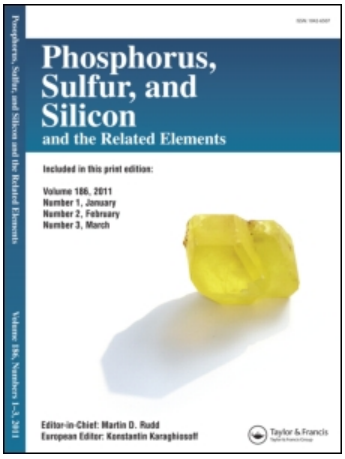


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Selected Aspects of the Chemistry and Biochemistry of Sulfur-Containing Nucleosides

Morris J. Robins[a]; Stanislaw F. Wnuk[a]
[a] Department of Chemistry, Brigham Young University, Provo, UT, U.S.A.

To cite this Article Robins, Morris J. and Wnuk, Stanislaw F.(1994) 'Selected Aspects of the Chemistry and Biochemistry of Sulfur-Containing Nucleosides', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 71 — 88
To link to this Article: DOI: 10.1080/10426509408034202
URL: http://dx.doi.org/10.1080/10426509408034202

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95-96, pp. 71-88
Reprints available directly from the publisher
Photocopying permitted by license only

SELECTED ASPECTS OF THE CHEMISTRY AND BIOCHEMISTRY OF SULFUR-CONTAINING NUCLEOSIDES

MORRIS J. ROBINS and STANISLAW F. WNUK
Department of Chemistry, Brigham Young University, Provo, UT 84602, U.S.A.

Synthetic nucleoside 5'-(α-halo)thioethers and derived 5'-halo(methylene) compounds function as potent mechanism-based inhibitors of *S*-adenosyl-L-homocysteine hydrolase. Nucleoside 5'-carboxaldehydes have been converted into 6'-tosyl(vinyl) derivatives. Radical-mediated stannyldesulfonylation of these homonucleoside vinyl sulfones gave 6'-stannyl(vinyl) derivatives. Stereoselective halodestannylation with electrophiles gave the 6-halo(homovinyl)nucleoside analogues. Some of these nucleoside analogue types have inhibitory activity against enzymes in the nucleic acid biochemical manifold and these effects correlate with *in vitro* anticancer and antiviral activities in certain cases.

Key Words: enzyme inhibitors, fluorination, α-fluoro thioethers, halodestannylation, nucleosides, thionucleosides, vinyl-sulfones.

INTRODUCTION

The sulfur-containing nucleoside *S*-adenosyl-L-methionine (AdoMet, SAM, **2**) is involved in a number of key biochemical pathways (Figure 1).[1,2] AdoMet (**2**) undergoes enzyme-mediated decarboxylation to give the aminopropyl donor for biosynthesis of the polyamines spermine and spermidine. The by-product of that process is 5'-*S*-methyl-5'-thioadenosine (MTA, **3**).[3] AdoMet (**2**) is the methyl donor for most enzyme-mediated methylation reactions. The by-product of these methyl transfer processes is *S*-adenosyl-L-homocysteine (AdoHcy, SAH, **1**).[4]

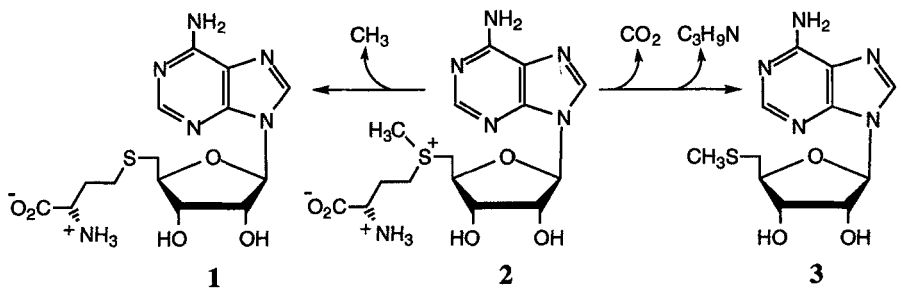


FIGURE 1

AdoHcy (**1**) functions as a potent feedback inhibitor of key methyltransferase enzymes required for post-synthetic modifications of nucleic acids and proteins, and biosynthesis of other molecules. Therefore, it is essential to have AdoHcy removed from the cytoplasm in order for protein biosynthesis and other processes to continue. The enzyme *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase) effects cleavage of AdoHcy **1** to adenosine (Ado, **6**) and L-homocysteine (Hcy) by a mechanism established by Palmer and Abels[5] (Figure 2) and reinforced by Borchardt,[6] Parry,[7] Porter,[8] and their coworkers. This reversible mechanism is initiated by oxidation of the hydroxyl function at C3' of AdoHcy **1** by enzyme-bound NAD^+ to give the 3'-ketonucleoside **4**. This activates H4' for elimination of Hcy to give enone **5**. Michael-type addition of water gives 3'-ketoAdo (**7**) which is reduced by enzyme-bound NADH to give Ado (**6**). It was demonstrated[5,7] that 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**8a**, X = H) also was accepted as an alternative substrate by AdoHcy hydrolase and oxidized at C3' to give enone **5** directly.

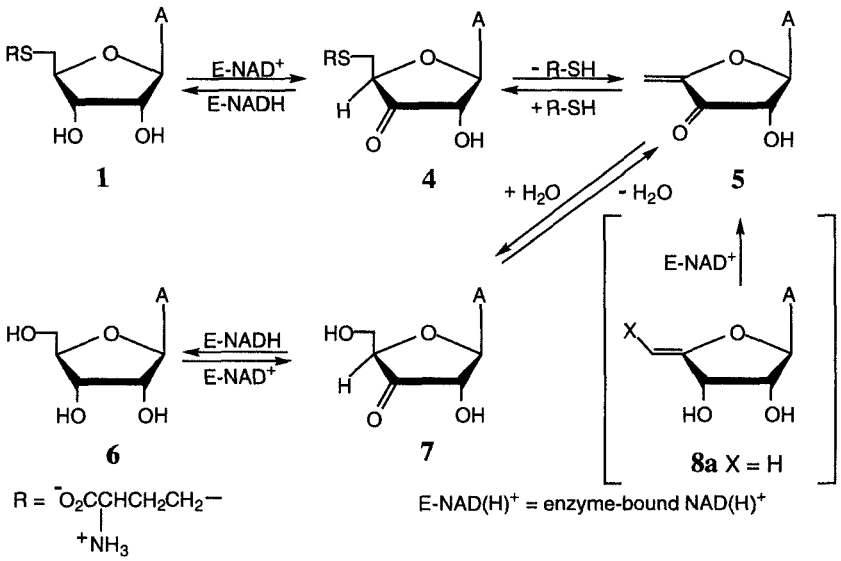
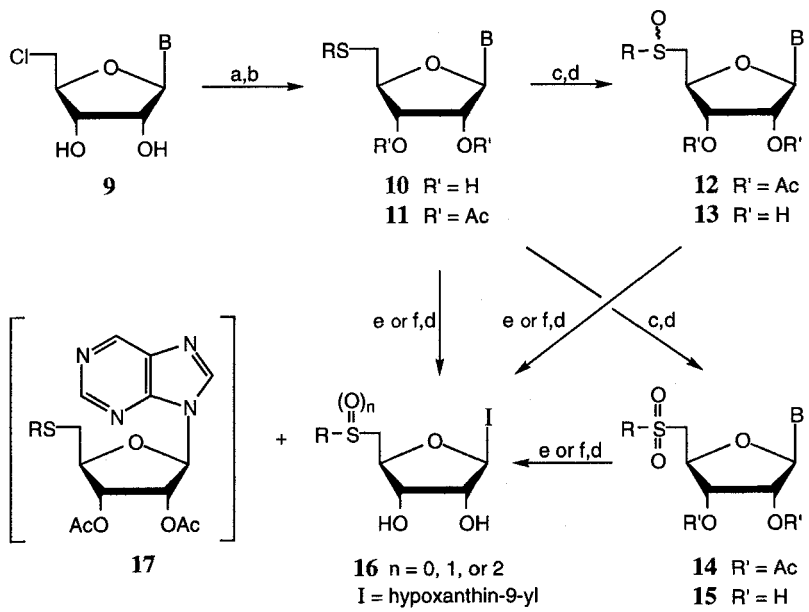


FIGURE 2

We anticipated that other 5'-substituted 4',5'-unsaturated Ado analogues **8** [X = F, Cl, CH_3O, HO (tautomeric hydroxy enol ether form of adenosine 5'-carboxaldehyde)] might be substrates/inhibitors of AdoHcy hydrolase. We also considered that appropriate nucleoside thioethers and α-fluorinated derivatives might function as substrates/inhibitors of methylthioadenosine phosphorylase (MTAPase) and purine nucleoside phosphorylase (PNPase), other crucial enzymes in the nucleic acid biochemical manifold.

SYNTHESIS OF NUCLEOSIDE 5'-THIOETHERS

Syntheses and chemistry of sulfur-modified nucleosides have been reviewed recently.[9] Treatment of ribonucleosides (e.g. **6**) with thionyl chloride and pyridine in acetonitrile resulted in quantitative formation of 5'-chloro-5'-deoxy-2',3'-*O*-sulfinylnucleosides, which upon treatment with aqueous ammonia gave **9**.[10] Displacement of the chloride in **9** with thiolates [derived by treatment of thiols in dimethylformamide (DMF) with sodium hydride] resulted in rapid and quantitative conversion to the corresponding 5'-*S*-alkyl(or aryl)-5'-thionucleoside derivatives[10] **10** which can be acetylated quantatively [11] to give **11** (Scheme 1). Oxidation of **11** with ~1 equivalent of *m*-CPBA (3-chloroperoxybenzoic acid) at low temperature gave diastereomeric (~1:1) sulfoxides **12** in the uridine[12] and adenosine[13] series. In some cases, column chromatography[14] (e.g. **12a**, R = An) or fractional crystallization[13] (e.g. **13a**, R = Ph) provided separation of the diastereomers. The acetylated uridine 5'-sulfoxide diastereomers[12] **12b** were separated and deprotected with methanolic ammonia to give the resolved **13b** (R = An) diastereomers.



Series **9** - **15**: **a** B = adenin-9-yl
b B = uracil-1-yl

R = Me, Ph, An [An = (4)$CH_3OC_6H_4$]

(a) RSH/NaH; (b) Ac_2O/pyridine; (c) *m*-CPBA; (d) NH_3/MeOH; (e) α-amylase; (f) *tert*-butyl nitrite/(EtOAc or THF).

SCHEME 1

The sulfoxide configurations (R_S or S_S) of the diastereomers of **12** and **13** were elucidated from ^1H and ^{13}C NMR spectra in conjunction with X-ray crystallography[13] of **13a**(R_S) (R = Ph). The (R_S)-sulfoxides were distinguished from their S_S diastereomers by differences in chemical shifts (e.g. H4' and H5',5") and the corresponding coupling constants.[13,14] Oxidation[15] of thioethers **11** with excess *m*-CPBA gave sulfones **14** which were deprotected and crystallized to give **15** in high yields.

5'-Deoxy-5'-[(4-methoxyphenyl)sulfonyl]uridine (15b; R = An).
(a) Oxidation. *m*-CPBA (4.34 g as 85% reagent; 21.4 mmol) in CH_2Cl_2 (150 mL) was added dropwise to a stirred solution of **11b** (R = An) (4.185 g, 9.3 mmol)[12] in CH_2Cl_2 (150 mL) at -30 °C. After 15 min, stirring was continued at ambient temperature until TLC ($CHCl_3$/MeOH, 12:1) indicated complete conversion of **11b** (R_f = 0.53) and **12b** (intermediate sulfoxide, R_f = 0.29) to **14b** (~5h). The reaction mixture was washed with ice-cold saturated $NaHCO_3/H_2O$ and the aqueous layer was extracted with $CHCl_3$ (2 x 60 mL). The combined organic phase was washed with H_2O and brine, dried (Na_2SO_4), and evaporated to give **14b** (R = An) (4.35 g, 97%; R_f = 0.41) as a white foam of sufficient purity for subsequent reactions and spectroscopic characterization: ^1H NMR (Me_2SO-d_6) δ 2.00, 2.06 (s, s; 3, 3; Ac's), 3.79 (dd, $J_{5"-5'}$ = 14.4 Hz, $J_{5"-4'}$ = 3.7 Hz, 1, H5"), 3.81 (s, 3, OCH_3), 4.00 (dd, $J_{5'-4'}$ = 8.8 Hz, 1, H5'), 4.34 (ddd, $J_{4'-3'}$ = 3.8 Hz, 1, H4'), 5.27 (dd, $J_{3'-2'}$ = 6.0 Hz, 1, H3'), 5.54 (dd, $J_{2'-1'}$ = 6.0 Hz, 1, H2'), 5.57 (d, J_{5-6} = 8.0 Hz, 1, H5), 5.80 (d, 1, H1'), 7.08 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.48 (d, 1, H6), 7.78 (d, 2, Ar), 11.40 (br s, 1, NH); MS *m/z* 482 (4, M^+), 371 (32, M - B), 171 (23), 139 (100). *(b) Deprotection.* Saturated NH_3/MeOH (200 mL) was added to a solution of **14b** (R = An) (3.5 g, 7.26 mmol) in MeOH (80 mL) at 0 °C and stirring was continued for 3 h, during which white crystals precipitated. The mixture was evaporated to a white solid that was recrystallized from MeOH/H_2O (900 mL, ~2:1) at reflux to give **15b** (R = An) (2.49 g, 86%) as fine white needles: mp 272-274 °C (dec); UV max 242 nm (ε 18 100), shoulder 259 nm (ε 9600), min 222 nm (ε 5400); ^1H NMR (Me_2SO-d_6) δ 3.64 (dd, $J_{5"-5'}$ = 14.6 Hz $J_{5"-4'}$ = 4.0 Hz, 1, H5"), 3.81 (dd, $J_{5'-4'}$ = 6.3 Hz, 1, H5'), 3.81 (s, 3, OCH_3), 3.87 (ddd, $J_{4'-3'}$ = 3.3 Hz, 1, H4'), 4.05 (ddd, $J_{3'-2'}$ = 4.8 Hz, $J_{3'-OH3'}$ = 4.7 Hz, 1, H3'), 4.14 (ddd, $J_{2'-1'}$ = 6.4 Hz, $J_{2'-OH2'}$ = 5.9 Hz, 1, H2'), 5.36 (d, 1, OH3'), 5.40 (d, 1, OH2'), 5.50 (d, J_{5-6} = 8.1 Hz, 1, H5), 5.67 (d, 1, H1'), 7.09 (d, J_{Ha-Hb} = 8.5 Hz, 2, Ar), 7.40 (d, 1, H6), 7.76 (d, 2, Ar), 11.30 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 55.80 (CH_3O), 58.37 (C5') 71.52, 72.87 (C2', C3'), 78.63 (C4'), 88.49 (C1') 102.10 (C5), 114.56, 130.50, 131.56, 163.64 (Ar), 141.50 (C6), 151.04 (C2), 163.30 (C4); MS *m/z* 286 (6, M - BH), 227 (75, M - $AnSO_2$), 172 (64), 155 (100), 112 (92, BH). Anal. Calcd. for $C_{16}H_{18}N_2O_8S$ (398.4): C, 48.24; H, 4.55; N, 7.03. Found: C, 47.99; H, 4.69; N, 7.08.

Compound **15b** (R = An) also was obtained from 2',3'-*O*-isopropylideneuridine (~75%) by: (i) 5'-*O*-tosylation; (ii) displacement [sodium (4-methoxy)thiophenoxide]; (iii) oxidation (*m*-CPBA); and (iv) deprotection (TFA/H_2O).

5'-Deoxy-5'-(phenylsulfonyl)uridine (15b; R = Ph).
(a) Oxidation of **11b** (R = Ph) [483 mg, 1.15 mmol; prepared by acetylation[12] of **10b** (R = Ph)[16]] with *m*-CPBA (538 mg as 85% reagent, 2.65 mmol), as described for **15b** (R = An), gave **14b** (R = Ph) (509 mg, 98%): ^1H NMR (Me_2SO-d_6) δ 2.01, 2.08 (s, s; 3, 3; Ac's), 3.86 (dd, $J_{5"-5'}$ = 14.5 Hz, $J_{5"-4'}$ = 3.9 Hz, 1, H5"), 4.06 (dd, $J_{5'-4'}$ = 8.5 Hz, 1, H5'), 4.35 (ddd, $J_{4'-3'}$ = 4.2 Hz, 1, H4'), 5.29 (dd, $J_{3'-2'}$ = 6.0 Hz, 1, H3'), 5.51 (dd, $J_{2'-1'}$ = 5.9 Hz, 1, H2'), 5.57 (d, J_{5-6} = 8.1 Hz, 1, H5), 5.79 (d, 1, H1'), 7.45 (d, 1, H6), 7.50-7.88 (m, 5, Ar), 11.39 (br s, 1, NH); MS *m/z* 452 (3, M^+), 341 (M - B, 62), 139 (100). *(b)* Deprotection of **14b** (300 mg, 0.66 mmol), as described for **15b** (R = An), and crystallization (MeOH) gave **15b** (R = Ph; 187 mg, 77%): mp 158-160 °C; UV (MeOH) max 259 nm (9800), min 230 nm (2050); ^1H NMR (Me_2SO-d_6) δ 3.72 (dd, $J_{5"-5'}$ = 13.5 Hz, $J_{5"-4'}$ = 3.8 Hz, 1, H5"), 3.88 (dd, $J_{5'-4'}$ = 6.0

Hz, 1, H5'), 3.88-3.94 (m, 1, H4'), 4.05-4.16 (m, 2, H2',3'), 5.41 (br s, 2, OH2',3'), 5.52 (d, $J_{5\text{-}6}$ = 8.1 Hz, 1, H5), 5.67 (d, $J_{1'\text{-}2'}$ = 6.2 Hz, 1, H1'), 7.43 (d, 1, H6), 7.57-7.70 (m, 3, Ar), 7.85-7.90 (m, 2, Ar), 11.37 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 57.99 (C5'), 71.59, 72.84 (C2', C3'), 78.37 (C4'), 88.56 (C1') 102.12 (C5), 128.08, 129.51, 134.07, 140.07 (Ar), 141.47 (C6), 151.01 (C2), 163.32 (C4); MS *m/z* 227 (3, M - $PhSO_2$), 197 (33), 142 (37), 125 (94), 112 (100, BH). Anal. Calcd. for $C_{15}H_{16}N_2O_7S$ (368.4): C, 48.91; H, 4.38; N, 7.60. Found: C, 49.01; H, 4.36; N, 7.75.

5'-Deoxy-5'-[(4-methoxyphenyl)sulfonyl]adenosine (15a; R = An).
Oxidation of **11a** (R = An) (946 mg, 12 mmol)[13] as described for **11a** (R = Ph),[17] deacetylation as described above for **15b** (R = An), and crystallization (MeOH) gave **15a** (R = An; 598 mg, 71% from **11a**): mp 157-158 °C (dec); UV (MeOH) max 246 nm (ε 18 800), shoulder 266 nm (ε 11 500), min 225 nm (3900); ^{1}H NMR (Me_2SO-d_6) δ 3.65-3.78 (m, 4, H5", OCH_3), 4.02-4.29 (m, 3, H3',4',5'), 4.93 (ddd, $J_{2'\text{-}3'}$ = 5.0 Hz, $J_{2'\text{-}1'}$ = 6.4 Hz, $J_{2'\text{-}OH2'}$ = 5.0 Hz, 1, H2'), 5.44-5.52 (m, 2, OH2',3'), 5.78 (d, 1, H1'), 6.85 (d, $J_{Ha\text{-}Hb}$ = 7.9 Hz, 2, Ar), 7.25(br s, 2, NH_2), 7.64 (d, 2, Ar), 8.11 (s, 1, H2), 8.17 (s, 1, H8); ^{13}C NMR (Me_2SO-d_6) δ 55.86 (OCH_3), 58.66 (C5'), 71.80, 73.65 (C2', C3'), 79.63 (C4'), 88.07 (C1'), 113.97, 130.25, 131.3, 163.17 (Ar), 119.66 (C5), 140.66 (C8), 149.25 (C4), 152.64 (C2), 156.28 (C6); MS *m/z* 421 (1, M^+), 172 (72), 164 (81), 155 (90), 135 (100, BH). Anal. Calcd. for $C_{17}H_{19}N_5O_6S\bullet 0.5H_2O$ (430.4): C, 47.44; H, 4.68; N, 16.27; S, 7.45. Found: C, 47.79; H, 4.69; N, 16.30; S, 7.34.

5'-Deoxy-5'-[(4-methoxyphenyl)sulfinyl(R_S and S_S)]uridine [13b(R_S) and 13b(S_S); R = An].
Chromatography (1%-3% $MeOH/CHCl_3$) of **12b** [$(R/S)_S$, ~1:1.2; R = An][12] gave partial separation of the sulfoxide diastereomers. Deacetylation of early fractions enriched in **12b**(R_S) and recrystallization ($MeOH/H_2O$) gave **13b**(R_S) (R = An; 82%): mp 258-260 °C (dec); UV (MeOH) max 250 nm (ε 18 300), min 228 nm (ε 11 300); ^{1}H NMR (Me_2SO-d_6) δ 3.07 (dd, $J_{5"\text{-}5'}$ = 13.1 Hz, $J_{5"\text{-}4'}$ = 3.6 Hz, 1, H5'), 3.22 (dd, $J_{5'\text{-}4'}$ = 9.5 Hz, 1, H5'), 3.82 (s, 3, OCH_3), 3.92-3.99 (m, 1, H3'), 4.14-4.28 (m, 2, H2',4'), 5.38 (d, $J_{OH3'\text{-}3'}$ = 4.8 Hz, 1, OH3'), 5.50 (d, $J_{OH2'\text{-}2'}$ = 5.5 Hz, OH2'), 5.66 (d, $J_{5\text{-}6}$ = 8.0 Hz, 1, H5), 5.81 (d, $J_{1'\text{-}2'}$ = 5.5 Hz, 1, H1'), 7.16 (d, $J_{Ha\text{-}Hb}$ = 8.1 Hz, 2, Ar), 7.67 (d, 2, Ar), 7.76 (d, 1, H6), 11.40 (br s, 1, NH); ^{13}C NMR (MeSO-d_6) δ 55.81 (OCH_3), 60.60 (C5'), 72.39, 72.83 (C2', C3'), 77.91 (C4'), 89.33 (C1'), 102.34 (C5), 115.01, 126.22, 135.77, 161.74 (Ar), 141.88 (C6), 150.96 (C2), 163.30 (C4); MS *m/z* 382 (1, M^+), 366 (20), 278 (66), 155 (61), 139 (100). Anal. Calcd. for $C_{16}H_{18}N_2O_7S$ (382.4): C, 50.26; H, 4.74; N, 7.33. Found: C, 50.27; H, 4.79; N, 7.21.

Deacetylation of fractions enriched in **12b**(S_S) and recrystallization ($MeOH/H_2O$) gave **13b**(S_S) (R = An; 78%): mp 203-205 °C (dec); UV (MeOH) max 252 nm (ε 18 500), min 223 nm (ε 7500); ^{1}H NMR (Me_2SO-d_6) δ 3.16 (dd, $J_{5"\text{-}5'}$ = 13.4 Hz, $J_{5"\text{-}4'}$ = 5.5 Hz, 1, H5"), 3.37 (dd, $J_{5'\text{-}4'}$ = 7.4 Hz, 1, H5'), 3.75-3.83 (m, 4, H4', OCH_3), 3.97-4.05 (m, 1, H3'), 4.16-4.24 (m, 1, H2'), 5.35 (d, $J_{OH3'\text{-}3'}$ = 4.4 Hz, 1, OH3'), 5.46 (d, $J_{OH2'\text{-}2'}$ = 5.6 Hz, 1, OH2'), 5.67 (d, $J_{5\text{-}6}$ = 8.0 Hz, 1, H5), 5.74 (d, $J_{1'\text{-}2'}$ = 5.6 Hz, 1, H1'), 7.16 (d, $J_{Ha\text{-}Hb}$ = 8.0 Hz, 2, Ar), 7.65 (d, 2, Ar), 7.70 (d, 2, H6), 11.40 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 55.77 (CH_3O), 59.13 (C5'), 72.06, 72.76 (C2', C3'), 78.78 (C4'), 88.79 (C1'), 102.39 (C5), 115.08, 126.73, 134.34, 161.88 (Ar), 141.55 (C6), 150.87 (C2), 163.24 (C4); MS *m/z* 366 (48, M - 16), 278 (C2), 139 (100). Anal. Calcd. for $C_{16}H_{18}N_2O_7S$ (382.4): C, 50.26; H, 4.74; N, 7.33. Found: C, 50.31; H, 4.81; N, 7.24.

The adenosine 5'-thioether **10a**, sulfoxide **13a**, and sulfone **15a** derivatives were deaminated to inosine 5'-analogues **16** by enzyme activity in a commercial α-amylase preparation from *Aspergillus oryzae*.[17] The adenosine deaminase from calf intestine did not deaminate **10a**, **13a**, and **15a**, which all lack the 5'-hydroxyl group determined to be essential for efficient substrate activity.[18] Treatment of the protected 5'-*S*-substituted-5'-

thioadenosines **11a**, **12a**, and **14a** with alkyl nitrites in ethyl acetate or tetrahydrofuran (THF) effected a mild nonaqueous conversion to their inosine derivatives which then were deprotected to give **16**.[17] The corresponding 5'-*S*-substituted-5'-thionebularine analogues **17** were formed as by-products from **11a** (R = Me or Ph), presumably by diazotization followed by abstraction of hydrogen from solvent by a purin-6-yl species.[17]

Biological Activities

AdoHcy hydrolase The chemically stable adenosine 5'-thioether **10a** (R = An), its sulfoxides **13a**, and sulfone **15a** were not alternative substrates or inhibitors of AdoHcy hydrolase and apparently were not oxidized to 3'-keto intermediates.[19] In contrast, the 5'-fluoro thioether derived from **10a** (R = An) was a potent inhibitor (*vide infra*).[13,19,20]

PNPase The 5'-*S*-substituted-5'-thioinosines **16** were poor alternative substrates and weak inhibitors of PNPase.[17] The thioether derivatives **16** (n = 0) were better substrates than their analogues **16** (n = 1 or 2) with sulfur in higher oxidation states.

MTAPase The adenosine 5'-thioethers **10a**, sulfoxides **13a**, and sulfone **15a** (and some 5'-fluorinated analogues) (*vide infra*) were evaluated as substrates of MTAPase.[21] Phosphorolytic glycosyl cleavage was effected by this enzyme with thioethers, but not with sulfoxides or sulfones (Professor Todd M. Savarese, unpublished data).

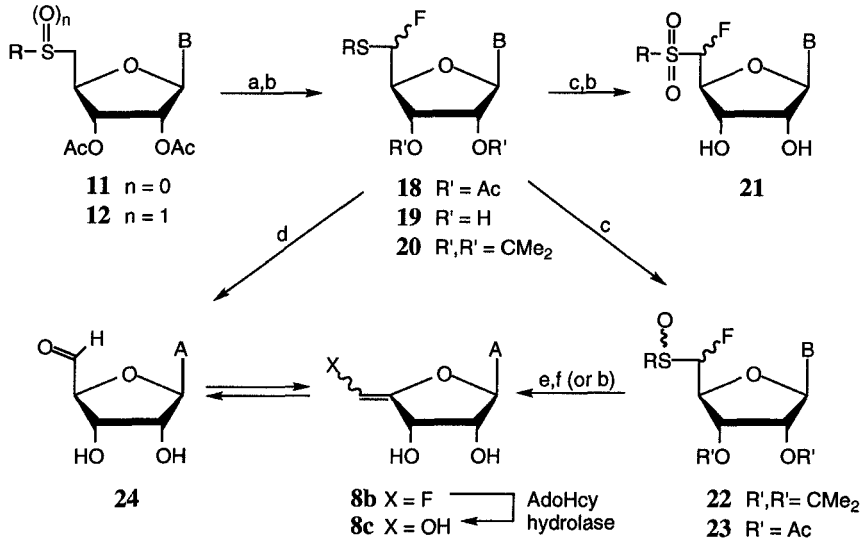
SYNTHESIS AND TRANSFORMATION OF NUCLEOSIDE α-FLUORO THIOETHERS

5'-Fluorination

Direct approaches for the synthesis of α-fluoro thioethers include: (i) treatment of dialkyl or alkyl aryl sulfoxides with (diethylamino)sulfur trifluoride[22] (DAST) with antimony(III) chloride as catalyst,[23] (ii) treatment of thioethers with XeF_2,[24] *N*-fluoropyridinium triflates,[25] DAST/$SbCl_3$,[26] and the new selectfluor® reagents[27] (1-alkyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane salts).

Treatment of the 2',3'-di-*O*-acetyl-protected adenosine sulfoxides **12a** with DAST and catalytic $SbCl_3$ gave the diastereomeric α-fluoro thioethers **18a** (5'*R/S*, ~2:3; ~70%) (Scheme 2).[11,13] Recrystallization of an analogous uridine 5'-α-fluoro thioether pair **18b** (5'*R/S*, ~1:1; ~85%, R = An) from methanol afforded one diastereomer whose 5'(*R*) configuration was established by X-ray crystallography.[12] The ^{19}F NMR spectrum of this compound had the lower field doublet of doublets at δ -157.50 ($^2J_{F\text{-}H5'}$ = 52.5 Hz, $^3J_{F\text{-}H4'}$ = 11.7 Hz) whereas that of the corresponding 5'(*S*)-fluoro diastereomer had this resonance at δ -159.27 (dd, $^2J_{F\text{-}H5'}$ = 52.5 Hz, $^3J_{F\text{-}H4'}$ = 17.0 Hz).[12] Deacetylation of **18a** (5'*R/S*, ~2:3; R = An) and fractional crystallization gave **19a**(5'*S*) whose ^{19}F NMR spectrum had the higher field signal at δ -160.24 (dd, $^3J_{F\text{-}H5'}$ = 53.5 Hz, $^3J_{F\text{-}H4'}$ = 18.8 Hz). The 5'(*S*)-fluoro configuration was confirmed by X-ray crystallography.[13]

It is noteworthy that $SbCl_3$-catalyzed fluorination with DAST is almost as efficient with phenyl sulfoxides **12a** (R = Ph) and even the deactivated 4-chlorophenyl sulfoxides **12a** (R = 4-ClC_6H_4) as with the more reactive and expensive 5'-*S*-(4-methoxyphenyl) analogues **12a** (R = An).[13] Stereochemistry in this deoxygenative fluorination process does not depend on the configuration of the precursor sulfoxides since treatment of **12a**(R_S) (R = Ph) with DAST resulted in formation of the same isomeric mixture of **18a** (5'*R/S*, ~2:3) as when **12a**[(*R/S*)$_S$] was used.[11,13] This lack of dependence on sulfoxide stereochemistry also was observed with C2' fluorinations of uridine 2'-sulfoxides, but 5'-sulfoxides of adenosine were chlorinated stereoselectively (*vide infra*).



Series **11**, **12**, **18** - **23**: **a** B = adenin-9-yl **b** B = uracil-1-yl R = Ph, An [An = (4)$CH_3OC_6H_4$], (4)ClC_6H_4

(a) DAST/$SbCl_3$ or XeF_2; (b) NH_3/MeOH; (c) *m*-CPBA; (d) phosphate buffer; (e) diglyme/145 °C; (f) TFA/H_2O

SCHEME 2

McCarthy and coworkers analogously prepared 5'-fluoro-2',3'-*O*-isopropylidene-5'-*S*-(4-methoxyphenyl)-5'-thioadenosine **20a** (R = An), oxidized it to sulfoxides **22a**, thermolyzed this mixture, and treated it with aqueous trifluoroacetic acid (TFA) to give the 4',5'-didehydro-5'-deoxy-5'-fluoroadenosines **8b** (*E/Z* ~1:2.5).[28,29] Similar chemistry was employed for syntheses of fluoromethylene analogues of **8b** beginning with 9-(β-D-arabinofuranosyl)adenine,[29] 2'-deoxyadenosine,[29] and the carbocyclic antibiotic aristeromycin.[30,31] The *Z* vinyl fluoride **8b** was a potent inhibitor of AdoHcy hydrolase and had significant biological activity.[28,29]

Possible inhibitory pathways included enzymatic oxidation at C3' followed by conjugate nucleophilic addition/elimination by functional groups on the enzyme.[28,29,32] Oxidation followed by hydrolysis also was noted.[32] However, Borchardt and coworkers observed that enzyme-mediated loss of fluoride from **8b** to give hydroxy enol ethers **8c** occurred 20 times faster than NAD^+-mediated oxidation at C3' of **8b**.[33] Intermediates **8c** are tautomers of adenosine 5'-carboxaldehyde **24** and its 4'-epimer, and the latter compounds were found to be potent inactivators of AdoHcy hydrolase (K_I = 40 nm).[34] Amazingly, the "hydrolytic activity" of this enzyme is sufficiently powerful to cause addition of water to the double bond of vinyl fluorides **8b**, thus making them enzymatic prodrugs of the "adenosine 5'-carboxaldehyde" tautomers.[33,34] Additionally, it was discovered that the 5'-(α-fluoro)thioethers **19a** underwent spontaneous hydrolysis in aqueous buffer to give the same "adenosine 5'-carboxaldehyde" species which caused analogously potent inactivation of AdoHcy hydrolase.[13,19,20] Thus, the vinyl fluorides **8b** are enzyme-activated prodrugs and the synthetic precursor 5'-(α-fluoro)thioethers **19a** are chemical hydrolysis prodrugs of these "adenosine 5'-carboxaldehyde" inhibitors.

Fluorination of the thioethers **11** (R = An) with xenon difluoride also gave the fluoro diastereomers in the uridine[12] [**18b** (5'*R/S*, ~1:1.3; ~90%)] and adenosine[13] [**18a** (5'*R/S*, ~3:2; ~ 70%)] series. Intriguingly, fluorination of **11a** (R = An) with XeF_2 and its sulfoxides **12a** with DAST/$SbCl_3$ gave inverted ratios of fluoro diastereomers **18a** (5'*R/S*, ~3:2 *vs.* ~2:3, respectively). Since the thioethers **11a** are converted directly to 5'-(α-fluoro)thioethers **18a** (R = Ph or An) in high yields with DAST/$SbCl_3$[26] and these diastereomeric ratios (5'*R/S*, ~2:3) are very close to those with the sulfoxide/DAST/$SbCl_3$ procedure,[13] an important question arises whether DAST/$SbCl_3$ deoxygenates sulfoxides to thioethers *in situ* prior to their conversion to α-fluoro thioethers. Compounds **18a** were purified on silica gel columns and then deacetylated, or deprotected and purified simultaneously on Dowex 1 × 2 (OH^-) columns (MeOH) to give **19a**.

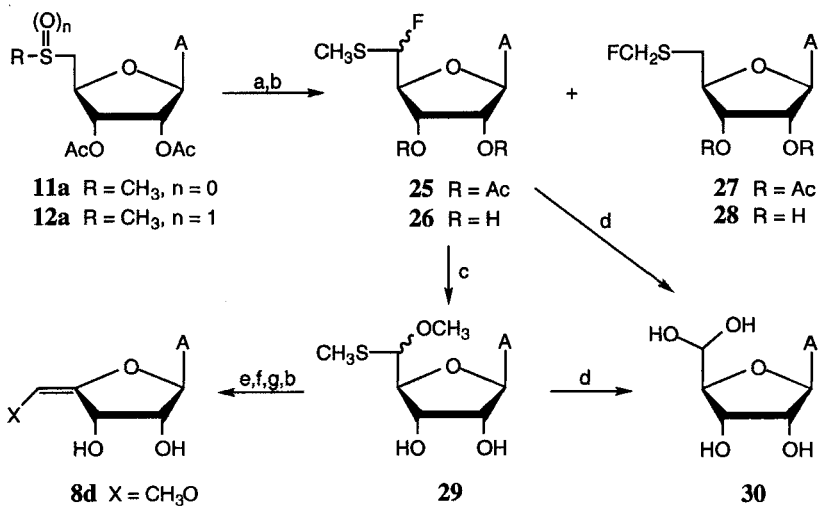
Treatment of α-fluoro sulfoxides with DAST[22] or α-fluoro thioethers with XeF_2[24a] was reported to give α,α-difluoro thioethers. However, nucleoside analogues did not undergo this second conversion.[12,13,26] Selective oxidation of **18** with *m*-CPBA afforded the α-fluoro sulfoxides **23** as mixtures of four diastereomers (^{19}F NMR).[12,13] However, treatment of **23** with DAST/$SbCl_3$ resulted in deoxygenation to give **18** with the same fluoro diasteromer ratios as prior to oxidation.[12,13] Treatment of **18** with XeF_2 failed to effect a second α-fluorination[12,13] as did attempts to increase the reactivity of **11b** or **12b** (R = Ph) by introduction of a 4-hydroxyl substituent on the phenyl ring.[12]

Oxidation of **18** (R = An) with an excess of *m*-CPBA followed by deacetylation gave the fluoro sulfones **21** as diastereomeric 5'(*R/S*) mixtures.[12,13] The 5'(*R* and *S*) isomers were separated in the uridine series.[12] The 1-*N*-oxide of fluoro sulfone **21a** also

was produced during oxidation of the adenosine α-fluoro thioether **18a** (R = An). This by-product was *N*-deoxygenated with hexachlorodisilane and deacetylated to give **21a**.[13] In marked contrast to the 5'-(α-fluoro)thioethers **19a** (*vide supra*), the adenosine 5'-(α-fluoro)sulfones **21a** did not undergo spontaneous solvolysis under neutral conditions, and did not cause inactivation of AdoHcy hydrolase.[19]

MTA fluorination

Treatment of the 2',3'-di-*O*-acetyl derivative of MTA **11a** with XeF_2[13] gave regio- and diastereomeric mixtures of protected 5'-*S*-(fluoromethyl)-5'-thioadenosine **27** and 5'-fluoro-5'-*S*-methyl-5'-thioadenosines **25** (~60% combined, silica chromatography) (Scheme 3). The ^{19}F NMR triplet for **27** at δ -184.63 ($^2J_{F\text{-}CH_2}$ = 52.0 Hz) and two doublets of doublets for **25** at δ -163.63 (F5'*R*) and -165.08 (F5'*S*) were diagnostic for regio- (**25/27**, ~2:3) and stereochemical (**25**; 5'*R/S*, ~1:1) compositions.[13] Fluorination of thioether[26] **11a** or sulfoxides[11,13] **12a** with DAST/$SbCl_3$ gave mixtures of **25/27** [~3:2, ~60%; **25** (5'*R/S*, ~1:2)] with parallel compositions of fluoro isomers, but again inverted in comparison with the thioether/XeF_2 reaction. The composition of **25/27** depends stongly upon work-up and purification conditions. Fluorination of **11a** with DAST/$SbCl_3$ proceeded quantitatively (^{19}F, ^1H NMR) and the ratio of fluoro isomers in the crude reaction mixture was **25/27** [~3.5:1; **25** (5'*R/S*, ~1:1.2)].[26] It was reported recently that fluorination of **11a** (or its completely benzoylated analogue) with XeF_2 at -60 °C in dichloromethane occurred exclusively at the methyl group to give **27** (~75%).[35]



(a) DAST/$SbCl_3$ or XeF_2; (b) NH_3/MeOH; (c) MeOH/$CHCl_3$/silica gel; (d) TFA/H_2O
(e) Ac_2O/pyridine; (f) *m*-CPBA; (g) diglyme/135 °C

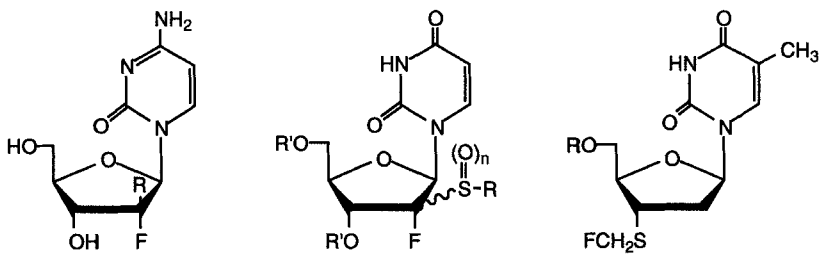
SCHEME 3

Deacetylation (NH_3/MeOH) of the crude **25/27** mixture and chromatography on Dowex 1 × 2 (OH^-) (washed extensively with MeOH) gave separation of fluoromethyl thioether **28** and the unstable 5'-fluoro-5'-methylthio diastereomers **26**.[26,36] Rapid deacetylation of crude **25/27** and slow passage of the mixture through a silica gel column ($CH_3OH/CHCl_3$) resulted in solvolysis to give the methoxy/methylthio diastereomers **29** (~4:1; ~40 % from **11a** via the DAST/$SbCl_3$ procedure).[13]

Mild acid-catalyzed hydrolysis of the mixed acetals **29** and HPLC purification gave adenosine 5'-carboxaldehyde hydrate (**30**).[34] Hydrolysis of the **26/28** mixture afforded **30** in lower yield. The methoxy/methylthio acetals **29** also served as starting materials for synthesis of the 5'(*E*)-*O*-methyl derivative **8d** of hydroxy enol ether **8c** (a tautomer of adenosine 5'-carboxaldehyde **24**). Thus, acetylation of **29**, oxidation to sulfoxides, thermolysis, deacetylation, and laborious purification gave a single methoxy vinyl ether **8d** in low yield.[13] The *E* configuration was tentatively assigned on the basis of NOE and NOSY ^1H NMR experiments. Vinyl diether **8d** was a moderately potent time-dependent inactivator of AdoHcy hydrolase. Since no spontaneous hydrolysis to give "adenosine 5'-carboxaldehydes" was observed in buffer solution, it was assumed that **8d** functioned as an enzyme-activated prodrug.[13]

2'-Fluorination

The potent anticancer agent 2'-deoxy-2',2'-difluorocytidine (**31**) (Figure 3) was prepared from its difluorosugar precursor.[37] We employed fluorination methodologies developed for nucleoside 5'-thioethers to synthesize 2'-fluoro-2'-methylsulfonyl analogue **32** from intact nucleoside precursors.[38] Compound **32** has geminal fluoro and electronegative methylsulfone substituents at C2' analogous to the *gem*-difluoro function in **31**.



31 R = F
32 R = $MeSO_2$
33 R = An
34 R = Me
35 R = Bz
36 R = H

Series **33** - **34**: **a** R' = Ac; **b** R' = H; **c** R' = (4-Cl)Bz; An = (4)$CH_3OC_6H_4$

FIGURE 3

Treatment of 3',5'-di-*O*-acetyl-2'-*S*-(4-methoxyphenyl)-2'-thiouridine with $XeFe_2$, or its sulfoxides [one diastereomer or $(R/S)_S$] with DAST/$SbCl_3$, gave the diastereomeric

2'-(α-fluoro)thioethers **33a** (n = 0; 2'*R/S*, ~1:4.5 to ~1:6.5; ~55%).[38] Compounds **33a** had ^{19}F NMR peaks at δ -128.27 (dd, $^{3}J_{F\text{-}1'} \cong {}^{3}J_{F\text{-}3'} \cong 16.5$ Hz, F2'*S*) and -139.26 (br s, F2'*R*). Deprotection of the sensitive **33a** (n = 0) resulted in decomposition. However, oxidation with *m*-CPBA afforded stable α-fluoro sulfones **33a** (n = 2; 2'*R/S*, ~1:4.5; 80%) and the major diastereomer was separated by HPLC. Deacetylation gave **33b** (n = 2; 2'*S*) whose configuration was established by X-ray crystallography.[38] Formation of major isomer **33a** (n = 2; 2'*S*) with fluorine in the *ribo* orientation might occur by attack of fluoride at the less hindered α face of the sugar ring at C2' of an intermediate species.

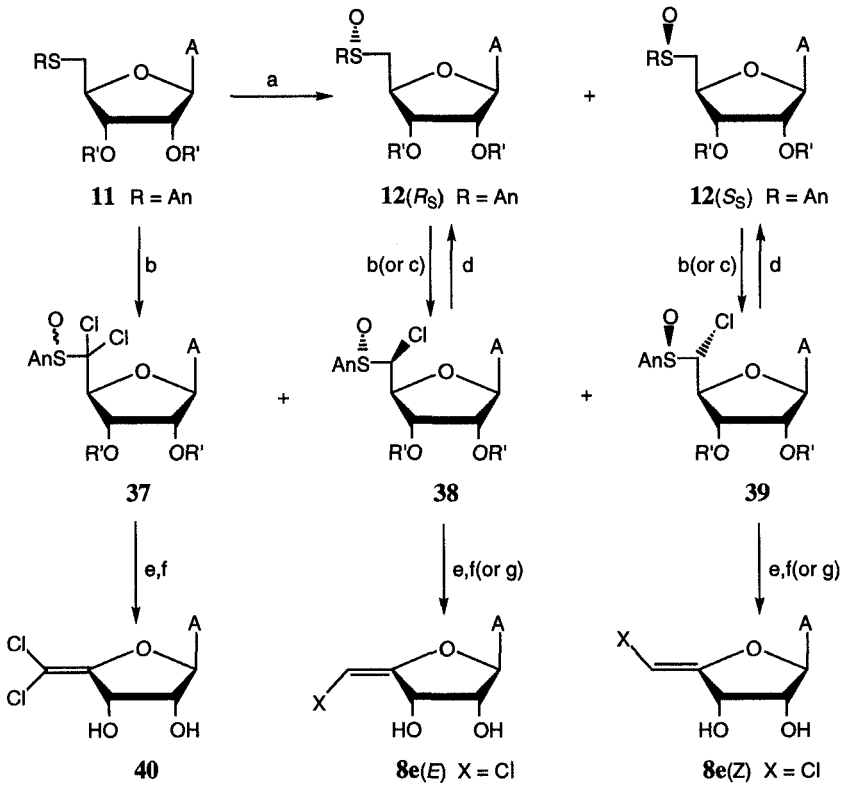
Analogous treatment of 3',5'-di-*O*-acetyl-2'-*S*-methyl-2'-thiouridine with $XeFe_2$ and oxidation of the resulting 2'-(α-fluoro)thioethers **34a** (n = 0) gave the diastereomeric α-fluoro sulfones **34a** (n = 2; 2'*R/S*, ~1:4.6; 46%).[38] Fractional crystallization and deprotection gave stable, crystalline **34b** (n = 2; 2'*S*). The 4-chlorobenzoyl-protected 2'-(α-fluoro)thioethers **34c** (n = 0; 2'*R/S*, ~1:7; 61%) (sulfoxide/DAST/$SbCl_3$) were sufficiently stable for silica gel chromatography and fractional crystallization to give **34c** (n = 2; 2'*S*) [^{19}F NMR δ -140.5 (m, F2'*S*)].[38] It is noteworthy that ^{19}F NMR spectra of the crude reaction mixture had peaks at δ -145.10 (m, F2'*R*) but not in the region of δ -180 to -185 where the triplet for the fluoromethylthio (FCH_2S) group usually appears. Thus, fluorination apparently occurred regiospecifically at C2'. Steric and electronic effects at the vicinal aminoacetal carbon (C1') might control this regiospecific fluorination at C2' to give **34c** (n = 0). The uridine 2'-(α-fluoro)sulfone **34a** (n = 2; 2'*S*) was converted to its cytidine counterpart and deprotected to give **32**(2'*S*).[38] In contrast, it recently was reported that fluorination of 5'-*O*-benzoyl-3'-*S*-methyl-3'-thiothymidine sulfoxides with DAST occurred at the methyl carbon to give the 3'-*S*-(fluoromethyl)-3'-thio analogue **35** (59%).[39] Compound **35** was oxidized to give the fluoromethyl sulfoxide and sulfone derivatives, and also was debenzoylated to give **36**.

5'-Chlorination

Treatment of 2',3'-di-*O*-acetyl-5'-*S*-(4-methoxyphenyl)-5'-thioadenosine (**11a**) with iodobenzene dichloride[40a] (2.25 equiv.) in acetonitrile with solid potassium carbonate as an acid acceptor resulted in the formation of 5'-chloro sulfoxide diastereomers **38a**, **39a**, and other diastereomers (including **37a**) in ratios of ~5.2:1.5:1 (67% combined yield) which were partially separated by silica gel chromatography (Scheme 4).[14] Deacetylation of **38a** and crystallization afforded **38b**(5'*S*, S_S) whose configurations at C5' and sulfur were determined by X-ray crystallography. Treatment of **11a** with excess $PhICl_2$ gave the 5',5'-dichloro sulfoxide diastereomers **37a** as major products.

Analogous treatment of the individual sulfoxides **12a**(R_S) and **12a**(S_S) with $PhICl_2$ (1.25 equiv.) gave **38a**(5'*S*, S_S) and **39a**(5'*R*, R_S), respectively, as the predominant

products.[14] Thus, chlorination of the 5'-thionucleoside sulfoxides under these conditions occurred primarily with retention of configuration at sulfur, in harmony with the studies of Colonna and coworkers.[40] Thermolysis of the 5'-(α-chloro)sulfoxides **38a** and **39a**, and the α,α-dichloro analogues **37a**, followed by deacetylation gave the geometric vinyl chloride isomers **8e**(*E*) and **8e**(*Z*), and dichloro analogue **40**, respectively. The known *syn* stereospecificity of sulfoxide thermolysis reactions coupled with the X-ray crystal structure of **38b**(5'*S*, S_S) and radical-mediated reductive dechlorinations of **38a** and **39a** to the precursor sulfoxides **12** of known configuration provided correlations for the configuration of **39a**(5'*R*, R_S).[14]



Series **11**, **12**, **37 - 39**: **a** R' = Ac; **b** R' = H; **c** R',R' = CMe_2; An = (4)$CH_3OC_6H_4$

(a) *m*-CPBA; (b) $PhICl_2/K_2CO_3/CH_3CN$; (c) SO_2Cl_2/pyridine; (d) Bu_3SnH; (e) diglyme/150 °C; (f) NH_3/MeOH; (g) TFA/H_2O

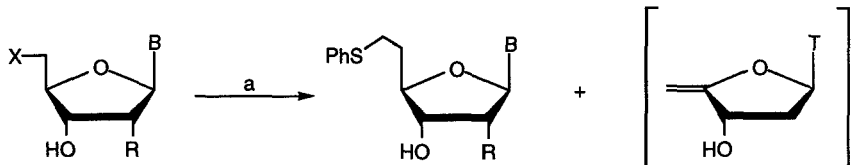
SCHEME 4

Jarvi *et al.* employed sulfuryl chloride in pyridine for the α-chlorination of 2',3'-*O*-isopropylidene-protected adenosine 5'-sulfoxides **12c**.[29] The major chlorination product **38c** was thermolyzed and deprotected to give 5'-chloromethylene analogue **8e**(*E*) which

was tentatively assigned the 5'(*Z*) configuration.[29] The authentic 5'(*Z*) compound **8e**(*Z*) functions as a potent time-dependent inactivator (K_I = 54 nm) of AdoHcy hydrolase.[14,19]

6'-HALO(VINYL) HOMONUCLEOSIDE ANALOGUES FROM VINYL-SULFONE PRECURSORS

Since 5'-chloro- **8e**(*Z*) and 5'-fluoro- **8b**(*Z*) 4',5'-unsaturated adenosine derivatives are potent inactivators of AdoHcy hydrolase, we considered that 6'-halo-5',6'-unsaturated homoadenosine analogues might also be inhibitors of this enzyme. Displacement of iodide from 5'-deoxy-5'-iodothymidine (**41**) with thioanisole anion was reported to give the 6'-thiohomothymidine derivative **42** (78%) plus the dehydrohalogenation by-product **44** (~10%).[41] However, analogous treatment of 5'-chloro-5'-deoxyadenosine (**9**) with (phenylthio)methyllithium did not give the desired 6'-thiohomoadenosine derivative **43**.



41 B = T, X = I, R = H
9 B = A, X = Cl, R = OH

42 B = T, R = H
43 B = A, R = OH

T = thymin-1-yl; A = adenin-9-yl

(a) $PhSCH_3$/BuLi/HMPA/THF

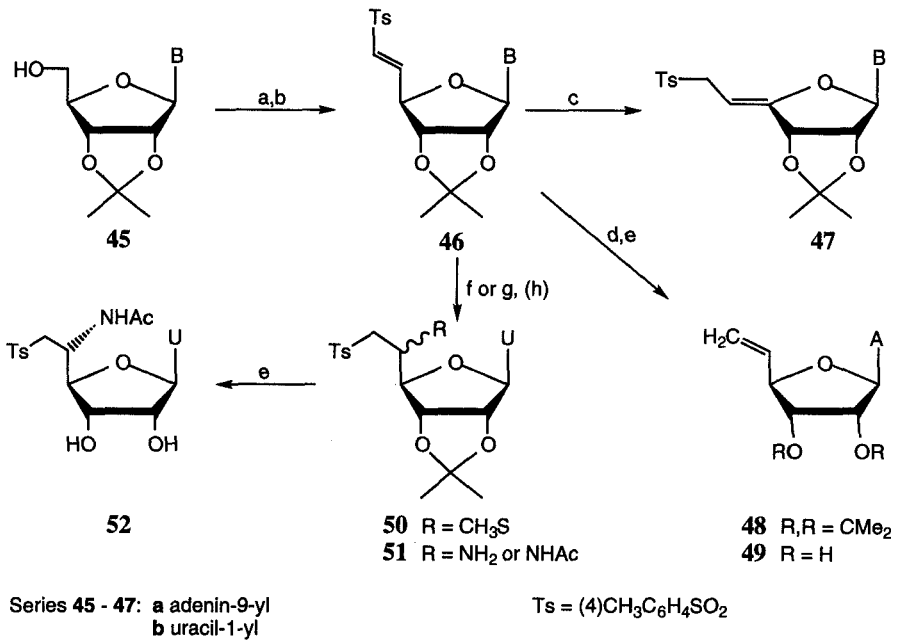
SCHEME 5

There is current interest in oligonucleotide analogues with sulfur-based linkages in place of the natural phosphodiester backbone.[9,42-44] However, convenient routes for the preparation of 6'-thiohomonucleosides such as **43** are lacking, and multi-step syntheses from non-sugar precursors have been employed.[44] Wittig reactions for the synthesis of 6'-halo(vinyl) homonucleosides which involved protected nucleoside 5'-carboxaldehydes and (halomethylene)triphenylphophoranes suffered from the instability of these aldehydes in the presence of the strong bases required for genetration of the Wittig reagents.[45,46] Therefore, we employed a stabilized sulfone Wittig reagent with subsequent vinyl-sulfone and organotin chemistry.

Synthesis of 6'(E)-tosyl(vinyl) homonucleosides

Moffatt oxidation[45b] of 2',3'-*O*-isopropylidenenucleosides **45** and treatment of the crude 5'-carboxaldehydes with (*p*-toluenesulfonylmethylene)triphenylphosphorane gave 6'(*E*)-tosyl(vinyl) homoadenosine[47] **46a** and homouridine[48] **46b** analogues in high yields (Scheme 6). Barton developed alternative routes to such vinyl 6'-sulfone derivatives via

radical-mediated chain extension at C4' with phenyl vinyl sulfone.[49] Compounds **46a** and **46b** rearranged under basic conditions to give single 4',5'-unsaturated allylic sulfone isomers presumed to be **47a** and **47b**.[47,48] Michael addition of sodium thiomethoxide or ammonia to **46b** gave the 5'-substituted-6'-tosyl-5',6'-dideoxy derivatives **50** and **51**, respectively, as diastereomeric mixtures (~1:1).[48] Chromatography and/or fractional crystallization followed by deprotection gave individual isomers [e.g. **52**, whose 5'(*R*) configuration was established by X-ray crystallography].



(a) DCC/Cl_2CHCO_2H/DMSO; (b) Ph_3P=CHTs; (c) DBU/THF; (d) Bu_3SnLi/THF; (e) TFA/H_2O; (f) CH_3SNa; (g) NH_3/H_2O; (h) Ac_2O/DMAP

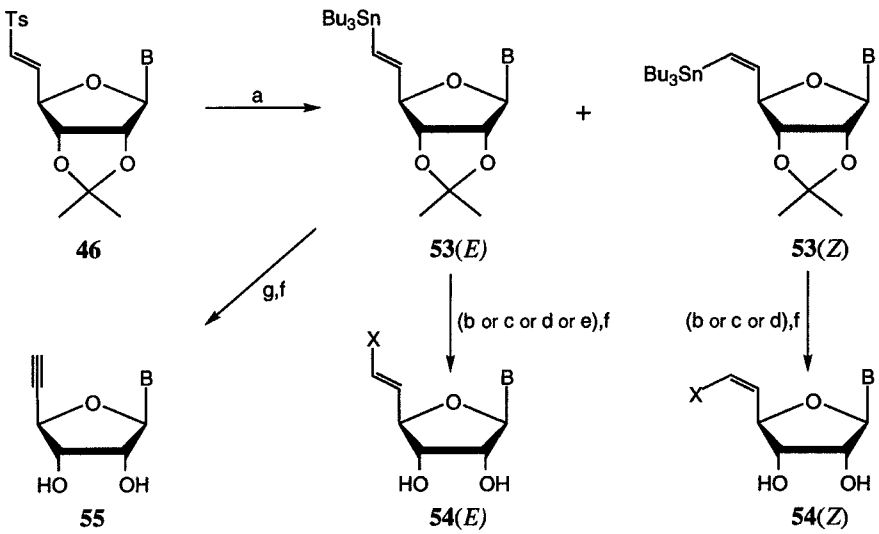
SCHEME 6

Reductive cleavage of the α,β-unsaturated sulfones **46** by Julia's sodium dithionite procedure[50] or with aluminum amalgam[51] failed to give **48**.[47,48] Tosyl removal from **46a** was effected via conjugate addition of tributylstannyllithium,[52] and 5'-deoxy-5'-methyleneadenosine **49** was obtained in moderate yields after deprotection.[47] Other vinyl sulfone chemistry[53] has been employed in syntheses of the 2'-deoxy-2'-fluoromethylene nucleosides;[54] and Chattopadhyaya *et al.* have used nucleoside vinyl 3'-arylsulfones[55] and vinyl 3'(and 2')-phenylselenones[56] for a variety of modifications in the sugar moiety.

6'-Halo(vinyl) homonucleosides from vinyl 6'-stannanes

Radical-mediated stannyldetosylation (Bu_3SnH/AIBN/toluene/Δ)[57] of the 6'(*E*)-sulfone

46 gave separable mixture of the vinyl 6'-stannanes **53a** (*E/Z*, ~4.2:1; 61%)[58] or its uracil analogues **53b** (*E/Z*, ~2.8:1; 87%)[59] (Scheme 7). Quantitative and stereospecific halodestannylation[60] of **53** (*E* and *Z*) occurred with bromine and iodine (or the respective *N*-halosuccinimides) to provide Wittig-type 6'-bromo(and iodo)homovinyl nucleosides **54** (*E* and *Z*) (X = Br and I) after deprotection.[58,59] Chlorine converted **53** (*E* and *Z*) to the 6'-chloro derivatives **54** (X = Cl; *E* and *Z*) with lower stereoselectivity, and some C5 chlorination of the uracil ring occurred with **53b.**[59] Fluorodestannylation of **53a**(*E*) with XeF_2/silver triflate[61] followed by deprotection and HPLC gave the 6'-fluoro(vinyl) homoadenosine **54a**(*E*) (X = F) plus the protiodestannylated by-product **49** (~3:1).[58] Oxidative-destannylation of **53**(*E/Z*) with lead tetraacetate followed by deprotection gave the 5'-deoxy-5'-methynylnucleosides **55**.[58,59] Acetylenic adenosine analogue **55a**, a potent mechanism-based inactivator of AdoHcy hydrolase, was prepared recently by a modified Wittig reaction that employed dimethyl diazomethylphosphonate.[62]



Series **46, 53 - 55:** **a** adenin-9-yl, **b** uracil-1-yl; X = F, Cl, Br, or I

(a) Bu_3SnH/AIBN/$PhCH_3$/Δ; (b) I_2 or NIS; (c) Br_2 or NBS; (d) Cl_2; (e) XeF_2/AgOTf; (f) TFA/H_2O; (g) $Pb(OAc)_4$

SCHEME 7

The 6'(*E/Z*)-halo(vinyl) homoadenosine analogues **54a** are concentration- and time-dependent inactivators of AdoHcy hydrolase. It is noteworthy that inhibition potencies were correlated with anticancer and antiviral activities of **54a** and found to be in the order I > Br > Cl > F (and *E* > *Z* for the geometric isomers of **54a**).[58] Amazingly, AdoHcy hydrolase possesses the catalytic power to effect addition of water to the "isolated" vinyl

double bonds of the 6'-halo(vinyl) homoadenosine analogues **54a**. These compounds are the first clear examples of alternative substrates in which separation of the "hydrolytic" (i.e. addition of water) and oxidative activities of AdoHcy hydrolase is apparent.[63,64]

ACKNOWLEDGMENTS. We thank the American Cancer Society and Brigham Young University development funds for generous financial support, and Mrs. Hazel Dunsmore for assistance with the manuscript.

REFERENCES

1. *Transmethylation and Methionine Biosynthesis*, edited by S.K. Shapiro and F. Schlenk (The University of Chicago Press, Chicago, 1965).
2. *The Biochemistry of S-Adenosylmethionine and Related Compounds*, edited by E. Usdin, R.T. Borchardt, and C.R. Creveling (Macmillan Press, London, 1982).
3. F. Schlenk, *Adv. Enzymol. Related Areas Mol. Biol.*, **54**, 195 (1983).
4. P.M. Ueland, *Pharmacol. Rev.*, **34**, 223 (1982).
5. J.L. Palmer and R.H. Abeles, *J. Biol. Chem.*, **254**, 1217 (1979).
6. A.K. Sinhababu, R.L. Bartel, N. Pochopin, and R.T. Borchardt, *J. Am. Chem. Soc.*, **107**, 1628 (1985).
7. R. Parry and L.J. Askonas, *J. Am. Chem. Soc.*, **107**, 1417 (1985).
8. D.J.T. Porter, *J. Biol. Chem.*, **268**, 66 (1993).
9. S.F. Wnuk, *Tetrahedron*, **49**, 9877 (1993).
10. M.J. Robins, F. Hansske, S.F. Wnuk, and T. Kanai, *Can. J. Chem.*, **69**, 1468 (1991).
11. M.J. Robins and S.F. Wnuk, *Tetrahedron Lett.*, **29**, 5729 (1988).
12. M.J. Robins, S.F. Wnuk, K.B. Mullah, and N.K. Dalley, *J. Org. Chem.*, **56**, 6878 (1991).
13. M.J. Robins, S.F. Wnuk, K.B. Mullah, N.K. Dalley, C.-S. Yuan, Y. Lee, and R.T. Borchardt, *J. Org. Chem.*, **59**, 544 (1994).
14. S.F. Wnuk, N.K. Dalley, and M.J. Robins, *J. Org. Chem.*, **58**, 111 (1993).
15. R. Kuhn and W. Jahn, *Chem. Ber.*, **98**, 1699 (1965).
16. I. Nakagawa, K. Akai, and T. Hata, *J. Chem Soc., Perkins Trans. 1*, 1315 (1983).
17. S.F. Wnuk, J.D. Stoeckler, and M.J. Robins, *Nucleosides Nucleotides*, **13**, 389 (1994).
18. A. Bloch, M.J. Robins, and J.R. McCarthy, Jr., *J. Med. Chem.*, **10**, 908 (1967).
19. M.J. Robins, S.F. Wnuk, K.B. Mullah, N.K. Dalley, R.T. Borchardt, Y. Lee, and C.-S. Yuan, "Adenosine-Derived 5'-α-Halo Thioether, Sulfoxide, Sulfone, and (5'-Halo)Methylene Analogues. Inhibition of *S*-Adenosyl-L-Homocysteine Hydrolase" in *Nucleosides as Antitumor and Antiviral Agents*, edited by C.K. Chu and D.C. Baker (Plenum Press, New York, 1993), Chapter 6, pp. 115-126.
20. C.-S. Yuan, S. Liu, S.F. Wnuk, M.J. Robins, and R.T. Borchardt, "Design and Synthesis of *S*-Adenosylhomocysteine Hydrolase Inhibitors as Broad-Spectrum Antiviral Agents" in *Advances in Antiviral Drug Design*, edited by E. De Clercq (JAI Press, London) in press.
21. T.M. Savarese, S.-H. Chu, M.-Y. Chu, and R.E. Parks, Jr., *Biochem. Pharmacol.*, **34**, 361 (1985).

22. J.R. McCarthy, N.P. Peet, M.E. LeTourneau, and M. Inbasekaran, *J. Am. Chem. Soc.*, **107**, 735 (1985).
23. S.F. Wnuk and M.J. Robins, *J. Org. Chem.*, **55**, 4757 (1990).
24. (a) M. Zupan, *J. Fluorine Chem.*, **8**, 305 (1976). (b) R.K. Marat and A.F. Janzen, *Can. J. Chem.*, **55**, 3031 (1977).
25. T. Umemoto and G. Tomizawa, *Bull. Chem. Soc. Jpn.*, **59**, 3625 (1986).
26. M.J. Robins and S.F. Wnuk, *J. Org. Chem.*, **58**, 3800 (1993).
27. G.S. Lal, *J. Org. Chem.*, **58**, 2791 (1993).
28. J.R. McCarthy, E.T. Jarvi, D.P. Matthews, M.L. Edwards, N.J. Prakash, T.L. Bowlin, S. Mehdi, P.S. Sunkara, and P. Bey, *J. Am. Chem. Soc.*, **111**, 1127 (1989).
29. E.T. Jarvi, J.R. McCarthy, S. Mehdi, D.P. Matthews, M.L. Edwards, N.J. Prakash, T.L. Bowlin, P.S. Sunkara, and P. Bey, *J. Med. Chem.*, **34**, 647 (1991).
30. S. Liu, M.S. Wolfe, C. Yuan, S.M. Ali, and R.T. Borchardt, *Bioorg. Med. Chem. Lett.*, **2**, 1741 (1992).
31. D.P. Matthews, M.L. Edwards, S. Mehdi, J.R. Koehl, J.A. Wolos, and J.R. McCarthy, *Bioorg. Med. Chem. Lett.*, **3**, 165 (1993).
32. S. Mehdi, E.T. Jarvi, J.R. Koehl, J.R. McCarthy, and P. Bey, *J. Enzyme Inhib.*, **4**, 1 (1990).
33. C.-S. Yuan, J. Yeh, S. Liu, and R.T. Borchardt, *J. Biol. Chem.*, **268**, 17030 (1993).
34. S. Liu, S.F. Wnuk, C.-S. Yuan, M.J. Robins, and R.T. Borchardt, *J. Med. Chem.*, **36**, 883 (1993).
35. G. Guillerm and M. Gatel, *J. Chem. Soc., Perkin Trans. 1*, 153 (1994).
36. J.R. Sufrin, A.J. Spiess, D.L. Kramer, P.R. Libby, and C.W. Porter, *J. Med. Chem.*, **32**, 997 (1989).
37. (a) L.W. Hertel, J.S. Kroin, J.W. Misner, and J.M. Tustin, *J. Org. Chem.*, **53**, 2406 (1988). (b) T.S. Chou, P.C. Heath, L.E. Patterson, L.M. Poteet, R.E. Lakin, and A.H. Hunt, *Synthesis*, 565 (1992).
38. M.J. Robins, K.B. Mullah, S.F. Wnuk, and N.K. Dalley, *J. Org. Chem.*, **57**, 2357 (1992).
39. P. Herdewijn, A. De Bruyn, P. Wigerinck, C. Hendrix, L. Kerremans, J. Rozenski, and R. Busson, *J. Chem. Soc., Perkin Trans. 1*, 249 (1994).
40. (a) M. Cinquini and S. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 1883 (1972). (b) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin Trans 1*, 1866 (1972). (c) P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Am. Chem. Soc.*, **95**, 7431 (1973).
41. P.S. Ray and A.A. Jaxa-Chamiec, *Heterocycles*, **31**, 1777 (1990).
42. Y.S. Sanghvi and P.D. Cook, "Towards Second-Generation Synthetic Backbones for Antisense Oligonucleosides" in *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, edited by C.K. Chu and D.C. Baker (Plenum Press, New York, 1993), Chapter 17, pp. 311-324.
43. R.S. Varma, *Synlett*, 621 (1993).
44. Z. Huang, K.C. Schneider, and S.A. Benner, *J. Org. Chem.*, **56**, 3869 (1991).
45. (a) J.G. Moffatt, "Chemical Transformations of the Sugar Moiety of Nucleosides" in *Nucleoside Analogues: Chemistry, Biology, and Medicinal Applications*, edited by R.T. Walker, E. De Clercq, and F. Eckstein (Plenum Press, New York, 1979),

Chapter 4, pp. 71-164. (b) R.S. Ranganathan, G.H. Jones, and J.G. Moffatt, *J. Org. Chem.*, **39**, 290 (1974).
46. R A. Sharma and M. Bobek, *J. Org. Chem.*, **43**, 367 (1978).
47. S.F. Wnuk and M.J. Robins, *Can. J. Chem.*, **69**, 334 (1991).
48. S.F. Wnuk, N.K. Dalley, and M.J. Robins, *Can. J. Chem.*, **69**, 2104 (1991).
49. (a) D.H.R. Barton, S.D. Géro, B. Quiclet-Sire, and M. Samadi, *J. Chem. Soc., Chem. Commun.*, 1372 (1988). (b) D.H.R. Barton and M. Samadi, *Tetrahedron*, **48**, 7083 (1992).
50. (a) J. Bremner, M. Julia, M. Launay, and J.-P. Stacino, *Tetrahedron Lett.*, **23**, 3265 (1982). (b) M. Julia, H. Lauron, J.-P. Stacino, and J.-N. Verpeaux, *Tetrahedron*, **42**, 2475 (1986).
51. V. Pascali and A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.*, 351 (1973).
52. M. Ochiai, T. Ukita, and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 619 (1983).
53. N.S. Simpkins, *Tetrahedron*, **46**, 6951 (1990).
54. (a) J.R. McCarthy, D.P. Matthews, D.M. Stemerick, E.W. Huber, P. Bey, B.J. Lippert, R.D. Snyder, and P.S. Sunkara, *J. Am. Chem. Soc.*, **113**, 7439 (1991). (b) D.P. Matthews, R.A. Persichetti, J.S. Sabol, K.T. Stewart, and J.R. McCarthy, *Nucleosides Nucleotides*, **12**, 115 (1993).
55. J.-C. Wu, T. Pathak, W. Tong, J.-M. Vial, G. Remaud, and J. Chattopadhyaya, *Tetrahedron*, **44**, 6705 (1988).
56. (a) J.-C. Wu and J. Chattopadhyaya, *Tetrahedron*, **45**, 4507 (1989). (b) W. Tong, Z. Xi, C. Gioeli, and J. Chattopadhyaya, *Tetrahedron*, **47**, 3431 (1991).
57. Y. Watanabe, Y. Ueno, T. Araki, T. Endo, and M. Okawara, *Tetrahedron Lett.*, **27**, 215 (1986).
58. S.F. Wnuk, C.-S. Yuan, R.T. Borchardt, J. Balzarini, E. De Clercq, and M.J. Robins, *J. Med. Chem.*, submitted.
59. S.F. Wnuk and M.J. Robins, *Can. J. Chem.*, **71**, 192 (1993).
60. M. Peryere, J.-P. Quintard, and A. Rahm, *Tin in Organic Synthesis* (Butterworths, London, 1987).
61. M.A. Tius and J.K. Kawakami, *Synlett*, 207 (1993).
62. R.J. Parry, A. Muscate, and L.J. Askonas, *Biochemistry*, **30**, 9988 (1991).
63. C.-S. Yuan, S. Liu, S.F. Wnuk, M.J. Robins, and R.T. Borchardt, *Biochemistry*, **33**, 3758 (1994).
64. C.-S. Yuan, S.F. Wnuk, S. Liu, M.J. Robins, and R.T. Borchardt, *Biochemistry*, submitted.