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# Developing of Germyldesulonylation 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 (α-FLUORO)VINYL SULFIDES.

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by

Pablo R. Sacasa

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To: Dean Kenneth Furton
College of Arts and Sciences

This dissertation, written by Pablo R. Sacasa, and entitled Developing of Germyldesulonylation 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

The dissertation of Pablo R. Sacasa is approved.

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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 work place.

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 (AdoHcy) hydrolase effects hydrolytic cleavage of AdoHcy to produce both adenosine and L-homocysteine and is a feedback inhibitor of *S*-adenosyl-L-methionine (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 germyldesulonylation utilizing less toxic germane hydrides. Treatment of the protected (*E*)-5'-deoxy-5'-[(*p*-toluenesulfonyl)-methylene]uridine and adenosine derivatives with tributyl- or triphenylgermane hydride effected radical-mediated germyldesulfonylations to give 5'-(tributyl- or triphenylgermyl)methylene-5'-deoxynucleoside derivatives as single (*E*)-isomers. Analogous treatment of 2'-deoxy-2'-[(phenylsulfonyl)methylene]uridine with $Ph_3GeH$ afforded the corresponding vinyl triphenylgermane product. Stereoselective halodegermylation of the (*E*)-5'-(tributylgermyl)-methylene-5'-deoxy nucleosides with NIS or NBS provided the Wittig-type (*E*)-5'-deoxy-5'-(halomethylene) nucleosides quantitatively.

Radical-mediated thiodesulfonylation of the readily available vinyl and (α-fluoro) vinyl sulfones with aryl thiols in organic or aqueous medium to provide a bench and environmentally friendly protocol to access (α-fluoro)vinyl sulfides were developed. Methylation of the vinyl or (α-fluoro)vinyl phenyl sulfide gave access to the corresponding vinyl or (α-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).[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]

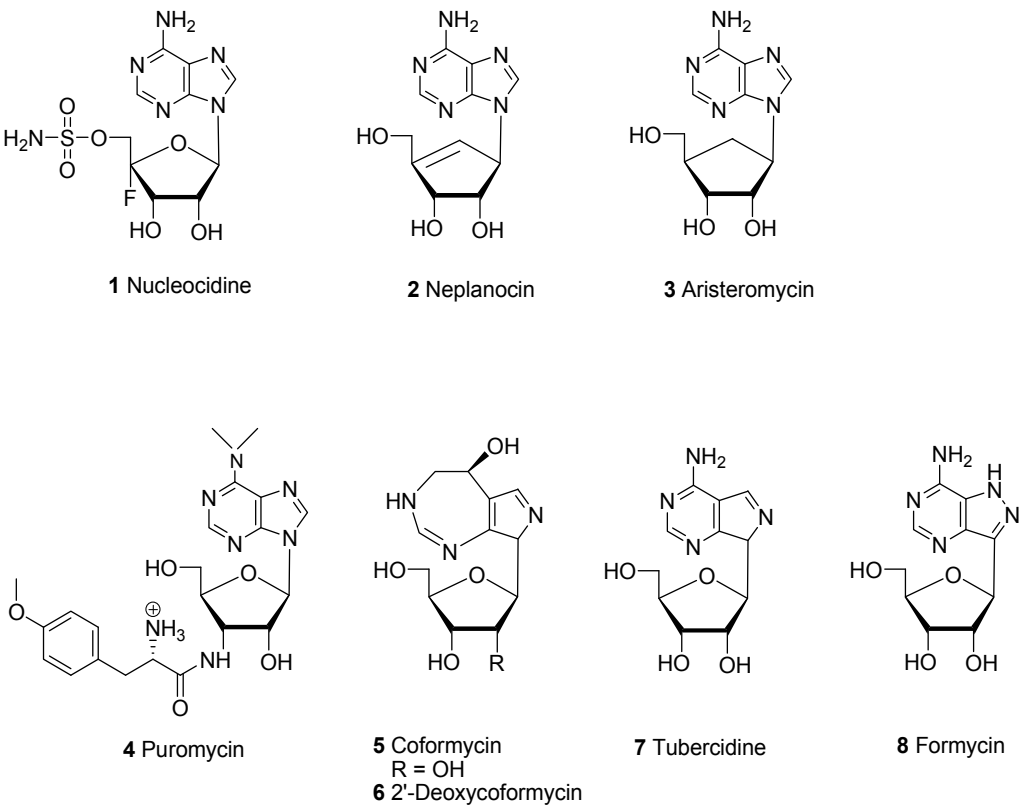



**Figure 1.** Selected Nucleoside Antibiotics.

Affinity labeling agents are reactive compounds that have an arrangement associated with that of the substrate of the target enzyme.[3] 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.[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. An overview of *S*-Adenosyl-L-Homocysteine Hydrolase.

### 1.1.1. Biological Functions of *S*-Adenosyl-L-Homocysteine Hydrolase

*S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase) effects hydrolytic cleavage of AdoHcy to produce both adenosine (Ado) and L-homocysteine (Hcy) and is a feedback inhibitor of *S*-adenosyl-L-methionine (SAM or AdoMet).[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.[8-10]

*S*-Adenosyl-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.[11] 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).[5-7]

A side-reaction catalyzed by AdoHcy hydrolase is the conversion of adenosine to adenine,[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 *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.

*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.[12] It has been proven in clinical studies that elevated plasma levels of Hcy in humans is linked to coronary heart disease.[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.[13,14]

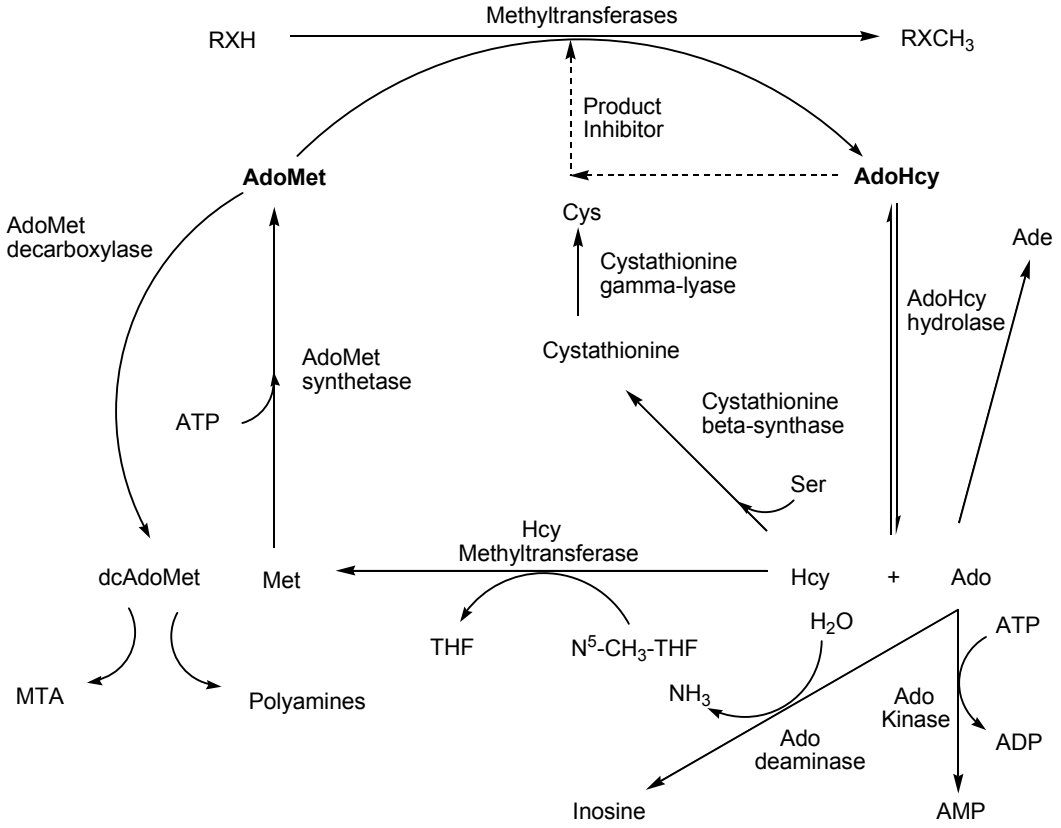



**Figure 2.** Biosynthesis Pathway and Metabolism of *S*-Adenosyl-L-Homocysteine and *S*-Adenosyl-L-Methionine.

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.[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.[15] In copper-deficient mice there is a 45% decrease in the hepatic level of AdoHcy.[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 $R_I$ 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 attacted 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.

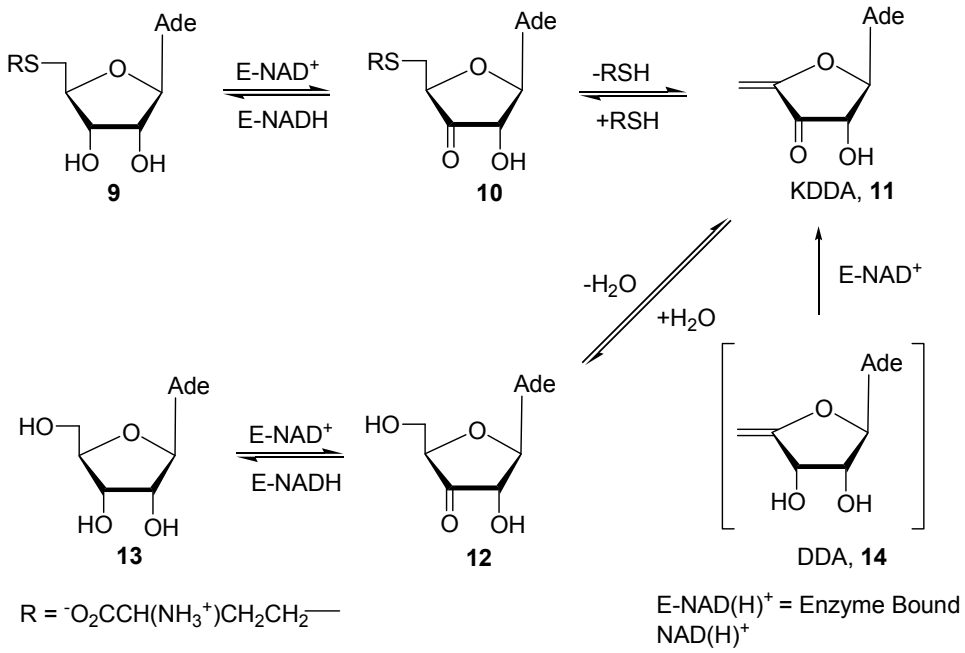



**Figure 3.** Proposed Mechanism for *S*-Adenosyl-L-Homocysteine Hydrolase.

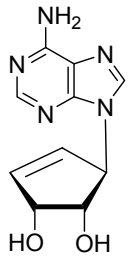
Porter and Boyd showed that neither the apoenzyme nor the reduced form of *S*-adenosyl-L-homocysteine hydrolase (E•NADH) was catalytically active.[24] Porter and Boyds' mechanism suggest that breakage of the C5'-S bond (elimination of the Hcy from the 3'-keto-AdoHcy) and the formation of C5'-O bond (addition of water to the KDDA, **11**) were dependent on the oxidative activity of the enzyme. Parry and Askonas studied

the stereochemistry of this reaction[25] and found *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 *syn* geometry.

Palmer and Abeles made the assumption that the mechanism;[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.[26] Borchardt and coworkers later demonstrated that these two catalytic activities of AdoHcy hydrolase were independent of one another.[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 ($NAD^+$) 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).[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.[14]

The x-ray crystal structure of substrate-bound NADH from human AdoHcy hydrolase was determined.[28] The pure NADH form of the enzyme was inactivated with 9-(2,3-dihyroxycyclopent-4-en-1-yl)adenine (DHCeA, **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.[14b,28] A crystal structure obtained from the liver of a rat in a substrate free $NAD^+$ showed an open catalytic site in the absence of substrate.[29] The experiment helped identify Glu55 as a proton acceptor from the 3'-OH during the abstraction of the H3' by $NAD^+$. 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 $NAD^+$. 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.




**15**

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

### 1.1.3. Hydrolytic Activity of *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).[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 *m*-chloroperoxybenzoic acid (*m*-CPBA) gave the α-fluoro sulfoxide diastereomers **22**.[30b,31] Thermal elimination of sulfenic acid (Figure 6) from **22** and deprotection gave the vinyl fluoride **16** as *E*/*Z* isomers.[30] The most important step in this reaction sequence was fluorination of sulfoxide **19**, or thioether **20** using DAST/$SbCl_3$ combinations developed by Wnuk and Robins.[32]

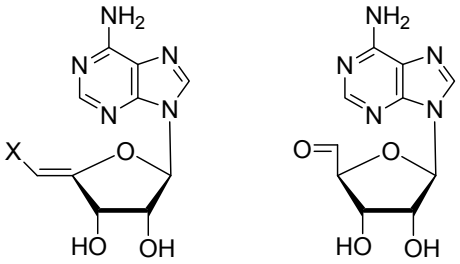



**Figure 5.** Selected Inhibitors of *S*-Adenosyl-L-Homocysteine Hydrolase.

Borchardt and coworkers proved[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.[27,33] The Ado-5'-aldehyde **18** was independently synthesized and shown to be a potent inhibitor of AdoHcy hydrolase.[34]

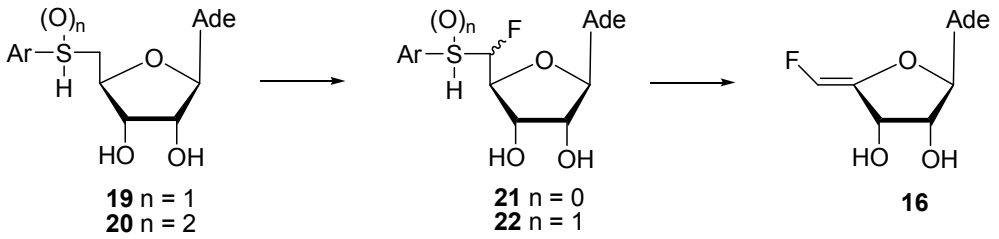
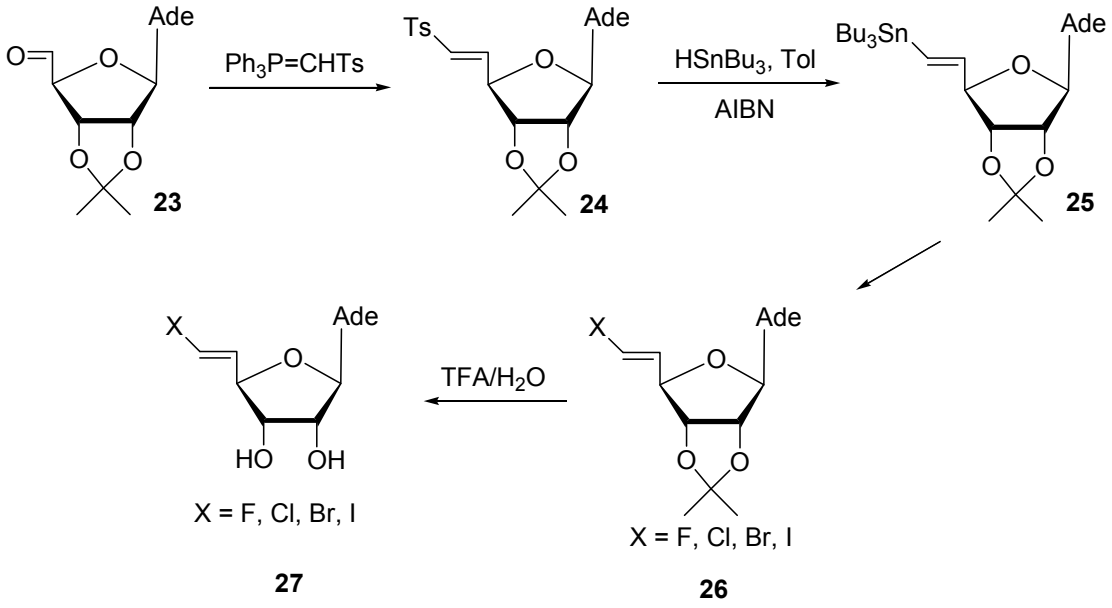



**Figure 6.** Synthesis of the 5'-Fluoro(vinyl)adenosine.

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).[35] Thus, Moffatt oxidation of the 2',3'-*O*-isopropylideneadenosine and treatment of the crude 5'-aldehyde **23** with [(*p*-tolylsulfonyl)methylene]-triphenylphosphorane, $Ph_3P$=CHTs, afforded the 6'-tosyl(vinyl)-sulfone **24** with the *E* isomer being the major product.[36] Radical stannyldesulfonylation[35] ($Bu_3SnH$/AIBN/toluene/Δ) of **24** produced separable mixtures of the vinyl 6'-stannane **25** (*E*/*Z*, > 6:1). Quantitative and stereospecific halodestannylation[35] 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[37] resulted in fluorodestannylation, **27** (X = F). Chlorine converted **25** to 6'-chloro derivative **27** (X = Cl, *E* and *Z*) but with less stereoselectivity.[35]




**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*).[35] Astonishingly, AdoHcy hydrolase exhibits the catalytic control to achieve the addition of water to the isolated double bonds of **27**.[38] 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'-hydroxyhomo-adenosine **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).[38] 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.[38b] Lys426 was shown to be a crucial residue for the enzymatic hydrolysis of **27** (X = F).[26]

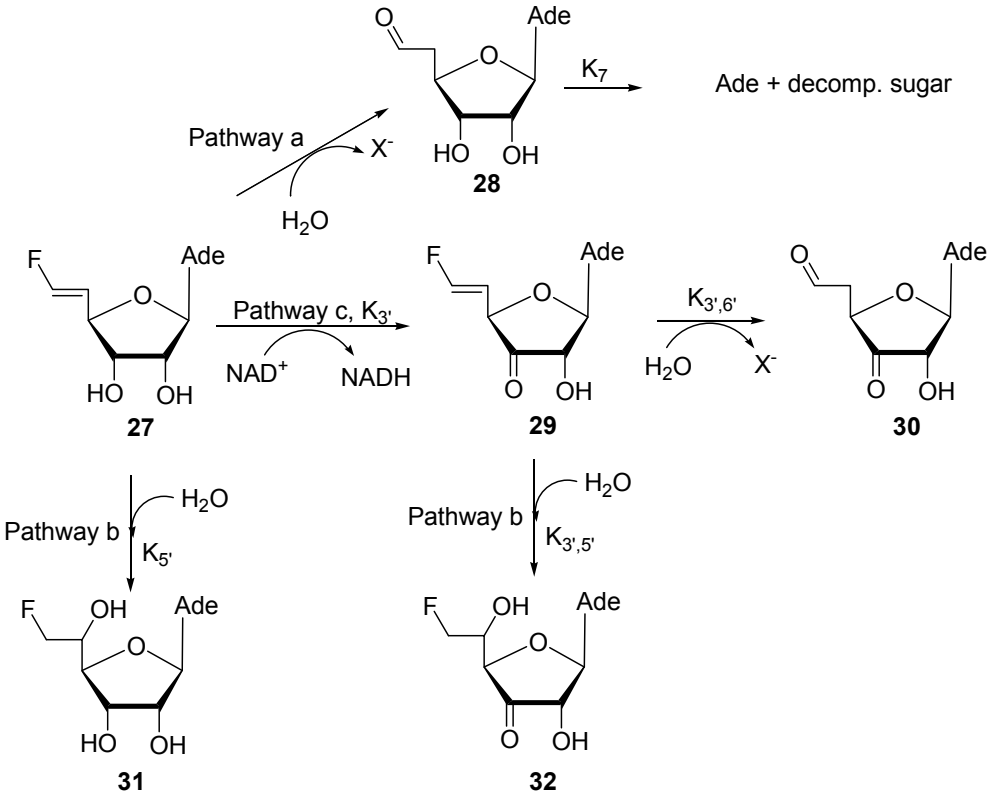



**Figure 7.** Inactivation of *S*-Adenosyl-L-Homocysteine Hydrolase by the 6'-Fluoro(vinyl) Homoadenosine.

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.[39] However, both **33a** and the independently synthesized aristeromycin 5'-aldehyde **33b** are potent type I inhibitors.[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.

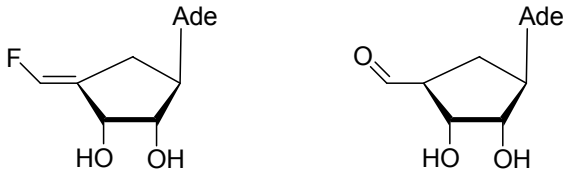



**Figure 8.** The 5'-Halo(vinyl)homoaristeromycin and 5'-Aldehyde Analogue.

To probe "pure" hydrolytic activity of the AdoHcy hydrolase,[26] analogues of vinyl halides **16** and **27** without an oxidizable functional group (hydroxyl group) at C3' have been targeted for studying.[41] 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**.[41] 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.

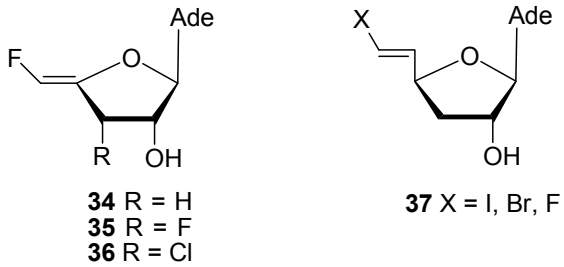



**Figure 9.** The 3'-Modified Vinyl Halides Analogues of Adenosine and Homoadenosine.

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

10).[42] Thus treatment of the crude Ado-5'-aldehyde **23** with (bromofluoromethylene)-triphenylphosphorane (generated in situ with $CBr_3F/Ph_3P/Zn$) and deprotection produced the bromofluorovinyl diastereomers **38** (*E*/*Z*, ~3:2).[42] 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.[42]

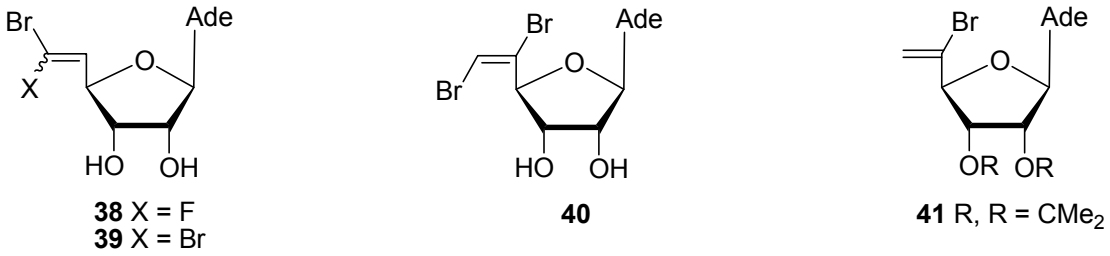
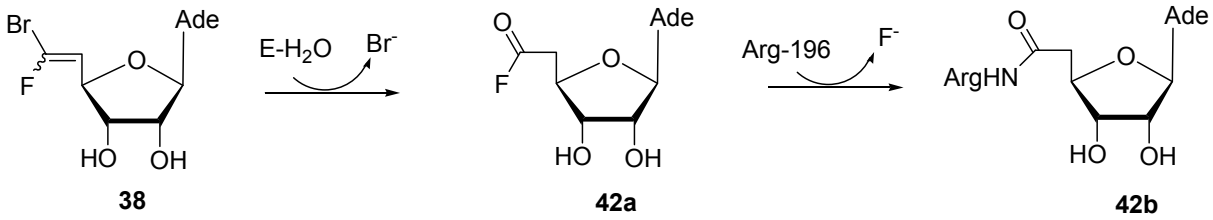



**Figure 10.** The Dihalo(homo)vinyladenosine Analogues.

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.[43] 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-$NH_2$ 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.[43]




**38** **42a** **42b**

**Figure 11.** Plausible Mechanism for the Inactivation of *S*-Adenosyl-L-Homocysteine Hydrolase by 6'-Bromo-6'-fluoro(homovinyl)adenosine.

## 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.[48]

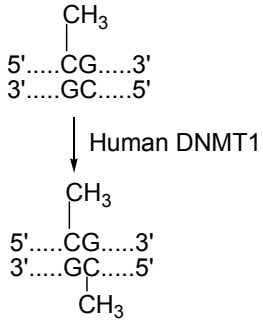



**Figure 12.** C-5 Methylation of Cytosine by Human DNA Methyltransferase (DNMT1).

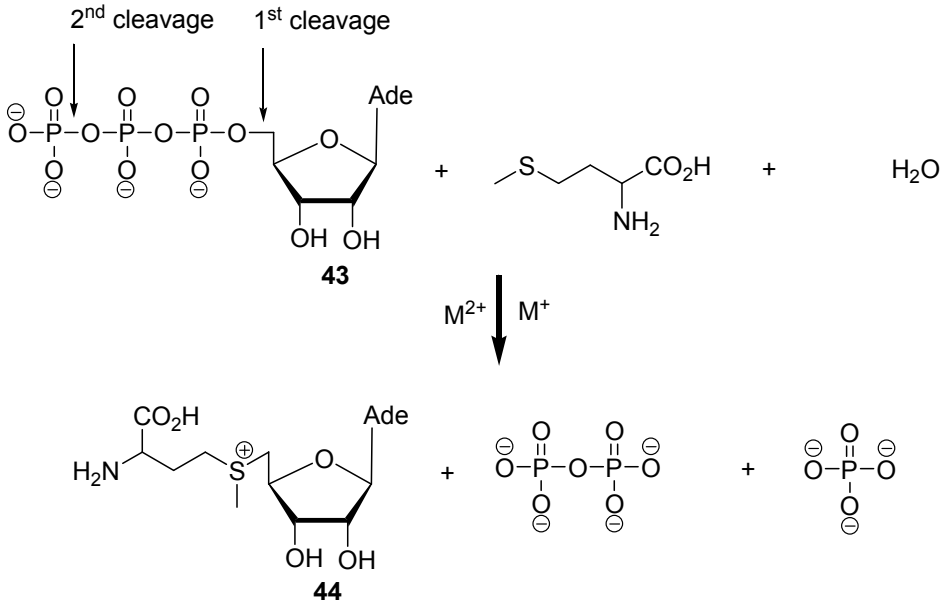
The SAM-dependent methylation of proteins and nucleic acids plays a fundamental role in gene transcription regulations.[49,50] Errors in the expression levels, and activities of eukaryotic DNA methyltransferases (MTase) DNMT1 was shown to be linked to oncogenic potential.[51] Therefore, compounds which 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.[52] These substances can undergo transfers to nucleic acids in MTase-dependent fashion serving as biological tools to better comprehend biological methylations.

### 1.2.2. *S*-Adenosyl-L-Methionine: A Methyl Group Donor.

*S*-adenosyl-L-methionine has been claimed to have played a diverse role in the "last universal common ancestor" (LUCA) of bacteria, *Archaea* and *Eukarya*.[53] Most probably, LUCA synthesized SAM *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.[54] 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.[55] Understanding the role of biological methylation, generally in gene transcription, has been hindered by the lack of tools for the identification of MTase substrates.[56] Owing to the methyl groups' lack of functionality, they are difficult to identify in complex biological environments.




**Scheme 2.** Biosynthesis of *S*-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.[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 α and β chains are methylated. The methyl transfer to hemoglobin from AdoMet is slow and inefficient ($(k_{cat}/K_m \sim 5 \times 10^{-2})$), 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.[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 tripoly-phosphate (**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 ~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.[59] 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.

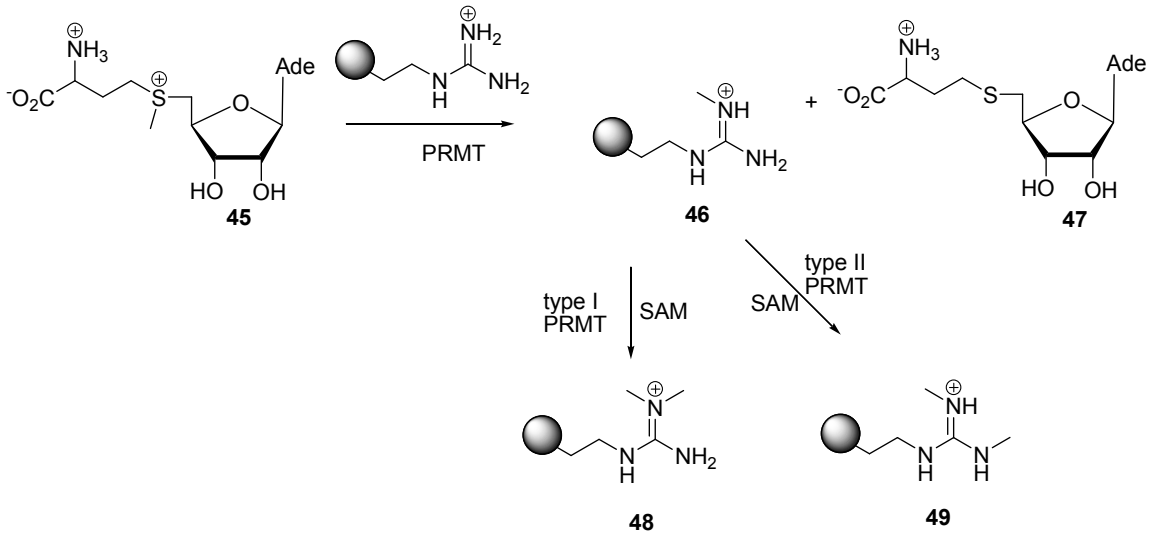
**1.2.3.1. By Glycine *N*-Methyltransferase**

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.[60] It was found that GNMT expression is down-regulated or even completely inhibited in liver, prostate tumor tissue[61] 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.[62] 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.[63]

**1.2.3.2. By Arginine *N*-Methyltransferase**

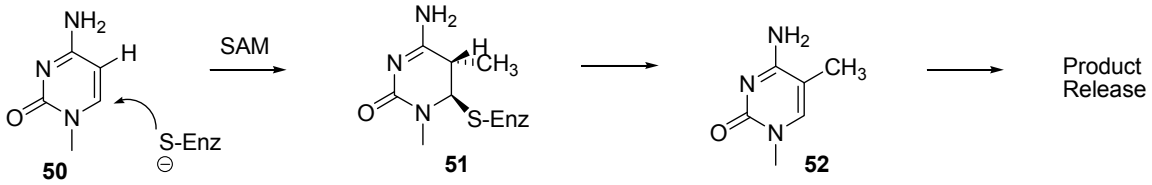
Enzymes which use SAM as methyl donors catalyze all post-translational formation of monomethylated Arg residues (MMA, Scheme 3). Protein arginine methyltransferases (PRMTs) are responsible for catalyzing the methylation of Arg residues, **46**, in various proteins which include histones (H2A, H3 and 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 (**49**, ADMA) or symmetric dimethylated Arg (**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.[64]




**Scheme 3.** Biosynthesis of Mono and Dimethylated Arginine Residues by *S*-Adenosyl-L-Methionine.

### 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.[65] 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).[65]




**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, **50**, 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'-deoxyuridiine. 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 group[65] 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 absense 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.[67]

Gromova proposed that stable covalent adducts **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 (**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 **58**, leading to the formation of **59** from the covalent intermediate.[67]

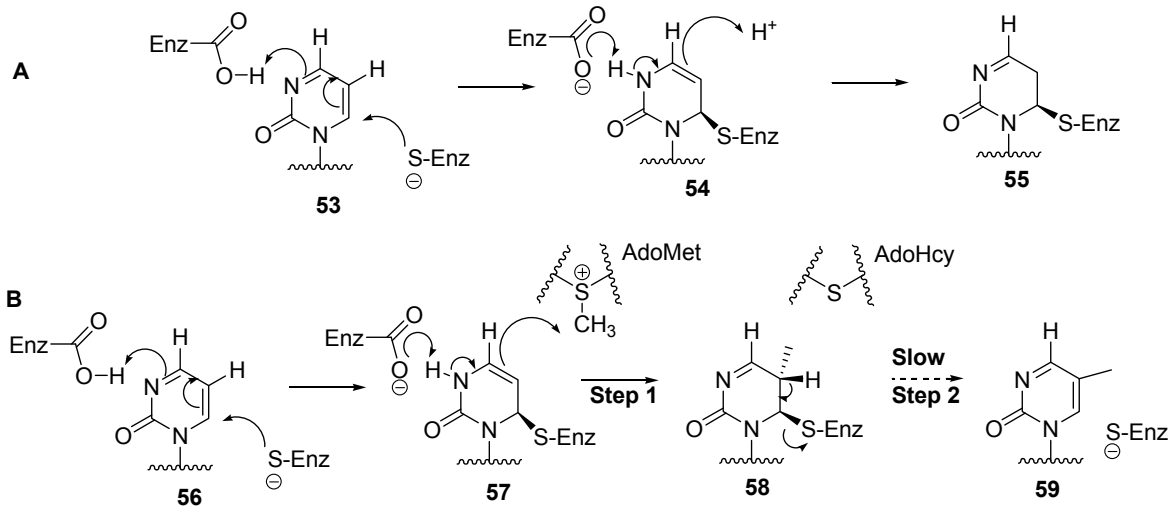



**Figure 13.** Proposed Mechanism for the Inhibition of M.EcoRII by 2-Pyrimidone Containing DNA Duplexs in the Absence (A) or in the Presence (B) of *S*-Adenosyl-L-Methionine.

## 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[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.[68] A wide array of monofluoro compounds display extraordinary biological activities,[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 bonds[69b-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.

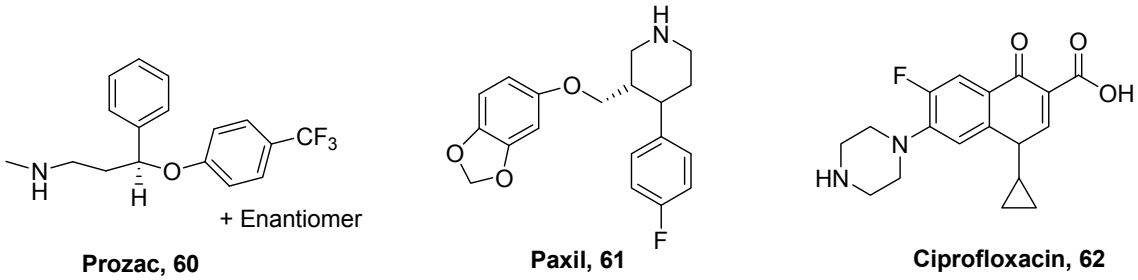


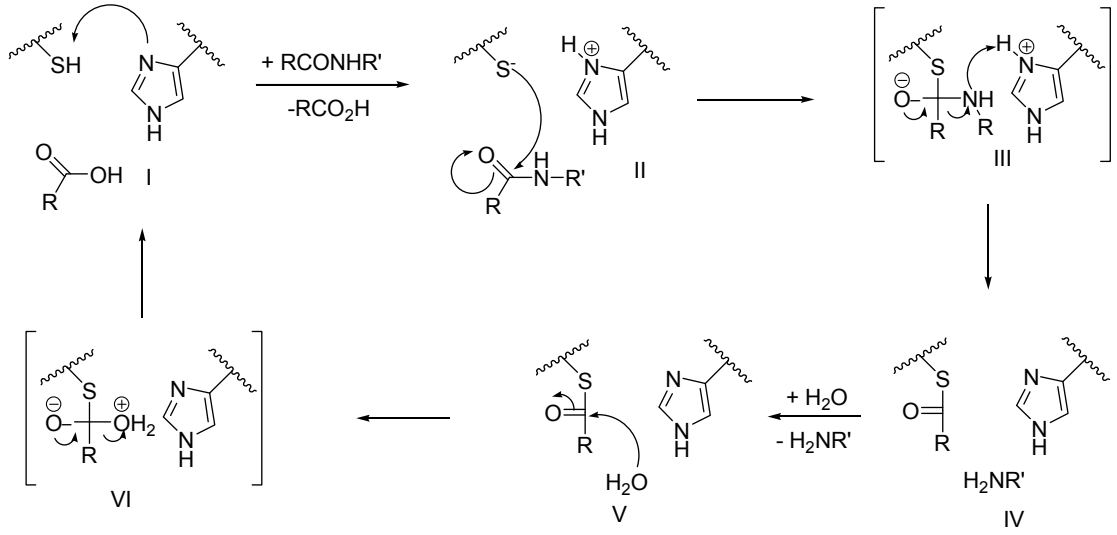

**Figure 14.** Selected Fluorinated Drugs.

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.[72] For example, fluoroolefins are significant, because of their application in the synthesis of biologically active mechanism-based inhibitors including materials like peptide isosteres.[73] To start a versatile synthetic method of desired fluorinated compounds, there must first be fluorine-containing building blocks which are frequently lacking.[74]

### 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.[75] 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.[76] Cysteine proteases also play a considerable role in protozoa such as *Plasmodium*, *Trypanosome and Leishmania* and inhibitors of falcipain and cruzain, whch are two key parasitic

cysteine proteases. These proteases are now under examination as probable treatment for Chagas' disease and malaria.[77]

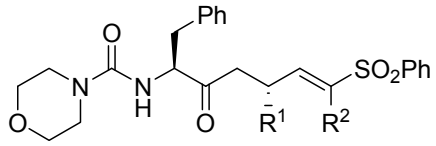



**Scheme 5**. Cysteine Protease Mechanism for the Hydrolysis of Amide Bond (Proteins).

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.[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.[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.[78] Vinyl sulfones selectively inhibit several cysteine proteases in a low nM range.[75] For example, compounds **63-65** inhibit falcipains and cruzains and are an important tool in antiprotozoal drug design and development (Figure 15).

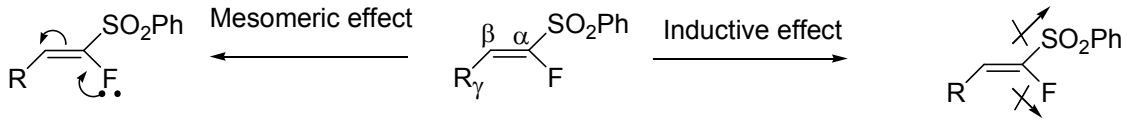



**63** $R^1 = CH_2CH_2Ph$; $R^2 = H$
**64** $R^1 = CH_2Ph$; $R^2 = H$
**65** $R^1 = CH_2Ph$; $R^2 = F$

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

Haemers' interest in fluoro-olefins allowed him to evaluate the influence of α-fluorine in a Michael acceptor type cysteine protease inhibitor.[75] The introduction of an inductively electron-withdrawing group on the α-carbon, such as, fluorine is assumed to increase the electron deficiency at the α-carbon. Alternatively, the lone pairs of electrons of the fluorine atom could then contribute and overlap with the existing conjugate π-system, contributing as a mesomeric donor. The insertion of a fluorine atom at the α-carbon resulted in an astonishing effect: the positive charge at the α-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.

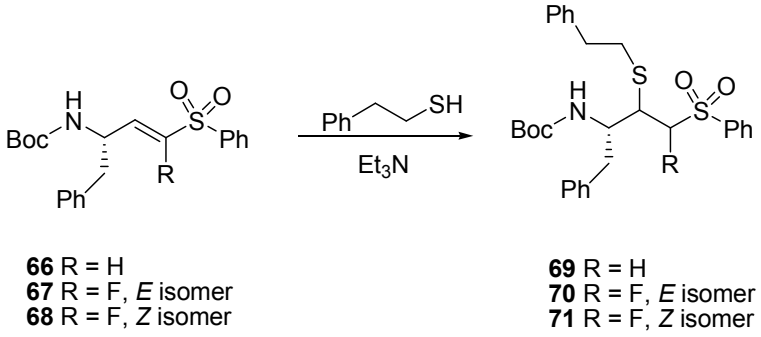



**Scheme 6**. Inductive Effect Vs Mesomeric Effect for the α-Fluorovinyl Sulfone.

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.[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 **64** and its α-fluoro derivative **65**. They found that compound **64** is a potent inhibitor of the *Leishmania cysteine* protease CPB, while compound **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.




**66** R = H
**67** R = F, *E* isomer
**68** R = F, *Z* isomer

**69** R = H
**70** R = F, *E* isomer
**71** R = F, *Z* isomer

**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[79] because of their role in parasite development.[80] *Plasmodium falciparum* contains four cysteine proteases from the papain family known as falcipains, for example, falcipain-2 (FP-2)[81] and falcipain-3 (FP-3)[81b,82] 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.[83] 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.[84]

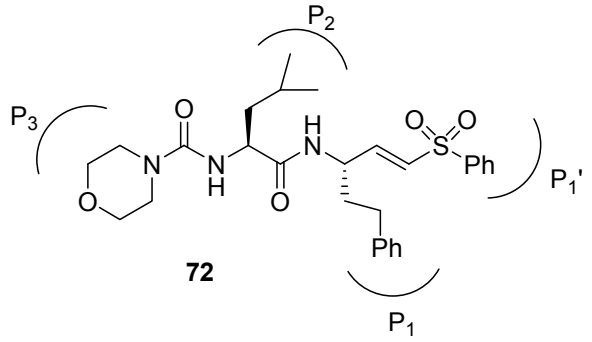
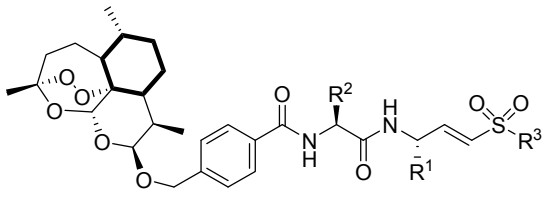



**Figure 16.** Structure of a Dipeptidyl Mu-Leu-hPhe-VSPh Containing Vinyl Sulfone.

In regards to the use of protease inhibitors as antimalarials, the concern is that selection of drug-resistant strains will eventually occur.[79] Parasites resistant to a dipeptidyl vinyl sulfone have been observed in Lopes' laboratory, although this resistance was somewhat limited.[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 *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, **72**, is very active. These vinyl sulfones have $IC_{50}$ values in the low-nM range.[81a,82,86] Hybrid molecule **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, **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.



**73** $R^1 = CH_2CH_2Ph, CH_2Ph$
$R^2 = CH_2CHMe_2, CH_2Ph$
$R^3 = Ph, Me$

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

### 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.[87] 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 sufonyl group attached to the phenyl ring. Sulindac sulfone has cancer chemopreventive activity[88] and inhibition of angiogenesis with sulindac or its sulfone metabolite may also contribute to their antineoplastic properties.[89]

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

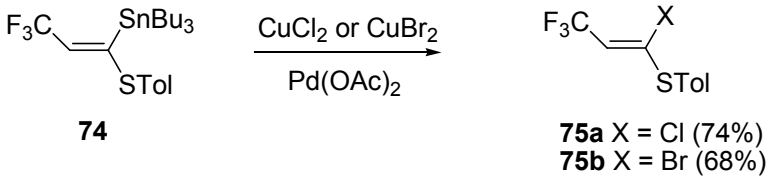
active, this can be attributed to their low p*K*a values. Leaving group properties of the sulfoxides have also been correlated to their biological activity.[90] Additionally, the antitumor activity of complexes of platinum containing substituted sulfoxides suggested that these complexes may act by binding to DNA with consequent loss of the sulfoxide ligand.[91] Brefeldin A (BFA), is a lactone antibiotic produced by fungal organisms such as *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.[92]

### 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.[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.[94]

α-(Halo)vinyl sulfides were synthesized as potential targets from compounds containing the trifluoromethyl motif. For example, vinyl chloride **75a** and vinyl bromide **75b** were obtained as the major products in good yields when the (*Z*)-1-stannyl-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]

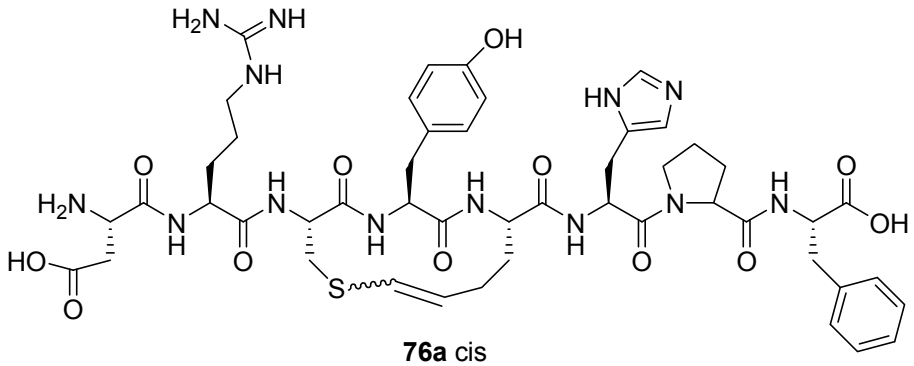



**74**

**75a** X = Cl (74%)
**75b** X = Br (68%)

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

Cyclization most often utilize disulfide or diamide bond formastion 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).

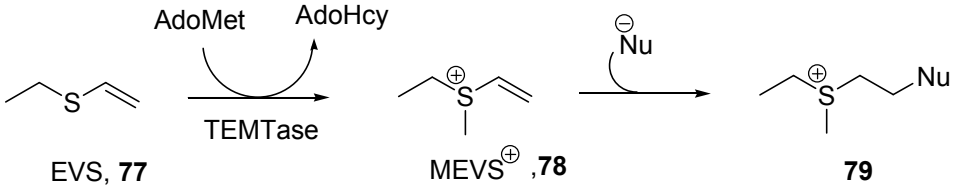



**76a** cis
**76b** trans

**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.[98] 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.[98] 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.

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 $MEVS^{+}$. 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.[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.[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.[99b] The natural element germanium has also been linked to the prevention of cancer and AIDS.[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.[99a]

#### 1.4.1. Organogermane alkenes: Synthesis and Reactivity.

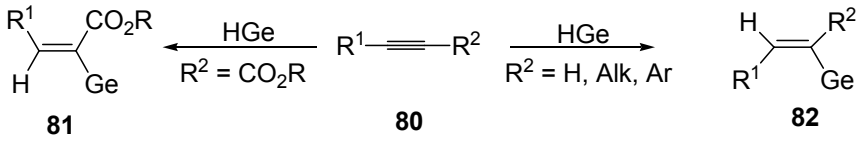
Since the chemistry and applications of organogermanes in the organic synthesis has been subject of recent reviews[99] in the following chapter of my dissertation only

selected aspects of germane 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 organogermanes 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 difficutly 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 germane isomers (*E*, *Z* and *gem*) with selectivity determined by both electronic and steric properties of the alkynes and germane hydride substrates.

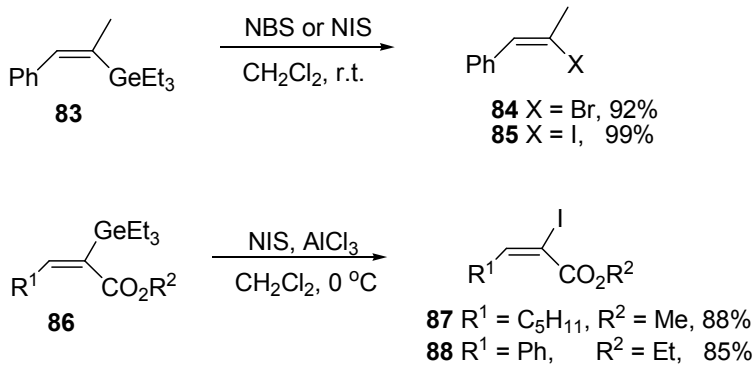
For example, vinylgermanes, e.g. **81** and **82** can be obtained via hydrometalation of alkyne, **80** as illustrated in Scheme 11. Generally, transition metal-catalyzed hydrometalation is utilized as a mild protocol to obtain the *cis*-addition products, **82**.[103] The *trans*-addition products 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 develope 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.[105]




**Scheme 11.** Lewis Acid Catalyzed Hydrogermylation of Alkynes.

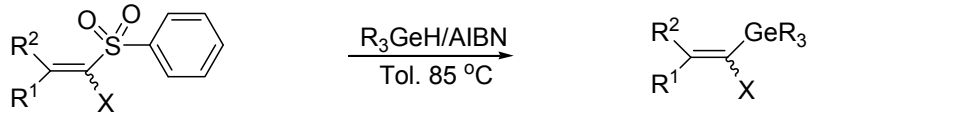
Hydrogermylation is a useful tool because it leads to the formation of vinylgermanes, which could be later transformed into the synthetically useful vinylhalides. As one might expect, halodegermylation of triethylgermanes **83** with NBS or NIS produced vinyl halides **84** and **85** in excellent yields (Scheme 12).[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.




**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,[107] techniques such as hydrogermylation are inapplicable for the synthesis of (α-fluoro)vinylgermanes,[108] The chemistry[109] and biological activity of the

organogermanium compounds have already been reviewed.[110] Wnuk and coworkers have developed stereoselective radical-mediated germyldesulfonylations of (α-fluoro)vinyl sulfones with germanium hydrides to provide access to (α-fluoro)vinyl germanes.[110] Such an approach provides a means to synthesizing 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 **90a** (*E*) with $(TMS)_3GeH$/ AIBN gave the corresponding vinyl germane **91a** (*E*) stereoselectively (Scheme 13). Analogous treatment of *E* vinyl sulfone **90** with $Bu_3GeH$, $Ph_3GeH$, and tri(2-furyl)germane produced the corresponding *E* germanes **91-94**. Radical germyldesulfonylation of **89** also allowed the synthesis of the previously unknown (α-fluoro)vinyl germanes **91'-94'** in high yields with retention of *E* stereochemistry. It was found that vinylgermanes bearing either a conjugated or an isolated double bond serve as versatile transmetalation reagents. The *E*-germanes could undergo coupling reactions with retention of stereochemistry under aqueous and anhydrous conditions. On the contrary, the coupling of *Z*-germanes occurs with less stereoselectivity to produce a mixture of *E* and *Z* isomers.[110]




**89** X = F
**90** X = H

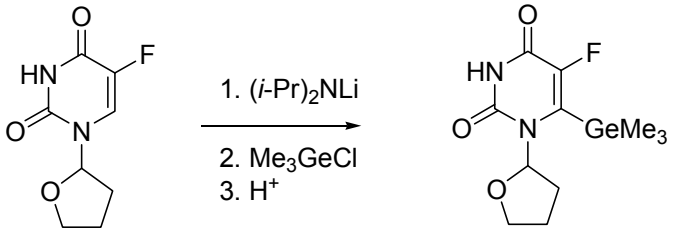
**91** R = $Me_3Si$, X = H **91'** R= $Me_3Si$, X = F
**92** R = Bu, X = H **92'** R = Bu, X = F
**93** R = Ph, X = H **93'** R = Ph, X = F
**94** R = 2-fury, X = H **94'** R = 2-fury, X = F

**Scheme 13**. Radical Mediated Germyldesulfonylation Reaction of Vinyl Sulfones.

### 1.4.2. Germanium Containing Nucleosides.

Previously, germaniums containing α-amino acids and peptides have been incorporated into biologically active decapeptides.[111] The 6-trialkylgermyl-5-fluorouridine derivatives are one of the very few known examples of germanium-containing nucleoside analogues.[112] 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.[113]

Lithiation of uracil acyclonucleosides was employed recently to obtain 6-substituted derivatives.[113] Lukevics' group has investigated the lithiation of another type of nucleoside analogues N-1 tetrahydrofuryl derivatives.[112] They decided to focus on an antitumor agent 1-(2-tetrahydrofuryl)-5-fluorouracil (**95**, Ftorafur)[112] for the introduction of an organometallic substituent at the C-6 position of uracil. Lithiation of Ftorafur was carried out in THF below -70 $^{o}$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 $^{o}$C. The 6-substituted organogermanium, **96**, isostructural derivative of Ftorafur, was obtained in moderate yield (Scheme 14).




**95** **96**

**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[114] and have the average value of 1.464 Å.[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.[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[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 stannydesulfonylation reaction is a critical step in the synthesis of two nucleoside-based drug candidates bearing an *exo*-fluoro methylene unit at a ribofuranosyl ring. The first drug is *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 a 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 germyldesulfonylation utilizing less toxic germane hydrides. Radical-mediated substitution of the arylsulfonyl group with the

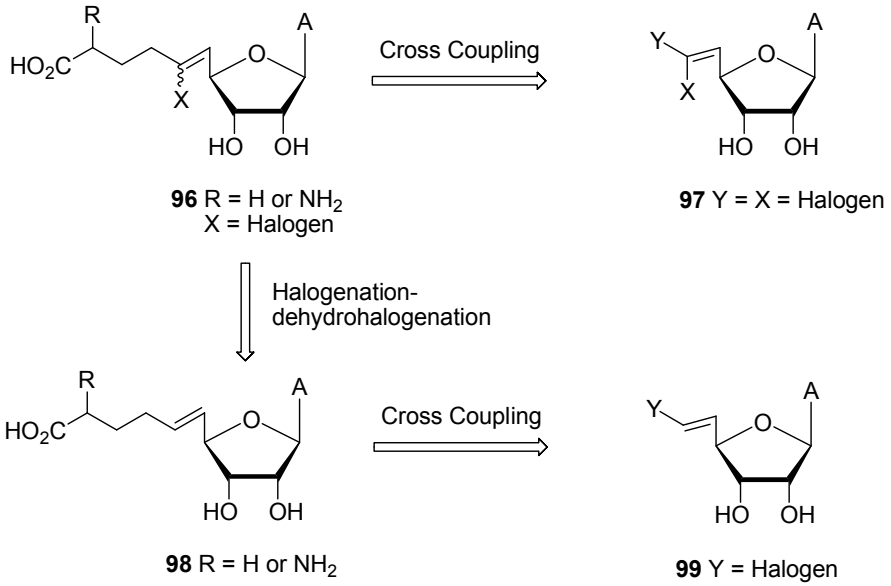
tributyl- or the triphenylgermanyl group at the vinylic carbon was expected to afford desired vinyl germanes. Moreover, the halodegermylation reaction should serve as an alternative approach for the synthesis of 5'-deoxy-5'-(halomethylene)nucleoside analogues.

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.

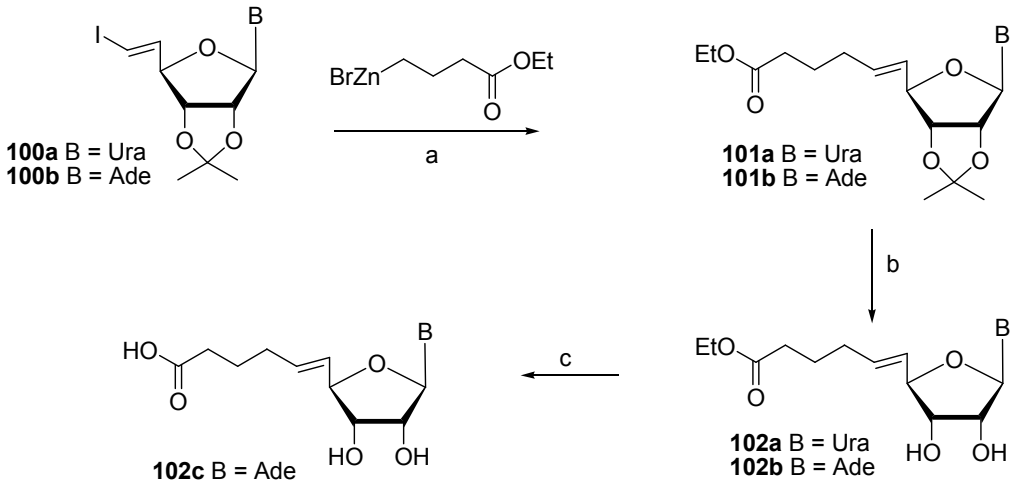



**Scheme 15**. Retrosynthetic Analysis for the Synthesis of *S*-Adenosyl-L-Homocysteine Analogues with C5' and Sulfur Atoms Replaced by Vinyl or Halovinyl Unit.

### 3.1.1. Synthesis of Vinyl *S*-Adenosyl-L-Homocysteine Analogues.

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 $EtO_2C(CH_2)_3ZnBr$ 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*)-enofuranuronate (**101b**, Scheme 16) in excellent yields after purification. $^1$H NMR of the product **101b** showed that coupling occurs with retention of stereochemistry ($J_{6'-5'}$ = 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.

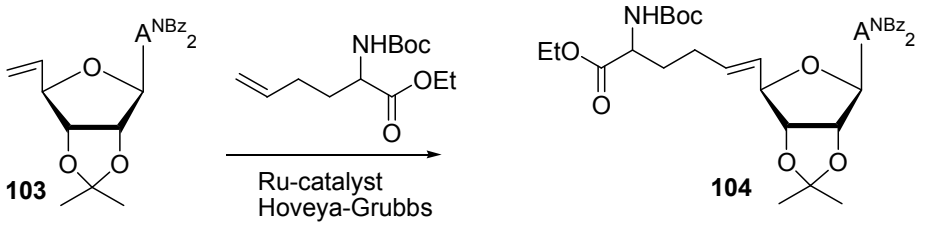
Deactonization of **101b** with TFA/$H_2O$ at 0 $^oC$ for 30 minutes produced ethyl 1-(adenine-9-yl)-1,5,6,7,8,9-hexadeoxy-β-D-*ribo*-dec-5(*E*)-enofuranuronate (**102b**, 49%) after column chromatography and recrystallization in MeOH. $^1H$ NMR analysis showed the disappearance of methyl signals from 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.




Reagents: (a) Tris(dibenzylideneacetone)-dipalladium/benzene
(b) TFA/$H_2O$ (9:1); (c) NaOH/$H_2O$

**Scheme 16.** Synthesis of *S*-Adenosyl-L-Homocysteine Analogues via Pd-catalyzed Coupling Utilizing 5'-Deoxy-5'-(Iodomethylene)adenosine.

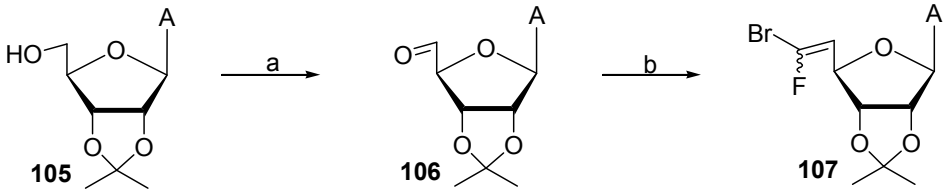
It has to be mentioned that Andrei and Wnuk synthesized the target molecule in the adenosine series, **104**, with an amino group at position C9'. [116] They employed a metathesis reaction between a 6 carbon amino acid (containing a terminal double bond) and 5'-deoxy-5'-methyleneadenosine, **103**, in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




**Scheme 17**. Metathesis Approach for the Synthesis of *S*-Adenosyl-L-Homocysteine Derivatives.

### 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 $CBr_3F/Ph_3P/Zn$ afforded bromo(fluoro)alkene **107** in 30% yield (Scheme 18). The $^{19}F$ NMR of **107** showed a mixture of *E/Z* (3:2) diastereomers. The two pairs of doublets at -64.28 ppm ($J_{F\text{-}H5'(cis)}$ = 10.7 Hz) and at -68.81 ppm ($J_{F\text{-}H5'(trans)}$ = 29.8 Hz) were diagnostic of the *E/Z* isomers**.**




Reagents and conditions: (a) $DCC/DMSO/Cl_2CHCO_2H$; (b) $Ph_3P/CBr_3F/Zn/CH_2Cl_2$

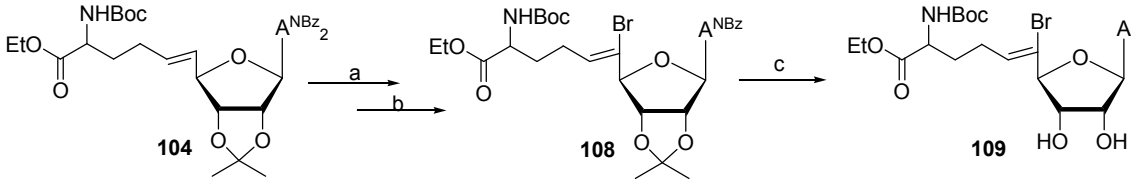
**Scheme 18**. Synthesis of 6',6''-Dihalovinyladenosine via Pd-Catalyzed Coupling Utilizing 5'-Deoxy-5'-(Bromofluoromethylene)adenosine.

### 3.1.3. Synthesis of 6'-Halovinyl *S*-Adenosyl-L-Homocysteine Analogues.

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 $NH_2$; 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 $NH_3$/MeOH and TFA/$H_2O$ followed by saponification with NaOH and HPLC purification gave **109** (*E*, 54%).

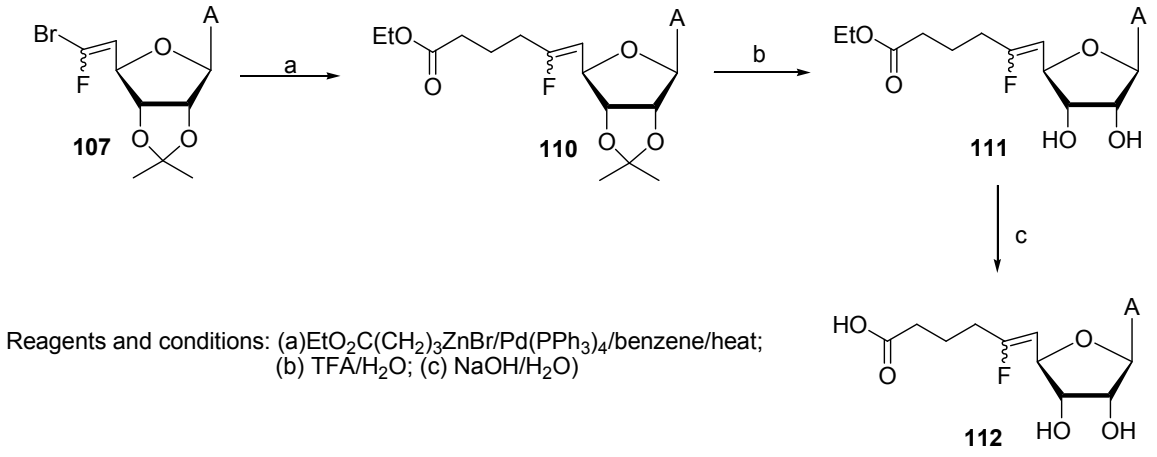



Reagents and conditions: (a) $C_5H_5NH\bullet Br_3$; (b) i.DBU/THF ii. MeOH/$NH_3$; (c) i. TFA. ii. NaOH

**Scheme 19.** Synthesis of 5'-Bromo(homo)vinyl *S*-Adenosyl-L-Homocysteine Analogues.

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 $Csp^3$ nucleophiles are very limited.[117] Andrei and Wnuk developed Pd-catalyzed Negishi coupling of 1-fluoro-1 bromoalkenes with alkylzinc, which provided stereoselective access to the internal fluoroalkenes.[116] After optimization of the coupling conditions, I discovered that treatment of the protected 5'-(bromofluoromethylene)-5'-deoxyadenosine[42] (**107**, *E/Z*, 3:2) with $EtO_2C(CH_2)_3ZnBr$/ $Pd(PPh_3)_4$ in refluxing benzene produced fluorovinyl AdoyHcy, **110**, (56%) as a mixture of geometric (*E/Z*, 2:3; Scheme 20) isomers. $^{19}F$ 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, $CH_3$) and at 1.61 (s, 3, $CH_3$). 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).[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 *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.[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 *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.

| Compound | % of enzyme inhibition[a,b] | |
|---|---|---|
| | 0.5 h[c] | 4 h[c] |
| **101b**[d] | 81 | |
| **102c** | 28.5 | 92.4 |
| **109** | 14.5 | 44.6 |
| **111**[d] | 14.1 | |
| **112** | 15.2 | 35.2 |

[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

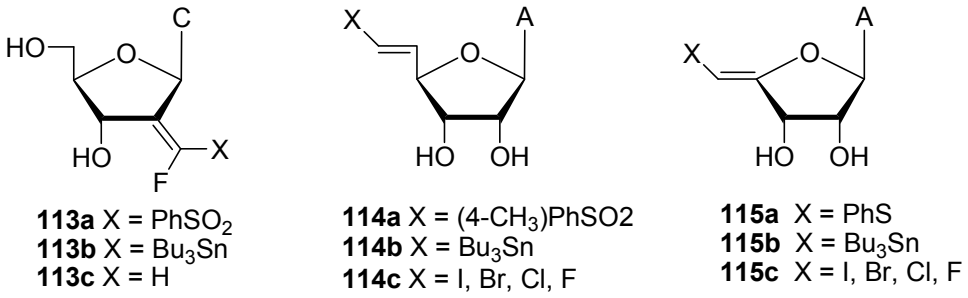
[c] Preincubation time of the inhibitors with the enzyme

[d] Esters were not tested with 4 h preincubation time due to chemical instability in the enzymatic assay.

## 3.2. Application of the Germyldesulfonylation Reactions to the Synthesis of Germanium-Containing Nucleosides.

### 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 α-halo vinyl functionality. For example, McCarthy and coworkers used a radical-mediated stannyldesulfonylation protocol (**113a → 113b)** for the synthesis of (*E*)-fluorovinyl cytidine **113c** (Tezacitabine; an inhibitor of ribonucleoside reductases with potent anticancer activity), from the protected (α-fluoro)vinyl sulfone **113a** (Figure 18).[109,118]




**113a** X = $PhSO_2$
**113b** X = $Bu_3Sn$
**113c** X = H

**114a** X = (4-$CH_3$)PhSO2
**114b** X = $Bu_3Sn$
**114c** X = I, Br, Cl, F

**115a** X = PhS
**115b** X = $Bu_3Sn$
**115c** X = I, Br, Cl, F

**Figure 18.** Nucleoside Analogues Synthesized via Tin Radical-Mediated Extrusion of Sulfur Atom.

Also, a radical mediated stannyldesulfonylation of the vinyl 6'-sulfone analogue of adenosine **114a** was achieved using a radical initiator and $Bu_3SnH$. 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*-cyclopropyladenosine[121] 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)[30]

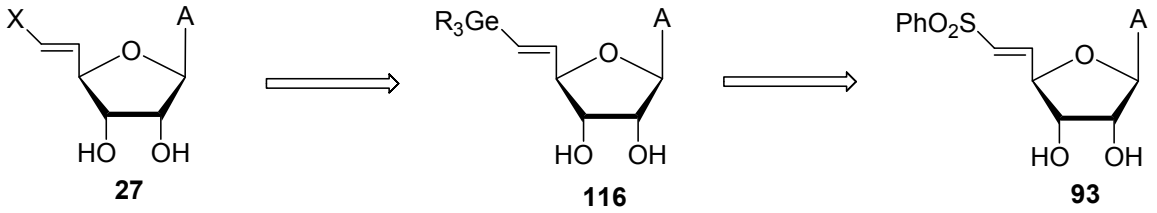
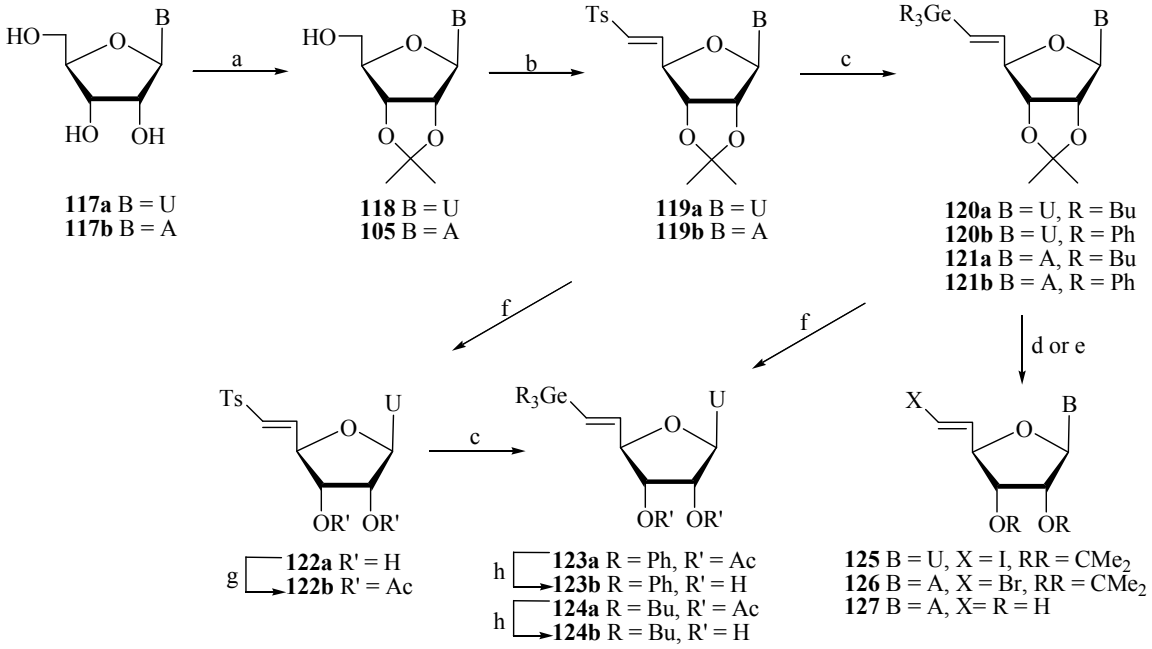



**Figure 19.** Germyldesulfonylation an Approach for the Synthesis of Novel Vinyl Germane Nucleosides. Application Towards Synthesis of 5'-Deoxy-5'-Halo(methylene)adenosines.

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'-tosylvinyluridine, **119a**, and 6'-tosylvinyladenine, **119b**, were obtained in good yields (~80%) after purification in silica gel. $^1$H NMR spectrum for **119b** confirmed the structure and was diagnostic to establish *trans* configuration ($J_{6'\text{-}5'}$ = 15.1 Hz). Two doublets at δ 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 germanyldesulfonylation via a radical process to give 5'-(tributylgermyl)methylene-5'-deoxyuridine, **120a**, as a single (*E*)-isomer ($J_{5'\text{-}6'(\text{trans})}$ = 18.5 Hz) in 57% yield. Sulfone **96b** also underwent a germyldesulfonylation reaction with $Bu_3GeH$ to yield the vinyl germane (*E*)-**121a** (46%). The analogous stannyldesulfonylation of **119a** and **119b** with $Bu_3SnH$ produced the corresponding (*E/Z*)-5'-(tributylstannyl)methylene-5'-deoxyuridine[111] and adenosine[35] 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.[35,111] Unlike the stannyldesulfonylation reactions,[35] the germyldesulfonylations 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 germyldesulfonylation reactions most probably occurs via the radical addition-elimination mechanism, similarly to the silyl- and stannyldesulfonylation reactions.[118]




Reagents and conditions: (a) Ethyl orthoformate/acetone/*p*-toluenesulfonic acid; (b) (i) DCC/DMSO/ $Cl_2CHO_2H$, (ii) $Ph_3P$=CHTs; (c) $Bu_3GeH$ or $Ph_3GeH$/AIBN/$PhCH_3$/heat; (d) NIS or NBS; (e) TFA/$H_2O$; (f) $Bu_3GeH$/ACCN/$HOCH_2CH_2SH$/$PhCH_3$/heat; (g) DMAP/$Ac_2O$; (h) $NH_3$/MeOH

**Scheme 21**. Synthesis of 6'-Vinylgermyluridine and Adenosine Analogues.

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 ($CH_2Cl_2$/-78 °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

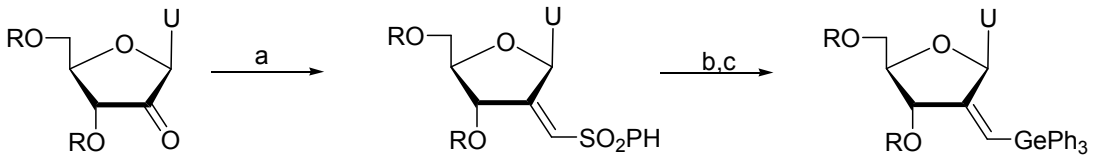
the nature of the substituents on the germanium atom;[125] most importantly it seems that $Csp^2$-Ge(alkyl)$_3$ bonds are more stable than that of the $Csp^2$-Ge(aryl)$_3$ bonds. I also observed same patterns of different reactivity for the protiodegermylation reactions of vinyl triarylgermanes and trialkylgermanes. For instance, treatment of the tributylgermane, **121a**, with aqueous trifluoroacetic acid (TFA) affected simultaneous protiodegermylation and deacetonization to afford 5'-deoxy-5'-methyleneadenosine, **127**. In contrast when triphenylgermane, **120b**, was treated with TFA only the isopropylidene protection group was removed affording germanonucleoside, **123b**.

I was, however, able to synthesize deprotected trialkylgermane, **124b**, using a base-labile protection strategy. For instance, treatment of 2',3'-*O*-diacetyl sulfone, **122b**, with $Bu_3GeH$/AIBN gave **124a** in 49% yield. Interestingly, germyldesulfonylation reaction performed in the presence of 2-mercaptoethanol, as a radical carrier,[117] and 1,1'-azobis(cyclohexanecarbonitrile), (ACCN) as a radical initiator also produced **124a** in even higer yield (58%). Treatment of **124a** with methanolic ammonia affected deacylation yielding the vinyl tributylgermane, **124b** (72%). The synthesis of the vinyl triphenylgermane, **123b** (65% overall yield), was analogously developed by germyldesulfonylation of 2',3'-*O*-acetyl protected uridine, **122b** with $Ph_3GeH$, followed by deacetylation of the resulting **123a**.

### 3.2.2. Synthesis of 2'-Vinyl Germane Nucleosides.

I also developed the germyldesulfonylation reaction for the removal of the vinyl sulfonyl group located on C2' of the nucleosides in Wnuk laboratory.[119] Thus, treatment of the protected 2'-ketouridine, **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.[108] Germyldesulfonylation reactions of **129** with $Ph_3GeH$ 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.




**128** R= TIPS

**129** R= TIPS

**130** R= TIPS
**131** R = H

Reagents and conditions: (a) $PhSO_2CH_2PO(OEt)_2$/LHDMS/THF; (b) $Ph_3GeH$/AIBN/ $PhCH_3$/heat; (c)TBAF/THF.

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

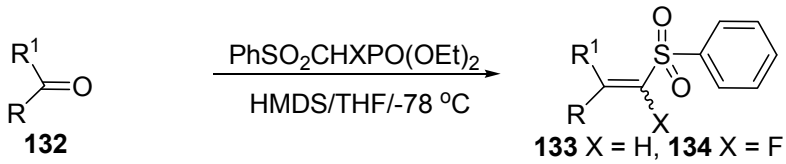
I have demonstrated that germyldesulfonylation reactions with trialkyl- and triarylgermane hydrides affect the removal of the sulfonyl group from the exomethylene and isolated double bonds of the sugar moieties of nucleosides. However, treatment of **130** with the more reactive tris(trimethylsilyl)germane [$(TMS)_3GeH$] provided the corresponding vinyl $(TMS)_3Ge$-uridine derivatives in relatively small yields (≤ 15%, $^1H$ NMR) despite numerous attempts. Therefore, no further efforts were made to optimize the germyldesulfonylation reactions utilizing the $(TMS)_3GeH$ reagent, although the vinyl tris(trimethylsilyl)germanes could serve as precursors for further modifications via Pd-catalyzed couplings reactions.[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.[110] 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 $^1$H 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.[127]

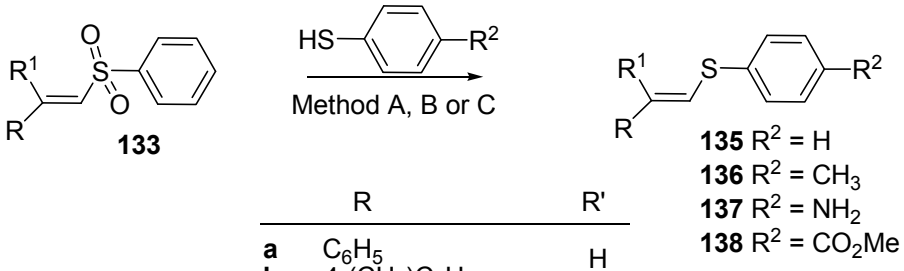



| series: | R | R' |
|---|---|---|
| **a** | $C_6H_5$ | H |
| **b** | 4-$(CH_3)C_6H_4$ | H |
| **c** | 4-$(CF_3)C_6H_4$ | H |
| **d** | 3,4-$(MeO)_2C_6H_3$ | H |
| **e** | $C_6H_5CH_2CH_2$ | H |
| **f** | *c*-$C_6H_{11}$ | H |
| **g** | -$(CH_2)_5$- | |
| **h** | $C_6H_5$ | $CH_3$ |

**Scheme 23.** Synthesis of *E*-Vinyl and (*E/Z*)-(α-Fluoro)vinyl Sulfones.

### 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 $sp^2$ 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).[127] 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 $^{o}$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 markedy influenced by the nature of the substituents. Thus, the alkyl (series b), electron-withdrawing ($CF_3$, 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).




| | R | R' |
|---|---|---|
| **a** | $C_6H_5$ | H |
| **b** | 4-$(CH_3)C_6H_4$ | H |
| **c** | 4-$(CF_3)C_6H_4$ | H |
| **d** | 3,4-$(MeO)_2C_6H_3$ | H |
| **e** | $C_6H_5CH_2CH_2$ | H |
| **f** | *c*-$C_6H_{11}$ | H |
| **g** | -$(CH_2)_5$- | |
| **h** | $C_6H_5$ | $CH_3$ |

**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 $H_2O$/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 $H_2O$/ACCN to produce the corresponding vinyl sulfides **136c** and **137c** (entries 16 and 17). Thiodesulfonylation of *E*-**133a** with 4-mercaptobenzoic acid ($R^1 = CO_2H$) 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-

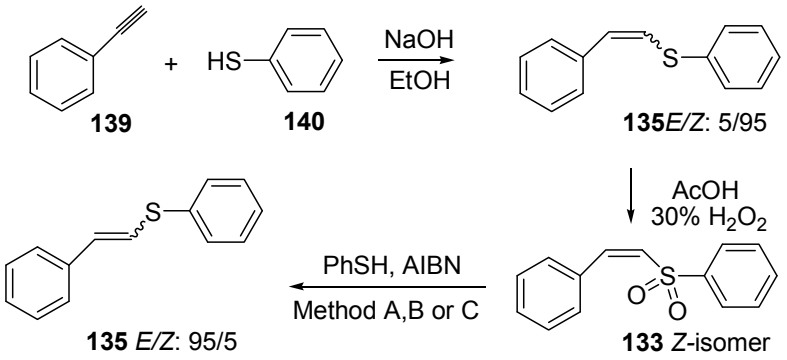
mercaptoethanol, 1-propanethiol or thioacetic acid) under radical conditions but the corresponding vinyl sulfides were not formed. Instead I only recovered the starting sulfones.

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

| Entry | Sulfone (*E/Z*) | Method[a] | Product[b] | (*E/Z*)[c] | Yield[d] |
|---|---|---|---|---|---|
| 1 | **133a (*E*)** | A | **135a** | 95:5 | 61 |
| 2 | **133a (*E*)** | B | **135a** | 95:5 | 71[e], 65[e,f], 10[e,g] |
| 3 | **133a (*E*)** | C | **135a** | 95:5 | 70[e] |
| 4 | **133a (*E*)** | C | **135a** | 95:5 | 20[e,k] |
| 5 | **133a (*E*)** | B | **136a** | 95:5 | 61 |
| 6 | **133a (*E*)** | B | **137a** | 98:2 | 55 |
| 7 | **133a (*E*)** | C | **138a** | 95:5 | 85 |
| 8 | **133a (Z)** | A | **135a** | 95:5 | 65[e] |
| 9 | **133a (Z)** | B | **135a** | 95:5 | 95[e] |
| 10 | **133a (Z)** | C | **135a** | 95:5 | 70, (80[e]) |
| 11 | **133b (*E*)** | A | **135b** | 85:15 | 55[e] |
| 12 | **133b (*E*)** | B | **135b** | 85:15 | 54, (63[e]) |
| 13 | **133c (*E*)** | A | **135c** | 95:5 | 59, (70[e]), 5[e,g] |
| 14 | **133c (*E*)** | B | **135c** | 95:5 | 85[e], 80[e,f], 50[g] |
| 15 | **133c (*E*)** | C | **135c** | 95:5 | 94[e], (96[e,i]) |
| 16 | **133c (*E*)** | B | **136c** | 95:5 | 58 |
| 17 | **133c (*E*)** | B | **137c** | 95:5 | 40, (55[e]) |
| 18 | **133d (*E*)** | A | **135d** | 75:25 | 55 |
| 19 | **133d (*E*)** | B | **135d** | 75:25 | 64[e] |
| 20 | **133d (*E*)** | C | **135d** | 85:15 | 70[e] |
| 21 | **133e (*E*)** | A,B,C | **135e** | | n.r |
| 22 | **133f (*E*)** | A,B,C | **135f** | | n.r. |
| 23 | **133g** | B | **135g** | | 55 |
| 24 | **133g** | C | **135g** | | 76[e] |
| 25 | **133g** | C | **136g** | | 62 |

[a] Method A: thiol/ACCN/toluene/110 $^{o}$C/12 h; Method B: thiol/ACCN/water/100 $^{o}$C/10 h; Method C: thiol/ACCN/MeOH/65 $^{o}$C/10 h. [b] 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. [c] Determined by GC-MS and/or $^{1}$H NMR. [d] Isolated yield. [e] Based on GC-MS. [f] AIBN instead of ACCN. [g] Without ACCN. [h] Disulfide instead of thiol, 16 h. [i] In EtOH.

Radical-mediated thiodesulfonylation 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 thiodesulfonylation reactions I also prepared pure *Z*-vinyl sulfone as a starting precursor.




**139** **140** **135***E/Z*: 5/95

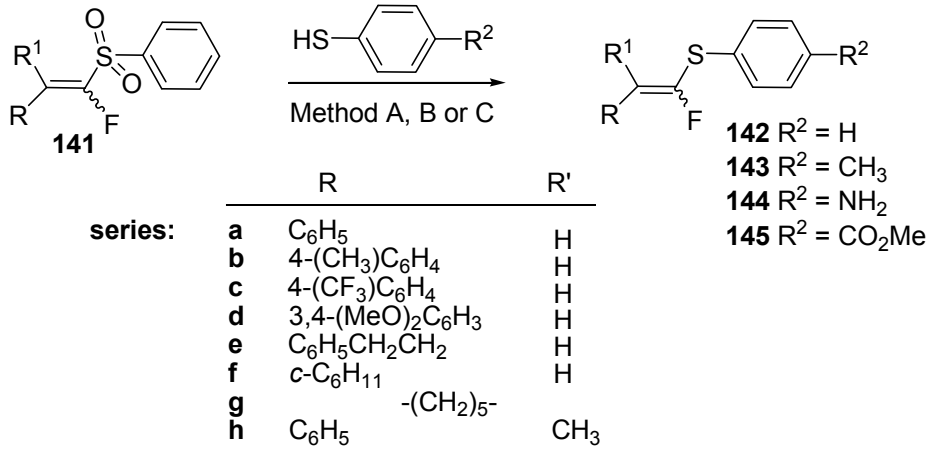
**135** *E/Z*: 95/5 **133** *Z*-isomer

**Scheme 25.** Synthesis of the *Z*-Vinyl Phenyl Sulfone and its Thiodesulfonylation.

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.[128] 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).[127] Similarly, for unfluorinated compounds, thiodesulfonylation appeared fairly general since sulfones **141b**, **141c** and **141d** bearing alkyl (Me), electron-withdrawing ($CF_3$), 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).




| series: | R | R' |
|---|---|---|
| **a** | $C_6H_5$ | H |
| **b** | 4-$(CH_3)C_6H_4$ | H |
| **c** | 4-$(CF_3)C_6H_4$ | H |
| **d** | 3,4-$(MeO)_2C_6H_3$ | H |
| **e** | $C_6H_5CH_2CH_2$ | H |
| **f** | *c*-$C_6H_{11}$ | H |
| **g** | -$(CH_2)_5$- | |
| **h** | $C_6H_5$ | $CH_3$ |

**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 (α-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 (α-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 (α-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.[127]

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

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

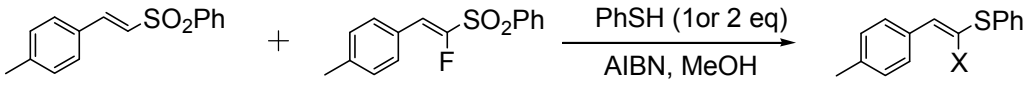
[a] Method A: thiol/ACCN/toluene /110 °C/6 h; Method B: thiol/ACCN/ $H_2O$ /100 °C/6 h; Method C: thiol/ACCN/MeOH/65 °C/5 h. [b] Reactions were performed on 0.1-0.5 mmol scale of sulfones (0.05 mM) with 1.25-2.0 equiv. of thiols and 0.25-0.50 equiv. of AACN or AIBN. [c] Determined by GC-MS and $^1$H or $^{19}$F 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 α-fluoro sulfone **141b** (*E/Z*, 84:16; 0.5 equiv) with PhSH (2.0 equiv; Method C) in the presence of the parent α-H sulfone *E*-**133b** (0.5 equiv) demonstrated that the thiodesulfonylation of α-fluorovinyl sulfone occurs at a faster rate than its nonfluorinated counterpart.[127] Differentiation of reactivity between vinyl and α-fluorovinyl sulfones towards thiodesulfonylation 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 Thiodesulfonylation Reactions.




*E*-**133b**, 0.5 eq. *E/Z* **141b**, 0.5 eq. *E/Z* **135b** X = H; *E/Z* **142b** X = F

| | Yield with 1 eq. thiol | | | Yield with 2 eq. thiol | | |
|---|---|---|---|---|---|---|
| **Time (min)** | **Yield** | **135b** | **142b** | **Yield** | **135b** | **142b** |
| 30 min | | 20% | 50% | | 35% | 70% |
| 1 h | | 25% | 65% | | 45% | 88% |
| 2h | | 25% | 70% | | 48% | 95% |
| 3h | | 10% | 75% | | 40% | 98% |
| 4h | | 5% | 75% | | 35% | 99% |
| 5h | | 5% | 80% | | 25% | 99% |

### 3.3.5. Synthesis of the Antibacterial Agent with (α-Fluoro)vinyl Sulfide Unit.

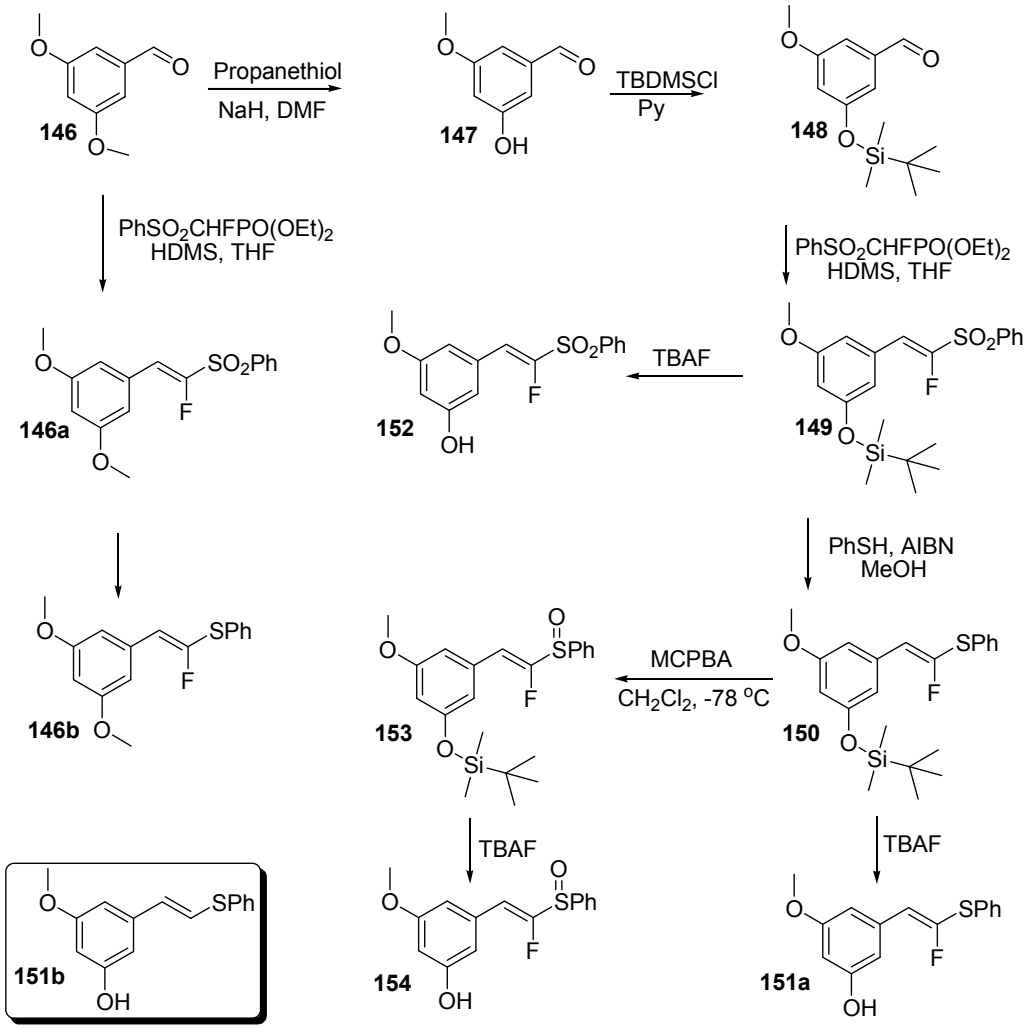
Next I applied my radical-mediated thiodesulfonylation procedure for the synthesis of the (*E/Z*)-1-fluoro-2-(3-hydroxy-5-methoxyphenyl)-1-phenylthioethene **151a**. The latter compound was expected to have enhanced biological activity when compared to its nonfluorinated analogue, 2-(3-hydroxy-5-methoxyphenyl)-1-

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 benzenthiol employing my radical mediated thiodesulfonylation methodology. In order to prepare the required 3-hydroxy-5-methoxybenzaldehyde substrate, **147**, the commercially available 3,5-dimethoxybenzaldehde, **146**, was selectively demethylated with propanethiol in the presence of sodium hydride at reflux following literature procedure[129b] (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). $^{1}$H NMR and $^{19}$F NMR showed a vicinal coupling constant of $^{3}J$ = 34.3 Hz, and $^{3}J$ = 21.9 Hz for *E* and *Z* isomers, respectively. Thiodesulfonylation reaction of the (α-fluoro)vinyl sulfone, **149**, with benzenethiol at 100 $^{o}$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 ($t_R$ = 28.60 min, *E,* $t_R$ = 27.31 min, *Z*). Desilylation of **150** with *tetra*-butylammonium fluoride in THF at 0 $^{o}$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*).




**Scheme 27.** Synthesis of (*E/Z*)-1-Fluoro-2-(3-Methoxy-5-Hydroxyphenyl)-1-Phenylthioethene and its Sulfone and Sulfoxide Derivatives.

I also synthesized the corresponding 3-hydroxy-5-methoxy-(α-fluoro)vinyl sulfoxide **154** and sulfone **152** derivatives to test if the oxidization state of sulfur will enhance antibacterial activity. Thus, (α-fluoro)vinyl sulfide, **150**, was dissolved in

methylene dichloride and treated with a solution of *m*-CPBA in $CH_2Cl_2$ for 1 hour to produce (*E/Z*)-1-fluoro-2-(3-methoxy-5-*tert*-butyl-dimethylsilyloxyphenyl)-1-phenyl-sulfinylethene, **153** in good yield (85%) after column chromatography. The $^{19}F$ NMR showed a doublet at δ -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 $^oC$ (ice-bath) for 25 minutes afforded (α-fluoro)vinyl sulfoxide, **154** (90%). The $^{19}F$ NMR in $CDCl_3$ showed δ -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 (α-fluoro)vinyl sulfone **152** (94%) after purification on silica gel column.

It was demonstrated in earlier literature reports[129] that in order for the vinyl sulfide to possess antibacterial activity the styryl group is required to have a *meta* hydroxyl/methoxy pattern. Therefore, I also prepared 3,5-dimethoxystyryl (α-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-fluoro-2-(3,5-dimethoxy)-1-phenylsulfonylethene, **146a**, in 80% yield (*E/Z*: 78/22) after column chromatography (hexane/EtOAc; 85:15). $^1H$ 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 (α-fluoro)vinyl sulfone, **146a**, with benzenethiol at 100 $^oC$ (oil bath) for 1.5 hours in MeOH produced the corresponding (α-fluoro)vinyl sulfide, **146b (**75%) as a mixture of *E/Z* isomers; $^1H$ 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 $IC_{50}$ 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 level[129c] 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]

| Compound | *Staphylococcus aureus* | *Bacillus cereus* | *Mycobacterium smegmatis* |
|---|---|---|---|
| | | | >512 |
| | >128 | >128 | >128 |
| **146b** | >128 | >128 | >128 |
| mean | **>128** | **>128** | **>128** |
| | | | 128 |
| | 16 | 32 | 128 |
| **151a** | 16 | 32 | 128 |
| mean | **16**[b] | **32**[c] | **128**[d] |
| | | | 256 |
| | 128 | 128 | >128 |
| **152** | 128 | 128 | >128 |
| mean | **128** | **128** | **>128** |
| | >128 | >128 | 256 |
| | >128 | >128 | >128 |
| **154** | | | >128 |
| mean | **>128** | **>128** | **>128** |

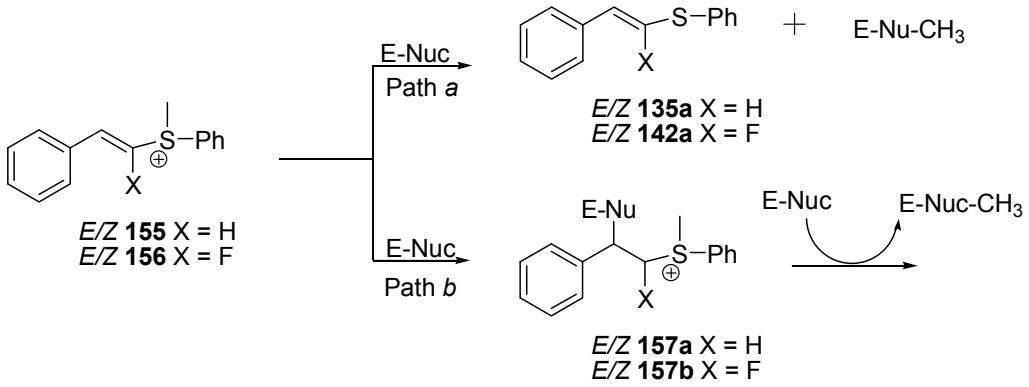
[a] Minimum inhibitory concentration $IC_{50}$ values in μg/mL. [b] Corresponds to $IC_{50}$ of 58 μM. [c] Corresponds to $IC_{50}$ of 116 μM. [d] Corresponds to $IC_{50}$ of 464 μM.

### 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 (*a*) methyl group donor to the amino acid functionalities

such as hydroxyphenol (present in tyrosine), sulfhydryl (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**).

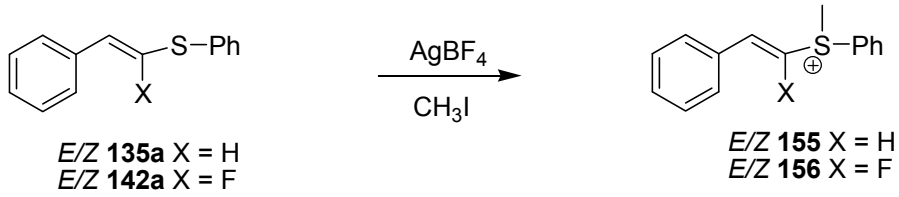



**Scheme 28.** Possible Dual Reactivity of Vinyl Sulfonium Ion with Enzyme-bound Nucleophiles.

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[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.




*E/Z* **135a** X = H
*E/Z* **142a** X = F

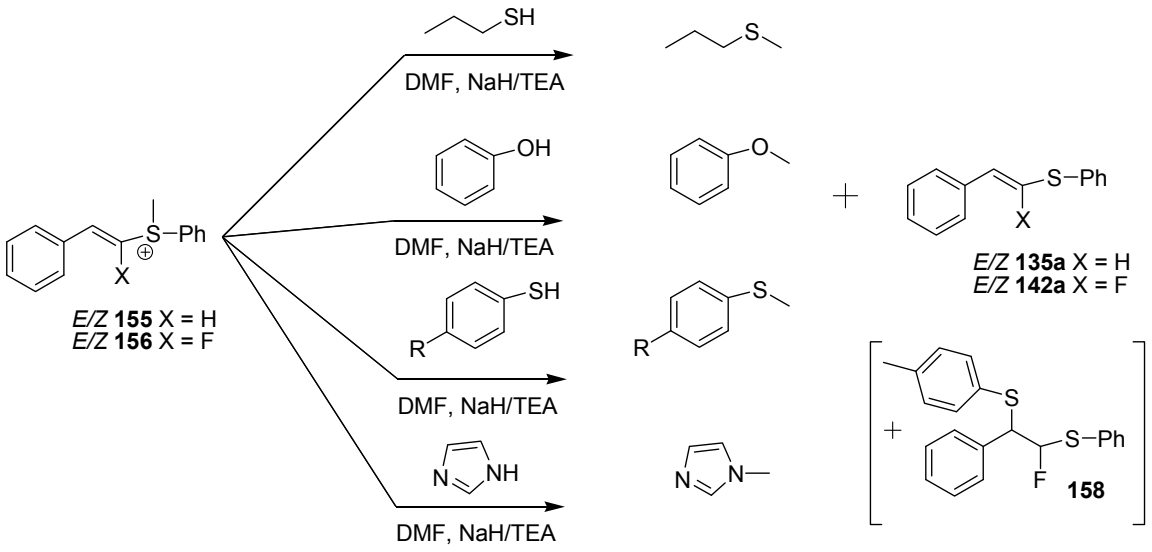
*E/Z* **155** X = H
*E/Z* **156** X = F

**Scheme 29**. Synthesis of Vinyl and α-Fluorovinyl Sulfonium Ions.

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 disapearance 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-CO*t*Bu 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. $^{1}H$ ($Me_4Si$) at 400 MHz and $^{13}C$ ($Me_4Si$) 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 $^{o}C$. Elemental analysis was determined at Galbraith Laboratories, Knoxville, TN. Merck Kiselgel 60-$F_{254}$ sheets were used for Thin Layer Chromatography (TLC) and products were detected with a 254 nm light. Merck Kiselgel 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/$H_2O$ (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 $EtO_2C(CH_2)_3ZnBr$ (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 $^oC$ for 8 h [additional $EtO_2C(CH_2)_3ZnBr$ (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/$H_2O$). The organic layer was washed (brine), dried ($Na_2SO_4$), evaporated, and the residue was column chromatographed (EtOAc/hexane, 85:15) to give **101a** (28 mg, 72%); $^1H$ NMR δ 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 δ 14.25 ($CH_3$), 24.03 (C8'), 25.32 and 27.16 (C*Me*$_2$), 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 (*C*$Me_2$), 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 $C_{19}H_{27}N_2O_7$ $[M+H]^+$ 395.1818, found 395.1811.

**Ethyl 5(*E*)-(5'-deoxy-2',3'-*O*-isopropylideneadenosin-5'-ylidene)pentanoate (101b)** Coupling of (*E*)-**100b**[35] (41 mg, 0.1 mmol) with $EtO_2C(CH_2)_3ZnBr$ (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, $CH_3$), 1.28 (s, 3, $CH_3$), 1.42 (s, 3, $CH_3$), 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, $CH_2$), 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, $NH_2$), 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 $C_{20}H_{28}N_5O_5$ $[M+H]^+$ 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/$H_2O$ (9:1, 2.5 mL) was stirred at 0 $^oC$ (ice-bath) for 1 h. The volatiles were evaporated under vacuum (< 15 $^oC$) and co-evaporated (3 x) with toluene. The residue was column chromatographed (1→6% MeOH/$CHCl_3$) to give **102a** (45 mg, 72%): mp 102–104 $^oC$ dec; UV max 262 nm (ε 9200), min 230 nm (ε 2100); $^1$H NMR ($Me_2SO$-$d_6$/$D_2O$) δ 1.18 (t, *J* = 7.1 Hz, 3, $CH_3$), 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',$CH_2$), 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 ($Me_2SO$-$d_6$) δ 14.91 ($CH_3$), 24.60 (C8'), 31.75 (C7'), 33.68 (C9'), 60.60 ($CH_2$), 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 $C_{16}H_{22}N_2O_7$ (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/$H_2O$ by procedure B gave **102b** (15 mg, 61%).

Purification on HPLC (10 → 60% $CH_3CN/H_2O$ 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 ($Me_2SO$-$d_6$) 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 $C_{17}H_{23}N_5O_5 \bullet H_2O$ (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/$H_2O$ (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% $CH_3CN/H_2O$ 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 $C_{15}H_{20}N_5O_5$ $[M+H]^+$ 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**[42] (*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 $^oC$ 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 $C_{20}H_{27}FN_5O_5$ $[M+H]^+$ 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, $CH_3$), 161 (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'), 7.86 (s, 1, H2), 8.34 (s, 1, H8). (*E*)- **110** had: $^1H$ NMR δ 1.21 (t, *J* = 7.1 Hz, 3, $CH_3$), 1.35 (s, 3, $CH_3$), 160 (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/$H_2O$ by procedure B and HPLC purification (15 →50% $CH_3CN/H_2O$, $t_R$ = 49 min) gave **111** (32 mg, 88%; *E/Z*, ~35:65): $^{19}F$ NMR (MeOH-$d_4$) δ -94.73 ('q', $J_{F–H5';7;7'}$ = 20.5 Hz, 0.35, *E*), -102.14 (dt, $J_{F–H5'}$ = 35.9 Hz; $J_{F–H7';7''}$ = 17.7 Hz, 0.65, *Z*); MS *m/z* 396 (100, $MH^+$); HRMS calcd for $C_{17}H_{23}FN_5O_5$ $[M+H]^+$ 396.1678, found 396.1680. (*Z*)-**111** had: $^1H$ NMR (MeOH-$d_4$) δ 1.24 (t, *J* = 7.1 Hz, 3, $CH_3$), 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, $CH_2$), 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); $^{13}C$ NMR (MeOH-$d_4$) δ 14.50 ($CH_3$), 22.34 (C8'), 31.99 (d, *J* = 27.2 Hz, C7'), 33.87 (C9'), 61.55 ($CH_2$), 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-$d_4$) δ 1.24 (t, *J* = 7.1 Hz, 3, $CH_3$), 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, $CH_2$), 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); $^{13}C$ NMR (MeOH-$d_4$) δ 14.50 ($CH_3$), 22.34 (C8'), 28.56 (d, *J* = 27.2 Hz, C7'), 33.78 (C9'), 61.55 ($CH_2$), 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'), 174.89 (C10').

**5-Fluoro-5(*E*)-(5'-deoxyadenosin-5'-ylidene)pentanoic acid (112)** Treatment of **111** (8 mg, 0.020 mmol; *E/Z*, 35:65) with NaOH as described for **102c** and HPLC purification (5 →50% $CH_3CN/H_2O$ for 1 h, $t_R$ = 42 min) gave **112** (6 mg, 82%; *E/Z*, 45:55); $^{19}F$ NMR (MeOH-$d_4$) δ -97.8 ('q', $J_{F–H5';7';7''}$ = 23.9 Hz, 0.45, *E*), -105.0 ('dt', $J_{F–H5'}$ = 35.6 Hz; $J_{F–H7';7''}$ =17.6 Hz, 0.55, *Z*); MS *m/z* 368 (100, $MH^+$); HRMS calcd for $C_{15}H_{19}FN_5O_5$ $[M+H]^+$ 368.1370, found 368.1375. (*Z*)-**112** had: $^1H$ NMR (MeOH-$d_4$) δ 1.85 ('quint', *J* = 7.4 Hz, 2, H8',8''), 2.32 (dt, *J* = 17.3, 7.4 Hz, 2, H7',7''), 2.38 (t, *J* = 7.3 Hz, 2, H9',9''), 4.23 (t, *J* = 4.8 Hz, 1, H3'), 4.83 ('t', *J* = 5.0 Hz, 1H, H2'), 4.92 (dd, *J* = 4.7, 9.3 Hz, 1, H4'), 5.20 (dd, *J* = 9.2, 36.0 Hz, 1, H5'), 6.01 (d, *J* = 5.2 Hz , 1, H1'), 8.24 (s, 1, H2), 8.27 (s, 1H, H8); $^{13}C$ NMR (MeOH-$d_4$) δ 23.02 (C8'), 32.05 (d, *J* = 27.4 Hz, C7'), 33.82 (C9'), 74.91 (C2'), 76.27 (C3'), 79.34 (d, *J* = 6.6 Hz, C4'), 90.27 (C1'), 105.90 (d, *J* = 11.0 Hz, C5'), 120.46 (C5), 141.36 (C8), 150.60 (C4), 153.88 (C2), 157.34 (C6), 163.30 (d, *J* = 258.6 Hz, C6'), 177.09 (C10'). (*E*)-**112** had: $^1H$ NMR (MeOH-$d_4$) δ 1.84 ('quint', *J* = 7.4 Hz, 2H, H8',8''), 2.39 (t, *J* = 7.3 Hz, 2, H9',9''), 2.45 (dt, *J* = 23.7, 7.3 Hz, 1, H7'), 2.46 (dt, *J* = 23.7, 7.3 Hz, 1, H7''), 4.28 (t, *J* = 5.6 Hz, 1, H3'), 4.60 (ddd, *J* = 1.8, 5.8, 9.7 Hz, 1, H4'), 4.72 (dd *J* = 4.0, 5.2 Hz, 1, H2'), 5.44 (dd, *J* = 9.8, 19.9 Hz, 1, H5'), 6.00 (d, *J* = 3.7 Hz, 1, H1'), 8.23 (s, 1, H2), 8.25 (s, 1, H8); $^{13}C$ NMR (MeOH-$d_4$) d 22.45 (C8'), 28.65 (d, *J* = 26.9 Hz, C7'), 33.82 (C9'), 75.17 (C2'), 76.12 (C3'), 81.04 (d, *J* = 14.8 Hz, C4'), 90.58 (C1'), 106.73 (d, *J* = 24.7 Hz, C5'), 120.53 (C5), 141.68 (C8), 150.49 (C4), 153.91 (C2), 157.34 (C6), 165.88 (d, *J* = 258.6 Hz, C6'), 177.09 (C10').

**1-[6-(Tributylgermyl)-5,6-dideoxy-2,3-*O*-isopropylidene-*β*-D-ribohex-5(*E*) enofuranosyl]uracil (120a)** A suspension of **119a** (48 mg, 0.11 mmol) in toluene (2 mL) was deoxygenated ($N_2$, 1 hour), and then $Bu_3GeH$ (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 ($CHCl_3$//$H_2O$/$NaHCO_3$). The organic layer was washed with brine, dried ($MgSO_4$) and was evaporated. The residue was column chromatographed [EtOAc/hexane (7:3)] to give **120a** (33 mg, 57%) as a syrup: $^1$H NMR $\delta$ 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); $^{13}$C NMR $\delta$ 12.71 (Bu), 13.77 (Bu), 25.37 (C*Me*$_2$), 26.42 (Bu), 27.15 (C*Me*$_2$), 27.29 (Bu), 83.99 (C3'), 84.83 (C2'), 89.79 (C4'), 93.47 (C1'), 102.41 (C5), 114.65 (*C*Me$_2$), 134.02 (C6'), 140.60 (C5'), 141.64 (C6), 149.77 (C2), 162.96 (C4); MS *m*/*z* 525 (100, MH$^+$, $^{74}$Ge), 523 (70, MH$^+$, $^{72}$Ge), 521 (50, MH$^+$, $^{70}$Ge); HRMS calcd for $C_{25}H_{43}{}^{74}GeN_2O_5$ [M+H]$^+$ 525.2384, found 525.2385.

**1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(triphenylgermyl)-$\beta$-D-ribo-hex-5(*E*) enofuranosyl]uracil (120b)** Treatment of **119a** (48 mg, 0.11 mmol) with $Ph_3GeH$ (60 mg, 0.20 mmol; as described for **120a**) gave **120b** (46 mg, 72%) as a foam: $^1$H NMR $\delta$ 1.26 (s, 3, $CH_3$), 1.50 (s, 3, $CH_3$), 4.61 (ddd, $J$ = 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 (C*Me*$_2$), 84.14 (C3'), 84.69 (C2'), 89.48 (C4'), 93.92 (C1'), 102.61 (C5), 114.63 (*C*Me$_2$), 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 $C_{31}H_{31}{}^{74}GeN_2O_5$ [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 $Bu_3GeH$ (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, CH3), 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 (C*Me*$_2$), 27.38 (Bu), 84.70 (C3'), 85.39 (C2'), 90.63 (C4'), 91.27 (C1'), 114.97 (*C*Me$_2$), 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 $C_{26}H_{44}{}^{74}GeN_5O_3$ [M+H]$^+$ 548.2656, found 548.2650.

**9-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(triphenylgermyl)-*β*-D-ribo-hex-5(*E*)-enofuranosyl]adenine (121b)** Treatment of **119b**[120] (50 mg, 0.11 mmol) with $Ph_3GeH$ (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, CH3), 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 $\delta$ 25.44 & 27.11 (C*Me*$_2$), 84.13 (C3'), 84.81 (C2'), 89.75 (C4'), 90.74 (C1'), 114.38 (*C*Me$_2$), 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 $C_{32}H_{32}{}^{74}GeN_5O_3$ [M+H]$^+$ 608.1717, found 608.1722.

**1-[2,3-Di-*O*-acetyl-5,6-dideoxy-6-(*p*-toluenesulfonyl)-$\beta$-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 $Ac_2O$ (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 ($CHCl_3$//$H_2O$/HCl) and the organic layer was washed with $NaHCO_3$/$H_2O$, brine, dried ($MgSO_4$) and was evaporated to give **122b** (83 mg, 96%) of sufficient purity to be used in next step: $^1$HNMR $\delta$ 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 $\delta$ 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)-$\beta$-D-ribo-hex-5(*E*)-enofuranosyl]uracil (123a)** Treatment of **122b** (90 mg, 0.19 mmol) with $Ph_3GeH$ (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, H4'), 5.27 (t, $J$ = 5.2 Hz, 1, H3'), 5.32 (t, $J$ = 5.4 Hz, 1, H2'), 5.65 (d, $J$ = 8.1 Hz, 1, H5), 6.10 (d, $J$ = 5.1 Hz, 1, H1'), 6.17 (dd, $J$ = 5.4, 18.3 Hz, 1, H5'), 6.73 (dd, $J$ = 1.4, 18.3 Hz, 1, H6'), 7.18 (d, $J$ = 8.2 Hz, 1, H6), 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 (C2'), 72.96 (C3'), 83.18 (C4'), 87.43 (C1'), 103.47 (C5), 128.48, 129.44, 134.96, 135.21 (Ph), 131.02 (C6'), 139.34 (C6), 142.87 (C5'), 150.22 (C2), 162.63 (C4), 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 $C_{32}H_{31}{}^{74}GeN_2O^7$ $[M+H]^+$ 629.1343, found 629.1335.

**1-[5,6-Dideoxy-6-(triphenylgermyl)-$\beta$-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, H3'), 4.19 (dd, $J$ = 3.5, 5.0 Hz, 1, H2'), 4.62 ("t", $J$ = 5.5 Hz, 1, H4'), 5.20 (br s, 2, 2 × OH), 5.58 (d, $J$ = 8.1 Hz, 1, H5), 5.82 (d, $J$ = 3.2 Hz, 1, H1'), 6.20 (dd, $J$ = 5.3, 18.4 Hz, 1, H5'), 6.71 (dd, $J$ = 1.4, 18.3 Hz, 1, H6'), 7.32–7.46 (m, 16H, Ph & H6), 8.92 (br s, 1, NH); $^{13}$C NMR $\delta$ 73.82 (C3'), 75.10 (C2'), 85.81 (C4'), 91.11 (C1'), 102.52 (C5), 128.43, 128.87, 130.98, 134.85 (Ph), 136.36 (C6'), 139.54 (C6), 144.29 (C5'), 151.21 (C2), 163.69 (C4); MS $m/z$ 545 (100, $MH^+$, $^{74}$Ge), 543 (75, $MH^+$, $^{72}$Ge), 541 (45, $MH^+$, $^{70}$Ge); HRMS calcd for $C_{28}H_{27}{}^{74}GeN_2O_5$ $[M+H]^+$ 545.1132, found 545.1132.

**Method B**. A solution of **120b** (29 mg, 0.05 mmol) in TFA/H2O (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-*β*-D-ribo-hex-5-(E) enofuranosyl]-uracil (124a) Method A.** Treatment of **122b** (39 mg, 0.08 mmol) with $Bu_3GeH$ (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 × 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 × Ac); MS $m/z$ 569 (100, $MH^+$, $^{74}$Ge), 567 (72, $MH^+$, $^{72}$Ge), 565 (51, $MH^+$, $^{70}$Ge); HRMS calcd for $C_{26}H_{43}{}^{74}GeN_2O_7$ $[M+H]^+$ 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 $Bu_3GeH$ (29 mg, 0.031 mL, 0.12 mmol) was added and deoxygenation was continued for an additional 1 hour. The 2-mercaptoethanol (2 mg, 2 $\mu$L, 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-*β*-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); $^{13}$C NMR (MeOH-*d*4) $\delta$ 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, $MH^+$, $^{74}$Ge), 483 (77, $MH^+$, $^{72}$Ge), 481 (52, $MH^+$, $^{70}$Ge); HRMS calcd for $C_{22}H_{39}{}^{74}GeN_2O_5$ $[M+H]^+$ 485.2071, found 485. 2065.

**1-[5,6-Dideoxy-6-iodo-2,3-*O*-isopropylidene-$\beta$-D-ribo-hex-5(*E*)-enofuranosyl]-uracil (125)** A solution of NIS (22 mg, 0.10 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) was added dropwise to a stirred solution of **120a** (48 mg, 0.09 mmol) in $CHCl_3/CH_2Cl_2$ (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 $NaHSO_3/H_2O$ and the separated organic layer was washed with brine, dried ($MgSO_4$) and was evaporated. Purification on a short silica gel column ($CHCl_3$/MeOH, 30:1) gave **125** (34 mg, 92%) with data as reported.[138]

**9-[6-Bromo-5,6-dideoxy-2,3-*O*-isopropylidene-$\beta$-D-ribo-hex-5(*E*) enofuranosyl]adenine (126)** A solution of NBS (18 mg, 0.10 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) was added dropwise to a stirred solution of **121a** (50 mg, 0.09 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) at 0°C. After 6 hours, the reaction mixture was washed with $NaHCO_3/H_2O$ and brine and the separated organic layer was dried ($Na_2SO_4$) and was evaporated. Purification on a short silica gel column ($CHCl_3$/MeOH, 20:1) gave **126** (28 mg, 81%) with data as reported.[37]

**9-(5,6-Dideoxy-$\beta$-D-ribo-hex-5-enofuranosyl)adenine[5'-deoxy-5'-methylene-adenosine] (127)** A solution of **121a** (22 mg, 0.04 mmol) in $CF_3CO_2H/H_2O$ (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, H3'), 4.48 (dd, *J* = 5.3, 6.5 Hz, 1, H4'), 4.74 (t, *J* = 4.9 Hz, 1, H2'), 5.26 ("dt", *J* = 1.4, 10.5 Hz, 1, H6"), 5.41 ("dt", *J* = 1.5, 17.1 Hz, 1, H6'), 6.04 (d, *J* = 5.0 Hz, 1, H1'), 6.11 ("ddd", *J* = 6.6, 10.5, 17.1 Hz, 1, H5'), 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. $NH_4Cl/H_2O$ (0.5 mL) was added and the volatiles were evaporated. The residue was partitioned ($CHCl_3$//H2O/$NaHCO_3$) 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, H4'), 3.99 (dd, *J* = 3.0, 12.8 Hz, 1, H5'), 4.06 (dd, *J* = 4.2, 12.8 Hz, 1, H5"), 5.35 (dt, *J* = 2.1, 8.5 Hz, 1, H3'), 5.70 (d, *J* = 8.0 Hz, 1, H5), 6.43 ("t", *J* = 1.8 Hz, 1, H1'), 6.48 ("t", *J* = 2.3 Hz, 1, H2"), 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 $\delta$ 0.91–0.97 (m, 24H, 8 × CH3), 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); $^{13}$C NMR $\delta$ 12.60, 12.66, 13.05, 13.65 (CH), 16.92, 17.02, 17.22, 17.24, 17.27, 17.31, 17.36 (CH3), 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, $MH^+$, $^{74}$Ge), 785 (35,$MH^+$, $^{72}$Ge), 783 (25,$MH^+$, $^{70}$Ge); HRMS calcd for $C_{40}H_{53}{}^{74}GeN_2O_6Si_2$ $[M+H]^+$ 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-*d*4) $\delta$ 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) $\delta$ 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 $C_{28}H_{26}{}^{74}GeN_2NaO_5$ $[M+Na]^+$ 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 $^o$C. After 30 minutes, **132d** (186 mg, 1.12 mmol) was added and the yellow reaction mixture was allowed to warm to -40 $^o$C over 2 h. Saturated $NH_4Cl/H_2O$ (~ 4 mL) was added and the volatiles were evaporated. The residue was partitioned ($H_2O//CHCl_3$) 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): $^{1}$H 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); $^{13}$C 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, Cα); $^{19}$F 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 ($M^+$; $t_R$ = 24.20 min, *E*, $t_R$ = 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): $^{1}$H 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); $^{13}$C 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, Cα); $^{19}$F NMR δ -62.82 (s, 0.07), -63.06 (s, 0.93F) -109.2 (d, *J* = 20.7 Hz, 0.07 F), -121.2 (d, *J* = 33.9 Hz, 0.93 F); MS *m/z* 329 (100, $MH^-$); GC-MS *m/z* 330 ($M^+$; $t_R$ = 24.53 min, *Z*, $t_R$ = 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 $^{o}$C (oil bath) for 8 h and then was evaporated. The resulting brownish residue was partitioned between $CHCl_3$/brine. The separated organic layer was dried ($MgSO_4$), 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 $H_2O$ (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 $^{o}$C (oil bath) for 8 hrs. The resulting brownish residue was partitioned ($CHCl_3$//$H_2O$/brine), and the organic layer was dried ($MgSO_4$), 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 $^{o}$C (oil bath) for 8 hrs and then evaporated. The resulting brownish residue was partitioned between ($CHCl_3$/brine). The separated organic layer was dried ($MgSO_4$), 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,

0.024 mmol)] gave **135a** (10.5 mg, 61%: *E/Z*, 95:5) $^1$H NMR δ 6.48 (d, *J* = 10.8 Hz, 0.10H), 6.58 (d, *J* = 10.8 Hz, 0.10H), 6.72 (d, *J* = 15.5 Hz, 0.90H), 6.87 ((d, *J* = 15.5 Hz, 0.90H), 7.20-7.42 (m, 10H); GC-MS *m/z* 212 ($M^+$; $t_R$ = 20.20 min, *E*, $t_R$ = 20.10 min, *Z*).

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 δ 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** (22.1mg, 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 **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 μL, 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 δ 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 δ; 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 μL, 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 μL, 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 μL, 0.16 mmol) by method A gave **135d** (12 mg, 55%: *E/Z*, 83:17): $^1$H NMR ($CDCl_3$) δ 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%): $^1$H 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%): $^1$H 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): $^1$H 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): $^{1}$H 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); $^{19}$F NMR δ; -62.7 Hz; GC-MS *m/z* 295 ($M^{+}$; $t_R$ = 28.74 min, *E*, $t_R$ = 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): $^{1}$H 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); $^{13}$C 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, Cα); $^{19}$F 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 ($M^{+}$; $t_R$ = 20.3 min, *E*; $t_R$ = 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 thiopheniol (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): $^{1}$H

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); $^{13}$C NMR (for *E*-**142b**) δ 21.2 ($CH_3$), 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); $^{19}$F 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 ($M^+$; $t_R$ = 19.95 min, *Z*; $t_R$ = 21.01 min, *E*).

Treatment of **134b** (22.1 mg, 0.08 mmol, *E/Z*, 86:14) with thiopheniol (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 thiopheniol (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): $^1$H 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); $^{13}$C NMR δ 115.2 (d, $J$ =12.3 Hz, Cβ), 125.5 ($CF_3$), 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); $^{19}$F 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 ($M^+$; $t_R$ = 23.09 min, *E*, $t_R$ = 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 $C_{16}H_{15}FNaO_2S$ $[M+Na]^+$: 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); $^{13}$C 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); $^{19}$F 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): $^1$H 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); $^{13}$C NMR δ 18.0, 18.1 ($CH_3$), 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); $^{19}$F 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 ($M^+$; $t_R$ = 20.61 min, *E*, $t_R$ = 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** (3.4mg, 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): $^1$H 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 NMR δ 21.1 ($CH_3$), 23.4 ($CH_3$), 117.2 ($J$ = 13.1 Hz, Cβ), 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, Cα); $^{19}$F NMR δ -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): $^1$H NMR δ 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 NMR δ 17.96, 18.00 ($CH_3$), 20.04, 21.06 ($CH_3$), 125.06 (d, $J$ = 15.4 Hz, Cβ), 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, Cα); $^{19}$F NMR δ -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): $^1$H NMR δ 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 NMR (for *E*-**144a**) δ 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 $C_{14}H_{13}FN_1S$ $[M+H]^+$: 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

(s, 1H), 6.71 (s, 1H), 6.97 (d, *J* = 34.3 Hz, 1H), 7.49-7.60 (m, 2H), 7.64-7.71 (m, 1H), 7.99 ("d", *J* = 7.5 Hz, 2H); *Z*-**149** had: $^{1}$H NMR δ 6.82 (d, *J* = 21.8 Hz).

**(*E/Z*)-1-Fluoro-2-(3-5-dimethox*y*)-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%): $^{19}$F NMR ($CDCl_3$) δ -79.6 (d, *J* = 16.4 Hz, 0.10F), -84.3 (d, *J* = 32.1 Hz, 0.90F); GC–MS (EI) m/z 290 ($M^+$; $t_R$ = 24.49 min, *Z*, $t_R$ = 25.84 min, *E*). *E*-**146b** had: $^{1}$H NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.24 (d, *J* = 32.0 Hz, 1H), 6.43 (t, *J* = 2.2 Hz, 1H), 6.71 (s, 1H), 6.72 (s, 1H), 6.49 ("t", *J* = 1.6 Hz, 1H), 7.28-7.32 (m, 1H), 7.34-7.39 (m, 2H), 7.49 ("d", *J* = 7.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 55.3 (2 x O*CH*$_3$), 100.3 (C4), 106.8 (C2), 107.0 (C6), 117.6 (d, *J* = 12.2 Hz, Cβ), 127.7 (C4'), 130.0 (C2'), 131.9 (d, *J* = 2.9 Hz, C1), 134.5 (d, *J* = 5.6 Hz, C1), 134.4 (d, *J* = 5.8 Hz, C1), 152.5 (d, *J* = 310.9 Hz, Cα), 160.8 (C3/C5). *Z*-**146b** had: $^{1}$H NMR δ 6.70 (d, *J* = 16.8 Hz).

***E/Z*)-1-Fluoro-2-(3-methoxy-5-*tert*-butyldimethylsilyloxyphenyl)-1-phenylsulfonylethene (149).** Treatment of diethyl fluoro(phenylsulfonyl)-methylphosphonate (135 mg, 0.044 mmol) in THF (5 mL) with **148**[136] (157 mg, 0.59 mmol) as described for **134b** gave **149** (136 mg, 75%; *E*/*Z*, 89:11): $^{19}$F NMR ($CDCl_3$) 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 ($M^+$; $t_R$ = 29.21 min, *Z*, $t_R$ = 30.89 min, *E*). *E*-**149** had: $^{1}$H NMR ($CDCl_3$) 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); $^{13}$C NMR ($CDCl_3$) δ -4.4 (Si*CH*$_3$), 18.2 [*C*$(CH_3)_3$], 25.7 [C(*CH*$_3$)$_3$], 55.4 (O*CH*$_3$), 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 -0.20 (s, 6H), 0.78 (s, 9H), 3.54 (s, 3H), 6.00 (d, *J* = 32.0 Hz, 1H), 6.15 (t, *J* = 2.2 Hz, 1H), 6.44 ("t", *J* = 1.6 Hz, 1H), 6.49 ("t", *J* = 1.6 Hz, 1H), 7.06-7.11 (m, 1H), 7.12-7.17 (m, 2H), 7.21-7.29 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ -4.4 (Si*CH*$_3$), 18.2 [*C*$(CH_3)_3$], 25.7 [C(*CH*$_3$)$_3$], 55.3 (O*CH*$_3$), 106.1 (C2'), 107.4 (d, *J* = 8.1 Hz, C4'), 113.3 (d, *J* = 7.6 Hz, C6'), 117.6 (d, *J* = 12.0 Hz, Cβ), 127.6 (C4), 129.3 (C3), 130.0 (C2), 132.1 (C1), 134.4 (d, *J* = 5.8 Hz, C1), 152.6 (d, *J* = 310.9 Hz, Cα), 156.8 (C5'), 160.6 (C3'). *Z*-**150** had: $^{1}$H NMR δ 6.71 (d, *J* = 16.3 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 $^{o}$C for 10 minutes. Add TBAF (1M/THF; 71 μL, 0.071 mmol) and stir for an additional 25 minutes at 0 $^{o}$C. The volatiles were evaporated in vacuo and the residue was partitioned ($CHCl_3$//$H_2O$/$NaHCO_3$). The organic layer was washed (brine), dried (MgSO4), 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 (O*CH*$_3$), 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, Cα), 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-phenylsulfonylethene (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 (O*CH*$_3$), 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, Cα), 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-phenylsulfinylethene (153).** Compound **150** (*E/Z,* 90:10, 50 mg, 0.13 mmol) was dissolved in $CH_2Cl_2$ and cooled to -40 $^{o}$C. *m*-CPBA (11.01 mg, 0.064 mmol) dissolved in $CH_2Cl_2$ was added to the sulfide solution at -40 $^{o}$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 $^{o}$C. The solution was washed with $Na_2S_2O_4$, aqueous $NaHCO_3$ and water, giving after silica gel column chromatography ($CHCl_3$) pure **153** (44 mg,

85%): $^{19}$F NMR ($CDCl_3$) δ -121.61 (d, *J* = 36.7 Hz, 1F); GC–MS (EI) m/z 406 ($M^+$; $t_R$ = 30.62 min, *E*). $^1$H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ -4.4 (Si*CH*$_3$), 18.2 [*C*($CH_3$)$_3$], 25.6 [C(*CH*$_3$)$_3$], 55.3 (O*CH*$_3$), 107.6 (C2'), 107.9 (C4'), 108.0 (C6'), 113.9 (d, *J* = 7.0 Hz, Cβ), 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, Cα), 160.8 (C3').

**(*E*)-1-Fluoro-2-(3-methoxy-5-hydroxyphenyl)-1-phenylsulfinylethene (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 ($CDCl_3$) δ -121.61 (d, *J* = 36.7 Hz, 1F); GC–MS (EI) m/z 292 ($M^+$; $t_R$ = 28.95 min, *E*). $^1$H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 55.4 (O*CH*$_3$), 103.1 (C4'), 107.4 (d, *J* = 7.2 Hz, C4'), 109.3 (d, *J* = 6.9 Hz, C6'), 112.9 (s, Cβ), 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, Cα), 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 $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield **155** (102 mg, 70%): $^1$H 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%): $^1$H 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); $^{19}$F 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., $^1$H 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, $^1$H 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, $^1$H 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 ($EtO_2C(CH_2)_3ZnBr$) afforded 5-(5'-deoxy-2',3'-*O*-isopropylideneadenosin-5'-ylidene)-pentanoate as a single *E*-isomer. Deacetonization with TFA/$H_2O$ followed by saponification with NaOH/$H_2O$ 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'-vinylic 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'-fluorovinylic 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 germyldesulfonylation 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 auxillary vinyl sulfone precursors were synthesized by treating nucleoside 5'-aldehyde derivatives with sulfonyl-stabilized Wittig reagents. The pyrimidine and purine nucleosides underwent desulfonylation with either trialkyl- or triarylgermanes giving single 1-{6-[tributyl- or triphenylgermyl]-5,6-dideoxy-2,3-*O*-isopropylidene-*β*-D-ribohex-5(*E*)-enofuranosyl} uracil and the corresponding adenine counterpart. The 5'-(tributylgermyl)methylene-5'-deoxyadenosine and uridine derivatives underwent efficient halodegermylation reaction upon treatment with *N*-bromosuccinimide (NBS) or *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.

Germydesulfonylation was also successfully applied to the synthesis of multi-substituted alkenes located at C2' of the nucleoside. The vinyl 2'-phenylsulfone underwent germyldesulfonylation with $Ph_3GeH$ to produce 2'-deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2'-[(triphenylgermyl)methylene]uridine as a single *Z*-isomer. Desilylation with TBAF produced 2'-deoxy-2'-[(triphenylgermyl)methylene] uridine. Thus, germyldesulfonylation 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 (α-fluoro)vinyl sulfones with aryl thiols to provide access to vinyl and the virtually unknown class of (α-fluoro)vinyl sulfides. Reaction involving the conjugated vinyl or α-(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 α-(fluoro)vinyl sulfides. This type of radical thiodesulfonylation reaction was also successful in aqueous medium. In both fluorinated or unfluorinated cases, thiodesulfonylation 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 (α-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 thiodesulfonylation of α-(fluoro)vinyl sulfones produced mostly inseparable mixture of *E/Z* isomers of α-(fluoro)vinyl sulfides. The relative kinetics of thiodesulfonylation reaction was studied with both vinyl and (α-fluoro)vinyl sulfones. It was found that (α-fluoro)vinyl sulfides were approximately formed 4 times faster than its vinyl sulfide counterpart.

Thiodesulfonylation 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. Thiodesulfonylation of the suitably constructed (α-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 (α-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 (α-fluoro)alkenyl phenyl sulfide with iodomethane and silver tetrafluoroborate generated quantitatively the alkenyl or (α-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**

1. Wnuk, S.F.; Ro, B-O.; Valdez, C. A.; Lewandowska, E.; Valdez, N. X.; Sacasa, P. R.; Yin, D.; Zhang, J.; Borchardt, R. T.; De Clercq, E.; Sugar-Modified Conjugated Diene Analogues of Adenosine and Uridine: Synthesis, Interaction with S-Adenosyl-L-homocysteine Hydrolase, and Antiviral and Cytostatic Effects. *J. Med. Chem*. **2002**, *45*(12), 2651-2658.
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4. Wnuk, S. F.; Sacasa, P. R.; Lewandowska, E.; Andrei, D.; Cai, S.; Borchardt, R. T. Synthesis of 5'-functionalized nucleosides: S-Adenosylhomocysteine analogs with the carbon-5' and sulfur atoms replaced by a vinyl or halovinyl unit. *Bioorg. Med. Chem*. **2008**, *16*, 5424-5433.
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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.

**2.** Wnuk, Stanislaw F.; Sacasa, Pablo R.; Lallama, Jennifer; Lawrence, Vernon J.; Lewandowska, Elzbieta. Synthesis of S-adenosyl-L-homocysteine analogs with the sulfur atom replaced by "vinyl unit" via cross-coupling reactions. 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003.

**3.** Sacasa, P.R.; Andrei, D.; Dang, T. P.; Wnuk, St. F.; S-Adenosyl-L-homocysteine analogues with Carbon 5' and Sulfur Atoms replaced by halovinyl Unit. 233rd ACS National Meeting, Chicago, Il, United States, March 25-29, 2007.

4. Restrepo, J. A.; Sacasa, P. R.; Pitteloud, J.-P.; Wnuk, S. F. Application of germyldesulfonylation reactions in nucleoside chemistry**.** 235th ACS National Meeting, New Orleans, LA, United States, April 6-10, 2008.

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7. Quirke, J. M. E.; Sacasa, P. Development of a rogues' gallery that illustrates practical errors in carrying out TLC analyses. 239th ACS National Meeting, San Francisco, CA, United States, March 21-25, 2010.

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