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# Synthesis of Novel 2'-Spirocyclopropanoid 4'-Deoxythreosyl Phosphonic Acid Nucleoside Analogues

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Efficient synthetic route to novel 2'-spirocyclopropanoid 4'-deoxythreosyl phosphonic acid nucleosides was described from 1,4-dihydroxy-2-butene. Cyclopropane moiety was prepared *via* ester enolate alkylation using (2-chloroethyl)dimethylsulfonium iodide. Synthesized nucleoside analogues **16**, **19**, **23** and **26** were tested for *anti*-HIV activity as well as cytotoxicity. However, none of them showed any *anti*-HIV activity or cytotoxicity up to 100 μM.

**Key Words :** Antiviral agent, Spironucleoside, Deoxythreosyl nucleoside, Phosphonic acid nucleoside

## Introduction

Phosphorus-modified nucleoside analogues, bearing a phosphonate group in the sugar moiety, have shown potent antiviral activity.[1] 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 nucleosides[2] such as PMDTA (**1**) and PMDTT (**2**) have been synthesized (Figure 1) because they can be assembled from natural precursor molecules.[3] Recently, we have synthesized threosyl 5'-deoxyphosphonic acid purine analogues.[4] 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.[5]

Various attempts to improve the selectivity index have led to rigid nucleoside analogues modified in their cyclopentane ring system by introduction of unsaturations, sometimes with an exomethylene moiety in 6'-position. Recently, nucleoside with an exomethylene or with a spirocyclopropane moiety in place of carbon atom of the furanose ring was reported to show antiviral activity. Among these compounds, entecavir[6] (**3**) is being clinically used as *anti*-HBV drugs (Figure 1). Furthermore, Chu *et al*. reported enantiomeric synthesis of 6'-spirocyclopropyl carbocyclic nucleoside (**4**) as potent *anti*-HCV agent.[7]

In the literature, several 5'-phosphate isosteres have been adopted to prepare nucleoside phosphonates. As shown in Figure 1, compounds (**5**)[8] and (**6**)[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. The potent antiviral activity of phosphonylated nucleobases is ascribed to their intracellular phosphorylation to their diphosphates and to refractory incorporation of the modified nucleosides in nucleic acids.[10]

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.[11] 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 for antiviral activity.[12] These atoms for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[13]

Stimulated by these findings that 6'-modified and threosyl nucleosides as well as 5'-deoxynucleoside phosphonic acid have excellent biological activities, we sought to synthesize a novel class of nucleosides comprising 2'-spirocyclopropanoid 4'-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.

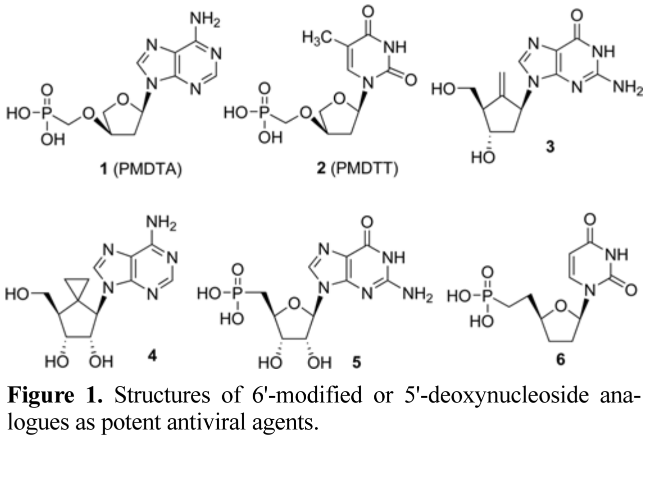



**Figure 1.** Structures of 6'-modified or 5'-deoxynucleoside analogues as potent antiviral agents.

## Results and Discussions

As shown in Scheme 1, the target compounds were prepared from 1,4-dihydroxy-2-butene **7** through an acyclic synthesis route.[14] Cyclopropylation of ester **8** was effected through a enolate intermediate followed by alpha-alkylation using (2-chloroethyl)-dimethylsulfonium iodide and potassium *tert*-butoxide[15] to give a cyclopropanoid **9**. The lactone derivative **10** was prepared from **9** *via* desilylation and cyclization in a 54% yield. The lactone **10** was reduced using DIBALH in toluene at –78 °C to give lactol **11**, which was acetylated in pyridine to furnish the key intermediate **12** as a glycosyl donor. The synthesis of adenine nucleoside was carried out by condensation of compound **12** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivative **13a** and **13b**, respectively. A complete NOE study allowed an unambiguous determination of their relative stereochemistry (Figure 2). For compound **13b**, strong NOE (0.9%) of H-1' ↔ CH-3', which showed 1',3'-*cis* relationships, was observed. According to this result, 3'-vinyl and 1'-purine base of **13b** were located on the b face. On the other hand, for **13a** compound, weak NOE (0.6%), such as H-1' ↔ CH-3', were assigned to the 1',3'-*trans* relationships.

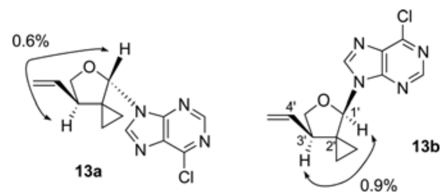


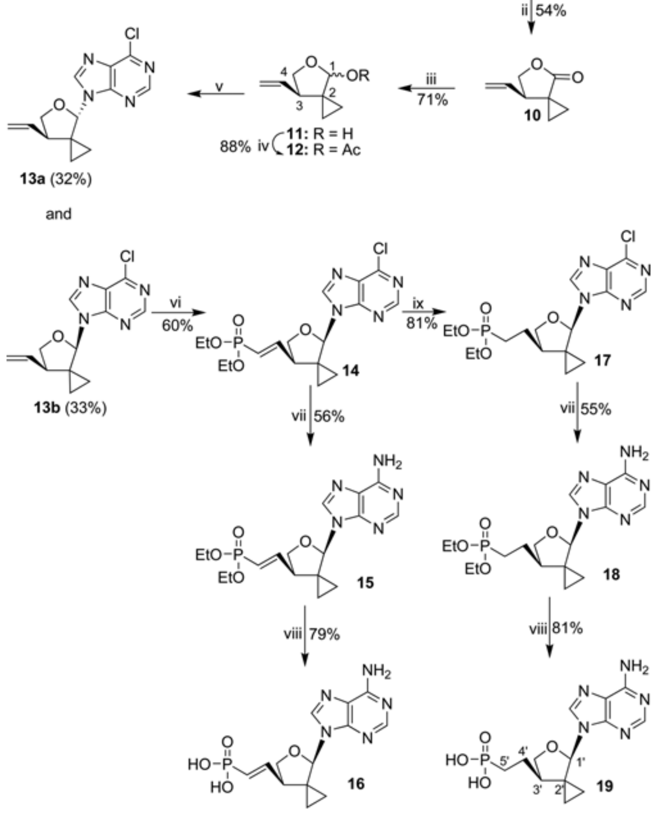
**Figure 2.** NOE differences between the proximal hydrogens of **13a** and **13b**.

Cross-metathesis[16] of **13b** with diethyl vinylphosphonate using 2nd generation Grubbs catalyst[17] gave (*E*)-vinylidene phosphonate nucleoside analogue **14** in a 60% yield. The stereochemistry of the olefin was confirmed $^1$H NMR and $^{31}$P NMR spectroscopy. The coupling constants of the *E* and Z olefinic protons ($J_{\text{Htrans-P}}$ = 22.5 Hz *vs* $J_{\text{Hcis-P}}$ = 41.5 Hz) were readily characterized. The coupling constant of the olefinic protonsThe chlorine group of purine analogue **14** was then converted to amine with methanolic ammonia at 63 °C to give a corresponding adenosine phosphonate derivative **15**, which was hydrolyzed by treatment with bromotrimethylsilane in $CH_3CN$ in the presence of 2,6-lutidine to give an adenosine phosphonic acid derivative **16**.[18] The vinylidene phosphonate **14** was saturated in transfer catalytic hydrogenation conditions to give ethyl phosphonate nucleoside analogue **17** in a 81% yield. Adenine phosphonic acid analogue **19** was prepared through the similar reaction conditions such as ammonolysis and hydrolysis described for the preparation of **16**.

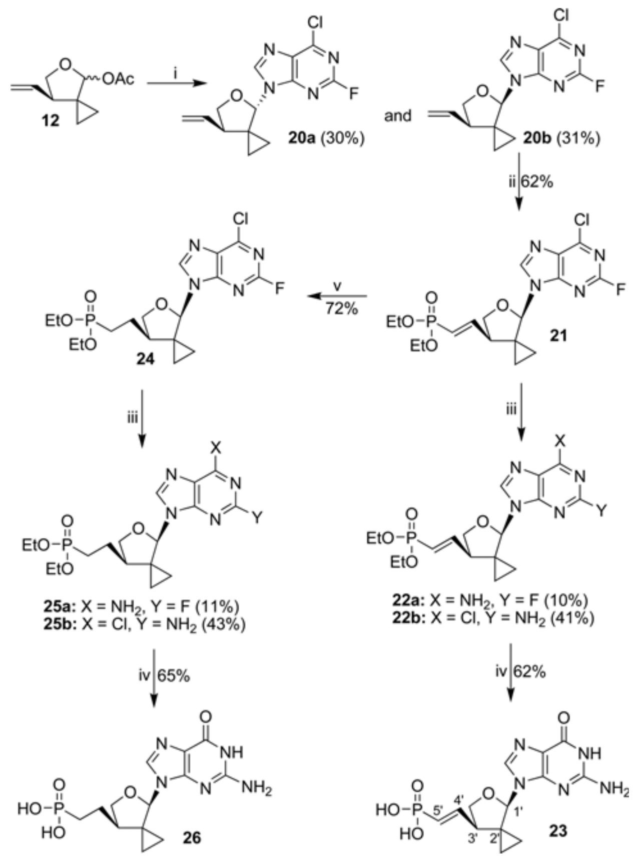
For the synthesis of guanine analogues, 2-fluoro-6-chloropurine[19] was condensed with glycosyl donor in the similar conditions used for the condensation of 6-chloropurine. Vorbruggen coupling[20] of the acetate **12** with 2-fluoro-6-chloropurine gave analogue **20a** (30%) and **20b** (31%), respectively. Cross-metathesis of **20b** and diethylvinylphosphonate gave **21** in a 62% yield. A complete NOE study allowed an unambiguous determination of their relative stereochemistry as described for **13a** and **13b**.

Bubbling ammonia into the compound **21** gave separable 2-fluoro-6-aminopurine **22a** (10%) and 2-amino-6-chloropurine **22b** (41%), respectively.[21] They are readily identified by UV spectral data. Fluorine acts as better leaving group than chlorine in nucleophilic aromatic substitution. 2-Amino-6-chloropurine derivative **22b** was treated with TMSBr and 2,6-lutidine to provide phosphonic acid and sequentially which was treated with sodium methoxide and 2-mercaptoethanol in methanol to give desired guanine vinylidene phosphonic acid **23** in a 62% yield (Scheme 2).[22] The guanine phosphonate **26** was synthesized from **21** *via* transfer catalytic hydrogenation, ammonolysis and hydrolysis using the similar conditions as described for the synthesis of **23**.

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.[23] The synthesized compounds **16**, **19**, **23**



**Scheme 1.** Synthesis of 2'-modified threosyl-4'-deoxyphosphonic acid adenine analogues.
Reagents: i) $ClCH_2CH_2SMe_2I$, KI, *t*-BuOK, *t*-BuOH; ii) TBAF, THF; iii) DIBALH, toluene, –78 °C; iv) $Ac_2O$, pyridine; v) silylated 6-chloropurine, TMSOTf, DCE; vi) diethyl vinylphosphonate, Grubbs cat.(II) $CH_2Cl_2$; vii) $NH_3$/MeOH; viii) TMSBr, 2,6-lutidine, $CH_3CN$; ix) Pd/C, cyclohexene, MeOH.




**Scheme 2.** Synthesis of 2'-modified threosyl-4'-deoxyphosphonic acid guanine analogues.
Reagents: i) silylated 2-fluoro-6-chloropurine, TMSOTf, DCE; ii) diethyl vinylphosphonate, 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.

and **26** were tested against HIV-1. However, none of them showed antiviral activity and cytotoxicity up to 100 μM (Table 1). This result indicates that the virus might not 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. Briefly, uninfected phytohemagglutinin-stimulated human PBMCs were infected with HIV-1 (strain LAV-1) (about 63,000 disintegrations of RT activity per minute per $10^7$ cells per 10 mL of medium) the drugs were then added to duplicate or triplicate cultures. Uninfected and untreated PBMCs were grown in parallel at equivalent cell concentrations as controls. The cultures were maintained in a humidified 5% $CO_2$-95% air incubator at 37 °C for 6 days after infection, at which point all cultures were sampled for supernatant RT activity. The supernatant was clarified, and the viral particles were then pelleted at 40,000 rpm for 30 min by using a rotor (70.1 Ti; Bechman Instruments, Inc., Fullerton, Calif.) and suspended in virus-disrupting buffer. The RT assay was performed by a modification of the method of Spira *et al.*[24] in 96-well microdilution plates by using $(rA)_n\cdot(dT)_{12-18}$ as the template primer. The RT results were expressed in disintegrations per minute per milliliter of originally clarified supernatant.[25] The compounds were evaluated for their potential toxic effects on uninfected phytohemagglutinin-stimulated human PBMCs and also in CEM and Vero cells. PBMCs were obtained from whole blood of healthy HIV-1 and hepatitis B virus-seronegative volunteers and collected by single-step Ficoll-Hypaque discontinuous gradient centrifugation. The CEM cells were maintained in RPMI 1640 medium supplemented with 20% heat-inactivated fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 μg/mL). The PBMCs and CEM cells were cultured with and without drug for 6 days, at which time portion were counted for cell proliferation and viability by the trypan blue exclusion method.[26] Only the effects on cell growth are reported, since these correlated well with cell viability. The toxicity of the compounds in Vero cells was assessed after 3 days of treatment with a hemacytometer.[27]

**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 |
| **16** | 62.8 | 95 | >100 | >100 | >100 |
| **19** | 49.2 | 80 | >100 | >100 | >100 |
| **23** | 66 | 95 | >100 | >100 | >100 |
| **26** | 80 | 95 | >100 | >100 | >100 |
| PMEA | 5.0 | ND | >100 | 40.0 | >100 |
| AZT | 0.128 | ND | >100 | 12.6 | 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.

## Conclusions

Based on the potent *anti*-HIV activity of 6'-electropositive nucleosides as well as threosyl phosphonic acid nucleoside analogues, we have designed and successfully synthesized novel 2'-spirocyclopropanoid 4'-deoxyphosphonic acid nucleo-

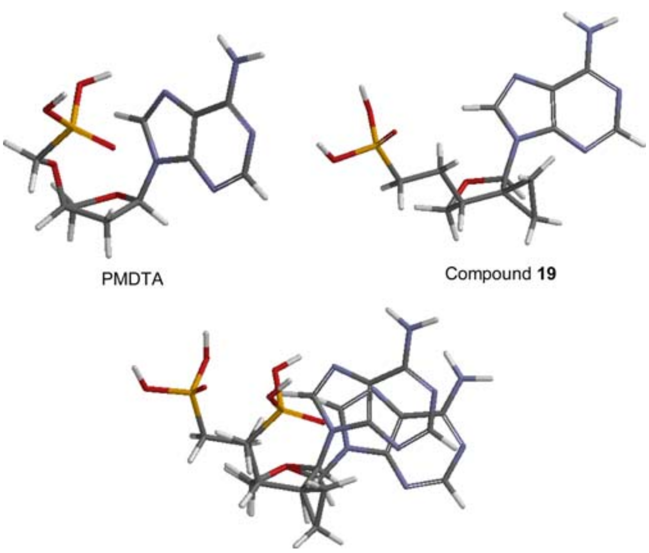



**Figure 3.** Superimpose of PMDTA **1** and **19**.

side analogues starting from 1,4-dihydroxy-2-butene. None of the synthesized nucleosides exhibits significant antiviral activity up to 100 μM. As shown in Figure 3, superimposed modeling of PMDTA (**1**) and **19** do not shows any similarity with two parts such as adenine base and phosphonic acid moiety. Furthermore, the sugar puckering of compound **19** is not positioned closer to that of adenine analogue PMDTA (**1**). Energy minimization was optimized with the framework of the density functional theory (DFT), with Spartan modeling software. The B3LYP functional with 6-31G* basis set was employed.

## 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.

**(±)-1-[1-(*t*-Butyldimethylsilanyloxymethyl) Allyl] Cyclo-Propanecarboxylic Acid Ethyl Ester (9).** A solution of ester derivative **8** (444 mg, 1.63 mmol) in *t*-butyl alcohol (5.0 mL) was added to a stirred mixture of potassium *t*-butoxide (738 mg, 6.60 mmol) in *t*-butyl alcohol (5.0 mL). After the mixture was stirred at room temperature for 20 min, potassium iodide (546 mg, 3.3 mmol) and (2-chloroethyl)dimethylsulfonium iodide (768 mg, 3.06 mmol) were added in portions under a stream of nitrogen. The mixture was stirred at room temperature for 2.0 h, diluted with saturated $NH_4Cl$ solution (50 mL), and extracted with ether (2 × 120 mL). The combined organic layer was washed with brine, dried under anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:20) on silica gel to give cyclopropanoid **9** (150 mg, 31%): $^1H$ NMR ($CDCl_3$, 300 MHz) δ 5.72-5.68 (m, 1H), 5.04-4.96 (m, 2H), 4.15 (q, $J$ = 6.8 Hz, 2H), 3.81 (m, 2H), 2.89 (m, 1H), 1.32 (m, $J$ = 6.8 Hz, 3H), 1.01-0.96 (m, 2H), 0.82 (s, 9H), 0.27-0.21 (m, 2H), 0.02 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 184.3, 143.2, 115.1, 65.3, 61.3, 51.4, 25.5, 24.1, 18.4, 10.2, −5.3; MS *m/z* 299 $(M+H)^+$.

**(±)-3-Vinyl-2-spiropropyl-dihydrofuran-1-one (10).** To a solution of **9** (1.1 g, 3.68 mmol) in THF (6 mL), TBAF (4.4 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, 8:1) to give **10** (274 mg, 54%): $^1H$ NMR ($CDCl_3$, 300 MHz) δ 5.71-5.67 (m, 1H), 5.04-4.98 (m, 2H), 4.34 (dd, $J$ = 6.6, 10.2 Hz, 1H), 4.24 (dd, $J$ = 8.2, 10.2 Hz, 1H), 2.78 (m, 1H), 1.02 (m, 2H), 0.55 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 184.8, 143.6, 115.3, 71.4, 44.3, 33.8, 15.7, 10.4; MS *m/z* 139 $(M+H)^+$.

**(±)-3-Vinyl-2-spiropropyl-dihydrofuran-1-ol (11).** To a cooled (-78 °C), stirred solution of lactone **10** (450 mg, 3.25 mmol) in dry toluene (10 mL) was added dropwise a 1.0 M solution of diisobutylaluminium hydride (DIBALH) (3.58 mL, 3.58 mmol). The reaction was stirred for 20 min. at −78 °C, followed by dropwise addition of methanol (3.5 mL) and diluted with ethyl acetate (50 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, 1:12) to give **11** (323 mg, 71%) as a colorless oil: $^1H$ NMR ($CDCl_3$, 300 MHz) δ 5.74-5.68 (m, 1H), 5.47 (m, 1H), 5.03-4.95 (m, 2H), 3.77-3.68 (m, 2H), 2.53-2.49 (m, 1H), 0.98-0.95 (m, 2H), 0.35-0.30 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 141.5, 140.9, 115.4, 110.2, 109.7, 62.2, 61.8, 45.3, 40.2, 39.8, 16.3, 15.9, 10.7; MS *m/z* 141 $(M+H)^+$.

**(±)-Acetic Acid 3-Vinyl-2-spiropropyl-dihydrofuran-1-yl Ester (12).** To a solution of compound **11** (124 mg, 0.88 mmol) in anhydrous pyridine (6 mL), $Ac_2O$ (132 mg, 1.31 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 $H_2O$ (60 mL), extracted with EtOAc (2 × 60 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 **12** (142 mg, 88%) as a colorless oil: $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.22-6.19 (m, 1H), 5.75-5.70 (m, 1H), 5.04-4.96 (m, 2H), 3.76-3.70 (m, 2H), 2.52-2.48 (m, 1H), 0.94-0.90 (m, 2H), 0.34-0.29 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 171.4, 171.1, 140.8, 114.6, 114.3, 112.2, 111.9, 61.5, 61.2, 44.7, 44.2, 32.8, 32.5, 18.7, 18.4, 16.0, 15.7, 11.2, 10.8; MS *m/z* 183 $(M+H)^+$.

***(rel)*-(1'*R*,3'*S*)-9-(3'-Vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 6-chloropurine (13a) and *(rel)*-(1'*S*,3'*S*)-9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 6-chloropurine (13b).** 6-Chloropurine (226 mg, 1.48 mmol), anhydrous HMDS (15 mL), and a catalytic amount of ammonium sulfate (20 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (15 mL). To this mixture, a solution of **12** (157 mg, 0.86 mmol) in dry DCE (15 mL) and TMSOTf (327 mg, 1.48 mmol) was added, and the resulting mixture was stirred for 4 h at rt. The reaction mixture was quenched with 3.0 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 (120 mL) and extracted with $CH_2Cl_2$ (2 × 100 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, 2:1:0.03) to give compound **13a** (76 mg, 32%) and **13b** (78 mg, 33%): data for **13a**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.25 (s, 1H), 5.95 (dd, $J$ = 5.8, 2.0 Hz, 1H), 5.71-5.68 (m, 1H), 5.03-4.95 (m, 2H), 3.76 (dd, $J$ = 10.6, 6.2 Hz, 1H), 3.65 (dd, $J$ = 10.5, 8.2 Hz, 1H), 2.53 (m, 1H), 0.94 (m, 1H), 0.45 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.5, 150.9, 144.7, 141.7, 132.5, 114.5, 97.3, 64.4, 48.3, 32.1, 13.5, 7.5; Anal. Calc. for $C_{13}H_{13}ClN_4O$ (+1.0 MeOH): C, 54.46; H, 5.55; N, 18.14. Found: C, 54.48; H, 5.53; N, 18.16; MS $m/z$ 277 $(M+H)^+$. data for **13b**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.23 (s, 1H), 5.94 (m, 1H), 5.74-5.69 (m, 1H), 5.06-5.01 (m, 2H), 3.77 (dd, $J$ = 10.8, 7.8 Hz, 1H), 3.65 (dd, $J$ = 10.8, 8.8 Hz, 1H), 2.54-2.51 (m, 1H), 1.01 (m, 1H), 0.43-0.38 (m, 2H), 0.11 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 150.8, 143.9, 141.5, 133.7, 115.0, 94.8, 65.7, 47.8, 33.5, 16.4, 8.0; Anal. Calc. for $C_{13}H_{13}ClN_4O$: C, 56.42; H, 4.74; N, 20.25. Found: C, 56.45; H, 4.73; N, 20.22; MS $m/z$ 277 $(M+H)^+$.

**(*rel*)-(1'*S*,3'*S*)-Diethyl {9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 6-chloropurine} phosphonate (14).** To a $CH_2Cl_2$ (6 mL) solution of 6-chloropurine derivative **13b** (57 mg, 0.21 mmol) and diethyl vinylphosphonate (169 mg, 1.03 mmol), 2$^{nd}$-generation Grubbs catalyst (8.7 mg, 0.01 mmol) was added. The reaction mixture was refluxed for 36 h under dry argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane/MeOH, 4:1:0.05) to give **14** (51 mg, 60%) as a form: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.28 (s, 1H), 6.64 (dd, $J$ = 16.8, 20.0 Hz, 1H), 6.11 (dd, $J$ = 16.8, 20.1 Hz, 1H), 5.97 (dd, $J$ = 5.8, 1.8 Hz, 1H), 4.10-4.05 (m, 4H), 3.77 (dd, $J$ = 10.0, 6.8 Hz, 1H), 3.61 (dd, $J$ = 10.1, 8.6 Hz, 1H), 2.53-2.49 (m, 1H), 1.31-1.28 (m, 6H), 0.95 (m, 1H), 0.39-0.36 (m, 2H), 0.11 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.2, 150.5, 149.4, 144.5, 135.2, 116.1, 97.8, 65.4, 63.7, 63.2, 49.4, 32.4, 16.7, 13.5, 7.9; Anal. Calc. for $C_{17}H_{22}ClN_4O_4P$ (+1.0 MeOH): C, 48.60; H, 5.89; N, 12.59; Found: C, 48.64; H, 5.91; N, 12.63; MS $m/z$ 413 $(M+H)^+$.

**(*rel*)-(4'*S*,7'*S*)-Diethyl {9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) adenine} phosphonate (15).** A solution of **14** (115 mg, 0.28 mmol) in saturated methanolic ammonia (6 mL) was stirred overnight at 63 °C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/$CH_2Cl_2$, 1:8) to give **15** (61.7 mg, 56%) as a white solid: mp 173-175 °C; UV (MeOH) $\lambda_{max}$ 260.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.38 (s, 1H), 8.17 (s, 1H), 6.65 (dd, $J$ = 17.0, 20.2 Hz, 1H), 6.12 (dd, $J$ = 16.9, 20.2 Hz, 1H), 5.95 (dd, $J$ = 5.8, 2.0 Hz, 1H), 4.09-4.05 (m, 4H), 3.73 (dd, $J$ = 10.1, 6.8 Hz, 1H), 3.60 (dd, $J$ = 10.2, 8.6 Hz, 1H), 2.53 (m, 1H), 1.29-1.25 (m, 6H), 0.97 (m, 1H), 0.40-0.37 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.7, 152.6, 150.4, 148.7, 141.6, 119.5, 115.5, 97.8, 66.3, 63.8, 63.2, 47.6, 32.7, 14.5, 13.7, 7.7; Anal. Calc. for $C_{17}H_{24}N_5O_4P$ (+1.0 MeOH): C, 50.82; H, 6.63; N, 16.46; Found: C, 50.79; H, 6.65; N, 16.44; MS $m/z$ 394 $(M+H)^+$.

**(*rel*)-(4'*S*,7'*S*)-9-(3'-Vinyl-2'-spiropropyl-dihydrofuran-1'-yl) adenine} phosphonic acid (16).** To a solution of the phosphonate **15** (95 mg, 0.24 mmol) in anhydrous $CH_3CN$ (6 mL) and 2,6-lutidine (0.562 mL, 4.80 mmol) was added trimethylsilyl bromide (0.269 mg, 2.41 mmol). The mixture was heated overnight at 80 °C under nitrogen gas and then concentrated *in vacuo*. The residue was partitioned between $CH_2Cl_2$ (60 mL) and purified water (60 mL). The aqueous layer was washed with $CH_2Cl_2$ (2 × 60 mL) and then freeze-dried to give phosphonic acid **16** (64 mg, 79%) as a yellowish foam: UV ($H_2O$) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.35 (s, 1H), 8.18 (s, 1H), 6.66 (dd, $J$ = 17.2, 20.2 Hz, 1H), 6.18 (dd, $J$ = 17.3, 19.9 Hz, 1H), 5.96 (dd, $J$ = 1.9, 6.0 Hz, 1H), 4.97 (br s, 1H), 3.74 (dd, $J$ = 10.2, 6.6 Hz, 1H), 3.60 (dd, $J$ = 10.0, 8.6 Hz, 1H), 2.56-2.53 (m, 1H), 1.01 (m, 1H), 0.42-0.38 (m, 2H), 0.11 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 154.9, 152.8, 151.7, 149.2, 142.0, 119.6, 115.3, 99.1, 63.3, 49.5, 32.6, 14.6, 8.1; Anal. Calc. for $C_{13}H_{16}N_5O_4P$ (+1.0 $H_2O$): C, 43.95; H, 5.11; N, 19.71; Found: C, 43.97; H, 5.09; N, 19.73; MS $m/z$ 338 $(M+H)^+$.

**(*rel*)-(4'*S*,7'*S*)-Diethyl {9-(3'-ethyl-2'-spiropropyl-dihydrofuran-1'-yl) 6-chloropurine} phosphonate (17).** To a solution of vinyl phosphonate nucleoside analogue **14** (197 mg, 0.48 mmol) in methanol (8 mL) was added 10% Pd/C (8 mg) and cyclohexene (3 mL) under argon gas. The reaction mixture was refluxed for 24 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using methanol and methylene chloride (12:1) to give ethyl phosphonate analogue **17** (387 mg, 81%) as a white solid: mp 176-178 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.26 (s, 1H), 5.99 (dd, $J$ = 5.8, 1.8 Hz, 1H), 4.14-4.08 (m, 4H), 3.73 (dd, $J$ = 10.4, 6.8 Hz, 1H), 3.62 (dd, $J$ = 10.3, 8.2 Hz, 1H), 2.16-2.11 (m, 4H), 1.86 (m, 1H), 0.96 (m, 1H), 0.40 (m, 2H), 0.13 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 151.8, 151.4, 151.1, 143.6, 134.7, 96.6, 65.7, 63.7, 63.2, 47.2, 31.6, 28.3, 18.3, 13.7, 6.9; Anal. Calc. for $C_{17}H_{24}ClN_4O_4P$: C, 49.22; H, 5.83; N, 13.51; Found: C, 49.18; H, 5.81; N, 13.49; MS $m/z$ 415 $(M+H)^+$.

**(*rel*)-(4'*S*,7'*S*)-Diethyl {9-(3'-ethyl-2'-spiropropyl-dihydrofuran-1'-yl) adenine} phosphonate (18).** Transformation of 6-chloropurine to adenine derivative **18** was performed from **17** by the similar ammonolysis procedure as described for **15**: yield 55%; mp 177-179 °C; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.35 (s, 1H), 8.16 (s, 1H), 5.96 (dd, $J$ = 5.9, 1.8 Hz, 1H), 4.16-4.10 (m, 4H), 3.75 (dd, $J$ = 10.2, 6.6 Hz, 1H), 3.63 (dd, $J$ = 10.2, 8.4 Hz, 1H), 2.22-2.17 (m, 4H), 1.83 (m, 1H), 0.96 (s, 1H), 0.42-0.38 (m, 2H), 0.12 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 154.9, 152.5, 151.4, 143.5, 119.6, 97.8, 64.2, 63.2, 62.8, 45.7, 32.3, 28.5, 18.4, 14.3, 7.2; Anal. Calc. for $C_{17}H_{26}N_5O_4P$ (+1.0 MeOH): C, 50.58; H, 7.07; N, 16.38; Found: C, 50.60; H, 7.09; N, 16.40; MS $m/z$ 396 $(M+H)^+$.

**(*rel*)-(4'*S*,7'*S*)-{9-(3'-Ethyl-2'-spiropropyl-dihydrofuran-**

**1'-yl) adenine} phosphonic acid (19).** Adenine phosphonic acid **19** was synthesized from **18** using the similar hydrolysis procedure as described for **16**: yield 81%, UV ($H_2O$) $\lambda_{max}$ 260.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.36 (s, 1H), 8.17 (s, 1H), 5.99 (dd, *J* = 5.8, 2.0 Hz, 1H), 3.74 (dd, *J* = 10.4, 6.6 Hz, 1H), 3.62 (dd, *J* = 10.3, 8.4 Hz, 1H), 2.20-2.16 (m, 4H), 1.85 (m, 1H), 1.02 (m, 1H), 0.42-0.38 (m, 2H), 0.13 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.2, 152.1, 149.4, 137.8, 119.3, 97.6, 64.6, 46.8, 32.2, 27.2, 17.6, 13.8, 7.7; Anal. Calc. for $C_{13}H_{18}N_5O_4P$ (+1.0 $H_2O$): C, 46.02; H, 5.35; N, 20.64; Found: C, 46.06; H, 5.36; N, 20.62; MS *m/z* 340 $(M+H)^+$.

***(rel)*-(1'*R*,3'*S*)-9-(3'-Vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-chloropurine (20a) and *(rel)*-(1'*S*,3'*S*)-9-(3'-Vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-chloropurine (20b).** Coupling of **12** with 2-fluoro-6-chloropurine under the similar condensation conditions as described for **13** to give **20a** and **20b**, respectively: Data for **20a**: yield 30%; UV (MeOH) $\lambda_{max}$ 269.0 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H), 5.91 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.71-5.67 (m, 1H), 5.05-4.97 (m, 2H), 3.75 (dd, *J* = 10.4, 6.2 Hz, 1H), 3.60 (dd, *J* = 10.3, 8.2 Hz, 1H), 2.48 (m, 1H), 1.03 (m, 1H), 0.40-0.35 (m, 2H), 0.10 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.2 (d, *J* = 235.8 Hz), 153.0, 147.9, 145.8, 136.8, 120.4, 114.6, 97.5, 64.2, 48.5, 31.3, 13.8, 7.8; Anal. Calc. for $C_{13}H_{12}ClFN_4O$: C, 52.98; H, 4.10; N, 19.01; Found: C, 52.95; H, 4.12; N, 18.99; MS *m/z* 295 $(M+H)^+$. Data for **20b**: yield 31%; UV (MeOH) $\lambda_{max}$ 269.5 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 5.94 (dd, *J* = 6.0, 1.8 Hz, 1H), 5.71 (m, 1H), 5.05-4.96 (m, 2H), 3.75 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.65 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.49 (m, 1H), 1.01-0.98 (m, 1H), 0.39-0.35 (m, 2H), 0.12 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, *J* = 233.8 Hz), 155.4, 152.2, 144.9, 141.6, 118.5, 113.8, 98.2, 63.9, 47.2, 33.0, 15.1, 9.4, 8.2; Anal. Calc. for $C_{13}H_{12}ClFN_4O$ (+1.0 MeOH): C, 51.46; H, 4.93; N, 17.14; Found: C, 51.43; H, 4.92; N, 17.12; MS *m/z* 295 $(M+H)^+$.

***(rel)*-(1'*S*,3'*S*)-Diethyl {9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-chloropurine} phosphonate (21).** Phosphonate nucleoside analogue **21** was prepared from **20b** using the same cross-metathesis procedure as described for **14**: yield 62%; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 6.61 (dd, *J* = 16.8, 19.8 Hz, 1H), 6.18 (dd, *J* = 16.8, 20.4 Hz, 1H), 5.97 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.12-4.08 (m, 4H), 3.73 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.62 (dd, *J* = 10.3, 6.8 Hz, 1H), 2.47 (m, 1H), 0.99 (m, 1H), 0.37-0.31 (m, 2H), 0.09 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.7 (d, *J* = 221.6 Hz), 153.6, 152.4, 147.8, 144.5, 128.1, 116.1, 96.8, 62.2, 49.6, 31.3, 14.8, 10.3, 7.8; Anal. Calc. for $C_{17}H_{21}ClFN_4O_4P$ (+1.0 MeOH): C, 46.71; H, 5.44; N, 12.10; Found: C, 46.68; H, 5.45; N, 12.08; MS *m/z* 431 $(M+H)^+$.

***(rel)*-(1'*S*,3'*S*)-Diethyl {9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-aminopurine} phosphonate (22a) and *(rel)*-(1'*S*,3'*S*)-diethyl {9-(3'-vinyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-amino-6-chloropurine} phosphonate (22b).** Dry ammonia gas was bubbled into a stirred solution of **21** (220 mg, 0.51 mmol) in DME (10 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/$CH_2Cl_2$, 1:10) to give **22a** (21 mg, 10%) and **22b** (89 mg, 41%), respectively: Data for **22a**; UV (MeOH) $\lambda_{max}$ 261.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.19 (s, 1H), 7.70 (br s, $NH_2$, 2H), 6.63 (dd, *J* = 20.2, 16.8 Hz, 1H), 6.19 (dd, *J* = 20.0, 16.9 Hz, 1H), 5.98 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.13-4.09 (m, 4H), 3.77 (dd, *J* = 10.2, 8.5 Hz, 1H), 3.64 (dd, *J* = 10.2, 6.7 Hz, 1H), 2.49 (m, 1H), 1.26-1.22 (m, 6H), 0.98 (m, 1H), 0.38-0.34 (m, 2H), 0.10 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 159.9 (d, *J* = 256.8 Hz), 155.7, 152.8, 144.1, 141.6, 118.6, 115.6, 96.6, 65.8, 63.2, 62.8, 48.3, 30.7, 15.2, 8.1; Anal. Calc. for $C_{17}H_{23}FN_5O_4P$ (+1.0 MeOH): C, 48.75; H, 6.13; N, 15.79; Found: C, 48.78; H, 6.11; N, 15.81; MS *m/z* 412 $(M+H)^+$. Data for **22b**; UV (MeOH) $\lambda_{max}$ 308.0 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.13 (s, 1H), 7.68 (br s, $NH_2$, 2H), 6.66 (dd, *J* = 20.0, 17.1 Hz, 1H), 6.19 (dd, *J* = 22.2, 17.0 Hz, 1H), 5.99 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.10 (m, 4H), 3.73-3.75 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.62 (dd, *J* = 10.3, 6.8 Hz, 1H), 2.51 (m, 1H), 1.29-1.26 (m, 6H), 1.01 (m, 1H), 0.39-0.33 (m, 2H), 0.10-0.09 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 155.0, 151.8, 149.7, 147.9, 144.0, 127.8, 115.9, 98.2, 66.5, 63.5, 62.9, 47.7, 32.1, 15.7, 11.7, 8.7; Anal. Calc. for $C_{17}H_{23}ClN_5O_4P$ (+1.0 MeOH): C, 47.01; H, 5.94; N, 15.23; Found: C, 46.98; H, 5.96; N, 15.25; MS *m/z* 428 $(M+H)^+$.

***(rel)*-(1'*S*,3'*S*)-9-{(3'-Vinyl-2'-spiropropyl-dihydrofuran-1'-yl) guanine} phosphonic acid (23).** To a solution of **22b** (216 mg, 0.51 mmol) dry $CH_3CN$ (18 mL) and 2,6-lutidine (1.88 mL, 17.6 mmol) was added trimethylsilyl bromide (1.35 g, 8.83 mmol) at room temperature. After this mixture was stirred for 24 h, the solvent was removed, coevaporating three times with methanol. The residue was dissolved in MeOH (17.0 mL) and 2-mercaptoethanol (158 mg, 2.03 mmol) and NaOMe (107.52 mg, 2.03 mmol) was added to the mixture. The mixture was refluxed for 16 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 **23** (110.6 mg, 62%) as a yellowish form. UV ($H_2O$) $\lambda_{max}$ 254.5 nm; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.11 (br s, NH, 1H), 8.17 (s, 1H), 7.09 (br s, $NH_2$, 2H), 6.66 (dd, *J* = 20.1, 17.2 Hz, 1H), 6.16 (dd, *J* = 20.2, 17.2 Hz, 1H), 5.95 (dd, *J* = 6.0, 1.9 Hz, 1H), 3.74 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.62 (dd, *J* = 10.5, 6.4 Hz, 1H), 2.56-2.54 (m, 1H), 0.98 (m, 1H), 0.39 (m, 2H), 0.09 (m, 1H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 157.4, 154.3, 152.6, 149.7, 136.4, 118.4, 115.5, 88.3, 64.2, 49.2, 32.0, 16.0, 8.9, 7.8; Anal. Calc. for $C_{13}H_{16}N_5O_5P$ (+2.0 $H_2O$): C, 40.10; H, 5.18; N, 17.99; Found: C, 40.08; H, 5.17; N, 18.01; MS *m/z* 354 $(M+H)^+$.

***(rel)*-(1'*S*,3'*S*)-Diethyl {9-(3'-ethyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-chloropurine} phosphonate (24).** Compound **24** was synthesized from **21** by the similar catalytic hydrogenation procedure as described for **17**: yield 72%; UV (MeOH) $\lambda_{max}$ 170.5 nm; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1H), 5.94 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.16-

4.11 (m, 4H), 3.74 (dd, $J$ = 10.4, 8.2 Hz, 1H), 3.60 (dd, $J$ = 10.3, 6.8 Hz, 1H), 2.20-2.16 (m, 4H), 1.99 (m, 1H), 1.00 (m, 1H), 0.34-0.30 (m, 2H), 0.10-0.08 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 158.1 (d, $J$ = 232.4 Hz), 153.7, 145.5, 136.3, 121.8, 97.8, 64.8, 63.6, 62.9, 47.1, 32.3, 28.4, 18.6, 14.7, 8.8.; Anal. Calc. for $C_{17}H_{23}ClFN_4O_4P$ (+1.0 MeOH): C, 46.51; H, 5.85; N, 12.05; Found: C, 46.48; H, 5.84; N, 12.03; MS $m/z$ 433 $(M+H)^+$.

**(*rel*)-(1'*S*,3'*S*)-Diethyl {9-(3'-ethyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-fluoro-6-aminopurine} phosphonate (25a) and (*rel*)-(1'*S*,3'*S*)-diethyl {9-(3'-ethyl-2'-spiropropyl-dihydrofuran-1'-yl) 2-amino-6-chloropurine} phosphonate (25b).** Ammonolysis of **24** was performed using the similar procedure as described for **22a** and **22b**: Data for **25a**: yield 11%; UV (MeOH) $\lambda_{max}$ 262.0 nm; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 8.28 (s, 1H), 7.71 (br s, $NH_2$, 2H), 5.98 (dd, $J$ = 5.9, 1.8 Hz, 1H), 4.18-4.14 (m, 4H), 3.74 (dd, $J$ = 10.2, 8.6 Hz, 1H), 3.63 (dd, $J$ = 10.2, 7.2 Hz, 1H), 2.30- 2.24 (m, 4H), 1.88 (m, 1H), 1.05-1.00 (m, 1H), 0.39-0.36 (m, 2H), 0.11-0.08 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 160.4 (d, $J$ = 258.2 Hz), 156.2, 151.7, 142.8, 119.2, 99.5, 65.2, 63.8, 63.4, 46.2, 32.4, 28.9, 18.6, 14.3, 7.3; Anal. Calc. for $C_{17}H_{25}FN_5O_4P$ (+1.0 MeOH): C, 48.54; H, 6.56; N, 15.72; Found: C, 48.55; H, 6.58; N, 15.70; MS $m/z$ 414 $(M+H)^+$. Data for **25b**: yield 43%; UV (MeOH) $\lambda_{max}$ 307.5 nm; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 8.15 (s, 1H), 7.67 (br s, $NH_2$, 2H), 5.95 (dd, $J$ = 6.0, 1.6, Hz, 1H), 4.20-4.16 (m, 4H), 3.76 (dd, $J$ = 10.6, 8.0 Hz, 1H), 3.61 (dd, $J$ = 10.5, 6.6 Hz, 1H), 2.20-2.16 (m, 4H), 1.82 (m, 1H), 0.93 (m, 1H), 0.40-0.37 (m, 2H), 0.12 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 156.8, 152.9, 150.7, 143.2, 125.2, 95.6, 65.2, 63.0, 62.5, 46.2, 31.8, 28.3, 18.7, 16.2, 10.3, 8.4; Anal. Calc. for $C_{17}H_{25}ClN_5O_4P$ (+1.0 MeOH): C, 46.80; H, 6.33; N, 15.16; Found: C, 46.84; H, 6.34; N, 15.14; MS $m/z$ 430 $(M+H)^+$.

**(*rel*)-(1'*S*,3'*S*)-9-{(3'-Ethyl-2'-spiropropyl-dihydrofuran-1'-yl) guanine} phosphonic acid (26).** Guanine nucleoside phosphonic acid **26** was prepared from **25b** by the same hydrolysis conditions used for **23**: yield 65%; UV ($H_2O$) $\lambda_{max}$ 253.0 nm; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 10.7 (br s, NH, 1H), 8.08 (s, 1H), 7.05 (br s, $NH_2$, 2H), 5.95 (dd, $J$ = 6.0, 1.9 Hz, 1H), 3.75 (dd, $J$ = 10.2, 8.5 Hz, 1H), 3.62 (dd, $J$ = 10.3, 6.4 Hz, 1H), 2.22-2.17 (m, 4H), 1.89 (m, 1H), 0.99 (m, 1H), 0.37-0.33 (m, 2H), 0.09-0.07 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 157.2, 153.9, 152.2, 135.8, 116.9, 88.2, 65.3, 46.2, 31.8, 28.9, 19.0, 15.2, 10.2, 8.7; Anal. Calc. for $C_{13}H_{18}N_5O_5P$ (+1.0 $H_2O$): C, 41.83; H, 5.40; N, 18.76; Found: C, 41.79; H, 5.38; N, 18.77; MS $m/z$ 356 $(M+H)^+$.

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