concentrations, and each concentration was tested five times. Dissociation constants (pA_2 values, Table I) were estimated by Schild plots[19] constrained to slope -1.0, as required by the theory.[25] When applying this method, it was always verified that the experimental data generated a line whose derived slope not significantly different from unity ($p > 0.05$).

Data are presented as means ± SE of n experiments. Differences between mean values were tested for significance by the Student's t test.

Acknowledgment. We acknowledge support by a grant from Ministry of Public Education ("Fondi 40%").

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Registry No. **1**, 613-67-2; **2**, 92642-94-9; **3**, 116635-64-4; **3**·HCl, 116635-75-7; **4**, 116635-65-5; **4**·HCl, 116635-76-8; **5**, 116635-66-6; **5**·HCl, 116635-77-9; **6**, 116635-67-7; **6**·$H_2C_2O_4$, 116635-78-0; **7**, 116635-68-8; **7**·$H_2C_2O_4$, 116663-45-7; **8**, 116635-69-9; **9**, 116635-70-2; **9**·$H_2C_2O_4$, 116635-80-4; **10**, 116663-44-6; **10**·$H_2C_2O_4$, 116663-46-8; **11**, 116635-71-3; **11**·$H_2C_2O_4$, 116635-81-5; **12**, 40516-01-6; **12**·HCl, 40516-02-7; **13**, 116635-72-4; **13**·HCl, 116635-82-6; **14**, 116635-73-5; **14**·HCl, 116635-83-7; **15**, 116635-74-6; **15**·$H_2C_2O_4$, 116635-84-8; **16**, 40515-98-8; **16**·HCl, 87780-27-6; 3-(chloromethyl)-1,4-benzoxathian, 65331-11-5; 4-chromanone, 491-37-2; thiochroman-4-one, 3528-17-4; chroman-2-carboxylic acid, 51939-71-0; 1-naphthoic acid, 86-55-5; 2-naphthoic acid, 93-09-4; indole-2-carboxaldehyde, 19005-93-7; *N*-[2-(2,6-dmethoxyphenoxy)ethyl]-3,4-dihydro-2*H*-1-benzopyran-2-carboxamide, 116635-85-9; 2-(2,6-dimethoxyphenoxy)-*N*-(1*H*-indol-2-ylmethylene)ethanamine, 116635-86-0.

Synthesis and Antiherpetic Activity of (±)-9-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]guanine and Related Compounds[1]

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A series of analogues of acyclovir and ganciclovir were prepared in which conformational constraints were imposed by incorporation of a cyclopropane ring or unsaturation into the side chain. In addition, several related base-modified compounds were synthesized. These acyclonucleosides were evaluated for enzymatic phosphorylation and DNA polymerase inhibition in a staggered assay and for inhibitory activity against herpes simplex virus types 1 and 2 in vitro. Certain of the guanine or 8-azaguanine derivatives were good substrates for the viral thymidine kinase and were further converted to triphosphate, but none was a potent inhibitor of the viral DNA polymerase. Nevertheless, one member of this group, (±)-9-[[(*Z*)-2-(hydroxymethyl)cyclopropyl]methyl]guanine (**3a**), displayed significant antiherpetic activity in vitro, superior to that of the corresponding cis olefin **4a**. Another group, typified by (±)-9-[[(*E*)-2-(hydroxymethyl)cyclopropyl]methyl]adenine (**17b**), possessed modest antiviral activity despite an apparent inability to be enzymatically phosphorylated. The relationship of side-chain conformation and flexibility to biological activity in this series is discussed.

The potent antiherpetic activity of acyclovir (ACV, **1a**)[2] has stimulated great interest in the area of acyclic nucleoside analogues. These efforts have intensified with the identification of the closely related ganciclovir (GCV, **2a**; also known variously as DHPG, 2'NDG, BW B759U, and BIOLF-62) as an agent with superior in vivo potency and somewhat broader spectrum of antiviral utility.[3-5] The corresponding carba analogues HBG (**1b**)[6] and carba-GCV (c-GCV, **2b**; also known as carba-DHPG, carba-2'NDG, 3HM-HBG, and BRL 39123)[7-10] have also demonstrated good inhibition of herpes simplex virus (HSV) in cell culture. All of the above compounds are believed to act by the same general mechanism.[3,5,6,11-14] The broadened substrate specificity of the HSV thymidine kinase enables these guanine acyclonucleosides to be selectively converted to monophosphate derivatives in infected cells. Further phosphorylation by host cell enzymes generates the acyclonucleoside triphosphate, which inhibits HSV DNA polymerase, thus blocking viral replication.

The effectiveness of an acyclic nucleoside analogue as a substrate (for phosphorylating enzymes) or inhibitor (for DNA polymerase) is likely to be dependent on the ability of the acyclic side chain to mimic the interaction of the

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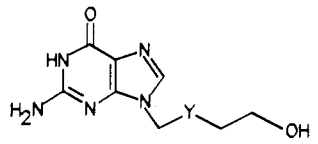
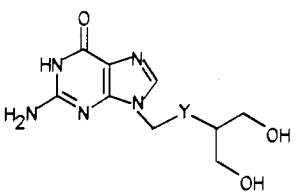
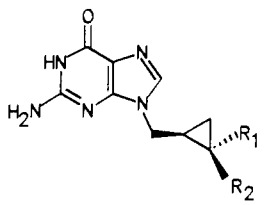
glycosyl portion of the natural substrate with the enzyme. The importance of side-chain conformation in the interactions of acyclic nucleosides with enzymes has been noted.[15-17] While the flexibility of the acyclic chain may allow it to adopt a conformation favorable for phosphorylation or inhibition, this may not correspond to a low-energy conformation in solution or may represent only a minor population among several low-energy rotamers. Consequently, if the side chain could be "frozen" into the conformation optimal for enzyme interaction (not necessarily the same, of course, for each enzyme), superior biological activity could result. With this in mind, we sought to prepare some more rigid analogues related to **1** and **2**. A constraint was imposed on side-chain flexibility by the internal incorporation of a cyclopropane ring or unsaturation, as exemplified by **3a-c**[18] and **4a-c**. Synthetic



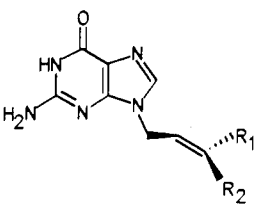
1a (ACV), Y=O
b (HBG), Y=CH_2



2a (GCV), Y=O
b (c-GCV), Y=CH_2



3



4

	R_1	R_2
a:	H	CH_2OH
b:	CH_2OH	H
c:	CH_2OH	CH_2OH

routes to these compounds and several base-modified analogues are presented. The effects of such side-chain alterations and base variations on enzymatic phosphorylation, DNA polymerase inhibition, and inhibition of HSV-1 and HSV-2 replication in cell culture are discussed. Subsequent to the completion of this work, recent reports from other laboratories have described several of the olefinic and acetylenic analogues.[19-22]

Chemistry

The syntheses of the 9-[[(Z)- and (E)-2-(hydroxymethyl)cyclopropyl]methyl]guanines **3a,b** are shown in Scheme I. Thermal reaction of ethyl diazoacetate and acrylonitrile according to the method of Ivanskii and Maksimov[23] furnished the racemic (Z)- and (E)-2-cyanocyclopropanecarboxylates **5a,b** in approximately a 1:2 ratio. Ivanskii and Maksimov reported isolating only the trans (E) isomer from this reaction, whereas Allan et al.[24] obtained both isomers but did not give the ratio. Likewise, a mixture of cis and trans isomers in low overall yield resulted from the corresponding reaction catalyzed by a chiral cobalt(II) complex, as described by Nakamura and co-workers.[25] However, neither the cis-trans ratio nor the optical purity was specified. In accordance with the results of other investigators,[25-27] we assigned the structure of the cis isomer **5a** to the higher boiling component. Our proton NMR spectra were consistent with the detailed spectral data for **5a** and **5b** reported by Nakamura et al.[25]

Reduction of **5a,b** with $LiAlH_4$ afforded the amino alcohols **6a,b**[28] (Scheme I). The remainder of the sequence employed a modification of the route introduced by Noell and Robins[29] for the synthesis of 9-alkylated guanines. The 6-(substituted-amino)isocytosines **7a,b** were normally used without isolation, as were the 5-formamidopyrimidines **9a,b**. Following ring closure in formamide-formic acid, brief heating with aqueous methylamine served to deprotect the partially formylated product, giving modest yields of the targets **3a,b**. Treatment of chromatographically isolated **7a** with chloroacetaldehyde[30] yielded the 7-deazaguanine derivative **10**. Also obtained from **8a** via reduction of the nitroso group and ring closure with nitrous acid[31] was the corresponding 8-azaguanine derivative **11**.

For the [2-(hydroxymethyl)cyclopropyl]methyl derivatives of other bases, an alternative approach was used (Scheme II). Following the procedure of Payne[26] and related work,[32-34] ethyl chloroacetate and ethyl acrylate were reacted in the presence of strong base to give diethyl 1,2-cyclopropanedicarboxylate **12a,b** as a cis-trans mixture. The isomers were separated by a combination of fractional distillation and preparative HPLC. Consistent with Payne's report,[26] the cis isomer **12a** predominated, although the isomer ratio varied depending on the conditions. Stereochemical assignments on the basis of NMR

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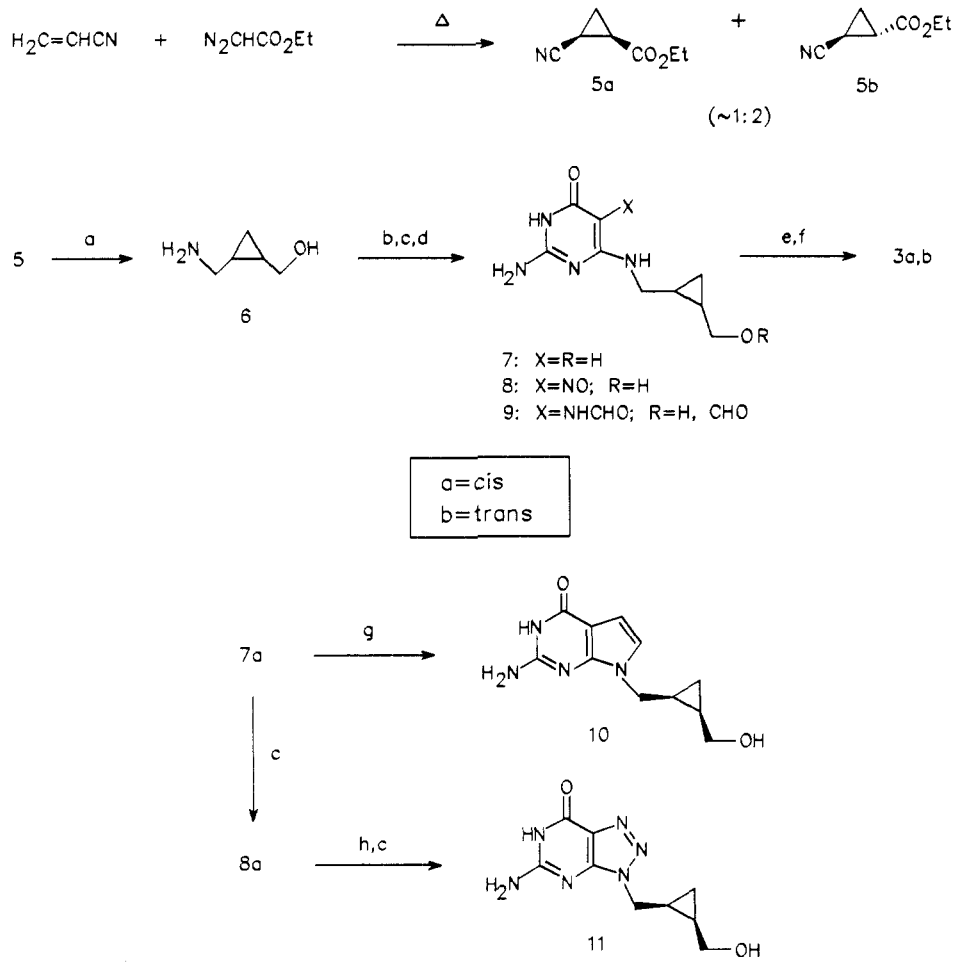
Scheme I[a]



[a] (a) $LiAlH_4$; (b) 6-chloroisocytosine, DABCO; (c) $NaNO_2$, AcOH–H_2O; (d) H_2, Pd/C, HCO_2H; (e) $HCONH_2$, HCO_2H; (f) 40% $MeNH_2$; (g) $ClCH_2CHO$; (h) H_2, Pd/C, AcOH.

spectra were straightforward, as symmetry considerations dictate that only the cis isomer can have different chemical shifts for the two geminal ring protons. The NMR spectrum of **12b** was in good agreement with that reported for the corresponding trans dimethyl ester.[35] A commercial sample (Aldrich Chemical Co.) of diethyl 1,2-cyclopropanedicarboxylate (isomer ratio unspecified) was indistinguishable from **12b** by NMR. Diols **13a**[36,37] and **13b**[38] were obtained by lithium aluminum hydride reduction of **12a,b**. In addition, a sample of **13a** identical with that described above was prepared from the cis cyano ester **5a** following acid hydrolysis to *cis*-1,2-cyclopropanedicarboxylic acid[32] and reduction. Monobenzoylation of **13a,b** gave **14a,b**, which were converted to chloro derivatives **15a,b** with thionyl chloride. Reaction of **15a,b** with adenine provided low yields of **16a,b**, subsequently deprotected with methanolic sodium methoxide to give **17a,b**. Similarly, reaction of **15a** with thymine yielded, after deprotection, the 1-substituted pyrimidine **19**.

The preparation of 2,2-bis(hydroxymethyl)cyclopropyl analogues is outlined in Scheme III. Diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**20**)[39,40] was reduced with lithium aluminum hydride to diol **21** and then converted to the dibenzoate **22**. Ozonolysis of the double bond followed by borohydride reduction afforded alcohol **23**, from which the tosylate **24** was derived. Reaction of **24** with 2-amino-6-chloropurine furnished the 9-alkylated purine derivative **25**. This was transformed to the deprotected guanine target **3c** upon acid hydrolysis. Similarly, treatment of the anion of adenine with **24** led to the 9-alkylated derivative **26**, which provided **27** upon deblocking with catalytic methoxide.

Our syntheses of 9-[(*Z*)- and (*E*)-4-hydroxy-2-buten-1-yl]guanine (**4a,b**) and the acetylenic analogue **36** are shown in Scheme IV. The key intermediates were the bromobutenyl or -butynyl benzoates **29**, **30**, **32**. Two of these (**29**, **32**) were obtained from commercially available diols via their monobenzoates **28**, **31**. The trans isomer **30** was made from the corresponding 1,4-dibromobutene. The remainder of the sequence, proceeding through the 9-alkylated 2-amino-6-chloropurines **33–35**, was analogous to that described above. Related approaches to **4a**,[19] **4b**,[20,21] and **36**[19] have recently been reported. The cis olefin **38** was prepared via **37**, the alkylation product derived from adenine and **29**. Our pathway to 9-[4-hydroxy-3-(hydroxymethyl)-2-buten-1-yl]guanine (**4c**) was very similar to that recently published in full by Haines et al.,[22] and consequently will not be detailed here. This material has also

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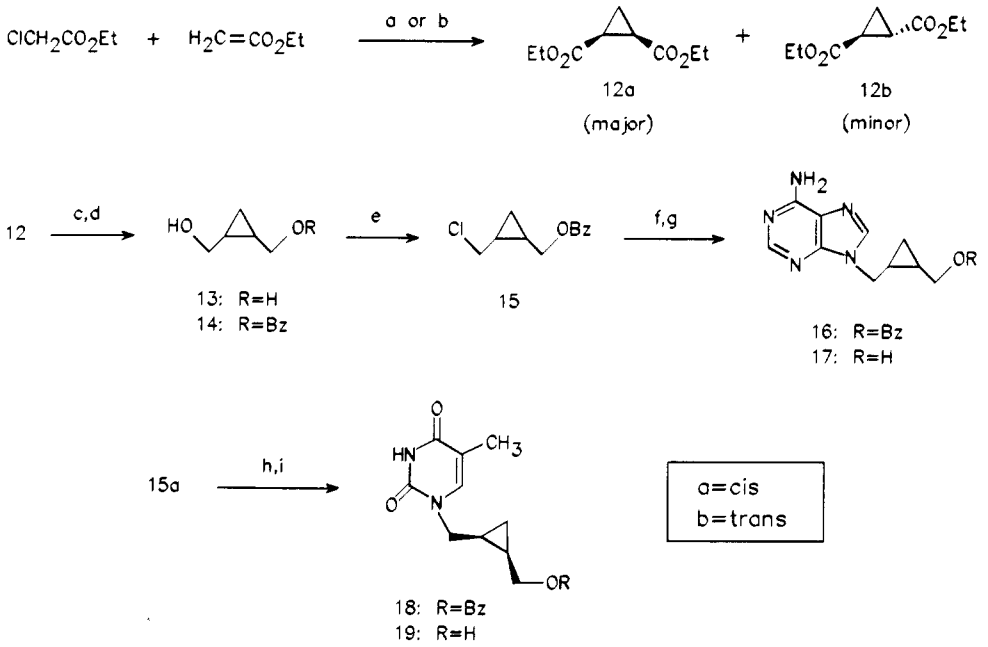
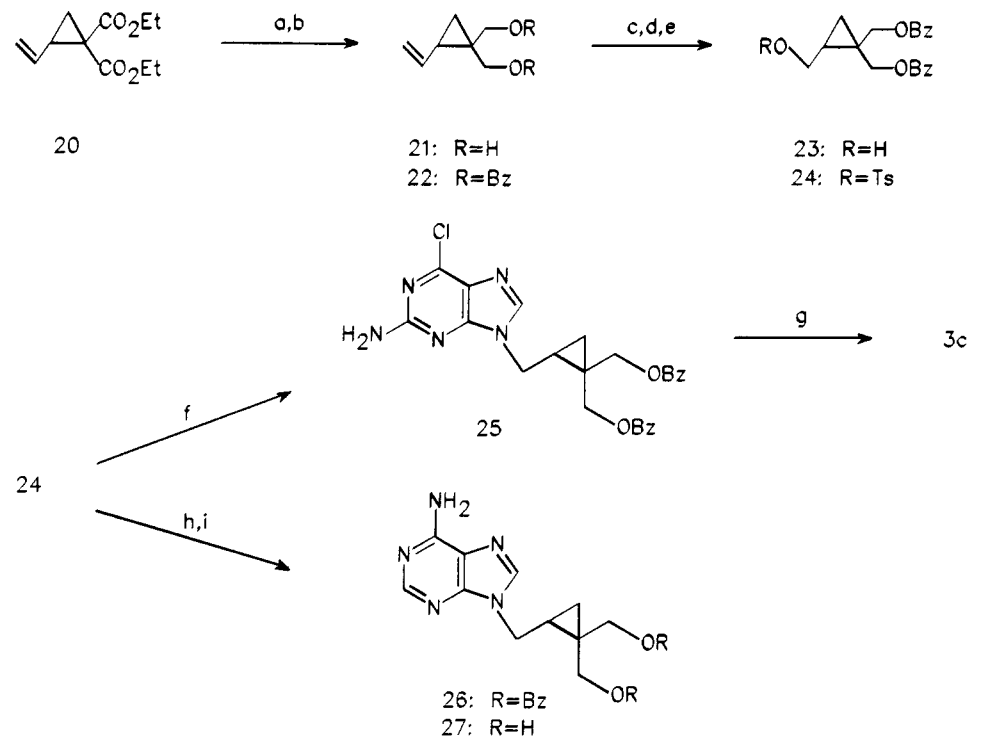
Scheme II[a]



[a] (a) NaH; (b) NaOEt; (c) $LiAlH_4$; (d) BzCl, C_5H_5N; (e) $SOCl_2$, C_5H_5N; (f) adenine, NaH, NaI; (g) NaOMe, MeOH; (h) thymine, K_2CO_3, NaI; (i) 40% $MeNH_2$.

Scheme III[a]



[a] (a) $LiAlH_4$; (b) BzCl, C_5H_5N; (c) O_3; (d) $NaBH_4$; (e) TsCl, C_5H_5N; (f) 2-amino-6-chloropurine, K_2CO_3; (g) 2.5 N HCl; (h) adenine, NaH; (i) NaOMe, MeOH.

been reported by other workers.[19]

For every compound prepared by alkylation of a purine or pyrimidine base, the site of alkylation was verified by relating the ultraviolet spectra, before or after deprotection, to those of model compounds. Thus, comparisons were made with reference spectra reported for the 9-benzyl, 7-benzyl, and 3-methyl derivatives of 2-amino-6-chloropurine;[41,42] 9-, 7-, 3-, and 1-methylguanines;[42-44] 9-, 7-, 3-, 1-, and N^6-methyladenines;[44-46] and the 1-methyl, 3-methyl, and 1-cyclopenten-4-yl derivatives of thymine.[47-49] In each

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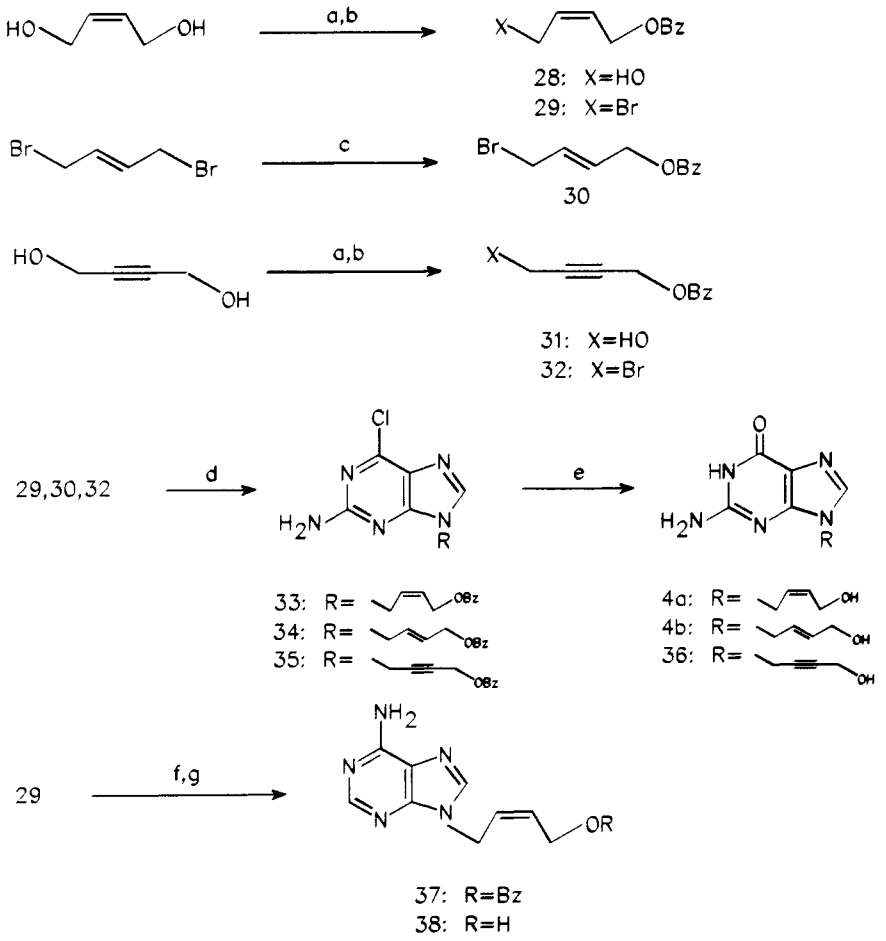
Scheme IV[a]



[a] (a) BzCl, C_5H_5N; (b) PBr_3; (c) NaOBz; (d) 2-amino-6-chloropurine, K_2CO_3; (e) 2 N HCl; (f) adenine, NaH; (g) NaOMe, MeOH.

case the comparison unequivocally supported the present isomeric assignment. When a minor isomer was isolated along with **25** from alkylation of 2-amino-6-chloropurine, the assignments as 7- and 9-isomers, respectively, were also corroborated by ^1H NMR evidence (i.e., the characteristic downfield shift of the C^8-H signal for the 7-isomer relative to the 9-isomer[50]).

Biological Studies

The acyclonucleoside analogues were tested for enzymatic phosphorylation in a "staggered" assay, as previously described.[51] After a 4-h incubation with HSV-1 thymidine kinase (TK), the amount of monophosphate formed was measured. Next, after addition of GMP kinase and crude extract of HSV-infected cells, the incubation was continued overnight. At this stage the extent of conversion to mono-, di-, and triphosphate was determined. Finally, an aliquot of this phosphorylation mixture was incubated for 1 h with a DNA polymerase system and assayed for inhibition.

As shown in Table I, in the (cyclopropylmethyl)guanine series both the *cis*- and *trans*-(hydroxymethyl) derivatives **3a,b** were reasonably good substrates for the HSV-1 TK in comparison with the reference compounds **1a,b** and **2a,b**. In the second step of the staggered assay, however, the cis isomer **3a** was converted efficiently to triphosphate (76%), while the trans isomer **3b** accumulated as diphosphate (48%) with little triphosphate detected. Curiously, the **3a** phosphorylation mixture very poorly inhibited the HSV-1 DNA polymerase (3%) in spite of the high triphosphate content, whereas that of **3b** appeared to be a better inhibitor (26%). This bis(hydroxymethyl) analogue **3c** was not phosphorylated to any measurable extent. The cis olefin **4a** was a good substrate for HSV-1 TK and was phosphorylated well to triphosphate (64%) in step II but was a weak DNA polymerase inhibitor (12%). Phosphorylation of **4a** by HSV-1 TK has also been reported by the Astra group.[13,14] The trans olefin **4b**, by contrast, was scarcely phosphorylated at all. Although the bis(hydroxymethyl) olefin **4c** was a poor TK substrate, a modest level of triphosphate (25%) was formed in step II. However, this did not lead to measurable DNA polymerase inhibition. The acetylenic analogue **36** was completely resistant to phosphorylation by the viral TK.

Among the analogues of **3a** in which the guanine was replaced by other bases, only the 8-azaguanine derivative **11** was a competent substrate for the herpes TK. In the second incubation step, more than half of this material was converted to triphosphate, but no inhibition of DNA polymerase was observed. Another close analogue of **3a**, the 7-deazaguanine compound **10**, was not phosphorylated at all in the initial TK incubation step, and only traces of monophosphate were detected after the overnight second incubation. Also a poor TK substrate, the thymine derivative **19** gave rise to a modest amount of monophosphate (23%) only after the second step. Interestingly, **8a**, the 5-nitrosoisocytosine precursor of **3a**, was itself significantly phosphorylated (21%) by HSV-1 TK, and further conversion to a similar level of triphosphate occurred in step II.

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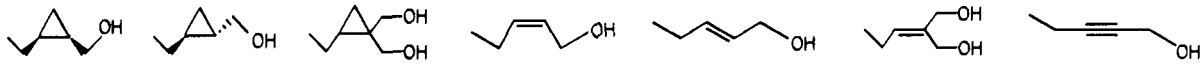
Table I. Biological Activity of Base R, Where R =



I II III IV V VI VII

			staggered assay							
			step I:[b,c]	step II[c,d]			DNA pol: % inhibn[e]		antiviral act.:[f] ED_{50}, μg/mL	
compd	base[a]	R	MP	MP	DP	TP	HSV-1	HeLa	HSV-1	HSV-2
1a (ACV)	G	*g*	17	3	9	60	79	40	3	3
1b (HBG)	G	*g*	55	0	10	17	20	20	3–12	12–25
2a (GCV)	G	*g*	90	3	10	84	60	22	3	3
2b (c-GCV)	G	*g*	37	3	13	75	0	8	6–12	12–50
3a	G	I	45	0	0	76	3	14	6	12–25
3b	G	II	45	9	48	2	26	30	NA	NA
3c	G	III	0	0	0	0	0	0	50	NA
4a	G	IV	50	12	16	64	12	8	12–25	50–100
4b	G	V	2	9	0	0	0	0	NA[h]	NA[h]
4c	G	VI	8	0	9	25	0	0	NA	NA
8a	5-NO-iC-6-NH-	I	21	0	0	21	8	0	NA	NA
8b	5-NO-iC-6-NH-	II	1	9	0	0	9	5	NA	NA
10	7-deazaG	I	0	9	0	0	14	0	NA[i]	NA[i]
11	8-azaG	I	39	2	41	55	0	1	NA[h]	NA[h]
17a	A	I	0	0	0	0	5	0	NA	NA
17b	A	II	0	0	0	0	0	0	50	50
19	T	I	0	23	0	0	22	0	NA	NA
27	A	III	0	0	0	0	0	12	50	50–100
36	G	VII	0	0	0	0	0	5	NA	NA
38	A	IV	0	0	0	0	0	3	NA	NA

[a] G = guanin-9-yl, iC = isocytosine, A = adenin-9-yl, T = thymin-1-yl. [b] Incubation with HSV-1 thymidine kinase. [c] MP, DP, TP = percent mono-, di-, triphosphate. Calculated percentages based on total phosphorylated and unphosphorylated compound, as measured by HPLC. [d] Continued incubation of the mixture from step 1 with GMP kinase and crude extract of HSV-1-infected HeLa cells. [e] Polymerase inhibition following further incubation of the mixture from step II as described in the Experimental Section. [f] Concentration required to prevent viral cytopathic effect in half of primary rabbit kidney cell cultures. NA = not active at 100 μg/mL (or highest nontoxic dose). [g] See structure diagrams in text. [h] Slightly toxic at 100 μg/mL. [i] Toxic at 100 μg/mL.

Evaluation of antiviral activity in primary rabbit kidney cell cultures (Table I) revealed that only a few of the compounds bearing conformationally constrained side chains inhibited HSV-induced cytopathology at ≤100 μg/mL. It should be noted that the conditions of this in vitro system[3,51] present a relatively severe test. Consequently, the ED_{50} values for the reference compounds tend to be higher than the ED_{50}'s determined in the plaque reduction assays frequently reported by other laboratories. The two most active compounds in this study were guanine derivatives **3a** (cis cyclopropane) and **4a** (cis olefin). Although less potent than ACV (**1a**) or GCV (**2a**), **3a** (ED_{50} = 6–25 μg/mL) was comparable in potency to HBG (**1b**) and carba-GCV (**2b**). The activity we observed for **4a** is consistent with that recently reported by the Astra group.[8,13,19] The corresponding trans olefin **4b**, devoid of activity in our assay, has likewise been reported inactive by one laboratory[21] but active by another.[20] The HSV inhibition observed by others[8,19,22] for the bis(hydroxymethyl) olefin **4c** was not evident in our assay. One additional guanine derivative, **3c** [bis(hydroxymethyl)cyclopropyl], had modest to borderline activity, as did two adenine derivatives: **17b** (trans cyclopropyl) and **28** [bis(hydroxymethyl)cyclopropyl]. In further testing, **3a** was found active at 3–25 μg/mL against several GCV-sensitive HSV-1 strains (Schooler, S, McKrae, McIntyre) but inactive at 100 μg/mL against an unrelated DNA virus (vaccinia) and an RNA virus (mengo). In our HSV-1 murine encephalitis model,[52] **3a** administered subcutaneously at up to 100 mg/kg per day was ineffective in preventing or delaying death.

Discussion

Conformational constraints were imposed on acyclonucleoside side chains by the introduction of unsaturation or by, in effect, fusing a cyclopropane ring onto the chain. This offered the opportunity to observe the effects of restricted flexibility and geometric isomerism in regard to enzyme interactions and antiviral activity. Replacement of guanine by other bases was also examined.

Two strategies were utilized for attachment of the side chains. The first, used for some of the (cyclopropylmethyl)guanines and related isosteres, involved a displacement on 6-chloroisocytosine with the side-chain amine followed by construction of the fused five-membered ring. In the other approach, the protected side chain was attached by alkylation of the base. Since direct alkylation of guanine was not practicable, 2-amino-6-chloropurine served as a satisfactory precursor for this purpose.

The HSV thymidine kinase displayed considerable specificity for both base and side chain. Good substrate activity was essentially limited to certain guanine derivatives and the 8-azaguanine **11**. The 8-aza analogue of acyclovir has been reported to be a substrate, albeit a slow one, of HSV-1 TK.[53] The importance of N^7 for interaction with the herpes TK can be seen from the virtually complete loss of substrate efficiency upon going from the guanine **3a** to the corresponding 7-deazaguanine **10**. In the cyclopropane series, HSV-1 TK appeared to process the *cis*- and *trans*-(hydroxymethyl) isomers **3a,b** equally well, whereas only the cis olefin **4a** was readily accepted by the enzyme. The bis(hydroxymethyl) analogues **3c** and

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4c contain both cis and trans substituents, either of which could in principle be phosphorylated. However, perhaps because of lack of bulk tolerance, 4c was a poor TK substrate and 3c a nonsubstrate. This is in marked contrast to the more flexible GCV (2a) and its carba analogue 2b, which contain a similar pair of hydroxyls but are well phosphorylated. The linear side chain carbon skeleton of the acetylenic analogue 36 was also incompatible with phosphorylation by HSV-1 TK. These results suggest that a "bent" side chain conformation, as in 3a and 4a, rather than a fully extended one, best fits the active site of the HSV thymidine kinase. Many details of the geometric requirements remain to be elucidated. For example, since 3a was tested only in racemic form, it is possible that one enantiomer is preferred by the enzyme. (The fact that 76% of racemic 3a was ultimately converted to triphosphate indicates that both enantiomers must be susceptible to phosphorylation, although the relative rates are unknown.)

In general, compounds that were satisfactory TK substrates were further converted to triphosphate in the second incubation step. A notable exception was 3b, which essentially stopped at the diphosphate stage. Even the few compounds (e.g., 3a, 4a, 11) from which high levels of triphosphate were generated proved to be poor inhibitors of the HSV DNA polymerase compared to ACV and GCV. In any case, there was no absolute correlation of either triphosphate formation or polymerase inhibition with in vitro antiviral activity. The two most efficiently phosphorylated of the new compounds, 3a and 4a, also had the best antiviral activity. However, the 8-azaguanine derivative 11, which was converted to >50% triphosphate, displayed no antiviral activity. The mechanism of antiviral action of the triphosphate-forming compounds 3a and 4a is open to speculation. Although the triphosphates of 3a and 4a were at best weak inhibitors of HSV-1 DNA polymerase in our cell-free assay, the possibility that these compounds may nevertheless impede viral DNA synthesis in cell culture has not been ruled out.

Particularly difficult to explain is the modest antiviral activity of 3c, 17b, and 27, which were not phosphorylated at all in the staggered assay. Conceivably these compounds may be phosphorylated by other enzymes in cell culture, or their antiviral activity may be unrelated to phosphorylation or DNA polymerase inhibition. Although not tested, inhibition of S-adenosylhomocysteine (SAH) hydrolase, the apparent mode of action of several antiviral acyclic and carbocyclic adenosine analogues,[54] is a possibility for 17b and 27. However, HSV is known to be relatively insensitive to SAH hydrolase inhibitors.[54] An interesting crossover in specificity can be seen in comparing two cis–trans pairs among the 9-[[2-(hydroxymethyl)-cyclopropyl]methyl]purines. With guanine as the base, only the cis isomer 3a had antiherpetic activity. In the corresponding adenine series, the cis isomer 17a was inactive, whereas the trans isomer 17b was active. Again, this may reflect a fundamental difference in mechanism between 3a and 17b.

The inactivity of 3a in a lethal murine HSV-1 encephalitis model is disappointing and without obvious explanation at present. (However, it should be noted that while GCV was highly active in this mouse model, ACV provided significant protection only at or above 50 mg/kg per day.[52]) A similar lack of effect against systemic HSV infection in mice has been observed for HBG (1b), and this has been tentatively attributed to rapid excretion and a resultant very short half-life in plasma.[55] Since the pharmacokinetics of 3a have not been examined, it is uncertain whether such factors could explain why its antiviral potency in vitro did not translate into therapeutic efficacy in the HSV-1 mouse model.

Experimental Section

Proton NMR spectra were obtained with a Varian XL-200, SC300, or T-60A spectrometer, using tetramethylsilane as internal standard (key: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets, br = broad, v = very, cyPr = cyclopropane, Bz = benzoyl, Ph = phenyl, Ts = *p*-toluenesulfonyl). UV spectra were recorded on a Perkin-Elmer Lambda 5 spectrophotometer. Mass spectra were obtained with a Varian MAT 731 instrument. Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover apparatus. Column chromatography was carried out on E. Merck silica gel 60 (70–230 mesh) or grade 62 (60–200 mesh). Preparative HPLC separations were run on a Waters Prep 500 instrument using Prep Pak silica gel cartridges. Compounds showed satisfactory purity by TLC on Analtech silica gel GF plates in the indicated solvent systems. Elemental combustion analyses, where indicated only by the elements, were within ±0.4% of theoretical values.

Ethyl (*Z*)- and (*E*)-2-Cyanocyclopropanecarboxylate (5a,b). On the basis of the procedure of Ivanskii and Maksimov,[23] acrylonitrile (38 g, 0.72 mol) was stirred under reflux in an oil bath as ethyl diazoacetate (40 g, 0.35 mol) was added portionwise over a period of 2.5 h. After completion of the addition, the mixture was stirred at reflux for an additional 1.5 h, and the excess acrylonitrile was removed by distillation. The bath temperature was then raised to 125–130 °C and maintained there until N_2 evolution ceased (about 2 h). Finally, the mixture was heated at 160–170 °C for 0.5 h and cooled under N_2. Distillation in vacuo afforded two major fractions. Fraction 1, bp 95–100 °C (4.75 mm), amounted to 17.2 g (35%) of colorless liquid, homogeneous by TLC (1:1 hexane–EtOAc), identified as the *E* isomer 5b [lit.[27] bp 76–78 °C (1.8 mm)]: MS, *m/e* 139 (M^+); 300-MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H, CH_3), 1.47 (ddd, J = 4.7, 5.9, 9.3 Hz,[56] 1 H, cyPr CH), 1.54 (ddd, J = 4.7, 6.2, 8.8 Hz, 1 H, cyPr CH), 1.95 (ddd, J = 4.3, 6.3, 9.1 Hz, 1 H, cyPr CH), 2.27 (ddd, J = 4.3, 6.0, 8.8 Hz,[56] 1 H, cyPr CH), 4.20 (q, J = 7 Hz, 2 H, CH_2CH_3). These data are consistent with those previously reported[25] for 5b.

Distillation fraction 2 [bp 110–122 °C (4.75 mm) and 80–90 °C (0.5 mm)] was filtered to remove a white solid contaminant, yielding 12 g of an oil. Because this material was impure by TLC (1:1 hexane–EtOAc), it was subjected to preparative HPLC (7:3 hexane–EtOAc, refractive index detection, three cycles). Chromatographic fractions containing clean product (lower R_f than that of distillation fraction 1 on TLC) were combined and concentrated in vacuo to give 8.53 g (18%) of the *Z* isomer 5a as a colorless liquid [lit.[27] bp 98–101 °C (2 mm)]: MS, *m/e* 139 (M^+); 300-MHz NMR ($CDCl_3$) 1.30 (t, J = 7 Hz, 3 H, CH_3), 1.41 (ddd, J = 6.3, 8.1, 9.0 Hz, 1 H, cyPr CH), 1.69 (ddd, J = 5.0, 6.5, 6.5 Hz, 1 H, cyPr CH), 1.84 (ddd, J = 6.7, 8.2, 9.0 Hz, 1 H, cyPr CH), 2.12 (ddd, J = 6.3, 8.1, 8.1 Hz, 1 H, cyPr CH), 4.25 (q, J = 7 Hz, 2 H, CH_2CH_3). These values are in accord with the NMR data previously reported[25] for 5a.

(*Z*)-2-(Aminomethyl)cyclopropanemethanol (6a). A mixture of 3.42 g (90 mmol) of $LiAlH_4$ and 100 mL of dry THF was stirred at gentle reflux under N_2 as a solution of 8.35 g (60 mmol) of 5a in 20 mL of THF was introduced dropwise (about 2 h) and maintained at reflux for an additional 2 h. The cooled mixture was stirred in an ice bath and kept under N_2 as 20 mL of H_2O was cautiously added dropwise at such a rate that the temperature remained below 20 °C. Vigorous gas evolution was followed by heavy precipitation. After several minutes, the solid was removed by filtration and washed with THF. The combined filtrate and washings were dried (Na_2SO_4), filtered, and concen-

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(56) These coupling constants determined in 1:5–1:7 $CDCl_3$–C_6D_6.

trated in vacuo. The residual oil was distilled through a short-path apparatus to give 3.67 g (60%) of colorless liquid: bp 51–58 °C (0.2 mm) [lit.[28] bp 55–58 °C (0.1 mm)]; TLC in 70:30:3 $CHCl_3$–MeOH–concentrated NH_4OH; 200-MHz NMR ($CDCl_3$) δ 0.17 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.77 (ddd, J = 5, 8.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.08, 1.32 (m, each 1 H, cyPr CH), 2.26 (dd, J = 11, 12 Hz, 1 H, C*H*HN), 3.03 (v br mound, 2 H, NH_2), 3.22 (dd, J = 11, 12 Hz, 1 H, C*H*HO), 3.40 (dd, J = 6.5, 12 Hz, 1 H, CH*H*N), 4.03 (dd, J = 5, 12 Hz, 1 H, CH*H*O), 4.92 (br s, 1 H, OH).

(*E*)-2-(Aminomethyl)cyclopropanemethanol (6b). This compound, prepared analogously to **6a**, was obtained in 53% yield as a pale yellow, somewhat viscous oil: bp 79–82 °C (1.2–1.4 mm) [lit.[28] bp 51 °C (0.5 mm)]; TLC in 70:30:3 $CHCl_3$–MeOH–concentrated NH_4OH; 300-MHz NMR ($CDCl_3$) δ 0.41 (m, 2 H, cyPr CH_2), 0.8–1.0 (m, 2 H, cyPr CH), 2.01 (br s, 3 H, NH_2, OH), 2.43 (dd, J = 8, 13 Hz, 1 H, C*H*HN), 2.72 (dd, J = 6, 13 Hz, 1 H, CH*H*N), 3.30 (dd, J = 8, 11.5 Hz, 1 H, C*H*HO), 3.59 (dd, J = 6, 11.5 Hz, 1 H, CH*H*O).

6-[[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]amino]-isocytosine (7a). A solution of 1.80 g (11 mmol) of 6-chloroisocytosine monohydrate and 3.33 g (33 mmol) of **6a** in 5 mL of 2-ethoxyethanol was stirred at reflux under N_2 for 2.5 h and then concentrated in vacuo. The viscous, amber residual oil was chromatographed on a column of silica gel (elution with a gradient of 5–20% MeOH in CH_2Cl_2). Evaporation of the product fractions gave an oil, which was crystallized from H_2O. There was obtained 488 mg (2 crops, 21%) of pale yellow solid: mp 163–168 °C; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; 200-MHz NMR (Me_2SO-d_6) δ 0.05–0.3 (m, 1 H, cyPr C*H*H), 0.55–0.75 (m, 1 H, cyPr CH*H*), 1.03 (m, 2 H, cyPr CH), 2.8–3.8 (m, 4 H, CH_2N, CH_2O), 4.45 (s, 1 H, C^5-H), 4.6 (v br mound, 1 H, OH), 6.23 (br s, 2 H, NH_2), 8.0 (v br mound, 1 H, C^6-NH). This material, although slightly impure, was suitable for use in the preparation of **10**.

6-[[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]-amino]-5-nitrosoisocytosine (8a). A solution of 3.28 g (20 mmol) of 6-chloroisocytosine monohydrate, 3.54 g (35 mmol) of **6a**, and 1.12 g (10 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO) in 9 mL of 2-ethoxyethanol was stirred at reflux under N_2 for 2.5 h. After concentration in vacuo, the residual gum was dissolved with heating in 15 mL of AcOH, diluted with 10 mL of H_2O, and cooled in ice. This solution was then stirred at ambient temperature as a solution of 2.76 g (40 mmol) of $NaNO_2$ in 15 mL of H_2O was added. The resulting solution immediately turned dark, followed rapidly by thick precipitation and foaming, which gradually subsided. After about 2 h, the precipitated solid was collected on a filter and washed thoroughly with H_2O, then with Me_2CO, to give 1.28 g (27%) of orange powder: mp 228.5–229 °C dec (analytical sample recrystallized from H_2O had mp 234–235 °C dec). TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; MS, m/e 239 (M^+); UV λ_{max} (MeOH) 321 nm (ε 16 600), λ_{max} (MeOH + H^+) 264 nm (ε 12 800), 318 nm (ε 7300), λ_{max} (MeOH + OH^-) 322 nm (ε 18 100); 200-MHz NMR (Me_2SO-d_6) δ 0.20 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.67 (ddd, J = 5, 8, 8 Hz, 1 H, cyPr CH*H*), 1.11 (m, 2 H, cyPr CH), 3.3–3.7 (m, 4 H, CH_2N, CH_2O), 4.60 (t, J = 5 Hz, 1 H, OH), 6.88, 8.24 (v br s, 3 H total, NH_2, C^6-NH), 10.70 (br s, 1 H, N^1-H). Anal. ($C_9H_{13}N_5O_3$) C, H, N.

6-[[[(*E*)-2-(Hydroxymethyl)cyclopropyl]methyl]-amino]-5-nitrosoisocytosine (8b). By the procedure used for **8a**, this compound was obtained in 29% yield as orange-tan crystals: mp 227–228 °C dec; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; MS, m/e 454 ($M^+ - 1$ for $(Me_3Si)_3$ derivative]; UV λ_{max} (MeOH) 321 nm (ε 17 300), λ_{max} (MeOH + H^+) 264 nm (ε 13 200), 318 nm (ε 7400), λ_{max} (MeOH + OH^-) 321 nm (ε 18 600); 200-MHz NMR (Me_2SO-d_6) δ 0.40 (dd, J = 6, 7 Hz, 2 H, cyPr CH_2), 0.92 (m, 2 H, cyPr CH), 3.2–3.5 (m, 4 H, CH_2N, CH_2O), 4.50 (br s, 1 H, OH), 6.90, 8.24 (v br s, 3 H total, NH_2, C^6-NH), 10.73 (br s, 1 H, N^1-H). Anal. ($C_9H_{13}N_5O_3 \cdot H_2O$) C, H, N.

9-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]guanine (3a). A mixture of 717 mg (3 mmol) of **8a**, 50 mg of 10% Pd/C, and 10 mL of 88% HCO_2H was shaken with H_2 (initial pressure 48 psig). Uptake of H_2 was complete within 30 min. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo (<5 mm). The residual gum (presumably **9a**) was dissolved with heating in 3 mL of $HCONH_2$ and treated with 0.3 mL of 95–97% HCO_2H. The solution was stirred under N_2 in an oil bath at approximately 170 °C for 2 h, then cooled, and concentrated in vacuo. The residual semisolid was extracted with MeOH, and the insoluble solid was removed by filtration. Evaporation of the filtrate gave an oil, which was dissolved in 2 mL of 40% $MeNH_2$ (aqueous). The solution was heated on a steam bath for a few minutes, then diluted with 10 mL of H_2O, treated with charcoal, and filtered through Super-Cel. The filtrate was concentrated by rotary evaporation and dried under high vacuum. The residual oil crystallized on trituration with a little H_2O. Recrystallization from a small volume of H_2O yielded 124 mg of golden crystals. The bulk of this material was recrystallized two more times from H_2O, giving 32 mg (4.4%) of light yellow crystals: mp 311–314 °C dec; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; MS, m/e 235 (M^+); UV λ_{max} (MeOH) 253 nm (ε 12 700), λ_{max} (MeOH + H^+) 256 nm (ε 11 700), λ_{max} (MeOH + OH^-) 267 nm (ε 10 900); 300-MHz NMR (Me_2SO-d_6) δ 0.29 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.66 (ddd, J = 5, 8, 8 Hz, 1 H, cyPr CH*H*), 1.14, 1.28 (m, each 1 H, cyPr CH), 3.35 (dd after D_2O spike, J = 8, 12 Hz, 1 H, C*H*HO), 3.70 (dd after D_2O spike, J = 6, 12 Hz, 1 H, CH*H*O), 3.87 (dd, J = 8, 14 Hz, 1 H, C*H*HN), 4.06 (dd, J = 6, 14 Hz, 1 H, CH*H*N), 4.65 (t, J = 5.5 Hz, 1 H, OH), 6.42 (br s, 2 H, NH_2), 7.78 (s, 1 H, C^8-H), 10.54 (br s, 1 H, NH). Anal. ($C_{10}H_{13}N_5O_2 \cdot {}^1/_3H_2O$) C, H, N.

9-[[(*E*)-2-(Hydroxymethyl)cyclopropyl]methyl]guanine (3b). By the procedure used for **3a**, this material was obtained in 24% yield as small, cream-colored plates: mp 273–275 °C; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; MS, m/e 379 [M^+ for $(Me_3Si)_2$ derivative]; UV λ_{max} (MeOH) 253 nm (ε 14 300), λ_{max} (MeOH + H^+) 256 nm (ε 12 500), λ_{max} (MeOH + OH^-) 268 nm (ε 11 200); 200-MHz NMR (Me_2SO-d_6) δ 0.42, 0.54 (m, each 1 H, cyPr CH_2), 1.08 (m, 2 H, cyPr CH), 3.19 (dd after D_2O spike, J = 6, 12 Hz, 1 H, C*H*HO), 3.34 (dd after D_2O spike, J = 5, 12 Hz, 1 H, CH*H*O), 3.82 (m, 2 H, CH_2N), 4.55 (t, J = 5 Hz, 1 H, OH), 6.43 (br s, 2 H, NH_2), 7.77 (s, 1 H, C^8-H), 10.47 (br s, 1 H, N^1-H). Anal. ($C_{10}H_{13}N_5O_2 \cdot 1.3H_2O$) C, H, N.

2-Amino-3,7-dihydro-7-[[(*Z*)-2-(hydroxymethyl)cyclopropyl]methyl]-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (10). A mixture of 210 mg (1 mmol) of **7a**, 100 mg (1.22 mmol) of NaOAc, and 2 mL of H_2O was added to 0.15 mL (1.05 mmol) of 45% (7 M) chloroacetaldehyde (aqueous). After 5 min, the mixture was cooled. The precipitate was collected on a filter and washed with H_2O to yield 69 mg (30%) of cream-colored solid: mp 278–279 °C dec (analytical sample recrystallized from H_2O); TLC in 80:20:2 and 90:10:1 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 263 nm (ε 11 900), λ_{max} (MeOH + H^+) 264 nm (ε 11 300), λ_{max} (MeOH + OH^-) 266 nm (ε 11 400); 200-MHz NMR (Me_2SO-d_6) δ 0.25 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.63 (ddd, J = 5, 9, 9 Hz, 1 H, cyPr CH*H*), 1.14 (m, 2 H, cyPr CH), 3.46 (dd, J = 8, 12 Hz after D_2O spike, 1 H, C*H*HOH), 3.67 (ddd, J = 5.5, 6, 12 Hz, 1 H, CH*H*OH), 3.82 (dd, J = 7.5, 14 Hz, 1 H, C*H*HN), 4.06 (dd, J = 6, 14 Hz, 1 H, CH*H*N), 4.61 (t, J = 5.5 Hz, 1 H, OH), 6.17 (br s, 2 H, NH_2), 6.21 (d, J = 3.5 Hz, 1 H, C^5-H), 6.86 (d, J = 3.5 Hz, 1 H, C^6-H), 10.19 (br s, 1 H, NH). Anal. ($C_{11}H_{14}N_4O_2 \cdot H_2O$) C, N; H: calcd, 6.39; found, 5.65.

5-Amino-3,6-dihydro-3-[[(*Z*)-2-(hydroxymethyl)cyclopropyl]methyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (11). A mixture of 287 mg (1.2 mmol) of **8a**, 50 mg of 10% Pd/C, and 15 mL of glacial AcOH was shaken with H_2 (approximately 3 atm) for 40 min, by which time TLC (80:20:2 $CHCl_3$–MeOH–H_2O) indicated complete reduction to the air-sensitive 5-amino intermediate. Following removal of catalyst (filtration through Celite under N_2), the pale yellow solution was treated with a solution of 83 mg (1.2 mmol) of $NaNO_2$ in 6 mL of H_2O, resulting in an immediate purple color. After 30 min, the solution was concentrated in vacuo. The residual solid was recrystallized from H_2O to give 82 mg (29%) of pale yellow powder: mp >250 °C dec; TLC in 70:30:3 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 253 nm (ε 13 600), λ_{max} (MeOH + H^+) 252 nm (ε 13 600), λ_{max} (MeOH + OH^-) 277 nm (ε 11 000); 200-MHz NMR (Me_2SO-d_6) δ 0.32 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.68 (ddd, J = 5, 8.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.15, 1.37 (m, each 1 H, cyPr CH), 3.46, 3.67 (m, each 1 H, CH_2O), 4.19 (dd, J = 8, 15 Hz, 1 H, C*H*HN), 4.45 (dd, J = 7, 15 Hz, 1 H, CH*H*N), 4.58 (t, J = 5.5 Hz, 1 H, OH), 6.91 (br s, 2 H, NH_2), 10.90 (br s, 1 H, NH). Anal. ($C_9H_{12}N_6O_2 \cdot 2H_2O$) C, H, N.

Diethyl (*Z*)- and (*E*)-Cyclopropane-1,2-dicarboxylate (12a,b). A. NaOEt Method.[31-33] To a mechanically stirred mixture of 108 mL (100 g, 1 mol) of ethyl acrylate and 107 mL

(123 g, 1 mol) of ethyl chloroacetate in a 1-L three-necked flask equipped with condenser, thermometer, and N_2 bubbler was added portionwise 68 g (1 mol) of freshly prepared, dry NaOEt while the temperature was maintained at 20–30 °C by cooling in an ice bath. After being stirred at room temperature overnight, the mixture was added to 1.3 L of cold H_2O and extracted with 1 L of Et_2O. The ethereal layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an orange oil. Distillation yielded, after collection of considerable lower boiling material, 31.6 g of liquid with bp 76–88 °C (2.5 mm). Further purification of this material by preparative HPLC (97:3 hexane–EtOAc) afforded 5.15 g of **12b** (eluted first) and 14.3 g of **12a** as colorless oils: MS, m/e 186 (M^+) for each; 200-MHz NMR ($CDCl_3$) of **12a** δ 1.25 (approximate, partially obscured m, 1 H, cyPr CHH), 1.26 (t, J = 7 Hz, 6 H, CH_2CH_3), 1.70 (ddd, J = 5, 6, 6 Hz, 1 H, cyPr CHH), 2.06 (dd, J = 6, 9 Hz, 2 H, cyPr CH), 4.17 (q, J = 7 Hz, 4 H, CH_2CH_3); 200-MHz NMR ($CDCl_3$) of **12b** δ 1.26 (t, J = 7 Hz, 6 H, CH_2CH_3), 1.43 (dd, J = 7, 8 Hz, 2 H, cyPr CH_2), 2.16 (dd, J = 7, 8 Hz, 2 H, cyPr CH), 4.16 (q, J = 7 Hz, 4 H, CH_2CH_3).

B. NaH Method.[32-34] In a three-necked flask equipped with addition funnel, thermometer, N_2 bubbler, and mechanical stirrer, a suspension of 40.0 g (1 mol) of NaH (60% dispersion in mineral oil) in 250 mL of dry toluene was stirred at room temperature as a mixture of 108.3 mL (100.1 g, 1 mol) of ethyl acrylate and 84.5 mL (122.5 g, 1 mol) of ethyl chloroacetate was added dropwise. To initiate the reaction, 0.5 mL of *tert*-BuOH was added, and the temperature was gradually raised to about 85 °C (oil bath). Within a few minutes at this temperature, the reaction became self-sustaining and the oil bath was removed. H_2 evolution continued as the temperature dropped, but after a few minutes an exotherm occurred (**caution**: vigorous foaming), and the reaction flask was immediately immersed in an ice bath. Cooling was continued until the mixture reached room temperature. The mixture was then added to cold H_2O and extracted with EtOAc. The organic phase was dried with $MgSO_4$, filtered, and concentrated to give 220 g of amber residual oil. Distillation afforded 88.8 g of product, bp 98–100 °C (4.5 mm) and 90–95 °C (2.5 mm), which was mainly cis isomer [lit.[31] bp 83–84 °C (1 mm)]. Further purification by preparative HPLC (97:3 hexane–EtOAc) provided 51.3 g (28%) of **12a**, identical with that obtained by the NaOEt method.

(*Z*)-1,2-Cyclopropanedimethanol (13a). A. From 12a. A three-necked flask equipped with addition funnel, condenser, and N_2 bubbler and containing 6.38 g (165 mmol) of $LiAlH_4$ was cooled in an ice bath as 160 mL of dry THF was added. The ice bath was removed, and the mixture was stirred at ambient temperature as a solution of 20.5 g (110 mmol) of **12a** in 40 mL of THF was added dropwise over 1.5 h. The mixture was stirred at reflux for 2 h and then overnight at room temperature. After being cooled in an ice–MeOH bath, the mixture was treated cautiously with 37 mL of saturated aqueous NH_4Cl (added dropwise) and then with 40 mL of EtOAc. The insoluble salts were removed by filtration, and the filtrate was evaporated in vacuo. A solution of the residue in EtOAc was dried over $MgSO_4$, filtered, and concentrated to give 6.32 g of oil. The salts that had been isolated from the reaction mixture were resuspended in a mixture of EtOAc and H_2O, neutralized with AcOH, and stirred overnight. The solid was then removed by filtration, and the filtrate was extracted with additional EtOAc. The organic solution was dried ($MgSO_4$), filtered, and concentrated to give an additional 2.56 g of product, for a total yield of 8.88 g (79%) of colorless oil: 200-MHz NMR ($CDCl_3$) δ 0.22 (dt, J = 5, 5 Hz, 1 H, cyPr CHH), 0.83 (dt, J = 5, 8 Hz, 1 H, cyPr CHH), 1.35 (m, 2 H, cyPr CH), 3.27 (dd, J = 11, 11 Hz, 2 H, CHHOH, superimposed on br mound, 2 H, OH), 4.14 (dd, J = 6, 11 Hz, 2 H, CHHOH).

B. From 5a. A solution of 20.0 g (144 mmol) of **5a** in 50 mL of concentrated HCl was heated at 95 °C for 1 h and then cooled, resulting in crystallization. The solid (NH_4Cl) was removed by filtration. Concentration of the filtrate in vacuo gave 21.9 g of colorless, waxy solid. By IR (neat), this material showed a C=O band at 1706 cm^{-1} and no C≡N band. The crude (*Z*)-1,2-cyclopropanedicarboxylic acid[32] thus obtained was reduced with $LiAlH_4$ (355 mmol total) in THF (310 mL) at reflux. After about 2.5 h, the cooled mixture was diluted with 200 mL of CH_2Cl_2 and stirred vigorously during the successive dropwise addition of 15 mL of H_2O, 15 mL of 15% NaOH, and 45 mL of H_2O (with cooling in ice bath as necessary). The mixture was filtered, and the solid was subjected to further extraction with 1:1 THF–CH_2Cl_2 (3 × 50 mL). The combined extracts were concentrated in vacuo to give 3.88 g of a yellow oil. Dissolution of the inorganics in concentrated HCl and further extraction with $CHCl_3$ provided an additional 0.41 g of oil, which was combined with the larger fraction and distilled, yielding 3.32 g (23%) of colorless oil: bp 82–83 °C (0.15 mm) [lit.[36] bp 107–109 °C (5 mm)]; NMR identical with that prepared from **12a**.

(*E*)-1,2-Cyclopropanedimethanol (13b). This material was prepared from **12b** in 69% yield by the method used for **13a** (procedure A). Colorless oil: 200-MHz NMR ($CDCl_3$) δ 0.44 (t, J = 6.5 Hz, 2 H, cyPr CH_2), 1.04 (m, 2 H, cyPr CH), 3.08 (dd, J = 9, 11 Hz, 2 H, CHHOH), 3.75 (br s, 2 H, OH), 3.86 (dd, J = 5 , 11 Hz, 2 H, CHHOH).

(*Z*)-2-[(Benzoyloxy)methyl]cyclopropanemethanol (14a). A mixture of 8.86 g (85 mmol) of **13a**, 10.3 mL (10.1 g, 128 mmol) of pyridine, and 90 mL of CH_2Cl_2 was stirred at 0 °C under N_2 as 9.87 mL (11.95 g, 85 mmol) of benzoyl chloride was added dropwise. After being stirred at room temperature for 3 days, the mixture was added to ice–H_2O and extracted with EtOAc. The organic layer was washed twice with H_2O, dried ($MgSO_4$), filtered, and concentrated. The residual oil was chromatographed on a column of silica gel initially packed in hexane. Dibenzoate was eluted with 9:1 hexane–EtOAc, and subsequent elution with 3:1 hexane–EtOAc yielded 5.6 g (32%) of the monobenzoyl ester **14a** as a colorless oil: TLC in 2:1 hexane–EtOAc; 200-MHz NMR ($CDCl_3$) δ 0.31 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr CHH), 0.93 (ddd, J = 5, 9, 9 Hz, 1 H, cyPr CHH), 1.43 (m, 2 H, cyPr CH), 2.6 (v br mound, 1 H, OH), 3.55 (dd, J = 8, 12 Hz, 1 H, CHHOH), 3.93 (dd, J = 6.5, 12 Hz, 1 H, CHHOH), 4.14 (dd, J = 10, 12 Hz, 1 H, CHHOBz), 4.73 (dd, J = 6, 12 Hz, 1 H, CHHOBz), 7.45–7.7 (m, 3 H, *m,p*-Ph H), 8.09 (d, J = 6 Hz, 2 H, *o*-Ph H).

(*E*)-2-[(Benzoyloxy)methyl]cyclopropanemethanol (14b). This material, prepared by the procedure used for **14a**, was obtained in 38% yield as a colorless oil: 200-MHz NMR ($CDCl_3$) δ 0.64 (m, 2 H, cyPr CH_2), 1.19 (m, 2 H, cyPr CH), 1.47 (s, 1 H, OH), 3.54 (m, 2 H, CH_2OH), 4.22 (m, 2 H, CH_2OBz), 7.4–7.6 (m, 3 H, *m,p*-Ph H), 8.06 (d, J = 7 Hz, 2 H, *o*-Ph H).

(*Z*)-1-[(Benzoyloxy)methyl]-2-(chloromethyl)cyclopropane (15a). A solution of 0.99 mL (1.61 g, 13.6 mmol) of $SOCl_2$ in 6 mL of $CHCl_3$ was added dropwise to a mixture of 2.8 g (13.6 mmol) of **14a**, 1.07 g (13.6 mmol) of pyridine, and 5 mL of $CHCl_3$ that was stirred at 0 °C under N_2. After completion of the addition, the mixture was heated at reflux for 1 h and then concentrated. The residual semisolid was taken up in a mixture of Et_2O and EtOAc, filtered, and concentrated to give 2.98 g (98%) of colorless oil, suitable for use without further purification: 200-MHz NMR ($CDCl_3$) δ 0.49 (ddd, J = 6, 6, 6 Hz, 1 H, cyPr CHH), 1.05 (ddd, J = 6, 8, 8 Hz, 1 H, cyPr CHH), 1.54 (m, 2 H, cyPr CH), 3.60 (dd, J = 8, 12 Hz, 1 H, CHHCl), 3.76 (dd, J = 7, 12 Hz, 1 H, CHHCl), 4.25 (dd, J = 8, 12 Hz, 1 H, CHHOBz), 4.57 (dd, J = 6, 12 Hz, 1 H, CHHOBz), 7.4–7.6 (m, 3 H, *m,p*-Ph H), 8.08 (d, J = 7 Hz, 2 H, *o*-Ph H).

(*E*)-1-[(Benzoyloxy)methyl]-2-(chloromethyl)cyclopropane (15b). By the procedure used for **15a**, this material was obtained in quantitative yield as a colorless oil: 200-MHz NMR ($CDCl_3$) δ 0.65–0.85 (m, 2 H, cyPr CH_2), 1.33 (m, 2 H, cyPr CH), 3.43, 3.56 (dd, J = 7, 12 Hz, each 1 H, CH_2Cl), 4.14 (dd, J = 7, 12 Hz, 1 H, CHHOBz), 4.29 (dd, J = 6, 12 Hz, 1 H, CHHOBz), 7.35–7.6 (m, 3 H, *m,p*-Ph H), 8.06 (d, J = 7 Hz, 2 H, *o*-Ph H).

9-[[(*Z*)-2-[(Benzoyloxy)methyl]cyclopropyl]methyl]-adenine (16a). To a stirred suspension of 1.01 g (7.5 mmol) of adenine in 10 mL of dry DMF was added 0.33 g (8.3 mmol) of NaH (60% in mineral oil). Owing to the insolubility of the resulting adenine sodium salt, the mixture was diluted with 7 mL of dry Me_2SO, stirred mechanically under N_2, and heated at 80 °C as a solution of 1.86 g (8.3 mmol) of **15a** in 1 mL of Me_2SO was added dropwise, followed by 112 mg (0.75 mmol) of NaI. After 10 h at 80 °C, an additional 1.01 g (6.75 mmol) of NaI was added. The temperature was raised to 100 °C and kept there overnight. The cooled mixture was concentrated (oil pump) to give a dark brown residue, which was taken up in CH_2Cl_2 and filtered. This solution was chromatographed on 24 1000-μm preparative silica gel plates (developed with 80:20:2 $CHCl_3$–MeOH–H_2O). The product bands (R_f about 0.7) were isolated from each plate,

combined, and extracted with DMF. The extracts were concentrated in vacuo. The residue was taken up in hot Me_2CO, filtered, and concentrated to give 220 mg (9%) of **16a** as an oil: 200-MHz NMR (Me_2SO-d_6) δ 0.63 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.89 (ddd, J = 5, 8.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.45 (m, 1 H, cyPr CH), 1.71 (m, 1 H, cyPr CH), 4.19 (dd, J = 8.5, 11.5 Hz, 1 H, C*H*HOBz), 4.25 (dd, J = 9, 14 Hz, 1 H, C*H*HN), 4.39 (dd, J = 7, 14 Hz, 1 H, CH*H*N), 4.73 (dd, J = 6.5, 11.5 Hz, 1 H, CH*H*OBz), 7.32 (br s, 2 H, NH_2), 7.5–7.7 (m, 3 H, *m,p*-Ph H), 7.81 (d, J = 7 Hz, 2 H, *o*-Ph H), 8.14, 8.30 (s, each 1 H, C^2-H, C^8-H).

9-[[(*E*)-2-[(Benzoyloxy)methyl]cyclopropyl]methyl]adenine (16b). By a procedure similar to that used for **16a**, this material was obtained in 7% yield as a solid: mp 174–176 °C; TLC 90:10:1 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 260 nm (ε 12 000); 200-MHz NMR (Me_2SO-d_6) δ 0.65–0.85 (m, 2 H, cyPr CH_2), 1.43 (m, 2 H, cyPr CH), 3.7–3.95, 4.2–4.4 (m, each 2 H, CH_2O, CH_2N), 7.4–7.7 (m, 5 H, Ph H), 8.14, 8.22 (s, each 1 H, C^2-H, C^8-H). Anal. ($C_{12}H_{17}N_5O_2$·0.45H_2O) C, H, N.

9-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]adenine (17a). A mixture of 123 mg (0.38 mmol) of **16a**, 1 mL of 40% $MeNH_2$ (aqueous), and 0.5 mL of MeOH was stirred at room temperature overnight and then at reflux for 2 h. The residual oil obtained upon concentration was triturated with CH_2Cl_2 to give a solid, which was collected on a filter. Recrystallization from *i*-PrOH yielded 18 mg (20%) of white solid: mp 185.5–187.5 °C; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 260 nm (ε 12 600), λ_{max} (MeOH + H^+) 259 nm (ε 16 900); 200-MHz NMR (Me_2SO-d_6) δ 0.30 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.65 (ddd, J = 5, 8.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.15, 1.34 (m, each 1 H, cyPr CH), 3.37, 3.72 (m, each 1 H, CH_2OH), 4.10, 4.24 (dd, J = 7, 14 Hz, each 1 H, CH_2N), 4.77 (t, J = 5 Hz, 1 H, OH), 7.19 (br s, 2 H, NH_2), 8.14, 8.23 (s, each 1 H, C^2-H, C^8-H). Anal. ($C_{10}H_{13}N_5O$·0.15H_2O) C, H, N.

9-[[(*E*)-2-(Hydroxymethyl)cyclopropyl]methyl]adenine (17b). A mixture of 200 mg (0.62 mmol) of **16b** and 4 mL of MeOH was treated with several drops of 1 N NaOMe in MeOH, stoppered, and stirred at room temperature for 3 days. The solution was neutralized with glacial AcOH and concentrated in vacuo to give a white solid, which was recrystallized from *i*-PrOH, yielding 85 mg (63%) of **17b**. An analytical sample was recrystallized from H_2O: mp 190–192 °C; TLC in 90:10:1 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 260 nm (ε 14 800), λ_{max} (MeOH + H^+) 258 nm (ε 17 600), λ_{max} (MeOH + OH^-) 260 nm (ε 16 100); 200-MHz NMR (Me_2SO-d_6) δ 0.42 (ddd, J = 5, 5, 8 Hz, 1 H, cyPr C*H*H), 0.56 (ddd, J = 5, 5, 8 Hz, 1 H, cyPr CH*H*), 1.14 (m, 2 H, cyPr CH), 3.17 (dd, J = 7, 11 Hz, 1 H, C*H*HO), 3.33 (dd, J = 6, 11 Hz, 1 H, CH*H*O), 4.02 (d, J = 8 Hz, 2 H, CH_2N), 4.58 (v br s, 1 H, OH), 7.22 (br s, 2 H, NH_2), 8.16, 8.25 (s, each 1 H, C^2-H, C^8-H). Anal. ($C_{10}H_{13}N_5O$·0.54H_2O) C, H, N.

1-[[(*Z*)-2-[(Benzoyloxy)methyl]cyclopropyl]methyl]thymine (18). A mixture of 1.26 g (10 mmol) of thymine, 2.47 g (11 mmol) of **15a**, 2.76 g (20 mmol) of anhydrous K_2CO_3, 1.50 g (10 mmol) of NaI, and 15 mL of dry Me_2SO was stirred under N_2 at 80–90 °C overnight. After removal of salts by filtration, the filtrate was concentrated in vacuo (oil pump). The residual oil was chromatographed on a column of silica gel initially packed in hexane. Elution with 1:1 hexane–EtOAc removed some dialkylated byproduct, while subsequent elution with EtOAc provided 1.26 g (40%) of **18** as a white solid. An analytical sample was recrystallized from *i*-PrOH: mp 153–155 °C; UV λ_{max} (MeOH) 272 nm (ε 9830); 200-MHz NMR (Me_2SO-d_6) δ 0.50 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.83 (ddd, J = 5, 8, 8 Hz, 1 H, cyPr CH*H*), 1.41 (m, 2 H, cyPr CH), 1.62 (s, 3 H, CH_3), 3.66 (dd, J = 8, 14 Hz, 1 H, C*H*HN), 3.87 (dd, J = 7, 14 Hz, 1 H, CH*H*N), 4.10 (dd, J = 9, 12 Hz, 1 H, C*H*HO), 4.65 (dd, J = 5, 12 Hz, 1 H, CH*H*O), 7.4–7.7 (m, 4 H, *m,p*-Ph H, C^6-H), 7.96 (d, J = 7 Hz, 2 H, *o*-Ph H), 11.07 (br s, 1 H, NH). Anal. ($C_{17}H_{18}N_2O_4$) C, H, N.

1-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]thymine (19). A mixture of 927 mg (2.95 mmol) of **18**, 8 mL of 40% $MeNH_2$ (aqueous), and 4 mL of MeOH was stirred at reflux for 2 h and then at room temperature overnight. The solution was next concentrated in vacuo. Trituration of the residual oil with EtOAc gave a white solid, which was collected on a filter. Following isolation of a smaller second crop from the mother liquor, there was obtained a total of 319 mg (51%) of **19**: mp 168–169 °C; TLC in 90:10:1 $CHCl_3$–MeOH–H_2O; UV λ_{max} (MeOH) 271 nm (ε 8930), λ_{max} (MeOH + H^+) 271 nm (ε 9010), λ_{max} (MeOH + OH^-) 268 nm (ε 7850); 200-MHz NMR (Me_2SO-d_6) δ 0.23 (ddd, J = 5, 5, 5 Hz, 1 H, cyPr C*H*H), 0.63 (ddd, J = 5, 8, 8 Hz, 1 H, cyPr CH*H*), 1.13 (m, 2 H, cyPr CH), 1.74 (s, 3 H, CH_3), 3.27 (dd after D_2O spike, J = 8, 12 Hz, 1 H, C*H*HO), 3.56 (dd, J = 8, 14 Hz, 1 H, C*H*HN), 3.66 (dd, J = 5, 12 Hz, 1 H, CH*H*O), 3.81 (dd, J = 6, 14 Hz, 1 H, CH*H*N), 4.61 (t, J = 5.5 Hz, 1 H, OH), 7.66 (s, 1 H, C^6-H), 11.16 (br s, 1 H, NH). Anal. ($C_{10}H_{14}N_2O_3$·0.1H_2O) C, H, N.

2-Vinyl-1,1-cyclopropanedimethanol (21). To 196 mL (196 mmol) of 1 M $LiAlH_4$ in THF stirred at reflux under N_2 was added dropwise over 30 min a solution of 23 g (108 mmol) of **20**[39,40] in 90 mL of dry THF. After heating for an additional 2 h, the mixture was cooled to 0 °C and treated cautiously with H_2O (200 mL total). The resulting mixture was stirred for 15 min and filtered. The solid on the filter was washed with THF. The combined filtrate and washings were concentrated to yield 12.9 g (93%) of an oil: TLC in 9:1 $CHCl_3$–MeOH; 200-MHz NMR ($CDCl_3$) δ 0.69 (dd, J = 5.5, 5.5 Hz, 1 H, cyPr C*H*H), 0.88 (dd, J = 5.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.64 (m, 1 H, cyPr CH), 3.31 (br s, 2 H, OH), 3.68 (s, 2 H, CH_2O), 3.74 (partially obscured d, J = 14 Hz, 1 H, C*H*HO), 3.98 (d, J = 14 Hz, 1 H, CH*H*O), 5.24 (ddd, J = 0.6, 2, 10 Hz, 1 H, CH=C*H*H), 5.36 (ddd, J = 0.8, 2, 16.5 Hz, 1 H, CH=CH*H*), 5.89 (ddd, J = 8, 10, 16.5 Hz, 1 H, C*H*=CH_2).

1,1-Bis[(benzoyloxy)methyl]-2-vinylcyclopropane (22). A solution of 5.5 g (43 mmol) of **21** in 40 mL of pyridine stirred at 0 °C under protection from moisture was treated with 15.2 mL (18.3 g, 130 mmol) of benzoyl chloride, added dropwise over 15 min. The reaction mixture was stirred at room temperature for 2 h, then treated with 8 mL of H_2O, and stirred overnight. The mixture was concentrated in vacuo. The residual oil was dissolved in 150 mL of EtOAc and washed successively with 50 mL of H_2O, 3 × 50 mL of 2 N HCl, and 4 × 50 mL of saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 11 g (75%) of an oil: TLC in 4:1 cyclohexane–EtOAc; 200-MHz NMR ($CDCl_3$) δ 0.98 (dd, J = 5.5, 5.5 Hz, 1 H, cyPr C*H*H), 1.16 (dd, J = 5.5, 8.5 Hz, 1 H, cyPr CH*H*), 1.88 (m, 1 H, cyPr CH), 4.30 (d, J = 12 Hz, 1 H, C_aHHO), 4.34 (d, J = 11.5 Hz, 1 H, C_bHHO), 4.44 (d, J = 11.5 Hz, 1 H, C_bHHO), 4.66 (d, J = 12 Hz, 1 H, C_aHHO), 5.13 (ddd, J = 0.8, 1.6, 10 Hz, 1 H, CH=C*H*H), 5.25 (ddd, J = 1, 1.7, 17 Hz, 1 H, CH=CH*H*), 5.79 (ddd, J = 7.5, 10, 17 Hz, 1 H, C*H*=CH_2), 7.4–7.6 (m, 6 H, *m,p*-Ph H), 8.06 (d, J = 7 Hz, 4 H, *o*-Ph H).

2,2-Bis[(benzoyloxy)methyl]cyclopropanemethanol (23). A solution of 11 g (33 mmol) of **22** in 200 mL of CH_2Cl_2 was stirred at −70 °C under protection from moisture as a stream of ozone was introduced over a period of 30 min, finally giving a permanent blue color. The mixture was treated with 6.6 g (174 mmol) of $NaBH_4$, and the cooling bath was removed. After an additional 1.5 h, the mixture was acidified by cautious dropwise addition of 200 mL of 2 N HCl. The CH_2Cl_2 was removed by rotary evaporation, and the remaining aqueous fraction was extracted with 3 × 100 mL of EtOAc. The combined EtOAc fractions were washed successively with 50 mL of H_2O, 100 mL of saturated $NaHCO_3$, and 50 mL of saturated NaCl, then dried over $MgSO_4$, filtered, and concentrated. The residual oil was chromatographed on a column of silica gel (elution with 5:2 and then 2:1 cyclohexane–EtOAc) to yield 4.0 g (36%) of **23** as an oil: 200-MHz NMR ($CDCl_3$) δ 0.68 (dd, J = 5.5, 5.5 Hz, 1 H, cyPr C*H*H), 1.03 (dd, J = 5.5, 9 Hz, 1 H, cyPr CH*H*), 1.53 (m, 1 H, cyPr CH), 2.03 (br s, 1 H, OH) 3.60 (dd, J = 9, 12 Hz, 1 H, C*H*HOH), 3.95 (dd, J = 5.5, 12 Hz, 1 H, CH*H*OH), 4.29 (d, J = 12 Hz, 2 H, $C_{a,b}H$HOBz), 4.41 (d, J = 12 Hz, 1 H, C_aH*HOBz*), 4.87 (d, J = 12 Hz, 1 H, C_bH*H*OBz), 7.35–7.6 (m, 6 H, *m,p*-Ph H), 8.03 (d, J = 7 Hz, 4 H, *o*-Ph H).

[2,2-Bis[(benzoyloxy)methyl]cyclopropyl]methyl *p*-Toluenesulfonate (24). A solution of 4.5 g (13.2 mmol) of **23** in 50 mL of dry pyridine was treated with 7.0 g (37 mmol) of *p*-toluenesulfonyl chloride and stirred at room temperature under protection from moisture for 1.5 h. The mixture was concentrated in vacuo. A solution of the residue in 150 mL of EtOAc was washed sequentially with 50 mL of H_2O, 100 mL of saturated $NaHCO_3$, 4 × 250 mL of H_2O, and 50 mL of saturated NaCl. The EtOAc phase was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a column of silica gel (elution with 5:1 cyclohexane–EtOAc) to give 3.36 g (54%) of **24** as an oil:

200-MHz NMR ($CDCl_3$) δ 0.76 (dd, J = 5.5, 5.5 Hz, 1 H, cyPr CHH), 1.09 (dd, J = 5.5, 9 Hz, 1 H, cyPr CHH), 1.54 (m, 1 H, cyPr CH), 2.41 (s, 3 H, CH_3), 4.06 (dd, J = 9, 11 Hz, 1 H, CHHOTs), 4.18 (d, J = 12 Hz, 1 H, C_aHHOBz), 4.29 (s, 2 H, C_bH_2OBz), 4.38 (dd, J = 7, 11 Hz, 1 H, CHHOTs), 4.68 (d, J = 12 Hz, 1 H, C_aHHOBz), 7.26 (d, J = 8 Hz, 2 H, tosyl 3,5-H), 7.35–7.6 (m, 6 H, m,p-Ph H), 7.74 (d, J = 8 Hz, 2 H, tosyl 2,6-H), 8.03 (d, J = 7 Hz, 4 H, o-Ph H).

2-Amino-9-[[2,2-bis[(benzoyloxy)methyl]cyclopropyl]methyl]-6-chloropurine (25). To a stirred mixture of 1.37 g (8.2 mmol) of 2-amino-6-chloropurine and 1.2 g of anhydrous K_2CO_3 in 20 mL of dry DMF was added a solution of 3.36 g (6.8 mmol) of **24** in 15 mL of dry DMF. The mixture was heated at 60 °C for 4 h and then concentrated to dryness. The residue was dissolved in 1:1 $CHCl_3$–MeOH and evaporated onto 20 mL of silica gel. This was added to the top of a 200-mL silica gel column, which was eluted with 97.5:2.5:0.15 $CHCl_3$–MeOH–H_2O. First eluted was 170 mg of the 7-alkylated isomer: UV λ_{max} (MeOH) 322 nm (ε 5500); 200-MHz NMR ($CDCl_3$) δ 8.22 (s, 1 H, C^8-H). Subsequently obtained was 1.79 g (53%) of the 9-alkylated isomer **25** as an oil: UV λ_{max} (MeOH) 308 nm (ε 7500); 200-MHz NMR ($CDCl_3$) δ 0.93 (dd, J = 5.5, 5.5 Hz, 1 H, cyPr CHH), 1.20 (dd, J = 5.5, 8 Hz, 1 H, cyPr CHH), 1.84 (m, 1 H, cyPr CH), 4.1–4.4 (m, 5 H, CH_2O, CH_2N), 4.87 (d, J = 12 Hz, 1 H, CHHO), 5.02 (br s, 2 H, NH_2), 7.3–7.9 (m, 10 H, Ph H), 7.92 (s, 1 H, C^8-H).

9-[[2,2-Bis(hydroxymethyl)cyclopropyl]methyl]guanine (3c). A suspension of 1.78 g (3.62 mmol) of **25** in 178 mL of 2.5 N HCl was stirred at reflux for 4.5 h. The resulting solution was cooled and concentrated in vacuo. Trituration of the residue with 3 × 20 mL of Et_2O afforded a solid. The isolated solid was dissolved in 5 mL of H_2O, and the pH was adjusted to 7 with 2 N NaOH. The solid that separated was collected on a filter and dried (600 mg). Concentration of the filtrate gave an additional 400 mg of solid. The combined solids were dissolved in a small volume of 1:1 $CHCl_3$–MeOH and applied to five 2000-μm silica gel preparative TLC plates, which were developed in 70:30:3 $CHCl_3$–MeOH–H_2O. The product bands (R_f 0.36) were isolated and eluted with 3:2 $CHCl_3$–MeOH. Concentration of the eluate yielded 430 mg of slightly impure product. A 260-mg sample was dissolved in 50 mL of warm MeOH and treated with 2 mL of Bio-Rad AG2-X8 (OH^-) resin (200–400 mesh). After being stirred for 5 min, the resin was collected on a filter, washed with MeOH, and then further extracted with warm 4:4:1 $CHCl_3$–MeOH–AcOH. The combined filtrates and washings were concentrated to give 123 mg (13%) of solid. An analytical sample was recrystallized from MeOH: mp 249–250 °C; UV λ_{max} (0.1 M phosphate buffer, pH 7) 254 nm (ε 11 700); 200-MHz NMR (Me_2SO-d_6) δ 0.42 (dd, J = 5, 5 Hz, 1 H, cyPr CHH), 0.55 (dd, J = 5, 8.5 Hz, 1 H, cyPr CHH), 1.16 (m, 1 H, cyPr CH), 3.17, 3.38, 3.45, 3.75 (dd, J = 5.5, 11 Hz, collapsed to d, J = 11 Hz, on D_2O addition, each 1 H, CH_2OH), 3.87 (dd, J = 8.5, 14 Hz, 1 H, CHHN), 4.08 (dd, J = 6.5, 14 Hz, 1 H, CHHN), 4.63, 4.73 (t, J = 5.5 Hz, each 1 H, OH), 6.82 (br s, 2 H, NH_2), 7.79 (s, 1 H, C^8-H), 10.92 (br s, 1 H, N^1-H). Anal. ($C_{11}H_{15}N_5O_3 \cdot 0.5H_2O$) C, H, N.

9-[[2,2-Bis[(benzoyloxy)methyl]cyclopropyl]methyl]adenine (26). To a suspension of 965 mg (7.14 mmol) of adenine in 25 mL of dry DMF stirred under protection from moisture was added 286 mg (7.14 mmol) of NaH (60% in oil). After evolution of H_2 had ceased (30 min), a solution of 3.00 g (6.5 mmol) of **24** in 10 mL of DMF was added, and the mixture was heated at 47 °C for 3 h. The mixture was concentrated to dryness in vacuo, and the residue was triturated with 3 × 20 mL of Et_2O. The resulting solid was collected on a filter, washed with several small volumes of H_2O, dried, and chromatographed on five 2000-μm silica gel preparative TLC plates (developed in 95:5:0.3 $CHCl_3$–MeOH–H_2O). The major product band (R_f 0.29) was isolated and eluted with 70:30:3 $CHCl_3$–MeOH–H_2O. Concentration of the eluate gave 670 mg (25%) of **26** as an oil: UV λ_{max} (MeOH) 260 nm (ε 16 000); 200-MHz NMR ($CDCl_3$) δ 0.96 (dd, J = 6, 6 Hz, 1 H, cyPr CHH), 1.18 (dd, J = 6, 8.5 Hz, 1 H, cyPr CHH), 1.90 (m, 1 H, cyPr CH), 4.3–4.45 (m, 5 H, CH_2N, CH_2O), 4.92 (d, J = 12.5 Hz, 1 H, CHHO), 5.79 (br s, 2 H, NH_2), 7.35–7.93 (m, 10 H, Ph H), 7.96, 8.32 (s, each 1 H, C^2-H, C^8-H).

9-[[2,2-Bis(hydroxymethyl)cyclopropyl]methyl]adenine (27). Deprotection of **26** with methanolic NaOMe (see preparation of **17b**) followed by preparative TLC (80:20:2 $CHCl_3$–MeOH–H_2O) and recrystallization from MeOH yielded 40% of colorless crystals: mp 159–160 °C; UV λ_{max} (0.1 M phosphate buffer, pH 7) 261 nm (ε 13 000); 200-MHz NMR (Me_2SO-d_6) δ 0.46 (dd, J = 5, 5 Hz, 1 H, cyPr CHH), 0.58 (dd, J = 5, 8.5 Hz, 1 H, cyPr CHH), 1.27 (m, 1 H, cyPr CH), 3.19 (dd, J = 5, 11 Hz, 1 H, C_aHHOH), 3.47 (m, 2 H, C_aHHOH, C_bHHOH), 3.80 (dd, J = 5, 11.5 Hz, 1 H, C_bHHOH), 4.12 (dd, J = 8, 14.5 Hz, 1 H, CHHN), 4.28 (dd, J = 7, 14.5 Hz, 1 H, CHHN), 4.53, 4.74 (t, J = 5 Hz, each 1 H, OH), 7.20 (br s, 2 H, NH_2), 8.15, 8.24 (s, each 1 H, C^2-H, C^8-H). Anal. ($C_{11}H_{15}N_2O_2 \cdot 0.2H_2O$) C, H, N.

(Z)-1-(Benzoyloxy)-4-bromo-2-butene (29). The compound was prepared from *cis*-2-butene-1,4-diol via **28** by a literature method[57] for the synthesis of **32**. Spectral data were in agreement with those reported for **29** (apparently the Z isomer, although not specified) prepared by a different route.[58]

(E)-1-(Benzoyloxy)-4-bromo-2-butene (30). A mixture of 6.3 g (30 mmol) of *trans*-1,4-dibromo-2-butene, 4.2 g (30 mmol) of anhydrous sodium benzoate, and 60 mL of dry DMF was stirred under N_2 at 60 °C for 5 h. After concentration in vacuo, the residue was taken up in EtOAc and filtered to remove insolubles. The filtrate was evaporated onto 4.5 g of silica gel, which was then applied to the top of a short column of 45 g of silica gel packed in 3:1 cyclohexane–$CHCl_3$. Elution with the same solvent afforded 1.64 g of product containing minor impurities. One half of this material was further purified by chromatogaphy on four 2000-μm preparative silica gel TLC plates (developed in 1:1 cyclohexane–$CHCl_3$). Isolation of the product band (R_f 0.57), elution with EtOAc, filtration, and concentration in vacuo yielded 415 mg (11%) of **30** as an oil. Spectral data agreed with those reported for **30** synthesized by an alternative route.[59]

1-(Benzoyloxy)-4-bromo-2-butyne (32). This material was prepared in two steps from 2-butyne-1,4-diol according to a literature procedure.[57]

2-Amino-9-[(Z)-4-(benzoyloxy)-2-buten-1-yl]-6-chloropurine (33). This compound was prepared from **29** by a procedure analogous to that used for **25**, except that the reaction was carried out at room temperature, and the column was eluted with 2:1 $CHCl_3$–EtOAc to give a 69% yield of **33**: TLC in 90:10:1 $CHCl_3$–MeOH–H_2O (R_f 0.7); UV λ_{max} (MeOH) 311 nm (ε 5340); 200-MHz NMR ($CDCl_3$) δ 4.93 (d, J = 7 Hz, 2 H, CH_2N or CH_2O), 5.12 (d, J = 6.5 Hz, 2 H, CH_2N or CH_2O), 5.13 (br s, 2 H, NH_2), 5.85–6.1 (m, 2 H, CH=CH), 7.4–7.65 (m, 3 H, m,p-Ph H), 7.91 (s, 1 H, C^8-H), 8.09 (d, J = 7 Hz, 2 H, o-Ph H).

2-Amino-9-[(E)-4-(benzoyloxy)-2-buten-1-yl]-6-chloropurine (34). Alkylation of 2-amino-6-chloropurine with **30** at 20 °C as described for **25** afforded a 95% yield of **34** suitable for use in the next step. Purification of a portion by preparative TLC on 1000-μm silica gel plates developed in 90:10:1 $CHCl_3$–MeOH–H_2O gave a white solid: mp 195–197 °C dec; 200-MHz NMR (Me_2SO-d_6) δ 4.77, 4.82 (overlapping d, J = 5.5 Hz, each 2 H, CH_2N and CH_2O), 5.75, 6.11 (dt, J = 15.5, 5.5 Hz, each 1 H, =CH), 6.97 (br s, 2 H, NH_2), 7.5–7.7 (m, 3 H, m,p-Ph H), 8.00 (d, J = 7 Hz, 2 H, o-Ph H), 8.17 (s, 1 H, C^8-H). Anal. ($C_{16}H_{14}ClN_5O_2 \cdot 0.1H_2O$) C, H, N.

2-Amino-9-[4-(benzoyloxy)-2-butyn-1-yl]-6-chloropurine (35). Reaction of **32**[57] with 2-amino-6-chloropurine at 20 °C by the method used for **26**, followed by preparative TLC on 2000-μm silica gel plates developed in 90:10:1 $CHCl_3$–MeOH–H_2O, gave a 26% yield of **35** as a yellow solid: mp 197–198 °C dec; 200-MHz NMR ($CDCl_3$) δ 4.92, 4.99 (t, J = 2 Hz, each 2 H, CH_2), 5.17 (br s, 2 H, NH_2), 7.49 (dd, J = 7, 7 Hz, 2 H, m-Ph H), 7.63 (t, J = 7 Hz, 1 H, p-Ph H), 8.10 (d, J = 7 Hz, 2 H, o-Ph H). Anal. ($C_{16}H_{12}N_5O_2Cl \cdot 0.35H_2O$) C, H, N.

9-[(Z)-4-Hydroxy-2-buten-1-yl]guanine (4a). Hydrolysis of **33** as described for **3c**, followed by crystallization of the hydrochloride from MeOH and neutralization with 2 N NaOH, yielded 61% of **4a** as white crystals: mp 264–266 °C; TLC in 80:20:2 $CHCl_3$–MeOH–H_2O; UV λ_{max} (0.1 M phosphate buffer, pH 7) 252 nm (ε 11 300), 270 nm (shoulder, ε 8500); NMR spectrum was in agreement with the reported data.[19]

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9-[(*E*)-4-Hydroxy-2-buten-1-yl]guanine (4b). This material was prepared from **34** as described for **4a** and **3c**. UV and NMR spectral data were in accord with literature values.[20,21]

9-(4-Hydroxy-2-butyn-1-yl]guanine (36). Hydrolysis of **35** by the method used for **3c**, followed by recrystallization from H_2O, gave a 68% yield of white solid: mp >235 °C dec (gradual); UV λ_{max} (0.1 M phosphate buffer, pH 7) 252 nm (ϵ 7160); NMR spectrum was in accord with reported values.[19]

9-[(*Z*)-4-(Benzoyloxy)-2-buten-1-yl]adenine (37). By a modification of the procedure used for **26** (reaction temperature 20 °C, preparative TLC plates developed in 90:10:1 $CHCl_3$–MeOH–H_2O, R_f 0.6), **37** was obtained from **29** in 50% yield as a cream-colored solid: mp 154–156 °C; UV λ_{max} (MeOH) 262 nm (ϵ 15 430); 200-MHz NMR ($CDCl_3$) δ 5.06, 5.10 (overlapping d, J = 5.5 Hz, each 2 H, CH_2N, CH_2O), 5.66 (br s, 2 H, NH_2), 5.85–6.1 (m, 2 H, =CH), 7.45–7.65 (m, 3 H, *m,p*-Ph H), 7.95, 8.42 (s, each 1 H, C^2-H, C^8-H), 8.10 (d, J = 7 Hz, 2 H, *o*-Ph H). Anal. ($C_{16}H_{15}N_5O_2$) C, H, N.

9-[(*Z*)-4-Hydroxy-2-buten-1-yl]adenine (38). Treatment of **37** with NaOMe as described for **17b** gave a 50% yield of white solid (recrystallized from MeOH): mp 196–199 °C; TLC in 90:10:1 $CHCl_3$–MeOH–H_2O (R_f 0.3); UV λ_{max} (0.1 M phosphate buffer, pH 7) 261 nm (ϵ 12 000); 200-MHz NMR (Me_2SO-d_6) δ 4.22 (d, J = 5.5 Hz, 2 H, CH_2O), 4.85 (d, J = 6.5 Hz, 2 H, CH_2N), 4.94 (br s, 1 H, OH), 5.55–5.8 (m, 2 H, =CH), 7.24 (br s, 2 H, NH_2), 8.14, 8.17 (s, each 1 H, C^2-H, C^8-H). Anal. ($C_9H_{11}N_5O{\cdot}0.1H_2O$) C, H, N.

Enzyme Assays. Full details of the "staggered" assay conditions have been reported.[51] Briefly, step I (thymidine kinase assay) entailed incubation of the test compound with HSV-1 thymidine kinase for 4 h at 37 °C followed by examination of an aliquot by HPLC for presence of the monophosphate. In step II (phosphorylation to di- and triphosphate), the remainder of the step I assay mixture was treated with extract of HSV-1-infected HeLa cells and hog brain GMP kinase. After incubation overnight at 30 °C, the amounts of mono-, di-, and triphosphate were determined by HPLC. Finally, the mixture from step II was incubated at 37 °C with activated salmon sperm DNA, deoxyribonucleotides including [^{3}H]dTTP, additional crude extract of HSV-1-infected cells, and other factors. The assay was conducted in the presence of $(NH_4)_2SO_4$ to determine viral polymerase activity and in the absence of $(NH_4)_2SO_4$ when the cellular polymerases were assayed. The extent of DNA synthesis was determined by measuring the radioactivity incorporated into washed nucleic acids precipitated by trichloroacetic acid.

In Vitro Antiviral Assays. As previously described,[3,51,52] quadruplicate confluent monolayers of primary rabbit kidney cell cultures, preincubated with serial dilutions of test compound in maintenance medium, were challenged with approximately 10 $TCID_{50}$ of either HSV-1, strain Schooler, or HSV-2, strain Curtis. Cultures were incubated at 37 °C and evaluated for virus-induced cytopathology on day 5. The ED_{50} was calculated as the concentration of drug required to completely suppress development of cytopathology in 50% of the cell monolayers.

Acknowledgment. We thank Corrille M. DeWitt for the in vivo testing of **3a**, Dr. Byron Arison for NMR spectral analyses of **5a,b**, Valorie Mayo for UV spectra, Jack Smith for mass spectra, and the laboratory of Jane Wu for elemental analyses. We are grateful to Alexander Matzuk and Glenn F. Reynolds for scale-ups of key intermediates.

Registry No. **3a**, 116663-96-8; **3b**, 116663-97-9; **3c**, 116664-10-9; **4a**, 99776-29-1; **4b**, 104715-61-9; **5a**, 116663-91-3; **5b**, 116663-90-2; **6a**, 116663-92-4; **6b**, 45467-35-4; **7a**, 116663-93-5; **8a**, 116663-94-6; **8b**, 116663-95-7; **10**, 116663-98-0; **11**, 116698-29-4; **12a**, 710-43-0; **12b**, 115109-28-9; **13a**, 2345-68-8; **13b**, 82442-59-9; **14a**, 116663-99-1; **14b**, 116664-00-7; **15a**, 116664-01-8; **15b**, 116664-02-9; **16a**, 116669-26-2; **16b**, 116669-27-3; **17a**, 116669-28-4; **17b**, 116669-29-5; **18**, 116664-03-0; **19**, 116664-04-1; **20**, 79930-08-8; **21**, 116664-05-2; **22**, 116664-06-3; **23**, 116664-07-4; **24**, 116664-08-5; **25**, 116664-09-6; **26**, 116664-11-0; **27**, 116664-12-1; **28**, 81121-63-3; **29**, 116664-13-2; **30**, 104311-79-7; **32**, 114978-77-7; **33**, 116664-14-3; **34**, 116664-15-4; **35**, 116664-16-5; **36**, 99776-30-4; **37**, 116664-17-6; **38**, 114978-80-2; H_2C=CHCN, 107-13-1; $N_2CHCOOEt$, 623-73-4; $ClCH_2CHO$, 107-20-0; H_2C=COOEt, 140-88-5; $ClCH_2COOEt$, 105-39-5; (*Z*)-$HOCH_2CH$=$CHCH_2OH$, 6117-80-2; (*E*)-$BrCH_2CH$=$CHCH_2Br$, 821-06-7; $HOCH_2C{\equiv}CCH_2OH$, 110-65-6; 6-chloroisocytosine, 1194-21-4; (*Z*)-1,2-cyclopropanedicarboxylic acid, 696-74-2; adenine, 73-24-5; thymine, 65-71-4; 2-amino-6-chloropurine, 10310-21-1.

Additions and Corrections

1987, Volume 30

Rosa L. Lopez de Compadre, R. A. Pearlstein, A. J. Hopfinger,* and J. K. Seydel: A Quantitative Structure–Activity Relationship Analysis of Some 4-Aminodiphenyl Sulfone Antibacterial Agents Using Linear Free Energy and Molecular Modeling Methods.

Page 904. The QSAR given by eq 3 is not valid because the intramolecular entropy, S, was incorrectly computed. The revised QSAR, which replaces eq 3, is

$$pC = 0.040\ (\pm 0.005)P_A + 0.469\ (\pm 0.052)\phi + 5.18\ (\pm 0.06)$$

$$N = 34,\ R = 0.90,\ \mathrm{SD} = 0.20,\ F = 63.0$$

P_A is the sum of the thermodynamic probabilities, see eq 2, p 902, of the four postulated active conformations, and ϕ is the direction of the dipole moment of the substituted phenyl ring relative to the corresponding dipole for the most active analogue. Compounds **30** and **31** of Table I, p 901, had to be deleted in constructing this QSAR. The values of P_A and ϕ are available upon request from A.J.H.

All other results are valid, and the conclusions made do not need to be altered. However, an additional conclusion is that the dipole moment of the substituted ring is important to inhibition potency. This may indicate some specific electrostatic interactions between the ligand and the receptor.

Alan R. Katritzky,* Kenneth C. Caster,† Thomas H. Maren,* Curtis W. Conroy, and Amir Bar-Ilan: Synthesis and Physicochemical Properties of Thiadiazolo[3,2-*a*]pyrimidinesulfonamides and Thiadiazolo[3,2-*a*]-triazinesulfonamides as Candidates for Topically Effective Carbonic Anhydrase Inhibitors.

Page 2061. The intraocular pressure was not "measured in anesthetized rabbits" as stated but in non-anesthetized awake rabbits given a local anesthetic (0.25% proparacaine) on the cornea.

In the measurement of the rate constant (k_{in}) for transcorneal penetration in the rabbit eye, the concentration of compound applied to the artifically created corneal well (C_{out}) was not (as stated) taken as constant. C_{out} was actually measured at the start and end (10 min later) of drug exposure time, and the mean concentration was used for C_{out} in the calculation of k_{in} as shown in Table I. For