1340, 1210, 1130, 1040 cm^{-1}. Anal. ($C_{11}H_{14}N_4O_4S \cdot {}^1/_2H_2O$) C, H, N, S.

Biological Experiments. In vitro testing was performed by incubation of L1210 cells with the compound for 24 h, followed by a 1:1 dilution with fresh medium and further incubation for 24 h. Total cell number was recorded as percent of control (untreated) growth.

In vivo tests were done on L1210 by the NCI according to the protocol described in Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen, Drug Evaluation Branch, Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. Tumor inoculum: 10^5 ascites cells implanted into BDF_1 mice. Each mouse was inoculated once and observed for 30 days. Evaluation: MST = median survival time in days. % T/C = MST of treated/MST of control × 100. Criteria: % T/C = 125 considered moderate; % T/C = 150 considered significant antitumor effect.

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Registry No. 1, 80851-32-7; 2, 86527-18-6; 3, 86527-17-5; 4, 86527-21-1; 5, 86527-22-2; 6, 86527-20-0; 7, 86527-19-7; 8, 86527-23-3; PNPase, 9030-21-1; bis(trimethylsilyl)hypoxanthine, 86527-16-4; (trimethylsilyl)-6-chloropurine, 32865-86-4.

An Evaluation of Certain Chain-Extended Analogues of 9-β-D-Arabinofuranosyladenine for Antiviral and Cardiovascular Activity[1]

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Several nucleosides modified and chain extended at the 5′-position have been synthesized as follows: N^6-benzamido-9-(2,3-di-*O*-benzoyl-β-D-*arabino*-pentodialdo-1,4-furanosyl)adenine, O=CHR, $\xrightarrow{a}$ (*E*)-EtOCOCH=CHR (**2**) $\xrightarrow{b}$ $EtOCOCH_2CH_2R$ (**3**) $\xrightarrow{c}$ $H_2NCOCH_2CH_2R$ (**6**) $\xrightarrow{d}$ 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronamide (**8**); **3** $\xrightarrow{e}$ ethyl 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronate (**5**) $\xrightarrow{f}$ 1-(adenin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronic acid (**4**); **5** $\xrightarrow{g}$ 9-(5,6-dideoxy-β-D-*arabino*-hepto-1,4-furanosyl)adenine (**7**) [where a = EtOCOCH=PPh_3; b = H_2, Pd/C; c = Me_2AlNH_2; d = NH_3/MeOH; e = NaOEt/EtOH; f = NaOH/MeOH; g = $LiAlH_4$]. Both **7** and **8** show activity against herpes simplex virus type 1. The mechanism for such activity is unknown. Compounds **5** and **8** exhibited weak coronary vasodilation effects in dogs.

Over the past 2 decades a number of 5′-modified, chain-extended nucleosides have been described in the literature.[2-10] The rationale behind the synthesis of such compounds has generally been that these derivatives would be isosteric with the nucleoside 5′-phosphates or their homologues and, thus, might function as chemotherapeutic agents by selective enzyme inhibition. Early examples include a "6′-deoxyhomoadenosine" phosphonate proposed by Montgomery and Hewson[2] and reported some years later by Jones and Moffatt[3,4] and a "homoadenosine-6′-phosphonic acid" described by Hampton and co-workers.[5] These compounds were found, in general, to be substrates or inhibitors for adenosine monophosphate (AMP) utilizing enzymes. A further extension of these compound types has been the carboxy analogues of the phosphonates that include both two-carbon[6,7,10] and one-carbon[8,9] chains at the 5′-position of both purines[6-9] and pyrimidines.[8-10] The adenosine analogues were also substrates for several AMP-metabolizing enzymes.[11,12] α-Diazo ketone derivatives of the pyrimidine analogues have been utilized as active-site-directed inhibitors for pyrimidine-metabolizing enzymes.[10]

Inasmuch as all the examples cited in the foregoing were derivatives of D-ribonucleosides, it was deemed worthwhile to investigate similar compounds derived from the antiviral purine nucleoside 9-β-D-arabinofuranosyladenine (**1a**, *ara*-A, VIRA-A). The carboxy analogues **4** and **8** (Scheme I), which in the D-ribonucleoside series had seemed the most interesting biologically,[12] were targeted for synthesis. Potential areas of biological interest included the antiviral, anticancer and cardiovascular[13,14] fields.

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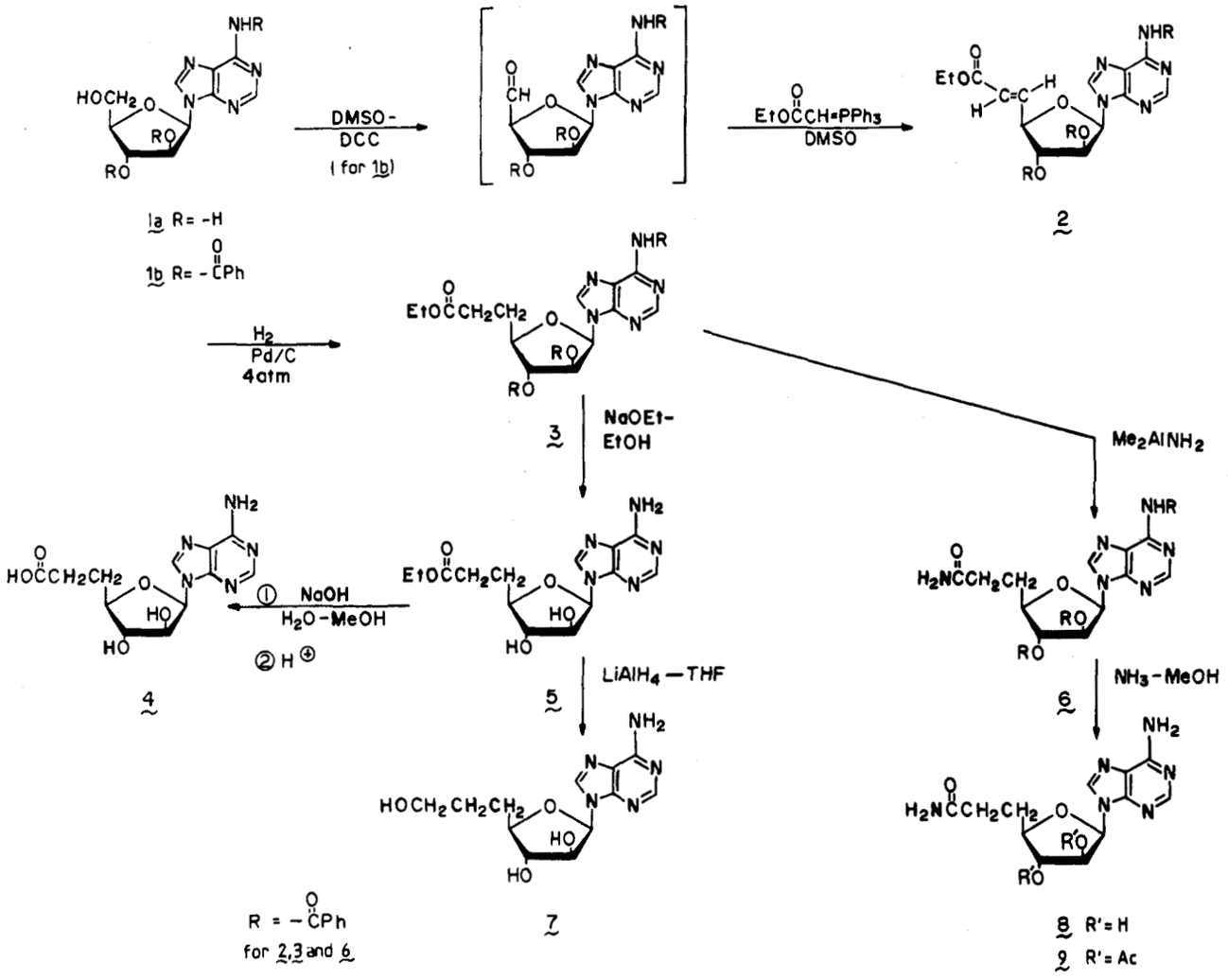
Scheme I



Results and Discussion

Chemical Syntheses. The syntheses of the chain-extended derivatives of **1a** were carried out by the processes outlined in Scheme I.

Oxidation of N^6-benzoyl-9-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)adenine (**1b**)[15,16] by the Pfitzner–Moffatt procedure afforded N^6-benzoyl-9-(β-D-*arabino*-2,3-di-*O*-benzoyl-1,5-pentodialdofuranosyl)adenine,[15] which was condensed directly, without isolation, with (carbethoxymethylene)triphenylphosphorane to give, in 65% yield, ethyl 1-(6-benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hept-5-eno-1,4-furanuronate (**2**) exclusively as the trans isomer, as determined by ^{1}H NMR and observed by TLC. Chromatographic procedures, combined with precipitation from alcohol-free solvents of *N,N'*-dicyclohexylurea, an annoying byproduct of the oxidation, rendered the product pure enough for use in subsequent reactions.

Attempts to deprotect **2** with sodium methoxide–methanol to give the free hydroxy, free amino compound were futile, owing to the participation of the conjugated carbonyl with H-4' giving rise to 3',4',5',6'-unsaturated[17] and possibly 4'-epimerized products as determined by ^{1}H NMR and TLC. Hydrogenation of **2** was accomplished at 60 psi over palladium on carbon catalyst to afford ethyl 1-(6-benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hepto-1,4-furanuronate (**3**) in 85% yield as a pure glassy solid. Complications arose when samples of **2** contained traces of *N,N'*-dicyclohexylurea, and additions of fresh catalyst were found necessary to achieve complete conversion of **2** to **3**. Compound **3** could be selectively deprotected with sodium ethoxide–ethanol to give ethyl 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronate (**5**) as a crystalline solid in 78% yield. No complicating side products in deprotecting **3** were observed by either TLC or ^{1}H NMR. Full deprotection of either **3** or **5** to give 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronic acid (**4**) required the use of aqueous sodium hydroxide. The carboxylic acid salt was isolated after DEAE-Sephadex

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(17) A compound, indicated to be 1-(6-aminopurin-9-yl)-1,3,5,6-tetradeoxy-α-L-*glycero*-hepta-3,5-dieno-1,4-furanuronate (i.e., the 3',4',5',6'-unsaturated analogue of **2**) was unequivocally identified by NMR (90 MHz methyl-d_6 sulfoxide with 10% D_2O): δ 1.20 (3 H, t, J = 7.5 Hz, CH_2CH_3), 4.12 (2 H, q, J = 7.5 Hz, CH_2CH_3), 5.09 (1 H, dd, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 2.5 Hz, H-2'), 5.90 (1 H, d, H-3'), 6.03 (1 H, d, $J_{5',6'}$ = 16 Hz, H-5'), 6.70 (1 H, d, *H*-1'), 7.18 (1 H, d, H-6'), 8.10 and 8.16 (1 H, 1 H, s, s, H-2, H-8).

chromatography, and the free acid was crystallized from methanolic hydrogen chloride to furnish pure **4** (by ^{1}H NMR and elemental analysis) in 38% yield. While direct conversion of **3** to **4** was possible, complicating products (including benzoic acid) made the two-step conversion through intermediate **5** a procedurally less troublesome route. The ester **5** was reduced by lithium aluminum hydride to give fully deprotected 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanose (**7**) in 91% crude yield. Purification by a modified Dekker procedure[18] using a column of HPLC-grade resin under medium pressure afforded analytically pure **7** as a lyophilized powder, whose structure was confirmed by ^{1}H NMR and elemental analysis.

In order to synthesize the amide **8**, conventional ammonolysis conditions (ammonia–methanol, sealed tube, 25–100 °C) were tried on **3**, and the reaction was found to be exceedingly slow and low yielding. A novel procedure[19] that makes use of dimethylaluminum amide was found to cleanly and selectively convert **3** to the protected 1-(6-benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hepto-1,4-furanuronamide (**6**) in 72% yield. The product, freed of contaminating aluminates by microporous filtration, was shown to be pure **6** by NMR, TLC, and elemental analysis. Noteworthy is the selectivity demonstrated by this reaction for a straight-chain ester over aromatic (benzoic) esters. Compound **6** could then be debenzoylated in the conventional manner to give 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronamide (**8**) in modest yield. Amide **8**, whose structure was ascertained by 200-MHz ^{1}H NMR, defied purification to give acceptable elemental analysis; however, the acetylated derivative, 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-acetyl-β-D-*arabino*-hepto-1,4-furanuronamide (**9**), confirmed the above structure by both ^{1}H NMR and elemental analysis.

Biological Evaluations. A. Reactivity toward Adenosine Deaminase. Compounds **4**, **5**, **7**, and **8** were each assayed by the procedure of Kalckar[20] for reaction with adenosine deaminase (Sigma Chemical Co., type III, calf-mucosal adenosine deaminase with 5×10^{-6} to 9×10^{-5} M adenosine as substrate). Neither of the four compounds was found to be either a substrate or inhibitor for the enzyme at concentrations in the 10^{-6}–10^{-4} M range. The lack of substrate activity is in agreement with the findings for nucleosides in general having the 5′-OH functionality replaced by alkyl groups.[21]

B. Cardiovascular Activity. Compounds **5** and **8** were evaluated for their effects on coronary vascular resistance in dogs. Mongrel dogs were anesthetized, their chests were opened, and, by means of extracorporeal shunt, coronary blood flow was increased to near normal levels of 20–25 mL min^{-1}, with an observed increase in coronary vascular resistance. With the flow rate fixed, the coronary vasodilation effects were then reflected in a decreased coronary perfusion pressure upon intravenous administration of the drugs. The reference standard was ethyl 9-(6-aminopurin-9-yl)-1-deoxy-β-D-ribofuranuronate,[22] a known vasoactive compound, which was administered intravenously at a dose of 0.10 mg kg^{-1}. Compound **5** showed 39% (at a dose of 1.0 mg kg^{-1}) of the maximum response achieved with the standard; compound **8** showed only a 10% response (at a dose of 1.0 mg kg^{-1}) under identical conditions. All effects were very short-lived, i.e., of less than 5 min duration, and no medicinally useful results were observed; however, these activities are significant when compared with those of adenosine and several derivatives thereof.[14]

Table I. Antiviral Activities of Compounds 4, 5, 7, and 8

compd	HSV-1 (strain 377) ID_{50}, μM	HSV-1 (strain 377) VR[a]	HSV-1 (strain HF) ID_{50}, μM	HSV-1 (strain HF) TI[b]
4		0.3		
5	729	1.0		
7	643	1.5	525	2.1
8	574	1.6		
1a (*ara*-A)	22	2.5	42	3.1

[a] Virus rating (VR) is a weighted measurement of in vitro antiviral activity, based on the inhibition of virus-induced cytopathogenic effects and on the cytotoxicity exhibited by the drug.[23] VR > 1.0, active; VR = 0.5–0.9, marginal; VR < 0.5, inactive. [b] The ID_{50} and in vitro therapeutic index (TI) were determined as described previously.[24] The in vitro TI is the ratio of the ID_{50} for inhibition of cellular DNA and protein synthesis to the ID_{50} (given above) for inhibition of virus replication.

Table II. Inhibition of DNA Synthesis by Compound 7 in an *ara*-A Resistant Cell Line[a]

compd	ID_{50},[b] μM wild-type cells	ID_{50},[b] μM *ara*-A resistant cells
7	1880 (1610-2200)	1510 (1200-1890)
1a (*ara*-A)	2.4 (1.7-3.5)	242 (188-311)

[a] *Ara*-A resistant cells were derived by the passaging of B-mix K-44/6 cells (a mammalian cell line that is devoid of adenosine deaminase activity[26]) in increasing concentrations of *ara*-A.[27] [b] ID_{50} concentrations and corresponding 95% confidence intervals are presented. Methods used to measure DNA synthesis, to construct dose–response lines, and to calculate the values presented above have been described previously.[28]

C. Antiviral Activity. Compounds **4**, **5**, **7**, and **8** were evaluated for activity against two strains of herpes simplex virus type 1 (HSV-1). Table I illustrates that, although none of the compounds had marked antiviral activity, two compounds (**7** and **8**) did show some selectivity against the virus (see VR and TI values).

Even though potent antiviral activity was not observed, it was of interest to conduct preliminary studies into the mode of action of one compound (**7**). Experiments performed as part of determining TI showed that **7** inhibited DNA synthesis in uninfected KB cells (Table II). By analogy, for *ara*-A to inhibit DNA synthesis it must be phosphorylated to *ara*-A 5′-triphosphate (*ara*-ATP), which is the active inhibitor of ribonucleoside diphosphate reductase and DNA polymerase.[25] As an indirect test of

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whether compound 7 was phosphorylated, the inhibitory potency of compound 7 was examined in a cell line that has a very limited capacity to phosphorylate *ara*-A (**1a**). Table II shows that compound 7 inhibited DNA synthesis equally well or better in this *ara*-A-resistant cell line than in corresponding wild-type cells. Thus, compound 7 either was phosphorylated to the same extent by both cell types or it did not need to be phosphorylated to be active. The latter possibility was explored by examining the effect of compounds 5, 7, and 8 on a DNA polymerase preparation from HSV-1-infected KB cells. All methods employed have been described previously.[29] At the highest concentration tested (1.5–1.7 mM), no inhibition (99–133% of control) of HSV-1 DNA polymerase was observed. In contrast, the ID_{50} for inhibition of the enzyme by *ara*-ATP was 1.5 μM.

Therefore, it is concluded that these chain-extended analogues of **1a** do not inhibit DNA polymerase directly. Nonetheless, the analogues do inhibit virus replication and cellular DNA synthesis by mechanisms that remain undefined.

Experimental Section

General. All evaporations were conducted at water aspirator vacuum at 40–45 °C. Chemicals and solvents were reagent grade and were used directly with the exception of tetrahydrofuran (distilled under nitrogen from potassium–benzophenone ketyl)), *N,N*-dimethylformamide (distilled in vacuo from calcium hydride), and methyl sulfoxide (dried over 4Å molecular sieves). All melting points are uncorrected and were determined with a Thomas-Hoover capillary apparatus (melting points up to 250 °C) or a Fisher-Jones hot-stage unit (melting points above 250 °C). Thin-layer chromatography was carried out on E. Merck aluminum-backed silica gel plates (E.M. catalog no. 5539) with either solvent A (45:45:10 ethyl acetate–chloroform–methanol), solvent B (80:20 chloroform–methanol), solvent C (70:15:15 acetonitrile–0.1 M ammonium chloride–0.1 M ammonium acetate), or solvent D (1:1 chloroform–ethyl acetate). Column chromatography was conducted with E. Merck silica gel 60 (70–200 mesh, E.M. catalog no. 7734) in gravity-fed columns with UV detection, where appropriate, by an Isco Model UA-5 unit. Preparative HPLC was carried out on a custom-built instrument (Milton-Roy minipump, Laboratory Data Control Cheminert fittings) of our own design. IR spectra were obtained on a Perkin-Elmer Model 710B spectrophotometer. Optical rotations were obtained in 1-dm cells on a Perkin-Elmer Model 241 spectropolarimeter. NMR spectra were carried out at 60 MHz on a Varian EM-360 spectrometer or at 200 MHz with a Nicolet NT-200 system with tetramethylsilane as the internal standard (δ = 0.0); spin–spin couplings are first-order values reported in hertz. Microanalyses were determined either by this department's microanalytical laboratory or by Atlantic Microlab, Inc., Atlanta, GA. The molecular formula followed by the elemental symbol indicates that the analyses were within ±0.3% of the theoretical values.

Ethyl 1-(6-Benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hept-5-eno-1,4-furanuronate (2). To a stirred suspension of 3.61 g (6.2 mmol) of **1b** in 40 mL of anhydrous methyl sulfoxide was added 5.00 g (24 mmol) of *N,N'*-dicyclohexylcarbodiimide (Aldrich Chemical Co.), followed by 0.40 mL (0.63 g, 4.8 mmol) of dichloroacetic acid. The mixture was stirred overnight with protection from moisture, after which time it was neutralized by the addition of 0.40 mL of pyridine. A precipitate of *N,N'*-dicyclohexylurea was removed by filtration, 5.00 g (14 mmol) of (carbethoxymethylene)triphenylphosphorane (Aldrich Chemical Co.) was added to the mother liquors, and the mixture was stirred for an additional 3 h. TLC (solvent A) indicated the formation of a new product at R_f 0.80, with absence of starting material at R_f 0.57.

The reaction was terminated by the slow addition (**caution: foaming!**) of 50 mL of a 10% aqueous solution of oxalic acid. The resulting suspension was filtered, and the mother liquors were extracted with 2 × 100 mL of ethyl acetate. The organic extract was washed with 2 × 100 mL of saturated aqueous sodium hydrogen carbonate solution and 100 mL of water, dried over anhydrous magnesium sulfate, and evaporated to yield a dark syrup. After the syrup was cooled at 0 °C overnight, an additional precipitate of *N,N'*-dicyclohexylurea was removed by filtration.

The crude, syrupy product was purified by rapid chromatography over a 4 × 30-cm (200-g) column of silica gel slurry packed in ethyl acetate. The column was eluted with ethyl acetate, the UV-active (280 nm) zones were pooled, and the solvent was evaporated to give a syrup somewhat free of *N,N'*-dicyclohexylurea. This product was then dissolved in ~3 mL of dichloromethane and chromatographed over a 4 × 40-cm (250-g) column of silica gel slurry packed in dichloromethane and eluted with a near-linear gradient of 450 mL of dichloromethane → 525 mL of 1:1 dichloromethane–ethyl acetate. The fractions containing the UV-active component were combined and concentrated to 20 mL, from which an additional amount of *N,N'*-dicyclohexylurea was filtered. The remaining solvent was evaporated, and the pure product was dried at 80 °C (0.1 torr) to yield 2.63 g (65%) of a glassy solid: R_f 0.80 (A); $[\alpha]^{20}_D$ −13° (*c* 0.9, chloroform); UV (MeOH) max 278 nm (ϵ 21 800), 232 (41 200); IR (KBr) 1710 (C=O) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.33 (3 H, t, CH_2CH_3), 4.26 (2 H, q, CH_2CH_3), 4.97 (1 H, sp, $J_{4',5'}$ = 5.1 Hz, $J_{4',6'}$ = 1.8 Hz, H-4'), 5.81 (1 H, dd, $J_{3',4'}$ = 3.4 Hz, H-3'), 5.99 (1 H, dd, $J_{2',3'}$ = 2.5 Hz, H-2'), 6.35 (1 H, dd, $J_{5',6'}$ = 15.7 Hz, H-5'), 6.94 (1 H, d, $J_{1',2'}$ = 4.1 Hz, H-1'), 7.31 (1 H, dd, H-6'), 7.39–8.16 (15 H, m, COPh), 8.32 and 8.86 (1, 1, s, s, H-2, H-8), 8.94 (1 H, s, NHR). Anal. ($C_{35}H_{29}N_5O_8$) C, H, N.

Ethyl 1-(6-Benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hepto-1,4-furanuronate (3). A solution of 1.29 g (1.99 mmol) of **2** in 100 mL of ethanol containing 0.5 mL of acetic acid was hydrogenated at 60 psi over 0.2 g of 10% palladium on carbon (Alfa-Ventron) for 24 h. At the end of this time, the mixture was filtered, fresh catalyst was added, and hydrogenation was continued for another 8 h. The catalyst was then removed by filtration, the solvent was evaporated, and the crude product was chromatographed rapidly over a 1.5 × 20-cm (20-g) column of silica gel with ethyl acetate as the eluent, collecting a single fraction. The solvent was evaporated, and the product was dried to yield 1.10 g (85%) of a clear glass that by ^1H NMR spectroscopy was shown to be the completely hydrogenated product **3**: R_f 0.80 (A); UV (MeOH) max 278 nm (ϵ 21 200), 232 (38 000); IR (KBr) 1715 (C=O) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.18 (3 H, t, CH_2CH_3) 2.48 [4 H, m (width = 31 Hz), H-5', H-5'a, H-6'], 4.13 (2 H, q, CH_2CH_3), 4.43 [1 H, m (width = 20 Hz), H-4'], 5.76 [1 H, dd (t), H-3'], 5.96 (1 H, dd, $J_{2',3'}$ = 2.5 Hz, H-2'), 6.84 (1 H, d, $J_{1',2'}$ = 4.2 Hz, H-1'), 7.25–8.22 (15 H, m, COPh), 8.37 and 8.78 (1, 1, s, s, H-2, H-8). Anal. ($C_{35}H_{31}N_5O_8$) C, H, N.

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronic Acid (4). To a solution of 0.40 g (0.1 mol) of sodium hydroxide in 100 mL of 1:1 methanol–water water was added 0.160 g (0.47 mmol) of **5**. After the solution was stirred for 8 h, TLC (C) indicated disappearance of **5**, with formation of a new zone at R_f 0.22. The solution was then neutralized with dilute sulfuric acid, and the methanol was removed by evaporation. The aqueous solution, diluted to 0.005 M, was loaded onto a 2.5 × 60-cm column of DEAE-Sephadex (HCO_3^-). Elution with a linear gradient of 1 L of 0.005 M triethylammonium bicarbonate → 1 L of 0.30 M triethylammonium bicarbonate and collection of the UV-active zone (254 nm continuous monitoring) afforded, after evaporation of the solvent and decomposition of the buffer by repeated methanol addition and evaporation, the triethylammonium salt of **4**. Crystallization was effected by dissolving the product in 3 mL of methanol at 0 °C and acidifying with cold, concentrated hydrochloric acid to pH 2.5: yield 0.055 g (38%); mp 191 °C dec; $[\alpha]^{20}_D$ +28° (*c* 0.8, methanol); R_f 0.22 (C); UV (MeOH) max 259 nm (ϵ 14 000); ^1H NMR (200 MHz, D_2O) δ 2.14 [2 H, m (width = 24 Hz), H-5', H-5'a], 2.52 [2 H, dd (t), H-6'], 3.99 (1 H, m, $J_{4',5'}$ = 7.6 Hz, $J_{4',5a'}$ = 5.8 Hz, H-4'), 4.22 [1 H, dd (t), $J_{3',4'}$ = 5.8 Hz, H-3'], 4.50 [1 H, dd (t), $J_{2',3'}$ = 5.0 Hz, H-2'], 6.38 (1 H, d, $J_{1',2'}$ = 5.3 Hz, H-1'), 8.27 and 8.31 (1, 1, s, s, H-2,

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H-8). Anal. ($C_{12}H_{15}N_5O_5 \cdot H_2O$) C, H, N.

Ethyl 1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronate (5). To 100 mL of a freshly prepared solution of sodium ethoxide, made by adding a small (50-mg) sliver of sodium to absolute ethanol (dried over 3Å molecular sieves), was added 3.00 g (4.62 mmol) of **3**. After the solution was stirred for 2 h, TLC (A) indicated complete conversion of **3** (R_f 0.80) to **5** (R_f 0.08). Dilute sulfuric acid was added to pH 7, and the solvent was evaporated. The residual syrup was chromatographed over a 2.5 × 50-cm (120-g) column of silica gel slurry packed in chloroform; elution was with a linear gradient of 350 mL of chloroform → 450 mL of 3:7 methanol–chloroform. Fractions containing the UV-active product were combined and evaporated to yield **5** as a colorless syrup, which was crystallized from hot ethanol to give 1.21 g (78%) of pure **5**: mp 196 °C; $[\alpha]^{20}_D$ +34° (*c* 1.4, methanol); UV (MeOH) max 259 nm (ε 15 700); IR (KBr) 1725 (C=O) cm^{-1}; ^1H NMR (200 MHz, Me_2SO-d_6) δ 1.17 (3 H, t, CH_2CH_3), 2.02 [2 H, m (width = 21 Hz), H-5′, H-5′a], 2.43 [2 H, dd (t), H-6′], 3.75 [1 H, m (width = 17 Hz), H-4′], 4.02 (2 H, q, CH_2CH_3), 4.03 [1 H, dd (t), H-3′], 4.13 [1 H, dd (t), $J_{2',3'}$ = 5.1 Hz, H-2′], 5.57 (1 H, d, *J* = 4.5 Hz, OH), 5.67 (1 H, d, *J* = 4.8 Hz, OH), 6.25 (1 H, d, $J_{1',2'}$ = 4.8 Hz, H-1′), 7.27 (2 H, s, NH_2), 8.12 and 8.16 (1, 1, s, s, H-2, H-8). Anal. ($C_{14}H_{19}N_5O_5$) C, H, N.

1-(6-Benzamidopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-benzoyl-β-D-*arabino*-hepto-1,4-furanuronamide (6). To 1 mL of a 2 M solution of ammonia in methylene chloride was added 1 mL of 2 M trimethylaluminum in toluene.[19] After allowing the mixture to stand for 5 min at room temperature, the solution was cooled to 0 °C and transferred to a 100-mL flask containing a cold, stirred solution (0 °C) of 0.65 g (1.0 mmol) of **3** in 20 mL of methylene chloride. The solution was slowly warmed to 42 °C and maintained at that temperature for 5 h, at which time TLC indicated the presence of a single new component [R_f 0.26 (A)]. The solution was frozen, and the reaction was terminated by the addition of 10 mL of cold, dilute hydrochloric acid, with gradual warming to room temperature. The precipitated salts were removed by filtration through Celite, and the solution was dried with anhydrous magnesium sulfate and evaporated to yield 0.45 g (72%) of a colorless glass that was homogeneous by TLC. An analytical sample was obtained by dissolving 100 mg of the crude product in distilled tetrahydrofuran, filtering through a 0.45-μm Teflon filter, and evaporating to give a glassy solid, which was dried at 80 °C (0.1 torr): UV (MeOH) max 278 nm (ε 20 300), 232 (35 500); IR (KBr) 1720 (C=O), 1675 (C=O) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.40 [4 H, m (width = 28 Hz), H-5′, H-5′a, H-6′], 4.27 [1 H, m (width = 20 Hz), H-4′], 5.65 [1 H, dd (t), H-3′], 5.87 [1 H, dd (t), H-2′], 6.3 (2 H, s, NH_2), 6.75 (1 H, d, $J_{1',2'}$ = 4.5 Hz, H-1′), 7.2–8.2 (15 H, m, COPh), 8.36 and 8.66 (1, 1, s, s, H-2, H-8), 9.6 (1 H, NHR). Anal. ($C_{32}H_{28}N_6O_7$) C, H, N.

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanose (7). To a stirred solution of 0.132 g (0.393 mmol) of **5** in 75 mL of anhydrous tetrahydrofuran was added 0.022 g (0.55 mmol) of lithium aluminum hydride (95% reagent, Alfa-Ventron), followed by an additional 0.025 g (0.63 mmol) after 30 min. At the end of 30 min (1 h, total reaction time), TLC (solvent B) indicated conversion to **7** (R_f 0.26). The reaction was terminated by the sequential addition of 0.047 mL of water, 0.047 mL of 15% aqueous sodium hydroxide, followed by 0.15 mL of water. The mixture was filtered, and a UV determination on the filtrate (5340 ODU, 259 nm) indicated a 91% yield of product.

An analytical sample (2460 ODU) was prepared via chromatography with a HPLC version of the Dekker procedure [1 × 60-cm column of Dowex-1 [OH^-], 37–74 μm (slurry packed in water), UV (254 nm) detection]. Elution with a linear gradient of 0.2 L of water → 0.2 L of methanol (2 mL min^{-1}, 350 psi) gave, upon evaporation and lyophilization of the solvent from the appropriate fractions, pure **7**, which was dried at 100 °C (0.01 torr): UV (H_2O) max 259 nm (ε 14 100); ^1H NMR (200 MHz, D_2O) δ 1.72 [2 H, m (width = 34 Hz), H-6′], 1.87 [2 H, m (width = 28 Hz), H-5′, H-5′a], 3.67 (2 H, t, $J_{6',7'}$ = 6.4, H-7′), 3.99 [1 H, m (width = 18 Hz), H-4′], 4.18 [1 H, dd (t), H-3′], 4.48 [H, dd (t), H-2′], 6.35 (1 H, d, $J_{1',2'}$ = 5.3 Hz, H-1′), 8.19 and 8.24 (1, 1, s, s, H-2, H-8). Anal. ($C_{12}H_{17}N_5O_4 \cdot 0.5H_2O$) C, H, N.

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*arabino*-hepto-1,4-furanuronamide (8). To a saturated solution of dry ammonia in methanol was added 0.150 g (0.241 mmol) of **6**. After 12 h at room temperature, TLC indicated that the reaction was complete (R_f 0.38, solvent C). The solvent was evaporated, and the residue was taken up in 50 mL of water and extracted with 50 mL of carbon tetrachloride, followed by 50 mL of chloroform. The aqueous layer, which contained the product, was freeze-dried to yield 0.056 g (80%) of **8**. The product was further purified by reverse-phase preparative HPLC (2.0 × 60-cm column of Lichrobsorb RP-18, 254-nm monitoring) to yield 0.032 g (46%) of pure product, which formed a glass upon removal of the solvent: ^1H NMR (200 MHz, D_2O) δ 2.15 [2 H, m (width = 29 Hz), H-5′, H-5′a], 2.48 (2 H, dd, $J_{5',6'}$ = 7.3 Hz, $J_{5a',6'}$ = 7.9 Hz, H-6′), 3.98 [1 H, m (width = 15 Hz), H-4′], 4.20 [1 H, dd (t), H-3′], 4.48 [1 H, dd (t), $J_{2',3'}$ = 4.7 Hz, H-2′], 6.35 (1 H, d, $J_{1',2'}$ = 5.1 Hz, H-1′), 8.26 and 8.20 (1, 1, s, s, H-2, H-8).

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-2,3-di-*O*-acetyl-β-D-*arabino*-hepto-1,4-furanuronamide (9). To a stirred solution of 0.047 g (0.15 mmol) of **8** in 15 mL of anhydrous pyridine at −5 °C was added dropwise 0.05 mL of acetic ahydride. The reaction was refrigerated at 0 °C for 48 h and quenched with the addition of 0.5 mL of water. After the solvents had been evaporated and the residue had been partitioned between 50 mL of water and 50 mL of ethyl acetate, the organic layer was washed with 50 mL of water, dried over anhydrous magnesium sulfate, and evaporated to yield a clear syrup. The syrup was taken up in 2 mL of chloroform and precipitated with hexane. The gummy precipitate was again taken up in 2 mL of chloroform, filtered through a 0.45-μm Teflon filter, and precipitated with hexane. The gummy precipitate was then collected by filtration and dried at 79 °C in vacuo for 12 h to yield 0.029 g of a powdery solid: R_f 0.51 (B); $[\alpha]^{20}_D$ +18° (*c* 0.7, methanol); UV (MeOH) max 259 nm (ε 14 700); IR (KBr) 1735 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.94 (3 H, s, OAc), 2.16 (3 H, s, OAc), 2.25 [2 H, m (width = 22.6 Hz), H-5′, H-5′a], 2.46 [2 H, m (width = 16.2 Hz), H-6′], 4.07 [1 H, m (width = 17.3 Hz), H-4′], 5.22 (1 H, dd, $J_{3',4'}$ = 3.6 Hz, H-3′), 5.44 (1 H, dd, $J_{2',3'}$ = 2.0 Hz, H-2′), 5.52 (2 H, s, NH_2), 5.89 (2 H, s, NH_2), 6.54 (1 H, d, $J_{1',2'}$ = 4.1 Hz, H-1′), 8.03 and 8.35 (1, 1, s, s, H-2, H-8). Anal. ($C_{16}H_{20}N_6O_6$) C, H, N.

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Registry No. **1b**, 57018-83-4; **2**, 86632-10-2; **3**, 86632-11-3; **4**, 86632-12-4; **4**·Me_3N^+, 86632-13-5; **5**, 86632-14-6; **6**, 86632-15-7; **7**, 86632-16-8; **8**, 86632-17-9; **9**, 86632-18-0; adenosine deaminase, 9026-93-1; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; ethyl 1-(6-aminopurin-9-yl)-1,3,5,6-tetradeoxy-β-L-*glycero*-hepta-3,5-diene-1,4-furanuronate, 86632-19-1.