Synthesis and Antiviral Activity of 2'-Substituted 9-[2-(Phosphonomethoxy)ethyl]guanine Analogues

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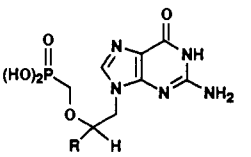
A series of 2'-substituted derivatives of 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG, 1) have been synthesized and evaluated *in vitro* for anti-human immunodeficiency virus (HIV) activity in the XTT assay and for anti-herpes activity in the plaque reduction assay. It has been observed that the anti-HIV activity of these derivatives depends on the size and the nature of the substituent as well as the chirality at the 2'-position of PMEG. In addition, these compounds generally demonstrated greater activity against HIV than herpes viruses. The most interesting analogues which emerged from these studies are (*R*)-2'-(azidomethyl)-PMEG [(*R*)-5] and (*R*)-2'-vinyl-PMEG [(*R*)-11]. The former showed anti-HIV activity with an IC_{50} of 5 μM and a cytotoxicity (CC_{50}) greater than 1.4 mM in CEM cells. The latter has an IC_{50} of 13 μM for anti-HIV activity and a CC_{50} of greater than 1.6 mM. Furthermore, we have demonstrated that replacement of the guanine base of these 2'-substituted PMEG analogues with cytosine drastically reduces anti-HIV and anti-herpes activity.

Introduction

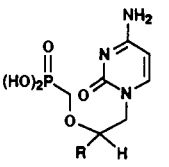
The initial report of the antiviral activity of (phosphonomethoxy)alkyl nucleotide analogues[1] has prompted several investigations exploring the structure–activity relationships for this exciting class of antiviral agents. As is the case for the well-studied nucleoside analogue family of antiviral agents, these nucleotide analogues most likely exert their antiviral effect following sequential activation to the corresponding triphosphate analogues.[2] However, as mimics of nucleoside monophosphates, these derivatives bypass the first and often rate-limiting step in the activation process, and therefore have the potential for greater potency and a broader spectrum of activity. The most potent member of this class reported to date is 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG, 1).[3] This acyclic guanine derivative shows *in vitro* activity against both herpes viruses and retroviruses such as human immunodeficiency virus (HIV). *In vivo*, PMEG is significantly more potent than acyclovir against herpes simplex virus (HSV) types 1 and 2, showing activity at doses as low as 0.1 mg/kg/day. However, PMEG also shows substantial toxicity at doses higher than 5 mg/kg/day and as a result has a narrower margin of safety than acyclovir.

A number of studies have appeared on efforts aimed at modifying the PMEG skeleton to provide new antiviral agents with improved selectivity.[4] One of the most promising derivatives to be identified from our studies is (*R*)-2'-methyl-PMEG [(*R*)-2]. While this compound was somewhat less potent against HIV and HSV 2 than PMEG *in vitro*, it showed significantly reduced cytotoxicity, thus demonstrating that antiviral activity and cellular toxicity could be varied independently. The corresponding (*S*)-isomer of 2'-methyl-PMEG was less potent and less selective as an anti-HIV agent. In the present report, we describe work focusing on additional modifications at the 2'-position of PMEG (Chart I). One derivative of this type, 9-[3-hydroxy-2-(phosphonomethoxy)propyl]guanine (HPMPG, 3), has already been described.[4,5] We were interested in evaluation of a series of guanine derivatives bearing other heteroatom substituents[6] attached by methylene and ethylene linkers at the 2'-position, and have also examined the effect of increasing the size of a hydrophobic substituent at the 2'-position. In most of the cases, both enantiomers of these PMEG analogues were synthesized in order to evaluate the effects of orientation of the substituent on biological activity. Based on the promising activity of (*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine [(*S*)-HPMPC, (*S*)-4],[5a,7] we also prepared several cytosine derivatives bearing a variety of substituents at the 2'-position. This report describes the synthesis and *in vitro* antiviral activity of these novel 2'-substituted (phosphonomethoxy)ethyl derivatives.

Chart I



1	R = H
2	R = CH_3
3	R = CH_2OH
5	R = CH_2N_3
6	R = CH_2F
7	R = CH_2Cl
8	R = CH_2CH_2OH
9	R = $CH_2CH_2N_3$
10	R = CH_2CH_2F
11	R = $CH{=}CH_2$
12	R = cyclopropyl
13	R = CH_2CH_3



4	R = CH_2OH
14	R = CH_2N_3
15	R = CH_2F
16	R = CH_2CH_2OH
17	R = $CH_2CH_2N_3$
18	R = CH_2CH_2F
19	R = $CH{=}CH_2$
20	R = cyclopropyl
21	R = CH_2CH_3

Chemistry

All of the analogues described in this report were prepared from the enantiomerically pure starting mate-

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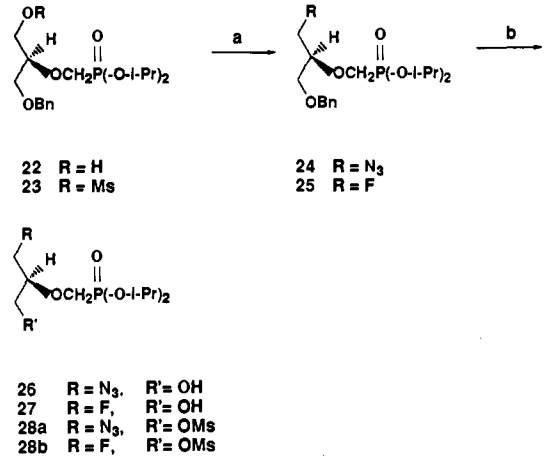
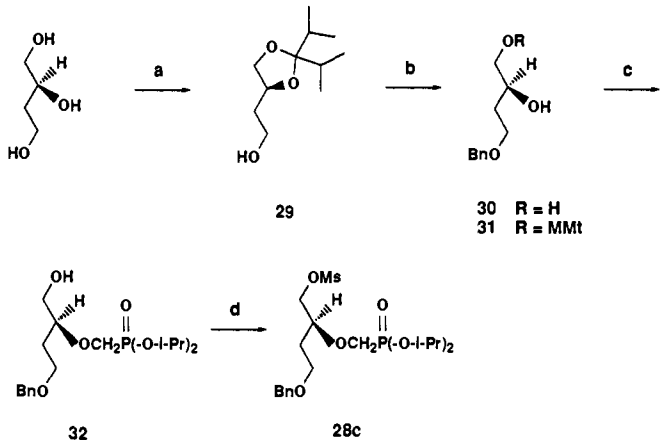
Scheme I[a]



[a] (a) NaN_3 or TBAF; (b) BCl_3; MsCl, Et_3N.

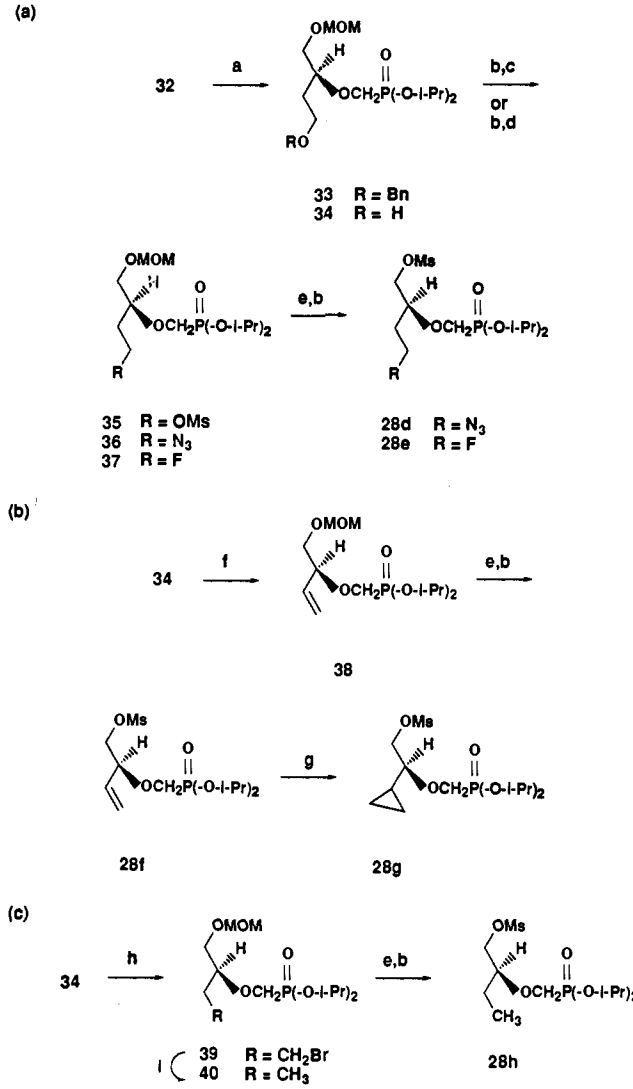
Scheme II[a]



[a] (a) 2,4-Dimethyl-3-pentanone, TsOH; (b) BnBr, NaOH; 1.5 M H_2SO_4; MMt-Cl, Et_3N; (c) NaH, $TsOCH_2PO(O\text{-}i\text{-}Pr)_2$, H^+; (d) MsCl, Et_3N.

rials, and no racemization was found in the preparation of these chiral analogues.[8] The general strategy employed for the synthesis of 2′-substituted PME analogues listed in Chart I involves coupling of the corresponding mesylates of the phosphonate side chains with a purine or pyrimidine base. An exception was 2′-(chloromethyl)-PMEG (**7**), which was prepared by functionalization of an intact guanine derivative bearing a free hydroxy group. The syntheses of the required mesylate side chains are depicted in Schemes I-III. For the 2′-azidomethyl analogue, nucleophilic substitution of mesylate **23**[4] with NaN_3 in DMF[9] at 105 °C afforded **24** in 78% yield (Scheme I). Initial attempts to prepare fluoromethyl intermediate **25** by treating **22**[4] with diethylamidosulfur trifluoride (DAST)[10] in methylene chloride resulted in significant elimination and many side products. On the other hand, mesylate **23** reacted smoothly with anhydrous tetrabutylammonium fluoride[11] in THF at room temperature to provide **25** in 77% yield. The trace of the elimination product which formed was easily separated by acidic hydrolysis of the product mixture followed by silica gel chromatography. Removal of the benzyl protecting group of **24** and **25** with BCl_3[12] gave **26** and **27**, respectively. Conversion to mesylates **28a** and **28b** proceeded in excellent yields upon treatment with mesyl chloride followed by addition of Et_3N. It is worth noting that the addition sequence of reagents is critical to obtain high yields and purity of the product in the mesylation reactions.

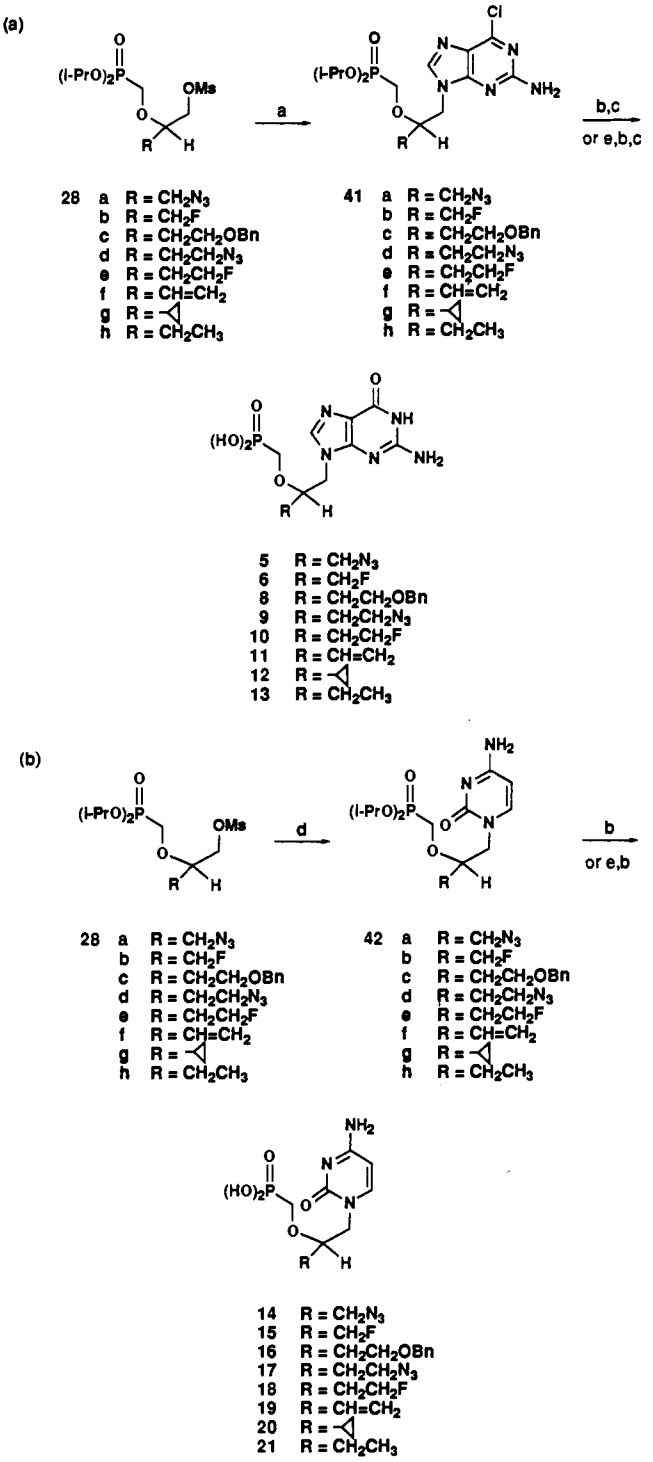
Scheme III[a]



[a] (a) MOM-Cl, diisopropylethylamine; cyclohexene, $Pd(OH)_2$; (b) MsCl, Et_3N; (c) NaN_3; (d) TBAF; (e) CSA-MeOH; (f) 2-nitrophenyl selenocyanate, $P(n\text{-}Bu)_3$; H_2O_2, NaOH; (g) CH_2N_2, $Pd(OAc)_2$; (h) CBr_4, PPh_3, imidazole; (i) H_2, Pd/C, Et_3N.

For the preparation of side chains of the 2′-ethyl substituted PME derivatives, alcohol **32** served as a common intermediate. Initial attempts to selectively protect the 1-hydroxy group of (*S*)-1,2,4-butanetriol using dibutyltin oxide[13] and benzyl bromide produced a 2:1 mixture of 1- and 4-O-benzyl 1,2,4-butanetriol. However, separation of these two regioisomers proved very tedious. Alternatively, a modified procedure of Clive[14] using 2,4-dimethyl-3-pentanone and TsOH in refluxing benzene resulted in selective protection of the 1,2-diol of (*S*)-1,2,4-butanetriol as a ketal to give **29** in 84% yield. Purification by flash chromatography afforded the desired product, free of the isomeric six-membered ketal. Interestingly, when the same reaction was carried out in refluxing toluene instead of benzene, the hemiketal which resulted from reaction of 4-hydroxy moiety of **29** with 2,4-dimethyl-3-pentanone was the only product. Phase-transfer alkylation of **29** with benzyl bromide followed by acidic hydrolysis of the resulting ketal provided diol **30** in 92% yield. The primary hydroxyl group of **30** was selectively protected with monomethoxyltrityl chloride (MMt-Cl) to give **31**. O-Alkylation of **31** with NaH and diisopropyl tosylmethanephosphonate[7] followed by removal of the MMt-pro-

Scheme IV[a]



[a] (a) 2-Amino-6-chloropurine, Cs_2CO_3; (b) TMSBr; H_2O; (c) aqueous HCl; (d) cytosine, Cs_2CO_3; (e) BCl_3.

tecting group furnished intermediate **32** in modest yield. Treatment of **32** with mesyl chloride afforded **28c** in 98% yield.

Elaboration of intermediate **32** to other substituted side chains is described in Scheme III. Protection of the hydroxyl group of **32** as a methoxymethyl (MOM) ether[15] (**33**), followed by catalytic transfer hydrogenation using cyclohexene and Pearlman's catalyst,[16] provided **34** (96% yield for two steps) (Scheme IIIa). Alcohol **34** was converted to mesylate **35** by treatment with mesyl chloride and triethylamine. Nucleophilic displacement of the mesylate group with azide or fluoride gave **36** and **37**, respectively. The MOM group was removed upon hydrolysis with camphorsulfonic acid in MeOH, and the resulting alcohols were converted into the corresponding mesylates **28d** and **28e** in excellent yields. Dehydration of **34** was achieved in two steps by reaction with 2-nitrophenyl selenocyanate[17] and tributylphosphine followed by oxidative elimination with H_2O_2–NaOH to afford **38** in 77% yield (Scheme IIIb). Deprotection of the MOM ether and conversion of the resulting alcohol to a mesylate gave **28f**. Cyclopropanation of **28f** was effected by treatment with CH_2N_2 in the presence of $Pd(OAc)_2$[18] to provide **28g** in quantitative yield. Ethyl derivative **28h** was prepared from alcohol **34** (Scheme IIIc) by reaction with CBr_4 and triphenylphosphine[19] followed by reduction of the resulting bromide **39** to provide **40**. Attempted use of an iodide intermediate was unsuccessful: formation of a complex product mixture resulted upon reaction of mesylate **35** with NaI in refluxing acetone or when **34** was treated with iodine–triphenylphosphine and imidazole in the presence or absence of Et_3N. Compound **40** was smoothly transformed into mesylate **28h** using the method described above.

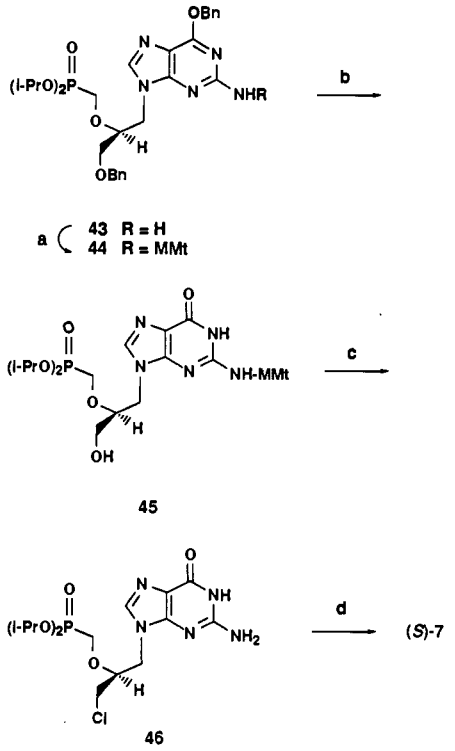
The mesylate side chains shown in Schemes I-III were coupled to 2-amino-6-chloropurine or cytosine in the presence of Cs_2CO_3[4] to give the corresponding phosphonate nucleotides as depicted in Scheme IV. For the guanine derivatives **41a,b,d-h**, cleavage of the phosphonate esters was effected by treatment with trimethylsilyl bromide (TMSBr)[20] in acetonitrile. The resulting 2-amino-6-chloropurine phosphonic acids were heated at reflux in aqueous HCl to provide target compounds **5**, **6**, and **9–13** (Scheme IVa). For preparation of the 2′-hydroxyethyl derivative **8**, the above sequence was preceded by treatment with BCl_3 to remove the benzyl group. Cytosine derivatives **14**, **15**, and **17–21** were obtained in good yields following TMSBr treatment of intermediates **42a,b,d-h** (Scheme IVb). In the case of intermediate **42c**, the benzyl group was removed first by treatment of BCl_3. Reaction with TMSBr then afforded cytosine derivative **16**.

2′-(Chloromethyl)-PMEG (**7**) was prepared from intermediate **43**[4] (Scheme V). Treatment with MMt-Cl afforded fully protected derivative **44**. Heating of **44** at reflux in a mixture of cyclohexene–ethanol in the presence of Pearlman's catalyst resulted in selective removal the *O*-benzyl groups to provide **45** in 51% yield. Reaction of alcohol **45** with CCl_4 and PPh_3–imidazole[21] followed by treatment with aqueous acetic acid gave **46** in modest yields. One of the major side products formed in the chlorination reaction was the 6-imidazole purine derivative. Sequential removal of the amino and the phosphonate protecting groups furnished (*S*)-**7** in 81% yield.

Results and Discussion

The analogues prepared were evaluated for anti-HIV activity using the XTT assay in CEM cells.[22] Results are shown in Table I. In previous work, we demonstrated that (*R*)-2′-methyl-PMEG [(*R*)-**2**] is more potent and less toxic than the corresponding (*S*)-isomer in the XTT assay.[4] Our objective in this SAR study was to investigate the effects of substitution at the 2′-position of PMEG and to see whether enantiomers of these new compounds exerted different biological effects. From Table I it can be seen that substitution on the methyl group of 2′-methyl PMEG with an azide or a halogen substituent (**5–7**) provided derivatives with retained anti-HIV activity (entries 6–11).

Scheme V[a]



[a] (a) MMt-Cl, Et_3N; (b) cyclohexene, $Pd(OH)_2$; (c) CCl_4, PPh_3, imidazole; 80% AcOH; (d) TMSBr; H_2O.

Table I. *In Vitro* Anti-HIV Activity of 2′-Substituted PMEG Derivatives

entry	2′-substituent	compd no	IC_{50} (μM)[a]	TC_{50} (μM)[b]	SI[c]	CC_{50} (μM)[d]
1	H	1	0.2	15	75	0.2
2	CH_3	(*R*)-2	1	>500	>500	180
3	CH_3	(*S*)-2	12	300	25	12
4	CH_2OH	(*R*)-3	500	>500	>1	
5	CH_2OH	(*S*)-3	>500	350	<1	
6	CH_2N_3	(*R*)-5	5	>1000	>200	>1400
7	CH_2N_3	(*S*)-5	51	>1000	>20	134
8	CH_2F	(*R*)-6	8	>500	>63	427
9	CH_2F	(*S*)-6	7	>500	>71	93
10	CH_2Cl	(*R*)-7	45	>500	>11	870
11	CH_2Cl	(*S*)-7	50	>500	>10	>1500
12	CH_2CH_2OH	(*R*)-8	NA	>450		
13	CH_2CH_2OH	(*S*)-8	NA	>500		
14	$CH_2CH_2N_3$	(*S*)-9	NA	>500		
15	CH_2CH_2F	(*S*)-10	NA	>500		
16	$CH{=}CH_2$	(*R*)-11	13	>1000	>77	>1586
17	$CH{=}CH_2$	(*S*)-11	49	>1000	>20	>1586
18	c-propyl	(*R*)-12	NA	>1000		
19	c-propyl	(*S*)-12	NA	91		
20	CH_2CH_3	(*R*)-13	54	1000	19	
21	CH_2CH_3	(*S*)-13	252	>500	>2	

[a] The 50% inhibitory concentration, determined by the XTT assay using CEM cells infected with HIV (entries 1–5, 8–15, LAV-BRU strain; entries 6, 7, 16–21, HIV-HRF strain). NA: not active at 100 μM. [b] The 50% toxic concentration, determined by the XTT assay in CEM cells. [c] Selectivity index, the ratio of the TC_{50} to IC_{50}. [d] The 50% cell growth toxicity concentration, determined by measuring the number of cells after treatment with drug for 72 h.

Although these modifications resulted in a 5–50-fold loss in potency, the cytotoxicity of these compounds also decreased. For example, (*R*)-2′-(azidomethyl)-PMEG [(*R*)-5] is 5 times less potent than (*R*)-2; however, the cytotoxicity (CC_{50}) of (*R*)-5 was lowered by a factor of 8. It is interesting to note that the enantiomers of 2′-(fluoromethyl)-PMEG (6) and 2′-(chloromethyl)-PMEG (7) showed very little difference in their anti-HIV activity. However, for 2′-(azidomethyl)-PMEG enantiomers (5), the (*R*)-isomer is more potent and less toxic than the corresponding (*S*)-isomer. Note that the 2′-substituent in (*R*)-5 is in the opposite orientation to the methyl group in (*R*)-2, indicating that the mode of binding to the target enzyme may be different, or that the two compounds may be acting by different mechanisms. In the 2′-ethyl-substituted series of PMEG derivatives, introduction of a heteroatom (entries 12–15) or cyclopropyl group (entries 18 and 19) resulted in complete loss of anti-HIV activity. However, 2′-vinyl-PMEG (11) and 2′-ethyl-PMEG (13) exhibited good activity against HIV, although both compounds are less potent and less cytotoxic than 2′-methyl-PMEG (2). The results from these homologues suggest that there is a limited steric tolerance at the binding sites for the 2′-substituted PMEG derivatives. Furthermore, in case of analogues 11 and 13, the (*R*)-isomers are more potent than the corresponding (*S*)-isomers, indicating that these compounds may have the same type of action as 2 in the biological system. When the guanine base of these analogues was replaced with cytosine, the anti-HIV activity of the resulting PME derivatives was completely eradicated (data not shown).

Table II. *In Vitro* Anti-Herpes Virus Activity of 2′-Substituted PMEG Derivatives

entry	2′-substituent	compd no.	IC_{50} (μM)[a] HCMV[b]	IC_{50} (μM)[a] HSV 2[c]	TC_{50}(μM)[a]
1	H	1	0.09	1.1	30,[b] 17[c]
2	CH_3	(*R*)-2	16	82	>330,[b] >330[c]
3	CH_3	(*S*)-2	16	43	>330,[b] >330[c]
4	CH_2OH	(*R*)-3	1.6	99	>310,[b] >310[c]
5	CH_2OH	(*S*)-3	0.8	97	>310,[b] >310[c]
6	CH_2N_3	(*R*)-5	33	NA	>300,[b] >300[c]
7	CH_2N_3	(*S*)-5	15	NA	300,[b] >300[c]
8	CH_2F	(*R*)-6	136	NA	>310,[b] >310[c]
9	CH_2F	(*S*)-6	150	256	>310,[b] >310[c]
10	CH_2Cl	(*R*)-7	51	NA	>300,[b] >300[c]
11	CH_2Cl	(*S*)-7	112	NA	300,[b] 300[c]
12	CH_2CH_2OH	(*R*)-8		NA	300[c]
13	CH_2CH_2OH	(*S*)-8	162	NA	>300,[b] 300[c]
14	$CH_2CH_2N_3$	(*S*)-9	NA	NA	300,[b] 300[c]
15	CH_2CH_2F	(*S*)-10	NA	NA	300,[b] 300[c]
16	$CH{=}CH_2$	(*R*)-11	NA[d]		>300[d]
17	$CH{=}CH_2$	(*S*)-11	NA	NA	>300,[b] 300[c]
18	c-propyl	(*R*)-12	NA[d]	NA[d]	>300,[d] >300[d]
19	c-propyl	(*S*)-12		NA	300[c]
20	CH_2CH_3	(*R*)-13	NA[d]	NA[d]	>300,[d] >300[d]
21	CH_2CH_3	(*S*)-13	NA[b]	NA[c]	300,[b] 300[c]

[a] IC_{50}, 50% inhibitory concentration; TC_{50}, 50% cellular toxicity concentration; NA, not active at 100 μM. [b] As determined in MRC-5 cells (HCMV, AD-169 strain). [c] As determined in vero cells (HSV 2, G strain). [d] As determined in WI-38 cells (HCMV, HSV 2).

The 2′-substituted PME analogues were also evaluated in the plaque reduction assay for anti-herpes activity.[23] The anti-HCMV (AD-169 strain) and anti-HSV 2 (G strain) assays of 2′-substituted PMEG analogues were conducted in MRC-5 and vero cells, respectively. The results are shown in Table II. In general, the 2′-methyl-substituted PMEG analogues 5–7 were less potent than (*R*)-2′-methyl-PMEG [(*R*)-2] against both HSV and HCMV. The homologue of HPMPG, 2′-(hydroxyethyl)-PMEG (8), was less potent than HPMPG (3) against HSV 2 and HCMV. All other substituted ethyl derivatives were inactive. These results show that there is a limited size allowable at the 2′-position of PMEG in terms of anti-herpes activity as well as for the anti-HIV activity previously discussed. The corresponding analogues bearing cytosine generally were weak anti-herpes agents or were inactive (data not shown).

In conclusion, our studies have shown that the therapeutic index of PMEG can be improved by adding a substituent such as azidomethyl or halomethyl at the 2'-position of PMEG. Large substituents, however, substantially decrease anti-HIV activity, indicating that there is limited steric tolerance at this position of the PMEG side chain. In addition, we have observed that the anti-HIV activity varies depending on the nature and chirality of the substituent at this position of PMEG derivatives. The most interesting analogues to emerge from these studies are (*R*)-2'-(azidomethyl)-PMEG [(*R*)-5] and 2'-vinyl-PMEG [(*R*)-11]. The former showed potent anti-HIV activity with an IC_{50} of 5 μM and a cytotoxicity CC_{50} of greater than 1.4 mM. The latter has an IC_{50} of 13 μM for anti-HIV activity and a CC_{50} of greater than 1.6 mM. The decreased cytotoxicity of guanine analogues is reflected in an improved *in vitro* therapeutic index relative to PMEG. However, further studies are needed to determine whether this translates into improved safety in *in vivo* models as well. Furthermore, we have demonstrated that replacement of the guanine base of these 2'-substituted PME analogues with cytosine drastically reduces anti-HIV and anti-herpes activity. The result is somewhat surprising in view of the potent activity of (*S*)-HPMPC [(*S*)-4][5a,7] against HSV and CMV, and stands in marked contrast to the activity seen for the wide variety of guanine derivatives.

Experimental Section

Melting points were determined on an electrothermal apparatus and are not corrected. Proton and carbon-13 nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker AM-300 or a Varian Gemini 300 spectrometer. All spectra were determined in $CDCl_3$, DMSO-d_6, or D_2O and chemical shifts are reported in δ units relative to tetramethylsilane (TMS) for $CDCl_3$ and DMSO-d_6 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; dd, doublet of doublets, and dt, doublet of triplets. 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 direct chemical ionization (DCI, isobutene) or fast atom bombardment (FAB). Preparative chromatography was performed with flash chromatography on silica gel from Universal Scientific or octadecyl (C18) from J. T. Baker Inc.

(*R*)-3-Azido-1-*O*-benzyl-2-*O*-[(diisopropylphosphono)methyl]-1,2-propanediol (24). A suspension of mesylate **23**[4] (9.00 g, 20.5 mmol) and sodium azide (4.00 g, 61.6 mmol) in 40 mL of anhydrous *N',N'*-dimethylformamide was stirred at 105 °C for 5 h and then allowed to cool to room temperature. After the solvent was removed under reduced pressure, the residue was diluted with 100 mL of CH_2Cl_2 and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone = 10:1 to 3:1) to give 6.15 g (78% yield) of the product as an oil: $[\alpha]^{20}_D$ 7.7° (*c* 0.42, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.35–7.22 (m, 5 H, Ar*H*), 4.77–4.62 (m, 2 H, POC*H*), 3.89 (dd, *J* = 8.7, 13.7 Hz, 1 H, CH_2P), 3.83 (dd, *J* = 8.7, 13.7 Hz, 1 H, CH_2P), 3.76–3.69 (m, 1 H, H-2), 3.57 (dd, *J* = 5.1, 10.2 Hz, 1 H, H-1), 3.50 (dd, *J* = 5.5, 10.2 Hz, 1 H, H-1), 3.50 (dd, *J* = 4.2, 13.0 Hz, 1 H, H-3), 3.43 (dd, *J* = 6.1, 13.0 Hz, 1 H, H-3), 1.31–1.25 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.6, 127.9, 127.8, 79.7 (d, $^3J_{C,P}$ = 10 Hz, C-2), 73.4 (OCH_2Ph), 71.1 (d, $^2J_{C,P}$ = 4 Hz, POCH), 69.3 (C-1), 65.0 (d, $^1J_{C,P}$ = 168 Hz, CH_2P), 51.8 (C-3), 23.8 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.6 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{17}H_{28}N_3O_5P$) C, H, N.

(*S*)-1-*O*-Benzyl-2-*O*-[(diisopropylphosphono)methyl]-3-fluoro-1,2-propanediol (25). Tributylammonium fluoride trihydrate (43.0 g, 165 mmol) was dried at 50 °C under vacuum for 2 days. To the residue was added mesylate **23** (9.88 g, 22.5 mmol) in 10 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere. The resulting thick mixture was stirred at room temperature for 6 h. The solvent was evaporated, and methanol (100 mL) and *p*-toluenesulfonic acid hydrate (1 g) were added to the residue. The mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (150 mL) and saturated sodium bicarbonate solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:3 to 1:0) to give 6.20 g (77% yield) of **27** as a thick oil: $[\alpha]^{20}_D$ 8.2° (*c* 1.19, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.35–7.23 (m, 5 H, Ar*H*), 4.78–4.65 (m, 2 H, 2 × POC*H*), 4.55 (ddd, $J_{H,H}$ = 3.7, 10.0 Hz, $J_{H,F}$ = 47.6 Hz, 1 H, CH_2F), 4.51 (s, 2 H, OCH_2Ph), 4.49 (ddd, $J_{H,H}$ = 5.5, 10.0 Hz, $J_{H,F}$ = 47.6 Hz, 1 H, CH_2F), 3.90 and 3.95–3.78 (d over m, *J* = 8.7 Hz, 3 H, CH_2P and H-2), 3.63–3.52 (m, 2 H, H-1), 1.31–1.27 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.7, 127.9, 127.8 (Ar), 83.1 (d, $^1J_{C,F}$ = 172 Hz, C-3), 79.3 (dd, $^2J_{C,F}$ = 19 Hz, $^3J_{C,P}$ = 11 Hz, C-2), 73.5 (OCH_2Ph), 71.1 (d, $^2J_{C,P}$ = 5 Hz, POCH), 71.0 (d, $^2J_{C,P}$ = 5 Hz, POCH), 65.2 (d, $^1J_{C,P}$ = 168 Hz, CH_2P), 23.8 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{17}H_{28}FO_5P$) C, H.

(*R*)-3-Azido-2-*O*-[(diisopropylphosphono)methyl]-1,2-propanediol (26). To a solution of **24** (6.15 g, 16.0 mmol) in 35 mL of anhydrous CH_2Cl_2, boron trichloride (1 M in CH_2Cl_2, 48.0 mL, 48.0 mmol) was slowly added at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 4 h, and then a saturated solution of sodium bicarbonate (100 mL) and CH_2Cl_2 (150 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 75 mL). The combined CH_2Cl_2 extracts were 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 = 5:1 to 1:1) to provide 4.39 g (93% yield) of **26** as an oil: $[\alpha]^{20}_D$ −21.8° (*c* 8.53, MeOH); ^1H NMR ($CDCl_3$) δ 4.82–4.65 (m, 2 H, POC*H*), 4.05 (dd, *J* = 6.9, 14.0 Hz, 1 H, CH_2P), 3.77 (dd, *J* = 8.9, 14.0 Hz, 1 H, CH_2P), 3.72 (dd, *J* = 2.1, 11.7 Hz, 1 H, H-1), 3.64–3.57 and 3.56 (m over dd, *J* = 5.4, 11.7 Hz, 2 H, H-1 and H-2), 3.41 (dd, *J* = 7.3, 12.9 Hz, 1 H, H-3), 3.23 (dd, *J* = 3.9, 12.9 Hz, 1 H, H-3), 1.34–1.28 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 82.5 (d, $^3J_{C,P}$ = 9 Hz, C-2), 71.7 (d, $^2J_{C,P}$ = 7 Hz, POCH), 71.2 (d, $^2J_{C,P}$ = 7 Hz, POCH), 64.9 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 61.4 (C-1), 51.5 (C-3), 23.6 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3), 23.4 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3).

(*R*)-3-Azido-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-propanediol (28a). To a solution of alcohol **26** (6.40 g, 21.7 mmol) and methanesulfonyl chloride (2.98 g, 26.0 mmol) in CH_2Cl_2 (100 mL) was added slowly triethylamine (4.39 g, 43.4 mmol) at 0 °C under a nitrogen atmosphere. The resulting solution was stirred at 0 °C for 1 h and then slowly warmed to room temperature over 1 h. Water (100 mL) was added to the solution and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 150 mL). The combined CH_2Cl_2 extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone = 10:1 to 3:1) to provide 7.21 g (87% yield) of the title compound as an oil: $[\alpha]^{20}_D$ 2.30° (*c* 16.76, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.78–4.63 (m, 2 H, POC*H*), 4.32 (dd, *J* = 4.6, 11.2 Hz, 1 H, H-1), 4.26 (dd, *J* = 5.1, 11.2 Hz, 1 H, H-1), 3.86 and 3.87–3.81 (d over m, *J* = 8.6 Hz, 3 H, CH_2P and H-2), 3.50 (dd, *J* = 4.7, 13.1 Hz, 1 H, H-3), 3.42 (dd, *J* = 5.7, 13.1 Hz, 1H, H-3), 3.05 (s, 3H, SO_2CH_3), 1.30 (d, *J* = 6.2, Hz, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 78.1 (d, $^3J_{C,P}$ = 10 Hz, C-2), 71.3 (apparent t, $^2J_{C,P}$ = 6 Hz, POCH), 65.2 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 50.5 (C-3), 37.2 (SO_2CH_3), 23.6 (apparent t, $^3J_{C,P}$ = 5 Hz, POCHCH_3); MS (DCI) *m/e* 374 (MH^+). Anal. ($C_{11}H_{24}N_3O_7PS$) C, H, N.

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-3-fluoro-1-*O*-(methylsulfonyl)-1,2-propanediol (28b). Mesylate **28b** was prepared in 83% yield for two steps from **25** by the same procedures used for the preparation of **28a**. The product was isolated as an oil: ^1H NMR ($CDCl_3$) δ 4.80–4.66 (m, 2 H, 2 × POC*H*), 4.56 (ddd, $J_{H,H}$ = 4.5, 10.3 Hz, $J_{H,F}$ = 47.0 Hz, 1 H, CH_2F), 4.51 (ddd, $J_{H,H}$ = 4.9, 10.3 Hz, $J_{H,F}$ = 47.0 Hz, 1 H, CH_2F), 4.39 (ddd, $J_{H,H}$ = 4.4, 11.3 Hz, $J_{H,F}$ = 1.5 Hz, 1 H, H-1), 4.30 (ddd,

$J_{H,H}$ = 5.5, 11.3 Hz, $J_{H,F}$ = 1.5 Hz, 1 H, H-1), 3.88 and 4.04–3.82 (d over m, J = 8.7 Hz, 3H, CH_2P and H-2), 3.06 (s, 3 H, SO_2CH_3), 1.31 (d, J = 6.2 Hz, 12 H, 4 × $POCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 81.1 (d, $^1J_{C,F}$ = 173 Hz, C-3), 77.5 (dd, $^2J_{C,F}$ = 20 Hz, $^3J_{C,P}$ = 10 Hz, C-2), 71.2 (apparent t, $^2J_{C,P}$ = 6 Hz, POCH), 65.2 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 37.3 (SO_2CH_3), 23.7 (d, $^3J_{C,P}$ = 4 Hz, $POCHCH_3$), 23.6 (d, $^3J_{C,P}$ = 5 Hz, $POCHCH_3$). Anal. ($C_{11}H_{24}FO_7PS$) C, H, N.

(*S*)-2,2-Diisopropyl-4-(2-hydroxyethyl)dioxolane (29). In a 1-liter, three-neck flask equipped with a mechanical stirrer, Dean–Stark trap, and condenser were combined (*S*)-1,2,4-butanetriol (48 g, 0.45 mol), 2,4-dimethyl-3-pentanone (145 g, 1.27 mol) and *p*-toluenesulfonic acid (0.35 g) in 300 mL of benzene. After the mixture was heated gently at reflux for 20 h, the mixture was allowed to cool to room temperature and 10 mL of triethylamine was added. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (acetone/CH_2Cl_2 = 1:10 to 1:2) to give 77.2 g (84% yield) of the product as an oil: $[\alpha]^{20}_D$ 1.55° (*c* 15.6 CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.33–4.23 (m, 1 H, H-4), 4.14 (t, J = 7.0 Hz, 1 H, H-5), 3.85–3.72 (m, 2 H, H-2′), 3.49 (t, J = 8.3 Hz, 1 H, H-5), 2.10–1.97 (m, 2 H, $CHCH_3$), 1.90–1.65 (m, 2 H, H-1′), 0.90–0.86 (m, 12 H, 4 × CH_3); ^{13}C NMR ($CDCl_3$) δ 116.7 (O-*C*-O), 77.2 (C-4), 72.2 (C-5), 60.9 (C-2′), 35.0 (C-1′), 34.3, 33.5 ($CHCH_3$), 14.3, 17.2, 17.0 ($CHCH_3$); MS (DCI) *m/e* 203 (MH^+). Anal. ($C_{11}H_{22}O_3$) C, H.

(*S*)-4-*O*-Benzyl-1,2,4-butanetriol (30). Alcohol **29** (76.2 g, 0.38 mol), benzylbromide (129 g, 0.75 mol), and tetrabutylammonium iodide (7.00 g, 19.0 mmol) were added to a concentrated sodium hydroxide solution (40.0 g in 90 mL of water, 2.26 mol) in a three-neck flask equipped with a mechanical stirrer and a condenser. After stirring at 110 °C for 18 h, the mixture was allowed to cool to room temperature, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was treated with 300 mL of 1.5 M sulfuric acid. After stirring at 100 °C for 8 h, the mixture was allowed to cool to room temperature, and 300 mL of hexane was added. The aqueous layer was washed with hexane (2 × 200 mL) and then adjusted to pH 8–9 with concentrated sodium sodium hydroxide. The solution was extracted with ethyl acetate (3 × 200 mL), and the combined ethyl acetate extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was purified by fractional distillation in vacuo (0.1 mm Hg, bp 150–170 °C) to give 68.3 g (92% yield) of **30** as an oil: ^1H NMR ($CDCl_3$) δ 7.48–7.24 (m, 5 H, Ar*H*), 4.51 (s, 2 H, CH_2Ph), 3.96–3.84 (m, 1 H, H-2), 3.74–3.42 (m, 4 H, H-1 and H-4), 2.24 (br s, 1 H, O*H*), 3.08 (br s, 1 H, O*H*), 1.88–1.58 (m, 2 H, H-3); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.6, 128.0, 127.9 (Ar), 73.3 (CH_2Ph), 71.2 (C-2), 68.1 (C-4), 66.5 (C-1), 32.6 (C-3).

(*S*)-4-*O*-Benzyl-1-*O*-[(*p*-methoxyphenyl)diphenylmethyl]-1,2,4-butanetriol (31). Alcohol **30** (68.3 g, 348 mmol) was mixed with triethylamine (70.4 g, 696 mmol) and 4-(dimethylamino)-pyridine (3.42 g, 28.0 mmol) in CH_2Cl_2 (300 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C and *p*-anisylchlorodiphenylmethane (129 g, 418 mmol) was added. After the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 5 h, 300 mL of saturated sodium bicarbonate solution was added and the resulting mixture was stirred at room temperature for 1 h. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined CH_2Cl_2 extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:5 to 1:1) to give 155.5 g (95% yield) of the title compounds as a thick oil: $[\alpha]^{20}_D$ −3.0° (*c* 3.29, MeOH); ^1H NMR ($CDCl_3$) δ 7.43–7.40, 7.32–7.15, 6.82–6.79 (m; 4 H, 8 H, and 2 H, respectively; Ar*H*), 4.44 (s, 2 H, CH_2Ph), 4.03–3.93 (m, 1 H, H-2), 3.76 (s, 3 H, OCH_3), 3.64–3.50 (m, 2 H, H-4), 3.12–3.05 (m, 2 H, H-1), 2.80 (d, J = 2.0 Hz, 1 H, O*H*), 1.80–1.70 (m, 2 H, H-3); ^{13}C NMR ($CDCl_3$) δ 158.7, 144.6, 138.2, 135.7, 130.5, 128.5, 127.9, 127.7, 127.0, 113.1, 88.2, 73.1 (CH_2Ph), 67.9 and 67.2 (C-4 and C-1), 65.0 (OCH_3), 33.2 (C-3). Anal. ($C_{31}H_{32}O_4$) C, H.

(*S*)-4-*O*-Benzyl-2-*O*-[(diisopropylphosphono)methyl]-1,2,4-butanetriol (32). To a solution of **31** (154 g, 328 mmol) in 700 mL of anhydrous tetrahydrofuran, sodium hydride (80% in mineral oil, 11.8 g, 393 mmol) was added portionwise under nitrogen atmosphere. After heating at reflux for 5 h, the mixture was cooled in an ice bath and a solution of diisopropyl (tosyloxy)-methyl phosphonate (138 g, 393 mmol) in 300 mL of anhydrous tetrahydrofuran was slowly added. The mixture was stirred at 0 °C for 30 min and at room temperature for 14 h. The resulting slurry was filtered through a pad of Celite. The filtrate was evaporated, and 400 mL of CH_2Cl_2 and 200 mL of water were added to the residue. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 200 mL), and the combined organic extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and to the residue were added methanol (400 mL) and toluenesulfonic acid (10 g). The reaction mixture was stirred at 60 °C for 8 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:3 to 1:0 and then ethyl acetate/ethanol = 10:1) to provide 44.1 g (37% yield) of the title compound as an oil: ^1H NMR ($CDCl_3$) δ 7.38–7.24 (m, 5 H, Ar*H*), 4.80–4.63 (m, 2 H, POC*H*), 4.49 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.44 (d, J = 12.0 Hz, 1 H, CH_2Ph), 3.87 (dd, J = 7.2, 14.1 Hz, 1 H, CH_2P), 3.72 and 3.80–3.60 (dd over m, J = 9.0, 14.1 Hz, 2 H, CH_2P and H-2), 3.60–3.47 (m, 4 H, H-1 and H-4), 1.82–1.70 (m, 2 H, H-3), 1.36–1.25 (m, 12 H, 4 × $POCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 138.8, 129.0, 128.3 (Ar), 82.1 (d, $^3J_{C,P}$ = 8.7 Hz, C-2), 73.4 (CH_2Ph), 72.0 (d, $^2J_{C,P}$ = 7 Hz, POCH), 71.6 (d, $^2J_{C,P}$ = 7 Hz, POCH), 66.7 (C-4), 65.4 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 64.9 (C-1), 31.8 (C-3), 24.2 (m, $POCHCH_3$).

(*S*)-4-*O*-Benzyl-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2,4-butanetriol (28c). Mesylate **28c** was prepared as an oil from **32** in 98% yield utilizing the same procedure used for the preparation of **28a**: ^1H NMR ($CDCl_3$) δ 7.37–7.20 (m, 5 H, Ar*H*), 4.78–4.63 (m, 2 H, POC*H*), 4.47 (s, 2 H, CH_2Ph), 4.36 (dd, J = 3.0, 11.1 Hz, 1 H, H-1), 4.18 (dd, J = 6.0, 11.1 Hz, 1 H, H-1), 3.83 and 3.80–3.87 (dd over m, J = 9.0, 13.3 Hz, 2 H, C*H*P and H-2), 3.74 (dd, J = 9.8, 13.3 Hz, 1 H, CH_2P), 3.60–3.50 (m, 2 H, H-4), 3.02 (s, 3 H, SO_2CH_3), 1.88–1.78 (m, 2 H, H-3), 1.29–1.27 (apparent t, 12 H, 4 × $POCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 137.9, 128.3, 127.5 (Ar), 77.04 (d, $^3J_{C,P}$ = 12.6 Hz, C-2), 72.7 (CH_2Ph), 65.3 (C-4), 64.7 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 36.9 (SO_2CH_3), 30.5 (C-3), 23.5 (apparent t, $^3J_{C,P}$ = 5 Hz, $POCHCH_3$).

(*S*)-4-*O*-Benzyl-2-*O*-[(diisopropylphosphono)methyl)]-1-*O*-(methoxymethyl)-1,2,4-butanetriol (33). To a solution of **32** (20.0 g, 53.4 mmol) and diisopropylethylamine (13.8 g, 107 mmol) in 100 mL of CH_2Cl_2 was slowly added chloromethyl methyl ether (6.45 g, 80.1 mmol) at 0 °C under a nitrogen atmosphere. After the solution was stirred at room temperature for 14 h, CH_2Cl_2 (100 mL) and 1 N HCl (100 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 75 mL), and the combined extracts were washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over magnesium sulfate, and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:1 to 1:0) to give 21.9 (98% yield) of the product as an oil: ^1H NMR ($CDCl_3$) δ 7.33–7.20 (m, 5 H, Ar*H*), 4.76–4.62 (m, 2 H, 2 × POC*H*), 4.58 (s, 2 H, OCH_2O), 4.47 (s, 2 H, CH_2Ph), 3.94 (dd, J = 8.7, 13.6 Hz, 1 H, CH_2P), 3.74 and 3.76–3.68 (dd over m, 2 H, CH_2P and H-2), 3.65–3.50 (m, 4 H, H-1 and H-4), 3.31 (s, 3 H, OCH_3), 1.80 (q, J = 6.2 Hz, 2 H, H-3), 1.32–1.26 (m, 12 H, 4 × $POCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 138.4, 128.3, 127.6, 96.4 (OCH_2O), 77.9 (d, $^3J_{C,P}$ = 13 Hz, C-2), 72.7 (CH_2Ph), 70.6 (d, $^2J_{C,P}$ = 6 Hz, POCH), 69.6 (C-1), 66.2 (C-4), 64.7 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 54.9 (OCH_3), 31.5 (C-3), 23.6 (apparent t, $^3J_{C,P}$ = 6 Hz, $POCHCH_3$); MS (DCI) *m/e* 419 (MH^+).

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-1,2,4-butanetriol (34). Palladium hydroxide on carbon (20%, 10.0 g) was added to a solution of **33** (21.9 g, 52.3 mmol) in ethanol and cyclohexene (200 mL of each). The resulting mixture was heated at reflux for 6 h, allowed to cool to room temperature, and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol = 20:1 to 10:1) to give 16.8 g (98% yield) of **34** as an oil: $[\alpha]^{20}_D$ 3.43° (*c* 2.33, MeOH); ^1H NMR ($CDCl_3$) δ 4.80–4.60 (m, 2 H, 2 × POC*H*), 4.60 (s, 2 H, OCH_2O), 4.03–3.80 and 3.67–3.48 (m, 7 H, H-1, H-2, H-4, and CH_2P), 1.80–1.50 (m, 2 H, H-3), 1.34–1.29 (m, 12 H, 4 × $POCHCH_3$); ^{13}C NMR ($CDCl_3$) δ 96.5 (OCH_2O), 77.7 (d, $^3J_{C,P}$ = 14 Hz, C-2), 71.1 (d, $^2J_{C,P}$ = 7 Hz, POCH), 70.2 (C-1), 64.7 (d, $^1J_{C,P}$ = 167 Hz, CH_2P), 57.9 (C-4),

55.0 (OCH_3), 34.3 (C-3), 23.6 (apparent t, $^3J_{C,P}$ = 5 Hz, POCHCH_3); MS (DCI) *m/e* 329 (MH^+). Anal. ($C_{13}H_{29}O_7P$) C, H.

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-4-*O*-(methylsulfonyl)-1,2,4-butanetriol (35). Compound **35** was prepared as an oil in 99% yield from **34** utilizing the same procedure used to prepared **28a**: $[\alpha]^{20}_D$ −17.9° (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.88–4.62 (m, 2 H, 2 × POC*H*), 4.58 (s, 2 H, OCH_2O), 4.42–4.28 (m, 2 H, H-4), 3.95 (dd, *J* = 8.8, 13.7 Hz, 1 H, C*H*$_2$P), 3.73 and 3.74–3.67 (dd over m, *J* = 9.3, 13.7 Hz, 2 H, C*H*$_2$P and H-2), 3.61–3.51 (m, 2 H, H-1), 3.32 (s, 3 H, OCH_3), 3.00 (s, 3 H, CH_3SO_2), 2.30–1.83 (m, 2 H, H-3), 1.31–1.27 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 96.3 (OCH_2O), 76.6 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.7 (d, $^2J_{C,P}$ = 7 Hz, POCH), 70.6 (d, $^2J_{C,P}$ = 7 Hz, POCH), 68.7 (C-4), 66.4 (C-1), 64.5 (d, $^1J_{C,P}$ = 170 Hz, C*H*$_2$P), 54.9 (OCH_3), 36.7 (SO_2CH_3), 31.2 (C-3), 23.5 (apparent t, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{14}H_{31}O_9PS$) C, H.

(*S*)-4-Azido-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-1,2-butanediol (36). Compound **36** was prepared as an oil from **35** (5.00 g, 12.3 mmol) utilizing the same procedure used to prepare **24**: ^{1}H NMR ($CDCl_3$) δ 4.79–4.60 (m, 2 H, POC*H*), 4.59 (s, 2 H, OCH_2O), 3.96 (dd, *J* = 8.7, 13.6 Hz, 1 H, C*H*$_2$P), 3.74 (dd, *J* = 9.5, 13.6 Hz, 1 H, C*H*$_2$P), 3.69–3.61 (m, 1 H, H-2), 3.55 (d, *J* = 4.5 Hz, 2 H, H-1), 3.43 (t, *J* = 6.8 Hz, 2 H, H-4), 3.33 (s, 3 H, OCH_3), 1.80–1.73 (m, 2 H, H-3), 1.30 (d, *J* = 6.2 Hz, 6 H, 2 × POCHCH_3), 1.29 (d, *J* = 6.2 Hz, 6 H, 2 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 96.5 (OCH_2O), 77.7 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.8 (apparent t, $^2J_{C,P}$ = 6 Hz, POC*H*), 69.1 (C-1), 64.7 (d, $^1J_{C,P}$ = 170 Hz, C*H*$_2$P), 55.1 (OCH_3), 47.4 (C-4), 30.8 (C-3), 23.6 (apparent t, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{13}H_{28}N_3O_6P$) C, H, N.

(*S*)-4-Azido-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-butanediol (28d). Compound **36** was heated with 0.5 g of camphorsulfonic acid in 50 mL of methanol at reflux for 16 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone = 5:1 to 2:1) to provide 2.53 g (67% yield for two steps) of (*S*)-4-azido-2-*O*-[(diisopropylphosphono)methyl]-1,2-butanediol as an oil: ^{1}H NMR ($CDCl_3$) δ 4.81–4.63 (m, 2 H, POC*H*), 3.91 (dd, *J* = 7.2, 14.1 Hz, 1 H, C*H*$_2$P), 3.73 and 3.76–3.68 (dd over m, *J* = 9.1, 14.1 Hz, 2 H, C*H*$_2$P and H-1), 3.58–3.46 (m, 2 H, H-1 and H-2), 3.40 (d, *J* = 5.9 Hz, 1 H, H-4), 3.37 (t, *J* = 5.9 Hz, 1 H, H-4), 1.88–1.60 (m, 2 H, H-3), 1.31 (d, *J* = 4.8 Hz, 6 H, 2 × POCHCH_3), 1.29 (d, *J* = 4.8 Hz, 6 H, POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 80.8 (d, $^3J_{C,P}$ = 9 Hz, C-2), 71.5 (d, $^2J_{C,P}$ = 7 Hz, POC*H*), 71.1 (d, $^2J_{C,P}$ = 7 Hz, POCH), 64.7 (d, $^1J_{C,P}$ = 170 Hz, C*H*$_2$P), 63.6 (C-1), 47.6 (C-4), 30.4 (C-3), 23.6 (m, POCHCH_3); IR (film): 3388 (OH), 2098 (N_3), 1240 (P=O), 1106 (C-O), 994 (P-O-C) cm^{-1}. Anal. Calcd for $C_{11}H_{24}N_3O_5P$: C, 42.71; H, 7.82; N, 13.58. Found: C, 42.74; H, 7.87; N, 13.32.

Mesylate **28d** was prepared as an oil in 97% yield from (*S*)-4-azido-2-[(diisopropylphonphono)methyl]-1,2-butanediol (2.50 g, 8.08 mmol) using the same procedure used for the preparation of **28a**: ^{1}H NMR ($CDCl_3$) δ 4.80–4.64 (m, 2 H, 2 × POC*H*), 4.34 (dd, *J* = 3.6, 11.2 Hz, 1 H, H-1), 4.26 (dd, *J* = 5.3, 11.2 Hz, 1 H, H-1), 3.87 (dd, *J* = 8.8, 13.6 Hz, 1 H, C*H*$_2$P), 3.75 and 3.83–3.74 (dd and m, *J* = 9.7, 13.6 Hz, 2 H, C*H*$_2$P and H-2), 3.48 (t, *J* = 6.6 Hz, 2 H, H-4), 3.06 (s, 3 H, SCH_3), 1.90–1.68 (m, 2 H, H-3), 1.32 (d, *J* = 6.2, Hz, 6 H, 2 × POCHCH_3), 1.31 (d, *J* = 6.2, Hz, 6 H, 2 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 76.7 (d, $^3J_{C,P}$ = 12 Hz, C-2), 71.1 (d, $^2J_{C,P}$ = 6 Hz, POCH), 71.0 (d, $^2J_{C,P}$ = 6 Hz, POCH), 69.9 (C-1), 65.1 (d, $^1J_{C,P}$ = 170 Hz, C*H*$_2$P), 47.0 (C-4), 37.3 (SO_2CH_3), 30.2 (C-3), 23.7 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3); MS (DCI) *m/e* 374 (MH^+).

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-4-fluoro-1-*O*-(methoxymethyl)-1,2-butanediol (37). To anhydrous tetrabutylammonium fluoride (prepared by heating tetrabutylammonium fluoride trihydrate at about 50 °C under vacuum for 24 h; 9.60 g, 36.7 mmol) in a 100 mL flask was added a solution of **35** (5.00 g, 12.3 mmol) in 5 mL of anhydrous tetrahydrofuran under nitrogen. The resulting mixture was stirred at room temperature for 16 h and at 50 °C for 5 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone = 1:0 to 5:1) to give 3.70 g (87%) of **40** as an oil: ^{1}H NMR ($CDCl_3$) δ 4.60 and 4.41–4.80 (s over m, 6 H, OCH_2O, 2 × POC*H* and C*H*$_2$F), 3.98 (dd, *J* = 8.6, 13.7 Hz, 1 H, C*H*$_2$P), 3.77 and 3.80–3.70 (dd over m, *J* = 9.5, 13.7 Hz, 2 H, C*H*$_2$P and H-2), 3.63–3.52 (m, 2 H, H-1), 3.34 (s, 3 H, OCH_3), 2.03–1.69 (m, 2 H, H-3), 1.36–1.29 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 96.4 (OCH_2O), 80.2 (d, $^1J_{C,F}$ = 164 Hz, C*H*$_2$F), 76.8 (dd, $^3J_{C,P}$ = 12 Hz, $^3J_{C,F}$ = 4 Hz, C-2), 70.6 (apparent t, $^2J_{C,P}$ = 5 Hz, POCH), 69.3 (C-1), 64.7 (d, $^1J_{C,P}$ = 169 Hz, C*H*$_2$P), 54.8 (OCH_3), 32.3 (d, $^2J_{C,F}$ = 20 Hz, C-3), 23.6 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3), 23.5 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3).

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-4-fluoro-1-*O*-(methylsulfonyl)-1,2-butanediol (28e). A mixture of fluoride **37** (3.60 g, 10.4 mmol) and camphorsulfonic acid (0.10 g, 0.43 mmol) in 20 mL of methanol was stirred at 55 °C for 20 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone = 5:1 to 3:1) to give 2.96 g of (*S*)-2-*O*-(diisopropylphosphono)methyl]-4-fluoro-1,2-butanediol. The alcohol was converted to the corresponding mesylate utilizing the same procedure used for preparation of **28a** to give 3.36 g of **28e** (89% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.75–4.40 (m, 4 H, 2 × POC*H* and C*H*$_2$F), 4.32 (dd, *J* = 3.4, 11.3 Hz, 1 H, H-1), 4.15 (dd, *J* = 5.6, 11.3 Hz, 1 H, H-1), 3.85 and 3.86–3.76 (dd over m, *J* = 9.5, 13.7 Hz, 2 H, C*H*$_2$P and H-2), 3.72 (dd, *J* = 9.7, 13.5 Hz, 1 H, C*H*$_2$P), 3.01 (s, 3 H, SO_2CH_3), 2.01–1.75 (m, 2 H, H-3), 1.30–1.20 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 79.7 ($^1J_{C,F}$ = 165 Hz, C*H*$_2$F), 76.2 (dd, $^3J_{C,P}$ = 12 Hz, $^3J_{C,F}$ = 3 Hz, C-2), 70.6 (br d, $^2J_{C,P}$ = 5 Hz, POCH), 70.4 (C-1), 65.1 (d, $^1J_{C,P}$ = 170 Hz, C*H*$_2$P), 37.3 (SO_2CH_3), 31.7 (d, $^2J_{C,F}$ = 20 Hz, C-3), 23.7 (apparent t, $^3J_{C,P}$ = 5 Hz, POCHCH_3); MS (DCI) *m/e* 365 (MH^+). Anal. ($C_{12}H_{28}FO_7PS$) C, H.

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-3-butene-1,2-diol (38). To a solution of **34** (9.00 g, 27.4 mmol) and 2-nitrophenyl selenocyanate (9.33 g, 41.1 mmol) in anhydrous tetrahydrofuran (100 mL), tributylphosphine (10.3 g, 41.1 mmol) was slowly added at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min and at room temperature for 24 h. Water (100 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were dried over magnesium sulfate and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1 to 1:0 and then ethyl acetate/acetone 10:1) to give (*S*)-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-4-*O*-[(2-nitrophenyl)selenyl]-1,2,4-butanetriol as a thick yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, *J* = 1.5, 8.3 Hz, 1 H, Ar*H*), 7.60–7.49, 7.32–7.26, (m, 3 H, Ar *H*), 4.80–4.67 (m, 2 H, POC*H*), 4.59 (s, 2 H, OCH_2O), 3.99 (dd, *J* = 8.6, 13.7 Hz, 1 H, C*H*$_2$P), 3.79 (dd, *J* = 9.3, 13.7 Hz, 1 H, C*H*$_2$P), 3.76–3.68 (m, 1 H, H-2), 3.60 (dd, 1 H, *J* = 5.1, 10.5 Hz, 1 H, H-1), 3.56 (dd, *J* = 4.8, 10.5 Hz, 1 H, H-1), 3.33 (s, 3 H, OCH_3), 2.90–3.01 and 3.17–3.06 (m, 2 H, H-4), 2.06–1.98 (m, 2 H, H-3), 1.26–1.34 (m, 12 H, 4 × POCHCH_3).

The selenium derivative obtained was dissolved in tetrahydrofuran (15 mL) and treated with hydrogen peroxide (29%, 20 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and then at room temperature for 16 h. Water (40 mL) and ethyl acetate (100 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (2 × 100 mL) and the combined extracts were washed with saturated $NaHCO_3$ (50 mL), dried over magnesium sulfate, and filtered. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane = 1:1 to 1:0) to give 6.59 g (77% yield) of **41** as an oil: ^{1}H NMR ($CDCl_3$) δ 5.75–5.63 (m, 1 H, H-3), 5.38–5.28 (m, 2 H, H-2), 4.78–4.62 (m, 2 H, 2 × POC*H*), 4.61 (s, 2 H, OCH_2O), 4.05–3.96 (m, 1 H, H-2), 3.79 (dd, *J* = 9.5, 13.5 Hz, 1 H, C*H*$_2$P), 3.63 (dd, *J* = 8.4, 13.5 Hz, 1 H, C*H*$_2$P), 3.62–3.50 (m, 2 H, H-1), 3.57 (s, 3 H, OCH_3), 1.35–1.28 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 134.5 (C-3), 119.8 (C-4), 96.5 (OCH_2O), 82.0 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.8 (apparent t, *J* = 5 Hz, POCH), 69.7 (C-1), 63.0 (d, $^1J_{C,P}$ = 169 Hz, C*H*$_2$P), 55.0 (OCH_3), 23.7 (t, *J* = 5 Hz, POCHCH_3). Anal. ($C_{13}H_{27}O_6P$) C, H.

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-3-butene (28f). (*S*)-2-*O*-[(Diisopropylphosphono)-methyl]-3-butene-1,2-diol and **28f** were obtained from **38** utilizing the same procedure used for preparation of **28d**. (*S*)-2-*O*-[(Diisopropylphosphono)methyl]-3-butene-1,2-diol was isolated as an oil: ^{1}H NMR ($CDCl_3$) δ 5.69–5.57 (m, 1 H, H-3), 5.32–5.23 (m, 2 H, H-4), 4.78–4.62 (m, 2 H, POC*H*), 3.82 (dd, *J* = 8.8, 13.5 Hz, 1 H, C*H*$_2$P), 3.56 (dd, *J* = 8.3, 13.5 Hz, 1 H, C*H*$_2$P), 3.92–3.83 (m, 1 H, H-2), 3.54 (d, *J* = 4.8 Hz, 2 H, H-1), 3.13 (b s, 1 H, O*H*),

1.34–1.26 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 134.1 (C-3), 119.0 (C-4), 84.0 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.5 (d, $^2J_{C,P}$ = 6 Hz, POCH), 70.7 (d, $^2J_{C,P}$ = 6 Hz, POCH), 64.3 (C-1), 62.8 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 23.3 (apparent t, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{11}H_{23}O_5P$) C, H.

Mesylate **28f** was isolated as an oil: ^{1}H NMR ($CDCl_3$) δ 5.69–5.58 (m, 1 H, H-3), 5.45–5.39 (m, 2 H, H-4), 4.77–4.62 (m, 2 H, POC*H*), 4.20 (d, *J* = 5.7 Hz, 2 H, H-1), 4.17–4.05 (m, 1 H, H-2), 3.77 (dd, *J* = 9.7, 13.6 Hz, 1 H, CH_2P), 3.57 (dd, *J* = 8.8, 13.6 Hz, 1 H, CH_2P), 3.05 (s, 3 H, SO_2CH_3), 1.34–1.23 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 131.8 (C-3), 121.7 (C-4), 80.3 (d, $^3J_{C,P}$ = 13 Hz, C-2), 70.8 and 70.7 (t over s, $^2J_{C,P}$ = 6 Hz, POCH and C-1), 62.8 (d, $^1J_{C,P}$ = 171 Hz, CH_2P), 37.33 (SO_2CH_3) 23.5 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3). Anal. ($C_{12}H_{25}O_7PS$) C, H.

(*S*)-2-Cyclopropyl-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-ethanediol (28g). Mesylate **28f** (1.10 g, 3.19 mmol) was dissolved in 50 mL of diazomethane in diethyl ether (containing 0.53 g of diazomethane). To the solution was added palladium acetate (10 mg) at 0 °C. The solution was stirred at 0 °C until nitrogen stopped evolving from the reaction mixture (approximate 15 min), and then the solvent was evaporated. The same procedure was repeated twice. The crude product was purified by flash chromatography (CH_2Cl_2/acetone = 3:1) to give 1.10 g (96% yield) of **28f** as an oil: ^{1}H NMR ($CDCl_3$) δ 4.78–4.63 (m, 2 H, POC*H*), 4.32 (dd, *J* = 3.1, 11.3 Hz, 1 H, H-1), 4.23 (dd, *J* = 6.7, 11.3 Hz, 1 H, H-1), 3.99 (dd, *J* = 9.3, 13.4 Hz, 1 H, CH_2P), 3.72 (dd, *J* = 9.7, 13.4 Hz, 1 H, CH_2P), 3.04 and 3.10–2.95 (s over m, 4 H, SO_2CH_3 and H-2), 1.29 (d, *J* = 6.2 Hz, 12 H, 4 × POCHCH_3), 0.85–0.62, 0.56–0.42, 0.20–0.10 (m; 1 H, 2 H, and 2 H, respectively; H-cyclopropyl); ^{13}C NMR ($CDCl_3$) δ 82.8 (d, $^3J_{C,P}$ = 13 Hz, C-2), 71.5 (CH_2OMs), 70.7 (d, $^2J_{C,P}$ = 4 Hz, POCH), 63.3 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 37.2 (SO_2CH_3), 23.4 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3), 10.0, 4.1, –0.3 (C-cyclopropyl).

(*S*)-4-Bromo-2-*O*-[(diisopropylphosphono)methyl]-1-*O*-(methoxymethyl)-1,2-butanediol (39). To a mixture of alcohol **35** (5.00 g, 15.2 mmol) were added triethylamine (4.65 g, 45.7 mmol) and triphenylphosphine (4.39 g, 16.8 mmol) in anhydrous tetrahydrofuran (40 mL), carbon tetrabromide (10.1 g, 30.5 mmol) and imidazole (0.10 g) at 0 °C. After stirring at 0 °C for 10 min, the cooling bath was removed. The solution was stirred at room temperature for 6 h. The resulting brown solution was evaporated and the residue was treated with ethyl ether (75 mL) and filtered. The filtrate was evaporated to give a dark brown material which was purified by flash chromatography (CH_2Cl_2/acetone = 5:1 to 3:1) to provide 5.20 g (87% yield) of the product as an oil: $[\alpha]^{20}_D$ –41.0° (*c* 0.62, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.78–4.62 (m, 2 H, POC*H*), 4.58 (s, 2 H, OCH_2O), 3.98 (dd, *J* = 8.4, 13.3 Hz, 1 H, CH_2P), 3.80–3.60 (m, 2 H, CH_2P and H-2), 3.60–3.43 (m, 4 H, H-1 and H-4), 3.32 (s, 3 H, OCH_3), 2.15–1.90 (m, 2 H, H-3), 1.31–1.28 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 96.5 (OCH_2O), 78.5 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.8 (d, $^2J_{C,P}$ = 3 Hz, POCH), 70.7 (d, $^2J_{C,P}$ = 3 Hz, POCH), 68.9 (C-1), 65.0 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 55.1 (OCH_3), 34.8 (C-4), 29.4 (C-3), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.6 (d, $^3J_{C,P}$ = 3 Hz, POCHCH_3). Anal. ($C_{13}H_{28}BrO_6P$) C, H.

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1,2-butanediol (40). Bromide **39** (5.10 g, 13.0 mmol), triethylamine (1.59 g, 15.7 mmol), and palladium on carbon (10%, 0.50 g) were mixed in 10 mL of methanol. The reduction was carried out in a Parr apparatus for 16 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned in a mixture of CH_2Cl_2 (100 mL) and 10% HCl solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated. The residue was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 4.78–4.63 (m, 2 H, POC*H*), 4.59 (s, 2 H, OCH_2O), 3.90 (dd, *J* = 8.6, 13.7 Hz, 1 H, CH_2P), 3.77 (dd, *J* = 9.2, 13.7 Hz, 1 H, CH_2P), 3.58–3.42 (m, 3 H, H-1 and H-2), 3.32 (s, 3 H, OCH_3), 1.58–1.48 (m, 2 H, H-3), 1.29 (q, *J* = 1.6, 6.3 Hz, 12 H, 4 × POCHCH_3), 0.91 (t, *J* = 7.4 Hz, 3 H, H-4); ^{13}C NMR ($CDCl_3$) δ 96.5 (OCH_2O), 81.9 (d, $^3J_{C,P}$ = 12 Hz, C-2), 70.6 (d, $^2J_{C,P}$ = 7 Hz, POCH), 69.1 (C-1), 64.3 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 54.9 (OCH_3), 23.8 (C-3), 23.6 (apparent t, $^3J_{C,P}$ = 6 Hz, POCHCH_3), 9.2 (C-4).

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-butanediol (28h). (*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1,2-butanediol and mesylate **28h** were obtained from **40** utilizing the procedure used for preparation of **28d**. 2-*O*-[(Diisopropylphosphono)methyl]-1,2-butanediol was isolated as a colorless oil: $[\alpha]^{20}_D$ –7.15° (*c* 1.34, MeOH); ^{1}H NMR ($CDCl_3$) δ 4.78–4.60 (m, 2 H, POC*H*), 3.88 (dd, *J* = 7.6, 14.1 Hz, 1 H, CH_2P), 3.69 (dd, *J* = 8.9, 14.1 Hz, 1 H, CH_2P), 3.65–3.44 (m, 2 H, H-1), 3.37–3.29 (m, 1 H, H-2), 1.55–1.30 (m, 2 H, H-3), 1.27 (dd, *J* = 4.1, 6.2 Hz, 12 H, 4 × POCHCH_3), 0.86 (t, *J* = 7.5 Hz, 3 H, H-4); ^{13}C NMR ($CDCl_3$) δ 85.6 (d, $^3J_{C,P}$ = 9 Hz, C-2), 71.4 (d, $^2J_{C,P}$ = 6 Hz, POCH), 71.0 (d, $^2J_{C,P}$ = 7 Hz, POCH), 64.7 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 64.1 (C-1), 23.8 (d, $^2J_{C,P}$ = 6 Hz, POCHCH_3), 23.7 (d, $^2J_{C,P}$ = 4 Hz, POCHCH_3), 23.6 (C-3), 9.5 (C-4); MS (DCI) *m/e* 269 (MH^+).

Mesylate **28h** was isolated as an oil: ^{1}H NMR ($CDCl_3$) δ 4.80–4.65 (m, 2 H, POC*H*), 4.28 (dd, *J* = 3.3, 11.1 Hz, H-1), 4.17 (dd, *J* = 6.0, 11.1 Hz, 1 H, H-1), 3.81 (dd, *J* = 9.2, 13.4 Hz, 1 H, CH_2P), 3.76 (dd, *J* = 9.4, 13.4 Hz, 1 H, CH_2P), 3.62–3.52 (m, 1 H, H-2), 3.05 (s, 3 H, SCH_3), 1.68–1.50 (m, 2 H, H-3), 1.30 (d, *J* = 6.2 Hz, 12 Hz, POCHCH_3), 0.94 (t, *J* = 7.5 Hz, 3 H, H-4); ^{13}C NMR ($CDCl_3$) δ 80.6 (d, $^3J_{C,P}$ = 11 Hz, C-2), 70.9 (apparent t, $^2J_{C,P}$ = 7 Hz, POCH), 70.3 (C-1), 64.5 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 37.3 (SO_2CH_3), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.6 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.1 (C-3), 8.9 (C-4). Anal. ($C_{12}H_{27}O_7PS$) C, H.

General Procedure for the Coupling Reactions of Mesylates with 2-Amino-6-chloropurine: (*S*)-2-Amino-9-[3-azido-2-[(diisopropylphosphono)methoxy]propyl]-6-chloropurine (41a). Mesylate **28a** (2.00 g, 5.22 mmol) was mixed with 2-amino-6-chloropurine (3.40 g, 10.4 mmol) and cesium carbonate (3.92 g, 12.0 mmol) in 15 mL of anhydrous *N',N'*-dimethylformamide. The mixture was stirred at 90 °C under a nitrogen atmosphere for 3 h, allowed to cool to room temperature, and filtered. The filtrate was evaporated under reduced pressure, and 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/methanol = 15:1 to 10:1) to give a thick oil which crystallized from ethyl acetate and diethyl ether to give 1.34 g (58% yield) of the title compound: mp 126–128 °C; $[\alpha]^{20}_D$ –9.9° (*c* 0.89, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1 H, H-8), 5.45 (br s, 2 H, NH_2), 4.72–4.56 (m, 2 H, 2 × POC*H*), 4.26 (dd, *J* = 4.3, 14.6 Hz, 1 H, H-1'), 4.18 (dd, *J* = 5.6, 14.6 Hz, 1 H, H-1'), 3.91–3.82 (m, 1 H, H-2'), 3.71 (dd, *J* = 8.9, 13.9 Hz, 1 H, CH_2P), 3.79 (dd, *J* = 8.6, 13.9 Hz, 1 H, CH_2P), 3.43 (dd, *J* = 5.1, 13.2 Hz, 1 H, H-3'), 3.25 (dd, *J* = 4.9, 13.2 Hz, 1 H, H-3'), 1.27–1.19 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.4, 154.3, 151.4, 143.6, 124.8, 77.6 (d, $^3J_{C,P}$ = 12 Hz, C-2'), 71.2 (apparent t, $^2J_{C,P}$ = 4 Hz, POCH), 65.0 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 47.1 and 45.4 (C-1' and C-4'), 30.7 (C-3'), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3). Anal. ($C_{15}H_{24}ClN_8O_4PS$) C, H, N.

(*S*)-2-Amino-6-chloro-9-[2-[(diisopropylphosphono)-methoxy]-3-fluoropropyl]purine (41b). The title compound was prepared from **28b** in 73% yield as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1 H, H-8), 5.10 (br s, 2 H, NH_2), 4.75–4.60 (m, 3 H, H-4 and 2 × POC*H*), 4.52–4.46 (m, 1 H, H-4), 4.35 (dd, *J* = 3.8, 14.6 Hz, 1 H, H-1'), 4.20 (dd, *J* = 3.8, 14.6 Hz, 1 H, H-1'), 4.11–3.98 (m, 1 H, H-2'), 3.84 (dd, *J* = 8.9, 13.9 Hz, 1 H, CH_2P), 3.75 (dd, *J* = 8.9, 13.9 Hz, 1 H, CH_2P), 1.31–1.22 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.5, 153.9, 151.0, 143.3, 124.4, 81.4 (d, $^1J_{C,F}$ = 174 Hz, C-4'), 77.8 (dd, $^2J_{C,F}$ = 20 Hz, $^3J_{C,P}$ = 10 Hz, C-2'), 71.0 (d, $^2J_{C,P}$ = 7 Hz, POCH), 64.8 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 43.0 (d, $^3J_{C,F}$ = 8 Hz, C-1'), 23.5 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 23.4 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3). Anal. ($C_{15}H_{24}ClFN_5O_4P$) C, H, N: calcd, 16.52; found, 16.06.

(*S*)-1-Amino-9-[4-(benzyloxy)-2-[(diisopropylphosphono)-methoxy]butyl]-6-chloropurine (41c). The title compound was prepared from **28c** in 66% yield as thick oil: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H, H-8), 7.30–7.18 (m, 5 H, Ar*H*), 5.44 (bs, 2 H, NH_2), 4.72–4.55 (m, 2 H, POC*H*), 4.44 (s, 2 H, CH_2Ph), 4.27 (dd, *J* = 3.2, 14.6 Hz, 1 H, H-1'), 4.07 (dd, *J* = 6.2, 14.6 Hz, 1 H, H-1'), 3.89–3.80 (m, 1 H, H-2'), 3.70 (dd, *J* = 9.5, 13.3 Hz, 1 H, CH_2P), 3.61 (dd, *J* = 9.5, 13.3 Hz, 1 H, CH_2P), 3.57–3.50 (m, 2 H, H-4'), 1.80–1.60 (m, 2 H, H-3'), 1.28–1.14 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.4, 154.2, 151.0, 143.7 (purine), 138.0, 127.7, 128.4 (Ph), 124.6 (purine), 77.9 (d, $^3J_{C,P}$ = 12 Hz, C-2'), 72.9 (CH_2-Ph), 70.9 (d, $^2J_{C,P}$ = 7 Hz, POCH), 70.8 (d, $^2J_{C,P}$ = 7 Hz, POCH), 65.5 (C-4'), 64.6 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 45.8 (C-1'), 31.3 (C-3'), 23.6 (d, $^3J_{C,P}$ = 7 Hz, POCHCH_3).

(S)-2-Amino-9-[4-azido-2-[(diisopropylphosphono)methoxy]butyl]-6-chloropurine (41d). The title compound was prepared from **28d** in 57% yield as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H, H-8), 5.14 (br s, 2 H, NH_2), 4.78–4.63 (m, 2 H, 2 × POC*H*), 4.30 (dd, J = 3.5, 14.7 Hz, 1 H, H-1′), 4.15 (dd, J = 5.2, 14.7 Hz, 1 H, H-1′), 3.89–3.81 (m, 1 H, H-2′), 3.76 (dd, J = 9.5, 13.5 Hz, 1 H, CH_2P), 3.72 (dd, J = 9.5, 13.5 Hz, 1 H, CH_2P), 3.47 (t, J = 5.9 Hz, 2 H, H-4′), 1.78–1.50 (m, 2 H, H-3′), 1.32–1.25 (m, 12 Hz, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.4, 154.3, 151.4, 143.6, 124.8, 77.6 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 71.2 (apparent t, $^2J_{C,P}$ = 4 Hz, POCH), 65.0 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 47.1 and 45.4 (C-1′ and C-4′), 30.7 (C-3′), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3); MS (DCI) m/e 461 (MH^+). Anal. ($C_{16}H_{26}ClN_8O_4P$) C, H, N.

(S)-2-Amino-6-chloro-9-[2-[(diisopropylphosphono)methoxy]-4-fluorobutyl]purine (41e). The title compound was prepared from **28e** in 69% yield as a solid: ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H, H-8), 5.32 (br s, 2 H, NH_2), 4.75–4.59 (m, 3 H, H-4 and 2 × POC*H*), 4.50–4.42 (m, 1 H, H-4), 4.30 (dd, J = 3.5, 14.7 Hz, 1 H, H-1′), 4.14 (dd, J = 5.7, 14.7 Hz, 1 H, H-1′), 3.94–3.86 (m, 1 H, H-2′), 3.74 (dd, J = 9.5, 13.4 Hz, 1 H, CH_2P), 3.69 (dd, J = 9.5, 13.4 Hz, 1 H, CH_2P), 1.98–1.57 (m, 2 H, H-3′), 1.29–1.22 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.4, 154.0, 150.8, 143.4, 124.1, 79.5 (d, $^1J_{C,F}$ = 165 Hz, C-4′), 76.6 (br d, $^3J_{C,P}$ = 9 Hz, C-2′), 70.9 (d, $^2J_{C,P}$ = 7 Hz, POCH), 64.5 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 45.4 (C-1′), 31.9 (d, $^2J_{C,F}$ = 20 Hz, C-3′), 23.3 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3).

(S)-2-Amino-6-chloro-9-[2-[(diisopropylphosphono)methoxy]-3-butenyl]purine (41f). The title compound was prepared from **28f** in 56% yield and crystallized from ethyl acetate/ethyl ether: mp 106–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H, H-8), 5.70–5.54 (m, 1 H, H-3′), 5.41–5.36 (m, 2 H, H-4′), 4.71 4.55 (m, 2 H, 2 × POC*H*), 4.27–4.05 (m, 3 H, 2 × H-1′ and H-2′), 3.75 (dd, J = 9.4, 13.6 Hz, 1 H, CH_2P), 3.49 (dd, J = 8.5, 13.6 Hz, 1 H, CH_2P), 1.29–1.19 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 159.3, 154.1, 151.3, 143.8 (G), 133.2 (C-3′), 124.9 (G), 121.9 (C-4′), 80.7 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 71.1 (d, $^2J_{C,P}$ = 7 Hz, POCH), 62.9 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 46.9 (C-1′), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3).

(S)-2-Amino-6-chloro-9-[2-cyclopropyl-2-[(diisopropylphosphono)methoxy]ethyl]purine (41g). The title compound was prepared from **28g** in 63% yield and crystallized from ethyl ether: mp 108–110 °C; $[\alpha]^{20}_D$ 42.4° (c 0.96, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H, H-8), 5.16 (br s, 2 H, NH_2), 4.73–4.56 (m, 2 H, POC*H*), 4.32 (dd, J = 3.2, 14.4 Hz, 1 H, H-1′), 4.15 (dd, J = 7.5, 14.4 Hz, 1 H, H-1′), 4.01 (dd, J = 9.1, 13.6 Hz, 1 H, CH_2P), 3.63 (dd, J = 9.5, 13.6 Hz, 1 H, CH_2P), 3.09–2.98 (m, 1 H, H-2′), 1.30–1.18 (m, 12 H, 4 × POCHCH_3), 0.76–0.62, 0.58–0.40, 0.22–0.12 (m; 1 H, 2 H, and 2 H, respectively; H-cyclopropyl); ^{13}C NMR ($CDCl_3$) δ 159.8, 154.7, 151.6, 144.4, 126.4, 83.9 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 71.5 (d, $^2J_{C,P}$ = 7 Hz, POCH), 63.7 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 47.6 (C-1′), 24.2 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3), 24.1 (d, $^3J_{C,P}$ = 5 Hz, POCHCH_3), 23.9, 11.7, 5.2 (C-cyclopropyl); MS (DCI) m/e 432 (MH^+). Anal. ($C_{17}H_{27}ClN_5O_4P$) C, H, N.

(S)-2-Amino-6-chloro-9-[2-[(diisopropylphosphono)methoxy]butyl]purine (41h). The title compound was prepared from **28h** in 60% yield as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H, H-8), 5.15 (br s, 2 H, NH_2), 4.75–4.61 (m, 2 H, 2 × POC*H*), 4.22 (dd, J = 3.3, 14.5 Hz, 1 H, H-1′), 4.07 (dd, J = 6.5, 14.5 Hz, 1 H, H-1′), 3.76 (dd, J = 9.2, 13.5 Hz, 1 H, CH_2P), 3.61 and 3.66–3.59 (dd over m, J = 9.6, 13.5 Hz, 2 H, CH_2P and H-2′), 1.60–1.42 (m, 2 H, H-3′), 1.31–1.22 (m, 12 Hz, 4 × POCHCH_3), 0.97 (t, J = 7.4 Hz, 3 H, H-4′); ^{13}C NMR ($CDCl_3$) δ 159.4, 154.1, 150.9, 143.6, 124.5, 81.1 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 70.9 (d, $^2J_{C,P}$ = 3 Hz, POCH), 70.8 (d, $^2J_{C,P}$ = 3 Hz, POCH), 63.9 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 45.2 (C-1′), 23.5 (m, POCHCH_3 and C-3′), 8.6 (C-4′); MS (DCI) m/e 420 (MH^+).

General Procedure for Converting Protected 6-Chloropurine Phosphonates to Guanine Phosphonates: (S)-9-[3-Azido-2-(phosphonomethoxy)propyl]guanine [(S)-5]. Bromotrimethylsilane (3.43 g, 22.4 mmol) was slowly added to phosphonate **41a** (1.00 g, 2.24 mmol) in 10 mL of anhydrous acetonitrile under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 14 h, and the solvent was removed under reduced pressure. The residue was dried in vacuo and then treated with acetone (8 mL) and water (2 mL). The resulting mixture was stirred at room temperature for 6 h. The solid was collected by filtration, washed with acetone and water, and then heated gently at reflux in 10 mL of 2 N HCl for 5 h. The solution was evaporated under reduced pressure, and the residue was recrystallized from water to give 533 mg of the title compound as pale yellow crystals. The mother liquor was concentrated to provide an additional 72 mg of the product (total 79% yield): mp 263 °C dec; $[\alpha]^{20}_D$ −18.4° (c 0.38, 1 N HCl); ^{1}H NMR (D_2O) δ 7.69 (s, 1 H, H-8), 4.13 (dd, J = 5.3, 14.8 Hz, 1 H, H-1′), 4.06 (dd, J = 5.3, 14.8 Hz, 1 H, H-1′), 3.79–3.74 (m, 1 H, H-2′), 3.46–3.40 (m, 2 H, CH_2P and H-3′), 3.34 (dd, J = 9.4, 12 2. Hz, 1 H, CH_2P), 3.18 (dd, J = 4.7, 13.3 Hz, 1 H, H-3′); ^{13}C NMR (D_2O, NaOD) δ 171.7, 164.6, 155.1, 142.7, 120.5, 80.8 (d, $^3J_{C,P}$ = 11 Hz, C-2′), 71.1 (d, $^1J_{C,P}$ = 151 Hz, CH_2P), 53.7 (C-3′), 46.5 (C-1′); MS (FAB) m/e 345 (MH^+). Anal. ($C_9H_{13}H_8O_5P\cdot0.5H_2O$) C, H, N.

(R)-9-[3-Azido-2-(phosphonomethoxy)propyl]guanine [(R)-6]: $[\alpha]^{20}_D$ 16.7° (c 0.63, 1 N HCl); MS (FAB) m/e 345 (MH^+). Anal. ($C_9H_{13}N_8O_5P\cdot0.66H_2O$) C, H, N.

(S)-9-[3-Fluoro-2-(phosphonomethoxy)propyl]guanine [(S)-6]. The title compound was prepared from **41b** in 53% yield, and purified by reverse-phase chromatography (C18, H_2O/methanol) and recrystallization (H_2O/methanol): mp 255–257 °C; $[\alpha]^{20}_D$ −51.8° (c 0.35, 1 N HCl); ^{1}H NMR (DMSO-d_6) δ 10.59 (b s, 1 H, N*H*), 7.74 (br s, 1 H, H-8), 6.47 (br s, 2 H, NH_2), 4.65–4.60, 4.49–4.42, 4.31–4.26 (m, 2 H, H-3′), 4.24–3.90 (m, 3 H, H-2′ and H-1′), 3.69–3.55 (m, 2 H, CH_2P); ^{13}C NMR (DMSO-d_6) δ 157.1, 154.0, 151.7, 138.4, 116.2, 82.2 (d, $^1J_{C,F}$ = 171 Hz, C-3′), 77.9 (dd, $^2J_{C,F}$ = 19 Hz, $^3J_{C,P}$ = 11 Hz, C-2′), 65.8 (d, $^1J_{C,P}$ = 163 Hz, CH_2P), 42.4 (d, $^3J_{C,F}$ = 7 Hz, C-1′). Anal. ($C_9H_{13}FN_5O_5P\cdot0.5H_2O$) C, H, N.

(R)-9-[3-Fluoro-2-(phosphonomethoxy)propyl]guanine [(R)-6]: $[\alpha]^{20}_D$ 45.6° (c 0.15, 1 N HCl), MS (FAB) m/e 322 (MH^+). Anal. ($C_9H_{13}FN_5O_5P\cdot H_2O$) C, H, N.

(S)-9-[4-Hydroxy-2-(phosphonomethoxy)butyl]guanine [(S)-8]. Boron trichloride (1 M in CH_2Cl_2, 13.2 mL, 13.2 mmol) was slowly added to the solution of **41c** (1.31 g, 2.49 mmol) in 15 mL of CH_2Cl_2 at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 4 h and at −40 °C for 2 h and then recooled to −78 °C. Anhydrous methanol (20 mL) was added and the mixture was allowed to slowly warm to room temperature and the solvent was evaporated. The residue was evaporated from methanol (3 × 20 mL) and dried in vacuo. Bromotrimethylsilane (7.53 g, 49.8 mmol) was slowly added to the residue in 15 mL of anhydrous acetonitrile under nitrogen atmosphere. The solution was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was dried in vacuo. To the residue, water (5 mL) and acetone (25 mL) were added, and the mixture was stirred at room temperature for 14 h. The solvent was evaporated, and the residue was partitioned between water (100 mL) and ethyl ether (30 mL). The aqueous layer was evaporated, and the residue was gently heated at reflux in 20 mL of 10% hydrochloric acid for 6 h. The solvent was evaporated, and the residue was purified by reverse-phase flash chromatography (C18, water/methanol = 1:0 to 10:1). The solid collected was recrystallized from water to provide 380 mg (46% yield) of the product: mp 254 °C dec; $[\alpha]^{20}_D$ 14.5° (c 0.40, 1 N HCl); ^{1}H NMR (DMSO-d_6) δ 10.54 (br s, 1 H, N*H*), 7.70 (s, 1 H, H-8), 6.41 (br s, 2 H, NH_2), 4.12 (dd, J = 3.8, 14.5 Hz, 1 H, H-1′), 3.96 (dd, J = 5.4, 14.4 Hz, 1 H, H-1′), 3.81–3.70 (m, 1 H, H-2′), 3.58 (dd, J = 9.3, 13.3 Hz, 1 H, CH_2P), 3.53–3.37 (m, 3 H, CH_2P and H-4′), 1.54–1.40 (m, 1 H, H-3′), 1.40–1.28 (m, 1 H, H-3′); ^{13}C NMR (DMSO-d_6) δ 157.2, 153.9. 151.8, 138.6, 116.1, 76.8 (d, $^3J_{C,P}$ = 11 Hz, C-2′), 65.3 (d, $^1J_{C,P}$ = 162 Hz, CH_2P), 56.7 (C-4′), 34.8 (C-3′), 45.0 (C-1′). Anal. ($C_{10}H_{16}N_5O_6P\cdot0.75H_2O$) C, H, N.

(R)-9-[4-Hydroxy-2-(phosphonomethoxy)butyl]guanine [(R)-8]: $[\alpha]^{20}_D$ −11.9° (c 0.68, 1 N HCl); MS (FAB, negative ion) m/e 332 (M − H). Anal. ($C_{10}H_{16}N_5O_6P\cdot1.25H_2O$) C, H, N.

(S)-9-[4-[Azido-2-(phosphonomethoxy)butyl]guanine [(S)-9]. The title compound was prepared from **41d** in 62% yield and crystallized from water: mp 245 °C dec; $[\alpha]^{20}_D$ −0.45° (c 0.44, 1 N HCl); ^{1}H NMR (DMSO-d_6) δ 10.6 (br s, 1 H, N*H*), 7.71 (s, 1 H, H-8), 6.44 (br s, 2 H, NH_2), 4.17 (dd, J = 3.9, 14.2 Hz, 1 H, H-1′), 4.02 (dd, J = 4.7, 14.2 Hz, 1 H, H-1′), 3.80–3.71 (m, 1 H, H-2′), 3.66 (dd, J = 9.3, 13.2 Hz, 1 H, CH_2P), 3.51 (dd, J = 9.8,

13.2 Hz, 1 H, CH_2P), 3.46 (t, J = 6.9 Hz, 2 H, H-4'), 1.65–1.50 (m, 1 H, H-3'), 1.50–1.38 (m, 1 H, H-3'); ^{13}C NMR (DMSO-d_6) δ 157.1, 154.0, 151.8, 138.6, 116.1, 77.0 (d, $^3J_{C,P}$ = 12 Hz, C-2'), 65.4 (d, $^1J_{C,P}$ = 162 Hz, CH_2P), 47.0 and 44.4 (C-1' and C-4'), 30.8 (C-3'); MS (FAB) m/e 359 (MH^+). Anal. ($C_9H_{15}N_6O_5P\cdot0.25H_2O$) C, H, N.

(*S*)-9-[4-Fluoro-2-(phosphonomethoxy)butyl]guanine [(*S*)-10]. The title compound was prepared from **41e** in 69% yield and purified by reverse-phase chromatography (C18, H_2O) and recrystallization from H_2O: mp 269 °C dec; $[\alpha]^{20}_D$ 23.4° (c 0.40, 1 N HCl); ^1H NMR (D_2O) δ 7.70 (s, 1 H, H-8), 4.69–4.53 (m, 1 H, H-4'), 4.53–4.39 (m, 1 H, H-4'), 4.11 (dd, J = 4.3, 14.9 Hz, 1 H, H-1'), 3.99 (dd, J = 5.7, 14.9 Hz, 1 H, H-1'), 3.67–3.79 (m, 1 H, H-2'), 3.29 (d, J = 9.6 Hz, 2 H, CH_2P), 1.89–1.45 (m, 2 H, H-3'); ^{13}C NMR (DMSO-d_6) δ 157.2, 154.0, 151.2, 138.6, 116.1, 82.2 (d, $^1J_{C,F}$ = 161 Hz, C-4'), 76.1 (dd, $^3J_{C,F}$ = 4 Hz, $^3J_{C,P}$ = 13 Hz, C-2'), 65.5 (d, $^1J_{C,P}$ = 162 Hz, CH_2P), 44.7 (C-1'), 32.4 (d, $^2J_{C,F}$ = 20 Hz, C-3'). Anal. ($C_{10}H_{15}FO_5N_5P$) C, H, N.

(*S*)-9-[2-(Phosphonomethoxy)-3-butenyl]guanine [(*S*)-11]. The title compound was prepared from **41f** in 66% yield, and purified by reverse-phase chromatography (C18, H_2O/methanol) and recrystallization (H_2O): mp 275 °C dec; ^1H NMR (D_2O) δ 8.82 (s, 1 H, H-8), 5.79–5.68 (m, 1 H, H-3'), 5.44–5.37 (m, 2 H, H-4'), 4.45–4.36 and 4.30–4.22 (m, 3 H, H-2' and H-1'), 3.69 (dd, J = 9.3, 13.0 Hz, 1 H, CH_2P), 3.38 (dd, J = 9.3, 13.0 Hz, 1 H, CH_2P); ^{13}C NMR (D_2O) δ 161.8, 157.5, 155.0, 144.0, 136.9 (C-3'), 124.2 (C-4'), 117.5, 83.8 (d, $^3J_{C,P}$ = 13 Hz, C-2'), 67.8 (d, $^1J_{C,P}$ = 158 Hz, CH_2P), 50.0 (C-1'); MS (FAB) m/e 316 (MH^+). Anal. ($C_{10}H_{14}N_5O_5P$) C, H, N.

(*R*)-9-[2-(Phosphonomethoxy)-3-butenyl]guanine [(*R*)-11]: mp 278 °C dec; $[\alpha]^{20}_D$ -27.2° (c 0.41, H_2O). Anal. ($C_{10}H_{14}N_5O_5P$) C, H, N.

(*S*)-9-[2-Cyclopropyl-2-(phosphonomethoxy)]ethyl]guanine [(*S*)-12]. Bromotrimethylsilane (3.48 g, 22.7 mmol) was slowly added to the solution of **41g** (0.98 g, 2.27 mmol) in 5 mL of anhydrous acetonitrile under a nitrogen atmosphere. The solution was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was dried in vacuo. To the residue were added water (1 mL) and acetone (20 mL). The mixture was stirred at room temperature for 16 h. The mixture was filtered, and the collected solid was stirred in 2 N NaOH solution (4.85 mL) at 120 °C for 2 h. The solution was acidified with 1 N HCl solution to pH 1. The solvent was evaporated under reduced pressure and the residue was purified by reverse-phase chromatography (C18, water/methanol = 1:0 to 10:1 to provide 0.304 g (48% yield) of the product as a solid: mp 239–241 °C; $[\alpha]^{20}_D$ 18.9° (c 0.38, H_2O); $[\alpha]^{20}_D$ 25.8° (c 0.38, 1 N HCl); ^1H NMR (DMSO-d_6) δ 10.56 (br s, 1 H, N*H*), 7.75 (s, 1 H, H-8), 6.44 (br s, 2 H, NH_2), 4.14 (dd, J = 5.1, 16.9 Hz, 1 H, H-1'), 4.07 (dd, J = 6.6, 16.9 Hz, 1 H, H-1'), 3.75 (dd, J = 9.6, 12.9 Hz, 1 H, CH_2P), 3.52 (dd, J = 11.1, 12.9 Hz, 1 H, CH_2P), 3.10–3.02 (m, 1 H, H-2'), 0.75–0.60, 0.60–0.28, -0.12–0 (m; 1 H, 3 H and 1 H, respectively; H-cyclopropyl); ^{13}C NMR (DMSO-d_6) δ 157.2, 153.9, 151.8, 138.6, 116.1, 82.8 (d, $^3J_{C,P}$ = 13 Hz, C-2'), 64.5 (d, $^1J_{C,P}$ = 163 Hz, CH_2P), 46.0 (C-1'), 11.8, 3.5, 0.4 (C-cyclopropyl); MS (FAB) m/e 330 (MH^+). Anal. ($C_{11}H_{16}N_5O_5P\cdot0.5H_2O$) C, H, N.

(*R*)-9-[2-Cyclopropyl-2-(phosphonomethoxy)ethyl]guanine [(*R*)-12]: mp 282 °C dec; $[\alpha]^{20}_D$ -22.4° (c 0.33, 1 N HCl). Anal. ($C_{11}H_{16}N_5O_5P\cdot0.25H_2O$) C, H, N.

(*S*)-9-[2-(Phosphonomethoxy)butyl]guanine [(*S*)-13]. The title compound was prepared from **41h** in 66% yield and purified by recrystallization from H_2O/methanol: mp 239–241 °C; $[\alpha]^{20}_D$ 22.2° (c 0.22, H_2O); $[\alpha]^{20}_D$ 34.2° (c 0.30, 1 N HCl); ^1H NMR (DMSO) δ 10.57 (br s, 1 H, NH), 7.74 (s, 1 H, H-8), 6.43 (br s, 2 H, NH_2), 4.10 (dd, J = 4.0, 14.2 Hz, 1 H, H-1'), 3.98 (dd, J = 5.3, 14.2 Hz, 1 H, H-1'), 3.62–3.45 (m, 3 H, CH_2P and H-2'), 1.40–1.22 (m, 2 H, H-3'), 0.97 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 157.2, 153.9, 151.8, 133.6, 116.1, 80.7 (d, $^3J_{C,P}$ = 12 Hz, C-2'), 65.1 (d, $^1J_{C,P}$ = 163 Hz, CH_2P), 44.3 (C-1'), 23.9 (C-3'), 9.1 (C-4'); MS (FAB) m/e 318 (MH^+). Anal. ($C_9H_{16}N_3O_5P\cdot0.75H_2O$) C, H, N.

(*R*)-9-[2-(Phosphonomethoxy)butyl]guanine [(*R*)-13]: mp 281–293 °C; $[\alpha]^{20}_D$ -35.4° (c 0.30, 1 N HCl). Anal. ($C_9H_{16}N_3O_5P\cdot0.25H_2O$) C, H, N.

General Procedure for the Coupling Reactions of Mesylates with Cytosine. (*S*)-1-[3-Azido-2-[(diisopropylphosphono)methoxy]propyl]cytosine (42a). Mesylate **28a** was mixed with cytosine (0.70 g, 6.26 mmol) and cesium carbonate (3.40 g, 10.4 mmol) in 15 mL of anhydrous N',N'-dimethylformamide. The mixture was stirred at 90 °C under a nitrogen atmosphere for 3 h, 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 (CH_2Cl_2/methanol = 15:1 to 5:1) to give 1.00 g (49% yield) of **45a** as a thick oil: $[\alpha]^{20}_D$ -37.6° (c 2.41, MeOH); ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 1 H, H-5), 5.69 (d, J = 7.2 Hz, 1 H, H-6), 4.75–4.61 (m, 2 H, 2 × POC*H*), 4.03 (dd, J = 3.7, 13.5 Hz, 1 H, H-1'), 3.86 and 3.87–3.82 (dd over m, J = 8.7, 13.6 Hz, 2 H, CH_2P and H-2'), 3.74 (dd, J = 6.7, 13.5 Hz, 1 H, H-1'), 3.69 (dd, J = 9.4, 13.6 Hz, 1 H, CH_2P), 3.62 (dd, J = 3.3, 13.3 Hz, 1 H, H-3'), 3.26 (dd, J = 5.2, 13.3 Hz, 1 H, H-3'), 1.30 (d, J = 6.3 Hz, 2 × POCHC*H*$_3$), 1.28 (d, J = 6.1 Hz, 2 × POCHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 166.7 (C-2), 157.1 (C-4), 146.7 (C-6), 94.8 (C-5), 79.0 (d, $^3J_{C,P}$ = 11 Hz, C-2'), 71.4 (d, $^2J_{C,P}$ = 6 Hz, POCH), 71.3 (d, $^2J_{C,P}$ = 6 Hz, POCH), 65.2 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 51.4 and 50.6 (C-1' and C-2'), 23.7 (apparent t, $^3J_{C,P}$ = 5 Hz, POCH*C*H$_3$); MS (DCI) m/e 389 (MH^+).

(*S*)-1-[2-[(Diisopropylphosphono)methoxy]-3-fluoropropyl]cytosine (42b). The title compound was prepared from **28b** in 61% yield and crystallized from ethyl acetate/ether: mp 165–168 °C; $[\alpha]^{20}_D$ -75.1° (c 1.37, MeOH); ^1H NMR ($CDCl_3$) δ 7.34 (d, J = 7.2 Hz, 1 H, H-5), 5.74 (d, J = 7.2 Hz, 1 H, H-6), 4.75–4.53 (m, 3 H, 2 × POC*H* and H-3'), 4.40 (ddd, $J_{H,F}$ = 47 Hz, $J_{H,H}$ = 4.5, 10.7 Hz, 1 H, H-3'), 4.09 (dd, J = 3.8, 13.3 Hz, H-1'), 4.06–3.91 (m, 1 H, H-2'), 3.87 (dd, J = 8.9, 13.6 Hz, 1 H, CH_2P), 3.72 (dd, J = 9.3, 13.6 Hz, 1 H, CH_2P), 3.70 (dd, J = 7.0, 13.3 Hz, H-1'), 1.28 (apparent t, J = 5.4 Hz, 12 H, 4 × POCHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 166.8 (C-2), 156.9 (C-4), 146.2 (C-6), 94.8 (C-5), 82.3 (d, $^1J_{C,F}$ = 174 Hz, C-3'), 78.4 (dd, $^2J_{C,F}$ = 18 Hz, $^3J_{C,P}$ = 12 Hz, C-2'), 71.0 (apparent t, $^2J_{C,P}$ = 7 Hz, POCH), 64.9 (d, $^1J_{C,P}$ = 169 Hz, CH_2P), 49.3 (d, $^3J_{C,F}$ = 8 Hz, C-3'), 23.6 (d, $^3J_{C,P}$ = 4 Hz, POCHC*H*$_3$), 23.5 (d, $^3J_{C,P}$ = 4 Hz, POCHC*H*$_3$). Anal. ($C_{14}H_{25}FN_3O_5P$) C, H, N.

(*S*)-1-[4-(Benzyloxy)-2-[(diisopropylphosphono)methoxy]butyl]cytosine [(*S*)-42c]. The title compound was prepared from **28c** in 42% yield and isolated as a thick oil: ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 6 H, Ph and H-6), 5.72 (d, J = 7.1 Hz, H-5), 4.70–4.57 (m, 2 H, POC*H*), 4.45 (s, 2 H, CH_2Ph), 4.10–4.02 (m, 1 H, H-1'), 3.85–3.75 (m, 1 H, H-2'), 3.73 (dd, J = 9.8, 13.4 Hz, 1 H, CH_2P), 3.66–3.52 (m, 4 H, H-4', CH_2P and H-1'), 1.90–1.66 (m, 2 H, H-3'), 1.30–1.19 (m, 12 H, 4 × POCHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 166.5 (C-2), 156.9 (C-4), 146.7 (C-6), 138.3, 128.4, 127.7, 127.6 (Ph), 94.3 (C-5), 78.1 (d, $^3J_{C,P}$ = 13 Hz, C-2'), 72.8 (CH_2Ph), 70.8 (apparent t, $^2J_{C,P}$ = 7 Hz, POCH), 65.7 (C-4'), 64.7 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 52.4 (C-1'), 31.5 (C-3'), 23.6 (d, $^3J_{C,P}$ = 5 Hz, POCH*C*H$_3$).

(*S*)-1-[4-Azido-2-[(diisopropylphosphono)methoxy]butyl]cytosine (42d). The title compound was prepared from **28d** in 42% yield and isolated as a thick oil: ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 1 H, H-5), 5.70 (d, J = 7.2 Hz, 1 H, H-6), 4.75–4.60 (m, 2 H, 2 × POC*H*), 4.00 (dd, J = 2.1, 12.9 Hz, 1 H, H-1'), 3.82–3.69 (m, 3 H, CH_2P, H-1' and H-2'), 3.63 (dd, J = 9.5, 13.5 Hz, 1 H, CH_2P), 3.52–3.38 (m, 2 H, H-4'), 1.90–1.63 (m, 2 H, H-3'), 1.31–1.27 (m, 12 H, 4 × POCHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 167.2 (C-2), 157.5 (C-4), 146.9 (C-6), 95.3 (C-5), 78.5 (d, $^3J_{C,P}$ = 5 Hz, C-2'), 71.6 (apparent t, $^2J_{C,P}$ = 5 Hz, 2 × POCH), 65.5 (d, $^1J_{C,P}$ = 171 Hz, CH_2P), 52.5 (C-1'), 47.6 (C-4'), 31.3 (C-3'), 24.2 (d, $^3J_{C,P}$ = 4 Hz, POCHC*H*$_3$); MS (DCI) m/e 403 (MH^+).

(*S*)-1-[2-[(Diisopropylphosphono)methoxy]-4-fluorobutyl]cytosine (42e). The title compound was prepared from **28e** in 60% yield and isolated as a thick oil: ^1H NMR ($CDCl_3$) δ 7.40 (d, J = 7.2 Hz, 1 H, H-5), 5.71 (d, J = 7.2 Hz, 1 H, H-6), 4.75–4.60 and 4.55–4.42 (m, 4 H, 2 × POC*H* and H-4'), 4.02 (dd, J = 3.1, 13.8 Hz, 1 H, H-1'), 3.90–3.80 (m, 1 H, H-2'), 3.77–3.69 (m, 2 H, CH_2P and H-1'), 3.63 (dd, J = 9.4, 13.4 Hz, 1 H, CH_2P), 2.10–1.70 (m, 2 H, H-4'), 1.28 (apparent t, J = 6.3 Hz, 12 H, 4 × POCHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C-2), 157.0 (C-4), 146.5 (C-6), 94.5 (C-5), 79.9 (d, $^1J_{C,F}$ = 165 Hz, C-4'), 77.3 (dd, $^3J_{C,F}$ = 2 Hz, $^3J_{C,P}$ = 12 Hz, C-2'), 71.0 (d, $^2J_{C,P}$ = 5 Hz, POCH), 70.9 (d, $^2J_{C,P}$ = 5 Hz, POCH), 65.0 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 52.2 (C-1'), 32.2 (d, $^2J_{C,F}$ = 20 Hz, C-3'), 23.6 (apparent

t, $^3J_{C,P}$ = 4 Hz, POCHCH_3); MS (DCI) *m/e* 380 (MH^+). Anal. ($C_9H_{15}N_6O_5P$) C, H, N.

(*S*)-1-[2-[(Diisopropylphosphono)methoxy]-3-butenyl]cytosine (42f). The title compound was prepared from **28f** in 60% yield and crystallized from ethyl acetate/ether: mp 137–138 °C; $[\alpha]^{20}_D$ 84.0° (*c* 0.96, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 1 H, H-6), 5.77 (d, *J* = 7.2 Hz, 1 H, H-5), 5.72–5.78 (m, 1 H, H-3′), 5.46–5.32 (m, 2 H, H-4′), 5.74–5.59 (m, 2 H, POC*H*), 4.22–4.10 (m, 2 H, H-1′), 3.74 (dd, *J* = 9.5, 13.6 Hz, 1 H, CH_2P), 3.45 and 3.54–3.41 (dd, over m, *J* = 9.5, 13.6 Hz, 2 H, CH_2P and H-2′), 1.36–1.22 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR ($CDCl_3$) δ 166.6 (C-2), 156.9 (C-4), 146.8 (C-6), 133.8 (C-3′), 128.8 (C-4′), 94.2 (C-5), 80.9 (d, $^3J_{C,P}$ = 13.6 Hz, H-2′), 63.0 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 70.9 (apparent t, $^2J_{C,P}$ = 6 Hz, POCH), 53.1 (C-1′), 23.7 (apparent t, $^3J_{C,P}$ = 5 Hz, POCHCH_3). Anal. ($C_{15}H_{28}N_3O_5P$) C, H, N.

(*S*)-1-[2-Cyclopropyl-2-[(diisopropylphosphono)methoxy]ethyl]cytosine (42g). The title compound was prepared from **28g** in 60% yield and isolated as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.32 (d, *J* = 7.2 Hz, 1 H, H-6), 5.70 (d, *J* = 7.2 Hz, 1 H, H-5), 4.71–4.57 (m, 2 H, POC*H*), 4.21 (dd, *J* = 2.7, 13.5 Hz, 1 H, H-1′), 3.81 (dd, *J* = 6.3, 13.5 Hz, 1 H, H-1′), 3.58–3.40 (m, 2 H, CH_2P), 3.03–2.94 (m, 1 H, H-2′), 1.25 (apparent t, *J* = 6.4 Hz, 12 H, 4 × POCHCH_3), 0.86–0.59, 0.58–0.35, 0.30–0.19 (m; 2 H, 2 H and 1 H, respectively; H-cyclopropyl); ^{13}C NMR ($CDCl_3$) δ 166.4 (C-2), 156.7 (C-4), 146.3 (C-6), 94.1 (C-5), 83.1 (d, $^3J_{C,P}$ = 14 Hz, C-2′), 70.6 (d, $^2J_{C,P}$ = 7 Hz, POCH), 62.9 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 53.2 (C-1′), 23.3 (apparent t, $^3J_{C,P}$ = 6 Hz, POCHCH_3), 11.1, 4.1, –0.6 (C-cyclopropyl).

(*S*)-1-[2-[(Diisopropylphosphono)methoxy]butyl]cytosine (42h). The product was prepared from **28h** in 58% yield and isolated as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 1 H, H-5), 5.62 (d, *J* = 7.2 Hz, 1 H, H-6), 4.75–4.60 (m, 2 H, 2 × POC*H*), 4.20 (dd, *J* = 2.3, 13.7 Hz, 1 H, H-1′), 3.74 (dd, *J* = 9.9, 13.3 Hz, 1 H, CH_2P), 3.65–3.55 (m, 1 H, H-2′), 3.52 (dd, *J* = 9.9, 13.3 Hz, 1 H, CH_2P), 3.43 (dd, *J* = 8.3, 13.7 Hz, 1 H, H-1′), 1.65–1.50 (m, 2 H, H-3′), 1.31–1.25 (m, 12 H, 4 × POCHCH_3), 0.96 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.6 (C-2), 157.0 (C-4), 148.9 (C-6), 94.1 (C-5), 81.6 (d, $^3J_{C,P}$ = 13 Hz, C-2′), 70.9 (apparent t, $^2J_{C,P}$ = 8 Hz, 2 × POCH), 64.5 (d, $^1J_{C,P}$ = 171 Hz, CH_2P), 52.4 (C-1′), 24.0 (C-3′), 23.8 (d, $^3J_{C,P}$ = 4 Hz, POCHCH_3), 8.7 (C-4′); MS (DCI) *m/e* 362 (MH^+).

General Procedure for the Hydrolysis of the Protected Cytosine Phosphonates. (*S*)-1-[3-Azido-2-(phosphonomethoxy)propyl]cytosine [(*S*)-14]. Phosphonate **42a** (0.85 g, 2.20 mmol) was dissolved in 9 mL of anhydrous acetonitrile and treated slowly with bromotrimethylsilane (4.06 g, 37.7 mmol) under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 12 h, and the solvent was removed under reduced pressure. The residue was dried in vacuo and then treated with acetone (10 mL) and water (2 mL). The resulting mixture was stirred at room temperature for 6 h and filtered. The solids collected were recrystallized from water/methanol to give 370 mg (55% yield) of the title compound as white crystals: mp 210 °C dec; $[\alpha]^{20}_D$ –75.0° (*c* 0.32, 1 N HCl); ^{1}H NMR (D_2O) δ 7.73 (d, *J* = 7.7 Hz, 1 H, H-5), 6.00 (d, *J* = 7.7 Hz, 1 H, H-6), 4.00 (dd, *J* = 6.6, 17.7 Hz, 1 H, H-1′), 3.81–3.72 (m, 2 H, H-1′ and H-2′), 3.66 (dd, *J* = 9.5, 13.1 Hz, 1 H, CH_2P), 3.57 (dd, *J* = 3.9, 13.5 Hz, 1 H, H-3′), 3.42 (dd, *J* = 9.5, 13.1 Hz, 1 H, CH_2P), 3.28 (dd, *J* = 3.6, 13.5 Hz, 1 H, H-3′); ^{13}C NMR (D_2O) δ 170.0 (C-2), 151.7 (C-4), 150.7 (C-6), 95.2 (C-5), 78.6 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 66.9 (d, $^1J_{C,P}$ = 158 Hz, CH_2P), 51.2, 51.0 (C-1′ and C-2′); MS (FAB) *m/e* 305 (MH^+). Anal. ($C_8H_{13}N_6O_5P$) C, H, N.

(*R*)-1-[3-Azido-2-(phosphonomethoxy)propyl]cytosine [(*R*)-14]: $[\alpha]^{20}_D$ 60.6° (*c* 0.46, 1 N HCl); MS (FAB) *m/e* 305 (MH^+). Anal. ($C_8H_{13}N_6O_5P\cdot0.33H_2O$) C, H, N.

(*S*)-1-[3-Fluoro-2-(phosphonomethoxy)propyl]cytosine [(*S*)-15]. The title compound was prepared from **42b** in 81% yield, purified by reverse-phase flash chromatography (C18, water), and recrystallized from water/methanol: mp 268 °C dec; $[\alpha]^{20}_D$ –87.4° (*c* 0.46, H_2O); ^{1}H NMR (D_2O) δ 7.86 (d, *J* = 7.7 Hz, 1 H, H-5), 6.14 (d, *J* = 7.7 Hz, 1 H, H-6), 4.65–4.60 and 4.47 (m and dd, *J* = 3.1, 10.7 Hz, 2 H, H-3′), 4.24–4.16 (m, 1 H, H-2′), 4.03–3.89 (m, 2 H, H-1′), 3.80 (dd, *J* = 9.5, 13.2 Hz, 1 H, CH_2P), 3.58 (dd, *J* = 9.5, 13.2 Hz, 1 H, CH_2P); ^{13}C NMR ($CDCl_3$) δ 166.7 (C-2), 157.0 (C-4), 146.5 (C-6), 94.5 (C-5), 79.9 (d, $^1J_{C,F}$ = 165 Hz, C-4′), 77.3 (dd, $^3J_{C,F}$ = 2 Hz, $^3J_{C,P}$ = 12 Hz, C-2′), 70.9 (d, $^2J_{C,P}$ = 5 Hz, POCH), 65.0 (d, $^1J_{C,P}$ = 170 Hz, CH_2P), 52.2 (C-1′), 32.2 (d, $^2J_{C,F}$ = 20 Hz, C-3′); MS (FAB) *m/e* 282 (MH^+). Anal. ($C_8H_{13}FN_3O_5P$) C, H, N.

(*R*)-1-[3-Fluoro-2-(phosphonomethoxy)propyl]cytosine [(*R*)-15]: $[\alpha]^{20}_D$ 115.5° (*c* 0.15, H_2O); MS (FAB) *m/e* 282 (MH^+). Anal. ($C_8H_{13}FN_3O_5P\cdot0.75\ H_2O$) C, H, N.

(*S*)-1-[4-Hydroxy-2-(phosphonomethoxy)butyl]cytosine [(*S*)-16]. Boron trichloride (1 M in CH_2Cl_2, 4.94 mL, 4.94 mmol) was slowly added to **42c** (0.77 g, 1.65 mmol) in 10 mL of anhydrous CH_2Cl_2 at –78 °C under a nitrogen atmosphere and the resulting mixture was stirred at –78 °C for 4 h. The solvent was removed under reduced pressure and the residue was evaporated from methanol (3 × 20 mL) and dried in vacuo. Anhydrous acetonitrile (8 mL) and bromotrimethylsilane (2.50 g, 16.5 mmol) were added to the residue under nitrogen and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, and the residue was dried in vacuo. To the residue were added water (4 mL) and acetone (16 mL). After stirring at room temperature for 24 h, the mixture was concentrated. The residue was dissolved in 50 mL of water and the resulting solution was washed with CH_2Cl_2 (2 × 15 mL). The aqueous layer was evaporated, and the residue was purified by reverse-phase flash chromatography (C_{18}; water/methanol = 1:0 to 10:1). The product collected was recrystallized from methanol and water to give 0.26 g (53%) of a white solid: mp 155–160 °C; $[\alpha]^{20}_D$ 43.7° (*c* 1.38, H_2O); $[\alpha]^{20}_D$ 64.0° (*c* 0.63, 1 N HCl); ^{1}H NMR (D_2O) δ 7.90 (d, *J* = 7.9 Hz, 1 H, H-6), 6.18 (d, *J* = 7.7 Hz, 1 H, H-5), 4.21–4.13, 3.92–3.83, 3.80–3.69 (m; 1 H, 2 H and 2 H, respectively; H-1′, H-2′ and H-4′), 3.72 (dd, *J* = 9.5, 13.1 Hz, 1 H, CH_2P), 3.59 (dd, *J* = 9.5, 13.1 Hz, 1 H, CH_2P), 1.81 (q, *J* = 6.1 Hz, 2 H, H-3′); ^{13}C NMR (D_2O) δ 165.8 (C-2), 156.3 (C-4), 153.1 (C-6), 94.0 (C-5), 80.5 (d, $^3J_{C,P}$ = 11 Hz, C-2′), 69.3 (d, $^1J_{C,P}$ = 158 Hz, CH_2P), 60.8, 58.0 (C-1′ and C-4′), 36.7 (C-3′); MS (FAB) *m/e* 294 (MH^+). Anal. ($C_9H_{16}N_3O_6P\cdot0.5H_2O$) C, H, N.

(*R*)-1-[4-Hydroxy-2-(phosphonomethoxy)butyl]cytosine [(*R*)-16]. The product was isolated as a monoammonium salt: $[\alpha]^{20}_D$ –24° (*c* 0.98, H_2O); high-resolution MS calcd for $C_9H_{16}N_3O_6P$ 294.0855, found 294.0852.

(*S*)-1-[4-Azido-2-(phosphonomethoxy)butyl]cytosine [(*S*)-17]. The title compound was prepared from **42d** in 63% yield and purified by reverse-phase column chromatography (C_{18}, water/methanol = 10:1 to 5:1) and recrystallized from methanol/water: mp 247 °C; $[\alpha]^{20}_D$ 32.6° (*c* 0.32, H_2O); ^{1}H NMR (D_2O) δ 7.86 (d, *J* = 7.7 Hz, 1 H, H-5), 6.13 (d, *J* = 7.7 Hz, 1 H, H-6), 4.12 (d, *J* = 11.5 Hz, 1 H, H-1′), 3.88–3.75 (m, 2 H, H-1′ and H-2′), 3.68 (dd, *J* = 9.7, 13.0 Hz, 1 H, CH_2P), 3.54 (dd, *J* = 9.7, 13.0 Hz, 1 H, CH_2P), 3.49 (t, *J* = 6.8 Hz, 2 H, H-4′), 1.81 (q, *J* = 6.6 Hz, 2 H, H-3′); ^{13}C NMR (D_2O) δ 164.2 (C-2), 154.3 (C-4), 153.7 (C-6), 97.7 (C-5), 80.6 (d, $^3J_{C,P}$ = 13 Hz, C-2′), 69.4 (d, $^1J_{C,P}$ = 158 Hz, CH_2P), 54.9 and 50.3 (C-1′ and C-4′), 33.2 (C-3′); MS (FAB) *m/e* 319 (MH^+); IR (KBr) 3500–2500 (OH, NH), 2100 (N_3), 1720 (C=O), 1114 (O-C), 1072, 930 (P-O), 770 (P-C) cm^{-1}. Anal. ($C_9H_{15}N_6O_5P$) C, H, N.

(*S*)-1-[4-Fluoro-2-(phosphonomethoxy)butyl]cytosine [(*S*)-18]. The title compound was prepared from **42e** in 88% yield, purified by reverse-phase column chromatography (C18, water/methanol = 10:1 to 5:1), and recrystallized from methanol/water: mp 257–259 °C dec; $[\alpha]^{20}_D$ 74.4° (*c* 0.49, H_2O); ^{1}H NMR (D_2O) δ 7.82 (d, *J* = 7.6 Hz, 1 H, H-5), 6.11 (d, *J* = 7.6 Hz, 1 H, H-6), 4.68 (dt, $J_{H,H}$ = 5.7 Hz, $J_{F,H}$ = 52.3 Hz, 2 H, H-4′), 4.15 (d, *J* = 11.7 Hz, 1 H, H-1′), 3.95–3.78 (m, 2 H, H-2′ and H-1′), 3.69 (dd, *J* = 9.7, 13.0 Hz, 1 H, CH_2P), 3.54 (dd, *J* = 9.7, 13.0 Hz, 1 H, CH_2P), 2.12–1.82 (m, 2 H, H-3′); ^{13}C NMR (D_2O) δ 165.7 (C-2), 156.3 (C-4), 153.2 (C-6), 97.9 (C-5), 84.5 (d, $^1J_{C,F}$ = 160 Hz, C-4′), 80.1 (t, $^3J_{C,P}$ = $^3J_{C,F}$ = 3 Hz, C-2′), 69.4 (d, $^1J_{C,P}$ = 158 Hz, CH_2P), 55.5 (C-1′), 34.8 (d, $^2J_{C,F}$ = 20 Hz, C-3′); MS (FAB) *m/e* 295 (MH^+). Anal. ($C_9H_{15}FN_3O_5P\cdot0.5H_2O$) C, H, N.

(*S*)-1-[2-(Phosphonomethoxy)-3-butenyl]cytosine [(*S*)-19]. The title compound was prepared from **42f** in 67% yield, purified by reverse-phase column chromatography (C18, water/methanol = 10:1 to 5:1), and recrystallized from methanol/water: mp 294 °C dec; $[\alpha]^{20}_D$ 84.0° (*c* 1.13, H_2O); ^{1}H NMR (D_2O) δ 7.86 (d, *J* = 7.7 Hz, 1 H, H-6), 6.11 (d, *J* = 7.7 Hz, 1 H, H-5), 5.78–5.66 (m, 1 H, H-3′), 5.44–5.37 (m, 2 H, H-4), 4.08 and 4.17–

4.05 (dd over m, J = 3.5, 14.0 Hz, 2 H, H-1′ and H-2′), 3.82 (dd, J = 7.9, 14.0 Hz, 1 H, H-1′), 3.67 (dd, J = 9.3, 13.2 Hz, 1 H, CH_2P), 3.38 (dd, J = 9.3, 13.2 Hz, 1 H, CH_2P); ^{13}C NMR (D_2O) δ 167.7 (C-2), 159.0 (C-4), 152.4 (C-6), 137.0 (C-3′), 123.7 (C-4′), 98.1 (C-5), 83.8 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 67.9 (d, J = 158 Hz, CH_2P), 55.6 (C-1′). Anal. ($C_9H_{14}N_3O_5P$) C, H, N.

(*S*)-1-[2-Cyclopropyl-2-(phosphonomethoxy)]ethyl]cytosine [(*S*)-20]. The title compound was prepared from **42g** in 58% yield, purified by reverse-phase column chromatography (C18, water/methanol = 10:1 to 5:1), and recrystallized from methanol/water: mp 281 °C dec; $[\alpha]^{20}_D$ 70.0° (c 1.18, H_2O); ^{1}H NMR (D_2O) δ 7.88 (d, J = 7.7 Hz, 1 H, H-6), 6.12 (d, J = 7.7 Hz, 1 H, H-5), 4.19 (dd, J = 3.4, 14.3 Hz, 1 H, H-1′), 3.95 (dd, J = 9.9, 13.0 Hz, 1 H, CH_2P), 3.90 (dd, J = 8.1, 14.3 Hz, 1 H, H-1′), 3.50 (dd, J = 9.9, 13.0 Hz, 1 H, CH_2P), 3.04–2.97 (m, 1 H, H-2′), 0.83–0.67, 0.57–0.50, 0.22–0.15 (m; 2 H, 2 H and 1 H, respectively; H-cyclopropyl); ^{13}C NMR (D_2O) δ 165.2 (C-2), 156.6 (C-4), 149.2 (C-6), 95.2 (C-5), 83.8 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 65.3 (d, $^1J_{C,P}$ = 159 Hz, CH_2P), 52.8 (C-1′), 11.4, 3.4, −3.2 (C-cyclopropyl). Anal. ($C_{10}H_{16}N_3O_5P$·0.25H_2O) H, N; C: calcd, 41.53; found, 40.96.

(*S*)-1-[2-(Phosphonomethoxy)butyl]cytosine [(*S*)-21]. The title compound was prepared from **42h** in 80% yield, purified by reverse-phase column chromatography (C18, water/methanol = 10:1 to 5:1), and recrystallized from methanol/water to provide the product: mp 282 °C; $[\alpha]^{20}_D$ 100.6° (c 0.36, H_2O); ^{1}H NMR (DMSO-d_6) δ 8.11 (br s, 1 H, NH), 8.02 (br s, 1 H, NH), 7.68 (d, J = 7.3 Hz, 1 H, H-5), 5.74 (d, J = 7.3 Hz, 1 H, H-6), 3.88 (br d, J = 12.3 Hz, 1 H, H-1′), 3.66–3.36 (m, 3 H, CH_2P and H-2′), 1.48–1.32 (m, 2 H, H-3′), 0.96 (t, J = 7.1 Hz, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 164.2 (C-2), 153.7 (C-4), 148.6 (C-6), 93.2 (C-5), 80.4 (d, $^3J_{C,P}$ = 11 Hz, C-2′), 65.8 (d, $^1J_{C,P}$ = 161 Hz, CH_2P), 50.6 (C-1′), 23.9 (C-3′), 9.2 (C-4′), MS (FAB) m/e 277 (MH^+). Anal. ($C_9H_{16}N_3O_5P$) C, H, N.

(*S*)-6-*O*-Benzyl-9-[3-(benzyloxy)-2-[(diisopropylphosphono)methoxy]propyl]-*N*^{2}-[(*p*-methoxyphenyl)diphenylmethyl]guanine (44). A solution of **43**[4] (9.20 g, 15.8 mmol), monomethoxytrityl chloride (7.30 g, 23.6 mmol), and 4-(dimethylamino)pyridine (1 g) under argon in anhydrous DMF (100 mL) was treated dropwise over 5 min with triethylamine (4.79 g, 47.3 mmol). The reaction mixture was heated at 40 °C for 20 h and then concentrated in vacuo. The residue was diluted with ethyl acetate (250 mL) and washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (150 mL), and the combined organic layers were washed with saturated NaCl solution (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give 15 g of a viscous oil. The residue was purified by column chromatography on silica gel (1% to 2% to 3% MeOH/CH_2Cl_2) to provide 10.9 g (81%) of the product: $[\alpha]^{20}_D$, −29.1° (c 0.67, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.57 (s, 1 H, H-8), 7.32–7.15 (m, 22 H, ArH), 6.73 (d, J = 8.9 Hz, 2 H, ArH), 6.22 (s, 1 H, NH), 4.99 (br s, 2 H, OCH_2Ph), 4.71–4.58 (m, 2 H, 2 × POCH), 4.45 (s, 2 H, OCH_2Ph), 4.09–3.85 (m, 2 H, 2 × H-1′), 3.73 (s, 3 H, OCH_3), 3.77–3.30 (m, 5 H, OCH_2P, H-2′, and 2 × H-3′), 1.29–1.19 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR (DMSO-d_6) δ 158.1, 15.7.7, 154.0, 145.9, 140.4, 138.1, 137.7, 136.6, 130.2, 129.0, 128.4, 128.2, 128.1, 127.8, 127.8, 127.6, 126.5, 114.8 (C-5), 112.9, 78.8 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 73.5 (3′-OCH_2Ph), 71.1 (d, $^2J_{C,P}$ = 7 Hz, POCH), 70.5 (CAr_3), 69.1 and 67.8 (C-3′ and 6-*O*-CH_2Ph), 65.1 (d, $^1J_{C,P}$ = 169 Hz, OCH_2P), 55.2 (OCH_3), 44.2 (C-1′), 24.0 (d, $^3J_{C,P}$ = 7 Hz, OCHCH_3), 23.9 (d, $^3J_{C,P}$ = 7 Hz, OCHCH_3); MS (FAB) m/e 856 (MH^+). Anal. ($C_{49}H_{54}N_5O_7P$) C, H, N.

(*S*)-9-[3-Hydroxy-2-[(diisopropylphosphono)methoxy]propyl]-*N*^{2}-[(*p*-methoxyphenyl)diphenylmethyl]guanine (45). Phosphonate **44** (10.1 g, 11.8 mmol) was dissolved in 1:1 cyclohexane/ethanol (200 mL) and treated in one portion with 20% Pd(OH)$_2$ on carbon (10 g). The mixture was heated at reflux for 14 h and then filtered while hot through a 1-inch pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (4% to 6% MeOH/CH_2Cl_2) to afford 4.04 g (51%) of the desired product: $[\alpha]^{20}_D$ −43.9° (c 0.95, MeOH); ^{1}H NMR (DMSO-d_6) δ 10.51 (br s, 1 H, NH), 7.60 (br s, 1 H, NH), 7.45 (s, 1 H, H-8), 7.31–7.15 (m, 12 H, ArH), 6.85 (d, J = 9.0 Hz, 2 H, ArH), 4.65 (t, J = 5.2 Hz, 1 H, OH), 4.52–4.39 (m, 2 H, 2 × POCH), 3.70 (s, 3 H, OCH_3), 3.64–3.46 (m, 2 H, 2 × H-1′), 3.32–3.21 (m, 3 H, 2 × OCH_2P and H-3′), 3.15–3.07 (m, 1 H, H-2′), 3.03–2.96 (m, 1 H, H-3′), 1.20–1.10 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR (DMSO-d_6) δ 157.8, 156.6, 150.7, 149.7, 145.1, 145.0, 138.4, 136.9, 130.0, 128.6, 127.7, 126.6, 116.9 (C-5), 113.0, 79.5 (d, $^3J_{C,P}$ = 13 Hz, C-2′), 70.3 (d, $^2J_{C,P}$ = 7 Hz, POCH), 69.8 (CAr_3), 63.6 (d, $^1J_{C,P}$ = 165 Hz, OCH_2P), 60.0 (C-3′), 55.0 (OCH_3), 43.7 (C-1′), 23.8 (d, $^3J_{C,P}$ = 7 Hz, OCHCH_3), 23.7 (d, $^3J_{C,P}$ = 7 Hz, OCHCH_3); MS (FAB) m/e 676 (MH^+). Anal. ($C_{35}H_{42}N_5O_7P$) C, H, N.

(*S*)-9-[3-Chloro-2-[(diisopropylphosphono)methoxy]propyl]guanine (46). A solution of **45** (1.35 g, 2.00 mmol) in anhydrous acetonitrile (10 mL) was treated with CCl_4 (3.07 g, 20.0 mmol), Ph_3P (1.05 g, 4.00 mmol), and imidazole (0.54 g, 8.0 mmol). The reaction mixture was stirred at room temperature for 2 h, treated with anhydrous pyridine (10 mL), and then heated at 80 °C for 15 h. Additional CCl_4 (1.50 g, 9.8 mmol), Ph_3P (0.52 g, 2.0 mmol), and imidazole (0.27 g, 4.0 mmol) were added, and the reaction mixture was heated at 80 °C for 5 h further. The resulting brown mixture was allowed to cool to room temperature, treated with ethanol (10 mL), and concentrated in vacuo. The residue (4.5 g) was purified by column chromatography on silica gel (1% to 3% to 5% MeOH/CH_2Cl_2) to afford 0.68 g of (*S*)-9-[3-chloro-2-[(diisopropylphosphono)methoxy]propyl]-*N*^{2}-[(*p*-methoxyphenyl)-diphenylmethyl]guanine contaminated with some imidazole and triphenyl phosphine.

A portion of the partially-purified material (0.50 g) was dissolved in 80% aqueous acetic acid (25 mL) and the solution was heated on a steam bath for 1 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (5% to 7.5% MeOH/CH_2Cl_2) to provide 0.22 g of the product (36% overall yield from **45**): ^{1}H NMR (DMSO-d_6) δ 7.60 (s, 1 H, H-8), 6.38 (br s, 2 H, NH_2), 4.56–4.33 (m, 2 H, 2 × POCH), 4.20–4.01 (m, 3 H, H-2′ and 2 × H-1′), 3.92–3.80 (m, 2 H, OCH_2P), 3.73–3.65 (m, 2 H, 2 × H-3′), 1.05–1.19 (m, 12 H, 4 × POCHCH_3); ^{13}C NMR (DMSO-d_6) δ 157.4, 154.0, 151.9, 138.3, 116.6 (C-5), 78.3 (d, $^3J_{C,P}$ = 13 Hz, C-2′), 70.5 (d, $^2J_{C,P}$ = 4 Hz, POCH), 63.5 (d, $^1J_{C,P}$ = 165 Hz, OCH_2P), 44.0 and 43.5 (C-3′ and C-1′), 23.8 (d, $^3J_{C,P}$ = 7 Hz, POCHCH_3), 23.6 (d, $^3J_{C,P}$ = 7 Hz, POCHCH_3); MS (FAB) m/e 422 (MH^+).

(*S*)-9-[3-Chloro-2-(phosphonomethoxy)propyl]guanine [(*S*)-7]. Bromotrimethylsilane (0.51 g, 3.3 mmol) was added dropwise to a solution of **46** (0.135 g, 0.320 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at room temperature for 14 h and then concentrated in vacuo. The residue was coevaporated from acetonitrile (25 mL) and then treated with water (0.5 mL). Upon addition of acetone (25 mL), the product precipitated from solution. Filtration of the slurry gave 0.088 g (81%) of the product as a pale orange solid: $[\alpha]^{20}_D$ −40.0° (c 0.07, H_2O); ^{1}H NMR (D_2O) δ 8.92 (s, 1 H, H-8), 4.55 (dd, J = 3.5, 14.6 Hz, 1 H, 1 × H-1′), 4.39 (dd, J = 8.1, 14.6 Hz, 1 H, 1 × H-1′), 4.19–4.10 (m, 1 H, H-2′), 3.89–3.70 (m, 3 H, 1 × H-3′ and OCH_2P), 3.55 (dd, J = 9.9, 13.2 Hz, 1 H, 1 × H-3′); ^{13}C NMR (D_2O) δ 157.4, 157.2, 152.1, 140.4 (C-8), 109.5 (C-5), 79.7 (d, $^3J_{C,P}$ = 12 Hz, C-2′), 67.3 (d, $^1J_{C,P}$ = 160 Hz, OCH_2P), 48.2 (C-3′), 44.1 (C-1′); MS (FAB) m/e 338 (MH^+). Anal. ($C_9H_{13}N_5O_5PCl$·0.66H_2O) C, H, N.

(*R*)-9-[3-Chloro-2-(phosphonomethoxy)propyl]guanine [(*R*)-7]. MS (FAB) m/e 338 (MH^+). Anal. ($C_9H_{13}N_5O_5$-PCl·0.125H_2O) H, N; C: calcd, 32.27; found, 31.80.

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