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: $[\alpha]^{22}_D = -130°$ (*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, Ar*H*); MS *m/z* 576 (M^+). Anal. ($C_{28}H_{32}O_{13}$) C, H.

(-)-4α[(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-glucose[18] (308 mg, 0.88 mmol), and BF_3–Et_2O (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: $[\alpha]^{20}_D = -119°$ (*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, Ar*H*; MS *m/z* 744 (M^+). Anal. ($C_{36}H_{40}O_{17}$) C, H.

(-)-4α-[2-(*N*,*N*-Dimethylamino)ethoxy]stegane [(-)-24]. A suspension of (-)-**5**[8] (23.7 mg, 0.057 mmol), *N*,*N*-dimethyl-2-hydroxyethylamine (14.6 mg, 0.60 mmol), BF_3–Et_2O (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: $[\alpha]^{22}_D = -125°$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (6 H, s, $N(CH_3)_2$), 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, Ar*H*); MS *m/z* 485 (M^+). Anal. ($C_{26}H_{31}NO_8$) C, H, N.

(-)-4α-Cyanostegane [(-)-25]. A solution of (-)-steganol (**5**[8]; 77.9 mg, 0.19 mmol), tetra-*O*-acetyl-α-D-glucopyranosyl bromide[16] (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; $[\alpha]^{20}_D = -201°$ (*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, $CH \times 3$), 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. ($C_{23}H_{21}NO_7$) C, H, N.

(18) Lemieux, R. U. *Methods in Carbohydrate Chemistry*; Whister, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol II, p 221.

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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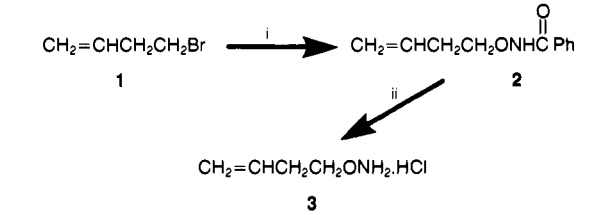
Reaction of alkenoxyamines (**3**, **5**) or (*R*,*S*)-, (*R*)-, and (*S*)-hydroxy-protected derivatives of hydroxyalkoxyamines (**20a**,**b**, **37a**–**c**) with 4,6-dichloro-2,5-diformamidopyrimidine (**4**) and cyclization of the resultant 6-[(alkenoxy)amino]- and 6-(alkoxyamino)pyrimidines (**6**, **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-(dihydroxypropoxy)methyl]guanine [(*S*)-INDG][4] and 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG),[5,6]

Scheme I[a]



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

(1) Part 1: Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. *J. Med. Chem.* **1990**, *33*, 187.
(2) Larsson, A.; Öberg, B.; Alenius, S.; Hagberg, C.-E.; Johansson, N.-G.; Lindborg, B.; Steyning, G. *Antimicrob. Agents Chemother.* **1983**, *23*, 664.
(3) Ericson, A.-C.; Larsson, A.; Aoki, F. Y.; Yisak, W.-A.; Johansson, N. G.; Öberg, B.; Datema, R. *Antimicrob. Agents Chemother.* **1985**, *27*, 753.
(4) Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M.-E. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. *J. Med. Chem.* **1985**, *28*, 926.

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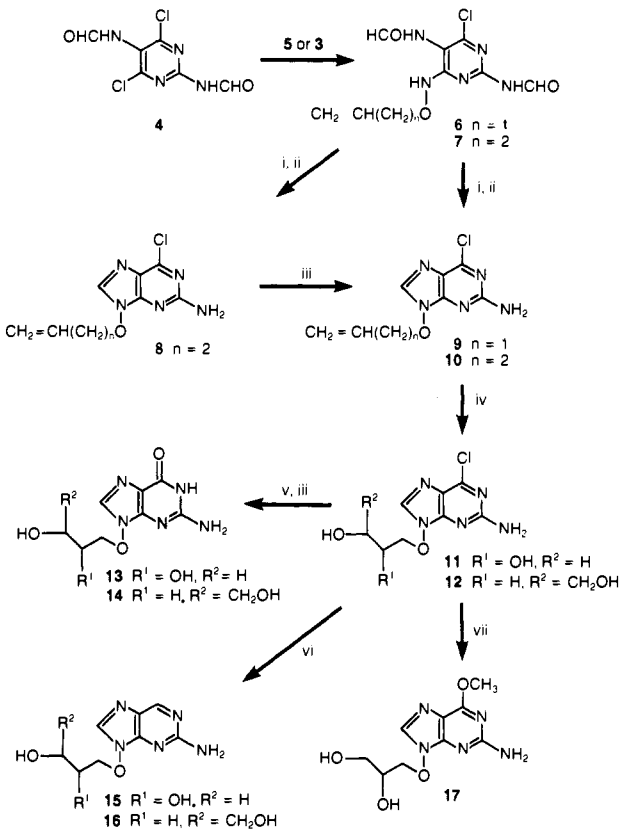
Scheme II[a]



[a] (i) $CH_3CO_2CH(OEt)_2$, 120 °C; (ii) MeOH–NH_3; (iii) NH_3; (iv) OsO_4, 4-methylmorpholine *N*-oxide, $(CH_3)_2C{=}O$, H_2O; (v) 80% HCO_2H, 100 °C; (vi) HCO_2NH_4, 10% Pd/C, MeOH; (vii) NaOMe, MeOH, 100 °C.

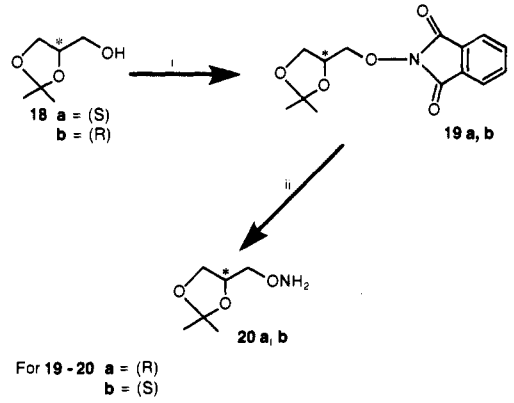
respectively. Some analogous 9-substituted derivatives of 2-aminopurine and 2-amino-6-methoxypurine have also been prepared.

Chemistry

The synthetic route employed in syntheses of the 9-alkoxypurines was similar to that described previously[7] 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-butenoxyamine 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 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**.

Scheme III[a]



[a] (i) *N*-Hydroxyphthalimide, Ph_3P, DEAD, THF; (ii) $MeHNNH_2$, CH_2Cl_2.

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.

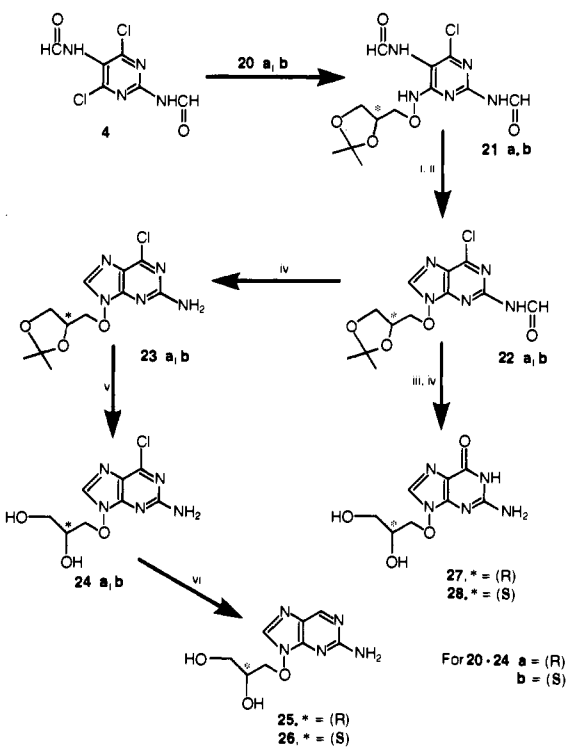
Diethyl azodicarboxylate (DEAD) catalyzed reaction of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (**18a**) with *N*-hydroxyphthalimide followed by treatment of the intermediary phthalimido compound **19a** with methylhydrazine gave the (*R*)-alkoxyamine **20a** (Scheme III). Reaction of **20a** with 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-oxy)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-

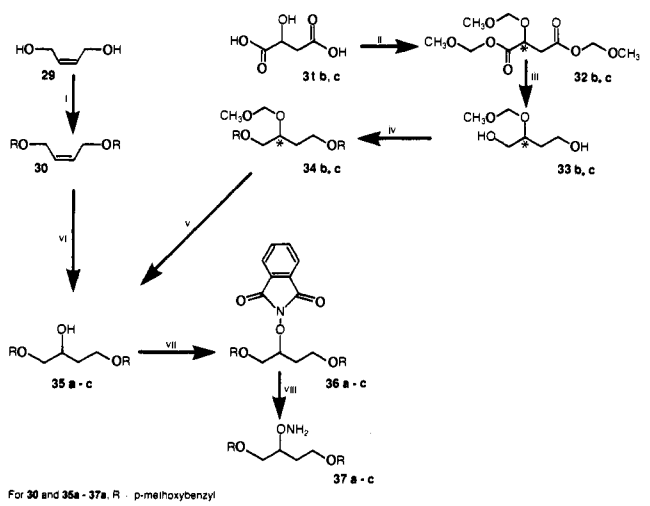
(5) Abele, G.; Karlstrom, A.; Harmenberg, J.; Shigeta, S.; Larsson, A.; Lindborg, B.; Wahren, B. *Antimicrob. Agents Chemother.* **1987**, *31*, 76.
(6) Abele, G.; Eriksson, B.; Harmenberg, J.; Wahren, B. *Antimicrob. Agents Chemother.* **1988**, *32*, 1137.
(7) Harnden, M. R.; Parkin, A.; Wyatt, P.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

Scheme IV[a]



[a] (i) $CH_3CO_2CH(OEt)_2$, 120 °C; (ii) MeOH–NH_3; (iii) HCO_2H, 100 °C; (iv) NH_3; (v) 80% CH_3CO_2H, 70 °C; (vi) HCO_2NH_4, 10% Pd/C, MeOH.

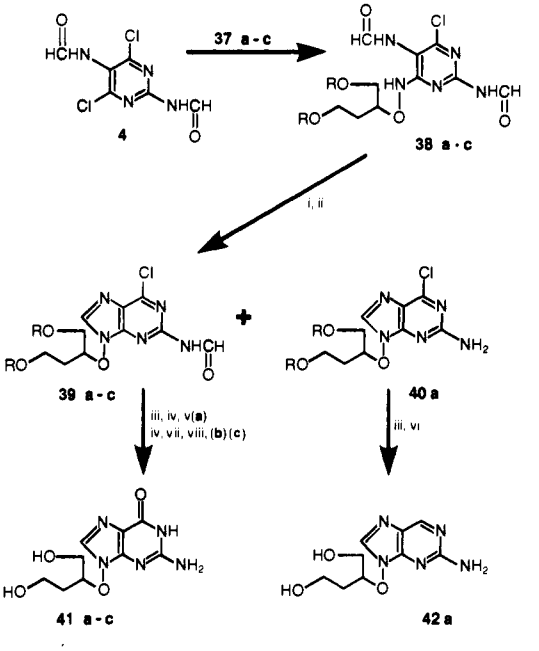
Scheme V[a]



[a] (i) NaH, DMF, 4-methoxybenzyl chloride; (ii) $(Pr^i)_2NEt$, $ClCH_2OCH_3$, DMF; (iii) 10 M BH_3–Me_2S, THF; (iv) NaH, DMF, $PhCH_2Br$; (v) HCL(g)–MeOH; (vi) $(CF_3CO_2)_2Hg$, THF, $NaBH_4$, NaOH; (vii) *N*-hydroxyphthalimide, Ph_3P, DEAD, THF; (viii) $MeHNNH_2$, CH_2Cl_2.

diformamidopyrimidine (**4**) gave the pyrimidine intermediate **38a**. Cyclization of **38a** with diethoxymethyl acetate followed by treatment with aqueous ammonia afforded a mixture of the 2-formamido (**37a**) and 2-amino (**40a**) purines. Guanine **41a** was obtained by sequential treatment of **39a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), refluxing 50% formic acid, and aqueous ammonia. The corresponding 2-aminopurine derivative (**42a**) was prepared by treatment of **40a** with DDQ followed by catalytic

Scheme VI[a]



[a] (i) $CH_3CO_2CH(OEt)_2$, 120 °C; (ii) MeOH–NH_3; (iii) DDQ, CH_2Cl_2, H_2O; (iv) 80% HCO_2H, 100 °C; (v) NH_3; (vi) HCO_2NH_4, 10% Pd/C, MeOH; (vii) 10% Pd/C, 80% HCO_2H; (viii) NH_3.

hydrogen transfer from ammonium formate.

As in the preparation of **20a,b**, it was necessary to modify the approach to the chiral alkoxyamines **37b,c** from that used to prepare the racemic alkoxyamine **37a**. Treatment of the enantiomers of malic acid (**31b,c**) with chloromethyl methyl ether in DMF gave diesters which upon further alkylation with chloromethyl methyl ether in dimethoxyethane gave **32b,c** (Scheme V). Reduction of **32b,c** with borane–dimethyl sulfide in THF gave diols **33b,c**. These were converted to the dibenzyl ethers **34b,c** by treatment with sodium hydride and benzyl bromide in DMF. Removal of the methoxymethyl protecting group was achieved with hydrogen chloride in methanol at ambient temperature, providing alcohols **35b,c**. DEAD-catalyzed treatment of **35b,c** with *N*-hydroxyphthalimide in THF then gave the phthalimide derivatives **36b,c**, the reaction proceeding with inversion of configuration. Cleavage of **36b,c** with methylhydrazine gave the alkoxyamines **37b,c**. Chloride displacements in **4** using **37b,c** and triethylamine in dioxane afforded pyrimidines **38b,c**, which were cyclized to chloropurines **39b,c** in diethoxymethyl acetate at 120 °C (Scheme VI). Hydrolysis of **39b,c** in 80% formic acid at 100 °C followed by hydrogenolytic debenzylation over palladium–charcoal then afforded guanines **41b,c**.

Biological Results

The acyclonucleosides (**13**, **14**, **27**, **28**, **41a–c**) prepared in this study were tested in plaque-reduction assays[8] for activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and against varicella zoster virus (VZV). The results obtained are given in Table I.

The racemic guanine derivative **13** has potent and selective activity against HSV-1 and HSV-2, but it is less active against VZV. Both enantiomers of **13** (**27** and **28**)

(8) Boyd, M. R.; Bacon, T. H.; Sutton, D.; Cole, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1238.

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

	IC_{50}, μM		
compd[b]	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 (IC_{50}). [b] Test compounds were prepared as 10 mg/mL solutions in Me_2SO 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 reported[9] to be substantially more active than its *S* enantiomer and to be less active against VZV[10] 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 reported[10] to be highly active against VZV.

None of the compounds for which IC_{50} data are given was cytotoxic for the MRC-5 cell monolayers when tested at concentrations up to 100 μg/mL (ca. 400 μM). 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 μM. 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 ±0.4% of the calculated values. Upon TLC of analytical samples, using silica gel $60F_{254}$ 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 (Me_2SO-d_6) δ 4.37 (2 H, d, J = 6.0 Hz, CH_2ON), 5.32 (2 H, m, CH=CH_2), 5.97 (1 H, m, CH=CH_2), 8.16 (1 H, s, CHO), 9.30 (1 H, s, CHO), 9.44 (1 H, br s, D_2O exchangeable, NH), and 10.87 (2 H, br s, D_2O exchangeable, 2 × NH); HRMS calcd for $C_9H_{10}ClN_5O_3$ 271.0469, found 271.0469. Anal. ($C_9H_{10}ClN_5O_3$) 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 (Me_2SO-d_6) δ 4.84 (2 H, d, J = 6.0 Hz, CH_2ON), 5.35 (2 H, m, CH_2=CH), 6.13 (1 H, m, CH=CH_2), 7.10 (2 H, br s, D_2O exchangeable, NH_2), and 8.35 (1 H, s, 8-H); HRMS calcd for $C_8H_8ClN_5O$ 225.0414, found 225.0406. Anal. ($C_9H_{13}N_5O_4$·0.1H_2O) 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 (Me_2SO-d_6) δ 3.42 (2 H, m, CH_2OH), 3.78 (1 H, m, CHOH), 4.20 (1 H, dd, J = 10.7, 7.3 Hz, CH_2ON), 4.41 (1 H, dd, J = 10.7, 3.2 Hz, CH_2ON), 4.74 (1 H, t, J = 5.7 Hz, D_2O exchangeable, OH), 5.14 (1 H, d, J = 5.2 Hz, D_2O exchangeable, OH), 7.13 (2 H, br s, D_2O exchangeable, NH_2), and 8.36 (1 H, s, 8-H); HRMS calcd for $C_8H_{10}ClN_5O_3$ 259.0469, found 259.0462. Anal. ($C_8H_{10}ClN_5O_3$·0.3H_2O) 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 (H_2O) λ_{max} 252 (ε 12600) nm; IR (KBr) ν_{max} 3330, 1690, 1640, 1605, 1540, and 1475 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.39 (2 H, m, CH_2OH), 3.72 (1 H, m, CHOH), 4.10 (1 H, dd, J = 10.5, 7.6 Hz, CH_2ON), 4.33 (1 H, dd, J = 10.5, 3.3 Hz, CH_2ON), 4.70 (1 H, t, J = 5.7 Hz, D_2O exchangeable, OH), 5.15 (1 H, d, J = 5.2 Hz, D_2O exchangeable, OH), 6.62 (2 H, br s, D_2O exchangeable, NH_2), 7.90 (1 H, s, 8-H), and 10.58 (1 H, br s, D_2O exchangeable, NH); HRMS calcd for $C_8H_{11}N_5O_4$ 241.0811, found 241.0813. Anal. ($C_8H_{11}N_5O_4$·0.8H_2O) 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 C_{18} 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 (H_2O) λ_{max} 221 (ε 25600), 305 (ε 7000) nm; IR (KBr) ν_{max} 3670, 3420, 3310, 3200, 1650, 1620,

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1570, 1520, 1480, and 1425 cm^{-1}; ^{1}H NMR (Me_2SO-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 $C_8H_{11}N_5O_3$ 225.0862, found 225.0865. Anal. ($C_8H_{11}N_5O_3$) 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 °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}; ^{1}H NMR (Me_2SO-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 $C_9H_{13}N_5O_4$ 255.0967, found 255.0968. Anal. ($C_9H_{13}N_5O_4 \cdot 0.5H_2O$) 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 °C. This solution was treated with 4-bromo-1-butene (1; 27 g, 0.2 mol) and the reaction was stirred at 100 °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}; ^{1}H NMR ($CDCl_3$) δ 2.44 (2 H, q, J = 7.0 Hz, CH_2CH_2O), 4.07 (2 H, t, J = 7.8 Hz, CH_2ON), 5.12 (2 H, m, CH_2=CH), 5.80 (1 H, m, CH=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 °C; IR (KBr) ν_{max} 3400, 3100–2900, 1650, 1590, 1550, and 1515 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.32 (2 H, m, CH_2CH_2ON), 4.06 (2 H, t, J = 7.0 Hz, CH_2ON), 5.07 (2 H, m, CH_2=CH), 5.72 (1 H, m, CH=CH_2), and 11.12 (3 H, br s, D_2O exchangeable, NH_3). Anal. ($C_4H_{10}ClNO$) 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 °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 °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 °C; IR (Nujol) ν_{max} 3250, 3180, 1710, 1650, 1590, 1560, and 1500 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.37 (2 H, q, J = 6.6 Hz, CH_2CH_2ON), 3.92 (2 H, t, J = 6.6 Hz, CH_2ON), 5.11 (2 H, m, CH_2=CH), 5.87 (1 H, m, CH=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 × NH). Anal. ($C_{10}H_{12}ClN_5O_3$) 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 °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 °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 °C; IR (KBr) ν_{max} 3420, 1720, 1610, 1580, 1540, and 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (2 H, m, CH_2CH_2ON), 4.47 (2 H, t, J = 7.0 Hz, CH_2ON), 5.20 (2 H, m, CH_2=CH), 5.84 (1 H, m, CH=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. ($C_{10}H_{10}ClN_5O_2 \cdot 0.3H_2O$) 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 °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 °C; IR (KBr) ν_{max} 3470, 3310, 1630, 1620, 1570, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.52 (2 H, m, CH_2CH_2ON), 4.42 (2 H, t, J = 7.0 Hz, CH_2ON), 5.22 (2 H, m, CH_2=CH), 5.40 (2 H, br s, D_2O exchangeable, NH_2), 5.82 (1 H, m, CH=CH_2), and 7.90 (1 H, s, 8-H). Anal. ($C_9H_{10}ClN_5O$) 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 °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 °C; IR (KBr) ν_{max} 3430, 3320, 3210, 1650, 1620, 1570, and 1520 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.74 (2 H, m, CH_2CH_2ON), 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 × OH), 7.10 (2 H, br s, D_2O exchangeable, NH_2), and 8.41 (1 H, s, 8-H); HRMS calcd for $C_9H_{12}ClN_5O_3$ 273.0629, found 273.0635. Anal. ($C_9H_{12}ClN_5O_3 \cdot 0.2H_2O$) 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 °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 °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 °C; UV (H_2O) λ_{max} 252 (ϵ 12900) nm; IR (KBr) ν_{max} 3330, 3170, 1690, 1640, 1600, 1540, and 1475 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.64 (1 H, m, CH_2CH_2ON), 1.88 (1 H, m, CH_2CH_2ON), 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 $C_9H_{13}N_5O_4$ 255.0967, found 255.0968. Anal. ($C_9H_{13}N_5O_4 \cdot 0.5H_2O$) C, H, N.

2-Amino-9-(3,4-dihydroxybutyloxy)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 °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}; ^{1}H NMR (Me_2SO-d_6) δ 1.65 (1 H, m, CH_2CH_2ON), 1.91 (1 H, m, CH_2CH_2ON), 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 $C_9H_{13}N_5O_3$ 239.1018, found 239.1022. Anal. ($C_9H_{13}N_5O_3$) 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 °C and treated with diethyl azodicarboxylate (66 mmol). The dark red solution was stirred for 18 h at 20 °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 °C; $[\alpha]^{20}_D$ = +15.6° (*c* 0.98, MeOH); IR (KBr) ν_{max} 1790, 1730, and 1610 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 1.35 (3 H, s, CH_3), 1.41 (3 H, s, CH_3), 3.99 (1 H, dd, J = 5.5, 8.8 Hz, CH_2ON or CH_2OCMe_2), 4.17 (2 H, m, 1 H of CH_2ON + 1 H of CH_2OCMe_2), 4.32 (1 H, dd, J = 5.7, 10.1 Hz, CH_2ON or CH_2OCMe_2), 4.50 (1 H, m, CH), and 7.75–7.87 (4 H, m, ArH). Anal. ($C_{14}H_{15}NO_5$) C, H, N.

(*S*)-*N*-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]phthalimide (19b): 69% yield; mp 99–100 °C; $[\alpha]^{25}_D$ = −14.6° (*c* 0.4, MeOH); IR and ^1H NMR are identical with those of the *R* enantiomer. Anal. ($C_{14}H_{15}NO_5$) 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 ($CDCl_3$) δ 1.38 (3 H, s, CH_3), 1.44 (3 H, s, CH_3), 3.73 (3 H, m, CH_2ON + 1 H of CH_2OCMe_2), 4.07 (1 H, dd, J = 6.4, 8.2 Hz, 1 H of CH_2OCMe_2), 4.35 (1 H, m, CH), and 5.56 (2 H, br s, D_2O exchangeable, NH_2). Anal. ($C_6H_{13}NO_3$) 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. ($C_6H_{13}NO_3$) 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 ($CDCl_3$) δ 1.39 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 3.81 (1 H, dd, J = 6.3, 8.2 Hz, CH_2OCMe_2), 4.03 (2 H, d, J = 5.5 Hz, CH_2ON), 4.11 (1 H, dd, J = 6.6, 8.2 Hz, CH_2OCMe_2), 4.41 (1 H, m, CH), 7.29 (1 H, s, D_2O exchangeable, NH), 7.97 (1 H, br d, J = 10.5 Hz, D_2O exchangeable, NH), 8.34 (1 H, s, HCO), 8.94 (1 H, br s, D_2O 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 ($CDCl_3$) δ 1.40 (3 H, s, CH_3), 1.44 (3 H, s, CH_3), 3.89 (1 H, m, CH_2OCMe_2), 4.16 (1 H, m, CH_2OCMe_2), 4.50 (3 H, m, CH + CH_2ON), 8.23 (1 H, s, 8-H), 8.45 (1 H, br d, J = 11.5 Hz, D_2O exchangeable, NH), and 9.59 (1 H, d, J = 11.5 Hz, *H*CONH). Anal. ($C_{12}H_{14}ClN_5O_4$) 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 $C_{12}H_{14}ClN_5O_4$ 327.0734, found 327.0734. Anal. ($C_{12}H_{14}ClN_5O_4$) 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; $[\alpha]^{25}_D$ = −14.9° (*c* 0.1, H_2O); UV (H_2O) λ_{max} 252 (ε 12200) nm; IR (KBr) ν_{max} 3380, 3180, 1690, 1640, 1600, and 1540 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.39 (2 H, m, CH_2OH), 3.73 (1 H, m, CH), 4.10 (1 H, dd, J = 7.7, 10.5 Hz, CH_2ON), 4.32 (1 H, dd, J = 3.3, 10.5 Hz, CH_2ON), 4.70 (1 H, t, J = 5.6 Hz, D_2O exchangeable, OH), 5.15 (1 H, d, J = 5.0 Hz, D_2O exchangeable, OH), 6.62 (2 H, br s, D_2O exchangeable, NH_2), 7.90 (1 H, s, 8-H), and 10.55 (1 H, br s, D_2O exchangeable, NH); HRMS calcd for $C_8H_{11}N_5O_4$ 241.0807, found 241.0797. Anal. ($C_8H_{11}N_5O_4$·0.5H_2O) H, N; C: calcd, 38.39; found, 37.91.

(*S*)-9-(2,3-Dihydroxypropoxy)guanine (28): 45% yield: mp 252–255 °C dec; $[\alpha]^{25}_D$ = +13.5° (*c* 0.16, H_2O); UV (H_2O) λ_{max} 252 (ε 12900) nm; IR and ^1H NMR are identical with those of the *R* enantiomer; HRMS calcd for $C_8H_{11}N_5O_4$ 241.0811, found 241.0820. Anal. ($C_8H_{11}N_5O_4$·0.4H_2O) 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 (Me_2SO-d_6) δ 1.28 (3 H, s, CH_3), 1.31 (3 H, s, CH_3), 3.77 (1 H, dd, J = 8.5, 5.8 Hz, CH_2OCMe_2), 4.08 (1 H, dd, J = 8.5, 5.8 Hz, CH_2OCMe_2), 4.40 (3 H, m, CH_2ON + CH), 7.11 (2 H, s, D_2O exchangeable, NH_2), and 8.38 (1 H, s, 8-H); HRMS calcd for $C_{11}H_{14}ClN_5O_3$ 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 ($CDCl_3$) δ 1.36 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 3.85 (1 H, m, CH_2OCMe_2), 4.14 (1 H, m, CH_2OCMe_2), 4.43 (3 H, m, CH_2ON + CH), 5.51 (2 H, br s, D_2O exchangeable, NH_2), and 8.00 (1 H, s, 8-H); HRMS calcd for $C_{11}H_{14}ClN_5O_3$ 299.0785, found 299.0795. Anal. ($C_{11}H_{14}ClN_5O_3$) 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 (Me_2SO-d_6) δ 3.41 (2 H, m, CH_2OH), 3.78 (1 H, m, CH), 4.19 (1 H, dd, J = 7.4, 10.7 Hz, CH_2ON), 4.40 (1 H, dd, J = 3.3, 10.7 Hz, CH_2ON), 4.72 (1 H, t, J = 5.6 Hz, D_2O exchangeable, OH), 5.13 (1 H, d, J = 5.0 Hz, D_2O exchangeable, OH), 7.12 (2 H, s, D_2O exchangeable, NH_2), and 8.35 (1 H, s, 8-H); HRMS calcd for $C_8H_{10}ClN_5O_3$ 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 $C_8H_{10}ClN_5O_3$ 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; $[\alpha]^{25}_D$ = −16.0° (*c* 0.1, H_2O); UV (H_2O) λ_{max} 221 (ε 24900) and 305 (ε 7000) nm; IR (KBr) ν_{max} 3380, 3320, 3200, 1660, 1650, 1620, 1580, and 1510 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.43 (2 H, m, CH_2OH), 3.77 (1 H, m, CH), 4.18 (1 H, dd, J = 7.8, 10.7 Hz, CH_2ON), 4.40 (1 H, dd, J = 2.5, 10.7 Hz, CH_2ON), 4.72 (1 H, t, J = 5.4 Hz, D_2O exchangeable, OH), 5.16 (1 H, d, J = 4.9 Hz, D_2O exchangeable, OH), 6.72 (2 H, s, D_2O exchangeable, NH_2),

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; $[\alpha]^{25}_D$ = +16.5° (*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 × CH_3), 4.02 (4 H, d, *J* = 4.5 Hz, 2 × $CHCH_2$), 4.43 (4 H, s, 2 × $ArCH_2$), 5.79 (2 H, t, *J* = 4.5 Hz, 2 × 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 × 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 × CH_3 and 2 × CH_2O), 4.25–4.55 (4 H, m, 2 × $ArCH_2$), 4.60 (1 H, m, CH), 6.7–7.3 (8 H, m, 2 × $CH_3OC_6H_4$), 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 × CH_2O), 3.80 (6 H, s, 2 × 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, Ar-H), and 7.25 (4 H, m, Ar-H); 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 × 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 × $ArCH_2$), 6.88 (4 H, m, ArH), 7.21 (4 H, m, ArH), 8.14 and 8.32 (total 1 H, 2 × s, HCO), 9.17–9.43 (2 H, m, D_2O exchange leaves s at 9.27, HCO and 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 × CH_2O), 3.73 (6 H, s, 2 × 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. ($C_{26}H_{28}ClN_5O_6$) 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 × CH_2O), 3.73 (6 H, s, 2 × 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. ($C_{25}H_{28}ClN_5O_5$) 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 (inflexion, 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 × 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 C_{18} 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 C_{18} 300 silica eluting with water and 10% methanol to afford **42a** (155 mg, 36%): mp 178–179 °C; UV (H_2O) 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 (Me_2SO-d_6) δ 1.84 (2 H, q, J = 6.4 Hz, CH_2CH_2O), 3.58 (4 H, m, 2 × CH_2O), 4.42 (1 H, m, CH), 4.63 (1 H, t, J = 5.2 Hz, D_2O exchangeable, OH), 4.98 (1 H, t, J = 5.9 Hz, D_2O exchangeable, OH), 6.70 (2 H, s, D_2O exchangeable, NH_2), 8.23 (1 H, s, 8-H), and 8.59 (1 H, s, 6-H). Anal. ($C_9H_{13}N_5O_3$) 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 × 50 mL). The combined organic solutions were washed with brine (2 × 50 mL) and dried ($MgSO_4$). 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 × 30 mL) and dried ($MgSO_4$), 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; $[\alpha]^{25}_D$ −42.7° (*c* 1.3, EtOH); IR (film) ν_{max} 3000, 2960, 2900, 2830, 1745, 1470, 1450, 1440, and 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (2 H, d, J = 6.0 Hz, CH_2CO_2), 3.40 (3 H, s, OCH_3), 3.48 (3 H, s, OCH_3), 3.50 (3 H, s, OCH_3), 4.56 (1 H, t, J = 6.0 Hz, CH), 4.75 (2 H, m, $CHOCH_2OCH_3$), 5.27 (2 H, s, CH_2), and 5.30 (4 H, m, 2 × CH_2). Anal. ($C_{10}H_{18}O_7$) 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): $[\alpha]^{25}_D$ = +47.6° (*c* 1.14, EtOH); IR and ^1H NMR are identical with those of the *S* enantiomer. Anal. ($C_{10}H_{18}O_7$) 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 × 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 ($CDCl_3$) δ 1.78 (2 H, m, $CHCH_2CH_2OH$), 2.96 (2 H, s, D_2O exchangeable, 2 × OH), 3.44 (3 H, s, OCH_3), 3.50–3.85 (5 H, m, CH and 2 × CH_2OH), 4.72 (1 H, d, J = 7 Hz, CH of CH_2OCH_3), and 4.77 (1 H, d, J = 7 Hz, CH of CH_2OCH_3).

A 60% suspension of sodium hydride in oil (1.34 g, 33 mmol) was washed with hexane (2 × 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 × 50 mL) and dried ($MgSO_4$), 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%): $[\alpha]^{25}_D$ = −16.0° (*c* 1.6, EtOH); IR (film) ν_{max} 3080, 3060, 3030, 2920, 2890, 2860, 1495, and 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (2 H, m, CH_2CH_2O), 3.35 (3 H, s, OCH_3), 3.60 (4 H, m, 2 × CH_2OCH_2Ar), 3.90 (1 H, m, CH), 4.50 (4 H, m, 2 × CH_2Ar), 4.68 (1 H, d, J = 7 Hz, CH of CH_2OCH_3), 4.74 (1 H, d, J = 7 Hz, CH of CH_2OCH_3), and 7.30 (10 H, m, ArH); CIMS (NH_3) m/z MH^+ 151, MNH_4^+ 168.

(*R*)-1,4-Bis(benzyloxy)-2-(methoxymethoxy)butane (34b) was prepared in an identical fashion from **32b**, in overall 45% yield: $[\alpha]^{25}_D$ = +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%): $[\alpha]^{25}_D$ = −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 ($CDCl_3$) δ 1.79 (2 H, m, CH_2CH_2O), 2.86 (1 H, d, J = 3 Hz, D_2O exchangeable, OH), 3.45 (2 H, m, CH_2OCH_2Ar), 3.65 (2 H, m, CH_2OCH_2Ar), 4.05 (1 H, m, CH), 4.51 (2 H, s, CH_2Ar), 4.55 (2 H, s, CH_2Ar), and 7.3 (10 H, m, ArH). Anal. ($C_{18}H_{22}O_3$) C, H, N.

(*R*)-1,4-Bis(benzyloxy)butan-2-ol (35b) was prepared in an identical fashion from **34b**, in 88% yield: $[\alpha]^{25}_D$ = 7.7° (*c* 0.46, EtOH); IR and ^1H NMR are identical with those of the *S* enantiomer. Anal. ($C_{18}H_{22}O_3$) 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%): $[\alpha]^{25}_D$ = −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 ($CDCl_3$) δ 2.05 (2 H, m, $CHCH_2CH_2O$), 3.75 (4 H, m, 2 × CH_2OCH_2Ar), 4.4–4.7 (5 H, m, 2 × OCH_2Ar and CH), and 7.1–7.9 (14 H, m, ArH); FABMS (positive ion, thioglycerol) m/z MH^+ 432. Anal. ($C_{26}H_{25}NO_5 \cdot 0.5H_2O$), 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: $[\alpha]^{25}_D$ = +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 ($MgSO_4$), 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%): $[\alpha]^{25}_D$ = −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 ($CDCl_3$) δ 1.85 (2 H, m, CH_2CH_2O), 3.55 (4 H, m, 2 × CH_2OCH_2Ar), 3.90 (1 H, m, CH), 4.49 (2 H, s, OCH_2Ar), 4.55 (2 H, s, OCH_2Ar), 5.36 (2 H, s, D_2O exchangeable, NH_2), and 7.30 (10 H, m, ArH). Anal. ($C_{18}H_{23}NO_3$) C, H, N.

(*R*)-1,4-Bis(benzyloxy)but-2-oxyamine (37b) was obtained in an identical fashion from **36b** in 81% yield: $[\alpha]^{25}_D$ = +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]

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(S)-4-Chloro-6-[[1,4-bis(benzyloxy)but-2-oxy]amino]-2,5-diformamidopyrimidine (38c). A solution of (S)-1,4-bis(benzyloxy)but-2-oxyamine (**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, CH_2CH_2O), 3.65 (4 H, m, 2 × CH_2OCH_2Ar), 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 × NH). Anal. ($C_{24}H_{25}ClN_5O_5$) C, H; N: calcd 14.04; found 13.40.

(R)-4-Chloro-6-[[1,4-bis(benzyloxy)but-2-oxy]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-oxy]-2-formamidopurine (39c). A solution of (S)-4-chloro-6-[[1,4-bis(benzyloxy)but-2-oxy]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 (Me_2SO-d_6) δ 2.04 (2 H, m, CH_2CH_2O), 3.55–3.80 (4 H, m, 2 × CH_2OCH_2Ar), 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 $C_{24}H_{24}ClN_5O_4$ 481.1517, found 481.1515.

(R)-6-Chloro-9-[1,4-bis(benzyloxy)but-2-oxy]-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-oxy)guanine (41c). A solution of (S)-6-chloro-9-[1,4-bis(benzyloxy)but-2-oxy]-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; $[\alpha]^{25}_D$ = −32.3° (c 0.16, H_2O); UV, IR, and ^1H NMR data are identical with those of **41a**; HRMS calcd for $C_9H_{13}N_5O_4$ 255.0968, found 255.0965. Anal. ($C_9H_{14}N_5O_4 \cdot 0.5H_2O$) C, H, N.

(R)-9-(1,4-Dihydroxybut-2-oxy)guanine (41b) was obtained in an identical fashion from **39b**, in 45% yield: $[\alpha]^{25}_D$ = +33.8° (c 0.24, H_2O); IR and ^1H NMR are identical with those of the S enantiomer. Anal. ($C_9H_{13}N_5O_4 \cdot 0.5H_2O$) C, H, N.

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

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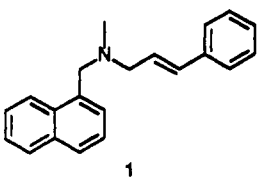
Benzo[*b*]thiophene analogues of the allylamine antimycotic terbinafine (**2**) bearing the side chain at various positions and optionally substituted by halogen have been prepared and their antifungal activity studied. Derivatives bearing the side chain at positions 3, 4, or 7 are bioequivalents of **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



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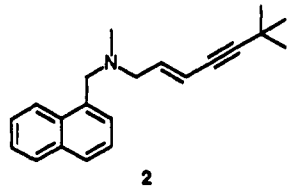

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a topical antimycotic. Exploration of structure–activity relationships (SAR) on the basis of naftifine, together with new synthetic strategies, has led to the discovery of terbinafine (SF 86-327, Lamisil, **2**), the first pharmaceutical agent to contain 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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