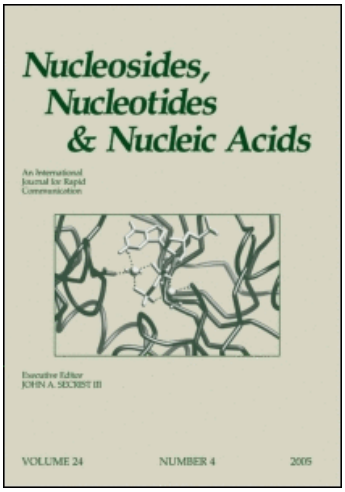

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SYNTHESIS OF 9-[1-(SUBSTITUTED)-3-(PHOSPHONOMETHOXY)PROPYL]ADENINE DERIVATIVES AS POSSIBLE ANTIVIRAL AGENTS

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

□ *Acyclic N^9 adenine nucleosides substituted at C-1′ position were prepared by the Mitsunobu reaction of 1-tert-butyldimethylsilyl-4-pivaloylbutan-1,2,4-triol* **(5)** *with adenine. Pivaloyl hydroxyl was modified to the phosphonomethoxy derivatives, and the tert-butyldimethylsilyl hydroxyl was converted to methoxy, azido, amino, fluoro, and α-hydroxyethyl and was eliminated to give vinyl. The resulting phosphonic acids were converted to prodrugs also.*

Keywords Acyclic nucleosides; Prodrugs; Antiviral

INTRODUCTION

Viral diseases are one of the major causes of deaths and economic losses in the world. Out of various viral diseases, HIV, HBV, and HCV infections are more important and responsible for a large number of deaths. There are some drugs for HIV, only a few for HBV but no good drug for HCV. Hepatitis C is a viral liver disease, caused by infection with the hepatitis C virus (HCV). There are approximately 170 million people worldwide with chronic HCV infection, of which about 2.7 million are in the United States.[1] HCV is a leading cause of cirrhosis, a common cause of hepatocellular carcinoma, and is the leading cause of liver transplantation in the United States.[2] Currently, α-interferon monotherapy and α-interferon-ribavirin combination therapy are the only approved treatments for HCV.[3]

Dedicated to the memory of John A. Montgomery.

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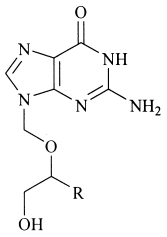
Acyclovir (**1a**, Chart 1)[4] and ganciclovir (**1b**, Chart 1)[5–7] are well-known antiviral drugs used for HIV and herpes virus. For most of the nucleosides to be active against DNA or RNA viral polymerases, first the formation of monophosphate occurs through specified kinases and then triphosphate is formed by cellular kinases. This triphosphate in turn acts as a viral polymerase inhibitor. A closely related drug, cidofovir, which is a phosphonic acid derivative and has cytidine base instead of guanine also is a drug used for herpes virus.[8]

The introduction of phosphonomethyl ether functionality in place of phosphoric acid ester may be important because: (a) it is expected to be chemically and metabolically more stable,[9] (b) the β-oxygen atom in phosphonomethyl ether functionality enhances the acidity of the phosphonate and brings its second pKa closer to that of the phosphate ester,[10] and (c) the oxygen atom in the immediate vicinity of phosphorus has been demonstrated to play a critical role for the enzymatic phosphorylation and thus for antiviral activity.[10]

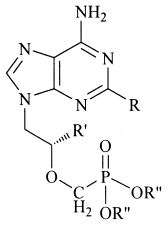
Thus, a number of acyclic nucleoside analogs containing the phosphonomethyl ether functional group in place of the phosphoric acid ester have been reported to have high activity against DNA viruses and retroviruses.[11,12] These compounds include (Chart 1), PMEA [9-(2-(phosphonomethoxy)ethyl]adenine (**2a**), PMPA [9-(2-phosphonomethoxy)propyl]adenine (**2c**), HPMPA [9-(3-hydroxy-(2-phosphonomethoxy)propyl)]adenine (**2e**), FPMPA [9-(3-fluoro-(2-phosphonomethoxy)propyl)]adenine (**2f**) and diaminopurine derivatives of PME (**2g**) and HPMP (**2h**). Some guanine derivatives, such as PMEG (**3a**), PMPG (**3b**) and HPMPG (**3c**) are also reported to have a very good profile of antiviral activities.[11–17] Out of these compounds, two drugs, adefovir dipivoxil (**2b**) and tenofovir disoproxil (**2d**), which are prodrugs of PMEA and PMPA, have been approved by FDA for HBV and HIV infections, respectively.

There are a number of reports in the literature on modifications of the base (purine and pyrimidine),[18,19] and substitutions on C-2′ of PMEA. With respect to the C-1′ position of PMEA or PMPA, there are a limited number of substitutions reported.[20–23] For example, methyl substitution from the C-1′ position with the guanine base as the phosphonic acid derivative has been reported.[10] Other substitutions at the C-1′ position are limited to only nucleosides; attempts have not been made to prepare phosphonomethyl ether derivatives and their prodrugs for the evaluation of antiviral activities. In spite of strong similarity in structures of these compounds, different modes of action and profiles of antiviral activity have been reported.

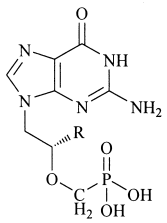
The important objective of this study was to examine the effect of the side chain from the C-1′ position of acyclic nucleosides, their phosphonomethyl ether derivatives and corresponding prodrugs on antiviral activity. Based upon the structure of acyclovir, we have synthesized these compounds



1a, R=H (Acyclovir)
1b, R=CH_2OH (Ganciclovir)



2a, R=H, R'=H, R"=H (PMEA)
2b, R=H, R'=H, R"=$CH_2OC(O)C(CH_3)_3$ (adefovir dipivoxil)
2c, R=H, R'=CH_3, R"=H (PMPA)
2d, R=H, R'=CH_3, R"=$CH_2OC(O)OCH(CH_3)_2$ (tenofovir disoproxil)
2e, R=H, R'=CH_2OH, R"=H (HPMPA)
2f, R=H, R'=CH_2F, R"=H (FPMPA)
2g, R=NH_2, R'=H, R"=H (PMEDAP)
2h, R=NH_2, R'=CH_2OH, R"=H (HPMPDAP)



3a, R=H (PMEG)
3b, R=CH_3 (PMPG)
3c, R=CH_2OH (HPMPG)

CHART 1

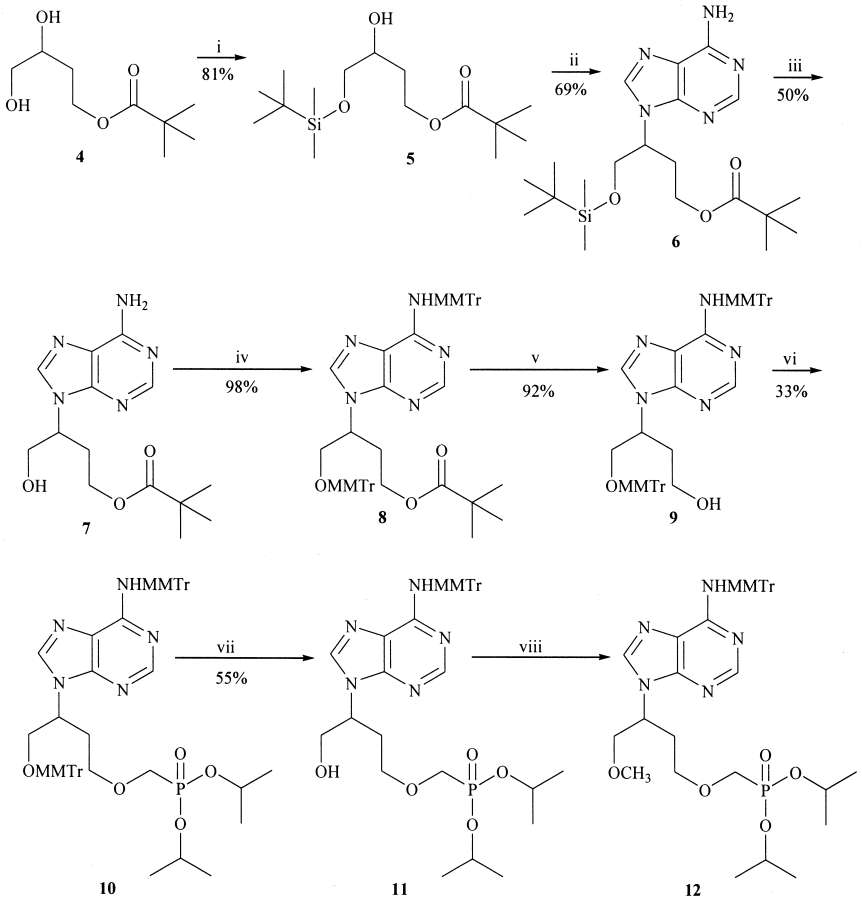
keeping the spacer of 5 atoms between the adenine nitrogen and the phosphorus atom (as in acyclovir) and the β-oxygen to the phosphorus atom. All the compounds synthesized here in this report are the substituted compounds at C-1′ of the acyclic chain.

RESULTS AND DISCUSSION

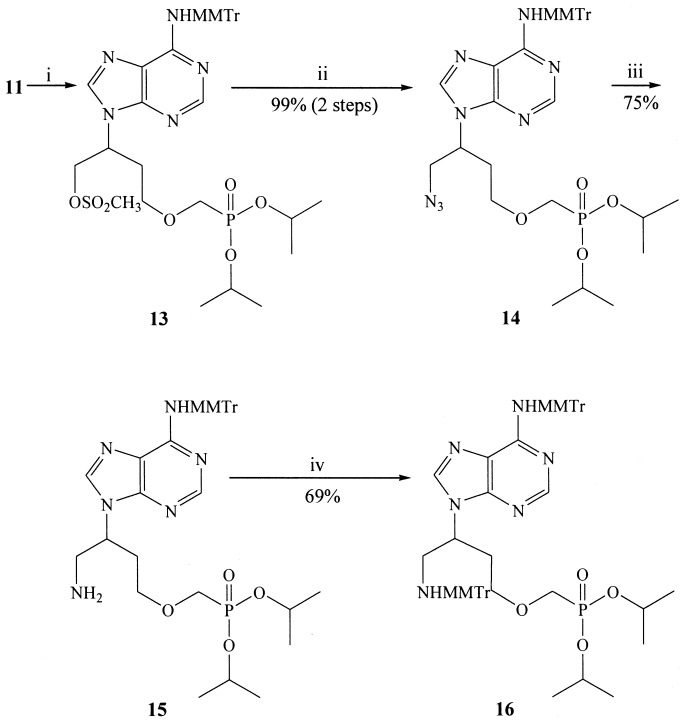
The synthesis of all the compounds reported here started from racemic butan-1,2,4-triol, which could be easily made available in each enantiomeric form from readily available (+) and (−) malic acid, when needed. There are some reports in the literature on the preparation of C-1′-substituted PMEA and PMPA derivatives for racemic and nonracemic nucleosides.[20–23] Racemic nucleosides were prepared from γ-butyrolactone[23] and diethylmaleate.[20] Nonracemic nucleosides were prepared from butan-1,2,4-triol and amino acids.[21,22] Jeffery et al.[22] starting from threonine, attempted

the preparation of the C-1′ hydroxymethyl PMPA derivative, but were not successful because of the migration of the *tert*-butylsilyl group. However, they successfully prepared the corresponding deoxygenated compound starting from D-alanine. In our synthesis, we have chosen the monomethoxytrityl group as the protecting group to avoid the problem of migration.

The synthesis of the appropriately protected desired phosphonomethyl ether derivatives is described in Schemes 1–5. Compound **4** (Scheme 1), the monopivaloyl ester of butan-1,2,4-triol, was prepared from literature procedures from butan-1,2,4-triol.[24,25] The other primary hydroxyl group was first protected with the trityl group and the resultant compound was subjected to the Mitsunobu reaction, but the yield of the Mitsunobu reaction

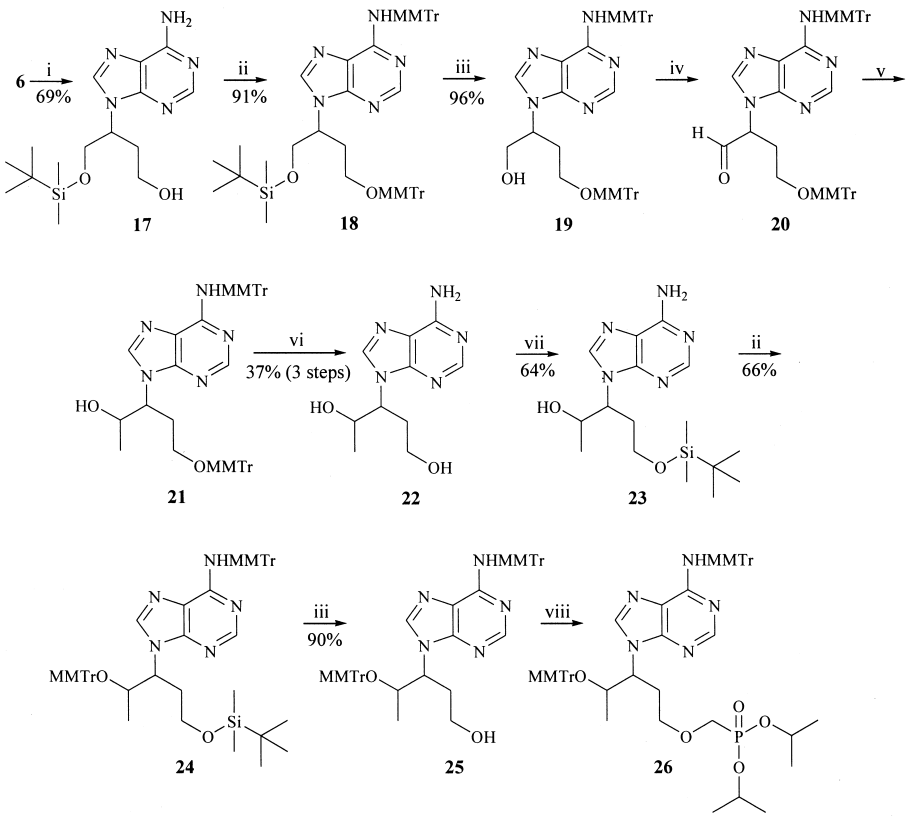


SCHEME 1 Reagents: i) TBDMS-Cl, imidazole; ii) Adenine, Ph_3P, DIAD; iii) Bu_4NF, THF; iv) MMTrCl, pyridine; v) NaOH; vi) NaH, TsO-CH_2-P(O)(O-iPr)$_2$; vii) HCl, CH_3CN; viii) NaH, CH_3I.



SCHEME 2 Reagents: i) MsCl; ii) NaN_3; iii) Ph_3P, H_2O, THF; iv) MMTrCl, pyridine.

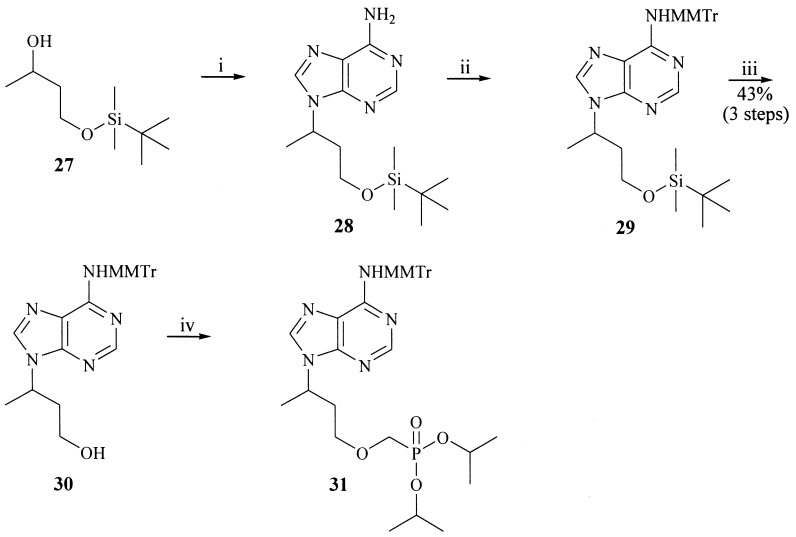
was very poor, probably because of the steric hindrance from the bulky trityl group. In the later experiments, the primary hydroxyl of **4** was first protected with the *tert*-butyldimethylsilyl (TBDMS) group in dichloromethane or DMF using imidazole as base. The resultant compound **5**, under Mitsunobu reaction conditions with adenine, triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD) in dioxane gave the desired compound **6** in good yield. The product obtained was identified as the N^9 derivative based upon the literature reports[26] and UV spectrum at different pH,[27] which did not show any shift in the absorption. On treatment with tetrabutylammonium fluoride (TBAF), compound **6** gave **7** in which both hydroxyl and amino functionalities were protected with the monomethoxytrityl (MMTr) group by treating with MMTr-chloride in pyridine to give **8**. The pivaloyl group in compound **8** was removed under basic conditions with sodium hydroxide to give **9**, and the free hydroxyl was reacted with *p*-toluenesulfonyloxymethylphosphonate using sodium hydride as base to give **10**, a precursor for the targets **37a** and **37i**. Methoxy derivative **12** was prepared from **10** by deprotecting the primary hydroxyl selectively, using 24 mM HCl in acetonitrile and alkylating the resultant **11** with methyl iodide using sodium hydride as base to give **12**, a precursor for the targets



SCHEME 3 Reagents: i) NaOMe; ii) MMTrCl, pyridine; iii) Bu_4NF, THF; iv) Dess-Martin; v) MeMgBr; vi) HCl; vii) TBDMS-Cl, imidazle; viii) NaH,TsO-CH_2-P(O)(O-ip)$_2$.

37b and **37j**. Similarly the treatment of **11** (Scheme 2) with mesyl chloride followed by azide displacement with sodium azide gave **14**, a precursor for target **37c**. The reduction of azide in **14** with TPP and water in THF gave **15** and again, the resultant amino group was protected with MMTr to give **16**, a precursor for target **37d**.

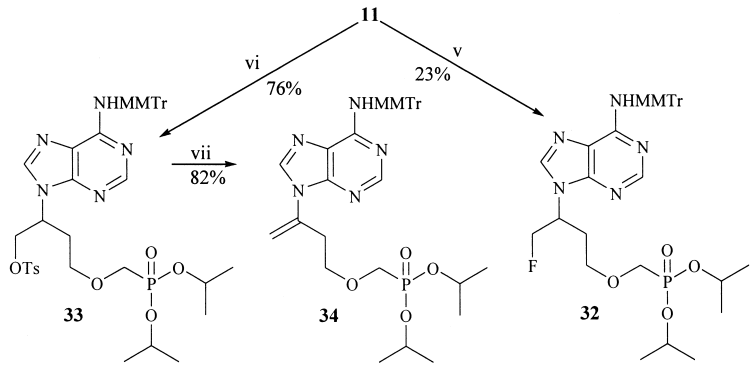
The introduction of the α-hydroxyethyl group in the side chain at the C-1′ position was achieved as per Scheme 3. The desired precursor **19**, to introduce the α-hydroxyethyl group, was prepared from **6** by removing pivaloyl under basic conditions (NaOMe), protecting with MMTr and then deprotecting the TBDMS group in resultant **18** with TBAF. Dess-Martin oxidation of **19** gave aldehyde **20**, which on reaction with methyl magnesium bromide introduced hydroxyl and methyl as a diastereomeric mixture to give **21**. The mixture was not separable by chromatography, therefore was taken as such for further modifications. Compound **21** was fully deprotected under acidic conditions to give **22**, the primary hydroxyl was protected with TBDMS to give **23** and amino and the secondary hydroxyl groups



SCHEME 4 Reagents: i) Adenine, Ph_3P, DIAD, 1,4-dioxane; ii) MMTr-Cl, pyridine; iii) Bu_4NF, THF; iv) NaH, $TsO\text{-}CH_2\text{-}P(O)(O\text{-}ip)_2$.

were protected with MMTr to give **24**. The primary hydroxyl group was now deprotected by reacting with TBAF and the resultant alcohol **25** was subjected to phosphonomethylation reaction to give the desired precursor **26** for target **37e**. Based upon ^1H NMR, the ratio of the diastereomers was 1:2 in all of these compounds (**22-25**, **36e**, and **37e**).

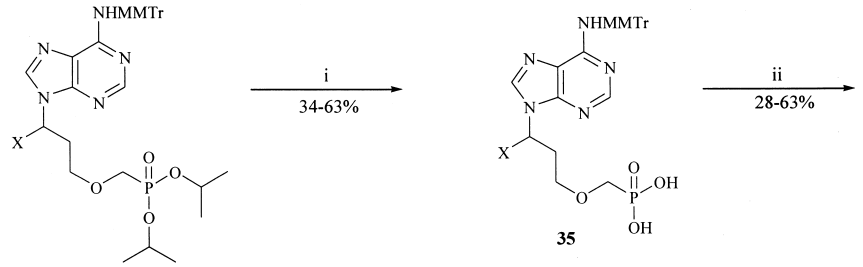
The synthesis of precursors **31**, **32**, and **34** for targets **37f**, **37g**, and **37h**, respectively, is described in Schemes 4 and 5. Since deoxygenation of **11** failed, the synthesis of **31** was achieved from known **27**[28] through the Mitsunobu reaction with adenine, protection of the amino group of resultant **28** with MMTr to give **29** and deprotection of TBDMS with TBAF to give **30.**



SCHEME 5 Reagents: v) DAST, Et_3N; vi) TsCl; vii) NaI, DBU.

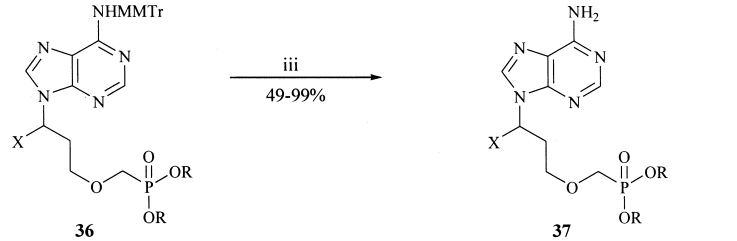
The phosphonomethylation reaction of **30** with *p*-toluenesulfonyloxymethylphosphonate and sodium hydride gave compound **31**. The preparation of **32** was first attempted from **13** by the reaction with silver fluoride but this reaction resulted in a mixture of **32** and the eliminated product **34** which were not separable by chromatography. Later, **32** was prepared from **11** by DAST reaction. Compound **34** was obtained through tosylate **33**, prepared from **11** followed by elimination of the tosyl group in **33** with sodium iodide and DBU.

The precursors **10**, **12**, **14**, **16**, **26**, **31**, **32**, and **34** on reaction with trimethylsilyliodide in the presence of triethylamine gave the desired free phosphonomethyl derivatives, **35a-35h** (Scheme 6). The use of triethylamine was essential to keep the MMTr protecting group intact, since the further



10, X=CH_2OMMTr **26**, X=$CH(OMMTr)CH_3$
12, X=CH_2OCH_3 **31**, X=CH_3
14, X=CH_2N_3 **32**, X=CH_2F
16, X=$CH_2NHMMTr$ **34**, X= =CH_2

a, X=CH_2OMMTr **e**, X=$CH(OMMTr)CH_3$
b, X=CH_2OCH_3 **f**, X=CH_3
c, X=CH_2N_3 **g**, X=CH_2F
d, X=$CH_2NHMMTr$ **h**, X= =CH_2



a, X=CH_2OMMTr **f**, X=CH_3
b, X=CH_2OCH_3 **g**, X=CH_2F
c, X=CH_2N_3 **h**, X= =CH_2
d, X=$CH_2NHMMTr$ **i**, X=CH_2OMMTr
e, X=$CH(OMMTr)CH_3$ **j**, X=CH_2OCH_3
(3.5% in 3 steps)

a, X=CH_2OH **f**, X=CH_3
b, X=CH_2OCH_3 **g**, X=CH_2F
c, X=CH_2N_3 **h**, X= =CH_2
d, X=CH_2NH_2 **i**, X=CH_2OH
e, X=$CH(OH)CH_3$ **j**, X=CH_2OCH_3

36a-f, h, R=$CH_2OC(O)C(CH_3)_3$
37a-f, h, R=$CH_2OC(O)C(CH_3)_3$
36g, i, j, and **37g, i, j**, R=$CH_2OC(O)OCH(CH_3)_2$

SCHEME 6 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.

reactions for the formation of prodrugs were not successful with the free amino and hydroxyl groups in our hands. The reaction of **35a-35h** with an appropriate chloromethyl pivalate or chloromethyl-2-propylcarbonate in the presence of triethylamine gave protected prodrugs **36a-36j** and the removal of the MMTr groups under mild acidic conditions yielded the desired targets **37a-37j**.

BIOLOGICAL ACTIVITY

These compounds showed poor activity against HCV virus in replicon assay.[29]

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. The elemental analysis (C, H, and N) were performed by Atlantic Microlab in Norcross, Georgia. The TLC solvent systems, CMA-80 and CMA-50, refer 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. 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.

(±)-4-Pivaloylbutan-1,2,4-triol (4). Butan-1,2,4-triol (139.0 g, 1.3 mol) was stirred with acetone (5.0 L) and *p*-toluenesulphonic acid monohydrate (7.0 g, 0.037 mol) at room temperature for 4 h. The mixture was neutralized with triethylamine and concentrated under vacuum below 40°C. It was

dissolved in 30% acetone in hexanes (0.5 L) and passed through a short plug of silica gel and further eluted with 30% acetone in hexanes. The fractions containing the product were pooled together and concentrated to give 186 g (98%) of 1,2-isopropylidenebutan-1,2,4-triol which was dissolved in pyridine (1.5 L) and pivaloyl chloride (161 g, 1.34 mol) added to it over a period of 1 h below 10°C. The mixture was further stirred at room temperature for 16 h and filtered to remove insoluble material and the pyridine removed under vacuum from the filtrate. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue was taken in 80% acetic acid (2.5 L) and heated at 55°C for 4 h. Acetic acid was removed under vacuum and the residue was purified on a silica gel column using ethyl acetate:hexanes as eluent to give 182 g (75%) of the desired target as an oil: ^{1}H NMR ($CDCl_3$): δ 4.25–4.42 (m, 1H), 4.08–4.22 (m, 1H), 3.60–3.81 (m, 3H), 3.42–3.52 (m, 1H), 2.02–2.12 (m, 1H), 1.65–1.80 (m, 2H), 1.17 (s, 9H).

(±)-1-*tert*-Butyldimethylsilyl-4-pivaloylbutan-1,2,4-triol (5). To a solution of **4** (70 g, 0.368 mol) in CH_2Cl_2 (2.0 L) was added imidazole (31.3 g, 0.46 mol) and *tert*-butyldimethylsilyl chloride (58.2 g, 0.386 mol) and stirred at room temperature for 3 h. The reaction mixture was diluted with water, the organic layer separated and washed with water and brine and then 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 to give 91.2 g (81%) of product as an oil: ^{1}H NMR (DMSO-d_6): δ 4.66 (d, $J = 5.2$ Hz, 1H), 4.14–3.90 (m, 2H), 3.54–3.25 (m, 3H), 1.84–1.72 (m, 1H), 1.51–1.39 (m, 1H), 1.10 (s, 9H), 0.83 (s, 9H), 0.01 (s, 6H).

(±)-9-[(1-*tert*-Butyldimethylsilyloxymethyl)(3-pivaloyloxy)propyl]adenine (6). To a mixture of **5** (80 g, 0.263 mol), triphenylphosphine (138 g, 0.525 mol) and adenine (71 g, 0.525 mol) in anhydrous dioxane (3.2 L) was added a solution of DIAD (104 mL, 0.525 mol) in dioxane (400 mL) over a period of 3.5 h at room temperature and the mixture was stirred further for 16 h. The reaction mixture was filtered through a short pad of Celite to remove insoluble materials and the residue purified on a column of silica gel eluting with chloroform:methanol (100:0 to 97:3) to provide the desired compound, which was crystallized from ethyl acetate:hexanes (1:3) to afford 77 g (69%) of **6** as a white solid, mp 175–177°C: ^{1}H NMR (DMSO-d_6): 8.14 (s, 1H), 8.08 (s, 1H), 7.15 (bs, 2H), 4.64 (m, 1H), 3.78–4.03 (m, 4H), 2.16–2.48 (m, 2H), 1.02 (s, 9H), 0.70 (s, 9H), −0.12 (s, 3H) and −0.18 (s, 3H). IR (KBr, cm^{-1}) 3352, 3166, 2958, 2859, 1721, 1656, 1597, and 1477. MS (ES^+) 422.46 $(M+H)^+$. Anal. calcd for $C_{20}H_{35}N_5O_3Si\bullet 0.25\ H_2O$: C, 56.37; H, 8.39; N, 16.43. Found: C, 56.16; H, 8.13; N, 16.36.

(±)-9-[(1-Hydroxymethyl)(3-*tert*-butylcarbonyloxy)propyl]adenine (7). Partially purified **6** (91.5 g, obtained from 60.5 g of **5**) was dissolved in THF (1 L) and treated with tetrabutyl ammonium fluoride (1 M in THF, 130 mL) and the reaction mixture stirred at room temperature for 2 h followed by concentration. The residue was purified on a silica gel column using chloroform:CMA-80 (1:0 to 1:1) as eluent to give 21.1 g (35%, 2 steps) of **7** as a white solid, mp 188°C: ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H), 8.13 (s, 1H), 7.22 (bs, 2H), 5.16 (t, $J = 5.4$ Hz, 1H), 4.69–4.59 (m, 1H), 4.04–3.71 (m, 4H), 2.44–2.19 (m, 2H), 1.07 (s, 9H). IR (KBr, cm^{-1}) 3334, 3172, 2968, 1727, 1676, 1607, and 1164. Anal. calcd for $C_{14}H_{21}N_5O_3$: C, 54.71; H, 6.89; N, 22.79. Found: C, 54.41; H, 6.90; N, 22.48.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-*tert*-butylcarbonyloxy)propyl]-N^6-monomethoxytrityladenine (8). A solution of **7** (21 g, 0.068 mol) in pyridine (370 mL) was treated with monomethoxytrityl chloride (86.2 g, 0.28 mol) and the reaction mixture heated at 70°C with stirring for 20 h. It was diluted with ethyl acetate (1.5 L) and washed with water (2×) and brine and the organic layer dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue purified on a silica gel column using ethyl acetate:hexanes as eluent (0:1 to 1:1) to give 60.0 g (98%) of product as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H), 7.72 (s, 1H), 7.29–6.81 (m, 25H), 6.75 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 9.1$ Hz, 2H), 4.77–4.65 (m, 1H), 3.93–3.73 (m, 2H), 3.62 (s, 6H), 3.40–3.29 (m, 1H), 3.16–3.05 (m, 1H), 2.58–2.43 (m, 1H), 2.10–1.97 (m, 1H), 1.90 (s, 9H). IR (KBr, cm^{-1}) 3419, 2959, 1730, 1605, 1508, and 1250. MS (ES$^+$) 874.27 (M+Na)$^+$.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-hydroxy)propyl]-N^6-monomethoxytrityladenine (9). A solution of **8** (59.5 g, 0.070 mol) in THF (375 mL) and methanol (150 mL) was treated with 2N NaOH (175 mL, 0.35 mol) at room temperature and stirred for 16 h. The reaction mixture was neutralized with acetic acid to pH 8.0 and diluted with ethyl acetate (1.0 L) 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 49.8 g (92%) of product as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1H), 7.70 (s, 1H), 7.28–6.83 (m, 25H), 6.74 (d, $J = 8.8$ Hz, 2H), 6.66 (d, $J = 9.1$ Hz, 2H), 4.78–4.67 (m, 1H), 4.46 (t, $J = 5.3$ Hz, 1H), 3.61 (s, 6H), 3.34–2.98 (m, 4H), 2.30–2.14 (m, 1H), 1.96–1.80 (m, 1H). IR (KBr, cm^{-1}) 3412, 2932, 1734, 1608, and 1508. MS (ES$^+$) 790.26 (M+Na)$^+$.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (10). A solution of **9** (32 g,

41.7 mmol) in DMF (360 mL) was treated with sodium hydride (60%, 6.7 g, 167.5 mmol) at room temperature and the mixture was stirred for 1 h. To this solution was then added a solution of *p*-toluenesulfonyloxymethylphosphonate (17.6 g, 50.2 mmol) in DMF (30 mL) and the mixture stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (2 L), neutralized with acetic acid and washed with water (2×) and brine and the organic layer 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 1:1:0.05) as eluent to give 13.2 g (33%) of product as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 7.78 (s, 1H), 7.36–6.85 (m, 25H), 6.82 (d, J = 9.1 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 4.80–4.67 (m, 1H), 4.55–4.40 (m, 2H), 3.69 (s, 6H), 3.60 (d, J = 7.7 Hz, 2H), 3.45–3.25 (m, 3H), 3.20–3.10 (m, 1H), 2.47–2.37 (m, 1H), 2.18–2.00 (m, 1H), 1.19–1.10 (m, 12H). IR (KBr, cm^{-1}) 3418, 2978, 1606, 1508, and 1250. Anal. calcd for $C_{56}H_{60}N_5O_{11}P\bullet 0.5\ H_2O\bullet 0.25$ EtOAc: C, 70.06; H, 6.50; N, 7.17. Found: C, 69.85; H, 6.49; N, 7.29.

(±)-9-[(1-Hydroxymethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (11). A solution of **10** (3.1 g, 3.3 mmol) in acetonitrile (125 mL) was treated with conc. HCl (0.25 mL) at room temperature and the mixture stirred for 1 h. The reaction was neutralized by adding triethylamine (1 mL) and diluted with ethyl acetate (300 mL). It was then washed with water (2×) and brine and the organic layer 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 1:1:0.2) as eluent to give 1.21 g (55%) of **11** as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.13 (s, 1H), 7.82 (s, 1H), 7.28–7.10 (m, 13H), 6.78 (d, J = 8.9 Hz, 2H), 4.97 (t, J = 5.3 Hz, 1H), 4.53–4.40 (m, 3H), 3.81–3.54 (m, 4H), 3.65 (s, 3H), 3.41–3.22 (m, 2H), 2.22–2.00 (m, 2H), 1.18–1.06 (m, 12H). IR (KBr, cm^{-1}) 3415, 2979, 1605, 1470, and 1250. Anal. calcd for $C_{36}H_{44}N_5O_6P\bullet 0.3\ H_2O\bullet 0.3$ EtOAc: C, 63.32; H, 6.71; N, 9.93. Found: C, 63.42; H, 6.80; N, 9.92.

(±)-9-[(1-Azidomethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (14). A solution of **11** (0.5 g, 0.74 mmol) in pyridine (10 mL) was treated with methanesulphonyl chloride (0.132 g, 1.15 mmol) at 0°C and the mixture stirred for 20 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2×) and brine and the organic layer dried over $MgSO_4$ followed by filtration and concentration. The residue (**13**) was dissolved in DMF (5 mL), treated with sodium azide (0.138 g, 2.1 mmol) and the mixture stirred for 4 h at 100°C. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2×) and brine and the organic layer dried over $MgSO_4$.

After filtration, the filtrate was concentrated to give 511 mg (99%, two steps) of product as a light yellow oil: ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.82 (s, 1H), 7.40–7.15 (m, 13H), 6.80 (d, $J = 9.0$ Hz, 2H), 4.81–4.67 (m, 3H), 4.21–4.10 (m, 1H), 3.82–3.55 (m, 4H), 3.78 (s, 3H), 3.35–3.25 (m, 1H), 2.49–2.19 (m, 2H), 1.39–1.29 (m, 12H). IR (KBr, cm^{-1}) 3418, 2979, 2104, 1605, 1472, and 1250. Anal. calcd for $C_{36}H_{43}N_8O_5P$: C, 61.88; H, 6.20; N, 16.04. Found: C, 61.80; H, 6.25; N, 15.38. HRMS calcd for $C_{36}H_{43}N_8O_5P$ $(M+H)^+$ 699.3172. Found 699.3149.

(±)-9-[(1-Aminomethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (15). A mixture of **14** (0.95 g, 1.36 mmol) in THF (9.5 mL) and water (1.9 mL) was treated with triphenylphosphine (0.76 g, 2.9 mmol) and stirred at room temperature for 15 h. The reaction mixture was concentrated and purified on a column using chloroform:CMA-80 (1:0 to 1:1) as eluent to give 0.687 g (75%) as a light yellow oil: ^{1}H NMR ($CDCl_3$): δ 8.01(s, 1H), 7.86 (s, 1H), 7.38–7.18 (m, 13H), 6.80 (d, $J = 8.8$ Hz, 2H), 4.80–4.66 (m, 2H), 4.65–4.55 (m, 1H), 3.78 (s, 3H), 3.64 (d, $J =$ 8.5 Hz, 2H), 3.62–3.53 (m, 1H), 3.43 (dd, $J = 13.5$, 8.1 Hz, 1H), 3.43–3.23 (m, 1H), 3.14 (dd, $J = 13.5$, 4.2 Hz, 1H), 2.41–2.17 (m, 2H), 2.10–1.70 (2H), 1.35–1.29 (m, 12H). HRMS calcd for $C_{36}H_{45}N_6O_5P$ $(M+H)^+$ 673.3267. Found 673.3292.

(±)-9-[(1-N-Monomethoxytritylaminomethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (16). It was prepared from **15** (652 mg) by following the same procedure as given for **8** except 2 equivalents of monomethoxytrityl chloride were used. 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 **16** as a light yellow oil (yield: 69%): ^{1}H NMR (DMSO-d_6): δ 8.21 (s, 1H), 7.79 (s, 1H), 7.37–6.85 (m, 25H), 6.81 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 8.8$ Hz, 2H), 4.62–4.39 (m, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.55 (dd, $J = 7.9$, 3.6 Hz, 2H), 3.37–3.21 (m, 2H), 2.80–2.65 (m, 1H), 2.57–2.37 (m, 1H), 2.19–2.05 (m, 1H), 2.00–1.85 (m, 1H), 1.17–1.07 (m, 12H). IR (KBr, cm^{-1}) 3419, 2978, 1605, 1508, and 1251. Anal. calcd for $C_{56}H_{61}N_6O_6P \bullet 1.0\ H_2O$: C, 70.50; H, 6.55; N, 8.81. Found: C, 70.34; H, 6.53; N, 8.57. HRMS calcd for $C_{56}H_{61}N_6O_6P$ $(M+H)^+$ 945.4468. Found 945.4474.

(±)-9-[(1-*tert*-Butyldimethylsilyloxymethyl)(3-hydroxy)propyl]adenine (17). To a solution of **6** (45 g, 0.107 mol) in MeOH (1.0 L) was added NaOMe (5.4 M solution in MeOH, 39 mL, 0.213 mol) and the reaction mixture was stirred at room temperature for 5 h. The solution was neutralized with acetic acid and concentrated. The residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:19:0 to 1:1:0.1) as eluent to

provide 25 g (69%) of **17** as a white solid, mp 112–114°C: ^{1}H NMR (DMSO-d_6): 8.09 (s, 1 H), 8.08 (s, 1H), 7.15 (bs, 2H), 4.62–4.70 (m, 1H), 4.58 (t, $J = 4.9$ Hz, 1H), 3.96–4.16 (m, 1H), 3.81–3.90 (m, 1H), 3.18–3.44 (m, 2H), 1.96–2.26 (m, 2 H). 0.70 (s, 9H), −0.14 (s, 3H), and −0.22 (s, 3H). IR (KBr, cm^{-1}) 3334, 3186, 2929, 2856, 1657, 1600, 1471, and 1414. MS (ES+) 338.49 (M+H). Anal. calcd for $C_{15}H_{27}N_5O_2Si$: C, 53.38; H, 8.06; N, 20.75. Found: C, 53.43; H, 8.29; N, 20.65.

(±)-9-[(1-*tert*-Butyldimethylsilyloxymethyl)(3-monomethoxytrityloxy)propyl]-N^6-monomethoxytrityladenine (18). It was prepared from **17** (25.0 g) by the same method used for **8** and obtained in 91% yield as a white solid, mp 88–92°C: ^{1}H NMR (DMSO-d_6): 8.16 (s, 1H), 7.88 (s, 1H), 7.02–7.36 (m, 25H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 4.84 (m, 1H), 3.70–3.94 (m, 2H), 3.71(s, 3H), 3.69 (s, 3H), 2.74–2.98 (m, 2H), 2.08–2.48 (m, 2H). 0.67 (s, 9H), −0.157 (s, 3H), and −0.24 (s, 3H). IR (KBr, cm^{-1}) 3416, 3030, 2951, 1604, 1508, 1467, and 1296. MS (ES$^+$) 882.53 (M+H)$^+$. Anal. calcd for $C_{55}H_{59}N_5O_4Si$: C, 74.48; H, 6.78; N, 7.78. Found: C, 74.79; H, 6.83; N, 7.43.

(±)-9-[(1-Hydroxymethyl)(3-monomethoxytrityloxy)propyl]-N^6-monomethoxytrityladenine (19). A solution of **18** (10.6 g, 12.02 mmol) in THF (120 mL) was treated with tetrabutyl ammonium fluoride (1 M in THF, 12.1 mL) and the reaction mixture 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 8.87 g (96%) of **19** as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.21 (s, 1H), 7.92 (s, 1H), 7.38–7.05 (m, 25H), 6.89 (d, $J = 9.1$ Hz, 2H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.09 (t, $J = 5.4$ Hz, 1H), 4.88–4.77 (m, 1H), 3.77–3.70 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 2.96–2.76 (m, 2H), 2.44–2.27 (m, 1H), 2.27–2.11 (m, 1H). IR (KBr, cm^{-1}) 3412, 2932, 1734, 1606, 1509, 1251, and 1033. Anal. calcd for $C_{49}H_{45}N_5O_4 \bullet 0.25$ $H_2O \bullet 0.4$ EtOAc: C, 75.25; H, 6.08; N, 8.67. Found: C, 75.35; H, 6.04; N, 8.50.

(±)-9-[(1-(2-Hydroxy)ethyl)(3-hydroxy)propyl]adenine (22). A solution of **19** (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 stirred at room temperature for 4 h. The reaction mixture was concentrated and purified on a silica gel column using hexanes:ethyl acetate (1:0 to 1:2) as eluent to provide **20** (white solid, 1.35 g) and its derivative with loss of one MMTr group (white solid, 1.18 g). The combined products (2.5 g) were dissolved in THF (150 mL), treated with 3 M methyl magnesium bromide (10.9 mL, 32.7 mmol) and the mixture stirred for 8 h at room temperature. The reaction mixture was diluted with chloroform (400 mL) and water (100 mL). After filtration through Celite and separation, the organic layer was dried over $MgSO_4$ followed by filtration and concentration. The residue (**21** and its

derivative with loss of one MMTr) was dissolved in acetonitrile (300 mL) and water (14 mL), treated with 2 M HCl (1.5 mL) at room temperature, and the mixture stirred for 14 h. The reaction mixture was diluted with water (100 mL) and neutralized by adding 0.5 N NaOH followed by concentration to remove most of the organic solvent. The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and concentrated to dryness. The residue was treated with MeOH (100 mL) and filtered. The filtrate was concentrated and purified on a silica gel column using chloroform:CMA-80 (1:0 to 0:1) as eluent to give 472 mg (37%, three steps) of **22** as a colorless oil: ^{1}H NMR (a mixture of diastereomers, DMSO-d_6): δ 8.17, 8.167, 8.11 (3s, 2H), 7.26, 7.25 (2s, 2H), 5.24, 5.17 (2d, J = 5.2 Hz each, 1H), 4.61–4.50 (m, 2H), 4.20–4.05 (m, 1H), 3.40–3.09 (m, 2H), 2.30–2.03 (m, 2H), 0.98, 0.96 (d, J = 6.2 Hz each, 3H). HRMS calcd for $C_{10}H_{15}N_5O_2$ $(M+H)^+$ 238.1304. Found 238.1307.

(±)-9-[(1-(α-Hydroxy)ethyl)(3-*tert*-butyldimethylsilyloxy)propyl]adenine (23). The same method was used as for compound **5**. The residue was purified on a silica gel column using chloroform:CMA-80 (1:0 to 1:1) to give 415 mg (64%) of **23** as a white solid: ^{1}H NMR (a mixture of diastereomers, DMSO-d_6): δ 8.24, 8.239, 8.18 (3s, 2H), 7.32, 7.30 (2s, 2H), 5.32, 5.24 (d, J = 5.0 Hz each, 1H), 4.72–4.51 (m, 1H), 4.22–4.10 (m, 1H), 3.70–3.60 (m, 1H), 3.49–3.35 (m, 1H), 2.45–2.12 (m, 2H), 1.06, 1.04 (d, J = 6.2 Hz each, 3H), 0.93, 0.91 (s, 9H), 0.00, −0.02 (2s, 6H). HRMS calcd for $C_{16}H_{29}N_5O_2Si$ $(M+H)^+$ 352.2168. Found 352.2176.

(±)-9-[(1-(α-Monomethoxytrityloxy)ethyl)(3-*tert*-butyldimethylsilyloxy)propyl]-N^6-monomethoxytrityladenine (24). It was prepared from **23** (392 mg) by following the same procedure as given for **8**. The crude product was purified on a silica gel column using ethyl acetate:hexanes (1:0 to 2:1) as eluent to give 66% of product as a colorless oil: ^{1}H NMR (a mixture of diastereomers, DMSO-d_6): δ 8.39, 8.38, 7.99, 7.95 (4s, 2H), 7.57–7.23 (m, 25H), 7.08–6.89 (m, 4H), 4.91–4.76 (1H), 3.93, 3.92, 3.91, 3.88 (4s, 6H), 3.87–3.35 (m, 3H), 2.97–2.43 (m, 2H), 0.99, 0.92 (d, J = 6.0 Hz each, 3H), 0.93 (s, 9H), 0.03, 0.01, 0.00, −0.04 (4s, 6H). HRMS calcd for $C_{56}H_{61}N_5O_4Si$ $(M+H)^+$ 1089.4891. Found 1089.4859.

(±)-9-[(1-(α-Monomethoxytrityloxy)ethyl)(3-hydroxy)propyl]-N^6-monomethoxytrityladenine (25). It was prepared from **24** (640 mg) by following the same procedure as given for **19**. The crude product was purified on a silica gel column using a mixture of ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.1) as eluent to give 90% of product as a colorless film: ^{1}H NMR (a mixture of diastereomers, DMSO-d_6): δ 8.26, 8.23 (2s, 1H), 7.79, 7.77 (2s, 1H), 7.45–6.71 (m, 29H), 4.73–4.50 (m, 2H), 3.76, 3.74, 3.72, 3.71 (4s, 6H), 3.54–3.40 (m, 1H), 3.27–3.12 (m, 1H), 3.09–2.93 (m, 1H), 2.59–2.12, 1.99–

1.83 (2m, 2H), 0.84, 0.80 (d, $J = 6.1$ Hz each, 3H). IR (KBr, cm^{-1}) 3414, 1737, 1606, 1508, 1250, and 1033.

(±)-9-[(1-Methyl)(3-hydroxy)propyl]-N^6-monomethoxytrityladenine (30). Compound **27** (1.93 g) was converted to **28** according to the procedure used for **6**. A small amount of the product was chromatographed two times (eluting with $CHCl_3$: MeOH, 100:0 to 95:5) to get the pure **28** for characterization: ^{1}H NMR (DMSO-d_6): δ 8.28 (s, 1H), 8.20 (s, 1H), 7.26 (s, 2H), 4.89–4.76 (m, 1H), 3.67–3.56 (m, 1H), 3.54–3.44 (m, 1H), 2.41–2.27 (m, 1H), 2.20–2.04 (m, 1H), 1.61 (d, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.006 (s, 3H), 0.00 (s, 3H). HRMS calcd for $C_{15}H_{27}N_5OSi$ $(M+H)^+$ 322.2063. Found 322.2066.

Impure compound **28** (chromatographed once) was converted to **29** with the method used for **8** (2 eq. of monomethoxytrityl chloride used) and the TBDMS group of **29** was removed by the procedure used for **19**. The resultant crude product was purified on a silica gel column using ethyl acetate:hexanes:methanol (1:1:0 to 1:1:0.2) as eluent to give 1.97 g (43%, three steps) of **30** as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H), 7.94 (s, 1H), 7.38–7.22 (m, 13H), 6.89 (d, $J = 9.0$ Hz, 2H), 4.82–4.73 (m, 1H), 4.59 (t, $J = 5.1$ Hz, 1H), 3.76 (s, 3H), 3.39–3.21 (m, 2H), 2.26–1.94 (m, 2H), 1.55 (d, $J = 6.8$ Hz, 3H). IR (KBr, cm^{-1}) 3410, 2933, 1605, 1470, and 1250. Anal. calcd for $C_{29}H_{29}N_6O_2 \bullet 0.2\ H_2O$: C, 72.09; H, 6.13; N, 14.49. Found: C, 71.99; H, 6.20; N, 14.33.

(±)-9-[(1-Fluoromethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (32). A solution of **11** (1.0 g, 1.48 mmol) in methylene chloride (20 mL) was treated with triethylamine (1.6 mL, 11.5 mmol) followed by DAST (0.6 mL, 4.54 mmol) and the reaction mixture stirred for 18 h at room temperature. This was then treated with 1 M TBAF (3.7 mL, 3.7 mmol) and stirred for 6 days and then concentrated. The residue was purified on a silica gel column using ethyl acetate:hexanes: methanol (1:1:0 to 1:1:0.3) as eluent to give 0.232 g (23%) of **32** as a colorless oil and 0.567 g (57%) of the starting material recovered: ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H), 7.79 (s, 1H), 7.29–7.05 (m, 13H), 6.73 (d, $J = 9.0$ Hz, 2H), 4.92–4.51 (m, 3H), 4.48–4.37 (m, 2H), 3.60 (s, 3H), 3.55 (dd, $J = 7.9$, 2.1 Hz, 2H), 3.40–3.20 (m, 2H), 2.20–2.00 (m, 2H), 1.12–1.00 (m, 12H). IR (KBr, cm^{-1}) 3418, 2979, 1606, 1511, and 1472. Anal. calcd for $C_{36}H_{43}FN_5O_5P \bullet 1.0\ H_2O$: C, 62.33; H, 6.54; N, 10.10. Found: C, 62.56; H, 6.38; N, 10.29.

(±)-9-[(1-Tosyloxymethyl)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (33). A solution of **11** (1.18 g, 1.75 mmol) in pyridine (25 mL) was treated with 4-toluenesulphonyl chloride (0.681 g, 3.5 mmol) at 5°C and the mixture was stirred for 15 h at room temperature.

The reaction was not complete so more 4-toluenesulphonyl chloride (0.34 g, 1.8 mmol) was added and again stirred at room temperature for 8 h. The reaction mixture was diluted with EtOAc (300 mL), washed with water (2×) and brine, and dried over $MgSO_4$. After filtration and concentration, 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 1.11 g (76%) of product as a white solid: ^{1}H NMR (DMSO-d_6): δ 8.03 (s, 1H), 7.55 (s, 1H), 7.26–6.97 (m, 17H), 6.72 (d, $J = 9.0$ Hz, 2H), 4.71–4.59 (m, 1H), 4.45–4.20 (m, 4H), 3.56 (s, 3H), 3.50–3.42 (m, 2H), 3.30–3.08 (m, 2H), 2.14 (s, 3H), 2.07–1.93 (m, 2H), 1.10–0.95 (m, 12H). IR (KBr, cm^{-1}) 3419, 2980, 1606, 1472, and 1250. Anal. calcd for $C_{43}H_{50}N_5O_8SP\bullet 0.25\ H_2O\bullet 0.1$ EtOAc: C, 61.96; H, 6.15; N, 8.33. Found: C, 61.87; H, 6.04; N, 8.17.

(±)-9-[(1-Methylene)(3-(diisopropylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (34). A solution of **33** (1.06 g, 1.28 mmol) in DMF (3.0 mL) was treated with sodium iodide (0.485 g, 3.20 mmol) and heated at 50°C for 6 h. The solution was cooled to room temperature and DBU (0.294 g, 1.93 mmol) in DMF (0.5 mL) added and heated at 80°C for 3 h. The solution on cooling was diluted with ethyl acetate (100 mL), washed with water and brine, and dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue purified on a silica gel column using ethyl acetate:methanol (19:0 to 19:1) as eluent to give 0.694 g (82%) of product as a pale yellow oil: ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.86 (s, 1H), 7.45–7.15 (m, 13H), 6.80 (d, $J = 8.9$ Hz, 2H), 5.47 (s, 1H), 5.27 (s, 1H), 4.80–4.66 (m, 2H), 3.78 (s, 3H), 3.80–3.64 (m, 4H), 3.07 (t, $J = 5.84$ Hz, 2H), 1.35–1.26 (m, 12H). IR (neat, cm^{-1}) 3020, 1604, 1471, 1216, and 766. Anal. calcd for $C_{36}H_{42}N_5O_5P\bullet 0.25\ H_2O\bullet 0.25$ EtOAc: C, 65.14; H, 6.57; N, 10.27. Found: C, 65.26; H, 6.52; N, 10.15.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35a). A suspension of **10** (16.7 g, 17.7 mmol) in DMF (170 mL) was treated with triethylamine (15 mL) followed by trimethylsilyliodide (25 mL, 174.9 mmol) and the reaction mixture flask covered with aluminum foil to protect from light and stirred for 14 h at room temperature. It was then diluted with TEAB buffer (500 mL), water (750 mL), and chloroform (1.5 L) and stirred for 1 h. The organic phase was collected and the aqueous phase extracted with chloroform (3×). The combined organic extracts were dried over $MgSO_4$. After filtration, the filtrate was concentrated and the residue 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 7.0 g (46%) of **35a** as a yellow solid: ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 1H), 7.67 (s, 1H), 7.30–6.81 (m, 25H), 6.75 (d, $J = 9.1$ Hz, 2H), 6.65 (d, $J = 9.1$ Hz, 2H), 4.78–4.65 (m, 1H), 3.61 (s, 3H), 3.60 (s, 3H), 3.40–2.99 (m, 6H), 2.36–2.20 (m, 1H), 2.04–1.87 (m, 1H). HRMS calcd for $C_{50}H_{48}N_5O_7P$ $(M+H)^+$ 862.3369. Found 862.3409.

(±)-9-[(1-Methoxymethyl)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35b). A solution of **11** (0.5 g, 0.74 mmol) in DMF (6.0 mL) was treated with sodium hydride (60%, 0.12 g, 3.0 mmol) at room temperature and the mixture stirred for 0.5 h. To this mixture was then added a solution of methyliodide (0.125 g, 0.88 mmol) in DMF (1 mL) and the mixture stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate (15 mL), neutralized with acetic acid and chloroform (200 mL) added. The mixture was washed with water (2×) and brine and the organic layer dried over $MgSO_4$ followed by filtration and concentration. The residue containing **12** was converted to **35b** with the same procedure used for **35a**. 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 222 mg (50%, two steps) of **35b** as an off-white film: ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1H), 7.87 (s, 1H), 7.38–7.16 (m, 13H), 6.84 (d, $J = 8.9$ Hz, 2H), 4.86–4.75 (m, 1H), 4.02–3.93 (m, 1H), 3.73–3.13 (m, 5H), 3.71 (s, 3H), 3.16 (s, 3H), 2.15–2.03 (m, 2H). HRMS calcd for $C_{31}H_{34}N_5O_6P$ $(M+H)^+$ 604.2325. Found 604.2345.

(±)-9-[(1-Azidomethyl)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35c). It was prepared from **14** (345 mg) with the same procedure as given for **35a**. 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 **35c** as a colorless film (yield, 63%): ^{1}H NMR (DMSO-d_6): δ 8.39 (s, 1H), 7.89 (s, 1H), 7.37–7.11 (m, 13H), 6.84 (d, $J = 9.0$ Hz, 2H), 4.85–4.74 (m, 1H), 4.11 (dd, $J = 11.7, 9.7$ Hz, 1H), 3.87 (dd, $J = 14.2$, 4.1 Hz, 1H), 3.71 (s, 3H), 3.49–3.37 (m, 1H), 3.32–3.12 (m, 3H), 2.23–2.06 (m, 2H). HRMS calcd for $C_{30}H_{31}N_8O_5P$ $(M+H)^+$ 615.2233. Found 615.2226.

(±)-9-[(1-N-Monomethoxytritylaminomethyl)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35d). It was prepared from **16** (540 mg) with the same procedure as given for **35a**. 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 **35d** as a colorless film (yield, 52%): ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H), 7.80 (s, 1H), 7.41–6.92 (m, 25H), 6.84 (d, $J = 9.0$ Hz, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 4.74–4.61 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.34–2.32 (m, 7H), 2.16–2.04 (m, 1H), 1.96-1.84 (m, 1H). HRMS calcd for $C_{50}H_{49}N_6O_6P$ $(M+H)^+$ 861.3529. Found 861.3568.

(±)-9-[(1-Methyl)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35f). Compound **30** (1.87 g) was converted to **31** with the same method used for compound **10** and the resultant **31** was converted to **35f**

following the same procedure used for **35a**. 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 760 mg (34%, two steps) of **35f** as a colorless film: ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H), 7.88 (s, 1H), 7.35–7.13 (m, 13H), 6.83 (d, J = 9.0 Hz, 2H), 4.79–4.66 (m, 1H), 3.70 (s, 3H), 3.45–3.31 (m, 1H), 3.31–3.12 (m, 3H), 2.23–2.10 (m, 1H), 2.10–1.97 (m, 1H), 1.51 (d, J = 6.8 Hz, 3H). HRMS calcd for $C_{30}H_{32}N_5O_5P$ $(M+H)^+$ 574.2219. Found 574.2243.

(±)-9-[(1-Methylene)(3-phosphonomethoxy)propyl]-N^6-monomethoxytrityladenine (35h). It was prepared from **34** (597 mg) with the same procedure as given for **35a**. 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 **35h** as an off-white solid (yield, 57%): ^{1}H NMR (DMSO-d_6): δ 8.41 (s, 1H), 7.92 (s, 1H), 7.40–7.15 (m, 13H), 6.84 (d, J = 8.9 Hz, 2H), 5.61 (s, 1H), 5.25 (s, 1H), 3.70 (s, 3H), 3.57 (t, J = 6.3 Hz, 2H), 3.31 (d, J = 8.3 Hz, 2H), 2.96 (t, J = 6.3 Hz, 2H). HRMS calcd for $C_{30}H_{30}N_5O_5P$ $(M+H)^+$ 572.2062. Found 572.2084.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36a). A solution of **35a** (500 mg, 0.58 mmol) in DMF (31 mL) was treated with triethylamine (31 mL) followed by chloromethyl pivalate (11.2 mL, 76.93 mmol) and stirred for 3 days at room temperature. It was then diluted with chloroform (300 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 174 mg (28%) of **36a** as a colorless film: ^{1}H NMR (DMSO-d_6): δ 8.13 (s, 1H), 7.54 (s, 1H), 7.14–6.65 (m, 25H), 6.60 (d, J = 9.1 Hz, 2H), 6.51 (d, J = 9.1 Hz, 2H), 5.38–5.26 (m, 4H), 4.57–4.43 (m, 1H), 3.59–3.40 (m, 2H), 3.46 (s, 6H), 3.25–2.85 (m, 4H), 2.29–2.17 (m, 1H), 1.91–1.76 (m, 1H), 0.88 (s, 18H). HRMS calcd for $C_{62}H_{68}N_5O_{11}P$ $(M+H)^+$ 1090.4731. Found 1090.4761.

(±)-9-[(1-Methoxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36b). It was prepared from **35b** (160 mg) with the same procedure as given for **36a**. 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 **36b** as a colorless film (yield, 63%): ^{1}H NMR (DMSO-d_6): δ 8.16 (s, 1H), 7.82 (s, 1H), 7.30–7.10 (m, 13H), 6.78 (d, J = 8.8 Hz, 2H), 5.58–5.48 (m, 4H), 4.73–4.62 (m, 1H), 3.86–3.73 (m, 1H), 3.76 (d, J = 7.5 Hz, 2H), 3.65 (s, 3H), 3.60–3.53 (m, 1H), 3.43–3.23 (m, 2H), 3.13 (s, 3H), 2.23–1.97 (m, 2H), 1.07 (s, 18H). HRMS calcd for $C_{43}H_{54}N_5O_{10}P$ $(M+H)^+$ 832.3686. Found 832.3707.

(±)-9-[(1-Azidomethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36c). It was prepared from **35c** (174 mg) with the same procedure as given for **36a**. 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 **36c** as a colorless film (yield, 56%): ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H), 7.87 (s, 1H), 7.38–7.20 (m, 13H), 6.79 (d, J = 9.0 Hz, 2H), 5.75–5.62 (m, 4H), 4.78–4.65 (m, 1H), 4.13 (dd, J = 12.7, 8.2 Hz, 1H), 3.81–3.57 (m, 4H), 3.78 (s, 3H), 3.34–3.20 (m, 1H), 2.50–2.35 (m, 1H), 2.30–2.16 (m, 1H), 1.23 (s, 9H), 1.226 (s, 9H). HRMS calcd for $C_{42}H_{51}N_8O_9P$ $(M+H)^+$ 843.3594. Found 843.3558.

(±)-9-[(1-N-Monomethoxytritylaminomethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36d). It was prepared from **35d** (150 mg) with the same procedure as given for **36a**. 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 **36d** as a colorless film (yield, 48%): ^{1}H NMR ($CDCl_3$): δ 7.964 (s, 1H), 7.958 (s, 1H), 7.47–6.95 (m, 25H), 6.78 (d, J = 8.9 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 5.76–5.60 (m, 4H), 4.66–4.52 (m, 1H), 4.20–4.02 (m, 1H), 3.79–3.65 (m, 2H), 3.72 (s, 6H), 3.58–3.44 (m, 1H), 3.31–3.16 (m, 1H), 2.88 (t, J = 10.8 Hz, 1H), 2.60–2.44 (m, 1H), 2.44–2.32 (m, 1H), 2.12–2.00 (m, 1H), 1.20 (m, 18H). HRMS calcd for $C_{62}H_{69}N_6O_{10}P$ $(M+H)^+$ 1089.4891. Found 1089.4859.

(±)-9-[(1-(α-Monomethoxytrityloxy)ethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36e). The conversions of **25** (427 mg) to **26**, **26** to **35e**, and **35e** to **36e** were done by the methods used for **10**, **35a**, and **36a**, respectively. 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 21 mg (3.5%, three steps) of **36e** as a colorless film: ^{1}H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.06, 7.89, 7.82 (3s, 2H), 7.43–7.05 (m, 25H), 6.92–6.66 (m, 4H), 5.73–5.60 (m, 4H), 5.00–4.02, 3.86–3.02 (2m, 6H), 3.78 (s, 3H), 3.72 (s, 3H), 2.69–2.24 (m, 2H), 1.22, 1.21 (2s, 18H), 0.99, 0.94 (2d, J = 6.6 Hz each, 3H). HRMS calcd for $C_{63}H_{70}N_5O_{11}P$ $(M+H)^+$ 1104.4887. Found 1104.4925.

(±)-9-[(1-Methyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36f). It was prepared from **35f** (240 mg) with the same procedure as given for **36a**. 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 **36f** as a colorless oil (yield, 47%): ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H), 7.72 (s, 1H), 7.17–7.00 (m, 13H), 6.68 (d, J = 9.1 Hz, 2H), 5.46–5.38 (m, 4H), 4.54–4.45 (m, 1H), 3.65 (d, J = 7.7 Hz,

2H), 3.55 (s, 3H), 3.32–3.10 (m, 2H), 2.14–1.84 (m, 2H), 1.35 (d, $J = 6.8$ Hz, 3H), 0.97 (s, 18H). IR (KBr, cm^{-1}) 3410, 2976, 1755, 1605, 1473, and 1252. Anal. calcd for $C_{42}H_{52}N_5O_9P$: C, 62.91; H, 6.54; N, 8.73. Found: C, 62.65; H, 6.76; N, 8.74.

(±)-9-[(1-Fluoromethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36g). Compound **32** (210 mg) was converted to **35g** and **35g** to **36g** with the methods used for **35a** and **36a**, respectively. In this case (**35g** to **36g**), chloromethyl-2-propylcarbonate was used in place of chloromethyl pivalate. The time of the reaction also increased to 7 days. The purification gave the desired **36g** in 29% yield: ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.82 (s, 1H), 7.31–7.12 (m, 13H), 6.73 (d, $J = 9.0$ Hz, 2H), 5.69–5.55 (m 4H), 5.05–4.51 (m, 5H), 3.75 (d, $J = 7.9$ Hz, 2H), 3.71 (s, 3H), 3.64–3.54 (m, 1H), 3.35–3.24 (m, 1H), 2.41–2.26 (m, 1H), 2.26–2.11 (m, 1H), 1.24 (d, $J = 6.2$ Hz, 6H), 1.23 (d, $J = 6.2$ Hz, 6H). HRMS calcd for $C_{40}H_{47}FN_5O_{11}P$ $(M+H)^+$ 824.3072. Found 824.3096.

(±)-9-[(1-Methylene)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36h). It was prepared from **35h** (193 mg) with the same procedure as given for **36a**. 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 **36h** as a colorless oil (yield, 55%): ^{1}H NMR (DMSO-d_6): δ 8.58 (s, 1H), 8.16 (s, 1H), 7.62–7.41 (m, 13H), 7.08 (d, $J = 8.9$ Hz, 2H), 5.86 (s, 1H), 5.84 (d, $J = 1.5$ Hz, 2H), 5.79 (d, $J = 1.1$ Hz, 2H), 5.46 (s, 1H), 4.12 (d, $J = 7.8$ Hz, 2H), 3.95 (s, 3H), 3.85 (t, $J = 6.4$ Hz, 2H), 3.26 (d, $J = 6.4$ Hz, 2H), 1.37 (s, 18H). IR (neat, cm^{-1}) 3020, 1753, 1604, and 1216. Anal. calcd for $C_{42}H_{50}N_5O_9P \bullet 0.25\ H_2O$: C, 62.71; H, 6.33; N, 8.71. Found: C, 62.92; H, 6.70; N, 8.62.

(±)-9-[(1-Monomethoxytrityloxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-N^6-monomethoxytrityladenine (36i). It was prepared from **35a** (216 mg) with the same procedure as given for **36a** but using chloromethyl-2-propylcarbonate in place of chloromethyl pivalate. The time of the reaction 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 **36i** as a colorless film (yield, 50%): ^{1}H NMR ($CDCl_3$): δ 7.99 (s, 1H), 7.90 (s, 1H), 7.41–7.00 (m, 25H), 6.79 (d, $J = 8.9$ Hz, 2H), 6.70 (d, $J = 8.7$ Hz, 2H), 5.73–5.58 (m, 4H), 4.96–4.86 (m, 2H), 4.81–4.71 (m, 1H), 3.79–3.65 (m, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.56–3.48 (m, 1H), 3.34–3.24 (m, 2H), 2.58–2.45 (m, 1H), 2.18–2.06 (m, 1H), 1.32–1.24 (m, 12H). HRMS calcd for $C_{60}H_{64}N_5O_{13}P$ $(M+H)^+$ 1094.4316. Found 1094.4316.

(±)-9-[(1-Methoxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)-propyl]-N^6-monomethoxytrityladenine (36j). It was prepared from **35b** (115 mg) with the same procedure as given for **36i**. 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 **36j** as a colorless film (yield, 42%): ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.90 (s, 1H), 7.39–7.19 (m, 13H), 6.80 (d, $J = 9.0$ Hz, 2H), 5.75–5.64 (m, 4H), 4.99–4.87 (m, 2H), 4.87–4.77 (m, 1H), 3.94 (dd, $J = 10.3$, 6.7 Hz, 1H), 3.81 (d, $J = 7.9$ Hz, 2H), 3.78 (s, 3H), 3.66 (dd, $J = 9.8$, 3.8 Hz, 1H), 3.63–3.56 (m, 1H), 3.41–3.32 (m, 1H), 3.32 (s, 3H), 2.43–2.12 (m, 2H), 1.31 (d, $J = 6.3$ Hz, 6H), 1.30 (d, $J = 6.2$ Hz, 6H). HRMS calcd for $C_{41}H_{50}N_5O_{12}P$ $(M+H)^+$ 836.3271. Found 836.3235.

(±)-9-[(1-Hydroxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-adenine (37a). A solution of **36a** (272 mg, 0.25 mmol) in acetonitrile (54 mL) was treated with 0.2 M HCl (2.7 mL) and stirred for 14 h at room temperature. It was then carefully neutralized with 0.5 N NaOH to pH 6.0 and diluted with water (20 mL) and concentrated to remove acetonitrile. The residual material was again diluted with water (20 mL) and extracted with chloroform:methanol (4:1, 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 chloroform:methanol (1:0 to 9:1) as eluent to give 102 mg (75%) of **37a** as a colorless oil. HPLC: $t_R = 22.240$ min, 97.06%.

Procedure for the fumarate salt of **37a**: A solution of **37a** (50.0 mg, 0.092 mmol) in 2-propanol (0.25 mL) was treated with a solution of fumaric acid in propanol (20.3 mg/mL, 1.62 mL, 0.092 mmol) followed by concentration. The fumaric salt was obtained as a white solid: ^{1}H NMR (DMSO-d_6): δ 13.21 (bs, 2H), 8.16 (s, 1H), 8.15 (s, 1H), 7.25 (s, 2H), 6.69 (s, 2H), 5.70–5.60 (m, 4H), 5.11 (bs, 1H), 4.68–4.52 (m, 1H), 4.00–3.70 (m, 2H), 3.87 (d, $J = 7.7$ Hz, 2H), 3.53–3.30 (m, 2H), 2.35–2.13 (m, 2H), 1.20 (s, 18H). Anal. calcd for $C_{22}H_{36}N_5O_9P\bullet 1.0\ C_4H_4O_4$: C, 47.18; H, 6.10; N, 10.59. Found: C, 47.30; H, 6.11; N, 10.31.

(±)-9-[(1-Methoxymethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-adenine (37b). It was prepared from **36b** (110 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37b** as a colorless oil (yield, 49%): A portion was purified by HPLC ($t_R = 21.260$ min). ^{1}H NMR ($CDCl_3$): δ 8.30 (s, 1H), 7.96 (s, 1H), 5.84 (s, 2H), 5.75–5.63 (m, 4H), 4.92–4.80 (m, 1H), 3.93 (dd, $J = 10.0$, 6.2 Hz, 1H), 3.75 (dd, $J = 7.9$, 1.3 Hz, 1H), 3.67 (dd, $J = 10.2$, 3.8 Hz, 1H), 3.64–3.56 (m, 1H), 3.37–3.30 (m, 1H), 3.38–3.28 (m, 1H), 3.32 (s, 3H), 2.44–2.30 (m,

1H), 2.30–2.16 (m, 1H), 1.23 (s, 9H), 1.22 (s, 9H). IR (neat, cm^{-1}) 3020, 2982, 1751, 1631, 1478, and 1216. HRMS calcd for $C_{23}H_{38}N_5O_9P$ $(M+H)^+$ 560.2485. Found 560.2468.

(±)-9-[(1-Azidomethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono) methoxy)propyl]-adenine (37c). It was prepared from **36c** (117 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37c** as a colorless oil (yield, 83%): ^1H NMR ($CDCl_3$): δ 8.30 (s, 1H), 7.91 (s, 1H), 5.80–5.62 (m, 6H), 4.84–4.70 (m, 1H), 4.23–4.12 (m, 1H), 3.83–3.69 (m, 3H), 3.67–3.56 (m, 1H), 3.34–3.21 (m, 1H), 2.56–2.40 (m, 1H), 2.32–2.16 (m, 1H), 1.24 (s, 9H), 1.23 (s, 9H). IR (neat, cm^{-1}) 3019, 2980, 2106, 1751, and 1633. HRMS calcd for $C_{22}H_{35}N_8O_8P$ $(M+H)^+$ 571.2393. Found 571.2386. HPLC: $t_R = 23.019$ min, 95.64%.

(±)-9-[(1-Aminomethyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono) methoxy)propyl]-adenine (37d). A solution of **36d** (67 mg, 0.062 mmol) in acetonitrile (10 mL) was treated with 0.2 M HCl (0.5 mL) and stirred for 16 h at room temperature. It was diluted with water (150 mL) and extracted with ethyl acetate (2×). The aqueous layer was concentrated to dryness to give **37d** as a gum. The product was dissolved in 3.5 mL of water and its concentration measured to be 13.07 mM (74%) by UV at 259 nm: ^1H NMR (D_2O): δ 8.32 (s, 1H), 8.31 (s, 1H), 5.57–5.43 (m, 4H), 5.03–4.91 (m, 1H), 3.78–3.45 (m, 5H), 3.30–3.20 (m, 1H), 2.43–2.29 (m, 1H), 2.25–2.12 (m, 1H), 1.08 (s, 9H), 1.07 (s, 9H). HRMS calcd for $C_{22}H_{37}N_6O_8P$ $(M+H)^+$ 545.2488. Found 545.2476. HPLC: $t_R = 18.720$ min, 95.61%.

(±)-9-[(1-(α-Hydroxy)ethyl)(3-(di-*tert*-butylcarbonyloxymethylphospho-no)methoxy)propyl]-adenine (37e). It was prepared from **36e** (21 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37e** as a colorless oil (yield, 72%): ^1H NMR (a mixture of diastereomers, $CDCl_3$): δ 8.29, 8.28, 7.96, 7.94 (4s, 2H), 6.06–5.65 (m, 7H), 4.64–4.14 (m, 2H), 3.89–3.50 (m, 3H), 3.14–3.00 (m, 1H), 2.37–2.17 (m, 2H), 1.33, 1.05 (d, $J = 6.7$ Hz each, 3H), 1.234, 1.231 (2s, 18H). IR (neat, cm^{-1}) 3321, 3019, 1753, 1635, and 1216. HRMS calcd for $C_{23}H_{38}N_5O_9P$ $(M+H)^+$ 560.2485. Found 560.2484. HPLC: $t_R = 21.865$ min, 97.66%.

(±)-9-[(1-Methyl)(3-(di-*tert*-butylcarbonyloxymethylphosphono)meth-oxy)propyl]adenine (37f). It was prepared from **36f** (127 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37f** as a colorless oil (yield, 97%): ^1H NMR ($CDCl_3$): δ 8.32 (s, 1H), 7.88 (s, 1H),

5.75–5.64 (m, 6H), 4.85–4.75 (m, 1H), 3.75 (d, J = 7.9 Hz, 2H), 3.60–3.52 (m, 1H), 3.35–3.24 (m, 1H), 2.46–2.32 (m, 1H), 2.24–2.10 (m, 1H), 1.67 (d, J = 6.8 Hz, 3H), 1.23 (s, 9H), 1.22 (s, 9H). IR (neat, cm^{-1}) 3020, 2981, 1751, 1630, 1478, and 1216. HRMS calcd for $C_{22}H_{36}N_5O_8P$ $(M+H)^+$ 530.2379. Found 530.2356. HPLC: t_R = 23.477 min, 99.03%.

(±)-9-[(1-Fluoromethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)propyl]-adenine (37g). It was prepared from **36g** (40 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37g** as a light yellow oil (yield, 96%): ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 1H), 7.96 (s, 1H), 5.79 (s, 2H), 5.76–5.64 (m, 4H), 5.13–4.60 (m, 5H), 3.81 (d, J = 7.8 Hz, 2H), 3.72–3.63 (m, 1H), 3.38–3.30 (m, 1H), 2.50–2.36 (m, 1H), 2.35–2.20 (m, 1H), 1.32 (d, J = 6.3 Hz, 6H), 1.31 (d, J = 6.4 Hz, 6H). IR (neat, cm^{-1}) 3334, 2987, 1759, 1646, 1599, and 1268. HRMS calcd for $C_{20}H_{31}FN_5O_{10}P$ $(M+H)^+$ 552.1870. Found 552.1847. HPLC: t_R = 21.739 min, 98.59%.

(±)-9-[(1-Methylene)(3-(di-*tert*-butylcarbonyloxymethylphosphono)methoxy)propyl]-adenine (37h) It was prepared from **36h** (135 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37h** as a colorless oil (yield, 95%): ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H), 7.94 (s, 1H), 5.79 (s, 2H), 5.73–5.63 (m, 4H), 5.48 (s, 1H), 5.29 (s, 1H), 3.80 (d, J = 7.9 Hz, 2H), 3.67 (t, J = 6.2 Hz, 2H), 3.11 (t, J = 6.2 Hz, 2H), 1.22 (s, 18H). IR (neat, cm^{-1}) 3019, 2981, 1751, 1633, and 1216. HRMS calcd for $C_{22}H_{34}N_5O_8P$ $(M+H)^+$ 528.2223. Found 528.2207. HPLC: t_R = 23.029 min, 95.79%.

(±)-9-[(1-Hydroxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)-propyl]adenine (37i). It was prepared from **36i** (122 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to give **37i** as a colorless film (yield, 69%): ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 7.90 (s, 1H), 5.73–5.58 (m, 6H), 4.87 (hept, J = 6.2 Hz, 2H), 4.72–4.62 (m, 1H), 4.03 (bs, 2H), 3.88–3.69 (m, 2H), 3.65–3.57 (m, 1H), 3.23–3.14 (m, 1H), 2.26–2.17 (m, 2H), 1.25, 1.24 (2d, J = 6.3 each, 12H). IR (neat, cm^{-1}) 3330, 2984, 1759, 1645, 1601, and 1472. HRMS calcd for $C_{20}H_{32}N_5O_{11}P$ $(M+H)^+$ 550.1914. Found 550.1930. HPLC: t_R = 20.352 min, 97.44%.

(±)-9-[(1-Methoxymethyl)(3-(di-isopropyloxycarbonyloxymethylphosphono)methoxy)-propyl]adenine (37j). It was prepared from **36j** (60 mg) with the same procedure as given for **37a**. The crude product was purified on a silica gel column using chloroform:methanol (1:0 to 9:1) as eluent to

give **37j** as a colorless oil (yield, 99%): ^{1}H NMR ($CDCl_3$): δ 8.30 (s, 1H), 7.96 (s, 1H), 6.09 (s, 2H), 5.81–5.62 (m, 4H), 5.03–4.81 (m, 3H), 3.95 (dd, J = 10.0, 6.4 Hz, 1H), 3.80 (d, J = 7.7 Hz, 2H), 3.72–3.58 (m, 2H), 3.40–3.30 (m, 1H), 3.32 (s, 3H), 2.46–2.32 (m, 1H), 2.32–2.20 (m, 1H), 1.32 (d, J = 6.2 Hz, 12H). IR (neat, cm^{-1}) 3020, 1761, 1631, and 1216. HRMS calcd for $C_{21}H_{34}N_5O_{11}P$ $(M+H)^+$ 564.2070. Found 564.2060. HPLC: t_R = 22.123 min, 96.91%.

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