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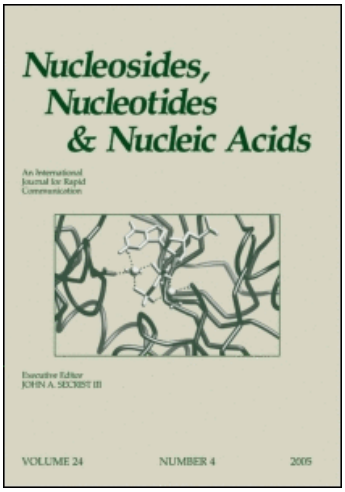

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Synthesis of Novel 4'-Cyclopropyl-5'-norcarbocyclic Adenosine Phosphonic Acid Analogues

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SYNTHESIS OF NOVEL 4′-CYCLOPROPYL-5′-NORCARBOCYCLIC ADENOSINE PHOSPHONIC ACID ANALOGUES

Guang Huan Shen and Joon Hee Hong
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□ *Novel 4′-cyclopropyl-5′-norcarbocyclic adenosine phosphonic acid analogues were designed and racemically synthesized from propionaldehyde* ***5*** *through a de novo acyclic stereoselective route using triple Grignard addition and ring-closing metathesis (RCM) as key reactions. To improve cellular permeability and enhance the anti-HIV activity of this phosphonic acid, SATE phosphonodiester nucleoside prodrug* ***23*** *was prepared. The synthesized adenosine phosphonic acids analogues* ***17, 18, 19, 21****, and* ***23*** *were subjected to antiviral screening against HIV-1. Compound* ***23*** *exhibits enhanced anti-HIV activity than its parent nucleoside phosphonic acid* ***18****.*

Keywords anti-HIV agents; 4′-cyclopropane branched nucleoside; phosphonic acid nucleosides

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INTRODUCTION

Several branched nucleosides[1] have been synthesized and evaluated as potent antiviral agents. Among them, 4′-vinyl-d4T (**1**)[2] and 4′-ethynyl-d4T (**2**),[2] which have an additional double or triple bond at the 4′-position, were reported to have potent anti-HIV activities (Figure 1). Molecular modeling studies demonstrated the presence of a hydrophobic 4′-pocket that could accommodate these substitutions and contribute to the observed enhancement in potency in anti-HIV activity.[3]

Recently, 4′-branched-5′-norcarbocyclic phosphonic acid analogues, such as 4′-vinyl-cpAP (**3**)[3] and 4′-ethynyl-cpAP (**4**),[3] have encouraged the search for novel nucleosides as potential anti-HIV agents among this class of compounds.[4] The phosphonate has certain advantages over its phosphate counterpart as it is metabolically stable because its phosphorus-carbon bond is not susceptible to hydrolytic cleavage.[5] The spatial location of the oxygen atom, namely the β-position from the phosphorus atom in the nucleoside analogue, plays a critical role in the antiviral activity. This increased antiviral

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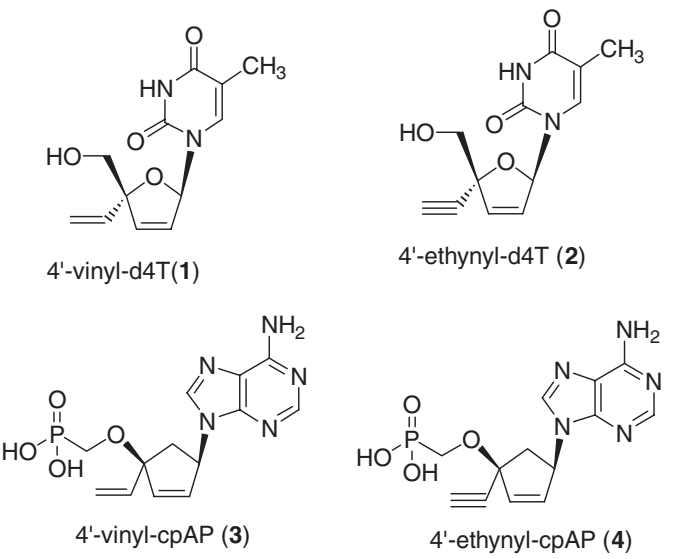

FIGURE 1 Synthesis of 4′-branched nucleoside analogues as potent anti-HIV agents.

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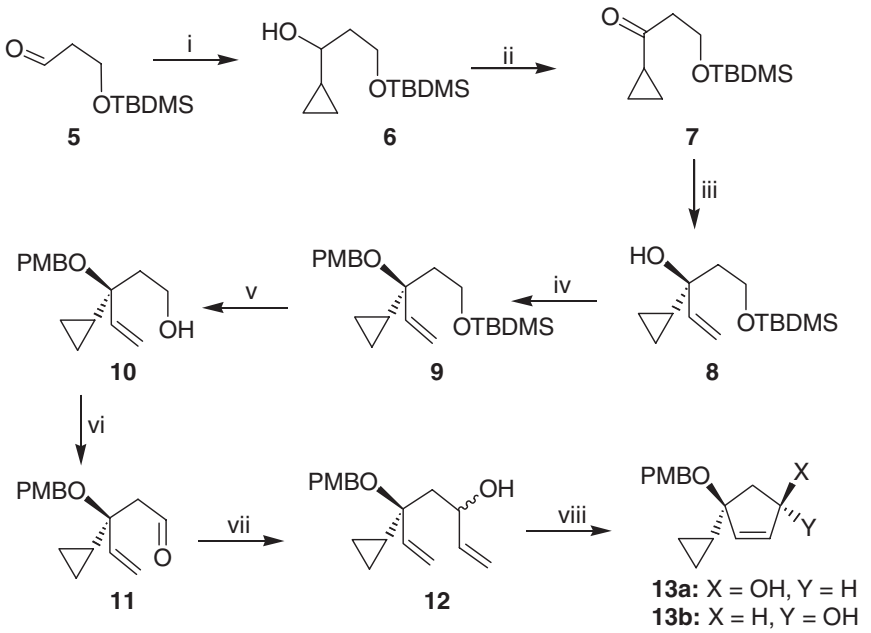
viral activity with this oxygen atom may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[6] Moreover, a phosphonate nucleoside analogue can skip the requisite first phosphorylation, which is a crucial step for the activation of nucleosides. This is frequently a limiting step in the phosphorylation sequence, which ultimately leads to triphosphates.[7]

Stimulated by these findings that 4′-branched nucleoside analogues and 5′-norcarbocyclic nucleoside phosphonate have excellent biological activities, we sought to synthesize a novel class of nucleosides comprising 4′-cyclopropane branched carbocyclic-5′-norcarbocyclic phosphonic acid analogues in order to search for more effective therapeutics against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the nucleoside kinases of nucleosides and nucleotides.

As depicted in Scheme 1, the target compounds were prepared from protected propionaldehyde, **5**.[8] The aldehyde functional group of **5** was subjected to carbonyl addition reaction by cyclopropylmagensium bromide to furnish the secondary alcohol **6**, which was subjected to oxidation using pyridium chlorochromate (PCC)[9] to provide ketone derivative **7**. The corresponding ketone group of **7** was again subjected to an addition reaction with vinylmagnesium bromide to give the tertiary hydroxyl analogue **8**, which was successfully protected using *p*-methoxybenzyl chloride (PMBCl)[10] to provide compound **9**. Removal of the silyl protecting group of **9** using *t*-butylammonium fluoride (TBAF) gave the primary alcohol **10**, which was oxidized to the aldehyde **11** using Swern oxidation conditions[11] (DMSO,



SCHEME 1 Synthesis of cyclopentenol intermediate. Reagents: i) cyclopropylMgBr, THF; ii) PCC, CH_2Cl_2; iii) vinylMgBr, THF; iv) PMBCI, NaH, DMF; v) TBAF, THF; vi) $(COCI)_2$, DMSO, TEA; vii) vinylMgBr, THF; viii) Grubbs (II), CH_2CI_2.

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oxalyl chloride, TEA). The aldehyde **11** was subjected to nucleophilic Grignard conditions[12] with vinylmagnesium bromide to give divinyl **12**, which was subjected to ring-closing metathesis (RCM) conditions using second generation Grubbs catalyst ($C_{46}H_{65}Cl_2N_2PRu$)[13] to provide cyclopropane-substituted cyclopentenol **13a** (36%) and **13b** (37%), which were readily separated by silica gel column chromatography. The nuclear Overhauser enhancement (NOE) experiments with cyclopentenols **13a** and **13b** confirmed these assignments. As expected, NOE enhancements were found between the cis-oriented hydrogens. Upon irradiation of C_1-*H*, weak NOE patterns were observed at the proximal hydrogens of compound **13b** [C_4-C*H*- (0.78%)] versus those of compound **13a** [C_4-C*H*- (1.21%)] (Figure 2).

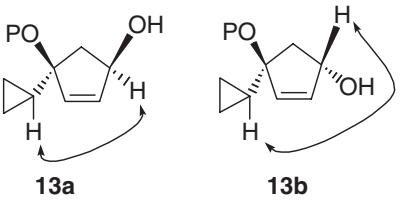
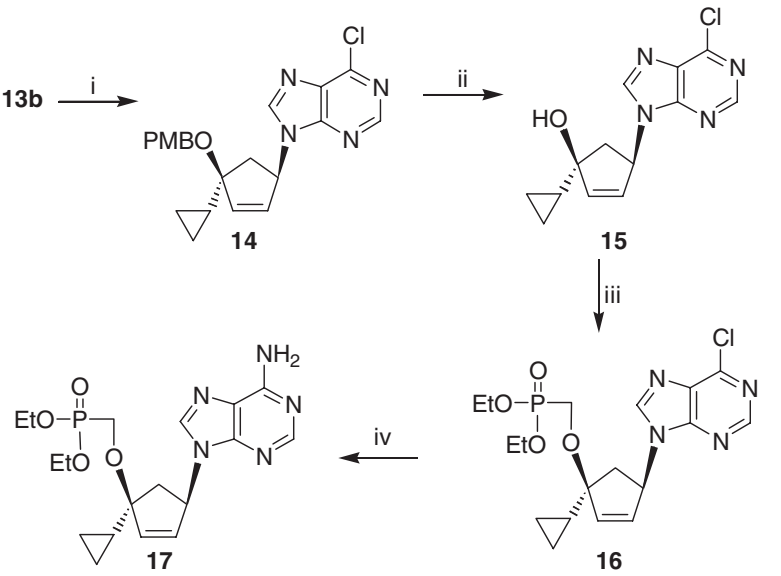


FIGURE 2 NOE differences between the proximal hydrogens of **13a** and **13b**.



SCHEME 2 Synthesis of 5′-norcarbocylic adenosine phosphonate. Reagents: i) 6-chloropurine, DEAD, PPh_3, THF; ii) DDQ, CH_2CI_2/H_2O (10:1); iii) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF, iv) NH_3/MeOH, 70°C.

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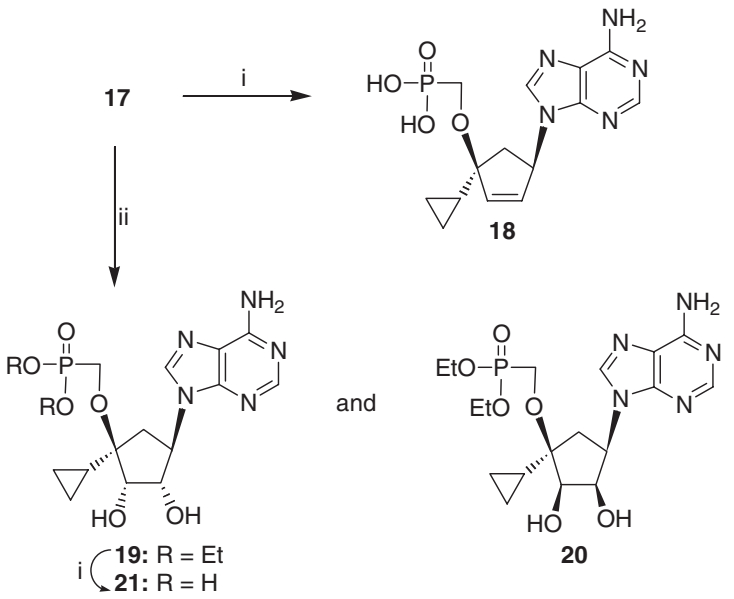
To synthesize the desired 5′-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **13b** was treated with 6-chloropurine under Mitsunobu conditions[14] (DEAD and PPh_3). Slow addition of diethyl azodicarboxylate (DEAD) to a mixture of cyclopentenol **13b**, triphenylphosphine and the 6-chloropurine in anhydrous tetrahydrofuran (THF) solvent gave a yellow solution, which was stirred for 2 hours at −40°C and further stirred overnight at room temperature to give the protected 6-chloropurine analogue **14** as an only N^9-regioisomer [UV (MeOH) λ_{max} 264.0 nm].[15] The PMB protection group was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[16] to produce the 5′-nornucleoside analogue **15**, which was treated with diethylphosphonomethyl triflate[17] using lithium *t*-butoxide to yield the nucleoside phosphonate analogue **16** (Scheme 2). The chlorine group of **16** was then converted to amine with methanolic ammonia at 70°C to give the corresponding adenine phosphonate derivative **17**.[4] Hydrolysis of **17** by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6-lutidine gave an adenine phosphonic acid derivative **18** (Scheme 3).[18]

In order to synthesize the 2′,3′-dihydroxy nucleoside analogues, the protected nucleosides **17** was subjected to vicinal hydroxylation conditions[19] using catalytic amount of OsO_4 and NMO to give the **19** (27%) and **20** (26%), respectively.[20] As shown in Figure 3, the stereochemistry was readily determined by NOE experiment. On irradiation of C_1-*H*, relatively strong



SCHEME 3 Synthesis of 5′-norcarbocyclic adenosine phosphonates and phosphonic acids. Reagents: i) TMSBr, 2,6-lutidine, CH_3CN; ii) OsO_4, NMO, acetone/*t*-BuOH/H_2O (6:1:1).

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NOE was observed at C_2-*H* and C_3-*H* of **20**, which showed 1′,2′,3′-*cis* relationships. But relatively weak NOE was observed at C_2-*H* and C_3-*H* of **19**, which means the 1′,2′- and 1′,3′-*trans* relationships. The adenosine phosphonic acid **21** was synthesized from **19** by the similar procedures described for **18** (Figure 3).

To synthesize the thioester prodrug analogue, compound **18** was reacted with thioester **22**[21] in the presence of 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT)[22] to provide the bis(SATE) derivative as a target compound **23** (Scheme 4).

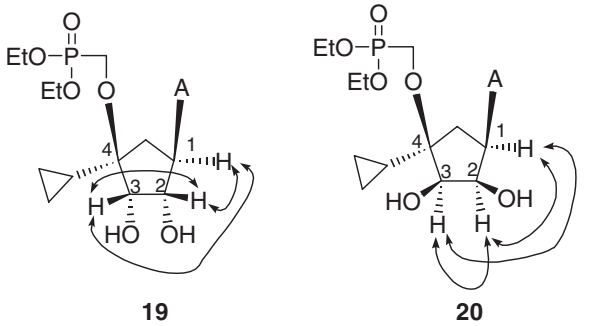
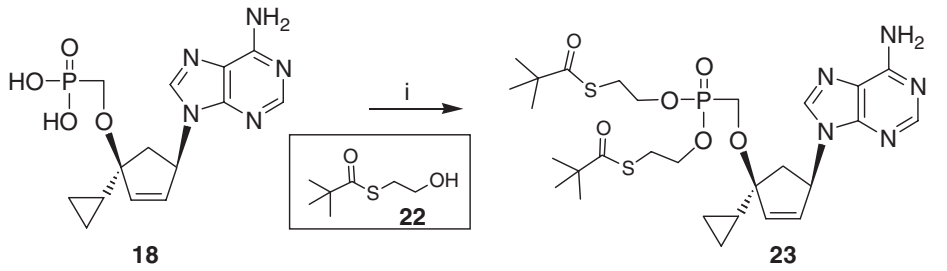


FIGURE 3 NOE relationships between the proximal hydrogens of **19** and **20**.



SCHEME 4 Synthesis of target bis(SATE) prodrug of adenine analogue **23**. Reagents: i) thioester, **22**, 1-(2-mestiylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole, pyridine.

The synthesized nucleoside phosphonate and phosphonic acid analogues **17**, **18**, **19**, **21**, and **23** were then evaluated for antiviral activity against human immunodeficiency virus. The procedures for measuring the antiviral activity toward wild-type HIV and cytotoxicity have been reported previously.[23] As shown in Table 1, nucleoside phosphonic acid **23** exhibited increased anti-HIV activity than its parent nucleoside phosphonic acid **18**. However, nucleoside analogues **17**, **19** and **21** did not show anti-HIV activity or cytotoxicity at concentrations up to 100 μM.

In summary, based on the potent anti-HIV activity of 4′-branched nucleoside and 5′-norcarbocyclic nucleoside analogues, we have designed and successfully synthesized novel 4′-cyclopropyl-5′-norcarbocyclic nucleoside analogues starting from propionaldehyde.

The synthesized nucleoside prodrug **23** exhibited slight improvement in cell-based activity compared with phosphonic acid **18**. Although SATE protecting group as a prodrug scaffold was introduced, the antiviral activity was slightly increased.

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TABLE 1 Anti-HIV activity of synthesized compounds

Compound no.	anti-HIV EC_{50} (μM)[c]	Cytotoxicity CC_{50} (μM)[d]
17	62.5	98
18	18.6	90
19	>100	>100
21	>100	>100
23	**9.8**	65
AZT[a]	0.01	100
PMEA[b]	0.51	10

[a]AZT: azidothymidine.
[b]PMEA: 9-[2-(phosphonomethoxy)ethyl]adenine.
[c]EC_{50}(μM): Concentration (μM) required to inhibit the replication of HIV-1 by 50%.
[d]CC_{50}(μM): Concentration (μM) required to reduce the viability of unaffected cells by 50%.

EXPERIMENTAL

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier 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). Ultraviolet (UV) spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). MS spectra were collected in electrospray ionization (ESI) mode. The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Thin layer chromatography (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 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.

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(±)-3-(t-Butyldimethylsilanyloxy)-1-cyclopropyl-propan-1-ol (6)

To a solution of **5** (2.0 g, 10.62 mmol) in dry THF (20 mL) was slowly added cyclopropylmagnesium bromide (25.49 mL, 0.5 M solution in THF) at −25°C; the mixture was stirred 4 hours at 0°C. Saturated NH_4Cl solution (15 mL) was added to the mixture, which was slowly warmed to room temperature (room temperature). The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, 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 **6** (1.93 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (t, J = 5.2 Hz, 2H), 3.21 (m, 1H), 1.61 (m, 2H), 0.92 (m, 1H), 0.81 (s, 9H), 0.39–0.18 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.6, 60.2, 41.5, 25.3, 19.5, 18.5, 3.1, 2.3, −5.3.

3-(t-Butyldimethylsilanyloxy)-1-cyclopropyl-propan-1-one (7): 4Å molecular sieves (3.8 g) and PCC (3.91 g, 18.13 mmol) were added slowly to a solution of compound **6** (1.66 g, 7.2 mmol) in CH_2Cl_2 (60 mL) at 0°C, and the mixture was stirred overnight at room temperature. An excess of diethyl ether (150 mL) was then added to the mixture. The mixture was stirred vigorously for 3 hours at room temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **7** (1.26 g, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 6.4 Hz, 1H), 2.29 (m, 1H), 1.23 (m, 2H), 1.03 (m, 2H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.6, 60.8, 43.2, 25.5, 18.9, 18.3, 11.4, −5.6.

(±)-5-(t-Butyldimethylsilanyloxy)-3-cyclopropyl-pent-1-en-3-ol (8): To a solution of **7** (3.5 g, 15.32 mmol) in dry THF (50 mL), vinylmagnesium bromide (18.46 mL, 1.0 M solution in THF) was slowly added at −10°C and stirred 5 hours at 0°C. Saturated NH_4Cl solution (18 mL) was added to the mixture, which was slowly warmed to room temperature. The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **8** (2.55 g, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (m, 1H), 5.26–5.19 (m, 2H), 3.80 (t, J = 5.8 Hz, 2H), 1.65 (dd, J = 5.7, 2.6 Hz, 2H), 0.95 (m, 1H), 0.82 (s, 9H), 0.46–0.23 (m, 4H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 114.2, 79.2, 59.1, 43.5, 25.5, 20.1, 18.2, 3.5, 2.9, -5.2; Anal. Calc. for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00; Found: C, 65.54; H, 10.98.

(±)-t-Butyl-[3-(4-methoxybenzyloxy)-3-cyclopropyl-pent-4-enyloxy]-dimethylsilane (9)

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NaH (60% in mineral oil, 330 mg, 8.3 mmol) was added portion-wise to a cooled (0°C) solution of tertiary alcohol **8** (1.77 g, 6.93 mmol) and *p*-methoxybenzyl chloride (1.03 mL, 7.62 mmol) in DMF (30 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was diluted with H_2O (110 mL) followed by extraction with diethyl ether (2 × 110 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **9** (1.98 g, 76%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.24 (m, 2H), 6.91–6.85 (m, 2H), 5.89 (m, 1H), 5.28–5.22 (m, 2H), 4.49 (s, 2H), 3.81 (s, 3H), 3.76 (t, J = 6.2 Hz, 2H), 1.62 (m, 2H), 0.98 (m, 1H), 0.81 (s, 9H), 0.44–0.23 (m, 4H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 143.7, 130.6, 129.3, 116.3, 114.1, 80.1, 73.0, 58.7, 56.2, 41.8, 25.3, 19.9, 18.4, 4.1, 3.6, -5.5; Anal. Calc. for $C_{22}H_{36}O_3Si$ (+0.5 EtOAc): C, 68.52; H, 9.58; Found: C, 68.48; H, 9.60.

(±)-3-(4-Methoxybenzyloxy)-3-cyclopropyl-pent-4-en-1-ol (10)

To a solution of **9** (1.05 g, 2.78 mmol) in THF (20 mL), TBAF (3.33 mL, 1.0 M solution in THF) was added at 0°C. The mixture was stirred overnight at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/EtOAc, 5:1) to give **10** (649 mg, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.27 (m, 2H), 6.95–6.87 (m, 2H), 5.90 (m, 1H), 5.25–5.19 (m, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.57 (t, J = 6.2 Hz, 2H), 1.60 (m, 2H), 0.93 (m, 1H), 0.41 (m, 2H), 0.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 144.0, 131.2, 129.7, 117.1, 114.8, 79.8, 72.6,

57.8, 54.8, 40.2, 18.9, 3.6, 3.2; Anal. Calc. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; Found: C, 73.28; H, 8.42.

(±)-3-(4-Methoxybenzyloxy)-3-cyclopropyl-pent-4-enal (11)

To a stirred solution of oxalyl chloride (215 mg, 1.7 mmol) in CH_2Cl_2 (14 mL) was added a solution of DMSO (265 mg, 3.4 mmol) in CH_2Cl_2 (5.0 mL) dropwise at –78°C. The resulting solution was stirred at –78°C for 10 minutes, and a solution of alcohol **10** (223 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at –78°C for 30 minutes and TEA (0.947 mL, 6.8 mmol) was added. The resulting mixture was warmed to 0°C and stirred for 30 minutes. H_2O (15 mL) was added, and the solution was stirred at room temperature for 30 minutes. The mixture was diluted with water (130 mL) and then extracted with EtOAc (2 × 130 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give aldehyde compound **11** (208 mg, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.86 (s, 1H), 7.30–7.25 (m, 2H), 6.94–6.88 (m, 2H), 5.91 (m, 1H), 5.27–5.21 (m, 2H), 4.66 (s, 2H), 3.74 (s, 3H), 2.58–2.49 (dd, J = 8.6, 4.0 Hz, 2H), 0.89 (m, 1H), 0.39 (m, 2H), 0.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 159.3, 142.9, 130.8, 129.1, 116.7, 114.2, 76.1, 71.2, 57.3, 51.9, 19.7, 4.8, 4.2.

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(*rel*)-(3*R* and *3S*,5*S*)- 5-(4-Methoxybenzyloxy)-5-cyclopropyl-hepta-1,6-dien-3-ol (12)

Divinyl analogue **12** was synthesized as a diastereomeric mixture from aldehyde **11** by a procedure similar to that described for **8**: yield 79%; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.31–7.26 (m, 2H), 6.91–6.85 (m, 2H), 5.96–5.87 (m, 2H), 5.17–4.99 (m, 4H), 4.64 (s, 2H), 3.91 (m, 1H), 3.76 (s, 3H), 1.67–1.58 (m, 2H), 0.93–0.84 (m, 1H), 0.40–0.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.4, 159.7, 141.5, 140.7, 131.8, 129.8, 128.4, 117.8, 116.7, 115.5, 114.7, 78.2, 72.0, 68.1, 56.9, 44.3, 20.2, 5.1, 4.6, 3.8.

(*rel*)-(1*S*,4*S*)-4-(4-Methoxy-benzyloxy)-4-cyclopropylcyclopent-2-enol (13a) and (*rel*)-(1*R*,4*S*)-4-(4-methoxy-benzyloxy)-4-cyclopropylcyclopent-2-enol (13b)

To a solution of **12** (260 mg, 0.901 mmol) in dry methylene chloride (7 mL) was added second generation Grubbs catalyst (40.0 mg, 0.0471 mmol). The reaction mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **13a** (84 mg, 36%) and **13b** (86 mg, 37%). Data for **13a**: ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 2H), 6.88–6.79 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.34 (m, 1H), 4.69 (s, 2H), 4.08 (m, 1H), 3.78 (s, 3H), 2.20 (dd, J = 13.6. 8.2 Hz, 1H), 2.06 (dd, J = 13.5, 6.6 Hz, 1H), 0.93 (m, 1H), 0.41–0.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 138.8, 136.9, 131.4, 128.5, 117.1, 88.7, 73.1, 67.9, 57.3, 39.2, 18.2, 5.9; Anal. Calc. for $C_{16}H_{20}O_3$ (+0.5 EtOAc): C, 71.02; H, 7.94; Found: C, 70.95; H, 7.97.

Data for **13b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.28 (m, 2H), 6.87 (m, 2H), 5.68 (d, J = 5.5 Hz, 1H), 5.38–5.34 (m, 1H), 4.71 (s, 2H), 4.01 (m, 1H), 3.75 (s, 3H), 2.28 (dd, J = 13.8. 8.6 Hz, 1H), 2.10–2.05 (dd, J = 13.7, 6.8 Hz, 1H), 0.97 (m, 1H), 0.43 (m, 2H), 0.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2, 139.1, 135.6, 131.8, 129.3, 118.0, 87.4, 72.2, 67.9, 56.9, 38.8, 17.9, 6.2, 5.7; Anal. Calc. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; Found: C, 73.79; H, 7.72.

(*rel*)-(1′*R*,4′*S*)-9-[4-Cyclopropyl-(4-methoxybenzyloxy)-cyclopent-2-enyl]-6-chloropurine (14)

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To a solution containing compound **13b** (161 mg, 0.62 mmol), triphenylphosphine (440 mg, 1.68 mmol) and 6-chloropurine (191 mg, 1.24 mmol) in anhydrous THF (12.0 mL), diethyl azodicarboxylate (DEAD) (0.226 mL, 1.24 mmol) was added dropwise at –40°C for 10 minutes under nitrogen. The reaction mixture was stirred for 2 hours at the same temperature under nitrogen and further stirred overnight at room temperature. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **14** (96 mg, 39%): m.p. 165–167°C; UV (MeOH) λ_{max} 264.0 nm: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.38 (s, 1H), 7.30–7.25 (m, 2H), 6.92–6.87 (m, 2H), 5.66 (d, J = 5.6 Hz, 1H), 5.36 (m, 1H), 4.69 (s, 2H), 4.44 (m, 1H), 3.72 (s, 3H), 2.31 (dd, J = 13.7. 8.8 Hz, 1H), 2.11–2.07 (dd, J = 13.8, 7.0 Hz, 1H), 0.92 (m, 1H), 0.41 (m, 2H), 0.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 151.8, 150.8, 145.7, 138.6, 134.9, 132.5, 131.5, 129.1, 117.6, 86.8, 73.5, 57.6, 54.7, 36.2, 19.3, 6.8; Anal. Calc. for $C_{21}H_{21}ClN_4O_2$ (+ 1.0 MeOH): C, 61.60; H, 5.87; N, 13.06; Found: C, 61.56; H, 5.90; N, 13.10.

(*rel*)-(1′*R*,4′*S*)-9-(4-Cyclopropyl-4-hydroxycyclopent-2-enyl)-6-chloropurine (15)

To a solution of compound **14** (420 mg, 1.058 mmol) in CH_2Cl_2/H_2O (12 mL, 10:1 v/v) was added DDQ (358 mg, 1.58 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (2.0 mL) was added to quench the reaction, which was then stirred for 1 hours at room temperature. The mixture was diluted with water (160 mL) and extracted with CH_2Cl_2 (3 × 160 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in

vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 4:1:0.03) to give compound **15** (199 mg, 68%): m.p. 176–178°C; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.74 (s, 1H), 8.39 (s, 1H), 5.64 (d, J = 5.4 Hz, 1H), 5.32 (dd, J = 5.5, 4.0 Hz, 1H), 4.51 (m, 1H), 2.28 (dd, J = 13.8. 8.7 Hz, 1H), 2.10–2.04 (m, 1H), 0.96 (m, 1H), 0.42 (m, 2H), 0.33 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.9, 150.3, 149.2, 137.2, 134.8, 132.4, 86.5, 56.7, 39.6, 18.6, 7.1, 6.7; Anal. Calc. for $C_{13}H_{13}ClN_4O$ (+1.5 MeOH): C, 62.55; H, 5.89; N, 17.25; Found: C, 62.59; H, 5.92; N, 17.20.

(*rel*)-(1′*R*,4′*S*)-Diethyl [9-(4-Hydroxy-4-cyclopropylcyclopent-2-en-1-yl)-6-chloropurine] methylphosphonate (16)

Both LiO*t*-Bu (2.32 mL of 0.5 M solution in THF, 1.24 mmol) and a solution of diethyl phosphonomethyltriflate (348 mg, 1.16 mmol) in 8.0 mL of THF were slowly added to a solution of the 6-chloropurine analogue **15** (160 mg, 0.58 mmol) in 7.0 mL of THF at –30°C and stirred overnight at room temperature under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (5 mL) and further diluted with additional H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.03:4:1) to give **16** (143 mg, 58%) as a foamy solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 8.50 (s, 1H), 5.65 (d, J = 5.3 Hz, 1H), 5.39 (dd, J = 5.5, 4.4 Hz, 1H), 4.51 (m, 1H), 4.31 (m, 4H), 3.98 (d, J = 8.0 Hz, 2H), 2.31–2.23 (dd, J = 13.8. 8.8 Hz, 1H), 2.09 (dd, J = 13.7, 6.8 Hz, 1H), 1.39 (m 6H), 0.97 (m, 1H), 0.43–0.35 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.9, 151.2, 150.5, 146.0, 137.7, 133.3, 132.5, 88.7, 66.3, 65.8, 64.5, 55.3, 36.7, 19.3, 17.2, 7.6, 6.6; Anal. Calc. for $C_{18}H_{24}ClN_4O_4P$ (+ 1.0 MeOH): C, 49.73; H, 6.15; N, 12.21; Found: C, 49.69; H, 6.18; N, 12.16.

(*rel*)-(1′*R*,4′*S*)-Diethyl [9-(4-Hydroxy-4-cyclopropylcyclopent-2-en-1-yl)-adenine] methylphosphonate (17)

A solution of **16** (202 mg, 0.473 mmol) in saturated methanolic ammonia (12 mL) was stirred overnight at 70°C in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:7) to give **17** (111 mg, 58%) as a white solid: m.p. 149–151°C; UV (MeOH) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 5.68 (d, J = 5.5 Hz, 1H), 5.39 (m, 1H), 4.50 (m, 1H), 4.35–4.41 (m, 4H), 4.02 (d, J = 8.1 Hz, 2H), 2.30–2.24 (dd, J = 13.7. 8.8 Hz, 1H), 2.12–2.06 (m, 1H), 1.41–1.35 (m 6H), 0.90 (m, 1H), 0.44 (m, 2H), 0.34 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 152.6, 150.7, 141.7,

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138.1, 134.7, 120.2, 89.3, 65.7, 64.1, 63.2, 54.9, 37.1, 20.2, 16.8, 7.5, 6.3; Anal. Calc. for $C_{18}H_{26}N_5O_4P$: C, 53.07; H, 6.43; N, 17.19; Found: C, 53.01; H, 6.38; N, 17.25.

(*rel*)-(1′*R*,4′*S*)-[9-(4-Cyclopropylcyclopenten-1-yl)-adenine] -4-methylphosphonic acid (18)

To a solution of the phosphonate **17** (149 mg, 0.35 mmol) in anhydrous CH_3CN (10 mL) and 2,6-lutidine (0.815 mL, 7.0 mmol) was added trimethylsilyl bromide (0.535 mg, 3.5 mmol). The mixture was heated overnight at 70°C under nitrogen gas and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (70 mL) and distilled purified water (70 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 50 mL) and then freeze-dried to give phosphonic acid **18** (88 mg, 72%) as a yellowish foam: UV (H_2O) λ_{max} 260.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.09 (s, 1H), 5.69 (d, J = 5.4 Hz, 1H), 5.37 (dd, J = 5.5, 4.2 Hz, 1H), 4.52 (m, 1H), 4.17 (d, J = 8.0 Hz, 2H), 2.31 (dd, J = 13.7, 8.8 Hz, 1H), 2.13–2.08 (dd, J = 13.8, 6.9 Hz, 1H), 0.88 (m, 1H), 0.37–0.31 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.8, 151.8, 149.5, 140.3, 138.6, 133.8, 119.6, 88.6, 64.7, 55.2, 36.7, 17.9, 6.7; Anal. Calc. for $C_{14}H_{18}N_5O_4P$ (+2.0 H_2O): C, 50.64; H, 5.72; N, 18.08; Found: C, 50.59; H, 5.68; N, 18.12.

(*rel*)-(1′*R*,2′*S*,3′*S*,4′*S*)-Diethyl [9-(2,3-dihydroxy-4-cyclopropylcyclopent-1-yl)-adenine]-4- methylphosphonate (19) and (*rel*)-(1′*R*,2′*R*,3′*R*,4′*S*)-diethyl [9-(2,3-dihydroxy-4-cyclopropylcyclopent-1-yl)-adenine]-4-methylphosphonate (20)

Compound **17** (236 mg, 0.58 mmol) was dissolved in a cosolvent system (10 mL) (acetone: *t*-BuOH: H_2O = 6:1:1) along with 4-methylmorpholine *N*-oxide (135 mg, 1.16 mmol). Subsequently, OsO_4 (0.29 mL, 4% wt% in H_2O) was added. The mixture was stirred overnight at room temperature and quenched with saturated Na_2SO_3 solution (5 mL). The resulting solid was removed by filtration through a pad of Celite, and filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give **19** (69 mg, 27%) and **20** (66 mg, 26%) as a solid: compound **19:** m.p. 151–153°C; UV (H_2O) λ_{max} 259.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1H), 8.17 (s, 1H), 4.23–4.16 (m, 4H), 4.10 (d, J = 8.0 Hz, 2H), 3.81 (m, 1H), 3.69 (d, J = 5.6 Hz, 1H), 3.31 (m, 1H), 2.15–2.08 (dd, J = 13.6, 8.7 Hz, 1H), 1.95–1.90 (dd, J = 13.8, 6.8 Hz, 1H), 1.35–1.32 (m 6H), 0.92 (m, 1H), 0.38 (m, 2H), 0.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.4, 152.6, 150.1, 142.7, 119.8, 86.2, 76.8, 70.5, 66.4, 64.6, 63.5, 47.5, 29.2, 19.6, 17.8, 7.8, 6.9; Anal. Calc. for $C_{18}H_{28}N_5O_6P$ (+ 1.5 MeOH): C, 47.85; H, 7.00; N, 14.30; Found: C, 47.79; H, 7.03; N, 14.26.

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Compound **20:** m.p. 144–146°C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 4.32–4.25 (m, 4H), 4.16 (d, J = 8.1 Hz, 2H), 3.82 (m, 1H), 3.62 (d, J = 5.5 Hz, 1H), 3.35 (dd, J = 5.6, 4.0 Hz, 1H), 2.17 (dd, J = 13.8, 8.6 Hz, 1H), 1.98–1.89 (dd, J = 13.7, 7.0 Hz, 1H), 1.36 (m 6H), 0.90 (m, 1H), 0.42 (m, 2H), 0.35 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.9, 152.2, 149.7, 143.2, 120.7, 85.6, 75.2, 67.5, 65.2, 64.7, 48.0, 27.8, 18.9, 17.2, 6.4; Anal. Calc. for $C_{18}H_{28}N_5O_6P$ (+1.0 MeOH): C, 48.20; H, 6.81; N, 14.79; Found: C, 48.15; H, 6.77; N, 14.84.

(*rel*)-(1′*R*,2′*S*,3′*S*,4′*S*)-[9-(2,3-Dihydroxy-4-cyclopropylcyclopent-1-yl)] adenine]-4- methylphosphonic acid (21)

Final adenosine phosphonic acid **21** was synthesized from **19** using the similar procedure described for **18** as a light yellow foamy solid: yield 67%; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.19 (s, 1H), 4.12 (d, J = 8.1 Hz, 2H), 3.67 (d, J = 5.4 Hz, 1H), 3.35 (m, 1H), 2.18–2.11 (dd, J = 13.8, 8.8 Hz, 1H), 1.93 (dd, J = 13.7, 6.9 Hz, 1H), 0.90 (m, 1H), 0.39–0.33 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.6, 153.7, 151.3, 143.2, 119.3, 87.1, 77.4, 68.52, 65.7, 48.1, 27.4, 18.8, 6.2, 5.7; Anal. Calc. for $C_{14}H_{20}N_5O_6P$ (+ 3.0 H_2O): C, 38.27; H, 5.96; N, 15.94; Found: C, 38.34; H, 6.01; N, 15.89.

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(*rel*)-(1′*R*,4′*S*)-Bis(SATE) phosphoester of [9-(4-methyloxyphosphonate-4-cyclopropylcyclopentyl)] adenine (23)

A solution of adenine phosphonic acid derivative **18** (59 mg, 0.169 mmol) and tri-*n*-butylamine (94 mg, 0.510 mmol) in methanol (3.8 mL) was mixed for 30 minutes and concentrated under reduced pressure. The residue was thoroughly dried with anhydrous ethanol and toluene. The resulting foamy solid was dissolved in anhydrous pyridine (10 mL) to which thioester **22** (519 mg, 3.2 mmol) and 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (201 mg, 0.678 mmol) were added. The mixture was stirred overnight at room temperature and quenched with tetrabutylammonium bicarbonate buffer (10.0 mL, 1 M solution, pH 8.0). The mixture was concentrated under reduced pressure and the residue was diluted with water (58 mL) and extracted with $CHCl_3$ (62 mL) two times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (MeOH/Hexane/EtOAc, 0.06:3:1) to give **23** (42 mg, 39%) as a white solid: m.p. 124–125°C; UV (MeOH) λ_{max} 262.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 8.15 (s, 1H), 5.58 (d, J = 5.6 Hz, 1H), 5.33 (dd, J = 5.7, 4.0 Hz, 1H), 4.51 (m, 1H), 4.20 (d, J = 8.1 Hz, 2H), 3.92 (m, 4H), 3.18–3.16 (m, 4H), 2.26 (dd, J = 13.6, 8.9 Hz, 1H), 2.12–2.08 (dd, J = 13.7, 6.7 Hz, 1H), 1.23–1.19 (m, 18), 0.89 (m, 1H), 0.38–0.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4, 154.5,

152.5, 149.0, 144.2, 128.2, 124.4, 118.2, 84.7, 65.3, 64.9, 62.3, 54.9, 48.3, 35.8, 31.4, 26.2, 17.3, 6.8; Anal. Calc. for $C_{28}H_{42}N_5O_6PS_2$ (+1.0 MeOH): C, 51.84; H, 6.90; N, 10.42; Found: C, 51.78; H, 6.87; N, 10.38.

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