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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.

Keywords

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

Introduction

Nucleoside analogs played a pivotal role in the development of antiviral and anti-cancer agents. Since the discovery by William Prusoff in 1962¹ 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, 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*-

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methylribonucleoside (**5a**) has been reported to inhibit both HCV¹³ 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 CF₃ group at this position remains underexplored. Herein, we wish to report the synthesis and antiviral evaluation of novel ribo, β -2'-methyl- or α -2'-fluoro- β -2'-methyl-D-ribofuranoses 7-deazapurine derivatives with a trifluoromethyl group at the 7-position using a key aromatic trifluoromethyl substitution (Figure 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 DMF¹⁹, 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 fluorosulfonyldifluoroacetate (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 analog²⁶ 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 ¹H-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.

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-deazapurine **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 (**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 HCV³¹ (clone B replicon), Ebola³² (Zaire ebola virus replicon) and Zika³³ (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 μ M against these viruses nor toxicities in PBM, CEM and Vero cells at concentration up to 100 μ M.

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.

Experimental

Nuclear magnetic resonance (NMR) spectra (¹H, ¹³C, ¹⁹F and ³¹P) were recorded on a Varian Unity Plus 400MHz and a Bruker Ascend™ 400MHz 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 (Rp/Sp) and the ¹³C 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 0.25mm silica gel. Purifications were carried out on silica gel column chromatography (60 Å, 63–200 μ m, or 40–75 μ m).

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 3:1 v/v) to give compound **8** in quantitative yield. ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 1H), 7.72 (s, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 151.7, 151.6, 150.2, 133.5, 116.3, 50.1; MS-ESI⁺ *m/z* 280 (M+H⁺).

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(4-chloro-5-iodo-7*H*-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 CH₃CN was added *N,O*-bis(trimethylsilyl)acetamide (0.50 g, 2.45 mmol) at room

temperature under N₂ 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 CH₃CN 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. The solution was cooled to room temperature and diluted with EtOAc (50 mL). The organic layer was washed with a saturated NHCO₃ aqueous solution (20 mL), cold water (20 mL) and brine (20 mL). The organic layer was then dried over Na₂SO₄, 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. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 8.21 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 6.8 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.64–7.49 (m, 6H), 7.43–7.35 (m, 4H), 6.67 (d, *J* = 5.6 Hz, 1H), 6.15 (t, *J* = 5.6 Hz, 1H), 6.11 (dd, *J* = 5.6, 4.4 Hz, 1H), 4.90 (dd, *J* = 12.4, 3.2 Hz, 1H), 4.80 (q, *J* = 3.6 Hz, 1H), 4.68 (dd, *J* = 12.4, 3.6 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃) 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 C₃₂H₂₄ClIN₃O₇ (M+H⁺) 724.0347, found 724.0331.

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(4-chloro-5-(trifluoromethyl)-7*H*-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 FSO₂CF₂CO₂Me (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 NH₄Cl (20 mL). The mixture was extracted with a mixture of hexanes and EtOAc (50 mL x 2, 1:2 v/v). The combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (20 mL), water (20 mL), brine (20 mL) then dried over Na₂SO₄ 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. ¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 1H), 8.11–8.08 (m, 2H), 8.02–8.00 (m, 2H), 7.93–7.91 (m, 2H), 7.86 (s, 1H), 7.62–7.34 (m, 9H), 6.68 (d, *J* = 5.6 Hz, 1H), 6.22 (t, *J* = 5.6 Hz, 1H), 6.15 (dd, *J* = 5.6, 4.4 Hz, 1H), 4.92 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.85 (q, *J* = 3.6 Hz, 1H), 4.72 (dd, *J* = 12.4, 3.6 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) δ –56.52; MS-ESI⁺ *m/z* 666 (M+H⁺); HRMS-ESI⁺: *m/z* calcd for C₃₃H₂₄ClF₃N₃O₇ (M+H⁺) 666.1255, found 666.1245.

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

In a steel bomb at 0 °C, NH₃ 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 (CH₂Cl₂: 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, CD₃OD) δ 8.20 (s, 1H), 8.03 (s, 1H), 6.11 (d, *J* = 6.0 Hz, 1H), 4.59 (t, *J* = 5.6 Hz, 1H), 4.30

(dd, $J = 4.8, 3.2$ Hz, 1H), 4.13 (q, $J = 3.2$ Hz, 1H), 3.87 (dd, $J = 12.4, 2.4$ Hz, 1H), 3.76 (dd, $J = 12.4, 2.8$ Hz, 1H); ^{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 ($\text{M}+\text{H}^+$); HRMS-ESI⁺: m/z calcd for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{N}_4\text{O}_4$ ($\text{M}+\text{H}^+$) 335.0967, found 335.0953.

Ethyl (((2*R*,3*S*,4*R*,5*R*)-5-(4-amino-5-(trifluoromethyl)-7*H*-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°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, 1H), 7.91–7.89 (m, 1H), 7.35–7.31 (m, 2H), 7.23–7.15 (m, 3H), 6.25–6.22 (m, 1H), 4.48–4.35 (m, 4H), 4.33–4.29 (m, 2H), 4.28–4.20 (m, 2H), 4.14–4.03 (m, 3H), 3.92–3.84 (m, 1H), 1.38–1.16 (m, 11H); ^{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 ($\text{M}+\text{H}^+$); HRMS-ESI⁺: m/z calcd for $\text{C}_{23}\text{H}_{28}\text{F}_3\text{N}_5\text{O}_8\text{P}$ ($\text{M}+\text{H}^+$) 590.1627, found 590.1609.

(2*S*/*R*,3*R*,4*R*,5*R*)-5-((Benzoyloxy)methyl)-3-methyltetrahydrofuran-2,3,4-triyl tribenzoate (9b**)**

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 $\text{LiAlH}(\text{O}i\text{-Bu})_3$ (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 **9b** (5.81 g, 10.01 mmol) in 95% yield.

¹H NMR (400 MHz, CDCl₃) δ 8.13–8.10 (m, 4H), 8.07–8.05 (m, 2H), 7.88 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.64–7.60 (m, 3H), 7.51–7.40 (m, 7H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 5.95 (d, *J* = 8.0 Hz, 1H), 4.80–4.77 (m, 1H), 4.68 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.54 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.95 (s, 3H); MS-ESI⁺ *m/z* 581 (M+H⁺).

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

To a solution of 6-chloro-7-iodo-7-deazapurine **8** (0.50 g, 1.79 mmol) in 20 mL of anhydrous CH₃CN was added *N,O*-bis(trimethylsilyl)acetamide (0.44 g, 2.16 mmol) at room temperature under N₂ atmosphere. After 20 min, 1,2,3,5-tetra-*O*-Bz-2-methylribose **9b** (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 N₂ 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 NHCO₃ (30 mL), cold water (30 mL), and brine (20 mL). The organic layer was then dried over Na₂SO₄, 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. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.12–8.09 (m, 4H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.69 (s, 1H), 7.63–7.53 (m, 3H), 7.48–7.44 (m, 4H), 7.34 (t, *J* = 7.6 Hz, 2H), 6.95 (s, 1H), 6.04 (d, *J* = 6.0 Hz, 1H), 4.96 (dd, *J* = 12.4, 3.6 Hz, 1H), 4.86 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.74–4.70 (m, 1H), 1.59 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₃H₂₆ClIN₃O₇ (M+H⁺) 738.0504, found 738.0488.

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

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 FSO₂CF₂CO₂Me (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 NH₄Cl (10 mL) and then extracted with a mixture of hexanes and EtOAc (30 mL x 2, 1:2 v/v). The combined organic layers were washed with a saturated solution of NaHCO₃ (10 mL), water (10 mL), brine (10 mL), dried over Na₂SO₄ 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. ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 8.13–8.08 (m, 4H), 7.97–7.94 (m, 3H), 7.64–7.52 (m, 3H), 7.48–7.43 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 6.96 (s, 1H), 6.03 (d, *J* = 5.2 Hz, 1H), 4.97–4.92 (m, 2H), 4.76–4.72 (m, 1H), 1.60 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) δ –56.29; MS-ESI⁺ *m/z* 680 (M+H⁺); HRMS-ESI⁺: *m/z* calcd for C₃₄H₂₆ClF₃N₃O₇ (M+H⁺) 680.1411, found 680.1400.

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

In a steel bomb at 0 °C, NH₃ 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 (CH₂Cl₂: MeOH = 20:1 to 10:1 v/v) to give compound **12b** (77.60 mg, 0.22 mmol) in 87% yield. ¹H NMR (400 MHz, CD₃OD) δ 8.32 (dd, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 6.31 (s, 1H), 4.13 (d, *J* = 9.2 Hz, 1H), 4.06–4.01 (m, 2H), 3.85 (dd, *J* = 12.4, 2.0 Hz, 1H), 0.85 (s, 3H); ¹³C NMR (100 MHz, CD₃OD) 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; ¹⁹F NMR (376 MHz, CD₃OD) δ –57.04; MS-ESI⁺ *m/z* 349 (M + H⁺); HRMS-ESI⁺: *m/z* calcd for C₁₃H₁₆F₃N₄O₄ (M + H⁺) 349.1123, found 349.1113.

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

To a solution of compound **12b** (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 °C under N₂ 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 NH₄Cl (0.10 mL). The resulting solution was poured into EtOAc (30 mL) and washed with saturated aqueous NH₄Cl (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (CH₂Cl₂: MeOH = 15:1 to 10:1 v/v) to give compound **14b** (42.0 mg, 0.07 mmol) as a mixture of *Rp*–/*Sp*–isomers (~1:1) in 58% yield. ¹H NMR (400 MHz, CD₃OD) δ 8.25 (s, 1H), 7.88–7.85 (m, 1H), 7.36–7.32 (m, 2H), 7.26–7.23 (m, 2H), 7.19–7.16 (m, 1H), 6.35–6.33 (s, 1H), 4.89–4.42 (m, 2H), 4.33–4.29 (m, 2H), 4.25–4.18 (m, 1H), 4.13–3.99 (m, 3H), 3.97–3.90 (m, 1H), 1.32–1.27 (m, 4H), 1.22–1.14 (m, 3H), 0.88–0.86 (s, 3H); ³¹P NMR (162 MHz, CD₃OD) δ 5.28, 4.94; ¹⁹F NMR (376 MHz, CD₃OD) δ –56.68, –56.78; MS-ESI⁺ *m/z* 604 (M + H⁺); HRMS-ESI⁺: *m/z* calcd for C₂₄H₃₀F₃N₅O₈P (M + H⁺) 604.1784.1627, found 604.1771.

((2*R*,3*R*,4*R*,5*R*)-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 N₂ 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 NH₄Cl (5.0 mL), poured into cold water (30 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were dried over Na₂SO₄ 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 CH₂Cl₂ was added acetyl chloride (0.79 g, 10.02 mmol) and Et₃N (1.22 g, 12.02 mmol) at 0 °C under N₂ 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 Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (CH₂Cl₂ to CH₂Cl₂: 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. ¹H NMR (400 MHz, CDCl₃) δ 8.13–8.10 (m, 2H), 8.06–8.03 (m, 2H), 7.66–7.62 (m, 1H), 7.57–7.53 (m, 1H), 7.52–7.48 (m, 2H), 7.41–7.37 (m, 2H), 6.25 (d, *J* = 8.7 Hz, 1H), 5.70 (dd, *J* = 23.6, 8.2 Hz, 1H), 4.74 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.69–4.66 (m, 1H), 4.46 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.00 (s, 3H), 1.55 (d, *J* = 22.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) 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 CH₂Cl₂ 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 CH₂Cl₂ and then washed with cold water (20 mL) and saturated aqueous NaHCO₃. The organic layer was dried over anhydrous MgSO₄ 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): ¹H NMR (400 MHz, CDCl₃) δ 8.17–8.14 (m, 2H), 8.06–8.04 (m, 2H), 7.66–7.59 (m, 2H), 7.52–7.45 (m, 4H), 6.37 (s, 1H), 5.31 (dd, *J* = 5.2, 2.8 Hz, 1H), 4.92–4.88 (m, 1H), 4.80 (dd, *J* = 12.4, 3.6 Hz, 1H), 4.65 (dd, *J* = 12.4, 4.4 Hz, 1H), 1.75 (d, *J* = 21.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ –151.36; MS-ESI⁺ *m/z* 437 (M+H⁺).

β -Isomer (upper spot on TLC): ¹H NMR (400 MHz, CDCl₃) δ 8.12–8.10 (m, 2H), 8.08–8.06 (m, 2H), 7.66–7.62 (m, 1H), 7.56–7.48 (m, 3H), 7.40–7.36 (m, 2H), 6.45 (d, *J* = 11.4 Hz, 1H), 6.07 (dd, *J* = 23.0, 7.7 Hz, 1H), 4.81 (m, 2H), 4.64 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.79 (d, *J* = 22.4 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ –160.06. OK

((2*R*,3*R*,4*R*,5*R*)-3-(Benzoyloxy)-5-(4-chloro-5-iodo-7*H*-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 CH₃CN was stirred for 15 min at room temperature under N₂ atmosphere. 6-Chloro-7-iodo-7-deazapurine **8** (0.41g, 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 CH₃CN 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 NH₄Cl (30 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over Na₂SO₄, 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. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.12–8.08 (m, 4H), 7.65–7.58 (m, 3H), 7.52–7.46 (m, 4H), 6.64 (d, *J* = 18.0 Hz, 1H), 5.90 (dd, *J* = 22.0, 5.6 Hz, 1H), 4.92 (dd, *J* = 12.8, 2.4 Hz, 1H), 4.78–4.74 (m, 1H), 4.62 (dd, *J* = 12.8, 2.4 Hz, 1H), 1.20 (d, *J* = 22.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ –158.15; MS-ESI⁺ *m/z* 636 (M+H⁺); HRMS-ESI⁺: *m/z* calcd for C₂₆H₂₁ClFIN₃O₅ (M+H⁺) 636.0198, found 636.0186.

((2*R*,3*R*,4*R*,5*R*)-3-(Benzoyloxy)-5-(4-chloro-5-(trifluoromethyl)-7*H*-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 FSO₂CF₂CO₂Me (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 NH₄Cl (20 mL) and then extracted with a mixture of hexanes and EtOAc (40 mL x 2, 1:2 v/v). The combined organic layers were washed with a saturated solution of NaHCO₃ (20 mL), water (20 mL), brine (20 mL), dried over Na₂SO₄ 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. ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H), 8.12–8.09 (m, 2H), 8.06–8.04 (m, 2H), 7.87 (s, 1H), 7.65–7.56 (m, 2H), 7.50–7.43 (m, 4H), 6.66 (d, *J* = 18.0 Hz, 1H), 5.92 (dd, *J* = 21.6, 9.2 Hz, 1H), 4.90 (dd, *J* = 12.8, 2.8 Hz, 1H), 4.81–4.77 (m, 1H), 4.67 (dd, *J* = 12.8, 4.0 Hz, 1H), 1.24 (d, *J* = 22.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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); ¹⁹F NMR (376 MHz, CDCl₃) δ –56.40, –157.73; MS-ESI⁺ *m/z* 578 (M+H⁺); HRMS-ESI⁺: *m/z* calcd for C₂₇H₂₁ClF₄N₃O₅ (M+H⁺) 578.1106, found 578.1126.

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

In a steel bomb at 0 °C, NH₃ 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 (CH₂Cl₂: MeOH = 20:1 to 10:1 v/v) to give compound **12c** (63.10 mg, 0.18 mmol) in 85% yield. ¹H NMR (400 MHz, CD₃OD) δ 8.28 (d, *J* = 1.2 Hz, 1H), 8.24 (s, 1H), 6.48 (d, *J* = 17.2 Hz, 1H), 4.59 (dd, *J* = 24.8, 9.6 Hz, 1H), 4.09–4.03 (m, 2H), 3.86 (dd, *J* = 12.8, 2.4 Hz, 1H), 1.07 (d, *J* = 22.0 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) 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); ¹⁹F NMR (376 MHz, CD₃OD) δ –57.26, –164.93; MS-ESI⁺ *m/z* 351 (M+H⁺); HRMS-ESI⁺: *m/z* calcd for C₁₃H₁₅F₄N₄O₃ (M+H⁺) 351.1080, found 351.1069.

Ethyl (((2*R*,3*R*,4*S*,5*R*)-5-(4-amino-5-(trifluoromethyl)-7*H*-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 $-78\text{ }^{\circ}\text{C}$ 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 $-78\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 6 h at room temperature and cooled down to $0\text{ }^{\circ}\text{C}$ 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.

^1H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 7.85 (d, $J = 1.6\text{ Hz}$, 1H), 7.36–7.32 (m, 2H), 7.24–7.22 (m, 2H), 7.20–7.15 (m, 1H), 6.54–6.49 (s, 1H), 4.65–4.60 (m, 1H), 4.52–4.47 (m, 1H), 4.26–4.22 (m, 2H), 4.19–4.08 (m, 2H), 4.92–3.88 (m, 1H), 1.29–1.26 (m, 5H), 1.21 (t, $J = 7.2\text{ Hz}$, 3H), 1.12–1.06 (s, 3H); ^{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, $J = 4.6\text{ Hz}$), 112.5, 103.0, 101.2, 100.1, 90.8, 81.4, 73.0, 65.8, 62.5, 51.8, 20.4 (d, $J = 7.0\text{ Hz}$), 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 ($\text{M}+\text{H}^+$); HRMS-ESI $^+$: m/z calcd for $\text{C}_{24}\text{H}_{29}\text{F}_4\text{N}_5\text{O}_7\text{P}$ ($\text{M}+\text{H}^+$) 606.1740, found 606.1723. OK

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1a: X = H (Tubercidin)

1b: X = CN (Toyocamycin)

1c: X = CONH₂ (Sangivamycin)

2a: X = H; R = furyl

2b: X = F; R = thienyl

2c: X = F; R = furyl

3a: X = NH₂; R = furyl

3b: X = OMe; R = thienyl

3c: X = NMe₂; R = furyl

4a: Y = H; Z = OH

4b: Y = Me; Z = OH

4c: Y = Me; Z = F

5a: X = H; Y = Me; Z = OH

5b: X = H; Y = ethynyl; Z = OH

5c: X = vinyl; Y = Me; Z = F

5d: X = 1,2,4-oxadiazole; Y = Me; Z = OH

6

Figure 1.

Biologically relevant 7-deazapurine nucleoside analogs

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

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) FSO₂CF₂CO₂Me, CuI, HMPA, DMF, 70 °C, 12h; d) sat. NH₃/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. $\text{LiAl}(\text{t-BuO})_3\text{H}$, 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 , $4 \text{ \AA}$ MS, CH_3CN , rt, 2 h; d) $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$, CuI , HMPA, DMF, 70°C , 12 h; e) sat. NH_3/MeOH , 90°C , 12 h, steel bomb; f) **13**, t-BuMgCl , THF, -78°C , 6 h.