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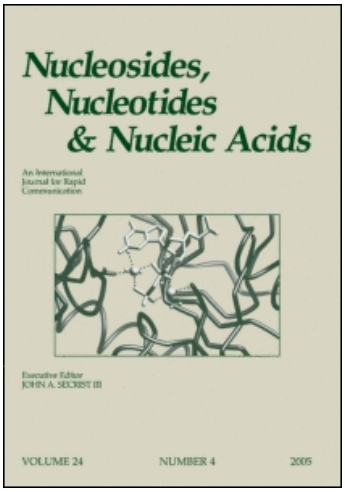

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Short Synthesis and Antiviral Activity of Acyclic Phosphonic Acid Nucleoside Analogues

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SHORT SYNTHESIS AND ANTIVIRAL ACTIVITY OF ACYCLIC PHOSPHONIC ACID NUCLEOSIDE ANALOGUES

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□ *An efficient route for synthesizing novel allylic and cyclopropanoid phosphonic acid nucleoside analogues is described. The condensation of the bromine derivatives* ***6*** *and* ***18*** *with nucleoside bases (A, U, T, C, G) under standard nucleophilic substitution and deprotection conditions, afforded the target phosphonic acid nucleoside analogues. These compounds were evaluated for their antiviral properties against various viruses. Cyclopropanoid phosphonic adenine nucleoside analogue* ***23*** *showed significant anti-HIV activity.*

Keywords PMPA; PMCG; HPMPC; PMEA; antiviral agents

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INTRODUCTION

The discovery of acyclovir[1] as an anti-herpes agent ignited the search for new antiviral nucleosides with a disconnected chain resulting from the omission of various bonds from the pentose or cyclopentane rings. During the past 20 years, many new synthetic schemes for acyclic nucleoside analogues[2] have been reported, and many of these molecules have exhibited promising antiviral activity,[3] particularly, ganciclovir,[4] a drug of choice for the treatment of HCMV infections, especially HCMV retinitis, which causes blindness in AIDS patients, and penciclovir,[5] which has a broad antiviral spectrum that includes anti-HSV-1 and 2, anti-HBV, and anti-VZV activity. These acyclic nucleosides are efficiently phosphorylated by viral TK (thymidine kinases) to the corresponding monophosphates and further phosphorylated by cellular kinases to the corresponding triphosphates. The efficacy of these drugs is limited by their toxicity and side effects, as well as the emergence of many drug-resistant viral strains.[6] Therefore, there is a

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need for less toxic and more effective antiviral agents that do not exhibit any cross-resistance with existing drugs.

Acyclic phosphonate nucleosides,[7] in which the 5′-hydroxy group has been replaced by either a phosphonate group or a phosphonate ester, can act as a stable mimic of nucleoside monophosphates and undergo further phosphorylation in cells to produce species that are analogous to nucleoside triphosphates and can inhibit polymerases. The advantage of these compounds is that primary phosphorylation of the parent nucleoside is unnecessary, which is often a stumbling block in attaining active compounds. Many new synthetic schemes for acyclic nucleoside phosphonate and phosphonic acid analogues have produced molecules with promising antiviral activity.[8] Among these analogues, the adenine derivative 9-(2-phosphonylmethoxyethyl) adenine (Adefovir, PMEA) and its congeners are effective in in vitro systems and in vivo.[9] Also, the cytosine analogue, HPMPC(Cidofovir), shows activity against herpes viruses, including CMV, adenoviruses, and pox viruses.[10] The recent FDA approval of bis(POC)PMPA (Tenofovir disoproxil)[11] as an anti-HIV agent highlights the need for further research into acyclic phosphonate analogues as potential therapeutic agents (Figure 1).

A cyclopropanoid version of acyclic nucleosides, PMCG,[12] {9-[1-phosphonomethoxy cyclopropyl) methyl] guanine} exhibits potent antiviral activity against HIV and HBV. As a part of our ongoing research into drug discovery and because of previous work on acyclic nucleoside analogues, we synthesized novel phosphonic analogues and examined their potential antiviral activity.

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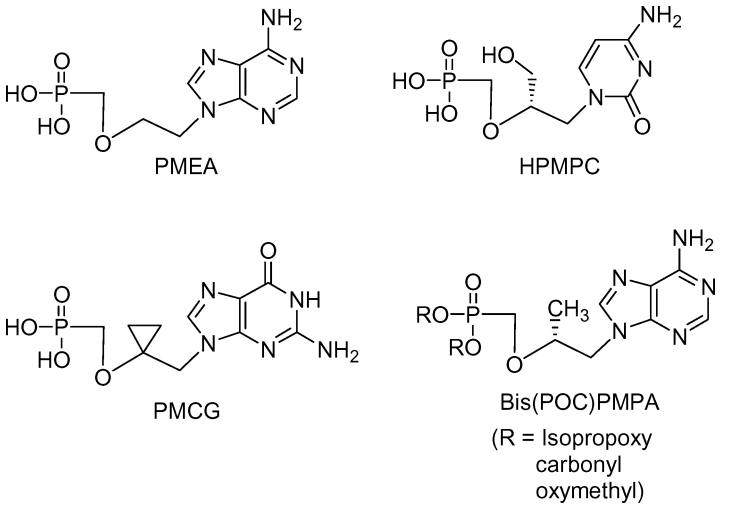
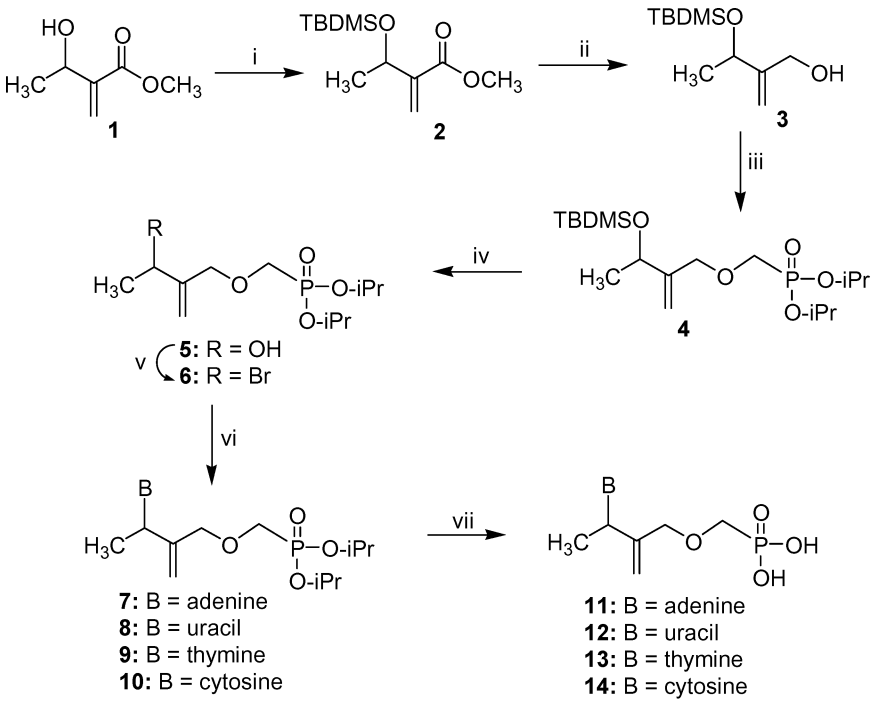


FIGURE 1 Structures of potent acyclic phosphonic antiviral agents.



Reagents: i) TBDMSCl, imidazole, CH_2Cl_2;ii) DIBALH, CH_2Cl_2; iii) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; iv) TBAF, THF; v) PPh_3, NBS, CH_2Cl_2; vi) bases, K_2CO_3, 18-*C*-6, DMF, vii) $(CH_3)_3SiBr$, CH_2Cl_2.

SCHEME 1 Synthesis of allylic phosphonic nucleosides.

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RESULTS AND DISCUSSION

First, the commercially available acrylic acid methyl ester derivative **1** was selected as a starting material for the synthesis of target allylic phosphonic nucleosides (Scheme 1). Silylation of the hydroxyl group of **1** gave an ester derivative **2**, which was reduced to allylic alcohol derivative **3** using diisobutylaluminum hydride (DIBALH). The corresponding hydroxy group of compound **3** was phosphonylated by treating it with diisopropyl bromomethylphosphonate in the presence of LiO*t*-Bu and LiI in anhydrous DMF solvent to give allylic phosphonate analogue **4**. A silyl protection group was removed by treatment with tetrabutylammonium fluoride (TBAF) to provide compound **5**. We attempted the mesylation of **5** because mesylate is a useful reactive intermediate for the replacement of a free hydroxyl group with nucleosidic bases. However, the mesylate that appeared in the reaction mixture disappeared during the work-up, resulting in decomposition into an unidentifiable byproduct and requiring an alternative coupling method. Then, alcohol derivative **5** was brominated by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine to give key

intermediate **6**.[13] The direct coupling of the bromine derivative **6** with the bases (A, U, T, C) in DMF containing potassium carbonate (K_2CO_3) and 18-crown-6 as catalysts provided the desired N^9-alkylated adenine derivative **7** in the case of purine base[14] and N^1-alkylated derivatives (**8**∼**10**) in the case of pyrimidine bases.[15] The *N*-9 isomer of the adenine base was confirmed by UV spectra data [λ_{max} (MeOH) 261 nm], which was in good agreement with those of the appropriate model compounds. The removal of the diisopropyl groups of compounds **7**∼**10** was accomplished using trimethylsilyl bromide[16] to afford the desired nucleoside phosphonic acids **11**∼**14**.

For the synthesis of the allylic guanine derivative **31**, the bromide **6** was coupled with the sodium salt of 2-amino-6-chloropurine, which was prepared by adding sodium hydride to 2-amino-6-chloropurine in DMF. The isopropyl groups of compound **27** was removed by a similar treatment of $(CH_3)_3SiBr$ to that used for compound **7** to produce compound **29**, which was subjected to hydrolysis conditions in a 2 N HCl solution to give the desired guanine phosphonic acid nucleoside **31** (Scheme 2).

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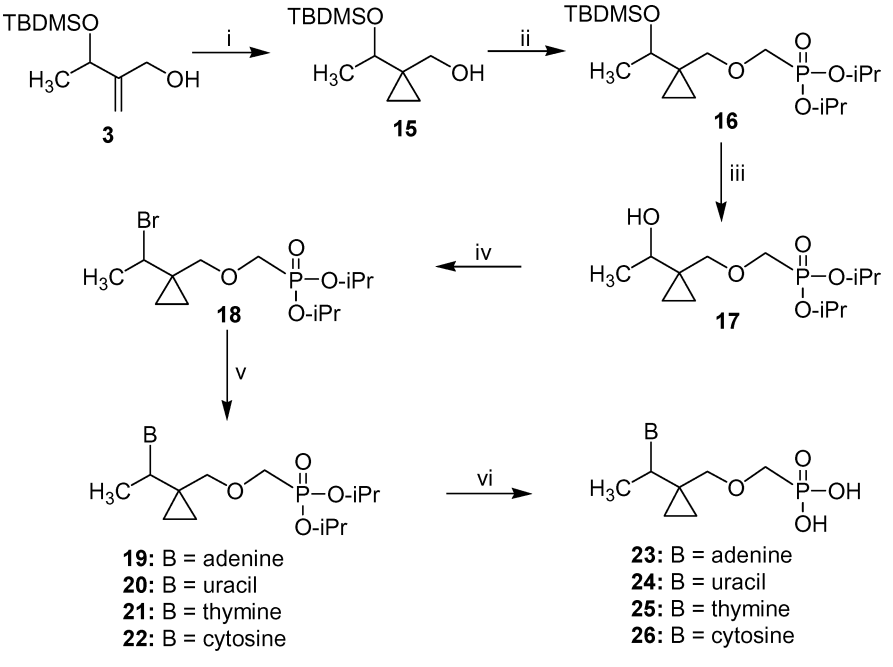
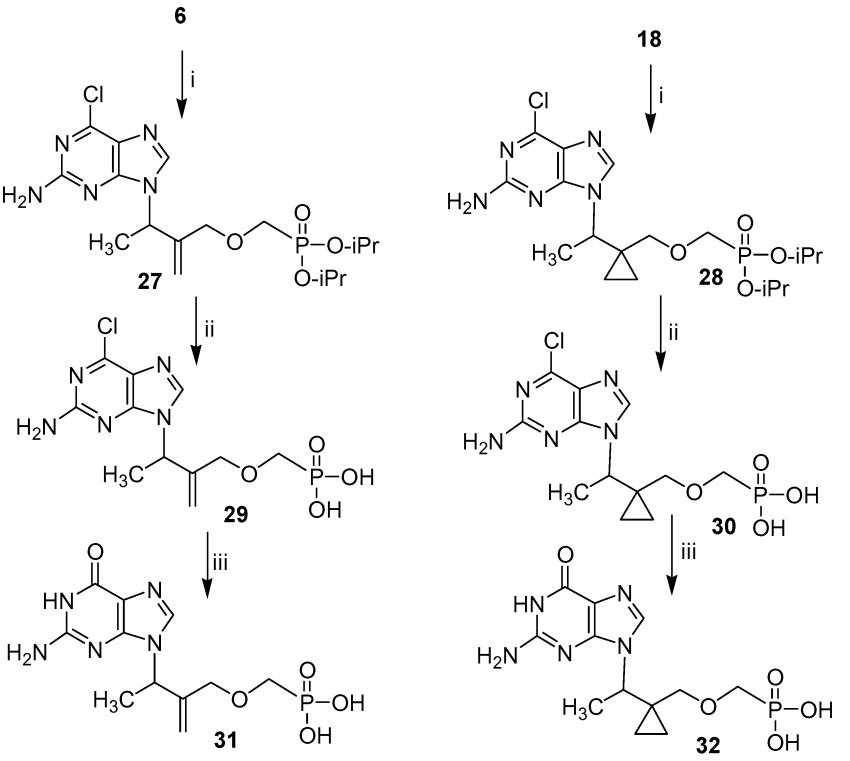


Reagents: i) $Zn(Et)_2$. CH_2I_2, CH_2Cl_2; ii) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; iii) TBAF, THF; iv) PPh_3, NBS, CH_2Cl_2; v) Bases, K_2CO_3, 18-*C*-6, DMF; vi) $(CH_3)_3SiBr$, CH_2Cl_2.

SCHEME 2 Synthesis of cyclopropanoid phosphonic nucleosides.



SCHEME 3 Synthesis of guanine phosphonic nucleosides.

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The synthesis of cyclopropanoid phosphonic nucleosides (Scheme 3), the intermediate allylic alcohol **3** described in Scheme 1 was subjected to Simmons-Smith carbenoid cycloaddition[17] using $Zn(Et)_2$ and CH_2I_2 to provide cyclopropanoid alcohol **15.** The conversion of the allylic alcohol **5** to the bromide derivative **15** was accomplished by a similar reaction described for the allylic bromide **6**. The targeted cyclopropanoid phosphonic acid nucleosides (A, U, T, C, G) were synthesized by the same procedure described in Schemes 1 and 3.

All the synthesized compounds were tested against several viruses such as HIV-1, HSV-1, and Coxsackie B3 (Table 1). The cyclopropanoid adenine phosphonic acid nucleoside **23** exhibited significant anti-HIV activity in the CEM cell line ($EC_{50} = 10.6$ μmol).

In Vitro Anti-HIV-1 Activity

The assay involved the killing of T4-lymphocytes by HIV-1. T4 lymphocytes were exposed to HIV at a virus-to-cell ratio of approximately 0.05

and treated with the compounds, dissolved in dimethylformamide, at doses ranging from 10^{-8} to 10^{-4} M. A complete cycle of virus reproduction is necessary to obtain the required cell killing (incubation at 37°C in a 5% carbon dioxide atmosphere for 6 days). Uninfected cells with the compounds served as a toxicity control, whereas the infected and uninfected cells without the compound served as basic controls. After incubation, the tetrazolium salt XTT was added to all wells, and cultures were incubated to allow formazan color development by viable cells. Formazan production was measured spectrophotometrically and protective activity was confirmed by microscopy. The effect of each compound on cell growth of HIV-infected and uninfected cells was compared to that of untreated uninfected cells. All tests were compared with AZT as a positive control performed under identical conditions.[18]

The arrangement between the purine base and the phosphorus atom may be conformationally similar to the natural nucleosides containing ribose, which would enhance the level of phosphorylation by kinases to produce the active diphosphate form. The antiviral activity in this series could provide a rationale for further development of acyclic cyclopropanoid phosphonic acid derivatives.

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EXPERIMENTAL

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier

TABLE 1 Antiviral activity of the synthesized compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	CoxB3 EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
11	80	77.3	>100	>100
12	26.9	>100	95.1	>100
13	>100	>100	61.2	>100
14	67.1	65.8	>100	>100
23	10.6	70	58	98
24	>100	>100	>100	>100
25	86.5	47.3	80.3	99
26	37.2	>100	89.5	>100
31	32.4	74.1	41.2	98
32	27.7	60.2	25.1	98
AZT	0.001	ND	ND	0.5
GCV	ND	1.25	ND	>10
RBV	ND	ND	30.77	>300

AZT: azidothymidine; GCV: ganciclovir; RBV: ribavirin
ND: not determined
EC_{50} (μM): concentration required to inhibit 50% of the virus-induced cytopathicity
CC_{50} (μM): concentration required to reduce cell viability by 50%.

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). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Mass spectra were measured with FAB-MS modified Finninggan MAT 312 spectrometer. 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.

(±)-2-[1-(tert-Butyldimethylsilanyloxy)ethyl]acrylic acid methyl ester (2): *t*-Butyldimethylsilyl chloride (6.37 g, 42.26 mmol) was added to a stirred solution of starting material **1** (5.0 g, 38.42 mmol) and imidazole (5.23 g, 76.84 mmol) in CH_2Cl_2 (150 mL) at 0°C. The mixture was stirred at room temperature for 5 hours, and quenched by adding a $NaHCO_3$ solution (20 mL). The mixture was extracted using EtOAc (250 mL)/water (250 mL), dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give compound **2** (8.54 g, 91%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (s, 1H), 5.89 (s, 1H), 4.64–4.58 (m, 1H), 3.69 (s, 3H), 1.27 (m, 3H), 0.89 (m, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.95, 164.76, 123.57, 66.81, 51.65, 25.80, 24.65, 18.19, -5.10.

(±)-2-[1-(tert-Butyldimethylsilanyloxy)ethyl]-prop-2-en-1-ol (3): To a solution of **2** (3.5 g, 14.32 mmol) in CH_2Cl_2 (100 mL), DIBALH (30.07 mL, 1.0 M solution in hexane) was added slowly at −20°C, and stirred for 2 hours at the same temperature. To the mixture, methanol (30 mL) was added. The mixture was stirred at room temperature for 2 hours, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give alcohol **3** (2.97 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.96 (s, 2H), 4.37 (dd, J = 12.3, 6.3 Hz, 1H), 4.20 (d, J = 13.2, 1H), 4.04 (d, J = 13.2 Hz, 1H), 2.26 (br s, 1H), 1.29 (m, 3H), 0.87 (m, 9H), 0.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 151.30, 110.42, 71.71, 63.74, 25.72, 23.71, 18.57, -5.19.

(±)-[2-(tert-Butyldimethylsilanyloxy)ethyl-allyloxymethyl] phosphonic acid diisopropyl ester (4): To a solution of **3** (1.146 g, 5.3 mmol) in 8 mL of DMF was added LiI (54 mg, 0.395 mmol) at 25°C. Li*O*t-Bu (8.55 mL of 1.0 M solution in THF, 8.55 mmol) and a solution of diisopropyl bromomethylphosphonate (1.875 g, 7.2 mmol) in 7 mL of DMF were slowly and simultaneously added to the reaction mixture for 5 hours at 60°C under anhydrous conditions. The mixture was quenched by adding

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water (40 mL), and the organic solvents (THF) were removed in vacuo. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give **4** (1.4 g, 67%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.17 (d, J = 13.2, 1H), 5.02 (d, J = 12.0 Hz, 1H), 4.68–4.64 (m, 2H), 4.14–4.09 (m, 3H), 3.68–3.57 (m, 2H), 1.28–1.22 (m, 15H), 0.88 (m, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 148.45, 147.99, 111.59, 70.21, 67.54, 65.63.74, 25.72, 24.71, 23.43, 18.43, -5.28; MS (FAB+) m/z 417 (M+Na).$^+$

(±)-[2-(Hydroxy)ethyl-allyloxymethyl]-phosphonic acid diisopropyl ester (5): To a solution of **4** (1.1 g, 2.79 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (4.18 mL, 1.0 M solution in THF) at 0°C and stirred for 5 hours at room temperature. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **5** (649 mg, 83%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.24 (d, J = 1.1 Hz, 1H), 5.10 (s, 1H), 4.81–4.68 (m, 2H), 4.18–4.05 (m, 3H), 3.78–3.62 (m, 2H), 1.50 (d, J = 7.2 Hz, 3H), 1.31 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 148.31, 113.79, 71.15, 68.62, 65.61, 63.37, 24.05, 22.04; MS (FAB+) m/z 303 (M+Na).$^+$

(±)-[2-(1-Bromoethyl)-allyloxymethyl] phosphonic acid diisopropyl ester (6): *N*-bromosuccinimide (616 mg, 3.46 mmol) was added slowly to a solution of compound **5** (485 mg, 1.73 mmol) and triphenylphosphine (907 mg, 3.46 mmol) in CH_2Cl_2 (15 mL) at 0°C, stirred overnight at room temperature, and diluted with CH_2Cl_2 (15 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate and filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by flash silica gel column chromatography (EtOAc/n-hexane, 1:20) to give the allylic bromide **6** (433 mg, 73%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.21 (d, J = 1.2 Hz, 1H), 5.07 (s, 1H), 4.79–4.65 (m, 2H), 4.16–4.05 (m, 2H), 3.77–3.60 (m, 3H), 1.51 (d, J = 7.3 Hz, 3H), 1.29 (dd, J = 6.2, 1.3 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 145.99, 111.32, 67.43, 65.32, 62.65, 41.77, 24.65, 23.05; MS (FAB+) m/z 343 (M+H).$^+$

(±)-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-allyl] adenine (7) A solution of the bromine derivative **6** (635 mg, 1.85 mmol), K_2CO_3 (552.8 mg, 4.0 mmol), 18-crown-6 (331 mg, 1.25 mmol), and adenine (304 mg, 2.25 mmol) in dry DMF (20 mL) was stirred overnight at 85–90 °C. The mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with brine (150 mL) and extracted with CH_2Cl_2 (150 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/EtOAc/hexane,

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0.1:3:1) to give compound **7** (146 mg, 39%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1H), 7.94 (s, 1H), 5.95 (br s, 2H), 5.19 (s, 1H), 4.98 (s, 1H), 4.82–4.74 (m, 2H), 4.10 (d, $J = 1.5$ Hz, 2H), 3.79–3.65 (m, 3H), 1.49 (d, $J =$ 7.2 Hz, 3H), 1.20 (d, $J = 6.1$ Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 155.97, 152.30, 150.21, 148.21, 141.52, 113.67, 72.11, 68.78, 66.87, 64.54, 24.82, 23.42; MS (FAB+) m/z 398 $(M+H)^+$.

Allylic phosphonate nucleosides **8**, **9**, and **10** were synthesized from the bromine intermediate **6** using the same procedures as described for synthesizing adenine derivative **7**.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-allyl] uracil (8): Yield 29%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, $J = 8.2$ Hz, 1H), 5.20 (s, 1H), 5.21 (d, $J = 8.2$ Hz, 1H), 5.01 (s, 1H), 4.79–4.66 (m, 2H), 4.06 (d, $J = 1.2$ Hz, 2H), 3.79–3.65 (m, 3H), 1.52 (d, $J = 7.2$ Hz, 3H), 1.34–1.29 (dd, $J = 6.3$, 1.2 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 163.94, 151.43, 147.88, 146.09, 112.38, 101.57, 70.87, 67.43, 65.29, 60.21, 23.54, 22.89; MS (FAB+) m/z 375 $(M+H)^+$, 397 $(M+Na)^+$.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-allyl] thymine (9): yield 25%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (s, 1H), 5.18 (s, 1H), 5.01 (s, 1H), 4.75–4.63 (m, 2H), 4.01 (d, $J = 1.2$ Hz, 2H), 3.82–3.69 (m, 3H), 1.59 (s, 3H), 1.49 (d, $J = 7.1$ Hz, 3H), 1.32–1.25 (d, $J = 6.2$ Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 164.32, 151.55, 147.38, 142.51, 113.78, 109.49, 69.92, 66.65, 64.19, 58.11, 24.48, 23.75, 13.10; MS (FAB+) m/z 389 $(M+H)^+$.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-allyl] cytosine (10): yield 34%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, $J = 7.2$ Hz, 1H), 5.51 (d, $J = 7.2$ Hz, 1H), 5.26 (s, 1H), 4.99 (s, 1H), 4.77–4.65 (m, 2H), 4.11 (d, $J = 1.5$ Hz, 2H), 3.79–3.68 (m, 3H), 1.48 (d, $J = 7.2$ Hz, 3H), 1.35–1.23 (dd, $J = 6.2$, 1.3 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 165.72, 156.50, 148.21, 145.78, 111.99, 92.70, 72.19, 68.39, 65.78, 59.53, 23.54, 22.49; MS (FAB+) m/z 396 $(M+Na)^+$.

(±)-9-[2-(Methoxymethyl)-1-methyl-allylphosphonic acid] adenine (11): $(CH_3)_3SiBr$ (0.566 g, 3.744 mmol) was added to a solution of the adenine phosphonate **7** (136 mg, 0.343 mmol) in 15 mL of anhydrous methylene chloride. The mixture was heated overnight under reflux and concentrated under reduced pressure. The residue was dissolved in distilled water and washed out with CH_2Cl_2 twice. The aqueous layer was lyophilized by freeze dryer to give compound **11** (72 mg, 67%): ^{1}H NMR (DMSO-d_6, 300 MHz) 8.09 (s, 1H), 7.97 (s, 1H), 5.20 (s, 1H), 5.21 (s, 1H), 4.98 (s, 1H), 4.01 (d, $J = 1.6$ Hz, 2H), 3.81–3.75 (m, 3H), 1.52 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 156.21, 150.43, 147.54, 141.43, 119.45, 112.67, 70.43, 64.67, 57.65, 22.90; MS (FAB+) m/z 314 $(M+H)^+$, 336 $(M+Na)^+$; Anal. calcd. for $C_{11}H_{16}N_5O_4P \cdot 1.0\ H_2O$: C, 39.88; H, 5.47; N, 21.14. Found: C, 40.13; H, 5.50; N, 21.11.

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The targeted allylic phosphonic acid nucleosides **12**, **13,** and **14** were synthesized from the corresponding phosphonate nucleosides using the procedure described for the adenine phsophonic acid derivative **11**.

(±)-1-[2-(Methoxymethyl)-1-methyl-allylphosphonic acid] uracil (12): Yield 56%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.24 (d, J = 8.0 Hz, 1H), 5.22 (s, 1H), 5.17 (d, J = 8.0 Hz, 1H), 5.01 (s, 1H), 4.09 (d, J = 1.3 Hz, 2H), 3.78–3.63 (m, 3H), 1.56 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.04, 150.99, 148.21, 145.98, 113.54, 101.57, 72.98, 62.32, 56.43, 23.50; MS (FAB+) m/z 291 $(M+H)^+$, 313 $(M+Na)^+$; Anal. calcd. for $C_{10}H_{15}N_2O_6P \cdot 1.0\ H_2O$: C, 38.96; H, 5.56; N, 9.09. Found: C, 39.15; H, 5.63; N, 9.17.

(±)-1-[2-(Methoxymethyl)-1-methyl-allylphosphonic acid] thymine (13): Yield 59%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36 (s, 1H), 5.17 (d, J = 1.2 Hz, 1H), 5.02 (s, 1H), 4.11–4.01 (m, 3H), 3.69 (m, 2H), 1.61 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 164.66, 150.87, 146.87, 141.78, 114.51, 108.67, 70.92, 63.43, 56.11, 22.99, 13.45; MS (FAB+) m/z 305 $(M+H)^+$, 327 $(M+Na)^+$; Anal. calcd. for $C_{11}H_{17}N_2O_6P \cdot 2.0\ H_2O$: C, 38.82; H, 6.22; N, 8.23. Found: C, 38.76; H, 6.15; N, 8.18.

(±)-1-[2-(Methoxymethyl)-1-methyl-allylphosphonic acid] cytosine (14): Yield 60%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.31 (d, J = 7.2 Hz, 1H), 5.60 (d, J = 7.2 Hz, 1H), 5.30 (d, J = 1.2 Hz, 1H), 5.01 (s, 1H), 4.19–4.10 (m, 2H), 3.96 (d, J = 7.8 Hz, 1H), 3.81–3.70 (m, 2H), 1.43 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 165.72, 156.50, 148.21, 145.78, 111.99, 92.70, 71.39, 65.78, 59.53, 23.54; MS (FAB+) m/z 290 $(M+H)^+$, 312 $(M+Na)^+$; Anal. calcd. for $C_{10}H_{16}N_3O_5P \cdot 2.0\ H_2O$: C, 36.92; H, 6.19; N, 12.92. Found: C, 37.03; H, 6.26; N, 12.87.

{1-[1-(tert-Butyldimethylsilanyloxy)-ethyl]-cyclopropyl}-methanol (15): To a solution of **3** (898 mg, 4.152 mmol) in CH_2Cl_2 (30 mL) at −30°C under nitrogen was added diethylzinc solution (1 M in hexanes, 14.8 mL, 14.8 mmol) followed by addition of diiodomethane (2.676 mL, 33.2 mmol) and stirred for 1 hour at −20°C. The reaction was quenched by addition of saturated NH_4Cl solution. The reaction mixture was extracted with chloroform, and the combined extracts were washed with saturated NaCl solution, dried ($NaSO_4$), filtered, and evaporated under reduced pressure. The residue was separated on a silica gel column with hexane:EtOAc (25:1) to give **15** (669.7 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.80-4.65 (m, 2H), 3.84-3.61 (m, 3H), 1.37 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.73–0.33 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 72.45, 65.21, 25.47, 24.46, 19.46, 18.32, 10.15. -5.70; MS (FAB+) m/z 230 $(M)^+$, 253 $(M+Na)^+$.

(±)-[2-(tert-Butyldimethylsilanyloxy)ethyl-cyclopropyl]-phosphonic acid diisopropyl ester (16): Phosphonylation of **15** was performed using a similar procedure as described for **4** to give **16**; yield 55%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83-4.69 (m, 2H), 3.87-3.69 (m, 4H), 3.22 (d, J = 9.8 Hz, 1H), 1.38–1.31 (m, 12H), 1.22 (d, J = 7.2 Hz, 3H), 0.88 (m, 9H), 0.75–0.34 (m,

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4H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 71.99, 68.20, 66.32, 65.21, 25.62, 23.39, 19.65, 18.22, 9.32. -5.42; MS (FAB+) m/z 409 $(M+H)^+$.

(±)-[2-(Hydroxy)ethyl-cyclopropyl]-phosphonic acid diisopropyl ester (17): Desilylated cyclopropanoid phosphonate **17** was synthesized from **16** by the similar procedure as described for **5**: yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.85-4.72 (m, 2H), 3.85-3.68 (m, 3H), 3.33 (d, $J = 9.8$ Hz, 1H), 3.26 (d, $J = 9.8$ Hz, 1H), 1.35 (m, 12H), 1.23 (d, $J = 7.2$ Hz, 3H), 0.71-0.32 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 73.01, 69.17, 67.71, 63.55, 24.17, 18.98, 10.54; MS (FAB+) m/z 295 $(M+H)^+$.

(±)-[1-(1-Bromoethyl)-cyclopropylmethoxymethyl] phosphonic acid diisopropyl ester (18): Bromine derivative **18** was synthesized from **17** by the same procedure as used for **6**: yield 75%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66–4.58 (m, 2H), 3.81–3.70 (m, 3H), 3.33 (d, $J = 9.6$ Hz, 1H), 3.27 (d, $J = 9.8$ Hz, 1H), 3.00 (s, 3H), 1.39–1.30 (m, 12H), 1.21 (d, $J = 7.2$ Hz, 3H), 0.76–0.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 68.21, 66.31, 63.71, 41.02, 24.58, 20.34, 10.72; MS (FAB+) m/z 357 $(M+H)^+$, 379 $(M+Na)^+$.

Cyclopropanoid phosphonate nucleoside analogues **19**, **20**, **21**, **22** were synthesized from the corresponding key intermediate **18** using the procedure described for the allylic adenine phosphonate **7** as show in Scheme 1.

(±)-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-cyclopropyl] adenine (19): Yield 36%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H), 7.99 (s, 1H), 4.85-4.71 (m, 2H), 3.77-3.68 (m, 2H), 3.21-3.12 (m, 2H), 2.92 (m 1H), 1.39-1.30 (m, 12H), 1.21 (d, $J = 7.0$ Hz, 3H), 0.75-0.34 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.00, 152.99, 151.87, 142.39, 120.77, 71.65, 67.91, 64.31, 57.63, 24.32, 19.76, 9.87; MS (FAB+) m/z 434 $(M+Na)^+$.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-cyclopropyl] uracil (20): Yield 30%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, $J = 8.0$ Hz, 1H), 5.58 (d, $J = 8.2$ Hz, 1H), 4.82–4.70 (m, 2H), 3.74 (m, 2H), 3.23-3.14 (m, 2H), 2.95-2.87 (m 1H), 1.30 (m, 12H), 1.20 (d, $J = 7.2$ Hz, 3H), 0.79–0.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.38, 152.72, 147.90, 102.33, 71.89, 68.08, 63.43, 56.41, 23.87, 19.70, 10.43; MS (FAB+) m/z 411 $(M+Na)^+$.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-cyclopropyl] thymine (21): Yield 29%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (s, 1H), 4.85-4.74 (m, 2H), 3.78-3.69 (m, 2H), 3.29-3.19 (m, 2H), 2.86 (m 1H), 1.80 (s, 3H), 1.33–1.29 (m, 12H), 1.23 (d, $J = 7.0$ Hz, 3H), 0.87-0.39 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.64, 151.76, 142.88, 110.87, 72.00, 67.96, 64.21, 55.32, 23.11, 19.32, 12.43, 9.54; MS (FAB+) m/z 425 $(M+Na)^+$.

(±)-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-cyclopropyl] cytosine (22): Yield 35%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

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7.32 (d, $J = 7.2$ Hz, 1H), 5.87 (d, $J = 7.2$ Hz, 1H), 4.81 (m, 2H), 3.70-3.59 (m, 2H), 3.18-3.11 (m, 2H), 2.81 (m 1H), 1.29 (m, 12H), 1.19 (d, $J = 7.0$ Hz, 3H), 0.77-0.31 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 165.74, 156.78, 146.38, 93.61, 71.43, 66.21, 63.62, 56.43, 23.29, 18.98, 9.21; MS (FAB+) m/z 388 $(M+H).^+$

Cyclopropanoid phosphonic acid nucleosides **23**, **24**, **25**, and **26** were also synthesized from the corresponding phosphonate analogues **19**, **20**, **21**, and **22** respectively using the procedures described for synthesizing adenine derivative **11**.

(±)-9-[2-(Methoxymethyl)-1-methyl-cyclopropylphosphonic acid] adenine (23): Yield 63%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.41 (s, 1H), 8.14 (s, 1H), 3.68–3.59 (m, 2H), 3.10 (d, $J = 8.0$ Hz, 1H), 2.99 (d, $J = 8.0$ Hz, 1H), 2.83 (m 1H), 1.62 (d, $J = 7.0$ Hz, 3H),), 0.80 (t, $J = 5.2$ Hz, 2H), 0.55 (t, $J = 5.1$ Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 155.54, 153.21, 151.43, 141.90, 118.43, 70.98, 65.31, 55.41, 20.01, 10.42; MS (FAB+) m/z 328 $(M+H)^+$, 450 $(M+Na)^+$; Anal. calcd. for $C_{12}H_{18}N_5O_4P \cdot 2.0\ H_2O$: C, 39.67; H, 6.10; N, 19.27. Found: C, 39.50; H, 6.20; N, 19.17.

(±)-1-[2-(Methoxymethyl)-1-methyl-cyclopropylphosphonic acid] uracil (24): Yield 65%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36 (d, $J = 7.8$ Hz, 1H), 5.59 (d, $J = 80$ Hz, 1H), 3.81 (br s, 2H), 3.30 (d, $J = 8.4$ Hz, 2H), 3.01 (m 1H), 1.58 (d, $J = 7.2$ Hz, 3H), 0.75–060 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 165.15, 153.49, 146.32, 103.67, 72.07, 63.71, 56.89, 20.19, 10.77; MS (FAB+) m/z 305 $(M+H)^+$, 327 $(M+Na)^+$; Anal. calcd. for $C_{11}H_{17}N_2O_6P \cdot 1.0\ H_2O$: C, 40.99; H, 5.94; N, 8.69. Found: C, 41.10; H, 6.03; N, 8.76.

(±)-1-[2-(Methoxymethyl)-1-methyl-cyclopropylphosphonic acid] thymine (25): Yield 60%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.39 (s, 1H), 3.81 (m, 2H), 3.13–3.01 (m, 2H), 2.80 (dd, $J = 6.8$, 1.5 Hz, 1H), 1.79 (s, 3H), 1.31 (d, $J = 7.2$ Hz, 3H), 0.80–0.39 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 164.31, 152.49, 143.21, 108.99, 71.54, 64.65, 54.90, 20.19, 12.87, 10.73; MS (FAB+) m/z 319 $(M+H)^+$, 341 $(M+Na)^+$; Anal. calcd. for $C_{12}H_{19}N_2O_6P \cdot 2.0\ H_2O$: C, 40.68; H, 6.54; N, 7.90. Found: C, 40.49; H, 6.43; N, 7.81.

(±)-1-[2-(Methoxymethyl)-1-methyl-cyclopropylphosphonic acid] cytosine (26): Yield 59%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.40 (d, $J = 7.0$ Hz, 1H), 5.91 (d, $J = 7.0$ Hz, 1H), 3.76 (m, 2H), 3.19-3.11 (m, 2H), 2.95 (m 1H), 1.29 (d, $J = 7.2$ Hz, 3H), 0.78 (dd, $J = 5.4$, 1.6 Hz, 2H), 0.51 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.05, 155.40, 145.39, 94.31, 71.32, 64.18, 55.32, 21.01, 11.00; MS (FAB+) m/z 304 $(M+H)^+$, 326 $(M+Na)^+$; Anal. calcd. for $C_{11}H_{18}N_3O_5P \cdot 2.0\ H_2O$: C, 38.94; H, 6.53; N, 12.38. Found: C, 38.80; H, 6.51; N, 12.45.

(±)-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-allyl] 2-amino-6-chloropurine (27): A solution of the 2-amino-6-chloropurine (288 mg, 1.75 mmol) and sodium hydride (49.2 mg, 2.04 mmol) in anhydrous DMF (13 mL) was stirred for 1 hour at room temperature.

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A solution of the bromide **6** (301 mg, 0.878 mmol) in DMF (7 mL) was then added to the mixture and stirred 4 hours at 80°C. The mixture was quenched by the addition of a saturated ammonium chloride solution (6 mL) and concentrated under reduced pressure. The residue was dissolved in water and extracted three times with CH_2Cl_2. The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane/MeOH, 4:1:0.5) to give compound **27** (108.9 mg, 29%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H), 5.41 (br s, 2H), 5.23 (d, J = 0.9 Hz, 1H), 5.11 (s, 1H), 4.80–4.69 (m, 2H), 4.18–4.11 (m, 3H), 3.78-3.62 (m, 3H), 1.56 (d, J = 6.8 Hz, 3H), 1.35-1.28 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 159.54, 154.23, 151.39, 147.88, 143.19, 124.97, 112.43, 71.67, 68.32, 65.21, 62.78, 24.53, 23.00; MS (FAB+) m/z 429 $(M+H)^+$, 451 $(M+Na)^+$.

(±)-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-1-methyl-cyclopropyl] 2-amino-6-chloropurine (28): Purine nucleoside phosphonate **28** was synthesized by the similar procedure as described for **27**: yield 32%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (s, 1H), 5.39 (br s, 2H), 4.82–4.71 (m, 2H), 4.21 (m, 1H), 3.77–3.63 (m, 2H), 1.52 (d, J = 7.0 Hz, 3H), 1.34–1.28 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 158.90, 154.03, 150.89, 143.21, 124.52, 72.03, 68.71, 64.10, 55.32, 22.65, 18.56, 10.78; MS (FAB+) m/z 443 $(M+H)^+$.

(±)-9-[2-(Methoxymethyl)-1-methyl-allylicphosphonic acid] 2-amino-6-chloropurine (29): The removal of the diisopropyl groups of compound **27** was performed using a similar procedure described for **11**: yield 78%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.93 (s, 1H), 5.27 (s, 1H), 5.10 (s, 1H), 4.09 (d, J = 2.4 Hz, 1H), 3.78–3.65 (d, J = 7.6 Hz, 2H), 1.53 (d, J = 2.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 158.74, 153.88, 151.01, 147.43, 143.19, 113.32, 71.99, 62.45, 57.21, 23.32; MS (FAB+) m/z 348 $(M+H)^+$, 370 $(M+Na)^+$.

(±)-9-[2-(Methoxymethyl)-1-methyl-cyclopropylphsophonic acid] 2-amino-6-chloropurine (30): Compound **30** was synthesized from **28** by the similar procedure as described for **11**: ^{1}H NMR (DMSO-d_6, 300 MHz): 158.61, 154.20, 150.76, 142.71, 125.36, 72.78, 64.02, 57.21, 22.43, 12.11; ^{13}C NMR (DMSO-d_6) δ 158.74, 153.88, 151.01, 147.43, 143.19, 113.32, 71.99, 62.45, 57.21, 23.32; MS (FAB+) m/z 362 $(M+H)^+$, 385 $(M+Na)^+$.

(±)-9-[2-(Methoxymethyl)-1-methyl-allylicphosphonic acid] guanine (31): Compound **29** (145 mg, 0.417 mmol) was dissolved in 2 N HCl (8 mL) and heated under reflux for 6 hours. The mixture was washed out by CH_2Cl_2 three times. The aqueous layer was dried by freeze dryer to give compound **31** (96 mg, 70%): UV (H_2O) λ_{max} 253.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 5.41 (d, J = 1.2 Hz, 1H), 5.09 (s, 1H), 4.12 (d, J = 2.2 Hz, 1H), 3.76–3.67 (d, J = 7.8 Hz, 2H), 1.50 (d, J = 2.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 158.71, 153.58, 151.69, 147.29, 142.70, 112.25,

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71.89, 62.32, 56.38, 21.90; MS (FAB+) m/z 330 $(M+H)^+$, 352 $(M+Na)^+$; Anal. calcd. for $C_{11}H_{16}N_5O_5P \cdot 2.0\ H_2O$: C, 36.16; H, 5.52; N, 9.77. Found: C, 36.22; H, 5.41; N, 9.63.

(±)-9-[2-(Methoxymethyl)-1-methyl-cyclopropylphsophonic acid] guanine (32): Guanine phosphonic acid derivative **32** was synthesized by the similar procedure as described for **31**: ^{1}H NMR (DMSO-d_6, 300 MHz): 158.61, 154.20, 150.76, 142.71, 125.36, 72.78, 64.02, 57.21, 22.43, 12.11; ^{13}C NMR (DMSO-d_6) δ 158.21, 154.03, 151.67, 148.28, 142.18, 113.24, 71.99, 63.78, 56.38, 22.95; MS (FAB+) m/z 343 $(M+H)^+$, 366 $(M+Na)^+$; Anal. calcd. for $C_{12}H_{19}N_2O_6P \cdot 1.0\ H_2O$: C, 39.89; H, 5.58; N, 19.38. Found: C, 39.78; H, 5.49; N, 19.41.

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