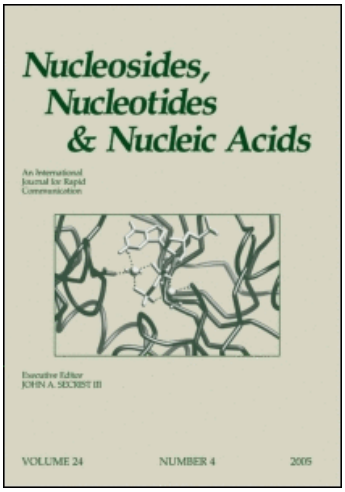

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Photo-Arbuzov Rearrangements of Benzyl Phosphites. Preparation of Acyclic Nucleoside Phosphonates Related to HPMPA

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PHOTO-ARBUZOV REARRANGEMENTS OF BENZYL PHOSPHITES. PREPARATION OF ACYCLIC NUCLEOSIDE PHOSPHONATES RELATED TO HPMPA#

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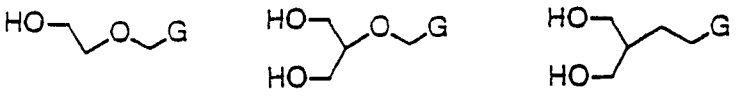
Abstract: Photo-Arbuzov rearrangement of the benzylic phosphite **18** affords the benzylphosphonate **19** which is converted to the bromo derivative **21.** The latter is a common precursor for the preparation of a series of branched-chain, acyclic nucleoside-based, benzylphosphonic acids, **25, 28, 32,** and **35.**

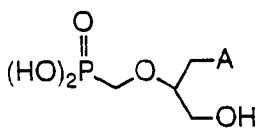
Two of the important classes of antivirals that have emerged in recent years are the acyclic nucleosides[1] and the closely related phosphonomethoxy derivatives.[2] The latter can be considered isosteres of the monophosphates that result from phosphorylation of acyclic nucleosides in the first step of their activation. Important examples of acyclic nucleosides are acyclovir, **1**, approved for use against HSV-1 infections, and ganciclovir, **2**, which is clinically effective against human cytomegalovirus.[3] The molecule penciclovir, **3**, also is a promising antiviral.[4]



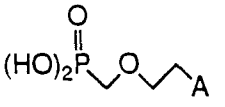
1 **2** **3**

Illustrative of the phosphonomethoxy derivatives are (S)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine (HPMPA), **4**, and 9-[2-(phosphonomethoxy)ethyl]adenine

#This paper is dedicated to the memory of Professor Roland K. Robins

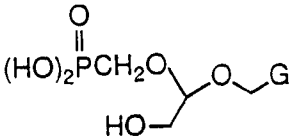


4 HPMPA



5 PMEA

(PMEA), **5**. The HPMP derivatives show promising broad spectrum activity against DNA viruses while PMEA has excellent anti-retroviral activity. The isostere of the monophosphate of ganciclovir, **6**, shows important anti-herpes activity.[5] An analogous compound, **7**, the phosphonate isostere of the monophosphonate of 2',3'-didehydro-2',3'-dideoxyadenosine, effectively inhibits



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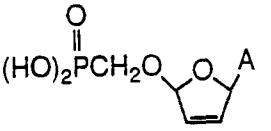
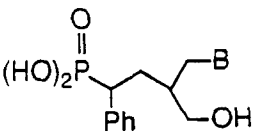


7

HIV replication.[6] Phosphonate analogs have the advantage over monophosphates that P-C bonds are not cleaved by the phosphatases which dephosphorylate monophosphates. In addition, drug-resistance resulting from loss of the viral or cellular kinase activity necessary for phosphorylation of acyclic nucleosides in the first step of their activation potentially is overcome by administration of phosphonates.

It is evident that a variety of phosphonate structures related to monophosphates of acyclic nucleosides show antiviral activity. We report here the use of the photo-Arbuzov rearrangement of benzyl phosphites, recently discovered in our laboratory,[7] to prepare a key intermediate, **21** (Scheme II), from which a series of acyclic nucleoside-based phosphonates, **25**, **28**, **32**, and **35**, was prepared.



25 B = guanin-9-yl **32** B = adenin-9-yl

28 B = 2,6-diaminopurin-9-yl **35** B = cytosin-1-yl

These molecules are related to the HPMP series but have an oxygen in the side chain of the HPMP structure replaced by CH_2 and a phenyl substituent on the carbon alpha

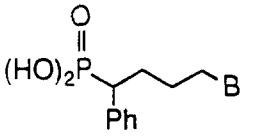
to phosphorus. Few phosphonates with substitution on the α carbon appear to have been prepared as potential antivirals.

The photo-Arbuzov reaction affords benzylphosphonates with a secondary carbon bonded to phosphorus in good yields.[7,8] By contrast the well-known thermal Arbuzov reaction between a trialkyl phosphite and a secondary halide is relatively slow even at high temperatures.[9] Furthermore, the alkylation of nucleophilic sites other than phosphorus is a potential complication in multifunctional molecules. Side product also is likely to result if the alkyl halide formed along with the desired phosphonate is a primary one, equations 1 and 2. We reported previously[8] the use

$$(EtO)_3P + PhCHBrR \rightarrow (EtO)_2P(O)CHRPh + EtBr \quad (1)$$

$$EtBr + (EtO)_3P \rightarrow EtBr + (EtO)_2P(O)Et \quad (2)$$

of the photo-Arbuzov rearrangement in the preparation of a series of benzylphosphonic acids, **8**, more analogous in structure to PMEA. The present paper illustrates the application of the photo-Arbuzov rearrangement to somewhat more elaborate molecules and demonstrates the desired inertness of the dimethyl benzylphosphonate functionality to reactions conditions that transform



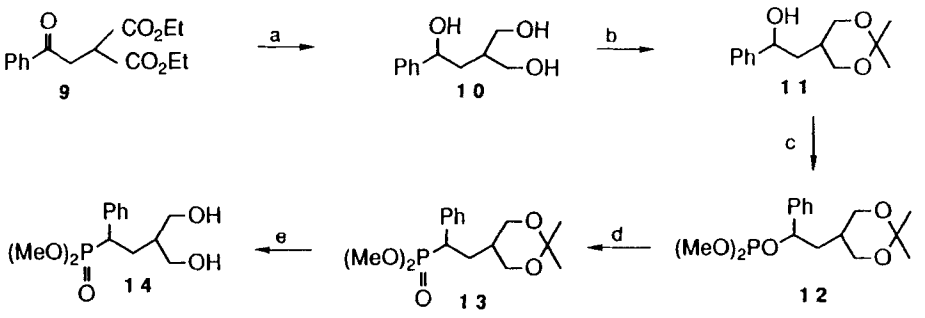
8

B = adenin-9-yl, guanin-9-yl,
2,6-diaminopurin-9-yl, cytosin-1-yl

intermediates **19** and **21** to acyclic nucleoside-based phosphonate targets with potential antiviral activity.

Results and Discussion

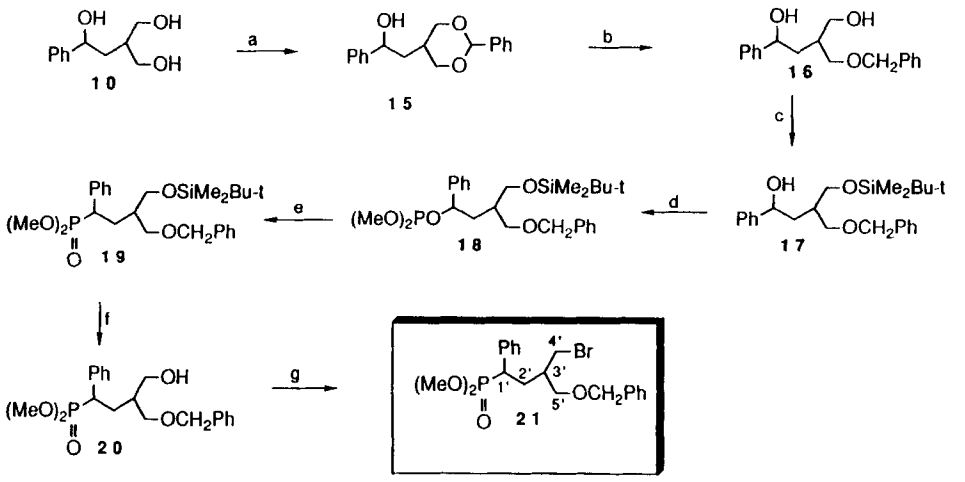
Approaches to the preparation of the key intermediates in the synthesis of the target acyclic nucleoside-based benzylphosphonates **25**, **28**, **32** and **35** are shown in Schemes I and II. Reaction of diethylmalonate with phenacyl chloride gave ketoester **9** in 98% yield which was then reduced to triol **10** in 82% yield on treatment with $NaBH_4$/*t*-BuOH/MeOH.[10] As we were interested in making secondary phosphonates,



(a) $NaBH_4$/t-BuOH/MeOH, 82%; (b) 2,2-Dimethoxypropane/PTSA, 75%; (c) $(MeO)_2PNEt_2$/tetrazole, quantitative; (d) 450 W Hanovia lamp/C_6H_6, 75%; (e) MeOH/1N HCl, 80%.

Scheme I

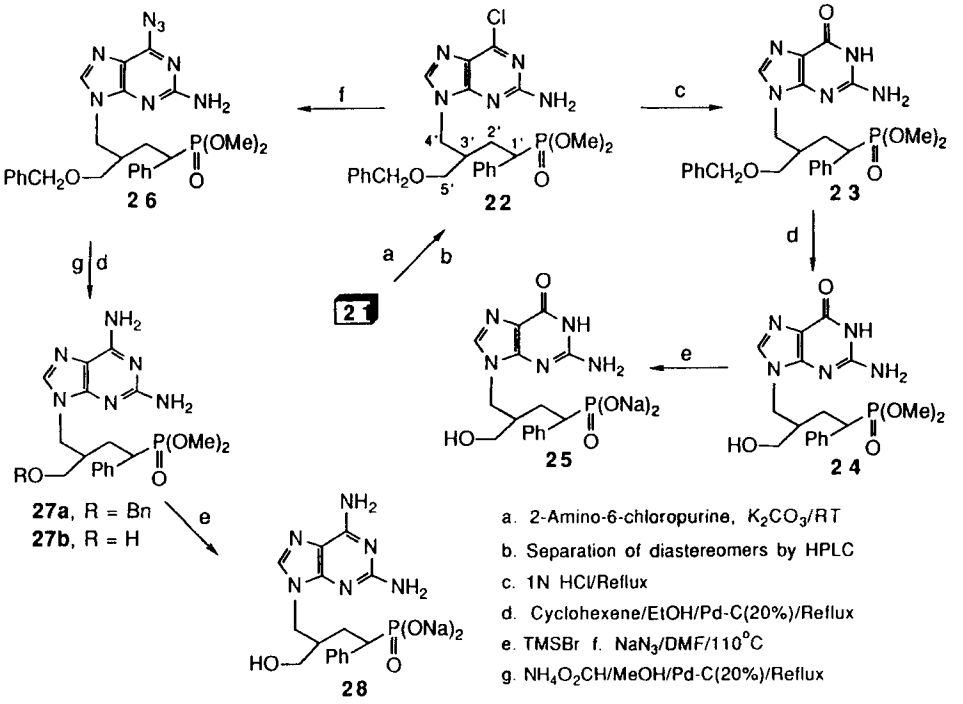
the primary alcohol functionalities were protected as the acetonide, **11**, isolated in 77% yield after chromatographic purification. Reaction of dimethyl N,N-diethyl phosphoramidite with **11** in the presence of tetrazole afforded **12**[11] quantitatively. Phosphite **12**, used without further purification, was totally consumed after 6 h of irradiation through quartz with a 450 W Hanovia ultraviolet lamp. The photoproduct, dimethyl phosphonate **13**, was isolated by column chromatography as a colorless liquid in 75% yield, based on alcohol **11**. Deprotection of the acetonide gave diol phosphonate **14** (80% yield) which was then converted to its mono tosyl derivative (62% yield) on treatment with *p*-toluenesulfonic acid in pyridine at 0 °C for 24 h and to its dimesyl derivative (83% yield) by treatment with methane sulfonyl chloride/triethylamine in CH_2Cl_2 at 0-5 °C. Unfortunately, the displacement reactions of these two derivatives of **14** with nucleic acid bases gave low yields (5-10%) of the corresponding nucleoside benzylphosphonates (adenine/NaH/DMF/25 °C, 24 h; 50 °C, 24 h, 48 h; 70 °C, 12 h, 24 h; 2-amino-6-chloropurine/K_2CO_3/DMF/25 °C, 24 h, 48 h; cytosine/NaH/DMF/25 °C, 24 h; 50 °C, 24 h, 48 h). Reaction above 50 °C led to decomposition of the mesyl and tosyl compounds but to no useful increase in yield of nucleoside-based benzylphosphonates. With cytosine O-alkylated and N-alkylated products were formed in approximately 1:1 ratio. Nonetheless, because of its potential as a diol for further transformation, details of the preparation of **14** via Scheme I are given in the Experimental Section.



(a) $PhCH(OMe)_2$/PTSA, 88%; (b) DIBAL, 84%; (c) t-$BuMe_2SiCl$/pyridine, 84%; (d) $(MeO)_2PNEt_2$/tetrazole, quantitative; (e) 450 W Hanovia lamp/C_6H_6, 78%; (f) TBAF, 84%; (g) Ph_3P/CBr_4, 74%

Scheme II

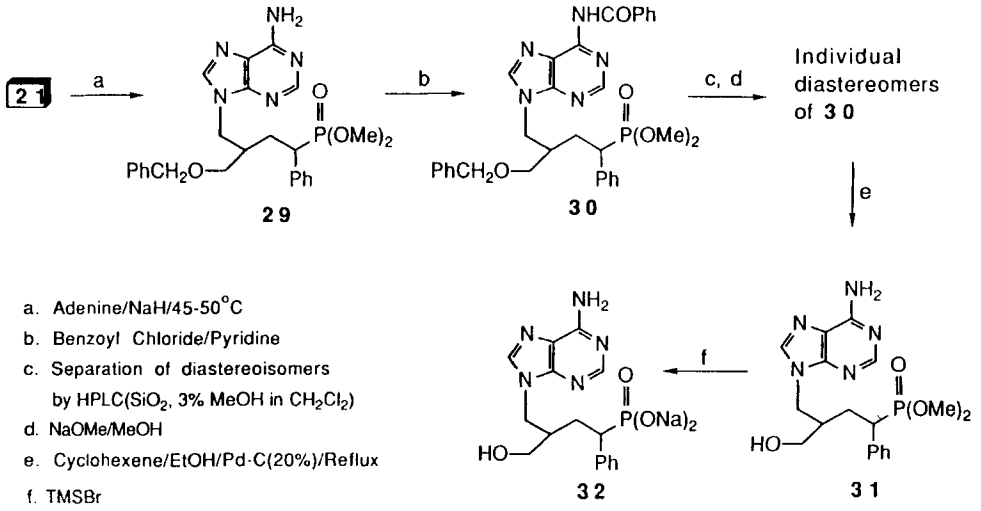
We reported earlier that the bromoalkyl functionality attached to benzylphosphonate diesters reacts with nucleic acid bases to give the corresponding nucleobase-substituted phosphonates (displacement of bromide by base) in good yields.[8] Therefore, bromophosphonate **21** was prepared by a modification of our synthetic strategy as shown in Scheme II. Triol **10** was converted to dioxane **15** (88% yield) which was then reacted with DIBAL[12] to give benzyl ether **16** in 84% yield as a mixture of diastereomers in ~55:45 ratio (^{1}H NMR). Crystallization of crude **15** afforded the *major* diastereomer. The mother liquor was a mixture of the two diastereomers, and pure *minor* diastereomer could not be isolated. However, the diastereomers of **16** were separated readily by HPLC (silica column, ethyl acetate: hexane, 1:1). The major isomer was obtained as a solid and the minor isomer as an oil. For the synthesis of purine-based phosphonates **25**, **28**, and **32**, the mixture of diastereomers of **16** was used as starting material, and the individual diastereomers were separated at a later stage. For pyrimidine-based **35**, the individual diastereomers of **16** were employed.



Scheme III

As shown in Scheme II, the primary hydroxyl of **16** was protected as its silyl ether, **17** (84% yield). Reaction of **17** with dimethyl N,N-diethyl phosphoramidite[11] afforded phosphite **18** in quantitative yield. Phosphonate **19** was obtained from a 6 h photoreaction in 78% isolated yield in a 55:45 ratio of diastereomers. Deprotection of the silyl ether moiety of **19** provided alcohol **20** (84% yield) which gave **21** in 74% isolated yield. The diastereomic ratio for both **20** and **21** was the same as that of **19** (~ 55:45, ^{31}P NMR).

With the key, monobromo, dimethyl benzylphosphonate (**21**) in hand, the target acyclic nucleoside phosphonic acids were synthesized by attachment of the appropriate nucleobase to yield intermediates **22**, **29**, and **33** followed by elaboration to **25**, **28**, **32** and **35** (Schemes III-V). Thus, treatment of **21** (mixture of diastereomers, ~55:45) with 2-amino-6-chloropurine in the presence of anhydrous K_2CO_3[13] afforded **22** in 65% yield as a colorless foam in ~55:45 (^{31}P NMR) ratio of diastereomers (Scheme III).

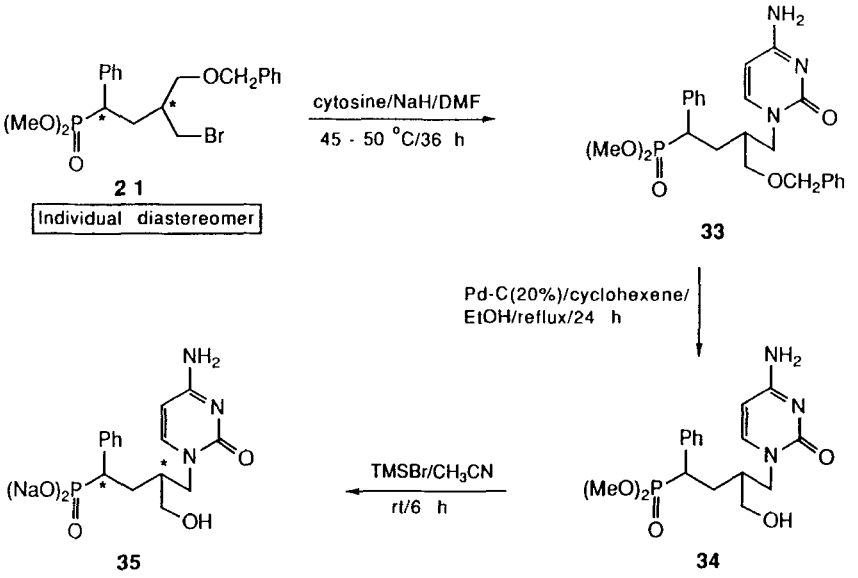


Scheme IV

The individual diastereomers of **22** were readily separated by HPLC (silica column, CH_2Cl_2:MeOH, 97:3). Acid hydrolysis of **22** afforded **23** (75%, major diastereomer; 76%, minor diastereomer). Compound **23** was debenzylated by transfer hydrogenolysis[13,14] to give **24** (80% major, 78% minor) which was demethylated ($BrSiMe_3$) and converted to the sodium salt, **25**.

Individual diastereomers of **22** were converted to 6-azidopurine intermediate **26** (66% major diastereomer, 65% minor diastereomer) on treatment with sodium azide at 100-105°C. Reduction of the azido group with ammonium formate[10] in refluxing methanol afforded the 2,6-diaminopurine-based product, **27a**, in high yield (92%, 93%). Debenzylation by transfer hydrogenolysis[13,14] to **27b** was followed by demethylation and conversion of the phosphonic acid derivative to its sodium salt, **28**, in good yield.

The synthesis of the adenine-based benzylphosphonate **32** is illustrated in Scheme IV. Reaction of a diastereomeric mixture of **21** (55:45 ratio) with adenine, which had first undergone reaction with NaH in DMF, afforded **29** in 60% isolated yield as a 55:45 (^{31}P NMR) mixture of diastereomers. At this stage the diastereomers could not be separated. However, protection of the amino group with the benzoyl moiety allowed their separation by HPLC (silica gel column, 3% MeOH in CH_2Cl_2).



Scheme V

Debenzoylation (86%, 84%) provided the pure diastereomers of **29** which were debenzylated (86%, 87%), demethylated, and converted to the individual diastereomers of **32** (81%, 80%).

Cytosine-based benzylphosphonic acid **35** was prepared from the reaction of individual diastereomers of **21** and cytosine (Scheme V), because the diastereomers of **33** could not be separated even by protecting the amino group with the acetyl, isobutyryl, or FMOC groups. Limited success was obtained when the amino group was benzoylated. The individual diastereomers of **21** were obtained from those of **16** by the procedure shown in Scheme II. The silyl ether **19** was deprotected by treating with 80% acetic acid instead of tetrabutylammonium fluoride, since deprotection of a pure diastereomer of **19** with TBAF afforded alcohol **20** as a mixture of diastereomers (final ratio, 55:45). Transformation of the readily obtained (**21** → **33**) individual diastereomers of **33** (58%, 59%) to those of the benzylphosphonic acid salt **35** (70%, 66%; yield based on **33**), by means analogous to those used for **29** → **32**, is shown in Scheme V.

The structural assignments for acyclic nucleoside-based benzylphosphonic acids **25**, **28**, **32** and **35** and their precursors were verified by ^{31}P, ^{1}H, and ^{13}C NMR and UV spectroscopy (Experimental). The numbering of the protons and carbons of the acyclic precursors is shown for **21** in Scheme II, and those of the benzylphosphonic acids and their nucleobase-substituted precursors are given for **22** in Scheme III. For the purine-based benzylphosphonates, the ^{1}H NMR resonances of the diastereotopic H4' protons (ABX spin system) of the minor isomer have more first-order character than those of the major isomer (larger $\Delta\delta_{AB}$). The H4' protons of both isomers of the cytosine-based benzylphosphonates appeared as very second-order ABX multiplets. The benzylic protons ($OCH_2C_6H_5$) of the minor isomers of all the nucleoside-based phosphonates appeared as AB quartets whereas those of the major isomer appeared as broad singlets, because the chemical shifts of the diastereotopic AB protons are close to equivalent. The 5'-CH_2 protons also were diastereotopic leading to ABX spectra. No correlation, however, could be made between the identity of the isomer and the extent of first-order character of the 5'-CH_2 protons. The methoxyl groups of the dimethyl benzylphosphonates (**13**, **14**, **20**, **21**, etc.) were diastereotopic as clearly demonstrated by their chemical shift nonequivalence in both ^{1}H and ^{13}C NMR spectra. Clearly, these correlations of spectral characteristic with diastereomeric structure should prove to be useful in identifying individual diastereomers. Unfortunately, X-ray quality crystals have not been readily obtainable, and the structures cannot be assigned at this time.

Nucleoside-based phosphonic acids **25**, **28**, **32** and **35** have not shown activity as antivirals during in vitro tests. These results will be reported separately along with the outcome of biochemical studies in collaboration with the group of Professor Eric De Clercq, Leuven, Belgium, aimed at defining the structural source of inactivity in the above phosphonic acids. The absence of antiviral inactivity makes the assignment of absolute configurations to the separated, individual diastereomers less important.

Summary. Readily available triol **10** is converted in four high-yield steps to phosphonite **18**. Irradiation through quartz converted **18** to the key benzylphosphonate dimethyl ester, **19**, in 78% isolated yield (Scheme II). Similarly, phosphonite **12** (Scheme I) was photorearranged to its phosphonate, **13**, in nearly identical yield. The further utilization of **13** through its deprotection to **14** and displacement of one of its

hydroxyls as the tosyl or mesyl derivative by a nucleobase anion was not successful. However, **18** was converted in three efficient steps to **21** which served as the precursor to the disodium phosphonates **25**, **28**, **32**, and **35** which are structurally related to the antiviral HPMP series. By use of the individual diastereomers of **21**, the individual diastereomers of **35** were obtained. Preparation of the other product benzylphosphonates diastereomerically pure was accomplished by HPLC separation of the diastereomers of precursor **22** in the case of **25** and **28** and those of precursor **30** prior to its conversion to **32**.

These syntheses, and those for the series of phosphonates more related to PMEA we reported previously,[8] show the utility of the dimethyl benzylphosphonate functionality when introduced rather early on in a reaction sequence for the preparation of phosphonates derived from acyclic nucleosides. The substitution of the alkyl chain by the requisite nucleobase is then done in the following step. In the reactions of Schemes I-V the dimethyl benzylphosphonate functionality remained intact to conditions of: 1 N HCl/MeOH; 1 M TBAF in THF; NaH and K_2CO_3 in DMF; NaN_3 in DMF at 110 °C (some demethylation); refluxing EtOH and MeOH; benzoyl chloride benzoylation; and mild MeONa/MeOH.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were taken on a Varian XL-300 spectrometer at 300 MHz. Listed J values in the ^{1}H NMR spectral data refer to proton-proton couplings unless otherwise stated. Designations of protons follow those of the carbon atoms. The H4' proton pair and H5' proton pair are diastereotopic. Where cleanly separated into four peaks, their resonances constitute the AB portion of an ABX system. Chemical shifts and J values recorded are based on first-order inspections of the AB portion of the spectrum and should not be considered to be precise values because of the variable degree of second-order character of the spectra. The benzyl protons of the benzyloxy substituents also are diastereotopic. Where AB quartets were clearly discernable, the measured J_{AB} values are recorded along with the range in ppm between the frequency extremes of the four peaks. ^{13}C NMR spectra were obtained on a Varian XL-300 MHz spectrometer at 75.4 MHz. The carbons of the base are designated as C1, C2, etc. (structures **21** and **22**); those of butyl chain C1', C2', etc.; those of the C_6H_5CH phenyl group C1", C2", etc.; those of benzyl phenyl group C1*, C2*, etc. Listed J values in the ^{13}C NMR spectral data refer to carbon-phosphorus couplings. Individual carbons of the phenyl groups (C1"-C4") were assigned with the aid of proton-coupled spectra. Ortho and meta carbons were arbitrarily assigned δ^{13}C (ortho) > δ^{13}C (meta). ^{31}P NMR spectra were recorded on a Varian XL-300 MHz spectrometer at 121.3 MHz.

UV absorption spectra were taken with a Hewlett Packard 8452A diode array spectrophotometer. Mass spectra were determined on a Finnigan MAT 95 mass spectrometer. Analytical tlc was performed on Merck 0.2 mm layer silica gel 60 F_{254}. Column chromatography employed Merck silica gel 60, 230-400 mesh. Sephadex A-25 (HCO_3^- form) was used for ion-exchange chromatography. C18 reverse phase column (HPLC) was used for final purification of some phosphonic acid derivatives. Anhydrous solvents were obtained as follows: acetonitrile by successive distillation from P_4O_{10} and then CaH_2; benzene, distillation from sodium; dimethylformamide and pyridine, distillation from CaH_2; tetrahydrofuran, distillation from sodium/benzophenone.

Ketoester 9. A solution of diethylmalonate (10.0 g, 62.5 mmol) in THF (50 mL) was added dropwise to a stirred suspension of NaH (2.75g of 60% reagent, 68.7 mmol) in THF (100 mL) at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred for 1 h. It was then cooled to 0 °C, and a solution of phenacyl chloride (9.63 g, 62.5 mmol) in THF (50 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed, and the residue was dissolved in EtOAc (150 mL) and washed with H_2O (2 x 70 mL) and NaCl/H_2O (1 x 60 mL). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound as a liquid (17.0 g, 98%); IR (neat) 1730, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7.0 Hz, CH_2CH_3), 3.60 (2H, d, J = 7.0 Hz, $COCH_2$), 4.05 (1H, t, J = 7.0 Hz, CH_2CH), 4.25 (4H, q, OCH_2CH_3), 7.50 (2H, apparent t, J = 8.0 Hz, C_6H_5), 7.62 (1H, m, C_6H_5), 7.88 (2H, m, C_6H_5); MS(CI): m/z 279 (M + 1). Anal. Calcd for $C_{15}H_{15}0_5$: C, 64.73; H, 6.52. Found: C, 64.60; H, 6.53.

3-Hydroxylmethyl-1-phenylbutan-1,4-diol (10). To a refluxing solution of ketoester **9** (16.0 g, 57.6 mmol) and sodium borohydride (5.03 g, 132 mmol) in *tert*-butyl alcohol (150 mL) was added methanol (20 mL) in three aliquots over 0.5 h. The solution was heated under reflux for a further 1 h, allowed to cool, and then was diluted with EtOH (300 mL). Hydrochloric acid (5 M) was added with care until the solution was neutral. The solution was filtered, and the residue was washed with ethanol (2 x 100 mL). The solutions were combined, and the solvent was removed. The triol was purified on a silica gel column eluting with EtOAc and was obtained as a colorless oil (9.25 g, 82%): IR (neat) 3650-2500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.52 (2H, m, $CHOHCH_2$), 1.62 (1H, m, CH_2CH), 4.31-4.48 (4H, m, CH_2OH), 4.39 (1H, t, J = 5.0 Hz, CH_2OH), 4.44 (1H, t, J = 5.0 Hz, CH_2OH), 4.62 (1H, unresolved dt, CHOH), 5.21 (1H, d, J = 4.5 Hz, CHOH), 7.25-7.36 (5H, m, C_6H_5). Anal. Calcd for $C_{11}H_{16}0_3$: C, 67.32, H, 8.22. Found: C, 67.23; H, 8.20.

5-(2-Hydroxyl-2-phenylethyl)-2,2-dimethyl-1,3-dioxane (11). To a solution of **10** (10.0 g, 51.0 mmol) in THF (50 mL) and 2,2-dimethoxypropane (5.46 g, 6.45 mL, 52.5 mmol) was added *p*-toluenesulfonic acid monohydrate (0.29 g, 1.55 mmol). The solution was stirred at room temperature for 4 h and then neutralized by addition of triethylamine. The solvent was removed, and the residue was purified by column chromatography on silica gel eluting with 10% EtOAc in hexane. Appropriate fractions were combined to give **11** as a thick oil (9.3 g, 77%): ^1H NMR ($CDCl_3$) δ 1.36 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.62 (2H, m, CH_2CH), 1.92 (1H, m, CH_2CH), 2.65 (1H, bs, OH), 3.56 (1H, dd, J = 8.5 Hz, 4.7 Hz, CH_2O), 3.60 (1H, dd, J = 8.5 Hz, 4.9 Hz, CH_2O), 3.79 (1H, ddd, J = 11.7 Hz, 4.6 Hz, 1.4 Hz, CH_2O), 3.90 (1H, ddd, J

= 11.7 Hz, 4.6 Hz, 1.4 Hz, CH_2O), 4.67 (1H, dd, J = 7.8 Hz, 5.6 Hz, C_6H_5CHOH), 7.22-7.35 (5H, m, C_6H_5). Anal. Calcd for $C_{14}H_{20}0_3$: C, 71.15; H, 8.53. Found: C, 71.22; H, 8.50.

Phosphonate (13). Tetrazole (700 mg, 10.0 mmol) was added to a stirred solution of alcohol **11** (5.9 g, 25 mmol) and dimethyl N,N-diethylphosphoramidite (4.95 g, 30 mmol) in CH_3CN (50 mL) at room temperature under argon. After 4 h CH_3CN was removed, and dry Et_2O (50 mL) was added. The tetrazolinium salt was filtered off, and ether was removed to give phosphite **12** as a colorless liquid (8.15 g, quantitative) which was used in the next step without further purification. (^{31}P NMR showed a single peak at δ 141.1, $CDCl_3$). Phosphite **12** was dissolved in benzene (0.1 M solution), dispersed into six, septum-capped quartz test tubes, flushed with argon and then irradiated (450W medium pressure Hg lamp) for 6 h. GC showed complete disappearance of phosphite **12**. The solvent was removed, and the product was purified by column chromatography on silica gel eluting with 1% MeOH in $CHCl_3$ to give phosphonate **13** as a colorless liquid (6.1 g, 75%): ^{31}P NMR ($CDCl_3$) δ 31.04; ^1H NMR ($CDCl_3$) δ 1.32 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.58-1.72 (1H, m, CH_2CH), 1.82-2.00 (2H, m, CH_2CH), 3.03 (1H, ddd, J_{HP} = 23.4 Hz, J = 11.7 Hz, 4.2 Hz, PCH), 3.42 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.45-3.84 (4H, m, CH_2O), 3.68 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 7.22-7.38 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 20.99 (CH_3), 26.48 (CH_3), 28.57 (d, J = 3.1 Hz, CH), 31.76 (d, J = 14.6 Hz, CH_2), 41.34 (d, J = 137.9 Hz, CHP), 52.50 (d, J = 7.4 Hz, OCH_3), 53.36 (d, J = 7.0 Hz, OCH_3), 63.39 (CH_2O), 64.61 (CH_2O), 97.63 $C(CH_3)_2$, 127.37 (d, J = 3.2 Hz, *p*-C_6H_5), 128.60 (d, J = 2.7 Hz, *m*-C_6H_5), 128.86 (d, J = 6.7 Hz, *o*-C_6H_5), 134.85 (d, J = 7.2 Hz, *ipso*-C_6H_5). Anal. Calcd for $C_{16}H_{25}O_5P$: C, 58.52, H, 7.67. Found: C, 58.53; H, 7.71.

Phosphonate Diol (14). To a stirred solution of phosphonate **13** (2.25 g, 6.85 mmol) in THF (40 mL), 2N HCl (8 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The solvent was removed by co-evaporation with CH_3CN and toluene to give a liquid which was purified by column on silica gel eluting with 5% MeOH in $CHCl_3$. Phosphonate **14** was obtained as a colorless liquid (1.58 g, 80%): ^{31}P NMR ($CDCl_3$) δ 31.99; ^1H NMR ($CDCl_3$) δ 1.62 (1H, m, CH), 1.94 (1H, ddd, J = 13.8 Hz, 9.6 Hz, 4.2 Hz, CH_2CH), 2.15 (1H, ddd, J=13.8 Hz, 9.6 Hz, 4.2 Hz, CH_2CH), 3.23 (1H, ddd, J_{HP} = 23.1 Hz, J = 11.7 Hz, 3.9 Hz, PCH), 3.47 (3H, d, J_{HP} = 10.5 Hz OCH_3), 3.65 (3H, J_{HP} = 10.5 Hz, OCH_3), 3.50-3.75 (4H, m, CH_2OH), 7.26-7.38 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 27.18 (d, J = 2.9 Hz, CH_2CH), 38.88, (d, J = 13.8 Hz, CH_2CH), 41.01 (d, J = 136.6 Hz, PCH), 52.58 (d, J = 7.4 Hz, OCH_3), 53.21 (d, J = 7.1 Hz, OCH_3), 62.11 (CH_2OH), 64.73 (CH_2OH), 127.07 (d, J = 3.3 Hz, *p*-C_6H_5), 128.36 (d, J = 2.6 Hz, *m*-C_6H_5), 128.90 (d, J = 6.8 Hz, *o*-C_6H_5), 134.99 (d, J = 7.3 Hz, *i*-C_6H_5). Anal. Calcd for $C_{13}H_{21}O_5P$: C, 54.16; H, 7.34. Found: C, 54.25; H, 7.26.

5-(2-Hydroxyl-2-phenylethyl)-2-phenyl-1,3-dioxane (15). Triol **10** (10.0 g, 51.0 mmol) was dissolved in THF (100 mL) to which was added benzaldehyde dimethyl acetal (7.75 g, 7.65 mL, 51.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (300 mg). The solution was stirred at room temperature for 4 h. Et_3N was added, and the THF was evaporated. The residue was dissolved in EtOAc (100 mL), washed with $NaHCO_3$(10% soln, 2 x 50 mL) and H_2O (2 x 50 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a low melting solid (14.2 g, 98%) which was directly used in the next step. Crystallization of the crude product gave the

major diastereoisomer as a crystalline solid, mp 105-106 °C. The mother liquor was a mixture of two diastereoisomers: ^{1}H NMR ($CDCl_3$) δ (major isomer) 1.40 (1H, ddd, J = 14.0 Hz, 6.6 Hz, 5.6 Hz, CH_2), 1.50 (1H, ddd, J = 14.0 Hz, 7.8 Hz, 6.6 Hz, CH_2), 1.98 (1H, d, J = 3.0 Hz, OH), 2.77 (1H, m, CH), 3.48 (1H, t, J = 11.1 Hz, CH_2O), 3.52 (1H, t, J = 11.1 Hz, CH_2O), 4.17 (1H, ddd, J = 11.1 Hz, 4.6 Hz, 2.4 Hz, CH_2O), 4.30 (1H, ddd, J = 11.1 Hz, 4.6 Hz, 2.4 Hz, CH_2O), 4.17 (1H, unresolved ddd, C_6H_5CHOH), 5.36 (1H, s, CHC_6H_5), 7.30-7.47 (10H, m, C_6H_5); Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.08. Found: C, 75.92; H, 7.07. (minor isomer): 2.05 (1H, m, CH), 4.00-4.14 (4H, m, CH_2O), 4.80 (1H, dd, J = 9.3 Hz, 3.6 Hz, C_6H_5CHOH), 5.47 (1H, s, CHC_6H_5). The rest of the protons had chemical shifts identical to those of major isomer.

3-Benzyloxymethyl-1-phenyl-butan-1,4-diol (16). Compound **15** (15.0 g, 52.82 mmol) was dissolved in toluene (150 mL) and cooled to 0 °C under argon. DIBAL (81 mL, 1.5 M in toluene) was added dropwise with vigorous stirring at a rate to maintain the temperature 0-5 °C. After the addition was complete, the reaction mixture was allowed to stir at room temperature overnight. A solution of MeOH (20 mL) in toluene (40 mL) was then added carefully with cooling at a rate to keep the temperature below 35 °C. After the addition of MeOH the reaction mixture became gelatinous. Water (30 mL) was then carefully added, and the resulting slurry was vigorously stirred until the mixture became granular (2 h). The precipitate was filtered through celite and washed with toluene. The filtrate was concentrated to an oil. The crude product was purified by column on silica gel eluting with 1:1 ethyl acetate/hexane to give a colorless liquid (12.7 g, 84% in ~55:45 ratio of isomers, ^{1}H NMR). The diastereomers were separated by HPLC (silica gel column, 1:1 EtOAc:hexane). The major isomer was obtained as a solid, mp 66-67 °C, the minor one as a thick oil: Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.70 (2H, t, J = 6.5 Hz, H2'), 1.97 (1H, m, H3'), 3.33-3.41 (2H, m, H4'), 3.49 (1H, dd, J = 10.8 Hz, 6.1 Hz, H5'), 3.61 (1H, dd, J = 10.8 Hz, 5.3 Hz. H5'), 4.36-4.45 (2H, ABq, J = 12.0 Hz, $CH_2C_6H_5$), 4.63 (1H, t, J = 6.6 Hz, H1'), 7.16-7.32 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 39.17 (C3'), 39.45 (C2'), 64.65 (C4'), 72.18 (C5'), 72.59 (C1'), 73.02 ($CH_2C_6H_5$), 125.51 (C3*), 127.02 (C4*), 127.40 (C2*), 127.45 (C4"), 128.09 (C3"), 128.18 (C2"), 137.75 (C1"), 144.84 (C1*) Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74; Found: C, 75.60; H, 7.79. Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.71-1.81 (2H, m, H2'), 1.96-2.05 (1H, m, H3'), 3.36 (1H, bs, OH), 3.40-3.50 (2H, m, H5'), 3.59 (2H, distorted d, H4'), 3.92 (1H, bs, OH), 4.38-4.46 (2H, ABq, J = 12.0 Hz, $CH_2C_6H_5$), 4.71 (1H, distorted dd, J = 7.5 Hz, 5.0 Hz, H1'), 7.20-7.32 (10H, m, C_6H_5): ^{13}C NMR ($CDCl_3$) δ 37.87 (C2'), 38.92 (C3'), 64.55 (C4'), 71.71 (C1'), 72.89 (C5'), 73.15 ($CH_2C_6H_5$), 125.54 (C3*), 127.06 (C4*), 127.51 (C2*), 127.59 (C4"), 128.17 (C3"), 128.28 (C2"), 137.67 (C1"), 144.70 (C1*). Anal. Calcd for $C_{18}H_{22}0_3$: C, 75.50; H, 7.74; Found: C, 75.58; H, 7.72.

3-Benzyloxymethyl-1-phenyl-4(*tert*-butyldimethylsilyoxy)butan-1-ol (17). *tert*-Butyldimethylsilyl chloride (3.32 g, 22.0 mmol) was added to a stirred solution of diol **16** (6.0 g, 21 mmol) in pyridine (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 h. Pyridine was evaporated, and the residue was dissolved in EtOAc (100 mL), washed with H_2O (2 x 70 mL) and NaCl/H_2O (1 x 100 mL). The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was passed through a short column. The column was first eluted with 1% EtOAc in hexane (200 mL) and then with 20% EtOAc in hexane (200 mL) to give **17** as a colorless liquid

(7.05 g, 84%): ^{1}H NMR ($CDCl_3$) δ (major isomer) 0.040 (6H, s, CH_3), 0.88 (9H, s, *t*-C_4H_9), 1.77 (2H, m, H2'), 2.05 (1H, m, H3'), 3.38 (1H, dd, J = 9.2 Hz, 6.0 Hz, H4') 3.45 (1H, dd, J = 9.2 Hz, 5.8 Hz, H4'), 3.55 (1H, dd, J = 10.0 Hz, 6.6 Hz, H5'), 3.68 (1H, dd, J = 10.0 Hz, 5.5 Hz, H5'), 3.93 (1H, bs, OH), 4.47 (2H, bs, $CH_2C_6H_5$), 4.76 (1H, dd, J = 8.0 Hz, 4.4 Hz, H1'), 7.17-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ -5.52 ($SiCH_3$), 18.16 (SiC), 25.82 (CH_3 of *t*-C_4H_9), 39.16 (C2'), 40.12 (C3'), 64.48 (C4'), 71.16 (C5'), 72.25 (C1'), 73.01 ($CH_2C_6H_5$), 125.54 (C3*), 126.77 (C4*), 127.40 (C2*), 127.41 (C4"), 128.01 (C3"), 128.16 (C2"), 137.93 (C1"), 145.07 (C1*). Anal. Calcd for $C_{24}H_{36}O_3Si$: C, 71.95; H, 9.05. Found: C, 72.04; H, 9.11. The minor isomer of **17** was prepared by an analogous procedure as a colorless liquid (83%): ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s, $SiCH_3$), 0.89 (9H, s, *t*-C_4H_9), 1.72-1.85 (2H, m, H2'), 2.03-2.12 (1H, m, H3'), 3.40 (1H, dd, J = 9.3 Hz, 6.0 Hz, H4'), 3.49 (1H, dd, J = 9.3 Hz, 6.6 Hz, H4'), 3.56 (1H, dd, J = 10.2 Hz, 6.6 Hz, H5'), 3.70 (1H, dd, J = 10.2 Hz, 5.8 Hz, H5'), 3.81 (1H, bs, OH), 4.50 (2H, bs, $CH_2C_6H_5$), 4.79 (1H, dd, J = 8.3 Hz, 4.5 Hz, H1'), 7.20-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ -5.54 ($SiCH_3$), 18.20 (SiC), 25.83 (CH_3 of *t*-C_4H_9), 39.03 (C2'), 40.26 (C3'), 64.16 (C4'), 71.62 (C5'), 72.20 (C1'), 73.18 ($CH_2C_6H_5$), 125.68 (C3*), 126.97 (C4*), 127.61 (C2*), 127.65 (C4"), 128.21 (C3"), 128.36 (C2"), 138.04 (C1"), 145.20 (C1*). Anal. Calcd for $C_{24}H_{36}O_3Si$: C, 71.95; H, 9.05. Found: C, 71.65; H, 9.30.

Dimethyl 1-Phenyl-3-benzyloxymethyl-4-(*tert* butyldimethylsilyloxy)butylphosphonate (19). Tetrazole (560 mg, 8.0 mmol) was added to a stirred mixture of alcohol **17** (8.0 g, 20 mmol) and dimethyl N,N-diethylphosphoramidite (4.29 g, 26.0 mmol) in CH_3CN (50 mL) under argon at room temperature. After 6 h CH_3CN was removed, and dry ether was added. The tetrazolinium salt was removed by quick filtration. Ether was removed, and the residual liquid was left under high vacuum overnight. Phosphite **18** was obtained as a colorless liquid (9.74 g, quantitative), and ^{31}P NMR showed only one peak, δ 141.26 ($CDCl_3$). Phosphite **18** was dissolved in dry benzene (200 mL). The solution was degassed by bubbling argon through it for 15 min. The solution was then irradiated by a 450 W medium pressure UV lamp. The conversion of **18** to phosphonate **19** was complete in 6 h. The benzene was removed, and the residual liquid was dissolved in $CHCl_3$ and applied to a silica gel column, eluted with $CHCl_3$ and then with 1% MeOH in $CHCl_3$. Phosphonate **19** was obtained as a colorless liquid (7.59 g, 78%) as a mixture of diastereomers, major/minor = 55/45 (^{31}P NMR): Major isomer: ^{31}P NMR ($CDCl_3$) δ 31.86; ^{1}H NMR ($CDCl_3$) δ 0.02 (3H, s, CH_3), 0.04 (3H, s, CH_3), 0.88 (9H, s, *t*-C_4H_9), 1.63 (1H, m, H3'), 2.00-2.20 (2H, m, H2'), 3.23 (1H, ddd, J_{HP} = 23.0 Hz, J = 11.0 Hz, 4.7 Hz, H1'), 3.27 (1H, dd, J = 9.0 Hz, 5.5 Hz, H4'), 3.36 (1H, dd, J = 9.0 Hz, 7.0 Hz, H4'), 3.43 (3H, d, J_{HP} = 10.4 Hz, OCH_3), 3.53 (1H, dd, J = 10.0 Hz, 4.8 Hz, H5'), 3.61 (1H, dd, J = 10.0 Hz, 4.0 Hz, H5'), 3.68 (3H, d, J_{HP} = 10.4 Hz, OCH_3), 4.36 (2H, bs, $CH_2C_6H_5$), 7.20-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ -5.53 ($SiCH_3$), -5.51 ($SiCH_3$), 18.24 (SiC), 25.85 (CH_3 of *t*-Bu), 27.52 (d, J = 3.0 Hz, C3'), 38.08 (d, J = 14.6 Hz, C2'), 41.61 (d, J = 137.0 Hz, C1'), 52.54 (d, J = 7.3 Hz, OCH_3), 53.30 (d, J = 7.0 Hz, OCH_3), 61.15 (C4'), 70.96 (C5'), 72.91 ($CH_2C_6H_5$), 127.13 (d, J = 3.4 Hz, C4"), 127.30 (C4*), 127.40 (C3*), 128.16 (C2*), 128.49 (d, J = 2.7 Hz, C3"), 129.25 (d, J = 6.6 Hz, C2"), 135.48 (d, J = 7.1 Hz, C1"), 138.39 (C1*); MS (FAB) m/z: 493.252644 (M+1). $C_{26}H_{41}O_5SiP$+1 requires 493.253917. Minor isomer: ^{31}P NMR ($CDCl_3$) δ 31.74; ^{1}H NMR ($CDCl_3$) δ 0.02 (3H, s, $SiCH_3$), 0.04 (3H,

s, $SiCH_3$), 0.85 (9H, s, t-C_4H_9), 1.63 (1H, m, H3'), 2.00-2.20 (2H, m, H2'), 3.20 (1H, ddd, J_{HP} = 23.2 Hz, J = 10.8 Hz, 5.0 Hz, H1'), 3.38 (2H, m, H4', partially hidden under OCH_3 signal; J could not be calculated), 3.41 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.45 (1H, dd, J = 11.5 Hz, 5.8 Hz, H5'), 3.53 (1H, dd, J = 11.5 Hz, 6.3 Hz, H5'), 3.65 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.37-4.50 (2H, ABq, J = 12.2 Hz, $CH_2C_6H_5$), 7.18-7.38 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ -5.52 ($SiCH_3$), -5.49 ($SiCH_3$), 18.08 (SiC), 25.74 ($(CH_3)_3C$), 27.87 (d, J = 2.8 Hz, C3'), 38.45 (d, J = 14.3 Hz, C2'), 41.42 (d, J = 136.5 Hz, C1'), 52.38 (d, J = 7.3 Hz, OCH_3), 53.06 (d, J = 7.0 Hz, OCH_3), 63.65 (C4'), 68.78 (C5'), 72.88, ($CH_2C_6H_5$), 126.91 (d, J = 3.3 Hz, C4"), 127.25 (C4*), 127.37 (C3*), 128.05 (C2*), 128.27 (d, J = 2.7 Hz, C3"), 129.12 (d, J = 6.6 Hz, C2"), 135.38 (d, J = 7.3 Hz, C1"), 138.27 (C1*). MS(FAB) m/z: 493.252648 (M+1). $C_{26}H_{41}O_5SiP$+1 requires 493.253917.

Dimethyl 1-Phenyl-3-benzyloxymethyl-4-hydroxybutylphosphonate (20). Tetrabutylammonium fluoride (1M solution in THF, 24 mL, 24.0 mmol) was added to a stirred solution of **19** (9.84 g, 20.0 mmol) in THF (50 mL) at room temperature. After 4 h 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 $CHCl_3$-MeOH (0-4% MeOH) gradient to give **20** as a colorless oil (6.35 g, 84%) as a mixture of diastereomers, major/minor = 55/45 (^{31}P NMR): Major isomer: ^{31}P NMR ($CDCl_3$) δ 31.30; ^1H NMR ($CDCl_3$) δ 1.66 (1H, m, H3'), 1.98-2.20 (2H, m, H2'), 3.26 (1H, ddd, J_{HP} = 23.2 Hz, J = 11.2 Hz, 4.2 Hz, PCH), 3.33-3.56 (4H, m, H4', H5'), 3.42 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.63 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.36 (2H, bs, $CH_2C_6H_5$), 7.19-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 27.53 (d, J = 2.6 Hz, C3'), 37.67 (d, J = 14.2 Hz, C2'), 41.18 (d, J = 136.5 Hz, C1'), 52.38 (d, J = 7.3 Hz, OCH_3), 53.06 (d, J = 7.0 Hz, OCH_3), 62.37 (C4'), 72.57 (C5'), 72.80 ($CH_2C_6H_5$), 126.94 (d, J = 3.0 Hz, C4"), 127.14 (C3*), 127.20 (C4*), 127.97 (C2*), 128.26 (d, J = 2.5 Hz, C3"), 128.93 (d, J = 6.8 Hz, C2"), 135.15 (d, J = 7.2 Hz, C1"), 137.78 (C1*). Minor isomer: ^{31}P NMR ($CDCl_3$) δ 31.73; ^1H NMR ($CDCl_3$) δ 1.64 (1H, m, H3'), 2.00-2.13 (2H, m, H2'), 3.17 (1H, ddd, J_{HP} = 23.3 Hz, J = 8.8 Hz, 6.4 Hz, H1'), 3.38 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.34-3.50 (4H, m, H4', H5'), 3.61 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.36-4.48 (2H ABq, J = 12.0 Hz, $CH_2C_6H_5$), 7.15-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 27.80 (d, J = 2.8 Hz, C3'), 37.73 (d, J = 14.2 Hz, C2'), 41.02 (d, J = 136.7 Hz, C1'), 52.32 (d, J = 7.3 Hz, OCH_3), 52.97 (d, J = 7.0 Hz, OCH_3), 64.30 (C4'), 69.88 (C5'), 72.80 ($CH_2C_6H_5$), 126.86 (d, J = 3.2 Hz, C4"), 127.25 (C3*, C4*), 127.96 (C2*), 128.18 (d, J = 2.6 Hz, C3"), 129.05 (d, J = 6.8 Hz, C2"), 134.96 (d, J = 7.2 Hz, C1"), 137.84 (C1*). MS (FAB): m/z 379.167363 (M+1); $C_{20}H_{27}O_5P$+1 requires 379.167438. Anal. Calcd for $C_{20}H_{27}O_5P$: C, 63.48; H, 7.19. Found: C, 61.78; H, 7.10.

Dimethyl 1-Phenyl-3-benzyloxymethyl-4-bromobutylphosphonate (21). Triphenylphosphine (6.29 g, 24.0 mmol) was added to a stirred solution of phosphonate **20** (7.50 g, 20.0 mmol) and carbon tetrabromide (7.96 g, 24.0 mmol) in CH_3CN (50 mL). The reaction mixture was stirred at room temperature for 6 h. Saturated $NaHCO_3$ (10 mL) and water (10 mL) were added, and the solution was stirred for 10 min. Solvent was removed, and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (1 x 50 mL) and NaCl/H_2O (2 x 50 mL), dried ($MgSO_4$), and evaporated to give a thick oil. Trituation with ether/pentane precipitated triphenylphosphine oxide which was removed by filtration. Product **21**

was purified as a mixture of diastereomers by column chromatography on silica gel eluting with $CHCl_3$-MeOH (0-2% MeOH) gradient, major/minor = 55/45, ^{31}P NMR. The product was obtained as a colorless oil (6.53 g, 74%): Major isomer: ^{31}P NMR ($CDCl_3$) δ 30.78; ^1H NMR ($CDCl_3$) δ 1.82 (1H, m, H3'), 2.05-2.20 (2H, m, H2'), 3.17 (1H, apparent dt, J_{HP} = 23.3 Hz, J = 7.8 Hz, H1'), 3.35-3.45 (3H, m, H4', H5'), 3.42 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.56 (1H, dd, J = 10.5 Hz, 3.3 Hz, H4'), 3.64 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.39 (2H, bs, $CH_2C_6H_5$), 7.20-7.35 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 28.71 (d, J = 2.6 Hz, C3'), 34.84 (C4'), 36.65 (d, J = 14.6 Hz, C2'), 40.73 (d, J = 137.3 Hz, C1'), 52.53 (d, J = 7.2 Hz, OCH_3), 53.21 (d, J = 7.0 Hz, OCH_3), 70.73 (C5'), 72.87 ($CH_2C_6H_5$), 127.10 (d, J = 3.2 Hz, C4"), 127.29 (C3*,C4*), 128.03 (C2*), 128.50 (d, J = 2.6 Hz, C3"), 128.91 (d, J = 6.6. Hz, C2"), 134.52 (d, J = 7.4 Hz, C1"), 137.75 (C1*). Minor isomer: ^{31}P NMR ($CDCl_3$) δ 30.93; ^1H NMR ($CDCl_3$) δ 1.82 (1H, m, H3'), 1.96-2.20 (2H, m, H2'), 3.12 (1H, ddd, J_{HP} = 23.4 Hz, J = 9.3 Hz, 6.5 Hz, PCH), 3.35-3.48 (4H, m, H4', H5'), 3.41 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.65 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.39-4.51 (2H, ABq, J = 12.0 Hz, $CH_2C_6H_5$), 7.20-7.38 (10H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 29.73 (d, J = 2.6 Hz, C3'), 36.27 (C4'), 37.70 (d, J = 14.5 Hz, C2'), 41.31 (d, J = 137.5 Hz, C1'), 52.40 (d, 7.2 Hz, OCH_3), 53.19 (d, J = 7.0 Hz, OCH_3), 68.98 (C5'), 72.88 ($CH_2C_6H_5$), 127.18 (d, J = 3.0 Hz, C4"), 127.29 (C3*, C4*), 128.08 (C2*), 128.42 (d, J = 2.6 Hz, C3"), 128.78 (d, J = 6.6 Hz, C2"), 134.73 (d, J = 7.2 Hz, C1"), 137.78 (C1*). Anal. Calcd for $C_{20}H_{26}O_4PBr$: C, 54.43; H, 5.93. Found: C, 54.22; H, 5.88.

2-Amino-6-chloro-9-(3-benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)purine (22). Anhydrous K_2CO_3[13] (1.85 g. 13.38 mmol) was added to a stirred solution of bromophosphonate **21** (3.61g, 8.20 mmol) and 2-amino-6-chloropurine (1.16g, 6.84 mmol) in dry DMF (30 mL) at room temperature. After 24 h the solid material was filtered off, and DMF was removed under reduced pressure to give an oil. Column chromatography on silica gel, eluting with $CHCl_3$-MeOH (0-2% MeOH), gave **22** (a 55:45 mixture of diastereoisomers) as a colorless foam (2.35g, 65%). The diastereoisomers were readily separated by HPLC on a silica gel column eluted with 3% MeOH in CH_2Cl_2: Major isomer: UV (MeOH) λ_{max} 248, 310 nm; ^{31}P NMR ($CDCl_3$) δ 28.66; ^1H NMR ($CDCl_3$) δ 2.00-2.10 (3H, m, H2', H3'), 3.08 (1H, dd, J = 9.4 Hz, 6.6 Hz, H5'), 3.20 (1H, dd, J = 9.4 Hz, 3.6 Hz, H5'), 3.48 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.64 (3H, d, J_{HP} = 10.5 Hz, OCH_3; H1' is partially hidden under this peak), 4.06 (1H, dd, J = 14.1 Hz, 3.9 Hz, H4'), 4.14 (1H, dd, J = 14.1 Hz, 4.2 Hz, H4'), 4.35 (2H, bs, $CH_2C_6H_5$), 5.60 (2H, s, NH_2), 7.24-7.38 (10H, m, C_6H_5), 7.55 (1H, s, H8); ^{13}C NMR ($CDCl_3$) δ 28.39 (d, J = 2.3 Hz, C3'), 36.30 (d, J = 14.7 Hz, C2'), 41.45 (d, J = 137.5 Hz, C1'), 42.37 (C4'), 52.69 (d, J = 6.9 Hz, OCH_3), 53.24 (d, J = 7.1 Hz, OCH_3), 69.69 (C5'), 73.04 ($CH_2C_6H_5$), 124.61 (C5), 127.37 (d, J = 3.2 Hz, C4"), 127.58 (C3*), 127.72 (C4*), 128.29 (C2*), 128.64 (d, J = 2.6 Hz, C3"), 129.08 (d, J = 6.8 Hz, C2"), 134.88 (d, J = 7.4 Hz, C1"), 137.31(C1*), 143.11 (C8), 150.74 (C4), 154.07 (C2), 159.16 (C6). Anal. Calcd for $C_{25}H_{29}N_5O_4PCl$: C, 56.64; H, 5.51; N, 13.21. Found: C, 56.66; H, 5.58; N, 13.11.

Minor isomer: UV (MeOH) λ_{max} 248, 310 nm; ^{31}P NMR ($CDCl_3$) δ 28.34; ^1H NMR ($CDCl_3$) δ 1.90-2.20 (3H, m, H2', H3'), 3.14 (1H, ddd, J_{HP} = 23.4 Hz, J = 11.7 Hz, 3.6 Hz, H1'), 3.22 (1H, dd, J = 9.9 Hz, 2.7 Hz, H5'), 3.31 (1H, dd, J = 9.9 Hz, 4.2 Hz, H5'), 3.42 (3H, d, J_{HP} = 10.8 Hz, OCH_3), 3.67 (3H, d, J_{HP} = 10.8 Hz, OCH_3), 3.96 (1H, dd, J = 13.5 Hz, 6.3 Hz, H4'), 4.10 (1H, dd, J = 13.5 Hz, 5.7 Hz, H4'), 4.41-4.51

(2H, ABq, J = 12.0 Hz, C*H*$_2$C$_6$H$_5$), 5.48 (2H, bs, NH$_2$), 7.05-7.35 (10H, m, C$_6$H$_5$), 7.54 (1H, s, H8); ^{13}C NMR ($CDCl_3$) δ 28.41 (d, J = 2.4 Hz, C3'), 35.83 (d, J = 14.8 Hz, C2'), 41.28 (d, J = 137.9 Hz, C1'), 45.37 (C4'), 52.59 (d, J = 7.4 Hz, OCH_3), 53.30 (d, J = 7.0 Hz, OCH_3), 67.71 (C5'), 73.03 (*C*H$_2$C$_6$H$_5$), 124.76 (C5), 127.28 (d, J = 3.1 Hz, C4"), 127.62 (C3*), 127.72 (C4*), 128.27 (C2*), 128.44 (d, J = 2.5 Hz, C3"), 128.74 (d, J = 6.6 Hz, C2"), 134.54 (d, J = 7.3 Hz, C1"), 137.46 (C1*), 142.59 (C8), 150.71(C4), 153.70 (C2), 158.85 (C6). Anal. Calcd for $C_{25}H_{29}N_5O_4PCl$: C, 56.64; H, 5.51; N, 13.21. Found: C, 56.65; H, 5.56; N, 13.30.

9-(3-Benzyloxymethyl-1-phenyl-1-dimethylphosphono-but-4-yl)guanine (23). The major diasteromer of **22** (680 mg, 1.22 mmol) was dissolved in EtOH/H_2O (1:1, 10 mL). A 1N HCl solution (3 mL) was added, and the mixture was refluxed for 10 h. The solution was cooled to room temperature and neutralized with 1N NaOH. The solvent was removed, the residue was dissolved in $CHCl_3$/MeOH (95:5, 10 mL), and applied to a column. Gradiant elution with $CHCl_3$-MeOH (5-10% MeOH) afforded the major isomer of **23** as a colorless solid (467 mg, 75%): mp 156-58 °C; UV (MeOH) λ_{max} 254, 274 nm; ^{31}P NMR ($CDCl_3$) δ 31.34; ^{1}H NMR ($CDCl_3$) δ 1.98-2.18 (3H, m, H2', H3'), 3.10-3.22 (2H, m, H5'), 3.43 (3H, d, J_{HP} = 10.5 Hz, OCH_3; H1' is hidden under OCH_3 peak), 3.60 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.94-4.08 (2H, unresolved dd, H4'), 4.33 (2H, bs, C*H*$_2$C$_6$H$_5$), 6.54 (2H, bs, NH$_2$), 7.21-7.35 (10H, m, C$_6$H$_5$), 7.42 (1H, s, H8), 12.14 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 28.65 (C3'), 36.75 (d, J = 14.5 Hz, C2'), 41.50 (d, J = 143.0 Hz, C1'), 42.61 (C4'), 52.84 (d, J = 7.3 Hz, OCH_3), 53.42 (d, J = 7.2 Hz, OCH_3), 69.84 (C5'), 73.02 (*C*H$_2$C$_6$H$_5$), 116.61 (C5), 127.42 (d, J = 3.0 Hz, C4"), 127.65 (C3*, C4*), 128.33 (C2*), 128.70 (d, J = 2.0 Hz, C3"), 129.26 (d, J = 6.6 Hz, C2"), 135.14 (d, J = 7.4 Hz, C1"), 137.72 (C1*), 138.45 (C8), 151.97 (C4), 153.73 (C2), 158.89 (C6), Anal. Calcd for $C_{25}H_{30}N_5O_5P$: C, 58.70; H, 5.91; N, 13.69. Found: C, 58.49; H, 6.00; N, 13.61.

An analogous procedure was used on the same scale to prepare the minor isomer of **23** (76%) from the minor **22** isomer as a colorless solid: mp 150-51 °C; λ_{max} 254, 275 nm; ^{31} P NMR ($CDCl_3$) δ 30.98; ^{1}H NMR ($CDCl_3$) δ 1.90-2.20 (3H, m, H2', H3'), 3.05-3.30 (3H, m, H1', H5'), 3.38 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.62 (3H, d, J = 10.5 Hz, OCH_3), 3.80-4.02 (2H, m, H4'), 4.36-4.51 (2H, ABq, J = 12.0 Hz, C*H*$_2$C$_6$H$_5$), 6.70 (2H, bs, NH$_2$), 7.03-7.40 (11 H, m, H$_8$, C$_6$H$_5$), 12.18 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 28.31 (C3'), 36.14 (d, J = 15.0 Hz, C2'), 41.22 (d, J = 137.4 Hz, C1'), 45.22 (C4'), 52.73 (d, J = 7.4 Hz, OCH_3), 53.38 (d, J = 7.1 Hz, OCH_3), 67.91 (C5'), 73.04 (*C*H$_2$C$_6$H$_5$), 116.34 (C5), 127.32 (d, J = 3.0 Hz, C4"), 127.70 (C4*), 127.74 (C3*), 128.32 (C2*), 128.55 (d, J = 2.0 Hz, C3"), 128.96 (d, J = 6.4 Hz, C2"), 134.61 (d, J = 7.3 Hz, C1"), 137.71 (C1*), 137.82 (C8), 151.74 (C4), 153.49 (C2), 159.06 (C6), Anal. Calcd for $C_{25}H_{30}N_5O_5P$: C, 58.70; H, 5.91; N, 13.69. Found: C, 58.35; H, 6.05; N, 13.48.

9-(3-Hydroxymethyl-1-phenyl-1-dimethylphosphono-but-4-yl) guanine (24). The major isomer of **23** (511 mg, 1.00 mmol) was debenzylated to give the major isomer of **24** (336 mg, 80%) following the procedure[13,14] described for **31**, except that an additional portion of catalyst were added every 8 h, and the reaction was continued for 24 h. The product was purified by column chromatography, eluting with 10% MeOH in $CHCl_3$, as white solid. An analytical sample was obtained by crystallization from EtOH/Et_2O: mp 244-46 °C (decomp.); UV (MeOH) λ_{max} 254, 274 nm; ^{31}P NMR (DMSO-d_6) δ 31.54; ^{1}H NMR (DMSO-d_6) δ 1.60-2.00 (3H, m, H2', H3'), 3.10-3.22

(3H, m, H1', H5'), 3.36 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.53 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.92 (2H, apparant d, J = 5.4 Hz, H4'), 4.80 (1H, bs, OH), 6.63 (2H, bs, NH_2), 7.20-7.37 (5H, m, C_6H_5), 7.52 (1H, s, H8), 10.90 (1H, bs, NH); ^{13}C NMR (DMSO-d_6) δ 28.56 (d, J = 2.5 Hz, C3'), 38.50 (d, J = 13.5 Hz, C2'), 39.89 (d, J = 137.5 Hz, C1'), 42.57 (C4'), 52.37 (d, J = 7.2 Hz, OCH_3), 52.69 (d, J = 6.9 Hz, OCH_3), 61.81 (C5'), 116.25 (C5), 126.91 (d, J = 2.9 Hz, C4"), 128.26 (d, J = 2.2 Hz, C3"), 129.12 (d, J = 6.8 Hz, C2"), 135.84 (d, J = 7.1 Hz, C1"), 137.62 (C8), 151.36 (C4), 153.62 (C2), 156.74 (C6). Anal. Calcd for $C_{18}H_{24}N_5O_5P$•1.5 H_2O: C, 48.21; H, 6.07; N, 15.62. Found: C, 48.48; H, 5.99; N, 15.17.

The minor isomer of **24** (78%) was obtained on the same scale from the minor isomer of **23** by an analogous procedure: mp 233-35 °C (decomp.); UV (MeOH) λ_{max} 254, 274 nm; ^{31}P NMR (DMSO-d_6) δ 31.78; ^1H NMR (DMSO-d_6) δ 1.58-1.72 (2H, m, H2'), 1.84-1.92 (1H, m, H3'), 3.27-3.38 (3H, m, H1', H5', partially hidden under OCH_3 signal), 3.37 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.56 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.80 (1H, dd, J = 13.6 Hz, 8.4 Hz, H4'), 3.86 (1H, dd, J = 13.6 Hz, 6.0 Hz, H4'), 4.79 (1H, bs, OH), 6.50 (2H, bs, NH_2), 7.00-7.06 (2H, m, C_6H_5), 7.15-7.20 (3H, m, C_6H_5), 7.51 (1H, s, H8), 10.72 (1H, bs, NH); ^{13}C NMR (DMSO-d_6) δ 28.95 (d, J = 2.2 Hz, C3'), 38.56 (d, J = 14.0 Hz, C2'), 40.10 (d, J = 137.6 Hz, C1'), 44.20 (C4'), 52.47 (d, J = 7.5 Hz, OCH_3), 53.01 (d, J = 7.3 Hz, OCH_3), 61.62 (C5'), 117.40 (C5), 127.02 (d, J = 2.8 Hz, C4"), 128.48 (d, J = 2.2 Hz, C3"), 129.32 (d, J = 6.4 Hz, C2"), 135.98 (d, J = 7.3 Hz, C1"), 139.04 (C8), 152.20 (C4), 153.85 (C2), 157.39 (C6); MS(FAB): m/z 422.15931 (M+1). $C_{18}H_{24}N_5O_5P$ + 1 requires 422.159332.

9-(3-Hydroxymethyl-1-phenyl-1-phosphonobut-4-yl)guanine Disodium salt (25). The disodium salt of the major isomer of **25** (102 mg, 76%) was obtained from the major isomer of **24** (130 mg, 0.321 mmol) by a procedure analogous to that described for compound **32**: UV (H_2O) λ_{max} 254, 274 nm; ^{31}P NMR (D_2O) δ 22.80; ^1H NMR (D_2O) δ 1.85-2.20 (3H, m, H2', H3'), 2.75 (1H, ddd, J_{HP} = 23.0 Hz, J = 12.5 Hz, 2.7 Hz, H1'), 3.40 (2H, apparent d, J = 4.3 Hz, H5'), 3.97 (2H, apparent d, J = 4.9 Hz, H4'), 7.07-7.27 (5H, m, C_6H_5), 7.65 (1H, s, H8); ^{13}C NMR (D_2O) δ 30.54 (C3'), 38.52 (d, J = 13.5 Hz, C2'), 44.62 (d, J = 128.4 Hz, C1'), 45.62 (C4'), 64.07 (C5'), 118.25 (C5), 127.31 (d, J = 2.8 Hz, C4"), 129.07 (d, J = 2.2 Hz, C3"), 129.84 (d, J = 5.6 Hz, C2"), 138.95 (d, J = 7.2 Hz, C1"), 140.25 (C8), 150.81 (C4), 154.24 (C2), 159.33 (C6). Anal. Calcd for $C_{16}H_{18}N_5O_5P$ Na_2•5H_2O: C, 36.44; H, 5.35; N, 13.28. Found: C, 36.39; H, 5.23, N, 13.27.

The minor isomer of **25** (78%) was prepared from minor **24** (140 mg, 0.345 mmol) by an analogous procedure: UV (H_2O) λ_{max} 256, 274 nm; ^{31}P NMR (D_2O) δ 23.16; ^1H NMR (D_2O) δ 1.47-1.57 (1H, m, H2'), 1.76-1.84 (1H, m, H2'), 1.88-1.98 (1H, m, H3'), 2.76 (1H, ddd, J_{HP} = 21.0 Hz, J = 12.0 Hz, 2.0 Hz, H1'), 3.63 (1H, dd, J = 11.7 Hz, 5.8 Hz, H5'), 3.69 (1H, dd, J = 11.7 Hz, 3.6 Hz, H5'), 3.73 (1H, dd, J = 14.2 Hz, 10.8 Hz, H4'), 3.94 (1H, dd, J = 14.2 Hz, 4.1 Hz, H4'), 6.84-6.87 (2H, m, C_6H_5), 6.98-7.02 (3H, m, C_6H_5), 7.64 (1H, s, H8); ^{13}C NMR (D_2O) δ 29.66 (C3'), 38.50 (d, J = 15.5 Hz, C2'), 45.35 (d, J = 130.2 Hz, C1'), 47.49 (C4'), 62.42 (C5'), 115.60 (C5), 127.15 (C4"), 128.75 (C3"), 129.13 (d, J = 6.3 Hz, C2"), 139.34 (d, J = 6.1 Hz, C1"), 140.75 (C8), 151.36 (C4), 153.83 (C2), 158.65 (C6). Anal. Calcd for $C_{16}H_{18}N_5O_5PNa_2$•4H_2O : C, 37.72; H, 5.14; N, 13.75. Found: C, 37.56; H, 5.18; N, 13.90.

2-Amino-6-azido-9-(3-benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)purine (26). A mixture of the major diastereomer of **22** (529 mg, 1.00 mmol) and sodium azide (78 mg. 1.2 mmol) in DMF (15 mL) was heated at 100-105 °C for 3 h. DMF was removed, and the product was purified by column chromatography eluting with 2% MeOH in $CHCl_3$. The major diasteromer of **26** was obtained as a colorless foam (349 mg, 66%): UV (MeOH) λ_{max} 270, 302 nm; ^{31}P NMR ($CDCl_3$) δ 31.02; ^1H NMR ($CDCl_3$)δ 1.94-2.12 (2H, m, H2'), 2.18-2.30 (1H, m, H3'), 3.02 (1H, dd, J = 9.4 Hz, 8.1 Hz, H5'), 3.23 (1H, dd, J = 9.4 Hz, 4.5 Hz, H5'), 3.60 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.63 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.84 (1H, ddd, J_{HP} = 24.6 Hz, J = 12.0 Hz, 3.6 Hz, H1'), 4.19 (1H, dd, J = 14.0 Hz, 4.5 Hz, H4'), 4.27 (1H, dd, J = 14.0 Hz, 4.2 Hz, H4'), 4.35 (2H, bs, $CH_2C_6H_5$), 7.13 (2H, bs, NH_2), 7.22-7.40 (10H, m, C_6H_5), 7.67 (1H, s, H8); ^{13}C NMR ($CDCl_3$) δ 28.32 (d, J = 2.0 Hz, C3'), 36.39 (d, J = 15.4 Hz, C2'), 41.65 (d, J = 137.3 Hz, C1'), 42.65 (C4'), 53.15 (d, J = 7.0 Hz, OCH_3), 53.19 (d, J = 7.3 Hz, OCH_3), 69.85 (C5'), 73.13 ($CH_2C_6H_5$), 113.11 (C5), 127.53 (d, J = 3.2 Hz, C4"), 127.61 (C3*), 127.76 C4*), 128.34 (C2*), 128.84 (d, J = 2.6 Hz, C3"), 129.10 (d, J = 6.5 Hz, C2"), 134.93 (d, J = 7.2 Hz, C1"), 137.35 (C1*), 141.00 (C8), 142.86 (C4), 144.67 (C2), 146.09 (C6); MS (FAB) m/z: 535.19714 (M^+-1); $C_{25}H_{29}N_8O_4P$ - 1 requires 535.19711.

The minor isomer of **26** was obtained from the minor isomer of **22** (480 mg, 0.907 mmol) in 65% yield by an analogous procedure: UV (MeOH) λ_{max} 270, 302 nm; ^{31}P NMR ($CDCl_3$) δ 30.69; ^1H NMR ($CDCl_3$) δ 1.90-2.05 (1H, m, H3'), 2.15-2.23 (2H, m, H2'), 3.14 (1H, ddd, J_{HP} = 23.5 Hz, J = 11.6 Hz, 3.4 Hz, H1'), 3.30 (1H, dd, J = 9.8 Hz, 3.2 Hz, H5'), 3.36 (1H, dd, J = 9.8 Hz, 4.3 Hz, H5'), 3.42 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.65 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.06 (1H, dd, J = 13.9 Hz, 6.8 Hz, H4'), 4.24 (1H, dd, J = 13.9 Hz, 6.1 Hz, H4'), 4.44-4.56 (2H, ABq, J = 12.0 Hz, $CH_2C_6H_5$), 6.84 (2H, bs, NH_2), 7.00-7.34 (10H, m, C_6H_5), 7.66 (1H, s, H8); ^{13}C NMR ($CDCl_3$) δ 28.54 (d, J = 2.2 Hz, C3'), 36.29 (d, J = 14.8 Hz, C2'), 41.46 (d, J = 138.0 Hz, C1'), 46.21 (C4'), 52.74 (d, J = 7.3 Hz, OCH_3), 53.38 (d, J = 7.0 Hz, OCH_3), 68.07 (C5'), 73.12 ($CH_2C_6H_5$), 113.28 (C5), 127.15 (d, J = 3.1 Hz, C4"), 127.64 (C3*), 127.74 (C4*), 128.29 (C2*), 128.41 (d, J = 2.6 Hz, C3"), 128.83 (d, J = 6.6 Hz, C2"), 134.65 (d, J = 7.2 Hz, C1"), 137.52 (C1*), 140.16 (C8), 142.33 (C4), 144.18 (C2), 145.96 (C6); MS (FAB) m/z: 535.19712 (M^+-1); $C_{25}H_{29}N_8O_4P$ - 1 requires 535.19711.

2,6-Diamino-9-(3-benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)purine (27a). Ammonium formate (1M solution in MeOH, 7.5 mL) followed by $Pd(OH)_2$ on carbon (80 mg, 20%) were added to a solution of the major isomer of **26** (400 mg, 0.750 mmol) in MeOH (15 mL). The mixture was heated under reflux for 1 h. The product was purified by column chromatography eluting with a $CHCl_3$-MeOH (0-5% MeOH) gradient. The major isomer of **27a** was obtained as a colorless foam (350 mg, 92%), UV (MeOH) λ_{max} 254, 284 nm; ^{31}P NMR ($CDCl_3$) δ 31.37; ^1H NMR ($CDCl_3$) δ 2.00-2.10 (3H, m, H2', H3'), 3.13 (1H, dd, J = 9.5 Hz, 6.1 Hz, H5'), 3.20 (1H, dd, J = 9.5 Hz, 3.9 Hz, H5'), 3.43 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.62 (3H, d, J_{HP} = 10.5 Hz, OCH_3; H1' is hidden under this peak), 4.00 (1H, dd, J = 14.0 Hz, 4.1 Hz, H4'), 4.09 (1H, dd, J = 14.0 Hz, 5.2 Hz, H4'), 4.42 (2H, bs, $CH_2C_6H_5$), 4.98 (2H, bs, NH_2), 5.80 (2H, bs, NH_2), 7.24-7.38 (11H, C_6H_5, H8); ^{13}C NMR ($CDCl_3$) δ 28.56 (d, J = 2.6 Hz, C3'), 36.60 (d, J = 14.7 Hz, C2'), 41.51 (d, J = 137.1 Hz, C1'), 42.22 (C4'), 52.73 (d, J = 7.2 Hz, OCH_3), 53.32 (d, J = 7.1 Hz, OCH_3), 69.99 (C5'), 73.05

($CH_2C_6H_5$), 113.90 (C5), 127.36 (d, J = 3.2 Hz, C4"), 127.67 (C3*), 127.73 (C4*), 128.36 (C2*), 128.66 (d, J = 2.6 Hz, C3"), 129.29 (d, J = 6.7 Hz, C2"), 135.22 (d, J = 7.3 Hz, C1"), 137.69 (C1*), 138.96 (C8), 152.44 (C4), 155.52 (C2), 159.62 (C6). Anal. Calcd for $C_{25}H_{31}N_6O_4P$: C, 58.81; H, 6.12; N, 16.46. Found: C, 58.88; H, 6.02; N, 16.30.

The minor isomer of **27a** was obtained by an analogous procedure from the minor isomer of **26** (536 mg, 1.00 mmol) in 93% yield as a foam: UV (MeOH) λ_{max} 256, 284 nm; ^{31}P NMR ($CDCl_3$) δ 31.08; ^1H NMR ($CDCl_3$) δ 1.92-2.20 (3H, m, H2', H3'), 3.14 (1H, ddd, J_{HP} = 23.2 Hz, J = 11.2 Hz, 3.5 Hz, H1'), 3.18 (1H, dd, J = 9.6 Hz, 3.5 Hz, H5'), 3.28 (1H, dd, J = 9.6 Hz, 4.0 Hz, H5'), 3.40 (3H, d, J = 10.5 Hz, OCH_3), 3.64 (3H, d, J = 10.5 Hz, OCH_3), 3.90 (1H, dd, J = 13.9 Hz, 6.1 Hz, H4'), 4.03 (1H, dd, J = 13.9 Hz, 6.1 Hz, H4'), 4.28-4.37 (2H, ABq, J = 11.9 Hz, $CH_2C_6H_5$), 5.10 (2H, bs, NH_2), 6.10 (2H, bs, NH_2), 7.05-7.38 (11H, m, C_6H_5, H8); ^{13}C NMR ($CDCl_3$) δ 28.26 (d, J = 2.0 Hz, C3'), 36.01 (d, J = 14.7 Hz, C2'), 41.26 (d, J = 137.6 Hz, C1'), 44.95 (C4'), 52.72 (d, J = 7.4 Hz, OCH_3), 53.39 (d, J = 7.0 Hz, OCH_3), 67.80 (C5'), 73.05 ($CH_2C_6H_5$), 113.98 (C5), 127.26 (d, J = 3.2 Hz, C4"), 127.70 (C4*), 127.73 (C3*), 128.32 (C2*), 128.49 (d, J = 2.5 Hz, C3"), 128.94 (d, J = 6.6 Hz, C2"), 134.69 (d, J = 7.3 Hz, C1"), 137.79 (C1*), 138.46 (C8), 152.03 (C4), 155.63 (C2), 159.45 (C6). Anal. Calcd for $C_{25}H_{31}N_6O_4P$: C, 58.81; H, 6.12; N, 16.46. Found: C, 58.57; H, 6.20; N, 16.10

2,6-Diamino-9-(-3-hydroxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)purine (27b). The major isomer of **27a** (510 mg, 1.0 mmol) was debenzylated[13,14] to give the major isomer of **27b** (336 mg, 80%) by the procedure described for the preparation of **31**, except that the reaction mixture was heated under reflex for 16 h. An analytical sample was prepared by crystallization from MeOH/Et_2O: mp 223-25 °C; UV (MeOH) λ_{max} 255, 282 nm; ^{13}P NMR (DMSO-d_6) δ 29.50; ^1H NMR (DMSO-d_6) δ 1.60-1.92 (3H, m, H2', H3'), 3.04-3.16 (2H, m, H5'), 3.32 (1H, ddd, J_{HP} = 22.5 Hz, J = 12.0 Hz, 3.7 Hz, H1'), 3.40 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.66 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.96 (2H, apparent d, J = 4.4 Hz, H4'), 5.03 (1H, bs, OH), 5.78 (2H, bs, NH_2), 6.71 (2H, bs, NH_2), 7.20-7.35 (5H, m, C_6H_5), 7.55 (1H, s, H8); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 28.10 (d, J = 2.7 Hz, C3'), 38.71 (d, J = 13.5 Hz, C2'), 41.42 (d, J = 138.6 Hz, C1'), 41.55 (C4'), 52.70 (d, J = 7.3 Hz, OCH_3), 53.35 (d, J = 7.1 Hz, OCH_3), 61.31 (C5'), 112.46 (C5), 127.50 (d, J = 3.1 Hz, C4"), 128.59 (d, J = 2.5 Hz, C3"), 128.91 (d, J = 6.7 Hz, C2"), 134.60 (d, J = 7.2 Hz, C1"), 138.83 (C8), 151.73 (C4), 155.13 (C2), 158.74 (C6). Anal. Calcd for $C_{18}H_{25}N_6O_4P$: C, 51.42; H, 5.99; N, 19.99. Found: C, 51.16; H, 6.08; N, 20.01.

The minor isomer of **27b** (254 mg, 81%) was obtained by debenzylation of the minor isomer of **27a** (383 mg, 0.75 mmol) by an analogous procedure. An analytical sample was prepared by crystallization from MeOH/Et_2O: mp 214-15 °C; UV (MeOH) λ_{max} 256, 282 nm; ^{31}P NMR (DMSO-d_6) δ 29.47; ^1H NMR (DMSO-d_6) δ 1.62-1.95 (3H, m, H2', H3'), 3.22-3.28 (2H, m, H5'), 3.32 (1H, ddd, J_{HP} = 23.1 Hz, J = 11.2 Hz, 3.4 Hz, H1'), 3.41 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.64 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.90 (1H, dd, J = 7.1 Hz, 2.5 Hz, H4'), 3.94 (1H, dd, J = 7.1 Hz, 2.5 Hz, H4'), 4.90 (1H, unresolved t, OH), 5.72 (2H, bs, NH_2), 6.67 (2H, bs, NH_2), 7.06-7.11 (2H, m, C_6H_5), 7.15-7.25 (3H, m, C_6H_5), 7.51 (1H, s, H8); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 27.97 (d, J = 2.5 Hz, C3'), 38.57 (d, J = 14.4 Hz, C2'), 41.52 (d, J = 138.0 Hz, C1'), 44.21 (C4'), 52.65 (d, J = 7.3 Hz, OCH_3), 53.26 (d, J = 7.0 Hz, OCH_3), 59.04

(C5'), 112.83 (C5), 127.46 (d, J = 3.2 Hz, C4"), 128.56 (d, J = 2.6 Hz, C3"), 128.87 (d, J = 6.7 Hz, C2"), 134.59 (d, J = 7.2 Hz, C1"), 138.34 (C8), 151.48 (C4), 155.70 (C6), 159.35 (C2). Anal. Calcd for $C_{18}H_{25}N_6O_4P$: C, 51.42; H, 5.99; N, 19.99. Found: C, 51.26; H, 6.16; N, 20.32.

2,6-Diamino-9-(3-hydroxymethyl-1-phenyl-1-phosphonobut-4-yl)purine Disodium Salt (28). The disodium salt of the major isomer of **28** (124 mg, 80%) was prepared from the major isomer of **27b** (150 mg, 0.36 mmol) by an analogous procedure to that described for compound **32**. UV (H_2O) λ_{max} 254, 282 nm; ^{31}P NMR (D_2O) δ 20.98; ^1H NMR (D_2O) δ 1.62-1.74 (1H, m, H3'), 1.90-2.10 (2H, m, H2'), 2.57 (1H, ddd, J_{HP} = 22.2 Hz, J = 12.0 Hz, 3.9 Hz, H1'), 3.22 (2H, d, J = 5.1 Hz, H5'), 3.73 (1H, dd, J = 14.1 Hz, 6.9 Hz, H4'), 3.82 (1H, dd, J = 14.1 Hz, 6.6 Hz, H4'), 6.98-7.14 (5H, m, C_6H_5), 7.33 (1H, s, H8); ^{13}C NMR (D_2O) δ 31.51 (C3'), 39.12 (d, J = 12.4 Hz, C2'), 44.44 (d, J = 124.6 Hz, C1'), 45.00 (C4'), 64.09 (C5'), 113.45 (C5), 126.42 (d, J = 2.4 Hz, C4"), 128.72 (d, J = 1.9 Hz, C3"), 129.96 (d, J = 5.3 Hz, C2"), 140.73 (C8), 141.54 (d, J = 6.4 Hz, C1"), 151.69 (C4), 156.31 (C6), 160.12 (C2). Anal. Calcd for $C_{16}H_{19}N_6O_4PNa_2 \cdot 3.5\ H_2O$: C, 38.48; H, 5.25; N, 16.83. Found: C, 38.22; H, 5.23; N, 16.64.

The minor isomer of **28** (117 mg, 81%) was obtained from the minor isomer of **27b** (140 mg, 0.33 mmol) by an analogous procedure. UV (H_2O) λ_{max} 256, 282 nm; ^{31}P NMR (D_2O) δ 20.87; ^1H NMR (D_2O) δ 1.40-1.62 (2H, m, H2'), 1.80-1.91 (1H, m, H3'), 2.60 (1H, ddd, J_{HP} = 21.0 Hz, J = 12.7 Hz, 1.7 Hz, H1'), 3.56 (2H, d, J = 4.9 Hz, H5'), 3.60 (1H, dd, J = 14.2 Hz, 10.0 Hz, H4'), 3.80 (1H, dd, J = 14.2 Hz, J = 4.4 Hz, H4'), 6.72-6.76 (2H, m, C_6H_5), 6.83-6.87 (3H, m, C_6H_5), 7.45 (1H, s, H8); ^{13}C NMR (D_2O) δ 30.30 (C3'), 38.92 (d, J = 14.3 Hz, C2'), 46.37 (d, J = 126.9 Hz, C1'), 46.99 (C4'), 62.37 (C5'), 113.91 (C5), 126.27 (C4"), 128.33 (C3"), 129.37 (d, J = 5.5 Hz, C2"), 141.12 (C8), 141.85 (d, J = 5.5 Hz, C1"), 151.02 (C4), 156.14 (C6), 159.76 (C2). Anal. Calcd for $C_{16}H_{19}N_6O_4PNa_2 \cdot 3H_2O$: C, 39.19; H, 5.14; N, 17.14. Found: C, 38.95; H, 5.19; N, 16.98.

9-(3-Benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)adenine (29). NaH (530 mg of 60% reagent in mineral oil, 13.1 mmol) was added to a stirred suspension of adenine (1.64 g, 12.1 mmol) in DMF (80 mL) under argon at room temperature. After 30 min a solution of bromophosphonate **21** (5.77 g, 13.1 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 $CHCl_3$ (15 mL) and applied to a silica gel column. The column was eluted with a $CHCl_3$-MeOH (0-5% MeOH) gradiant to give **29** (mixture of diastereomers) as a colorless foam (3.59 g, 60%). Major isomer: UV (MeOH) λ_{max} 260 nm; ^{31}P NMR ($CDCl_3$) δ 28.68; ^1H NMR ($CDCl_3$) δ 1.92-2.20 (3H, H2', H3'), 3.19 (2H, m, H5'), 3.40 (1H, ddd, J_{HP} = 23.4 Hz, J = 10.7 Hz, 4.2 Hz, H1'), 3.40 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.62 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.18 (1H, dd, J = 14.0 Hz, 5.0 Hz, H4'), 4.25 (1H, dd, J = 14.0 Hz, 4.8 Hz, H4'), 4.32 (2H, bs, $CH_2C_6H_5$), 6.66 (2H, bs, NH_2), 7.20-7.38 (10H, m, C_6H_5), 7.57 (1H, s, H8), 8.33 (1H, s, H2); ^{13}C NMR ($CDCl_3$) δ 28.92 (d, J = 2.3 Hz, C3'), 37.05 (d, J = 14.2 Hz, C2'), 41.78 (d, J = 137.2 Hz, C1'), 43.21 (C4'), 52.56 (d, J = 7.2 Hz, OCH_3), 53.36 (d, J = 7.0 Hz, OCH_3), 69.72 (C5'), 72.87 ($CH_2C_6H_5$), 118.90 (C5), 127.13 (d, J = 3.0 Hz, C4"), 127.54 (C3*), 127.56 (C4*), 128.18 (C2*), 128.37 (d, J = 2.3 Hz, C3"), 129.14 (d, J = 6.7 Hz, C2"), 135.43 (d, J = 7.1 Hz, C1"), 137.49 (C1*), 140.84 (C8), 150.05 (C4), 152.48 (C2), 155.50

(C6). Anal. Calcd for $C_{25}H_{30}N_5O_4P$: C, 60.06; H, 6.10; N, 14.13. Found: C, 60.16; H, 6.08; N, 14.10. Minor isomer: UV (MeOH) λ_{max} 260 nm; ^{31}P NMR ($CDCl_3$) δ 28.41; ^1H NMR ($CDCl_3$) δ 1.98 (1H, m, H3'), 2.10-2.21 (2H, m, H2'), 3.16 (1H, ddd, J_{HP} = 23.2 Hz, J = 11.8 Hz, 3.7 Hz, H1'), 3.23 (1H, dd, J = 10.0 Hz, 3.1 Hz, H5'), 3.33 (1H, dd, J = 10.0 Hz, 4.4 Hz, H5'), 3.40 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.65 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.11 (1H, dd, J = 14.0 Hz, 6.6 Hz, H4'), 4.22 (1H, dd, J = 14.0 Hz, 6.1 Hz, H4'), 4.40-4.53 (2H, ABq, J = 11.9 Hz, $CH_2C_6H_5$), 6.34 (2H, bs, NH_2), 7.05-7.40 (10H, m, C_6H_5), 7.57 (1H, s, H8), 8.22 (1H, s, H2); ^{13}C NMR ($CDCl_3$) δ 28.36 (d, J = 2.2 Hz, C3'), 36.18 (d, J = 15.0 Hz, C2'), 41.44 (d, J = 138.0 Hz, C1'), 45.42 (C4'), 52.58 (d, J = 7.3 Hz, OCH_3), 53.32 (d, J = 7.0 Hz, OCH_3), 67.83 (C5'), 73.06 ($CH_2C_6H_5$), 119.13 (C5), 127.06 (d, J = 3.1 Hz, C4"), 127.61 (C3*, C4*), 128.19 (C2*), 128.25 (d, J = 2.6 Hz, C3"), 128.74 (d, J = 6.5 Hz, C2"), 134.72 (d, J = 7.2 Hz, C1"), 137.54 (C1*), 140.58 (C8), 149.63 (C4), 151.98 (C2), 155.47 (C6). Anal. Calcd for $C_{25}H_{30}N_5O_4P$: C, 60.60; H, 6.10; N, 14.13. Found: C, 60.25; H, 6.15; N, 14.23.

9-(3-Benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)-N^6-benzoyladenine (30). Benzoyl chloride (936 mg, 0.77 mL, 6.66 mmol) was added to a stirred solution of **29** (3.0 g, 6.06 mmol) in pyridine at room temperature. After 6 h the pyridine was removed, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 x 50 mL) and saturated NaCl/H_2O (1 x 70 mL). The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography eluting with 0-2% MeOH in $CHCl_3$. Product **30** was obtained as a colorless foam (3.05 g, 84%). The diastereomers were separated by HPLC (silica gel column, 3% MeOH in CH_2Cl_2). Major isomer: UV (MeOH) λ_{max} 250, 276 nm; ^{31}P NMR ($CDCl_3$) δ 28.28; ^1H NMR ($CDCl_3$) δ 1.91-2.17 (3H, m, H2', H3'), 3.18 (2H, m, H5'), 3.39 (1H, ddd, J_{HP} = 23.4 Hz, J = 11.0 Hz, 4.5 Hz, H1'), 3.42 (d, J_{HP} = 10.5 Hz, OCH_3), 3.65 (d, J_{HP} = 10.5 Hz, OCH_3), 4.30 (4H, m, H4', $CH_2C_6H_5$), 7.21-7.49 (13H, m, C_6H_5), 7.83 (3H, m, C_6H_5, NH), 7.90 (1H, s, H8), 8.63 (1H, s, H2); ^{13}C NMR ($CDCl_3$) δ (N^6 benzoyl carbons of **30** are designated as $C1^+$, $C2^+$ etc.) 29.21 (d, J = 2.4 Hz, C3'), 36.93 (d, J = 14.1 Hz, C2'), 41.94 (d, J = 137.8 Hz, C1'), 43.55 (C4'), 52.64 (d, J = 7.2 Hz, OCH_3), 53.25 (d, J = 7.0 Hz, OCH_3), 69.79 (C5'), 73.12 ($CH_2C_6H_5$), 126.97 (C5), 127.41 (d, J = 3.2 Hz, C4"), 127.62 (C3*, C4*), 127.79 (C2*), 128.39 ($C4^+$), 128.58 ($C3^+$), 128.65 (d, J = 2.5 Hz, C3"), 129.24 (d, J = 6.2 Hz, C2"), 129.33 ($C2^+$), 132.79 ($C1^+$), 134.07 (C1*), 135.33 (d, J = 7.0 Hz, C1"), 137.50 (C8), 145.69 (C4), 151.92 (C2), 153.51 (C6), 172.14 (CO). Anal. Calcd for $C_{32}H_{34}N_5O_5P$: C, 64.06; H, 5.71; N, 11.67. Found: C, 64.30; H, 5.90; N, 11.29.

Minor isomer: UV (MeOH) λ_{max} 250, 274 nm; 31P NMR ($CDCl_3$) δ 28.50; ^1H NMR ($CDCl_3$) δ 1.90-2.30 (3H, m, H2', H3'), 3.10 (1H, ddd, J_{HP} = 23.4 Hz, J = 11.7 Hz, 3.9 Hz, H1'), 3.21 (1H, dd, J = 10.2 Hz, 3.3 Hz, H5'), 3.32 (1H, dd, J = 10.2 Hz, 4.8 Hz, H5'), 3.41 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.66 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 4.18 (1H, dd, J = 14.1 Hz, 5.7 Hz, H4'), 4.30 (1H, dd, J = 14.1 Hz, 6.6 Hz, H4'), 4.38-4.51 (2H, ABq, J = 11.7 Hz, $CH_2C_6H_5$), 7.04-7.50 (13H, m, C_6H_5), 7.85 (3H, m, C_6H_5, NH), 7.91 (1H, s, H8), 8.53 (1H, s, H2); ^{13}C NMR ($CDCl_3$) δ 28.58 (d, J = 2.1 Hz, C3'), 36.24 (d, J = 14.7 Hz, C2'), 41.77 (d, J = 138.0 Hz, C1'), 45.87 (C4'), 52.55 (d, J = 7.3 Hz, OCH_3), 53.20 (d, J = 7.1 Hz, OCH_3), 67.65 (C5'), 73.20 ($CH_2C_6H_5$), 127.17 (C5), 127.33 (d, J = 3.1 Hz, C4"), 127.75 (C3*, C4*), 127.85 (C2*), 128.43 ($C4^+$), 128.58 ($C3^+$), 128.76 (d, J = 3.2 Hz, C3"), 128.90 (d, J = 6.5 Hz,

C2"), 129.32 (C2⁺), 132.79 (C1⁺), 134.07 (C1*), 134.84 (d, J = 7.2 Hz, C1"), 137.62 (C8), 145.51 (C4), 151.84 (C2), 153.30 (C6), 172.13 (CO). MS (FAB): m/z 600.229840 (M+1). $C_{32}H_{34}N_5O_5P+1$ requires 600.229740.

9-(3-Hydroxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)adenine (31). A mixture of the major diastereoisomer of **29** (495 mg, 1.00 mmol) and $Pd(OH)_2$ on carbon (530 mg, 20%) in ethanol/cyclohexene (1:1, 12 mL) was heated at reflux for 4 h.[13,14] The catalyst was filtered off, and a second portion of catalyst (200 mg, 20%) was added. The mixture was refluxed for another 3 h. The catalyst again was filtered off, and the product was purified by column on silica gel eluting with 10% MeOH in $CHCl_3$ to give the major isomer of **31** as a colorless foam (372 mg, 86%). UV(MeOH) λ_{max} 260 nm; ^{31}P NMR ($CDCl_3$) δ 29.18; ^1H NMR ($CDCl_3$) δ 1.90-2.00 (3H, m, H2', H3'), 3.17 (1H, dd, J = 12.0 Hz, 6.3 Hz, H5'), 3.26-3.38 (2H, m, H1', H5'), 3.40 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.65 (3H, d, J_{HP} = 10.5, OCH_3), 4.23 (1H, dd, J = 14.7 Hz, 5.0 Hz, H4'), 4.32 (1H, dd, J = 14.7 Hz, 3.3 Hz, H4'), 4.50 (2H, bs, NH_2), 7.20-7.40 (5H, m, C_6H_5), 7.86 (1H, s, H8), 8.26 (1H, s, H2); ^{13}C NMR ($CDCl_3$) δ 28.32 (d, J = 2.8 Hz, C3'), 38.89 (d, J = 13.3 Hz, C2'), 41.53 (d, J = 138.5 Hz, C1'), 42.27 (C4'), 52.30 (d, J = 7.2 Hz, OCH_3), 53.34 (d, J = 7.0 Hz, OCH_3), 61.44 (C5'), 118.29 (C5), 127.51 (d, J = 3.2 Hz, C4"), 128.59 (d, J = 2.6 Hz C3"), 128.89 (d, J = 6.6 Hz, C2"), 134.69 (d, J = 7.0 Hz, C1"), 141.22 (C8), 149.74 (C4), 152.35 (C2), 155.33 (C6). Anal. Calcd for $C_{18}H_{24}N_5O_4$ P: C, 53.33; H, 5.96; N, 17.27. Found: C, 53.58; H, 6.25; N, 17.00.

The minor isomer of **31** was prepared by an analogous procedure from the minor isomer of **29** (410 mg, 0.828 mmol) in 87% yield. UV(MeOH)λ_{max} 260 nm; ^{31}P NMR ($CDCl_3/CD_3OD$) δ 28.66; ^1H NMR ($CDCl_3/CD_3OD$) δ 1.88-2.20 (3H, m, H2', H3') 3.25 (1H, ddd, J_{HP} = 23.4 Hz, 11.6 Hz, 3.8 Hz, H1'), 3.41 (3H, d, J_{HP} = 10.6 Hz, OCH_3), 3.46 (2H, two ddd collapsed, H5'), 3.63 (3H, d, J_{HP} = 10.6 Hz, OCH_3), 4.15 (1H, dd, J = 14.1 Hz, 6.6 Hz, H4'), 4.25 (1H, dd, J = 14.1 Hz, 6.3 Hz, H4'), 4.60 (2H, bs, NH_2), 7.14-7.37 (5H, m, C_6H_5), 7.88 (1H, s, H8), 8.16 (1H, s, H2); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 27.56 (d, J = 2.6 Hz, C3'), 38.02 (d, J = 15.1 Hz, C2'), 41.10 (d, J = 138.1 Hz, C1'), 44.76 (C4'), 52.16 (d, J = 7.1 Hz, OCH_3), 53.36 (d, J = 7.0 Hz, OCH_3), 59.28 (C5'), 118.27 (C5), 127.07 (d, J = 3.1 Hz, C4"), 128.12 (d, J = 2.3 Hz, C3"), 128.47 (d, J = 6.7 Hz, C2"), 134.20 (d, J = 7.4 Hz, C1"), 141.02 (C8), 149.13 (C4), 151.82 (C2), 155.11 (C6). Anal. Calcd for $C_{18}H_{24}N_5O_4P$: C, 53.33; H, 5.96; N, 17.27. Found: C, 53.10; H, 6.08; N, 17.16.

9-(3-Hydroxymethyl-1-phenyl-1-phosphonobut-4-yl)adenine Disodium Salt (32). Bromotrimethylsilane (671 mg, 0.58 mL, 4.3 mmol) was added to a solution of the major isomer of **31** (190 mg, 0.430 mmol) in DMF (10 mL) under argon at room temperature. The reaction mixture was stirred for 6 h. The volatile materials were removed under vacuum, and the residual oil was placed under high vacuum overnight. Water (5 mL) was added, and the pH was adjusted to 8 by the addition of a NH_4HCO_3 solution. The solution was applied to a Sephadex A-25 column and eluted first with H_2O (200 mL) and then with 0.2 M NH_4HCO_3. Volatile materials were removed. Excess buffer was removed by coevaporation with H_2O after neutralization to pH 8-9 with 0.1 N NaOH. The product was then purified by HPLC on a C-18 reverse phase column eluted with H_2O. The major isomer of **32** was obtained as a white solid (147 mg, 81%): UV(H_2O) λ_{max} 262 nm; ^{31}P NMR (D_2O) δ 20.37; ^1H NMR (D_2O) δ 1.80 (1H, m, H3'), 1.90-2.15 (2H, m, H2'), 2.51 (1H, ddd, J_{HP} = 21.7 Hz, J = 11.9 Hz, 4.0

Hz, H1'), 3.27 (2H, apparent d, J = 5.4 Hz, H5'), 3.84 (1H, dd, J = 14.4 Hz, 6.6 Hz, H4'), 3.93 (1H, dd J = 14.4 Hz, 6.8 Hz, H4'), 6.88-7.07 (5H, m, C_6H_5), 7.54 (1H, s, H8), 7.69 (1H, s, H2); ^{13}C NMR (D_2O) δ 31.67 (C3'), 39.21 (d, J = 12.5 Hz, C2'), 45.44 (d, J = 123.4 Hz, C1'), 45.82 (C4'), 64.29 (C5'), 118.65 (C5), 126.20 (d, J = 2.3 Hz, C4"), 128.60 (d, J = 1.7 Hz, C3"), 129.78 (d, J = 5.0 Hz, C2"), 141.82 (d, J = 6.8 Hz, C1"), 142.92 (C8), 149.26 (C4), 152.51 (C2), 155.59 (C6). Anal. Calcd for $C_{16}H_{18}N_5O_4PNa_2 \cdot 2H_2O$: C, 42.02; H, 4.85; N, 15.31. Found: C. 41.94; H, 4.86; N, 15.25.

The minor isomer of **32** was obtained in similar amounts (80% yield) from the minor isomer of **31** in an analogous procedure: UV(H_2O) λ_{max} 262 nm; ^{31}P NMR (D_2O) δ 20.60; ^1H NMR (D_2O) δ 1.38 (1H, m, H2'), 1.59 (1H, m, H2'), 1.87 (1H, m, H3'), 2.54 (1H, ddd, J_{HP} = 20.3 Hz, J = 12.7 Hz, 1.9 Hz, H1'), 3.60 (2H, d, J = 4.5 Hz, H5'), 3.72 (1H, dd, J = 14.0 Hz, 11.0 Hz, H4'), 3.92 (1H, dd, J = 14.0 Hz, 4.0 Hz, H4'), 6.62-6.74 (5H, m, C_6H_5), 7.54 (1H, s, H8), 7.75 (1H, s, H2); ^{13}C NMR (D_2O) δ 30.51 (C3'), 39.19 (d, J = 14.7 Hz, C2'), 46.46 (d, J = 126.9 Hz, C1'), 47.61 (C4'), 62.44 (C5'), 119.10 (C5), 126.11 (C4"), 128.22 (C3"), 129.18 (d, J = 5.6 Hz, C2"), 141.90 (d, J = 5.6 Hz, C1"), 143.31 (C8), 148.69 (C4), 152.11 (C2), 155.60 (C6). Anal. Calcd for $C_{16}H_{18}N_5O_4PNa_2 \cdot 3H_2O$: C, 40.42; H, 5.09; N, 14.73. Found: C, 40.43; H, 5.17; N, 14.69.

1-(3-Benzyloxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)cytosine (33). Sodium hydride (317 mg of a 60% dispersion in mineral oil, 7.93 mmol) was added to a suspension of cytosine (800 mg, 7.21 mmol) in DMF (30 mL) under argon at room temperature. After 30 min a solution of the major diasteroisomer of **21** (3.5 g, 7.93 mmol) in DMF (10 mL) was 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, eluted with a $CHCl_3$-MeOH (0-10% MeOH) gradient, to give the major diasteroisomer of **33** as a colorless foam (1.96 g, 58%). UV (MeOH) λ_{max} 238, 276 nm; ^{31}P NMR ($CDCl_3$) δ 31.30; ^1HNMR ($CDCl_3$) δ 1.90-2.10 (3H, m, H2', H3'), 3.10-3.21 (2H, m, H5'), 3.43 (3H, d, J_{HP} = 10.5 Hz, OCH_3, H1' is hidden under this peak, and J values could not be calculated), 3.65 (3H, d, J_{HP} = 10.5 Hz, OCH_3; one of H4' protons is hidden under this peak), 3.84 (1H, dd, J = 11.7 Hz, 2.5 Hz, H4'), 4.24 (2H, bs, $CH_2C_6H_5$), 5.87 (1H, d, J = 7.1 Hz, H5), 6.98 (1H, d, J = 7.1 Hz, H6), 7.14-7.50 (12H, m, NH_2, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 29.60 (C3'), 36.41 (d, J = 13.5 Hz, C2'), 41.45 (d, J = 136.5 Hz, C1'), 49.88 (C4'), 52.49 (d, J = 7.4 Hz, OCH_3), 53.24 (d, J = 7.1 Hz, OCH_3), 69.19 (C5'), 72.64 ($CH_2C_6H_5$), 94.51 (C5), 127.08 (d, J = 2.8 Hz, C4"), 127.41 (C3*, C4*), 128.08 (C2*), 128.35 (d, J = 2.2 Hz, C3"), 129.01 (d, J = 6.5 Hz, C2"), 135.49 (d, J = 7.2 Hz, C1"), 137.51 (C1*), 145.53 (C6), 156.33 (C2), 165.41 (C4). Anal. Calcd for $C_{24}H_{30}N_3OP$: C, 61.13; H, 6.41; N, 8.91. Found: C, 61.17; H, 6.44; N, 8.94.

The minor isomer of **33** was obtained from the reaction of the minor isomer of bromophosphonate **21** (2.62 g, 5.94 mmol) and cytosine (600 mg, 5.40 mmol) in an analogous reaction condition as described above in 59% yield as a colorless foam: UV (MeOH) λ_{max} 234, 276 nm; ^{31}P NMR ($CDCl_3$) δ 31.24; ^1H NMR ($CDCl_3$) δ 1.80-2.10 (3H, m, H2', H3'), 3.10 (1H, dd, J = 8.4 Hz, 1.7 Hz, H5'), 3.20 (1H, dd, J = 8.4 Hz, 2.8 Hz, H5'), 3.30-3.40 (2H, m, H1', H4'), 3.45 (3H, d, J = 10.5 Hz, OCH_3), 3.46 (1H, dd, J = 10.5 Hz, 5.4 Hz, H4'), 3.62 (3H, d, J = 10.5 Hz, OCH_3), 4.26-4.38 (2H,

ABq, J = 12.0 Hz, $CH_2C_6H_5$), 5.88 (1H, d, J = 7.3 Hz, H5), 6.96 (1H, d, J = 7.3 Hz, H6) 7.14-7.37 (12H, m, NH_2, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 28.10 (C3'), 35.24 (d, J = 15.1 Hz, C2'), 40.97 (d, J = 137.1 Hz, C1'), 51.21 (C4'), 52.49 (d, J = 7.3 Hz, OCH_3), 53.19 (d, J = 7.0 Hz OCH_3), 67.34 (C5'), 72.81 ($CH_2C_6H_5$), 95.52 (C5), 127.20 (d, J = 2.9 Hz, C4"), 127.54 (C4*), 127.60 (C3*), 128.15 (C2*), 128.36 (d, J = 2.2 Hz, C3"), 128.79 (d, J = 6.5 Hz, C2"), 134.42 (d, J = 7.6 Hz, C1"), 137.56 (C1*), 145.51 (C6), 156.32 (C2), 165.41 (C4). Anal. Calcd for $C_{24}H_{30}N_3OP$: C, 61.13; H, 6.41; N, 8.91. Found: C, 61.32; H, 6.35; N, 8.98.

1-(3-Hydroxymethyl-1-phenyl-1-dimethylphosphonobut-4-yl)cytosine (34). A mixture of the major isomer of **33** (680 mg, 1.44 mmol) and $Pd(OH)_2$ on carbon (770 mg, 20%) in ethanol/cyclohexene (1:1, 20 mL) was heated at reflux for 8 h.[13,14] The reaction mixture was filtered through a pad of celite, and the pad was washed with hot ethanol. Chromatography on silica gel, eluted with a $CHCl_3$-MeOH (2-15% MeOH) gradient, provided the major isomer of **34** as a colorless foam (473 mg, 86%): UV(MeOH) λ_{max} 238, 276 nm; ^{31}P NMR (DMSO-d_6) δ 32.09; ^1H NMR (DMSO-d_6) δ 1.53 (1H, m, H3'), 1.68-1.98 (2H, m, H2'), 3.14 (2H, m, H5'), 3.24-3.53 (2H, m, H1', H4'), 3.38 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.58 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.68 (1H, dd, J = 13.2 Hz, 4.9 Hz, H4'), 4.68 (1H, bs, OH), 5.64 (1H, d, J = 7.2 Hz, H5), 7.10 (2H, bs, NH_2), 7.18-7.31 (5H, m, C_6H_5), 7.37 (1H, d, J = 7.2 Hz, H6); ^{13}C NMR (DMSO-d_6) δ 29.44 (d, J = 2.6 Hz, C3'), 38.25 (d, J = 13.3 Hz, C2'), 39.42 (d, J = 137.5 Hz, C1', partially hidden under DMSO-d_6 peak; J found from CD_3OD spectrum), 48.56 (C4'), 52.45 (d, J = 7.0 Hz, OCH_3), 52.72 (d, J = 6.8 Hz, OCH_3), 61.52 (C5'), 93.32 (C5), 126.87 (d, J = 3.0 Hz, C4"), 128.26 (d, J = 2.1 Hz, C3"), 129.18 (d, J = 6.7 Hz, C2"), 136.27 (d, J = 7.0 Hz, C1"), 146.25 (C6), 156.34 (C2), 165.76 (C4). MS: M/z 381.14534. $C_{17}H_{24}N_3O_5P$ requires 381.14536.

The minor isomer of **34** was prepared in similar quantities by an analogous route in 83% yield as a colorless foam: UV (MeOH) λ_{max} 236, 274 nm; ^{31}P NMR (DMSO-d_6) δ 32.00; ^1H NMR (DMSO-d_6) δ 1.53 (1H, m, H3'), 1.69-1.98 (2H, m, H2'), 3.28-3.50 (5H, m, H1', H4', H5'), 3.38 (3H, d, J_{HP} = 10.5 Hz, OCH_3), 3.58 (3H, d, J = 10.5 Hz, OCH_3) 4.68 (1H, bs, OH), 5.61 (1H, d, J = 7.2 Hz, H5), 7.13 (2H, bs, NH_2), 7.18-7.31 (5H, m, C_6H_5), 7.38 (1H, d, J = 7.2 Hz, H6); ^{13}C NMR (DMSO-d_6) δ 27.21 (d, J = 1.6 Hz, C3'), 37.10 (d, J = 14.7 Hz, C2'), 40.32 (d, J = 137.7 Hz, C1', J determined from a spectrum run in CD_3OD), 50.20 (C4'), 52.52 (d, J = 7.0 Hz, OCH_3), 52.72 (d, J = 6.8 Hz, OCH_3), 58.78 (C5'), 93.23 (C5), 126.88 (d, J = 2.9 Hz, C4"), 128.25 (d, J = 2.2 Hz, C3"), 129.02 (d, J = 6.5 Hz, C2"), 135.57 (d, J = 7.3 Hz, C1"), 146.19 (C6), 156.20 (C2), 165.76 (C4). Anal. Calcd for $C_{17}H_{24}N_3O_5P$: C, 53.54; H, 6.34; N, 11.02: Found: C, 53.36; H, 6.38; N, 10.92.

1-(3-Hydroxymethyl-1-phenyl-1-phosphonobut-4-yl)cytosine Disodium salt (35). The disodium salt of the major isomer of **35** (128 mg, 82%) was obtained from the major isomer of **34** (150 mg, 0.39 mmol) by an analogous procedure to that described for compound **32**: UV (H_2O) λ_{max} 276 mm; ^{31}P NMR (D_2O) δ 20.56; ^1H NMR (D_2O) δ 1.62-1.74 (1H, m, H3'), 1.92-2.20 (2H, m, H2'), 2.85 (1H, ddd, J_{HP} = 21.7 Hz, J = 12.3 Hz, 3.40 Hz, H1'), 3.35 (2H, d, J = 4.7 Hz, H5'), 3.70 (1H, dd, J = 14.1 Hz, 8.8 Hz, H4'), 3.79 (1H, dd, J = 14.1 Hz, 5.4 Hz, H4'), 5.86 (1H, d, J = 7.3 Hz, H5), 7.15-7.33 (5H, m, C_6H_5), 7.36 (1H, d, J = 7.3 Hz, H6); ^{13}C NMR (D_2O) δ 32.06 (d, J = 1.7 Hz, C3'), 39.10 (d, J = 13.0 Hz, C2'), 45.77 (d, J = 124.9 Hz, C1'), 51.20 (C4'), 63.87 (C5'), 96.44 (C5), 126.39 (d, J = 2.6 Hz, C4"), 128.93 (d, J = 2.0

Hz, C3"), 130.27 (d, J = 5.4 Hz, C2"), 142.64 (d, J = 6.5 Hz, C1"), 147.98 (C6), 159.44 (C2), 167.06 (C4). Anal. Calcd for $C_{15}H_{18}N_3O_5PNa_2 \cdot 2H_2O$: C, 41.57; H, 5.11; N, 9.69; Found: C, 41.18; H, 5.09; N, 9.52.

The disodium salt of the minor isomer of **35** (116 mg, 80%) was obtained from the minor isomer of **34** (140 mg, 0.36 mmol) by an analogous procedure: UV (H_2O) λ_{max} 276 mm; ^{31}P NMR (D_2O) δ 20.47; ^1H NMR (D_2O) δ 1.61-1.70 (1H, m, H3'), 1.75-2.04 (2H, m, H2'), 2.78 (1H, ddd, J_{HP} = 21.3 Hz, J = 12.4 Hz, 2.9 Hz, H1'), 3.54 (3H, m, H4', H5'), 3.69 (1H, dd, J = 13.6 Hz, 5.2 Hz, H4'), 5.87 (1H, d, J = 7.5 Hz, H5), 7.15-7.33 (5H, m, C_6H_5), 7.38 (1H, d, J = 7.5 Hz, H6); ^{13}C NMR (D_2O) δ 29.99 (C3'), 39.15 (d, J = 14.2 Hz, C2'), 46.23 (d, J = 124.1 Hz, C1'), 53.02 (C4'), 61.71 (C5'), 96.38 (C5), 126.32 (d, J = 2.8 Hz, C4"), 128.93 (d, J = 2.0 Hz, C3"), 129.96 (d, J = 5.5 Hz, C2"), 142.65 (d, J = 6.5 Hz, C1"), 148.02 (C6), 159.21 (C2), 167.06 (C4). Anal. Calcd for $C_{15}H_{18}N_3O_5PNa_2 \cdot 2H_2O$: C, 41.57; H, 5.11; N, 9.69. Found: C, 41.19; H, 5.13; N, 9.49.

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