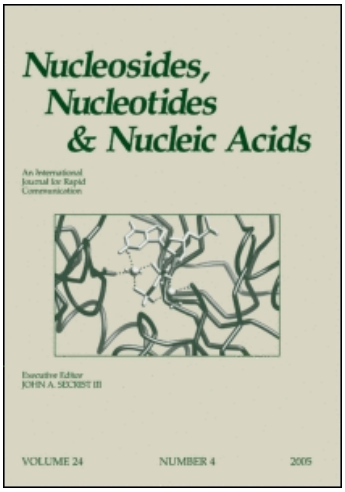

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SYNTHESIS AND ANTI-HCMV ACTIVITY OF NOVEL CYCLOPROPYL PHOSPHONIC ACID NUCLEOSIDES

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□ *A simple synthetic route for novel acyclic phosphonate nucleosides is described. The characteristic cyclopropyl moiety* ***8*** *was constructed employing the Simmons-Smith reaction as key step starting from simple acyclic 2-butene-1,4-diol. The condensation of the mesylate* ***11*** *with natural nucleosidic bases (A,C,T,U) under nucleophilic substitution conditions (K_2CO_3, 18-Crown-6, DMF) and hydrolysis afforded the target nucleosides* ***16, 17, 18,*** *and* ***19****. In addition, the antiviral evaluations against various viruses were performed.*

Keywords Antiviral agent; Cyclopropyl phosphonic acid nucleosides; Simmons-Smith reaction

INTRODUCTION

Recently, novel nucleosides containing a cyclopropane moiety also were synthesized as conformationally constrained analogues of acyclic nucleosides. Among them, *trans*-configuration of the cyclopropyl adenine nucleoside (**1**) showed moderate antiviral activity.[1] The purine derivatives such as synadenol (**2**)[2] and synguanol (**3**),[3] of which the ribofuranoside moiety is replaced with a methylene cyclopropane ring, were found to have potent antiviral activity, particularly against human cytomegalovirus (HCMV). Also, the guanine derivative (A-5021) (**4**),[4] which was one of trisubstituted cyclopropane nucleosides with an additional hydroxymethyl group at 1′-position, showed more potent antiviral activity against HSV-1 than acyclovir (Figure 1).

Furthermore, a number of acyclic nucleoside analogues with phosphonate group have been synthesized and evaluated for antiviral activity. Among

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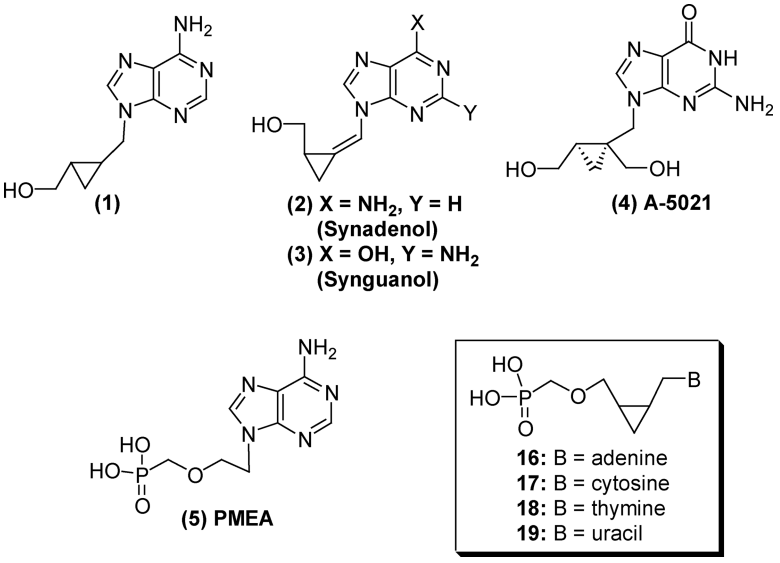
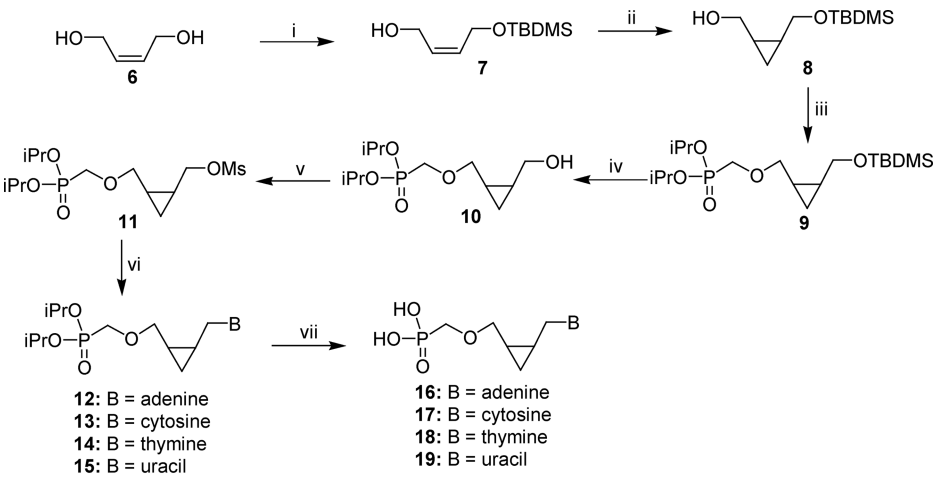


FIGURE 1 Rationale to the design of target nucleosides.

them, PMEA (**5**)[5,6] shows a broad spectrum of antiviral activity against human immunodeficiency virus (HIV)[7] and also the herpes simplex virus (HSV).[8] Unlike nucleoside agents, a phosphonate nucleoside has the advantage of skipping the requisite initial phosphorylation, which is the crucial step for the activation of nucleosides.[9] Encouraged by the interesting structures of cyclopropyl nucleosides and antiviral activities of acyclic phosphonate nucleosides, this study aimed to synthesize novel classes of cyclopropyl phosphonic acids as potential antiviral agents.

RESULTS AND DISCUSSION

For the synthesis of target cyclopropyl nucleoside phosphonic acid, cis-2-butene-1,4-diol **6** was selected as the starting material. As shown in Scheme 1, the synthetic route is very simple and straightforward. Selective monosilylation of diol **6** provided the alcohol derivative **7**, which was subjected to the Simmons-Smith carbene cycloaddition condition[10] using $Zn(Et)_2$ and CH_2I_2 to give cyclopropyl alcohol **8**. The hydroxyl group of **8** was phosphonated by treating with diisopropyl bromomethanephosphonate in anhydrous DMF to give the key intermediate **9**.[11] The silyl protecting group was then readily removed by the treatment of tetrabutylammonum fluoride (TBAF) to provide **10**. Compound **10** was methanesulfonylated with MsCl and TEA in anhydrous CH_2Cl_2 to give **11**, which was coupled with natural bases (adenine, cytosine, thymine, uracil) under well-known nucleophilic S_N2 substitution conditions[12] to give the acyclic nucleoside phosphonates **12**∼**15**, respectively. The diisopropyl groups of phosphonates



Reagents: i) TBDMSCl, imidazole, CH_2Cl_2; ii) CH_2I_2, $Zn(Et)_2$, 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 cyclopropyl phosphonic acid nucleosides.

were readily hydrolyzed using trimethylsilylbromide[13] to give final nucleoside phosphonic acids **16**∼**19.**

The antiviral assays against HIV-1, HSV-1, HCMV, and CoxB3 were performed and the results are shown in Table 1. As shown in Table 1, only the adenine analogue **16** was found to show moderate activities against HCMV, without significant toxicities to the host cell.

In conclusion, we successfully synthesized novel cyclopropyl nucleoside phosphonic acids **16**∼**19** starting from acyclic 2-butene-1,4-diol, employing the Simmons-Smith reaction as the key step. Only adenine derivative **18** exhibited moderate anti-HCMV activity. The information obtained in the present study will be useful for the development of novel cyclopropyl nucleoside phosphonic acids. Studies toward this end and to clarify the mechanism are underway.

TABLE 1 The antiviral activities of the synthesized 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	22.80	>100	>100
17	>100	>100	>100	>100	>100
18	>100	>100	>100	>100	>100
19	>100	>100	>100	>100	>100
AZT	0.0008	ND	ND	ND	1.0
Ganciclovir	ND	1.34	0.77	ND	>10
Ribavirin	ND	ND	ND	25.43	>300

ND: not determined.

EXPERIMENTAL

The melting points were determined on a Mel-tem II laboratory device and are uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer (JEOL, Tokyo, Japan). 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. 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.

*cis-4-(tert-Butyldimethylsilanyloxy)-but-2-en-1-ol (**7**).* To a stirred solution of **6** (5.0 g, 56.74 mmol) and imidazole (7.72 g, 0.113 mol) in CH_2Cl_2 (250 mL), *t*-butyldimethylsilyl chloride (8.55 g, 56.74 mmol) was added slowly at 0°C. The mixture was stirred for 5 hours at 0°C, and concentrated in vacuo. The residue was extracted using EtOAc/H_2O, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **7** (7.0 g, 61%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (d, J = 4.8 Hz, 2H), 4.17 (d, J = 4.5 Hz, 2H), 4.11 (d, J = 4.5 Hz, 2H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 131.31, 130.08, 59.58, 58.83, 25.90, 18.32, −5.24.

*(±)-cis-[2-(tert-Butyldimethylsilanyloxymethyl)-cyclopropyl]-methanol (**8**).* To a mixture of **7** (3.5 g, 17.29 mmol) in 50 mL of CH_2Cl_2 at 0°C was added $Zn(Et)_2$ (34.58 mL, 1 M in hexane) and CH_2I_2 (69.16 mmol). The mixture was stirred at 0°C for 3 hours and quenched with a saturated NH_4Cl. After the mixture was concentrated to one-third of the 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, 1:10) to give **8** (2.95 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.07 (dd, J = 11.1, 5.4 Hz, 1H), 3.84 (m, 1H), 3.10 (m, 2H), 1.25 (m, 1H), 1.13 (m, 1H), 0.97 (s, 9H), 0.78 (m, 1H), 0.32 (m, 1H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 63.85, 63.09, 25.81, 18.45, 18.15, 15.36, 8.35, −5.56.

*(±)-cis-[2-(tert-Butyldimethylsilanyloxymethyl)-cyclopropyl–methoxymethyl]-phosphonic acid diisopropyl ester (**9**).* To a solution of **8** (3.07 g, 14.22 mmol) in 10 mL of DMF was added LiI (143 mg, 1.06 mmol) at 25°C. Li*O*t-Bu (22.8 mL of 1.0M solution in THF, 22.8 mmol) and a solution of diisopropyl bromomethylphosphonate (4.99 g, 19.27 mmol) in 10 mL of DMF were slowly and simultaneously added to the reaction mixture for 3 hours at 60°C under anhydrous condition. The mixture was quenched by adding water (70 mL), and the organic solvents (THF) were removed in vacuo. The aqueous layer was extracted with EtOAc (3 × 70 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, 1:1.5) to give **9** (3.70 g, 66%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.67 (m, 2H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.50 (m, 4H), 1.35 (m, 13H), 1.18 (m, 1H), 0.91 (s, 9H), 0.72 (m, 1H), 0.35 (m, 1H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 69.81, 66.87, 64.34, 63.77, 25.80, 23.81, 18.78, 18.21, 17.35, 7.64, −5.41; Anal calc for $C_{18}H_{39}O_5PSi$: C, 54.79; H, 9.96. Found: C, 54.99; H, 9.70.

*(±)-cis-[2-(Hydroxymethyl)-cyclopropylmethoxymethyl]-phosphonic acid diisopropyl ester (**10**).* To a solution of **9** (2.0 g, 5.07 mmol) in tetrahydrofuran (15 mL) was added tetrabutylammonium fluoride (6.08 mL, 1.0 M solution in THF) at 0°C and stirred for 3 hours 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** (1.15 g, 81%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (m, 2H), 3.82 (d, $J =$ 8.2Hz, 2H), 3.67 (m, 4H), 1.41 (m, 12H), 1.29 (m, 2H), 0.86 (m, 1H), 0.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 71.21, 66.72, 65.98, 64.12, 23.85, 18.23, 14.65, 7.98.

*(±)-cis-Methanesulfonic acid-2-(diisopropoxy-phosphorylmethoxym-ethyl)-cyclopropylmethyl ester (**11**).* To a solution of the phosphonate **10** (874 mg, 3.12 mmol) in anhydrous CH_2Cl_2 (30 mL), anhydrous triethylamine (1.0 mL) and MsCl (428 mg, 3.74 mmol) was added at 0°C. The mixture was stirred at the same temperature for 5 hours, and quenched by a cold saturated $NaHCO_3$ solution (1.5 mL). The mixture was extracted with CH_2Cl_2 (150 mL)/water (150 mL). The 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 give **11** (693 mg, 62%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.80 (m, 2H), 3.73 (d, $J = 8.2$ Hz, 2H), 3.64–4.55 (m, 4H), 3.05 (s, 3H), 1.37 (m, 12H), 1.21 (m, 2H), 0.83 (m, 1H), 0.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 71.45, 65.43, 63.45, 65.67, 36.43, 23.93, 20.34, 18.55, 14.32, 7.12.

*(±)-cis-9-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmethyl ester]adenine (**12**).* A solution of the mesylate **11** (200 mg, 0.558 mmol), K_2CO_3 (154 mg, 1.17 mmol), 18-crown-6 (221 mg, 0.837 mmol), and adenine (90.53 mg, 0.67 mmol) in dry DMF (5.0 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 (20 mL) and extracted with CH_2Cl_2 (20 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 give compound **12** (90.9 mg, 41%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 8.05 (s, 1H), 5.61 (br s, 2H), 4.85 (m, 2H), 4.33 (dd, $J = 14.4$, 6.3 Hz, 1H), 4.11–3.96 (m, 2H), 3.71 (d, $J = 8.4$, Hz, 2H), 3.50 (dd, $J = 11.7$,

8.7 Hz, 1H), 1.38–1.23 (m, 14H), 0.87 (m, 1H), 0.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.96, 152.30, 140.84, 118.62, 71.23, 66.45, 62.21, 42.96, 23.56, 18.21, 15.83, 7.56.

*(±)-cis-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmethyl ester]-cytosine (**13**).* Compound **13** was prepared from **11** using the method as described for **12**: yield 41%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J = 7.5 Hz, 1H), 5.60 (d, J = 7.5 Hz, 1H), 4.81 (m, 2H), 4.10 (dd, J = 14.4, 5.7 Hz, 1H), 3.90 (dd, J = 12.3 Hz, 1H), 3.72 (d, J = 8.1 Hz, 2H), 3.49–3.33 (m, 2H), 1.30–1.23 (m, 14H), 0.80 (m, 1H), 0.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 165.63, 156.79, 145.96, 93.52, 69.87, 65.98, 62.35, 47.78, 23.59, 18.27, 15.23, 6.89.

*(±)-cis-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmet-hyl ester]thymine (**14**).* Compound **14** was prepared from **12** using the method as described for **12**: yield 40%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (s, 1H), 4.87 (m, 2H), 3.96–3.88 (m, 2H), 3.70 (d, J = 8.3 Hz, 2H), 3.52 (dd, J = 14.7, 7.2 Hz, 1H), 3.37 (dd, J = 11.4, 8.1 Hz, 1H), 1.84 (s, 3H), 1.36–1.20 (m, 14H), 0.79 (m, 1H), 0.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.65, 153.63, 138.76, 109.21, 71.05, 65.65, 63.23, 45.56, 24.09, 18.12, 15.87, 13.02, 7.34.

*(±)-cis-1-[2-(Diisopropoxy-phosphorylmethoxymethyl)-cyclopropylmethyl ester]uracil (**15**).* Compound **15** was prepared from **11** using the method as described for **12**: yield 44%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, J = 6.8 Hz, 1H), 5.62 (d, J = 6.8 Hz, 1H), 4.80 (m, 2H), 4.09 (dd, J = 14.1, 5.1 Hz, 1H), 3.99 (dd, J = 11.7, 4.8 Hz, 1H), 3.66 (s, 2H), 3.33–3.29 (m, 2H), 1.30 (m, 12H), 1.21 (m, 2H), 0.82 (m, 1H), 0.29 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.75, 151.09, 144.91, 101.79, 70.99, 65.21, 62.18, 46.18, 23.67, 18.30, 15.01, 6.70.

*(±)-cis-9-[2-(Methoxymethyl)-cyclopropylmethyl-phosphonic acid] adenine (**16**).* To a solution of the phosphonate **12** (304 mg, 0.765 mmol) in 25 mL of anhydrous methylene chloride was added $(CH_3)_3SiBr$ (1.26 g, 8.32 mmol). The mixture was refluxed for overnight and concentrated in vacuo. The residue was partitioned between distilled water and washed with CH_2Cl_2 2 times. The aqueous layer was dried by freezer dryer to give **16** (177 mg, 74%) as a solid: UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.19 (s, 1H), 8.01 (s, 1H), 5.61 (br s, 2H), 7.07 (br s 2H), 4.68 (t, J = 5.6 Hz, 1H), 4.12 (dd, J = 13.5, 6.6 Hz, 1H), 3.97 (dd, J = 14.4, 7.2 Hz, 1H), 3.71 (d, J = 8.0 Hz, 2H), 3.62–3.52 (m, 1H), 3.28–3.24 (m, 2H), 1.29–0.96 (m 2H), 0.57 (m, 1H), 0.20 (m,1H); ^{13}C NMR (DMSO-d_6) δ 155.89, 152.21, 149.76, 140.78, 112.41, 71.46, 60.17, 42.42, 18.71, 15.81, 7.74.

*(±)-cis-1-[2-(Methoxymethyl)-cyclopropylmethyl-phosphonic acid] cytosine (**17**).* Compound **17** was prepared from **13** using the method as described for **16**: yield 79%; UV (H_2O) λ_{max} 271.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.48 (d, J = 7.2 Hz, 1H), 6.77 (br d, 2H), 5.45 (d, J = 7.5 Hz, 1H), 4.67 (t, J = 5.1 Hz, 1H), 3.81 (dd, J = 13.8, 6.6 Hz, 1H), 3.68–3.52 (m, 4H), 3.26 (m, 1H), 1.16–1.05 (m, 2H), 0.60 (m, 1H), 0.21 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 165.90, 156.12, 145.99, 93.13, 69.87, 60.39, 47.56, 23.59, 18.51, 15.27, 7.20.

*(±)-cis-1-[2-(Methoxymethyl)-cyclopropylmethyl phosphonic acid]thymine (**18**).* Compound **18** was prepared from **14** using the method as described for **16**: yield 84%; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.45 (s, 1H), 4.67 (t, J = 6.0 Hz, 1H), 3.82–3.94 (m, 2H), 3.73 (d, J = 8.4 Hz, 2H), 3.41 (dd, J = 13.7, 7.0 Hz, 1H), 3.27 (dd, J = 12.4, 7.8 Hz, 1H), 1.80 (s, 3H), 1.31–1.21 (m, 2H), 0.81 (m, 1H), 0.27 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.56, 154.76, 137.12, 104.98, 69.78, 61.76, 44.87, 23.88, 18.43, 14.98, 13.43, 7.23.

*(±)-cis-1-[2-(Methoxymethyl)-cyclopropylmethyl phosphonic acid]uracil (**19**).* Compound **19** was prepared from **15** using the method as described for **16**: yield 74%; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.89 (d, J = 6.6 Hz, 1H), 5.70 (d, J = 6.7 Hz, 1H), 4.78 (t, J = 5.8 Hz, 1H), 3.98 (dd, J = 14.4, 6.2 Hz, 1H), 3.76 (dd, J = 12.7, 5.0 Hz, 1H), 3.68 (d, J = 7.9 Hz, 2H), 3.43–3.30 (m, 2H), 1.25 (m, 2H), 0.80 (m, 1H), 0.31 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 163.79, 152.65, 145.90, 100.81, 71.23, 61.99, 45.31, 18.34, 14.87, 7.12.

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