Total Synthesis of Griseolic Acid Derivatives from D-Glucose

Deen Tulshian,* Ronald J. Doll, and Mary F. Stansberry

Schering-Plough Research, Schering-Plough Corporation, 60 Orange Street, Bloomfield, New Jersey 07003

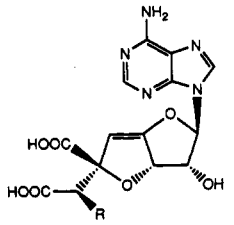
Andrew T. McPhail

Department of Chemistry, P. M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

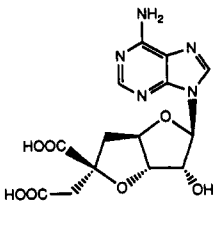
Received April 2, 1991

Griseolic acid, **1**, is a potent nonselective cyclic nucleotide-phosphodiesterase inhibitor isolated from *Streptomyces Griseoaurantiacus*. Recently, preparation of several griseolic acid derivatives, including **3**, has been reported. We have completed the chiral total synthesis of several griseolic acid derivatives. Here, we report on total syntheses of two cis-fused 4′,5′-dihydro-7′-deoxy griseolic acid derivatives, **4** and **5**, from D-glucose.

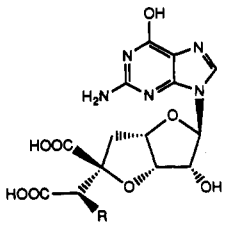
Griseolic acids A, B, and C are nucleotide-phosphodiesterase inhibitors isolated from the cultured broth of *Streptomyces griseoaurantiacus*.[1] On the basis of spectroscopic data, chemical transformations, and X-ray crystallography, they were structurally characterized as **1a**, **1b**, and **2**, respectively.[2] These compounds have been the subject of numerous biochemical studies on account of their potent inhibitory activities.[3]



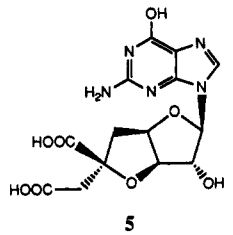
1a R=H
1b R=OH



2



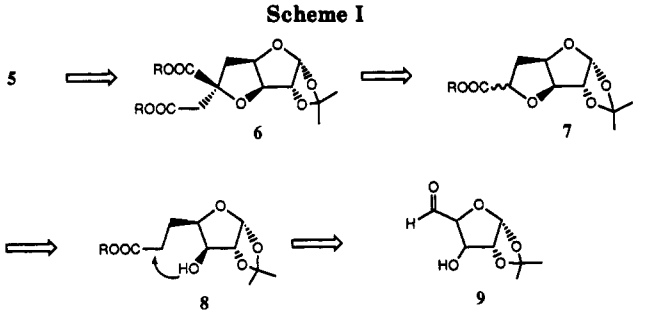
3 R=OH
4 R=H



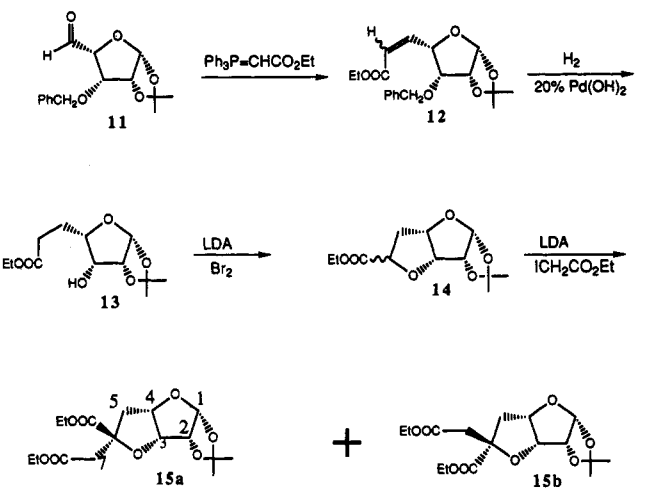
5

Recent reports have described the synthesis of various derivatives[3] of griseolic acid including **3**,[3c] a cis-fused analogue of griseolic acid C. These derivatives were all prepared by modification of the natural product itself. In order to investigate the biological activities of this class of compounds, a facile synthesis of derivatives was highly desirable. In our view, a totally synthetic route to these targets was preferable to modification of natural griseolic acid. Herein we report on the total synthesis of two chiral cis ring-fused 4′,5′-dihydro-7′-deoxy griseolic acid derivatives, **4** and **5**, containing a guanine rather than an adenine heterocycle. Our synthetic strategy was to prepare bicyclic compound **6** from aldehyde **9** derived from a sugar possessing the desired stereochemistry at C_2, C_3, and C_4. Functionalization of the proposed aldehyde would generate **8** which could be cyclized to **7** by a bromination/displacement sequence. Alkylation of **7** with iodoacetate, followed by an acetolysis,[4] would then produce a bis-acetate derivative, which could be converted to guanine derivatives **4** and **5** using the Vorbruggen[5] procedure (Scheme I).

Scheme I



Scheme II



Results and Discussion

Synthesis of **4** began with the known functionalized sugar aldehyde **11** which was obtained from diacetone glucose using the literature procedure.[6] A Wittig reaction

(1) Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. *J. Antibiotics* **1985**, *38*, 823.
(2) Takahaski, S.; Nakagawa, F.; Sato, S. *J. Antibiotics* **1988**, *41*, 705.
(3) (a) Iijima, Y.; Nakagawa, F.; Handa, S.; Oda, T.; Naito, A.; Yamezaki, M. *FEBS Lett.* **1985**, *192*(2), 179. (b) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneko, M. *Chem. Pharm. Bull.* **1987**, *35*, 1036. (c) Murofushi, Y.; Kimura, M.; Kuwano, H.; Iijima, Y.; Mitsuo, Y.; Kaneka, M. *Nucleic Acid Res., Symp. Ser.* **1986**, *17*, 45. (d) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneka, M. *Chem. Pharm. Bull.* **1987**, *35*, 4442; *Ibid* **1988**, *36*, 1309.
(4) Rosenthal, A.; Sprinzl, M. *Can. J. Chem.* **1969**, *47*, 3941.
(5) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1235.
(6) Kuzuhara, H.; Terayama, H.; Ohrui, H.; Emoto, S. *Carbohydr. Res.* **1971**, *20*, 165.

0022-3263/91/1956-6819$02.50/0

Scheme III

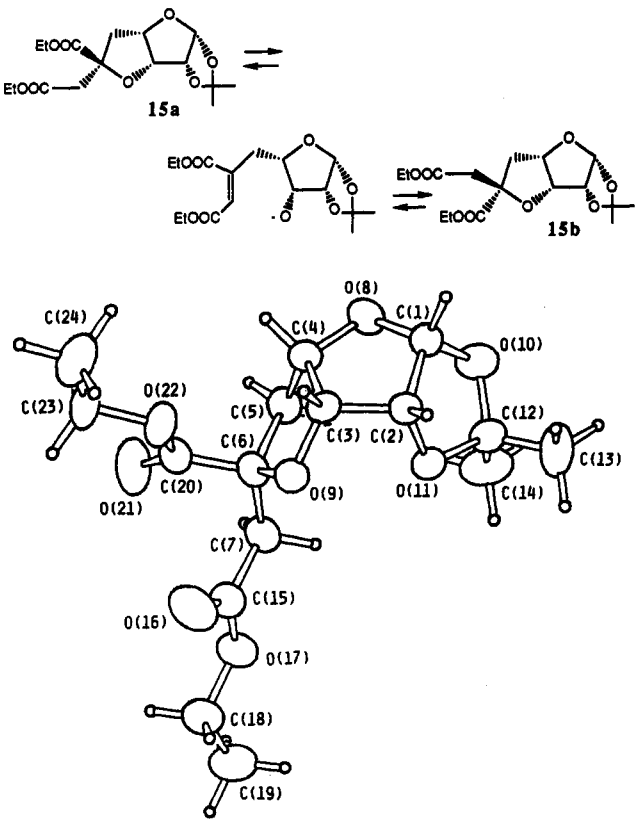


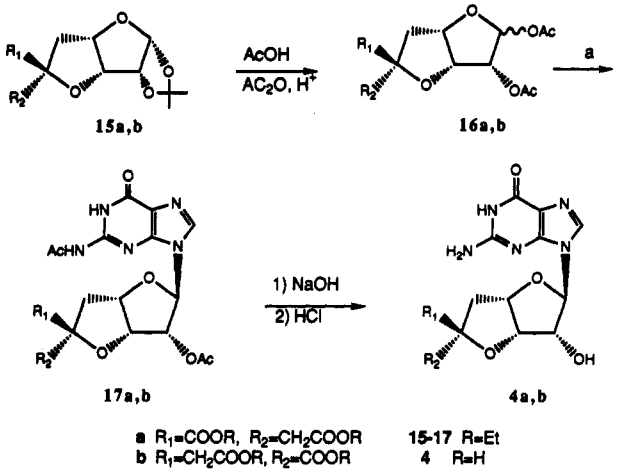
Figure 1. ORTEP diagram showing the atomic numbering scheme and solid-state conformation of **15a**; small circles represent hydrogen atoms.

on 11 produced alkene **12** as a mixture of *E* and Z isomers. Hydrogenation of **12** with 20% palladium hydroxide in the presence of a catalytic amount of hydrochloric acid resulted in both olefin reduction and debenzylation to produce **13**. Treatment of **13** with bromine and 2 equiv of lithium diisopropylamide led directly to bicyclic ester **14** predominantly as the α-isomer (9:1 ratio). The stereochemistry of the major isomer of **14** was established by ^{1}H NMR spectroscopy which showed an NOE between the proton α to the ester and ring junction protons H-3 and H-4, indicating a syn relationship. Alkylation of **14** with ethyl iodoacetate then gave both **15a** and **15b** in a 4:1 ratio. Formation of **15a** as the major product was surprising, since this requires alkylation to occur on the more hindered face. Treatment of either **15a** or **15b** under identical alkylation conditions also produced a 4:1 mixture, leading to the conclusion that these compounds equilibrate with each other via a ring opening conjugate addition sequence (Scheme III). The absolute configuration at C_6 in **15a** was established by ^{1}H NMR studies which revealed an NOE between the C_7 methylene protons, one of the isopropylidene methyl groups, and one of the protons at C_5. The C_7 methylene protons of **15b** exhibited an NOE involving H-3 and one of the protons at C_5. No NOE was observed between H-3 and the C_7 methylene protons of **15a**. An X-ray crystallographic analysis[8] of **15a** corroborated the structural assignment based on the NMR data. The crystal structure was solved by direct methods. A view of the solid-state conformation is presented in Figure 1.

(7) Wolform, M. L.; Thomas, G. H. S. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolform, M. L., Eds.; Academic Press: New York, 1963; Vol. 2, p 32.

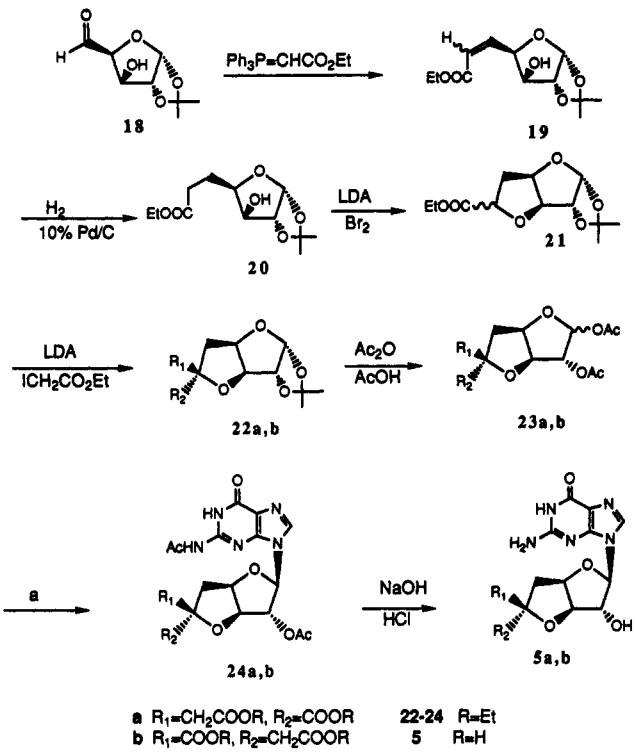
(8) Supplementary material. See the paragraph at the end of this paper.

Scheme IV[a]



[a] Key: (a) Silylated N^2-acetylguanine, TMSOTf, CH_2ClCH_2Cl.

Scheme V[a]



[a] Key: (a) Silylated N^2-acetylguanine, TMSOTf, CH_2ClCH_2Cl.

The absolute stereochemistry shown follows from that of the starting aldehyde **11**. Bond lengths and angles are all in accord with expected values.[9] The central tetrahydrofuran ring is in a half-chair conformation with the C_2 symmetry axis passing through O_8 and the mid-point of the C_2–C_3 bond, while the other two five-membered rings adopt envelope forms with C_5 and O_{11} as the out-of-plane atoms.

Transformation of **15a** and **15b** to the final products is shown in Scheme IV. Acetolysis[4] of **15** followed by guaninylation[5] of diacetate **16** produced **17**. This displacement was always accompanied by a small amount of N^7 alkylation (less than 10%), but the desired N^9 product is easily isolated using chromatography and regioisomers were characterized by NMR methods.[10] Subsequent base

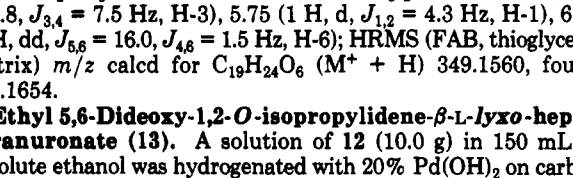
(9) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S2.

hydrolysis of **17** produced **4a**.

The synthetic sequence for the preparation of **5**, starting with known aldehyde[7] **18**, is shown in Scheme V and is vary similar to that depicted in Scheme II. Alkylation of **21** with ethyl iodoacetate was much less stereoselective than that involving compound **14**, the ratio of products being 1.5:1 in favor of **22a**. The absolute stereochemistry of both compounds was again established using NOE experiments. Thus, **22a** showed an NOE between the C_7 methylene protons and one of the protons at C_5, but no NOE with H-3 and H-4, whereas for **22b**, an NOE was observed between the C_7 methylene protons and H-3 and H-4, as well as one of the protons at C_5. Conversion of these compounds to guanine derivatives using the procedure described above for **17** was followed by hydrolysis to furnish **5**. Compounds **4** and **5** have been evaluated for in vitro activity against Ca-Cam-phosphodiesterase isolated from bovine aorta. Compound **4a** exhibited greater activity and selectivity relative to griseolic acid **1**.[11]

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 200 or 400 MHz. The progress of reaction was monitored by TLC using Analtech silica gel GF plates. The chromatograms were viewed under an ultraviolet light, sprayed with concentrated H_2SO_4, and briefly heated on a hot plate. All column chromatography was done using silica gel (Baker silica gel 40 μm). The compounds were named using tentative rules for carbohydrate nomenclature.[12] For the purpose of NMR interpretation, the following numbering scheme has been adopted:



Ethyl 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-hept-5-enofuranuronate (12). A solution of aldehyde **11**[6] (8.50 g, 30.6 mmol) and (carbethoxymethylene)triphenylphosphorane (13.85 g, 39.7 mmol) in 100 mL of CH_3CN was refluxed for 2 h. Solvent was removed, and the residue was purified via flash chromatography (40% EtOAc–PE) to afford compound **12** as an oil (9.60 g, 90%) which was a mixture of cis and trans isomers. For major isomer trans: TLC, R_f = 0.6 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (3 H, t, J = 7.0 Hz, OCH_2CH_3) 1.32 and 1.65 (6 H, s, $C(CH_3)_2$), 4.10 (1 H, dd, $J_{2,3}$ = 5.8, $J_{3,4}$ = 7.5 Hz, H-3), 5.75 (1 H, d, $J_{1,2}$ = 4.3 Hz, H-1), 6.05 (1 H, dd, $J_{5,6}$ = 16.0, $J_{4,6}$ = 1.5 Hz, H-6); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{19}H_{24}O_6$ (M^+ + H) 349.1560, found 349.1654.

Ethyl 5,6-Dideoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-heptofuranuronate (13). A solution of **12** (10.0 g) in 150 mL of absolute ethanol was hydrogenated with 20% $Pd(OH)_2$ on carbon (3.0 g) and few drops of dioxane saturated with HCl gas for 5 h. A saturated solution of $NaHCO_3$ (5 mL) was then added, the reaction mixture was filtered, and the filtrate was dried ($MgSO_4$). Removal of solvent gave **13** as an oil (7.1 g, 95%): (7.1 g, 95%): TLC R_f = 0.6 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.42 and 1.65 (6 H, s, $C(CH_3)_2$), 2.15 (2 H, m, H-5, and H-5′), 2.50 (2 H, m, H-6, H-6′), 4.65 (1 H, dd, $J_{1,2}$ = 4.3, $J_{2,3}$ = 5.8 Hz, H-2), 5.85 (1 H, d, $J_{1,2}$ = 4.3 Hz, H-1); MS (EI) m/e 261 (M^+ + H, 100); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{12}H_{20}O_6$(M^+ + H) 261.1338, found 261.1331.

Ethyl 3,6-Anhydro-5-deoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-heptofuranuronate (14). A solution of **13** (3.0 g, 11.5 mmol) in 50 mL of dry THF was cooled to −78 °C, to this was added a solution of lithium diisopropylamide (25.5 mmol), and the reaction mixture was stirred at −78 °C for 0.5 h. This solution was then added dropwise to a solution of Br_2 (1.18 mL) in 50 mL of THF maintained at −78 °C. The reaction mixture was then warmed up to 0 °C slowly, 20 mL of the saturated NH_4Cl was added, and solvent was removed. Residue was redissolved in 200 mL of CH_2Cl_2. The solution was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified via flash chromatography (45% EtOAc–PE) to afford **14** as an oil (1.93 g, 65%): TLC R_f = 0.5 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (3 H, t, J = 6.85, OCH_2CH_3), 1.35 and 1.50 (6 H, s, $C(CH_3)_2$), 2.30 (1 H, ddd, $J_{5,5'}$ = 14.0, $J_{4,5}$ = 9.0, $J_{5,6}$ = 4.0 Hz, H-5), 2.55 (1 H, bd, $J_{5,5'}$ = 14.0 Hz, H-5′), 4.20 (2 H, q, J = 6.8 Hz, OCH_2CH_3), 4.72 (1 H, dd, $J_{2,3}$ = $J_{3,4}$ = 4.1 Hz, H-3), 4.82 (1 H, dd, $J_{1,2}$ = 4.2, $J_{2,3}$ = 4.1 Hz, H-2), 5.80 (1 H, d, $J_{1,2}$ = 4.2 Hz, H-1); MS (FAB thioglycerol matrix) m/z 259 (M^+ + H). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.79; H, 7.03. Found: C, 55.76; H, 7.05.

Ethyl 3,6-Anhydro-6-β- and Ethyl 3,6-Anhydro-6-α-carbethoxy-5,7-dideoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-nonofuranuronate (15a and 15b). A solution of **14** (0.52 g, 2.0 mmol) in 20 mL of dry THF was cooled to −78 °C and treated with lithium diisopropylamide (2.2 mmol) for 0.5 h. To this was added ethyl iodoacetate (0.43 g, 2.0 mmol), and the reaction mixture was warmed to 0 °C slowly. Reaction was worked up as described for the previous compound to produce a 4:1 mixture of compounds **15a** as a solid and **15b** as an oil (0.55 g, 80%) which were separated via flash chromatography (50% EtOAc–PE). For compound **15a**: TLC R_f = 0.75 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 and 1.55 (6 H, s, $C(CH_3)_2$), 2.30 (1 H, dd, $J_{5,5'}$ = 13.50, $J_{4,5}$ = 7.5 Hz, H-5), 2.70 (1 H, dd, $J_{5,5'}$ = 13.50, $J_{4,5}$ = 6.1 Hz, H-5), 3.10 and 3.15 (2 H, AB, J_{AB} = 15.0 Hz, H-7, H-7′), 4.55 (1 H, dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 5.5 Hz, H-2), 5.85 (1 H, d, $J_{1,2}$ = 3.6 Hz, H-1); mp 74–75 °C. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.79; H, 7.03. Found: C, 55.77; H, 6.98. For compound **15b**: TLC R_f = 0.68 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ, 1.28 and 1.30 (6 H, 2t, J = 7.0 Hz, $2OCH_2CH_3$), 1.32 and 1.58 (6 H, 2s, $2C(CH_3)$, 2.65 (1 H, dd, $J_{4,5'}$ = 5.0, $J_{5,5'}$ = 13.0 Hz, H-5′), 2.75 and 2.85 (2 H, AB, $J_{A,B}$ = 14.0 Hz, H-7a, H-7b), 4.58 (1 H, dd, $J_{1,2}$ = 3.1, $J_{2,3}$ = 6.2 Hz, H-2), 4.78 (1 H, dd, $J_{2,3}$ = 6.2, $J_{3,4}$ = 6.1 Hz, H-3), 4.95 (1 H, m, H-4), 5.80 (1 H, d, $J_{1,2}$ = 3.1 Hz, H-1); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{16}H_{24}O_8$ (M^+ + H) 345.1549, found 345.1541. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.79; H, 7.03. Found: C, 55.72; H, 6.96. **X-ray Crystal Structure Analysis of 15a.** $C_{16}H_{14}O_8$, M_r 344.36, monoclinic, a = 13.539 (4) Å, b = 5.428 (1) Å, c = 11.776 (3) Å, β = 90.97 (2)° (from 25 reflections, 35° < θ < 51°), V = 865.3 (6) Å^3, Z = 2, D_{calcd} = 1.322 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 8.6 cm^{-1}; crystal dimensions 0.06 × 0.10 × 0.60 mm. Space group $P2_1$ from the systematic absences, $0k0$ when $k \neq 2n$, and **15a** is chiral.

The following general procedure was used for guaninylation. A solution of isopropylidene compound (1.0 mmol) in 20 mL of CH_2Cl_2 was stirred and cooled at 0 °C as 20 mL of acetic anhydride and acetic acid (7:10 ratio) and catalytic amount of H_2SO_4 were added. The reaction mixture was stirred at rt for 4 h, diluted with 100 mL of CH_2Cl_2, washed with saturated $NaHCO_3$, water, and brine, and dried ($MgSO_4$). Flash chromatography with 50% EtOAc–PE gave a mixture of two anomeric acetates by TLC. The acetate mixture from the above experiment was dissolved in 1,2-dichloroethane and cooled to 0 °C. Trisilylated N^2-acetylguanine[5] (1.3 mmol) was added followed by trimethylsilyl triflate (1.3 mmol), and the reaction mixture was refluxed for 2 h. It was then diluted with CH_2Cl_2, washed with a cold solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (10% methanol–benzene). A small amount of N^7 alkylation product was also isolated during this purification. The pure compound was then treated with 6 equiv of 1 N NaOH in aqueous ethanol for 4 h. The reaction mixture was then neutralized with 1 N HCl, and the volume of the reaction mixture was reduced to half. This was then put on a CHP20P (MCI^R gel, Mitsubishi Chemical Industries Ltd) column and eluted first with water to remove all

(10) Kjellberg, J.; Johansson, N. G. *Tetrahedron* **1986**, *42*, 6541.
(11) Tulshian, D.; Doll, R. J.; Czarniecki, M.; Stansberry, M. Presented at ACS National Meeting, Division of Medacinal Chemistry, New York, NY, Aug 25–30, 1991; Paper No. MEDI 117.
(12) Tentative Rules for Carbohydrate Nomenclature *Biochemistry*, **1971**, *10*, 3983.
(13) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$; GOF = $[\sum w\Delta^2/(N_{observations} - N_{parameters})]^{1/2}$.
(14) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

NaCl and than with 10% acetone in water.

1,6-Dihydro-2-amino-9-(3′,6′-anhydro-5′-deoxy-6′(*S*)- and 1,6-Dihydro-2-amino-9-(3′,6′-anhydro-5′-deoxy-6′(*R*)-carboxy-6′-(carboxymethyl)-β-D-gulofuranosyl)-6-hydroxypurine (4a and 4b). Compounds **15a** (0.5 g, 1.5 mmol) and **15b** (0.4 g, 1.2 mmol) were guaninylated using the general procedure. Crude products **17a** and **17b** were purified via liquid column chromatography (10% methanol in benzene). For compound **17a** (a solid, 0.55 g, 72%): TLC R_f = 0.10 (10% methanol–benzene); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 and 2.32 (6 H, 2s, $OCOCH_3$ and $HNCOCH_3$), 2.35 (1 H, d, $J_{5',5''}$ = 14.5 Hz, H-5′), 2.65 (1 H, dd, $J_{4',5''}$ = 4.5, $J_{5',5''}$ = 14.5 Hz, H-5″), 3.05 (2 H, m, CH_2COOEt), 4.95 (1 H, dd, $J_{4',5''}$ = 4.5, $J_{3,4'}$ = 6.0 Hz, H-4′), 5.21 (1 H, t, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 6.0 Hz, H-3′), 5.92 (1 H, dd, $J_{2',3'}$ = 6.0, $J_{1',2'}$ = 5.85 Hz, H-2′), 6.0 (1 H, d, $J_{1',2'}$ = 5.85 Hz, H-1′), 7.5 (1 H, s, H-8); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{22}H_{27}N_5O_{10}$ (M^+ + H) 522.1836, found 522.1839. For compound **17b** (a solid, 0.45 g, 74%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 and 2.30 (6 H, 2s, $HNCOCH_3$, and $OCOCH_3$), 2.45 (1 H, dd, $J_{4',5'}$ = 4.0, $J_{5',5''}$ = 14.0 Hz, H-5′), 2.55 (1 H, d, $J_{5',5''}$ = 14.0 Hz, H-5″), 2.72 and 2.95 (2 H, AB, $J_{A,B}$ = 15.0 Hz, CH_2COOEt), 4.88 (1 H, dd, $J_{4',5'}$ = 4.0, $J_{3',4'}$ = 5.5 Hz, H-4′), 5.22 (1 H, dd, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 5.5 Hz, H-3′), 5.82 (1 H, dd, $J_{2',3'}$ = 6.0, $J_{1',2'}$ = 5.75 Hz, H-2′), 6.07 (1 H, d, $J_{1',2'}$ = 5.75 Hz, H-1′), 7.35 (1 H, s, $HNCOCH_3$), 7.7 (1 H, s, H-8), 9.8 (1 H, bs, OH); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{22}H_{27}N_5O_{10}$ (M^+ + H) 522.1836, found 522.1843. Hydrolysis of these compounds was done as described in the general procedure to give **4a** (a solid, decomposed at 250 °C, 0.38 g, 90%) and **4b** (a solid, decomposed at 225 °C, 0.30 g, 88%). For compound **4a**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.15 (1 H, d, $J_{5',5''}$ = 15.0 Hz, H-5″), 2.65 (1 H, dd, $J_{4',5'}$ = 6.0, $J_{5',5''}$ = 15.0 Hz, H-5′), 2.80 and 2.95 (2 H, AB, $J_{A,B}$ = 13.0 Hz, H-7″ and H-7′), 4.58 (1 H, dd, $J_{4',5'}$ = 6.0, $J_{3',4''}$ = 4.2 Hz, H-4′), 4.83 (1 H, m, H-3′), 5.05 (1 H, dd, $J_{1',2'}$ = 5.5 Hz, H-2′), 5.63 (1 H, d, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.75 (1 H, d, $J_{2',OH}$ = 4.3 Hz, C_2OH), 6.52 (2 H, s, NH_2), 8.0 (1 H, s, H-8), 10.35 (1 H, bs, OH), 12.35 (1 H, bs, COOH). Anal. Calcd for $C_{14}H_{15}N_5O_8$: C, 44.08; H, 3.97; N, 18.37. Found: C, 44.17; H, 3.92; N, 18.32. For compound **4b**: ^{1}H NMR (D_2O, 200 MHz) δ 2.5 (2 H, m, H-5′ and H-5″), 2.73 and 3.02 (2 H, AB, J_{AB} = 15.8 Hz, CH_2COOEt), 4.85 (2 H, m, H-3′ and H-4′), 5.16 (1 H, m, H-2′), 5.80 (1 H, d, $J_{1',2'}$ = 4.5 Hz, H-1′), 7.8 (1 H, s, H-8); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{14}H_{15}N_5O_8$ (M^+ + H) 382.0998, found 382.0993.

Ethyl 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate (19). A solution of aldehyde **18**[7] (5.80 g, 30.6 mmol) and (carbethoxymethylene)triphenylphosphorane (21.50 g, 61.7 mmol) in 100 mL of CH_3CN was refluxed for 2 h. Solvent was removed, and residue was purified via flash chromatography (50% EtOAc–PE) to give **19** as an oil (7.0 g, 86%). For the major trans compound: TLC R_f = 0.50 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 and 1.55 (6 H, 2s, $OC(CH_3)_2$), 4.63 (1 H, d, $J_{1,2}$ = 4.0 Hz, H-2), 4.85 (1 H, m, H-4), 6.05 (1 H, d, $J_{1,2}$ = 4.0 Hz, H-1), 6.22 (1 H, bd, $J_{4,6}$ = 1.8 Hz, H-6), 6.95 (1 H, dd, $J_{4,5}$ = 4.0, $J_{5,6}$ = 16.0 Hz, H-5); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{12}H_{18}O_6$ (M^+ + H) 259.1181, found 259.1176.

Ethyl 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptofuranuronate (20). A solution of **19** (5.0 g) in 75 mL of absolute ethanol was hydrogenated (60 psi) with 10% palladium on carbon (0.3 g) for 2 h. The reaction mixture was then filtered and solvent was removed to give **20** as an oil (4.75 g, 95%): TLC R_f = 0.5 (50% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (2 H, m, H-5, H-5′), 2.55 (1 H, dt, *J* = 7.0, $J_{6,6'}$ = 18.0 Hz, H-6a), 3.18 (1 H, d, $J_{3,4}$ = 4.5 Hz, H-3), 4.05 (1 H, m, H-4), 4.55 (1 H, d, $J_{1,2}$ = 4.0 Hz, H-2), 5.95 (1 H, d, $J_{1,2}$ = 4.0 Hz, H-1); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{12}H_{20}O_6$ (M^+ + H) 261.1338, found 261.1332.

Ethyl 3,6-Anhydro-5-deoxy-1,2-*O*-isopropylidene-α-D-heptofuranuronate (21). Compound **20** (1.50 g, 5.7 mmol) was treated under reaction conditions described for compound **13** to produce crude **21** which was purified via flash chromatography (20% EtOAc–PE) to give pure **21** as an oil (1.0 g, 70%): TLC R_f = 0.35 (30% EtOAc–PE); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.35 and 1.50 (6 H, 2s, $OC(CH_3)_2$), 2.30 (1 H, ddd, $J_{5,5'}$ = 14.0, $J_{5,6}$ = 9.0, $J_{4,5}$ = 4.0 Hz, H-5), 2.55 (1 H, bd, $J_{5,5'}$ = 14.0 Hz, H-5), 4.2 (2 H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.70 (1 H, m, H-3), 5.04 (1 H, m, H-4), 5.80 (1 H, d, $J_{1,2}$ = 4.1 Hz, H-1). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.79; H, 7.03. Found: C, 55.80; H, 6.98.

Ethyl 3,6-Anhydro-6-α- and Ethyl 3,6-Anhydro-6-β-(carboxyethyl)-5,7-dideoxy-α-D-*xylo*-nanofuranuronate (22a and 22b). Compound **21** (1.0 g, 4.0 mmol) was alkylated with ethyl iodoethylacetate using the procedure described for compound **14** to produce a 1.5:1 mixture of two compounds **22a** and **22b** (0.96 g, 70%) which were separated by flash chromatography (45% EtOAc–PE). For major compound **22a** (an oil): TLC R_f = 0.48, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 and 1.32 (6 H, 2t, *J* = 7.0 Hz, $2OCH_2CH_3$), 1.30 and 1.50 (6 H, 2s, $C(CH_3)_2$), 2.37 (1 H, d, $J_{5',5}$ = 14.50 Hz, H-5), 2.50 (1 H, dd, $J_{5',5}$ = 14.50, $J_{4,5'}$ = 4.15 Hz, H-5′), 2.92 and 3.05 (2 H, AB, $J_{A,B}$ = 15.5 Hz, H-7′, H-7), 4.18 and 4.28 (4 H, 2q, *J* = 7.0 Hz, $2OCH_2CH_3$), 4.65 (1 H, d, $J_{3,4}$ = 2.8 Hz, H-3), 4.75 (1 H, d, $J_{1,2}$ = 3.7 Hz, H-2), 4.90 (1 H, dd, $J_{4,5'}$ = 4.15, $J_{3,4}$ = 2.8 Hz, H-4), 5.95 (1 H, d, $J_{1,2}$ = 3.7 Hz, H-1); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{16}H_{24}O_8$ (M^+ + H) 345.1549, found 345.1539. For compound **22b** (an oil): TLC R_f = 0.4; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 and 1.32 (6 H, 2t, $2OCH_2CH_3$), 1.30 and 1.45 (6 H, 2s, $C(CH_3)_2$), 2.20 (1 H, dd, $J_{4,5}$ = 4.0, $J_{5',5}$ = 14.0 Hz, H-5), 2.66 (1 H, d, $J_{5',5}$ = 14.0 Hz, H-5′), 2.68 and 2.99 (2 H, AB, $J_{A,B}$ = 15.2 Hz, H-7′, H-7), 4.65 (1 H, d, $J_{1,2}$ = 3.4 Hz, H-2), 4.90 (1 H, m, H-4), 5.82 (1 H, d, $J_{1,2}$ = 3.4 Hz, H-1); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{16}H_{24}O_8$ (M^+ + H) 345.1549, found 345.1542.

1,6-Dihydro-2-amino-9-(3′,6′-anhydro-5′-deoxy-6′(*R*)- and 1,6-Dihydro-2-amino-9-(3′,6′-anhydro-5′-deoxy-6′(*S*)-carboxy-6′-(carboxymethyl)-β-D-glucofuranosyl)-6-hydroxypurine (5b and 5a). Compound **22a** (0.3 g, 0.9 mmol) and **22b** (0.5 g, 1.5 mmol) both were guaninylated using general procedure to give **24a** (a solid, 0.3 g, 65%) and **24b** (a solid, 0.55 g, 72%). For compound **24b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 and 2.30 (6 H, 2s, $OCOCH_3$ and $HNCOCH_3$), 2.55 (1 H, dd, $J_{5',5''}$ = 14.0, $J_{4',5'}$ = 4.0 Hz, H-5′), 2.78 (1 H, d, $J_{5',5''}$ = 14.0 Hz, H-5″), 2.85 and 3.02 (2 H, AB, $J_{A,B}$ = 15.0 Hz, CH_2COOEt), 4.85 (1 H, bd, $J_{3',4'}$ = 4.0 Hz, H-3′), 4.95 (1 H, t, $J_{3',4'}$ = 4.0, $J_{4',5'}$ = 4.0 Hz, H-4′), 5.80 (1 H, d, $J_{1',2'}$ = 5.0 Hz, H-2′), 6.05 (1 H, d, $J_{1',2'}$ = 5.0 Hz, H-1′), 8.10 (1 H, s, H-8); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{22}H_{27}N_5O_{10}$ (M^+ + H) 522.1836, found 522.1835. Compound **24a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 and 2.30 (6 H, 2s, $OCOCH_3$, $HNCOCH_3$), 2.40 (1 H, d, $J_{5',5''}$ = 16.0 Hz, H-5′), 2.50 (1 H, dd, $J_{5',5''}$ = 16.0, $J_{4',5''}$ = 5.2 Hz, H-5″), 3.27 and 3.40 (2 H, AB, $J_{A,B}$ = 15.0 Hz, CH_2COOEt), 4.88 (1 H, dd. $J_{4',5''}$ = 5.2, $J_{3',4'}$ = 6.5 Hz, H-4′), 5.00 (1 H, dd, $J_{3',4'}$ = 6.5, $J_{1,3}$, = 1.9 Hz, H-3′); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{22}H_{27}N_5O_{10}$ (M^+ + H) 522.1836, found 522.1841. Hydrolysis of these compounds was done according to the general procedure to produce **5a** (a solid, 0.19 g, 87%) and **5b** (a solid, 0.34 g, 85%). For compound **5a**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.20 (1 H, d, $J_{5',5''}$ = 15.2 Hz, H-5′), 2.65 (1 H, dd, $J_{5',5''}$ = 15.2, $J_{4',5''}$ = 4.2 Hz, H-5″), 2.80 and 2.90 (2 H, AB, J_{AB} = 15.0 Hz, H-7′ and H-7″), 4.60 (1 H, m, H-4′), 4.72 (1 H, m, H-3′), 5.75 (1 H, d, $J_{1',2'}$ = 4.85 Hz, H-2′), 6.05 (1 H, d, $J_{1',2'}$ = 4.85 Hz, H-1′), 6.55 (2 H, bs, NH_2), 7.85 (1 H, s, H-8); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{14}H_{15}N_5O_8$ (M^+ + H) 382.0998, found 382.0986. Anal. Calcd for $C_{14}H_{15}N_5O_8$: C, 44.08; H, 3.97: N, 18.37. Found: C, 44.05; H, 3.93; N, 18.34. For compound **5b**: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.65 and 2.88 (2 H, AB, $J_{A,B}$ = 15.0 Hz, H-7′, H-7″), 4.73 (1 H, m, H-4′), 4.53 (1 H, bd, $J_{3',4'}$ = 4.4 Hz, H-3′), 5.50 (d, 1 H, $J_{1',2'}$ = 5.5 Hz, H-2′), 5.95 (1 H, d, $J_{1',2'}$ = 5.5 Hz, H-1′), 6.5 (2 H, bs, NH_2), 7.85 (1 H, s, H-8); HRMS (FAB, thioglycerol matrix) *m/z* calcd for $C_{14}H_{15}N_5O_8$ (M^+ + H) 382.0998, found 382.0992. Anal. Calcd for $C_{14}H_{15}N_5O_8$: C, 44.08; H, 3.97; N, 18.37. Found: C, 44.03; H, 3.92; N, 18.34.

Acknowledgment. We thank Dr. M. Czarniecki for his invaluable information and discussion and Dr. T. M. Chan for performing the NOE experiments.

Supplementary Material Available: Tables of crystallographic data, fractional atomic coordinates, thermal parameters, bond lengths, bond angles, and torsion angles for **15a** and proton NMR spectra for **4b**, **12**, **13**, **19**, **22a**, and **22b** (13 pages). Ordering information is given on any current masthead page.