Nucleic Acid Related Compounds. Part 76. Synthesis of 5′(E- and Z)- Chloro-4′,5′-didehydro-5′-deoxyadenosines via Chlorination and Thermolysis of Adenosine 5′-Sulfoxides. Mechanism...

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Nucleic Acid Related Compounds. 76. Synthesis of 5'(*E* and *Z*)-Chloro-4',5'-didehydro-5'-deoxyadenosines via Chlorination and Thermolysis of Adenosine 5'-Sulfoxides. Mechanism-Based Inhibition of *S*-Adenosyl-L-homocysteine Hydrolase[1]

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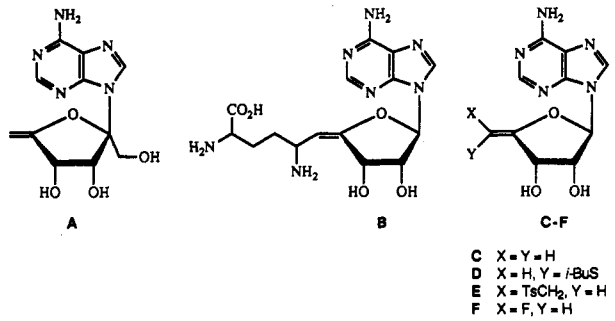
Treatment of 2',3'-di-*O*-acetyl-5'-*S*-(4-methoxyphenyl)-5'-thioadenosine (**1a**), or its sulfoxides **2a**(S_R) and **3a**(S_S), with iodobenzene dichloride and potassium carbonate in acetonitrile resulted in formation of the 5'-chloro(and 5',5'-dichloro)-5'-deoxy-5'-[(4-methoxyphenyl)sulfinyl]adenosines **4a**, **5a**, **6a**, and minor diastereomers. Deprotection of **5a** gave 5'(*S*)-chloro-5'-deoxy-5'-[(4-methoxyphenyl)-sulfinyl(S_S)]adenosine [**5b**(5'*S*,S_S)] whose stereochemistry and conformation were established by X-ray crystallography. The α-chlorination of sulfoxides **2a**(S_R) and **3a**(S_S) occurred with predominant retention of configuration at sulfur. Thermolysis of the α-chloro sulfoxides and deprotection gave the chloromethylene derivatives. The 5'(*Z*)-chloro-4',5'-didehydro-5'-deoxyadenosine [**9b**(5'*Z*)] diastereomer was found to be a potent time-dependent inhibitor of *S*-adenosyl-L-homocysteine hydrolase.

Interest in the modification of nucleosides at C4', especially the introduction of a 4',5'-double bond in the carbohydrate moiety, has been stimulated by the presence of this structural feature in the nucleoside antibiotics angustmycin A (decoyinine) (**A**)[2a] and the 4',5'-didehydrosinefungin derivative A9145C (**B**).[2b] The latter is an inhibitor of methyl transferase enzymes, and this inhibition can be reversed by the addition of *S*-adenosylmethionine.[2b] It also was found that synthetic 4',5'-didehydro-5'-deoxyadenosine (**C**)[3] was accepted as an alternative substrate[4] by *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase, EC 3.3.1.1) (see Figure 1). Inhibition of AdoHcy hydrolase results in higher cellular concentrations of AdoHcy which causes suppression of the methylation of crucial biomolecules by feedback inhibition of methyl transferase enzymes.[5] Therefore, the development of mechanism-based inhibitors of AdoHcy hydrolase is an attractive chemotherapeutic goal.[6]



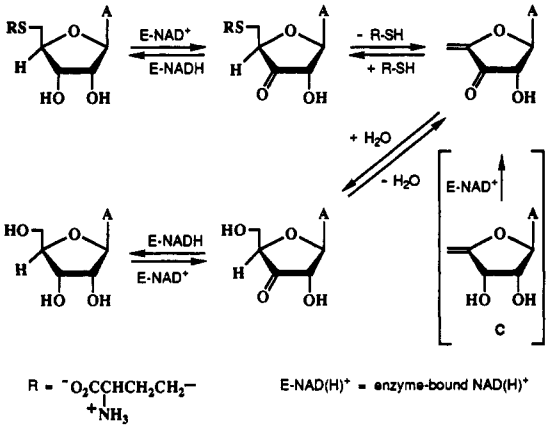


Figure 1. Proposed mechanism for *S*-adenosyl-L-homocysteine hydrolase.

Syntheses of unsubstituted 4',5'-unsaturated nucleosides[7] have employed base- or silver fluoride-promoted eliminations with protected 5'-deoxy-5'-iodonucleosides, base-promoted eliminations with 5'-*O*-sulfonyl nucleosides including the synthesis of angustmycin A (**A**),[3] and thermal eliminations with 5'-selenoxides.[8] Nucleoside 4',5' enol acetate[9a] and enamine[9b] derivatives were prepared from protected nucleoside 5'-aldehydes. Vinyl thioether compound **D** was prepared by treatment of the 5'-dithioacetal of a benzoylated adenosine 5'-aldehyde derivative with bromine and DBU.[10] A protected 4',5'-didehydro-5'-

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deoxy-5′-iodoadenosine derivative was formed during efforts to synthesize the antibiotic nucleocidin.[11] An ethylidene (4′,5′-didehydro-5′-deoxy-5′-methyladenosine) analogue was prepared by coupling a sugar derivative with the chloromercury salt of 6-benzamido purine.[12] Isomerization of tosylmethylene derivatives of adenosine[13a] (and uridine[13b]) to give the 4′,5′-unsaturated allylic tosyl compound **E** occurred under mildly basic conditions.

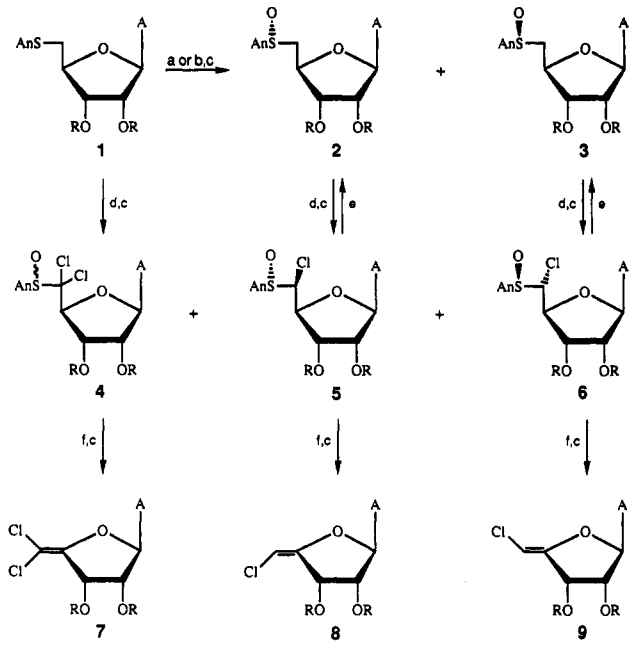
Parallel efforts by our laboratory[14] and the Marion Merrell Dow group[15,16] have resulted in syntheses of 5′-fluoro-5′-*S*-alkyl(and aryl)-5′-thionucleosides and derived 5′-halo, 5′,5′-dihalo, and other 4′,5′-modified nucleoside derivatives. Several of these are antiviral and antineoplastic agents, and 4′,5′-didehydro-5′-deoxy-5′(*Z*)-fluoroadenosine (**F**) is a potent mechanism-based inhibitor of AdoHcy hydrolase[15] with antiretroviral,[15a,b] antimalarial,[16a] and antiinflamitory[16b] activity. During the course of this work, the synthesis and biological activity of 5′-halogenated-4′,5′-unsaturated adenosine derivatives including "5′(*Z*)-chloro-4′,5′-didehydro-5′-deoxyadenosine" were reported.[15b] McCarthy and co-workers employed sulfuryl chloride/pyridine[17] for the α-chlorination of protected adenosine 5′-sulfoxides.[15b]

We now report alternative syntheses of 5′-chloro(and 5′,5′-dichloro)-4′,5′-didehydro-5′-deoxyadenosine derivatives via chlorination of 3′,5′-di-*O*-acetyl-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**1a**), or its **2a**(S_R) and **3a**(S_S) sulfoxides, with iodobenzene dichloride followed by thermolysis of the α-chloro sulfoxides (Scheme I). Our stereochemical assignments were made with X-ray crystallography, NMR spectroscopy, and stannyl radical-mediated hydrodechlorination reactions. The *authentic* 5′(*Z*)-chloro-4′,5′-didehydro-5′-deoxyadenosine (**9b**) diastereomer causes potent time-dependent inactivation of AdoHcy hydrolase.

Results and Discussion

From available procedures for the synthesis of α-chloro thioethers[18] and α-chloro sulfoxides,[19] we examined transformations with *N*-chlorosuccinimide (NCS) and iodobenzene dichloride. The latter was reported to give cleavage products with phenyl trityl sulfide and benzyl trityl sulfide, presumably via *S*-chlorosulfonium intermediates.[20] However, Colonna and co-workers reported conversions of other thioethers and sulfoxides to α-chloro sulfoxides with $PhICl_2$ and studied stereochemical consequences at the sulfur and α-carbon atoms.[21]

Scheme I[a]



A = adenin-9-yl; An = (*p*)$CH_3OC_6H_4$; Series **a**: R = CH_3CO, **b**: R = H.

[a] Key: (a) *m*-CPBA/CH_2Cl_2/−40 °C; (b) $PhICl_2$ (1.05 equiv)/(CH_3CN or pyridine)/−20 °C; (c) NH_3/MeOH; (d) $PhICl_2$/K_2CO_3/MeCN; (e) Bu_3SnH/AIBN/C_6H_6/Δ; (f) *i*-Pr_2NEt/(diglyme or Me_2SO)/Δ.

Conversion[22] of adenosine to 5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (**1b**) (via 5′-chloro-5′-deoxyadenosine) followed by acetylation efficiently afforded protected sulfide **1a**. Treatment of **1a** (or its *S*-phenyl analogue[14a,c,22]) with 1 equiv of NCS or $PhICl_2$ under various conditions gave complex reaction mixtures which contained unchanged **1a** and its sulfoxide diastereomers **2a** and **3a**. It is noteworthy that the latter sulfoxides gave mainly deoxygenated starting material **1a** upon treatment with thionyl chloride, since other thioethers and sulfoxides were converted to α-chloro thioethers with this reagent.[18]

Treatment of **1a** with 3 equiv of NCS or $PhICl_2$ overnight at ambient temperature resulted in its disappearance (TLC). ^1H NMR spectra of the reaction mixture confirmed the absence of **1a** and its sulfoxides **2a** and **3a**. Addition of K_2CO_3 to the initial mixture of **1a** and $PhICl_2$ resulted in accelerated reaction rates and improved yields of α-chlorination products. Potassium carbonate might promote the conversion of intermediate *S*-chlorosulfonium

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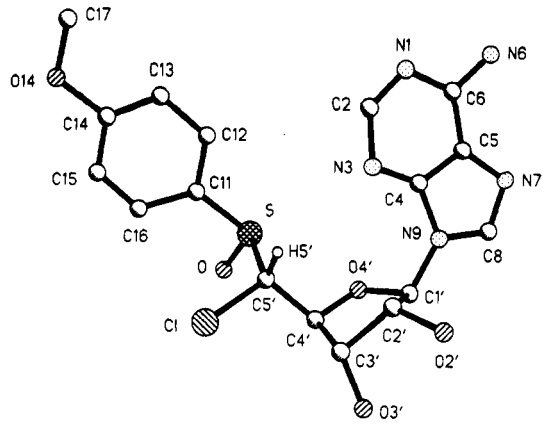

Figure 2. Computer-generated X-ray crystal structure of 5′(*S*)-chloro-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl(S_S)]adenosine [**5b**(5′*S*,S_S)].

species to 5′-chloro sulfoxides by proton abstraction from C5′. Iodobenzene dichloride gave higher yields, and reactions were easier to work up than those with NCS.

Treatment of **1a** with $PhICl_2$ (2.25 equiv) in CH_3CN in the presence of K_2CO_3 gave the 5′-chloro sulfoxide diastereomers **5a** and **6a** in 68% combined yield. Partial chromatographic separation of **5a** (^{1}H NMR δ 5.42 (d, $^3J_{5'-4'}$ = 10.2 Hz, H5′)) and **6a** (δ 4.94 (d, $^3J_{5'-4'}$ = 4.2 Hz, H5′)) from the other products was achieved. Diastereomer **5a**[5′*S*,*S* at sulfur (S_S)] was produced in ~46% yield (67% of the total α-chloro sulfoxides), **6a**(5′*R*,S_R) in ~14% yield, and other diastereomers including 5′,5′-dichloro sulfoxides **4a** in ~9% yield (**5a**/**6a**/other isomers ~5.2:1.5:1). Deacetylation (NH_3/MeOH) of **5a** and crystallization afforded **5b**(5′*S*,S_S) whose configurations at sulfur and C5′ were determined by X-ray crystallography (Figure 2). The configuration of **6a**(5′*R*,S_R) was deduced by chemical interconversions (see below). The attempted analogous deacetylation of **6a** resulted in spontaneous decomposition with release of adenine.

The computer drawing of **5b**(5′*S*,S_S) is shown in Figure 2. The sugar ring has a pseudorotation angle of 168° indicating a $^2T_3$ conformation.[23] Both the adenine and benzene rings are planar, as expected. The dihedral angle between the least-squares planes of these rings is 15.7° which makes the extended or open conformation of these two aromatic ring systems essentially coplanar. In fact, the average deviation of a ring atom from the least-squares plane calculated for the nine adenine and six benzene heavy atoms is 0.30 Å and the maximum deviation of a ring atom from that plane is 0.76 Å. Interestingly, the average deviation of heavy atoms from the least-squares plane calculated for all non-hydrogen atoms in the molecule is 0.63 Å and the largest deviation of any heavy atom is 2.36 Å [O (sulfoxide)]. Because of the scarcity of observed data, only the atoms Cl, S, and O were refined anisotropically. As a result, only one of the hydrogen atoms, HO3′, which could be involved in hydrogen bonds was located in difference maps. However, it appears that all hydrogen atoms bonded to oxygen and nitrogen atoms are involved in intermolecular hydrogen bonding. Criteria used for this inference are the short donor–acceptor interatomic distances and C–D--A angles near 109°. There is no evidence for intramolecular hydrogen bonding, which is consistent with the "planar" conformation of the molecule.

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The glycosyl torsion angle C8–N9--C1′–O4′ is −115 (2)° and the C3′–C4′--C5′–S torsion angle has a value of 166 (1)°. Experimental details, crystallographic parameters, and structural data are available.[24]

Thermolysis of **5a**(5′*S*,S_S) (150 °C, 36 h) with Hünig's base in diglyme gave the 5′(*E*)-chloromethylene compound **8a**. More mild treatment of **6a**(5′*R*,S_R) (145 °C, 5 h) gave the less thermally-stable 5′(*Z*)-chloromethylene diastereomer **9a**. Marked differences in the rates of syn-elimination from sulfoxides **5a** and **6a** allowed the preparation of **8a** and **9a** from mixtures of the precursor α-chloro sulfoxides. Thermolysis of **5a**/**6a** (~3.5:1) at ~145 °C for 4–5 h resulted in formation of **8a**/**9a** (~1:5.7). The more thermally stable, unreacted **5a** was readily recovered by chromatography. Deacetylation of the **8a**/**9a** mixture, HPLC, and crystallization gave the 5′-chloromethylene products **8b**(*E*) and **9b**(*Z*).

^{1}H NMR spectra of these isomers had singlets for H5′ at δ 5.90 for **8b**(*E*) and 5.60 for **9b**(*Z*). These shifts compare well with values reported[15b] for the corresponding 5′-fluoromethylene analogues (H5′ peak for the Z isomer is 0.48 ppm upfield from that for the E; confirmed by us with samples prepared by thermolysis of 5′-fluoro sulfoxide derivatives whose structures were verified by X-ray crystallography and NMR[14c,d]). Protected chloromethylene compound **8a**(5′*E*) had a vinyl proton signal at δ 5.84 (d, $^4J_{5'-3'}$ = 1.14 Hz, H5′) [**9a**(5′*Z*): δ 5.64 (d, $^4J_{5'-3'}$ = 0.72 Hz, H5′)] in harmony with the usual trans > cis allylic coupling constants.[5c,25] The ^{13}C NMR signal for C5′ was at δ 95.31 for **8b** and 90.93 for **9b**. Finally, NOE difference spectroscopy experiments showed ~5% enhancement of the vinyl proton signal at δ 5.60 for **9b** upon irradiation of the signal for H3′ at δ 4.75 whereas parallel experiments with **8b** showed little or no enhancement at δ 5.90. Availability of only the more stable *E* diastereomer **8b** by the Marion Merrell Dow group[15b] and slight enhancements of its H5′ signal upon irradiation at H3′ in some NOE experiments apparently resulted in an erroneous tentative assignment of the 5′(*Z*) stereochemistry to **8b**.

Since thermolyses of **5a** gave **8a**(5′*E*), and **6a** gave **9a**(5′*Z*), and thermal sulfoxide eliminations proceed with syn stereochemistry, the C5′ configurations for **5a**(5′*S*) and **6a**(5′*R*) were indicated. The large differences in proton coupling constants for compounds **5a** ($^3J_{5'-4'}$ = 10.2 Hz) and **6a** ($^3J_{5'-4'}$ = 4.2 Hz) suggested different chirality at sulfur as well. The configuration for **6a** was established as S_R by stannyl radical-mediated hydrodehalogenation[26] and comparison of the product **3a** NMR spectra with those of 2′,3′-di-*O*-acetyl-5′-deoxy-5′-phenylsulfinyl(S_S)adenosine.[14c,d] [Note that the absolute configurations at sulfur in sulfoxide **2a** and α-chloro sulfoxide **5a** (or **3a** and **6a**) are the same, but the *R*/*S* configuration descriptors change owing to the change in Cahn–Ingold–Prelog priority of C5′ when a chloro substituent is present.] Thus, treatment of **5a**(5′*S*,S_S) with Bu_3SnH/AIBN/C_6H_6/Δ gave **2a**(S_R) [and **6a**(5′*R*,S_R) gave **3a**(S_S)] in high yields. Independent control treatments of **2a**(S_R) and **3a**(S_S) with Bu_3SnH/AIBN/C_6H_6/Δ demonstrated the stable stereochemistry at sulfur under these reaction conditions.

Our chlorination results are in agreement with Colonna's

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Table I. ^{13}C NMR Spectral Data[a,b]

compd	C2	C4	C5	C6	C8	C1′	C2′[c]	C3′[c]	C4′	C5′	aromatic C1″	aromatic C2″	aromatic C3″	aromatic C4″	CH_3O
1b	152.62	149.47	119.20	156.05	139.94	87.33	72.57	72.52	82.96	37.41	125.50	132.99	114.71	158.46	55.71
2b(S_R)	152.94	149.60	119.78	156.54	140.95	88.36	73.39	72.42	78.59	61.09	135.89	126.02	115.12	161.82	55.63
3b(S_S)	152.99	149.72	119.55	156.49	140.43	87.82	73.34	72.54	79.12	59.02	134.49	126.70	114.93	161.91	55.56
4b(S_S)	153.45	150.17	119.54	156.27	139.51	87.88	72.12	71.08	86.67	102.97	128.72	129.35	114.76	163.62	55.77
4b(S_R)[f]	153.45	150.27	118.84	156.27	139.66	86.52	72.07	71.35	85.66	100.65	127.56	130.32	114.42	163.64	55.74
5a(5′*S*,S_S)[d]	153.43	149.48	119.64	156.69	140.55	85.76	71.97	70.70	81.06	76.42	130.54	126.77	115.04	162.34	55.67
5b(5′*S*,S_S)	153.17	149.56	119.73	156.38	141.31	88.22	72.63	71.20	83.79	77.38	130.48	126.79	115.00	162.72	55.66
6a(5′*R*,S_R)[e]	153.32	149.49	119.27	156.57	139.94	85.59	71.67	70.56	80.82	77.36	131.01	127.30	114.99	162.51	55.68
7b	153.53[g]	150.05	119.29	156.30	140.47	88.25	71.43	68.83	153.53[g]	99.06					
8b(*E*)	153.35	150.19	119.50	156.56	140.38	87.63	71.42	67.59	158.10	95.31					
9b(*Z*)	153.37	149.94	119.50	156.60[c]	140.47	88.16	72.02	69.44	156.73[c]	90.93					
10b	153.26	149.87	118.96	156.14	140.00	88.25[c]	71.94	70.91	86.95[c]	72.21[c]					

[a] Chemical shifts (δ) in Me_2SO-d_6 at 50.0 MHz. [b] Proton decoupled peaks appeared as singlets. [c] Assignments may be reversed. [d] Peaks also at 20.10, 20.43, 169.55, 169.64 (Ac's). [e] Peaks also at 20.15, 20.32, 169.54, 169.59 (Ac's). [f] Assignments were made from a spectrum of the diastereomeric mixture ($S_{R/S}$, ~3.1). [g] Unresolved peaks were distinguished by an APT experiment.

studies on the stereochemistry of conversions of thioethers and sulfoxides to α-halo sulfoxides.[21b-g] Oxidation of **1a** with 3-chloroperoxybenzoic acid (*m*-CPBA) followed by silica column chromatography gave clean samples of sulfoxides **2a**(S_R) and **3a**(S_S). Treatment of **2a**(S_R) with $PhICl_2$ (1.25 equiv) gave a mixture of **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/others (~15.5:3.5:1; ^1H NMR) in 84% yield. Analogous treatment of **3a**(S_S) gave **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/others (~5.5:8:1) in 82% yield. Thus, chlorination under these conditions gave predominant retention of configuration at sulfur. Treatment of **2a**(S_R) with $PhICl_2/AgNO_3/CH_3CN$[21c] gave predominant inversion of configuration at sulfur to give **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/others (~2.5:5.5:1) in 25% yield in harmony with the prior studies.[21c]

Direct treatment of **1a** with 4.5 equiv of $PhICl_2$ gave the 5′,5′-dichloro sulfoxide diastereomers **4a** [$S_{R/S}$(~1:1), 67%] plus ~15% of the 5′-chloro isomers [mainly **5a**(5′*S*,S_S)]. Deacetylation and crystallization gave a sample of **4b** [$S_{R/S}$ (~1:24), HPLC] whose S_S configuration was assigned by comparison of relative ^{13}C NMR shifts (Table I) of C5′ and C1″ with those of **2b**(S_R) and **3b**(S_S). Configurations of the latter compounds were assigned by comparisons of ^{13}C and ^1H NMR spectra with those of 5′-deoxy-5′-phenylsulfinyl(S_R)adenosine, whose structure was established by X-ray crystallography.[14c,d]

Thermolysis (145 °C, 2.5 h) of mixed **4a** gave the 5′,5′-dichloromethylene product **7a** plus 2′,3′-di-*O*-acetyl-5′,5′-dichloro-5′-deoxyadenosine (**10a**) in low combined yield. Thermolyses of **4a** in DMSO (**7a**/**10a**; ~1.5:1) or diglyme (**7a**/**10a**; ~1:2) gave significantly different product ratios. Deacetylation of these mixtures and reversed-phase HPLC gave clean samples of 5′,5′-dichloro-4′,5′-didehydro-5′-deoxyadenosine (**7b**) and 5′,5′-dichloro-5′-deoxyadenosine (**10b**).

As noted previously[15b] [with incorrect tentative assignment of the 5′(*Z*) configuration], the 5′(*E*)-chloromethylene analogue **8b**(5′*E*) did not cause time-dependent inactivation of AdoHcy hydrolase.[14c,15b] However, our *authentic* 9-[5(*Z*)-chloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl]adenine [**9b**(*Z*)] did function as a potent time-dependent inactivator of this enzyme (K_I = 54.5 nM and k_2 = 0.046 min^{-1}) with kinetic parameters comparable to those of the 5′(*Z*)-fluoromethylene analogue **F** (K_I = 22 nM and k_2 = 0.042 min^{-1}) in Borchardt's beef liver AdoHcy hydrolase assay.[14c] Possible mechanisms involving conversions of these prodrug 5′-halomethylene **F** and **9b**(*Z*) analogues of **C** (Figure 1) to active (oxidized) 5′-aldehyde agent(s) have been discussed,[14c,15b,c] and further studies are in progress (R. T. Borchardt et al., unpublished results).

Experimental Section

Uncorrected melting points were determined on a microstage block. ^1H (200-MHz) and ^{13}C (50-MHz) NMR spectra were determined with Me_2SO-d_6 solutions unless otherwise noted. NOE experiments were performed at 500 MHz. UV spectra were determined with MeOH solutions. Iodobenzene dichloride was prepared as described.[27] TLC was performed on Merck Kieselgel 60 F_{254} sheets with: S_1, MeOH/EtOAc (2:25), and S_2, MeOH/$CHCl_3$ (1:9). "Chromatography" was performed on silica columns. Reagent-grade chemicals were used, and solvents were redistilled. CH_3CN was dried by reflux over and distillation from CaH_2. Preparative and analytical HPLC were performed on C_{18} reversed-phase columns.

2′,3′-Di-*O*-acetyl-5′-*S*-(4-methoxyphenyl)-5′-thioadenosine (1a). A stirred suspension of 5′-*S*-(4-methoxyphenyl)-5′-thioadenosine[22] (**1b**, 3.89 g, 10 mmol) in Ac_2O (2.86 mL, 3.08 g, 27.5 mmol) was cooled in an ice bath, and pyridine (17 mL) was added. Stirring was continued at ~0 °C for 7 h or until TLC (S_2) indicated complete reaction. MeOH (50 mL) was added, stirring was continued for 30 min, and the solution was evaporated. The residue was partitioned (2% AcOH/H_2O//$CHCl_3$), and the organic phase was washed (H_2O, $NaHCO_3/H_2O$, brine, and H_2O), dried (Na_2SO_4), and evaporated to give **1a** (4.64 g, 98%) as a white solid foam (TLC homogeneous) used directly in subsequent reactions: ^1H NMR ($CDCl_3$) δ 2.02, 2.12 (s, s; 3, 3; Ac's), 3.30 (d, $J_{5'',5'-4'}$ = 5.9 Hz, 2, H5′,5″), 3.76 (s, 3, OCH_3), 4.33 (ddd, $J_{4'-3'}$ = 3.7 Hz, 1, H4′), 5.61 (dd, $J_{3'-2'}$ = 5.3 Hz, 1, H3′), 5.73 (br s, 2, NH_2), 6.03 (dd, $J_{2'-1'}$ = 6.1 Hz, 1, H2′), 6.11 (d, 1 H1′), 6.78 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.34 (d, 2, Ar), 7.90 (s, 1, H2), 8.32 (s, 1, H8); MS *m/z* 473.1377 (3, $M^+[C_{21}H_{23}N_5O_6S]$ = 473.1369).

2′,3′-Di-*O*-acetyl-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl($S_{R/S}$)]adenosine [2a(S_R) and 3a(S_S)]. A solution of *m*-CPBA (414 mg as 85% reagent, 2.04 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a cold (−50 °C) stirred solution of **1a** (946 mg, 2 mmol) in CH_2Cl_2 (25 mL). TLC indicated complete reaction as soon as the addition was finished. The solution was poured into ice-cold saturated $NaHCO_3/H_2O$ (50 mL), and the mixture was extracted with $CHCl_3$ (2 × 35 mL). The combined organic phase was washed with brine and then H_2O, dried ($MgSO_4$), and evaporated to give **2a**(S_R)/**3a**(S_S) (~1:1.2; 0.97 g, 99%) as a white foam used directly in subsequent reactions: MS *m/z* 489.1324 (9.2, $M^+[C_{21}H_{23}N_5O_7S]$ = 489.1318), 155.0173 (76, ArSO), 136.0620 (61, BH_2). Chromatography (2% MeOH/$CHCl_3$) gave **2a**(S_R) (312 mg, 32%) followed by **2a**(S_R/**3a**(S_S) (~1:1.9; 286 mg, 29%), and **3a**(S_S) (333 mg, 34%). **2a**(S_R): ^1H NMR ($CDCl_3$) δ 2.05, 2.12 (s, s; 3, 3; Ac's), 3.10 (dd, $J_{5'',-5'}$ = 13.1 Hz, $J_{5''-4'}$ = 2.4 Hz, 1, H5″), 3.55 (dd, $J_{5'-4'}$ = 10.9 Hz, 1, H5′), 3.83 (s, 3, OCH_3), 4.78 (ddd, $J_{4'-3'}$ = 4.9 Hz, 1, H4′), 5.63 (br s, 2, NH_2), 5.75 (dd, $J_{3'-2'}$ = 5.4 Hz, 1,

(27) Lucas, H. J.; Kennedy, E. R. *Organic Syntheses*; Wiley: New York, 1955; Coll. Vol. III, pp 482–483.

H3′), 6.05 (d, $J_{1'-2'}$ = 4.9 Hz, 1, H1′), 6.17 (dd, 1, H2′), 6.99 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.51 (d, 2, Ar), 7.85 (s, 1, H2), 8.28 (s, 1, H8). **3a**(S_S): ^{1}H NMR ($CDCl_3$) δ 2.02, 2.12 (s, s; 3, 3; Ac's), 3.22 (dd, $J_{5''-5'}$ = 13.6 Hz, $J_{5''-4'}$ = 5.2 Hz, 1, H5″), 3.58 (dd, $J_{5'-4'}$ = 6.8 Hz, 1, H5′), 3.80 (s, 3, OCH_3), 4.56 (ddd, $J_{4'-3'}$ = 4.0 Hz, 1, H4′), 5.73 (br s, 2, NH_2), 5.79 (dd, $J_{3'-2'}$ = 5.6 Hz, 1, H3′), 6.03 (d, $J_{1'-2'}$ = 5.7 Hz, 1, H1′), 6.20 (dd, 1, H2′), 6.86 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.50 (d, 2, Ar), 7.89 (s, 1, H2), 8.31 (s, 1, H8).

Treatment of **1a** (150 mg, 0.32 mmol) in CH_3CN (15 mL) with $PhICl_2$ (93 mg, 0.34 mmol) at −20 °C for 10 min gave **2a**(S_R)/**3a**(S_S) (~2:3; 117 mg, 75%) and recovered **1a** (15 mg, 10%) after analogous workup. Treatment of **1a** (100 mg, 0.21 mmol) in pyridine (10 mL) with $PhICl_2$ (61 mg, 0.22 mmol) gave **2a**(S_R)/**3a**(S_S) (~1.2:1; 65 mg, 63%) and recovered **1a** (8 mg, 8%).

5′-Deoxy-5′-[(4-methoxyphenyl)sulfinyl(S_R)]adenosine [2b(S_R)]. A solution of **2a**(S_R) (98 mg, 0.2 mmol) in MeOH (5 mL) was stirred with NH_3/MeOH (10 mL) at ambient temperature for 2 h. Evaporation of volatiles and crystallization of the residual white solid from MeOH gave **2b**(S_R) (71 mg, 88%): mp 264–265 °C dec; UV max 250 nm (ε 22 100), min 223 nm (ε 6700); ^{1}H NMR δ 3.08 (dd, $J_{5''-5'}$ = 13.4 Hz, $J_{5''-4'}$ = 2.5 Hz, 1, H5″), 3.44 (dd, $J_{5'-4'}$ = 10.6 Hz, 1, H5′), 3.82 (s, 3, OCH_3), 4.18 (ddd, $J_{3'-4'}$ = 2.8 Hz, $J_{OH-3'}$ = 4.3 Hz, $J_{3'-2'}$ = 4.6 Hz, 1, H3′), 4.32 (ddd, 1, H4′), 4.86 (ddd, $J_{2'-1'}$ = 6.0 Hz, $J_{OH-2'}$ = 5.9 Hz, 1, H2′), 5.47 (d, 1, OH3′), 5.55 (d, 1, OH2′), 5.95 (d, 1, H1′), 7.12 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.58 (d, 2, Ar), 7.32 (br s, 2, NH_2), 8.13 (s, 1, H2), 8.38 (s, 1, H8); MS CI (NH_3) *m/z* 406 (18, MH^+). Anal. Calcd for $C_{17}H_{19}N_5O_5S$ (405.4): C, 50.36; H, 4.72; N, 17.27; S, 7.91. Found: C, 50.30; H, 4.61; N, 17.09; S, 7.94.

5′-Deoxy-5′-[(4-methoxyphenyl)sulfinyl(S_S)]adenosine [3b(S_S)]. Deacetylation of **3a**(S_S) (98 mg, 0.2 mmol) [as described for **2b**(S_R)] gave **3b**(S_S) (64 mg, 79%): mp 212–213 °C dec; UV max 252 nm (ε 22 800), min 223 nm (ε 7900); ^{1}H NMR δ 3.25 (dd, $J_{5''-5'}$ = 13.2 Hz, $J_{5''-4'}$ = 4.9 Hz, 1, H5″), 3.56 (dd, $J_{5'-4'}$ = 8.3 Hz, 1, H5′), 3.78 (s, 3, OCH_3), 3.86 (ddd, $J_{4'-3'}$ = 3.5 Hz, 1, H4′), 4.23 (ddd, $J_{OH-3'}$ = 4.8 Hz, $J_{3'-2'}$ = 4.6 Hz, 1, H3′), 4.83 (ddd, $J_{OH-2'}$ = 5.6 Hz, $J_{2'-1'}$ = 5.9 Hz, 1, H2′), 5.42 (d, 1, OH3′), 5.54 (d, 1, OH2′), 5.82 (d, 1, H1′), 7.06 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.31 (br s, 2, NH_2), 7.58 (d, 2, Ar), 8.16 (s, 1, H2), 8.38 (s, 1, H8); MS CI (NH_3) *m/z* 406 (31, MH^+). Anal. Calcd for $C_{17}H_{19}N_5O_5S$ (405.4): C, 50.36; H, 4.72; N, 17.27; S, 7.91. Found: C, 50.26; H, 4.80; N, 17.23; S, 7.81.

2′,3′-Di-*O*-acetyl-5′-chloro-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl($S_{R/S}$)]adenosine [5a(5′*S*,S_S) and 6a(5′*R*,S_R)]. Method A (from Sulfide). General Procedure for Chlorination. $PhICl_2$ (1.55 g, 5.63 mmol) was added in one portion to a stirred mixture of dried K_2CO_3 (300 mg, 2.17 mmol) in a solution of **1a** (1.18 g, 2.5 mmol) in anhydrous CH_3CN (60 mL) under N_2 at ambient temperature. The **1a** [R_f ~0.55, TLC (S_1)] and intermediate sulfoxides **2a**/**3a** (R_f ~0.35–0.43) observed during earlier stages of the reaction were replaced by new compounds (R_f ~0.46–0.52) after 16 h. The mixture was evaporated (<30 °C), the residue was partitioned (H_2O/$CHCl_3$), and the aqueous layer was extracted ($CHCl_3$). The combined organic phase was washed with $Na_2S_2O_3/H_2O$, $NaHCO_3/H_2O$, and brine, dried ($MgSO_4$), concentrated, and chromatographed on a silica column (2% followed by 3.5% MeOH/AcOEt) to give **5a**/**6a** (890 mg, 68%) as a white solid foam. Analysis and combination of homogeneous fractions allowed separation of the fastest migrating **5a**(5′*S*,S_S) [206 mg, 16%; the total yield of this isomer was 46% (~67% of the chlorinated diastereomers by ^{1}H NMR analysis of all fractions)] and the slowest migrating **6a**(5′*R*,S_R) [63 mg, 5%; the total yield of this isomer was 14% (~20% of the chlorinated diastereomers)]. Diastereomer ratios varied slightly from run to run. **5a**(5′*S*,S_S): ^{1}H NMR ($CDCl_3$) δ 1.99, 2.16 (s,s; 3,3; Ac's), 3.85 (s, 3, OCH_3), 4.70 (dd, $J_{4'-5'}$ = 10.2 Hz, $J_{4'-3'}$ = 2.1 Hz, 1, H4′), 5.42 (d, 1, H5′), 5.75 (br s, 2, NH_2), 5.94 (dd, $J_{3'-2'}$ = 5.1 Hz, 1, H3′), 6.12 (d, $J_{1'-2'}$ = 6.7 Hz, 1, H1′), 6.46 (dd, 1, H2′), 7.00 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.42 (d, 2, Ar), 7.88 (s, 1, H2), 8.33 (s, 1, H8); MS *m/z* 525 (3.8, $M^+[^{37}Cl]$), 523 (10.5, $M^+[^{35}Cl]$), 370 (19, M − ArSO[^{37}Cl]), 368 (58, M − ArSO[^{35}Cl]), 278 (28), 155 (100), 156 (36), 139 (40), 135 (89, BH). **6a**(5′*R*,S_R): ^{1}H NMR ($CDCl_3$) δ 2.03, 2.14 (s,s; 3,3; Ac's), 3.82 (s, 3, OCH_3), 4.57 (dd, $J_{4'-5'}$ = 4.2 Hz, $J_{4'-3'}$ = 3.6 Hz, 1, H4′), 4.94 (d, 1, H5′), 5.77 (br s, 2, NH_2), 5.83–5.87 (m, 2, H2′,3′), 6.20 (d, $J_{1'-2'}$ = 5.4 Hz, 1, H1′), 6.99 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.61 (d, 2, Ar), 7.95 (s, 1, H2), 8.31 (s, 1, H8); MS CI (CH_4) *m/z* 526 (13, $MH^+[^{37}Cl]$), 524 (35, $MH^+[^{35}Cl]$), 370 (32, M − ArSO[^{37}Cl]), 368 (88, M − ArSO[^{35}Cl]), 136 (100, BH_2).

Method B (from Sulfoxide). $PhICl_2$ (344 mg, 1.25 mmol) was added in one portion to a stirred mixture of dried K_2CO_3 (100 mg, 0.72 mmol) in a solution of **2a**(S_R)/**3a**(S_S) (~1:1.2, 489 mg, 1 mmol) in anhydrous CH_3CN (20 mL) under N_2 at ambient temperature. After 9 h the mixture was evaporated, worked up, and purified as described in method A to give **5a**(5′*S*,S_S) (157 mg, 30%; purity ≥95%), **6a**(5′*R*,S_R) (115 mg, 22%; purity ≥95%), and a mixture of diastereomers (148 mg, 28%) for a total yield of **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/other diastereomers (~8:5.5:1; 420 mg, 80%).

Solvent, sulfoxide stereochemistry, $PhICl_2$ quantities, and other variables were found to affect the ratios of chloro sulfoxide diastereomers formed. (a) Treatment of **2a**(S_R)/**3a**(S_S) (~1:1.2; 244 mg, 0.5 mmol) in pyridine/CH_2Cl_2 (1:3, 8 mL) with $PhICl_2$ (172 mg, 0.625 mmol) at −20 °C to ambient temperature for 5 h gave **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/other diastereomers (~7:5:1; 196 mg, 75%). (b) Treatment of **2a**(S_R) (147 mg, 0.3 mmol) with $PhICl_2$ (103 mg, 0.375 mmol) and K_2CO_3 (42 mg, 0.3 mmol) in CH_3CN (6 mL) at ambient temperature for 7 h gave **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/other diastereomers (~15.5:3.5:1; 132 mg, 84%). (c) Treatment of **3a**(S_S) (147 mg, 0.3 mmol) with $PhICl_2$ (103 mg, 0.375 mmol) and K_2CO_3 (42 mg, 0.3 mmol) in CH_3CN (6 mL) at ambient temperature for 7 h gave **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/other diastereomers (~5.5:8:1; 129 mg, 82%). (d) Treatment of **2a**(S_R) (30 mg, 0.061 mmol) with $PhICl_2$ (21 mg, 0.077 mmol), K_2CO_3 (18 mg, 0.13 mmol), and $AgNO_3$[21c] (54 mg, 0.32 mmol) in CH_3CN (4 mL) at ambient temperature for 4 h gave **5a**(5′*S*,S_S)/**6a**(5′*R*,S_R)/other diastereomers (~2.5:5.5:1; 8 mg, 25%).

2′,3′-Di-*O*-acetyl-5′-deoxy-5′,5′-dichloro-5′-[(4-methoxyphenyl)sulfinyl($S_{R/S}$)]adenosine [4a($S_{R/S}$)]. Treatment of **1a** (860 mg, 1.82 mmol) with $PhICl_2$ (2.25 g, 8.19 mmol) and dried K_2CO_3 (350 mg, 2.54 mmol) in anhydrous CH_3CN (80 mL) under N_2 at ambient temperature for 24 h gave **4a**[$S_{R/S}$(1:1)]//**5a**(5′*S*,S_S)/**6a**(5′*R*,S_R) (**5a** ≫ **6a**) [~5.7:1; 679 mg 67%] after workup and purification as described for **5a**(5′*S*,S_S). The dichloro sulfoxides **4a** migrated slightly faster [TLC (S_1)] than **5a**(5′*S*,S_S) which allowed partial separation of **4a**: ^{1}H NMR ($CDCl_3$) δ 1.96, 1.99 (2 s, 3, Ac), 2.12, 2.13 (2 s, 3, Ac), 3.84, 3.85 (2 s, 3, OCH_3), 4.56 (d, $J_{4'-3'}$ = 2.3 Hz, 0.5 H, H4′), 4.96 (d, $J_{4'-3'}$ = 2.8 Hz, 0.5 H, H4′), 6.01–6.08 (m, 2, H3′,2′), 6.22 (br s, 2, NH_2), 6.34–6.40 (m, 1, H1′), 7.00, 7.02 (2 d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.69, 7.70 (2 d, 2, Ar), 8.09, 8.14 (2 s, 1, H2), 8.36 (s, 1, H8); MS *m/z* 561 (0.4, $M^+[^{37}Cl_2]$), 559 (2.2, $M^+[^{35}Cl,\ ^{37}Cl]$), 557 (3.3, $M^+[^{35}Cl_2]$), 406 (8, M − ArSO[$^{37}Cl_2$]), 404 (45, M − ArSO[^{35}Cl, ^{37}Cl]), 402 (67, M − ArSO[$^{35}Cl_2$]), 378 (57), 155 (100), 139 (60), 136 (23, BH_2).

5′(*S*)-Chloro-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl(S_S)]adenosine [5b(5′*S*,S_S)]. NH_3/MeOH (6 mL) was added to a solution of **5a**(5′*S*,S_S) (79 mg, 0.15 mmol) in MeOH (2 mL), and stirring was continued at ~0 °C (ice bath) for 45 min. Evaporation of volatiles gave a cream-colored solid which was recrystallized (MeOH) to give **5b**(5′*S*,S_S) (28 mg, 42%) as colorless needles. RP-HPLC purification of the mother liquor (20 → 30% CH_3CN/H_2O; 2.5 mL/min, 120 min) gave additional **5b**(5′*S*,S_S) (21 mg, 32%; t_R ~85 min): mp 220–224 °C dec; UV max 254 nm (ε 25 700), min 224 nm (ε 9300); ^{1}H NMR δ 3.81 (s, 3, OCH_3), 4.20 (d, $J_{4'-5'}$ = 10.3 Hz, 1, H4′), 4.30 (dd, $J_{3'-2'}$ = 4.6 Hz, $J_{OH-3'}$ = 4.1 Hz, 1, H3′), 5.15 (ddd, $J_{2'-1'}$ = 7.9 Hz, $J_{OH-2'}$ = 6.8 Hz, 1, H2′), 5.46 (d, 1, H5′), 5.62 (d, 1, OH3′), 5.80 (d, 1, OH2′), 6.05 (d, 1, H1′), 7.19 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.39 (br s, 2, NH_2), 7.45 (d, 2, Ar), 8.22 (s, 1, H2), 8.45 (s, 1, H8); MS CI (CH_4) *m/z* 442 (5.9, $MH^+[^{37}Cl]$), 440 (15, $MH^+[^{35}Cl]$), 2.86 (7, M − ArSO[^{37}Cl]), 284 (17, M − ArSO[^{35}Cl]), 157 (42), 141 (98), 136 (100, BH_2). Anal. Calcd for $C_{17}H_{18}ClN_5O_5S$ (439.9): C, 46.42; H, 4.12; N, 15.92. Found: C, 46.77; H, 4.33; N, 15.83.

Attempted Deacetylation of 6a(5′*R*,S_R). Analogous treatment of **6a**(5′*R*,S_R) resulted in decomposition with release of adenine.

5′,5′-Dichloro-5′-deoxy-5′-[(4-methoxyphenyl)sulfinyl($S_{R/S}$)]adenosine [4b($S_{R/S}$)]. NH_3/MeOH (20 mL) was added to a solution of the crude dichloro sulfoxide mixture **4a**[$S_{R/S}$(~1:1), containing ~15% of **5a**(5′*S*,S_S); 200 mg, ~0.36 mmol] in MeOH (10 mL), and stirring was continued at ~0 °C (ice bath) for 1 h. Volatiles were evaporated, and the residue was crystallized

(MeOH) and recrystallized (MeOH/H_2O (9:1)) to give **4b**[$S_{R/S}$(1:24, HPLC)] (61 mg, 36%) as colorless crystals: mp 236–238 °C dec; UV max 262 nm (ε 26 100), min 225 (ε 6600); ^1H NMR [**4b**(S_S)] δ 3.82 (s, 3, OCH_3), 4.00 (d, $J_{4'-3'}$ = 3.2 Hz, 1, H4'), 4.53 (ddd, $J_{3'-2'}$ = 5.9 Hz, $J_{OH-3'}$ = 6.2 Hz, 1, H3'), 4.85 (ddd, $J_{2'-1'}$ = 6.6 Hz, $J_{OH-2'}$ = 5.9 Hz, 1, H2'), 5.77 (d, 1, OH3'), 5.82 (d, 1, OH2'), 6.01 (d, 1, H1'), 7.18 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.35 (br s, 2, NH_2), 7.71 (d, 2, Ar), 8.20 (s, 1, H2), 8.40 (s, 1, H8); MS CI (CH_4) *m/z* 247 (2), 235 (2), 157 (14), 155 (31), 143 (100), 141 (100), 139 (34), 136 (13, BH_2). Anal. Calcd for $C_{17}H_{17}Cl_2N_5O_5S$ (474.3): C, 43.05; H, 3.61; N, 14.77. Found: C, 43.09; H, 3.61; N, 14.60.

Precipitation of **4b**[$S_{R/S}$(~3:1)] (45 mg, 26%) occurred in the first mother liquor: ^1H NMR **4b**(S_R) δ 3.82 (s, 3, OCH_3), 4.46–4.54 (m, 2, H4',3'), 4.84 (ddd, $J_{2'-3'}$ = 5.6 Hz, $J_{2'-1'}$ = 6.9 Hz, $J_{OH-2'}$ = 6.1 Hz, 1, H2'), 5.81 (d, $J_{OH-3'}$ = 6.6 Hz, 1, OH3'), 5.91 (d, 1, OH2'), 6.08 (d, 1, H1'), 7.16 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.38 (br s, 2, NH_2), 7.71 (d, 2, Ar), 8.20 (s, 1, H2), 8.44 (s, 1, H8).

The combined mother liquors were purified by silica column chromatography (MeOH/$CHCl_3$ (3:47)). The first eluted residue was crystallized (MeOH/H_2O (9:1)) to give additional **4b**[$S_{R/S}$(~4:1)] (22 mg, 13%) [mp 218–220 °C dec; UV max 260 nm (ε 27 500) min 225 nm (ε 7800)], and the second was crystallized (MeOH/EtOAc) to give **5b**(5′*S*,S_S) (19 mg, 12%). RP-HPLC (20 → 30% CH_3CN/H_2O at 2.5 mL/min for 180 min) gave **5b**(5′*S*,S_S) (t_R ~75 min), **4b**(S_S) (t_R ~130 min), and **4b**(S_R) (t_R ~145 min).

9-(2,3-Di-*O*-acetyl-5(*E*)-chloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine [8a(*E*)]. General Thermolysis Procedure. A solution of **5a**(5′*S*,S_S) (400 mg, 0.765 mmol) in diglyme (20 mL) containing EtN(*i*-Pr)$_2$ (395 mg, 0.53 mL, 3.06 mmol) was purged (N_2) for 30 min and placed in an oil bath at 150 ± 2 °C. Progress of the reaction was monitored by TLC (S_1). After 18 h, EtN(*i*-Pr)$_2$ (247 mg, 0.33 mL, 1.91 mmol) was added, and heating was continued for 18 h. Volatiles were evaporated in vacuo (~60 °C), and the residue was chromatographed on silica (MeOH/EtOAc (1:39)) to give **8a**(*E*) (116 mg, 41%) as a slightly yellow foam: ^1H NMR ($CDCl_3$) δ 1.98, 2.15 (s, s; 3, 3; Ac's), 5.62 (br s, 2, NH_2), 5.84 (d, $J_{5'-3'}$ = 1.14 Hz, 1, H5'), 6.12 (dd, $J_{2'-3'}$ = 5.8 Hz, $J_{2'-1'}$ = 6.9 Hz, 1, H2'), 6.33 (dd, 1, H3'), 6.36 (d, 1, H1'), 7.86 (s, 1, H2), 8.32 (s, 1, H8); MS *m/z* 369 (35, M^+[^{37}Cl]), 367 (96, M^+[^{35}Cl]), 326 (21), 324 (60), 308 (93), 272 (82), 248 (62), 230 (100), 178 (76), 177 (73), 136 (95), 135 (89, BH). Further elution of the column (MeOH/EtOAc (1:24)) gave recovered **5a**(5′*S*,S_S) (45 mg, 11%).

Longer thermolysis resulted in greater relative product decomposition. When thermolysis was stopped at 22 h, **8a**(*E*) (89 mg, 32%) and **5a**(5′*S*,S_S) (125 mg, 31%) were isolated. The use of DMSO as solvent reduced the time required for thermal elimination, but also reduced product yields.

9-(2,3-Di-*O*-acetyl-5(*Z*)-chloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine [9a(*Z*)]. Analogous thermolysis of **6a**(5′*R*,S_R) (150 mg, 0.29 mmol) in diglyme (10 mL) containing EtN(*i*-Pr)$_2$ (150 mg, 0.2 mL, 1.16 mmol) at 145 ± 2 °C (bath temperature) for 5 h, workup, and chromatography gave **9a**(*Z*) (62 mg, 58%) as a slightly yellow foam: ^1H NMR ($CDCl_3$) δ 2.04, 2.15 (s, s; 3, 3; Ac's), 5.64 (d, $J_{5'-3'}$ = 0.72 Hz, 1, H5'), 5.74 (br s, 2, NH_2), 6.08 (dd, $J_{2'-3'}$ = 5.8 Hz, $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 6.16 (dd, 1, H3'), 6.43 (d, 1, H1'), 7.92 (s, 1, H2), 8.35 (s, 1, H8); MS *m/z* 369 (30, M^+[^{37}Cl]), 367 (88, M^+[^{35}Cl]), 326 (20), 324 (52), 310 (28), 308 (84), 272 (70), 250 (26), 248 (75), 230 (100), 178 (56), 177 (59), 136 (88), 135 (82, BH).

Thermolysis of the Mixed Chloro Sulfoxides. A solution of chloro sulfoxides after chromatographic purification (**5a**/**6a**/others isomers, ~7:2:1; 700 mg, 1.34 mmol) in diglyme (35 mL) containing EtN(*i*-Pr)$_2$ (693 mg, 0.93 mL, 5.36 mmol) was purged (N_2) for 30 min and then heated at 145 ± 2 °C (bath temperature) for 4.5 h. Volatiles were evaporated in vacuo (~60 °C), and the residue was partitioned (HCl/H_2O//$CHCl_3$). The H_2O layer was extracted ($CHCl_3$), and the combined organic phase was washed with $NaHCO_3/H_2O$ and brine, dried ($MgSO_4$), and chromatographed on a silica column. Elution gave **8a**(*E*)/**9a**(*Z*) (~1:6, plus minor contaminants; 105 mg, ~21%) (MeOH/EtOAc (1:49)) and recovered **5a**(5′*S*,S_S) (390 mg, 56%; purity ≥95%) (MeOH/EtOAc (3.5:96.5)).

Treatment of this recovered **5a**(5′*S*,S_S) by the general thermolysis procedure (~150 °C, 26 h) gave additional **8a**(*E*) (115 mg, 42%; 24% based on the starting mixture) plus recovered **5a**(5′*S*,S_S) (125 mg, 32%; 18% based on the starting mixture).

9-(2,3-Di-*O*-acetyl-5,5-dichloro-β-D-*erythro*-pent-4-enofuranosyl)adenine (7a) and 2′,3′-Di-*O*-acetyl-5′-deoxy-5′,5′-dichloroadenosine (10a). Thermolysis of the Dichloro Sulfoxide Diastereomers. A solution of **4a**[$S_{R/S}$(~1:1)]/**5a**(5′*S*,S_S) (~9:1; 400 mg, ~0.72 mmol) in DMSO (10 mL) containing EtN(*i*-Pr)$_2$ (372 mg, 0.500 mL, 2.88 mmol) was heated at 145 ± 2 °C (bath temperature) for 2.5 h. Workup and silica column chromatography gave **7a**/**10a** [~1.5:1 (plus ~5% of impurities, ^1H NMR); 67 mg, ~23%] as a yellow foam: MS *m/z* 407 (8, M^+[$^{37}Cl_2$], **10a**), 405 (56), 403 (98), 401 (38, M^+[$^{35}Cl_2$], **7a**), 367 (30), 344 (41), 269 (49), 164 (100), 136 (52, BH_2). **7a**: ^1H NMR ($CDCl_3$, ~1.5:1 mixture of **7a**/**10a**) δ 2.00, 2.19 (s, s; 3, 3; Ac's), 6.00 (br s, 2, NH_2), 6.24 (dd, $J_{2'-3'}$ = 5.9 Hz, $J_{2'-1'}$ = 6.9 Hz, 1, H2'), 6.33 (d, 1, H3'), 6.47 (d, 1, H1'), 7.93 (s, 1, H2), 8.33 (s, 1, H8). **10a**: ^1H NMR ($CDCl_3$, ~1:6 mixture of **7a**/**10a**) δ 2.02, 2.17 (s, s; 3, 3; Ac's), 4.55 (dd, $J_{4'-5'}$ = 4.9 Hz, $J_{4'-3'}$ = 3.1 Hz, 1, H4'), 5.80 (br s, 2, NH_2), 5.86 (dd, $J_{3'-2'}$ = 5.9 Hz, 1, H3'), 5.98 (dd, $J_{2'-1'}$ = 6.5 Hz, 1, H2'), 6.14 (d, 1, H5'), 6.26 (d, 1, H1'), 8.00 (s, 1, H2), 8.36 (s, 1, H8).

The use of diglyme as solvent under these conditions gave **7a**/**10a** [~1:2 (plus ~5% impurities); ~21%]. With both solvents ~26% of the starting dichloro sulfoxides [diastereomer ratio now ~5.7:1; ^1H NMR doublets at δ 4.96 and 4.56 (H4'), respectively] were recovered. More vigorous thermolysis in diglyme (150 ± 2 °C, 4 h) gave **7a**/**10a** (~1:6, 29%). A minor amount of the unchanged monochloro sulfoxide **5a** (~6–8%) also was recovered from these thermolyses as the last fraction eluted from silica columns.

9-[5(*Z*)-Chloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl]adenine [9b(*Z*)]. General Deacetylation Procedure. NH_3/MeOH (5 mL) [saturated at ~0 °C (ice bath)] was added to a solution of **9a** (40 mg, 0.11 mmol) in MeOH (2 mL), and stirring was continued for 1 h. Volatiles were evaporated, and the residue was crystallized (MeOH) to give **9b**(*Z*)/**8b**(*E*) [~24:1 (HPLC); 16 mg, 51%]. The crystals and mother liquor were combined and evaporated, and the residue was dissolved (H_2O/CH_3CN (1:1)) and subjected to RP-HPLC (CH_3CN/H_2O (3:17); 2.5 mL/min). Evaporation of appropriate fractions gave **8b**(*E*) (t_R ~75 min, see below) and **9b**(*Z*) [t_R 89 min; 25 mg, 80%; "diffusion crystallized"[28] (MeOH/EtOAc)]: mp 210–213 °C dec; UV max 258 nm (ε 14 100), min 230 nm (ε 3800); ^1H NMR δ 4.75 (dd, $J_{3'-2'}$ = 4.8 Hz, $J_{OH-3'}$ = 5.0 Hz, 1, H3'), 4.99 (ddd, $J_{2'-1'}$ = 6.3 Hz, $J_{OH-2'}$ = 6.2 Hz, 1, H2'), 5.60 (s, 1, H5'), 5.81 (d, 1, OH3'), 5.86 (d, 1, OH2'), 6.27 (d, 1, H1'), 7.40 (br s, 2, NH_2), 8.18 (s, 1, H2), 8.45 (s, 1, H8); MS *m/z* 285 (21, M^+[^{37}Cl]), 283 (56, M^+[^{35}Cl]), 248 (26), 178 (23), 148 (23), 136 (100), 135 (30, BH). Anal. Calcd for $C_{10}H_{10}ClN_5O_3 \cdot 0.15H_2O \cdot 0.1C_4H_8O_2$ (295.2) (^1H NMR integration of residual EtOAc): C, 42.32; H, 3.79; N, 23.73. Found: C, 42.22; H, 3.78; N, 23.48.

9-[5(*E*)-Chloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl]adenine [8b(*E*)]. Deacetylation of **8a** (103 mg, 0.28 mmol), RP-HPLC [as described for **9b**(*Z*)], and crystallization (Me_2CO) gave **8b**(*E*) (66 mg, 83%): mp 132–135 °C softening, 203–205 °C dec; UV max 258 nm (ε 14 500), min 232 nm (ε 5500); ^1H NMR δ 4.73 (dd, $J_{3'-2'}$ = 5.0 Hz, $J_{OH-3'}$ = 5.1 Hz, 1, H3'), 5.07 (ddd, $J_{2'-1'}$ = 8.0 Hz, $J_{OH-2'}$ = 7.0 Hz, 1, H2'), 5.79 (d, 1, OH3'), 5.85 (d, 1, OH2'), 5.90 (s, 1, H5'), 6.23 (d, 1, H1'), 7.38 (br s, 2, NH_2), 8.16 (s, 1, H2), 8.47 (s, 1, H8); MS *m/z* 285 (21, M^+[^{37}Cl]), 283 (56, M^+[^{35}Cl]), 248 (21), 178 (22), 148 (24), 136 (100), 135 (33, BH). Anal. Calcd for $C_{10}H_{10}ClN_5O_3 \cdot 0.15H_2O \cdot 0.1C_3H_6O$ (292.2) (^1H NMR integration of residual Me_2CO): C, 42.34; H, 3.76; N, 23.97. Found: C, 42.12; H, 3.72; N, 23.69.

9-(5,5-Dichloro-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (7b) and 5′,5′-Dichloro-5′-deoxyadenosine (10b). Deacetylation of **7a**/**10a** (~1.5:1; 72 mg, 0.18 mmol) and RP-HPLC (15 → 25% gradient of CH_3CN/H_2O, 2.5 mL/min, 150 min) gave **10b** (t_R ~105 min; 14 mg, 24%; crystallized from MeOH/EtOAc) and **7b** (t_R ~125 min; 27 mg, 47%; crystallized from Me_2CO). [RP-HPLC with a 15 → 25% gradient of CH_3CN/H_2O allowed resolution of of the deacetylated products **8b**, **9b**, **10b**, and **7b** (order of elution) when different mixtures of protected

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chloro sulfoxides were thermolyzed.] **7b**: mp 176–183 °C dec; UV max 258 nm (ε 15 000), min 235 nm (ε 7700); ^{1}H NMR δ 4.73 (dd, $J_{3'-2'}$ = 5.2 Hz, $J_{OH-3'}$ = 5.5 Hz, 1, H3′), 5.11 (ddd, $J_{2'-1'}$ = 7.7 Hz, $J_{OH-2'}$ = 5.9 Hz, 1, H2′), 5.95 (d, 1, OH3′), 5.99 (d, 1, OH2′), 6.34 (d, 1, H1′), 7.42 (br s, 2, NH_2), 8.18 (s, 1, H2), 8.50 (s, 1, H8); MS *m/z* 321 (3.8, $M^+[^{37}Cl_2]$), 319 (28, $M^+[^{37}Cl, ^{35}Cl]$), 317 (44, $M^+[^{35}Cl_2]$), 284 (1.5, {$M[^{37}Cl_2] - ^{37}Cl$} and {$M[^{37}Cl, ^{35}Cl] - ^{35}Cl$}), 282 (4.2, {$M[^{37}Cl, ^{35}Cl] - ^{37}Cl$} and {$M[^{35}Cl_2] - ^{35}Cl$}), 178 (21), 161 (41), 136 (54, BH_2), 133 (46), 103 (42), 59 (100). Anal. Calcd for $C_{10}H_9Cl_2N_5O_3$ (318.1): C, 37.76; H, 2.85; N, 22.02. Found: C, 37.49; H, 2.93; N, 22.31. **10b**: mp 179–181 °C dec; UV max 259 nm (ε 14 500), min 226 nm (ε 2600); ^{1}H NMR δ 4.17 (dd, $J_{4'-3'}$ = 2.5 Hz, $J_{4'-5'}$ = 6.2 Hz, 1, H4′), 4.30 (ddd, $J_{3'-2'}$ = 5.1 Hz, $J_{OH-3'}$ = 5.2 Hz, 1, H3′), 4.82 (ddd, $J_{2'-1'}$ = 6.9 Hz, $J_{OH-2'}$ = 6.6 Hz, 1, H2′), 5.70 (d, 1, OH3′), 5.74 (d, 1, OH2′), 6.00 (d, 1, H1′), 6.56 (d, 1, H5′); 7.35 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.37 (s, 1, H8); MS *m/z* 323 (2.1, $M^+[^{37}Cl_2]$), 321 (10, $M^+[^{37}Cl, ^{35}Cl]$), 319 (13, $M^+[^{35}Cl_2]$), 286 (4, {$M[^{37}Cl_2] - ^{37}Cl$} and {$M[^{37}Cl, ^{35}Cl] - ^{35}Cl$}), 284 (12, {$M[^{37}Cl, ^{35}Cl] - ^{37}Cl$} and {$M[^{35}Cl_2] - ^{35}Cl$}), 236 (9), 164 (100), 136 (94), 135 (54, BH). Anal. Calcd for $C_{10}H_{11}Cl_2N_5O_3$ (320.1): C, 37.52; H, 3.46; N, 21.88. Found: C, 37.41; H, 3.58; N, 21.99.

Stannyl Radical-Mediated Hydrodechlorination of Chloro Sulfoxides. A solution of **5a**(5′*S*,S*S*) (35 mg, 0.067 mmol) in benzene (5 mL) was deoxygenated (Ar) for 45 min. Bu_3SnH (116 mg, 0.108 mL, 0.4 mmol) and AIBN (5 mg) were added, and the mixture was refluxed for 5 h. Volatiles were evaporated, and the residue was chromatographed (silica; MeOH/EtOAc (1:39)) to give **2a**(S_R) (22 mg, 67%) and recovered **5a**(5′*S*,S*S*) (6 mg, 17%) (^{1}H NMR). Identical treatment of **6a**(5′*R*,S*R*) (35 mg, 0.067 mmol) gave **3a**(S_S) (23 mg, 70%) and recovered **6a** (9 mg, 26%).

Identical independent treatment of **2a**(S_R) and **3a**(S_S) resulted in quantitative recovery of unchanged starting materials without detected (^{1}H NMR) alteration of stereochemistry at sulfur.

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