count was adjusted to (3-4) × $10^5$ platelets/μL.

The PICA was used to obtain aggregation data as follows. Fibrinogen (1.2 μg) in 100 μL of buffer was added to 0.9 mL of platelet suspension. The cuvette was placed in the PICA, 37 °C, with stirring at 1100 rpm. After 15 s, the vehicle (95% ethanol) or test compound in vehicle was added, and 1 min later the agonist (collagen, 5 μg in 5 μL of buffer) was added. Aggregation was recorded for 5 min, the IC% and $IC_{50}$ being determined as described for ADP-stimulated aggregation. Luminescence data, related to calcium flux, were obtained in parallel from the above experiment and will be reported elsewhere.

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# Synthesis and Antiviral Activity of Methyl Derivatives of 9-[2-(Phosphonomethoxy)ethyl]guanine[1]

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A number of methyl derivatives of 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG, 1) have been synthesized and tested in vitro for anti-herpes and anti-human immunodeficiency virus (HIV) activity. Among these analogues, (*R*)-2′-methyl-PMEG [(*R*)-3] and 2′,2′-dimethyl-PMEG (7) demonstrated potent anti-HIV activity in the XTT assay with $EC_{50}$ values of 1.0 and 2.6 μM, respectively. The corresponding (*S*)-2′-methyl-PMEG [(*S*)-3] was found to be less potent against HIV. In addition, the (*R*) and (*S*) enantiomers of 9-[3-hydroxy-2-(phosphonomethoxy)propyl]guanine (HPMPG, 8) were prepared for comparison of biological activity, and shown to be active and equipotent against herpesviruses, but inactive against HIV.

## Introduction

With the increasing worldwide problems of viral diseases, particularly acquired immunodeficiency syndrome (AIDS),[2] there continues to be a significant need for safe and effective antiviral agents. Several approaches including chemical synthesis, natural products screening, and biotechnology have been utilized to identify compounds having antiviral activity.[3] Since the discovery of selective antiviral agents such as acyclovir (ACV)[4] and zidovudine (AZT),[5] nucleoside analogues have become one of the major classes of compounds that might meet the need. Many of these analogues are converted to their corresponding triphosphates in vitro and in vivo, and terminate elongation of polynucleotide synthesis or destabilize the structure of DNA or RNA when incorporated into the viral genome. Alternatively, the triphosphates may act as inhibitors of viral polymerase and inhibit viral replication. Preferential interaction of the nucleoside triphosphate analogue with viral enzymes instead of host enzymes is an important factor in determining the ultimate selectivity of these nucleoside derivatives.

Recently, analogues of phosphorylated nucleosides have been investigated for their potential as antiviral agents.[6] (*S*)-9-[3-Hydroxy-2-(phosphonomethoxy)propyl]adenine, ((*S*)-HPMPA), an acyclic nucleotide analogue reported by Holy and De Clercq,[7] is a representative of a new structural type of antiviral agent which possesses broad spectrum antiviral activity. Acyclic phosphonate nucleotides[8] are analogues of monophosphorylated nucleosides in which the furanose ring is replaced with an acyclic side chain and the $POCH_2$ unit of the monophosphate is replaced with a bioisostere, $PCH_2O$. These modifications lead to molecules which are chemically more stable than nucleoside monophosphate derivatives: nucleotide analogues such as HPMPA are not prone to enzymatic or chemical hydrolysis of the phosphonate group or to cleavage of the purine or pyrimidine base from the side chain. In cells, mono-

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(1) Part of this paper was presented at the 3rd International Conference on Antiviral Research, Brussels, Belgium, April 1990. Bronson, J. J.; Yu, K. L.; Kim, C. U.; Yang, H.; Brankovan, V.; Hitchcock, M. J. M.; Martin, J. C. Synthesis and Antiviral Activity of Substituted Derivatives of the Potent Antiviral Agent 9-[2-(Phosphonylmethoxy)ethyl]guanine (PMEG). The abstract was shown in *Antiviral Res. Suppl. 1*, 1990, 54.

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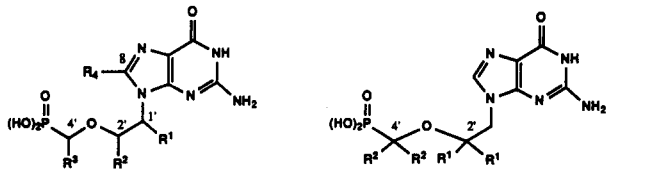
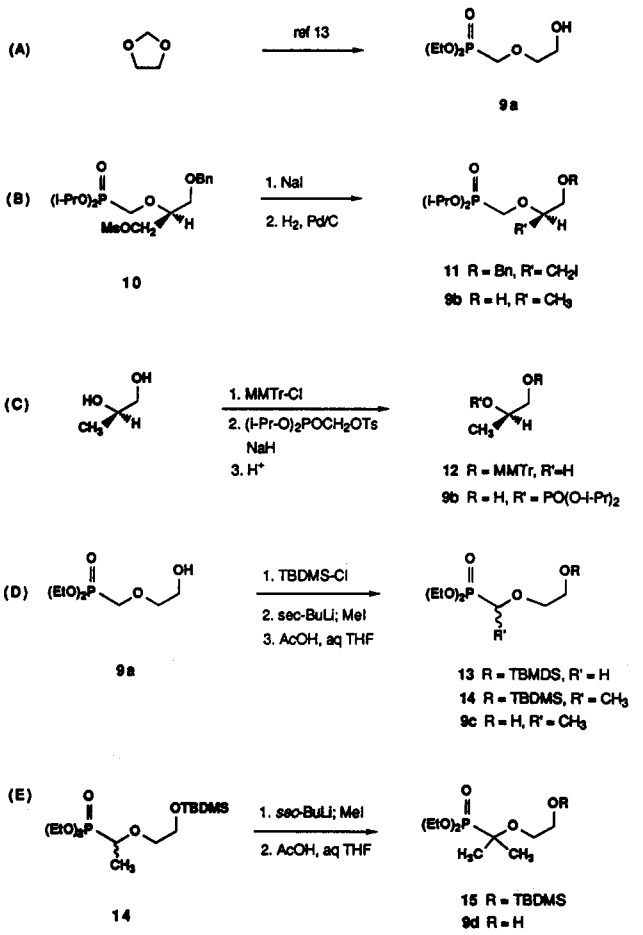
**Chart I**



1 PMEG: $R^1$-$R^4$ = H
2 1'-Methyl PMEG: $R^1$ = Me; $R^2$-$R^4$ = H
3 2'-Methyl PMEG: $R^2$ = Me; $R^1$, $R^3$, $R^4$ = H
4 4'-Methyl PMEG: $R^3$ = Me; $R^1$, $R^2$, $R^4$ = H
5 8-Methyl PMEG: $R^4$ = Me; $R^1$-$R^3$ = H
6 4',4'-Dimethyl PMEG: $R^1$ = H, $R^2$ = Me
7 2',2'-Dimethyl PMEG: $R^1$ = Me, $R^2$ = H
8 HPMPG: $R^2$ = $CH_2OH$; $R^1$, $R^3$, $R^4$ = H

phosphate analogues bypass the first step of phosphorylation and are converted sequentially to the corresponding di- and triphosphate analogues by cellular kinases. This distinct property gives the phosphonate derivatives a potential advantage over conventional nucleoside analogues, such as ACV and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), which require initial activation by viral kinases.[9] Among the phosphonate nucleotides, 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG)[10] (1) is the most potent, broad spectrum antiviral agent reported to date. In vitro, PMEG has demonstrated more potent activity than ganciclovir (DHPG)[11] against human cytomegalovirus (HCMV) ($EC_{50}$ values are 0.3 and 7.4 $\mu$M, respectively). In vivo, PMEG exerted antiviral efficacy at doses 10–50-fold lower than ACV in herpes simplex virus type 2 (HSV-2) infected mice. PMEG is active in vitro against a thymidine kinase (TK) deficient mutant of herpes simplex type 1 virus (HSV 1) ($EC_{50}$ 0.13 $\mu$M)[10] indicating that, as expected, the antiviral activity of this phosphonate derivative is viral thymidine kinase independent. However, the cytotoxicity of PMEG precludes it from being used as a selective agent ($CC_{50}$ 0.2 $\mu$M in CEM cells). In order to improve the therapeutic window of PMEG, several structure–activity relationship (SAR) studies have been reported.[12] In our continued efforts to study the SAR of PMEG, we have introduced methyl groups at various positions of the molecule to probe the steric requirements of its biological activity. This report presents the syntheses of the parent compound, PMEG, and the methyl PMEG analogues, and the in vitro biological activities of these nucleotide analogues.

**Scheme I**




## Chemistry

PMEG (1) and the proposed methyl-PMEG analogues **2–7** are illustrated in Chart I. The synthesis and biological activity of racemic 1′-methyl-PMEG (**2**) have been previously reported.[12b] For the synthesis of PMEG (**1**) and the side-chain methyl PMEG analogues, a general approach was employed which involves coupling of the appropriate heterocyclic base with a side-chain fragment bearing the phosphonomethyl ether group. The syntheses of the side-chain fragments **9a–d** are depicted in Scheme I. The side chain **9a**, required for the synthesis of PMEG, was prepared from commercially available 1,3-dioxolane as previously reported (Scheme IA).[10,13] For the synthesis

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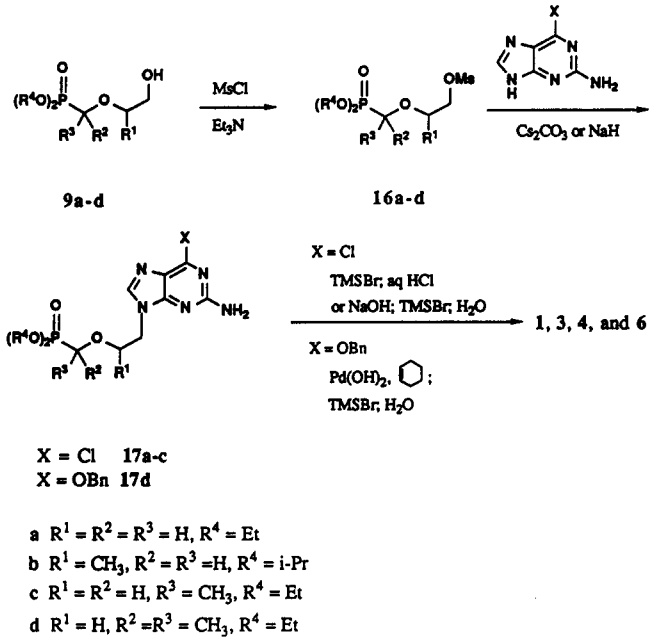
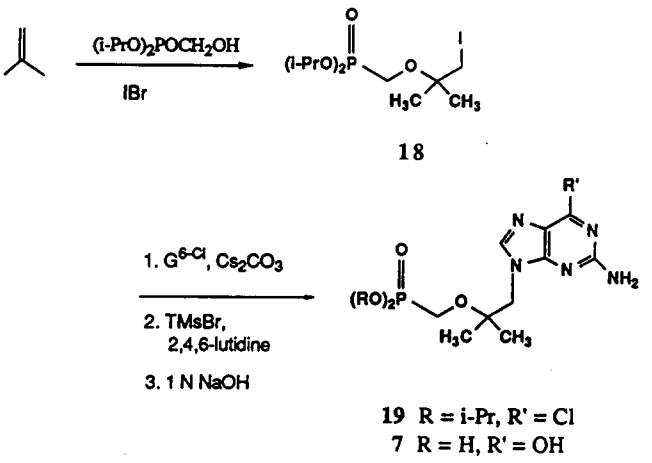
**Scheme II**




a $R^1 = R^2 = R^3 = H$, $R^4 = Et$
b $R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = i\text{-}Pr$
c $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = Et$
d $R^1 = H$, $R^2 = R^3 = CH_3$, $R^4 = Et$

of the acyclic chain of 2′-methyl-PMEG (**3**), mesylate **10**[14] was treated with sodium iodide in refluxing acetone to provide **11** in 89% yield; catalytic hydrogenation of iodide **11** followed by removal of the benzyl group using $Pd(OH)_2$ and cyclohexene[15] gave alcohol **9b** in 87% yield. Subsequently, we found that alcohol **9b** was more efficiently prepared on a large scale from (*R*)-1,2-propanediol[16] (Scheme IC). The primary hydroxyl group of (*R*)-1,2-propanediol was selectively protected as a monomethoxytrityl (MMTr) ether. Alkylation of the secondary hydroxyl group of **12** with diisopropyl [(*p*-tosyloxy)-methyl]phosphonate,[17] followed by removal of the MMTr protecting group with camphorsulfonic acid in methanol gave **9b**. For construction of the side chain of racemic 4′-methyl-PMEG (**4**), alcohol **9a** was first protected as its *tert*-butyldimethylsilyl (TBDMS) ether,[18] and the resulting phosphonate **13** was treated with 1.2 equiv of *sec*-butyllithium[19] and methyl iodide at −78 °C to afford the α-methylphosphonate **14** in 90% yield (Scheme ID). Hydrolysis of the TBDMS moiety of **14** with acetic acid in aqueous tetrahydrofuran proceeded smoothly to provide **9c**. Repeating the metalation–alkylation process with **14** (Scheme IE) gave α,α-dimethylphosphonate **15**, which was hydrolyzed to provide the acyclic fragment required for 4′,4′-dimethyl-PMEG, **9d**, in excellent yields.

**Scheme III**




Alcohols **9a–d** were treated with mesyl chloride and triethylamine to provide the corresponding mesylates **16a–d** (Scheme II) in good to excellent yields. Couplings of the mesylates with 2-amino-6-chloropurine or 6-*O*-benzylguanine in the presence of cesium carbonate or sodium hydride[14] provided the phosphonate esters **17a–d**. Ester cleavage of **17a** and **17b** with excess bromotrimethylsilane (TMSBr)[20] followed by hydrolysis of the halopurine to a guanine in aqueous HCl gave PMEG (**1**) and (*R*)-2′-methyl-PMEG, (*R*)-**3**, in good yields. The procedure used for the preparation of (*R*)-2′-methyl-PMEG was also utilized to prepare its enantiomer, (*S*)-2′-methyl-PMEG, (*S*)-**3**. The enantiomeric purity of (*R*)- and (*S*)-2′-methyl-PMEG was determined by HPLC using cupric sulfate and L-phenylalanine in 4% aqueous acetonitrile as eluent.[21] Each compound was found to contain less than 1% of the other antipode. To prepare racemic 4′-methyl-PMEG (**4**), **17c** was treated with sodium hydroxide followed by reaction of the phosphonate monoester with TMSBr. The desired final product **4** was obtained in 64% overall yield for the two steps. Cleavage of the *O*-benzyl group of **17d** by catalytic hydrogenation and hydrolysis of the resulting phosphonate ester with TMSBr yielded 4′,4′-dimethyl-PMEG (**6**).

Our approach to the synthesis of the side-chain for 2′,2′-dimethyl-PMEG **18** (Scheme III) involved reaction of isobutene and diisopropyl phosphonylmethanol in the presence of an electrophile. Use of iodine and cupric acetate[22] in this reaction proved unsuccessful; however, when the same reaction was performed using IBr[23] as the

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(20) McKenna, C. E.; Schmidhauser, J. Functional Selectivity in Phosphonate Ester Dealkylation with Bromotrimethylsilane. *J. Chem. Soc. Chem. Commun.* **1979**, 739.
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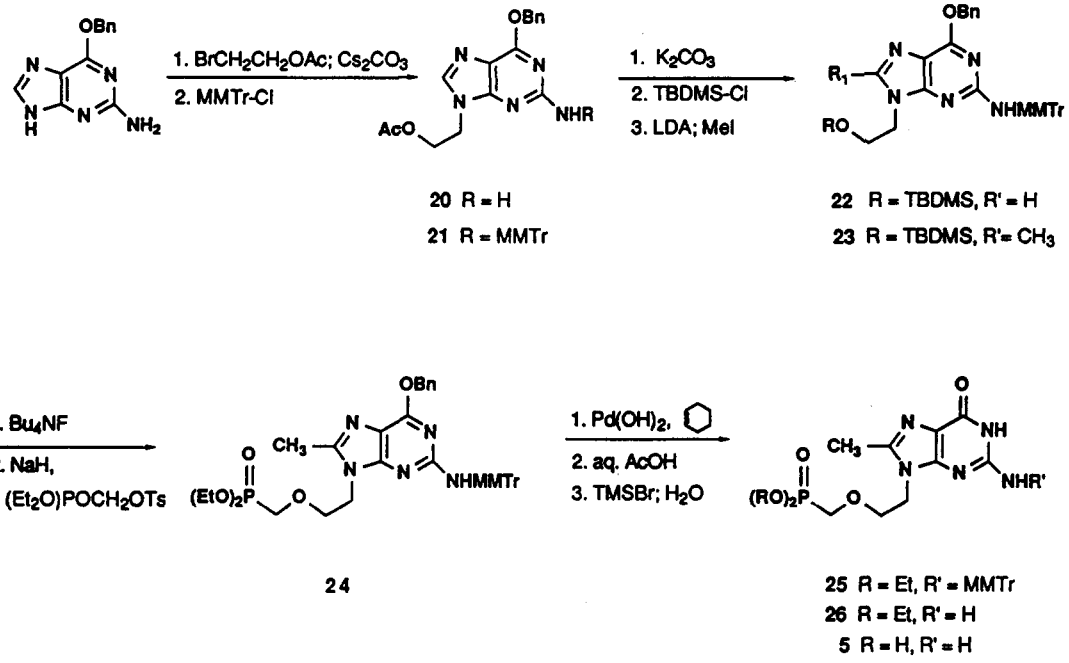
**Scheme IV**

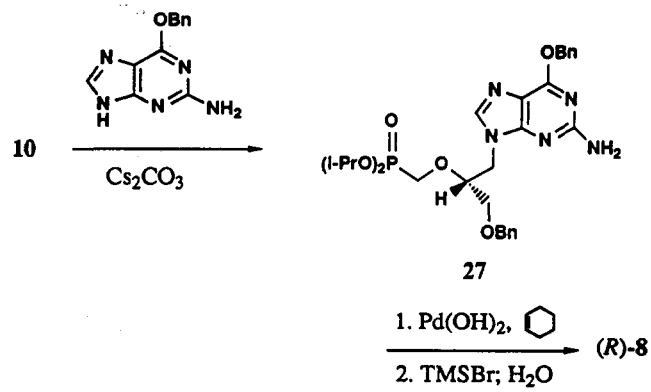



iodonium source, **18** was produced exclusively in 49% yield. Condensation of **18** with 2-amino-6-chloropurine afforded nucleotide **19**. Unexpectedly, **19** underwent extensive decomposition upon treatment with TMSBr, possibly because of the hydrogen bromide released in the reaction and the sensitivity of the tertiary ether moiety of **19**. This decomposition was prevented by deprotection of the phosphonate ester with TMSBr in the presence of excess 2,4,6-collidine. Hydrolysis of the halopurine moiety of **19** with 1 N NaOH produced target compound **7**, which was purified by ion-exchange chromatography and isolated as an ammonium salt.

8-Methyl-PMEG (**5**) was prepared using the approach illustrated in Scheme IV. Reaction of 6-*O*-benzylguanine and bromoethyl acetate in the presence of cesium carbonate in DMF, followed by protection of the guanine base with monomethoxytrityl chloride provided compound **21**. The acetate protecting group of **21** was replaced with a *tert*-butyldimethylsilyl group, and then methylation at the 8-position of **22** was effected with lithium diisopropylamide (LDA) and iodomethane at −78 °C to give **23** in 54% yield. The silylether **23** was cleaved using tetrabutylammonium fluoride,[18] and the resulting alcohol was alkylated with diethyl [(*p*-tosyloxy)methyl]phosphonate[17] to afford **24**. Sequential removal of all the protecting groups of **24** provided 8-methyl-PMEG (**5**).

It is worth noting that both N-9 and N-7 alkylated purine products were obtained in the coupling reaction between the phosphonate mesylates and the heterocyclic base. We have found that the ratio of the N-9 versus N-7 regioisomers is dependent on the nature of purine base used in the coupling reaction,[10,24] varying from 1:2 for $N^2$-acetylguanine to 2:1 for 6-*O*-benzylguanine to >6:1 for 2-amino-6-chloropurine. The use of either the preformed sodium salt of the heterocycle for the coupling or cesium carbonate as a base in the reaction does not significantly change the ratio of the isomers. The N-9 and N-7 isomers of the guanine derivatives were easily separated by chromatography and characterized by using 2-dimensional long range coupling nuclear magnetic resonance techniques. Furthermore, a side product (5–10%), $N^9$-ethylguanine, was isolated from the coupling reaction when ethyl phosphonate esters were used. This side reaction could be prevented by use of isopropyl phosphonate esters.

During the course of our studies, we also prepared both (*R*)- and (*S*)-HPMPG (**8**)[25] for comparison of biological activity. Thus, reaction of mesylate **10** with 6-*O*-benzylguanine in the presence of cesium carbonate gave phosphonate derivative **27**. Catalytic transfer hydrogenation followed by hydrolysis of the phosphonate ester with TMSBr provided (*R*)-HPMPG, (*R*)-**8**. (*S*)-HPMPG was prepared in the same manner using the enantiomer of **10** as starting material. By HPLC analysis, each enantiomer prepared through this route contained approximately 5% of the other enantiomer.




## Results and Discussion

The methyl derivatives of PMEG were evaluated for their activity against human immunodeficiency virus (HIV) and two members of the herpesvirus family, HSV-2 and HCMV. The antiviral effect of these compounds was compared with that of the parent compound PMEG and enantiomers of the related guanine derivative HPMPG,

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Table I. In Vitro Anti-HIV Activity of Methyl-PMEG Derivatives

| entry | compound | $EC_{50}$ ($\mu$M)[a] | $TC_{50}$ ($\mu$M)[b] | SI[c] | $CC_{50}$ ($\mu$M)[d] |
|---|---|---|---|---|---|
| 1 | PMEG (1) | 0.2 | 15 | 75 | 0.2 |
| 2 | (±)-1′-Me-PMEG (2)[12b] | 5 | 250 | 25 | - |
| 3 | (*R*)-2′-Me-PMEG [(*R*)-3] | 1 | >500 | >500 | 180 |
| 4 | (*S*)-2′-Me-PMEG [(*S*)-3] | 12 | 300 | 25 | 12 |
| 5 | 4′-Me-PMEG (4)[e] | >100 | >100 | >1 | - |
| 6 | 8-Me-PMEG (5)[e] | >100 | >100 | >1 | - |
| 7 | 2′,2′-$Me_2$-PMEG (7) | 2.6 | >100 | >38 | - |
| 8 | (*S*)-HPMPG [(*S*)-8] | >500 | 350 | <1 | - |
| 9 | (*R*)-HPMPG [(*R*)-8] | 500 | >500 | >1 | - |
| 10 | PMEA | 18 | >500 | >27 | - |

[a] The 50% effective concentration, determined by the XTT assay using CEM cells infected with HIV (entries 1–4, 7–10. LAV-BRU strain; entries 5, 6: HIV-HRF strain). [b] The 50% toxic concentration, determined by the XTT assay in CEM cells. [c] Selectivity index, or the ratio of the $TC_{50}$ to $EC_{50}$. [d] The 50% cell growth toxicity concentration, determined by measuring the number of cells after treatment with drug for 72 h. [e] The compounds were tested by Southern Research Institute.

8.[25] Measurement of cellular toxicity in a variety of cell lines was also important, since the aim of this study was to determine whether activity and toxicity could be varied independently to give a more selective compound than PMEG. The selectivity index (SI) is calculated as the ratio of the toxic concentration to the effective concentration ($TC_{50}/EC_{50}$).

The results for evaluation of compounds 1–8 against HIV using the XTT[3c] assay are shown in Table I. The antiviral activity is determined as the concentration of compound required to increase the number of viable cells to 50% that of uninfected controls ($EC_{50}$). The toxicity ($TC_{50}$) of each compound is measured under the same assay conditions but in the absence of virus. Selected compounds were also evaluated for cell growth inhibition by measuring the concentration of compound that causes a 50% decrease in cell number compared to untreated cells after 72 h ($CC_{50}$). The $CC_{50}$ assay is a more sensitive test for toxicity since it is measured in growing rather than stationary cells. The data show that all of the methyl-substituted PMEG derivatives prepared are less potent than PMEG against HIV. However, for the (*R*)-2′-methyl derivative 3, the antiviral potency was decreased only 5-fold relative to PMEG, while the toxicity was lessened more than 30-fold, resulting in a substantial increase in the selectivity index for (*R*)-3. The (*S*)-enantiomer of 2′-methyl-PMEG is also active against HIV, but it is somewhat less potent and more toxic than the (*R*)-isomer, and thus, has lower selectivity. (*R*)-2′-methyl-PMEG was also substantially less toxic than PMEG or (*S*)-2′-methyl-PMEG when evaluated for its effects on cell growth. Interestingly, 2′,2′-dimethyl-PMEG (7) was also active against HIV, having an $EC_{50}$ between that for (*R*)- and (*S*)-2′-methyl-PMEG. This indicates that the acyclic side chain can adopt a conformation such that two groups at the 2′-position can be accommodated. The data for 1′-methyl-PMEG (2) shows that this compound has decreased selectivity relative to PMEG, although it should be noted that since the compound is in racemic form, the effect of the individual isomers was not defined. Derivatives of PMEG with the methyl group substituted at the 4′- and 8-positions were found to be inactive against HIV, as were the enantiomers of HPMPG. Note that the 2′-methyl-PMEG derivatives can be viewed as 3′-deoxy-HPMPG analogues, indicating that the lack of the 3′-hydroxyl substituent is important for the anti-HIV activity.

The dramatic improvement in selectivity for (*R*)-2′-methyl-PMEG over PMEG is illustrated more clearly in

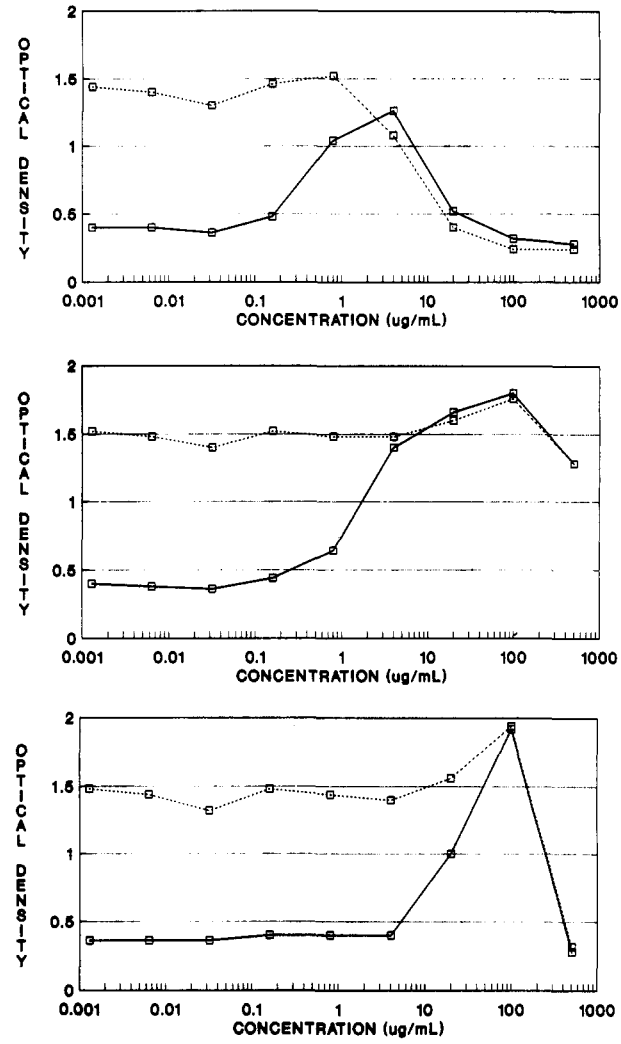


Figure 1. (a, top) Anti-HIV activity of PMEG. (b, middle) Anti-HIV activity of (*R*)-2′-methyl-PMEG. (c, bottom) Anti-HIV activity of (*S*)-2′-methyl-PMEG. HIV-infected cells (—); uninfected cells (- - -).

the dose–response curves shown in Figure 1a–c, in which the toxicity and anti-HIV activity are plotted over a range of concentrations. The optical density values plotted on the *y*-axis are directly proportional to the number of viable cells, as determined by the colorimetric XTT-assay in infected and uninfected cells. For PMEG (Figure 1a), a 50% protective dose can be determined; however, the toxic effects of the compound are seen before full protection is achieved. By comparison, (*R*)-2′-methyl-PMEG provides complete protection from the virus over a wide range of concentrations, with slight cytotoxicity seen only at the highest dose tested (Figure 1b). The (*S*)-isomer of 2′-methyl-PMEG also affords complete protection from the virus, but over a much narrower concentration range (Figure 1c). Thus, the data show that (*R*)-2′-methyl-PMEG is significantly more selective as an anti-HIV agent than either its enantiomer or the parent compound PMEG.

The anti-herpesvirus activity of methyl-PMEG derivatives was evaluated using the plaque reduction assay for cells infected with HSV-2 (G strain) or HCMV (AD-169 strain) (Table II). The antiviral activity is given as the concentration of compound required to decrease the number of virus plaques by 50% ($EC_{50}$), while the $TC_{50}$ is the concentration of compound which reduces the number of viable uninfected cells by 50%. Again, the effect of placing a methyl substituent at the 1′-, 2′-, 4′-, or 8-positions of the PMEG skeleton was to decrease potency

Table II. In Vitro Antiherpesvirus Activity of Methyl-PMEG Derivatives

| compound | $IC_{50}$ (μM)[a] HCMV | HSV-2 | $TC_{50}$ (μM)[b] |
|---|---|---|---|
| PMEG (1) | 0.09 | 1.1 | 30,[c] 17[d] |
| (±)-1′-Me-PMEG (2) | 1.3 | 11 | >330,[c] 200[d] |
| (R)-2′-Me-PMEG [(R)-3] | 16 | 82 | >330,[c] >330[d] |
| (S)-2′-Me-PMEG [(S)-3] | 16 | 43 | >330,[c] >330[d] |
| 4′-Me-PMEG (4) | – | 158 | >330[d] |
| 8′-Me-PMEG (5) | – | 172 | >330[d] |
| 4′,4′-$Me_2$-PMEG (6) | – | >300 | >330[d] |
| 2′,2′-$Me_2$-PMEG (7) | >300 | >300 | >330[e] |
| (S)-HPMPG [(S)-8] | 0.8 | 97 | >310,[c] >310[d] |
| (R)-HPMPG [(R)-8] | 1.6 | 99 | >310,[c] >310[d] |
| acyclovir | – | 1.2–5.3 | – |
| ganciclovir | 4 | – | – |

[a] Inhibitory concentration, as determined in MRC-5 cells (HCMV, AD-169 strain) and vero cells (HSV-2, G strain) for compounds 1–6 and 8, and in WI-38 cells (HCMV, HSV-2) for compound 7. [b] 50% cellular toxicity in stationary cells. [c] Determined in MRC-5 cells. [d] Determined in vero cells. [e] Determined in WI-38 cells.

relative to PMEG, although each compound tested showed some anti-herpesvirus activity. Substitution at the 1′-position resulted in the smallest decrease in antiviral potency against HCMV and HSV-2; however the cellular toxicity was lessened to a similar degree, and therefore no increase in selectivity was obtained. The (R)- and (S)-isomers of 2′-methyl-PMEG are equipotent against HCMV, with both compounds showing a >175-fold decrease in potency relative to PMEG. However, it is interesting to note that the $EC_{50}$ values for both isomers of 3 are comparable to that for ganciclovir, a compound currently being evaluated in the clinic for treatment of CMV infections in AIDS patients.[26] In the HSV-2 assay, both compounds were found to have only moderate activity, with the (S)-2′-methyl isomer having somewhat greater potency than the (R)-enantiomer. The 2′,2′-dimethyl derivative of PMEG was also evaluated for its anti-herpesvirus effect. Surprisingly, this disubstituted compound was found to be completely inactive. The related hydroxyl derivatives of (R)- and (S)-2′-methyl-PMEG, (S)- and (R)-HPMPG, were found to have good anti-HCMV activity, although both showed only weak potency against HSV-2. These results indicate that anti-herpesvirus activity is not dependent on the presence or absence of the hydroxyl group, although the potency may be affected. Substitution at the 4′- and 8-positions also resulted in a substantial loss of potency against HSV-2. The results obtained for 8-methyl-PMEG are particularly interesting in comparison with those reported for acyclovir (ACV) and 8-methyl-ACV.[27] In the case of 8-methyl-ACV, the antiviral potency decreased only 10-fold relative to ACV but the cellular toxicity decreased more than 30-fold, for a net increase in the selectivity index. Substitution with the 8-methyl group in PMEG, however, resulted in a much greater loss in potency, so that the same improvement in selectivity was not realized. The results described in Table II therefore indicate that while cellular toxicity could be reduced relative to PMEG, the concomitant loss in potency against herpesviruses means that no improvement in selectivity was realized.

Our studies have shown that simple modification of the PMEG skeleton can have a profound effect on antiviral activity and cellular toxicity, and that these properties can be varied in an independent fashion. Of particular interest is the finding that both enantiomers of 2′-methyl-PMEG and HPMPG are active as antiviral agents, since in the case of the related adenine and cytosine derivatives HPMPA[7] and HPMPC,[1,14] only the (S)-isomers have antiviral activity. The implication of our findings for SAR studies in the area of nucleotide analogues is that seemingly small changes can have a large effect on antiviral activity. This phenomenon is illustrated clearly in the present study, which explores the effect of substitution and provides additional examples of the different antiviral properties of enantiomers.

Of the derivatives prepared, 2′-(R)-methyl-PMEG was identified as a potent and highly selective anti-HIV agent. The anti-HCMV activity of this compound gives it additional potential as a therapy for the treatment of AIDS. It should be noted that the in vitro antiviral activity of each of the phosphonates tested is a reflection of several factors, the most important of which are the efficiency of phosphorylation by cellular kinases to give the corresponding triphosphate analogue[28] and the effectiveness of the triphosphate analogue as an inhibitor of the viral polymerase. Biochemical studies have been initiated to elucidate the origin of the selectivity of (R)-2′-methyl-PMEG.[29] The results show that the diphosphate of (R)-2′-methyl-PMEG, a triphosphate analogue, has a higher affinity for HIV reverse transcriptase than either PMEG diphosphate or (S)-2′-methyl-PMEG diphosphate, but a lower affinity for cellular DNA polymerase α. Thus, the selectivity of (R)-2′-methyl-PMEG may be attributed to its selective inhibition of viral DNA synthesis. Details of the biochemical evaluation as well as results from in vivo evaluation will be presented shortly.

## Experimental Section

Melting points were determined on an electrothermal apparatus and are not corrected. Proton and carbon-13 magnetic resonance ($^1H$ and $^{13}C$ NMR) spectra were recorded on a Bruker AM 300, Varian Gemini 300, or Varian VXR 200 spectrometer. All spectra were determined in $CDCl_3$, DMSO-$d_6$, $CD_3OD$, or $D_2O$, and chemical shifts are reported in δ units relative to tetramethylsilane (TMS) for $CDCl_3$, DMSO-$d_6$, and $CD_3OD$, and relative to sodium 3-(trimethylsilyl)tetradeuteriopropionate for $D_2O$. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; and dd, doublet of doublet. Optical rotations $[\alpha]^{20}_D$ were determined on a Perkin-Elmer 41 polarimeter. Mass spectra were recorded on a Kratos MS-50 or a Finnegan 4500 instrument utilizing the electron ionization (EI), fast atom bombardment (FAB), or direct chemical ionization (DCI) technique. Preparative chromatography was performed with flash chromatography on silica gel from Universal Scientific Inc. or octadecyl (C18) from J.T. Baker Inc.

**(R)-3-O-Benzyl-2-O-[(diisopropylphosphono)methyl]-1-O-(methylsulfonyl)glycerol (10).** Compound 10 was prepared

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(29) Ho, H.-T.; De Boeck, H.; Woods, K. L.; Konrad, S. A.; Hitchcock, M. J. M.; Datema, R. Structure and Activity Correlation-Studies of Anti-HIV Acyclic Guanine Nucleotide Analogues at Enzyme Level. *J. Acquired Immune Defic. Syndr.* **1991**, *4*, 353.

from (*S*)-2,3-*O*-isopropylideneglycerol following the procedure described by J. J. Bronson et al.:[14] $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.38 (m, 5 H, PhH), 4.63–4.77 (m, 2 H, 2 × POCH), 4.51 (s, 2 H, $OCH_2Ph$), 4.39 (dd, *J* = 3.6, 11.2 Hz, 1 H, $CH_2OMs$), 4.29 (dd, *J* = 5.7, 11.2 Hz, 1 H, $CH_2OMs$), 3.90 (dd, *J* = 8.8, 13.7 Hz, 1 H, $OCH_2P$), 3.84–3.91 (m, 1 H, H-2), 3.83 (dd, *J* = 8.7, 13.7 Hz, 1 H, $OCH_2P$), 3.61 (dd, *J* = 5.0, 10.1 Hz, 1 H, $CH_2OBn$), 3.56 (dd, *J* = 5.5, 10.1 Hz, 1 H, $CH_2OBn$), 3.03 (s, 3 H, $CH_3SO_2$), and 1.27–1.32 (m, 12 H, 4 × $POCHCH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.7, 128.1, 127.9, 78.4 (d, $^3J_{c,p}$ = 11 Hz, C-2), 73.5 ($CH_2Ph$), 71.2 (t, $^2J_{c,p}$ = 5 Hz, POCH), 69.2 and 68.2 ($CH_2OBn$ and $CH_2OMs$), 65.1 (d, $^1J_{c,p}$ = 169 Hz, $OCH_2P$), 37.3 ($CH_3SO_2$), 23.9 (d, $^3J_{c,p}$ = 5 Hz, $POCHCH_3$), and 23.8 (d, $^3J_{c,p}$ = 4 Hz, $POCHCH_3$); MS (methane, DCI) *m/e* 439 ($MH^+$). Anal. ($C_{18}H_{31}O_8PS$) C, H, N.

**(*S*)-1-(Benzyloxy)-2-[(diisopropylphosphono)methoxy]-3-iodopropane (11).** A mixture of **10** (10.0 g, 22.8 mmol) and sodium iodide (5.15 g, 34.4 mmol) in 70 mL of acetone was heated at reflux for 14 h. The mixture was concentrated to about 30-mL volume, and insoluble material was removed by filtration. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel ($CH_2Cl_2$–acetone = 1:0 to 5:1) to give 9.51 g (89%) of the title compound as an oil: $[\alpha]^{20}_D$ −0.82° (*c* 2.30, $CH_3OH$); $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.35 (m, 5 H, PhH), 4.66–4.80 (m, 2 H, 2 × POCH), 4.52 (s, 2 H, $OCH_2Ph$), 3.88 (dd, *J* = 8.7, 13.6 Hz, 1 H, $OCH_2P$), 3.82 (dd, *J* = 8.7, 13.6 Hz, 1 H, $OCH_2P$), 3.52–3.68 (m, 3 H, $CH_2OBn$ and H-2), 3.37 (dd, *J* = 3.6, 10.5 Hz, 1 H, $CH_2I$), 3.31 (dd, *J* = 6.0, 10.5 Hz, 1 H, $CH_2I$), and 1.23–1.34 (m, 12 H, 4 × $POCHCH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 137.9, 128.4, 127.8, 127.7, 79.4 (d, $^3J_{c,p}$ = 11 Hz, C-2), 73.3 ($OCH_2Ph$), 71.1 ($CH_2OBn$), 71.0 (d, $^2J_{c,p}$ = 3 Hz, POCH), 64.6 (d, $^1J_{c,p}$ = 168 Hz, C-P), 23.7 (t, $^3J_{c,p}$ = 4 Hz, $POCHCH_3$), and 4.9 ($CH_2I$); MS (isobutane, DCI) *m/e* 471 ($MH^+$).

**(*R*)-2-*O*-[(Diisopropylphosphono)methyl]-1,2-propanediol (9b).** Compound 11 (11.1 g, 23.5 mmol) was mixed with triethylamine (2.85 g, 28.2 mmol) in 15 mL of $CH_3OH$. To this solution, 10% palladium on carbon (2.0 g) was added under nitrogen atmosphere. The reaction was performed in a Parr apparatus at a hydrogen pressure of 40 psi. After 3 h, the catalyst was removed by filtration, the filtrate was concentrated, and the residue was purified by flash chromatography on silica gel ($CH_2Cl_2$–acetone = 1:0 to 5:1) to give 7.91 g (98%) of (*R*)-1-*O*-benzyl-2-*O*-[(diisopropylphosphono)methyl]-1,2-propanediol as an oil: $[\alpha]^{20}_D$ −7.28° (*c* 0.29, $CH_3OH$); $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.35 (m, 5 H, PhH), 4.66–4.80 (m, 2 H, 2 × POCH), 4.52 (s, 2 H, $OCH_2Ph$), 3.84 (dd, *J* = 8.8, 13.6 Hz, 1 H, $OCH_2P$), 3.70–3.84 (m, 2 H, H-2 and $OCH_2P$), 3.50 (dd, *J* = 6.0, 10.2 Hz, 1 H, $CH_2OBn$), 3.41 (dd, *J* = 4.4, 10.2 Hz, 1 H, $CH_2OBn$), 1.26–1.35 (m, 12 H, 4 × $POCHCH_3$), and 1.16 (d, *J* = 6.4 Hz, 3 H, H-3); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 138.3, 128.4, 127.7, 76.9 (d, $^3J_{c,p}$ = 12 Hz, C-2), 74.0 and 73.2 ($CH_2OBn$ and $OCH_2Ph$), 70.8 (d, $^2J_{c,p}$ = 7 Hz, POCH), 63.9 (d, $^1J_{c,p}$ = 169 Hz, $OCH_2P$), 23.7 (q, $^3J_{c,p}$ = 4 Hz, $POCHCH_3$), and 16.5 (C-3); MS (isobutane, DCI) *m/e* 345 ($MH^+$). Anal. ($C_{17}H_{29}O_5P$) C, H.

(*R*)-1-*O*-Benzyl-2-*O*-[(diisopropylphosphono)methyl]-1,2-propanediol (7.75 g, 22.5 mmol) was dissolved in a mixture of cyclohexene (30 mL) and $CH_3OH$ (30 mL). To the solution, 20% palladium hydroxide on carbon (1.5 g) was added. The resulting mixture was heated at reflux for 16 h, and the catalyst was removed by filtration. The filtrate was concentrated in vacuo, and the residue containing **9b** was used in the next reaction without further purification: $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.62–4.80 (m, 2 H, 2 × POCH), 3.88 (dd, *J* = 8.0, 13.9 Hz, 1 H, $OCH_2P$), 3.67 (dd, *J* = 9.0, 13.9 Hz, 1 H, $OCH_2P$), 3.52–3.68 (m, 2 H, H-2 and $CH_2OH$), 3.46 (dd, *J* = 7.2, 12.0 Hz, 1 H, $CH_2OH$), 2.19 (d, *J* = 6.0 Hz, 3 H, H-3), and 1.28–1.32 (m, 12 H, 4 × $POCHCH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 79.0 (d, $^3J_{c,p}$ = 10 Hz, C-2), 70.8 (d, $^2J_{c,p}$ = 7 Hz, POCH), 70.6 (d, $^2J_{c,p}$ = 7 Hz, POCH), 65.3 (C-1), 63.3 (d, $^1J_{c,p}$ = 170 Hz, $OCH_2P$), 23.4 (d, $^3J_{c,p}$ = 4 Hz, $POCHCH_3$), 23.2 (d, $^3J_{c,p}$ = 5 Hz, $POCHCH_3$), and 15.4 (C-3).

**(*R*)-1-*O*-[(*p*-Methoxyphenyl)diphenylmethyl]-1,2-propanediol (12).** Triethylamine (234 g, 2.31 mol) and 4-(dimethylamino)pyridine (1 g, 8 mmol) were added to (*R*)-1,2-propanediol[16] ($[\alpha]^{20}_D$ −17.3° (neat)) (80 g, 1.05 mol) in a mixture of EtOAc and $CH_2Cl_2$ (2:1, 0.8 L) under a nitrogen atmosphere. To this mixture, *p*-anisylchlorodiphenylmethane (356.5 g, 1.16 mol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 15 h. The solid was removed by filtration. The filtrate was concentrated, and the residue was put on a silica gel column and eluted with a mixture of EtOAc:hexane (1:5 to 1:2). The product **12** (367 g) was dried under vacuum and used without further purification: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.45 (m, 12 H, ArH), 6.80–6.83 (m, 2 H, ArH), 3.90–4.00 (m, 1 H, H-2), 3.77 (s, 3 H, $OCH_3$), 3.10 (dd, *J* = 3.4, 9.2 Hz, 1 H, H-1), 2.95 (dd, *J* = 7.9, 9.2 Hz, 1 H, H-1), 2.35 (br d, 1 H, OH), and 1.07 (d, *J* = 6.4 Hz, 3 H, H-3); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.8, 144.6, 135.7, 130.5, 128.0, 127.7, 127.1, 113.2, 86.3, 68.8 (C-1), 67.0 (C-2), 55.1 ($OCH_3$), and 18.7 (C-3).

**(*R*)-2-*O*-[(Diisopropylphosphono)methyl)]-1,2-propanediol (9b).** Sodium hydride (80% in mineral oil, 24 g, 0.80 mol) was added in five portions to a solution of crude **12** obtained previously (232 g, 0.66 mol) in 1 L of anhydrous tetrahydrofuran at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then heated at reflux for 5 h. The resulting reaction mixture was cooled to 0 °C, and a solution of diisopropyl (*p*-tosyloxy)methanephosphonate (280 g, 0.80 mol) in 300 mL of anhydrous tetrahydrofuran was added via a cannula. The mixture was stirred in ice-bath and slowly warmed to room temperature overnight (18 h). The resulting brown slurry was filtered through a pad of Celite and washed with $CH_2Cl_2$. After the solvent was removed, the residue was filtered through a silica gel column and eluted with mixtures of EtOAc and hexane (1:5 to 1:0) to give a partially-purified product of (*R*)-2-*O*-[(diisopropylphosphono)methyl)]-1-*O*-[(*p*-methoxyphenyl)diphenylmethyl]-1,2-propanediol as an oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, *J* = 7.0 Hz, 3 H, ArH), 7.16–7.33 (m, 9 H, ArH), 6.81 (d, *J* = 8.1 Hz, 2 H, ArH), 4.56–4.80 (m, 2 H, 2 × POCH), 3.86 (dd, *J* = 9.1, 13.6 Hz, 1 H, $OCH_2P$), 3.76 and 3.76–3.88 (s over m, 4 H, $OCH_3$ and $OCH_2P$), 3.77–3.68 (m, 1 H, H-2), 3.16 (dd, *J* = 5.9, 9.6 Hz, 1 H, H-1), 3.01 (dd, *J* = 4.1, 9.6 Hz, 1 H, H-1), 1.27–1.32 (m, 12 H, 4 × $POCHCH_3$), and 1.14 (d, *J* = 6.1 Hz, 3 H, H-3); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 158.6, 144.6, 135.7, 130.4, 128.5, 127.8, 126.8, 113.0, 86.2, 77.4 (d, $^3J_{c,p}$ = 12 Hz, C-2), 70.7 (t, $^2J_{c,p}$ = 6 Hz, POCH), 67.0 (C-1), 64.1 (d, $^1J_{c,p}$ = 169 Hz, $OCH_2P$), 54.9 ($OCH_3$), 23.8 (d, $^3J_{c,p}$ = 3 Hz, $POCHCH_3$), 23.7 (d, $^3J_{c,p}$ = 3 Hz, $POCHCH_3$), and 16.8 (C-3).

10-Camphorsulphonic acid (21 g) was added to a solution of the crude (*R*)-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-[(*p*-methoxyphenyl)diphenylmethyl]-1,2-propanediol in 1.8 L of $CH_3OH$. The solution was heated at reflux for 7 h. After the solvent was evaporated, the residue was purified by column chromatography on silica gel (first time, EtOAc:hexane = 1:2 to 1:0 and then EtOAc:EtOH = 10:1; second time, $CH_2Cl_2$:acetone = 5:1 to 0:1) to give 40.8 g (24% yield from **12**) of the product.

**1-(*tert*-Butyldimethylsiloxy)-2-[(diethylphosphono)-methoxy]ethane (13).** A mixture of 2-[(diethylphosphono)-methoxy]ethanol (21.3 g, 100 mmol),[10,13] *tert*-butyldimethylsilyl chloride (16.6 g, 110 mmol), triethylamine (15.2 g, 151 mmol), and 4-(dimethylamino)pyridine (0.5 g) in anhydrous $CH_2Cl_2$ (200 mL) was stirred at room temperature for 14 h under argon. The reaction mixture was then diluted with EtOAc (500 mL), washed with 10% aqueous $K_2CO_3$ (250 mL) and saturated NaCl solution (250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give 32 g of a yellow oil. Purification by column chromatography on silica gel (EtOAc) provided 27.4 g (84%) of the product as a clear, colorless oil: $^1$H NMR ($CDCl_3$, 200 MHz) δ 4.18 (apparent quintet, *J* = 7 Hz, 4 H, 2 × $POCH_2$), 3.88 (d, *J* = 8.2 Hz, 2 H, $OCH_2P$), 3.78 (t, *J* = 5 Hz, 2 H, $CH_2O$), 3.66 (t, *J* = 5 Hz, 2 H, $CH_2O$), 1.35 (t, *J* = 8 Hz, 6 H, 2 × $POCH_2CH_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), and 0.07 (s, 6 H, $Si(CH_3)_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 74.7 (d, $^2J_{c,p}$ = 10 Hz, $CH_2OCH_2P$), 65.6 (d, $^1J_{c,p}$ = 165 Hz, $OCH_2P$), 62.6 ($CH_2OSi$), 62.3 (d, $^1J_{c,p}$ = 6 Hz, $POCH_2$), 25.9 ($(CH_3)_3CSi$), 18.4 ($(CH_3)_3CSi$), 16.5 (d, $^3J_{c,p}$ = 6 Hz, $POCH_2CH_3$), and −5.3 ($(CH_3)_3Si$); MS (EI) *m/e* 311 ($M^+ - CH_3$), 269 ($M^+ - C_4H_9$).

**1-(*tert*-Butyldimethylsiloxy)-2-[1-(diethylphosphono)-ethoxy]ethane (14).** To a solution of *sec*-BuLi (47.5 mL, 1.3 M in hexanes, 61.7 mmol) in anhydrous THF (150 mL) cooled to −78 °C under argon was added a solution of compound **13** (16.8 g, 51.5 mmol) in THF (20 mL). The reaction mixture was stirred at −78 °C for 0.5 h, and then methyl iodide (14.6 g, 103 mmol) was added rapidly via syringe. The mixture was allowed to warm

to room temperature, then was diluted with diethyl ether (300 mL), and washed with $H_2O$ (150 mL) and saturated NaCl solution (150 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 19 g of a yellow oil. Column chromatography on silica gel (EtOAc) gave 15.7 g (90%) of **14** as a clear, colorless oil: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.25 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.67–3.95 (m, 5 H, OC$H_2$C$H_2$OCHP), 1.49 (dd, $J$ = 7, 17 Hz, 3 H, OCH(C$H_3$)P), 1.42 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$), 1.41 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$), 0.97 (s, 9 H, SiC(C$H_3$)$_3$), and 0.14 (s, 6 H, Si(C$H_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 72.5 (d, $^2J_{c,p}$ = 5 Hz, C$H_2$OCH$_2$P), 72.2 (d, $^1J_{c,p}$ = 165 Hz, OCHP), 62.8 (C$H_2$OSi), 62.3 (d, $^1J_{c,p}$ = 6 Hz, POCH$_2$), 62.2 (d, $^1J_{c,p}$ = 6 Hz, POCH$_2$), 25.9 ((C$H_3$)$_3$CSi), 16.6 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$CH$_3$), 15.6 (OCH(CH$_3$)P), and −5.3 ((C$H_3$)$_3$Si); MS (EI) $m/e$ 325 ($M^+ - CH_3$), 283 ($M^+ - C_4H_9$).

**2-[1-(Diethylphosphono)ethoxy]ethanol (9c).** Compound **14** (15.6 g, 45.9 mmol) was treated with THF (45 mL), $H_2O$ (45 mL), and glacial acetic acid (135 mL). The mixture was stirred at room temperature for 12 h and then concentrated in vacuo. The residue was coevaporated from toluene (2 × 100 mL), and crude alcohol **9c** was used without purification: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.22 (apparent quintet, $J$ = 8 Hz, 2 H, POC$H_2$), 4.18 (apparent quintet, $J$ = 8 Hz, 2 H, POC$H_2$), 3.59–3.95 (m, 5 H, C$H_2$C$H_2$OCH), 3.29 (br s, 1 H, OH), 1.42 (dd, $J$ = 8, 17 Hz, 3 H, OCH(C$H_3$)P), 1.36 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$), and 1.35 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 73.4 (d, $^3J_{c,p}$ = 7 Hz, C$H_2$OCHP), 72.3 (d, $^1J_{c,p}$ = 165 Hz, OCHP), 62.9 (d, $^2J_{c,p}$ = 7 Hz, POC$H_2$), 62.3 (d, $^2J_{c,p}$ = 7 Hz, POC$H_2$), 61.8 (C$H_2$OH), 16.5 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$CH$_3$), and 15.8 (OCH(C$H_3$)P).

**2-[1-(Diethylphosphono)-1-methylethoxy]ethanol (9d).** A solution of *sec*-BuLi (15.2 mL, 1.3 M in hexanes, 19.8 mmol) was added dropwise over 10 min to a −78 °C solution of compound **14** (6.13 g, 18.0 mmol) in anhydrous THF (90 mL) under argon. The resulting clear, yellow solution was stirred at −78 °C for 1 h, and then methyl iodide (5.11 g, 36.0 mmol) was added rapidly via syringe. The reaction mixture was stirred at −78 °C for 1 h further, allowed to warm to room temperature, and then poured into a separatory funnel containing saturated $NH_4Cl$ solution (150 mL) and EtOAc (200 mL). The organic layer was separated and washed with saturated NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 6.5 g of (*tert*-butyldimethylsiloxy)-2-[1-(diethylphosphono)-1-methylethoxy]ethane (**15**) as a yellow oil which was used without purification. On a separate run, the product was purified by column chromatography on silica gel (50% to 75% EtOAc/hexanes) to give a pure sample of **15**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.16 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.64–3.74 (m, 4 H, OC$H_2$C$H_2$OCP), 1.42 (d, $J$ = 15 Hz, 6 H, OC(C$H_3$)$_2$P), 1.33 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$), 0.88 (s, 9 H, SiC(C$H_3$)$_3$), and 0.05 (s, 6 H, Si(C$H_3$)$_2$); MS (FAB) $m/e$ 355 ($MH^+$).

The unpurified silyl ether **15** was dissolved in 3:1:1 AcOH/THF/$H_2O$ (90 mL) and the mixture was stirred at room temperature for 12 h. The resulting clear solution was concentrated in vacuo, and the residue (4.7 g) was purified by column chromatography on silica gel (2% MeOH/$CH_2Cl_2$). Fractions containing the desired product were pooled and concentrated to give 3.83 g (89% overall) of **9d** as a clear, colorless oil: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.20 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.73 (br s, 4 H, C$H_2$C$H_2$O), 3.05 (br s, 1 H, OH), 1.46 (d, $J$ = 15 Hz, 6 H, OC(C$H_3$)$_2$P), and 1.36 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 74.4 (d, $^1J_{c,p}$ = 165 Hz, OCP), 65.0 (d, $^3J_{c,p}$ = 5 Hz, C$H_2$OCP), 62.5 (d, $^2J_{c,p}$ = 7 Hz, POC$H_2$), 62.0 (C$H_2$OH), 22.2 (OC(C$H_3$)$_2$P), and 16.4 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$C$H_3$); MS (FAB) $m/e$ 241 ($MH^+$).

**(*R*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-propanediol (16b).** Crude **9b** obtained previously (39.8 g, 157 mmol) was dissolved in 400 mL of $CH_2Cl_2$ and cooled to 0 °C. Methanesulfonyl chloride (21.5 g, 188 mmol) was added slowly to the solution, and then triethylamine (31.7 g, 313 mmol) was added dropwise. After the addition was complete, the mixture was stirred at 0 °C for 30 min and then allowed to warm slowly to room temperature. Water (150 mL) and $CH_2Cl_2$ (150 mL) were added to the solution. The aqueous layer was extracted with $CH_2Cl_2$ (2 × 150 mL). The combined $CH_2Cl_2$ extracts were washed with brine and dried over magnesium sulfate. Filtration and concentration under reduced pressure gave a residue which was purified by flash chromatography on silica gel ($CH_2Cl_2$–acetone = 10:1 to 5:1) to provide 42.0 g of **16b** as an oil (81% yield for 2 steps): $[\alpha]^{20}_D$ −7.45° (*c* 1.45, $CH_3OH$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.52–4.69 (m, 2 H, 2 × POC*H*), 4.10 (dd, $J$ = 3.6, 11.1 Hz, 1 H, C$H_2$OMs), 4.03 (dd, $J$ = 6.1, 11.1 Hz, 1 H, C$H_2$OMs), 3.65–3.78 (m, 2 H, OC$H_2$P and H-2), 3.61 (dd, $J$ = 9.3, 13.4 Hz, 1 H, OC$H_2$P), 2.95 (s, 3 H, C$H_3$SO$_2$), 1.20 (d, $J$ = 6.4 Hz, 12 H, 4 × POCHC$H_3$), and 1.10 (d, $J$ = 6.5 Hz, 3 H, H-3); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 75.3 (d, $^3J_{c,p}$ = 12 Hz, C-2), 72.0 (CH$_2$OMs), 71.1 (d, $^2J_{c,p}$ = 4 Hz, POCH), 71.0 (d, $^2J_{c,p}$ = 4 Hz, POCH), 63.72 (d, $^1J_{c,p}$ = 171 Hz, OCH$_2$P), 37.4 (CH$_3$SO$_2$), 23.4 (d, $^3J_{c,p}$ = 4 Hz, POCHCH$_3$), 23.2 (d, $^3J_{c,p}$ = 4 Hz, POCHCH$_3$), and 15.3 (C-3).

**2-[1-(Diethylphosphono)ethoxy]ethyl Methanesulfonate (16c).** Sulfonate **16c** was prepared in 97% yield from unpurified alcohol **9c** (obtained as described previously from 45.9 mmol of **14**) by the same procedure used for the preparation of **16b**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.34 (t, $J$ = 4.5 Hz, 2 H, C$H_2$OMs), 4.20 (apparent quintet, $J$ = 8 Hz, 2 H, POC$H_2$), 4.19 (apparent quintet, $J$ = 8 Hz, 2 H, POC$H_2$), 3.97 (dt, $J$ = 4.5, 12 Hz, 1 H, CH$_2$CH$_2$OCH), 3.83 (dt, $J$ = 4.5, 12 Hz, 1 H, CH$_2$CH$_2$OCH), 3.73 (apparent quintet, $J$ = 7 Hz, 1 H, OCH(CH$_3$)P), 3.04 (s, 3 H, C$H_3$SO$_3$), 1.40 (dd, $J$ = 7, 17 Hz, 3 H, OCH(C$H_3$)P), 1.32 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$), and 1.31 (t, $J$ = 7 Hz, 3 H, POCH$_2$C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 72.3 (d, $^1J_{c,p}$ = 165 Hz, OCHP), 69.1 (CH$_2$OMs), 68.7 (d, $^3J_{c,p}$ = 6 Hz, CH$_2$OCHP), 62.5 (d, $^2J_{c,p}$ = 7 Hz, POCH$_2$), 62.4 (d, $^2J_{c,p}$ = 7 Hz, POCH$_2$), 37.7 (CH$_3$SO$_3$), 16.5 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$CH$_3$), and 15.5 (OCH(CH$_3$)P); MS (DCI) $m/e$ 305 ($MH^+$).

**2-[1-(Diethylphosphono)-1-methylethoxy]ethyl Methanesulfonate (16d).** Sulfonate **16d** was prepared from **9d** (3.80 g, 15.8 mmol) in 85% yield by the same procedure used to convert **9b** to **16b**: $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 4.26–4.30 (m, 2 H, C$H_2$OMs), 4.07 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.79–3.83 (m, 2 H, C$H_2$OCP), 3.17 (s, 3 H, C$H_3$SO$_3$), 1.33 (d, $J$ = 15 Hz, 6 H, 2 × OC(C$H_3$)$_2$P), and 1.24 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 74.0 (d, $^1J_{c,p}$ = 165 Hz, OCP), 70.0 (CH$_2$OMs), 61.9 (d, $^2J_{c,p}$ = 7 Hz, POCH$_2$), 61.5 (d, $^3J_{c,p}$ = 5 Hz, CH$_2$OCP), 36.8 (CH$_3$SO$_3$), 21.8 (OC(CH$_3$)$_2$P), and 16.3 (d, $^3J_{c,p}$ = 5 Hz, POCH$_2$CH$_3$); MS (FAB) $m/e$ 319 ($MH^+$).

**2-Amino-6-chloro-9-[2-[(diethylphosphono)methoxy]ethyl]purine (17a).** 2-Amino-6-chloropurine (17.1 g, 101 mmol) was added portionwise to a slurry of NaH (3.02 g, 80% dispersion in oil, 101 mmol) in anhydrous DMF (500 mL) at room temperature under argon. The mixture was stirred for 1 h, and then the resulting clear, pale yellow solution was treated with a solution of **9a**[10,13] (26.6 g, 91.6 mmol) in DMF (50 mL). The mixture was heated at 80 °C for 5 h, allowed to cool to room temperature, and then concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ (300 mL) and $H_2O$ (300 mL), and the aqueous layer was extracted further with $CH_2Cl_2$ (300 mL). The combined organic layers were washed with saturated NaCl solution (300 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 32.5 g of a yellow, viscous residue. Purification by column chromatography on silica gel (MeOH/$CH_2Cl_2$ 2% to 6%) gave 17.5 g (53%) of the product as an off-white solid: mp 119–121 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.92 (s, 1 H, H-8), 5.34 (br s, 2 H, N$H_2$), 4.31 (t, $J$ = 5 Hz, 2 H, 2 × H-1′), 4.12 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.93 (t, $J$ = 5 Hz, 2 H, 2 × H-2′), 3.81 (d, $J$ = 8 Hz, 2 H, OC$H_2$P), and 1.31 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 159.0, 153.6, 151.0, 143.1 (C-8), 124.9 (C-5), 70.9 (d, $^3J_{c,p}$ = 9 Hz, C-2′), 65.3 (d, $^1J_{c,p}$ = 165 Hz, OCH$_2$P), 62.5 (d, $^2J_{c,p}$ = 7 Hz, POCH$_2$), 43.4 (C-1′), and 15.5 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$CH$_3$); MS (FAB) $m/e$ 364 ($MH^+$).

**(*R*)-2-Amino-6-chloro-9-[2-[(diisopropylphosphono)-methoxy]propyl]purine (17b).** Compound **16b** (42.0 g, 127 mmol) was mixed with 2-amino-6-chloropurine (25.7 g, 152 mmol) and cesium carbonate (61.8 g, 190 mmol) in 180 mL of anhydrous DMF. The mixture was gently heated at 95 °C under nitrogen atmosphere for 4 h, then allowed to cool to room temperature, and filtered. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel twice (first time, $CH_2Cl_2$–acetone = 3:1 to 0:1; second time, $CH_2Cl_2$–$CH_3OH$ = 15:1 to 10:1). The product was isolated as a glassy material which was crystallized from EtOAc–$Et_2O$ to give 31.0 g of white crystals (60% yield): mp 133–135 °C; $[\alpha]^{20}_D$ −41.56°

(c 0.99, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 1 H, H-8), 5.06 (br s, 2 H, $NH_2$), 4.58–4.72 (m, 2 H, 2 × POCH), 4.20 (dd, J = 2.6, 14.3 Hz, 1 H, H-1′), 4.03 (dd, J = 7.2, 14.3 Hz, 1 H, H-1′), 3.82–3.95 (m, 1 H, H-2′), 3.76 (dd, J = 9.2, 13.4 Hz, 1 H, $OCH_2P$), 3.57 (dd, J = 9.8, 13.7 Hz, 1 H, $OCH_2P$), 1.18–1.31 (m, 15 H, 4 × $POCHCH_3$ and H-3′); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 159.2, 154.2, 151.4, 144.0, 125.1, 75.9 (d, $^3J_{c,p}$ = 12 Hz, C-2′), 71.2 (d, $^2J_{c,p}$ = 7 Hz, POCH), 63.5 (d, $^1J_{c,p}$ = 170 Hz, $OCH_2P$), 47.9 (C-1′), 23.8 ($POCHCH_3$), and 16.3 (C-3′); MS (FAB) m/e 406 ($MH^+$). Anal. ($C_{15}H_{25}N_5O_4PCl$) C, H, N.

**2-Amino-6-chloro-9-[2-[1-(diethylphosphono)ethoxy]ethyl]purine (17c).** Reaction of **16c** (7.60 g, 25.0 mmol) with the sodium salt of 2-amino-6-chloropurine (4.66 g, 27.5 mmol) in DMF (125 mL) and purification as in the procedure used for the synthesis of **17a** gave 5.80 g (61%) of **17c** as a white powder: mp 101–103 °C; $^1H$ NMR ($CDCl_3$, 200 MHz) δ 7.95 (s, 1 H, H-8), 5.24 (br s, 2 H, $NH_2$), 4.29 (t, J = 4.5 Hz, 2 H, 2 × H-1′), 4.02–4.18 (m, 5 H, 2 × $POCH_2$ and $OCH(CH_3)P$), 3.87 (dt, J = 4.5, 13 Hz, 1 Hz, H-2′), 3.68 (dt, J = 4.5, 13 Hz, 1 H, H-2′), 1.36 (dd, J = 7, 14 Hz, 3 H, $OCH(CH_3)P$), 1.30 (t, J = 7 Hz, 3 H, $POCH_2CH_3$), and 1.29 (t, J = 7 Hz, 3 H, $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 159.0, 153.7, 151.1, 143.4 (C-8), 125.1 (C-5), 72.4 (d, $^1J_{c,p}$ = 165 Hz, OCHP), 68.8 (d, $^3J_{c,p}$ = 6 Hz, C-2′), 62.5 (d, $^2J_{c,p}$ = 7 Hz, $POCH_2$), 62.3 (d, $^2J_{c,p}$ = 7 Hz, $POCH_2$), 43.7 (C-1′), 16.5 (d, $^3J_{c,p}$ = 6 Hz, $POCH_2CH_3$), and 15.5 ($OCH(CH_3)P$); MS (FAB) m/e 378 ($MH^+$).

**6-O-Benzyl-9-[2-[1-(diethylphosphono)-1-methylethoxy]ethyl]guanine (17d).** Sodium hydride (0.44 g, 80% dispersion in oil, 14.7 mmol) was added portionwise to a solution of 6-O-benzylguanine (3.22 g, 13.3 mmol) in anhydrous DMF (75 mL) at room temperature under argon. The resulting clear, yellow solution was stirred for 45 min, and then a solution of **16d** (4.25 g, 13.4 mmol) in DMF (10 mL) was added via cannula. The solution was heated at 80 °C for 14 h, then allowed to cool to room temperature, and concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ (200 mL) and $H_2O$ (200 mL). The layers were agitated and separated, and the aqueous layer was extracted with $CH_2Cl_2$ (200 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give 7.5 g of a viscous yellow-brown oil. Purification by column chromatography on silica gel (2% to 5% $MeOH/CH_2Cl_2$) afforded 2.95 g (48%) of the product as a pale yellow solid: $^1H$ NMR ($CDCl_3$, 200 MHz) δ 7.74 (s, 1 H, H-8), 7.26–7.53 (m, 5 H, Ph*H*), 5.57 (br s, 2 H, $NH_2$), 4.81 (br s, 2 H, $OCH_2Ph$), 4.21 (t, J = 5 Hz, 2 H, 2 × H-1′), 4.07 (apparent quintet, J = 7 Hz, 4 H, 2 × $POCH_2$), 3.92 (t, J = 5 Hz, 2 H, 2 × H-2′), 1.32 (d, J = 16 Hz, 6 H, $OC(CH_3)_2P$), and 1.28 (t, J = 7 Hz, 6 H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 161.2, 159.1, 140.6 (C-8), 136.5, 128.3, 128.2, 127.9, 115.5 (C-5), 74.5 (d, $^1J_{c,p}$ = 165 Hz, OCP), 68.0 ($OCH_2Ph$), 62.3 (d, $^3J_{c,p}$ = 6 Hz, C-2′), 62.1 (d, $^2J_{c,p}$ = 7 Hz, $POCH_2$), 43.8 (C-1′), 22.2 ($OC(CH_3)_2P$), and 16.5 (d, $^3J_{c,p}$ = 6 Hz, $POCH_2CH_3$); MS (isobutane-DCI) m/e 464 ($MH^+$).

**9-[2-(Phosphonomethoxy)ethyl]guanine (1).** A solution of **17a** (17.5 g, 48.1 mmol) in anhydrous DMF (250 mL) at room temperature under argon was treated dropwise via addition funnel with bromotrimethylsilane (73.7 g, 480 mmol). The reaction mixture was stirred for 14 h and then concentrated in vacuo. The residue was treated with $H_2O$ (100 mL) and acetone (250 mL), and the resulting precipitate was collected by filtration and dried in vacuo to provide 14.8 g (100%) of 2-amino-6-chloro-9-[2-(phosphonomethoxy)ethyl]purine as an off-white solid, which was used without further purification: $^1H$ NMR (DMSO-$d_6$, 200 MHz) δ 8.10 (s, 1 H, H-8), 7.00 (br s, 2 H, $NH_2$), 4.24 (t, J = 5 Hz, 2 H, 2 × H-1′), 3.86 (t, J = 5 Hz, 2 H, 2 × H-2′), and 3.62 (d, J = 8.8 Hz, 2 H, $OCH_2P$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz) δ 159.6, 153.9, 149.2, 143.3 (C-8), 123.1 (C-5), 69.8 (d, $^3J_{c,p}$ = 11 Hz, C-2′), 66.2 (d, $^1J_{c,p}$ = 160 Hz, $OCH_2P$), and 42.4 (C-1′); MS (FAB) m/e 308 ($MH^+$).

The crude product was suspended in 10% aqueous HCl solution (v/v, 200 mL), and the mixture was heated at reflux for 6 h. The resulting yellow solution was concentrated in vacuo. The residue was placed under high vacuum for 4 h, then dissolved in hot $H_2O$, and treated with activated charcoal. Filtration of the slurry through Celite gave a pale yellow solution. The decolorizing process was repeated twice, and the final filtrate was concentrated to a volume of 400 mL, treated with EtOH (200 mL), and allowed to cool slowly to room temperature. The white solid that formed was collected by filtration to give 9.5 g (70%) of 1 as a white solid: mp 292–295 °C; $^1H$ NMR (DMSO-$d_6$, 200 MHz) δ 10.60 (br s, 1 H, N*H*), 7.71 (s, 1 H, H-8), 6.46 (br s, 2 H, $NH_2$), 4.11 (t, J = 5 Hz, 2 H, 2 × H-1′), 3.79 (t, J = 5 Hz, 2 H, 2 × H-2′), and 3.58 (d, J = 9 Hz, 2 H, $OCH_2P$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz) δ 157.0 (C-6), 153.6 (C-2), 151.3 (C-4), 139.0 (C-8), 116.1 (C-5), 70.5 (d, $^3J_{c,p}$ = 10 Hz, C-2′), 66.4 (d, $^1J_{c,p}$ = 160 Hz, $OCH_2P$), and 42.6 (C-1′); MS (FAB) m/e 290 ($MH^+$). Anal. ($C_8H_{12}N_5O_5P\cdot 2H_2O$) C, H, N.

**(R)-9-[2-(Phosphonomethoxy)propyl]guanine [(R)-3].** To a solution of **17b** (31.0 g, 76 mmol) in 150 mL of anhydrous acetonitrile was slowly added bromotrimethylsilane (117 g, 760 mmol) under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 16 h, and the solvent was removed under reduced pressure. The residue was dried in vacuo and then treated with acetone (170 mL) and water (30 mL). The resulting mixture was stirred at room temperature for 16 h. The mixture was evaporated, and the residue was washed with acetone and water. The resulting solid was heated gently at reflux in 250 mL of 10% HCl for 4 h. The solution was evaporated under reduced pressure, and the residue was crystallized from water–$CH_3OH$ to give 12.95 g of (R)-3 as pale yellow crystals. The mother liquor was concentrated to provide an additional 1.3 g of the product (total 62% yield): mp 282–285 °C; $[\alpha]^{20}_D$ −26.74° (c 0.43, $H_2O$); $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 10.58 (br s, 1 H, N*H*), 7.74 (s, 1 H, H-8), 6.46 (br s, 2 H, $NH_2$), 4.04 (dd, J = 4.4, 14.3 Hz, 1 H, H-1′), 3.95 (dd, J = 5.8, 14.3 Hz, 1 H, H-1′), 3.78–3.88 (m, 1 H, H-2′), 3.58 (dd, J = 9.3, 13.0 Hz, 1 H, $OCH_2P$), 3.51 (dd, J = 9.9, 13.0 Hz, 1 H, $OCH_2P$), and 1.02 (d, J = 6.3 Hz, 3 H, H-3′); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 157.2, 154.0, 151.8, 138.6, 116.1, 75.4 (d, $^3J_{c,p}$ = 12 Hz, C-2′), 64.4 (d, $^1J_{c,p}$ = 152 Hz, $OCH_2P$), 46.5 (C-1′), and 16.8 (C-3′); MS (FAB) m/e 304 ($MH^+$). Anal. ($C_9H_{14}N_5O_5P\cdot 1.25H_2O$) C, H, N.

**(S)-9-[2-(Phosphonomethoxy)propyl]guanine [(S)-3]**: mp 270–272 °C; $[\alpha]^{20}_D$ +34.66° (c 0.68, $H_2O$); MS (methane, DCI) m/e 304 ($MH^+$). Anal. ($C_9H_{14}N_5O_5P\cdot 1.66H_2O$) C, H, N.

**9-[2-(1-Phosphonoethoxy)ethyl]guanine (4).** Compound **17c** (4.7 g, 12.4 mmol) was treated with 1 N NaOH solution (125 mL), and the mixture was heated at reflux for 2 h and then allowed to cool to room temperature and treated with 10% HCl solution (125 mL). Concentration in vacuo gave 12 g of a pale yellow solid. The solid was dissolved in $H_2O$ (30 mL), and EtOH (150 mL) was added. The precipitate (NaCl) was removed by filtration, and the filtrate was concentrated in vacuo to give 7.5 g of a yellow solid. Purification by column chromatography on C18 adsorbent ($H_2O$ to 10% $MeOH/H_2O$) gave 3.92 g of a white solid. The solid was further purified by recrystallization from $EtOH/H_2O$ to afford 3.07 g (75%) of 9-[2-[1-(monoethylphosphono)ethoxy]ethyl]guanine as a white powder: $^1H$ NMR ($D_2O$, 200 MHz) δ 8.89 (s, 1 H, H-8), 4.43 (t, J = 5 Hz, 2 H, 2 × H-1′), 3.95–4.11 (m, 2 H, 2 × H-2′), 3.85 (apparent quintet, J = 7 Hz, 2 H, $POCH_2$), 3.69 (dq, J = 7.5, 8 Hz, 1 H, $OCH(CH_3)P$), 1.29 (dd, J = 7.5, 15 Hz, 3 H, $OCH(CH_3)P$), and 1.17 (t, J = 7 Hz, 3 H, $POCH_2CH_3$); $^{13}C$ NMR ($D_2O$, 50 MHz) δ 158.6, 158.2, 153.3, 141.6 (C-8), 111.7 (C-5), 75.6 (d, $^1J_{c,p}$ = 160 Hz, OCHP), 70.0 (d, $^3J_{c,p}$ = 9 Hz, C-2′), 64.3 (d, $^2J_{c,p}$ = 6 Hz, $POCH_2$), 48.2 (C-1′), 19.12 (d, $^3J_{c,p}$ = 6 Hz, $POCH_2CH_3$), and 17.5 ($OCH(CH_3)P$); MS (FAB) m/e 332 ($MH^+$). Anal. ($C_{11}H_{18}N_5O_5P$) C, H, N.

A suspension of the monoethyl ester (2.60 g, 7.85 mmol) in anhydrous DMF (80 mL) was treated with bromotrimethylsilane (12.0 g, 78.5 mmol) under argon. The resulting clear, yellow solution was stirred at room temperature for 4.5 h, and then concentrated in vacuo. The residue was placed under high vacuum for 12 h, and then purified by reverse-phase column chromatography on C18 adsorbent ($H_2O$ to 10% $MeOH/H_2O$). Fractions containing the desired product were pooled and concentrated in vacuo to give 2.28 g of a white solid. The solid was further purified by recrystallization from $H_2O/EtOH$ to provide 2.15 g (85%) of the title compound as a fluffy white solid: mp 290–292 °C; $^1H$ NMR (DMSO-$d_6$, 200 MHz) δ 10.59 (s, 1 H, N*H*), 7.75 (s, 1 H, H-8), 4.06 (br t, J = 5 Hz, 2 H, 2 × H-1′), 3.77–3.95 (m, 2 H, 2 × H-2′), 3.53 (apparent quintet, J = 7 Hz, 1 H, $OCH(CH_3)P$), and 1.19 (dd, J = 7, 16 Hz, 3 H, $OCH(CH_3)P$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz) δ 156.6 (C-6), 153.6 (C-2), 151.0 (C-4), 137.8 (C-8), 115.6

(C-5), 72.1 (d, $^1J_{c,p}$ = 165 Hz, OCHP), 68.1 (d, $^3J_{c,p}$ = 6 Hz, C-2'), 42.8 (C-1'), and 15.5 (OCH($CH_3$)P). Anal. ($C_9H_{14}N_5O_5P\cdot0.5H_2O$) C, H, N.

**9-[2-(1-Methyl-1-phosphonoethoxy)ethyl]guanine (6).** Compound **17d** (2.90 g, 6.26 mmol) was dissolved in 1:1 EtOH–cyclohexene (100 mL) and treated in one portion with $Pd(OH)_2$ (1.5 g, 10% on carbon). The mixture was heated at reflux for 14 h and then filtered through a 1-in. pad of Celite. The collected solid was washed with hot EtOH (3 × 50 mL), and the filtrate was concentrated to give 2.25 g (95%) of 9-[2-[1-(diethylphosphono)-1-methylethoxy]ethyl]guanine. The white solid was used without further purification: $^1$H NMR (DMSO-$d_6$, 200 MHz) δ 10.57 (s, 1 H, N*H*), 7.62 (s, 1 H, H-8), 6.45 (br s, 2 H, N$H_2$), 4.06 (t, $J$ = 5 Hz, 2 H, 2 × H-1'), 3.95 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.82 (t, $J$ = 5 Hz, 2 H, 2 × H-2'), 1.23 (d, $J$ = 16 Hz, 6 H, OC($CH_3$)$_2$P), and 1.19 (t, $J$ = 7 Hz, 6 H, 2 × $POCH_2CH_3$); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) δ 156.7, 153.4, 151.0, 137.7 (C-8), 116.2 (C-5), 73.9 (d, $^1J_{c,p}$ = 165 Hz, OCP), 61.7 (d, $^2J_{c,p}$ = 7 Hz, POC$H_2$), 61.3 (d, $^3J_{c,p}$ = 5 Hz, C-2'), 43.2 (C-1'), 21.6 (OC($CH_3$)$_2$P), and 16.2 (d, $^3J_{c,p}$ = 5 Hz, $POCH_2CH_3$); MS (FAB) $m/e$ 374 ($MH^+$).

Bromotrimethylsilane (5.33 g, 34.8 mmol) was added dropwise via syringe to a solution of the diethyl ester (1.30 g, 3.48 mmol) in anhydrous DMF (30 mL) at room temperature under argon. After 4 h, the solution was concentrated in vacuo, and the residue was treated with $H_2O$ (10 mL) and acetone (15 mL). The slurry was kept at −20 °C for 14 h, and then the desired product (0.95 g, 86%) was isolated by filtration: mp 263–266 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.52 (s, 1 H, NH), 7.65 (s, 1 H, H-8), 6.43 (br s, 2 H, N$H_2$), 4.00 (t, $J$ = 5 Hz, 2 H, 2 × H-1'), 3.77 (t, $J$ = 5 Hz, 2 H, 2 × H-2'), and 1.15 (d, $J$ = 14 Hz, 6 H, OC($CH_3$)$_2$P); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) δ 156.8, 153.6, 151.1, 138.1 (C-8), 116.2 (C-5), 73.4 (d, $^1J_{c,p}$ = 160 Hz, OCP), 61.5 (d, $^3J_{c,p}$ = 4 Hz, C-2'), 43.5 (C-1'), and 22.2 (OC($CH_3$)$_2$P); MS (FAB) $m/e$ 318 ($MH^+$). Anal. ($C_{10}H_{16}N_5O_5P\cdot H_2O$) C, H, N.

**Diisopropyl [[1-(Iodomethyl)-1-methylethoxy]methyl]-phosphonate (18).** Isobutene was passed into a solution of diisopropyl (hydroxymethyl)phosphonate (20.0 g, 121 mmol) in 50 mL of anhydrous $CH_2Cl_2$ at −78 °C under nitrogen atmosphere. After 30 min, iodine bromide (4.0 g, 19.34 mmol) was added in one portion. The mixture was stirred at −78 °C for 30 min, then slowly warmed to 0 °C, and stirred at 0 °C for 4 h. The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by flash chromatography ($CH_2Cl_2$–acetone = 10:0 to 10:1) to give 3.61 g (49% yield) of the product as a light yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.68–4.80 (m, 2 H, POC*H*), 3.60 (d, $J$ = 11.7 Hz, 2 H, C$H_2$P), 3.24 (s, 2 H, C$H_2$I), 1.33 (s, 6 H, H-3'), and 1.31 (d, $J$ = 6.2 Hz, 12 H, 4 × POCHC$H_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 74.6 (d, $^3J_{c,p}$ = 15 Hz, C-2'), 71.0 (d, $^2J_{c,p}$ = 7 Hz, POCH), 57.3 (d, $^1J_{c,p}$ = 173 Hz, C$H_2$P), 24.0 (t, $^3J_{c,p}$ = 4 Hz, POCHC$H_3$), and 16.0 (C$H_2$I); MS (FAB) $m/e$ 379 ($MH^+$). Anal. ($C_{11}H_{24}IO_5P$) C, H.

**2-Amino-6-chloro-9-[2-[(diisopropylphosphono)methoxy]-2-methylpropyl]purine (19).** Compound **18** (3.55 g, 9.39 mmol) was mixed with 2-amino-6-chloropurine (2.39 g, 14.09 mmol) and cesium carbonate (6.12 g, 18.78 mmol) in 10 mL of anhydrous DMF. The mixture was stirred at 100 °C under nitrogen atmosphere for 16 h. The mixture was allowed to cool to room temperature and filtered. The solid was washed with $CH_2Cl_2$, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel ($CH_2Cl_2$–$CH_3OH$ = 20:1 to 10:1) to give 0.78 g (22%) of the starting material and 0.54 g (18% yield) of the product as an oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.03 (s, 1 H, H-8), 5.27 (br s, 2 H, N$H_2$), 4.63–4.76 (m, 2 H, POC*H*), 4.06 (s, 2 H, H-1'), 3.60 (d, $J$ = 11.6 Hz, 2 H, OC$H_2$P), 1.30 (d, $J$ = 6.2 Hz, 6 H, 2 × POCHC$H_3$), 1.26 (d, $J$ = 6.2 Hz, 6 H, 2 × POCHC$H_3$), and 1.13 (s, 6 H, H-3'); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 159.3, 154.3, 150.4, 144.0, 123.8, 76.0 (d, $^3J_{c,p}$ = 14 Hz, C-2'), 70.7 (d, $^2J_{c,p}$ = 7 Hz, POCH), 57.5 (d, $^1J_{c,p}$ = 174 Hz, C$H_2$P), 51.1 (C-1'), 23.3 (t, $^3J_{c,p}$ = 4 Hz, POCHC$H_3$), and 21.2 (C-3'); MS (FAB) $m/e$ 420 ($MH^+$).

**9-[2-Methyl-2-(phosphonomethoxy)propyl]guanine Monoammonium Salt (7).** To a solution of compound **19** (0.22 g, 0.52 mmol) and 2,4,6-collidine (0.95 g, 7.8 mmol) in 5 mL of anhydrous $CH_2Cl_2$ was slowly added bromotrimethylsilane (0.68 g, 5.24 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and at room temperature for 16 h. The solvent was evaporated, and the residue was dried in vacuo. Acetone (10 mL) and water (1 mL) were added to the residue, and the mixture was stirred at room temperature for 14 h. The solvent was evaporated, and the residue was dissolved in 10 mL of 1 N NaOH. After washing with $CH_2Cl_2$ (10 mL × 5), the aqueous solution was stirred at 100 °C for 2 h. The solvent was evaporated, and the residue was purified by reverse-phase chromatography (C18, $H_2O$). The crude product collected was further purified by anion-exchange chromatography (Pharmacia, Trisacryl M DEAE, ammonium carbonate buffer pH 8, 0.01 to 0.25 M gradient) to give 96 mg (55%) of the product as white powder: $^1$H NMR ($D_2O$, 300 MHz) δ 8.0 (s, 1 H, H-8), 4.12 (s, 2 H, H-1'), 3.58 (d, $J$ = 11.3 Hz, 2 H, C$H_2$P), and 1.18 (s, 6 H, H-3'); $^{13}$C NMR ($D_2O$, 75 MHz) δ 162.5, 157.1, 155.6, 145.0, 118.6, 79.4 (d, $^3J_{c,p}$ = 13 Hz, C-2'), 61.0 (d, $^1J_{c,p}$ = 161 Hz, C$H_2$P), 53.8 (C-1'), and 24.6 (C-3'); MS (FAB) $m/e$ 318 ($MH^+$).

**9-(2-Acetoxyethyl)-6-*O*-benzylguanine (20).** A solution of 2-bromoethyl acetate (8.35 g, 50.0 mmol) in anhydrous DMF (50 mL) was heated to 75 °C under argon, and cesium carbonate (16.3 g, 50.0 mmol) and 6-*O*-benzylguanine (6.03 g, 25.0 mmol) were added in single portions. The mixture was stirred for 1 h at 75 °C and then allowed to cool to room temperature. Insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in hot EtOAc, and additional insoluble material was removed by filtration. The filtrate was concentrated, and the residue (9.5 g) was purified by column chromatography on silica gel (EtOAc to 4% EtOH/EtOAc). Fractions containing the desired product were pooled and concentrated to give 4.37 g (54%) of **20** as an off-white solid: $^1$H NMR (DMSO-$d_6$, 200 MHz) δ 7.88 (s, 1 H, H-8), 7.37–7.54 (m, 5 H, Ph*H*), 6.49 (br s, 2 H, N$H_2$), 5.51 (s, 2 H, OC$H_2$Ph), 4.28–4.36 (m, 4 H, 2 × H-1' and 2 × H-2'), and 1.98 (s, 3 H, C$H_3$C=O); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) δ 170.0 (C=O), 162.2, 159.6, 154.5, 140.0 (C-8), 136.6, 128.4, 128.3, 127.9, 113.5 (C-5), 66.8 (OC$H_2$Ph), 61.8 (C-2'), 41.8 (C-1'), and 20.5 ($CH_3$C=O).

**9-(2-Acetoxyethyl)-6-*O*-benzyl-$N^2$-(monomethoxytrityl)-guanine (21).** Compound **20** (4.60 g, 14.1 mmol) was dissolved in anhydrous DMF (140 mL) and treated with monomethoxytrityl chloride (6.5 g, 21.1 mmol), triethylamine (4.3 g, 42.2 mmol), and 4-(dimethylamino)pyridine (0.03 g) under argon. The reaction mixture was stirred at 45 °C for 16 h, allowed to cool to room temperature, and then concentrated in vacuo. The residue (15.3 g) was purified by column chromatography on silica gel (75% EtOAc/hexane to EtOAc) to provide 8.2 g (98%) of **21** as a crisp foam: $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.51 (s, 1 H, H-8), 7.16–7.36 (m, 17 H, Ar*H*), 6.76 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.27 (br s, 1 H, N*H*), 5.00 (s, 2 H, OC$H_2$Ph), 4.07–4.18 (m, 4 H, 2 × H-1' and 2 × H-2'), 3.77 (s, 3 H, OC$H_3$), and 2.01 (s, 3 H, C$H_3$C=O); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ 170.4 (C=O), 162.4, 158.1, 157.8, 145.9, 139.3, 138.0, 136.5, 130.2, 129.0, 128.3, 128.1, 127.8, 127.0, 126.6, 115.0 (C-5), 112.9, 70.6 (C$Ar_3$), 67.9 (OC$H_2$Ph), 62.1 (C-2'), 55.2 ($CH_3$O), 42.2 (C-1'), and 20.7 ($CH_3$C=O); MS (FAB) $m/e$ 600 ($MH^+$).

**6-*O*-Benzyl-9-[2-(*tert*-butyldimethylsiloxy)ethyl]-$N^2$-(monomethoxytrityl)guanine (22).** Potassium carbonate (3.99 g, 28.9 mmol) was added in one portion to a solution of compound **21** (14.4 g, 24.1 mmol) in $CH_3OH$ (75 mL) at room temperature. After 1 h, the solvent was removed in vacuo, and the residue was partitioned between $CH_2Cl_2$ (200 mL) and water (200 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (150 mL). The combined organic layers were washed with saturated NaCl solution (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give 13.9 g of 6-*O*-benzyl-9-(2-hydroxyethyl)-$N^2$-(monomethoxytrityl)guanine as a pale yellow glass. The alcohol was used without purification: $^1$H NMR ($CDCl_3$, 200 MHz) δ 7.47 (s, 1 H, H-8), 7.18–7.40 (m, 17 H, Ar*H*), 6.75 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.25 (br s, 1 H, N*H*), 5.00 (s, 2 H, OC$H_2$Ph), 3.90–4.08 (m, 4 H, 2 × H-1' and 2 × H-2'), and 3.75 (s, 3 H, OC$H_3$).

A solution of the alcohol in anhydrous $CH_2Cl_2$ (120 mL) was treated with *tert*-butyldimethylsilyl chloride (5.45 g, 36.2 mmol), triethylamine (4.88 g, 48.2 mmol), and 4-(dimethylamino)pyridine (0.05 g) under argon. After 16 h at room temperature, the reaction mixture was poured into a separatory funnel containing $CH_2Cl_2$ (200 mL) and water (150 mL). The layers were agitated and separated, and the aqueous layer was extracted with $CH_2Cl_2$ (100

mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give 18 g of a yellow residue. Column chromatography on silica gel (25% to 75% EtOAc/hexanes) gave 15.8 g (98%) of the product as a white foam: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.72 (s, 1 H, H-8), 7.30–7.46 (m, 17 H, Ar*H*), 6.90 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.38 (br s, 1 H, N*H*), 5.15 (s, 2 H, OC$H_2$Ph), 4.00–4.18 (m, 2 H, 2 × H-1′), 3.91 (s, 3 H, OC$H_3$), 3.72–3.90 (m, 2 H, 2 × H-2′), 0.97 (s, 9 H, SiC($CH_3$)$_3$), and −0.01 (s, 6 H, Si($CH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 159.9, 158.1, 157.7, 153.5, 146.0, 140.4, 138.2, 136.6, 130.3, 129.1, 128.2, 128.0, 127.9, 127.7, 127.6, 126.5, 115.0 (C-5), 112.8, 70.6 (C$Ar_3$), 67.8 (OC$H_2$Ph), 61.2 (C-2′), 55.2 (C$H_3$O), 45.8 (C-1′), 25.8 (SiC($CH_3$)$_3$), 18.1 (Si*C*($CH_3$)$_3$), and −5.7 (Si$CH_3$)$_2$); MS (methane-DCI) $m/e$ 672 ($MH^+$).

**6-*O*-Benzyl-9-[2-(*tert*-butyldimethylsiloxy)ethyl]-$N^2$-(monomethoxytrityl)-8-methylguanine (23).** A solution of diisopropylamine (5.78 g, 57.1 mmol) in anhydrous THF (40 mL) was cooled to −40 °C and treated with *n*-BuLi solution (18.0 mL, 2.5 M in hexanes, 45.2 mmol) under argon. The resulting pale yellow solution was allowed to warm to 0 °C over 0.5 h, stirred at 0 °C for 0.5 h, and then cooled to −78 °C. A solution of compound **22** (7.60 g, 11.3 mmol) in THF (40 mL) was added dropwise via addition funnel, and the mixture was stirred at −78 °C for 4 h. Meanwhile, a solution of methyl iodide (25.1 g, 176 mmol) in THF (20 mL) was cooled to −78 °C. The above anionic solution was added dropwise via cannula over 0.5 h to the MeI solution, and the resulting bright yellow mixture was allowed to warm to room temperature. After 14 h, the reaction was quenched by slow addition of EtOH (15 mL). The mixture was then partitioned between EtOAc (300 mL) and water (200 mL), and the organic layer was washed with saturated NaCl solution (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue (8.1 g) was purified by column chromatography on silica gel (25% to 50% EtOAc/hexanes) to afford 4.21 g (54%) of the desired product as a white foam: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.35–7.53 (m, 17 H, Ar*H*), 6.92 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.33 (br s, 1 H, N*H*), 5.18 (s, 2 H, OC$H_2$Ph), 3.95–4.12 (m, 2 H, 2 × H-1′), 3.93 (s, 3 H, OC$H_3$), 3.74–3.95 (m, 2 H, 2 × H-2′), 2.63 (s, 3 H, C$^8$-C$H_3$), 0.96 (s, 9 H, SiC($CH_3$)$_3$), and 0.00 (s, 6 H, Si($CH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 158.8, 158.0, 157.0, 154.6, 148.9 (C-8), 146.1, 138.3, 136.7, 130.3, 129.1, 128.2, 127.6, 127.5, 126.4, 113.8 (C-5), 112.8, 70.5 (C$Ar_3$), 67.7 (OC$H_2$Ph), 61.4 (C-2′), 55.1 (C$H_3$O), 45.0 (C-1′), 25.8 (SiC($CH_3$)$_3$), 18.2 (Si*C*($CH_3$)$_3$), 14.1 (C$^8$-C$H_3$), and −5.7 (Si($CH_3$)$_2$); MS (methane-DCI) $m/e$ 686 ($MH^+$).

**6-*O*-Benzyl-9-[2-[(diethylphosphono)methoxy]ethyl]-$N^2$-(monomethoxytrityl)-8-methylguanine (24).** Compound **23** (5.47 g, 7.99 mmol) was dissolved in THF (65 mL) and treated dropwise with a solution of tetrabutylammonium fluoride in THF (12 mL, 1 M in THF, 12.0 mmol). The reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo to give 6 g of a yellow residue. Purification by column chromatography on silica gel (2% to 5% MeOH/$CH_2Cl_2$) afforded 4.26 g (93%) of 6-*O*-benzyl-9-(2-hydroxyethyl)-$N^2$-(monomethoxytrityl)-8-methylguanine as a white crisp foam: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.22–7.36 (m, 17 H, Ar*H*), 6.77 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.25 (br s, 1 H, N*H*), 5.31 (s, 1 H, O*H*), 5.03 (s, 2 H, OC$H_2$Ph), 3.83–3.97 (m, 2 H, 2 × H-1′), 3.78 (s, 3 H, OC$H_3$), 3.65–3.80 (m, 2 H, 2 × H-2′), and 2.41 (s, 3 H, C$^8$-C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 159.1, 158.1, 156.9, 154.6, 148.2 (C-8), 145.8, 138.0, 136.5, 130.2, 129.0, 128.2, 127.8, 127.7, 126.6, 113.9 (C-5), 112.9, 70.6 (C$Ar_3$), 67.8 (OC$H_2$Ph), 61.0 (C-2′), 55.2 (C$H_3$O), 46.5 (C-1′), and 14.1 (C$^8$-C$H_3$); MS (FAB) $m/e$ 572 ($MH^+$).

A solution of the alcohol (4.20 g, 7.36 mmol) in anhydrous DMF (50 mL) was cooled to 0 °C under argon and treated with NaH (0.45 g, 80% dispersion in oil, 14.7 mmol). After 1 h, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 4 h. The solution was then transferred via cannula to a solution of diethyl (*p*-tosyloxy)methanephosphonate (3.56 g, 11.0 mmol) in DMF (25 mL) that had been precooled to 0 °C. The mixture was allowed to warm to room temperature and was stirred for 14 h. Following treatment with EtOH (10 mL), the reaction mixture was concentrated in vacuo. The orange residue was slurried in hot 5% EtOH/EtOAc, and the mixture was filtered to remove insoluble material. Concentration of the filtrate gave 6.5 g of an orange, viscous oil which was purified by column chromatography on silica gel (3% to 7% EtOH/EtOAc) to provide 2.42 g (46%) of the desired product as a white foam: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.19–7.36 (m, 17 H, Ar*H*), 6.76 (d, $J$ = 7 Hz, 2 H, Ar*H*), 6.20 (br s, 1 H, N*H*), 5.06 (s, 2 H, OC$H_2$Ph), 4.04 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.85–3.97 (m, 2 H, 2 × H-1′), 3.77 (s, 3 H, OC$H_3$), 3.59 (d, $J$ = 8 Hz, 2 H, OC$H_2$P), 3.45–3.60 (m, 2 H, 2 × H-2′), 2.45 (s, 3 H, C$^8$-C$H_3$), and 1.23 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 158.5, 157.7, 156.6, 148.3 (C-8), 145.7, 137.8, 136.3, 129.9, 128.7, 127.8, 127.3, 127.2, 126.1, 113.4 (C-5), 112.5, 70.9 (d, $^3J_{c,p}$ = 12 Hz, C-2′), 70.1 (C$Ar_3$), 67.3 (OC$H_2$Ph), 64.9 (d, $^1J_{c,p}$ = 165 Hz, OC$H_2$P), 61.9 (d, $^2J_{c,p}$ = 6 Hz, POC$H_2$), 54.8 (C$H_3$O), 42.1 (C-1′), 16.0 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$C$H_3$), and 13.5 (C$^8$-C$H_3$); MS (methane-DCI) $m/e$ 722 ($MH^+$).

**9-[2-[(Diethylphosphono)methoxy]ethyl]-$N^2$-(monomethoxytrityl)-8-methylguanine (25).** Palladium hydroxide (1.2 g, 10% on carbon) was added in one portion to a solution of compound **24** (2.40 g, 3.32 mmol) in 1:1 EtOH/cyclohexene (30 mL). The mixture was heated at reflux for 45 min and then was filtered while hot through a 1-in. pad of Celite. The collected solid was washed with hot EtOH (3 × 50 mL), and the combined filtrates were concentrated in vacuo. The residue (2.2 g) was purified by column chromatography on silica gel (2% to 7% MeOH/$CH_2Cl_2$) to provide 2.00 g (95%) of **25** as a white foam: $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 10.48 (s, 1 H, N*H*), 7.59 (s, 1 H, NHC$Ar_3$), 7.15–7.35 (m, 17 H, Ar*H*), 6.87 (d, $J$ = 7 Hz, 2 H, Ar*H*), 3.93 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.73 (s, 3 H, OC$H_3$), 3.50–3.65 (m, 4 H, 2 × H-1′ and OC$H_2$P), 3.10–3.22 (m, 2 H, 2 × H-2′), 2.24 (s, 3 H, C$^8$-C$H_3$), and 1.17 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 157.6, 156.0, 150.2, 150.1, 145.3 (C-8), 145.0, 136.8, 129.8, 128.41, 127.5, 126.4, 115.2 (C-5), 112.8, 70.4 (d, $^3J_{c,p}$ = 13 Hz, C-2′), 69.6 (C$Ar_3$), 64.1 (d, $^1J_{c,p}$ = 165 Hz, OC$H_2$P), 61.6 (d, $^2J_{c,p}$ = 6 Hz, POC$H_2$), 54.9 (C$H_3$O), 41.7 (C-1′), 16.1 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$C$H_3$), and 13.2 (C$^8$-C$H_3$); MS (methane-DCI) $m/e$ 632 ($MH^+$).

**9-[2-[(Diethylphosphono)methoxy]ethyl]-8-methylguanine (26).** A solution of compound **25** (2.02 g, 3.20 mmol) in 80% aqueous acetic acid (30 mL) was heated at 70 °C for 1.5 h, allowed to cool to room temperature, and concentrated in vacuo. The residue was suspended in hot EtOAc, and EtOH was added dropwise until a clear solution was obtained. The solution was allowed to cool slowly to room temperature, and the resulting solid was collected by filtration to give 0.84 g (74%) of **26** as a white solid. HPLC analysis on a Waters Bondapak C18 column (4.6 × 300 mm), eluting with 20% MeOH/7.5 mM phosphate buffer at pH 3.4, showed <1% of 9-[2-[(diethylphosphono)methoxy]-ethyl]guanine: mp 225–228 °C dec; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 10.48 (s, 1 H, N*H*), 6.30 (br s, 2 H, N$H_2$), 4.09 (t, $J$ = 5 Hz, 2 H, 2 × H-1′), 3.96 (apparent quintet, $J$ = 7 Hz, 4 H, 2 × POC$H_2$), 3.81 (d, $J$ = 8 Hz, 2 H, OC$H_2$P), 3.77 (t, $J$ = 5 Hz, 2 H, 2 × H-2′), 2.37 (s, 3 H, C$^8$-C$H_3$), and 1.19 (t, $J$ = 7 Hz, 6 H, 2 × POCH$_2$C$H_3$); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 156.3 (C-6), 153.1 (C-2), 151.9 (C-4), 145.0 (C-8), 114.9 (C-5), 70.7 (d, $^3J_{c,p}$ = 13 Hz, C-2′), 64.1 (d, $^1J_{c,p}$ = 165 Hz, OC$H_2$P), 61.6 (d, $^2J_{c,p}$ = 6 Hz, POC$H_2$), 41.6 (C-1′), 16.1 (d, $^3J_{c,p}$ = 6 Hz, POCH$_2$C$H_3$), and 13.4 (C$^8$-C$H_3$); MS (methane-DCI) $m/e$ 360 ($MH^+$).

**8-Methyl-9-[2-(phosphonomethoxy)ethyl]guanine (5).** Bromotrimethylsilane (3.5 g, 23 mmol) was added dropwise to a solution of compound **26** (0.82 g, 2.3 mmol) in anhydrous DMF (20 mL) at room temperature under argon. The mixture was stirred at room temperature for 16 h and concentrated in vacuo. The yellow residue was treated with $H_2O$ (10 mL) and acetone (20 mL) to give a white slurry. The mixture was kept at 0 °C for 14 h, and the solid was collected by filtration to afford 0.60 g (87%) of the product as a white solid: mp 220–225 °C dec; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 10.59 (s, 1 H, N*H*), 6.48 (br s, 2 H, N$H_2$), 4.11 (t, $J$ = 5 Hz, 2 H, 2 × H-1′), 3.76 (t, $J$ = 5 Hz, 2 H, 2 × H-2′), 3.48 (d, $J$ = 8 Hz, 2 H, OC$H_2$P), and 2.43 (s, 3 H, C$^8$-C$H_3$); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 155.9 (C-6), 153.3 (C-2), 151.6 (C-4), 145.4 (C-8), 113.9 (C-5), 70.3 (d, $^3J_{c,p}$ = 13 Hz, C-2′), 66.8 (d, $^1J_{c,p}$ = 165 Hz, OC$H_2$P), 41.8 (C-1′), and 13.3 (C$^8$-C$H_3$); MS (methane-DCI) $m/e$ 304 ($MH^+$). Anal. ($C_9H_{14}N_5O_5P\cdot H_2O$) C, H, N.

**(*R*)-6-*O*-Benzyl-9-[3-(benzyloxy)-2-[(diisopropylphosphono)methoxy]propyl]guanine (27).** Compound **10** (13.8 g, 31.5 mmol), 6-*O*-benzylguanine (9.07 g, 37.8 mmol), and cesium carbonate (12.3 g, 37.76 mmol) were mixed in 150 mL of dry

acetonitrile under nitrogen atmosphere. The mixture was heated gently at reflux for 16 h. The solvent was removed under reduced pressure, and then $CH_2Cl_2$ (150 mL) was added to the residue. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure to give a residue which was purified by flash chromatography on silica gel (first time, $CH_2Cl_2$–$CH_3OH$ = 30:1 to 10:1; second time, $CH_2Cl_2$–acetone = 2:1 to 0:1) to provide 10.9 g (59% yield) of **27** as a thick mass. The product crystallized upon standing at room temperature. The solid was triturated with $Et_2O$ to give **27** as white crystals: mp 75–79 °C; $[\alpha]^{20}_D$ +16.7° (*c* 1.02, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1 H, H-8), 7.45–7.52 and 7.20–7.35 (2 m, 10 H, Ar*H*), 5.54 (s, 2 H, 6-OC$H_2$Ph), 4.84 (br s, 2 H, N$H_2$), 4.59–4.71 (m, 2 H, 2 × POC*H*), 4.50 (s, 2 H, 3′-OC$H_2$Ph), 4.30 (dd, *J* = 4.1, 14.4 Hz, 1 H, H-1′), 4.17 (dd, *J* = 6.5, 14.4 Hz, 1 H, H-1′), 3.90–3.98 (m, 1 H, H-2′), 3.83 (dd, *J* = 8.7, 13.6 Hz, 1 H, OC$H_2$P), 3.75 (dd, *J* = 8.0, 13.6 Hz, 1 H, OC$H_2$P), 3.50 (d, *J* = 5.0 Hz, 2 H, C$H_2$OBn), and 1.16–1.32 (m, 12 H, 4 × POCHC$H_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 161.2, 159.5, 154.5, 140.7, 137.7, 136.7, 128.6, 128.4, 128.3, 128.0, 127.9, 115.1, 78.8 (d, $^3J_{c,p}$ = 11 Hz, C-2′), 73.5 (3′-OC$H_2$Ph), 71.1 (d, $^2J_{c,p}$ = 5 Hz, POCH), 71.0 (d, $^2J_{c,p}$ = 7 Hz, POCH), 68.8 and 67.8 (C-3′ and 6-O-C$H_2$Ph), 64.9 (d, $^1J_{c,p}$ = 168 Hz, OC$H_2$P), 43.9 (C-1′), 23.8 (d, $^3J_{c,p}$ = 4 Hz, POCHC$H_3$), and 23.7 (d, $^3J_{c,p}$ = 4 Hz, POCHC$H_3$); MS (FAB) *m/e* 584 ($MH^+$). Anal. ($C_{29}H_{38}N_5O_6P$) C, H, N.

**(*R*)-9-[3-Hydroxy-2-(phosphonomethoxy)propyl]guanine [(*R*)-8].** A solution of compound **27** (4.00 g, 5.85 mmol) in EtOH and cyclohexene (30 mL of each) was treated with 20% palladium hydroxide on carbon (1.0 g). The mixture was heated gently at reflux for 3 days. The catalyst was collected by filtration and boiled in $CH_3OH$ (100 mL) for 2 min, and the resulting slurry was filtered. The process was repeated three times. The combined filtrates were concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel ($CH_2Cl_2$–$CH_3OH$ = 10:1 to 5:1). The crude product was recrystallized from $CH_3OH$–EtOAc to give 2.16 g (92% yield) of (*R*)-9-[2-[(diisopropylphosphono)methoxy]-3-hydroxypropyl]-guanine as a crystalline solid. A sample of the solid product was recrystallized from water to give crystals of the alcohol: $[\alpha]^{20}_D$ +23.7° (*c* 1.95, $CH_3OH$); $^1$H NMR (300 MHz, $CD_3OD$) δ 7.49 (s, 1 H, H-8), 4.65 (s, 2 H, N$H_2$), 4.34–4.46 (m, 2 H, 2 × POC*H*), 4.05 (dd, *J* = 4.0, 14.5 Hz, 1 H, H-1′), 3.95 (dd, *J* = 6.6, 14.5 Hz, 1 H, H-1′), 3.71 (dd, *J* = 8.9, 13.8 Hz, 1 H, OC$H_2$P), 3.63 (dd, *J* = 9.5, 13.8 Hz, 1 H, OC$H_2$P), 3.58–3.66 (m, 1 H, H-2′), 3.39 (dd, *J* = 5.0, 12.2 Hz, 1 H, H-3′), 3.33 (dd, *J* = 5.0, 12.2 Hz, 1 H, H-3′), and 1.00–1.10 (m, 12 H, 4 × POCHC$H_3$); $^{13}$C NMR ($CD_3OD$, 75 MHz) δ 159.8, 155.7, 153.7, 140.9, 117.4, 81.9 (d, $^3J_{c,p}$ = 12 Hz, C-2′), 73.3 (d, $^2J_{c,p}$ = 6 Hz, POCH), 65.0 (d, $^1J_{c,p}$ = 169 Hz, OC$H_2$P), 61.5 (C-3′), 44.6 (C-1′), and 24.1 (d, $^3J_{c,p}$ = 4 Hz, POCH$CH_3$). Anal. ($C_{15}H_{26}N_5O_6P \cdot 0.25H_2O$) C, H, N.

A solution of (*R*)-9-[2-[(diisopropylphosphono)methoxy]-3-hydroxypropyl]guanine (0.20 g, 0.50 mmol) in 5 mL of anhydrous acetonitrile was treated with bromotrimethylsilane (0.99 g, 6.45 mmol) under nitrogen atmosphere. The resulting solution was protected from light and stirred at room temperature for 14 h. The solvent was removed under reduced pressure, and the residue was dried under vacuum. To the residue were added water (1 mL) and acetone (4 mL). The mixture was stirred at room temperature overnight and then the solvent removed. The residue was triturated with $CH_2Cl_2$ and filtered. The collected solid was recrystallized from water–$CH_3OH$ to give 127 mg (80% yield) of (*R*)-8 as white crystals: mp 249 °C dec; $[\alpha]^{20}_D$ +32.3° (*c* 1.11, $H_2O$); $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 7.73 (s, 1 H, H-8), 6.49 (br s, 2 H, N$H_2$), 4.17 (dd, *J* = 4.1, 14.3 Hz, 1 H, H-1′), 3.98 (dd, *J* = 6.6, 14.3 Hz, 1 H, H-1′), 3.61–3.73 (m, 1 H, H-2′), 3.64 (dd, *J* = 8.9, 13.3 Hz, 1 H, OC$H_2$P), 3.58 (dd, *J* = 9.3, 13.3 Hz, 1 H, OC$H_2$P), and 3.32–3.45 (m, 2 H, H-3′); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ 157.1, 154.1, 151.6, 138.6, 115.9, 80.5 (d, $^3J_{c,p}$ = 10 Hz, C-2′), 65.6 (d, $^1J_{c,p}$ = 161 Hz, OC$H_2$P), 60.2 (C-3′), and 43.2 (C-1′). Anal. ($C_9H_{14}N_5O_6P$) C, H, N.

**(*S*)-9-[3-Hydroxy-2-(phosphonomethoxy)propyl]guanine [(*S*)-8]**: mp 180–182 °C; $[\alpha]^{20}_D$ −35.83° (*c* 0.49, $H_2O$). Anal. ($C_9H_{14}N_5O_6P$) C, H, N.

**Evaluation of Compounds against Herpesviruses.** Plaque reduction assays for compounds 1–6 and 8 were conducted with vero cells infected with HSV-2 (G strain) or MRC-5 cells infected with HCMV (AD-169 strain) and then treated with the phosphonate analogues as previously described.[12b] Analogue **7** was tested in WI-38 cell monolayers infected with HSV-2 and HCMV as previously described.[25] The antiviral effectiveness of each compound was determined as the $EC_{50}$, the concentration of compound necessary to reduce the number of plaques to 50% those in the virus control cultures. The cellular toxicity of each compound ($TC_{50}$) in stationary cells was determined as the drug concentration required to disrupt 50% of the cell monolayer in uninfected cell cultures.

**Evaluation of Compounds against Human Immunodeficiency Virus.** Compounds were evaluated for activity against HIV (LAV-BRU strain) in CEM cells using the XTT assay described by Weislow et al.[3c] The antiviral effect is expressed as the concentration of compound which increases the number of viable cells in infected cultures to 50% that of untreated controls ($TC_{50}$). The inhibitory effect on growing cells ($CC_{50}$) was determined in CEM cells as the concentration of compound which caused 50% inhibition in cell growth after at least three rounds of replication when compared with untreated control cell cultures.