

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

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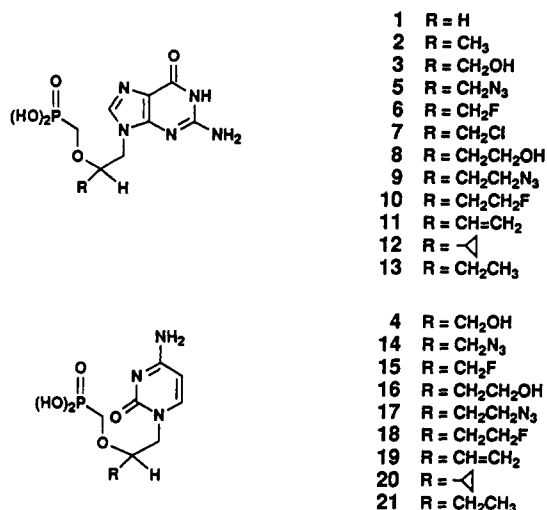
A series of 2'-substituted derivatives of 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG, 1) have been synthesized and evaluated *in vitro* for anti-human immunodeficiency virus (HIV) activity in the XTT assay and for anti-herpes activity in the plaque reduction assay. It has been observed that the anti-HIV 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 μ M and a cytotoxicity (CC_{50}) greater than 1.4 mM in CEM cells. The latter has an IC_{50} of 13 μ M 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 analogues¹ 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

Chart I



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 substituents⁶ 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.

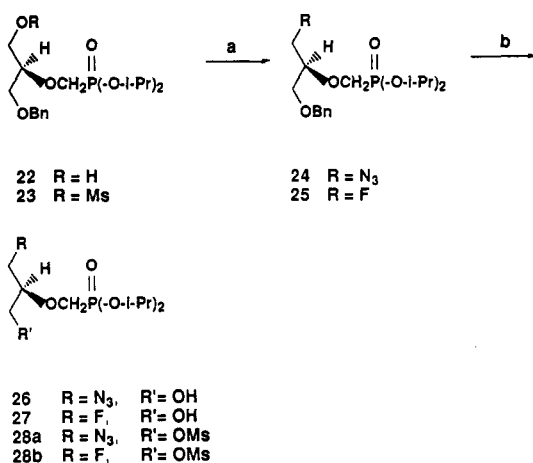
Chemistry

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

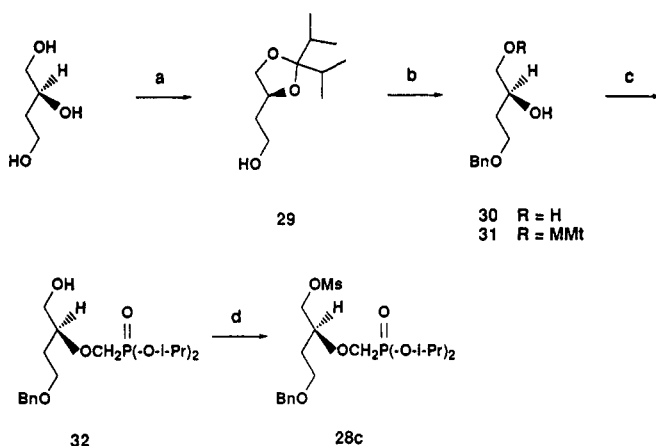
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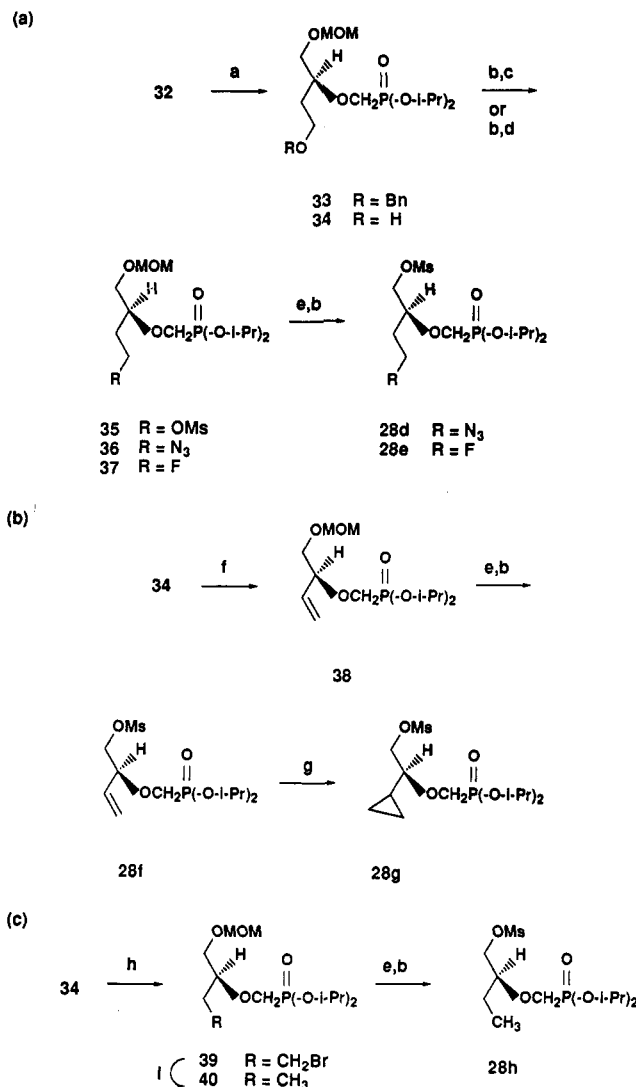
Scheme I^a

^a (a) NaN₃ or TBAF; (b) BCl₃; MsCl, Et₃N.

Scheme II^a

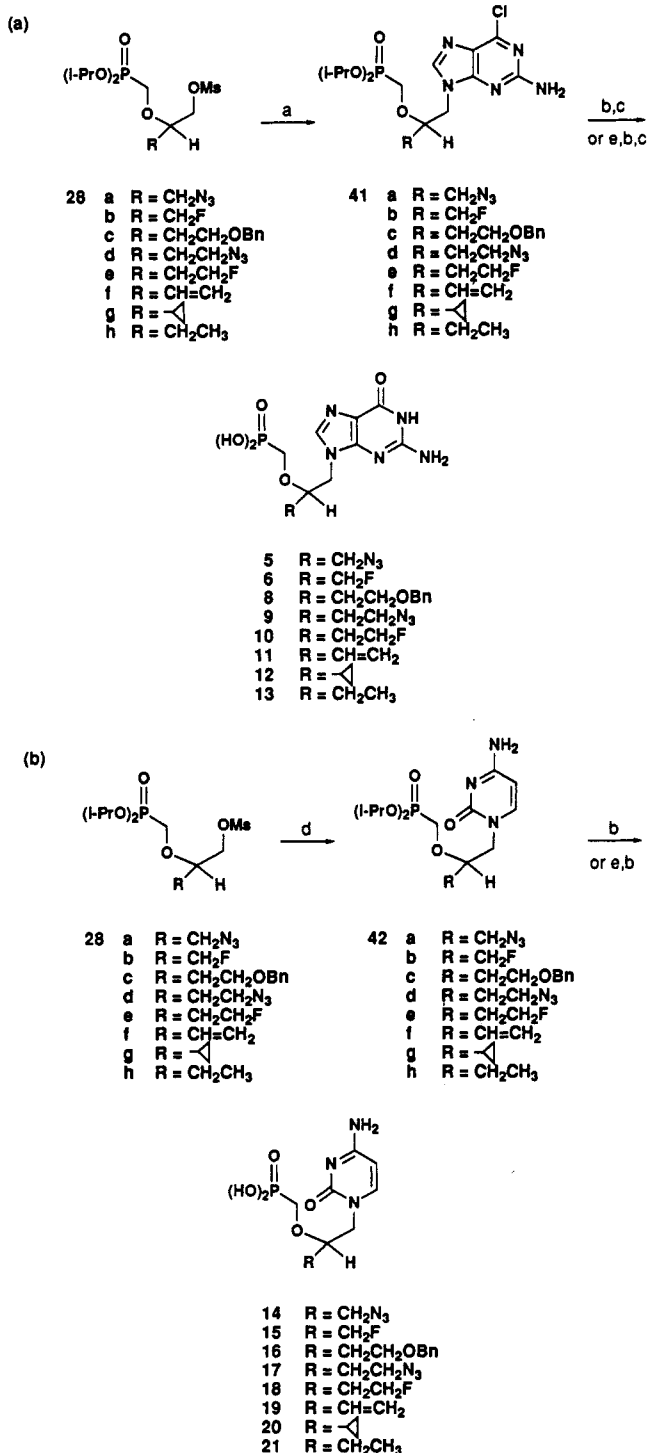
^a (a) 2,4-Dimethyl-3-pentanone, TsOH; (b) BnBr, NaOH; 1.5 M H₂SO₄; MMT-Cl, Et₃N; (c) NaH, TsOCH₂PO(O-*i*-Pr)₂, H⁺; (d) MsCl, Et₃N.

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 23⁴ with NaN₃ in DMF⁹ at 105 °C afforded 24 in 78% yield (Scheme I). Initial attempts to prepare fluoromethyl intermediate 25 by treating 22⁴ with diethylamidodisulfur 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 fluoride¹¹ 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 BCl₃¹² gave 26 and 27, respectively. Conversion to mesylates 28a and 28b proceeded in excellent yields upon treatment with mesyl chloride followed by addition of Et₃N. 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, Et₃N; (c) NaN₃; (d) TBAF; (e) CSA-MeOH; (f) 2-nitrophenyl selenocyanate, P(n-Bu)₃; H₂O₂, NaOH; (g) CH₂N₂, Pd(OAc)₂; (h) CBr₄, PPh₃, imidazole; (i) H₂, Pd/C, Et₃N.

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 oxide¹³ 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 Clive¹⁴ 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 monomethoxytrityl chloride (MMT-Cl) to give 31. O-Alkylation of 31 with NaH and diisopropyl tosylmethanephosphonate⁷ followed by removal of the MMT-pro-

Scheme IV^a

protecting 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) ether¹⁵ (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,

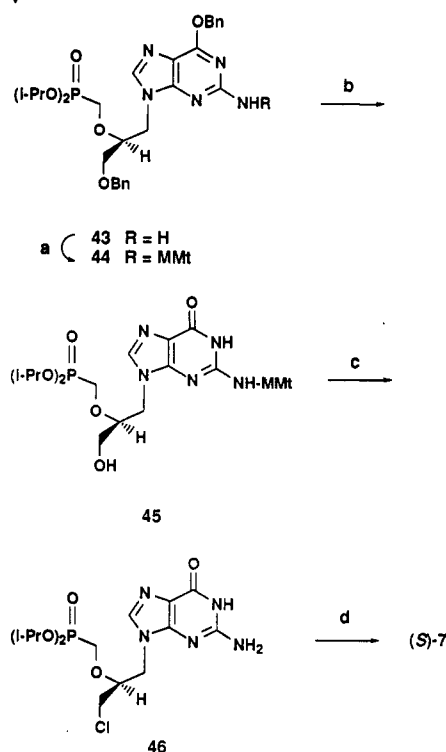
respectively. The MOM group was removed upon hydrolysis with camphorsulfonic acid in MeOH, and the resulting alcohols were converted into the corresponding mesylates 28d and 28e in excellent yields. Dehydration of 34 was achieved in two steps by reaction with 2-nitrophenyl selenocyanate¹⁷ and tributylphosphine followed by oxidative elimination with H₂O₂-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 CH₂N₂ in the presence of Pd(OAc)₂¹⁸ to provide 28g in quantitative yield. Ethyl derivative 28h was prepared from alcohol 34 (Scheme IIIc) by reaction with CBr₄ and triphenylphosphine¹⁹ 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 Et₃N. 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 Cs₂CO₃⁴ 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 BCl₃ 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 BCl₃. Reaction with TMSBr then afforded cytosine derivative 16.

2'-(Chloromethyl)-PMEG (7) was prepared from intermediate 43⁴ (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 of the *O*-benzyl groups to provide 45 in 51% yield. Reaction of alcohol 45 with CCl₄ and PPh₃-imidazole²¹ 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, Et₃N; (b) cyclohexene, Pd(OH)₂; (c) CCl₄, PPh₃, imidazole; 80% AcOH; (d) TMSBr; H₂O.

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 ₂ OH	(R)-3	500	>500	>1	
5	CH ₂ OH	(S)-3	>500	350	<1	
6	CH ₂ N ₃	(R)-5	5	>1000	>200	>1400
7	CH ₂ N ₃	(S)-5	51	>1000	>20	134
8	CH ₂ F	(R)-6	8	>500	>63	427
9	CH ₂ F	(S)-6	7	>500	>71	93
10	CH ₂ Cl	(R)-7	45	>500	>11	870
11	CH ₂ Cl	(S)-7	50	>500	>10	>1500
12	CH ₂ CH ₂ OH	(R)-8	NA	>450		
13	CH ₂ CH ₂ OH	(S)-8	NA	>500		
14	CH ₂ CH ₂ N ₃	(S)-9	NA	>500		
15	CH ₂ CH ₂ F	(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 ₂ CH ₃	(R)-13	54	1000	19	
21	CH ₂ CH 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 TC₅₀ to IC₅₀. ^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 (CC₅₀) 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

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

entry	2'-substituent	compd no.	IC ₅₀ (μM) ^a		
			HCMV ^b	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 ₂ OH	(R)-3	1.6	99	>310, ^b >310 ^c
5	CH ₂ OH	(S)-3	0.8	97	>310, ^b >310 ^c
6	CH ₂ N ₃	(R)-5	33	NA	>300, ^b >300 ^c
7	CH ₂ N ₃	(S)-5	15	NA	300, ^b >300 ^c
8	CH ₂ F	(R)-6	136	NA	>310, ^b >310 ^c
9	CH ₂ F	(S)-6	150	256	>310, ^b >310 ^c
10	CH ₂ Cl	(R)-7	51	NA	>300, ^b >300 ^c
11	CH ₂ Cl	(S)-7	112	NA	300, ^b 300 ^c
12	CH ₂ CH ₂ OH	(R)-8	NA	NA	300 ^c
13	CH ₂ CH ₂ OH	(S)-8	162	NA	>300, ^b 300 ^c
14	CH ₂ CH ₂ N ₃	(S)-9	NA	NA	300, ^b 300 ^c
15	CH ₂ CH ₂ F	(S)-10	NA	NA	300, ^b 300 ^c
16	CH=CH ₂	(R)-11	NA ^d	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, ^b >300 ^c
19	c-propyl	(S)-12	NA	NA	300 ^c
20	CH ₂ CH ₃	(R)-13	NA ^d	NA ^d	>300, ^b >300 ^c
21	CH ₂ CH ₃	(S)-13	NA ^b	NA ^c	300, ^b 300 ^c

^a IC₅₀, 50% inhibitory concentration; TC₅₀, 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).

(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).

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 μ M and a cytotoxicity CC_{50} of greater than 1.4 mM. The latter has an IC_{50} of 13 μ M 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)tetrauteriopropionate 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 23⁴ (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 $^{\circ}C$ 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 $^{\circ}$ (c 0.42, CH_2Cl_2); 1H NMR ($CDCl_3$) δ 7.35–7.22 (m, 5 H, ArH), 4.77–4.62 (m, 2 H, POCH), 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 \times POCHCH₃); ^{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 (OCH₂Ph), 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, POCHCH₃), 23.6 (d, $^3J_{C,P}$ = 4 Hz, POCHCH₃). Anal. (C₁₇H₂₈N₃O₈P) 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 $^{\circ}C$ 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 \times 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 $^{\circ}$ (c 1.19, CH_2Cl_2); 1H NMR ($CDCl_3$) δ 7.35–7.23 (m, 5 H, ArH), 4.78–4.65 (m, 2 H, 2 \times POCH), 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, OCH₂Ph), 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 \times POCHCH₃); ^{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 (OCH₂Ph), 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, POCHCH₃), 23.7 (d, $^3J_{C,P}$ = 4 Hz, POCHCH₃). Anal. (C₁₇H₂₈FO₈P) 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 $^{\circ}C$ under a nitrogen atmosphere. The mixture was stirred at –78 $^{\circ}C$ 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 \times 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 $^{\circ}$ (c 8.53, MeOH); 1H NMR ($CDCl_3$) δ 4.82–4.65 (m, 2 H, POCH), 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 \times POCHCH₃); ^{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, POCHCH₃), 23.4 (d, $^3J_{C,P}$ = 5 Hz, POCHCH₃).

(*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 $^{\circ}C$ under a nitrogen atmosphere. The resulting solution was stirred at 0 $^{\circ}C$ 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 \times 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 $^{\circ}$ (c 16.76, CH_2Cl_2); 1H NMR ($CDCl_3$) δ 4.78–4.63 (m, 2 H, POCH), 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, 1 H, H-3), 3.05 (s, 3 H, SO₂CH₃), 1.30 (d, J = 6.2, Hz, 12 H, 4 \times POCHCH₃); ^{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 (SO₂CH₃), 23.6 (apparent t, $^3J_{C,P}$ = 5 Hz, POCHCH₃); MS (DCI) *m/e* 374 (MH⁺). Anal. (C₁₁H₂₄N₃O₇PS) 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 \times POCH), 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,

$J_{\text{H,H}} = 5.5, 11.3 \text{ Hz}$, $J_{\text{H,P}} = 1.5 \text{ Hz}$, 1 H, H-1), 3.88 and 4.04–3.82 (d over m, $J = 8.7 \text{ Hz}$, 3H, CH_2P and H-2), 3.06 (s, 3 H, SO_2CH_3), 1.31 (d, $J = 6.2 \text{ Hz}$, 12 H, 4 \times POCHCH_3); ^{13}C NMR (CDCl_3) δ 81.1 (d, $^1J_{\text{C,P}} = 173 \text{ Hz}$, C-3), 77.5 (dd, $^2J_{\text{C,P}} = 20 \text{ Hz}$, $^3J_{\text{C,P}} = 10 \text{ Hz}$, C-2), 71.2 (apparent t, $^2J_{\text{C,P}} = 6 \text{ Hz}$, POCH), 65.2 (d, $^1J_{\text{C,P}} = 169 \text{ Hz}$, CH_2P), 37.3 (SO_2CH_3), 23.7 (d, $^3J_{\text{C,P}} = 4 \text{ Hz}$, POCHCH_3), 23.6 (d, $^3J_{\text{C,P}} = 5 \text{ Hz}$, POCHCH_3). Anal. ($\text{C}_{11}\text{H}_{24}\text{FO}_7\text{PS}$) 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/ $\text{CH}_2\text{Cl}_2 = 1:10$ to 1:2) to give 77.2 g (84% yield) of the product as an oil: $[\alpha]_D^{20} 1.55^\circ$ (c 15.6 CH_2Cl_2); ^1H NMR (CDCl_3) δ 4.33–4.23 (m, 1 H, H-4), 4.14 (t, $J = 7.0 \text{ Hz}$, 1 H, H-5), 3.85–3.72 (m, 2 H, H-2'), 3.49 (t, $J = 8.3 \text{ Hz}$, 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 \times 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. ($\text{C}_{11}\text{H}_{22}\text{O}_3$) 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 \times 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 \times 200 mL) and then adjusted to pH 8–9 with concentrated sodium hydroxide. The solution was extracted with ethyl acetate (3 \times 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, ArH), 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, OH), 3.08 (br s, 1 H, OH), 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 \times 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: $[\alpha]_D^{20} -3.0^\circ$ (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; ArH), 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, $J = 2.0 \text{ Hz}$, 1 H, OH), 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. ($\text{C}_{31}\text{H}_{32}\text{O}_4$) 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 \times 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, ArH), 4.80–4.63 (m, 2 H, POCH), 4.49 (d, $J = 12.0 \text{ Hz}$, 1 H, CH_2Ph), 4.44 (d, $J = 12.0 \text{ Hz}$, 1 H, CH_2Ph), 3.87 (dd, $J = 7.2, 14.1 \text{ Hz}$, 1 H, CH_2P), 3.72 and 3.80–3.60 (dd over m, $J = 9.0, 14.1 \text{ Hz}$, 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 \times POCHCH_3); ^{13}C NMR (CDCl_3) δ 138.8, 129.0, 128.3 (Ar), 82.1 (d, $^3J_{\text{C,P}} = 8.7 \text{ Hz}$, C-2), 73.4 (CH_2Ph), 72.0 (d, $^2J_{\text{C,P}} = 7 \text{ Hz}$, POCH), 71.6 (d, $^2J_{\text{C,P}} = 7 \text{ Hz}$, POCH), 66.7 (C-4), 65.4 (d, $^1J_{\text{C,P}} = 170 \text{ Hz}$, 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-(methanesulfonyl)-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, ArH), 4.78–4.63 (m, 2 H, POCH), 4.47 (s, 2 H, CH_2Ph), 4.36 (dd, $J = 3.0, 11.1 \text{ Hz}$, 1 H, H-1), 4.18 (dd, $J = 6.0, 11.1 \text{ Hz}$, 1 H, H-1), 3.83 and 3.80–3.87 (dd over m, $J = 9.0, 13.3 \text{ Hz}$, 2 H, CHP and H-2), 3.74 (dd, $J = 9.8, 13.3 \text{ Hz}$, 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 \times POCHCH_3); ^{13}C NMR (CDCl_3) δ 137.9, 128.3, 127.5 (Ar), 77.04 (d, $^3J_{\text{C,P}} = 12.6 \text{ Hz}$, C-2), 72.7 (CH_2Ph), 65.3 (C-4), 64.7 (d, $^1J_{\text{C,P}} = 170 \text{ Hz}$, CH_2P), 36.9 (SO_2CH_3), 30.5 (C-3), 23.5 (apparent t, $^3J_{\text{C,P}} = 5 \text{ Hz}$, 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 \times 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 g (98% yield) of the product as an oil: ^1H NMR (CDCl_3) δ 7.33–7.20 (m, 5 H, ArH), 4.76–4.62 (m, 2 H, 2 \times POCH), 4.58 (s, 2 H, OCH_2O), 4.47 (s, 2 H, CH_2Ph), 3.94 (dd, $J = 8.7, 13.6 \text{ Hz}$, 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, $J = 6.2 \text{ Hz}$, 2 H, H-3), 1.32–1.26 (m, 12 H, 4 \times POCHCH_3); ^{13}C NMR (CDCl_3) δ 138.4, 128.3, 127.6, 96.4 (OCH_2O), 77.9 (d, $^3J_{\text{C,P}} = 13 \text{ Hz}$, C-2), 72.7 (CH_2Ph), 70.6 (d, $^2J_{\text{C,P}} = 6 \text{ Hz}$, POCH), 69.6 (C-1), 66.2 (C-4), 64.7 (d, $^1J_{\text{C,P}} = 170 \text{ Hz}$, CH_2P), 54.9 (OCH_3), 31.5 (C-3), 23.6 (apparent t, $^3J_{\text{C,P}} = 6 \text{ Hz}$, 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: $[\alpha]_D^{20} 3.43^\circ$ (c 2.33, MeOH); ^1H NMR (CDCl_3) δ 4.80–4.60 (m, 2 H, 2 \times POCH), 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 \times POCHCH_3); ^{13}C NMR (CDCl_3) δ 96.5 (OCH_2O), 77.7 (d, $^3J_{\text{C,P}} = 14 \text{ Hz}$, C-2), 71.1 (d, $^2J_{\text{C,P}} = 7 \text{ Hz}$, POCH), 70.2 (C-1), 64.7 (d, $^1J_{\text{C,P}} = 167 \text{ Hz}$, CH_2P), 57.9 (C-4),

55.0 (OCH₃), 34.3 (C-3), 23.6 (apparent t, ³J_{C,P} = 5 Hz, POCHCH₃); MS (DCI) *m/e* 329 (MH⁺). Anal. (C₁₃H₂₈O₇P) 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 prepare 28a: [α]_D²⁰ -17.9° (c 0.67, MeOH); ¹H NMR (CDCl₃) δ 4.88–4.62 (m, 2 H, 2 \times POCH), 4.58 (s, 2 H, OCH₂O), 4.42–4.28 (m, 2 H, H-4), 3.95 (dd, *J* = 8.8, 13.7 Hz, 1 H, CH₂P), 3.73 and 3.74–3.67 (dd over m, *J* = 9.3, 13.7 Hz, 2 H, CH₂P and H-2), 3.61–3.51 (m, 2 H, H-1), 3.32 (s, 3 H, OCH₃), 3.00 (s, 3 H, CH₃SO₂), 2.30–1.83 (m, 2 H, H-3), 1.31–1.27 (m, 12 H, 4 \times POCHCH₃); ¹³C NMR (CDCl₃) δ 96.3 (OCH₂O), 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, CH₂P), 54.9 (OCH₃), 36.7 (SO₂CH₃), 31.2 (C-3), 23.5 (apparent t, ³J_{C,P} = 4 Hz, POCHCH₃). Anal. (C₁₄H₃₁O₈PS) 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: ¹H NMR (CDCl₃) δ 4.79–4.60 (m, 2 H, POCH), 4.59 (s, 2 H, OCH₂O), 3.96 (dd, *J* = 8.7, 13.6 Hz, 1 H, CH₂P), 3.74 (dd, *J* = 9.5, 13.6 Hz, 1 H, CH₂P), 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, OCH₃), 1.80–1.73 (m, 2 H, H-3), 1.30 (d, *J* = 6.2 Hz, 6 H, 2 \times POCHCH₃); ¹³C NMR (CDCl₃) δ 96.5 (OCH₂O), 77.7 (d, ³J_{C,P} = 12 Hz, C-2), 70.8 (apparent t, ²J_{C,P} = 6 Hz, POCH), 69.1 (C-1), 64.7 (d, ¹J_{C,P} = 170 Hz, CH₂P), 55.1 (OCH₃), 47.4 (C-4), 30.8 (C-3), 23.6 (apparent t, ³J_{C,P} = 4 Hz, POCHCH₃). Anal. (C₁₃H₂₈N₃O₆P) 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 (CH₂Cl₂/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: ¹H NMR (CDCl₃) δ 4.81–4.63 (m, 2 H, POCH), 3.91 (dd, *J* = 7.2, 14.1 Hz, 1 H, CH₂P), 3.73 and 3.76–3.68 (dd over m, *J* = 9.1, 14.1 Hz, 2 H, CH₂P 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 \times POCHCH₃), 1.29 (d, *J* = 4.8 Hz, 6 H, POCHCH₃); ¹³C NMR (CDCl₃) δ 80.8 (d, ³J_{C,P} = 9 Hz, C-2), 71.5 (d, ²J_{C,P} = 7 Hz, POCH), 71.1 (d, ²J_{C,P} = 7 Hz, POCH), 64.7 (d, ¹J_{C,P} = 170 Hz, CH₂P), 63.6 (C-1), 47.6 (C-4), 30.4 (C-3), 23.6 (m, POCHCH₃); IR (film): 3388 (OH), 2098 (N₃), 1240 (P=O), 1106 (C-O), 994 (P-O-C) cm⁻¹. Anal. Calcd for C₁₁H₂₄N₃O₆P: 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-O-[(diisopropylphosphono)methyl]-1,2-butanediol (2.50 g, 8.08 mmol) using the same procedure used for the preparation of 28a: ¹H NMR (CDCl₃) δ 4.80–4.64 (m, 2 H, 2 \times POCH), 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, CH₂P), 3.75 and 3.83–3.74 (dd and m, *J* = 9.7, 13.6 Hz, 2 H, CH₂P and H-2), 3.48 (t, *J* = 6.6 Hz, 2 H, H-4), 3.06 (s, 3 H, SCH₃), 1.90–1.68 (m, 2 H, H-3), 1.32 (d, *J* = 6.2, Hz, 6 H, 2 \times POCHCH₃), 1.31 (d, *J* = 6.2, Hz, 6 H, 2 \times POCHCH₃); ¹³C NMR (CDCl₃) 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, CH₂P), 47.0 (C-4), 37.3 (SO₂CH₃), 30.2 (C-3), 23.7 (d, ³J_{C,P} = 5 Hz, POCHCH₃); 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 (CH₂Cl₂/acetone = 1:0 to 5:1) to give 3.70 g (87%) of 40 as an oil: ¹H NMR (CDCl₃) δ 4.60 and 4.41–4.80 (s over m, 6 H, OCH₂O, 2 \times POCH and CH₂F), 3.98 (dd, *J* = 8.6, 13.7 Hz, 1 H, CH₂P), 3.77 and 3.80–3.70 (dd over m, *J* = 9.5, 13.7 Hz, 2

H, CH₂P and H-2), 3.63–3.52 (m, 2 H, H-1), 3.34 (s, 3 H, OCH₃), 2.03–1.69 (m, 2 H, H-3), 1.36–1.29 (m, 12 H, 4 \times POCHCH₃); ¹³C NMR (CDCl₃) δ 96.4 (OCH₂O), 80.2 (d, ¹J_{C,F} = 164 Hz, CH₂F), 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, CH₂P), 54.8 (OCH₃), 32.3 (d, ²J_{C,F} = 20 Hz, C-3), 23.6 (d, ³J_{C,P} = 5 Hz, POCHCH₃), 23.5 (d, ³J_{C,P} = 5 Hz, POCHCH₃).

(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 (CH₂Cl₂/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: ¹H NMR (CDCl₃) δ 4.75–4.40 (m, 4 H, 2 \times POCH and CH₂F), 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, CH₂P and H-2), 3.72 (dd, *J* = 9.7, 13.5 Hz, 1 H, CH₂P), 3.01 (s, 3 H, SO₂CH₃), 2.01–1.75 (m, 2 H, H-3), 1.30–1.20 (m, 12 H, 4 \times POCHCH₃); ¹³C NMR (CDCl₃) δ 79.7 (¹J_{C,F} = 165 Hz, CH₂F), 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, CH₂P), 37.3 (SO₂CH₃), 31.7 (d, ²J_{C,F} = 20 Hz, C-3), 23.7 (apparent t, ³J_{C,P} = 5 Hz, POCHCH₃); MS (DCI) *m/e* 365 (MH⁺). Anal. (C₁₂H₂₈FO₇PS) 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 \times 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)selenenyl]-1,2,4-butanetriol as a thick yellow oil: ¹H NMR (CDCl₃) δ 8.27 (dd, *J* = 1.5, 8.3 Hz, 1 H, ArH), 7.60–7.49, 7.32–7.26 (m, 3 H, Ar H), 4.80–4.67 (m, 2 H, POCH), 4.59 (s, 2 H, OCH₂O), 3.99 (dd, *J* = 8.6, 13.7 Hz, 1 H, CH₂P), 3.79 (dd, *J* = 9.3, 13.7 Hz, 1 H, CH₂P), 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, OCH₃), 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 \times POCHCH₃).

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 \times 100 mL) and the combined extracts were washed with saturated NaHCO₃ (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: ¹H NMR (CDCl₃) 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 \times POCH), 4.61 (s, 2 H, OCH₂O), 4.05–3.96 (m, 1 H, H-2), 3.79 (dd, *J* = 9.5, 13.5 Hz, 1 H, CH₂P), 3.63 (dd, *J* = 8.4, 13.5 Hz, 1 H, CH₂P), 3.62–3.50 (m, 2 H, H-1), 3.57 (s, 3 H, OCH₃), 1.35–1.28 (m, 12 H, 4 \times POCHCH₃); ¹³C NMR (CDCl₃) δ 134.5 (C-3), 119.8 (C-4), 96.5 (OCH₂O), 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, CH₂P), 55.0 (OCH₃), 23.7 (t, *J* = 5 Hz, POCHCH₃). Anal. (C₁₃H₂₇O₆P) C, H.

(S)-2-O-[(Diisopropylphosphono)methyl]-1-O-(methylsulfonyl)-3-butene-1,2-diol (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: ¹H NMR (CDCl₃) 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, POCH), 3.82 (dd, *J* = 8.8, 13.5 Hz, 1 H, CH₂P), 3.56 (dd, *J* = 8.3, 13.5 Hz, 1 H, CH₂P), 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, OH),

1.34–1.26 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) 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, CH₂P), 23.3 (apparent t, ³J_{C,P} = 4 Hz, POCHCH₃). Anal. (C₁₁H₂₃O₅P) C, H.

Mesylate **28f** was isolated as an oil: ¹H NMR (CDCl₃) 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, POCH), 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, CH₂P), 3.57 (dd, *J* = 8.8, 13.6 Hz, 1 H, CH₂P), 3.05 (s, 3 H, SO₂CH₃), 1.34–1.23 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) 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, CH₂P), 37.33 (SO₂CH₃) 23.5 (d, ³J_{C,P} = 5 Hz, POCHCH₃). Anal. (C₁₂H₂₅O₇PS) 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 (CH₂Cl₂/acetone = 3:1) to give 1.10 g (96% yield) of **28g** as an oil: ¹H NMR (CDCl₃) δ 4.78–4.63 (m, 2 H, POCH), 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, CH₂P), 3.72 (dd, *J* = 9.7, 13.4 Hz, 1 H, CH₂P), 3.04 and 3.10–2.95 (s over m, 4 H, SO₂CH₃ and H-2), 1.29 (d, *J* = 6.2 Hz, 12 H, 4 × POCHCH₃), 0.85–0.62, 0.56–0.42, 0.20–0.10 (m; 1 H, 2 H, and 2 H, respectively; H-cyclopropyl); ¹³C NMR (CDCl₃) δ 82.8 (d, ³J_{C,P} = 13 Hz, C-2), 71.5 (CH₂OMs), 70.7 (d, ²J_{C,P} = 4 Hz, POCH), 63.3 (d, ¹J_{C,P} = 170 Hz, CH₂P), 37.2 (SO₂CH₃), 23.4 (d, ³J_{C,P} = 5 Hz, POCHCH₃), 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 (CH₂Cl₂/acetone = 5:1 to 3:1) to provide 5.20 g (87% yield) of the product as an oil: [α]_D²⁰ –41.0° (c 0.62, MeOH); ¹H NMR (CDCl₃) δ 4.78–4.62 (m, 2 H, POCH), 4.58 (s, 2 H, OCH₂O), 3.98 (dd, *J* = 8.4, 13.3 Hz, 1 H, CH₂P), 3.80–3.60 (m, 2 H, CH₂P and H-2), 3.60–3.43 (m, 4 H, H-1 and H-4), 3.32 (s, 3 H, OCH₃), 2.15–1.90 (m, 2 H, H-3), 1.31–1.28 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) δ 96.5 (OCH₂O), 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, CH₂P), 55.1 (OCH₃), 34.8 (C-4), 29.4 (C-3), 23.7 (d, ³J_{C,P} = 4 Hz, POCHCH₃), 23.6 (d, ³J_{C,P} = 3 Hz, POCHCH₃). Anal. (C₁₃H₂₈BrO₆P) 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 CH₂Cl₂ (100 mL) and 10% HCl solution (50 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (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: ¹H NMR (CDCl₃) δ 4.78–4.63 (m, 2 H, POCH), 4.59 (s, 2 H, OCH₂O), 3.90 (dd, *J* = 8.6, 13.7 Hz, 1 H, CH₂P), 3.77 (dd, *J* = 9.2, 13.7 Hz, 1 H, CH₂P), 3.58–3.42 (m, 3 H, H-1 and H-2), 3.32 (s, 3 H, OCH₃), 1.58–1.48 (m, 2 H, H-3), 1.29 (q, *J* = 1.6, 6.3 Hz, 12 H, 4 × POCHCH₃), 0.91 (t, *J* = 7.4 Hz, 3 H, H-4); ¹³C NMR (CDCl₃) δ 96.5 (OCH₂O), 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, CH₂P), 54.9 (OCH₃), 23.8 (C-3), 23.6 (apparent t, ³J_{C,P} = 6 Hz, POCHCH₃), 9.2 (C-4).

(*S*)-2-*O*-[(Diisopropylphosphono)methyl]-1-*O*-(methylsulfonyl)-1,2-butanediol (**28h**). (*S*)-2-*O*-[(Diisopropylphospho-

no)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: [α]_D²⁰ –7.15° (c 1.34, MeOH); ¹H NMR (CDCl₃) δ 4.78–4.60 (m, 2 H, POCH), 3.88 (dd, *J* = 7.6, 14.1 Hz, 1 H, CH₂P), 3.69 (dd, *J* = 8.9, 14.1 Hz, 1 H, CH₂P), 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 × POCHCH₃), 0.86 (t, *J* = 7.5 Hz, 3 H, H-4); ¹³C NMR (CDCl₃) 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, CH₂P), 64.1 (C-1), 23.8 (d, ³J_{C,P} = 6 Hz, POCHCH₃), 23.7 (d, ³J_{C,P} = 4 Hz, POCHCH₃), 23.6 (C-3), 9.5 (C-4); MS (DCI) *m/e* 269 (MH⁺).

Mesylate **28h** was isolated as an oil: ¹H NMR (CDCl₃) δ 4.80–4.65 (m, 2 H, POCH), 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, CH₂P), 3.76 (dd, *J* = 9.4, 13.4 Hz, 1 H, CH₂P), 3.62–3.52 (m, 1 H, H-2), 3.05 (s, 3 H, SCH₃), 1.68–1.50 (m, 2 H, H-3), 1.30 (d, *J* = 6.2 Hz, 12 H, POCHCH₃), 0.94 (t, *J* = 7.5 Hz, 3 H, H-4); ¹³C NMR (CDCl₃) 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, CH₂P), 37.3 (SO₂CH₃), 23.7 (d, ³J_{C,P} = 4 Hz, POCHCH₃), 23.6 (d, ³J_{C,P} = 4 Hz, POCHCH₃), 23.1 (C-3), 8.9 (C-4). Anal. (C₁₂H₂₇O₇PS) 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, CH₂Cl₂/acetone = 3:1 to 0:1; second time, CH₂Cl₂/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; [α]_D²⁰ –9.9° (c 0.89, MeOH); ¹H NMR (CDCl₃) δ 7.87 (s, 1 H, H-8), 5.45 (br s, 2 H, NH₂), 4.72–4.56 (m, 2 H, 2 × POCH), 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, CH₂P), 3.79 (dd, *J* = 8.6, 13.9 Hz, 1 H, CH₂P), 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 × POCHCH₃); ¹³C NMR (CDCl₃) 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, CH₂P), 47.1 and 45.4 (C-1' and C-4'), 30.7 (C-3'), 23.7 (d, ³J_{C,P} = 4 Hz, POCHCH₃). Anal. (C₁₅H₂₄ClN₅O₄PS) 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: ¹H NMR (CDCl₃) δ 7.89 (s, 1 H, H-8), 5.10 (br s, 2 H, NH₂), 4.75–4.60 (m, 3 H, H-4 and 2 × POCH), 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, CH₂P), 3.75 (dd, *J* = 8.9, 13.9 Hz, 1 H, CH₂P), 1.31–1.22 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) 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, CH₂P), 43.0 (d, ³J_{C,P} = 8 Hz, C-1'), 23.5 (d, ³J_{C,P} = 4 Hz, POCHCH₃), 23.4 (d, ³J_{C,P} = 5 Hz, POCHCH₃). Anal. (C₁₅H₂₄ClF₂N₅O₄P) 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: ¹H NMR (CDCl₃) δ 7.90 (s, 1 H, H-8), 7.30–7.18 (m, 5 H, ArH), 5.44 (bs, 2 H, NH₂), 4.72–4.55 (m, 2 H, POCH), 4.44 (s, 2 H, CH₂Ph), 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, CH₂P), 3.61 (dd, *J* = 9.5, 13.3 Hz, 1 H, CH₂P), 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 × POCHCH₃); ¹³C NMR (CDCl₃) 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 (CH₂Ph), 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, CH₂P), 45.8 (C-1'), 31.3 (C-3'), 23.6 (d, ³J_{C,P} = 7 Hz, POCHCH₃).

(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: ^1H 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 \times POCH), 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 \times POCHCH₃); ^{13}C NMR (CDCl_3) δ 159.4, 154.3, 151.4, 143.6, 124.8, 77.6 (d, $^3J_{\text{C,P}} = 12$ Hz, C-2'), 71.2 (apparent t, $^2J_{\text{C,P}} = 4$ Hz, POCH), 65.0 (d, $^1J_{\text{C,P}} = 170$ Hz, CH_2P), 47.1 and 45.4 (C-1' and C-4'), 30.7 (C-3'), 23.7 (d, $^3J_{\text{C,P}} = 4$ Hz, POCHCH₃); MS (DCI) m/e 461 (MH^+). Anal. ($\text{C}_{16}\text{H}_{26}\text{ClN}_5\text{O}_4\text{P}$) 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: ^1H 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 \times POCH), 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 \times POCHCH₃); ^{13}C NMR (CDCl_3) δ 159.4, 154.0, 150.8, 143.4, 124.1, 79.5 (d, $^1J_{\text{C,F}} = 165$ Hz, C-4'), 76.6 (br d, $^3J_{\text{C,P}} = 9$ Hz, C-2'), 70.9 (d, $^2J_{\text{C,P}} = 7$ Hz, POCH), 64.5 (d, $^1J_{\text{C,P}} = 170$ Hz, CH_2P), 45.4 (C-1'), 31.9 (d, $^2J_{\text{C,F}} = 20$ Hz, C-3'), 23.3 (d, $^3J_{\text{C,P}} = 4$ Hz, POCHCH₃).

(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; ^1H 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 \times POCH), 4.27–4.05 (m, 3 H, 2 \times 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 \times POCHCH₃); ^{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, $^3J_{\text{C,P}} = 12$ Hz, C-2'), 71.1 (d, $^2J_{\text{C,P}} = 7$ Hz, POCH), 62.9 (d, $^1J_{\text{C,P}} = 170$ Hz, CH_2P), 46.9 (C-1'), 23.7 (d, $^3J_{\text{C,P}} = 4$ Hz, POCHCH₃).

(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; $[\alpha]_D^{20}$ 42.4° (c 0.96, CH_2Cl_2); ^1H 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, POCH), 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 \times POCHCH₃), 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, $^3J_{\text{C,P}} = 12$ Hz, C-2'), 71.5 (d, $^2J_{\text{C,P}} = 7$ Hz, POCH), 63.7 (d, $^1J_{\text{C,P}} = 170$ Hz, CH_2P), 47.6 (C-1'), 24.2 (d, $^3J_{\text{C,P}} = 5$ Hz, POCHCH₃), 24.1 (d, $^3J_{\text{C,P}} = 5$ Hz, POCHCH₃), 23.9, 11.7, 5.2 (C-cyclopropyl); MS (DCI) m/e 432 (MH^+). Anal. ($\text{C}_{17}\text{H}_{27}\text{ClN}_5\text{O}_4\text{P}$) 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: ^1H 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 \times POCH), 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 \times POCHCH₃), 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, $^3J_{\text{C,P}} = 12$ Hz, C-2'), 70.9 (d, $^2J_{\text{C,P}} = 3$ Hz, POCH), 70.8 (d, $^3J_{\text{C,P}} = 3$ Hz, POCH), 63.9 (d, $^1J_{\text{C,P}} = 170$ Hz, CH_2P), 45.2 (C-1'), 23.5 (m, POCHCH₃ 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; $[\alpha]_D^{20}$ -18.4° (c 0.38, 1 N HCl); ^1H 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, $^3J_{\text{C,P}} = 11$ Hz, C-2'), 71.1 (d, $^1J_{\text{C,P}} = 151$ Hz, CH_2P), 53.7 (C-3'), 46.5 (C-1'); MS (FAB) m/e 345 (MH^+). Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_5\text{P} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

(R)-9-[3-Azido-2-(phosphonomethoxy)propyl]guanine [(R)-6]: $[\alpha]_D^{20}$ 16.7° (c 0.63, 1 N HCl); MS (FAB) m/e 345 (MH^+). Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_5\text{P} \cdot 0.66\text{H}_2\text{O}$) 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 (C_{18} , H_2O /methanol) and recrystallization (H_2O /methanol): mp 255–257 °C; $[\alpha]_D^{20}$ -51.8° (c 0.35, 1 N HCl); ^1H NMR ($\text{DMSO}-d_6$) δ 10.59 (b s, 1 H, NH), 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 ($\text{DMSO}-d_6$) δ 157.1, 154.0, 151.7, 138.4, 116.2, 82.2 (d, $^1J_{\text{C,F}} = 171$ Hz, C-3'), 77.9 (dd, $^2J_{\text{C,F}} = 19$ Hz, $^3J_{\text{C,P}} = 11$ Hz, C-2'), 65.8 (d, $^1J_{\text{C,P}} = 163$ Hz, CH_2P), 42.4 (d, $^3J_{\text{C,F}} = 7$ Hz, C-1'). Anal. ($\text{C}_9\text{H}_{13}\text{FN}_5\text{O}_5\text{P} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

(R)-9-[3-Fluoro-2-(phosphonomethoxy)propyl]guanine [(R)-6]: $[\alpha]_D^{20}$ 45.6° (c 0.15, 1 N HCl); MS (FAB) m/e 322 (MH^+). Anal. ($\text{C}_9\text{H}_{13}\text{FN}_5\text{O}_5\text{P} \cdot \text{H}_2\text{O}$) 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 \times 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 (C_{18} , 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; $[\alpha]_D^{20}$ 14.5° (c 0.40, 1 N HCl); ^1H NMR ($\text{DMSO}-d_6$) δ 10.54 (br s, 1 H, NH), 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 ($\text{DMSO}-d_6$) δ 157.2, 153.9, 151.8, 138.6, 116.1, 76.8 (d, $^3J_{\text{C,P}} = 11$ Hz, C-2'), 65.3 (d, $^1J_{\text{C,P}} = 162$ Hz, CH_2P), 56.7 (C-4'), 34.8 (C-3'), 45.0 (C-1'). Anal. ($\text{C}_{10}\text{H}_{16}\text{N}_5\text{O}_6\text{P} \cdot 0.75\text{H}_2\text{O}$) C, H, N.

(R)-9-[4-Hydroxy-2-(phosphonomethoxy)butyl]guanine [(R)-8]: $[\alpha]_D^{20}$ -11.9° (c 0.68, 1 N HCl); MS (FAB, negative ion) m/e 332 (M^-). Anal. ($\text{C}_{10}\text{H}_{16}\text{N}_5\text{O}_6\text{P} \cdot 1.25\text{H}_2\text{O}$) 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; $[\alpha]_D^{20}$ -0.45° (c 0.44, 1 N HCl); ^1H NMR ($\text{DMSO}-d_6$) δ 10.6 (br s, 1 H, NH), 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, CH₂P), 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'); ¹³C NMR (DMSO-*d*₆) δ 157.1, 154.0, 151.8, 138.6, 116.1, 77.0 (d, ³*J*_{C,P} = 12 Hz, C-2'), 65.4 (d, ¹*J*_{C,P} = 162 Hz, CH₂P), 47.0 and 44.4 (C-1' and C-4'), 30.8 (C-3'); MS (FAB) *m/e* 359 (MH⁺). Anal. (C₉H₁₅N₅O₅P·0.25H₂O) 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, H₂O) and recrystallization from H₂O: mp 269 °C dec; [α]_D²⁰ 23.4° (c 0.40, 1 N HCl); ¹H NMR (D₂O) 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, CH₂P), 1.89–1.45 (m, 2 H, H-3'); ¹³C NMR (DMSO-*d*₆) δ 157.2, 154.0, 151.2, 138.6, 116.1, 82.2 (d, ¹*J*_{C,P} = 161 Hz, C-4'), 76.1 (dd, ³*J*_{C,P} = 4 Hz, ³*J*_{C,P} = 13 Hz, C-2'), 65.5 (d, ¹*J*_{C,P} = 162 Hz, CH₂P), 44.7 (C-1'), 32.4 (d, ²*J*_{C,F} = 20 Hz, C-3'). Anal. (C₁₀H₁₆FO₅N₅P) 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, H₂O/methanol) and recrystallization (H₂O): mp 275 °C dec; ¹H NMR (D₂O) 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, CH₂P), 3.38 (dd, *J* = 9.3, 13.0 Hz, 1 H, CH₂P); ¹³C NMR (D₂O) δ 161.8, 157.5, 155.0, 144.0, 136.9 (C-3'), 124.2 (C-4'), 117.5, 83.8 (d, ³*J*_{C,P} = 13 Hz, C-2'), 67.8 (d, ¹*J*_{C,P} = 158 Hz, CH₂P), 50.0 (C-1'); MS (FAB) *m/e* 316 (MH⁺). Anal. (C₁₀H₁₄N₅O₅P) C, H, N.

(R)-9-[2-(Phosphonomethoxy)-3-butenyl]guanine [(R)-11]. mp 278 °C dec; [α]_D²⁰ -27.2° (c 0.41, H₂O). Anal. (C₁₀H₁₄N₅O₅P) 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; [α]_D²⁰ 18.9° (c 0.38, H₂O); [α]_D²⁰ 25.8° (c 0.38, 1 N HCl); ¹H NMR (DMSO-*d*₆) δ 10.56 (br s, 1 H, NH), 7.75 (s, 1 H, H-8), 6.44 (br s, 2 H, NH₂), 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, CH₂P), 3.52 (dd, *J* = 11.1, 12.9 Hz, 1 H, CH₂P), 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); ¹³C NMR (DMSO-*d*₆) δ 157.2, 153.9, 151.8, 138.6, 116.1, 82.8 (d, ³*J*_{C,P} = 13 Hz, C-2'), 64.5 (d, ¹*J*_{C,P} = 163 Hz, CH₂P), 46.0 (C-1'), 11.8, 3.5, 0.4 (C-cyclopropyl); MS (FAB) *m/e* 330 (MH⁺). Anal. (C₁₁H₁₆N₅O₅P·0.5H₂O) C, H, N.

(R)-9-[2-Cyclopropyl-2-(phosphonomethoxy)ethyl]guanine [(R)-12]. mp 282 °C dec; [α]_D²⁰ -22.4° (c 0.33, 1 N HCl). Anal. (C₁₁H₁₆N₅O₅P·0.25H₂O) 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 H₂O/methanol: mp 239–241 °C; [α]_D²⁰ 22.2° (c 0.22, H₂O); [α]_D²⁰ 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, NH₂), 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, CH₂P and H-2'), 1.40–1.22 (m, 2 H, H-3'), 0.97 (t, *J* = 7.4 Hz, 3 H, CH₃); ¹³C NMR (DMSO-*d*₆) δ 157.2, 153.9, 151.8, 133.6, 116.1, 80.7 (d, ³*J*_{C,P} = 12 Hz, C-2'), 65.1 (d, ¹*J*_{C,P} = 163 Hz, CH₂P), 44.3 (C-1'), 23.9 (C-3'), 9.1 (C-4'); MS (FAB) *m/e* 318 (MH⁺). Anal. (C₉H₁₆N₅O₅P·0.75H₂O) C, H, N.

(R)-9-[2-(Phosphonomethoxy)butyl]guanine [(R)-13]. mp 281–293 °C; [α]_D²⁰ -35.4° (c 0.30, 1 N HCl). Anal. (C₉H₁₆N₅O₅P·0.25H₂O) 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 (CH₂Cl₂/methanol = 15:1 to 5:1) to give 1.00 g (49% yield) of 45a as a thick oil: [α]_D²⁰ -37.6° (c 2.41, MeOH); ¹H NMR (CDCl₃) 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 × POCH), 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, CH₂P 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, CH₂P), 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 × POCHCH₃), 1.28 (d, *J* = 6.1 Hz, 2 × POCHCH₃); ¹³C NMR (CDCl₃) δ 166.7 (C-2), 157.1 (C-4), 146.7 (C-6), 94.8 (C-5), 79.0 (d, ³*J*_{C,P} = 11 Hz, C-2'), 71.4 (d, ²*J*_{C,P} = 6 Hz, POCH), 71.3 (d, ²*J*_{C,P} = 6 Hz, POCH), 65.2 (d, ¹*J*_{C,P} = 169 Hz, CH₂P), 51.4 and 50.6 (C-1' and C-2'), 23.7 (apparent t, ³*J*_{C,P} = 5 Hz, POCHCH₃); 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; [α]_D²⁰ -75.1° (c 1.37, MeOH); ¹H NMR (CDCl₃) 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 × POCH 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, CH₂P), 3.72 (dd, *J* = 9.3, 13.6 Hz, 1 H, CH₂P), 3.70 (dd, *J* = 7.0, 13.3 Hz, H-1'), 1.28 (apparent t, *J* = 5.4 Hz, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) δ 166.8 (C-2), 156.9 (C-4), 146.2 (C-6), 94.8 (C-5), 82.3 (d, ¹*J*_{C,P} = 174 Hz, C-3'), 78.4 (dd, ²*J*_{C,P} = 18 Hz, ³*J*_{C,P} = 12 Hz, C-2'), 71.0 (apparent t, ³*J*_{C,P} = 7 Hz, POCH), 64.9 (d, ¹*J*_{C,P} = 169 Hz, CH₂P), 49.3 (d, ³*J*_{C,F} = 8 Hz, C-3'), 23.6 (d, ²*J*_{C,P} = 4 Hz, POCHCH₃), 23.5 (d, ³*J*_{C,P} = 4 Hz, POCHCH₃). Anal. (C₁₄H₂₅FN₅O₅P) C, H, N.

(S)-1-[4-(Benzzyloxy)-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 (CDCl₃) 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, POCH), 4.45 (s, 2 H, CH₂Ph), 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, CH₂P), 3.66–3.52 (m, 4 H, H-4', CH₂P and H-1'), 1.90–1.66 (m, 2 H, H-3'), 1.30–1.19 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (CDCl₃) 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, ³*J*_{C,P} = 13 Hz, C-2'), 72.8 (CH₂Ph), 70.8 (apparent t, ³*J*_{C,P} = 7 Hz, POCH), 65.7 (C-4'), 64.7 (d, ¹*J*_{C,P} = 170 Hz, CH₂P), 52.4 (C-1'), 31.5 (C-3'), 23.6 (d, ³*J*_{C,P} = 5 Hz, POCHCH₃).

(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 (CDCl₃) 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 × POCH), 4.00 (dd, *J* = 2.1, 12.9 Hz, 1 H, H-1'), 3.82–3.69 (m, 3 H, CH₂P, H-1' and H-2'), 3.63 (dd, *J* = 9.5, 13.5 Hz, 1 H, CH₂P), 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 × POCHCH₃); ¹³C NMR (CDCl₃) δ 167.2 (C-2), 157.5 (C-4), 146.9 (C-6), 95.3 (C-5), 78.5 (d, ³*J*_{C,P} = 5 Hz, C-2'), 71.6 (apparent t, ³*J*_{C,P} = 5 Hz, 2 × POCH), 65.5 (d, ¹*J*_{C,P} = 171 Hz, CH₂P), 52.5 (C-1'), 47.6 (C-4'), 31.3 (C-3'), 24.2 (d, ³*J*_{C,P} = 4 Hz, POCHCH₃); 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 (CDCl₃) 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 × POCH 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, CH₂P and H-1'), 3.63 (dd, *J* = 9.4, 13.4 Hz, 1 H, CH₂P), 2.10–1.70 (m, 2 H, H-4'), 1.28 (apparent t, *J* = 6.3 Hz, 12 H, 4 × POCHCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 166.7 (C-2), 157.0 (C-4), 146.5 (C-6), 94.5 (C-5), 79.9 (d, ¹*J*_{C,F} = 165 Hz, C-4'), 77.3 (dd, ³*J*_{C,F} = 2 Hz, ³*J*_{C,P} = 12 Hz, C-2'), 71.0 (d, ²*J*_{C,P} = 5 Hz, POCH), 70.9 (d, ²*J*_{C,P} = 5 Hz, POCH), 65.0 (d, ¹*J*_{C,P} = 170 Hz, CH₂P), 52.2 (C-1'), 32.2 (d, ²*J*_{C,F} = 20 Hz, C-3'), 23.6 (apparent

t , $^3J_{C,P} = 4$ Hz, POCHCH₃); MS (DCI) m/e 380 (MH⁺). Anal. (C₉H₁₅N₆O₅P) 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; $[\alpha]_D^{20}$ 84.0° (c 0.96, CH₂Cl₂); 1H NMR (CDCl₃) 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, POCH), 4.22–4.10 (m, 2 H, H-1'), 3.74 (dd, $J = 9.5, 13.6$ Hz, 1 H, CH₂P), 3.45 and 3.54–3.41 (dd, over m, $J = 9.5, 13.6$ Hz, 2 H, CH₂P and H-2'), 1.36–1.22 (m, 12 H, 4 \times POCHCH₃); ^{13}C NMR (CDCl₃) 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, CH₂P), 70.9 (apparent t , $^3J_{C,P} = 6$ Hz, POCH), 53.1 (C-1'), 23.7 (apparent t , $^3J_{C,P} = 5$ Hz, POCHCH₃). Anal. (C₁₈H₂₆N₈O₅P) 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: 1H NMR (CDCl₃) 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, POCH), 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, CH₂P), 3.03–2.94 (m, 1 H, H-2'), 1.25 (apparent t , $J = 6.4$ Hz, 12 H, 4 \times POCHCH₃), 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 (CDCl₃) 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, CH₂P), 53.2 (C-1'), 23.3 (apparent t , $^3J_{C,P} = 6$ Hz, POCHCH₃), 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: 1H NMR (CDCl₃) 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 \times POCH), 4.20 (dd, $J = 2.3, 13.7$ Hz, 1 H, H-1'), 3.74 (dd, $J = 9.9, 13.3$ Hz, 1 H, CH₂P), 3.65–3.55 (m, 1 H, H-2'), 3.52 (dd, $J = 9.9, 13.3$ Hz, 1 H, CH₂P), 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 \times POCHCH₃), 0.96 (t, $J = 7.5$ Hz, 3 H, CH₃); ^{13}C NMR (CDCl₃) 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 \times POCH), 64.5 (d, $^1J_{C,P} = 171$ Hz, CH₂P), 52.4 (C-1'), 24.0 (C-3'), 23.8 (d, $^3J_{C,P} = 4$ Hz, POCHCH₃), 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; $[\alpha]_D^{20}$ –75.0° (c 0.32, 1 N HCl); 1H NMR (D₂O) 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, CH₂P), 3.57 (dd, $J = 3.9, 13.5$ Hz, 1 H, H-3'), 3.42 (dd, $J = 9.5, 13.1$ Hz, 1 H, CH₂P), 3.28 (dd, $J = 3.6, 13.5$ Hz, 1 H, H-3'); ^{13}C NMR (D₂O) 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, CH₂P), 51.2, 51.0 (C-1' and C-2'); MS (FAB) m/e 305 (MH⁺). Anal. (C₈H₁₃N₆O₅P) C, H, N.

(R)-1-[3-Azido-2-(phosphonomethoxy)propyl]cytosine [(R)-14]. $[\alpha]_D^{20}$ 60.6° (c 0.46, 1 N HCl); MS (FAB) m/e 305 (MH⁺). Anal. (C₈H₁₃N₆O₅P·0.33H₂O) 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; $[\alpha]_D^{20}$ –87.4° (c 0.46, H₂O); 1H NMR (D₂O) 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, CH₂P), 3.58 (dd, $J = 9.5, 13.2$ Hz, 1 H, CH₂P); ^{13}C NMR (CDCl₃) 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, CH₂P), 52.2 (C-1'), 32.2 (d, $^2J_{C,F} = 20$ Hz, C-3'); MS (FAB) m/e 282 (MH⁺). Anal. (C₈H₁₃FN₆O₅P) C, H, N.

(R)-1-[3-Fluoro-2-(phosphonomethoxy)propyl]cytosine [(R)-15]. $[\alpha]_D^{20}$ 115.5° (c 0.15, H₂O); MS (FAB) m/e 282 (MH⁺). Anal. (C₈H₁₃FN₆O₅P·0.75 H₂O) C, H, N.

(S)-1-[4-Hydroxy-2-(phosphonomethoxy)butyl]cytosine [(S)-16]. Boron trichloride (1 M in CH₂Cl₂, 4.94 mL, 4.94 mmol) was slowly added to 42c (0.77 g, 1.65 mmol) in 10 mL of anhydrous CH₂Cl₂ 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 \times 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 CH₂Cl₂ (2 \times 15 mL). The aqueous layer was evaporated, and the residue was purified by reverse-phase flash chromatography (C18; 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; $[\alpha]_D^{20}$ 43.7° (c 1.38, H₂O); $[\alpha]_D^{20}$ 64.0° (c 0.63, 1 N HCl); 1H NMR (D₂O) 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, CH₂P), 3.59 (dd, $J = 9.5, 13.1$ Hz, 1 H, CH₂P), 1.81 (q, $J = 6.1$ Hz, 2 H, H-3'); ^{13}C NMR (D₂O) 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, CH₂P), 60.8, 58.0 (C-1' and C-4'), 36.7 (C-3'); MS (FAB) m/e 294 (MH⁺). Anal. (C₉H₁₆N₆O₆P·0.5H₂O) C, H, N.

(R)-1-[4-Hydroxy-2-(phosphonomethoxy)butyl]cytosine [(R)-16]. The product was isolated as a monoammonium salt: $[\alpha]_D^{20}$ –24° (c 0.98, H₂O); high-resolution MS calcd for C₉H₁₆N₆O₆P 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 (C18, water/methanol = 10:1 to 5:1) and recrystallized from methanol/water: mp 247 °C; $[\alpha]_D^{20}$ 32.6° (c 0.32, H₂O); 1H NMR (D₂O) 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, CH₂P), 3.54 (dd, $J = 9.7, 13.0$ Hz, 1 H, CH₂P), 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 (D₂O) 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, CH₂P), 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 (N₃), 1720 (C=O), 1114 (O-C), 1072, 930 (P-O), 770 (P-C) cm^{–1}. Anal. (C₉H₁₅N₆O₆P) 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; $[\alpha]_D^{20}$ 74.4° (c 0.49, H₂O); 1H NMR (D₂O) 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, CH₂P), 3.54 (dd, $J = 9.7, 13.0$ Hz, 1 H, CH₂P), 2.12–1.82 (m, 2 H, H-3'); ^{13}C NMR (D₂O) 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, CH₂P), 55.5 (C-1'), 34.8 (d, $^2J_{C,F} = 20$ Hz, C-3'); MS (FAB) m/e 295 (MH⁺). Anal. (C₉H₁₅FN₆O₆P·0.5H₂O) 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; $[\alpha]_D^{20}$ 84.0° (c 1.13, H₂O); 1H NMR (D₂O) 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, CH₂P), 3.38 (dd, $J = 9.3, 13.2$ Hz, 1 H, CH₂P); ¹³C NMR (D₂O) 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, CH₂P), 55.6 (C-1'). Anal. (C₉H₁₄N₈O₅P) 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, H₂O); ¹H NMR (D₂O) 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, CH₂P), 3.90 (dd, $J = 8.1, 14.3$ Hz, 1 H, H-1'), 3.50 (dd, $J = 9.9, 13.0$ Hz, 1 H, CH₂P), 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); ¹³C NMR (D₂O) 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, CH₂P), 52.8 (C-1'), 11.4, 3.4, –3.2 (C-cyclopropyl). Anal. (C₁₀H₁₆N₈O₅P·0.25H₂O) 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, H₂O); ¹H 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, CH₂P and H-2'), 1.48–1.32 (m, 2 H, H-3'), 0.96 (t, $J = 7.1$ Hz, 3 H, CH₃); ¹³C 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, CH₂P), 50.6 (C-1'), 23.9 (C-3'), 9.2 (C-4'), MS (FAB) m/e 277 (MH⁺). Anal. (C₉H₁₆N₈O₅P) C, H, N.

(S)-6-O-Benzyl-9-[3-(benzyloxy)-2-[(diisopropylphosphono)methoxy]propyl]-N²-(*p*-methoxyphenyl)diphenylmethyl]guanine (44). A solution of 43^a (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/CH₂Cl₂) to provide 10.9 g (81%) of the product: $[\alpha]^{20}_D$ –29.1° (c 0.67, MeOH); ¹H 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, OCH₂Ph), 4.71–4.58 (m, 2 H, 2 × POCH), 4.45 (s, 2 H, OCH₂Ph), 4.09–3.85 (m, 2 H, 2 × H-1'), 3.73 (s, 3 H, OCH₃), 3.77–3.30 (m, 5 H, OCH₂P, H-2', and 2 × H-3'), 1.29–1.19 (m, 12 H, 4 × POCHCH₃); ¹³C NMR (DMSO-*d*₆) δ 158.1, 157.7, 154.0, 145.9, 140.4, 138.1, 137.7, 136.6, 130.2, 129.0, 128.4, 128.2, 128.1, 127.8, 127.6, 127.6, 126.5, 114.8 (C-5), 112.9, 78.8 (d, $^3J_{C,P} = 12$ Hz, C-2'), 73.5 (3'-OCH₂Ph), 71.1 (d, $^2J_{C,P} = 7$ Hz, POCH), 70.5 (CAr₃), 69.1 and 67.8 (C-3' and 6-O-CH₂Ph), 65.1 (d, $^1J_{C,P} = 169$ Hz, OCH₂P), 55.2 (OCH₃), 44.2 (C-1'), 24.0 (d, $^3J_{C,P} = 7$ Hz, OCHCH₃), 23.9 (d, $^3J_{C,P} = 7$ Hz, OCHCH₃); MS (FAB) m/e 856 (MH⁺). Anal. (C₄₉H₅₄N₈O₇P) C, H, N.

(S)-9-[3-Hydroxy-2-[(diisopropylphosphono)methoxy]propyl]-N²-(*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/CH₂Cl₂) to afford 4.04 g (51%) of the desired product: $[\alpha]^{20}_D$ –43.9° (c 0.95, MeOH); ¹H 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, OCH₃), 3.64–3.46 (m, 2 H, 2 × H-1'), 3.32–3.21 (m, 3 H, 2 × OCH₂P 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 × POCHCH₃); ¹³C 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 (CAr₃), 63.6 (d, $^1J_{C,P} = 165$ Hz, OCH₂P), 60.0 (C-3'), 55.0 (OCH₃), 43.7 (C-1'), 23.8 (d, $^3J_{C,P} = 7$ Hz, OCHCH₃), 23.7 (d, $^3J_{C,P} = 7$ Hz, OCHCH₃); MS (FAB) m/e 676 (MH⁺). Anal. (C₃₅H₄₂N₈O₇P) 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 CCl₄ (3.07 g, 20.0 mmol), Ph₃P (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 CCl₄ (1.50 g, 9.8 mmol), Ph₃P (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/CH₂Cl₂) to afford 0.68 g of (S)-9-[3-chloro-2-[(diisopropylphosphono)methoxy]propyl]-N²-(*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/CH₂Cl₂) to provide 0.22 g of the product (36% overall yield from 45): ¹H NMR (DMSO-*d*₆) δ 7.60 (s, 1 H, H-8), 6.38 (br s, 2 H, NH₂), 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, OCH₂P), 3.73–3.65 (m, 2 H, 2 × H-3'), 1.05–1.19 (m, 12 H, 4 × POCHCH₃); ¹³C 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, OCH₂P), 44.0 and 43.5 (C-3' and C-1'), 23.8 (d, $^3J_{C,P} = 7$ Hz, POCHCH₃), 23.6 (d, $^3J_{C,P} = 7$ Hz, POCHCH₃); 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, H₂O); ¹H NMR (D₂O) 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 OCH₂P), 3.55 (dd, $J = 9.9, 13.2$ Hz, 1 H, 1 × H-3'); ¹³C NMR (D₂O) 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, OCH₂P), 48.2 (C-3'), 44.1 (C-1'); MS (FAB) m/e 338 (MH⁺). Anal. (C₉H₁₃N₆O₅PCl·0.66H₂O) C, H, N.

(R)-9-[3-Chloro-2-(phosphonomethoxy)propyl]guanine [(R)-7]. MS (FAB) m/e 338 (MH⁺). Anal. (C₉H₁₃N₆O₅PCl·0.125H₂O) H, N; C: calcd, 32.27; found, 31.80.

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