

in EtOH (4 mL) was stirred at reflux for 14 h and diluted with CHCl_3 -i-PrOH (4:1, 50 mL). The mixture was washed with water and saturated NaCl and dried over Na_2SO_4 . Concentration and silica gel column chromatography (CHCl_3 -MeOH (10:1)) afforded (-)-22 (143 mg) as a white solid with a melting point of 219° (dec) in 77% yield: $[\alpha]_D^{25} = -130^\circ$ (c 0.152, CHCl_3 -MeOH (9:1)); IR (KBr) 3400, 1752 cm^{-1} ; NMR (CDCl_3 - CD_3OD (9:1)) δ 2.3-2.8 (3 H, m), 2.8-5.0 (8 H, m), 3.75, 3.84, and 3.87 (each 3 H, s, OCH_3), 5.96 (2 H, s, OCH_2O), 6.38, 6.46, and 6.84 (each 1 H, s, ArH); MS m/z 576 (M^+). Anal. ($\text{C}_{28}\text{H}_{32}\text{O}_{13}$) C, H.

(-)-4 α [(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)oxy]-stegane [(-)-23]. A solution of (-)-steganol (5^8 , 204 mg, 0.49 mmol), tetra-*O*-acetyl- α -D-glucose¹⁸ (308 mg, 0.88 mmol), and BF_3 -Et₂O (181 mg, 1.28 mmol) in 1,2-dichloroethane (23 mL) was stirred at -20 °C for 1 h and then quenched with pyridine (0.5 mL). After dilution with ethyl acetate (50 mL), the mixture was washed with saturated NaCl and dried over MgSO_4 . Concentration and purification by silica gel column chromatography (benzene-ethyl acetate (3:1)) afforded (-)-23 (309 mg) as a colorless amorphous in 85% yield: $[\alpha]_D^{20} = -119^\circ$ (c 0.91, CHCl_3); IR (KBr) 1754 cm^{-1} ; NMR (CDCl_3) δ 1.90 (6 H, s, Ac), 1.94 and 1.99 (each 3 H, s, Ac), 2.2-3.2 (4 H, m), 3.3-5.2 (10 H, m), 3.84, 3.87, and 3.98 (each 3 H, s, OCH_3), 5.98 (2 H, s, OCH_2O), 6.40, 6.43, and

6.70 (each 1 H, s, ArH; MS m/z 744 (M^+). Anal. ($\text{C}_{36}\text{H}_{40}\text{O}_{17}$) C, H.

(-)-4 α -[2-(*N,N*-Dimethylamino)ethoxy]stegane [(-)-24]. A suspension of (-)-5⁸ (23.7 mg, 0.057 mmol), *N,N*-dimethyl-2-hydroxyethylamine (14.6 mg, 0.60 mmol), BF_3 -Et₂O (207 mg, 1.40 mmol), and 4A molecular sieve (1 g) in 1,2-dichloroethane (8 mL) was stirred at room temperature for 3 h. After dilution with ethyl acetate (30 mL), the mixture was washed with 10% NaOH and saturated NaCl and dried over MgSO_4 . Concentration and purification by silica gel column chromatography (CHCl_3 -MeOH (4:1)) afforded (-)-24 (6.3 mg) as an oil in 23% yield: $[\alpha]_D^{25} = -125^\circ$ (c 0.32, CHCl_3); IR (CHCl_3) 1770 cm^{-1} ; NMR (CDCl_3) δ 2.25 (6 H, s, $\text{N}(\text{CH}_3)_2$), 2.2-4.8 (11 H, m), 3.70, 3.82, and 3.87 (each 3 H, s, OCH_3), 5.98 (2 H, s, OCH_2O), 6.35, 6.51, 6.68 (each 1 H, s, ArH); MS m/z 485 (M^+). Anal. ($\text{C}_{26}\text{H}_{31}\text{NO}_7$) C, H, N.

(-)-4 α -Cyanostegane [(-)-25]. A solution of (-)-steganol (5^8 , 77.9 mg, 0.19 mmol), tetra-*O*-acetyl- α -D-glucopyranosyl bromide¹⁶ (124 mg, 0.30 mmol), and mercuric cyanide (84 mg, 0.332 mmol) in acetonitrile (2 mL) was stirred at reflux for 3 h. After dilution with ethyl acetate (20 mL), the mixture was washed with saturated NaCl and dried over MgSO_4 . Concentration and purification by silica gel column chromatography (hexane-ethyl acetate (3:2)) afforded (-)-25 (35.4 mg) as a solid in 45% yield: mp 233.5-234.5 °C; $[\alpha]_D^{20} = -201^\circ$ (c 0.40, CHCl_3). IR (KBr) 2230, 1775 cm^{-1} ; NMR (CDCl_3) δ 1.8-2.2 (2 H, m, ArCH_2), 2.3-3.2 (3 H, m, $\text{CH} \times 3$), 3.6-4.7 (2 H, m, CH_2O), 3.76, 3.85, and 3.88 (each 3 H, s, OCH_3), 5.99 (2 H, s, OCH_2O), 6.43, 6.60, and 6.68 (each 1 H, s, ArH). MS m/z 423 (M^+). Anal. ($\text{C}_{23}\text{H}_{21}\text{NO}_7$) C, H, N.

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Synthesis and Antiviral Activity of 9-Alkoxypurines. 2. 9-(2,3-Dihydroxypropoxy)-, 9-(3,4-Dihydroxybutoxy)-, and 9-(1,4-Dihydroxybut-2-oxy)purines

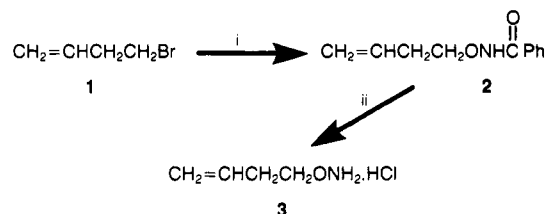
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Reaction of alkenoxyamines (3, 5) or (*R,S*)-, (*R*)-, and (*S*)-hydroxy-protected derivatives of hydroxyalkoxyamines (20a,b, 37a-c) with 4,6-dichloro-2,5-diformamidopyrimidine (4) and cyclization of the resultant 6-[(alkenoxy)amino]- and 6-(alkoxyamino)pyrimidines (6, 7, 21a,b, 38a,b,c) by heating with diethoxymethyl acetate afforded 9-alkenoxy- and 9-alkoxy-6-chloropurines (9, 10, 22a,b, 39a-c, 40a). These were subsequently converted to 9-(2,3-dihydroxypropoxy)-, 9-(3,4-dihydroxybutoxy)-, and 9-(1,4-dihydroxybut-2-oxy) derivatives of guanine and 2-aminopurine (13-16, 25-28, 41a-c, 42a). A 2-amino-6-methoxypurine derivative (17) was also prepared. The racemic guanine derivative 13 showed potent and selective activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), but was less active against varicella zoster virus (VZV). Its antiviral activity is attributable to the *S* isomer (28), which was found to be more active than acyclovir against HSV-1 and HSV-2 and about 4 times less active than acyclovir against VZV. The *S* enantiomer of 9-(1,4-dihydroxybut-2-oxy)guanine (41c) also showed noteworthy antiviral activity in cell culture. Although this acyclonucleoside (41c) is only weakly active against HSV-1 and inactive against HSV-2, it is about twice as active as acyclovir against VZV.

In part 1 of this series of publications on novel 9-alkoxypurines,¹ the synthesis and antiviral activity of 9-(3-hydroxypropoxy)- and 9-[3-hydroxy-2-(hydroxymethyl)propoxy]purines were reported. In this publication we describe the synthesis and antiviral properties of 9-(2,3-dihydroxypropoxy)-, 9-(3,4-dihydroxybutoxy)-, and 9-(1,4-dihydroxybut-2-oxy) derivatives of guanine and their stereoisomers. The latter compounds can be regarded as analogues of the antiviral acyclonucleosides (*R*)-9-(3,4-dihydroxybutyl)guanine (buciclovir),^{2,3} (*S*)-9-[2,3-(di-

Scheme I^a

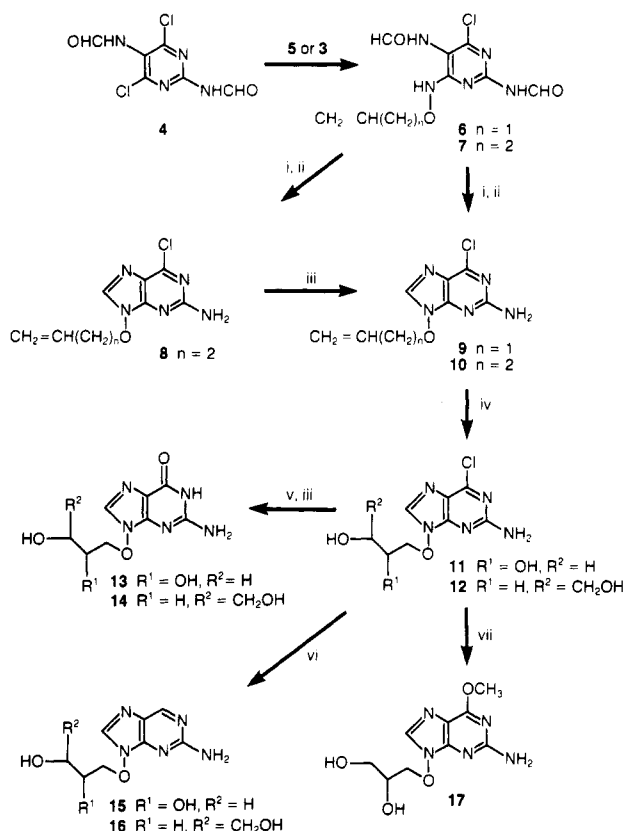


^a (i) PhC(O)NHOH , NaH, DMF; (ii) concentrated HCl, EtOH, reflux, 3 h.

hydroxypropoxy)methyl]guanine [(*S*)-INDG]⁴ and 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG),^{5,6}

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Scheme II^a

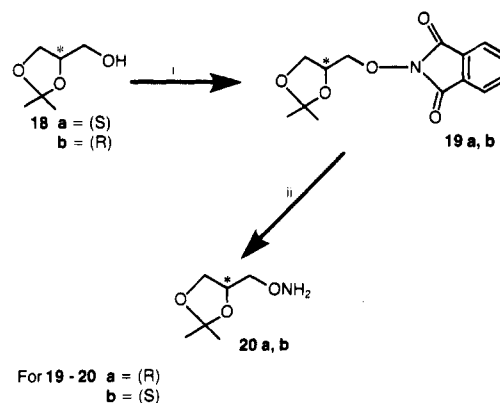
^a (i) $\text{CH}_3\text{CO}_2\text{CH}(\text{OEt})_2$, 120 °C; (ii) MeOH-NH_3 ; (iii) NH_3 ; (iv) OsO_4 , 4-methylmorpholine *N*-oxide, $(\text{CH}_3)_2\text{C}=\text{O}$, H_2O ; (v) 80% HCO_2H , 100 °C; (vi) HCO_2NH_4 , 10% Pd/C , MeOH ; (vii) NaOMe , MeOH , 100 °C.

respectively. Some analogous 9-substituted derivatives of 2-aminopurine and 2-amino-6-methoxypurine have also been prepared.

Chemistry

The synthetic route employed in syntheses of the 9-alkoxypurines was similar to that described previously⁷ and involved displacement of chloride from 4,6-dichloro-2,5-diformamidopyrimidine with a hydroxyl-protected alkoxyamine, followed by cyclization of the intermediate 6-(alkoxyamino)pyrimidine using diethoxymethyl acetate.

9-(2,3-Dihydroxypropoxy)- and 9-(3,4-Dihydroxybutoxy)purines. Racemic acyclonucleosides in the 2,3-dihydroxypropoxy (13, 15, 17) and 3,4-dihydroxybutoxy (14, 16) series (Scheme II) were prepared via the alkenoxyamines 5 and 3. 2-Propenoxyamine hydrochloride (5) was commercially available and 3-butenyloxyamine hydrochloride (3) was synthesized from 4-bromo-1-butene via benzohydroxamate 2 (Scheme I). Reaction of 5 and 3 with 4,6-dichloro-2,5-diformamidopyrimidine (4) in dioxane in the presence of triethylamine then provided the pyrimidine intermediates 6 and 7. Closure of the imidazole ring was achieved by heating at 120 °C with diethoxymethyl acetate followed by ammonia treatment, affording purines 9 and 10. In the butenyl case (7), the 2-formamidopurine in-

Scheme III^a

^a (i) *N*-Hydroxyphthalimide, Ph_3P , DEAD, THF; (ii) MeHNHNH_2 , CH_2Cl_2 .

intermediate 8 was isolated and was subsequently converted to 10 by ammonia treatment. Cis-hydroxylation of 9 and 10 using osmium tetroxide gave diols 11 and 12 in good yields. Guanine derivatives 13 and 14 were obtained by treatment of 11 and 12 with refluxing 80% formic acid, followed by ammonia at ambient temperature. The corresponding 2-aminopurine derivatives 15 and 16 were prepared from 11 and 12 by catalytic hydrogen transfer from ammonium formate. Treatment of 11 with sodium methoxide afforded the 6-methoxy derivative 17.

Our synthesis of the *R* and *S* enantiomers (25, 26) of the 2,3-dihydroxypropoxy derivative 13 commenced from the enantiomers of isopropylidene glycerol (18a,b). These chiral glycerols (18a,b) undergo facile racemization and therefore, in order to conserve chirality, acid-free conditions were employed in the early stages of the reaction sequence.

Diethyl azodicarboxylate (DEAD) catalyzed reaction of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (18a) with *N*-hydroxyphthalimide followed by treatment of the intermediary phthalimido compound 19a with methylhydrazine gave the (*R*)-alkoxyamine 20a (Scheme III). Reaction of 20a with 4,6-dichloro-2,5-diformamidopyrimidine (4) afforded 21a in only 20% yield. The *N*-formyl derivative of alkoxyamine 20a and the 2-amino analogues of the pyrimidines 4 and 21a were also isolated from this reaction. Cyclization of 21a with diethoxymethyl acetate, followed by treatment with aqueous ammonia afforded purine 22a. Conversion of 22a into guanine 27 was accomplished by treatment of 22a with refluxing 80% formic acid followed by aqueous ammonia. Treatment of 22a with aqueous methanolic ammonia gave 2-amino-6-chloropurine 23a. The isopropylidene protection in 23a was removed with acetic acid at 70 °C, and dechlorination of the resultant diol 24a, using catalytic hydrogen transfer from ammonium formate, afforded the (*R*)-2-aminopurine derivative 25 (Scheme IV).

Repetition of this reaction sequence starting from (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol (18b) afforded the corresponding (*S*)-guanine analogue 28 and the (*S*)-2-aminopurine derivative 26 through intermediates 19b–24b (Scheme IV).

9-(1,4-Dihydroxybut-2-oxo)purines. 2-Butene-1,4-diol (29) was protected by treatment with sodium hydride and 4-methoxybenzyl chloride to give diether 30 (Scheme V). Hydration of 30 using mercury(II) trifluoroacetate afforded 35a in 91% yield. Alcohol 35a was then converted to alkoxyamine 37a (via 36a) by DEAD-catalyzed reaction with *N*-hydroxyphthalimide followed by deprotection with methylhydrazine. Reaction of 37a with 4,6-dichloro-2,5-

- (5) Abele, G.; Karlstrom, A.; Harmenberg, J.; Shigeta, S.; Larsson, A.; Lindborg, B.; Wahren, B. *Antimicrob. Agents Chemother.* 1987, 31, 76.
 (6) Abele, G.; Eriksson, B.; Harmenberg, J.; Wahren, B. *Antimicrob. Agents Chemother.* 1988, 32, 1137.
 (7) Harnden, M. R.; Parkin, A.; Wyatt, P. G. *Tetrahedron Lett.* 1988, 29, 701.

Scheme IV^a

Table I. Antiviral Activity in Plaque-Reduction Assays^a against Herpes Simplex Virus Types 1 and 2 and Varicella Zoster Virus

compd ^b	IC ₅₀ , μ M		
	HSV-1 (SC16)	HSV-2 (MS)	VZV (Ellen)
13	7.9	2.8	154
27	>415	>415	>415
28	2.7	0.46	62
14	>390	>390	>390
41a	43	>390	30
41b	390	>390	>390
41c	36	>390	8.3
acyclovir	4.8	1.2	15

^a Plaque-reduction assays were performed as previously described,⁸ using MRC-5 cell monolayers infected with about 50 PFU of HSV-1, HSV-2, or VZV. Monolayers were treated with various concentrations of the compounds which were present throughout the incubation period. Plaques were counted when they were clearly visible (usually 3 days for HSV-1, 1 day for HSV-2, and 5 days for VZV). The compound concentration required to reduce the plaque count to 50% of that in untreated control cultures was calculated (IC₅₀). ^b Test compounds were prepared as 10 mg/mL solutions in Me₂SO and aliquots were further diluted in cell culture medium.

were prepared and the antiviral activity was found to be attributable to the *S* enantiomer **28**, which was about twice as active as acyclovir against HSV-1 and HSV-2 and about 4 times less active than acyclovir against VZV. It is interesting to note that the analogous acyclonucleoside (*R*)-9-(3,4-dihydroxybutyl)guanine (buciclovir), which has the same absolute stereochemistry as **28**, has also been reported⁹ to be substantially more active than its *S* enantiomer and to be less active against VZV¹⁰ than against HSV-1 and HSV-2.

Another compound with significant antiviral activity in cell culture is (*S*)-9-(1,4-dihydroxybut-2-oxy)guanine (**41c**). Although **41c** is only weakly active against HSV-1 and inactive against HSV-2, it is about twice as active as acyclovir against VZV. Again, it is noteworthy that the structurally analogous (*R,S*)-[4-hydroxy-2-(hydroxymethyl)butyl]guanine has also been reported¹⁰ to be highly active against VZV.

None of the compounds for which IC₅₀ data are given was cytotoxic for the MRC-5 cell monolayers when tested at concentrations up to 100 μ g/mL (ca. 400 μ M). Furthermore, in a cell-growth experiment in which MRC-5 cells were incubated for 72 h with compound **28**, the concentration required to inhibit the increase in cell number by 50% was 170 μ M. The cell number in untreated control cultures increased 12-fold.

In summary, the *S* enantiomers of 9-(2,3-dihydroxypropoxy)guanine (**28**) and 9-(1,4-dihydroxybut-2-oxy)guanine (**41c**) show potent and selective activity against herpes viruses in cell culture, **28** against HSV-1 and HSV-2 and **41c** against VZV.

Experimental Section

Melting points were determined by using a Reichert Kofler apparatus and are uncorrected. ¹H NMR spectra were recorded with a Varian EM-390 90-MHz or a JEOL GX-270 270-MHz spectrometer. Infrared spectra were recorded with a Perkin-Elmer 580 spectrometer and ultraviolet spectra were recorded with a UVikon 810 spectrometer. Mass spectra were recorded on a VG 70-70 instrument, and accurate masses were measured on a VG ZAB spectrometer. Microanalyses were performed on a Carlo-

Erba Model 1106 analyzer and, where only the symbols for the elements are recorded, were within $\pm 0.4\%$ of the calculated values. Upon TLC of analytical samples, using silica gel 60F₂₅₄ precoated aluminum sheets (Merck Art. No. 5554), in each case only a single component was detected.

4-[2-(Propenyloxy)amino]-6-chloro-2,5-diformamidopyrimidine (6). A mixture of 4,6-dichloro-2,5-diformamidopyrimidine (**4**; 3.75 g, 16 mmol), *O*-2-propenylhydroxylamine hydrochloride (**5**; 1.8 g, 16.4 mmol), and triethylamine (6.65 g, 66 mmol) in dioxane (80 mL) was stirred at 100 °C for 6 h. The reaction was cooled and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with chloroform-methanol (10:1), and the product was recrystallized from chloroform-methanol, affording **6** as a white solid (2.05 g, 47%): mp 179–181 °C; IR (KBr) ν_{\max} 3100–3350, 1700, 1650, 1590 and 1570 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 4.37 (2 H, d, *J* = 6.0 Hz, CH₂ON), 5.32 (2 H, m, CH=CH₂), 5.97 (1 H, m, CH=CH₂), 8.16 (1 H, s, CHO), 9.30 (1 H, s, CHO), 9.44 (1 H, br s, D₂O exchangeable, NH), and 10.87 (2 H, br s, D₂O exchangeable, 2 \times NH); HRMS calcd for C₉H₁₀ClN₅O₃ 271.0469, found 271.0469. Anal. (C₉H₁₀ClN₅O₃) C, H; N: calcd, 25.78; found, 25.34.

9-(2-Propenyloxy)-2-amino-6-chloropurine (9). A solution of **6** (1.23 g, 4.53 mmol) in diethoxymethyl acetate (20 mL) was stirred at 120 °C for 4 h. The solvent was removed in vacuo and the residue was dissolved in methanol (5 mL) and concentrated aqueous ammonia (10 mL) and stirred for 16 h at 25 °C. The solvents were removed in vacuo; the residue was absorbed on silica gel and chromatographed. Elution with ethyl acetate-hexane (1:1) afforded **9** (520 mg, 51%): mp 137–139 °C; IR (KBr) ν_{\max} 3480, 3400, 3310, 3200, 1630, 1615, 1560, and 1510 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 4.84 (2 H, d, *J* = 6.0 Hz, CH₂ON), 5.35 (2 H, m, CH₂=CH), 6.13 (1 H, m, CH=CH₂), 7.10 (2 H, br s, D₂O exchangeable, NH₂), and 8.35 (1 H, s, 8-H); HRMS calcd for C₈H₈ClN₅O 225.0414, found 225.0406. Anal. (C₈H₈ClN₅O \cdot 0.1H₂O) C, H, N.

2-Amino-6-chloro-9-(2,3-dihydroxypropoxy)purine (11). A solution of **9** (374 mg, 1.66 mmol) and osmium tetroxide (catalytic) in acetone (10 mL) and water (10 mL) was treated with 4-methylmorpholine *N*-oxide (290 mg, 2.49 mmol) and stirred under nitrogen at 20 °C for 16 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with acetone, affording **11** (325 mg, 76%): mp 173–175 °C; IR (KBr) ν_{\max} 3500, 3410, 3330, 3200, 3100, 1645, 1630, 1615, 1560 and 1520 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.42 (2 H, m, CH₂OH), 3.78 (1 H, m, CHOH), 4.20 (1 H, dd, *J* = 10.7, 7.3 Hz, CH₂ON), 4.41 (1 H, dd, *J* = 10.7, 3.2 Hz, CH₂ON), 4.74 (1 H, t, *J* = 5.7 Hz, D₂O exchangeable, OH), 5.14 (1 H, d, *J* = 5.2 Hz, D₂O exchangeable, OH), 7.13 (2 H, br s, D₂O exchangeable, NH₂), and 8.36 (1 H, s, 8-H); HRMS calcd for C₈H₁₀ClN₅O₃ 259.0469, found 259.0462. Anal. (C₈H₁₀ClN₅O₃ \cdot 0.3H₂O) C, H; N: calcd, 26.35; found, 25.91.

9-(2,3-Dihydroxypropoxy)guanine (13). A solution of **11** (100 mg, 0.39 mmol) in 80% formic acid was stirred at 100 °C for 2.5 h. The solvent was removed in vacuo and the residue was treated with methanol (5 mL) and concentrated aqueous ammonia solution (3 mL). After stirring the reaction at 60 °C for 2 h, the solvents were removed in vacuo, and the residue was recrystallized from water, yielding **13** (35 mg, 38%): mp 252–253 °C; UV (H₂O) λ_{\max} 252 (ϵ 12 600) nm; IR (KBr) ν_{\max} 3330, 1690, 1640, 1605, 1540, and 1475 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.39 (2 H, m, CH₂OH), 3.72 (1 H, m, CHOH), 4.10 (1 H, dd, *J* = 10.5, 7.6 Hz, CH₂ON), 4.33 (1 H, dd, *J* = 10.5, 3.3 Hz, CH₂ON), 4.70 (1 H, t, *J* = 5.7 Hz, D₂O exchangeable, OH), 5.15 (1 H, d, *J* = 5.2 Hz, D₂O exchangeable, OH), 6.62 (2 H, br s, D₂O exchangeable, NH₂), 7.90 (1 H, s, 8-H), and 10.58 (1 H, br s, D₂O exchangeable, NH); HRMS calcd for C₈H₁₁N₅O₄ 241.0811, found 241.0813. Anal. (C₈H₁₁N₅O₄ \cdot 0.8H₂O) C, H, N.

2-Amino-9-(2,3-dihydroxypropoxy)purine (15). A mixture of **11** (150 mg, 0.58 mmol), ammonium formate (146 mg, 2.32 mmol), and 10% palladium-on-charcoal (15 mg) in methanol (5 mL) was stirred under reflux for 4 h. The reaction was evaporated under reduced pressure and the residue was dissolved in water and passed through a SEP-PAK C₁₈ cartridge for decolorization. After elution with water, the water was evaporated under reduced pressure and the residue was recrystallized from ethanol, affording **15** (58 mg, 45%): mp 183–185 °C; UV (H₂O) λ_{\max} 221 (ϵ 25 600), 305 (ϵ 7000) nm; IR (KBr) ν_{\max} 3670, 3420, 3310, 3200, 1650, 1620,

(9) Ericson, A.-C.; Larsson, A.; Aoki, F. Y.; Yisak, W.-A.; Johansson, N.-G.; Öberg, B.; Datema, R. *Antimicrob. Agents Chemother.* 1985, 27, 753.

(10) Abele, G.; Karlström, A.; Harmenberg, J.; Shigeta, S.; Larsson, A.; Lindborg, B.; Wahren, B. *Antimicrob. Agents Chemother.* 1987, 31, 76.

1570, 1520, 1480, and 1425 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.41 (2 H, m, CH_2OH), 3.76 (1 H, m, CHOH), 4.18 (1 H, dd, $J = 7.6, 10.7$ Hz, CH_2ON), 4.39 (1 H, dd, $J = 3.2, 10.7$ Hz, CH_2ON), 4.72 (1 H, t, $J = 5.6$ Hz, D_2O exchangeable, OH), 5.15 (1 H, d, $J = 5.2$ Hz, D_2O exchangeable, OH), 6.72 (2 H, br s, D_2O exchangeable, NH_2), 8.27 (1 H, s, 8-H), and 8.59 (1 H, s, H-6); HRMS calcd for $\text{C}_9\text{H}_{11}\text{N}_5\text{O}_3$ 225.0862, found 225.0865. Anal. ($\text{C}_9\text{H}_{11}\text{N}_5\text{O}_3$) H, N; C: calcd, 42.67; found, 42.17.

2-Amino-9-(2,3-dihydroxypropoxy)-6-methoxypurine (17). To a 1.3 M sodium methoxide solution in methanol (0.55 mL, 0.68 mmol) was added 11 (60 mg, 0.23 mmol) and the solution was stirred at 100 $^\circ\text{C}$ for 1.5 h. The solvent was removed in vacuo; the residue was absorbed on silica gel and chromatographed. Elution with chloroform-methanol (20:1) afforded 17 (30 mg, 51%) as a hygroscopic foam: IR (KBr) ν_{max} 3400, 3220, 1620, 1590, 1500, 1480, and 1400 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 3.40 (2 H, m, CH_2OH), 3.75 (1 H, m, CHOH), 3.96 (3 H, s, CH_3), 4.13 (1 H, dd, $J = 7.7, 10.5$ Hz, CH_2ON), 4.36 (1 H, dd, $J = 3.3, 10.5$ Hz, CH_2ON), 4.71 (1 H, t, $J = 5.8$ Hz, D_2O exchangeable, OH), 5.18 (1 H, d, $J = 5.2$ Hz, D_2O exchangeable, OH), 6.64 (2 H, br s, NH_2), and 8.08 (1 H, s, 8-H); HRMS calcd for $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$ 255.0967, found 255.0968. Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

3-Butenyl Benzohydroxamate (2). To a suspension of 60% sodium hydride (8 g, 0.2 mol) in anhydrous DMF (200 mL) was added benzohydroxamic acid (27.5 g, 0.2 mol) over 20 min and the reaction was stirred for 1 h at 25 $^\circ\text{C}$. This solution was treated with 4-bromo-1-butene (1; 27 g, 0.2 mol) and the reaction was stirred at 100 $^\circ\text{C}$ for 6 h. After cooling, water (400 mL) was added and the solution was extracted with hexane (3×200 mL). The aqueous layer was evaporated under reduced pressure, the residue was suspended in ethyl acetate (600 mL), washed with water (2×200 mL), and dried (MgSO_4). The solvent was removed in vacuo to give an oil which was distilled under high vacuum, affording 2 (19.4 g 51%): IR (film) ν_{max} 3200, 1640, 1600, 1580, and 1510 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.44 (2 H, q, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{O}$), 4.07 (2 H, t, $J = 7.8$ Hz, CH_2ON), 5.12 (2 H, m, $\text{CH}_2=\text{CH}$), 5.80 (1 H, m, $\text{CH}=\text{CH}_2$), 7.26–7.9 (5 H, m, ArH), and 9.44 (1 H, br s, D_2O exchangeable, NH).

O-3-Butenylhydroxylamine Hydrochloride (3). A solution of 2 in ethanol (30 mL) was treated with concentrated hydrochloric acid (15 mL) and boiled under reflux for 3 h. The reaction was cooled, diluted with water (60 mL), and extracted with chloroform (3×100 mL). The aqueous layer was evaporated to dryness and the residue was recrystallized from ethanol-ether, affording 3 (4.6 g, 71%) as white plates: mp 136–140 $^\circ\text{C}$; IR (KBr) ν_{max} 3400, 3100–2900, 1650, 1590, 1550, and 1515 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.32 (2 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 4.06 (2 H, t, $J = 7.0$ Hz, CH_2ON), 5.07 (2 H, m, $\text{CH}_2=\text{CH}$), 5.72 (1 H, m, $\text{CH}=\text{CH}_2$), and 11.12 (3 H, br s, D_2O exchangeable, NH_3). Anal. ($\text{C}_4\text{H}_{10}\text{ClNO}$) H, N; C: calcd, 38.87; found, 38.23.

4-[(3-Butenyloxy)amino]-6-chloro-2,5-diformamidopyrimidine (7). A solution of 3 (1.94 g, 15.7 mmol) and triethylamine (3.96 g, 5.5 mL, 39.3 mmol) in dioxane (80 mL) was stirred for 1 h at 50 $^\circ\text{C}$. The suspension was cooled and filtered, before addition of 4,6-dichloro-2,5-diformamidopyrimidine (3.35 g, 14.3 mmol) to the filtrate. The solution was stirred at 100 $^\circ\text{C}$ for 4 h, cooled, filtered, and evaporated to dryness. The residue was chromatographed on silica gel eluting with ethyl acetate-hexane (5:1), affording 7 (1.31 g 32%): mp 151–152 $^\circ\text{C}$; IR (Nujol) ν_{max} 3250, 3180, 1710, 1650, 1590, 1560, and 1500 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.37 (2 H, q, $J = 6.6$ Hz, $\text{CH}_2\text{CH}_2\text{ON}$), 3.92 (2 H, t, $J = 6.6$ Hz, CH_2ON), 5.11 (2 H, m, $\text{CH}_2=\text{CH}$), 5.87 (1 H, m, $\text{CH}=\text{CH}_2$), 8.15 (1 H, s, CHO), 9.26 (1 H, s, CHO), 9.41 (1 H, br s, D_2O exchangeable, NH), 10.85 (2 H, br s, D_2O exchangeable, $2 \times \text{NH}$). Anal. ($\text{C}_{10}\text{H}_{12}\text{ClN}_5\text{O}_3$) C, H, N.

9-(3-Butenyloxy)-6-chloro-2-formamidopurine (8). A solution of 7 (1.2 g, 4.2 mmol) in diethoxymethyl acetate (20 mL) was stirred at 120 $^\circ\text{C}$ for 4 h. The solution was cooled, the solvent was removed in vacuo, and the residue was dissolved in methanol (20 mL) and concentrated aqueous ammonia (0.5 mL) and stirred for 1 h at 25 $^\circ\text{C}$. The solvents were removed, in vacuo, and the residue was chromatographed on silica gel eluting with chloroform, yielding 8 (600 mg, 55%) as a pale yellow solid: mp 149–151 $^\circ\text{C}$; IR (KBr) ν_{max} 3420, 1720, 1610, 1580, 1540, and 1510 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.53 (2 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 4.47 (2 H, t, $J = 7.0$ Hz, CH_2ON), 5.20 (2 H, m, $\text{CH}_2=\text{CH}$), 5.84 (1 H, m, $\text{CH}=\text{CH}_2$),

8.14 (1 H, s, 8-H), 8.33 (1 H, br d, $J = 11.0$ Hz, D_2O exchangeable, NH), and 9.56 (1 H, d, $J = 11.0$ Hz, CHO). Anal. ($\text{C}_{10}\text{H}_{10}\text{ClN}_5\text{O}_2 \cdot 0.3\text{H}_2\text{O}$) C, H, N.

2-Amino-9-(3-butenyloxy)-6-chloropurine (10). A solution of 8 (600 mg, 2.24 mmol) in methanol (5 mL) was treated with concentrated aqueous ammonia (10 mL) and stirred at 80 $^\circ\text{C}$ for 1 h. The reaction was cooled, and the solvents were removed in vacuo. The residue was absorbed on silica gel and chromatographed, eluting with chloroform, affording 10 (420 mg, 78%): mp 114–119 $^\circ\text{C}$; IR (KBr) ν_{max} 3470, 3310, 1630, 1620, 1570, and 1500 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.52 (2 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 4.42 (2 H, t, $J = 7.0$ Hz, CH_2ON), 5.22 (2 H, m, $\text{CH}_2=\text{CH}$), 5.40 (2 H, br s, D_2O exchangeable, NH_2), 5.82 (1 H, m, $\text{CH}=\text{CH}_2$), and 7.90 (1 H, s, 8-H). Anal. ($\text{C}_9\text{H}_{10}\text{ClN}_5\text{O}$) C, H, N.

2-Amino-6-chloro-9-(3,4-dihydroxybutoxy)purine (12). Compound 10 (395 mg, 1.65 mmol) was dissolved in acetone (10 mL) and water (10 mL) containing a catalytic amount of osmium tetroxide. The reaction was treated with 4-methylmorpholine *N*-oxide (293 mg, 2.51 mmol) and stirred for 16 h under nitrogen at 25 $^\circ\text{C}$. The solvents were removed in vacuo and the residue was absorbed on silica gel and chromatographed. Elution with acetone-hexane (3:1) afforded 12 (320 mg, 70%): mp 159–164 $^\circ\text{C}$; IR (KBr) ν_{max} 3430, 3320, 3210, 1650, 1620, 1570, and 1520 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.74 (2 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 3.27 (2 H, m, CH_2OH), 3.62 (1 H, m, CHOH), 4.42 (2 H, t, $J = 7.0$ Hz, CH_2ON), 4.60 (2 H, m, D_2O exchangeable, $2 \times \text{OH}$), 7.10 (2 H, br s, D_2O exchangeable, NH_2), and 8.41 (1 H, s, 8-H); HRMS calcd for $\text{C}_9\text{H}_{12}\text{ClN}_5\text{O}_3$ 273.0629, found 273.0635. Anal. ($\text{C}_9\text{H}_{12}\text{ClN}_5\text{O}_3 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

9-(3,4-Dihydroxybutoxy)guanine (14). A solution of 12 (100 mg, 0.37 mmol) in 80% formic acid (7 mL) was stirred at 100 $^\circ\text{C}$ for 1.5 h. The solvent was removed in vacuo and the residue was dissolved in methanol (5 mL) and concentrated aqueous ammonia (5 mL) and stirred for 0.5 h at 25 $^\circ\text{C}$. The solvents were removed in vacuo, and the residue was dissolved in hot water and filtered through a glass-fiber paper to remove colored material. The filtrate was slowly cooled, affording 14 (65 mg, 70%) as a pale brown solid: mp 254–258 $^\circ\text{C}$; UV (H_2O) λ_{max} 252 (ϵ 12900) nm; IR (KBr) ν_{max} 3330, 3170, 1690, 1640, 1600, 1540, and 1475 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.64 (1 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 1.88 (1 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 3.31 (2 H, m, CH_2OH), 3.61 (1 H, CHOH), 4.34 (2 H, m, CH_2ON), 4.58 (1 H, t, $J = 5.5$ Hz, D_2O exchangeable, OH), 4.64 (1 H, d, $J = 4.9$ Hz, D_2O exchangeable, OH), 6.59 (2 H, br s, D_2O exchangeable, NH_2), 7.91 (1 H, s, H-8), and 10.38 (1 H, br s, D_2O exchangeable, NH); HRMS calcd for $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$ 255.0967, found 255.0968. Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

2-Amino-9-(3,4-dihydroxybutoxy)purine (16). A mixture of 12 (150 mg, 0.55 mmol), ammonium formate (140 mg, 2.2 mmol), 10% palladium-on-charcoal (20 mg), and methanol (5 mL) was heated under reflux for 3 h. The solution was filtered through a glass-fiber paper and the solvent was removed in vacuo. The residue was recrystallized from hot ethanol, affording 16 (100 mg, 76%): mp 157–158 $^\circ\text{C}$; UV (H_2O) λ_{max} 221 (ϵ 24700) and 305 (ϵ 7100) nm; IR (KBr) ν_{max} 3420, 3310, 3200, 1640, 1620, 1580, 1520, 1480, and 1450 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.65 (1 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 1.91 (1 H, m, $\text{CH}_2\text{CH}_2\text{ON}$), 3.32 (2 H, m, CH_2OH), 3.63 (1 H, m, CHOH), 4.41 (2 H, m, CH_2ON), 4.59 (1 H, t, $J = 5.7$ Hz, D_2O exchangeable, OH), 4.71 (1 H, d, $J = 5.2$ Hz, D_2O exchangeable, OH), 6.71 (2 H, br s, D_2O exchangeable, NH_2), 8.30 (1 H, s, 8-H), and 8.59 (1 H, s, 6-H); HRMS calcd for $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_3$ 239.1018, found 239.1022. Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_3$) C, H, N.

(R)- and (S)-N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]phthalimide (19a and 19b). A solution of *N*-hydroxyphthalimide (50 mmol), triphenylphosphine (50 mmol), and either (S)-2,2-dimethyl-1,3-dioxolane-4-methanol (18a) or (R)-2,2-dimethyl-1,3-dioxolane-4-methanol (18b) in anhydrous THF (200 mL) was cooled to 0 $^\circ\text{C}$ and treated with diethyl azodicarboxylate (66 mmol). The dark red solution was stirred for 18 h at 20 $^\circ\text{C}$ and the solvent was removed in vacuo. The residue was extracted once with ether (200 mL) and the ether was evaporated in vacuo. Chromatography of the residue on silica gel eluting with hexane-acetone (3:1) afforded the *R* enantiomer (19a) or *S* enantiomer (19b).

(R)-N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]phthalimide (19a): 55% yield; mp 100–102 $^\circ\text{C}$; $[\alpha]_D^{20} = +15.6^\circ$ (c 0.98, MeOH); IR (KBr) ν_{max} 1790, 1730, and 1610 cm^{-1} ; ^1H NMR

(CDCl₃) δ 1.35 (3 H, s, CH₃), 1.41 (3 H, s, CH₃), 3.99 (1 H, dd, J = 5.5, 8.8 Hz, CH₂ON or CH₂OCMe₂), 4.17 (2 H, m, 1 H of CH₂ON + 1 H of CH₂OCMe₂), 4.32 (1 H, dd, J = 5.7, 10.1 Hz, CH₂ON or CH₂OCMe₂), 4.50 (1 H, m, CH), and 7.75–7.87 (4 H, m, ArH). Anal. (C₁₄H₁₅NO₅) C, H, N.

(*S*)-*N*-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]phthalimide (19b): 69% yield; mp 99–100 °C; $[\alpha]_D^{25} = -14.6^\circ$ (c 0.4, MeOH); IR and ¹H NMR are identical with those of the *R* enantiomer. Anal. (C₁₄H₁₅NO₅) C, H, N.

(*R*)- and (*S*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxyamine (20a and 20b). A solution of 19a or 19b (36 mmol) in dichloromethane (150 mL) was cooled to 0 °C and treated with methylhydrazine (72 mmol). The reaction was stirred at 20 °C for 1 h and filtered, and the solvent was removed in vacuo. The residue was suspended in ether and filtered, and the solvent was removed in vacuo. Chromatography of the residue on silica eluting with ethyl acetate afforded 20a or 20b as clear liquids.

(*R*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxyamine (20a): 89% yield; IR (film) ν_{\max} 3550, and 1600 cm⁻¹; ¹H NMR (CDCl₃) δ 1.38 (3 H, s, CH₃), 1.44 (3 H, s, CH₃), 3.73 (3 H, m, CH₂ON + 1 H of CH₂OCMe₂), 4.07 (1 H, dd, J = 6.4, 8.2 Hz, 1 H of CH₂OCMe₂), 4.35 (1 H, m, CH), and 5.56 (2 H, br s, D₂O exchangeable, NH₂). Anal. (C₆H₁₃NO₃) C, H, N: calcd, 9.52; found 9.02.

(*S*)-2,2-(Dimethyl-1,3-dioxolan-4-yl)methoxyamine (20b): 91% yield; IR and ¹H NMR are identical with those of the *R* enantiomer. Anal. (C₆H₁₃NO₃) C, H, N.

(*R*)- and (*S*)-4-Chloro-2,5-diformamido-6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]amino]pyrimidine (21a and 21b). A solution of 20a or 20b (30 mmol), 4,6-dichloro-2,5-diformamidopyrimidine (30 mmol), and diisopropylethylamine (60 mmol) in diglyme (125 mL) was stirred at 100 °C for 4 h. The reaction was cooled to 20 °C and filtered, and the solvent was removed in vacuo. Chromatography of the residue on silica gel eluting with chloroform–methanol (15:1) afforded 21a or 21b as yellow foams.

(*R*)-4-Chloro-2,5-diformamido-6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]amino]pyrimidine (21a): 20% yield; IR (KBr) ν_{\max} 3400, 3250, 1690, 1590, and 1470 cm⁻¹; ¹H NMR (CDCl₃) δ 1.39 (3 H, s, CH₃), 1.47 (3 H, s, CH₃), 3.81 (1 H, dd, J = 6.3, 8.2 Hz, CH₂OCMe₂), 4.03 (2 H, d, J = 5.5 Hz, CH₂ON), 4.11 (1 H, dd, J = 6.6, 8.2 Hz, CH₂OCMe₂), 4.41 (1 H, m, CH), 7.29 (1 H, s, D₂O exchangeable, NH), 7.97 (1 H, br d, J = 10.5 Hz, D₂O exchangeable, NH), 8.34 (1 H, s, HCO), 8.94 (1 H, br s, D₂O exchangeable, NH), and 9.43 (1 H, d, J = 10.5 Hz, HCO).

(*S*)-4-Chloro-2,5-diformamido-6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]amino]pyrimidine (21b): 24% yield; IR and ¹H NMR are identical with those of the *R* enantiomer.

(*R*)- and (*S*)-6-Chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-2-formamidopurine (22a and 22b). A solution of 21a or 21b (6 mmol) in diethoxymethyl acetate (30 mL) was stirred at 120 °C for 3 h. The solvent was removed in vacuo; the residue was dissolved in methanol (40 mL) and concentrated aqueous ammonia (1 mL) and stirred for 1 h at 20 °C. The solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:1) to afford 22a or 22b.

(*R*)-6-Chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-2-formamidopurine (22a): 62% yield; mp 145–148 °C; IR (KBr) ν_{\max} 3420, 3200, 1700, 1600, and 1580 cm⁻¹; ¹H NMR (CDCl₃) δ 1.40 (3 H, s, CH₃), 1.44 (3 H, s, CH₃), 3.89 (1 H, m, CH₂OCMe₂), 4.16 (1 H, m, CH₂OCMe₂), 4.50 (3 H, m, CH + CH₂ON), 8.23 (1 H, s, 8-H), 8.45 (1 H, br d, J = 11.5 Hz, D₂O exchangeable, NH), and 9.59 (1 H, d, J = 11.5 Hz, HCONH). Anal. (C₁₂H₁₄ClN₅O₄) C, H, N.

(*S*)-6-Chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-2-formamidopurine (22b): 65% yield; mp 147–148 °C; IR and ¹H NMR are identical with those of the *R* enantiomer; HRMS calcd for C₁₂H₁₄ClN₅O₄ 327.0734, found 327.0734. Anal. (C₁₂H₁₄ClN₅O₄) C, H, N.

(*R*)- and (*S*)-9-(2,3-Dihydroxypropoxy)guanine (27 and 28). A solution of 22a or 22b (0.5 mmol) in 80% formic acid (6 mL) was stirred at 100 °C for 2.5 h. The solvent was removed in vacuo, the residue was dissolved in methanol (1 mL) containing concentrated aqueous ammonia (1 mL), and the solution was stirred for 1 h at 20 °C. Evaporation of the solvents under reduced

pressure gave a residue which was recrystallized from hot water, affording 27 or 28 as tan solids.

(*R*)-9-(2,3-Dihydroxypropoxy)guanine (27): 45% yield; mp 255 °C dec; $[\alpha]_D^{25} = -14.9^\circ$ (c 0.1, H₂O); UV (H₂O) λ_{\max} 252 (ε 12 200) nm; IR (KBr) ν_{\max} 3380, 3180, 1690, 1640, 1600, and 1540 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.39 (2 H, m, CH₂OH), 3.73 (1 H, m, CH), 4.10 (1 H, dd, J = 7.7, 10.5 Hz, CH₂ON), 4.32 (1 H, dd, J = 3.3, 10.5 Hz, CH₂ON), 4.70 (1 H, t, J = 5.6 Hz, D₂O exchangeable, OH), 5.15 (1 H, d, J = 5.0 Hz, D₂O exchangeable, OH), 6.62 (2 H, br s, D₂O exchangeable, NH₂), 7.90 (1 H, s, 8-H), and 10.55 (1 H, br s, D₂O exchangeable, NH); HRMS calcd for C₈H₁₁N₅O₄ 241.0807, found 241.0797. Anal. (C₈H₁₁N₅O₄·0.5H₂O) H, N; C: calcd, 38.39; found, 37.91.

(*S*)-9-(2,3-Dihydroxypropoxy)guanine (28): 45% yield; mp 252–255 °C dec; $[\alpha]_D^{25} = +13.5^\circ$ (c 0.16, H₂O); UV (H₂O) λ_{\max} 252 (ε 12 900) nm; IR and ¹H NMR are identical with those of the *R* enantiomer; HRMS calcd for C₈H₁₁N₅O₄ 241.0811, found 241.0820. Anal. (C₈H₁₁N₅O₄·0.4H₂O) C, H, N.

(*R*)- and (*S*)-2-Amino-6-chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]purine (23a and 23b). A solution of 22a or 22b (1.2 mmol) in methanol (10 mL) and concentrated aqueous ammonia (10 mL) was stirred at 20 °C for 4 h. The solvents were removed in vacuo, and the residue was chromatographed on silica gel. Elution with ethyl acetate–hexane (2:1) afforded 23a or 23b as white solids.

(*R*)-2-Amino-6-chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]purine (23a): 77% yield; mp 118–119 °C; IR (KBr) ν_{\max} 3450, 3320, 3210, 1650, 1630, 1620, 1560, and 1510 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.28 (3 H, s, CH₃), 1.31 (3 H, s, CH₃), 3.77 (1 H, dd, J = 8.5, 5.8 Hz, CH₂OCMe₂), 4.08 (1 H, dd, J = 8.5, 5.8 Hz, CH₂OCMe₂), 4.40 (3 H, m, CH₂ON + CH), 7.11 (2 H, s, D₂O exchangeable, NH₂), and 8.38 (1 H, s, 8-H); HRMS calcd for C₁₁H₁₄ClN₅O₃ 299.0785, found 299.0786.

(*S*)-2-Amino-6-chloro-9-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]purine (23b): 74% yield; mp 118–120 °C; IR is identical with that of the *R* enantiomer; ¹H NMR (CDCl₃) δ 1.36 (3 H, s, CH₃), 1.42 (3 H, s, CH₃), 3.85 (1 H, m, CH₂OCMe₂), 4.14 (1 H, m, CH₂OCMe₂), 4.43 (3 H, m, CH₂ON + CH), 5.51 (2 H, br s, D₂O exchangeable, NH₂), and 8.00 (1 H, s, 8-H); HRMS calcd for C₁₁H₁₄ClN₅O₃ 299.0785, found 299.0795. Anal. (C₁₁H₁₄ClN₅O₃) C, H, N.

(*R*)- and (*S*)-2-Amino-6-chloro-9-(2,3-dihydroxypropoxy)purine (24a and 24b). A solution of 23a or 23b (0.8 mmol) in 80% aqueous acetic acid (20 mL) was stirred at 20 °C for 2 h and then at 70 °C for 1 h. The solvents were removed in vacuo, and the residue was absorbed on silica gel and chromatographed. Elution with acetone–hexane (3:1) afforded 24a or 24b as white, crystalline solids.

(*R*)-2-Amino-6-chloro-9-(2,3-dihydroxypropoxy)purine (24a): 63% yield; mp 155–158 °C; IR (KBr) ν_{\max} 3340, 3200, 1660, 1640, 1570, and 1520 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.41 (2 H, m, CH₂OH), 3.78 (1 H, m, CH), 4.19 (1 H, dd, J = 7.4, 10.7 Hz, CH₂ON), 4.40 (1 H, dd, J = 3.3, 10.7 Hz, CH₂ON), 4.72 (1 H, t, J = 5.6 Hz, D₂O exchangeable, OH), 5.13 (1 H, d, J = 5.0 Hz, D₂O exchangeable, OH), 7.12 (2 H, s, D₂O exchangeable, NH₂), and 8.35 (1 H, s, 8-H); HRMS calcd for C₈H₁₀ClN₅O₃ 259.0472, found 259.0478.

(*S*)-2-Amino-6-chloro-9-(2,3-dihydroxypropoxy)purine (24b): 78% yield; mp 155–158 °C; IR and ¹H NMR are identical with those of the *R* enantiomer; HRMS calcd for C₈H₁₀ClN₅O₃ 259.0472, found 259.0475.

(*R*)- and (*S*)-2-Amino-9-(2,3-dihydroxypropoxy)purine (25 and 26). A mixture of 24a or 24b (0.2 mmol), 10% palladium-on-charcoal (10 mg), and ammonium formate (0.8 mmol) in methanol (2 mL) was heated under reflux for 3 h. The reaction was cooled and filtered, and the solvents were removed in vacuo. The residue was recrystallized from ethanol, affording 25 or 26 as pale tan solids.

(*R*)-2-Amino-9-(2,3-dihydroxypropoxy)purine (25): 55% yield; mp 145–147 °C; $[\alpha]_D^{25} = -16.0^\circ$ (c 0.1, H₂O); UV (H₂O) λ_{\max} 221 (ε 24 900) and 305 (ε 7000) nm; IR (KBr) ν_{\max} 3380, 3320, 3200, 1660, 1650, 1620, 1580, and 1510 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 3.43 (2 H, m, CH₂OH), 3.77 (1 H, m, CH), 4.18 (1 H, dd, J = 7.8, 10.7 Hz, CH₂ON), 4.40 (1 H, dd, J = 2.5, 10.7 Hz, CH₂ON), 4.72 (1 H, t, J = 5.4 Hz, D₂O exchangeable, OH), 5.16 (1 H, d, J = 4.9 Hz, D₂O exchangeable, OH), 6.72 (2 H, s, D₂O exchangeable, NH₂),

8.27 (1 H, s, 8-H), and 8.59 (1 H, s, 6-H); HRMS calcd for $C_8H_{11}N_5O_3$ 225.0862, found 225.0872. Anal. ($C_8H_{11}N_5O_3 \cdot 1.5H_2O$) C, H, N.

(S)-2-Amino-9-(2,3-dihydroxypropoxy)purine (26): 72% yield; mp 153–155 °C; $[\alpha]_D^{25} = +16.5^\circ$ (c 0.1, H_2O); UV (H_2O) λ_{max} 221 (ϵ 25 000) and 305 (ϵ 7250) nm; IR and 1H NMR are identical with those of the *R* enantiomer; HRMS calcd for $C_8H_{11}N_5O_3$ 225.0862, found 225.0870. Anal. ($C_8H_{11}N_5O_3 \cdot 0.5H_2O$) C, H, N.

1,4-Bis[(4-methoxybenzyl)oxy]but-2-ene (30). To a solution of 2-butene-1,4-diol (**29**; 4.94 g, 60 mmol) in DMF (120 mL) was added sodium hydride (60% dispersion in oil; 5.28 g, 132 mmol) and the mixture was stirred at 20 °C for 100 min. To this solution was added 4-methoxybenzyl chloride (17.9 mL, 132 mmol) in DMF (30 mL) dropwise over 45 min, and the mixture was stirred for a further 40 min. The mixture was partitioned between ether (150 mL) and water (150 mL). The organic layer was further washed with water (150 mL), dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane–acetone (4:1, 3:1) to afford **30** as a clear, colorless liquid (13.7 g, 70%); IR (film) ν_{max} 2840, 1615, and 1515 cm^{-1} ; 1H NMR ($CDCl_3$) δ 3.80 (6 H, s, $2 \times CH_3$), 4.02 (4 H, d, $J = 4.5$ Hz, $2 \times CHCH_2$), 4.43 (4 H, s, $2 \times ArCH_2$), 5.79 (2 H, t, $J = 4.5$ Hz, $2 \times CH$), 6.88 (4 H, d, $J = 9$ Hz, ArH), and 7.27 (4 H, d, $J = 9$ Hz, ArH).

1,4-Bis[(4-methoxybenzyl)oxy]butan-2-ol (35a). To a solution of mercury(II) trifluoroacetate (17.1 g, 40 mmol) in aqueous THF (1:1, 80 mL) was added a solution of **30** (12.8 g, 39 mmol) in THF (10 mL) over 5 min. The resulting two-phase mixture was stirred vigorously at room temperature for 15 min. To the mixture was added aqueous sodium hydroxide (3 M, 40 mL) followed by sodium borohydride (0.5 M solution in 3 M sodium hydroxide; 40 mL) with water-bath cooling. The solution was saturated with sodium chloride and allowed to stand. The organic layer was collected, dried ($MgSO_4$), and filtered through Celite. The solvent was removed in vacuo to afford **35a** as an oily solid (12.27 g, 91%); IR (KBr) ν_{max} 3440, 2940, 2860, 1610, and 1510 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.76 (2 H, q, $J = 6.0$ Hz, CH_2CH_2O), 2.90 (1 H, br s, D_2O exchangeable, OH), 3.41 (2 H, AB of ABX, $J_{ax} = 6.9$ Hz, $J_{bx} = 4.2$ Hz, and $J_{ab} = 9.5$ Hz, $CHCH_2O$), 3.62 (2 H, m, CH_2CH_2O), 3.80 (6 H, s, $2 \times CH_3$), 4.00 (1 H, m, CH), 4.43 (2 H, s, $ArCH_2$), 4.48 (2 H, s, $ArCH_2$), 6.86 (4 H, m, ArH), and 7.24 (4 H, m, ArH).

N-[1,4-Bis[(4-methoxybenzyl)oxy]but-2-oxy]phthalimide (36a). A solution of *N*-hydroxyphthalimide (10.8 g, 66 mmol), triphenylphosphine (17.3 g, 66 mmol), and **35a** (12.12 g, 35 mmol) in anhydrous THF (140 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (10.4 mL, 66 mmol). The dark red solution was stirred for 24 h at 20 °C and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane–ethyl acetate (2:1, 7:5) to afford **36a** as a clear colorless oil (10.9 g, 63%); IR (film) ν_{max} 2940, 2860, 1790, 1735, 1615, and 1520 cm^{-1} ; 1H NMR ($CDCl_3$) δ 2.04 (2 H, m, CH_2CH_2O), 3.7–3.8 (10 H, m, $2 \times CH_3$ and $2 \times CH_2O$), 4.25–4.55 (4 H, m, $2 \times ArCH_2$), 4.60 (1 H, m, CH), 6.7–7.3 (8 H, m, $2 \times CH_3OC_6H_4$), and 7.73 (4 H, m, phthaloyl-H).

1,4-Bis[(4-methoxybenzyl)oxy]but-2-oxyamine (37a). A solution of **36a** (10.3 g, 21 mmol) in dichloromethane (80 mL) was cooled to 0 °C and treated with methylhydrazine (1.71 mL, 32 mmol) and the reaction was stirred at room temperature for 40 min and filtered, and the filtrate was washed with a 3% aqueous solution of sodium carbonate. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane–ethyl acetate (1:1) to afford **37a** as a clear colorless oil (5.1 g, 68%); IR (film) ν_{max} 2860, 1615, and 1515 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.80 (2 H, m, CH_2CH_2O), 3.54 (4 H, m, $2 \times CH_2O$), 3.80 (6 H, s, $2 \times CH_3$), 3.86 (1 H, m, CH), 4.42 (2 H, s, $ArCH_2$), 4.48 (2 H, s, $ArCH_2$), 5.37 (2 H, s, D_2O exchangeable, NH_2), 6.87 (4 H, m, ArH), and 7.25 (4 H, m, ArH); HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1882.

6-[[1,4-Bis[(4-methoxybenzyl)oxy]but-2-oxy]amino]-4-chloro-2,5-diformamidopyrimidine (38a). A solution of 4,6-dichloro-2,5-diformamidopyrimidine (3.27 g, 13.9 mmol), **37a** (5.06 g, 14 mmol), and triethylamine (5.88 mL, 42 mmol) in dioxane (100 mL) was stirred at 100 °C for 90 min. The solution was cooled

to 20 °C and filtered, and the solvent was removed. The residue was chromatographed on silica gel eluting with chloroform–methanol (30:1) to afford **38a** as a pale yellow foam (4.8 g, 62%); IR (KBr) ν_{max} 3240, 2920, 2860, 1690, 1615, 1590, and 1515 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.88 (2 H, m, CH_2CH_2O), 3.54 (4 H, m, $2 \times CH_2O$), 3.73 (3 H, s, CH_3), 3.74 (3 H, s, CH_3), 4.07 (1 H, m, CH), 4.37 (4 H, m, $2 \times ArCH_2$), 6.88 (4 H, m, ArH), 7.21 (4 H, m, ArH), 8.14 and 8.32 (total 1 H, $2 \times s$, HCO), 9.17–9.43 (2 H, m, D_2O exchangeable, NH), 10.67 (1 H, br s, D_2O exchangeable, NH), and 10.85 (1 H, br, D_2O exchangeable, NH); FABMS (positive ion, thioglycerol) m/z MH^+ 560/562. Anal. ($C_{26}H_{30}ClN_5O_7$) C, H, N: calcd, 12.51; found, 11.99.

9-[1,4-Bis[(4-methoxybenzyl)oxy]but-2-oxy]-6-chloro-2-formamidopurine (39a) and 2-Amino-9-[1,4-bis[(4-methoxybenzyl)oxy]but-2-oxy]-6-chloropurine (40a). A solution of **38a** (4.71 g, 8.4 mmol) in diethoxymethyl acetate (45 mL) was stirred at 120 °C for 1 h. The solvent was removed in vacuo; the residue was dissolved in methanol (60 mL) and concentrated aqueous ammonia (20 mL) and stirred at 50 °C for 1 h and then left at room temperature for 4 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with chloroform to afford purines **39a** and **40a** in a total yield of 54%. Fractions 8–12 yielded **39a** as a clear glass (0.66 g, 15%); IR (film) ν_{max} 3230, 3120, 2930, 2860, 1705, 1610, 1575, 1515, and 1440 cm^{-1} ; 1H NMR (Me_2SO-d_6) δ 2.00 (2 H, m, CH_2CH_2O), 3.57–3.70 (4 H, m, $2 \times CH_2O$), 3.73 (6 H, s, $2 \times CH_3$), 4.31 (2 H, AB, $J = 11.4$ Hz, $ArCH_2$), 4.39 (2 H, s, $ArCH_2$), 4.71 (1 H, m, CH), 6.85 (4 H, m, ArH), 7.06 (2 H, d, $J = 8.8$ Hz, ArH), 7.21 (2 H, d, $J = 8.8$ Hz, ArH), 8.61 (1 H, s, 8-H), 9.33 (1 H, s, HCO), and 11.27 (1 H, s, D_2O exchangeable, 2-NH). Anal. ($C_{26}H_{26}ClN_5O_6$) C, H, N.

Fractions 13–15 yielded a mixture of **39a** and **40a** (0.61 g, 14%). Fractions 16 and 17 yielded **40a** as a clear glass (1.06 g, 25%); IR (film) ν_{max} 3320, 3200, 2930, 2860, 1700, 1615, 1560, 1510, and 1465 cm^{-1} ; 1H NMR (Me_2SO-d_6) δ 1.96 (2 H, m, CH_2CH_2O), 3.46–3.65 (4 H, m, $2 \times CH_2O$), 3.73 (6 H, s, $2 \times CH_3$), 4.33 (2 H, AB, $J = 11.3$ Hz, $ArCH_2$), 4.36 (2 H, s, $ArCH_2$), 4.62 (1 H, m, CH), 6.86 (4 H, m, ArH), 7.03 (2 H, s, D_2O exchangeable, NH_2), 7.11 (2 H, d, $J = 8.5$ Hz, ArH), 7.19 (2 H, d, $J = 8.5$ Hz, ArH), and 8.21 (1 H, s, 8-H). Anal. ($C_{25}H_{26}ClN_5O_6$) C, H, N.

9-(1,4-Dihydroxybut-2-oxy)guanine (41a). To a solution of **39a** (0.27 g, 0.5 mmol) in dichloromethane (2.7 mL) and water (0.15 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.25 g, 1.1 mmol), and the solution was stirred at 20 °C for 1 h. The solution was diluted with dichloromethane (3 mL) and extracted with water (2×5 mL). The aqueous layers were combined and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with chloroform–methanol (10:1). The product was dissolved in 50% formic acid and the solution was heated at 100 °C for 1 h. The solvent was removed and the residue was coevaporated with water. The residue was dissolved in concentrated aqueous ammonia (2 mL) and the solution was stirred at 80 °C for 20 min. The solvent was removed in vacuo and the residue was purified by reverse-phase column chromatography on Spherisorb C18 300 silica eluting with water followed by 5% and 10% methanol to afford **41a** (28 mg, 23%); mp >215 °C dec; UV (H_2O) λ_{max} 252 (ϵ 12 400) and 265 (inflection, 9740) nm; IR (KBr) ν_{max} 3360, 3200, 1735, 1690, 1640, 1600, 1540, 1475, and 1400 cm^{-1} ; 1H NMR (Me_2SO-d_6) δ 1.82 (2 H, m, CH_2CH_2O), 3.56 (4 H, m, $2 \times CH_2O$), 4.34 (1 H, m, CH), 4.63 (1 H, t, $J = 5.4$ Hz, D_2O exchangeable, OH), 4.97 (1 H, t, $J = 6.1$ Hz, D_2O exchangeable, OH), 6.59 (2 H, s, D_2O exchangeable, NH_2), 7.87 (1 H, s, 8-H), and 10.67 (1 H, s, D_2O exchangeable, NH); HRMS calcd for $C_9H_{13}N_5O_4$ 255.0968, found 255.0973. Anal. ($C_9H_{13}N_5O_4 \cdot 0.7H_2O$) C, H, N.

2-Amino-9-(1,4-dihydroxybut-2-oxy)purine (42a). To a solution of **40a** (0.94 g, 1.8 mmol) in dichloromethane (7.2 mL) and methanol (0.8 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.91 g, 4.0 mmol) and the solution was stirred at 20 °C for 80 min. The solution was diluted with dichloromethane (8 mL) and extracted with water (3×8 mL). The aqueous layers were combined and filtered, and the solvent was removed in vacuo. The residue was purified by reverse-phase column chromatography on Spherisorb C18 300 silica eluting with 10% methanol in water followed by column chromatography on silica gel eluting with chloroform–methanol (12:1). The product was suspended in a

solution of ammonium formate (208 mg, 3.3 mmol) in methanol (8 mL), 10% palladium-on-charcoal was added (35 mg), and the mixture was heated under reflux for 90 min. The mixture was allowed to cool and water (2 mL) was added. The solution was filtered and the solvent was removed in vacuo. The residue was purified by reverse-phase column chromatography on Spherisorb C₁₈ 300 silica eluting with water and 10% methanol to afford **42a** (155 mg, 36%): mp 178–179 °C; UV (H₂O) λ_{max} 222 (ϵ 24 100) and 304 (ϵ 7020 nm); IR (KBr) ν_{max} 3330, 3210, 3070, 1655, 1640, 1580, 1510, 1480, and 1435 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 1.84 (2 H, q, *J* = 6.4 Hz, CH₂CH₂O), 3.58 (4 H, m, 2 \times CH₂O), 4.42 (1 H, m, CH), 4.63 (1 H, t, *J* = 5.2 Hz, D₂O exchangeable, OH), 4.98 (1 H, t, *J* = 5.9 Hz, D₂O exchangeable, OH), 6.70 (2 H, s, D₂O exchangeable, NH₂), 8.23 (1 H, s, 8-H), and 8.59 (1 H, s, 6-H). Anal. (C₉H₁₃N₅O₃) C, H, N.

(S)-2-(Methoxymethoxy)butanedioic Acid, Bis(methoxymethyl ester) (32c). To a solution of (S)-2-hydroxybutanedioic acid (**31c**; 10 g, 75 mmol) in anhydrous DMF (100 mL) was added diisopropylethylamine (29 mL, 165 mmol). The mixture was cooled to 0 °C and treated dropwise with a solution of chloromethyl methyl ether (13 mL, 165 mmol) in anhydrous DMF (25 mL). After stirring at 20 °C for 18 h, the solvent was removed in vacuo and the residue was treated with ethyl acetate (100 mL). The mixture was filtered and the precipitate was washed with ethyl acetate (2 \times 50 mL). The combined organic solutions were washed with brine (2 \times 50 mL) and dried (MgSO₄). The solvent was removed in vacuo; the residual oil was dissolved in anhydrous dimethoxyethane (50 mL) and diisopropylethylamine (19.5 mL, 112 mmol) and treated dropwise with a solution of chloromethyl methyl ether (8.8 mL, 112 mmol) in dimethoxyethane (10 mL). The solution was heated at 80 °C for 2 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate (100 mL) and filtered. The filtrate was washed with brine (3 \times 30 mL) and dried (MgSO₄), and the solvent was removed in vacuo to leave a liquid which was distilled to give **32c** (15 g, 75%): bp 116–122 °C, 0.04 mmHg; $[\alpha]_{\text{D}}^{25}$ -42.7° (*c* 1.3, EtOH); IR (film) ν_{max} 3000, 2960, 2900, 2830, 1745, 1470, 1450, 1440, and 1410 cm⁻¹; ¹H NMR (CDCl₃) δ 2.88 (2 H, d, *J* = 6.0 Hz, CH₂CO₂), 3.40 (3 H, s, OCH₃), 3.48 (3 H, s, OCH₃), 3.50 (3 H, s, OCH₃), 4.56 (1 H, t, *J* = 6.0 Hz, CH), 4.75 (2 H, m, CHOC₂H₅OCH₃), 5.27 (2 H, s, CH₂), and 5.30 (4 H, m, 2 \times CH₂). Anal. (C₁₀H₁₈O₇) C, H, N.

(R)-2-(Methoxymethoxy)butanedioic acid, bis(methoxymethyl ester) (32b), was prepared in an identical fashion from **31b** in 82% yield after chromatography on silica gel, eluting with ethyl acetate–hexane (1:2): $[\alpha]_{\text{D}}^{25}$ +47.6° (*c* 1.14, EtOH); IR and ¹H NMR are identical with those of the *S* enantiomer. Anal. (C₁₀H₁₈O₇) C, H, N.

(S)-1,4-Bis(benzyloxy)-2-(methoxymethoxy)butane (34c). A solution of (S)-2-(methoxymethoxy)butanedioic acid, bis(methoxymethyl ester) (**32c**; 10 g, 37.5 mmol), in anhydrous THF (10 mL) under dry nitrogen was treated with borane–dimethyl sulfide (8.3 mL, 83 mmol). The solution was heated between 60 and 80 °C over a period of 5.5 h and then cooled in ice and treated dropwise with methanol (50 mL). After effervescence had ceased, the solution was stirred at 20 °C for 18 h, and the solvent was removed in vacuo. The residue was evaporated to dryness with methanol (2 \times 50 mL) and the residue was chromatographed on silica gel, eluting with chloroform–methanol (5:1) to give **33c** (3.9 g, 69%): IR (film) ν_{max} 3400, 2940, 2890, 2820, 1470, 1440, and 1410 cm⁻¹; ¹H NMR (CDCl₃) δ 1.78 (2 H, m, CHCH₂CH₂OH), 2.96 (2 H, s, D₂O exchangeable, 2 \times OH), 3.44 (3 H, s, OCH₃), 3.50–3.85 (2 H, m, CH and 2 \times CH₂OH), 4.72 (1 H, d, *J* = 7 Hz, CH of CH₂OCH₃), and 4.77 (1 H, d, *J* = 7 Hz, CH of CH₂OCH₃).

A 60% suspension of sodium hydride in oil (1.34 g, 33 mmol) was washed with hexane (2 \times 20 mL) under an atmosphere of dry nitrogen. After decanting off the hexane, the solid was suspended in anhydrous DMF (20 mL) and treated with a solution of **33c** (2 g, 13 mmol) in DMF (5 mL). After stirring at room temperature for 6 h, the mixture was treated with a solution of benzyl bromide (3.9 mL, 33 mmol) in DMF (5 mL) and stirred at 20 °C for 18 h. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic phase was washed with water (2 \times 50 mL) and dried (MgSO₄), and the solvent was removed in vacuo. The residual oil was chromatographed on silica gel eluting with ethyl acetate–hexane (1:2) to give **34c** (3.6 g, 82%): $[\alpha]_{\text{D}}^{25}$ = -16.0° (*c*

1.6, EtOH); IR (film) ν_{max} 3080, 3060, 3030, 2920, 2890, 2860, 1495, and 1450 cm⁻¹; ¹H NMR (CDCl₃) δ 1.90 (2 H, m, CH₂CH₂O), 3.35 (3 H, s, OCH₃), 3.60 (4 H, m, 2 \times CH₂OCH₂Ar), 3.90 (1 H, m, CH), 4.50 (4 H, m, 2 \times CH₂Ar), 4.68 (1 H, d, *J* = 7 Hz, CH of CH₂OCH₃), 4.74 (1 H, d, *J* = 7 Hz, CH of CH₂OCH₃), and 7.30 (10 H, m, ArH); CIMS (NH₃) *m/z* MH⁺ 151, MNH₃⁺ 168.

(R)-1,4-Bis(benzyloxy)-2-(methoxymethoxy)butane (34b) was prepared in an identical fashion from **32b**, in overall 45% yield: $[\alpha]_{\text{D}}^{25}$ = +16.8° (*c* 1.09, EtOH); IR and ¹H NMR are identical with those of the *S* enantiomer.

(S)-1,4-Bis(benzyloxy)butan-2-ol (35c). To a solution of (S)-1,4-bis(benzyloxy)-2-(methoxymethoxy)butane (**34c**; 2 g, 6 mmol) in methanol (14 mL) was added a 2% solution of methanolic hydrogen chloride (6 mL, 2.5 mmol). The solution was stirred at 20 °C for 7 h, and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:1) to give **35c** (1.47 g, 84%): $[\alpha]_{\text{D}}^{25}$ = -7.34° (*c* 1.1, EtOH); IR (film) ν_{max} 3450, 3080, 3060, 3015, 2920, 2860, 2800, 1950, 1870, 1810, 1605, 1585, 1495, and 1450 cm⁻¹; ¹H NMR (CDCl₃) δ 1.79 (2 H, m, CH₂CH₂O), 2.86 (1 H, d, *J* = 3 Hz, D₂O exchangeable, OH), 3.45 (2 H, m, CH₂OCH₂Ar), 3.65 (2 H, m, CH₂OCH₂Ar), 4.05 (1 H, m, CH), 4.51 (2 H, s, CH₂Ar), 4.55 (2 H, s, CH₂Ar), and 7.3 (10 H, m, ArH). Anal. (C₁₈H₂₂O₃) C, H, N.

(R)-1,4-Bis(benzyloxy)butan-2-ol (35b) was prepared in an identical fashion from **34b**, in 88% yield: $[\alpha]_{\text{D}}^{25}$ = 7.7° (*c* 0.46, EtOH); IR and ¹H NMR are identical with those of the *S* enantiomer. Anal. (C₁₈H₂₂O₃) C, H, N.

(S)-N-[1,4-Bis(benzyloxy)but-2-oxy]phthalimide (36c). A solution of *N*-hydroxyphthalimide (6.8 g, 42 mmol), triphenylphosphine (11 g, 42 mmol), and (R)-1,4-bis(benzyloxy)butan-2-ol (**35b**; 8 g, 28 mmol) in anhydrous THF (150 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (6.6 mL, 42 mmol). The dark red solution was stirred for 16 h at 20 °C, then treated with additional *N*-hydroxyphthalimide (1.35 g, 8.5 mmol), triphenylphosphine (2.25 g, 8.5 mmol), and diethyl azodicarboxylate (1.35 mL, 8.5 mmol). After stirring for a further 24 h at 20 °C, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate–hexane (1:1) (50 mL) and cooled at 5 °C for 2 h. After filtration, the filtrate was evaporated to dryness. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (1:2) to give the *S* enantiomer **36c** as an oil (11 g, 91%): $[\alpha]_{\text{D}}^{25}$ = -17.4° (*c* 0.76, EtOH); IR (film) ν_{max} 3087, 3065, 3031, 2930, 2863, 2804, 1809, 1790, 1734, 1608, 1496, 1468, 1454, and 1411 cm⁻¹; ¹H NMR (CDCl₃) δ 2.05 (2 H, m, CHCH₂CH₂O), 3.75 (4 H, m, 2 \times CH₂OCH₂Ar), 4.4–4.7 (5 H, m, 2 \times OCH₂Ar and CH), and 7.1–7.9 (14 H, m, ArH); FABMS (positive ion, thio-glycerol) *m/z* MH⁺ 432. Anal. (C₂₆H₂₅NO₅·0.5H₂O), C, H, N.

(R)-N-[1,4-Bis(benzyloxy)but-2-oxy]phthalimide (36b) was prepared in an identical fashion from the *S* enantiomer **35c**, in 80% yield: $[\alpha]_{\text{D}}^{25}$ = +16.4° (*c* 1.3, EtOH); IR and ¹H NMR are identical with those of the *S* enantiomer.

(S)-1,4-Bis(benzyloxy)but-2-oxyamine (37c). A solution of (S)-N-[1,4-bis(benzyloxy)but-2-oxy]phthalimide (**36c**; 5 g, 11.6 mmol) in dichloromethane (50 mL) was cooled to 0 °C and treated with methylhydrazine (0.8 mL, 15 mmol). The reaction was stirred at 20 °C for 1 h and filtered, and the filtrate was washed with a 3% aqueous solution of sodium carbonate. After drying (MgSO₄), the solvent was removed in vacuo. The residual oil was chromatographed on silica gel eluting with ethyl acetate–hexane (5:1) to give **37c** (2.66 g, 76%): $[\alpha]_{\text{D}}^{25}$ = -13.2° (*c* 0.29, EtOH); IR (film) ν_{max} 3315, 3284, 3087, 3062, 3030, 2922, 2861, 1588, 1496, and 1454 cm⁻¹; ¹H NMR (CDCl₃) δ 1.85 (2 H, m, CH₂CH₂O), 3.55 (4 H, m, 2 \times CH₂OCH₂Ar), 3.90 (1 H, m, CH), 4.49 (2 H, s, OCH₂Ar), 4.55 (2 H, s, OCH₂Ar), 5.36 (2 H, s, D₂O exchangeable, NH₂), and 7.30 (10 H, m, ArH). Anal. (C₁₈H₂₃NO₃) C, H, N.

(R)-1,4-Bis(benzyloxy)but-2-oxyamine (37b) was obtained in an identical fashion from **36b** in 81% yield: $[\alpha]_{\text{D}}^{25}$ = +12.6° (*c* 0.55, EtOH); IR and ¹H NMR are identical with those of the *S* enantiomer. The stereochemical purities of **37b** and **37c** were determined as >95% from the ¹H NMR 270-MHz spectra of their Moscher amides.¹¹

(S)-4-Chloro-6-[[1,4-bis(benzyloxy)but-2-oxyl]amino]-2,5-diformamidopyrimidine (38c). A solution of (S)-1,4-bis(benzyloxy)but-2-oxylamine (37c) (2.17 g, 7.2 mmol), 4,6-dichloro-2,5-diformamidopyrimidine (1.7 g, 7.2 mmol), and triethylamine (3 mL, 2.4 mmol) in dioxane (50 mL) was stirred at 100 °C for 1.5 h. The reaction was cooled to 20 °C and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with chloroform-methanol (30:1) to give, as an oil, 38c (2.59 g, 71%): IR (film) ν_{\max} 3241, 3062, 3031, 2924, 2863, 1695, 1635, 1587, 1567, 1496, 1477, 1454, and 1417 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.98 (2 H, m, $\text{CH}_2\text{CH}_2\text{O}$), 3.65 (4 H, m, $2 \times \text{CH}_2\text{OCH}_2\text{Ar}$), 4.28 (1 H, m, CH), 4.50 (2 H, s, OCH_2Ar), 4.55 (2 H, s, OCH_2Ar), 7.30 (10 H, m, ArH), 7.84 (1 H, s, HCO), and 8.5-9.5 (3 H, m, D_2O exchange leaves s at 9.30, HCO and $2 \times \text{NH}$). Anal. ($\text{C}_{24}\text{H}_{25}\text{ClN}_5\text{O}_5$) C, H, N: calcd 14.04; found 13.40.

(R)-4-Chloro-6-[[1,4-bis(benzyloxy)but-2-oxyl]amino]-2,5-diformamidopyrimidine (38b) was obtained in an identical fashion from 37b, in 83% yield; IR and ^1H NMR are identical with those of the S enantiomer.

(S)-6-Chloro-9-[1,4-bis(benzyloxy)but-2-oxyl]-2-formamidopurine (39c). A solution of (S)-4-chloro-6-[[1,4-bis(benzyloxy)but-2-oxyl]amino]-2,5-diformamidopyrimidine (38c; 0.7 g, 1.4 mmol) in diethoxymethyl acetate (15 mL) was stirred at 100 °C for 1.5 h. The solvent was removed in vacuo, the residue was dissolved in methanol (20 mL) and concentrated aqueous ammonia (0.5 mL) and stirred for 0.5 h at 20 °C. The solvent was removed in vacuo and the residue was coevaporated with methanol (3×20 mL). The residue was chromatographed on silica gel eluting with chloroform-methanol (60:1) to give, as an oil, 39c (0.57 g, 84%): IR (film) ν_{\max} 3226, 3168, 3120, 3089, 3063, 3030, 3007, 2920, 2864, 1704, 1612, 1576, 1504, 1476, 1454, and 1439 cm^{-1} ; ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.04 (2 H, m, $\text{CH}_2\text{CH}_2\text{O}$), 3.55-3.80 (4 H, m, $2 \times \text{CH}_2\text{OCH}_2\text{Ar}$), 4.30-4.55 (4 H, m, OCH_2Ar), 4.76 (1 H, m, CH),

7.05-7.40 (10 H, m, ArH), 8.64 (1 H, s, 8-H), 9.33 (1 H, s, HCO), and 11.21 (1 H, s, D_2O exchangeable, NH); HRMS calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_5\text{O}_4$ 481.1517, found 481.1515.

(R)-6-Chloro-9-[1,4-bis(benzyloxy)but-2-oxyl]-2-formamidopurine (39b) was obtained in an identical fashion from 38b, in 91% yield; IR and ^1H NMR are identical with those of the S enantiomer.

(S)-9-(1,4-Dihydroxybut-2-oxyl)guanine (41c). A solution of (S)-6-chloro-9-[1,4-bis(benzyloxy)but-2-oxyl]-2-formamidopurine (39c; 0.4 g, 0.8 mmol) in 80% formic acid (20 mL) was stirred at 100 °C for 1 h and cooled to 20 °C. To the solution was added 10% palladium-on-charcoal (200 mg), the mixture was hydrogenated under atmospheric pressure for 1 h and then filtered, and the solvent was removed in vacuo. The residue was dissolved in methanol (2 mL) and concentrated aqueous ammonia (2 mL) and stirred at room temperature for 0.5 h. The solvent was removed in vacuo and the residue was chromatographed on reverse-phase silica gel eluting with water, 5% methanol-water, and 10% methanol-water. The product eluted in the 5% and 10% methanol fractions and crystallized from these fractions, giving 41c (0.12 g, 57%): mp 248 °C dec; $[\alpha]_D^{25} = -32.3^\circ$ (c 0.16, H_2O); UV, IR, and ^1H NMR data are identical with those of 41a; HRMS calcd for $\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4$ 255.0968, found 255.0965. Anal. ($\text{C}_9\text{H}_{14}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

(R)-9-(1,4-Dihydroxybut-2-oxyl)guanine (41b) was obtained in an identical fashion from 39b, in 45% yield: $[\alpha]_D^{25} = +33.8^\circ$ (c 0.24, H_2O); IR and ^1H NMR are identical with those of the S enantiomer. Anal. ($\text{C}_9\text{H}_{13}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$) C, H, N.

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Synthesis and Structure-Activity Relationships of Benzo[b]thienylallylamine Antimycotics

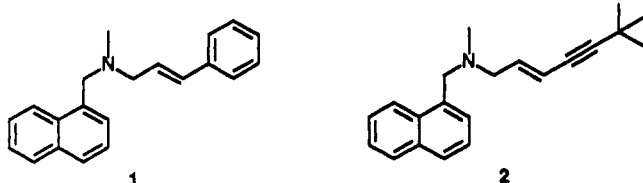
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Benzo[b]thiophene analogues of the allylamine antimycotic terbinafine (2) bearing the side chain at various positions and optionally substituted by halogen have been prepared and their antifungal activity studied. Derivatives bearing the side chain at positions 3, 4, or 7 are bioequivalents of 2. Compounds containing the allylamine side chain at position 7, with a further substituent at position 3, showed significantly enhanced activity against *Candida albicans*, an effect which appears to be specifically linked only to this particular substitution pattern. 3-Chloro-7-benzo[b]thienyl derivative 7m was found to be the most potent allylamine antimycotic identified so far. In general, substituted benzo[b]thiophenes can be used not only as potential equivalents of naphthalene in bioactive compounds but also as a tool to selectively modify biological activities.

Introduction

The allylamine derivatives are a new class of synthetic antifungal agents selectively inhibiting fungal squalene epoxidase.¹ The first representative, naftifine [(E)-N-methyl-N-(3-phenyl-2-propenyl)-1-naphthalenemethanamine, 1], has recently become commercially available as



a topical antimycotic. Exploration of structure-activity relationships (SAR) on the basis of naftifine, together with

new synthetic strategies, has led to the discovery of terbinafine (SF 86-327, Lamisil, 2), the first pharmaceutical agent to contain an (E)-1,3-enyne structural element.² Terbinafine exhibits considerably higher activity than the original lead structure naftifine both in vitro and in vivo; it is also up to 1 order of magnitude more effective than clinical standards in various chemotherapeutic animal tests after oral or topical administration.^{3,4} According to ad-

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