969.4349; Found 969.4348.

Ethyl ((2-((2R,3R,4R,5R)-5-(2-acetamido-6-((diphenylcarbamoyl)oxy)-9H-purin-9-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)tetrahydrofuran-2-yl)vinyl)(phenoxy)phosphoryl)-L-alaninate (19d) as a mixture of E-/Z-and Rp-/Sp-isomers

Compound 19d was prepared with the same procedure as compound 19a (0.09 g, 0.08 mmol) as a mixture of E-/Z-isomers in 61% yield as a white solid. The ratio of E-/Z-isomers was ~1:0.7 by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.76 (s, 1H), 9.41 (s, 0.7H), 7.95 (s, 1H), 7.91 (s, 0.7H), 7.46-7.42 (m, 6H), 7.36-7.31 (m, 7.4H), 7.23-7.20 (m, 7.4H), 7.17-7.09 (m, 3.7H), 6.91-6.82 (m, 4H), 6.31-6.15 (m, 1.7H), 5.86 (dd, $J$ = 6.8 Hz, 7.6 Hz, 1.7H), 5.06-5.03 (m, 1H), 5.01-4.99 (m, 0.7H), 4.61-4.56 (m, 2H), 4.14-4.09 (m, 5H), 3.92 (d, $J$ = 4.0 Hz, 1H), 3.69 (t, $J$ = 10.4 Hz, 1H), 3.53 (t, $J$ = 9.6 Hz, 10.8 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 2.1H), 1.36-1.32 (m, 6H), 1.26-1.22 (m, 4.5H), 0.95 (s, 6H), 0.94 (s, 9H), 0.73 (s, 6H), 0.72 (s, 9H), 0.13 (d, $J$ = 3.6 Hz, 4.2 H), 0.10 (s, 6H), -0.12 (s, 2.1H), -0.15 (s, 3H), -0.52 (s, 2.1H), -0.54 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 173.7, 173.6, 173.4, 137.4, 156.5, 156.4, 156.0, 154.0, 154.0, 152.5, 152.4, 150.4, 150.4, 150.3, 148.6, 147.7, 147.7, 144.2, 143.9, 131.2, 129.7, 129.6, 129.5, 129.1, 125.1, 124.9, 124.5, 121.8, 121.2, 120.6, 120.6, 120.3, 120.5, 120.2, 119.5, 115.3, 89.8, 89.7, 86.1, 85.9, 85.7, 72.6, 72.3, 70.8, 70.7, 61.6, 61.5, 61.3, 49.5, 49.4, 48.8, 29.6, 25.7, 25.5, 24.8, 24.7, 22.0, 22.0, 21.5, 21.4, 21.2, 19.0, 18.0, 17.7, 14.1, 14.1, 14.0, 14.0, -4.5, -4.6, -4.6, -3.4, -5.4, -5.4. $^{31}$P NMR (243 MHz, CDCl$_3$) $\delta$ 20.47, 19.95, 18.52, 17.23. HRMS (ESI) $m/z$: [M + Na]$^+$ Calcd for C$_{49}$H$_{66}$N$_7$NaO$_{10}$PSi$_2$ 1022.4040; Found 1022.4044.
4. Reference for supporting information


5. NMR spectra

$^1$H NMR of compound 2 (400 MHz, CDCl$_3$)

$^1$H NMR of compound 3a (400 MHz, CDCl$_3$)
$^1$H NMR of compound 3c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 3c (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 3e (202 MHz, CDCl$_3$)

$^1$H NMR of compound 3d (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 3d (100 MHz, CDCl$_3$)

$^{31}$P NMR of compound 3d (202 MHz, CDCl$_3$)
$^1$H NMR of compound 3e (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 3e (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 3e (202 MHz, CDCl$_3$)

$^1$H NMR of compound 3f (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 3f (100 MHz, CDCl$_3$)

$^{31}$P NMR of compound 3f (202 MHz, CDCl$_3$)
$^1$H NMR of compound 4b (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 4b (100 MHz, CDCl$_3$)
$^1$H NMR of compound 5 (400 MHz, CDCl$_3$)

$^1$H NMR of compound 6a (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 6a (100 MHz, CDCl$_3$)

$^{31}$P NMR of compound 6a (202 MHz, CDCl$_3$)
$^1$H NMR of compound 6b (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 6b (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 6b (202 MHz, CDCl$_3$)

$^1$H NMR of compound 7 (400 MHz, CDCl$_3$)
$^{13}\text{C} \text{ NMR of compound 7 (100 MHz, CDCl}_3\text{)}$

$^{31}\text{P} \text{ NMR of compound 7 (202 MHz, CDCl}_3\text{)}$
$^1$H NMR of compound 9a (400 MHz, CD$_3$OD)

$^{13}$C NMR of compound 9a (100 MHz, CD$_3$OD)
\(^{31}\)P NMR of compound 9a (202 MHz, CD\(_{3}\)OD)

\(^{1}\)H NMR of compound 9b (400 MHz, D\(_2\)O)
$^{13}$C NMR of compound 9b (100 MHz, D$_2$O)

$^{31}$P NMR of compound 9b (202 MHz, D$_2$O)
$^1$H NMR of compound 9c (400 MHz, CD$_3$OD)

$^{13}$C NMR of compound 9c (100 MHz, CD$_3$OD)
$^{31}$P NMR of compound 9e (202 MHz, CD$_3$OD)

$^1$H NMR of compound 9d (400 MHz, CD$_3$OD)
$^{13}$C NMR of compound 9d (100 MHz, CD$_3$OD)

$^{31}$P NMR of compound 9d (202 MHz, CD$_3$OD)
$^1$H NMR of compound 9e (400 MHz, CD$_3$OD)

$^{13}$C NMR of compound 9e (100 MHz, CD$_3$OD)
$^{31}$P NMR of compound 9e (202 MHz, CD$_3$OD)

$^1$H NMR of compound 10 (400 MHz, CDCl$_3$)
$^1$H NMR of compound 11a (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 11a (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 11a (202 MHz, CDCl$_3$)

$^1$H NMR of compound 11b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 11b (100 MHz, CDCl$_3$)

$^{31}$P NMR of compound 11b (202 MHz, CDCl$_3$)
$^1$H NMR of compound 11c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 11c (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 11c (202 MHz, CDCl$_3$)

$^1$H NMR of compound 11d (400 MHz, CD$_2$OD)
$^{13}$C NMR of compound 11d (100 MHz, CD$_3$OD)

$^{31}$P NMR of compound 11d (202 MHz, CD$_3$OD)
$^1$H NMR of compound 11f (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 11f (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 11f (202 MHz, CDCl$_3$)

$^1$H NMR of compound 13a (400 MHz, CDCl$_3$)
$^1$H NMR of compound 14a (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 14a (100 MHz, CDCl$_3$)
$^1$H NMR of compound 15a (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 15a (100 MHz, CDCl$_3$)

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$^1$H NMR of compound 13b (400 MHz, CDCl₃)

$^1$H NMR of compound 14b (400 MHz, CDCl₃)
$^{13}$C NMR of compound 14b (100 MHz, CDCl$_3$)

![13C NMR spectrum of 14b](image)

$^1$H NMR of compound 15b (400 MHz, CDCl$_3$)

![$^1$H NMR spectrum of 15b](image)
$^1$H NMR of compound 13c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 15b (100 MHz, CDCl$_3$)
$^1$H NMR of compound 14c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 14c (100 MHz, CDCl$_3$)
$^1$H NMR of compound 15c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 15c (100 MHz, CDCl$_3$)
$^1$H NMR of compound 16 (α-form), (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 16 (α-form), (100 MHz, CDCl$_3$)
$^1$H NMR of compound 16 ($\beta$- form), (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 16 ($\beta$- form), (100 MHz, CDCl$_3$)
$^1$H NMR of compound 18 (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 18 (100 MHz, CDCl$_3$)
$^{1}\text{H} \text{ NMR of compound } 15\text{d} \ (400 \text{ MHz, CDCl}_3)$

$^{13}\text{C} \text{ NMR of compound } 15\text{d} \ (100 \text{ MHz, CDCl}_3)$
$^1$H NMR of compound 19a (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 19a (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 19a (243 MHz, CDCl$_3$)

$^1$H NMR of compound 19b (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 19b (100 MHz, CDCl$_3$)

$^{31}$P NMR of compound 19b (243 MHz, CDCl$_3$)
$^1$H NMR of compound 19c (400 MHz, CDCl$_3$)

$^{13}$C NMR of compound 19c (100 MHz, CDCl$_3$)
$^{31}$P NMR of compound 19c (243 MHz, CDCl$_3$)

$^1$H NMR of compound 19d (400 MHz, CDCl$_3$)
$^{13}$C NMR of compound 19d (100 MHz, CDCl$_3$)

$^3$P NMR of compound 19d (243 MHz, CDCl$_3$)