9-{[3-Fluoro-2-(hydroxymethyl)cyclopropylidene]methyl}adenines and -guanines. Synthesis and Antiviral Activity of All Stereoisomers[1]

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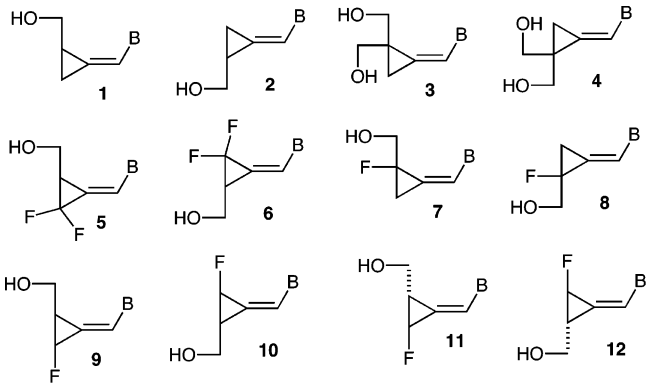
All stereoisomers of adenine and guanine methylene-3-fluoromethylenecyclopropane analogues of nucleosides **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **12a**, and **12b** were synthesized and their antiviral activities were evaluated. A highly convergent approach permitted the synthesis of all these analogues using a single intermediate **15**. Reaction of aldehyde **13** with fluorotrichloromethane and tri-*n*-butylphosphine gave fluoroalkenes **14a** + **14b** (83:17). Addition of carbene derived from ethyl diazoacetate gave cyclopropane **15** as the major product. Reduction (**19**), bromination (**20**), and phenylselenenylation (**21**), followed by Se oxidation and β-elimination gave *cis*-methylenecyclopropane **22**. Addition of bromine provided the reagent **23** for alkylation−elimination. Reaction of **23** with adenine led to an isomeric mixture **25a** + **26a** that after deprotection afforded analogues **9a** and **10a**. The 2-amino-6-chloropurine furnished **25e** + **26e** and after deblocking (**9e** and **10e**) and hydrolysis gave targets **9b** and **10b**. Intermediate **15** provided, after debenzylation (**27**), 2-nitrophenylselenenylation (**28**), reduction (**29**), benzylation (**30**), and oxidation−elimination *trans*-methylenecyclopropane **31**. Addition of bromine gave reagent **32**. Further transformations followed the sequence outlined for analogues **9a**, **9b**, **10a**, and **10b**. Analogue **9b** was effective against human cytomegalovirus (HCMV; Towne) with EC_{50} 2.9 μM. The *trans*-isomer **10b** inhibited AD169 strain of HCMV (EC_{50} 15 μM) and the murine virus MCMV (EC_{50} 2.5 μM). Compound **12a** was effective against Epstein−Barr virus (EC_{50} < 0.03 μM). Analogue **9a** inhibited varicella zoster virus (EC_{50} 5.9 μM) and human immunodeficiency virus type 1 (EC_{50} 5.2 μM). Analogues **9a**, **10a**, and **11a** are moderate substrates for adenosine deaminase. The structure−activity relationships will be discussed in context with other methylenecyclopropane analogues.

Methylenecyclopropane analogues of nucleosides are antiviral agents effective especially against human cytomegalovirus (HCMV) and Epstein−Barr virus (EBV).[2,3] The antiviral potency of the first generation series resides mostly in purine *Z*-(*cis*)-isomers **1** (Chart 1), whereas the *E*-(*trans*)-isomers **2** and pyrimidine analogues are active only exceptionally. The second generation *Z*-(*cis*)-isomers **3** have a more narrow antiviral effect,[4−6] but the guanine analogue cyclopropavir (**3**, B = Gua) is effective in vivo[7] and it is currently being developed as a potential drug against HCMV infections. As in the first generation series, the *E*-(*trans*)-isomers **4** lack anti-HCMV activity, but some EBV potency has been noted.[4,6]

Frequently, fluoro analogues of biologically active compounds have yielded effective agents in many areas of biology and biochemistry.[8,9] For these reasons, we focused our attention on methylenecyclopropane analogues of nucleosides fluorinated in the cyclopropane moiety. In the previous work, we reported on 3,3-difluoromethylenecyclopropane analogues[10] **5** and **6** and, more recently, 2-fluoro-substituted compounds[11] **7** and **8**. Although activity of compounds **5** and **6** was limited to a moderate potency[10] of the *E*-(*cis*)-isomer **5a** against HCMV, several *Z*-(*cis*)- and *E*-(*trans*)-isomers of the series **7** and **8** were effective[11] against HCMV and EBV. Also, the methylene-3,3-difluorocyclopropanes **5** and **6** have limited stability[10] that may have affected the biological activity, but monofluoro compounds **7** and **8** are stable.[11] It was then of interest to investigate the isomeric methylene-3-fluorocyclopropane analogues **9**, **10**, **11**, and **12**.

Chart 1. [a]



[a] B = nucleic acid base: series a, B = Ade; series b, B = Gua; series c, B = Cyt; series d, B = Thy; series e, B = 2-amino-6-chloropurine.

Synthesis. At the outset, it was clear that a convergent approach utilizing a single intermediate for synthesis of all antici-

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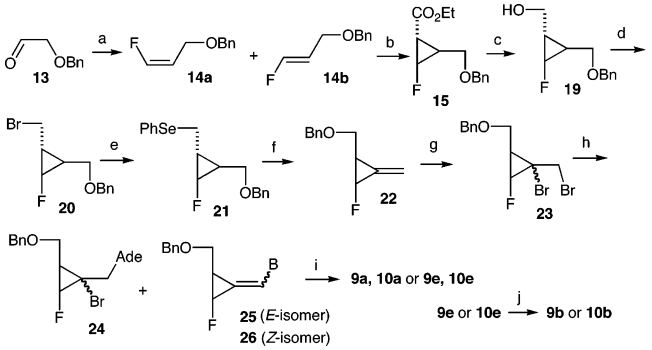
Scheme 1[a]

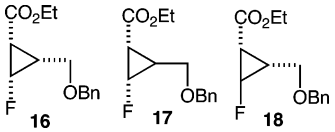


[a] Reaction conditions: (a) (1) $CFCl_3$, Bu_3P, CH_2Cl_2; (2) NaOH (10%); (b) N_2CHCO_2Et, $Cu(AcAc)_2$, CH_2Cl_2, Δ; (c) DIBALH, THF; (d) Ph_3P, Br_2, CH_2Cl_2; (e) Ph_2Se_2, NaOH, $NaBH_4$, EtOH; (f) (1) H_2O_2, THF, 0 °C; (2) (*i*-Pr)$_2$NEt, toluene, Δ; (g) pyridine·HBr_3, CH_2Cl_2; (h) B-H, K_2CO_3, DMF, Δ; (i) (1) BCl_3, CH_2Cl_2, −78 °C; (2) $NaHCO_3$, MeOH; (j) (1) 80% HCO_2H, Δ; (2) NH_3, MeOH. For series a, b, and e, see Chart 1.

pated analogues **9**, **10**, **11**, and **12** would be most convenient. Such a key compound should comprise the fluorocyclopropane ring carrying two different but modifiable substituents at the remaining cyclopropane carbon atoms. The different fluorocyclopropane stereochemistry necessary for *cis*-fluoro analogues **9** and **10** versus *trans*-isomers **11** and **12** could then be generated by manipulation of the cyclopropane substituents.

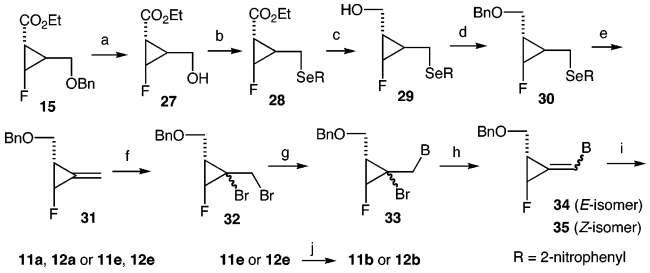
The synthesis of such a key intermediate, compound **15**, is described in Scheme 1.

Benzyloxyacetaldehyde **13** was converted to an isomeric mixture of fluoroalkenes **14a** + **14b** (*Z*/*E* = 83:17) in 68% yield by a modified Wittig reaction using fluorotrichloromethane and tri-*n*-butylphosphine in dichloromethane followed by alkaline hydrolysis.[12] Addition of carbene[13] derived from ethyl diazoacetate catalyzed by copper(II) acetylacetonate in dichloromethane gave a mixture of four cyclopropane stereoisomers **15**, **16**, **17**, and **18** (65% conversion) and two unidentified fluorine-containing components. The major stereoisomer **15** was formed by addition of carbene from a less-hindered side of the double bond of the *cis*-isomer **14a**. It was readily obtained by chromatography on a silica gel column in 42% yield. The other three stereoisomers **16**, **17**, and **18** were obtained as an unresolvable mixture identified by ^{19}F NMR spectroscopy. Reduction of **15**



with diisobutylaluminum hydride in tetrahydrofuran afforded hydroxymethylcyclopropane **19** (95%). Bromination using bromine−triphenylphosphine complex[14] in dichloromethane gave crude bromomethylcyclopropane **20** (91%), which was, in turn, converted to phenylselenenylcyclopropane **21** in 94% yield using sodium phenylselenide generated in situ from diphenyl diselenide.[5] Oxidation with 30% hydrogen peroxide was followed by *β*-elimination, catalyzed by diisopropylethylamine in toluene[10] at 80−85 °C to give methylenecyclopropane **22** (68%). Addition of bromine via pyridinium tribromide in dichloromethane afforded dibromide **23** (83%), obtained as a single stereoisomer of 95% isomeric purity. Alkylation-elimination protocol with adenine (K_2CO_3, DMF, 100−105 °C, 48 h) led to the alkylated product **24** and isomeric mixture of methylenecyclopropanes **25a** + **26a**. The elimination procedure was repeated with **24** to give additional **25a** + **26a** (total yield

Scheme 2[a]



[a] Reaction conditions: (a) (1) BCl_3, CH_2Cl_2, −78 °C; (2) $NaHCO_3$; (b) 2-nitrophenyl selenocyanate, Bu_3P, THF; (c) DIBALH, THF; (d) BnBr, NaH, THF; (e) (1) H_2O_2, THF, 0 °C; (2) toluene, Δ; (f) pyridine·HBr_3, CH_2Cl_2; (g) B-H, K_2CO_3, DMF; (h) K_2CO_3, DMF, Δ; (i) Me_2S·BCl_3, CH_2Cl_2; (j) (1) 80% HCO_2H, Δ; (2) NH_3, MeOH. For series a, b, and e, see Chart 1.

46%). Finally, debenzylation with boron trichloride in dichloromethane at −78 °C furnished, after chromatographic separation, analogues **9a** and **10a** in 47% yield each. Alkylation-elimination with 2-amino-6-chloropurine and **23** under the conditions described for adenine isomers **25a** + **26a** gave isomeric mixture **25e** + **26e** (56%). Debenzylation gave the *E*- and *Z*-isomers **9e** and **10e** in 47% yield each. Hydrolysis with 80% formic acid afforded guanine analogues **9b** and **10b** (both in 95% yield).

The key intermediate **15** served also as a starting material for the synthesis of the isomeric series **11** and **12** (Scheme 2). The *O*-debenzylation of **15** with boron trichloride in dichloromethane at −78 °C furnished hydroxyester **27** (83%). Reaction with 2-nitrophenyl selenocyanate and tri-*n*-butylphosphine in tetrahydrofuran (THF) using the procedure described[10] for difluoro analogues **5** and **6** gave 2-nitrophenylselenenyl derivative **28** in 92% yield. Reduction with diisobutylaluminum hydride in THF afforded hydroxymethylcyclopropane **29** (95%). Benzylation with benzyl bromide using sodium hydride in THF led to intermediate **30** (71%). Oxidation with hydrogen peroxide in THF, followed by *β*-elimination (see also Scheme 1, **21** → **22**) provided methylenecyclopropane **31** (*trans*-isomer of **22** from Scheme 1) in 73% yield. Addition of bromine furnished dibromocyclopropane **32** (83%), obtained, in contrast to isomeric derivative **23**, as a mixture of *cis*- and *trans*-isomers. Further transformations followed those described in Scheme 1, but the alkylation and elimination steps were separated. Alkylation of adenine (K_2CO_3, DMF, 25−40 °C) with **32** gave alkylated product **33a** in 86% yield.

β-Elimination was effected with K_2CO_3 in DMF at 100 °C to furnish *E*- and *Z*-isomers **34a** and **35a**, which were separated by chromatography in 27 and 18% yields, respectively. The *O*-debenzylation afforded adenine analogues **11a** and **12a** (74−79%). The reaction sequence with 2-amino-6-chloropurine proceeded in a similar fashion: **32** → **33e** (87%) → **34e** and **35e** (29 and 33%) → **11e** and **12e** (74% each). Hydrolysis then provided guanine analogues **11b** and **12b** in 73−76% yield.

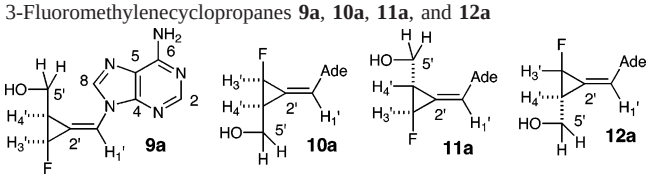
Isomeric Structure of Analogues 9, 10, 11, and 12. A preliminary isomeric assignment of *cis*- and *trans*-alkene isomers **9** versus **10** and **11** versus **12** was made on the basis of chromatographic mobility that followed the pattern observed previously[3] for other methylenecyclopropane analogues. The isomers **9** and **11** with a *cis*-configured base are faster moving than the respective *trans*-isomers **10** and **12**. Although this "rule" may be of value for distinguishing *cis*- and *trans*-isomers at the alkene bond, it has little relevance for determining the *cis*- and *trans*-configuration at the cyclopropane moiety in **9** versus **11** and **10** versus **12**. All these isomeric structures were readily established from ^1H and ^{19}F NMR spectra (Table 1). The

Table 1. Chemical Shifts (δ) and Coupling Constants $^3J_{F,H}$ of the Relevant ^{1}H NMR Signals of Fluorinated Methylenecyclopropanes **5a**, **6a**, **9a**, **10a**, **11a**, and **12a**

compound[a]	$H_{1'}$	H_8	OH	$^3J_{F,H}$ (Hz)
5a	8.19	8.68	5.39	<1, 7.5
6a	7.64	8.16	5.24	<1, 6.3
9a	7.89	8.72	5.21	<1
10a	7.55	8.35	5.03	<1
11a	7.93	8.71	5.17	12.2
12a	7.58	8.34	5.02	10.9

[a] DMSO-d_6 as solvent. Values for **5a** and **6a** were taken from ref 10.

Table 2. NOE Enhancements of Relevant ^{1}H NMR Signals of 3-Fluoromethylenecyclopropanes **9a**, **10a**, **11a**, and **12a**



compound[a]	H_{iir}	δ	H_{obs}	δ	NOE (%)
9a	H_8	8.72	$H_{4'}$	2.48	2.84
	$H_{4'}$	2.48	H_8	8.72	2.20
	OH	5.21	H_8	8.72	1.98
	$H_{4'}$	2.48	$H_{3'}$	5.32, 5.49[a]	1.87, 2.40
10a	H_8	8.35	$H_{3'}$	5.53, 5.70[a]	2.47, 2.44
	$H_{3'}$	5.53, 5.70[a]	H_8	8.35	5.23, 3.67
	$H_{4'}$	2.37	$H_{3'}$	5.53, 5.70[a]	3.33, 3.76
	$H_{3'}$	5.53, 5.70[a]	$H_{4'}$	2.37	13.05, 12.57
11a	H_8	8.71	$H_{4'}$	2.60	1.54
	$H_{4'}$	2.60	H_8	8.71	3.36
	H_8	8.71	OH	5.17	0.30
	OH	5.17	H_8	8.71	2.58
12a	H_8	8.34	$H_{3'}$	5.28, 5.45[a]	1.08, 0.68
	$H_{3'}$	5.28, 5.45[a]	H_8	8.34	4.44, 2.33

[a] Doublets of the $H_{3'}$ signals of **9a** and **10a** were treated separately as two singlets. Likewise, the doublets of doublets of **11a** and **12a** were treated as two doublets.

chemical shifts of the *cis*-isomers of the purine H_8, alkene $H_{1'}$, and OH of **9a** and **11a** are all located downfield from the respective *trans*-isomers **10a** and **12a**. A similar deshielding pattern was observed previously[10] for the corresponding 3,3-difluoromethylene analogues **5a** and **6a**. The $^3J_{F,H}$ coupling constants were then instrumental for isomeric assignment of the substituents in the cyclopropane moiety. The fluorine signals of isomers **9a** and **10a** with *trans*-situated proton and fluorine appear as doublets with $^3J_{F,H} < 1$ Hz, whereas compounds **11a** and **12a** having *cis*-configured protons, exhibit $^3J_{F,H} = 12.2$ and 10.9 Hz, respectively. This is in accord with the general pattern in fluorocyclopropanes,[15] where the $^3J_{F,H-cis}$ are much larger than $^3J_{F,H-trans}$. As expected, *cis*- and *trans*-located *geminal* fluorine atoms of difluoro analogues **5a** and **6a** also follow these trends.[10] Similar relationships were observed for analogues containing bases other than adenine, compounds **9b**, **10b**, **9e**, and **10e**. The $^3J_{F,H}$ values of a similar magnitude, <1 and 13.9 Hz, were also observed for *cis*- and *trans*-methylenecyclopropanes **22** and **31** lacking the heterocyclic bases.

The NOE experiments with analogues **9a**, **10a**, **11a**, and **12a** confirmed these assignments (Table 2). As expected, in compounds **9a** and **11a**, with a *cis*-configured adenine, the NOE enhancements were observed between the H_8 and $H_{4'}$ and OH and H_8. In *trans*-isomers **10a** and **12a**, an interaction between the H_8 and $H_{3'}$ was observed. The NOE enhancements between the *cis*-configured cyclopropane protons $H_{3'}$ and $H_{4'}$ were noted for analogues **9a** and **10a**, but they were absent in **11a** and **12a**, where this relationship is *trans*.

Table 3. Inhibition of HCMV and HSV-1 Replication by 3′-Fluoromethylenecyclopropane Analogues of Nucleosides

	EC_{50}/CC_{50} (μM)		
	HCMV/HFF		
compound	Towne[a,b]	AD169[c,d]	HSV-1/BSC-1[e]
9a	31/>100	44.3/>100	80/>100
10a	>100/>100	>100/>100	>100/>100
9b	2.9/>100	>12/>300	70/>100
10b	>100/>100	15/266[a,f]	20/>100
11a	>100/>100	45/>300	20/>100
12a	>100/>100	285/>300	50/>100
11b	>100/>100	>60/255	>100/>100
12b	>100/>100	>60/183	>100/>100
control	1.8/>100[g]	0.15/>100[g]	3.5/>100[h]

[a] Plaque reduction assay. [b] Visual cytotoxicity. [c] Cytopathic effect (CPE) inhibition assay. [d] Cytotoxicity by neutral red uptake. [e] ELISA. Cytotoxicity was determined in KB cells. All listed compounds were inactive against HSV-1 or HSV-2 in Vero (EC_{50}/CC_{50} >50/>50 μM)[a] and HFF cells (EC_{50}/CC_{50} >100/>100 μM)[c] culture. [f] Against MCMV/MEF[a] the EC_{50}/CC_{50} was 2.5/>100 μM. Because of a lack of significant potency against HCMV/AD169, other compounds listed in Table 1 were not tested. [g] Ganciclovir. [h] Acyclovir.

Table 4. Inhibition of EBV, VZV, HIV-1, and HBV Replication by 3′-Fluoromethylenecyclopropane Analogues of Nucleosides

	EC_{50}/CC_{50} (μM)				
	EBV		VZV	$HIV\text{-}1_{LAI}$	HBV
compound	Daudi[a]	H-1[b,c]	HFF[d,e]	MT-2[d]	2.2.15[b,c]
9a	>50/>50	>20/>100	5.9[f]	5.2/>10	>20
10a	>50/>50	>20/>100	54.6[f]	>10/>10	>20
9b	>100/>100	13/74	>100[f]	>10/>10	>20
10b	>100/>100	>20/>100	68.3[f]	>10/>10	>20
11a	>100/>100	>10/9	33.6[f]	>10/>10	>10
12a	<0.03/>100	>10/>100	>60	>10/>10	>10
11b	>100/>100	>30/>100	>100	>10/>10	>30
12b	91.6/>100	>30/>100	>60	>10/>10	>30
control	0.33/>100[g]	5[h]	0.03[g]	0.02/>10[i]	0.02/>100[j]

[a] Viral capsid antigen (VCA) ELISA. [b] DNA hybridization assay. [c] Cytotoxicity was determined in CEM cells. [d] Cytopathic effect (CPE) assay. [e] Only the EC_{50} values are listed, for CC_{50} values, see HCMV(AD169)/HFF in Table 1. [f] Plaque reduction assay. [g] Acyclovir. [h] Ganciclovir. [i] AZT. [j] Lamivudine.

Biological Activity. Antiviral Activity. Analogues **9a**, **9b**, **10a**, **10b**, **11a**. **11b**, **12a**, and **12b** were tested against the following viruses: HCMV, herpes simplex virus 1 and 2 (HSV-1 and HSV-2), EBV, varicella zoster virus (VZV), human immunodeficiency virus type 1 (HIV-1), and hepatitis B virus (HBV). The results are summarized in Tables 3 and 4. Analogue **9b** was active against HCMV/HFF (EC_{50}/CC_{50} 2.9/>100 μM) in Towne strain of the virus (Table 3) but it had little effect against the AD169 strain. Conversely, *trans*-isomer **10b** was somewhat effective against HCMV/HFF in the AD169 strain (EC_{50}/CC_{50} 15/266 μM) and inactive against Towne strain. It was active with 2.5/>100 μM against the murine virus MCMV/MEF. Analogues **11a**, **11b**, **12a**, and **12b** were without significant effect.

Moderate antiviral effects were detected by ELISA against HSV-1/BSC-1. The most potent compounds **10b** and **11a** had EC_{50}/CC_{50} 20/>100 μM. Against EBV/Daudi (VCA-ELISA), the *trans*-isomer **12a** was the most effective analogue, with EC_{50}/CC_{50} <0.03/>100 μM, but it was devoid of potency in H-1 cells, as determined by DNA hybridization assay (Table 4).

Under the latter conditions, guanine analogue **9b** was moderately active with EC_{50}/CC_{50} 13/74 μM. It was inactive in Daudi cells. The adenine analogue **9a** was the most potent compound against VZV/HFF with EC_{50}/CC_{50} 5.9/>100 μM, and it also

inhibited HIV-1/MT-2 (EC_{50}/CC_{50} 5.2/>10 μM). The tested compounds were inactive against HBV in 2.2.15 cells, and they were noncytotoxic, with the exception of analogue **11a** with CC_{50} 9 μM in CEM cells.

The analogues described herein conclude the first generation of methylenecyclopropanes **1** and **2** with a single fluorine atom in the cyclopropane moiety. Therefore, some generalizations regarding the structure−activity relationships of antiviral activity in this whole series of compounds can be made. The antiviral activity of the purine methylenecyclopropane analogues with a *cis* configuration of the nucleobase follows approximately the order **1** > **7** > **9** > **11** > **5**. Introduction of the fluorine appears to narrow the antiviral effects.[10,11] Two *geminal* fluorines (**5a**, **5b**, **6a**, and **6b**) decrease the chemical stability of the analogues.[10] Compounds with a *trans*-configured nucleobase **10** and **12** were mostly devoid of significant antiviral activity. Strong potency, sometimes in submicromolar range, was detected against EBV/Daudi by VCA-ELISA but it was not always reproduced in DNA hybridization assays. Analogues **8a**, **8b**, **8c** (ref 11), and **12a** serve as examples. It is likely that the mechanism of action of active analogues of this series follows the conversion to the corresponding triphosphates, which then inhibit the relevant DNA polymerase or reverse transcriptase. This was documented[16] for nonfluorinated analogues **1** and **2**.

Adenosine Deaminase (ADA). Adenine fluoroanalogues **9a**, **10a**, **11a**, and **12a** were investigated as substrates for adenosine deaminase from calf intestine, whereas compounds **9a**, **10a**, and **11a** are moderate substrates, which were about 50% deaminated after 24 h; analogue **12a** was resistant to deamination up to 48 h.

Experimental Section

General Methods. The UV spectra were measured in ethanol and NMR spectra were determined at 300 or 400 MHz (^{1}H), 75 or 100 MHz (^{13}C), and 376 MHz (^{19}F). For ^{19}F NMR, $CFCl_3$ was used as a reference. For atom numbering of 3-fluoromethylenecyclopropane analogues, see Table 2, formula **9a**. Mass spectra were determined in electron-impact (EI-MS) or electrospray ionization (ESI-MS, methanol−NaCl) mode. Benzyloxyacetaldehyde[17] (**13**) and 2-nitrophenyl selenocycanate[18] were prepared as described. For the nomenclature of compounds with a double *cis*−*trans* isomerism in the cyclopropane ring, an *r*,*c*,*t* system[19] was adopted. The substituents were denoted as follows: *r* (reference), *c* (*cis*), and *t* (*trans*). Adenosine deaminase from calf intestine, ×6B8577, 19.8 units/mg solid, was the product of Worthington, Lakewood, New Jersey.

(*Z*,*E*)-1-Benzyloxymethyl-2-fluoroethene (14a + 14b). Tri-*n*-butylphosphine (205 mL, 0.825 mmol) was added dropwise with stirring at 0 °C to a mixture of CH_2Cl_2 (270 mL) and $CFCl_3$ (25.7 mL, 0.275 mol). The stirring was continued for 1 h at 0 °C and then 3 h at room temperature. Benzyloxyacetaldehyde[17] (**13**, 33.3 g, 0.22 mol) in CH_2Cl_2 (20 mL) was added at 0 °C with stirring, which was continued for 16 h at room temperature. Sodium hydroxide solution (10%, 330 mL) was then added, and the stirring was continued for 24 h. The reaction mixture was cooled to 0 °C, and the pH was adjusted to 5.0 by a careful addition of HCl. The organic phase was separated, washed with 5% HCl (5%, 2 × 150 mL), and dried over $MgSO_4$. The solvents were removed in vacuo, the residue was dissolved in hexanes, and the solution was filtered through a silica gel pad. After removal of hexanes, the crude product was chromatographed on a silica gel column in hexanes to hexanes−Et_2O (40:1) to give *Z*- and *E*-isomers **14a** and **14b** (25.2 g, yield 68%, 83% **14a**, and 17% **14b**, as determined by ^{19}F NMR) as a colorless oil, which was of sufficient purity to be used in the next step. ^{1}H NMR ($CDCl_3$) δ 3.98 (dt, J = 7.2, 1.6 Hz, **14b**), 4.22 (dt, 2H, J = 7.2, 2.0 Hz, **14a**, CH_2O), 4.54 (s, **14b**), 4.56 (s, 2H, CH_2Ph, **14a**), 5.09 (ddt, J = 42.0, 7.2, 4.8 Hz, **14a**), 5.60 (ddt, 1H, J = 18.4, 11.2, 7.2 Hz, 1H, **14b**, CH=), 6.67 (ddd, J = 84.4, 4.8, 1.6 Hz, **14a**), 6.75 (ddd, 1H, J = 83.6, 11.2, 1.6 Hz, **14b**, CHF=), 7.36 (m), 7.41 (m, 5H, Ph). ^{13}C NMR 61.9 (d, J = 6.7 Hz, **14a**), 64.8 (d, J = 14.2 Hz), **14b**, CH_2O), 72.2 (**14b**), 72.5 (**14a**, CH_2Ph), 108.5 (d, J = 3.7 Hz, **14a**), 108.9 (d, J = 9.8 Hz, **14b**, CH=), 128.0 (**14a**), 128.1 (**14b**), 128.2 (**14a**, **14b**), 128.7 (**14a**), 128.8 (**14b**), 138.2 (**14b,**) 138.4 (**14a**, Ph), 149.9 (d, J = 261.9 Hz, **14a**), 152.1 (d, J = 261.2 Hz, **14b**, CHF=). ^{19}F NMR −126.07 (dd, J = 83.9, 44.4 Hz, **14a**), −125.54 (ddt, J = 83.9, 18.1, 3.0 Hz, **14b**). EI-MS 166 (M, 3.0), 165 (M − H, 4.2), 91 ($PhCH_2$, 100.0). EI−HRMS calcd for $C_{10}H_{11}OF$, 166.0794; found, 166.0791.

Ethyl *t*-2-Benzyloxymethyl-*t*-3-fluorocyclopropane-*r*-1-carboxylate (15). Ethyl diazoacetate (11.5 g, 100 mmol) was added to a refluxing solution of **14a** + **14b** (16.0 g, 96.38 mmol) and copper acetylacetonate (0.75 g, 2.87 mmol) in CH_2Cl_2 (120 mL) using a syringe pump (0.34 mL/h) with stirring. The stirring was continued for 1 h, solvent was evaporated, and the residue was put on a silica gel column that was eluted with hexane−EtOAc (100:0 to 10:1) to give unreacted **14a** + **14b** (5.6 g, 35%), followed by a mixture of products. Solvents were evaporated, the residue was dissolved in ether (150 mL), and $KMnO_4$ (15 g) in water (60 mL) was added with external ice-cooling and stirring to remove unsaturated impurities. The stirring was continued for 6 h, and excess $KMnO_4$ was removed by addition of solid $Na_2S_2O_3$. The mixture was filtered through a short silica gel pad that was eluted with ether. The organic phase was washed successively with saturated $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL), and it was dried over $MgSO_4$. The crude product was chromatographed on a silica gel column in hexane−Et_2O, 50:1 to give a faster moving isomer **15** as a colorless oil (6.65 g, 42%). The slower moving fraction was an inseparable mixture consisting of the three remaining isomers **16**, **17**, and **18** and two unidentified fluorine-containing impurities.

Isomer 15: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz, CH_3), 1.91−1.99 (m, 2H, H_2, H_1), 3.78−3.58 (2 partly overlapped AB's, 2H, CH_2OBn), 4.08 (2q, 2H, J = 7.2 Hz, CH_2 of Et), 4.52, 4.59 (AB, 2H, J = 11.7 Hz, CH_2Ph), 4.92 (ddd, 1H, J = 63.2, 5.6, 2.4 Hz, H_3), 7.28−7.36 (m, 5H, Ph). ^{13}C NMR 14.4 (CH_3), 24.9 (d, J = 12.7 Hz, C_1), 26.3 (d, J = 8.3 Hz, C_2), 61.3 (CH_2 of Et), 65.6 (d, J = 7.5 Hz, CH_2OBn), 73.0 (CH_2Ph), 76.1 (d partly overlapped with $CDCl_3$, J = 230.5 Hz, C_3), 127.95, 127.98, 128.7, 138.2 (Ph), 170.7 (C=O). ^{19}F NMR −220.05 (ddd, J = 64.0, 18.1, 7.5 Hz). EI-MS 252 (M, 5.1), 91 ($PhCH_2$, 100.0). EI−HRMS calcd for $C_{14}H_{17}FO_3$, 252.1162; found, 252.1164. Anal. $C_{14}H_{17}FO_3$ (C, H).

Ethyl *c*-2-Benzyloxymethyl-*c*-3-fluorocyclopropane-*r*-1-carboxylate (16). ^{19}F NMR ($CDCl_3$) −232.66 (dt, J = 65.5, 9.0 Hz).

Ethyl *t*-2-Benzyloxymethyl-*c*-3-fluorocyclopropane-*r*-1-carboxylate (17). ^{19}F NMR ($CDCl_3$) −220.66 (ddd, J = 64.0, 18.1, 7.5 Hz).

Ethyl *c*-2-Benzyloxymethyl-*t*-3-fluorocyclopropane-*r*-1-carboxylate (18). ^{19}F NMR ($CDCl_3$) −205.84 (dt, J = 64.0, 18.4 Hz).

***t*-2-Benzyloxymethyl-*t*-3-fluorocyclopropyl-*r*-1-methanol (19).** Diisobutylaluminum hydride (DIBALH) in hexanes (1M, 45.80 mL, 45.80 mmol) was added to a solution of ester **15** (4.62 g, 18.33 mmol) in hexane (40 mL) with stirring at 0 °C during 10 min under N_2. The stirring was continued for 1 h. The reaction was quenched by a dropwise addition of HCl (5%, 50 mL) and then it was extracted with ether (4 × 30 mL). The organic phase was washed successively with saturated $NaHCO_3$ (2 × 30 mL) and water (2 × 30 mL). The solvents were evaporated, and the residue was chromatographed on a silica gel column in hexanes−EtOAc = 10:1 to 5:1 to give compound **19** as a colorless oil (3.66 g, 95%). ^{1}H NMR ($CDCl_3$) δ 1.18 (ddd, 1H, J = 13.0, 6.6 Hz, H_2), 1.34 (dddd, 1H, J = 22.0, 13.6, 6.4, 1.6 Hz, H_1), 2.95 (br s, 1H, OH), 3.33 (m, 1H), 3.31−3.46 (m, 1H, CH_2OH), 3.57−3.71 (m, 2H, CH_2OBn), 4.50 (ddd, 1H, J = 64.0, 6.4, 2.4 Hz, H_3), 4.44, 4.60 (split AB partly overlapped with H_3, 2H, CH_2Ph), 4.52 (ddd partly overlapped with CH_2Ph, 1H, J = 63.6, 6.0, 2.1 Hz, H_3), 7.28−7.36 (m, 5H, Ph). ^{13}C NMR 21.6 (d, J = 10.5 Hz), 25.1 (d, J = 9.7 Hz, $C_{1'}$, C_2), 61.8 (CH_2OH), 67.3 (d, J = 8.2 Hz, CH_2OBn), 73.0 (CH_2Ph), 75.1 (d, J = 223.5 Hz, C_3), 128.0, 128.1, 128.7, 138.3 (Ph). ^{19}F NMR

−223.80 (ddd, J = 64.0, 21.5, 4.5 Hz). EI-MS 210 (M, 1.2), 91 ($PhCH_2$, 100.0). EI−HRMS calcd for $C_{12}H_{15}FO_2$, 210.1056; found, 210.1057. Anal. $C_{12}H_{15}FO_2$ (C, H).

***t*-2-Benzyloxymethyl-*t*-3-fluoro-*r*-1-bromomethylcyclopropane (20).** Bromine (2.60 g,16.24 mmol) was added with stirring to a solution of PPh_3 (4.65 g, 17.71 mmol) in CH_2Cl_2 (20 mL) over 20 min, maintaining the temperature below −30 °C. Compound **19** (3.10 g, 14.76 mmol) in CH_2Cl_2 (8 mL) was then added dropwise, and the mixture was allowed to warm to room temperature. It was diluted with hexanes (150 mL), whereupon it was filtered through a silica gel plug (10 g). The plug was washed with hexanes−ethyl acetate (30:1, 150 mL), and the combined filtrates were evaporated to provide compound **20** as a colorless oil containing <10% PPh_3 (3.65 g, 91%). This product was used for preparation of phenylselenenyl derivative **21**.

The experiment performed on a 1-mmol scale of **19** gave after chromatography on a silica gel column in hexanes−Et_2O (50:1 to 30:1) compound **20** (250 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 1.32 (ddd, J = 12.0, 6.0, 2.0 Hz, 1H, H_2), 1.60 (dddd, J = 21.6, 10.8, 6.4, 2.0 Hz, 1H, H_1), 3.28 (dd, 2H, J = 7.6, 2.0 Hz, CH_2Br), 3.55 (poorly resolved dd, 1H), 3.77 (poorly resolved ddd, 1H, CH_2OBn), 4.54, 4.60 (AB, 2H, J = 12.2 Hz, CH_2Ph), 4.56 (ddd, 1H, J = 63.0, 6.0, 1.6 Hz, H_3), 7.30−7.37 (m, 5H, Ph). ^{13}C NMR 25.2 (d, J = 11.2), 26.6 (d, J = 10.5 Hz, C_1, C_2), 32.8 (CH_2Br), 66.6 (d, J = 7.5 Hz, CH_2OBn), 72.9 (CH_2Ph), 77.6 (d, J = 226.8 Hz, C_3), 128.0, 128.1, 128.7, 138.4 (Ph). ^{19}F NMR −219.63 (ddd, J = 64.0, 20.0, 5.6 Hz). ESI-MS (MeOH − KOAc) 311, 313 (M + K, 92.8 and 100.0). Anal. $C_{12}H_{14}BrFO$ (C, H).

***t*-2-Benzyloxymethyl-*t*-3-fluoro-*r*-1-(phenylselenenylmethyl)-cyclopropane (21).** Ph_2Se_2 (1.71 g, 5.50 mmol) was refluxed in ethanol (25 mL) until a clear solution was obtained. After cooling, NaOH (4M, 2.75 mL, 11 mmol) was added, followed by $NaBH_4$ (0.835 g, 11 mmol). The reaction mixture was refluxed for 30 min and then it was cooled again to room temperature. A solution of compound **20** (3.0 g, 11 mmol) in ethanol (10 mL) was slowly added with stirring. After 3 h, water (125 mL) was added, the mixture was extracted with EtOAc, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column in hexane−EtOAc (30:1) to give compound **21** (3.63 g, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.20 (dd, J = 14.0, 6.4 Hz, H_2), 1.35−1.46 (m, 1H, H_1), 2.75−2.90 (poorly resolved 2 AB's, 2H, CH_2SePh), 3.49 (poorly resolved dd, 1H), 3.72 (dd, 1H, J = 10.4, 5.6 Hz, CH_2OBn), 4.47 (poorly resolved dd, 1H, J = 63.2, 6.8 Hz, H_3), 4.52, 4.59 (AB, 2H, J = 12.0 Hz, CH_2Ph, partly overlapped with H_3), 7.29−7.34 (m, 4H), 7.37 (br d, 4H), 7.56−7.58 (m, 2H, 2 × Ph). ^{13}C NMR 23.3, 25.8 (2d, J = 10.5 Hz, C_1, C_2), 28.3 (CH_2SePh), 67.1 (d, J = 8.3 Hz, CH_2OBn), 72.8 (CH_2Ph), 77.8 (d, J = 227.6 Hz, C_3), 127.6, 127.9, 128.0, 128.7, 129.4, 129.6, 133.8, 138.6 (2 × Ph). ^{19}F NMR −219.63 (ddd, J = 64.0, 21.5 Hz, <1 Hz). EI-MS 350, 348 (M, 1.90, 0.87), 91 ($PhCH_2$, 100.0). EI−HRMS calcd for $C_{18}H_{19}FO^{80}Se$, 350.0585; found, 350.0585. Anal. $C_{18}H_{19}FOSe$ (C, H).

***cis*-2-(Benzyloxymethyl)-3-fluoro-1-methylenecyclopropane (22).** Hydrogen peroxide (30%, 11.19 mL, 98.7 mmol) was added dropwise with stirring to a solution of compound **21 (** 3.49 g, 10 mmol) in THF (30 mL) at −60 °C. The mixture was allowed to warm to room temperature. After 14 h, water (100 mL) and EtOAc (100 mL) were added, the organic phase was washed with $NaHCO_3$ (5%) and water, it was dried ($MgSO_4$), and the solvents were evaporated. The residue was dissolved in toluene (15 mL), diisopropylethylamine (3.50 mL, 20 mmol) was added, and the reaction mixture was stirred at 80−85 °C for 2 h. After removal of solvents, the crude product was chromatographed on silica gel in hexanes−EtOAc (30:1) to give compound **22** (1.30 g, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.08−2.17 (m, 1H, H_2), 3.60 (poorly resolved dd, 1H), 3.82 (ddd, 1H, J = 10.7, 5.6, 1.2 Hz, CH_2OBn), 4.56, 4.63 (AB, 2H, J = 12.0 Hz, CH_2Ph), 5.08 (dd, 1H, J = 69.0, 7.5 Hz, H_3), 5.66, 5.90 (2 poorly resolved t, 2H, CH_2═), 7.30−7.39 (2m, 5H, Ph). ^{13}C NMR 23.9 (d, J = 15.1 Hz, C_2), 66.5 (d, J = 2.0 Hz, CH_2OBn), 69.3 (d, J = 231.7 Hz, C_3), 72.8 (CH_2Ph), 110.8 (J = 3.0 Hz, CH_2═), 130.9 (C_1), 127.9, 128.0, 128.6, 138.6 (Ph). ^{19}F NMR −218.27 (dd, J = 68.9, <1 Hz). EI-HRMS calcd for $C_{12}H_{13}FO$, 192.0950; found, 192.0955. Anal. $C_{12}H_{13}FO$ (C, H).

***r*-2-Benzyloxymethyl-*c*, or *t*-1-bromo-*c*, or *t*-1-Bromomethyl)-*c*-2-fluorocyclopropane (23).** Pyridinium tribromide (3.20 g, 10.24 mmol) was added with stirring to a solution of compound **22** (1.2 g, 6.25 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was allowed to warm to room temperature. After 16 h, it was diluted with EtOAc (100 mL), and the resultant solution was washed sequentially with saturated $Na_2S_2O_3$, $NaHCO_3$, and water. The organic phase was dried over $MgSO_4$, and the solvents were evaporated. The crude product was chromatographed on a silica gel column in hexanes−Et_2O (40:1) to afford compound **23** (1.82 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.52−1.60 (m, 1H, H_2), 3.6−3.80 (cluster of m, 4H, CH_2Br and CH_2OBn), 4.47 (dd, 1H, J = 64.0, 7.6 Hz, H_3), 4.58 (s, CH_2Ph), 7.30−7.37 (cluster of m, 5H, Ph). ^{13}C NMR 29.1 (d, J = 9.7 Hz, C_2), 38.8 (d, J = 9.0 Hz, C_1), 40.5 (d, J = 1.8 Hz, CH_2Br), 66.9 (d, J = 5.9 Hz, CH_2-OBn), 73.3 (CH_2Ph), 74.6 (d, J = 235.8 Hz, C_3), 128.04, 128.06, 128.7, 138.1 (Ph). ^{19}F NMR −213.89 (dd, J = 64.0, 9.0 Hz).[20] ESI-MS (MeOH + KOAc) 389, 391, 393 (M + K, 52.7, 100.0, 51.8). Anal. $C_{12}H_{13}Br_2FO$ (C, H).

(*Z*,*E*)-9-{[*cis*-(3-Fluoro-2-benzyloxymethyl)cyclopropylidene]-methyl}adenine (25a + 26a) and *c*- or *t*-9-{[*c*- or *t*-1-Bromo-*c*-3-fluoro-*r*-2-(benzyloxymethyl)cyclopropyl]methyl}adenine (24). A mixture of adenine (287 mg, 2.2 mmol), compound **23** (704 mg, 2.0 mmol), and K_2CO_3 (1.66 g, 12.0 mmol) in DMF (10 mL) was stirred under N_2 for 4 h at 40 °C and then at 100−105 °C for 45 min. The mixture was rapidly cooled to −78 °C and then it was allowed to warm to room temperature. The insoluble solid was filtered off using a silica gel pad (5 g) that was washed with DMF (70 mL). The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column in EtOAc−MeOH (40:1 to 30:1) to give the faster moving *E*,*Z*-isomeric mixture **25a** + **26a** and slower moving intermediate **24** (490 mg, 1.21 mmol). The elimination procedure was repeated with **24** using K_2CO_3 (0.83 g, 6 mmol) and DMF (5.0 mL). The product was chromatographed as described above to give *Z*,*E*-mixture **25a** + **26a** and bromo derivative **24** (120 mg, 14.8%). Both portions of **25a** + **26a** were combined and they were rechromatographed in EtOAc−MeOH (50:1 to 30:1) to give *E*,*Z*-isomers **25a** + **26a** (300 mg, 46%, *E*/*Z* = 1:1).

***E*,*Z*-Isomers 25a + 26a:** Mp 166−170 °C. UV λ_{max} 237 nm (ϵ 25 700), 280 (ϵ 8500). ^{1}H NMR ($CDCl_3$) δ 2.46 (br m, 1H, $H_{4'}$), 3.68, 3.85 (2m, 2H, $H_{5'}$), 4.47−4.63 (m, 2H, OCH_2Ph), 5.21, 5.37 (2 partially overlapped dd, J = 69.0, 69.6, 6.4 Hz, 1H, $H_{3'}$), 6.50, 6.53 (2s, 2H, NH_2), 7.26−7.36 (m, 5H, Ph), 7.59, 7.98 (2br s, 1H, $H_{1'}$), 8.38, 8.20, 8.75 (3s, 2H, H_2 and H_8). ^{19}F NMR −214.83 and −215.88 (2d, J = 70.0, <1 Hz). EI-MS 325 (M, 0.36), 91 (100.0). ESI-MS (MeOH) 326 (M + H, 100.0). EI−HRMS calcd for $C_{17}H_{16}N_5FO$, 325.1339; found, 325.1339.

Compound 24: Mp 161−163 °C. UV λ_{max} 209 nm (ϵ 21 800), 261 (ϵ 12 200). ^{1}H NMR ($CDCl_3$) δ 1.79−1.87 (m, 1H, $H_{4'}$), 3.65−3.75 (m, 2H, $H_{5'}$), 4.36−4.52 (overlapped m of CH_2Ph and $H_{1'}$, 4H), 4.92 (dd, 1H, J = 64.0, 7.2 Hz, $H_{3'}$), 5.85 (s, 2H, NH_2), 7.26−7.36 (m, 5H, Ph), 8.02, 8.32 (2s, 2H, H_2, H_8). ^{13}C NMR 26.9 (d, J = 10.5 Hz, $C_{4'}$), 39.1 (d, J = 9.8 Hz, $C_{2'}$), 51.9 ($C_{1'}$), 66.5 (d, J = 5.2 Hz, $C_{5'}$), 73.1 (d, J = 234.2 Hz, $C_{3'}$), 73.2 (CH_2 of Bn), 119.7 (C_5), 127.9, 128.0, 128.7, 138.0 (Ph), 140.9 (C_8), 150.4 (C_4), 153.4 (C_2), 155.8 (C_6). ^{19}F NMR −216.85 (ddd, J = 64.0, 9.2 Hz). ESI-MS 406, 408 (M + H, 97.0, 100.0).

(*E*)-9-{[*cis*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]-methyl}adenine (9a) and (*Z*)-9-{[*cis*-(3-Fluoro-2-hydroxymethyl)-cyclopropylidene]methyl}adenine (10a). Boron trichloride (1 M in CH_2Cl_2, 5.7 mL, 5.7 mmol) was added to a solution of the *Z*,*E*-isomers **25a** + **26a** (230 mg, 0.71 mmol) in CH_2Cl_2 (55 mL) at −78 °C under N_2 over 10 min with stirring. The stirring was continued for 3.5 h at −78 °C, whereupon the reaction was quenched with methanol (25 mL) and $NaHCO_3$ (6.0 g, 71.4 mmol). The reaction mixture was allowed to warm to room temperature and it was stirred for 4 h. The insoluble solid was filtered off using a short silica gel pad (3.5 g) that was washed with CH_2Cl_2−MeOH (2:1, 60 mL).

After removal of solvents, the residue was chromatographed on a silica gel column in EtOAc−MeOH (50:1) to give the *E*-isomer **9a** (64 mg, 38%), followed by *Z*-isomer **10a** (56 mg, 33%).

***E*-Isomer 9a:** Mp 243−245 °C. UV max λ_{max} 237 nm (ϵ 24 500), 280 (ϵ 8300). ^{1}H NMR (DMSO-d_6) δ 2.48 (overlapped with DMSO-d_5, $H_{4'}$), 3.69 (br s, 2H, $H_{5'}$), 5.21 (poorly resolved t, 1H, OH), 5.41 (dd, 1H, J = 70.8 and 6.0 Hz, $H_{3'}$), 7.42 (s, 2H, NH_2), 7.89 (br s, 1H, $H_{1'}$), 8.20 (s, 1H, H_2), 8.72 (s, 1H, H_8). ^{13}C NMR 27.3 (d, J = 14.1 Hz, $C_{4'}$), 58.2 ($C_{5'}$), 69.1 (d, J = 229.1 Hz, $C_{3'}$), 111.7, 116.5 ($C_{1'}$, $C_{2'}$), 119.2 (C_5), 138.5 (C_8), 149.1 (C_4), 154.0 (C_2), 156.8 (C_6). ^{19}F NMR −215.47 (d, J = 70.0 Hz). EI-MS 235 (M, 28.0), 218 (M − OH, 77.9), 205 (M − CH_2O, 24.9), 135 (adenine, 91.7), 136 (adenine + H, 100.0). EI−HRMS calcd for $C_{10}H_{10}FN_5O$, 235.0869; found, 235.0865. Anal. $C_{10}H_{10}FN_5O\cdot 0.1H_2O$ (C, H, N).

***Z*-Isomer 10a:** Mp 230−232 °C. UV λ_{max} 237 nm (ϵ 25 200), 280 (ϵ 8000). ^{1}H NMR (DMSO-d_6) δ 2.35−2.38 (br m, 1H, $H_{4'}$), 3.51 (m, 1H), 3.69 (poorly resolved td, 1H, $H_{5'}$), 5.03 (t, 1H, J = 5.2 Hz, OH), 5.61 (dd, 1H, J = 69.0 and 6.6 Hz, $H_{3'}$), 7.45 (s, 2H, NH_2), 7.55 (s, 1H, $H_{1'}$), 8.20 (s, 1H, H_2), 8.35 (s, 1H, H_8). ^{13}C NMR 26.3 (d, J = 14.2 Hz, $C_{4'}$), 58.1 ($C_{5'}$), 70.0 (d, J = 229.9 Hz, $C_{3'}$), 112.1, 114.9 (d, J = 3.2 Hz, $C_{1'}$, $C_{2'}$), 119.1 (C_5), 138.0 (C_8), 148.9 (C_4), 154.2 (C_2), 156.8 (C_6). ^{19}F NMR −215.45 (d, J = 70.0 Hz). EI-MS 235 (M, 8.4), 218 (M − OH, 100.0), 135 (adenine, 22.9), 136 (adenine + H, 48.0). EI-HRMS calcd for $C_{10}H_{10}FN_5O$, 235.0869; found, 235.0870. Anal. $C_{10}H_{10}FN_5O\cdot 0.1\ H_2O$ (C, H, N).

(*E*)-2-Amino-6-chloro-9-{[*cis*-(3-fluoro-2-hydroxymethyl)-cyclopropylidene]methyl}purine (9e) and (*Z*)-2-Amino-6-chloro-9-{[*cis*-(3-fluoro-2-hydroxymethyl)cyclopropylidene]-methyl}-purine (10e). A mixture of 2-amino-6-chloropurine (170 mg, 1.0 mmol), compound **23** (352 mg, 1.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (5 mL) was stirred at room temperature for 48 h and then at 100−105 °C for 45 min under N_2. The reaction mixture was worked up as described for the isomeric mixture **25a** + **26a**, but the elimination procedure was not repeated. The crude product was chromatographed in EtOAc−hexanes (1:1) to give the (*Z*,*E*)- isomeric mixture **25e** + **26e** (200 mg, 56%). Boron trichloride (1 M in CH_2Cl_2, 4.44 mL, 4.44 mmol) was added dropwise to a solution of compound **25e** + **26e** (200 mg, 0.56 mmol) in CH_2Cl_2 (40 mL) at −78 °C under N_2 over 10 min with stirring, which was continued for 5 h. The reaction was quenched with methanol (20 mL) and $NaHCO_3$ (4 g, 47.6 mmol). After 20 min, the mixture was allowed to warm to room temperature, and the stirring was continued for 4 h. The insoluble solid was filtered off using a silica gel pad (3.5 g), which washed with CH_2Cl_2−MeOH (2:1, 60 mL). The solvents were evaporated, and the residue was chromatographed in hexanes−EtOAc = 1.5:1 to 1:1 to give the faster moving *E*-isomer **9e** (70 mg, 46.5%), followed by *Z*-isomer **10e** (70 mg, 46.5%).

***E*-Isomer 9e:** Mp 209−211 °C. UV λ_{max} 239 nm (ϵ 26 300), 310 (ϵ 7400). ^{1}H NMR (DMSO-d_6) δ 2.44−2.48 (1H, $H_{4'}$, overlapped with DMSO-d_5), 3.66 (t, 2H, J = 6.0 Hz, $H_{5'}$), 5.15 (t, 1H, J = 5.4 Hz, OH), 5.41 (dd, 1H, J = 70.4, 6.4 Hz, $H_{3'}$), 7.10 (s, 2H, NH_2), 7.71 (s, 1H, $H_{1'}$), 8.66 (s, 1H, H_8). ^{13}C NMR 27.6 (d, J = 13.5 Hz, $C_{4'}$), 58.2 ($C_{5'}$), 69.1 (d, J = 229.1 Hz, $C_{3'}$), 112.5, 116.0 (2d, J = 2 Hz, $C_{1'}$, $C_{2'}$), 123.8 (C_5), 140.5 (C_8), 150.5 (C_4), 153.4 (C_2), 160.9 (C_6). ^{19}F NMR −215.58 (d, J = 71.9 Hz). EI-MS 269, 271 (M, 17.6, 6.1), 252, 254 (M − OH, 16.2, 5.6), 169, 171 (2-amino-6-chloropurine, 37.9, 21.4), 170, 172 (2-amino-6-chloropurine + H, 100.0, 31.5). EI-HRMS calcd for $C_{10}H_9{}^{35}ClFN_5O$, 269.0480; found, 269.0476.

***Z*-Isomer 10e:** Mp 193−195 °C. UV λ_{max} 239 nm (ϵ 27 200), 310 (ϵ 7200). ^{1}H NMR (DMSO-d_6) δ 2.35 (1H, poorly resolved dd, $H_{4'}$), 3.51 (dt, 1H, J = 11.6, 7.4 Hz, $H_{5'}$) and 3.66 (dt, 1H, J = 11.2, 5.6 Hz, $H_{5'}$), 5.0 (t, 1H, J = 5.8 Hz, OH), 5.62 (dd, 1H, J = 69.0, 6.6 Hz, $H_{3'}$), 7.12 (s, 2H, NH_2), 7.37 (s, 1H, $H_{1'}$), 8.31 (s, 1H, H_8). ^{13}C NMR 26.4 (d, J = 14.2 Hz, $C_{4'}$), 58.0 ($C_{5'}$), 70.0 (d, J = 229.8 Hz, $C_{3'}$), 113.0, 114.5 (d, J = 3.5 Hz, $C_{1'}$, $C_{2'}$), 123.8 (C_5), 140.2 (C_8), 150.6 (C_4), 153.2 (C_2), 161.0 (C_6). ^{19}F NMR −216.25 (d, J = 68.9 Hz). EI-MS 269, 271 (M, 14.9, 5.2), 252, 254 (M − OH, 14.9, 4.7), 169, 171 (2-amino-6-chloropurine, 39.0, 21.1), 170, 172 (2-amino-6-chloropurine + H, 100.0, 32.4). EI-HRMS calcd for $C_{10}H_9{}^{35}ClFN_5O$, 269.0480; found, 269.0484.

(*E*)-9-{[*cis*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]-methyl}guanine (9b). A solution of the *E*-isomer **9e** (90 mg, 0.33 mmol) in 80% HCO_2H (80%, 10 mL) was heated at 80 °C with stirring for 4 h. After cooling, formic acid and water were evaporated in vacuo, the crude product was dissolved in methanol (30 mL), and NH_3 (20% in methanol, 10 mL) was added at 0 °C. The reaction mixture was stirred for 4 h at 0 °C. The solvents were removed to give the *E*-isomer **9b** (80 mg, 95%), mp > 300 °C. UV λ_{max} 242 λ_{nm} (ϵ 26 300), 273 (ϵ 10 200). ^{1}H NMR (DMSO-d_6) δ 2.39 (m, 1H, $H_{4'}$), 3.65 (d, 2H, J = 5.6 Hz, $H_{5'}$), 5.16 (s, 1H, OH), 5.36 (dd, 1H, J = 71.2, 6.2 Hz, $H_{3'}$), 6.62 (s, 2H, NH_2), 7.58 (s, 1H, $H_{1'}$), 8.29 (s, 1H, H_8), 10.69 (br s, 1H, NH). ^{13}C NMR 27.1 (d, J = 14.2 Hz, $C_{4'}$), 58.1 ($C_{5'}$), 69.0 (d, J = 229.0 Hz, $C_{3'}$), 111.3 (d, J = 3.0 Hz), 116.2 (d, J = 2.2 Hz, $C_{1'}$, $C_{2'}$), 117.0 (C_5), 134.8 (C_8), 150.8 (C_4), 154.8 (C_2), 157.3 (C_6). ^{19}F NMR −215.43 (d, J = 71.9 Hz). ESI-MS (MeOH) 252 (M + H, 100.0). Anal. $C_{10}H_{10}FN_5O_2$ (C, H, N).

(*Z*)-9-{[*cis*-3-Fluoro-2-(hydroxymethyl)cyclopropylidene]-methyl}guanine (10b). The procedure described above for **9b** was performed with the *Z*-isomer **10e** (90 mg, 0.33 mmol) to give compound **10b** (80 mg, 95%), mp > 300 °C. UV λ_{max} (EtOH) 242 nm (ϵ 27 900), 274 (ϵ 10 800). ^{1}H NMR (DMSO-d_6) δ 2.31 (m, 1H, $H_{4'}$), 3.49 (dd, 1H, J = 10.8, 8.8 Hz), 3.65 (dd, 1H, J = 10.4, 5.6 Hz, $H_{5'}$), 4.99 (br s, 1H, OH), 5.58 (dd, 1H, J = 68.8, 5.6 Hz, $H_{3'}$), 6.67 (s, 2H, NH_2), 7.26 (s, 1H, $H_{1'}$), 7.91 (s, 1H, H_8), 10.88 (br s, 1H, NH). ^{13}C NMR 26.2 (d, J = 15.2 Hz, $C_{4'}$), 58.0 ($C_{5'}$), 69.0 (d, J = 231.7 Hz, $C_{3'}$), 111.8, 114.8 (d, J = 3.0 Hz, $C_{1'}$, $C_{2'}$), 117.1 (C_5), 134.3 (C_8), 150.6 (C_4), 155.0 (C_2), 157.3 (C_6). ^{19}F NMR −216.82 (d, J = 68.5 Hz). ESI-MS (MeOH − KOAc) 252 (M + H, 90.0), 290 (M + K, 100.0), 503 (2M + H, 33.0), 541 (2M + K, 50.0). Anal. $C_{10}H_{10}FN_5O_2$ (C, H, N).

Ethyl *t*-3-Fluoro-*t*-2-hydroxymethylcyclopropane-*r*-1-carboxylate (27). Boron trichloride (1.0 M in CH_2Cl_2, 40 mL, 40 mmol) was added dropwise with stirring to ester **15** (5.0 g, 19.8 mmol) in CH_2Cl_2 at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C, 15 min at 0 °C, it was then re-cooled to −78 °C, and $NaHCO_3$ (6.72 g, 80 mmol) was added. The reaction mixture was warmed to room temperature and it was stirred for 4 h. Water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (5 × 50 mL). The organic phase was dried over $MgSO_4$, solvent was evaporated, and the crude product was chromatographed on a silica gel column in hexanes/Et_2O = 10:1 to 3:1 to give ester **27** (2.66 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.4 Hz, CH_3), 1.85 (dd, 1H, J = 14.0, 7.6 Hz, H_2), 1.94 (ddd, 1H, J = 18.4, 6.4, 1.6 Hz, H_1), 2.79 (br s, 1H, OH), 3.84, 3.69 (J_{AB} = 11.8 Hz), 3.83, 3.71 (J_{AB} = 11.4 Hz, 2 overlapped AB's, 2H, CH_2OH), 4.08 (2q, 2H, J = 7.6 Hz, CH_2 of Et), 4.88 (ddd, 1H, J = 64.0, 6.4, 1.6 Hz, H_3). ^{13}C NMR 14.3 (CH_3 of Et), 24.9 (d, J = 12.7 Hz, C_1), 28.6 (d, J = 8.2 Hz, C_1, C_2), 58.6 (d, J = 9.0 Hz, CH_2OH), 61.4 (CH_2 of Et), 76.4 (d, J = 229.8 Hz, C_3), 171.0 (C=O). ^{19}F NMR −221.34 (ddd, J = 64.4, 18.3, 7.7 Hz). EI-MS 163 (M + H, 0.4), 145 (M − OH, 1.2), 131 (M − CH_2OH, 44.5), 73 (100.0). EI-HRMS calcd for $C_7H_{10}FO_2$ (M − OH), 145.0665; found, 145.0665. Anal. $C_7H_{10}FO_2$ (C, H).

Ethyl *t*-2-Fluoro-*t*-3-(2-nitrophenylselenenyl)cyclopropane-*r*-1-carboxylate (28). Tributylphosphine (2.49 g, 14.8 mmol) was added to a mixture of ester **27** (2.0 g, 12.33 mmol) and 2-nitrophenyl selenocyanate[18] (3.36 g, 14.8 mmol) in THF (40 mL) at room temperature with stirring, which was continued for 2 h. The solvent was evaporated, and the crude product was chromatographed on a silica gel column using hexanes/Et_2O (10:1 to 5:1) to give product **28** (3.93 g, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 1.91 (dd, 1H, J = 13.8, 6.6 Hz, H_2), 1.98 (ddd, 1H, J = 18.2, 5.6, 2.4 Hz, H_1), 3.06, 3.11 (J_{AB} = 12.2 Hz), 3.08, 3.14 (J_{AB} = 12.0 Hz, 2 overlapped AB, 2H, CH_2Se), 4.12 (2 overlapped q, 2H, J = 7.2 Hz, CH_2 of Et), 4.94 (ddd, 1H, J = 64.4, 6.4, 1.6 Hz, H_3), 7.33 (ddd, 1H, J = 8.0, 5.6, 2.4 Hz), 7.52 (br s, 1H), 7.54 (dd, 1H, J = 8.0, 1.6 Hz), 8.27 (d, 1H, J = 8.4 Hz, 2-NO_2Ph). ^{13}C NMR 14.4 (CH_3), 21.4 (d, J = 7.5 Hz, CH_2Se),

25.3 (d, $J = 8.2$ Hz), 28.0 (d, $J = 11.8$ Hz), 61.5 (CH_2 of Et), 76.8 (d, $J = 231.3$ Hz, C_3), 126.0, 126.8, 129.2, 133.0, 134.1 (2-NO_2-Ph), 170.3 (C═O). ^{19}F NMR −220.22 (ddd, $J = 64.0$, 18.1, 6.0 Hz). EI-MS 347 (M + H, 5.4), 346 (M, 1.4), 125 (100.0). EI-HRMS calcd for $C_{13}H_{14}FNO_4{}^{80}Se$, 347.0072; found, 347.0066.

***t*-3-Fluoro-*t*-2-(2-nitrophenylselenenylmethyl)cyclopropane-*r*-1-methanol (29).** DIBALH in hexane (1 M, 21.67 mL, 21.67 mmol) was added to a solution of ester **28** (3.0 g, 8.67 mmol) in hexane (30 mL) at 0 °C over a period of 10 min under N_2. The stirring was continued for 1 h. The reaction was quenched by a dropwise addition of HCl (5%, 50 mL) and then it was extracted with Et_2O (4 × 30 mL). The combined organic phase was washed successively with saturated $NaHCO_3$ (2 × 30 mL) and water (2 × 30 mL). The solvent was evaporated, and the crude product was chromatographed on a silica gel column using hexane/EtOAc (10:1 to 5:1) to give product **29** as a colorless oil (2.49 g, 95%). ^{1}H NMR ($CDCl_3$) δ 1.27 (ddd, 1H, $J = 13.6$, 6.8, 1.6 Hz, H_2), 1.44 (ddd, 1H, $J = 21.2$, 12.8, 6.4 Hz, H_1), 1.68 (br s, 1H, OH), 3.08, 3.12 ($J_{AB} = 11.6$ Hz), 3.06, 3.14 ($J_{AB} = 12.0$ Hz, 2 overlapped AB, 2H, CH_2Se), 3.51−3.60 (m, 2H, CH_2O), 4.65 (ddd, 1H, $J = 64.0$, 6.4, 2.4 Hz, H_3), 7.32 (ddd, 1H, $J = 8.0$, 5.6, 2.4 Hz), 7.54 (dd, 2H, $J = 8.0$, 1.6 Hz), 8.29 (d, 1H, $J = 8.8$ Hz, 2-NO_2Ph). ^{13}C NMR 19.8 (d, $J = 10.4$ Hz, C_1), 23.1 (d, $J = 7.5$ Hz, CH_2Se), 28.3 (d, $J = 9.0$ Hz, C_2), 61.8 (CH_2O), 76.0 (d, $J = 235.4$ Hz, C_3), 125.8, 126.7, 129.4, 134.0 (2-NO_2Ph). ^{19}F NMR −223.87 (ddd, $J = 64.0$, 21.5, 3.0 Hz). EI-MS 303 (M + H, 4.9), 186 (100.0). EI-HRMS calcd for $C_{11}H_{12}FNO_3{}^{78}Se$, 302.9974; found, 302.9966.

***r*-1-Benzyloxymethoxymethyl-*t*-2-fluoro-*t*-3-(2-nitrophenylselenenylmethyl)cyclopropane (30).** Sodium hydride (50%, 0.63 g, 13.1 mmol) was added to a solution of compound **29** (2.0 g, 6.6 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred for 5 h and then 1 h at room temperature. Benzyl bromide (2.57 g, 15 mmol) was added at 0 °C, the reaction mixture was slowly warmed to room temperature, and it was stirred for 16 h. The solvent was evaporated, and the crude product was chromatographed on a silica gel column in hexane/Et_2O (30:1 to 5:1) to give compound **30** (1.84 g, 71%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 1H, H_2), 1.46 (ddd, 1H, $J = 20.9$, 6.5, 2.5 Hz, H_1), 3.10 (d, 2H, $J = 7.6$ Hz, CH_2Se), 3.41 (poorly resolved dd, 1H, $J = 6.8$, 2.0 Hz, CH_2O), 4.51, 4.48 (AB, 2H, $J_{AB} = 11.8$ Hz, CH_2Ph), 4.63 (ddd, 1H, $J = 64.0$, 6.4, 2.4 Hz, H_3), 7.28−7.36 (m, 6H), 7.48−7.56 (m, 2H), 8.30 (dd, 1H, $J = 8.0$, 1.6 Hz, Ph + 2-NO_2Ph). ^{13}C NMR 20.0 (d, $J = 11.3$ Hz, C_1), 23.1 (d, $J = 6.6$ Hz, CH_2Se), 25.9 (d, $J = 9.8$ Hz, C_2), 68.6 (CH_2O), 72.9 (CH_2Ph), 76.3 (d partly overlapped with $CDCl_3$, $J = 240.0$ Hz, C_3), 125.7, 126.7, 127.8, 128.0, 128.7, 129.4, 133.9 (Ph + 2-NO_2Ph). ^{19}F NMR −223.69 (ddd, $J = 65.0$, 21.1, 4.5 Hz). EI-MS 395 (M, 0.29), 91 (100.0). EI-HRMS calcd for $C_{18}H_{18}FNO_3{}^{80}Se$, 395.0436; found, 395.0434.

***trans*-3-Benzyloxymethyl-2-fluoromethylenecyclopropane (31).** Hydrogen peroxide (30%, 1.6 mL, 15.66 mmol) was added dropwise to a solution of compound **30** (1.8 g, 4.58 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h and then 12 h at room temperature, whereupon it was partitioned between water (50 mL) and Et_2O (100 mL). The organic phase was washed with water (2 × 50 mL), $Na_2S_2O_3$ (5%, 2 × 20 mL), and $NaHCO_3$ (5%, 2 × 50 mL), it was dried over $MgSO_4$, and the solvent was evaporated. A solution of the crude product in toluene (25 mL) was heated at 80−85 °C for 6 h. The solvent was evaporated, and the residue was chromatographed on a silica gel column in hexanes/Et_2O (50:1) to give compound **31** (640 mg, 73%) as an oil. ^{1}H NMR ($CDCl_3$) δ 2.20−2.22 (m, 1H, H_2), 3.35−3.39 (poorly resolved dd, 1H), 3.37 (poorly resolved dd, 1H), 3.49 (m, 1H, CH_2O), 4.55 (s, 2H, $PhCH_2$), 4.76 (d, 1H, $J = 67.2$ Hz, H_3), 5.70, 5.92 (2s, 2H, CH_2═), 7.30−7.36 (m, 5H, Ph). ^{13}C NMR 25.0 (d, $J = 13.0$ Hz, C_2), 68.7 (CH_2O), 70.6 (d, $J = 230.3$ Hz, C_3), 72.8 ($PhCH_2$), 111.4 (CH_2═), 127.9, 128.0, 128.7, 131.8, 138.2 (C_1 + Ph). ^{19}F NMR −203.67 (dd, $J = 67.4$, 13.9 Hz). ESI-MS 215 (M + Na, 42.3), 91 ($PhCH_2$, 100.0).

***r*-2-Benzyloxymethyl-*c*,*t*-1-bromo-*c*,*t*-1-bromomethyl-*t*-fluorocyclopropane (32).** Pyridinium tribromide (2.0 g, 6.27 mmol) was added to a solution of compound **31** (600 mg, 3.13 mmol) in CH_2Cl_2 (15 mL) at −20 °C with stirring. The reaction mixture was warmed to room temperature, and the stirring was continued for 10 h. After removal of the solvent, the crude mixture was chromatographed on a silica gel column in hexanes/Et_2O (50:1 to 20:1) to give product **32** (910 mg, 83%). ^{1}H NMR ($CDCl_3$) δ 1.73, 2.21 (2m, 1H, H_1), 3.58−3.72 (m, 2H, CH_2Br), 3.76−3.97 (m, 2H, CH_2O), 4.45 (dd, $J = 63.8$, 4.1 Hz), 4.82 (dd, $J = 63.0$, 3.6 Hz, 1H, H_3), 4.51, 4.52, 4.59 (3s, 2H, CH_2Ph), 7.33−7.40 (m, 5H, Ph). ^{13}C NMR 33.2, 35.8 (2d, $J = 11.1$, 10.0 Hz, C_2), 38.0−38.1 (2 overlapped d, CH_2Br), 38.5, 40.3 (2d, $J = 10.1$ Hz, C_1), 64.37, 68.90, 73.2, 73.5 (CH_2O), 76.1, 81.3 (2d, $J = 241.7$, 243.7 Hz, C_3), 77.0, 77.4, 77.8 (CH_2Ph), 128.1, 128.14, 128.3, 128.8, 128.85, 137.5, 138.0 (Ph). ^{19}F NMR −201.56 (dd, $J = 64.0$, 20.0 Hz), −207.76 (dd, $J = 62.9$, 22.8 Hz). ESI-MS 373, 375, 377 (M + Na, 49.0, 100.0, 48.0).

***c*,*t*-9-{[*c*,*t*-1-Bromo-*t*-3-fluoro-*r*-2-(benzyloxymethyl)cyclopropyl]methyl}adenine (33a).** A mixture of K_2CO_3 (280 mg, 2.22 mmol), adenine (50 mg, 0.37 mmol), and compound **32** (120 mg, 0.34 mmol) was stirred in DMF (2.0 mL) at room temperature for 8 h and at 40 °C for 2 h under N_2. The insoluble solid was filtered off, and DMF was evaporated in vacuo. The residue was chromatographed on a silica gel column using EtOAc−MeOH (100:0 to 20:1) to give compound **33a** (0.12 g, 86%), mp 112−115 °C. UV λ_{max} 261 nm (ϵ 11 700), 203 (ϵ 23 400). ^{1}H NMR ($CDCl_3$) δ 2.19−2.33 (1H, m, $H_{4'}$), 3.46−3.51, 3.57−3.67 (2m, 2H, $H_{5'}$), 4.43−5.00 (overlapped m, 5H, CH_2Ph, $H_{1'}$, $H_{3'}$), 5.84 (s, 2H, NH_2), 7.21−7.34 (m, 5H, Ph), 8.03, 8.06, 8.33 and 8.37 (4s, 1H, H_2, H_8). ^{19}F NMR −203.35 (ddd, $J = 64.0$, 19.6, 4.5 Hz), −206.81 (dd, $J = 62.5$, 23.0 Hz). ESI-MS 406, 408 (M + H, 94.0, 100.0), 428, 430 (M + Na, 24.3, 27.3).

(*E*)-{[*trans*-(3-Fluoro-2-benzyloxymethyl)cyclopropylidene]methyl}adenine (34a) and (*Z*)-{[*trans*-(3-Fluoro-2-benzyloxymethyl)cyclopropylidene]methyl}adenine (35a). A mixture of compound **33a** (0.40 g, 0.98 mmol) and K_2CO_3 (410 mg, 3 mmol) in DMF (5 mL) was stirred for 55 min at 100 °C. The mixture was cooled to 0 °C, and the insoluble portion was filtered off using a silica gel (3.5 g) pad that was washed with DMF (10 mL). The solvent was evaporated, and the residue was chromatographed on a silica gel column using hexanes/EtOAc (1:4 to 100% EtOAc) to give the *E*,*Z*-isomeric mixture **34a** + **35a** (50 mg, 16%), followed by starting material **33a** (260 mg, 59%). The latter was subjected to another two cycles of elimination and chromatography to give **34a** + **35a** (105 mg, 33%). The isomeric mixture **34a** + **35a** (390 mg, 1.2 mmol, *E*/*Z* = 1.5:1) combined from several experiments was chromatographed on silica gel using hexanes−EtOAc = 1:1 to 1:2 to 100% EtOAc to give the faster moving *E*-isomer **34a** (220 mg, 56%), followed by the *Z*-isomer **35a** (150 mg, 38%).

***E*-Isomer 34a:** Mp 173−175 °C. UV λ_{max} 280 nm (ϵ 9500), 238 (ϵ 26 600). ^{1}H NMR ($CDCl_3$) δ 2.62 (m, 1H, $H_{4'}$), 3.30 (t, 1H, $J = 9.2$ Hz), 3.91 (dd, 1H, $J = 9.6$, 5.6 Hz, $H_{5'}$), 4.55 (s, 2H, CH_2-Ph), 4.97 (d, 1H, $J = 68.8$ Hz, $H_{3'}$), 6.08 (s, 2H, NH_2), 7.26−7.33 (m, 5H, Ph), 7.99 (s, 1H, $H_{1'}$), 8.38, 8.76 (2s, 2H, H_2, H_8). ^{13}C NMR ($CDCl_3$) δ 26.6 (d, $J = 13.4$ Hz, $C_{4'}$), 68.8 (d, $J = 234.3$ Hz, $C_{3'}$), 68.9 (d, $J = 3.7$ Hz, $C_{5'}$), 73.6 (CH_2Ph), 111.4 (d, $J = 4.4$ Hz), 117.0 (d, $J = 3.7$ Hz, $C_{1'}$, $C_{2'}$), 119.6 (C_5), 128.0, 128.3, 128.8, 137.5 (Ph), 138.3 (C_8), 149.3 (C_4), 153.7 (C_2), 155.8 (C_6). ^{19}F NMR −201.70 (dd, $J = 68.9$, 10.5 Hz). ESI-MS 326 (M + H, 100.0), 348 (M + Na, 31.6).

***Z*-Isomer 35a:** Mp 159−162 °C. UV λ_{max} 279 nm (ϵ 10 000), 237 (ϵ 29 400). ^{1}H NMR ($CDCl_3$) δ 2.58 (m, 1H, $H_{4'}$), 3.49 (poorly resolved dd, 1H), 3.60 (m, 1H, $H_{5'}$), 4.56 (s, 2H, CH_2Ph), 5.09 (d, 1H, $J = 68.0$ Hz, $H_{3'}$), 6.11 (s, 2H, NH_2), 7.29−7.34 (m, 5H, phenyl), 7.63 (s, 1H, $H_{1'}$), 8.19, 8.38 (2s, 2H, H_2, H_8). ^{13}C NMR 25.2 (d, $J = 12.7$ Hz, $C_{4'}$), 68.1 (d, $J = 3.7$ Hz, $C_{5'}$), 70.0 (d, $J = 229.8$ Hz, $C_{3'}$), 73.2 (CH_2Ph), 111.9, 116.1 ($C_{1'}$, $C_{2'}$), 119.6 (C_5), 128.0, 128.2, 128.8, 137.8 (Ph), 138.0 (C_8), 149.0 (C_4), 153.9 (C_2), 155.8 (C_6). ^{19}F NMR −202.17 (dd, $J = 68.3$, 10.0 Hz). ESI-MS 326 (M + H, 100.0), 348 (M + Na, 48.2).

(*E*)-{[*trans*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]methyl}adenine (11a). A solution of BCl_3·SMe_2 complex in CH_2Cl_2 (2.0 M, 1.37 mL, 2.74 mmol) was added dropwise to a solution

of compound **34a** (150 mg, 0.46 mmol) in CH_2Cl_2 (10 mL) at room temperature with stirring, which was continued for 5 h. The reaction was quenched by adding $NaHCO_3$ (4.0 g, 47.6 mmol) and methanol (15 mL) at −78 °C and then it was stirred for 2 h at room temperature. The insoluble solid was filtered off through a silica gel (2.5 g) pad, and it was washed with CH_2Cl_2−MeOH (2:1, 50 mL). The filtrate was concentrated, and the residue was chromatographed on a silica gel column to give product **11a** (80 mg, 74%), mp 218−220 °C. UV λ_{max} 280 nm (ϵ 11 000), 237 (ϵ 32 600). ^{1}H NMR (DMSO-d_6) δ 2.60−263 (m, 1H, $H_{4'}$), 3.48, 3.67 (2m, $H_{5'}$), 5.17 (t, 1H, J = 5.6 Hz, OH), 5.21 (d, 1H, J = 70.4 Hz, $H_{3'}$), 7.41 (s, 2H, NH_2), 7.93 (s, 1H, $H_{1'}$), 8.19 (s, 1H, H_2), 8.71 (s, 1H, H_8). ^{13}C NMR 29.5 (d, J = 11.2 Hz, $C_{4'}$), 60.2 (d, J = 3.7 Hz, $C_{5'}$), 70.0 (d, J = 229.8 Hz, $C_{3'}$), 112.5 (d, J = 2.9 Hz), 116.8 (d, J = 3.7 Hz, $C_{1'}$, $C_{2'}$), 119.2 (C_5), 138.4 (C_8), 149.1 (C_4), 154.0 (C_2), 156.8 (C_6). ^{19}F NMR −200.81 (dd, J = 70.2, 12.2). EI-MS 235 (M, 14.9), 218 (M − OH, 100.0), 136 (Ade + H, 48.4), 135 (Ade, 36.0). EI-HRMS calcd for $C_{10}H_{10}N_5FO$, 235.0869; found, 235.0871. Anal. $C_{10}H_{10}FN_5O$ (C, H, N).

(*Z*)-{[*trans*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]methyl}adenine (12a). The procedure described above for the *E*-isomer **11a** was repeated with the *Z*-isomer **35a** to give compound **12a** (85 mg, 79%), mp 239−242 °C. UV λ_{max} 280 nm (ϵ 11 300), 237 (ϵ 31 100). ^{1}H NMR (DMSO-d_6) δ 2.42−2.45 (m, 1H, $H_{4'}$), 3.37 (poorly resolved dd, 1H), 3.51−3.54 (m, 1H, $H_{5'}$), 5.02 (br s, 1H, OH), 5.36 (d, 1H, J = 68.8 Hz, $H_{3'}$), 7.44 (s, 2H, NH_2), 7.58 (s, 1H, $H_{1'}$), 8.21 (s, 1H, H_2), 8.34 (s, 1H, H_8). ^{13}C NMR 27.6 (d, J = 11.1 Hz, $C_{4'}$), 60.3 (d, J = 4.4 Hz, $C_{5'}$), 70.8 (d, J = 229.8 Hz, $C_{3'}$), 112.7 (d, J = 2.2 Hz), 115.7 (d, J = 2.3 Hz, $C_{1'}$, $C_{2'}$), 119.2 (C_5), 138.1 (C_8), 148.9 (C_4), 154.0 (C_2), 156.7 (C_6). ^{19}F NMR −201.15 (dd, J = 68.9, 10.9 Hz). EI-MS 235 (M, 17.1), 218 (M − OH, 100.0), 136 (adenine + H, 37.7), 135 (adenine, 28.1). EI-HRMS calcd for $C_{10}H_{10}N_5FO$, 235.0869; found, 235.0871. Anal. $C_{10}H_{10}FN_5O$ (C, H, N).

2-Amino-6-chloro-*c*,*t*-9-{[*c*,*t*-1-bromo-*t*-3-fluoro-*r*-2-(benzyloxymethyl)cyclopropyl]methyl}purine (33e). A mixture of 2-amino-6-chloropurine (580 mg, 3.43 mmol), compound **32** (1.2 g, 3.41 mmol) in DMF (20 mL), and K_2CO_3 (1.4 g, 10.1 mmol) was stirred for 5 h at 40 °C under N_2. The insoluble solid was filtered off using a short silica gel pad, which was washed with DMF (100 mL). The solvent was evaporated in vacuo at room temperature, and the residue was chromatographed on a silica gel column in hexanes−EtOAc (3:1 to 2:1) to give compound **33e** (1.30 g, 87%), mp 75−79 °C. UV λ_{max} 311 nm (ϵ 10 700), 244 (ϵ 11 100), 223 (ϵ 34 700). ^{1}H NMR ($CDCl_3$) δ 2.14−2.27 (cluster of m, 1H, $H_{4'}$), 3.46, 3.65 and 3.90 (3m, 2H, $H_{5'}$), 4.42−4.57 (s and m), 4.69−4.91 (m, 5H, $H_{1'}$, $H_{3'}$, CH_2Ph), 5.16, 5.24 (2s, 2H, NH_2), 7.21−7.37 (2m, 5H, Ph), 7.98, 8.00 (2s, 1H, H_8). ^{19}F NMR −203.69 (dd, J = 64.0, 20.0 Hz), −206.74 (dd, J = 62.5, 24.5 Hz). ESI-MS 440, 442, 444 (M + H, 76.9, 100.0, 24.3), 462, 464, 466 (M + Na, 65.7, 87.6, 18.3).

(*E*)-2-Amino-6-chloro-9-{[*trans*-(3-fluoro-2-(benzyloxymethyl)cyclopropylidene]methyl}purine (34e) and (*Z*)-2-Amino-6-chloro-9-{[*trans*-(3-fluoro-2-benzyloxymethyl)-cyclopropylidene]methyl}-purine (35e). A mixture of compound **33e** (700 mg, 1.59 mmol) and K_2CO_3 (660 mg, 4.78 mmol) in DMF (8 mL) was stirred for 45 min at 100 °C. After the workup (see **33e**), the crude product was chromatographed on a silica gel column using hexanes−EtOAc (3:1 to 2:1) to give the *E*-isomer **34e** (70 mg, 18%) followed by *Z*-isomer **35e** (110 mg, 29%) and unreacted starting material **33e** (230 mg, 33%).

***E*-Isomer 34e:** Mp 93−95 °C. UV λ_{max} 307 nm (ϵ 9000), 226 (ϵ 25 800). ^{1}H NMR ($CDCl_3$) δ 2.59−2.61 (m, 1H, $H_{4'}$), 3.20 (t, 1H, J = 9.0 Hz, $H_{5'}$), 3.87 (dd, 1H, J = 10.0, 1.6 Hz, H_5), 4.55 (s, 2H, CH_2Ph), 4.94 (d, J = 68.8 Hz, $H_{3'}$), 5.24 (s, 2H, NH_2), 7.26−7.34 (m, 5H, phenyl), 7.81 (s, 1H, $H_{1'}$), 8.73 (s, 1H, H_8). ^{13}C NMR 26.7 (d, J = 12.7 Hz, $C_{4'}$), 68.5 (d, J = 3.0 Hz, $C_{5'}$), 68.8 (d, J = 235.1 Hz, $C_{3'}$), 73.5 (CH_2Ph), 111.7 (d, J = 3.7 Hz), 116.5 (d, J = 2.9 Hz, $C_{1'}$, $C_{2'}$), 125.5 (C_5), 128.1, 128.3, 128.8, 137.4 (Ph), 139.9 (C_8), 151.8 (C_4), 152.8 (C_2), 159.6 (C_6). ^{19}F NMR −201.82 (dd, J = 68.5, 12.1 Hz). ESI-MS 360, 362 (M + H, 54,2, 29.2), 382, 384 (M + Na, 100.0, 32.7), 741, 743 (2M + Na, 49.4, 35.7).

***Z*-Isomer 35e:** Mp 99−101 °C. UV λ_{max} 307 nm (ϵ 8500), 226 (ϵ 24 300). ^{1}H NMR ($CDCl_3$) δ 2.54−2.60 (m, 1H, $H_{4'}$), 3.50−3.60 (m, 2H, $H_{5'}$), 4.56 (s, 2H, CH_2Ph), 5.07 (d, J = 68.4 Hz, $H_{3'}$), 5.21 (s, 2H, NH_2), 7.30−7.38 (m, 5H, phenyl), 7.45 (s, 1H, $H_{1'}$), 8.12 (s, 1H, H_8). ^{13}C NMR 25.2 (d, J = 12.7 Hz, $C_{4'}$), 68.1 (d, J = 4.5 Hz, $C_{5'}$), 69.9 (d, J = 235.7 Hz, $C_{3'}$), 73.2 (CH_2Ph), 112.2 (d, J = 2.2 Hz), 115.6 (d, J = 2.9 Hz, $C_{1'}$, $C_{2'}$), 125.5 (C_5), 128.0, 128.2, 128.8, 137.8 (Ph), 139.5 (C_8), 152.0 (C_4), 152.5 (C_2), 159.7 (C_6). ^{19}F NMR −202.05 (dd, J = 65.5, 12.2 Hz). ESI-MS 360, 362 (M + H, 54.2, 28.6), 382, 384 (M + Na, 100.0, 32.7), 741, 743 (2M + Na, 49.1, 35.7).

(*E*)-2-Amino-6-chloro-9-{[*trans*-(3-fluoro-2-hydroxymethyl)-cyclopropylidene]methyl}purine (11e). The procedure described for adenine analogue **11a** was followed with the *E*-isomer **34e** (200 mg, 0.56 mmol) to give compound **11e** (110 mg, 74%), mp 209−211 °C. UV λ_{max} 311 nm (ϵ 8300), 239 (ϵ 29 400). ^{1}H NMR (DMSO-d_6) δ 2.60−2.66 (m, 1H, $H_{4'}$), 3.42−3.48 (m, 1H), 3.63−3.69 (m, 1H, $H_{5'}$), 5.11 (t partly overlapped with $H_{3'}$, 1H, J = 5.6 Hz, OH), 5.20 (d, 1H, J = 71.2 Hz, $H_{3'}$), 7.10 (s, 2H, NH_2), 7.74 (s, 1H, $H_{1'}$), 8.67 (s, 1H, H_8). ^{13}C NMR 29.6 (d, J = 11.9 Hz, $C_{4'}$), 60.1 (d, J = 3.8 Hz, $C_{5'}$), 70.0 (d, J = 229.1 Hz, $C_{3'}$), 113.2 (d, J = 3.7 Hz), 116.3 (d, J = 3.0 Hz, $C_{1'}$, $C_{2'}$), 123.8 (C_5), 140.5 (C_8), 150.5 (C_4), 153.4 (C_2), 160.9 (C_6). ^{19}F NMR −201.13 (dd, J = 68.9, 12.4 Hz). ESI-MS 270, 272 (M + H, 100.0, 31.0), 292, 294 (M + Na, 50.0, 15.2).

(*Z*)-2-Amino-6-chloro-9-{[*trans*-(3-fluoro-2-hydroxymethyl-cyclopropylidene]methyl}purine (12e). The procedure described for compound **11a** was performed with the *Z*-isomer **35e** (360 mg, 1.0 mmol) to give **12e** (200 mg, 74%), mp 201−203 °C. UV λ_{max} 311 nm (ϵ 7900), 239 (ϵ 28 700). ^{1}H NMR (DMSO-d_6) δ 2.40−2.46 (m, 1H, $H_{4'}$), 3.34−3.40 (overlapped with water), 3.47−3.53 (m, 1H, $H_{5'}$), 5.01 (t, 1H, J = 5.8 Hz, OH), 5.36 (d, 1H, J = 67.2 Hz, $H_{3'}$), 7.11 (s, 2H, NH_2), 7.40 (s, 1H, $H_{1'}$), 8.28 (s, 1H, H_8). ^{13}C NMR 27.7 (d, J = 11.2 Hz, $C_{4'}$), 60.2 (d, J = 4.4 Hz, $C_{5'}$), 70.9 (d, J = 229.8 Hz, $C_{3'}$), 113.5 (d, J = 2.2 Hz), 115.3 (d, J = 2.2 Hz, $C_{1'}$, $C_{2'}$), 123.8 (C_5), 140.1 (C_8), 150.6 (C_4), 153.1 (C_2), 161.0 (C_6). ^{19}F NMR −200.70 (dd, J = 68.9, 12.4 Hz). ESI-MS 270, 272 (M + H, 100.0, 3.6), 292, 294 (M + Na, 50, 15.8).

(*E*)-9-{[(*trans*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]-methyl}guanine (11b). The procedure described for compound **9b** was followed using the *E*-isomer **11e** (120 mg, 0.45 mmol) to give guanine analogue **11b** (82 mg, 73%), mp > 300 °C. UV λ_{max} 273 nm (ϵ 10 200), 242 (ϵ 26 300). ^{1}H NMR (DMSO-d_6) δ 2.48−2.53 (m, 1H, $H_{4'}$), 3.61−3.65 (m overlapped with H_2O, $H_{5'}$), 5.16 (t overlapped with $H_{3'}$, 1H, OH), 5.35 (d, 1H, J = 68.2 Hz, $H_{3'}$), 6.59 (s, 2H, NH_2), 7.61 (s, 1H, $H_{1'}$), 8.28 (s, 1H, H_8), 10.69 (br s, 1H, NH). ^{13}C NMR 29.3 (d, J = 11.2 Hz, $C_{4'}$), 60.1 (d, J = 3.7 Hz, C_5), 69.9 (d, J = 229.9 Hz, $C_{3'}$), 112.2 (d, J = 3.7 Hz), 116.5 (d, J = 2.9 Hz, $C_{1'}$, $C_{2'}$), 117.1 (C_5), 134.8 (C_8), 150.8 (C_4), 154.8 (C_2), 157.3 (C_6). ^{19}F NMR −200.84 (dd, J = 70.2, 10.7 Hz). ESI-MS (MeOH − KOAc) 252 (M + H, 100.0), 290 (M + K, 20.9), 503 (2M + H, 16.1), 541 (2M + K, 6.0). Anal. $C_{10}H_{10}FN_5O_2$ (C, H, N).

(*Z*)-9-{[(*trans*-(3-Fluoro-2-hydroxymethyl)cyclopropylidene]-methyl}guanine (12b). Procedure described for compound **9b** was followed with the *Z*-isomer **12e** (200 mg, 0.74 mmol) to give *E*-isomer **12b** (140 mg, 75.5%), mp > 300 °C. UV λ_{max} 274 nm (ϵ 9900), 241 nm (ϵ 26 000). ^{1}H NMR (DMSO-d_6) δ 2.36−2.40 (m, 1H, $H_{4'}$), 3.46−3.53 (m, 1H), 3.64−3.66 (m, 1H, $H_{5'}$), 4.96 (t, 1H, 5.2 Hz, OH), 5.32 (d, 1H, J = 68.0 Hz, $H_{3'}$), 6.88 (s, 2H, NH_2), 7.29 (s, 1H, $H_{1'}$), 7.86 (s, 1H, H_8), 10.74 (s, 1H, NH). ^{13}C NMR 27.5 (d, J = 11.2 Hz, $C_{4'}$), 60.2 (d, J = 4.4 Hz, $C_{5'}$), 70.8 (d, J = 229.9 Hz, $C_{3'}$), 112.3 (d, J = 1.5 Hz), 115.6 (d, J = 2.3 Hz, $C_{1'}$, $C_{2'}$), C_5 (117.0), 134.2 (C_8), 150.6 (C_4), 155.2 (C_2), 157.2 (C_6). ^{19}F NMR −201.23 (dd, J = 67.9, 11.5 Hz). ESI-MS (MeOH + KOAc) 252 (M + H, 100.0), 290 (M + K, 11.9), 503 (2M + H, 11.3), 541 (2M + K, 3.0). Anal. $C_{10}H_{10}FN_5O_2$ (C, H, N).

Antiviral Assays. The antiviral assays were performed as described previously.[11] The HCMV assays were performed with Towne and AD169 strains of the virus in HFF culture by plaque

reduction or cytopathic effect (CPE) inhibition assay. The HSV-1 was run in BSC-1 cells by ELISA. In addition, HSV-1 and HSV-2 assays were performed in HFF (CPE inhibition) and Vero cells (plaque reduction). The EBV assays were run in Daudi culture (viral capsid antigen, VCA-ELISA) and in H-1 culture (DNA hybridization). The VZV was assayed in HFF cells (CPE inhibition or plaque reduction), HIV-1 in MT-2 cells (CPE inhibition), and HBV in 2.2.15 cells. The cytotoxicity assays were performed in HFF, KB, or CEM cells. The results are summarized in Tables 3 and 4.

Adenosine Deaminase (ADA) Assay.[11] Compounds **9a**, **10a**, **11a**, and **12a** (2.0−2.4 μmol) were incubated with ADA (1.1 unit/mL) in 0.05 M Na_2HPO_4 (pH 7.5, 0.47−0.54 mL). Aliquots were periodically withdrawn and examined by TLC in CH_2Cl_2−MeOH (9:1, multiple development, **10a**, **11a**) and EtOAc−MeOH (10:1, multiple development, **9a**, **12a**). The extent of deamination of **9a**, **10a**, and **11a** was approximately 50% after 24 and 48 h, whereas **12a** was not deaminated after 48 h.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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