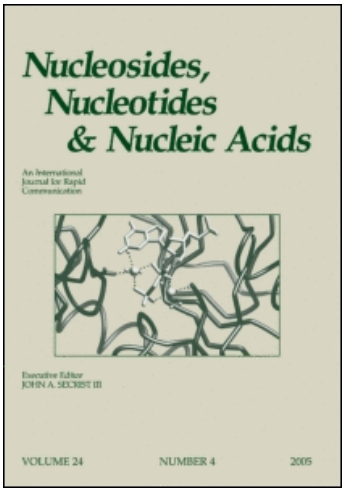

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THE SYNTHESIS OF 2-AMINO 7-SUBSTITUTED PURINES

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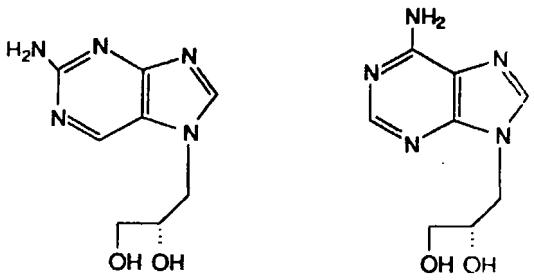
ABSTRACT: The putative antiviral agent, (S)-2-amino-7-(2,3-dihydroxypropyl)purine (1b), and its achiral analogue, 2-amino-7-(2-hydroxyethyl) purine (2), were synthesized by a procedure involving alkylation at N7 of guanosine followed by deribosylation and deoxygenation. Evidence for the stereochemical integrity of the former preparation was obtained from the X-ray diffraction structure of the novel tricyclic compound, (S)-6H,7H,8H-2-amino-7-hydroxy-[1,4]oxazepino[1,2,3-d,e]purine (17), obtained by a similar synthetic sequence. Compound (1a), a regioisomer of the known antiviral agent, (S)-9-(2,3-dihydroxypropyl)adenine ((S)-DHPA), was tested and found to be inactive in tissue culture against herpes virus type-2, rotavirus, poliovirus, and parainfluenza virus.

Recent work has demonstrated the feasibility of using acyclic nucleoside analogues as antiviral chemotherapeutic agents, with purine derivatives being among the most widely studied.[1-4] As a result, much current effort is being devoted to determining what effect alterations of the purine ring have upon antiviral activity in synthetic nucleosides.[5-8] Although to date many modified 9-substituted purines have been prepared and studied,[9-16] only a few reports of 7-substituted purines have appeared.[17] Certain 7-substituted purines might, however, show interesting physiological properties. This class of compounds thus constitutes a potentially interesting series of synthetic targets.

We considered acyclic 2-amino 7-substituted purines to be particularly attractive candidates for initial studies; they are structurally similar to 9-substituted adenosine-like nucleosides. Both classes of compounds contain, for instance, a fully oxidized pyrimidine ring bearing one exocyclic amino group and show a similar, but not identical, substitution pattern for the pyrimidine ring nitrogens. This resemblance is illustrated for a specific case in Figure 1, which provides a



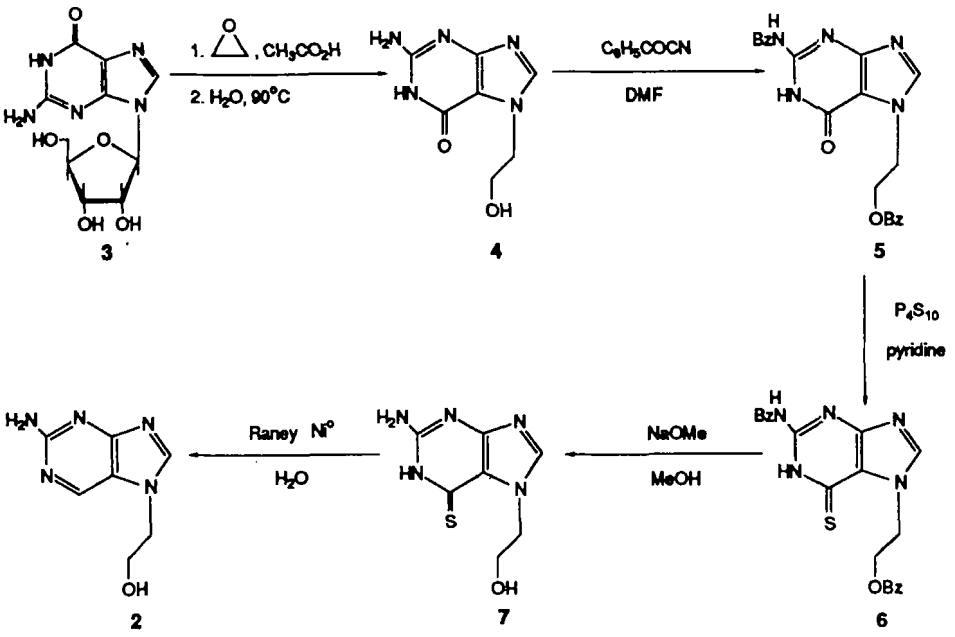
1b (S)-DHPA

FIGURE 1

Schematic representations of (S)-2-amino-7-(2,3-dihydroxypropyl)purine (1b) and (S)-9-(2,3-dihydroxypropyl)adenine ((S)-DHPA).

schematic comparison between the hitherto unreported substance, (S)-2-amino-7-(2,3-dihydroxypropyl)purine (1b), and the known[18] compound, (S)-9-(2,3-dihydroxypropyl)adenine ((S)-DHPA). The latter broad-spectrum antiviral has been shown to inhibit reversibly the enzyme S-adenosyl-L-homocysteine hydrolase (SAH)[19] and presumably derives its antiviral activity at least in part from this ability.[8] Since it has been shown that the position of the exocyclic amino group on the heterocycle is not essential for substrate activity,[20] the apparent stereoelectronic similarity between (S)-DHPA and (1b) led us to consider that (1b), with its adenine-like structure, might be an interesting isostere with which to probe further the structure activity relationship of SAH. We report here the synthesis of (1) in both its racemic (1a) and enantiomerically pure (S) (1b) forms, and present indirect structural evidence to support the stereochemical integrity of the latter. We also report the results of antiviral testing studies carried out with the racemic form of compound (1).

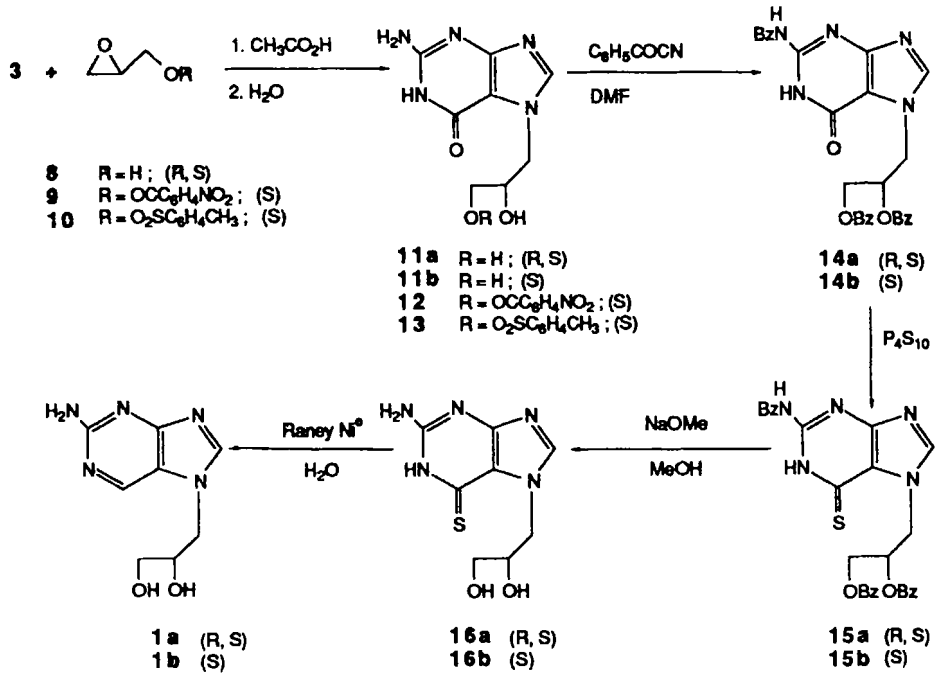
RESULTS AND DISCUSSION: The basic strategy for preparing acyclic 2-amino-7-substituted purines was worked out using a simple achiral compound, 2-amino-7-(2-hydroxyethyl)purine (2), as the synthetic target (Scheme I). It is based on extending a deoxygenation sequence first reported by J. J. Fox and co-workers,[21] to 7-alkylated guanines. The 7-(2-hydroxyethyl)guanine derivative (4) was obtained in two steps from



Scheme I

guanosine (3).[22] Treatment with benzoyl cyanide in N,N-dimethylformamide produced the dibenzoyl protected alcohol (5), which, following thiation with phosphorus pentasulfide in pyridine, afforded the requisite thione (6). Although dethiation could be effected at this stage, it was found to be more convenient to deprotect (6) first using sodium methoxide in methanol to produce (7). Dethiation of (7) then occurred readily using Raney nickel[23] in water to give (2). As expected,[21] dethiation resulted in a blue shift in the absorption spectrum (from λ_{max} = 351 nm for (7) to λ_{max} = 315 nm for (2)). It also led to the appearance of a second resonance in the aromatic portion of the ^1H NMR spectrum (δ 8.15, 8.63). Importantly, both the proton coupled and proton decoupled ^{13}C NMR spectra of (2) were consistent with the assigned structure. Furthermore, satisfactory high resolution mass spectrometric and microanalytic data were obtained for this compound.

The racemic form of (1) was prepared by a sequence analogous to that used to obtain (2) starting with commercially available (R,S)-glycidyl alcohol (8). The use of a nonsymmetric epoxide did not introduce

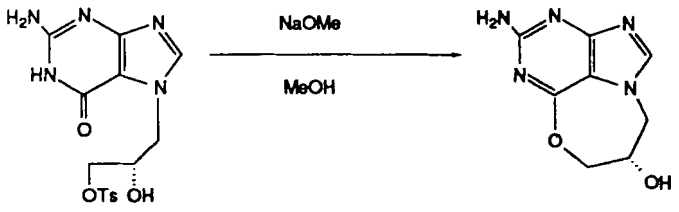


The designations (R, S) and (S) refer to the configuration at the exocyclic 2' position.

Scheme II

regiochemical complications in the initial step of the synthesis; as was implied in an earlier mechanistic study,[24] the less substituted isomer (11a) is formed exclusively in the course of this alkylation (Scheme II). The regiochemical assignment for (11a) was made initially on the basis of ^1H and ^{13}C NMR. The observed spectra are consistent with the depicted structure; they do not display the simple patterns expected for symmetrical, isopropyl-like substitution. Further confirmation of the regiochemistry of (11a) came from the X-ray structure of (17) which was produced following a similar regioselective epoxidation (see below). From the key intermediate (11a), all further steps in the synthesis of (1a), *viz.* protection, thiation, deprotection and reductive dethiation (Scheme II), proceeded in analogy to those used to prepare compound (2).

If an enantiomerically pure epoxide is used, the initial alkylation at N7 proceeds with both regio- and stereochemical control. This was established using two commercially available chiral epoxides: (2S)-



13 17

Scheme III

glycidyl 4-nitrobenzoate (9) and (2S)-glycidyl tosylate (10), which following deribosylation gave compounds (12) and (13), respectively. Treatment of (12) with sodium methoxide in methanol led to trans-esterification and formation of (11b) in nearly quantitative yield. The ^{1}H NMR spectrum of (11b) was identical to that of (11a), indicating that the regiochemical outcome of the two alkylation reactions was the same.

In the case of (13) the analogous transesterification did not occur. As judged by thin layer chromatography (TLC), a new product, distinct from (11b), was being formed. Following work up, the new compound (17) was obtained, in *crystalline form*, as the sole product of the reaction (Scheme III). It was assigned the novel tricyclic structure shown in Figure 2 on the basis of an X-ray diffraction study. The X-ray structure confirmed the enantiomerically pure nature of (17) but could not distinguish between the two possible enantiomorphs (see below). On the basis of the synthetic sequence employed, the absolute configuration at the chiral center was assigned as (S). The direct correspondence between (13) and (17), coupled with the strong spectral similarity between (12) and (13), establishes that the key alkylation step leading to (1b) proceeds with regio- and stereochemical control. Importantly, none of the reactions used to convert (12) to (1b) involve conditions which could lead to racemization and/or inversion at the chiral center.

X-RAY CRYSTALLOGRAPHY: The data crystal was a colorless needle, cut from a larger crystal of (17), 0.25 x 0.25 x 0.58 mm, obtained by recrystallization from water. The crystal system is orthorhombic, space group is $P2_12_12_1$, Z = 4, F(000) = 432, ρ_x = 1.64 g/cc (163 K); lattice

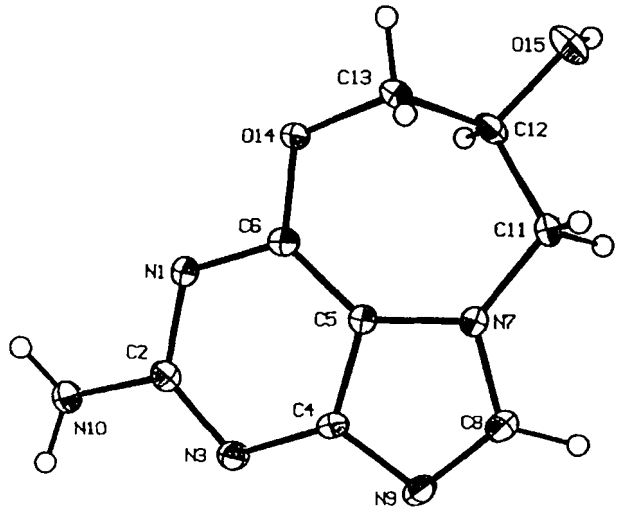


Figure 2.
Computer drawing of molecule (17) showing atom labeling.
Thermal ellipsoids are at 50% probability.

parameters from least-squares refinement of 30 reflections with $27.3^\circ < 2\theta < 33.1^\circ$; a = 6.646(3), b = 8.175(2), c = 15.459(5) Å, V = 839.9(5) Å^3. The data were collected on a Syntex $P2_1$ diffractometer, with a graphite monochromator using Mo Kα radiation (λ = 0.71069 Å) at 163 K and corrected for L_p effects, absorption (based on crystal shape; μ = 1.161 cm^{-1}, transmission factor range 0.958-0.976) and decay (maximum correction on I was 1.5%). The data were reduced as described elsewhere[25] and the structure solved by direct methods[26] with refinement by full-matrix least-squares procedures[27] using anisotropic thermal parameters for the non-H atoms. Neutral atom scattering factors were used for all atoms,[28,29] with anomalous dispersion corrections for non-H atoms;[30] linear absorption coefficient from the International Tables for X-ray Crystallography.[31] The least-squares planes program was supplied by Cordes;[32] other computer programs from reference 11 of Gadol and Davis.[33] All H atom positions from a ΔF map. 172 parameters refined. Final R = 0.0334 for 1352 reflections, wR = 0.0345 (R_{all} = 0.0361, wR_{all} = 0.0347) and a goodness of fit, S, = 2.543. The absolute configuration was

Table 1. Bond Lengths (Å) and Angles (°) for (17) (non-H).

1	2	3	1-2	1-2-3
C2	N1	C6	1.358(2)	118.59(13)
C6	N1		1.328(2)	
N3	C2	N10	1.336(2)	117.82(14)
N3	C2	N1		127.41(13)
N10	C2	N1	1.376(2)	114.72(13)
C4	N3	C2	1.354(2)	112.81(13)
C5	C4	N9	1.401(2)	110.40(13)
C5	C4	N3		124.16(13)
N9	C4	N3	1.372(2)	125.41(13)
C6	C5	N7	1.390(2)	136.78(14)
C6	C5	C4		117.59(13)
N7	C5	C4	1.389(2)	105.61(13)
O14	C6	N1	1.337(2)	113.77(13)
O14	C6	C5		126.89(14)
N1	C6	C5		119.32(14)
C8	N7	C11	1.357(2)	126.62(12)
C8	N7	C5		105.35(12)
C11	N7	C5	1.462(2)	128.02(13)
N9	C8	N7	1.323(2)	114.49(13)
C4	N9	C8		104.14(13)
C12	C11	N7	1.524(2)	111.11(12)
C13	C12	O15	1.523(2)	106.89(14)
C13	C12	C11		112.58(15)
O15	C12	C11	1.428(2)	106.46(13)
O14	C13	C12	1.453(2)	113.37(14)
C6	O14	C13		117.76(12)

assigned on the basis of internal comparison to that at C-12. The enantiomorph refined to a wR = 0.0347 and, therefore, discrimination between enantiomers could not be made on the basis of X-ray results. Selected bond lengths and bond angles are in Table 1. A table of atomic parameters for non-H atoms and a crystal packing diagram for (17) is available from the authors upon request.

The X-ray structure of compound (17) showed it to be nearly planar (Figure 3). Not surprisingly, the largest deviations from the mean plane of the tricyclic ring system are found for the bridging atoms C12 and C13, which are 0.493(2) Å and -0.443(2) Å, respectively. The remaining ring atoms are all within 0.11 Å of this plane. The seven membered ring formed by the inclusion of the four atom bridge from C6 to N7 appears to result in some slight deformation of the purine ring

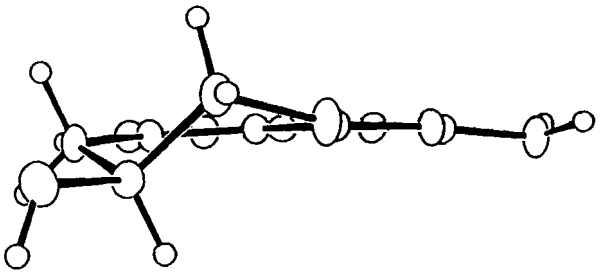


Figure 3.
End on view of compound (17) showing the nearly planar arrangement of all nonhydrogen atoms.

system. In order to minimize this strain, atoms C11 and O14 lie on opposite sides of the purine ring plane. In addition, the exocyclic bond angle at C6 is enlarged compared to that found in guanine monohydrate[34] and 9-ethyl-7-methylguaninium.[35]

ANTIVIRAL TESTING: Compound (1a) and its precursor (16a) were tested for antiviral activity against herpes virus type-2, rotavirus, poliovirus, and parainfluenza virus. Activity was assessed using a standard plaque reduction assay.[36] To provide the most likely procedure for producing activity, cells were preincubated with the putative drug and supplied with the same in an overlay. After preincubation with the proper drug or control, virus (approx. 100 pfu) was added and adsorbed for one hour at 37 °C. An agarose overlay containing the diluted drug or control was then added. After incubation as shown the cells were stained with crystal violet and the plaques enumerated.

Virus	Cell Type	Incubation Time
Enterovirus: Poliovirus (Chat strain)	RD	2 days
Herpes Virus: HSV-2 (MS strain)	RK	3 days
Paramyxoviruses: Parainfluenza 3	CV-1	3 days
Rotavirus: Wa strain	Ma-104	4 days

Compounds (1a) and (16a) were evaluated at 10-fold dilutions ranging from 100 to 1μg/ml. No significant reduction of plaque forming units (pfu) relative to control was observed for any of these viral systems, even at the highest concentration tested (100 μg/ml).[37]

These results indicate that, at least as far as these viral systems are concerned, the 2-amino 7-substituted purines (1a) and (16a) fail to act as adenosine analogues. More recently, compounds (1a) and (2) were tested for *in vitro* anti-HIV activity in the National Cancer Institute's developmental therapeutics program, but showed no antiviral activity and only weak cytotoxicity (IC50 = 4.15×10^1 μg/mL for (1a)). Interestingly, compound (1a) was, however, found to act as a weak competitive inhibitor for adenosine deaminase (ADA),[38] showing an approximate K_i of 0.37 mM.[39] This suggests that, in spite of the negative results obtained with (1a), further studies with other 2-amino 7-substituted purines could lead to the discovery of compounds with more interesting biological properties. We are currently exploring this possibility.

EXPERIMENTAL SECTION

General Methods: NMR spectra were obtained in DMSO-d_6, using the residual solvent peak as internal standard, or in 1M NaOD in D_2O, using TMSPS as a standard, as indicated. All NMR spectra were recorded on either a Varian EM-390 or Nicolet FT-360 spectrometer. Mass spectra, where obtained, were measured with either a Finnigan MAT 4023 or a Bell and Howell 21-110B instrument. Chemical ionization mass spectral data were obtained for compounds (5), (6), and (12)-(15), which fragment under electron impact conditions. Elemental analyses were performed by Oneida Research Services, Inc. and by Galbraith Laboratories, Inc. Electronic spectra were measured in water at pH 7 or acetonitrile and recorded from 190 nm to 500 nm on a Beckmann Instruments DU-7 using a built-in computer difference program to correct for background cell and solvent absorbances. Specific rotations were measured on a Perkin-Elmer 141 Polarimeter. Guanosine hydrate, racemic glycidyl alcohol, (2S)-glycidyl 4-nitrobenzoate, and (2S)-glycidyl tosylate were obtained from Aldrich Chemical Co. and used without further purification. Ethylene oxide was purchased from Eastman Kodak Co. (Caution: ethylene oxide is a known carcinogen; observe manufacturer's recommendations for handling

and storage). TLC was carried out on silica plates (Whatman K6F) using 12:7:1 $CHCl_3$: MeOH: H_2O (solvent 1) or 10% MeOH in $CHCl_3$ (solvent 2). Column chromatography was performed using Merck silica gel 60. MeOH and pyridine were dried with, and then distilled from, $Mg(OCH_3)_2$ and Na, respectively. Melting points were measured on a Mel-temp apparatus and are uncorrected.

7-(2-Hydroxyethyl)guanine (4).[22] Guanosine hydrate (25.0 g, 88 mmol) was suspended in acetic acid (AcOH) (500 mL) and stirred under nitrogen for several minutes. Ethylene oxide (20 mL, 404 mmol) was transferred into the vessel using a cold syringe, and the reaction was allowed to proceed for 6 h or until judged complete by TLC (solvent 1, guanosine R_f = 0.30, product nonmobile). Following evaporation of excess ethylene oxide and solvent in vacuo, water (250 mL) was added to form a clear solution. This was heated at 80-100° for 2 h. The white precipitate which formed upon cooling was filtered, washed with cold water (100 mL), and recrystallized from hot water to give (4) as white needles (11.4 g, 66%), mp dec >300°. ^1H NMR (DMSO): δ 3.68 (2H, t, CH_2CH_2OH), 4.19 (2H, t, CH_2CH_2OH), 4.85 (1H, t, CH_2OH), 6.07 (2H, s, NH_2), 7.82 (1H, s, C^8H); ^{13}C NMR: δ 48.3, 60.0, 108.1, 143.6, 152.5, 154.9, 160.1; UV-vis λ_{max} in nm (log ε), at pH 7, 216.0 (4.56), 242.0 (4.01) (sh.), 283.5 (4.11) (lit.[22]: 245 (3.74) (sh.), 284 (3.86)); mass spectrum: m/e 195.

2-Benzamido-7-(2-O-benzoyl-2-hydroxyethyl)purin-6-one (5). 7-(2-Hydroxyethyl)guanine (4) (19.00 g, 97.4 mmol) was suspended in dry pyridine (400 mL) containing benzoyl cyanide (38.3 g, 292 mmol). After the addition of 4-dimethylaminopyridine (DMAP) (11.90 g, 97.4 mmol) the mixture was allowed to stir under nitrogen at 75° for 3 h and allowed to cool for 3 h. The reaction was then quenched by the addition of H_2O (200 mL). The resulting precipitate was collected by filtration and washed with $CHCl_3$ (3 x 60 mL) and dried in vacuo to produce 30.9 g solid. This crude material was recrystallized from CH_3CN (10.5 L) to produce purified (5) as very fine crystals (25.37 g, 64.6%), mp 259-260°. TLC: R_f = 0.57, solvent 2. ^1H NMR(DMSO): δ 4.68 (2H, t, CH_2CH_2OBz), 4.70 (2H, t, CH_2CH_2OBz), 7.51 (4H, m, BzH), 7.63 (2H, m, BzH), 7.87 (2H, d, BzH), 8.04 (2H, d, BzH), 8.31 (1H, s, C^8H), 11.85 (1H, s, NH), 12.38 (1H, s, NH); UV-vis λ_{max} in nm (log ε), in CH_3CN, 207.0 (4.46), 229.0 (4.47), 274.5 (4.17), 292.0 (sh.); mass spectrum: m/e 404. *Anal.* Calcd for $C_{21}H_{17}N_5O_4$: C, 62.53; H, 4.25; N, 17.36. Found: C, 62.70; H, 4.29; N, 17.53.

2-Benzamido-7-(2-O-benzoyl-2-hydroxyethyl)purin-6-thione (6). Compound (5) (5.00 g, 12.4 mmol), water (0.89 g, 49 mmol), and P_4S_{10} (11.03 g, 24.8 mmol) were added to dry pyridine (250 mL), and the resulting mixture heated for 24 h at 110° under nitrogen. After cooling to 50°, water (100 mL) was slowly added. The solvents were then removed in vacuo to produce a gum. This was suspended in water (250 mL), stirred for 1 h, then filtered and washed with additional water (3 x 150 mL). After air drying, the yellow precipitate was dried in vacuo, suspended in hot CH_3CN (1000 mL), filtered, and allowed to recrystallize. Yellow tetrahedral crystals of purified (6) formed on standing at 4° (4.95 g, 86.6%). TLC: R_f = 0.61, solvent 2. A minor product, having a slightly higher R_f on TLC (R_f = 0.65, solvent 2) could be removed by column chromatography to provide an analytically pure sample, mp 224-225°, but in general (6) was used directly without further purification. ^1H NMR (NaOD): δ 3.74 (2H, t, $CH_2C\underline{H}_2OBz$), 4.18 (2H, t, $C\underline{H}_2CH_2OBz$), 7.34 (5H, m, ArH), 7.76 (5H, m, ArH), 8.40 (1H, s, C^8H); ^{13}C NMR: δ 45.5, 63.9, 123.6, 127.6, 127.8, 128.4, 129.0, 131.6, 133.1, 140.8, 146.8, 149.0, 153.5, 165.1, 169.5, 201.7; UV-vis λ_{max} in nm (log ε), in CH_3CN, 205.0 (4.71), 231.5 (4.61), 345.5 (4.38); mass spectrum: m/e 420. *Anal.* Calcd for $C_{21}H_{17}N_5O_3S \cdot H_2O$: C, 57.66; H, 4.61; N, 16.01. Found: C, 57.70; H, 4.37; N, 16.09.

2-Amino-7-(2-hydroxyethyl)purin-6-thione (7). Compound (6) (2.00 g, 4.77 mmol) prepared as described above was added to anhydrous MeOH (100 mL) containing NaOMe (1.03 g, 19.1 mmol), and heated at reflux for 4 h. After cooling to room temperature, the solution was neutralized with HCl (12 N). The yellow crystals which formed upon standing at 4° were filtered, washed with MeOH (2 x 50 mL), and dried in vacuo to give crude (7). This was recrystallized from H_2O (500 mL) to provide (7) as yellow needles (0.588 g, 58.4%). This product does not migrate on TLC, solvent 1. ^1H NMR (NaOD): δ 4.01 (2H, t, $CH_2C\underline{H}_2OH$), 4.84 (2H, t, $C\underline{H}_2CH_2OH$), 8.10 (1H, s, C^8H); UV-vis λ_{max} in nm (log ε), at pH 7, 205.0 (4.33), 221.0 (4.25), 258.0 (sh.), 352.0 (4.27); mass spectrum: m/e 211; high resolution mass spectrum: m/e calcd for $C_7H_9N_5OS$ (M^+): 211.05278, obsd (M^+): 211.05248. *Anal.* Calcd for $C_7H_9N_5OS$: C, 39.80; H, 4.29; N, 33.15. Found: C, 40.01; H, 4.51; N, 30.73.

2-Amino-7-(2-hydroxyethyl)purine (2). Compound (7) (0.50 g, 2.37 mmol) was added to water (250 mL), and heated to reflux. Raney nickel

(600 mg), prepared by the method of Fieser,[23] was then added with caution. Reflux was continued for 1 h, and the hot solution then filtered to remove the catalyst, which in turn was washed with boiling water (250 mL). The combined filtrate and washings were evaporated on a rotary evaporator to give (2) as a white precipitate. This was heated in absolute ethanol (250 mL), filtered, and allowed to cool at 4° to produce small white crystals (0.35 g, 83%) mp 230-233°. Compound (2) appeared as a bright blue spot on TLC, R_f = 0.65, solvent 1. ^{1}H NMR (DMSO): δ 3.69 (2H, t, CH_2CH_2OH), 4.21 (2H, t, CH_2CH_2OH), 8.15 (1H, s, C^8H), 8.63 (1H, s, C^6H); ^{13}C NMR: δ 48.8, 60.5, 120.1, 143.3, 149.1, 160.8, 162.3; UV-vis λ_{max} in nm (log ε), at pH 7, 219.0 (4.29), 254.0 (3.60), 314.0 (3.66), at pH 1, 2.19.5 (4.30), 263.0 (3.54), 326.5 (3.48), at pH 13, 220.0 (4.42), 255.0 (3.71), 314.0 (3.76); mass spectrum: m/e 179; high resolution mass spectrum: m/e calcd for $C_7H_9N_5O$ (M^+): 179.08071, obsd (M^+): 179.08099. *Anal.* Calcd. for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.81; H, 5.17; N, 38.97.

(R,S)-7-(2,3-Dihydroxypropyl)guanine (11a). This compound was prepared using a modification of the Brookes and Lawley procedure used to produce (4).[22] In this case, due to difficulties in work-up, a large excess of alkylating agent could not be employed. This problem was circumvented by increasing the reaction times to compensate for the lower stoichiometry. Guanosine hydrate (15.0 g, 53 mmol) was suspended in AcOH (500 mL) and stirred for several minutes under nitrogen. Glycidyl alcohol (7.86 g, 106 mmol) was then added and the alkylation allowed to proceed for 5 days. The solvent was then removed in vacuo, and the resulting gum dissolved in water (250 mL) and heated to 80-100° for 3 h. The white precipitate which forms was filtered upon cooling, washed with water (250 mL), followed by MeOH (100 mL), and recrystallized from boiling water (1000 mL). Filtration and drying in vacuo provided (7) (8.67 g, 73%) as white needles, mp dec >275°. ^{1}H NMR (NaOD): δ 3.60 (2H, m, CH_2OH), 4.15 (1H, m, CHOH), 4.42 (2H, m, $ArCH_2$), 7.84 (1H, s, C^6H); ^{13}C NMR: δ 51.3, 65.5, 73.4, 112.9, 145.7, 162.1, 163.7, 168.0; UV-vis λ_{max} in nm (log ε), at pH 7, 216.0 (4.38), 240.0 (sh.), 284.0 (3.95); mass spectrum: m/e 225; high resolution mass spectrum: m/e calcd for $C_8H_{11}N_5O_3$ (M^+): 225.08619, obsd (M^+): 225.08689. *Anal.* Calcd for $C_8H_{11}N_5O_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.17; H, 4.72; N, 31.60.

(S)-7-(3-O-p-Nitrobenzoyl-2,3-dihydroxypropyl)guanine (12). Guanosine hydrate (3) (6.34 g, 22.4 mmol) was suspended in acetic acid (100 mL). (S)-glycidyl 4-nitrobenzoate (9) (5.0 g, 22.4 mmol) was added and the mixture allowed to stir under nitrogen at 25° for 7 days. The solvent was removed in vacuo at <50°, and the resulting solids dissolved in H_2O (200 mL). This aqueous solution was extracted with $CHCl_3$ (2 x 50 mL) and filtered to remove the crude (12) which had prematurely deribosylated. The filtrate was heated at 100° for 1 h and allowed to cool at 5°. The orange/white precipitate which formed was filtered and washed with H_2O (100 mL) to produce (12) (4.87 g, 58%), mp dec >200°. An analytically pure sample could not obtained due to the fact that (12) undergoes decomposition during recrystallization or drying. TLC: R_f = 0.72 (solvent 1); $[\alpha]_D$ = -69.6° (c. 0.0205, DMSO); ^1H NMR (DMSO): δ 4.25 (2H, m, CH_2OPNB), 4.42 (2H, m, $ArCH_2$), 5.62 (1H, s, CHOH), 6.19 (2H, s, NH_2), 7.87 (1H, s, C^8H), 8.25 (4H, m, ArH), 10.94 (1H, s, OH); ^{13}C NMR: δ 49.0, 66.7, 67.2, 108.1, 123.3, 130.5, 135.0, 143.7, 150.1, 152.5, 154.6, 159.8, 163.9; UV-vis λ_{max} in nm (log ε), at pH 7, 200.5 (4.53), 213.5 (sh.), 254.0 (sh.), 271.5 (4.21); mass spectrum: m/e 375.

(S)-7-(3-O-p-Toluenesulfonyl-2,3-dihydroxypropyl)guanine (13). Guanosine hydrate (3) (3.72 g, 13.1 mmol) was suspended in acetic acid (50 mL). (S)-glycidyl tosylate (10) (3.00 g, 13.1 mmol) was added and the mixture allowed to stir under nitrogen at 25° for 5 days. The solvent was removed in vacuo at <50°, and the resulting solids dissolved in H_2O (50 mL). This aqueous solution was extracted with 2 portions of chloroform (10 mL) and filtered to remove the prematurely deribosylated (13) which formed. The filtrate was heated at 100° for 1 h and allowed to cool at 5°. The white precipitate which formed was dried in vacuo to yield crude (13) (4.62 g, 55.8%). An analytical sample, mp dec >175°, was obtained using column chromatography with solvent 1. TLC: R_f = 0.70 (solvent 1). $[\alpha]_D$ = -36.3° (c. 0.0195, DMSO); ^1H NMR (DMSO): δ 2.43 (3H, s, CH_3), 3.95 (2H, m, CH_2OTs), 4.10 (2H, m, $ArCH_2$), 5.62 (1H, s, CHOH), 6.36 (2H, s, NH_2), 7.61 (4H, m, ArH), 7.86 (1H, s, C_8H); ^{13}C NMR: δ 20.9, 48.7, 66.8, 71.4, 107.8, 125.3, 127.3, 127.8, 129.8, 142.8, 144.6, 152.8, 154.3; UV-vis λ_{max} in nm (log ε), at pH 7, 200.0 (4.43), 215.5 (4.21), 244.0 (sh.), 284.5 (3.58); mass spectrum: m/e 380. *Anal.* Calcd for $C_{15}H_{17}N_5O_5S$: C, 47.49; H, 4.52; N, 18.46. Found: C, 46.86; H, 4.57; N, 18.46.

(S)-7-(2,3-Dihydroxypropyl)guanine (11b). (S)-7-(3-O-*p*-Nitrobenzoyl-2,3-dihydroxypropyl)guanine (12) (3.28 g, 8.79 mmol) was added to 0.1 N NaOMe/MeOH (125 mL) and stirred for 0.5 h. The solution was neutralized with 2N HCl (6.5 mL) and cooled at 5° for 3 h. The white precipitate which formed was filtered, washed with MeOH (50 mL), and dried in vacuo to produce (11b) (1.92 g, 97%). $[\alpha]_D$ = -75.5° (c. 0.0051, DMSO); other features as per (11a).

(R,S)-2-Benzamido-7-(2,3-di-O-benzoyl-2,3-dihydroxypropyl)purin-6-one (14a). (R,S)-7-(2,3-dihydroxypropyl)guanine (11a) (5.00 g, 22.2 mmol) was suspended in dry pyridine (125 mL) and stirred under nitrogen for several minutes. Benzoic anhydride (25.14 g, 111 mmol) and DMAP (3.26 g, 26.7 mmol) were added, and the mixture heated at 70° for 3 h. Benzoyl cyanide (8.73 g, 66.6 mmol) was then added, heating continued for an additional hour, and the solution allowed to cool. After the adddition of 2 N $KHCO_3$ (200 mL), the solution was permitted to stir overnight. Following extraction with $CHCl_3$ (2 x 125 mL), solvents from the combined $CHCl_3$ washings were removed in vacuo. The resulting gum was recrystallized from hot CH_3CN (1000 mL) to produce purified (14a) as very fine tan crystals, mp 223-227° (6.80 g, 60%). TLC: R_f = 0.57 (solvent 2); ^1H NMR (DMSO): δ 4.68 (2H, m, CH_2OH), 4.92 (2H, m, $ArCH_2$), 5.88 (1H, m, CHOH), 7.58 (8H, m, ArH), 7.98 (7H, m, ArH), 8.28 (1H, s, C^8H), 11.88 (1H, s, NH), 12.53 (1H, s, NH); UV-vis λ_{max} in nm (log ε), in CH_3CN, 206.5 (4.64), 229.0 (4.73), 275.0 (4.32), 292.5 (sh.); mass spectrum: m/e 538. *Anal.* Calcd. for $C_{29}H_{23}N_5O_6 \cdot H_2O$: C, 62.70; H, 4.54; N, 12.61. Found: C, 62.10; H, 4.62; N, 12.72.

(S)-2-Benzamido-7-(2,3-di-O-benzoyl-2,3-dihydroxypropyl)purin-6-one (14b). This compound was prepared from (11b) by the above procedure; $[\alpha]_D$ = -101.1° (c. 0.0099, DMSO); other features as per (14a).

(R,S)-2-Benzamido-7-(2,3-di-O-benzoyl-2,3-dihydroxypropyl)purin-6-thione (15a). (R,S)-2-Benzamido-7-(2,3-di-O-benzoyl-2,3-dihydroxypropyl)purin-6-one (14a) (2.25 g, 4.19 mmol) and water (0.30 g, 16.7 mmol) were suspended in dry pyridine (125 mL). P_4S_{10} (3.72 g, 8.37 mmol) was then added, and the reaction carried out as per the procedure used to prepare (6). Following work up, crude material was obtained as a bright yellow precipitate. This was recrystallized from CH_3CN (500 mL) to provide purified (15a) (1.58 g, 68.2%) as yellow needles, mp 237-239°. For (15a): TLC R_f = 0.67 (solvent 2). A small amount of

dithiated material, R_f = 0.70, remained in this product. It could be removed by column chromatography to provide an analytically pure sample, but in general (15a) was used directly with no further purification. ^{1}H NMR (DMSO): δ 4.82 (2H, m, C$\underline{H}_2$OBz), 4.82 (2H, m, ArC$\underline{H}_2$), 5.75 (1H, m, C$\underline{H}$OBz), 7.43 (8H, m, ArH), 8.11 (7H, m, ArH), 8.21(1H, s, C^{8}H), 10.83 (1H, s, NH); UV-vis λ_{max} in nm (log ε), in CH_3CN, 201.5 (4.83), 230.0 (4.83), 345.5 (4.44); mass spectrum: m/e 554. *Anal.* Calcd. for $C_{29}H_{23}N_5O_5S \cdot H_2O$: C, 60.94; H, 4.41; N, 12.25; S, 5.61. Found: C, 61.16; H, 4.37; N, 12.14; S, 5.72.

(S)-2-Benzamido-7-(2,3-di-O-benzoyl-2,3-dihydroxypropyl)purin-6-thione (15b). This was prepared from (14b) using the above procedure. $[\alpha]_D$ = -213.2° (c. 0.0189, DMSO); other features as per (15a).

(R,S)-2-Amino-7-(2,3-dihydroxypropyl)purin-6-thione (16a). Compound (15a) (1.00 g, 1.81 mmol) and NaOMe (0.488 g, 9.04 mmol) were placed in dry MeOH (50 mL) and heated at reflux for 4 h. After cooling to room temperature, and neutralizing with HCl (12 N), a gold color was produced. The crystals which formed upon sitting at 4° were collected, washed with MeOH (30 mL), and recrystallized from H_2O (125 mL). The yellow needles which formed on cooling were filtered, washed with a small amount of H_2O and dried in vacuo to produce (16a) (0.120 g, 27.5%), mp dec >290°. TLC: R_f = 0.59 (solvent 1); ^{1}H NMR (NaOD): δ 3.58 (2H, m, C$\underline{H}_2$OH), 4.12 (1H, m, C$\underline{H}$OH), 4.57 (2H, m, ArC$\underline{H}_2$), 8.01 (1H, s, C^{8}H); ^{13}C NMR: δ 51.5, 65.8, 74.1, 123.8, 148.5, 158.8, 161.2, 175.3; UV-vis λ_{max} in nm (log ε), at pH 7, 206.5 (4.12), 225.5 (4.15), 256.0 (sh.), 351.5 (4.20); mass spectrum: m/e (M^+-H_2O) 223; high resolution mass spectrum: m/e calcd for $C_8H_9N_5OS$ (M^+-H_2O): 223.05278, obsd (M^+-H_2O): 223.05247. *Anal.* Calcd for $C_8H_{11}N_5O_2S$: C, 39.83; H, 4.60, N, 29.03. Found: C, 39.85; H, 4.62; N, 28.96.

(S)-2-Amino-7-(2,3-dihydroxypropyl)purin-6-thione (16b). This compound was prepared from (15b) using the above procedure. $[\alpha]_D$ = -181.0° (c. 0.0092, DMSO); other features as per (16a).

(R,S)-2-Amino-7-(2,3-dihydroxypropyl)purine (1a). (R,S)-2-Amino-7-(2,3-dihydroxypropyl)purin-6-thione (16a) was dethiated using a procedure identical to that used to convert (7) into (2). From 0.50 g (16a) (2.24 mmol), 0.37 g (1a) was obtained as a white precipitate, mp dec >160° (85%). Compound (1a) appeared as a bright blue spot on TLC, R_f = 0.50 (solvent 1). ^{1}H NMR (DMSO, D_2O): δ 3.31 (2H, m, C$\underline{H}_2$OH), 3.79 (1H,

m, CHOH), 4.21 (2H, m, $ArCH_2$), 8.13 (1H, s, C^8H), 8.62 (1H, s, C6H); ^{13}C NMR: δ 48.2, 62.7, 69.9, 119.7, 141.9, 147.9, 160.4, 161.9; UV-vis λ_{max} in nm (log ε), at pH 7, 219.5 (4.35), 253.5 (3.71), 314.5 (3.72), at pH 1, 220.0 (4.34), 261.0 (3.60), 327.5 (3.49), at pH 13, 219.0 (4.40), 254.5 (3.70), 315.0 (3.73); mass spectrum: m/e 209; high resolution mass spectrum: m/e calcd for $C_8H_{11}N_5O_2$ (M^+): 209.09127, obsd (M^+): 209.09180. *Anal.* Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.83; H, 5.31; N, 33.02.

(S)-7-(2,3-Dihydroxypropyl)-2-aminopurine (1b). This compound was prepared from (16b) using a procedure similar to that used to prepare (1a). $[\alpha]_D$ = -45.5° (c. 0.0106, DMSO); other features as per (1a).

(S)-6H,7H,8H-2-amino-7-hydroxy-[1,4]oxazepino[1,2,3-d,e]purine (17). Compound (12) (250 mg, 0.661 mmol) was added to dry MeOH (25 mL) containing NaOMe (107 mg, 1.98 mmol) and allowed to stir under nitrogen for 0.5 h. The resulting suspension was neutralized with 2N HCl, and solvent was removed on a rotary evaporator. The solids were recrystallized from H_2O (20 mL) to produce white crystals of (17) (130 mg, 95%), mp dec >270°. TLC: R_f = 0.57 (solvent 1). $[\alpha]_D$ = -29.4° (c. 0.0099, DMSO); ^1H NMR (DMSO): δ 4.26 (2H, m, CH_2OAr), 4.41 (2H, m, CH_2NAr), 5.65 (1H, s, CHOH), 6.00 (2H, s, NH_2), 8.15 (1H, s, C^8H); ^{13}C NMR: δ 52.6, 66.0, 72.8, 106.7, 145.4, 157.6, 159.7, 164.6; UV-vis λ_{max} in nm (log ε), at pH 7, 216.0 (4.43), 236.0 (sh.), 297.5 (3.78), at pH 1, 217.0 (4.55), 243.5 (sh.), 294.5 (4.10), at pH 13, 217.5 (4.56), 236.0 (sh.), 293.5 (3.81); mass spectrum: m/e 207; high resolution mass spectrum: m/e calcd for $C_8H_9N_5O_2$ (M^+): 207.07562, obsd (M^+): 207.07627. *Anal.* Calcd for $C_8H_9N_5O_2$: C, 46.38; H, 4.38; N, 33.80. Found: C, 46.05; H, 4.36; N, 33.49.

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