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Developing of Germyldesulfonylation and Thiodesulfonylation Reactions for the Synthesis of Novel Nucleoside Analogues. Efficient Synthesis of Novel (α-Fluoro)vinyl Sulfides

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DEVELOPING OF GERMYLDESULFONYLATION AND THIODESULFONYLATION REACTIONS FOR THE SYNTHESIS OF NOVEL NUCLEOSIDE ANALOGUES. EFFICIENT SYNTHESIS OF NOVEL \((\alpha\text{-FLUORO})\text{VINYL SULFIDES.}\)

A dissertation submitted in partial fulfillment of the requirements for the degree of

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by

Pablo R. Sacasa

2010
To: Dean Kenneth Furton  
College of Arts and Sciences

This dissertation, written by Pablo R. Sacasa, and entitled Developing of Germylidesulfonylation and Thiodesulfonylation Reactions for the Synthesis of Novel Nucleoside Analogues. Efficient Synthesis of Novel (α-Fluoro)vinyl Sulfides, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Date of Defense: July 19, 2010

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Florida International University, 2010
DEDICATION

I dedicate this dissertation to my family:

Pablo, Ruth, Juan Pablo and Ruth Paola Sacasa for all of their love and support.
ACKNOWLEDGMENTS

I am extremely grateful to my major Professor, Dr. Stanislaw F. Wnuk for all of his guidance, support, understanding, patience, friendship and most important of all for believing in me. I would also like to thank Dr. J. Martin Quirke for all of his friendship, help, suggestions, and for being there for me. I also want to thank Dr. Kevin O'shea and Dr. Piero Gardinali for their guidance and friendship throughout the years. I also want to thank Dr. Rene Herrera for all the helpful insights and support. Finally, I would like to also thank all of my coworkers in the lab for providing a family atmosphere in the workplace.
ABSTRACT OF THE DISSERTATION

DEVELOPING OF GERMYLDESULFONYLATION AND THIODESULFONYLATION REACTIONS FOR THE SYNTHESIS OF NOVEL NUCLEOSIDE ANALOGUES. EFFICIENT SYNTHESIS OF NOVEL (α-FLUORO)VINYL SULFIDES.

by

Pablo R. Sacasa

Florida International University, 2010

Miami, Florida

Professor Stanislaw F. Wnuk, Major Professor

*S*-adenosyl-\(L\)-homocysteine (\(S\)-AdoHcy) hydrolase effects hydrolytic cleavage of AdoHcy to produce both adenosine and \(L\)-homocysteine and is a feedback inhibitor of \(S\)-adenosyl-\(L\)-methionine (\(S\)-SAM). Nucleoside analogues bearing an alkenyl or fluoroalkenyl chain between sulfur and \(C5'\) utilizing Negishi coupling reactions were synthesized. Palladium-catalyzed cross-coupling between the \(5'\)-deoxy-\(5'\)-(iodomethylene) nucleosides and alkylzinc bromides gives analogues with the alkenyl unit. Palladium-catalyzed selective monoalkylation of \(5'\)-(bromofluoromethylene)-\(5'\)-deoxy-adenosine with alkylzinc bromide afford adenosylhomocysteine analogues with a \(6'\)-(fluoro)vinyl motif. The vinylic adenine nucleosides produced time-dependent inactivation of the \(S\)-adenosyl-\(L\)-homocysteine hydrolases.

Stannydesulfonylation reaction is a critical step in the synthesis of \(E\)-fluorovinyl cytidine (Tezacitabine) a ribonucleoside reductase inhibitor with a potent anticancer activity. The synthesis involves the removal of the sulfonyl group by a radical-mediated
stannyldesulfonylation reaction using tributyltin hydride. In order to eliminate the toxicity of tin, I developed a radical-mediated germyldesulfonylation utilizing less toxic germane hydrides. Treatment of the protected \((E)-5'\text{-deoxy}-5'\text{-}[\(\rho\text{-toluenesulfonyl}\)\-methylene]uridine and adenosine derivatives with tributyl- or triphenylgermane hydride effected radical-mediated germyldesulfonylations to give \(5'\text{-}(\text{tributyl- or triphenylgermyl})\text{methylene-5'\text{-deoxynucleoside derivatives as single } (E)\text{-isomers}}.

Analogous treatment of \(2'\text{-deoxygen-2'\-[\(\text{phenylsulfonyl}\)\-methylene]uridine with Ph}_{3}\text{GeH afforded the corresponding vinyl triphenylgermane product. Stereoselective halodegermylation of the } (E)-5'-(\text{tributylgermyl})\text{-methylene-5'\-deoxygen nucleosides with NIS or NBS provided the Wittig-type } (E)-5'\text{-deoxygen-5'-(halomethylene) nucleosides quantitatively.}

Radical-mediated thiodesulfonylation of the readily available vinyl and \((\alpha\text{-fluoro})\) vinyl sulfones with aryl thiols in organic or aqueous medium to provide a bench and environmentally friendly protocol to access \((\alpha\text{-fluoro})\) vinyl sulfides were developed. Methylation of the vinyl or \((\alpha\text{-fluoro})\) vinyl phenyl sulfide gave access to the corresponding vinyl or \((\alpha\text{-fluoro})\) vinyl sulfonium salts. These sulfonium ions were tested as possible methyl group donors during reactions with thiols, phenols or amino groups which are commonly present in natural amino acids.
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1. INTRODUCTION

Nucleoside analogues have been synthesized as potential anticancer and antiviral chemotherapeutic agents to mimic those created by microorganisms (1-8, figure 1). There are enzymes which apply nucleosides and/or nucleotides as cofactors or substrates that can intervene with targets for antibiotic as well as synthetic antiviral and antitumor agents. In nucleic acid replication, deviant nucleosides inhibit elongation of embryonic nucleic acid strands or can severely suspend certain normal functions or activities of completed nucleic acids. For instance, certain nucleoside antibiotics can interrupt protein synthesis. An example of this interruption that takes place in the ribosome causing premature chain termination during translation involves puromycin, 4, which is derived from the *Streptomyces alboniger* bacterium, an aminonucleoside antibiotic. Part of puromycin resembles the 3' end of the aminoacylated tRNA. Puromycin enters the A site and transfers to the growing chain, causing premature chain release. How this action takes place is still unknown, but, the 3' position instead of containing the normal ester linkage of tRNA contains an amide linkage. Thus, the amide linkage makes the molecule much more resistant to hydrolysis and causes complete blockage of the ribosome.1b

Transition state inhibitors bind rigidly to the enzymes active site, owing to their resemblance to the transition state that occurs during a normal enzyme reaction. Coformycin, 5, and 2'-deoxycoformycin, 6, are transition state inhibitors that are potent inhibitors of adenosine deaminase. Both 5 and 6 mimic the transition state structures of the adenosine and 2'-deoxyadenosine substrates during their hydrolysis to form inosine and 2'-deoxyinosine by adenosine deaminase.2,3
Figure 1. Selected Nucleoside Antibiotics.

Affinity labeling agents are reactive compounds that have an arrangement associated with that of the substrate of the target enzyme. After the formation of the reversible enzyme-inhibitor complex, acylation or alkylation reaction mechanisms tend to occur with the active site nucleophiles forming a stable covalent bond to the enzyme. Affinity labeling agents contain many reactive functional groups. As a result, these agents not only react with the active site of the enzyme, but also with nucleophiles associated with other enzymes and biomolecules. For that reason, these inactivators are potentially toxic, and are not useful in drug design as other types of enzyme inhibitors.

A mechanism-based enzyme inhibitor is an inactive compound that bears structural resemblance either to the substrate or the product of a specific enzyme. Once
this compound binds to the active site of the target enzyme its normal catalytic mechanism alters it to a transitional state that is usually very reactive. Prior to escaping from the active site, this species can form a covalent bond to the enzyme; however, a tight-binding inhibitor-enzyme complex may be sufficient. The deactivator must first be transformed by the target enzyme into the actual deactivating species, and the deactivation must occur before the release of this species from the active site of the enzyme.\textsuperscript{2-4} Therefore, the activation of the mechanism-based inhibitors depends on the catalytic mechanism of the target enzyme. As a result, these inhibitors can be designed by coherent organic mechanistic approaches.


1.1.1. Biological Functions of \textit{S}-Adenosyl-\textit{L}-Homocysteine Hydrolase

\textit{S}-adenosyl-\textit{L}-homocysteine hydrolase (AdoHcy hydrolase) effects hydrolytic cleavage of AdoHcy to produce both adenosine (Ado) and \textit{L}-homocysteine (Hcy) and is a feedback inhibitor of \textit{S}-adenosyl-\textit{L}-methionine (SAM or AdoMet).\textsuperscript{5-7} The methyl group from AdoMet is transferred to a variety of acceptor macromolecules, for example, nucleic acids, phospholipids, proteins and small molecules such as neurotransmitters and hormones from specific methyl transferases in AdoMet-dependent transmethylation reactions. Biomethylation reactions have an effect on various aspects of metabolism, gene regulation and cell function.\textsuperscript{8-10}

\textit{S}-Adenosyl-\textit{L}-homocysteine (AdoHcy), the product of the AdoMet-dependent methyl transferases must be efficiently eliminated because it is an effective competitive product inhibitor of methyltransferases. The AdoHcy hydrolase provides the only known mechanism for AdoHcy metabolism in eukaryotes by catalyzing its hydrolysis to
adenosine (Ado) and L-homocysteine (Hcy). This catalytic reaction is reversible, with the equilibrium favoring the synthetic direction. Nevertheless, under physiological conditions, the reaction is driven in the hydrolytic direction by successive metabolic conversions of adenosine (e.g., to ATP, inosine) and homocysteine (e.g., to methionine, cystathionine)\textsuperscript{5-7}.

A side-reaction catalyzed by AdoHcy hydrolase is the conversion of adenosine to adenine,\textsuperscript{5} This reaction is very important because it is the only source of cellular adenine in the body. Another way to express this reaction is by enzymatic synthesis and hydrolysis of AdoHcy but it is inefficient \textit{in vitro}. The main features of the role of AdoHcy hydrolase in the metabolism of purine and sulfur containing compounds are summarized in Figure 2.

\textit{S}-adenosyl-L-homocysteine hydrolase plays an important part in controlling cellular level of Hcy, which is a cystathionine synthetase-catalyzed precursor to cysteine and methionine. The metabolism of AdoHcy by this enzyme is the only known source of Hcy in mammalian cells.\textsuperscript{12} It has been proven in clinical studies that elevated plasma levels of Hcy in humans is linked to coronary heart disease.\textsuperscript{13} Inhibitors of AdoHcy hydrolase have the potential to reduce the risk of developing coronary heart disease by lowering the plasma levels of Hcy. It is known that by taking supplements containing folic acid and vitamin B there is a drastic effect in lowering the plasma Hcy levels in patients with homocysteinemia with residual activities of cystathionine synthetase.\textsuperscript{13,14}
A distribution study was performed on AdoHcy hydrolase in a variety of mammalian tissues and it revealed that the enzyme activity was lowest in the heart and brain; intermediary in the spleen and testes; and highest in the liver, pancreas and kidneys.\textsuperscript{5} It was found that the liver of the mouse contains about twelve times more AdoHcy hydrolase then in the kidneys, which in turn has five times more AdoHcy hydrolase then in the brain. A one molar equivalent of copper is bound per subunit of mouse liver enzyme.\textsuperscript{15} In copper-deficient mice there is a 45\% decrease in the hepatic level of AdoHcy.\textsuperscript{16} Therefore, binding of copper by enzyme plays a role in copper metabolism.

\textbf{Figure 2.} Biosynthesis Pathway and Metabolism of \textit{S}-Adenosyl-\textit{L}-Homocysteine and \textit{S}-Adenosyl-\textit{L}-Methionine.

A distribution study was performed on AdoHcy hydrolase in a variety of mammalian tissues and it revealed that the enzyme activity was lowest in the heart and brain; intermediary in the spleen and testes; and highest in the liver, pancreas and kidneys.\textsuperscript{5} It was found that the liver of the mouse contains about twelve times more AdoHcy hydrolase then in the kidneys, which in turn has five times more AdoHcy hydrolase then in the brain. A one molar equivalent of copper is bound per subunit of mouse liver enzyme.\textsuperscript{15} In copper-deficient mice there is a 45\% decrease in the hepatic level of AdoHcy.\textsuperscript{16} Therefore, binding of copper by enzyme plays a role in copper metabolism.
The AdoHcy hydrolase from *Dictyostelium discoideum* can be reversibly inactivated by cAMP by causing dissociation of enzyme bound NAD\(^+\). Interestingly, cAMP is secreted by the amoebas to attract neighboring cells to a central location. This suggests a viable regulation mechanism by cAMP for AdoHcy or AdoMet metabolism. Another way to inactivate the AdoHcy hydrolase from the liver of the rat is by means of ATP. The binding site for cAMP of the hydrolase is particularly different from the cAMP-binding site of the R\(_1\) regulatory subunit of cAMP-dependent protein kinase. These observations indicate that AdoHcy hydrolase competes for cAMP or ATP against some unknown receptors or kinases.\(^8\)

Recently, AdoHcy hydrolase has attracted attention as a target for drug design,\(^6,17\) because inhibitors of this enzyme exhibit antiviral,\(^17-19\) antiparasitic,\(^20\) antiarthritic\(^21\) and immunosuppressive effects.\(^22\) Inhibition of cellular AdoHcy hydrolase results in intracellular buildup of AdoHcy, as a result, it causes an increase in the intracellular AdoHcy/AdoMet ratios and subsequent inhibition of fundamental AdoMet-dependent methylation reactions. The established relationships are particularly well recognized for the antiviral effect of AdoHcy hydrolase inhibitors. A linear correlation between log IC\(_{50}\) values (inhibition concentration which inhibits viral replication by 50%) and their log K\(_i\) values (inhibition potency of AdoHcy hydrolase) for a series of AdoHcy hydrolase inhibitors has been observed.\(^1\)

**1.1.2. Mechanism of Action for S-Adenosyl-L-Homocysteine Hydrolase.**

Palmer and Abeles\(^23\) proposed a mechanism by which AdoHcy hydrolase catalyzes the conversion of AdoHcy 9 to Ado 13 and Hcy (Figure 3). The first step (oxidative activity) of the mechanism involves the oxidation of the 3'-hydroxyl group of
AdoHcy by the enzyme-bound NAD$^+$ (E•NAD$^+$) to form E•NADH and 3'-keto-AdoHcy 10, which then undergoes a β-elimination to Hcy to form the 3'-keto-4',5'-didehydro-5'-deoxyAdo (KDDA, 11). This is then followed by a Michael type addition of water to this tightly bound intermediate (hydrolytic activity) to give the 3'-ketoAdo 12, which is then reduced by E•NADH to yield Ado 13 and E•NAD$^+$. The 4',5'-didehydro-5'-deoxyadenosine, (DDA, 14, Figure 3) was found to be an alternative substrate of the enzyme.

**Figure 3.** Proposed Mechanism for S-Adenosyl-L-Homocysteine Hydrolase.

Porter and Boyd showed that neither the apoenzyme nor the reduced form of S-adenosyl-L-homocysteine hydrolase (E•NADH) was catalytically active.$^{24}$ Porter and Boyds’ mechanism suggest that breakage of the C5'-S bond (elimination of the Hcy from the 3'-keto-AdoHcy) and the formation of C5'-O bond (addition of water to the KDDA, 11) were dependent on the oxidative activity of the enzyme. Parry and Askonas studied
the stereochemistry of this reaction\textsuperscript{25} and found \textit{syn} geometry of the addition of Hcy to KDDA. This geometry results because of the reaction, which is catalyzed by AdoHcy hydrolase, occurs with retention of the configuration in C5'. The elimination step is catalyzed by an enzyme also containing \textit{syn} geometry.

Palmer and Abeles made the assumption that the mechanism;\textsuperscript{23} is operated in a sequential manner in which the oxidation of the hydroxyl functionality at C3' forms the 3'-ketone. The "oxidative activity" was said to be a prerequisite for the conjugate addition of water ("hydrolytic activity") across the double bond of the activated enone.\textsuperscript{26} Borchardt and coworkers later demonstrated that these two catalytic activities of AdoHcy hydrolase were independent of one another.\textsuperscript{27} They first defined type I mechanism-based inhibitors of AdoHcy hydrolase as inhibitors that serve as substrates for the "oxidative" activities of the enzyme. These inhibitors were oxidized to the corresponding 3'-keto derivatives which converted the enzyme from its active form (NAD\textsuperscript{+}) to its inactive form (NADH; cofactor depletion mechanism). Secondly, they defined type II mechanism-based inhibitors of AdoHcy hydrolase as compounds that use the "oxidative" and/or "hydrolytic" activity of the enzyme to produce electrophiles on the active site of the enzyme. The electrophiles react with the enzymes nucleophiles to modify the enzyme (covalent inactivation mechanism).\textsuperscript{6a,14,26} Finally, they defined type III inhibitors as those that use neither "oxidative" nor the "hydrolytic" activity, but that they are reversibly bound to the enzyme.\textsuperscript{14}

The x-ray crystal structure of substrate-bound NADH from human AdoHcy hydrolase was determined.\textsuperscript{28} The pure NADH form of the enzyme was inactivated with 9-(2,3-dihydroxycyclopent-4-en-1-yl)adenine (DHCeA, \textbf{15}, figure 4) to produce crystals of
the 3'-ketoDHCeA/NADH form of human AdoHcy hydrolase which was appropriate for X-ray crystallographic analysis. The sequestered water molecules in the active site were found to hydrogen bond to His55, Asp131 and His301. Water has a dual role in the catalytic mechanism; it is not just used for the catalytic base responsible for the H4' abstraction initiating Hcy elimination, but it may also add to the intermediate enone in the formation of 3'-ketoAdo.\textsuperscript{14b,28} A crystal structure obtained from the liver of a rat in a substrate free NAD\textsuperscript{+} showed an open catalytic site in the absence of substrate.\textsuperscript{29} The experiment helped identify Glu55 as a proton acceptor from the 3'-OH during the abstraction of the H3' by NAD\textsuperscript{+}. Also it is indicated that either His54 or Asp130 acts as a general acid-base catalyst. The Cys194 was expected to modulate the oxidation state of the bound NAD\textsuperscript{+}. Unfortunately, these two crystal structures do not unambiguously define the binding site of the homocysteine moiety of AdoHcy at the active sites of the enzyme.

\textbf{Figure 4.} 9-(2,3-Dihydroxycyclopent-4-en-1-yl)adenosine (DHCeA). A Potential Inhibitor of \textit{S}-Adenosyl-L-Homocysteine Hydrolase.

\subsection*{1.1.3. Hydrolytic Activity of \textit{S}-Adenosyl-L-Homocysteine Hydrolase with Halovinyl Adenosine Analogues.}

McCarthy and coworkers designed and synthesized vinyl fluoride 16 (4',5'-didehydro-5'-deoxy-5'-fluoroAdo) and vinyl chloride 17 as feasible type II mechanism
based inhibitors that also displayed significant biological activity (Figure 5).\textsuperscript{30} The synthesis of 16 was performed by fluorination of a protected 5'-S-aryl-5'-thioadenosine analogue, 19, with (diethylamino)sulfur trifluoride (DAST) to produce the α-fluorothioesters 21. Subsequent oxidation with \textit{m}-chloroperoxybenzoic acid (\textit{m}-CPBA) gave the α-fluoro sulfoxide diastereomers 22.\textsuperscript{30b,31} Thermal elimination of sulfenic acid (Figure 6) from 22 and deprotection gave the vinyl fluoride 16 as \textit{E}/\textit{Z} isomers.\textsuperscript{30} The most important step in this reaction sequence was fluorination of sulfoxide 19, or thioether 20 using DAST/SbCl\textsubscript{3} combinations developed by Wnuk and Robins.\textsuperscript{32}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{inhibitors.png}
\caption{Selected Inhibitors of \textit{S}-Adenosyl-L-Homocysteine Hydrolase.}
\end{figure}

Borchardt and coworkers proved\textsuperscript{27} that vinyl fluoride 16 is not a type II based inhibitor. Instead, 16, is a "pro-inhibitor" that was altered by the AdoHcy hydrolase to form both adenosine 5'-aldehyde 18 and its 4'-epimers which inactivates the enzyme by a type I mechanism. The elimination of the fluorine from 16 was executed by the "hydrolytic" activity of the enzyme and was found to be independent of the enzymes "oxidative" activity.\textsuperscript{27,33} The Ado-5'-aldehyde 18 was independently synthesized and shown to be a potent inhibitor of AdoHcy hydrolase.\textsuperscript{34}
Figure 6. Synthesis of the 5'-Fluoro(vinyl)adenosine.

It was found that AdoHcy hydrolase also adds water across the isolated 5',6' double bond of the 6'-halo(vinyl)homoAdo derivative. A combination of a sulfonyl-stabilized Wittig-type reagent and organotin chemistry was utilized for the synthesis of homovinyl halides 27 (scheme 1). Thus, Moffatt oxidation of the 2',3'-O-isopropylideneadenosine and treatment of the crude 5'-aldehyde 23 with [(p-tolylsulfonyl)methylene]-triphenylphosphorane, Ph$_3$P=CHTs, afforded the 6'-tosyl(vinyl)-sulfone 24 with the $E$ isomer being the major product. Radical stannyldesulfonylation ($\text{Bu}_3\text{SnH/AIBN/toluene/\Delta}$) of 24 produced separable mixtures of the vinyl 6'-stannane 25 ($E/Z$, $> 6:1$). Quantitative and stereospecific halodestannylation of 25 ($E$ or $Z$ isomers) occurred with I$_2$ or Br$_2$ (or the respective $N$-halosuccinimides) gave the Wittig type 6'-iodo (or bromo) homovinylAdo 26 ($E/Z$ isomers). Deprotection and purification afforded 27. Treatment of 25 with XeFe$_2$/silver triflate resulted in fluorodestannylation, 27 ($X = F$). Chlorine converted 25 to 6'-chloro derivative 27 ($X = Cl$, $E$ and $Z$) but with less stereoselectivity.
Scheme 1. Synthesis of 6'-Halo(vinyl)homoadenosine Analogues.

The 6'-halo(homo)vinylAdo analogues 27 were found to be concentration and time-dependent inactivators of AdoHcy hydrolase. The inhibition potencies which were linked with anticancer and antiviral activities of 27, were found to be in the following order: I > Br > Cl > F (and E > Z). Astonishingly, AdoHcy hydrolase exhibits the catalytic control to achieve the addition of water to the isolated double bonds of 27. AdoHcy hydrolase effected hydrolysis of the 6'-halogen from 27 by the addition of water at C6' (path a). Subsequent halogen elimination produced homoadenosine 6'-aldehyde 28, which undergoes a spontaneous decomposition to Ade (figure 7). Addition of water at C5' of 27 (X = F) resulted in the formation of 6'-deoxy-6'-fluoro-5'-hydroxyhomoadenosine 31 (path b). In the third pathway, the enzymatic oxidation of 27 provided 3'-ketone 29 which may further react with water at either the C5' of the C6' position (path c). The hydrolytic (C5'/C6') and oxidative (C3') activities of AdoHcy hydrolase are differentiated effectively by the 6'-fluoro analogue 27 (X = F) with the following partition.
ratio among three pathways: $k_3': k_5': k_6' = 1:79:29$.\textsuperscript{38b} Lys426 was shown to be a crucial residue for the enzymatic hydrolysis of 27 ($X = F$).\textsuperscript{26}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Inactivation of S-Adenosyl-L-Homocysteine Hydrolase by the 6'-Fluoro(vinyl) Homoadenosine.}
\end{figure}

Interestingly, the 4', 5'-didehydro-5'-deoxy-5'-fluoroaristeromycin (33a, Figure 8) is not a substrate for the hydrolytic activities of the enzyme. Incubation of AdoHcy hydrolase with 33a did not show the release of the fluoride ion.\textsuperscript{39} However, both 33a and the independently synthesized aristeromycin 5'-aldehyde 33b are potent type I inhibitors.\textsuperscript{39,40} Thus, it is reasonable to assume that enzyme mediated protonation of the ribosyl ring oxygen in 16 (as well as in 27) enhances the electrophilicity of the C5', hence allowing the 5' position to be more vulnerable to the attack by the enzyme bound water.
To probe "pure" hydrolytic activity of the AdoHcy hydrolase, analogues of vinyl halides 16 and 27 without an oxidizable functional group (hydroxyl group) at C3' have been targeted for studying. The 3'-deoxy modified analogues (34 and 37) lack a hydrogen bounding acceptor-donor hydroxyl group at C3' (Figure 9). In other series, the 3'-hydroxyl group was replaced with a fluoro 35 or chloro 36 substituent to give a closer stereoelectronic analogue to the natural substrates, but still preventing the oxidative activity at C3'. The 3' modified analogues 34-36 were found to be weak inhibitors of AdoHcy hydrolase in a sharp contrast to the 3'-hydroxy analogues 16 and 27. Thus, it is reasonable to conclude that the 3'-hydroxyl group is necessary for the effective inhibitor/substrate binding to the AdoHcy hydrolase, and such binding is required for the execution of the "hydrolytic" activity of the enzyme.

The geminal and vicinal dihalo(homo)vinyl analogues 38-40 were also designed as potential novel substrates for the "hydrolytic" activity of AdoHcy hydrolase (figure

**Figure 8.** The 5'-Halo(vinyl)homoaristeromycin and 5'-Aldehyde Analogue.

**Figure 9.** The 3'-Modified Vinyl Halides Analogues of Adenosine and Homoadenosine.
Thus treatment of the crude Ado-5'-aldehyde 23 with (bromofluoromethylene)-triphenylphosphorane (generated in situ with CBr₃F/Ph₃P/Zn) and deprotection produced the bromofluorovinyl diastereomers 38 (E/Z, ~3:2). The analogous treatment of 23 with dibromomethylene-Wittig reagent provided the geminal dibromo derivatives 39. Bromination of the 5'-bromo(homo)vinyl derivatives 41 gave the 5',5'',6'-tribromo compound and the subsequent amine-mediated dehydrobromination and deprotection produced the vicinal 5',6'-dibromo(homo)vinyl derivative 40 as a single diastereomer.

Figure 10. The Dihalo(homo)vinyladenosine Analogues.

The [bromo(fluoro)](homo)vinyl analogue 38 covalently modified the human placental AdoHcy hydrolase and was also found to be the first type II inhibitor that uses only "hydrolytic" activity. Thus, the enzyme mediated addition of water to 38 at C6' of the 5', 6'-double bond (followed by elimination of bromide ion) generated an electrophilic acyl fluoride 42a (figure 11). Nucleophilic attack by a proximal Arg196-NH₂ group formed a covalent adduct 42b (a lethal event). The enzyme maintained its original NAD⁺/NADH content indicating no oxidation at C3'. In the second non-lethal event depurination and hydrolysis of 42a (with elimination of fluoride ion) produced the hexose derived 6-carboxylic acid.
1.2. An Overview of S-Adenosyl-L-Methionine

1.2.1. Biological Functions of S-Adenosyl-L-Methionine

Giulio Cantoni discovered S-adenosyl-L-methionine (SAM or AdoMet) in 1953.44,45 S-adenosyl-L-methionine was formed from the reaction catalyzed by methionine adenosyltransferase (MAT or SAM synthetase) with methionine and the adenosyl moiety of adenosine triphosphate (ATP). S-adenosyl-L-methionine was used as a source of methylation for a wide array of biological reactions, giving AdoMet the title of one of the most used enzyme substrates after ATP. S-adenosyl-L-methionine can donate to a wide array of chemical groups including ribosyl, aminoalkyl, methylene and amino groups, as well as a source of 5'-deoxyadenosyl radicals. More or less 15 subfamilies have been found containing different structural folds and domains which execute all of these chemical reactions.44

Thus, DNA methyltransferases catalyze the alteration of adenine and cytosine methylations, which are critical in many cellular events especially those involving DNA replication, defense against phage invasion, gene regulation and mismatch repair.46 Human homologues DNMT1, DNMT2, DNMT3a and DNMT3b all are known to modify DNA at cytosine C5 (Figure 12), which are essential for gene regulation, host defense mechanisms and genetic imprinting.47 Owing to their contribution in bacterial virulence
and tumorigenesis, both human and bacterial enzyme are targets for antibiotic and chemotherapeutic drugs.\textsuperscript{48} 

\begin{center}
\begin{tikzpicture}
  \node[align=center] at (0,0) {
  \begin{array}{c}
  \text{CH}_3 \\
  5'.....\text{CG}.....3' \\
  3'.....\text{GC}.....5' \\
  \end{array}
  \\
  \downarrow \\
  \begin{array}{c}
  \text{CH}_3 \\
  5'.....\text{CG}.....3' \\
  3'.....\text{GC}.....5' \\
  \end{array}
  \\
  \text{Human DNMT1}
\end{tikzpicture}
\end{center}

**Figure 12.** C-5 Methylation of Cytosine by Human DNA Methyltransferase (DNMT1).

The SAM-dependent methylation of proteins and nucleic acids plays a fundamental role in gene transcription regulations.\textsuperscript{49,50} Errors in the expression levels, and activities of eukaryotic DNA methyltransferases (MTase) DNMT1 was shown to be linked to oncogenic potential.\textsuperscript{51} Therefore, compounds which can undergo DNMT1-dependent transfer to DNA might prove useful in a novel chemotherapeutic strategy by asset of altered transcriptional repression mechanisms which are connected with promoter methylation.\textsuperscript{52} These substances can undergo transfers to nucleic acids in MTase-dependent fashion serving as biological tools to better comprehend biological methylations.


*S*-adenosyl-\textit{L}-methionine has been claimed to have played a diverse role in the "last universal common ancestor" (LUCA) of bacteria, Archaea and Eukarya.\textsuperscript{53} Most probably, LUCA synthesized SAM \textit{de novo} (44, Scheme 2) and used to (i) affect translation by methylating both RNA and proteins, (ii) decarboxylate SAM (yielding decarboxylated SAM, dcSAM) through the synthesis of polyamines, (iii) generate SAM
(5'-deoxyadenosyl) radicals. Approximately 95% of SAM is employed for methylation and 3-5% is used for the generation of the decarboxylated SAM. In humans, it is believed that 85% of the methylation reactions and around 50% of methionine metabolisms takes place in the liver.

*S*-adenosyl-L-methionine is coined "mother nature's methyl iodide" because it is a potent nonspecific alkylating agent, which is very specific when it guides MTases capable of alkylating DNA, RNA and proteins. SAM is also used as a biosynthetic tool for the production of secondary metabolites. Understanding the role of biological methylation, generally in gene transcription, has been hindered by the lack of tools for the identification of MTase substrates. Owing to the methyl groups' lack of functionality, they are difficult to identify in complex biological environments.

\[ \text{Scheme 2. Biosynthesis of } S\text{-Adenosyl-L-Methionine.} \]

The SAM-dependent methyltransferases catalyze the transfer of the activated methyl group from the substrate to a carbon, sulfur, nitrogen or oxygen containing...
acceptor of small entities, phospholipids, proteins, RNA and DNA with a good specificity.\textsuperscript{57} Kimzeys' group noted that the methyl group is transferred into the proteins of hemoglobin without any apparent involvement of an enzyme. The methyl group can be incorporated into multiple sites into hemoglobin, because both \( \alpha \) and \( \beta \) chains are methylated. The methyl transfer to hemoglobin from AdoMet is slow and inefficient \((k_{\text{cat}}/K_m \sim 5 \times 10^{-2})\), the reaction rate tends toward a plateau with increasing AdoMet concentrations signifying that saturable binding of AdoMet to hemoglobin is involved in methyl transfer. The rate of hemoglobin methylation is inhibited by \( S \)-adenosylhomocysteine, the known inhibitor of methyltransferases, an additional sign that methyl group transfer involves binding and catalysis by a specific site (or sites) in the hemoglobin molecule.\textsuperscript{58}

1.2.3. Regulation of \( S \)-Adenosyl-L-Methionine Levels

\( S \)-adenosyl-L-methionine is created from ATP and methionine by methionine adenosyltransferase which are present in all cells in virtually all organisms, including archaea, eubacteria, and eukaryotes. The reaction involves, primarily, the transfer of the adenosyl group of ATP to methionine, with the remnants of the ATP being transformed to enzyme-bound triply-phosphate (\textsuperscript{43}, Scheme 2). The final compound is hydrolyzed to pyrophosphate and phosphate, which are then expelled from the cell. \( S \)-adenosyl-L-methionine, a sulfonium compound, provides a large amount of free energy \((20 \sim \text{kcal/mol})\) needed for methyl group transfers. It is possibly the most multitalented compound in nature; it is a not just a source of methyl groups but, in assorted reactions in various organisms, provides methylene groups, four-carbon moieties, ribosyl groups, amino groups, and, after decarboxylation, three-carbon moieties for polyamines and
ethylene. It may be converted to a 5'-deoxyadenosyl free radical that participates in a
great variety of “radical SAM” reactions. It also functions as a regulator of many
metabolic pathways in mammals, plants, and bacteria.

In mammals, more than 90% of AdoMet is used for methylation reactions, which
involve at least 50 different methyltransferases. Methylation of both small molecules (e.g. phosphatidylethanolamine) and macromolecules (DNA, RNA, proteins) plays vital roles in cellular metabolism. For instance, methylations of DNA and histones are major events in epigenetics [changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence]. As a result, the level of AdoMet must be carefully regulated to maintain cellular homeostasis. Recent evidence has established that glycine N-methyltransferase (GNMT) plays a major role in maintaining normal AdoMet levels in mammals.

1.2.3.1. By Glycine N-Methyltransferase

Enzymatically catalyzed direct transfer of a methyl group from AdoMet to glycine (forming sarcosine, e.g. N-methylglycine) was confirmed in 1960. AdoMet was shown to have activity in liver extracts from guinea pig, rat, rabbit, and mouse, but unfortunately, the enzyme was not purified until 1972 after Heady and Kerr, found that glycine was a better acceptor of AdoMet methyl groups than tRNA. They proceeded to purify the GNMT activity from rabbit liver. It was found that GNMT expression is down-regulated or even completely inhibited in liver, prostate tumor tissue and in most cultured cells. Even though not much is known about the properties of the GNMT gene promoters of experimental animals, it has been shown that GNMT activity is induced by vitamin A, glucocorticoids, and glucagon. Decreased levels of GNMT in prostate tumor
tissues might be negatively correlated with that the level of sarcosine in prostate tissue. However, sarcosine is found in elevated amounts in metastatic prostate tissue compared with normal human prostate and localized prostate cancer. It is found that sarcosine is increased in the urine of men with metastatic prostate cancer, which implies that this metabolite may be a marker for progression of the cancer.\textsuperscript{63}

1.2.3.2. By Arginine N-Methyltransferase

Enzymes which use SAM as methyl donors catalyze all post-translational formation of monomethylated Arg residues (MMA, Scheme 3). Protein arginine methyltransferases (PRMTs) are responsible for catalyzing the methylation of Arg residues,\textsuperscript{46} in various proteins which include histones (H2A, H3 and H4) and various other proteins involved in cell signaling and RNA splicing. These Arg residues are then further processed to form either asymmetric dimethylated Arg (\textsuperscript{49}, ADMA) or symmetric dimethylated Arg (\textsuperscript{48}, SDMA) by utilizing either Type I or II PRMTs. In humans, there are at least nine different PRMTs which are known to play a physiological role in a number of cellular processes (transcriptional regulation). For instance, PRMT1 and PRMT4/CARM1 (coactivator associated arginine methyltransferase 1), act as transcriptional coactivators for a variety of transcriptional forces. The PRMTs are interesting because dysregulated PRMT activities appear to be associated with heart disease and cancer, making them a potential target for therapeutic design.\textsuperscript{64}

1.2.3.3. By C5 Methylation of Cytosine.

Contrary to the well-established methylation of C5 of 2'-deoxyuridine by thymidylate synthase, it was reported that SAM can perform C5 methylation of cytidine catalyzed by methyltransferases. The positioning of the AdoHcy and AdoMet methylsulfonium to the C5 of cytosine base provides an ideal trajectory and distance for methyltransfer reaction to occur (Scheme 4).

Scheme 4. C5 Methylation of Cytidine by Methyltransferases.

The DNA (cytosine-5)-methyltransferase (C5 MTases) are recognized for their ability to catalyze the transfer of the methyl group from AdoMet to cytosine, C5 atom in specific DNA sequences. Thus, the methylation reaction of C5 MTases arises with the addition of a cysteine thiol group from the preserved Pro-Cys motif to the C6 position of
the target cytosine, 51, in a step which resembles action of thymidylate on 2'-deoxyuridyliine. It is then followed by the methyl transfer from AdoMet to C5 of the target base and the release of the methylated substrate, 52. The source of the methyl group (Tetrahydrofolate; THF in the case of thymidylate synthase) is the biggest difference between these two enzymes. There are some cytosine analogues, 5-fluorocytosine (FC), 5-azacytosine (AzaC) and 2-pyrimidinone (2P), which have been identified as mechanism-based inhibitors of C5 MTases.65,66 When a fluorine atom is introduced to the C5 position of the target cytosine, it results in an irreversible covalent attack of a cysteine residue and transfer of a methyl group to the C5 position of the target base.

The Gromovas group65 studies the mechanism of inhibition of EcoRII DNA methyltransferases (M.EcoRII) by DNA containing 2-pyrimidinone, as well as, DNA containing 2 pyrimidinone which they used to probe contacts of M.EcoRII with functional groups of pyrimidine bases of the recognition sequence. 2-Pyrimidinone is a cytosine analogue, in which the exocyclic amino group is replaced by a hydrogen atom. It is known that removing the exocyclic amino group from the cytosine results in an increase of reactivity at the C6 position in 2-Pyrimidinone and in a reduction of the energy barrier for base flipping.

The reaction mechanism involves the addition of a cysteine thiol group of the enzyme to the C6 position of 2-pyrimidinone, 53, followed by proton transfer to the C5 position, 54. Owing to the absence of the exocyclic amino group in 55, β-elimination of the proton from the C5 position is deinhibited. It is noteworthy, that 1-(β-D-ribofuranosyl)-2-pyrimidinone, which is also known as Zebularine. It is used in vivo as
an antitumor drug. It is known that its antitumor properties are probably attributed to inhibition of C5 MTase activity in tumor cells.\textsuperscript{67}

Gromova proposed that stable covalent adducts \textbf{56} between M.EcoRII and 2-Pyrimidinone residue in DNA were formed, and that the quantity grew with the increasing enzyme concentration. For that reason, inhibition of M.EcoRII by 2-Pyrimidinone containing DNA occurs with methyl group transfer to the C5 position of 2-Pyrimidinone. All active enzyme molecules become covalently bound to 2-Pyrimidinone-containing DNA (Fig. 13B, step 1). It is suggested that a covalent adduct with M.EcoRII is formed within the first few minutes of the reaction. In the absence of AdoMet, proton transfer to the C5 position of 2-pyrimidinone occurs instead (Fig. 13A). In the presence of AdoMet, methyl transfer to the C5 position of 2-pyrimidinone occurs (\textbf{57}, Fig. 13B). The formation of stable covalent intermediate between M.EcoRII and 2-Pyrimidinone-containing DNA in the presence of AdoMet causes the inhibition of the methylation. From these results, 2-pyrimidinone is seen as a potent inhibitor that arises from the retardation of proton elimination from \textbf{58}, leading to the formation of \textbf{59} from the covalent intermediate.\textsuperscript{67}
Figure 13. Proposed Mechanism for the Inhibition of M.EcoRII by 2-Pyrimidone Containing DNA Duplexs in the Absence (A) or in the Presence (B) of S-Adenosyl-L-Methionine.

1.3. Overview of the Biological Activity of the Vinyl and α-(Fluoro)vinyl Sulfone, Sulfoxide, Sulﬁde and Sulfonium Compounds Containing Fluorine.

Since the synthesis of the fluoro organic compounds have been extensively reviewed\textsuperscript{68,70,71} the next section of my dissertation will mostly deal with the literature review of the biological activity of the vinyl and α-(fluoro)vinyl sulfones, sulfoxides, sulfides and sulfonium salts. Special attention will be placed on the rational that can be used for design of the novel mechanism-based inhibitors.

1.3.1. General Importance of the Fluorine Containing Drugs.

Signiﬁcant alterations in biological activity are often observed in organic compounds associated with the replacement of an H-atom in a molecule by an F-atom. The replacement not only enhances the biological activity of parent compounds, but it also increases their thermal and oxidative stabilities.\textsuperscript{68} A wide array of monofluoro compounds display extraordinary biological activities,\textsuperscript{68} and medical and biological
sciences put forth an increasing demand for fluorinated organic compounds. Compounds with a fluorine atom attached to a vinylic group are of great importance, as this moiety is present in a number of enzyme inhibitors. Therefore, the synthesis of selectively fluorinated building blocks, such as phenyl-substituted fluoro alkenes has become an important area for research.

Fluorinated compounds make up some of the most successful pharmaceutical drugs (Figure 14) on the market today ranging from antidepressants, for example, Prozac® (60, Eli Lilly), Paxil®, 61 to the most prescribed antibiotic Ciprofloxacin® (62, Bayer). The integration of a fluorine atom is considered a simple method for the modification that often results in a improved bioactivity as compared to the original drug.69 In general, fluorinated compounds require a lower dosage than their non-fluorinated drugs or compounds counterpart to be effective.69a For example, the introduction of a fluorine atom into Ciprofloxacin 62, increases the rate of cell penetration by up to 70 times.70 The fluorine atom is strongly electronegative,69,71 possibly leading to increased interactions between calcitriol and the vitamin D receptor (VDR). Fluorine is sterically comparable to hydrogen atom; therefore it creates no increased steric hindrance for VDR binding. Furthermore, fluorine is known to form the strongest covalent bonds69b-71 with carbon which may encumber the catabolic pathway. These encouraging characteristics, in addition to the synthetic simplicity of fluorine incorporation, make fluorine an excellent candidate for drug design and synthesis.
The importance of the fluorinated compounds have increased significantly owing to the unique influence of the fluorine atom on the chemical, physical, and physiological properties. For example, fluoroolefins are significant, because of their application in the synthesis of biologically active mechanism-based inhibitors including materials like peptide isosteres. To start a versatile synthetic method of desired fluorinated compounds, there must first be fluorine-containing building blocks which are frequently lacking.

1.3.2. Biological Activity of the Vinyl and α-(Fluoro)vinyl Sulfones.

Enzymes that degrade polypeptides are known as proteases. Cysteine proteases are widely found in fruits including papaya, pineapple, and kiwi. They are prevalent in nature and hold a fundamental position in the metabolism of both eukaryotic and prokaryotic organisms. Numerous inhibitors are studied in drug development programs that target human proteases for diseases such as osteoporosis, rheumatoid arthritis, metastasis, arterial thrombosis, tumor invasion and Alzheimer’s disease. Cysteine proteases also play a considerable role in protozoa such as Plasmodium, Trypanosome and Leishmania and inhibitors of falcipain and cruzain, which are two key parasitic
cysteine proteases. These proteases are now under examination as probable treatment for Chagas’ disease and malaria.\textsuperscript{77}

Scheme 5. Cysteine Protease Mechanism for the Hydrolysis of Amide Bond (Proteins).

The general catalytic mechanism of the cysteine proteases (Scheme 5) involves a nucleophilic attack of one of the cysteine thiol. The initial step is the deprotonation of the thiol in the enzyme's active site by an adjacent basic amino acid (I). The pathway continues with a nucleophilic attack by the deprotonated cysteine anion (II) on the substrate carbonyl carbon via the proposed transition state of type III. The amino acid residue in the protease is then returned to its deprotonated form, and a thioester intermediate connecting to the new carboxy-terminus of the substrate to the cysteine thiol and the fragment of the substrate with an amine terminus are formed (IV). Finally, the thioester bond is hydrolyzed to generate the carboxylic acid (V) on the remaining substrate fragment, while regenerating the free enzyme (I).

A great number of these inhibitors were designed from the corresponding peptide substrate of the target enzyme which are modified at the P1 position where the amide
group is substituted by a “warhead”: an electrophilic group with high affinity for the active site thiol group.\textsuperscript{75} Warheads tend to consist of ketones and nitriles, producing reversible tight binding inhibitors, epoxides and Michael acceptors. These groups are then capable of reacting covalently with the thiolate, affording irreversible inhibitors.\textsuperscript{76} Peptide vinyl sulfones and their analogues such as vinyl sulfonamides and vinyl sulfonate esters are some of the most interesting Michael acceptors to be developed as cysteine protease inhibitors.\textsuperscript{78} Vinyl sulfones selectively inhibit several cysteine proteases in a low nM range.\textsuperscript{75} For example, compounds 63-65 inhibit falcipains and cruzains and are an important tool in antiprotozoal drug design and development (Figure 15).

\begin{center}
\includegraphics[width=0.8\textwidth]{figure15.png}
\end{center}

**Figure 15.** Fluorinated and Nonfluorinated Vinyl Sulfones as Potential Cysteine Protease Inhibitors.

Haemers' interest in fluoro-olefins allowed him to evaluate the influence of $\alpha$-fluorine in a Michael acceptor type cysteine protease inhibitor.\textsuperscript{75} The introduction of an inductively electron-withdrawing group on the $\alpha$-carbon, such as, fluorine is assumed to increase the electron deficiency at the $\alpha$-carbon. Alternatively, the lone pairs of electrons of the fluorine atom could then contribute and overlap with the existing conjugate $\pi$-system, contributing as a mesomeric donor. The insertion of a fluorine atom at the $\alpha$-carbon resulted in an astonishing effect: the positive charge at the $\alpha$-carbon entails that the fluorine atom influences the charge density by way of a field effect, rather than a
mesomeric donating effect (Scheme 6). Nevertheless, this field effect did not interfere with the β-carbon. The bond between the α-carbon and the β-carbon is further polarized, creating a partial negative charge on the latter. Consequently, the β-carbon is no longer an appropriate place for a nucleophilic attack.

\[
\begin{array}{c}
\text{SO}_2\text{Ph} \\
\text{F} \\
\text{R} \\
\end{array}
\quad \text{Mesomeric effect}
\quad \begin{array}{c}
\text{β} \\
\text{α} \\
\text{SO}_2\text{Ph} \\
\end{array}
\quad \text{Inductive effect}
\quad \begin{array}{c}
\text{β} \\
\text{γ} \\
\text{SO}_2\text{Ph} \\
\end{array}
\]

Scheme 6. Inductive Effect Vs Mesomeric Effect for the α-Fluorovinyl Sulfone.

The negative charge on the β-carbon does not have an effect on the charge of the γ-carbon. As an alternative, the hydrogen atom located on the β-carbon becomes a more positive species. The negative charge on the β-carbon could also be influenced by a mesomeric effect. In one of the likely mesomeric forms, an alkene is formed between the fluorine and the α-carbon, resulting in a negative charge on the β-carbon. However, when bond lengths between the α- and β-carbons are studied, no considerable changes are seen on the substitution by a fluorine atom, the changes being less than 0.01 a.u.\textsuperscript{75} On the other hand a mesomeric effect would cause lengthening to this bond. Lastly, Haemers tested the influence of α-fluorine on the activity of Michael acceptor cysteine protease inhibitors using Leishmania CPB cysteine protease. The reactivity of the addition might be improved if the electrophilicity of the β-carbon of the Michael acceptor is increased. Haemers used the vinyl phenylsulfone acceptor system and prepared reference compound \textbf{64} and its α-fluoro derivative \textbf{65}. They found that compound \textbf{64} is a potent inhibitor of the Leishmania cysteine protease CPB, while compound \textbf{65} was found to be a weak inhibitor. These in vitro observations confirmed the theoretical predictions that the
introduction of α-fluorine in a Michael acceptor such as vinyl sulfones should not result in increasing Michael acceptor properties of these enzymatic substrates.

The fluorovinyl sulfone compounds 67 and 68 (Scheme 7) were found to be unreactive towards thiols and remained unchanged. Contrary to this lack of reactivity, the H-vinyl sulfone 66 reacted to completion with thiols within 45 minutes producing the desired addition at carbon β. Thus, there is lower reactivity of the sulfone as a Michael acceptor towards thiolate nucleophiles when α-fluorine was present in the vinyl sulfone moiety.

Scheme 7. Conjugated Addition of Thiolates to Vinyl Phenyl Sulfones.

1.3.2.1. Vinyl Sulfones as Cysteine Protease Inhibitors.

Cysteine proteases from malaria parasites are of great interest as therapeutic targets because of their role in parasite development. \( \text{Plasmodium falciparum} \) contains four cysteine proteases from the papain family known as falcipains, for example, falcipain-2 (FP-2) and falcipain-3 (FP-3) which are widely used as therapeutic targets. Peptidyl vinyl sulfone, 72 (Figure 16), was found to be a potent irreversible inhibitor of falcipains, which acts as Michael acceptor for the catalytic cysteine residue. Falcipain inhibitors are believed to inhibit the development of cultured erythrocytic
parasites by blocking the hydrolysis of the host hemoglobin. They also cure mice infected with lethal malaria infections.\textsuperscript{84}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure16.png}
\caption{Structure of a Dipeptidyl Mu-Leu-hPhe-VSPh Containing Vinyl Sulfone.}
\end{figure}

In regards to the use of protease inhibitors as antimalarials, the concern is that selection of drug-resistant strains will eventually occur.\textsuperscript{79} Parasites resistant to a dipeptidyl vinyl sulfone have been observed in Lopes' laboratory, although this resistance was somewhat limited.\textsuperscript{85} Dipeptidyl vinyl sulfones are good candidates for combination antimalarial therapy as a strategy to retard the development of resistance; as a result, Lopes designed artemisinin–vinyl sulfone hybrid molecules for the potential prevention of multi-drug resistance in \textit{P. falciparum}.

The structure activity relationship (SAR) data for the inhibition of FP-2 exposed that peptidyl vinyl sulfones containing a Leu residue at the P2 position and an hPhe (homophenylalanine) at the P1 position, \textbf{72}, is very active. These vinyl sulfones have IC\textsubscript{50} values in the low-nM range.\textsuperscript{81a,82,86} Hybrid molecule \textbf{73} bearing an endoperoxide motif was also designed and synthesized (Figure 17). In this inhibitor the vinyl sulfone component is linked to the endoperoxide moiety via the N-terminus, using a 4-hydroxymethylbenzoic acid linker. This hybrid molecule, \textbf{73}, displays potent
antiplasmodial activity against a panel of *P. falciparum* chloroquine-sensitive and multidrug-resistant strains, with IC$_{50}$ values ranging from 2 to 5 nM.

**Figure 17.** Structure of a Hybrid Vinyl Sulfone with Activity Towards *P. falciparum*.

### 1.3.3. Selected Biological Properties of Vinyl Sulfoxide.

The biological activity of sulfoxides is usually credited to their capability of either being reduced to the corresponding sulfides or oxidized to the corresponding sulfones. In tumor cells, the solid center is usually deprived of oxygen and is similar to a low oxygen tension (hypoxia) area resistant to both radiotherapy and chemotherapy. The use of bioreductive agents which are selectively toxic to hypoxic cells upon enzymatic reduction has been reported.\(^8^7\) For example, Sulindac which is marketed in the UK & U.S. by Merck as Clinoril ® as a non-steroidal anti-inflammatory drug of the arylalkanoic acid class with a methyl sulfonyl group attached to the phenyl ring. Sulindac sulfone has cancer chemopreventive activity\(^8^8\) and inhibition of angiogenesis with sulindac or its sulfone metabolite may also contribute to their antineoplastic properties.\(^8^9\)

Santelli-Rouvier states that it could be deduced, from a comparison of sulfides and sulfoxides that sulfoxides are not sulfide prodrugs as their activity against human cancer cell lines are usually greater as compared to the corresponding sulfides because, sulfoxides can undergo redox type reactions. While the analogous sulfones are far less
active, this can be attributed to their low pKa values. Leaving group properties of the sulfoxides have also been correlated to their biological activity.\textsuperscript{90} Additionally, the antitumor activity of complexes of platinum containing substituted sulfoxides suggested that these complexes may act by binding to DNA with consequent loss of the sulfoxide ligand.\textsuperscript{91} Brefeldin A (BFA), is a lactone antibiotic produced by fungal organisms such as \textit{Eupenicillium brefeldianum}. Brefeldin A has antitumor activity by inducing apoptosis in cancer cells although clinical use was prohibited because of undesirable pharmacokinetic properties. The sulfoxide derivatives present activities comparable to that of BFA. One was shown to be more active than BFA. The sulfide analogues were less active than the sulfoxides. This could be attributed to the ability of the sulfoxide and not the sulfide to undergo elimination, which leads to the regeneration of BFA.\textsuperscript{92}

\textbf{1.3.4. Selected Biological Properties of Vinyl Sulfides.}

Not a lot of work has been performed in the cyclization of peptides bearing preconstructed vinyl sulfides unit within. Crescenza’s work showed that a vinyl sulfide could be formed by an elimination-addition of an enol triflate. The reaction occurred via an intermediate allene in the synthesis of a 7-membered dipeptide unit.\textsuperscript{93} The vinyl sulfide motif should possess properties to be used for conformational fine-tuning of structure activity relationships (SARs) for cyclic peptide analogues. Pharmacologically these vinyl sulfide ring systems should exhibit higher metabolic stability as well as higher affinity and full agonist properties in the AT1 receptor.\textsuperscript{94}

\textit{α-}(Halo)vinyl sulfides were synthesized as potential targets from compounds containing the trifluoromethyl motif. For example, vinyl chloride \textsuperscript{75a} and vinyl bromide \textsuperscript{75b} were obtained as the major products in good yields when the (Z)-1-stanny1-2-
tributylstannyl-1-(4-methylphenylthio)ethene 74 was treated with CuCl$_2$ or CuBr$_2$ in the presence of Pd(OAc)$_2$ catalyst (Scheme 8).$^{95}$

![Chemical structure](image)

**Scheme 8.** Synthesis of α-Bromo and α-Chlorovinyl Sulfides by Halodestannylation Reaction.

Cyclization most often utilize disulfide or diamide bond formation in a process which imposes conformational constraints.$^{96}$ Hallberg’s group formulated methods to deliver active angiotensin II (Ang II) derivatives that contain ring systems which have similar conformational properties to those of disulfide. However, there is a vinyl sulfide unit instead of the redox-sensitive disulfide bridge. The Ang II derivatives 76a and 76b were synthesized containing a 13-member ring with a cis and trans vinyl sulfide bridge, as a valuable tool in the search for Ang II conformation bioactivity.$^{97}$ (Scheme 9).

![Chemical structure](image)

**Scheme 9.** Vinyl Sulfide Analogues of Angiotensin II.
1.3.5. Selected Biological Properties of Vinyl Sulfonium Ions.

Thioether S-methyltransferase (TEMTase) is a key enzyme in the metabolism of sulfur and selenium containing compounds in animals. Ethyl vinyl sulfide (EVS) was found to be a substrate for this enzyme yielding methyl ethyl vinyl sulfonium ion (MEVS+) upon reaction with S-adenosylmethionine. Studies revealed that MEVS+ is a substrate for TEMTase and can act as a possible suicide inhibitor (Scheme 10). MEVS+ is a very reactive species because of the ability of the sulfonium ions to stabilize the neighboring carbanion generated during the nucleophilic attack on the β-carbon of the vinyl motif. Scheme 10 exhibits the proposed mechanism of TEMTase inactivation caused by the methylation of EVS to form MEVS+ and subsequently, interaction of MEVS+ with nucleophilic amino acid residues in or around the active site of the enzyme.

![Scheme 10. Proposed Mechanism for Thioether S-Methyltransferase Inactivation by Ethyl Vinyl Sulfide.](image)

Warner and Hoffman incubated TEMTase with EVS and AdoMet in order to test its ability to methylate dimethyl sulfide (DMS) to form the trimethyl sulfonium ion (TMS+). The data obtained demonstrated that TEMTase was inactivated by EVS in a time-dependent, pseudo-first-order process, which is a basic requirement for a suicide inhibitor. It was noted that activity of the TEMTase diminished logarithmically for 12 min, but the loss of activity began to equilibrate after 15 min. No further loss of activity was seen after 30 min. Warner and Hoffman explained that this inability to attain further
inactivation was a result of the AdoHcy generated after 15 min by methylation of EVS with AdoMet, which acts as a feedback inhibitor of the remaining active TEMTase. The EVS has to bind initially to the active site of the enzyme to generate MEVS\textsuperscript{+}. As stated, from the kinetics of inactivation dimethyl sulfide (DMS) should compete with EVS for this site and block inactivation by EVS. As a result, DMS was confirmed to be an effective competitor of EVS inactivation in a concentration-dependent manner.\textsuperscript{98}

1.4. Gemanium in Health and Chemistry.

Germanium is a natural trace mineral with a wide range of health benefits. For example, propagermanium, which was released in Japan in 1994, boosts the immune system, heptoprotection, protects against viruses and has low toxicity.\textsuperscript{99a} Orally administered organic germanium stimulates interferon production, while renovating the previously impaired immune response. Organogermanium compounds have been prepared for hypotensive, neurotropic, antitumor, radioprotective and immunomodulating properties.\textsuperscript{99b} The natural element germanium has also been linked to the prevention of cancer and AIDS.\textsuperscript{99c} In the organic form, germanium is considered as one of the most potent developments in the nutritional treatment of cancer. Germanium is a biological-response modifier; it allows the organism to change its response to tumors. It does not directly attack cancer cells; instead it stimulates the body's immune system, making it effective in the treatment of cancer as well as other degenerative diseases.\textsuperscript{99a}

1.4.1. Organogermane alkenes: Synthesis and Reactivity.

Since the chemistry and applications of organogermanes in the organic synthesis has been subject of recent reviews\textsuperscript{99} in the following chapter of my dissertation only
selected aspects of germaine chemistry directly related to the goals of my dissertation will be addressed.

Metals located in group 14 are crucial elements for cross-coupling reactions between organometallics and organic halides. In spite of the wide application of Stille (Sn)\(^{99d,e,100}\) and Hiyama (Si)\(^{99d,e,101}\) couplings, coupling involving organogermaines has received limited attention,\(^{102a}\) even though the germanium element is situated between silicon and tin in the periodic table. The lack of popularity of germanium could be due to the challenge in the difficulty in synthesizing vinyl germanyl derivatives as well as the poorer reactivity of these compounds.\(^{102}\) The most significant route to vinylgermanes involves the hydrogermylation of alkynes; which can be done either by utilizing radical initiators or by using a transition metal complex as a catalyst. The end product is the formation of the three vinyl germene isomers (\(E, Z\) and \(gem\)) with selectivity determined by both electronic and steric properties of the alkynes and germaine hydride substrates.

For example, vinylgermanes, e.g. 81 and 82 can be obtained via hydrometalation of alkyne, 80 as illustrated in Scheme 11. Generally, transition metal-catalyzed hydrometalation is utilized as a mild protocol to obtain the \(cis\)-addition products, 82.\(^{103}\) The \(trans\)-addition products can be achieved via Lewis acid catalyzed hydrometalations of C-C multiple bonds.\(^{104}\) Unfortunately, these methods exhibit low functional group tolerance.\(^{105}\) Thus, it is necessary to develop milder \(trans\)-selective general hydrometalation.\(^{106}\) Gevorgyan's group performed the first Lewis acid catalyzed hydrogermylation reaction, which not only showed a higher functional group tolerance when compared to the previously reported Lewis acid catalyzed hydrometalation.
reactions but also displayed stereospecific trans-addition (81) for alkynes and cis-addition for propiolates.\textsuperscript{105}

\[
\begin{align*}
\begin{array}{c}
\text{H} \quad \text{Ge} \\
\text{R}^1 \quad \text{CO}_2\text{R} \\
\text{R}^2 = \text{CO}_2\text{R} \\
\end{array}
\quad \xrightarrow{\text{HGe}} \quad \\
\begin{array}{c}
\text{H} \quad \text{Ge} \\
\text{R}^1 \quad \text{=} \quad \text{R}^2 \\
\text{R}^2 = \text{H}, \text{Alk}, \text{Ar} \\
\end{array}
\quad \xrightarrow{\text{HGe}} \quad \\
\begin{array}{c}
\text{H} \quad \text{Ge} \\
\text{R}^1 \quad \text{=} \quad \text{R}^2 \\
\end{array}
\end{align*}
\]

Scheme 11. Lewis Acid Catalyzed Hydrogermylation of Alkynes.

Hydrogermylation is a useful tool because it leads to the formation of vinylgermanes, which could be later transformed into the synthetically useful vinylhalides. As one might expect, halodegermylation of triethylgermanes 83 with NBS or NIS produced vinyl halides 84 and 85 in excellent yields (Scheme 12).\textsuperscript{106} Iododegermylation of 86 under standard conditions occurred on efficiently, producing vinyl iodides 87 and 88 in good yields. It is worth noting that all halodegermylation reactions proceed with stereospecific retention of the double-bond geometry.

\[
\begin{align*}
\begin{array}{c}
\text{Ph} \quad \text{GeEt}_3 \\
\end{array} \quad \xrightarrow{\text{NBS or NIS}} \quad \\
\begin{array}{c}
\text{Ph} \quad \text{X} \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \quad \text{GeEt}_3 \\
\text{R}^1 \quad \text{CO}_2\text{R}^2 \\
\end{array} \quad \xrightarrow{\text{NIS, AlCl}_3} \quad \\
\begin{array}{c}
\text{R}^1 \quad \text{CO}_2\text{R}^2 \\
\end{array}
\]

Scheme 12. Halodegermylation Reaction of Vinyl Germanes with NBS and NIS with and Without Lewis Acids.

Since compounds like 1-fluoroalkynes are very unstable and nearly unknown,\textsuperscript{107} techniques such as hydrogermylation are inapplicable for the synthesis of (α-fluoro)vinylgermanes.\textsuperscript{108} The chemistry\textsuperscript{109} and biological activity of the
organogermanium compounds have already been reviewed.\textsuperscript{110} Wnuk and coworkers have developed stereoselective radical-mediated germyledesulfonylations of (α-fluoro)vinyl sulfones with germanium hydrides to provide access to (α-fluoro)vinyl germanes.\textsuperscript{110} Such an approach provides a means to synthesizing \textit{1-fluoroalkenyl} tris(trimethylsilyl)germanes, which were employed as substrates in Pd-catalyzed cross-coupling reactions with aryl halides. Thus, treatment of vinyl phenyl sulfone 90\textsubscript{a} \textit{(E)} with (TMS)\textsubscript{3}GeH/ AIBN gave the corresponding vinyl germane 91\textsubscript{a} \textit{(E)} stereoselectively (Scheme 13). Analogous treatment of \textit{E} vinyl sulfone 90 with Bu\textsubscript{3}GeH, Ph\textsubscript{3}GeH, and tri(2-furyl)germane produced the corresponding \textit{E} germanes 91-94. Radical germyledesulfonylation of 89 also allowed the synthesis of the previously unknown (α-fluoro)vinyl germanes 91'-94' in high yields with retention of \textit{E} stereochemistry. It was found that vinylgermanes bearing either a conjugated or an isolated double bond serve as versatile transmetalation reagents. The \textit{E}-germanes could undergo coupling reactions with retention of stereochemistry under aqueous and anhydrous conditions. On the contrary, the coupling of \textit{Z}-germanes occurs with less stereoselectivity to produce a mixture of \textit{E} and \textit{Z} isomers.\textsuperscript{110}

![Scheme 13. Radical Mediated Germyledesulfonylation Reaction of Vinyl Sulfones.](image)
1.4.2. Germanium Containing Nucleosides.

Previously, germaniums containing α-amino acids and peptides have been incorporated into biologically active decapeptides. The 6-trialkylgermyl-5-fluorouridine derivatives are one of the very few known examples of germanium-containing nucleoside analogues. Also, 5-trimethylgermyl-2'-deoxyuridine was shown to inhibit HSV-1 replication in vitro and blocked incorporation of thymidine into DNA of ovarian cancer cells.

Lithiation of uracil acyclonucleosides was employed recently to obtain 6-substituted derivatives. Lukevics' group has investigated the lithiation of another type of nucleoside analogues N-1 tetrahydrofuryl derivatives. They decided to focus on an antitumor agent 1-(2-tetrahydrofuryl)-5-fluorouracil (95, Ftorafur) for the introduction of an organometallic substituent at the C-6 position of uracil. Lithiation of Ftorafur was carried out in THF below -70 °C using 4.2 equiv. of lithium diisopropylamide (LDA) and after 1 h the C-6 lithiated Ftorafur was treated with the corresponding trialkylchlorogermane at -70 °C. The 6-substituted organogermanium, 96, isostructural derivative of Ftorafur, was obtained in moderate yield (Scheme 14).

Scheme 14. The Synthesis 6-Trimethylgermane-5-Fluorouracil Analogues.
The glycosyl bond length in compound 96 is slightly shorter than in other nucleoside structures reported\textsuperscript{114} and have the average value of 1.464 Å.\textsuperscript{115} It was found that atoms of the uracil ring in molecule of compound 96 deviate from the average plane and have the screw ($1S_2$) conformation. The configuration of the THF ring in both compounds are C3'-exo-C4'-endo. It was also found that in 96 the uracil moiety exhibits a syn orientation with respect to the THF ring, while an anti conformation was found for compounds described.\textsuperscript{114a-d} This could be the result of the introduction of bulky substituents in the 5-fluorouracil ring at C6. For instance, the large GeMe$_3$ groups change molecular conformations and bond lengths. Careful analysis of the bond lengths for the compound indicated that the C6 Ge is significantly longer than Ge-C bonds with methyl groups' carbon.

The results obtained from Lukevic's lab\textsuperscript{112} demonstrated the ability of the germanium-modified nucleoside analogues to interfere with transcription and, probably with the replication processes, because of the conformation changes induced by the presence of the germanium atom.
2. RESEARCH OBJECTIVE

The purpose of this dissertation is to design and to synthesize novel inhibitors of \( S \)-adenosyl-L-homocysteine hydrolase and \( S \)-adenosyl-L-methionine transferases. The first targets were adenosine and uridine analogues with the C5' and sulfur atoms replaced by a fluoroalkenyl unit. The adenine analogues were expected to act as substrates for the "hydrolytic" activity of \( S \)-adenosyl-L-homocysteine hydrolase. These targets could be prepared via Negishi and other Pd-catalyzed cross-coupling reactions. Stereoselective Pd-catalyzed monoalkylation of 5'-(bromofluoromethylene)-5'-deoxyadenosine with alkylzinc bromides derived from the homocysteine-like precursors could produce \( S \)-adenosyl-L-homocysteine analogues with a 6'- (fluoro)vinyl motif. These novel vinylic adenine nucleosides were planned to be tested for time-dependent inactivation of the \( S \)-adenosyl-L-homocysteine hydrolases.

The stannydesulfonylationreaction is a critical step in the synthesis of two nucleoside-based drug candidates bearing an \textit{exo}-fluoro methylene unit at a ribofuranosyl ring. The first drug is \textit{E}-fluorovinyl cytidine (Tezacitabine) which is a ribonucleoside reductase inhibitor with a potent anticancer activity. The second compound is 5'-deoxy-5'- (fluoromethylene)adenosine which is an inhibitor of \( S \)-adenosyl-L-homocysteine hydrolase with potent antiviral activity. The critical step in the synthesis of these two compounds (drugs) was the removal of the auxiliary sulfonyl group employing a radical-mediated stannyldesulfonylation reaction using tributyltin hydride. In order to eliminate the synthetic drawback associated with the toxicity of the tin reagent, the second aim of this dissertation was to develop a radical-mediated germyl desulfonylation utilizing less toxic germane hydrides. Radical-mediated substitution of the arylsulfonyl group with the
tributyl- or the triphenylgermyl group at the vinylic carbon was expected to afford desired vinyl germanes. Moreover, the halodegermylation reaction should serve as an alternative approach for the synthesis of 5'-deoxy-5'-((halomethylene)nucleoside analogues.

I was also planning to study radical-mediated thiodesulfonylation of the readily available vinyl and (α-fluoro) vinyl sulfones with aryl thiols in organic or aqueous medium. Such a procedure would provide a bench and environmentally friendly protocol to access both vinyl and the virtually unknown (α-fluoro)vinyl sulfides. The thioldesulfonylation was expected to proceed with controlled stereochemistry. These thiodesulfonylation reactions would provide an alternative methodology to the hydrothiolation of alkynes with thiols which occur under metal catalysis conditions. Since vinyl sulfide 2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene is a potent antibacterial agent active against drug-resistant strains of tuberculosis and anthrax surrogates, I am planning to apply my methodology for the synthesis of its (α-fluoro) vinyl analogue. This would allow us to determine whether the incorporation of the fluorine atom into the vinyl sulfide unit would enhance its biological activity. I also intended to perform methylation to the vinyl or (α-fluoro)vinyl phenyl sulfide to get access to the corresponding vinyl or (α-fluoro)vinyl methyl phenyl sulfonium salts. These sulfonium ions were selected as possible methyl group donors during reactions with thiols, phenols or amino groups which are commonly present in natural amino acids.
3. RESULTS AND DISCUSSIONS

3.1. Design and Synthesis of S-Adenosyl-L-Homocysteine Analogues with the Carbon-5' and Sulfur Atoms Replaced by a Vinyl or Halo(vinyl) Unit via Cross-Coupling Reactions.

The first targets of this dissertation were S-adenosyl-L-homocysteine analogues 96 and 98 (Scheme 15). These compounds could serve as substrates for the "hydrolytic" activity of the enzyme, because they should form stable complexes with the enzyme and in turn help identify key binding groups at the active site. Such analogues (e.g. 96 and 98) should be resistant to elimination because the homocysteine-type unit is attached to C5' via an olefinic double bond. As a result, they can freeze the elimination steps catalyzed by AdoHcy hydrolase allowing the proteins in the active site of the enzyme to be identified. These unsaturated S-adenosyl-L-homocysteine analogues 96 and 98 could be synthesized from their corresponding vinyl halides 99 and dihalide 97 utilizing Negishi cross-coupling procedures. The Pd-catalyzed approaches extended my earlier attempts to synthesize AdoHcy analogues 96 or 98 employing metathesis and Wittig reaction methodology.
Scheme 15. Retrosynthetic Analysis for the Synthesis of S-Adenosyl-L-Homocysteine Analogues with C5’ and Sulfur Atoms Replaced by Vinyl or Halovinyl Unit.


Negishi cross-coupling reaction is a palladium catalyzed stereospecific carbon-carbon bond formation between aryl or vinyl halides with zinc-derived organometallic reagents. After various optimization attempts which included testing different Pd-catalyst, solvents, temperature and additives. I found that treatment of iodovinyl adenosine precursor, 100b(E) with 1.5 equivalent of EtO₂C(CH₂)₃ZnBr in the presence of a catalytic amount of Pd(0) in benzene produced ethyl 1-(adenine-9-yl)-1,5,6,7,8,9-hexadeoxy-2,3-O-isopropylidene-β-D-ribo-dec-5(E)-enofuranonate (101b, Scheme 16) in excellent yields after purification. ¹H NMR of the product 101b showed that coupling occurs with retention of stereochemistry (J₆-₅ = 15.4 Hz), while the mass spectrum showed an ion at m/z 418 (MH⁺, 100) which corresponds to its molecular ion. Analogous treatment of the iodovinyl uridine, 100a, gave the desired uracil-based product 101b in good yields.
Deactonization of 101b with TFA/H2O at 0 °C for 30 minutes produced ethyl 1-(adenine-9-yl)-1,5,6,7,8,9-hexadeoxy-β-D-ribo-dec-5(E)-enofuranuronate (102b, 49%) after column chromatography and recrystallization in MeOH. ¹H NMR analysis showed the disappearance of methyl signals from the isopropyl unit and the mass spectrum indicated a molecular ion at m/z 378 (MH⁺, 100). Analogously, the uridine analogue 101a was deprotected to give 102a. Saponification of the ester, 102b, afforded 102c, a 10-carbon AdoHcy analogue with C5’ and sulfur atoms replaced by a vinyl unit.


It has to be mentioned that Andrei and Wnuk synthesized the target molecule in the adenosine series, 104, with an amino group at position C9’. ¹¹⁶ They employed a metathesis reaction between a 6 carbon amino acid (containing a terminal double bond) and 5’-deoxy-5’-methyleneadenosine, 103, in the presence of a Grubbs catalyst to obtain the desired product (104, Scheme 17).

3.1.2. Synthesis of 6,6'-Dihalo(homo)vinyl Adenosine Precursors.

The geminal dihalovinyl analogue 107 was envisioned to be a potential substrate for the Pd-catalyzed selective monoalkylation reaction. Thus, a Moffat oxidation of the isopropylidene protected adenosine, 105, gave the crude aldehyde 106. A subsequent Wittig reaction with (bromofluoromethylene)triphenylphosphonate (generated in situ using CBr₃F/Ph₃P/Zn afforded bromo(fluoro)alkene 107 in 30% yield (Scheme 18). The ¹⁹F NMR of 107 showed a mixture of E/Z (3:2) diastereomers. The two pairs of doublets at -64.28 ppm ($J_{F-H5' (cis)} = 10.7$ Hz) and at -68.81 ppm ($J_{F-H5' (trans)} = 29.8$ Hz) were diagnostic of the E/Z isomers.

Reagents and conditions: (a) DCC/DMSO/Cl₂CH₂CO₂H; (b) Ph₃P/CBr₃F/Zn/CH₂Cl₂

Scheme 18. Synthesis of 6',6''-Dihalovinyladenosine via Pd-Catalyzed Coupling Utilizing 5'-Deoxy-5'-(Bromofluoromethylene)adenosine.


Adenosine analogues with the 5',6'-halovinyl or vinyl motif 96 and 98 incorporated in place of the C5' and sulfur atoms might act as substrates for the
"oxidative" and/or "hydrolytic" activity of AdoHcy hydrolase. For instance, enzyme-mediated addition of water to 96 (X = F, R = H or NH2; Scheme 14) might occur at C5' or C6'. With the addition of water, this would generate a new species bearing a hydroxyl or keto (after β-elimination of HF) binding site within the enzyme.

Andrei and Wnuk have synthesized the AdoHcy analogue bearing the amino moiety on C9' and an alkenyl unit between C5' and C6' employing metathesis approaches.116a Their attempts to install a halogen at C6' via bromination-dehydrobromination methodology led however to the synthesis of 5'-bromo analogue 109. Thus, compound 104 was treated with pyridinium tribromide followed by 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to form 108 as a single isomer in 70% yield (Scheme 19). Deprotection of 108 with NH3/MeOH and TFA/H2O followed by saponification with NaOH and HPLC purification gave 109 (E, 54%).

In order to prepare the 6'-halovinyl analogue, 96, I turned my attention to the Pd-catalyzed selective monoalkylation of 5'-deoxy-5'-(dihalomethylene) nucleoside precursor. Enlightened by the results obtained from the Negishi reactions between the 6'-halovinyl nucleoside precursor and the commercially available Negishi reagent (alkylzinc bromide) I have targeted a selective monoalkylation of dihalovinyl nucleoside substrates (e.g., 107). It is noteworthy to mention that the mono cross-coupling reactions of 1,1-
dihalovinyl electrophiles with Csp³ nucleophiles are very limited. Andrei and Wnuk developed Pd-catalyzed Negishi coupling of 1-fluoro-1-bromoalkenes with alkylzinc, which provided stereoselective access to the internal fluoroalkenes. After optimization of the coupling conditions, I discovered that treatment of the protected 5′-(bromofluoromethylene)-5′-deoxyadenosine⁴² (107, E/Z, 3:2) with EtO₂C(CH₂)₃ZnBr/Pd(PPh₃)₄ in refluxing benzene produced fluorovinyl AdoHcy, 110, (56%) as a mixture of geometric (E/Z, 2:3; Scheme 20) isomers. ¹⁹F NMR indicated the formation of both geometric isomers at δ -95.78 ('q', $J_{F-H5';7';7''}$ = 21.8 Hz, 0.4, $E$), and -101.80 (dt, $J_{F-H5'}$ = 35.5 Hz; $J_{F-H7';7''}$ = 17.3 Hz, 0.6, $Z$); the mass spectrum showed a molecular ion at $m/z$ 436 (MH⁺, 100) as base peak. Selective acid-catalyzed deprotection of 110 gave the corresponding ester 111; ¹H NMR proved deacetonization by the disappearance of the methyl groups at δ 1.36 (s, 3, CH₃) and at 1.61 (s, 3, CH₃). Saponification of the ester afforded a free carboxylic acid analogue, 112, a 10-carbon AdoHcy analogue with C5′ and sulfur atoms replaced by 6'-fluorovinyl unit.

**Scheme 20. Synthesis of 6'-Halo(homo)vinyl S-Adenosyl-L-Homocysteine Analogues.**
3.1.4. Inactivation of the S-Adenosyl-L-Homocysteine Hydrolase.

The homovinyl adenine nucleosides were tested against human AdoHcy hydrolase using a protocol involving a 0.5 or a 4 h preincubation with the enzyme followed by a 12 min incubation that measured the residual enzyme activity (Table 1).\textsuperscript{116} Esters 101b and 111 were found to be unstable either by chemically or enzymatically under the assay conditions. These compounds had also very similar activity toward the \textit{Trypanosoma cruzi} AdoHcy hydrolase. Interestingly, the most active inhibitors were found to be the 10-carbon, 102b and 102c, vinylic analogues. With a 30 min preincubation, ester 102b was found to be more active than the corresponding acid 102c. The 6'-fluoro vinylic analogues 111 and 112 were expected to have higher activity against the enzyme; but instead they showed a lower activity than the non-halogenated derivatives 102b and 102c, perhaps in accordance with the fact that 5'-deoxy-5'-(fluoromethylene) adenosine showed the lowest enzyme inactivation efficiency among all of the 5'-halomethylene derivatives.\textsuperscript{118} The 5'-bromovinylic analogue, 109, with the amino group located at C9' also showed a lower enzyme inhibition compared to 102b. The analogues 109 and 112 bearing a free carboxylic group produced similar time-dependent inactivation of the human (Table 1) and \textit{T. cruzi} AdoHcy hydrolases. No further enzymatic studies have been performed on these compounds.
Table 1. Inhibition of S-Adenosyl-L-Homocysteine Hydrolase by 5',6'-Vinylic Adenosine Derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% of enzyme inhibition (^{a,b})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 h(^{c})</td>
</tr>
<tr>
<td>101b(^d)</td>
<td>81</td>
</tr>
<tr>
<td>102c</td>
<td>28.5</td>
</tr>
<tr>
<td>109</td>
<td>14.5</td>
</tr>
<tr>
<td>111(^d)</td>
<td>14.1</td>
</tr>
<tr>
<td>112</td>
<td>15.2</td>
</tr>
</tbody>
</table>

\(^a\) AdoHcy hydrolase (204 nM) was incubated with the inhibitors (281 uM) at 37 °C for 12 min and the remaining enzyme activity was assayed as described\(^{152}\).

\(^b\) Data are the averages of duplicate determinations.

\(^c\) Preincubation time of the inhibitors with the enzyme.

\(^d\) Esters were not tested with 4 h preincubation time due to chemical instability in the enzymatic assay.


3.2.1. Synthesis of 6'-Vinyl Germane Nucleosides.

Radical-mediated replacement of an arylsulfonyl group with a tributylstannyl group at the vinylic carbon is an important approach for the synthesis of various nucleoside and amino acid analogues bearing an \(\alpha\)-halo vinyl functionality. For example, McCarthy and coworkers used a radical-mediated stannyldesulfonylation protocol (113\(^a\) \\(\rightarrow\) 113\(^b\)) for the synthesis of (\(E\))-fluorovinyl cytidine 113\(^c\) (Tezacitabine; an inhibitor of ribonucleoside reductases with potent anticancer activity), from the protected (\(\alpha\)-fluoro)vinyl sulfone 113\(^a\) (Figure 18).\(^{109,118}\)
Also, a radical mediated stannyldesulfonylation of the vinyl 6'-sulfone analogue of adenosine 114a was achieved using a radical initiator and Bu3SnH. Subsequent halodestannylation of the resulting vinyl 6'-stannanes 114b afforded 5'-deoxy-5'-(halomethylene)adenosine 114c. These 6'-halovinyladenosine analogues were found to be potent inhibitors of S-adenosyl-L-homocysteine (AdoHcy) hydrolase and valuable probes to study the "hydrolytic" activity of the enzyme.35,38,116 The stannyldesulfonylation/protiodestannylation of the (α-fluoro)vinyl sulfones and stannyldesulfonylation/halodestannylation of the vinyl sulfones procedures allowed for the synthesis of various 5'-deoxy-5'-(halomethylene)nucleoside analogues derived from uridine,111 L-adenosine,120 3'-deoxyadenosine,41 6-N-cyclopropyladenosine121 and 5'-deoxy-5'-(halomethylene)ribose derivatives.122 Moreover, the replacement of the sulfide group from 115a with tributyltin hydride has been elaborated for the synthesis of the known 4',5'-unsaturated-5'-haloadenosine analogue 115c (a potent AdoHcy hydrolase inhibitor) employing halodestannylation of the intermediary vinyl stannane 115b.123

I envisioned the possibilities for the removal of the toxicity factors associated with tributyltin hydride reagent in a stannyldesulfonylation reaction by developing a
stereoselective and chemoselective radical-mediated germyldesulfonylation of vinyl and
(α-fluoro)vinyl sulfones with less toxic germanium hydrides to produce 116 (Figure 19)\textsuperscript{30}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure19.png}
\caption{Germymdesulfonylation an Approach for the Synthesis of Novel Vinyl Germane Nucleosides. Application Towards Synthesis of 5'-Deoxy-5'-Halo(methylene)adenosines.}
\end{figure}

In order to prepare the 2',3'-O-isopropylidiene protected uridine/adenosine (117a/b), the sugar was dissolved in acetone and treated with 1 equivalent of p-toluenesulfonic acid monohydrate and 4 equivalents of ethyl orthoformate. Crystallization of the crude product from methanol gave the 2',3'-O-isopropylidieneadenosine/uridine (105/118) in more than 95% yields (Scheme 21). Moffatt oxidation of the 5'-OH group in (105/118) with 3 equivalents of dicyclohexylcarbodiimide (DCC) in DMSO and half an equivalent of dichloroacetic acid at ambient temperature gave the crude 5'-aldehyde. Treatment of the 5'-aldehyde with 1.1 equivalents of (p-toluenesulfonylmethylene)triphenylphosphorane produced a less polar product in an exothermic reaction. The 6'-tosylyvinuridine, 119a, and 6'-tosylyvinladenine, 119b, were obtained in good yields (~80%) after purification in silica gel. \textsuperscript{1}H NMR spectrum for 119b confirmed the structure and was diagnostic to establish trans configuration (\(J_{6',5'} = 15.1\) Hz). Two doublets at \(\delta\) 7.29 (d, \(J = 8.2\) Hz, Ar, 2H) and 7.62 (d, \(J = 8.3\) Hz, Ar, 2H) indicated the presence of the p-toluenesulfonyl group located at C6' (Figure 19).
Reflux of 119a in toluene with tributylgermanium hydride in the presence of AIBN effected germanyl-desulfonylation via a radical process to give 5'- (tributylgermyl)methylene-5'-deoxyuridine, 120a, as a single (E)-isomer \( J_{5'-6'(\text{trans})} = 18.5 \) Hz) in 57% yield. Sulfone 96b also underwent a germyl-desulfonylation reaction with Bu3GeH to yield the vinyl germane (E)-121a (46%). The analogous stannyldesulfonylation of 119a and 119b with Bu3SnH produced the corresponding (E/Z)-5'(tributylstannyl)methylene-5'-deoxyuridine and adenosine derivatives in 87% and 61% yields, respectively. Thus, treatment of 119a and 119b with triphenylgermane hydride gave (E)-5'-deoxy-5'-(triphenylgermyl)methylene nucleosides correspondingly gave 120b (72%) and 121b (42%). The desulfonylation reaction was performed on both purine and pyrimidine nucleoside analogues using either trialkyl- or triarylgermanes. I found that the yields were significantly higher for the uridine analogues. This is similar to what was observed in the case of the stannyldesulfonylation reactions. Unlike the stannyldesulfonylation reactions, the germyl-desulfonylations of the vinyl sulfones derived from the sugar modified nucleosides are stereoselective since the analogous (Z)-isomers of vinyl germanes 120 or 121 were not isolated from the crude reaction mixtures. The germyl-desulfonylation reactions most probably occurs via the radical addition-elimination mechanism, similarly to the silyl- and stannyldesulfonylation reactions.
I found that stereoselective iododegermylation reaction of tributylgermane, \(120a\), and \(N\)-iodosuccinimide (NIS) gave 5'-deoxy-5'-(iodomethylene) uridine, \([(E)-125, 92\%]\). Similarly the tributylgermane, \(121a\), reacts with \(N\)-bromosuccinimide (NBS) to yield the 5'-deoxy-5'-(bromomethylene)adenosine \((E)-126 (81\%)\) with retention of double bond geometry. It is worth noting, that treatment of triphenylgermanes \(120b\) and \(121b\) with either NBS or NIS did not produce the corresponding halomethylene nucleosides \(125\) or \(126\), giving instead the recovered vinyl triphenylgermanes \(120b\) and \(121b\). Even halodegermylation of the triphenylgermane, \(120b\), with iodine (\(\text{CH}_2\text{Cl}_2/-78\degree\text{C to room temperature for 14 hours}\)) did not give the desired halosubstituted product, \(125\), only recovered starting materials. In the literature, \(124\) iododestannylation reactions are known for vinyl triaryltin derivatives. I believe that the strength of the Ge-Csp\(^2\) bond depends on

**Scheme 21.** Synthesis of 6'-Vinylgermyluridine and Adenosine Analogues.
the nature of the substituents on the germanium atom;\textsuperscript{125} most importantly it seems that Csp\textsuperscript{2}-Ge(alkyl)\textsubscript{3} bonds are more stable than that of the Csp\textsuperscript{2}-Ge(aryl)\textsubscript{3} bonds. I also observed same patterns of different reactivity for the protiodegermylation reactions of vinyl triarylgermanes and trialkylgermanes. For instance, treatment of the tributylgermane, \textsuperscript{121a}, with aqueous trifluoroacetic acid (TFA) affected simultaneous protiodegermylation and deacetonization to afford 5'-deoxy-5'-methyleneadenosine, \textsuperscript{127}. In contrast when triphenylgermane, \textsuperscript{120b}, was treated with TFA only the isopropylidene protection group was removed affording germanonucleoside, \textsuperscript{123b}.

I was, however, able to synthesize deprotected trialkylgermane, \textsuperscript{124b}, using a base-labile protection strategy. For instance, treatment of 2',3'-\textit{O}-diacetyl sulfone, \textsuperscript{122b}, with Bu\textsubscript{3}GeH/AIBN gave \textsuperscript{124a} in 49\% yield. Interestingly, germylodesulfonylation reaction performed in the presence of 2-mercaptoethanol, as a radical carrier,\textsuperscript{117} and 1,1'-azobis(cyclohexanecarbonitrile), (ACCN) as a radical initiator also produced \textsuperscript{124a} in even higher yield (58\%). Treatment of \textsuperscript{124a} with methanolic ammonia affected deacylation yielding the vinyl tributylgermane, \textsuperscript{124b} (72\%). The synthesis of the vinyl triphenylgermane, \textsuperscript{123b} (65\% overall yield), was analogously developed by germylodesulfonylation of 2',3'-\textit{O}-acetyl protected uridine, \textsuperscript{122b} with Ph\textsubscript{3}GeH, followed by deacetylation of the resulting \textsuperscript{123a}.

3.2.2. Synthesis of 2'-Vinyl Germane Nucleosides.

I also developed the germylodesulfonylation reaction for the removal of the vinyl sulfonyl group located on C2' of the nucleosides in Wnuk laboratory.\textsuperscript{119} Thus, treatment of the protected 2'-ketouridine, \textsuperscript{128}, with a sulfonyl-stabilized enolate derived from diethyl (phenylsulfonyl)methylphosphonate gave the Horner-Wittig-type vinyl 2'-
phenylsulfone, **129**, as a single (Z)-isomer (Scheme 22). The Z stereochemistry was established by NOESY NMR experiments as well as by comparing my results with the data of McCarthy’s work that utilized the fluoro(phenylsulfonyl)methylphosphonate reagent.\textsuperscript{108} Germyl desulfonylation reactions of **129** with Ph\textsubscript{3}GeH produced the 2'-deoxy-2'-(triphenylgermyl)methylene]uridine, **130** (51%) as a single (Z)-isomer. The triphenylgermanyl protected nucleoside **130** was desilylated with TBAF affording the vinyl triphenylgermane **131** in 73% yield.

\[
\begin{align*}
\text{RO} & \quad \text{O} & \quad \text{U} & \quad \text{a} & \quad \text{RO} & \quad \text{O} & \quad \text{U} & \quad \text{b,c} & \quad \text{RO} & \quad \text{O} & \quad \text{SO}_2\text{PH} & \quad \text{GePh}_3 \\
128 & \quad \text{R= TIPS} & \quad 129 & \quad \text{R= TIPS} & \quad 130 & \quad \text{R= TIPS} & \quad 131 & \quad \text{R = H}
\end{align*}
\]

Reagents and conditions: (a) PhSO\textsubscript{2}CH\textsubscript{2}PO(OEt)\textsubscript{2}/LHDMS/THF; (b) Ph\textsubscript{3}GeH/AIBN/ PhCH\textsubscript{3}/heat; (c) TBAF/THF.

**Scheme 22.** Synthesis of 2'-Vinylgermyluridine Analogues.

I have demonstrated that germyl desulfonylation reactions with trialkyl- and triarylgermane hydrides affect the removal of the sulfonyl group from the exomethylene and isolated double bonds of the sugar moieties of nucleosides. However, treatment of **130** with the more reactive tris(trimethylsilyl)germane [(TMS)\textsubscript{3}GeH] provided the corresponding vinyl (TMS)\textsubscript{3}Ge-uridine derivatives in relatively small yields (≤ 15%, \textsuperscript{1}H NMR) despite numerous attempts. Therefore, no further efforts were made to optimize the germyl desulfonylation reactions utilizing the (TMS)\textsubscript{3}GeH reagent, although the vinyl tris(trimethylsilyl)germanes could serve as precursors for further modifications via Pd-catalyzed couplings reactions.\textsuperscript{110,126}
3.3. Radical-Mediated Thiodesulfonylation of Vinyl Sulfones

3.3.1. Synthesis of Vinyl Sulfones and α-(Fluoro)vinyl Sulfones

The vinyl and α-(fluoro)vinyl sulfones were prepared following literature methodology utilizing Horner-Emmons-Woodward reactions. Thus, the condensation reaction of the sulfonyl-stabilized enolates generated from diethyl (phenylsulfonyl)-methylphosphonate with aliphatic and aromatic aldehydes and ketones 132a–g gave the corresponding vinyl sulfones 133a–f and cyclic vinyl sulfone 133g (72–95%, Scheme 22). It is important to note that these condensations produced the corresponding E isomers as either the major or the sole products with only traces of the Z sulfones observed in the crude 1H NMR or gas chromatographic analysis.

Analogous condensations utilizing the sulfonyl-stabilized enolates generated from diethyl fluoro(phenylsulfonyl)methylphosphonate with aliphatic and aromatic aldehydes and ketones 132a–h afforded the corresponding α-(fluoro)vinyl sulfones 134a–h (Scheme 23). Unlike the vinyl sulfones, the α-(fluoro)vinyl sulfones are obtained mostly as unseparable mixtures of E/Z isomers.

![Scheme 23. Synthesis of E-Vinyl and (E/Z)-(α-Fluoro)vinyl Sulfones.](image-url)
3.3.2. Thiodesulfonylation of Vinyl Sulfones: Synthesis of Vinyl Sulfides.

After several attempts to identify the conditions for radical replacement of the sulfonyl group with thiol groups at sp² hybridized carbon, I was fortunate to discover that the reaction between the conjugated vinyl sulfone $E$-$133a$ with benzenethiol (2 equiv) in the presence of ACCN as a radical initiator in refluxing toluene (12 h) produced the vinyl sulfide $135a$ (61%; Scheme 24; Table 2, entry 1). This type of radical thiodesulfonylation reaction was also successful in an aqueous medium. For instance, treatment of $E$-$133a$ with benzenethiol/ ACCN or AIBN in water (100 °C) produced vinyl sulfide $135a$ in 71% and 65% yields (entry 2). When a polar protic solvent was used such as methanol or ethanol, I produced a homogenous reaction mixture which effected thiodesulfonylation (entry 3). The thiodesulfonylation reactions were not markedly influenced by the nature of the substituents. Thus, the alkyl (series b), electron-withdrawing (CF₃, series c), or electron-donating (MeO, series d) groups on the phenyl ring attached to the double bond had only modest effect on rate and yield of thiodesulfonylation reactions with benzenethiol (entries 11–15, 18–20).

Scheme 24. Thiodesulfonylation of Vinyl Sulfones and Synthesis of Vinyl Sulfides.
Treatment of the unconjugated vinyl sulfones derived from aliphatic aldehydes (series e and f) with benzenethiol/AIBN or ACCN under protic and aprotic conditions did not yield the corresponding vinyl sulfides (entries 21 and 22). Interestingly, dialkyl alkenyl sulfone, 133g, derived from cyclohexanone, underwent a thiodesulfonylation reaction affording vinyl sulfide, 135g (entries 23 and 24), demonstrating that the thiodesulfonylation can serve as a convenient method for the synthesis of the trisubstituted vinyl sulfides.

The thermal reaction of \(E\)-133a with benzenethiol without any radical initiator produced 135a but in significantly lower yield (10%, entry 2) than when an initiator was used. Similarly, the replacement of benzenethiol with phenyl disulfide also effected the conversion of the sulfone 133a to the vinyl sulfide 135a in lower yield (20%, entry 4); The reaction proceed required longer time and subsequent addition of radical initiator. However, reaction of 133a with phenyl disulfide without radical initiator failed to produce the corresponding vinyl sulfide 135a by using any of the three approaches.

Treatment of \(E\)-132a with 4-methylbenzenethiol or 4-aminobenzenethiol in H\(_2\)O/ACCN produced the corresponding vinyl sulfides 136a (61%) and 137a (55%) (entries 5 and 6). Analogously, \(E\)-133c was reacted with 4-methylbenzenethiol or 4-aminobenzenethiol in H\(_2\)O/ACCN to produce the corresponding vinyl sulfides 136c and 137c (entries 16 and 17). Thiodesulfonylation of \(E\)-133a with 4-mercaptobenzoic acid (\(R^1 = \text{CO}_2\text{H}\)) in methanol afforded the methyl ester 138a (85%; entry 7). Thus, I could assume that thiodesulfonylation protocol is compatible with amino and carboxylate derivative functional groups, which are vulnerable to oxidative and reductive procedures. I also attempted thiodesulfonylation reactions on 133a and 133c, with alkanethiols (2-
mercaptoethanol, 1-propanethiol or thioacetic acid) under radical conditions but the corresponding vinyl sulfides were not formed. Instead I only recovered the starting sulfones.

Table 2. Synthesis of E-Vinyl Sulfides via Thiodesulfonylation of Vinyl Sulfones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone (E/Z)</th>
<th>Method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt; (E/Z)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133a (E)</td>
<td>A</td>
<td>135a</td>
<td>95:5  61</td>
</tr>
<tr>
<td>2</td>
<td>133a (E)</td>
<td>B</td>
<td>135a</td>
<td>95:5  71&lt;sup&gt;e&lt;/sup&gt;, 65&lt;sup&gt;ef&lt;/sup&gt;, 10&lt;sup&gt;eg&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>133a (E)</td>
<td>C</td>
<td>135a</td>
<td>95:5  70&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>133a (E)</td>
<td>C</td>
<td>135a</td>
<td>95:5  20&lt;sup&gt;ek&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>133a (E)</td>
<td>B</td>
<td>136a</td>
<td>95:5  61</td>
</tr>
<tr>
<td>6</td>
<td>133a (E)</td>
<td>B</td>
<td>137a</td>
<td>98:2  55</td>
</tr>
<tr>
<td>7</td>
<td>133a (E)</td>
<td>C</td>
<td>138a</td>
<td>95:5  85</td>
</tr>
<tr>
<td>8</td>
<td>133a (Z)</td>
<td>A</td>
<td>135a</td>
<td>95:5  65&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>133a (Z)</td>
<td>B</td>
<td>135a</td>
<td>95:5  95&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>133a (Z)</td>
<td>C</td>
<td>135a</td>
<td>95:5  70, (80&lt;sup&gt;e&lt;/sup&gt;)</td>
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<tr>
<td>11</td>
<td>133b (E)</td>
<td>A</td>
<td>135b</td>
<td>85:15 55&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>133b (E)</td>
<td>B</td>
<td>135b</td>
<td>85:15 54, (63&lt;sup&gt;e&lt;/sup&gt;)</td>
</tr>
<tr>
<td>13</td>
<td>133c (E)</td>
<td>A</td>
<td>135c</td>
<td>95:5  59, (70&lt;sup&gt;e&lt;/sup&gt;), 5&lt;sup&gt;e&lt;/sup&gt;-g</td>
</tr>
<tr>
<td>14</td>
<td>133c (E)</td>
<td>B</td>
<td>135c</td>
<td>95:5  85&lt;sup&gt;e&lt;/sup&gt;, 80&lt;sup&gt;ef&lt;/sup&gt;, 50&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>133c (E)</td>
<td>C</td>
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<td>16</td>
<td>133c (E)</td>
<td>B</td>
<td>136c</td>
<td>95:5  58</td>
</tr>
<tr>
<td>17</td>
<td>133c (E)</td>
<td>B</td>
<td>137c</td>
<td>95:5  40, (55&lt;sup&gt;e&lt;/sup&gt;)</td>
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<tr>
<td>18</td>
<td>133d (E)</td>
<td>A</td>
<td>135d</td>
<td>75:25 55</td>
</tr>
<tr>
<td>19</td>
<td>133d (E)</td>
<td>B</td>
<td>135d</td>
<td>75:25 64&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>133d (E)</td>
<td>C</td>
<td>135d</td>
<td>85:15 70&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td>133e (E)</td>
<td>A,B,C</td>
<td>135e</td>
<td>n.r</td>
</tr>
<tr>
<td>22</td>
<td>133f (E)</td>
<td>A,B,C</td>
<td>135f</td>
<td>n.r.</td>
</tr>
<tr>
<td>23</td>
<td>133g</td>
<td>B</td>
<td>135g</td>
<td>55</td>
</tr>
<tr>
<td>24</td>
<td>133g</td>
<td>C</td>
<td>135g</td>
<td>76&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>25</td>
<td>133g</td>
<td>C</td>
<td>136g</td>
<td>62</td>
</tr>
</tbody>
</table>

<sup>a</sup> Method A: thiol/ACCN/toluene/110 °C/12 h; Method B: thiol/ACCN/water/100 °C/10 h; Method C: thiol/ACCN/MeOH/65 °C/10 h. <sup>b</sup> Reactions were performed on 0.1-1.0 mmol scale of sulfones (0.05 mM) with 1.25-2.00 equiv. of thiols and 0.25-0.50 equiv. of AACN or AIBN. <sup>c</sup> Determined by GC-MS and/or <sup>1</sup>H NMR. <sup>d</sup> Isolated yield. <sup>e</sup> Based on GC-MS. <sup>f</sup> AIBN instead of ACCN. <sup>g</sup> Without ACCN. <sup>h</sup> Disulfide instead of thiol, 16 h. <sup>i</sup> In EtOH.
Radical-mediated thio-desulfonylation of the vinyl sulfone 133 occurred mainly with retention of the E stereochemistry although small amounts of the Z isomers were detectable by GC–MS and $^1$H NMR of the crude reaction mixtures (Table 2). In order to study the stereochemical outcome of the thio-desulfonylation reactions I also prepared pure Z-vinyl sulfone as a starting precursor.


The Z-vinyl sulfone 133a was prepared by anti-Markovnikov addition of PhSH to phenylacetylene in the presence of NaOH (139, Scheme 25). Subsequent oxidation of the resulting (Z)-2-phenyl-1-phenylthioethene 135 gave the corresponding sulfone Z-133a as described in the literature. The magnitude for the vicinal olefinic coupling constant was $J = 12.1$ Hz indicating Z stereochemistry (the E isomer has $J = 15.1$ Hz). This sulfone, Z-133a was later treated with PhSH in aqueous or organic medium to produce the vinyl sulfide 135a in very good yields with inversion of stereochemistry (E/Z, 95:5; entries 8–10). Thus, I concluded that the vinyl sulfides were formed predominantly with E stereochemistry independent of the stereochemistry of the starting vinyl sulfones.
3.3.3. Thiodesulfonylation of α-(Fluoro)vinyl Sulfones: Synthesis of α-(Fluoro)vinyl Sulfides.

Reactions involving radical-mediated thiodesulfonylation provided me access to the synthesis of the virtually unknown (α-fluoro)vinyl sulfides 142-145 in relatively good yields (Scheme 26). I started with the reactions of 141a (E/Z, 96:4) with benzenethiol in organic or aqueous medium in the presence of the radical initiator, ACCN, which formed the (α-fluoro)vinyl sulfide, E/Z-142a, in good to excellent yields with the "overall" retention of stereochemistry (Table 3, entries 1 and 2). Similarly, for unfluorinated compounds, thiodesulfonylation appeared fairly general since sulfones 141b, 141c and 141d bearing alkyl (Me), electron-withdrawing (CF₃), or electron-donating (MeO) substituents on the phenyl ring attached to the double bond also produced (α-fluoro)vinyl sulfides (entries 4–6, 9, and 10).

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\text{a:} & \quad \text{C}_6\text{H}_5 & \quad \text{H} \\
\text{b:} & \quad 4-(\text{CH}_3)\text{C}_6\text{H}_4 & \quad \text{H} \\
\text{c:} & \quad 4-(\text{CF}_3)\text{C}_6\text{H}_4 & \quad \text{H} \\
\text{d:} & \quad 3,4-(\text{MeO})_2\text{C}_6\text{H}_3 & \quad \text{H} \\
\text{e:} & \quad \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2 & \quad \text{H} \\
\text{f:} & \quad \text{c-C}_6\text{H}_{11} & \quad \text{H} \\
\text{g:} & \quad \text{C}_6\text{H}_5 & \quad -(\text{CH}_2)_5^- \\
\text{h:} & \quad \text{C}_6\text{H}_5 & \quad \text{CH}_3
\end{align*}
\]

**Scheme 26.** Thiodesulfonylation of (E/Z)-(α-Fluoro)vinyl Sulfones and Synthesis of (E/Z)-(α-Fluoro)vinyl Sulfides.

Treatment of the unconjugated sulfone 141e or 141f with benzenethiol produced the vinyl sulfide 142e or 142f in low yields (entries 11 and 12). Careful analysis of the crude reaction mixture indicated, however, that only the Z-141e or the Z-141f isomer of
the starting sulfones were consumed during reactions to produce primarily $E$-sulfides, while the $E$-sulfones remained mostly unreacted. These indicated the lack of reactivity of $E$-133e and $E$-133f vinyl sulfones since only the $Z$ sulfone was consumed during reactions. Cyclohexylidiene sulfone 141g was the only nonconjugated sulfone that gave promising results. It produced the tetrasubstituted vinyl sulfide, 141g upon treatment with benzenethiol (entry 13).

Reactions involving sulfone 141h ($E/Z$, 57:43) derived from acetophenone with benzenethiol also afforded tetrasubstituted ($\alpha$-fluoro)-vinyl sulfide 142h ($E/Z$, 50:50; entries 14 and 15). I later tested the stereospecificity of the thiodesulfonylation reactions by testing thiodesulfonylation with pure $E/Z$ isomers of some ($\alpha$-fluoro)vinyl sulfones. I observed that thiodesulfonylation is not stereospecific since reactions of pure $E$-141h or $Z$-141h with benzenethiol each gave 142h as mixture of both $E/Z$-isomers (entries 16 and 17). The $E$ product is the predominant isomer, most probably due to its greater thermodynamic stability (Scheme 26).

Thiodesulfonylation also occurred with other aromatic thiols such as 4-methylbenzenethiol, 4-aminobenzenethiol and with 4-mercaptobenzoic acid yielding various vinyl sulfides (entries 3, 7 and 8, 18–20). It is noteworthy that transmetalation of the carboxylate group to methyl ester occurred in MeOH. My methodology is particularly important for the synthesis of ($\alpha$-fluoro)vinyl sulfides since the 1-fluoroalkynes are unstable and virtually unknown in literature, therefore, the hydrothiolation approaches are inapplicable. It is also worth emphasizing that my thiodesulfonylation methodology can be viewed as as reductive deoxygenation of sulfones to the corresponding sulfides—a
transformation which requires harsh conditions incompatible with most functional groups.  

Table 3. Synthesis of (α-Fluoro)vinyl Sulfides via Thiodesulfonylation of (α-Fluoro)vinyl Sulfones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone (E/Z)</th>
<th>Method</th>
<th>Product</th>
<th>E/Z</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a (96:4)</td>
<td>A</td>
<td>142a</td>
<td>92:8</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>141a (96:4)</td>
<td>B</td>
<td>142a</td>
<td>94:6</td>
<td>65c</td>
</tr>
<tr>
<td>3</td>
<td>141a (96:4)</td>
<td>A</td>
<td>144a</td>
<td>83:17</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>141b (86:14)</td>
<td>A</td>
<td>142b</td>
<td>93:7</td>
<td>82, 62f</td>
</tr>
<tr>
<td>5</td>
<td>141b (86:14)</td>
<td>B</td>
<td>142b</td>
<td>92:8</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>141b (86:14)</td>
<td>C</td>
<td>142b</td>
<td>92:8</td>
<td>92f</td>
</tr>
<tr>
<td>7</td>
<td>141b (86:14)</td>
<td>C</td>
<td>143b</td>
<td>92:8</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>141b (86:14)</td>
<td>C</td>
<td>144b</td>
<td>94:6</td>
<td>69f</td>
</tr>
<tr>
<td>9</td>
<td>141c (90:10)</td>
<td>B</td>
<td>142c</td>
<td>93:7</td>
<td>60f,72</td>
</tr>
<tr>
<td>10</td>
<td>141d (97:3)</td>
<td>B</td>
<td>142d</td>
<td>93:7</td>
<td>73</td>
</tr>
<tr>
<td>11</td>
<td>141e (90:10)</td>
<td>B</td>
<td>142e</td>
<td>70:30</td>
<td>10g</td>
</tr>
<tr>
<td>12</td>
<td>141f (86:14)</td>
<td>C</td>
<td>142f</td>
<td>70:30</td>
<td>12h</td>
</tr>
<tr>
<td>13</td>
<td>141g</td>
<td>B</td>
<td>142g</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>14</td>
<td>141h (57:43)</td>
<td>B</td>
<td>142h</td>
<td>50:50</td>
<td>58</td>
</tr>
<tr>
<td>15</td>
<td>141h (57:43)</td>
<td>C</td>
<td>142h</td>
<td>50:50</td>
<td>68</td>
</tr>
<tr>
<td>16</td>
<td>141h (100:0)</td>
<td>C</td>
<td>142h</td>
<td>50:50</td>
<td>85</td>
</tr>
<tr>
<td>17</td>
<td>141h (0:100)</td>
<td>C</td>
<td>142h</td>
<td>33:67</td>
<td>70</td>
</tr>
<tr>
<td>18</td>
<td>141h (100:0)</td>
<td>C</td>
<td>143h</td>
<td>64:36</td>
<td>96</td>
</tr>
<tr>
<td>19</td>
<td>141h (57:43)</td>
<td>B</td>
<td>143h</td>
<td>50:50</td>
<td>59</td>
</tr>
<tr>
<td>20</td>
<td>141h (57:43)</td>
<td>C</td>
<td>145h</td>
<td>55:45</td>
<td>42</td>
</tr>
</tbody>
</table>

a Method A: thiol/ACCN/toluene /110 °C/6 h; Method B: thiol/ACCN/ H₂O /100 °C/6 h; Method C: thiol/ACCN/MeOH/65 °C/5 h. b Reactions were performed on 0.1-0.5 mmol scale of sulfones (0.05 mM) with 1.25-2.0 equiv. of thiols and 0.25-0.50 equiv. of AACN or AIBN. c Determined by GC-MS and ¹H or ¹⁹F NMR. d Isolated yield. e Reaction with phenyl disulfided gave 142a (55%, Method B or C). f AIBN instead of ACCN. g 83% based on Z-141e. h 75% based on Z-141f.

3.3.4. Kinetics of Thiodesulfonylation Reaction.

The relative kinetics for the thiodesulfonylation reaction of vinyl sulfone and α-fluorovinyl sulfone were studied using 4-methylphenyl vinyl sulfone 133b and its α-fluorovinyl counterpart 141b as convenient starting materials. Thus, equivalent amounts of sulfones 133b (0.5 eq) and 141b (0.5 eq) were mixed together with one or two equivalent of benzenethiol. The progress of the reaction was followed by analyzing
 aliquots by GC-MS and $^1$HNMR (see Table 4 for results). For example, treatment of $\alpha$-fluoro sulfone $141b$ ($E/Z$, 84:16; 0.5 equiv) with PhSH (2.0 equiv; Method C) in the presence of the parent $\alpha$-H sulfone $E-133b$ (0.5 equiv) demonstrated that the thioadesulfonylation of $\alpha$-fluorovinyl sulfone occurs at a faster rate than its nonfluorinated counterpart. Differentiation of reactivity between vinyl and $\alpha$-fluorovinyl sulfones towards thioadesulfonation reactions with aryl thiols was more evident when only one equivalent of benzenethiol was used resulting in a 3-fold difference after 2 h (70% yield of $142b$ vs 25% yield of $135b$).

**Table 4. Relative Kinetics of Thioadesulfonylation Reactions.**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Yield $135b$</th>
<th>Yield $142b$</th>
<th>Yield $135b$</th>
<th>Yield $142b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>20%</td>
<td>50%</td>
<td>35%</td>
<td>70%</td>
</tr>
<tr>
<td>1 h</td>
<td>25%</td>
<td>65%</td>
<td>45%</td>
<td>88%</td>
</tr>
<tr>
<td>2h</td>
<td>25%</td>
<td>70%</td>
<td>48%</td>
<td>95%</td>
</tr>
<tr>
<td>3h</td>
<td>10%</td>
<td>75%</td>
<td>40%</td>
<td>98%</td>
</tr>
<tr>
<td>4h</td>
<td>5%</td>
<td>75%</td>
<td>35%</td>
<td>99%</td>
</tr>
<tr>
<td>5h</td>
<td>5%</td>
<td>80%</td>
<td>25%</td>
<td>99%</td>
</tr>
</tbody>
</table>

3.3.5. **Synthesis of the Antibacterial Agent with ($\alpha$-Fluoro)vinyl Sulfide Unit.**

Next I applied my radical-mediated thioadesulfonylation procedure for the synthesis of the ($E/Z$)-1-fluoro-2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene $151a$. The latter compound was expected to have enhanced biological activity when compared to its nonfluorinated analogue, 2-(3-hydroxy-5-methoxyphenyl)-1-
phenylthioethene 151b, which is active against drug resistant strains of tuberculosis and anthrax surrogates.129

I proposed the synthesis of 151a by starting with suitably protected 3,5-dihydroxybenzaldehyde into (α-fluoro)vinyl sulfone utilizing the Wittig-Horner reaction followed by replacement of sulfonyl group with benzenthio employing my radical mediated thiodesulfonfylolation methodology. In order to prepare the required 3-hydroxy-5-methoxybenzaldehyde substrate, 147, the commercially available 3,5-dimethoxybenzaldehyde, 146, was selectively demethylated with propanethiol in the presence of sodium hydride at reflux following literature procedure129b (Scheme 27). Subsequent protection of the free hydroxyl group in 147 was performed by dissolving the compound in anhydrous pyridine and treating it with 3 equivalents of tert-butylchlorodimethylsilane to yield 148 (53%).

Treatment of the aldehyde, 148 with the Wittig reagent generated from diethyl fluoro(phenylsulfonyl)methylphosphonate and lithium bis(trimethylsilyl) amide in THF gave (E/Z)-1-fluoro-2-(3-methoxy-5-tert-butyldimethylsilyloxyphenyl)-1-phenylsulfonyl-ethene, 149, in 80% yield (E/Z: 89/11) after column chromatography (hexane/EtOAc; 9:1). 1H NMR and 19F NMR showed a vicinal coupling constant of 3J = 34.3 Hz, and 3J = 21.9 Hz for E and Z isomers, respectively. Thiodesulfonymation reaction of the (α-fluoro)vinyl sulfone, 149, with benzenethiol at 100 °C (oil bath) for 1.5 hours in MeOH produced the corresponding (α-fluoro)vinyl sulfide, 150, in 90% yield after purification in silica gel as a mixture of E/Z isomers as conveniently judged by NMR and GC/MS (tR = 28.60 min, E, tR = 27.31 min, Z). Desilylation of 150 with tetra-butylammonium fluoride in THF at 0 °C in an ice-bath for 25 minutes afforded (E/Z)-1-fluoro-2-(3-
hydroxy-5-methoxyphenyl)-1-phenylthioethene, 151a, in 98% yield. $^1$HNMR showed the disappearance of the signals from the silyl protection at 0.21 and 0.98 ppm. The GC-MS spectrum indicated a molecule ion at $m/z$ 276 (M+, 100; $t_R = 25.39$ min, Z, $t_R = 26.64$ min, $E$).


I also synthesized the corresponding 3-hydroxy-5-methoxy-(α-fluoro)vinyl sulfoxide 154 and sulfone 152 derivatives to test if the oxidation state of sulfur will enhance antibacterial activity. Thus, (α-fluoro)vinyl sulfide, 150, was dissolved in
methylene dichloride and treated with a solution of \textit{m}-CPBA in CH$_2$Cl$_2$ for 1 hour to produce \((E/Z)-1\text{-fluoro-2-(3-methoxy-5-\textit{tert}-butyl-dimethylsilyloxyphenyl)-1-phenyl-sulfinylethene, 153\) in good yield (85\%) after column chromatography. The $^{19}$F NMR showed a doublet at $\delta$ -121.61 (d, $J = 36.7$ Hz, 1F) and the GC–MS analysis showed a molecular ion at \(m/z\) 406 (M$^+$; \(t_R = 30.62\) min, \(E\)). Desilylation of 153 with TBAF in THF at 0 \(^\circ\)C (ice-bath) for 25 minutes afforded (\(\alpha\)-fluoro)vinyl sulfoxide, 154 (90\%). The $^{19}$F NMR in CDCl$_3$ showed $\delta$ -121.61 (d, $J = 36.7$ Hz, 1F) and the GC–MS showed an ion peak at \(m/z\) 292 (M$^+$; \(t_R = 28.95\) min, \(E\)). Standard desilylation of 149 with TBAF provided the (\(\alpha\)-fluoro)vinyl sulfone 152 (94\%) after purification on silica gel column.

It was demonstrated in earlier literature reports\textsuperscript{129} that in order for the vinyl sulfide to possess antibacterial activity the styryl group is required to have a \textit{meta} hydroxyl/methoxy pattern. Therefore, I also prepared 3,5-dimethoxystyril (\(\alpha\)-fluoro)vinyl sulfide, 146b to check for the existing pattern of reactivity. Thus, readily available aldehyde 146 underwent a Wittig reaction with diethyl fluoro(phenylsulfonyl)-methylphosphonate in the presence of lithium bis(trimethylsilyl)amide in THF to give \((E/Z)-1\text{-fluoro-2-(3,5-dimethoxy)-1-phenylsulfonylethene, 146a, in 80\% yield (E/Z: 78/22) after column chromatography (hexane/EtOAc; 85:15). $^1$H NMR and $^{19}$F NMR showed a vicinal coupling constant of $^3J = 34.2$ Hz, and $^3J = 21.8$ Hz for \(E\) and \(Z\) isomers, respectively. Thiodesulfonylation of (\(\alpha\)-fluoro)vinyl sulfone, 146a, with benzenethiol at 100 \(^\circ\)C (oil bath) for 1.5 hours in MeOH produced the corresponding (\(\alpha\)-fluoro)vinyl sulfide, 146b (75\%) as a mixture of \(E/Z\) isomers; $^1$H NMR and $^{19}$F NMR showed a vicinal coupling constant of $^3J = 32.0$ Hz, and $^3J = 16.9$ Hz for \(E\) and \(Z\) isomers, respectively.
3.3.5.1. Biological Activity of the (α-Fluoro)vinyl Sulfide, Sulfoxide and Sulfone Analogues

Table 5 summarizes the in vitro cytotoxic activity of 3-hydroxy-5-methoxy-(α-fluoro)vinyl sulfone 152, sulfoxide 154, and sulfide 151a as well as 3,5-dimethoxy-(α-fluoro)vinyl sulfide 146b against three different gram positive bacterial lines. Tests were performed in the laboratory of Professor A. Monte at University of Wisconsin La Crosse. The minimum inhibitory concentration IC₅₀ values were determined as an average of at least three experiments with standard error of the mean. It was found that (α-fluoro)vinyl sulfide 151a showed activity against M. smegmatis, the surrogate for tuberculosis, at the similar level¹²⁹c as the nonfluorinated analogue 151b (Table 5). Sulfone 152 and sulfoxide 154 have no cytotoxic activity as compared to 151a for both S. aureus and B. cereus. The 3,5-dimethoxy-(α-fluoro)vinyl sulfide 146b also showed no activity reinforcing the literature finding that m-hydroxy/methoxy pattern is required for antibacterial activity.
Table 5. Antibacterial Activity of the (α-Fluoro)vinyl Sulfone, Sulfoxide and Sulfide Analogues Against Gram Positive Bacteria.\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th><em>Staphylococcus aureus</em></th>
<th><em>Bacillus cereus</em></th>
<th><em>Mycobacterium smegmatis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>146b</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>mean</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>151a</td>
<td>16</td>
<td>32</td>
<td>128</td>
</tr>
<tr>
<td>mean</td>
<td>16(^b)</td>
<td>32(^c)</td>
<td>128(^d)</td>
</tr>
<tr>
<td>152</td>
<td>128</td>
<td>128</td>
<td>256</td>
</tr>
<tr>
<td>mean</td>
<td>128</td>
<td>128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>154</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>mean</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>

\(^a\) Minimum inhibitory concentration IC\(_{50}\) values in µg/mL. \(^b\) Corresponds to IC\(_{50}\) of 58 µM. \(^c\) Corresponds to IC\(_{50}\) of 116 µM. \(^d\) Corresponds to IC\(_{50}\) of 464 µM.

3.3.6. Synthesis of Vinyl and α-(Fluoro)vinyl Methyl Phenyl Sulfonium Ions.

3.3.6.1. Attempted Transfer of a Methyl Group to Alkyl or Aryl Thiols, Phenols and Amino Groups

Methyl group transfers (e.g., from SAM) catalyzed by methyltransferases are one of the most fundamental reactions catalyzed by proteins. These processes are frequently used for the alkylation (methylation) of viral RNA fragments and/or different amino acid residues to alert their natural activity. I envisioned that in Wnuk lab (α-fluoro)vinyl sulfides synthesized can be converted to the corresponding sulfonium salt (i.e. 155 or 156); which in turn could act as (α) methyl group donor to the amino acid functionalities.
such as hydroxyphenol (present in tyrosine), sulphydryl (cysteine/homocysteine), amino (lysine/histidine) or hydroxyl (serine) groups (path a, Scheme 28) or alternatively might act as a (b) powerful Michael acceptor to induce covalent inhibition of the protein proximal amino acid residues prior to transferring CH$_3$ group (path b, Scheme 28, 157a/b).

![Scheme 28](image)

**Scheme 28.** Possible Dual Reactivity of Vinyl Sulfonium Ion with Enzyme-bound Nucleophiles.

Pathway (a) resembles a typical methylation reaction catalyzed by various transferases enzyme, while pathway (b) was demonstrated by Warner and Hoffman who reported$^{98}$ a nucleophilic addition of the enzyme-bound protein to the β position of the MEVS$^+$ (see Scheme 10). They reported that vinyl sulfonium ions act as an inhibitor for thioether methyltransferase (TEMTase)$^{98}$ postulating that ethyl methyl vinyl sulfonium ion inactivates the enzymes activity by covalently modifying TEMTase.

In order to check my hypothesis, and to examine a possible dual reactivity of vinyl sulfonium ions with nucleophiles, I converted vinyl 135a and (α-fluoro)vinyl 142a sulfides to the corresponding methyl phenyl styryl or (β-fluoro)styryl sulfonium salts 155 and 156, respectively. The (β-fluoro)styryl sulfonium ion, 156, will also allow me to
determine the effect of the fluorine substituent on the reactivity of vinyl sulfonium substrates. Thus, treatment of 135a or 142a with iodomethane and silver tetrafluoroborate\textsuperscript{129d} yielded quantitatively the alkenyl or (α-fluoro)alkenyl methyl phenyl sulfonium salts 155 and 156, respectively (Scheme 29). $^1$H NMR and $^{19}$F NMR analysis showed that methylation of the sulfide occurred with retention of the $E$ stereochemistry at the alkenyl unit.

![Scheme 29. Synthesis of Vinyl and α-Fluorovinyl Sulfonium Ions.](image)

Vinyl sulfonium salts, 155 and 156, were treated with an array of nucleophiles mimicking functionalities present in natural amino acid (Scheme 30). Thus treatment of the sulfonium salt 155 with propanethiol in DMF in the presence of triethylamine (TEA) resulted in a quick disappearance of the substrate and formation of the corresponding sulfide 135a. Treatment of 155 with phenol, thiophenol and/or imidazole also resulted in a rapid formation of the vinyl sulfide 135a. Analogous treatment of propanethiol, thiophenol, phenol and imidazole with β-styryl fluorinated sulfonium salt 156 also resulted in a quick formation of the corresponding fluorovinyl sulfide 142a. Treatment of 156 with $p$-toluenethiol in DMF with TEA also led to the formation of the vinyl sulfide 142a and the new minor product whose structure was tentatively assigned as the β-addition adduct of type 158. These results indicated an efficient transfer of the methyl
group from substrate 155/156. However, treatment of 156 with protected $N$-Boc-Hcy-COtBu under analogous conditions led to the formation of complex reaction mixture.

The preliminary kinetic result of the methylation reactions reveals that the transfer of a methyl group from the fluorinated sulfonium salt precursor 56 occurs only slightly faster than from the corresponding unfluorinated methyl sulfonium counterpart, 55.

**Scheme 30.** Reaction of Vinyl and α-Fluorovinyl Sulfonium Ions with Selected Amino Acid Residues.
4. EXPERIMENTAL SECTION

4.1. General Procedure

Melting points were obtained with a capillary apparatus and are uncorrected. UV spectra were measured in MeOH using a Shimadzu UV-2101 PC scanning spectrometer. $^1$H (Me$_4$Si) at 400 MHz and $^{13}$C (Me$_4$Si) at 100.6 MHz were recorded on a Bruker Avance NMR spectrometer with solutions in CDCl$_3$, unless otherwise specified. Mass spectra were obtained by atmospheric pressure chemical ionization (APCI) technique using a Finnigan navigator LC/MS and MeOH as a solvent. Gas chromatography data was obtained by a Hewlett Packard HP6890 series GC system equipped with a 5973 Mass Selective Detector and a 7683 Series Injector. Evaporation was effected with a Büchi rotary evaporator under water aspirator or mechanical oil pump at < 35 °C. Elemental analysis was determined at Galbraith Laboratories, Knoxville, TN. Merck Kieselgel 60-F$_{254}$ sheets were used for Thin Layer Chromatography (TLC) and products were detected with a 254 nm light. Merck Kieselgel 60 (230-400 mesh) was used for column chromatography. Unless otherwise specified solvents used for column chromatography and TLC were as follows: (S1) CHCl$_3$/MeOH (9:1); (S2) CHCl$_3$/MeOH (95:5); (S3) CHCl$_3$; (S4) EtOAc; (S5) EtOAc/hexane (1:1); (S6) EtOAc/hexane (7:3); (S7) EtOAc/hexane (3:7); (S8) EtOAc/hexane (1:9); (S9) SSE [the upper phase of EtOAc/i-PrOH/H$_2$O (4:1:2)]. Reagent grade chemicals were used for reactions. Solvents were dried by reflux over and distillation from CaH$_2$ under argon except THF which was dried with a VAC Atmospheres Co. solvent purifier. Sonication was performed with a Branson 5200 ultrasound bath.
4.2. Synthesis

**Ethyl 5(E)-(5'-deoxy-2',3'-O-isopropylideneuridin-5'-ylidene)pentanoate (101a).** Procedure A Tris(dibenzylideneacetone)dipalladium (9.2 mg, 0.01 mmol) was added to a solution of (E)-100a\[111\] (40 mg, 0.1 mmol) in benzene (2 mL) followed by dropwise addition of EtO\(_2\)C(CH\(_2\))\(_3\)ZnBr (0.5 M/THF, 0.3 mL, 0.15 mmol) via syringe at ambient temperature under N\(_2\). The resulting mixture was heated at 55 °C for 8 h [additional EtO\(_2\)C(CH\(_2\))\(_3\)ZnBr (0.1 mL, 0.05 mmol) was added after 5 h] and progress of the reaction was monitored (TLC) by the formation of slightly more polar compound. The volatiles were evaporated and the brown residue was partitioned (EtOAc/H\(_2\)O). The organic layer was washed (brine), dried (Na\(_2\)SO\(_4\)), evaporated, and the residue was column chromatographed (EtOAc/hexane, 85:15) to give 101a (28 mg, 72%); \(^1\)H NMR \(\delta\) 1.25 (t, \(J = 7.1\) Hz, 3, CH\(_3\)), 1.38 (s, 3, CH\(_3\)), 1.58 (s, 3, CH\(_3\)), 1.72 (quint, \(J = 7.6\) Hz, 2, H8',8''), 2.12 (q, \(J = 7.1\) Hz, 2, H7',7''), 2.32 (t, \(J = 7.6\) Hz, 2, H9'), 4.14 (q, \(J = 7.1\) Hz, 2, CH\(_2\)), 4.50 (dd, \(J = 4.3, 7.8\) Hz, 1, H4'), 4.74 (dd, \(J = 4.4, 6.2\) Hz, 1, H3'), 5.02 (dd, \(J = 1.7, 6.5\) Hz, 1, H2'), 5.60 (d, \(J = 1.6\) Hz, 1, H1'), 5.62 (dd, \(J = 8.0, 14.6\) Hz, 1, H5'), 5.73 (d, \(J = 8.2\) Hz, 1, H5), 5.82 (dt, \(J = 6.8, 14.6\) Hz, 1, H6'), 7.28 (d, \(J = 8.2\) Hz, 1, H6), 9.40 (s, 1, NH); \(^{13}\)C NMR \(\delta\) 14.25 (CH\(_3\)), 24.03 (C8'), 25.32 and 27.16 (CMe\(_2\)), 31.53 (C7'), 33.62 (C9'), 60.35 (CH\(_2\)), 84.22 (C3'), 84.84 (C2'), 88.63 (C4'), 94.29 (C1'), 102.45 (C5), 114.57 (CMe\(_2\)), 128.57 (C6'), 131.96 (C5'), 142.23 (C6), 149.77 (C2), 163.03 (C4), 173.45 (C10'); MS m/z 395 (100, MH\(^+\)); HRMS calcd for C\(_{19}\)H\(_{27}\)N\(_2\)O\(_7\) [M+H\(^+\)] 395.1818, found 395.1811.

**Ethyl 5(E)-(5'-deoxy-2',3'-O-isopropylidenedenosin-5'-ylidene)pentanoate (101b)** Coupling of (E)-100b\[35\] (41 mg, 0.1 mmol) with EtO\(_2\)C(CH\(_2\))\(_3\)ZnBr (0.5 M/THF,
0.4 mL, 0.2 mmol) by procedure A [column chromatography (1→2% MeOH/EtOAc)] gave **101b** (27 mg, 68%); \(^1\)H NMR (600 MHz) δ 1.25 (t, J = 7.2 Hz, 3, CH₃), 1.28 (s, 3, CH₃), 1.42 (s, 3, CH₃), 1.68 (quint, J = 7.5 Hz, 2, H₈',₈''), 2.04 (q, J = 7.2 Hz, 2, H₇',₇''), 2.28 (t, J = 7.5 Hz, 2, H₉',₉''), 4.08 (q, J = 7.1 Hz, 2, CH₂), 4.65 (dd, J = 3.3, 7.5 Hz, 1, H₄'), 4.98 (dd, J = 3.5, 6.2 Hz, 1, H₃'), 5.51 (dd, J = 1.9, 6.3 Hz, 1, H₂'), 5.59 (ddt, J = 1.2, 7.6, 15.4 Hz, 1, H₅'), 5.72 (dt, J = 15.4, 6.6 Hz, 1, H₆'), 5.90 (br s, 2, NH₂), 6.09 (d, J = 1.9 Hz, 1, H₁'), 7.91 (s, 1, H₂), 8.38 (s, 1, H₈); MS m/z 418 (100, MH⁺); HRMS calcd for C₂₀H₂₈N₅O₅ [M+H]^+ 418.2090, found 418.2082.

**Ethyl 5(E)-(5'-deoxyuridin-5'-ylidene)pentanoate (102a) Procedure B.** A solution of **101a** (70 mg, 0.78 mmol) with TFA/H₂O (9:1, 2.5 mL) was stirred at 0 °C (ice-bath) for 1 h. The volatiles were evaporated under vacuum (< 15 °C) and co-evaporated (3 x) with toluene. The residue was column chromatographed (1→6% MeOH/CHCl₃) to give **102a** (45 mg, 72%): mp 102–104 °C dec; UV max 262 nm (ε 9200), min 230 nm (ε 2100); \(^1\)H NMR (Me₂SO-d₆/D₂O) δ 1.18 (t, J = 7.1 Hz, 3, CH₃), 1.62 ('quint', J = 7.3 Hz, 2, H₈',₈''), 2.08 (q, J = 6.8 Hz, 2, H₇',₇''), 2.32 (t, J = 7.4 Hz, 2, H₉',₉''), 3.81 (t, J = 5.3 Hz, 1, H₃'), 4.04–4.10 (m, 3, H₂',CH₂), 4.15 ('t', J = 6.4 Hz, 1, H₄'), 5.57–5.72 (m, 4, H₁',5,5',6'), 7.58 (d, J = 8.1 Hz, 1, H₆); \(^1³\)C NMR (Me₂SO-d₆) δ 14.91 (CH₃), 24.60 (C₈'), 31.75 (C₇'), 33.68 (C₉'), 60.60 (CH₂), 73.73 (C₃'), 74.40 (C₂'), 84.81 (C₄'), 89.62 (C₁'), 102.79 (C₅), 129.58 (C₆'), 134.44 (C₅'), 141.89 (C₆), 151.49 (C₂), 163.95 (C₄), 173.61 (C₁₀'); MS m/z 355 (100, MH⁺). Anal. Calcd for C₁₆H₂₂N₂O₇ (354.36): C, 54.23; H, 6.26; N, 7.91. Found: C, 54.34; H, 6.28; N, 7.68.

**Ethyl 5(E)-(5'-deoxyadenosin-5'-ylidene)pentanoate (102b) Treatment of 101b** (27 mg, 0.065 mmol) with TFA/H₂O by procedure B gave **102b** (15 mg, 61%).

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Purification on HPLC (10 → 60% CH$_3$CN/H$_2$O for 1 h, t$_R$ = 43 min) and recrystallization (MeOH) gave white crystals: mp 91–93 °C dec; UV max 260 nm (ε 12,700), min 230 nm (ε 1840); $^1$H NMR (MeOH-$d_6$, 600 MHz) δ 1.05 (t, J = 7.2 Hz, 3, CH$_3$), 1.55 (quint, J = 7.3 Hz, 2, H8',8'"), 1.98 (q, J = 7.0 Hz, 2, H7',7'"), 2.16 (t, J = 7.4 Hz, 2, H9',9'"), 3.94 (q, J = 7.0 Hz, 2, CH$_2$), 4.04 (t, J = 5.2 Hz, 1, H3'), 4.25 (dd, J = 5.4, 6.6 Hz, 1, H4'), 4.59 (t, J = 4.8 Hz, 1, H2'), 5.58 (dd, J = 6.8, 15.4 Hz, 1, H5'), 5.65 (dt, J = 15.4, 6.4 Hz, 1, H6'), 5.84 (d, J = 4.5 Hz, 1, H1'), 8.08 (s, 1, H2), 8.10 (s, 1, H8); $^{13}$C NMR (Me$_2$SO-$d_6$) δ 14.90 (CH$_3$), 24.46 (C8'), 31.57 (C7'), 33.62 (C9'), 60.74 (CH$_2$), 73.54 (C3'), 74.69 (C20), 85.40 (C4'), 88.33 (C1'), 119.76 (C5), 129.64 (C6'), 133.98 (C5'), 140.95 (C8), 150.11 (C4), 153.53 (C2), 156.56 (C6), 173.97 (C10'); MS m/z 378 (100, MH$^+$). Anal. Calcd for C$_{17}$H$_{23}$N$_5$O$_5$•H$_2$O (395.41): C, 51.64; H, 6.37; N, 17.71. Found: C, 51.53; H, 6.42; N, 17.37.

5(E)-(5'-Deoxyadenosin-5'-ylidene)pentanoic acid (102c) NaOH/H$_2$O (1 M, 0.35 mL) was added to a solution of 102b (10 mg, 0.026 mmol) in MeOH (2.5 mL) and stirring was continued at ambient temperature overnight. The resulting mixture was neutralized with AcOH to pH ~ 7. Volatiles were evaporated and the residue was purified on HPLC (10 → 30% CH$_3$CN/H$_2$O for 50 min, t$_R$ = 28 min) to give 102c (7.5 mg, 82%); $^1$H NMR (MeOH-$d_4$) δ 1.74 (quint', J = 7.4 Hz, 2, H8',8'"), 2.15 (q, J = 7.1 Hz, 2, H7',7'"), 2.32 (t, J = 7.4 Hz, 2, H9',9'"), 4.21 (t, J = 5.2 Hz, 1, H3'), 4.43 (dd, J = 5.5, 6.8 Hz, 1, H4'), 4.72 (t, J = 4.9 Hz, 1, H2'), 5.75 (dd, J = 7.0, 15.4 Hz, 1, H5'), 5.83 (dt, J = 15.5, 6.5 Hz, 1, H6'), 6.01 (d, J = 4.5 Hz, 1, H1'), 8.16 (s, 1, H2), 8.22 (s, 1, H8); $^{13}$C NMR (MeOH-$d_4$) δ 25.37 (C8'), 32.64 (C7'), 34.32 (C9'), 75.12 (C3'), 75.70 (C2'), 86.43 (C4'), 90.14 (C1'), 120.10 (C5), 129.76 (C6'), 135.18 (C5'), 141.28 (C8), 150.66 (C4), 153.93
(C2), 157.36 (C6), 177.59 (C10'); MS m/z 350 (100, MH+); HRMS calcd for C_{15}H_{20}N_{5}O_{5} [M+H]^+ 350.1464, found 350.1469.

**Ethyl 5-fluoro-5-(5'-deoxy-2',3'-O-isopropylideneadenosin-5'-ylidene)pentanoate** (110) Pd(PPh_3)_4 (25.6 mg, 0.022 mmol) was added to a solution of 107^{12} (E/Z, ~60:40; 80 mg, 0.2 mmol) in benzene (5 mL) followed by dropwise addition of EtO_2C(CH_2)_3ZnBr (0.5 M/THF, 0.88 mL, 0.44 mmol) via syringe at ambient temperature under N_2. The resulting mixture was heated at 55 °C for 8 h. The volatiles were evaporated and the brown residue was partitioned (EtOAc/NaHCO_3/H_2O). The organic layer was washed (brine), dried (Na_2SO_4), evaporated, and the residue was column chromatographed (1 → 3% MeOH/CHCl_3) to give 110 (49 mg, 56%; E/Z, ~40:60); ^{19}F NMR δ -95.78 ('q', J_{F-H5';7';7''} = 21.8 Hz, 0.4, E), -101.80 (dt, J_{F-H5'} = 35.5 Hz; J_{F-H7';7''} = 17.3 Hz, 0.6, Z); MS m/z 436 (MH^+); HRMS calcd for C_{20}H_{27}FN_{5}O_{5} [M+H]^+ 436.1996, found 436.1991. (Z)-87 had: ^1H NMR δ 1.23 (t, J = 7.1 Hz, 3, CH_3), 1.36 (s, 3, CH_3), 1.61 (s, 3, CH_3), 1.84 ('quint', J = 7.3 Hz, 2, H8',8''), 2.15 (dt, J = 17.1, 7.7 Hz, 2, H7',7''), 2.30 (t, J = 7.5 Hz, 2, H9',9''), 4.09 (q, J = 7.2 Hz, 2, CH_2), 4.85 (dd, J = 9.2, 35.5 Hz, 1, H5'), 4.97 ('dd', J = 3.3, 6.2 Hz, 1, H3'), 5.15 (dd, J = 3.1, 9.2 Hz, 1, H4'), 5.54 (dd, J = 1.9, 6.2 Hz, 1, H2'), 5.88 (br s, 2, NH_2), 5.98 (d, J = 1.7 Hz, 1, H1'), 7.84 (s, 1, H8). (E)- 110 had: ^1H NMR δ 1.21 (t, J = 7.1 Hz, 3, CH_3), 1.35 (s, 3, CH_3), 1.60 (s, 3, CH_3), 1.74 ('quint', J = 7.2 Hz, 2, H8',8''), 2.26 (t, J = 7.4 Hz, 2, H9',9''), 2.35 (dt, J = 23.3, 7.3 Hz, 2, H7',7''), 4.11 (q, J = 7.2 Hz, 2, CH_2), 4.75 (ddd, J = 1.8, 3.2, 10.1 Hz, 1, H4'), 4.97 ('dd', J = 3.3, 6.2 Hz, 1, H3'), 5.30 (dd, J = 10.1, 19.6 Hz, 1, H5'), 5.50 (dd, J = 1.7, 6.3 Hz, 1, H2'), 5.88 (br s, 2, NH_2), 5.97 (d, J = 1.5 Hz, 1, H1'), 7.84 (s, 1, H2), 8.34 (s, 1, H8).
Ethyl 5-fluoro-5-(5'-deoxyadenosin-5'-ylidene)pentanoate (111) Treatment of 110 (40 mg, 0.092 mmol; E/Z, 40:60) with TFA/H₂O by procedure B and HPLC purification (15 → 50% CH₃CN/H₂O, tᵣ = 49 min) gave 111 (32 mg, 88%; E/Z, ~35:65):

¹⁹F NMR (MeOH-ᵈ) δ -94.73 ('q', Jᵢ₋H₅';₇;₇' = 20.5 Hz, 0.35, E), -102.14 (dt, J₁₋H₅' = 35.9 Hz; J₅⁻H₇';₇'' = 17.7 Hz, 0.65, Z); MS m/z 396 (100, MH⁺); HRMS calcd for C₁₇H₂₃FN₅O₅ [M+H]^+ 396.1678, found 396.1680. (Z)-111 had: ¹H NMR (MeOH-ᵈ) δ 1.24 (t, J = 7.1 Hz, 3, CH₃), 1.86 ('quint', J = 7.4 Hz, 2, H₈',₈''), 2.32 ('dt', J = 17.6, 7.3 Hz, 2, H₇',₇''), 2.40 (t, J = 7.4 Hz, 2, H₉',₉''), 4.13 (q, J = 7.1 Hz, 2, CH₂), 4.23 (t, J = 4.7 Hz, 1, H₃'), 4.86 ('t', J = 4.4 Hz, 1, H₂'), 4.94 (dd, J = 4.5, 9.2 Hz, 1, H₄'), 5.20 (dd, J = 9.2, 36.5 Hz, 1, H₅'), 5.99 (d, J = 4.8 Hz, 1, H₁'), 8.24 (s, 1, H₂), 8.26 (s, 1, H₈); ¹³C NMR (MeOH-ᵈ) δ 14.50 (CH₃), 22.34 (C₈'), 31.99 (d, J = 27.2 Hz, C₇'), 33.87 (C₉'), 61.55 (CH₂), 74.89 (C₂'), 76.29 (C₃'), 79.34 (d, J = 6.5 Hz, C₄'), 90.38 (C₁'), 106.01 (d, J = 11.3 Hz, C₅'), 120.82 (C₅), 141.69 (C₈), 150.62 (C₄), 153.90 (C₂), 157.37 (C₆), 163.50 (d, J = 260.9 Hz, C₆'), 174.86 (C₁₀'). (E)-111 had: ¹H NMR (MeOH-ᵈ) δ 1.24 (t, J = 7.1 Hz, 3, CH₃), 1.84 ('quint', J = 7.4 Hz, 2, H₈',₈''), 2.39 (t, J = 7.3 Hz, 2, H₉',₉''), 2.43–2.55 (m, 2, H₇',₇''), 4.12 (q, J = 7.1 Hz, 2, CH₂), 4.28 (t, J = 5.5 Hz, 1, H₃'), 4.60 (ddd, J = 1.9, 5.8, 9.8 Hz, 1, H₄'), 4.72 (dd, J = 4.0, 5.1 Hz, 1, H₂'), 5.44 (dd, J = 9.7, 19.9 Hz, 1, H₅'), 6.00 (d, J = 3.6 Hz, 1, H₁'), 8.25 (s, 1, H₂), 8.23 (s, 1, H₈); ¹³C NMR (MeOH-ᵈ) δ 14.50 (CH₃), 22.34 (C₈'), 28.56 (d, J = 27.2 Hz, C₇'), 33.78 (C₉'), 61.55 (CH₂), 75.21 (C₂'), 76.11 (C₃'), 81.03 (d, J = 14.4 Hz, C₄'), 90.57 (C₁'), 106.83 (d, J = 24.4 Hz, C₅'), 120.70 (C₅), 141.31 (C₈), 150.54 (C₄), 153.94 (C₂), 157.37 (C₆), 165.42 (d, J = 255.3 Hz, C₆').
5-Fluoro-5(\textit{E})-(5'-deoxyadenosin-5'-ylidene)pentanoic acid (112) Treatment of 111 (8 mg, 0.020 mmol; \textit{E/Z}, 35:65) with NaOH as described for 102c and HPLC purification (5 →50% CH₃CN/H₂O for 1 h, \textit{t}_R = 42 min) gave 112 (6 mg, 82%; \textit{E/Z}, 45:55); \textit{19}F NMR (MeOH-\textit{d}_4) \delta -97.8 ('q', \textit{J}_{\text{F-H5';7';7''}} = 23.9 Hz, 0.45, \textit{E}), -105.0 ('dt', \textit{J}_{\text{F-H7';7''}} = 17.6 Hz, 0.55, \textit{Z}); MS \textit{m/z} 368 (100, MH⁺); HRMS calcd for C₁₅H₁₉FN₅O₅ [M+H⁺] 368.1370, found 368.1375. (\textit{Z})-112 had: \textit{1H} NMR (MeOH-\textit{d}_4) \delta 1.85 ('quint', \textit{J} = 7.4 Hz, 2, H\textit{8',8''}), 2.32 (dt, \textit{J} = 17.3, 7.4 Hz, 2, H\textit{7',7''}), 2.38 (t, \textit{J} = 7.3 Hz, 2, H\textit{9',9''}), 4.23 (t, \textit{J} = 4.8 Hz, 1, H\textit{3'}), 4.83 ('t', \textit{J} = 5.0 Hz, 1H, H\textit{2'}), 4.92 (dd, \textit{J} = 4.7, 9.3 Hz, 1, H\textit{4'}), 5.20 (dd, \textit{J} = 9.2, 36.0 Hz, 1, H\textit{5'}), 6.01 (d, \textit{J} = 5.2 Hz, 1, H\textit{1'}), 8.24 (s, 1, H\textit{2}), 8.27 (s, 1H, H\textit{8}); \textit{13C} NMR (MeOH-\textit{d}_4) \delta 23.02 (C\textit{8'}), 32.05 (d, \textit{J} = 27.4 Hz, C\textit{7'}), 33.82 (C\textit{9'}), 74.91 (C\textit{2'}), 76.27 (C\textit{3'}), 79.34 (d, \textit{J} = 6.6 Hz, C\textit{4'}), 90.27 (C\textit{1'}), 105.90 (d, \textit{J} = 11.0 Hz, C\textit{5'}), 120.46 (C\textit{5}), 141.36 (C\textit{8}), 150.60 (C\textit{4}), 153.88 (C\textit{2}), 157.34 (C\textit{6}), 163.30 (d, \textit{J} = 258.6 Hz, C\textit{6'}), 177.09 (C\textit{10'}). (\textit{E})-112 had: \textit{1H} NMR (MeOH-\textit{d}_4) \delta 1.84 ('quint', \textit{J} = 7.4 Hz, 2H, H\textit{8',8''}), 2.39 (t, \textit{J} = 7.3 Hz, 2, H\textit{9',9''}), 2.45 (dt, \textit{J} = 23.7, 7.3 Hz, 1, H\textit{7'}), 2.46 (dt, \textit{J} = 23.7, 7.3 Hz, 1, H\textit{7''}), 4.28 (t, \textit{J} = 5.6 Hz, 1, H\textit{3'}), 4.60 (ddd, \textit{J} = 1.8, 5.8, 9.7 Hz, 1, H\textit{4'}), 4.72 (dd \textit{J} = 4.0, 5.2 Hz, 1, H\textit{2'}), 5.44 (dd, \textit{J} = 9.8, 19.9 Hz, 1, H\textit{5'}), 6.00 (d, \textit{J} = 3.7 Hz, 1, H\textit{1'}), 8.23 (s, 1, H\textit{2}), 8.25 (s, 1, H\textit{8}); \textit{13C} NMR (MeOH-\textit{d}_4) \delta 22.45 (C\textit{8'}), 28.65 (d, \textit{J} = 26.9 Hz, C\textit{7'}), 33.82 (C\textit{9'}), 75.17 (C\textit{2'}), 76.12 (C\textit{3'}), 81.04 (d, \textit{J} = 14.8 Hz, C\textit{4'}), 90.58 (C\textit{1'}), 106.73 (d, \textit{J} = 24.7 Hz, C\textit{5'}), 120.53 (C\textit{5}), 140.58 (C\textit{8}), 150.49 (C\textit{4}), 153.91 (C\textit{2}), 157.34 (C\textit{6}), 165.88 (d, \textit{J} = 258.6 Hz, C\textit{6'}), 177.09 (C\textit{10'}).  

1-[6-(Tributylgermyl)-5,6-dideoxy-2,3-\textit{O}-isopropylidene-\textit{\beta}-\textit{D}-ribohex-5(\textit{E}) enofuranosyl]uracil (120a) A suspension of 119a (48 mg, 0.11 mmol) in toluene (2 mL) was deoxygenated (N₂, 1 hour), and then Bu₃GeH (49 mg, 0.052 mL, 0.20 mmol) was
added. Deoxygenation was continued for 30 minutes, and AIBN (8.2 mg, 0.05 mmol) was added. The resulting solution was refluxed for 14 hours [additional AIBN (16.4 mg, 0.1 mmol) in degassed toluene (1 mL) was added to the reaction mixture periodically]. Volatiles were evaporated (TLC analysis showed a formation of the less polar product) and the residue was partitioned (CHCl₃//H₂O/NaHCO₃). The organic layer was washed with brine, dried (MgSO₄) and was evaporated. The residue was column chromatographed [EtOAc/hexane (7:3)] to give 120a (33 mg, 57%) as a syrup: ¹H NMR δ 0.72–0.78 (m, 6H, Bu), 0.84–0.88 (m, 9H, Bu), 1.24–1.33 (m, 12H, Bu), 1.39 (s, 3, CH3), 1.56 (s, 3, CH3), 4.52 ("dd", J = 4.0, 6.0 Hz, 1, H4'), 4.69 (dd, J = 4.3, 6.4 Hz, 1, H3'), 4.92 (dd, J = 2.0, 6.4 Hz, 1, H2'), 5.70 (dd, J = 1.5, 8.2 Hz, 1, H5), 5.72 (d, J = 2.1 Hz, 1, H1'), 5.95 (dd, J = 6.3, 18.5 Hz, 1, H5'), 6.14 (dd, J = 1.1, 18.5 Hz, 1, H6'), 7.20 (d, J = 8.1 Hz, 1, H6), 8.75 (br s, 1, NH); ¹³C NMR δ 12.71 (Bu), 13.77 (Bu), 25.37 (CMe₂), 26.42 (Bu), 27.15 (CMe₂), 27.29 (Bu), 83.99 (C3'), 84.83 (C2'), 89.79 (C4'), 93.47 (C1'), 102.41 (C5), 114.65 (CMe₂), 134.02 (C6'), 140.60 (C5'), 141.64 (C6), 149.77 (C2), 162.96 (C4); MS m/z 525 (100, MH⁺, ⁷⁴Ge), 523 (70, MH⁺, ⁷²Ge), 521 (50, MH⁺, ⁷⁰Ge); HRMS calcd for C₂₅H₄₃⁷⁴GeN₂O₅ [M+H]⁺ 525.2384, found 525.2385.

1-[5,6-Dideoxy-2,3-O-isopropylidene-6-(triphenylgermyl)-β-D-ribo-hex-5(É)
enofuranosyl]uracil (120b) Treatment of 119a (48 mg, 0.11 mmol) with Ph₃GeH (60 mg, 0.20 mmol; as described for 120a) gave 120b (46 mg, 72%) as a foam: ¹H NMR δ 1.26 (s, 3, CH₃), 1.50 (s, 3, CH₃), 4.61 (dd, J = 1.2, 4.2, 5.6 Hz, 1, H4'), 4.71 (dd, J = 4.1, 6.3 Hz, 1, H3'), 4.90 (dd, J = 1.9, 6.4 Hz, 1, H2'), 5.55 (d, J = 8.1 Hz, 1, H5), 5.64 (d, J = 1.9 Hz, 1, H1'), 6.12 (dd, J = 5.7, 18.3 Hz, 1, H5'), 6.52 (dd, J = 1.3, 18.3 Hz, 1, H6'), 7.10 (d, J = 8.1 Hz, 1, H6), 7.26–7.33 (m, 9H, Ph), 7.36–7.42 (m, 6H, Ph), 8.65 (br s, 1,
NH); $^{13}$C NMR $\delta$ 25.34 & 27.11 (CMe$_2$), 84.14 (C3'), 84.69 (C2'), 89.48 (C4'), 93.92 (C1'), 102.61 (C5), 114.63 (CMe$_2$), 128.35, 128.53, 129.26, 135.03 (Ph), 135.64 (C6'), 141.80 (C5'), 145.00 (C6), 149.75 (C2), 162.99 (C4); MS $m/z$ 585 (100, MH$^+$, $^{74}$Ge), 583 (70, MH$^+$, $^{72}$Ge), 581 (50, MH$^+$, $^{70}$Ge); HRMS calcd for C$_{31}$H$_{31}$GeN$_2$O$_5$ [M+H]$^+$ 585.1485, found 585.1447.

9-[6-(Tributylgermyl)-5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5(E)-enofuranosyl]adenine (121a) Treatment of 119b (50 mg, 0.11 mmol) with Bu$_3$GeH (47 mg, 0.050 mL, 0.19 mmol; as described for 120a) gave 121a (27 mg, 46%) as a syrup: $^1$HNMR $\delta$ 0.66–0.71 (m, 6H, Bu), 0.85–0.89 (m, 9H, Bu), 1.26–1.34 (m, 12H, Bu) 1.42 (s, 3, CH$_3$), 1.62 (s, 3, CH$_3$), 4.71 (dd, $J = 3.1$, 5.0 Hz, 1, H4'), 5.02 (dd, $J = 3.1$, 6.2 Hz, 1, H3'), 5.57 (dd, $J = 1.8$, 6.3 Hz, 1, H2'), 5.64 (br s, 2, NH$_2$), 5.95 (dd, $J = 5.1$, 18.6 Hz, 1, H5'), 6.01 (d, $J = 18.5$ Hz, 1, H6'), 6.12 (d, $J = 1.8$ Hz, 1, H1'), 7.88 (s, 1, H2), 8.35 (s, 1, H8); $^{13}$C NMR $\delta$ 12.69 (Bu), 13.85 (Bu), 26.54 (Bu), 26.63 & 27.26 (CMe$_2$), 27.38 (Bu), 84.70 (C3'), 85.39 (C2'), 90.63 (C4'), 91.27 (C1'), 114.97 (CMe$_2$), 120.99 (C5), 133.70 (C6'), 140.89 (C5'), 142.02 (C8), 150.44 (C4), 154.05 (C2), 156.36 (C6); MS $m/z$ 548 (100, MH$^+$, $^{74}$Ge), 546 (70, MH$^+$, $^{72}$Ge), 544 (50, MH$^+$, $^{70}$Ge); HRMS calcd for C$_{26}$H$_{44}$GeN$_2$O$_3$ [M+H]$^+$ 548.2656, found 548.2650.

9-[6-(Triphenylgermyl)-5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5(E)-enofuranosyl]adenine (121b) Treatment of 119b$^{120}$ (50 mg, 0.11 mmol) with Ph$_3$GeH (57 mg, 0.19 mmol; as described for 120a) gave 121b (28 mg, 42%) as a foam: $^1$H NMR $\delta$ 1.39 (s, 3, CH$_3$), 1.62 (s, 3, CH$_3$), 4.83 (ddd, $J = 1.3$, 3.2, 5.8 Hz, 1, H4'), 5.09 (dd, $J = 3.2$, 6.3 Hz, 1, H3'), 5.55 (dd, $J = 1.9$, 6.3 Hz, 1, H2'), 5.61 (br s, 2, NH$_2$), 6.11 (d, $J = 1.9$ Hz, 1, H1'), 6.20 (dd, $J = 5.9$, 18.3 Hz, 1, H5'), 6.46 (dd, $J = 1.4$, 18.3 Hz, 1, H6'), 7.31–
7.40 (m, 15H, Ph), 7.85 (s, 1, H2), 8.11 (s, 1, H8); $^{13}$C NMR δ 25.44 & 27.11 (CMe$_2$), 84.13 (C3'), 84.81 (C2'), 89.75 (C4'), 90.74 (C1'), 114.38 (CMe$_2$), 120.13 (C5), 127.96, 128.26, 129.13, 134.95 (Ph), 135.67 (C6'), 140.03 (C5'), 145.44 (C8), 149.44 (C4), 153.04 (C2), 155.31 (C6) MS $m/z$ 608 (100, MH$^+$, $^{74}$Ge), 606 (68, MH$^+$, $^{72}$Ge), 604 (50, MH$^+$, $^{70}$Ge); HRMS calcd for C$_{32}$H$_{32}$$^{74}$GeN$_5$O$_3$ [M+H]$^+$ 608.1717, found 608.1722.

1-[2,3-Di-O-acetyl-5,6-dideoxy-6-(p-toluenesulfonyl)-β-D-ribo-hex-5(E)-enofuranosyl]uracil (122b) DMAP (5 mg, 0.04 mmol) was added to a stirred solution of 122a$_{130}$ (80 mg, 0.18 mmol) in Ac$_2$O (4 mL) at ambient temperature. After 14 hours, MeOH (10 mL) was added and stirring was continued for 1 hour. Volatiles were evaporated and the residue was co-evaporated with MeOH (2 × 5 mL). The crude product was partitioned (CHCl$_3$/H$_2$O/HCl) and the organic layer was washed with NaHCO$_3$/H$_2$O, brine, dried (MgSO$_4$) and was evaporated to give 122b (83 mg, 96%) of sufficient purity to be used in next step: $^1$HNMR δ 2.05 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.38 (s, 3, CH$_3$), 4.64 (ddd, $J$ = 1.6, 4.6, 6.0 Hz, 1, H4'), 5.24 (t, $J$ = 6.1 Hz, 1, H3'), 5.36 (t, $J$ = 5.5Hz, 1, H2'), 5.70 (d, $J$ = 8.1 Hz, 1, H5), 5.86 (d, $J$ = 4.8 Hz, 1, H1'), 6.62 (dd, $J$ = 1.6, 15.1 Hz, 1, H6'), 6.98 (dd, $J$ = 4.4, 15.1 Hz, 1, H5'), 7.18 (d, $J$ = 8.1 Hz, 1, H6), 7.28 (d, $J$ = 8.2 Hz, 2H, Ar), 7.71 (d, $J$ = 8.3 Hz, 2H, Ar), 9.45 (br s, 1, NH); $^{13}$C NMR δ 20.39 (2×) & 21.65 (CH$_3$ & 2 × Ac), 72.16 (C3'), 72.39 (C2'), 79.17 (C4'), 89.35 (C1'), 103.68 (C5), 127.94 (Ar), 129.78 (Ar), 133.33 (C6'), 136.47 (Ar), 138.66 (C5'), 140.21 (C6), 145.01 (Ar), 149.98 (C2), 162.67 (C4), 169.44 & 169.58 (2 × Ac); MS $m/z$ 479 (100, MH$^+$).

1-[2,3-Di-O-acetyl-5,6-dideoxy-6-(triphenylgermyl)-β-D-ribo-hex-5(E)-enofuranosyl]uracil (123a) Treatment of 122b (90 mg, 0.19 mmol) with Ph$_3$GeH (104 mg, 0.34 mmol; as described for 120a) gave 123a (81 mg, 68%) as an amorphous solid:
$^1$HNMR $\delta$ 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 4.66 (ddd, $J = 1.5, 5.2, 5.4$ Hz, 1, H$^4'$), 5.27 (t, $J = 5.2$ Hz, 1, H$^3'$), 5.32 (t, $J = 5.4$ Hz, 1, H$^2'$), 5.65 (d, $J = 8.1$ Hz, 1, H$^5$), 6.10 (d, $J = 5.1$ Hz, 1, H$^1'$), 6.17 (dd, $J = 5.4$, 18.3 Hz, 1, H$^5'$), 6.73 (dd, $J = 1.4$, 18.3 Hz, 1, H$^6$), 7.18 (d, $J = 8.2$ Hz, 1, H$^6$), 7.37–7.43 (m, 9H, Ph), 7.45–7.50 (m, 6H, Ph), 8.98 (br s, 1, NH); $^{13}$C NMR $\delta$ 20.43 & 20.54 (2 × Ac), 72.55 (C$^2'$), 72.96 (C$^3'$), 83.18 (C$^4'$), 87.43 (C$^1'$), 103.47 (C$^5$), 128.48, 129.44, 134.96, 135.21 (Ph), 131.02 (C$^6'$), 139.34 (C$^6$), 142.87 (C$^5$), 150.22 (C$^2$), 162.63 (C$^4$), 169.61 (2 × Ac); MS m/z 629 (100, MH$^+$, $^{74}$Ge), 627 (70, MH$^+$, $^{72}$Ge), 625 (50, MH$^+$, $^{70}$Ge); HRMS calcd for C$_{32}$H$_{31}$GeN$_2$O$_7$ [M+H]$^+$ 629.1343, found 629.1335.

1-[5,6-Dideoxy-6-(triphenylgermyl)-β-D-ribo-hex-5(E)-enofuranosyl]uracil

(123b) Method A. A solution of 123a (32 mg, 0.05 mmol) in NH$_3$/MeOH (2 mL) was stirred at ~0°C for 2 hours, and was evaporated and co-evaporated (MeOH). The residue was column chromatographed (EtOAc/hexane, 4:1) to give 123b (26 mg, 96%) as a white powder: $^1$HNMR $\delta$ 4.01 (t, $J = 5.5$ Hz, 1, H$^3'$), 4.19 (dd, $J = 3.5$, 5.0 Hz, 1, H$^2'$), 4.62 ("t", $J = 5.5$ Hz, 1, H$^4'$), 5.20 (br s, 2, 2 × OH), 5.58 (d, $J = 8.1$ Hz, 1, H$^5$), 5.82 (d, $J = 3.2$ Hz, 1, H$^1'$), 6.20 (dd, $J = 5.3$, 18.4 Hz, 1, H$^5'$), 6.71 (dd, $J = 1.4$, 18.3 Hz, 1, H$^6$), 7.32–7.46 (m, 16H, Ph & H$^6$), 8.92 (br s, 1, NH); $^{13}$C NMR $\delta$ 73.82 (C$^3'$), 75.10 (C$^2'$), 85.81 (C$^4'$), 91.11 (C$^1'$), 102.52 (C$^5$), 128.43, 128.87, 130.98, 134.85 (Ph), 136.36 (C$^6'$), 139.54 (C$^6$), 144.29 (C$^5$), 151.21 (C$^2$), 163.69 (C$^4$); MS m/z 545 (100, MH$^+$, $^{74}$Ge), 543 (75, MH$^+$, $^{72}$Ge), 541 (45, MH$^+$, $^{70}$Ge); HRMS calcd for C$_{28}$H$_{27}$GeN$_2$O$_7$ [M+H]$^+$ 545.1132, found 545.1132.

Method B. A solution of 120b (29 mg, 0.05 mmol) in TFA/H$_2$O (9:1, 1.5 mL) was stirred at ~0°C for 1 hour. The volatiles were evaporated, co-evaporated (3×) with toluene
and the residue was column chromatographed (EtOAc) to give 123b (18 mg, 66%) with data identical as above.

1-[2,3-Di-O-acetyl-6-(tributylgermyl)-5,6-dideoxy-\(\beta\)-D-ribo-hex-5-(E)-enofuranosyl]-uracil (124a) Method A. Treatment of 122b (39 mg, 0.08 mmol) with Bu\(_3\)GeH (39 mg, 0.041 mL, 0.16 mmol; as described for 120a) gave 124a (22 mg, 49%) as a foam: \(^1\)HNMR \(\delta\) 0.78–0.92 (m, 15H, Bu), 1.26–1.38 (m, 12H, Bu), 2.08 (s, 3H, Ac), 2.10 (s, 3H, Ac), 4.52 ("t", \(J = 5.5\) Hz, 1, H4'), 5.22 (t, \(J = 5.3\) Hz, 1, H3'), 5.30 (t, \(J = 5.4\) Hz, 1, H2'), 5.75 (d, \(J = 8.1\) Hz, 1, H5), 5.95 (dd, \(J = 5.7, 18.5\) Hz, 1, H5'), 6.02 (d, \(J = 5.2\) Hz, 1, H1'), 6.26 (dd, \(J = 1.2, 18.5\) Hz, 1, H6'), 7.26 (d, \(J = 8.1\) Hz, 1, H6), 8.27 (s, 1, NH); \(^13\)C NMR \(\delta\) 12.71 (Bu), 13.73 (Bu), 26.35 (Bu), 27.32 (Bu), 20.42 & 20.49 (2 x Ac), 72.78 (C3'), 72.91 (C2'), 83.57 (C4'), 87.73 (C1'), 103.24 (C5), 135.65 (C6'), 138.84 (C5'), 139.50 (C6), 149.89 (C2), 162.27 (C4); 169.56 & 169.57 (2 x Ac); MS m/z 569 (100, MH\(^+\), \(^{74}\)Ge), 567 (72, MH\(^+\), \(^{72}\)Ge), 565 (51, MH\(^+\), \(^{70}\)Ge); HRMS calcd for C\(_{26}\)H\(_{43}\)\(^{74}\)GeN\(_2\)O\(_7\) [M+H]\(^+\) 569.2282, found 569.2289.

Method B. A suspension of 122b (29 mg, 0.06 mmol) in toluene (4 mL) was degassed (N\(_2\), 1 hour), and then Bu\(_3\)GeH (29 mg, 0.031 mL, 0.12 mmol) was added and deoxygenation was continued for an additional 1 hour. The 2-mercaptoethanol (2 mg, 0.02 mmol) and ACCN (14.5 mg, 0.06 mmol) were added and the resulting solution was refluxed for 20 hours. The aqueous work-up and column chromatography (as described for 120a) gave 124a (20 mg, 58%) with data as reported above.

1-[6-(Tributylgermyl)-5,6-dideoxy-\(\beta\)-D-ribo-hex-5-(E)-enofuranosyl]uracil (124b) Treatment of 124a (23 mg, 0.04 mmol) with NH\(_3\)/MeOH (2 mL; as described for 123a) gave 124b (14 mg, 72%) as a white powder: \(^1\)H NMR (MeOH-\(d\)4) \(\delta\) 0.83–0.97 (m,
15H, Bu), 1.30–1.46 (m, 12H, Bu), 3.96 ("t", J = 5.7 Hz, 1, H3'), 4.18 (dd, J = 3.8, 5.3 Hz, 1, H2'), 4.35 (t, J = 5.8 Hz, 1, H4'), 5.69 (d, J = 8.1 Hz, 1, H5), 5.83 (d, J = 3.8 Hz, 1, H1'), 6.11 (dd, J = 5.3, 18.5 Hz, 1, H5'), 6.20 (d, J = 18.6 Hz, 1, H6'), 7.55 (d, J = 8.1 Hz, 1, H6); 13C NMR (MeOH- d4) δ 13.71 (Bu), 14.09 (Bu), 27.46 (Bu), 28.56 (Bu), 75.12 & 75.13 (C2'/3'), 87.08 (C4'), 92.09 (C1'), 102.78 (C5), 133.15 (C6'), 142.39 (C5'), 143.20 (C6), 152.22 (C2), 166.08 (C4); MS m/z 485 (100, MH+, 74Ge), 483 (77, MH+, 72Ge), 481 (52, MH+, 70Ge); HRMS calcd for C22H39GeN2O5 [M+H]+ 485.2071, found 485.2065.

1-[5,6-Dideoxy-6-iodo-2,3-O-isopropylidene-β-D-ribo-hex-5(E)-enofuranosyl]-uracil (125) A solution of NIS (22 mg, 0.10 mmol) in CHCl3/CH2Cl2 (1:1, 5 mL) was added dropwise to a stirred solution of 120a (48 mg, 0.09 mmol) in CHCl3/CH2Cl2 (1:1, 5 mL) at 0°C. After 1 hour (TLC showed exclusive formation of a more polar product), the pink reaction mixture was treated with NaHSO3/H2O and the separated organic layer was washed with brine, dried (MgSO4) and was evaporated. Purification on a short silica gel column (CHCl3/MeOH, 30:1) gave 125 (34 mg, 92%) with data as reported.138

9-[6-Bromo-5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hex-5(E)-enofuranosyl]adenine (126) A solution of NBS (18 mg, 0.10 mmol) in CHCl3/CH2Cl2 (1:1, 5 mL) was added dropwise to a stirred solution of 121a (50 mg, 0.09 mmol) in CHCl3/CH2Cl2 (1:1, 5 mL) at 0°C. After 6 hours, the reaction mixture was washed with NaHCO3/H2O and brine and the separated organic layer was dried (Na2SO4) and was evaporated. Purification on a short silica gel column (CHCl3/MeOH, 20:1) gave 126 (28 mg, 81%) with data as reported.37

9-(5,6-Dideoxy-β-D-ribo-hex-5-enofuranosyl)adenine[5'-deoxy-5'-methylene-adenosine] (127) A solution of 121a (22 mg, 0.04 mmol) in CF3CO2H/H2O (9:1, 1 mL)
was stirred at 0°C for 1 hour. The volatiles were evaporated and the residue was co-
evaporated (2×) with toluene. The residue was column chromatographed (1 → 5% MeOH/EtOAc) to give 127 (8 mg, 76%): $^1$H NMR (MeOH-$d_4$) $\delta$ 4.25 (t, $J = 5.1$ Hz, 1, H$3'$), 4.48 (dd, $J = 5.3$, 6.5 Hz, 1, H$4'$), 4.74 (t, $J = 4.9$ Hz, 1, H$2'$), 5.26 ("dt", $J = 1.4$, 10.5 Hz, 1, H$6'$), 5.41 ("dt", $J = 1.5$, 17.1 Hz, 1, H$6'$), 6.04 (d, $J = 5.0$ Hz, 1, H$1'$), 6.11 ("ddd", $J = 6.6$, 10.5, 17.1 Hz, 1, H$5'$), 8.23 (s, 1, H2), 8.26 (s, 1, H8).

2'-Deoxy-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-[(phenylsulfonyl)-methylene] uridine [129 (Z)] Lithium bis(trimethylsilyl)amide (1 M/THF; 0.18 mL, 0.18 mmol) was added dropwise to a stirred solution of diethyl (phenylsulfonyl)methylphosphonate (53 mg, 0.18 mmol) in THF (2 mL) at -78°C under nitrogen. After 30 minutes, ketone 128$^{131}$(78 mg, 0.16 mmol) was added and the resulting solution was allowed to warm up to -30°C over 2 hours and then to ~0°C over 15 minutes. NH$_4$Cl/H$_2$O (0.5 mL) was added and the volatiles were evaporated. The residue was partitioned (CHCl$_3$/H$_2$O/NaHCO$_3$) and the organic layer was washed with brine, dried (MgSO$_4$) and was evaporated. Column chromatography (30→40% EtOAc/hexane) gave 129 (62 mg, 62%) as a pale-yellow powder: $^1$H NMR $\delta$ 0.97–1.05 (m, 28H, 4 × i-Pr), 3.62 (ddd, $J = 3.0$, 4.2, 8.7 Hz, 1, H$4'$), 3.99 (dd, $J = 3.0$, 12.8 Hz, 1, H$5'$), 4.06 (dd, $J = 4.2$, 12.8 Hz, 1, H$5'$), 5.35 (dt, $J = 2.1$, 8.5 Hz, 1, H$3'$), 5.70 (d, $J = 8.0$ Hz, 1, H$5'$), 6.43 ("t", $J = 1.8$ Hz, 1, H$1'$), 6.48 ("t", $J = 2.3$ Hz, 1, H$2'$), 7.27 (d, $J = 8.1$ Hz, 1, H6), 7.51 ("t", $J = 7.4$ Hz, 2H, Ph), 7.60 ("tt", $J = 1.3$, 7.4 Hz, 1H, Ph), 7.68 ("dd", $J = 1.4$, 7.1 Hz, 2H, Ph), 8.30 (s, 1, NH); $^{13}$CNMR $\delta$ 12.58 (CH), 16.86, 16.94, 17.05, 17.13, 17.20, 17.21, 17.23, 17.35 (CH$_3$), 61.21 (C5'), 73.02 (C3'), 81.38 (C4'), 85.83 (C1'), 102.06
(C5), 124.17 (C2") , 126.57, 129.56, 134.02, 140.57 (Ph), 145.08 (C6), 148.65 (C2), 156.65 (C2"), 162.91 (C4); MS m/z 623 (100, MH^+).

2'-Deoxy-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-[(triphenylgermyl)methylene]uridine [130 (Z)] Treatment of 129 (43 mg, 0.07 mmol) with Ph_3GeH (40 mg, 0.13 mmol; as described for 120a) gave 130 (28 mg, 51%) as a white powder: ^1^H NMR δ 0.91–0.97 (m, 24H, 8 × CH_3), 1.03 (s, 4H, 4 × CH), 3.50 (dt, J = 3.2, 8.7 Hz, 1, H4'), 3.86 (dd, J = 3.2, 12.1 Hz, 1, H5'), 3.91 (dd, J = 3.6, 12.1 Hz, 1, H5''), 4.88 ("dt", J = 2.2, 8.4 Hz, 1, H3'), 5.15 (d, J = 8.1 Hz, 1, H5), 5.83 (t, J = 1.7 Hz, 1, H1'), 6.29 (d, J = 8.1 Hz, 1, H6), 6.77 (t, J = 2.1 Hz, 1, H2''), 7.20–7.26 (m, 9H, Ph), 7.30–7.36 (m, 6H, Ph), 8.28 (s, 1, NH); ^1^C NMR δ 12.60, 12.66, 13.05, 13.65 (CH), 16.92, 17.02, 17.22, 17.24, 17.27, 17.31, 17.36 (CH_3), 61.31 (C5'), 73.50 (C3'), 82.12 (C4'), 85.37 (C1'), 102.24 (C5), 122.63 (C2''), 128.62, 129.53, 134.63, 135.29 (Ph), 141.17 (C6), 149.03 (C2), 155.27 (C2''), 162.21 (C4); MS m/z 787 (50, MH^+, ^7^4Ge), 785 (35, MH^+, ^7^2Ge), 783 (25,MH^+, ^7^0Ge); HRMS calcd for C_{40}H_{53}^{'7^4}GeN_2O_6Si_2 [M+H]^+ 787.2654, found 787.2663.

2'-Deoxy-2'-'[(triphenylgermyl)methylene]uridine [131 (Z)] Bu_4NF (1 M/THF, 0.12 mL, 0.12 mmol) was added to a solution of 130 (31 mg, 0.04 mmol) in THF (2 mL) and the resulting mixture was stirred at ~0°C for 3 hours. Volatiles were evaporated and the residue was partitioned between diethyl ether and water. The aqueous layer was evaporated and the oily residue was column chromatographed (EtOAc) to give 131 (16 mg, 73%) as an amorphous solid: ^1^H NMR (MeOH-d4) δ 3.66–3.73 (m, 2, H4',5'), 3.83–3.89 (m, 1, H5''), 4.77 (dt, J = 2.2, 8.0 Hz, 1, H3'), 5.32 (d, J = 8.0 Hz, H5), 6.14 (t, J = 1.7 Hz, 1, H1'), 6.86 (t, J = 2.2 Hz, 1, H2''), 7.04 (d, J = 8.0 Hz, 1, H6), 7.37–7.43 (m, 9H,
Ph), 7.49–7.52 (m, 6H, Ph); $^{13}$C NMR MeOH-$d_4$ δ 62.33 (C5'), 73.43 (C3'), 85.44 (C4'), 86.93 (C1'), 102.93 (C5), 124.67 (C2''), 129.65, 130.54, 135.76, 136.76 (Ph), 143.85 (C6), 151.61 (C2), 159.02 (C2'), 166.01 (C4); MS $m/z$ 545 (50, MH$^+$, $^{74}$Ge), 543 (35, MH$^+$, $^{72}$Ge), 541 (25, MH$^+$, $^{70}$Ge); HRMS (ESI) calcd for C$_{28}$H$_{26}$N$_2$GeNaO$_5$ [M+Na]$^+$ 567.0951, found 567.0960.

The vinyl sulfones $2a^{117}$, $2b^{132}$, $2c^{132}$, $2e^{117}$, $2f^{133}$, $2g^{134}$, $2h^{117}$ and (α-fluoro)vinyl sulfones $3a^{134}$, $3d^{134}$, $3e^{134}$, $3f^{135}$, $3g^{117}$, $3h^{117}$ were prepared as reported.

$(E)$-2-(3,4-dimethoxyphenyl)-1-phenylsulfonylethene (133d). LHDMS (1.0M; 1.12 mL, 1.12 mmol) was added dropwise to a stirred solution of diethyl (phenylsulfonyl)-methylphosphonate$^{110}$ (292 mg, 1.0 mmol) in THF (10 mL) under N$_2$ at -78 °C. After 30 minutes, 132d (186 mg, 1.12 mmol) was added and the yellow reaction mixture was allowed to warm to -40 °C over 2 h. Saturated NH$_4$Cl/H$_2$O (~ 4 mL) was added and the volatiles were evaporated. The residue was partitioned (H$_2$O//CHCl$_3$) and the organic layer was washed (brine), dried (MgSO$_4$), evaporated and column chromatographed (hexane/EtOAc; 9:1) to give 133d (358 mg, 47%): $^1$H NMR δ 3.78 (s, 3H), 3.82 (s, 3H), 6.73 (d, $J = 15.3$ Hz, 1H), 6.79 (d, $J = 8.3$ Hz, 1H), 6.94 (d, $J = 2.0$ Hz, 1H), 7.03 (dd, $J = 2.0$, 8.3 Hz, 1H), 7.46 ("tt", $J = 1.3$, 8.3 Hz, 2H), 7.52 ("dt", $J = 1.4$, 8.7 Hz, 1H), 7.57 (d, $J = 15.3$ Hz, 1H), 7.88 ("dt", $J = 1.5$, 8.6 Hz, 2H); $^{13}$C NMR δ 55.9 (CH$_3$), 56.0 (CH$_3$), 110.1 (C2), 111.1 (Cα), 123.5 (C5), 124.7 (C6), 125.2 (C1), 127.5 (C2'), 129.3 (C3'), 133.2 (Cβ), 141.2 (C4'), 142.6 (C1'), 149.3 (C4), 151.9 (C3); GC-MS $m/z$ 272 (M$^+$; $t_R = 26.47$ min, E, $t_R = 26.12$ min, Z). MS $m/z$ 304.8 (100, MH$^+$).

$(E/Z)$-1-Fluoro-2-(4-methylphenyl)-1-phenylsulfonylethene (134b). Treatment of diethyl fluoro(phenylsulfonyl)methylphosphonate (515 mg, 1.66 mmol) in THF (10
mL) with 132b (0.22 mL, 1.86 mmol) as described for 133d gave 134b (358 mg, 70%; E/Z, 86:14): 1H NMR δ 2.38 (s, 3 × 0.86H), 2.40 (s, 3 × 0.14H), 6.90 (d, J = 22.5 Hz, 0.14H), 7.05 (d, J = 34.2 Hz, 0.86H), 7.22 (d, J = 7.9 Hz, 2 × 0.86H), 7.40 (d, J = 7.9 Hz, 2 × 0.14H), 7.48 (d, J = 8.0 Hz, 2 × 0.86H), 7.55 (d, J = 7.9 Hz, 2 × 0.14H), 7.61 ("t", J = 7.4 Hz, 2 × 0.86H), 7.70 ("t", J = 6.9 Hz, 0.86H), 7.93 (d, J = 7.9 Hz, 2 × 0.14H), 8.05 (d, J = 7.9 Hz, 2 × 0.86H); 13C NMR (for E-134b) δ 21.4 (CH 3), 119.2 (J = 18.7 Hz, Cβ), 126.7 (C4'), 128.6 (C2), 128.7 (C4), 129.4 (C3), 129.7 (C3'), 130.2 (C2'), 137.7 (C1'), 140.9 (C1), 153.0 (d, J = 302.9 Hz, Ca); 19F NMR δ -112.45 (d, J = 22.0 Hz, 0.14F), -125.85 (d, J = 34.0 Hz, 0.86F); GC-MS m/z 276 (M+; tR = 24.20 min, E, tR = 22.58 min, Z).

(E/Z)-1-Fluoro-2-(4-trifluoromethylphenyl)-1-phenylsulfonylethene (134c).

Treatment of diethyl fluoro(phenylsulfonyl)methylphosphonate (467 mg, 1.6 mmol) in THF (10 mL) with 132c (0.24 mL, 1.8 mmol) as described for 133d gave 134c (475 mg, 95%; E/Z, 9:1): 1H NMR δ 6.89 (d, J = 20.6 Hz, 0.07H, H1), 7.07 (d, J = 33.9 Hz, 0.93H, H1), 7.57-7.72 (m, 7H), 8.01 (d, J = 8.7 Hz, 2H); 13C NMR δ 113.8 (Cβ), 125.9 (CF 3), 127.8 (C4'), 128.7 (C4), 128.8 (C3), 129.5 (C2), 130.3 (C3'), 130.4 (C2'), 134.7 (C1), 137.0 (C1'), 155.2 (J = 308.6 Hz, Ca); 19F NMR δ -62.82 (s, 0.07), -63.06 (s, 0.93F) -109.2 (d, J = 20.7 Hz, 0.07 F), -109.2 (d, J = 33.9 Hz, 0.93 F); MS m/z 329 (100, MH+); GC-MS m/z 330 (M+; tR = 24.53 min, Z, tR = 26.13 min, E).

General Procedure for Thiodesulfonylation. Method A. The vinyl sulfones 133a-g or (α-fluoro)vinyl sulfones 134a-h (0.10 mmol) were dissolved in toluene (2 mL) under a nitrogen atmosphere in a sealed tube. The reaction mixture was degassed for 1 h at ambient temperature, and then thiol (0.20 mmol) and the radical initiator (ACCN or
AIBN; 0.031 mmol) were added. The resulting solution was heated at 115 °C (oil bath) for 8 h and then was evaporated. The resulting brownish residue was partitioned between CHCl₃/brine. The separated organic layer was dried (MgSO₄), evaporated and purified by column chromatography (hexane) to give the corresponding sulfides 135-138(a-g) or (α-fluoro)vinyl sulfides 142-145(a-h).

**Method B.** The vinyl sulfones 133a-g or (α-fluoro)vinyl sulfones 134a-h (0.10 mmol) were suspended in H₂O (2 mL) under a nitrogen atmosphere in a sealed tube. The reaction mixture was degassed for 1 h at ambient temperature, and then thiol (0.20 mmol) and radical initiator (ACCN or AIBN; 0.031 mmol) was added to the heterogenous solution and the reaction mixture was heated at 105 °C (oil bath) for 8 hrs. The resulting brownish residue was partitioned (CHCl₃/H₂O/brine), and the organic layer was dried (MgSO₄), evaporated and purified by column (hexane/EtOAc, 9:1) to give the corresponding sulfides 135-138(a-g) or (α-fluoro)vinyl sulfides 142-145(a-h).

**Method C.** The vinyl sulfones 133a-g or (α-fluoro)vinyl sulfones 134a-h (0.10 mmol) were dissolved in MeOH (2 mL) under a nitrogen atmosphere in a sealed tube. The reaction mixture was degassed for 1 h at ambient temperature, and then thiol (0.20 mmol) and the radical initiator (ACCN or AIBN; 0.031 mmol) were added. The resulting solution was heated at 85 °C (oil bath) for 8 hrs and then evaporated. The resulting brownish residue was partitioned between (CHCl₃/brine). The separated organic layer was dried (MgSO₄), evaporated and purified by column chromatography (hexane) to give the corresponding sulfides 135-138(a-g) or (α-fluoro)vinyl sulfides 142-145(a-h).

*(E/Z)-2-phenyl-1-phenylthioethene (135a).* Treatment of 133a (20 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [AIBN (3.9 mg,
Treatment of 133a (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [ACCN (5.8 mg, 0.024 mmol)] gave 135a (12 mg, 71%: E/Z, 95:5). Treatment of 133a (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [no initiator] gave 135a (1.7 mg, 10%: E/Z, 95:5). Treatment of 133a (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method A [ACCN (5.8 mg, 0.024 mmol)] gave 135a (9.3 mg, 55%: E/Z, 95:5). Treatment of 133a (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method C [AIBN (3.9 mg, 0.024 mmol), EtOH or MeOH (2 mL)] gave 135a (12 mg, 70%: E/Z, 95:5).

*(Z)-2-phenyl-1-phenylthioethene [135a (Z)].* Treatment of 133a (Z) (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method A [AIBN (3.9 mg, 0.024 mmol)] gave 135a (10.2 mg, 60%: E/Z, 95:5). Treatment of 133a (Z) (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [AIBN (3.9 mg, 0.024 mmol)] gave 135a (16.1 mg, 95%: E/Z, 95:5).

Treatment of 133a (Z) (20mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method C [AIBN (3.9 mg, 0.024 mmol), EtOH (2 mL)] gave 135a (13.6mg, 80%: E/Z, 95:5).

*(E/Z)-2-(4-methylphenyl)-1-phenylthioethene (135b).* Treatment of 133b (22.1 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [ACCN
(5.8 mg, 0.024 mmol)] gave 135b (11.4 mg, 63%: E/Z, 85:15): \(^1\)H NMR \(\delta\) 2.25 (s, 3 × 0.85H), 2.27 (s, 3 × 0.15H), 6.36 (d, \(J = 11.0\) Hz, 0.15H), 6.50 (d, \(J = 11.0\) Hz, 0.15H), 6.66 (d, \(J = 16.1\) Hz, 0.85H), 6.76 ((d, \(J = 16.1\) Hz, 0.85H), 7.05 (d, \(J = 8.0\) Hz, 1H), 7.12-7.27 (m, 6H), 7.31-7.43 (m, 2H); GC-MS \(m/z\) 226 (M\(^+\); \(t_R = 21.72\) min, E, \(t_R = 21.53\) min, Z).

Treatment of 133b (22.1 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 \(\mu\)L, 0.16 mmol) by method A [AIBN (3.9 mg, 0.024 mmol)] gave 135b (10 mg, 55%: E/Z, 85:15).

2-(4-Trifluoromethylphenyl)-1-phenylthioethene (135c). Treatment of 133c (25 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 \(\mu\)L, 0.16 mmol) by method A [AIBN (3.9 mg, 0.024 mmol)] gave 135c (13 mg, 59%: E/Z, 95:5): \(^1\)H NMR \(\delta\) 6.56 (d, \(J = 10.8\) Hz, 0.05H), 6.62 (d, \(J = 15.5\) Hz, 0.95H), 6.64 (d, \(J = 10.8\) Hz, 0.05H), 7.01 (d, \(J = 15.6\) Hz, 0.95H), 7.28-7.62 (m, 9H); \(^13\)C NMR \(\delta\); GC-MS \(m/z\) 280 (M\(^+\); \(t_R = 20.55\) min, Z, \(t_R = 20.82\) min, E).

Treatment of 133c (25 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 \(\mu\)L, 0.16 mmol) by method B [AIBN (3.9 mg, 0.024 mmol)] gave 135c (19 mg, 85%: E/Z, 95:5).

Treatment of 133c (25 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 \(\mu\)L, 0.16 mmol) by method C [AIBN (3.9 mg, 0.024 mmol)] gave 135c (21 mg, 95%: E/Z, 95:5).

(E/Z)-2-(3,4-dimethoxyphenyl)-1-phenylthioethene (135d). Treatment of 133d (24.3 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 \(\mu\)L, 0.16 mmol) by method A gave 135d (12 mg, 55%: E/Z, 83:17): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.86 & 3.87 (s, 2 × 3H, 0.83H), 3.88 & 3.92 (s, 2 × 3H, 0.17H), 6.36 (d, \(J = 10.6\) Hz, 0.17H), 6.52 (d, \(J = 10.6\) Hz, 0.17H), 6.72 (s, 0.83H), 6.88 (s, 0.83H), 7.21-7.47 (m, 8H); GC-MS \(m/z\) 272 (M\(^+\); \(t_R = 26.55\) min, E, \(t_R = 26.21\) min, Z).
Treatment of 133d (24.3 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B gave 135d (9.6 mg, 44%: E/Z, 54:45).

Treatment of 133d (24.3 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method C gave 135d (10.9 mg, 50%: E/Z, 85:15).

(Cyclohexylidene)methyl phenyl sulfide (135g). Treatment of 133g (18.9 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) and ACCN (5.8 mg, 0.024 mmol) by Method B gave 135g (5.8 mg, 35%): 1H NMR δ 1.55-1.63 (m, 6H), 2.24 ("t", J = 5.7 Hz, 2H), 2.39 ("t", J = 5.7 Hz, 2H), 5.86 ("s", 1H), 7.18-7.31 (m, 4H), 7.49 (m, 1H); GC-MS m/z 204 (M+; t_R = 21.95 min).

Treatment of 133g (18.9 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method C gave 135g (12 mg, 74%).

2-(4-Methylphenyl)-1-(cyclohexylidene)methyl phenyl sulfide (136g). Treatment of 133g (18.9 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) and AIBN (3.9 mg, 0.024 mmol) by Method C gave 136g (10.5 mg, 60%): 1H NMR δ 1.54-1.59 (m, 6H), 2.20 ("t", J = 5.5 Hz, 2H), 2.29 (s, 3H), 2.36 ("t", J = 5.5 Hz, 2H), 5.86 ("s", 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H); GC-MS m/z 218 (M+; t_R = 20.11 min).

2-Phenyl-1-(4-aminophenylthio)ethene (137a). Treatment of 133a (20 mg, 0.08 mmol) with 4-aminobenzenethiol (20 mg, 0.16 mmol) by method B gave 137a (10 mg, 55%; E/Z, 65:35): 1H NMR δ 3.79 (bs, 2H), 6.36 (d, J = 11.7 Hz, 0.35H), 6.41 (d, J = 15.4 Hz, 0.65H), 6.42 (d, J = 11.8 Hz, 0.35H), 6.80 (d, J = 15.5 Hz, 0.65H) 7.15-7.29 (m, 9H); GC-MS m/z 227 (M+; t_R = 29.20 min, E, t_R = 30.24 min, Z).
4-Trifluoromethylphenyl-1-(4-aminophenylthio)ethene (137c). Treatment of 133c (25 mg, 0.08 mmol) with 4-aminobenzenethiol (20 mg, 0.16 mmol) by method B gave 137c (4.7 mg, 20%; E/Z, 70:30): 1H NMR δ 3.82 (bs, 2H), 6.31 (d, J = 15.4 Hz, 0.7H), 6.41 (d, J = 11.0 Hz, 0.3H), 6.51 (d, J = 10.8 Hz, 0.3H), 6.93 (d, J = 15.6 Hz, 0.7H) 7.25-7.32 (m, 2H), 7.45-7.66 (m, 6H); 19F NMR δ; -62.7 Hz; GC-MS m/z 295 (M⁺; t<sub>R</sub> = 28.74 min, E, t<sub>R</sub> = 28.56 min, Z).

(E/Z)-1-Fluoro-2-phenyl-1-phenylthioethene (142a). Treatment of 134a (22.1 mg, 0.08 mmol; E/Z, 96:4) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [AIBN (3.9 mg, 0.024 mmol)] gave 142a (12 mg, 65%; E/Z, 94:6): 1H NMR δ 6.28 (d, J = 32.5 Hz, 0.94H), 6.76 (d, J = 16.3 Hz, 0.06H), 7.26-7.37 (m, 6H), 7.44-7.53 (m, 4H); 13C NMR (for E-142a) δ 117.9 (d, J = 12.7 Hz, Cβ), 127.2 (C4'), 127.6 (C2), 128.2 (C4), 128.7 (C3), 129.3 (C3'), 129.9 (C2'), 132.2 (C1'), 137.1 (C1), 152.2 (d, J = 310 Hz, Ca); 19F NMR δ -80.33 (d, J = 16.3 Hz, 0.06F), -85.55 (d, J = 32.4 Hz, 0.94F). GC-MS m/z 230 (M⁺; t<sub>R</sub> = 20.3 min, E; t<sub>R</sub> = 19.3 min, Z).

Treatment of 134a (22.1 mg, 0.08 mmol, E/Z, 96:4) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method A [AIBN (3.9 mg, 0.024 mmol)] gave 142a (17 mg, 92%; E/Z, 92:8).

Treatment of 134a (22.1 mg, 0.08 mmol; E/Z, 96:4) with phenyl disulfide (35 mg, 0.16 mmol) method B and C [no thiol, AIBN (3.9 mg, 0.024 mmol)] afforded 142a (55%). Analogous reaction without AIBN gave unchanged 134a (~95%).

(E/Z)-1-Fluoro-2-(4-methylphenyl)-1-phenylthioethene (142b). Treatment of 134b (22.1 mg, 0.08 mmol; E/Z, 86:14) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [ACCN (5.8 mg, 0.024 mmol)] gave 142b (11 mg, 56%; E/Z, 92:8): 1H
NMR δ 2.20 (s, 3H), 6.15 (d, J = 32.6 Hz, 0.92H), 6.64 (d, J = 16.3 Hz, 0.08H), 7.15 (d, J = 8.0 Hz, 2H), 7.25-7.35 (m, 3H), 7.40-7.46 (m, 4H); 13C NMR (for E-142b) δ 21.2 (CH₃), 118.3 (d, J = 13.4 Hz, Cβ), 127.4 (C4'), 128.2 (C2), 128.2 (C4), 129.2 (C3), 129.3 (C3'), 129.6 (C2'), 132.6 (C1'), 138.3 (C1), 151.5 (d, J = 309.0 Hz, Cα); 19F NMR δ -81.33 (d, J = 16.3 Hz, 0.08F), -86.45 (d, J = 32.6 Hz, 0.92F); GC-MS m/z 244 (M⁺; tᵣ = 19.95 min, Z; tᵣ = 21.01 min, E).

Treatment of 134b (22.1 mg, 0.08 mmol, E/Z, 86:14) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method A [AIBN (3.9 mg, 0.024 mmol] gave 142b (11 mg, 82%; E/Z, 93:7).

Treatment of 3b (22.1 mg, 0.08 mmol, E/Z; 86:14) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method C [AIBN (3.9 mg, 0.024 mmol)] gave 142b (18 mg, 92%; E/Z, 92:8).

(E/Z)-1-Fluoro-2-(4-trifluoromethylphenyl)-1-phenylthioethene (142c).

Treatment of 134c (25 mg, 0.08 mmol; E/Z, 9:1) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [AIBN (3.9 mg, 0.024 mmol)] gave 142c (17 mg, 72%; E/Z, 93:7): 1H NMR δ 6.24 (d, J = 32.1 Hz, 0.93H), 6.72 (d, J = 15.7 Hz, 0.07H), 7.18-7.38 (m, 5H), 7.48 ("dd", J = 1.4, 7.5 Hz, 2H), 7.58 (s, 2H); 13C NMR δ 115.2 (d, J =12.3 Hz, Cβ), 125.5 (CF₃), 127.2 (C4'), 127.6 (C3'), 128.2 (C4), 128.8 (C2), 128.9 (C3), 129.1 (C2'), 129.4 (C1), 130.8 (C1'), 137.6 (d, J = 324.0 Hz, Cα); 19F NMR δ -77.14 (d, J = 15.6 Hz, 0.07F), -82.8 (d, J = 32.0 Hz, 0.93F); MS m/z 299 (100, MH⁺); GC-MS m/z 298 (M⁺; tᵣ = 23.09 min, E, tᵣ = 23.18 min, Z).
(E/Z)-1-Fluoro-2-(3,4-dimethoxyphenyl)-1-phenylthioethene (142d).

Treatment of 134d (25.8 mg, 0.08 mmol; E/Z, 97:3) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [ACCN (5.8 mg, 0.024 mmol)] gave 142d (17 mg, 73%; E/Z, 93:7): $^{19}$F NMR δ -81.5 (d, $J = 16.3$ Hz, 0.07F), -88.2 (d, $J = 32.4$ Hz, 0.93F); HRMS calcd for C$_{16}$H$_{15}$FNaO$_2$S [M+Na]$^+$: 313.0675; found: 313.0687; GC-MS (EI) m/z 290 (M$^+$; $t_R = 29.32$ min, E, $t_R = 30.04$ min, Z). E-142d had: $^1$H NMR (CDCl$_3$) δ 3.86 (s, 3H), 3.88 (s, 3H), 6.24 (d, $J = 32.4$ Hz, 0.93H), 6.82 (d, $J = 8.4$ Hz, 0.07H), 7.04 (dd, $J = 2.1$, 8.4 Hz, 1H), 7.15 (d, $J = 1.7$ Hz, 1H), 7.24-7.35 (m, 3H), 7.42-7.46 (m, 2H); $^{13}$C NMR δ 55.8 & 55.9 (CH$_3$), 110.1 (C5), 111.6 (d, $J = 10.1$ Hz, C2), 118.3 (d, $J = 13.2$ Hz, Cβ), 122.2 (d, $J = 7.5$ Hz, C6), 125.9 (d, $J = 6.0$ Hz, C1), 127.5 (C4'), 129.3 (C3'), 129.5 (C4), 132.6 (d, $J = 3.7$ Hz, C1'), 148.8 (C4), 149.1 (d, $J = 3.1$ Hz, C3), 150.6 (d, $J = 301.7$ Hz, Cα); Z-142a had: $^1$H NMR δ 6.74 (d, $J = 16.4$ Hz).

(E/Z)-1-Flouro-4-(phenylbutyl)-1-phenylthioethene (142e). Treatment of 134e (22.3 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) by methods B and C [AIBN (3.9 mg, 0.024 mmol)] gave 142e (2 mg, 10%: E/Z, 70:30): Note: I observed that only the (Z)-sulfone reacts to form the corresponding (E/Z)-sulfide; $^1$H NMR δ 2.47 ("dq", $J = 5.1$, 10.8 Hz, 0.7H), 2.52 (m, 0.3H), 2.64 (t, $J = 8.9$ Hz, 0.3H), 2.67 (t, $J = 10.4$ Hz, 0.3H), 5.38 (dt, $J = 7.6$, 30.3 Hz, 0.7H), 5.68 (dt, $J = 7.8$, 14.2 Hz, 0.3H), 7.11-7.44 (m, 10H); $^{19}$F NMR δ -85.76 (d, $J = 14.1$ Hz, 0.3F), -91.78 ("dt", $J = 2.14$, 30.68 Hz, 0.7F); MS m/z 258 (100, MH$^+$).

[(Cyclohexylidene)(fluoro)methyl phenyl sulfide (142g). Treatment of 134g (20.3 mg, 0.08 mmol) with thiophenol (14.4 mg, 13.4 μL, 0.16 mmol) and AIBN (3.9 mg, 0.024 mmol) by Method B gave 142g (11.6 mg, 65%): $^1$H NMR δ 1.50-1.63 (m, 3H),
2.35-2.43 (m, 2H), 7.16-7.33 (m, 4H), 7.49 (dd, J = 1.5, 8.0 Hz, 1H); 13C NMR δ 26.9, 27.0 (C5), 27.2, 27.3 (C3), 27.6, 27.7 (C4), 126.4, 128.0, 129.1, 137.0 (Ar), 132.2 (d, J = 17.9 Hz, Cβ), 143.4 (d, J = 285.4 Hz, Cα); 19F NMR δ -96.81 (s, 1F); MS m/z 221 (100, MH+).

(E/Z)-1-Fluoro-2-methyl-2-phenyl-1-phenylthioethene (142h). Treatment of 134h (22.1 mg, 0.08 mmol; E/Z, 57:43) with thiopheniol (14.4 mg, 13.4 μL, 0.16 mmol) by method B [AIBN (3.9 mg, 0.024 mmol)] gave 142h (11.3 mg, 58%; E/Z, 50:50): 1H NMR δ 2.19 (d, J = 4.4 Hz, 1.5H), 2.27 (d, J = 4.2 Hz, 1.5H), 7.19-7.51 (m, 10H); 13C NMR δ 18.0, 18.1 (CH3), 126.0, 126.1 (d, J = 15.6 Hz, Cβ), 126.9, 127.0 (C4'), 127.7, 127.8 (C2), 128.1 (C4), 128.1, 128.2 (C3), 128.7, 128.8 (C3'), 129.2, 129.3 (C2'), 133.0, 133.5 (C1'), 139.0, 139.5 (C1), 147.9, 148.3 (d, J = 295.0 Hz, Cα); 19F NMR δ -89.77 (q, J = 4.3, 8.8 Hz, 0.5F), -89.90 ("q", J = 1.8 Hz, 0.5F); GC-MS m/z 244 (M+; tR = 20.61 min, E, tR = 19.30 min, Z).

Analogous treatment of the E-134h (15 mg, 0.05 mmol) with thiophenol (9.0 mg, 8.4 μL, 0.10 mmol) by Method C [AIBN (2.5 mg, 0.015 mmol)] gave 142h (3.1 mg, 85%; E/Z, 1:1).

Analogous treatment of the Z-134h (18 mg, 0.065 mmol) with thiophenol (11.6 mg, 10.8 μL, 0.13 mmol) by Method C [AIBN (3.2 mg, 0.02 mmol)] gave 142h (3.4 mg, 70%; E/Z, 67:33).

(E/Z)-1-Fluoro-2-(4-methylphenyl)-1-(4-methylphenylthio)ethene (143b). Treatment of 134b (44.2 mg, 0.16 mmol; E/Z, 86:14) with p-toluenethiol (59.6 mg, 0.48 mmol) and AIBN (7.8 mg, 0.024 mmol) by Method C gave 143b (37.1 mg, 90%; E/Z, 92:8): 1H NMR δ 2.32 (s, 3H), 2.34 (s, 3H), 6.26 (d, J = 32.8 Hz, 0.92H), 6.72 (d, J =
16.5 Hz, 0.08H), 7.10 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.34-7.42 (m, 4H); 
^{13}C\text{ NMR } \delta 21.1 (CH_3), 23.4 (CH_3), 117.2 (J = 13.1 Hz, C\beta), 128.6 (C2), 128.8 (C4), 129.3 (C3), 129.6 (C3'), 130.1 (C2'), 134.3 (C4'), 136.9 (C4), 137.3 (C1'), 137.9 (C1), 152.2 (d, J = 309.2 Hz, Ca); \ ^{19}F\text{ NMR } \delta -81.6 (d, J = 16.3 Hz, 0.08F), -86.6 (d, J = 32.6 Hz, 0.92F); GC-MS m/z 258 (M^+); t_R = 22.13, Z, t_R = 23.20 min, E).

**(E/Z)-1-Fluoro-2-methyl-2-phenyl-1-(4-methylphenylthio)ethene (143h).**

Treatment of 134h (22.1 mg, 0.08 mmol; E/Z, 57:43) with p-toluenethiol (29.8 mg, 0.24 mmol) and AIBN (3.9 mg, 0.024 mmol) by method B gave 143h (12.0 mg, 59%; E/Z, 50:50): \ ^1H\text{ NMR } \delta 2.15 (d, J = 4.4 Hz, 0.5H), 2.27 (d, J = 3.2 Hz, 0.5H), 2.30 (s, 3H), 2.32 (s, 3H), 7.08-7.43 (m, 9H); \ ^{13}C\text{ NMR } \delta 17.96, 18.00 (CH_3), 20.04, 21.06 (CH_3), 125.06 (d, J = 15.4 Hz, C\beta), 127.57, 127.63 (C4'), 128.04, 128.09 (C2), 128.12, 128.17 (C4), 128.27, 128.31 (C3), 129.49, 129.62 (C3'), 129.93, 130.04 (C2'), 137.14, 137.31 (C1'), 139.38, 139.43 (C1), 148.40, 148.82 (d, J = 291.8 Hz, Ca); \ ^{19}F\text{ NMR } \delta -89.74 (q, J = 4.1, 8.3 Hz, 0.5F), -89.89 (d, J = 1.5 Hz, 0.5F). GC-MS m/z 258 (M^+); t_R = 20.74 min, E, t_R = 22.06 min, Z).

Analogous treatment of the E-134h (15 mg, 0.05 mmol) with p-toluenethiol (18.6 mg, 0.15 mmol) by Method C [AIBN (2.5 mg, 0.015 mmol)] gave 143h (12.4 mg, 96%; E/Z, 64:36).

**(E/Z)-1-Fluoro-2-phenyl-1-(4-aminophenylthio)ethene (144a).**

Treatment of 134a (22.1 mg, 0.08 mmol; E/Z, 96:4) with 4-mercaptoaniline (30 mg, 0.24 mmol) and AIBN (3.9 mg, 0.024 mmol) by method C gave 144a (9 mg, 50%; E/Z, 83:17): \ ^1H\text{ NMR } \delta 3.76 (s, 2H), 6.07 (d, J = 33.3 Hz, 0.83H), 6.53 (d, J = 16.9 Hz, 0.17H), 6.64 (d, J = 8.6 Hz, 2H), 7.18-7.34 (m, 5H), 7.44 (d, J = 8.7 Hz, 2H); \ ^{13}C\text{ NMR (for E-144a) } \delta 114.0 (d, J
= 12.4 Hz, Cβ), 127.6 (C4'), 127.7 (C2), 128.2 (C4), 128.5 (C3), 128.6 (C3'), 128.8 (C2'), 129.1 (C1'), 129.3 (C1), 152.3 (d, J = 310 Hz, Cα); $^{19}$F NMR δ -81.40 (d, $J = 16.9$ Hz, 0.17F), -86.51 (d, $J = 33.2$ Hz, 0.83F); GC-MS $m/z$ 245 (M$^+$; $t_R$ = 24.95 min, Z, $t_R$ = 25.05 min, E); HRMS calcd for C$_{14}$H$_{13}$FN$_1$S [M+H]$^+$: 246.0753; found: 246.0755.

($E$/Z)-1-Fluoro-2-(4-methylphenyl)-1-(4-carboxyphenylthio)ethene  (145b). Treatment of 134b (22.1 mg, 0.08 mmol; E/Z, 86:14) with 4-mercaptobenzoic acid (36.9 mg, 0.24 mmol) and AIBN (5.8 mg, 0.024 mmol) by method C and recrystallized in MeOH gave 145b (16 mg, 69%; E/Z, 94:6): $^1$H NMR δ 2.35 (s, 3H), 6.36 (d, $J = 32.5$ Hz, 0.94H), 6.9 (d, $J = 15.9$ Hz, 0.06H), 7.31-7.59 (m, 7H), 8.12 (d, $J = 8.2$ Hz, 1H); $^{19}$F NMR δ -81.92 (d, $J = 16.0$ Hz, 0.06F), -87.25 (d, $J = 32.3$ Hz, 0.94F).

($E$/Z)-1-Fluoro-2-methyl-2-phenyl-1-(4-carboxyphenylthio)ethene  (145h). Treatment of 134h (22.1 mg, 0.08 mmol; E/Z, 57:43) with 4-mercaptobenzoic acid (36.9 mg, 0.24 mmol) and AIBN (3.9 mg, 0.024 mmol) by method C gave 145h (10.2 mg, 42%; E/Z, 55:45): $^1$H NMR δ 2.22 (d, $J = 4.4$ Hz, 3 × 0.55H), 2.27 (d, $J = 3.3$ Hz, 3 × 0.45H), 3.86 (s, 3 × 0.55H), 3.87 (s, 3 × 0.45H), 7.22-7.47 (m, 7H), 7.91-7.97 (m, 2H); $^{19}$F NMR δ -90.51 ("q" $J = 4.1$, 8.5 Hz, 0.55H), -90.57 (d, $J = 1.9$ Hz, 0.45H); GC-MS ($t_R$ = 24.60 min, E; $t_R$ = 25.84 min, Z).

($E$/Z)-1-Fluoro-2-(3,5-dimethoxy)-1-phenylsulfonylethene  (146a). Treatment of 146 (181 mg, 1.09 mmol) with diethyl fluoro(phenylsulfonyl)-methylphosphonate (250 mg, 0.08 mmol) in THF (5 mL) as described for 134b gave 146a (285 mg, 81%; E/Z, 78:22): $^{19}$F NMR (CDCl$_3$) δ -111.05 (d, $J = 21.8$ Hz, 0.22F), -123.58 (d, $J = 34.2$ Hz, 0.78F); $E$-146a had: $^1$H NMR (CDCl$_3$) δ 3.76 (s, 6H, 6.48 (t, $J = 2.2$ Hz, 1H), 6.69...
(E/Z)-1-Fluoro-2-(3-5-dimethoxy)-1-phenylthioethene (146b). Treatment of 146a (E/Z, 78:22, 103 mg, 0.32 mmol) with thiophenol (57.6 mg, 53.6 μL, 0.64 mmol) by method B gave 146b (E/Z, 90:10, 70 mg, 75%): 1H NMR (CDCl3) δ 6.82 (d, J = 21.8 Hz).

Z-146b had: 1H NMR δ 6.70 (d, J = 16.8 Hz).

E/Z-1-Fluoro-2-(3-methoxy-5-tert-butylidemethylsilyloxyphenyl)-1-phenylsulfonylethene (149). Treatment of diethyl fluoro(phenylsulfonyl)methylphosphonate (135 mg, 0.044 mmol) in THF (5 mL) with 148136 (157 mg, 0.59 mmol) as described for 134b gave 149 (136 mg, 75%; E/Z, 89:11): 19F NMR (CDCl3) δ -111.1 (d, J = 21.9 Hz, 0.11F), -123.9 (d, J = 34.2 Hz, 0.89F); GC–MS (EI) m/z 422 (M⁺; tR = 29.21 min, Z, tR = 30.89 min, E). E-149 had: 1H NMR (CDCl3) δ 0.16 (s, 6H), 0.95 (s, 9H), 3.74 (s, 3H), 6.42 (t, J = 2.2 Hz, 1H), 6.66 ("t", J = 1.7 Hz, 1H), 6.71 ("t", J = 1.8 Hz, 1H), 6.94 (d, J = 34.3 Hz, 1H), 7.50-7.60 (m, 2H), 7.62-7.70 (m, 1H), 7.99 ("d", J = 7.5 Hz, 2H); 13C NMR (CDCl3) δ -4.4 (SiCH3), 18.2 [C(CH3)3], 25.7 [C(CH3)3], 55.4 (OCH3), 108.5 (d, J = 7.7 Hz, C2'), 108.7 (C4'), 114.5 (d, J = 7.6 Hz, C6'), 118.7 (d, J = ...
20.3 Hz, Cβ), 128.7 (C2), 129.5 (C3), 130.8 (d, J = 3.7 Hz, C4), 134.4 (C1'), 137.5 (C1), 153.8 (d, J = 305.9 Hz, Cα), 157.0 (C5'), 160.9 (C3'). Z-149 had: \(^1\)H NMR δ 6.80 (d, J = 21.9 Hz).

**(E/Z)-1-Fluoro-2-(3-methoxy-5-tert-butyldimethylsilyloxyphenyl)-1-phenylthioethene (150).** Treatment of 149 (E/Z, 89:11, 135 mg, 0.32 mmol) with thiophenol (50.4 mg, 47.2 µL, 0.56 mmol) by method C gave 150 (E/Z, 90:10, 101 mg, 81%): \(^{19}\)F NMR (CDCl\(_3\)) δ -79.6 (d, J = 16.3 Hz, 0.10F), -84.6 (d, J = 32.1 Hz, 0.90F); GC–MS (EI) m/z 390 (M\(^+\); t\(_R\) = 27.31 min, Z, t\(_R\) = 28.60 min, E). E-150 had: \(^1\)H NMR (CDCl\(_3\)) δ 6.80 (d, J = 21.9 Hz).

**(E/Z)-1-Fluoro-2-(3-methoxy-5-hydroxyphenyl)-1-phenylthioethene (151a).** Compound 150 (40 mg, 0.10 mmol) was dissolved in THF (1.5 mL) and placed in an ice-bath at 0 °C for 10 minutes. Add TBAF (1M/THF; 71 µL, 0.071 mmol) and stir for an additional 25 minutes at 0 °C. The volatiles were evaporated in vacuo and the residue was partitioned (CHCl\(_3\)/H\(_2\)O/NaHCO\(_3\)). The organic layer was washed (brine), dried (MgSO\(_4\)), evaporated and purified on column chromatography (CHCl\(_3\)) to give 151a (27 mg, 98%, E/Z, 90:10): \(^{19}\)F NMR (CDCl\(_3\)) δ -79.4 (d, J = 16.5 Hz, 0.10F), -84.0 (d, J = 32.0 Hz, 0.90F); GC–MS (EI) m/z 276 (M\(^+\); t\(_R\) = 25.39 min, Z, t\(_R\) = 26.64 min, E). E-
**151a** had: $^1$H NMR (CDCl$_3$) δ 3.71 (s, 3H), 6.13 (d, $J = 31.9$ Hz, 1H), 6.32 (t, $J = 2.2$ Hz, 1H), 6.60 ("t", $J = 1.9$ Hz, 2H), 7.22-7.27 (m, 1H), 7.28-7.33 (m, 2H), 7.36-7.44 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 55.4 (OCH$_3$), 101.7 (C4'), 107.2 (d, $J = 7.7$ Hz, C2'), 108.3 (d, $J = 8.6$ Hz, C6'), 117.2 (d, $J = 12.3$ Hz, Cβ), 127.8 (C4), 129.3 (C3), 130.1 (C2), 131.9 (d, $J = 3.0$ Hz, C1), 134.8 (d, $J = 5.7$ Hz, C1), 152.9 (d, $J = 311.0$ Hz, Ca), 156.7 (C5'), 160.9 (C3'). Z-151a had: $^1$H NMR δ 6.63 (d, $J = 16.7$ Hz).

*(E/Z)-1-Fluoro-2-(3-methoxy-5-hydroxyphenyl)-1-phenylsulfonylethylene* (152). Desilylation of 149 (E/Z, 89:11, 35 mg, 0.083 mmol) in THF (1 mL) with TBAF (1M/THF; 59 µL, 0.059 mmol) as described for 151 gave 152 (24 mg, 94%, E/Z, 91:9): $^{19}$F NMR (CDCl$_3$) δ -111.0 (d, $J = 21.8$ Hz, 0.09F), -123.5 (d, $J = 34.0$ Hz, 0.91F); $^1$H NMR (CDCl$_3$) δ 3.72 (s, 3H), 6.44 (t, $J = 2.3$ Hz, 1H), 6.64 ("t", $J = 2.1$ Hz, 1H), 6.66 ("t", $J = 2.0$ Hz, 1H), 6.92 (d, $J = 34.2$ Hz, 1H), 7.49-7.60 (m, 2H), 7.63-7.70 (m, 1H), 7.98 ("d", $J = 7.4$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 55.4 (OCH$_3$), 108.5 (C2'), 108.3 (d, $J = 7.3$ Hz, C4'), 109.7 (d, $J = 7.6$ Hz, C6'), 118.7 (d, $J = 19.8$ Hz, Cβ), 128.7 (C2), 129.5 (C3), 131.0 (C1'), 134.5 (C4), 137.3 (C1), 153.7 (d, $J = 305.0$ Hz, Ca), 157.2 (C5'), 161.1 (C3'); Z-152 had: $^1$H NMR δ 6.78 (d, $J = 21.8$ Hz).

*(E)-1-Fluoro-2-(3-methoxy-5-tert-butyldimethylsilyloxyphenyl)-1-phenylsulfinylene* (153). Compound 150 (E/Z, 90:10, 50 mg, 0.13 mmol) was dissolved in CH$_2$Cl$_2$ and cooled to -40 °C. m-CPBA (11.01 mg, 0.064 mmol) dissolved in CH$_2$Cl$_2$ was added to the sulfide solution at -40 °C with continuous stirring. Additional portion of m-CPBA (11.0 mg, 0.064 mmol) solution was added dropwise and continued stirring for 30 mins at -40 °C. The solution was washed with Na$_2$S$_2$O$_4$, aqueous NaHCO$_3$ and water, giving after silica gel column chromatography (CHCl$_3$) pure 153 (44 mg,
85%): $^{19}$F NMR (CDCl$_3$) $\delta$ -121.61 (d, $J$ = 36.7 Hz, 1F); GC–MS (EI) m/z 406 (M$^+$; $t_R$ = 30.62 min, $E$). $^1$H NMR (CDCl$_3$) $\delta$ 0.16 (s, 6H), 0.95 (s, 9H), 3.74 (s, 3H), 6.37 (t, $J$ = 2.2 Hz, 1H), 6.53 (d, $J$ = 36.7 Hz, 1H), 6.62 ("t", $J$ = 1.6 Hz, 1H), 6.69 ("t", $J$ = 1.7 Hz, 1H), 7.51-7.56 (m, 6H), 7.72-7.77 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ -4.4 (SiCH$_3$), 18.2 [C(CH$_3$)$_3$], 25.6 [C(CH$_3$)$_3$], 55.3 (OCH$_3$), 107.6 (C2'), 107.9 (C4'), 108.0 (C6'), 113.9 (d, $J$ = 7.0 Hz, C$\beta$), 125.4 (C3), 129.5 (C2), 131.9 (C1'), 132.1 (C4), 140.6 (C1), 156.9 (C5'), 158.8 (d, $J$ = 319.7 Hz, C$\alpha$), 160.8 (C3').

**(E)-1-Fluoro-2-(3-methoxy-5-hydroxyphenyl)-1-phenylsulfineylethene** (154). Desilylation of 153 (44 mg, 0.11 mmol) with TBAF (1M/THF; 44 µL, 0.044 mmol) in THF (1 mL) as described for 151 gave 154 (29 mg, 90%): $^{19}$F NMR (CDCl$_3$) $\delta$ -121.61 (d, $J$ = 36.7 Hz, 1F); GC–MS (EI) m/z 292 (M$^+$; $t_R$ = 28.95 min, $E$). $^1$H NMR (CDCl$_3$) $\delta$ 3.72 (s, 3H), 6.42 (t, $J$ = 2.1 Hz, 1H), 6.54 (d, $J$ = 36.4 Hz, 1H), 6.61 ("t", $J$ = 1.5 Hz, 1H), 6.74 ("t", $J$ = 1.6 Hz, 1H), 7.00 (s, 1H), 7.49-7.55 (m, 6H), 7.71-7.74 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 55.4 (OCH$_3$), 103.1 (C4'), 107.4 (d, $J$ = 7.2 Hz, C4'), 109.3 (d, $J$ = 6.9 Hz, C6'), 112.9 (s, C$\beta$), 125.5 (C3), 129.6 (C2), 131.8 (C1'), 132.3 (C4), 139.7 (C1), 157.7 (C5'), 157.9 (d, $J$ = 319.7 Hz, C$\alpha$), 161.1 (C3').

**Methyl phenyl styryl sulfonium ion** (155). To a solution of silver tetrafluoroborate (647 mg, 3.29 mmol) compound 135a (100 mg, 0.47 mmol) was added in dry 1,2-dichloroethane (15 mL) at room temperature under a nitrogen atmosphere. To the resulting mixture, a solution of methyl iodide (456 mg, 200 µL, 3.29 mmol) in 1,2-dichloroethane (5 mL) was added dropwise via syringe, whereupon the reaction mixture became cloudy and a yellow solid (silver iodide) slowly precipitated out. The heterogeneous mixture was stirred at ambient temperature for 2 days. The mixture was
filtered off using a fritted Buchner funnel to remove AgI. The yellow solid was washed with 1,2-dichloroethane (2 x 10 mL) and the combined filtrates were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure to yield 155 (102 mg, 70%): ¹H NMR δ 1.24 (s, 3H), 6.84 (d, J = 15.4 Hz, 1H), 7.66 (d, J = 15.4 Hz, 1H), 7.38-8.10 (m, 10H).

**Methyl (β-fluorostyryl) phenyl sulfonium ion (156).** Treatment of 142a (100 mg, 0.44 mmol) with silver tetrafluoroborate (524 mg, 3.1 mmol), as described for 155, gave 156 (117 mg, 80%): ¹H NMR δ 1.18 (s, 3H), 7.28 (d, J = 37.5 Hz, 1H), 7.61-7.74 (m, 6H), 7.90-7.96 (m, 4H); ¹⁹F NMR δ -121.13 (d, J = 36.0 Hz, 1F).

**Attempted methylation of selected nucleophiles with methyl phenyl styryl sulfonium ion (155).**

A solution of propanethiol (2.8 mg, 3 µL, 0.03 mmol) containing TEA (2.8 mg, 3 µL, 0.03 mmol) in DMF (0.25 mL) was added to a stirred solution of 155 (5 mg, 0.017 mmol) in DMF (0.3 mL). The reaction mixture was stirred at ambient temperature for 15 minutes to give vinyl sulfide 135a as judged by T.L.C., ¹H NMR and GC/MS analysis.

Analogous treatment of phenol (2.8 mg, 3 µL, 0.03 mmol) with 155 (5 mg, 0.017 mmol) afforded vinyl sulfide 135a as judged by TLC, ¹H NMR and GC/MS.

Treatment of imidazole (2.0 mg, 0.03 mmol) containing NaH (1.0 mg, 0.03 mmol) in DMF (0.25 mL) with 155 (5 mg, 0.017 mmol) dissolved in DMF (0.3 mL) at ambient temperature for 15 minutes yielded vinyl sulfide 135a as judged by TLC, ¹H NMR and GC/MS.
Attempted methylation of selected nucleophiles with methyl (β-fluorostyryl) phenyl sulfonium ion (156).

A solution of propanethiol (5.7 mg, 7 µL, 0.075 mmol) containing NaH (2.0 mg, 0.075 mmol) in DMF (0.25 mL) was added to a stirred solution of 156 (15 mg, 0.05 mmol) in DMF (0.3 mL). The reaction mixture was stirred at ambient temperature for 15 minutes to afford α-(fluoro)vinyl sulfide 142a as judged by TLC, \(^1\)H NMR, \(^{19}\)F NMR and GC/MS.

Analogous treatment of benzenethiol (3.4 mg, 2 µL, 0.06 mmol) with 156 (10 mg, 0.03 mmol) in DMF (0.3 mL) afforded α-(fluoro)vinyl sulfide 142a as judged by TLC, \(^1\)H NMR, \(^{19}\)F NMR and GC/MS. The thioanisole (MeSPh) was also detected from the reaction mixture with GC/MS [\(m/z\) 124 (M\(^+\); \(t_R = 7.51\) min)]

A solution of \(p\)-toluenethiol (6.1 mg, 0.05 mmol) containing TEA (3.7 mg, 4.7 µL, 0.05 mmol) in DMF (0.20 mL) was added to a stirred solution of 156 (10 mg, 0.03 mmol) in DMF (0.2 mL). The reaction mixture was stirred at ambient temperature for 35 minutes to afford α-(fluoro)vinyl sulfide 142a as judged by TLC, \(^1\)H NMR, \(^{19}\)F NMR and GC/MS. Also detected from the reaction mixture was addition product 158; GC/MS [\(m/z\) 354 (M\(^+\); \(t_R = 9.34\) min)] proving that the thiol was added to the β-carbon, while the methyl group was transferred to an amino acid residue.
5. CONCLUSION

I have designed and synthesized S-adenosyl-L-homocysteine analogues with the C5' and sulfur atom in the adenosylhomocysteine moiety replaced by a vinyl or (α-halo)vinyl unit to further probe the "hydrolytic" activity of the enzyme. Negishi Pd-catalyzed cross-coupling between the protected 5'-deoxy-5'-(iodomethylene)adenosine and the readily available alkylzinc bromide (EtO$_2$C(CH$_2$)$_3$ZnBr) afforded 5-(5'-deoxy-2',3'-O-isopropylideneadenosin-5'-ylidene)-pentanoate as a single $E$-isomer. Deacetonization with TFA/H$_2$O followed by saponification with NaOH/H$_2$O provided the fully deprotected 10-carbon analogue of S-adenosyl-L-homocysteine. Palladium-catalyzed selective monoalkylation between ($E/Z$) 5'- (bromofluoromethylene)-5'-deoxy-adenosine with alkylzinc bromides yielded a mixture of geometrical isomers of ethyl 5-fluoro-5-(5'-deoxy-2',3'-O-isopropylideneadenosin-5'-ylidene)pentanoate. Deprotection of this compound afforded a 10-carbon analogue of S-adenosyl-L-homocysteine with a 6'-fluoro(vinyl) unit.

The 5',6'-vinyl adenine nucleosides were tested against human *T. cruzi* and AdoHcy hydrolase. The most active inhibitors were found to be 10-carbon non-halogenated vinylic analogues. The 6'-fluorovinylc analogues proved to have a lower activity then its non-fluorinated counterpart, perhaps in accordance with the fact that 5'-deoxy-5'-(fluoromethylene)adenosine showed the lowest enzyme inactivation efficiency among all 5'-halomethylene derivatives. It was also found that the free carboxylic acid derivatives have a time-dependent inactivation of the enzyme.

I developed the germyl desulfonylation methodology for the synthesis of novel pyrimidine and purine nucleoside analogues modified at the sugar moieties with vinyl
germane functionalities, and further tested their application towards the synthesis of vinyl halides. The auxiliary vinyl sulfone precursors were synthesized by treating nucleoside 5'-aldehyde derivatives with sulfonyl-stabilized Wittig reagents. The pyrimidine and purine nucleosides underwent desulfonation with either trialkyl- or triarylgermanes giving single 1-\{6-[tributyl- or triphenylgermyl]-5,6-dideoxy-2,3-O-isopropylidene-\beta-D-ribohex-5(\textit{E})-enofuranosyl\} uracil and the corresponding adenine counterpart. The 5'-(tributylgermyl)methylene-5'-deoxyadenosine and uridine derivatives underwent efficient halodegermylation reaction upon treatment with \textit{N}-bromosuccinimide (NBS) or \textit{N}-iodosuccinimide (NIS) to give the 5'-deoxy-5-halomethylene nucleosides. It was found that TFA effected simultaneous protiodegermylation and removal of the isopropylidene protecting group from the vinyl 6'-tributylgermanes (alkyl germanes) to produce 5'-deoxy-5'-methyleneadenosine. On the other hand, the vinyl triphenylgermane (aryl germanes) counterparts were found to be stable under acidic conditions and towards treatment with NBS or NIS.

Germydesulfonation was also successfully applied to the synthesis of multi-substituted alkenes located at C2' of the nucleoside. The vinyl 2'-phenylsulfone underwent germyldesulfonation with \textit{Ph}_3\text{GeH} to produce 2'-deoxy-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-[\{triphenylgermyl\}methylene]uridine as a single \textit{Z}-isomer. Desilylation with TBAF produced 2'-deoxy-2'-[\{triphenylgermyl\}methylene]uridine. Thus, germyldesulfonation reaction was found to effectively remove the sulfonyl group from either the exomethylene or isolated double bond present in the sugar moieties of nucleosides.
I developed radical-mediated thiodesulfonylations of vinyl and ($\alpha$-fluoro)vinyl sulfones with aryl thiols to provide access to vinyl and the virtually unknown class of ($\alpha$-fluoro)vinyl sulfides. Reaction involving the conjugated vinyl or $\alpha$-(fluoro)vinyl sulfones with benzenethiol in the presence of 1,1'-azobis(cyclohexane-carbonitrile) as a radical initiator at reflux in toluene produced the corresponding vinyl or $\alpha$-(fluoro)vinyl sulfides. This type of radical thiodesulfonylation reaction was also successful in aqueous medium. In both fluorinated or unfluorinated cases, thiodesulfonilation appeared fairly general since sulfones with the alkyl (Me), electron-withdrawing (CF$_3$), or electron-donating (MeO) substituents on the phenyl ring attached to the double bond also proceeded efficiently to afford either vinyl or ($\alpha$-fluoro)vinyl sulfides. GC–MS and $^1$H NMR analysis showed that radical-mediated thiodesulfonylation of the vinyl sulfones occurred with retention of the $E$ stereochemistry although small amounts of the $Z$ isomers were also detected. In contrast, the thiodesulfonilation of $\alpha$-(fluoro)vinyl sulfones produced mostly inseparable mixture of $E/Z$ isomers of $\alpha$-(fluoro)vinyl sulfides. The relative kinetics of thiodesulfonylation reaction was studied with both vinyl and ($\alpha$-fluoro)vinyl sulfones. It was found that ($\alpha$-fluoro)vinyl sulfides were approximately formed 4 times faster than its vinyl sulfide counterpart.

Thiodesulfonilation methodology was applied towards the synthesis of the fluorinated analogue of the known antibacterial agent, 2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene, which contains vinyl sulfide functionality. Thiodesulfonilation of the suitably constructed ($\alpha$-fluoro)vinyl sulfone precursor with benzenethiol effected thiodesulfonylation and subsequent deprotection afforded ($E/Z$)-1-fluoro-2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene. I also synthesized other ($\alpha$-fluoro)vinyl analogues
of 2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene, containing a sulfonyl or sulfoxide moiety. These analogues were tested against *Mycobacterium smegmatis*. Results showed that the fluorinated and non-fluorinated vinyl sulfides have a similar antibacterial activity. Data obtained also showed that oxidization of the sulfur atom to the sulfoxide or sulfone actually removes activity from the analogue; and that the styryl group is required to have a meta hydroxy/methoxy pattern in order to possess antibacterial activity.

*S*-Alkylation of alkenyl or \((\alpha\text{-fluoro})\)alkenyl phenyl sulfide with iodomethane and silver tetrafluoroborate generated quantitatively the alkenyl or \((\alpha\text{-fluoro})\)alkenyl methyl phenyl sulfonium salts. \(^1\)H NMR and \(^{19}\)F NMR analysis showed that methylation of the sulfide occurred with retention of the \(E\) stereochemistry of the double bond. These sulfonium ions were found to be a good alkyl group donor and transfer a methyl group to common functionalities present in amino acids such as alkyl or aryl thiols, phenols and amino groups in the presence of a base.
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Publications

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**Communications**

1. **Wnuk, S. F.; Sacasa, P. R.; Lewandowska, E.** Stereocontrolled synthesis of sugar-modified diene analogues of adenosine and uridine via Stille coupling. 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002.


**Affiliations**

- Chemistry GSO
- American Chemical Society
- South Florida American Chemical Society
- Sigma Xi