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Sulfur- and Seleno-Sugar Modified Nucleosides. Synthesis, Chemical Transformations and Biological Properties.

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Contents

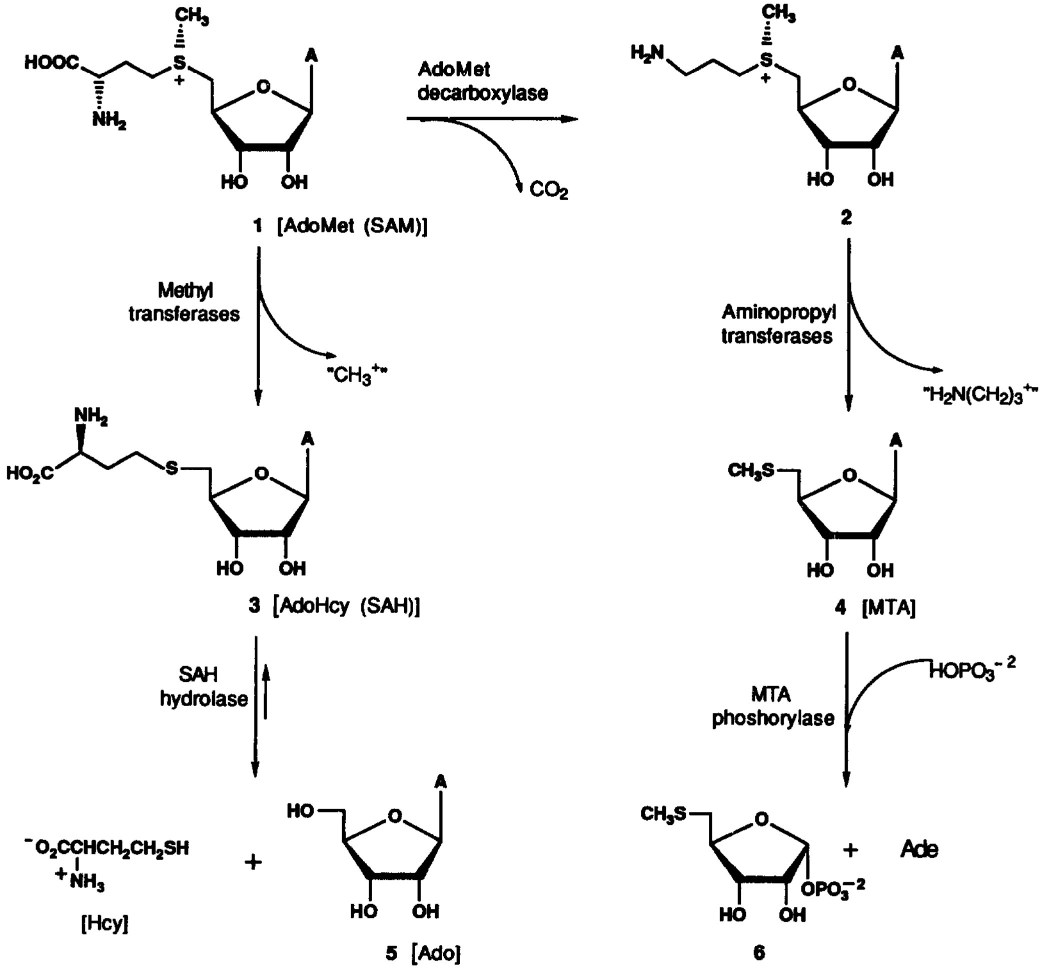
INTRODUCTION

Chemical modifications of naturally occurring nucleosides have been of interest for over 30 years and have been reviewed extensively.[2-4] Nucleoside analogues display a wide range of biological activities as anti-tumor, anti-viral and chemotherapeutic agents.[5-7] Furthermore, nucleoside chemistry has gained enormous importance in recent years since 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxynucleoside analogues were found to inhibit the human immunodeficiency viruses (HIV) that cause the AIDS disease.[8-10] The number of publications in this field has increased tremendously; specialized reviews on the synthesis of sugar-fluorinated nucleosides,[11] dideoxynucleosides from sugar precursors,[12] C5-substituted nucleosides,[13] carbocyclic nucleosides,[14] acyclonucleosides[15a] (including thioacyclonucleosides[15b,c]), and AIDS-driven nucleoside chemistry[16] have recently appeared.

However, a review of thionucleosides has not appeared although some aspects of their chemistry have been included in general nucleoside reviews.[2-4] Chemistry of nucleoside phosphorothioates and phosphorodithioates was the subject of a recent review and will not be discussed here.[17] This article will attempt a selective overview of the synthesis and chemistry of sulfur- and seleno-modified nucleosides in which a hydroxyl oxygen, or an oxygen or carbon atom of the sugar ring is replaced by a sulfur or selenium atom. In the past four years such nucleosides have gained increased attention since sulfur or selenium functionalities present in sugar precursors play a pivotal role in directing β-selective coupling reactions with bases. These functionalities can be readily removed from final nucleosides either thermally or reductively to produce anti-HIV dideoxynucleosides. Moreover, the application of newly developed reactions such as McCarthy's conversion of sulfoxides to α–fluorothioethers with DAST[18,19] allows fascinating modifications of nucleosides and synthesis of biologically potent derivatives.

The central role played by *S*-adenosyl-L-methionine (**1**; SAM, AdoMet)[20] in biological methylation reactions has stimulated considerable interest in the preparation of 5'-thionucleosides analogues. SAM (**1**) serves as the methyl donor for most enzyme-mediated methylations, producing *S*-adenosyl-L-homocysteine (**3**; SAH, AdoHcy). Alternatively, enzymatic decarboxylation of SAM (**1**) gives the corresponding 5'-aminopropyl sulfonium compound (**2**) that serves as an aminopropyl donor for the biosynthesis of the polyamines spermidine and spermine. The nucleoside by-product of that pathway is 5'-*S*-methyl-5'-thioadenosine (**4**; MTA).[21] Methylthioadenosine phosphorylase (MTAPase) effects glycosyl cleavage of MTA (**4**) to adenine (Ade) and 5-*S*-methyl-5-thioribose 1-phosphate (**6**) which is converted to methionine by a salvage pathway.[22] SAH (**3**) functions as a feedback inhibitor of crucial methylation enzymes,[20] and MTA (**4**) exerts feedback inhibition on polyamine biosynthesis.[21]

The enzyme *S*-adenosyl-L-homocysteine hydrolase (SAH hydrolase) catalyzes the hydrolysis of SAH (**3**) to adenosine (**5**; Ado) and L-homocysteine (Hcy) via a reversible oxidation, elimination, Michael addition, reduction mechanism.[20,23,24] Since it is crucial for continuing metabolism to remove intracellular SAH (3) in order for enzymatic methylation to proceed, inhibition of SAH hydrolase presents a rational target for anticancer and antiviral chemotherapy[25,26] and, in fact, antiviral activity has been correlated with SAH hydrolase inhibitory effects.[27,28] Additionally, it was found that 5'-*S*-isobutyl-5'-thioadenosine (**10**; R = *i*-Bu, SIBA) has significant inhibitory activity in some cells,[29] and 5'-*S*-phenyl-5'-thioadenosine (**10**; R = Ph) has been reported to have antiviral activity.[30] Recently, 9-(5-*S*-methyl-5-thio-β-D-xylofuranosyl)adenine, the first naturally occurring analogue of MTA (**4**), has been isolated from the Mediterranean nudibranch *Doris verrucosa*[31] and synthesized.[32]

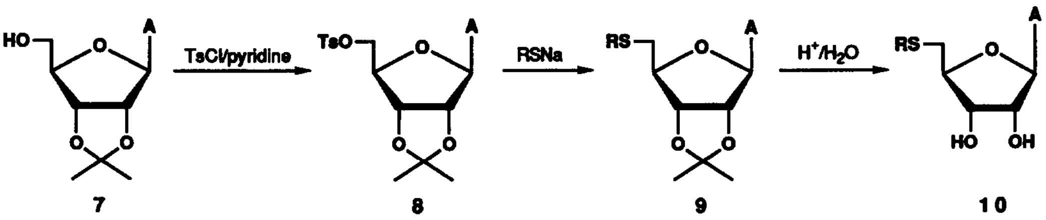


A = adenin-9-yl

1. 5'-*S*-ALKYL(or ARYL)-5'-THIONUCLEOSIDES

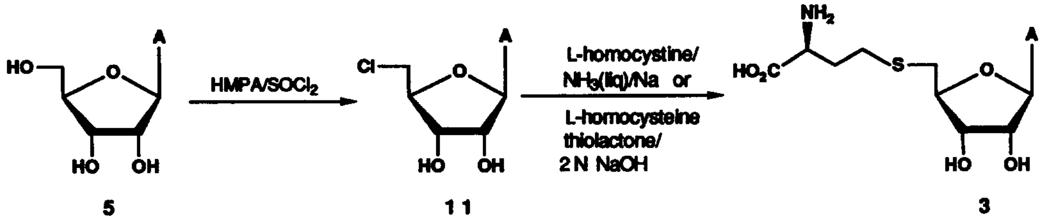
1.1. S-*Adenosylhomocysteine and related compounds*

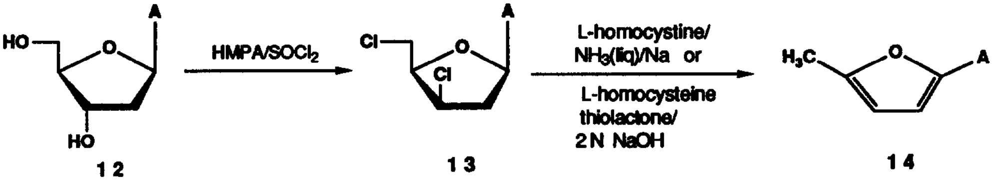
The first general route for the synthesis of 5'-thionucleoside analogues was modeled after the procedure developed by Baddiley and Jamieson for MTA (**4**),[33a] SAM (**1**),[33b] and SAH (**3**).[33c] The route involves: (i) protection of the 2' and 3'-hydroxyl groups of adenosine **5** using the isopropylidene group to give derivative **7**, (ii) activation of the nucleoside 5'-position in **7** by formation of the corresponding 5'-*O*-tosyl derivative **8**, (iii) displacement of the latter with sodium salts of thiols to give protected 5'-thioether **9**, and (iv) removal of the isopropylidene group with dilute acid to yield desired products of type **10**. This procedure has proved to be quite successful for the synthesis of a variety of 5'-thionucleosides of type **10**.[2-4,34,35]



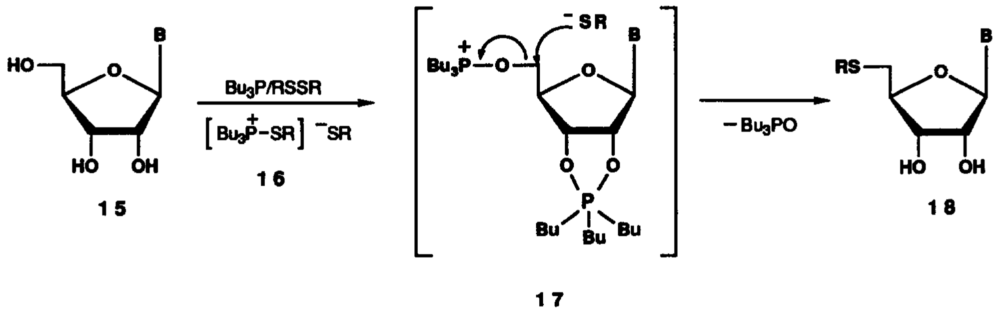
Ts = (4)$CH_3C_6H_4SO_2$

Borchardt *et al*. developed a shorter procedure for the preparation of SAH (**3**) and related compounds (including a 2'-deoxyadenosine analogue) by condensing 5'-chloro-5'-deoxyadenosine (**11**) and L-homocystine (disulfide of L-homocysteine) in liquid ammonia in the presence of sodium.[36] Treatment of **11** with homocysteine thiolactone in 2 N alkali also gave SAH (**3**).[37] Both methods employ the thionyl chloride-hexamethylphosphoramide (HMPA) reagent of Kikugawa and Ichino[38] to prepare 5'-chloro derivative **11** from adenosine (**5**). These routes eliminate the necessity for protection and deprotection of the 2',3'-cis diol function as well as the concern regarding the stability of 2',3'-*O*-isopropylidene-5'-*O*-tosyladenosine (**8**). Wang and Hogenkamp reinvestigated the synthesis of an SAH analogue involving 2'-deoxyadenosine under the reaction conditions used in both methods.[39] They found that chlorination of 2'-deoxyadenosine (**12**) under Kikugawa and Ichino conditions[38] did not yield 5'-chloro-2',5'-dideoxyadenosine but rather dichlorinated nucleoside 9-(3,5-dichloro-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)adenine (**13**). The latter under condensation conditions with homocysteine derivatives as in previous reports[36a,37] underwent double elimination and isomerization to form 9-(5-methyl-2-furyl)adenine (**14**).[39] Borchardt's procedure[36] seemed to be the most universal at the time and was widely used for preparing SAH analogues modified in the sugar, base or amino acid moiety[40,41] which act as inhibitors of *S*-adenosylmethionine-dependent methyltransferases.[40]



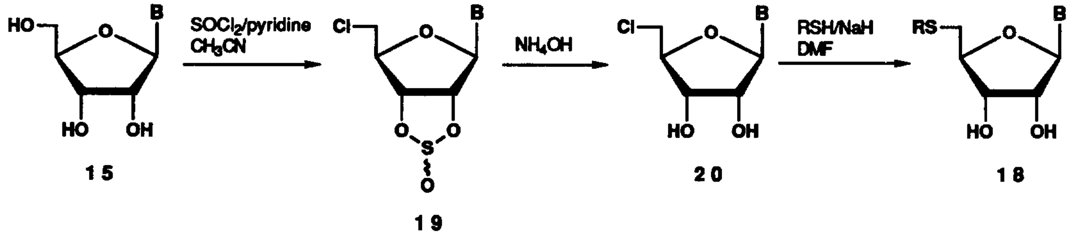


Hata *et al.* developed a one-step procedure for the synthesis of 5'-*S*-alkyl(or aryl)-5'-thionucleosides (**18**) by reacting unprotected purine and pyrimidine nucleosides **15** or 2'-deoxynucleosides with dialkyl or diaryl disulfides (especially 2,2'-dipyridyl disulfide) in the presence of tributylphoshine in pyridine.[42] The reaction apparently proceeds through phosphonium salt **16** which in turn reacts with nucleoside **15** to form the 5'-*O*-phosphonium salt **17**. The latter intermediate decomposes upon attack by alkyl(or aryl)thiolate anion to afford 5'-thionucleosides **18** and tributylphosphine oxide. Formation of the 2',3'-cyclic oxyphosphorane **17**, acting as a protective group for 2' and 3' hydroxyl groups, was also suggested.[42b] When an unsymmetrical disulfide (e.g. ethyl phenyl disulfide) was used, only the phenylthio group was introduced at the 5'-position to give **18** (R = Ph).[42b] Holy used 2-mercaptopyrimidine in the presence of dimethylformamide dialkyl acetals in a one-step procedure to prepare 5'-*S*-(pyrimidin-2-yl)-5'-thionucleosides from protected or unprotected nucleosides.[43]



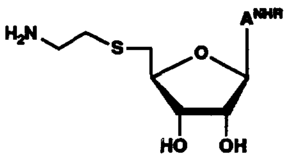
Serafinowski reported that condensation of *N*,*N*-bis[trifluoroacetyl]-L-homocystine dimethyl ester (disulfide of suitably protected L-homocysteine) with unprotected adenosine (or 3- or 7-deazaadenosine) in the presence of tributylphoshine (Hata method[42]) gave SAH (3) or the the corresponding deaza analogues[44a] with *S*-

tubercidinyl-L-homocysteine propyl ester showing potent aniviral activity.[44b] *S*-Formycinyl-L-homocysteine and its 3'-deoxy analogue have been prepared by condensation of the corresponding 5'-chloro-5'-deoxy derivatives with L-homocysteine sodium salt in liquid ammonia (Borchardt method[36]).[44c] Robins *et al.*[45] reported a convenient high-yield conversion of nucleosides **15** to 5'-*S*-aryl(or alkyl)-5'-thionucleosides **18** via 5'-chloro-5'-deoxynucleosides **20** without the use of HMPA or liquid ammonia. Treatment of ribonucleosides **15** with thionyl chloride and pyridine in acetonitrile resulted in quantitative formation of 5'-chloro-5'-deoxy-2',3'-*O*-sulfinylnucleosides (**19**), which upon treatment with aqueous methanolic ammonia gave **20** (94%). Reaction of the latter with sodium thiolate (derived from the thiol and sodium hydride in DMF) afforded 5'-thionucleoside derivatives **18** (86-94%).[45] Borchardt *et al.* have adopted this procedure.[46]

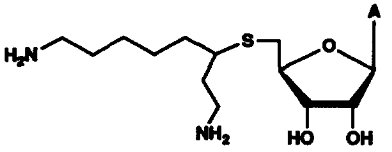


Reese *et al.* reported a general route to 5'-thionucleosides by treatment of 5'-chloro-5'-deoxynucleosides **20** with the conjugate base of 9-(4-methoxyphenyl)xanthen-9-thiol followed by acid-promoted removal of the 5'-*S*-[9-(4-methoxyphenyl)xanthen-9-yl] in the presence of pyrrole in high yields.[47] Such methodology appears to be advantageous relative to the standard generation of thiol functions from acetylthio precursors in basic media in which spontaneous oxidation to disulfides sometime occurs (see section 2). Reaction of **20** (in the purine series) with sodium thiosulfate in aqueous solution gave 5'-thiosulfuric acid derivatives which were also converted to purine 5'-thionucleosides.[48]

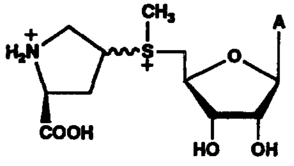
Using the above procedures, a wide range of sugar-, base-, and amino acid(or thiol)-modified SAH analogues was prepared for biological evaluation.[49-56] Particularly noteworthy were 5'-*S*-(2-aminoethyl)-N^6-(4-nitrobenzyl)-5'-thioadenosine (**21a**), a novel ligand for polypeptides associated with nucleoside transport,[49] and *S*-adenosyl-1,8-diamino-3-thiooctane[50a] (**21b**), or its structural analogues, which are potent inhibitors of polyamine biosynthesis.[50] A series of *S*-adenosylmethionine analogues of type **21c**, with restricted rotation in the amino acid fragment, were synthesized and shown to inhibit *S*-adenosylmethionine decarboxylase.[51] Furthermore, 8-amino-5'-*S*-phenyl-5'-thioguanosine was found to inhibit purine nucleoside phosphorylase.[52] Parry *et al.* synthesized selectively labeled 5'(*R* and *S*)-deuteriated analogues of SAM (1), SAH (3), and MTA (4),[54] and showed that the conversion of adenosine (5) to SAH (3) catalyzed by SAH hydrolase occurred with overall retention of configuration at C5'.[54b] Chiral deuteriated (*S*-adenosyl-*S*-methylsulfonio)propylamines and spermidines have been used to show that transfer of the aminopropyl group occurs with inversion of configuration during biosynthesis of polyamines.[55]



21a

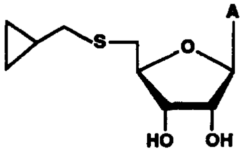


21b

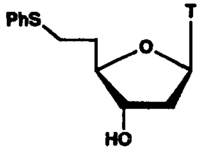


21c

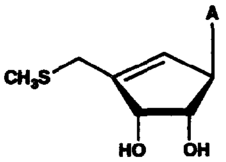
R = $(4)O_2NC_6H_4CH_2$



22a

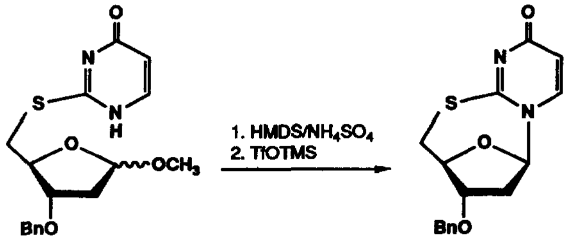


22b



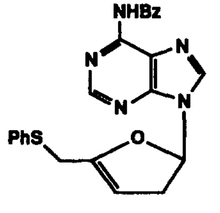
23

Furthermore, synthesis of a cyclopropyl analogue of SIBA (**10**, R = *i*-Bu), 5'-*S*-(cyclopropyl)methyl-5'-thioadenosine (**22a**), has been reported.[56] Examples of homothionucleosides such as 6'-phenylthio thymidine derivative **22b** (by iodide displacement from 5'-deoxy-5'-iodothymidine with the anion of thioanisole)[57a] and 7'-phenylthio[57b] analogues have been prepared. Also the 5'-methylthio derivative of the carbocyclic neplanocin A **23** has been synthesized by replacement of the 5'-chloro function with sodium thiomethoxide in DMF, but the product did not show significant biological activity.[58] ^{13}C NMR spectra of 5'-thionucleosides were investigated,[59] and a technique was developed for identification of 5'-*S*-methyl-5'-thioguanosine in the urine of lung cancer patients by gas chromatography/mass spectroscopy.[60]



24 **25**

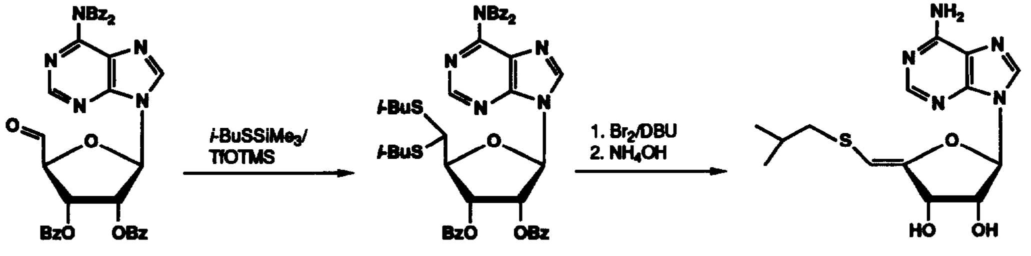
Bn = $C_6H_5CH_2$ Bz = C_6H_5CO



26

2,5'-*S*-thioanhydropyrimidine nucleosides[3,61,62] **25** and 8,5'-*S*-thioanhydropurine nucleosides[4,63] have been prepared as useful intermediates for further chemical transformations. Thus, treatment of 2-thiouridine with triphenylphosphine and diethyl azodicarboxylate in aqueous dioxane gave 2,5'-*S*-thioanhydrouridine.[61] Compound **24**, with uracil attached to the sugar precursor through a 2,5'-thioether linkage, was subjected to silylation with hexamethyldisilazane (HMDS). Intramolecular coupling in the presence of trimethylsilyl triflate occurred to provide a stereospecific synthesis of the thioanhydro pyrimidine β-D-2'-deoxynucleoside **25**.[62]

Moffatt *et al.* synthesized the vinyl thioether, 9-[5-deoxy-5(*Z*)-(isobutylthio)-β-D-*erythro*-pent-4-enofuranosyl]adenine (**29**), a molecule that incorporated structural features of both SIBA and the antibiotic 4',5'-didehydrosinefungin.[64a] Treatment of benzoylated adenosine 5'-aldehyde **27** with (isobutylthio)trimethylsilane and trimethylsilyl triflate in the presence of zinc(II) iodide gave thioacetal **28**. The latter when treated with bromine and DBU led to the elimination product which, after debenzoylation, provided **29** (plus the minor *E* isomer).[64a] They also observed that reaction of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine or its 5'-aldehyde with isobutyl disulfide/Bu_3P (Hata conditions[42]) led to formation of $5',N^3$-cycloadenosine derivatives rather than the desired 5'-thiosubstituted products.[64b] Addition of benzenethiyl radical to a 2'-deoxy-4',5'-unsaturated adenosine nucleoside having a good ionic leaving group at the 3'-position (e.g. phosphonate) gave the 5'-phenylthio-3',4'-unsaturated analogue **26** via a proposed single electron transfer and cleavage of the carbon-oxygen bond at the 3' position.[65] Such reactions can be used as model probes for radical induced DNA strand cleavages.[65]

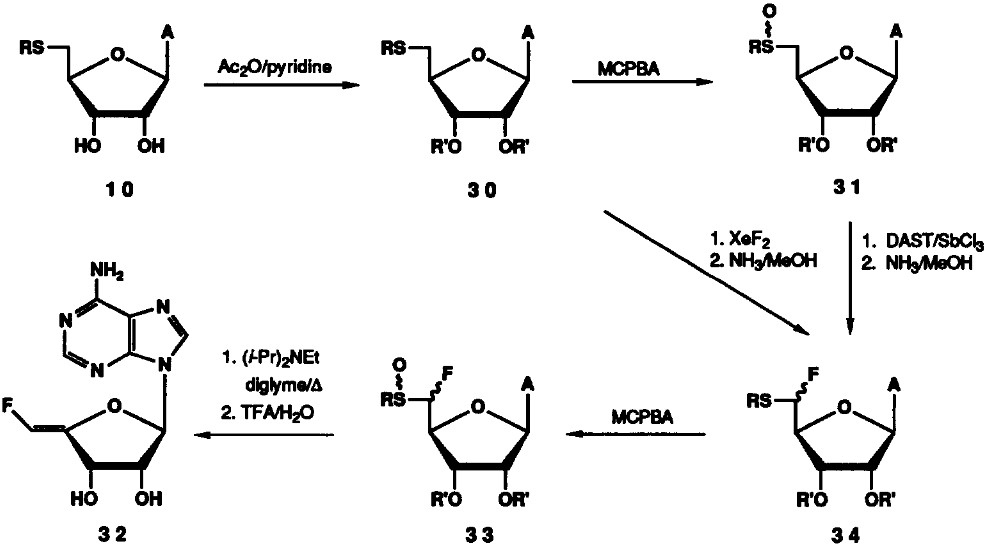


27 **28** **29**

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

1.2. *5'-Fluoro(or chloro)-5'-*S*-aryl-5'-thionucleosides and their transformation to 4',5'-unsaturated-5'-fluoro(or chloro)nucleosides as* S*-adenosylhomocysteine hydrolase inhibitors*

The discovery of McCarthy and co-workers that treatment of sulfoxides with DAST [(diethylamino)sulfur trifluoride] gave α-fluoro thioethers[18] in high yields opened possibilities for the synthesis of biologically attractive nucleoside α-fluoro thioether derivatives. Robins and Wnuk hypothesized that adenosine 5'-α-fluoro thioethers (thioacetal analogue) **34** (R' = H) or their oxidized analogues might function as mechanism-based inhibitors of SAH hydrolase if bound and converted into inhibitory species by the oxidation/elimination processes.[66] Treatment of phenyl sulfoxide **31** (R = Ph), derived by selective oxidation of acetylated sulfide **30** [~1 equiv. of MCPBA (3-chloroperoxybenzoic acid)/-40 °C] with DAST/ZnI_2/CH_2Cl_2 gave protected diastereomers of 5'-fluoro-5'-*S*-phenyl-5'-thioadenosine **34** (R' = Ac) as minor products plus deoxygenated starting material **30**. It was found that DAST/$SbCl_3$ provided rapid conversion of **31** (R = Ph) to **34** (5'*R*/*S*, ~2/3) in 68% purified yield with minimal color and by-product formation.[66,67] The sulfoxide/DAST/$SbCl_3$ procedure[19] proved to be general, giving good fluorination yields not only with the more reactive 4-methoxyphenyl thioether **31** (R = 4-$CH_3OC_6H_4$) but also with deactivated 4-chlorophenyl thioether **31** (R = 4-ClC_6H_4) and 5'-*S*-methyl thioether **48** as well.[66-68]

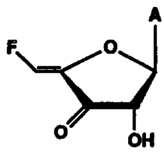


R = C_6H_5, $(4)CH_3OC_6H_4$, or $(4)ClC_6H_4$ R' = H, Ac, or CMe_2

Fluorination of protected nucleoside thioethers with xenon difluoride proceeds smoothly.[67-69] Treatment of sulfide **30** (R = 4-$CH_3OC_6H_4$; R' = Ac) with XeF_2/CH_2Cl_2 at low temperature gave the 5'-fluoro diastereomers **34** (5'*R*/*S*, ~ 3/2). Yields from these two fluorination processes were comparable, and diastereomeric ratios were in some cases opposite. The cost and manipulations required for oxidation of nucleoside thioethers to their sulfoxides, plus the ratios of excess DAST noted,[18,19] sometimes justify the cost of using stoichiometric amounts of XeF_2. Deacetylation and fractional crystallization in some cases gave single 5'-fluoro diastereomers **34** (R' = H). It was established by X-ray crystallography that in all cases 5'*R* fluoro diastereomers has lower-field ^{19}F NMR peaks than their *S* counterparts.[67-69] Similar chemistry has been successfully applied in the uridine series.[69]

McCarthy *et al.* reported parallel studies on the preparation of isopropylidene-protected 5'-fluoro-5'-*S*-(4-methoxyphenyl)-5'-thioadenosine diastereomers **34** (R' = CMe_2) by treatment of the corresponding sulfoxide of type **31** with DAST. Oxidation of crude **34** with MCPBA, followed by thermolysis (diglyme, Hunig's base, 145 °C, 48 h) of the resulting α-fluoro sulfoxide diastereomers **33** (*syn* 1,2-elimination of the sulfenic acid), gave a mixture of geometric *E* and *Z* isomer of 4',5'-didehydro-5'-deoxy-5'-fluoroadenosines (**32**) after acid deprotection.[70,71] The 5'(*Z*)-fluoromethylene isomer **32** is a potent mechanism-based inhibitor of SAH hydrolase[70,71] with antiretroviral,[70,71] antimalarial,[72] and antiinflammatory[73] activity. Similar chemistry has been applied for the preparation of fluoromethylene analogues of **32**, from araA and 2'-deoxyadenosine, which were competitive inhibitors of SAH hydrolase with lower biological activity.[71] 4',5'-Didehydro-5'-deoxy-5'-fluoro analogues of carbocyclic aristeromycin were also synthesized, employing a similar approach, and shown to be 2-3 times less potent as inhibitors of SAH hydrolase than the ribosyl vinyl fluoride **32**.[46,74]

Vinyl fluoride **32** was reported to inactivate the SAH hydrolase enzyme by reducing the enzyme-bound NAD$^+$ to NADH and quantitatively releasing fluoride ion as demonstrated by ^{19}F NMR (singlet at δ -118.8 ppm).[70,71,75] This was consistent with enzymatic oxidation of the 3'-OH group of **32** to a 3'-keto function forming a powerful Michael acceptor enone **35**. The latter was postulated to be attacked by an active nucleophile from the enzyme followed by release of fluoride ion in an addition-elimination process, which inactivated the enzyme.[70] It was also suggested that enone **35** might react with enzyme-sequestered water, releasing fluoride ion and generating the 3'-keto-5'-carboxaldehydes **36**.[71] In an effort to prove this mechanism, adenosine 5'-carboxaldehyde **37** (in a hydrated form) has been synthesized and shown to be a potent mechanism-based inhibitor of SAH hydrolase.[68,76] Additionally, the nucleoside 5'-α-fluoro thioethers **34** (R' = H) underwent spontaneous hydrolysis in aqueous buffer to give adenosine 5'-aldehyde-derived species which caused potent time-dependent inactivation of *S*-adenosyl-L-homocysteine hydrolase.[67,68] It was suggested that hydrolysis of the 5'-α-fluoro thioethers **34** (R' = H) involved loss of fluoride to give a cationic species that underwent nucleophilic attack by water and loss of a proton to give an intermediate thiohemiacetal **39**. Further elimination of thiol afforded aldehyde **37** (in tautomeric equilibrium with the hydroxy enolether form **38**).



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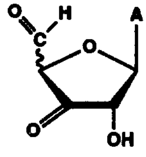

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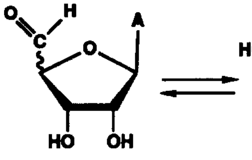

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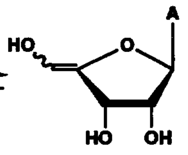

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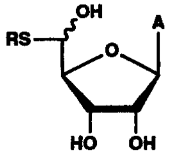

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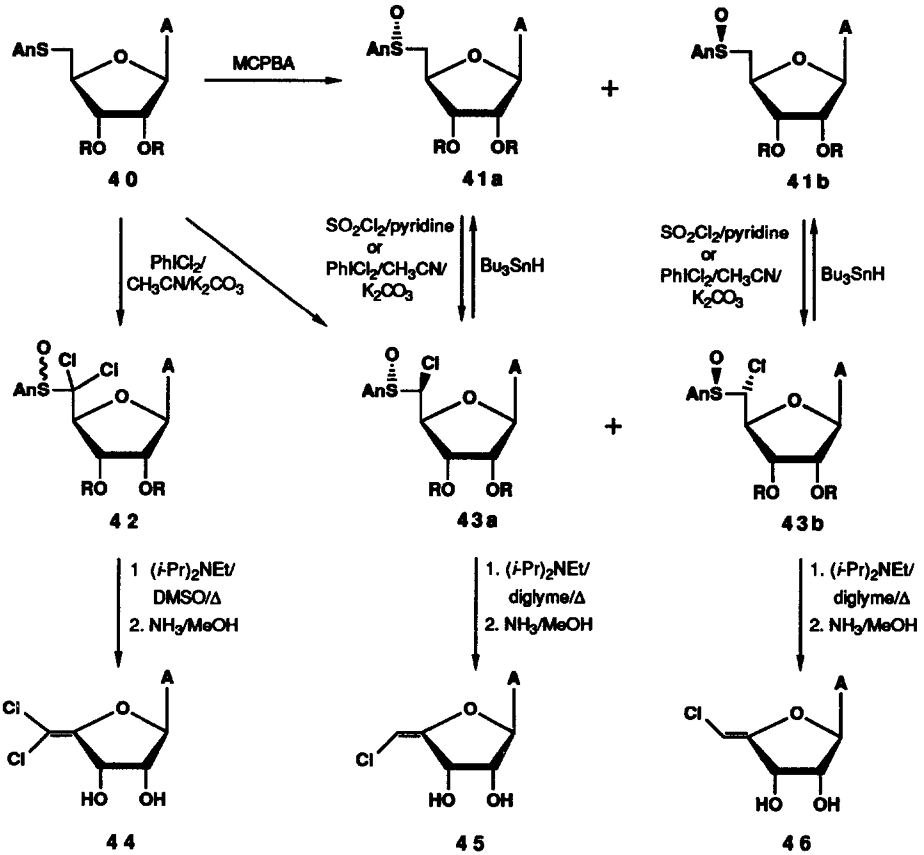
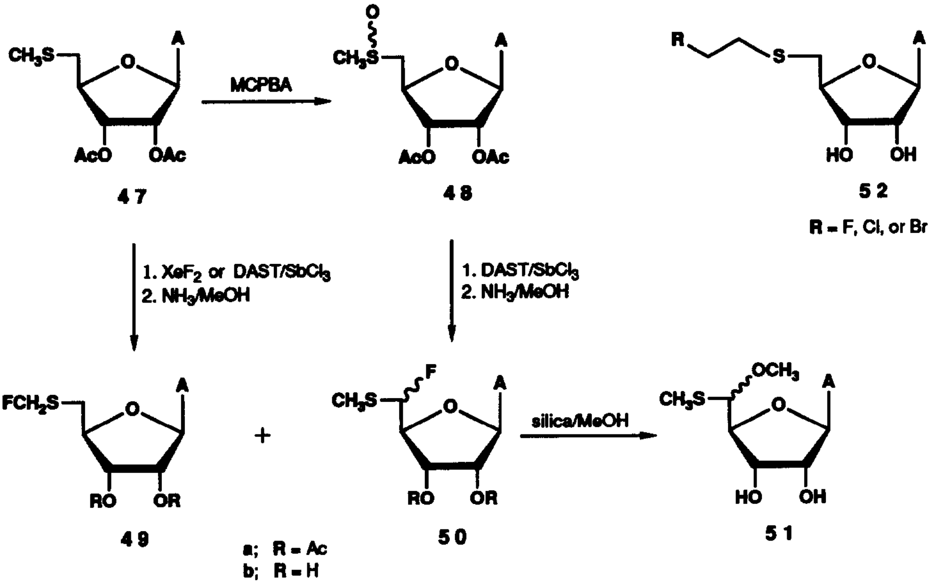
5'-Chloro-4',5'-unsaturated adenosine derivatives **45** and **46** have also been synthesized utilizing α-chloro sulfoxides **43a-b** as key intermediates.[71,77] Jarvi *et al.* employed sulfuryl chloride/pyridine for the α-chlorination of isopropylidene-protected adenosine 5'-sulfoxide diastereomers **41a-b** (R,R = CMe$_2$).[71] Thermolysis of the resulting α-chloro sulfoxide diastereomers **43a-b** and acid deprotection gave as a major product 5'-chloromethylene analogue **45**, whose stereochemistry was erroneously assigned as 5'(*Z*). Wnuk *et* *al.* reported that treatment of 2',3'-di-*O*-acetyl-5'-*S*-(4-methoxyphenyl)-5'-thioadenosine (**40**, R = Ac), or its sulfoxides **41a**(S_R) and **41b**(S_S) (with defined configuration at sulfur), with iodobenzene dichloride and potassium carbonate in acetonitrile resulted in the formation of 5'-chloro(and 5',5'-dichloro)-5'-deoxy-5'-[(4-methoxyphenyl)sulfinyl]adenosines (**42**, **43a-b**).[77] The α-chlorination of sulfoxides **41a**(S_R) and **41b**(S_S) occurred with predominant retention of configuration at sulfur to give **43a**(5'*S*, S_S) and **43b**(5'*R*, S_R), respectively. The sulfur and C5' stereochemistry resulting from this conversion were determined by X-ray crystallography in conjunction with radical-mediated reductive dechlorination. Thermolysis of the α-chloro sulfoxides and deprotection gave the 5'-chloromethylene derivatives (**45** and **46**). The authentic 5'(*Z*)-chloro-4',5'-didehydro-5'-deoxyadenosine (**46**) diastereomer was found to be a potent time-dependent inhibitor of *S*-adenosyl-L-homocysteine hydrolase.[68,77]



An = (4)$CH_3OC_6H_4$ R = H, Ac, or CMe_2

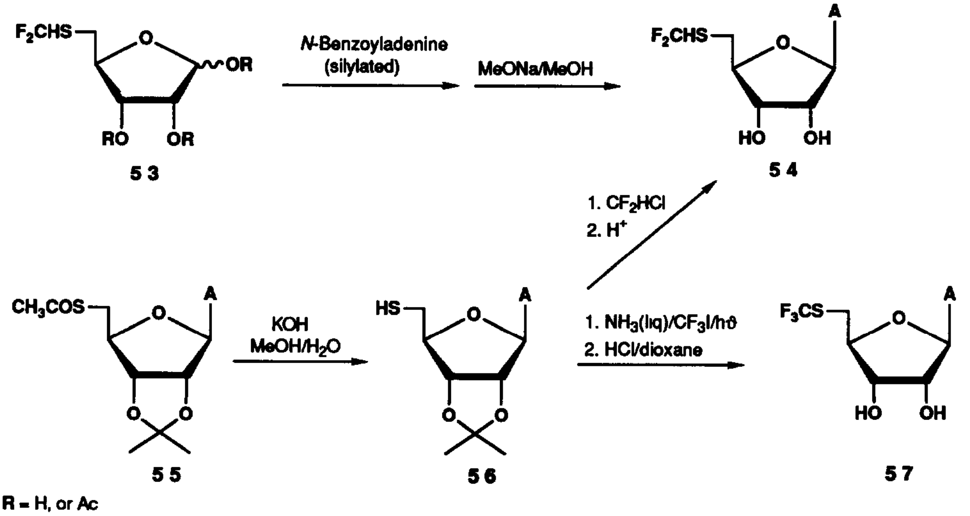
1.3. *5'-Fluorinated analogues of 5'-S-methyl-5'-thioadenosine as inhibitors of MTA phosphorylase and S-adenosylhomocysteine hydrolase*

Treatment of 2',3'-di-*O*-acetyl-5'-*S*-methyl-5'-thioadenosine (**47**) with XeF_2, or its sulfoxide **48** with DAST/$SbCl_3$,[66-68] or DAST[78] gave the regio- and diastereomeric mixture of 5'-*S*-(fluoromethyl)-5'-thio- (**49a**) and 5'-fluoro-5'-*S*-methyl-5'-thioadenosine (**50a**) derivatives in good yield. Recently, it was discovered that thioether **47** reacts directly with DAST/$SbCl_3$ to afford the regioisomeric mixture **49a**/**50a** in good yield, thus indicating that oxidation of thioethers to sulfoxides is unnecessary for the synthesis of α-fluorothioethers from thioethers utilizing DAST.[79] The sensitive fluoromethyl thioether **49a** was stable enough for chromatographic purification, deprotection to **49b**, and gentle manipulation. However, the 5'-fluoro-5'-methylthio diastereomers **50a** were labile and, after deprotection, decomposed significantly on silica in methanol-containing solvents to give mixed methoxy/methylthio acetals **51**.[66,67] However, deprotection and careful basic ion-exchange chromatography with MeOH did allow isolation of the very sensitive 5'-fluoro-5'-*S*-methyl-5'-thioadenosine (**50b**) diastereomers.[78a] Compound **49b** and to a lesser extent compound **50b** (rapid nonenzymatic degradation observed) were found to be potent inhibitors of MTAPase, with antiproliferative properties.[78a] The methylthio diastereomers **50b** were especially prone to decomposition in aqueous buffer solution, underwent hydrolysis to adenosine 5'-aldehyde **37** and were potent inhibitors of SAH hydrolase.[67] Compound **49b** inhibited SAH hydrolase to a lesser degree.



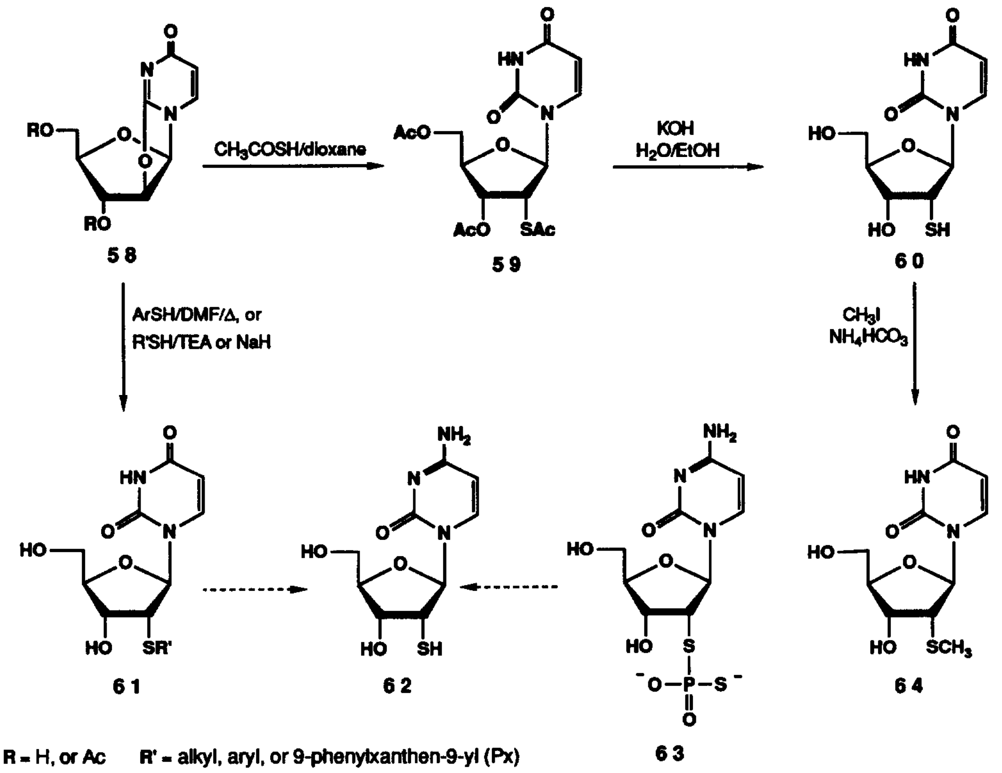
Suffrin *et al.* synthesized other 5'-haloalkyl analogues of MTA **52** with extended carbon chains.[80] Treatment of 5'-chloro-5'-deoxyadenosine (**11**) with 2-mercaptoethanol gave the 5'-[(2-hydroxylethyl)]thio derivative, which reacted with thionyl chloride, thionyl bromide, or DAST (isopropylidene-protected starting material used) to give corresponding 5'-[(2-haloethyl)thio] derivatives **52** in low yield, and the 5'-[(3-fluoropropyl)thio] derivative was prepared analogously.[80a] The fluoroalkyl derivative **52** (R = F) proved to be stable and showed potent growth inhibition of MTA phosphorylase-deficient or wild-type leukemia cell lines, and modest inhibition of SAH hydrolase activity.[80a]

Treatment of the sodium salt of methyl 2,3-*O*-isopropylidene-5-thioribofuranoside with FCH_2Cl, F_2CHCl,[81] or CF_3I[82] gave 5-deoxy-5-*S*-(mono, di, or trifluoro)methyl-5-thioribose, respectively after deprotection. The mono and difluoro **53** (R = H) analogues have antitumor activity,[81] and the trifluoromethyl compound is an inhibitor of a 5-*S*-methyl-5-thioribose kinase.[82] 5'-*S*-(difluoromethyl)-5'-thioadenosine (**54**), prepared by coupling of the acetylated 5-deoxy-5-*S*-difluoromethyl-5-thioribose **53** (R = Ac) with trimethylsilylated *N*-benzoyladenine, has been found to be an inhibitor, but not alternative substrate, of MTAPase.[83] 5'-*S*-Fluoroalkyl-substituted analogues of MTA were more efficiently prepared from an adenosine precursor. Treatment of 2',3'-*O*-isopropylidene-5'-*O*-tosyladenosine (**8**) with potassium thioacetate gave thioacetate **55**.[84] Generation of the 5'-mercapto function under basic conditions gave **56** which underwent alkylation with fluoroalkyl halogenated or triflated reagents to give 5'-[(fluoroalkyl)thio] derivatives **54** and **57** after deprotection. Monofluoroethylthioadenosine **52** (R = F), due to its decreased stability to acid deprotection was prepared analogously from the deprotected 5'-thioacetate.[84] Treatment of 5'-deoxy-5'-iodouridine with a mercury(II) trifluoromethylthio complex in acetonitrile for 2 days at 80 °C gave 5'-*S*-(trifluoromethyl)-5'-thiouridine in 59% yield.[85] Mono-, di-, and trifluoromethylhomocysteine (α-fluoromethylmethionine) have been prepared employing sulfide/XeF_2,[86a] and sulfoxide/DAST,[78b,86b] or by homocysteine mercaptide displacements with chlorodifluoromethane[86b,c] or trifluoroiodomethane.[86b]



2. 2'-*S*-ALKYL(or ARYL)-2'-THIONUCLEOSIDES

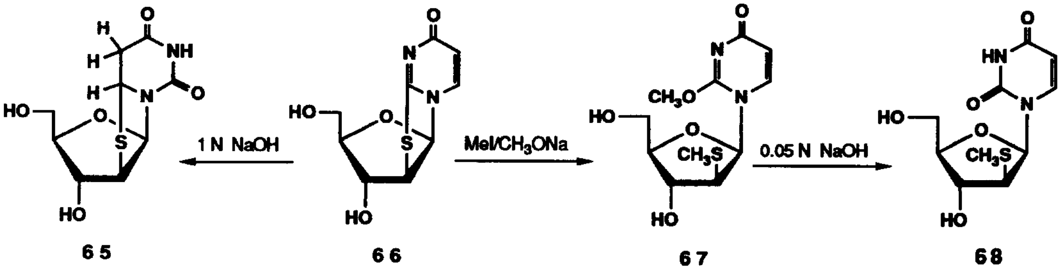
Synthesis of 2'-*S*-alkyl(or aryl)-2'-thionucleosides in the pyrimidine series can be achieved most conveniently by cleavage of the anhydro linkage in readily accessible 2,2'-cyclonucleosides **58** with alkyl or aryl thiols or their precursors. Thus, heating **58** (R = Ac) with thioacetic acid in dioxane at 110 °C gave the 2'-acetylthio derivative **59** in 65% yield.[87] Interestingly, when potassium acetate or benzoate was used for 2,2'-anhydro ring opening in **58**, uracil was detected as the main product. Deacetylation of **59** with ammonia or methanolic alkali also gave uracil predominantly, presumably via the neighboring attack of the 2'-mercapto function on anomeric carbon with elimination of uracil. However, hydrolysis of **59** with KOH at low temperature afforded deprotected, crystalline, and stable 2'-mercapto compound **60** in high yield.[87] Oxidation of **60** with iodine gave the corresponding disulfide, whereas treatment with methyl iodide afforded 2'-*S*-methyl-2'-thiouridine (**64**). Analysis of proton coupling constants[88] indicated a C2' endo or 80% S type conformation for the 2'-thioribonucleosides.[87]



The 2,2'-anhydrouridine **58** (R = H) reacts with a variety of substituted thiophenols in refluxing DMF to give 2'-*S*-aryl-2'-thiouridines **61** (R' = Ar) in high yield.[89] Reese *et al.* reported the synthesis of 2'-thio derivatives **61** by cleavage of **58** with arene and alkane thiolates (including ethanethiolate), formed with triethylamine and N^1,N^1,N^3,N^3-tetramethylguanidine as bases,[90] and application of sodium hydride was also described.[91] Opening of the anhydro linkage in the pyridazine cyclonucleosides under similar conditions afforded the corresponding 2'-*S*-benzylthio derivatives.[92] Heating of 2'-*S*-(4-methoxybenzyl)-2'-thiouridine **61** (R' = $4\text{-}CH_3OC_6H_4CH_2$) with thiophenol in the presence of trifluoroacetic acid gave 2'-deoxy-2'-mercaptouridine (**60**), which was indirectly converted to cytidine analogue **62** using the relatively easily acid-removable 9-phenylxanthen-9-yl (Px) protecting group for the 2'-mercapto function.[93] The latter compound was also reported to be synthesized by an intramolecular ring opening reaction on 2,2'-anhydrocytidine with a 3'-phosphorodithioate intermediate, followed by acid phosphatase-promoted hydrolysis of the putative 2'-phosphorodithioate **63**,[94] but spectroscopic characterization differed from that of Reese *et al.*[93]

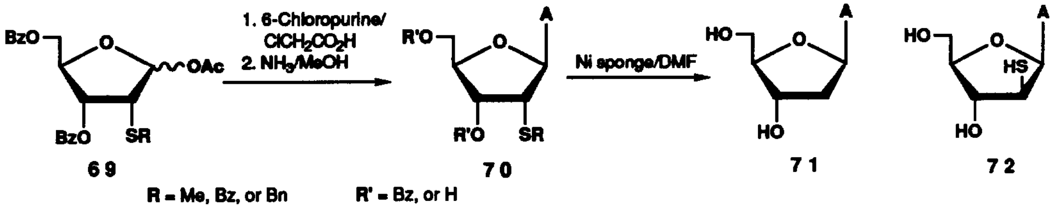
Brown *et al.*[95a] and Furukawa *et al.*[95b] had reported that treatment of **58** (R = H) or its 3',5'-diacetyl derivative with excess sodium ethanethiolate in DMF gave the *xylo* 3'-deoxy-3'-ethylthio derivative, presumably via a 2',3'-anhydro (*ribo* epoxide) or a 2',3'-acetoxonium ion intermediate, but their results (assignments) were questionable.[90] Proof that direct substitution of **58** with thiols occurred at C2' to give *ribo* configuration thioethers was provided by X-ray crystallography of 2'-deoxy-2'(S_S)-[(4-methoxyphenyl)sulfinyl]uridine (**91**; R = $4\text{-}MeOC_6H_4$, R' = H).[91] In addition, it was shown that **91** had a $^2T_3$ conformation (with a furanose pseudorotation angle of 179.4°), close to that predicted by Ueda (C2' endo conformation) for 2'-thioribonucleosides.[87] Furthermore, the *ribo* **61** and *arabino* **68** 2'-thionucleosides had vicinal $J_{1'\text{-}2'}$ coupling constants of about 9.0 and 6.5 Hz, respectively.

Shibuya and Ueda also reported the synthesis of the *arabino* 2'-*S*-methyl-2'-thio-uracil nucleoside **68** and cytosine analogues by ring opening of the corresponding 2,2'-*S*-thioanhydro compound **66** with methyl iodide and sodium methoxide in methanol.[96a] Initial methylation of the sulfur atom of the S-cyclo linkage was followed by nucleophilic substitution with methoxide to give **67**. Treatment of **67** with aqueous alkali afforded **68** in good overall yield. Interestingly, sodium methoxide did not cleave the sulfur bridge in **66**. However, alkaline hydrolysis of **66** gave the 2'-deoxy-2',6-epithio-5,6-dihydro derivative **65**, presumably via Michael addition of the intermediate *arabino* 2'-mercapto function across the 5,6 double bond of the uracil moiety.[87,96a]



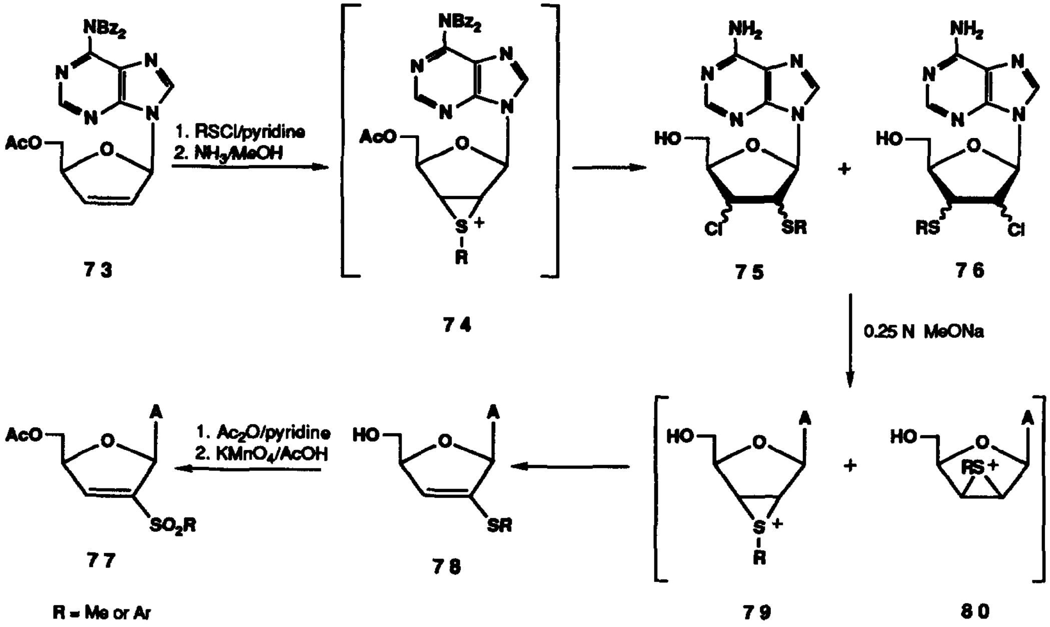
Uridine thioepoxides with both the *ribo* and *lyxo* configuration were prepared by Ueda *et al.* and were desulfurized by treatment with triphenylphosphine in refluxing dioxane to give 2',3'-didehydro-2',3'-dideoxyuridine.[96b] Interestingly the *ribo* thioepoxide was quite stable in contrast to the *ribo* epoxide which underwent spontaneous conversion to the 2,2'-anhydrouridine derivatives. 2'-Thiouridine (**60**) has been converted via its 2'-*S*, 3'-*O*-alkylidene derivatives into the corresponding 3'-*O*-alkyl-2'-deoxyuridines under tin radical-mediated conditions, but other 2'-thionucleosides did not undergo this transformation.[97] Recently 2',3'-di-*S*-(4-toluyl)-2',3'-dithiouridine and its *xylo* analog were prepared by displacement of mesylates with toluene-4-thiolate. Oxidation to the corresponding bis-sulfones and radical desulfonylation gave 2',3'-didehydro-2',3'-dideoxyuridine.[98] Other bis-thioether derivatives including 2',5'-di-*S*-phenyl-2',5'-dithiouridine and 3',5'-bis analogues have been reported.[99]

2'-Thioadenosine derivatives **70** (R' = H) were prepared by coupling the corresponding protected 2-thio-D-ribofuranoside **69** with 6-chloropurine in the presence of chloroacetic acid (β/α, ~2:1), followed by amination and debenzoylation with methanolic ammonia;[100a] also a 1,2-dithiosugar precursor has been used in such a coupling approach.[100b] Attempts to prepare free 2'-mercapto derivatives by debenzoylation of **70** (R and R' = Bz) in basic MeOH gave adenine, presumably through 1,2-episulfide formation and ejection of the base.[100a] However, Reese *et al.* used the 9-(4-methoxyphenyl)xanthen-9-yl protecting group[47] on the 2'-thio function to obtain 2'-thioadenosine as a crystalline solid in 78% yield.[101] Desulfurization of 2'-*S*-methyl-, 2'-*S*-benzoyl-, and 2'-*S*-benzyl-2'-thioadenosines **70** gave 2'-deoxyadenosine **71**.[100a]



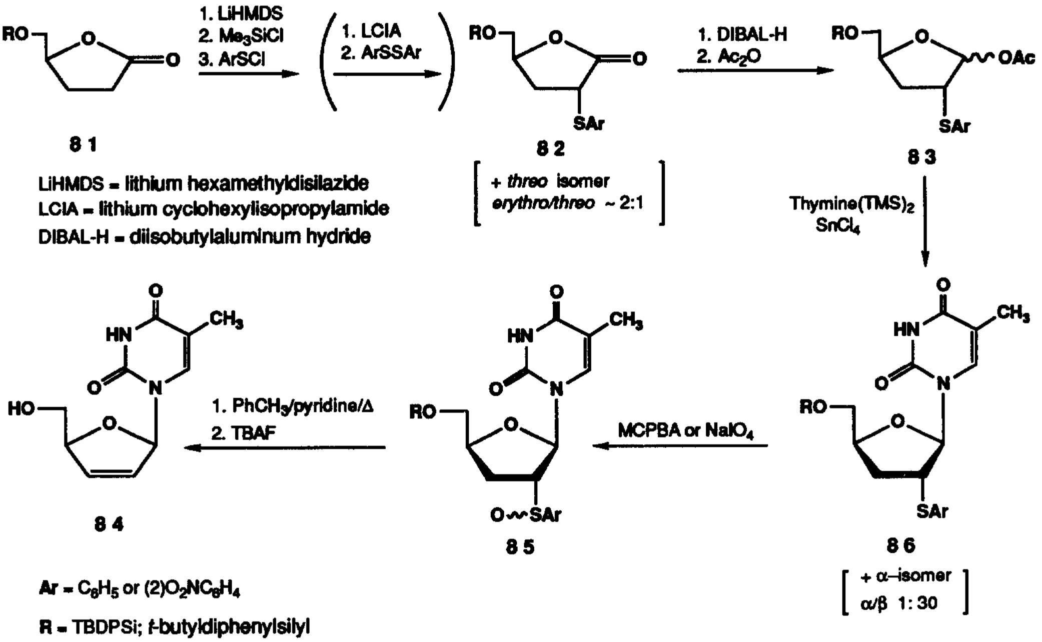
In the purine series, various 2'-thio analogues have been prepared by methods developed for other substituents and these approaches have been reviewed.[2,4] These methodologies involve: (i) protection of 3' and 5'-hydroxyls, (ii) activation of the 2'-hydroxyl group, and (iii) substitution at C2' with inversion of configuration followed by deprotection; or epoxide ring opening. These strategies have been used, for example, to synthesize 2'-thio-arabinofuranosyladenine **72**[101,102] and 2'(*R*)-thioneplanocin A.[103a] The X-ray structure of the latter *arabino* carbocyclic analogue had a C2'-exo conformation.[103b] A number of 2'-deoxynucleosides have been prepared for the first time by desulfurization of 2'-thio derivatives using Raney nickel.[2]

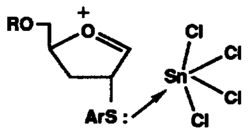
Reaction of the protected 2',3'-didehydro-2',3'-dideoxyadenosine **73** with arene- or methanesulfenyl chloride gave regioisomeric mixtures of β-chloro sulfides **75** and **76**.[104] The reaction proceeded through the *ribo* thiiranium ion intermediate **74** (or the corresponding *lyxo* isomer) followed by nucleophilic attack of chloride ion in a *trans* fashion. Methanesulfenyl chloride gave a mixture of the four possible *trans* β-chloroalkane sulfides, whereas the arenesulfenyl chloride gave three isomers since the *arabino* 2'-chloro analogue was not formed due to the steric effect of the base. Treatment of *trans* β-chloroarene/alkane sulfides **75** and **76** with sodium methoxide in MeOH gave a single 2'-ene sulfide **78** in all cases. The reaction presumably took place via *ribo* thiiranium intermediate **79** or its *lyxo* isomer **80**, from which H2' is abstracted by base followed by cleavage of the 3'-carbon-sulfur bond. Acetylation of **78** (R = CH_3), followed by oxidation, gave the 2'-ene sulfone **77**. Also, the separated β-chloroalkane sulfides **75** and **76** (R = CH_3) were acetylated (Ac_2O/pyridine), oxidized ($KMnO_4$/AcOH), and subjected to *cis* elimination (25% solution of pyridine in dioxane at 50 °C) to produce 2'-ene sulfone **77** and the analogous 3'-ene sulfone, respectively.[104]



2.1 *Precursors to 2',3'-unsaturated nucleosides*

Recently, Wilson and Liotta[105] and Kawakami *et al.*,[106] reported synthesis of 2'-*S*-phenyl-2'-thiopyrimidine nucleoside **86** using a novel convergent approach that has already been reviewed.[12] They discovered high stereoselectivity (β/α; ~10:1 to ~30:1) in the coupling reaction between 2,3-dideoxy-2-phenylthio-D-*erythro*-pentofuranose derivative **83** and silylated pyrimidine bases in the presence of tin(IV) chloride. Sugar precursor **83** was obtained by sulfenylation of the readily available γ-lactone **81**, followed by reduction of the resulting *erythro* 2-phenylthio γ-lactone **82** with diisobutylaluminum hydride (DIBAL-H), and subsequent acetylation. High β-selectivity was believed to be directed by formation of episulfonium ion 88[105] similar to the neighboring group participation of 2-acyloxy group 89 in the *ribo* series.[107] Tin(IV) chloride was also thought to be coordinated to the phenylthio group during the coupling reaction to form complex 87 raising β-selectivity due to steric hindrance at the α-face of cation 87.[106] Oxidation of sulfides 86 to sulfoxides 85 and thermal elimination gave the desired 2',3'-didehydro-2',3'-dideoxynucleosides derivative 84 in good yield.

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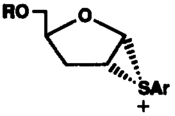
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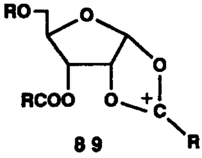
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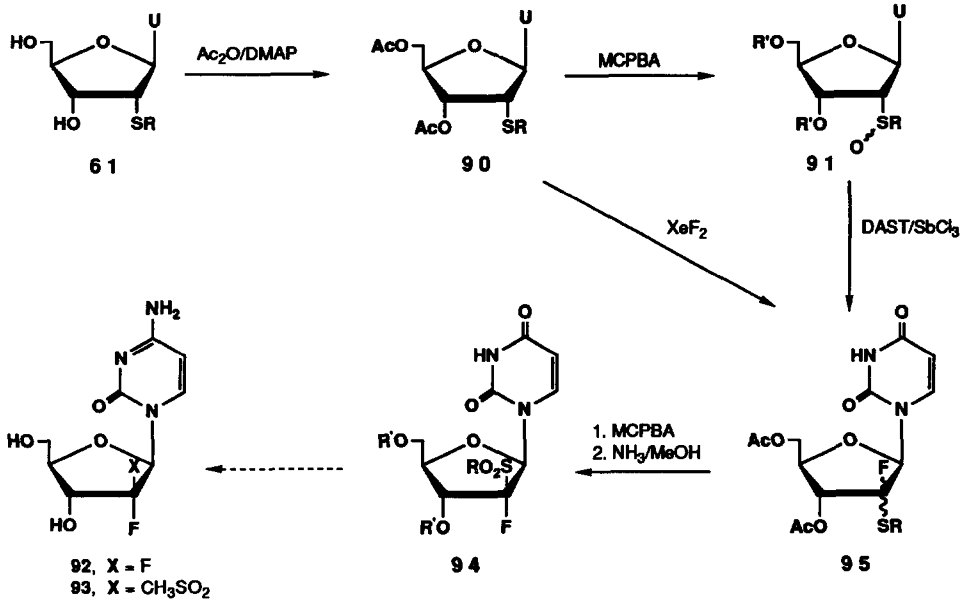
Liotta's[105] and Kawakami's[106] methodology, which employed easily removable thio substituents at C2 in the sugar precursor, not only gave access to 2',3'-didehydro-2',3'-dideoxynucleosides from 2',3'-dideoxy furanoses but also increased the β-selectivity for preparation of 2'-deoxy or 2',3'-dideoxynucleosides. A 2,2-diphenylthio analogue of 83 was recently introduced by Kawakami *et al.* in order to overcome the stereoselectivity problem in the phenylsulfenylation reaction of γ-lactone 81.[108] Unfortunately, such a 2,2-diphenylthio precursor, when coupled with silylated pyrimidine bases, gave the desired nucleosides with lower stereoselectivity (β/α, ~4:1) and lower yield. Wilson and Liotta have developed a diastereoselective phenylsulfenylation procedure for **81** employing *N*-(phenylthio)lactams under nonbasic conditions.[109]

2.2 ***2'-[Alkyl(or aryl)sulfonyl]-2'-deoxy-2'-fluoronucleosides as potential inhibitors of ribonucleoside diphosphate reductase***

A multistep synthesis of 2'-deoxy-2',2'-difluorocytidine **92** via coupling of 2-deoxy-2,2-difluoro-D-ribose was reported a few years ago.[110,111] Compound **92** has potent anticancer activity against solid tumors[6] and its 5'-diphosphate functions as a potent mechanism-based inhibitor of the ribonucleoside diphosphate reductase (RDPR) from *Escherichia coli*.[112] Robins *et al*. designed and synthesized compound **93** from its parent nucleoside.[91] The electronic analogue **93** of the 2',2'-difluoro nucleoside **92** has geminal electronegative fluoro and methylsulfonyl substituents at C2'. Treatment of the 2,2'-anhydrouridine **58** (R = H) with 4-methoxybenzenethiolate or methylthiolate (RSH/NaH/DMF) gave 2'-thio derivatives **61**. Acetylation of **61** gave protected sulfides **90**, which were oxidized to the corresponding sulfoxides **91** (R' = Ac) in high overall yield. Treatment of sulfides **90** with XeF_2, or their sulfoxides **91** (R' = Ac) with DAST/$SbCl_3$, gave the α-fluoro diastereomers **95** (2'*R*/*S*, ~1:5.5) in good yield. 2'-Methylthio analogue **95** (R = CH_3) was unstable, but *in situ* oxidation of the crude reaction mixture with MCPBA gave the stable α-fluoro sulfones **94** (R'= Ac; 2'*R*/*S*, ~1:4.6). Recrystallization gave the major diastereomer **94** (R' = Ac) with a higher field ^{19}F NMR resonance whose *S* configuration at C2' (fluorine down) was confirmed by X-ray crystallography. Compound **94**(2'*S*) was converted to its cytidine counterpart **93**(2'*S*) and deprotected with methanolic ammonia.[91]

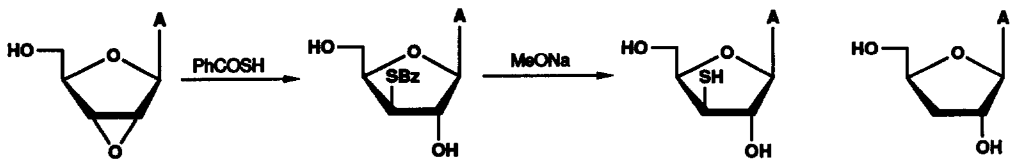


R = (4)$MeOC_6H_4$, or CH_3 R' = H, or Ac   U = Uracil-1-yl

Interestingly, fluorination of 2'-methylthio sulfide **90** with XeF_2, or its sulfoxide **91** with DAST, occurred in a regiospecific fashion giving no detectable fluorination at the methyl group in either method. In contrast, reaction of acetylated MTA derivatives **47** with XeF_2 and **48** with DAST (section 1.3) produced regioisomeric mixtures. These results are contrary to literature reports, in which fluorination of mixed thioether derivatives occurred exclusively at the methyl group.[18,19,86a,b] Steric and electronic effects at the vicinal azaacetal carbon (C1') might direct attack of fluoride to the less hindered α-face at C2' of an intermediate sulfenium cation to give fluorinated products with the *ribo* orientation.

3. 3'-*S*-ALKYL(or ARYL)-3'-THIONUCLEOSIDES

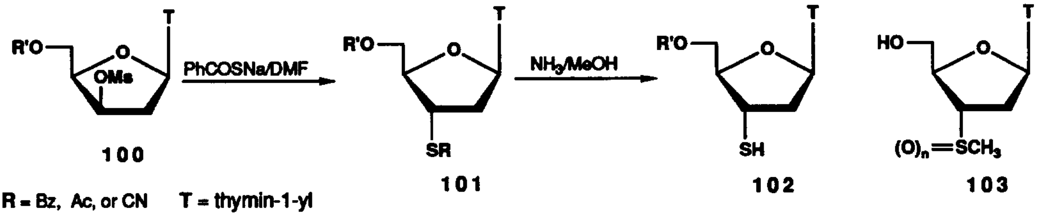
3' Sulfur-substituted nucleosides were prepared by: (i) coupling of sulfur-modified sugar derivatives with heterocyclic bases,[106b,113-115] (ii) direct nucleophilic displacement of activated 3'-hydroxyl groups with inversion of configuration at C3',[10,116-119] (iii) opening of *ribo*/*lyxo* epoxides or thioepoxides,[96b,117a,120,121] and (iv) cleavage of 2,3'-anhydronucleosides or cyclonucleosides bridged by sulfur.[122-125] Related chemistry has been previously reviewed[2-4] and similar approaches have been discussed in the case of 2'-sulfur modified analogues (section 2). It is noteworthy that opening of 2',3'-anhydroadenosine **96** with thiobenzoic acid is highly regioselective and only the *xylo* 3'-thio product **97** was isolated.[117a] The thiobenzoate **97** (or its *ribo* isomer), upon careful hydrolysis with sodium methoxide under nitrogen, gave the 3'-thiol *xylo* product **98** (or its *ribo* isomer).[113,117] Although the 3'-thiol compounds are more stable than their 2'-mercapto counterparts with respect to glycosylic bond cleavage, they also are easily oxidized to disulfides and participate in migration of protecting groups. Desulfurization of 3'-thio substituted derivatives (e.g. **97**) with Pd/C or Ni-sponge gave 3'-deoxyadenosine (cordycepin) **99** in good yield.[117a] Similarly, opening of *ribo* epoxides derived from tubercidin with sodium benzylthioate in hot THF gave only the *xylo* 3'-*S*-benzylthio derivative, which was isomerized (after 2'-OH mesylation) with sodium benzoate in DMF to give the *arabino* 2'-*S*-benzylthio isomer via an episulfonium intermediate. Desulfurization of the 2'(or 3')-*S*-benzylthio isomers with Raney Ni gave 2'(or 3')-deoxytubercidin, respectively.[120]



96 **97** **98** **99**

Recently 3' sulfur-substituted analogues of AZT have been prepared by several research groups. Treatment of protected 3'-*O*-mesyl *xylo* thymidine **100** with sodium thiobenzoate in DMF gave 3'-thiobenzoate

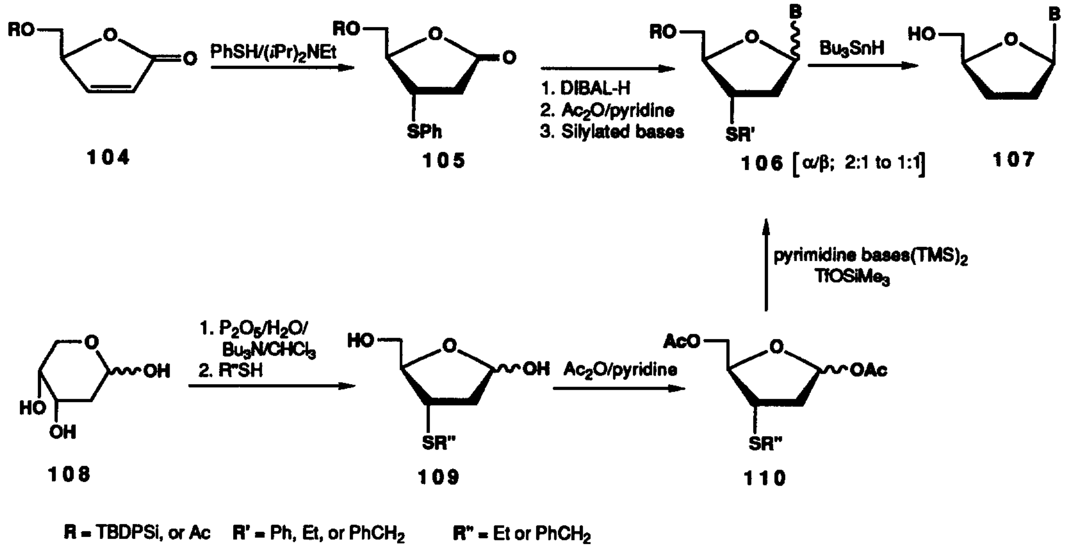
101 (R = PhCO) which, when reacted with saturated methanolic ammonia for 1 h, gave the 3'-thiol **102** (R' = MMTr).[119] In contrast, deprotection of 3'-(acetylthio)-3'-deoxythymidine (**101**; R = Ac) with ammonia in MeOH led to the formation of a crystalline disulfide dimer.[10a] Mansuri *et al.* synthesized 3'-methylthio derivatives **103** (n = 0) in 45% yield by ring opening of the 5'-protected 2,3'-anhydrothymidine with sodium thiomethoxide.[125] Oxidation with the appropriate amount of MCPBA followed by removal of the 5'-trityl protecting group afforded 3'-deoxy-3'-(methylsulfinyl)thymidine **103** (n = 1) and its sulfone analogue **103** (n = 2). Unfortunately, these AZT analogues **103**, with different polarity at sulfur,[125] and other 3'-thiosubstituted analogues[10,115] including 3'-deoxy-3'-thiocyanatothymidine **101** (R = CN, R' = H)[126] were not active against HIV infected cells. Interestingly, 3'-mercapto-2',3'-dideoxynucleoside 5'-triphosphates selectively and irreversibly terminated DNA chain elongation by HIV reverse transcriptase.[127]



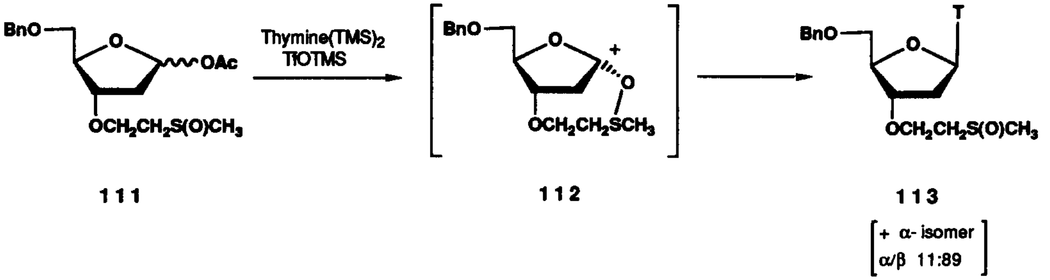
100 **101** **102** **103**

R = Bz, Ac, or CN T = thymin-1-yl
R' = Tr; trityl (triphenylmethyl), or MMTr; monomethoxytrityl

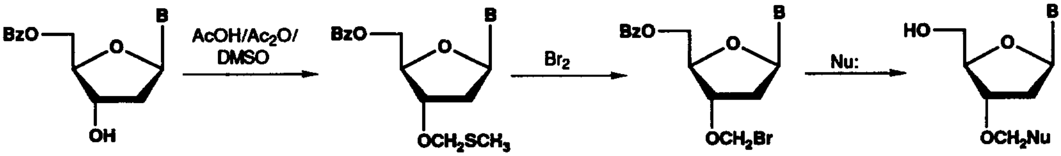
Chu *et al.* reported the synthesis of 2',3'-dideoxynucleosides employing 3'-phenylthio substituted lactone **105** as the sugar precursor.[114] The α,β–unsaturated lactone **104** was substituted at the 3-position by Michael addition of thiophenol in the presence of base to afford the desired *erythro*-isomer **105** (*erythro*/*threo*; ~19:1). Subsequent reduction with diisobutylaluminum hydride and acetylation gave the 1-acetate, which was condensed with various pyrimidine and purine bases. Unfortunately, a mixture of 3'-thiosubstituted nucleosides **106** (α/β; ~1:1) was obtained. Chromatographic separation was achieved after removal of the 5'-protecting group. Radical-mediated desulfurization with tributyltin hydride gave the desired dideoxynucleosides **107**.[114] In a parallel effort, 2-deoxy-D-ribose (**108**) was treated with the Pedersen phosphorus pentoxide reagent (P_2O_5/H_2O; $Bu_3N/CHCl_3$) in the presence of ethyl or benzylmercaptans to give the 3-alkyl(or aryl)thio-2,3-dideoxy-D-*erythro*-pentofuranoses **109** and *threo*-pyranoses as anomeric mixtures in ~80% yield.[115] After acetylation, the separated furanoses **110** were exposed to a standard coupling procedure to give a mixture of 3'-thiosubstituted pyrimidine nucleosides **106** (α/β; ~2:1).[115] This approach showed that the 3-alkyl(or aryl)thio substituent on sugar precursors, unlike the 2-thio or 2-seleno substituents, did not enhance β-stereoselectivity in coupling reactions.[106b,114,115]



A stereoselective method for the preparation of β-2'-deoxyribonucleosides has been developed employing remote interaction of an alkyl linker with a sulfinyl group attached at the 3-position with the cation at C1, which was generated by activation with a Lewis acid.[128] Thus, condensation of 1-*O*-acetyl-2-deoxyribose derivative **111** with the 3-*O*-[2-(methylsulfinyl)ethyl] linker and silylated thymine (or other pyrimidine bases) in the presence of trimethylsilyl triflate gave nucleoside **113** (α/β; ~11:89) in 89% yield. Since the 3'-*O*-benzyl analogue under similar coupling conditions gave lower β-stereoselectivity (α/β; ~2:3), the authors suggested that intramolecular α-side attack by the sulfinyl group on the cation at the 1-position, as shown in **112**, is a plausible explanation for the enhanced β-stereoselectivity. Sulfoxides **113** were oxidized (NaIO$_4$/RuCl$_3$) to the sulfone and deprotected with lithium diisopropylamide (to remove the 3' group quantitatively) followed by catalytic hydrogenolysis with Pd/C (to remove the 5'-benzyl group) to give thymidine.[128]



Treatment of appropriately protected nucleosides (mainly 2'-deoxy) having a free 3'-hydroxyl group **114** with a mixture of acetic acid and acetic anhydride in DMSO for 60 h at 20 °C, gave 3'-*O*-methylthiomethyl derivatives **115** in good yield via a Pummerer rearrangement.[129] This reaction was general since other dialkyl sulfoxides were successfully employed in place of DMSO to yield *O*-(1-alkylthioalkylated)nucleosides. In addition to 3'-*O*-methylthiomethyl substituted 2'-deoxyribonucleosides **115**, their 5'-*O*- and 3'-*O*-substituted ribonucleoside analogues were prepared in a similar manner. Formation of *O*-methylthiomethyl by-products during oxidation of sugar hydroxyls with a mixture of Ac_2O/DMSO is well known.[32a,130] Displacement of the methylthio group (*O,S*-acetal) with bromine gave 3'-*O*-bromomethyl nucleosides **116**, which were converted via nucleophilic displacement of bromine to various 3'-*O*-substituted nucleosides of type **117** (over twenty substituents). Compounds **115** were oxidized to the sulfoxides and sulfones.[129]



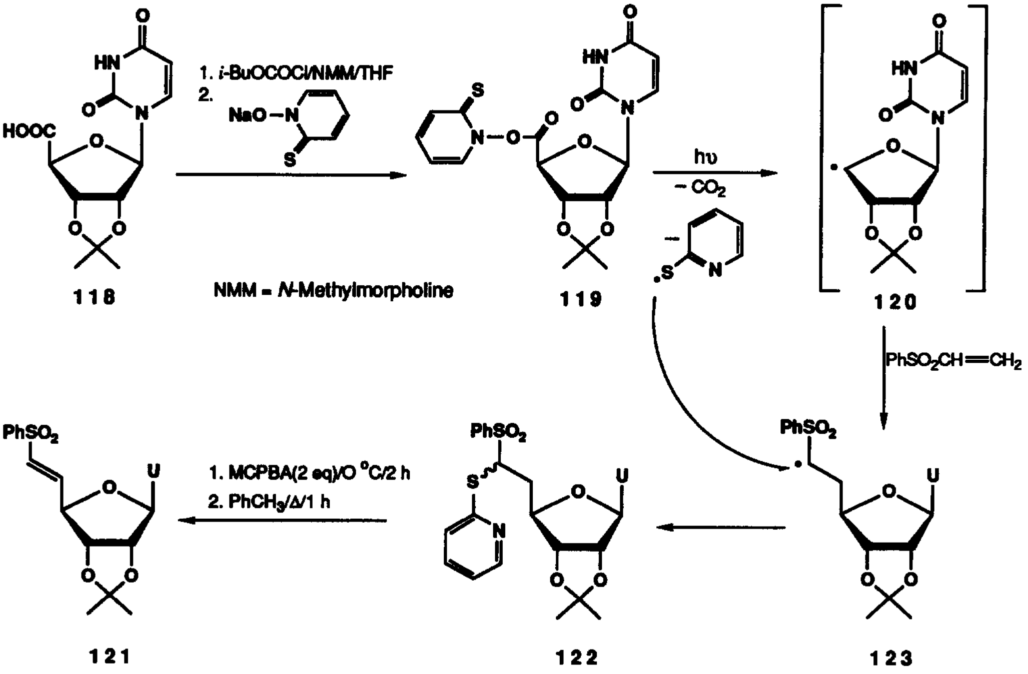
114 **115** **116** **117**

Novel radical-mediated rearrangement of 3'-*O*-alkyl xanthates into a 3'-*S*-alkyl xanthates with *O*-alkyl tin dithiocarbonate reagents offer a new route to thionucleosides.[131] Cosstick *et al.* reported syntheses of protected 3'-thiothymidine[119] and 2'-deoxy-3'-thioadenosine,[132a] conversion to 3'-*S*-phosphorothioamidite building blocks, and incorporation into a DNA fragment[119,132] using a solid phase approach.[132b] DNA oligomers with a terminal 3'-mercapto group crosslinked to a fluorescent probe also have been described.[133]

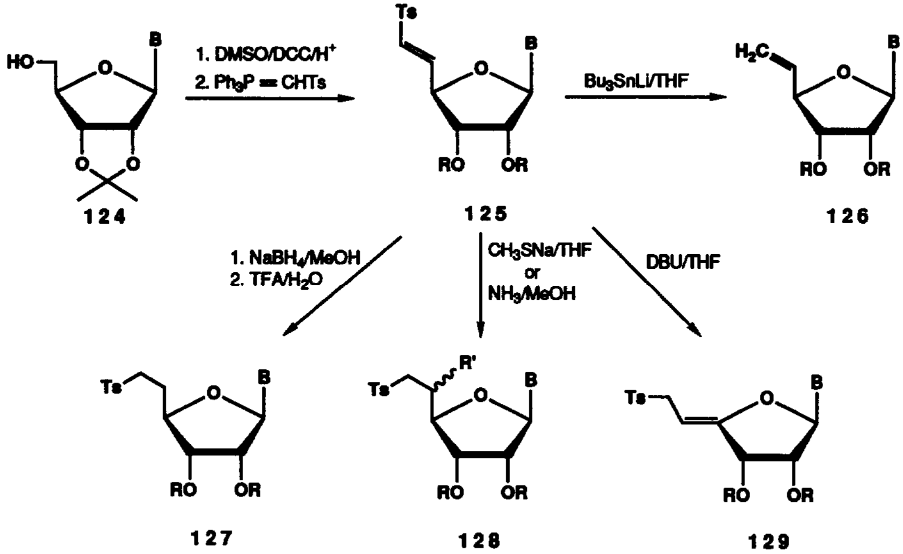
4. SYNTHESIS AND TRANSFORMATION OF VINYL-SULFONYL(OR SELENONYL) DERIVATIVES

5'-Modification

In recent years vinyl sulfones[134] and vinyl sulfonate moieties (see section 7) have been incorporated into nucleosides and converted to a variety of functionalities. Barton *et al.* developed a radical-mediated strategy at C4' for stereocontrolled synthesis of chain-lengthened vinyl 6'-sulfone homonucleosides **121**.[135a] The C4' radical **120** was generated upon photolysis of the *N*-hydroxy-2-thiopyridone derivative **119** of isopropylidene protected uridine 5'-carboxylic acid, or its adenosine analogue. Phenyl vinyl sulfone was used as an electron-deficient radical trap to form the C6' radical **123** which then reacted with the thiocarbonyl function from the precursor to give 2-thiopyridyl derivative **122** as a mixture of diastereoisomers.[135] Oxidation to sulfoxide and thermal elimination afforded the *trans* vinyl 6'-sulfone **121**.[135a] Intermediate **122** could also be reduced with tin hydride reagents with removal of the 2-thiopyridyl residue to give the saturated analogue of **121**. The bulky acetal group controls chirality, thus affording isomer **123**.[135] Similar radical-mediated methodology has been used in syntheses of natural *S*-sinefungin,[136a] its uracil analogue,[136b] 6'-homophosphonates[137a] and a phosphonate analogue of 3'-azido-3'-deoxythymidine 5'-monophosphate,[137b,c] where different electron-deficient olefins were used as traps for radicals analogous to **120**.

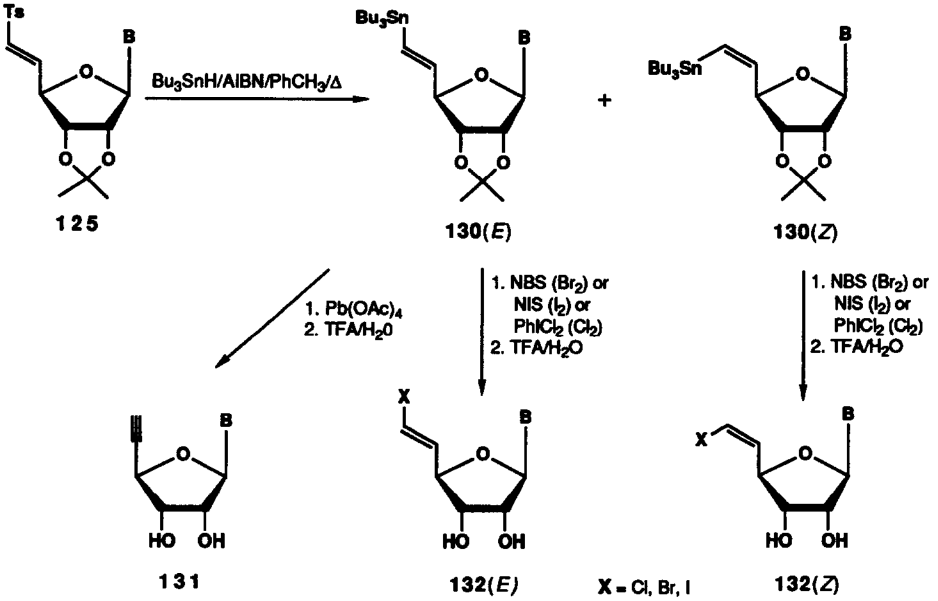


Wnuk and Robins reported that treatment of crude 2',3'-*O*-isopropylidenenucleoside 5'-aldehydes (derived from **124** by Moffatt oxidation) with a sulfonyl-stabilized Wittig reagent gave high yields of *trans* vinyl 6'-sulfones **125** in the adenosine[138] and uridine[139] series. Compounds **125** readily underwent isomerization under basic conditions to give a single geometric isomer of the 4',5'-unsaturated allylic sulfone **129**. Treatment of **125** with sodium borohydride, sodium thiomethoxide, or ammonia resulted in conjugate addition at C5' to give the 5'-substituted-5',6'-dideoxy derivatives **127** and **128**. Removal of the isopropylidene group was effected with aqueous trifluoroacetic acid. Attempted desulfonylation by various classical methods failed to give the 5'-deoxy-5'-methylenenucleosides **126**.[138,139] However, removal of the tosyl group from the adenosine vinylsulfone derivative **125** was effected via conjugate addition of tributylstannyllithium to give **126** in moderate yield.[138]



R = H, or CMe$_2$ R' = NH$_2$, or CH$_3$S DCC = *N,N*-dicyclohexylcarbodiimide

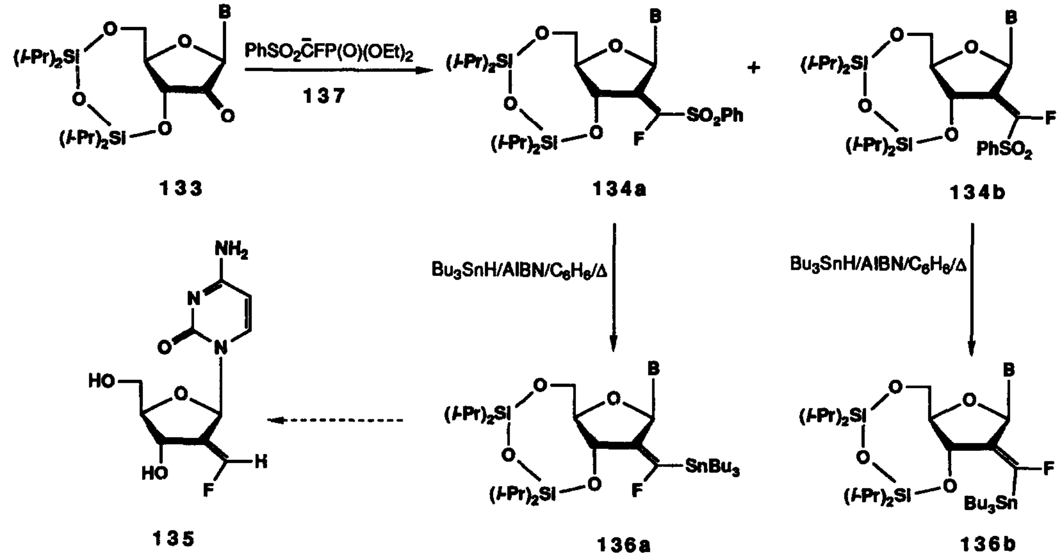
Radical desulfonylation of vinyl 6'-sulfone derivatives **125** with tributyltin hydride in the presence of AIBN in refluxing toluene gave separable mixtures of synthetically useful vinyl 6'-stannanes **130** (*E*/*Z*, ~2.8:1; ~85% in the uridine series).[140]



Stereospecific halogenodestannylation of the geometric isomers of **130** with iodine, *N*-iodosuccinimide (NIS), bromine, *N*-bromosuccinimide (NBS), chlorine, or iodobenzene dichloride, followed by deprotection, gave smooth conversion to Wittig-type 5'-deoxy-5'-halomethylenenucleosides **132** in high yields.[140] Such conversions represent an alternative route to an otherwise limited Wittig reaction between halophosphorane reagents and nucleoside 5'-aldehydes presumably owing to the instability of the latter carbonyl compounds under experimental conditions.[2,141] Treatment of **130** with ammonium fluoride in refluxing methanol[142] resulted in cleavage of the carbon-tin bond to give 5'-deoxy-5'-methylenenucleosides **126**. Trifluoroacetic acid effected protiodestannylation and deprotection in one step to give **126**. Treatment of vinyl 6'-stannanes **130** with lead tetraacetate followed by deprotection gave the 5'-acetylenic derivatives **131**.[140] Adenosine 5'-acetylenic derivative **131** was also recently synthesized in a modified Wittig reaction employing dimethyl diazomethylphosphonate, and was found to be a novel irreversible inhibitor of SAH hydrolase.[143]

2' And 3' modification

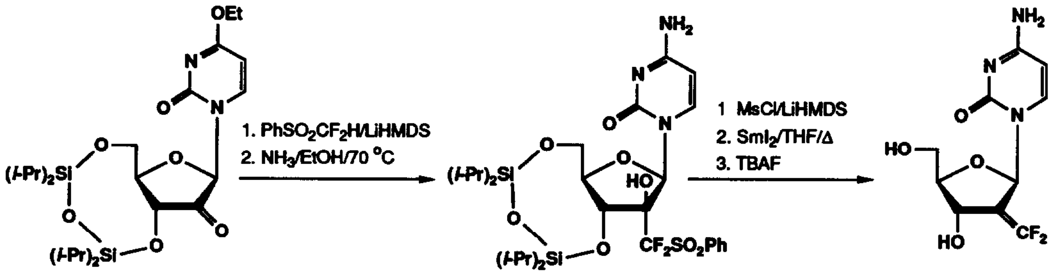
McCarthy *et al.* designed and synthesized 2'-deoxy-2'-fluoromethylene nucleosides (e.g. **135**) as potential inhibitors of ribonucleoside diphosphate reductase (RDPR), employing 2'-fluorovinyl sulfone **134** as a key intermediate.[144] Treatment of protected 2'-ketonucleosides **133** with carbanion **137**, generated *in situ* from fluoromethyl phenyl sulfone, diethyl chlorophosphate and lithium hexamethyldisilazide (LiHMDS) at -78 °C, gave a mixture of readily separable fluorovinyl sulfones **134a,b** in high yield.[144a]



137 [$PhSO_2CH_2F/(EtO)_2P(O)Cl/LiHMDS$]

Lack of success with direct reduction of the fluorovinyl sulfones **134a,b** to fluoro olefins of type **135** led to the discovery of a new stereospecific method for the synthesis of fluoro olefins.[144b] Thus, fluorovinyl sulfones **134a,b** were transformed into fluorovinyl(stannanes) **136a,b** under radical conditions via a proposed radical addition-elimination process with retention of configuration. Refluxing methanolic sodium methoxide gave cleaner stereospecific destannylation to fluoro olefins **135** than methanolic ammonia or cesium fluoride in refluxing methanol. 2'-Deoxy-2'(*E*)-(fluoromethylene)cytidine (**135**) is a potent cytotoxic agent and inhibited RDPR activity in tumor cells by 97% within 3 h, whereas *Z*-isomer (obtained from **136b**) is less active.[144b]

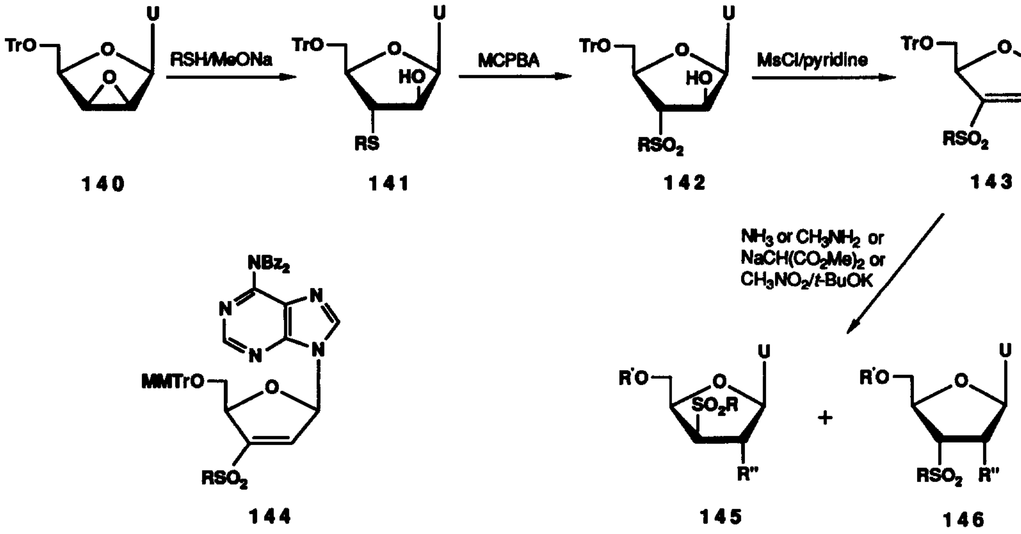
2'-Deoxy-2'-difluoromethylenecytidine **139** also was prepared employing fluoro sulfonyl-mediated chemistry.[145] Addition of difluoromethyl phenyl sulfone to the protected ketone **137** in the presence of lithium hexamethyldisilazide afforded adduct **138** (85% yield), with addition occurring mainly from the α-face. Mesylation of the 2'-hydroxyl group and reductive elimination with a freshly prepared samarium iodide-THF complex gave the desired difluoromethylene compound **139**.



137 **138** **139**

Ms = CH_3SO_2

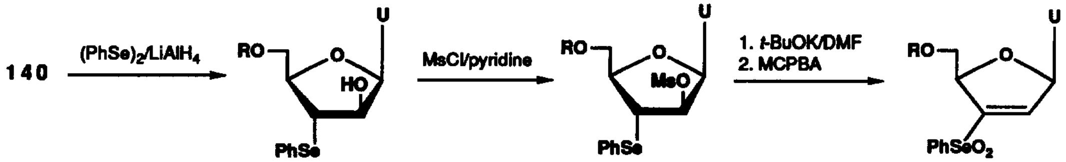
In a series of papers, Chattopadhyaya *et al.* described new syntheses of 2',3'-dideoxy-2',3'-di(or 2'-mono)substituted uridine and adenosine derivatives employing vinyl 3'-arylsulfones **143** and **144** or 3'(or 2')-arylselenones **149** or **163** as Michael acceptors.[146-150] (See also section 2 for related chemistry of vinyl 3'(or 2')-alkylsulfones[104]). Treatment of 1-(5-*O*-trityl-2,3-anhydrolyxofuranosyl)uracil (**140**) with p-toluenethiolate gave the separable isomeric mixture of *arabino* 3'-toluenethio **141** and its *xylo* 2'-toluenethio isomer in a 2:1 ratio and high yield. Oxidation of **141** with MCPBA gave sulfone **142** (99%), which gave the 2'-mesylate upon treatment with excess methanesulfonyl chloride in pyridine. The mesylate underwent base catalyzed *cis*-β-elimination spontaneously affording the vinyl 3'-sulfone **143** (72%). Compound **143** served as a key intermediate for many functionalizations.[146] Thus, treatment of **143** with ammonia, primary or secondary amines, or carbon nucleophiles such as sodium dimethyl malonate or the conjugate base of nitromethane, gave a mixture of 2'-substituted products **145** and **146** in good yield. These nucleophilic additions occurred at C2' exclusively from the α-face of the vinyl 3'-sulfone **143** to give mainly the *trans* 2',3'-disubstituted adducts **145** via *cis* addition of a proton at C3'. The stereochemistry of the addition reactions depended upon the nucleophile structure and reaction conditions. In some cases, reactions gave the *trans* adducts **145** exclusively, reportedly due to stereoelectronic factors which controlled stabilization (protonation) of the intermediate chiral α-sulfonyl 3'-carbanions.[146]



R = (4)$CH_3C_6H_4$ R' = Tr, or H   R" = NH_2, $NHCH_3$, $CH(CO_2CH_3)_2$, or CH_2NO_2

A similar strategy was applied for the preparation and modification of vinyl 3'-sulfone derivative **144** in the adenosine series starting from 2',3'-anhydroadenosine **96**.[146] Although this methodology represents a regiospecific and highly stereoselective route for the preparation of 2'-amino derivatives, removal of the acid labile 5' protecting group, and especially desulfonylation at C3', proved to be troublesome.[146]

Subsequently, this research group employed the uridine vinyl 3'-selenone **149** as a powerful intermediate for simultaneously functionalizing both the 2' and 3' carbons.[147] The pronounced electron-withdrawing effect and much better leaving group ability of the selenonyl substituent, compared to sulfonyl, made this vinyl 3'-selenone synthetically equivalent to the dication $^{+}CH_2$-CH_2^{+}. Opening of the 2',3'-anhydrolyxo ring in **140** with phenylselenide ion in THF gave a separable mixture of the *arabino* 3'-deoxy-3'-phenylselenouridine derivative **147** (55%) and the *xylo* 2'-deoxy-2'-phenylseleno isomer (26%). Mesylation of the 2'-hydroxyl group of **147** and elimination of the resulting 2'-mesylate from **148** with potassium *t*-butoxide in dry DMF, gave a vinyl 3'-selenide which, upon oxidation with MCPBA, gave vinyl 3'-selenone **149** in 68% overall yield. The 5'-trityl group was removed by brief treatment with 80% aqueous acetic acid.



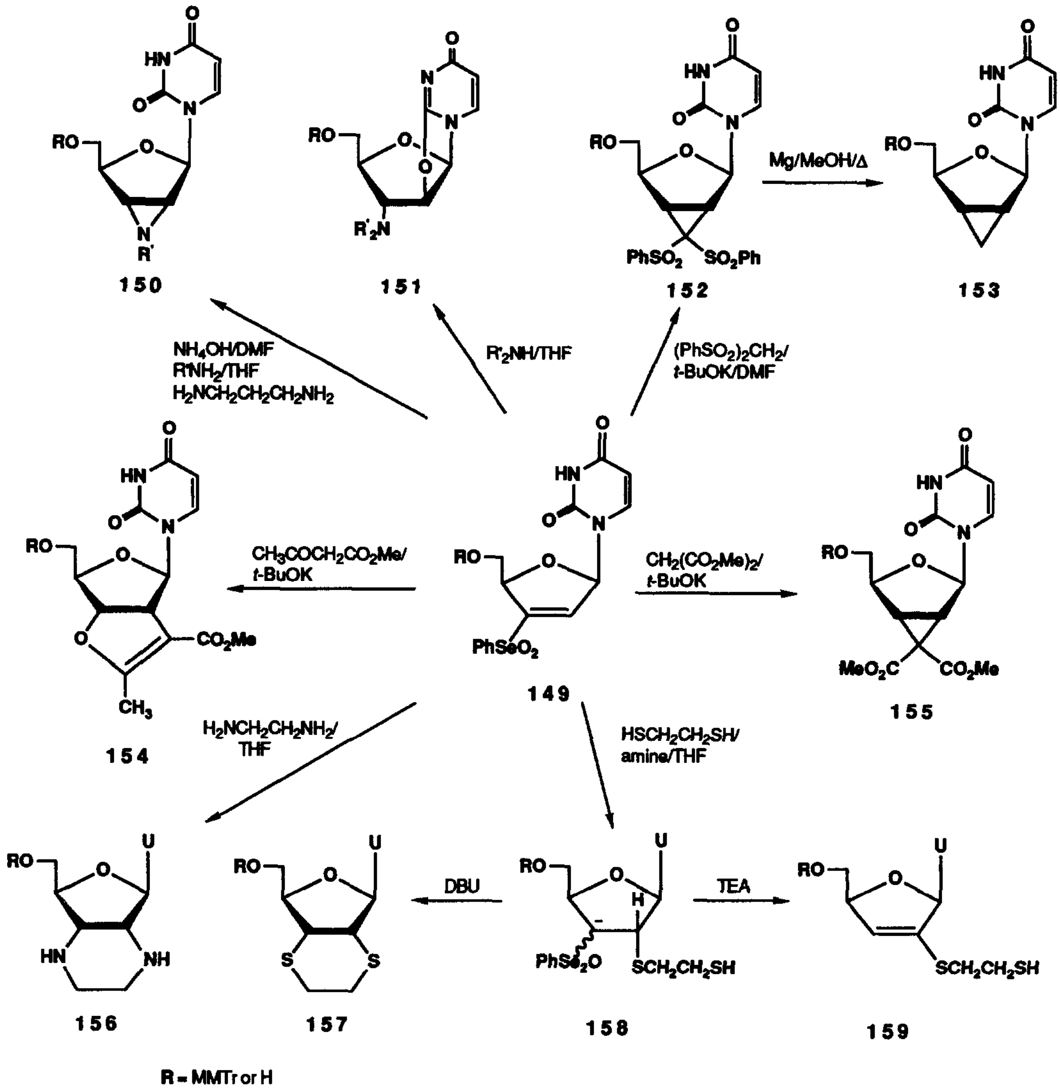
147 148 149

R = Tr, MMTr, or H

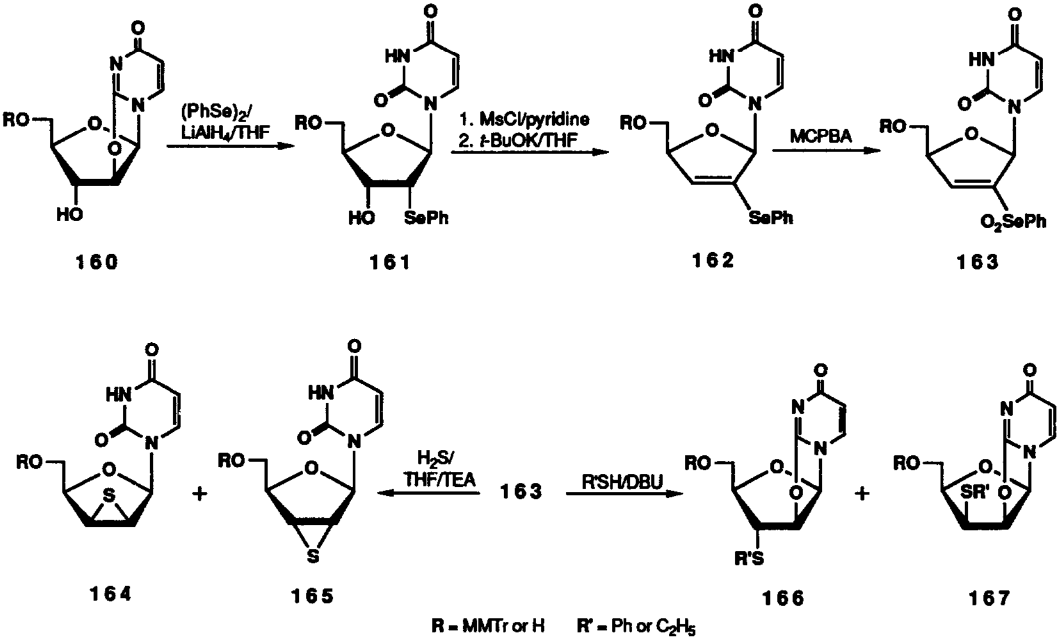
As expected, stereospecific nucleophilic addition of ammonia or primary amines to the α-face of 3'-eneselenone **149** gave the *trans* 2',3'-addition product, which instantaneously underwent a 2'-amino promoted S_N2 displacement reaction at C3' to give the 2',3'-*ribo* aziridines **150**.[147] Secondary amines reacted with **149** to give 3'-amino-3'-deoxy-2,2'-anhydrouridine derivative **151** via formation of the 2',3'-*ribo* aziridinium ion and subsequent nucleophilic attack by the O2 of uracil.[147] Compound **149** also served as a convenient synthon for unique 2',3'-fused bicyclic nucleosides such as **154** or **155** upon treatment with methyl acetoacetate or dimethyl malonate, respectively.[147] Treatment of **149** with bis(phenylsulfonyl)methane, followed by reductive desulfonylation (Mg/MeOH) of the resulting **152**, afforded the bicyclic [3.1.0]-cyclopropano-dideoxyuridine **153** in low yield.[148]

Conjugate addition at C2' in **149** with bis-functionalized reagents such as 1,2-ethylenediamine or 1,2-ethanedithiol gave the 2',3'-α-fused heterocyclic derivatives **156** and **157**, respectively.[149] Interestingly, treatment of **149** with 1,3-diaminopropane gave the 2',3'-*ribo* aziridine **150** (R' = $CH_2CH_2CH_2NH_2$), presumably because a second nucleophilic attack at C3' by the 2'-secondary amino group to close the 3-membered ring is favored entropicaly over closure by the primary γ-amino group to form a 7-membered ring. In the reaction with 1,2-ethanedithiol, the 2'-substituted-2',3'-unsaturated analogue **159** is probably arises via *cis*-elimination of phenylselenic acid from intermediate **158**. However, a competing ring closure occurs giving product **157** by an intramolecular S_N2 displacement at C3'. Compound **149** also functions as a dienophile and dipolarophile in Diels-Alder and 1,3-cycloaddition reactions.[149]

Vinyl 2'-phenylselenone **163** has opposite 2',3'-double bond polarity compared to that of compounds **143** and **149** and also proved to be a powerful Michael acceptor and synthetic equivalent of a $^{+}CH_2$-CH_2^{+} dication.[150] Ring opening of the 5'-protected 2,2'-anhydrouridine **160** with phenyl selenide anion gave 2'-deoxy-2'-phenylseleno derivative **161**. Mesylation of the 3'-hydroxyl group of **161** and elimination of the 3'-mesylate with potassium *t*-butoxide in dry THF gave the 2'-ene-2'-selenide **162**. Oxidation of **162** with MCPBA gave the vinyl 2'-selenone **163** in 63% overall yield.[150] Treatment of **163** with various sulfur, nitrogen, oxygen and carbon nucleophiles gave numerous 3'-substituted 2',3'-modified uridine nucleosides including 2',3'-fused nucleoside derivatives.[150]



However, in contrast to vinyl 3'-selenone **149**, addition to vinyl 2'-selenone **163** (R = H or MMTr) was not stereoselective and gave mixtures of 3' "up" and "down" substituted products. In addition, concomitant 2,2'-anhydro ring closure occurred readily, providing in most cases 3'-substituted-2,2'-anhydro derivatives. Thus, tratment of **163** with ethanethiol and thiophenol in THF in the presence of DBU gave mixtures (~1:1) of 3'-thio substituted cyclouridine derivatives **166** and **167**. Acid-catalyzed hydrolysis of 2,2'-anhydro nucleosides **166** and **167** gave the corresponding 3'-substituted-thio *arabino* and *lyxo* derivatives, respectively. Treatment of **163** with dilute hydrogen sulfide in THF gave a mixture of the 2',3'-*ribo* **165** and *lyxo* **164** epithio nucleosides (89%),[150] whose structural properties have been studied in detail.[151]



160 **161** **162** **163**

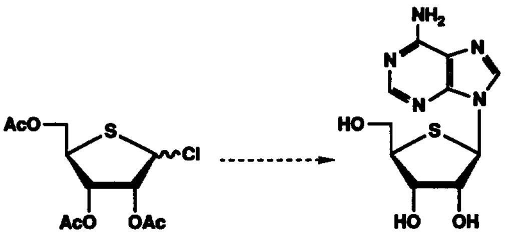
164 **165** **163** **166** **167**

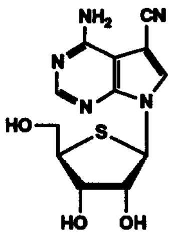
R = MMTr or H R' = Ph or C_2H_5

5. NUCLEOSIDES WITH SULFUR IN THE PENTOSE RING

5.1. *Oxygen replaced by a sulfur atom*

4'-Thionucleosides in which the oxygen atom of the pentose ring has been replaced by a sulfur atom were synthesized from the corresponding thiosugar precursors by coupling approaches and showed interesting biological activities.[152-157] Coupling of the acetylated 4-thio-D-ribosyl chloride **168**, prepared by a multistep procedure from L-lyxose, with the chloromercury salt of 6-benzamidopurine followed by deprotection gave 4'-thioadenosine **169**.[152] Using sugar precursor **168**, Bobek *et al.* prepared various base-modified 4'-thionucleosides, including the modified antibiotic 4'-thiotoyocamycin **170**[153b] and 5-fluorouridine[155] derivatives. The Hilbert-Johnson silyl coupling procedure was used for the preparation of a variety of 4'-thiopyrimidine nucleosides.[154-157] Some of these 4'-thionucleosides showed marked inhibitory activity against leukemia L-1210 and other cells,[153-156] but did not show antiviral properties against HIV or herpes simplex viruses.[157] 4'-Thioadenosine **169** was found to inhibit SAH hydrolase,[158] and 4'-thioinosine showed resistance to cleavage by purine nucleoside phosphorylase.[159] However, the high cytotoxicities shown by many of these 4'-thionucleosides precluded further pharmacological applications. The naturally occurring antibiotic albomycin δ_1 **171**, isolated[160] from *Streptomyces Spec.* and shown to be a thionucleoside (composed of a thiosugar, 3-methyluracil, and amino acid fragments),[161] prompted further interest in the 4'-thionucleosides.[162]


168 **169**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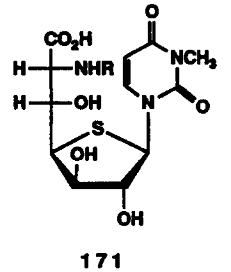
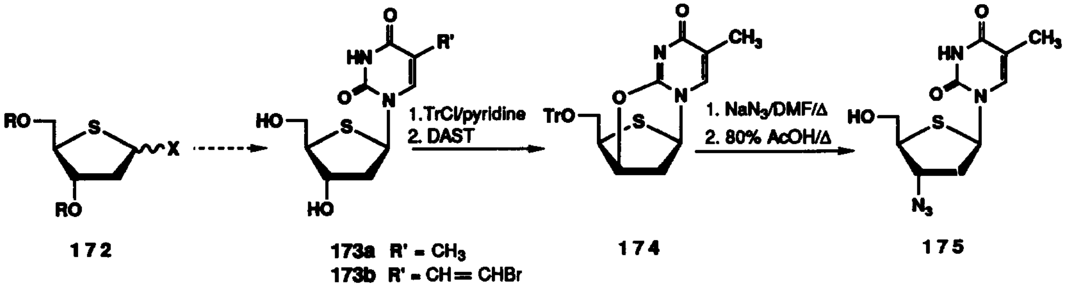

171

In search of new potential therapeutic agents against HIV Secrist *et al.*,[163,164] Walker *et al.*,[165] Uenishi *et al.*,[166] and Huang and Hui[167] simultaneously reported the synthesis of 4'-thio-2'-deoxy(or 2',3'-dideoxy)nucleosides including the 4'-thio analogue of AZT.[164,165] Coupling of protected 2-deoxy-4-thio-D-*erythro*-pentofuranose **172** (X = OAc, prepared in 14 steps from L-arabinose) with silylated pyrimidine bases in the presence of trimethylsilyl triflate, gave the corresponding 2'-deoxy-4'-thionucleosides as anomeric mixtures (α/β; ~1:1). Fractional crystallization followed by deprotection afforded pure β-anomers e.g. 4'-thiothymidine **173a**.[163] The latter was converted to its 5'-*O*-trityl derivative and treated with DAST to afford the 4'-thio-2,3'-anhydrothymidine **174**. Anhydro ring opening of **174** with sodium azide followed by deprotection gave the 4'-thio analogue of AZT **175** (36%).[164] 5(*E*)-(2-Bromovinyl)-2'-deoxy-4'-thiouridine **173b** was prepared in a similar fashion by condensing **172** (X = Br, prepared in 10 steps from 2-deoxy-D-ribose) with the base precursor;[165] its conformation was studied in detail by 500-MHz ^{1}H NMR spectroscopy and X-ray crystallography.[168] 5-Fluoro derivative **173c** was prepared analogously. [167,169]



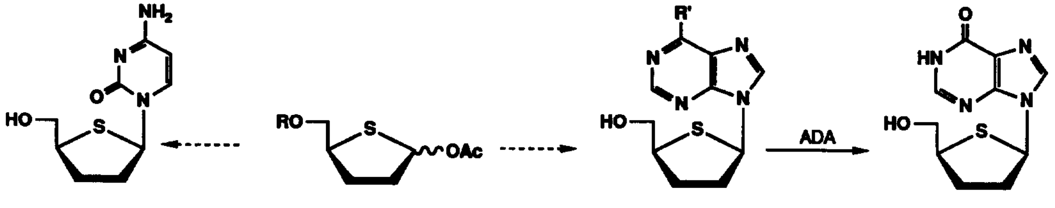
172
R = (4)CH$_3$C$_6$H$_4$CO

173a R' = CH$_3$
173b R' = CH=CHBr
173c R' = F

174

175

The 2',3'-dideoxy-4'-thiosugar precursor **177**, prepared stereospecifically from L-glutamic acid, afforded 2',3'-dideoxy-4'-thionucleosides.[164] Coupling of **177** with 6-chloropurine using diethylaluminum hydride as catalyst, gave an anomeric mixture (α/β; ~1:1) in 60% yield. Pure β-anomer **178** (R' = Cl) was obtained in low yield after desilylation with TBAF and laborious separation by preparative TLC. Treatment of the α/β-anomers of **178** (R' = Cl) with adenosine deaminase (ADA), converted the β-anomer to 2',3'-dideoxy-4'-thioinosine (**179**) which was easily separated from the unreacted 6-chloro α-anomer. Treatment of the α/β-anomers of **178** (R' = Cl) with ammonia followed by ion-exchange chromatography afforded the adenosine analogue **178** (R' = NH_2) in modest yield. 2',3'-Dideoxy-4'-thiocytidine (**176**) and the 2,6-diaminopurine analogue were prepared analogously from **177**, but the isolation of pure β-anomers was troublesome.[164] Tests with these compounds showed that only 2',3'-dideoxy-4'-thiocytidine (**176**) exhibited significant anti-HIV activity;[164] the 4'-thioAZT analogue **175** was not active.[165b] Interestingly, the 5-bromovinyl thio analogue **173b** was not toxic and had significant activity against herpes viruses[165b] whereas 4'-thiothymidine **173a** was active but also toxic.[163,165b]

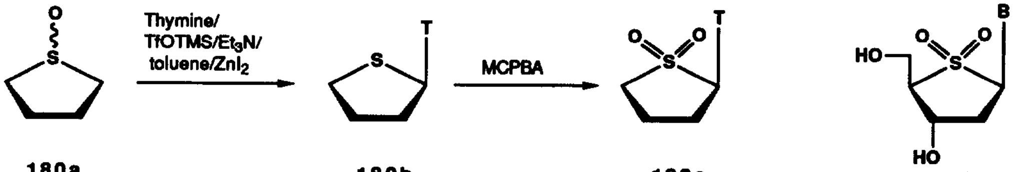


176 **177** **178** **179**

R = TBDPSi R' = Cl or NH_2

[+ α-anomer α/β; ~1:1]

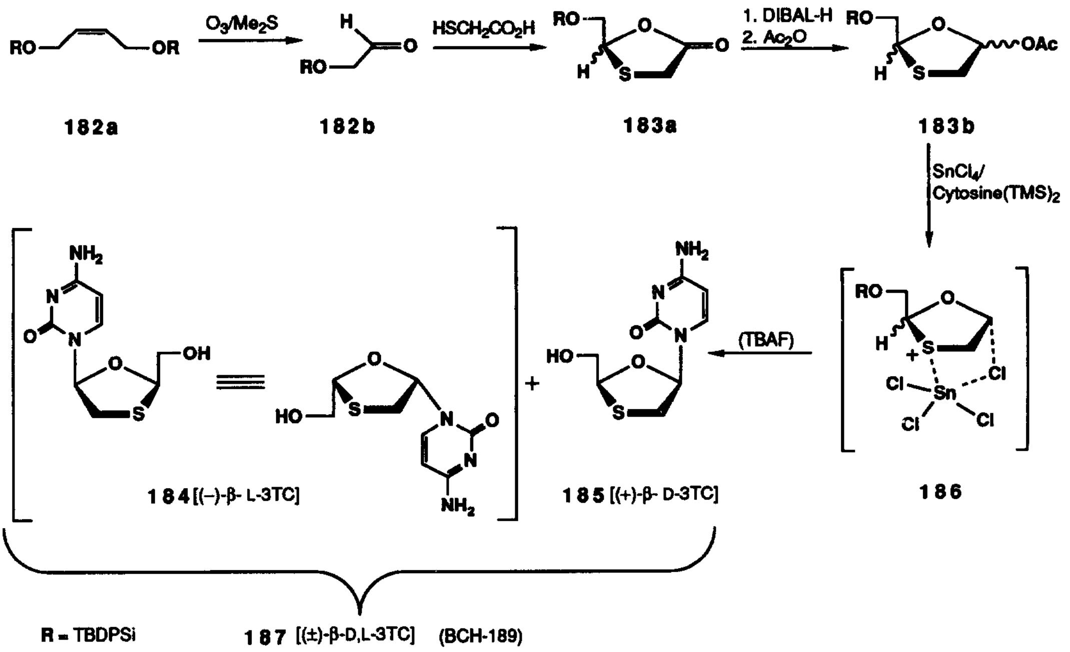
Dideoxy thionucleoside analogue **180b** lacking the 4'-hydroxymethyl group was recently synthesized by a novel coupling procedure employing a silicon-mediated Pummerer reaction.[170] Treatment of thymine, or other natural or non-natural bases, with tetramethylene sulfoxide **180a** in the presence of TfOTMS and ZnI_2 gave **180b** in 84% yield, presumably via a sulfenium ion. Oxidation of **180b** gave sulfone **180c**. It was suggested that phosphorylation of 2'-deoxy sulfone analogue **181** at the 5'-hydroxyl group and enzyme-mediated elimination might produce the 4',5'-unsaturated sulfone-intermediate, which could function as a Michael acceptor to inhibit key viral enzymes by covalently binding nucleophilic sites of enzymes.[170]



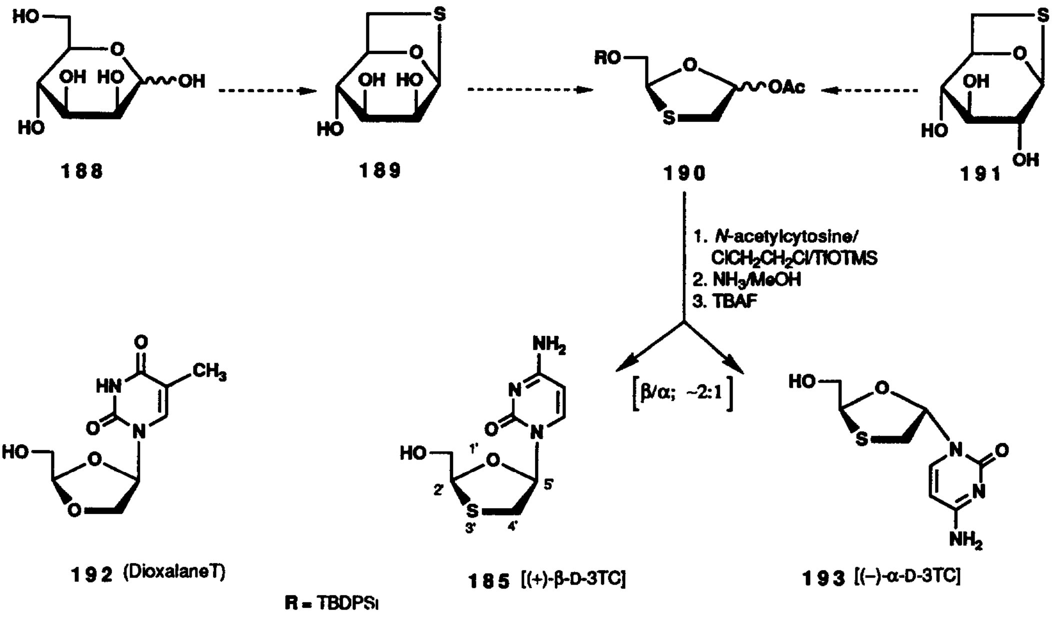
180a **180b** **180c** **181**

5.2. *Carbon replaced by a sulfur atom*

The search for more effective and less toxic anti-AIDS drugs has included analogues of dideoxynucleosides in which the 3'-CH_2 group has been replaced by a heteroatom such as sulfur (**187**, BCH-189) or oxygen (**192**, Dioxalane T). The synthesis, anti-HIV activity and low in vitro toxicity of racemic 2'-deoxy-3'-thiacytidine (**187**, BCH-189; [(±)-β-D,L-3TC]) were first reported by Belleau *et al.*[171] Liotta *et al.* developed a highly stereoselective coupling procedure for the synthesis of racemic 3TC **187** by the reaction of thiosugar precursor **183b** and cytosine in the presence of stannic chloride.[172] The key intermediate thiolactone **183a** was synthesized in two steps in high yield (81%) from cheap starting materials by ozonolysis of silylated 2-butene-1,4-diol **182a**, followed by condensation of the resulting protected aldehyde **182b** with mercaptoacetic acid and ring closure. Reduction of **183a** with diisobutylaluminum hydride, followed by acetylation, gave **183b** as an anomeric mixture. Coupling of **183b** with silylated cytosine in the presence of stannic chloride at ambient temperature gave the β products **187** (β/α >300:1, by HPLC) after deprotection. With this coupling, application of common Lewis acids such as trimethylsilyl triflate gave inseparable mixtures of β/α-adducts (1:1).[172] The stereoselectivity in this glycosylation reaction, involving a 2-deoxysugar analogue, was rationalized by the postulated precomplexation of stannic chloride with the ring sulfur atom. Such complexation presumably hinders α approach of the silylated base via formation of an intermediate α-chloro derivative **186**, which undergoes S_N2 attack to form the β-N-glycoside.



Chu *et al.* synthesized enantiomerically pure stereoisomers of 3TC in order to determine specific anti-HIV activities.[173-175] The synthesis of (+)-(2*S*, 5*R*)-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (**185**) provided the (+)-β-D-3TC, D-like isomer, since β-D-like nucleosides are generally found to be more biologically active. D-Mannose **188** was converted to 1,6-thioanhydro-D-mannose **189** in 5 steps. The latter was converted in 13 steps to **190**, which was coupled with *N*-acetylcytosine in the presence of trimethylsilyl triflate to give a separable mixture (2:1) of (+)-β-D-3TC **185** and its α-isomer **193** [(−)-α-D-3TC] after deprotection.[173] Precursor **190** and (+)-β-D-3TC have been prepared more efficiently from D-galactose via 1,6-thioanhydro-D-galactose (**191**).[174] Surprisingly, it was found that enantiomericaly pure (+)-β-3TC (**185**, D-like isomer) exhibited lower anti-HIV activity than racemic (±)-3TC **187**, whereas (−)-α-D-3TC **193** did not show significant anti-HIV activity, as expected.[173]



188 **189** **190** **191**

192 (DioxalaneT)

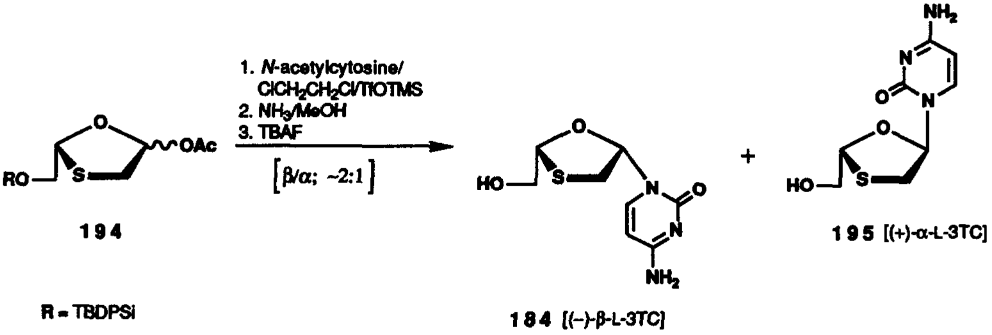
185 [(+)-β-D-3TC]

193 [(−)-α-D-3TC]

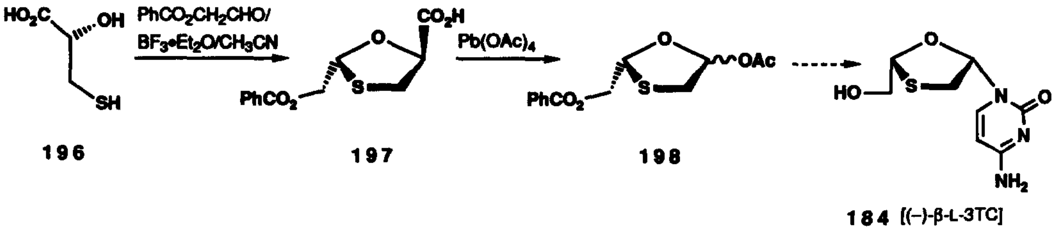
R = TBDPSi

The multistep synthesis of enantiomerically pure (−)-β-L-3TC [**184**; (2'*R*, 5'*S*), L-like isomer] and its α-anomer **195** [(+)-α-L-3TC] from L-gulose via 1,6-thioanhydro-L-gulose, has been accomplished in Chu's laboratory.[175] Precursor **194** was condensed with *N*-acetylcytosine (and with other pyrimidine and purine bases[175b]) in the presence of TfOTMS to give a separable mixture (2:1) of (−)-β-L-3TC **184** and its α-isomer **195** [(+)-α-L-3TC] after deprotection. It was found that the use of stannic chloride[172] instead of TfOTMS as the Lewis acid gave the β-isomer exclusively. Unfortunately, it also caused racemization to give the mixture **187**,[175a] presumably via ring opening at the thioacetal carbon of sugar analogue **194**.[176] Surprisingly, (−)-β-L-3TC **184** was found to be the most potent and least toxic among the four oxathiolanyl isomers tested against

HIV and hepatitis B virus (HBV) [the (+)-α-L-3TC **195** isomer showed moderate activity]. This finding represents the first example in which an L-like nucleoside **184** is more potent than its D-like analogue **185** by at least an order of magnitude.[175]



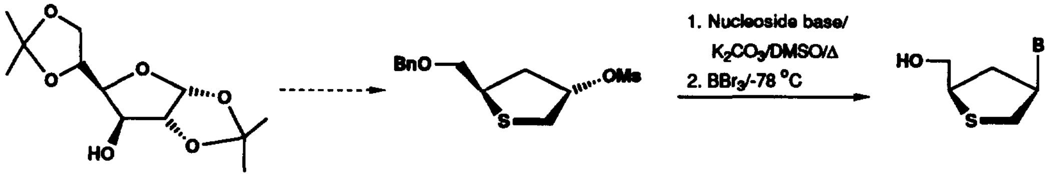
The four-step synthesis of enantiomerically pure (−)-2'-deoxy-3'-thiacytidine [**184**, (−)-3TC] from (+)-thiolactic acid has been recently reported.[176] In this approach, (+)-thiolactic acid (**196**) was condensed with benzoyloxyacetaldehyde in the presence of boron trifluoride etherate, to give a mixture (2:1) of oxathiolane acid **197** and its C2 diastereomer. Separation on silica and treatment of **197** with lead tetraacetate in DMF afforded anomeric acetates **198** (64%). Coupling of **198** with silylated cytosine in the presence of iodotrimethylsilane gave (−)-3TC **184** and the α-anomer **195** in a ~1.3:1 ratio after debenzoylation with basic resin. When stannic chloride was used as catalyst[172] in this reaction, a higher ratio (~10:1) of **184** to **195** was obtained. However, this catalyst gave racemic product (chiral HPLC), again suggesting oxathiolane ring cleavage (at C2) under the reaction conditions.[176]



The biologically active racemate (±)-β-D,L-3TC **187** has been separated on HPLC with a chiral column.[173,177] Furthermore, racemic (±)-2'-deoxy-3'-thiacytidine (3TC) and (±)-2'-deoxy-5-fluoro-3'-thiacytidine (FTC) were both resolved by enzyme-catalyzed hydrolysis of their 5'-*O*-butyryl ester derivatives,[178] and enzymic resolution of the monophosphate derivative of (±)-3TC was reported.[179] Racemic (±)-β-D,L-3TC

187, its enantiomers **184** and **185**, and FTC were the subject of biological investigations.[171,175,177,180-182] In addition to potent anti-HIV activity and very low toxicity, 3TC has been found to inhibit the replication of the hepatitis B virus in vitro,[180] and its 5'-triphosphate affects human immunodeficiency virus reverse transcriptase and mammalian DNA polymerases.[182b] Interestingly, tetrazole oxathiolane nucleoside analogues were found to be inactive against the HIV-1 retrovirus,[183a] and phosphonate derivatives of (±)-3TC were less potent than the parent compounds.[183b]

Chu *et al.* also reported the asymmetric synthesis and anti-HIV activity of related 1,3-dioxalane-pyrimidine nucleoside derivatives **192** (Dioxalane T).[184] In an attempt to obtain less toxic anti-HIV agents, the Glaxo Research Group prepared 2',3'-dideoxy carbocyclic nucleosides enantiospecifically with the 3'-carbon atom replaced either by an oxygen or a sulfur atom. This would prevent phosphorylase-mediated cleavage of the glycosidic linkage.[185] The targeted 3'-thia analogues **201** (tetrahydrothiophene nucleosides) were prepared with both purine and pyrimidine bases but did not show any anti-HIV activity. Tetrahydrothiophene **200** was prepared in 15 steps starting from diacetone D-glucose **199**. S_N2 displacement of the mesylate group from **200** by a variety of nucleoside bases, followed by 5'-*O*-debenzylation with boron tribromide at low temperature, gave the 3'-thia carbocyclic nucleoside derivatives **201**.[185]



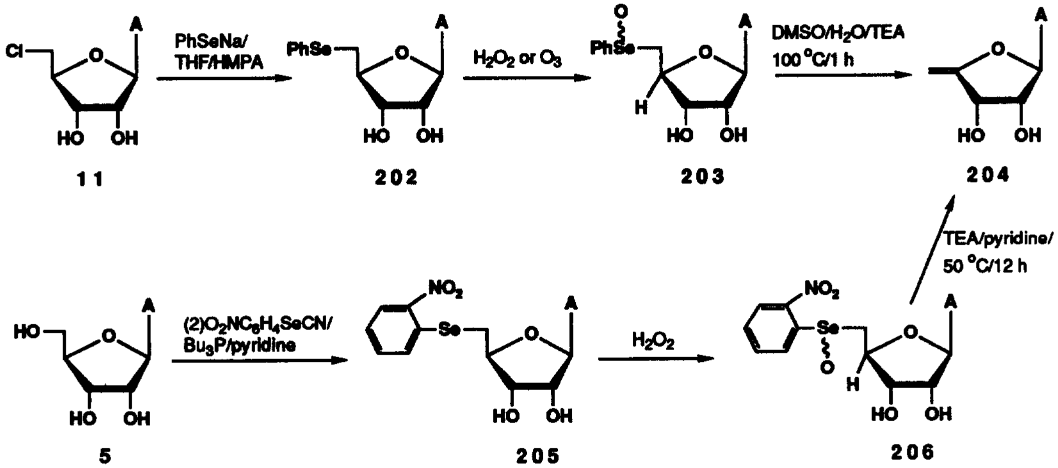
199 **200** **201**

6. SELENONUCLEOSIDES

Organoseleno fragments have mainly been incorporated into nucleoside sugar moieties in order to synthesize C4'-C5' exocyclic double bonds or to make 2',3'-unsaturated and 2',3'-dideoxy derivatives via removal of the organoseleno portion by selenoxide elimination or reductive methods. In the search for new synthetic methods to construct dideoxynucleosides from cheaper sugar precursors, a 2-phenylseleno sugar substituent gave high β-selectivity in coupling reactions with nucleoside bases. Some aspects of selenonucleoside chemistry (vinyl-selenonyl compounds) have been discussed in section 4.

6.1. *Precursors to 4',5'-unsaturated nucleosides*

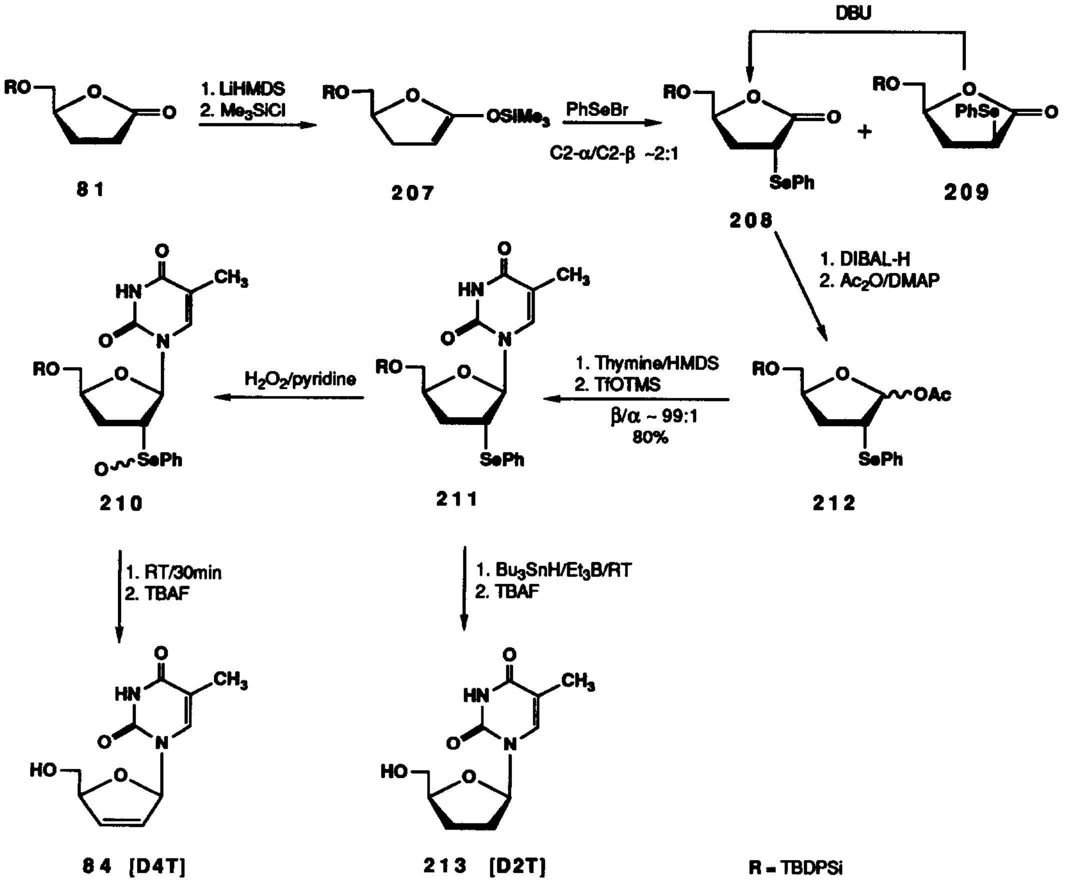
Zylber *et al.* first employed the selenoxide fragmentation to introduce a C4'-C5' exocyclic double bond into the sugar unit of adenosine.[186] Treatment of 5'-chloro-5'-deoxyadenosine **11** with sodium benzeneselenoate gave 5'-*Se*-phenyl-5'-selenoadenosine (**202**) (60%). Oxidation of crude **202** *in situ* with hydrogen peroxide or ozone gave the diastereomeric selenoxides **203**. Diastereomer **203**(Se$_S$) was obtained in 54% yield and the *S* configuration at selenium was established by X-ray crystallography.[187] Interestingly, selenoxide **203**(Se$_S$) was stable in boiling EtOH but underwent epimerization at selenium in water. *Syn*-elimination occurred upon heating **203**(Se$_S$) at 100 °C for 1 h in DMSO/H_2O in the presence of triethylamine (TEA) affording the 4',5'-unsaturated adenosine **204** (94%).[186] The presence of water was beneficial since thermolysis of **203**(Se$_S$) in DMSO gave a mixture of products. Epimerization at selenium in the presence of water presumably gave the Se$_R$ diastereomer which underwent *syn*-elimination more readily.



To facilitate the epimerization at selenium and *syn*-elimination, 5'-*Se*-(2-nitrophenyl)-5'-selenoadenosine (**205**) was prepared in high yield by treatment of adenosine (**5**) with 2-nitrophenylselenocyanate and tributylphosphine.[188] (For an analogous reaction involving 5'-thionucleosides see section 1.1). Oxidation of **205** gave the stable selenoxides **206**, which were directly thermolyzed (pyridine/triethylamine/12 h/50 °C) to give **204** (90%). Thus, compound **204** was obtained in 85% yield from adenosine in two steps.[188] Townsend *et al.* employed this methodology for construction of the C4'-C5' exocyclic double bond of the naturally occurring pyrrolo[2,3-*d*]pyrimidine nucleoside mycalisine A from toyocamycin.[189]

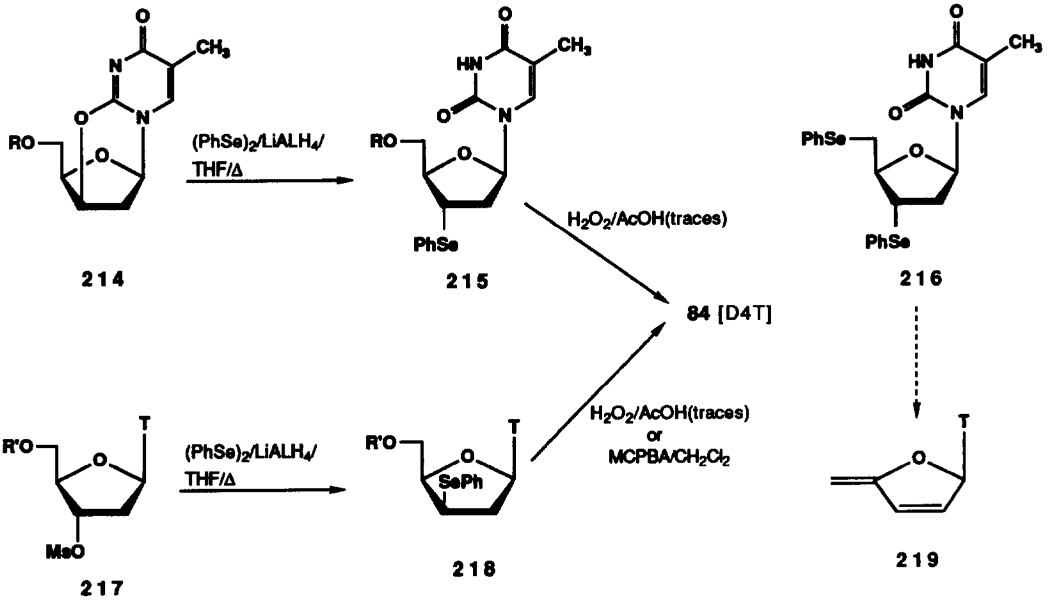
6.2. *Precursors to 2',3'-unsaturated nucleosides*

Chu *et al.* developed highly stereoselective syntheses of dideoxynucleosides which differed from the Liotta[105] and Kawakami[106] methodology by the use of a 2-seleno instead of a 2-sulfur substituent on the sugar precursor.[190-192] The mild selenoxide elimination relative to sulfoxide thermolysis is advantageous with the sensitive 2',3'-didehydro-2',3'-dideoxynucleoside (e.g. **84**) targets. Attempts to α-selenylate the lithium enolate of dideoxy γ-lactone **81** did not give high yields of **208**. However, formation of the trimethylsilyl enol ether **207** followed by treatment with phenylselenenyl bromide gave the desired C2-α isomer **208** (*erythro*) in 65% yield. The overall yield was increased to 83% by equilibration of the C2-β isomer **209** (*threo*) with DBU.[192] Reduction of lactone **208** with DIBAL-H followed by acetylation afforded **212** (77% from **81**). Condensation of the latter with silylated thymine in the presence of trimethylsilyl triflate gave the 2'-phenylselenenyl thymidine derivative **211** plus traces of the α anomer (99:1). The high stereoselectivity in this coupling reaction was attributed to neighboring group participation by the phenylselenenyl group.



Oxidative elimination of the phenylselenenyl group from **211** via the intermediary selenoxide **210** and deprotection gave 3'-deoxy-2',3'-didehydrothymidine (**84**, D4T; 60%). Alternatively, reductive removal of the phenylselenenyl group from **211** and deprotection afforded 3'-deoxythymidine (**213**, D2T; 71%).[190,192] This strategy was general, and a series of 2',3'-dideoxy and 2',3'-didehydro-2',3'-dideoxynucleosides was prepared in high yield. The β-stereoselectivity for glycosylation was as high as 99:1 in the pyrimidine series (e.g. ddC, ddT) and 95:5 in the purine series (e.g. ddI, ddA).[190-192] 6-Chloropurine was used in the coupling reaction to prepare 2'-selenenyl substituted purine nucleosides.[191,192]

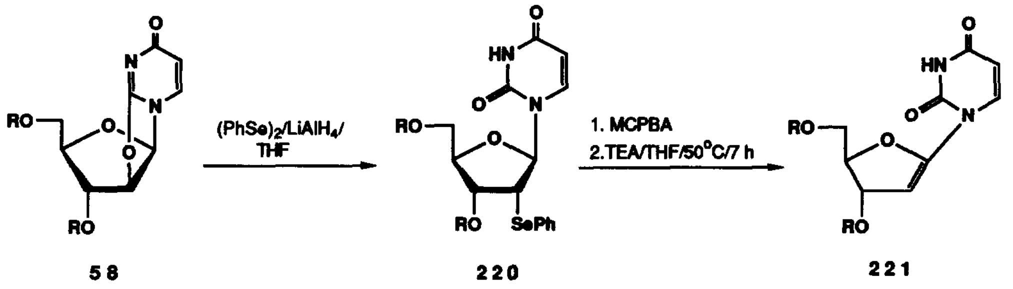
As found with 3-aryl(or alkyl)sulfenyl sugar substituents[106b,114,115,193] e.g. in **110**, (see section 3) the 3-phenylselenenyl substituent also did not enhance the coupling stereoselectivity.[193] However, Chattopadhyaya *et al.*,[194] Cosford and Schinazi,[195] Miyasaka *et al.*,[196] and Reese *et al.*[197] have utilized 3'-phenylselenenyl modified nucleosides prepared from parent nucleosides. Thus, treatment of the 5'-protected 2,3'-anhydrothymidine **214** with $(PhSe)_2/LiAlH_4$ in THF at reflux gave the 3'-phenylselenenyl-3'-deoxythymidine derivative **215** in good yield.[195a,196] Attempts to open the anhydro ring in **214** with selenium reagents, generated with other bases or reducing agents (NaH, $NaBH_4$), gave 3'-*threo* hydroxy compounds. Miyasaka *et al.* also observed similar difficulties with other anhydro systems.[196,198] Interestingly, treatment of unprotected **214** with either NaH in *N,N*-dimethylacetamide[197a] or sodium metal in HMPA/THF[195b] gave D4T (**84**). Enhancing the soft nature of the selenide nucleophile by complexation with AlH_3 might favor attack at the 3'-position rather than at the harder sp^2 C2.[195a] Joshi and Reese studied reactions of the unprotected 2,3'-anhydrothymidine **214** (R = H) with sodium phenylselenoate (and propane-2-thiolate) and observed that minor amounts of 5'-seleno(or thio) substituted derivatives were also formed (ratio of ~9:1).[197b] Equilibration between the 2,3'- and 2,5'-anhydrothymidines under basic conditions apparently led to formation of the 5'-substituted products.

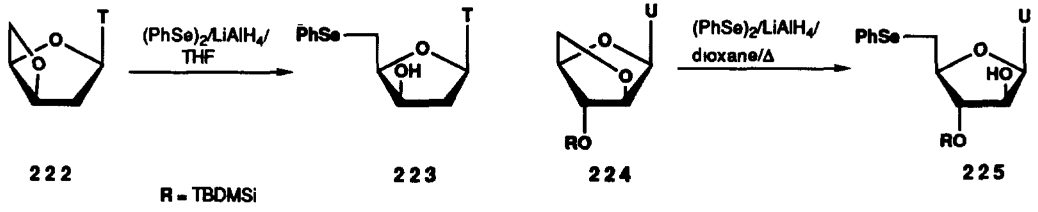


R = Tr, or TBDMSi; *t*-butyldimethylsilyl R' = Tr, MMTr, or pivaloyl

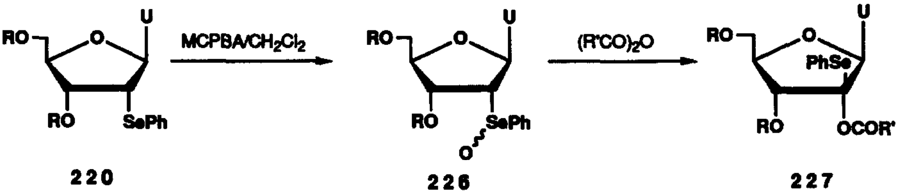
Under the same selenylation conditions, 3'-mesylate **217** was converted to the 3'-phenylselenenyl isomer **218**.[194,195a] Mildly acidic oxidation of **215** and **218** resulted in spontaneous *syn*-elimination to afford D4T **84** after deprotection. Interestingly, since phenylseleninyl is a good leaving group, oxidation of **215** in the presence of base gave the 2,3'-anhydrothymidine derivative.[195a] From 3',5'-bis(methanesulfonyl)thymidine, Chattopadhyaya *et al.* prepared the 3',5'-dideoxy-3',5'-bis(phenylselenenyl)thymidine **216**, which was oxidized with MCPBA. Elimination of the 3'-phenylseleninyl and 5'-phenylselenonyl groups occurred to give the bis-unsaturated derivative **219**.[194]

Miyasaka *et al.* have extensively studied the synthesis and chemistry of seleno-modified uracil nucleosides.[196,198-202] They first generated the phenylselenide anion from diphenyl diselenide and lithium aluminum hydride and utilized this highly nucleophilic species in several cyclonucleoside ring opening reactions.[198] Treatment of the silyl-protected 2,2'-anhydrouridine **58** with selenide anion at ambient temperature gave 2'-phenylselenated product **220** in quantitative yield,[196,198] and this procedure was general.[203] Silyl-protected 2,3'- and 2,5'-cyclonucleosides gave 3'- or 5'-phenylselenenyl derivatives, respectively.[196] Similar ring openings of nucleosidic oxetane **222** (3',5'-anhydro) and oxolane **224** (2',5'-anhydro) derivatives provided 5'-seleno derivatives **223** and **225**, respectively.[196,199] Treatment of the selenonucleosides with MCPBA gave regioselective *syn*-elimination of phenylselenic acid to provide a variety of unsaturated nucleosides including those with a 1',2'-double bond such as **221**.[196] The case of selenoxide fragmentation depends on the position of the phenylseleninyl substituent on the ribose ring and the neighboring environment. For example, 3'-phenylseleninyl nucleoside intermediates are hardly ever detected (TLC) and undergo almost instantaneous elimination. Other selenoxides (e.g. at the 5'-position) are quite stable and must be heated to effect elimination.



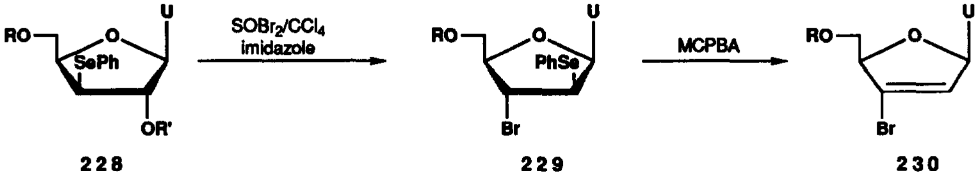


Miyasaka *et al.* found that Pummerer-type rearrangements of uracil nucleosides with a phenylselenenyl group at the 2', 3', or 5' position occurred upon oxidation (MCPBA) and treatment with acid anhydrides to afford α-acyloxyselenides such as **227**.[200] The stereochemistry at C2' of **227** with the phenylseleno group "up" was established by a NOESY experiment and correlated with Robins' results[91] for a fluoro-Pummerer reaction of a 2'-sulfoxide with DAST (section 2.2). Presumably attack at the less hindered α-face of the selenonium intermediate gave the single diastereomer **227**. Under similar conditions the 5'-phenylselenide gave 5'-acyloxyselenide diastereomers (~1:1.7). The authors postulated that **227** could serve as useful synthon for the formation of new carbon-carbon bonds by radical cleavage of the carbon-selenium bond.[200]



R = TBDMSi R' = Me or CMe$_3$

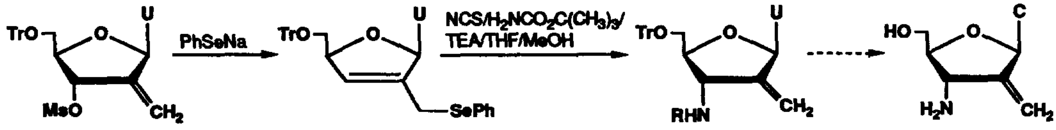
Treatment of 3'-phenylseleno derivative **228** (R' = H) with thionyl bromide gave a mixture of the *arabino* 3'-bromo-2'-phenylseleno derivative **229** and its *xylo* 2'-bromo-3'-phenylseleno isomer. Subsequent oxidation and selenoxide fragmentation afforded 3'-vinyl bromide **230** (73%).[201] A minor amount (15%) of the corresponding 2'-vinyl bromide was formed, presumably via initial opening of a *lyxo* seleniranium intermediate by bromide anion preferentially (but not exclusively) at the 3'-position.[201] 3'-Vinyl bromide **230** (or its 2'-isomer) underwent palladium-catalyzed cross-coupling and halogen-lithium exchange reactions to give 2' or 3'-carbon substituted derivatives of 2',3'-didehydro-2',3'-dideoxynucleosides. Treatment of the 3'-phenylseleno derivative **228** (R' = C_2H_5CO) with MCPBA and selenoxide fragmentation gave an enol ester, which was reacted with methyl lithium followed by an electrophilic aldehyde to give 3'-carbon substituted products.[202]



R = TBDMSi R' = H, or C_2H_5CO

Treatment of 2'-methylene derivative **231** with phenylselenide anion gave 2',3'-didehydro-2',3'-dideoxy-2'-phenylselenomethyl derivative **232** via a S_N2' process in excellent yield instead of the product from direct substitution at C3'.[204] Based on this conversion, Hassan and Matsuda reported the synthesis of 3'-amino-

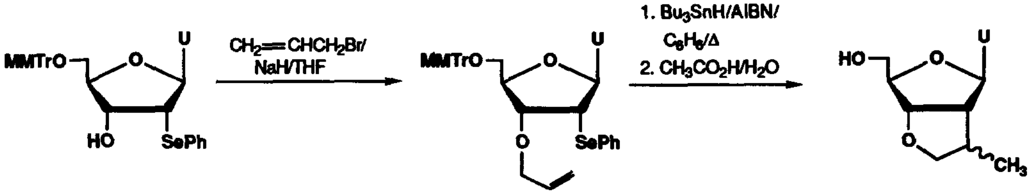
2',3'-dideoxy-2'-methylenecytidine 234 via an oxidative [2,3]-sigmatropic rearrangement of allylic selenide 232 via allyl amine intermediate 233.[204] Compound 234 resembles the antineoplastic and antiviral nucleosides 2'-deoxy-2'-methylenecytidine and 3'-amino-3'-deoxycytidine.



231 232 233 234

C = cytosin-1-yl $R = CO_2C(CH_3)_3$

Alkylation of 2'(or 3')-phenylseleno uridine derivatives (e.g. 235) with allyl bromide gave the 2'(or 3')-phenylseleno-3'(or 2')-*O*-allyl ethers (e.g. 236).[205a] Upon treatment of 236 with tributyltin hydride the C2' radical intermediate underwent intramolecular free radical addition from the α-face to provide diastereomeric 237 after deprotection. Interestingly, similar radical addition-cyclization at the β-face was diastereospecific. Various 3',5'-fused nucleosides were prepared when free radicals generated at C3' from 3'-phenylseleno nucleosides were trapped by olefin or alkyne functions attached to the 5' oxygen.[205b] Structural properties of 237 (and its *lyxo* isomers) have been studied.[206] Such a stereocontrolled radical cyclization with a silicon-bearing allyl group tethered to the 3'-hydroxyl of 235 led to formation of a seven membered siloxane ring, which was oxidized to give C2 branched nucleosides.[207]

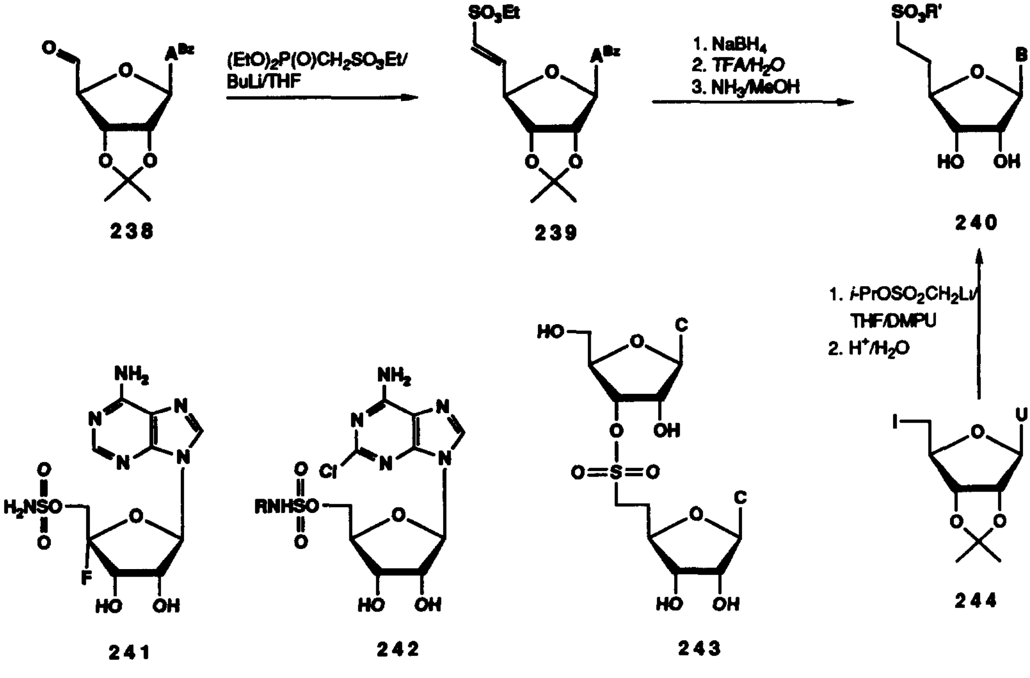


235 236 237

7. SULFONATE NUCLEOSIDES AND OLIGONUCLEOTIDE ANALOGUES WITH SULFUR-BASED LINKAGES

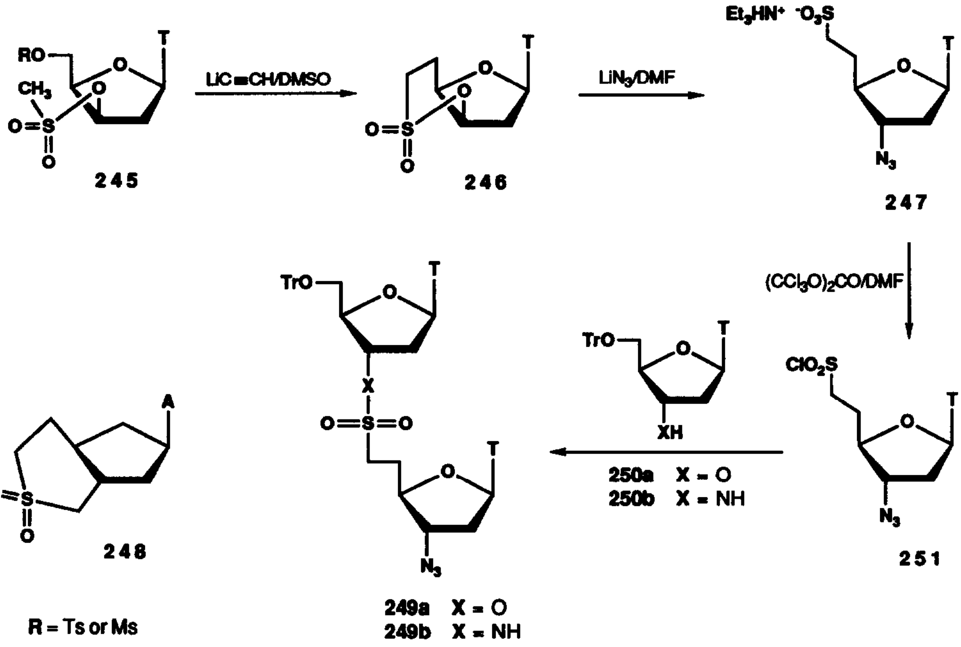
Sulfur-linked DNA and RNA fragments having the phosphate backbone replaced by dimethylene-sulfide, -sulfoxide, or -sulfone linkages, as well as thioformacetal, sulfonate, sulfonamide, and sulfamate (sulfamoyl) based bridges have recently been reported by several groups.[208-218] Such sulfur derivatives are non-ionic, achiral, and some are isosteric and isoelectronic analogues of phosphate diesters. Furthermore, they generally are more stable toward both chemical and biochemical degradation. The 5'-*O*-sulfamoyl moiety is present in the nucleoside antibiotics nucleocidin[219] **241** and ascamycin[220] **242**, produced by *Streptomyces*. Syntheses and biological evaluations of *O*-sulfamoyl nucleosides have been reported.[221-223]

Musicki and Widlanski described the synthesis of 5'-homologated sulfonate nucleosides **240** and 5-sulfonate derivatives of D-ribose.[208] Sulfonate **240** was prepared by alkylation of protected uridine 5'-iodide **244** with isopropyl lithium methanesulfonate (52%)[208b] or by addition of a sulfonate-stabilized Horner-Emmons reagent to protected adenosine 5'-aldehyde **238**.[208a] The double bond in the resulting α,β-unsaturated sulfonate ester **239** was reduced to give **240** after deprotection. Sulfonate **240** and 3'-*O*-sulfonate dinucleotide analogue **243** also were prepared from the corresponding sugar or disaccharide precursors, respectively, by glycosyl coupling with nucleic acid bases.[208a]



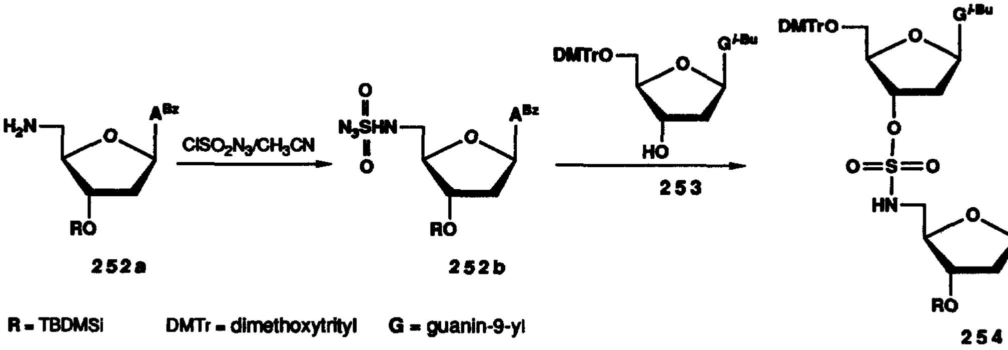
R = L-$H_2NCH(CH_3)CO$ R' = Et, or *i*-Pr

6',3'-Cyclic sulfonate (sultone) **246** (and its *erythro* isomer) were prepared via intramolecular cyclization by treatment of 5'-*O*-tosyl(or mesyl) derivative **245** with a lithium acetylide-ethylenediamine complex in DMSO.[209] The stable sultone **246** was utilized in a variety of ring opening reactions to give 3'-substituted nucleoside 6'-sulfonic acid derivatives. For example, treatment of **246** with LiN_3 in DMF gave ring-opened sulfonate **247** as a novel isostere of 3'-azidothymidine (AZT) monophosphate. Treatment of **246** with hot ethanolic NaOH afforded the 2',3'-didehydro-2',3'-dideoxy 6'-sulfonate in high yield.[209]



Treatment of **247** with triphosgene in DMF gave sulfonyl chloride **251**[210a] which was coupled with 5'-protected thymidine **250a** or its 3'-amino analogue **250b** in DMF to give thymidine dimers **249a** and **249b** connected by sulfonate or sulfonamide linkages, respectively. The 3'-azido-terminated dimer **249b** was reduced to the 3'-amino-terminated dimer, which could undergo further reaction with **251** to extend the oligonucleotide analogue. Attempted coupling of sulfonic acid **247** with **250** under a variety of conditions failed to give **249** in reasonable yields.[210a] Conformational studies of thymidine sulfonate dimer **249a** and 3'-amino-terminated sulfonamide dimer analogous to **249b** using NMR spectroscopy have been reported.[210b]

Dinucleotide analogues having a nuclease-resistant sulfamate (sulfamoyl) internucleotide linkage **254** have been reported.[211] Treatment of 5'-amino derivatives **252a** with chlorosulfonylazide gave the stable precursor **252b**. This compound underwent base catalyzed coupling with the free 3'OH of protected 2'-deoxyguanosine **253** to give the sulfamate dimer **254**. Under standard conditions, dimer **254** can be deprotected or converted to its 3'-*O*-(β-cyanoethyl)-phosphoroamidite. By standard automated oligonucleotide methodology this phosphoroamidite unit was incorporated into an oligodeoxynucleotide segment.[211]

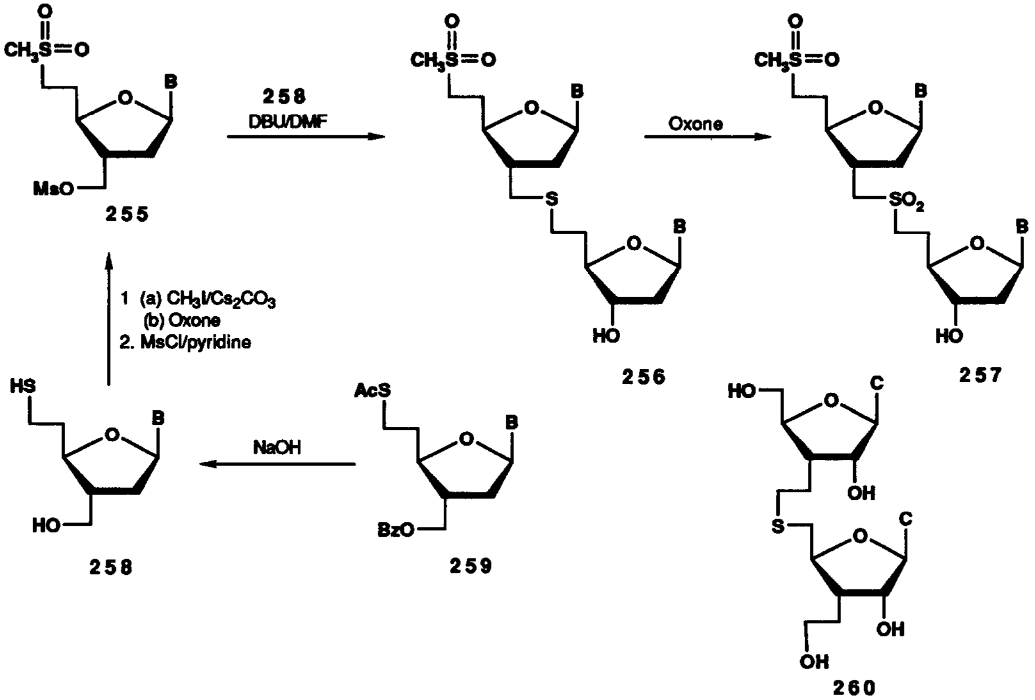


252a **252b** **253** **254**

R = TBDMSi DMTr = dimethoxytrityl G = guanin-9-yl

Incorporation of a sulfone unit into oligonucleotides by replacement of the phosphodiester (-O-PO_2-O-) bridge with an uncharged sulfone (-CH_2-SO_2-CH_2-) group is of interest due to potential applications as probes and in "antisense" studies.[212-214] The 3',5'-bis(homodeoxy)ribonucleoside building blocks **259** bearing 6'-thio functionalization have been synthesized. The multistep preparation involved: (i) construction of the sugar skeleton from a non-sugar precursor, (ii) enzymatic chiral resolution, and (iii) chromatographic separation of the α- and β-anomers.[212,213] Alternatively, nucleosides **259** were obtained from D-glucose.[213] The 6'-thioacetate group was introduced into **259** in the last step by standard Mitsunobu conditions. These protected building blocks were stable and were deprotected with sodium hydroxide to give **258** immediately prior to coupling. The coupling procedure involved: (i) capping of the 6'-thiol in **258** by conversion to the methyl sulfide, followed by oxidation to give the 6'-methylsulfonyl derivatives, (ii) activation of the 3'-hydroxyl by mesylation to give the monomers **255**, (iii) coupling of **255** with **258** to give thioether-linked dimer **256**, and (iv) oxidation *in situ* to give the sulfone-linked dimers **257**.[213]

Recently a selective protection/deprotection strategy for thiols and hydroxyls with dimethoxytrityl groups was developed to synthesize a dimer analogous to **256**. In this case displacement of a 6'-mesylate by a 3'-branched mercapto function was used to construct an identical internucleoside thioether linkage.[214] Dimer **260** in the ribonucleoside series, containing an "isomeric" internucleoside thioether linkage compared to **256**, has also been prepared from 3'-branched-chain nucleoside precursors.[215a] In this approach intermolecular displacement of a 3'-branched mesylate by a 5'-mercapto function afforded **260**.[215] Carbocyclic building blocks analogous to **259** with a methylene unit in place of the endocyclic ring oxygen were synthesized via modified Mitsunobu chemistry to give the 6'-thioacetate functionality.[216] Such a building block was converted via intramolecular displacement to the novel uncharged analog **248** of adenosine 3',5'-monophosphate[216b] as well as to the carbocyclic thioether-dimer analogous to **256**.[216c] Matteucci *et al.* reported synthesis and binding properties of pyrimidine oligodeoxynucleoside analogues containing 3'-formacetal and 3'-thioformacetal internucleoside linkages.[217,218]



CONCLUDING REMARKS

Discovery of the anti-HIV activity of dideoxynucleosides and recent developments with oxathiolanyl nucleoside analogues has had an impact on nucleoside chemistry including enhanced interest in sulfur and seleno chemistry. In the most convenient synthesis of dideoxynucleosides, 2-phenylsulfenyl(or selenenyl) substituted sugars were developed as precursors for coupling procedures.[105,106,192] Synthesis of the most potent drug candidates 32[70] and 135[144] and a variety of other nucleoside derivatives[146-150] was achieved through sulfur(or selenium)-mediated nucleoside chemistry.

More exploration in this area of nucleoside chemistry is warranted despite the fact that sulfur and selenium have been introduced at almost every position on the sugar moiety. Recently, for example, a series of carbon-4' substituted nucleosides has been prepared by the Syntex Research Group, but no 4'-sulfur substituted analogues were reported.[224,225] Further improvements in coupling procedures, including methods for 2'-deoxynucleosides and 2',3'-dideoxynucleosides, were recently extended by the use of phenyl(or methyl) 1-thioribosides[226,227] or 1-phenylsulfinyl analogues.[228] Selenoglycosides might also be useful.[229]

Improved syntheses of mercapto-modified nucleosides, now readily available by Reese's 9-(aryl)xanthen-9-yl strategy,[47,93] might provide more convenient approaches to thiooligonucleotides. Early work by Chladek and Nagyvary[230] and recent studies by Cosstick *et al.*[119,132] represent examples in which a sulfur atom replaced one of the bridging phosphodiester oxygen atoms in oligodeoxynucleotides. 4'-Thionucleosides have also been incorporated into antisense thiooligonucleotides and these oligomers retained Watson-Crick base pairing.[231]

APPENDIX

AZT	3'-Azido-3'-deoxythymidine
DAST	(Diethylamino)sulfur trifluoride
DIBAL-H	Diisobutylaluminum hydride
D2T	3'-Deoxythymidine
D4T	2',3'-Didehydro-3'-deoxythymidine
Hcy	L-Homocysteine
HIV	Human immunodeficiency viruses
HMPA	Hexamethylphosphoramide
HMDS	Hexamethyldisilazane
MCPBA	*meta*-Chloroperbenzoic acid
MMTr	Monomethoxytrityl
MTA	5'-*S*-Methyl-5'-thioadenosine
MTAPase	Methylthioadenosine phosphorylase
NAD^+/NADH	Nicotinamide adenine dinucleotide
RDPR	Ribonucleoside diphosphate reductase
SAH	*S*-Adenosyl-L-homocysteine (AdoHcy)
SAH hydrolase	*S*-Adenosyl-L-homocysteine hydrolase
SAM	*S*-Adenosyl-L-methionine (AdoMet)
SIBA	5'-*S*-Isobutyl-5'-thioadenosine
TBAF	Tetrabutylammonium fluoride
TBDMSi	*tert*-Butyldimethylsilyl
TBDPSi	*tert*-Butyldiphenylsilyl
TfOTMS	Trimethylsilyl triflate
Tr	Trityl (triphenylmethyl)

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