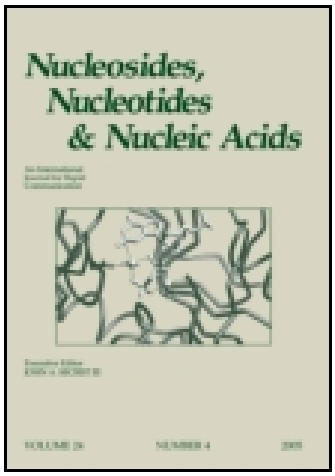

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Synthesis of 9-[1-(Substituted)-2-(Phosphonomethoxy)Ethyl]Adenine Derivatives as Possible Antiviral Agents

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SYNTHESIS OF 9-[1-(SUBSTITUTED)-2-(PHOSPHONOMETHOXY)ETHYL]ADENINE DERIVATIVES AS POSSIBLE ANTIVIRAL AGENTS

Minwan Wu, Yahya El-Kattan, Tsu-Hsing Lin, Ajit Ghosh, V. Satish Kumar, Pravin L. Kotian, Xiaogang Cheng, Shanta Bantia, Yarlagadda S. Babu, and Pooran Chand □ *BioCryst Pharmaceuticals, Inc., Birmingham, Alabama, USA*

□ *Various C-1′-substituted acyclic N^9 adenine nucleosides were prepared from 9-[(1-hydroxymethyl)(3-monomethoxytrityloxy)propyl]-N^6-monomethoxytrityladenine. The hydroxymethyl was modified to the phosphonomethoxy derivative, and the 3-monomethoxytrityloxy was converted to hydroxyl, methoxy, azido, and amino. Other substituents, such as ethyl and α-hydroxyethyl were also prepared. The resulting phosphonomethoxy derivatives were converted to prodrugs.*

Keywords Acyclic nucleosides; Prodrugs; Antiviral

INTRODUCTION

Extensive studies have been done on 9-[2-(phosphonomethoxy)ethyl]-adenine and guanine derivatives.[1–5] A number of lead compounds (Chart 1), such as PMEA, PMEDAP, PMEG evolved from those studies and adefovir dipivoxil (**1a**), the prodrug of PMEA, was approved by FDA for HBV infections.[6–12] All these compounds are unsubstituted acyclic nucleoside derivatives. Substituting the C-2′ position by methyl, hydroxymethyl, and fluoromethyl resulted into some more lead compounds (Chart 1), such as PMPA, HPMPA, FPMPA, HPMPDAP, PMPG, and HPMPG. One 2′-methyl compound, tenofovir disoproxil (**1b**), the prodrug of PMPA, was approved by FDA for HIV infections.[6–12] Very little work has been done on the C-1′-substituted compounds.[13–16]

Dedicated to the memory of John A. Montgomery.

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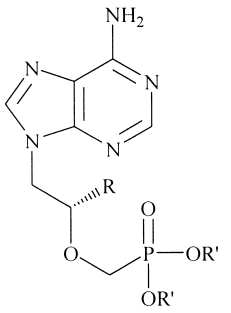


1a, R=H, R'=$CH_2OC(O)C(CH_3)_3$ (Adefovir dipivoxil)
1b, R=CH_3, R'=$CH_2OC(O)OCH(CH_3)_2$ (Tenofovir disoproxil)

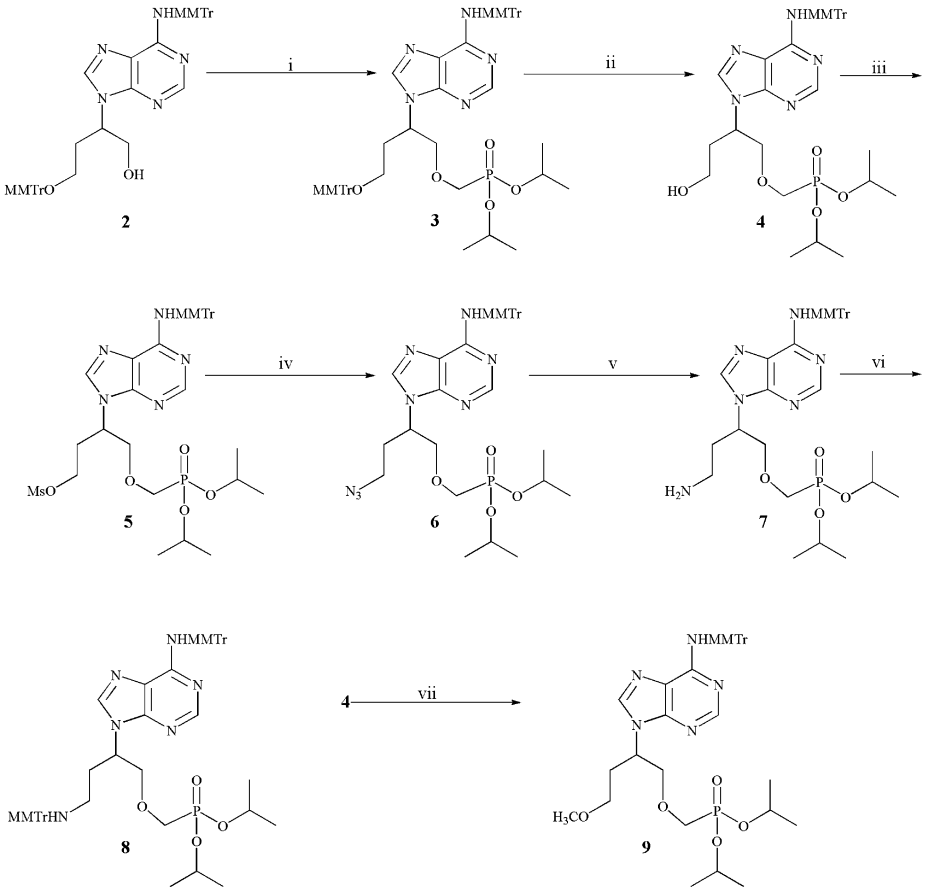
CHART 1

In continuation of our work in the preceding paper, we have now prepared the compounds to examine the effect of the side chain from the C-1′ position of acyclic nucleosides, their phosphonomethyl ether derivatives and corresponding prodrugs on antiviral activity. Based upon the structure of adefovir and tenofovir, we have synthesized these compounds keeping the spacer of 4 atoms between the adenine nitrogen and the phosphorus atom, and the oxygen β- to the phosphorus atom. All the compounds synthesized here in this report are the substituted compounds at C-1′ of the acyclic chain.

RESULTS AND DISCUSSION

The synthesized compounds are racemic. The synthesis of the compounds with hydroxyl, methoxy, azido, and amino groups in the C-1′ substitution started from 9-[(1-hydroxymethyl)(3-monomethoxoxytrityloxy)propyl]-N^6-monomethoxytrityladenine (**2**) reported in the preceding paper. In this case also, the hydroxyl protecting group was chosen as the monomethoxytrityl group to avoid the problem of migration as reported with the *tert*-butyldimethylsilyl group.[15]

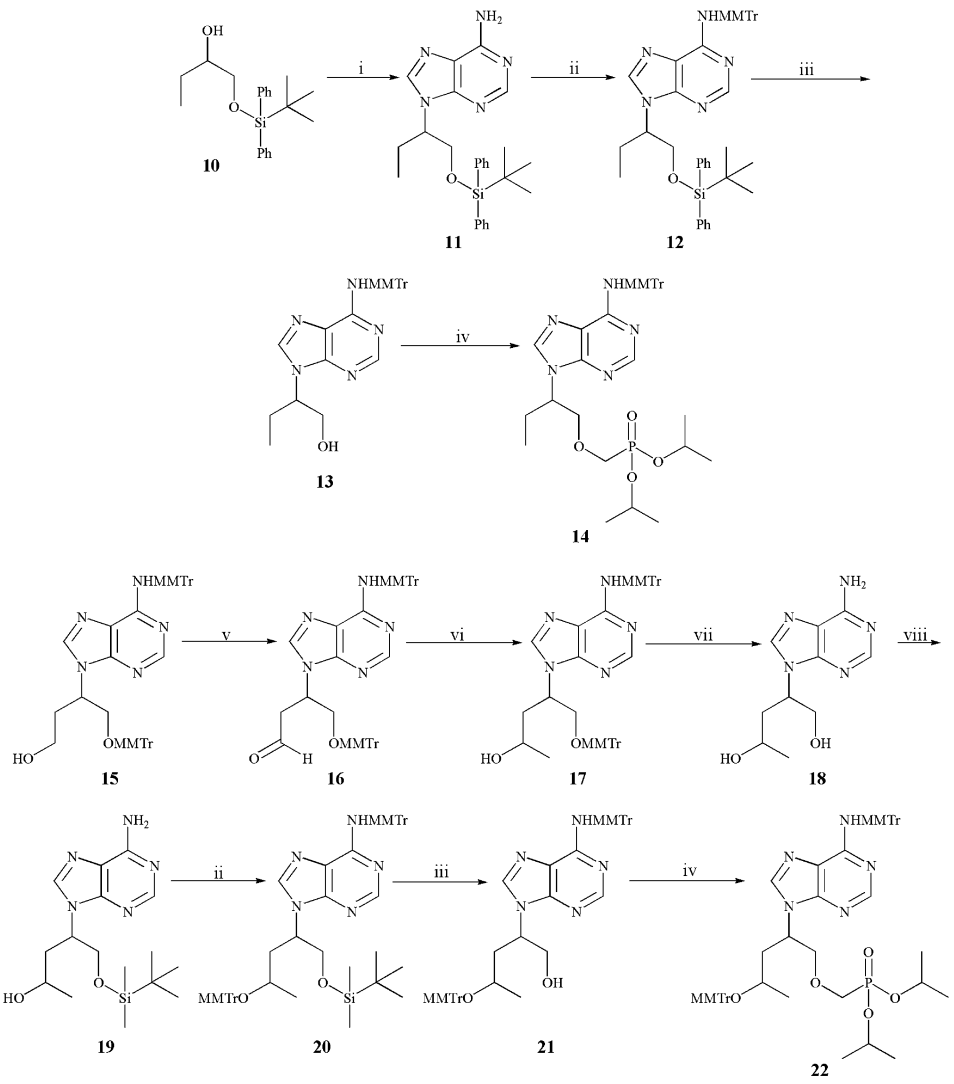
Compound **2** (Scheme 1) on reaction with diisopropyl p-toluenesulfonyloxymethylphosphonate using sodium hydride as base gave compound **3**, a precursor for the target **25a**. Azido derivative **6**, precursor for target **25b**, was obtained by selectively deprotecting the primary hydroxyl of compound **3** with 25 mM HCl in acetonitrile to give compound **4** which was converted to azido **6** through mesylate **5**. The precursor **8** for amino target **25c** was obtained by reduction of azide **6** to give **7** and protection with monomethoxytrityl chloride. Methoxy derivative **9**, a precursor for target **25d**, was obtained by alkylation of **4** with methyl iodide and sodium hydride.



SCHEME 1 Reagents: i) NaH, TsO-$CH_2P(O)(O\text{-ipr})_2$; ii) HCl, CH_3CN; iii) MsCl; iv) NaN_3; v) Ph_3P, H_2O, THF; vi) MMTrCl; vii) NaH, CH_3I.

The preparation of the C-1′ ethyl derivative **25e** started from known **10**[17] (Scheme 2), which under Mitsunobu reaction conditions with adenine, triphenylphosphine (TPP), and diisopropylazodicarboxylate (DIAD) in dioxane gave desired compound **11**. The amino group of adenine was protected with MMTr-chloride in pyridine to give **12**, which on tetrabutylammonium fluoride (TBAF) reaction gave compound **13** with the free hydroxyl. The hydroxyl of **13** was reacted with diisopropyl p-toluenesulfonyloxymethylphosphonate using sodium hydride as the base to give compound **14**, a precursor for the target **25e**.

The introduction of 2-hydroxypropyl could not be achieved from the suitable phosphonomethyl compound **4** because of the complications during oxidation of the primary hydroxyl group. Therefore, we chose 9-[(1-monomethoxytrityloxymethyl)(3-hydroxy)propyl]adenine **15** (Scheme 2)



SCHEME 2 Reagents: i) Adenine, Ph_3P, DIAD; ii) MMTr-Cl; iii) Bu_4NF, THF; iv) NaH, TsO-CH_2-P(O)(O-iPr)$_2$; v) Dess-Martin; vi) CH_3MgBr; vii) HCl; viii) TBDMS-Cl, imidazole.

reported in the preceding paper as our starting material. The oxidation of the primary hydroxyl with Dess-Martin reagent gave aldehyde **16**, which on reaction with Grignard reagent, CH_3MgBr, yielded 2-hydroxypropyl compound **17**. In this case, both MMTr protecting groups were removed under acidic conditions to give **18**, and the primary hydroxyl was blocked with the *tert*-butyldimethylsilyl (TBDMS) group to give **19**. Forcing reaction conditions with MMTr-chloride resulted in the protection of both the amino and

secondary hydroxyl to give **20**. The desired free hydroxyl compound **21** was now obtained by deprotection of the TBDMS group with TBAF and the precursor **22** for the target **25f** was obtained by reaction of **21** with diisopropyl p-toluenesulfonyloxymethylphosphonate using sodium hydride as base.

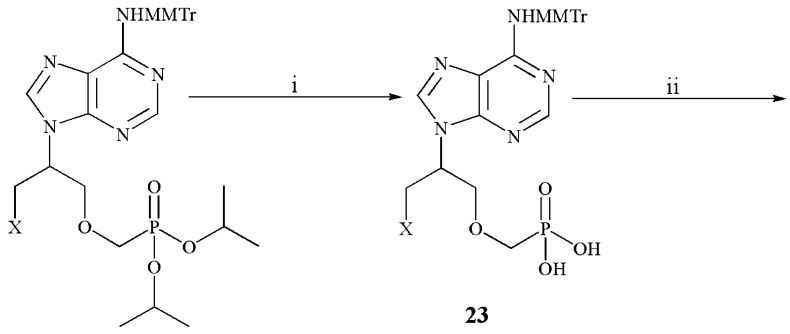
The precursors **3**, **6**, **8**, **9**, **14**, and **22** on reaction with trimethylsilyl iodide in the presence of triethylamine gave the desired phosphonomethoxy compounds **23a-23f** (Scheme 3). The use of triethylamine was essential to keep the MMTr protecting group intact, since the further reactions for the formation of prodrugs were not successful with the free amino group. The reaction of **23a-23f** with an appropriate chloromethyl pivalate or chloromethyl-2-propylcarbonate in the presence of triethylamine gave diprotected prodrugs **24a-24f** and the removal of the MMTr groups under mild acidic conditions yielded the desired targets **25a-25f**.

BIOLOGICAL ACTIVITY

These compounds showed poor activity against HCV virus in replicon assay.[18]

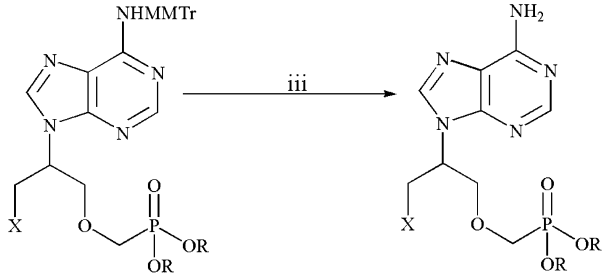
EXPERIMENTAL

All reagents and solvents were purchased from Aldrich and used as received. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) referenced to TMS at 0.00 or respective deuterated solvent peak. Coupling constants (J) are reported in HERTZ. IR spectra were obtained from films on NaCl plates for oils or KBr pellets for solids with a scan range of 4000–500 cm^{-1} on a FT-IR spectrometer (BioRad FTS-3500GX). Mass spectra data were acquired on a Waters ZMD mass spectrometer coupled with a Waters System 2695 for loading of the samples in ES positive or negative mode. HRMS data were recorded on Bruker Bioapex 4.7E. UV spectroscopy was carried out on an Agilent 8453 spectrophotometer. The elemental analysis (C, H, and N) were performed by Atlantic Microlab in Norcross, Georgia. The TLC solvent system CMA-80 and CMA-50 refers to chloroform:methanol:conc. NH_4OH (80:18:2) and chloroform:methanol: conc. NH_4OH (50:40:10), respectively. Tetraethyl ammonium bicarbonate is abbreviated as TEAB. The non-UV active compounds were visualized by charring the TLC plate sprayed with ammonium molybdate/cesium sulfate spray prepared by dissolving conc. H_2SO_4 (22.4 mL), $CeSO_4$ (45 mg), $(NH_4)_6Mo_7O_{24}\bullet 4\ H_2O$ (7 g) in 100 mL water. The olefin compounds were visualized by using $KMnO_4$ spray. The following conditions were used for HPLC analysis.



3, X=CH_2OMMTr
6, X=CH_2N_3
8, X=$CH_2NHMMTr$
9, X=CH_2OCH_3
14, X=CH_3
22, X=$CH(OMMTr)CH_3$

23
a, X=CH_2OMMTr
b, X=CH_2N_3
c, X=$CH_2NHMMTr$
d, X=CH_2OCH_3
e, X=CH_3
f, X=$CH(OMMTr)CH_3$



24
a, X=CH_2OMMTr
b, X=CH_2N_3
c, X=$CH_2NHMMTr$
d, X=CH_2OCH_3
e, X=CH_3
f, X=$CH(OMMTr)CH_3$

25
a, X=CH_2OH
b, X=CH_2N_3
c, X=CH_2NH_2
d, X=CH_2OCH_3
e, X=CH_3
f, X=$CH(OH)CH_3$

24-25a, b, e, f, R=$CH_2OC(O)C(CH_3)_3$
24-25c, d, R=$CH_2OC(O)OCH(CH_3)_2$

SCHEME 3 Reagents: i) TMSI, Et_3N; ii) $ClCH_2OC(O)C(CH_3)_3$ or $ClCH_2OC(O)OCH(CH_3)_2$, Et_3N; iii) HCl.

Column: Spherisorb ODS 4.6 × 250 mm. Mobile phase: solvent A: water, solvent B: MeOH.
Gradient: time: 0 min., A: 95%, B 5%; time: 20 min, A: 0%, B: 100%; then isocratic for 5 min.
Time: 25.1 min., A: 95, B: 5% then isocratic for 5 min. Flow rate 1.0 mL/min. Run time 30 min. Detection UV at 259 nm.

(±)-9-[1-[(Diisopropylphosphono)methoxy]methyl][(3-monomethoxytrityloxy)-propyl]-N^6-monomethoxytrityladenine (3). A solution of **2** (72.45 g, 94.35 mmol) in DMF (810 mL) was treated with sodium hydride (60%, 15.1 g, 377.5 mmol) at room temperature and the mixture was stirred for 1 h. To this solution was added a solution of diisopropyl p-toluenesulfonyloxymethylphosphonate (39.65 g, 113.17 mmol) in DMF (70 mL) and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate (3 L), neutralized with acetic acid and washed with water (2×) and brine and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 61.2 g (69%) of product as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H), 7.87 (s, 1H), 7.32–7.03 (m, 25H), 6.84 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 5.01–4.90 (m, 1H), 4.45–4.32 (m, 2H), 4.03–3.94 (m, 1H), 3.82–3.63 (m, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 2.93–2.81 (m, 1H), 2.81–2.70 (m, 1H), 2.40–2.20 (m, 1H), 2.20–2.03 (m, 1H), 1.11 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H). IR (KBr, cm^{-1}) 3420, 2978, 1605, 1508 and 1250. Anal. Calcd for $C_{56}H_{60}N_5O_7P\bullet 0.5\ H_2O\bullet 0.25$ EtOAc: C, 70.06; H, 6.50; N, 7.17. Found: C, 69.62; H, 6.55; N, 7.21.

(±)-9-[1-[(Diisopropylphosphono)methoxy]methyl][(3-hydroxy)propyl]-N^6-monomethoxytrityladenine (4). A solution of **3** (52.2 g, 55.18 mmol) in acetonitrile (2 L) was treated with conc. HCl (4 mL) at room temperature and the mixture was stirred for 24 h. The reaction was neutralized with 2N NaOH and diluted with water (250 mL). It was then concentrated to remove most of acetonitrile and treated with ethyl acetate (500 mL) and water (200 mL). The organic layer was separated and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.2) as eluent to give 6.18 g (17%) of **4** as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.27 (s, 1H), 7.93 (s, 1H), 7.38–7.20 (m, 13H), 6.89 (d, J = 9.0 Hz, 2H), 4.92–4.80 (m, 1H), 4.64 (t, J = 5.1 Hz, 1H), 4.50–4.36 (m, 2H), 4.14 (t, J = 9.8 Hz, 1H), 3.89–3.65 (m, 3H), 3.76 (s, 3H), 3.42–3.18 (m, 2H), 2.22–1.95 (m, 2H), 1.18–1.11 (m, 6H), 1.06 (d, J = 6.2 Hz, 6H). IR (KBr, cm^{-1}) 3418, 2978,

1605, 1503, and 1250. Anal. Calcd for $C_{36}H_{44}N_5O_6P\bullet 0.5\ H_2O$: C, 63.33; H, 6.64; N, 10.26. Found: C, 63.31; H, 6.47; N, 10.19.

(±)-9-[1-[(Diisopropylphosphono)methoxy]methyl][(3-azido)propyl]-N^6-monomethoxytrityladenine (6). A solution of **4** (1.00 g, 1.48 mmol) in pyridine (20 mL) was treated with methanesulphonyl chloride (539 mg, 97%, 3.00 mmol) and the mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with ethyl acetate (200 mL), was washed with water (2×) and brine and the organic layer dried over $MgSO_4$ followed by filtration and concentration. The residue containing **5** was dissolved in DMF (9 mL), treated with sodium azide (260 mg, 3.96 mmol) and the mixture was stirred for 4 h at 100°C. The reaction mixture was diluted with ethyl acetate (300 mL), washed with water (2×) and brine and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.2) as eluent to give 458 mg (44%, two steps) of product as a colorless film: ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H), 7.89 (s, 1H), 7.40–7.18 (m, 13H), 6.79 (d, $J = 8.8$ Hz, 2H), 4.87–4.76 (m, 1H), 4.73–4.60 (m, 2H), 4.19–3.68 (m, 4H), 3.77 (s, 3H), 3.41–3.32 (m, 1H), 3.22–3.10 (m, 1H), 2.47–2.32 (m, 1H), 2.24–2.12 (m, 1H), 1.29 (d, $J = 6.0$ Hz, 6H), 1.24 (d, $J = 6.7$ Hz, 6H). IR (neat, cm^{-1}) 3017, 2103, 1605, and 1216. HRMS Calcd for $C_{36}H_{43}N_8O_5P$ $(M+H)^+$ 699.3172. Found: 699.3152.

(±)-9-[1-[(Diisopropylphosphono)methoxy]methyl][(3-amino)propyl]-N^6-monomethoxytrityladenine (7). A mixture of **6** (805 mg, 1.15 mmol) in THF (8 mL) and water (1.6 mL) was treated with triphenylphosphine (640 mg, 2.44 mmol) and was stirred at room temperature for 14 h. The reaction mixture was concentrated and purified on silica gel column using chloroform:CMA-80 (1:0 to 1:1) as eluent to give 660 mg (85%) as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.09 (s, 1H), 7.72 (s, 1H), 7.17–7.00 (m, 13H), 6.67 (d, $J = 9.0$ Hz, 2H), 4.70–4.59 (m, 1H), 4.28–4.16 (m, 2H), 3.95 (t, $J = 9.2$ Hz, 1H), 3.68–3.45 (m, 3H), 3.54 (s, 3H), 2.29–2.05 (m, 2H), 1.93–1.60 (m, 4H), 0.96–0.91 (m, 6H), 0.84 (d, $J = 6.1$ Hz, 6H). IR (neat, cm^{-1}) 3414, 3020, 1605, 1511, and 1216. Anal. Calcd for $C_{36}H_{45}N_6O_5P\bullet 1.5\ H_2O$: C, 61.79; H, 6.91; N, 12.01. Found: C, 61.70; H, 6.63; N, 12.07.

(±)-9-[1-[(Diisopropylphosphono)methoxy]methyl][(3-monomethoxytritylamino)propyl]-N^6-monomethoxytrityladenine (8). A solution of compound **7** (600 mg, 0.89 mmol) in pyridine (5 mL) was treated with monomethoxytrityl chloride (561 mg, 1.78 mol) and the reaction mixture was heated at 70°C with stirring for 16 h. It was diluted with ethyl acetate (150 mL) and washed with water (2×) and brine and the organic layer dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue

was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 645 mg (87%) of product as a light yellow film: ^{1}H NMR (DMSO-d_6): δ 7.99 (s, 1H), 7.66 (s, 1H), 7.12–6.79 (m, 25H), 6.61 (d, $J = 9.0$ Hz, 2H), 6.50 (d, $J = 9.1$ Hz, 2H), 4.88–4.75 (m, 1H), 4.22–4.09 (m, 2H), 3.80–3.68 (m, 1H), 3.63–3.40 (m, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 2.37–1.93 (m, 2H), 1.83–1.49 (m, 3H), 0.89–0.84 (m, 6H), 0.80–0.75 (m, 6H). IR (KBr, cm^{-1}) 3418, 2978, 1605, 1503, 1250, and 989. Anal. Calcd for $C_{56}H_{61}N_6O_6P\bullet 0.5\ H_2O$: C, 70.50; H, 6.55; N, 8.81. Found: C, 70.38; H, 6.52; N, 8.72.

(±)-9-[1-(*tert*-Butyldiphenylsilyloxy)methyl]propyladenine (11). To a mixture of **10** (19 g, 55.5 mol), triphenylphosphine (29 g, 0.11 mol) and adenine (15 g, 0.11 mol) in anhydrous dioxane (300 mL) was added a solution of DIAD (21.8 mL) in dioxane (30 mL) over a period of 2 h at room temperature and the mixture was stirred further for 16 h. The reaction mixture was evaporated to dryness and the residue was purified on a column of silica gel eluting with chloroform:methanol (100:0 to 95:5) to provide 20 g (81%) of **11** as a white foam: ^{1}H NMR (DMSO-d_6): 7.99 (s, 1H), 7.85 (s, 1H), 7.4–7.00 (m, 12H), 4.34 (m, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 1.87 (m, 1H), 1.70 (m, 1H), 0.58 (m, 12H). IR (KBr, cm^{-1}) 3147, 2962, 2931, 2857, 1674, 1601, 1472, and 1303.

(±)-9-[1-(*tert*-Butyldiphenylsilyloxy)methyl]propyl-N^6-monomethoxytrityladenine (12). A solution of **11** (20 g, 0.044 mol) in pyridine (500 mL) was treated with MMTr-chloride (27.75 g, 0.088 mol) and the reaction mixture was heated at 70°C with stirring for 20 h. It was evaporated to dryness, diluted with ethyl acetate (1.5 L) and was washed with water (2 × 500 mL) and brine and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes as eluent (0:1 to 1:1) to give 22 g (69%) of product as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 8.32 (s, 1H), 7.84 (s, 1H), 7.4–6.8 (m, 24H), 4.55 (m, 1H), 4.00 (m, 1H), 3.88 (m, 1H), 3.70 (s, 3H), 2.09 (m, 1H), 1.92 (m, 1H), 0.77 (m, 12H). IR (KBr, cm^{-1}) 2931, 2856, 2361, 1734, 1604, 1467, 1249, and 1111.

(±)-9-[1-Hydroxymethyl]propyl-N^6-monomethoxytrityladenine (13). Compound **12** (22 g, 30.0 mmol) was dissolved in THF (200 L) and was treated with TBAF (1M in THF, 30.68 mL) and the reaction mixture was stirred at room temperature for 2 h followed by concentration. The residue was purified on a silica gel column using chloroform:methanol (100:0 to 90:10) as an eluent to give 10 g (70%) of **13** as a white foam, mp 188°C: ^{1}H NMR (DMSO-d_6): δ 8.23 (s, 1H), 7.89 (s, 1H), 7.4–6.9 (m, 14H), 5.01 (bs, 1H), 4.36 (m, 1H), 3.84 (m, 1H), 3.71 (s, 3H), 3.67 (m, 1 H, partially

masked by CH_3 peak), 1.90 (m, 2H), 0.73 (t, $J = 7.3$ Hz, 3H). IR (KBr, cm^{-1}) 3408, 3313, 2966, 1715, 1605, 1469, and 1249.

(±)-9-[1-[(Monomethoxytrityloxy)methyl][3-oxopropyl]-N^6-monomethoxytrityladenine (16). A solution of **15** (4.16 g, 5.42 mmol) in methylene chloride (300 mL) was treated with Dess-Martin reagent (4.74 g, 97%, 10.84 mmol) and was stirred at room temperature for 4 h. The reaction mixture was concentrated and was purified on a silica gel column using ethyl acetate:hexanes (0:1 to 2:1) as eluent to provide 2.9 g (70%) of **16** as a white solid: ^{1}H NMR (DMSO-d_6): δ 9.58 (s, 1H), 8.44 (s, 1H), 7.80 (s, 1H), 7.43–6.67 (m, 29H), 5.24–5.12 (m, 1H), 4.08–3.89 (m, 1H), 3.70 (s, 6H), 3.65–3.48 (m, 1H), 3.18 (d, $J = 10.3$ Hz, 2H). MS (ES^+) 766.58 $(M+H)^+$.

(±)-9-[1-[(*tert*-Butyldimethylsilyloxy)methyl][(3-hydroxy)butyl]adenine (19). A solution of **16** (2.8 g, 3.66 mmol) in THF (150 mL) was treated with 3M methyl magnesium bromide (6.1 mL, 18.3 mmol) and the mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with ethyl acetate (400 mL) and was washed with water (2×) and brine and the organic layer dried over $MgSO_4$. After filtration and concentration, a white solid (**17**) was obtained (2.65 g).

A solution of **17** (2.55 g, 3.26 mmol) in acetonitrile (300 mL) and water (14 mL) was treated with 2M HCl (1.5 mL) at room temperature and the mixture stirred for 14 h. The reaction mixture was neutralized by adding 0.5N NaOH followed by dilution with water (100 mL) and concentration to remove most of the organic solvent. The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and concentrated to give 830 mg of **18** as light yellow film.

To a solution of **18** in DMF (8 mL) was added imidazole (375 mg, 5.45 mmol) and TBDMS-chloride (332 mg, 2.18 mmol) and stirred at room temperature for 31 h. The reaction mixture was diluted with chloroform (300 mL), washed with water (2×), and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using chloroform:CMA-80 (1:0 to 1:1) to give 338 mg (49%) of **19** as a colorless film: ^{1}H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.28, 8.275, 8.12, 7.93 (4s, 2H), 5.79, 5.76 (2s, 2H), 4.85–4.75 (m, 1H), 4.01 (d, $J = 3.8$ Hz, 2H), 3.88–3.76, 3.28–3.18 (2m, 2H), 2.18–1.98, 1.73–1.62 (2m, 2H), 1.19, 1.10 (2d, $J = 6.2$ Hz each, 3H), 0.83, 0.78 (2s, 9H), 0.00, −0.11, −0.12 (3s, 6H). HRMS Calcd for $C_{16}H_{29}N_5O_2Si$ $(M+H)^+$ 352.2168. Found: 352.2177.

(±)-9-[1-(Hydroxymethyl)[(3-monomethoxytrityloxy)butyl]-N^6-monomethoxytrityladenine (21). A solution of **19** (320 mg, 0.91 mmol) in pyridine (5 mL) was treated with monomethoxytrityl chloride (1.15 g, 98%,

3.65 mmol) and the reaction mixture heated at 70°C with stirring for 14 h. It was diluted with ethyl acetate (150 mL) and washed with water (2×) and brine and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using ethyl acetate:hexanes as eluent (0:1 to 1:3) to give 1.07 g of **20** as a colorless syrup.

A solution of **20** in THF (9 mL) was treated with TBAF (1M in THF, 0.91 mL) and the reaction mixture was stirred at room temperature for 2 h followed by concentration. The residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) to give 507 mg (71%, two steps) of **21** as a white solid: ^{1}H NMR (a mixture of diastereomers, DMSO-d_6): δ 8.11, 7.94, 7.91, 7.85 (4s, 2H), 7.39–7.13 (m, 25H), 6.93–6.75 (m, 4H), 5.02 (t, $J = 5.8$ Hz, 1H), 4.72–4.64, 4.52–4.44 (2m, 1H), 3.77, 3.76, 3.75, 3.73 (4s, 6H), 3.71–3.51, 3.31–3.11 (2m, 3H), 2.27–2.14, 1.99–1.72 (2m, 2H), 0.81, 0.70 (2d, $J = 6.0$ Hz each, 3H). IR (KBr, cm^{-1}) 3414, 2931, 1606, 1508, and 1250. Anal. Calcd for $C_{50}H_{47}N_5O_4$•0.3 EtOAc: C, 76.07; H, 6.16; N, 8.66. Found: C, 75.92; H, 6.29; N. 8.59.

(±)-9-[1-[(Diisopropylphosphonomethoxy)methyl][(3-monomethoxytrityloxy)butyl]-N^6-monomethoxytrityladenine (22). This compound was prepared from **21** by the same procedure as given for **3**. The crude product was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give **22** in 57% yield as a colorless oil: ^{1}H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.08, 8.02, 8.01, 7.89 (4s, 2H), 7.39–7.13 (m, 25H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 4.98–4.89 (m, 1H), 4.78–4.63 (m, 2H), 4.19–3.15 (m, 5H), 3.79, 3.78 (2s, 6H), 2.29–1.70 (m, 2H), 1.35–1.22 (m, 12H), 1.20, 1.14 (2d, $J = 6.2$ Hz each, 3H). HRMS Calcd for $C_{57}H_{62}N_5O_7P$ $(M+H)^+$ 960.4465. Found: 960.4417.

(±)-9-[1-[(Phosphonomethoxy)methyl][(3-monomethoxytrityloxy)propyl]-N^6-monomethoxytrityladenine (23a). A solution of **3** (17.7 g, 18.71 mmol) in DMF (170 mL) was treated with triethylamine (15 mL) followed by trimethylsilyl iodide (25 mL, 174.9 mmol) and the reaction mixture flask was covered with aluminum foil to protect from light and was stirred for 16 h at room temperature. It was then diluted with TEAB buffer (0.5 L), water (0.75 L) and chloroform (1.5 L) and was stirred for 1 h. The organic phase was collected and the aqueous phase was re-extracted with chloroform (3×). The combined organic extracts were dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using chloroform:methanol (1:0 to 85:15), then CMA-80:CMA-50 (1:0 to 0:1) as eluent to give 7.5 g (47%) of **23a** as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1H), 7.86 (s, 1H), 7.34–7.01 (m, 25H), 6.85 (d, $J =$ 9.1 Hz, 2H), 6.78 (d, $J = 8.9$ Hz, 2H), 4.97–4.86 (m, 1H), 3.94–3.85 (m,

1H), 3.80–3.72 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.37 (d, $J = 7.6$ Hz, 2H), 2.89–2.72 (m, 2H), 2.42–2.26 (m, 1H), 2.23–2.07 (m, 1H). HRMS Calcd for $C_{50}H_{48}N_5O_7P$ $(M+H)^+$ 862.3369. Found: 862.3387.

(±)-9-[1-[(Phosphonomethoxy)methyl][(3-monomethoxytritylamino) propyl]-N^6-monomethoxytrityladenine (23c). This compound was prepared from **8** by the same procedure as given for **23a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 85:15), then CMA-80:CMA-50 (1:0 to 0:1) as eluent to give 45% yield of **23c** as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H), 7.83 (s, 1H), 7.32–6.99 (m, 25H), 6.82 (d, $J = 9.1$ Hz, 2H), 6.70 (d, $J = 9.1$ Hz, 2H), 5.00–4.83 (m, 1H), 3.92–3.79 (m, 1H), 3.76–3.66 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.37 (d, $J = 7.5$ Hz, 2H), 2.28–2.14 (m, 1H), 2.06–1.90 (m, 1H), 1.84–1.62 (m, 2H). HRMS Calcd for $C_{50}H_{49}N_6O_6P$ $(M+H)^+$ 861.3529. Found: 861.3562.

(±)-9-[1-[(Phosphonomethoxy)methyl][(3-methoxy)propyl]-N^6-monomethoxytrityladenine (23d). A solution of **4** (1.0 g, 1.48 mmol) in DMF (12 mL) was treated with sodium hydride (60%, 0.24 g, 6.0 mmol) at room temperature and the mixture was stirred for 1 h. To this solution was then added a solution of methyl iodide (0.11 mL, 1.77 mmol) in DMF (2 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (30 mL), neutralized with acetic acid and chloroform (400 mL) added. The mixture was washed with water (2×) and brine and the organic layer was dried over $MgSO_4$ followed by filtration and concentration to give **9** which was converted to **23d** following the same procedure as used for **23a**. The product was purified on a silica gel column using chloroform:methanol (1:0 to 85:15), then CMA-80:CMA-50 (1:0 to 0:1), as eluent to give 296 mg (33%, two steps) of **23d** as an off-white film: ^{1}H NMR (DMSO-d_6): δ 8.34(s, 1H), 7.89 (s, 1H), 7.36–7.16 (m, 13H), 6.84 (d, $J = 9.1$ Hz, 2H), 4.80–4.67 (m, 1H), 4.02–3.90 (m, 1H), 3.87–3.77 (m, 1H), 3.71 (s, 3H), 3.36–3.26 (m, 2H), 3.27–3.18 (m, 1H), 3.14–3.03 (m, 1H), 3.10 (s, 3H), 2.24–2.04 (m, 2H). HRMS Calcd for $C_{31}H_{34}N_5O_6P$ $(M+H)^+$ 604.2325. Found: 604.2335.

(±)-9-[1-[(Phosphonomethoxy)methyl]propyl]-N^6-monomethoxytrityladenine (23e). Compound **13** was converted to **14** in 30% yield with the same procedure as used for **3** and **14** was converted to **23e** by the same method used for **23a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 85:15), then CMA-80:CMA-50 (1:0 to 0:1) as eluent to give 47% of **23e** as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 7.87 (s, 1H), 7.4–6.8 (m, 14H), 6.50 (bs, 2H), 4.56 (m, 1H), 3.95 (m, 1H), 3.82 (m, 1H), 3.69 (s, 3H), 3.32 (m, 2H), 1.86 (m, 2H), 0.67 (t, $J = 7.1$ Hz, 3H). IR (KBr, cm^{-1}) 3408, 3159, 1604, 1469, 1401, and 1249.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl][(3-monomethoxytrityloxy)propyl]-N^6-monomethoxytrityladenine (24a). A solution of **23a** (400 mg, 0.46 mmol) in DMF (24 mL) was treated with triethylamine (24 mL) followed by chloromethyl pivalate (8.9 mL, 97%, 59.9 mmol) and stirred for 3 days at room temperature. It was then diluted with chloroform (250 mL) and washed with water (2×). The organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 83 mg (17%) of **24a** as a colorless film: ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1H), 8.10 (s, 1H), 7.57–7.25 (m, 25H), 7.08 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 5.78 (s, 2H), 5.74 (s, 2H), 5.24–5.12 (m, 1H), 4.22–4.10 (m, 3H), 4.10–4.00 (m, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.15–3.05 (m, 1H), 3.05–2.92 (m, 1H), 2.68–2.50 (m, 1H), 2.43–2.28 (m 1H), 2.23 (s, 18H). IR (KBr, cm^{-1}) 3420, 2972, 1753, 1605, 1511, 1471, and 1251. Anal. Calcd for $C_{62}H_{68}N_5O_{11}P\bullet 0.75\ H_2O\bullet 0.25$ EtOAc: C, 67.22; H, 6.40; N, 6.22. Found: C, 67.09; H, 6.37; N, 6.01.

(±)-9-[1-[(di-Isopropyloxycarbonyloxymethylphosphonomethoxy)methyl][(3-monomethoxytritylamino)propyl]-N^6-monomethoxytrityladenine (24c). This compound was prepared from **23c** with the same procedure as given for **24a** but using chloromethyl-2-propylcarbonate in place of chloromethyl pivalate. The time of the reaction was also increased to 7 days. The crude product was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 27% yield of product as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H), 7.87 (s, 1H), 7.38–7.07 (m, 25H), 6.80 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 5.68–5.56 (m, 4H), 5.08–4.95 (m, 1H), 4.95–4.84 (m, 2H), 4.05–3.80 (m, 2H), 3.86 (d, J = 7.4 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 2.37–2.20 (m, 1H), 2.12–1.78 (m, 4H), 1.28 (d, J = 6.2 Hz, 6H), 1.27 (d, J = 6.2 Hz, 6H). HRMS Calcd for $C_{60}H_{65}N_6O_{12}P$ $(M+H)^+$ 1093.4476. Found: 1093.4483.

(±)-9-[1-[(di-Isopropyloxycarbonyloxymethylphosphonomethoxy)methyl][(3-methoxy)propyl]-N^6-monomethoxytrityladenine (24d). This compound was prepared from **23d** by the same procedure as given for **24c**. The crude product was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 35% yield of product as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.87 (s, 1H), 7.38–7.19 (m, 13H), 6.80 (d, J = 9.0 Hz, 2H), 5.68–5.58 (m, 4H), 4.96–4.81 (m, 3H), 4.20–4.12 (m, 1H), 3.95–3.82 (m, 3H), 3.78 (s, 3H), 3.41–3.32 (m, 1H), 3.24 (s, 3H), 3.18–3.08 (m, 1H), 2.38–2.15 (m, 2H), 1.31 (d, J = 6.2 Hz, 12H). IR (neat, cm^{-1}) 3020, 1605, and 1216. Anal. Calcd for $C_{41}H_{50}N_5O_{12}P$: C, 58.92; H, 6.03; N, 8.38. Found: C, 58.89; H, 6.17; N. 8.23.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl][(3-monomethoxytrityloxy)butyl]-N^6-monomethoxytrityladenine (24f). Compound **22** was converted to **23f** by the same method used for **23a** and **23f** was converted to **24f** by the method used for **24a**. The product **24f** was obtained in 17% yield (two steps) as a colorless oil: ^{1}H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.00, 7.93, 7.62 (3s, 2H), 7.46–7.10 (m, 25H), 6.90–6.68 (m, 4H), 5.64–5.52 (m, 4H), 4.94–4.64 (m, 1H), 3.95–3.85, 3.79–3.44, 3.35–3.25 (3m, 5H), 3.77 (m, 3H), 3.73 (s, 3H), 2.20–1.81, 1.76–1.56 (2m, 2H), 1.20, 1.19, 1.18 (3s, 18H), 0.92, 0.86 (2d, J = 6.2 Hz each, 3H). HRMS Calcd for $C_{63}H_{70}N_5O_{11}P$ $(M+H)^+$ 1104.4887. Found: 1104.4882.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl][(3-hydroxy)propyl]adenine (25a). A solution of **24a** (138 mg, 0.13 mmol) in acetonitrile (28 mL) was treated with 0.2 M HCl (1.4 mL) and stirred for 14 h at room temperature. It was then carefully neutralized with 0.5 N NaOH to pH 6.0 and was diluted with water (15 mL) and was concentrated to remove acetonitrile. The residual material was again diluted with water (20 mL) and was extracted with chloroform:methanol (4:1, 2×). The organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was purified on a silica gel column using chloroform: methanol (1:0 to 9:1) as eluent to give 42 mg (59%) of **25a** as a colorless oil.

Procedure for the fumarate salt of **25a**: A solution of **25a** (14.1 mg, 0.026 mmol) in 2-propanol (1.2 mL) was treated with a solution of fumaric acid in propanol (20.3 mg/mL, 0.45 mL, 0.026 mmol) followed by slow concentration under vacuum. The fumaric salt was obtained as a white solid: ^{1}H NMR (DMSO-d_6): δ 12.95 (bs, 2H), 7.89 (s, 1H), 7.87 (s, 1H), 6.97 (s, 2H), 6.40 (s, 2H), 5.31 (d, J = 3.4 Hz, 2H), 5.27 (d, J = 3.5 Hz, 2H), 4.64–4.48 (bs, 1H), 4.44–4.24 (bs, 1H), 3.85 (t, J = 9.1 Hz, 1H), 3.73–3.60 (m, 3H), 3.16–2.91 (m, 2H), 1.97–1.84 (m, 1H), 1.84–1.68 (m, 1H), 0.90 (s, 18H). HRMS Calcd for $C_{22}H_{36}N_5O_9P$ $(M+H)^+$ 546.2329. Found: 546.2325.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl][(3-azido)propyl]adenine (25b). Compound **6** was converted to **23b** in 44% yield with the same method as used for **23a** and **23b** was converted to **24b** in 64% yield by the method used for **24a**. The resultant **24b** was deprotected by the same method used for **25a** to give **25b**. The compound **25b** was obtained in 82% yield as a colorless oil: ^{1}H NMR (DMSO-d_6): 8.16 (s, 1H), 8.10 (s, 1H), 7.22 (bs, 2H), 5.52 (dd, J = 12.6, 3.5 Hz, 4H), 4.77 (m, 1H), 4.03 (m, 1H), 3.92 (m, 3H), 3.29 (m, 1H), 3.16 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 1.13 (m, 18H). MS (ES^+) 571.24 $(M+H)^+$. Anal. Calcd for $C_{22}H_{35}N_8O_8P$: C, 46.31; H, 6.18; N, 19.6. Found: C, 46.67; H, 6.22; N, 18.56. HPLC: t_R = 23.42 min., 95.44%.

(±)-9-[1-[(di-Isopropyloxycarbonyloxymethylphosphonomethoxy)methyl][(3-amino)propyl]adenine (25c). A solution of **24c** (45 mg, 0.041 mmol) in acetonitrile (6.6 mL) was treated with 0.2 M HCl (0.99 mL) and was stirred for 16 h at room temperature. It was diluted with water (100 mL) and was extracted with ethyl acetate (2×) and chloroform (2×). The aqueous layer was concentrated to dryness to give **25c** as a gum. The product was dissolved in 2.0 mL of water and its concentration was measured to be 11.9 mM (58%) by UV at 259 nm using adenosine monophosphate as standard. ^{1}H NMR (D_2O): δ 8.32 (s, 1H), 8.29 (s, 1H), 5.47–5.36 (m, 4H), 4.90–4.72 (m, 3H), 4.05–3.86 (m, 4H), 3.04–2.90 (m, 1H), 2.84–2.70 (m, 1H), 2.49–2.35 (m, 1H), 2.35–2.20 (m, 1H), 1.17 (d, J = 6.5 Hz, 6H), 1.16 (d, J = 6.3 Hz, 6H). HRMS Calcd for $C_{20}H_{33}N_6O_{10}P$ $(M+H)^+$ 549.2074. Found: 549.2070. HPLC: t_R = 15.11 min., 95.0%.

(±)-9-[1-[(di-Isopropyloxycarbonyloxymethylphosphonomethoxy)methyl][(3-methoxy)propyl]adenine (25d). This compound was prepared from **24d** by the same procedure as given for **25a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give 83% yield of product as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 1H), 7.94 (s, 1H), 5.73 (s, 2H), 5.68–5.60 (m, 4H), 4.96–4.84 (m, 3H), 4.18 (dd, J = 10.0, 6.6 Hz, 1H), 3.92 (dd, J = 9.9, 3.8 Hz, 1H), 3.86 (dd, J = 7.6, 1.1 Hz, 2H), 3.42–3.32 (m, 1H), 3.23 (s, 3H), 3.15–3.02 (m, 1H), 2.41–2.16 (m, 2H), 1.32 (d, J = 6.2 Hz, 6H), 1.31 (d, J = 6.3 Hz, 6H). IR (neat, cm^{-1}) 3328, 2928, 1761, 1646, 1598, and 1267. HRMS Calcd for $C_{21}H_{34}N_5O_{11}P$ $(M+H)^+$ 564.2070. Found: 564.2071. HPLC: t_R = 21.65 min., 95.0%.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl]propyl]adenine (25e). Compound **23e** was converted to **24e** in 78% yield with the method used for **24a** and the resultant **24e** was converted to **25e** by the same method as used for **25a**. Compound **25e** was obtained in 32% yield as a colorless oil: ^{1}H NMR (DMSO-d_6): δ 8.4 (s, 1H), 8.35 (s, 1H), 7.45 (bs, 2H), 5.80 (m, 2H), 5.74 (m, 2H), 5.83 (m, 1H), 4.30 (m, 1H), 4.15 (m, 2H), 4.10 (m, 1H), 2.20 (m, 2H), 1.32 (s, 18H), 0.95 (t, J = 7.1 Hz, 3H). MS (ES^+) 552.29 $(M+Na)^+$. Anal. Calcd for $C_{22}H_{36}N_5O_8P$: C, 49.90; H, 6.85; N, 13.22. Found: C, 49.97; H, 6.73; N, 13.21. HPLC: t_R = 22.92 min., 98.26%.

(±)-9-[1-[(di-*tert*-Butylcarbonyloxymethylphosphonomethoxy)methyl][(3-hydroxy)butyl]adenine (25f). This compound was prepared from **24f** by the same procedure as given for **25a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give 89% yield of product as a colorless oil: ^{1}H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.31, 8.12, 7.97 (3s, 2H), 6.11, 6.01 (2s, 2H), 5.74–5.58 (m, 4H), 5.04–4.91 (m, 1H), 4.25–3.78, 3.34–3.24 (2m, 4H), 3.92, 3.85 (2d, J =

7.2 Hz each, 2H), 2.28–2.01, 1.86–1.74 (2m, 2H), 1.24, 1.15 (2d, $J = 6.2$ Hz each, 3H), 1.21 (s, 18H). IR (neat, cm^{-1}) 3020, 1754, 1632, 1216, and 764. HRMS Calcd for $C_{23}H_{38}N_5O_9P$ $(M+H)^+$ 560.2485. Found: 560.2469. HPLC: $t_R = 22.01$ min., 96.0%.

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