in the range -18.4° to -12.7° with the exception of the cAMP case mentioned above. In the solid state, intermolecular association may play a role more important than the dipole–dipole interactions between the 2'-OH and the base proposed to be the factor that determines ribose ring conformation in solution.[36]

Conformation of Nucleobases and Intramolecular Association. Since the interest of this paper is in the conformations of the phosphate and ribose rings of nucleoside cyclic 3',5'-monophosphates and derivatives thereof, we have not complied available information on the conformations of the nucleobases with regard to C(1')–N rotation, i.e., the glycosyl torsion angle. Comparisons of glycosyl torsion angles for the diesters (**1**, **2**, **5**–**9**) of Table I can be found in refs 15 and 17. Glycosyl torsion angles for **10**–**19** show no evident systematic correlation with phosphorus configuration. The related question of the nature of intramolecular interactions in the solid state, which can involve H bonding between nucleobases and also nucleobase–phosphate oxyanion interactions, has not been addressed.

Conclusions

X-ray crystal structure data for nucleoside cyclic 3',5'-monophosphates and their derivatives with substituents on phosphorus either trans and cis to the heterocyclic base have been compared. The six-membered, phosphorus-containing, 1,3,2-dioxaphosphorinane rings lack the mirror symmetry of the simple, monocyclic analogues. This is clearly shown by certain dihedral and bond angles involving atoms endocyclic to the ring. The dihedral angles ω and ω' show that the 1,3,2-dioxaphosphorinane rings that are derivatized at phosphorus to form triesters, phosphoramidates, and methylphosphonates are more flattened about phosphorus than are the anionic, nucleoside cyclic 3',5'-monophosphate diesters. This is also revealed by comparisons of the bond angles P–O(3')–C(3') and P–O(5')–C(5'). Moreover, the neutral derivatives with substituents axial on phosphorus are more flattened about phosphorus than are those with equatorial substituents on phosphorus. This is most clearly revealed by the torsion angles ω and ω'. These findings, along with effects on the P–O(3') and P–O(5') bond distances seen in comparing all three types of 1,3,2-dioxaphosphorinanes can be understood in terms of two effects: (1) the greater repulsive steric interactions of axial P–Z compared to axial P=O and (2) variations in the degree of n/σ^* stabilization involving the higher energy, p-orbital electron lone pair on oxygen and the axial P–Z or P=O antibonding σ orbital. Both cis and trans neutral derivatives (**8**–**17**) display effects of a greater n/σ^*, anomeric-effect-like stabilization than do the negatively charged anionic diesters. Moreover, the n/σ^* stabilization involving the O(5') lone pair and the larger P–O–C angle (P–O(5')–C(5')) is greater than that for the O(3') lone pair. Furthermore, the repulsive 1,3-syn axial repulsions between axial P–Z are almost certainly greater for H(3') than for H(5') as the former is closer to Z in the distorted chair **3**. These two structural features are distinctive for the cyclic nucleotide-based derivatives as compared to the symmetrical monocyclic 1,3,2-dioxaphosphorinanes. The results in the cyclic nucleotide systems are generally consistent with what was delineated earlier for highly symmetrical, simple, monocyclic 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes.[9] However, not all of the well-correlated bond distance and bond angle differences between P=O axial and P=O equatorial isomers for the simple monocyclic neutral derivatives were found for the cyclic nucleotide based molecules. The majority of the bond length and angle correlations found for monocyclic 2-oxo-1,3,2-dioxaphosphorinanes, and predicted by the previously reported ab initio calculations,[9a] were also revealed in the present study by calculations at the semiempirical MNDO level.

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Photo-Arbuzov Rearrangement Route to Acyclic Nucleoside Benzylphosphonates

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The recently discovered photo-Arbuzov rearrangement was carried out with a series of *tert*-butyldimethylsilyl-protected dimethyl benzyl phosphites, **9**, **15**, **18**, **20**, and **22**, easily derived from alcohol precursors, to afford the corresponding dimethyl benzylphosphonates in 67–74% isolated yields. One of the phosphonates, **10**, was further converted to the primary bromide which underwent reaction with the sodium salts of adenine, cytosine, and 2-amino-6-chloropurine to give the desired N-alkylated acyclic nucleoside dimethyl benzylphosphonates. The 2-amino-6-chloro compound was further elaborated to the guaninyl and 2,6-diamino derivatives. Demethylation afforded the acyclic nucleoside-based benzylphosphonic acids **25**, **27**, **29**, **31**, and **32** in good overall yields. These molecules are closely related structurally to the active antiviral 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) and the potent human erythrocyte purine nucleoside phosphorylase (PNP) inhibitors 9-(5-phosphonopentyl)guanine and 9-(5,5-difluoro-5-phosphonopentyl)guanine.

Acyclic nucleosides have been shown in recent years to have considerable potential as antiviral agents.[1] Amongst key advances in this area has been the discovery of the potent, selective antiherpes activity of 9-[(2-hydroxyeth-

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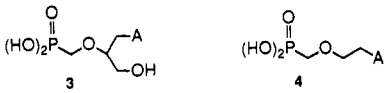
oxy)methyl]guanine (acyclovir), **1**, in clinical use for several years and of the structurally related antiviral 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, ganciclovir), **2**, recently approved for clinical use. DHPG is especially effective against human CMV (cytomegalovirus) infections.[2]

The first step in the activation of many acyclic nucleoside antivirals is their selective monophosphorylation by a virally induced kinase. Mutation, however, may render the kinase inactive toward the antiviral and the virus drug resistant. Consequently, isosteric and sometimes isoelectronic *phosphonate* analogues have been synthesized. These phosphate substitutes are not rapidly metabolized by the rapid dephosphorylation to which monophosphates are subject.

Examples of phosphonates of widespread current interest[3] are the phosphonomethyl derivatives (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine (HPMPA), **3**, and 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA), **4**, and their congeners containing other purine and pyrimidine bases. These phosphonic acids have shown promising activities against a broad spectrum of viruses including HIV.[3] Very recent work[4] has suggested that a

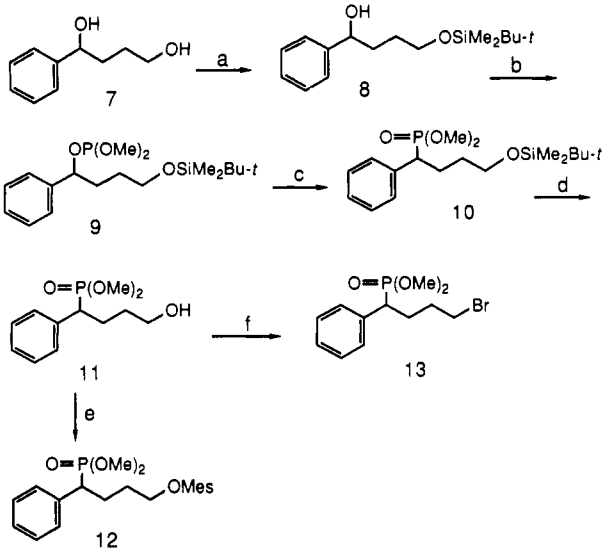


mechanism of active membrane transport is operative with **4**.

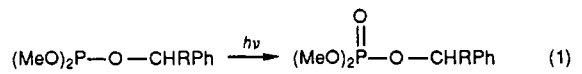
Acyclic nucleoside-based phosphonates also have been found to be "multisubstrate" inhibitors of purine nucleoside phosphorylase (PNP).[5-7] Examples are 9-(5-phosphonopentyl)guanine, **5**,[6] and its 5,5-difluoro analogue, **6**,[7] which inhibit human erythrocyte PNP. PNP is a key enzyme in the purine salvage pathway. Its inhibition has been targeted for the control of metabolic disorders leading to disease and as an effective way to maximize the efficacies of drugs.

Recently, the efficient photorearrangement of benzyl phosphites to benzylphosphonates was reported by this laboratory.[8] This reaction, a kind of intramolecular, photo-Arbuzov process (eq 1), was shown to proceed with

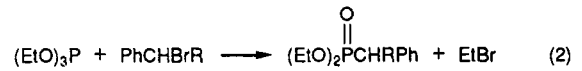
Scheme I[a]

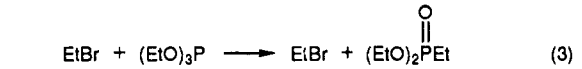


[a] Key: (a) *t*-$BuMe_2SiCl$, pyridine; (b) $(MeO)_2PNEt_2$/tetrazole; (c) *hν*/benzene; (d) Bu_4NF/THF; (e) $MeSO_2Cl/Et_3N$/0 °C; (f) Ph_3P/CBr_4.



retention of configuration at both phosphorus and the migrating benzyl carbon center. Of special interest is the ease in which secondary benzylphosphonate diesters are prepared by this approach (eq 1, R = alkyl). By contrast, the well-known thermal Arbuzov reaction between a trialkyl phosphite and a secondary alkyl halide is relatively slow, even at high temperatures.[9] Furthermore, if the alkyl halide formed along with the desired phosphonate is a primary one, as in eq 2, side product will be formed (eq 3) because of the intrinsically greater reactivity of the product primary halide.





In this paper, we report the application of the photo-Arbuzov rearrangement to the synthesis of a series of benzylphosphonate diesters, **10**, **16**, **19**, **21**, and **23**, which are potential precursors to new acyclic nucleoside-based phosphonates. Benzylphosphonate diester **10** was then further elaborated to the five acyclic nucleoside phosphonic

(1) (a) For recent reviews of antiviral research see: *Design of Anti-Aids Drugs*; De Clercq, E., Ed.; Vol. 14. *Pharmacochemistry Library*; Timmerman, H., Ed.; Elsevier: Amsterdam, 1990. (b) *Nucleotide Analogues as Antiviral Agents*; Martin, J. C., Ed.; ACS Symposium Series No. 401; American Chemical Society: Washington, DC, 1989. (c) De Clercq, E. *Actual. Chim. Ther.* **1991**, *18*, 133. (d) De Clercq, E. *Microbiologia* **1990**, *13*, 165. (e) De Clercq, E. *Konink. Acad. Geneesk. Belg.* **1990**, 69. (f) De Clercq, E. *Drugs Exptl. Clin. Res.* **1990**, *16*, 319. (g) De Clercq, E. In *Trends in Drug Research*; Claassen, V., Ed.; Elsevier: Amsterdam, 1990; pp 133–152. (h) De Clercq, E. *Trends Pharmacol. Sci. (TIPS)* **1990**, *11*, 198. (i) Holy, A.; Votruba, I.; Merta, A.; Cerny, J.; Vesely, J.; Vlach, J.; Sediva, K.; Rosenberg, I.; Otmar, M. *Antiviral Res.* **1990**, *13*, 295. (j) Broder, S.; Mitsuya, H.; Yarchoan, R.; Pavlakis, G. N. *Ann. Intern. Med.* **1990**, *113*, 604. (k) De Clercq, E. *New Methods in Drug Res.* **1989**, *3*, 103. (l) Prusoff, W. H.; Lin, T. S.; August, E. M.; Wood, T. G.; Marongiu, M. E.; Birks, E.; Qian, H. Y. *Mol. Aspects Chemother. Proc. Int. Symp. 2nd* **1988**, 11.

(2) Balfour, H. H., Jr. *Rev. Infect. Dis.* **1990**, *12*, S849.

(3) (a) For a recent review of [(phosphonomethoxy)alkyl]purines and -pyrmidines as antiviral agents see refs 1f and 1i. See also: (b) Cerny, J.; Votruba, I.; Vonka, V.; Rosenberg, I.; Otmar, M.; Holy, A. *Antiviral Res.* **1990**, *13*, 253. (c) Votruba, I.; Travnicek, M.; Rosenberg, I.; Otmar, P. *Antiviral Res.* **1990**, *13*, 287. (d) De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464.

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(6) Nakamura, C. E.; Chu, S.-H.; Stoeckler, J. D.; Parks, R. E., Jr. *Nucleosides Nucleotides* **1989**, *8*, 1039.

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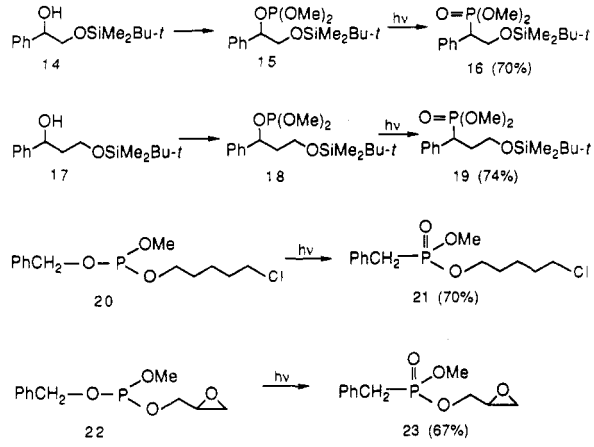
(8) (a) Cairns, S. M.; Bentrude, W. G. *Tetrahedron Lett.* **1989**, *30*, 1025. (b) Omelanzcuk, J.; Sopchik, A. E.; Lee, S.-G.; Akutagawa, K.; Cairns, S. M.; Bentrude, W. G. *J. Am. Chem. Soc.* **1988**, *110*, 6908.

(9) For reviews concerning the Arbuzov reaction, see: Bhattacharya, A. K.; Thygarajan, G. *Chem. Rev.* **1981**, *81*, 415. Brill, T. S.; Landon, S. J. *Ibid.* **1984**, *84*, 577.

Scheme II



acids **25**, **27**, **29**, **31**, and **32** by attachment of the appropriate base and dealkylation of the phosphonate ester functionality.

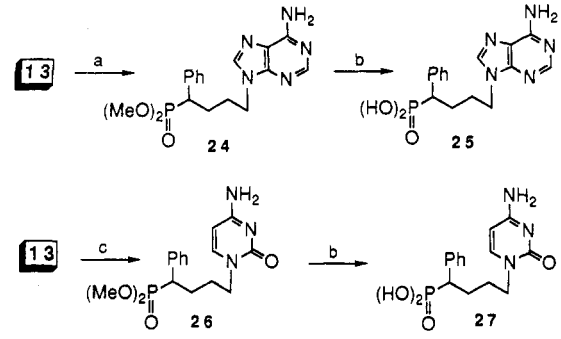
Few if any secondary phosphonates derived from acyclic nucleosides have been previously prepared. The secondary benzylphosphonates reported here were selected for the purpose of demonstrating the facility of the photorearrangement in the preparation of precursors to nucleoside-based phosphonates. The synthesis of derivatives with optimal potential for antiviral activity, based on structural analogy to molecules with known antiviral properties, will be the subject of future work.

Results and Discussion

Photogeneration of Benzylphosphonate Precursors. The synthesis of the key mesyl and monobromo dimethyl benzylphosphonates, **12** and **13**, is shown in Scheme I. These derivatives contain active leaving groups, Br and mesyl. Reaction of dimethyl *N,N*-diethylphosphoramidite with **8** in the presence of tetrazole afforded **9**.[10] Phosphite **9**, used without further purification, was totally consumed after 8 h of irradiation by a 450-W Hanovia ultraviolet lamp. The photoproduct, dimethyl phosphonate **10**, was isolated by column chromatography as a colorless liquid in 72% yield, based on starting diol. Deprotection of the silyl ether moiety of **10** provided alcohol **11** (84% yield) which was converted to **12** in 83% isolated yield on reaction with methanesulfonyl chloride in the presence of triethylamine and also to the bromide **13** in 75% yield.

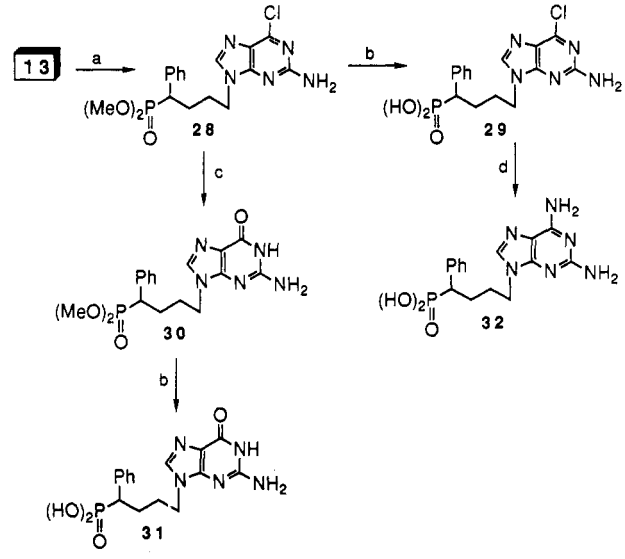
Scheme II depicts similar transformations for the preparations of dimethyl benzylphosphonates **16** and **19**, which are completely analogous to **10** except for differences in the lengths of the carbon chains. The transformations **20** to **21** and **22** to **23** (Scheme II) provide two more examples of the subject photorearrangement to generate benzylphosphonates which should be reactive with anionic nucleobases to yield acyclic nucleoside-based benzylphosphonates. The final products of demethylation of such derivatives of **21** and **23** would be benzylphosphonate monoesters. Use of epoxy intermediates related to **23** for the synthesis of acyclic nucleoside analogues has been reported very recently.[11,12]

Scheme III[a]



[a] Key: (a) adenine/NaH/DMF/rt; (b) Me_3SiBr/CH_3CN/rt; (c) cytosine/NaH/DMF/45–50 °C.

Scheme IV[a]



[a] Key: (a) 2-amino-6-chloropurine/K_2CO_3/DMF/rt; (b) Me_3SiBr/CH_3CN; (c) 1 N HCl/reflux; (d) $MeOH/NH_3$/80 °C.

Acyclic Nucleoside-Based Phosphonates from 13. Attempted reactions of **12** under a variety of conditions with the sodium salt formed from reaction of adenine with NaH (Scheme III) gave the target acyclic-nucleoside-based dimethyl benzylphosphonate **24** in only 5–10% yield (DMF, 25 °C, 48 h; 50 °C, 24 h, 48 h; 70 °C, 24 h; CH_3CN, 25 °C, 48 h; 50 °C, 48 h; reflux, 24 h). Reaction above 50 °C led to decomposition of **12** and no useful increase in yield of **24**.

Similarly, on reaction with **12**, the sodium salt of cytosine gave only a 5% yield of the desired N-1 alkylated product along with 6% of O-2 alkylated material. Again, variations in solvent and reaction temperature, as given above for reaction of **12** with the adenine sodium salt, failed to improve the product yield. Likewise, the use of K_2CO_3 or $CsCO_3$ with either cytosine or adenine, a procedure shown[13] to effect the efficient coupling of these bases with straight-chain mesylates, proved unsuccessful.

As an alternative and ultimately successful route, reaction of **13** for 24 h at room temperature with adenine, which had first undergone reaction with NaH in DMF, afforded **24** in 65% isolated yield. Demethylation of the latter with bromotrimethylsilane at room temperature gave the desired nucleoside-based phosphonic acid **25** (75% yield), which was converted quantitatively to the disodium

(10) This sort of chemistry is used routinely in the preparations of oligonucleotides. See, e.g., Caruthers, M. H. In *Synthesis and Applications of DNA and RNA*; Narang, S. A., Ed.; Academic Press: Orlando, FL, *1989*; pp 47–94.

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(13) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R., II; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 1457.

salt (NaOH) and isolated by lyophilysis. Similarly, phosphonate **26** was formed in 60% isolated yield (chromatography) on reaction at 45–50 °C of cytosine/NaH/DMF with **13** followed by demethylation ($BrSiMe_3$) to yield **27**, which was purified as its triethylammonium salt, converted to the more water-soluble sodium salt (0.1 N NaOH) and then recrystallized (62% yield based on **26**).

The three purine-based acyclic nucleoside phosphonic acids **29**, **31**, and **32** (Scheme IV) were derived from dimethyl benzylphosphonate ester **28**, prepared in 62% isolated yield from reaction of **13** with 2-amino-6-chloropurine in the presence of anhydrous K_2CO_3. Thus, benzylphosphonic acid **29** was obtained from **28** in 76% yield as the sodium salt. Acid hydrolysis of **28** afforded **30** in 75% yield. The latter was demethylated ($BrSiMe_3$) and converted to the sodium salt of **31**, isolated by lyophilysis. Phosphonic acid **32** resulted in 60% yield (Na salt) upon facile ammonolysis of **29**. The structures of the above acyclic nucleoside-based benzylphosphonic acids and their precursors were verified by UV spectroscopy, which showed that the N-alkylations on the purine and pyrimidine bases had occured at the desired positions, and were confirmed by ^1H and ^{13}C NMR spectroscopy.

In summary, the synthesis of acyclic nucleoside-based benzylphosphonic acids **25**, **27**, **29**, **31**, and **32** in good overall yields from dimethyl (1-phenyl-4-bromobutyl)-phosphonate, **13**, is readily accomplished. The ease of preparation of **10** by photorearrangement of **9**, and its easy conversion to **13**, along with the good yields obtained for **16**, **19**, **21**, and **23**, suggests the general use of this photorearrangement process to give phosphonate derivatives which should be easily convertible to nucleoside-based, benzylphosphonic acids with potential antiviral activity. Biological tests of the above phosphonates are incomplete at this time and will be reported separately.

Experimental Section

Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. ^1H NMR spectra were taken on a Varian XL-300 spectrometer at 300 MHz. ^{13}C NMR spectra were obtained on a Varian XL-300 MHz spectrometer at 75.5 MHz. For **24–32** the carbons of the base are designated C_1, C_2, etc.; those of the butyl chain C'_1, C'_2, etc.; those of the phenyl group, C''_1, C''_2, etc. ^{31}P NMR spectra were recorded on a Varian XL-300 MHz spectrometer at 121.3 MHz. Listed J values in the ^1H NMR spectral data refer to proton–proton couplings unless otherwise stated. UV absorption spectra were taken with a Cary-17D spectrophotometer. Mass spectra were determined on a VG Micromass 7050E mass spectrometer equipped with a VG 2000 Data System. Analytical TLC was performed on aluminum sheets coated with a 0.2-mm layer of silica gel 60 F_{254} (Merck). Flash column chromatography utilized silica gel 60, 230–400 mesh (Merck). Dowex (OH^- form) and Sephadex A-25 (HCO_3^- form) were used for ion-exchange chromatography. Compounds were detected by UV light (254 nm). Anhydrous solvents were obtained as follows: acetonitrile by successive distillations from phosphorus pentoxide and then calcium hydride; benzene, distillation from sodium; dichloromethane, distillation from phosphorus pentoxide; dimethylformamide and pyridine, distillation from calcium hydride.

Phenyl-1,2-ethanediol was converted to silyl ether **14** in 90% yield on treatment with *tert*-butyldimethylsilyl chloride in pyridine. Reaction of cinnamyl alcohol with MCPBA gave the corresponding epoxide in 80% yield. Reduction of the epoxide with Red-Al following the procedure of Sharpless et al.[14] provided 1-phenyl-1,3-dihydroxypropane in 96% yield which was converted to its silyl ether **17** in 93% yield. (*N,N*-diisopropylamino)-methoxychlorophosphine was prepared from the reaction of methyl phosphorodichloridite[15] and diisopropylamine in 60% yield following a literature procedure.[16] Treatment of (*N,N*-diisopropylamino)methoxychlorophosphine with benzyl alcohol in the presence of diisopropylethylamine gave benzyl methyl *N,N*-diisopropylphosphoramidite in 82% yield after distillation under reduced pressure (bp 68–70 °C (0.05 mmHg)).

1-Phenyl-1,4-butanediol (7). A solution of 3-benzoylpropionic acid[17] (8.0 g, 44.9 mmol) in THF (200 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (5.12 g, 135 mmol) in THF (200 mL) at 0 °C. The reaction mixture was then heated under reflux for 24 h. The reaction mixture was cooled, and excess $LiAlH_4$ was destroyed by dropwise addition of ethyl acetate. H_2O (100 mL) and then 2 N HCl (10 mL) were added, and the reaction mixture was filtered. The filtrate was evaporated and then coevaporated with CH_3CN and toluene to give diol **7** as a thick liquid which turned solid overnight under high vacuum. The solid product was dried in a desiccator containing P_2O_5 to a powder form (6.94 g, 93%) and used in the next step without further purification. An analytical sample was prepared by crystallization from ether as colorless solid: mp 64–65 °C (lit.[18] mp 65–66 °C); ^1H NMR (DMSO-d_6) δ 7.25–7.38 (m, 5 H, C_6H_5), 5.17 (d, 1 H, J = 4.2 Hz, 1-OH), 4.53 (unresolved q, 1 H, H1; on D_2O exchange the peak became a t), 4.42 (t, 1 H, J = 5 Hz, 4-OH), 3.39 (unresolved q, 2 H, D_2O exchange spectrum, t, H4), 1.30–1.70 (m, 4 H, H2 and H3); MS(EI) m/z 166 (M^+, 1.3), 148 ($M^+ - 18$, 5.4). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.37; H, 8.54.

Mono-*tert*-butyldimethylsilyl Ether (8) of 7. *tert*-Butyldimethylsilyl chloride (4.17 g, 27.8 mmol) was added in one portion to a stirred solution of **7** (4.40 g, 26.5 mmol) in pyridine (50 mL) at 0 °C. After 2 h the reaction mixture reached room temperature and was stirred for 18 h. Pyridine was removed, and the residue was dissolved in EtOAc (150 mL). The solution was washed with 1 N HCl (1 × 30 mL), H_2O (2 × 50 mL), and brine (1 × 50 mL) and then dried over $MgSO_4$, concentrated, and applied to a silica gel column. Elution with 2% EtOAc in hexane gave **8** as a colorless liquid (7.10 g, 96%) after evaporation: ^1H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5 H, C_6H_5), 4.69 (dd, 1 H, J = 7.2, 5.1 Hz, H1), 3.68 (dd, 1 H, J = 6.0, 1.8 Hz, H4), 3.66 (dd, 1 H, J = 6.0, 2.4 Hz, H4), 1.84 (m, 2 H, H3), 1.64 (m, 2 H, H2), 0.91 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, CH_3); MS (FAB^+) m/z 281 (M + 1, 1).

1-Phenyl-4-[(*tert*-butyldimethylsilyl)oxy]butyl Dimethyl Phosphite (9). Tetrazole (560 mg, 8.0 mmol) was added to a stirred mixture of **8** (5.60 g, 20.0 mmol) and dimethyl *N,N*-diethylphosphoramidite (3.96 g, 24.0 mmol) in CH_3CN (50 mL) under argon at room temperature. After 6 h CH_3CN was removed, and dry ether (50 mL) was added. The tetrazolinium salt was removed by filtration. Ether was removed, and the residual liquid was left under high vacuum overnight. Phosphite **9** was obtained as a colorless liquid (7.5 g, 99%). Both the ^1H NMR and ^{31}P NMR spectra indicated that the product was at least 98% pure, and this material was directly used in the next step: ^{31}P NMR ($CDCl_3$) δ 140.78; ^1H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5 H, C_6H_5), 5.06 (ddd, 1 H, J_{HP} = 9.0 Hz, apparent J = 6.3, 6.0 Hz, H1), 3.61 (t, 1 H, J = 6.3 Hz, CH_2OSi), 3.60 (t, 1 H, J = 6.3 Hz, CH_2OSi), 3.45 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.35 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 1.80–1.99 (m, 2 H, H3), 1.35, 1.67 (m, 2 H, H2), 0.88 (s, 9 H, *t*-Bu), 0.03 (s, 3 H, CH_3), 0.01 (s, 3 H, CH_3).

Dimethyl [1-Phenyl-4-[(*tert*-butyldimethylsilyl)oxy]butyl]phosphonate (10). A solution of phosphite **9** (5.94 g, 16.0 mmol) in benzene (160 mL) was divided between six quartz test tubes. The solution was degassed by bubbling argon through it for 15 min. The solution was then irradiated by a 450-W Hanovia medium-pressure UV lamp. The conversion of **9** was complete in 8 h. Benzene was removed, and the yellowish liquid residue was dissolved in $CHCl_3$ and applied to a silica gel column. The column was first eluted with $CHCl_3$ and then with 1% MeOH in $CHCl_3$. Phosphonate **10** was obtained as a colorless liquid (4.2 g, 72%): ^{31}P NMR ($CDCl_3$) δ 31.70; ^1H NMR ($CDCl_3$) δ 7.22–7.36 (m, 5 H, C_6H_5), 3.68 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.54 (t, 2 H, J = 6.6 Hz, CH_2OSi), 3.46 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.03

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(ddd, 1 H, J_{HP} = 22.5 Hz, J = 11.4, 3.9 Hz, H1), 1.81–2.24 (m, 2 H, H3), 1.32–1.46 (m, 2 H, H2), 0.86 (s, 9 H, *t*-Bu), 0.01 (s, 6 H, CH_3); MS (FAB) 373 (M + 1, 38.8%).

Dimethyl (1-Phenyl-4-hydroxybutyl)phosphonate (11). Tetrabutylammonium fluoride (1 M solution in THF, 12 mL, 12.0 mmol) was added to a stirred solution of **10** (4.09, 10.7 mmol) in THF (30 mL) at room temperature. The reaction mixture was stirred for 4 h, and the THF was removed to give a yellow liquid which was dissolved in $CHCl_3$ and applied to a silica gel column. The column was eluted with a $CHCl_3$–MeOH (0–5% MeOH) gradient to give **11** as a colorless liquid (2.0 g, 84%): ^{31}P NMR ($CDCl_3$) δ 31.63; ^1H NMR ($CDCl_3$) δ 7.30–7.45 (m, 5 H, C_6H_5), 3.68 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.58 (t, 2 H, J = 6.3 Hz, $-CH_2OH$), 3.47 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.06 (ddd, 1 H, J_{HP} = 22.8 Hz, J = 11.1 Hz, 4.5 Hz, H1), 2.86 (bs, 1 H, CH_2OH), 1.80–2.35 (m, 2 H, H3), 1.31–1.52 (m, 2 H, H2); ^{13}C NMR ($CDCl_3$) δ (J_{PC}) 135.42 (d, J = 6.8 Hz, Cl′), 128.90 (d, J = 6.9 Hz, C2′), 128.33 (d, J = 12.3 Hz, C3′), 127.00 (d, J = 3.0 Hz, C4′), 61.52 (C4), 53.23 (d, J = 7.0 Hz, OCH_3), 52.49 (d, J = 7.0 Hz, OCH_3), 43.70 (d, J = 136.0 Hz, C1), 30.41 (d, J = 14.6 Hz, C2), 26.01 (d, J = 3.1 Hz, C3); MS (EI) m/z 258 (M^+, 38.9). Anal. Calcd for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.41; P, 11.99. Found: C, 55.57; H, 7.50; P, 12.00.

Dimethyl [1-Phenyl-4-(mesyloxy)butyl]phosphonate (12). Methanesulfonyl chloride (868 mg, 0.60 mL, 7.58 mmol) was added dropwise to a stirred solution of phosphonate **11** (1.81 g, 7.02 mmol) and triethylamine (922 mg, 1.27 mL, 9.13 mmol) in CH_2Cl_2 (30 mL) at −5 °C. The reaction mixture was warmed to room temperature over a 5-h period, diluted with CH_2Cl_2 (50 mL), and then washed with H_2O (1 × 50 mL), $NaHCO_3$ (1 × 50 mL), and brine (2 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated, and applied to a silica gel column. The column was eluted with $CHCl_3$–MeOH (0–2% MeOH) to give **12** as a colorless liquid (1.96 g, 83%): ^{31}P NMR ($CDCl_3$) δ 31.19; ^1H NMR ($CDCl_3$) δ 7.25 – 7.38 (m, 5 H, C_6H_5), 4.18 (t, 1 H, J = 6.3 Hz, CH_2OMs), 4.16 (t, 1 H, J = 6.3 Hz, CH_2OMs), 3.70 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.47 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.04 (ddd, 1 H, J_{HP} = 22.8 Hz, J = 11.1, 4.5 Hz, H1), 2.97 (s, 3 H, SO_2CH_3), 2.00–2.30 (m, 2 H, H3), 1.68 (m, 2 H, H2); MS (FAB) m/z 337 (M + 1, 100%).

Dimethyl (1-Phenyl-4-bromobutyl)phosphonate (13). Triphenylphosphine (3.45 g, 13.2 mmol) was added to a stirred solution of **11** (2.85 g, 11.0 mmol) and carbon tetrabromide (4.38 g, 13.2 mmol) in CH_3CN (50 mL). The reaction mixture was stirred at room temperature for 6 h. Saturated $NaHCO_3$ (10 mL) and then H_2O (10 mL) were added and stirred for 10 min. Solvent was removed, and the residue was dissolved in $CHCl_3$ (100 mL). The solution was washed with H_2O (1 × 50 mL) and saturated brine (2 × 50 mL), dried ($MgSO_4$), and evaporated to give a thick oil. Trituation with Et_2O/pentane precipitated triphenylphosphine oxide which was removed by filtration. Product **13** was purified by column chromatography on silica gel eluted with $CHCl_3$–MeOH (0–2% MeOH). The pure product was obtained as a colorless liquid (2.48 g, 75%): ^{31}P NMR ($CDCl_3$) δ 30.75; ^1H NMR ($CDCl_3$) δ 7.26–7.38 (m, 5 H, C_6H_5), 3.70 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.50 (d, 3 H, J_{HP} = 10.8 Hz), 3.33 (t, 1 H, J = 6.6 Hz, CH_2Br), 3.29 (t, 1 H, J = 6.6 Hz, CH_2Br), 3.04 (ddd, 1 H, J_{HP} = 22.8 Hz, J = 11.1, 4.2 Hz, H1), 2.11–2.32 (m, 2 H, H2), 1.65–1.80 (m, 2 H, H3); ^{13}C NMR ($CDCl_3$) δ (J_{PC}) 135.12 (d, J = 6.8 Hz, C1′), 128.94 (d, J = 6.7 Hz, C2′), 128.58 (d, J = 2.5 Hz, C3′), 127.32 (d, J = 3.1 Hz, C4′), 53.39 (d, J = 6.9 Hz, OCH_3), 52.64 (d, J = 7.2 Hz, OCH_3), 43.49 (d, J = 136.9 Hz, C1), 32.83 (C4), 30.60 (d, J = 15.5 Hz, C2), 28.31 (d, J = 3.0 Hz, C3); MS (EI) m/z 320 (M^+, 4.7), 322 (M^+ + 2, 4.7). Anal. Calcd for $C_{12}H_{18}O_3PBr$: C, 44.88; H, 5.65; P, 9.64. Found: C, 45.16; H, 5.80; P, 9.50.

Preparations of Phosphites 15, 18, 20, and 22 and Phosphonates 16, 19, 21, and 23. The phosphites were obtained according to the procedure for phosphite **2** given in detail above. Preparations were on a 5–10 mmol scale and yielded the phosphites virtually quantitatively (96–98%) as colorless liquids >95% pure as indicated by their ^1H and ^{31}P NMR spectra (Spectral parameters are given below as proof of structure). They were used without further purification in the subsequent photorearrangement to the benzylphosphonate following the detailed procedure described above for phosphonate **8**. Product phosphonates were purified by gravity column filtration on silica gel, eluting first with $CHCl_3$ and then 1% MeOH in $CHCl_3$. Quantities of reactant phosphites and yields of product phosphonates are given in the brief procedures recorded below. A small portion of each phosphonate was further purified for quantitative elemental analysis by isocratic HPLC on silica gel (1% MeOH in $CHCl_3$).

1-Phenyl-2-[(*tert*-butyldimethylsilyl)oxy]ethyl dimethyl phosphite (15) was prepared from **14**: ^{31}P NMR ($CDCl_3$) δ 140.60; ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H, C_6H_5), 5.11 (ddd, 1 H, J_{HP} = 9.0 Hz, J = 7.4, 4.8 Hz, H1), 3.84 (dd, 1 H, J = 10.6, 7.4 Hz, H2), 3.72 (dd, 1 H, J = 10.6, 4.8 Hz, H2), 3.49 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.42 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 0.88 (s, 9 H, *t*-Bu), 0.02 (s, 6 H, CH_3).

Dimethyl [1-Phenyl-2-[(*tert*-butyldimethylsilyl)oxy]-ethyl]phosphonate (16). Phosphite **15** (1.72 g, 5.0 mmol) was converted to phosphonate **16** (1.20 g) in 70% yield: ^{31}P NMR ($CDCl_3$) δ 29.15; ^1H NMR ($CDCl_3$) δ 7.25–7.38 (m, 5 H, C_6H_5), 4.33 (ddd, 1 H, J = 12.8, 10.5, 5.4 Hz, H2), 4.04 (ddd, 1 H, J = 12.8, 8.7 Hz, H2), 3.71 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.48 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.32 (ddd, 1 H, J_{HP} = 22.2 Hz, J = 8.4, 5.4 Hz, H1), 0.78 (s, 9 H, *t*-Bu), −0.04 (s, 3 H, CH_3), −0.12 (s, 3 H, CH_3); MS (EI) m/z 344.15784 (0.6), $C_{16}H_{29}O_4PSi$ requires 344.15727. Anal. Calcd for $C_{16}H_{29}O_4PSi$: C, 55.79; H, 8.49; P, 9.00. Found: C, 55.70; H, 8.44; P, 9.36.

1-Phenyl-3-[(*tert*-butyldimethylsilyl)oxy]propyl dimethyl phosphite (18) was prepared from **17**: ^{31}P NMR ($CDCl_3$) δ 141.0; ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H, C_6H_5), 5.24 (ddd, 1 H, J_{HP} = 8.1 Hz, J = 7.5, J = 5.4 Hz, H1), 3.72 (m, 1 H, H3), 3.56 (m, 1 H, H3), 3.45 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.33 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 2.11 (m, 1 H, H2), 1.93 (m, 1 H, H2), 0.90 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, CH_3), 0.03 (s, 3 H, CH_3).

Dimethyl [1-Phenyl-3-[(*tert*-butyldimethylsilyl)oxy]-propyl]phosphonate (19). Phosphite **18** (1.79 g, 5.0 mmol) was converted to phosphonate **19** (1.32 g) in 74% yield: ^{31}P NMR ($CDCl_3$) δ 32.36; ^1H NMR ($CDCl_3$) δ 7.24–7.35 (m, 5 H, C_6H_5), 3.71 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.58 (m, 1 H, H3), 3.48 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.36 (ddd, 1 H, J_{HP} = 22.2 Hz, J = 11.4, 3.9 Hz, H1), 3.30 (m, 2 H, H3), 2.29 (m, 1 H, H2), 2.08 (m, 1 H, H2), 0.86 (s, 9 H, *t*-Bu), −0.04 (s, 3 H, CH_3) −0.07 (s, 3 H, CH_3); MS (EI) m/z 358.17121 (0.3), $C_{17}H_{31}O_4PSi$ requires 358.17293. Anal. Calcd for $C_{17}H_{31}O_4PSi$: C, 56.95; H, 8.72; P, 8.64. Found: C, 56.88; H, 8.74; P, 8.77.

Benzyl 5-chloropentyl methyl phosphite (20) was prepared from 5-chloropentan-1-ol and $PhCH_2OP(NEt_2)OMe$: ^{31}P NMR ($CDCl_3$) δ 140.44; ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H, C_6H_5), 4.87 (d, 2 H, J_{HP} = 8.1 Hz, $C_6H_5CH_2O$), 3.80 (dt, 2 H, J_{HP} = 7.8 Hz, J = 6.6 Hz, OCH_2), 3.51 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.50 (t, 2 H, J = 6.6 Hz, CH_2Cl), 1.77 (m, 2 H, CH_2), 1.61 (m, 2 H, CH_2), 1.48 (m, 2 H, CH_2).

5-Chloropentyl methyl benzylphosphonate (21) (1.09 g, 70%) was obtained from phosphite **20** (1.15 g, 5.0 mmol): ^{31}P NMR ($CDCl_3$) δ 28.20; ^1H NMR ($CDCl_3$) δ 7.25–7.40 (m, 5 H, C_6H_5), 3.94 (apparent q, 2 H, J_{HP} = J = 6.6 Hz, OCH_2), 3.65 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.47 (t, 2 H, J = 6.6 Hz, CH_2Cl), 3.16 (d, 2 H, J_{HP} = 21.6 Hz, $PCH_2C_6H_5$), 1.72 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 1.44 (m, 2 H, CH_2); MS (EI) m/z 290.08401 (20); $C_{13}H_{20}O_3PCl$ requires 290.08386. Anal. Calcd for $C_{13}H_{20}O_3PCl$: C, 53.71; H, 6.93; P, 10.65. Found: C, 52.83; H, 6.83; P, 10.52.

Benzyl glycidyl methyl phosphite (22) was prepared from $PhCH_2OP(NEt_2)OMe$ and the epoxy alcohol: ^{31}P NMR ($CDCl_3$) δ 140.52, 140.56 diastereomers; ^1H NMR ($CDCl_3$) δ 7.26–7.40 (m, 5 H, C_6H_5), 4.89 (d, 2 H, J_{HP} = 8.1 Hz, $OCH_2C_6H_5$), 4.00 (m, 1 H, $POCH_2$), 3.78 (m, 1 H, $POCH_2$), 3.54, 3.53 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.14, 2.79, 2.63 (m, 1 H each, oxirane).

Methyl glycidyl benzylphosphonate (23) (810 mg) was obtained from phosphite **22** (1.21 g, 5.0 mmol) as a colorless liquid in 67% yield: ^{31}P NMR ($CDCl_3$) δ 28.74, 28.64 diastereomers; ^1H NMR ($CDCl_3$) δ 7.24–7.38 (m, 5 H, C_6H_5), 4.19 (ddd, 1 H, J_{HP} = 11.0 Hz, J = 8.4, 3.0 Hz, $POCH_2$), 3.88 (ddd, 1 H, J_{HP} = 11.0 Hz, J = 8.4, 6.0 Hz, $POCH_2$), 3.68, 3.67, (d, 3 H, J_{HP} = 11.0 Hz, OCH_3), 3.21 (d, 2 H, J_{HP} = 21.9 Hz, $PCH_2C_6H_5$), 3.12, 2.77, 2.57 (m, 1 H each, oxirane); MS (EI) m/z 242.07017 (58), $C_{11}H_{15}O_4P$ requires 242.07079. Anal. Calcd for $C_{11}H_{15}O_4P$: C, 54.54; H, 6.24; P, 12.78. Found: C, 53.07; H, 6.10; P, 12.57.

9-[4-Phenyl-4-(dimethylphosphono)but-1-yl]adenine (24). NaH (530 mg, 60% in oil, 13.1 mmol) was added to a stirred suspension of adenine (1.64 g, 12.1 mmol) in DMF (100 mL) under

argon at room temperature. After 30 min, a solution of **13** (3.91 g, 12.1 mmol) in DMF (15 mL) was added, and the reaction mixture was stirred for 24 h. DMF was removed under reduced pressure, and the residue was dissolved in 10% MeOH in $CHCl_3$ (10 mL) and applied to a silica gel column. The column was eluted with 2% MeOH in $CHCl_3$ to give **24** as a colorless solid (2.97 g, 65%). An analytical sample was prepared by crystallization from CH_3CN: mp 179 °C; UV (MeOH) λ_{max} 260 (14750) nm; ^{31}P NMR (DMSO-d_6) δ 31.63; ^1H NMR (DMSO-d_6) δ 8.09 (s, 1 H, H-8), 8.08 (s, 1 H, H2), 7.18–7.32 (m, 5 H, C_6H_5), 4.10 (t, 2 H, J = 6.9 Hz, H1′), 3.56 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.38 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.28 (ddd, 1 H, J_{HP} = 22.2 Hz, J = 10.0, 4.8 Hz, H4′), 1.82 (m, 2 H, H3′), 1.60 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 155.91 (C6), 152.31 (C2), 149.44 (C4), 140.74 (C8), 135.94 (d, J = 6.8 Hz, C1″), 128.94 (d, J = 6.8 Hz, C2″), 128.34 (d, J = 2.2 Hz, C3″), 126.95 (d, J = 2.8 Hz, C4″), 118.71 (C5), 52.65 (d, J = 6.8 Hz, OCH_3), 52.31 (d, J = 7.0 Hz, OCH_3), 42.26 (C1′), 41.51 (d, J = 135.0 Hz, C4′), 27.35 (d, J = 14.8 Hz, C3′), 26.30 (d, J = 2.8 Hz, C2′); MS (EI) m/z 375 (M^+, 6.4). Anal. Calcd for $C_{17}H_{22}N_5O_3P$: C, 54.39; H, 5.90; N, 18.65; P, 8.25. Found: C, 54.46; H, 5.89; N, 18.71; P, 8.54.

9-(4-Phenyl-4-phosphonobut-1-yl)adenine (25). Bromotrimethylsilane (2.17 g, 1.87 mL, 14.2 mmol) was added dropwise to stirred suspension of **24** (880 mg, 2.36 mmol) in CH_3CN (25 mL) under argon at room temperature. The reaction mixture was stirred for 6 h. The volatiles were removed under vacuum, and the residual oil was placed under high vacuum for 1 h. Then H_2O (15 mL) was added to precipitate a white solid. The solid was crystallized from MeOH–H_2O to give **25** as a colorless solid (624 mg, 75%), mp 162–165 °C (changed in form, then melted over a wide range): UV (MeOH) λ_{max} 260 (11971) nm. ^{31}P NMR (DMSO-d_6) δ 23.92; ^1H NMR (DMSO-d_6) δ 8.07 (s, 1 H, H8), 8.06 (s, 1 H, H2), 7.10–7.30 (m, 5 H, C_6H_5), 4.07 (t, 2 H, J = 6.0 Hz, H1′) 2.80 (unresolved ddd, 1 H, H4′), 1.95 (m, 1 H, H3′), 1.65 (m, 1 H, H3′, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 155.69 (C6), 152.07 (C2), 149.22 (C4), 140.66 (C8), 139.38 (d, J = 5.5 Hz, C1″), 128.86 (d, J = 5.62 Hz, C2″), 127.60 (bs, C3″, J = ~1 Hz), 125.56 (C4″), 118.58 (C5), 45.15 (d, J = 130.8 Hz, C4′), 42.65 (C1′), 28.11 (d, J = 14.0 Hz, C3′), 27.35 (bs, C2′, J = ~1 Hz); MS (FAB^+) m/z 348 (M + 1, 28). Anal. Calcd for $C_{15}H_{18}N_5O_3P$·1.75 H_2O: C, 47.56; H, 5.72; N, 18.48; P, 8.17. Found: C, 47.48; H, 5.38; N, 18.42; P, 8.13.

The sodium salt of **25** was prepared for in vitro studies by treating a suspension of **25** in H_2O with 0.5 N NaOH. The resulting solution was lyophilized to give a white powder.

1-[4-Phenyl-4-(dimethylphospho)but-1-yl]cytosine (26). Sodium hydride (595 mg, 60% in oil, 14.9 mmol) was added to a suspension of cytosine (1.50 g, 13.2 mmol) in DMF (80 mL) under argon at room temperature. After 30 min a solution of **13** (4.25 g, 13.2 mmol) in DMF (15 mL) was slowly added. The reaction mixture was heated at 45–50 °C for 24 h. DMF was removed under reduced pressure, and the residue was treated with 15% MeOH in $CHCl_3$. Insoluble material was filtered off. The filtrate was concentrated and applied to a silica gel column. The column was eluted with $CHCl_3$–MeOH (0–15% MeOH) gradient to give **26** as a colorless foam (2.83 g, 60%). A white, crystalline analytical sample was obtained by crystallization from acetone: mp 152–53 °C; UV (MeOH) λ_{max} 238 (6700), 272 (7977) nm; ^{31}P NMR (DMSO-d_6) δ 31.04; ^1H NMR (DMSO-d_6) δ 7.48 (d, 1 H, J = 7.0 Hz, H6), 7.15–7.35 (m, 5 H, C_6H_5), 6.95 (bs, 2 H, NH_2), 5.58 (d, 1 H, J = 7.0 Hz, H5), 3.59 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.57 (t, 2 H, H1′, partially hidden under OCH_3 signal; J could not be determined), 3.40 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.26 (ddd, 1 H, J_{HP} = 21.9 Hz, J = 10.8, 4.8 Hz, H4′), 1.82 (m, 2 H, H3′), 1.40 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 165.88 (C4), 156.41 (C2), 144.38 (C6), 135.03 (d, J = 6.8 Hz, C1″), 128.75 (d, J = 6.8 Hz, C2″), 128.41 (d, J = 2.2 Hz, C3″), 127.10 (d, J = 2.9 Hz, C4″), 94.86 (C5), 53.31 (d, J = 7.0 Hz, OCH_3), 52.51 (d, J = 7.2 Hz, OCH_3), 49.03 (C1′), 43.53 (d, J = 136.2 Hz, C4′), 27.38 (d, J = 14.8 Hz, C3′), 26.78 (d, J = 2.5 Hz, C2′); MS (EI) m/z 351 (M^+, 0.4). Anal. Calcd for $C_{16}H_{22}N_3O_4P$: C, 54.69; H, 6.31; N, 11.96; P, 8.82. Found: C, 54.65; H, 6.35; N, 11.89; P, 9.05.

1-(4-Phenyl-4-phosphonobut-1-yl)cytosine (27). Bromotrimethylsilane (608 mg, 0.52 mL, 3.97 mmol) was added dropwise to a stirred solution of **26** (465 mg, 1.32 mmol) in CH_3CN (15 mL) under argon at room temperature. After 12 h the volatiles were removed, and the residue was dissolved in H_2O (10 mL). The pH was adjusted to 7 with 1 N NaOH. This solution was then applied to a Dowex (OH^-) column (10 cm × 2.5 cm). The expected product was obtained by eluting with 0.1 N triethylammonium bicarbonate. Volatiles were removed, and excess buffer was removed by coevaporation with H_2O and neutralization to pH 8–9 with 0.1 N NaOH. The residue was recrystallized from EtOH/H_2O to give **27** as a fluffy white solid (383 mg, 70%): no mp <300 °C; UV (H_2O) λ_{max} 274 (9175) nm; ^{31}P NMR (DMSO-d_6) δ 22.57; ^1H NMR (DMSO-d_6) δ 7.49 (d, 1 H, J = 6.9 Hz, H6), 7.0–7.22 (m, 5 H, C_6H_5), 6.98 (bs, 2 H, NH_2), 5.57 (d, 1 H, H5), 3.53 (unresolved ddd, 2 H, H1′), 2.66 (ddd, 1 H, J_{HP} = 21.9 Hz, J = 11.7, 3.5 Hz, H4′), 1.95 (m, 1 H, H3′), 1.70 (m, 1 H, H3′), 1.35 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 165.51 (C4), 155.39 (C2), 145.92 (C6), 140.15 (d, J = 6.3 Hz, C1″), 128.89 (d, J = 5.9 Hz, C2″), 127.52 (C3″), 125.31 (C4″), 90.93 (C5), 48.45 (C′1), 45.76 (d, J = 130.0 Hz, C4′), 27.60 (d, J = 14.5 Hz, C3′), 27.53 (C2′); MS (FAB^+) m/z 324 (M + 1, 30); HRMS calcd for $C_{14}H_{18}N_3O_4P$ 324.11130, found 324.11053. Anal. Calcd for $C_{14}H_{17}N_3O_4PNa$·0.5H_2O: C, 47.46; H, 5.12; N, 11.86; P, 8.74. Found: C, 47.68; H, 5.40; N, 11.95; P, 8.61.

2-Amino-6-chloro-9-[4-phenyl-4-(dimethylphosphono)-but-1-yl]purine (28). Compound **28** was prepared following a literature procedure.[19] To a solution of **13** (2.75 g, 8.30 mmol) in DMF (50 mL) were added 2-amino-6-chloropurine (1.41 g, 8.30 mmol) and anhydrous K_2CO_3 (1.87 g, 13.5 mmol). The solution was stirred at room temperature for 6 h and then at 4 °C overnight. The solution was filtered, and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$–MeOH (0–4% MeOH) to afford **28** (2.10 g, 62%) as a foam. An analytical sample was prepared by crystallization from acetone: mp 113–114 °C; UV (MeOH) λ_{max} 245 (5570), 305 (7500) nm; ^{31}P NMR ($CDCl_3$) δ 30.65; ^1H NMR ($CDCl_3$) δ 7.66 (s, 1 H, H8), 7.25–7.38 (m, 5 H, C_6H_5), 5.16 (bs, 2 H, NH_2), 4.02 (t, 2 H, J = 6.9 Hz, H1′), 3.67 (d, 3 H, J_{HP} = 10.8 Hz, OCH_3), 3.45 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.10 (ddd, 1 H, J_{HP} = 23.1 Hz, J = 10.8, 4.5 Hz, H4′), 1.90–2.20 (m, 2 H, H3′), 1.78 (quintet, 2 H, H2′); ^{13}C NMR ($CDCl_3$) δ (J_{PC}) 158.88 (C6), 153.27 (C4), 150.29 (C2), 141.67 (C8), 134.57 (d, J = 6.8 Hz, C1″), 128.49 (d, J = 6.8 Hz, C2″), 128.23 (d, J = 2.1 Hz, C3″), 127.01 (d, J = 3.1 Hz, C4″), 124.25 (C5), 53.08 (d, J = 6.9 Hz, OCH_3), 52.30 (d, J = 7.2 Hz, OCH_3), 42.99 (d, J = 137.1 Hz, C4′), 42.67 (C1′), 27.20 (d, J = 15.0 Hz, C3′), 26.36 (d, J = 2.6 Hz, C2′); MS m/z 409 (M^+, 12.1). Anal. Calcd for $C_{17}H_{20}N_5O_3PCl$: C, 49.82; H, 5.16; N, 17.08; P, 7.55. Found: C, 49.95; H, 5.20; N, 17.01; P, 7.36.

2-Amino-6-chloro-9-(4-phenyl-4-phosphonobut-1-yl)purine (29). Deprotection of **28** to give **29** was carried out as described for **24**. H_2O (5 mL) was then added followed by 0.5 N NaOH to bring the pH to 8–9. The solution was then applied to a Sephadex A-25 column (HCO_3^- form). The column was first eluted with H_2O (200 mL) and then with a gradient of NH_4CO_3 (0–0.2 M) solution. Appropriate fractions were collected and evaporated to give **29** as the ammonium salt which was dissolved in H_2O (5 mL) and applied to a Dowex column (Na^+ form). Elution with H_2O gave the sodium salt of **29** which was crystallized from H_2O–CH_3CN to yield a white solid (261 mg, 76%): UV (H_2O) λ_{max} 240 (5106), 300 (7488) nm; ^{31}P NMR (D_2O) δ 22.64; ^1H NMR (D_2O) δ 7.78 (s, 1 H, H8), 6.95–7.15 (m, 5 H, C_6H_5), 3.80–3.98 (m, 2 H, H1′), 2.66–2.81 (ddd, 1 H, J_{HP} = 21.3 Hz, J = 12.0, 2.4 Hz, H4′), 2.0–2.2 (m, 1 H, H3′), 1.5–1.9 (m, 3 H, H2′, H3′); ^{13}C NMR (D_2O) δ (J_{PC}) 160.07 (C2), 153.91 (C4 or C6), 151.31 (C4 or C6), 145.88 (C-8), 140.59 (d, J = 6.3 Hz, C1″), 130.12 (d, J = 6.1 Hz, C2″), 129.46 (d, J = 1.8 Hz, C3″), 127.62 (d, J = 2.6 Hz, C4″), 125.03 (C-5), 47.77 (d, J = 128.5 Hz, C4′), 45.54 (C1′), 28.48 (C2′, J = ~1 Hz), 27.96 (d, J = 16.4 Hz, C3′); MS (FAB^+) m/z 426 (M + 1, 13.6). Anal. Calcd for $C_{15}H_{15}N_5O_3PC1Na_2$·1.5$H_2O$: C, 39.79; H, 4.00; N, 15.46; P, 6.84. Found: C, 40.18; H, 4.31; N, 15.61; P, 6.64.

9-[4-Phenyl-4-(dimethylphosphono)but-1-yl]guanine (30). 1 N HCl (1.5 mL) was added to a suspension of **28** (600 mg, 1.46 mmol) in H_2O (3 mL). The reaction mixture was heated under reflux for 1.5 h and then neutralized by 1 N NaOH. The volatiles were removed. The residue was dissolved in MeOH and slurried

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with silica gel. The solvent was removed, and the slurry was applied to the top of a silica gel column packed in 5% MeOH/95% $CHCl_3$ solvent. The column was eluted with a $CHCl_3$–MeOH gradient (5–12% MeOH) to give **30** as a colorless solid (434 mg, 75%). An analytical sample was obtained by recrystallization of **30** from EtOH/H_2O as white crystals: mp 179–80 °C; UV (MeOH) λ_{max} 253 (12001), 270 (sh, 9120) nm; ^{31}P NMR (DMSO-d_6) δ 31.99; ^1H NMR (DMSO-d_6) δ 10.53 (bs, 1 H, NH), 7.62 (s, 1 H, H8), 7.23–7.31 (m, 5 H, C_6H_5), 6.42 (bs, 2 H, NH_2), 3.88 (t, 2 H, J = 6.9 Hz, H1′), 3.56 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.39 (d, 3 H, J_{HP} = 10.5 Hz, OCH_3), 3.25 (ddd, 1 H, J_{HP} = 22.2 Hz, J = 10.2, 4.8 Hz, H4′), 1.70–1.90 (m, 2 H, H3′), 1.46–1.60 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 157.28 (C6), 153.53 (C2), 151.47 (C4), 138.20 (C8), 135.87 (d, J = 6.8 Hz, C1″), 129.31 (d, J = 6.6 Hz, C2″), 128.87 (d, J = 2.2 Hz, C3″), 127.58 (d, J = 2.9 Hz, C4″), 116.58 (C5), 53.37 (d, J = 6.7 Hz, OCH_3), 53.06 (d, J = 6.7 Hz, OCH_3), 42.48 (C1′), 41.91 (d, J = 134.7 Hz, C4′), 27.77 (d, J = 15.2 Hz, C3′), 26.49 (d, J = 2.4 Hz, C2′); MS (FAB) m/z 392 (M + 1, 98.4). Anal. Calcd for $C_{17}H_{22}N_5O_4P\cdot0.5H_2O$: C, 51.00; H, 5.79; N, 17.49; P, 7.74. Found: C, 51.07; H, 5.71; N, 17.72; P, 7.70.

9-(4-Phenyl-4-phosphonobut-1-yl)guanine (31). Compound **31** was obtained by deprotection of **30** as described for **24**. Product **31** was purified by crystallization from EtOH/H_2O as a white solid (200 mg, 77%): mp 220–22 °C. UV (MeOH) λ_{max} 254 (12100), 270 (11646) nm; ^{31}P NMR (DMSO-d_6) δ 24.36; ^1H NMR (DMSO-d_6) δ 10.52 (bs, 1 H, NH), 7.61 (s, 1 H, H8), 7.15–7.30 (m, 5 H, C_6H_5), 6.41 (bs, 2 H, NH_2), 3.87 (t, 2 H, J = 6.9 Hz, H1′), 2.81 (ddd, 1 H, J_{HP} = 21.9 Hz, J = 10.8, 4.2 Hz, H4′), 1.90 (m, 1 H, H3′), 1.70 (m, 1 H, H3′), 1.52 (m, 2 H, H2′); ^{13}C NMR (DMSO-d_6) δ (J_{PC}) 156.75 (C6), 153.44 (C2), 151.04 (C4), 138.35 (d, J = 6.5 Hz, C1″), 137.39 (C8), 129.01 (d, J = 6.3 Hz, C2″), 127.98 (d, J = 1.9 Hz, C3″), 126.17 (d, J = 2.6 Hz, C4″), 116.42 (C5), 44.69 (d, J = 133.2 Hz, C4′), 42.31 (C1′), 28.00 (d, J = 14.4 Hz, C3′), 26.96 (bs, J = ~1.5 Hz, C2′); MS (FAB$^+$) m/z 364 (M + 1, 27). Anal. Calcd for $C_{15}H_{18}N_5O_4P\cdot H_2O$: C, 47.24; H, 5.28; N, 18.36; P, 8.12. Found: C, 47.02; H, 5.12; N, 18.15; P, 8.42.

2,6-Diamino-9-(4-phenyl-4-phosphonobut-1-yl)purine (32). Compound **29** (280 mg) was dissolved in 10 mL of methanolic ammonia and heated in a bomb at 80 °C for 24 h. The solution was concentrated, and H_2O (5 mL) was added, followed by a few drops of NH_4HCO_3. The solution was applied to a DEAE-cellulose column and eluted first with H_2O (200 mL) and then with a NH_4HCO_3 gradient (0–0.3 M). Evaporation gave the monoammonium salt of **32**. The sodium salt of **32** was prepared on a Dowex (Na^+ form) column. Crystallization from H_2O/EtOH gave **32** as a white solid (196 mg, 66%): UV (H_2O) λ_{max} 255 (7308), 280 (9338) nm; ^{31}P NMR (D_2O) δ 21.02; ^1H NMR (D_2O) δ 7.56 (s, 1 H, H8), 7.02–7.20 (m, 5 H, C_6H_5), 3.86 (m, 2 H, H1′), 2.62 (ddd, 1 H, J_{HP} = 20.7 Hz, J = 11.4, 3.0 Hz, H4′), 2.0–2.15 (m, 1 H, H3′), 1.15–1.18 (m, 3 H, H2′, H3′); ^{13}C NMR (D_2O) δ (J_{PC}) 160.82 (C2), 157.12 (C6), 151.96 (C4), 142.96 (d, J = 5.9 Hz, C1″), 141.56 (C8), 130.43 (d, J = 5.6 Hz, C2″), 129.22 (d, J = 1.8 Hz, C3″), 126.89 (d, J = 2.4 Hz, C4″), 114.46 (C5), 48.79 (d, J = 125.1 Hz, C4′), 45.21 (C1′), 29.22 (C2′), 29.01 (d, J = 15.2 Hz, C3′); MS (FAB$^+$) m/z 363 (M + 1, 4). Anal. Calcd for $C_{15}H_{17}N_6O_3PNa_2\cdot2H_2O$: C, 40.73; H, 4.78; N, 18.99; P, 7.26. Found: C, 41.04; H, 4.89; N, 18.76; P, 7.10.

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Registry No. **7**, 4850-50-4; **8**, 137333-75-6; **9**, 137333-76-7; **10**, 137333-77-8; **11**, 137333-78-9; **12**, 137333-79-0; **13**, 137333-80-3; **14**, 71009-09-1; **15**, 137333-81-4; **16**, 137333-82-5; **17**, 137333-83-6; **18**, 137333-84-7; **19**, 137333-85-8; **20**, 137333-86-9; **21**, 137333-87-0; **22** (isomer 1), 137333-88-1; **22** (isomer 2), 137334-00-0; **23** (isomer 1), 137333-89-2; **23** (isomer 2), 137334-01-1; **24**, 137333-90-5; **25**, 137333-91-6; **25**·2Na, 137334-02-2; **26**, 137333-92-7; **27**, 137333-93-8; **28**, 137333-94-9; **29**·2Na, 137333-95-0; **30**, 137333-96-1; **31**, 137333-97-2; **32**·2Na, 137333-98-3; $PhCH_2OP(NEt_2)OMe$, 137333-99-4; adenine, 73-24-5; cytosine, 71-30-7; 2-amino-6-chloropurine, 10310-21-1; 3-benzoylpropionic acid, 2051-95-8; 5-chloro-1-pentanol, 5259-98-3; glycidol, 556-52-5.

Accumulation of Hydrogen-Bonding and Electrostatic Binding Sites: Stabilization of Salts in Hydroxylic Media via Intramolecular Hydrogen Bonding[1]

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Pyridyl–bisresorcinol derivative **1a** and dodecyl phosphate (**5**) form a pyridinium–phosphate salt which is stabilized via hydrogen-bonding interaction between the bisresorcinol moiety and bound phosphate anion. The salt-formation constants (K) are relatively insensitive to solvent polarities; $K_{1a}(5)$ = 1.2 × 10^3 (water–methanol (2:1)), 1.2 × 10^3 (methanol), 1.1 × 10^3 (ethanol), and 6.9 × 10^2 M^{-1} (2-propanol). On the other hand, the salt formation with 2-picoline (**3**) as a less crowded reference host takes place with much difficulty and is highly solvent dependent; $K_3(5)$ = 2.1 × 10^2 (water–methanol (2:1)), 3.2 × 10 (methanol), 1.6 × 10 (ethanol), and 9.2 (2-propanol). The selectivities $K_{1a}(5)/K_3(5)$ thus increase with respect to change in solvents in the order, water–methanol (2:1) (6) < methanol (37) < ethanol (72) < 2-propanol (75). The role of a pair of hydroxyl groups in the bisresorcinol moiety is discussed in terms of intramolecular microsolvation.

Multipoint hydrogen bonding is a general guiding principle for the molecular recognition of complicated biorelevant molecules such as amino acids,[2] dicarboxylic acids,[3] diols,[4] sugars,[5] quinones,[6] and nucleobases and related nitrogen heterocycles[7] in apolar organic media. Biorelevant anions as guests, especially phosphates, can also be solubilized in organic solvents upon formation of salts with lipophilic cations as hosts.[8] The resulting salts

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