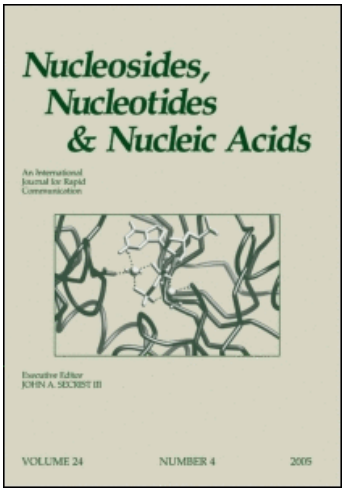

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Synthesis Of 9-(1-Deoxy-1-phosphono-β-D-psicofuranosyl)-1,9-dihydro-6H-purin-6-one as a Potential Transition State Analog Inhibitor of Purine Nucleoside Phosphorylase

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SYNTHESIS OF 9-(1-DEOXY-1-PHOSPHONO-β-D-PSICOFURANOSYL)-1,9-DIHYDRO-6*H*-PURIN-6-ONE AS A POTENTIAL TRANSITION STATE ANALOG INHIBITOR OF PURINE NUCLEOSIDE PHOSPHORYLASE

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ABSTRACT

A fifteen-step synthesis of the proposed purine nucleoside phosphorylase (PNP) transition state analog inhibitor 9-(1-deoxy-1-phosphono-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purine-6-one (**2**) is described starting with 1,2:4,5-disopropylidene-β-D-psicopyranose (**12**). Catalytic hydrogenation of 9-[3-*O*-benzyl-1-(dibenzyloxy-phosphinyl)-1-deoxy-β-D-psicofuranosyl]-6-benzyloxypurine (**27b**) under basic conditions gave the unstable **2** which was found to have a half-life of 39 min at pH 7 and 81 min at pH 8. The low PNP inhibitory activity found for **2** (IC_{50} = 25 μM at 50 mM phosphate concentration) may be due entirely to the presence of the decomposition product hypoxanthine which is itself an inhibitor (IC_{50} = 8.6 μM).

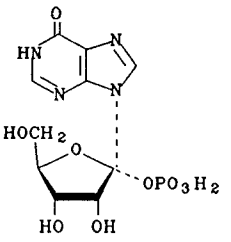
* * * * * * * *

Purine nucleoside phosphorylase (PNP) is a purine-metabolizing enzyme that catalyzes the phosphorolysis of nucleosides such as inosine, guanosine, and their 2'-deoxy forms. The products of this reversible reaction are purine bases and their corresponding 1-ribose and deoxyribose phosphates. PNP deficiency has been identified as a genetic defect associated with severe T-cell immune deficiency.[1] Since proliferating T-cells have been associated with transplant rejection, T-cell leukemia, rheumatoid arthritis, and other autoimmune diseases, the synthesis of PNP inhibitors which can regulate T-cell populations could lead to useful new drugs.

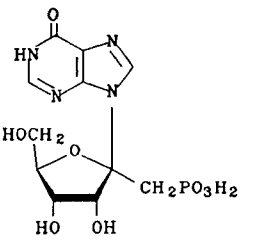
PNP inhibitors can also potentiate the cytotoxicity of nucleosides used an antitumor or antiviral agents by inhibiting their breakdown by phosphorolysis. This potentiation has been demonstrated by 8-aminoguanine and 8-aminoguanosine,[2] competitive inhibitors of human PNP that markedly potentiate the toxicity of 2'-deoxyguanosine for, and the accumulation of dGTP in, T lymphoblasts.[3-5] Accumulation of dGTP in T-cells causes cell death and blocks lymphocytes clonal expansion.

A transition state represented by structure **1** has been suggested for the PNP catalyzed reversible conversion of inosine and phosphate to hypoxanthine and ribose-1-phosphate.[6] We have proposed **2** as a multisubstrate analog which could mimic the transition state **1** and bind to PNP

at the position normally occupied by **1**. The concept of transition-state analogs has been a successful one for the design of potent enzyme inhibitors.[7] The rational for this approach is the recognition that additional, favorable binding interactions develop between an enzyme and the substrate as their complex approaches its transition-state conformation. The substitution of a methylene for the oxygen in the phosphate ester linkage of **1** was expected to add stability to the structure by eliminating the possibility of normal enzymatic phosphate hydrolysis.[8]



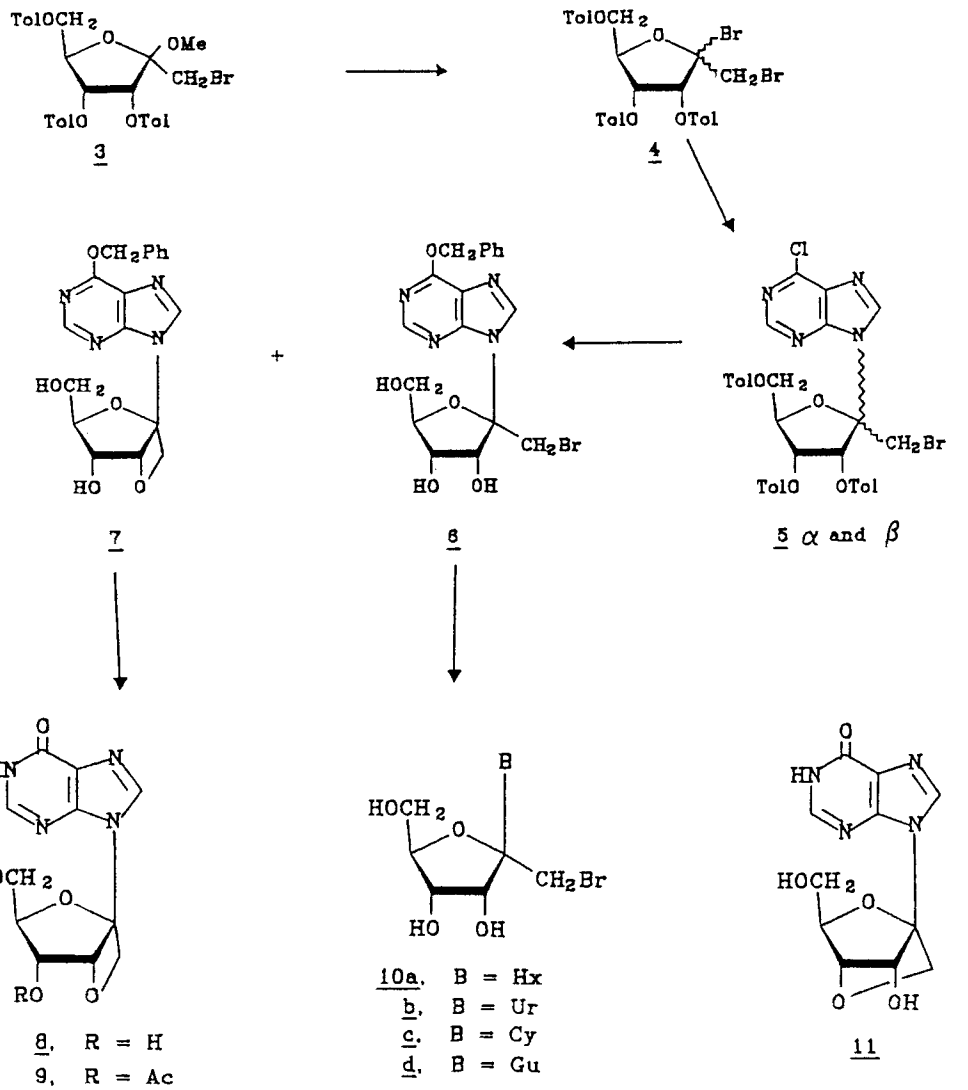
1



2

An initial attempt to prepare **2** involved the synthesis of 9-(1-bromo-1-deoxy-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purin-6-one (**10a**). This synthesis (Scheme 1) was modeled after previously reported syntheses of the corresponding uracil,[9] cytosine,[9] and guanine[10] psicofuranosyl nucleosides (**10b,c,d**). Treatment of methyl 1-bromo-1-deoxy-3,4,6-tri-*O*-*p*-toluoyl-β-D-psicofuranoside **3**[9] with hydrogen bromide in acetic acid gave the bromosugar **4** which was coupled with 6-chloropurine in the presence of mercuric cyanide to give a 61% yield of the β-nucleoside **5**β and a 2% yield of the corresponding α-anomer (**5**α). The anomeric configuration is based on Baker's rule,[11] the greater downfield shift of H-3′ in the β-anomer,[12] and the later formation of the anhydronucleosides **7** and **8** from the β-anomer. Treatment of **5**β in benzyl alcohol with a slight excess of sodium hydride gave a 49% yield of the 6-*O*-benzyl derivative **6** and a 15% yield of the anhydronucleoside **7**. Hydrogenolysis of the benzyl group of **6** and **7** gave the unblocked nucleosides **10a** and **8**. Evidence to support the 1′,3′-anhydronucleoside structure for **8** as opposed to the possible 1′,4′-anhydronucleoside structure **11** was provided by acetylation of **8** to give the diacetate **9**. The ^{1}H NMR spectra of **8** and **9** show a downfield shift of 0.26 ppm for the 3′-H and a downfield shift of 1.06 ppm for the 4′-H in going from non-acetylated to acetylated nucleoside. This well known "acylation shift" of approximately 1.1 ppm for the protons α to secondary alcohols[13] favors structure **8** over the 1′,4′-anhydronucleoside **11**. Similar anhydronucleoside formations have been reported from alkaline methanolysis of the 3′,4′,6′-tri-*O*-tolyl ester of **10b** and **10c**.[14] Although the structures of the anhydronucleosides formed from **10b** and **10c** were not assigned, published ^{1}H NMR data[14] indicate the 1′,3′-anhydronucleosides are the likely products based on the same evidence used for selection of structure **8**.

Scheme 1

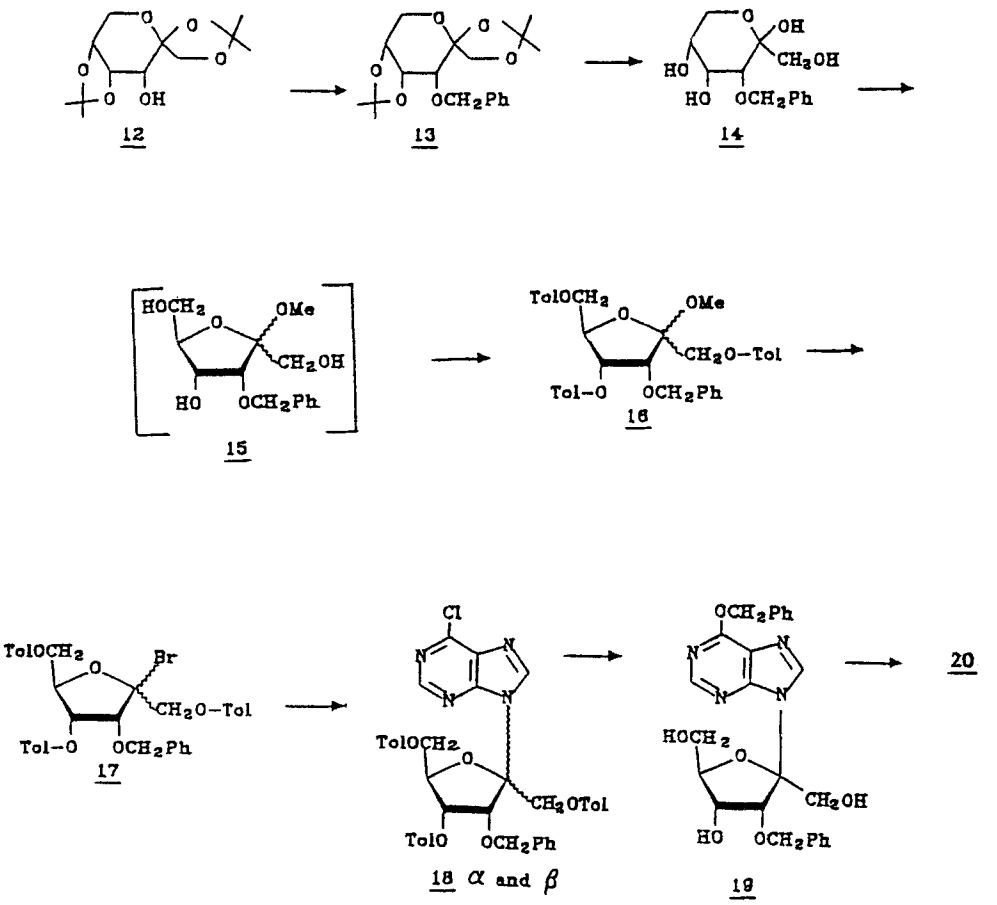


A comparison of the energy values from computer generated lowest energy conformations for structures **8** and **11** indicates a lower energy by 32.8 kcal for the 1′,4′-anhydronucleoside structure **11**. The computed value for **8** was 69.7 kcal and for **11** was 36.9 kcal. If this computed energy difference can be considered a true reflection of the actual energies of **8** and **11**, the formation of the higher energy **8** must be attributed to preferential attack of benzyloxy anion on the 3′-*O*-tolyl ester of **5**β to give the 3′-oxygen anion which rapidly displaces bromide to form anhydronucleoside. The greater reactivity of the 2′-*O*-acyl group in 2′,3′,5′-tri-*O*-acylribonucleosides is well documented.[15] Although a Michaelis-Arbuzov reaction on a 1′-deoxy-1′-iodopsicofuranosyl-nucleoside has been reported to give a trace amount of the corresponding phosphonate,[16] all attempts to carry out this reaction on **6** and **10a** to give phosphonates were unsuccessful. The reaction of **10a** with highly nucleophilic azide ion gave only anhydronucleoside **8**. The conversion of **10a** to **8** can be explained by analogy to the greater acidity and preferred alkylation of the 2′-OH in related ribonucleosides.[15,17]

The successful synthesis of **2** was carried out by the route shown in Scheme 2. 1,2:4,5-Diisopropylidene-β-D-psicopyranose[18] (**12**) was prepared in three steps from D-fructose, and benzylated in 76% yield with benzyl bromide and sodium hydride in *N,N*-dimethylacetamide. The crystalline **13** was hydrolyzed in aqueous oxalic acid to give a quantitative yield of 3-*O*-benzyl-D-psicose (**14**) as a syrup. Treatment of **14** with methanolic hydrogen chloride gave a ~1:1 mixture of anomeric methyl D-psicofuranosides **15** which was isolated as the anomeric mixture of *p*-toluates **16** α and β. The bromopsicose derivative **17** from **16** and hydrogen bromide in acetic acid was coupled with 6-chloropurine in the presence of mercuric cyanide to give a 38% yield of a 1:1 mixture of the α- and β-anomers **18**α **and** β. The anomers were separated by chromatography on silica gel. The absence of an anomeric proton in the nucleosides **18** α and **18** β makes the assignment of their anomeric configuration difficult. However, Moffatt, *et al.*[12] have shown that for α- and β-psicofuranosyl purine nucleosides the assignment of the stereochemistry can be made by comparison of the δ of H-3′ for the α- and β-anomeric pair. They found that H-3′ for the β-psicofuranosyl nucleoside occurs at a δ = 0.5 ppm downfield from the corresponding α-anomer. We found, that H-3′ for **18**-β occurs at δ = 5.57 ppm and H-3′ for the **18**-α occurs at δ 4.86 ppm. This is in good agreement with that found by Moffatt and makes the assignment of the anomeric configuration possible. The pure β-anomer was treated with sodium hydride in benzyl alcohol to give a 52% yield of the deblocked 6-benzyloxypurine nucleoside **19**. The 4′- and 6′-hydroxyl groups of **19** were protected by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyl-disiloxane (TIPSCl) and imidazole in DMF at -55 °C to give a 45% yield of the disiloxane derivative **20**.

In a second experiment carried out at -35 °C, the yield of **20** was reduced to 35% and a 22% yield of the dimeric product **21** isolated (Scheme 3). At the lower reaction temperature initial reaction of TIPSCl apparently takes place primarily at the less hindered 6′-primary OH. At the slightly higher reaction temperature less selectivity might be expected and some reaction could

SCHEME 2



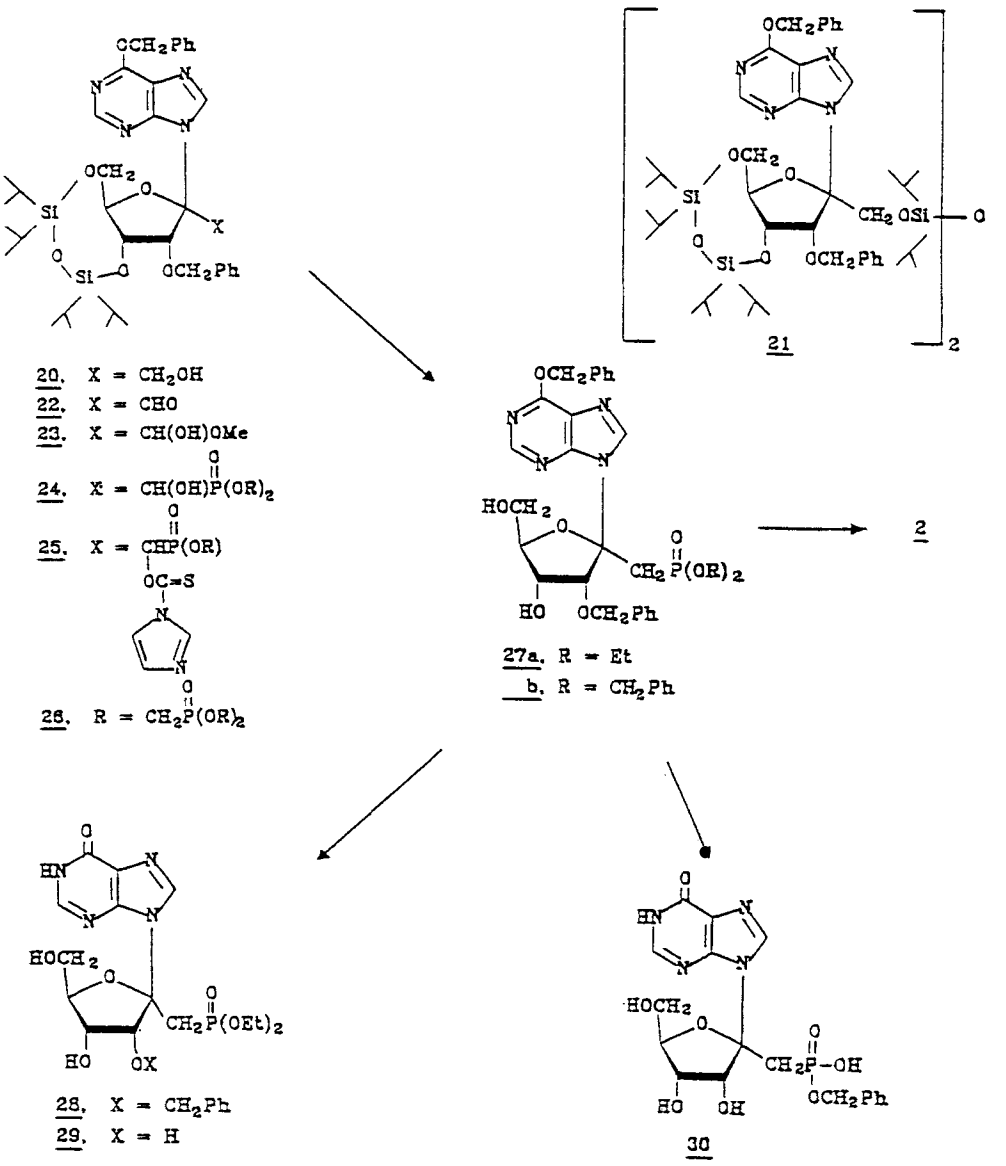
take place at the 1′-OH which could lead to formation of dimer **21**. The dimeric structure **21** is supported by the mass spectrum which gives an $(M + H)^+$ of 1684. The ^1H NMR spectrum is also consistent with structure **21**. Oxidation of **20** with Me_2SO-DCC containing a catalytic amount of trifluroacetic acid and pyridine in benzene gave the aldehyde **22** which was isolated as the hemiacetal **23**. Reaction of the aldehyde equivalent **23** with diethyl phosphite gave a mixture of the *R* and *S* isomers of the diethyl phosphonate **24a**. The overall yield from **20** to **24a** was 84%. The C-P bond formation was confirmed by coupling between P and the proton at C-1′ and the 1′-OH. The hydroxyl group at C-1′ was removed in two steps by conversion to the imidazole thioester **25a** followed by reduction with tributyltin hydride to give **26a**. Cleavage of the silyl protecting group of **26a** gave the diethyl phosphonate **27a**. Catalytic hydrogenation of **27a** over palladium on carbon resulted in initial removal of the 6-*O*-benzyl group to give **28**. Further hydrogenation cleaved the 3′-*O*-benzyl group to give the diethyl phosphonate **29**. An attempt to cleave the ethyl groups from **29** with trimethylsilylbromide resulted in glycoside cleavage. Treatment of **29** with phosphodiesterase from *Crotalus atrox* gave a mixture of products which could not be separated or identified by MS or ^1H NMR.

Our inability to convert the diethyl phosphonate **29** to the free phosphonic acid **2** prompted the synthesis of the corresponding dibenzyl phosphonate **27b** which was anticipated to be more amenable to conversion under mild hydrogenation conditions[19] to the free phosphonate **2**. Replacement of diethyl phosphite with dibenzyl phosphite in the conversion of **23** to **24** gave a 47% and 30% yield of the two diastereomers (**24b**). The ^1H-NMR spectra did not provide sufficient information to distinguish between *R* and *S* isomers. Treatment of the faster traveling (TLC) isomer of **24b** with 1,1′-thiocarbonyldimidazole gave a 57% yield of the thioester **25b** which was reduced with tributyltin hydride to give a 72% yield of **26b**. Removal of the silyl blocking group gave a 67% yield of the dibenzyl phosphonate **27b**.

Synthesis and isolation of the target phosphonate **2** was complicated by the unexpected instability of the free acid. An initial attempt to remove the benzyl groups from **27b** by hydrogenation in the presence of palladium-on-carbon in aqueous ethanol gave only hypoxanthine and a non-UV-absorbing sugar component. Reduction in the presence of calcium carbonate to neutralize the free acid still permitted an estimated 50% sugar cleavage. The reaction conditions which were found to give a minimum of sugar cleavage required 30% palladium-on-carbon in the presence of triethylamine and 2 equivalents of 1*N* sodium hydroxide in order to stabilize the product by immediate neutralization of the unstable phosphonic acid as it was formed. The reduction product mixture containing the sodium salt of **2**, the monobenzyl ester **30** and hypoxanthine was separated by silica gel flash chromatography in acetonitrile-1*N* ammonium hydroxide to give a 37% yield of **2** and a 28% yield of **30**, both as crude ammonium salts.

The half-life of **2** in aqueous solution as determined by HPLC is 81 min at pH 8 and 39 min at pH 7. The monobenzyl ester **30** was more stable with a half-life of about 7 h at pH 8.

SCHEME 3



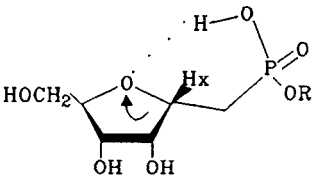


Figure 1

The instability of these phosphonate nucleosides can be explained by intramolecular protonation of the psicose ring oxygen by a phosphonic acid proton via a 6-membered ring intermediate (Fig. 1) leading to glycosidic ring opening followed by nucleoside cleavage. The psicose nucleoside 9-β-D-psicofuranosyladenine (psicofuranine) is reported to be somewhat unstable in acid[20] (half-life at pH 2 is 18 h). The presence of the appropriately-positioned, built-in proton source in **2** markedly increases this instability.

The molar absorptivity of **2** at 250 nm was determined by allowing a solution of crude **2** in pH 7 buffer to stand for 18 h during which time the **2** had hydrolyzed completely to hypoxanthine, and the UV absorbance at 250 nm had changed from 0.210 to 0.190. Since the sample of crude **2** was known to contain 16 mol % of hypoxanthine as determined by HPLC, the absorbance of pure **2** (0.214) could be estimated by extrapolation of a linear plot of absorbance *vs* hypoxanthine concentration to 0% hypoxanthine concentration. Since the total molar concentration does not change in going from **2** to hypoxanthine, and **2** and hypoxanthine have absorption maxima at 250 nm, the following equations hold true: $e_2/e_{Hx} = A_2/A_{Hx}$ and $e_2 = e_{Hx}(A_2/A_{Hx})$. Substitution of the reported[21] molar absorptivity of 10.5 x 10^{-3} $L \cdot mol^{-1} \cdot cm^{-1}$ for e_{Hx} gives a molar absorptivity of 11.8 x 10^{-3} for **2**.

Assay for inhibition of purine nucleoside phosphorylase (PNP). Assays for inhibition of PNP were performed by measuring the effects of the inhibitor on the conversion of [8-^{14}C]inosine to [8-^{14}C]hypoxanthine in the presence of calf spleen PNP (Sigma Chemical Co., St. Louis, MO). The procedure used was a modification of Sicar, *et al.*[22] The incubation mixtures contained the inhibitor at various concentrations; 10 μM [8-^{14}C]inosine (560 nCi); 0.001 units of PNP; and 50 mM phosphate buffer (pH 7.4) in a final volume of 0.5 mL. After incubation for 10 min at 25 °C, the reaction was stopped by immersion in a boiling water bath. Carrier inactive hypoxanthine and inosine were added to an aliquot of the reaction mixture; 50 μL of the mixture was subjected to paper chromatography (Whatman 3MM, 4.5 cm x 57 cm strips) in a solvent consisting of equal parts of 93.8% aqueous 1-butanol and 44% aqueous propionic acid. The spots of hypoxanthine and inosine were located by inspection of the chromatogram under ultraviolet light, cut out, and

assayed for radioactivity by liquid scintillation spectrometry. The inhibitor was assayed at multiple concentrations in the range 1 nM to 300 μM, and the concentration giving 50% inhibition was determined from a plot of percent inhibition *vs* concentration. Since the inhibitor was known to contain about 16% hypoxanthine a standard curve was plotted for inhibition of the enzymes by hypoxanthine; the IC_{50} for hypoxanthine was 8.6 μM.

The observed IC_{50} for the inhibitor was 25 μM. About half of the observed inhibition could be accounted for by the amount of hypoxanthine present in the IC_{50} concentration of the inhibitor; some additional hypoxanthine is formed by hydrolysis of the inhibitor, which has a half-life of 39 min at pH 7. Since about 45 min (*i.e.*, about one half-life) elapsed between putting the inhibitor in solution and termination of the reaction, the concentration of hypoxanthine could have been as high as 16.5 μM; thus all of the observed inhibition could be due to hypoxanthine.

Discussion

The failure of **2** to effectively inhibit PNP is consistent with results from other studies reported since the initiation of this project. A series of 9-(phosphonoalkyl)hypoxanthines was synthesized, and the K_i values for PNP inhibition at 1 mM phosphate concentration for the propyl, butyl, and pentyl compounds were reported as 2700, 65, and 1.1 μM, respectively.[23] The efficacy of this homologous class of inhibitors increased with increasing side chain length up to five methylenes after which no further advantage was gained. In agreement with these findings, acyclovir diphosphate, a highly effective PNP inhibitor,[24] has a spacing of 5 and 7 atoms from the 9-nitrogen to the phosphorus atoms. The location of the phosphate binding site in human erythrocyte PNP has been determined from X-ray crystallographic studies with formycin B, and the phosphorus atom was found to be spaced 6.1 Å from the 3-position of the pyrazolopyrimidine ring corresponding to the 9-position of inosine or guanosine.[25] Since the maximum distance of the phosphorus from the 9-nitrogen in **2** is 4.2 Å,[25] tight binding of both the purine ring and the phosphonate group to their respective binding sites in the enzyme active site is not possible.

Experimental Section

All evaporations were carried out *in vacuo* with a rotary evaporator or by short-path distillation into a dry ice/acetone-cooled receiver under high vacuum. Analytical samples were normally dried *in vacuo* over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated aqueous $(NH_4)_2SO_4$. All analytical samples were homogeneous by TLC. Melting points were determined with a Mel-Temp apparatus unless otherwise specified. Purifications by "gravity column" and by "flash chromatography"[26] were carried out on Merck silica gel 60 (230-400 mesh) using the slurry method of column packing. The UV absorption spectra were determined in 0.1*N* HCl (pH 1), pH 7 buffer, and 0.1*N* NaOH (pH 13) with a Cary 17 spectrophotometer and a Perkin Elmer ultraviolet-visible near-infrared spectrophotometer Model Lambda 9: the maxima are reported in nanometers (ϵ x 10^{-3} M^{-1} cm^{-1}).

The NMR spectra of all compounds except **2** were determined with a Nicolet/GE NT 300NB spectrometer operating at 300.35 MHz for ^{1}H-NMR spectra and 75.6 MHz for ^{13}C NMR spectra with tetramethylsilane as an internal reference. The ^{1}H NMR spectrum of **2** was recorded at 600.138 MHz with a Brucker AM 600 spectrometer.[31] D_2O solvent (pD 6.6) was used as an internal lock and acetone (δ = 2.12 ppm) was used as an external reference. Chemical shifts (δ, ppm) quoted in the case of multiplets are measured from the approximate center. The mass spectra were obtained with a Varian-MAT 311A mass spectrometer in the fast-atom-bombardment mode. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. High-pressure liquid chromatography (HPLC) was carried out on a Hewlett Packard 1084B liquid chromatograph. Linear gradients of 0.01M $NH_4H_2PO_4$ (pH 5.1) and MeOH (5% to 90% MeOH) were carried out over 20 min at a flow rate of 1 mL per minute using a 30 cm x 4 mm (i.d.) column of μ-Bondapak C_{18} (Waters Associates, Inc.).

Molecular modeling was performed on an Evans and Sutherland PS 390 graphics facility linked to a Digital Equipment Corp. VAX 8550 computer. Models were built interactively using the MACROMODEL software package (Version 2)[27], and refined by molecular mechanics methods[28] using the AMBER force field.[29] Subsequently, global conformational searches for both molecules were conducted using Monte Carlo methods[30] as implemented by the BATCHMIN V. 2.2 module of MACROMODEL. A total of 5000 structures were minimized for each model using the block diagonal Newton-Raphson algorithm. Cartesian searching was employed for the sugar ring atoms, *i.e.*, at each Monte Carlo step, a randomly selected fraction of these atoms was given a displacement of up to 250 pm; terminal atoms were moved with their parent atom to minimize chirality inversions. In order to maintain planarity of the purine ring, the torsion of the anomeric bond was varied randomly at each step, but the relative positions of the ring atoms were held fixed. The lowest energy structures were refined to a gradient rms of approximately 0.01.

9-(1-Bromo-1-deoxy-3,4,6-tri-*O*-4-toloyl-β-D-psicofuranosyl)-6-chloro-9*H*-purine (5β) and 9-(1-Bromo-1-deoxy-3,4,6-tri-*O*-*p*-toloyl-α-D-psicofuranosyl)-6-chloro-9*H*-purine (5α). A solution of methyl 1-bromo-1-deoxy-3,4,6-tri-*O*-*p*-toloyl-β-D-psicofuranoside[9] (**3**, 2.50 g, 4.09 mmol) in anhydrous CH_2Cl_2 (15 ml) in an ice bath was treated with 30% HBr in acetic acid (13.5 mL) and stirred at 0 °C for 30 min and at 25 °C for 20 min. The mixture was diluted with $CHCl_3$ (21 mL) and poured into ice-H_2O. The organic layer was washed with cold H_2O (5 mL), then freshly prepared cold $NaHCO_3$ solution (3 x 15 mL), dried ($MgSO_4$) and evaporated to a foam under high vacuum. A solution of the resulting bromosugar (**4**) in anhydrous $MeNO_2$ (9 mL) was added to a cold solution of $Hg(CN)_2$ (1.04 g, 4.09 mmol) and 6-chloropurine (634 mg, 4.09 mmol) in $MeNO_2$ (140 mL). The mixture was stirred at 0 °C for 5 min and at 25 °C for 2 h, then filtered with charcoal through Celite and evaporated to dryness *in vacuo*. A solution of the residue in benzene (50 mL) was filtered and evaporated *in vacuo* to a solid which was dissolved in a minimum of 94:6 benzene-

EtOAc, applied to a flash column of 125 g of silica gel and eluted with the same solvent. The major fraction (Rf 0.35 in 9:1 benzene-EtOAc) was evaporated to give 1.83 g (61%) of **5β** which was recrystallized from hot MeOH (125 mL) to give pure **5β**, mp 188 °C; MS, *m/z* 733 $(M + H)^+$; UV λ_{max} (ϵ x 10^{-3}) EtOH, 241 (49.8); ^1H NMR (Me_2SO-d_6) δ 8.81 (s, 1, H_2), 8.64 (s, 1, H_8), 8.01, 7.73, 7.49, 7.36, 7.25, 7.07 (d's, 12, ortho and meta aromatic H's), 6.88 (d, 1, $H_{3'}$, $J_{3',4'}$ = 5.2 Hz), 6.04 (t, 1, $H_{4'}$, $J_{4',5'}$ = 5.0 Hz), 5.17 (m, 1, $H_{5'}$), 4.83 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 3.0 Hz, $J_{6a',6'b}$ = 12.0 Hz), 4.59 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 3.2 Hz), 4.47 (s, 2, $H_{1'}$), 2.42, 2.35, and 2.33 (3s, 9, 3 CH_3's). Anal. ($C_{35}H_{30}BrClN_4O_7$) C,H,N.

The minor slightly faster traveling α-anomer fraction (Rf 0.4 in 9:1 benzene-EtOAc) was evaporated to give 64 mg (2%) of **5α** which was triturated with MeOH (1 mL) to give 31 mg of pure **5α**, mp 177 °C; MS, *m/z* 733 $(M + H)^+$; UV λ max (ϵ x 10^{-3}) EtOH, 242 (48.9); ^1H NMR (Me_2SO-d_6) δ 9.19 (s, 1, H_8), 8.26 (s, 1, H_2), 8.02, 7.40, 7.37, 7.18, 7.12, 7.04 (d's, 12, ortho and meta aromatic H's), 6.38 (d, 1, $H_{3'}$, $J_{3',4'}$ = 5.8 Hz), 6.06 (dd, 1, $H_{4'}$, $J_{4',5'}$ = 1.9 Hz), 5.60 (m, 1, $H_{5'}$), 4.95 (d, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 11.9 Hz), 4.78 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 4.3 Hz, $J_{6'a,6'b}$ = 4.3 Hz, $J_{6'a,6'b}$ = 11.0 Hz), 4.72 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 5.2 Hz), 2.42, 2.35, 2.28 (3s, 9, 3 CH_3's). Anal. ($C_{35}H_{30}BrClN_4O_7$) C,H,N.

6-Benzyloxy-9-(1-bromo-1-deoxy-β-D-psicofuranosyl)-9*H*-purine (6) and 9-(1,3-Anhydro-β-D-psicofuranosyl)-6-benzyloxy-9*H*-purine (7). A solution of **5β** (1.52 g, 2.07 mmol) in anhydrous (dried over Linde 4A Molecular Sieve) benzyl alcohol (115 mL) under N_2 was cooled in an ice bath, treated with 50% NaH/mineral oil emulsion (109 mg, 2.28 mmol) and stirred at 0 °C for 2 h and 25 °C for 2.5 days. The reaction mixture was neutralized with Dowex 50W-X4 (H^+) ion-exchange resin, filtered and evaporated under high vacuum at 30 °C. The resulting syrup was triturated with 35-60 °C petroleum ether to give a white solid which was dissolved in a minimum of 95:5 $CHCl_3$-MeOH, applied to a flash column of 80 g of silica gel, and eluted with the same solvent. The major fraction (Rf 0.4 in 9:1 $CHCl_3$-MeOH) was evaporated to give pure **6** as a white crystalline solid which was dried at 56 °C *in vacuo*; yield 460 mg (49%), mp 126-130 °C; MS, m/z 451 $(M + H)^+$; UV λ_{max} (ϵ x 10^{-3}) pH 1, 252 (13.5); pH 7, 253 (14.1); pH 13, 253 (13.8); ^1H NMR (Me_2SO-d_6) δ 8.64 (s, 1, H_8 or H_2), 8.57 (s, 1, H_2 or H_8), 7.54-7.51 (m, 2, ortho aromatic H's), 7.44-7.36 (m, 3, meta and para aromatic H's), 6.11 (d, 1, 3'-OH, $J_{3',3'\text{-OH}}$ = 5.4 Hz), 5.62 (s, 2, CH_2), [5.19(d, 4'-OH, $J_{4',4'\text{-OH}}$ = 6.9 Hz) and 5.16 (t, 6'-OH, $J_{6',6'\text{-OH}}$ = 5.1 Hz)] (2H), 4.67 (t, 1, $H_{3'}$, $J_{3',4'}$ = 4.3 Hz), 4.60 (d, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 11.5 Hz), 4.09-3.99 (m, 2, $H_{1'a}$ and $H_{5'}$), 3.85 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 2.1 Hz, $J_{6'a,6'b}$ = 12.6 Hz), 3.58 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 2.8 Hz). Anal. ($C_{18}H_{19}BrN_4O_5$) C,H,N. A second fraction from the flash column (Rf 0.36 in 9:1 $CHCl_3$-MeOH) was evaporated to give 123 mg (15%) of **7** which was triturated with MeOH (1 mL) to give pure **7** as a crystalline solid, mp 115 °C (Kofler-Heizbank); MS, *m/z* 371 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.56 (s, 2, H_2, H_8),

7.52-7.49 (m, 2, ortho aromatic H's), 7.44-7.35 (m, 3, meta and para aromatic H's), 5.64 (s, 2, CH_2), 5.55 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.4 Hz), 5.45 (d, 1, $H_{1'a}$, $J_{1'a,1'b}$ = 8.0 Hz), 4.88 (d, 1, $H_{1'b}$), 4.25 (m, 2, $H_{5'}$, $H_{4'}$), 3.79 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 11.7 Hz), 3.56 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 4.9 Hz). Anal. ($C_{18}H_{18}N_4O_5 \cdot 0.5H_2O$) C,H,N. By using a larger molar ratio of NaH to **5**β (*e.g.*, 2.25:1), **7** could be obtained as the major product.

9-(1,3-Anhydro-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purin-6-one (8). A solution of **7** (92 mg, 0.237 mmol) in MeOH (50 mL) containing 5% Pd/C (20 mg) was hydrogenated at atmospheric pressure for 11 min, filtered through Celite and evaporated to give 69 mg (100%) of crystalline **8**. The analytical sample, mp 236 °C dec (Mel-Temp), was obtained by recrystallization from MeOH and dried at 100 °C *in vacuo*; MS (FAB), *m/z* 281 $(M + H)^+$; UV λ_{max} (ϵ x 10^{-3}) pH 1, 248 (11.9); pH 7, 248 (12.3); pH 13, 253 (13.1); ^{1}H NMR (Me_2SO-d_6) δ 12.5 (br s, 1, NH), 8.26 (s, 1, H_8), 8.06 (s, 1, H_2), 5.52 (d, 1, $H_{3'}$, $J_{3',4'}$ = 4.0 Hz), 5.34 (d, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 8.0 Hz), 4.85 (d, 1, $H_{1'a}$), 4.25 (m, 1, $H_{5'}$), 4.19 (m, 1, $H_{4'}$, $J_{4',5'}$ = 8.6 Hz), 3.80 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 2.1 Hz), 3.55 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 5.6 Hz, $J_{6'a,6'b}$ = 12.3 Hz). Anal. ($C_{11}H_{12}N_4O_5$) C,H,N.

9-(1,3-Anhydro-4,6-di-*O*-acetyl-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purin-6-one (9). A solution of **8** (2.9 mg, 0.0103 mmol) in anhydrous pyridine (0.4 mL) was treated with Ac_2O (0.2 mL), allowed to stand for 3 days at 25 °C, treated with EtOH (0.4 mL), let stand for 2 h, and evaporated under reduced pressure to give a crystalline residue; yield 3 mg (80%); Rf 0.15 in 95:5 $CHCl_3$-MeOH; MS, *m/z* 365 $(M + H)^+$; ^{1}H NMR (Me_2SO-d_6) δ 12.5 (br s, 1, NH), 8.32 (s, 1, H_8), 8.11 (s, 1, H_2), 5.76 (d, 1, $H_{3'}$, $J_{3',4'}$ = 4.4 Hz), 5.44 (B part of an AB spin system, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 8.2 Hz), 5.26 (dd, 1, $H_{4'}$, $J_{4',5'}$ = 8.5 Hz), 4.97 (A part of an AB spin system, 1, $H_{1'a}$), 4.71 (m, 1, $H_{5'}$, $J_{5',6'a}$ = 2.7 Hz, $J_{5',6'b}$ = 5.9 Hz), 4.49 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{6'a,6'b}$ = 12.3 Hz), 4.16 (B part of an ABX spin system, 1, $H_{6'b}$), 2.11 (s, 3, CH_3), 1.98 (s, 3, CH_3-).

9-(1-Bromo-1-deoxy-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purin-6-one (10a). A solution of **6** (116 mg, 0.257 mmol) in MeOH (10 mL) containing 5% Pd/C (35 mg) was hydrogenated at atmospheric pressure for 15 min, filtered and evaporated to dryness. The residue was crystallized from hot MeOH to give pure **10a**; yield 56 mg (58%), mp 185 °C dec (Kofler-Heizbank); MS, *m/z* 361 $(M + H)^+$; UV λ_{max} (ϵ x 10^{-3}) pH 1, 249 (12.0); pH 7, 248 (12.6), pH 13, 253 (13.7); ^{1}H NMR (Me_2SO-d_6) 11.42 (br s, 1, NH), 8.36 (s, 1, H_8), 8.07 (s, 1, H_2), 6.03 (br s, 1, 3'-OH) 5.20 (br s, 1, 4'-OH), 5.13 (br t, 1, 5'-OH), 4.58 (br s, 1, $H_{3'}$, $J_{3',4'}$ = 6.4 Hz), 4.49 (d, 1, $H_{1'b}$, $J=_{1'a,1'b}$ = 11.3 Hz), 4.06-3.99 (m, 3, $H_{1'a}$, $H_{4'}$, $H_{5'}$), 3.84 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 2 Hz), 3.58 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 3 Hz, $J_{6'a,6'b}$ = 12 Hz). Anal. ($C_{11}H_{13}BrN_9O_5 \cdot 0.5CH_3OH$) C,H,N.

3-*O*-Benzyl-1,2:4,5-diisopropylidene-β-D-psicopyranose (13). A solution of 1,2:4,5-diisopropylidene-β-D-psicopyranose[18] (**12**, 107 g, 0.411 mol) in anhydrous DMAC (16 mL) was treated in small portions under N_2 with NaH (10.9 g, 0.452 mol), cooled to 5 °C, treated dropwise with benzyl bromide (77.3 g, 0.452 mol) over 30 min and stored at 25 °C for 24 h. The solution was cooled to 5 °C and treated with Et_3N (40 mL) followed by H_2O (350 mL). The mixture was treated with solid NaCl, filtered and evaporated under high vacuum. The residue in CH_2Cl_2 (1500 mL) was washed with H_2O (2 x 200 mL), dried ($MgSO_4$), and evaporated to dryness. A solution of the residue in warm Et_2O (200 mL) was diluted with *n*-pentane (250 mL) and refrigerated to give crystalline **13**; yield 111 g (76%) mp 85 °C; MS, *m/z* 351 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 7.42-7.25 (m, 5, $-C_6H_5$), 4.85 (B part of an AB spin system, 1, $-CH_aH_b-C_6H_5$, J = 12.0 Hz), 4.73 (A part of an AB spin system, 1, $-CH_aH_bC_6H_5$), 4.48 (d, 1, H_{1b}, $J_{1a,1b}$ = 9.2 Hz), 4.43 (dd, 1, H_4, $J_{3,4}$ = 2.6 Hz, $J_{4,5}$ = 7.7 Hz), 4.21 (m, 1, H_5), 3.95 (d, 1, H_{1a}), [3.73 (d, H_3, $J_{3,4}$ = 2.6 Hz) and 3.71 (m, H_{6a}, H_{6b})] (3H), 1.50, 1.48, 1.47, 1.31 (4s, 12, four CH_3's). Anal. ($C_{19}H_{26}O_6$) C,H.

3-*O*-Benzyl-β-D-psicopyranose (14). A mixture of **13** (110 g, 314 mmol) oxalic acid (18.0 g) and water (2 L) was stirred at 65 °C for 4 h to give a clear solution which was cooled to 25 °C and stirred with powdered $CaCO_3$ (66 g) for 18 h. The resulting mixture was filtered and the filtrate (pH 5) was evaporated under high vacuum at 40-45 °C to give **14** as a syrup (85 g) which was used without further purification for the synthesis of **16**; MS, *m/z* 271 $(M + H)^+$.

Methyl 3-*O*-Benzyl-1,4,6-tri-*O*-*p*-toluyl-β-D-psicofuranoside (16). A solution of **14** (85 g, 314 mmol) in 0.1*N* HCl in MeOH (1500 mL) was allowed to stand at 25 °C for 4 h and neutralized by stirring with Ag_2CO_3 (33 g) for 40 min. The precipitate was filtered off, washed with MeOH (2 x 100 mL) and the combined filtrate and wash evaporated under reduced pressure. The residue of **15** was evaporated twice from anhydrous pyridine to remove traces of H_2O. A solution of the residue in pyridine (900 mL) was cooled in an ice bath, treated dropwise with *p*-toluyl chloride (205 g, 176 mL, 1.33 mol). After 2 days at 25 °C, the solution was poured onto ice and extracted with cold Et_2O (2 x 1 L). The extract was washed with 5% H_3PO_4 until the aqueous layer remained acidic, then with saturated $NaHCO_3$ and evaporated to a syrup. This mixture was purified on a gravity column of 4 Kg of silica gel eluting with benzene-EtOAc (99:1), then (98:2) and finally (95:5) to give a mixture of α- and β-anomers (Rf 0.6 and 0.85 in 95:5 benzene-EtOAc); yield 119 g (68%); MS, *m/z* 639 $(M + H)^+$. The ^1H NMR and elemental analysis were obtained on a small quantity of the slower-traveling anomer which crystalized from the mixture of anomers. ^1H NMR $CDCl_3$ δ 7.94-7.89 (m, 6, aromatic H's), 7.24-7.11 (m, 11, aromatic H's), 5.74 (dd, 1, H_4, $J_{3,4}$ - 4.4 Hz, $J_{4,5}$ = 8.0 Hz), [4.77 (d, $-CH_aH_bC_6H_5$, J = 12.2 Hz) and 4.74 (m, H_5)] (2H), 4.66-4.58 (m, 3, H_{1a}, H_{1b}, H_{6b}, $J_{5,6b}$ = 5.1 Hz, $J_{6a,6b}$ = 12.0 Hz), 4.49 (d, 1, $-CH_aH_bC_6H_5$, J = 12.2 Hz), [4.43 (dd, H_{6a}, $J_{5,6a}$ = 3.7 Hz, $J_{6a,6b}$ = 12.0 Hz), and 4.42 (d, H_3, $J_{3,4}$ = 4.4 Hz)] (2H), 3.29 (s, 3, $-OCH_3$), 2.42, 2.41, 2.38 (3s, 9, $3CH_3$'s). Anal. ($C_{38}H_{38}O_9 \cdot 0.3C_6H_6$) C,H,N.

9-(3-*O*-Benzyl-1,4,6-tri-*O*-*p*-toluyl-α- and β-D-psicofuranosyl)-6-chloro-9*H*-purine (18). A solution of **16** (26.4 g, 41.4 mmol) in anhydrous CH_2Cl_2 (142 mL) was cooled to 0 °C, treated with 30% HBr-AcOH (139 mL), maintained at 0 °C for 20 min and 25 °C for 30 min. The mixture was diluted with CH_2Cl_2 (212 mL) and poured onto ice. The organic layer was washed with H_2O (55 mL) then cold saturated $NaHCO_3$ solution (2 x 147 mL), dried over $MgSO_4$ and evaporated to give the bromosugar **17** as a foam.

A solution of **17** in $MeNO_2$ (12 mL) was added to a solution of 6-chloropurine (6.40 g, 41.5 mmol) and $Hg(CN)_2$ (10.5 g, 41.4 mmol) in $MeNO_2$ (750 mL) and the stirred mixture refluxed for 45 min, cooled to 25 °C, filtered, and evaporated to dryness *in vacuo*. A solution of the residue in $CHCl_3$ (150 mL) was washed with H_2O, dried ($MgSO_4$) and evaporated to a syrup. The residue in 95:5 benzene-EtOAc was applied to a gravity column of 1 Kg of silica gel and eluted with the same solvent. The β-nucleoside fraction (Rf 0.38 in 9:1 benzene-EtOAc) was evaporated under high vacuum to give **18-β** as a solvate with benzene and $CHCl_3$; yield 6.36 g (19%); MS, *m/z* 761 $(M + H)^+$, 607 $(sugar)^+$; ^1H NMR ($CDCl_3$) δ 8.66 (s, 1, H_8), 8.47 (s, 1, H_2), 7.96, 7.64, 7.58 (3 d, 6, ortho aromatic H's), 7.37 (C_6H_6), 7.28-7.06 (m, 11, other aromatic H's), 5.67 (d, 1, $H_{3'}$, $J_{3',4'}$ = 5.1 Hz), 5.57 (t, 1, $H_{4'}$, $J_{4',5'}$ = 6.2 Hz), 5.15 (B part of an AB spin system, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 12.3 Hz), [4.95 (m, $H_{5'}$) and 4.91 (m, $H_{1'a}$ and $-CH_bH_a-C_6H_5$)] (3H), 4.82 (m, 2, $H_{6'b}$, $-CH_6H_aC_6H_5$), 4.49 (B part of an ABX spin system, 1, $H_{6'a}$, $J_{6'a,6'b}$ = 12.7 Hz, $J_{5',6'a}$ = 3.2 Hz), 2.44, 2.38, 2.36 (3 s, 9H, 3 CH_3's). ^{13}C NMR ($CDCl_3$) δ 165.76, 165.60, and 165.44 (C=O), 151.55 (C-2, $^1J_{C,H}$ = 209.7 Hz), 151.16 (C-6, $^3J_{C,H}$ = 13.4 Hz), 150.36 (C-4, $^3J_{C,H}$ = 5.0 Hz, $^3J_{C,H}$ = 12.3 Hz), 144.21 (C-8, $^1J_{C,H}$ = 217.4 Hz), 132.50 (C-5, $^3J_{C,H}$ = 12.4 Hz), 144.63, 144.27, 144.18, 136.51, 129.94, 129.56, 129.31, 129.14, 129.01, 128.41, 128.34, 128.20, 126.12, 125.96, and 125.88 (aromatic C's), 97.16 (C-2'), 81.04 and 80.78 (c-4' and C-5'), 74.90 (benzyl CH_2), 71.83 (C-3'), 64.37 and 62.51 (C-1' and C-6'), 21.76 and 21.65 (CH_3). Anal. ($C_{42}H_{37}ClN_4O_8 \cdot 0.3C_6H_6 \cdot 0.2CHCl_3$) C,H,N. The α-anomer fraction (Rf 0.28 in 9:1 benzene-EtOAc) was evaporated to give **18α** as a solvate with benzene and $CHCl_3$; yield 5.86 g (18%); MS, *m/z* 761 $(M + H)^+$, 607 $(sugar)^+$; ^1H NMR ($CDCl_3$) 8.63 (s, 1, H_2), 8.57 (s, 1, H_8), 7.81, 7.75, 7.62 (3 d, 6, ortho aromatic H's), 7.37 (C_6H_6), 7.19-7.07 (m, 9, aromatic H's), 6.83 (m, 2, meta aromatic H's), 5.76 (t, 1, $H_{4'}$, $J_{3',4'}$ = 5.1 Hz, $J_{4',5'}$ = 4.8 Hz), 5.14, 5.13 (AB spin system, 2, $-CH_aH_bC_6H_5$, J = 12.4 Hz), 5.01 (m, 1, $H_{5'}$), 4.86 (d, 1, $H_{3'}$), 4.70 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5'6'b}$ = 3.4 Hz, $J_{6'a,6'b}$ = 12.3 Hz), [4.61 (B part of an AB spin system, $H_{1'b}$) and 4.57 (A part of an ABX spin system, $H_{6'a}$, $J_{5',6'a}$ = 4.2 Hz)] (2 H), 4.42 (A part of an AB spin system, 1, $H_{1'a}$, $J_{1'a,1'b}$ = 11.4 Hz), 2.40, 2.39, 2.37 (3 s, 9, 3 CH_3's). ^{13}C NMR ($CDCl_3$) δ 165.94, 165.55, and 165.52 (C=O), 151.57 (C-2, $^1J_{C,H}$ = 13.2 Hz), 151.50 (C-4, $^3J_{C,H}$ = 5.0 Hz, $^3J_{C,H}$ = 12.3 Hz), 144.21 (C-8, $^3J_{C,H}$ = 217.0 Hz), 132.7 (C-5, $^3J_{C,H}$ = 11.9 Hz), 144.73, 144.24, 144.01, 135.97, 129.70, 129.66, 129.60, 129.28, 129.18, 129.16, 128.32, 128.20, 127.41, 126.38, 125.97, and 125.56 (aromatic carbons), 96.42 (C-2'), 81.47 and 79.37 (C-4' and C-5'), 74.48 (benzyl CH_2), 72.00

(C-3′), 64.90 and 63.27 (C-1′ and C-6′), 21.70 and 21.67 (CH_3). Anal. ($C_{42}H_{37}ClN_4O_8 \cdot 0.04C_6H_6 \cdot 0.18CHCl_3$) C,H,N.

9-(3-*O*-Benzyl-β-D-psicofuranosyl)-6-benzyloxy-9*H*-purine (19). A solution of **18β** (2.70 g, 3.55 mmol) in anhydrous benzyl alcohol (210 mL) was stirred with NaH (213 mg, 8.87 mmol) in a stoppered flask for 20 h, filtered, neutralized with Dowex 50W-X4 (H^+) ion-exchange resin (pH followed with wet pH paper), and evaporated to dryness under high vacuum at 45 °C. The residual syrup was purified by flash chromatography on 125 g of silica gel using 96:4 $CHCl_3$-MeOH as eluant. The product fraction (Rf 0.29 in 95:5 $CHCl_3$-MeOH) was evaporated under high vacuum to give a gum which was triturated with Et_2O to give pure **19**, mp 124-125 °C; yield 880 mg (52%); MS, *m/z* 478 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.52 and 8.50 (2 s, 2, H_8 and H_2), 7.53-7.27 (m, 10, aromatic H's), 5.29 (m, 1, 4′-OH, $J_{4',4'\text{-OH}}$ = 6.0 Hz), 5.05 (t, 1, 6′-OH, $J_{6',6'\text{-OH}}$ = 5.4 Hz), 4.98-4.94 (m, 2, $H_{3'}$, -CH_aH_b-C_6H_5), 4.90 (t, 1, 1′-OH), 4.76 (A part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 11.7 Hz), 4.22 (dd, 1, $H_{1'b}$, $J_{1'b,1'\text{-OH}}$ = 6.7 Hz, $J_{1'a,1'b}$ = 12.0 Hz), 4.15 (m, 2, $H_{4'}$,$H_{5'}$), 3.94 (dd, 1, $H_{1'a}$, $J_{1'a,1'\text{-OH}}$ = 5.5 Hz), 3.79 (br dd, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 12.2 Hz), 3.53 (br dd, 1, $H_{6'a}$). Anal. ($C_{25}H_{26}N_4O_6$) C,H,N.

9-[3-*O*-Benzyl-4,5-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine (20) and 1′,1′-*O*-[1,1,3,3-Tetrakis (1-methylethyl)-1,3-disiloxanediyl]bis-9-[3-*O*-benzyl-4,6-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine (21). A solution of **19** (500 mg, 1.05 mmol) and imidazole (845 mg, 12.4 mmol) in anhydrous DMF (2 mL) at -55 °C was treated dropwise with 90% 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl) (403 mg, 1.15 mmol), stirred at -55 °C for 6 h and stored in the freezer overnight. Solvent was removed *in vacuo* and the residue purified by flash chromatography on 45 g of silica gel using hexane-ethyl acetate (4:1) as eluant. The fraction containing **20** (Rf 0.22 in 4:1 hexane-ethyl acetate) was evaporated to give a white crystalline solid, yield 340 mg (45%), mp 87-88 °C (Kofler-Heizbank); MS, *m/z* 721 $(M + H)^+$; UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 260 (28.3); pH 7, 259 (24.4); ^1H NMR (Me_2SO-d_6) δ 8.51 (s, 1, H_2), 8.27 (s, 1, H_8), 7.52-7.32 (m, 10, aromatic H's), 5.65 (B part of an AB spin system, 1, CH_bH_a-C_6H_5, J = 12.3 Hz), 5.61 (A part of an AB spin system, 1, -CH_bH_a-C_6H_5), 5.40 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.6 Hz), [4.99 (B part of an AB spin system, -$CH_bH_aC_6H_5$) and 4.97 (t, 1′-OH, $J_{1',1'\text{-OH}}$ = 6.0 Hz, exchanges with D_2O)] (2H), 4.88 (A part of an AB spin system, 1, -CH_bH_a-C_6H_5, J = 11.7 Hz), 4.31-4.19 (m, 3, $H_{1'b}$, $H_{4'}$, $H_{5'}$), 4.11 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.2 Hz), 3.95-3.85 (m, 2, $H_{1'a}$, $H_{6'a}$), 1.00 - 0.65 (m, 28, four-$CH(CH_3)_2$'s). ^{13}C NMR (Me_2SO-d_6) δ 159.61 (C-6, $^3J_{C,H}$ = 11.2 Hz), 150.75 (C-2, $^1J_{C,H}$ = 205.2 Hz), 150.75 (C-4, $^3J_{C\text{-}4,H\text{-}2}$ = 4.7 Hz, $^3J_{C\text{-}4,H\text{-}8}$ = 12.8 Hz), 142.26 (C-8, $^1J_{C,H}$ = 215.8 Hz), 138.07, 136.27, 128.33, 128.18, 128.14, 128.11, 128.03, and 127.54 (aromatic carbons), 121.80 (C-5, $^3J_{C5,H8}$ = 12.2 Hz), 97.53 (C-2′), 81.09 and 80.11 (C-3′ and C-5′), 73.65 (benzyl CH_2), 69.91 (C-4′), 67.57 (benzyl CH_2), 61.84 (C-1′), 59.91 (C-6′), 17.20, 17.05, 16.77, 16.66, 16.60, and 16.50 (CH_3), 12.61, 12.33, 12.17, and 11.79 (CH). Anal. ($C_{37}H_{52}N_4O_7Si_2$) C,H,N.

In a second experiment using 3.97 mmol of **19**, the conditions above were followed except that the reaction temperature fluctuated between -55 °C and -15 °C for 4.5 h. These conditions gave a slightly reduced yield (35%) of **20** and a 22% yield of the dimeric product (**21**). This faster-moving byproduct (Rf, 0.77 in 4:1 cyclohexane-EtOAc) was collected during the flash column purification and further purified on a second column of 45 g of silica gel using 9:1 hexane-EtOAc as solvent. Evaporation of the product fraction gave pure **21** solvated with $CHCl_3$ and EtOAc as a solid glass; yield 732 mg; MS, *m/z* 1684 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.39 (s, 2, H_2's or H_8's), 8.26 (s, 2, H_8's or H_2's), 7.53-7.29 (m, 20, aromatic H's), 5.65 (s, 4, -CH_2 C_6H_5's), 5.12 (d, 2, $H_{3'}$'s, $J_{3',4'}$ = 3.8 Hz), 5.05 (B part of an AB spin system, 2, -$CH_bH_aC_6H_5$'s, J = 11.5 Hz), 4.81 (A part of an AB spin system, 2, -CH_bH_a-C_6H_5's, J = 11.5 Hz), 4.55 (B part of an AB spin system, 2, $H_{1'b}$'s, $J_{1'a,1'b}$ = 11.1 Hz), 4.29 (B part of an ABX spin system, 2, $H_{4'}$'s, $J_{4',5'}$ = 9.3 Hz), 4.21, 4.16, 4.14 (m, 6, $H_{5'}$'s, $H_{6'b}$'s, $H_{1'a}$'s), 3.95 (A part of an ABX spin system, 2, $H_{6'a}$'s, $J_{6'a,6'b}$ = 13.1 Hz, $J_{5',6'a}$ = 2.5 Hz), 1.63 (s, 1/2 mol H_2O), 1.04-0.53 (m, 70, ten-$CH(CH_3)_2$'s). Anal. $C_{86}H_{130}N_8O_{15}Si_6$•0.8$CHCl_3$•3EtOAc) C,H,N.

9-[3-*O*-Benzyl-1-C-(diethoxyphosphinyl)-4,6-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine, (*R*) and (*S*) (24a). A solution of **20** (300 mg, 0.416 mmol) in anhydrous benzene (5 mL) was treated with 1,3-dicyclohexylcarbodiimide (257 mg, 1.24 mmol) and a mixture of trifluroacetic acid (16.0 μL), pyridine (33.6 μL) and anhydrous Me_2SO (296 μL). The reaction mixture was stirred for 27 h and evaporated to a syrup under high vacuum. A solution of this crude aldehyde **22** in MeOH (5 mL) was treated with a solution of oxalic acid (105 mg) in MeOH (2 mL), stirred for 30 min, filtered, and evaporated *in vacuo* to a syrup. This residue of crude hemiacetal **23** [MS, *m/z* 751 $(M + H)^+$] was washed with 35-60 °C petroleum ether, dissolved in anhydrous THF (5 mL), treated with triethylamine (48 μL, 0.416 mmol) and diethyl phosphite (216 μL, 1.67 mmol) and stirred for 17 h. Solvent was removed *in vacuo* and the residue in 7:3 hexane-EtOAc applied to a flash column of 25 g of silica gel and eluted with the same solvent. The fraction containing *R* and *S* isomers of **24a** was evaporated under high vacuum to give 300 mg (84% yield). A small quantity was separated by preparative TLC (1000μ, silica gel GF, using 9:1 $CHCl_3$-MeOH) to provide samples of *R* and *S* isomers for MS and ^1H NMR. No attempt was made to determine the configuration at C-1. Sample **24a** (*R* or *S*, Rf 0.22 in 9:1 $CHCl_3$-MeOH); MS, *m/z* 857 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.49 and 8.48 (2 s, 2, H_2 and H_8), 7.56-7.30 (m, 10, aromatic H's), 6.95 (d, 1, 1'-OH, $^3J_{HOCP}$ = 11.0 Hz), 5.73 (B part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 12.2 Hz), 5.68 (A part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 12.2 Hz), 5.05 (B part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 10.2 Hz), 4.98 (A part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 10.2 Hz), 4.74 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.4 Hz), 4.70 (d, 1, $H_{1'}$, $^2J_{HCP}$ = 10.4 Hz), 4.45 (m, 1, $H_{5'}$, $J_{5',6'a}$ = 2.6, $J_{4',5'}$ = 9.5 Hz), 4.36-4.27 (m, 2, $H_{4'}$, $H_{6'b}$, $J_{5',6'a}$ = 2.6 Hz, $J_{4',5'}$ = 9.5 Hz), 4.00 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{6'a,6'b}$ = 13.7 Hz), 3.91-3.76 (m, 4, two-CH_2CH_3's), 1.07-0.84 (m, 34, two-CH_2CH_3's and

four-C*H*$(CH_3)_2$'s). Sample **24a** (*S* or *R*, Rf 0.15 in 9:1 $CHCl_3$-MeOH): MS, *m/z* 857 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1, H_8 or H_2), 8.32 (s, 1, H_2 or H_8), 7.55-7.29 (m, 10, aromatic H's), 5.66 (B part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.59 (A part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.31 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.8 Hz), 5.21 (dd, 1, $H_{1'}$, $^2J_{HCP}$ = 12.5 Hz, $J_{H',1'\text{-}OH}$ = 3.4 Hz), 5.12 (d, 1, -CH_aH_b-C_6H_5, J = 10.5 Hz), 4.88 (d, 1, -CH_aH_b-C_6H_5, J = 10.5 Hz), [4.37 (m, 1, 1'-OH, $J_{1',1'\text{-}OH}$ = 3.4, $^3J_{HOCP}$ = 27.5 Hz, exchanges with D_2O)] (2 H), 4.31 (m, 1, $H_{4'}$, $J_{4',5'}$ = 9.6), 4.21 (broad d, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.4), 3.94 (dd, 1, $H_{6'a}$, $J_{5',6'a}$ = 2.3 Hz), 3.92-3.76 (m, 4, two-CH_2CH_3's), 1.06-0.80 (m, 34, two-CH_2CH_3's and four-C*H*$(CH_3)_2$'s).

9-[3-*O*-Benzyl-1-*C*-(dibenzyloxyphosphinyl)-4,6-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine, (*R*) and (*S*) (24b). A solution of **20** (979 mg, 1.36 mmol) in anhydrous benzene (15 mL) was treated with 1,3-dicyclohexylcarbodiimide (808 mg, 3.92 mmol) and a mixture of trifluoroacetic acid (52.4 μL, 0.68 mmol), anhydrous pyridine (110 μL, 1.36 mmol) and anhydrous Me_2SO (1.26 mL). The reaction mixture was stirred for 27 h and evaporated to a syrup under high vacuum. A solution of this residue of crude aldehyde **22** in MeOH (15 mL) was treated with a solution of oxalic acid (230 mg, 2.56 mmol) in MeOH, stirred for 30 min, filtered to remove dicyclohexylurea and evaporated *in vacuo* to a syrup. The residue of crude hemiacetal **23** was washed with 35-60 °C petroleum ether, dissolved in anhydrous THF (15 mL), treated with *N,N*-di-isopropylethylamine (238 μL, 1.36 mmol) and dibenzyl phosphite (1.20 mL, 5.44 mmol) and the mixture stirred for 20 h. Solvent was removed *in vacuo* and a solution of the residue in 5:2 cyclohexane-EtOAc applied to a flash column of 125 g of silica gel and eluted with the same solvent. The fraction containing the faster-moving diastereomer of **24b** (Rf 0.45 in 2:1 cyclohexane-EtOAc) was evaporated to give a crystalline solid; yield 631 mg (47%), mp *ca.* 90-92 °C; MS, *m/z* 981 $(M + H)^+$; UV λ *max* (ϵ x 10^{-3}) (EtOH) 252 (10.4); ^1H NMR ($CDCl_3$) δ 8.44 (s, 1, H_8 or H_2), 8.32 (s, 1, H_2 or H_8), 7.57-7.07 (m, 20, aromatic H's), 5.64 (B part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.53 (A part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.01 (B part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 10.3 Hz), 4.95 (A part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 10.3 Hz), 4.87-4.75 (m, 5, 2-$CH_2C_6H_5$'s, $H_{1'}$), 4.60 (br d, 1, $H_{3'}$, $J_{3',4'}$ = 3.5 Hz), 4.36 (m, 1, $H_{5'}$, $J_{4',5'}$ = 10.0 Hz), 4.24 (A part of an ABX spin system, 1, $H_{4'}$, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 10.0 Hz), 4.08 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.6 Hz), 3.89 (A part of an ABX spin system, 1,$H_{6'a}$, $J_{5',6'a}$ = 2.6 Hz), 1.07-0.81 (m, 28, four-C*H*$(CH_3)_2$'s). Anal. ($C_{51}H_{65}N_4O_{10}PSi_2$) C,H;N:calcd 5.71; found 5.25. The fraction containing the slower-moving diastereomer of **24b** (Rf, 0.19 in 2:1 cyclohexane-EtOAc) was evaporated to give a crystalline solid; yield 399 mg (30%), mp *ca.* 120-140 °C; MS, *m/z* 981 $(M + H)^+$; UV λ_{max} (ϵ x 10^{-3}) (EtOH) 252 (12.7); ^1H NMR ($CDCl_3$) δ 8.34 (s, 1, H_8 or H_2), 8.31 (s, 1, H_2 or H_8), 7.54-7.05 (m, 20, aromatic H's), 5.57 (B part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.46 (A part of an AB spin system, 1, -CH_aH_b-C_6H_5, J = 12.3 Hz), 5.39 (dd,

1, $H_{1'}$, $J_{1',1'\text{-OH}}$ = 3.4 Hz, $^2J_{HCP}$ = 12.3 Hz), 5.32 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.9 Hz), 5.12 (d, 1, -CH_aH_b-C_6H_5, J = 10.5 Hz), 4.87-4.66 (m, 5, -CH_aH_b-C_6H_5 and two other $CH_2C_6H_5$'s), 4.52 (dd, 1, 1'-OH, $J_{1',1'\text{-OH}}$ = 3.4 Hz, $^3J_{HOCP}$= 27.1 Hz), 4.39 (B part of an ABX spin system, 1, $H_{5'}$, $J_{4',5'}$ = 9.6 Hz), 4.32 (A part of an ABX spin system, 1, $H_{4'}$, $J_{4',5'}$ = 9.6 Hz, $J_{3',4'}$ = 3.4 Hz), 4.14 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.4 Hz), 3.92 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 2.5 Hz, $J_{6'a,6'b}$ = 13.4 Hz), 1.05-0.78 (m, 28, four -$CH(CH_3)_2$'s). Anal. ($C_{51}H_{65}N_4O_{10}PSi_2$) C,N,H: calcd 6.68; found 7.35.

9-[3-*O*-Benzyl-1-*C*-(diethoxyphosphinyl)-1-*O*-[(imidizol-1-yl)thioxomethyl]-4,6-*O*-[1,1,3,3-tetrakis-(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine, (*R*) and (*S*) (25a). A solution of *R* and *S* isomers of **24a** (300 mg, 0.350 mmol) in anhydrous 1,2-dichloroethane (3 mL) was treated with 1,1'-thiocarbonyldiimidazole (125 mg, 0.700 mmol), stirred under argon for 18 h, concentrated *in vacuo* to a syrup and purified by flash chromatography on 25 g of silica gel using 4:1 $CHCl_3$-EtOAc as solvent; yield 178 mg; MS, *m/z* 967 $(M + H)^+$. This compound was used without further characterization for the preparation of **26a**.

9-[3-*O*-Benzyl-1-*C*-(dibenzyloxyphosphinyl)-1-*O*-[(imidizol-1-yl)thioxomethyl]-4,6-*O*-[1,1,3,3-tetrakis-(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine, (*R* or *S*) (25b). A solution of the faster-moving (TLC) diastereomer of **24b** (500 mg, 0.510 mmol) in anhydrous CH_2Cl_2 (5 mL) under N_2 was treated with 1,1'-thiocarbonyldiimidazole (182 mg, 1.02 mmol), stirred in a stoppered flask for 9 days, and evaporated to a syrup. A solution of the syrup in 2:1 cyclohexane-EtOAc was applied to a flash column of 45 g of silica gel and eluted with the same solvent. The product fraction (Rf 0.2 in 2:1 cyclohexane-EtOAc) was evaporated to give **25b** as a syrup; yield 315 mg (57%); MS, *m/z* 1091 $(M + H)^+$; This material was used without further characterization for the preparation of **26b**.

9-[3-*O*-Benzyl-1-*C*-(diethoxyphosphinyl)-1-deoxy-4,6-*O*-[1,1,3,3-tetrakis-(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine (26a). A solution of **25a** (178 mg, 0.184 mmol) in anhydrous toluene (10 mL) under argon was treated with tributyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) (10 mg), and heated in a stoppered flask at 86 °C for 2 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography on 25 g of silica gel using 9:1 $CHCl_3$-MeOH as eluant. The product fraction was evaporated to give **26a** as a syrup; yield 120 mg (77%); MS, *m/z* 841 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 8.45 (s, 1, H_8 or H_2), 8.38 (s, 1, H_2 or H_8), 7.56-7.29 (m, 10, aromatic H's), 5.72 (B part of an AB spin system, 1,-$CH_aH_bC_6H_5$, J = 12.3 Hz), 5.64 (A part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 12.3 Hz), 5.07 (B part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 11.4 Hz), 4.90 (A part of an AB spin system, 1, -$CH_aH_bC_6H_5$, J = 11.4 Hz), 4.68 (bs, 1, $H_{3'}$), 4.31 (bs, 2, $H_{4'}$, $H_{5'}$), 4.27 (B part of an AB spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.4 Hz), 3.99 (A part of an AB spin system, $H_{6'a}$), 3.91-3.63 (m, 4, two CH_2CH_3's), 3.33 (dd, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 16.1 Hz, $^2J_{1'b,P}$ = 18.7 Hz), 2.95 (dd, 1, $H_{1'a}$, $^2J_{1'a,P}$ = 17.3 Hz), 1.13-0.80 (m, 34, two -CH_2CH_3's and four -$CH(CH_3)_2$'s). This material was used without further purification for conversion to **28** and **29**.

9-[3-*O*-Benzyl-1-(dibenzyloxyphosphinyl)-1-deoxy-4,6-*O*-[1,1,3,3-tetrakis-(1-methylethyl)-1,3-disiloxanediyl]-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine (26b). A solution of **25b** (301 mg, 0.276 mmol) in anhydrous toluene (10 mL) under argon was treated with AIBN (15 mg) and tributyltin hydride (296 μL, 1.10 mmol) and heated in a stoppered flask at 85 °C (oil bath) for 2 h. The solvent was removed *in vacuo* and the residue in a minimum of 3:1 cyclohexane-EtOAc, applied to a flash column of 25 g of silica gel, and eluted with the same solvent. The product fraction (Rf 0.3 in 2:1 cyclohexane-EtOAc) was evaporated to give **26b** as a syrup; yield 193 mg (72%); MS, *m/z* 965 $(M + H)^+$, 921 $(M - i\text{-}Pr)^+$, 857 $(M - PhCH_2)^+$; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1, H_2 or H_8), 8.36 (s, 1, H_8 or H_2), 7.56-7.03 (m, 20, aromatic H's), 5.60 (B part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 12.4 Hz), 5.54 (A part of an AB spin system, 1, $CH_aH_bC_6H_5$, J = 12.4 Hz), 5.03 (B part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 11.4 Hz), 4.85 (A part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 11.4 Hz), 4.80-4.66 (m, 4, two $CH_2C_6H_5$'s), 5.06 (d, 1, $H_{3'}$, $J_{3',4'}$ = 3.4 Hz), 4.27 (B part of an ABX spin system, 1, $H_{4'}$, $J_{3',4'}$ = 3.4 Hz, $J_{4',5'}$ = 9.7 Hz), 4.22 (A part of an ABX spin system, 1, $H_{5'}$, $J_{4',5'}$ = 9.7 Hz), 4.11 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{6'a,6'b}$ = 13.4 Hz), 3.90 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 2.2 Hz, $J_{6'a,6'b}$ = 13.4 Hz), 3.44 (dd, 1, $H_{1'b}$, $^2J_{1'b,P}$ = 18.6 Hz, $J_{1'a,1'b}$ = 15.9 Hz), 3.05 (dd, 1, $H_{1'a}$, $^2J_{1'a,P}$ = 17.6 Hz, $J_{1'a,1'b}$ = 15.9 Hz), 1.06-0.78 (m, 28, four $-CH(CH_3)_2$'s). This material was used without further characterization for the preparation of **27b**.

9-[3-*O*-Benzyl-1-(dibenzyloxyphosphinyl)-1-deoxy-β-D-psicofuranosyl]-6-benzyloxy-9*H*-purine (27b). A solution of **26b** (180 mg, 0.187 mmol) in anhydrous THF (4 mL) under N_2 was treated dropwise with a 1*M* solution of tetrabutylammonium fluoride in THF (373 μL, 0.373 mmol), stirred for 20 min, and evaporated to a syrup. The syrup in a minimum of 98:2 $CHCl_3$-MeOH was applied to a flash column of 25 g of silica gel and eluted with the same solvent. The product fraction (Rf 0.3 in 97:3 $CHCl_3$-MeOH) was evaporated to give 92 mg (67%) of **27b** as a waxy solid, mp 40-58; MS, *m/z* 723 $(M + H)^+$; UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 255 (10.3); pH 7, 255 (18.6); pH 13, 255 (12.4); ^1H NMR ($CDCl_3$) δ 8.40 (s, 1, H_8 or H_2), 8.15 (s, 1, H_2 or H_8), 7.58-7.15 (m, 20, aromatic CH's), 5.65 (B part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 13.0 Hz), 5.62 (A part of an AB spin system, 1, $CH_aH_bC_6H_5$, J = 13.0 Hz), 4.93-4.77 (m, 4, two $CH_2C_6H_{5's}$), 4.67-4.56 (m, 4, $-CH_2C_6H_5$, $H_{3'}$, 6'-OH, $J_{3',4'}$ = 4.0 Hz), 4.32-4.22 (m, 2, H_4, $H_{5'}$), 3.90 (m, 1, $H_{6'b}$, $J_{5',6'b}$ = 2.0 Hz, $J_{6'a,6'b}$ = 3.0 Hz), 3.71 (m, 1, $H_{6'a}$, $J_{5',6'a}$ = 3.0 Hz), 3.31 (dd, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 16.0 Hz, $^2J_{1'b,P}$ = 20.0 Hz), 3.08 (ψt, 1, $H_{1'a}$, $J_{1'a,1'b}$ = 16.0 Hz, $^2J_{1'a,P}$ = 20.0 Hz), 2.69 (d, 1, 4'-OH, $J_{4',4'\text{-OH}}$ = 5.7 Hz), 1.63 (s, 2 mole H_2O). Anal. ($C_{39}H_{38}N_4O_8P \cdot 0.5H_2O$) C,H,N.

9-[3-*O*-Benzyl-1-(diethoxyphosphinyl)-1-deoxy-β-D-psicofuranosyl]-1,9-dihydro-6*H*-purin-6-one (28). To a stirred solution of **26a** (45 mg, 0.0535 mmol) in anhydrous THF (1 mL) under N_2 was added a 1*M* solution of tetrabutylammonium fluoride in THF (107 μL, 0.107 mmol). A TLC indicated the desililation was complete in 2 min. The reaction mixture was evaporated *in vacuo* and the residue of crude **27a** dissolved in 95% EtOH (10 mL) was hydrogenated at amospheric

pressure for 1 h in the presence of 5% Pd/C (10 mg), filtered, and evaporated under reduced pressure. The residue of crude **28** was purified on a Chromatatron (1 mm silica gel plate) using 9:1 $CHCl_3$-MeOH as solvent. The product fraction (Rf 0.69 in 12:6:1 $CHCl_3$-MeOH-HOAc) was evaporated to give **28** as a crystalline solid; yield 18 mg (66%), mp 98-100 °C; MS, *m/z* 509 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 12.34 (broad d, 1, 1-NH, J = 3.5 Hz), 8.31 (s, 1, H_8), 8.03 (d, 1, H_2, J = 3.5 Hz), 7.47-7.30 (m, 5, aromatic H's), 5.33 (bs, 1, 4′-OH), 5.10 (bs, 1, 6′-OH), 4.91 (B part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 11.7 Hz), 4.72 (A part of an AB spin system, 1, $CH_aH_bC_6H_5$, J = 11.7 Hz), 4.37 (d, 1, $H_{3'}$, $J_{3'4'}$ = 3.4 Hz), 4.06 (m, 2, $H_{4'}$,$H_{5'}$), 3.82-3.71 (m, 5, $H_{6'b}$ and two CH_2CH_3's), 3.57 (br d, 1, $H_{6'a}$, $J_{6'a,6'b}$ = 12.3 Hz), 3.14 (dd, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 15.7 Hz, $^2J_{1'b,P}$ = 18.1 Hz), 2.76 (dd, 1, $H_{1'a}$, $J_{1'a,1'b}$ = 15.7 Hz, $^2J_{1'a,P}$ = 17.5 Hz), 1.07-0.99 (m, 6, two CH_2CH_3's).

9-[1-Deoxy-1(diethoxyphosphinyl)-β-D-psicofuranosyl]-1,9-dihydro-6*H*-purin-6-one (29). A solution of **28** (16 mg) in 95% ethanol (15 ml) was hydrogenated at amospheric pressure in the presence of 5% Pd/C (15 mg) for 3 h, filtered and evaporated to dryness under reduced pressure; yield 11 mg (83%); MS, *m/z* 419 $(M + H)^+$. This product which was homogeneous by TLC (Rf 0.29 in 12:6:1 $CHCl_3$-MeOH-HOAc) was used for the attempted synthesis of **2** without further purification.

9-(1-Deoxy-1-phosphono-β-D-psicofuranosyl)-1,9-dihydro-6*H*-purin-6-one (2) and Monobenzyl Ester (30). A solution of **27b** (30 mg, 0.0410 mmol) in 1:1 EtOH-H_2O (20 mL) was treated with 1*N* NaOH (82.1 μL, 0.0821 mmol) and Et_3N (300 μL). The solution was hydrogenated at room temperature and atmospheric pressure in the presence of 30% Pd/C (15 mg). Although hydrogenation appeared to be complete after 1 h 40 min (H_2 uptake 99% of theory), a TLC showed 2 nucleoside products. Further hydrogenation for 1.5 h with added catalyst (14 mg) gave no change in product composition. The solution was quickly filtered, concentrated on a rotary evaporator to remove EtOH, and lyophilized to remove H_2O. The residual solid (28 mg) now containing hypoxanthine in addition to the 2 nucleoside products was dissolved in 0.5 mL of 65:35 MeCN-1*N* NH_4OH and applied to a flash column (1 cm dia.) containing 4 g of silica gel and eluted with the same solvent. The faster-traveling nucleoside fraction (Rf 0.22 in 65:35 MeCN-1*N* NH_4OH) was lyophilized to give crude **30** as the ammonium salt; yield 5 mg (28%); MS, *m/z* 110 $(NH_4^+ + \text{glycerin})^+$, 137 $(\text{hypoxanthine} + H)^+$, 317 $(\text{sugar-phosphonic acid})^+$, 453 (M as free acid + $H)^+$; ^1H NMR (D_2O) 8.19 (s, 1, H_2 or H_8), 7.97 (s, 1, H_8 or H_2), 7.30-7.20 (m, 5, C_6H_5), 4.79 (B part of an AB spin system, 1, $-CH_aH_bC_6H_5$, J = 11.7 Hz), 4.66 (A part of an AB spin system, 1, $CH_aH_bC_6H_5$, J = 11.7 Hz), 4.45 (d, 1, $H_{3'}$, $J_{3',4'}$ = 5.1 Hz), 4.21 (m, 1, $H_{5'}$), 4.13 (m, 1, $H_{4'}$, $H_{4',5'}$ = 6.4 Hz), 3.84 (B part of an ABX spin system, 1, $H_{6'b}$, $J_{5',6'b}$ = 2.4 Hz, $J_{6'a,6'b}$ = 12.7 Hz), 3.70 (A part of an ABX spin system, 1, $H_{6'a}$, $J_{5',6'a}$ = 4.8 Hz), 2.85 (ψt, 1, $H_{1'b}$, $J_{1'a,1'b}$ = 16.0 Hz, $^2J_{1'bP}$ = 16.5 Hz), 2.73 (dd, 1, $H_{1'a}$, $^2J_{1'b,P}$ = 17.8 Hz, $J_{1'a,1'b}$ = 16.0 Hz). The slower-traveling nucleoside fraction (Rf 0.14 in 65:35 MeCN-1*N* NH_4OH) was lyophilized to

ELEMENTAL ANALYSES

Compound	Molecular Formula	Calcd/Found C	H	N
5α	$C_{35}H_{30}BrClN_4O_7$	57.27	4.12	7.63
		57.11	4.12	7.41
5β	$C_{35}H_{30}BrClN_4O_7$	57.27	4.12	7.63
		57.43	4.07	7.54
6	$C_{18}H_{19}BrN_4O_5$	47.91	4.24	12.41
		48.00	4.27	12.60
7	$C_{18}H_{18}N_4O_5 \cdot 0.5H_2O$	56.99	5.05	14.77
		57.06	4.87	14.65
8	$C_{11}H_{12}N_4O_5$	47.15	4.32	19.99
		46.89	4.51	19.79
10a	$C_{11}H_{13}BrN_9O_5 \cdot 0.5CH_3OH$	36.62	4.01	14.85
		36.81	4.03	14.76
13	$C_{19}H_{26}O_6$	65.12	7.47	
		65.08	7.58	
16	$C_{38}H_{38}O_9 \cdot 0.3C_6H_6$	72.20	6.06	
		72.25	6.14	
18α	$C_{42}H_{37}ClN_4O_8 \cdot 0.18CHCl_3$	64.84	4.80	7.13
		64.70	5.20	7.09
18β	$C_{42}H_{37}ClN_4O_8 \cdot 0.3C_6H_6 \cdot 0.2CHCl_3$	65.36	4.86	6.93
		65.44	5.17	6.97
19	$C_{25}H_{26}N_4O_6$	62.75	5.47	11.70
		62.44	5.74	12.09
20	$C_{37}H_{52}N_4O_7Si_2$	61.63	7.21	7.71
		61.61	7.46	7.48
21	$C_{86}H_{130}N_8O_{15}Si_6 \cdot 0.8CHCl_3 \cdot 3EtOAc$	58.05	7.63	5.48
		58.16	7.62	5.48
24b-1	$C_{51}H_{65}N_4O_{10}PSi_2$	62.43	6.68	5.71
		62.69	6.80	5.25
24b-2	$C_{51}H_{65}N_4O_{10}PSi_2$	62.43	6.68	5.71
		62.69	7.35	5.80

give crude **2** as an ammonium salt; yield 8 mg (37%); MS, *m/z* 110 $(NH_4^+ + \text{glycerin})^+$, 137 $(Hx + H)^+$, 363 $(M \text{ as free acid} + H)^+$; MS (NEG. FAB) *m/z* 135 $(Hx - H)^-$, 361 $(M - H)^-$; UV λ_{max} (ϵ x 10^{-3}) pH 7, 250 (11.8); ^1H NMR (600.138 MHz, D_2O, pD = 6.6) δ 8.08 (s, 1, H_8), 7.86 (s, 1, H_2), 4.64 (d, 1, $H_{3'}$, $J_{3',4'}$ = 4.64 Hz), 3.98 (m, 1, $H_{5'}$), 3.84 (dd, 1, $H_{4'}$, $J_{4',5'}$ = 8.6 Hz), 3.57 (dd, 1, $H_{6'b}$, $J_{5',6'b}$ = 2.4 Hz, $J_{6'a,6'b}$ = 12.8 Hz), 3.40 (dd, 1, $H_{6'b}$), 2.43 (t, 1, $H_{1'b}$, $J_{1'b,P} = J_{1'a,1'b}$ = 16.3 Hz), 2.31 (t, 1, $H_{1'a}$, $J_{1'a,1'b}$ = 16.3 Hz).

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