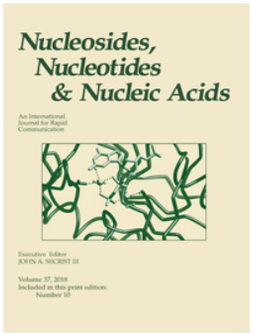

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# Synthesis of 7-trifluoromethyl-7-deazapurine ribonucleoside analogs and their monophosphate prodrugs

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# Synthesis of 7-trifluoromethyl-7-deazapurine ribonucleoside analogs and their monophosphate prodrugs

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**ABSTRACT**

Novel 7-trifluoromethyl-7-deazapurine ribonucleoside analogs (**13a-c**) and their Protides (**15a-c**) were successfully synthesized from ribolactol or 1-α-bromo-ribose derivatives using Silyl-Hilbert-Johnson or nucleobase-anion substitution reactions followed by key aromatic trifluoromethyl substitution. Newly prepared compounds were evaluated against a panel of RNA viruses, including HCV, Ebola or Zika viruses.

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7-trifluoromethyl-7-deazapurine ribonucleoside; protides; Silyl-Hilbert-Johnson; RNA viruses

## 1. Introduction

Nucleoside analogs played a pivotal role in the development of antiviral and anti-cancer agents. Since the discovery by William Prussoff in 1962[1] of idoxuridine, the first antiviral drug approved for the treatment of herpes virus, more than 25 nucleoside derivatives have been approved to treat human infectious diseases. 7-Deazapurine nucleoside derivatives are an extremely interesting class of analogs due to their innate biological activity.[2] Over the past 50 years, more than twenty 7-deazapurine derivatives have been discovered from terrestrial and marine sources.[3] Among them, naturally occurring tubercidin (**1a**),[4] toyocamycin (**1b**),[5] and sangivamycin (**1c**)[6] display a broad spectrum of activity and have driven extensive SAR studies towards the development of new antiviral and anticancer agents. Thus, 7-deazaadenosine derivatives of 6-hetaryl-7-deazapurine (**2a**) and 7-fluoro-7-deazapurine ribonucleosides (**2b-c**)[7] as well as 7-hetaryl-7-dazaapurine ribonucleoside (**3a**)[8] displayed potent cytostatic activity in multiple cancer cell lines. Recently, a series of 6-substituted 7-furyl or ethynyl-7-deazapurine ribonucleoside analogs (**3b-c**)[9] showed significant cytostatic, antimicrobial and promising anti-HCV activity. Furthermore,

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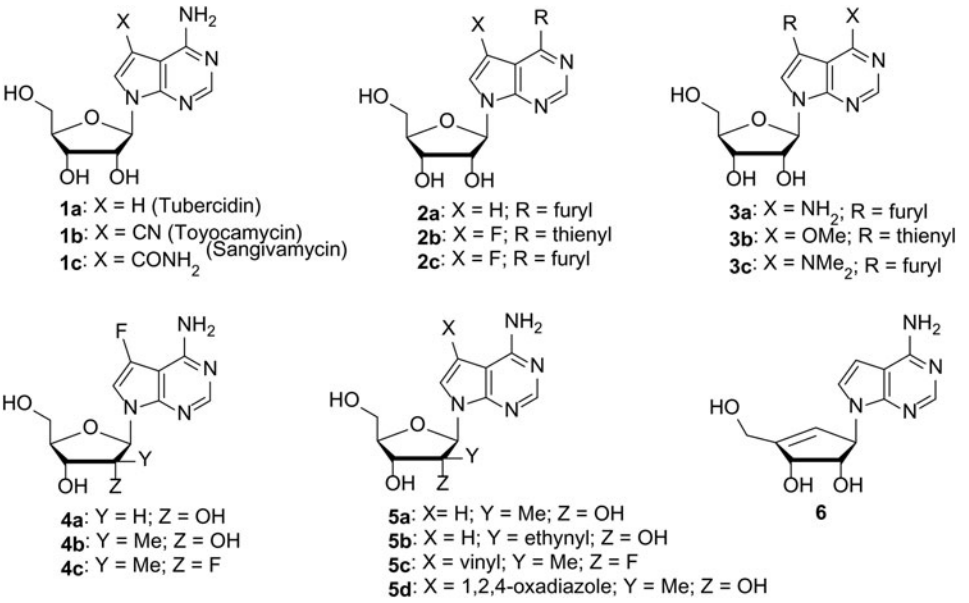



**Figure 1.** Biologically relevant 7-deazapurine nucleoside analogs.

7-fluoro-7-deazapurine ribonucleoside (**4a**)[10] showed improved anti-cancer activity and reduced cytotoxicity when compared with its parent tubercidin (**1a**). 7-Fluoro-7-deazapurine-2′-*C*-methyl and 2′-deoxy-2′-fluoro-2′-*C*-methyl ribonucleosides (**4b**)[11] and (**4c**)[12] were highly potent inhibitors of HCV replication. Interestingly, 7-deazapurine-2′-*C*-methylribonucleoside (**5a**) has been reported to inhibit both HCV[13] and Zika virus replication.[14] Additionally, 7-deazapurine-2′-*C*-ethynylribonucleoside (**5b**, NITD008) potentially inhibited dengue and Zika viruses.[15] Furthermore, 7-vinyl-7-deazapurine-2′-deoxy-2′-fluoro-2′-*C*-methyl ribonucleoside (**5c**) exhibited promising anti-HCV activity as well as weak anti-HIV activity.[16] The 1,2,4-oxadiazole-7-deazapurine-2′-*C*-methylribonucleoside (**5d**) showed high antiviral potency against HCV replication cells.[17] 7-Deazaneplanocin A analog (**6**) exhibited potent antiviral activity against cowpox and vaccinia viruses.[18]

If a large variety of groups has been introduced at the 7-position of 7-deazapurine nucleosides (Figure 1), the effect of a $CF_3$ group at this position remains underexplored. Herein, we wish to report the synthesis and antiviral evaluation of novel ribo, $\beta$-2′-methyl- or $\alpha$-2′-fluoro-$\beta$-2′-methyl-D-ribofuranoses 7-deazapurine derivatives with a trifluoromethyl group at the 7-position using a key aromatic trifluoromethyl substitution (Figure 2).

## 2. Results and discussion

6-Chloro-7-iodo-7-deazapurine (**8**), prepared from commercially available 6-chloro-7-deazapurine (**7**) by treatment with *N*-iodosuccinimide (NIS) in

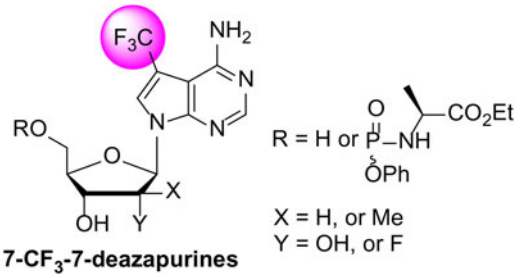
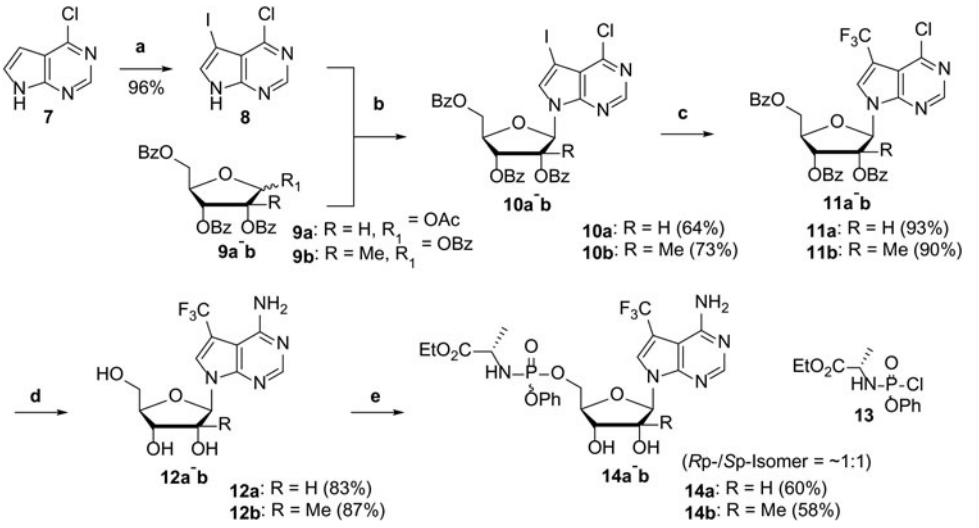


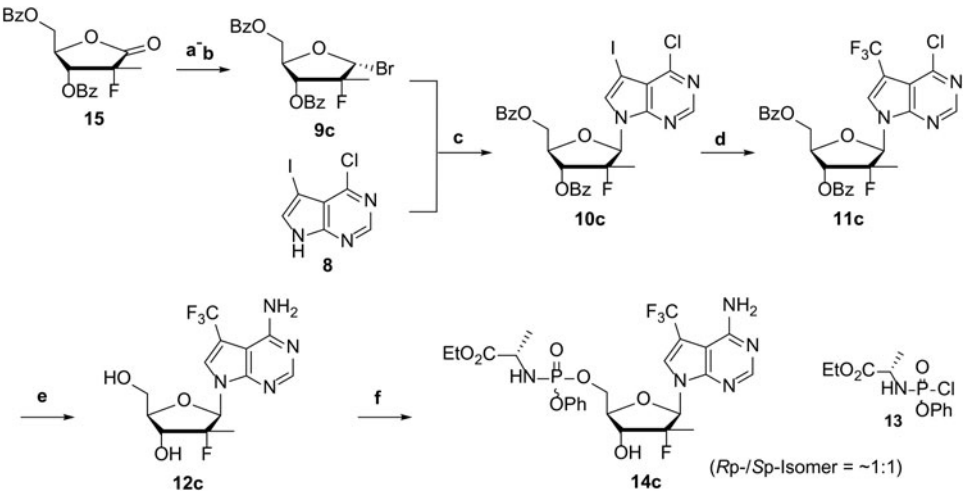

**Figure 2.** Target 7-trifluoromethyl-7-deazapurine analogs.

DMF,[19] was reacted with 1-α-/*β*-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose (**9a**) and 1-α-/*β*-*O*-benzoyl-2,3,5-tri-*O*-benzoyl-2′-*C*-methyl-D-ribose (**9b**) under classical Vorbrüggen glycosylation conditions[20–22] to give *β*- 6-chloro-7-iodo-7-deazapurine ribonucleosides **10a** and **10b**. Next, aromatic trifluoromethylation reaction[23,24] of compound **10a** and **10b** was carried out by treatment with methyl fluorosulfonyldifuoroacetate (MFSDA) and CuI in a mixture hexamethylphosphoramide (HMPA) and *N*,*N*-dimethylformamide (DMF) to give 7-trifluoromethyl-7-deazapurine nucleoside derivatives **11a** and **11b** in 90–93% yield.[25] Subsequent treatment with a saturated solution of ammonia in MeOH gave 7-trifluoromethyl-7-deazapurine nucleosides **12a** and **12b** in good yields. Finally, since the monophosphorylation of a nucleoside analog[26] can be the limiting step to the formation of the active triphosphate form, nucleosides **12a** and **12b** were converted into their corresponding phosphoramidate prodrug **14a** and **14b** by reaction with chlorophosphoramidate derivative **13** in presence of *t*-BuMgCl.[27] Prodrugs **14a** and **14b** were obtained as 1/1 Rp/Sp-mixtures, as determined by $^{1}$H-NMR and 31P-NMR. It is noteworthy that when *N*-methylimidazole (NMI) was employed instead of *t*-BuMgCl, prodrugs **14a** and **14b** were obtained in poor yields due to incomplete reactions and formation of 3′,5′-bis-phosphoramidate by-products (Scheme 1).

2′-*C*-Me,2′-F nucleoside analog **12c** and its phosphoramidate prodrug **14c** were prepared according to the chemistry described in Scheme 2. 1-α-Bromo-3,5-di-*O*-benzoyl-2′-deoxy-2′-fluoro-2′-*C*-methylribose (**9c**), synthesized from commercially available 3,5-di-*O*-benzoyl-2′-deoxy-2′-fluoro-2′-*C*-methyl ribolactone (**15**),[28,29] was coupled with 7-deaza purine **8** in presence of KOH and tris-[2-(2-methoxyethoxy)]ethylamine (TDA-1)[30] to give 3,5-di-*O*-benzoyl-2′-deoxy-2′-fluoro-2′-*C*-methyl-6-chloro-7-iodo-7-deazapurine ribonucleoside (**10c**) in 68% yield. Subsequent reaction with MFSDA and CuI in a mixture of DMF and HMPA afforded 3,5-di-*O*-benzoyl-2′-deoxy-2′-fluoro-2′-*C*-methyl-6-chloro-7-tri-fluoromethyl-7-deazapurine ribonucleoside (**11c**) in 97% yield. Finally, treatment of **11c** with a saturated solution of ammonia in MeOH provided 2′-deoxy-2′-fluoro-2′-*C*-methyl-7-trifluoromethyl-7-deazapurine ribonucleoside




**Scheme 1.** Synthesis of compound **12a-b** and **14a-b**.
Reagents and reaction conditions: (a) NIS, DMF, rt, 12h; (b) BSA, TMSOTf, 0 °C → 80 °C, 12h for **10a**; 8h for **10b**; (c) $FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 70 °C, 12h; (d) sat. $NH_3$/MeOH, 90 °C, 12h, steel bomb; (e) **13**, *t*-BuMgCl, THF, −78 °C → rt, 8h for **14a**; 12h for **14b.**




**Scheme 2.** Synthesis of compound **12c** and **14c**.
Reagents and reaction conditions: (a) i. LiAl(*t*-BuO)$_3$H, THF, −20 °C, 4 h: ii. AcCl, DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C, 3 h; (b) 33% HBr in AcOH, $CH_2Cl_2$, 0 °C then rt 4 h; (c) TDA-1, KOH, 4 Å MS, $CH_3CN$, rt, 2 h; (d) $FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 70 °C, 12 h; (e) sat. $NH_3$/MeOH, 90 °C, 12 h, steel bomb; (e) **13**, *t*-BuMgCl, THF, −78 °C, 6 h.

(**12c**) in 85% yield. Phosphoramidate prodrug **14c** was prepared by reaction of nucleoside **12c** with chlorophosphoramidate **13** in presence of *t*-BuMgCl (Rp/Sp = 1/1 ratio).

Nucleosides **12a-c** and their corresponding phosphoramidate prodrugs **14a-c** were evaluated against a panel of RNA viruses including HCV[31]

(clone B replicon), Ebola[32] (Zaire ebola virus replicon) and Zika[33] (cytopathic effect reduction assay) viruses. In addition, cytotoxicity was determined in primary human peripheral blood mononuclear (PBM) cells, human lymphoblastoid CEM, African Green monkey Vero cells and HepG2 cells.[34] Unfortunately, none of these derivatives exhibited significant activity at concentration up to 20 μM against these viruses nor toxicities in PBM, CEM and Vero cells at concentration up to 100 μM.

In conclusion, several novel 7-trifluoromethyl-7-deazapurine ribonucleoside analogs (**12a**-**c**) were synthesized by using a key aromatic trifluoromethylation with MFSDA and CuI using HMPA and DMF as co-solvents. Unfortunately, none of the synthesized compounds (**12a**-**c** and **14a**-**c**) showed marked activity when tested against HCV, Ebola or Zika viruses.

## 3. Experimental

Nuclear magnetic resonance (NMR) spectra ($^1$H, 13C, 19F and 31P) were recorded on a Varian Unity Plus 400 MHz and a Bruker Ascend$^{TM}$ 400 MHz Fourier transform spectrometer at RT, with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), or ddd (doublet of doublets of doublets). The phosphoramidates are an approximate 50:50 mixture of diastereomers ($R_P/S_P$) and the $^{13}$C NMR data is reported as observed, that is, some carbon signals overlap. High-resolution mass spectra (HRMS) were recorded on a Micromass Autospec high-resolution mass spectrometer with electrospray ionization (ESI). Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel. Purifications were carried out on silica gel column chromatography (60 Å, 63–200 μm, or 40–75 μm).

### 3.1. Compound 8

To a solution of 6-chloro-7-deazapurine (1.0 g, 6.51 mmol) in 20 mL of anhydrous DMF was added *N*-iodosuccinimide (1.60 g, 7.16 mmol). The reaction mixture was stirred for 2 h at room temperature and the solvent removed under vacuum. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 1:1 to 3;1v/v) to give compound **8** in quantitative yield. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.55 (s, 1 H), 7.72 (s, 1 H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 151.7, 151.6, 150.2, 133.5, 116.3, 50.1; MS-ESI$^+$ m/z 280 ($M + H^+$).

#### 3.1.1. (2R,3R,4R,5R)-2-((benzoyloxy)methyl)-5-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)tetrahydrofuran-3,4-diyl dibenzoate (10a)

To a solution of 6-chloro-7-iodo-7-deazapurine **8** (0.55 g, 1.96 mmol) in 10 mL of anhydrous $CH_3CN$ was added *N*,*O*-bis(trimethylsilyl)acetamide (0.50 g, 2.45 mmol) at room temperature under $N_2$ atmosphere. After 30 min, a solution of 1-*O*-Ac-2,3,5-tri-*O*-Bz-ribose **9a** (0.90 g, 1.79 mmol) in 10 mL of anhydrous $CH_3CN$ and TMSOTf (0.56 g, 2.45 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was then heated to 80 °C over 1 h and stirred for 12 h at this temperature e. The solution was cooled to room temperature and diluted with EtOAc (50 mL). The organic layer was washed with a saturated $NHCO_3$ aqueous solution (20 mL), cold water (20 mL) and brine (20 mL). The organic layer was then dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 5:1 to 2:1 v/v) to give compound **10a** (0.83 g, 1.15 mmol) in 64% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1 H), 8.21 (d, $J$ = 7.2 Hz, 2 H), 7.99 (d, $J$ = 6.8 Hz, 2 H), 7.92 (d, $J$ = 8.4 Hz, 2 H), 7.64-7.49 (m, 6 H), 7.43-7.35 (m, 4 H), 6.67 (d, $J$ = 5.6 Hz, 1 H), 6.15 (t, $J$ = 5.6 Hz, 1 H), 6.11 (dd, $J$ = 5.6, 4.4 Hz, 1 H), 4.90 (dd, $J$ = 12.4, 3.2 Hz, 1 H), 4.80 (q, $J$ = 3.6 Hz, 1 H), 4.68 (dd, $J$ = 12.4, 3.6 Hz, 1 H), $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.8, 165.3, 153.3, 151.5, 151.2, 134.1, 134.0, 133.8, 132.2, 130.1, 129.9, 129.5, 129.1, 128.9, 128.8, 128.7, 128.6, 118.0, 87.0, 80.9, 74.4, 71.6, 63.7, 53.9; MS-ESI$^+$ m/z 724 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{32}H_{24}ClIN_3O_7$ ($M + H^+$) 724.0347, found 724.0331.

#### 3.1.2. (2R,3R,4R,5R)-2-((benzoyloxy)methyl)-5-(4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)tetrahydrofuran-3,4-diyl dibenzoate (11a)

To a solution of compound **10a** (0.51 g, 0.71 mmol) in 20 mL of anhydrous DMF and hexamethylphosphoric triamide (HMPA, 8.50 mL) was added $FSO_2CF_2CO_2Me$ (170.0 mg, 0.88 mmol) and CuI (160.0 mg, 0.85 mmol) under argon atmosphere. The reaction mixture was stirred for 13 h at 70 °C and then cooled down to room temperature before addition of a saturated aqueous solution of $NH_4Cl$ (20 mL). The mixture was extracted with a mixture of hexanes and EtOAc (50 mL × 2, 1:2 v/v). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL) then dried over $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexanes: EtOAc = 10:1 to 5:1 v/v) to give compound **11a** (0.44 g, 0.66 mmol) in 93% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1 H), 8.11-8.08 (m, 2 H), 8.02-8.00 (m, 2 H), 7.93-7.91 (m, 2 H), 7.86 (s, 1 H), 7.62-7.34 (m, 9 H), 6.68 (d, $J$ = 5.6 Hz, 1 H), 6.22 (t, $J$ = 5.6 Hz, 1 H), 6.15 (dd, $J$ = 5.6, 4.4 Hz, 1 H), 4.92 (dd, $J$ = 9.2, 3.2 Hz, 1 H), 4.85 (q, $J$ = 3.6 Hz, 1 H), 4.72 (dd, $J$ = 12.4, 3.6 Hz, 1 H), $^{13}$C NMR

(100 MHz, $CDCl_3$) δ 166.2, 165.5, 165.2, 152.7, 152.4, 152.1, 134.0, 133.9, 130.0, 129.8, 128.9, 128.8, 128.7, 87.6, 81.1, 74.4, 71.6, 63.5; $^{19}F$ NMR (376 MHz, $CDCl_3$) δ -56.52; MS-ESI$^+$ m/z 666 ($M+H^+$); HRMS-ESI$^+$: m/z calcd for $C_{33}H_{24}ClF_3N_3O_7$ ($M+H^+$) 666.1255, found 666.1245.

#### 3.1.3. (2R,3R,4S,5R)-2-(4-Amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (12a)

In a steel bomb at 0 °C, $NH_3$ was bubbled through a solution of compound **11a** (0.16 g, 0.24 mmol) in 30 mL of MeOH for 20 min. The reaction was heated at 90 °C for 12 h before being cooled down to 0 °C. After evaporation of the volatiles under reduced pressure, the residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 20:1 to 10:1 v/v) to give compound **12a** (58.60 mg, 0.18 mmol) in 83% yield. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.20 (s, 1 H), 8.03 (s, 1 H), 6.11 (d, $J = 6.0$ Hz, 1 H), 4.59 (t, $J = 5.6$ Hz, 1 H), 4.30 (dd, $J = 4.8$, 3.2 Hz, 1 H), 4.13 (q, $J = 3.2$ Hz, 1 H), 3.87 (dd, $J = 12.4$, 2.4 Hz, 1 H), 3.76 (dd, $J = 12.4$, 2.8 Hz, 1 H); $^{13}C$ NMR (100 MHz, $CD_3OD$) δ 158.1, 153.9, 152.7, 152.2, 129.9, 126.3, 123.7, 105.8, 100.7, 91.2, 87.5, 76.0, 72.3, 63.2; $^{19}F$ NMR (376 MHz, $CD_3OD$) δ -57.14; MS-ESI$^+$ m/z 335 ($M+H^+$); HRMS-ESI$^+$: m/z calcd for $C_{12}H_{14}F_3N_4O_4$ ($M+H^+$) 335.0967, found 335.0953.

#### 3.1.4. Ethyl ((((2R,3S,4R,5R)-5-(4-amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (14a)

To a solution of compound **12a** (0.05 g, 0.15 mmol) in 3.0 mL of anhydrous THF was added *t*-BuMgCl (0.53 mL, 1.0 M in THF) at –78 0 °C under $N_2$ atmosphere. After 30 minutes at this temperature and an additional 10 min at room temperature, a solution of phosphoramidate chloride **13** (67.0 mg, 0.23 mmol) in 2.0 mL of anhydrous THF was added to the reaction at –78 °C. The reaction mixture was stirred for 6 h at room temperature and cooled down to 0 °C before addition of a saturated aqueous solution of $NH_4Cl$ (0.25 mL). The resulting solution was poured into EtOAc (50 mL) and the organic layer was washed with a saturated aqueous solution of $NH_4Cl$ (20 mL) and brine (20 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 20:1 to 10:1 v/v) to give compound **14a** (53.0 mg, 0.09 mmol) as a mixture of Rp-/Sp-isomers (~1:1) in 60% yield. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.23 (s, 1 H), 7.91-7.89 (m, 1 H), 7.35-7.31 (m, 2 H), 7.23-7.15 (m, 3 H), 6.25-6.22 (m, 1 H), 4.48-4.35 (m, 4 H), 4.33-4.29 (m, 2 H), 4.28-4.20 (m, 2 H), 4.14-4.03 (m, 3 H), 3.92-3.84 (m, 1 H), 1.38-1.16 (m, 11 H); $^{31}P$ NMR (162 MHz, $CD_3OD$) δ 5.06, 4.83; $^{19}F$ NMR (376 MHz, $CD_3OD$) δ -56.99,

–57.03; MS-ESI$^+$ m/z 590 ($M+H^+$); HRMS-ESI$^+$: m/z calcd for $C_{23}H_{28}F_3N_5O_8P$ ($M+H^+$) 590.1627, found 590.1609.

#### 3.1.5. (2S/R,3R,4R,5R)-5-((benzoyloxy)methyl)-3-methyltetrahydrofuran-2,3,4-triyl tribenzoate (9 b)

To a solution of 2-C-methyl-, 2,3,5-tribenzoyl ribolactone (5.0 g, 10.54 mmol) in 50 mL of anhydrous THF was added LiAlH(O*t*-Bu)$_3$ (1.1 M in THF, 15 mL) over 10 min at 0 °C under $N_2$ atmosphere. After stirring for 1 h, the reaction was warmed up to room temperature and stirred for 2 h. The reaction was then quenched with a saturated solution of $NH_4Cl$ (10 mL), poured into cold water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (hexanes:EtOAc = 10:1 to 2:1 v/v) to give a 2-C-methyl-, 2,3,5-tribenzoyl ribolactol in quantitative yield. To a solution of the lactol (2.08 g, 10.25 mmol) in 100 mL of anhydrous $CH_2Cl_2$ was added benzoyl chloride (2.16 g, 15.38 mmol) and $Et_3N$ (1.25 g, 20.50 mmol) at 0 °C under $N_2$ atmosphere. After being stirred for 12 h at room temperature, the reaction mixture was quenched with MeOH (10 mL) at 0 °C, stirred for 1 h at room temperature, and then poured into cold water (50 mL). The organic layer was separated and washed with 0.1 *N* HCl aqueous solution (30 mL), water (30 mL), brine (30 mL), dried over $Na_2SO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CH_2Cl_2$ to $CH_2Cl_2$: MeOH = 50:1 v/v) to give compound **9 b** (5.81 g, 10.01 mmol) in 95% yield.

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 4 H), 8.07-8.05 (m, 2 H), 7.88 (dd, $J$ = 8.4, 1.2 Hz, 2 H), 7.64-7.60 (m, 3 H), 7.51-7.40 (m, 7 H), 7.15 (t, $J$ = 8.0 Hz, 2 H), 7.06 (s, 1 H), 5.95 (d, $J$ = 8.0 Hz, 1 H), 4.80-4.77 (m, 1 H), 4.68 (dd, $J$ = 12.4, 4.0 Hz, 1 H), 4.54 (dd, $J$ = 12.4, 4.8 Hz, 1 H), 1.95 (s, 3 H); MS-ESI$^+$ m/z 581 ($M+H^+$).

#### 3.1.6. (2R,3R,4R,5R)-5-((benzoyloxy)methyl)-2-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (10 b)

To a solution of 6-chloro-7-iodo-7-deazapurine **8** (0.50 g, 1.79 mmol) in 20 mL of anhydrous $CH_3CN$ was added *N*,*O*-bis(trimethylsilyl)acetamide (0.44 g, 2.16 mmol) at room temperature under $N_2$ atmosphere. After 20 min, 1,2,3,5-tetra-O-Bz-2-methylribose **9 b** (1.04 g, 1.80 mmol) and then TMSOTf (0.49 g, 2.16 mmol) were added to the reaction mixture at 0 °C under $N_2$ atmosphere. The mixture was warmed up to room temperature for 30 min and then heated at 80 °C for additional 8 h. The solution was cooled down to room temperature and diluted with EtOAc (50 mL). The

organic layer was washed with a saturated solution of $NHCO_3$ (30 mL), cold water (30 mL), and brine (20 mL). The organic layer was then dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1 to 3:1 v/v) to give compound **10b** (0.97 g, 1.31 mmol) in 73% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 8.12-8.09 (m, 4 H), 7.96 (d, $J$ = 7.6 Hz, 2 H), 7.69 (s, 1 H), 7.63-7.53 (m, 3 H), 7.48-7.44 (m, 4 H), 7.34 (t, $J$ = 7.6 Hz, 2 H), 6.95 (s, 1 H), 6.04 (d, $J$ = 6.0 Hz, 1 H), 4.96 (dd, $J$ = 12.4, 3.6 Hz, 1 H), 4.86 (dd, $J$ = 12.4, 5.6 Hz, 1 H), 4.74-4.70 (m, 1 H), 1.59 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.5, 165.3, 153.3, 151.4, 150.9, 133.9, 133.8, 133.6, 133.2, 130.1, 130.0, 129.9, 129.8, 129.7, 128.9, 128.8, 128.7, 117.9, 89.2, 85.1, 80.2, 75.8, 63.5, 52.9, 29.9, 18.1; MS-ESI$^+$ m/z 738 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{33}H_{26}ClIN_3O_7$ ($M + H^+$) 738.0504, found 738.0488.

### 3.1.7. (2R,3R,4R,5R)-5-((benzoyloxy)methyl)-2-(4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3-methyltetrahydrofuran-3,4-diyl dibenzoate (11 b)

To a solution of compound **10b** (0.24 g, 0.32 mmol) in 10 mL of anhydrous DMF and 7.0 mL of HMPA was added $FSO_2CF_2CO_2Me$ (80.0 mg, 0.40 mmol) and CuI (73.0 mg, 0.38 mmol) under argon atmosphere. After being stirred for 12 h at 70 °C, the reaction mixture was cooled down to temperature and treated with a saturated solution of $NH_4Cl$ (10 mL) and then extracted with a mixture of hexanes and EtOAc (30 mL × 2, 1:2 v/v). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexanes: EtOAc = 10:1 to 5:1 v/v) to give compound **11b** (0.20 g, 0.29 mmol) in 90% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.13-8.08 (m, 4 H), 7.97-7.94 (m, 3 H), 7.64-7.52 (m, 3 H), 7.48-7.43 (m, 4 H), 7.33 (t, $J$ = 7.6 Hz, 2 H), 6.96 (s, 1 H), 6.03 (d, $J$ = 5.2 Hz, 1 H), 4.97-4.92 (m, 2 H), 4.76-4.72 (m, 1 H), 1.60 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.5, 165.3, 152.9, 152.4, 151.9, 134.90, 133.7, 130.2, 130.0, 129.9, 129.7, 129.6, 128.8, 128.7, 89.5, 84.8, 80.7, 75.9, 63.4, 18.2; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −56.29; MS-ESI$^+$ m/z 680 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{34}H_{26}ClF_3N_3O_7$ ($M + H^+$) 680.1411, found 680.1400.

### 3.1.8. (2R,3S,4R,5R)-2-(4-Amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-5-(hydroxymethyl)-3-methyltetrahydrofuran-3,4-diol (12 b)

In a steel bomb at 0 °C, $NH_3$ was bubbled through a solution of compound **11b** (0.20 g, 0.26 mmol) in 30 mL of MeOH for 20 min. The reaction was

then heated at 90 °C for 12 h and then cooled down to 0 °C. The volatiles were concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 20:1 to 10:1 v/v) to give compound **12b** (77.60 mg, 0.22 mmol) in 87% yield. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.32 (dd, $J$ = 1.2 Hz, 1 H), 8.23 (s, 1 H), 6.31 (s, 1 H), 4.13 (d, $J$ = 9.2 Hz, 1 H), 4.06-4.01 (m, 2 H), 3.85 (dd, $J$ = 12.4, 2.0 Hz, 1 H), 0.85 (s, 3 H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 158.1, 154.1, 152.3, 151.5, 126.5, 125.2, 125.1, 123.8, 106.2, 105.8, 100.0, 92.9, 84.2, 80.6, 73.3, 60.7, 20.2; $^{19}$F NMR (376 MHz, $CD_3OD$) δ -57.04; MS-ESI$^+$ m/z 349 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{13}H_{16}F_3N_4O_4$ ($M + H^+$) 349.1123, found 349.1113.

### 3.1.9. Ethyl ((((2R,3R,4S,5R)-5-(4-amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3,4-dihydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (14 b)

To a solution of compound **12 b** (40.0 mg, 0.12 mmol) in 2.0 mL of anhydrous THF was added *t*-BuMgCl (0.42 mL, 1.0 M in THF) at −78 0 °C under $N_2$ atmosphere. After being stirred for 30 min at this temperature and for 10 min at room temperature, a solution of phosphoramidate chloride **13** (49.60 mg, 0.17 mmol) in 2.0 mL of anhydrous THF was added to the solution −78 °C. The reaction mixture was stirred for 12 h at room temperature and then cooled down to 0 °C before addition of saturated aqueous solution of $NH_4Cl$ (0.10 mL). The resulting solution was poured into EtOAc (30 mL) and washed with saturated aqueous $NH_4Cl$ (10 mL) and brine (10 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 15:1 to 10:1 v/v) to give compound **14 b** (42.0 mg, 0.07 mmol) as a mixture of Rp-/Sp-isomers (~1:1) in 58% yield. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.25 (s, 1 H), 7.88-7.85 (m, 1 H), 7.36-7.32 (m, 2 H), 7.26-7.23 (m, 2 H), 7.19-7.16 (m, 1 H), 6.35-6.33 (s, 1 H), 4.89-4.42 (m, 2 H), 4.33-4.29 (m, 2 H), 4.25-4.18 (m, 1 H), 4.13-3.99 (m, 3 H), 3.97-3.90 (m, 1 H), 1.32-1.27 (m, 4 H), 1.22-1.14 (m, 3 H), 0.88-0.86 (s, 3 H); $^{31}$P NMR (162 MHz, $CD_3OD$) δ 5.28, 4.94; $^{19}$F NMR (376 MHz, $CD_3OD$) δ −56.68, −56.78; MS-ESI$^+$ m/z 604 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{24}H_{30}F_3N_5O_8P$ ($M + H^+$) 604.1784.1627, found 604.1771.

### 3.1.10. ((2R,3R,4R,5R)-3-(benzoyloxy)-5-bromo-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (9c, α-isomer)

To a solution of 3,5-*O*-di-Bz-2-F-2-Me-ribolactone (3.0 g, 8.10 mmol) in 40 mL of anhydrous THF was added LiAlH(O*t*-Bu)$_3$ (1.1 M in THF, 8.80 mL) over 10 min at 0 °C under $N_2$ atmosphere. After being stirred for

2 h at this temperature, the reaction was warmed up to room temperature and stirred for an additional 1 h. The reaction was then quenched with a saturated solution of $NH_4Cl$ (5.0 mL), poured into cold water (30 mL) and extracted with EtOAc (40 mL × 3). The combined organic layers were dried over $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column (hexanes:EtOAc = 10:1 to 2:1 v/v) to give 3,5-*O*-di-Bz-ribolactol in quantitative yield. To a solution of the lactol (3.0 g, 8.01 mmol) in 50 mL of anhydrous $CH_2Cl_2$ was added acetyl chloride (0.79 g, 10.02 mmol) and $Et_3N$ (1.22 g, 12.02 mmol) at 0 °C under $N_2$ atmosphere. After being stirred for 3 h, the reaction mixture was quenched with MeOH (10 mL) at 0 °C and poured into cold water (50 mL). The organic layer was separated and washed with 0.1 *N*-HCl (20 mL), water (20 mL), brine (20 mL) and then dried over $Na_2SO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CH_2Cl_2$ to $CH_2Cl_2$: MeOH = 50:1 v/v) to give 1-*O*-Ac-3,5-*O*-di-Bz-2-F-2-Me-ribose (3.20 g, 7.69 mmol) as an α-/*β*-isomers (1:1) in 95% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2 H), 8.06-8.03 (m, 2 H), 7.66-7.62 (m, 1 H), 7.57-7.53 (m, 1 H), 7.52-7.48 (m, 2 H), 7.41-7.37 (m, 2 H), 6.25 (d, $J$ = 8.7 Hz, 1 H), 5.70 (dd, $J$ = 23.6, 8.2 Hz, 1 H), 4.74 (dd, $J$ = 12.0, 4.0 Hz, 1 H), 4.69-4.66 (m, 1 H), 4.46 (dd, $J$ = 12.0, 4.4 Hz, 1 H), 2.00 (s, 3 H), 1.55 (d, $J$ = 22.4 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.9, 165.7, 133.9, 133.2, 130.1, 129.7, 129.6, 128.6, 128.3, 100.4, 98.4 (d, $J$ = 34.8 Hz), 78.7, 73.7 (d, $J$ = 15.1 Hz), 63.6, 20.9, 16.5 (d, $J$ = 23.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -170.72; MS-ESI$^+$ m/z 417 ($M + H^+$). To a solution of 1-*O*-Ac-3,5-*O*-di-Bz-2-F-2-Me-ribose (2.0 g, 4.80 mmol) in 20 mL of $CH_2Cl_2$ was added 2.5 mL of 33% HBr in acetic acid solution at room temperature. The solution was stirred for 16 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in 50 mL of $CH_2Cl_2$ and then washed with cold water (20 mL) and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated and purified by silica gel column chromatography to give α-isomer (**9c**) (1.80 g, 4.13 mmol) in 86% yield and β-Isomer (0.21 g, 0.48 mmol) in 10% of yield.

α-Isomer (bottom spot on TLC): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2 H), 8.06-8.04 (m, 2 H), 7.66-7.59 (m, 2 H), 7.52-7.45 (m, 4 H), 6.37 (s, 1 H), 5.31 (dd, $J$ = 5.2, 2.8 Hz, 1 H), 4.92-4.88 (m, 1 H), 4.80 (dd, $J$ = 12.4, 3.6 Hz, 1 H), 4.65 (dd, $J$ = 12.4, 4.4 Hz, 1 H), 1.75 (d, $J$ = 21.6 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.8, 133.7, 133.4, 130.1, 129.7, 129.3, 128.8, 128.6, 128.5, 95.6, 93.6, 92.0 (d, $J$ = 23.6 Hz), 81.9 (d, $J$ = 1.9 Hz), 73.4 (d, $J$ = 15.4 Hz), 62.4, 22.9 (d, $J$ = 26.3 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -151.36; MS-ESI$^+$ m/z 437 ($M + H^+$).

$\beta$-Isomer (upper spot on TLC): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.12-8.10 (m, 2 H), 8.08-8.06 (m, 2 H), 7.66-7.62 (m, 1 H), 7.56-7.48 (m, 3 H), 7.40-7.36 (m, 2 H), 6.45 (d, $J = 11.4$ Hz, 1 H), 6.07 (dd, $J = 23.0$, 7.7 Hz, 1 H), 4.81 (m, 2 H), 4.64 (dd, $J = 13.2$, 6.6 Hz, 1 H), 1.79 (d, $J = 22.4$ Hz, 3 H); $^{19}$F NMR (376 MHz, $CDCl_3$) δ −160.06. OK

#### 3.1.11. ((2R,3R,4R,5R)-3-(benzoyloxy)-5-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (10c)

A solution of powdered KOH (0.23 g, 3.52 mmol, 85%) and TDA-1 (0.03 g, 0.09 mmol) in 10 mL of anhydrous $CH_3CN$ was stirred for 15 min at room temperature under $N_2$ atmosphere. 6-Chloro-7-iodo-7-deazapurine **8** (0.41 g, 1.47 mmol) was then added to the solution. After stirring for 20 min, a solution of compound **9c** (0.77 g, 1.76 mmol) in 10 mL of anhydrous $CH_3CN$ was added to the mixture at once. The reaction mixture was stirred to 40 °C for 48 h and then quenched with a saturated solution of $NH_4Cl$ (30 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:EtOAc = 10:1 to 5:1 v/v) to give compound **10c** (0.76 g, 1.20 mmol) in 68% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1 H), 8.12-8.08 (m, 4 H), 7.65-7.58 (m, 3 H), 7.52-7.46 (m, 4 H), 6.64 (d, $J = 18.0$ Hz, 1 H), 5.90 (dd, $J = 22.0$, 5.6 Hz, 1 H), 4.92 (dd, $J = 12.8$, 2.4 Hz, 1 H), 4.78-4.74 (m, 1 H), 4.62 (dd, $J = 12.8$, 2.4 Hz, 1 H), 1.20 (d, $J = 22.8$ Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.7, 153.5, 151.6, 150.7, 134.2, 133.6, 131.4, 130.3, 129.9, 129.1, 128.9, 128.6, 117.7, 101.3, 99.5, 89.8 (d, $J = 39.4$ Hz), 72.5 (d, $J = 16.2$ Hz), 62.3, 53.8, 17.4 (d, $J = 24.7$ Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ −158.15; MS-ESI$^+$ m/z 636 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{26}H_{21}ClFIN_3O_5$ ($M + H^+$) 636.0198, found 636.0186.

#### 3.1.12. ((2R,3R,4R,5R)-3-(benzoyloxy)-5-(4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-fluoro-4-methyltetrahydrofuran-2-yl)methyl benzoate (11c)

To a solution of compound **10c** (0.25 g, 0.39 mmol) in anhydrous DMF (20 mL) and 8.50 mL of hexamethylphosphoric triamide was added $FSO_2CF_2CO_2Me$ (63.0 mg, 0.49 mmol) and CuI (90.0 mg, 0.47 mmol) under argon atmosphere. The reaction mixture was stirred for 24 h at 70 °C under argon atmosphere. The solution was then cooled down to room temperature and treated with a saturated aqueous solution of $NH_4Cl$ (20 mL) and then extracted with a mixture of hexanes and EtOAc (40 mL × 2, 1:2 v/v). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL), dried over $Na_2SO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue

was purified by silica gel column chromatography (hexanes: EtOAc = 10:1 to 5:1 v/v) to give compound **11c** (0.22 g, 0.38 mmol) in 98% yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 8.12-8.09 (m, 2 H), 8.06-8.04 (m, 2 H), 7.87 (s, 1 H), 7.65-7.56 (m, 2 H), 7.50-7.43 (m, 4 H), 6.66 (d, $J$ = 18.0 Hz, 1 H), 5.92 (dd, $J$ = 21.6, 9.2 Hz, 1 H), 4.90 (dd, $J$ = 12.8, 2.8 Hz, 1 H), 4.81-4.77 (m, 1 H), 4.67 (dd, $J$ = 12.8, 4.0 Hz, 1 H), 1.24 (d, $J$ = 22.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.4, 165.6, 153.0, 152.7, 151.7, 134.2, 133.7, 130.3, 129.9, 129.8, 129.4, 128.8, 128.5, 127.2, 123.2, 120.5, 114.1, 107.3 (q, $J$ = 38.5 Hz), 101.2, 99.3, 90.4 (d, $J$ = 40.1 Hz), 77.7, 72.6 (d, $J$ = 16.2 Hz), 62.2, 29.6, 17.6 (d, $J$ = 24.7 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) δ −56.40, −157.73; MS-ESI$^+$ m/z 578 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{27}H_{21}ClF_4N_3O_5$ ($M + H^+$) 578.1106, found 578.1126.

### 3.1.13. (2R,3R,4S,5R)-5-(4-Amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-fluoro-2-(hydroxymethyl)-4-methyltetrahydrofuran-3-ol (12c)

In a steel bomb at 0 °C, $NH_3$ was bubbled through a solution of compound **11c** (0.12 g, 0.21 mmol) in 20 mL of MeOH for 20 min and heated to 80 °C for 12 h. The volatiles were concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 20:1 to 10:1 v/v) to give compound **12c** (63.10 mg, 0.18 mmol) in 85% yield. $^{1}$H NMR (400 MHz, $CD_3OD$) δ 8.28 (d, $J$ = 1.2 Hz, 1 H), 8.24 (s, 1 H), 6.48 (d, $J$ = 17.2 Hz, 1 H), 4.59 (dd, $J$ = 24.8, 9.6 Hz, 1 H), 4.09-4.03 (m, 2 H), 3.86 (dd, $J$ = 12.8, 2.4 Hz, 1 H), 1.07 (d, $J$ = 22.0 Hz, 1 H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 158.1, 154.4, 152.4, 126.3, 124.8 (d, $J$ = 6.2 Hz), 123.6, 106.7 (q, $J$ = 37.8 Hz), 103.4, 101.6, 100.0, 90.2 (d, $J$ = 38.6 Hz), 83.6, 72.2 (d, $J$ = 17.8 Hz), 60.3, 16.8 (d, $J$ = 25.5 Hz); $^{19}$F NMR (376 MHz, $CD_3OD$) δ −57.26, −164.93; MS-ESI$^+$ m/z 351 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{13}H_{15}F_4N_4O_3$ ($M + H^+$) 351.1080, found 351.1069.

### 3.1.14. Ethyl ((((2R,3R,4S,5R)-5-(4-amino-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (14c)

To a solution of compound **12c** (45.0 mg, 0.13 mmol) in 5.0 mL of anhydrous THF was added *t*-BuMgCl (0.39 mL, 1.0 M in THF) at −78.0 °C under $N_2$ atmosphere. After being stirred for 30 min at this temperature and for 10 min at room temperature, a solution of phosphoramidate chloride **13** (75.0 mg, 0.26 mmol) in 2.0 mL of anhydrous THF was added to the reaction at −78 °C. The reaction mixture was stirred for 6 h at room temperature and cooled down to 0 °C before treatment with a saturated solution of $NH_4Cl$ (0.20 mL). The resulting solution was poured into EtOAc (30 mL) and washed with a saturated solution of $NH_4Cl$ (20 mL) and brine (10 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under

reduced pressure. The crude residue was purified by silica gel column chromatography ($CH_2Cl_2$: MeOH = 20:1 to 10:1 v/v) to give compound **14c** (54.50 mg, 0.09 mmol) as a mixture of Rp-/Sp-isomers (1:1) in 69% yield.

$^1$H NMR (400 MHz, $CD_3OD$) δ 8.25 (s, 1 H), 7.85 (d, $J = 1.6$ Hz, 1 H), 7.36-7.32 (m, 2 H), 7.24-7.22 (m, 2 H), 7.20-7.15 (m, 1 H), 6.54-6.49 (s, 1 H), 4.65-4.60 (m, 1 H), 4.52-4.47 (m, 1 H), 4.26-4.22 (m, 2 H), 4.19-4.08 (m, 2 H), 4.92-3.88 (m, 1 H), 1.29-1.26 (m, 5 H), 1.21 (t, $J = 7.2$ Hz, 3 H), 1.12-1.06 (s, 3 H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 175.1, 158.1, 154.6, 152.6, 152.3, 130.9, 126.3, 121.6 (d, $J = 4.6$ Hz), 112.5, 103.0, 101.2, 100.1, 90.8, 81.4, 73.0, 65.8, 62.5, 51.8, 20.4 (d, $J = 7.0$ Hz), 17.0, 16.7,14.6; $^{31}$P NMR (162 MHz, $CD_3OD$) δ 5.23; $^{19}$F NMR (376 MHz, $CD_3OD$) δ -56.99, -57.04, -163.59; MS-ESI$^+$ m/z 606 ($M + H^+$); HRMS-ESI$^+$: m/z calcd for $C_{24}H_{29}F_4N_5O_7P$ ($M + H^+$) 606.1740, found 606.1723. OK.

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