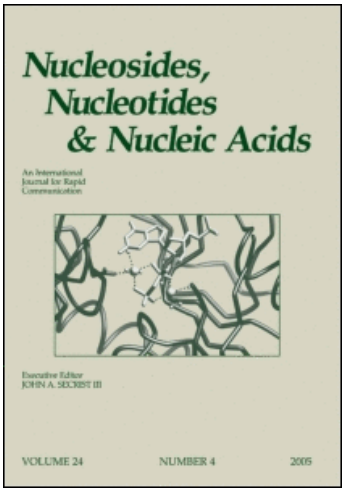

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SIMPLE SYNTHESIS AND ANTI-HIV ACTIVITY OF NOVEL CYCLOPENTENE PHOSPHONATE NUCLEOSIDES

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□ *A very simple synthetic route for novel cyclopentene phosphonate nucleosides is described. The characteristic cyclopentene moiety* ***6*** *was constructed via a ring-closing metathesis of divinyl* ***5****, which could be readily prepared from diethylmalonate. The condensation of the mesylate* ***11*** *with nucleobases (A,C,T,U) under nucleophilic substitution conditions (K_2CO_3, 18-*Crown-*6, DMF) afforded the target nucleosides* ***12****,* ***13****,* ***14****, and* ***15****. In addition, the antiviral evaluations against various viruses were performed.*

Keywords Acyclic phosphonate nucleoside; PMEA; Adefovir dipivoxil

INTRODUCTION

Nucleoside analogues have been the cornerstone of antiviral therapy over the past 30 years. In the effort to discover effective antiviral agents, a large number of nucleoside analogues have been synthesized and evaluated. Although structure-activity relationship studies have not led to a pharmacophore model for the antiviral activities of nucleosides, some structural features have been particularly successful. So far, seven nucleoside analogues (AZT, ddC, ddI, d4T, 3TC, abacavir, and *bis*(POC)PMPA) were approved by the FDA for the treatment of AIDS. Recently, a number of acyclic nucleoside analogues with phosphonate group have been synthesized and evaluated for antiviral activity. Among them, tenofovir disoproxil (**1**)[1,2] has been synthesized and reported to have anti-HIV activity through inhibition of HIV reverse transcriptase. For HBV therapy, the FDA recently approved adefovir dipivoxil[3,4] (**2**), which is a prodrug of the phosphonate nucleoside, 9-[2-(phosphonomethoxy)ethyl] adenine (PMEA). In addition

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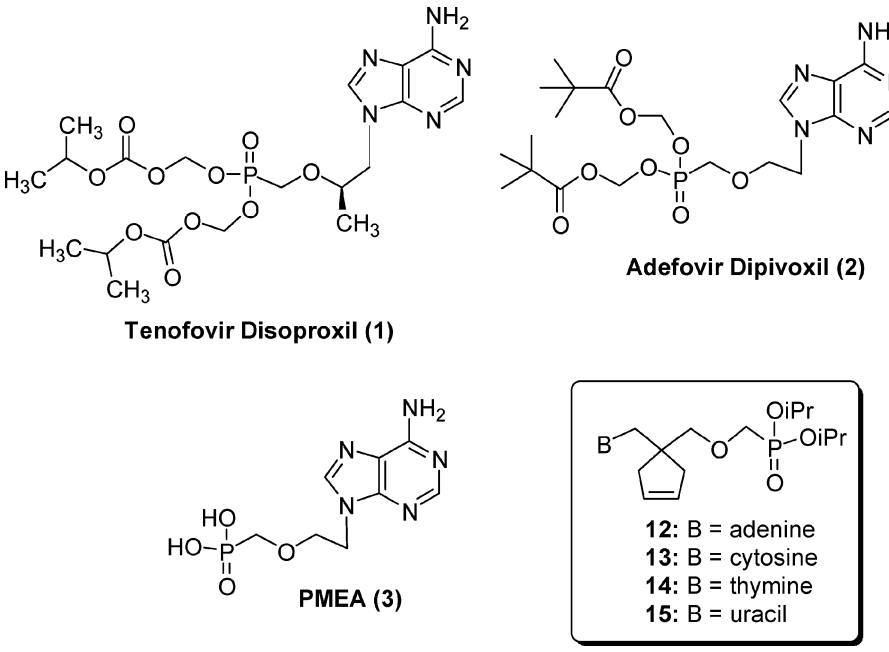
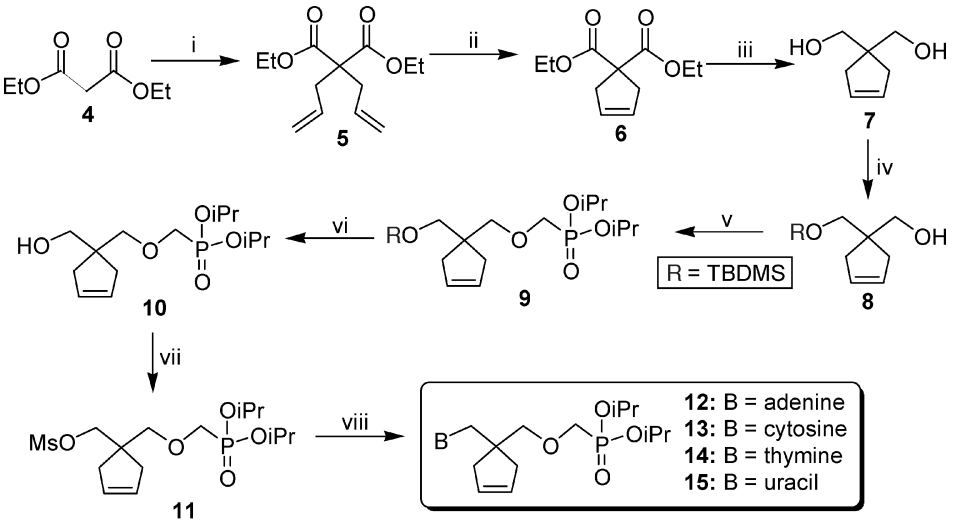


FIGURE 1 Rationale to the design of target nucleosides.

to anti-HBV activity, PMEA (**3**)[5,6] shows a broad spectrum of antiviral activity against human immunodeficiency virus (HIV)[7] and the herpes simplex virus (HSV) (Figure 1).[8] Unlike nucleoside agents, a phosphonate nucleoside has the advantage of skipping the requisite first phosphorylation, which is crucial step for the activation of nucleosides.[9] Encouraged by these interesting structures and antiviral activities of acyclic phosphonate nucleosides, this study is aimed to synthesize novel classes of cyclopentene phosphonate nucleosides.

RESULTS AND DISCUSSION

For the synthesis of 1,1-cyclopentenyl geminated acyclic nucleosides, diethyl malonate **4** was selected as starting material. As shown in Scheme 1, the synthetic route is very simple and straightforward. Double allylation of active methylene group of **4** and ring-closing metathesis (RCM) of corresponding divinyl **5** provided cyclopentene derivative **6** in a high yield.[10,11] Reduction of the ester functional group of **6** followed by a monosilylation of diol **7** provided the alcohol derivative **8**. The hydroxyl group of **8** was phosphonated by treating with diisopropyl bromomethylphosphonate in an anhydrous THF to give the key intermediate **9**, which was readily desilylated



SCHEME 1 Synthesis of acyclic phosphonate nucleosides.

by the tetrabutylammonium fluoride (TBAF) to provide **10**. Compound **10** was activated by methanesulfonylation with MsCl and TEA in anhydrous CH_2Cl_2 to give **11**, which was coupled with natural bases (adenine, cytosine, thymine, uracil) under nucleophilic S_N2 substitution conditions (K_2CO_3, 18-*C*-6, DMF)[12] to give the cyclopentene nucleoside phosphonates **12–15**, respectively.

The antiviral assays (13) against human immunodeficiency virus 1 (HIV-1) and herpes simplex virus 1 and 2 (HSV-1,2) were performed and the results are shown in Table 1. As shown in Table 1, any tested compounds did not display antiviral activity except cytosine nucleoside **13**, which exhibited moderate anti-HIV activity in MT-4 cell ($EC_{50} = 20.5$ μmol).

TABLE 1 Antiviral Activities of the Synthesized Compounds

	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HSV-2 EC_{50} (μg/mL)	Cytotoxicity IC_{50} (μg/mL)
16	>100	>100	>100	>100
17	**20.5**	>100	>100	>100
18	>100	>100	>100	>100
19	60.0	>100	>100	>100
AZT	0.0009	ND	ND	1.02
ACV	ND	0.98	5.21	250

ND: Not determined.

EXPERIMENTAL SECTION

The melting points were determined on a Meltem II laboratory device and are 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. The elemental analyses were performed using an elemental analyzer system (EA 1112). 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 distillation from CaH_2. The dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

2,2-Diallyl-malonic Acid Diethyl Ester (5). To a stirred suspension of sodium hydride (3.74 g, 0.156 mol) in tetrahydrofuran (250 mL) was slowly added diethyl malonate **4** (10 g, 62.4 mmol) at 0°C and stirred 2 h at room temperature. To this mixture was slowly added allyl bromide (15.8 g, 0.131 mol) at 0°C and further stirred for 4 h at RT before quenching with saturated NH_4Cl solution (10 mL). The mixture was extracted using EtOAc (300 mL)/water (300 mL); the organic layer was dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **5** (14.7 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72–5.58 (m, 2H), 5.13 (m, 2H), 5.08 (s, 2H), 4.17 (q, J = 6.9 Hz, 4H), 2.64 (d, J = 8.4 Hz, 4H), 1.25 (t, J = 6.9 Hz, 6H).

Cyclopent-3-ene-1,1-dicarboxylic Acid Diethyl Ester (6). To a stirred solution of **5** (5.0 g, 20.8 mmol) in anhydrous CH_2Cl_2 (100 mL) was added Grubbs' reagent [$Cl_2(Cy_3P)RuCHC_6H_5$] (855 mg, 1.04 mmol) at 0°C and stirred for 5 h at rt. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **6** (4.19 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (s, 2H), 4.18 (q, J = 6.9 Hz, 4H), 3.00 (s, 4H), 1.24 (t, J = 6.9 Hz, 6H).

(1-Hydroxymethyl-cyclopent-3-enyl)-methanol (7). To a suspension of lithium aluminum hydride (1.2 g, 31.6 mmol) in dry tetrahydrofuran (40 mL) was added a solution of diethylester **6** (2.37 g, 11.2 mmol) in dry tetrahydrofuran (30 mL) dropwise at 0°C. The resulting suspension was stirred overnight at 0°C. The suspension was quenched with water (1.24 mL), 15% sodium hydroxide (1.24 mL), and water (3.7 mL) at the same temperature. The mixture was stirred at room temperature for 2 h. The white gel suspension was filtered through a pad of Celite and concentrated *in vacuo*. The residue

was purified by silica gel column chromatography (EtOAc/n-Hexane, 4:1) to give diol **7** (1.17 g, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (s, 2H), 3.67 (s, 4H), 2.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 128.74, 69.83, 47.54, 38.63; Anal calc for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.38; H, 9.30.

[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclopent-3-enyl]-methanol (8). To a stirred solution of **7** (451 mg, 3.52 mmol) and imidazole (477 mg, 7.02 mmol) in CH_2Cl_2 (25 mL), *t*-butyldimethylsilyl chloride (531 mg, 3.52 mmol) was added at 0°C. The mixture was stirred for 5 h at 0°C, and quenched by adding a $NaHCO_3$ solution (3 mL). The mixture was extracted using EtOAc (100 mL), dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **8** (810 mg, 95%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.53 (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, 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.

Diisopropyl{[1-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclopent-3-enyl]-oxy}methylphosphonate (9). To a solution of the cyclopentenol **8** (2.3 g, 9.48 mmol) in 5 mL of DMF was added LiI (95 mg, 0.71 mmol) at 25°C. Both Li*O*t-Bu (15.2 mL of 1.0 M solution in THF, 15.2 mmol) and a solution of diisopropyl bromomethylphosphonate (3.33 g, 12.85 mmol) in 5 mL of DMF were slowly added to the reaction mixture and stirred for 2 h at 60°C under anhydrous condition. The mixture was quenched by adding water (50 mL), and the organic solvents were removed in *vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give **9** (2.55 g, 64%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.53 (s, 2H), 4.72 (m, 2H), 3.72 (d, J = 8.1 Hz, 2H), 3.45 (d, J = 3.6 Hz, 4H), 2.13 (s, 4H), 1.30 (m, 12H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 128.79, 76.90, 76.76, 70.72, 67.31, 65.86, 65.09, 47.82, 31.74, 25.53, 23.92, 18.15, −5.57; Anal calc for $C_{20}H_{41}O_5PSi$: C, 57.11; H, 9.83. Found: C, 57.02; H, 10.01.

Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate (10). To a solution of **9** (3.5 g, 8.32 mmol) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (9.98 mL, 1.0 M solution in THF) at 0°C and stirred for 4 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 **10** (2.21 g, 87%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (s, 2H), 4.76 (m, 2H), 3.74 (dd, J = 6.6, 0.9 Hz, 2H), 3.62 (s, 2H), 3.52 (s, 2H), 2.25 (d, J = 15.3 Hz, 2H), 2.16 (d, J = 15.2 Hz, 2H), 1.35 (d, J = 6.3 Hz, 12H); ^{13}C NMR ($CDCl_3$)

δ 128.68, 78.35, 78.27, 71.17, 67.16, 66.79, 64.59, 47.52, 38.84, 23.96; Anal calc for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88. Found: C, 54.67; H, 8.73.

Methanesulfonic Acid 1-[Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate] Ester (11). To a solution of the alcohol **10** (637 mg, 2.08 mmol) in anhydrous CH_2Cl_2 (20 mL), anhydrous triethylamine (0.61 mL) and MsCl (292 mg, 2.52 mmol) were added at 0°C. The mixture was stirred at the same temperature for 4 h and quenched by a cold saturated $NaHCO_3$ solution (1.5 mL). The mixture was extracted with CH_2Cl_2 (150 mL) and water (150 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under vacuum, and the residue was purified by flash silica gel column chromatography (EtOAc/hexane, 4:1) to give **11** (600 mg, 75%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (s, 2H), 4.72 (m, 2H), 4.16 (s, 2H), 3.75 (d, J = 9.3 Hz, 2H), 3.52 (s, 3H), 2.26 (s, 4H), 1.34 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 128.42, 75.88, 75.73, 72.38, 70.97, 67.23, 65.00, 46.02, 38.79, 36.88, 23.99; Anal calc for $C_{15}H_{29}O_7PS$: C, 46.86; H, 7.60. Found: C, 46.78; H, 7.72.

9-[1-[Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate]] Adenine (12). A solution of the mesylate **11** (395 mg, 1.03 mmol), K_2CO_3 (288 mg, 2.08 mmol), 18-crown-6 (410 mg, 1.57 mmol), and adenine (142 mg, 1.05 mmol) in dry DMF (12.0 mL) was stirred overnight at 90°C. The mixture was cooled to room temperature and concentrated under high vacuo. The residue was diluted with brine (50 mL) and extracted with CH_2Cl_2 (50 mL $\times$ 3). The combined organic layer were 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 give compound **12** (227 mg, 52%) as a yellow solid: UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1H), 8.11 (s, 1H), 6.83 br s, 2H), 5.62 (s, 2H), 4.84 (m, 2H), 4.33 (s, 2H), 3.80 (d, J = 8.4 Hz, 2H), 3.37 (s, 2H), 2.52 (d, J = 14.7 Hz, 2H), 2.20 (d, J = 14.7 Hz, 2H), 1.38 (dd, J = 6.3, 2.7 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 155.72, 152.78, 150.56, 142.00, 128.49, 119.05, 70.98, 67.03, 64.80, 47.83, 47.56, 40.05, 24.00, 22.56; Anal calc for $C_{19}H_{30}N_5O_4P$: C, 53.89; H, 7.14; N, 16.54. Found: C, 54.11; H, 6.97; N, 16.36.

1-[1-[Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate]] Cytosine (13). Compound **13** was prepared from **11** using the method as described for **12**: yield 42%; UV (MeOH) λ_{max} 271.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 6.0 Hz, 1H), 6.11 (d, J = 6.0 Hz, 1H), 5.60 (s, 2H), 4.72 (m, 2H), 4.20 (s, 2H), 3.76 (d, J = 7.8 Hz, 2H), 3.63

(s, 2H), 2.32 (s, 2H), 1.28 (t, J = 6.0 Hz, 12H); ^{13}C NMR ($CDCl_3$) δ 164.96, 156.42, 145.60, 128.76, 99.50, 71.08, 69.65, 67.24, 65.04, 46.05, 39.15, 23.98; Anal calc for $C_{18}H_{30}N_3O_5P$: C, 54.13; H, 7.57; N, 10.52. Found: C, 54.33; H, 7.42; N, 10.59.

1-[1-[Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate]] Thymine (14). Compound **14** was prepared from **11** using the method as described for **12**: yield 38%; UV (MeOH) λ_{max} 266.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1H), 5.60 (s, 1H), 5.55 (s, 1H), 4.72 (m, 2H), 4.15 (s, 1H), 3.88 (s, 1H), 3.70 (t, J = 7.5 Hz, 2H), 3.48 (s, 1H), 3.85 (s, 1H), 2.30 (d, J = 14.4 Hz, 2H), 1.95 (d, J = 14.4 Hz, 2H), 1.34 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 165.34, 153.34, 139.93, 128.83, 109.16, 79.08, 70.80, 67.13, 64.90, 52.41, 48.56, 48.06, 46.28, 39.68, 39.19, 24.04, 13.06; Anal calc for $C_{19}H_{31}N_2O_6P$: C, 55.06; H, 7.54; N, 6.76. Found: C, 54.87; H, 7.40; N, 6.89.

1-[1-[Diisopropyl{[1-(hydroxymethyl)-cyclopent-3-enyl]oxy}methylphosphonate]] Uracil (15). Compound **15** was prepared from **11** using the method as described for **12**: yield 40%; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.41 (br s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 5.65 (s, 2H), 5.52 (d, J = 7.8 Hz, 1H), 4.77 (m, 2H), 4.23 (s, 2H), 3.81 (d, J = 7.8 Hz, 2H), 3.63 (s, 2H), 2.12 (s, 2H), 1.30 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 164.76, 150.45, 147.23, 128.65, 100.25, 71.45, 69.62, 66.90, 65.12, 45.87, 39.81, 23.99; Anal calc for $C_{18}H_{29}N_2O_6P$: C, 53.99; H, 7.30; N, 7.00. Found: C, 54.23; H, 7.40; N, 6.81.

CONCLUSION

We have completed the synthesis and biological evaluation of novel cyclopentene phosphonate nucleosides, starting from diethylmalonate. None of the synthesized compounds exhibited antiviral activity except cytosine derivative **13**, which showed moderate anti-HIV activity.

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