Nucleic Acid Related Compounds. 101. *S*-Adenosyl-L-homocysteine Hydrolase Does Not Hydrate (5′-Fluoro)vinyl or (6′-Halo)homovinyl Analogues Derived from 3′-Deoxyadenosine or 3′-(Chloro or Fluoro)-3′-deoxyadenosine[1]

Morris J. Robins,*[,†] Vladimir Neschadimenko,[†] Bong-Oh Ro,[†,‡] Chong-Sheng Yuan,[§] Ronald T. Borchardt,[§] and Stanislaw F. Wnuk*[,†,⊥]

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700, and Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas

Received September 16, 1997

S-Adenosyl-L-homocysteine (AdoHcy) hydrolase is crucial for the maintenance of biomethylation. The usual mechanistic sequence involves oxidation of AdoHcy at C3′ followed by elimination of L-homocysteine, Michael addition of water, and reduction to give adenosine. A 6′-fluorohomovinyladenosine analogue (EDDFHA) undergoes hydration of the 5′,6′ double bond (hydrolytic activity) at a more rapid rate than oxidation at C3′. Three 4′,5′-didehydro-5′-deoxy-5′-fluoro nucleoside analogues were prepared from 3′-deoxy- and 3′-(chloro and fluoro)-3′-deoxyadenosine via generation of the vinyl fluorides by thermolysis of 5′-fluoro-5′-thioether sulfoxides. The 3′-deoxy analogues of 6′-halohomovinyladenosines were prepared by Wittig extension with a 3′-deoxy-5′-carboxaldehyde and halodestannylation of vinyl stannanes. The 3′-hydroxyl group appears to be essential for binding to AdoHcy hydrolase. No hydrolytic activity at C5′ or C6′ was observed with the nonoxidizable 3′-deoxy or 3′-(chloro or fluoro) analogues in contrast with their 3′-hydroxy counterparts (ZDDFA and EDDFHA). These 3′-modified analogues cannot reduce enzyme-bound NAD^+ to NADH and do not produce time-dependent inhibition of AdoHcy hydrolase, but are weak competitive inhibitors (K_i = 150−200 μM).

Introduction

The cellular enzyme *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase; EC 3.3.1.1) effects hydrolytic cleavage of AdoHcy to give adenosine and L-homocysteine. AdoHcy is a potent feedback inhibitor of crucial transmethylation enzymes, and the alteration of cellular AdoMet/AdoHcy ratios results in serious perturbation of biological methylation of viral RNA and various cellular substrates. Therefore, the design of inhibitors of AdoHcy hydrolase represents a rational strategy for mechanism-based antiviral and anticancer chemotherapy.[2]

Palmer and Abeles investigated the mechanism of AdoHcy hydrolase (Figure 1) and also discovered that 4′,5′-didehydro-5′-deoxyadenosine **A** (Figure 2) functioned as an alternative substrate.[3] The vinyl fluoride[4,5] **B** (ZDDFA) and chloride[6] **C** analogues were prepared and found to be potent mechanism-based inhibitors of the enzyme. The fluoromethylene compound **B** has been shown to have significant biological activity,[4] but its mechanism of inactivation of AdoHcy hydrolase involves its conversion to the (4′-epimeric) adenosine-5′-carboxaldehyde **D**. It was demonstrated that release of fluoride anion from **B** could be effected by the "hydrolytic activity" of this enzyme that was independent of its oxidative activity.[7] The adenosine-5′-carboxaldehyde **D** was synthesized and shown to be an equally potent inhibitor of

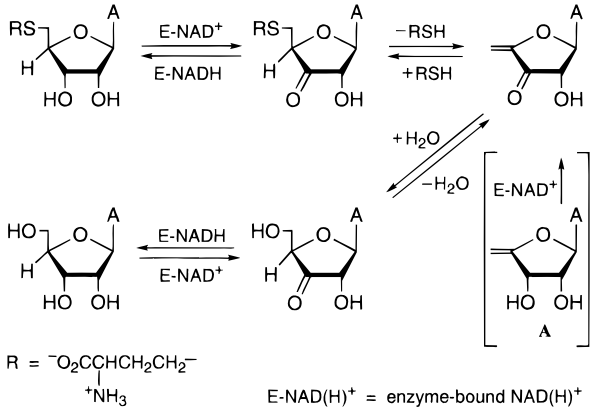


Figure 1. Proposed mechanism for *S*-adenosyl-L-homocysteine hydrolase.

* To whom correspondence should be addressed at Brigham Young University. Fax: (801) 378-5474.

† Brigham Young University.

‡ Sabbatical leave from Chosun University, Kwangju City, Korea.

§ University of Kansas.

⊥ Current address: Department of Chemistry, Florida International University, Miami, FL.

(1) Part 100: Robins, M. J.; Sarker, S.; Wnuk, S. F. *Nucleosides Nucleotides*, in press.

(2) (a) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223−253. (b) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521−1530. (c) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 41−88.

(3) Palmer, J. L.; Abeles, R. H. *J. Biol. Chem.* **1979**, *254*, 1217−1226.

(4) (a) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127−1128. (b) Jarvi, E. T.; McCarthy, J. R.; Mehdi, S.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Sunkara, P. S.; Bey, P. *J. Med. Chem.* **1991**, *34*, 647−656.

(5) Robins, M. J.; Wnuk, S. F.; Mullah, K. B.; Dalley, N. K.; Yuan, C.-S.; Lee, Y.; Borchardt, R. T. *J. Org. Chem.* **1994**, *59*, 544−555.

(6) Wnuk, S. F.; Dalley, N. K.; Robins, M. J. *J. Org. Chem.* **1993**, *58*, 111−117.

(7) Yuan, C.-S.; Yeh, J.; Liu, S.; Borchardt, R. T. *J. Biol. Chem.* **1993**, *268*, 17030−17037.

S0022-3263(97)01741-6 CCC: $15.00
Published on Web 01/23/1998

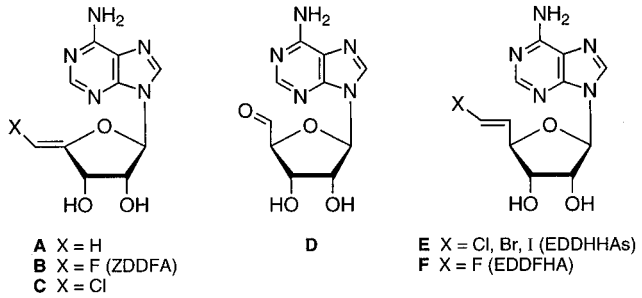


Figure 2.

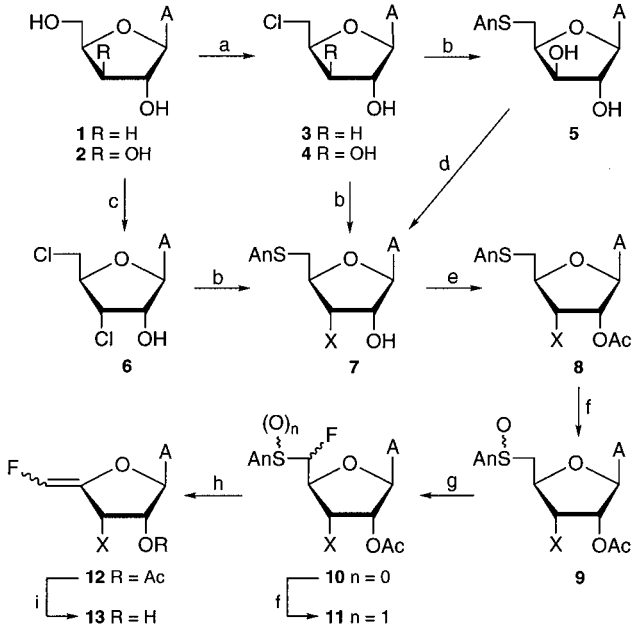
AdoHcy hydrolase.[8] The synthetic precursor 5′-*S*-aryl-5′-fluoro-5′-thioadenosines were found to undergo spontaneous hydrolysis in aqueous buffers to give **D** and cause time-dependent enzyme inactivation.[5] We then investigated oxime derivatives[9] of **D**, which were enzymatically converted into **D** with concomitant inhibition of AdoHcy hydrolase[9b] and accompanying cancer cell cytotoxicity and antiviral activity.[9a]

We had demonstrated that the (*E*)-5′,6′-didehydro-6′-deoxy-6′-halohomoadenosines[10a] **E** (EDDHHAs), and especially the homovinyl fluoride[10b] **F** (EDDFHA), could undergo addition of water at C5′ and C6′ by AdoHcy hydrolase (hydrolytic activity) without prior oxidation at C3′.[11] In contrast with these results,[10] and the enzymatic hydrolysis of oximes,[9] amide and ester derivatives of adenosine-5′-carboxylic acid underwent oxidation at C3′ by AdoHcy hydrolase (type I, NAD^+ cofactor-depletion inhibitors[2b]) without observed hydrolysis to the carboxylic acid.[12] We now report analogues of ZDDFA and EDDHHAs that do not contain the 3′-hydroxyl group (which is oxidized to give 3′-keto intermediates) and their interaction with AdoHcy hydrolase. The 3′-deoxy analogues have major differences in stereoelectronic effects and lack a hydrogen-bond acceptor at C3′. In two other series, the 3′-hydroxyl group was replaced with fluoro or chloro functions to give closer similarities with the natural hydroxy substituent, but still preclude substrate oxidation at C3′. If addition of water to these modified halovinyl nucleoside analogues were executed by AdoHcy hydrolase, more detailed investigations of the uncoupled "hydrolytic activity" function of the enzyme could be pursued with such "half-substrate" analogues.

Chemistry

The somewhat unstable 3′-deoxyZDDFA **13a**(*Z*) and its *E* isomer were prepared in low yields from 3′-deoxyadenosine (**1**; Scheme 1) with procedures that were developed for ZDDFA.[4,5] Thus, **1**[13] was converted into 5′-chloro-3′,5′-dideoxyadenosine **3** ($SOCl_2$/HMPA)[14] which was treated with AnSH/NaH/DMF[15] to give the 4-methoxyphenyl thioether **7a** (~70% from **1**). Acetylation of **7a** and oxidation of **8a** (1 equiv of *m*-CPBA) gave the sulfoxides **9a** [$(R/S)_S$ ~1:1], which were treated with (diethylamino)sulfur trifluoride (DAST)/$SbCl_3$[16a] to give the 2′-*O*-acetyl-3′-deoxy-5′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thioadenosines (**10a**, 54%). The ratio of fluoro diastereomers of **10a** (5′*R*/*S*, ~3:2) was inverted relative to that in the adenosine series (5′*R*/*S*, ~2:3)[5] with the analogous fluorination. Oxidation of **10a** gave the α-fluoro sulfoxides **11a** (four diastereomers, ^{19}F NMR). Thermolysis of **11a** (Hünig's base/diglyme) and deacetylation gave **13a** (*E* and *Z*) in low yields after repeated chromatography.

Scheme 1[a]



An = 4-MeOC$_6$H$_4$–; **7–13**: series a: X = H, b: X = F, c: X = Cl.

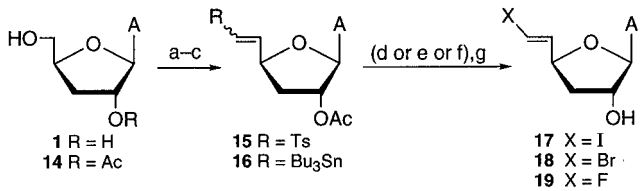
[a] Key: (a) $SOCl_2$/HMPA/6 h; (b) AnSH/NaH/DMF; (c) $SOCl_2$/HMPA/10 days; (d) DAST/DMF/−40 °C; (e) Ac_2O/pyridine; (f) *m*-CPBA/CH_2Cl_2; (g) DAST/$SbCl_3$/CH_2Cl_2; (h) EtN(*i*-Pr)$_2$/diglyme/145 °C; (i) NH_3/MeOH.

The 3′-fluoro analogue **13b** was prepared from 9-(β-D-xylofuranosyl)adenine (**2**) via its 5′-chloro-5′-deoxy[14] **4** and 5′-(4-methoxyphenyl) thioether **5** analogues (60% overall). Treatment of **5** with DAST (−40 °C, 3.5 h) effected replacement of the 3′-OH group by fluoride with inversion to give **7b** (30%) plus recovered **5** (41%). Longer reaction times or elevated temperatures gave more complex mixtures.[16b] Acetylation of **7b** and oxidation of **8b** gave **9b**, which was treated with DAST/$SbCl_3$ to give the 3′,5′-difluoro diastereomers **10b** (5′*R*/*S*, 36:64; 68% from **7b**). Oxidation of **10b**, thermolysis of **11b**, and deacetylation and chromatography gave the 3′-fluoro-3′-deoxy vinyl fluorides **13b**(*E*) and **13b**(*Z*) (major).

Extended treatment of **2** with the chlorination mixture gave 3′,5′-dichloro-3′,5′-dideoxyadenosine[14] (**6**). The 3′-

(8) Liu, S.; Wnuk, S. F.; Yuan, C.-S.; Robins, M. J.; Borchardt, R. T. *J. Med. Chem.* **1993**, *36*, 883−887.
(9) (a) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1997**, *40*, 1608−1618. (b) Huang, H.; Yuan, C.-S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *Arch. Biochem. Biophys.* **1997**, *343*, 109−117.
(10) (a) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *Biochemistry* **1994**, *33*, 3758−3765. (b) Yuan, C. S.; Wnuk, S. F.; Liu, S.; Robins, M. J.; Borchardt, R. T. *Biochemistry* **1994**, *33*, 12305−12311.
(11) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1994**, *37*, 3579−3587.
(12) Wnuk, S. F.; Liu, S.; Yuan, C.-S.; Borchardt, R. T.; Robins, M. J. *J. Med. Chem.* **1996**, *39*, 4162−4166.
(13) Robins, M. J.; Wilson, J. S.; Madej, D.; Low, N. H.; Hansske, F.; Wnuk, S. F. *J. Org. Chem.* **1995**, *60*, 7902−7908.
(14) Robins, M. J.; Sporns, P.; Muhs, W. H. *Can. J. Chem.* **1979**, *57*, 274−281.
(15) Robins, M. J.; Hansske, F.; Wnuk, S. F.; Kanai, T. *Can. J. Chem.* **1991**, *69*, 1468−1474.
(16) (a) Wnuk, S. F.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4757−4760. (b) Robins, M. J.; Wnuk, S. F. *J. Org. Chem.* **1993**, *58*, 3800−3801.

Scheme 2[a]



Ts = 4-$CH_3C_6H_4SO_2$–

[a] Key: (a) (i) TBDPSCl/pyridine; (ii) Ac_2O/pyridine; (iii) (TBAF/THF or NH_4F/MeOH/Dowex (H^+)/Δ or TFA/H_2O); (b) (i) DMSO/DCC/Cl_2CHCO_2H; (ii) $Ph_3P{=}CHTs$; (c) Bu_3SnH/AiBN/toluene/Δ; (d) NIS; (e) NBS; (f) XeF_2/AgOTf; (g) NH_3MeOH.

Table 1. Concentration-Dependent Inhibition of AdoHcy Hydrolase by 3′-Deoxy and 3′-(Chloro and Fluoro) Analogues

	% of activity remaining			
compd	0.1 μM	1 μM	10 μM	100 μM
13a(*Z*)	105.2	102.5	99.2	74.4
13b(*Z*)	98.8	96.3	93.8	73.9
13c(*Z*)	103.4	101.1	88.9	53.3
17	98.2	94.8	83.9	71.8
18	97.8	96.4	92.1	69.9
19	94.0	93.5	83.2	45.7

chloro-5′-fluoro thioether **10c** (5′*R*/*S*, 34:66) was prepared via an analogous sequence of **6** → **7c** → **8c** → **9c** → **10c**. Oxidation of **10c**, thermolysis of **11c**, deacetylation of **12c**, and chromatography gave the 3′-chloro-3′-deoxy vinyl fluorides **13c**(*E*) and **13c**(*Z*) (major). Stereochemical assignments for the sulfoxides **9a**−**c** (S), α-fluoro thioethers **10a**−**c** (C5′), and vinyl fluorides **13a**−**c** (C5′) are based on ^{1}H and ^{19}F NMR data (Experimental Section), which are in harmony with results for adenosine analogues that were corroborated with X-ray crystal structure data.[5]

Moffatt oxidation of 2′-*O*-acetyl-3′-deoxyadenosine (**14**; prepared from **1** by O5′ silylation, O2′ acetylation, and desilylation;[9a] Scheme 2) and treatment of the resulting 5′-aldehyde with [(*p*-tolylsulfonyl)methylene]triphenylphosphorane[17] gave the (*E*)-tosyl vinyl sulfone **15**(*E*) (48%). Stannyldesulfonylation (Bu_3SnH/AIBN/toluene/Δ)[11,18] of **15** gave mixtures of the vinylstannanes **16** (*E*/*Z*, >6:1; 42%; plus minor byproducts). Iodo- or bromodestannylation of **16** (NIS or NBS) gave the (*E*)-6′-(iodo or bromo)homovinyl-3′-deoxyadenosines **17** or **18**, respectively, in good yields after deprotection and purification. Treatment of **16** with XeF_2/silver triflate[19] effected fluorodestannylation to give 3′-deoxyEDDFHA **19** after deprotection and purification (some protiodestannylated homovinyl byproduct was formed).

Interaction of the Halovinyl and Halohomovinyl Analogues with *S*-Adenosyl-L-homocysteine Hydrolase

The 3′-modified analogues were weak competitive inhibitors of AdoHcy hydrolase, and enzyme inhibition was observed at inhibitor concentrations greater than 10 μM (Table 1; K_i = 197, 191, and 143 μM with compounds **17**, **18**, and **19**, respectively). Inhibition by **13a**−**c** (*Z*-isomers) and **17**−**19** was not time-dependent and did not involve reduction of enzyme-bound NAD^+ to NADH (data not shown). In contrast with the 3′-hydroxy compounds (ZDDFA and EDDFHA),[7,10] these 3′-modified analogues were not substrates for the hydrolytic activity of AdoHcy hydrolase. Incubation of the enzyme with these compounds did not result in detected formation of any reaction products including F^-, 5′-carboxaldehyde analogues, 6′-halo-5′-hydroxy analogues, or adenine (data not shown). These results indicate that the 3′-hydroxyl group is critical for proper substrate binding with the AdoHcy hydrolase, and such binding apparently is prerequisite for the hydrolytic action of the enzyme, as well as its oxidative activity.

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. UV spectra were determined with solutions in MeOH. ^{1}H (200 or 500 MHz), ^{13}C (50 MHz), and ^{19}F (470.3 MHz, CCl_3F) NMR spectra were determined with solutions in Me_2SO-d_6 unless otherwise noted. Mass spectra (MS and HRMS) were obtained with electron impact (EI, 20 eV), chemical ionization (CI, isobutane), or fast atom bombardment (FAB, 5% trifluoroacetic acid/thioglycerol matrix) techniques. Reagent-grade chemicals were used and solvents were dried by reflux over and distillation from CaH_2 (except diglyme// $LiAlH_4$) under an argon atmosphere. TLC was performed on Merck Kieselgel 60-F_{254} sheets with: S_1 (MeOH/$CHCl_3$, 1:9), S_2 (EtOAc/*i*-PrOH/H_2O, 4:1:2; upper layer), S_3 (hexanes/EtOAc, 1:4), or S_4 (MeOH/EtOAc, 1:12); products were detected with 254 nm light. Merck Kieselgel 60 (230−400 mesh) was used for column chromatography. Analytical and preparative RP-HPLC were performed with a Spectra Physics SP 8800 ternary pump system and Dynamax C_{18} columns. "Diffusion crystallization" was performed with the noted solvent combinations as described.[20] Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. Treatment of adenosine with α-acetoxyisobutyryl bromide followed by debromination (Bu_3SnH/AIBN) and ion-exchange chromatography [Dowex 1 × 2 (OH^-)] gave 3′-deoxyadenosine (**1**, ∼60%),[13] which was O5′ silylated, O2′ acetylated, and desilylated to give 2′-*O*-acetyl-3′-deoxyadenosine (**14**).[9a] Coupling ($SnCl_4$/MeCN)[21] of adenine and 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose followed by deprotection (NH_3/MeOH) and chromatography [Dowex 1 × 2 (OH^-), 50 → 80% MeOH/H_2O] gave 9-(β-D-xylofuranosyl)adenine (**2**, ∼65% overall) with data as reported.[22] Chlorination ($SOCl_2$/HMPA)[14] of **1** (6 h), **2** (6 h), or **2** (10 days) followed by ion-exchange chromatography [Dowex 1 × 2 (OH^-), MeOH/H_2O] gave the 5′-chloro-5′-deoxy compounds **3**[23] (80%, mp 213-215 °C dec), **4**[14] (78%), or **6**[14] (52%), respectively, with data as reported.[14,23]

9-[5-*S*-(4-Methoxyphenyl)-5-thio-β-D-xylofuranosyl]-adenine (5). Procedure A. Sodium hydride (0.29 g of 50% NaH/mineral oil, 6 mmol) was washed (dried Et_2O, 10 mL; dried DMF, 5 mL), and suspended in dried DMF (15 mL) at −20 °C under N_2, and 4-methoxybenzenethiol (0.646 mL, 736 mg, 5.25 mmol) was injected slowly via syringe. When evolution of H_2 ceased, **4** (1.43 g, 5 mmol) in dried DMF (20 mL) was added dropwise and stirring was continued at −20 °C for 1 h and then at ambient temperature overnight. Volatiles were evaporated, and the residue was neutralized (pH ∼7, 5% AcOH/H_2O). Volatiles were evaporated, and the residue was crystallized (MeOH/H_2O) to give **5** (1.51 g, 77%): mp 107−108 °C; UV max 258, 230 nm (ε 23 300, 12 000), min

(17) Van Leusen, A. M.; Reith, B. A.; Iedema, A. J. W.; Strating, J. *Rec. Trav. Chim. Pays-Bas* **1972**, *91*, 37−49.
(18) Watanabe, Y.; Ueno, Y.; Araki, T. Endo, T.; Okawara, M. A. *Tetrahedron Lett.* **1986**, *27*, 215−218.
(19) Tius, M. A.; Kawakami, J. K. *Synlett* **1993**, 207−208.
(20) Robins, M. J.; Mengel, R.; Jones, R. A.; Fouron, Y. *J. Am. Chem. Soc.* **1976**, *98*, 8204−8213.
(21) Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull.* **1979**, *27*, 2518−2521.
(22) Cheng, X.; Zhang, J.-D.; Zhang, L.-H. *Synthesis* **1989**, 383−384.
(23) Serafinowski, P. *Nucleic Acids Res.* **1987**, *15*, 1121−1137.

236, 226 nm (ϵ 11 300, 11 800); ^{1}H NMR δ 3.18 (dd, J = 13.6, 7.0 Hz, 1H), 3.26 (dd, J = 13.6, 6.9 Hz, 1H), 3.76 (s, 3H), 4.04 (ddd, J = 5.5, 3.6, 2.8 Hz, 1H), 4.20 (ddd, J = 7.0, 6.9, 2.8 Hz, 1H), 4.36 (ddd, J = 4.0, 3.6, 1.0 Hz, 1H), 5.87 (d, J = 1.0 Hz, 1H), 5.97 (d, J = 4.0 Hz, 1H), 6.15 (d, J = 5.5 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 7.37 (br s, 2H), 7.39 (d, J = 8.6 Hz, 2H), 8.18 (s, 1H), 8.27 (s, 1H); ^{13}C NMR δ 33.14, 55.34, 75.12, 80.73, 81.44, 89.87, 114.96, 118.80, 125.76, 132.35, 140.00, 148.73, 152.61, 156.04, 158.60; MS (CI) m/z 390 (100, MH$^+$), 255 (20). Anal. Calcd for $C_{17}H_{19}N_5O_4S\cdot H_2O$ (407.4): C, 50.11; H, 5.20; N, 17.19. Found: C, 49.96; H, 5.14; N, 16.73.

3′-Deoxy-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (7a). Treatment of **3** (1.34 g, 5 mmol) by procedure A and crystallization (MeOH/H_2O, 2:1) gave **7a** (1.64 g, 88%; two crops) as off-white crystals: mp 153−155 °C; UV max 257, 229 nm (ϵ 21 800, 10 400), min 235, 225 nm (ϵ 10 000, 10 000); ^{1}H NMR δ 2.07 (ddd, J = 13.1, 5.7, 2.6 Hz, 1H), 2.62 (ddd, J = 13.1, 8.9, 5.9 Hz, 1H) 3.19 (d, J = 6.1 Hz, 2H), 3.75 (s, 3H), 4.31−4.44 (m, 1H), 4.63−4.71 (m, 1H), 5.72 (d, J = 4.2 Hz, 1H), 5.88 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.30 (br s, 2H), 7.37 (d, J = 8.8 Hz, 2H), 8.16 (s, 1H), 8.26 (s, 1H); ^{13}C NMR δ 38.52−41.03 (C3′, C5′, and Me_2SO-d_6), 55.45, 74.68, 78.85, 90.94, 115.01, 119.26, 125.87, 132.40, 139.35, 149.29, 152.89, 156.31, 158.66; MS (CI) m/z 374 (100, MH$^+$). Anal. Calcd for $C_{17}H_{19}N_5O_3S$ (373.4): C, 54.68; H, 5.13; N, 18.75. Found: C, 54.42; H, 5.15; N, 19.08.

3′-Deoxy-3′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (7b). DAST (7.72 mL, 9.40 g, 58.4 mmol) was added (syringe) to a suspension of **5** (3.79 g, 9.73 mmol) in DMF (50 mL) at −40 °C, and stirring was continued at 0 °C for 3.5 h. NH_3/MeOH was added (to pH ∼8), volatiles were evaporated, the solid residue was washed (H_2O), and the solid was dissolved (MeOH). The aqueous wash was extracted (EtOAc), and these extracts were combined with the MeOH solution. The solution was concentrated, silica gel was added, and volatiles were evaporated. Chromatography ($CHCl_3$ → 5% MeOH/$CHCl_3$) and crystallization (MeOH/H_2O) gave **7b** (1.16 g, 30%; two crops): mp 129−130 °C; UV max 258, 230 nm (ϵ 22 700, 12 000), min 224, 236 nm (11 000, 11 800); ^{1}H NMR δ 3.29 (dd, J = 14.0, 6.9 Hz, 1H), 3.33 (dd, J = 14.0, 7.3 Hz, 1H), 3.75 (s, 3H), 4.19 (dddd, J = 24.9, 7.3, 6.9, 1.6 Hz, 1H), 5.11 (ddd, J = 53.8, 4.4, 1.6 Hz, 1H), 5.25 (dddd, J = 25.6, 7.8, 6.4, 4.4 Hz, 1H), 5.93 (d, J = 7.8 Hz, 1H), 6.01 (d, J = 6.4 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 7.38 (br s, 2H), 7.40 (d, J = 8.6 Hz, 2H), 8.18 (s, 1H), 8.40 (s, 1H); ^{19}F NMR δ −195.83 (ddd, J = 53.8, 25.6, 24.9 Hz); ^{13}C NMR δ 36.31 (d, J = 9.5 Hz), 55.36, 70.61 (d, J = 15.8 Hz), 81.54 (d, J = 23.0 Hz), 86.39, 93.63 (d, J = 183.0 Hz), 115.02, 119.36, 124.70, 132.96, 140.44, 149.70, 152.91, 156.11, 158.88; MS (CI) m/z 392 (100, MH$^+$). Anal. Calcd for $C_{17}H_{18}FN_5O_3S$ (391.4): C, 52.16; H, 4.64; N, 17.89. Found: C, 52.31; H, 4.60; N,18.00. Further elution of the column gave recovered **5** (1.56 g, 41%).

3′-Chloro-3′-deoxy-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (7c). Treatment of **6** (1.41 g, 4.63 mmol) by procedure A and crystallization (MeOH/H_2O) gave **7c** (1.61 g, 85%; two crops) as a white solid: mp ∼146 °C; UV max 258, 230 nm (ϵ 22 700, 11 800), min 224, 236 nm (10 900, 11 700); ^{1}H NMR δ 3.28 (dd, J = 13.9, 6.9 Hz, 1H), 3.39 (dd, J = 13.9, 5.5 Hz, 1H), 3.72 (s, 3H), 4.18 (ddd, J = 6.9, 5.5, 4.4 Hz, 1H), 4.81 (dd, J = 5.1, 4.4 Hz, 1H), 5.19 (ddd, J = 5.6, 5.2, 5.1 Hz, 1H), 5.96 (d, J = 5.6 Hz, 1H), 6.22 (d, J = 5.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 H, 2H), 7.38 (br s, 2H), 8.19 (s, 1H), 8.39 (s, 1H); ^{13}C NMR δ 37.57, 55.30, 62.13, 71.41, 83.77, 87.72, 114.88, 119.27, 124.89, 132.87, 140.42, 149.34, 152.83, 156.08, 158.76; MS (CI) m/z 408 (100, MH$^+$, ^{35}Cl), 410 (40, MH$^+$, ^{37}Cl and [^{35}Cl, ^{34}S]). Anal. Calcd for $C_{17}H_{18}ClN_5O_3S$ (407.9): C, 50.06; H, 4.45; N, 17.17. Found C, 49.89; H, 4.55; N, 16.93.

9-(3,5-Dideoxy-5-fluoro-*β*-D-*glycero*-pent-4-enofuranosyl)adenine [13a(*Z*) and 13a(*E*)]. Procedure B. Pyridine (8 mL) was added to a suspension of **7a** (1.5 g, 4.0 mmol) in Ac_2O (0.53 mL, 571 mg, 5.6 mmol) at ∼0 °C (ice bath), and stirring was continued for 9 h (TLC indicated complete reaction). MeOH (20 mL) was added, and stirring was continued for 30 min. Volatiles were evaporated, and the residue was partitioned (5% AcOH/H_2O//$CHCl_3$). The organic phase was washed ($NaHCO_3$/H_2O, brine, H_2O) and dried (Na_2SO_4), and volatiles were evaporated. The residue was chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give the less polar 6-*N*-acetyl-**8a** [(200 mg, 14%; MS m/z 457 (30, M$^+$)], followed by 2′-*O*-acetyl-3′-deoxy-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**8a**, 1.34 g, 81%) as a TLC-homogeneous solid foam: ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.28 (ddd, J = 13.9, 5.6, 1.4 Hz, 1H), 2.61 (ddd, J = 13.9, 9.9, 6.1 Hz, 1H), 3.14 (dd, J = 13.7, 6.6 Hz, 1H), 3.26 (dd, J = 13.7, 5.7 Hz, 1H), 3.79 (s, 3H), 4.46−4.60 (m, 1H), 5.69 (dt, J = 6.1, 1.4 Hz, 1H), 5.79 (br s, 2H), 6.02 (d, J = 1.4 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.91 (s, 1H), 8.33 (s, 1H); MS m/z 415 (30, M$^+$), 220 (100), 139 (90); HRMS (FAB) m/z 416.1381 (100, MH$^+$ [$C_{19}H_{22}N_5O_4S$] = 416.1393).

Procedure C. *m*-CPBA (447 mg of 78% reagent, 2.03 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a cold (−78 °C) solution of **8a** (830 mg, 2 mmol) in CH_2Cl_2 (20 mL), and stirring was continued for ∼5 min (TLC indicated complete reaction). The solution was poured into $NaHCO_3$/H_2O (25 mL) and extracted ($CHCl_3$, 3 × 15 mL). The combined organic phase was washed (brine and H_2O), dried (Na_2SO_4), and evaporated to give 3′-*O*-acetyl-3′,5′-dideoxy-5′-[(4-methoxyphenyl)sulfinyl]adenosine [**9a**, (R/S)$_S$ ∼1:1; 819 mg, 95%] as a solid foam. Column chromatography ($CHCl_3$ → 3% MeOH/$CHCl_3$) gave **9a** (R_S, 259 mg, 30%), **9a** [(R/S)$_S$ ∼1:1; 276 mg, 32%], and **9a** (S_S, 233 mg, 27%). **9a**(R_S): ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.33 (ddd, J = 13.9, 6.6, 1.2 Hz, 1H), 2.87 (ddd, J = 13.9, 10.3, 5.9 Hz, 1H), 3.10 (dd, J = 13.2, 3.3 Hz, 1H), 3.24 (dd, J = 13.2, 9.2 Hz, 1H), 3.84 (s, 3H), 4.90−5.05 (m, 1H), 5.71 (br d, J = 5.9 Hz, 1H), 6.00 (d, J = 1.3 Hz, 1H), 6.08 (br s, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.87 (s, 1H), 8.26 (s, 1H); HRMS (CI) m/z 432.1340 (100, MH$^+$ [$C_{19}H_{22}N_5O_5S$] = 432.1342). **9a**(S_S): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.43 (dd, J = 13.9, 5.5 Hz, 1H), 2.95 (ddd, J = 13.9, 10.1, 6.2 Hz, 1H), 3.12 (dd, J = 13.3, 6.2 Hz, 1H), 3.43 (dd, J = 13.3, 6.2 Hz, 1H), 3.85 (s, 3H), 4.57−4.70 (m, 1H), 5.73 (br d, J = 6.2 Hz, 1H), 5.98 (s, 1H), 6.01 (br s, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.89 (s, 1H), 8.31 (s, 1H).

Procedure D. DAST (0.53 mL, 645 mg, 4.0 mmol) was added (by syringe) to a solution of **9a** [(R/S)$_S$ ∼1:1; 864 mg, 2 mmol] and $SbCl_3$ (46 mg, 0.20 mmol) in CH_2Cl_2 (17 mL) under argon, and stirring was continued at ambient temperature for 8 h (TLC indicated complete reaction). Excess DAST was destroyed by addition of ice-cold, saturated $NaHCO_3$/H_2O, and stirring was continued for 30 min. The organic layer was separated, and the aqueous layer was extracted ($CHCl_3$). The combined organic phase was washed ($NaHCO_3$/H_2O, brine, H_2O), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue ($CHCl_3$ → 2% MeOH/$CHCl_3$) gave **10a** (5′*R*/*S* ∼6:4; 468 mg, 54%) as a yellow solid foam: ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.20−2.98 (m, 2H), 3.81 (s, 3H), 4.57−4.77 (m, 1H), 5.68−5.75 (m, 1H), 5.78 (br s, 2H), 5.80 (dd, J = 54.3, 5.8 Hz, 0.6H), 5.94 (dd, J = 54.3, 3.8 Hz, 0.4H), 6.12 (s, 0.6H), 6.17 (s, 0.4H), 6.83−7.50 (d's, J = 8.8 Hz, 4H), 8.01 (s, 1, H2), 8.30 (s, 0.6H), 8.33 (s, 0.4H); ^{19}F NMR ($CDCl_3$) δ −162.21 (dd, J = 54.9, 17.8 Hz, 0.4F), −156.51 (dd, J = 54.9, 14.6 Hz, 0.6F); MS m/z 433 (2, M$^+$), 135 (100).

m-CPBA (287 mg of 78% reagent, 1.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of **10a** (468 mg, 1.08 mmol) in CH_2Cl_2 (15 mL) at −40 °C, and stirring was continued (−20 to −10 °C) for 3 h. Workup as in procedure C and flash chromatography (EtOAc → 6% MeOH/EtOAc) gave **11a** (412 mg, 85%) as a solid foam: ^{19}F NMR ($CDCl_3$) δ −201.82 (dd, J = 48.5, 9.7 Hz, 0.05F), −194.64 (dd, J = 48.5, 19.9 Hz, 0.13F), −194.18 (dd, J = 48.5, 25.9 Hz, 0.58F), −190.72 (dd, J = 48.4, 19.4 Hz, 0.24F); MS (CI) m/z 450 (100, MH$^+$).

A solution of isomeric **11a** (412 mg, 0.92 mmol; predried in vacuo at 65 °C for 16 h) and EtN(i-Pr)$_2$ (0.96 mL, 713 mg, 5.52 mmol) in dried diglyme (8 mL) was purged with N_2 for 1 h and heated at 145 ± 2 °C (oil bath temperature). Stirring was continued for 24 h, EtN(i-Pr)$_2$ (0.48 mL, 356 mg, 2.76 mmol) was added, and thermolysis was continued for 24 h. Volatiles were evaporated, and the residue was chromatographed

(EtOAc → 10% S_2/EtOAc) to give **12a** as a brown solid (∼150 mg; purity ∼70%, ^{1}H NMR). This material was stirred with NH_3/MeOH (10 mL) for 2 h at ∼0 °C, volatiles were evaporated, and the brown residue was purified (RP-HPLC, preparative column, 2×; program: 20% MeCN/H_2O for 30 min, 20 → 50% MeCN/H_2O for 50 min, 2.8 mL/min) to give **13a**(*Z*) (11 mg, 4% from **10a**; t_R = 70 min) and **13a**(*E*) (22 mg, 8%; t_R = 75 min). **13a**(*Z*): ^{1}H NMR (CD_3OD) δ 2.60−2.73 (m, 1H), 3.10−3.25 (m, 1H), 4.90−4.99 (m, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 6.37 (dt, *J* = 76.0, 1.8 Hz, 1H), 8.20 (s, 1H), 8.23 (s, 1H); ^{19}F NMR (CD_3OD) δ −166.15 (dm, *J* = 76.0 Hz); HRMS *m*/*z* 251.0813 (100, M^+ [$C_{10}H_{10}FN_5O_2$] = 251.0819). **13a**(*E*): ^{1}H NMR (CD_3OD) δ 2.89 (dm, *J* = 14.6 Hz, 1H), 3.30−3.45 (m, 1H), 4.91−5.00 (m, 1H), 6.22−6.25 (m, 1H), 7.14 (dt, *J* = 78.9, 2.4 Hz, 1H), 8.19 (s, 1H), 8.23 (s, 1H); ^{19}F NMR (CD_3OD) δ −182.56 (dtd, *J* = 78.9, 4.0, 1.5 Hz); HRMS *m*/*z* 251.0811 (100, M^+ [$C_{10}H_{10}FN_5O_2$] = 251.0819).

9-(3,5-Dideoxy-3,5-difluoro-β-D-*erythro*-pent-4-enofuranosyl]adenine [13b(*Z*) and 13b(*E*)]. Acetylation of **7b** (785 mg, 2.01 mmol) with Ac_2O (0.27 mL, 292 mg, 2.86 mmol) by procedure B (7.5 h, ice−salt bath, workup only) gave 2′-*O*-acetyl-3′-deoxy-3′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**8b**, 862 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.25 (dd, *J* = 14.5, 5.6 Hz, 1H), 3.30 (dd, *J* = 14.5, 7.8 Hz, 1H), 3.80 (s, 3H), 4.45 (ddd, *J* = 24.4, 7.8, 5.6, 1.5 Hz, 1H), 5.43 (ddd, *J* = 53.6, 4.4, 1.5 Hz, 1H), 5.74 (br s, 2H), 6.12 (d, *J* = 7.0 Hz, 1H), 6.16 (ddd, *J* = 19.4, 7.0, 4.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 1H), 8.34 (s, 1H); ^{19}F NMR ($CDCl_3$) δ −197.91 (ddd, *J* = 53.6, 24.4, 19.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.60, 37.27 (d, *J* = 8.5 Hz), 55.61, 72.98 (d, *J* = 16.0 Hz), 83.06 (d, *J* = 24.2 Hz), 86.12, 90.73 (d, *J* = 190.0 Hz), 115.06, 121.5, 124.53, 134.36, 141.06, 149.98, 154.22, 159.84, 169.83; HRMS (FAB) *m*/*z* 434.1295 (100, MH^+ [$C_{19}H_{21}FN_5O_4S$] = 434.1298).

Treatment of **8b** (869 mg, 2 mmol) by procedure C gave 2′-*O*-acetyl-3′,5′-dideoxy-3′-fluoro-5′-[(4-methoxyphenyl)sulfinyl]-adenosine [**9b**, (*R*/*S*)$_S$ ∼48:52; 787 mg, 88%] as an amorphous solid: HRMS (FAB) *m*/*z* 450.1243 (100, MH^+ [$C_{19}H_{21}FN_5O_5S$] = 450.1247). Chromatography (EtOAc → 5% MeOH/EtOAc) gave partial separation. Less polar **9b**(R_S): ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.10 (dd, *J* = 12.8, 2.6 Hz, 1H), 3.78 (dd, *J* = 12.8, 10.8 Hz, 1H), 3.85 (s, 3H), 5.00 (dddd, *J* = 21.9, 10.8, 2.6, 1.9 Hz, 1H), 5.41 (ddd, *J* = 53.6, 4.4, 1.9 Hz, 1H), 6.11 (br s, 2H), 6.13 (d, *J* = 6.9 Hz, 1H), 6.33 (ddd, *J* = 19.5, 6.9, 4.4 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.89 (s, 1H), 8.22 (s, 1H); ^{19}F NMR ($CDCl_3$) δ −199.61 (ddd, *J* = 53.6, 21.9, 19.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.51, 55.72, 60.87 (d, *J* = 6.9 Hz), 72.30 (d, *J* = 15.3 Hz), 77.93 (d, *J* = 24.8 Hz), 87.46, 91.55 (d, *J* = 193.8 Hz), 115.13, 121.18, 125.92, 134.79, 141.23, 149.56, 153.17, 156.13, 162.51, 169.90. More polar **9b**(S_S): ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.31 (dd, *J* = 13.7, 5.4 Hz, 1H), 3.58 (dd, *J* = 13.7, 7.3 Hz, 1H), 3.80 (s, 3H), 4.69 (dddd, *J* = 24.2, 7.3, 5.4, 1.5 Hz, 1H), 5.58 (ddd, *J* = 53.6, 4.4, 1.5 Hz, 1H), 6.09 (d, *J* = 7.3 Hz, 1H), 6.26 (br s, 2H), 6.32 (ddd, *J* = 19.2, 7.3, 4.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.93 (s, 1H), 8.30 (s, 1H); ^{19}F NMR ($CDCl_3$) δ −196.82 (ddd, *J* = 53.6, 24.2, 19.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.48, 55.61, 56.84 (d, *J* = 6.5 Hz), 72.35 (d, *J* = 15.6 Hz), 77.45 (d, *J* = 25.9 Hz), 86.32, 91.62 (d, *J* = 191.5 Hz), 114.75, 120.71, 126.23, 133.21, 140.32, 149.69, 153.36, 156.13, 162.23, 169.68.

A solution of **9b** (788 mg, 1.75 mmol) in CH_2Cl_2 (15 mL) was treated with DAST/$SbCl_3$ by procedure D (4 h), and the residue was flash chromatographed (EtOAc) to give amorphous 2′-*O*-acetyl-3′-deoxy-3′,5′-difluoro-5′-*S*-(methoxyphenyl)-5′-thioadenosine (**10b**, 5′*R*/*S* ∼36:64; 611 mg, 77%): ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 1.08H), 2.12 (s, 1.92H), 3.82 (s, 3H), 4.59 (ddd, *J* = 24.0, 15.6, 4.9 Hz, 0.36H), 4.69 (dddd, *J* = 20.0, 18.5, 4.2, 2.0 Hz, 0.64H), 5.51 (dd, *J* = 52.7, 4.4 Hz, 0.36H), 5.56 (ddd, *J* = 52.7, 4.9, 4.2 Hz, 0.64H), 5.77 (ddd, *J* = 23.6, 7.3, 4.9 Hz, 0.64H), 5.88 (ddd, *J* = 21.3, 7.3, 4.4 Hz, 0.36H), 5.99 (dd, *J* = 53.1, 4.2 Hz, 0.64H), 6.03 (dd, *J* = 54.0, 4.9 Hz, 0.36H), 6.32 (d, *J* = 7.3 Hz, 0.36H), 6.36 (d, *J* = 7.3 Hz, 0.64H), 6.49 (br s, 0.72H), 6.55 (br s, 1.28H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 0.72H), 7.48 (d, *J* = 9.0 Hz, 1.28H), 8.04 (s, 0.36H), 8.17 (s, 0.64H), 8.27 (s, 0.36H), 8.34 (s, 0.64H); ^{19}F NMR ($CDCl_3$) δ −199.79 (ddd, *J* = 52.7, 23.6, 18.5 Hz, 0.64F), −199.38 (ddd, *J* = 52.7, 24.0, 21.3, Hz, 0.36F), −160.00 (dd, *J* = 53.1, 20.0 Hz, 0.64F), −159.72 (dd, *J* = 54.0, 15.6 Hz, 0.36F); HRMS (CI) *m*/*z* 452.1197 (66, MH^+ [$C_{19}H_{20}F_2N_5O_4S$] = 452.1204.

m-CPBA (299 mg of 78% reagent, 1.35 mmol) in CH_2Cl_2 (20 mL) was added dropwise to **10b** (611 mg, 1.35 mmol) in CH_2Cl_2 (20 mL) at −78 °C, and stirring was continued for 2 h at −20 °C and 1 h at 0 °C. Workup as in procedure C and chromatography (EtOAc → 5% MeOH/EtOAc) gave recovered **10b** (47 mg, 7%) and then **11b** (588 mg, 93%) as a solid foam: ^{19}F NMR ($CDCl_3$) δ −201.59 (ddd, *J* = 51.7, 21.5, 15.8 Hz, 0.52F), −199.38 (dd, *J* = 47.4, 8.6 Hz, 0.06F), −198.97 (ddd, *J* = 53.1, 23.0, 20.1 Hz, 0.06F), −198.43 (ddd, *J* = 51.7, 24.4, 20.8 Hz, 0.28F), −197.08 (ddd, *J* = 51.7, 24.5, 19.4 Hz, 0.14F), −194.42 (dd, *J* = 47.4, 24.4 Hz, 0.14F), −193.07 (dd, *J* = 47.4, 30.2 Hz, 0.52F), −185.68 (dd, *J* = 48.1, 15.1, Hz, 0.28F).

A solution of isomeric **11b** (588 mg, 1.26 mmol; dried in vacuo at 60 °C for 12 h) and EtN(*i*-Pr)$_2$ (2.2 mL, 1.6 g, 12.6 mmol) in dried diglyme (20 mL) was purged with argon for 0.5 h and heated at 143 ± 1 °C (oil bath temperature). Stirring was continued for 24 h, EtN(*i*-Pr)$_2$ (1.1 mL, 0.82 g, 6.3 mmol) was added, and heating was continued for 48 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc → 5% MeOH/EtOAc) to give **12b** (*E*/*Z* ∼36:64; 283 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 5.91 (dd, *J* = 56.1, 4.2 Hz, 0.64H), 6.18 (dd, *J* = 55.1, 4.2 Hz, 0.36H), 6.34 (ddd, *J* = 18.3, 6.6, 4.2 Hz, 0.36H), 6.39 (ddd, *J* = 20.6, 7.7, 4.2 Hz, 0.64H), 6.64 (d, *J* = 6.6 Hz, 0.36H), 6.70 (d, *J* = 7.7 Hz, 0.64H), 7.16 (dd, *J* = 72.8, 8.0 Hz, 0.64H), 7.51 (dd, *J* = 77.0, 6.7 Hz, 0.36H), 7.57 (br s, 2H), 8.22 (s, 1H), 8.46 (s, 0.36H), 8.49 (s, 0.64H); ^{19}F NMR ($CDCl_3$) δ −190.08 (dddd, *J* = 55.1, 18.3, 10.3, 6.7 Hz, 0.36F), −183.36 (dddd, *J* = 56.1, 20.6, 10.3, 8.0 Hz, 0.64F), −173.06 (dd, *J* = 77.0, 10.3 Hz, 0.36F), −155.80 (dd, *J* = 72.8, 10.3 Hz, 0.64F).

A solution of **12b** (37 mg, 0.12 mmol) in NH_3/MeOH (20 mL) was stirred for 2 h at ambient temperature. Volatiles were evaporated, and "diffussion crystallization" (EtOAc/hexane) of the residue gave **13b** (*E*/*Z* ∼36:64; 22 mg, 69%). RP-HPLC: (*Z*)t_R = 38.3 min, (*E*)t_R = 41.4 min [preparative column, H_2O/MeOH/MeCN (55:30:15)]. **13b**(*Z*): mp ∼239 °C dec [MeOH/EtOAc (∼1:1)//hexanes]; UV max 259 nm (ε 14 800); ^{1}H NMR δ 5.42 (ddd, *J* = 24.9, 8.3, 3.4 Hz, 1H), 5.50 (dd, *J* = 56.7, 3.4 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 1H), 6.35 (br s, 1H), 7.03 (dd, *J* = 73.7, 7.8 Hz, 1H), 7.44 (br s, 2H), 8.17 (s, 1H), 8.48 (s, 1H); ^{19}F NMR δ −184.30 (dddd, *J* = 56.7, 24.9, 10.3, 7.8 Hz, F3′), −156.83 (dd, *J* = 73.7, 10.3 Hz, F5′); ^{13}C NMR δ 70.43 (d, *J* = 19.1 Hz), 87.22, 87.87 (dd, *J* = 183.1, 8.0 Hz), 119.5, 133.76 (dd, *J* = 254.6, 13.5 Hz), 138.27 (dd, *J* = 13.9, 5.2 Hz), 140.59, 149.85, 153.19, 156.40; MS *m*/*z* 269 (100, M^+), 252 (20), 135 (34). Anal. Calcd for $C_{10}H_9N_5O_2F_2$·0.25 H_2O (273.7): C, 43.88; H, 3.50; N, 25.59. Found: C, 43.71; H, 3.68; N, 25.68. **13b**(*E*): mp 239−240 °C dec; UV max 259 nm (ε 14 500); ^{1}H NMR δ 5.38 (dddd, *J* = 24.0, 8.3, 6.8, 4.4 Hz, 1H), 5.83 (ddd, *J* = 56.2, 4.4, 2.1 Hz, 1H), 6.21 (d, *J* = 8.3 Hz, 1H), 6.33 (d, *J* = 6.8 Hz, 1H), 7.38 (dd, *J* = 77.7, 7.4 Hz, 1H), 7.42 (br s, 2H), 8.17 (s, 1H), 8.46 (s, 1H); ^{19}F NMR δ −190.06 (dddd, *J* = 56.2, 24.0, 11.6, 7.4 Hz, F3′), −172.88 (ddd, *J* = 77.7, 11.6, 2.1 Hz, F5′); ^{13}C NMR δ 70.12 (d, *J* = 17.6 Hz), 85.38 (d, *J* = 181.8 Hz), 86.87, 119.42, 138.24, (dd, *J* = 238.2, 11.1 Hz), 140.45, 143.93 (dd, *J* = 29.4, 13.4 Hz), 149.82, 153.15, 156.37; MS *m*/*z* 269 (100, M^+), 252 (22), 135 (36). Anal. Calcd for $C_{10}H_9N_5O_2F_2$ (269.2): C, 44.62; H, 3.37; N, 26.01. Found: C, 44.44; H, 3.36; N, 25.83.

RP-HPLC of the mother liquor (preparative column, program: 15% MeCN/H_2O for 15 min, 15 → 40% MeCN/H_2O for 30 min; 2.5 mL/min) gave **13b**(*Z*) (3 mg, 9%; t_R = 36.2 min), **13b**(*E*/*Z*) (1.5 mg, 5%), and **13b**(*E*) (1.5 mg, 5%, t_R = 39.2 min) [to give **13b** (88% overall)].

9-(3-Chloro-3,5-dideoxy-5-fluoro-β-D-*erythro*-pent-4-enofuranosyl)adenine [13c(*Z*) and 13c(*E*)]. Treatment of **7c** (1.29 g, 3.16 mmol) by procedure B (7.5 h, ice−salt bath, workup only) gave 2′-*O*-acetyl-3′-chloro-3′-deoxy-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**8c**, 1.41 g, 99%): ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.23 (dd, *J* = 14.3, 6.5 Hz, 1H), 3.41 (dd, *J* =

14.3, 5.0 Hz, 1H), 3.79 (s, 3H), 4.38−4.41 (m, 1H), 5.11 (dd, J = 5.5, 6.0 Hz, 1H), 5.75 (br s, 2H), 6.05 (d, J = 4.0 Hz, 1H), 6.10 (dd, J = 5.5, 4.0 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 9.0 Hz, 2H), 7.87 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.70, 38.26, 55.52, 57.55, 74.39, 84.86, 87.58, 114.88, 120.45, 125.11, 133.76, 140.42, 149.38, 152.28, 155.34, 159.49, 169.71; HRMS (FAB) m/z 450.0990/452.0986 (100/40, MH^+ [$C_{19}H_{21}{}^{35}Cl/{}^{37}ClN_5O_4S$] = 450.1003/452.0973).

Treatment of **8c** (1.42 g, 3.16 mmol) by procedure C gave amorphous 2′-*O*-acetyl-3′-chloro-3′,5′-dideoxy-5′-[(4-methoxyphenyl)sulfinyl]adenosine [**9c**, $(R/S)_S$ ∼41:59; 1.44 g, 98%]; HRMS (FAB) m/z 466.0934/468.0925 (100/40, MH^+ [$C_{19}H_{21}{}^{35}Cl/{}^{37}ClN_5O_5S$] = 466.0952/468.0922). Chromatography (EtOAc → 5% MeOH/EtOAc) gave partial separation of the less polar **9c**(R_S) [^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.22 (dd, J = 13.7, 1.8 Hz, 1H), 3.38 (dd, J = 13.7, 10.8 Hz, 1H), 3.86 (s, 3H), 4.83 (ddd, J = 10.8, 6.9, 1.8 Hz, 1H), 5.21 (dd, J = 6.9, 5.5 Hz, 1H), 5.97 (br s, 2H), 6.06 (d, J = 3.3 Hz, 1H), 6.08 (dd, J = 5.5, 3.3 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.66, 55.73, 57.92, 61.11, 74.61, 79.64, 88.80, 115.18, 120.32, 126.04, 134.94, 140.94, 153.31, 156.06, 162.56, 169.93] and the more polar **9c**(S_S): δ 2.16 (s, 3H), 3.30 (dd, J = 13.7, 4.4 Hz, 1H), 3.52 (dd, J = 13.7, 7.3 Hz, 1H), 3.83 (s, 3H), 4.55 (ddd, J = 7.3, 6.4, 4.4 Hz, 1H), 5.32 (dd, J = 6.4, 5.4 Hz, 1H), 5.90 (br s, 2H), 6.02 (d, J = 3.9 Hz, 1H), 6.10 (dd, J = 5.4, 3.9 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 8.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.66, 55.69, 58.05, 58.31, 74.12, 80.51, 88.12, 114.91, 121.05, 126.35, 133.86, 140.43, 149.10, 153.42, 155.93, 162.46, 169.74.

Treatment of **9c** (1.44 g, 3.1 mmol) by procedure D gave 2′-*O*-acetyl-3′-chloro-3′-deoxy-5′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**10c**, 5′*R*/*S* ∼34:66; 668 mg, 46%): ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 1.02H), 2.15 (s, 1.98H), 3.79 (s, 3H), 4.59 (ddd, J = 14.3, 5.5, 4.6 Hz, 0.34H), 4.62 (ddd, J = 20.0, 5.8, 3.2 Hz, 0.66H), 5.06 (dd, J = 5.8, 4.8 Hz, 0.66H), 5.09 (dd, J = 5.8, 5.5 Hz, 0.34H), 5.94 (dd, J = 4.8, 4.3 Hz, 0.66H), 5.96 (dd, J = 53.6, 3.2 Hz, 0.66H), 5.98 (dd, J = 5.8, 4.3 Hz, 0.34H), 6.04 (dd, J = 53.6, 4.6 Hz, 0.34H), 6.26 (d, J = 4.3 Hz, 1H), 6.53 (br s, 0.68H), 6.59 (br s, 1.32H), 6.85 (d, J = 9.0 Hz, 0.68H), 6.87 (d, J = 9.0 Hz, 1.32H), 7.42 (d, J = 9.0 Hz, 0.68H), 7.48 (d, J = 9.0 Hz, 1.32H), 8.02 (s, 0.34H), 8.11 (s, 0.66H), 8.27 (s, 0.34H), 8.31 (s, 0.66H); ^{19}F NMR ($CDCl_3$) δ −162.18 (dd, J = 53.6, 20.0 Hz, 0.66F), −158.35 (dd, J = 53.6, 14.3 Hz, 0.34F); HRMS (FAB) m/z 468.0890 (100, MH^+ [$C_{19}H_{20}{}^{35}ClFN_5O_4S$] = 468.0909).

Oxidation of **10c** (681 mg, 1.46 mmol) as described for **13b** (**10b** → **11b**; 2h, −20 °C) gave recovered **10c** (51 mg, 8%) and **11c** (589 mg, 81%): ^{19}F NMR ($CDCl_3$) δ −199.53 (dd, J = 47.9, 5.3 Hz, 0.07F), −196.85 (dd, J = 47.2, 28.6 Hz, 0.50F), −196.37 (dd, J = 47.2, 23.6 Hz, 0.14 F), −186.48 (dd, J = 47.9, 13.1 Hz, 0.29F).

Thermolysis of isomeric **11c** (322 mg, 0.665 mmol) as described for **13b** (141 ± 1 °C, 100 h) gave **12c** (*E*/*Z* ∼36:64; 119 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 5.45 (d, J = 5.4 Hz, 0.64H), 5.67 (ddd, J = 5.4, 2.0, 1.0 Hz, 0.36H), 6.24 (dd, J = 7.8, 5.4 Hz, 0.36H), 6.26 (dd, J = 6.8, 5.4 Hz, 0.64H), 6.39 (d, J = 7.8 Hz, 0.36H), 6.41 (d, J = 6.8 Hz, 0.64H), 6.55 (d, J = 72.8 Hz, 0.64H), 6.92 (dd, J = 76.2, 1.0 Hz, 0.36H), 7.49 (br s, 2H), 7.92 (s, 0.36H), 7.93 (s, 0.64H), 8.31 (s, 0.64H), 8.33 (s, 0.36H); ^{19}F NMR ($CDCl_3$) δ −172.80 (dd, J = 76.2, 2.0 Hz, 0.36 F), −158.93 (d, J = 72.8 Hz, 0.64F); ^{13}C NMR ($CDCl_3$) δ 20.48, 52.64, 54.30 (d, J = 5.7 Hz), 72.42, 72.78, 85.77, 86.64, 120.41, 132.83 (d, J = 257.0 Hz), 137.14 (d, J = 246.0 Hz), 139.54, 139.82, 139.92 (d, J = 9.6 Hz), 145.00 (d, J = 36.9 Hz), 149.95, 150.11, 153.53, 153.58, 156.15, 169.64, 169.71.

A solution of **12c** (88 mg, 0.27 mmol) in NH_3/MeOH was treated as described for **13b** to give **13c** (*E*/*Z* ∼36:64; 40 mg, 52%). RP-HPLC gave (*Z*)t_R = 46.6 min and (*E*)t_R = 48.8 min (preparative column, program: 15% MeCN/H_2O for 15 min, 15 → 60% MeCN/H_2O for 60 min, 2.5 mL/min). **13c**(*Z*): mp ∼182 °C dec; UV max 258 nm (ϵ 13 900); ^{1}H NMR δ 5.37 (d, J = 5.0 Hz, 1H), 5.60 (ddd, J = 7.7, 5.5, 5.0 Hz, 1H), 6.26 (d, J = 7.7 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 6.93 (d, J = 74.0 Hz, 1H), 7.42 (br s, 2H), 8.17 (s, 1H), 8.49 (s, 1H); ^{19}F NMR δ −161.12 (d, J = 74.0 Hz); ^{13}C NMR δ 58.98 (d, J = 6.8 Hz), 70.21, 87.06, 119.40, 132.13 (d, J = 252.0 Hz), 140.32 (d, J = 7.1 Hz), 140.63, 149.68, 152.99, 156.25; MS m/z 285 (100, M^+, ^{35}Cl), 287 (33, M^+, ^{37}Cl), 250 (58), 135 (53). Anal. Calcd for $C_{10}H_9ClFN_5O_2\cdot 0.5\ H_2O$ (294.7): C, 40.76; H, 3.42; N, 23.77. Found: C, 40.58; H, 3.35; N, 23.58. **13c**(*E*): mp ∼182 °C dec; UV max 258 nm (ϵ 15 400); ^{1}H NMR δ 5.58 (d, J = 4.9 Hz, 1H), 5.61 (dt, J = 7.3, 4.9 Hz, 1H), 6.21 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 4.9 Hz, 1H), 7.28 (d, J = 77.2 Hz, 1H), 7.43 (br s, 2H), 8.17 (s, 1H), 8.48 (s, 1H); ^{19}F NMR δ −174.87 (d, J = 77.2 Hz); ^{13}C NMR δ 56.13, 69.81, 86.60, 119.36, 136.37 (d, J = 236.3 Hz), 140.53, 145.74 (d, J = 37.2 Hz), 149.66, 152.97, 156.21; MS 285 (100, M^+, ^{35}Cl), 287 (33, M^+, ^{37}Cl), 250 (44), 135 (39). Anal. Calcd for $C_{10}H_9ClFN_5O_2\cdot 0.5\ H_2O$ (294.7): C, 40.76; H, 3.42; N, 23.77. Found: C, 40.92; H, 3.48; N, 23.53. RP-HPLC of the mother liquor gave **13c**(*Z*) (13 mg, 17%), **13c**(*E*/*Z*) (7 mg, 9%), and **13c**(*E*) (4 mg, 5%) [to give **13c** (83% overall)].

9-[2-*O*-Acetyl-3,5,6-trideoxy-6-(*p*-toluylsulfonyl)-*β*-D-*erythro*-hex-5-enofuranosyl]adenine [15(*E*)]. A solution of **14**[9a] (410 mg, 1.4 mmol) and DCC (1.16 g, 5.6 mmol) in dried Me_2SO (4.5 mL) was cooled (ice bath), and Cl_2CHCO_2H (0.06 mL, 90 mg, 0.7 mmol) was added. Stirring was continued at ambient temperature for 2 h, [(*p*-toluylsulfonyl)methylene]triphenylphosphorane[17] (662 mg, 1.54 mmol) was added, and stirring was continued overnight. Oxalic acid dihydrate (529 mg, 4.2 mmol) in MeOH was added, the mixture was stirred for 30 min, and *N*,*N*′-dicyclohexylurea was filtered. Volatiles were evaporated from the filtrate in vacuo and the residue was partitioned (EtOAc/H_2O). The organic layer was washed (H_2O, $NaHCO_3$/H_2O, brine) and dried ($MgSO_4$), and volatiles were evaporated. Chromatography of the brown residue ($CHCl_3$ → 4% MeOH/$CHCl_3$) gave **15**(*E*) (298 mg, 48%) as a colorless solid: mp 188−190 °C; UV 258, 237 nm (ϵ 13 750, 18 200), min 252, 222 nm (ϵ 13 250, 11 700); ^{1}H NMR δ 2.10 (s, 3H), 2.40−2.53 (m, 1H), 2.78 (ddd, J = 13.9, 10.2, 6.0 Hz, 1H), 4.92−5.02 (m, 1H), 5.69 (br d, J = 5.9 Hz, 1H), 6.16 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 15.0 Hz, 1H), 7.02 (dd, J = 15.0, 4.9 Hz, 1H), 7.37 (br s, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 8.06 (s, 1H), 8.28 (s, 1H); ^{13}C NMR δ 20.98, 21.36, 40.46 (C3′ overlap with Me_2SO-d_6 peaks), 77.51, 77.68, 89.03, 119.28, 127, 130.34, 131.7, 137.14, 140.03, 143.34, 144.72, 149.03, 152.97, 156.40, 170.11; MS (CI) m/z 444 (10, MH^+), 336 (100). Anal. Calcd for $C_{20}H_{21}N_5O_5S$ (443.5): C, 54.17; H, 4.77; N, 15.79. Found: C, 53.91; H, 5.00; N, 15.66.

9-[3,5,6-Trideoxy-6(*E*)-iodo-*β*-D-*erythro*-hex-5-enofuranosyl]adenine (17). Procedure E. A suspension of **15**(*E*) (443 mg, 1 mmol) in toluene (15 mL) was deoxygenated (Ar, 1 h), Bu_3SnH (1.07 mL, 1.16 g, 4 mmol) was added, and the solution was purged with argon for 15 min. AIBN (25 mg, 0.15 mmol) was added and the solution was heated at reflux for 3 h. AIBN (25 mg, 0.15 mmol) was added, heating was continued for 3 h (TLC showed a less polar product), and volatiles were evaporated. Slow chromatography of the residue (20% hexanes/EtOAc → EtOAc) gave a mixture (243 mg) containing 9-[3-*O*-acetyl-6-(tributylstannyl)-3,5,6-trideoxy-*β*-D-*erythro*-hex-5-enofuranosyl]adenine (**16**) as a viscous oil, and further elution (3% MeOH/EtOAc) gave recovered **15** (62 mg, 14%). Product **16** was a mixture [*E*/*Z* ∼6:1; containing ∼15% of byproduct(s) and Bu_3SnX (^{1}H NMR)] that was used for the halodestannylation reactions. **16**(*E*): ^{1}H NMR ($CDCl_3$) δ 0.85−1.65 (m, 27H), 2.01 (s, 3H), 2.25−2.60 (m, 2H), 4.72−4.86 (m, 1H), 5.70 (br d, J = 5.5 Hz, 1H), 5.80 (br s, 2H), 6.10 (s, 1H), 6.11 (dd, J = 18.6, 5.8 Hz, 1H), 6.38 (d, J = 18.6, 1H), 7.91 (s, 1H), 8.35 (s, 1H); MS (CI) m/z 580 (100, MH^+, ^{120}Sn), 578 (78, MH^+, ^{118}Sn), 576 (42, MH^+, ^{116}Sn).

NIS (47 mg, 0.21 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a solution of **16** [115 mg; ∼98 mg, 0.17 mmol of **16**) in CH_2Cl_2/CCl_4 (∼1:1, 10 mL) at −20 °C, and stirring was continued for 1 h (TLC showed more polar product). The faint-pink mixture was poured into $NaHCO_3$/H_2O and extracted ($CHCl_3$). The combined organic phase was washed (dilute $NaHSO_3$/H_2O, brine) and dried ($MgSO_4$), and volatiles were evaporated.

NH_3/MeOH (10 mL) was added to a solution of the iodo product in MeOH (10 mL) at ~0 °C (ice bath), and stirring was continued for 3 h. Volatiles were evaporated, and short-column flash chromatography of the residue (EtOAc → 10% S_2/EtOAc) gave **17** (60 mg, ~95%). RP-HPLC (preparative column, program: 20% MeCN/H_2O for 20 min, 20 → 60% for 70 min, 2.8 mL/min; t_R = 81 min) and crystallization (MeOH/H_2O, ~1:1) gave **17** (52 mg, ~83% from **16**) as fine colorless needles: mp 195−197 °C; UV max 259 nm (ϵ 14 000), min 235 nm (ϵ 4000); ^{1}H NMR δ 2.05−2.43 (m, 2H), 4.60−4.82 (m, 2H), 5.77 (d, J = 4.0 Hz, 1H), 5.89 (d, J = 1.5 Hz, 1H), 6.71 (d, J = 13.6 Hz, 1H), 6.82 (dd, J = 13.6, 6.7 Hz, 1H), 7.32 (br s, 2H), 8.17 (s, 1H), 8.26 (s, 1H); ^{13}C NMR δ (C3′ overlap with Me_2SO-d_6 peaks), 74.77, 81.90, 82.35, 90.79, 119.25, 139.26, 145.32, 149.24, 152.91, 156.32; MS (CI) m/z 374 (100, MH^+). Anal. Calcd for $C_{11}H_{12}IN_5O_2$ (373.2): C, 35.41; H, 3.24; N, 18.77. Found: C, 35.17; H, 3.50; N, 18.77.

9-[6(*E*)-Bromo-3,5,6-trideoxy-β-D-*erythro*-hex-5-enofuranosyl]adenine (18). NBS (57 mg, 0.32 mmol) in CH_2Cl_2/CCl_4 (1:1, 10 mL) was added dropwise to a solution of **16** (173 mg; ~147 mg, 0.25 mmol of **16**; from procedure E) in CH_2Cl_2/CCl_4 (1:1, 10 mL) at −30 °C, and stirring was continued for 2 h. The mixture was poured into saturated $NaHCO_3$/H_2O and extracted ($CHCl_3$). The organic phase was washed (brine) and dried ($MgSO_4$), and volatiles were evaporated.

Treatment of the bromo product (as described for **17**) with NH_3/MeOH (15 mL), flash chromatography, RP-HPLC (t_R = 75 min), and crystallization (MeOH/H_2O, ~5:1) gave **18** (64 mg, ~78% from **16**): mp 198−200 °C; UV max 259 nm (ϵ 15 800), min 229 nm (ϵ 5200); ^{1}H NMR δ 2.10−2.40 (m, 2H), 4.62−4.70 (m, 1H), 4.74−4.85 (m, 1H), 5.81 (d, J = 3.6 Hz, 1H), 5.92 (d, J = 1.7 Hz, 1H), 6.53 (dd, J = 13.5, 7.9 Hz, 1H), 6.77 (d, J = 13.5 Hz, 1H), 7.32 (br s, 2H), 8.17 (s, 1H), 8.26 (s, 1H); ^{13}C NMR δ (C3′ overlap with Me_2SO-d_6 peaks), 74.85, 79.74, 90.88, 110.07, 119.26, 137.69, 139.26, 149.23, 152.91, 156.33; MS (CI) m/z 328 (20, MH^+, ^{81}Br), 326 (21, MH^+, ^{79}Br), 247 (84), 136 (100). Anal. Calcd for $C_{11}H_{12}BrN_5O_2$ (326.2): C, 40.51; H, 3.71; N, 21.47. Found: C, 40.70; H, 3.88; N, 21.27.

9-[3,5,6-Trideoxy-6(*E*)-fluoro-β-D-*erythro*-hex-5-enofuranosyl]adenine (19). A solution of **16** (150 mg; ~128 mg, 0.22 mmol of **16**; from procedure E) in dried CH_2Cl_2 (8 mL) was injected into a stirred suspension of AgOTf (103 mg, 0.4 mmol) in dried CH_2Cl_2 (3 mL) under Ar at ambient temperature in a flame-dried flask with a rubber septum. XeF_2 (76 mg, 0.45 mmol) in dried CH_2Cl_2 (4 mL) was injected, the flask was covered with aluminum foil, and stirring was continued for 45 min. The mixture was poured into $NaHCO_3$/H_2O (15 mL) and extracted [$CHCl_3$ (3×), EtOAc (2×), and EtOAc/MeOH (9:1; 3×)]. The combined organic phase was dried ($MgSO_4$), volatiles were evaporated, and the residue was dissolved [NH_3/MeOH (30 mL)] and stirred overnight at ambient temperature. Volatiles were evaporated, and column chromatography of the residue (EtOAc → 50% S_2/EtOAc) gave a mixture (48 mg) containing **19**: ^{19}F NMR δ −125.61 [dd, J = 83.9, 17.8 Hz, 0.77, F6′(*E*)], −126.26 [dd, J = 83.9, 43.2 Hz, 0.23, F6′(*Z*)]; the ^{1}H NMR (CD_3OD) signal for H6′ in **19**(*Z*) was at δ 6.70 (dd, J = 83.9, 4.6 Hz), and visible peaks for the protiodestannylated 5′-methylene byproduct were at δ 5.22 (d, J = 10.4 Hz, $H6'_{cis}$), 5.36 (d, J = 17.1 Hz, $H6'_{trans}$), 6.07 (ddd, J = 17.4, 10.4, 6.8 Hz, H5′). Integration idicated the ratios of **19**, the (*Z*)-isomer, and the methylene analogue (~3.5:1:3). RP-HPLC (preparative column, program: 15% MeCN/H_2O for 40 min, 15 → 45% for 50 min, 2.8 mL/min) and crystallization (MeOH) gave **19** (10 mg, ~15% from **16**;t_R = 81 min): mp 197−199 °C; UV max 260 nm (ϵ 13 300), min 226 nm (ϵ 1000); ^{1}H NMR (CD_3OD) δ 2.14 (ddd, J = 13.6, 6.2, 2.1 Hz, 1H), 2.26 (ddd, J = 13.6, 9.8, 5.5 Hz, 1H), 4.68−4.85 (m, 2H), 5.68 (ddd, J = 17.4, 11.1, 8.9 Hz, 1H), 5.97 (d, J = 1.3 Hz, 1H), 6.95 (dd, J = 83.9, 11.1 Hz, 1H), 8.15 (s, 1H), 8.20 (s, 1H); ^{19}F NMR δ −125.61 (dd, J = 83.9, 17.8 Hz); MS (CI) m/z 266 (100, MH^+). Anal. Calcd for $C_{11}H_{12}FN_5O_2 \cdot H_2O \cdot 0.5$ MeOH (299.3): C, 46.15; H, 5.39; N, 23.40. Found: C, 46.45; H, 5.58; N, 23.09.

Concentration-Dependent Enzyme Inhibition. AdoHcy hydrolase (1 μg) was incubated with various concentrations of the inhibitors in 500 μL of phosphate buffer (pH 7.2) containing 1 mM EDTA at 37 °C for 10 min. Adenosine deaminase (4 units) and 50 μL of [2,8-^{3}H]AdoHcy (1 mM) were added to the reaction mixture and incubation was continued for 5 min. Formic acid (5 M, 100 μL) was added to quench the reaction, and enzyme activity was determined by scintillation counting as described previously.[7] Lineweaver−Burk analysis with various concentrations of adenosine (4−64 μM) as substrate and the inhibitors (10−80 μM) gave the noted K_i values for compounds **17**−**19** as competitive inhibitors.

Acknowledgment. We thank the American Cancer Society (Grant No. DHP-34), Brigham Young University development funds, Chosun University (B.-O.R.), and the United States Public Health Service (Grant No. GM-29332) for support and Mrs. Jeanny Gordon for assistance with the manuscript.

JO971741U