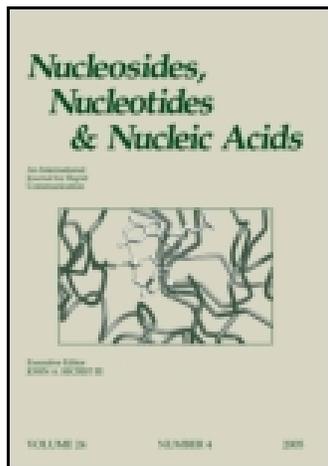


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## Nucleosides, Nucleotides and Nucleic Acids

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### Synthesis of 9-[1-(1-Hydroxyethyl)-3-(Phosphonomethoxy)Propyl] Adenine and Prodrug as Possible Antiviral Agents

Ajit Ghosh<sup>a</sup>, Pooran Chand<sup>a</sup>, Yahya El-Kattan<sup>a</sup>, Minwan Wu<sup>a</sup>, Tsu-Hsing Lin<sup>a</sup>, Satish Vadlakonda<sup>a</sup>, Pravin L. Kotian<sup>a</sup> & Yarlagadda S. Babu<sup>a</sup>

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## SYNTHESIS OF 9-[1-(1-HYDROXYETHYL)-3-(PHOSPHONOMETHOXY)PROPYL] ADENINE AND PRODRUG AS POSSIBLE ANTIVIRAL AGENTS

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

□ *The appropriately protected C-1'-hydroxyethyl-3-hydroxypropyl-N<sup>9</sup>-adenine nucleoside was prepared from 1-pivaloyloxy-5-tert-butylidiphenylsilyloxy-3-pentanol and adenine through the Mitsunobu reaction. One of the terminal hydroxyls was converted to the phosphonomethoxy derivative and the prodrug.*

**Keywords** Acyclic nucleosides; Prodrugs; Antiviral

### INTRODUCTION

Since the discovery of phosphonomethyl ether functionality as an important replacement of phosphoric acid ester, a lot of work has been done on acyclic nucleosides.<sup>[1,2]</sup> As a result, a number of adenine derivatives (Chart 1), PMEA (**1a**), PMPA (**1c**), HPMPA (**1e**), and FPMPA (**1f**); 2,6-diaminopurine derivatives, PMEDAP (**1g**) and HPMPDAP (**1h**); and guanine derivatives, PMEG (**2a**), PMPG (**2b**), and HPMPG (**2c**) have been extensively studied.<sup>[3–6]</sup> Prodrugs of two phosphonomethyl adenine derivatives, adefovir dipivoxil (**1b**) and tenofovir disoproxil (**1d**), were approved by FDA for HBV and HIV infections, respectively.

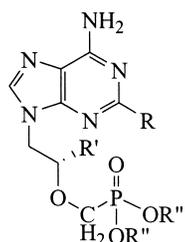
Most of these compounds have no substitution on the acyclic moiety or have substitutions such as methyl, hydroxymethyl and fluoromethyl coming from the C-2' position of the acyclic moiety. There are only a few reports

Dedicated to the memory of John A. Montgomery.

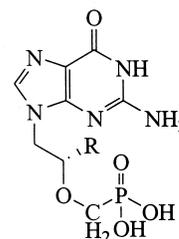
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- 1a**, R=H, R'=H, R''=H (PMEA)  
**1b**, R=H, R'=H, R''=CH<sub>2</sub>OC(O)C(CH<sub>3</sub>)<sub>3</sub> (Adefovir dipivoxil)  
**1c**, R=H, R'=CH<sub>3</sub>, R''=H (PMPA)  
**1d**, R=H, R'=CH<sub>3</sub>, R''=CH<sub>2</sub>OC(O)OCH(CH<sub>3</sub>)<sub>2</sub> (Tenofovir disoproxil)  
**1e**, R=H, R'=CH<sub>2</sub>OH, R''=H (HPMPA)  
**1f**, R=H, R'=CH<sub>2</sub>F, R''=H (FPMPA)  
**1g**, R=NH<sub>2</sub>, R'=H, R''=H (PMEDAP)  
**1h**, R=NH<sub>2</sub>, R'=CH<sub>2</sub>OH, R''=H (HPMPDAP)



- 2a**, R=H (PMEG)  
**2b**, R=CH<sub>3</sub> (PMPG)  
**2c**, R=CH<sub>2</sub>OH (HPMPG)

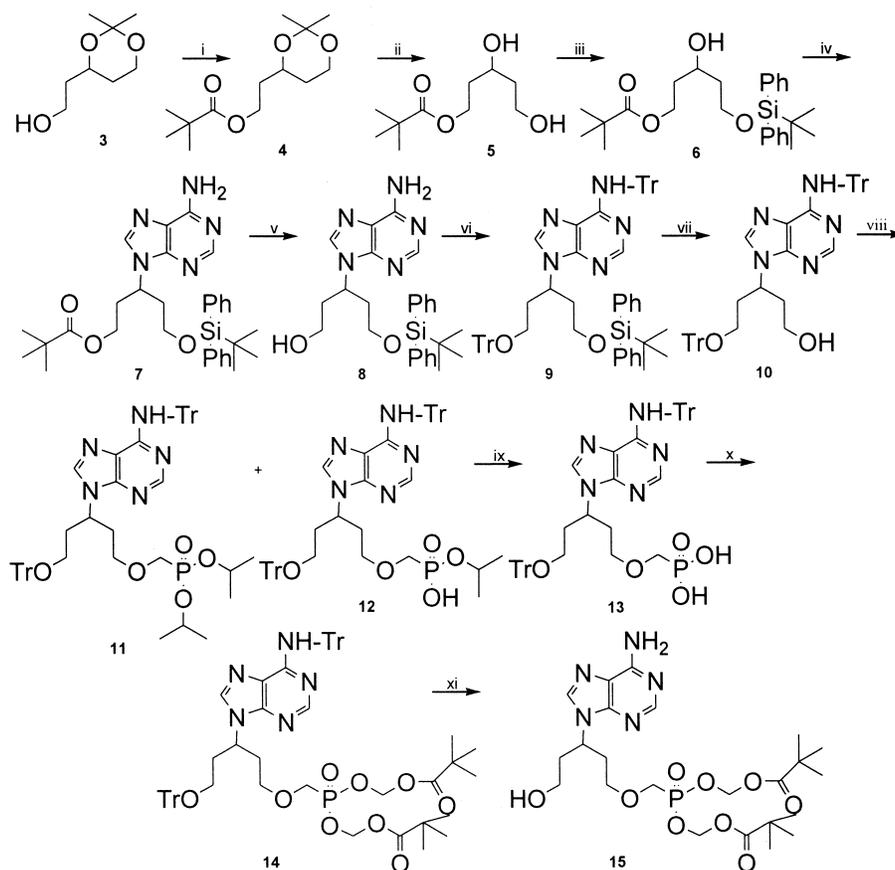
#### CHART 1

on C-1' position substitutions, and most of those reports describe only the acyclic nucleosides.<sup>[7–10]</sup> Phosphonomethyl ether derivatives have not been prepared for the compounds branching from the C-1' position except when substitution is methyl. In our preceding papers we have disclosed the compounds substituted at the C-1' position keeping the number of spacer atoms between the phosphorus of the phosphonomethyl group and joining nitrogen of adenine as 5 in one case and 4 in other case. In one of the papers, when we have 5 spacer atoms, the substitutions from the C-1' position are methyl derivatives, such as methyl, hydroxymethyl, fluoromethyl, amino methyl, azidomethyl, methoxymethyl, etc. In another paper, we have 4 spacer atoms and the substitutions from the C-1' position are ethyl, hydroxyethyl, aminoethyl, azidoethyl, and methoxyethyl.

The compounds in this report have the number of spacer atoms between the adenine nitrogen and phosphorus as 5 while the substituent, hydroxyethyl is coming from the C-1' position of the acyclic moiety. The synthesis of the corresponding nucleoside, phosphonomethyl ether derivative, and the prodrug will be described.

## RESULTS AND DISCUSSION

All synthesized compounds are racemic mixtures. The synthesis started from known racemic 3,5-isopropylidene-1,3,5-pentanetriol (**3**, Scheme 1).<sup>[11]</sup> The hydroxyl group of **3** was protected with the pivaloyl group by the reaction of pivaloyl chloride in pyridine and the isopropylidene was removed from the resultant **4** with 80% acetic acid. The primary hydroxyl group of dihydroxy compound **5** was selectively protected with the *tert*-butyldiphenylsilyl



**SCHEME 1** Reagents: i) Pivaloyl chloride, pyridine; ii) 80% aq. AcOH; iii) TBDPS-Cl, imidazole; iv) Adenine,  $\text{Ph}_3\text{P}$ , DEAD; v) NaOMe, MeOH; vi) Tr-Cl, pyridine; vii)  $\text{N}(\text{n-Bu})_4\text{F}$ , THF; viii) NaH, TSO- $\text{CH}_2\text{-P}(\text{O})(\text{O-iPr})_2$ ; ix) TMSI,  $\text{Et}_3\text{N}$ ; x)  $\text{ClCH}_2\text{OC}(\text{O})\text{C}(\text{CH}_3)_3$ ,  $\text{Et}_3\text{N}$ ; xi) HCl.

(TBDPS) group on reaction with TBDPS-Cl and the secondary hydroxyl of resultant **6** underwent the Mitsunobu reaction with adenine, triphenylphosphine and diethylazodicarboxylate (DEAD) in dioxane to give compound **7**. The product obtained was identified as the  $\text{N}^9$  derivative based upon the literature reports<sup>[12]</sup> and UV spectrum at different pH, which did not show any shift in the absorption.<sup>[13]</sup> We then had to remove one of the protecting groups from the hydroxyls to prepare the phosphonomethyl ether derivatives. We chose to remove the pivaloyl because we had to prepare prodrugs which are base sensitive and the pivaloyl group could not have been removed at the end in the presence of the prodrug. Removal of the pivaloyl group from **7** with sodium methoxide in methanol gave **8**. From our previous experience, it was necessary: a) to protect the amino of adenine for the preparation of the phosphonomethyl ether derivative, and b) not to have

the TBDPS group as the protecting group on the hydroxyl. Therefore, we chose to protect both the amino and the free hydroxyl with a group which could easily come off under very mild acidic conditions. We decided to protect both groups with the trityl group and the tritylation of compound **8** was achieved with trityl chloride in pyridine at 70°C in several days after adding a lot of excess of the reagent and also triethylamine base. Compound **9** was obtained although in low yield. The TBDPS group of **9** was removed with tetrabutylammonium fluoride (TBAF) and the resultant compound **10** was taken for the reaction with *p*-toluenesulfonyloxymethyl phosphonate in the presence of sodium hydride to give the desired compound **11** and also **12**, which was the mono-isopropoxy derivative. Both could be easily separated by silica gel column chromatography. Phosphonomethyl derivative **13** was obtained from **11** and **12** with a TMS-iodide reaction in the presence of triethylamine to avoid the deprotection of trityl, because of the acid generated from TMS-iodide alone. The formation of the prodrug of **13** with chloromethylpivalate in the presence of triethylamine as base occurred over several days and the resultant **14** was finally deprotected under mild acidic conditions (HCl) to give the desired target **15**.

### BIOLOGICAL ACTIVITY

These compounds showed poor activity against HCV virus in replicon assay.<sup>[14]</sup>

### EXPERIMENTAL

All reagents and solvents were purchased from Aldrich and used as received. <sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded on a Bruker 300 MHz instrument. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) referenced to TMS at 0.00 or the respective deuterated solvent peak. <sup>31</sup>P NMR chemical shifts are reported with respect to D<sub>3</sub>PO<sub>4</sub> in D<sub>2</sub>O as the external standard. 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<sup>-1</sup> 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, USA. The TLC solvent system CMA-80 and CMA-50 refers to chloroform:methanol:conc. NH<sub>4</sub>OH (80:18:2) and chloroform:methanol:conc. NH<sub>4</sub>OH (50:40:10), respectively. The non-UV active compounds were visualized by charring the TLC plate sprayed with an ammonium molybdate/cesium sulfate spray prepared by dissolving conc.

H<sub>2</sub>SO<sub>4</sub> (22.4 mL), CeSO<sub>4</sub> (45 mg), (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>•4 H<sub>2</sub>O (7 g) in 100 mL water. The olefin compounds were visualized by using a KMnO<sub>4</sub> spray.

**(±)-1-Pivaloyl-3,5-isopropylidene-pentan-1,3,5-triol (4).** To a solution of 3,5-isopropylidene-pentan-1,3,5-triol<sup>[11]</sup> **3** (6.2 g, 38.69 mmol) in pyridine (125 mL) was added pivaloyl chloride (5.7 mL, 46.43 mmol) and the resulting reaction mixture was stirred at room temperature for 17 h. After evaporation of most of the solvent, water (200 mL) was added and then extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated to dryness to give 9.35 g of **4** (98%) as an oil: <sup>1</sup>HNMR (CDCl<sub>3</sub>): 4.13–4.17 (m, 2H), 3.92–4.04 (m, 2H), 3.80–3.89 (m, 1H), 1.74–1.81 (m, 2H), 1.54–1.72 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H) and 1.19 (s, 9H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>): 2959, 2918, 2872, 1726, 1458, and 1369.

**(±)-5-Pivaloylpentan-1,3,5-triol (5).** A mixture of **4** (10 g, 40.92 mmol) and 80% aqueous acetic acid (125 mL) was heated at 50–55°C for 15 h. The reaction mixture was evaporated to dryness under vacuum and then co-evaporated with toluene (3 × 35 mL) to give 8.0 g (96%) of **5** as an oil: <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 4.48 (d, *J* = 5.65 Hz, 1H), 4.34 (t, *J* = 5.08 Hz, 1H), 4.0–4.12 (m, 2H), 3.60–3.71 (m, 1H), 3.45–3.51 (m, 2H), 1.43–1.72 (m, 4H) and 1.12 (s, 9H). IR (KBr, cm<sup>-1</sup>): 3405, 2963, 1722, 1477, 1288, 1166, and 1057.

**(±)-1-tert-Butyldiphenylsilyl-5-pivaloylpentan-1,3,5-triol (6).** To a solution of **5** (8.0 g, 39.16) and imidazole (3.0 g, 43.07 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (170 mL) was added TBDPS-chloride (11.20 mL, 39.16 mmol) over a period of 1 h at room temperature. After stirring for 1 more h, the solvent was removed and the residue was purified on a silica gel column using ethyl acetate:hexanes as eluent to provide 13 g (75%) of **6**, as a colorless oil: <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 7.57–7.67 (m, 4H), 7.36–7.47 (m, 6H), 4.55 (d, *J* = 5.8 Hz, 1H), 4.06–4.11 (m, 2H), 3.66–3.85 (m, 3H), 1.53–1.73 (m, 4H), 1.11 (s, 9H), and 0.97 (s, 9H). IR (KBr, cm<sup>-1</sup>): 3514, 2959, 2858, 1726, 1473, and 1428. HRMS calcd for C<sub>26</sub>H<sub>38</sub>O<sub>4</sub>Si (M+H)<sup>+</sup> 443.2617. Found 443.2598.

**(±)-9-[(1-tert-Butyldiphenylsilyloxyethyl)(3-pivaloyloxy)propyl]adenine (7).** To a stirring mixture of **6** (10.0 g, 22.59 mmol), triphenylphosphine (11.85 g, 45.18 mmol), and adenine (6.1 g, 45.18 mmol) in anhydrous dioxane (250 mL) was added a solution of DEAD (7.15 mL, 45.18 mmol) in dioxane (50 mL) over a period of 3 h at room temperature. The reaction mixture was further stirred for 19 h, then filtered through a short pad of Celite and the filtrate concentrated. The residue was purified on a silica gel column using chloroform:methanol (100:0 to 99:2) as eluent to give the

desired product **7**, but it was contaminated with tri-phenylphosphine oxide and the DEAD derivative. Two more purifications on silica gel gave 8.8 g of pure **7** (70%), as a white solid, mp 137–139°C:  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ): 8.13 (s, 1H), 8.09 (s, 1H), 7.22–7.66 (m, 10H), 7.21 (br, 2H, exchangeable with  $\text{D}_2\text{O}$ ), 4.92 (m, 1H), 3.64–3.98 (m, 2H), 3.24–3.58 (m, 2H), 2.06–2.46 (m, 4H), 1.05 (s, 9H), 0.9 (s, 9H). IR (KBr,  $\text{cm}^{-1}$ ): 3313, 3153, 2962, 1711, 1667, 1601, and 1472. MS ( $\text{ES}^+$ ) 560.31 ( $\text{M}+\text{H}$ ). Anal. calcd for  $\text{C}_{31}\text{H}_{41}\text{N}_5\text{O}_3\text{Si}$ : C, 66.51; H, 7.38; N, 12.51. Found: C, 66.26; H, 7.37; N, 12.70.

( $\pm$ )-**9**-[(1-*tert*-Butyldiphenylsilyloxyethyl)(3-hydroxy)propyl]adenine (**8**). To a solution of **7** (7.6 g, 13.57 mmol) in anhydrous MeOH (300 mL) was added NaOMe (5.4 M solution in MeOH, 5.0 mL, 27.15 mmol), and then the reaction mixture was stirred at room temperature for 17 h. The mixture was neutralized to pH 7.0 with acetic acid and concentrated. The residue was purified on a silica gel column eluting with chloroform:methanol (100:0 to 95:5) to provide 4.2 g (65%) of **8** as a white solid, mp 144–147°C:  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ): 8.09 (s, 1H), 8.07 (s, 1H), 7.24–7.56 (m, 10H), 7.19 (br, 2H, exchangeable with  $\text{D}_2\text{O}$ ), 4.85 (m, 1H), 4.55 (t,  $J = 4.7$  Hz, 1H exchangeable with  $\text{D}_2\text{O}$ ), 3.42–3.56 (m, 1H), 3.1–3.42 (m, 3H), 2.30–2.46 (m, 1H), 1.92–2.44 (m, 3H), 0.89 (s, 9H). IR (KBr,  $\text{cm}^{-1}$ ): 3341, 3185, 2929, 2854, 1668, 1607, 1412, and 1317. MS ( $\text{ES}^+$ ) 476.33 ( $\text{M}+\text{H}$ ). Anal. calcd for  $\text{C}_{26}\text{H}_{33}\text{N}_5\text{O}_2\text{Si}\cdot 0.5 \text{H}_2\text{O}$ : C, 64.43; H, 7.07; N, 14.44. Found: C, 64.52; H, 7.14; N, 14.16.

( $\pm$ )-**9**-[(1-*tert*-Butyldiphenylsilyloxyethyl)(3-trityloxy)propyl]- $\text{N}^6$ -trityl-adenine (**9**). To a solution of **8** (1.9 g, 3.99 mmol) and DMAP (180 mg) in anhydrous pyridine (100 mL) was added tritylchloride (4.4 g, 15.97 mmol), and then the reaction mixture was heated at 65°C for 16 h. More tritylchloride (4.4 g) was added and heated another 8 h at 65°C. Another 4.4 g of trityl chloride and triethyl amine (1.0 mL) was added and heated for 17 h. The solvent was removed and the residue was purified on a silica gel column eluting with hexanes:ethanol (100:0 to 70:30) to provide 2.1 g (54%) of **9** as a white solid, mp 202–204°C:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 7.90 (s, 1H), 7.14–7.62 (m, 41H), 6.88 (s, 1H), 4.95–5.12 (m, 1H), 3.55–3.66 (m, 1H), 3.26–3.37 (m, 1H), 3.04–3.14 (m, 1H), 2.63–2.74 (m, 1H), 2.29–2.51 (m, 2H), 2.0–2.24 (m, 2H), and 1.63 (s, 9H). IR (KBr,  $\text{cm}^{-1}$ ): 3417, 3055, 2855, 1602, 1469, and 1442. MS ( $\text{ES}^+$ ) 960.27 ( $\text{M}+\text{H}$ ). Anal. calcd for  $\text{C}_{64}\text{H}_{61}\text{N}_5\text{O}_2\text{Si}\cdot 0.5 \text{H}_2\text{O}$ : C, 79.30; H, 6.44; N, 7.23. Found: C, 79.33; H, 6.39; N, 7.25.

( $\pm$ )-**9**-[(1-Trityloxyethyl)(3-hydroxy)propyl]- $\text{N}^6$ -trityl-adenine (**10**). To a solution of **9** (2 g, 2.08 mmol) in THF (80 mL) was added 1 M solution of TBAF in THF (2.2 mL, 2.2 mmol) and then the reaction mixture was

stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue was purified on a silica gel column eluting with chloroform:methanol (100:0 to 98:2) to provide 1.2 g (80%) of **10** as a white solid, mp 160–170°C: <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.18 (s, 1H), 7.83 (s, 1H), 7.1–7.4 (m, 31H), 4.84 (m, 1H), 4.54 (t, *J* = 5.0 Hz, 1H) 3.1–3.4 (m, 2H), 2.62–2.88 (m, 2H), 1.88–2.44 (m, 4H). IR (KBr, cm<sup>-1</sup>): 3054, 2926, 1605, 1470, 1444, and 1216. HRMS calcd for C<sub>48</sub>H<sub>43</sub>N<sub>5</sub>O<sub>2</sub> (M+H)<sup>+</sup> 722.3495. Found 722.3528. Anal. calcd for C<sub>48</sub>H<sub>43</sub>N<sub>5</sub>O<sub>2</sub>•0.2 CHCl<sub>3</sub>: C, 77.62; H, 5.83; N, 9.39. Found: C, 77.32; H, 5.82; N, 9.34.

(±)-**9-[(1-Trityloxyethyl)(3-diisopropylphosphonomethoxy)propyl]-N<sup>6</sup>-trityladenine (11)** and (±)-**9-[(1-Trityloxyethyl)(3-mono-isopropylphosphonomethoxy)propyl]-N<sup>6</sup>-trityladenine (12)**. To a solution of **10** (0.54 g, 0.748 mmol) in DMF (6 mL) was added NaH (120 mg, 60% dispersion in oil, 2.99 mmol) under N<sub>2</sub> atmosphere. After stirring the mixture for 0.5 h at room temperature, a solution of p-toluenesulfonyloxymethyl phosphonate in DMF (1.0 mL) was added over a period of 5 min. The reaction mixture was stirred at room temperature for 18 h and then neutralized slowly with acetic acid at 0–5°C. After removing most of the solvent, the mixture was extracted with chloroform (60 mL), the organic layer washed with water (2 × 30 mL), dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (100:0:0 to 70:25:5) as eluent to provide 0.204 g (30%) of **11** as a gum: <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.18 (s, 1H), 7.8 (s, 1H), 7.13–7.33 (m, 31H), 4.84 (m, 1H), 4.46–4.59 (m, 2H), 3.62 (d, *J* = 7.9 Hz, 2H), 3.20–3.46 (m, 4H), 1.98–2.8 (m, 4H), 1.14–1.20 (m, 12H). IR (KBr, cm<sup>-1</sup>): 3417, 3057, 2976, 1605, 1471, and 1220. HRMS calcd for C<sub>55</sub>H<sub>58</sub>N<sub>5</sub>O<sub>5</sub>P (M+H)<sup>+</sup> 900.4254. Found 900.4269. Anal. calcd for C<sub>55</sub>H<sub>58</sub>N<sub>5</sub>O<sub>5</sub>P•0.5 H<sub>2</sub>O: C, 72.66; H, 6.54; N, 7.70. Found: C, 72.55; H, 6.37; N, 7.72. Further elution of the column with CMA-80 afforded 0.200 g (31%) of **12** as a light yellow gum: MS (ES<sup>-</sup>) 856.04 (M–H).

(±)-**9-[(1-Trityloxyethyl)(3-phosphonomethoxy)propyl]-N<sup>6</sup>-trityladenine (13)**. To a solution of **11** (0.13 g, 0.144 mmol) and **12** (0.2 g, 0.233 mmol) in DMF (6.0 mL) were added Et<sub>3</sub>N (0.4 mL) and TMSI (1.07 mL, 7.54 mmol) and stirred at room temperature for 13 h (in the dark). To this reaction mixture was added TEAB (35 mL), water (60 mL), and chloroform (100 mL) and stirred at room temperature for 1.5 h. The chloroform layer was separated and the water layer was re-extracted with chloroform (3 × 30 mL). Combined chloroform extracts were dried over MgSO<sub>4</sub>, filtered, and the filtrate concentrated. The residue was purified on a silica gel column eluting with chloroform:methanol:NH<sub>4</sub>OH (100:0:0 to 50:40:10) to provide 0.15 g (48%) of **13**: <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.22 (s, 1H), 7.8 (s, 1H), 7.06–7.35 (m, 31H), 4.74–4.84 (m, 1H), 3.0–3.6 (m, 6H), 2.56–2.84 (m, 2H), 1.95–2.2

(m, 2H). IR (KBr,  $\text{cm}^{-1}$ ): 3415, 3028, 2876, 1605, 1472, 1446, and 1219. HRMS calcd for  $\text{C}_{49}\text{H}_{46}\text{N}_5\text{O}_5\text{P}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 816.3315. Found 816.3331.

**(±)-9-[(1-Trityloxyethyl)(3-di-*tert*-butylcarbonyloxymethylphosphonmethoxy)propyl]-N<sup>6</sup>-trityladenine (14).** To a solution of **13** (0.14 g, 0.17 mmol) in DMF (6 mL) were added  $\text{Et}_3\text{N}$  (6.2 mL, 42.89 mmol) and chloromethyl pivalate (3.1 mL, 21.45 mmol) under  $\text{N}_2$  atmosphere and the reaction mixture stirred at room temperature for 4 days. The mixture was diluted with water (40 mL) and then extracted with chloroform (3 × 30 mL). Combined chloroform extracts were dried over  $\text{MgSO}_4$ , filtered, and the filtrate concentrated. The residue was purified on a silica gel column using ethyl acetate:hexanes:methanol (90:10:0 to 50:49:1) to provide 0.093 g (52%) of **14** as a light yellow solid, mp 73–75°C:  $^1\text{H}$ NMR ( $\text{DMSO-d}_6$ ): 8.16 (s, 1H), 7.82 (s, 1H), 7.12–7.33 (m, 31H), 5.60 (s, 2H), 5.56 (s, 2H), 4.72–4.87 (m, 1H), 3.79 (d,  $J = 7.9$  Hz, 2H), 3.15–3.48 (m, 4H), 1.95–3.0 (m, 4H), and 1.11 (bs, 18H). IR (KBr,  $\text{cm}^{-1}$ ): 3419, 3028, 2973, 1753, 1605, 1473, 1448, and 1280. HRMS calcd for  $\text{C}_{61}\text{H}_{66}\text{N}_5\text{O}_9\text{P}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 1044.4676. Found 1044.4629. Anal. calcd for  $\text{C}_{61}\text{H}_{66}\text{N}_5\text{O}_9\text{P}\cdot 0.25$  EtOAc: C, 69.84; H, 6.42; N, 6.56. Found: C, 69.61; H, 6.32; N, 6.47.

**(±)-9-[(1-Hydroxyethyl)(3-di-*tert*-butylcarbonyloxymethylphosphonmethoxy)propyl]adenine (15).** A mixture of **14** (0.16 g, 0.15 mmol), HCl (2.0 N, 15 mL), and MeCN (15 mL) was stirred at room temperature for 15 h. The reaction mixture was neutralized with  $\text{Et}_3\text{N}$ , and then diluted with water (40 mL). After evaporating the organic volatiles, the residue was extracted with chloroform (3 × 70 mL), dried ( $\text{MgSO}_4$ ), filtered, and the filtrate evaporated to dryness. The residue was purified over a silica gel column eluting with chloroform:methanol (100:0 to 96:4). First, a compound (60 mg) (49%) with one trityl group still attached was obtained. Further elution of the column gave 24 mg (28%) of the desired **15** as a gum:  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.27 (s, 1H, aromatic), 7.89 (s, 1H, aromatic), 6.17 (brs, 2H,  $\text{NH}_2$ ), 5.58–5.79 (m, 4H, 2 ×  $\text{OCH}_2\text{O}$ ), 4.92 (m, 1H,  $\text{NCH}$ ), 3.75 (d,  $J = 7.9$  Hz, 2H,  $\text{OCH}_2\text{P}$ ), 3.52–3.64 (m, 2H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 3.1–3.42 (m, 2H,  $\text{CH}_2\text{OH}$ ), 2.11–2.56 (m, 4H,  $\text{NCH}(\text{CH}_2)_2$ ), 1.22 (s, 18H, *t*-butyl). IR (KBr,  $\text{cm}^{-1}$ ): 3341, 2974, 2876, 1752, 1646, 1611, 1479. MS ( $\text{ES}^+$ ) 582.43 ( $\text{M}+\text{Na}$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{38}\text{N}_5\text{O}_9\text{P}\cdot 0.75$   $\text{H}_2\text{O}$ : C, 48.20; H, 6.94; N, 12.22. Found: C, 48.26; H, 7.04; N, 11.94.

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