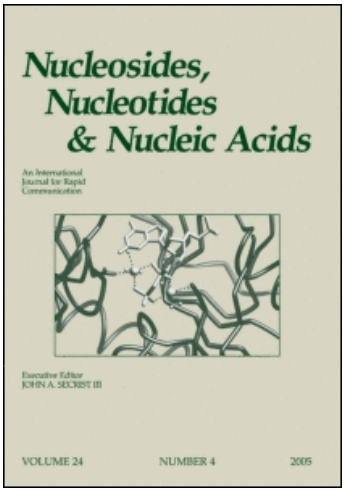

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SYNTHESIS AND ANTIVIRAL EVALUATION OF NOVEL 5′-NORCARBOACYCLIC PHOSPHONIC ACID NUCLEOSIDES

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□ *This article describes a very simple route for synthesizing a novel 5′-norcarboacyclic nucleotides. The condensation of the mesylates* ***17*** *and* ***18*** *with the natural nucleosidic bases (A,U,T,C) under standard nucleophilic substitution (K_2CO_3, 18-*Crown-*6, DMF) and deprotection afforded the target nucleotide analogues* ***27–34****. In addition, these compounds were evaluated for their antiviral properties against various viruses.*

Keywords 5′-Noraristeromycin; Carboacyclic nucleoside; Nucleotide; Antiviral agent

INTRODUCTION

Acyclic nucleosides[1] in which the 5′-hydroxy group has been replaced by a phosphonate or phosphonate ester can act as stable mimics of nucleoside monophosphates and undergo further phosphorylation in cells to afford species that are analogous to nucleoside triphosphates and are capable of inhibiting polymerases. The advantage of these compounds is to circumvent the need for primary phosphorylation of the parent nucleoside, which is often the stumbling block in attaining active compounds. During the past 20 years, many new synthetic schemes for various acyclic nucleoside phosphonic acid analogues[2] have been reported, and many of these molecules have exhibited promising antiviral activity.[3] Among them, PMEA **1**,[4] (S)-HPMPA **2,**[5] and (S)-HPMPC **3**[6] exhibit potent antiviral activity against HIV, HBV, and HSV. Furthermore, the recent approval of *bis*(POC)PMPA[7] **4** by the FDA as an anti-HIV agent warrants further study for acyclic nucleotide analogues as chemotherapeutic agents (Figure 1).

5′-Norcarbocyclic nucleosides have been found to have a variety of meaningful biological properties. Among them, 5′-noraristeromycin **5**[8]

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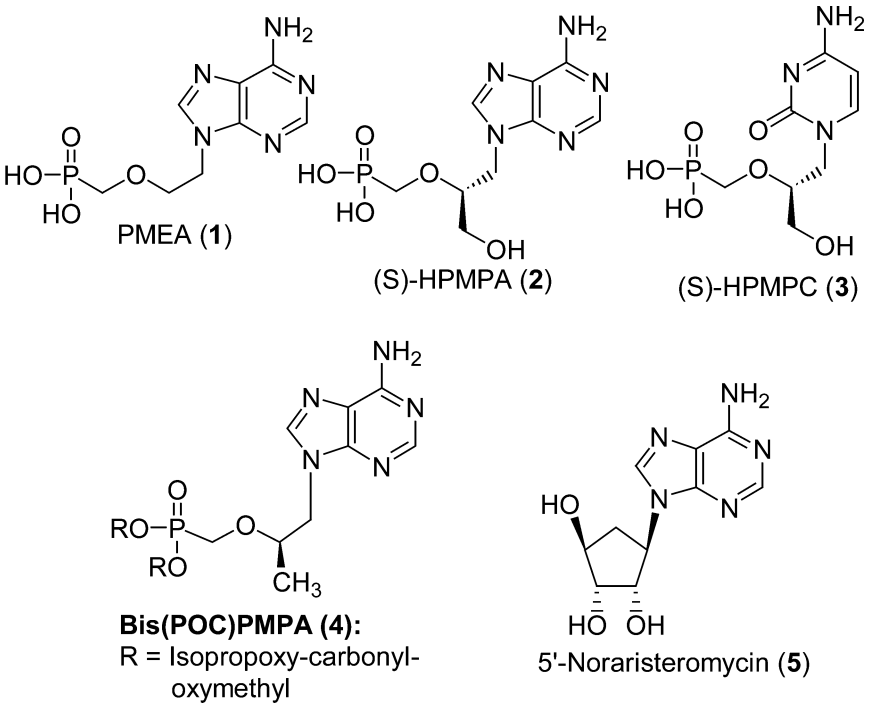
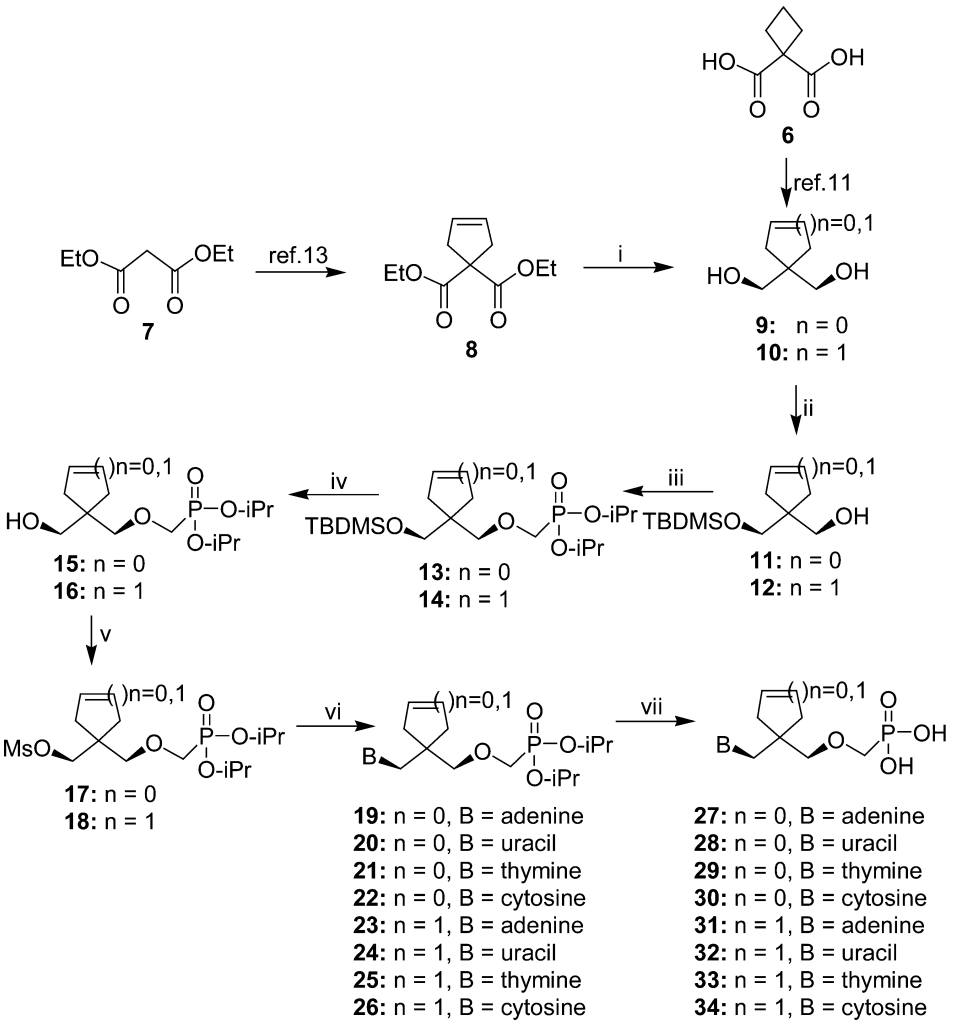


FIGURE 1 Synthesis rationale of target nucleotide analogues.

was reported to be more potent against the HCMV than the licensed anti-HCMV agent, ganciclovir.[9] Nevertheless, the efficacy of these drugs is limited by their toxicity and side effects, as well as the emergence of many drug- resistant viral strains.[10] Therefore, there is a need for less toxic and more effective antiviral agents that do not have any cross-resistance with existing drugs. In view of the stimulating results reported for acyclic nucleoside phosphonic acids and as a part of our ongoing drug discovery efforts, the aim of this study was to synthesize novel 5′-norcarboacyclic nucleotide analogues.

RESULTS AND DISCUSSION

First, for the synthesis of 5′-norcyclobutyl carboacyclic nucleoside phosphonic acids, the commercially available cyclobutyl dicarboxylic acid **6** was selected as a starting material (Scheme 1). A reduction[11] of the carboxylic functional groups of the starting material **6**, followed by a monosilylation of the diol **9** afforded the alcohol derivative **11**. The hydroxy group of compound **11** was phosphonylated by treating with diisopropyl bromomethylphosphonate in the presence of anhydrous DMF to give **13**. Silyl protection group was removed by the treatment of tetrabutylammonium



Reagents:i) $LiAlH_4$, THF; ii) TBDMSCl, imidazole, CH_2Cl_2; iii) Diisopropyl bromomethylphosphonate, LiO*t*-Bu, LiI, DMF; iv) TBAF, THF; v) MsCl, TEA, CH_2Cl_2; vi) Bases, K_2CO_3, 18-*C*-6, DMF; vii) $(CH_3)_3SiBr$, CH_2Cl_2.

SCHEME 1 Synthesis of 5′-norcyclo-butane and -pentene carboacyclic nucleotide analogues.

fluoride (TBAF) to form **15**, which was mesylated by treating it with methanesulfonyl chloride (MsCl) in an anhydrous CH_2Cl_2 to give the key intermediate **17**. The mesylate **17** was coupled with the natural nucleobases (adenine, uracil, thymine, cytosine) using well-known standard nucleophilic substitution conditions (K_2CO_3, 18-*C*-6, DMF)[12] to provide the nucleoside phosphonic ester derivatives **19–22**, respectively. The removal of the diisopropyl groups of compounds **19–22** was accomplished using trimethylsilyl bromide[13] to provide desired nucleoside phosphonic acids **27–30**.

TABLE 1 Antiviral Activities of the Synthesized Compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	HSV-2 EC_{50} (μM)	HCMV EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
27	52.7	45.9	>100	>100	>100
28	>100	>100	>100	>100	>100
29	>100	>100	>100	>100	>100
30	16.5	>100	>100	72.1	>100
31	>100	>100	>100	>100	>100
32	>100	>100	>100	>100	>100
33	66.2	>100	>100	>100	>100
34	>100	>100	>100	>100	>100
AZT	0.008	ND	ND	ND	1.15
GCV	ND	ND	ND	0.6	>10
ACV	ND	0.15	ND	ND	>100

ND: Not determined.
EC_{50} (μM): Concentration required to inhibit 50% of virus-induced cytopathicity.
CC_{50} (μM): Concentration required to reduce cell viability by 50%.

For the synthesis of the 5′-norcyclopentenyl carboacyclic nucleoside phosphonic acids, a similar reaction procedure described for synthesizing **27–30** was used. Starting material **8** was readily synthesized by double allylation of diethylmalonate **7** (CH_2 = CH-CH_2Br, NaH, DMF) using the reported procedure.[14] The ester functional group of compound **8** was reduced with lithium aluminum hydride (LAH) to give the diol **10**, which was monoprotected using *tert*-butyldimethylchlorosilane (TBDMSCl) to give compound **12**. Compound **12** was subjected to similar reaction conditions as described above (phosphonylation, mesylation, base coupling, and deprotection) to provide the target nucleoside phosphonic acids **31–34**.

All the synthesized compounds were tested against several viruses such as HIV-1 (MT-4 cells), HSV-1,2 (CCL 18 cells), and HCMV (AD-169). As shown in Table 1, none of the tested compounds showed antiviral activity except for the cytosine nucleotide **30**, which exhibited moderate anti-HIV activity in the MT-4 cell (EC_{50} = 16.5 μmol).

In conclusion, we studied the synthesis and biological evaluation of novel 5′-norcarbacyclic nucleotide analogues, starting from cyclobutane dicarboxylic acid and diethyl malonate, respectively.

EXPERIMENTAL

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA (JEOL, Tokyo, Japan) 300 spectrometer. The chemical shifts are reported as parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer

(Beckman, South Pasadena, CA). The elemental analyses were performed using an Elemental Analyzer System (EA 1112) (Leco Corp., St. Joseph, MI). The TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under N_2 unless otherwise specified. Dry dichloromethane, benzene, and pyridine were obtained by the distillation from CaH_2. The dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

*[1-(*tert-*Butyldimethylsilanyloxymethyl)cyclobutyl]methanol (**11**).* To a stirred solution of compound **9** (294 mg, 2.35 mmol) and imidazole (318 mg, 4.68 mmol) in CH_2Cl_2 (15 mL), *t*-butyldimethylsilyl chloride (354 mg, 2.35 mmol) was added at 0°C. The mixture was stirred at room temperature for 4 h and quenched by adding a $NaHCO_3$ solution (2 mL). The mixture was extracted using EtOAc (50 mL), dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **11** (857 mg, 98%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.62 (s, 2H), 3.60 (s, 2H), 1.86–1.59 (m, 6H), 0.81 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 71.16, 70.24, 43.07, 25.80, 18.20, 15.45, -5.56; Anal calc for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.72; H, 11.45.

*[1-(*tert-*Butyldimethylsilanyloxymethyl) Cyclobutyl] Methyl Phosphonic Acid Diisopropyl Ester (**13**).* To a solution of **11** (818 mg, 3.55 mmol) in 4 mL of DMF was added LiI (36 mg, 0.27 mmol) at 25°C. LiO*t*-Bu (5.7 mL of 1.0 M solution in THF) and a solution of diisopropyl bromomethylphosphonate (1.25 g, 4.81 mmol) in 3 mL of DMF were slowly and simultaneously added to the reaction mixture for 5 h at 60°C under anhydrous conditions. The mixture was quenched by adding water (18 mL), and the organic solvents (THF) were removed *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 40 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 **13** (899 mg, 62%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.76 (m, 2H), 3.74 (d, J = 8.0 Hz, 2H), 3.65 (s, 2H), 3.60 (s, 2H), 1.82–1.60 (m, 6H), 1.37 (m 12H), 0.87 (s, 9H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 72.75, 70.67, 70.02, 65.31, 43.34, 25.56, 23.78, 18.58, 15.45, -5.45; Anal calc for $C_{19}H_{41}O_5PSi$: C, 55.85; H, 10.11. Found: C, 55.71; H, 10.03.

*[1-(Hydroxymethyl) Cyclobutyl] Methyl Phosphonic Acid Diisopropyl Ester (**15**).* To a solution of **13** (1.55 g, 3.8 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (5.7 mL, 1.0 M solution in THF) at 0°C and stirred for 6 h at room temperature. The reaction mixture was concentrated in *vacuo* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give **15** (861 mg, 77%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.78 (m, 2H), 3.70 (d, J = 8.2 Hz, 2H), 3.66 (s, 2H), 3.61 (s, 2H), 1.80–1.61 (m, 6H), 1.36 (m 12H); ^{13}C NMR ($CDCl_3$) δ 71.89, 71.13, 70.23, 65.63, 44.12, 23.69, 15.38.

*Methanesulfonate-1-(*tert*-butyldimethylsilanyloxymethyl)-Cyclobutylmethyl Phosphonic Acid Diisopropyl Ester (**17**).* To a solution of the alcohol **15** (818 mg, 2.78 mmol) in anhydrous CH_2Cl_2 (20 mL), anhydrous triethylamine (0.76 mL) and MsCl (390 mg, 3.36 mmol) was added at 0°C. The mixture was stirred at the same temperature for 4 h and quenched by adding a cold saturated $NaHCO_3$ solution (3.0 mL). The mixture was extracted with CH_2Cl_2 (200 mL) and water (150 mL) two times. The combined organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash silica gel column chromatography (EtOAc/hexane, 4:1) to give compound **17** (724 mg, 70%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.76 (m, 2H), 4.16 (s, 2H), 3.72 (d, J = 7.8 Hz, 2H), 3.58 (s, 2H), 3.01 (s, 3H), 1.90–1.70 (m, 6H), 1.35 (m 12H); ^{13}C NMR ($CDCl_3$) δ 72.87, 71.67, 66.65, 65.63, 43.12, 36.72, 23.77, 15.71.

*9-[1-(Diisopropoxy-phosphorylmethoxymethyl)-cyclobutylmethyl]adenine (**19**).* A solution of the mesylate **17** (231 mg, 0.62 mmol), K_2CO_3 (173 mg, 1.25 mmol), 18-crown-6 (247 mg, 0.945 mmol), and adenine (85 mg, 0.63 mmol) in dry DMF (8 mL) was stirred overnight at 90°C. The mixture was cooled to room temperature and concentrated under high vacuum. The residue was diluted with brine (20 mL) and extracted with CH_2Cl_2 (30 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 (EtOAc/hexane/MeOH, 2:1:0.2) to give compound **19** (133 mg, 52%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 8.03 (s, 1H), 4.74 (m, 2H), 4.18 (s, 2H), 3.70 (d, J = 7.6 Hz, 2H), 3.61 (s, 2H), 1.88–1.68 (m, 6H), 1.34 (m 12H); ^{13}C NMR ($CDCl_3$) δ 154.72, 153.03, 142.65, 118.67, 71.83, 71.21, 67.92, 64.39, 44.28, 27.63, 23.61, 15.75.

*1-[1-(Diisopropoxy-phosphorylmethoxymethyl)-cyclobutylmethyl]uracil (**20**).* Compound **20** was prepared from compound **17** using the method described for synthesizing compound **19**: yield 23%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 7.8 Hz, 1H), 5.64 (d, J = 7.8 Hz, 1H), 4.80 (m, 2H), 3.97 (s, 2H), 3.70 (d, J = 7.6 Hz, 2H), 3.60 (s, 2H), 1.90–1.71 (m, 6H), 1.36 (m 12H); ^{13}C NMR ($CDCl_3$) δ 164.65, 152.59, 143.63, 103.88, 72.48, 71.72, 66.35, 63.85, 43.65, 26.74, 23.21, 15.23.

*1-[1-(Diisopropoxy-phosphorylmethoxymethyl)-cyclobutylmethyl]thymine (**21**).* Compound **21** was obtained from compound **17** using the similar method described for **19**: yield 22%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 1H), 4.82 (m, 2H), 3.90 (s, 2H), 3.73 (d, J = 7.8 Hz, 2H), 3.67 (s, 2H), 1.76 (s, 3H), 1.89–1.68 (m, 6H), 1.40 (m 12H); ^{13}C NMR ($CDCl_3$) δ 164.92, 154.25, 139.63, 107.61, 71.66, 70.32, 67.72, 64.76, 44.28, 26.11, 23.83, 14.97, 11.59.

*1-[1-(Diisopropoxy-phosphorylmethoxymethyl)-cyclobutylmethyl]cytosine (**22**).* Compound **22** was synthesized from compound **17** using the similar procedure described for **19**: yield 43%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 7.6 Hz, 1H), 6.84 (br d, 2H), 5.67 (d, J = 7.6 Hz, 1H), 4.79 (m, 2H), 4.02

(s, 2H), 3.75 (d, J = 8.0 Hz, 2H), 3.65 (s, 2H), 1.88–1.67 (m, 6H), 1.39 (m 12H); ^{13}C NMR ($CDCl_3$) δ 165.67, 155.84, 146.26, 93.38,, 72.76, 70.94, 67.45, 65.36, 43.31, 27.25, 22.99, 15.03.

*9-[1-(Hydromethyl)-cyclobutylmethylphosphonic Acid]-adenine (**27**).* To a solution of the phosphonate **19** (79 mg, 0.191 mmol) in 5 mL of anhydrous methylene chloride was added $(CH_3)_3SiBr$ (0.315 g, 2.08 mmol). The mixture was refluxed for overnight and concentrated *in vacuo*. The residue was dissolved in distilled water and washed out by CH_2Cl_2. The aqueous layer was dried by freeze dryer to give **27** (48 mg, 78%) as a solid: mp 136–138°C; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.08 (s, 1H), 7.71 (s, 1H), 4.05 (s, 2H), 3.73 (d, J = 8.0 Hz, 2H), 3.67 (s, 2H), 1.90–1.68 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 154.95, 151.23, 143.12, 114.87, 65.56, 64.40, 58.34, 43.76, 26.76, 14.82; Anal calc for $C_{12}H_{18}N_5O_4P \cdot 1.5H_2O$: C, 40.68; H, 5.97; N, 19.77. Found: C, 40.77; H, 6.11; N, 19.64.

*1-[1-(Hydroxymethyl)-cyclobutylmethylphosphonic Acid]-uracil (**28**).* Compound **28** was obtained from compound **20** using the method described for synthesizing compound **27**: yield 76%; mp 142–144°C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.23 (br s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 5.57 (d, J = 6.8 Hz, 1H), 4.12 (s, 2H), 3.70 (d, J = 8.2 Hz, 2H), 3.62 (s, 2H), 1.86–1.66 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 163.78, 153.23, 144.29, 102.65, 66.34, 64.73, 57.65, 44.59, 26.12, 14.66; Anal calc for $C_{11}H_{17}N_2O_6P \cdot 0.2$MeOH: C, 43.30; H, 5.78; N, 9.02. Found: C, 43.11; H, 5.65; N, 8.87.

*1-[1-(Hydroxymethyl)-cyclobutylmethylphosphonic acid]-thymine (**29**).* Compound **29** was synthesized from compound **21** using the similar method described for **27**: yield 72%; mp 128–130°C; UV (H_2O) λ_{max} 267.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.38 (br s, 1H), 7.42 (s, 1H), 3.99 (s, 2H), 3.72 (d, J = 8.2 Hz, 2H), 3.52 (s, 2H), 1.79 (s, 3H), 1.80–1.61 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 164.76, 152.21, 141.74, 107.43, 65.39, 64.63, 52.76, 43.37, 27.25, 14.85, 12.19; Anal calc for $C_{12}H_{19}N_2O_6P$: C, 45.29; H, 6.02; N, 8.80. Found: C, 45.41; H, 5.92; N, 8.98.

*1-[1-(Hydroxymethyl)-cyclobutylmethylphosphonic Acid]-cytosine (**30**).* Compound **30** was synthesized from compound **22** using the similar procedure described for compound **27**: yield 75%; mp 133–136°C; UV (H_2O) λ_{max} 272.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.76 (d, J = 7.0 Hz, 1H), 7.09 (br d, 2H), 5.69 (d, J = 7.0 Hz, 1H), 3.93 (s, 2H), 3.69 (d, J = 7.8 Hz, 2H), 3.58 (s, 2H), 1.86–1.62 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 165.81, 156.48, 145.51, 94.65, 65.87, 63.34, 53.76, 43.76, 26.43, 14.81; Anal calc for $C_{11}H_{18}N_3O_5P \cdot 2H_2O$: C, 38.94; H, 6.54; N, 12.38. Found: C, 39.12; H, 6.47; N, 12.10.

*(1-Hydroxymethyl-cyclopent-3-enyl)-methanol (**10**).* To a suspension of lithium aluminum hydride (0.8 g, 21.1 mmol) in dry tetrahydrofuran (40 mL), a solution of compound **8** (1.59 g, 7.49 mmol) in dry tetrahydrofuran (40 mL) was added dropwise at 0°C. The resulting suspension was stirred overnight, which was followed by cooling to 0°C. The suspension was quenched with water (0.83 mL), 15% sodium hydroxide (0.83 mL) and

water (2.48 mL) at the same temperature. The mixture was stirred at room temperature for a further 1 h. The white gel suspension was filtered through a celite pad and was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/n-hexane, 5:1) to give the diol **10** (787 mg, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (s, 2H), 3.67 (s, 4H), 2.20 (4H); ^{13}C NMR ($CDCl_3$) δ 128.74, 69.83, 47.54, 38.63.

*[1-(tert-Butyl-dimethyl-silanyloxymethyl)-cyclopent-3-enyl]-methanol (**12**).* Compound **12** was obtained from compound **10** using the method described for compound **11**: yield 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (s, 2H), 3.57 (d, J = 5.7 Hz, 4H), 2.20–2.01 (m, 4H), 0.83 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 128.74, 70.79, 70.27, 47.51, 38.51, 25.63, 18.06, -5.70; Anal calc for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.22; H, 10.91.

*[1-(tert-Butyldimethylsilanyloxymethyl) cyclopent-3-enyl] Methyl Phosphonic Acid Diisopropyl Ester (**14**).* Compound **14** was synthesized from **12** using the method for compound **13**: yield 62%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.61 (s, 2H), 4.73 (m, 2H), 3.76 (d, J = 8.0 Hz, 2H), 3.61 (s, 2H), 3.56 (s, 2H), 2.23–2.05 (m, 4H), 1.36 (m 12H), 0.89 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 127.92, 71.67, 70.89, 69.63, 65.31, 48.12, 38.64, 25.67, 23.23, 18.72, -5.57; Anal calc for $C_{20}H_{41}O_5PSi$: C, 57.11; H, 9.83. Found: C, 56.92; H, 10.09.

*[1-(Hydroxymethyl) cyclopent-3-enyl] Methyl Phosphonic Acid Diisopropyl Ester (**16**).* Compound **16** was synthesized from **14** using the method described for synthesizing compound **15**: yield 76%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66 (s, 2H), 4.75 (m, 2H), 3.78 (d, J = 8.0 Hz, 2H), 3.66 (s, 2H), 3.60 (s, 2H), 2.20–2.07 (m, 4H), 1.40 (m 12H); ^{13}C NMR ($CDCl_3$) δ 127.82, 71.58, 70.46, 69.26, 66.27, 48.12, 37.99, 23.23.

*Methanesulfonate [1-(hydroxymethyl) cyclopent-3-enyl] Methyl Phosphonic Acid Diisopropyl Ester (**18**).* Compound **18** was synthesized from **16** using the method described for synthesizing compound **17**: yield 80%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79 (s, 2H), 4.78 (m, 2H), 4.12 (s, 2H), 3.75 (d, J = 8.2 Hz, 2H), 3.71 (s, 2H), 3.03 (s, 3H), 2.20–2.11 (m, 4H), 1.39 (m 12H); ^{13}C NMR ($CDCl_3$) δ 128.21, 72.15, 71.67, 70.36, 65.78, 48.27, 38.81, 36.36, 23.78.

*9-[1-(Diisopropoxyphosphorylmethoxymethyl)-cyclopent-3-enyl-methyl]-adenine (**23**).* Compound **23** was synthesized from **28** using the method described for compound **19**: yield 44%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.79 (s, 1H), 4.74 (m, 2H), 4.06 (s, 2H), 3.78 (d, J = 7.8 Hz, 2H), 3.62 (s, 2H), 2.19–2.04 (m, 4H), 1.40 (m 12H); ^{13}C NMR ($CDCl_3$) δ 154.76, 151.78, 142.71, 128.21, 118.63, 71.67, 71.12, 69.56, 48.31, 47.78, 36.22, 22.89.

*1-[1-(Diisopropoxyphosphorylmethoxymethyl)-cyclopent-3-enyl-methyl]-uracil (**24**).* Compound **24** was prepared from compound **28** using the method described for synthesizing compound **19**: yield 28%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81 (br s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 5.54 (d, J = 7.4 Hz, 1H),

4.83 (m, 2H), 4.10 (s, 2H), 3.72 (d, J = 7.8 Hz, 1H), 3.58 (s, 2H), 2.28 (s, 4H), 1.36 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 164.45, 152.56, 146.72, 128.42, 102.55, 70.56, 69.32, 66.78, 48.45, 46.74, 37.78, 23.56.

*1-[1-(Diisopropoxyphosphorylmethoxymethyl)-cyclopent-3-enyl-methyl]-thymine (**25**).* Compound **25** was synthesized from compound **18** using the similar method for compound **19**: yield 28%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (br s, 1H), 7.62 (s, 1H), 4.87 (m, 2H), 4.12 (s, 2H), 3.65 (d, J = 8.2 Hz, 2H), 3.55 (s, 2H), 2.25 (s, 4H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.36, 152.54, 141.73, 128.27, 104.72, 71.76, 70.77, 67.85, 47.65, 46.18, 37.65, 24.01, 11.89.

*1-[1-(Diisopropoxyphosphorylmethoxymethyl)-cyclopent-3-enyl-methyl]-cytosine (**26**).* Compound **26** was synthesized from compound **18** using the method described for synthesizing compound **19**: yield 52%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 5.8 Hz, 1H), 6.05 (d, J = 5.8 Hz, 1H), 4.85 (m, 2H), 4.13 (s, 2H), 3.81 (d, J = 8.0 Hz, 1H), 3.67 (s, 2H), 2.25 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 165.45, 157.32, 143.76, 128.25, 98.34, 70.87, 69.76, 66.62, 48.81, 47.27, 37.65, 23.62.

*9-[1-(Hydroxymethyl)-cyclopent-3-enyl-methylphosphonic Acid]-adenine (**31**).* Compound **31** was synthesized from compound **23** using a similar procedure described for **27**: yield 78%; mp 140–143°C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.22 (s, 1H), 7.97 (s, 1H), 7.26 (br d, 2H), 4.13 (s, 2H), 3.80 (d, J = 7.8 Hz, 2H), 3.66 (s, 2H), 2.25 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 155.42, 151.67, 141.35, 128.55, 117.26, 71.12, 69.56, 49.78, 48.78, 37.20; Anal calc for $C_{13}H_{18}N_5O_4P \cdot 0.5$MeOH: C, 45.63; H, 5.67; N, 19.71. Found: C, 45.82; H, 5.44; N, 19.86.

*1-[1-(Hydroxymethyl)-cyclopent-3-enylmethylphsphonic Acid]-uracil (**32**).* Compound **32** was obtained from compound **24** using the method described for synthesizing compound **27**: yield 75%; mp 135–137°C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.36 (br s, 1H), 7.52 (d, J = 5.8 Hz, 1H), 5.55 (d, J = 5.8 Hz, 1H), 4.14 (s, 2H), 3.71 (d, J = 7.6 Hz, 1H), 3.62 (s, 2H), 2.26 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 164.65, 151.33, 145.71, 128.74, 102.76, 71.56, 69.91, 48.45, 47.02, 37.32; Anal calc for $C_{12}H_{17}N_2O_6P$: C, 45.59; H, 5.42; N, 8.86. Found: C, 45.47; H, 5.28; N, 8.69.

*1-[1-(Hydroxymethyl)-cyclopent-3-enylmethylphosphonic Acid]-thymine (**33**).* Compound **33** was prepared from compound **25** using the procedure described for synthesizing compound **27**: yield 70%; mp 145–147°C; UV (H_2O) λ_{max} 267.1 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.32 (br s, 1H), 7.51 (s, 1H), 4.27 (s, 2H), 3.80 (d, J = 8.0 Hz, 1H), 3.68 (s, 2H), 2.31 (s, 4H), 1.68 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.67, 153.39, 141.64, 128.65, 108.16, 70.67, 68.71, 48.28, 47.65, 38.31, 12.04; Anal calc for $C_{13}H_{19}N_2O_6P \cdot 0.7H_2O$: C, 45.53; H, 5.99; N, 8.17. Found: C, 45.65; H, 5.90; N, 8.33.

*1-[1-(Hydroxymethyl)-cyclopent-3-enylmethylphosphonic Acid]-cytosine (**34**).* Compound **34** was synthesized from compound **26** using the method described for compound **27**: yield 78%; mp 131–133°C; UV (H_2O) λ_{max}

272.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.82 (d, J = 5.8 Hz, 1H), 7.01 (br d, 2H), 5.69 (d, J = 5.8 Hz, 1H), 4.24 (s, 2H), 3.81 (d, J = 7.8 Hz, 2H), 3.62 (s, 2H), 2.26 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 165.72, 158.65, 145.94, 128.62, 97.45, 70.62, 69.53, 49.71, 47.25, 38.25; Anal calc for $C_{12}H_{18}N_3O_5P \cdot H_2O$: C, 43.25; H, 6.05; N, 12.61. Found: C, 43.11; H, 5.94; N, 12.48.

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