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Synthesis and Some Properties of 4'-Phenyl-5'-Norcarbocyclic Adenosine Phosphonic Acid Analogues

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Steric and electronic parameters of 4'-substituents play significant roles in steering the conformation of nucleoside analogues. In order to investigate the relationship of 4'-substituent with antiviral enhancement, novel 4'-phenyl-5'-norcarbocyclic adenosine phosphonic acid analogues were racemically synthesized *via de novo* acyclic stereoselective route from propionaldehyde **5**. The phenyl substituted cyclopentenols **15a** and **15b** as key intermediates were successfully constructed *via* reiterative carbonyl addition of Grignard reagents and ring-closing metathesis of corresponding divinyl **14**. The synthesized nucleoside phosphonic acids analogues **19**, **20**, **21**, and **23** were subjected to antiviral screening against HIV-1.

Key Words : Anti-HIV agent, 4'-Branched nucleoside, 5'-Norcarbocyclic nucleoside phosphonic acid

Introduction

The development of new effective antiviral agent is essential for overcoming viral diseases, such as acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV). Recently, several branched nucleosides[1] have been synthesized and evaluated as potent antiviral agents. Among them, 4'-ethynylthymidine (**1**)[2] and 4'-vinylthymidine (**2**)[3] which have an additional triple or double bond at the 4'-position, were reported to have potent anti-HIV activities (Fig. 1). Molecular modeling studies demonstrated the presence of a relatively hydrophobic 4'-pocket that can accommodate these substitutions, contributes to the observed enhancement in potency.[4]

5'-Norcarbocyclic nucleoside phosphonic acid analogues such as 4'-ethynyl-cpAP (**3**) and 4'-vinyl-cpAP (**4**)[4] have encouraged the search for novel nucleosides in this class of compounds (Fig. 1).[5] 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.[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 event in the phosphorylation sequence, which ultimately leads to triphosphates.[7] The spacial location of the oxygen atom, namely the β-position from the phosphorus atom in the nucleoside analogue, has been demonstrated to play a critical role for antiviral activity. This oxygen atom for antiviral activity may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[8]

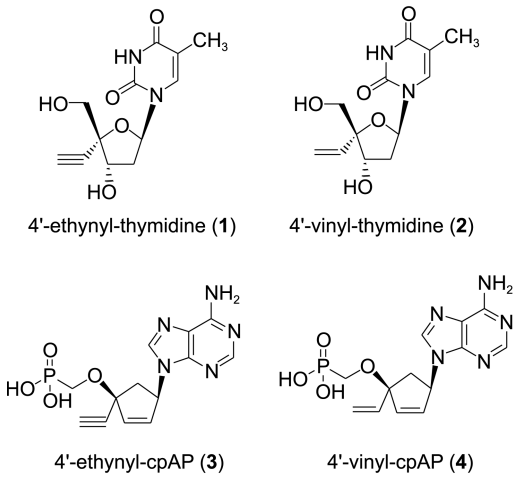
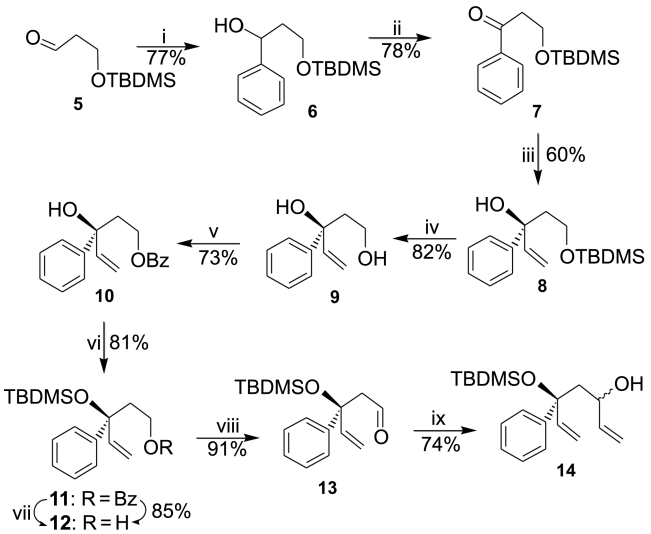


Figure 1. Structures of 4'-branched nucleoside analogues as potent anti-HIV agents.

Actually, the exact role of substituent in 4'-position in nucleoside analogues in inhibiting reverse transcriptase (RT) has not been explored clearly. In continuation of our effort to find more detailed structure activity relationship of branched nucleoside as RT inhibitor, we have designed and prepared a novel class of nucleosides comprising branched-5'-norcarbocyclic phosphonic acid analogues bearing phenyl group which has bigger van der Waals radius than ethynyl or ethenyl functional group.

As shown in Scheme 1, the target compounds were prepared from protected propionaldehyde, **5**, which was readily synthesized from 1,3-propanediol using known procedure.[9] The aldehyde functional group of **5** was subjected to carbonyl addition reaction by phenylmagnesium bromide to give the secondary alcohol **6**, which was subjected to oxidation condition using Corey-Kim's oxidation procedure[10] to provide corresponding ketone derivative **7**. The ketone functional group of **7** was again subjected to addition reaction by vinylmagnesium bromide to give tertiary hydroxyl analogue **8**.

In order to differentiate the two hydroxyl groups, the silicon protection group of the primary hydroxyl was replaced with a benzoyl group by sequential desilylation and benzoylation to provide **10**. Silylation of the tertiary hydroxyl group of **10** was successfully accomplished using *t*-



Scheme 1. Synthesis of divinyl intermediate **14**.
Reagents: i) phenylMgBr, THF; ii) NCS, DMS, toluene; iii) vinylMgBr, THF; iv) TBAF, THF/CH_3CN; v) BzCl, DMAP, pyridine; vi) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; vii) NH_3/MeOH; viii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; ix) vinylMgBr, THF.

butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf, 2,6-lutidine)[11] to give the fully protected compound **11**. Removal of the benzoyl protecting group of **11** under methanolic ammonium condition (NH_3/MeOH) provided the primary alcohol **12**, which was oxidized to the aldehyde **13** using Swern oxidation conditions (Oxalyl chloride, DMSO, TEA).[12] The aldehyde **13** was subjected to nucleophilic Grignard conditions with vinylmagnesium bromide to give divinyl **14** which was subjected to ring-closing metathesis (RCM) conditions using 2nd generation Grubbs catalyst[13] to provide phenyl substituted cyclopentenol **15a** (34%) and **15b** (35%), which were readily separated by silica gel column chromatography. The NOE experiments with cyclopentenols **15a** and **15b** confirmed these assignments. Also, the exact structural determinations were performed in the latter stage of compounds **22** and **23** (Fig. 2).

To synthesize the desired 5'-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol **15b** was treated with 6-chloropurine under Mitsunobu conditions[14] (DIAD and PPh_3). Slow addition of diisopropyl azodicarboxylate (DIAD) to a mixture of cyclopentenol **15b**, triphenylphosphine and the 6-chloropurine in anhydrous tetrahydrofuran (THF) gave a yellow solution which was stirred

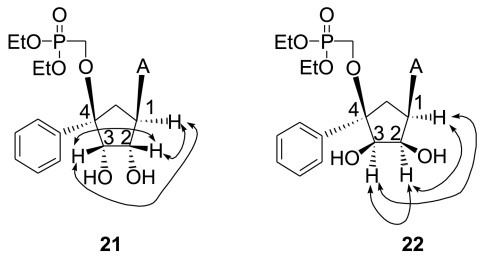
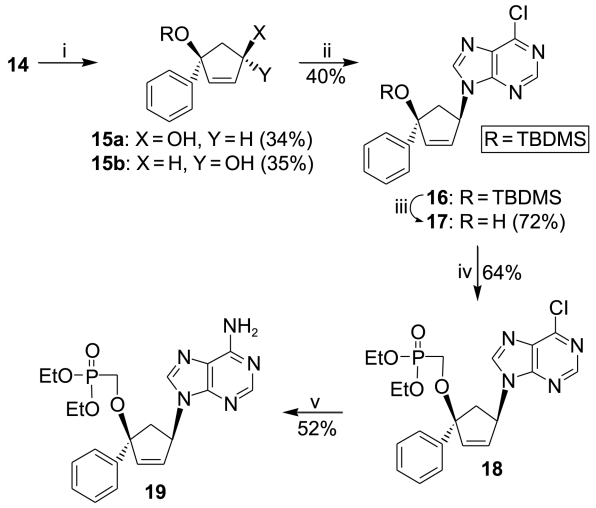


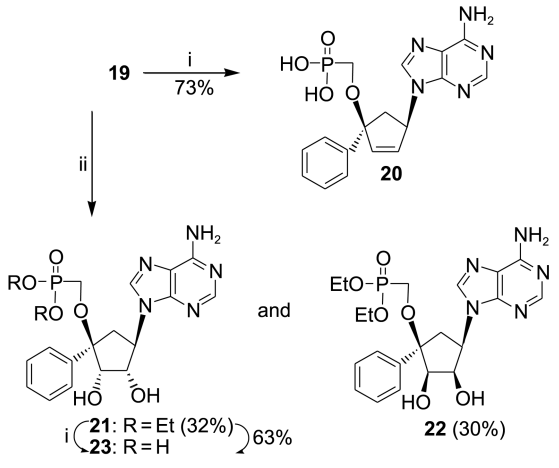
Figure 2. NOE differences between the proximal hydrogens of **21** and **22**.



Scheme 2. Synthesis of 5'-norcarbocyclic adenosine phosphonate.
Reagents: i) Grubbs(II), CH_2Cl_2; ii) 6-chloropurine, DIAD, PPh_3, THF; iii) TBAF, THF/CH_3CN; iv) $(EtO)_2POCH_2OTf$, *t*-BuOLi, THF; v) NH_3/MeOH, 65 °C.

for 3 h at −10 °C to give the 6-chloropurine analogue **16** (Scheme 2).[15] The silicon protection group was removed with tetrabutylammonium fluoride (TBAF) to provide 5'-norcarbocyclic nucleoside analogue **17**. The hydroxyl group was phosphonated with diethylphosphonomethyl triflate[16] using lithium *t*-butoxide to give the nucleoside phosphonate **18**. The chlorine group of purine analogue **18** was then converted to amine with methanolic ammonia at 65 °C to give a corresponding adenosine phosphonate derivative **19**. Hydrolysis of diethyl phosphonate functional groups of **19** by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6-lutidine gave an adenosine phosphonic acid derivative **20**.[17]

Bishydroxylation[18] of the double bond in **19** was accom-



Reagents: i) TMSBr, 2,6-lutidine, CH_3CN; ii) OsO_4, NMO, acetone / *t*-BuOH / H_2O: 8 / 1 / 1 /.

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: 8/1/1/.

Table 1. Anti-HIV activity of synthesized compounds

Compound No.	anti-HIV IC_{50} (μM)[b]	Cytotoxicity CC_{50} (μM)[c]
19	>1 00	> 100
20	28.3	90
21	> 100	> 100
23	80	> 100
ABC[a]	0.13	> 10

[a]**ABC**: Abacavir. [b]IC_{50} (μM): Concentration (μM) of the inhibitor required to reduce the activity of the enzyme by 50%. [c]CC_{50} (μM): Concentration (μM) required to reduce the viability of unaffected cells by 50%

plished with a catalytic amount of osmium tetraoxide (OsO_4) and 4-methyl-morpholine *N*-oxide (NMO) as an oxidant to give the dihydroxylated isomer **21** (32%) and **22** (30%) with almost equal amount (Scheme 3).[19] A complete NOE study allowed an unambiguous determination of their respective stereochemistry (Fig. 2). For compound **22**, strong NOE of H-1' ↔ H-2' as well as H-1' ↔ H-3', which showed 1',2',3'-*cis* relationships, was observed. According to this result, 2'- and 3'-hydroxyl groups of **22** were located on the b face. On the other hand, for **21** compound, weak NOE, such as H-1' ↔ H-2' and H-1' ↔ H-3', were assigned to the 1',2'- and 1',3'-*trans* relationships and a face stereochemicals of 2'- and 3'-hydroxyl groups. Hydrolysis of diethyl phosphonate functional groups of **21** by the similar procedure described for **20** gave an adenosine phosphonic acid derivative **23**.

The synthesized nucleoside phosphonate and phosphonic acid analogues **19**, **20**, **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.[20]

As shown in Table 1, adenosine phosphonic acid **20** exhibited moderate anti-HIV activity with IC_{50} = 28.3 μM. Also, nucleotide analogues **19**, **21** and **23** did not show anti-HIV activity nor cytotoxicity up to 100 μM.

After demonstrating that adenine nucleoside analogue **20** slightly inhibits HIV-1 polymerase, we decide to study its properties computationally. Figure 3 shows the superposition of the calculated low energy conformers of **3**, **4** and **20**, underscoring the overall similarity of the three analogues and also highlighting the difference at purine base. Furthermore, the position of sterically bulky group such as phenyl group at 4'-position leads to the predicted difference in location of the phosphonic acid group. Figure 4 shows a pronounced difference in the 4'-cavity of the synthesized compound **20** compared to the selected nucleoside **3** bounds to the active site. The location of the wider cavity below 4'-substitents is formed by residue M184 and Y115 in the synthesized analogue **20** than the 4'-ethynyl-cpAP **3**.

In summary, on the basis of potent anti-HIV activity of 4'-olefin branched nucleoside and 5'-norcarbocyclic nucleoside analogues, we have designed and successfully synthesized novel 4'-phenyl-5'-norcarbocyclic nucleoside analogues

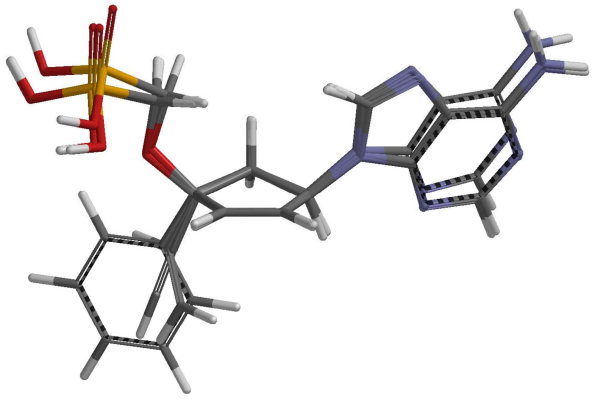


Figure 3. Superimposed low energy conformations of 4'-branched nucleoside **3**, **4** as anti-HIV-1 agents and an adenosine phosphonic acid derivative **20**. The lowest energy conformation for each of all three molecules was calculated with the modeling package Spartan using B3LYP/6-31G**.

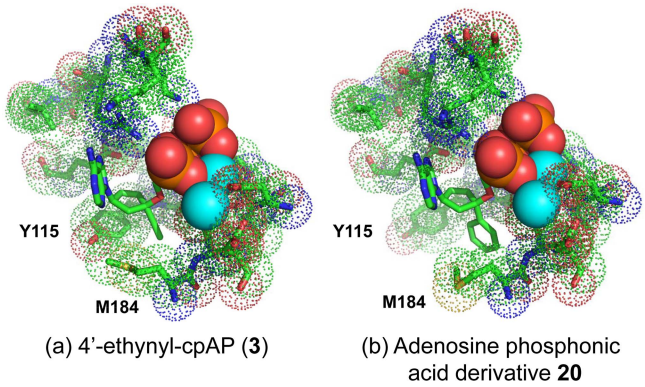


Figure 4. Model of the active site of HIV-1 RT crystal structure. (a) 4'-ethynyl-cpAP (**3**) and (b) the synthesized nucleoside phosphonic acid analogue **20** are in stick representation; Protein is a dot rendering and a stick model; Mg ions are cyan spheres and the diphosphophosphonates are red spheres. The lowest energy conformations are calculated by the modeling package Spartan using MMFF force field. The labels represent amino acids so called "primer grip".

starting from propionaldehyde **5**. 4'-Ethynyl analogue (**3**) and 4'-vinyl analogue (**4**) were found to inhibit RT with IC_{50} = 0.14 μM and 0.65 μM, respectively.[4] Taking these data into account, the proposed 4'-pocket in the active site of RT is sensitive to changes in the 4'-substituent, especially when this involves increasing the van der Waals radius or possibly changes in the bulkiness. Compounds **20** and **23** exhibited weak anti-HIV activity, indicating that the bulky hydrophobic pocket such as phenyl group at 4'-position of 5'-norcarbocyclic nucleosides system are not perfect mimics for nucleoside analogues with small 4'-substituent. Therefore, the mechanisms of virus inhibition, that is, either phosphorylation or inhibition of RNA synthesis, might be impaired in these compounds.

Experimental Section

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). 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). 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 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.

(±)-3-(*t*-Butyldimethylsilanyloxy)-1-phenylpropan-1-ol (6). To a solution of **5** (4.01 g, 21.31 mmol) in dry THF (60 mL) was slowly added phenylmagnesium bromide (25.6 mL, 1.0 M solution in THF) at −10 ºC and stirred 5 h at 0 ºC under nitrogen. Saturated NH_4Cl solution (25 mL) was added to the mixture, which was slowly warmed to rt. The mixture was further diluted with water (150 mL) and extracted with EtOAc (2 × 150 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, 1:8) to give **6** (4.37 g, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.20 (m, 5H), 4.52 (dd, *J* = 5.4, 2.8 Hz, 1H), 3.81 (m, 2H), 1.97 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 128.7, 127.7, 127.1, 72.1, 60.3, 44.6, 25.6, 18.4, −5.4.

3-(*t*-Butyldimethylsilanyloxy)-1-phenylpropan-1-one (7). *N*-Chlorosuccinimide (NCS, 3.15 g, 23.5 mmol) was suspended in toluene (80 mL) and the mixture was cooled in an ice bath. Methyl sulfide (2.95 mL, 39.5 mmol) was added and a white precipitate formed immediately. The solution was attired for 30 min at 0 ºC and then cooled to −20 ºC. A solution of alcohol **6** (4.26 g, 16 mmol) in toluene (25 mL) was slowly added to the mixture. The mixture was kept under nitrogen for 3 h, whereupon TEA (3.3 mL, 23.5 mmol) was added, and the solution was allowed to warm to room temperature and was then stirred for 2 h. The mixture was extracted with ethyl acetate, washed with 1 N HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **7** (3.3 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, *J* = 5.4 Hz, 2H), 7.43-7.38 (m, 3H), 3.99 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.6, 139.1, 133.4, 128.7, 128.0, 60.3, 44.6, 25.7, 18.3, −5.5.

(±)-5-(*t*-Butyldimethylsilanyloxy)-3-phenylpent-1-en-3-ol (8). To a solution of **7** (4.95 g, 18.72 mmol) in dry THF (80 mL) was slowly added vinylmagnesium bromide (22.46 mL, 1.0 M solution in THF) at −20 ºC and stirred 6 h at 0 ºC under nitrogen. Saturated NH_4Cl solution (22 mL) was added to the mixture, which was slowly warmed to rt. The mixture was further diluted with water (120 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, 1:14) to give **8** (3.28 g, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.21 (m, 5H), 5.99 (m, 1H), 5.14-5.05 (m, 2H), 3.81 (t, *J* = 6.8 Hz, 2H), 1.98 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 139.7, 129.5, 128.3, 127.3, 125.6, 115.7, 74.2, 58.5, 47.6, 25.6, 18.4, -5.6; Anal. Calc. for $C_{17}H_{28}O_2Si$·0.5 EtOAc: C, 67.80; H, 9.58; Found: C, 67.76; H, 9.56.

(±)-3-Phenylpent-4-ene-1,3-diol (9). TBAF (9.22 mL, 1.0 M solution in THF) was added to a solution of **8** (1.8 g, 6.15 mmol) in cosolvent (12 mL, THF/CH_3CN 1:1 v/v) at 0 ºC. The mixture was stirred overnight at room temperature and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to give **9** (898 mg, 82%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.26-7.22 (m, 5H), 5.90 (dd, *J* = 17.4, 11.1 Hz, 1H), 5.34 (dd, *J* = 17.3, 3.2 Hz, 1H), 5.14 (dd, *J* = 11.2, 2.4 Hz, 1H), 5.12 (s, 1H), 4.88 (t, *J* = 4.8 Hz, 1H), 3.67 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 144.3, 138.7, 128.5, 124.2, 112.3, 74.4, 56.1, 47.1; Anal. Calc. for $C_{11}H_{14}O_2$·0.5 MeOH: C, 71.10; H, 8.30; Found: C, 71.13; H, 8.28.

(±)-Benzoic Acid 3-Hydroxy-3-phenylpent-4-enyl Ester (10). To a solution of **9** (1.25 g, 7.01 mmol) in anhydrous pyridine (12 mL) was added benzoyl chloride (1.08 g, 7.71 mmol) and DMAP (43 mg, 0.355 mmol) at 0 ºC. The reaction mixture was stirred overnight at rt. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), stirred for 20 minutes and concentrated under reduced pressure. The residue was poured into water (100 mL) and extracted with EtOAc (100 mL) twice. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **10** (1.44 g, 73%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 7.25-7.21 (m, 5H), 5.89 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.50-4.40 (m, 2H), 2.10-1.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.5, 144.2, 137.5, 132.9, 130.1, 129.5, 128.9, 128.3, 124.7, 112.3, 76.3, 58.6, 44.3; Anal. Calc. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.50; H, 6.38.

(±)-Benzoic Acid 3-(*t*-Butyldimethylsilanyloxy)-3-phenylpent-4-enyl Ester (11). To a solution of **10** (1.6 g, 5.66 mmol) in anhydrous CH_2Cl_2 (12 mL) was added 2,6-lutidine (2.42 g, 22.6 mmol) at 0 ºC. *t*-Butyldimethylsilyl trifluomethanesulfonate (TBDMSOTf) (2.24 g, 8.49 mmol) was added to this mixture and the reaction mixture was stirred overnight at rt and quenched with cold H_2O (10 mL). The mixture was diluted with water (80 mL) and extracted with EtOAc (2 × 80 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromato-

graphy (EtOAc/hexane, 1:25) to give **11** (1.82 g, 81%) as colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (m, 2H), 7.45 (m, 1H), 7.31-7.23 (m, 7H), 5.87 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 4.36-4.30 (m, 2H), 1.95-1.87 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.5, 144.8, 139.2, 132.7, 130.4, 129.5, 128.2, 123.9, 112.2, 74.4, 63.8, 45.1, 25.8, 18.2, –5.56; Anal. Calc. for $C_{24}H_{32}O_3Si$·0.5 EtOAc: C, 70.87; H, 8.23; Found: C, 70.92; H, 8.24.

(±)-3-(*t*-Butyldimethylsilanyloxy)-3-phenylpent-4-en-1-ol (12). A solution of **11** (670 mg, 1.69 mmol) in methanolic ammonia (10 mL) 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 **12** (420 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.21 (m, 5H), 5.98-5.91 (m, 1H), 5.14-5.05 (m, 2H), 3.64 (m, 2H), 1.99 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 138.3, 128.7, 127.4, 125.7, 115.3, 75.7, 58.3, 46.1, 25.4, 18.6, –5.3; Anal. Calc. for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; Found: C, 69.77; H, 9.59.

(±)-3-(*t*-Butyldimethylsilanyloxy)-3-phenylpent-4-enal (13). To a stirred solution of oxalyl chloride (190 mg, 1.5 mmol) in CH_2Cl_2 (11 mL) was added a solution of DMSO (234 mg, 3.0 mmol) in CH_2Cl_2 (5.0 mL) dropwise at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min under nitrogen, and a solution of alcohol **12** (219 mg, 0.75 mmol) in CH_2Cl_2 (12 mL) was added dropwise. The mixture was stirred at –78 ºC for 30 min and TEA (607 mg, 6.0 mmol) was added. The resulting mixture was warmed to 0 ºC and stirred for 30 min under nitrogen. H_2O (17 mL) was added, and the solution was stirred at room temperature for 30 min. The mixture was further diluted with water (110 mL) and then extracted with EtOAc (2 × 110 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, 1:12) to give aldehyde compound **13** (198 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, 1H), 7.26-7.23 (m, 5H), 6.01-5.93 (m, 1H), 5.11-4.99 (m, 2H), 2.89 (dd, *J* = 10.2, 6.8 Hz, 2H), 0.87 (s, (H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 142.6, 138.9, 129.3, 128.2, 127.2, 117.5, 115.3, 71.2, 58.5, 25.4, 18.6, –5.5.

(±)-3*R* and 3*S*,5*S*)-5-(*t*-Butyldimethylsilanyloxy)-5-phenyl-hepta-1,6-dien-3-ol (14). Divinyl analogue **14** was synthesized from aldehyde **13** by the similar procedure as described for **8** as a diastereomeric mixture: yield 74%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.22 (m, 5H), 5.98-5.85 (m, 2H), 5.13-4.96 (m, 4H), 3.87 (m, 1H), 1.95-1.88 (m, 2H), 0.88 (m, 9H), 0.02 (m, 6H).

(±)-(1*S*,4*S*)-4-(*t*-Butyldimethylsilanyloxy)-4-phenylcyclopent-2-enol (15a) and (±)-(1*R*,4*S*)-4-(*t*-butyldimethylsilanyloxy)-4-phenyl-cyclopent-2-enol (15b). To a solution of **14** (259 mg, 0.814 mmol) in dry methylene chloride (8 mL) was added 2nd generation Grubbs catalyst (42.8 mg 0.0497 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 **15a** (80 mg, 34%) and **15b** (82 mg, 35%). Data for **15a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.23 (m, 5H), 5.63 (d, *J* = 5.2 Hz, 1H), 5.39 (m, 1H), 4.01 (m, 1H), 3.79 (s, 3H), 2.18 (dd, *J* = 13.0. 8.8 Hz, 1H), 2.09 (dd, *J* = 13.0, 6.8 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 137.7, 129.1, 128.3, 127.6, 124.9, 81.2, 67.8, 48.9, 25.4, 18.5, -5.3; Anal. Calc. for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02; Found: C, 70.33; H, 9.05.

Data for **15b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.21 (m, 5H), 5.60 (d, *J* = 5.3 Hz, 1H), 5.42 (dd, *J* = 5.4, 4.2 Hz, 1H), 4.03 (m, 1H), 2.14 (dd, *J* = 12.8. 8.4 Hz, 1H), 2.05 (dd, *J* = 12.9, 6.6 Hz, 1H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 137.3, 133.8, 127.6, 125.6, 80.5, 68.2, 47.6, 25.6, 18.4, –5.5; Anal. Calc. for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02; Found: C, 70.25; H, 8.96.

(±)-(1'*R*,4'*S*)-9-[4-Phenyl-(*t*-butyldimethylsilanyloxy)-cyclopent-2-enyl]-6-chloropurine (16). To a solution containing compound **15b** (162 mg, 0.56 mmol), triphenylphosphine (440 mg, 1.68 mmol) and 6-chloropurine (173 mg, 1.12 mmol) in anhydrous THF (10.0 mL), diisopropyl azodicarboxylate (DIAD) (226 mg, 1.12 mmol) was added dropwise at –10 ºC for 30 min under nitrogen. The reaction mixture was stirred for 4 h at –10 ºC under nitrogen and further stirred overnight at rt. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/hexane, 2.5:1) to give compound **16** (95 mg, 40%): mp 176-178 ºC; UV (MeOH) λ_{max} 263.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.45 (s, 1H), 7.27-7.23 (m, 5H), 5.63 (d, *J* = 5.4 Hz, 1H), 5.37 (d, *J* = 5.4 Hz, 1H), 4.47 (m, 1H), 2.67 (dd, *J* = 13.1. 8.6 Hz, 1H), 2.26 (dd, *J* = 13.2, 6.8 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.1, 148.2, 143.7, 140.7, 138.2, 137.2, 134.8, 132.3, 127.4, 126.9, 81.8, 53.5, 46.1, 25.4, 18.7, -5.4; Anal. Calc. for $C_{22}H_{27}ClN_4OSi$·0.5 EtOAc: C, 61.19; H, 6.63; N, 11.89; Found: C, 61.23; H, 6.59; N, 11.92.

(±)-(1'*R*,4'*S*)-9-(4-Phenyl-4-hydroxycyclopent-2-enyl)-6-chloropurine (17). Desilylation of **16** was performed using the similar procedure as described for **9**: yield 72%; mp 160-163 ºC; UV (MeOH) λ_{max} 264.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.71 (s, 1H), 8.43 (s, 1H), 7.34-7.26 (m, 5H), 5.61 (d, *J* = 5.2 Hz, 1H), 5.39 (m, 1H), 5.10 (br s, 1H), 4.45 (m, 1H), 2.22 (dd, *J* = 13.2. 8.8 Hz, 1H), 2.03 (dd, *J* = 13.1, 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.2, 151.7, 147.5, 138.7, 137.8, 135.4, 132.3, 129.6, 81.2, 54.2, 45.8; Anal. Calc. for $C_{16}H_{13}ClN_4O$·1.0 MeOH: C, 59.22; H, 4.97; N, 16.25; Found: C, 59.18; H, 4.99; N, 16.27.

(±)-(1'*R*,4'*S*)-Diethyl [9-(4-hydroxy-4-phenylcyclopent-2-en-1-yl)-6-chloropurine] methylphosphonate (18). Both Li*Ot*-Bu (2.48 mL of 0.5 M solution in THF, 1.24 mmol) and a solution of diethyl phosphonomethyltriflate (372 mg, 1.24 mmol) in 10.0 mL of THF were slowly added to a solution of the 6-chloropurine analogue **17** (194 mg, 0.62 mmol) in 7.0 mL of THF at –30 °C and stirred overnight at rt

under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (5 mL) and further diluted with additional H_2O (120 mL). The aqueous layer was extracted with EtOAc (3 × 120 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, 0.02:5:1) to give **18** (183 mg, 64%) as a formy solid: UV (MeOH) λ_{max} 263.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.76 (s, 1H), 8.50 (s, 1H), 7.31-7.23 (m, 5H), 5.65 (d, J = 5.3 Hz, 1H), 5.39 (m, 1H), 4.49 (m, 1H), 4.23 (m, 4H), 4.04 (d, J = 8.2 Hz, 2H), 2.25-2.19 (dd, J = 13.2. 8.6 Hz, 1H), 2.06 (dd, J = 13.2, 6.8 Hz, 1H), 1.36-1.33 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.4, 151.2, 149.3, 138.6, 137.3, 134.8, 130.2, 129.3, 128.7, 84.9, 65.2, 64.7, 63.2, 53.7, 40.4, 17.0; Anal. Calc. for $C_{21}H_{24}ClN_4O_4P$: C, 54.49; H, 5.23; N, 12.10; Found: C, 54.55; H, 5.20; N, 12.12.

(±)-(1'*R*,4'*S*)-Diethyl [9-(4-hydroxy-4-phenylcyclopent-2-en-1-yl)-adenine] methylphosphonate (19). A solution of **18** (187 mg, 0.404 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at 65 ºC in a steel bomb, and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to give **19** (93 mg, 52%) as a solid: mp 156-158 ºC; UV (MeOH) λ_{max} 260.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.35 (s, 1H), 8.11 (s, 1H), 7.15 (br s, 2H), 7.30-7.24 (m, 5H), 5.68 (d, J = 5.2 Hz, 1H), 5.37 (dd, J = 5.4, 4.2 Hz, 1H), 4.56 (m, 1H), 4.19 (m, 4H), 4.03 (d, J = 8.2 Hz, 2H), 2.24 (dd, J = 13.2. 8.8 Hz, 1H), 2.07 (dd, J = 13.1, 6.6 Hz, 1H), 1.35-1.31 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.6, 152.7, 146.7, 138.2, 133.2, 129.8, 128.6, 127.8, 126.2, 119.2, 87.0, 64.6, 63.3, 62.2, 54.1, 41.2, 17.2; Anal. Calc. for $C_{21}H_{26}N_5O_4P$·0.5 MeOH: C, 56.20; H, 6.14; N, 15.24; Found: C, 56.17; H, 6.11; N, 15.21.

(±)-(1'*R*,4'*S*)-[9-(4-Phenylcyclopenten-1-yl)-adenine]-4-methylphosphonic Acid (20). To a solution of the phosphonate **19** (142 mg, 0.32 mmol) in anhydrous CH_3CN (10 mL) and 2,6-lutidine (685 mg, 6.4 mmol) was added trimethylsilyl bromide (0.42 mL, 3.2 mmol). The mixture was heated overnight at 60 ºC and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and distilled clean water (80 mL). The aqueous layer was washed out with CH_2Cl_2 two times and then freeze-dried to give phosphonic acid **20** (73 mg, 70%) as a yellowish form: UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.11 (s, 1H), 7.16 (br s, 2H), 7.32-7.26 (m, 5H), 5.66 (d, J = 5.2 Hz, 1H), 5.36 (m, 1H), 4.49 (m, 1H), 4.14 (d, J = 8.2 Hz, 2H), 2.27 (dd, J = 13.2, 8.6 Hz, 1H), 2.07 (dd, J = 13.3, 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.4, 152.4, 143.6, 138.2, 135.5, 133.2, 130.4, 128.3, 127.6, 125.2, 120.2, 87.1, 63.8, 54.8, 39.2; Anal. Calc. for $C_{17}H_{18}N_5O_4P$·3.0 H_2O: C, 46.26; H, 5.48; N, 15.86; Found: C, 46.31; H, 4.52; N, 15.83.

(±)-(1'*R*,2'*S*,3'*S*,4'*S*)-Diethyl [9-(2,3-dihydroxy-4-phenylcyclopent-1-yl)-adenine]-4-methylphosphonate (21) and (±)-(1'*R*,2'*R*,3'*R*,4'*S*)-diethyl [9-(2,3-dihydroxy-4-phenylcyclopent-1-yl)-adenine]-4-methylphosphonate (22). Compound **19** (244 mg, 0.55 mmol) was dissolved in in a cosolvent system (12 mL) (acetone: *t*-BuOH: H_2O = 8:1:1) along with 4-methylmorpholine *N*-oxide (128 mg, 1.1 mmol). Subsequently, OsO_4 (0.22 mL, 0.03 mmol, 4% wt. % in H_2O) was added. The mixture was stirred overnight at rt 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 **21** (84 mg, 32%) and **22** (78 mg, 30%): compound **21** as formy solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.16 (br s, 2H), 7.32-7.26 (m, 5H), 4.21-4.17 (m, 4H), 4.13 (d, J = 8.1 Hz, 2H), 4.04 (d, J = 5.6 Hz, 1H), 3.68 (m, 1H), 3.26 (dd, J = 5.6, 2.6 Hz, 1H), 2.16-2.09 (dd, J = 13.1, 8.8 Hz, 1H), 1.91 (dd, J = 13.2, 7.6 Hz, 1H), 1.33 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.2, 152.7, 146.6, 138.5, 137.3, 128.7, 127.4, 125.9, 119.6, 82.5, 80.7, 69.3, 67.8, 64.7, 63.7, 62.5, 46.3, 31.5, 17.1; Anal. Calc. for $C_{21}H_{28}N_5O_6P$·2.0 MeOH: C, 51.01; H, 6.70; N, 12.93; Found: C, 50.96; H, 6.74; N, 12.88; Compound **22**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.18 (s, 1H), 7.19 (br s, 2H), 7.30-7.22 (m, 5H), 4.19 (m, 4H), 4.08 (d, J = 8.2 Hz, 2H), 3.99 (d, J = 5.8 Hz, 1H), 3.70 (m, 1H), 3.30 (m, 1H), 2.17 (dd, J = 13.0, 8.7 Hz, 1H), 1.94 (dd, J = 13.1, 7.8 Hz, 1H), 1.34 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.6, 152.1, 147.4, 138.6, 136.9, 128.6, 127.4, 126.2, 120.1, 81.4, 78.2, 68.7, 66.2, 65.3, 64.8, 63.2, 47.3, 32.1, 17.6; Anal. Calc. for $C_{21}H_{28}N_5O_6P$·1.0 MeOH: C, 51.86; H, 6.33; N, 13.74; Found: C, 51.91; H, 6.28; N, 13.69.

(±)-(1'*R*,2'*S*,3'*S*,4'*S*)-[9-(2,3-Dihydroxy-4-phenylcyclopent-1-yl)] adenine]-4-methylphosphonic Acid (23). Final adenosine phosphonic acid **23** was synthesized from **21** using the similar procedure described for **20** as a light yellow formy solid: yield 63%; UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.18 (s, 1H), 7.32-7.25 (m, 5H), 4.09 (d, J = 8.1 Hz, 2H), 3.97 (d, J = 6.0 Hz, 1H), 3.71 (m, 1H), 3.31 (m, 1H), 2.17 (dd, J = 13.3, 8.6 Hz, 1H), 1.92 (dd, J = 13.2, 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.1, 153.4, 146.7, 133.5, 138.3, 128.4, 127.8, 126.2, 120.6, 81.7, 79.6, 68.3, 64.5, 63.6, 46.7, 32.1; Anal. Calc. for $C_{17}H_{20}N_5O_6P$·2.0 H_2O: C, 44.64; H, 5.29; N, 15.31; Found: C, 44.59; H, 5.35; N, 15.26.

Molecular Modeling. The low energy conformations are calculated by quantum mechanics method using B3LYP/6-31G**. For modeling of the complex form, the structure of the ternary complex of HIV-1 RT (PDB code 1RTD) was used as the starting point. The dTTP of the active site was modified into our anti-HIV-1 RT agent analogues. All template positions of the enzyme are fixed except M184 and Y115 so called 'primer grip' in the minimization of the complex. For maintaining the bind site, Mg ions and diphosphophosphonates group are also fixed. Therefore, the agents and primer grip region are flexible. All modeling studies and the calculations are performed by the modeling package Spartan software. For minimization of the complex, molecular mechanics force field such as MMFF was used.

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