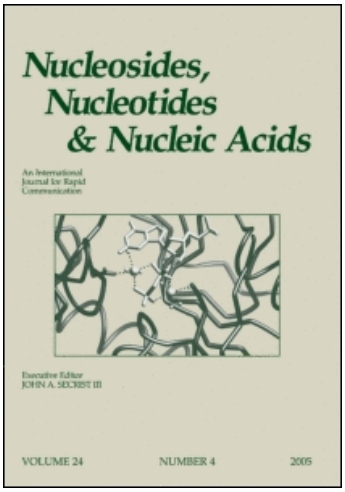

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Synthesis of Chiral 1',2'-SECO-Nucleosides OF Guanine AND Uracil

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SYNTHESIS OF CHIRAL 1',2'-SECO-NUCLEOSIDES OF GUANINE AND URACIL

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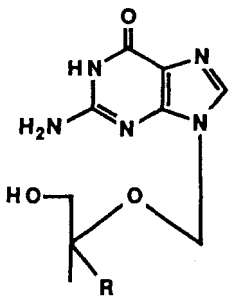
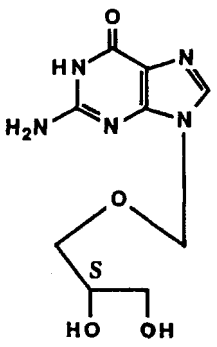
Abstract: 2R-Chloromethoxy-1,3S-dibenzyloxybutane (6a) and 2R-chloro methoxy-1,3S,4-tribenzyloxybutane (6b) chirons readily available from D-isoascorbic acid, were used in the preparation of 1',2'-seco-nucleosides of uracil and guanine.

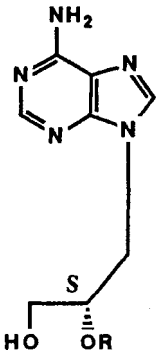
Since the discovery of acyclovir (1) as an antiviral agent[1], interest in the preparation of other acyclic nucleosides has steadily increased resulting in the synthesis of a large number of analogs.[2,3] One of these, i.e., 9-(dihydroxypropoxymethyl)guanine (DHPG, 2), has emerged as a potent antiviral.[4] For the most part, these compounds were either achiral or racemic.[2,5] The importance of chirality to antiviral activity was clearly demonstrated with certain optically



1 : R = H
2 : R = CH_2OH



3



4 : R = H
5 : R = $CH_2PO(OH)_2$

active adenine and guanine analogs where only one enantiomer proved to be active. Among these are iso-NDG (3)[6], S-DHPA (4)[7], and most recently 9-(3-hydroxy-2S-phosphonylmethoxypropyl)adenine (S-HPMPA, 5).[8]

As the carbon framework of the acyclic side chain approaches that of the naturally occurring pentoses, the number of chiral centers increases, and the preparation of optically pure isomers becomes more difficult. 1',2'-seco-Nucleosides have two chiral centers and, to the best of our knowledge, only one report has appeared in the literature which described in detail the synthesis of all four isomers of 1',2'-seco-guanosine.[9,10]

We have recently reported a practical method to prepare chiral, selectively protected butanetriols and butanetetrols from D-isoascorbic acid.[11] These chirons have now been chloromethylated[12] and used to synthesize 1',2'-seco-nucleosides of uracil and guanine, which is the subject of this paper.

The target acyclonucleosides 8a, 8b, 12a, and 12b were obtained as illustrated in Scheme 1. Reaction of the chloromethyl ethers (6a or 6b) with persilylated uracil in dichloromethane and in the presence of a catalytic amount of tetraethylammonium iodide afforded the corresponding blocked analogs of 1',2'-seco-uridine 7a and 7b. In each case, a small amount of the N3-isomer was isolated. Debenzylation of the acyclic side chain was accomplished by transfer hydrogenation over Pearlman's catalyst[13] to provide 8a and 8b, respectively.

For the preparation of the 1',2'-seco-guanosines (12a and 12b) two pathways were used. The route employed for the synthesis of 1',2'-seco-guanosine (12b) involved direct alkylation of the sodium salt of 2-amino-6-benzyloxypurine[9b] with 6b. The blocked intermediate 9 was obtained in 33% yield. Subsequent deprotection of 9 by transfer hydrogenation furnished 12b. This reaction was monitored by tlc and it was found that debenzylation of the purine moiety occurred first[14] followed by the three benzyl groups on the acyclic side chain.

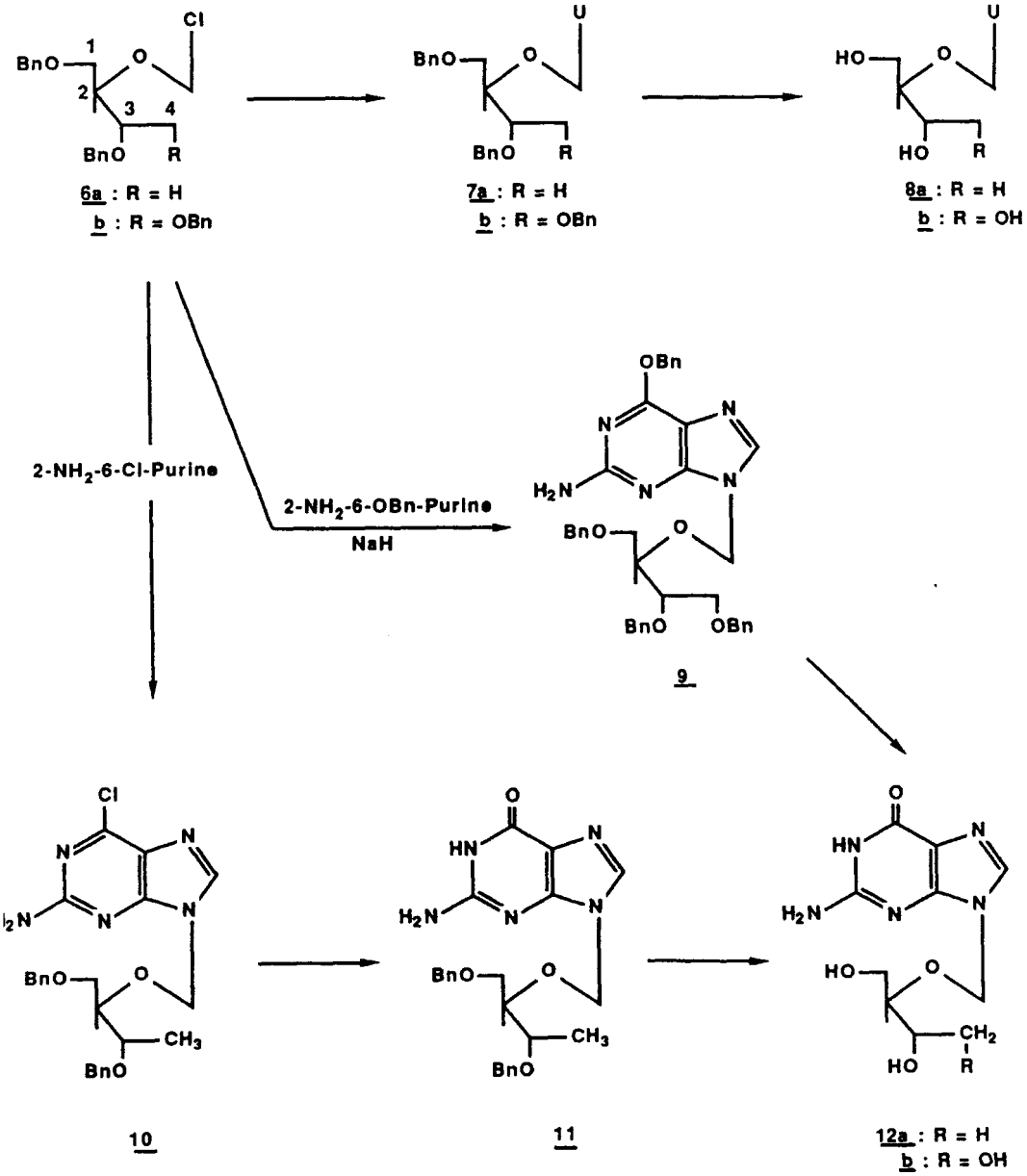
The other pathway, which was employed to prepared 2'-deoxy-1',2'-seco-guanosine (12a), used the silyl-alkylation procedure. Silylated 2-amino-6-chloropurine was reacted with the chloromethyl ether 6a to provide 10 (65%) and a small amount of the N7-isomer (5%).

Conversion of the 6-chloro group to the oxo function followed by deprotection provided 12a. Starting with 2-amino-6-chloropurine, the overall yield of this pathway was 40%. It is worth mentioning that mixtures of the N7 and N9-acyclo-2-amino-6-chloropurines, e.g., 10 and its N7-isomer, could be rearranged exclusively to the N9-isomer by Ogilvie's method.[15] The site of alkylation of the target 1',2'-seco-nucleosides prepared in this study was determined by UV-spectroscopy and in the case of the guanosines also by ^{1}H NMR spectroscopy.[16]

Experimental

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton spectra were obtained on a Varian EM-390 spectrometer. Chemical shifts are in parts per million with respect to TMS. Optical rotations were obtained with a Perkin-Elmer Model 141 digital readout polarimeter. Silica gel (60-140 mesh) suitable for chromatographic use was purchased from Aldrich Chemical Company. Thin layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

1-[(1,3S-Dibenzyloxy-2R-butoxy)methyl]uracil (7a). Uracil (2.5 g, 0.022 mol) and 0.82 g of ammonium sulfate were added to 70 mL of HMDS. The mixture was stirred and heated at reflux overnight with the exclusion of moisture. The excess HMDS was then removed under reduced pressure and the residue was dried under high vacuum. A solution of 6a[12] (9.02 g, 82.7% pure, 0.022 mol) in 100 mL of dry dichloromethane and 30 mg of tetraethylammonium iodide were added to the persilylated uracil and stirred at reflux for 4.5 h. The reaction mixture was diluted with 68 mL of water and 27 mL of methanol, stirred for 2 min, evaporated to dryness and the residue was dissolved in 100 mL of dichloromethane. The organic layer was washed successively with 40 mL of saturated sodium chloride solution and 40 mL of water, and then dried over anhydrous $MgSO_4$. The viscous material (11.08 g), obtained after removing the solvent, was chromatographed on a silica gel (200 g)



Bn = Benzyl, U = Uracil

Scheme 1

column. Elution with hexane-EtOAc (6:4) gave 5.36 g (58.6%, yield based on uracil) of pure 7a, as a gum, and 0.64 g (7%) of the N3-isomer. Physical constants of 7a are: $[\alpha]_D$ = +3.73 (c = 0.885, EtOH); ^{1}H nmr ($CDCl_3$),δ1.15 (d, J = 6 Hz, 3, CH_3), 3.38-4.12 (m, 4), 4.32-4.68 (m, 4, $CH_2C_6H_5$), 5.22 (s, 2 OCH_2N), 5.54 (d, J = 7.5 Hz, 1, C(5)H), 7.25 (br s, 11, $CH_2C_6H_5$ and C(6)H), 9.35 (br s, 1, NH, D_2O exchangeable).

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.31; H, 6.38; N, 6.83. Found: C, 67.17; H, 6.33; N, 6.80.

1-[(1,3S,4-Tribenzyloxy-2R-butoxy)methyl]uracil (7b). Compound 7b was prepared in the same manner as 7a. To the persilylated uracil (obtained from 2.27 g (0.02 mol) of uracil) was added 8.91 g (81.1% pure, 0.016 mol) of the chloromethyl ether 6b in 75 mL of dry dichloromethane and 28 mg of tetraethylammonium iodide. This mixture was stirred and heated at reflux for 9 h and at room temperature for an additional 15 h. After work up and column chromatography, 10.5 g of crude material afforded 6.44 g (61.7%) of pure 7b, as a mobile syrup, and 1.00 g (10.4%, yields based on uracil) of the N3-isomer. Physical constants of 7b are: $[\alpha]_D$ = +1.49 (c = 2.55, EtOH); ^{1}H nmr ($CDCl_3$),δ 3.32-41.8 (m, 6), 4.33-6.73 (m, 6, $CH_2C_6H_5$), 5.17 (s, 2, OCH_2N), 5.5 (d, J = 9 Hz, 1, C(5)H), 7.12 (d, J = 9 Hz, 1, C(6)H), 7.25 (br s, 15, $CH_2C_6H_5$), 9.4 (br s, 1, NH, D_2O exchangeable).

Anal. Calcd. for $C_{30}H_{32}N_2O_6$: C, 69.76; H, 6.24; N, 5.42. Found: C, 69.85; H, 6.31; N, 5.43.

1-[(1,3S-Dihydroxy-2R-butoxymethyl]uracil (8a). Compound 7a (2.85 g, 6.96 mmol) was dissolved in absolute ethanol (36 mL) and to this solution was added 20% $Pd(OH)_2/C$ (0.91 g) and cyclohexene (15.4 mL). The reaction mixture was stirred and heated at reflux for 32 h. After this time period, debenzylation was not complete (monitored by TLC) and additional amounts of 20% $Pd(OH)_2/C$ (0.46 g) and cyclohexene (15 mL) were added to the reaction mixture and heating continued for another 16 h. The reaction mixture was then filtered through celite and the filter cake washed with warm ethanol. The filtrate and wash were combined and concentrated under diminished pressure to furnish 8a (1.35 g, 85%) as a gum. Lypholization of this hygroscopic material furnished a foam: $[\alpha]_D$ = -4.13 (c = 1.21, EtOH); ^{1}H nmr (DMSO-d_6),δ0.98 (d, J =

6 Hz, 3, CH_3), 2.97-3.9 (m, 4), 4.27-4.92 (m, 2, OH, D_2O exchangeable), 5.23 (s, 2H, OCH_2N), 5.57 (d, J = 8 Hz, 1, C(5)H), 7.73 (d, J = 8 Hz, 1, C(6)H); UV λ_{max} (pH1) 259 nm (ε8,952); λ_{max} (water) 259 nm (ε 8,801); λ_{max} (pH11) 258 nm (ε6,190).

Anal. Calcd. for $C_9H_{14}N_2O_5 \cdot 0.25\ H_2O$: C, 46.05; H, 6.22; N, 11.93. Found: C, 46.15; H, 6.27; N, 11.96.

1-[1,3S,4-Trihydroxy-2R-butoxy)methyl]uracil (8b). Catalytic transfer hydrogenation of 7b (3.43 g, 6.65 mmol) in absolute ethanol (36 mL) was carried out, as described for 8a, in the presence of 20% $Pd(OH)_2/C$ (0.87 g) and cyclohexene (15 mL). The reaction mixture was stirred and heated at reflux for 13 h. The reaction was then filtered through celite and the residue was washed with warm ethanol. The filtrate was concentrated under diminished pressure to give a quantitative yield of pure 8b, as a gum. This hygroscopic gum was dissolved in a minimal amount of water and lypholized to afford 8b as a foam: $[\alpha]_D$ = -8.15 (c = 1.815, EtOH); ^1H nmr (DMSO-d_6), δ3.07-3.88 (m, 6), 4.18-4.87 (m, 3, OH, exchangeable with D_2O), 5.17 (s, 2, OCH_2N), 5.55 (d, J = 9 Hz, 1, C(5)H), 7.62 (d, J = 9 Hz, 1, C(6)H), 11.1 (br s, 1, NH, exchangeable with D_2O); UV λ_{max} (pH1) 260 nm (ε11,889); λ_{max} (water) 259 nm (ε6,745); λ_{max} (pH11) 258 nm (ε6,745).

Anal. Calcd. for $C_9H_{14}N_2O_6$: C, 43.91; H, 5.73; N, 11.38. Found: C, 44.10; H, 5.83; N, 11.17.

2-Amino-6-benzyloxy-9-[(1,3S,4-tribenzyloxy-2-butoxy)methyl]purine (9). Sodium hydride (0.5 g, 0.021 mol, prewashed with petroleum ether) was suspended in dry DMF (100 mL). To this stirred suspension was added dropwise 3.4 g (0.014 mol) of 2-amino-6-benzyloxypurine dissolved in 20 mL of dry DMF over a 15 min period. After stirring for an hour, the chloromethyl ether 6b (7.76 g, 90% pure, 0.016 mol) in 65 mL of dry DMF was added dropwise to this mixture. After stirring for 18 h, the reaction was concentrated to 100 mL and added to 800 mL of ice-water. The suspension was extracted with ethyl acetate. The aqueous solution was saturated with NaCl and extracted further with EtOAc until the extracts became colorless. The combined extract was backwashed with brine and then dried over anhydrous Na_2SO_4. The crude product, obtained after removing the solvent, was chromatographed on a silica

gel column using a solvent gradient of 10⟶50% EtOAc in hexane. Elution with 40⟶50% EtOAc in hexane gave 3.04 g (33.4%) of pure 9, as a crystalline solid. m.p. 92-94°C; $[\alpha]_D^{25}$ = -5.10 (c = 1.745, MeOH); ^{1}H nmr ($CDCl_3$), δ3.35-3.77 (m, 5H), 3.85-4.23 (m, 1H), 4.35 (s, 2H, OCH_2Ph), 4.4 (s, 2H, OCH_2PH), 4.45 (ABq, J = 12 Hz, 2H, OCH_2N), 4.9 (br s, 2H, NH_2), 5.48 and 5.5 (two s, 4H, OCH_2N, C(6)OCH_2Ph), 7.03-7.53 (m, 20H, C_6H_5), 7.58 (s, 1H, C(8)H).

Anal. Calcd. for $C_{38}H_{39}N_5O_5$: C, 70.68; H, 6.09; N, 10.84. Found: C, 70.73; H, 6.20; N, 10.75.

9-[(1,3S,4-Trihydroxy-2R-butoxy)methyl]guanine (12b). To a solution of 9 (2.57 g, 3.98 mmol) in absolute ethanol (20 mL) was added 20% $Pd(OH)_2/C$ (0.45 g) and cyclohexene (10 mL). After 23 h of stirring and heating at reflux, the reaction had not reached completion[14], thus additional amounts of 20% $Pd(OH)_2/C$ (1.4 g) cyclohexene (10 mL) and ethanol (30 mL) were added and the reaction was continued at reflux for another 18 h. After the usual workup as described for 8a, a viscous liquid was obtained. This material solidified when stirred with ether (10 mL). The solid obtained after filtration was crystallized from methanol to provide pure 12b (0.59 g, 52.2%): m.p. 200-203°C (dec.); $[\alpha]_D^{25}$ = -13.93 (c = 1.485, DMF); ^{1}H nmr (DMSO-d_6), δ 3.00-3.80 (m, 6H), 4.20-4.75 (m, 3H, OH), 5.40 (s, 2H, OCH_2N), 6.38 (s, 2H, NH_2), 7.72 (s, 1H, C(8)H), 10.50 (s, 1H, NH); UV λ_{max} (pH1) 255 nm (ε10,454), sh 282 (ε6,527); λ_{max} (water) 251.5 nm (ε11,892), sh 274.5 (ε7,854); λ_{max} (pH11) 263 nm (ε9,845).

Anal. Calcd. for $C_{10}H_{15}N_5O_5$: C, 42.11; H, 5.30; N, 24.55. Found: C, 41.95; H, 5.50; N, 24.28.

2-Amino-6-chloro-9-[(1,3S-dibenzyloxy-2R-butoxy)methyl]purine (10). Silylation of 2-amino-6-chloropurine (4.0 g, 0.024 mol) was carried out, as described for 7a, with 80 mL of HMDS in the presence of ammonium sulfate (0.87 g). Mercuric cyanide (6.4 g, 0.025 mol) and dry benzene (67 mL) were added to the silylated 2-amino-6-chloropurine and the mixture heated at reflux. To the reaction mixture was added the chloromethyl ether 6a (19.8 g, 86.5% pure, 0.024 mol) in dry benzene (67 mL). The reaction mixture was stirred and heated at reflux under nitrogen atmosphere for 3 h. The benzene was removed under diminished

pressure and the remaining residue was stirred with 400 mL of dichloromethane for 15 min. The solution was filtered and washed with 30% aq potassium iodide (2 x 80 mL), 10% aq potassium carbonate (2 x 80 mL), water (2 x 80 mL) and finally with a saturated sodium chloride solution (2 x 80 mL). It was dried over $MgSO_4$ and concentrated under diminished pressure to afford 12.8 g of a crude, viscous material. Silica gel (200 g) column chromatography using hexane-EtOAc (1:1) as eluent gave first 7.25 g (65.3%) of pure 10, as a gummy material, followed by 0.54 g (4.8%) of the N7-isomer. Physical constants of 10 are: $[\alpha]_D$ = +0.64 (c = 7.085, EtOH); ^{1}H nmr ($CDCl_3$), δ1.07 (d, J = 6 Hz, 3, CH_3), 3.38-4.03 (m, 4), 4.42 (s, 2, $\underline{CH_2}C_6H_5$), 4.47 (q_{AB}, J = 12 Hz, 2, $\underline{CH_2}C_6H_5$), 5.52 (br s, 2, NH_2, D_2O exchangeable), 5.62 (s, 2, OCH_2N), 7.27 (br s, 10, $CH_2C_6\underline{H_5}$), 7.8 (s, 1, C(8)H).

Anal. Calcd. for $C_{24}H_{26}ClN_5O_3$: C, 61.60; H, 5.60; N, 14.97; Cl, 7.58. Found: C, 61.48; H, 5.59; N, 15.04; Cl, 7.61.

9-[(1,3S-Dibenzyloxy-2R-butoxy)methyl]guanine (11). Sodium (1.0 g, 0.043 g atoms) in 44 mL of absolute methanol, 2-mercaptoethanol (3.5 mL) and water (0.22 g) were successively added to a solution of 10 (5.1 g, 0.011 mol) in 100 mL of absolute methanol. The resulting solution was heated at reflux for 2 h under a nitrogen atmosphere. At this point, an additional amount of sodium (0.655 g, 0.028 g atoms) in 11 mL of absolute methanol was added and heating was continued for an additional hour. The reaction solution was then concentrated to ca. 16 mL and diluted with water (87 mL). The solution was adjusted to pH 6 with glacial acetic acid. The pale, yellow solid which precipitated (5.14 g), was collected by filtration and washed with water (100 mL) and ether (20 mL). Crystallization of this material from ethanol or DMSO containing a few drops of water afforded 3.6 g (73.7%) of crystalline 11, mp 198-199°C; $[\alpha]_D$ = -3.13 (c = 1.085, DMF); ^{1}H nmr ($CDCl_3$), δ0.98 (d, J = 6 Hz, 3, CH_3), 3.07-4.0 (m, 4); 4.23-4.6 (m, 4, $\underline{CH_2}C_6H_5$), 5.62 (s, 2, OCH_2N), 6.43 (s, 2, NH_2, D_2O exchangeable), 7.23 (br s, 10, $CH_2C_6\underline{H_5}$), 7.77 (s, 1, C(8)H), 10.58 (br s, 1, NH, D_2O exchangeable).

Anal. Calcd. for $C_{26}H_{27}N_5O_4$: C, 64.13; H, 6.05; N, 15.58. Found: C, 64.16; H, 5.96; N, 15.73.

9-[(1,3S-Dihydroxy-2R-butoxy)methyl]guanine (12a). Catalytic transfer hydrogenation of 11 (3.30 g, 7.359 mol) in ethanol (164 mL) and cyclohexene (82 mL) was carried out over 3.1 g of 20% $Pd(OH_2/C$ at reflux for 13.5 h. The catalyst was collected by filtration on a celite pad and the filter cake was washed with hot DMF (8 x 50 mL). The filtrate and DMF washings were combined and evaporated to furnish a white solid. This was dissolved in 100 mL of hot ethanol-water (1:1) and filtered through celite containing activated charcoal. The solid, obtained after removal of the solvent, was crystallized from ethanol-water (4:1) to furnish 1.64 g (82.6%) of crystalline 12a, mp 300°C (dec): $[\alpha]_D$ = -16.59 (c = 1.115, DMF); ^{1}H nmr (DMSO-d_6),δ0.82 (d, J = 6 Hz, 3, CH_3), 3.06-3.76 (m, 4), 4.23-4.73 (m, 2, OH, D_2O exchangeable), 5.42 (s, 2, OCH_2N), 6.45 (s, 2, NH_2, D_2O exchangeable), 7.75 (s, 1, C(8)H), 10.65 (br s, 1, NH, D_2O exchangeable); UV λ_{max} (pH1) 255 nm (ε11,148), sh 281 (ε6,992); λ_{max} (water) 251 nm (ε12,137), sh 277 (ε7,586); λ_{max} (pH11) 258 nm (ε10,290), 264 (ε10,290).

Anal. Calcd. for $C_{10}H_{15}N_5O_4$: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.40; H, 5.59; N, 26.14.

Conversion of 2-amino-6-chloro-7-[(1,3S-dibenzyloxy-2R-butoxy)-methyl]purine and 10 to 11. A mixture of 10 and the corresponding N7-isomer (N9/N7 = 9:2, 1.66 g, 3.54 mmol) was dissolved in methanol (88 mL). To this solution was added water (6.2 mL) and sodium hydroxide (24.54 g, 614 mmol). This mixture was stirred and heated at reflux for 1.5 h and then allowed to cool to room temperature. The solution was neutralized with acetic acid, extracted with chloroform (3 x 100 mL), and dried over anhydrous sodium sulfate. The dried chloroform layer was filtered and then evaporated under diminished pressure to dryness. The solid residue was crystallized from absolute ethanol to furnish 11 (1.07 g, 67.4%). This compound was identical to 11 prepared from 10 by the sodium-methanol-2-mercaptoethanol method.

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10. 9-(1,3,4-Trihydroxy-2-butoxymethyl)guanine, was described by H. J. Schaeffer, ref. 3, but neither the experimental details nor the stereochemistry were given.

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14. If after 23 h the reaction was worked up, 9-[(1,3S,4-tribenzyloxy-2R-butoxy)methyl]guanine[9c] was the product. This material was crystallized from absolute ethanol {mp 168-170°C; $[\alpha]_D^{25}$ = -3.56 (c = 0.90, MeOH)} and was identical (tlc and ^{1}H NMR) to an authentic sample provided by Drs. M. MacCoss and R. L. Tolman (Merck).

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