JOC*Note*

Synthesis of Griseolic Acid Analogues: Regioselective α-Facial [1,2]-Migration in the Rhodium Acetate Catalyzed Reaction of D-Glucose Derived α-Diazo-β-keto Ester

Navnath P. Karche, Santosh M. Jachak, and Dilip D. Dhavale*

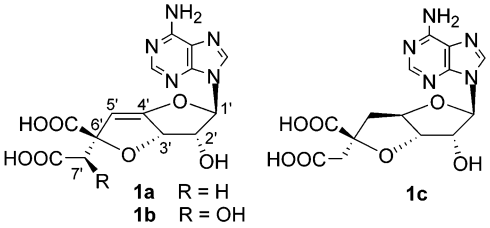
Department of Chemistry, Garware Research Centre, University of Pune, Pune-411 007, India

ddd@chem.unipune.ernet.in

Received December 17, 2002

Abstract: This paper describes an efficient route for the synthesis of known and novel griseolic acid analogues **1d** and **1e**, respectively. The key intermediate dioxabicyclo derivative **6**, with the required stereochemical orientation at C6, was obtained by rhodium acetate catalyzed reaction of D-*glucose* derived α-diazo-β-keto ester **5** in a novel high-yielding methodology.

In rhodium(II)-catalyzed oxonium-ylide formation reactions of α-diazo-β-keto esters, the product derived from either [2,3]-sigmatropic rearrangement or [1,2]-migration is routinely observed;[1] however, [1,4]-migration as a prominent process has been demonstrated by us only recently.[2] During this study, we have noticed an interesting observation that the reactions of D-*glucose* derived α-diazo-β-keto esters follow selective α-facial [1,2]-migration of the substituent along with the formation of a 1,5-dioxabicyclo[3.3.0]octane ring skeleton—the core structural component of griseolic acids. Griseolic acids A, B, and C (**1a**, **1b**, and **1c**), isolated from the cultural broths



of *Streptomyces griseoaurantiacus*,[3] have been shown to have inhibitory activity against cyclic nucleotide-phosphodiesterase and structural analogues of these compounds have been found to show greater activity and selectivity.[3,4]

The total synthesis of griseolic acid and analogues is restricted due to the stereochemical and structural challenges that include key steps such as preparation of a strained 1,5-dioxabicyclo[3.3.0]oct-3-ene ring system and the distereoselective formation of a quaternary carbon with −COOH and $-CH_2COOH$ substituents. In general, the known strategies first involve construction of the dioxabicyclic ring skeleton with −OR and −COOR groups and then the stereoselective introduction of two carbon acid units using carbanion chemistry.[5]Recently, Knapp and co-workers reported π-face-dependent radical cyclization to achieve the bicyclic system with required substituents at C6.[6] We thought of exploring the application of rhodium carbenoid chemistry toward the synthesis of griseolic acid analogues. In this direction, we have investigated the reaction of D-*glucose*-derived α-diazo-β-keto ester **5** with rhodium(II) acetate, which directly led to the key intermediate needed for the synthesis of griseolic acid analogues **1d** and **1e**.

Reaction of diacetone-D-*glucose* with ethyl bromoacetate in the presence of NaH in THF afforded 3-*O*-carbethoxymethylene-D-*glucose* derivative **2** (Scheme 1). Selective deprotection of the 5,6-*O*-isopropylidene group in **2** and sodium periodate oxidation gave 3-*O*-carbethoxymethylene-α-D-*xylo*-pentodialdo-1,4-furanose (**3**). Treatment of **3** with ethyl diazoacetate and BF_3-OEt_2 in dichloromethane afforded sugar β-keto ester **4**,[7] which on reaction with mesyl azide and triethylamine provided the α-diazo-β-keto ester **5**. The rhodium(II) acetate catalyzed reaction of **5** (benzene reflux) afforded **6** in which formation of the dioxabicyclic skeleton, with both substituents (−COOR and $-CH_2COOR$) in the required (*R*) absolute configuration at C6, was achieved in one step.

We assumed that the reaction involves generation of a rhodium carbenoid species **A** (Scheme 2) followed by a metal-bound five-membered oxonium ylide **B** as the first step. As the reaction proceeds, the migration of the $-CH_2COOEt$ group from oxygen to rhodium is completed, via the intermediacy of four-centered oxabicyclo[3.2.0]heptane transition state (TS) **C**, to afford TS **D**. Subsequently, the cleavage of the $Rh-CH_2COOEt$ bond followed by formation of a new carbon−carbon bond (between C6 and $-CH_2COOEt$) and rupture of the Rh−C6 bond with the loss of Rh(II) acetate in a three-membered TS **E**, by a concerted process, afforded [1,2]-rearranged product **6**.[2b]

(1) For general reviews of rhodium-carbenoids see: (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765−1795. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5402. (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1112. (d) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. (e) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (f) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145−3169.

(2) The selectivity in [1,2]- versus [1,4]-migration is controlled by the electronic factor associated with the migratory group, see: (a) Dhavale, D. D.; Desai, V. N.; Saha, N. N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 147−151. (b) Dhavale, D. D.; Karche, N. P.; Jachak, S. M. *J. Org. Chem.* **2001**, *66*, 6323−6332.

(3) Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. *J. Antibiot.* **1985**, *38*, 823−829.

(4) (a) Murofushi, Y.; Kimura, M.; Kuwano, H.; Iijima, H.; Yamazaji, M.; Kaneko, M. *Chem. Pharm Bull.* **1988**, *36*, 3760−3763. (b) Miyakoshi, S.; Haruyama, H.; Shioiri, T.; Takahashi, S.; Torikata, A.; Yamazaki, M. *J. Antibiot.* **1992**, *45*, 395−399. (c) Kaneko, M.; Kimura, M.; Murofushi, Y.; Yasumoto, T.; Iijima, Y.; Yamazaki, M. *Nucleosides Nucleotides* **1992**, *11*, 865−887. (d) Pickering, L.; Nair, V. *Nucleosides Nucleotides* **1996**, *15*, 1751−1769.

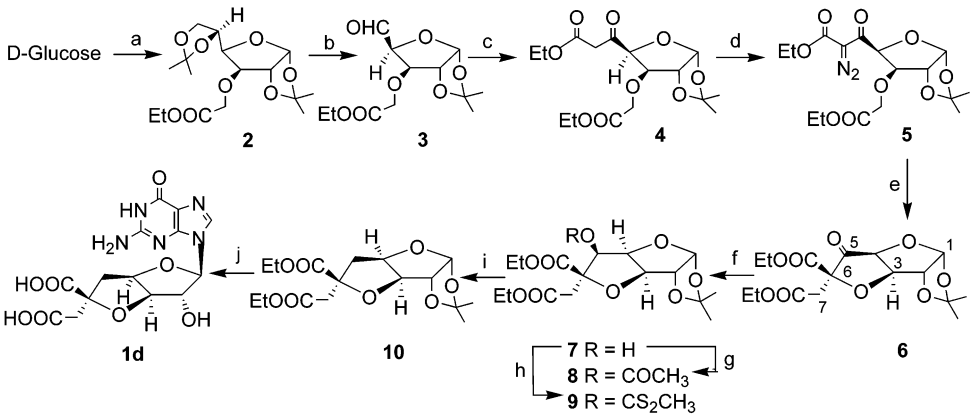
(5) (a) Tulshian, D.; Doll, R. J.; Stansberry, M. F. *J. Org. Chem.* **1991**, *56*, 6819−6822. (b) Tulshian, D.; Czarniecki, M.; Doll, R. J.; Ahn, H. S. *J. Med. Chem.* **1993**, *36*, 1210−1220. (c) Tulshian, D. B.; Czarniecki, M. *J. Am. Chem. Soc.* **1995**, *117*, 7009−7010. (d) Pickering, L.; Nair, V. *Nucleosides Nucleotides* **1997**, *16*, 1435−1438.

(6) Knapp, S.; Madduru, M. R.; Lu, Z.; Morriello, G. J.; Emge, T. J.; Doss, G. A. *Org. Lett.* **2001**, *3*, 3583−3585.

(7) Dhavale, D.; Bhujbal, N.; Joshi, P.; Desai, S. *Carbohydr. Res.* **1994**, *263*, 303−307.

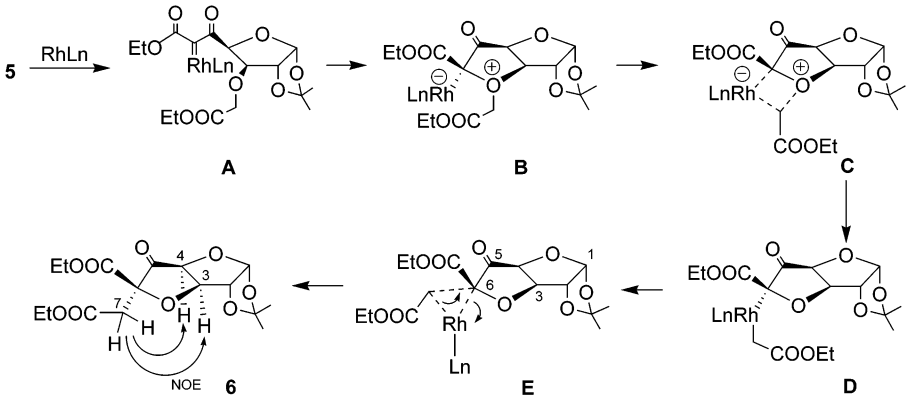
10.1021/jo026858j CCC: $25.00
Published on Web 04/24/2003

SCHEME 1. Synthesis of 1d[a]



[a] Reagents and conditions: (a) [i] Acetone, I_2 (0.2 equiv), 25 °C, 6 h, 72%; [ii] NaH (1.5 equiv), $BrCH_2COOEt$ (1.2 equiv), TBAI (0.03 equiv), THF, 25 °C, 12 h, 78%. (b) [i] 10% H_2SO_4, EtOH, 25 °C, 6 h, 89%; [ii] $NaIO_4$ (1.5 equiv), acetone, H_2O, 0 °C, 2 h, 86%. (c) Ethyl diazoacetate (1.5 equiv), BF_3-etherate (0.6 equiv), CH_2Cl_2, 0 °C, 2 h, 76%. (d) MsN_3 (1.1 equiv), Et_3N (2.0 equiv), CH_3CN, 25 °C, 2.5 h, 83%. (e) $Rh_2(OAc)_4$ (0.002 equiv), C_6H_6, 80 °C, 10 min, 74%. (f) $NaBH_4$ (0.5 equiv), CH_3OH, 0 °C, 2 h, 89%. (g) Pyridine (19.0 equiv), $(CH_3CO)_2O$ (10.0 equiv), DMAP (0.05 equiv), 25 °C, 12 h, 94%. (h) NaH (1.5 equiv), CS_2 (8.0 equiv), imidazole (0.005 equiv), CH_3I (1.8 equiv), THF, 25 °C, 1 h, 86%. (i) nBu_3SnH (2.2 equiv), AIBN (0.05 equiv), toluene, 110 °C, 4 h, 69%. (j) Reference 5a.

SCHEME 2. Mechanism for the Formulation of 6



The absolute configuration at the newly generated stereocenter C6 was established by NOEDIF studies wherein irradiation of C7 methylene protons showed NOE with H3 and H4 ring protons. This requires the $-CH_2COOEt$ group to have a cis relationship with H3 and H4 resulting in (*R*) absolute configuration at C6. In the subsequent step, sodium borohydride reduction of the keto group in **6** afforded only D-*gluco*-isomer **7** wherein the addition of hydride has taken place from the lower face of **6** (*Re* face attack at the carbonyl group). Acylation of **7** with acetic anhydride/pyridine produced **8** in almost quantitative yields. The relative configuration at C5 in **8** was established by NOEDIF studies which revealed an NOE between H5 and H4 and one of the H7 protons (methylene protons) thus indicating β-orientation of the $-OAc$ group at C5 and confirming D-*gluco*-configuration for **8**. Therefore, (*S*) absolute configuration was assigned at C5 in **7** and **8**.

Protection of the $-OH$ group in **7** with carbon disulfide and methyl iodide in the presence of NaH gave the *S*-methyl dithiocarbonate **9**. Reduction of the dithiocarbonate group in **9** with tributyltin hydride and AIBN afforded the reduced product **10**. The ^1H NMR spectrum of **10** was found to be in consonance with that reported.[5a] The conversion of **10** to griseolic acid analogue **1d**, via deprotection of the 1,2-acetonide group followed by guaninylation, is reported. Therefore, our route constitutes the formal synthesis of **1d**. In an attempt to synthesize a new analogue of griseolic acid **1e**, the acetyl derivative **8** was subjected to acetolysis ($AcOH-Ac_2O$ and catalytic H_2SO_4) to afford triacetate derivative **11** as an anomeric mixture. Vorbrüggen glycosylation with bis-(trimethylsilyl)-N^6-benzoyladenine and *tert*-butyldimethylsilyl triflate in refluxing acetonitrile afforded **12**.[8] Deprotection of **12** with 1 N NaOH−ethanol gave griseolic acid analogue **1e** (Scheme 3).

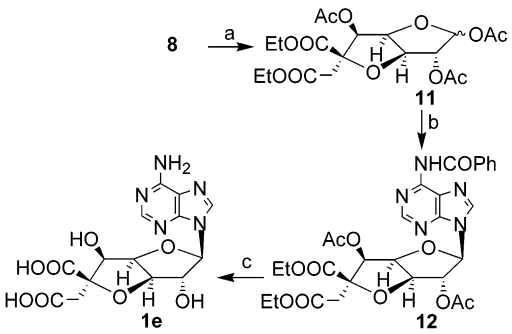
In summary, we have demonstrated the applicability of rhodium carbenoid chemistry in the formation of the otherwise difficult to obtain oxa-bicyclo ring system and providing the α-facial selectivity in a [1,2]-migration that allows a novel approach to access griseolic acid analogues.

Experimental Section

General. Melting points were recorded with melting point apparatus and are uncorrected. IR spectra were recorded with an FTIR spectrophotometer as a thin film or in Nujol mull

(8) Vorbrüggen, H.; Ruh-polenz, C. *Org. React.* **2000**, *55*, 1−630. In this reaction, small amounts (<10%) of unwanted anomeric α-nucleoside and *N*-7 alkylated product were also formed. An analogous observation was also noticed by others.[4a,5c]

SCHEME 3. Synthesis of 1e[a]



[a] Reagents and conditions: (a) CH_3COOH, $(CH_3CO)_2O$, CH_2Cl_2, H_2SO_4 (0.01 equiv), 25 °C, 4 h, 74%. (b) Bis(trimethysilyl)-*N*-benzoyladenine (1.5 equiv), TBDMSOTf (1.5 equiv), CH_3CN, 75 °C, 3 h, 73%. (c) 1 N NaOH (8.0 equiv) in aq EtOH, 25 °C, 24 h, 63%.

(expressed in cm^{-1}). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ as a solvent unless otherwise noted. NMR chemical shifts are reported in δ (ppm) downfield from TMS. Elemental analyses were carried out with an elemental analyzer. Optical rotations were measured with a polarimeter, using sodium light (D line 589.3 nm) at 25 °C. TLC was performed on precoated plates (0.25 mm, silica gel 60 F_{254}). Flash chromatography was performed on 200−400-mesh silica gel and column chromatography was carried out with 100−200-mesh silica gel. The reactions were carried out in oven-dried glassware under dry N_2. Acetonitrile, benzene, dichloromethane, and THF were purified and dried before use. Petroleum ether (PE) is a distillation fraction between 40 and 60 °C. Rhodium acetate dimer was purchased from Aldrich and was activated by heating at 100 °C under reduced pressure (3 mm of Hg) for 3 h prior to use. After workup, the organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated at reduced pressure.

3-*O*-Carbethoxymethylene-1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (2). To a 0 °C cooled solution of 1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-1,4-furanose (1000 mg, 3.85 mmol) in dry THF was added NaH (230 mg, 5.77 mmol) and the reaction mixture was allowed to attain room temperature and stirred for 6 h. Ethyl bromoacetate (0.51 mL, 4.62 mmol) in THF was added dropwise followed by addition of TBAI (45 mg, 0.12 mmol). The reaction mixture was stirred for an additional 12 h. Workup and purification by column chromatography (PE/ethyl acetate 9.5:0.5) afforded **2** as a white solid: mp 65−67 °C (1038 mg, 78% yield); R_f 0.46 (40% EtOAc in hexanes); $[\alpha]_D$ −48.00 (*c* 0.30, $CHCl_3$); IR (Nujol) 1749, 1160, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, J = 3.6 Hz, 1H), 4.70 (d, J = 3.6 Hz, 1H), 4.32 (t, J = 4.2 Hz, 1H), 4.22 (s, 2H), 4.20 (m, 2H), 4.12 (m, 2H), 4.09 (m, 2H), 1.48 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.28 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 111.7, 108.9, 105.0, 83.5, 83.1, 80.9, 72.5, 68.3, 67.1, 61.0, 26.8 (strong), 26.2, 25.4, 14.2. Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.46; H, 7.56. Found: C, 55.58; H, 7.37.

3-*O*-Carbethoxymethylene-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (3). A solution of **2** (1000 mg, 2.88 mmol) in 10% H_2SO_4 (5 mL) in ethanol (15 mL) was stirred at 25 °C for 6 h. The reaction mixture was neutralized with a saturated solution of potassium carbonate, ethanol was evaporated, and residue was extracted with chloroform. Purification by column chromatography (PE/ethyl acetate 6.5:3.5) gave diol as a thick oil (776 mg, 89% yield). The diol (700 mg, 2.31 mmol) was treated with sodium metaperiodate (744 mg, 3.46 mmol) in acetone−water (7:3, 10 mL) at 0 °C. After 2 h, ethylene glycol (0.5 mL) was added, acetone was evaporated, and the residue was extracted with $CHCl_3$ (3 × 20 mL). Purification by column chromatography (PE/ethyl acetate 9:1) afforded **3** as a thick oil (546 mg, 86% yield); R_f 0.36 (40% EtOAc in hexanes); $[\alpha]_D$ −32.00 (*c* 0.50, $CHCl_3$); IR (neat) 1735, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 6.11 (d, J = 3.6 Hz, 1H), 4.74 (d, J = 3.6 Hz, 1H), 4.61 (d, J = 3.6 Hz, 1H), 4.35 (d, J = 3.6 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.10 (s, 2H), 1,48 (s, 3H), 1.34 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 169.4, 112.6, 105.9, 85.1, 84.5, 82.6, 67.8, 61.3, 27.0, 26.4, 14.2. Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.52; H, 6.61. Found: C, 52.76; H, 6.36.

Ethyl 6-Deoxy-1,2-*O*-isopropylidene-3-*O*-carbethoxymethylene-α-D-*xylo*-hept-5-ulo-1,4-furanuronate (4). To a 0 °C cooled solution of **3** (500 mg, 1.82 mmol) and ethyl diazoacetate (0.29 mL, 2.73 mmol) in dry CH_2Cl_2 (15 mL) under N_2 was added dropwise BF_3−etherate (0.10 mL, 1.08 mmol) in dry CH_2Cl_2 (2 mL) with control of the evolution of N_2 (20 min). The mixture was stirred at 0 °C for 2 h and quenched with a saturated solution of sodium bicarbonate (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). After workup, the residue thus obtained was purified with column chromatography (PE/ethyl acetate 9:1) to give **4** as thick oil (498 mg, 76% yield); R_f 0.41 (40% EtOAc in hexanes); $[\alpha]_D$ −52.00 (*c* 0.50, $CHCl_3$); IR (neat) 1747, 1733, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 3.6 Hz, 1H), 4.74 (d, J = 3.5 Hz, 1H), 4.28 (d, J = 3.5 Hz, 1H), 4.26−4.14 (m, 4H), 4.10 (AB quartet, J = 12.3 Hz, 2H), 3.70 (AB quartet, J = 16.2 Hz, 2H), 1.47 (s, 3H), 1.33 (s, 3H), 1.32−1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 169.6, 167.0, 112.5, 105.8, 85.3, 84.9, 82.4, 68.2, 61.1 (strong), 47.3, 26.9, 26.3, 14.1, 14.0. Anal. Calcd for $C_{16}H_{24}O_9$: C, 53.30; H, 6.71. Found: C, 53.16; H, 6.76. (The ^1H and ^{13}C NMR spectrum showed ∼5% enol contribution.)

Ethyl 6-Deoxy-6-diazo-1,2-*O*-isopropylidene-3-*O*-carbethoxymethylene-α-D-*xylo*-hept-5-ulo-1,4-furanuronate (5). To a stirred solution of β-keto ester **4** (300 mg, 0.83 mmol) in dry acetonitrile (30 mL) was added methanesulfonyl azide (111 mg, 0.91 mmol) and triethylamine (0.23 mL, 1.65 mmol). The reaction mixture was stirred at room temperature for 2.5 h and quenched with aqueous 2 N NaOH (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layer after workup and purification by column chromatography (PE/ethyl acetate 8.5:1.5) afforded **5** as a pale yellow solid; mp 106−108 °C (266 mg, 83% yield); R_f 0.38 (40% EtOAc in hexanes); $[\alpha]_D$ +15.64 (*c* 0.20, $CHCl_3$); IR (Nujol) 2150, 1751, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, J = 3.6 Hz, 1H), 5.54 (d, J = 3.6 Hz, 1H), 4.65 (d, J = 3.5 Hz, 1H), 4.53 (d, J = 3.5 Hz, 1H), 4.39−4.28 (m, 2H), 4.27−3.90 (m, 4H), 1.51 (s, 3H), 1.34 (s, 3H), 1.32−1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 169.3, 161.3, 112.5, 105.3, 83.9, 83.3, 82.3, 77.3, 66.8, 61.5, 60.9, 27.0, 26.5, 14.2, 14.1. Anal. Calcd for $C_{16}H_{22}N_2O_9$: C, 49.72; H, 5.74. Found: C, 49.96; H, 5.56.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-oct-5-ulo-1,4 -furanuronate (6). A solution of **5** (250 mg, 0.65 mmol) and rhodium(II) acetate (3 mg, 0.013 mmol) in benzene (10 mL) was refluxed for 10 min under N_2. On cooling, the reaction mixture was directly loaded on a silica gel (100−200 mesh) column and eluted (PE/ethyl acetate 9:1) to afford **6** as an oil (172 mg, 74% yield); R_f 0.43 (40% EtOAc in hexanes); $[\alpha]_D$ +32.63 (*c* 0.25, $CHCl_3$); IR (neat) 1778, 1747, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, J = 3.6 Hz, 1H), 4.97 (d, J = 3.6 Hz, 1H), 4.90 (d, J = 3.9 Hz, 1H), 4.83 (d, J = 3.9 Hz, 1H), 4.28−4.18 (m, 2H), 4.14 (q, J = 7.5 Hz, 2H), 3.49−2.98 (AB quartet, J = 18.0 Hz, 2H), 1.50 (s, 3H), 1.38 (s, 3H), 1.33−1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 170.2, 166.8, 113.4, 107.9, 85.7, 84.9, 83.5, 79.8, 62.8, 61.6, 41.7, 27.6, 26.9, 14.0, 13.9. Anal. Calcd for $C_{16}H_{22}O_9$: C, 53.60; H, 6.19. Found: C, 53.46; H, 6.36.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-oct-1,4-furanuronate (7). To a cooled solution of **6** (500 mg, 1.40 mmol) in methanol (20 mL) was added sodium borohydride (28 mg, 0.70 mmol) and the reaction mixture was stirred at 0 °C. After 2 h 1 N HCl (3 mL) was added, methanol was evaporated, and the residue was extracted with ethyl acetate (10 mL × 3). Workup and purification by column chromatography (PE/ethyl acetate 8:2) gave **7** as a white solid; mp 68 °C (445 mg, 89% yield); R_f 0.33 (40% EtOAc in hexanes); $[\alpha]_D$ =+30.26 (*c* 0.40, $CHCl_3$); IR (Nujol) 3468, 1746, 1720 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (d, J = 3.6 Hz, 1H), 4.92 (d, J = 4.2 Hz, 1H), 4.81 (t, J = 4.2 Hz, 1H), 4.64 (d, J = 3.6 Hz, 1H), 4.30 (d, J = 4.2 Hz, 1H), 4.28−4.20 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.10 (d, J = 16.0 Hz, 1H), 2.71 (d, J = 16.0 Hz, 1H), 1.75−1.60 (br, 1H, exchanges with D_2O), 1.47 (s, 3H), 1.33−1.22 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 169.0 113.4, 107.9, 85.7, 84.9, 84.5, 83.5, 79.8, 62.8, 61.6, 41.7, 27.6, 26.9, 14.0, 13.9. Anal. Calcd for $C_{16}H_{24}O_9$: C, 53.30; H, 6.71. Found: C, 53.66; H, 6.36.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7-deoxy-1,2-*O*-isopropylidene-5-*O*-acetoxy-α-D-*gluco*-oct-1,4-furanuronate (8). To a stirred solution of **7** (300 mg, 0.83 mmol) in pyridine (1.3 mL, 15.7 mmol) at 0 °C was added acetic anhydride (0.78 mL, 8.3 mmol) and DMAP (5 mg, 0.04 mmol). The reaction mixture was allowed to attain room temperature. After 12 h ethyl acetate (10 mL) was added and the organic layer separated and worked up. Evaporation of solvent and purification by column chromatography (PE/ethyl acetate 8.5:1.5) afforded **8** as thick oil (314 mg, 94% yield); R_f 0.42 (40% EtOAc in hexanes); $[\alpha]_D$ +8.60 (*c* 0.30, $CHCl_3$); IR (neat) 1747, 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, J = 3.5 Hz, 1H), 5.42 (d, J = 4.4 Hz, 1H), 4.93 (m, 2H), 4.73 (d, J = 3.7 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.20−2.77 (AB quartet, J = 16.5 Hz, 2H), 2.12 (s,3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1,0.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 169.4, 169.2, 112.3, 107.8, 86.2, 84.9, 83.9, 80.9, 77.3, 61.7, 60.9, 42.2, 27.4, 26.8, 20.7, 14.3, 14.2. Anal. Calcd for $C_{18}H_{26}O_{10}$: C, 53.70; H, 6.51. Found: C, 53.46; H, 6.76.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7-deoxy-1,2-*O*-isopropylidene-5-*O*-(*S*-methyldithiocarbonate)-α-D-*gluco*-oct-1,4-furanuronate (9). To a solution of **7** (100 mg, 0.28 mmol) in dry THF was added NaH (17 mg, 0.42 mmol) and imidazole (1 mg, 0.0056 mmol) and the reaction mixture was stirred for 1 h at room temperature. Carbon disulfide (0.13 mL, 2.24 mmol) was added, the solution was stirred 1 h, and then methyl iodide (0.03 mL, 0.50 mmol) was added. After an additional 20 min of stirring dichloromethane (40 mL) was added and the organic layer was worked up. Purification by column chromatography (PE/ethyl acetate 9.5:0.5) gave **9** as a thick oil (109 mg, 86% yield); R_f 0.40 (40% EtOAc in hexanes); $[\alpha]_D$ +21.17 (*c* 0.15, $CHCl_3$); IR (neat) 1745, 1723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J = 4.5 Hz, 1H), 6.03 (d, J = 4.2 Hz, 1H), 5.08 (t, J = 4.2, 3.9 Hz, 1H), 4.96 (d, J = 3.9 Hz, 1H), 4.78 (d, J = 4.5 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.18 (d, J = 16.2 Hz, 1H), 2.83 (d, J = 16.2 Hz, 1H), 2.57 (s, 3H), 1.46 (s, 3H), 1.33−1.22 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 169.2, 169.1, 112.4, 108.1, 86.9, 86.3, 83.9, 83.4, 83.2, 61.8, 60.9, 41.8, 27.4, 27.1, 26.8, 14.2, 13.9. Anal. Calcd for $C_{18}H_{26}S_2O_9$: C, 46.54; H, 5.97. Found: C, 46.26; H, 5.56.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7,5-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-oct-1,4-furanuronate (10). A solution of **9** (100 mg, 0.22 mmol) in dry toluene (5 mL) was added to a refluxing solution of tributyltin hydride (69 mg, 0.48 mmol) and AIBN (2 mg, 0.011 mmol) in toluene under N_2. The solution was refluxed for 4 h, toluene was evaporated, and residue was dissolved in ethyl acetate (30 mL). Workup and purification by column chromatography (PE/ethyl acetate 8.5:1.5) afforded **10** as a thick oil (52 mg, 69% yield); R_f 0.38 (40% EtOAc in hexanes); $[\alpha]_D$ +15.60 (*c* 0.65, $CHCl_3$); IR (neat) 1742 1729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 3.9 Hz, 1H), 4.92−4.88 (m, 2H), 4.63 (d, J = 3.9 Hz, 1H), 4.28−4.08 (m, 4H), 2.97 (d, J = 15.3 Hz, 1H), 2.68 (d, J = 14.1 Hz, 1H), 2.64 (d, J = 15.3 Hz, 1H), 2.22 (dd, J = 14.1, 4.2 Hz, 1H), 1.45 (s, 3H), 1.30 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 168.9, 111.5, 106.9, 89.0, 84.8, 84.5, 82.8, 61.4, 60.8, 42.8, 42.3, 27.2, 26.6,14.2 (strong). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.78; H, 7.02. Found: C, 55.96; H, 6.76.

Ethyl 3,6-Anhydro-6-(*R*)-carbethoxy-7-deoxy-1,2,5-*O*-triacetoxy-α- and *β*-D-*gluco*-oct-1,4-furanuronate (11). To a stirred solution of compound **8** (250 mg, 0.62 mmol) in dichlorometane (20 mL) at 0 °C was added a mixture of acetic acid and acetic anhydride (1:1.5, 20 mL) and H_2SO_4 (0.01 mL). The reaction mixture was allowed to attain room temperature. After 4 h, dichloromethane (100 mL) was added. The organic layer on workup and evaporation of solvent afforded **11** as an anomeric mixture. Separation by column chromatography (PE/ethyl acetate 8:2) gave α-anomer as thick oil (164 mg; 59% yield); R_f 0.38 (40% EtOAc in hexanes); IR (neat) 1751, 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (d, J = 4.8 Hz, 1H), 5.63 (dd, J = 4.8 and 2.4 Hz, 1H), 5.41 (d, J = 5.1 Hz, 1H), 4.98 (t, J = 5.1 Hz, 1H), 4.92 (dd, J = 5.1 and 2.4 Hz, 1H), 4.28−420 (dq, J = 7.2 and 3.0 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.14 (d, J = 16.0 Hz, 1H), 2.79 (d, J = 16.0 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.22. (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.2, 169.1, 169.0, 168.7, 96.4, 85.7, 85.6, 79.6, 77.6, 76.0, 61.8, 60.8, 41.5, 20.7, 20.4, 20.2, 14.0, 13.9. Anal. Calcd for $C_{19}H_{26}O_{12}$: C, 51.09; H, 5.87. Found: C, 51.26; H, 5.76. Further elution gave a mixture of α- and *β*-anomer (41 mg, 15% yield).

Ethyl 1,7-Dideoxy-6-*c*-carbethoxy-3,6-anhydro-1-(6-*N*-benzoyl-amino-9-*H*-purin-9-yl)-2,5-diacetoxy-α-D-*gluco*-oct-1,4-furanuronate (12). To a stirred solution of **11** (100 mg, 0.23 mmol) in acetonitrile (5 mL) was added bis(trimethylsilyl)-*N*-benzoyladenine (130 mg, 0.345 mmol) followed by *tert*-butyl dimethylsilyl triflate (0.05 mL, 0.345 mmol) and the reaction mixture was refluxed. After 3 h, ethyl acetate was added and the organic layer was washed with a cold solution of $NaHCO_3$ and evaporated. The crude product was purified by column chromatography (PE/ethyl acetate 5:4) to give **12** as a semisolid (102 mg, 73% yield); R_f 0.45 (80% EtOAc in hexane); $[\alpha]_D$ +77.80 (*c* 0.65, $CHCl_3$); IR (neat) 3346, 1745, 1610, 1587; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 8.79 (s, 1H), 8.01 (s, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 2H), 6.95 (d, J = 5.1 Hz, 1H), 5.83 (dd, J = 5.1 and 1.2 Hz, 1H), 5.58 (d, J = 5.7 Hz, 1H), 5.45 (dd, J = 5.7 and 4.5 Hz, 1H), 5.12 (dd, J = 4.5 and 1.2 Hz, 1H), 4.34 (dq, J = 6.9 and 2.5 Hz, 2H), 4.17 (q, J = 6.9 Hz, 2H), 3.21 (d, J = 16.8 Hz, 1H), 2.92 (d, J = 16.8 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.38 (t, J = 6.9 Hz, 3H), 1.28 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.3, 169.1, 169.0, 168.6, 152.7, 149.2, 142.4, 133.4, 132.7, 128.8 (strong), 127.7 (strong), 122.3, 86.4, 86.0, 85.8, 81.5, 77.3, 77.2, 62.2, 61.1, 41.5, 20.6, 20.2, 14.3, 14.2. Anal. Calcd for $C_{29}H_{31}N_5O_{11}$: C, 55.65; H, 4.99. Found: C, 55.76; H, 4.76.

1,7-Dideoxy-6-*c*-carboxy-3,6-anhydro-1-(6-amino-9-*H*-purin-9-yl)-α-D-*gluco*-oct-1,4-furanuronic Acid (1e). A solution of **12** (100 mg, 0.16 mmol) in ethanol−water (7:3, 2 mL) and NaOH (51 mg, 1.28 mmol) was stirred at room temperature. After 24 h, the reaction mixture was neutralized with 1 N HCl and the volume of the reaction mixture was reduced to half by evaporation at reduced pressure. The solution was loaded on a Chromabond C18 ec (Macherey-Nagel) column and eluted first with water to remove all inorganic salt and then with 10% acetone in water. Evaporation of solvent gave a semisolid that was repeatedly washed with chloroform (3 × 2 mL) to give **1e** as a solid (38 mg, 63% yield); mp 232−235 °C; $[\alpha]_D$ +32.30 (*c* 0.15, CH_3OH); IR (KBr) 3442, 1737, 1627 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.30 (s, 1H), 7.92 (s, 1H), 5.85 (d, J = 6.0 Hz, 1H), 4.83 (m, 2H), 4.22 (d, J = 5.1 Hz, 1H), 3.52 (s, 1H), 2.66−2.44. (AB quartet, J = 15.3 Hz, 2H); ^{13}C NMR (75 MHz, D_2O) δ 172.3, 172.2, 155.2, 152.4, 149.0, 140.8, 118.8, 89.6, 86.3, 81.7, 79.5, 76.0, 75.1, 42.6. Anal. Calcd for $C_{14}H_{15}N_5O_8$: C, 44.08; H, 3.96. Found: C, 44.32; H, 3.77.

Acknowledgment. We thank the Department of Science and Technology (SP/S1/G-23/2000) and the University Grants Commission for financial support and for procuring the high field NMR facility.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of all new compounds **2**−**12** and **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026858J