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Synthesis and Conformation of Novel 4'-Fluorinated 5'-Deoxythreosyl Phosphonic Acid Nucleosides as Antiviral Agents

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Efficient synthetic route to novel 4'-fluorinated 5'-deoxythreosyl phosphonic acid nucleosides was described from glyceraldehyde using Horner-Emmons reaction in the presence of triethyl α-fluorophosphonoacetate. Glycosylation reaction of nucleosidic bases with glycosly donor **14** gave the nucleosides which were further phosphonated and hydrolyzed to reach desired nucleoside analogues. Synthesized nucleoside analogues **18**, **21**, **25** and **28** were tested for *anti*-HIV activity as well as cytotoxicity. Adenine derivatives **18** and **21** showed significant *anti*-HIV activity up to 100 μM.

Key Words : Antiviral agent, 4'-Fluorinated nucleoside, Deoxythreosyl nucleoside, Phosphonic acid nucleoside

Introduction

Nucleoside reverse transcriptase inhibitors (NRTIs) continue to be the cornerstone of *anti*-HIV (human immunodeficiency virus) therapy. Side effects of the existing regimens with NRTIs, such as lactic acidosis, pancreatitis and hepatotoxicity however, have been main drawbacks in HIV patient therapy.[1] It has also been found that the introduction of a lipophilic group into the 4'-position of nucleosides in general, and of purine nucleosides in particular, result in the interesting biological activity as exemplified by 4'-ethynyl-cpAP.[2] So far, there have been limited reports on the synthesis of 4'-fluorinated nucleosides.[3] Furthermore, relatively little effort has been devoted to the synthesis of nucleoside analogues with 4'-fluorinated threose-type modification.[4]

Phosphorus-modified nucleoside analogues, bearing a phosphonate group in the sugar moiety, have shown potent antiviral activity.[5] Since the antiviral activity is often associated with nucleoside analogues bearing a phosphonomethoxy group in the sugar moiety, little attention has been paid to exploring the properties and scope of other phosphonate functions in relationship to biological activity. Threose phosphonate nucleosides[6] such as PMDTA (**1**) and PMDTT (**2**) have been synthesized (Figure 1) because they can be assembled from natural precursor molecules.[7] It has been demonstrated that threose nucleic acids (TNA) form duplex with DNA and RNA of thermal stability, similar to that of the natural nucleic acid association. The phosphonoalkoxy group of the proposed threose nucleoside phosphonates is bound at the 3'-position, bring the phosphorus atom and the nucleobase closer to each other than in previously synthesized nucleoside phosphonates where the phosphonate group is bound to the primary hydroxyl group of the nucleoside.

In the literature, several 5'-phosphate isosteres have been adopted to prepare nucleoside phosphonates. As shown in Figure 1, compounds **3**[8] and **4**[9] are simple 5'-deoxynucleoside phosphonic acid, in which the 5'-oxygen of a nucleoside phosphate is replaced by methylene group. Phosphorylation by kinases and incorporation into nucleic acid (eventually leading to chain termination) is considered as an important mechanism to explain the antiviral activity of nucleosides.[10] The potent antiviral activity of phosphonylated nucleobases is ascribed to their intracellular phosphorylation leading to their diphosphates and to refractory incorporation of the modified nucleosides in nucleic acids.[11]

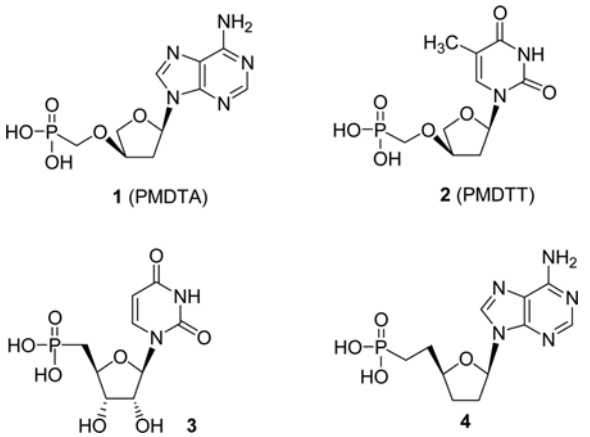
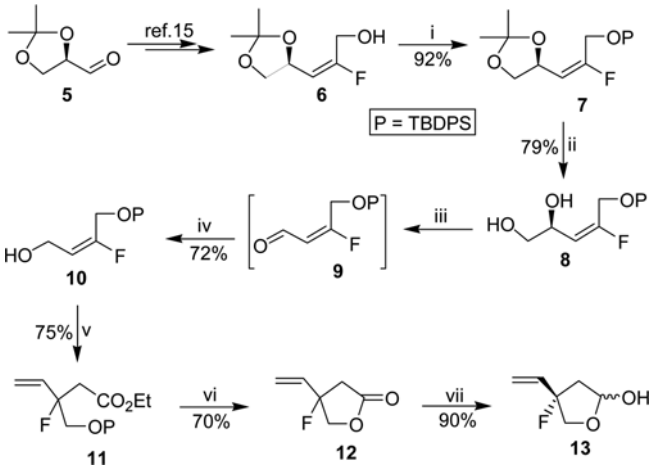


Figure 1. Structures of threosyl or 5'-deoxyphosphonic acid nucleosides as potent antiviral agents.

The phosphonate has certain advantages over its phosphate counterpart as it is metabolically stable because its phosphorus-carbon bond is not susceptible to hydrolytic cleavage.[12] Moreover, the spacial location of the carbon atom, namely the β-position from the phosphorus atom in the nucleoside analogue, has been demonstrated to play a critical role in antiviral activity.[13] These atoms for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[14]

Stimulated by these findings that 4'-modified and threose modification nucleosides as well as 5'-deoxynucleoside



Scheme 1. Synthesis of lactol intermediate **13**
Reagents: i) TBDPSCl, imidazole, CH_2Cl_2; ii) 1,4-dioxane, 2 N HCl solution; iii) $NaIO_4$, MeOH, H_2O; iv) $NaBH_4$, MeOH; v) $(EtO)_3CCH_3$, $CH_3CH_2CO_2H$; vi) TBAF, THF; vii) DIBALH, toluene.

phosphonic acid have excellent biological activities, we sought to synthesize a novel class of nucleosides comprising 4'-fluorinated 5'-deoxythreosyl nucleoside phosphonic acid analogues in order to search for more effective therapeutics against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the nucleoside kinases of nucleosides and nucleotides.

Results and Discussions

As shown in Scheme 1, the starting D-glyceraldehyde **5** was reacted under Horner-Wadsworth-Emmons conditions with triethylfluorophosphonoacetate and reduction with DIBALH to give fluoroallylic alcohol **6** using known procedure.[15] Silylation of alcohol **7** was effected with TBDPSCl and hydrolysis of isopropylidene group in 2 N HCl solution to give diol derivative **8**. Oxidative cleavage of diol with $NaIO_4$ and then reduction of corresponding aldehyde **9** with $NaBH_4$ gave alcohol derivative **10**.[16] This substrate was subjected to the Claisen rearrangement condition in the presence of excess triethyl orthoacetate and catalytic amounts of propionic acid to give γ,δ-unsaturated tertiary fluorinated ethylester **11** in 75% yield.[17] The lactone derivative **12** was prepared *via* desilylation and cyclization from **11** in a 70% yield. The lactone **10** was reduced using DIBALH in toluene at –78 °C to give lactol **13**, which was acetylated in pyridine to furnish the key intermediate **14** as a glycosyl donor. The synthesis of adenine nucleoside was carried out by condensation of compound **14** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivative **15a** and **15b**, respectively. A complete NOE study allowed an unambiguous determination of their relative stereochemistry (Figure 2). For compound **15b**, strong NOE (0.8%) of H-1' ↔ CF-4', which showed 1',4'-*cis* relationships, was observed. According to this result, 4'-vinyl and 1'-purine base of **15b** were located on the b face.

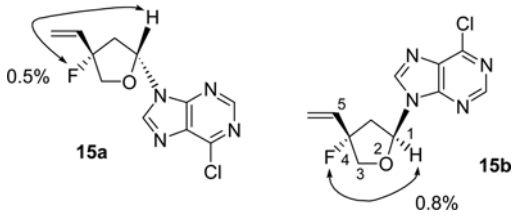
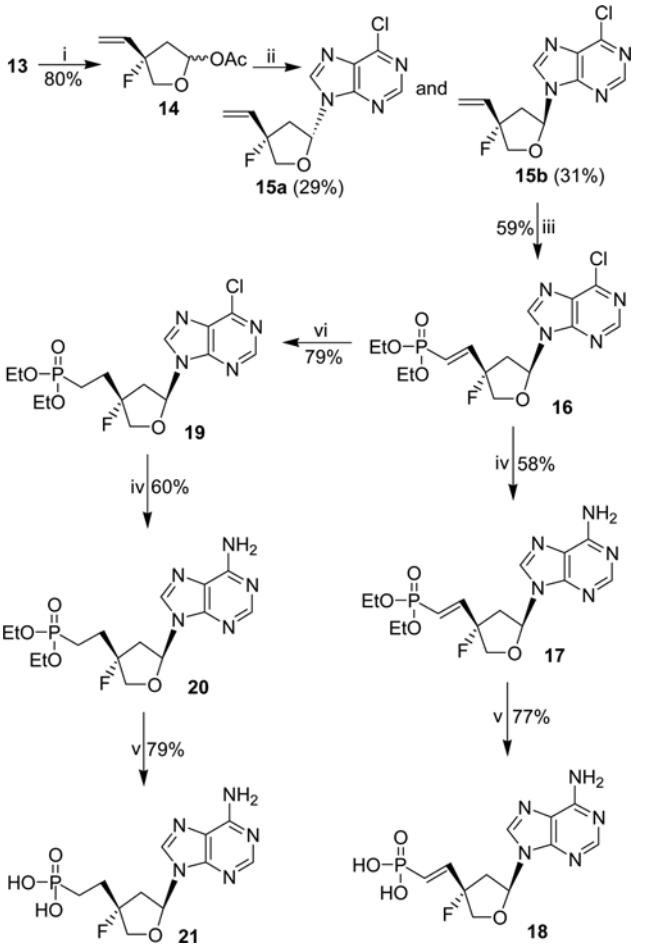


Figure 2. NOE differences between the proximal hydrogens of **15a** and **15b**.

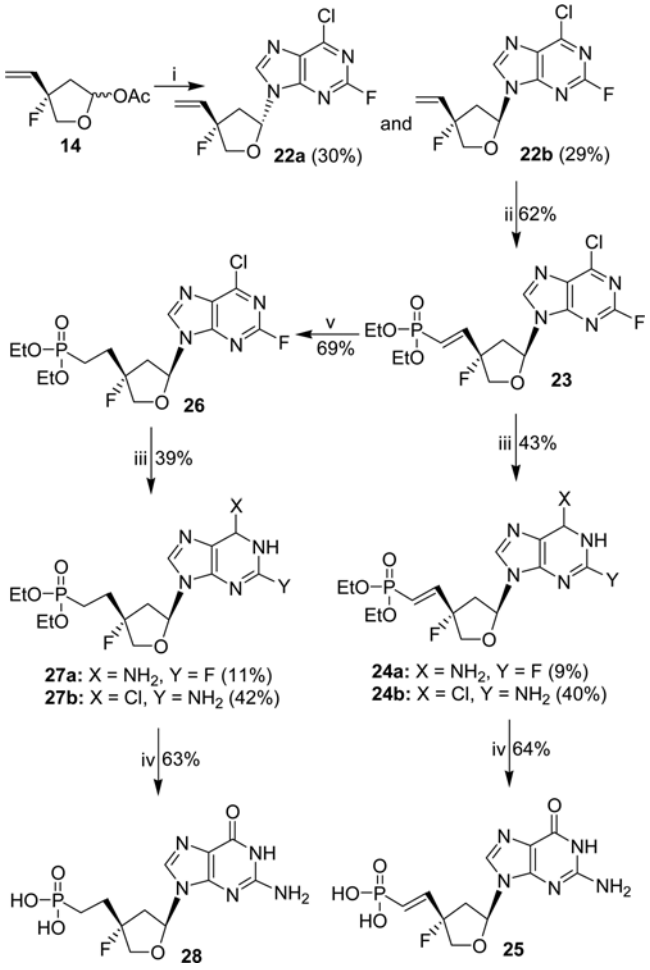
On the other hand, for **15a** compound, weak NOE (0.5%), such as H-1' ↔ CF-4', were assigned to the 1',4'-*trans* relationships.

Cross-metathesis[18] of **15b** with diethylphosphonate using 2nd generation Grubbs catalyst[19] gave vinylidene phosphonate nucleoside analogue **16** in a 59% yield. The chlorine group of purine analogue **16** was then converted to amine with methanolic ammonia at 65 °C to give a corresponding adenosine phosphonate derivative **17**, which was hydrolyzed by treatment with bromotrimethylsilane in CH_3CN in the



Reagents: i) Ac_2O, DMAP, pyridine; ii) silylated 6-chloropurine, TMSOTf, DCE; iii) vinyldiethylphosphonate, Grubbs cat.(II) CH_2Cl_2; iv) NH_3/MeOH; v) TMSBr, 2,6-lutidine, CH_3CN; vi) Pd/C, cyclohexene, MeOH.

Scheme 2. Synthesis of 4'-fluorinated threosyl-5'-deoxyphosphonate adenine analogues.



Reagents: i) silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) vinyldiethylphosphonate, Grubbs cat.(II) CH_2Cl_2; iii) NH_3, DME, rt; iv) (a) TMSBr, 2,6-lutidine, CH_3CN; (b) NaOMe, $HSCH_2CH_2OH$, MeOH; v) Pd/C, cyclohexene, MeOH

Scheme 3. Synthesis of 4'-fluorinated threosyl-5'-deoxyphosphonate guanine analogues.

presence of 2,6-lutidine to give an adenosine phosphonic acid derivative **18**.[20] The vinylidene phosphonate **16** was saturated in transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside analogue **19** in a 79% yield. Adenine phosphonic acid analogue **21** was prepared through the similar reaction conditions such as ammonolysis and hydrolysis described for the preparation of **18**.

For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[21] was condensed with glycosyl donor in the similar conditions used for the condensation of 6-chloropurine. Vorbruggen coupling[22] of the acetate **14** with 2-fluoro-6-chloropurine gives analogue **22a** (30%) and **22b** (29%), respectively. Cross-metathesis of **22b** and diethylvinylphosphonate gave **23** in a 62% yield. A complete NOE study allowed an unambiguous determination of their relative stereochemistries as described for **13a** and **13b**.

Bubbling ammonia into the compound **23** gave separable 2-fluoro-6-aminopurine analogue[23] analogue **24a** (9%) and 2-amino-6-chloropurine analogue **24b** (40%), respectively. Usually, fluorine acts as better leaving group than chlorine in nucleophilic aromatic substitution. 2-Amino-6-chloropurine derivative **24b** was treated with TMSBr and 2,6-lutidine to provide phosphonic acid and sequentially which was treated sodium methoxide and 2-mercaptoethanol in methanol to give desired guanine vinylidene phosphonic acid **25** in a 64% yield (Scheme 2).[24] The guanine phosphonate **28** was synthesized from **23** *via* transfer catalytic hydrogenation, ammonolysis and hydrolysis using the similar conditions as described for the synthesis of **25**.

The antiviral activity of phosphonate nucleoside is mostly explained by their intracellular metabolism to their diphosphates followed by incorporation into the viral genome and chain termination.[25] The synthesized compounds **18**, **21**, **25** and **28** were tested against HIV-1. Adenine derivatives **18** and **21** show some antiviral activity and cytotoxicity up to 100 mM (Table 1). This result indicates that the virus might allow the sugar moiety for diphosphorylation or any affinity of its diphosphate toward viral polymerases. *Anti*-HIV activity was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain *LAI*. PBM cells (1×10^5 cell/mL) were infected with HIV-1 at a multiplicity of infection (MOI) of 0.02 and cultured in the presence of various concentrations of the test compounds. After 4 days of incubation at 37 °C, numbers of viable cells were determined using the 3-(4,5-di-methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide method. The cytotoxicities of the

Table 1. The antiviral activities of the synthesized compounds

Compound	HIV-1		Cytotoxicity IC_{50} (μM)		
	EC_{50} (μM)	EC_{90} (μM)	PBM	CEM	Vero
18	18	90	>100	>100	>100
21	10	80	>100	>100	>100
25	42	95	>100	>100	>100
28	53	95	>100	>100	>100
PMEA	4.2	ND	>100	40.0	>100
AZT	0.0843	ND	>100	15.8	50.0

ND: Not Determined. PMEA: 9-[2-(Phosphonomethoxy)ethyl]adenine. AZT: Azidothymidine. EC_{50} (μM): EC_{50} values are for 50% inhibition of virus production as indicated by supernatant RT levels. EC_{90} (μM): EC_{90} values are for 90% inhibition of virus production as indicated by supernatant RT levels. IC_{50} (μM): IC_{50} values indicate 50% inhibition of cell growth.

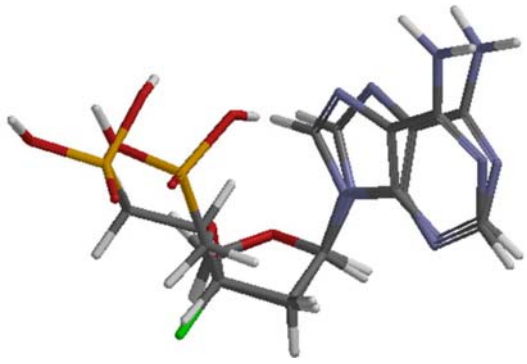


Figure 3. Superimpose of PMDTA and **21**.

compounds were evaluated in parallel with their antiviral activities, which were assessed based on the viabilities of mock-infected cells.[26] As shown in the superimposition model of PMDTA (**1**) and the corresponding analogue **21** (Figure 3), discrepancy of phosphonic acid parts are more pronounced compared to base moiety. Note the furanose puckering of PMDTA (**1**) is positioned closer to that of adenine analogue **21**.[27]

Conclusions

Based on the potent *anti*-HIV activity of 4'-branched nucleosides as well as threosyl phosphonic acid nucleosides, we have designed and successfully synthesized novel 4'-fluorinated 5'-deoxyphosphonic acid nucleoside analogues starting from glyceraldehyde. Biological data presented indicates that these phosphonates have modest *anti*-viral activity with the best compound **21** exhibiting EC_{50} of 10 μM, albeit 100 times less active than AZT, but similar to PMEA and that reported for PMDTA.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). MS spectra were collected in electrospray ionization (ESI) mode. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were carried out under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

***t*-Butyl-[3-(2,2-dimethyl-[1,3]dioxolan-4-yl) 2-fluoro-allyloxy]diphenylsilane (7).** To a solution of the alcohol **6** (1.69 g, 9.6 mmol) and imidazole (0.98 g, 14.4 mol) in dry CH_2Cl_2 (40 mL), TBDPSCl (2.90 g, 10.56 mmol) was slowly added at 0 °C and the mixture was stirred for 3 h at rt. The reaction mixture was quenched using a saturated aqueous $NaHCO_3$ solution (10 mL) and further diluted with water (100 mL). The mixture was extracted with CH_2Cl_2 (100 mL) two times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **7** (3.66 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.40 (m, 10H), 5.48 (d, *J* = 16.8 Hz, 1H), 4.59 (m, 1H), 4.45 (d, *J* = 18.0 Hz, 2H), 3.98 (dd, *J* = 11.8, 6.8 Hz, 1H), 3.89 (dd, *J* = 11.7, 8.4 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6 (d, *J* = 170.3 Hz), 135.9, 135.8, 133.1, 132.8, 130.2, 128.3, 104,6, 94.3 (d, *J* = 30.5 Hz), 76.2, 73.1, 68.6 (d, *J* = 28.5 Hz), 28.3, 27.7, 27.2, 19.6.

5-(*t*-Butyldiphenylsilanyloxy) 4-fluoro-pent-3-ene-1,2-diol (8). To a solution of compound **7** (4.23 g, 10.2 mmol) in 1,4-dioxane (20 mL), 2 N aqueous HCl solution (50 mL) was added and stirred for 2 h at 0 °C. The mixture was neutralized by the slow addition of a saturated $NaHCO_3$ solution and diluted with brine (100 mL). The mixture was extracted with EtOAc (100 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give the diol **8** (3.01 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.39 (m, 10H), 5.54 (d, *J* = 17.0 Hz, 1H), 4.51 (dd, *J* = 17.9, 2.8 Hz, 2H), 3.99 (m, 1H), 3.75-3.70 (m, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2 (d, *J* = 172.2 Hz), 135.6, 135.4, 133.2, 133.0, 130.6, 128.4, 116.4, 95.2 (d, *J* = 28.8 Hz), 71.2, 68.5 (d, *J* = 22.4 Hz), 67.5, 27.9, 19.3; Anal. Calc. for $C_{21}H_{27}FO_3Si$: C, 67.35; H, 7.27. Found: C, 67.38; H, 7.29.

4-(*t*-Butyldiphenylsilanyloxy) 3-fluoro-but-2-en-1-ol (10). A solution of $NaIO_4$ (1.12 g, 5 mmol) in H_2O (15 mL) was added dropwise to a solution of **8** (1.31 g, 3.5 mmol) in MeOH (15 mL) for 10 min at 0 °C and stirred for further 15 min at the same temperature. $NaBH_4$ (397 mg, 10.5 mmol) was added, and the reaction mixture was stirred for 10 min at 0 °C. The white solid was filtrate off, and the solid was washed with MeOH (30 mL). The combined filtrate was carefully neutralized by 0.5 N HCl and concentrated to dryness and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give the allylic alcohol **10** (3.01 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.41 (m, 10H), 5.58 (d, *J* = 18.4 Hz, 1H), 4.51 (d, *J* = 17.8 Hz, 2H), 4.24 (d, *J* = 4.8 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8 (d, *J* = 176.0 Hz), 136.0, 135.8, 133.7, 132.9, 131.3, 128.7, 120.1, 119.5, 96.0 (d, *J* = 28.4 Hz), 68.3 (d, *J* = 25.3 Hz), 57.1, 28.2, 19.5; Anal. Calc. for $C_{20}H_{25}FO_2Si$: C, 69.73; H, 7.31. Found: C, 69.68; H, 7.28.

(±)-3-(*t*-Butyldiphenylsilanyloxymethyl) 3-Fluoro-pent-4-enoic Acid Ethyl Ester (11). A solution of the allylic alcohol **10** (1.17 g, 3.41 mmol) in triethyl orthoacetate (15 mL) and 0.1 mL of propionic acid was heated at 135-140 °C overnight with constant stirring to allow for the removal of ethanol. An excess of triethyl orthoacetate was removed by distillation, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **11** (1.06 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.38 (m, 10H), 5.86 (m, 1H), 5.22-5.15 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.72 (m, 2H), 2.82 (dd, *J* = 18.4, 15.2 Hz, 1H), 2.73 (dd, *J* = 15.2, 15.0 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 141.2 (d, *J* = 19.2 Hz), 135.8, 135.1, 133.6, 133.0, 132.2, 128.4, 123.3, 119.2, 112.5, 94.7 (d, *J* = 178.4 Hz), 67.8 (d, *J* = 26.4

Hz), 60.4, 40.3 (d, J = 26.0 Hz), 28.2, 20.1, 14.5; Anal. Calc. for $C_{24}H_{31}FO_3Si$: C, 69.53; H, 7.54. Found: C, 69.49; H, 7.56; MS *m/z* 415 $(M+H)^+$.

(±)-4-Fluoro-4-vinyl-dihydrofuran-2-one (12). To a solution of **11** (550 mg, 1.32 mmol) in THF (10 mL), TBAF (1.58 mL, 1.0 M solution in THF) was added at 0 °C. The mixture was stirred overnight at rt and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 12:1) to give **12** (120 mg, 70%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88-5.81 (m, 1H), 5.25-5.14 (m, 2H), 4.48 (dd, J = 18.6, 10.2 Hz, 1H), 4.30 (dd, J = 19.0, 10.2 Hz, 1H), 2.68 (dd, J = 18.4, 8.2 Hz, 1H), 2.44 (dd, J = 17.8, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 142.6 (d, J = 19.4 Hz), 93.8 (d, J = 172.8 Hz), 79.7 (d, J = 24.2 Hz), 49.5 (d, J = 21.3 Hz); MS *m/z* 131 $(M+H)^+$.

(±)-4-Fluoro-4-vinyl-tetrahydrofuran-2-ol (13). To a cooled (−78 °C), stirred solution of lactone **12** (250 mg, 1.92 mmol) in dry toluene (7 mL) was added dropwise a 1.0 M solution of diisobutylaluminium hydride (DIBALH) (2.1 mL, 2.1 mmol). The reaction was stirred for 15 min. at −78 °C, followed by dropwise addition of methanol (2.0 mL) and diluted with ethyl acetate (30 mL). The reaction mixture was warmed to room temperature and stirred for 1 h, and the precipitate was removed by filtration through a pad of Celite, washed with ethyl acetate. The filtrate and washings were concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:8) to give **13** (228 mg, 90%) as mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81-5.70 (m, 1H), 5.51 (m, 1H), 5.18-5.10 (m, 2H), 3.89-3.72 (m, 2H), 2.35-2.22 (m, 2H).

(±)-Acetic Acid 4-Fluoro-4-vinyl-tetrahydrofuran-2-yl Ester (14). To a solution of compound **13** (233 mg, 1.76 mmol) in anhydrous pyridine (10 mL) and DMAP (10 mg), Ac_2O (267 mg, 2.62 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene. The residue was diluted with H_2O (100 mL), extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **14** (245 mg, 80%) as a mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21-6.17 (m, 1H), 5.90-5.78 (m, 1H), 5.24-5.11 (m, 2H), 3.94-3.80 (m, 2H), 2.31-2.19 (m, 2H), 2.02 (s, s, 3H).

(*rel*)-(2'*R*,4'*S*)-9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) 6-chloropurine (15a) and (*rel*)-(2'*S*,4'*S*)-9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) 6-Chloropurine (15b). 6-Chloropurine (188 mg, 1.22 mmol), anhydrous HMDS (11 mL), and a catalytic amount of ammonium sulfate (10 mg) were refluxed overnight, and the solvent was distilled under anhydrous condition. The residue was dissolved in anhydrous 1,2-dichloroethane (11 mL). To this mixture, a solution of **14** (106 mg, 0.61 mmol) in dry DCE (11 mL) and TMSOTf (271 mg, 1.22 mmol) was added, and the resulting mixture was stirred for 5 h at rt. The reaction mixture was quenched with 2.0 mL of saturated $NaHCO_3$ and stirred for 1 h. The resulting solid was filtered through a Celite pad, and the filtrate was diluted with water (80 mL) and extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 3:1:0.01) to give compound **15a** (47 mg, 29%) and **15b** (50 mg, 31%): data for **15a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.21 (s, 1H), 6.02 (dd, J = 5.4, 1.8 Hz, 1H), 5.91-5.78 (m, 1H), 5.25-5.14 (m, 2H), 3.93 (dd, J = 17.5, 10.6 Hz, 1H), 3.81 (dd, J = 18.2, 10.5 Hz, 1H), 2.58 (dd, J = 17.4, 8.2 Hz, 1H), 2.39 (dd, J = 16.8, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.3, 150.6, 144.1, 142.6 (d, J = 19.4 Hz), 141.2, 132.8, 113.1, 101.9 (d, J = 175.2 Hz), 80.3, 73.7 (d, J = 27.6 Hz), 42.2 (d, J = 23.3 Hz); Anal. Calc. for $C_{11}H_{10}ClFN_4O$ (+1.0 MeOH): C, 47.93; H, 4.69; N, 18.63. Found: C, 47.90; H, 4.71; N, 18.65; MS *m/z* 269 $(M+H)^+$. data for **15b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H), 8.24 (s, 1H), 5.99 (t, J = 5.2 Hz, 1H), 5.90-5.77 (m, 1H), 5.27-5.16 (m, 2H), 3.98 (dd, J = 16.8, 8.6 Hz, 1H), 3.81 (dd, J = 17.2, 8.6 Hz, 1H), 2.60 (dd, J = 17.6, 8.4 Hz, 1H), 2.41 (dd, J = 18.2, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.0, 151.5, 150.8, 144.5, 142.8 (d, J = 21.0 Hz), 140.8, 133.5, 112.6, 102.3 (d, J = 176.2 Hz), 81.2, 73.5 (d, J = 26.8 Hz), 41.8 (d, J = 22.7 Hz); Anal. Calc. for $C_{11}H_{10}ClFN_4O$: C, 49.17; H, 3.75; N, 20.85. Found: C, 49.21; H, 3.72; N, 20.83; MS *m/z* 269 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl [9-(4-fluoro-4-vinyl-tetrahydrofuran-2-yl) 6-Chloropurine] Phosphonate (16). To a CH_2Cl_2 (10 mL) solution of 6-chloropurine derivative **15b** (110 mg, 0.412 mmol) and diethyl vinylphosphonate (338 mg, 2.06 mmol), 2nd-generation Grubbs catalyst (17.4 mg, 0.0206 mmol) was added. The reaction mixture was refluxed for 48 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane/MeOH, 4:1:0.04) to give **16** (98 mg, 59%) as a form: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.22 (s, 1H), 6.68 (dd, J = 17.2, 21.4 Hz, 1H), 6.21-6.10 (m, 1H), 5.97 (dd, J = 5.4, 1.8 Hz, 1H), 4.08-4.04 (m, 4H), 3.94 (dd, J = 17.0, 8.6 Hz, 1H), 3.79 (dd, J = 17.2, 8.7 Hz, 1H), 2.56 (dd, J = 17.4, 9.2 Hz, 1H), 2.40 (dd, J = 18.0, 9.2 Hz, 1H), 1.28-1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.9, 151.3, 150.5, 148.8 (d, J = 20.8 Hz), 143.5, 141.5, 133.6, 111.3, 99.5 (d, J = 177.1 Hz), 80.7, 74.5 (d, J = 26.5 Hz), 63.7, 63.1, 42.2 (d, J = 23.4 Hz), 14.6; Anal. Calc. for $C_{15}H_{19}ClFN_4O_4P$ (+1.0 MeOH): C, 43.99; H, 5.31; N, 12.83. Found: C, 44.02; H, 5.29; N, 12.85; MS *m/z* 405 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) Adenine} Phosphonate (17). A solution of **16** (125 mg, 0.309 mmol) in saturated methanolic ammonia (8 mL) was stirred overnight at 65 °C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:10) to give **17** (64.3 mg, 54%) as a white solid: mp 176-178 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.33 (s, 1H), 8.16 (s, 1H), 6.70 (dd, J = 17.3, 21.2 Hz, 1H),

6.24-6.12 (m, 2H), 4.09-4.04 (m, 4H), 3.96 (dd, *J* = 16.8, 8.8 Hz, 1H), 3.79 (dd, *J* = 17.8, 8.7 Hz, 1H), 2.58 (dd, *J* = 17.8, 9.0 Hz, 1H), 2.42 (dd, *J* = 17.2, 9.0 Hz, 1H), 1.29-1.25 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.3, 152.7, 151.9 (d, *J* = 20.8 Hz), 150.5, 141.5, 120.3, 112.6, 98.8 (d, *J* = 176.8 Hz), 81.4, 74.5 (d, *J* = 25.8 Hz), 63.9, 63.4, 41.8 (d, *J* = 24.4 Hz), 14.6; Anal. Calc. for $C_{15}H_{21}FN_5O_4P$ (+1.0 MeOH): C, 46.04; H, 6.04; N, 16.78; Found: C, 46.08; H, 6.02; N, 16.80; MS *m/z* 386 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-{9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) Adenine} Phosphonic Acid (18). To a solution of the phosphonate **17** (185 mg, 0.482 mmol) in anhydrous CH_3CN (15 mL) and 2,6-lutidine (1.124 mL, 9.6 mmol) was added trimethylsilyl bromide (0.538 mg, 4.82 mmol). The mixture was heated overnight at 75 ºC under nitrogen gas and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (130 mL) and purified water (130 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 130 mL) and then freeze-dried to give phosphonic acid **18** (122 mg, 77%) as a yellowish foam: UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.13 (s, 1H), 6.69 (dd, *J* = 17.8, 21.4 Hz, 1H), 6.21-6.10 (m, 1H), 5.99 (dd, *J* = 5.5, 1.8 Hz, 1H), 3.94 (dd, *J* = 17.1, 8.8 Hz, 1H), 3.80 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.52 (dd, *J* = 17.2, 9.0 Hz, 1H), 2.42 (dd, *J* = 16.8, 9.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.7, 152.2, 150.4 (d, *J* = 19.8 Hz), 149.8, 142.2, 122.6, 111.3, 99.4 (d, *J* = 177.2 Hz), 81.7, 75.6 (d, *J* = 27.2 Hz), 42.2 (d, *J* = 25.4 Hz); Anal. Calc. for $C_{11}H_{13}FN_5O_4P$ (+2.0 H_2O): C, 36.17; H, 4.69; N, 19.17; Found: C, 36.21; H, 4.71; N, 19.15; MS *m/z* 330 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) 6-Chloropurine} Phosphonate (19). A solution of vinyl phosphonate nucleoside analogue **16** (202 mg, 0.5 mmol) in methanol (10 mL) was added 10% Pd/C (10 mg) and cyclohexene (5 mL) under argon gas. The reaction mixture was refluxed for 36 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography (EtOAc/*n*-Hexane/MeOH, 3:1:0.1) to give ethyl phosphonate analogue **19** (160 mg, 79%) as a white solid: mp 178-180 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.20 (s, 1H), 5.99 (dd, *J* = 5.6, 1.8 Hz, 1H), 4.11-4.07 (m, 4H), 3.89 (dd, *J* = 17.4, 10.0 Hz, 1H), 3.72 (dd, *J* = 17.0, 9.9 Hz, 1H), 2.51 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.40 (dd, *J* = 17.8, 9.1 Hz, 1H), 2.14-1.77 (m, 4H), 1.26-1.22 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 151.0, 150.4, 144.1, 132.7, 102.5 (d, *J* = 174.8 Hz), 82.2, 73.2 (d, *J* = 25.8 Hz), 64.2, 63.6, 62.0, 41.7 (d, *J* = 25.6 Hz), 26.8 (d, *J* = 23.2 Hz), 19.9, 15.1; Anal. Calc. for $C_{15}H_{21}ClFN_4O_4P$ (+1.0 MeOH): C, 43.79; H, 5.74; N, 12.76; Found: C, 43.83; H, 5.76; N, 12.79; MS *m/z* 407 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) Adenine} Phosphonate (20). Transformation of 6-chloropurine to adenine derivative **20** was performed from **19** by the similar ammonolysis procedure as described for **17**: yield 60%; mp 180-182 ºC; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.33 (s, 1H), 8.16 (s, 1H), 6.00 (dd, *J* = 5.5, 1.8 Hz, 1H), 4.12-4.07 (m, 4H), 3.86 (dd, *J* = 17.5, 10.0 Hz, 1H), 3.70 (dd, *J* = 16.8, 10.0 Hz, 1H), 2.55 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.42 (dd, *J* = 17.2, 8.8 Hz, 1H), 2.12-1.87 (m, 4H), 1.24-1.19 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.5, 152.5, 150.7, 141.5, 120.2, 98.8 (d, *J* = 177.2 Hz), 81.6, 75.5 (d, *J* = 24.5 Hz), 63.6, 62.5, 40.9 (d, *J* = 22.7 Hz), 28.6, 21.4 (d, *J* = 21.8 Hz), 14.7; Anal. Calc. for $C_{15}H_{23}FN_5O_4P$ (+1.0 MeOH): C, 45.82; H, 6.49; N, 16.70; Found: C, 45.78; H, 6.51; N, 16.73; MS *m/z* 388 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-{9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) Adenine} Phosphonic Acid (21). Adenine phosphonic acid 21 was synthesized from 20 using the similar hydrolysis procedure as described for 18: yield 79%, UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.36 (s, 1H), 8.17 (s, 1H), 5.98 (dd, *J* = 5.4, 1.8 Hz, 1H), 3.83 (dd, *J* = 17.2, 9.6 Hz, 1H), 3.68 (dd, *J* = 17.2, 9.7 Hz, 1H), 2.58 (dd, *J* = 16.7, 9.6 Hz, 1H), 2.45 (dd, *J* = 17.4, 9.8 Hz, 1H), 2.12-1.87 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.9, 152.5, 150.7, 141.5, 120.2, 100.3 (d, *J* = 177.2 Hz), 81.6, 75.5 (d, *J* = 24.5 Hz), 40.9 (d, *J* = 22.7 Hz), 28.6, 18.4 (d, *J* = 21.8 Hz); Anal. Calc. for $C_{11}H_{15}FN_5O_4P$ (+1.0 H_2O): C, 37.83; H, 4.90; N, 20.05; Found: C, 37.79; H, 4.91; N, 20.07; MS *m/z* 332 $(M+H)^+$.

(*rel*)-(2'*R*,4'*S*)-9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) 2-fluoro-6-chloropurine (22a) and (*rel*)-(2'*S*,4'*S*)-9-(4-fluoro-4-vinyl-tetrahydrofuran-2-yl) 2-Fluoro-6-chloropurine (22b). Coupling of **14** with 2-fluoro-6-chloropurine under the similar condensation conditions as described for **15** to give **22a** and **22b**, respectively: data for **22a**: yield 30%; UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H), 5.98 (dd, *J* = 5.2, 2.0 Hz, 1H), 5.90-5.79 (m, 1H), 5.24-5.13 (m, 2H), 3.95 (dd, *J* = 17.6, 9.8 Hz, 1H), 3.79 (dd, *J* = 18.0, 9.8 Hz, 1H), 2.54 (dd, *J* = 17.2, 8.6 Hz, 1H), 2.39 (dd, *J* = 16.9, 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8 (d, *J* = 228.4 Hz), 153.6, 145.7, 142.6 (d, *J* = 19.4 Hz), 136.6, 122.9, 110.5, 100.4 (d, *J* = 174.8 Hz), 79.3, 73.3 (d, *J* = 26.6 Hz), 41.2 (d, *J* = 24.4 Hz); Anal. Calc. for $C_{11}H_9ClF_2N_4O$: C, 46.09; H, 3.16; N, 19.54. Found: C, 46.13; H, 3.17; N, 19.56; MS *m/z* 287 $(M+H)^+$. data for **22b**: yield 29%; UV (MeOH) λ_{max} 268.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (s, 1H), 6.01 (dd, *J* = 5.3, 1.8 Hz, 1H), 5.89-5.76 (m, 1H), 5.22-5.13 (m, 2H), 3.91 (dd, *J* = 17.2, 9.8 Hz, 1H), 3.75 (dd, *J* = 18.1, 9.9 Hz, 1H), 2.49 (dd, *J* = 17.6, 8.2 Hz, 1H), 2.34 (dd, *J* = 16.8, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8 (d, *J* = 238.4 Hz), 153.6, 146.9, 144.8, 141.6 (d, *J* = 19.6 Hz), 137.2, 122.8, 111.4, 99.6 (d, *J* = 175.2 Hz), 81.2, 73.7 (d, *J* = 27.6 Hz), 42.2 (d, *J* = 23.3 Hz); Anal. Calc. for $C_{11}H_9ClF_2N_4O$: C, 46.09; H, 3.16; N, 19.54. Found: C, 46.12; H, 3.18; N, 19.55; MS *m/z* 287 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) 2-Fluoro-6-chloropurine} Phosphonate (23). Phosphonate nucleoside analogue **23** was prepared from **22b** using the same cross-metathesis procedure as described for **16**: yield 62%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 6.62 (dd, *J* = 16.8, 20.4 Hz, 1H), 6.25-6.13 (m, 1H), 5.99 (dd, *J* = 5.2, 1.8 Hz, 1H), 4.10-4.06 (m, 4H), 3.87 (dd, *J* = 17.4, 8.8 Hz, 1H), 3.74 (dd, *J* = 17.8, 8.8 Hz, 1H), 2.53 (dd, *J*

= 17.4, 9.4 Hz, 1H), 2.39 (dd, *J* = 18.0, 9.4 Hz, 1H), 1.25-1.20 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6 (d, *J* = 235 Hz), 153.6, 152.8 (d, *J* = 20.6 Hz), 146.6, 145.2, 138.5, 122.4, 111.6, 98.8 (d, *J* = 176.6 Hz), 79.4, 73.5 (d, *J* = 24.6 Hz), 63.7, 63.1, 62.5, 41.4 (d, *J* = 25.4 Hz), 14.1; Anal. Calc. for $C_{15}H_{18}ClF_2N_4O_4P$ (+1.0 MeOH): C, 42.25; H, 4.87; N, 12.32; Found: C, 42.20; H, 4.89; N, 12.30; MS *m/z* 423 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) 2-Fluoro-6-aminopurine} phosphonate (24a) and (*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-fluoro-4-vinyl-tetrahydrofuran-2-yl) 2-Amino-6-chloropurine} Phosphonate (24b). Dry ammonia gas was bubbled into a stirred solution of **23** (250 mg, 0.59 mmol) in DME (15 mL) at room temperature overnight. The salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:12) to give **24a** (21 mg, 9%) and **24b** (99 mg, 40%), respectively: Data for **24a**; UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40 (s, 1H), 6.71 (dd, *J* = 17.6, 21.6 Hz, 1H), 6.29-6.13 (m, 1H), 6.03 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.11-4.06 (m, 4H), 3.92 (dd, *J* = 17.6, 10.2 Hz, 1H), 3.72 (dd, *J* = 17.0, 10.1 Hz, 1H), 2.49 (dd, *J* = 16.4, 9.2 Hz, 1H), 2.34 (dd, *J* = 18.2, 92 Hz, 1H), 1.22-1.17 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.3 (d, *J* = 226.4 Hz), 154.6, 152.8 (d, *J* = 20.2 Hz), 149.2, 142.1, 119.4, 114.6, 99.3 (d, *J* = 172.8 Hz), 81.2, 75.0 (d, *J* = 22.8 Hz), 63.7, 62.9, 42.2 (d, *J* = 22.6 Hz), 14.6; Anal. Calc. for $C_{15}H_{20}F_2N_5O_4P$ (+1.0 MeOH): C, 44.67; H, 5.00; N, 17.36; Found: C, 44.14; H, 5.55; N, 16.08; MS *m/z* 404 $(M+H)^+$.

Data for **24b**; UV (MeOH) λ_{max} 308.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.19 (s, 1H), 6.69 (dd, *J* = 17.0, 22.2 Hz, 1H), 6.19-6.09 (m, 1H), 5.98 (dd, *J* = 5.3, 1.8 Hz, 1H), 4.10-4.05 (m, 4H), 3.86 (dd, *J* = 18.2, 10.0 Hz, 1H), 3.72 (dd, *J* = 17.8, 10.0 Hz, 1H), 2.47 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.32 (dd, *J* = 17.4, 9.2 Hz, 1H), 1.23-1.16 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.7, 155.1, 151.7, 148.2 (d, *J* = 22.7 Hz), 143.6, 125.6, 116.3, 94.8 (d, *J* = 169.7 Hz), 78.8, 73.0 (d, *J* = 24.0 Hz), 62.8, 62.3, 40.8 (d, *J* = 21.2 Hz), 13.8; Anal. Calc. for $C_{15}H_{20}ClFN_5O_4P$ (+1.0 MeOH): C, 42.53; H, 5.35; N, 15.50; Found: C, 42.49; H, 5.37; N, 15.53; MS *m/z* 420 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-9-{(4-Fluoro-4-vinyl-tetrahydrofuran-2-yl) Guanine} Phosphonic Acid (25). To a solution of **24b** (148 mg, 0.353 mmol) dry CH_3CN (10 mL) and 2,6-lutidine (0.94 mL, 12.32 mmol) was added trimethylsilyl bromide (0.945 g, 6.18 mmol) at room temperature. After this mixture was stirred for 15 h, the solvent was removed, coevaporating three times with methanol. The residue was dissolved in MeOH (10.0 mL) and 2-mercaptoethanol (110 mg, 1.417 mmol) and NaOMe (75.26 mg, 1.417 mmol) was added to the mixture. The mixture was refluxed for 10 h under N_2, cooled, neutralized with glacial AcOH, and evaporated to dryness under vacuum. The residue was purified by chromatography on a column of reversed-phase C18 silica gel eluting water to give **25** (79 mg, 64%) as a yellowish form. UV (H_2O) λ_{max} 253.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (s, 1H), 6.72 (dd, *J* = 17.2, 22.0 Hz, 1H), 6.21-6.12 (m, 1H), 5.97 (dd, *J* = 5.2, 2.0 Hz, 1H), 3.90 (dd, *J* = 16.8, 9.8 Hz, 1H), 3.71 (dd, *J* = 17.5, 9.8 Hz, 1H), 2.51 (dd, *J* = 17.6, 9.4 Hz, 1H), 2.34 (dd, *J* = 17.8, 9.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.9, 154.8, 152.6, 149.2 (d, *J* = 20.7 Hz), 137.9, 119.2, 113.6, 99.1 (d, *J* = 176.2 Hz), 79.9, 73.2 (d, *J* = 23.4 Hz), 64.4, 63.3, 62.8, 42.0 (d, *J* = 19.9 Hz); Anal. Calc. for $C_{11}H_{13}FN_5O_5P$ (+1.0 H_2O): C, 36.37; H, 4.16; N, 20.19; Found: C, 36.35; H, 4.18; N, 20.21; MS *m/z* 346 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) 2-Fluoro-6-chloropurine} Phosphonate (26). Compound **26** was synthesized from **23** by the similar catalytic hydrogenation procedure as described for **19**: yield 69%; UV (MeOH) λ_{max} 270.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 6.01 (dd, *J* = 5.0, 2.2 Hz, 1H), 4.16-4.09 (m, 4H), 3.86 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.72 (dd, *J* = 17.0, 8.7 Hz, 1H), 2.57 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.42 (dd, *J* = 17.4, 10.0 Hz, 1H), 2.13-1.78 (m, 4H), 1.22-1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8 (d, *J* = 248.2 Hz), 152.8, 146.6, 138.5, 121.7, 102.2 (d, *J* = 168.4 Hz), 78.6, 71.2 (d, *J* = 23.4 Hz), 63.1, 62.7, 43.1 (d, *J* = 23.6 Hz), 22.6 (d, *J* = 22.6 Hz), 20.2, 14.6; Anal. Calc. for $C_{15}H_{20}ClF_2N_4O_4P$: C, 42.41; H, 4.75; N, 13.19; Found: C, 42.37; H, 4.76; N, 13.22; MS *m/z* 425 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) 2-Fluoro-6-aminopurine} Phosphonate (27a) and (*rel*)-(2'*S*,4'*S*)-Diethyl {9-(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) 2-Amino-6-chloropurine} Phosphonate (27b). Ammonolysis of **26** was performed using the similar procedure as described for **27a** and **27b**: Data for **27a**; yield 11%; UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 1H), 6.00 (t, *J* = 2.4 Hz, 1H), 4.18-4.09 (m, 4H), 3.88 (dd, *J* = 18.2, 8.8 Hz, 1H), 3.74 (dd, *J* = 17.4, 8.9 Hz, 1H), 2.58-2.48 (m, 1H), 2.37 (dd, *J* = 17.4, 10.1 Hz, 1H), 2.16-1.85 (m, 4H), 1.25-1.20 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 159.6 (d, *J* = 252.4 Hz), 154.7, 152.5, 142.2, 120.2, 94.2 (d, *J* = 173.6 Hz), 79.6, 70.7 (d, *J* = 22.4 Hz), 63.9, 62.9, 41.3 (d, *J* = 21.8 Hz), 27.6 (d, *J* = 20.5 Hz), 21.2, 14.1; Anal. Calc. for $C_{15}H_{22}F_2N_5O_4P$ (+1.0 MeOH): C, 43.94; H, 5.99; N, 16.01; Found: C, 43.96; H, 6.02; N, 15.97; MS *m/z* 406 $(M+H)^+$.

Data for **27b**; yield 42%; UV (MeOH) λ_{max} 308.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.19 (s, 1H), 5.90 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.21-4.14 (m, 4H), 3.90 (dd, *J* = 18.0, 9.8 Hz, 1H), 3.72 (dd, *J* = 17.8, 9.8 Hz, 1H), 2.54-2.43 (dd, *J* = 17.2, 8.8 Hz, 1H), 2.37 (m, 1H), 2.21-1.90 (m, 4H), 1.21-1.17 (m, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.4, 154.3, 151.2, 144.2, 125.6, 98.8 (d, *J* = 178.6 Hz), 80.2, 71.2 (d, *J* = 24.7 Hz), 63.2, 62.5, 61.9, 40.6 (d, *J* = 24.1 Hz), 29.7 (d, *J* = 24.6 Hz), 22.6, 15.1; Anal. Calc. for $C_{15}H_{22}ClFN_5O_4P$ (+1.0 MeOH): C, 42.34; H, 5.77; N, 15.43; Found: C, 42.29; H, 5.78; N, 15.40; MS *m/z* 422 $(M+H)^+$.

(*rel*)-(2'*S*,4'*S*)-9-{(4-Fluoro-4-ethyl-tetrahydrofuran-2-yl) Guanine} Phosphonic Acid (28). Guanine nucleoside phosphonic acid **28** was prepared from **27b** by the same hydrolysis conditions used for **25**: yield 65%; UV (H_2O)

λ_{max} 253.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89 (s, 1H), 5.97 (dd, J = 5.2, 2.0 Hz, 1H), 3.89 (dd, J = 17.6, 9.6 Hz, 1H), 3.69 (dd, J = 18.0, 9.6 Hz, 1H), 2.54-2.43 (dd, J = 17.6, 9.2 Hz, 1H), 2.37 (dd, J = 16.8, 9.2 Hz, 1H), 2.26-1.95 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.6, 154.4, 152.7, 138.6, 119.5, 95.5 (d, J = 176.8 Hz), 79.8, 72.6 (d, J = 22.8 Hz), 63.0, 62.3, 42.2 (d, J = 23.8 Hz), 29.5 (d, J = 22.8 Hz), 20.2; Anal. Calc. for $C_{11}H_{15}FN_5O_5P$ (+2.0 H_2O): C, 34.47; H, 4.99; N, 18.27; Found: C, 34.51; H, 5.02; N, 18.25; MS *m/z* 348 $(M+H)^+$.

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