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Synthesis and Antiviral Evaluation of Novel Methyl Branched Cyclopropyl Phosphonic Acid Nucleosides

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A simple synthetic route for the synthesis of novel methyl branched cyclopropyl phosphonic acid nucleosides is described. The characteristic cyclopropyl moiety **8** was constructed by employing Simmons-Smith reaction as a key step. The condensation of mesylate **11** with natural nucleosidic bases (A,C,T,U) under standard nucleophilic substitution conditions (K_2CO_3, 18-*Crown*-6, DMF) and after subsequent hydrolysis resulted in the formation of target nucleosides, **16**, **17**, **18**, and **19**. In addition, the antiviral evaluations of the synthesized nucleotides against various viruses were also performed.

Key words: Antiviral reagent, Nucleoside, Nucleophilic substitution, Simmons-smith reaction

INTRODUCTION

Recently, novel nucleosides containing a cyclopropane moiety have been synthesized as conformationally constrained analogues of acyclic nucleosides. Amongst them, *trans*-configuration of the cyclopropyl adenine nucleoside (**1**) has been reported to exhibit moderate antiviral activity (Ashton *et al.*, 1988). The purine derivatives such as synadenol (**2**) (Qiu *et al.*, 1998a) and synguanol (**3**) (Qiu *et al.*, 1998b), in which the ribofuranoside moiety is replaced with a methylene cyclopropane ring were found to have potent antiviral activity, particularly against human cytomegalovirus (HCMV). Also, it has been reported that the guanine derivative (A-5021) (**4**) (Sekiyama *et al.*, 1998), which is one of the trisubstituted cyclopropane nucleosides with an additional hydroxymethyl group, exhibits more potent antiviral activity against HSV-1 than acyclovir (Fig. 1).

Furthermore, a number of acyclic nucleoside analogues bearing phosphonic acid group have been synthesized and evaluated for antiviral activity. Amongst them, PMEA (**5**) (Balzarini *et al.*, 1989; De Clercq *et al.*, 1987) shows a broad spectrum of antiviral activity against human immunodeficiency virus (HIV) (Noble and Goa 1999) and herpes simplex virus (HSV) (Starrett *et al.*, 1994). Unlike other nucleoside antiviral agents, a phosphonic acid nucleoside has the advantage of skipping the initially required phosphorylation step which is crucial for the activation of nucleosides (Bischofberger and Jones 1995).

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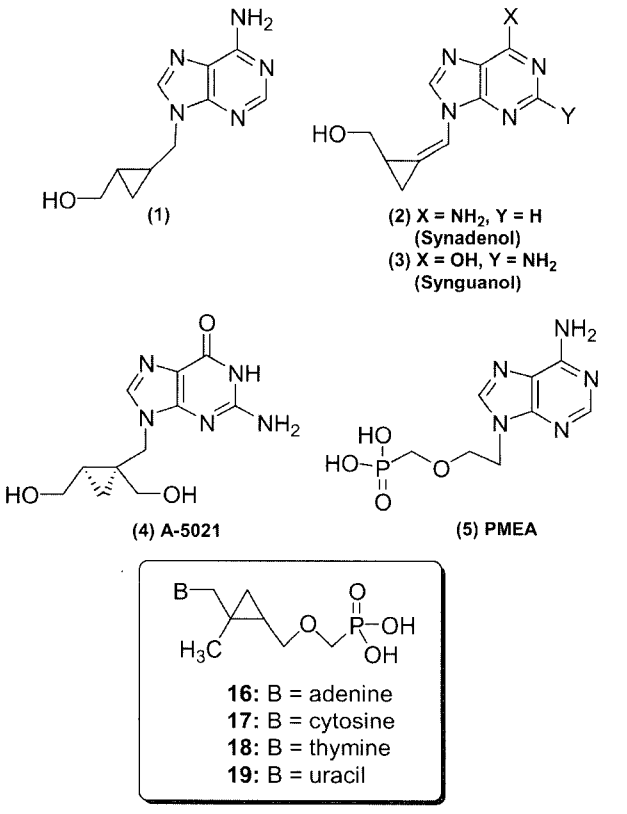


Fig. 1. Rationale for the design of target nucleosides

Based on the alluring structures of cyclopropyl nucleosides and the antiviral activities shown by acyclic phosphonic acid nucleosides, we were inspired to to synthesize novel classes of methyl branched cyclopropyl phosphonic acids as potential antiviral agents.

MATERIALS AND METHODS

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 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. Thin Layer Chromatography (TLC) was performed on Uniplates (silica gel) which were purchased from Analtech Co. All reactions were carried out under N_2 unless otherwise 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.

(±)-*trans*-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-cyclopropyl]-methanol (8)

To a mixture comprising of allylic alcohol (**7**) (1.87 g, 8.64 mmol) in 30 mL of CH_2Cl_2, $ZnEt_2$ (17.3 mL, 1 M in hexane) and CH_2I_2 (9.26 g, 34.58 mmol) were added at 0 °C. The mixture was stirred for 4 h at the same temperature and was quenched by the addition of a saturated solution of NH_4Cl. After the mixture was concentrated to 1/3 of its original volume, the aqueous layer was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to form **8** (1.61 g, 81%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.69 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.47 (dd, *J* = 10.8, 8.7 Hz, 1H), 3.39 (d, *J* = 9.9 Hz, 1H), 3.27 (d, *J* = 9.9 Hz, 1H), 1.10 (s, 3H), 0.99 (m, 1H), 0.85 (s, 9H), 0.61 (m, 1H), 0.15 (m, 1H), 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 70.54, 63.43, 25.94, 23.30, 22.12, 18.36, 15.33, 14.82, -5.30.

(±)-*trans*-[2-(*tert*-Butyldimethylsilanyloxymethyl)-2-methyl-cyclopropylmethoxymethyl]-phosphonic acid diisopropyl ester (9)

To a solution of **8** (1.64 g, 7.11 mmol) in 6 mL of DMF, LiI (72 mg, 0.53 mmol) was added at 25°C. Li*Ot*-Bu (11.4 mL of 1.0 M solution in THF, 11.4 mmol) and a solution of diisopropyl bromomethylphosphonate (2.5 g, 9.63 mmol) in 6 mL of DMF were slowly and simultaneously added to the reaction mixture for 4 h at 60°C under anhydrous condition. The mixture was quenched by adding water (35 mL), and the organic solvents (THF) were removed *in vacuo*. The aqueous layer was extracted with EtOAc (3×60 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 form **9** (1.89 g, 65%) as a colorless syrup: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.75 (m, 2H), 3.71 (d, J = 8.0 Hz, 2H), 3.68 (m, 2H), 3.40 (d, *J* = 9.8 Hz, 1H), 3.28 (d, *J* = 9.8 Hz, 1H), 1.31 (m, 12H), 1.09 (s, 3H), 1.00 (m, 1H), 0.82 (s, 9H), 0.56 (m, 1H), 0.21 (m, 1H), 0.12 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 71.71, 68.31, 66.54, 64.21, 25.67, 23.99, 23.45, 22.11, 18.45, 15.78, 14.65, -5.45; Anal calc for $C_{19}H_{41}O_5PSi$: C, 55.85; H, 10.11. Found: C, 56.02; H, 10.22.

(±)-*trans*-[2-(Hydroxymethyl)-2-methyl-cyclopropyl-methoxymethyl]-phosphonic acid diisopropyl ester (10)

To a solution of **9** (3.1 g, 7.60 mmol) in tetrahydrofuran (20 mL), tetrabutylammonium fluoride (9.88 mL, 1.0 M solution in THF) was added at 0°C and stirred for 5 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 form **10** (1.85 g, 83%) as a colorless syrup: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.70 (m, 2H), 3.73 (d, *J* = 8.2 Hz, 2H), 3.71 (m, 2H), 3.41 (m, 2H), 1.33 (m, 12H), 1.12 (s, 3H), 1.07 (m, 1H), 0.60 (m, 1H), 0.23 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 70.89, 69.45, 67.33, 65.12, 23.90, 23.23, 21.76, 14.88, 14.01.

(±)-*trans*-[Methanesulfonic acid-2-(diisopropoxy-phosphorylmethoxymethyl)-2-methyl-cyclopropyl-methyl] ester (11)

To a solution of phosphonate **10** (1.37 g, 4.68 mmol) in anhydrous CH_2Cl_2 (2 mL), anhydrous triethylamine (1.5 mL) and MsCl (642 mg, 5.61 mmol) were added at 0°C. The mixture was stirred at the same temperature for 5 h, and was quenched by the addition of cold saturated $NaHCO_3$ solution (2.0 mL). The mixture was extracted twice with CH_2Cl_2 (120 mL)/water (120 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to form **11** (1.16 g, 67%) as a colorless syrup: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.71 (m, 2H), 3.75 (d, *J* = 7.8 Hz, 2H), 3.70-3.66 (m, 2H), 3.44 (dd, *J* = 13.5, 8.8 Hz, 2H), 3.04 (s, 3H), 1.33 (m, 12H), 1.04 (s, 3H), 1.01 (m, 1H), 0.61 (m, 1H), 0.26 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 70.67, 69.12, 68.56, 65.21, 36.76, 24.21, 23.67, 22.17, 15.67, 14.32.

(±)-*trans*-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-2-methyl-cyclopropylmethylester]-adenine (12)

Mixture of mesylate **11** (311 mg, 0.837 mmol), K_2CO_3 (231 mg, 1.75 mmol), 18-crown-6 (221 mg, 0.837 mmol), and adenine (135.8 mg, 1.00 mmol) in dry DMF (9.0 mL) was stirred overnight at 90°C. The mixture was cooled to room temperature and concentrated *in high vacuo*. The residue was diluted with brine (30 mL) and extracted with CH_2Cl_2 (50 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 ($MeOH/CH_2Cl_2$, 1:10) to form compound **12** (130.8 mg, 38%) as a yellowish solid: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 8.02 (s, 1H), 4.72 (m, 2H), 4.61 (dd, *J* = 14.7, 6.6 Hz, 1H), 4.22 (dd, *J* = 14.4, 8.7 Hz, 1H), 3.71 (d, *J* = 8.4 Hz, 2H), 3.61 (d, *J* = 10.2 Hz, 1H), 3.22 (d, *J* = 10.2 Hz, 1H), 1.30 (m, 12H), 1.11 (s, 3H), 1.02 (m, 1H), 0.59 (m, 1H), 0.39 (t, J = 5.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 154.28, 152.65, 141.54, 118.76, 71.31, 70.22, 65.77, 50.61, 23.45, 23.15, 18.33, 15.66, 15.59.

(±)-*trans*-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-2-methyl-cyclopropylmethyl ester]-cytosine (13)

Compound **13** was prepared from **11** by following the method as described for **12**: the yield of **13** was 31%: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 7.5 Hz, 1H), 6.95 (br d, 2H), 5.63 (d, *J* = 7.5 Hz, 1H), 4.75 (m, 2H), 3.71-3.53 (m, 4H), 3.48 (d, *J* = 10.2 Hz, 1H), 3.32 (d, *J* = 10.2 Hz, 1H), 1.35 (m, 12H), 1.09 (s, 3H), 0.52 (m, 1H), 0.26 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 165.74, 155.92, 145.01, 92.91, 70.35, 69.48, 66.35, 48.02, 23.23, 22.01, 17.93, 15.26, 14.35.

(±)-*trans*-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmethyl ester]-thymine (14)

Compound **14** was prepared from **11** by following the method as described for **12**: the yield of **14** was 33%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.87 (s, 1H), 4.79 (m, 2H), 4.01 (dd, J = 13.5, 8.6 Hz, 1H), 3.74 (d, *J* = 7.8 Hz, 2H), 3.68 (d, *J* = 10.0 Hz, 1H), 3.47 (dd, *J* = 14.0, 9.9 Hz, 1H), 3.11 (d, J = 11. 1 Hz, 1H), 1.97 (s, 3H), 1.24 (m, 12H), 1.12 (s, 3H), 1.00 (m, 1H), 0.66 (m, 1H), 0.29 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 164.45, 153.34,139.91, 108.17, 71.76, 68.54, 64.23, 47.51, 23.77, 22.45, 17.43, 15.87, 13.87, 12.99.

(±)-*trans*-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmethyl ester]-uracil (15)

Compound **15** was prepared from **11** by following the method as described for **12**: the yield of **15** was 44%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, *J* = 8.1 Hz, 1H), 5.66 (d, *J* = 8.2 Hz, 1H), 4.87 (m, 2H), 4.05 (dd, *J* = 15.9, 6.6 Hz, 2H), 3.71 (d, *J* = 8.2 Hz, 2H), 3.66 (d, *J* = 9.9 Hz, 1H), 4.40 (dd, *J* = 15.0, 8.8 Hz, 1H), 3.09 (d, *J* = 11.1 Hz, 1H), 1.32 (m, 12H), 1.10 (s, 3H), 0.98 (m, 1H), 0.52 (m, 1H), 0.23 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 163.53, 151.12, 143.35, 101.82, 71.02, 70.87, 66.45, 47.67, 23.67, 22.64, 19.17, 15.49, 15.09.

(±)-*trans*-9-[2-(Methoxymethyl)-2-methyl-cyclopropylmethyl-phosphonic acid]-adenine (16)

To a solution of phosphonate **12** (157 mg, 0.382 mmol) in 10 mL of anhydrous methylene chloride $(CH_3)_3SiBr$ (0.63 g, 4.16 mmol)was added. The mixture was refluxed for overnight and concentrated *in vacuo*. The residue was partitioned between distilled water and washed out by CH_2Cl_2. The aqueous layer was dried by freez dryer to give **16** (96 mg, 77%) as a solid: UV (H_2O) λ_{max} 261.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.02 (s, 1H), 7.70 (s, 1H), 4.07 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.82 (dd, *J* = 13.8, 8.4 Hz, 1H), 3.71 (d, *J* = 8.1 Hz, 2H), 2.78 (m, 2H), 1.11 (s, 3H), 0.97 (m, 1H), 0.57 (m, 1H), 0.21 (m, 1H); ^{13}C-NMR (DMSO-d_6) δ 154.94, 152.42, 142.93, 115.87, 68.45, 65.82, 49.57, 23.10, 19.72, 15.50, 14.92.

(±)-*trans*-1-[2-(Methoxymethyl)-2-methyl-cyclopropylmethyl-phosphonic acid]-cytosine (17)

Compound **17** was prepared from **13** by following the method as described for **16**: the yield of **17** was 80%; UV (H_2O) λ_{max} 272.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.43 (d, *J* = 6.9 Hz, 1H), 6.69 (br d, 2H), 5.42 (d, *J* = 6.9 Hz, 1H), 3.91 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.51 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.30-2.85 (m, 2H), 1.00-0.83 (m, 4H), 0.55 (dd, *J* = 8.4, 3.9 Hz, 1H), 0.21 (t, *J* = 5.1 Hz, 1H); ^{13}C-NMR (DMSO-d_6) δ 165.81, 156.02, 145.42, 92.99, 68.69, 64.65, 48.25, 22.29, 19.68, 15.56, 14.67.

(±)-*trans*-1-[2-(Methoxymethyl)-2-methyl-cyclopropylmethyl phosphonic acid]-thymine (18)

Compound **18** was prepared from **14** by following the method as described for **16**: the yield of **18** was 72%; UV (H_2O) λ_{max} 267.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.74 (s, 1H), 3.98 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.71 (d, *J* = 8.2 Hz, 2H), 3.47 (dd, *J* = 14.5, 9.0 Hz, 1H), 3.02 (m, 2H), 1.92 (s, 3H), 1.12-0.99 (m, 4H), 0.63 (m, 1H), 0.30 (t, *J* = 5.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6) δ 164.67, 154.23, 140.65, 105.23, 68.54, 65.27, 46.35, 22.99, 17.71, 15.12, 14.89, 13.02.

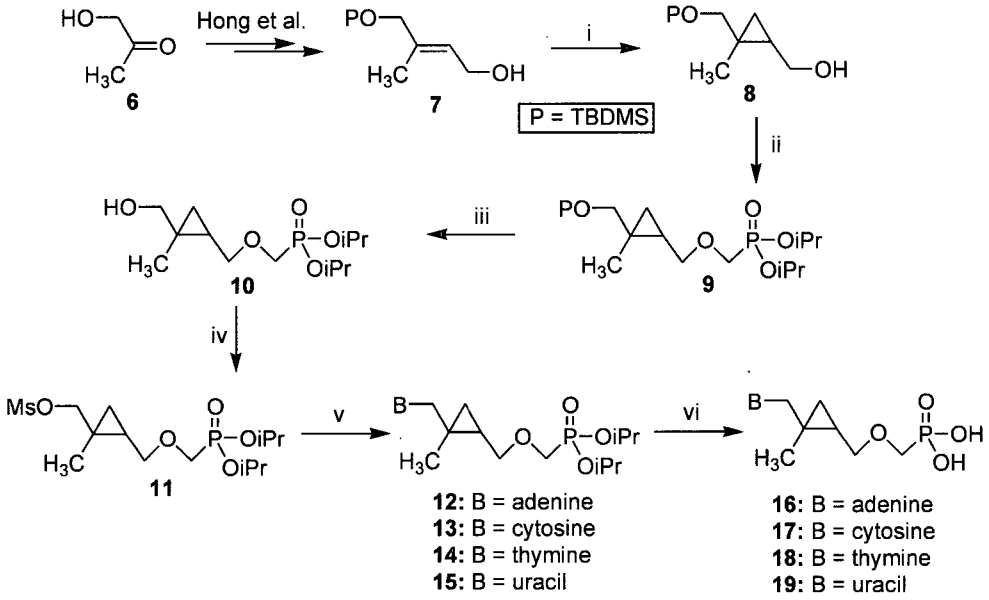
(±)-*trans*-1-[2-(Methoxymethyl)-2-methyl-cyclopropylmethyl phosphonic acid]-uracil (19)

Compound **19** was prepared from **15** by following the method as described for **16**: the yield of **19** was 74%; UV (H_2O) λ_{max} 262.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ

7.45 (d, J = 7.8 Hz, 1H), 5.30 (d, J = 7.7 Hz, 1H), 3.76 (d, J = 7.9 Hz, 2H), 3.55 (dd, J = 13.8, 81. Hz, 1H), 3.34 (dd, J = 14.4, 8.1 Hz, 1H), 2.96 (dd, J = 11.1, 6.0 Hz, 1H), 2.84 (dd, J = 11.1, 4.5 Hz, 1H), 1.02-0.98 (m, 4H), 0.59 (m, 1H), 0.29 (t, J = 5.2 Hz, 1H); ^{13}C-NMR (DMSO-d_6) δ 163.70, 151.04, 145.24, 100.67, 68.48, 64.87, 47.38, 22.49, 19.38, 15.52, 14.62.

RESULTS AND DISCUSSION

For the synthesis of target cyclopropyl nucleoside phosphonic acid, acetol **6** was selected as a starting material. As can be seen from Scheme 1, the synthetic route applied for the synthesis of target nucleosides is very simple and straightforward. Allylic alcohol **7** was readily synthesized by following the previously reported procedure (Hong *et al.*, 2003), which was subsequently subjected to Simmons-Smith carbene cycloaddition (Zhao *et al.*, 1995) in the presence of $ZnEt_2$ and CH_2I_2 to form cyclopropyl alcohol **8**. The hydroxyl group of **8** was phosphonated by treating it with diisopropyl bromomethylphosphonate in the presence of anhydrous DMF to form the key intermediate **9**. Silyl protection group was readily removed by the treatment with tetabutylammonum fluoride (TBAF) to form **10**. Compound **10** was methanesulfonylated in the presence of MsCl and TEA in anhydrous CH_2Cl_2 to form **11**, which was coupled with natural bases (adenine, cytosine, thymine, uracil) under well-known classical nucleophilic S_N2 substitution conditions (Hossain *et al.*, 1996) to form the acyclic nucleoside phosphonates **12-15**, respectively. Isopropyl groups of phosphonates were readily hydrolyzed by treatment with trimethylsilylbromide (CH_3SiBr) (El Subbagh *et al.*, 1996) to form final nucleoside phosphonic acids, **16-19**.



Reagents: i) CH_2I_2, $ZnEt_2$, CH_2Cl_2; ii) Diisopropyl bromomethylphosphonate, LiOt-Bu, LiI, DMF; iii) TBAF, THF; iv) MsCl, TEA, CH_2Cl_2; v) Bases, K_2CO_2, 18-C-6, DMF; vi) $(CH_3)_3SiBr$, CH_2Cl_2.

Scheme 1. Synthesis of cyclopropyl phosphonic acid nucleosides

Table I. The antiviral activities of the synthesized compounds

Compounds	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HCMV EC_{50} (μg/mL)	CoxB3 EC_{50} (μg/mL)	cytotoxicity IC_{50} (μg/mL)
16	>100	>100	>100	>100	>100
17	55.7	>100	>100	43.56	>100
18	>100	>100	>100	>100	>100
19	>100	>100	>100	>100	>100
AZT	0.0007	ND	ND	ND	0.5
Ganciclovir	ND	1.24	ND	ND	>10
Ribavirin	ND	ND	ND	30.43	>300

ND: Not Determined

The antiviral assays of the target nucleosides were performed against HIV-1, HSV-1, HCMV, and CoxB3 and the results are shown in Table I. None of the compound exhibited excellent antiviral activity. In the case of cytosine analogue **17**, weak activities against HIV-1 and CoxB3 were observed, without any significant toxicity to the host cell.

To conclude, we have successfully synthesized novel methyl branched cyclopropyl nucleoside phosphonic acids by employing acetol as a starting material and by following Simmons-Smith reaction as a key step. However, when compared with other nucleoside derivatives, cytosine derivative **17** exhibited weak anti-HIV-1 and CoxB3 activity. The results derived from the present study will be useful for the further development of novel cyclopropyl nucleoside phosphonic acids.

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