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Role of Hydroxymethyl Group as a New Hydrophilic 4'-Pocket in 5'-Norcarbocyclic Nucleoside 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'-group with antiviral enhancement, novel 4'-hydroxymethyl-5'-norcarbocyclic adenosine phosphonic acid analogues were designed and synthesized from 2,2-dimethyl-1,3-dioxolane-4-ethanol (**5**) using reiterative Grignard addition and ring-closing metathesis (RCM) as key reactions. The synthesized adenosine phosphonic acids analogues (**22**) and (**23**) were subjected to antiviral screening against HIV-1. Compound (**23**) exhibited moderate anti-HIV activity (EC_{50} = 8.61 μM) in the CEM cell line.

Key Words: Anti-HIV agents, 4'-Hydroxymethyl branched nucleoside, Phosphonic acid nucleosides

Introduction

The resistance of glycoside bond to enzymatic hydrolysis catalyzed by nucleoside phosphorylase[1] is one of the critical points in nucleoside antiviral chemotherapy. In order to avoid such enzymatic degradation as well as to improve the antiviral activity, a great number of structural modifications have been carried out on both the sugar and the heterocycle moiety of nucleosides. One strategy has been to replace the oxygen of the furanose ring by a methylene group, which gives rise to carbocyclic nucleosides.[2] Although these two classes of rings are far from being identical, the cyclopentene or cyclopentane ring allows carbocyclic nucleosides to be recognized as substrates or inhibitors of various enzymes.[3]

Recently, 4'-homologated nucleosides such as 4'-fluoromethyl-2'-deoxycytidine (**1**)[4] and 4'-hydroxymethylthymidine (**2**)[5] analogues are molecules of considerable interest (Figure 1). One of reasons for this prominence arises from the notable biological activities as anti-HIV agents. Modeling studies demonstrated the presence of a narrow, relatively hydrophobic 4'-pocket that can accommodate these substitutions, contributing to the observed enhancement in potency.[6]

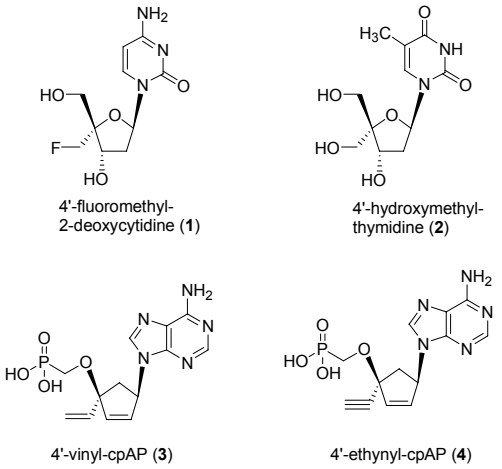
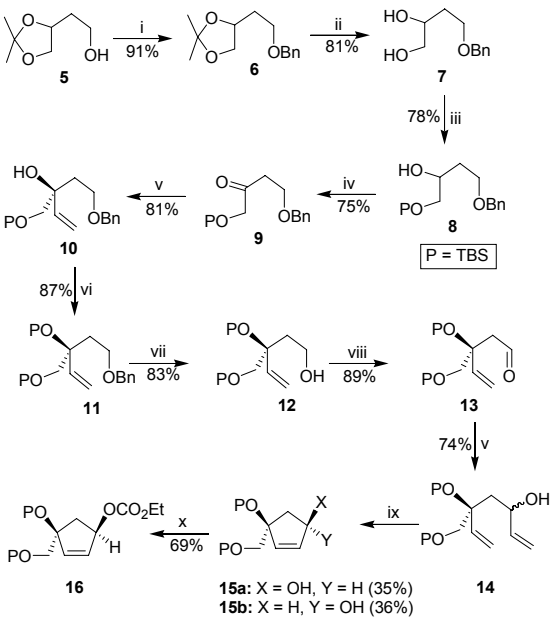


Figure 1. Structures of 4'-branched nucleoside analogues as potent anti-HIV agents.

More recently, 4'-branched-5'-norcarbocyclic phosphonic acid analogues, such as 4'-vinyl-cpAP (**3**) and 4'-ethynyl-cpAP (**4**)[6] have encouraged the search for novel nucleosides as potential anti-HIV agents among this class of compounds (Figure 1).[7] 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.[8] The spacial 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 activity with this oxygen atom may be attributed to the increased binding capacity of the phosphonate analogues to target enzymes.[9] 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.[10]

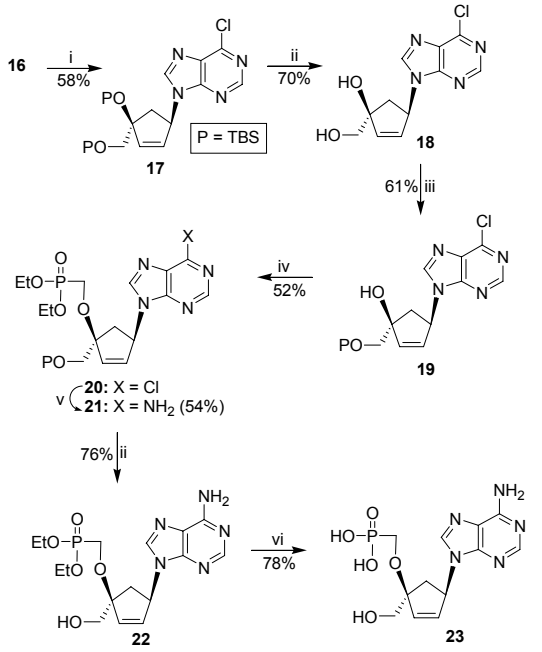
Actually, the exact role of the substituents in 4'-position of nucleoside analogues has not been fully explored. In continuation of our effort to find more efficient therapeutic agents against HIV and to provide analogues for probing the conformational preferences of enzymes associated with the metabolism of nucleosides and nucleotides, we have designed and prepared a novel class of nucleosides comprising 4'-hydroxymethyl-5'-norcarbocyclic phosphonic acid analogues.

As depicted in Scheme 1, the target compounds were prepared from commercially available 2,2-dimethyl-1,3-dioxolane-4-ethanol, (**5**). The hydroxyl functional group of (**5**) was subjected to protection reaction by benzyl bromide (BnBr, NaH, DMF) to furnish the acetonide (**6**), which was subjected to hydrolysis to provide diol derivative (**7**). The selective protection of primary hydroxyl group of (**7**) was successfully accomplished under mild silylation conditions (TBDMSCl, imidazole) to give the secondary alcohol (**8**).[11] The secondary hydroxyl group of (**8**) was oxidized to the ketone (**9**) using Corey and Kim's oxidation conditions (NCS, DMS).[12] The corresponding ketone functional group of (**9**) was subjected to an addition re-



Reagents: i) BnBr, NaH, THF; ii) HCl, MeOH; iii) TBDMSCl, imidazole, CH_2Cl_2; iv) NCS, DMS, toluene; v) vinylMgBr, THF; vi) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; vii) Li, NH_3/THF; viii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; ix) Grubb's (II), CH_2Cl_2; x) $ClCO_2Et$, DMAP, pyridine.

Scheme 1. Synthesis of key cyclopentene ethylformate intermediate **16**



Reagents: i) 6-chloropurine, $Pd_2(dba)_3.CHCl_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO; ii) TBAF, CH_3CN; iii) TBDMSCl, imidazole, CH_2Cl_2; iv) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; v) NH_3/MeOH, 70 °C; vi) TMSBr, lutidine, CH_3CN,

Scheme 2. Synthesis of target 4'-hydroxymethyl-5'-norcarbocyclic adenosine phosphonic acid

action by vinylmagnesium bromide to give the tertiary hydroxyl analogue (**10**), which was again silylated (TBDMSOTf, 2.6-lutidine)[13] to give the protected compound (**11**).

Removal of the benzyl protecting group of (**11**) under dissolving metal reduction[14] for a prolonged time (*ca* 25 min) furnished the desired alcohol (**12**), which was oxidized to the aldehyde (**13**) using Swern oxidation conditions[15] (DMSO, oxalyl chloride, TEA). The aldehyde (**13**) was again subjected to nucleophilic Grignard conditions[16] by vinylmagnesium bromide to yield divinyl (**14**), which was subjected to ring-closing metathesis (RCM) conditions using 2nd generation Grubbs catalyst ($C_{46}H_{65}Cl_2N_2PRu$)[17] to provide cyclopentenol (**15a**) (35%) and (**15b**) (36%), which were readily separated by silica gel column chromatography. The nuclear Overhauser enhancement (NOE) experiments with cyclopentenols (**15a**) and (**15b**) 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 (**15b**) [C_4-C*H*- (0.78%)] compared with those of compound (**15a**) [C_4-C*H*- (1.21%)] (Figure 2).

Initially, to synthesize the desired 5'-norcarbocyclic adenosine nucleoside analogues, the protected cyclopentenol (**15b**) was treated with 6-chloropurine under Mitsunobu coupling conditions[18] (DIAD and PPh_3). However, the reaction produced a very low yield and was not reproducible. Alternatively, to couple the 6-chloropurine to cyclopentenol derivative (**15a**) using well known palladium(0)-catalysis,[19] hydroxyl group of (**15a**) was transformed to the allylic formate analogue (**16**) using ethyl chloroformate. Compound (**16**) was coupled with the nucleosidic base anions generated by NaH/DMSO using a catalyst [tris(dibenzylidene-acetone)-dipalladium(0)-chloroform] adduct to provide the 5'-norcarbocyclic nucleoside analogues (**17**) (Scheme 2).[20] Sequential double desilylation of (**17**) and selective monosilylation of corresponding diol (**18**) produced the 5'-norcarbocyclic nucleoside analogue (**19**), which was treated with diethylphosphonomethyl triflate[21] using lithium *t*-butoxide to yield the nucleoside phosphonate analogue (**20**). The chlorine group of (**20**) was then converted to amine with methanolic ammonia at 70 °C to give the corresponding adenine phosphonate derivative (**21**).[4] Desilylation of silicon protection group followed by hydrolysis of diethyl phosphonate functional groups of (**22**) gave the adenosine phosphonic acid derivative (**23**).

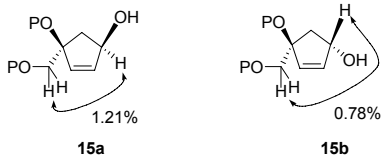


Figure 2. NOE differences between the proximal hydrogens of **15a** and **15b**.

The synthesized nucleoside phosphonate and phosphonic acid analogues (**22**) 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.[22] As shown in Table 1, nucleoside phosphonic acid (**23**) exhibited significantly more anti-HIV activity than its parent nucleoside diethyl phosphonate (**22**) at concentrations up to 100 μM. Further develop-

Table 1. Anti-HIV activity of synthesized compounds

Compound No.	anti-HIV EC_{50} (μM)[c]	Cytotoxicity CC_{50} (μM)[d]
22	47.5	98
23	**8.61**	90
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%.

ment toward optimal prodrugs will likely allow efficient delivery of the phosphonate to the lymphatic system and provide a novel nucleotide RT inhibitor for the treatment of HIV.

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'-hydroxymethyl-5'-norcarbocyclic nucleoside analogues starting from 2,2-dimethyl-1,3-dioxolane-4-ethanol. 4'-Vinyl analogue (**3**) and ethynyl analogue (**4**) were found to inhibit RT with an IC_{50} =0.67 μM, and 0.15 μM, respectively.[6] Taking these data into account, the proposed 4'-pocket in the active site of RT is sensitive to steric and electronic changes in the 4'-substituent, especially when this involves increasing the van der Waals radius or possibly changes in the projection angle of the 4'-substituent into the pocket. Compounds **22** and **23** exhibited weak anti-HIV activity, indicating that the hydrophilic pocket such as hydroxymethyl group at 4'-position of 5'-norcarbocyclic nucleosides system makes the conformation to be unfavorable for interaction with enzymes associated with the kinases of nucleosides and nucleotides.

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 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.

(±)-4-(2-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (6). To a suspension of NaH (60% in mineral oil, 495 mg, 12.45 mmol) in THF (50 mL) was slowly added a solution of alcohol **5** (1.52 g, 10.39 mmol) in THF (50 mL). Benzyl bromide (1.95 g, 11.43 mmol) in THF (50 mL) was added to the mixture at 0 °C and stirred overnight at rt. The reaction was quenched by water (10 mL) and further diluted with water (150 mL). The mixture was extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **6** (2.23 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.20 (m, 5H), 4.59 (s, 2H), 3.92-3.85 (m, 3H), 3.41 (t, J = 6.8 Hz, 2H), 1.61 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H).

(±)-4-Benzyloxy-butane-1,2-diol (7). To a solution of **6** (120 mg, 0.508 mmol) dissolved in MeOH (10 mL), con. HCl (1 mL) was added. The mixture was stirred at rt for 12 h and neutralized with TEA. The mixture was concentrated in vacuo and the residue was dissolved in H_2O (50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give **7** (80 mg, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.19 (m, 5H), 4.61 (s, 2H), 3.78 (dd, J = 6.8, 4.8 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 3.31 (m, 1H), 1.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8, 128.5, 127.8, 127.2, 76.4, 72.2, 71.1, 63.8, 35.7.

(±)-4-Benzyloxy-1-(*t*-butyldimethylsilanyloxy)-butan-2-ol (8). To a stirred solution of diol **7** (2.2 g, 11.25 mmol) and imidazole (1.14 g, 16.87 mmol) in CH_2Cl_2 (80 mL), *t*-butyldimethylsilyl chloride (1.86 g, 12.37 mmol) was slowly added at −10 °C. The mixture was stirred at 0 °C for 2 h, and further stirred for 3 h at rt. The mixture was quenched by adding a $NaHCO_3$ solution (5 mL) and further diluted with water (100 mL). The mixture was extracted using CH_2Cl_2 (150 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give compound **8** (2.72 g, 78%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.20 (m, 5H), 4.65 (s, 2H), 3.91 (dd, J = 7.0, 5.0 Hz, 2H), 3.38 (t, J = 6.8 Hz, 2H), 3.32 (m, 1H), 1.63-1.60 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 128.6, 127.7, 127.1, 75.8, 74.5, 72.6, 64.2, 36.0, 25.7, 18.4, −5.2.

(±)-4-Benzyloxy-1-(*t*-butyldimethylsilanyloxy)-butan-2-one (9). *N*-Chlorosuccinimide (NCS, 1.57 g, 11.75 mmol) was suspended in toluene (40 mL) and the mixture was cooled in an ice bath. Methyl sulfide (1.47 mL, 19.75 mmol) was added and a white precipitate formed immediately. The solution was attired for 30 min at 0 °C and then cooled to −20 °C. A solution of alcohol **8** (2.48 g, 8 mmol) in toluene (15 mL) was slowly added to the mixture. The mixture was kept under nitrogen for 4 h, whereupon TEA (1.65 mL, 11.75 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, 1:15) to give **9** (1.85 g, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.21 (m, 5H), 4.98 (s, 2H), 4.62 (s, 2H), 3.66 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.9 Hz, 2H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.2, 139.6, 128.9, 128.0, 127.3, 76.8, 75.5, 64.6, 38.5, 25.5, 18.6, −5.4.

(±)-5-Benzyloxy-3-(*t*-butyldimethylsilanyloxymethyl)-

pent-1-en-3-ol (10). To a solution of **9** (1.5 g, 4.86 mmol) in dry THF (20 mL) was slowly added vinylmagnesium bromide (5.8 mL, 1.0 M solution in THF) at −20 °C and the mixture was stirred 4 h at 0 °C. Saturated NH_4Cl solution (5 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, 1:12) to give **10** (1.32 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.20 (m, 5H), 5.72 (dd, *J* = 16.8, 10.5 Hz, 1H), 5.33 (dd, *J* = 17.0, 3.6 Hz, 1H), 5.17 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.65 (s, 2H), 3.98 (dd, *J* = 6.9, 5.0 Hz, 2H), 3.40 (m, 2H), 1.63 (m, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 140.3, 128.7, 127.6, 127.0, 112.5, 77.4, 74.6, 62.2, 39.3, 25.6, 18.5, −5.6; Anal. Calc. for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58; Found: C, 67.77; H, 9.61.

(±)-[3-(*t*-Butyldimethylsilanyloxy)-3-(*t*-butyldimethylsilanyloxymethyl)-pent-4-enyloxymethyl]-benzene (11). To a cooled, stirred solution of tertiary alcohol **10** (242 mg, 0.72 mmol) and 2,6-lutidine (0.6 mL, 6.14 mmol) in dry methylene chloride (12 mL) was added *t*-butyldimethylsilyl trifluoromethane sulfonate (TBDMSOTf, 0.9 mL, 3.07 mmol). The reaction mixture was warmed to room temperature, and stirred for 3 h at the same temperature. The mixture was quenched by saturated sodium bicarbonate (5 mL) and water (80 mL) was added. The mixture was extracted with ethyl acetate (80 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:25) to give **11** (282 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.21 (m, 5H), 5.74-5.72 (dd, *J* = 16.9, 10.4 Hz, 1H), 5.34 (dd, *J* = 17.0, 3.8 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.64 (s, 2H), 4.01 (dd, *J* = 6.8, 5.0 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 1.65 (m, 2H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 139.6, 128.5, 127.7, 113.6, 76.7, 73.5, 64.1, 38.9, 25.3, 18.6, −5.4; Anal. Calc. for $C_{25}H_{46}O_3Si_2 \cdot 0.5$ EtOAc: C, 65.53; H, 10.18; Found: C, 65.49; H, 10.12.

(±)-3-(*t*-Butyldimethylsilanyloxy)-3-(*t*-butyldimethylsilanyloxymethyl)-pent-4-en-1-ol (12). Anhydrous ammonia (approximately 12 mL) was condensed into a flask containing a solution of benzyl ether **11** (246 mg, 0.546 mmol) in dry tetrahydrofuran (4 mL) at −78 °C. To this mixture was added a piece of metallic lithium sufficient to maintain a blue color, and the resulting deep blue solution was stirred at −78 °C for 3 min. Methanol was added dropwise at the same temperature until the blue color disappeared. The colorless solution was stirred for 30 min at −78 °C, and then solid ammonium chloride (*ca*. 3.5 g) was added. After stirring for 1 h at −78 °C, the ammonia was allowed to evaporate. Diethyl ether (40 mL) was added, and the mixture was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **12** (163 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79-5.74 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.34 (dd, *J* = 17.1, 3.6 Hz, 1H), 5.18 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.98 (dd, *J* = 6.8, 4.8 Hz, 2H), 3.54 (t, *J* = 6.8, 2H), 1.66 (m, 2H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 112.2, 78.5, 70.2, 56.2, 42.4, 25.5, 18.4, −5.5; Anal. Calc. for $C_{18}H_{40}O_3Si_2$: C, 59.94; H, 11.18; Found: C, 59.97; H, 11.15.

(±)-3-(*t*-Butyldimethylsilanyloxy)-3-(*t*-butyldimethylsilanyloxymethyl)-pent-4-enal (13). To a stirred solution of oxalyl chloride (264 mg, 2.08 mmol) in CH_2Cl_2 (15 mL) was added a solution of DMSO (244 mg, 3.12 mmol) in CH_2Cl_2 (4.5 mL) dropwise at −78 °C. The resulting solution was stirred at −78 °C for 10 min, and a solution of alcohol **12** (375 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min and TEA (632 mg, 6.24 mmol) was added. The resulting mixture was warmed to 0 °C and stirred for 30 min. H_2O (15 mL) was added, and the solution was stirred at room temperature for 30 min. The mixture was diluted with water (150 mL) and then extracted with EtOAc (2 × 150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give aldehyde compound **13** (332 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.73 (s, 1H), 5.81-5.76 (dd, *J* = 17.0, 10.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 3.5 Hz, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 3.96 (dd, *J* = 6.9, 5.0 Hz, 2H), 2.57 (dd, *J* = 6.6, 4.8 Hz, 2H), 0.82 (m, 18H), 0.03 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 143.6, 111.9, 77.8, 67.1, 52.6, 25.7, 18.5, −5.3.

(*rel*)-(3*R* and 3*S*,5*S*)-5-(*t*-Butyldimethylsilanyloxy)-5-(*t*-butyldimethylsilanyloxymethyl)-hepta-1,6-dien-3-ol (14). Divinyl analogue **14** was synthesized as a diastereomeric mixture from aldehyde **13** by a procedure similar to that described for **10**: yield 74%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82-5.74 (m, 2H), 5.35-31 (m, 2H), 5.18-5.13 (m, 2H), 3.97-3.90 (m, 2H), 1.65-1.60 (m, 2H), 0.81 (m, 18H), 0.02 (m, 12H).

(*rel*)-(1*R*,4*S*)-4-(*t*-Butyldimethylsilanyloxy)-4-(*t*-butyldimethylsilanyloxymethyl)-cyclopent-2-enol (15a) and (*rel*)-(1*S*,4*S*)-4-(*t*-butyldimethylsilanyloxy)-4-(*t*-butyldimethylsilanyloxy-methyl)-cyclopent-2-enol (15b). To a solution of **14** (417 mg, 1.08 mmol) in dry methylene chloride (10 mL) was added 2nd generation Grubbs catalyst (48.0 mg, 0.0565 mmol). The reaction mixture was refluxed overnight and cooled to rt. The mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **15a** (135 mg, 35%) and **15b** (139 mg, 36%).

Data of 15a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (d, *J* = 5.6 Hz, 1H), 5.38 (dd, *J* = 5.5, 2.8 Hz, 1H), 4.04 (m, 1H), 3.98 (dd, *J* = 6.2, 4.6 Hz, 2H), 2.22 (dd, *J* = 13.8. 8.8 Hz, 1H), 2.08 (dd, *J* = 13.7, 6.8 Hz, 1H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.2, 128.8, 78.3, 77.5, 69.1, 41.3, 25.6, 18.7, −5.4; Anal. Calc. for $C_{18}H_{38}O_3Si_2 \cdot 0.5$ EtOAc: C, 59.65; H, 10.51; Found: C, 59.69; H, 10.46.

Data of 15b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (d, *J* = 5.6 Hz, 1H), 5.36 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.06 (m, 1H), 3.93 (dd, *J* = 6.4, 5.0 Hz, 2H), 2.20 (dd, *J* = 13.7. 8.6 Hz, 1H), 2.04 (dd, *J* = 13.6, 6.6 Hz, 1H), 0.81 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0, 129.1, 78.7, 76.7, 68.4, 42.0, 25.4, 18.3, −5.6; Anal. Calc. for $C_{18}H_{38}O_3Si_2$: C, 60.28; H, 10.68; Found: C, 60.33; H, 10.72.

(*rel*)-(1'*R*,4'*S*)-1-Ethoxycarbonyloxy-4-(*t*-butyldimethyl-

silanyloxy)-4-(*t*-butyldimethyl silanyloxymethyl) cyclopent-2-ene (16). To a solution of compound **15a** (839 mg, 2.34 mmol) in anhydrous pyridine (15 mL), ethyl chloroformate (273 mg, 2.52 mmol) and DMAP (49 mg, 0.4 mmol) were added. The reaction mixture was stirred overnight at 65 °C. The reaction mixture was then quenched using a saturated $NaHCO_3$ solution (0.5 mL) and evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer extracts were washed with brine, dried over $MgSO_4$ and filtered. The organic solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:13) to give **16** (695 mg, 69%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.63 (d, J = 5.5 Hz, 1H), 5.43 (dd, J = 5.6, 3.2 Hz, 1H), 4.76 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.97 (dd, J = 6.6, 5.2 Hz, 2H), 2.31 (dd, J = 13.5. 8.8 Hz, 1H), 2.09 (dd, J = 13.6, 6.7 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.82 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2, 137.8, 127.8, 78.2, 77.5, 76.2, 64.6, 38.5, 25.6, 18.5, 13.8, −5.6; Anal. Calc. for $C_{21}H_{42}O_5Si_2$: C, 58.56; H, 9.83; Found: C, 58.61; H, 9.79.

(*rel*)-(1'*R*,4'*S*)-9-[4-(*t*-Butyldimethylsilanyloxy)-4-(*t*-butyldimethylsilanyloxymethyl) cyclopent-2-enyl]-6-chloropurine (17). 6-Chloropurine (145 mg, 0.94 mmol) was added to a solution of NaH (22.5 mg, 0.94 mmol) in anhydrous DMSO (5.0 mL). The reaction mixture was stirred for 30 min at 50 - 55 °C and cooled to room temperature. Simultaneously, P(O-*i*-Pr)$_3$ (78 mg, 0.374 mmol) was added to a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (50 mg, 4.8 μmol) in anhydrous THF (4.5 mL), which was stirred for 30 min. The catalyst solution in THF and **16** (357 mg, 0.83 mmol) dissolved in anhydrous THF (6.0 mL) was sequentially added to the purine base solution in DMSO. The reaction mixture was refluxed overnight, and then cooled and quenched with water (2.5 mL). The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (Hexane/EtOAc, 1:2.5) to give compound **17** (238 mg, 58%) as a white solid. mp 167 - 169 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (s, 1H), 8.39 (s, 1H), 5.62 (d, J = 5.6 Hz, 1H), 5.41 (dd, J = 5.6, 3.3 Hz, 1H), 4.51 (m, 1H), 3.97 (dd, J = 6.6, 5.2 Hz, 2H), 2.42 (dd, J = 13.6. 8.2 Hz, 1H), 2.07 (dd, J = 13.7, 5.3 Hz, 1H), 0.82 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.7, 151.4, 151.2, 145.2, 135.3, 132.4, 128.5, 79.3, 77.7, 54.7, 37.6, 25.5, 18.4, −5.4; Anal. Calc. for $C_{23}H_{39}ClN_4O_2Si_2 \cdot 0.5$ MeOH: C, 55.21; H, 8.08; N, 10.96; Found: C, 55.15; H, 8.12; N, 10.91.

(*rel*)-(1'*R*,4'*S*)-9-[4-(Hydroxy)-4-(hydroxymethyl) cyclopent-2-enyl]-6-chloropurine (18). To a solution of **17** (160 mg, 0.323 mmol) in acetonitrile (6.0 mL), TBAF (0.807 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 (MeOH/CH_2Cl_2, 1:10) to give **18** (60 mg, 70%) as a white solid: mp 171 - 173 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (s, 1H), 8.43 (s, 1H), 5.60 (d, J = 5.6 Hz, 1H), 5.39 (m, 1H), 5.13 (s, 1H, D_2O exchangeable), 4.91 (t, 1H, D_2O exchangeable), 4.54 (m, 1H), 3.67 (dd, J = 6.7, 5.4 Hz, 2H), 2.48 (dd, J = 13.8. 8.0 Hz, 1H), 2.11 (dd, J = 13.7, 5.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.9, 151.3, 146.4, 135.7, 133.2, 128.5, 78.4, 74.2, 55.2, 36.4; Anal. Calc. for $C_{11}H_{11}ClN_4O_2 \cdot 1.5$ MeOH: C, 47.70; H, 5.44; N, 17.80; Found: C, 47.76; H, 5.39; N, 17.77.

(*rel*)-(1'*R*,4'*S*)-9-[4-(Hydroxy)-4-(*t*-butyldimethylsilanyloxymethyl) cyclopent-2-enyl]-6-chloropurine (19). Nucleoside analogue **19** was prepared from **18** using the similar selective silylation procedure as described for **8**: yield 61%: mp 169 - 171 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1H), 8.42 (s, 1H), 5.63 (d, J = 5.6 Hz, 1H), 5.42 (dd, J = 5.5, 4.2 Hz, 1H), 4.52 (m, 1H), 3.89 (dd, J = 6.8, 5.2 Hz, 2H), 2.51 (dd, J = 13.7. 8.2 Hz, 1H), 2.13 (dd, J = 13.7, 5.3 Hz, 1H), 0.82 (m, 9H), 0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.1, 150.8, 145.7, 135.8, 132.6, 127.5, 79.5, 77.6, 54.7, 37.2, 25.6, 18.5, −5.6; Anal. Calc. for $C_{17}H_{25}ClN_4O_2Si$: C, 53.60; H, 6.61; N, 14.71; Found: C, 53.64; H, 6.56; N, 14.67.

(*rel*)-(1'*R*,4'*S*)-Diethyl {9-[(4-Hydroxy)-4-(*t*-butyldimethylsilanyloxymethyl) cyclopent-2-en-1-yl]-6-chloropurine} 4-methylphosphonate (20). Both Li*Ot*-Bu (2.976 mL of 0.5 M solution in THF, 1.488 mmol) and a solution of diethyl phosphonomethyltriflate (417 mg, 1.392mmol) in 8.0 mL of THF were slowly added to a solution of the 6-chloropurine analogue **19** (265 mg, 0.696 mmol) in 10 mL of THF at −20 °C and stirred overnight at rt under nitrogen. The mixture was quenched by adding saturated NH_4Cl solution (8 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, 0.02:4:1) to give **20** (192 mg, 52%) as a foam: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (s, 1H), 8.48 (s, 1H), 5.68 (d, J = 5.4 Hz, 1H), 5.41 (dd, J = 5.5, 2.8 Hz, 1H), 4.50 (m, 1H), 4.28 (m, 4H), 3.95 (d, J = 8.1 Hz, 2H), 3.81 (dd, J = 6.7, 4.2 Hz, 2H), 2.41-2.35 (dd, J = 13.8. 8.7 Hz, 1H), 2.08 (dd, J = 13.8, 6.8 Hz, 1H), 1.37 (m 6H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.0, 151.6, 150.9, 147.3, 138.2, 133.8, 130.2, 85.8, 75.1, 67.8, 65.6, 64.8, 54.8, 35.8, 25.4, 18.6, 15.9, −5.4; Anal. Calc. for $C_{22}H_{36}ClN_4O_5PSi$: C, 49.76; H, 6.83; N, 10.55; Found: C, 49.70; H, 6.88; N, 10.49.

(*rel*)-(1'*R*,4'*S*)-Diethyl {9-[(4-Hydroxy)-4-(*t*-butyldimethylsilanyloxymethyl) cyclopent-2-en-1-yl] adenine} 4-methylphosphonate (21). A solution of **20** (224 mg, 0.423 mmol) in saturated methanolic ammonia (10 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 **21** (116 mg, 54%) as a white solid: mp 162 - 164 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.10 (s, 1H), 6.08 (br s, 2H, D_2O exchangeable), 5.66 (d, J = 5.5 Hz, 1H), 5.38 (m, 1H), 4.49 (m, 1H), 4.30 (m, 4H), 3.96-3.88 (m, 4H), 2.43 (dd, J = 13.8. 8.8 Hz, 1H), 2.10 (m, 1H), 1.39-1.36 (m 6H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.7, 151.6, 148.4, 142.5, 137.9, 132.9, 120.1, 84.6, 76.3, 68.1, 65.2, 64.4, 55.0, 36.4, 25.5, 18.4, 16.3, −5.3; Anal. Calc. for $C_{22}H_{38}N_5O_5PSi \cdot 1.0$ MeOH: C, 50.81; H, 7.78; N, 12.88; Found: C, 50.75; H, 7.84; N, 12.91.

(*rel*)-(1'*R*,4'*S*)-Diethyl {9-[(4-Hydroxy)-4-(hydroxymethyl) cyclopent-2-en-1-yl] adenine} 4-methylphosphonate (22). Nucleoside analogue **22** was synthesized from **21** using the

similar desilyation procedure describe for **18**: yield 76%; mp 145 - 147 °C; UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.30 (s, 1H), 8.14 (s, 1H), 6.11 (br s, 2H, D_2O exchangeable), 5.68 (d, J = 5.6 Hz, 1H), 5.42 (dd, J = 5.7, 2.4 Hz, 1H), 4.93 (t, J = 4.8 Hz, 1H, D_2O exchangeable), 4.52 (m, 1H), 4.32 (m, 4H), 3.95-3.86 (m, 4H), 2.45 (m, 1H), 2.11 (dd, J = 13.7, 6.4 Hz, 1H), 1.38-1.35 (m 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.8, 151.7, 147.8, 143.4, 138.3, 134.1, 119.7, 86.5, 75.4, 67.8, 66.0, 65.6, 54.5, 37.1, 16.3; Anal. Calc. for $C_{16}H_{24}N_5O_5P \cdot 1.0$ MeOH: C, 47.54; H, 6.57; N, 16.31; Found: C, 47.49; H, 6.60; N, 16.26.

(*rel*)-(1'*R*,4'*S*)-{9-[(4-Hydroxy)-4-(hydroxymethyl) cyclopent-2-en-1-yl] adenine}4-methylphosphonic acid (23). To a solution of the phosphonate **22** (167 mg, 0.42 mmol) in anhydrous CH_3CN (10 mL) and 2,6-lutidine (0.978 mL, 8.4 mmol) was added trimethylsilyl bromide (0.642 mg, 4.2 mmol). The mixture was heated overnight at 60 °C under nitrogen gas and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (80 mL) and distilled purified water (80 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 60 mL) and then freeze-dried to give phosphonic acid **23** (112 mg, 78%) as a yellowish foam: UV (H_2O) λ_{max} 261.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 6.07 (br s, 2H, D_2O exchangeable), 5.66 (d, J = 5.7 Hz, 1H), 5.43 (dd, J = 5.6, 2.4 Hz, 1H), 4.89 (br s, 1H, D_2O exchangeable), 4.54 (m, 1H), 3.81 (dd, J = 6.7, 4.8 Hz, 2H), 2.48-2.38 (dd, J = 13.7, 8.7 Hz, 1H), 2.15 (dd, J = 13.6, 6.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.6, 151.4, 148.3, 141.9, 137.8, 132.8, 119.8, 85.2, 74.6, 65.2, 64.8, 55.8, 36.8; Anal. Calc. for $C_{12}H_{16}N_5O_5P \cdot 2.0$ H_2O: C, 38.20; H, 5.34; N, 18.56; Found: C, 38.14; H, 5.39; N, 18.49.

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References

1. Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *J. Med. Chem*. **1985**, *28*, 550.
2. Cookson, R.; Dudfield, P.; Newton, R. *Eur. J. Med. Chim. Ther*. **1985**, *20*, 375.
3. (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.
4. Kitano, K.; Miura, S.; Ohrui, H.; Meguro, H. *Tetrahedron* **1997**, *53*, 13315.
5. (a) Yossefyeh, R. D.; Tegg, D.; Verheyden, J. P. H.; Jones, G. H.; Moffatt, J. G. *Teterahedron Lett*. **1992**, *33*, 37. (b) Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem*. **1979**, *44*, 1301. (c) Jones, G. H.; Taniguchi, M.; Tegg, D.; Moffatt, J. G. *J. Org. Chem*. **1979**, *44*, 1309.
6. Boojamra, C. G.; Parrish, J. P.; Sperandio, D.; Gao, Y.; Petrakovsky, O. V.; Lee, S. K.; Markevich, D. Y.; Vela, J. E.; Laflamme, G.; Chen, J. M.; Ray, A. S.; Barron, A. C.; Sparacino, M. L.; Desai, M. C.; Kim, C. U.; Cihlar, T.; Mackman, R. L. *Bioorg. Med. Chem*. **2009**, *17*, 1739.
7. (a) Ray, A. S.; Vela, J. E.; Boojamra, C. G.; Zhang, L.; Hui, H.; Callebaut, C.; Stray, K.; Lin, K. Y.; Gao, Y.; Mackman, R. L.; Cihlar, T. *Antimicrob. Agents Chemother*. **2008**, *52*, 648. (b) Boojamra, C. G.; Mackman, R. L.; Markevitch, D.Y.; Prasad, V.; Ray, A. S.; Douglas, J.; Grant, D.; Kim, C. U.; Cihlar, T. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1120. (c) Cihlar, T.; Ray, A. S.; Boojamra, C. G.; Zhang, L.; Hui, H.; Laflamme, G.; Vela, J. E.; Grant, D.; Chen, J.; Myrick, F.; White, K. L.; Gao, Y.; Lin, K. Y.; Douglas, J. L.; Parkin, N. T.; Carey, A.; Pakdaman, R.; Mackman, R. L. *Antimicrob. Agents Chemother*. **2008**, *52*, 655.
8. Wu, T.; Froeyen, M.; Kempeneers, V.; Pannecouque, C.; Wang, J.; Busson, R.; De Clercq, E.; Herdewijn, P. *J. Am. Chem. Soc*. **2005**, *127*, 5056.
9. Kim, C. U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem*. **1990**, *33*, 1207.
10. Kim, C. U.; Luh, B. Y.; Martin, J. C. *J. Org. Chem*. **1991**, *56*, 2642.
11. Ermolenko, L.; André Sasaki, N.; Potier, P. *Tetrahedron Lett*. **1999**, *40*, 5187.
12. Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc*. **1972**, *94*, 7586.
13. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett*. **1981**, *22*, 3455.
14. Philips, K. D.; Zemlicka, J.; Horowitz, J. P. *Carbohydr. Res*. **1973**, *30*, 281.
15. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem*. **1978**, *43*, 2480.
16. Ko, O. H.; Hong, J. H. *Tetrahedron Lett*. **2002**, *43*, 6399.
17. (a) Jeong, L. S.; Lee, J. A. *Antiviral Chem. Chemother*. **2004**, *15*, 235. (b) Amblard, F.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 7067.
18. Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Pavan Kumar, K. V. P. *Chem. Rev*. **2009**, *109*, 2551.
19. Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev*. **2003**, *103*, 1875.
20. (a) Trost, B. M.; Kallander, L. S. *J. Org. Chem*. **1999**, *64*, 5427. (b) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc*. **1996**, *118*, 3037.
21. Phillion, D. P.; Andrew, S. S. *Tetrahedron Lett*. **1986**, *27*, 1477. (b) Xu, Y.; Flavin, M. T.; Xu, Z.-Q. *J. Org. Chem*. **1996**, *61*, 7697.
22. Lian, L. J.; Yoo, J. C.; Hong, J. H. *Nucleosides Nucleotides Nucleic Acids* **2009**, *28*, 150.