Synthesis and Antiviral Activity of Novel Acyclic Nucleosides: Discovery of a Cyclopropyl Nucleoside with Potent Inhibitory Activity against Herpesviruses

Takaaki Sekiyama, Satoshi Hatsuya, Yasuhiro Tanaka, Mamoru Uchiyama, Nobukazu Ono, Satoshi Iwayama, Miki Oikawa, Katsuya Suzuki, Masahiko Okunishi, and Takashi Tsuji*

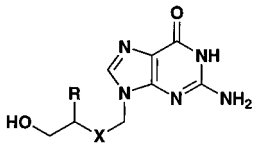
Central Research Laboratories, Ajinomoto Company, Inc., 1-1 Suzuki-cho, Kawasaki 210, Japan

Received September 3, 1997

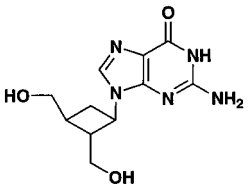
A series of acyclic nucleosides with two hydroxymethyl groups mimicking the 3′- and 5′-hydroxyl groups of the 2′-deoxyribose moiety were prepared and evaluated for their antiherpetic activity. Among those, 9-[[*cis*-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine (**3**) showed extremely potent antiviral activity against herpes simplex virus type-1 (HSV-1) with good selectivity. Both enantiomers of **3** were synthesized starting from chiral epichlorohydrins, and only one of the enantiomers with 1′*S*,2′*R*-configuration (**3a**) exhibited strong antiherpetic activity (IC_{50} of 0.020 μg/mL against HSV-1 Tomioka vs 0.81 μg/mL for acyclovir). Enantiomer **3a** was also more inhibitory than acyclovir against varicella-zoster virus (VZV) but ineffective against human immunodeficiency virus (HIV). Compound **3a** is phosphorylated by HSV-1 thymidine kinase (TK) very efficiently. The relationship between conformation and antiherpetic activity in this series of compounds is discussed.

Introduction

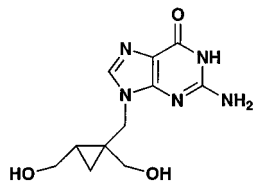
Since the discovery of acyclovir (ACV, **1a**) as a potent antiherpetic agent,[1] acyclic nucleosides have attracted interest of medicinal chemists as well as virologists. The efforts in search of a new agent with superior activity over ACV resulted in the finding of ganciclovir[2] (GCV, **1b**), with broader antiviral activity, and penciclovir[3] (PCV, **1c**) as new therapeutic agents. As represented by these two drugs, one of the approaches to improve antiherpetic activity is to design a compound with two hydroxyl groups mimicking the 3′- and 5′-hydroxyl groups of the 2′-deoxyribose moiety of nucleosides. The recent report on the crystal structure of HSV-1 thymidine kinase (TK), a key enzyme to activate antiherpetic nucleosides, complexed with GCV indicates the importance of the two hydroxyl groups of GCV for substrate recognition.[4]



1a ACV R = H, X = O
1b GCV R = CH_2OH, X = O
1c PCV R = CH_2OH, X = CH_2



2 cyclobut-G



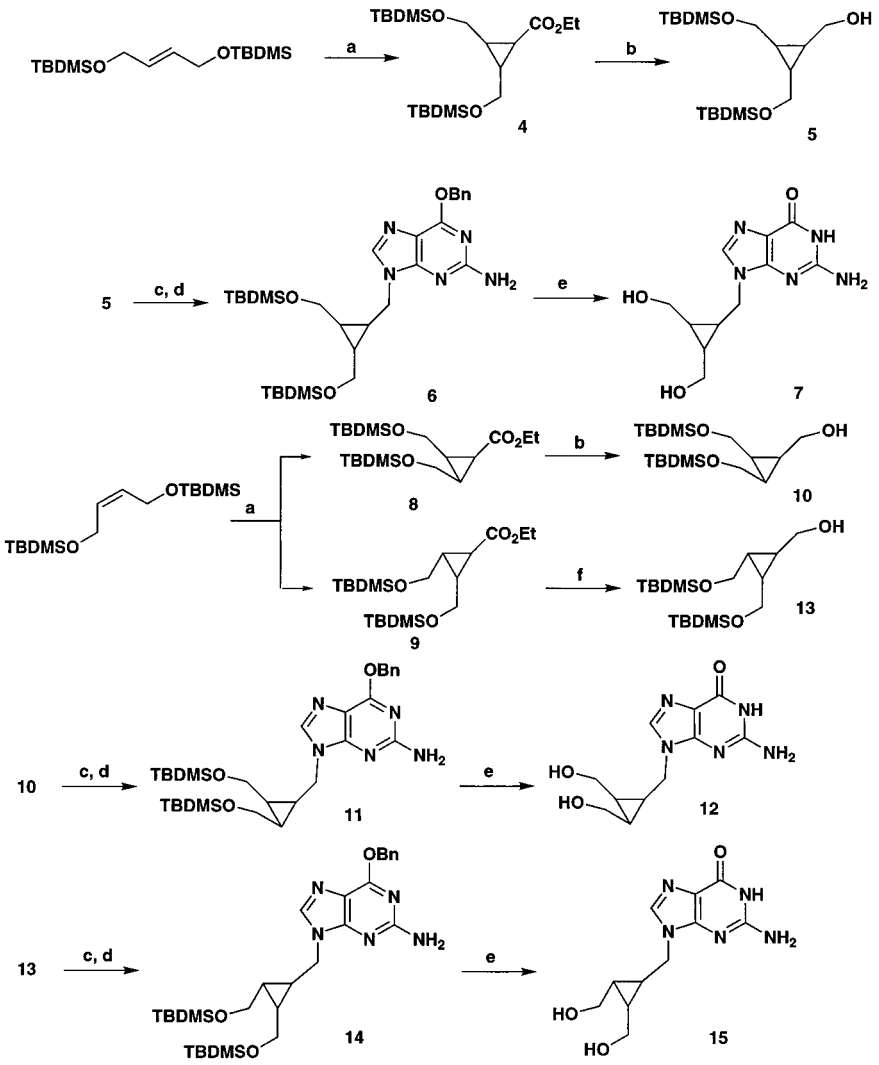
3

The discovery of oxetanocins[5] has led to a related carbocyclic analogue, cyclobut-G[6] (BHCG, **2**), as a highly potent inhibitor of broad spectrum against herpesviruses including herpes simplex virus type-1 and -2 (HSV-1, HSV-2), varicella-zoster virus (VZV), and human cytomegalovirus (HCMV). The characteristic structural feature of oxetanocins is the two hydroxymethyl groups located on a rigid four-membered ring. These findings have prompted us to design compounds by introducing conformational restriction on acyclic nucleosides with two hydroxymethyl groups mimicking the 3′- and 5′-hydroxyl groups of the 2′-deoxyribose moiety. Nucleosides with olefinic and cyclopropyl C_4 alcohols were reported previously,[7] and among them, 9-[[(*Z*)-2-(hydroxymethyl)cyclopropan-1-yl]methyl]guanine and 9-[(*Z*)-4-hydroxy-2-buten-1-yl]guanine showed moderate activity against HSV-1 and -2. These acyclic nucleosides are efficiently phosphorylated by viral TK and further phosphorylated by cellular kinases. These results suggest that the position of the hydroxyl group mimicking the 5′-hydroxyl group of nucleosides is suitable for phosphorylation in this series of compounds and that the introduction of the second hydroxyl group mimicking the 3′-hydroxyl group of nucleosides in this series of compounds will lead to a more potent antiherpetic compound.

In this study, we introduced rotational restriction between the C2 and C3 positions in a C_4 alcohol attached to a nucleoside base with olefinic, cyclopropyl, and oxiranic moieties and located the second hydroxymethyl group corresponding to the 3′-hydroxyl group of 2′-deoxyribose at the appropriate position. Among the compounds we synthesized, 9-[[*cis*-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine (**3**) showed extremely potent antiviral activity against HSV-1 with good selectivity. The two enantiomers of **3** were prepared starting from chiral epichlorohydrins, and among the enantiomers the 1′*S*,2′*R*-form (**3a**) was proved to be active. Antiviral spectra and mode of antiviral action of the series of compounds are also presented. The relationship of the side-chain conformation and flex-

S0022-2623(97)00586-4 CCC: $15.00
Published on Web 03/24/1998

Scheme 1[a]



[a] (a) N_2CHCO_2Et, $Rh_2(OAc)_4$; (b) Red-Al; (c) TsCl, DMAP; (d) 2-amino-6-(benzyloxy)purine, K_2CO_3, 18-crown-6; (e) HCl/MeOH; (f) $LiAlH_4$.

ibility to antiherpetic activity and phosphorylation by HSV-1 TK in this series of compounds are also discussed.

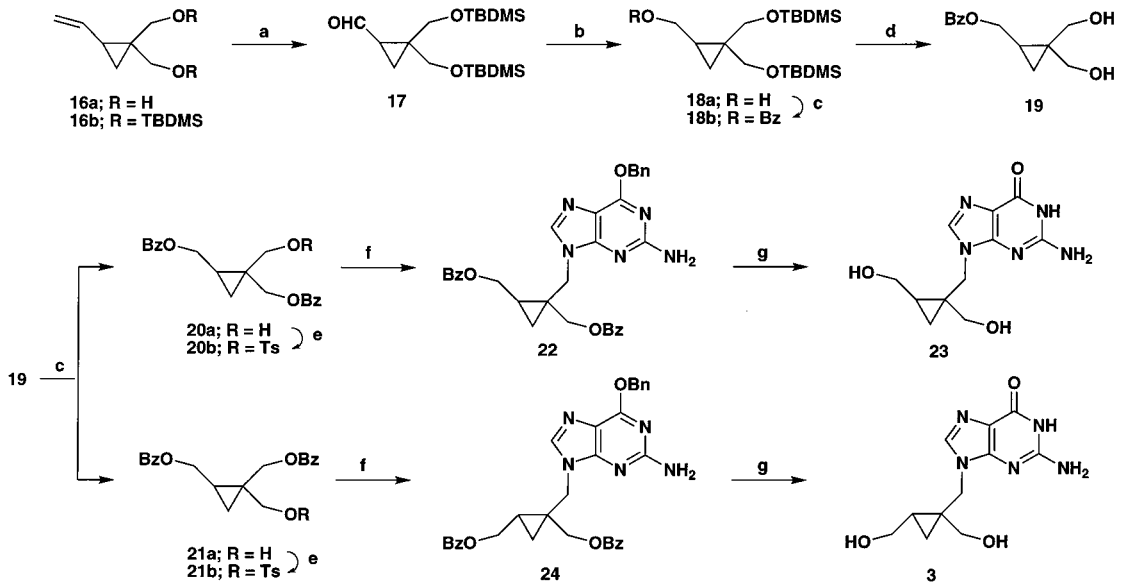
Chemistry

The synthesis of *trans*-2,3-bis(hydroxymethyl)cyclopropane derivative **7** is shown in Scheme 1. Cycloaddition of ethyl diazoacetate to the protected *trans*-1,4-butenediol in the presence of rhodium acetate gave 1,2,3-trisubstituted cyclopropane **4** which was reduced to alcohol **5** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), and the resultant alcohol was converted to its tosylate. Without purification the tosylate was used for coupling with 2-amino-6-(benzyloxy)purine to yield the desired 9-alkyl derivative **6** in 34% yield.[8] The 7-isomer was also obtained in 27% yield. Deprotection of **6** with 0.2 N hydrochloric acid in methanol gave **7**.

The syntheses of *cis*-2,3-bis(hydroxymethyl)cyclopropane derivatives are also outlined in Scheme 1. The silyl-protected *cis*-1,4-butenediol was treated with ethyl diazoacetate in the presence of rhodium acetate to give 1,2,3-trisubstituted cyclopropanes **8** and **9** in 8% and 7% yield, respectively. Stereochemistry of **8** and **9** was confirmed by vicinal coupling constant between protons on the cyclopropane ring.[9] Compound **8** was reduced to alcohol **10**, and its tosylate was coupled with 2-amino-6-(benzyloxy)purine to give the desired 9-alkyl derivative **11**. Deprotection of **11** afforded **12**. In a similar manner **9** was converted to **15**.

Scheme 2 shows the syntheses of 1,2-bis(hydroxymethyl)cyclopropane derivatives. 1,1,2-Tris(hydroxymethyl)cyclopropane (**16a**) was synthesized as described previously with modification[7] and converted to the disilyl ether **16b** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl). Oxidation of the double bond of **16b** with osmium tetraoxide, followed by oxidation with sodium metaperiodate, gave aldehyde **17**, which was converted to alcohol **18a** by reduction with $NaBH_4$. Benzoylation of the resulting hydroxyl group and acid hydrolysis of the silyl ether gave diol **19**. Treatment with an equimolar amount of benzoyl chloride gave two monobenzoates (**20a** and **21a**.) The regioisomers were separated by silica gel column chromatography, and their configuration was determined by NOE experiments.[10] Tosylation of **20a** and **21a** to **20b** and **21b** followed by treatment with 2-amino-6-(benzyloxy)purine afforded 9-alkylated

Scheme 2[a]



[a] (a) OsO_4, MNO then $NaIO_4$; (b) $NaBH_4$; (c) BzCl, pyridine; (d) aq HCl; (e) TsCl, DMAP; (f) 2-amino-6-(benzyloxy)purine, K_2CO_3, 18-crown-6; (g) MeONa/MeOH then 1 N HCl.

purine derivatives **22** and **24**, both in 61% yield, which were then deprotected to yield **23** and **3**.

The syntheses of olefinic derivatives are described in Scheme 3. Reaction of triethyl phosphonoacetate with ketone **25**, derived from dihydroxyacetone dimer by the method of Shibasaki et al.,[11] in the presence of sodium hydride produced bis-TBDMS ether **26** in 88% yield. Reduction of the ester group of **26** with diisobutylaluminun hydride (DIBAL-H) yielded alcohol **27a** which was subsequently converted to diol **28** by benzoylation followed by acid hydrolysis of the silyl ethers. Treatment of **28** with an equimolar amount of benzoyl chloride gave dibenzoate **29a**, as an *E*- and *Z*-mixture, which was converted to bromide **29b** with PBr_3 and coupled with 2-amino-6-(benzyloxy)purine without purification. Two 9-alkylated purine derivatives, **30** and **31**, were obtained, both in 20% yield, after separation on a silica gel column. The configuration of these stereoisomers was determined by NOE experiments.[12] Deprotection of **30** and **31** gave guanine derivatives **32** and **33**, respectively.

The syntheses of epoxides **38** and **39** are shown in Scheme 3. Oxidation of dibenzoate **29a** with *m*-CPBA yielded epoxide **34**. Tosylation of **34** and coupling of tosylate **35** with 2-amino-6-(benzyloxy)purine gave 9-alkylated purine derivatives **36** and **37** in 23% and 24% yield, respectively, after separation by reversed-phase column chromatography.[13] Deprotection by catalytic hydrogenation followed by sodium methoxide treatment yielded **38** and **39**.

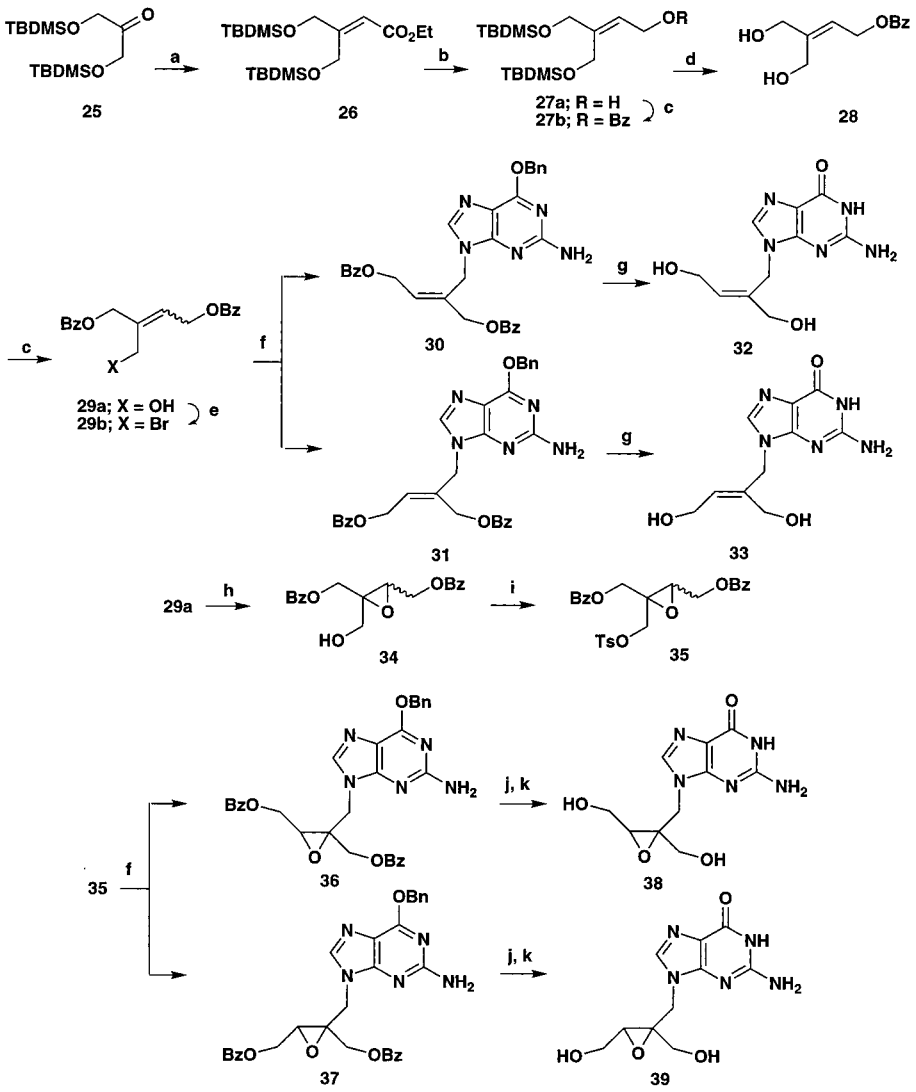
Derivatives of nucleosides bearing bases other than guanine were prepared as shown in Scheme 4. Tosylate or bromide **20b**, **21b**, and **29b** were coupled with adenine, thymine, and cytosine base. After coupling of **29b**, the stereoisomers were separated by reversed-phase column chromatography and the stereochemistry was determined by NOE experiments.[12] Deprotection of the benzoyl groups gave a series of adenine, thymine, and cytosine derivatives (**40**−**42**). Hypoxanthine derivatives **43a**,**b** were prepared from adenine derivatives **40a**,**b** by diazotization with sodium nitrite. 2,6-Diamino- and 2-aminopurine derivatives of **3** were prepared by coupling of **21b** with 2-amino-6-chloropurine followed by either amination or catalytic hydrogenation.

The compounds described above were synthesized as racemates. The enantiomers of the most active compound in the series, 9-[[*cis*-1′,2′-bis(hydroxymethyl)-cycloprop-1′-yl]methyl]guanine (**3**), were synthesized by the route shown in Scheme 5. Optically active cyclopropane lactone **47** was synthesized in the manner previously described by Pirrung et al.[14] with modification. Condensation of diethyl malonate and (*R*)-(−)-epichlorohydrin in ethanol under reflux gave **47** in 65% yield with >97% ee. The optical purity of **47** was established by chiral HPLC. Selective reduction of the lactone moiety was performed by $NaBH_4$ at room temperature to give diol ester **48** in 69% yield, which was converted to an acetonide and then reduced to alcohol **50a** by $LiBH_4$. Compound **50a** was converted to benzyl ether **50b** and subsequently hydrolyzed to diol **51a** by aqueous HCl. Benzoylation of **51a**, followed by palladium-catalyzed hydrogenation, gave dibenzoate **52** which was converted to **3a** in a similar manner as shown in Scheme 2.[15] The other enantiomer, **3b**, was prepared from (*S*)-(+)-epichlorohydrin in the same way.

Biological Studies

Antiherpetic activities of the series of compounds were measured by a quantitative CPE reduction assay[16] against HSV-1 Tomioka strain. Results are summarized in Table 1. Among the compounds tested, **3** showed extremely potent activity against HSV-1 and is nearly 20 times as potent as ACV (**1a**) with better selectivity. Of the two enantiomers of **3**, 1′*S*,2′*R*-form **3a** is the active form and is about 40 times as potent as ACV. The weak activity of the other enantiomer **3b** is possibly due to contamination of **3a** (<3%). The stereoisomer of **3**, the *trans*-cyclopropane **23**, is only marginally active. In contrast, the olefin analogues are weakly active, and both *E*- and *Z*-forms are equally active. Among the epoxide analogues only the *E*-epoxide **38** is active, and the *Z*-form is inactive. However, in this case,

Scheme 3[a]



[a] (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (b) DIBAL-H; (c) BzCl, pyridine; (d) aq HCl; (e) PBr_3; (f) 2-amino-6-(benzyloxy)purine, NaH; (g) MeONa/MeOH then aq HCl; (h) *m*-CPBA; (i) TsCl, pyridine; (j) H_2, Pd/C; (k) MeONa/MeOH.

decomposition of the epoxide ring under assay conditions was observed possibly by an intramolecular attack of N3 of purine to the epoxide. The 1′,2′,3′-trisubstituted cyclopropane analogues **7**, **12**, and **15** are completely devoid of activity.

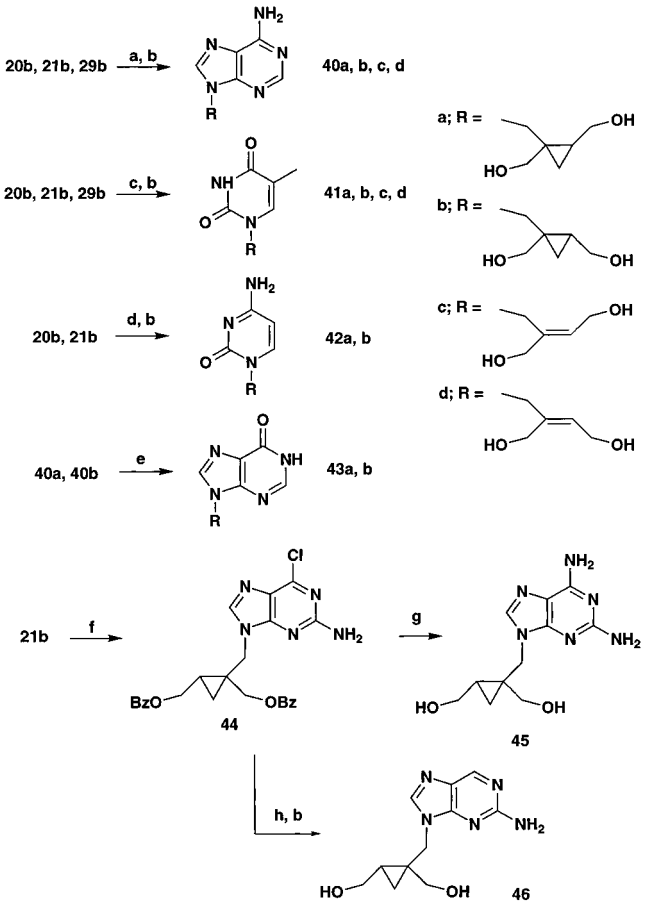
Among the compounds with base moieties other than guanine, **40b** with adenine, **45** with 2,6-diaminopurine, and **46** with 6-aminopurine, all with the *cis*-1′,2′-bis-(hydroxymethyl) moiety, are weakly active. The activity of the latter two compounds may be due to intracellular conversion to **3**.

The compounds were also tested against HIV-1. In contrast to the strong activity against HSV-1, **3a** was inactive against HIV. Among the compounds tested **41b**, a cytosine derivative of **3**, was moderately active, and some thymine, hypoxanthine, and 2,6-diaminopurine derivatives showed weak activity.

Anti-VZV activity of some of the compounds was evaluated by inhibition of plaque formation. The results are summarized in Table 2. All the compounds which are active against HSV-1 showed inhibitory activity against VZV, and among them, **3a** is more than 10 times as potent as ACV. *E*-Olefin **32** is more than 10 times as active as *Z*-olefin **33** in contrast to their anti-HSV-1 activity in which both isomers show equal activity.

Most of the antiherpetic acyclic nucleosides are phosphorylated by viral TK, and this step is critical for activity and selectivity. To study the phosphorylation of **3** and other compounds, they were incubated with an extract of HSV-1-infected BU25 cells lacking cellular TK[17] and amounts of monophosphates were measured by HPLC analysis.[18] Conversion of each nucleoside to the corresponding monophosphate is summarized in Table 3. Though the inactive compounds **7**, **12**, and **15** showed no or slow phosphorylation, the most potent (**3a**) is 7−8 times more efficiently phosphorylated than ACV by the cellular extract. The less active enantiomer, **3b**, is also phosphorylated, more slowly than **3a** but faster than ACV. **23**, **32**, and **33** are better substrates than acyclovir for the viral TK despite their weaker anti HSV-1 activity. The two enantiomers of **23** were separated by chiral HPLC, and phosphorylation of both enantiomers were studied. Although the absolute configuration of each enantiomer was not identified, one of the enantiomers showed highly efficient phosphorylation and the other showed no phosphorylation. No

Scheme 4[a]



[a] (a) Adenine, NaH; (b) MeONa/MeOH; (c) thymine, Na_2CO_3; (d) cytosine, NaH; (e) $NaNO_2$/AcOH; (f) 2-amino-6-chloropurine, K_2CO_3, 18-crown-6; (g) NH_3/MeOH; (h) 10% Pd/C, HCO_2NH_4.

phosphate formation was observed when these compounds were incubated with an extract of uninfected BU25 cells.

Discussion

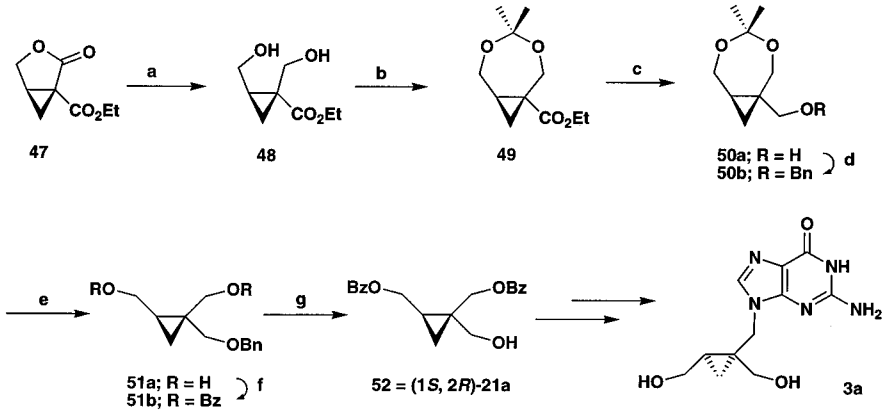
Rotational restrictions were introduced into flexible acyclosugar moieties of nucleosides, and their effects on antiviral activity were examined. Among the compounds synthesized, **3**, which is considered to be a 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG[19]) analogue with a cyclopropane ring in the 2,3-position of the side chain, showed extremely potent antiviral activity against HSV-1. Concerning the chirality around the carbon atom bearing the hydroxymethyl group corresponding to the 3′-hydroxyl of a nucleoside, the 2*R*-form of 2HM-HBG is the active form and, in case of **3**, the 1′*S*-form is the active configuration. Because of the characteristics of a cyclopropane ring, the direction of the side chain leading to the hydroxyl group corresponding to the 5′-hydroxyl group of a nucleoside is different in **3** and 2HM-HBG even with the same chirality around the 1′- and 2-carbon atoms, respectively, and it is not surprising that the opposite enantiomers are the active forms. Among the other com-

Table 1. Anti-HSV-1 Activity (Tomioka in Vero Cells) by Quantitative CPE Assay and Anti-HIV-1 Activity (RF in CEM Cells) by Plaque Reduction Assay of the Compounds

				HSV-1		HIV-1	
compd[a]	type[b]	position[c]	base[d]	IC_{50}[e]	CC_{50}	IC_{50}	CC_{25}
1a (ACV)				0.81	820	–	–
AZT				– [f]	–	0.003	35.6
ddC				–	–	0.02	0.49
3	cp	1′,2′-*c*	G	0.046	530	–	–
3a	cp	1′,2′-*c*	G	0.020	240	>100	>100
3b	cp	1′,2′-*c*	G	2.2	>500	–	–
7	cp	2′,3′-*t*	G	>500	>500	–	–
12	cp	2′,3′-*c*	G	>500	>500	–	–
15	cp	2′,3′-*c*	G	>500	>500	–	–
23	cp	1′,2′-*t*	G	10	>500	>100	>100
32	ol	2,3-*E*	G	4.2	>500	>100	>100
33	ol	2,3-*Z*	G	4.2	>500	>100	>100
38	ep	2,3-*E*	G	14	>500	–	–
39	ep	2,3-*Z*	G	>500	>500	–	–
40a	cp	1′,2′-*t*	A	>500	260	>100	>100
40b	cp	1′,2′-*c*	A	47	120	>100	19.8
40c	ol	2,3-*E*	A	>500	260	>100	>100
40d	ol	2,3-*Z*	A	>500	260	>100	>100
41a	cp	1′,2′-*t*	T	>500	>500	>100	>100
41b	cp	1′,2′-*c*	T	>500	>500	3.2	>100
41c	ol	2,3-*E*	T	>500	>500	>100	>100
41d	ol	2,3-*Z*	T	>500	>500	>100	>100
42a	cp	1′,2′-*t*	C	120	>500	23.7	>100
42b	cp	1′,2′-*c*	C	>500	>500	>100	>100
43a	cp	1′,2′-*t*	HX	>500	>500	20.1	>100
43b	cp	1′,2′-*c*	HX	>500	>500	25.7	>100
45	cp	1′,2′-*c*	DAP	29	>500	32.1	>100
46	cp	1′,2′-*c*	2AP	30	>500	–	–

[a] All compounds except AZT, ddC, and **3a**,**b** are racemates. [b] Type of bonds in the side chains: cp, cyclopropane; ol, olefin; ep, epoxide. [c] Positions of the two hydroxymethyl groups in the side chains. [d] G, guanine; T, thymine; C, cytosine; A, adenine; HX, hypoxanthine; DAP, 2,6-diaminopurine; 2AP, 2-aminopurine. [e] Concentrations in μg/mL. [f] Not measured.

Scheme 5[a]



[a] (a) $NaBH_4$; (b) 2,2-dimethoxypropane, cat. TsOH; (c) $LiBH_4$; (d) benzyl bromide, NaH; (e) aq HCl; (f) BzCl, pyridine; (g) H_2, Pd/C.

Table 2. Anti-VZV Activity (DM625 in HFF Cells) by Plaque Reduction Assay of the Compounds

compd[a]	IC_{50}[b]	MTC[c]	SI[d]
1a (ACV)	2.7	>320	>83
3a	0.20	320	1600
7	240	320	1.3
23	19.4	320	16
32	3.2	320	100
33	52.8	>320	>6.1
40a	220	320	1.5
40b	19.8	320	16

[a] All compounds except **3a** are racemates. [b] Concentrations in μg/mL. [c] Minimum cytotoxic concentration determined by microscopic examination of the drug-treated uninfected cells. [d] Selectivity index = IC_{50}/minimum cytotoxic concentration of drugs.

Table 3. Conversion of Nucleosides to Their Monophosphates

compd[a]	conversion (%)[b]	compd[a]	conversion (%)[b]
2′-dG	0	**15**	14
1a (ACV)	6	**23**	46
3a	46	**23a**	0
3b	11	**23b**	94
7	16	**32**	39
12	0	**33**	32

[a] All compounds except 2′-dG, **3a**,**b**, and **23a**,**b** are racemates. [b] Calculated percentage based on phosphorylated and unphosphorylated compound after incubation for 24 h at 37 °C.

pounds, **32** and **33** which are the *E*- and *Z*-olefinic analogues of 2HM-HBG are moderately active. Though in the olefinic version the *E*- and *Z*-isomers showed almost identical antiherpetic activity, **23**, which is the *trans*-cyclopropyl analogue of **3**, showed a dramatic decrease in antiherpetic activity compared to the corresponding cis form. There is only a small difference in the possible location of the two hydroxyl groups in the *E*- and *Z*-forms of the olefinic and cyclopropyl derivatives; however, this small change in the side-chain orientation caused by the different type of restriction plays a critical role in the antiviral activity. Among the oxirane analogues only the *E*-form **38** showed weak activity. The side-chain orientations of the oxirane derivatives are almost identical to that of the cyclopropyl derivatives except for the presence of the oxygen atom. The low activity of the oxirane derivatives may be due to the disturbance of interaction with the target enzymes by the presence of the oxygen atom. Another possibility might be the instability of the compounds under the assay conditions as described in the previous section.

Although less active against HSV-1 and -2 than ACV, 2HM-HBG shows superior activity over ACV against VZV.[19] Similar to 2HM-HBG, anti-VZV activity of **3a** is more than 10 times as potent as ACV; thus, **3a** is proved to be one of the most potent anti-VZV acycloguanine nucleosides ever known. Unlike PCV and GCV, the carbon skeleton of the sugar moiety does not trace that of deoxyribose in **3a** and 2HM-HBG and the position of the 3′-hydroxyl group is closer to the guanine base. This structural feature will be one of the reasons for the high activity against VZV.

The 1′,2′,3′-trisubstituted type compounds are all inactive. These compounds resemble cyclobut-G **2** but have an extra methylene between the guanine base and the ring. Other base analogues of this type of compounds were synthesized by Katagiri et al.,[20] and none of them showed antiviral activity. By the simple analogy to **2**, compounds in which a cyclopropyl moiety is attached directly to a nucleoside base were also synthesized previously, but these analogues are only weakly or not at all active against herpesviruses.[21] In the compounds with a cyclopropane ring directly attached to the nucleoside base, the hydroxyl group to be phosphorylated is too close to the base in comparison to **2**. Thus, the compounds with an extra methylene group were synthesized in this study. However, the relative positions of the two hydroxyl groups and the base moiety are proved to be unsuitable in these compounds. In contrast, ring expansion of **2** has also been tried to find a unique adenine nucleoside active against HIV.[22]

Cyclopropyl and olefinic derivatives of 9-(4-hydroxybutyl)guanine (HBG) and PCV were reported previously,[7,23] and the (*Z*)-cyclopropyl analogue which lacks the 1′-hydroxymethyl group of **23** showed moderate activity. In contrast to our results, the corresponding (*E*)-cyclopropyl analogue which lacks the 1′-hydroxymethyl group of **3** was inactive against HSV-1 and -2. Importance of the relative positioning of the two hydroxyl groups in the side chain should be noted.

Since exhibition of the antiherpetic activity of these nucleoside analogues is the sum of several steps of enzymatic processes including phosphorylation to monophosphates by a viral TK, further phosphorylation to triphosphates by cellular kinases, and finally inhibition of viral DNA replication,[24] to make detailed discussion in structure−activity relationships studies on each step are required. In the present study the first step of activation was studied, since this step is known to be critical for the selectivity and activity of antiherpes acyclic nucleosides. All the compounds tested which are active against HSV-1 to some extent were phosphorylated more efficiently than acyclovir. The most active compound (**3a**) is not the best compound in terms of the efficacy of phosphorylation. The inactive enantiomer (**3b**) is also phosphorylated to some extent. In the case of PCV the major form of the monophosphate produced by HSV-TK is the (*S*)-PCV monophosphate, but the (*R*)-monophosphate is also formed.[25] Quite surprisingly, one of the enantiomers of **23** is the best substrate of viral TK. Enantiomeric selectivity observed in **23** is similar to that in GCV in which a single enantiomeric monophosphate is formed.[26] In case of cyclobut-G, efficiency of phosphorylation of each enantiomer by HSV-TK does not correlate with their antiherpesvirus activity.[27] Though there is no clear parallel relationship between efficacy of phosphorylation by viral TK and antiviral activity, efficient phosphorylation by herpes TK is apparently one of the reasons for the strong antiherpetic activity of **3a**.

Recently, crystal structures of the thymidine kinase of HSV-1 and its complexes with thymidine and GCV were solved.[4] As shown in the crystal structure of the complexes, the binding modes of thymidine and GCV are different from each other. Combining the information from the crystal structure with the fact that 2′-deoxyguanosine is not a good substrate of the HSV-TK,[28] the resemblance of the acycloguanine nucleoside to 2′-deoxyguanosine is unfavorable in the step of phosphorylation. However, in the steps of further phosphorylation by cellular kinases and the triphosphate inhibition of DNA polymerases, structural simi-

larity to 2′-deoxyguanosine nucleotides is supposed to be important. In fact carbocyclic 2′-deoxyguanosine[29] and its 2′-fluoro derivative[30] which are structurally closest to 2′-deoxyguanosine show potent antiherpetic activity. Since these compounds are also active against HCMV lacking the viral thymidine kinase, they might be phosphorylated by the cellular guanosine kinases.

Effect of the cyclopropane ring should be the introduction of restriction which arranges the relative orientation of the two hydroxyl groups while maintaining a certain amount of flexibility. From our preliminary results on conformational studies using molecular mechanics, the two hydroxyl groups of **3a** can take positions close to those of 2′-deoxyguanosine in one of their stable conformations. At the same time, it was revealed that the rotational barriers around the bonds between the cyclopropane ring and the methylene carbon attached to the ring were lowered compared to the normal single bond, which means the entire molecule is flexible enough to adopt different conformers suitable for further phosphorylation and DNA polymerase inhibition after phosphorylation. The structural requirement for the highly active compounds is not described with a single conformation. They should have proper conformations, both in themselves and in phosphorylated forms, against several enzymes, viral and cellular kinases, and viral DNA polymerase, and **3a** is one of such compounds, in terms of conformational rigidity and flexibility, especially for HSV-1. To introduce conformational rigidity is one of the approaches to decide the active conformation, and a cyclopropane ring has also been used recently to fix sugar ring puckering by introducing it into carbocyclic 2′-deoxynucleosides.[31] In contrast to such trials to give complete rigidity in the molecule, rigidity is limited in the present study, and this partial conformational restriction has led to a highly potent antiviral compound.

Since **3a** exhibits superior activity against a wide variety of herpesviruses with a good selectivity index and preliminary in vivo experiments showed a superior therapeutic potential of this compound,[32] it may provide a new therapeutic tool with better clinical efficacy over the existing drugs. Further studies such as antiviral spectrum against various strains of herpesviruses in different cell lines and in vivo efficacy will be reported elsewhere.[32]

Experimental Section

General. Reagents used were the highest quality available commercially. (*R*)- and (*S*)-epichlorohydrin (>98% ee) were obtained from Daiso (Osaka, Japan). Unless otherwise noted, organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4, and temperature refers to the temperature of the bath. Melting points (uncorrected) were determined on a Yanaco MP-S3 micromelting point apparatus. ^{1}H NMR spectra were recorded with a Varian XL-300 300-MHz or a JEOL JNM-GX-400 400-MHz spectrometer, using tetramethylsilane as an internal standard, and ultraviolet spectra were recorded with a HITACHI U-3200 spectrophotometer. Mass spectra were recorded on a JEOL JMS-DX300 spectrophotometer, and accurate masses were measured on a JEOL JMS-HX110 spectrometer. Thin-layer chromatography was carried out on silica gel 60F254 precoated plates (Merck art. 5715), and silica gel column chromatography was conducted on silica gel 60 (70−230 mesh; Merck art. 7734). Preparative reversed-phase column chromatography was conducted on Merck LiChroprep RP-18 (40−63 μm). Elemental combustion analyses, where indicated only by the elements, were within ±0.4% of theoretical values. Anti-VZV and anti-HIV assays were performed under contract by Southern Research Institute. All antiviral titrations were done in either triplicate or quadruplicate.

Ethyl *c*-2,*t*-3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanecarboxylate (4). To an ice-cooled mixture of ethyl glycinate HCl (5.60 g, 40 mmol) in H_2O (10 mL) and CH_2Cl_2 (23 mL) was added aqueous $NaNO_2$ (3.28 g, 47.5 mmol, 10 mL), and then 5% aqueous H_2SO_4 (3.90 mL) was added dropwise at −20 °C. After stirring for 10 min at −20 °C, the mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated $NaHCO_3$. The organic layer was combined and concentrated to 7.5 mL in vacuo. The solution was added dropwise over 6 h to a solution of (*E*)-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-2-butene (10.38 g, 32.8 mmol) and rhodium(II) acetate dimer (90 mg, 0.20 mmol) in CH_2Cl_2 (20 mL) at room temperature. After stirring for 14 h, the solvent was removed in vacuo and the residue was chromatographed on silica gel eluting with 4−10% Et_2O in hexane to yield **4** as a colorless oil (4.01 g, 30%): ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 12H), 0.86 (s, 18H), 1.25 (t, J = 7.2 Hz, 3H), 1.55−1.65 (m, 2H), 1.73 (dd, J = 5.4, 9.0 Hz, 1H), 3.61 (dd, J = 4.8, 10.5 Hz, 1H), 3.66 (dd, J = 4.5, 10.5 Hz, 1H), 3.71 (dd, J = 7.8, 11.0 Hz, 1H), 3.90 (dd, J = 5.7, 11.0 Hz, 1H), 4.11(q, J = 7.2 Hz, 1H), 4.12 (q, J = 7.2 Hz, 1H); FD MS m/z 402 (M^+).

***c*-2,*t*-3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanemethanol (5).** A solution of **4** (2.24 g, 5.56 mmol) in anhydrous THF (25 mL) was cooled to −5 °C and treated with a 3.3 M solution of Red-Al in toluene (2.8 mL, 9.24 mmol). After stirring at −5 °C for 20 min, saturated NH_4Cl was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 15−20% Et_2O in hexane to yield **5** as a colorless oil (1.34 g, 67%): ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.89 (m, 1H), 0.90 (s, 9H), 1.17 (m, 1H), 1.30 (m, 1H), 3.28 (m, 1H), 3.34 (m, 1H), 3.51 (dd, J = 5.7, 10.8 Hz, 1H), 3.55 (dd, J = 5.7, 10.8 Hz, 1H), 3.94 (dd, J = 5.1, 11.3 Hz, 1H), 4.13 (dd, J = 5.6, 11.3 Hz, 1H); FD MS m/z 361 (MH^+).

2-Amino-6-(benzyloxy)-9-[[*c*-2′,*t*-3′-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]cycloprop-*r*-1′-yl]methyl]-purine (6). *p*-TsCl (3.39 g, 17.8 mmol) was added to a solution of **5** (2.14 g, 5.93 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (4.35 g, 35.6 mmol) in CH_2Cl_2 (80 mL) at 0 °C, and the mixture was stirred at 0−5 °C for 2.5 h. The solution was diluted with EtOAc−hexane (1:1) and washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine. The organic layer was concentrated in vacuo, and the resulting residue was dissolved in DMF (10 mL). The solution was added to a suspension of 2-amino-6-(benzyloxy)purine (1.43 g, 5.93 mmol), K_2CO_3 (0.82 g, 5.93 mmol), and 18-crown-6 (1.42 g, 5.93 mmol) in DMF (40 mL). After stirring at 110 °C for 16 h, the mixture was cooled to room temperature, diluted with EtOAc−hexane (1:1, 100 mL), and then washed with brine. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 2% MeOH in CH_2Cl_2 to yield **6** as a white solid (1.19 g, 34%): ^{1}H NMR ($CDCl_3$) δ −0.01 (s, 6H), 0.06 (s, 6H), 0.84 (s, 9H), 0.89 (s, 9H), 1.08 (m, 1H), 1.21 (m, 1H), 1.31 (m, 1H), 3.48 (dd, J = 6.0, 10.8 Hz, 1H), 3.57−3.67 (m, 2H), 3.97 (dd, J = 4.8, 11.4 Hz, 1H), 4.10 (dd, J = 7.2, 14.4 Hz, 1H), 4.30 (dd, J = 7.2, 14.4 Hz, 1H), 4.92 (bs, 2H), 5.56 (s, 2H), 7.25−7.36 (m, 3H), 7.48−7.52 (m, 2H), 7.91 (s, 1H); FD MS m/z 584 (MH^+).

9-[[*c*-2′,*t*-3′-Bis(hydroxymethyl)cycloprop-*r*-1′-yl]methyl]guanine (7). To a solution of **6** (552 mg, 0.945 mmol) in MeOH (25 mL) was added 1 N HCl (5 mL), and the mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the solvent was removed in vacuo and the residue was dissolved in H_2O and washed with EtOAc. The aqueous layer was concentrated in vacuo, and the residue was recrystallized from MeOH to yield the HCl salt of **7** as white crystals (53.5 mg, 19%): mp 265−267 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.02−1.20 (m, 2H), 1.26−1.37 (m, 1H), 3.12 (dd, J = 7.2, 11.4 Hz,

1H), 3.31 (dd, J = 9.3, 11.7 Hz, 1H), 3.47 (dd, J = 5.4, 11.4 Hz, 1H), 3.76 (dd, J = 5.4, 11.7 Hz, 1H), 4.06 (dd, J = 8.1, 14.4 Hz, 1H), 4.24 (dd, J = 7.2, 14.4 Hz, 1H), 7.18 (bs, 2H), 9.11 (s, 1H), 11.61 (bs, 1H); FD MS m/z 266 (MH^+); HRMS calcd for $C_{11}H_{16}O_3N_5$ (MH^+) 266.1253, found 266.1247. Anal. ($C_{11}H_{16}O_3N_5Cl$) C, H, N.

Ethyl 2,3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-cyclopropanecarboxylate (8 and 9). (*Z*)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2-butene (10.00 g, 31.6 mmol) was treated in the same manner as described in preparation of **4**. After chromatography, 1.06 g of **8** (8.3%) and 0.93 g of **9** (7.3%) were obtained as a colorless oil along with 5.73 g (57%) of starting material. Ethyl *c*-2,*c*-3-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanecarboxylate **8**: ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H, CH_3Si), 0.05 (s, 6H, CH_3Si), 0.88 (s, 18H, *t*-Bu), 1.25 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.67 (m, 2H, C^2H, C^3H), 1.83 (dd, J = 8.1, 9.3 Hz, 1H, C^1H), 3.94 (m, 2H, CH_2O), 4.02 (m, 2H, CH_2O), 4.09 (q, J = 7.2 Hz, 2H, CH_2CH_3). Ethyl *t*-2,*t*-3-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanecarboxylate, **9**: ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H, CH_3Si), 0.05 (s, 6H, CH_3Si), 0.89 (s, 18H, *t*-Bu), 1.25 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.57 (m, 1H, C^1H), 1.77 (m, 2H, C^2H, C^3H), 3.73 (m, 4H, CH_2O), 4.12 (q, J = 7.2 Hz, 2H, CH_2CH_3).

***c*-2,*c*-3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanemethanol (10).** Treatment of **8** (2.17 g, 5.39 mmol) as described in preparation of **5** gave **10** as a colorless oil (0.530 g, 27%): ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 12H), 0.90 (s, 18H), 1.31−1.51 (m, 3H), 3.11 (t, J = 6.6 Hz, 1H), 3.64−3.76 (m, 4H), 3.86−3.92 (m, 2H).

2-Amino-6-(benzyloxy)-9-[[*c*-2′,*c*-3′-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]cycloprop-*r*-1′-yl]methyl]-purine (11). Compound **10** (530 mg, 1.47 mmol) was treated as described in preparation of **6** to give **11** as a white solid (137 mg, 16%): ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 12H), 0.90 (s, 18H), 1.36−1.54 (m, 3H), 3.75−3.81 (m, 2H), 3.90−3.96 (m, 2H), 4.23 (d, J = 6.9 Hz, 2H), 4.90 (bs, 2H), 5.57 (s, 2H), 7.28−7.37 (m, 3H), 7.48−7.52 (m, 2H), 7.98 (s, 1H).

9-[[*c*-2′,*c*-3′-Bis(hydroxymethyl)cycloprop-*r*-1′-yl]methyl]guanine (12). Treatment of 137 mg of **11** (0.235 mmol) as described in preparation of **7** afforded the HCl salt of **12** as white crystals (30.7 mg, 43%): mp 235−237 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.23−1.36 (m, 2H), 1.48−1.62 (m, 1H), 3.50 (dd, J = 8.7, 11.7 Hz, 2H), 3.69 (dd, J = 5.4, 11.7 Hz, 2H), 4.26 (d, J = 7.8 Hz, 2H), 7.10 (bs, 2H), 8.91 (s, 1H), 11.49 (bs, 1H); FAB MS m/z 266 (MH^+); HRMS calcd for $C_{11}H_{16}O_3N_5$ (MH^+) 266.1253, found 266.1241. Anal. ($C_{11}H_{16}O_3N_5Cl$) C, H, N.

***t*-2,*t*-3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-*r*-1-cyclopropanemethanol (13).** A solution of **9** (1.09 g, 2.71 mmol) in anhydrous THF (10 mL) was treated with 1.0 M $LiAlH_4$ in THF (10 mL, 10 mmol) at 0 °C. After stirring at 0 °C for 30 min, saturated NH_4Cl was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 15−20% Et_2O in hexane to yield **13** as a colorless oil (0.769 g, 79%): ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 12H), 0.90 (s, 18H), 1.03−1.12 (m, 3H), 1.45 (bs, 1H), 3.48 (d, J = 6.6 Hz, 2H), 3.60−3.66 (m, 2H), 3.71−3.76 (m, 2H).

2-Amino-6-(benzyloxy)-9-[[*t*-2′,*t*-3′-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]cycloprop-*r*-1′-yl]methyl]-purine (14). Compound **13** (667 mg, 1.85 mmol) was treated as described in preparation of **6** to yield **14** as a pale-yellow solid (319 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 12H), 0.88 (s, 18H), 1.20−1.35 (m, 3H), 3.6−3.7 (m, 2H), 3.7−3.8 (m, 2H), 3.96 (d, J = 6.9 Hz, 2H), 4.78 (bs, 2H), 5.57 (s, 2H), 7.28−7.37 (m, 3H), 7.48−7.52 (m, 2H), 7.95 (s, 1H).

9-[[*t*-2′,*t*-3′-Bis(hydroxymethyl)cyclopropan-*r*-1′-yl]-methyl]guanine (15). Treatment of **14** (319 mg, 0.546 mmol) as described in preparation of **7** gave the HCl salt of **15** as white crystals (121 mg, 73%): mp 295−298 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.12−1.21 (m, 1H, H1), 1.22−1.32 (m, 3H), 3.37−3.48 (m, 4H), 3.99 (d, J = 7.2 Hz, 2H), 7.22 (bs, 2H), 9.11 (s, 1H), 11.5 (bs, 1H); FAB MS m/z 266 (MH^+); HRMS calcd for $C_{11}H_{16}O_3N_5$ (MH^+) 266.1253, found 266.1245. Anal. ($C_{11}H_{16}O_3N_5Cl\cdot 0.2H_2O$) C, H, N.

1,1-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-vinylcyclopropane (16b). To a solution of diethyl 2-vinyl-1,1-cyclopropyldicarboxylate (17.5 g, 82.3 mmol) in anhydrous THF (82.3 mL) was added dropwise 0.1 M $LiAlH_4$ in anhydrous THF (90.5 mL, 90.5 mmol) at 0 °C. After stirring at room temperature for 30 min, 33 mL of MeOH was added at 0 °C. MeOH (300 mL) and H_2O (15 mL) were added, and the mixture was stirred at room temperature overnight. The resulting emulsion was filtered over Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and filtered, and the filtrate was concentrated in vacuo. The residue containing **16a** (7.0 g, 55 mmol) and imidazole (16.5 g, 242 mmol) were dissolved in DMF (105 mL), and *tert*-butyldimethylsilyl chloride (18.2 g, 121 mmol) was added at 0 °C. After stirring overnight at room temperature, the solvent was removed in vacuo. The residue was dissolved in Et_2O and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 3% EtOAc in hexane to yield **16b** as a colorless oil (16.5 g, 56%): ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6H), 0.03 (s, 6H), 0.56 (dd, J = 4.8, 4.8 Hz, 1H), 0.80 (dd, J = 4.8, 8.4 Hz, 1H), 0.88 (s, 9H), 0.89 (s, 9H), 1.50 (m, 1H), 3.43 (d, J = 9.9 Hz, 1H), 3.51 (d, J = 10.5 Hz, 1H), 3.68 (d, J = 9.9 Hz, 1H), 3.71 (d, J = 10.5 Hz, 1H), 4.97 (ddd, J = 0.6, 2.1, 10.2 Hz, 1H), 5.18 (ddd, J = 0.9, 2.1, 17.1 Hz, 1H), 5.69 (ddd, J = 8.1, 10.2, 17.1 Hz, 1H).

2,2-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-cyclopropanecarbaldehyde (17). Osmium tetraoxide in acetone (0.1 M solution, 23.2 mL, 2.32 mmol) was added to a solution of **16b** (16.5 g, 46.4 mmol) and 4-methylmorpholine *N*-oxide (10.9 g, 92.8 mmol) in H_2O/THF (1:2, 165 mL), and the mixture was stirred at room temperature for 84 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was treated with $NaIO_4$ (11.9 g, 55.7 mmol) in H_2O/THF (1:2, 248 mL) at room temperature overnight. The solvent was removed in vacuo, and the residue was dissolved in Et_2O and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on a silica gel column eluting with 7% Et_2O in hexane to yield **17** as a colorless oil (13.5 g, 81%): ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.04 (s, 6H), 0.86 (s, 9H), 0.88 (s, 9H), 1.20 (dd, J = 5.1, 7.8 Hz, 1H), 1.42 (dd, J = 5.1, 5.1 Hz, 1H), 1.91 (ddd, J = 5.1, 5.1, 7.8 Hz, 1H), 3.46 (d, J = 10.2 Hz, 1H), 3.58 (d, J = 11.1 Hz, 1H), 3.80 (d, J = 10.2 Hz, 1H), 3.95 (d, J = 11.1 Hz, 1H), 9.46 (d, J = 4.5 Hz, 1H); FAB MS m/z 301 ($M^+ - t$-Bu).

2,2-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-cyclopropanemethanol (18a). $NaBH_4$ (3.56 g, 94.0 mmol) was added in portions to a stirred solution of **17** (13.5 g, 37.6 mmol) in MeOH (200 mL) at 0 °C. After 30 min, the solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with saturated NH_4Cl. The organic layer was concentrated in vacuo, and the residue was chromatographed on a silica gel column eluting with 10% Et_2O in hexane to yield **18a** as a colorless oil (11.8 g, 87%): ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.03 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.34 (t, J = 5.1 Hz, 1H), 0.70 (dd, J = 5.1, 8.4 Hz, 1H), 0.89 (s, 9H), 0.91 (s, 9H), 1.19 (m, 1H), 2.87 (d, J = 10.5 Hz, 1H), 3.20−3.32 (m, 3H), 3.94 (m, 1H), 4.11 (d, J = 10.5 Hz, 1H), 4.27 (dd, J = 10.8 Hz, 1H); FD MS m/z 361 (MH^+), 403 ($M^+ - t$-Bu).

[2,2-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]cycloprop-1-yl]methyl Benzoate (18b). BzCl (5.69 mL, 49.1 mmol) was added to a solution of **18a** (11.8 g, 32.7 mmol) in pyridine (177 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then, ice−water was added at 0 °C, and the mixture was stirred for 15 min. The solvent was removed in vacuo, and the residue was dissolved in Et_2O and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo and the residue was chromatographed on a silica gel column with 3% Et_2O in hexane to yield **18b** as a colorless oil (14.7 g, 97%): ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 6H), 0.04 (s,

3H), 0.55 (dd, J = 5.1, 5.1 Hz, 1H), 0.76 (dd, J = 5.1, 8.4 Hz, 1H), 0.87 (s, 18H), 1.29 (m, 1H), 3.44 (d, J = 10.2 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.63 (d, J = 11.1 Hz, 1H), 3.86 (d, J = 11.1 Hz, 1H), 4.34 (dd, J = 7.8, 11.7 Hz, 1H), 4.43 (dd, J = 7.8, 11.7 Hz, 1H), 7.43 (m, 2H), 7.55 (m, 1H), 8.06 (m, 2H); FD MS m/z 464 (M^+), 407 (M^+ − t-Bu).

[2,2-Bis(hydoxymethyl)cycloprop-1-yl]methyl Benzoate (19). To a solution of **18b** (21.2 g, 45.5 mmol), in MeOH (683 mL) was added 1 N HCl (137 mL, 137 mmol), and the mixture was stirred at room temperature for 40 min. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column with 4% MeOH in CH_2Cl_2 to yield **19** as a colorless oil (10.9 g, 100%): ^{1}H NMR ($CDCl_3$) δ 0.52 (dd, J = 5.4, 5.4 Hz, 1H), 0.82 (dd, J = 5.1, 8.7 Hz, 1H), 1.41 (m, 1H), 2.95 (bs, 2H), 3.55 (d, J = 11.4 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 3.69 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 12.0 Hz, 1H), 4.29 (dd, J = 8.7, 12.0 Hz, 1H), 4.57 (dd, J = 6.3, 12.0 Hz, 1H), 7.44 (m, 2H), 7.56 (m, 1H), 8.04 (m, 2H); FD MS m/z 236 (M^+).

***trans*-[2-[(Benzoyloxy)methyl]-1-(hydroxymethyl)-cycloprop-1-yl]methyl Benzoate (20a) and *cis*-[2-[(Benzoyloxy)methyl]-1-(hydroxymethyl)cycloprop-1-yl]-methyl Benzoate (21a).** A solution of **19** (1.06 g, 4.49 mmol) in pyridine (16 mL) was cooled to 0 °C and treated with BzCl (0.52 mL, 4.49 mmol). After stirring at room temperature for 40 min, ice−water was added and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 1% MeOH in CH_2Cl_2. The first elute gave **20a** as a colorless oil (455 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 0.68 (dd, J = 5.7, 5.7 Hz, 1H, C^3*H*H), 1.04 (dd, J = 5.7, 9.3 Hz, 1H, C^{3}H*H*), 1.57 (dddd, J = 5.7, 5.7, 9.3, 9.3 Hz, 1H, C^{2}H), 1.78 (bs, 1H, OH), 3.70 (d, J = 12.6 Hz, 1H, C*H*HOH), 3.94 (d, J = 12.6 Hz, 1H, CH*H*OH), 4.18 (dd, J = 9.3, 12.0 Hz, 1H, 2-C*H*HOBz), 4.33 (d, J = 11.4 Hz, 1H, 1-C*H*HOBz), 4.38 (d, J = 11.4 Hz, 1H, 1-CH*H*OBz), 4.74 (dd, J = 5.7, 12.0 Hz, 1H, 2-CH*H*OBz), 7.39 (m, 4H, Ar), 7.55 (m, 2H, Ar), 8.01 (m, 4H, Ar); FD MS m/z 341 (M^+ + H). The second elute gave **21a** as a colorless oil (455 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 0.74 (dd, J = 6.0, 6.0 Hz, 1H, C^3*H*H), 0.98 (dd, J = 6.0, 9.0 Hz, 1H, C^{3}H*H*), 1.50 (dddd, J = 6.0, 6.0, 9.0, 9.0 Hz, 1H, C^{2}H), 1.99 (bs, 1H, OH), 3.41 (d, J = 12.0 Hz, 1H, C*H*HOH), 3.71 (d, J = 12.0 Hz, 1H, CH*H*OH), 4.28 (dd, J = 9.0, 12.3 Hz, 1H, 2-C*H*HOBz), 4.29 (d, J = 12.3 Hz, 1H, 1-C*H*HOBz), 4.64 (dd, J = 6.0, 12.3 Hz, 1H, 2-CH*H*OBz), 4.85 (d, J = 12.3 Hz, 1H, 1-CH*H*OBz), 7.35 (m, 4H, Ar), 7.52 (m, 2H, Ar), 7.98 (m, 4H, Ar); FD MS m/z 340 (M^+).

***cis*-[1,2-Bis[(benzoyloxy)methyl]cycloprop-1-yl]methyl *p*-Toluenesulfonate (20b).** *p*-TsCl (3.58 g, 18.8 mmol) was added to a solution of **20a** (2.13 g, 6.26 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (4.59 g, 37.6 mmol) in 32 mL of CH_2Cl_2 at 0 °C, and the mixture was stirred at 0 °C for 1 h. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the concentrate was chromatographed on a silica gel column eluting with hexanes−EtOAc (3:1) to yield **20b** as a white solid (2.59 g, 84%): ^{1}H NMR ($CDCl_3$) δ 0.81 (dd, J = 6.0, 6.0 Hz, 1H), 1.08 (dd, J = 6.0, 8.7 Hz, 1H), 1.66 (m, 1H), 2.27 (s, 3H), 4.02 (dd, J = 9.3, 12.3 Hz, 1H), 4.05 (d, J = 12.0 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 4.26 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.1 Hz, 1H), 4.64 (dd, J = 6.0, 12.3 Hz, 1H), 7.18 (m, 2H), 7.27−7.41 (m, 4H), 7.55 (m, 2H), 7.74 (m, 2H), 7.85 (m, 2H), 7.97 (m, 2H); FD MS m/z 494 (M^+).

2-Amino-6-(benzyloxy)-9-[[*trans*-1′,2′-bis[(benzoyloxy)-methyl]cyclopropan-1′-yl]methyl]purine (22). A solution of **20b** (287 mg, 0.580 mmol) in DMF (7.5 mL) was added to the mixture of 2-amino-6-(benzyloxy)purine (168 mg, 0.70 mmol), K_2CO_3 (96 mg, 0.70 mmol), and 18-crown-6 (167 mg, 0.70 mmol) in DMF (4 mL), and the resulting mixture was stirred at 60 °C for 2 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on a silica gel column with 2−7% MeOH in CH_2Cl_2. Compound **22** was eluted first and obtained as a white solid (199 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 1.05 (dd, J = 6.0, 9.3 Hz, 1H), 1.15 (dd, J = 6.0, 6.0 Hz, 1H), 1.74 (dddd, J = 6.0, 6.0, 9.3, 9.3 Hz, 1H), 3.95 (d, J = 12.3 Hz, 1H), 4.22 (d, J = 15.3 Hz, 1H), 4.33 (dd, J = 9.3, 12.3 Hz, 1H), 4.35 (d, J = 12.3 Hz, 1H), 4.57 (d, J = 15.3 Hz, 1H), 4.90 (bs, 2H), 4.92 (dd, J = 6.0, 12.3 Hz, 1H), 5.47 (d, J = 12.3 Hz, 1H), 5.52 (d, J = 12.3 Hz, 1H), 7.30−7.39 (m, 7H), 7.47−7.57 (m, 4H), 7.83 (s, 1H), 7.92−7.98 (m, 4H); FD MS m/z 563 (M^+). The 7-isomer was obtained as the second elute (82.6 mg, 25%).

9-[[*trans*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]-methyl]guanine (23). NaH (60%, 42.4 mg, 1.06 mmol) in MeOH (2 mL) was added to a solution of **22** (199 mg, 0.35 mmol) in MeOH (2 mL), and the mixture was stirred at 40 °C for 30 min. Then 1, N HCl (1.77 mL, 1.77 mmol) was added, and the mixture was stirred at 50 °C for 0.5 h. After cooling to room temperature, the solvent was removed in vacuo and the residue was dissolved in H_2O and washed with EtOAc. The aqueous layer was concentrated in vacuo, and the residue was purified by reversed-phase chromatography eluting with 0−30% MeOH in H_2O to yield **23** as a white solid (80.5 mg, 86%): mp 273.5−275 °C; ^{1}H NMR (DMSO-d_6) δ 0.52−0.59 (m, 2H), 1.12 (dddd, J = 6.0, 6.0, 8.4, 8.4 Hz, 1H), 3.03 (dd, J = 4.5, 11.4 Hz, 1H), 3.15 (dd, J = 4.5, 11.4 Hz, 1H), 3.47 (m, 1H), 3.72 (m, 1H), 3.99 (d, J = 14.4 Hz, 1H), 4.14 (d, J = 14.4 Hz, 1H), 4.64 (m, 2H), 6.40 (bs, 2H), 7.75 (s, 1H), 10.56 (bs, 1H); HRMS calcd for $C_{11}H_{16}O_3N_5$ (MH^+) 266.1253, found 266.1244. Anal. ($C_{11}H_{15}O_3N_5$) C, H, N.

***trans*-[1,2-Bis[(benzoyloxy)methyl]cycloprop-1-yl]-methyl *p*-Toluenesulfonate (21b).** Treatment of 11.5 g of **21a** (33.8 mmol) as described in the preparation of **20b** afforded **21b** as a white solid (15.6 g, 93%): ^{1}H NMR ($CDCl_3$) δ 0.83 (dd, J = 6.0, 6.0 Hz, 1H), 1.07 (dd, J = 6.0, 9.0 Hz), 1.56 (dddd, J = 6.0, 6.0, 9.0, 9.0 Hz, 1H), 2.28 (s, 3H), 3.93 (d, J = 10.5 Hz, 1H), 4.16 (dd, J = 9.0, 12.0 Hz, 1H), 4.22 (d, J = 12.3 Hz, 1H), 4.23 (d, J = 10.5 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 4.63 (dd, J = 6.0, 12.0 Hz, 1H), 7.20 (m, 2H), 7.31 (m, 4H), 7.52 (m, 2H), 7.76 (m, 2H), 7.85 (m, 2H), 7.91 (m, 2H); FD MS m/z 494 (M^+).

2-Amino-6-(benzyloxy)-9-[[*cis*-1′,2′-bis[(benzoyloxy)-methyl]cycloprop-1′-yl]methyl]purine (24). Coupling of 92.1 mg of **21b** (0.186 mmol) with 2-amino-6-(benzyloxy)purine as described in preparation of **22** gave **24** as a white solid (64.1 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, J = 6.0, 6.0 Hz, 1H), 1.29 (dd, J = 5.7, 9.0 Hz, 1H), 2.02 (m, 1H), 4.10 (d, J = 14.7 Hz, 1H), 4.11 (dd, J = 9.6, 12.3 Hz, 1H), 4.25 (d, J = 12.3 Hz, 1 Hz), 4.30 (d, J = 14.7 Hz, 1H), 4.55 (d, J = 12.3 Hz, 1H), 4.72 (dd, J = 6.0, 12.3 Hz, 1H), 4.92 (bs, 2H), 5.47 (s, 2H), 7.26−7.40 (m, 7H), 7.43−7.51 (m, 4H), 7.79−7.87 (m, 5H); FD MS m/z 563 (M^+). The 7-isomer was also obtained as a white solid (27.8 mg, 27%).

9-[[*cis*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]methyl]-guanine (3). Deprotection of 64.1 mg of **24** (0.114 mmol) as described in the preparation of **23** afforded **3** as a white solid (24.4 mg, 81%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 0.40 (t, J = 5.1 Hz, 1H), 0.88 (dd, J = 4.8, 8.7 Hz, 1H), 1.23 (m, 1H), 3.24−3.37 (m, 2H), 3.41 (dd, J = 6.0, 12.0 Hz, 1H), 3.58 (dt, J = 12.0, 6.0 Hz, 1H), 3.81 (d, J = 14.1 Hz, 1H), 4.00 (d, J = 14.1 Hz, 1H), 4.49 (m, 1H), 4.64 (m, 1H), 6.38 (bs, 2H), 7.71 (s, 1H), 10.49 (bs, 1H); HRMS calcd for $C_{11}H_{16}O_3N_5$ (MH^+) 266.1253, found 266.1263. Anal. ($C_{11}H_{15}O_3N_5$) C, H, N.

Ethyl 4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(*tert*-butyldi-methylsilyl)oxy]methyl]-2-butenate (26). Triethyl phosphonoacetate (2.07 mL, 10.0 mmol) was added to a suspension of 420 mg of NaH (60%, 10.5 mmol) in benzene (50 mL) at 0 °C; then **25** (3.15 g, 9.9 mmol) was added dropwise at room temperature over 0.5 h. The precipitate was dissolved in EtOH, H_2O was added, and the mixture was extracted with EtOAc. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with hexanes−EtOAc (10:1) to yield **26** as a pale-yellow oil (3.4 g, 88%): ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 6H), 0.89 (s, 9H), 0.93 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 4.43 (m, 2H), 4.86 (m, 2H), 5.97 (t, J = 2.0 Hz, 1H); FD MS m/z 389 (MH^+), 331 (M^+ − *t*-Bu).

4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-buten-1-ol (27a). Compound **26** (3.4 g, 8.8 mmol) in CH_2Cl_2 (6 mL) was treated with 1.0 M DIBAL-H in toluene (17.5 mL, 17.5 mmol) at −78 °C. After stirring at 0 °C for 30 min, H_2O and 3 mL of 1 N NaOH were added to dissolve the precipitate, and the resulting solution was extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with hexanes−EtOAc (10:1) to yield **27a** as a colorless oil (2.28 g, 75%): ^{1}H NMR ($CDCl_3$) δ 0.07−0.1 (m, 12H), 0.90 (s, 9H), 0.92 (s, 9H), 4.15−4.35 (m, 6H), 5.8 (m, 1H); FD MS *m*/*z* 289 ($M^+ - t$-Bu).

4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-buten-1-yl Benzoate (27b). Benzoylation of **27a** (2.28 g, 6.6 mmol) as described in the preparation of **18b** gave **27b** as a colorless oil (2.97 g, 100%): ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 12H), 0.90 (s, 9H), 0.92 (s, 9H), 4.24 (s, 2H), 4.31 (s, 2H), 4.96 (d, J = 7.0 Hz, 2H), 5.81 (t, J = 7.0 Hz, 1H), 7.4−7.6 (m, 3H), 8.0−8.1 (m, 2H); FD MS *m*/*z* 451 (MH^+), 393 ($M^+ - t$-Bu).

4-Hydroxy-3-(hydroxymethyl)-2-buten-1-yl Benzoate (28). A mixture of **27b** (14.25 g, 31.7 mmol) in MeOH (500 mL) and 1 N HCl (95 mL, 95 mmol) was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was chromatographed on silica gel eluting with CH_2Cl_2−MeOH (10:1) to yield **28** as a colorless oil (5.87 g, 83%): ^{1}H NMR ($CDCl_3$) δ 4.27 (s, 2H), 4.39 (s, 2H), 4.96 (d, J = 7.2 Hz, 2H), 5.79 (t, J = 7.2 Hz, 1H), 7.4−7.6 (m, 3H), 8.03 (m, 2H); FD MS *m*/*z* 222 (M^+).

4-(Benzoyloxy)-2-(hydroxymethyl)-2-buten-1-yl Benzoate (29a). Compound **28** (5.55 g, 25 mmol) was benzoylated as described in the preparation of **18b** to give **29a** as a pale-yellow oil of a 1:1 mixture of *E* and *Z*-forms (3.81 g, 47%): ^{1}H NMR (recorded as a sum of two isomers, $CDCl_3$) δ 2.1 (bs, 1H), 2.65 (bs, 1H), 4.28 (d, J = 6.0 Hz, 2H), 4.39 (d, J = 6.3 Hz, 2H), 4.96 (s, 2H), 4.99−5.06 (m, 2H, 2H), 5.06 (s, 2H), 5.92 (t, J = 6.9 Hz, 1H), 6.04 (t, J = 7.0 Hz, 1H), 7.38−7.6 (m, 6H, 6H), 8.0−8.7 (m, 4H, 4H); FD MS *m*/*z* 327 (MH^+).

4-(Benzoyloxy)-2-(bromomethyl)-2-buten-1-yl Benzoate (29b). PBr_3 (0.12 mL, 1.26 mmol) was added to **29a** (410 mg, 1.26 mmol) in benzene (3 mL) at 0 °C. After stirring at room temperature for 2 h, ice−water was added and the mixture was extracted with EtOAc. The organic layer was concentrated in vacuo to give **29b** (360 mg, 70%): ^{1}H NMR (recorded as a sum of two isomers, $CDCl_3$) δ 4.18 (s, 2H), 4.20 (s, 2H), 4.98−5.11 (m, 4H, 4H), 6.08 (t, J = 6.8 Hz, 1H), 6.16 (t, J = 6.8 Hz, 1H), 7.38−7.65 (m, 6H, 6H), 8.03−8.12 (m, 4H, 4H); FD MS *m*/*z* 309 (M^+ − Br).

2-Amino-9-[(*E*)-4-(benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]-6-(benzyloxy)purine (30) and 2-Amino-9-[(*Z*)-4-(benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]-6-(benzyloxy)purine (31). Compound **29b** (360 mg, 0.888 mmol) in DMF (1 mL) was added to a suspension of 2-amino-6-(benzyloxy)purine (241 mg, 1.0 mmol) and K_2CO_3 (600 mg, 4.34 mmol) in DMF (2 mL), and the resulting mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was dissolved in EtOAc and washed with H_2O. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with CH_2Cl_2−MeOH (10:1). The *E*-isomer **30** was obtained as the first elute: white solid (145 mg, 30%); ^{1}H NMR ($CDCl_3$) δ 4.76 (s, 2H, 2-CH_2OBz), 4.77 (s, 2H, C$^1H_2$), 4.95 (bs, 2H, NH_2), 5.26 (d, J = 6.6 Hz, 2H, C$^4H_2$), 5.52 (s, 2H, CH_2Ph), 6.16 (t, J = 6.6 Hz, 1H, C^{3}H), 7.3−7.6 (m, 11H, Ar), 7.74 (s, 1H, C^{8}H), 7.95 (m, 2H, Ar), 8.06 (m, 2H, Ar); FD MS *m*/*z* 549 (M^+). The *Z*-isomer **31** was eluted later: pale-yellow foam (142 mg, 29%); ^{1}H NMR ($CDCl_3$) δ 4.71 (s, 2H, 2-CH_2OBz), 4.84 (s, 2H, C$^1H_2$), 4.97 (bs, 2H, NH_2), 5.04 (d, J = 6.7 Hz, 2H, C$^4H_2$), 5.53 (s, 2H, CH_2Ph), 5.90 (t, J = 6.7 Hz, 1H, C^{3}H), 7.3−7.6 (m, 11H, Ar), 7.64 (s, 1H, C^{8}H), 7.95 (m, 2H, Ar), 8.00 (m, 2H, Ar); FD MS *m*/*z* 549 (M^+).

(*E*)-9-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]guanine (32). Deprotection of **30** (250 mg, 0.45 mmol) as described in the preparation of **23** and purification by reversed-phase chromatography eluting with 15% MeOH in H_2O afforded **32** as a white solid (86.1 mg, 76%): mp 268−268.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.77 (d, J = 5.3 Hz, 2H), 4.17 (dd, J = 6.1, 5.4 Hz, 2H), 4.58 (s, 2H, H1′), 4.76 (t, J = 5.4 Hz, 1H), 4.91 (t, J = 5.3 Hz, 1H), 5.78 (t, J = 6.1 Hz, 1H), 6.40 (bs, 2H), 7.57 (s, 1H), 10.57 (bs, 1H); HRMS calcd for $C_{10}H_{14}O_3N_5$ (MH^+) 252.1096, found 252.1095. Anal. ($C_{10}H_{13}O_3N_5$) C, H, N.

(*Z*)-9-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]guanine (33). Treatment of **31** as above yielded **33** in 76% yield as a white solid: mp 269−271 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (m, 4H), 4.59 (s, 2H), 4.88 (bs, 1H), 5.10 (bs, 1H), 5.78 (t, J = 6.1 Hz, 1H), 6.44 (bs, 2H), 7.58 (s, 1H), 10.6 (bs, 1H); HRMS calcd for $C_{10}H_{14}O_3N_5$ (MH^+) 252.1096, found 252.1090. Anal. ($C_{10}H_{13}O_3N_5$) C, H, N.

(*E*)- and (*Z*)-4-(Benzoyloxy)-2,3-epoxy-2-(hydroxymethyl)but-1-yl Benzoate (34). A solution of **29a** (2.0 g, 6.13 mmol) in CH_2Cl_2 (20 mL) was treated with *m*-chloroperbenzoic acid (1.32 g, 6.13 mmol) at 4 °C. After stirring at 4 °C for 4 days, saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 5% MeOH in CH_2Cl_2 to yield the mixture of **34** as a colorless oil (1.77 g, 84%).

(*E*)- and (*Z*)-4-(Benzoyloxy)-2-[(benzoyloxy)methyl]-2,3-epoxybut-1-yl *p*-Toluenesulfonate (35). A solution of **34** (1.10 g, 3.21 mmol) in CH_2Cl_2 (30 mL) containing pyridine (1.04 mL, 16.1 mmol) was treated with *p*-TsCl (642 mg, 3.37 mmol) at 0 °C. After 15 h, ice−water was added and the mixture was extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 2% MeOH in CH_2Cl_2 to yield **35** as a colorless oil (790 mg, 50%).

2-Amino-9-[(*E*)-4(benzoyloxy)-2,3-epoxy-2-[(benzoyloxy)methyl]but-1-yl]-6-(benzyloxy)purine (36) and 2-Amino-9-[(*Z*)-4-(benzoyloxy)-2,3-epoxy-2-[(benzoyloxy)methyl]but-1-yl]-6-(benzyloxy)purine (37). 2-Amino-6-(benzyloxy)purine (300 mg, 1.24 mmol) was added to 50 mg of NaH (60%, 1.25 mmol) in anhydrous DMF (15 mL). After stirring at room temperature for 1 h, **35** (500 mg, 1.01 mmol) in DMF (10 mL) was added and the mixture was stirred at 60 °C for 1.5 h. The mixture was cooled to room temperature, poured into brine, and extracted with EtOAc. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 4% MeOH in CH_2Cl_2 to yield a mixture of **36** and **37**. Then the mixture was purified by reversed-phase chromatography eluting with CH_3CN−H_2O (3:2). The first elute was the *E*-isomer **36** isolated as a colorless oil (130 mg, 23%): ^{1}H NMR ($CDCl_3$) δ 3.56 (dd, J = 4.8, 6.0 Hz, 1H, C^{3}H), 4.23 (d, J = 12.6 Hz, 1H, 2-C*H*HOBz), 4.31 (d, J = 12.6 Hz, 1H, 2-CH*H*OBz) 4.41 (d, J = 15.0 Hz, 1H, C^1*H*H), 4.57 (d, J = 15.0 Hz, 1H, C^{1}H*H*), 4.63 (dd, J = 12.6, 6.0 Hz, 1H, C^4*H*H), 4.88 (bs, 2H, NH_2), 5.02 (dd, J = 12.6, 4.8 Hz, 1H, C^{4}H*H*), 5.49 (s, 2H, CH_2Ph), 7.28−7.62 (m, 11H, Ar), 7.74 (s, 1H, C^{8}H), 7.91−7.79 (m, 4H, Ar). The second elute was the *Z*-isomer **37**: colorless oil (135 mg, 24%); ^{1}H NMR ($CDCl_3$) δ 3.49 (dd, J = 4.5, 6.6 Hz, 1H, C^{3}H), 4.43 (s, 2H, 2-CH_2OBz), 4.46 (dd, J = 6.6, 12.3 Hz, 1H, C^4*H*H), 4.48 (s, 2H, C$^1H_2$), 4.71 (dd, J = 4.5, 12.3 Hz, 1H, C^{4}H*H*), 4.74 (bs, 2H, NH_2), 5.50 (s, 2H, CH_2Ph), 7.30−7.60 (m, 12H, Ar), 7.67 (s, 1H, C^{8}H), 7.96−8.02 (m, 3H, Ar).

(*E*)-9-[2,3-Epoxy-4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (38). A suspension of **36** (130 mg, 0.23 mmol) in MeOH (10 mL) was hydrogenated in the presense of 10% Pd/C (100 mg) at room temperature under atomospheric pressure for 10 h. After filtration, the filtrate was treated with 28% MeONa/MeOH (96.5 mg, 0.50 mmol). After 0.5 h, the solution was neutralized with 2 N HCl and washed with EtOAc. The aqueous layer was concentrated, and the residue was purified by reversed-phase chromatography eluting with 10% MeOH/H_2O to yield **38** as a white solid (10 mg, 16%): mp 265−268 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.12 (dd, J = 5.1, 6.3 Hz, 1H), 3.15−3.35 (m, 2H), 3.63 (ddd, J = 5.7, 6.3, 12.9 Hz, 1H), 3.79 (ddd, J = 5.1, 5.4, 12.9 Hz, 1H), 4.18 (d, J = 14.7 Hz, 1H), 4.22 (d, J = 14.7 Hz, 1H), 5.01 (m, 1H), 5.09 (m, 1H, 6.42 (bs,

2H), 7.62 (s, 1H), 10.66 (bs, 1H); HRMS calcd for $C_{10}H_{14}O_4N_5$ (MH^+) 268.1046, found 268.1042. Anal. ($C_{10}H_{13}O_4N_5$) C, H, N.

(*Z*)-9-[2,3-Epoxy-4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (39). Treatment of **37** (135 mg, 0.24 mmol) as above afforded **39** as a white solid (14 mg, 22%): mp 272−275 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.63 (dd, J = 3.6, 6.9 Hz, 1H), 3.1−3.4 (m, 2H), 3.50 (m, 1H), 3.64 (ddd, J = 3.6, 5.7, 12.6 Hz, 1H), 4.17 (d, J = 15.0 Hz, 1H), 4.37 (d, J = 15.0 Hz, 1H), 4.90 (bs, 1H), 5.15 (bs, 1H), 6.52 (bs, 2H), 7.53 (s, 1H), 10.6 (bs, 1H); HRMS calcd for $C_{10}H_{14}O_4N_5$ (MH^+) 268.1046, found 268.1034. Anal. ($C_{10}H_{13}O_4N_5$) C, H, N.

9-[[*trans*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]-methyl]adenine (40a). Adenine (386 mg, 2.85 mmol) was treated with 114 mg of NaH (60%, 2.85 mmol) in anhydrous DMF (12 mL) at room temperature for 20 min, and **20b** (1.18 g, 2.38 mmol) in DMF (6 mL) was added. The mixture was stirred at 60 °C for 3 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 4% MeOH in CH_2Cl_2 to yield 9-[[*trans*-1′,2′-bis-[(benzoyloxy)methyl]cycloprop-1′-yl]methyl]adenine as a white gum (844 mg, 77%). The protected adenine derivative (844 mg, 1.84 mmol) in MeOH (2 mL) was treated with MeONa/MeOH (5.53 mmol, 7 mL) at 40 °C for 30 min. The solution was neutralized with 1 N HCl (5.5 mL, 5.5 mmol) and concentrated in vacuo. The residue was dissolved in H_2O and washed with EtOAc. The aqueous layer was concentrated in vacuo, and the residue was purified by reversed-phase chromatography eluting with 0−30% MeOH/H_2O to yield **40a** as a white solid (424 mg, 92%). Recrystallization from MeOH gave white crystals (389 mg, 85%): mp 211−213 °C; ^{1}H NMR (DMSO-d_6) δ 0.53−0.60 (m, 2H), 1.14 (dt, J = 6.0, 8.4 Hz, 1H), 3.05 (dd, J = 5.7, 11.4 Hz, 1H), 3.12 (dd, J = 5.7, 11.4 Hz, 1H), 3.51 (ddd, J = 5.1, 8.4, 12.0 Hz, 1H), 3.77 (ddd, J = 5.1, 6.0, 11.4 Hz, 1H), 4.24 (d, J = 14.7 Hz, 1H), 4.32 (d, J = 14.7 Hz, 1H), 4.75 (t, J = 5.7 Hz, 1H), 4.85 (m, 1H), 7.19 (bs, 2H), 8.13 (s, 1H), 8.18 (s, 1H); HRMS calcd for $C_{11}H_{16}O_2N_5$ (MH^+) 250.1304, found 250.1295. Anal. ($C_{11}H_{15}O_2N_5$) C, H, N.

9-[[*cis*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]methyl]-adenine (40b). Compound **21b** (1.50 g, 3.03 mmol) was treated as above to afford 9-[[*cis*-1′,2′-bis[(benzoyloxy)methyl]-cycloprop-1′-yl]methyl]adenine as a white foam (1.12 g, 80%). Deprotection gave **40b** as a white solid (489 mg, 80%). Recrystallization from MeOH gave white crystals (445 mg, 73%): mp 189−190.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.41 (t, J = 5.1 Hz, 1H), 0.93 (dd, J = 5.1, 8.7 Hz, 1H), 1.32 (m, 1H), 3.23−3.44 (m, 3H), 3.58 (m, 1H), 4.02 (d, J = 14.2 Hz, 1H), 4.19 (d, J = 14.2 Hz, 1H), 4.56 (t, J = 5.2 Hz, 1H), 4.74 (t, J = 5.2 Hz, 1H), 7.20 (bs, 2H), 8.13 (s, 1H), 8.16 (s, 1H); HRMS calcd for $C_{11}H_{16}O_2N_5$ (MH^+) 250.1304, found 250.1310. Anal. ($C_{11}H_{15}O_2N_5$ 0.2H_2O) C, H, N.

(*E*)-9-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]-adenine (40c) and (*Z*)-9-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]adenine (40d). Coupling of **29b** (834 mg, 2.14 mmol) with adenine in a similar manner as described in the preparation of **40a** afforded (*E*)-9-[4-(benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]adenine and (*Z*)-9-[4-benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]adenine which were separated by chromatography on silica gel eluting with 4% MeOH in CH_2Cl_2. The *E*-isomer, colorless oil (290 mg, 31%), was eluted first: ^{1}H NMR ($CDCl_3$) δ 5.00 (s, 4H, 2-CH_2OBz, C^1H_2), 5.06 (d, J = 6.6 Hz, 2H, C^4H_2), 5.70 (bs, 2H, NH_2), 5.94 (t, J = 6.6 Hz, 1H, C^3H), 7.38−7.44 (m, 4H, Ar), 7.53−7.58 (m, 2H, Ar), 7.85 (s, 1H, C^2H or C^8H), 7.91−7.93 (m, 2H, Ar), 7.99−8.22 (m, 2H, Ar), 8.31 (s, 1H, C^8H or C^2H). The second elute was the *Z*-isomer: colorless oil (360 mg, 38%); ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 2H, 2-CH_2OBz), 5.12 (s, 2H, C^1H_2), 5.21(d, J = 6.9 Hz, 2H, C^4H_2), 5.6 (bs, 2H, NH_2), 6.2 (t, J = 6.9 Hz, 1H, C^3H), 7.38−7.48 (m, 4H, Ar), 7.52−7.61 (m, 2H, Ar), 7.87−7.91 (m, 2H, Ar), 7.96 (s, 1H, C^2H or C^8H), 8.04−8.08 (m, 2H, Ar), 8.29 (s, 1H, C^8H or C^2H). Both products were separately deprotected as above. Purification by reversed-phase chromatography eluting with 0−15% MeOH/H_2O afforded **40c** as a white solid (75%): mp 181−182.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.79 (d, J = 4.8 Hz, 2H), 4.22 (t, J = 6.1 Hz, 2H), 4.80 (s, 2H), 4.89 (bs, 1H), 4.94 (bs, 1H), 5.79 (t, J = 6.1 Hz, 1H), 7.18 (bs, 2H), 8.03 (s, 1H), 8.13 (s, 1H); HRMS calcd for $C_{10}H_{14}O_2N_5$ (MH^+) 236.1147, found 236.1158. Anal. ($C_{10}H_{13}O_2N_5$) C, H, N. **40d**: white solid (82%); mp 202−204 °C; ^{1}H NMR (DMSO-d_6) δ 3.80 (d, J = 4.8 Hz, 2H), 4.23 (t, J = 6.0 Hz, 2H), 4.81 (s, 2H), 4.89−4.97 (bs, 2H), 5.80 (t, J = 6.0 Hz, 1H), 7.19 (bs, 2H), 8.05 (s, 1H), 8.14 (s, 1H); HRMS calcd for $C_{10}H_{14}O_2N_5$ (MH^+) 236.1147, found 236.1137. Anal. ($C_{10}H_{13}O_2N_5$) C, H, N.

1-[[*trans*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]-methyl]thymine (41a). To a mixture of thymine (215 mg, 1.70 mmol), K_2CO_3 (236 mg, 1.70 mmol), and 18-crown-6 (409 mg, 1.70 mmol) in DMF (6 mL) was added a solution of **20b** (700 mg, 1.42 mmol) in DMF (10 mL), and the resulting mixture was stirred at 60 °C for 2 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 2% MeOH in CH_2Cl_2 to yield 1-[[*trans*-1′,2′-bis-[(benzoyloxy)methyl]cycloprop-1′-yl]methy]thymine as a white foam (370 mg, 58%). Deprotection by the procedure described in the preparation of **40a** yielded **41a** as a white solid (113 mg, 57%): mp 169.5−171 °C; ^{1}H NMR (DMSO-d_6) δ 0.48 (m, 1H), 0.55 (dd, J = 4.5, 8.7 Hz, 1H), 1.06 (m, 1H), 1.76 (d, J = 0.9 Hz, 3H), 3.08 (dd, J = 5.1, 11.7 Hz, 1H), 3.24 (dd, J = 5.7, 11.7 Hz, 1H), 3.37 (m, 1H), 3.66 (m, 1H), 3.77 (d, J = 14.4 Hz, 1H), 3.86 (d, J = 14.4 Hz, 1H), 4.55−4.63 (m, 2H), 7.60 (m, 1H), 11.20 (bs, 1H); HRMS calcd for $C_{11}H_{17}O_4N_2$ (MH^+) 241.1188, found 241.1193. Anal. ($C_{11}H_{16}O_4N_2$) C, H, N.

1-[[*cis*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]methyl]-thymine (41b). Treatment of **21b** (321 mg, 0.649 mmol) as above gave 1-[[*cis*-1′,2′-bis[(benzoyloxy)methyl]cycloprop-1′-yl]-methyl]thymine as a white gum (188 mg, 65%). Deprotection gave **41b** as a white solid (83.6 mg, 83%): mp 164−166 °C; ^{1}H NMR (DMSO-d_6) δ 0.37 (m, 1H), 0.80 (dd, J = 4.5, 8.4 Hz, 1H), 1.19 (m, 1H), 1.76 (s, 3H), 3.26−3.40 (m, 2H), 3.46−3.63 (m, 2H), 3.61 (d, J = 14.1 Hz, 1H), 3.67 (d, J = 14.1 Hz, 1H), 4.55 (bs, 2H), 7.50 (s, 1H), 11.20 (bs, 1H); HRMS calcd for $C_{11}H_{17}O_4N_2$ (MH^+) 241.1188, found 241.1189. Anal. ($C_{11}H_{16}O_4N_2$) C, H, N.

(*E*)-1-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]-thymine (41c) and (*Z*)-1-[4-Hydroxy-2-(hydroxymethyl)-2-buten-1-yl]thymine (41d). To a mixture of thymine (190 mg, 1.5 mmol)and K_2CO_3 (320 mg, 2.32 mmol) in DMF (2 mL) was added a solution of **29** (584 mg, 1.5 mmol) in DMF (3 mL), and the resulting mixture was stirred at 70 °C for 15 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with CH_2Cl_2−MeOH (20:1) followed by preparative TLC with hexanes−EtOAc (1:2) to give (*E*)-1-[4-(benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]thymine as a colorless oil (45 mg): ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H, 5-CH_3), 4.66 (s, 2H, 2-CH_2OBz), 4.81 (s, 2H, C^1H_2), 5.08 (d, J = 6.9 Hz, 2H, C^4H_2), 6.18 (t, J = 6.6 Hz, 1H, C^3H), 7.17 (s, 1H, C^6H), 7.39−7.61 (m, 6H, Ar), 7.96−8.14 (m, 4H, Ar), 8.4 (bs, 1H, N^3H). The product having a lower R_f was (*Z*)-1-[4-(benzoyloxy)-2-[(benzoyloxy)methyl]-2-buten-1-yl]thymine: colorless oil (45 mg); ^{1}H NMR ($CDCl_3$) δ 1.81 (d, 3H, J = 0.9 Hz, 5-CH_3), 4.51 (s, 2H, 2-CH_2OBz), 4.99 (s, 2H, C^1H_2), 5.09 (d, J = 6.6 Hz, 2H, C^4H_2), 5.96 (t, J = 6.6 Hz, 1H, C^3H), 6.98 (q, J = 0.9 Hz, 1H, C^6H), 7.37−7.58 (m, 6H, Ar), 7.96−8.14 (m, 4H, Ar), 8.4 (bs, 1H, N^3H). Both products were deprotected separately as described in the preparation of **41a**. Compound **41c** was isolated as a white solid (15 mg, 75%): mp 132−134 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3H) 3.80 (s, 2H), 4.12 (d, J = 6.3 Hz, 2H), 4.31 (s, 2H), 4.70 (bs, 1H), 4.86 (bs, 1H), 5.77 (t, J = 6.3 Hz, 1H), 7.34 (s, 1H), 11.2 (bs, 1H); HRMS calcd for $C_{10}H_{15}O_4N_2$ (MH^+) 227.1032, found 227.1015. Anal. ($C_{10}H_{14}O_4N_2$) C, H, N. Compound **41d** (16 mg, 80%) was obtained as a white solid: mp 170.5−172 °C; ^{1}H NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.94 (s, 2H), 4.02 (d, J = 6.0 Hz, 2H), 4.28

(s, 2H), 4.66 (bs, 1H), 4.8 (bs, 1H), 5.28 (t, J = 6.0 Hz, 1H), 7.34 (s, 1H), 11.2 (bs, 1H); HRMS calcd for $C_{10}H_{15}O_4N_2$ (MH^+) 227.1032, found 227.1016. Anal. ($C_{10}H_{14}O_4N_2$) C, H, N.

1-[[*trans*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]-methyl]cytosine (42a). Compound **20b** (104 mg, 0.21 mmol) was coupled with cytosine (28 mg, 0.25 mmol) followed by deprotection in a similar manner as described in the preparation of **40a**. Chromatography on silica gel eluting with 5−10% MeOH in CH_2Cl_2 yielded 1-[[*trans*-1′,2′-bis[(benzoyloxy)methyl]-cycloprop-1′-yl]methyl]cytosine as a white gum (54.2 mg, 60%). Deprotection gave **42a** as a white solid (38.2 mg, 79%): mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 0.43 (t, J = 4.8 Hz, 1H), 0.49 (dd, J = 4.8, 8.7 Hz, 1H), 1.02 (m, 1H), 3.02 (dd, J = 6.0, 11.7 Hz, 1H), 3.10 (dd, J = 6.0, 11.7 Hz, 1H), 3.38 (m, 1H), 3.65 (m, 1H), 3.76 (d, J = 14.4 Hz, 1H), 3.89 (d, J = 14.4 Hz, 1H), 4.71 (t, J = 5.4 Hz, 1H), 4.77 (t, J = 6.0 Hz, 1H), 5.68 (d, J = 7.2 Hz, 1H), 7.04 (bs, 1H), 7.09 (bs, 1H), 7.65 (d, J = 7.2 Hz, 1H); HRMS calcd for $C_{10}H_{16}O_3N_3$ (MH^+) 226.1191, found 226.1204. Anal. ($C_{10}H_{15}O_3N_3$) C, H, N.

1-[[*cis*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]methyl]-cytosine (42b). Treatment of **21b** (500 mg, 1.01 mmol) as above gave 1-[[*cis*-1′,2′-bis[(benzoyloxy)methyl]cycloprop-1′-yl]-methyl]cytosine as a white gum (284 mg, 65%). Deprotection gave **42b** as a white solid (118 mg, 80%). Recrystallization from MeOH gave white crystals (107 mg, 73%): mp 207−208 °C; ^{1}H NMR (DMSO-d_6) δ 0.32 (t, J = 5.1 Hz, 1H), 0.82 (dd, J = 5.1, 9.0 Hz, 1H), 1.15 (m, 1H), 3.16−3.44 (m, 3H), 3.53 (m, 1H), 3.58 (d, J = 14.1 Hz, 1H), 3.74 (d, J = 14.1 Hz, 1H), 4.42 (bs, 1H), 4.71 (t, J = 5.7 Hz, 1H), 5.66 (d, J = 7.2 Hz, 1H), 7.02 (bs, 2H), 7.57 (d, J = 7.2 Hz, 1H); HRMS calcd for $C_{10}H_{16}O_3N_3$ (MH^+) 226.1191, found 226.1194. Anal. ($C_{10}H_{15}O_3N_3$) C, H, N.

9-[[*trans*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]-methyl]hypoxanthine (43a). To a solution of **40a** (97.0 mg, 0.389 mmol) in AcOH (11.7 mL) was added a solution of $NaNO_2$ (805 mg, 11.7 mmol) in H_2O (3.9 mL), and the mixture was stirred at 60 °C for 5 h. After cooling to room temperature, the pH was adjusted to 7 with 2 N NaOH and the solvent was removed in vacuo. The residue was purified by reversed-phase chromatography eluting with 0−15% MeOH in H_2O to yield **43a** as a white solid (86.0 mg, 88%): mp 238−240 °C; ^{1}H NMR (DMSO-d_6) δ 0.54−0.60 (m, 2H), 1.16 (m, 1H), 3.04 (dd, J = 5.1, 11.4 Hz, 1H), 3.18 (m, 1H), 3.48 (m, 1H), 3.75 (m, 1H), 4.20 (d, J = 14.7 Hz, 1H), 4.36 (d, J = 14.7 Hz, 1H), 4.61 (m, 1H), 4.67 (m, 1H), 8.03 (s, 1H), 8.15 (s, 1H), 12.23 (bs, 1H); HRMS calcd for $C_{11}H_{15}O_3N_4$ (MH^+) 251.1144, found 251.1149. Anal. ($C_{11}H_{14}O_3N_4 \cdot 0.2H_2O$) C, H, N.

9-[[*cis*-1′,2′-Bis(hydroxymethyl)cycloprop-1′-yl]methyl]-hypoxanthine (43b). Deamination of **40b** as above afforded **43b** as a white solid (28.2 mg, 63%): mp 234.5−237 °C; ^{1}H NMR (DMSO-d_6) δ 0.43 (t, J = 5.4 Hz, 1H), 0.90 (dd, J = 4.8, 8.7 Hz, 1H), 1.32 (m, 1H), 3.25−3.37 (m, 2H), 3.41 (dd, J = 6.0, 12.0 Hz, 1H), 3.60 (dt, J = 12.0, 6.0 Hz, 1H), 4.05 (d, J = 14.1 Hz, 1H), 4.17 (d, J = 14.1 Hz, 1H), 4.54 (m, 1H, OH), 4.61 (m, 1H), 8.02 (s, 1H), 8.11 (s, 1H), 12.23 (bs, 1H); HRMS calcd for $C_{11}H_{15}O_3N_4$ (MH^+) 251.1144, found 251.1157. Anal. ($C_{11}H_{14}O_3N_4$) C, H, N.

2-Amino-9-[[*cis*-1′,2′-bis[(benzoyloxy)methyl]cycloprop-1′-yl]methyl]-6-chloropurine (44). A solution of **21b** (400 mg, 0.809 mmol) in DMF (8 mL) was added to a mixture of 2-amino-6-chloropurine (165 mg, 0.973 mmol), K_2CO_3 (134 mg, 0.970 mmol) and 18-crown-6 (233 mg, 0.970 mmol), in DMF (8 mL) and stirred at 60 °C for 1.5 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 2−7% MeOH in CH_2Cl_2 to give **44** as a white solid (323 mg, 81%): ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.0 Hz, 1H), 1.26 (dd, J = 6.0, 9.0 Hz, 1H), 2.04 (tt, J = 6.0, 9.0 Hz, 1H), 4.02 (d, J = 14.4 Hz, 1H), 4.11 (dd, J = 9.0, 12.3 Hz, 1H), 4.27 (d, J = 12.9 Hz, 1H), 4.32 (d, J = 14.4 Hz, 1H), 4.55 (d, J = 12.9 Hz, 1H), 4.74 (dd, J = 6.0, 12.3 Hz, 1H), 4.91 (bs, 2H), 7.31−7.37 (m, 4H), 7.49−7.56 (m, 2H), 7.76−7.84 (m, 4H), 7.90 (s, 1H); FD MS m/z 491 (M^+). The 7-isomer was eluted afterward: white crystalline solid (45.2 mg, 11%).

2,6-Diamino-9-[[*cis*-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]purine (45). Compound **44** (550 mg, 1.12 mmol) was dissolved in saturated NH_3/MeOH (56 mL), and the mixture was stirred at 90 °C for 7 days. The solvent was removed in vacuo and the residue was taken up in H_2O (5 mL) and washed with EtOAc. The aqueous layer was concentrated in vacuo, and the residue was purified by reversed-phase chromatography eluting with 0−20% MeOH/H_2O to yield **45** as a white solid (150 mg, 51%): mp 186−188.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.38 (t, J = 5.1 Hz, 1H), 0.90 (dd, J = 4.8, 8.7 Hz, 1H), 1.24 (m, 1H), 3.16−3.44 (m, 3H), 3.56 (m, 1H), 3.81 (d, J = 14.4 Hz, 1H), 4.02 (d, J = 14.4 Hz, 1H), 4.47 (m, 1H), 4.87 (m, 1H), 5.76 (bs, 2H), 6.65 (bs, 2H), 7.73 (s, 1H); HRMS calcd for $C_{11}H_{17}O_2N_6$ (MH^+) 265.1427, found 265.1423. Anal. ($C_{11}H_{16}O_2N_6$) C, H, N.

2-Amino-9-[[*cis*-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]purine (46). A mixture of **44** (1.41 g, 2.87 mmol), ammonium formate (724 mg, 11.5 mmol), and 10% Pd/C (86 mg) in MeOH (29 mL) was refluxed at 75 °C for 3 h. After filtration the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 4−10% MeOH in CH_2Cl_2 to yield 2-amino-9-[[*cis*-1′,2′-bis[(benzyloxy)methyl]-cycloprop-1′-yl]methyl]purine as a white gum (1.10 g, 84%). The benzoyl group was removed by treating the dibenzoate (242 mg, 0.529 mmol) in MeONa/MeOH (1.59 mmol, 2 mL) at 40 °C for 30 min. The solution was neutralized with 2 N HCl (0.79 mL, 1.58 mmol) and concentrated in vacuo. The residue was dissolved in H_2O and washed with EtOAc. The aqueous layer was concentrated in vacuo, and the residue was purified by reversed-phase chromatography eluting with 0−20% MeOH/H_2O to yield **46** as a white solid (116 mg, 88%): mp 159−162 °C; ^{1}H NMR (DMSO-d_6) δ 0.43 (t, J = 5.1 Hz, 1H), 0.93 (dd, J = 5.1, 9.0 Hz, 1H), 1.29 (m, 1H), 3.16 (s, 0.6H, CH_3OH), 3.26−3.38 (m, 2H), 3.42 (dd, J = 5.4, 12.0 Hz, 1H), 3.60 (m, 1H), 3.96 (d, J = 14.4 Hz, 1H), 4.01 (s, 0.2H, CH$_3$OH), 4.79 (d, J = 14.4 Hz, 1H), 4.54 (t, J = 5.4 Hz, 1H), 4.64 (t, J = 5.4 Hz, 1H), 6.44 (bs, 2H), 8.10 (s, 1H), 8.55 (s, 1H); HRMS calcd for $C_{11}H_{16}O_2N_5$ (MH^+) 250.1304, found 250.1316. Anal. ($C_{11}H_{15}O_2N_5 \cdot 0.2$MeOH) C, H, N.

Ethyl (3a*S*,4a*R*)-3,3a,4,4a-Tetrahydro-3-oxo-1*H*-cyclopropa[*c*]furan-3a-carboxylate (47). Sodium (2.42 g, 105 mmol) was dissolved in EtOH (195 mL), and diethyl malonate (16.7 mL, 110 mmol) was added at 0 °C over 5 min to the solution. (*R*)-(−)-Epichlorohydrin (7.8 mL, 100 mmol) in EtOH (5 mL) was added dropwise to the solution at room temperature over 1 h, and the mixture was stirred at 75 °C for 20 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 15−50% EtOAc in hexane to yield **47** as a colorless oil (12.0 g, 70%): ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 1.37 (dd, J = 4.8, 5.4 Hz, 1H), 2.08 (dd, J = 4.8, 8.0 Hz, 1H), 2.72 (m, 1H), 4.18 (d, J = 9.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.36 (dd, J = 4.5, 9.6 Hz, 1H); FAB MS m/z 170 (M^+); $[\alpha]^{25}_D$ = −146.58 (c = 1.22, EtOH). The optical purity of **47** was analyzed by chiral HPLC using Chiralpak AD (Daicel, Tokyo) by an isocratic elution using hexanes−EtOAc−Et_2NH (75:25:0.2) at a detection wavelength of 235 nm. The optical purity of **47** obtained by this procedure was >97% ee. The other enantiomer derived from (*S*)-(+)-epichlorohydrin showed $[\alpha]^{25}_D$ = +145.48 (c = 1.22, EtOH).

Ethyl (1*R*,2*R*)-1,2-Bis(hydroxymethyl)-1-cyclopropanecarboxylate (48). $NaBH_4$ (2.0 g, 53 mmol) was added portionwise to a solution of **47** (12 g, 70 mmol) in EtOH (200 mL), and the mixture was stirred at room temperature for 2 h. HCl (2 N, 27 mL, 54 mmol) and EtOAc (100 mL) were added at 0 °C, and the mixture was filtered. After concentration in vacuo the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was concentrated in vacuo, and

the residue was chromatographed on silica gel eluting with 4% MeOH in CH_2Cl_2 to yield **48** as a colorless oil (8.35 g, 69%): ^{1}H NMR ($CDCl_3$) δ 0.76 (dd, J = 4.8, 6.6 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.49 (dd, J = 4.8, 9.0 Hz, 1H), 2.05 (m, 1H), 3.06 (bs, 1H), 3.23 (d, J = 12.8 Hz, 1H), 3.24 (bs, 1H), 3.33 (dd, J = 11.1, 12.5 Hz, 1H), 4.08 (dd, J = 5.1, 12.5 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.52 (d, J = 12.8 Hz, 1H); FD MS m/z 175 (MH^+).

Ethyl (1*R*,7*R*)-4,4-Dimethyl-3,5-dioxabicyclo[5.1.0]-octane-1-carboxylate (49). To a solution of **48** (8.35 g, 47.9 mmol) in DMF (100 mL) were added *p*-TsOH monohydrate (57 mg, 0.3 mmol) and dimethoxypropane (12 mL, 100 mmol), and the mixture was stirred at room temperature for 12 h. A mixture of 150 mL each of hexane and EtOAc was added, and the mixture was washed with H_2O. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with EtOAc−hexane (1:5) to yield **49** as a colorless oil (4.99 g, 49%): ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.2−1.3 (m, 4H), 1.37 (s, 3H), 1.41 (dd, J = 3.8, 9.5 Hz, 1H), 1.80 (m, 1H), 3.75 (d, J = 13.5 Hz, 1H), 3.76 (dd, J = 4.2, 13.2 Hz, 1H), 4.05−4.21 (m, 3H), 4.62 (d, J = 13.5 Hz, 1H); FD MS m/z 214 (M^+).

(1*S*,7*R*)-4,4-Dimethyl-3,5-dioxabicyclo[5.1.0]octane-1-methanol (50a). To a solution of **49** (7.92 g, 37.0 mmol) in anhydrous THF (18.5 mL) was added 2 M $LiBH_4$ in anhydrous THF (18.5 mL, 37.0 mmol) over 5 min, and the mixture was refluxed at 72 °C for 12 h. Saturated NH_4Cl was added at 0 °C, and the resulting clear solution was extracted with EtOAc. The organic layer was concentrated in vacuo, and the resulting colorless oil **50a** was used in the next step without further purification (4.07 g, 64%): ^{1}H NMR ($CDCl_3$) δ 0.67 (dd, J = 4.4, 8.9 Hz, 1H), 0.90 (dd, J = 4.4, 5.8 Hz, 1H), 1.06 (m, 1H), 1.28 (s, 3H), 1.38 (s, 3H), 1.5−1.7 (bs, 1H), 3.45 (bs, 2H), 3.69 (dd, J = 4.2, 13.2 Hz, 1H), 3.78 (d, J = 12.9 Hz, 1H), 4.12 (dd, J = 5.7, 13.2 Hz, 1H), 4.17 (d, J = 12.9 Hz,1H); FD MS m/z 173 (MH^+).

(1*S*,2*R*)-1-[(Benzyloxy)methyl]-1,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane (50b). Crude **50a** (4.07 g, 23.6 mmol) was added to a suspension of 1.2 g of NaH (60%, 30 mmol) in anhydrous DMF (80 mL). After stirring for 5 min, benzyl bromide (3.97 mL, 30 mmol) was added and the mixture was stirred at room temperature for 14 h. After cooling to 0 °C, the pH was adjusted to 7 with saturated NH_4Cl (about 5 mL), and the solution was diluted with hexanes−EtOAc (1:1) and washed with H_2O. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 15% EtOAc in hexane to yield **50b** as a colorless oil (5.56 g, 90%): ^{1}H NMR ($CDCl_3$) δ 0.67 (dd, J = 4.2, 8.4 Hz, 1H), 0.92 (m, 1H), 1.00 (m, 1H), 1.28 (s, 3H), 1.37 (s, 3H), 3.13 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H), 3.70 (dd, J = 3.9, 13.2 Hz, 1H), 3.78 (d, J = 13.1 Hz, 1H), 4.12 (dd, J = 5.1, 13.2 Hz, 1H), 4.15 (d, J = 13.1 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 7.32 (m, 5H); FD MS m/z 262 (M^+).

(1*R*,2*R*)-1-[(Benzyloxy)methyl]-2-(hydroxymethyl)-1-cyclopropanemethanol (51a). A solution of **50b** (5.56 g, 21.1 mmol) in THF (50 mL) was treated with 1 N HCl (50 mL) at 0 °C for 30 min and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was concentrated in vacuo, and the resulting colorless oil **51a** was used in the next step without further purification (4.08 g, 86%): ^{1}H NMR ($CDCl_3$) δ 0.41 (t, J = 5.4 Hz, 1H), 0.66 (dd, J = 5.4, 8.7 Hz, 1H), 1.32 (m, 1H), 2.0−2.2 (bs, 2H), 3.25−3.40 (m, 3H), 3.60 (d, J = 9.3 Hz, 1H), 4.06 (dd, J = 5.4, 12.6 Hz, 1H), 4.22 (d, J = 12.3 Hz, 1H), 4.56 (s, 2H), 7.34 (m, 5H); FD MS m/z 223 (MH^+).

(1*S*,2*R*)-[2-[(Benzoyloxy)methyl]-1-[(benzyloxy)methyl]cycloprop-1-yl]methyl Benzoate (51b). A solution of **51a** (4.08 g, 18.2 mmol) in $CHCl_3$ (64 mL) containing pyridine (11.8 mL, 146 mmol) was treated with BzCl (8.45 mL,72.8 mmol) at 0 °C for 12 h. Saturated NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 15% EtOAc in hexane to yield **51b** as a colorless oil (5.35 g, 68%): ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 5.5 Hz, 1H), 0.98 (dd, J = 5.4, 9.0 Hz, 1H), 1.51 (m, 1H), 3.39 (d, J = 10.1 Hz, 1H), 3.62 (d, J = 10.1 Hz, 1H), 4.22 (dd, J = 9.0, 12.0 Hz, 1H), 4.35 (d, J = 11.9 Hz, 1H), 4.55 (s, 2H), 4.66 (dd, J = 6.6, 12.0 Hz, 1H), 4.76 (d, J = 11.9 Hz, 1H), 7.2−7.35 (m, 9H), 7.5 (m, 2H), 7.94 (m, 4H); FD MS m/z 430 (M^+).

(1*S*,2*R*)-[2-[(Benzoyloxy)methyl]-1-(hydroxymethyl)-cycloprop-1-yl]methyl Benzoate (52) = (1*S*,2*R*)-21a. A solution of **51b** (5.35 g, 12.4 mmol) in EtOH (50 mL) containing AcOH (15 mL) was hydrogenated at room temperature under atmospheric pressure for 3 days in the presence of 10% Pd/C (500 mg). After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in water, neutralized with 2 N NaOH, and then extracted with CH_2Cl_2. The organic layer was concentrated in vacuo, and the residue was chromatographed on silica gel eluting with 2% MeOH in CH_2Cl_2 to yield **52** as a colorless oil (4.20 g, 99%). ^{1}H NMR was identical to that of **21a**.

(1′*S*,2′*R*)-9-[[1′,2′-Bis(hydroxymethyl)cyclopropan-1′-yl]methyl]guanine (3a) and (1′*R*,2′*S*)-9-[[1′,2′-Bis-(hydroxymethyl)cyclopropan-1′-yl]methyl]guanine (3b). Compounds **3a**,**b** were synthesized as described in the preparation of racemate **3** by using **52** or its enatiomer instead of **21a.** ^{1}H MNR spectra of **3a**,**b** were identical to that of **3**. **3a**: mp 297−298.5 °C; $[\alpha]^{20}_D$ = −11.18 (c = 1%, DMSO). Anal. ($C_{11}H_{15}O_3N_5$) C, H, N. **3b**: mp 296−298 °C; $[\alpha]^{20}_D$ = +11.08 (c = 1%, DMSO). Anal. ($C_{11}H_{15}O_3N_5 \cdot 0.2H_2O$) C, H, N.

Quantitative CPE Reduction Assay (HSV-1). The activities of test compounds were determined by neutral red dye uptake method[16] with modification. Dilutions (3-fold) of the test compounds were prepared in 100-μL volumes of Eagle minimum essential medium (EMEM) supplemented with 2% FBS in the wells of 96-well culture plates; 60 μL of Vero cells (3×10^5 cells/mL, EMEM 10% FBS) were then dispensed into each well. HSV-1 Tomioka strain was diluted in medium (EMEM 2% FBS) to approximately 100 $TCID_{50}$/40 μL, as determined by prior titration in a similar dye uptake assay, and 40-μL volumes of viral suspension were added to the respective wells. Control wells containing no test compound and no virus (cell control) or no cells (blank control) were included in each plate. After the plates were incubated for 3 days at 37 °C in an atmosphere of 5% CO_2, 50 μL of neutral red dye (0.15% in saline, pH 5.5) was dispensed into each well, and the cultures were incubated for a further 45 min at 37 °C (pH 4.2, equal volumes of 0.1 M Sorensen citrate buffer and ethanol). The medium was removed, and the well was rinsed with 150 μL of PBS; 100 μL of citrate−ethanol buffer (pH 4.2, equal volumes of 0.1 M Sorensen citrate buffer and ethanol) was added, and absorbance at 550 nm was measured. The mean OD of the cell control wells was assigned a value of 100% and that of the control blank wells a value of 0%, and the concentration of the test compounds producing a 50% OD reading was determined as IC_{50}. For determining cytotoxic activity of the test compounds, the same method without viral infection was performed to give CC_{50}. All experiments were performed in quadruplicate.

Plaque Reduction Assays (VZV). Anti-VZV assay was performed as described.[33] Briefly, subconfluent monolayers of human foreskin fibroblasts (HFF) cells in 12-well plates were rinsed with MEM and exposed to 0.5 mL/well of a suspension of VZV DM625 strain (a clinical isolate from Dr. Rich Whitley's laboratory at University of Alabama, Birmingham) and diluted in MEM + 2% FBS for 2 h at 37 °C to allow virus adsorption. The fluids were removed, and the cell layers were rinsed with MEM + 2% FBS. The test compounds in 1 mL of overlay medium (MEM, 2% FBS in 0.25% agarose) were added, and the plates were incubated at 37 °C in a humidified atmosphere of 5% CO_2. After 5 days the plaques were counted and the effect of each drug concentration on plaque formation was determined by comparing the mean number of plaques in the drug-treated cultures with the mean plaque counts of the untreated virus control cultures. The concentration of the test compounds which conferred 50% inhibition of plaque formation compared to virus control (untreated control) was

interpolated from the dose−response curve and was defined as IC_{50}. The drug cytotoxicity control cultures were examined microscopically for gross morphologic changes and then treated with MTT and 30% SDS for quantitative measurement. Since all the compounds tested were not toxic to give CC_{25} at the highest concentration (320 μg/mL), minimum concentrations to give morphologic changes were determined microscopically. All experiments were performed in triplicate.

Anti-HIV Assay. Anti-HIV assay was performed as described.[34] Briefly, CEM cells were pregrown as monolayers in wells of 96-well tissue culture plates containing RPMI 1640 medium supplemented with 10% FCS. Stock viruses (HIV-1 RF strain, from the National Institutes of Health AIDS Research and Reference Reagent Respository) were pretitered and diluted in cell culture medium to yield 32−100 $CCID_{50}$ units/0.1 mL. To each of the cell cultures were added 0.1 mL of the test compound solution and 0.1 mL of virus suspension. The plates were incubated at 37 °C in a humidified atmosphere of 5% CO_2 for 7 days, and CPE inhibition (IC_{50}) and cytotoxicity (CC_{25}) were determined by a dye uptake (MTT) procedure. All experiments were performed in triplicate.

Phosphorylation by HSV-1 TK. Crude HSV-1 TK fraction was prepared from the HSV-1 (KOS)-infected BU25 cells by ammonium sulfate precipitation as described.[17] Briefly, monolayer of BU25 (TK^-) cells was infected with HSV-1 (KOS) at a multiplicity of infection of 10 pfu/cell and then was incubated at 37 °C for 18 h. Cells were harvested with 50 mM Tris-HCl buffer (pH 8.0) containing 0.9% NaCl and were washed four times with the same buffer. After centrifugation the cell pellet was resuspended with 0.1 M Tris-HCl (pH 8.0) containing 20 mM 2-mercaptoethanol and disrupted by sonication at 4 °C. The sonicated suspension was centrifuged at 600*g* for 60 min. Ammonium sulfate was added to the supernatant to give 30% saturation. The mixture was allowed to stand for 30 min on ice, and then the precipitate was removed by centrifugation at 900*g* for 30 min. Additional ammonium sulfate was added to the supernatant to give 50% saturation, and then the mixture was allowed to stand for 30 min on ice. The precipitate was collected by centrifugation at 900*g* for 30 min. The pellet was resuspended in 50 mM Tris-HCl (pH 8.0) containing 20 mM 2-mercaptoethanol and dialyzed overnight with the same buffer containing 10% glycerol. The extract was stored at −80 °C until use.

TK reaction was performed at 37 °C for 24 h using the above crude HSV-1 TK extract. Test compounds (final concentration of 400 μM) were incubated in an assay buffer containing 50 mM Tris-HCl (pH 8.0), 5 mM ATP, 5 mM $MgCl_2$, 9 mM KF, 5 mM phosphoenol pyruvate, 10 mM 2-mercaptoethanol, and 15 μg of protein/mL crude HSV-1 TK extract. Monophosphates were analyzed by HPLC as described previously[18] except that a Partisil 10 SAX was used with 0−1 M KH_2PO_4 (pH 3.5) linear gradient at a flow rate of 1.5 mL/min for analysis. Amounts of monophosphate were determined by absorbance at 254 nm.

23 was separated by SUMICHIRAL OA-6100 using 2 mM $CuSO_4$ and acetonitrile (90:10) into each enantiomer and used as a substrate in this experiment. Fast eluting enantiomer was designated **23a**, and latter was designated **23b**.

Acknowledgment. The authors thank Noriko Takesada, Toshimi Mizukoshi, Uno Tagami, Reiko Yuji, and Dr. Tomoko Akashi for measurement of NMR and mass spectra. We are also grateful to Dr. Kohki Ishikawa for X-ray crystallographic analysis and to Katsutoshi Sakata for efficient technical assistance.

References

(1) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. Selectivity of Action of an Antiherpetic Agent, 9-(2-Hydroxyethoxymethyl)guanine. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716−5720.

(2) (a) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Julien, P. H.; Verheyden, J. P. H. 9-[(1,3-Dihydroxy-2-propyloxy)methyl]guanine: A New Potent and Selective Antiherpes Agent. *J. Med. Chem.* **1983**, *26*, 759−761. (b) Smee, D. F.; Martin, J. C.; Verheyden, J. P. H.; Matthews, T. R. Antiherpesvirus Activity of the Acyclic Nucleosides 9-(1,3-Dihydroxy-2-propoxymethyl)guanine. *Antimicrob. Agents Chemother.* **1983**, *23*, 676−682. (c) Field, E. K.; Davies, M. E.; DeWitt, C.; Perry, H. C.; Liou, R.; Germershausen, J.; Karkas, J. D.; Ashton, W. T.; Johnston, D. B.; Tolman, R. L. 9-([2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl)guanine: A Selective Inhibitor of Herpes Group Virus Replication. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 4139−4143.

(3) (a) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. Synthesis and Antiviral Activity of 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]purines. *J. Med. Chem.* **1987**, *30*, 1636−1643. (b) Vere Hodge, R. A.; Perkins, R. M. Mode of Action of 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanine (BRL 39123) against Herpes Simplex Virus in MRC-5 Cells. *Antimicrob. Agents Chemother.* **1989**, *33*, 223−229.

(4) Brown, D. G.; Visse, R.; Sandhu, G.; Davies, A.; Rizkallah, P. J.; Melitz, C.; Summers, W. C.; Sanderson, M. R. Crystal Structures of the Thymidine Kinase from Herpes Simplex Virus Type-I in Complex with Deoxythymidine and Ganciclovir. *Nature Struct. Biol.* **1995**, *2*, 876−881.

(5) (a) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. Oxetanocin, A Novel Nucleoside from Bacteria. *J. Antibiot.* **1986**, *39*, 1623−1625. (b) Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. X-ray Structure Determination of Oxcetanocin. *J. Antibiot.* **1986**, *39*, 1626−1629. (c) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. Inhibition of Infectivity of Human Immunodeficiency Virus by Oxetanocin. *J. Antibiot.* **1987**, *40*, 1077−1078. (d) Nishiyama, Y.; Yamamoto, N.; Takahashi, K.; Shimada, N. Selective Inhibition of Human Cytomegalovirus Replication by a Novel Nucleoside, Oxetanocin G. *Antimicrob. Agents Chemother.* **1988**, *32*, 1053−1056. (e) Sakuma, T.; Saijo, M.; Suzutani, T.; Yoshida, I.; Saito, S.; Kitagawa, M.; Hasegawa, S.; Azuma, M. Antiviral Activity of Oxetanocins against Varicella-Zoster Virus. *Antimicrob. Agents Chemother.* **1991**, *35*, 1512−1514.

(6) (a) Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. Synthesis of SQ-33,054. *Tetrahedron Lett.* **1989**, *30*, 6453−6456. (b) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takahashi, K. Anti-Herpesvirus Activity of Carbocyclic Oxetanocin G In Vitro. *J. Antibiot.* **1989**, *42*, 1854−1859. (c) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erikson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. Cyclobut-A and Cyclobut-G: Broad-Spectrum Antiviral Agents with Potential Utility for the Therapy of AIDS. *J. Med. Chem.* **1990**, *33*, 1281−1285. (d) Bisacchi, G. S.; Braitman, A.; Cianti, C. W.; Clark, J. M.; Field, A. K.; Hagan, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. Synthesis and Antiviral Activity of Enantiomeric Forms of Cyclobutyl Nucleoside Analogues. *J. Med. Chem.* **1991**, *34*, 1415−1421.

(7) Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wager, A. F.; Walton, E.; Tolman, R. L. Synthesis and Antiherpetic Activity of (±)-9-[(*Z*)-2-(Hydroxymethyl)cyclopropyl]methyl]-guanine and Related Compounds. *J. Med. Chem.* **1988**, *31*, 2304−2315.

(8) The site of alkylation was verified by the same method in ref 7 by comparing the ultraviolet spectra to those of model compounds. For purine analogues NMR spectra were also used for assignments; see: Kjellberg, J.; Johansson, N. G. Characterization of N7 and N9 Alkylated Purine Analogues by ^1H and ^{13}C NMR. *Tetrahedron* **1986**, *42*, 6541−6544.

(9) The vicinal coupling constants between C1 and C2 protons of the cyclopropane ring are 8.06 Hz for **8** (all-cis) and 4.64 Hz for **9**, respectively.

(10) NOE was observed between the methylene protons of 1-hydroxymethyl and the methylene protons of 2-(benzoyloxy)methyl.

(11) Sodeoka, M.; Yamada, H.; Shibasaki, M. A New Method for the Stereocontrolled Synthesis of Silyldienol Ether Using (Naphthalene) Chromium Tricarbonyl Catalyzed Isomerization. *J. Am. Chem. Soc.* **1990**, *112*, 4906−4911.

(12) NOE was observed between the olefinic proton and the methylene protons adjacent to the purine ring in *Z*-olefin **31** and the protected forms of **40d** and **41d**.

(13) The stereochemistry of **36** was confirmed by identity with the compound synthesized from (*E*)-**29a** in a separate run.

(14) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. Synthesis and Study of Racemic, (1*R*,2*S*)-, and (1*S*,2*R*)-1-Amino-2-(hydroxymethyl)-cyclopropane Carboxylic Acid. *Helv. Chim. Acta* **1989**, *72*, 1301−1310.

(15) Since it is reported in ref 14 that condensation of diethyl malonate and epichlorohydrin proceeds by sequential alkylations with inversion of stereochemistry, the absolute configuration of the cyclopropane lactone prepared from (*R*)-(−)-epichlorohydrin should be that of **47**. To confirm the stereochemistry, 4-bro-

mophenacyl ester of **47** was prepared and the absolute structure was determined by X-ray crystallography. Since there is no chance of racemization in the preparation of **3a** from **47**, the absolute conformation of **3a** prepared from (*R*)-(−)-epichlorohydrin is 1′*S*,2′*R*.

(16) McLaren, C.; Corey, L.; Dekket, C.; Barry, D. W. In Vitro Sensitivity to Acyclovir in Genital Herpes Simplex Viruses from Acyclovir-Treated Patients. *J. Infect. Diseases* **1983**, *14*, 868−875.

(17) Cheng, Y.-C.; Ostrander, M. Deoxythymidine Kinase Induced in Hela TK$^-$ Cells by Herpes Simplex Virus Type I and Type II. *J. Biol. Chem*. **1976**, *251*, 2605−2610.

(18) Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davis, E.-M. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. Synthesis and Antiherpetic Activity of (*S*)-, (*R*)-, and (±)-9-[(2,3-Dihydroxy-1-propoxy)methyl]guanine, Linear Isomers of 2′-Nor-2′-deoxyguanosine. *J. Med. Chem*. **1985**, *28*, 926−933.

(19) (a) Larsson, A.; Stenberg, K.; Ericson, A.-C.; Haglund, U.; Yisak, W.-A.; Johansson, N. G.; Oeberg, B.; Detama, R. Mode of Action, Toxicity, Pharmacokinetics, and Efficacy of Some New Antiherpesvirus Guanosine Analogues Related to Buciclovir. *Antimicrob. Agents Chemother*. **1986**, *30*, 598−605. (b) Lake-bakkar, D. M.; Abele, G.; Lindborg, B.; Soike, K. F.; Detama, R. Pharmacokinetics and Antiviral Activity in Simian Varicella-Infected Monkeys with (*R,S*)-9-(4-Hydroxymethyl)butyl)guanine, and Anti-Varicella-Zoster Virus Drug. *Antimicrob. Agents Chemother*. **1988**, *32*, 1−6. (c) Abele, G.; Karlstroem, A.; Harmenberg, J.; Shigeta, S.; Larsson, A.; Lindborg, B.; Wahren, B. Inhibiting Effect of (*RS*)-9-[4-Hydroxy-2-(hydroxymethyl)butyl]guanine on Varicella-zoster Virus Replication in Cell Culture. *Antimicrob. Agents Chemother*. **1987**, *31*, 76−80.

(20) Katagiri, N.; Sato, H.; Kaneko, C. Synthesis of Nucleosides and Related Compounds. 24. Synthesis and Biological Evaluation of 9-(c-2,t-3-bis(hydroxymethyl)-r-1-cyclopropylmethyl)-9H-adenine (a Lower Methylene Homologue of Carbocyclic Oxcetanocin) and Related Compounds. *Nucleosides Nucleotides* **1992**, *11*, 707−718.

(21) (a) Norbeck, D. W.; Rosen, T. J.; Sham, H. L. U.S. Patent 4,-988,703, 1991. (b) Norbeck, D. W.; Sham, H. L.; Herrin, T.; Rosenbrook, W.; Plattner, J. J. Synthesis of (±)-cycloprop-G, the Cyclopropyl Analogue of the Broad Spectrum Antiviral Agent Cyclobut-G. *J. Chem. Soc., Chem. Commun*. **1992**, 128−129.

(22) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T. Synthesis and Anti-HIV Activity of 9-[c-4,t-5-Bis(hydroxymethyl)cyclopent-2-en-r-1-yl]-9H-adenine. *J. Med. Chem*. **1992**, *35*, 1882−1886.

(23) Haines, D.; Tseng, C. K. H.; Marquez, V. E. Synthesis and Biological Activity of Unsaturated Carbocyclic Purine Nucleoside Analogues. *J. Med. Chem*. **1987**, *30*, 943−947.

(24) Derse, D.; Cheng, Y.-C.; Furman, P. A.; St. Char, M. H.; Elion, G. B. Inhibition of Purified Human and Herpes Simplex Virus-induced DNA Polymerases by 9-(2-hydroxyethoxymethyl)guanine Triphosphate. *J. Biol. Chem*. **1957**, *67*, 602−610.

(25) Jarvest, R. L.; Barnes, R. D.; Earnshaw, D. L.; O'Toole, K. J.; Sime, J. T.; Vere Hodge, R. A. Synthesis of Isotopically Chiral [^{13}C]-Penciclovir (BRL 39123) and its Use to Determine the Absolute Configuration of Penciclovir Triphosphate Formed in Herpes Virus Infected Cells. *J. Chem. Soc., Chem. Commun*. **1990**, 555−556.

(26) Karkas, J. D.; Germershausen, J. G.; Tolman, R. L.; MacCoss, M.; Wagner, A. F.; Liou, R.; Bostedor, R. Stereochemical Considerations in the Enzymatic Phosphorylation and Antiviral Activity of Acyclonucleosides. I. Phosphorylation of 2′-Nor-2′-deoxyguanosine. *Biochim. Biophys. Acta* **1987**, *911*, 127−135.

(27) Kohlbrenner, W. E.; Carter, C. D.; Fesik, S. W.; Norbeck, D. W.; Erickson, J. Efficiency of Phosphorylation of of the Cyclobut-G (A-69992) Enantiomers by HSV-1 Thymidine Kinase Does Not Correlate with Their Anti-Herpesvirus Activity. *Biochem. Pharmacol*. **1990**, *40*, R5−R10.

(28) Fyfe, J. A.; Keller, P. M.; Furman, P. A.; Miller, R. L.; Elion, G. B. *J. Biol. Chem*. **1978**, *253*, 8721−8727.

(29) Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. Synthesis and Antiviral Activity of Carbocyclic Analogues of 2′-Deoxyribofuranosides of 2-Amino-6-substituted-purines and of 2-Amino-6-substituted-8-azapurines. *J. Med. Chem*. **1984**, *27*, 1416−1421.

(30) (a) Borthwick, A. D.; Butt, S.; Biggadike, K.; Exall, A. M.; Roberts, S. M.; Youds, P. M.; Kirk, B. E.; Booth, B. R.; Cameron, J. M.; Cox, S. W.; Marr, C. L. P.; Shill, M. D. Synthesis and Enzymatic Resolution of Carbocyclic 2′-Ara-fluoro-guanosine: A potent New Anti-herpetic Agent. *J. Chem. Soc., Chem. Commun*. **1988**, 656−658. (b) Borthwick, A. D.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Butt, S.; Roberts, S. M.; Knight, D. J.; Coates, J. A. V.; Ryan, D. M. Fluorocarbocyclic Nucleosides: Synthesis and Antiviral Activity of 2′- and 6′-Fluorocarbocyclic 2′-Deoxy Guanosines. *J. Med. Chem*. **1991**, *34*, 907−914.

(31) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. Nucleosides with a Twist. Can Fixed Forms of Sugar Ring Pucker Influence Biological Activity in Nucleosides and Oligonucleotides? *J. Med. Chem*. **1996**, *39*, 3739−3747.

(32) Iwayama, S.; Ono, N.; Ohmura, Y.; Suzuki, K.; Aoki, M.; Nakazawa, H.; Oikawa, M.; Kato, T.; Okunishi, M.; Nishiyama, Y.; Yamanishi, K. Unpublished results.

(33) Vince, R.; Turakhia, R. H.; Shannon, W. M.; Arnett, G. Synthesis and Antiviral Activity of Carbocyclic Analogues of Xylofuranosides of 2-Amino-6-substituted-purines and 2-Amino-6-substituted-8-azapurines. *J. Med. Chem*. **1987**, *30*, 2026−2030.

(34) Comber, R. N.; Reynolds, R. C.; Friedrich, J. D.; Manguikian, R. A.; Buckheit, R. W., Jr.; Truss, J. W.; Shannon, W. M.; Secrist, J. A., III. 5,5-Disubstituted Hydantoins: Synthesis and Anti-HIV Activity. *J. Med. Chem*. **1992**, *35*, 3567−3572.

JM9705869