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RECENT DEVELOPMENTS IN THE SYNTHESIS, CHEMICAL MODIFICATIONS AND BIOLOGICAL APPLICATIONS OF SULFUR MODIFIED NUCLEOSIDES, NUCLEOTIDES AND OLIGONUCLEOTIDES

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**RECENT DEVELOPMENTS IN THE SYNTHESIS, CHEMICAL MODIFICATIONS AND
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INTRODUCTION

Chemical modifications of natural occurring nucleosides and nucleotides have led to a large number of analogs used for their therapeutic properties especially their antiviral and antitumor activities.¹⁻⁷

In the search for new bioactive agents and tools for biological studies, many sulfur nucleosides, nucleotides and oligonucleotides have been synthesized over 40 years. Some of them present interesting therapeutic activities and a majority have been efficient tools in studies of protein or nucleic acid structures and functions, protein-nucleic acid interactions and for antisense modulation of gene expression. Sulfur containing nucleosides are also interesting intermediates in the synthesis of other modified nucleosides.

A review of sulfur and seleno nucleosides in which an oxygen or a carbon atom of the sugar is substituted for sulfur or selenium was written by Wnuk⁸ and aspects of the chemistry of sulfur modified nucleosides, nucleotides and oligonucleotides have appeared in several books.⁹⁻¹³

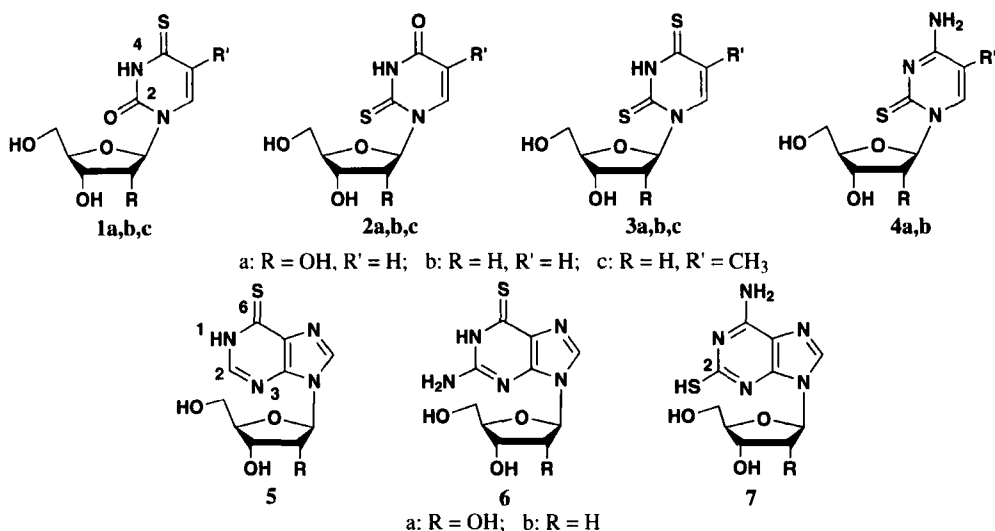
In regard to the extensive development of sulfur nucleoside chemistry, we are summarizing here some recent aspects of the chemistry of sulfur modified nucleosides, nucleotides and oligonucleotides including modifications of the base and the sugar but not on the phosphorus atom. This review illustrates different aspects of sulfur nucleoside chemistry.

I. MODIFICATIONS IN THE HETEROCYCLIC BASE

1. Thiobases Containing Nucleosides, Nucleotides

A large number of methods were developed in the past to introduce a thiol function at different positions on the base of natural occurring nucleosides or nucleotides. In order to prepare

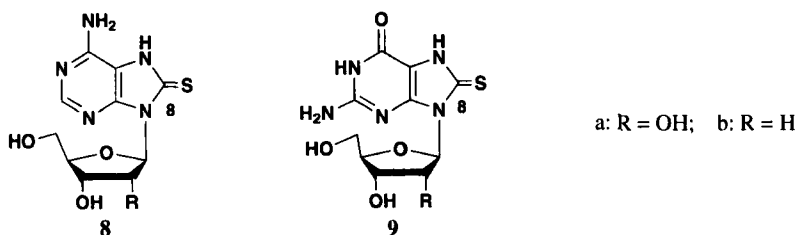
these modified nucleosides, an oxygen atom in an uracil, thymine or guanine ring was often transformed into a leaving group which was substituted, obtaining the corresponding thionucleoside or its protected form. 4-Thiouridine **1a**, 2'-deoxy-4-thiouridine **1b**, 4-thiothymidine **1c** and 6-thiopurine nucleosides, for example **5** and **6** (*Scheme 1*) and derivatives were prepared in such a way.¹⁴⁻¹⁷ One step substitution of an oxygen for a sulfur atom is also possible using phosphorous pentasulfide, for example in the synthesis of 4-thiothymidine.¹⁸ 2-, 2,4-Thiopyrimidine and 2-thiopurine nucleosides (for example **2-4** and **7**, *Scheme 1*) and nucleotides were synthesized in different ways. 1-β-D-arabino-furanosyl-2-thiouracil can be obtained by ring-opening of 2,2'-anhydrouridine **85** with



Scheme 1

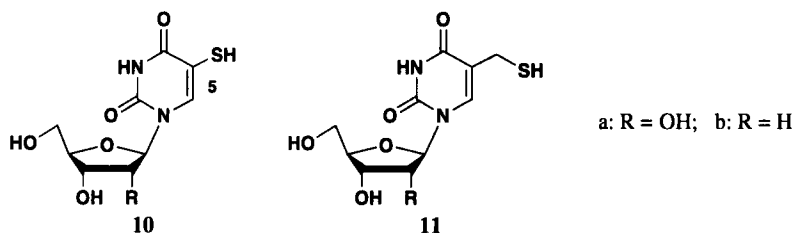
hydrogen sulfide.¹⁹ 2-Thiouridine **2a**, 2-thiothymidine **2c** and 2-thiocytidine **4a** derivatives were obtained by chemical²⁰⁻²² or enzymatic glycosylation.²³ In the purine series, for example, 2-thioadenosine **7** which was found to inhibit platelet aggregation was synthesized from a 6-chloro derivative of guanosine²⁴ and its 5'-monophosphate were prepared by ring-opening of adenosine 5'-monophosphate N¹-oxide with aqueous sodium hydroxide followed by recyclization with carbon disulfide.²⁵

In these compounds, the thiol functions were often found in the form of the corresponding stable thione. Introduction of a thione function at the 8-position of purine nucleosides (for example, **8** and **9** in *Scheme 2*) or nucleotides was achieved by displacement of a bromine atom introduced by bromination of the natural adenine and guanine nucleosides or nucleotides.^{10,26,27}



Scheme 2

2'-Deoxy-5-thiocyanatouridine derivatives were used as intermediates in the preparation of 2'-deoxy-5-thiouridine **10b** (Scheme 3) and its phosphoramidite.^{28,29} The easily oxidizable nucleoside, 2'-deoxy-5-thiomethyluridine **11b** (Scheme 3) can also be obtained by photochemical bromination of 3',5'-diacetylthymidine and then reaction with sodium hydrogen sulfide³⁰ or after hydroxymethylation of 2'-deoxyuridine.³¹



Scheme 3

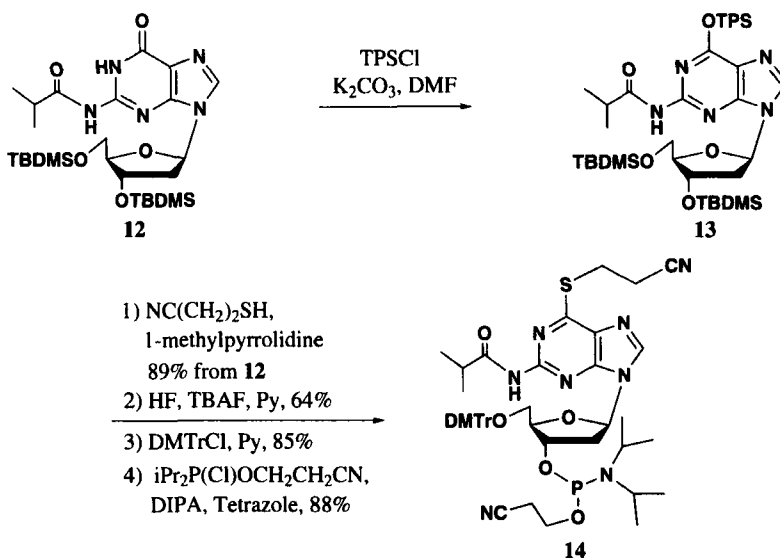
Different modifications were introduced in thiobase containing nucleosides and nucleotides. For example arabino, 2'-deoxy-5-fluoro and 2'-azido-2'-deoxythiopyrimidine nucleosides and/or nucleotides were prepared.³²⁻³⁵ In the search for new anti-HIV agents, 2',3'-dideoxy-2-thiouridine, thymidine and cytidine were recently synthesized but exhibited low activities in comparison with their 2-oxy analogs.³⁶ 2',3'-Dideoxy-4-thiouridine significantly inhibits uridine phosphorylase purified from mouse leukemic L-1210 cells.³⁷

2. Thiobases Containing Oligonucleotides, Photochemical Probes and Tools

In the last decade, methods were developed for the synthesis of oligonucleotides bearing a thiol or a thione function on the base. The drug, 6-mercaptopurine, has been used since the 1950's for the treatment of acute leukemia³⁸ and the 6-protected derivative, azothioprine, is a useful immunosuppressant. 6-Mercaptopurine is thought to be transformed *in vivo* into 6-mercaptopguanine which is incorporated into DNA. Oligodeoxynucleotides incorporating the corresponding nucleosides **5b** and **6b** respectively were synthesized and the stability of the corresponding duplexes was studied.³⁹ The synthesis and study of 2'-deoxy-6-thiomethylguanosine containing oligonucleotides revealed that the cytotoxicity of 6-mercaptopguanine depends upon *S*-methylation by *S*-adenosylmethionine **138** after incorporation into DNA.⁴⁰

4-Thiouridine **1a** is a natural constituent of t-RNA⁴¹ which can be used as an intrinsic photo-label in the study of nucleic acids.⁴² The inherent photo-crosslinking ability of 4-thiopyrimidine and 6-thiopurine nucleosides has been widely used to study three dimensional interactions such as between RNA-RNA (for example in t-RNAs or in catalytic RNAs called ribozymes) or RNA-proteins. 4-Thiopyrimidine or 6-thiopurine nucleotides can be activated selectively by UVA light (330-350 nm) and photocrosslinking allows specific contacts to be mapped. Natural RNAs were studied but the full development of this photoaffinity technique required efficient methods for the introduction of thiobases in oligonucleotides.⁴²⁻⁴⁷

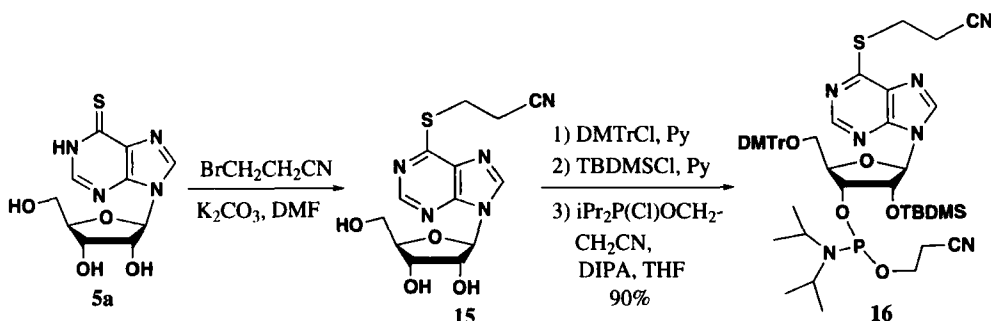
In this approach, modified oligodeoxynucleotides were synthesized incorporating thiopurine nucleosides such as 2'-deoxy-6-thioinosine **5b**⁴⁸⁻⁵² (6-mercaptapurine) and 2'-deoxy-6-thioguanosine **6b**^{51,53-59} (*Scheme 4*) or thiopyrimidine nucleosides such as 2'-deoxy-4-thiouridine **1b**^{49,50,60-62} and 4-thiothymidine **1c**.^{49-52,58,62-66}



Scheme 4

The synthesis of 4-thiothymidine 5'-triphosphate was reexamined recently.⁶⁷ This nucleotide was found to be an excellent substrate for the Klenow fragment (DNA polymerase) and HIV-1 reverse transcriptase and was used for incorporation of 4-thiothymidine into oligodeoxynucleotides.⁶⁸

Less work has been reported with thioribonucleosides. This is largely due to the problem of finding suitable protecting groups for the 2'-hydroxyl and the thione functions. Oligoribonucleotides containing 6-thioinosine **5a**⁶⁸ (thiopurine ribonucleoside; *Scheme 5*) or 4-thiouridine **1a** were synthesized.⁶⁹⁻⁷²



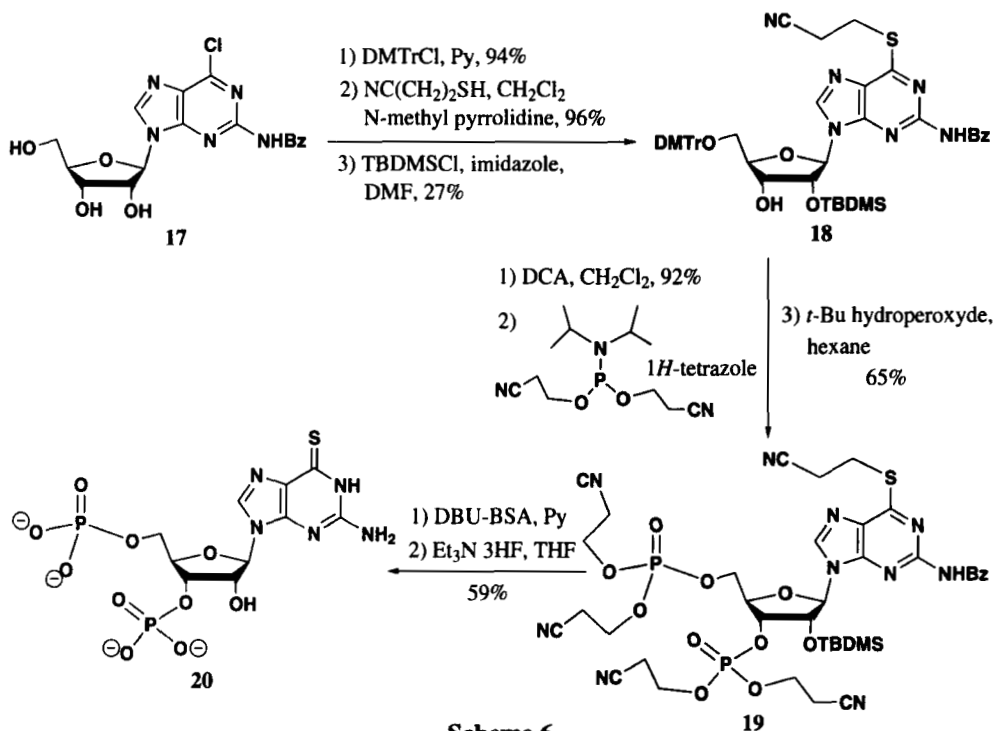
Scheme 5

In the automated solid phase synthesis of such oligodeoxyribonucleotides and oligoribonucleotides using phosphoramidite or H-phosphonate chemistry, different protective groups for the

SULFUR MODIFIED NUCLEOSIDES, NUCLEOTIDES AND OLIGONUCLEOTIDES

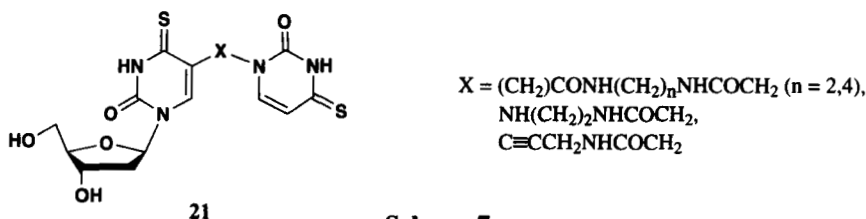
thione function were used, the methylsulfenyl group⁶³, the 2-cyanoethyl^{53,56,57,60,61,68,69} (Scheme 4 and 5), the phenyl or the 4-nitrophenyl⁶⁴, the 2,4-dinitrophenyl³⁹, the mesitylene sulfonyl⁵⁴⁻⁷³ and the pivaloyloxymethyl group.^{49-51,72}

6-Thioguanosine, 6-thioinosine, 4-thiouridine and their 3',5'-bisphosphates (for example 20) were synthesized recently in good yields by improved methods and were enzymatically incorporated into RNA (Scheme 6).¹⁷ The 4-thiouridine 3',5'-bisphosphate derivative was found to serve as the most active substrate of T4 RNA ligase with a reaction efficiency of 96%.



Scheme 6

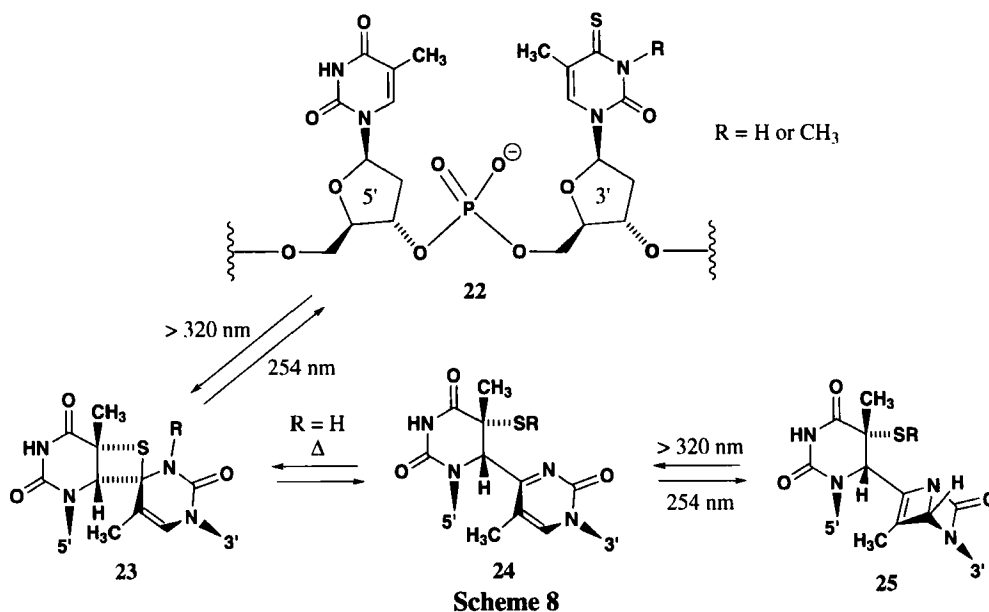
Oligodeoxynucleotides containing the *bis*-thiouracil nucleoside probe **21** (Scheme 7) were also synthesized and showed moderate irreversible photobinding with complementary DNA and RNA targets.^{74,75} Peptide nucleic acid (PNA) dimer duplexes incorporating 4-thiothymidine were not able



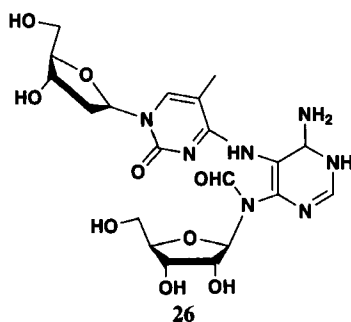
Scheme 7

to fully mimic the photochemical behavior observed in the dinucleotide series.⁷⁶ A study of the self-association properties of 4-thiouridine **1a** showed a strong decrease in self-association constant compared to uridine.⁷⁷

4-Thiouracil and 6-thiopurine systems undergo two types of light-induced reactions with the natural bases: cycloaddition and radical reactions which produce stable photoadducts.^{66,76,78-80} For example, 4-thiouridine, 4-thiothymidine and derivatives photoreact with natural pyrimidine nucleoside to lead to a thietane **23** which interconverts with the corresponding (6-4) product **24** (Scheme 8).⁸¹ Upon irradiation the latter forms the Dewar valence isomer **25**.⁸¹ The thietane adducts appeared more stable than the corresponding oxo analogs. A remarkable photoreversal of the thio Dewar valence isomers **25** was recently reported (Scheme 8).



In a mechanistic study of the photoreaction between 4-thiothymidine **1c** and adenosine, the structure of the major adduct **26** isolated in a 90% yield was determined by X-ray diffraction (Scheme 9).⁸²⁻⁸³ In order to prevent formation of G-quartets in G-rich sequences in triple helix forming oligonucleotides used as tools for modulation of gene expression⁸⁴⁻⁸⁶, 2'-deoxy-6-thioguanosine **6b**



Scheme 9

(dS⁶G) containing oligonucleotides were employed.⁵³ The presence of a central dC-dS⁶G base pair in an octameric duplex affects the overall structure.⁸⁷ Polyribonucleotides containing 1-methyl-6-thioguanosine or 1-methyl-6-thioinosine are shown to be potent inhibitors of various strains of HIV-1 and HIV-2.⁸⁸ These oligomers were proposed to bind and fill the RNA binding site of HIV reverse transcriptase.

2'-Deoxy-2-thiouridine **2b** and 2-thiothymidine **2c** were also incorporated as probes in oligodeoxynucleotides giving stable hybrids with unmodified oligonucleotides.^{63,89-91} In one of these syntheses⁸⁹, *N*³ or *O*⁴-acylation with toluoyl chloride was used as protection during the synthesis. This protection prevents the oxidative desulfurization observed for the unprotected thiobase induced by the aqueous oxidation reagent used in the phosphoramidite DNA synthesis.

Incorporation of a 2-thiopyrimidine ribonucleoside into oligoribonucleotides appeared more attractive to study the intramolecular hydrogen bonding in RNA structures.⁹² For example, the formation of the HIV TAR-TAR RNA complex (« kissing hairpin ») was studied after incorporation of 2-thiouridine **2a**.⁹³ Methods of synthesis and incorporation of this modified nucleoside were developed from the corresponding phosphoramidite without base protection.⁹⁴

2-Thiouridine **2a** and C5-modified 2-thiouridines are found predominantly at the wobble position of tRNAs. For structural studies, 2-thiouridine has also been incorporated into various diribonucleotides^{95,96} and oligoribonucleotides.⁹⁷

5-Methylaminomethyl-2-thiouridine is an hypermodified nucleoside present in the anticodon domain of tRNA^{Lys}. For biophysical investigation, this nucleoside was recently incorporated with other modified nucleotides in the 17 nucleotide anticodon stem-loop of *E. coli* tRNA^{Lys} using the corresponding *O*-2-cyanoethyl-*N,N*-diisopropylphosphoramidite.^{98,99}

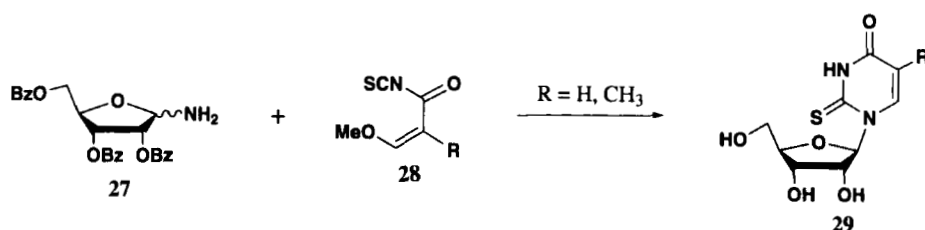
Other hypermodified thionucleosides were synthesized and incorporated into oligonucleotides. 5-Carbomethoxymethyl-2-thiouridine, which appears to be directly involved in RNA and protein recognition during HIV-1 reverse transcription initiation, was incorporated chemically into tRNA anticodon stem-loop domains¹⁰⁰ and 2'-*O*-methyl-2-thiouridine containing oligoribonucleotides have been described.¹⁰¹

Incorporation of 2'-deoxy-5-thiouridine **10b** into oligodeoxynucleotides was achieved using the 5-thiocyanato or the 5-*S*-(2,4-dinitrophenyl)thio group in the phosphoramidite intermediate.^{28,29,102} These oligonucleotides were conjugated to fluorescent or spin-labelled molecules.²⁹

3. Synthesis and Modifications of Nucleosides and Oligonucleotides Using Sulfur Chemistry

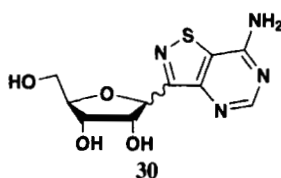
a) Sulfur in Glycosidation Methods, Synthesis of Thiobases Containing Nucleosides, Control of Stereochemistry

Sulfur chemistry was extensively developed both for the synthesis of thionucleosides, and for the synthesis of non-sulfur containing nucleosides.^{103,104} The synthesis of the 2-thiopyrimidine nucleosides **29** can be illustrated by a method of glycosidation developed by Shaw *et al.* (Scheme 10).¹⁰⁵ Some different methods were developed more recently.²⁰⁻²² Different nucleosides incorporating



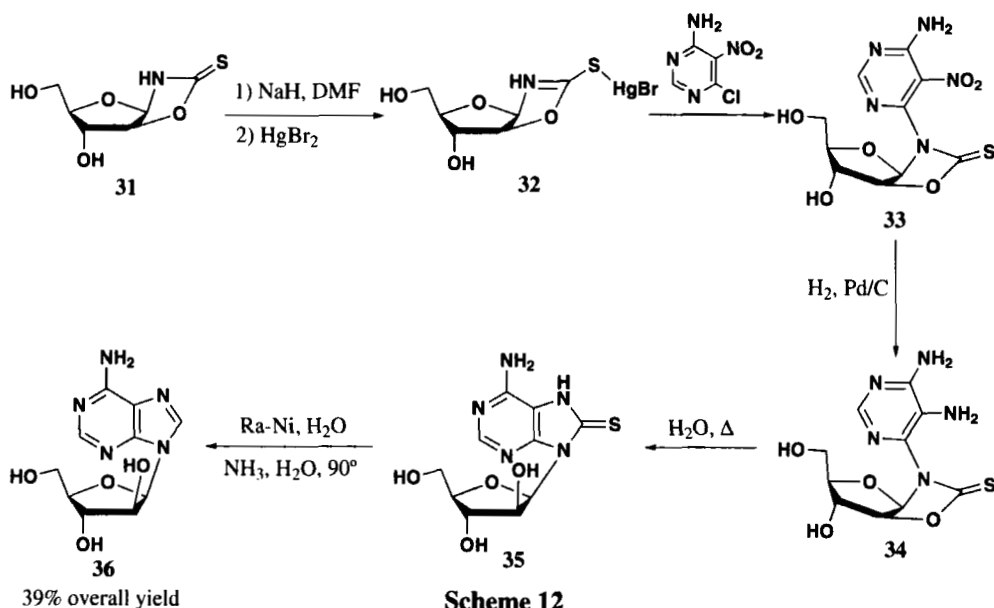
Scheme 10

a sulfur atom in the base ring were also synthesized, for example analogs of bioactive *C*-nucleosides **30** (Scheme 11).¹⁰⁶⁻¹⁰⁷ The pyrimidine ring was formed by cyclization of intermediates 4-aminoisothiazole-5-carboxylate *C*-nucleosides. In the condensation of a sugar with a base, a sulfur atom was



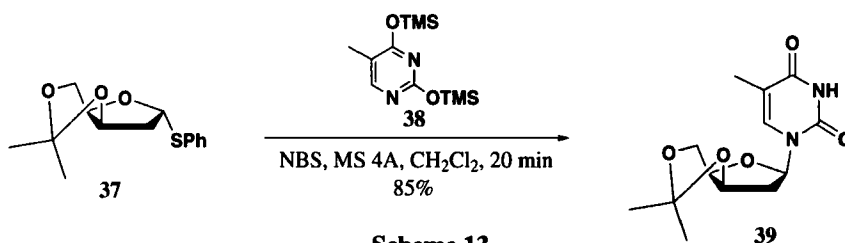
Scheme 11

used in a different manner in order to control the stereochemistry. Introduction of a sulfur atom on the sugar allows control of the anomeric stereochemistry, for example in the synthesis of 9- β -D-arabinofuranosyladenine **36** from the arabinofurano-thionoxazolidine **31** (Scheme 12).¹⁰⁸

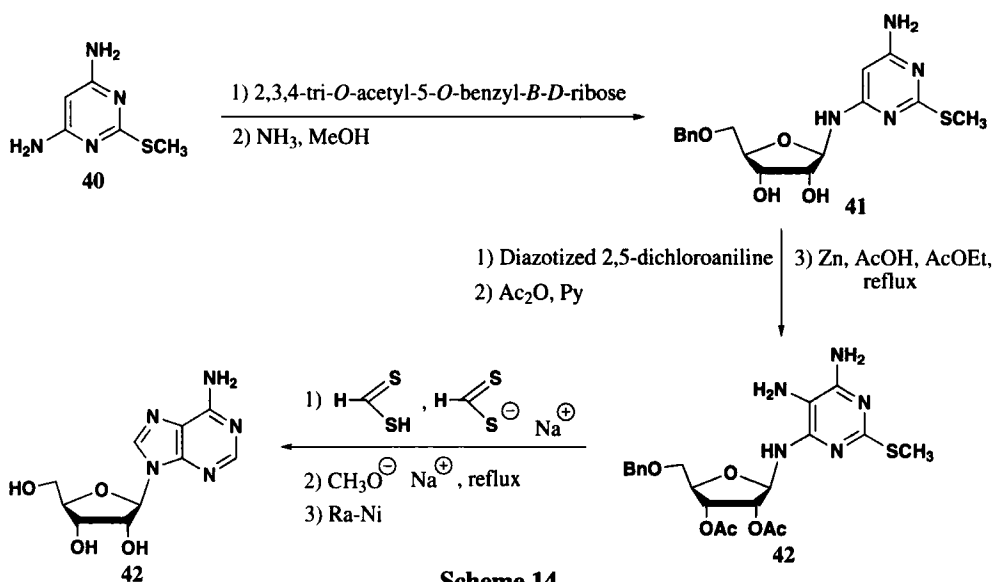


Scheme 12

The NBS-promoted coupling reaction of 3,5-*O*-isopropylidene-2-deoxy-1-thiophenyl- α -D-threo-pentafuranoside **37** with silylated bases such as **38** was found to proceed in a highly stereoselective manner (α : β = 1:50) (Scheme 13).¹⁰⁹



A thiomethyl group can also be used for regioselectivity control in the glycosidation step (Scheme 14).¹¹⁰ An interesting protection of the 4-thione function in pyrimidines as 4-benzylsulfanyl uracil and thymine illustrates the use of a sulfur protecting group in glycosylation reactions for preparing cyclobutyl nucleosides.¹¹¹

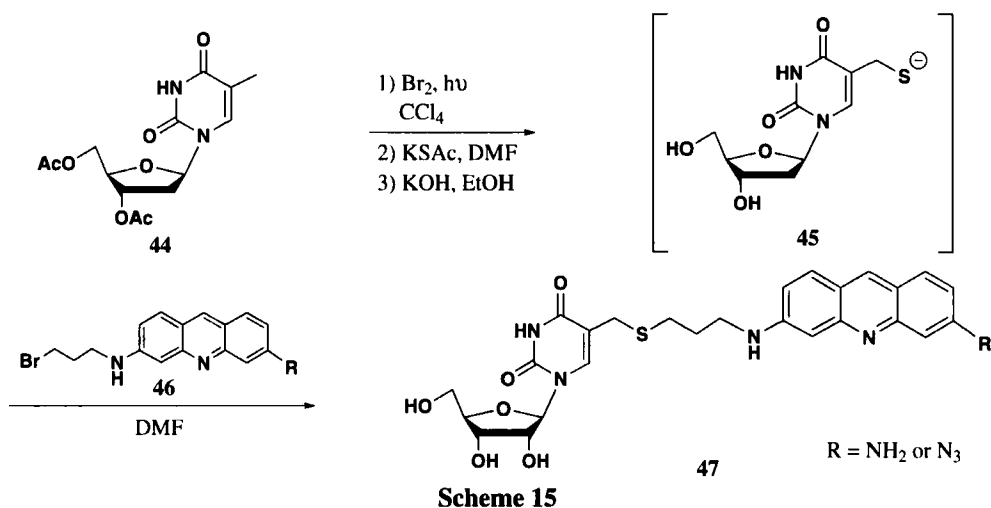


b) Modifications of Thionucleosides and Nucleotides

In the past, a number of reactive biological probes have been prepared from thiopyrimidine and thiopurine nucleosides. Typical examples are a reactive bromoacyl derivative of 2-thioadenosine 5'-monophosphate synthesized from the corresponding adenosine 1-oxide derivative and used as an affinity label of pyruvate kinase^{24,25} and a 4-azidophenacyl derivative 5'-triphosphate used as a phoaffinity label of the DNA polymerase I Klenow fragment.¹¹² 2-Thioethers of adenosine 5'-triphosphate derivatives synthesized from 2-bromoadenosine have been reported as novel P_{2Y-R} receptor ligands and potential insulin secretagogues^{113,114} whereas their 8-thioether analogs have little or no effect.¹¹⁴ 2-Thioethers of adenosine 5'-triphosphate modified on the phosphate group are the first very potent antagonists of the human platelet P_{2T} receptor which have significant potential as antithrombotic agents.¹¹⁵ 2'-Deoxy-8-thioadenosine and its phosphate derivatives were also used as intermedi-

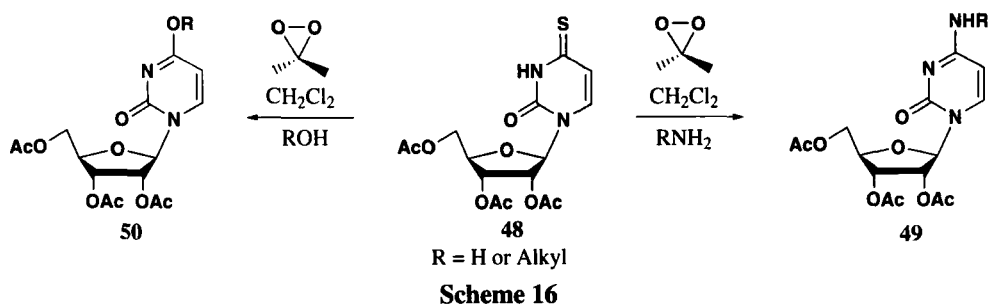
ates in the synthesis of various (photo)reactive nucleosidic, nucleotidic and oligonucleotidic probes. In a recent application, 8-[(4-azidophenacyl)thio]adenosine 5'-triphosphate was used as a photocrosslinking agent.¹¹⁶

Sulfur modification of thymidine on the 5-methyl group was achieved in the past *via* the 5-chloro derivative. The 5-thiomethyl derivatives were prepared from this intermediate and revealed efficient anti-herpes activity.¹¹⁷ Photochemical bromination of 3',5'-diacetylthymidine **44** on the 5-methyl group led to 2'-deoxy-3',5'-diacetyl-5-bromomethyluridine which can be transformed into the easily oxidable 2'-deoxy-5-thiomethyluridine or into the corresponding thioacetate (*Scheme 15*).³⁰ We used this latter compound and its α -isomer for preparing α and β -thymidine conjugates to the intercalating drug proflavine or its azido derivative, for example **47**, in order to study ring-ring stacking interactions (*Scheme 15*).¹¹⁸ A one pot hydrolysis of the thioacetate under basic conditions to form the thiolate **45** and coupling with the bromopropyl proflavin derivative **46** led to the conjugates **47** and avoided oxidation of the thiol function (*Scheme 15*).

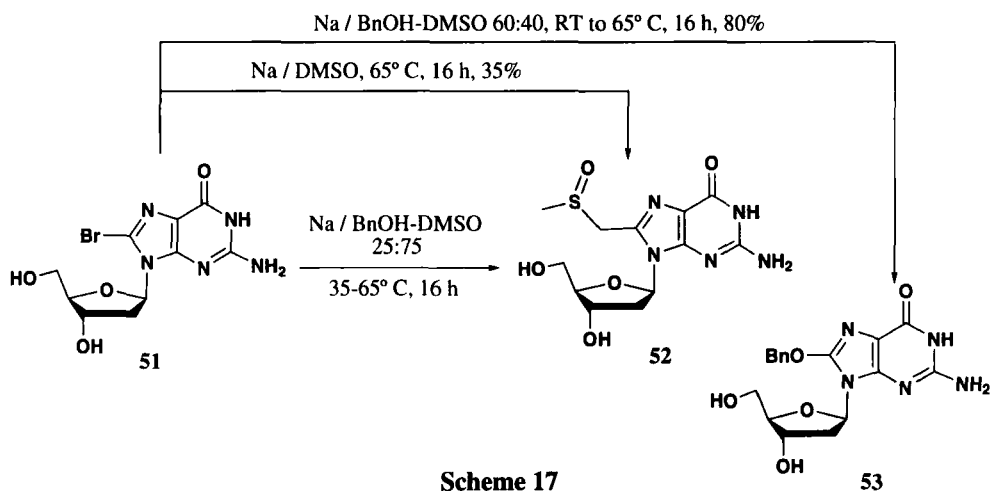


In the recent development of chemistry of thiopyrimidine and thiopurine nucleosides, some new reactions have been reported. Ozonation of 4-thiouracil and 6-thioguanine nucleosides in the presence of amines afforded under mild conditions cytidine and adenosine or their *N*-alkylated derivatives, respectively.¹¹⁹ Desulfurization of thiopyrimidine or thiopurine nucleosides with dimethyldioxirane alone or in the presence of an amine led to various *N*- or *O*- derivatives like *N*⁴-cytidine, *N*⁶ and *C*⁸-adenosine derivatives (*Scheme 16*).^{120,121}

The first direct aminolysis of 2-thiouracil nucleosides to 2-thiocytosine nucleosides have been reported.¹²² In the thio purine series, heating at elevated temperature of peracetylated 6-thioguanosine induces a transglycosylation to form a stable 9,*S*⁶-*bis*(ribose) derivative and *N*²-acetyl-6-thioguanine.¹²³ A synthesis of 9-(2-deoxy- β -D-ribofuranosyl)purine-2-thione from 2'-deoxy-6-thioguanosine has been also recently reported.¹²⁴ An interesting reaction was observed in the synthesis



of 8-oxodG, a DNA oxidative damage product, from 8-bromodG **51** via the 8-benzyloxy intermediate **53**.¹²⁵⁻¹²⁶ 2'-Deoxy-8-dimsylguanosine **52** was obtained as the major product in a $\text{S}_{\text{RN}}1$ reaction with sodium metal conducted in a benzylic alcohol-DMSO mixture (Scheme 17).



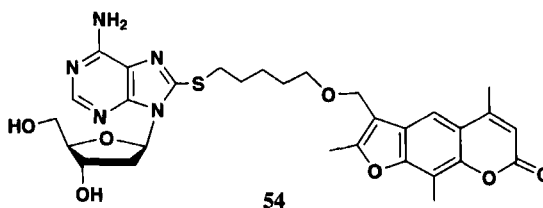
Thiols are antioxidants and have been used as radioprotecting agents. Under some conditions, thiols are believed to enhance DNA damage. Chemical evidence for thiyl radical addition to the C6-position of a pyrimidine double bond of nucleosides resulting in the formation of an intermediate 5,6-dihydropyrimidine 5-yl radical was recently obtained.¹²⁷

A lot of work has been developed for the synthesis of « activated » pyrimidine and purine nucleosides and their transformation into substituted-base nucleosides. In this regard, it has been reported recently that, in the purine series, the 6-(benzylsulfonyl) group undergoes $\text{S}_{\text{N}}\text{Ar}$ displacement with an arylamine at ambient temperature.¹²⁹

c) Modifications of Oligonucleotides

In the study of proteins and/or nucleic acids, 2'-deoxy-8-thioadenosine was used as an intermediate in the synthesis of (photo)reactive nucleosidic, nucleotidic and oligonucleotidic probes (see

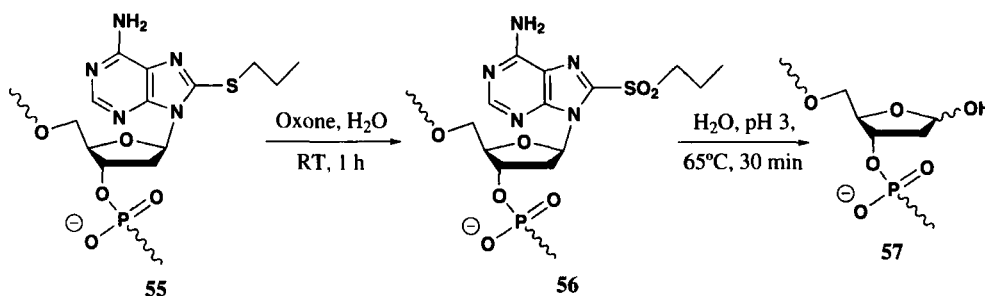
previous part). 4,5',8-Trimethylpsoralen was attached at the C8-position of 2'-deoxy-8-thioadenosine **8b** via the sulfur atom and a five carbon atom linker and the resulting modified nucleoside **54** was incorporated into oligonucleotides.¹²⁹ These oligonucleotides are efficiently able to form, photochemically with their complementary DNA target, a specific sequence crosslink (*Scheme 18*).



Scheme 18

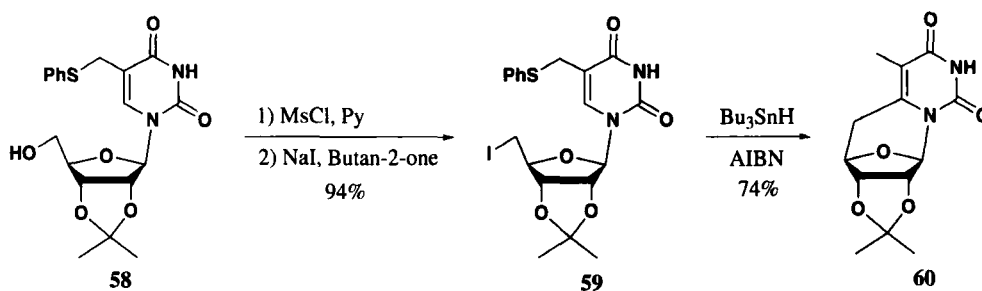
Post-synthetic modification of 4-thio-2'-deoxyuridine **1b** containing oligonucleotide strand have been reported for incorporating a wide range of functional groups at any base position within a DNA.⁶⁴ Such a post-modification was used to derivatize, with *p*-azidophenacyl bromide, 4-thiouridine residues incorporated enzymatically into a RNA fragment from the corresponding triphosphate.¹³⁰

We synthesized different 2'-deoxy-8-sulfur modified purine nucleosides for preparing oligonucleotides containing one of the most frequent chemical damage product in DNA, the abasic site **57**, which results from hydrolysis of the glycosidic bond with removal of the base. In these modified nucleosides, a fragility of the glycosidic bond induces loss of the base and rapid hydrolysis especially for 8-alkylsulfonyl nucleosides.¹³¹ This property was used for synthesizing abasic oligonucleotides. 2'-Deoxy-8-propylthioadenosine prepared from 2'-deoxy-8-thioadenosine **8b** was incorporated into oligodeoxynucleotides **55** and then the sulfide function on the base was oxidized to the corresponding sulfone **56** increasing the fragility of the glycosidic bond. A simple hydrolysis led to the abasic oligonucleotides **57** (*Scheme 19*).¹³²



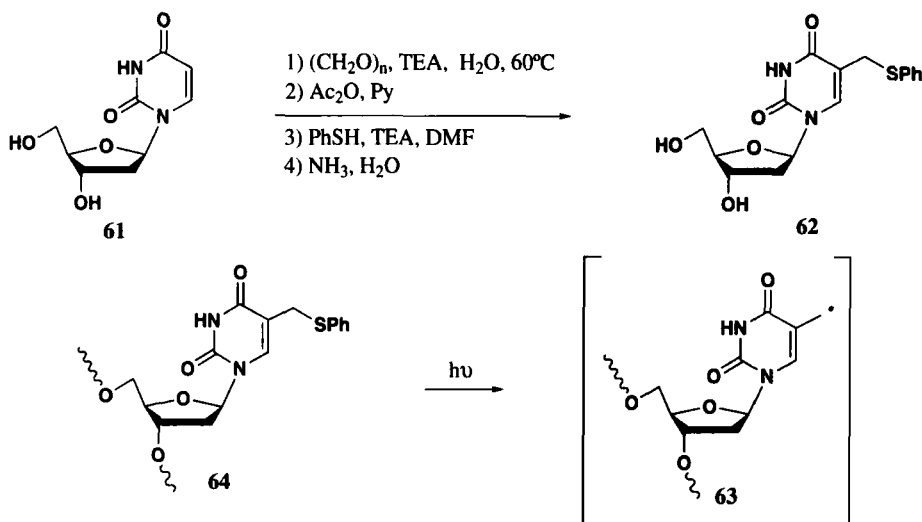
Scheme 19

5-Phenylthiouridine derivatives such as **58** have been used as intermediates in the synthesis of modified nucleosides and nucleotides. 6,5'-Cyclothymidine **60** was prepared from 3'-acetyl-2',5'-dideoxy-5'-iodo-5-phenylthiomethyluridine **59** (*Scheme 20*).³¹



Scheme 20

2'-Deoxy-5-phenylthiouridine **62** prepared from 2'-deoxyuridine **61** (Scheme 21) was incorporated into DNA oligomers using the corresponding 3'-phosphoramidite.¹³³ Under UV exposure and different conditions, these oligomers **64** were used to generate specific base lesions from the radical species **63** (Scheme 21).

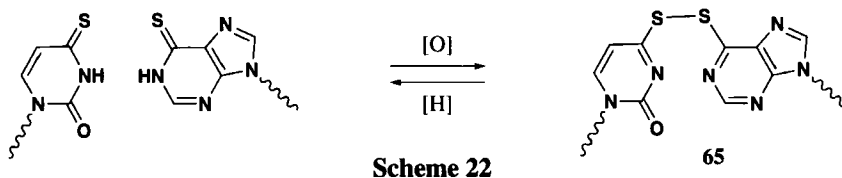


Scheme 21

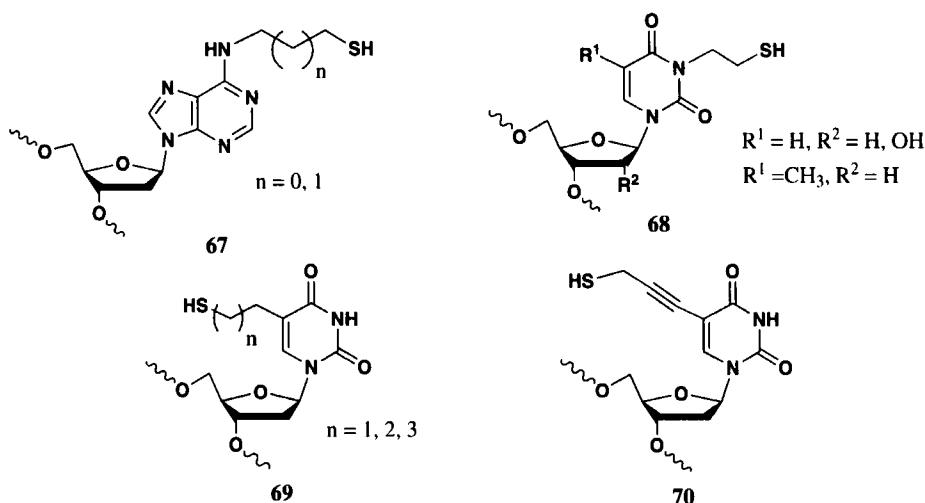
4. Others Properties of Thiopyrimidine and Thiopurine Nucleosides, Nucleotides and Oligonucleotides

Specific interactions of the sulfur atom in 4-thiouridine and 6-mercaptapurine with metallic ions such as Tl(II) , Hg(II) , Au(III) and Pt(II) were evidenced.¹³⁴ Recently, reactions of 4-thiouridine, 2'-deoxy-6-thioinosine and their 5'-monophosphates with chloro(diethylenetriamine)palladium(II) were investigated in acidic aqueous solution.¹³⁵ The labile chloro ligand is directly replaced by the thione unit in the Pd(II) complex and incorporation of both thionucleosides into single-stranded oligonucleotides increased the rate of adduct formation by a factor 2-3. Gold(III) complexes with thione-containing nucleosides and oligonucleotides were also studied for evaluation of reactivity of short oligonucleotides in different environment.^{134,136}

Several research groups have successfully introduced thiol or thione groups into DNA for the purpose of disulfide cross-linking (for example, *Scheme 22*).¹³⁷⁻¹³⁹ If the thiols or the thiones are placed into opposite strands of a duplex-forming sequence, the two strands are linked covalently by

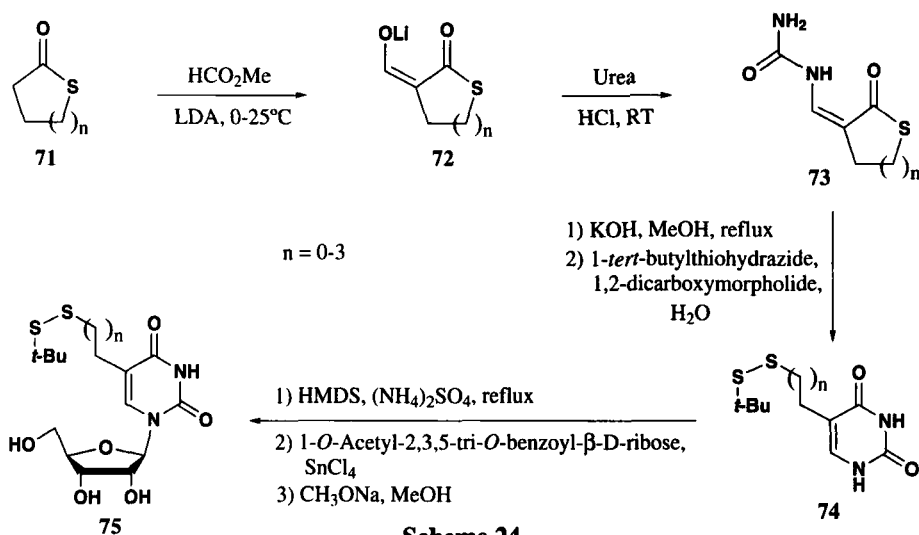


oxidation and the duplex is stabilized. A similar approach was used to stabilize intramolecular hairpins in short catalytic RNA or DNA.¹⁴⁰⁻¹⁴¹ Various sulfur-modified pyrimidine and purine nucleosides have been incorporated in oligonucleotides for preorganization of two binding domains in recognition of single-stranded DNA or RNA targets by duplex or triplex formation (for example, oligonucleotides **67**^{142,143}, **68**¹⁴⁴⁻¹⁴⁸, **69**¹⁴⁹⁻¹⁵⁰, **70**¹⁵¹, *Scheme 23*).

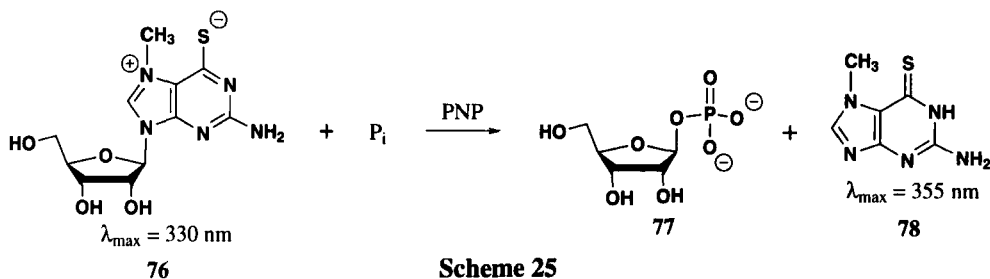


For example in this approach, different 5-thioalkyluridines and their phosphoramidites were efficiently synthesized by conversion of thiolactones **71** into ureidomethylene thiolactones **73**, rearrangement to the corresponding 5-thioalkyl uracil derivatives **74** and then Hilbert-Johnson glycosylation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribose (*Scheme 24*).¹⁴⁹

Finally another biological application of a nucleoside carrying a sulfur atom on the base can be mentioned. In the presence of inorganic phosphate, 2-amino-6-mercapto-7-methylpurine ribonucleoside **76**, obtained by methylation of 6-thioguanosine **6a**, is enzymatically converted by purine nucleoside phosphorylase (PNP) to ribose 1-phosphate **77** and 2-amino-6-mercapto-7-



methylpurine **78** (Scheme 25). The spectrophotometric detection of the free base permits the continuous assay of ATPase activity, and potentially of other enzymes such as GTPases and phosphatases that produce inorganic phosphate.¹⁵²⁻¹⁵⁴



II. SULFUR MODIFICATIONS IN THE SUGAR, SUBSTITUTION OF THE HYDROXYL FUNCTIONS

1. Modifications at the 2' or 3' Position

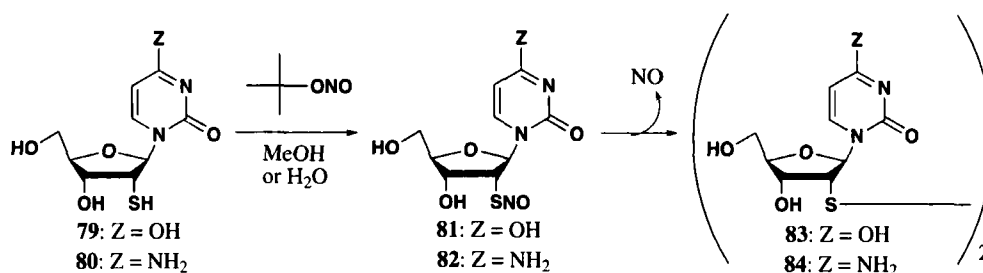
a) Modifications at the 2' Position

Substitution of the 2'-hydroxyl function by a thiol group in ribonucleosides appeared attractive in the search for new therapeutic agents or for the study of RNA chemistry and biology, especially in the field of catalytic RNA (ribozymes).¹⁵⁵

2'-Deoxy-2'-thiouridine **79**, cytidine **80** and adenosine have been prepared.^{8,156-158} These nucleosides undergo glycosidic cleavage in aqueous solution at room temperature above pH 6.5.¹⁵⁹ Elimination of the base probably results from intramolecular reaction of the thiolate at position 2'. These nucleosides are also easily oxidized to the corresponding disulfide.¹⁵⁹

In the search for new bioactive nucleotides, we showed that 2'-deoxy-2'-thiouridine 5'-diphosphate strongly inactivates *in vitro* *E. coli* ribonucleotide diphosphate reductase.¹⁶⁰ This enzyme catalyzes the reduction of the four natural ribonucleotides to the corresponding 2'-deoxyribonucleotides and thus is a key enzyme in the synthesis of DNA.¹⁶¹⁻¹⁶⁴ The 2'-thiol function of the modified nucleotide interacts with a cysteine residue at the active site to lead to a perthiyl radical on the enzyme. This nucleotide was obtained using a mixed propyl disulfide intermediate which can be reduced easily *in situ* with dithiothreitol to lead to the active compound.¹⁶⁵ This protection proved useful for the introduction of a diphosphate function at the 5'-position.

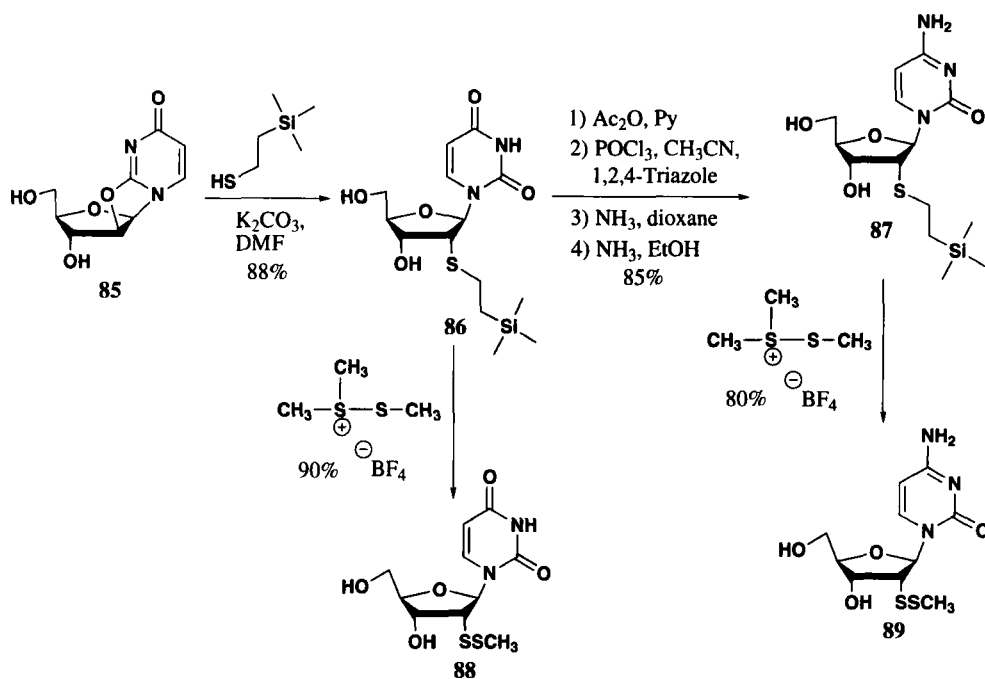
We reported the synthesis of pyrimidine nucleosides carrying a thionitrite function (Scheme 26).¹⁶⁵ Treatment of 2'-deoxy-2'-thiouridine **79** or cytidine **80** with a nearly stoichiometric amount of *tert*-butyl nitrite in methanol led quantitatively to the corresponding red, unstable, 2'-S-nitroso nucleosides **81**, **82** which can be purified if chromatographed rapidly. As a solid or in aqueous



Scheme 26

solution, these compounds decompose rapidly to yield the corresponding disulfides **83**, **84** and nitric oxide. The rate of decomposition decreases in aqueous solution in the presence of desferrioxamine, a strong iron chelator, or bathocuproine, a strong copper chelator, or in water treated with Chelex resin to remove metallic impurities. This suggests that the decomposition is catalyzed by iron and copper ions. More recently, we developed a new method for preparing methyl disulfides of thionucleosides such as 2'-thiouridine **79**, cytidine **80** and 3'-thiothymidine using 2-(trimethylsilyl)ethanethiol (Scheme 27).¹⁶⁶

The first synthesis of a diribonucleotide incorporating 2'-deoxy-2'-thiouridine **79** was achieved by Reese *et al.* in 1994 using the 9-(*p*-anisyl)xanthen-9-yl protective group for the thiol, which is removed under acidic conditions.¹⁶⁷ A study of this dinucleotide showed that the 2'-thiol function does not interact with the internucleotide phosphodiester linkage under either basic or acidic conditions.¹⁵⁹ Furthermore, the dinucleotide is not a substrate for ribonuclease A. To provide insight into the reactivity of phosphodiester group adjacent to the 2'-thiol function, 2'-deoxy-2'-thiouridine 3'-(*p*-nitrophenyl phosphate) was synthesized.¹⁶⁸ The major reaction pathway found is transphosphorylation to afford 2',3'-cyclic phosphorothioate followed by hydrolysis to produce 2'-deoxy-2'-thiouridine 2'-phosphorothioate. However, the results confirmed the previous report of Reese *et al.*¹⁵⁹, at pH 7.4, the thiol containing ribonucleotide is hydrolyzed 27-fold slower than its 2'-hydroxyl analog. This



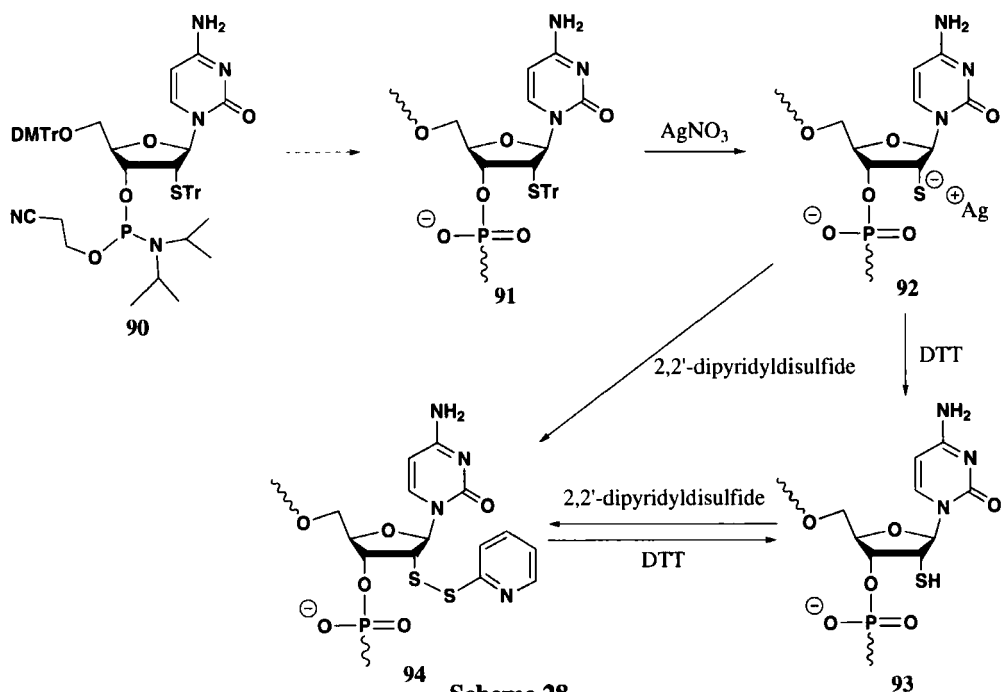
Scheme 27

study highlighted the potential of 2'-thiol-containing oligonucleotides for the study of an array of RNA processes, especially those in which the 2'-substituent plays a critical role.^{169,170}

2'-Deoxy-2'-thiouridine **79** and cytidine **80** were incorporated into oligodeoxynucleotides using a trityl group for the protection of the thiol function (Scheme 28).¹⁷¹ This protective group allows solid phase phosphoramidite DNA synthesis using standard reagents and protocols. Following oligonucleotide synthesis and deprotection, the tritylthio moiety is readily cleaved with silver nitrate followed by DTT treatment or, is converted to the (2-pyridyldithio) derivative **94** via treatment with silver nitrate and 2,2'-dipyridyldisulfide (Scheme 28).

Short oligodeoxynucleotides containing 2'-S-3'-O-cyclic phosphorothiolate termini were obtained after synthesis of 2'-S-phosphorothiolate linkage containing oligonucleotides from the 2'-deoxy-2'-thiocytidine 2'-S-phosphoramidite derivative and then base catalyzed cleavage.¹⁷² These constitute new probes for exploring the biological structure and function of macromolecules that interact with 2',3'-cyclic phosphates.

The interest in 2'-modified oligoribonucleotides was recently highlighted with a recent study of the cleavage mechanism of the hairpin ribozyme. Among the different 2'-modified oligoribonucleotides prepared and assembled into the hairpin, an oligoribonucleotide containing 2'-deoxy-2'-thiocytidine synthesized from the S-trityl 3'-O-phosphoramidite derivative was employed. The corresponding cleavage rate was found to be 2500-fold lower than that of the unmodified ribozyme.¹⁷³



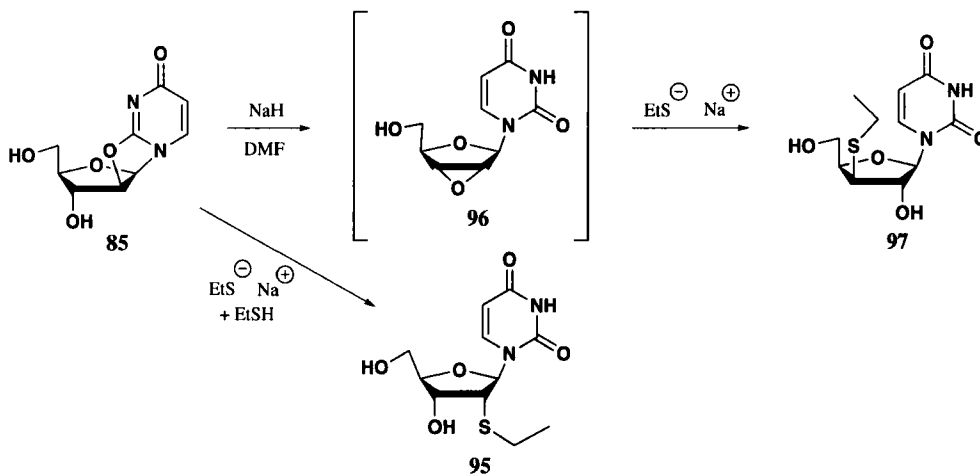
Oligonucleotides containing a 2'-S-hexyl group at the 2'-position were prepared to study their duplex stability. It was found that this stability was decreased compared to the unmodified counterparts.¹⁷⁴ Oligodeoxynucleotides bearing 2'-methoxycarbonylmethylthio-2'-uridine were also used for post-synthetic functionalization with amino derivatives.¹⁷⁵

b) Modifications at the 3' Position

3'-deoxy-3'-thionucleosides and especially 3'-deoxy-3'-thiothymidine received attention in the last ten years. 2',3'-Dideoxy-3'-thionucleosides 5'-triphosphates (T, C, A, G) irreversibly stopped DNA chain elongation by AMV and HIV reverse transcriptases, and the corresponding nucleosides display interesting antiviral activities.¹⁷⁶⁻¹⁷⁸ However, the antiviral activity of these nucleosides was controversial.¹⁷⁸ We prepared the stable methyl disulfide precursor of 3'-deoxy-3'-thiothymidine using the 2-(trimethylsilyl)ethanethiol approach¹⁶⁶ and found an anti-HIV reverse transcriptase effect for this compound.¹⁷⁹

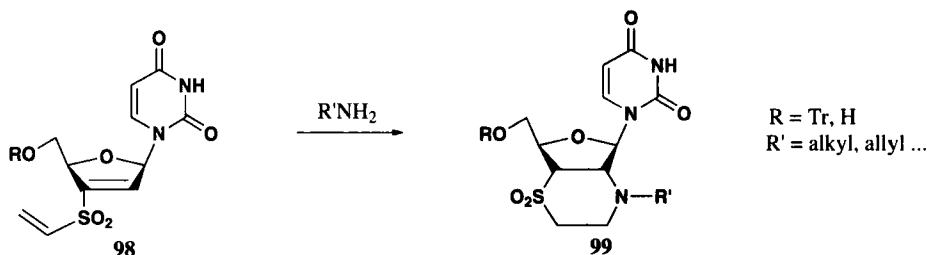
In the synthesis of 3'-sulfur modified nucleosides, an old question mentioned by Reese¹⁸⁰ concerns the selectivity of the ring opening of 2,2'-anhydrouridine **85** by nucleophiles, especially by alkyl thiolate. Brown *et al.* reported that when 2,2'-anhydrouridine was heated with a large excess of sodium ethanethiolate in DMF and the product desulfurized with Raney nickel, 3'-deoxyuridine, rather the expected 2'-isomer was obtained.¹⁸¹ Furukawa *et al.* described similar results with 2',3'-anhydroadenosine.¹⁸² In contrast, Reese *et al.* reported that reaction of 2,2'-anhydrouridine in DMF or methanol with an alkyl or arylthiolate in the presence of triethylamine or *N*¹,*N*¹,*N*³,*N*³-tetramethyl-

guanidine led exclusively in good to high yield to the corresponding 2'-deoxy-2'-mercaptouridine derivatives.¹⁸⁰ Robins *et al.*, and us later, observed the same selectivity using as reagents in DMF sodium hydride-thiophenol and potassium carbonate-2-(trimethylsilyl)ethanethiol, respectively^{183,166} (RX structure of product or derivatives). Brown *et al.* rationalized their results by suggesting that 2,2'-anhydrouridine is first converted under the basic conditions of the reaction into the 2',3'-isomeric epoxide. Recently, Reese *et al.* explained the discrepancy between the reported results.^{184,185} Treatment of 2,2'-anhydrouridine **85** with sodium ethanethiolate or the sodium salt of benzylmercaptan in the presence of an excess of thiol gives 2'-deoxy-2'-S-ethyluridine **95** or 2'-deoxy-2'-S-benzyluridine in high yield. However, treatment of 2,2'-anhydrouridine first with sodium hydride and then with a deficiency, with respect to sodium hydride, of ethanethiol or benzylmercaptan leads to the 3'-S-ethyl or 3'-S-benzyl isomer **97** in high yield (Scheme 29). This difference can be explained by conversion of 2,2'-anhydrouridine into the 2',3'-anhydrouridine **96** by reaction of sodium hydride (quantitative conversion in DMSO, isolated in 69% yield). This is a particularly versatile and interesting route for preparing 3'-deoxy-3'-substituted uridine and cytosine derivatives.



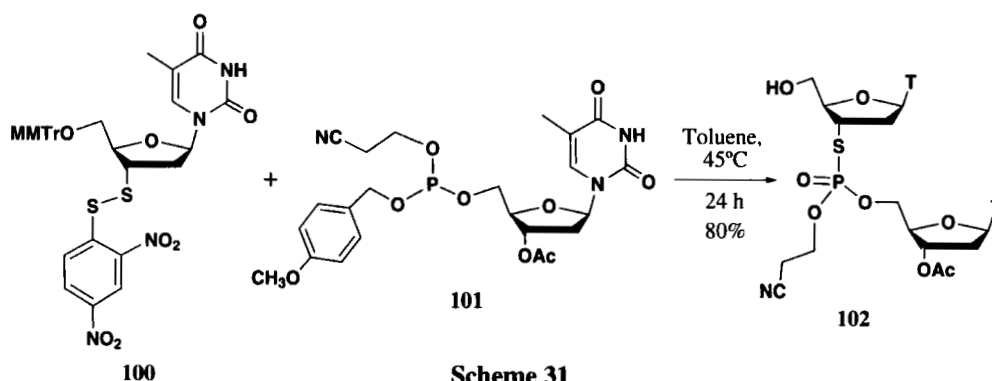
Scheme 29

Another sulfur modification achieved at the 3'-position is the introduction of a bisvinylsulfone functionality into the sugar moiety of uridine (compound **98**).¹⁸⁶ From this Michael acceptor, different monosubstituted nucleosides were obtained (Scheme 30).



Scheme 30

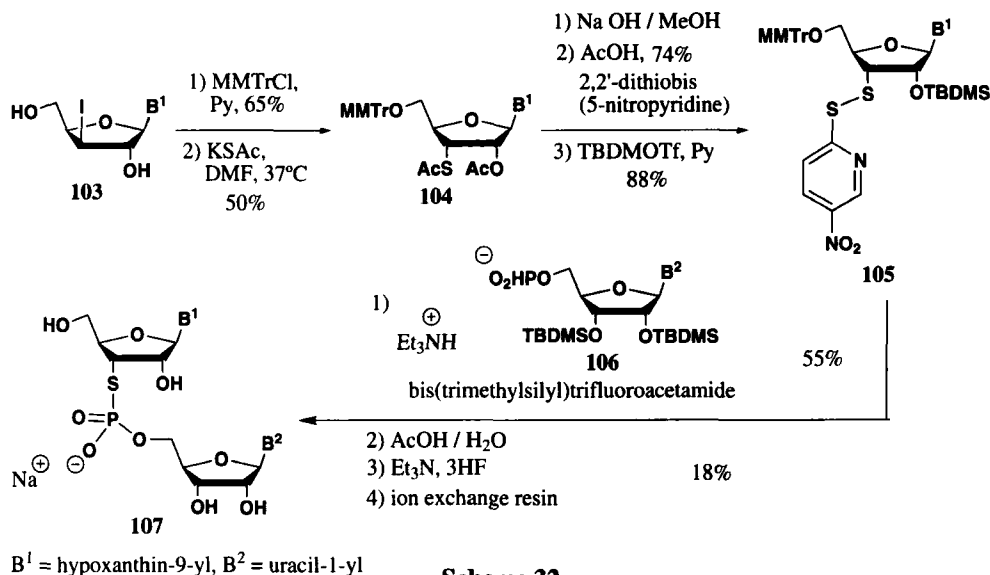
Replacement of the 3'-bridging oxygen with sulfur in a dinucleotide was first reported by Cosstick *et al.* in 1988.¹⁸⁷ From the initial synthesis, the method has been developed for preparing various oligodeoxynucleotides using for example a 3'-deoxy-3'-thiothymidine 3'-S-phosphoramidite.¹⁸⁶⁻¹⁸⁸ Oligonucleotides containing a 3'-S-phosphorothiolate linkage were used for mapping protein-DNA interfaces and studying the interactions between the two macromolecules.¹⁹²⁻¹⁹⁴ These oligonucleotides appeared resistant to certain nucleases such as *EcoRV*. The phosphorus-sulfur bond could be cleaved chemically under mild conditions by aqueous solutions of either iodine or silver nitrate.¹⁹² A high resolution X-ray crystallographic study of the restriction endonuclease *EcoRV* bound to a duplex DNA substrate analog with deoxyribo-3'-S-phosphorothiolate linkages was recently described.¹⁹⁵ In the original method developed by Cosstick *et al.* for preparing oligodeoxynucleotides containing a 3'-S-phosphorothiolate linkage, 3'-deoxy-3'-thiothymidine 3'-S-(*O*-2-cyanoethyl-*N,N*-diisopropylamino)phosphoramidite derivatives were found to be less reactive than the corresponding *O*-phosphoramidites in the coupling step in the presence of tetrazole. In the presence of the more acidic 5-(4-nitrophenyl)-tetrazole, side reactions were observed. Cosstick *et al.* investigated alternative coupling methods using the Michaelis-Arbusov reaction or a phosphotriester approach (*Scheme 31*).^{196,197} More recently, a general procedure for preparing the 3'- and 5'-S-nucleosidyl-S-aryl disulfide intermediates such as **100** was developed in the 2'-deoxyribose and ribose series.¹⁹⁸ Thymidine 3'-S-phosphorodithioate and dithymidine 3'-S-phosphorodithioate derived from 3'-thiothymidine were synthesized in excellent yield by ring opening of 2,3'-anhydrothymidine with phosphorodithioic acids.¹⁹⁹



Scheme 31

2',3'-Dideoxy-3'-thiouridine containing oligodeoxynucleotides were obtained from the corresponding phosphoramidite and used in the study of catalysis by *Tetrahymena* ribozymes.²⁰⁰ Analysis of cleavage of a DNA substrate with a 3'-S-phosphorothiolate at the scissile phosphate identified a specific metal interaction that contributes to ribozyme catalysis. Use of DNA substrate complicated the study because 2'-OH at the cleavage site enhances reactivity of RNA.²⁰¹ It is advantageous to be able to make functional group substitution in a ribose context.²⁰² Purine-pyrimidine diribonucleotides^{198,202,203} (for example *Scheme 32*) and a pyrimidine-pyrimidine ribonucleotide (Us)pU^{204,205}

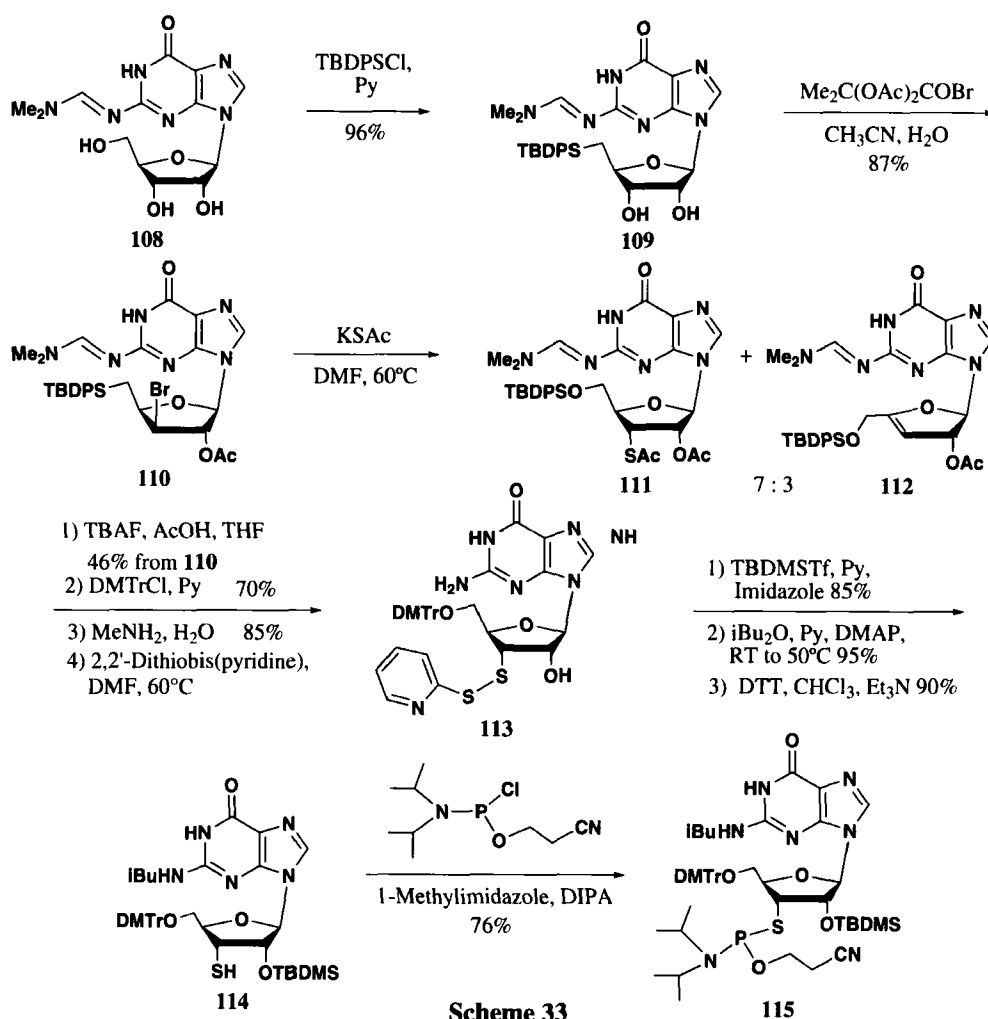
were synthesized by coupling a 3'-disulfide with a *O,O*-bis(trimethylsilyl)phosphite generated in situ from the corresponding H-phosphonate.



Scheme 32

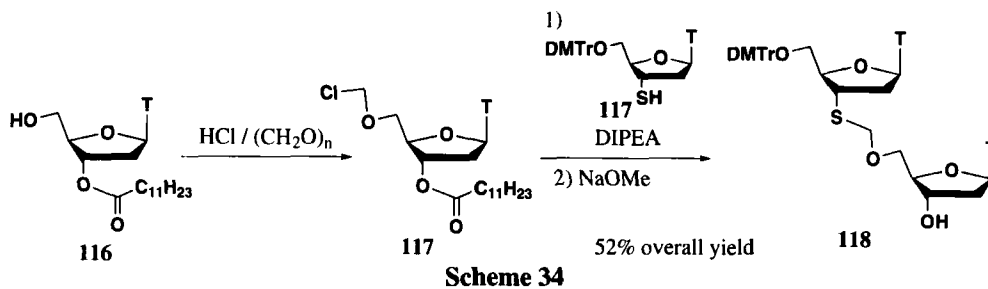
The stability of these diribonucleotides was studied under different pH conditions. It has been known that under acidic conditions, the natural diribonucleotide UpU both isomerizes to uridylyl-(2'→5')-uridine and undergoes hydrolytic cleavage; (Us)pU was found less stable than UpU in aqueous acetic acid at 30°. ^{204,205} At pH 2, in aqueous hydrochloric acid, the behavior of 3'-deoxy-3'-thioinosylyl-(3'→5')-uridine (Is)pU appeared to be similar to that of UpU. ²⁰³ This difference has not been explained. ²⁰⁵ Base-catalyzed cleavage of (Is)pU is accelerated (≈ 2000-fold) relative to that of the phosphate-linked dinucleotide IpU. ²⁰² The same result was found, at pH 10 and 50°, with (Us)pU which leads to uridine and the 2',3'-cyclic phosphorothioate intermediate. ^{204,205} (Is)pU and (Us)pU were found to be substrate for several enzymes including T4 polynucleotide kinase, snake venom phosphodiesterase and ribonuclease T₂. ^{202, 204,205} The hydrolytic reactions of the dimethyl ester of 3'-deoxy-3'-thioinosine-3'-S-phosphorothiolate ²⁰⁶ and of the cis-methyl ester of 3'-thiothymidine 3',5'-cyclicphosphorothiolate ²⁰⁷ were studied recently. At pH > 3, isomerization to the 2'-dimethylphosphate takes place whereas under more acidic conditions, hydrolysis to the 2'-monomethylphosphate and 3'-S-monomethylphosphorothiolate competes.

Sun *et al.* described the synthesis of uridine, cytosine, guanosine and inosine 3'-S-phosphoramidites and their incorporation into RNA by standard phosphoramidite solid-phase synthesis. ²⁰⁸ With regard to the interest in 3'-S-phosphorothiolate linkage containing oligoribonucleotides in the study and the search for new ribozymes ^{155,169,170,209}, improved methods of 3'-thioribonucleoside synthesis have been reported, for example the synthesis of 3'-thiouridine derivatives ¹⁹⁸ and 3'-thioguanosine and its phosphoramidite **115** (Scheme 33). ²¹⁰



Scheme 33

Oligonucleotides incorporating 3'-thioformacetal internucleoside linkages were synthesized²¹¹ (Scheme 34) in the search for new antisense and anti-DNA oligonucleotides.^{84-86,212-214} Pyrimidine dimer blocks such as **118** have been prepared and incorporated into oligonucleotides. Dithymidine monophosphate analogs in which the phosphodiester linkage is replaced by a 3'-C-S-S-5' or a 3'-S-S-5' linkage have been prepared from 3'-(3-nitropyridinyl)disulfide thymidine derivatives.²¹⁵



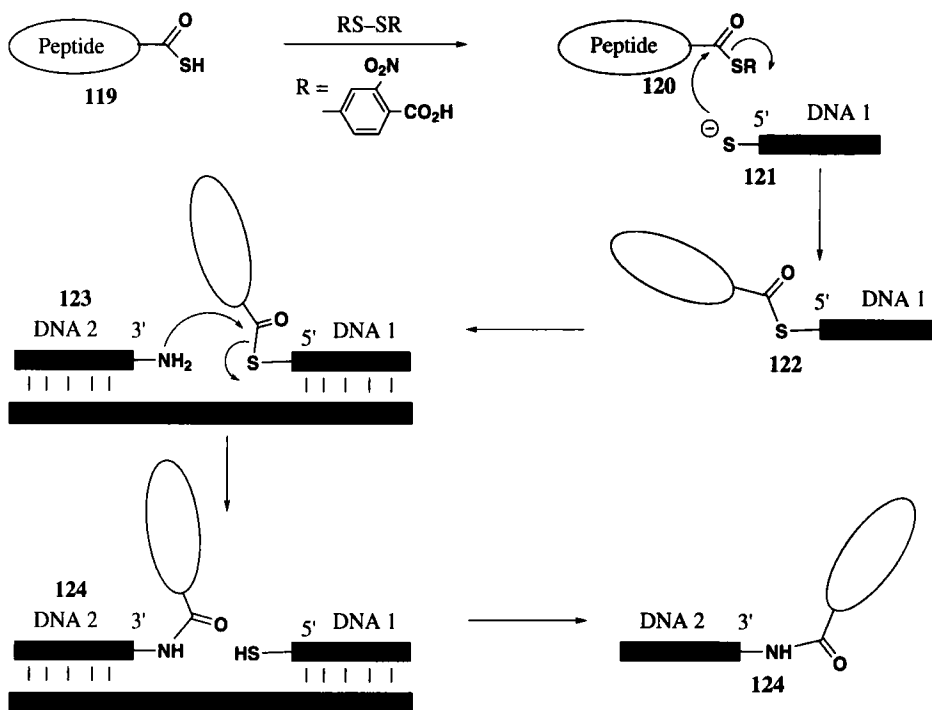
Scheme 34

2. Modifications at the 5' Position

a) 5'-Thionucleosides and Related Oligonucleotides

5'-Deoxy-5'-thioribonucleosides and nucleotides and their 2'-deoxy derivatives can be prepared efficiently from the corresponding natural nucleosides.^{8,216} 2'-Deoxy-5'-thionucleosides and 2',3'-dideoxy-5'-thionucleosides were used for preparing oligodeoxynucleotides with modified inter-nucleoside linkages as tools for biochemical studies^{169,170,209} and/or in view of their potential use as antisense agents which might present an improved stability towards cellular nucleases.²¹⁴

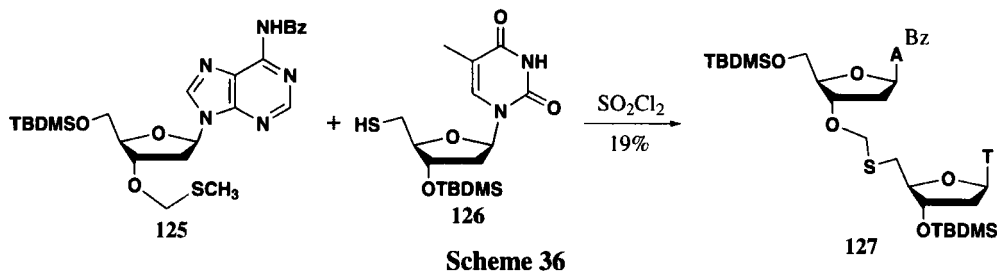
The potentialities of the sulfur chemistry for the design of new biological tools can be illustrated by the nice work of Bruick *et al.*²¹⁷ An oligonucleotide template was used to direct the ligation of peptides to oligodeoxynucleotides possessing a 5'-thiol end *via* a stable amide linkage (Scheme 35). Peptides **120**, ending in a carboxylic-terminal thioester, were converted to thioester linked oligonucleotide-peptide intermediates **122** using an oligonucleotide possessing a terminal 2'-deoxy-5'-thiouridine **121**. The oligonucleotide portion of the intermediate binds to a complementary sequence template, placing the peptide in close proximity to an adjacent template bound oligonucleotide **123** that terminates in a 3'-amino group. The ensuing reaction results in an efficient formation of an amide-linked oligonucleotide-peptide conjugate **124**.



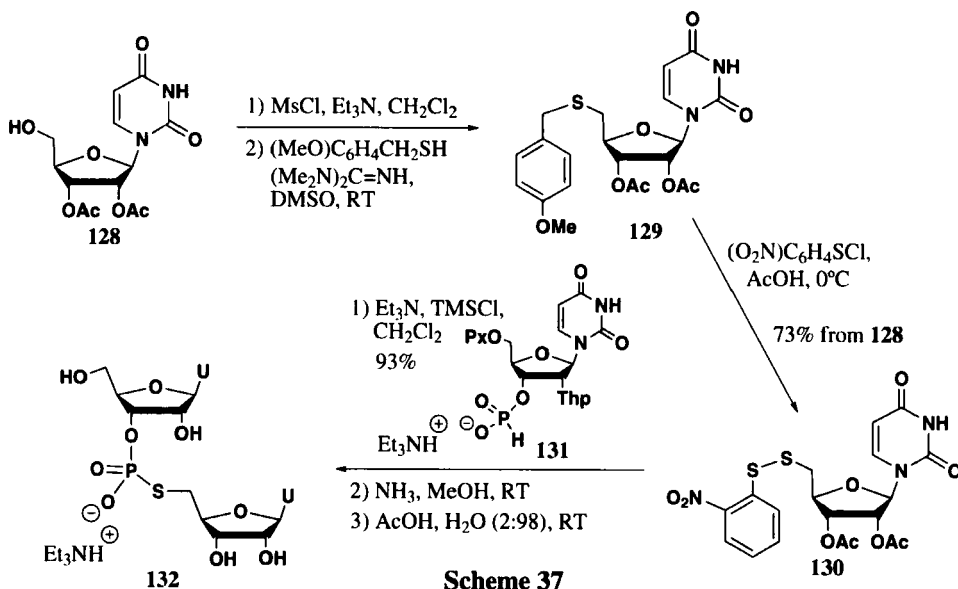
Scheme 35

5'-Deoxy-5'-thionucleoside incorporating oligodeoxynucleotides were used with other modified oligonucleotides to investigate DNA ligation by DNA topoisomerase I.²¹⁸ Oligodeoxynucleotides incorporating sulfur containing linkages without a phosphorous atom were also synthesized

from 5'-thionucleosides. 5'-Thiothymidine was used to prepare dialkyl sulfide linked thymidine dimer and the corresponding dimer 3'-phosphoramidite was incorporated into oligodeoxynucleotides.^{219,220} The four 2'-deoxy-5'-thionucleosides were incorporated in short oligonucleotides such as **127** containing 5'-thioformacetal internucleoside linkages with a new coupling method using 3'-*O*-chloromethyl intermediates (Scheme 36).^{221,222} 5'-*S*-Phosphorothiolate linkage containing



diribonucleotides such as **132**^{223,224} (Scheme 37) and oligoribonucleotides²²⁶ were synthesized, these latter from the *N*-benzoyl-2'-deoxy-5'-thioadenosine 3'-*O*-phosphoramidite derivative. This linkage was found particularly susceptible to isomerization and/or cleavage when compared to the corresponding oxo, deoxy and thio deoxy derivatives. It is hydrolyzed rapidly under neutral and mildly basic conditions.²²³⁻²²⁵ Divalent metal cations increase the cleavage rate.²²³⁻²²⁶ Such oligonucleotides

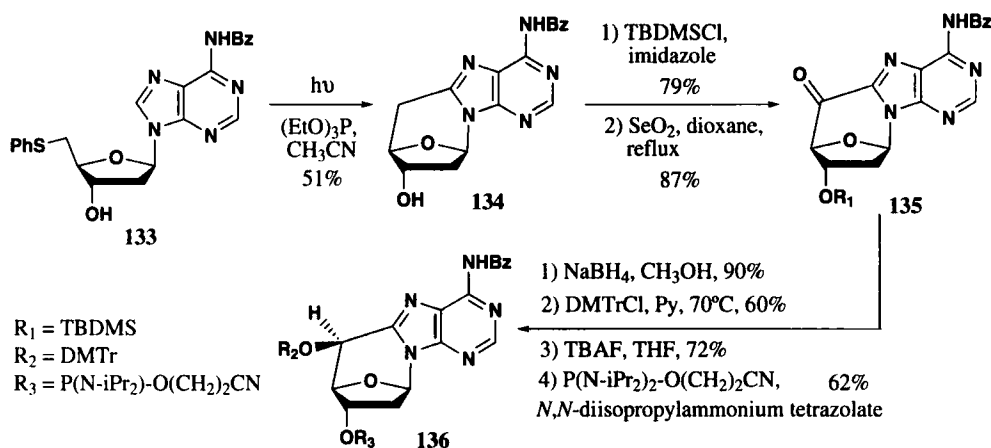


were used as tools in the study of natural ribozymes, and in the search for ribozymes possessing new catalytic properties.^{90,155,225,227,228}

5'-Deoxy-5'-thioguanosine 5'-monophosphate was obtained after deprotection of 2',3'-isopropylidene-5'-deoxy-5'-iodoguanosine (2.5 days, with 50% aqueous formic acid) and subsequent

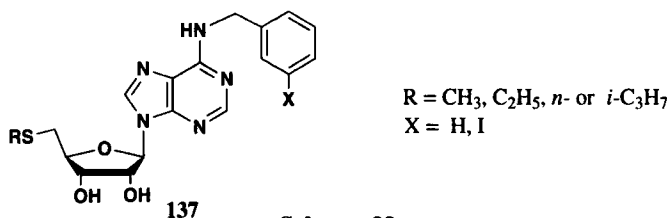
reaction with trisodium thiophosphate in 68% yield.²²⁹ This nucleotide was incorporated into RNA with T7 RNA polymerase. Dephosphorylation with alkaline phosphatase led to the corresponding RNA carrying a 5'-thiol function which reacts with different thiol-reactive agents.

One of the main radiation-induced decomposition products of 2'-deoxyadenosine, (5'*S*)-5',8-cyclo-2'-deoxyadenosine **136**, was prepared photochemically from 5'-deoxy-5'-thiophenyladenosine **133** and was incorporated into oligonucleotides (Scheme 38).²³⁰ This method was applied to the synthesis of (5'*S*)- and (5'*R*)-5',8-cyclo-2'-deoxyguanosines which were incorporated into oligonucleotides.²³¹



Scheme 38

Many 5'-modified 5'-deoxynucleosides possessing a sulfur atom at the 5'-position have been synthesized in the search for new therapeutic agents. Such 5'-modified adenosine derivatives inactivate *S*-adenosyl-L-homocysteine hydrolase (see next part) and it was demonstrated that 5'-alkylthio-substituted analogs of *N*⁶-benzyl and *N*⁶-(3-iodobenzyl)adenosine **137** are selective ligands for the A_3 receptor with K_d 's in the nanomolar range (Scheme 39).²³² Stimulation of the rat A_3 receptor causes bronchoconstriction and the release of allergic mediators; partial agonists should circumvent these effects.

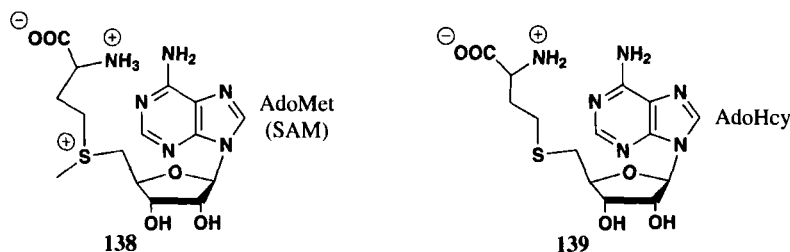


Scheme 39

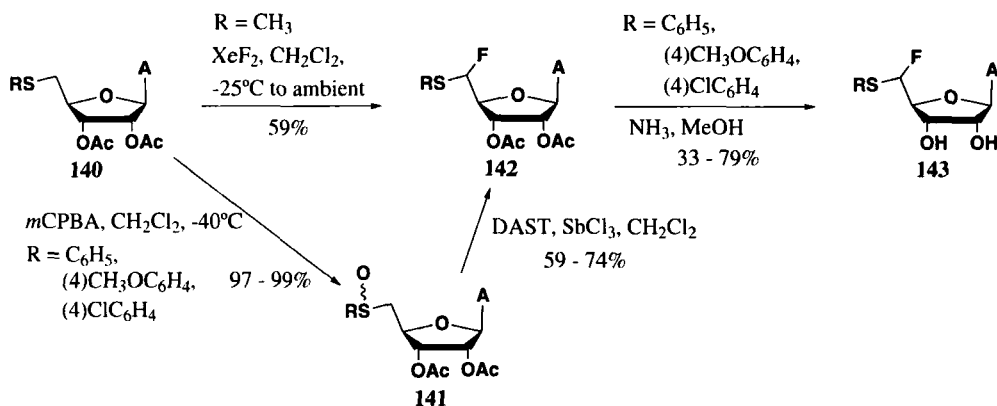
In the search for inhibitors of cytoplasmic-thymidine kinase endowed with antitumor or antiviral agents, 5'-alkylthio-5'-deoxythymidine derivatives were synthesized.²³³⁻²³⁵

b) 5'-Thionucleosides and Derivatives in the Search for Therapeutic Agents, S-Adenosyl-L-methionine Analogs and Mechanism-based Inhibitors of S-Adenosyl-L-Homocysteine Hydrolase

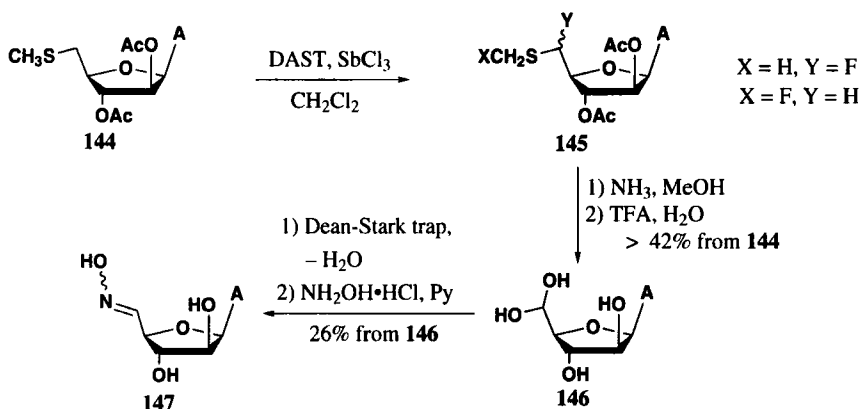
S-adenosyl-L-methionine **138** (AdoMet, SAM; *Scheme 40*) is a cofactor in numerous enzymatic reactions like methylation performed by methyl transferases. AdoMet decarboxylase leads to the 5'-aminopropylsulfonium used by the cell as an aminopropyl donor for the biosynthesis of the polyamines, spermidine and spermine. After enzymatic methylation, AdoMet is transformed into S-adenosyl-L-homocysteine **139** (AdoHcy; *Scheme 40*). This product is hydrolyzed to adenosine and L-homocysteine by the enzyme AdoHcy hydrolase after reversible oxidation of the 3'-hydroxyl group of AdoHcy by NAD^+ and then β -elimination of L-homocysteine to give the α,β unsaturated ketone. Michael addition of water to the intermediate affords 3'-ketoadenosine which is then reduced by NADH to adenosine.²³⁶⁻²³⁷ It is crucial for the cell to remove AdoHcy for performing methylations and thus inhibitors of AdoHcy hydrolase are interesting compounds in the search for antiviral and antitumor compounds.²³⁸



The design and synthesis of inhibitors and mechanism-based inhibitors of AdoHcy hydrolase have received attention. 5'-Deoxy-5'-methylthioadenosine has been shown in the past to inactivate AdoHcy hydrolase. Robins *et al.* synthesized 5'-deoxy-5'-fluoro-5'-thioalkyl or aryl adenosines **143** (*Scheme 41*) and found that some of them present antiviral activities.²³⁹⁻²⁴⁰ They showed that α -fluoro thioethers undergo spontaneous chemical hydrolysis in aqueous buffer to give 4'-epimeric adenosine-5'-carboxaldehyde species that causes inactivation of AdoHcy hydrolase.



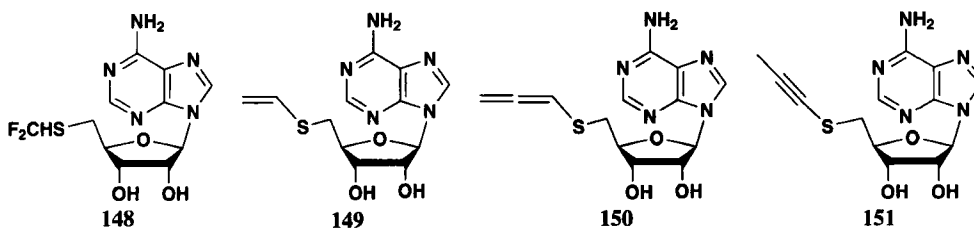
5'-Deoxy-5'-fluoro-5'-S-methyl-5'-thioadenosine derivatives and their 5'-deoxy-5'-S-(fluoromethyl)-5'-thio regio-isomers were used as intermediates in the synthesis of 5'-carboxaldehydes of 2' and 3'-deoxyadenosine and their oximes. This reaction was applied to the synthesis of the 5'-carboxaldehyde of 9-(β -D-arabinofuranosyl)adenine (Ara A) **146** (Scheme 42).²⁴¹



Scheme 42

3'-Deoxy-3'-chloro and 3'-fluoro derivatives of 4',5'-didehydro-5'-deoxy-5'-fluoroadenosine were prepared by generation of the vinyl fluorides from thermolysis of 5'-fluoro-5'-thioethersulfoxides.^{242,243} These 3'-modified derivatives do not produce time-dependent inhibition of AdoHcy hydrolase but are weak competitive inhibitors.

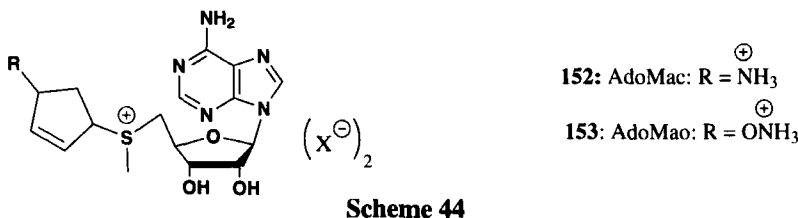
Guillerm *et al.* investigated the mechanism of inactivation of AdoHcy hydrolase by 5'-deoxy-5'-S-difluoromethyl-5'-thioadenosine **148**.²⁴⁴⁻²⁴⁶ They showed that the reactive adenosine derivatives 5'-vinylthio **149**, 5'-allenylthio **150** and 5'-propynylthio **151** cause potent time dependent inactivation of this enzyme (Scheme 43).^{247,248} This group studied, with different 5'-S-methylthioadenosine analogs, the mechanism of the hydrolysis reaction catalyzed by another enzyme AdoHcy/methylthioadenosine nucleosidase from *E. coli*.²⁴⁹ This enzyme is required for regeneration of free homocysteine from AdoHcy in various prokaryotes and plays a significant role in the regulation of methylthioadenosine concentration, a potent inhibitor of spermine and spermidine synthase.



Scheme 43

In the polyamine biosynthetic pathway²⁵⁰, AdoMet decarboxylase (AdoMet-DC) inhibitors have been developed as potential antitumor and/or antiparasitic agents. The diastereoisomers of the AdoMet analog, AdoMac **152**, were synthesized and used to probe the stereorequirements of

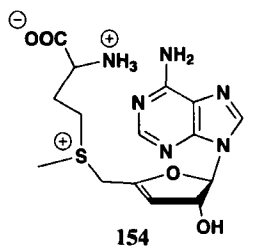
AdoMet-DC from *E. coli*²⁵¹⁻²⁵³ (Scheme 44) and the human form of the enzyme.²⁵³ These compounds act as enzyme inactivators. A related analog, AdoMao 153, inhibited trypanosomal growth with an IC_{50} of 0.9 μM (Scheme 44).²⁵⁴



Scheme 44

In order to study the structural determinant for cofactor binding of the DNA methyltransferase *M.HhaI*, *S*-adenosyl-L-homocysteine analogs and 5'-thio-5'-deoxyadenosine were synthesized from 5'-acetylthio-5'-deoxy-2',3'-*O*-isopropyleneadenosine obtained by reaction of 2',3'-*O*-isopropyleneadenosine and thiolacetic acid under Mitsunobu conditions.²⁵⁵ Another analog of *S*-adenosyl-L-homocysteine, a 4-*C*-methyl derivative, was synthesized from the β -methyl 4-*C*-methylribofuranoside prepared efficiently by a new strategy involving an enzymatic step.²⁵⁶

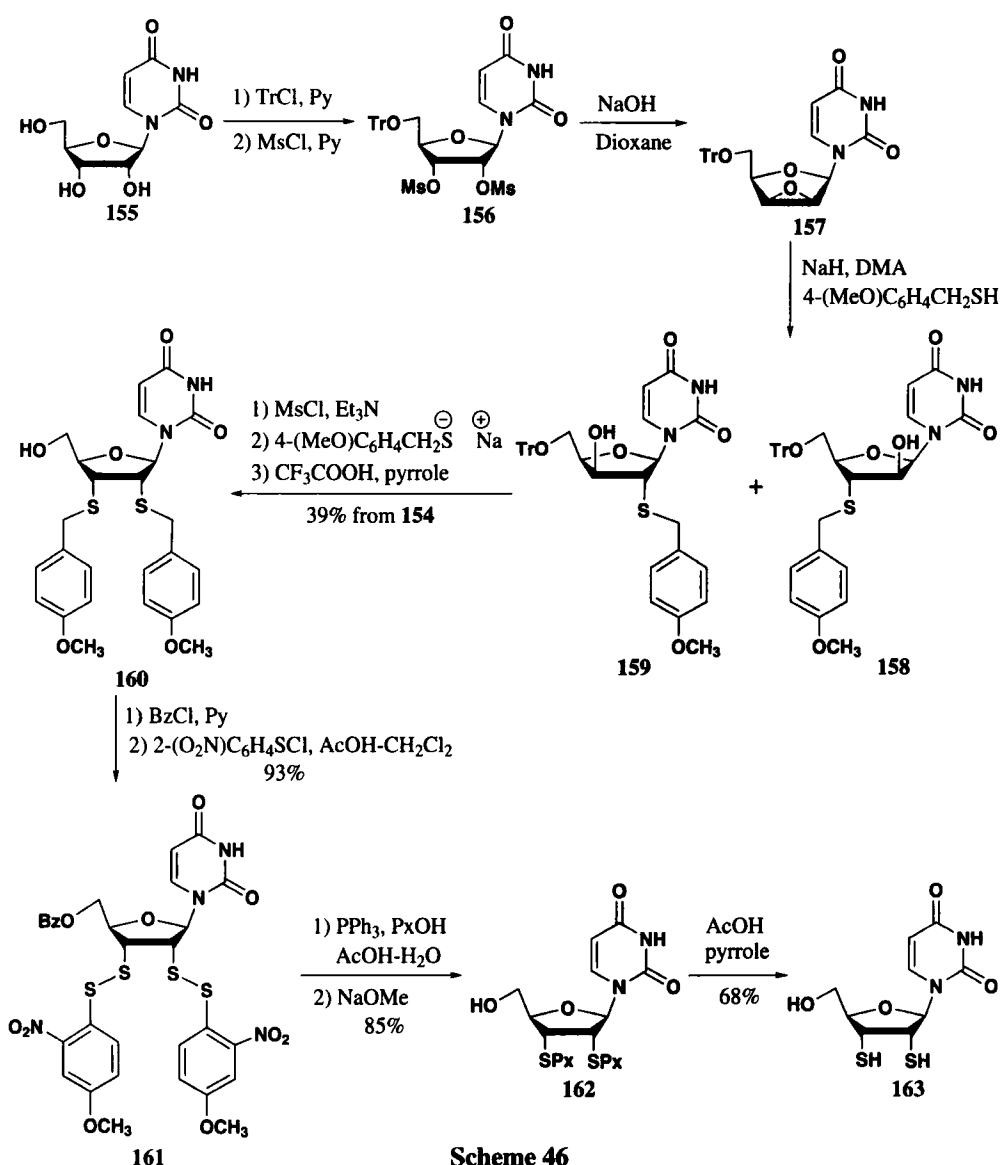
Analogues of AdoMet were designed and synthesized for mechanistic studies. For example, free radical intermediates have been identified in the interconversion of L- α -lysine and L- β -lysine catalyzed by the enzyme lysine 2,3-aminomutase in bacteria with AdoMet as a cofactor. A 5'-deoxyadenosyl radical was supposed to be formed from AdoMet during the enzymatic reaction. In order to observe a stabilized allylic radical analog formed at the carbon 5', *S*-3',4'-anhydro-5'-deoxyadenosyl-L-methionine 154 was prepared and used to characterize the 3',4'-anhydro-5'-deoxyadenosine-5'-yl radical (Scheme 45).²⁵⁷



Scheme 45

3. Modifications at the 2' and 3' or at the 3' and 5' Positions

The first 2',3'-deoxy-2',3'-dithionucleoside was described by Reese *et al.* in 1994 (Scheme 46).²⁵⁸ The corresponding dinucleotide was synthesized by the same researchers using the phosphotriester methodology of coupling.¹⁶⁷ More recently, Reese *et al.* have prepared 3',5'-dithiothymidine and related compounds.²⁵⁹



Scheme 46

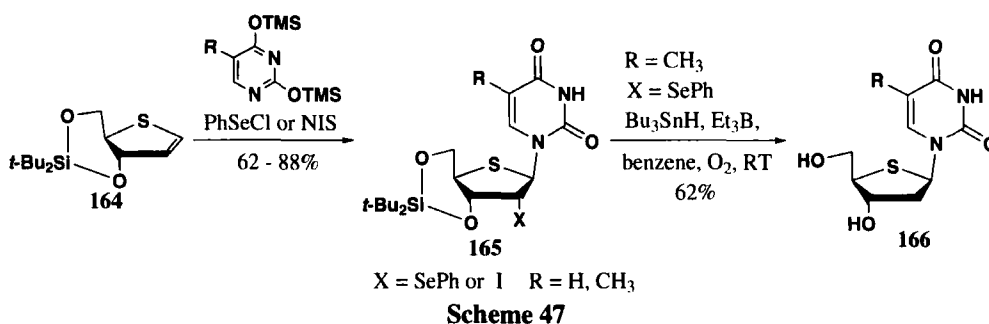
III. SULFUR MODIFICATION IN THE SUGAR RING

1. 4'-Thionucleosides

4'-thionucleosides in which the furanose oxygen atom is replaced by a sulfur atom exhibit interesting biological properties such as antibiotic, antitumor and antiviral activities. This class of bioactive agents has been reported in the 2'-deoxy series by Secrist *et al.*²⁶⁰ and Walker *et al.*²⁶¹ The replacement of oxygen by sulfur also provides higher chemical stability of the glycosidic linkage and higher metabolic stability of the nucleoside, and of the corresponding oligonucleotides.²⁶²

a) 2'-Deoxy-4'-thionucleosides and Derivatives

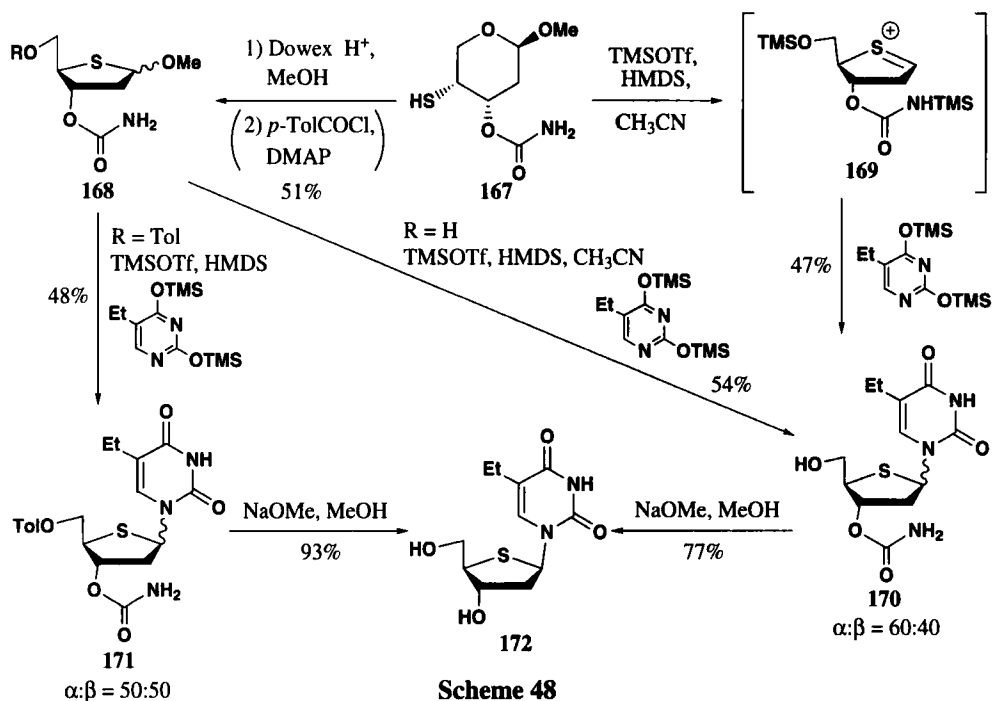
The synthesis of 2'-deoxy-4'-thionucleosides has been reviewed.^{8,262} For example, 4'-thiothymidine was prepared using several strategies.^{260,261,263,264} The X-ray structure of the corresponding sulfone has been reported.²⁶⁵ Glycosidation methods using 2-deoxy-4'-thiosugar derivatives lead to mixtures in which the α -anomer is predominant.^{266,267} A *trans* glycosidation method using *trans*-N-deoxyribosylase was developed for selectively preparing the β -purine anomers from the 2'-deoxy-4'-thiouridine β -anomer prepared in mixtures with its α -anomer.²⁶⁷ A stereoselective entry to 2'-deoxy-4'-thio pyrimidine nucleosides **166** was described by electrophilic addition to 4-thio furanoid glycal (Scheme 47).²⁶⁸



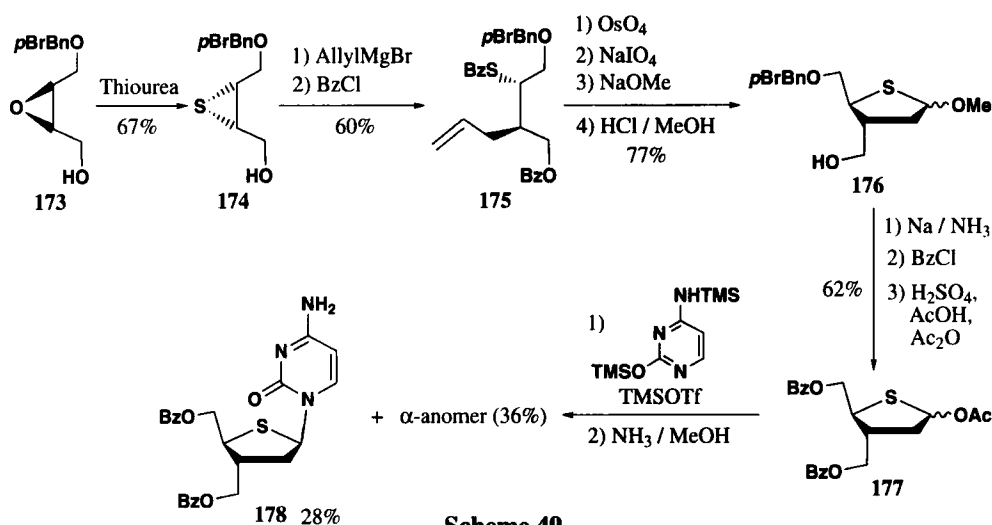
The stability of 2'-deoxy-4'-thioribonucleosides under acidic conditions was investigated. These 4'-thionucleosides were shown to be from 7 to 70 times more stable than their 4'-oxo natural analogs (pH 1-4).²⁶⁹ Assuming that 4'-thio substitution does not change the mechanism of hydrolysis of purine nucleosides, it was proposed that the rate decrease reflects a lower resonance stabilization of the developing thiocarbenium ion compared to that of the corresponding oxocarbenium.²⁷⁰ Under acidic conditions, it was observed that the glycosidic bond cleavage in 4'-thiopyrimidine α and β nucleosides competes with the reversible isomerization between the furano and pyrano ring systems.²⁷⁰

The potent antitumor activities of 2'-deoxy-4'-thiopyrimidine nucleosides have been reported by Secrist *et al.*²⁶⁰, Dyson *et al.*²⁶¹ and Uenishi *et al.*²⁷¹ They revealed potent anti-HSV (herpes simplex virus) and antitumor activities and their purine analogs showed potent anti-HBV (hepatitis B virus) and anti-HCMV (human cytomegalovirus) activities.^{260,267,271,272} These compounds have moderate to severe cytotoxicity *in vitro* and the most potent and selective purine nucleoside, 2-amino-6-(cyclopropylamino)purine 2'-deoxy-4'-thioriboside, was found to be highly nephrotoxic *in vivo*.²⁶⁷ During the last decade, in the search for new bio-active compounds, 2'-deoxy-4'-thionucleosides which present an additional modification in comparison with the corresponding natural nucleoside were synthesized. Analogs possessing a modified base were prepared.^{266,272-279} For example, the anti-herpes agent, 2'-deoxy-5-ethyl-4'-thiouridine **172**, was prepared *via in situ* pyranose-furanose rearrangement (Scheme 48).²⁸⁰ Its enantiomer was prepared more recently utilizing the iodolactonisa-

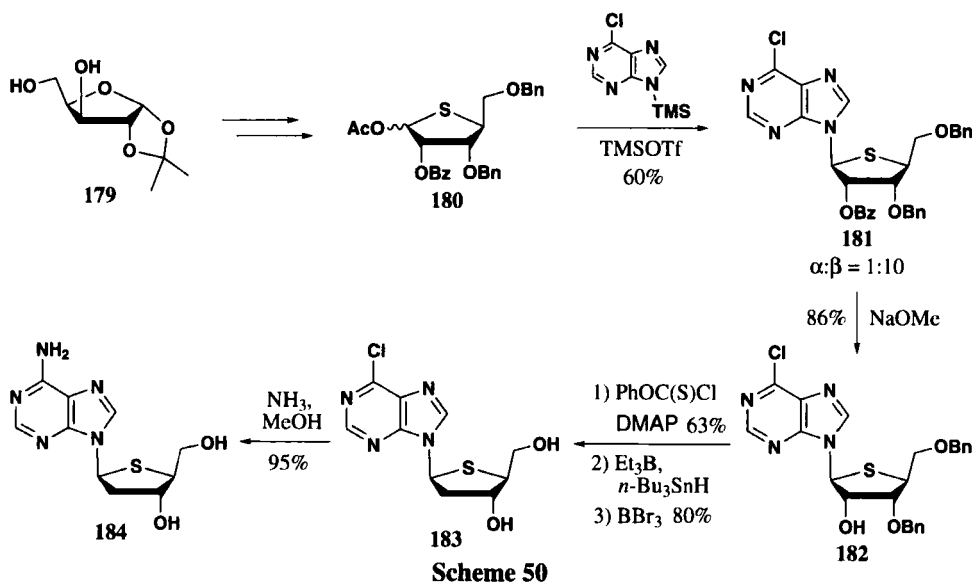
tion of 3-(*tert*-butyldimethylsilyl)oxy-*N,N*-dimethyl-4-pentenamide.²⁸¹ An alternative synthesis of the 4'-thio analog of the anti-herpes agent, (E)-5(2-bromovinyl)-2'-deoxyuridine (BVDU), was described recently.²⁸²



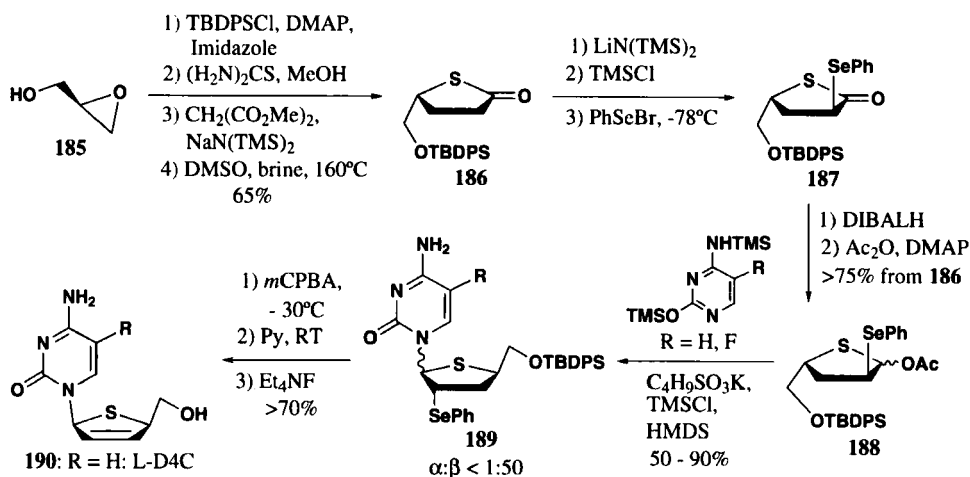
Additional modifications were introduced in the sugar, for example, at the 3'-position, an alternative synthesis of 3'-azido-3'-deoxynucleosides from D-xylose has been reported²⁸³, or at the



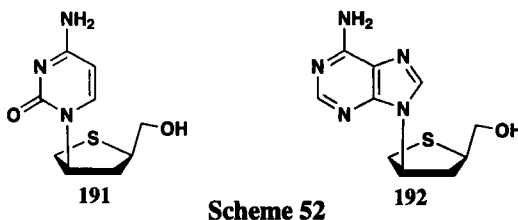
5'-position, with the synthesis of 5'-difluorophosphonate analogs.²⁸⁴ 2'-Deoxy-4'-thio-L-threo pyrimidine nucleosides²⁸⁵ and 3'-C-methyl-4'-thio apionucleosides were prepared, this latter via [3,3]-sigmatropic Claisen rearrangement.²⁸⁶ 2',3'-Dideoxy-3'-C-hydroxymethyl-4'-thionucleosides (thymine, cytosine, adenine) were synthesized via regioselective opening of the episulfide **174** with allylmagnesium bromide and were found inactive against HIV-1 (Scheme 49).²⁸⁷⁻²⁸⁹ The same nucleosides were prepared from (+)-diethyl-L-tartrate via (*S,S*)-1,4-bis(benzyloxy)-2,3-epoxybutane.²⁹⁰ L-Enantiomers of 2'-deoxy-4'-thionucleosides were also synthesized (Scheme 50).^{266,267,271,272,281,291,292}



During the search for anti-HIV agents, 2',3'-dideoxy-4'-thionucleosides^{293,294} and 2',3'-dideoxy-2',3'-dideoxy-4'-thionucleosides (Scheme 51) were synthesized.²⁹⁵ Among the 2',3'-dideoxynucleosides prepared, L-2',3'-dideoxy-didehydro-4'-thiocytidine **190** (L-D4C) has potent anti-HIV



activity. 4',5'-Didehydro-2',5'-dideoxy-4'-thiothymidine was prepared from 4'-thio-5'-tosylthymidine.²⁹⁶ Enantiospecific total syntheses of D and L-2',3'-dideoxy-4'-thioisnucleosides (*Scheme 52*) and their oxo analogs have been reported *via* regioselective opening of optically active C₂-symmetric 1,4-pentadiene *bis*-epoxide.^{297,298}



Scheme 52

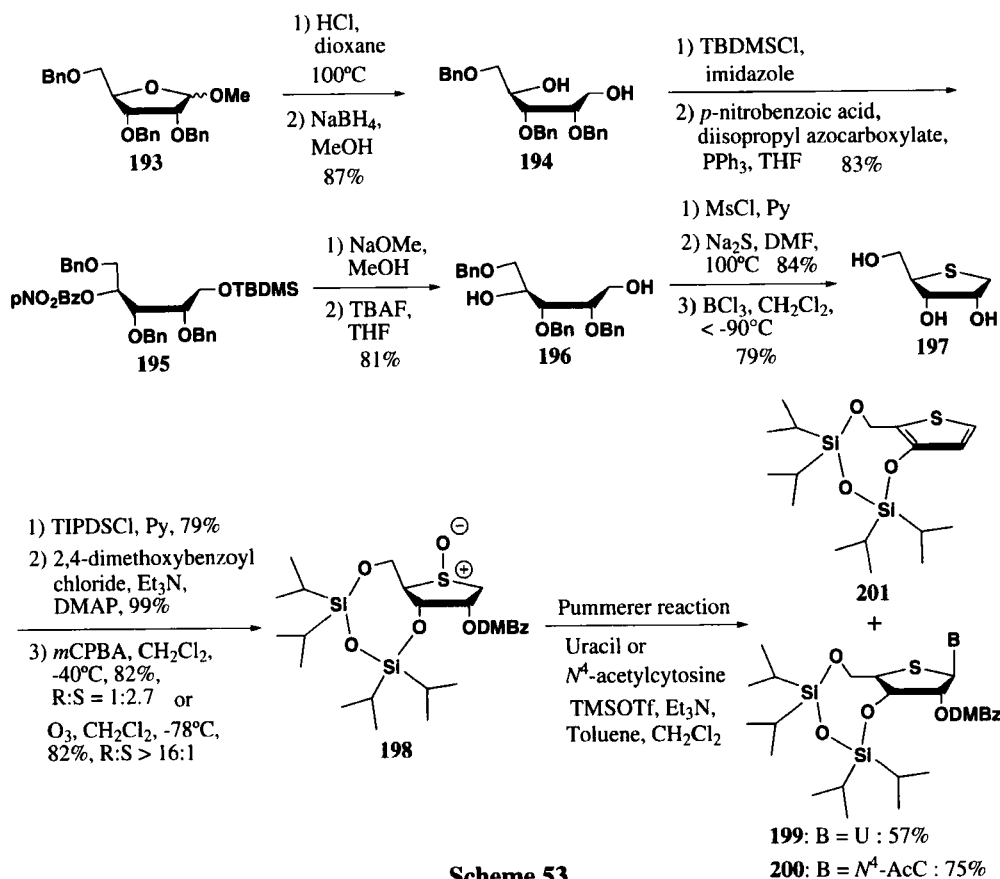
Sulfoxidation of 2'-deoxy-5-ethyl-4'-thiouridine and separation of the diastereoisomers followed by treatment with sodium deuteroxide allows exchange of the H-4' proton for deuterium.²⁹⁹ The yield (32%) was limited by side reactions like formation of the L-xylo isomer. Reduction of the deuteriated sulfoxide with TFA/TMSBr furnished 4'-deuteriated 2'-deoxy-5-ethyl-4'-thiouridine (54%). Surprisingly after these results, 1'-substituted sulfoxides were obtained selectively by formation of the carbanion at the 1'-position of the corresponding sulfoxide with LDA and then reaction with an electrophilic reagent.³⁰⁰ Surprisingly, no reaction at the 4'-position, or epimerization was observed in the reaction with diphenyl sulfide or with an excess of methyl iodide. Unfortunately, the configuration α or β at the 1'-position of the products could not be ascertained.

In order to investigate the role of the sugar in DNA-protein interactions, oligodeoxynucleotides incorporating 4'-thiothymidine were synthesized by the automated solid phase technique using the corresponding O-2-cyanoethyl-N,N-diisopropylphosphoramidite.^{193,301}

b) 4'-Thioribonucleosides and Related Oligonucleotides

The synthesis of 4'-thioribonucleosides (uracil, cytosine, adenine) was reviewed in 1993.⁸ Adenosine mediates a wide variety of physiological functions including vasodilatation, vasoconstriction, lipolysis and platelet aggregation. Its 4'-thio analog could possess interesting biological activities. It was found 3.2-fold more potent than adenosine for A_{2a} receptors of G-proteins while at A₁ receptors, affinity diminished 32-fold. Thus, the thio modification induces a 15-fold increase in selectivity relative to that of adenosine.³⁰²

Imbach *et al.* have reported a multistep synthesis of 4'-thiocytidine and adenosine from D-ribose leading to β -anomers in moderate yields, especially for the β -adenine nucleoside.³⁰³ The anomeric selectivity was improved in the preparation of 2-chloro-2'-deoxy-4'-thioadenosine using additional steps.²⁷⁴ Recently, the first stereoselective chemical synthesis of 4'- β -thioribonucleosides was described *via* the Pummerer reaction (*Scheme 53*).³⁰⁴ 4'- β -Thiouridine **199** and 4'- β -thiocytidine **200** were obtained in 66 and 75% yields, respectively (Pummerer reaction and deprotection steps). For the reaction with purine bases, 6-chloropurine and 2-amino-6-chloropurine were found the most suitable (65 and 56% for the Pummerer reaction, respectively). The nucleosides obtained were then



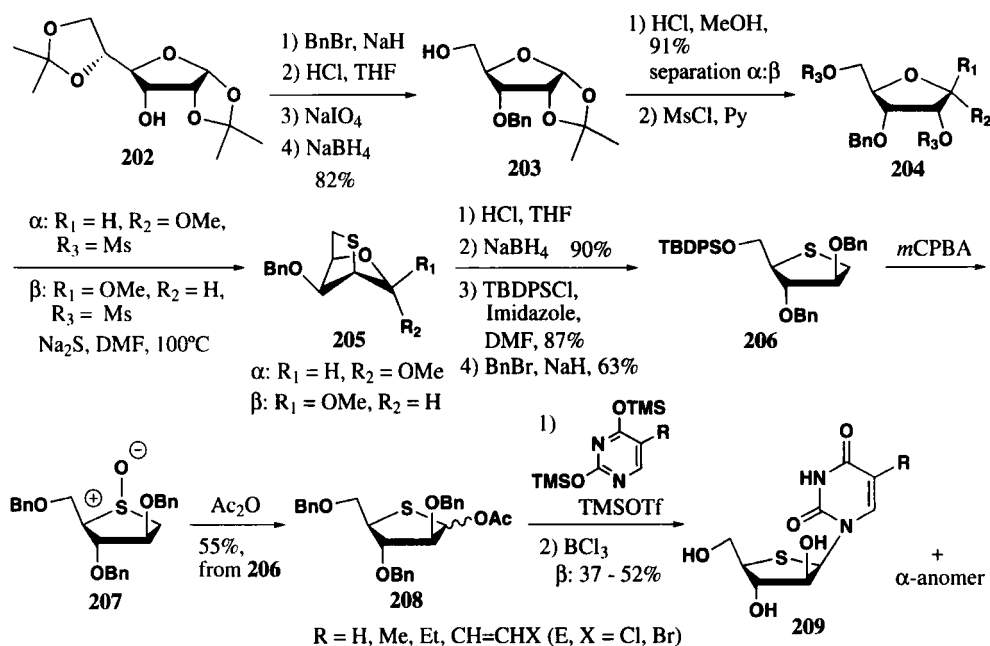
Scheme 53

converted to 4'- β -thioadenosine and 4'- β -thioguanosine under usual conditions. When separated, the *R*-sulfoxide and the *S*-sulfoxide intermediates gave the protected 4'- β -thiouridine derivative in 87% and 60% yields, respectively. Formation of the thiophene derivative **201** from the *S*-sulfoxide was observed in 22% yield. A likely explanation for this difference is that the Pummerer reaction proceeds via an E2 type pathway, which prefers anti elimination.

4'-Thioribonucleosides carrying modification on the base has been synthesized, for example, chloroadenosine derivatives^{265,274} and a 4'-thio analog of tiazofurin, a synthetic thiazole *C*-nucleoside which has demonstrated clinical efficacy as an antitumor agent, and related derivatives.^{305,306} The first 4'-thiooligoribonucleotides synthesized and studied by Imbach *et al.* were obtained by oligomerization of 4'-thiouridine 3'-phosphoramidite using classical RNA chemistry on solid support.³⁰⁷ Different 4'-thiooligoribonucleotides then were synthesized and studied in view of their application for anti-sense modulation of gene expression in regard to their resistance towards nuclease degradation and their binding characteristics with complementary DNA and RNA strands.^{308,309} The synthesis of the first oligoribonucleotide containing 4'-thioguanosine has been reported in 1999 by the same group.³¹⁰

c) 2'-Modified-4'-thionucleosides

The synthesis of modified 4'-thioribonucleosides was described and reviewed in 1993. More recently, the synthesis of 4'-thio-D-arabinonucleosides such as **209** from 4-thio-D-arabinofuranose intermediates has been reported by Secrist *et al.*^{266,311-313} In the synthesis developed from D-glucose by Yoshimura *et al* (Scheme 54),³¹¹ 1-O-acetyl-2,3,5-tri-O-benzyl-4-thio-D-arabinofuranose **208** was the key intermediate used in the glycosylation step.^{314,315}

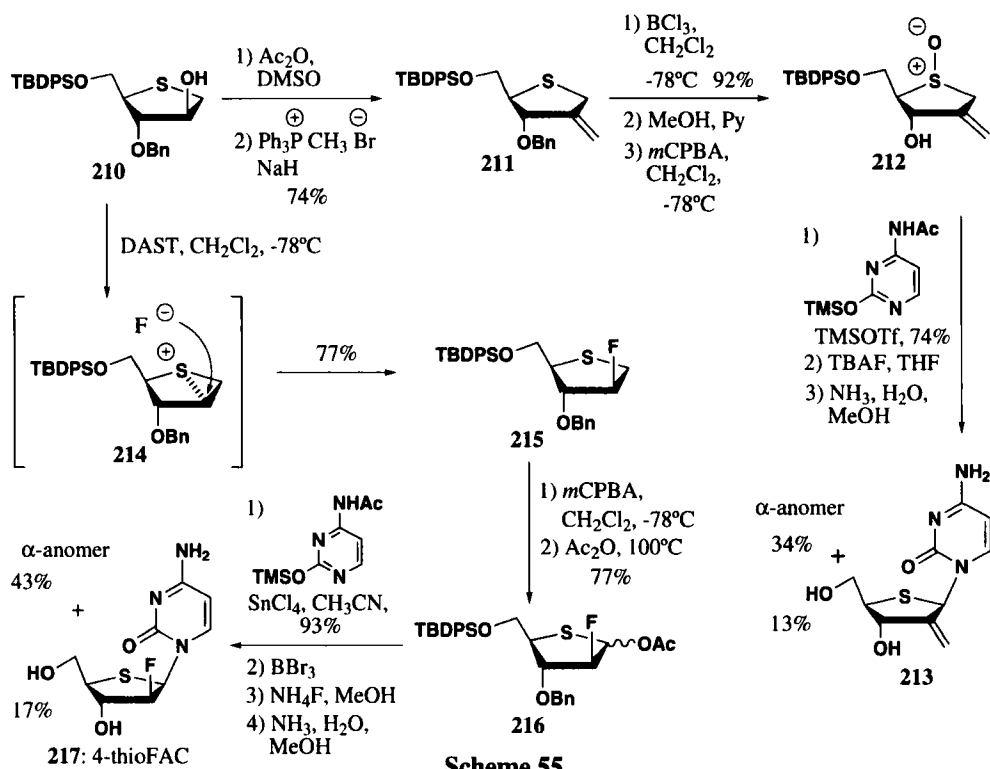


Scheme 54

Another method of preparation of this intermediate from L-xylose was described and used for preparing 4'-thioarabinofuranosylpurine nucleosides modified on the base.³¹² 4'-Thio-L-arabinofuranosylpyrimidine nucleosides were obtained more recently from D-xylose and then 1-methyl-2,3,5-tri-O-benzyl-D-xylofuranose leading to the 1,4-anhydro-4-thio-L-arabitol intermediate³¹⁶ or *via* the 1-thiobenzyl derivative of 2,3,5-tri-O-benzyl-4-thio-L-arabinofuranose.³¹⁷ Thio-L-arabinofuranosyl-5-halopyrimidine nucleosides were also prepared from 1-O-acetyl-2,3,5-tri-O-benzyl-4-thio-L-arabinofuranose and no antiviral activity was found.^{317,318}

9-(4-Thioxylofuranosyl)adenine was obtained through glycosylation of *N*⁶-benzoylated adenine with 2,3,5-tri-O-benzyl-1-thiobenzyl-4-thio-D-xylofuranose activated with *N*-iodosuccinimide.³¹⁹ Formation of a transient thiocarbenium intermediate could explain the relatively good yield of β -anomer. Other 2'-modifications of 4'-thionucleosides received a lot attention in the recent years for obtaining 4-thio analogs of nucleosides presently used for their therapeutic activities. 2'-Deoxy-2'-methylenecytidine, 2'-deoxy-2'-fluoromethylenecytidine, 2'-deoxy-2',2'-difluorocytidine (Gemcitabine) inhibit a key enzyme in the synthesis of DNA, ribonucleoside diphosphate reductase, and are

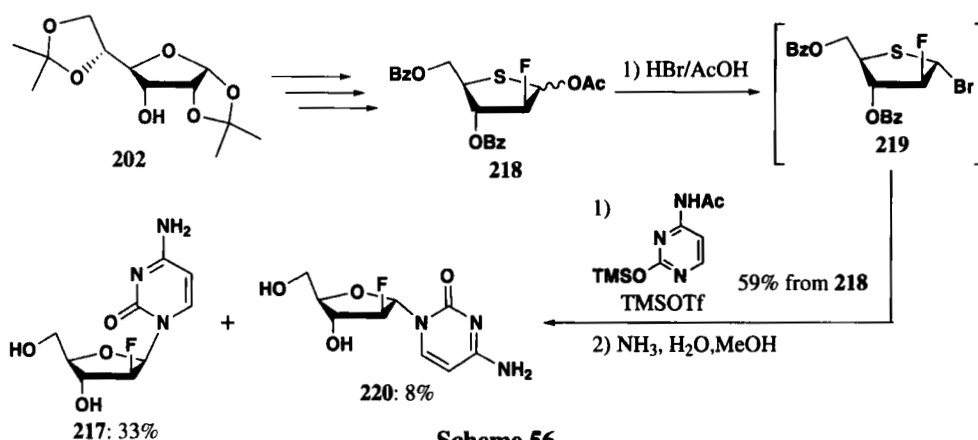
incorporated into DNA *in vivo*.¹⁶¹⁻¹⁶⁴ These 2'-modified ribonucleotides possess interesting antitumor activities and Gemcitabine and 2'-deoxy-2'-fluoromethylenecytidine are used presently as antitumor drugs. The 4'-thio analogs of 2'-deoxy-2',2'-difluorocytidine, 2'-deoxy-2'-methylenecytidine and other 2'-modified ribonucleotides were synthesized from D-glucose by Yoshira *et al.* (Scheme 55).^{314,315,320} 2'-Deoxy-2'-methylene 4'-thiocytidine **213** and 1-(2-deoxy-2-fluoro-β-D-4-thioarabinofuranosyl)cytosine **217** (4'-thioFAC) revealed respectively potent antiviral and antineoplastic properties.^{314,315,320} 4'-ThioFAC **217** has prominent and broad antitumor activities against various human solid tumor cell lines *in vitro* as well as *in vivo*.³²¹



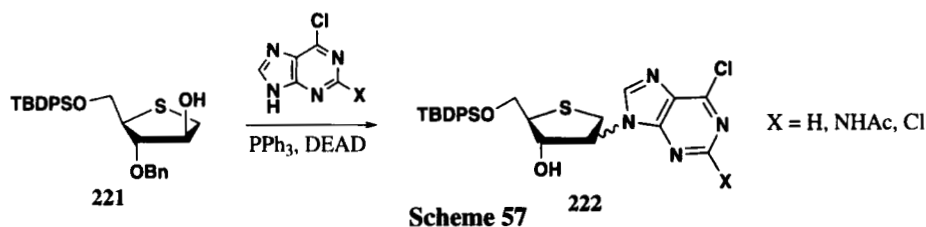
Scheme 55

The synthesis of such a thionucleoside is long and difficult and an alternative synthesis was recently reported to overcome these problems (Scheme 56).³²²⁻³²⁴ In the original method starting from D-glucose, the C1 to C5 atoms were used. In the new method, C2-C6 atoms closer to the tail were employed. This method was applied to the synthesis of the guanine analog (4'-ThioFAG) and 4'-thiocytarazid in which the fluorine atom is substituted for an azido group.^{322,324}

During DAST fluorination in the synthesis of L-2'-« up »-fluoro-4'-thiothymidine, a 4'-thioanalogue of an anti-HBV agent undergoing preclinical toxicological studies, ring contraction and rearrangement of 4-thiofuranose derivatives were observed.³²⁵ A short and efficient synthesis of a L-thioarabinose intermediate for the synthesis of L-2'-deoxy-2,2'-disubstituted-4'-thionucleosides has



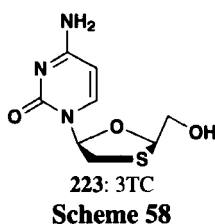
been reported starting from 1,2-isopropylidene-D-xylose.^{326,327} 2,2'-Anhydro-4'-thio- β - and α -nucleosides were prepared and undergo ring-opening with azide or chloride ion to lead to the corresponding 2'-fluoro and chloro derivatives, respectively.³²⁸ Treatment with cyanide or fluoride sources lead to unsaturated derivatives. The 5-substituted uracil analogs of 2'-deoxy-2'-methylene-4'-thiocytidine are active against herpes simplex virus (HSV) type I.^{311,329} The purine analogs have shown broad antiviral activities against HSV-1, HSV-2 and human cytomegalovirus (HCMV) but are cytotoxic. Uracil and purine modified analogs of 4'-ThioFAC were recently synthesized by Yoshimura *et al.*³³⁰ The 5-ethyl, 5-iodo, 5-chloroethyluracil derivatives and the 5-iodocytosine analog showed potent anti-HSV-1 and HSV-2 activities. The 5-fluoro-4'-thioFAC has an antitumor spectrum similar to 4'-thioFAC but it is about ten times less active. The L-enantiomers of 4'-thioFAC and of pyrimidine and adenine analogs prepared from L-glucose showed moderate antiviral activities.^{326,327} Novel iso-4'-thionucleosides were synthesized by Yoshimura *et al.* using the Mitsunobu reaction (Scheme 57).³³¹ With both purines and *N*³-benzoyluracils, the reaction predominantly gives the β -anomers suggesting that these were produced *via* an episulfonium intermediate.



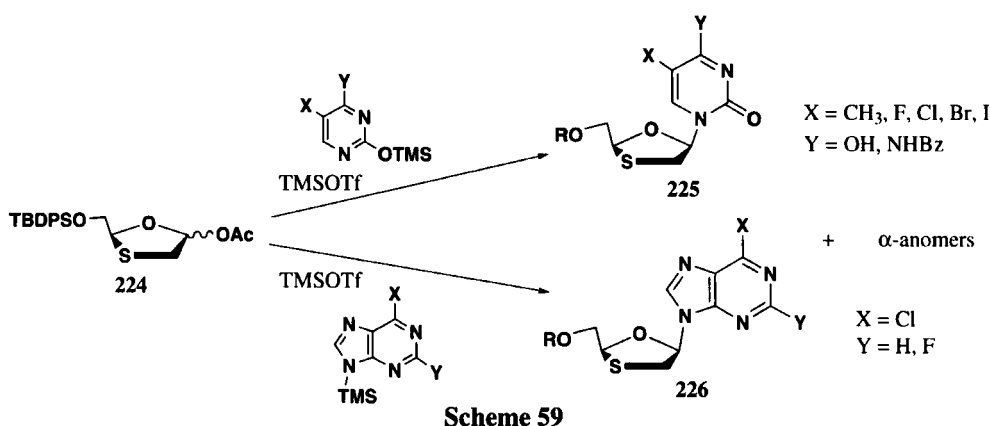
2. 1,3-Oxathiolanyl Nucleosides

(-)-L- β -1,3-oxathiolanyl cytosine **223** (Lamivudine, 3TC, Scheme 58) is an anti-HIV dideoxynucleoside incorporating a sulfur atom used in the treatment of AIDS. This therapeutic agent has a unique structural feature: it is a L-nucleoside with an oxathiolane ring. The synthesis of 3TC

was reviewed previously.⁸ Mechanistic studies of incorporation of 3TC 5'-triphosphate into DNA was recently reported.³³²



Different 1,3-oxathiolanylpurimidine and purine nucleosides possessing the natural D-configuration such as **225** and **226** were synthesized by Chu *et al.* and some of them showed interesting anti-HIV activities (Scheme 59).³³³ The key intermediate **224** used in the glycosylation step was

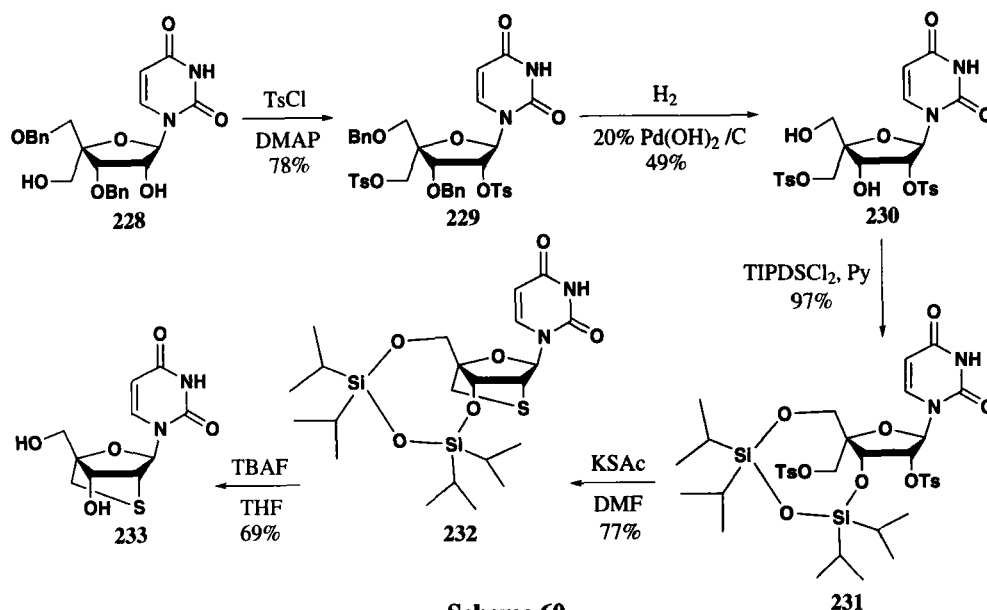
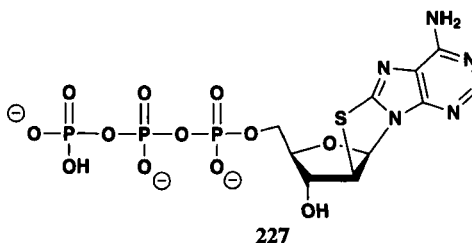


prepared from L-gulose *via* 1,6-thioanhydro-L-gulopyranose. More recently, 1,3-oxathiolanyl pyrimidine nucleosides with a 5-fluoro^{334,335} or with a 2'- or a 5'-hydroxymethyl substituent^{336,337} were synthesized and evaluated for antiviral activities. The synthesis of the (E)-5-(2-bromovinyl)uracil analogs of 3TC was recently reported.³³⁸ An asymmetric synthesis of 1,3-oxathiolane nucleosides was developed from benzyloxyethanal for preparing a wide range of heterosubstituted sulfur containing nucleosides.^{339,340} 1,3-Dithiolane analogs of 3TC were synthesized and some of them showed anti-HIV activity but were found less active than 3TC.³⁴¹ Lipophilic prodrugs of 3TC in which phosphonoformic acid or phosphonoacetic acid was attached to the 5'-O or N⁴ atom were prepared.³⁴² These nucleosides may exert their effects by extracellular or intracellular hydrolysis leading to 3TC. 5'-Polyaminated 3TC prodrugs were also prepared and evaluated.³⁴³

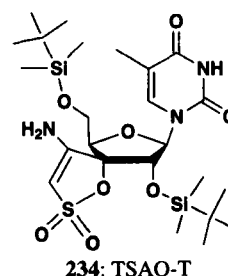
IV. SULFUR CONTAINING CYCLONUCLEOSIDES AND NUCLEOTIDES, LOCKED NUCLEOSIDES AND UNUSUAL BRANCHED NUCLEOSIDES

In the past, a lot of cyclopurine and cyclopyrimidine nucleosides and nucleotides incorporating a sulfur atom in the additional ring have been synthesized¹³ and studied.³⁴⁴ They are interesting

intermediates for chemical transformations of nucleosides and nucleotides.¹³ Some of them were studied as putative agonists for P2-purinergeric receptors (compound **227**).³⁴⁵ In the last decade, modified antisense oligonucleotides were synthesized in which conformational restriction may lead to favourable hybridization with the complementary RNA target due to entropic advantage. With this aim, a number of new nucleosides were synthesized in which additional rings lead to conformational restriction favorable to base pairing.^{141,346-349} In some of them, a sulfur atom was incorporated in the additional ring. Locked nucleic acids (LNA) incorporating a locked nucleoside such as **233** containing a sulfur atom in the additional ring were efficiently oligomerized using phosphoramidite chemistry.³⁵⁰⁻³⁵² They showed, with their oxo and amino analogs, an unprecedented thermal stability of duplexes towards complementary DNA or RNA, stability towards 3'-exonucleolytic degradation, and good solubility in water (Scheme 60).



Nucleosides possessing a sulfur containing spiro ring at the 3'-position were synthesized recently, and represent a new class of anti-HIV agents, for example TSAO-T **234**. The presence of the *tert*-butyldimethylsilyl groups at positions 2' and 5' are essential for antiviral efficacy. These nucleosides are potent and highly specific inhibitors of HIV-1 replication that are able to interfere at the interface between the p51 and p66 reverse transcriptase subunits.³⁵³⁻³⁵⁶



V. CONCLUSION

In this article, we show that a large number of sulfur containing nucleosides, nucleotides, oligonucleotides are bioactive agents or can be used as essential tools for biochemical and biological studies. Incorporation of a sulfur atom in nucleosides has led to efficient antiviral or antitumor agents. Among them, we can mention 3TC, a L-nucleoside with an oxathiolane ring, which is now used in the treatment of AIDS and 4'-thioFAC which is a promising orally active antitumor agent. We illustrate here the large interest in sulfur nucleoside chemistry for preparing non-sulfur and sulfur modified nucleosides in the search for potent nucleoside drugs or tools. With regard to the diversity of the sulfur chemistry and to the numerous possible modifications in nucleosides, it is certain that in the future, other sulfur containing nucleosides, nucleotides, oligonucleotides should emerge as therapeutic agents or as major tools in biology.

REFERENCES

1. D. Bergstrom, X. Lin, G. Wang, D. Rotstein, P. Beal, K. Norrix and J. Ruth, *Synlett*, 179, (1992).
2. C. Périgaud, G. Gosselin and J.-L. Imbach, *Nucleosides & Nucleotides*, **11**, 903 (1992).
3. D. M. Huryn and M. Okabe, *Chem. Rev.*, **92**, 1745 (1992).
4. K. Burgess and D. Cook, *Chem. Rev.*, **100**, 2047 (2000).
5. E. De Clercq, *Rev. Med. Virol.*, **10**, 255 (2000).
6. H. Jonckheere, J. Anné and E. De Clercq, *Med. Res. Rev.*, **20**, 129 (2000).
7. B. Fischer, *Drug Develop. Res.*, **50**, 338 (2000).
8. S. F. Wnuk, *Tetrahedron*, **49**, 9877 (1993).
9. "Nucleoside Analogues", R. T. Walker, E. De Clercq and F. Eckstein, Plenum Press, 1979.
10. "Nucleotide Analogs", K. H. Scheit, John Wiley & Sons, 1980.
11. "Nucleic Acid Chemistry, Part Three", L. B. Townsend and R. S. Tipson, John Wiley & Sons, 1986.
12. "Chemistry of Nucleosides and Nucleotides", Vol. 3, L. B. Townsend, Plenum Press, 1994.
13. "The Organic Chemistry of Nucleic Acids, Studies in Organic Chemistry", Vol. 24, Y. Mizuno, Elsevier, 1986.
14. W. L. Sung, *J. Chem. Soc., Chem. Commun.*, 522 (1982).

15. Y.-Z. Xu, Q. Zheng and P. F. Swann, *Tetrahedron Lett.*, **32**, 2817 (1991).
16. R. S. Coleman and J. M. Siedlecki, *Tetrahedron Lett.*, **32**, 3033 (1991).
17. M. Kadokura, T. Wada, K. Seio and M. Sekine, *J. Org. Chem.*, **65**, 5104 (2000).
18. A. Roget, H. Bazin and R. Teoule, *Nucleic Acids Res.*, **17**, 7643 (1989).
19. T. Sekiya and T. Ukita, *Chem. Pharm. Bull.*, **15**, 1498 (1967).
20. H. Vorbrüggen and P. Strehlke, *Chem. Ber.*, **106**, 3039 (1973).
21. R. G. Kuimelis H. Hope and K. P. Nambiar, *Nucleosides & Nucleotides*, **12**, 737 (1993).
22. I. M. Abdou and L. Strekowski, *Tetrahedron*, **56**, 8631 (2000).
23. W.-G. Chae, T. C. K. Chan and C.-J. Chang, *Tetrahedron*, **54**, 8661 (1998).
24. K. Kikugawa, H. Suehiro and M. Ichino, *J. Med. Chem.*, **16**, 1381 (1973).
25. E. Kapetanovic, J. M. Bailey and R. F. Colman, *Biochemistry*, **24**, 7586 (1985).
26. M. Ikehara, E. Ohtsuka and S. Uesugi, *Chem. Pharm. Bull.*, **21**, 444 (1973).
27. J. Come, L. Burr and R. Chen, *Tetrahedron Lett.*, **32**, 4823 (1991).
28. D. H. Bradley and M. M. Hanna, *Tetrahedron Lett.*, **33**, 6223 (1992).
29. K. L. Meyer and M. M. Hanna, *Bioconjugate Chem.*, **7**, 401 (1996).
30. D. Bärwolff, P. Langen, Ger. (East) 114, 949, 1974; CA 87, 1977 – 39770.
31. Y. Suzuki, A. Matsuda and T. Ueda, *Chem. Pharm. Bull.*, **35**, 1085 (1987).
32. E. Palomino, B. R. Meltsner, D. Kessel and J. P. Horwitz, *J. Med. Chem.*, **33**, 258 (1990).
33. M. Bretner, T. Kulikowski, J. M. Dzik, M. Balinska, W. Rode and D. Shugar, *J. Med. Chem.*, **36**, 3611 (1993).
34. T.-S. Lin, M.-Z. Luo and M.-C. Liu, *Tetrahedron*, **51**, 1055 (1995).
35. M. Bretner, M. Balinska, K. Krawiec, B. Kierdaszuk, D. Shugar and T. Kulikowski, *Nucleosides & Nucleotides*, **14**, 657 (1995).
36. B. V. Joshi, C. B. Reese and C. V. N. S. Varaprasad, *Nucleosides & Nucleotides*, **14**, 209 (1995).
37. I. Votruba, M. Krecmerova, H. Hrebabecky and A. Holy, *Nucleosides & Nucleotides*, **18**, 2551 (1999).

38. G. B. Elion, *Science*, **244**, 41 (1989).
39. Y.-Z. Xu, Q. Zheng and P. F. Swann, *Tetrahedron Lett.*, **33**, 5837 (1992).
40. T. R. Waters and P. F. Swann, *Biochemistry*, **36**, 2501 (1997).
41. R. Kambampati and C. T. Lauhon, *Biochemistry*, **38**, 16561 (1999).
42. A. Favre and J.-L. Fourrey, *Acc. Chem. Res.*, **28**, 375 (1995).
43. L. Wang and D. E. Ruffner, *Nucleic Acids Res.*, **25**, 4355 (1997).
44. Y.-T. Yu and J. A. Steitz, *Proc. Natl. Acad. Sci USA.*, **94**, 6030 (1997).
45. Y. H. Ping, Y. Liu, X. Wang, H. R. Neenhold and T. M. Rana, *RNA*, **3**, 850 (1997).
46. P. V. Baranov, O. L. Gurvich, A. A. Bogdanov, R. Brimacombe and O. A. Donstova, *RNA*, **4**, 658 (1998).
47. Z. Wang and T. M. Rana, *Biochemistry*, **37**, 4235 (1998).
48. A. Woisard, A. Favre, P. Clivio and J.-L. Fourrey, *J. Am. Chem. Soc.*, **114**, 10072 (1992).
49. P. Clivio, J.-L. Fourrey and J. Gasche, *Tetrahedron Lett.*, **33**, 65 (1992).
50. P. Clivio, J.-L. Fourrey, J. Gasche and A. Favre, *Tetrahedron Lett.*, **33**, 69 (1992).
51. P. Clivio, J.-L. Fourrey and A. Favre, *J. Chem. Soc., Perkin Trans. 1*, 2585 (1993).
52. J. Milton, B. A. Connolly, T. T. Nikiforov and R. Cosstick, *J. Chem. Soc., Chem. Commun.*, 779 (1993).
53. T. S. Rao, R. H. Durland, D. M. Seth, M. A. Myrick, V. Bodepudi and G. R. Revankar, *Biochemistry*, **34**, 765 (1995).
54. H. P. Rappaport, *Nucleic Acids Res.*, **16**, 7253 (1988).
55. F. C. Richardson, S. M. Bronstein, WO 89/09778.
56. M. S. Christopherson and A. D. Broom, *Nucleic Acids Res.*, **19**, 5719 (1991).
57. T. S. Rao, K. Jayaraman, R. H. Durland and G. R. Revankar, *Tetrahedron Lett.*, **33**, 7651 (1992).
58. T. T. Nikiforov and B. A. Connolly, *Nucleic Acids Res.*, **20**, 1209 (1992).
59. Y.-Z. Xu, Q. Zheng and P. F. Swann, *Tetrahedron*, **48**, 1729 (1992).

60. R. S. Coleman and J. M. Siedlecki, *J. Am. Chem. Soc.*, **114**, 9229 (1992).
61. R. S. Coleman and E. A. Kesicki, *J. Am. Chem. Soc.*, **116**, 11636 (1994).
62. P. Clivio, J.-L. Fourrey, J. Gasche and A. Favre, *J. Chem. Soc., Perkin Trans. 1*, 2383 (1992).
63. B. A. Connolly and P. C. Newman, *Nucleic Acids Res.*, **17**, 4957 (1989).
64. T. T. Nikiforov and B. A. Connolly, *Tetrahedron Lett.*, **32**, 3851 (1991).
65. Y.-Z. Xu, Q. Zheng and P. F. Swann, *J. Org. Chem.*, **57**, 3839 (1992).
66. J. Liu and J.-S. Taylor, *Nucleic Acids Res.*, **26**, 3300 (1998).
67. H. Bazin and S. Sauvaigo, *Nucleosides & Nucleotides*, **18**, 965 (1999).
68. T. V. S. Rao, M. T. Haber, J. M. Sayer and D. M. Jerina, *Bioorg. Med. Chem. Lett.*, **10**, 907 (2000).
69. C. J. Adams, M. A. Farrow, J. B. Murray, S. M. Kelly, N. C. Price and P. G. Stockley, *Tetrahedron Lett.*, **36**, 4637 (1995).
70. C. J. Adams, J. B. Murray, J. R. P. Arnold and P. G. Stockley, *Tetrahedron Lett.*, **35**, 765 (1994).
71. A. McGregor, M. Vaman Rao, G. Duckworth, P. G. Stockley and B. A. Connolly, *Nucleic Acids Res.*, **24**, 3173 (1996).
72. H. F. Becker, H. Grosjean and J.-L. Fourrey, *Nucleosides & Nucleotides*, **17**, 2403 (1998).
73. Rappaport WO 89020, *Chem. Abstr.*, **112**, 119350k (1990).
74. C. Saintomé, P. Clivio, A. Favre, J.-L. Fourrey and P. Laugâa, *Chem. Commun.*, 167 (1997).
75. C. Saintomé, P. Clivio, J.-L. Fourrey, A. Woisard, P. Laugâa and A. Favre *Tetrahedron*, **56**, 1197 (2000).
76. P. Clivio, D. Guillaume, M.-T. Adeline, J. Hamon, C. Riche and J.-L. Fourrey, *J. Am. Chem. Soc.*, **120**, 1157 (1998).
77. A. Dunger, H.-H. Limbach and K. Weisz, *Chem. Eur. J.*, **4**, 621 (1998).
78. J.-L. Fourrey, *Tetrahedron Lett.*, 297 (1976).
79. A. Favre, "Bioorganic Photochemistry: Photochemistry and the Nucleic Acids", Vol. 1, p. 317, H. Morrison, John Wiley & Sons, 1990.
80. P. Clivio, J.-L. Fourrey, T. Szabo and J. Stawinski, *J. Org. Chem.*, **59**, 7273 (1994).

81. J. Liu and J.-S. Taylor, *J. Am. Chem. Soc.*, **118**, 3287 (1996).
82. C. Saintomé, P. Clivio, A. Favre, J.-L. Fourrey and C. Riche, *J. Am. Chem. Soc.*, **118**, 8142 (1996).
83. C. Saintomé, P. Clivio, A. Favre and J.-L. Fourrey, *J. Org. Chem.*, **62**, 8125 (1997).
84. C. Hélène, *Anticancer Drug Design*, **6**, 569 (1991).
85. N. T. Thuong and C. Hélène, *Angew. Chem., Int. Ed. Engl.*, **32**, 666 (1993).
86. S. O. Doronina and J.-P. Behr, *Chem. Soc. Rev.*, **63** (1997).
87. M. S. Christopherson and A. D. Broom, *Nucleosides & Nucleotides*, **13**, 351 (1994).
88. A. D. Broom, V. K. Agrawal, M. G. Tutonda, H. D. Fain and R. W. Buckheit, Jr, *J. Med. Chem.*, **38**, 3253 (1995).
89. R. G. Kuimelis and K. P. Nambiar, *Nucleic Acids Res.*, **22**, 1429 (1994).
90. R. G. Kuimelis and L. W. McLaughlin, *Biochemistry*, **35**, 5308 (1996).
91. I. V. Kutyavin, R. L. Rhinehart, E. A. Lukhtanov, V. V. Gorn, R. B. Meyer, Jr. and H. B. Gamper, Jr., *Biochemistry*, **35**, 11170 (1996).
92. C. Houssier, P. Degee, K. Nicoghsian and H. Grosjean, *J. Biomol. Struct. Dyn.*, **5**, 1259 (1988).
93. T. M. Nair, D. G. Myszkas and D. R. Davis, *Nucleic Acids Res.*, **28**, 1935 (2000).
94. R. K. Kumar and D. R. Davis, *J. Org. Chem.*, **60**, 7726 (1995).
95. P. F. Agris, H. Sierzputowska-Gracz, W. Smith, A. Malkiewicz, E. Sochacka and B. Nawrot, *J. Am. Chem. Soc.*, **114**, 2652 (1992).
96. W. S. Smith, H. Sierzputowska-Gracz, E. Sochacka, A. Malkiewicz and P. F. Agris, *J. Am. Chem. Soc.*, **114**, 7989 (1992).
97. R. K. Kumar and D. R. Davis, *Nucleosides & Nucleotides*, **16**, 1469 (1997).
98. M. Sundaram, P. C. Durant and D. R. Davis, *Biochemistry*, **39**, 12575 (2000).
99. M. Sundaram, P. F. Crain and D. R. Davis, *J. Org. Chem.*, **65**, 5609 (2000).
100. A. C. Bajji and D. R. Davis, *Org. Lett.*, **2**, 3865 (2000).
101. K. Shohda, I. Okamoto, T. Wada, K. Seio and M. Sekine, *Bioorg. Med. Chem. Lett.*, **10**, 1795 (2000).

102. E. Yuriev, D. Scott and M. M. Hanna, *J. Mol. Recognit.*, **12**, 337 (1999).
103. G. M. Blackburn and M. J. Gait, *Nucleic Acids in Chemistry and Biology*, (1996), Oxford University Press.
104. "Comprehensive Organic Chemistry", R. T. Walker, Pergamon Press, **5**, 53, 1971.
105. G. Shaw, R. N. Warrener, M. H. Maguire and R. K. Ralph, *J. Chem. Soc.*, 2294 (1958).
106. H. Wamhoff, R. Berressem and M. Nieger, *J. Org. Chem.*, **58**, 5181 (1993).
107. H. Wamhoff, R. Berressem and M. Nieger, *J. Org. Chem.*, **59**, 1912 (1994).
108. R. Ranganathan, *Tetrahedron Lett.*, 1185 (1975).
109. H. Sugimura, K. Osumi, Y. Kodaka and K. Sujino, *J. Org. Chem.*, **59**, 7653 (1994).
110. G. W. Kenner, C. W. Taylor and A. R. Todd, *J. Chem. Soc.*, 1620 (1949).
111. M. Frieden, M. Giraud, C. B. Reese and Q. Song, *J. Chem. Soc., Perkin Trans. 1*, 2827 (1998).
112. B. M. Moore, II, R. K. Jalluri and M. B. Doughty, *Biochemistry*, **35**, 11642 (1996).
113. B. Fisher, A. Chulkin, J. L. Boyer, K. T. Harden, F.-P. Gendron, A. R. Beaudoin, J. Chapal, D. Hillaire-Buys and P. Petit, *J. Med. Chem.*, **42**, 3636 (1999).
114. E. Halbfinger, D. T. Major, M. Ritzmann, J. Ubl, G. Reiser, J.-L. Boyer, K. T. Harden and B. Fisher, *J. Med. Chem.*, **42**, 5325 (1999).
115. A. H. Ingall, J. Dixon, A. Bailey, M. E. Coombs, D. Cox, J. I. McNally, S. F. Hunt, N. D. Kindon, B. J. Teobald, P. A. Willis, R. G. Humphries, P. Leff, J. A. Clegg, J. A. Smith and W. Tomlinson, *J. Med. Chem.*, **42**, 213 (1999).
116. C. Costas, E. Yuriev, K. L. Meyer, T. S. Guion and M. M. Hanna, *Nucleic Acids Res.*, **28**, 1849 (2000).
117. C. L. Schmidt, C. T.-C. Chang, E. De Clercq, J. Descamps and M. P. Mertes, *J. Med. Chem.*, **23**, 252 (1980).
118. N. Habboub, PhD Thesis, Grenoble University (1989).
119. R. Saladino, C. Crestini, F. Occhionero and R. Nicoletti, *Tetrahedron*, **51**, 3607 (1995).
120. C. Crestini, R. Saladino, R. Bernini and E. Mincione, *Tetrahedron Lett.*, **34**, 7785 (1993).
121. R. Saladino, E. Mincione, C. Crestini and M. Mezzetti, *Tetrahedron*, **52**, 6759 (1996).
122. L. Strekowski, I. M. Abdou, A. M. E. Attia and S. E. Patterson, *Tetrahedron Lett.*, **41**, 4757 (2000).

123. A. Manikowski and J. Boryski, *Nucleosides & Nucleotides*, **18**, 2367 (1999).
124. H. P. Rappaport, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 839 (2000).
125. S. Nampalli, I. Livshin and S. Kumar, *Nucleosides & Nucleotides*, **18**, 697 (1999).
126. S. Nampalli and S. Kumar, *Bioorg. Med. Chem. Lett.*, **10**, 1677 (2000).
127. K. N. Carter, T. Taverner, C. H. Schiesser and M. M. Greenberg, *J. Org. Chem.*, **65**, 8375 (2000).
128. X. Lin and M. J. Robins, *Org. Lett.*, **2**, 3497 (2000).
129. U. Pies, B. S. Sproat, P. Neuner and F. Cramer, *Nucleic Acids Res.*, **17**, 8967 (1989).
130. M. Osswald and R. Brimacombe, *Nucleic Acids Res.*, **27**, 2283 (1999).
131. A. Laayoun, J.-L. Décout and J. Lhomme, *Tetrahedron Lett.*, **35**, 4989 (1994).
132. A. Laayoun, J.-L. Décout, E. Defrancq and J. Lhomme, *Tetrahedron Lett.*, **35**, 4991 (1994).
133. A. Romieu, S. Bellon, D. Gasparutto and J. Cadet, *Org. Lett.*, **2**, 1085 (2000).
134. A. Ericson, J. L. McCary, R. S. Coleman and S. K. C. Elmroth, *J. Am. Chem. Soc.*, **120**, 12680 (1998).
135. A. Ericson, Y. Iljina, J. L. McCary, R. S. Coleman and S. K. C. Elmroth, *Inorg. Chim. Acta*, **297**, 56 (2000).
136. A. Ericson, J. C. Arthur, R. S. Coleman, L. I. Elding and S. K. C. Elmroth, *J. Chem. Soc., Dalton Trans.*, 1687 (1998).
137. R. S. Coleman and J. L. McCary, *Bioorg. Med. Chem. Lett.*, **8**, 3039 (1998).
138. R. S. Coleman, J. L. McCary and R. J. Perez, *Tetrahedron Lett.*, **40**, 13 (1999).
139. R. S. Coleman, J. L. McCary and R. J. Perez, *Tetrahedron*, **55**, 12009 (1999).
140. S. E. Osborne and A. D. Ellington, *Chem. Rev.*, **97**, 349 (1997).
141. E. T. Kool, *Chem. Rev.*, **97**, 1473 (1997).
142. A. E. Ferentz and G. L. Verdine, *J. Am. Chem. Soc.*, **113**, 4000 (1991).
143. A. E. Ferentz, T. A. Keating and G. L. Verdine, *J. Am. Chem. Soc.*, **115**, 9006 (1993).
144. G. D. Glick, *J. Org. Chem.*, **56**, 6746 (1991).

145. G. D. Glick, S. E. Osborne, D. S. Knitt and J. P. Marino, Jr., *J. Am. Chem. Soc.*, **114**, 5447 (1992).
146. S. E. Osborne, J. Völker, S. Y. Stevens, K. J. Breslauer and G. D. Glick, *J. Am. Chem. Soc.*, **118**, 11993 (1996).
147. J. T. Goodwin, S. E. Osborne, E. J. Scholle and G. D. Glick, *J. Am. Chem. Soc.*, **118**, 5207 (1996).
148. J. T. Goodwin and G. D. Glick, *Tetrahedron Lett.*, **35**, 1647 (1994).
149. S. Sun, X.-Q. Tang, A. Merchant, P. S. R. Anjaneyulu and J. A. Piccirilli, *J. Org. Chem.*, **61**, 5708 (1996).
150. J. T. Goodwin and G. D. Glick, *Tetrahedron Lett.*, **34**, 5549 (1993).
151. N. C. Chaudhuri and E. T. Kool, *J. Am. Chem. Soc.*, **117**, 10434 (1995).
152. "Handbook of Fluorescent Probes and Research Chemicals, Sixth Edition", R. P. Haugland, Molecular Probes, Inc., 1996.
153. M. R. Webb, *Proc. Natl. Acad. Sci.*, **89**, 4884 (1992).
154. F. C. Wedler, B. W. Ley and M. L. Moyer, *Anal. Biochem.*, **218**, 449 (1994).
155. "Nucleic Acids and Molecular Biology", Vol. 10, F. Eckstein and D. M. J. Lilley, Springer Berlin, 1997.
156. M. Imazawa, T. Ueda and T. Ukita, *Chem. Pharm. Bull.*, **23**, 604 (1975).
157. K. J. Divakar, A. Mottoh, C. B. Reese and Y. S. Sanghvi, *J. Chem. Soc., Perkin Trans. 1*, 969 (1990).
158. J. H. Marriott, M. Mottahedeh and C. B. Reese, *Carbohydr. Res.*, **216**, 257 (1991).
159. R. Johnson, C. B. Reese and Z. Pei-Zhuo, *Tetrahedron*, **51**, 5093 (1995).
160. J. Covès, L. Le Hir de Fallois, L. Le Pape, J.-L. Décout and M. Fontecave, *Biochemistry*, **35**, 8595 (1996).
161. J. Stubbe and W. A. van der Donk, *Chem. Biol.*, **2**, 793 (1995).
162. M. Fontecave, *Cell. Mol. Life Sci. 1*, 684 (1998).
163. A. Jordan, P. Reichard, *Annu. Rev. Biochem.*, **67**, 71 (1998).
164. M. J. Robins, *Nucleosides & Nucleotides*, **18**, 779 (1999).

165. L. Le Hir de Fallois, J.-L. Décout and M. Fontecave, *J. Chem. Soc., Perkin Trans. 1*, 2587 (1997).
166. S. Chambert, I. Gautier-Luneau, M. Fontecave and J.-L. Décout, *J. Org. Chem.*, **65**, 249 (2000).
167. C. B. Reese, C. Simons and Z. Pei-Zhuo, *J. Chem. Soc., Chem. Commun.*, 1809 (1994).
168. C. L. Dantzman and L. L. Kiessling, *J. Am. Chem. Soc.*, **118**, 11715 (1996).
169. D.-M. Zhou and K. Taira, *Chem. Rev.*, **98**, 991 (1998).
170. M. Oivanen, S. Kuusela and H. Lönnberg, *Chem. Rev.*, **98**, 961 (1998).
171. M. L. Hamm and J. A. Piccirilli, *J. Org. Chem.*, **62**, 3415 (1997).
172. M. L. Hamm and J. A. Piccirilli, *J. Org. Chem.*, **64**, 5700 (1999).
173. D. J. Earnshaw, M. L. Hamm, J. A. Piccirilli, A. Karpeisky, L. Beigelman, B. S. Ross, M. Manoharan and M. J. Gait, *Biochemistry*, **39**, 6410 (2000).
174. H. Ozaki, Y. Sato, S. Azuma and H. Sawai, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 593 (2000).
175. H. Ozaki, S. Momiyama, K. Yokotsuda and H. Sawai, *Tetrahedron Lett.*, **42**, 677 (2001).
176. A. A. Yuzhakov, Z. G. Chidgeavadze and R. S. Beabealashvilli, *F. E. B. S.*, **306**, 185 (1992).
177. A. A. Yuzhakov, Z. G. Chidgeavadze, R. S. Beabealashvilli, A. A. Kraevskii, G. A. Galegov, M. N. Korneeva, D. N. Nosik and T. Y. Kileso, *Bioorg. Khim.*, **17**, 504 (1991).
178. K. L. Dueholm, Y. L. Aly, P. T. Joergensen, A. A. El-Barbary, E. B. Pedersen and C. Nielsen, *Monatsh. Chem.*, **124**, 37 (1993).
179. A.-M. Aubertin unpublished results; S. Chambert, I. Gautier-Luneau, M. Fontecave and J.-L. Décout, *J. Org. Chem.*, **65**, 249 (2000).
180. K. J. Divakar and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1625 (1982).
181. D. M. Brown, D. B. Parihar, A. Todd and S. Varadarajan, *J. Chem. Soc., Perkin Trans. 1*, 3028 (1958).
182. Y. Furukawa, Y. Yoshioka, K.-I. Imai and M. Honjo, *Chem. Pharm. Bull.*, **18**, 554 (1970).
183. M. J. Robins, K. B. Mullah, S. F. Wnuk and N. K. Dalley, *J. Org. Chem.*, **57**, 2357 (1992).
184. A. Miah, C. B. Reese and Q. Song, *J. Chem. Soc., Chem. Commun.*, 407 (1997).
185. A. Miah, C. B. Reese, Q. Song, Z. Sturdy, S. Neidle, I. J. Simpson, M. Read and E. Rayner, *J. Chem. Soc., Perkin Trans. 1*, 3277 (1998).

186. S. Bera, G. J. Langley and T. Pathak, *J. Org. Chem.*, **63**, 1754 (1998).
187. R. Cosstick and J. S. Vyle, *J. Chem. Soc., Chem. Commun.*, 992 (1988).
188. R. Cosstick and J. S. Vyle, *Tetrahedron Lett.*, **30**, 4693 (1989).
189. R. Cosstick and J. S. Vyle, *Nucleic Acids Res.*, **18**, 829 (1990).
190. R. Cosstick, X. Li and J. S. Vyle, *Tetrahedron Lett.*, **33**, 3017 (1992).
191. X. Li, D. M. Andrews and R. Cosstick, *Tetrahedron*, **48**, 2729 (1992).
192. J. S. Vyle, B. A. Connolly, D. Kemp and R. Cosstick, *Biochemistry*, **31**, 3012 (1992).
193. M. D. Szczelkun and B. A. Connolly, *Biochemistry*, **34**, 10724 (1995).
194. E. J. Sontheimer, S. Sun and J. A. Piccirilli, *Nature*, **388**, 801 (1997).
195. N. C. Horton, B. A. Connolly and J. J. Perona, *J. Am. Chem. Soc.*, **122**, 3314 (2000).
196. J. S. Vyle, X. Li and R. Cosstick, *Tetrahedron Lett.*, **33**, 3017 (1992).
197. X. Li, G. K. Scott, A. D. Baxter, R. J. Taylor, J. S. Vyle and R. Cosstick, *J. Chem. Soc., Perkin Trans. 1*, 2123 (1994).
198. A. P. Higson, G. K. Scott, D. J. Earnshaw, A. D. Baxter, R. A. Taylor and R. Cosstick, *Tetrahedron*, **52**, 1027 (1996).
199. W. Dabkowski, M. Michalska and I. Tworowska, *J. Chem. Soc., Chem. Commun.*, 427 (1998).
200. J. A. Piccirilli, J. S. Vyle, M. H. Caruthers and T. R. Cech, *Nature*, **361**, 85 (1993).
201. D. Herschlag, F. Eckstein and T. R. Cech, *Biochemistry*, **32**, 8312 (1993).
202. L. B. Weinstein, D. J. Earnshaw, R. Cosstick and T. R. Cech, *J. Am. Chem. Soc.*, **118**, 10341 (1996).
203. M. I. Elzagheid, M. Oivanen, K. D. Klika, B. C. N. M. Jones, R. Cosstick and H. Lönnberg, *Nucleosides & Nucleotides*, **18**, 2093 (1999).
204. X. Liu and C. B. Reese, *Tetrahedron Lett.*, **37**, 925 (1996).
205. X. Liu and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2227 (2000).
206. M. I. Elzagheid, E. Mäki, U. Kaukinen, M. Oivanen and H. Lönnberg, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 827 (2000).
207. M. I. Elzagheid, K. Mattila, M. Oivanen, B. C. N. M. Jones, R. Cosstick and H. Lönnberg, *Eur. J. Org. Chem.*, 1987 (2000).

208. S. Sun, A. Yoshida and J. A. Piccirilli, *RNA*, **3**, 1352 (1997).
209. R. G. Kuimelis and L. W. McLaughlin, *Chem. Rev.*, **98**, 1027 (1998).
210. J. Matulic-Adamic and L. Beigelman, *Helv. Chim. Act.*, **82**, 2141 (1999).
211. R. J. Jones, K.-Y. Lin, J. F. Milligan, S. Wadwani and M. D. Matteucci, *J. Org. Chem.*, **58**, 2983 (1993).
212. J. J. Toulmé and C. Hélène, *Gène*, **72**, 51 (1988).
213. M. D. Matteucci and R. W. Wagner, *Nature*, **384**, 20 (1996).
214. W. Zhou, *Drugs of the future*, **25**, 183 (2000).
215. E. M. Witch and R. Cosstick, *Tetrahedron Lett.*, **38**, 6745 (1997).
216. B. Kumar Patel and F. Eckstein, *Tetrahedron Lett.*, **38**, 1021 (1997).
217. R. K. Bruick, P. E. Dawson, S. B. Kent, N. Usman and G. F. Joyce, *Chemistry & Biology*, **3**, 49 (1996).
218. K. A. Henningfeld, T. Arslan and S. M. Hecht, *J. Am. Chem. Soc.*, **118**, 11701 (1996).
219. S. H. Kawai, D. Wang, P. A. Giannaris, M. J. Damha and G. Just, *Nucleic Acids Res.*, **21**, 1473 (1993).
220. D. Wang, B. Meng, M. J. Damha and G. Just, *Nucleosides & Nucleotides*, **14**, 1961 (1995).
221. Y. Ducharme and K. A. Harrison, *Tetrahedron Lett.*, **36**, 6643 (1995).
222. Y. Ducharme and K. A. Harrison, *Can. J. Chem.*, **77**, 1410 (1999).
223. X. Liu and C. B. Reese, *Tetrahedron Lett.*, **36**, 3413 (1995).
224. J. B. Thomson, B. K. Patel, V. Jiménez, K. Eckart and F. Eckstein, *J. Org. Chem.*, **61**, 6273 (1996).
225. R. G. Kuimelis and L. W. McLaughlin, *Nucleic Acids Res.*, **23**, 4753 (1995).
226. B. K. Patel, J. B. Thomson, V. Jiménez, K. Eckart and F. Eckstein, *Nucleosides & Nucleotides*, **16**, 1443 (1997).
227. R. G. Kuimelis and L. W. McLaughlin, *J. Am. Chem. Soc.*, **117**, 11019 (1995).
228. D.-M. Zhou, N. Usman, F. E. Wincott, J. Matulic-Adamic, M. Orita, L.-H. Zhang, M. Komiya, P. K. R. Kumar and K. Taira, *J. Am. Chem. Soc.*, **118**, 5862 (1996).
229. B. Zhang, Z. Cui and L. Sun, *Org. Lett.*, **3**, 275 (2001).

230. A. Romieu, D. Gasparutto, D. Molko and J. Cadet, *J. Org. Chem.*, **63**, 5245 (1998).
231. A. Romieu, D. Gasparutto and J. Cadet, *Chem. Res. Toxicol.*, **12**, 412 (1999).
232. E. W. van Tilburg, J. von Frijtag Drabbe Kunzel, M. de Groote, R. C. Vollinga, A. Lorenzen and A. P. Ijzerman, *J. Med. Chem.*, **42**, 1393 (1999).
233. F. Girard, S. Léonce and L. A. Agrofoglio, *Tetrahedron Lett.*, **38**, 7535 (1997).
234. L. A. Agrofoglio, F. Girard, F. Fleury and S. Leonce, *Nucleosides & Nucleotides*, **18**, 599 (1999).
235. N. A. Al-Masoudi, *Tetrahedron Lett.*, **40**, 4795 (1999).
236. J. L. Palmer and R. H. Abeles, *J. Biol. Chem.*, **254**, 1217 (1979).
237. C.-S. Yuan, J. Yeh, S. Liu and R. T. Borchardt, *J. Biol. Chem.*, **268**, 17030 (1993).
238. C.-S. Yuan, S. Liu, S. F. Wnuk, M. J. Robins and R. T. Borchardt, *Nucleosides & Nucleotides*, **14**, 439 (1995).
239. M. J. Robins and S. F. Wnuk, *J. Org. Chem.*, **58**, 3800 (1993).
240. M. J. Robins, S. F. Wnuk, K. B. Mullah, N. K. Dalley, C-S. Yuan, Y. Lee and R. T. Borchardt, *J. Org. Chem.*, **59**, 544 (1994).
241. S. F. Wnuk, C.-S. Yuan, R. T. Borchardt, J. Balzarini, E. De Clercq and M. J. Robins, *J. Med. Chem.*, **40**, 1608 (1997).
242. S. F. Wnuk, N. K. Dalley and M. J. Robins, *J. Org. Chem.*, **58**, 111 (1993).
243. M. J. Robins, V. Neschadimenko, B.-O. Ro, C.-S. Yuan, R. T. Borchardt and S. F. Wnuk, *J. Org. Chem.*, **63**, 1205 (1998).
244. M. Muzard, D. Guillerme, C. Vandenplas and G. Guillerme, *Bioorg. Med. Chem. Lett.*, **7**, 1037 (1997).
245. D. Guillerme, G. Guillerme and C. Vandenplas-Witkowski, *Nucleosides, Nucleotides & Nucleic acids*, **20**, in press.
246. M. Muzard, C. Vandenplas, D. Guillerme and G. Guillerme, *J. Enzyme Inhib.*, **13**, 443 (1998).
247. C. Vandenplas, D. Guillerme and G. Guillerme, *Nucleosides & Nucleotides*, **18**, 569 (1999).
248. G. Guillerme, D. Guillerme and C. Vandenplas-Witkowski, , *Nucleosides, Nucleotides & Nucleic acids*, **20**, in press.
G. Guillerme, D. Guillerme, C. Vandenplas-Witkowski, H. Rogniaux, N. Carte, E. Leize, A. Van Dorssele, E. De Clercq and C. Lambert, *J. Med. Chem.*, **44**, in press.

249. B. Allart, D. Guillermin and G. Guillermin, *Nucleosides & Nucleotides*, **18**, 861 (1999).
250. R. A. Casero, Jr. and P. M. Woster, *J. Med. Chem.*, **44**, 1 (2001).
251. Y. Q. Wu and P. M. Woster, *J. Med. Chem.*, **35**, 3196 (1992).
252. Y. Q. Wu and P. M. Woster, *Bioorg. Med. Chem.*, **1**, 349 (1993).
253. Y. Q. Wu and P. M. Woster, *Biochem. Pharmacol.*, **49**, 1125 (1995).
254. J. Guo, Y. Q. Wu, D. Rattendi, C. J. Bacchi and P. M. Woster, *J. Med. Chem.*, **38**, 1770 (1995).
255. M. Pignot, G. Pljevaljcic and E. Weinhold, *Eur. J. Org. Chem.*, 549 (2000).
256. C. R. Johnson, J. L. Esker, M. C. Van Zandt, *J. Org. Chem.*, **59**, 5854 (1994).
257. O. T. Magnusson, G. H. Reed and P. A. Frey, *J. Am. Chem. Soc.*, **121**, 9764 (1999).
258. R. Johnson, B. V. Joshi and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 133 (1994).
259. A. Eleuteri, C. B. Reese and Q. Song, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1996).
260. J. A. Secrist III, K. N. Tiwari, J. M. Riordan and J. A. Montgomery, *J. Med. Chem.*, **34**, 2361 (1991).
261. M. R. Dyson, P. L. Coe and R. T. Walker, *J. Med. Chem.*, **34**, 2782 (1991).
262. R. T. Walker, *4'-Thio-2'-Deoxyribonucleosides, Their Chemistry and Biological Properties - A Review.*, Vol. 198, p. 203, R. T. Walker, Ed., (1997).
263. J. Uenishi, M. Motoyama, Y. Nishiyama and S. Wakabayashi, *J. Chem. Soc., Chem. Commun.*, 1421 (1991).
264. B. Huang and Y. Hui, *Nucleosides & Nucleotides*, **12**, 139 (1993).
265. E. L. Hancox, T. A. Hamor and R. T. Walker, *Tetrahedron Lett.*, **35**, 1291 (1994).
266. J. A. Secrist III, W. B. Parker, K. N. Tiwari, L. Messini, S. C. Shaddix, L. M. Rose, L. Lee Bennett, Jr. and J. A. Montgomery, *Nucleosides & Nucleotides*, **14**, 675 (1995).
267. N. A. Van Draanen, G. A. Freeman, S. A. Short, R. Harvey, R. Jansen, G. Szczech and G. W. Koszalka, *J. Med. Chem.*, **39**, 538 (1996).
268. K. Haraguchi, A. Nishikawa, E. Sasakura, H. Tanaka, K. T. Nakamura and T. Miyasaka, *Tetrahedron Lett.*, **39**, 3713 (1998).
269. M. I. Elzagheid, M. Oivanen, R. T. Walker and J. A. Secrist III, *Nucleosides & Nucleotides*, **18**, 181 (1999).

270. G. P. Otter, M. I. Elzagheid, G. D. Jones, A. C. MacCulloch, R. T. Walker, M. Oivanen and K. D. Klika, *J. Chem. Soc., Perkin Trans. 2*, 2343 (1998).
271. J. Uenishi, K. Takahashi, M. Motoyama, H. Akashi and T. Sasaki, *Nucleosides & Nucleotides*, **13**, 1347 (1994).
272. S. G. Rahim, N. Trivedi, M. V. Bogunovic-Batchelor, G. W. Hardy, G. Mills, J. W. T. Selway, W. Snowden, E. Littler, P. L. Coe, I. Basnak, R. F. Whale and R. T. Walker, *J. Med. Chem.*, **39**, 789 (1996).
273. K. N. Tiwari, J. A. Secrist III and J. A. Montgomery, *Nucleosides & Nucleotides*, **13**, 1819 (1994).
274. S. Shaw-Ponter, G. Mills, M. Robertson, R. D. Bostwick, G. W. Hardy and R. J. Young, *Tetrahedron Lett.*, **37**, 1867 (1996).
275. G. Inguaggiato, M. Jasamai, J. E. Smith, M. Slater and C. Simons, *Nucleosides & Nucleotides*, **18**, 457 (1999).
276. Y. Wang, G. Inguaggiato, M. Jasamai, M. Shah, D. Hughes, M. Slater and C. Simons, *Bioorg. Med. Chem.*, **7**, 481 (1999).
277. L. Cappellacci, K. N. Tiwari, J. A. Montgomery and J. A. Secrist III, *Nucleosides & Nucleotides*, **18**, 613 (1999).
278. L. Messini, K. N. Tiwari, J. A. Montgomery and J. A. Secrist III, *Nucleosides & Nucleotides*, **18**, 683 (1999).
279. J. Wirsching, J. Voss, G. Adiwidjaja, A. Giesler and J. Kopf, *Eur. J. Org. Chem.*, 1077 (2001).
280. K. S. Jandu and D. L. Selwood, *J. Org. Chem.*, **60**, 5170 (1995).
281. D. L. Selwood, K. Carter, R. J. Young and K. S. Jandu, *Bioorg. Med. Chem. Lett.*, **6**, 991 (1996).
282. I. Basnak, G. P. Otter, R. J. Duncombe, N. B. Westwood, M. Pietrarelli, G. W. Hardy, G. Mills, S. G. Rahim and R. T. Walker, *Nucleosides & Nucleotides*, **17**, 29 (1998).
283. B. Tber, N.-E. Fahmi, G. Ronco, P. Villa, D. F. Ewing and G. Mackenzie, *Carbohydr. Res.*, **267**, 203 (1995).
284. J. Boivin, L. Ramos and S. Z. Zard, *Tetrahedron Lett.*, **39**, 6877 (1998).
285. C. Birk, J. Voss and J. Wirsching, *Carbohydr. Res.*, **304**, 239 (1997).
286. J. H. Hong, M.-Y. Gao and C. K. Chu, *Tetrahedron Lett.*, **40**, 231 (1999).
287. J. Brånalt, I. Kvarnström, G. Niklasson, S. C. T. Svensson, B. Classon and B. Samuelsson, *J. Org. Chem.*, **59**, 1783 (1994).

288. J. Brånalt, I. Kvarnström, S. C. T. Svensson, B. Classon and B. Samuelsson, *J. Org. Chem.*, **59**, 4430 (1994).
289. J. Mann, A. J. Tench, A. C. Weymouth-Wilson, S. Shaw-Ponter and R. J. Young, *J. Chem. Soc., Perkin Trans. 1*, 677 (1995).
290. K. Kato and S. Yamamura, *Nucleosides & Nucleotides*, **18**, 657 (1999).
291. F. De Valette, J.-L. Barascut and J.-L. Imbach, *Nucleosides & Nucleotides*, **17**, 2289 (1998).
292. H. O. Kim, L. S. Jeong, S. N. Lee, S. J. Yoo, H. R. Moon, K. S. Kim and M. W. Chun, *J. Chem. Soc., Perkin Trans. 1*, 1327 (2000).
293. J. A. Secrist III, R. M. Riggs, K. N. Tiwari and J. A. Montgomery, *J. Med. Chem.*, **35**, 533 (1992).
294. G. Rassu, P. Spanu, L. Pinna, F. Zanardi and G. Casiraghi, *Tetrahedron Lett.*, **36**, 1941 (1995).
295. R. J. Young, S. Shaw-Ponter, J. B. Thomson, J. A. Miller, J. G. Cumming, A. W. Pugh and P. Rider, *Bioorg. Med. Chem. Lett.*, **5**, 2599 (1995).
296. E. L. Hancox and R. T. Walker, *Nucleosides & Nucleotides*, **15**, 135 (1996).
297. M. E. Jung and O. Kretschik, *J. Org. Chem.*, **63**, 2975 (1998).
298. M. E. Jung, C. J. Nichols, O. Kretschik and Y. Xu, *Nucleosides & Nucleotides*, **18**, 541 (1999).
299. A. C. MacCulloch and R. T. Walker, *Tetrahedron*, **54**, 12457 (1998).
300. A. C. MacCulloch, P. L. Coe and R. T. Walker, *J. Chem. Soc., Perkin Trans. 1*, 335 (1999).
301. L. Hancox, B. A. Connolly and R. T. Walker, *Nucleic Acids Res.*, **21**, 3485 (1993).
302. S. M. Siddiqi, K. A. Jacobson, J. L. Esker, M. E. Olah, X. Ji, N. Melman, K. N. Tiwari, J. A. Secrist III, S. W. Schneller, G. Cristalli, G. L. Stiles, C. R. Johnson and A. P. Ijzerman, *J. Med. Chem.*, **38**, 1174 (1995).
303. C. Leydier, L. Bellon, J.-L. Barascut, J. Deydier, G. Maury, H. Pelicano, M. A. El Alaoui and J.-L. Imbach, *Nucleosides & Nucleotides*, **13**, 2035 (1994).
304. T. Naka, N. Minakawa, H. Abe, D. Kaga and A. Matsuda, *J. Am. Chem. Soc.*, **122**, 7233 (2000).
305. P. Franchetti, S. Marchetti, L. Cappellacci, M. Grifantini, B. M. Goldstein, D. Dukhan, J.-L. Barascut and J.-L. Imbach, *Nucleosides & Nucleotides*, **18**, 679 (1999).
306. P. Franchetti, S. Marchetti, L. Cappellacci, H. N. Jayaram, J. A. Yalowitz, B. M. Goldstein, J.-L. Barascut, D. Dukhan, J.-L. Imbach and M. Grifantini, *J. Med. Chem.*, **43**, 1264 (2000).

307. L. Bellon, J.-L. Barascut, G. Maury, G. Divita, R. Goody and J.-L. Imbach, *Nucleic Acids Res.*, **21**, 1587 (1993).
308. C. Leydier, L. Bellon, J.-L. Barascut and J.-L. Imbach, *Nucleosides & Nucleotides*, **14**, 1027 (1995).
309. C. Leydier, L. Bellon, J.-L. Barascut, F. Morvan, B. Rayner and J.-L. Imbach, *Antisense Res. Dev.*, **5**, 167 (1995).
310. D. Dukhan, F. De Valette, R. Marquet, B. Ehresmann, C. Ehresmann, F. Morvan, J.-L. Barascut and J.-L. Imbach, *Nucleosides & Nucleotides*, **18**, 1423 (1999).
311. Y. Yoshimura, M. Watanabe, H. Satoh, N. Ashida, K. Ijichi, S. Sakata, H. Machida and A. Matsuda, *J. Med. Chem.*, **40**, 2177 (1997).
312. J. A. Secrist III, K. N. Tiwari, A. T. Shortnacy-Flower, L. Messini, J. M. Riordan and J. A. Montgomery, *J. Med. Chem.*, **41**, 3865 (1998).
313. K. N. Tiwari, A. T. Shortnacy-Fowler, L. Cappellacci, W. B. Parker, W. R. Waud, J. A. Montgomery and J. A. Secrist III, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 329 (2000).
314. Y. Yoshimura, K. Kitano, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki and A. Matsuda, *J. Org. Chem.*, **61**, 822 (1996).
315. Y. Yoshimura, K. Kitano, K. Yamada, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki and A. Matsuda, *J. Org. Chem.*, **62**, 3140 (1997).
316. H. Satoh, Y. Yoshimura, S. Sakata, S. Miura, H. Machida and A. Matsuda, *Bioorg. Med. Chem. Lett.*, **8**, 989 (1998).
317. J. Wirsching and J. Voss, *Eur. J. Org. Chem.*, 691 (1999).
318. J. Wirsching, J. Voss, J. Balzarini and E. De Clercq, *Bioorg. Med. Chem. Lett.*, **10**, 1339 (2000).
319. S. A. Hartsel and W. S. Marshall, *Tetrahedron Lett.*, **39**, 205 (1998).
320. Y. Yoshimura, K. Kitano, M. Watanabe, H. Satoh, S. Sakata, S. Miura, N. Ashida, H. Machida and A. Matsuda, *Nucleosides & Nucleotides*, **16**, 1103 (1997).
321. S. Miura, Y. Yoshimura, M. Endo, H. Machida, A. Matsuda, M. Tanaka and T. Sasaki, *Cancer Lett.*, **129**, 103 (1998).
322. Y. Yoshimura, M. Endo, S. Miura and S. Sakata, *J. Org. Chem.*, **64**, 7912 (1999).
323. Y. Yoshimura, M. Endo and S. Sakata, *Tetrahedron Lett.*, **40**, 1937 (1999).
324. Y. Yoshimura, M. Endo, K. Kitano, K. Yamada, S. Sakata, S. Miura and H. Machida, *Nucleo-*

- sides & Nucleotides*, **18**, 815 (1999).
325. L. S. Jeong, H. R. Moon, S. J. Yoo, S. N. Lee, M. W. Chun and Y.-H. Lim, *Tetrahedron Lett.*, **39**, 5201 (1998).
 326. L. S. Jeong, H. R. Moon, Y. J. Choi, M. W. Chun and H. O. Kim, *J. Org. Chem.*, **63**, 4821 (1998).
 327. L. S. Jeong, H. R. Moon, S. J. Yoo, S. N. Lee, H.-D. Kim and M. W. Chun, *Nucleosides & Nucleotides*, **18**, 571 (1999).
 328. J. A. Miller, A. W. Pugh and G. M. Ullah, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 1475 (2000).
 329. H. Satoh, Y. Yoshimura, M. Watanabe, N. Ashida, K. Ijichi, S. Sakata, H. Machida and A. Matsuda, *Nucleosides & Nucleotides*, **17**, 65 (1998).
 330. Y. Yoshimura, K. Kitano, K. Yamada, S. Sakata, S. Miura, N. Ashida and H. Machida, *Bioorg. Med. Chem.*, **8**, 1545 (2000).
 331. K. Yamada, S. Sakata and Y. Yoshimura, *J. Org. Chem.*, **63**, 6891 (1998).
 332. J. Y. Feng and K. S. Anderson, *Biochemistry*, **38**, 55 (1999).
 333. L. S. Jeong, R. F. Schinazi, J. W. Beach, H. O. Kim, K. Shanmuganathan, S. Nampalli, M. W. Chun, W.-K. Chung, B. G. Choi and C. K. Chu, *J. Med. Chem.*, **36**, 2627 (1993).
 334. T. S. Mansour, H. Jin, W. Wang, E. U. Hooker, C. Ashman, N. Cammack, H. Salomon, A. R. Belmonte and M. A. Wainberg, *J. Med. Chem.*, **38**, 1 (1995).
 335. T. S. Mansour, H. Jin, W. Wang, D. M. Dixit, C. A. Evans, H. L. A. Tse, B. Belleau, J. W. Gillard, E. Hooker, C. Ashman, N. Cammack, H. Salomon, A. R. Belmonte and M. A. Wainberg, *Nucleosides & Nucleotides*, **14**, 627 (1995).
 336. M. W. Chun, D. H. Shin, H. R. Moon, J. Lee, H. Park and L. S. Jeong, *Bioorg. Med. Chem. Lett.*, **7**, 1475 (1997).
 337. M. W. Chun, S. P. Choi, M. J. Kim, C. J. Bae, H. R. Moon, H.-D. Kim and L. S. Jeong, *Nucleosides & Nucleotides*, **18**, 615 (1999).
 338. Y. Choi, L. Li, S. Grill, E. Gullen, C. S. Lee, G. Gumina, E. Tsujii, Y.-C. Cheng and C. K. Chu, *J. Med. Chem.*, **43**, 2538 (2000).
 339. R. Caputo, A. Guaragna, G. Palumbo and S. Pedatella, *Nucleosides & Nucleotides*, **17**, 1739 (1998).
 340. R. Caputo, A. Guaragna, G. Palumbo and S. Pedatella, *Eur. J. Org. Chem.*, 1455 (1999).

341. N. Nguyen-Ba, W. L. Brown, L. Chan, N. Lee, L. Brasili, D. Lafleur and B. Zacharie, *J. Chem. Soc., Chem. Commun.*, 1245 (1999).
342. A.-S. Charvet, M. Camplo, P. Faury, J.-C. Graciet, N. Mourier, J.-C. Chermann and J.-L. Kraus, *J. Med. Chem.*, **37**, 2216 (1994).
343. M. Camplo, N. Mourier, J.-C. Chermann and J.-L. Kraus, *Nucleosides & Nucleotides*, **18**, 879 (1999).
344. A. Karpeisky, S. Zavgorodny, M. Hotokka, M. Oivanen and H. Lönnberg, *J. Chem. Soc., Perkin Trans. 2*, 741 (1994).
345. G. Tusa and J. K. Reed, *Nucleosides, Nucleotides & Nucleic acids*, **19**, 805 (2000).
346. P. Herdewijn, *Liebigs Ann.*, 1337 (1996).
347. M. Egli, *Antisense Nucleic Drug Dev.*, **8**, 123 (1998).
348. P. Herdewijn, *Biochem. Biophys. Acta*, **1489**, 167 (1999).
349. M. Meldgaard and J. Wengel, *J. Chem. Soc., Perkin Trans. 1*, 3539 (2000).
350. R. Kumar, S. K. Singh, A. A. Koshkin, V. K. Rajwanshi, M. Meldgaard and J. Wengel, *Bioorg. Med. Chem. Lett.*, **8**, 2219 (1998).
351. S. K. Singh, R. Kumar and J. Wengel, *J. Org. Chem.*, **63**, 6078 (1998).
352. J. Wengel, A. Koshkin, S. K. Singh, P. Nielsen, M. Meldgaard, V. K. Rajwanshi, R. Kumar, J. Skouv, C. B. Nielsen, J. P. Jacobsen, N. Jacobsen and C. E. Olsen, *Nucleosides & Nucleotides*, **18**, 1365 (1999).
353. M. J. Perez, A. Sanfeliix, M. J. Camasara, J. Balzarini and E. De Clercq, *Tetrahedron Lett.*, **33**, 3029 (1992).
354. R. Alvarez, M. L. Jimeno, F. Gago, J. Balzarini, M. J. Perez-Perez and M. J. Camarasa, *Antivir. Chem. Chemother*, **9**, 333 (1998).
355. S. Velazquez, R. Alvarez, C. Perez, F. Gago, E. De Clercq, J. Balzarini and M. J. Camarasa, *Antivir. Chem. Chemother*, **9**, 481 (1998).
356. N. Sluis-Cremer, G. I. Dmitrienko, J. Balzarini, M.-J. Camarasa and M. A. Parniak, *Biochemistry*, **39**, 1427 (2000).

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