An Enantiospecific Synthesis of the Human Cytomegalovirus Antiviral Agent [(*R*)-3-((2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-hydroxybutyl]phosphonic Acid

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The racemic isosteric phosphonate of ganciclovir monophosphate (BW2482U89, SR3745, [3-((2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-hydroxybutyl]phosphonic acid, 1) has potent and selective *in vitro* activity against human cytomegalovirus. An enantiospecific synthesis of the *R*-enantiomer of compound 1 starting from L-arabinose was developed. The synthesis involved (1) the preparation of a chiral acyclic moiety, (2) the coupling of the chiral acyclic moiety to diacetylguanine, (3) the introduction of phosphorus, and (4) the final deprotection. The *R*-enantiomer, which has stereochemistry analogous to the natural compound GMP, was tested against human cytomegalovirus and had an IC_{50} of 1.7 μM, which was approximately 2-fold more active than the racemic material. Both racemic and chiral compounds were less toxic than ganciclovir to bone marrow progenitor cells in an *in vitro* assay.

Introduction

The isosteric phosphonate of ganciclovir monophosphate, [3-((2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)-methoxy)-4-hydroxybutyl]phosphonic acid (ganciclovir phosphonate, 1), is an effective *in vitro* and *in vivo* inhibitor of human cytomegalovirus (HCMV) replication.[1] This compound has only been synthesized as the racemic mixture[1b,c] and has not been resolved. A chiral synthesis or resolution of 1 would allow each enantiomer to be evaluated for its antiviral activity and cellular toxicity.

The published methods leading to the formation of racemic ganciclovir phosphonate are difficult and low yielding or require the use of a toxic mercury salt to catalyze a key step in the synthetic scheme. These drawbacks, along with the additional difficulties of separating and identifying the enantiomers at some stage of the synthesis, led us to develop a chiral synthesis for the *R*-enantiomer of ganciclovir phosphonate starting from readily available L-arabinose. This paper discloses the synthetic scheme and reports the anti-HCMV activity and *in vitro* bone marrow progenitor cell toxicity data for this enantiomer.

Synthesis

The phosphonate and hydroxyl moieties of the *R*-enantiomer of ganciclovir phosphonate (**R-1**) can be superimposed on the phosphorous and 3′-hydroxyl groups of the naturally occurring guanosine monophosphate (GMP). This is not possible with the *S*-enantiomer (**S-1**) (Figure 1). This structural similarity between **R-1** and GMP suggests that the *R*-enantiomer may be more readily phosphorylated to the di- and triphosphate analogues by host-cell enzymes than the *S*-enantiomer and, therefore, may be the more potent inhibitor of the HCMV DNA polymerase. This assumption is supported by studies on the two enantiomers of ganciclovir monophosphate which show that the enantiomer which can be superimposed on GMP is the preferred substrate for GMP kinase.[2]

The overall strategy for the synthesis of the *R*-enantiomer was divided into four stages: (1) the preparation of

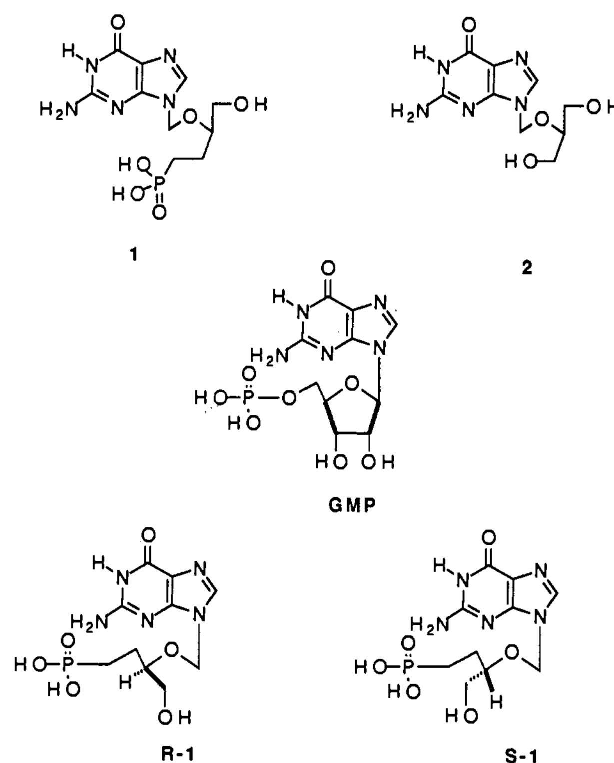

Figure 1.

a suitably functionalized four-carbon 'chiron' from a carbohydrate "chiral template",[3] (2) the coupling of this chiron to an appropriate guanine precursor, (3) the introduction of the phosphonate moiety, and (4) the deprotection. The strategy of introducing the phosphonate after coupling the chiron to the heterocycle was adopted after numerous discouraging attempts to couple a phosphonate side chain to the heterocycle without the use of mercurial salts.

A limited number of methods exist for constructing the desired four-carbon chiron (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-chloro-2-(methoxymethoxy)butane.[4,5] We chose a novel approach using L-arabinose as the chiral template for entry into this class of compounds. The L-arabinose

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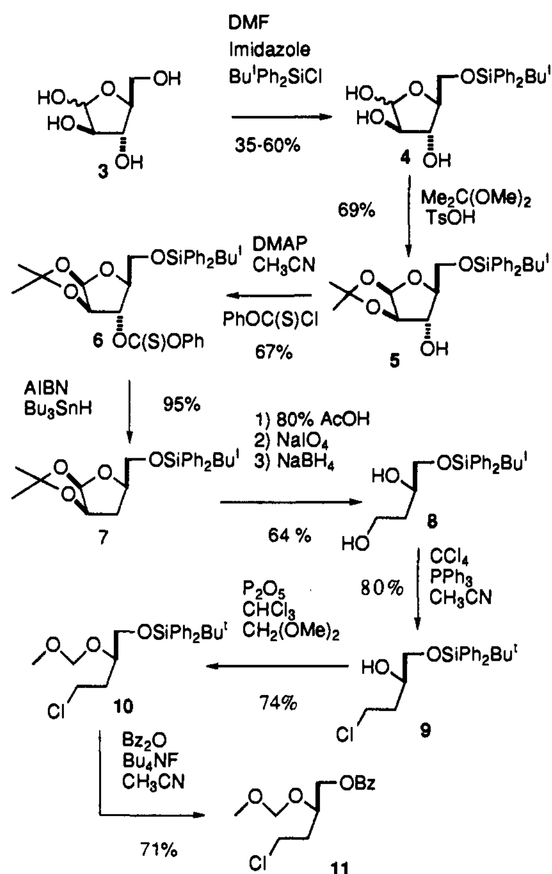
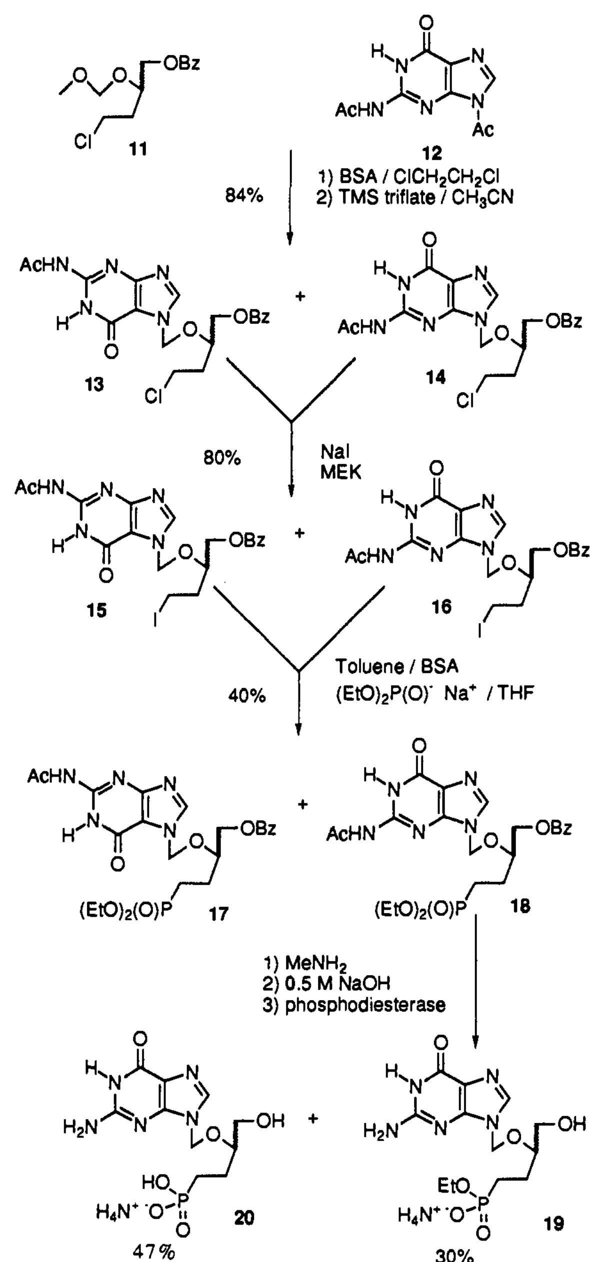
Scheme 1



Scheme 2



(3) was locked in a furanose configuration by synthesizing the 5-*O*-*tert*-butyldiphenylsilyl derivative 4 (Scheme 1).[6] The C-1 and C-2 hydroxyl groups were protected as the acetonide to give 5 in 69% yield utilizing a modified Dahlman[6] procedure. The free secondary hydroxyl of 5 was deoxygenated in two steps using the procedure of Barton and McCombie.[7] Thus, reaction of 5 with phenyl chlorothionoformate and 4-(dimethylamino)pyridine gave phenyl thiocarbonate 6, which was then reduced to 7. Selective removal of the isopropylidene in the presence of the *tert*-butyldiphenylsilyl group was accomplished in 80% acetic acid, and the resulting crude diol was cleaved to the aldehyde with sodium periodate. Reduction with sodium borohydride provided silylated triol 8 in an overall yield of 64% from 7. Selective conversion of the primary alcohol to the chloride gave compound 9 in a 75% yield.[8] Treatment of 9 with dimethoxymethane in chloroform in the presence of phosphorus pentoxide provided the methoxymethyl ether 10 in a 65% yield.[9] Celite was added to this reaction to maintain a free-stirring heterogeneous mixture.

At this point, acyclic acetal chiron 10 was ready for coupling. Cyclic acetals, such as methyl furanosides, have been coupled to purines under Vorbrüggen conditions, although generally the more reactive acetoxy or halo intermediates are preferred.[10] Similarly, there are many examples in acyclic nucleoside chemistry of coupling chloromethyl ethers or acetoxymethyl ethers,[11] but coupling an acyclic methylene acetal has not been done to the best of our knowledge. Since the same carbonium intermediate would be involved in coupling as would be in activating 10 to a chloromethyl ether or acetoxymethyl ether, it was decided to directly couple 10 to a silylated guanine precursor using a Lewis acid catalyst. The guanine precursor selected was diacetylguanine 12. Generally, N^2-acetylguanine, not diacetylguanine, is used in Vorbrüggen-type coupling reactions.[12] However, diacetylguanine has been used in other acid-catalyzed coupling reactions.[13]

Reaction of silylated 12 with 10 in the presence of trimethylsilyl triflate produced coupled product in low yield (40%). This result may be due to loss of the *tert*-butyldiphenylsilyl protecting group since desilylated, coupled product was also isolated. In an attempt to improve the yield of this reaction, the primary alcohol was deblocked and converted to benzoate ester 11 with an overall yield of 71%.

Coupling 11 with silylated diacetylguanine in the presence of trimethylsilyl triflate improved the yield of coupled product more than 2-fold, to 84% (Scheme 2). However, this material was predominantly the N-7 regioisomer 13; less than 5% of the N-9 regioisomer 14 could be detected by ^{1}H NMR. By using a less polar solvent, more of the desired N-9 regioisomer 14 was obtained, but longer reaction times and higher temperatures were required. The yields and regioisomeric ratios for the

Table 1. N-9 and N-7 Regioisomeric Ratios for the Coupling Reactions of Diacetylguanine 12 and (*R*)-4-Chloro-2-(methoxymethoxy)butyl Benzoate (11) in Three Different Solvents[a]

solvent	time (h)	T (°C)	yield[b] (%)	ratio[c] N-9/N-7
CH_3CN	0.5	25	84	<1/19
$ClCH_2CH_2Cl$	0.5	83	60	2/3
$PhCH_3$	4.5	111	61	5/6

[a] Reaction mixtures included 1.5 equiv of diacetylguanine, 9 equiv of *N,O*-bis(trimethylsilyl)acetamide, and 5 equiv of trimethylsilyl triflate. [b] Yield of the mixture of N-9 and N-7 regioisomers after column chromatography. [c] Ratio determined by integration of the H-8 and pseudoanomeric protons in the ^1H NMR spectra.

coupling reactions in three solvents are summarized in Table 1. In each case, N^2-acetylguanine could be isolated as a reaction byproduct. Although the side-product 9/7-(methoxymethyl)-2-acetamidoguanine could have formed, we did not detect it. Compounds **13** and **14** were not easily separated by column chromatography. However, **14** could be isolated with less than 5% **13** by using a chromatotron, and its structural data are reported (Experimental Section).

Although the major product, **13**, was the undesired regioisomer, it could be readily isomerized to the N-9 regioisomer. Such isomerizations have been utilized in nucleoside synthesis, and it is a well-recognized process in the context of a Vorbrüggen coupling reaction.[12a,14] In this case, **13** underwent facile isomerization to predominantly the N-9 regioisomer in the next two steps, thus making it unnecessary to optimize the coupling reaction for **14** or to separate the two regioisomers.

Assignment of **13** as the N-7 regioisomer was based on ^{13}C NMR data which showed the C-5 resonance at 111.0 ppm which is characteristic of N-7-substituted purines.[15] In addition, the ^1H NMR data for **13** were consistent with literature values for other N-7-substituted N^2-acetylguanines.[12b]

Because attempts to displace the chloro group of **13** were unsuccessful with either trialkyl phosphites or the anion of diethyl phosphite, the chloride was converted to an iodide by a halide-exchange (Finkelstein) reaction. Moderate to good yields (50–80%) of the iodo were obtained by refluxing **13** in the presence of dry sodium iodide and freshly distilled 2-butanone (Scheme 2). Surprisingly, these conditions also affected isomerization of the N-7 regioisomer to a mixture of **15** and **16**. This reaction was repeated several times, and the ratio of **15** to **16** varied from 70:30 to 30:70 as a function of time over 2–5 h at reflux. The conditions which provided the best combined yield of **15** and **16** are reported in the Experimental Section.

Sodium iodide was necessary for the isomerization, since heating **13** in 2-butanone alone did not result in formation of the N-9 regioisomer. In addition, if both the sodium iodide and the 2-butanone were not dried prior to use, product yields decreased and N^2-acetylguanine was isolated. It is worth noting that the addition of sodium bicarbonate to the reaction mixture stopped the isomerization from occurring but did not stop the halide-exchange reaction. Isomerization of a purine nucleoside analogue from N-7 to N-9 with sodium iodide in a ketone solvent is unknown, although molecular iodine has been reported to be a catalyst for nucleoside-coupling reactions under fusion conditions.[16]

Initial attempts to synthesize the phosphonate **18** by an Arbuzov reaction[17] in refluxing triethyl phosphite or trimethyl phosphite were unsuccessful. The elevated temperatures required for solubilizing the iodo nucleoside caused the starting material to decompose.

A second approach was to use the sodium salt of diethyl phosphite.[18] Thus, a 70:30 mixture of **15** and **16** was silylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) in toluene and subsequently reacted with the anion of diethyl phosphite generated with sodium hydride in tetrahydrofuran (Scheme 2). Diethyl phosphonate was obtained as a 40:60 mixture of **17** and **18** in 41% yield along with starting material (24%). The pure N-9 regioisomer **18** was isolated in 23% yield after further chromatography. When potassium *tert*-butoxide was used as the base, pure **18** was isolated in a 35% yield along with 12% of **17** (data not shown). Examination of the reaction by thin-layer chromatography showed that isomerization from **15** to **16** occurred during the silylation in refluxing toluene. However, when the N-7 chloride **13** was heated with BSA in toluene, no isomerization was observed. In general, literature examples have shown that such isomerization of N-7-substituted purines to N-9 purines require a Lewis acid catalyst such as trimethylsilyl triflate or tin tetrachloride.[10] In this case, small amounts of HI may have catalyzed the isomerization.

Comparison of the ^1H NMR data for the mixture of crude phosphonates **17** and **18** with those of purified **18** showed the H-8 proton for **17** at 8.6 ppm and for **18** at 8.2 ppm. The pseudoanomeric protons for **17** and **18** appeared at 5.8 and 5.6 ppm, respectively. This is consistent with the assignment of **18** as the N-9 regioisomer.[19] The presence of phosphorus was confirmed by ^{31}P NMR which showed a single peak at 32.4 ppm. Carbon to phosphorus couplings were observed for the carbon atoms α, β, and γ to the phosphorus in the ^{13}C NMR of compound **18** (Experimental Section).

Phosphonate **18** was deprotected by sequential treatment with methylamine, aqueous sodium hydroxide, and snake venom phosphodiesterase I, providing a 47% yield of phosphonic acid **20** as the monoammonium salt after ion-exchange chromatography (Scheme 2).[20] The ester **19** was also obtained from the ion-exchange column (30%). Enzymatic cleavage of the phosphonate monoethyl ester was used instead of the more practical trimethylsilyl bromide to avoid possible isomerization to the N-7 regioisomer. Compound **20** was fully characterized by ^1H, ^{13}C, and ^{31}P NMR, quantitative UV, HPLC, and CHN combustion analysis. The ^{31}P NMR spectrum showed a single resonance at 24.5 ppm, and 10 carbon resonances were observed in the ^{13}C NMR spectrum, three being coupled to phosphorus. Compound **20** was confirmed as the monoammonium salt by an ammonium ion assay. The final product had a negative optical rotation (Experimental Section).

Biological Activity

The monoethyl phosphonate ester **19** and the *R*-phosphonic acid **20** were tested for anti-HCMV activity using a DNA hybridization assay.[21] The antiviral activities of these compounds, racemic ganciclovir phosphonate (**1**), and ganciclovir (**2**) are presented in Table 2. The IC_{50} for ganciclovir is consistent with literature values.[22] The *R*-enantiomer **20** was as active as ganciclovir and more than twice as active as the racemate **1** (2 vs 5 μM, respectively). Interestingly, the *R*-monoethyl ester **19** inhibited HCMV replication with an IC_{50} within 3-fold of

Table 2. *In Vitro* Anti-HCMV Activity and Human Bone Marrow Progenitor Cell Toxicity of Racemic Phosphate 1, the *R*-Enantiomer 20, the *R*-Enantiomeric Monoester 19, and Ganciclovir (2)

	IC_{50}		
compound	HCMV[a] (μM)	CFU-GM[b] (μM)	BFU-E[b] (μM)
1[c]	5.6	280 ± 26	200 ± 9
20	1.7	96 ± 11	126 ± 9
19	6.8		
ganciclovir (2)	1.7	19 ± 3	29 ± 6

[a] *In vitro* antiviral activities assessed against the HCMV strain AD169 in MRC-5 lung fibroblasts using a DNA-hybridization assay (Danker, W. M. *et al. J. Virol. Methods* **1990**, *28*, 293–298); drug concentrations were tested in triplicate, and data were analyzed by a linear regression program (PROBIT Version 79.2; Statistical Analyses Systems, Cary, NC). Standard errors were less than 20%. [b] IC_{50} values from 7 to 12 experiments with standard errors. [c] Obtained from E. J. Reist, SRI International, Menlo Park, CA 94025.

that of **20** and ganciclovir. Compounds **1**, **19**, **20**, and ganciclovir were not toxic to uninfected MRC-5 cells at 100 μM, the highest concentration tested.

The toxicity of **1**, **2**, and **20** with bone marrow progenitor cells was also examined,[23] and the results are reported in Table 2. The racemic ganciclovir phosphonate (**1**) was approximately half as toxic as the *R*-enantiomer **20** to both the CFU-GM (colony-forming-unit-granulocyte-macrophage) and BFU-E (burst-forming-unit-erythroid) progenitor cells. Both **1** and **20** were relatively nontoxic when compared to ganciclovir. The IC_{50} values for **20** were 4–5-fold higher than those for ganciclovir.

The *R*-enantiomer **20** was shown to be inactive in a variety of other antiviral screens including: HSV-1, HSV-2,[24] HIV-1,[25] and HBV.[26] **20** was also nontoxic to IM-9, CEM,[27] and MOLT4[25] cells (IC_{50} > 100 μM).

Conclusion

The first synthesis of the *R*-enantiomer (**20**) of ganciclovir phosphonate was completed. The synthesis utilized a chiral-template-based approach by which a novel entry into the synthesis of chiral 1,2,4-butanetriols was developed. The synthesis also involved an isomerization of an N-7-substituted guanine to an N-9 guanine and a novel strategy for introducing the phosphorus moiety of an acyclic nucleoside phosphonate after coupling to the heterocyclic base. This later methodology could facilitate the synthesis of a series of dialkyl phosphonate esters of **20** as potential prodrugs. However, this synthesis is clearly limited by its length and overall yield to milligram amounts of the *R*-enantiomer. The *in vitro* testing data indicated that **20** had approximately twice the antiviral activity as racemic mixture **1**, which suggested that the majority of the anti-HCMV activity was associated with the *R*-enantiomer. In addition, **20** was twice as toxic as **1** in the progenitor cell toxicity assay, which indicated that the cellular toxicity resided primarily with the *R*-enantiomer as well. After completion of this work, sufficient amounts of the *S*-enantiomer were obtained by other methods for antiviral testing. These results will be reported separately.

Experimental Section

General. Diacetylguanine **12** was synthesized as described in the literature.[28] 5-*O*-(*tert*-Butyldiphenylsilyl)-L-arabinofuranose (**4**) was synthesized as described by Dahlman *et al.*[6] Racemic ganciclovir phosphonate (**1**) was obtained from E. J. Reist at SRI International, Menlo Park, CA 94025. Phenyl chlorothionoformate was purchased from Lancaster Chemical Co. 2,2′-Azobis-(2-methylpropionitrile) (AIBN) was purchased from Kodak Chemicals. 2-Butanone was distilled from P_2O_5. 2,2-Dimethoxypropane was distilled from calcium chloride. Toluene and acetonitrile were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium and benzophenone ketal. Snake venom phosphodiesterase I was purchased from Pharmacia LKB Biotechnology (Uppsala, Sweden). All other chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used directly unless otherwise indicated. Thin-layer chromatography (TLC) was performed on silica gel plates (E. Merck, silica gel 60 F-254), and components were visualized by UV_{254} or charring with anisaldehyde/H_2SO_4/ethanol (1/1/9). Column chromatography was performed on silica gel 60 (230–400 mesh), eluting either with a positive pressure of nitrogen or with an FMI lab pump. A chromatotron (Harrison Research, Palo Alto, CA), fitted with 1000- or 2000-μm silica gel rotors (Analtech, Newark, DE), was used in some purifications. Analytical HPLC for compounds **19** and **20** was performed with a Perkin-Elmer LC 480 diode array detector and a Alltech cartridge packed with Whatman Partisil 10-μm SAX (strong anion exchange) resin.

Melting points were determined on a Thomas-Hoover UniMelt apparatus and are uncorrected. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on either a Varian GEMINI-200, XL-300, UNITY-400, or UNITY-500 spectrometer and reported relative to tetramethylsilane. Mass spectra were recorded by Oneida Research Services (Whitesboro, NY). Elemental analyses were performed by Atlantic Microlabs (Atlanta, GA). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

5-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-β-L-arabinofuranose (5). Compound **4** (30.8 g, 79 mmol) was combined with *p*-toluenesulfonic acid monohydrate (0.33 g, 1.7 mmol) and 2,2-dimethoxypropane (65 mL). The suspension was stirred for 2 h and then diluted with dichloromethane (250 mL) and extracted with 5% $NaHCO_3$ (100 mL) and then water (2 × 150 mL). The organics were dried ($MgSO_4$), filtered, and concentrated. The resulting thick yellow oil was purified on a silica gel column (10 × 20 cm^2) (ethyl acetate:hexanes (1:4)). Compound **5** was obtained as a gold oil, 23.6 g (69%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H, Ar-H), 7.43–7.36 (m, 6H, Ar-H), 5.88 (d, 1H, H-1, *J* = 4.1 Hz), 4.54 (d, 1H, H-2, *J* = 4.0 Hz), 4.45–4.42 (m, 1H, H-3), 4.08–4.00 (m, 1H, H-4), 3.83–3.80 (m, 2H, H-5), 2.12 (d, 1H, 3-OH, *J* = 4.3 Hz), 1.32 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 127.7, 112.5, 105.5, 87.4, 87.0, 76.3, 63.7, 26.8, 26.0, 19.2; MS (CI) *m/e* (% rel intensity) 353 (26.86, $M^+ - C_3H_7O_2$). Anal. ($C_{24}H_{32}O_5Si$) C, H.

5-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-3-*O*-(phenoxythiocarbonyl)-β-L-arabinofuranose (6). Compound **5** (16 g, 37 mmol) was combined with DMAP (8.2 g, 67 mmol) and acetonitrile (anhydrous, 150 mL). Phenyl chlorothionoformate was added (6.2 g, 45 mmol), and the solution was flushed with nitrogen and stirred at room temperature. After 18 h, a solution of ethyl acetate:hexanes (1:1) (200 mL) was added and the reaction mixture was filtered. The precipitate was washed with ethyl acetate, and the combined filtrate and washings were concentrated under reduced pressure to a thick yellow oil which was purified on a silica gel column (10 × 20 cm^2) (ethyl acetate: hexanes (1:10)). Pure product **6** was obtained as a colorless oil, 14 g (67%): ^1H NMR (200 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H, Ar-H), 7.48–7.30 (m, 9H, Ar-H), 7.14–7.09 (m, 2H, Ar-H), 5.96 (d, 1H, H-1, *J* = 4.0 Hz), 5.80 (d, 1H, H-3, *J* = 1.3 Hz), 4.76 (d, 1H, H-2, *J* = 4.0 Hz), 4.46 (t, 1H, H-4, *J* = 7.0 Hz), 3.90–3.83 (m, 2H, H-5), 1.32 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$), 1.05 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 193.6, 153.3, 135.6, 133.0, 129.7, 129.6, 129.5, 128.0, 127.7, 126.8, 121.8, 112.8, 105.9, 85.9, 85.3, 84.3, 63.4, 26.8, 26.4, 25.8, 19.2; MS (CI) *m/e* (% rel intensity) 565 (1.30, $M^+ + H$), 507 (100, $M^+ - C_4H_9$). Anal. ($C_{31}H_{36}O_6SSi$) C, H.

5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (7). Compound **6** (13 g, 23 mmol) was combined with AIBN (0.30 g, 1.8 mmol) and toluene (anhydrous 200 mL). The solution was degassed under reduced pressure for 15 min. Tributyltin hydride (7 mL, 26 mmol) was added, and the reaction mixture was stirred under nitrogen at 90 °C for 6 h and then concentrated under reduced pressure. The resulting thick yellow oil was purified on a silca gel column (10 × 15 cm^2) (ethyl acetate:hexanes (1:20)). Pure product **7** was

obtained as a colorless oil, 9.3 g (95%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H, Ar-H), 7.41–7.32 (m, 6H, Ar-H), 5.77 (d, 1H, H-1, J = 3.9 Hz), 4.74–4.69 (m, 1H, H-2), 4.30–4.22 (m, 1H, H-4), 3.81–3.76 (m, 1H, H-5), 2.25–2.10 (m, 2H, H-3), 1.31 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.04 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 135.6, 133.5, 129.6, 127.7, 127.6, 112.1, 106.6, 81.2, 80.7, 65.8, 33.5, 27.0, 26.8, 25.9, 19.2; MS (EI) *m/e* (% rel intensity) 355 (13.01, $M^+ - C_4H_9$). Anal. ($C_{24}H_{32}O_4Si{\cdot}0.10C_4H_8O_2$) C, H.

(*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-1,2,4-butanetriol (8). Compound 7 (33.5 g, 81.2 mmol) was stirred with 80% acetic acid (300 mL) for 30 min at 90 °C and then concentrated under reduced pressure to a thick oil. After coevaporation with 95% ethanol (3 × 50 mL), the residue was dissolved in methanol (450 mL) and treated with sodium periodate (34.9 g, 163 mmol) dissolved in water (300 mL). This solution was stirred at room temperature for 1.5 h, filtered, cooled in an ice bath, and treated with excess sodium borohydride (13.1 g, 346 mmol). After 50 min, the solution was neutralized with concentrated HCl (20 mL, to pH 7.5). The neutral solution was filtered, and the solids were washed with methanol. The filtrate and washings were concentrated to 500 mL and extracted with ethyl acetate:hexanes (2:1) (3 × 300 mL). The combined organic layers were extracted with 5% sodium bisulfite (300 mL), dried ($MgSO_4$), filtered, and concentrated to a clear yellow oil. This material was purified on a silica gel column (10 × 20 cm^2) with 3 L of ethyl acetate:hexanes (1:2) and then with ethyl acetate:hexanes (1:1). Pure **8**, 18.0 g (64%), was obtained as a light yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H, Ar-H), 7.45–7.36 (m, 6H, Ar-H), 4.01–3.94 (m, 1H, H-2), 3.81 (dt, 2H, H-4, J = 5.4, 5.5 Hz), 3.64 (dd, 1H, H-1, J = 3.8, 10.1 Hz), 3.54 (dd, 1H, H-1′, J = 7.3, 10.1 Hz), 2.80 (d, 1H, 2-OH, J = 3.2 Hz), 2.44 (t, 1H, 4-OH, J = 5.4 Hz), 1.68–1.63 (m, 2H, H-3), 1.06 (s, 9H, $C(CH_3)_3$); MS (CI) *m/e* 345 (2.84, $M^+ + H$), 267 (76.78), 189 (100). Anal. ($C_{20}H_{28}O_3Si$) C, H.

(*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-4-chloro-1,2-butanediol (9). Compound 8 (1.5 g, 4.3 mmol) was dried by coevaporation with toluene and then dissolved in anhydrous acetonitrile (50 mL) and carbon tetrachloride (4.2 mL, 43.5 mmol). A solution of triphenylphosphine (2.3 g, 8.7 mmol) in anhydrous acetonitrile (50 mL) was added over 5 h so that all the starting material and triphenylphosphine were consumed. The reaction mixture was concentrated to a volume of 60 mL under reduced pressure and applied to a silica gel column (5 × 18 cm^2) (ethyl acetate:hexanes (1:10)). Compound **9**, 1.25 g (80%), was obtained pure by ^{1}H NMR and used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H, Ar-H), 7.46–7.40 (m, 6H, Ar-H), 4.00–3.90 (m, 1H, H-2), 3.72–3.66 (m, 3H, H-1, H-4), 3.56–3.50 (dd, 1H, H-1′, J = 3.9, 10.1 Hz), 2.46 (d, 1H, 2-OH, J = 5.0 Hz), 1.98–1.75 (m, 2H, H-3), 1.08 (s, 9H, $C(CH_3)_3$).

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-4-chloro-2-(methoxymethoxy)butane (10). Phosphorus pentoxide (7.0 g, 49.3 mmol) and chloroform (anhydrous, 75 mL) were combined in a dry flask. Dimethoxymethane (15 mL, 170 mmol) was added, and the solution was stirred at room temperature for 15 min. Compound **9** (1.38 g, 3.8 mmol), dissolved in chloroform (anhydrous, 25 mL), was added, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was decanted from the phosphorus pentoxide, and the solids were washed with chloroform (2 × 50 mL). The combined organic layers were extracted with H_2O (3 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oil which was purified on a silica gel column (2.5 × 22 cm^2) (ethyl acetate:hexanes (1:15)). Pure **10** (1.13 g, 74%) was obtained as a colorless oil after drying: ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.69–7.65 (m, 4H, Ar-H), 7.44–7.36 (m, 6H, Ar-H), 4.71 (d, 1H, OCH_2O, J = 6.8 Hz), 4.62 (d, 1H, OCH_2O, J = 6.7 Hz), 3.88–3.84 (m, 1H, H-2), 3.73–3.61 (m, 4H, H-1, H-4), 3.34 (s, 3H, OCH_3), 2.06–1.99 (m, 2H, H-3), 1.06 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 135.6, 133.3, 129.8, 127.7, 96.3, 74.9, 65.8, 55.7, 41.5, 35.1, 26.8, 19.2; MS (CI) *m/e* 371 (11.40, $M^+ - Cl$). Anal. ($C_{22}H_{31}O_3ClSi{\cdot}0.15C_6H_{14}$) C, H.

(*R*)-4-Chloro-2-(methoxymethoxy)butyl Benzoate (11). Compound 10 (0.50 g, 1.23 mmol) and benzoic anhydride (1.1 g, 4.9 mmol) were combined in a dry flask fitted with a constant addition funnel. Anhydrous acetonitrile (20 mL) was added, and a 1 M solution of tetrabutyl ammonium fluoride in tetrahydrofuran (2.5 mL) was added in two portions at 1-h intervals. The reaction was stirred at room temperature for 20 h. An additional 1.0 mL (1 mmol) of tetrabutyl ammonium fluoride was added, and the reaction was continued for an additional 20 h. The reaction mixture was passed through a silica gel filter pad (5 × 5 cm^2), which was then washed with ethyl acetate:hexanes (1:10). The UV-absorbing fractions were concentrated under reduced pressure and purified on a silica gel column (2.5 × 18 cm^2) (ethyl acetate:hexanes (1:10)). Compound 11 was obtained as a colorless oil (0.24 g, 71%): ^{1}H NMR (300 MHZ, $CDCl_3$ δ 8.05 (d, 2H, Ar-H, J = 7.1 Hz), 7.58 (t, 1H, Ar-H, J = 6.7 Hz), 7.45 (t, 2H, ArH, J = 7.5 Hz), 4.82 (d, 1H, OCH_2O, J = 6.9 Hz), 4.73 (d, 1H, OCH_2O, J = 6.9 Hz), 4.46 (dd, 1H, H-1, J = 4.4, 11.7 Hz), 4.36 (dd, 1H, H-1′, J = 5.0, 11.7 Hz), 4.20–4.12 (m, 1H, H-2), 3.74–3.69 (m, 2H, H-4), 3.40 (s, 3H, OCH_3), 2.17–2.04 (m, 2H, H-3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 133.2, 129.8, 129.6, 128.4, 96.5, 72.5, 66.3, 55.8, 41.0, 35.3; MS (CI) *m/e* 273 (3.71, $^{35}M^+ + H$), 237 (18.22, $M^+ - Cl$). Anal. ($C_{13}H_{17}O_4Cl{\cdot}0.15C_6H_{14}$) C, H.

(*R*)-2-((2-Acetamido-1,6-dihydro-6-oxo-7*H*-purin-7-yl)methoxy)-4-chlorobutyl Benzoate (13) and (*R*)-2-((2-Acetamido-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-chlorobutyl Benzoate (14). N-2,9(7)-Diacetylguanine (12) (0.35 g, 1.4 mmol) was silylated with *N,O*-bis(trimethylsilyl)acetamide (1.8 mL, 7.3 mmol) in 1,2-dichloroethane (anhydrous, 10 mL). The solution was stirred for 1.5 h at room temperature. The 1,2-dichloroethane was removed under vacuum, and the residue was dissolved in anhydrous acetonitrile. Trimethylsilyl triflate (2.0 mL, 10 mmol) was added, and the solution was stirred for 15 min. A solution of compound 11 (0.27 g, 1.0 mmol) in anhydrous acetonitrile (5 mL) was added. After 30 min at room temperature, the reaction mixture was diluted with ethyl acetate (150 mL) and hexanes (50 mL) and extracted with H_2O (2 × 50 mL). The organic phase was extracted with 5% $NaHCO_3$ (25 mL) and then with H_2O (25 mL), dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to a colorless oil (0.48 g). Purification on a silica gel column (2.5 × 18 cm^2) (methanol:dichloromethane (1:10)) provided 0.37 g (84%) of **13** as an amorphous solid (<5% of **14** present): ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 12.1 (s, 1H, NH), 11.6 (s, 1H, NH), 8.40 (s, 1H, H-8), 7.90 (d, 2H, Ar-H, J = 6.9 Hz), 7.66 (t, 1H, Ar-H, J = 7.4 Hz), 7.51 (t, 2H, ArH, J = 7.6 Hz), 5.82 (d, 1H, OCH_2O, J = 10.9 Hz), 5.73 (d, 1H, OCH_2O, J = 10.9 Hz), 4.53 (dd, 1H, CH_2, J = 3.0, 11.7 Hz), 4.23 (dd, 1H, CH_2, J = 5.6, 11.7 Hz), 4.18–4.14 (m, 1H, CH), 3.64–3.60 (m, 1H, CH_2Cl), 3.48–3.45 (m, 1H, CH_2Cl), 2.18 (s, 3H, $CH_3C(O)NH$-), 2.02–1.96 (m, 2H, CH_2); ^{13}C NMR (75.43 MHz, Me_2SO-d_6) δ 173.3, 165.4, 157.5, 152.4, 147.1, 145.1, 133.3, 129.2, 129.0, 128.6, 111.0, 73.6, 72.0, 65.2, 41.2, 33.9, 23.6; MS (CI) *m/e* 434 (9.00, $^{35}M^+ + H$), 436 (3.34, $^{37}M^+ + H$), 194 (10.07). Anal. ($C_{19}H_{20}N_5O_5Cl{\cdot}0.20CH_4O{\cdot}0.05CH_2Cl_2$) C, H, N. Compound **14** was obtained as an amorphous solid with less then 5% **13** after purification of the mixture of **13** and **14** from the toluene- and 1,2-dichloroethane-coupling reactions (Table 1), using a chromatotron fitted with a 2000-μm rotor (methanol:dichloroemthane (1:20)): ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 11.95 (s, 1H, NH), 11.69 (s, 1H, NH), 8.17 (s, 1H, H-8), 7.82 (d, 2H, Ar-H, J = 7.3 Hz), 7.65 (t, 1H, Ar-H, J = 7.4 Hz), 7.49 (t, 2H, ArH, J = 7.6 Hz), 5.61 (d, 1H, OCH_2O, J = 11.6 Hz), 5.54 (d, 1H, OCH_2O, J = 11.4 Hz), 4.47 (dd, 1H, CH_2, J = 3.0, 12 Hz), 4.22 (dd, 1H, CH_2, J = 5.6, 12 Hz), 4.11–4.04 (m, 1H, CH), 3.67–3.60 (m, 1H, CH_2Cl), 3.53–3.44 (m, 1H, CH_2Cl), 2.17 (s, 3H, $CH_3C(O)NH$-), 2.03–1.94 (m, 2H, CH_2); ^{13}C NMR (75.43 MHz, Me_2SO-d_6) δ 173.4, 165.3, 154.7, 148.7, 147.9, 139.9, 133.3, 129.2, 128.9, 128.6, 120.3, 72.6, 71.3, 65.0, 41.1, 33.9, 23.7; MS (EI) *m/e* 433 (2.68, $^{35}M^+$), 435 (0.92, $^{37}M^+$), 193 (1.74). Anal. ($C_{16}H_{20}N_5O_5Cl{\cdot}0.25CH_6O{\cdot}0.20H_2O$) C, H, N.

(*R*)-2-((2-Acetamido-1,6-dihydro-6-oxo-7*H*-purin-7-yl)methoxy)-4-iodobutyl Benzoate (15) and (*R*)-2-((2-Acetamido-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-iodobutyl Benzoate (16). Distilled 2-butanone (100 mL) was combined with compound **13** (1.38 g, 3.2 mmol) and sodium iodide (anhydrous, 2.38 g, 16 mmol). This solution was stirred under nitrogen at 80 °C. After 3 h, the solution was filtered and concentrated to give 4.7 g of crude product. This residue was purified on a silica gel column (2.5 × 20 cm^2) (methanol:dichloromethane (1:9)). Product was obtained as a light yellow

glass, 1.35 g (80%) as a mixture of **15** (60%) and **16** (40%): ^1H NMR (300 MHz, Me_2SO-d_6) δ 12.10 (s, 1H, NH, N-7), 12.00 (s, 1H, NH, H-9), 11.71 (s, 1H, NH, N-9), 11.61 (s, 1H, NH, N-7), 8.43 (s, 1H, H-8, N-7), 8.40 (s, 1H, H-8, N-9), 8.20–7.82 (m, Ar-H, N-7 and -9), 7.70–7.64 (m, Ar-H, N-7 and -9), 7.54–7.48 (m, Ar-H, N-7 and -9), 5.82 (d, 1H, OCH_2O, J = 10.9 Hz, N-7), 5.73 (d, 1H, OCH_2O, J = 10.9 Hz, N-7), 5.62 (d, 1H, OCH_2O, J = 11.4 Hz, N-9), 5.56 (d, 1H, OCH_2O, J = 11.4 Hz, N-9), 4.58–4.47 (m, CH_2-OSi, N-7 and -9), 4.28–4.21 (m, CH_2OSi, N-7 and -9), 4.00–3.93 (m, CH, N-7 and -9), 3.35–3.20 (m, CH_2I, N-7 and -9), 3.15–3.00 (m, CH_2I, N-7 and -9), 2.17 (s, 3H, $CH_3C(O)N$, N-7), 2.15 (s, 3H, $CH_3C(O)N$, N-9), 2.20–2.00 (m, CH_2, N-7 and -9); MS (CI) *m/e* 526 (0.86, M^+ + H), 333 (13.45). Anal. ($C_{19}H_{20}N_5O_5I{\cdot}0.15C_4H_8O$) C, H, N.

(*R*)-Diethyl [3-((2-Acetamido-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-(benzoyloxy)butyl]phosphonate (18). A mixture of 70% **15** and 30% **16** (0.31 g, 0.60 mmol) was added to toluene (4 mL) and *N,O*-bis(trimethylsilyl)acetamide (0.3 mL, 1.2 mmol) and heated at 80 °C. After 2 h, the solution was cooled to ambient temperature. In a separate flask, a 60% dispersion of sodium hydride in mineral oil (0.12 g, 3.0 mmol) was treated with anhydrous tetrahydrofuran (20 mL) and cooled to −78 °C. A solution of diethyl hydrogen phosphite (0.7 mL, 5.4 mmol) dissolved in tetrahydrofuran (10 mL) was added, and the mixture was stirred at −78 °C for 30 min and then at 0 °C for an additional 45 min. The two solutions were combined and stirred at 0 °C for 6 h. The reaction mixture was diluted with dichloromethane (200 mL) and H_2O (50 mL). The solution was neutralized with 1 N HCl, separated, and further extracted with dichloromethane (150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column (2.5 × 18 cm^2) (methanol: dichloromethane (1:10)) to give 0.13 g (41%) of **17** and **18** (40% and 60%, respectively, by ^1H NMR). This product was combined with 70 mg of similar material from a previous reaction (total 200 mg, 0.37 mmol) and further purified on a silica gel column (2.5 × 14 cm^2) (methanol:dichloromethane (1:15)) to give 120 mg (23% from **15** and **16**) of pure **18** as a clear glass: UV λ_{max} (ϵ) pH = 7.0, 260 (13 400), 236 nm (14 500), 0.1 N HCl, 262 (14 000), 236 nm (14 400), 0.1 N NaOH, 263 nm (12 000); ^1H NMR (300 MHz, Me_2SO-d_6) δ 11.9 (s, 1H, NH), 11.7 (s, 1H, NH), 8.19 (s, 1H, H-8), 7.79 (d, 2H, Ar-H, J = 7.3 Hz), 7.65 (t, 1H, Ar-H, J = 7.4 Hz), 7.48 (t, 2H, ArH, J = 7.7 Hz), 5.62 (d, 1H, OCH_2O, J = 11.4 Hz), 5.56 (d, 1H, OCH_2O, J = 11.4 Hz), 4.37 (dd, 1H, CH_2OBz, J = 3.3, 11.9 Hz), 4.22 (dd, 1H, CH_2OBz, J = 6.3, 11.8 Hz), 3.99–3.88 (m, 5H, CH and OCH_2CH_3), 2.16 (s, 3H, $CH_3C(O)NH$-), 1.75–1.50 (m, 4H, PCH_2CH_2), 1.20 (t, 6H, OCH_2CH_3, J = 7.0 Hz); ^{13}C NMR (50.3 MHz, Me_2SO-d_6) δ 173.8, 165.7, 155.1, 149.0, 148.3, 140.4, 133.7, 129.5, 129.2, 128.9, 120.2, 75.6 (d, CH, $J_{C,P}$ = 17.5 Hz), 71.8, 65.3, 61.2 (d, OCH_2CH_3, $J_{C,P}$ = 6.3 Hz), 24.2 (d, CH_2, $J_{C,P}$ = 4.1 Hz), 23.9, 20.3 (d, CH_2, $J_{C,P}$ = 141 Hz), 16.7 (d, OCH_2CH_3, $J_{C,P}$ = 5.7 Hz); ^{31}P NMR (121.4 MHz, Me_2SO-d_6) δ 32.43; MS (CI) *m/e* 536 (16.45, M^+ + H), 343 (37.83). Anal. ($C_{23}H_{30}N_5O_8P{\cdot}0.10CH_4O{\cdot}0.15CH_2Cl_2$) C, H, N.

(*R*)-Ethyl Hydrogen [3-((2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-hydroxybutyl]phosphonate (19) and [(*R*)-3-((2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-hydroxybutyl]phosphonic Acid (20). Compound **18** (0.10 g, 0.19 mmol) was stirred with a saturated solution of methylamine in methanol (100 mL) for 18 h at 0–5 °C. The solution was concentrated under reduced pressure and then redissolved in 0.5 N NaOH (50 mL) and stirred at room temperature for 24 h. The solution was neutralized (pH 7.5) by the slow addition of dry ice and then extracted with dichloromethane (3 × 50 mL). The aqueous phase was concentrated under reduced pressure while maintaining a neutral pH. The white solid residue (0.26 g) was dissolved in 10 mL of 50 mM $NaHCO_3$ buffer (pH 9), and snake venom phosphodiesterase I (100 units) was added. The solution was incubated at 37 °C for 5 days. The reaction was determined to be 50% complete by HPLC on a SAX column eluted at 2 mL/min with isocratic 10 mM ammonium phosphate (pH 5.5) with 5% methanol. After additional enzyme (100 units) was added and the reaction mixture was kept at 37 °C for an additional 41 h, the reaction was 65% complete. The resulting reaction mixture was diluted with 40 mL of deionized water, adjusted to pH 9 with 0.1 N HCl, and separated on a Sephadex DEAE A-25 ion-exchange column equilibrated in 50 mM ammonium bicarbonate, pH 9.0. (*R*)-Ethyl hydrogen [3-((2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy)-4-hydroxybutyl]phosphonate (**19**) was eluted from the column with 50 mM ammonium bicarbonate and repeatedly concentrated from deionized water to give 0.023 g (30%) of a white solid: ^1H NMR (400 MHz, D_2O) δ 7.80 (s, 1H, H-8), 5.49 (d, 1H, OCH_2O, J = 11.4 Hz), 5.38 (d, 1H, OCH_2O, J = 11.4 Hz), 3.58–3.50 (m, 4H, OCH_2CH_3, CH, and CH_2OH), 3.39 (dd, 1H, CH_2OH, J = 6.9, 13.0 Hz), 1.50–1.00 (m, 4H, PCH_2CH_2), 0.99 (t, 3H, OCH_2CH_3, J = 7.1 Hz). HPLC analysis on a SAX column with isocratic 10 mM ammonium phosphate (2 mL/min, pH 5.5, 5% methanol) showed one peak with a retention time of 72 s. A linear gradient from 50 to 500 mM ammonium bicarbonate eluted phosphonic acid **20** early in the gradient. The product was repeatedly concentrated from deionized water yielding a white solid (0.034 g, 47%). Compound **20** was the monoammonium salt by a spectrophotometric assay:[29] $[\alpha]^{20}_D$ = −4.5° (c 0.09, H_2O); UV λ_{max} (ϵ) pH = 7.00, 252 (12 000), 270 nm (9500), 0.1 N HCl, 255 (10 900), 275 nm (8300), 0.1 N NaOH, 265.0 nm (10 000); ^1H NMR (300 MHz, D_2O) δ 7.78 (s, 1H, H-8), 5.40 (br s, 2H, OCH_2O), 3.55–3.32 (m, 3H, CH_2OH and CH), 1.56–1.46 (m, 2H, PCH_2CH_2), 1.32–1.13 (m, 2H, PCH_2CH_2); ^{13}C NMR (75.4 MHz, D_2O δ 158.8, 153.9, 151.5, 139.8, 115.9, 79.9 (d, $J_{C,P}$ = 17.6 Hz), 71.7, 62.7, 24.7 (d, $J_{C,P}$ = 3.1 Hz), 23.5 (d, $J_{C,P}$ = 134 Hz); ^{31}P NMR (121.4 MHz, D_2O) δ 24.51. HPLC analysis on a SAX column with isocratic 10 mM ammonium phosphate (2 mL/min, pH 5.5, 5% methanol) showed one peak with a retention time of 120 s. Anal. ($C_{10}H_{16}N_5O_6P{\cdot}1.0NH_3{\cdot}1.5H_2O$) C, H, N.

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