Novel Acyclonucleotides: Synthesis and Antiviral Activity of Alkenylphosphonic Acid Derivatives of Purines and a Pyrimidine

Michael R. Harnden, Ann Parkin, Martin J. Parratt,* and Robert M. Perkins

SmithKline Beecham Pharmaceuticals, Great Burgh, Epsom, Surrey KT18 5XQ, U.K.

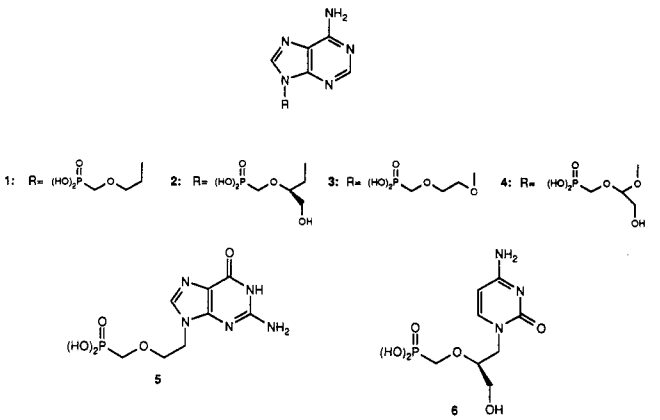
Received February 9, 1993

A series of phosphonoalkenyl and (phosphonoalkenyl)oxy derivatives of purines and a pyrimidine were synthesized. These compounds are the first reported acyclonucleotides which incorporate the α,β-unsaturated phosphonic acid moiety as the phosphate mimic and include compounds in which the acyclic substituent is attached to N-9 of a purine or N-1 of a pyrimidine by either a nitrogen–carbon or a nitrogen–oxygen bond. The phosphonoalkenyl-substituted compounds **7a–c**, **8a–c**, **9**, **10**, and **12** were prepared either by Mitsunobu coupling of alcohols with purine or pyrimidine derivatives or by alternative alkylations of the heterocyclic bases. The (phosphonoalkenyl)oxy derivatives **7d–g**, **8d–g**, and **11** were synthesized by coupling of alcohols with 9-hydroxypurines or a 1-hydroxypyrimidine under Mitsunobu conditions. The novel acyclonucleotides were tested for activity against herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), visna virus, and human immunodeficiency virus type 1 (HIV-1). Guanine derivatives were moderately to extremely cytotoxic, but the adenines were less toxic to cells. At the concentrations tested, (*Z*)-isomers in the unbranched series had no activity against herpes viruses or HIV-1. (*E*)-9-[(4-Phosphonobut-3-enyl)oxy]adenine (**7d**) displayed selective activity against HIV-1, (*E*)-2,6-diamino-9-(4-phosphonobut-3-enyl)purine (**9**) showed selective antiretrovirus activity, and (*E*)-9-[2-(hydroxymethyl)-4-phosphonobut-3-enyl]adenine (**7c**) showed selective antiherpesvirus (VZV and CMV) activity.

Introduction

In recent years it has been shown that acyclic phosphonomethoxy analogues of nucleoside 5′-monophosphates can lead to broad-spectrum antiviral agents[1] which do not require activation by viral thymidine kinase. The selectivity of these compounds is dependent upon the ability of their diphosphate derivatives (acting as triphosphate equivalents) to inhibit viral polymerases at concentrations lower than those required for inhibition of host cell DNA polymerases.[2-4] Two discrete series embracing the most promising candidates emerged, namely the 9-[2-(phosphonomethoxy)ethyl] (PME) and (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl] [(*S*)-HPMP] series. In the former series 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) (**1**) (Chart I) has selective activity against retroviruses including human immunodeficiency virus (HIV),[5] the causative agent of acquired immunodeficiency syndrome (AIDS), and 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG) (**5**) has broad-spectrum antiviral activity.[5] In the latter series (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)-propyl]adenine [(*S*)-HPMPA] (**2**) exhibits broad-spectrum anti-DNA virus activity[1] including activity against herpes simplex virus types 1 and 2 (HSV-1 and -2), and the corresponding cytosine derivative [(*S*)-HPMPC] (**6**) has selective activity against cytomegalovirus (CMV).[5,6] We have recently reported the synthesis of a series of 9-[(phosphonomethoxy)alkoxy]purines in which the acyclic substituent is attached by an N–O bond. Some of these compounds, such as 9-[(2-phosphonomethoxy)-ethoxy]adenine (BRL 47923) (**3**), have potent activity against retroviruses including HIV.[7,8] This strategy has been adopted by others to produce the acetal-containing HPMPA analogue (**4**) which has selective activity against HSV-2 and CMV.[9] Since the ethenyl unit has an appreciable electron-withdrawing effect,[10] the important second dissociation constant of alkenylphosphonic acids should closely mirror those of the natural phosphate monoesters[11]

Chart I



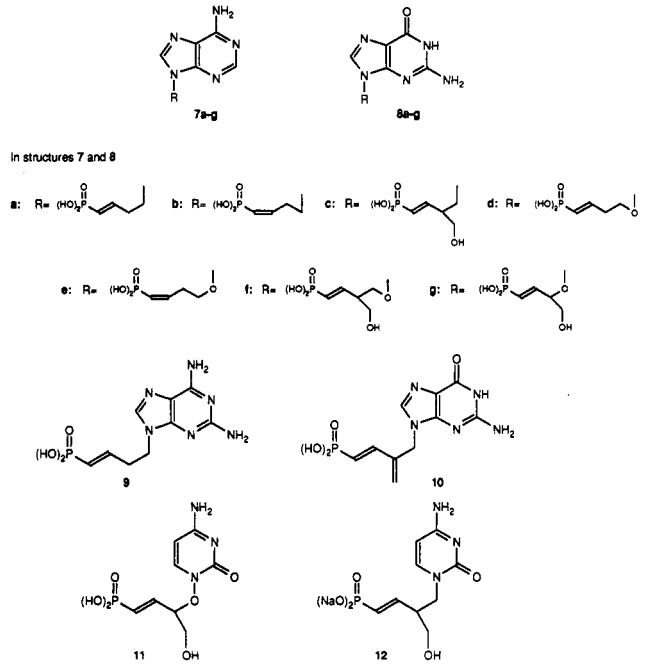
and the phosphonomethoxy analogues.[12] Encouragingly, the *trans*-alkenylphosphonic acid analogue of adenosine monophosphate (AMP) has been shown to be a substrate for rabbit muscle AMP kinase,[13] though antiviral data for this type of nucleotide analogue is lacking. Acyclic nucleotide analogues incorporating the alkenylphosphonic acid group as the phosphate mimic therefore appeared to have high potential for being effective antiviral agents. In this report the synthesis and antiviral activity of a series of alkenylphosphonic acid derivatives of purines and a pyrimidine (**7a–g**, **8a–g**, **9–12**) (Chart II) are described.[14] These novel acyclonucleotide analogues include both N–C and N–O linked derivatives.

Chemistry

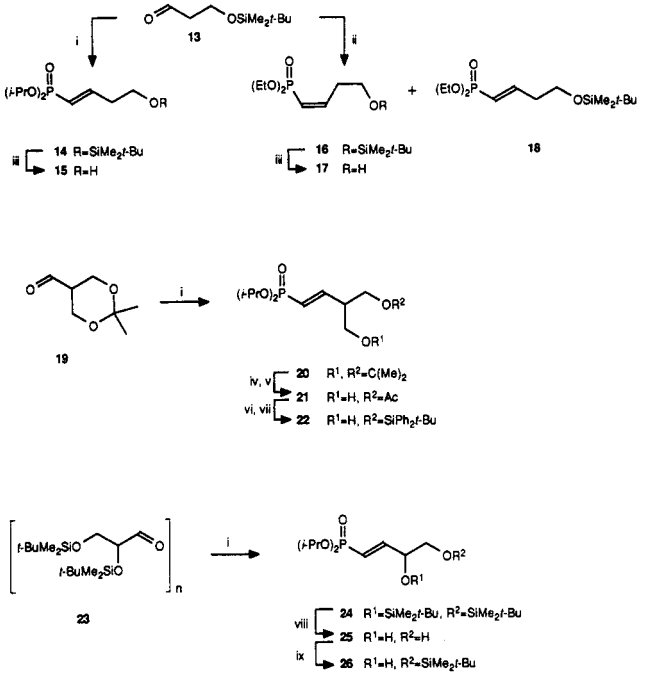
The alkenylphosphonate moiety of the acyclic substituents was introduced by Wadsworth–Emmons[15a] or Peterson[15b] olefination of aldehydes **13**, **19**, and **23** (Scheme I). Aldehydes **13** and **19** were prepared by pyridinium chlorochromate mediated oxidation of the respective alcohols,[16] and **23** was obtained by silylation of (*R*/*S*)-

0022-2623/93/1836-1343$04.00/0

Chart II



Scheme I[a]

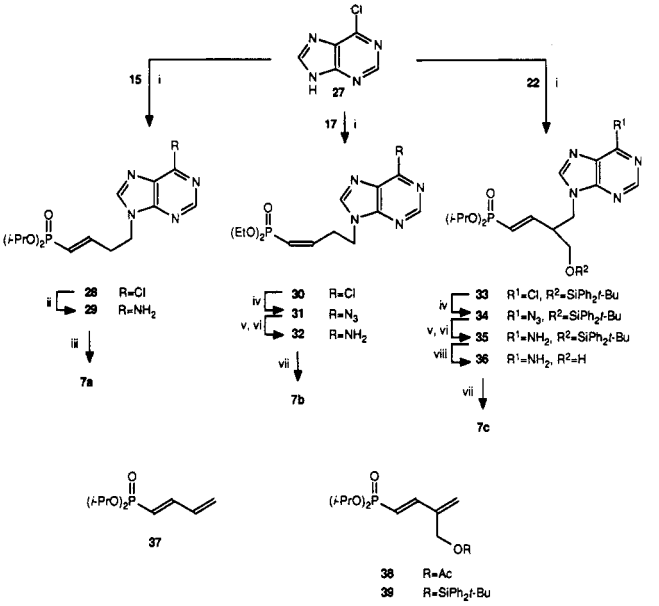


[a] (i) $[(i\text{-PrO})_2P(O)]_2CHLi$, *n*-heptane; (ii) $(EtO)_2P(O)CHLiSiMe_3$, THF; (iii) CH_3CO_2H–H_2O (2:1); (iv) HCl, MeOH; (v) (a) $(CH_3O)_3CCH_3$, *p*-TSA, THF, (b) H_2O; (vi) *t*-$BuPh_2SiCl$, imidazole, THF; (vii) K_2CO_3, MeOH; (viii) CH_3CO_2H–H_2O–THF (2:1:1); (ix) *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2.

glyceraldehyde. Wadsworth–Emmons reaction[17-19] of tetraisopropyl methylenediphosphonate with the aldehydes **13**, **19**, and **23** gave exclusively the (*E*)-alk-1-enylphosphonates **14**, **20**, and **24**. Peterson reaction of **13** with diethyl [(trimethylsilyl)methyl]phosphonate[17,20] provided the chromatographically separable (*Z*)- and (*E*)-alkenes **16** and **18** in the ratio of 5:2, thereby proving a useful route to both isomers. Deprotection/protection procedures were performed on intermediates **14**, **16**, **20**, and **24** to give the desired alcohols **15**, **17**, **22**, and **26**.

Attempted base-catalyzed alkylation of purine derivatives using the mesylate derived from **15** produced only

Scheme II[a]

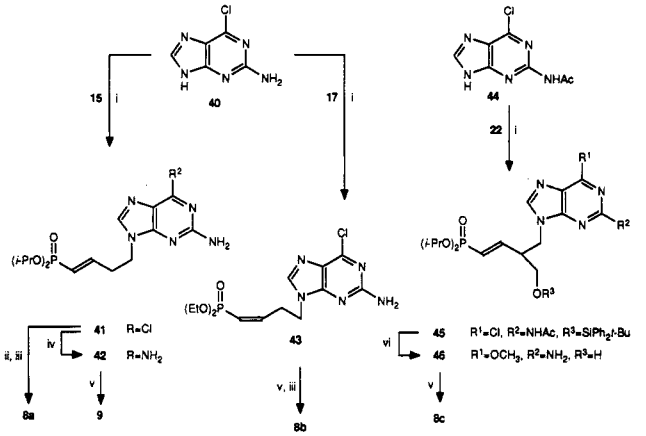


[a] (i) PPh_3, DEAD, THF; (ii) NH_3, EtOH; (iii) Me_3SiBr, CH_2Cl_2; (iv) NaN_3, DMF; (v) PPh_3, THF; (vi) H_3O^+; (vii) Me_3SiBr, DMF; (viii) HCl, MeOH.

the elimination product **37**. However, effective coupling was achieved directly from the alcohol **15** under Mitsunobu conditions[21] (Scheme II). Exclusive alkylation at the N-9 position of the purine occurred upon Mitsunobu coupling of 6-chloropurine[22] (**27**) with the alcohol **15** to give the product **28** in 37% yield, along with a substantial quantity of the diene **37**. Similar coupling of **27** with **17** gave **30**. Attempted Mitsunobu coupling using the acetate **21** produced only the diene **38**. The protecting group was therefore exchanged and the *tert*-butyldiphenylsilyl derivative **22** coupled successfully to afford the purine derivative **33** in 28% yield along with a 56% yield of the diene **39**. Dienes were observed as byproducts in all Mitsunobu reactions involving alcohols **15**, **17**, and **22**. Treatment of **28** with ethanolic ammonia gave the adenine derivative **29**. Similar treatment of **30** and **33**, however, caused partial migration of the double bond leading to inseparable mixtures of alk-1-enyl- and alk-2-enylphosphonates. The intermediates **30** and **33**, however, were both cleanly transformed into the 6-azidopurine derivatives **31** and **34** upon treatment with the less basic reagent sodium azide. Reduction[23] of the azido function of **31** gave the adenine derivative **32**. Similarly, reduction of **34** gave the adenine derivative **35** which was not isolated but was deprotected to afford **36**. Compounds **29**, **32**, and **36** were deesterified to the phosphonic acids **7a–c** using bromotrimethylsilane.

Mitsunobu reaction of 2-amino-6-chloropurine (**40**) with **15** and **17** gave the desired purine derivative **41** and **43** (Scheme III). However, even with **22** the sole reaction pathway was toward elimination upon attempted alkylation of **40**. Acetylation of the amino group was found to partially suppress elimination, the desired product **45** being obtained in 36% yield from reaction of **22** with 2-acetamido-6-chloropurine (**44**). Compounds **41** and **43** were transformed into the guanine derivatives **8a,b** by sequential deesterification and hydrolysis. Compound **41** was also treated with ethanolic ammonia to give the 2,6-diaminopurine derivative **42** which was deesterified to the phosphonic acid **9**. Removal of the *tert*-butyldiphenylsilyl protecting group from **45** using methanolic hydrogen

Scheme III[a]



[a] (i) PPh_3, DEAD, DMF; (ii) Me_3SiBr, CH_2Cl_2; (iii) HCl; (iv) NH_3, EtOH; (v) Me_3SiBr, DMF; (vi) HCl, MeOH.

chloride concurrently removed the *N*-acetyl group and exchanged the 6-chloro group for a 6-methoxy function, giving compound **46**. Deesterification conditions also caused cleavage of the 6-methoxy function giving the phosphonic acid **8c** in 58% yield.

Reaction of 9-hydroxy-6-*N*-phthalimidopurine[7b,24] **47** with the alcohols **15**, **17**, **22**, and **26** under Mitsunobu conditions furnished the coupled products **48**, **50**, **52**, and **55** (Scheme IV). Mitsunobu reactions with 9-hydroxypurines were generally higher yielding than with purines themselves. N-Deprotection of **48** and **50** gave the unbranched adenine derivatives **49** and **51** and sequential N- and O-deprotection of **52** and **55** gave the branched derivatives **54** and **57**. The phosphonates **49**, **51**, **54**, and **57** were deesterified to the phosphonic acids **7d–g**.

Mitsunobu coupling of 2-[bis(*tert*-butoxycarbonyl)-amino]-9-hydroxy-6-methoxypurine[7b,24] (**58**) with **15**, **17**, **22**, and **26** provided the intermediates **59–61** and **63** (Scheme V). Complete deprotection of **59–61** and **63** gave the phosphonic acids **8d–g**.

Attempted 1,6-addition of **40** to the diene **39** (Scheme VI) gave none of the desired product but interestingly afforded the diene **64** in 52% yield by allylic displacement of the *tert*-butyldiphenylsilyloxy moiety.[25] Deesterification and hydrolysis of **64** gave the guanine derivative **10**.

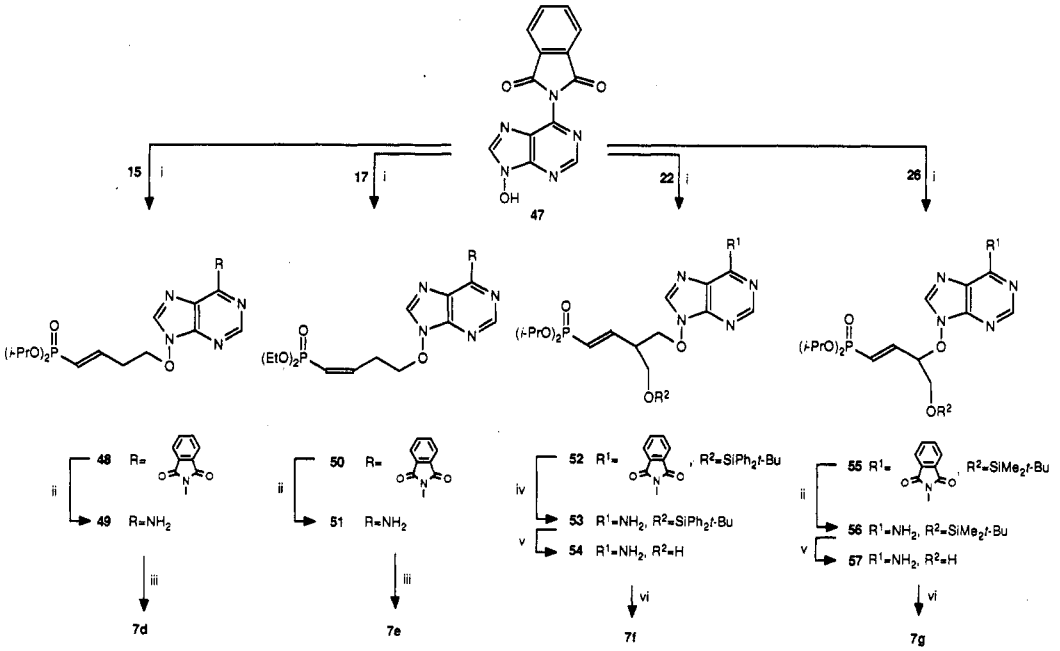
N^4-Benzoyl-1-hydroxycytosine[26] (**65**) was also successfully alkylated to give **66** when treated with **26** under Mitsunobu conditions (Scheme VII). The intermediate **66** was concurrently N- and O-deprotected using methanolic hydrogen chloride to give the cytosine derivative **67** which upon treatment with bromotrimethylsilane provided the phosphonic acid **11**.

Preparation of the N–C linked HPMPC analogue **12** was more problematical. Cytosine itself did not couple with **22** under Mitsunobu conditions, the diene **39** being the sole product. Our success with the *N*-acetylpurine **44** suggested that N^4-acetylcytosine might couple more efficiently with **22**. However, this reaction was similarly unsuccessful. A recent literature report[27] of the successful Mitsunobu reaction of N^3-benzoyluracil with alcohols in the synthesis of carbocyclic nucleoside analogues prompted investigation of the reaction of N^3-benzoyluracil with **22**. Although a very small amount of material was obtained and tentatively assigned as the desired product, this route could not be made viable. However, alkylation[6] of cytosine **68** with the mesylate **69** under basic conditions gave the desired N-1-isomer **70** together with the less polar O-isomer **71** in the ratio of 2:1 (Scheme VIII). Isomers **70** and **71** were initially assigned by comparison of their NMR (^1H and ^{13}C) spectra with data for similarly alkylated intermediates obtained in the synthesis of PMEC and (*S*)-HPMPC.[6] Additional confirmation of the assignments was obtained from a 2D NMR ^1H–^{13}C correlation experiment. For the product designated as the *N*-1-alkyl derivative **70**, a three-bond coupling interaction was observed between C-1′ and the proton at C-6 of the cytosine ring. No such interaction was observed for the O-alkylated isomer **71**. Sequential deacetalization, N-acetylation, and O-monomethoxytritylation gave the alcohol **74**. Moffatt oxidation of **74** followed by Wittig reaction with diphenyl [(triphenylphosphoranylidene)methyl]phosphonate[28–30] provided the alkenylphosphonate **75**. Deprotection of **75** gave the diphenyl phosphonate **76**. Transesterification[31] of **76** using cesium fluoride in methanol gave the dimethyl phosphonate **77** which was then amenable to deesterification to the phosphonic acid **12** by bromotrimethylsilane.

Biological Results

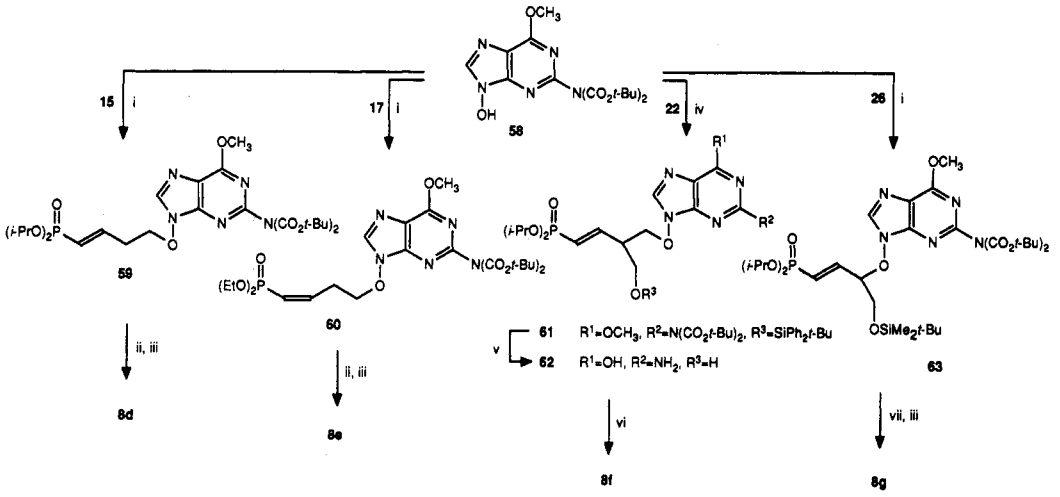
The acyclonucleotide analogues (**7a–g**, **8a–g**, **9–12**) were tested in cell culture for activity against HSV-1 and -2, varicella zoster virus (VZV), CMV, and HIV-1. Additionally, several compounds were tested against visna virus, a lentivirus related to HIV. The results obtained for active compounds (IC_{50} <300 μM) are given in Table I. At the concentrations tested **7b**, **7c**, **7g**, **8b**, **8g**, **10**, **11**, and **12** showed no significant activity. The compounds were evaluated for cytotoxicity by determination of their ability to inhibit DNA synthesis (as measured by incorporation of [^3H]thymidine) in uninfected cells (Table I). The analogue **7d** of BRL 47923 (**3**) showed selective anti-HIV activity albeit with reduced potency relative to **3**[8] (Table I). Interestingly the saturated derivative of **7d** showed no significant anti-HIV activity at concentrations up to 300 μM.[32] Surprisingly the PMEA analogue **7a** was inactive against HIV although it was moderately active against visna virus. However, the analogue **9** of 2,6-diamino-9-(2-phosphonomethoxy)ethylpurine (PMEDAP) exhibited selective anti-HIV activity but was less potent than the prototype (which has an IC_{50} value of 1.0 μM[5,33]). The guanine derivatives **8a,c–f** displayed a variety of apparent antiviral effects. However, although many of these derivatives were not toxic to the cell monolayers used in the antiviral tests, in most cases at concentrations similar to those inhibiting virus replication they inhibit DNA synthesis in uninfected cells. It is therefore unlikely that in these cases their activity is attributable to inhibition of a virus specific process. The guanine derivative **8d** proved to be a very cytotoxic compound. Similarly compound **8a** [which is the direct analogue of PMEG (**5**)] showed a high level of cytotoxicity comparable to the value for PMEG itself (CD_{50} 8.6 μM[5]). Although PMEG has selective activity against many viruses, its potential as an anti-papilloma virus[34] and anticancer[35] agent is likely to be a manifestation of its relatively high toxicity to proliferating cells. None of the (*Z*)-isomers in the unbranched series showed significant activity against herpes viruses or HIV at the concentrations tested although the guanine derivative **8e** showed selective activity against visna virus. Again the guanine derivatives **8c** [the analogue of 9-[3-hydroxy-2-(phosphonomethoxy)propyl]guanine[5] (HPMPG)] and **8f** proved to be moderately cytotoxic compounds. The racemic adenine derivative **7c** [the analogue of (*S*)-

Scheme IV[a]



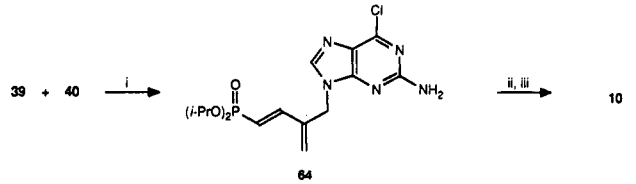
[a] (i) PPh_3, DEAD, THF; (ii) $MeNHNH_2$, EtOH; (iii) Me_3SiBr, CH_2Cl_2; (iv) $MeNHNH_2$, CH_2Cl_2; (v) HCl, MeOH; (vi) Me_3SiBr, DMF.

Scheme V[a]



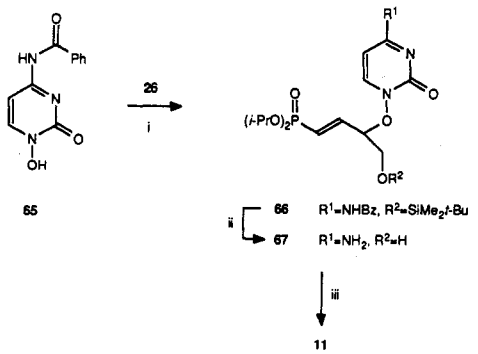
[a] (i) PPh_3, DEAD, THF; (ii) Me_3SiBr, CH_2Cl_2; (iii) H_3O^+; (iv) PPh_3, DEAD, DMF; (v) HCl, EtOH, H_2O; (vi) Me_3SiBr, DMF; (vii) Me_3SiBr, CH_2Cl_2, DMF.

Scheme VI[a]



[a] (i) K_2CO_3, DMF; (ii) Me_3SiBr, DMF; (iii) HCl.

Scheme VII[a]

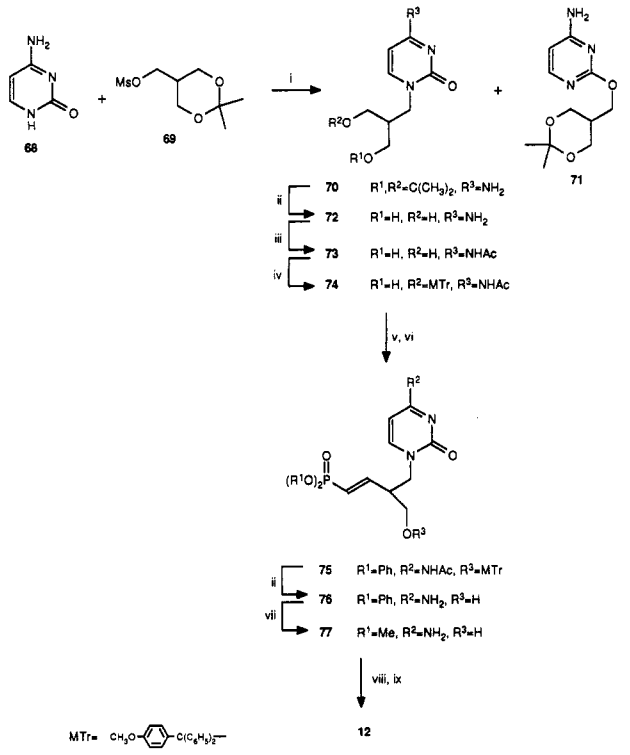


[a] (i) PPh_3, DEAD, DMF; (ii) HCl, MeOH; (iii) Me_3SiBr, CH_2Cl_2, DMF.

HPMPA (2)], however, exhibited selective antiherpesvirus (particularly VZV and CMV) activity, but was less potent than the prototype (which has IC_{50} values of 0.07 and 0.49 μM against VZV and CMV, respectively[5]). Surprisingly (in the light of results obtained[9] with 4) this activity was neither improved nor retained in the N–O linked (*S*)-HPMPA analogue **7g**.

The inactivity of the (*Z*)-isomers may be due to the cis-double bond fixing the acyclic substituent in an unfavorable orientation for interaction with at least one of the enzymes involved in phosphorylating the phosphonic acids to their diphosphate forms (triphosphate equivalents), or with the viral DNA polymerase. The relatively modest performance of the (*E*)-isomers as selective antiviral agents is more surprising. The restriction of

Scheme VIII[a]



[a] (i) Cs_2CO_3, DMF; (ii) HCl, MeOH; (iii) Ac_2O, MeOH; (iv) 4-$MeOC_6H_4C(C_6H_5)_2Cl$, Et_3N, DMF; (v) DCC, $CHCl_2CO_2H$, DMSO; (vi) $(PhO)_2P(O)CHPPh_3$, DMSO; (vii) CsF, MeOH; (viii) Me_3SiBr, CH_2Cl_2, DMF; (ix) Dowex 50W-X8 (Na^+).

conformational flexibility imposed by the double bond may be partly responsible, but other factors are also likely to be involved. The second dissociation constant, pK_a^2, for compound **8g** was determined to be 6.6, thereby correlating extremely well with the values reported[12] for PMEG (pK_a^2 6.5) and various analogues. Thus, as expected, the introduction of unsaturation into the alkyl chain enhances the acidity of the phosphonic acid moiety by the desired amount. However, it appears that achieving a pK_a^2 comparable to that of the parent phosphate is a necessary but insufficient requirement for attaining potent and selective antiviral agents.[12] Nonetheless the range of biological activities seen for these alkenylphosphonic acids suggests that this novel approach could also be used for analogues of other biologically active phosphates.

Experimental Section

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. NMR spectra were recorded with a Varian EM-390 90 MHz, JEOL GX-270 270 MHz, or a Bruker AMX400 400 MHz spectrometer. IR spectra were recorded with a Perkin-Elmer 580 spectrometer and UV spectra with a Uvikon 810 spectrometer. The electron-impact (EIMS), chemical ionization (CIMS), and fast-atom bombardment (FABMS) mass spectra were recorded, and accurate masses were measured on a JEOL JMS-SX102 spectrometer; the abbreviation TDE/NaCl is used for thiodiethanol/sodium chloride. Microanalyses were performed on a Carlo Erba Model 1106 analyzer, and where only the symbols for the elements are recorded, were within ±0.4% of the calculated values. Determinations of pK_a values were carried out using a Metrohm 670 Titroprocessor. All intermediates were homogeneous by TLC on silica gel $60F_{254}$ coated glass plates. All phosphonic acids were homogeneous by TLC on cellulose F coated aluminum sheets.

3-[(*tert*-Butyldimethylsilyl)oxy]propanal (13).[38] To a suspension of pyridinium chlorochromate (8.50 g, 39.4 mmol) in dichloromethane (53 mL), stirred at ambient temperature, was added 3-[(*tert*-butyldimethylsilyl)oxy]propan-1-ol[16] (5.00 g, 26.3 mmol). After 1.5 h, dry ether (50 mL) was added and the supernatant liquid was decanted from a black gum. The residual gum was washed with ether (3 × 50 mL), and the combined organic portions were passed through a column of Florisil. The solvent was removed, and then the residue was taken up in dichloromethane and passed through fresh Florisil. The solvent was removed to leave crude **13** as a liquid (2.75 g) which was shown by ^1H NMR analysis to be ~40% pure (~22% yield) and was used without further purification: ^1H NMR ($CDCl_3$) δ 0.10 (6H, s, CH_3), 0.93 (9H, s, $C(CH_3)_3$), 2.63 (2H, dt, J = 2 Hz and 6 Hz, CH_2), 4.03 (2H, t, J = 6 Hz, CH_2O), 9.97 (1H, t, J = 2 Hz, CHO).

Diisopropyl [(*E*)-4-(*tert*-Butyldimethylsilyloxy)but-1-enyl]phosphonate (14). To a solution of tetraisopropyl methylenediphosphonate (2.50 g, 7.26 mmol) in *n*-heptane (50 mL) was added *n*-butyllithium (2.70 mL of 2.7 M solution in *n*-hexanes; 7.29 mmol) and the mixture stirred at ambient temperature under dry nitrogen for 15 min. To the solution was added crude **13** (2.75 g, ~40% pure, ~5.85 mmol), and the mixture was heated under reflux for 0.5 h and then stirred at ambient temperature for 64 h. The mixture was filtered, and then the solvent was removed. The residue was purified by column chromatography on silica gel eluting with dichloromethane–ethyl acetate (9:1, 4:1) to afford **14** as a colorless oil (1.10 g, 43%): IR (film) ν_{max} 2940, 1625, 1460, 1380, 1250, 1105, 980, and 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (6H, s, 2 × $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 1.29 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.32 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.43 (2H, m, CH_2), 3.72 (2H, t, J = 7 Hz, CH_2O), 4.65 (2H, m, 2 × $CH(CH_3)_2$), 5.72 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.75 (1H, ddt, J = 7, 17 and 20 Hz, PCH=C*H*); FABMS (positive ion, thioglycerol) m/z MH^+ 351. Anal. ($C_{16}H_{35}O_4PSi$) C, H.

Diisopropyl [(*E*)-4-Hydroxybut-1-enyl]phosphonate (15). A solution of **14** (0.84 g, 2.40 mmol) in acetic acid–water (2:1) (10 mL) was stirred at 70 °C for 2 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with acetone–hexane (1:1) to give **15** as a gum (0.43 g, 76%); IR (film) ν_{max} 3380, 2970, 1625, 1460, 1380, 1370, 1220, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.32 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.85 (1H, br s, OH), 2.50 (2H, m, CH_2), 3.76 (2H, t, J = 6 Hz, CH_2O), 4.69 (2H, m, 2 × $CH(CH_3)_2$), 5.80 (1H, dd, J = 16 and 18 Hz, PC*H*=CH), 6.75 (1H, ddt, J = 7, 17, and 22 Hz, PCH=C*H*); CIMS (isobutane) m/z MH^+ 237.

Diethyl [(*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-1-enyl]-phosphonate (16). To a solution of diethyl [(trimethylsilyl)-methyl]phosphonate[39] (5.60 g, 25.0 mmol) in dry THF (40 mL) stirred at −78 °C under dry nitrogen was added *n*-butyllithium (15.6 mL of 1.6 M solution in *n*-hexanes; 25.0 mmol). The mixture was stirred for 10 min before crude **13** (6.59 g, ~40% pure, ~14.0 mmol) was added rapidly. The mixture was allowed to warm to 0 °C and maintained at this temperature while being neutralized by addition of 5 M hydrochloric acid. Water (20 mL) was added, and the mixture was extracted with ether (150 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to leave an oil which was purified by column chromatography eluting with hexane–ethyl acetate (3:1, 1:1) to give **16** as a colorless liquid (4.11 g, 51%) along with diethyl [(*E*)-4-[(*tert*-butyldimethylsilyl)-oxy]but-1-enyl]phosphonate (**18**) as a liquid (1.65 g, 21%). For **16**: IR (film) ν_{max} 2940, 1625, 1390, 1245, 1095, 1055, 1030, and 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (6H, s, 2 × $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 1.30 (6H, t, J = 7 Hz, 2 × CH_3), 2.83 (2H, m, CH_2), 3.73 (2H, t, J = 7 Hz, CH_2OSi), 4.10 (4H, qu, J = 7 Hz, 2 × CH_2O), 5.70 (1H, dd, J = 14 and 20 Hz, PC*H*=CH), 6.70 (1H, ddt, J = 7, 14, and 54 Hz, PCH=C*H*); HRMS calcd for $C_{14}H_{31}O_4PSi$ (MH^+) 323.1808, found 323.1808. For **18**: ^1H NMR ($CDCl_3$) δ 0.03 (6H, s, 2 × $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 1.30 (6H, t, J = 7 Hz, 2 × CH_3), 2.40 (2H, m, CH_2), 3.73 (2H, t, J = 7 Hz, CH_2OSi), 4.07 (4H, qu, J = 7 Hz, 2 × CH_2O), 5.70 (1H, dd, J = 18 and 21 Hz, PC*H*=CH), 6.80 (1H, ddt, J = 7, 18, and 21 Hz, PCH=C*H*).

Diethyl [(*Z*)-4-Hydroxybut-1-enyl]phosphonate (17). A solution of **16** (1.32 g, 4.09 mmol) in acetic acid–water (2:1) (35 mL) was stirred at ambient temperature for 2 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1) to give **17** as a colorless liquid (0.50 g, 59%): IR (film) ν_{max}

Table I. Antiviral Activity and Cytotoxicity in Cell Culture[a]

compd	anti-herpesvirus activity, IC_{50} (μM)[b] HSV-1 (SC16)	HSV-2 (MS)	VZV (Ellen)	CMV (AD169)	anti-retrovirus activity IC_{50} (μM)[c] HIV-1 (D_{34})	MIC (μM)[d] Visna virus (K184)	inhibition of cell replication, CD_{50} (μM)[e] MRC-5 cells	PBL's	SCP cells
7a	na[f]	na	na	na	na	20	260		137
7c	137	91	16	35	na		189		
7d	na	na	na	na	10.2	82	330	130	
8a	na	90	190	52	na	0.35	4.5		1.3
8c	60	66	17	<9.0	na		20		
8d	<10	<10	<10	0.53	0.10	<0.01	0.10	0.23	0.13
8e	na	na	na	178	na	0.10	26		11.7
8f	295	177	15	44	8.9		19		
9	na	na	na	na	9.8	2.1	222		95
BRL 47923 (3)	na	270	280	na	0.24	8.0	173		173
zidovudine					0.006	5.6	72	13	>370
acyclovir	3.9	4.3	21	93			355		

[a] All assays were performed as previously described.[7b,36,37] [b] Concentration of compound which inhibited by 50% the number of plaques (HSV-2, VZV, and CMV) or cytopathic effect (HSV-1) in infected human fibroblast (MRC-5) cells. [c] The compounds were first subjected to a prescreen for determination of cytotoxicity to human peripheral blood lymphocytes (PBL's). Antiviral activity against the Diagen strain of HIV (D_{34}) was then determined at a single concentration equivalent to $^1/_{10}$ of the cytotoxic concentration (CD_{50}). The activity of compounds of particular interest was determined in full dose–response titrations. [d] Minimum concentration which completely inhibited the cytopathic effect in infected sheep choroid plexus (SCP) cells. [e] Concentration of compound which inhibited by 50% the incorporation of ^{3}H-dT into uninfected cells. [f] na = not active.

3380, 2980, 1720, 1620, 1390, 1230, and 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, t, J = 7 Hz, CH_3), 2.70 (2H, m, CH_2), 3.15 (1H, s, OH), 3.73 (2H, t, J = 7 Hz, CH_2O), 4.00 (4H, qu, J = 7 Hz, 2 × CH_3CH_2), 5.70 (1H, dd, J = 14 and 20 Hz, PC*H*=CH), 6.60 (1H, ddt, J = 7, 14, and 54 Hz, PCH=C*H*); HRMS calcd for $C_8H_{17}O_4P$ 209.0943, found 209.0942.

2,2-Dimethyl-1,3-dioxane-5-carbaldehyde (19). A solution of (2,2-dimethyl-1,3-dioxan-5-yl)methanol[16] (2.04 g, 14.0 mmol) in dichloromethane (5 mL) was added dropwise to pyridinium chlorochromate (4.4 g, 20 mmol) in dichloromethane (30 mL). The mixture was stirred at ambient temperature for 2 h and then treated with ether (30 mL). After being stirred for a further 10 min at ambient temperature, the mixture was filtered through silica, the residue was extracted with ether (50 mL) and filtered, and the combined filtrates were evaporated under reduced pressure to give **19** as an oil (0.75 g) which was shown by ^{1}H NMR analysis to be ~60% pure (~23% yield): ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.30 (1H, m, CH), 4.00–4.30 (4H, m, 2 × CH_2), 9.55 (1H, s, CHO).

Diisopropyl [(*E*)-2-(2,2-Dimethyl-1,3-dioxan-5-yl)ethenyl]phosphonate (20). A solution of tetraisopropyl methylenediphosphonate (1.07 g, 3.12 mmol) in *n*-heptane (25 mL) was treated with *n*-butyllithium (1.15 ml of 2.7 M solution in *n*-hexanes; 3.1 mmol). After the mixture was stirred at ambient temperature for 15 min, crude **19** (0.75 g, ~60% pure, 3.12 mmol), suspended in *n*-heptane (5 mL), was added. After the mixture was stirred at ambient temperature for 15 min, the solvent was removed and the residue was purified by column chromatography on silica gel, eluting with acetone–hexane (1:4) to give **20** as an oil (0.88 g, 92%): IR (KBr) ν_{max} 3386, 2979, 2938, 2870, 1740, 1627, 1470, and 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.33 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.42 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.65 (1H, m, CH), 3.85 (4H, m, 2 × CH_2), 4.55 (2H, m, 2 × $CH(CH_3)_2$), 5.79 (1H, ddd, J = 2, 17, and 19 Hz, PC*H*=CH), 6.60 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*). Anal. ($C_{14}H_{27}O_5P$) C, H.

Diisopropyl [(*E*)-3-(Acetoxymethyl)-4-hydroxybut-1-enyl]phosphonate (21). A solution of **20** (0.73 g, 2.38 mmol) in 3% methanolic HCl (10 mL) was stirred at ambient temperature for 1.5 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with ethyl acetate, increasing polarity to ethyl acetate–methanol (20:1) to give diisopropyl [(*E*)-4-hydroxy-3-(hydroxymethyl)but-1-enyl]phosphonate as an oil (0.40 g, 63%): IR (film) ν_{max} 3391, 2979, 2933, 2877, 1738, 1630, 1467, and 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.32 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.61 (1H, m, CH), 3.40 (2H, br s, D_2O exchangeable, 2 × OH), 3.80 (4H, m, 2 × CH_2OH), 4.65 (2H, m, 2 × $CH(CH_3)_2$), 5.82 (1H, ddd, J = 1, 17, and 20 Hz, PC*H*=CH), 6.71 (1H, ddd, J = 7, 17, and 23 Hz, PCH=C*H*). Anal. ($C_{11}H_{23}O_5P$) C, H.

A solution of diisopropyl [(*E*)-4-hydroxy-3-(hydroxymethyl)-but-1-enyl]phosphonate (5.00 g, 18.5 mmol), trimethyl orthoacetate (7 mL, 56 mmol), and *p*-toluenesulfonic acid monohydrate (0.36 g, 1.9 mmol) in THF (50 mL) was stirred at room temperature for 1.5 h. The solution was treated with water (5 mL), stirred for a further 30 min, and then treated with triethylamine (0.1 mL). The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (30:1) to give **21** as an oil (4.94 g, 85%): IR (film) ν_{max} 3382, 2980, 2934, 2877, 2361, 2333, 1741, 1631, 1468, and 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.34 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.06 (3H, s, CH_3CO), 2.40 (1H, br s, D_2O exchangeable, OH), 3.68 (2H, m, CH_2OH), 4.24 (2H, m, CH_2), 4.64 (2H, m, 2 × $CH(CH_3)_2$), 5.83 (1H, ddd, J = 1, 17, and 19 Hz, PC*H*=CH), 6.67 (1H, ddd, J = 8, 17, and 22 Hz, PCH=C*H*); HRMS calcd for $C_{13}H_{25}O_6P$ (MH^+) 309.1467, found 309.1466. Anal. ($C_{13}H_{25}O_6P \cdot 0.25H_2O$) C, H.

Diisopropyl [(*E*)-3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-hydroxybut-1-enyl]phosphonate (22). To a solution of **21** (3.00 g, 9.70 mmol) and imidazole (1.70 g, 25.0 mmol) in anhydrous THF (60 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (3.49 g, 12.7 mmol). After the mixture was stirred at room temperature for 3 h, the solvent was removed and the residue was partitioned between chloroform (100 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$), the solvent was removed, and the residue was purified by column chromatography on silica gel, eluting with chloroform, increasing polarity to chloroform–methanol (100:1) to give diisopropyl [(*E*)-3-(acetoxymethyl)-4-[(*tert*-butyldiphenylsilyl)oxy]but-1-enyl]phosphonate as an oil (5.00 g, 94%): IR (film) ν_{max} 3071, 3050, 2977, 2931, 2858, 1743, 1630, 1582, 1472, and 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, $C(CH_3)_3$), 1.26 (3H, d, J = 6 Hz, $CHCH_3$), 1.27 (3H, d, J = 6 Hz, $CHCH_3$), 1.32 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.98 (3H, s, CH_3CO), 2.74 (1H, m, CH), 3.72 (2H, m, CH_2), 4.22 (2H, m, CH_2), 4.65 (2H, m, 2 × $CH(CH_3)_2$), 5.76 (1H, ddd, J = 1, 17, and 18 Hz, PC*H*=CH), 6.99 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*), 7.3–7.7 (10H, m, 2 × C_6H_5). Anal. ($C_{29}H_{43}O_6PSi$) C, H.

A solution of diisopropyl [(*E*)-3-(acetoxymethyl)-4-[(*tert*-butyldiphenylsilyl)oxy]but-1-enyl]phosphonate (5.00 g, 9.16 mmol) in methanol (50 mL) was stirred with potassium carbonate (62 g, 0.45 mmol) for 5 h at room temperature. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (100:1, 30:1) to give **22** as an oil (3.40 g, 74%): IR (film) ν_{max} 3381, 3071, 3025, 2940, 2931, 2858, 2360, 2332, 1631, 1585, 1471, and 1428 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, J = 6 Hz, $CHCH_3$), 1.27 (3H, d, J = 6 Hz, $CHCH_3$), 1.31 (6H, d, J = 6 Hz, 2 × $CH(CH_3)_2$), 2.15 (1H, t, J = 6 Hz, D_2O exchangeable, OH), 2.65 (1H, m, CH), 3.80 (4H, m, 2 × CH_2), 4.65 (2H, m, 2 × $CH(CH_3)_2$), 5.76 (1H, ddd, J = 1, 17, and 19 Hz, PC*H*=CH), 6.64 (1H, ddd, J = 8, 17, and 23 Hz, PCH=C*H*), 7.4–7.7 (10H, m, 2 × C_6H_5); HRMS calcd for $C_{27}H_{41}O_5PSi$ 504.2461, found 504.2444. Anal. ($C_{27}H_{41}O_5PSi \cdot 0.25H_2O$) C, H.

Diisopropyl [(*E*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-but-1-enyl]phosphonate (24). To a solution of imidazole (7.7 g, 113 mmol) and D,L-glyceraldehyde (3.0 g, 33.3 mmol) in DMF (50 mL) was added *tert*-butylchlorodimethylsilane (12.5 g, 83.2 mmol). The mixture was stirred at ambient temperature for 1.5 h. Hexane (250 mL) was added, and the solution was washed with 1 M hydrochloric acid (100 mL) and saturated sodium bicarbonate solution (100 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed to leave 2,3-bis[(*tert*-butyldimethylsilyl)oxy]propanal (**23**) as a colorless liquid (12.0 g) which was used without further purification.

To a solution of tetraisopropyl methylenediphosphonate (4.3 g, 12.5 mmol) in *n*-heptane (80 mL) stirred at −78 °C under dry nitrogen was added *n*-butyllithium (8.60 mL of 1.6 M solution in *n*-hexane; 13.8 mmol). The mixture was stirred at −78 °C for 0.5 h, and then crude **23** (4.0 g, ~12.5 mmol) was added dropwise. The solution was heated at 100 °C for 1 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (99:1, 49:1) to give **24** as a colorless oil (2.1 g, 34%): IR (film) ν_{max} 2935, 1465, 1395, 1255, 1110, 1010, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (12H, s, 4 × $SiCH_3$), 0.90 (18H, s, 2 × $C(CH_3)_3$), 1.30 (12H, m, 2 × $CH(CH_3)_2$), 3.53 (2H, m, CH_2), 4.30 (1H, m, CH), 4.66 (2H, m, 2 × $CH(CH_3)_2$), 5.98 (1H, dd, J = 17 and 22 Hz, PC*H*=CH), 6.83 (1H, ddd, J = 4, 17, and 22 Hz, PCH=C*H*); HRMS calcd for $C_{22}H_{49}O_5PSi_2$ (MH^+) 481.2935, found 481.2934. Anal. ($C_{22}H_{49}O_5PSi_2$) C, H.

Diisopropyl [(*E*)-3,4-Dihydroxybut-1-enyl]phosphonate (25). A solution of **24** (2.0 g, 4.16 mmol) in acetic acid–water–tetrahydrofuran (2:1:1) (40 mL) was stirred at 80 °C for 16 h. The solvent was removed, and the residue was purified by column chromatography on silica gel, eluting with dichloromethane–methanol (24:1, 9:1) to give **25** as a colorless oil (0.57 g, 54%): IR (film) ν_{max} 3350, 2980, 1635, 1470, 1380, 1230, and 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.21 (12H, m, 2 × $CH(CH_3)_2$), 3.35 (2H, m, CH_2), 4.10 (1H, m, CH), 4.48 (2H, m, 2 × $CH(CH_3)_2$), 4.76 (1H, t, J = 6 Hz, D_2O exchangeable, CH_2OH), 5.17 (1H, d, J = 5 Hz, D_2O exchangeable CHO*H*), 5.89 (1H, dd, J = 17 and 22 Hz, PC*H*=CH), 6.68 (1H, ddd, J = 4, 17, and 22 Hz, PCH=C*H*); HRMS calcd for $C_{10}H_{21}O_5P$ (MH^+) 253.1205, found 253.1187. Anal. ($C_{10}H_{21}O_5P$·0.1H_2O) C, H.

Diisopropyl [(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxybut-1-enyl]phosphonate (26). A solution of **25** (0.55 g, 2.18 mmol), triethylamine (0.265 g, 2.62 mmol), *tert*-butylchlorodimethylsilane (0.36 g, 2.38 mmol), and 4-(dimethylamino)-pyridine (11 mg, 0.088 mmol) in dichloromethane (20 mL) was stirred at room temperature for 66 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (49:1, 19:1) to give **26** as a colorless gum (0.54 g, 68%): IR (film) ν_{max} 3345, 2930, 1635, 1470, 1385, 1250, 1230, and 1105 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.03 (6H, s, 2 × $SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 1.23 (12H, m, 2 × $CH(CH_3)_2$), 3.53 (2H, m, CH_2), 4.13 (1H, m, CH), 4.50 (2H, m, 2 × $CH(CH_3)_2$), 5.23 (1H, d, J = 6 Hz, D_2O exchangeable, OH), 5.90 (1H, dd, J = 18 and 22 Hz, PC*H*=CH), 6.73 (1H, ddd, J = 4, 18, and 22 Hz, PCH=C*H*); HRMS calcd for $C_{16}H_{35}O_5PSi$ (MH^+) 367.2070, found 367.2069. Anal. ($C_{16}H_{35}O_5PSi$·0.2H_2O) C, H.

General Procedure for the Preparation of Compounds 28, 30, 33, 41, 43, 45, 48, 50, 52, 55, 59–61, 63, and 66. A mixture of alcohol **15**, **17**, **22**, or **26** (1.00 mmol), compound **27**, **40**, **44**, **47**, **58**, or **75** (1.00–1.30 mmol), and triphenylphosphine (PPh_3) (1.30–2.00 mmol) in anhydrous THF or DMF, cooled to 0 °C, was treated with diethyl azodicarboxylate (DEAD) (1.3–2.0 mmol). After the mixture was stirred at ambient temperature for 1.3–27.5 h, the solvent was removed and the residue was purified by column chromatography on silica gel.

(*E*)-6-Chloro-9-[4-(diisopropoxyphosphoryl)but-3-enyl]-purine (28): obtained as a white solid in 37% yield [2.67-mmol scale, THF solvent (30 mL), using alcohol **15**, 1.0 equiv of **27**, and 1.5 equiv of PPh_3 and DEAD, 27.5 h, eluent: dichloromethane–methanol (24:1, 13:1)]; mp 105 °C; UV (EtOH) λ_{max} 266 (ϵ 9260) nm; IR (KBr) ν_{max} 3435, 2980, 1590, 1560, 1330, 1230, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.29 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.88 (2H, m, CH_2), 4.45 (2H, t, J = 7 Hz, CH_2N), 4.55 (2H, m, 2 × $CH(CH_3)_2$), 5.68 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.70 (1H, ddt, J = 7, 17, and 22 Hz, PCH=C*H*), 8.10 (1H, s, 2-H/8-H), 8.77 (1H, s, 2-H/8-H); FABMS (thioglycerol) m/z MH^+ 373. Anal. ($C_{15}H_{22}ClN_4O_3P$) C, H, N.

(*Z*)-6-Chloro-9-[4-(diethoxyphosphoryl)but-3-enyl]purine (30): obtained as a gum in 64% yield [2.67-mmol scale, THF solvent (30 mL), using alcohol **17**, 1.0 equiv of **27** and 1.5 equiv of PPh_3 and DEAD, 16 h, eluent: dichloromethane–methanol (13:1)]; UV (EtOH) λ_{max} 265 (ϵ 8570) nm; ^1H NMR (Me_2SO-d_6) δ 1.09 (6H, t, J = 7 Hz, 2 × CH_3), 3.10 (2H, m, CH_2), 3.75 (4H, m, 2 × CH_2O), 4.48 (2H, t, J = 6 Hz, CH_2N), 5.67 (1H, dd, J = 13 and 19 Hz, PC*H*=CH), 6.55 (1H, ddt, J = 7, 13, and 52 Hz, PCH=C*H*), 8.67 (1H, s, 2-H/8-H), 8.78 (1H, s, 2-H/8-H); EIMS m/z M^+ 344. Anal. ($C_{13}H_{18}ClN_4O_3P$·0.1H_2O) C, H, N.

(*E*)-9-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]-6-chloropurine (33): obtained as a gum in 28% yield along with diisopropyl [(*E*)-3-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-butadienyl]-phosphonate (**39**) as an oil in 56% yield [1.37-mmol scale, DMF solvent (22 mL), using alcohol **22**, 1.0 equiv of **27**, and 1.5 equiv of PPh_3 and DEAD, 16 h, eluents: hexane–acetone (4:1; 2:1) then ethyl acetate–methanol (99:1; 9:1)]. For **33**: UV (EtOH) λ_{max} 265 (ϵ 9215) nm; IR (film) ν_{max} 2980, 2930, 1590, 1560, 1425, 1385, 1335, and 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (9H, s, $C(CH_3)_3$), 1.14 (3H, d, J = 6 Hz, $CHCH_3$), 1.18 (3H, d, J = 6 Hz, $CHCH_3$), 1.26 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 3.10 (1H, m, CH), 3.69 (2H, d, J = 6 Hz, CH_2O), 4.50 (4H, m, CH_2N and 2 × $CH(CH_3)_2$), 5.57 (1H, t, J = 17 Hz, PC*H*=CH), 6.66 (1H, ddd, J = 8, 17, and 26 Hz, PCH=C*H*), 7.30–7.70 (10H, m, 2 × C_6H_5), 8.00 (1H, s, 2-H/8-H), 8.73 (1H, s, 2-H/8-H); HRMS calcd for $C_{32}H_{42}ClN_4O_4PSi$ 641.2479, found 641.2459. For **39**: IR (film) ν_{max} 3440, 2975, 2930, 2855, 1590, 1430, 1385, 1250, 1110, 1010, and 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, $C(CH_3)_3$), 1.25 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.34 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 4.34 (2H, s, CH_2), 4.64 (2H, m, 2 × $CH(CH_3)_2$), 5.45 (1H, br s, H_A of C=CH_2), 5.60 (1H, t, J = 18 Hz, PC*H*=CH), 5.71 (1H, br s, H_B of C=CH_2), 7.10 (1H, dd, J = 18 and 23 Hz, PCH=C*H*), 7.30–7.70 (10H, m, 2 × C_6H_5); HRMS calcd for $C_{27}H_{39}O_4PSi$ (MH^+) 487.2433, found 487.2429. Anal. ($C_{27}H_{39}O_4PSi$·0.5H_2O) C, H.

(*E*)-2-Amino-6-chloro-9-[4-(diisopropoxyphosphoryl)but-3-enyl]purine (41): obtained as a gum in 35% yield [3.81-mmol scale, DMF solvent (30 mL), using alcohol **15**, 1.0 equiv of **40**, and 2.0 equiv of PPh_3 and DEAD, 1.3 h, eluent: dichloromethane–methanol (9:1)]; mp 150 °C; UV (EtOH) λ_{max} 311 (ϵ 6760), 249 (ϵ 5420) and 224 (ϵ 24 320) nm; IR (KBr) ν_{max} 3385, 3320, 3208, 1635, 1615, 1560, 1520, 1410, and 1240 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.08 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.16 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.77 (2H, m, CH_2), 4.27 (4H, m, CH_2N and $CH(CH_3)_2$), 5.69 (1H, dd, J = 17 and 21 Hz, PC*H*=CH), 6.52 (1H, ddt, J = 6, 17, and 22 Hz, PCH=C*H*), 6.89 (2H, br s, D_2O exchangeable, NH_2), 8.11 (1H, s, H-8); HRMS calcd for $C_{15}H_{23}ClN_5O_3P$ 388.1305, found 388.1288.

(*Z*)-2-Amino-6-chloro-9-[4-(diethoxyphosphoryl)but-3-enyl]purine (43): obtained as a gum in 42% yield [2.67-mmol scale, DMF solvent (20 mL), using alcohol **17**, 1.0 equiv of **40**, and 2.0 equiv of PPh_3 and DEAD, 2.5 h, eluent: dichloromethane–methanol (32:1; 13:1)]; UV (EtOH) λ_{max} 310 (ϵ 7890), 248 (ϵ 6510), 223 (ϵ 29 880) nm; IR (KBr) ν_{max} 3320, 3205, 2980, 1610, 1560, 1520, 1465, 1410, and 1240 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.13 (6H, t, J = 7 Hz, 2 × CH_3), 3.00 (2H, m, CH_2), 3.80 (4H, m, 2 × CH_2O), 4.20 (2H, m, CH_2N), 5.70 (1H, dd, J = 13 and 19 Hz, PC*H*=CH), 6.55 (1H, ddt, J = 7, 13, and 52 Hz, PCH=C*H*), 6.90 (2H, br s, D_2O exchangeable, NH_2), 8.09 (1H, s, 8-H); HRMS calcd for $C_{13}H_{19}ClN_5O_3P$ 359.0922, found 359.0914.

(*E*)-2-Acetamido-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]-6-chloropurine (45): obtained as a gum in 36% yield [1.54-mmol scale, DMF solvent (40 mL), using alcohol **22**, 1.0 equiv of **44**,[40] and 1.5 equiv of PPh_3 and DEAD, 16 h, eluent: ethyl acetate increasing polarity to ethyl acetate–methanol (19:1)]; UV (EtOH) λ_{max} 224 (ϵ 29 735), 260 (ϵ 8593), and 289 (ϵ 9915) nm; IR (KBr) ν_{max} 2980, 2930, 1695, 1610, 1575, 1515, 1375, 1285, and 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (9H, s, $C(CH_3)_3$), 1.16 (6H, pseudo-t, J = 6 Hz, 2 × $CHCH_3$), 1.30 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.53 (3H, s, $NCOCH_3$), 3.00 (1H, m, CH), 3.67 (2H, m, CH_2O), 4.25–4.60 (4H, m, CH_2N and 2 × $CH(CH_3)_2$), 5.58 (1H, t, J = 18 Hz, PC*H*=CH), 6.67 (1H, ddd, J = 8, 17, and 22 Hz, PCH=C*H*), 7.50 (10H, m,

2 × C_6H_5), 7.86 (1H, s, 8-H), 8.29 (1H, br s, D_2O exchangeable, NH); HRMS calcd for $C_{34}H_{45}ClN_5O_5PSi$ 698.2695, found 698.2697.

(*E*)-9-[[4-(Diisopropoxyphosphoryl)but-3-enyl]oxy]-6-*N*-phthalimidopurine (48): obtained as a gum in 80% yield [0.50-mmol scale, THF solvent (5 mL), using alcohol **15**, 1.0 equiv of **47**, and 1.5 equiv of PPh_3 and DEAD, 2 h, eluent: dichloromethane–methanol (49:1; 16:1)]; UV (EtOH) λ_{max} 273 (ϵ 14 380) nm; IR (film) ν_{max} 2970, 1730, 1590, 1570, 1355, 1240, and 975 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.24 (12H, pseudo-t, J = 6 Hz, 2 × $CH(CH_3)_2$), 2.77 (2H, m, CH_2), 4.60 (2H, m, 2 × $CH(CH_3)_2$), 4.66 (2H, t, J = 6 Hz, CH_2O), 6.07 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.75 (1H, ddt, J = 6, 17, and 22 Hz, PCH=C*H*), 8.00–8.25 (4H, m, C_6H_4), 9.00 (1H, s, 2-H/8-H), 9.08 (1H, s, 2-H/8-H); HRMS calcd for $C_{23}H_{26}N_5O_6P$ 499.1621, found 499.1620.

(*Z*)-9-[[4-(Diethoxyphosphoryl)but-3-enyl]oxy]-6-*N*-phthalimidopurine (50): obtained as a gum in 60% yield [1.14-mmol scale, THF solvent (11 mL), using alcohol **17**, 1.0 equiv of **47**, and 1.5 equiv of PPh_3 and DEAD, 2.3 h, eluent: acetone–hexane (1:1; 4.3)]; UV (EtOH) λ_{max} 271 (ϵ 14 680) nm; IR (KBr) ν_{max} 2980, 1735, 1595, 1575, 1360, 1330, 1245, and 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.23 (6H, t, J = 7 Hz, 2 × CH_3), 3.05 (2H, m, CH_2), 3.98 (4H, dq, J = 7 and 8 Hz, 2 × CH_2CH_3), 4.63 (2H, t, J = 6 Hz, CH_2O), 5.90 (1H, dd, J = 14 and 20 Hz, PC*H*=CH), 6.75 (1H, ddt, J = 7, 14, and 52 Hz, PCH=C*H*), 8.05 (4H, m, C_6H_4), 9.05 (1H, s, 2-H/8-H), 9.10 (1H, s, 2-H/8-H); HRMS calcd for $C_{21}H_{22}N_5O_6P$ (MH^+) 472.1386, found 472.1384. Anal. ($C_{21}H_{22}N_5O_6P$) C, H, N.

(*E*)-9-[[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]oxy]-6-*N*-phthalimidopurine (52): obtained as a glass in 62% yield [2.60-mmol scale, THF solvent (20 mL), using alcohol **22**, 1.3 equiv of **47**, and 1.3 equiv of PPh_3 and DEAD, 18 h, eluent: ethyl acetate–dichloromethane (1:1), increasing polarity to ethyl acetate]: IR (KBr) ν_{max} 3447, 3071, 2978, 2931, 2858, 1792, 1737, 1598, 1577, 1468, 1455, 1428, and 1406 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (9H, s, $C(CH_3)_3$), 1.29 (3H, d, J = 6 Hz, $CHCH_3$), 1.30 (3H, d, J = 6 Hz, $CHCH_3$), 1.34 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 3.00 (1H, s, CH), 3.90 (2H, m, CH_2), 4.70 (4H, m, CH_2, 2 × $CH(CH_3)_2$), 6.00 (1H, ddd, J = 1, 17, and 19 Hz, PC*H*=CH), 6.81 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*), 7.30–8.20 (15H, m, C_6H_4, 2 × C_6H_5, 2-H/8-H), 9.04 (1H, s, 2-H/8-H). Anal. ($C_{40}H_{46}N_5O_7PSi$·0.5H_2O) C, H, N.

(*E*)-9-[[1-[(*tert*-Butyldimethylsilyl)oxy]-4-(diisopropoxyphosphoryl)but-3-en-2-yl]oxy]-6-*N*-phthalimidopurine (55): obtained as a gum in 68% yield [0.74-mmol scale, THF solvent (12 mL), using alcohol **26**, 1.0 equiv of **47**, and 1.5 equiv of PPh_3 and DEAD, 3 h, eluent: ethyl acetate–dichloromethane (1:1), increasing polarity to ethyl acetate]; UV (EtOH) λ_{max} 270 (ϵ 18 000) nm; IR (KBr) ν_{max} 3435, 2930, 1735, 1600, 1575, 1365, 1250, and 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (6H, s, 2 × $SiCH_3$), 0.90 (9H, s, $C(CH_3)_3$), 1.30 (12H, m, 2 × $CH(CH_3)_2$), 3.99 (2H, d, J = 5 Hz, CH_2), 4.64 (2H, m, 2 × $CH(CH_3)_2$), 5.10 (1H, m, CH), 6.18 (1H, t, J = 17 Hz, PC*H*=CH), 6.85 (1H, ddd, J = 6, 17, and 22 Hz, PCH=C*H*), 7.80–8.10 (4H, m, C_6H_4), 8.30 (1H, s, 2-H/8-H), 9.05 (1H, s, 2-H/8-H); FABMS (positive ion, TDE/NaCl) m/z MH^+ 630, MNa^+ 652.

(*E*)-2-[Bis(*tert*-butoxycarbonyl)amino]-9-[[4-(diisopropoxyphosphoryl)but-3-enyl]oxy]-6-methoxypurine (59): obtained as a gum in 62% yield [0.40-mmol scale, THF solvent (4 mL), using alcohol **15**, 1.0 equiv of **58**, and 1.5 equiv of PPh_3 and DEAD, 2.3 h, eluent: ethyl acetate–methanol (20:1)]; UV (EtOH) λ_{max} 255 (ϵ 12 300) nm; IR (KBr) ν_{max} 3440, 3220, 2975, 1790, 1600, 1370, 1280, and 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.21 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.23 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.40 (18H, s, 2 × $C(CH_3)_3$), 2.70 (2H, m, CH_2), 4.08 (3H, s, CH_3O), 4.53 (4H, m, CH_2O and 2 × $CH(CH_3)_2$), 5.98 (1H, dd, J = 17 and 19 Hz, PC*H*=CH), 6.25 (1H, ddt, J = 6, 17, and 22 Hz, PC*H*=CH), 8.71 (1H, s, 8-H); HRMS calcd for $C_{26}H_{42}N_5O_9P$ 599.2720, found 599.2724.

(*Z*)-2-[Bis(*tert*-butoxycarbonyl)amino]-9-[[4-(diethoxyphosphoryl)but-3-enyl]oxy]-6-methoxypurine (60): obtained as a gum in 61% yield [1.28-mmol scale, THF solvent (15 mL), using alcohol **17**, 1.0 equiv of **58**, and 1.5 equiv of PPh_3 and DEAD, 1.5 h, eluent: acetone–hexane (1:1)]; UV (EtOH) λ_{max} 256 (ϵ 10 920) nm; IR (KBr) ν_{max} 2980, 2360, 1790, 1760, 1590, 1475, 1370, 1280, and 1255 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.21 (6H, t, J = 7 Hz, 2 × CH_2CH_3), 1.40 (18H, s, 2 × $C(CH_3)_3$), 2.97 (2H, m, CH_2), 3.95 (4H, qu, J = 7 Hz, 2 × CH_2CH_3), 4.08 (3H, s, OCH_3), 4.50 (2H, t, J = 7 Hz, CH_2O), 5.83 (1H, dd, J = 14 and 19 Hz, PC*H*=CH), 6.68 (1H, ddt, J = 7, 14, and 52 Hz, PCH=C*H*), 8.75 (1H, s, 8-H); CIMS (NH_3) m/z MH^+ 572. Anal. ($C_{24}H_{35}N_5O_9P$) C, H, N.

(*E*)-2-[Bis(*tert*-butoxycarbonyl)amino]-9-[[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]oxy]-6-methoxypurine (61): obtained as a gum in 66% yield [1.20-mmol scale, THF solvent (15 mL), using alcohol **22**, 1.3 equiv of **58**, and 1.3 equiv of PPh_3 and DEAD, 18 h, eluent: hexane–acetone (2:1)]; IR (KBr) ν_{max} 2975, 2930, 2860, 1790, 1755, 1735, 1590, 1470, and 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, $SiC(CH_3)_3$), 1.30 (12H, m, 2 × $CH(CH_3)_2$), 1.43 (18H, s, 2 × $OC(CH_3)_3$), 2.92 (1H, m, CH), 3.85 (2H, m, CH_2), 4.15 (3H, s, OCH_3), 4.40–4.75 (4H, m, CH_2 and 2 × $CH(CH_3)_2$), 5.91 (1H, ddd, J = 1, 17, and 19 Hz, PC*H*=CH), 6.77 (1H, ddd, J = 8, 17, and 25 Hz, PCH=C*H*), 7.30–7.85 (11H, m, 2 × C_6H_5, 8-H). Anal. ($C_{43}H_{62}N_5O_{10}PSi$) C, H, N.

(*E*)-2-[Bis(*tert*-butoxycarbonyl)amino]-9-[[1-[(*tert*-butyldimethylsilyl)oxy]-4-(diisopropoxyphosphoryl)but-3-en-2-yl]oxy]-6-methoxypurine (63): obtained as a gum in 75% yield [0.82-mmol scale, THF solvent (14 mL), using alcohol **26**, 1.0 equiv of **58**, and 1.5 equiv of PPh_3 and DEAD, 3 h, eluent: ethyl acetate–methanol (30:1)]; UV (EtOH) λ_{max} 256 (ϵ 12 116) nm; IR (KBr) ν_{max} 2975, 1795, 1760, 1590, 1475, 1395, 1370, 1255, 1155, and 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (6H, s, 2 × $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.30 (12H, m, 2 × $CH(CH_3)_2$), 1.47 (18H, s, 2 × $OC(CH_3)_3$), 3.95 (2H, d, J = 4 Hz, CH_2), 4.15 (3H, s, OCH_3), 4.63 (2H, m, 2 × $CH(CH_3)_2$), 5.10 (1H, m, CH), 6.02 (1H, t, J = 17 Hz, PC*H*=CH), 6.75 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*), 8.01 (1H, s, 8-H); HRMS calcd for $C_{32}H_{56}N_5O_{10}PSi$ (MH^+) 730.3614, found 730.3614.

(*E*)-N^4-Benzoyl-1-[[1-[(*tert*-butyldimethylsilyl)oxy]-4-(diisopropoxyphosphoryl)but-3-en-2-yl]oxy]cytosine (66): obtained as a gum in 91% yield [0.74-mmol scale, DMF solvent (10 mL), using alcohol **26**, 1.0 equiv of **65**, and 1.5 equiv of PPh_3 and DEAD, 16 h, eluent: dichloromethane–ethyl acetate (9:1; 3:1), increasing polarity to dichloromethane–methanol (19:1)]; UV (EtOH) λ_{max} 261 (ϵ 22 520) and 306 (ϵ 10 200) nm; IR (KBr) ν_{max} 3435, 2930, 1690, 1615, 1555, 1480, 1330, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (6H, s, 2 × $SiCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 1.30 (12H, m, 2 × $CH(CH_3)_2$), 3.93 (2H, m, CH_2), 4.67 (2H, m, 2 × $CH(CH_3)_2$), 5.17 (1H, m, CH), 6.10 (1H, t, J = 18 Hz, PC*H*=CH), 6.83 (1H, ddd, J = 6, 18, and 22 Hz, PCH=C*H*), 7.47–8.05 (7H, m, C_6H_5, 5-H and 6-H), 8.95 (1H, br s, NH); FABMS (positive ion, TDE/NaCl) m/z MH^+ 580, MNa^+ 602. Anal. ($C_{27}H_{42}O_7N_3PSi$·0.2H_2O) C, H, N.

(*E*)-9-[4-(Diisopropoxyphosphoryl)but-3-enyl]adenine (29). A solution of **28** (0.31 g, 0.83 mmol) in saturated ethanolic ammonia (35 mL) was heated at 80 °C in a stainless steel autoclave for 5 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with ethyl acetate–methanol (3:1) to give **29** as a white solid (0.205 g, 70%): mp 121–122 °C; UV (EtOH) λ_{max} 262 (ϵ 11 855) nm; IR (KBr) ν_{max} 3320, 3175, 2935, 1650, 1600, 1575, 1475, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 1.29 (6H, d, J = 6 Hz, 2 × $CHCH_3$), 2.84 (2H, m, CH_2), 4.35 (2H, t, J = 7 Hz, CH_2N), 4.55 (2H, m, 2 × $CH(CH_3)_2$), 5.69 (1H, dd, J = 17 and 19 Hz, PC*H*=CH), 5.76 (2H, s, NH_2), 6.70 (1H, ddt, J = 7, 17, and 22 Hz, PCH=C*H*), 7.79 (1H, s, 2-H/8-H), 8.37 (1H, s, 2-H/8-H); HRMS calcd for $C_{15}H_{24}N_5O_3P$ 354.1695, found 354.1695.

General Procedure for the Preparation of Compounds 7a–g, 8a–g, and 9–12. A solution of compound **29**, **32**, **36**, **41–43**, **46**, **49**, **51**, **54**, **57**, **59**, **60**, **62–64**, **67**, or **77** (1.00 mmol) in anhydrous dichloromethane, DMF, or dichloromethane–DMF mixtures was treated at ambient temperature with bromotrimethylsilane (15.0–20.0 mmol). After the mixture was stirred for 16–48 h, the solvent was removed, coevaporating several times with methanol. For compounds **8a**, **8b**, **8d**, **8e**, **8g**, and **10**, the residue underwent the following additional treatments prior to purification:

For compounds **8a**, **8b**, and **10** the residue was dissolved in 2 M hydrochloric acid, and the solution was heated at 100 °C for 1.0–1.7 h before the cooled solution was neutralized by addition of 2.5 M sodium hydroxide solution and evaporated to dryness.

For compounds **8d**, **8e**, and **8g** the residue was dissolved in water and the solution was heated at 100 °C for 2–30 min before being cooled and evaporated to dryness.

The crude products (except **8d**) were purified by column chromatography on C_{18} reverse-phase silica gel eluting with water; **8d** was purified by recrystallization from methanol–water (4:1).

(*E*)-9-(4-Phosphonobut-3-enyl)adenine (7a): obtained as a white solid in 81% yield [0.31-mmol scale, dichloromethane solvent (6 mL)]; mp 263–266 °C; UV (MeOH) λ_{max} 261 (ϵ 10 810) nm; IR (KBr) ν_{max} 3360, 3095, 1685, 1605, 1520, 1415, and 1228 cm^{-1}; ^1H NMR (D_2O + NH_3) δ 2.63 (2H, m, CH_2), 4.31 (2H, t, J = 7 Hz, CH_2N), 5.72 (1H, t, J = 17 Hz, PC*H*=CH), 6.14 (1H, tt, J = 7 and 17 Hz, PCH=C*H*), 8.13 (1H, s, 2-H/8-H), 8.19 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 270. Anal. ($C_9H_{12}N_5O_3P$·0.25HBr) C, H, N.

(*Z*)-9-(4-Phosphonobut-3-enyl)adenine (7b): obtained as a white solid in 87% yield [0.19-mmol scale, dichloromethane–DMF (5:1) solvent (12 mL)]; mp 260–262 °C; UV (MeOH) λ_{max} 262.5 (ϵ 13 750) nm; IR (KBr) ν_{max} 3086, 1690, 1515, 1415, 1225, 1145, and 1030 cm^{-1}; ^1H NMR (D_2O + NH_3) δ 3.00 (2H, m, CH_2), 4.32 (2H, t, J = 7 Hz, CH_2N), 5.83 (1H, dd, J = 13 and 17 Hz, PC*H*=CH), 6.05 (1H, ddt, J = 7, 13, and 44 Hz, PCH=C*H*), 8.17 (1H, s, 2-H/8-H), 8.19 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 270. Anal. ($C_9H_{12}N_5O_3P$·0.1HBr) C, H, N.

(*E*)-9-[2-(Hydroxymethyl)-4-phosphonobut-3-enyl]adenine (7c): obtained as a white solid in 40% yield [0.28-mmol scale, DMF solvent (5 mL)]; mp >300 °C; UV (MeOH) λ_{max} 262 (ϵ 10 704) nm; IR (KBr) ν_{max} 3435, 1695, 1640, 1415, 1263, 1229, and 1030 cm^{-1}; ^1H NMR [(Me_2SO-d_6)–D_2O] δ 2.73 (1H, m, CH), 3.37 (2H, d, J = 6 Hz, CH_2O), 4.13 (1H, dd, J = 7 and 14 Hz, CH_2N), 4.30 (1H, dd, J = 7 and 14 Hz, CH_2N), 5.65 (1H, t, J = 17 Hz, PC*H*=CH), 6.06 (1H, ddd, J = 8 and 19 Hz, PCH=C*H*), 8.10 (1H, s, 2-H/8-H), 8.17 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 300. Anal. ($C_{10}H_{14}N_5O_4P$·H_2O) C, H, N.

(*E*)-9-(4-Phosphonobut-3-enyl)guanine (8a): obtained as a white solid in 53% yield [0.43-mmol scale, dichloromethane solvent (8 mL)]; mp 290–294 °C dec; UV (MeOH) λ_{max} 257 (ϵ 8660) nm; IR (KBr) ν_{max} 3425, 3150, 2745, 1740, 1635, 1490, 1240, and 1190 cm^{-1}; ^1H NMR (D_2O + NH_3) δ 2.62 (2H, m, CH_2), 4.15 (2H, t, J = 7 Hz, CH_2N), 5.78 (1H, t, J = 17 Hz, PC*H*=CH), 6.15 (1H, tt, J = 7 and 18 Hz, PCH=C*H*), 7.80 (1H, s, 8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 286. Anal. ($C_9H_{12}N_5O_4P$·0.2H_2O) C, H, N.

(*E*)-2,6-Diamino-9-(4-phosphonobut-3-enyl)purine (9): obtained as a white solid in 27% yield [0.39-mmol scale, DMF solvent (10 mL)]; mp >325 °C; UV (MeOH) λ_{max} 256 (ϵ 6570) and 285 (ϵ 6490) nm; IR (KBr) ν_{max} 3410, 1710, 1670, 1630, 1590, 1420, 1220, and 1135 cm^{-1}; ^1H NMR [(Me_2SO-d_6) + NH_3] δ 2.50 (2H, m, CH_2), 4.05 (2H, t, J = 7 Hz, CH_2N), 5.70 (1H, t, J = 17 Hz, PC*H*=CH), 5.81 (2H, s, NH_2), 6.10 (1H, tt, J = 7 and 20 Hz, PCH=C*H*), 6.69 (2H, s, NH_2), 7.76 (1H, s, 8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 285.

(*Z*)-9-(4-Phosphonobut-3-enyl)guanine (8b): obtained as a white solid in 61% yield [0.56-mmol scale, DMF solvent (5 mL)]; UV (EtOH) λ_{max} 255 (ϵ 6500) nm; IR (KBr) ν_{max} 3395, 3140, 3015, 2790, 1695, 1605, 1545, 1480, 1375, and 1151 cm^{-1}; ^1H NMR [(Me_2SO-d_6)–D_2O (1:1)] δ 2.91 (2H, m, CH_2), 4.10 (2H, t, J = 7 Hz, CH_2N), 5.75 (1H, dd, J = 13 and 17 Hz, PC*H*=CH), 5.95 (1H, ddt, J = 7, 13, and 50 Hz, PCH=C*H*), 7.84 (1H, s, 8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 286. Anal. ($C_9H_{12}N_5O_4P$·1.7H_2O) H, N; C: calcd, 34.22; found, 35.29.

(*E*)-9-[2-(Hydroxymethyl)-4-phosphonobut-3-enyl]guanine (8c): obtained as a white solid in 40% yield [0.33-mmol scale, DMF solvent (5 mL)]; mp >300 °C; UV (MeOH) λ_{max} 256 (ϵ 7402) nm; IR (KBr) ν_{max} 3425, 1715, 1640, 1610, 1480, 1410, 1380, and 1160 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.50–6.00 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 2.80 (1H, m, CH), 3.40 (2H, d, J = 5 Hz, CH_2O), 4.04 (2H, m, CH_2N), 5.73 (1H, t, J = 18 Hz, PC*H*=CH), 6.35 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*), 6.50 (2H, br s, D_2O exchangeable, NH_2), 7.60 (1H, s, 8-H), 10.56 (1H, br s, D_2O exchangeable, 1-H); FABMS (positive ion, thioglycerol) m/z MH^+ 316. Anal. ($C_{10}H_{14}N_5O_5P$·0.2H_2O·0.2DMF) C, H, N.

(*E*)-9-[(4-Phosphonobut-3-enyl)oxy]adenine (7d): obtained as a white solid in 84% yield [0.28-mmol scale, dichloromethane solvent (5 mL)]; mp 249–251 °C; UV (MeOH) λ_{max} 260 (ϵ 11 985) nm; IR (KBr) ν_{max} 3110, 2300, 1695, 1470, 1410, 1330, and 1030 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.62 (2H, m, CH_2), 4.50 (2H, t, J = 7 Hz, CH_2O), 5.94 (1H, dd, J = 17 and 22 Hz, PC*H*=CH), 6.50 (1H, ddt, J = 6, 17, and 22 Hz, PCH=C*H*), 7.39 (2H, br s, NH_2), 8.16 (1H, s, 2-H/8-H), 8.35 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 286. Anal. ($C_9H_{12}N_5O_4P$·0.2HBr) C, H, N, Br.

(*Z*)-9-[(4-Phosphonobut-3-enyl)oxy]adenine (7e): obtained as a white solid in 81% yield [0.42-mmol scale, dichloromethane solvent (10 mL)]; mp 238 °C; UV (MeOH) λ_{max} 260 (ϵ 13 515) nm; IR (KBr) ν_{max} 3420, 3200, 3085, 2970, 1700, 1610, 1485, 1415, and 1335 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.94 (2H, m, CH_2), 4.43 (2H, t, J = 7 Hz, CH_2O), 5.77 (1H, dd, J = 14 and 17 Hz, PC*H*=CH), 6.40 (1H, ddt, J = 7, 14, and 47 Hz, PCH=C*H*), 7.40 (2H, br s, NH_2), 8.15 (1H, s, 2-H/8-H), 8.42 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 286. Anal. ($C_9H_{12}N_5O_4P$·0.4H_2O) C, H, N.

(*E*)-9-[[2-(Hydroxymethyl)-4-phosphonobut-3-enyl]oxy]adenine (7f): obtained as a white solid in 17% yield [0.63-mmol scale, DMF solvent (5 mL)]; UV (H_2O) λ_{max} 260 (ϵ 13 111) nm; IR (KBr) ν_{max} 3434, 1717, 1690, 1653, 1640, 1472, and 1414 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.78 (1H, m, CH), 3.38 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 3.60 (2H, m, CH_2OH), 4.48 (2H, m, CH_2ON), 5.99 (1H, m, PC*H*=CH), 6.48 (1H, m, PCH=C*H*), 7.37 (2H, br s, D_2O exchangeable NH_2), 8.14 (1H, s, 2-H/8-H), 8.34 (1H, s, 2-H/8-H). Anal. ($C_{10}H_{14}N_5O_5P$·0.9H_2O) C, H; N: calcd, 21.13; found 20.49.

(*E*)-9-[(1-Hydroxy-4-phosphonobut-3-en-2-yl)oxy]adenine (7g): obtained as a white solid in 50% yield [0.27-mmol scale, DMF solvent (4 mL)]; mp >300 °C; UV (MeOH) λ_{max} 260 (ϵ 7440) nm; IR (KBr) ν_{max} 3425, 3110, 1695, 1405, 1335, 1295, 1200, and 1045 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.70–5.70 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 3.69 (2H, m, CH_2), 5.00 (1H, m, CH), 6.06 (1H, pseudo-t, J = 17 Hz, PC*H*=CH), 6.54 (1H, ddd, J = 6, 17, and 21 Hz, PCH=C*H*), 7.41 (2H, br s, D_2O exchangeable, NH_2), 8.16 (1H, s, 2-H/8-H), 8.29 (1H, s, 2-H/8-H); FABMS (positive ion, thioglycerol) m/z MH^+ 302. Anal. ($C_9H_{12}N_5O_5P$·0.8H_2O) C, H, N.

(*E*)-9-[(4-Phosphonobut-3-enyl)oxy]guanine (8d): obtained as a cream-colored crystals in 84% yield [0.18-mmol scale, dichloromethane solvent (5 mL)]; mp >330 °C; UV (EtOH) λ_{max} 255, 266 nm; IR (KBr) ν_{max} 3200, 3120, 2740, 1760, 1690, 1635, 1470, 1235, and 1160 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.60 (2H, m, CH_2), 4.40 (2H, t, J = 7 Hz, CH_2O), 5.92 (1H, dd, J = 17 and 19 Hz, PC*H*=CH), 6.50 (1H, ddt, J = 6, 17, and 22 Hz, PCH=C*H*), 6.60 (2H, br s, NH_2), 7.90 (1H, s, 8-H), 10.65 (1H, br s, 1-H); FABMS (positive ion, thioglycerol) m/z MH^+ 302. Anal. ($C_9H_{12}N_5O_5P$·0.2H_2O) C, H, N.

(*Z*)-9-[(4-Phosphonobut-3-enyl)oxy]guanine (8e): obtained as a white solid in 42% yield [0.47-mmol scale, dichloromethane solvent (15 mL)]; mp 240–242 °C; UV (MeOH) λ_{max} 255 (ϵ 13 000) nm; IR (KBr) ν_{max} 3390, 3140, 1695, 1650, 1610, 1475, 1385, and 1165 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.91 (2H, m, CH_2), 4.32 (2H, t, J = 7 Hz, CH_2O), 5.75 (1H, dd, J = 13 and 17 Hz, PC*H*=CH), 6.30 (1H, ddt, J = 7, 13, and 47 Hz, PCH=C*H*), 6.61 (2H, br s, D_2O exchangeable, NH_2), 7.95 (1H, s, 8-H), 10.63 (1H, br s, D_2O exchangeable, 1-H); FABMS (positive ion, thioglycerol) m/z MH^+ 302. Anal. ($C_9H_{12}N_5O_5P$·0.4H_2O) C, H, N.

(*E*)-9-[[2-(Hydroxymethyl)-4-phosphonobut-3-enyl]oxy]guanine (8f): obtained as a white solid in 17% yield [0.38-mmol scale, DMF solvent (4 mL)]; UV (H_2O) λ_{max} 253 (ϵ 12 277) nm; IR (KBr) ν_{max} 3422, 3125, 2922, 2852, 2752, 1691, 1639, 1611, 1552, 1533, 1474, and 1451 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.70 (1H, m, CH), 3.30 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 3.55 (2H, m, CH_2OH), 4.35 (2H, m, CH_2ON), 5.95 (1H, t, J = 18 Hz, PC*H*=CH), 6.45 (1H, m, PCH=C*H*), 6.60 (2H, br s, D_2O exchangeable, NH_2), 7.85 (1H, s, 8-H), 10.63 (1H, br s, 1-H). Anal. ($C_{10}H_{14}N_5O_6P$·0.4H_2O) C, H, N.

(*E*)-9-[(1-Hydroxy-4-phosphonobut-3-en-2-yl)oxy]guanine (8g): obtained as a white solid in 36% yield [0.51-mmol scale, dichloromethane–DMF (15:1) solvent (16 mL)]; mp >300 °C; UV (MeOH) λ_{max} 255 (ϵ 11 750) nm; IR (KBr) ν_{max} 3415, 1700,

1640, 1605, 1475, 1385, and 1165 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.70–5.70 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 3.65 (2H, m, CH_2), 4.88 (1H, m, CH), 6.03 (1H, t, J = 17 Hz, PC*H*=CH), 6.50 (1H, ddd, J = 6, 17, and 21 Hz, PCH=C*H*), 6.64 (2H, br s, D_2O exchangeable, NH_2), 7.84 (1H, s, 8-H), 10.68 (1H, br s, D_2O exchangeable, 1-H); FABMS (positive ion, thioglycerol), m/z MH^+ 318; pK_a^2 6.6. Anal. ($C_9H_{12}N_5O_6P$·1.1H_2O) H, N; C: calcd, 32.08; found, 32.49.

(*E*)-9-(2-Methylene-4-phosphonobut-3-enyl)guanine (10): obtained as a cream-colored solid in 90% yield [0.31-mmol scale, DMF solvent (6 mL)]; mp >315 °C; UV (MeOH) λ_{max} 272 (ε 7885), 255 (ε 10 890), and 233 (ε 18 400); IR (KBr) ν_{max} 3435, 1690, 1635, 1605, 1540, 1485, 1395, 1300, and 1225 cm^{-1}; ^{1}H NMR [(Me_2SO-d_6)–D_2O (1:1)] δ 4.90 (1H, br s, H_A of C=CH_2), 4.95 (2H, br s, CH_2N), 5.53 (1H, br s, H_B of C=CH_2), 6.10 (1H, dd, J = 15 and 18 Hz, PC*H*=CH), 6.92 (1H, dd, J = 18 and 21 Hz, PCH=C*H*), 7.87 (1H, s, 8-H); ^{13}C NMR (D_2O) δ 44.82 (s, CH_2N), 116.60 (s), 121.91 (s, C=CH_2), 123.22 (d, $^1J_{CP}$ = 177 Hz, P*C*=C), 140.68 (d, $^3J_{CP}$ = 22 Hz, *C*=CH_2), 140.96 (s), 141.64 (d, $^2J_{CP}$ = 5 Hz, PC=*C*), 152.33 (s), 154.65 (s), 159.70 (s); FABMS (positive ion, thioglycerol) m/z MH^+ 298. Anal. ($C_{10}H_{12}N_5O_4P$·1.3H_2O) C, H, N.

(*E*)-1-[(1-Hydroxy-4-phosphonobut-3-en-2-yl)oxy]cytosine (11): obtained as a white solid in 53% yield [0.41-mmol scale, dichloromethane–DMF (30:1) solvent (15 mL)]; mp 184–186 °C; UV (MeOH) λ_{max} 278 (ε 8564) nm; IR (KBr) ν_{max} 3340, 1735, 1675, 1525, 1290, 1185, and 1065 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.70–6.50 (>3H, br s, D_2O exchangeable, $P(OH)_2$, OH and H_2O), 3.59 (2H, m, CH_2), 4.74 (1H, m, CH), 5.61 (1H, d, J = 7 Hz, 5-H), 6.03 (1H, t, J = 17 Hz, PC*H*=CH), 6.44 (1H, ddd, J = 5, 17, and 21 Hz, PCH=C*H*), 7.34 (1H, br s, D_2O exchangeable, NH), 7.41 (1H, br s, D_2O exchangeable, NH), 7.76 (1H, d, J = 7 Hz, 6-H); FABMS (positive ion, thioglycerol) m/z MH^+ 278. Anal. ($C_8H_{12}N_3O_6P$·0.3H_2O) C, H, N.

(*E*)-1-[2-(Hydroxymethyl)-4-phosphonobut-3-enyl]cytosine Disodium Salt (12). The phosphonic acid was obtained as a gum [0.19-mmol scale, dichloromethane–DMF (5:2) solvent (14 mL)]. This material was dissolved in water and passed through a column of Dowex 50W-X8 (Na^+) resin eluting with water to afford **12** as a white solid (37.6 mg, 62%): UV (H_2O) λ_{max} 275 (ε 5080) nm; IR (KBr) ν_{max} 3400, 1720, 1660, 1530, 1490, 1400, 1160, and 1080 cm^{-1}; ^{1}H NMR [(Me_2SO-d_6)–D_2O] δ 2.62 (1H, m, CH), 3.45 (2H, m, CH_2OH), 3.62 (1H, dd, J = 8 and 13 Hz, H_A of CH_2N), 3.86 (1H, dd, J = 6 and 13 Hz, H_B of CH_2N), 5.68 (1H, t, J = 17 Hz, PC*H*=CH), 5.82 (1H, d, J = 7 Hz, 5-H), 6.10 (1H, ddd, J = 8, 17, and 19 Hz, PCH=C*H*), 7.51 (1H, d, J = 7 Hz, 6-H); FABMS (positive ion, TDE/NaCl) m/z MH^+ 320.

(*Z*)-6-Azido-9-[4-(diethoxyphosphoryl)but-3-enyl]purine (31). A mixture of **30** (0.33 g, 0.957 mmol) and sodium azide (62 mg, 0.957 mmol) in DMF (10 mL) was heated at 70 °C for 2 h. The solvent was removed and the residue was purified by column chromatography, eluting with dichloromethane–methanol (33:1, 13:1) to give **31** as a colorless gum (0.25 g, 74%): IR (KBr) ν_{max} 2980, 2130, 1640, 1495, 1440, 1405, 1370, and 1245 cm^{-1}; UV (EtOH) λ_{max} 286 (ε 6240) nm; ^{1}H NMR (Me_2SO-d_6) δ 1.09 (6H, t, J = 7 Hz, 2 × CH_3), 3.16 (2H, m, CH_2), 3.77 (4H, m, 2 × CH_2O), 4.57 (2H, t, J = 7 Hz, CH_2N), 5.70 (1H, dd, J = 13 and 19 Hz, PC*H*=CH), 6.60 (1H, ddt, J = 7, 13, and 52 Hz, PCH=C*H*), 8.65 (1H, s, 2-H/8-H), 10.14 (1H, s, 2-H/8-H); HRMS calcd for $C_{13}H_{18}N_7O_3P$ (MH^+) 352.1287, found 352.1287. Anal. ($C_{13}H_{18}N_7O_3P$·0.4H_2O) C, H, N.

(*Z*)-9-[4-(Diethoxyphosphoryl)but-3-enyl]adenine (32). To a solution of **31** (0.235 g, 0.669 mmol) in THF stirred at ambient temperature was added triphenylphosphine (0.298 g, 1.14 mmol). After 18 h, water (4 mL) was added and the solution was acidified by addition of Amberlite IR-120 (H^+) resin. The mixture was heated at 80 °C for 0.5 h, neutralized by addition of sodium bicarbonate solution, and filtered. The filtrate was evaporated, and the residue was purified by column chromatography eluting with dichloromethane–methanol (19:1, 4:1) to give **32** as a white solid (65 mg, 30%): mp 142–143 °C; UV (EtOH) λ_{max} 261 (ε 13 810) nm; IR (KBr) ν_{max} 3260, 3100, 1665, 1600, 1480, 1415, 1320, and 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7 Hz, 2 × CH_3), 3.20 (2H, m, CH_2), 4.00 (4H, qu, J = 7 Hz, 2 × CH_2O), 4.33 (2H, t, J = 7 Hz, CH_2N), 5.70 (1H, dd, J = 13 and 18 Hz, PC*H*=CH), 6.33 (2H, br s, NH_2), 6.50 (1H, ddt, J = 7, 13, and 51 Hz, PCH=C*H*), 7.97 (1H, s, 2-H/8-H), 8.37 (1H, s, 2-H/8-H); HRMS calcd for $C_{13}H_{20}N_5O_3P$ 325.1304, found 325.1303.

(*E*)-6-Azido-9-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]purine (34). A mixture of **33** (0.244 g, 0.381 mmol) and sodium azide (25 mg, 0.381 mmol) in DMF (7 mL) was heated at 70 °C for 2.8 h. The solvent was removed and the residue purified by column chromatography on silica gel eluting with acetone–hexane (1:4, 1:1) to give **34** as a gum (0.186 g, 75%): UV (EtOH) λ_{max} 282 (ε 10 363) nm; IR (film) ν_{max} 2980, 2935, 2155, 1640, 1375, 1250, and 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00–1.40 (21H, m, 2 × CH(CH_3)$_2$ and C(CH_3)$_3$), 3.05 (1H, m, CH), 3.70 (2H, m, 2 × CH_2O), 4.30–4.80 (4H, m, CH_2N and 2 × C*H*(CH_3)$_2$), 5.58 (1H, m, PC*H*=CH), 6.70 (1H, m, PCH=C*H*), 7.30–7.70 (10H, m, 2 × C_6H_5), 7.86 (0.35H, s, 2-H/8-H), 8.05 (0.65H, s, 2-H/8-H), 8.64 (0.35H, s, 2-H/8-H), 9.44 (0.65H, s, 2-H/8-H) [mixture of azido and tetrazolo tautomers[41]]; FABMS (TDE/NaCl) m/z MNa^+ 670, MH^+ 648.

(*E*)-9-[4-(Diisopropoxyphosphoryl)-2-(hydroxymethyl)but-3-enyl]adenine (36). A solution of **34** (0.32 g, 0.494 mmol) and triphenylphosphine (0.194 g, 0.741 mmol) in tetrahydrofuran (15 mL) was stirred at ambient temperature for 21 h. The solution was heated to 70 °C, and 5 M hydrochloric acid (0.258 mL, 1.29 mmol) was added. After 2 h, the solvent was removed, the crude **35** was dissolved in 3% methanolic hydrogen chloride (10 mL), and the solution was stirred at ambient temperature for 2 h. The solvent was removed, the residue was dissolved in water, and the solution was neutralized by addition of aqueous sodium bicarbonate solution. The solution was evaporated to dryness, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (9:1, 6:1) to give **36** as a white solid (0.124 g, 63%): mp 130 °C; UV (EtOH) λ_{max} 261 (ε 13 074) nm; IR (KBr) ν_{max} 3325, 2980, 1645, 1600, 1475, 1420, 1240, and 990 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.10 (12H, m, 2 × CH(CH_3)$_2$), 3.07 (1H, m, CH), 3.50 (2H, t, J = 5 Hz, CH_2O), 4.10 (1H, m, C*H*(CH_3)$_2$)), 4.27 (3H, m, CH_2N and C*H*(CH_3)$_2$), 4.99 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 5.59 (1H, dd, J = 17 and 21 Hz, PC*H*=CH), 6.52 (1H, ddd, J = 8, 17, and 22 Hz, PCH=C*H*), 7.16 (2H, br s, D_2O exchangeable, NH_2), 8.07 (1H, s, 2-H/8-H), 8.12 (1H, s, 2-H/8-H); CIMS (NH_3) 384 (MH^+). Anal. ($C_{16}H_{26}N_5O_4P$·0.5H_2O) C, H, N.

(*E*)-2,6-Diamino-9-[4-(diisopropoxyphosphoryl)but-3-enyl]purine (42). A solution of **41** (0.37 g, 0.954 mmol) in saturated ethanolic ammonia (60 mL) was heated at 100 °C in a stainless steel autoclave for 7 h. The solution was allowed to cool, and then the solvent was removed. The residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 9:1) to give **42** as a white solid (0.175 g, 50%): mp 211–213 °C; UV (MeOH) λ_{max} 256 (ε 7860) and 283 (ε 9670) nm; IR (KBr) ν_{max} 3460, 3325, 3174, 1630, 1590, 1470, 1410, and 1250 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.11 (6H, d, J = 6 Hz, 2 × CH(CH_3)), 1.17 (6H, d, J = 6 Hz, 2 × CH(CH_3)), 2.50 (2H, m, CH_2), 4.12 (2H, t, J = 7 Hz, CH_2N), 4.33 (2H, m, 2 × C*H*(CH_3)$_2$), 5.73 (2H, s, D_2O exchangeable, NH_2), 5.73 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.55 (1H, ddt, J = 7, 17, and 20 Hz, PCH=C*H*), 6.60 (2H, s, D_2O exchangeable, NH_2), 7.68 (1H, s, 8-H); HRMS calcd for $C_{15}H_{25}N_6O_3P$ 369.1804, found 369.1803.

(*E*)-2-Amino-9-[4-(diisopropoxyphosphoryl)-2-(hydroxymethyl)but-3-enyl]-6-methoxypurine (46). A solution of **45** (0.33 g, 0.473 mmol) in 7% methanolic hydrogen chloride (15 mL) was stirred at room temperature for 7 h. The solution was reduced to 1/3 volume and then neutralized by addition of saturated sodium bicarbonate solution. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 6:1) to give **46** as a colorless gum (140 mg, 72%): UV (EtOH) λ_{max} 249 (ε 8632) and 283 (ε 9086) nm; IR (KBr) ν_{max} 3335, 2980, 1610, 1585, 1475, 1410, 1400, and 1250 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.10 (12H, m, 2 × CH(CH_3)$_2$), 3.02 (1H, m, CH), 3.50 (2H, t, J = 5 Hz, CH_2O), 3.94 (3H, s, CH_3O), 4.10–4.40 (4H, m, CH_2N and 2 × C*H*(CH_3)$_2$), 4.97 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 5.61 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.43 (2H, br s, D_2O exchangeable, NH_2), 6.50 (1H, ddd, J = 8, 17, and 22 Hz, PCH=C*H*), 7.80 (1H, s, 8-H); HRMS calcd for $C_{17}H_{28}N_5O_5P$ 414.1906, found 414.1900.

(*E*)-9-[[4-(Diisopropoxyphosphoryl)but-3-enyl]oxy]adenine (49). A mixture of **48** (0.186 g, 0.370 mmol) and methylhydrazine (18 mg, 0.390 mmol) in ethanol (4 mL) was stirred at

room temperature for 1.5 h. The solvent was removed and the residue purified by column chromatography on silica gel eluting with dichloromethane–methanol (4:1) to afford **49** as a gum (0.12 g, 88%): UV (EtOH) λ_{max} 260 (ϵ 12 860) nm; IR (film) ν_{max} 3310, 3170, 2970, 1640, 1590, 1290, 1230, and 980 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.26 (12H, pseudo-t, J = 6 Hz, 2 × CH(CH_3)$_2$), 2.67 (2H, m, CH_2), 4.50 (4H, m, CH_2O and 2 × CH(CH$_3$)$_2$), 6.05 (1H, dd, J = 17 and 22 Hz, PCH=CH), 6.70 (1H, ddt, J = 6, 17, and 22 Hz, PCH=CH), 7.38 (2H, br s, NH_2), 8.14 (1H, s, 2-H/8-H), 8.36 (1H, s, 2-H/8-H); HRMS calcd for $C_{15}H_{24}N_5O_4P$ 369.1566, found 369.1568.

(*Z*)-9-[[4-(Diethoxyphosphoryl)but-3-enyl]oxy]adenine (51). A mixture of **50** (0.305 g, 0.647 mmol) and methylhydrazine (31.3 mg, 0.679 mmol) in ethanol (7 mL) was stirred at room temperature for 1.5 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 9:1) to afford **51** as a colorless gum (0.177 g, 80%): UV (EtOH) λ_{max} 260 (ϵ 13 045) nm; IR (KBr) ν_{max} 3320, 3175, 2980, 1645, 1595, 1325, 1295, and 1240 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (6H, t, J = 7 Hz, 2 × CH_3), 2.95 (2H, m, CH_2), 3.97 (4H, pseudo qu, J = 7 Hz, CH_2CH$_3$), 4.46 (2H, t, CH_2O), 5.85 (1H, dd, J = 14 and 20 Hz, PCH=CH), 6.65 (1H, ddt, J = 7, 14, and 52 Hz, PCH=CH), 7.38 (2H, br s, NH_2), 8.15 (1H, s, 2-H/8-H), 8.41 (1H, s, 2-H/8-H); HRMS calcd for $C_{13}H_{20}N_5O_4P$ 341.1253, found 341.1253. Anal. ($C_{13}H_{20}N_5O_4P$·0.3H_2O) C, H, N.

(*E*)-9-[[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(diisopropoxyphosphoryl)but-3-enyl]oxy]adenine (53). A solution of **52** (1.17 g, 1.5 mmol) in dichloromethane (25 mL) at 0 °C was treated dropwise with methylhydrazine (0.12 mL, 2.2 mmol). After the mixture was stirred at room temperature for 1 h, the solvent was removed and the residue was dissolved in acetone–hexane (1:1) (30 mL). The mixture was filtered, the solvent was removed, and the residue was purified by column chromatography on silica gel, eluting with acetone–hexane (1:1), increasing polarity to (2:1), to give **53** as a gum (0.72 g, 74%): IR (KBr) ν_{max} 3325, 3175, 2978, 2931, 2858, 2230, 1641, 1593, 1471, 1427, and 1415 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, C(CH$_3$)$_3$), 1.27 (3H, d, J = 6 Hz, CHCH_3), 1.28 (3H, d, J = 6 Hz, CHCH_3), 1.33 (6H, d, J = 6 Hz, 2 × CHCH_3), 2.92 (1H, m, CH), 3.85 (2H, m, CH_2), 4.47–4.75 (4H, m, 2 × CH(CH$_3$)$_2$ and CH_2ON), 5.69 (2H, s, D_2O exchangeable, NH_2), 5.96 (1H, ddd, J = 1, 17, and 19 Hz, PCH=CH), 6.78 (1H, ddd, J = 7, 17, and 22 Hz, PCH=CH), 7.30–7.75 (11H, m, 2 × C_6H_5, 2-H/8-H), 8.34 (1H, s, 2-H/8-H); HRMS calcd for $C_{32}H_{44}N_5O_5PSi$ 638.2928, found 638.2909.

(*E*)-9-[[4-(Diisopropoxyphosphoryl)-2-(hydroxymethyl)but-3-enyl]oxy]adenine (54). A solution of **53** (0.27 g, 0.4 mmol) in 3% methanolic hydrogen chloride (5 mL) was heated at 60 °C for 5.5 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (20:1; 10:1) to give **54** as a glass (0.14 g, 83%): IR (KBr) ν_{max} 3391, 3204, 2980, 2934, 1689, 1642, 1599, 1468, and 1400 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.23 (12H, m, 2 × CH(CH_3)$_2$), 2.87 (1H, m, CH), 3.60 (>3H, m, CH_2, D_2O exchangeable OH's), 4.55 (4H, m, 2 × CH(CH$_3$)$_2$ and CH_2ON), 6.07 (1H, ddd, J = 1, 17, and 18 Hz, PCH=CH), 6.65 (1H, ddd, J = 7, 17, and 23 Hz, PCH=CH), 7.80 (2H, s, D_2O exchangeable, NH_2), 8.23 (1H, s, 2-H/8-H), 8.46 (1H, s, 2-H/8-H); HRMS calcd for $C_{16}H_{26}N_5O_5P$ (MH^+) 400.1750, found 400.1750. Anal. ($C_{16}H_{26}N_5O_5P$·0.85$CHCl_3$) C, H, N.

(*E*)-9-[[4-(Diisopropoxyphosphoryl)-1-hydroxybut-3-en-2-yl]oxy]adenine (57). A solution of **55** (0.251 g, 0.39 mmol) and methylhydrazine (18 mg, 0.39 mmol) in ethanol (5 mL) was stirred at room temperature for 1 h. The solvent was removed, and the residue of crude (*E*)-9-[[1-[(*tert*-butyldimethylsilyl)oxy]-4-(diisopropoxyphosphoryl)but-3-en-2-yl]oxy]adenine (**56**) was used without further purification.

A solution of crude **56** (~0.39 mmol) in 5% methanolic hydrogen chloride was stirred at room temperature for 3 h. The solution was neutralized using saturated aqueous sodium bicarbonate solution. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with ethyl acetate–methanol (20:1, 5:1) to give **57** as a colorless gum (0.121 g, 62%): UV (EtOH) λ_{max} 260 (ϵ 14 650) nm; IR (KBr) ν_{max} 3325, 1645, 1595, 1295, 1240, and 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (12H, m, 2 × CH(CH_3)$_2$), 3.80 (2H, m, CH_2), 4.69 (2H, m, 2 × CH(CH$_3$)$_2$), 4.87 (1H, m, CH), 5.48 (1H, br s, OH), 5.82 (2H, br s, NH_2), 6.14 (1H, t, J = 17 Hz, PCH=CH), 6.80 (1H, ddd, J = 6, 17, and 22 Hz, PCH=CH), 7.91 (1H, s, 2-H/8-H), 8.35 (1H, s, 2-H/8-H); CIMS (NH_3) m/z MH^+ 386. Anal. ($C_{15}H_{24}N_5O_5P$·0.5H_2O) C, H, N.

(*E*)-9-[[4-(Diisopropoxyphosphoryl)-2-(hydroxymethyl)but-3-enyl]oxy]guanine (62). A solution of **61** (0.45 g, 0.5 mmol) in ethanol (10 mL) and 5 M hydrochloric acid (1 mL, 5 mmol) was heated under reflux for 4.5 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with chloroform–methanol (10:1) to give **62** as a solid (0.16 g, 74%): IR (KBr) ν_{max} 3381, 3160, 2981, 2935, 2751, 1685, 1632, 1596, and 1472 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (12H, m, 2 × CH(CH_3)$_2$), 2.82 (1H, m, CH), 3.57 (2H, m, CH_2), 4.30–4.60 (4H, m, 2 × CH(CH$_3$)$_2$ and CH_2ON), 4.91 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 6.00 (1H, ddd, J = 1, 17, and 18 Hz, PCH=CH), 6.65 (3H, m, D_2O exchangeable, NH_2 and PCH=CH), 7.87 (1H, s, 8-H), 10.69 (1H, s, D_2O exchangeable, 1-H); FABMS (positive ion, thioglycerol) m/z MH^+ 416, MNa^+ 438.

(*E*)-2-Amino-6-chloro-9-[4-(diisopropoxyphosphoryl)-2-methylenebut-3-enyl]purine (64). A mixture of 2-amino-6-chloropurine (**40**) (0.115 g, 0.678 mmol), **39** (0.33 g, 0.678 mmol), and potassium carbonate (141 mg, 1.02 mmol) in DMF (10 mL) was heated at 70 °C for 16 h. The solvent was removed, and the residue was purified by column chromatography eluting with dichloromethane–methanol (19:1, 9:1) to give **64** as a gum (0.13 g, 48%): UV (EtOH) λ_{max} 310 (ϵ 7920), 238 (ϵ 8680), and 223 (ϵ 42 330) nm; IR (KBr) ν_{max} 3320, 3210, 2980, 1610, 1560, 1520, 1470, 1410, 1385, 1375, and 1240 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.17 (6H, d, J = 6 Hz, 2 × CHCH_3), 1.22 (6H, d, J = 6 Hz, 2 × CHCH_3), 4.46 (2H, m, CH(CH$_3$)$_2$), 4.92 (2H, br s, CH_2N), 5.06 (1H, br s, H_A of C=CH_2), 5.66 (1H, br s, H_B of C=CH_2), 6.08 (1H, t, J = 17 Hz, PCH=CH), 6.97 (2H, br s, D_2O exchangeable, NH_2), 7.04 (1H, dd, J = 17 and 23 Hz, PCH=CH), 8.11 (1H, s, 8-H); HRMS calcd for $C_{16}H_{23}ClN_5O_3P$ 399.1226, found 399.1225.

(*E*)-1-[[4-(Diisopropoxyphosphoryl)-1-hydroxybut-3-en-2-yl]oxy]cytosine (67). A solution of **66** (0.382 g, 0.66 mmol) in 5% methanolic hydrogen chloride (13 mL) was stirred at room temperature for 66 h. The solution was reduced to half volume and neutralized using saturated sodium bicarbonate solution. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (9:1, 4:1) to give **67** as a hygroscopic white solid (0.170 g, 71%): mp 70–75 °C; UV (EtOH) λ_{max} 276 (ϵ 6100) nm; IR (KBr) ν_{max} 3395, 3190, 2980, 1645, 1485, 1375, and 1235 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.20 (12H, m, 2 × CH(CH_3)$_2$), 3.60 (2H, m, CH_2), 4.47 (2H, m, 2 × CH(CH$_3$)$_2$), 4.82 (1H, m, CH), 5.17 (1H, t, J = 6 Hz, D_2O exchangeable, OH), 5.57 (1H, d, J = 7 Hz, 5-H), 6.10 (1H, pseudo-t, J = 19 Hz, PCH=CH), 6.63 (1H, ddd, J = 7, 17, and 22 Hz, PCH=CH), 7.18 (1H, br s, D_2O exchangeable, NH), 7.24 (1H, br s, D_2O exchangeable, NH), 7.77 (1H, d, J = 7 Hz, 6-H); CIMS (NH_3) m/z MH^+ 362. Anal. ($C_{14}H_{24}N_3O_6P$·1.0H_2O) C, H, N.

(2,2-Dimethyl-1,3-dioxan-5-yl)methyl Methanesulfonate (69). To a solution of (2,2-dimethyl-1,3-dioxan-5-yl)methanol[16] (5.75 g, 39.3 mmol) and triethylamine (5.97 g, 59.0 mmol) in dichloromethane (90 mL) stirred at −5 °C under dry nitrogen was added methanesulfonyl chloride (5.40 g, 47.2 mmol) dropwise, maintaining the internal temperature <0 °C. The resulting mixture was stirred at 0 °C for 1 h before being washed with 0.5 M hydrochloric acid (40 mL) and saturated aqueous sodium bicarbonate solution (40 mL). The solution was dried ($MgSO_4$), and the solvent was removed to leave 8.49 g (96%) of **69** as a colorless oil which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, s, CH_3), 1.47 (3H, s, CH_3), 2.07 (1H, m, CH), 3.07 (3H, s, SO_2CH_3), 3.67–4.20 (4H, m, 2 × CH_2), 4.42 (2H, d, J = 7 Hz, CH_2OS).

1-[(2,2-Dimethyl-1,3-dioxan-5-yl)methyl]cytosine (70). A mixture of cytosine (4.19 g, 37.7 mmol), **69** (8.45 g, 37.7 mmol), and cesium carbonate (14.74 g, 45.2 mmol) in DMF (100 mL) was heated at 90 °C for 18 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 4:1) to afford **70** as a pale yellow solid (3.94 g, 44%) along with O^2-[(2,2-dimethyl-1,3-dioxan-5-yl)methyl]cytosine (**71**) as a pale yellow gum (2.12

g, 23%). For **70**: mp 243–246 °C; UV (MeOH) λ_{max} 275 (ϵ 7800) nm; IR (KBr) ν_{max} 3345, 3110, 1660, 1655, 1485, 1380, 1245, 1195, and 1070 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.32 (3H, s, CH_3), 1.33 (3H, s, CH_3), 2.04 (1H, m, CH), 3.51 (2H, dd, J = 6.2 and 12.0 Hz, 2 × H_{ax}), 3.83 (2H, dd, J = 3.9 and 12.0 Hz, 2 × H_{eq}), 3.70 (2H, d, J = 7.3 Hz, CH_2N), 5.64 (1H, d, J = 7.2 Hz, 5-H), 7.00 (2H, br s, NH_2), 7.48 (1H, d, J = 7.2 Hz, 6-H); ^{13}C NMR (Me_2SO-d_6) δ 23.6 (CH_3), 24.1 (CH_3), 33.2 (CH), 48.1 (CH_2N), 61.0 (2 × CH_2O), 93.1 (5-C), 97.4 ($C(CH_3)_2$), 146.3 (6-C), 155.9 (2-C), 165.9 (4-C); HRMS calcd for $C_{11}H_{17}N_3O_3$ (MH^+) 240.1348, found 240.1349. Anal. ($C_{11}H_{17}N_3O_3$) C, H, N. For **71**: UV (MeOH) λ_{max} 228 (ϵ 7655) nm, 272 (ϵ 6360) nm; IR (film) ν_{max} 3335, 3205, 3000, 1640, 1590, 1555, 1415, 1365, 1295, 1250, 1200, 1155, 1090, and 1040 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 2.01 (1H, m, CH), 3.71 (2H, dd, J = 6.3 and 11.8 Hz, 2 × H_{ax}), 3.94 (2H, dd, J = 4.1 and 11.8 Hz, 2 × H_{eq}), 4.18 (2H, d, J = 7.1 Hz, CH_2O), 6.08 (1H, d, J = 5.7 Hz, 5-H), 6.83 (2H, br s, NH_2), 7.85 (1H, d, J = 5.7 Hz, 6-H); ^{13}C NMR (Me_2SO-d_6) δ 23.7 (CH_3), 24.0 (CH_3), 33.4 (CH), 60.5 (2 × CH_2O), 64.5 (CH_2O), 97.3 ($C(CH_3)_2$), 99.4 (5-C), 156.2 (6-C), 164.7 (2-C), 165.3 (4-C); HRMS calcd for $C_{11}H_{17}N_3O_3$ (MH^+) 240.1348, found 240.1348. Anal. ($C_{11}H_{17}N_3O_3$) C, H; N: calcd, 17.56; found, 16.85.

1-[3-Hydroxy-2-(hydroxymethyl)prop-1-yl]cytosine (72). A solution of **70** (3.15 g, 13.16 mmol) in 5% methanolic hydrogen chloride (87 mL) was stirred at ambient temperature for 1.25 h before the solution was neutralized by addition of saturated aqueous sodium bicarbonate solution. The solution was evaporated to dryness, and the residue was partially purified by column chromatography on silica gel eluting with dichloromethane–methanol (1:1) gradually increasing polarity to methanol. The product (which contained sodium chloride) was further purified by column chromatography on C_{18} reverse-phase silica gel eluting with water to afford **72** as a white solid (2.3 g, 88%): mp 204–206 °C; UV (MeOH) λ_{max} 275 (ϵ 7860); ^1H NMR (Me_2SO-d_6) δ 1.87 (1H, m, CH), 3.32 (4H, partially obscured by H_2O, d upon D_2O exchange, J = 6 Hz, 2 × CH_2OH), 3.62 (2H, d, J = 7 Hz, CH_2N), 4.55 (2H, t, J = 5 Hz, D_2O exchangeable, 2 × OH), 5.65 (1H, d, J = 7 Hz, 5-H), 7.00 (2H, br s, D_2O exchangeable, NH_2), 7.49 (1H, d, J = 7 Hz, 6-H); FABMS (positive ion, thioglycerol) m/z MH^+ 200. Anal. ($C_{18}H_{13}N_3O_3 \cdot 0.2H_2O$) C, H, N.

N^3-Acetyl-1-[3-hydroxy-2-(hydroxymethyl)prop-1-yl]cytosine (73). To a solution of **72** (2.17 g, 10.89 mmol) in methanol (225 mL) heated under reflux was added acetic anhydride (2.45 g, 24.0 mmol). After 0.5 and 1.0 h two further portions of acetic anhydride (2.17 g, 10.89 mmol) were added. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 5:1) to afford **73** as a white solid (1.74 g, 66%): mp 157–159 °C; UV (MeOH) λ_{max} 216 (ϵ 17 770), 247 (ϵ 14 155), 300 (ϵ 7065) nm; IR (KBr) ν_{max} 3410, 1720, 1705, 1655, 1630, 1565, 1495, 1435, 1375, 1335, 1305, 1245, 1230, and 1180 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.96 (1H, m, CH), 2.09 (3H, s, CH_3), 3.38 (4H, t, J = 5 Hz, collapsing to d upon D_2O exchange, 2 × CH_2OH), 3.79 (2H, d, J = 7 Hz, CH_2N), 4.54 (2H, t, J = 5 Hz, D_2O exchangeable, 2 × OH), 7.13 (1H, d, J = 7 Hz, 5-H), 7.99 (1H, d, J = 7 Hz, 6-H), 10.79 (1H, s, D_2O exchangeable, NH); CIMS (NH_3) m/z MH^+ 242. Anal. ($C_{10}H_{15}N_3O_4$) C, H, N.

N^3-Acetyl-1-[3-hydroxy-2-[[(4-methoxyphenyl)diphenylmethoxy]methyl]prop-1-yl]cytosine (74). To a solution of **73** (1.84 g, 7.63 mmol) and triethylamine (1.08 g, 10.7 mmol) in DMF (25 mL) stirred at ambient temperature was added (4-methoxyphenyl)chlorodiphenylmethane (3.06 g, 9.91 mmol). The solution was stirred for 1 h. The solvent was removed, and the residue was purified by column chromatography on silica eluting with dichloromethane–methanol (39:1; 19:1) to afford **74** as a white solid (2.26 g, 58%): mp 110–120 °C; UV (EtOH) λ_{max} 206 (ϵ 57 770), 236 (ϵ 20 405), 302 (ϵ 6385) nm; IR (KBr) ν_{max} 3440, 1720, 1655, 1560, 1490, 1370, 1305, 1250, 1220, and 1180 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.09 (3H, s, CH_3), 2.25 (1H, m, CH), 3.00 (2H, m, CH_2O), 3.45 (2H, m, CH_2O), 3.73 (3H, s, CH_3O), 3.82 (2H, d, J = 7 Hz, CH_2N), 4.63 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 6.87 (1H, d, J = 9 Hz, 2 of C_6H_4), 6.99 (1H, d, J = 7 Hz, 5-H), 7.19 (1H, d, J = 9 Hz, 2 of C_6H_4), 7.33 (10H, m, 2 × C_6H_5), 7.76 (1H, d, J = 7 Hz, 6-H), 10.76 (1H, s, D_2O exchangeable, NH); HRMS calcd for $C_{30}H_{31}N_3O_5$ (MH^+) 514.2342, found 514.2333.

(*E*)-N^3-Acetyl-1-[4-(diphenoxyphosphoryl)-2-[[(4-methoxyphenyl)diphenylmethoxy]methyl]but-3-enyl]cytosine (75). To a solution of **74** (1.13 g, 2.20 mmol) and dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) in anhydrous DMSO (10 mL) was added dichloroacetic acid (0.1 mL). The mixture was stirred at ambient temperature for 1 h before being cooled to 0 °C. A solution of oxalic acid dihydrate (1.11 g, 8.80 mmol) in methanol (6 mL) was added, and the mixture was stirred at ambient temperature for 0.5 h. The mixture was filtered, and the methanol was removed under reduced pressure before the residue was partitioned between saturated aqueous sodium chloride solution (100 mL) and dichloromethane (100 mL, 2 × 50 mL). The combined organic portions were dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in anhydrous DMSO, and diphenyl[(triphenylphosphoranylidene)methyl]phosphonate[42] (1.12 g, 2.20 mmol) was added. The mixture was heated at 80 °C for 18 h. The solvent was removed, and the residue was partially purified by column chromatography on silica gel eluting with acetone–hexane (3:2). The product was further purified by column chromatography on silica gel eluting with dichloromethane–methanol (39:1, 19:1) to afford **75** as a gum (0.178 g, 21%): ^1H NMR ($CDCl_3$) δ 2.20 (3H, s, CH_3), 3.05 (1H, m, CH_2O), 3.15 (1H, m, CH), 3.30 (1H, m, CH_2O), 3.77 (3H, s, CH_3O), 4.00 (2H, m, CH_2N), 6.05 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.75–7.40 (27 H, m, PCH=C*H*, 5-H, 6-H, C_6H_4 and 4 × C_6H_5), 9.10 (1H, br s, NH); FABMS (positive ion, TDE/NaCl) m/z MH^+ 742, MNa^+ 764.

(*E*)-1-[4-(Diphenoxyphosphoryl)-2-(hydroxymethyl)but-3-enyl]cytosine (76). A solution of **75** (0.178 g, 0.234 mmol) in 5% methanolic hydrogen chloride (10 mL) was stirred at ambient temperature for 1.8 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (19:1, 4:1) to afford **76** as a hygroscopic white solid (0.10 g, 97%): UV (EtOH) λ_{max} 276 nm; ^1H NMR (Me_2SO-d_6) δ 2.87 (1H, m, CH), 3.20–3.50 (2H, m, partially obscured by H_2O, CH_2OH), 3.76 (2H, m, CH_2N), 4.90 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 5.58 (1H, d, J = 7 Hz, 5-H), 6.10 (1H, dd, J = 17 and 23 Hz, PC*H*=CH), 6.85 (1H, ddd, J = 7, 17, and 23 Hz, PCH=C*H*), 7.00 (1H, br s, D_2O exchangeable, NH), 7.10 (1H, br s, D_2O exchangeable, NH), 7.10–7.50 (11H, m, 6-H and 2 × C_6H_5); HRMS calcd for $C_{21}H_{22}N_3O_5P$ (MH^+) 428.1375, found 428.1380.

(*E*)-1-[2-(Hydroxymethyl)-4-(dimethoxyphosphoryl)but-3-enyl]cytosine (77). A mixture of **76** (98 mg, 0.229 mmol) and cesium fluoride (0.217 g, 1.43 mmol) in methanol (40 mL) was stirred at ambient temperature for 24 h. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with dichloromethane–methanol (9:1, 3:1) to afford **77** as a gum (58 mg, 83%): ^1H NMR (Me_2SO-d_6) δ 2.80 (1H, m, CH), 3.45 (2H, m, CH_2OH), 3.53 (3H, d, J = 6 Hz, CH_3), 3.57 (3H, d, J = 6 Hz, CH_3), 3.75 (2H, m, CH_2N), 4.87 (1H, t, J = 5 Hz, D_2O exchangeable, OH), 5.62 (1H, d, J = 7 Hz, 5-H), 5.70 (1H, dd, J = 17 and 20 Hz, PC*H*=CH), 6.60 (1H, ddd, J = 7, 17, and 22 Hz, PCH=C*H*), 6.90 (1H, br s, D_2O exchangeable, NH), 7.05 (1H, br s, D_2O exchangeable, NH), 7.50 (1H, d, J = 7 Hz, 6-H).

Acknowledgment. We thank Mr. M. R. Boyd and Dr. D. N. Planterose and their colleagues for antiviral data, Dr. S. C. Connor for NMR studies, Mr. C. J. Salter for pK_a data, and Dr. A. G. Brown for his support of this work.

References

(1) De Clercq, E.; Holý, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. A Novel Selective Broad-Spectrum Anti-DNA Virus Agent. *Nature* **1986**, *323*, 464–467.

(2) Votruba, I.; Bernaerts, R.; Sakuma, T.; De Clercq, E.; Merta, A.; Rosenberg, I.; Holý, A. Intracellular Phosphorylation of Broad-Spectrum Anti-DNA Virus Agent (*S*)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine and Inhibition of Viral DNA Synthesis. *Mol. Pharmacol.* **1988**, *32*, 524–529.

(3) Merta, A.; Votruba, I.; Rosenberg, I.; Otmar, M.; Hřebabecký, H.; Bernaerts, R.; Holý, A. Inhibition of Herpes Simplex Virus DNA Polymerase by Diphosphates of Acyclic Phosphonylmethoxyalkyl Nucleotide Analogues. *Antiviral Res.* **1990**, *13*, 209–218.

(4) Balzarini, J.; Hoa, Z.; Herdewijn, P.; Johns, D. G.; De Clercq, E. Intracellular Metabolism and Mechanism of Anti-Retrovirus Action of 9-(2-Phosphonylmethoxyethyl)adenine, a Potent Anti-Human Immunodeficiency Virus Compound. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1499–1503.
(5) De Clercq, E.; Sakuma, T.; Baba, M.; Pauwels, R.; Balzarini, J.; Rosenberg, I.; Holý, A. Antiviral Activity of Phosphonylmethoxyalkyl Derivatives of Purine and Pyrimidines. *Antiviral Res.* **1987**, *8*, 261–272.
(6) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R.; Martin, J. C. Synthesis and Antiviral Activity of the Nucleotide Analogue (*S*)-1-[3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine. *J. Med. Chem.* **1989**, *32*, 1457–1463.
(7) (a) Duckworth, D. M.; Harnden, M. R.; Perkins, R. M.; Planterose, D. N. 9-[2-(Phosphonomethoxy)alkoxy]purines, A New Series of Antiviral Acyclonucleotides. *Nucleosides Nucleotides* **1991**, *10*, 427–430. (b) Duckworth, D. M.; Harnden, M. R.; Perkins, R. M.; Planterose, D. N. Antiviral 9-[2-(phosphonomethoxy)alkoxy]purines. *Antiviral Chem. Chemother.* **1991**, *2*, 229–241.
(8) Perkins, R. M.; Patience, C.; Ashton, R. J.; Love, S.; Barnes, K.; Jenkins, O.; Donker, G.; Reynolds, K.; Elphick, L. M.; Planterose, D. N.; Kenig, M. D.; Darlison, S. J.; Vere Hodge, R. A.; Duckworth, D. M.; Serafinowska, H. T.; Harnden, M. R.; Weiss, R. A.; Brown, A. G. 9-[2-(Phosphonomethoxy)ethoxy]adenine, BRL 47923, A Potent and Selective Inhibitor of HIV Replication. *J. Cell. Biochem., Suppl. 16E* **1992**, 86.
(9) Kim, C. U.; Luh, B. Y.; Martin, J. C. A Novel Synthesis of 1-Oxa-HPMPA: A Potent Antiviral Agent Against Herpesviruses. *Tetrahedron Lett.* **1992**, *33*, 25–28.
(10) Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979; p 52.
(11) Blackburn, G. M. *Chem. Ind.* **1981**, 134–138.
(12) Kim, C. U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. Acyclic Purine Phosphonate Analogues as Antiviral Agents. Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1990**, *33*, 1207–1213.
(13) Hampton, A.; Kappler, F.; Perini, F. Evidence for the Conformation About the C(5′)-O(5′) Bond of AMP Complexed to AMP Kinase. *Bioorg. Chem.* **1976**, *5*, 31–35.
(14) During the course of this work some 2-alkenyl- and 1,3-dienylphosphonic acid analogues of acyclonucleotides have been reported: (a) Phadtare, S.; Zemlicka, J. Unsaturated Analogues of Acyclic Nucleoside Phosphonates: An Unusual Arbusov Reaction with Unactivated Triple Bond. *Nucleosides Nucleotides* **1991**, *10*, 275–278. (b) Screenivasulu, M.; Phadtare, S.; Zemlicka, J. Unsaturated Phosphonates as Acyclic Nucleotide Analogues. Anomalous Michaelis-Arbusov and Michaelis-Becker Reactions with Multiple Bond Systems. *J. Org. Chem.* **1992**, *57*, 2320–2327.
(15) (a) For a recent review see: Maryanoff, B. E.; Reitz, A. B. The Wittig Olefination Reaction and Modifications Involving Phosphoryl-Stabilized Carbanions. Stereochemistry, Mechanism and Selected Synthetic Applications. *Chem. Rev.* **1989**, *89*, 863–927. (b) For a recent review, see: Ager, D. J. The Peterson Olefination Reaction. *Org. React.* **1990**, *38*, 1–223.
(16) Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. Synthesis and Antiviral Activity of 9-Alkoxypurines. 1. 9-(3-Hydroxypropoxy)- and 9-[3-Hydroxy-2-(hydroxymethyl)propoxy]purines. *J. Med. Chem.* **1990**, *33*, 187–196.
(17) Paulsen, H.; Bartsch, W. Phosphorus-Containing Carbohydrates. XII. Preparation of Olefinic Sugar Phosphonates and Allenic Sugar Phosphonates. *Chem. Ber.* **1975**, *108*, 1732–1744.
(18) Gupta, A.; Sacks, K.; Khan, S.; Tropp, B. E.; Engel, R. An Improved Synthesis of Vinylic Phosphonates from Ketones. *Synth. Commun.* **1980**, *10*, 299–304.
(19) Zyablikova, T. A.; Il'yasov, A. V.; Mukhametzyanova, E. K.; Shermergorn, I. M. Synthesis and Investigation of the PMR Spectra of β-Substituted Vinylphosphonates. *J. Gen. Chem. USSR (Engl. Transl.)* **1982**, *52*, 249–252.
(20) Carey, F. A.; Court, A. S. Silicon-Containing Carbanions. I. Synthesis of Vinyl Thioethers and Vinylphosphonates via Silicon-Modified Organolithium Reagents. *J. Org. Chem.* **1972**, *37*, 939–943.
(21) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1–28.
(22) Iwakawa, M.; Pinto, B. M.; Szarek, W. A. Synthetic Routes to Nucleoside Analogues of N-Substituted 1,3-Thiazolidines. *Can. J. Chem.* **1978**, *56*, 326–335.
(23) Vaultier, M.; Knouzi, N.; Carrie, R. Reduction of Azides to Primary Amines by a General Method Using the Staudinger Reaction. *Tetrahedron Lett.* **1983**, *24*, 763–764.
(24) Harnden, M. R.; Wyatt, P. G. Synthesis of 9-Hydroxypurines: Intermediates to Novel Antiviral Acyclonucleosides. *Tetrahedron Lett.* **1990**, *31*, 2185–2188.
(25) Midgley, J. M.; Millership, J. S.; Whalley, W. B. The Chemistry of Fungi. Part LXXVII. The Trimethylsilyloxy-substituent as a Leaving Group. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1384–1385.
(26) Parkin, A. Analogues of Acyclonucleoside Diphosphates. The Synthesis of a Series of Diphosphonate Derivatives of Pyrimidines and Purines. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2983–2990.
(27) Jenny, T. F.; Previsani, N.; Benner, S. A. Carbocyclic Analogues of Nucleosides via Modified Mitsunobu Reactions. *Tetrahedron Lett.* **1991**, *32*, 7029–7032.
(28) Martin, J. C.; Verheyden, J. P. H. Synthesis of 4′-(Hydroxymethyl)-guanosine and a Phosphonate Analogue of Guanylic Acid. *Nucleosides Nucleotides* **1988**, *7*, 365–374.
(29) Prisbe, E. J.; Martin, J. C.; McGee, D. P. C.; Barker, M. F.; Smee, D. F.; Duke, A. E.; Matthews, T. R.; Verheyden, J. P. H. Synthesis and Antiherpes Virus Activity of Phosphate and Phosphonate Derivatives of 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine. *J. Med. Chem.* **1986**, *29*, 671–675.
(30) Jones, G. H.; Moffatt, J. G. The Synthesis of 6′-Deoxyhomonucleoside-6′-phosphonic Acids. *J. Am. Chem. Soc.* **1968**, *90*, 5337–5338.
(31) Lejczak, B.; Kafarski, P.; Szewczyk, J. Transesterification of Diphenyl Phosphonates using the Potassium Fluoride/Crown Ether/Alcohol System; Part 2. The Use of Diphenyl 1-Aminoalkanephosphonates in Phosphonopeptide Synthesis. *Synthesis* **1982**, 412–414.
(32) Serafinowska, H. T., SmithKline Beecham Pharmaceuticals. Unpublished results.
(33) Pauwels, R.; Balzarini, J.; Schols, D.; Baba, M.; Desmyter, J.; Rosenberg, I.; Holý, A.; De Clercq, E. Phosphonylmethoxyethyl Purine Derivatives, a New Class of Anti-Human Immunodeficiency Virus Agents. *Antimicrob. Agents Chemother.* **1988**, 1025–1030.
(34) Kreider, J. W.; Balogh, K.; Olson, R. O.; Martin, J. C. Treatment of Latent Rabbit and Human Papillomavirus Infections with 9-(2-Phosphonylmethoxy)ethylguanine (PMEG). *Antiviral Res.* **1990**, *14*, 51–58.
(35) Rose, W. C.; Crosswell, A. R.; Bronson, J. J.; Martin, J. C. In Vitro Antitumor Activity of 9-[(2-Phosphonylmethoxy)ethyl]guanine and Related Phosphonate Nucleotide Analogues. *J. Nat. Cancer Inst.* **1990**, *82*, 510–512.
(36) Boyd, M. R.; Bacon, T. H.; Sutton, D.; Cole, M. Antiherpesvirus Activity of 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanine (BRL 39123) in Cell Culture. *Antimicrob. Agents Chemother.* **1987**, *31*, 1238–1242.
(37) Harnden, M. R.; Jennings, L. J. Antiviral 9-[2-(Phosphonomethylthio)alkoxy]purines. *Antimicrob. Agents Chemother.* In press.
(38) Harnden, M. R.; Jarvest, R. L. Synthesis of (9-Hydroxyalkylamino)-guanines, Novel Antiviral Acyclonucleosides. *Tetrahedron Lett.* **1988**, *29*, 5995–5998.
(39) Gilbert, A. R. Organosilicon Compounds Containing Phosphorus. U.S. Patent 2,768,193; 1956; *Chem. Abstr.* **1957**, *51*, 5816h.
(40) Bowles, W. A.; Schneider, F. H.; Leland, R. L.; Robins, R. K. Synthesis and Antitumor Activity of 9-(Tetrahydro-2-furanyl)purine Analogues of Biologically Important Deoxynucleosides. *J. Med. Chem.* **1963**, *6*, 471–480.
(41) Temple, C.; Kussner, C. L.; Montgomery, J. A. Studies on the Azidoazomethine-Tetrazole Equilibrium. *J. Org. Chem.* **1966**, *31*, 2210–2215.
(42) Jones, G. H.; Hamamura, E. K.; Moffatt, J. G. A New Wittig Reagent Suitable for the Synthesis of α,β-Unsaturated Phosphonates. *Tetrahedron Lett.* **1968**, 5731–5734.