Chemical Synthesis of Heterocyclic−Sugar Nucleoside Analogues

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Contents

1. Introduction

A variety of nucleoside analogues have now been discovered which expand the antiviral and anticancer spectrum and/or modify the pharmacological and/or pharmacokinetic properties of the parent compounds.[1] In terms of their structure nucleosides can be considered to be constituted by three key elements: (i) the hydroxymethyl group, which is necessary for the phosphorylation of the molecule by kinases in order to achieve biological activity, (ii) the heterocyclic base moiety, which is implied in the recognition process of the nucleoside through specific hydrogen bonds, and (iii) the furanose ring, which in several instances seems to act as a spacer presenting the hydroxymethyl group and the base in the correct orientation (Figure 1).

A lot of structural modifications have been described, many of them having been successfully developed as therapeutic agents in medicine.[2] Indeed, several compounds modified in the sugar have been developed as antiviral agents.[3] Most of them have several common features. For instance, they do not have the 3′ hydroxyl group. An exception is fialuridine, which has that group but inhibits reverse transcription (it has a potent anti-HBV activity). Some variations of the base moiety are also present, and only variations on the substituents of the furanose ring were studied extensively; in this way substances like the well-known AZT or other 2′,3′-deoxynucleosides have appeared (Figure 2).[4] However, it has also been found that nucleoside analogues with modified substituents in the furanose ring have several disadvantages, including chemical instability and clinical toxicity.[5]

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Giovanni Romeo was born in Giarre (CT), Italy. He received his Doctoral degree in Chemistry from the University of Messina. After a postdoctoral position at the University of Messina, he was appointed as Associate Professor of Chemistry at the Department Farmaco-Chimico of the University of Messina in 1982 and in 1990 was promoted to Full Professor of Organic Chemistry. He has held visiting positions at University Chemical Laboratory, Cambridge (U.K.), at the Department of Organic Chemistry of the University of Zaragoza (Spain), and at the Department of Chemistry University of Bergen (Norway). He is coauthor of more than 180 publications. His research interests focus on heterocyclic chemistry, asymmetric dipolar cycloaddition, and synthesis of bioactive heterocycles. Currently, his activity is focused on topics related to the synthesis of potential antiviral drugs and carrier models for their intracellular delivery.

With the aim of overcoming these drawbacks, several studies have been directed to analogues in which the furanose ring has been replaced by a different five-membered ring system including carbocycles. Pioneering examples of this new generation of compounds are carbovir,[6] lobucavir,[7] dioxolane T,[8] or lamivudine[9] (Figure 3).

It is also worth noting, in the case of lamivudine, that if we consider the sulfur atom as an additional one within the furanose ring, lamivudine can be seen as a nucleoside of L-series.[10] Accordingly, both series of enantiomers in nucleoside analogues synthesis should be taken into consideration.[11]

The main theme of this section deals with the synthesis of nucleoside analogues in which the spacer is a heterocyclic system different from tetrahydrofuran, which are referred to as *heterocyclic nucleosides*[12] by analogy to *carbocyclic nucleosides*. The latter compounds are not considered, and the reader should refer to other reviews that have previously been reported.[13]

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Ugo Chiacchio was born in Catania, Italy. He received his Doctoral degree in Chemistry in 1972 from the University of Catania. In 1974 he worked as Ricercatore Universitario in the Department of Chemical Sciences of the University of Catania. From 1977 to 1979 he had a postdoctoral position at the State University of New York in Buffalo with Professor Albert Padwa and from 1982 to 1984 as a NATO fellow at Emory University, Atlanta, GA. He was appointed Associate Professor at the University of Catania in 1987, and in 2000 he was nominated Full Professor. He is coauthor of more than 140 publications. His recent research interests focus on asymmetric dipolar cycloaddition, synthesis of bioactive heterocycles, and modified nucleosides.

Antonino Corsaro, born in 1945 in S. Gregorio of Catania (Italy), is Full Professor of Organic Chemistry in the Faculty of Pharmacy at Catania University. His scientific activity, performed at the Department of Chemical Sciences of Catania University, is concerned with organic synthetic methodologies, reactive intermediates, and reaction mechanisms, mainly in the field of the chemistry regarding 1,3-dipolar cycloaddition reactions and that of carbohydrates. Recently, his main interest is directed toward the study of nitrone, nitril oxide, and thiocarbonyl ylid reactions affording suitably substituted heterocycles which act as nucleoside analogues. His secondary interest is the chemical valorization of lactose that he pursues by conducting research on (a) modulation of the chemical and physical properties of new lactose-based prodrugs and (b) simplification of lactose chemical and stereochemical iper functionalities in order to approach simpler chiral molecules equipped with distinct functional groups to be used on a medium to large scale as chiral building blocks for the fine and secondary chemistry.

Among the several possibilities for heterocyclic nucleosides we considered both only replacement of the oxygen atom of the furanose by a different heteroatom, like in thioanalogues and azanucleosides, and addition of a second heteroatom, that is, the case of isoxolanyl, oxathiolanyl, thiazolidinyl, oxazolidinyl, and isoxazolidinyl analogues (Figure 4). The chemistry of these nucleoside analogues will be described according to the heterocyclic ring acting as a spacer.

Pedro Merino graduated with an Honors M.Sc. degree in Chemistry from the University of Zaragoza in 1986. After earning his Ph.D. degree in Organic Chemistry from the same university in 1989 under the guidance of Professor Enrique Melendez, he spent two years as a postdoctoral fellow with Professor Alessandro Dondoni at the University of Ferrara (Italy), working on thiazole chemistry applied to asymmetric synthesis. In 1992 he returned to the University of Zaragoza as an Assistant Professor, where he started his independent research. In 1994 he was promoted to Associate Professor, and in 2005 he got his habilitation as Full Professor in Organic Chemistry. In 2006 he won a Chair in Organic Chemistry at the Department of Organic Chemistry of the University of Zaragoza. He is coauthor of more than 150 papers, and his research interests span the areas of asymmetric synthesis of biologically active compounds such as nucleoside analogues, amino acids, target-oriented synthesis, organometallic chemistry, and asymmetric metal-assisted and organic catalysis.

2. Heterocyclic Nucleosides with One Heteroatom

2.1. Pyrrolidinyl Nucleosides

The chemistry of pyrrolidinyl nucleosides, also referred to as azanucleosides, has been reviewed elsewhere.[14] Typical analogues are those in which the furanose ring has been replaced by a pyrrolidine ring and the glycosyl bond is maintained between C-2 and the nitrogen atom of the base

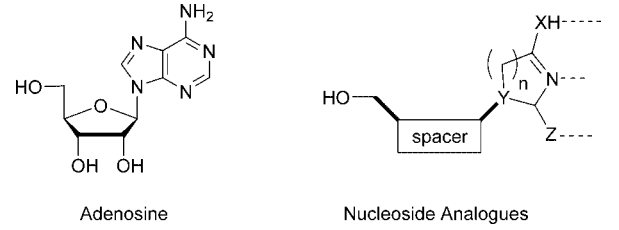


Figure 1.

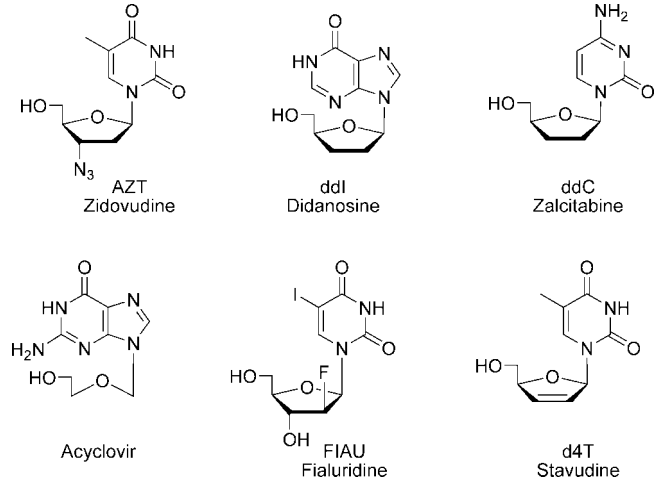


Figure 2.

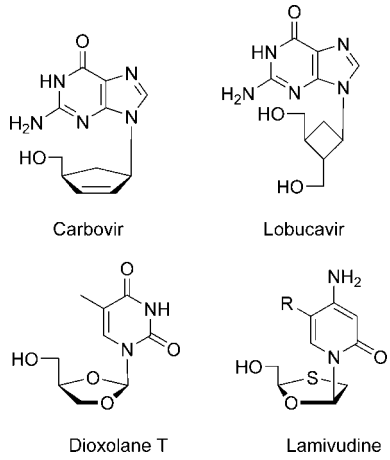


Figure 3.

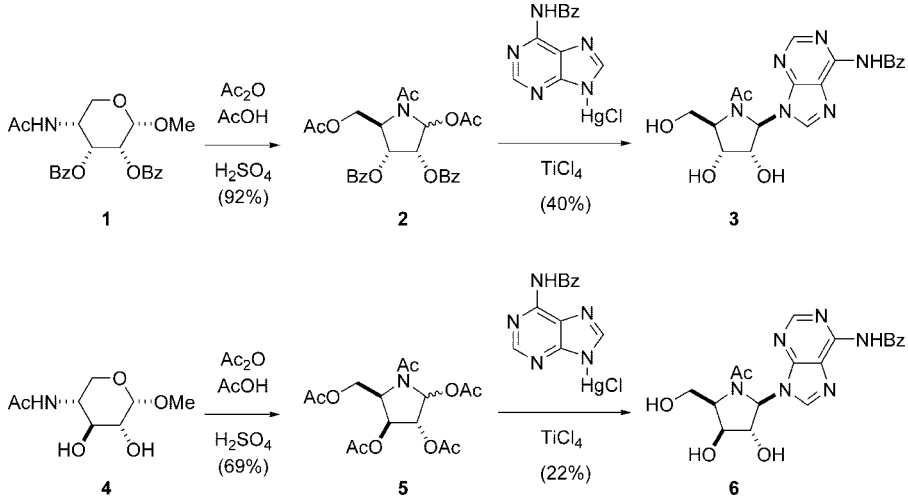
moiety. In most cases, the endocyclic nitrogen atom is conveniently protected, although in several instances it can be deprotected too.

Transformation of protected aminosugars into pyrrolidines ready to N-glycosylation processes has been a typical method for the synthesis of pyrrolidinyl nucleosides. As a first example in 1966, compound **1** was transformed into pyrrolidine **2**, which was subjected to N-glycosylation to give nucleoside **3** (Scheme 1).[15] The same methodology was applied to diastereoisomer **5**, although in this case the chemical yields were lower.[16] Open-chain aminosugar derivatives can also be used as starting materials. Thus, compound **7** was converted to **8**, which was treated with bis(trimethylsilyl)thymine to afford **9** (Scheme 2).[17]

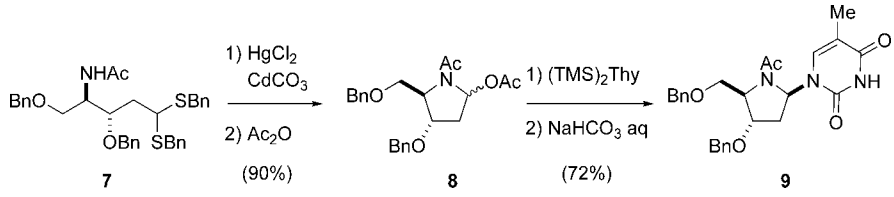
The 2-alkoxy pyrrolidines precursors (e.g., **2**, **5**, or **8**) can also be prepared from the corresponding 2-pyrrolidinones by reductive methods. The reduction is achieved with $LiEt_3BH$, which furnishes the free hemiaminal, which is in situ methylated for further coupling with silylated bases. An example of this methodology has been described by Rassu et al. for the synthesis of **12** (Scheme 3).[18]

The same authors described the synthesis of **15** by acetylating the intermediate hemiaminal. In this case, the

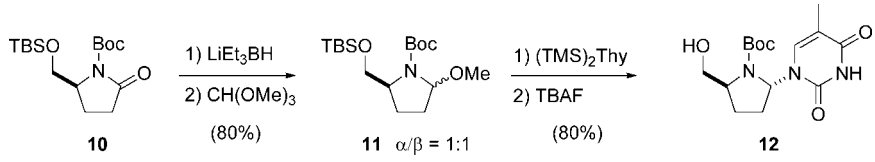
Scheme 1



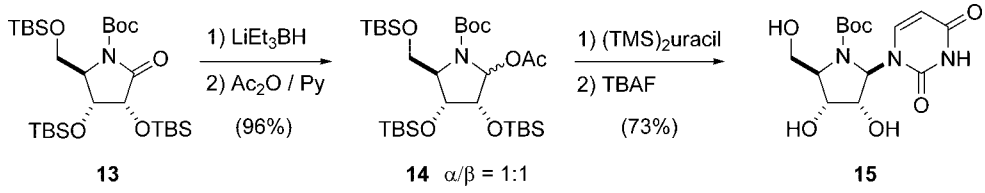
Scheme 2



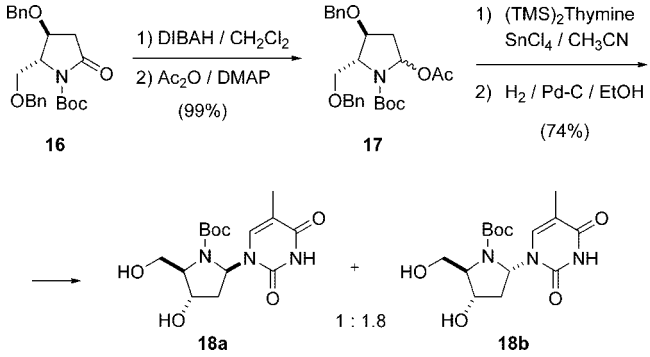
Scheme 3



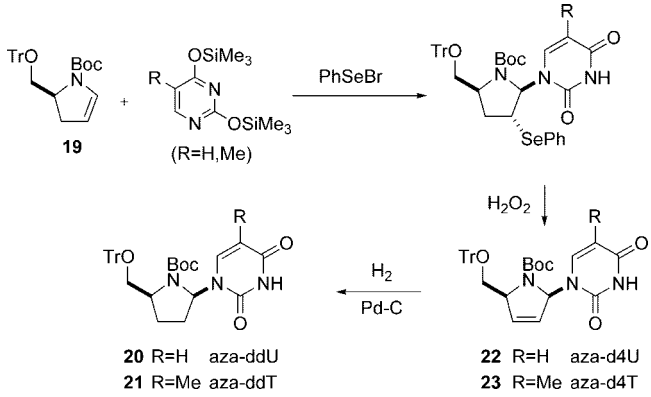
Scheme 4



Scheme 5



Scheme 6



presence of substituents at the pyrrolidine ring allowed the obtention of the cis isomer (Scheme 4).

Although the reduction of the lactam moiety has usually been performed with superhydride ($LiEt_3BH$), it is also possible to use other reducing agents such as DIBAH. Huang et al. described the preparation of nucleosides **18** using as a starting material pyrrolidinone **16**.[19] The reduction took place with an almost quantitative yield, and the final nucleoside analogues were obained in quite high overall yield and in a 1.8:1 α/β ratio (Scheme 5).

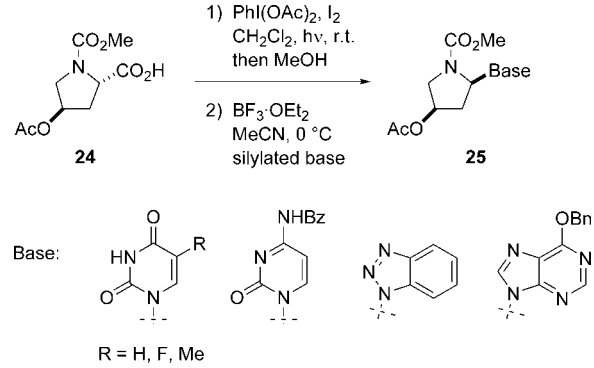
Particularly interesting is the last deprotection step, in which the benzyl groups are eliminated by hydrogenolysis without affecting the double bond of the thymine.

The direct addition of a silylated base to a cyclic enamine **19** in the presence of an activant such as *N*-iodosuccinimide or phenylselenyl bromide has also been described for preparing pyrrolidinyl nucleosides. By using the latter, the corresponding analogues to d4T, d4U, ddU, and ddT were obtained (Scheme 6).[20]

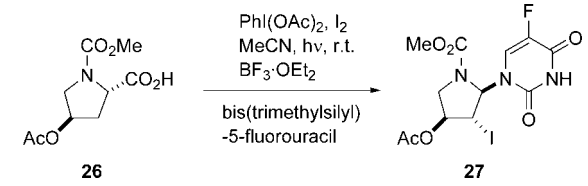
Cyclic amino acids, derived from both proline and *trans*-4-hydroxyproline, were readily transformed into azanucleosides in a one-pot procedure through a radical decarboxylation process initiated by (diacetoxy)iodobenzene and iodine under visible light irradiation.[21] The process showed a good scope, being compatible with several bases, and the corresponding azanucleosides **25** were obtained in good yields (Scheme 7).

When excess of iodine was added and acetonitrile was used as a solvent, a scission−β-iodination−base addition process took place (Scheme 8). The authors invoked a polar mechanism favored by the polarity of the solvent in contrast to the radical mechanism postulated when dichloromethane was used as a solvent. Such a polar mechanism caused generation in situ of enamine, which reacted with iodine when regenerating the intermediate iminium ion. The introduction of an extra iodine atom gives the possibility of further functionalization of the pyrrolidine ring.

Scheme 7



Scheme 8



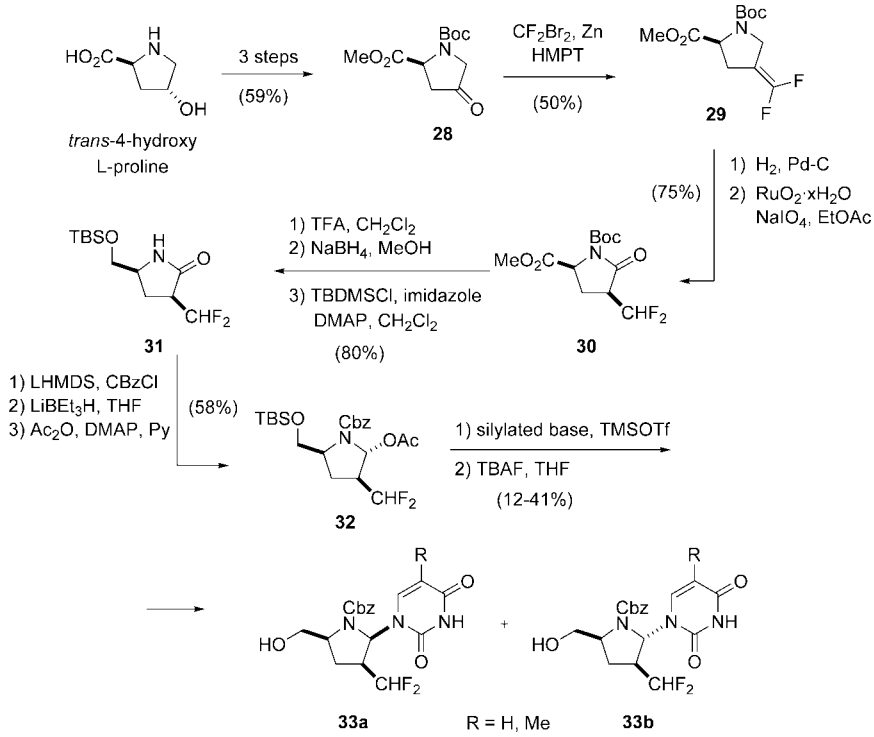
The presence of a fluorine atom in biologically active molecules has been widely implemented as the strong carbon−fluoride bond is particularly resistant to metabolic transformations. 2′,3′-Dideoxy-2′-difluoromethyl azanucleosides have been prepared from *trans*-4-hydroxy proline via a difluoromethylenation reaction of the oxidized starting material (Scheme 9).[22] The N-Boc-protected intermediate **30** could not be reduced at the lactam moiety, and it was necessary to exchange the Boc protecting group by the Cbz group. After reduction and acetylation intermediate **32** was obtained in 58% yield. Glycosylation of **32** with silylated thymine and uracil afforded the corresponding azanucleosides **33**. Noteworthy, when glycosylation was carried out with uracil the cis isomer was predominant (cis/trans 2.5:1), whereas in the case of thymine the trans adduct was obtained preferentially (cis/trans 1:3.5). In this case, illustrated in Scheme 9, the chemical yields of the final glycosylation step were lower than usual; this behavior was attributed to the presence of fluorine atoms.

The same authors used the strategy depicted in Scheme 9 for preparing 3′-deoxy-3′-difluoromethyl azanucleosides **38** and **39**.[23] The introduction of the additional hydroxyl group was carried out from the unsaturated derivative **34**, which was further transformed into intermediate **35**. Interestingly, the two diastereomers **36** and **37** could be prepared in a preferential way by selecting hydrogenation conditions. Starting from these hydrogenated adducts both *cis*- and *trans*-azanucleosides **38** and **39** were prepared using thymine and uracil as heterocyclic bases (Scheme 10).

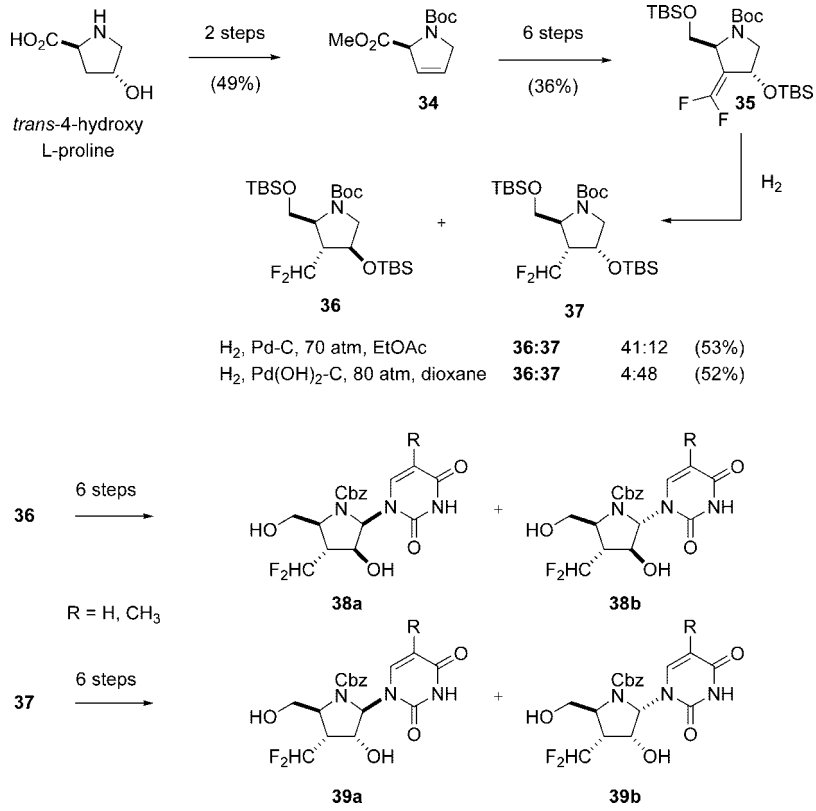
Aza analogues of ganciclovir have been prepared from pyrrolidin-2-one **41** obtained from nitrodioxirane **40**.[24] Both purine and pyrimidine nucleobases could be introduced by activation with trimethylsilyl triflate. Further deprotection of intermediates afforded the corresponding nucleoside analogues (Scheme 11).

Homonucleoside analogues containing a pyrrolidine ring as a spacer has also been reported by Wong et al.[25] Compounds **44** were prepared from precursor **43** in only 9% isolated yield after the deprotection steps (Scheme 12).

Scheme 9



Scheme 10



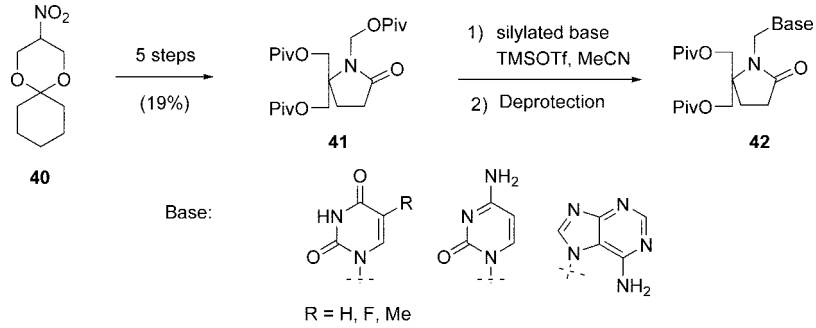
A Mitsunobu reaction was employed by Verdine et al.[26] to introduce the base moiety into homonucleoside **46** (Scheme 13). This product was further used in the preparation of the mimic transition state **47** for DNA hydrolysis. The key intermediate **45** was prepared from L-serine in 9 steps.

The same type of substitution reaction was used by Peterson and Vince for synthesizing pyrrolidinyl nucleosides in which the base moiety is linked to the C-4 of the pyrrolidine ring (Scheme 14).[27]

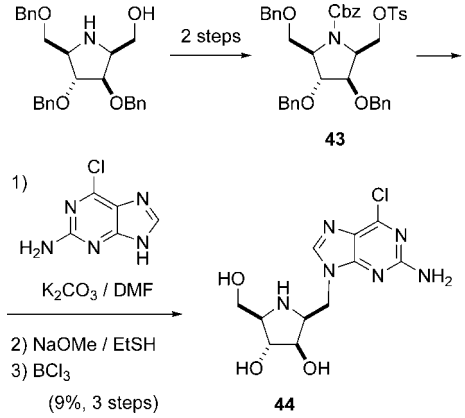
Nucleoside analogues similar to **49** were prepared by constructing the heterocyclic ring as illustrated in Scheme 15.[28] The corresponding L-enantiomers were also prepared following the same reaction sequence.[29]

Intermediates of type **48** are also of importance because they are constituents of peptide nucleic acids. Starting from

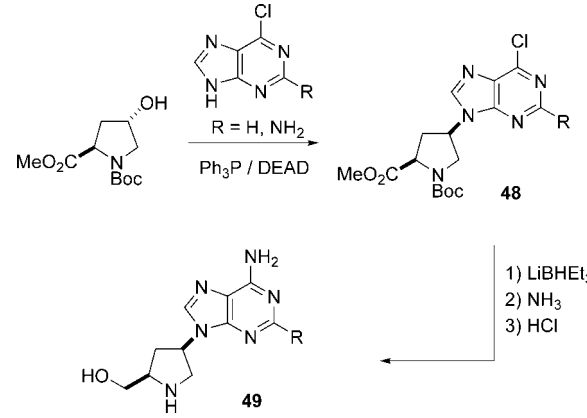
Scheme 11



Scheme 12



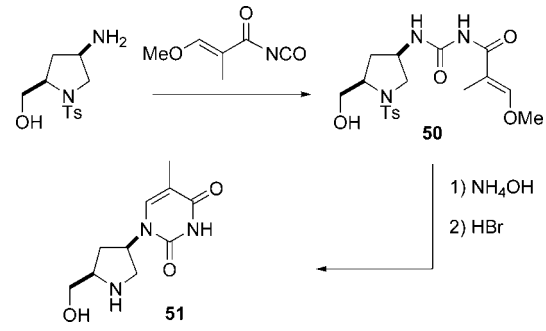
Scheme 14



trans-4-hydroxy-L-proline Lowe et al.[30] synthesized a series of proline nucleosides **52** which were used for preparing peptide nucleic acids like oligothymine **53** (Scheme 16).

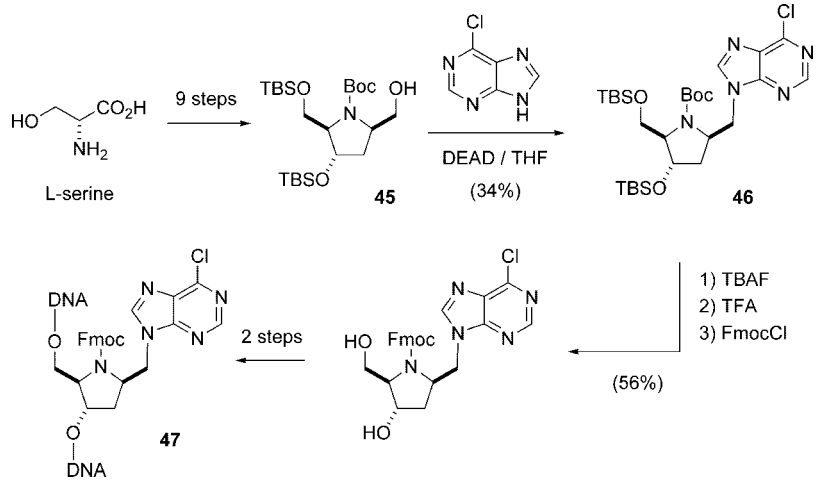
Structural modifications of **53** such as the insertion of proline and lysine spacers led to increasing binding between PNA analogues and DNA.[31] However, many different structures are possible for PNA analogues,[32] and a considerable effort has been made by several groups in order to prepare the corresponding monomers. Common features for these monomers are the presence of amino and acid groups connected by a pyrrolidine bearing a heterocyclic base. Compounds **54** and **55** are examples of monomers easily accessible from the corresponding 4-hydroxyproline isomer. Oligomers formed from those compounds led to the formation of DNA:PNA chimeras.[33] Compounds **56** and **57** are examples of oligomers capable of forming duplexes with DNA[34] and RNA (Figure 5).[35]

Scheme 15

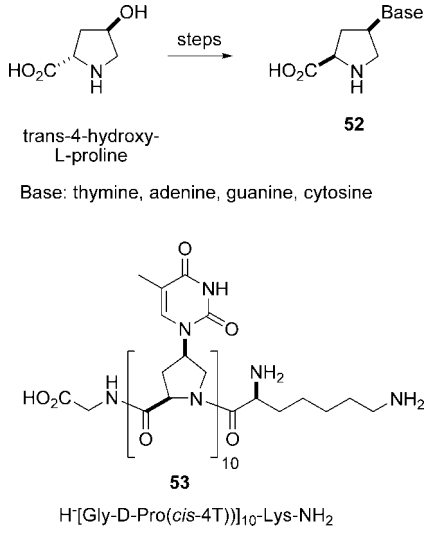


Nielsen et al. prepared pyrrolidinyl nucleoside **58** starting from *cis*-4-hydroxy-D-proline (Scheme 22) in 13 steps and 2.8% overall yield.[36] PNA oligomers prepared from **59** showed strong affinity toward both DNA and RNA. Struc-

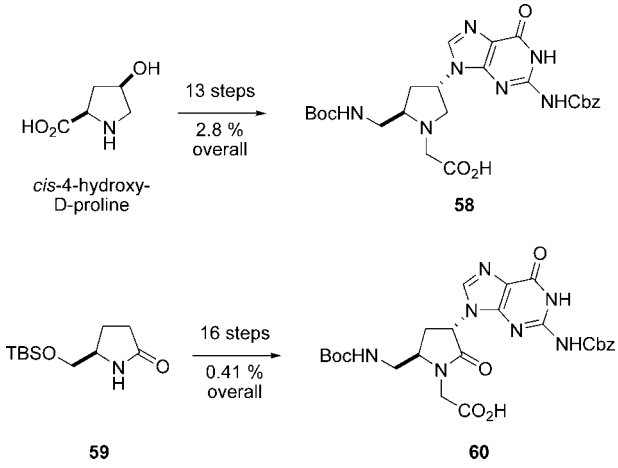
Scheme 13



Scheme 16

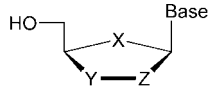


Scheme 17



tural modification of the pyrrolidine ring by addition of a carbonyl, thus transforming the heterocycle into a lactam, was achieved starting from pyroglutamic acid derivative **59**. Compound **60** was prepared in 16 steps and only 0.41% overall yield (Scheme 17).[37]

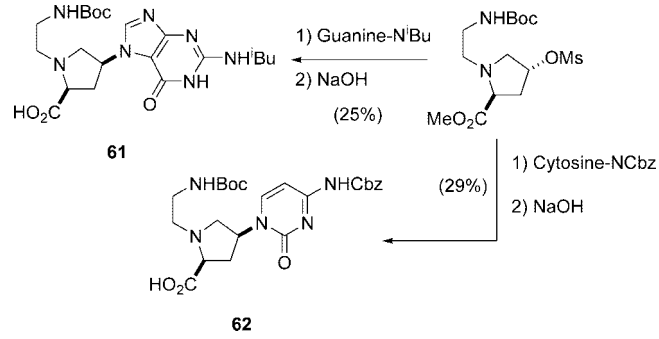
Kumar et al. reported the synthesis of PNA monomers **61** and **62** in which the N-terminal was linked to the endocyclic nitrogen through a two-carbon bridge (Scheme 18).[38] As usual in this type of reaction the substitution reaction took place with low chemical yield.



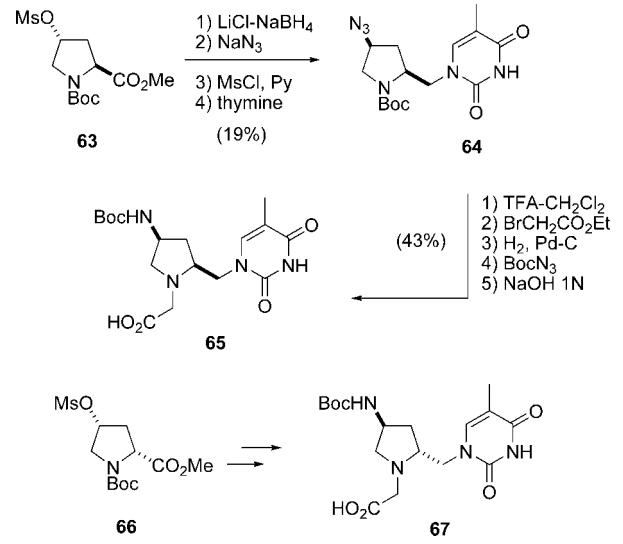
Conventional	X = O	Y, Z = CHOH, CH_2, CH=CH, $CHNH_2$
Thioanalogs	X = S	Y, Z = CHOH, CH_2, CH=CH, $CHNH_2$
Aza Nucleosides	X = NR	Y, Z = CHOH, CH_2, CH=CH, $CHNH_2$
Carbocyclic	X = CH_2	Y, Z = CHOH, CH_2, CH=CH, $CHNH_2$
Dioxolanyl	X = O	Y = CH_2 Z = O; or Y = O Z = CH_2
Oxathiolanyl	X = O	Y = S Z = CH_2; or Y = CH_2 Z = S
Thiazolidinyl	X = NR	Y = CH_2 Z = S
Oxazolidinyl	X = NR	Y = CH_2 Z = O
Isoxazolidinyl	X = CH_2	Y = NR Z = O

Figure 4.

Scheme 18



Scheme 19



A modification to PNA monomers consisting of the addition of a methylene bridge between the base moiety and the pyrrolidine has been reported by the same authors. Compound **65** was obtained from the adequately functionalized *trans*-4-hydroxy-D-proline **63** in 9 steps and 8.2% overall yield (Scheme 19). In a similar way, the trans isomer **67** was obtained following the same reaction sequence from the commercially available *cis*-4-hydroxy-D-proline.[39]

Novel PNA oligomers **70** have been prepared by employing solid-phase techniques and using monomers **69** (Scheme 20). These monomers were prepared from aminoalcohol **68**, easily accessible from *trans*-4-hydroxy-D-proline, in 23−27% overall yield.[40]

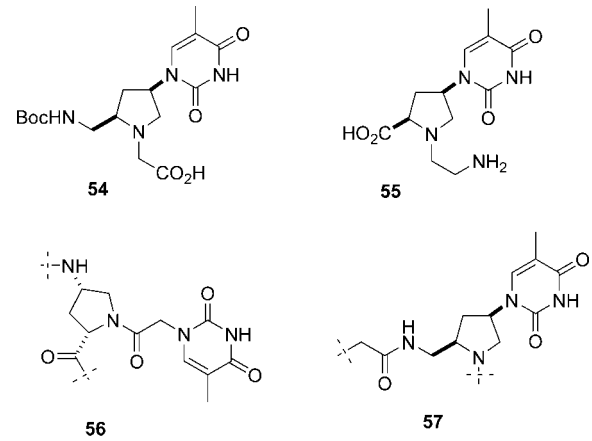
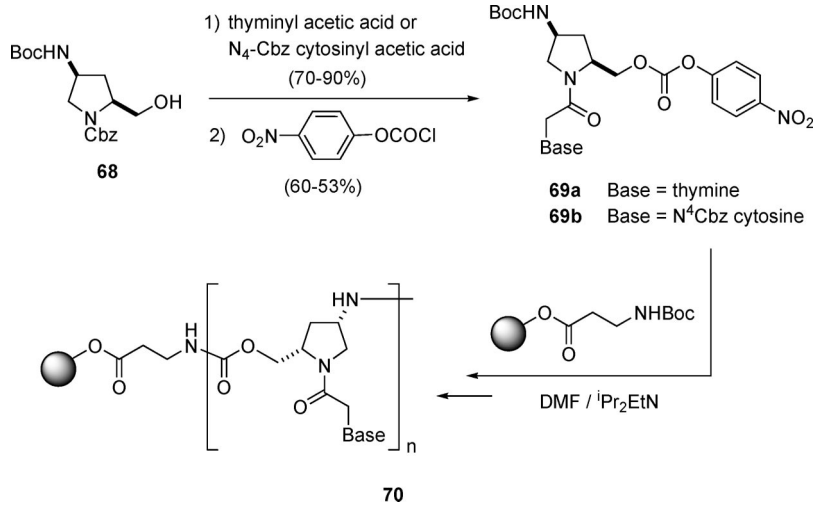
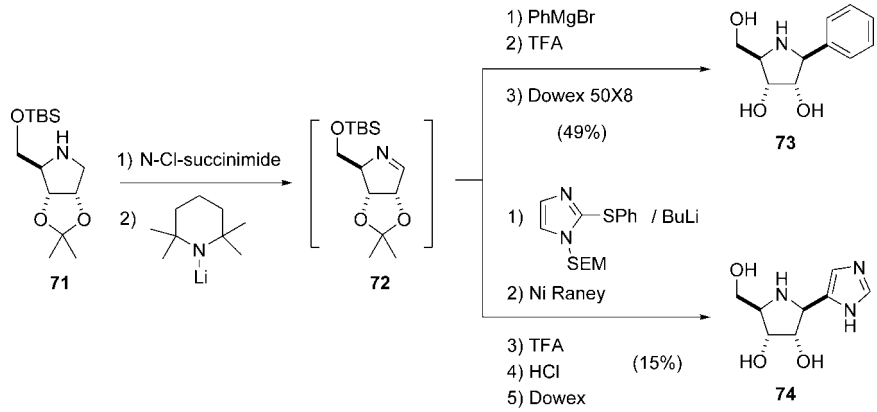


Figure 5.

Scheme 20



Scheme 21



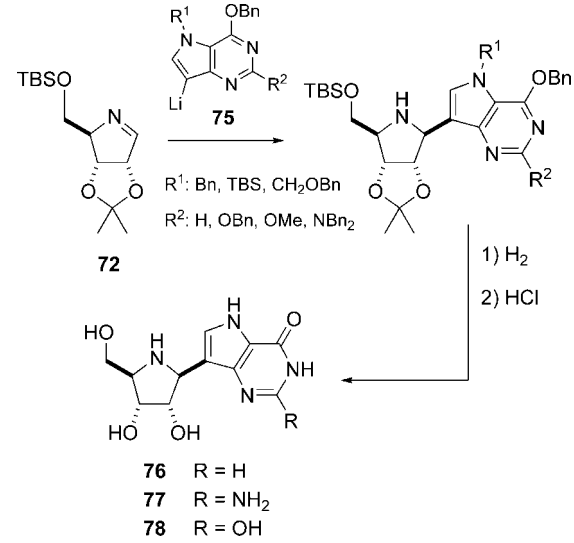
Another class of pyrrolidinyl nucleosides that has gained attention during the past decade is that in which the base moiety is directly linked to the pyrrolidine ring by a nonhydrolizable carbon−carbon bond. The resulting compounds are the so-called C-azanucleosides. The introduction of the base into the pyrrolidine ring can be carried out either by a direct addition of the heterocycle to a cyclic imine (or enamine) or by constructing the heterocyclic base over an adequate substituent of the pyrrolidine ring.

The nucleophilic addition of phenylmagnesium bromide and lithiated imidazole to the cyclic imine **72** generated in situ from pyrrolidine **71** afforded the corresponding adducts which after suitable deprotection led to nucleoside analogues **73** and **74**, respectively (Scheme 21).[41] The low overall yield observed for **74** was due to the addition step which took place with only 26% isolated yield.

Other C-azanucleosides similar to **73** have been prepared by using substituted phenyl rings and further explored for biological activity as trypanosomal nucleoside hydrolases inhibitors.[42] Indeed, several C-azanucleosides, referred to as immucillins, have been described to be potent inhibitors of purine nucleoside phosphorylase[43] and other hydrolases from protozoan parasites.[44] Such a biological activity makes it so that immucillins can be considered as potential therapeutic agents for the treatment of important pathologies like malaria[45] and several autoimmune diseases.[46]

Immucillins **76**−**78** were prepared by stereoselective nucleophilic addition of lithiated 9-deazapurines **75** to imine **72** (Scheme 22).[47]

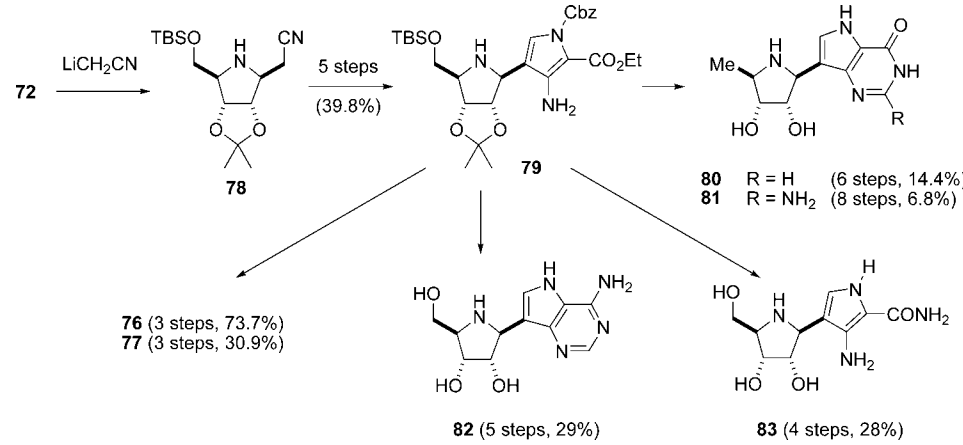
Scheme 22



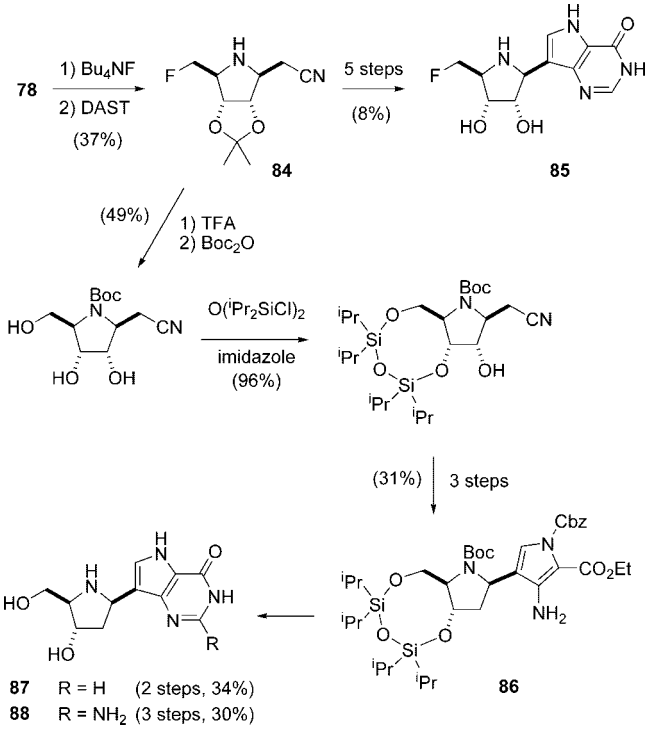
Different analogues of immucillins were also prepared by constructing the heterocyclic ring over the adequate substituents of the pyrrolidine ring. Tyler et al.[48] reported the preparation of several immucillins including **76**, **77**, and **80**−**83** starting from **72**. The common key intermediate **79** was prepared by constructing the pyrrole ring from the previously introduced acetonitrile at C-2 (Scheme 23).

5′-Deoxy-5-fluoroimmucillin **85** was prepared in a similar way starting from **84**, which was obtained in moderate overall

Scheme 23



Scheme 24



yield after substitution of the hydroxy group in **78** by a fluorine using DAST as a reagent. Intermediate **84** was also converted into 2′-deoxyimmucillins **87** and **88** as indicated in Scheme 24. After preparation of intermediate **86**, a reaction sequence similar to those mentioned above allowed the synthesis of compounds **87** and **88**.

Compound **72** was also used by Tyler et al.[49] for the preparation of 8-azaimmucillins **90** and **91** by a similar protocol to that illustrated in Scheme 25. Starting from imine **72** several immucillins analogues, including compounds **92**−**95**, have been prepared by Tyler's group.[50]

The same group reported the preparation of difluoro-derivatives **98** starting from D-serine derivative **96** through fluorinated intermediate **97** (Scheme 26).[51]

The direct construction of the heterocyclic base has also been used for preparing other pyrrolidinyl nucleoside analogues of biologically important C-nucleosides. Just et al. reported[52] the synthesis of the aza analogue of showdomycin **101** from pyrrolidine **99**. After formation of the heterocycle and the final deprotection step, the analogue **101** was obtained in 24% overall yield (6 steps) from **99** (Scheme 27).

The pyrrolidinyl analogue of tiazofurin **104** was prepared by synthesizing the thiazole ring from 2-cyano pyrrolidine **103**, which, in turn, was prepared from the aminosugar **102** in 3 steps and 36.4% overall yield (Scheme 28).[53]

Palladium-mediated coupling of 5-iodoracil with enamine **105** provided after deprotecting steps the azanucleoside **106** (Scheme 29). The enamine **105** was prepared from *trans*-3-hydroxy-L-proline in 7 steps and 50.5% overall yield.

A novel type of C-aza nucleosides in which the base is linked to the endocyclic nitrogen atom has been described by Pedersen et al.[54] Both pyrrolidinyl and piperidinyl derivatives have been described, only the former being illustrated in Scheme 30. By refluxing unprotected pyrrolidine **107** with 5-bromouracil **108** the analogue **109** was obtained in 61% isolated yield.

2.2. Thionucleosides

Thionucleoside analogues are among the most active heterocyclic nucleosides. Both the syntheses and biological properties of thionucleosides were reviewed comprehensively by Yokoyama in 2000.[55]

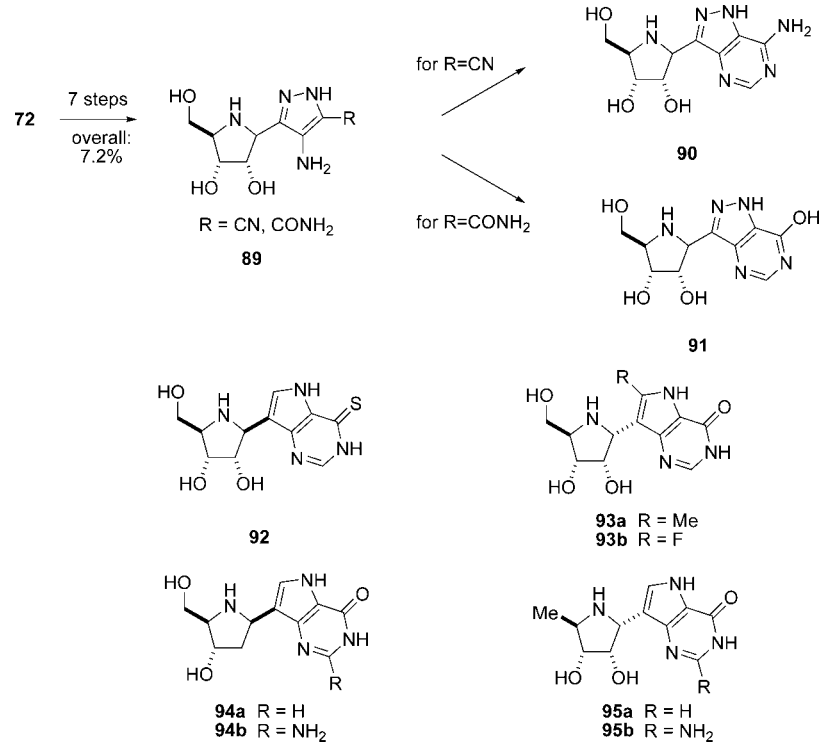
Miller et al. reported the synthesis of 2-deoxy-4′-thio-nucleosides **111** from thioglycosides **110** by reaction with silylated bases in the presence of *N*-bromosuccinimide.[56] After deprotection steps a 2:3 mixture of β:α anomers was obtained in 53% overall yield (Scheme 31). Although the α isomer **111b** was obtained predominantly, it showed a potent antiherpetic activity.[57]

The same research group reported the reaction of silylated bases with thioglycal **112**, accessible from the corresponding thioglycoside. In this case the reaction afforded cis isomers as major adducts (cis:trans = 20:1).[58] Elimination of iodine atom was performed by tributyltin hydride and debenzylation with boron trichloride, thus leading to unprotected thio-nucleoside **114** (Scheme 32).

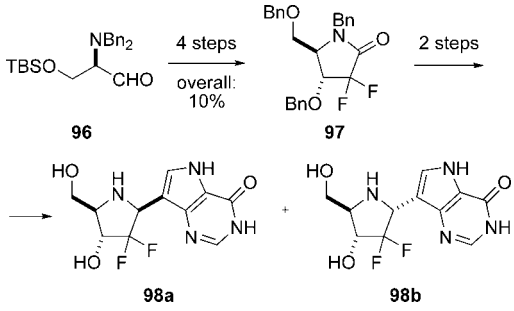
Condensation between thioglycosides **115** and 4,5-dicyanoimidazole in the presence of *N*-iodosuccinimide led to mixtures of thionucleosides **116** (Scheme 33).[59] The authors conducted a study on the use of 3′-directing groups to varying α:β ratios in the glycosylation reaction.

Direct coupling of nucleobases with cyclic sulfoxides has been described by Corsaro et al.[60] as a straightforward route to 4′-thionucleosides. The key step in the obtention of the

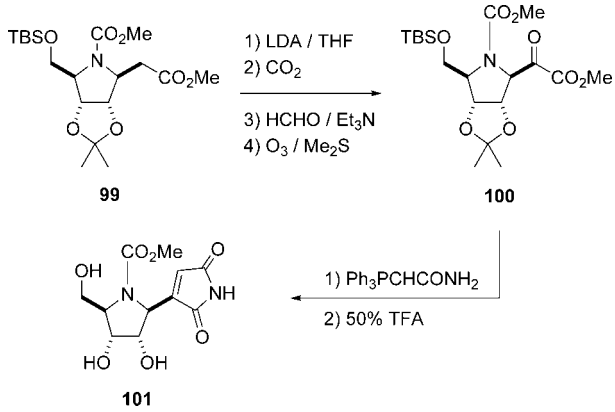
Scheme 25



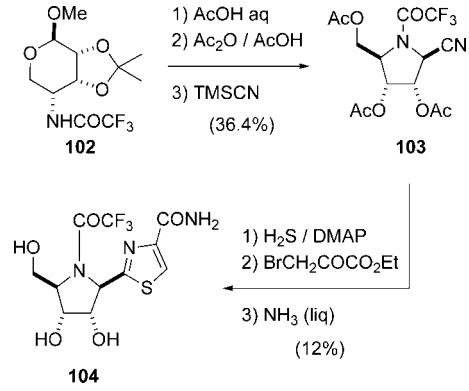
Scheme 26



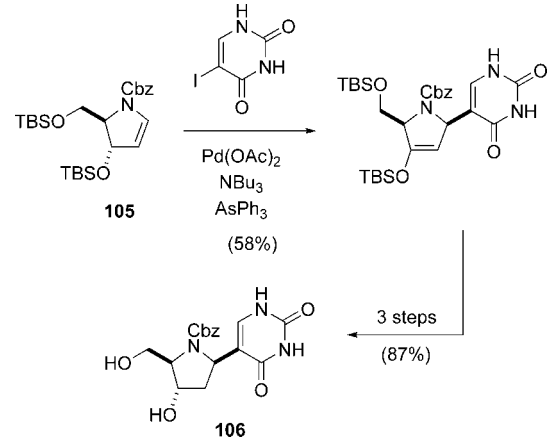
Scheme 27



Scheme 28



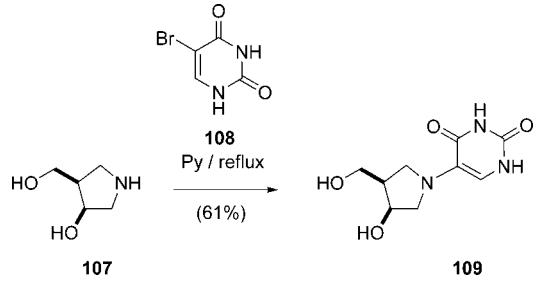
Scheme 29



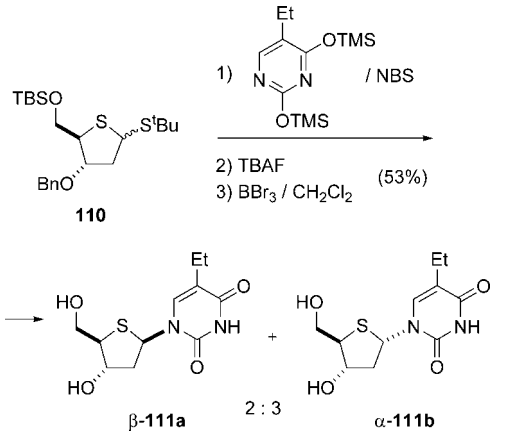
sulfoxides **120** and **121** was the reaction of thiocarbonyl ylide **119** generated in situ with dimethyl fumarate **117** and dimethyl maleate **118**, respectively (Scheme 34). The nucleobase was introduced through a Pummerer-type reaction, which afforded in all cases the β-anomer predominantly.

By using optically active alkene **122** as a starting material, the same strategy allowed the preparation of deoxy- and isoderivatives, in this case in a enantiomerically pure form (Scheme 35). Cycloaddition and further transformations allowed preparation of the common intermediate **124**. Isonucleoside analogues **125** were obtained by S_N2 reaction of the silylated nucleobase, and deoxyderivatives **127** were prepared by phenylselenylation of **126** in the presence of the base.

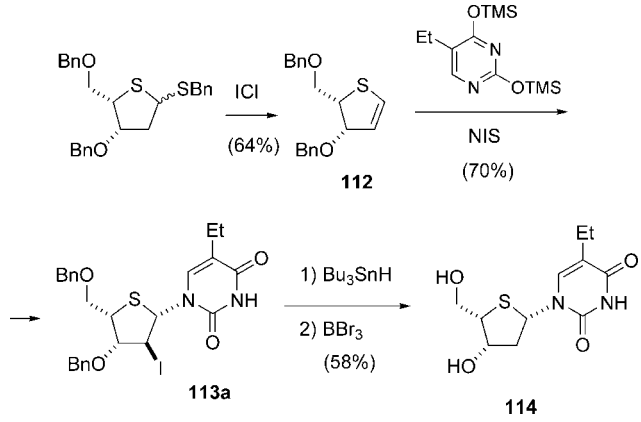
Scheme 30



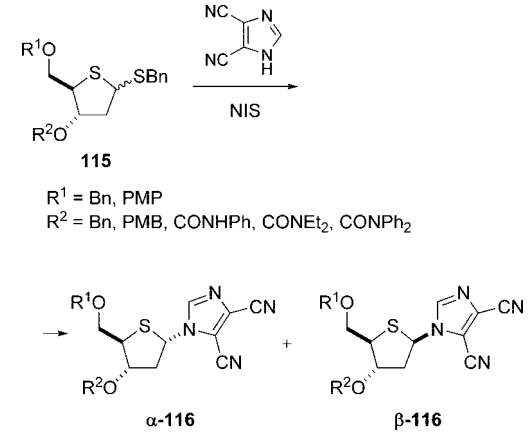
Scheme 31



Scheme 32

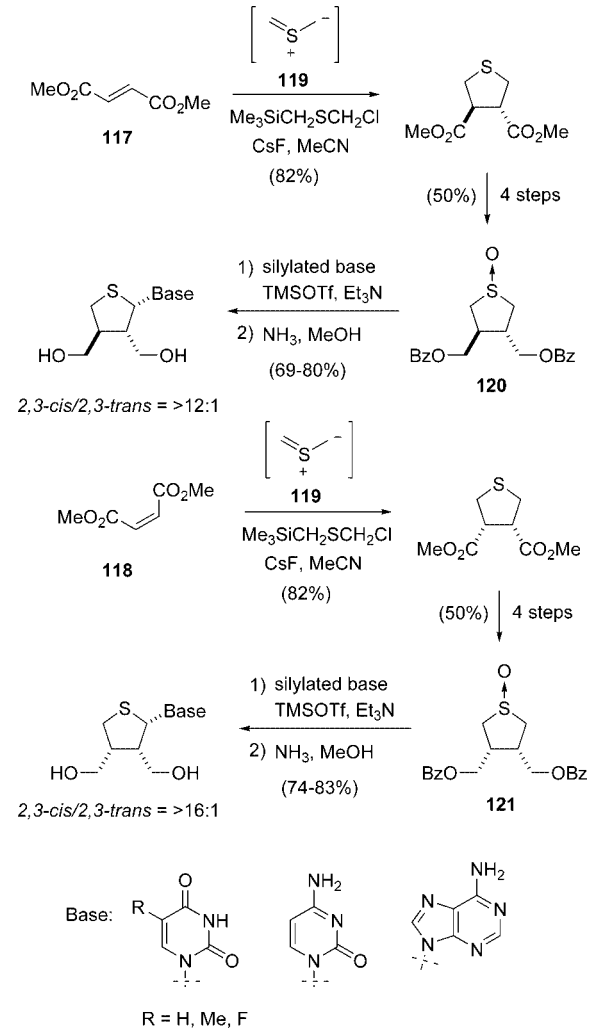


Scheme 33



Jeong et al. synthesized dehydrothionucleosides **128** to study differences between sulfur and oxygen by comparison with the parent apionucleosides.[61] Their synthesis involved

Scheme 34



the formation of the endocyclic double bond via the selenenyl intermediate **127** prepared in 3 steps from thiolactone **126** (Scheme 36).

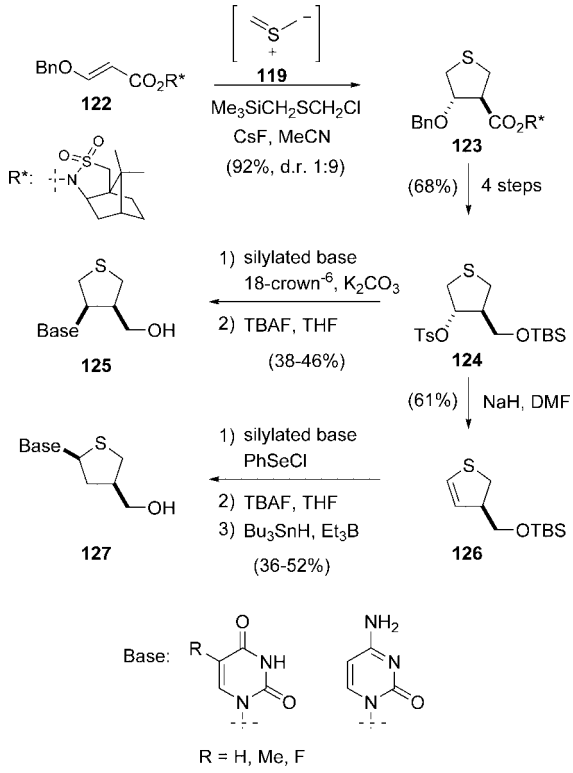
The thioanalogue of the antineoplastic agent 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl) cytosine **130** has been prepared from thiofuranoside **129** (Scheme 37).[62] The β-isomer showed antitumoral activity against several human solid tumor cell lines.[63] By using the same strategy 2′-deoxy-2′-fluoro-4′-thionucleosides **131**−**133** were also synthesized by the same research group, and potent antiviral activities were found.[64]

Fluorinated thionucleoside **136** was prepared from the precursor **134** and tested against solid tumor and leukemic cells.[65] Compound **134** was coupled with CF_2Br_2 in the presence of zinc; the incorporation of the base was made by reaction with *m*-chloroperbenzoic acid and then silylated *N*-acetylcytosine in the presence of trimethylsilyltriflate as an activator of the glycosylation reaction. After deprotection compound **136** was obtained in 22% overall yield (3 steps) (Scheme 38).

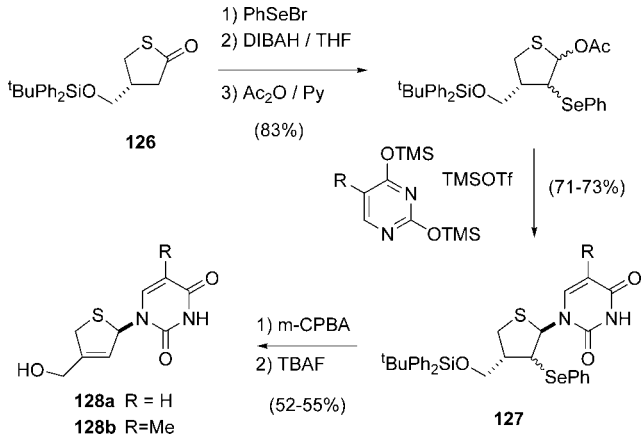
By combining the methodologies outlined in Schemes 37 and 38, 2′-fluoro-2′,3′-dehydro-4′-thionucleosides **138**−**140** were prepared from intermediate **137** to test their antiviral activity.[66] The more active compounds were found to be **139** and **140** (Scheme 39).

2′,3′-Dideoxy-2′-fluoro-4′-thionucleosides **143** are also accessible from thiolactone **141** (1:1 cis/trans mixture).[67]

Scheme 35

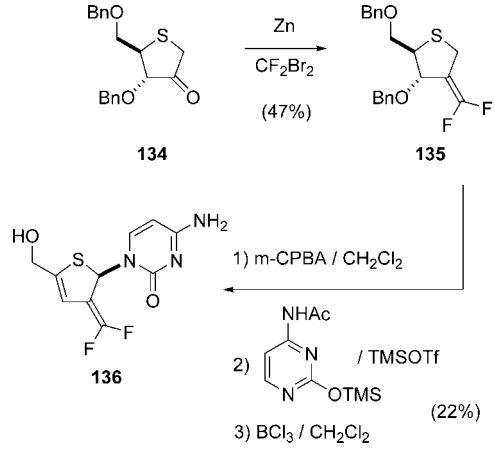


Scheme 36

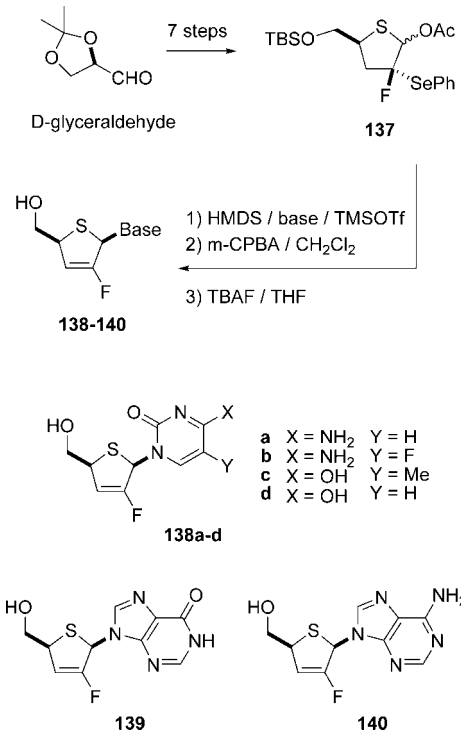


Reduction of **141** under strict temperature conditions (in order to avoid ring-opening reaction by the solvent) followed by

Scheme 38

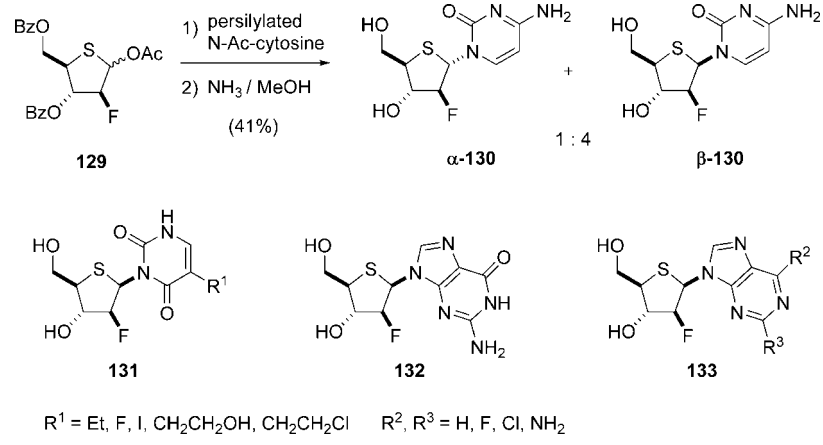


Scheme 39

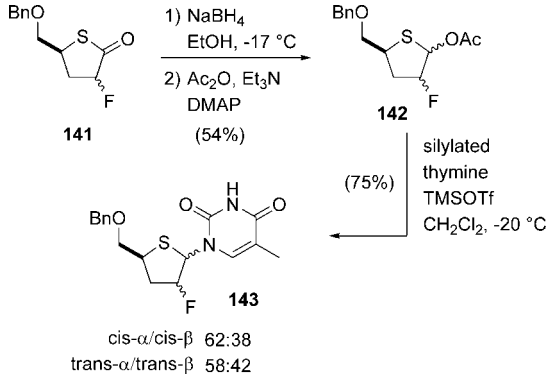


acetylation afforded precursor **142**, which was glycosylated under typical Vörbruggen conditions. Under such conditions a mixture of 4 isomers was obtained (Scheme 40).

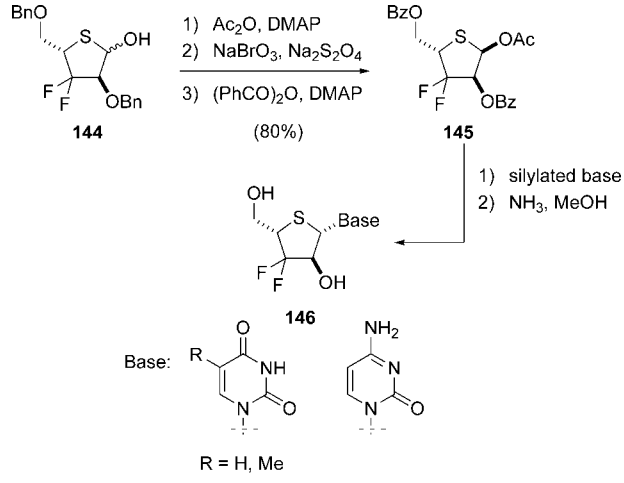
Scheme 37



Scheme 40



Scheme 41



Difluorothionucleosides analogues of gemcitabine were prepared from thiofuranose **144**. After acetylation and N-glycosylation the corresponding protected thionucleosides **146** were obtained. Both thymine and cytosine analogues were prepared in good yields (Scheme 41).[68]

Branched 4′-thionucleosides **150** were prepared starting from protected thioglycal **147**. Incorporation of the base in the presence of phenylselenenyl chloride afforded intermediate **148** in 40% yield. After the deprotection steps the final analogue **150** was obtained (Scheme 42).[69]

By using a similar strategy, the same authors prepared 2′-β-carbon-substituted 2′-deoxy-4′-thionucleosides.[70] In this case, β-substituted glycals **152** and **153** were prepared from 2-chloroderivatives **151** by direct lithiation, subsequent nucleophilic substitution, and dechlorination. Phenylselenylation of **152** and **153** in the presence of silylated thymine and silylated *N*-acetylcytosine followed by selenium elimination afforded protected derivatives **154** (Scheme 43). Other derivatives such as analogues **155**−**160** were prepared by conventional chemistry starting from previously synthesized thionucleosides.[71]

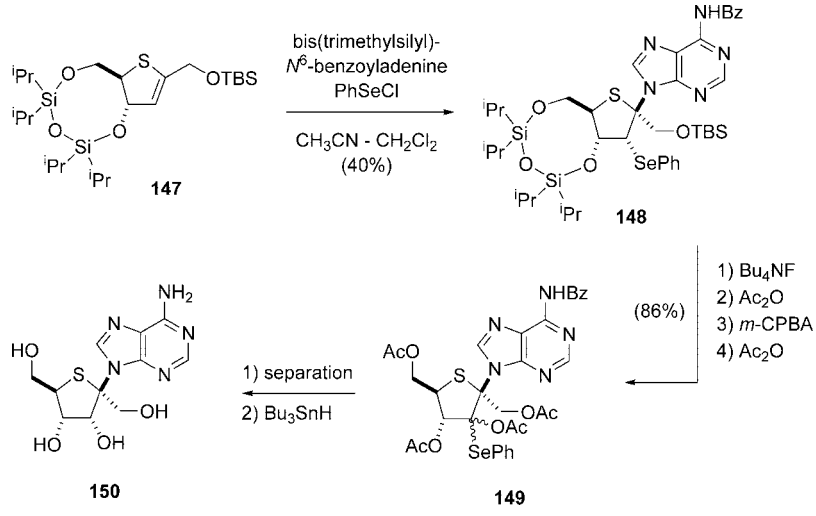
The 4′-thio analogue of the antihuman immunodeficiency virus type 1 (HIV-1) 4′-ethynylstavudine was synthesized from thioglycals **161** as depicted in Scheme 44.[72] Activation of the double bond with *N*-iodosuccinimide in the presence of silylated thymine afforded 1:10 mixtures of α/β anomers in 88% combined yield. Further synthetic transformations of the β-anomer led to intermediate **163**, which was transformed into the target compound by reaction with 1-diazo-(2-oxopropyl)phosphonate in combination with potassium carbonate in methanol.

Starting from unsaturated 4′-thiothymidine, prepared from glycal **165**, several 4′-substituted 4′-thiothymidines have been prepared.[73] The key step was the vicinal diacetoxylation of compound **167** by using lead(IV) tetracetate (Scheme 45). From intermediate **168** a series of 5′-substituted thioanalogues **169** has been prepared utilizing diverse synthetic routes.

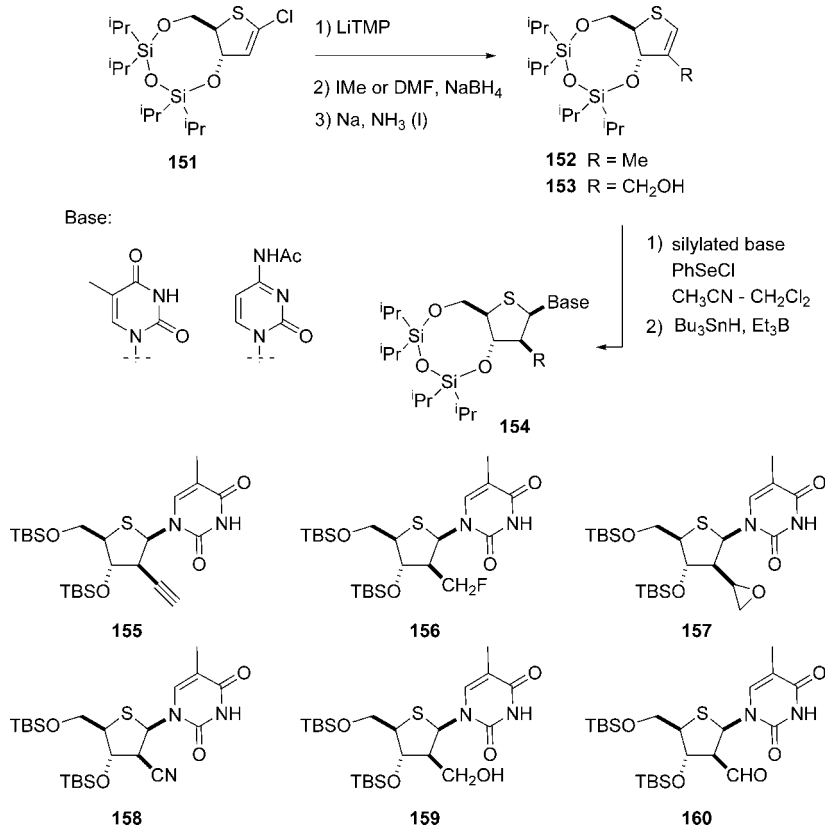
The asymmetric synthesis of 3′-*C*-methyl-4′-thioapionucleosides was accomplished starting from chiral nonracemic **170**. The thioglycoside **171** was coupled with protected cytosine in the presence of *N*-iodosuccinimide followed by deprotection to furnish nucleoside analogue **172** in 8.8% overall yield (Scheme 46).[74]

Spirocyclic thioanalogues have been prepared from enantiopure acetonide **173** using the Pummerer reaction approach of the corresponding sulfoxide **174**.[75] After removal of protecting groups the corresponding thioanalogues were obtained. The methodology was applied to both pyrimidine and purine classes, and both possible configurations at 5′ were described (Scheme 47). The same strategy was applied to the epimer **176** from the anti series, thus affording the corresponding nucleoside analogues **177** in good yields. Although differences in reactivity between the two studied series were noted in all cases, minimum formation of α-anomers was observed.

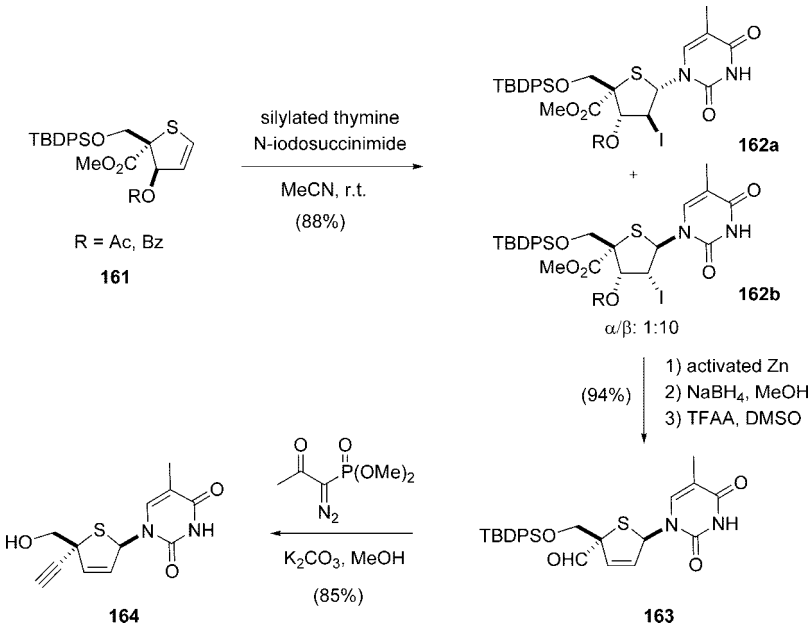
Scheme 42



Scheme 43



Scheme 44

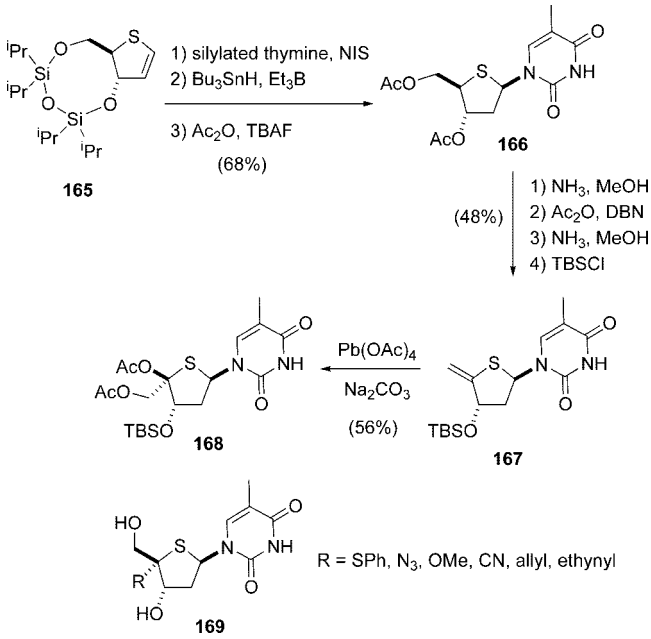


Several examples of L-thionucleosides have also been described. The Pummerer rearrangement was used as the key step for the synthesis of 1-*O*-acetylthiofuranoses **179**, which were used as the precursors of novel L-thiocytidines **180** (Scheme 48).[76]

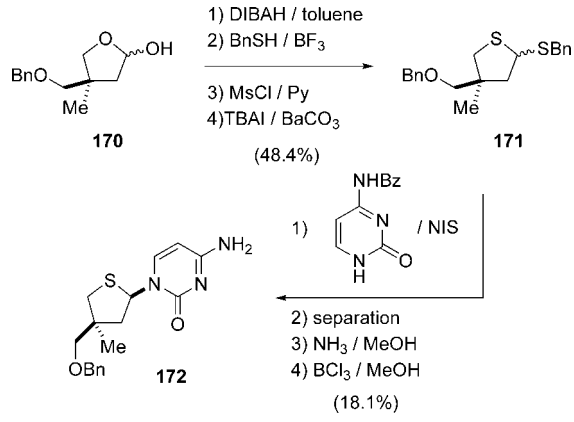
Methyl α-D-lyxopyranoside **181** was used as starting material for synthesizing compound **182**, a key intermediate in the preparation of 4′-thionucleoside analogues **183**−**185** (Scheme 49).[77] L-Nucleosides were prepared by in situ formation of the persilylated bases and further glycosylation in the presence of trimethylsilyl triflate. All of them have been tested for their antitumor activity, only moderate activity being found against HTB14 human glioma cells (41.5−83.3 μM).

Yoshimura et al. reported the synthesis of 2′-modified-4′-thionucleosides in order to test their antiviral and antitumoral activities.[78] The glycosylation reactions of **186** with several pyrimidine bases afforded the corresponding protected nucleoside analogues which after deprotection steps were converted into thionucleosides **187** and **188** (Scheme 50). By introducing purine bases in the presence of trim-

Scheme 45



Scheme 46



ethylsilyl triflate as an activator, compound **186** was also used for preparing thionucleosides **189**.

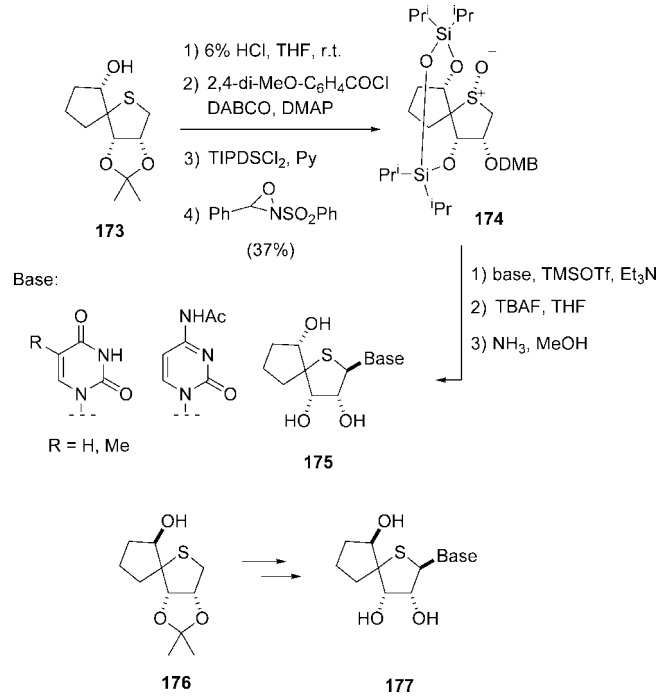
Thionucleosides in which the base moiety is linked to the C-3 of the tetrahydrothiophene ring have been named as *N*-isothionucleosides. This sort of compound can be prepared by introducing the base moiety through a classical S_N2 reaction or a Mitsunobu reaction, although as in the case of the corresponding pyrrolidinyl analogues low chemical yields are usually obtained for such a step.

Activation of compound **190** via mesylation and condensation with uracil furnished protected *N*-isothionucleoside **191,** which was transformed into the *N*-isothionucleoside **192** (Scheme 51).[79]

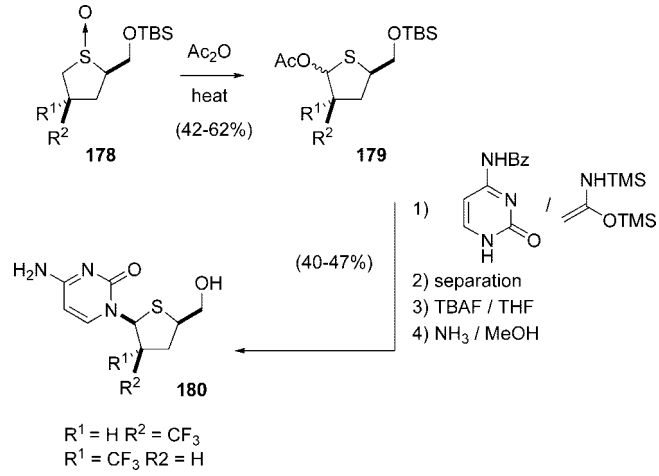
Yoshimura et al.[80] utilized the Mitsunobu reaction for obtaining *N*-isothionucleoside **194** from alcohol **193**. Several bases were tested, the best results corresponding to 4-acetoxyamino-6-chloropurine, which afforded the corresponding adduct in 38% isolated yield (Scheme 52).

A series of furan *C*-4′-thionucleosides was prepared by direct cyclization of the precursor furan intermediate **195**.[81] Both α- and *β*-anomers were obtained in a 2:3 ratio. Starting from compound **196** the sulfoxides **198** and the methyl sulfonium salts **199** were prepared (Scheme 53). All compounds were tested as glycosidase inhibitors; unfortunately, no substantial inhibitory properties were observed.

Scheme 47



Scheme 48



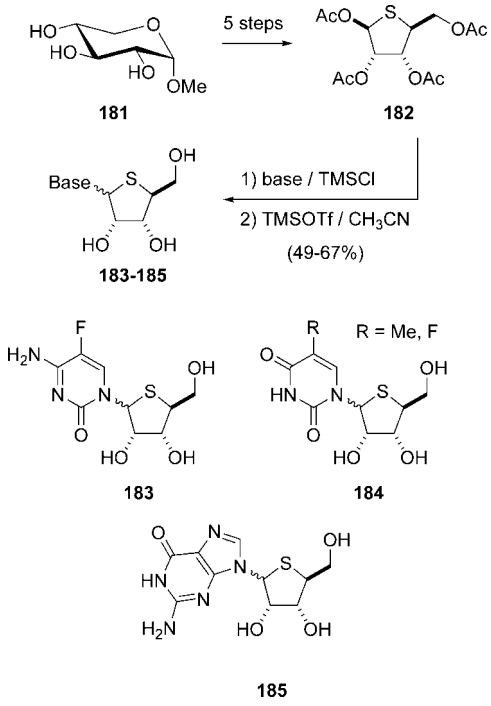
3. Heterocyclic Nucleosides with Two Heteroatoms

3.1. Dioxolanyl Nucleosides

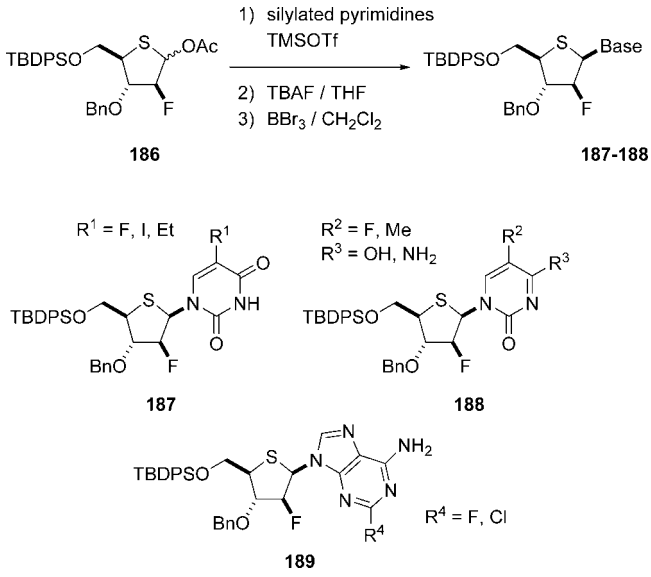
Liotta et al. prepared racemic pyrimidine dioxolane nucleoside analogues from 1,3-dioxolan-4-one **200**. After reduction with *tert*-butoxy lithium aluminum hydride and acetylation of the resulting lactol, the pyrimidine bases were introduced by conventional methods (Scheme 54).[82]

Mansour et al.[83] described the synthesis of dioxolane T **204** and purine dioxolane analogues **207** from the corresponding acetoxy derivatives **203** and **206**, respectively, via a classical Vörbruggen N-glycosylation.[84] The acetoxy intermediates are easily prepared from L-ascorbic acid, which could be transformed into carboxylic acids **202** and **205** in a enantiodivergent way. After conversion of the carboxylic acids into the acetoxy derivatives **203** and **206**, the resulting nucleoside analogues belong to enantiomeric D- and L-series. The intermediate carboxylic acids **202** and **205** can also be

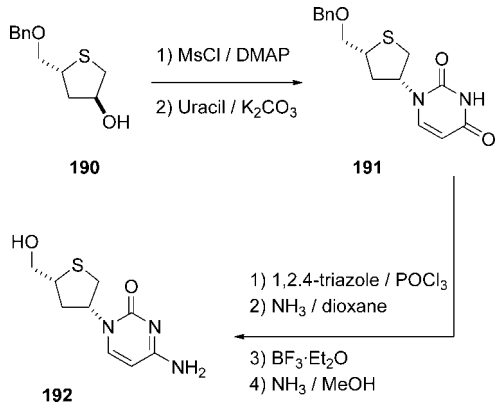
Scheme 49



Scheme 50

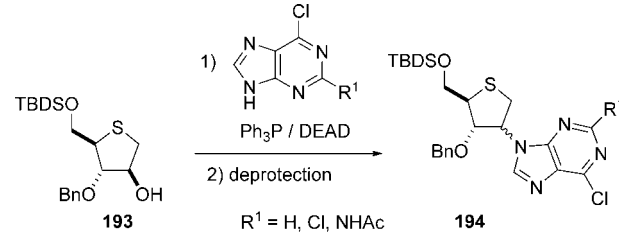


Scheme 51

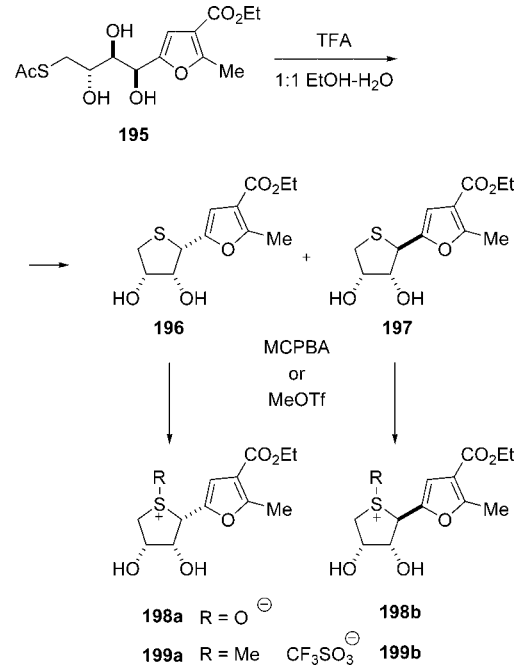


synthesized in a straightforward way by chemoenzymatic methods (Scheme 55).[85]

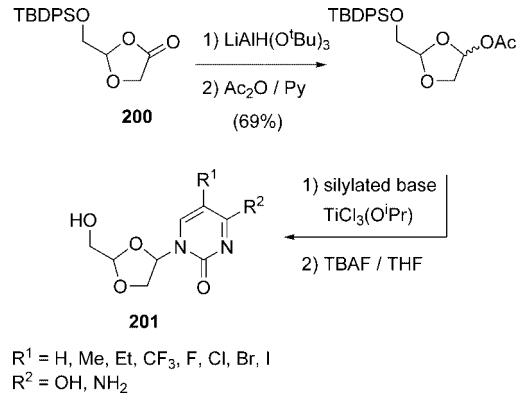
Scheme 52



Scheme 53



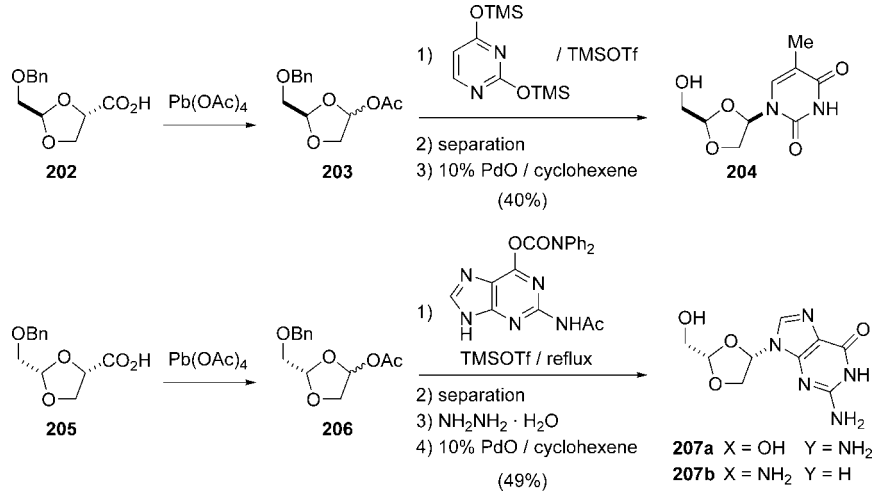
Scheme 54



Dioxolane analogues **208**−**211** (Figure 6) bearing different pyrimidine and purine bases have also been prepared and their activity against the Epstein−Barr virus evaluated.[86] Other biological activities including antiherpetic,[87] anti-HCMV,[88] anti-HBV,[89] and anti-HIV-1[90] have also been evaluated as well as their activity profiles,[91] pharmacokinetics,[92] and virus resistance.[93] In particular, troxacitabine **209** emerged as a promising anticancer agent.[94] Compound **209** is a complete DNA chain terminator that incorporates itself into the growing DNA chain of cancer cells, showing activity against pancreatic cancer[95] and leukemic tumors.[96]

Mansour et al. also reported the preparation of racemic dioxolane analogues **214** as biomimetics of phosphorylated nucleosides by coupling between the in situ generated

Scheme 55



silylated bases and the corresponding acetoxy precursor **213** (Scheme 56), which had been phosphorylated previously.[97]

The typical Vörbruggen N-glycosylation has also been utilized for the preparation of branched analogues **216** and **217** (Scheme 57).[98]

Chu et al.[99] utilized orthoester **218** as a substrate for the condensation with silylated bases, thus obtaining unsubsti-

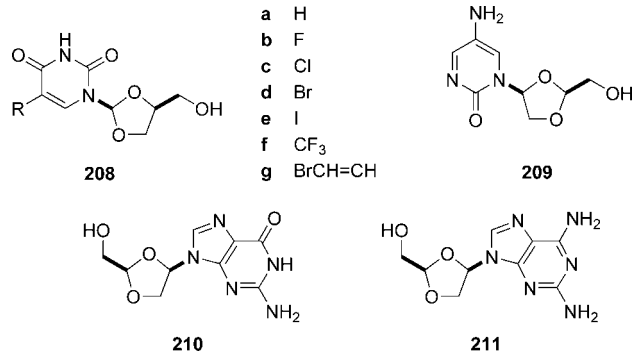
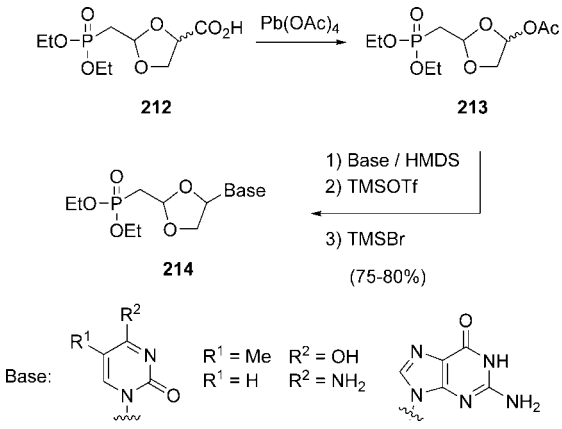
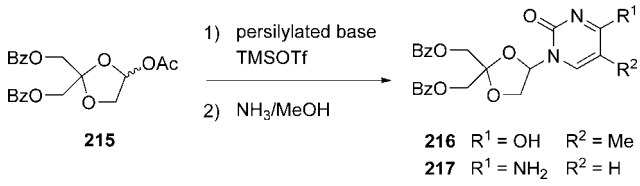


Figure 6.

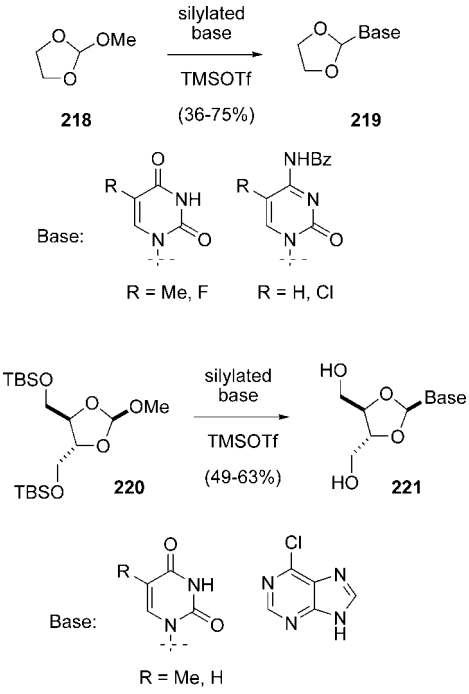
Scheme 56



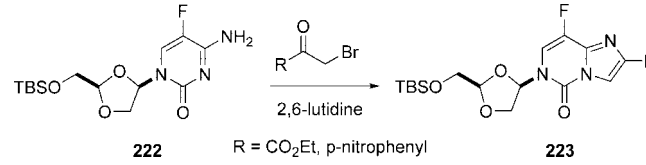
Scheme 57



Scheme 58



Scheme 59

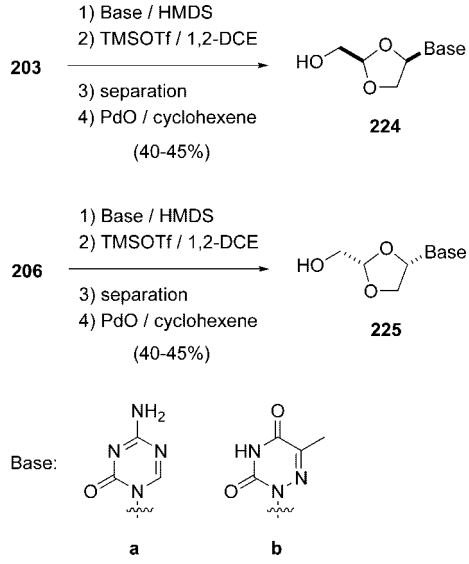


tuted dioxolanyl nucleosides **219**. The same strategy was employed by Samuelsson et al.[100] to prepare nucleoside analogues **221** bearing two hydroxymethyl groups attached to the heterocyclic ring (Scheme 58).

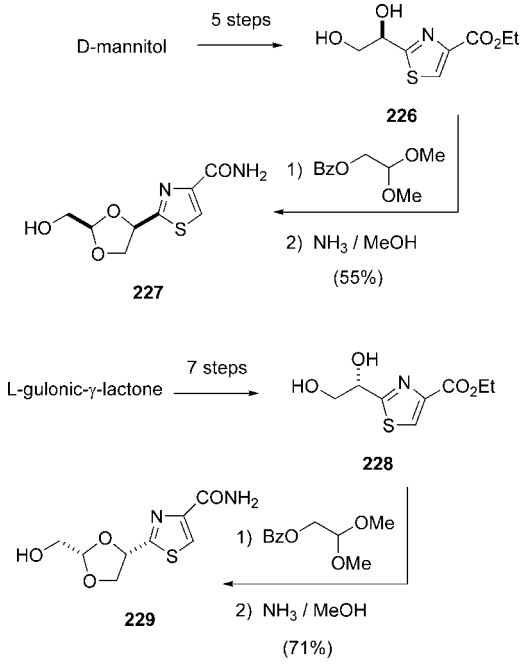
Dioxolane nucleosides with modified bases have been reported by Mansour et al.[101] The novel imidazo[1,2-*c*]pyrimidines **223** were prepared starting from the corresponding dioxolane pyrimidine nucleoside **222** by constructing the fused imidazole ring. The direct incorporation of the heterocyclic base is also possible (Scheme 59).

Sartorelli et al. reported the synthesis of 5-azacytosine and 6-azathymine dioxolane analogues **224** and **225**. These

Scheme 60



Scheme 61



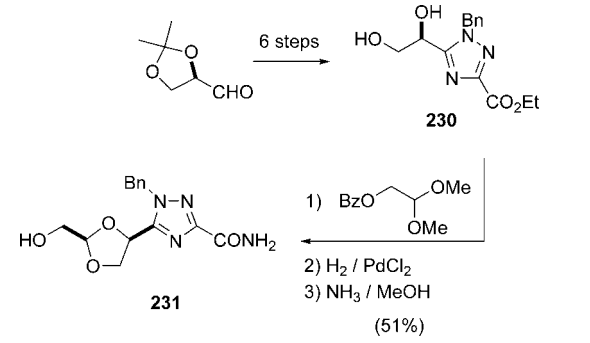
compounds have been prepared from acetoxydioxolanes **203** and **206** by condensation with the persilylated modified bases following the same synthetic strategy outlined in Scheme 60.[102]

Chu et al.[103] reported the synthesis of enantiomeric dioxolanyl analogues of tiazofurin. The synthesis was carried out by condensation of key thiazolyl intermediates **226** and **228**, obtained from D-mannitol and L-gulonic-γ-lactone, respectively, with 2-benzoyloxy acetaldehyde dimethyl acetal. Further treatment with liquid ammonia in methanol afforded analogues **227** and **229** (Scheme 61).

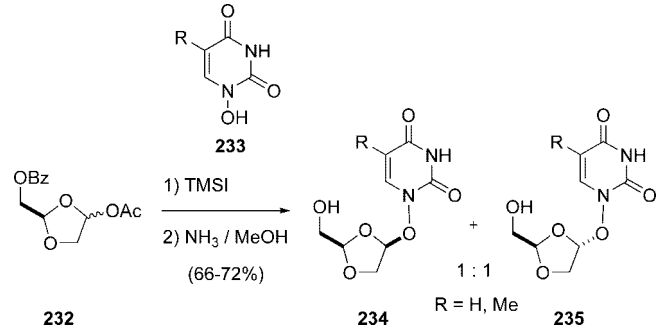
The same authors reported the synthesis of D-1,3-dioxolanyl triazole C-nucleoside **231** through key intermediate **230** obtained from D-glyceraldehyde (Scheme 62).[104] The enantiomer of **230** was also prepared by starting from L-glyceraldehyde.

Zacharie et al.[105] reported on an approach to dioxolane nucleosides containing *N*-1-oxypyrimidine as a base. Condensation of acetoxy derivative **232** with *N*-hydroxypyrimidines **233** in the presence of TMSI or TMSBr afforded a 1:1 mixture of nucleoside analogues **234** and **235** (Scheme 63). By using the same reaction conditions, the same group carried out the synthesis of the purine nucleoside analogues **238** and **239** (Scheme 64).[106]

Scheme 62



Scheme 63



Lonnberg et al.[107] described the synthesis of dioxolane homonucleosides **241** and **245**. The tosyl derivative **240** was made to react with the corresponding base anion, and after deprotection a mixture of nucleoside analogues was obtained. The phosphonate derivatives **245** were obtained by condensing 2-bromoacetaldehyde diethyl acetate with modified base **243**. Incorporation of the phosphonate moiety and deprotection mediated by trimethylsilyl bromide furnished the phosphorylated nucleoside analogues **245** (Scheme 65).

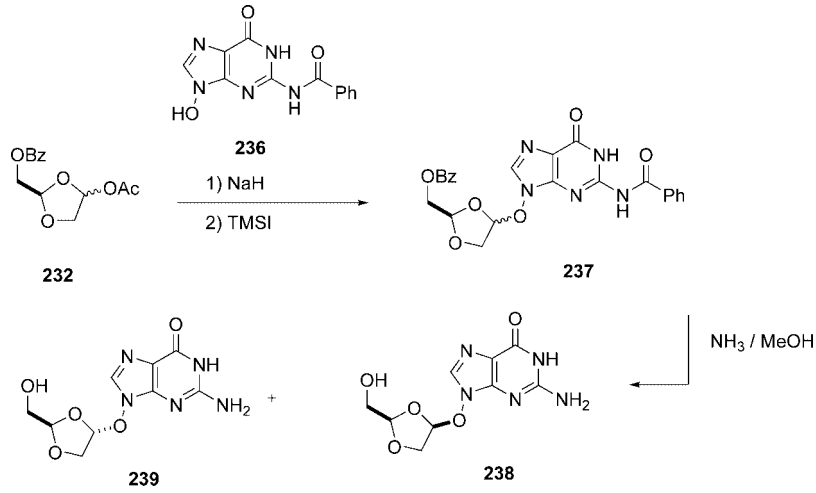
Scheiner et al.[108] prepared ring-expanded dioxolane nucleosides (dioxane nucleosides) for designing novel analogues with increased biological activity. Compounds **249** were prepared by construction of the 1,3-dioxolane after N-alkylation of the monoprotected base. The cytosine analogues **250** were prepared from **249** in 3 steps. In all cases the cis isomers were obtained preferentially. No antiviral activity was found for nucleosides **249** and **250** (Scheme 66).

3.2. Dithiolanyl Nucleosides

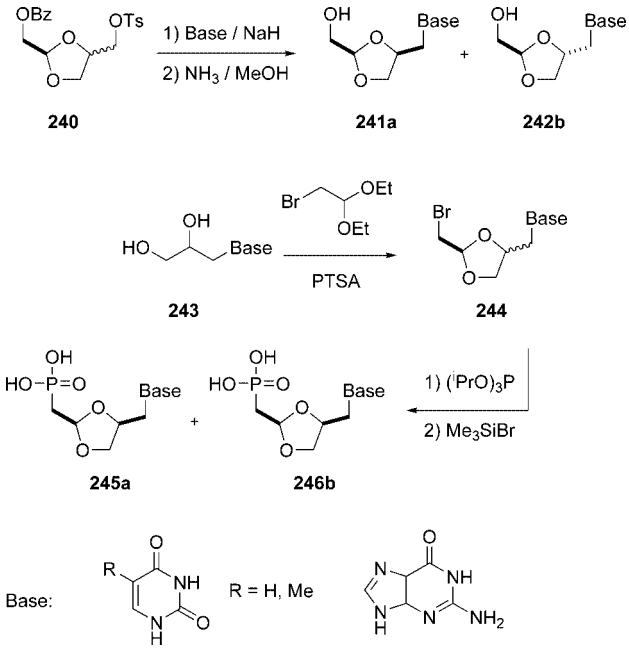
Zacharie et al.[109] synthesized racemic **253** in 3 steps from compound **251** (Scheme 67). Condensation of intermediate **252** with silylated *N*-acetylcytosine in the presence of iodotrimethylsilane and further deprotection with liquid ammonia in methanol afforded a 1:2 mixture of anomers, the β isomer being the major one. The procedure is amenable to be used in multigram preparations.

The same authors prepared pyrimidine analogues **255** from the corresponding 4-acetoxy-1,3-dithiolane **254**.[110] Condensation between **254** and silylated pyrimidine in the presence of tin tetrachloride afforded a mixture of analogues **255**, with a slight predominance of the cis isomer (Scheme 68).

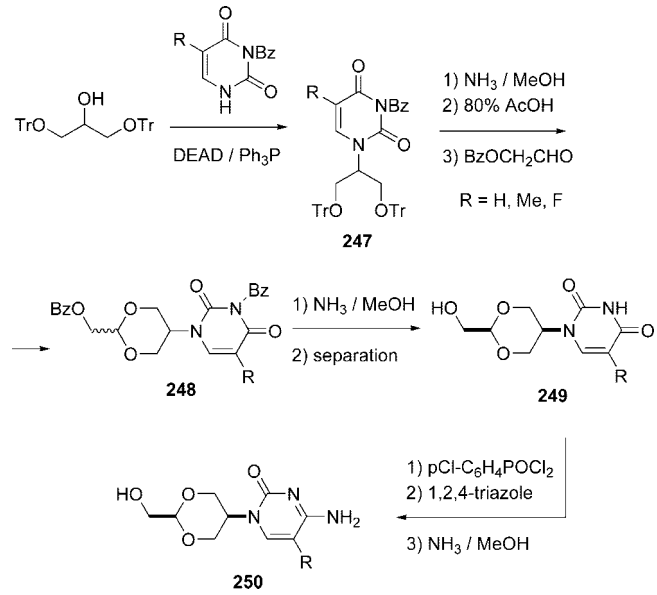
Scheme 64



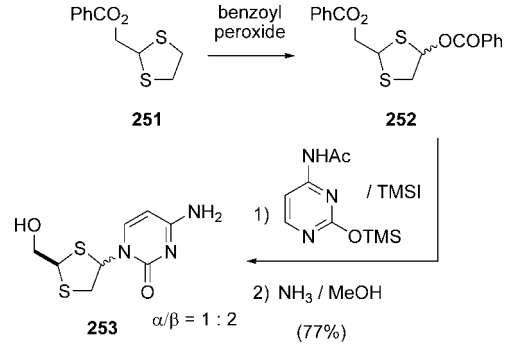
Scheme 65



Scheme 66



Scheme 67



The oxidation of dithiolane **256** in the presence of D-diethyl tartrate afforded a mixture of chiral compounds from which (*E*)-**257** could be separated. This compound reacted in situ with silylated bases, under modified Pummerer rearrangement conditions, to furnish **258** and **259** in good yields (Scheme 69).[111]

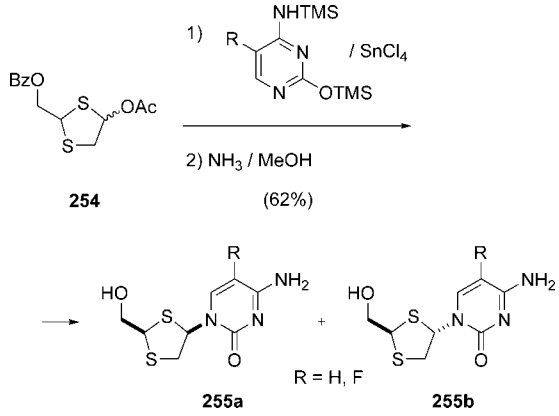
3.3. Oxathiolanyl Nucleosides

Both enantiomers of the anti-AIDS drug lamivudine **262** have been synthesized through a stereoselective N-glycosylation reaction from the corresponding acetoxy derivative **260**, which was obtained by fractional recrystallization using L-menthol as a resolving agent.[112] Only the synthesis of the (−)-3TC is shown in Scheme 70. Previous syntheses of racemic **262** were described by Dwyer,[113] starting from racemic **260**, and by Huang et al.[114] The intermediate **260** was also used for the synthesis of oxathiolanyl analogues with modified bases.[115] Such a modification was carried out from intermediate **263** in 4 steps, giving rise to nucleoside analogue **264**.

Rayner et al.[116] prepared lamivudine **262** by a chemoenzymatic approach which involved resolution of racemic **265** with *Pseudomonas fluorescens* lipase. The obtained enantiomeric compound was transformed into oxathiolane **266** and then into lamivudine **262** in 4 steps and 35.6% overall yield (Scheme 71).

Large-scale synthesis of enantiomerically pure lamivudine **262** was achieved by means of dynamic kinetic resolution.[117] By heating menthyl glyoxylate hydrate **267** with dithiane diol **268** in toluene, optically pure crystalline **269** was

Scheme 68

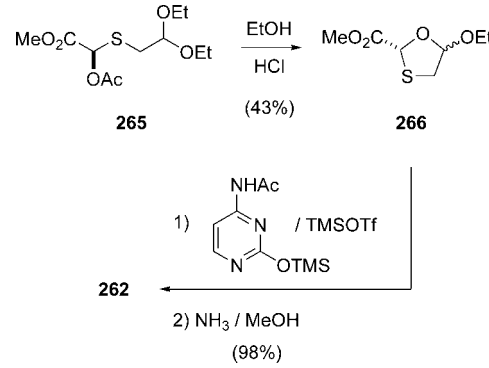


obtained in 80% combined yield after crystallization from *n*-hexane in the presence of a catalytic amount of triethylamine. Further treatment of **269** with thionyl chloride and presilylated cytosine afforded pure **270**, which was transformed into lamivudine **262** by reduction with borohydride to eliminate the menthyl moiety. The overall yield from the starting glyoxylate was 43.82% for 6 steps (Scheme 72).

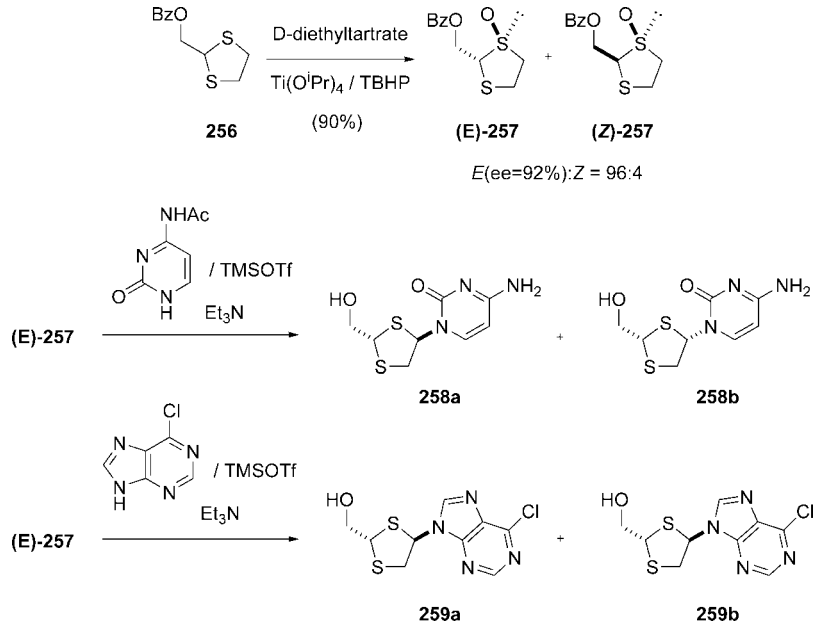
Scheiner et al.[118] synthesized L-homolamivudine **275** and its 5-fluoro congener **276** starting from (+)-*R*-glycidol **271** (Scheme 73). Condensation of oxathiolane **272** with 3-benzoyl fluorouracil (or 3-benzoyl-5-fluorouracil) under Mitsunobu conditions afforded intermediates **273** and **274**, which were converted into **275** and **276**, respectively, in 5 steps. The enantiomers of lamivudine **275** and FTC **276** have also been prepared[119] and their antiviral activity against HIV and HBV evaluated. In all cases, the obtained values were found to be lower than those observed for the L-analogues.

Jin et al.[120] developed a new synthesis for oxathiolane nucleosides in which the heterocyclic base is vicinal to the sulfur atom. Condensation between compound **277** and silylated *N*-acetyl cytosine afforded cis and trans nucleosides **278** and **279** (Scheme 74). Conversion to unprotected

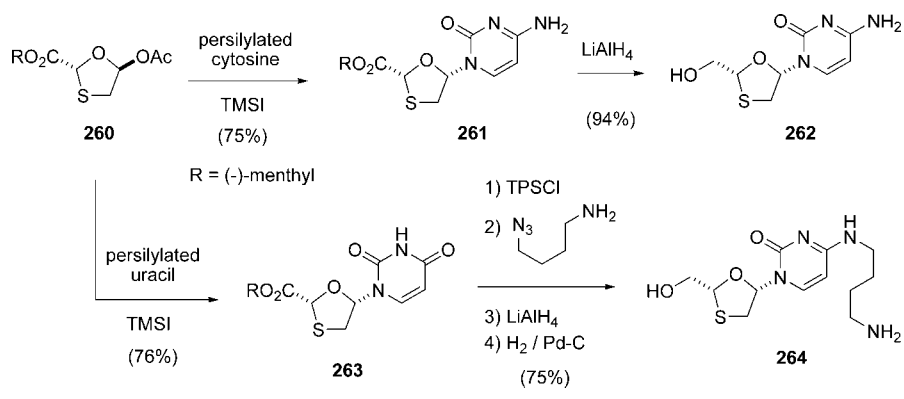
Scheme 71



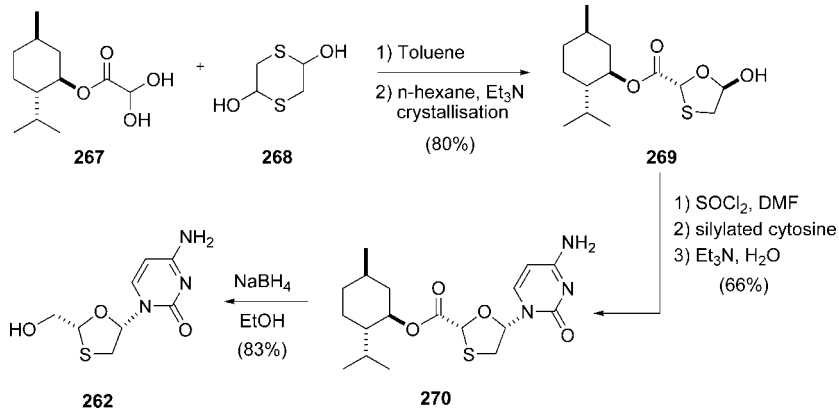
Scheme 69



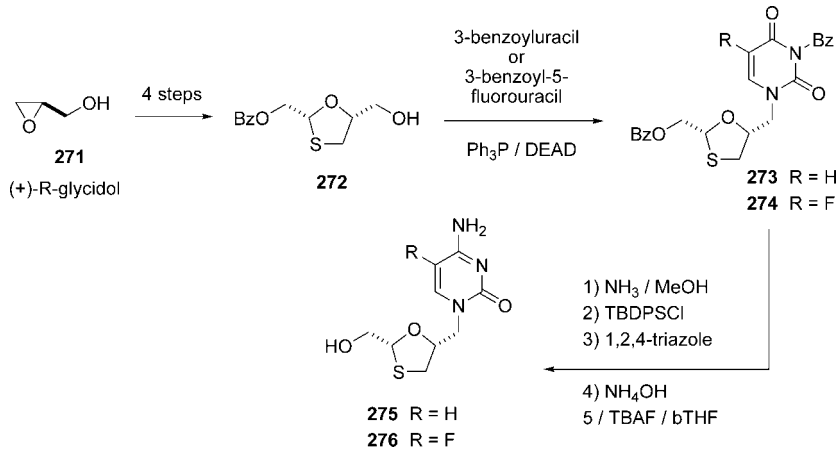
Scheme 70



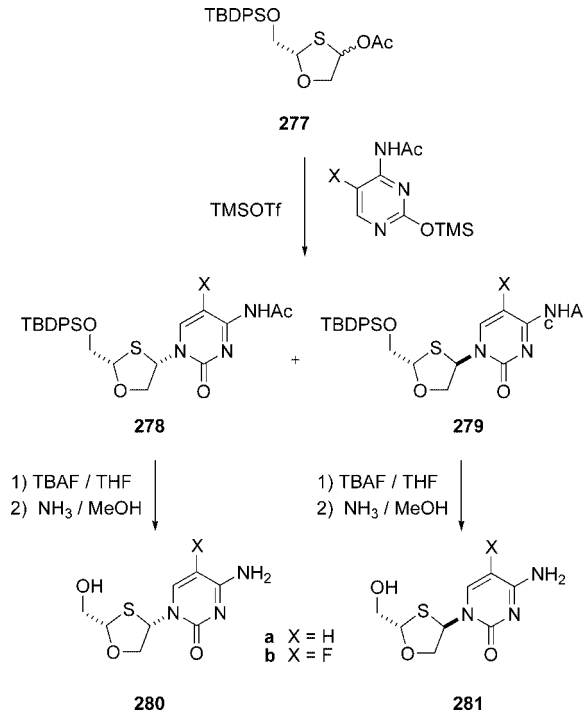
Scheme 72



Scheme 73



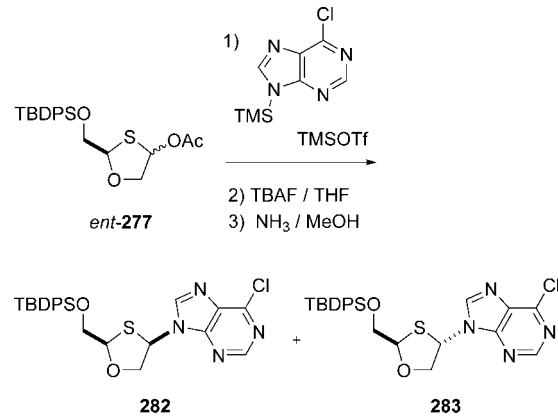
Scheme 74



oxathiolane nucleosides **280** and **281** was carried out by conventional methods.

Similarly, starting from the enantiomer of **277** the corresponding antipodes *ent*-**280** and *ent*-**281** were prepared. Compound *ent*-**277** was also used for preparing purine

Scheme 75

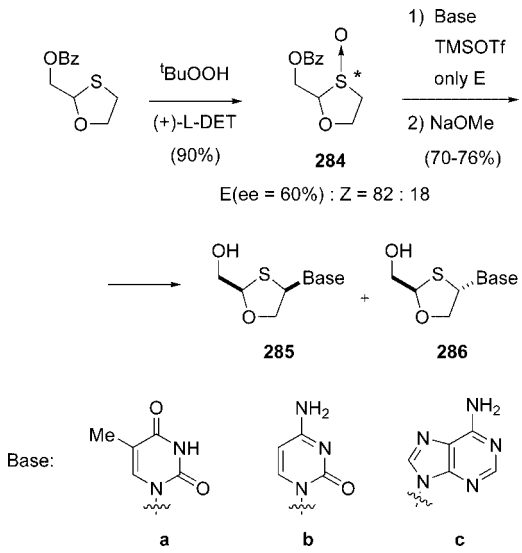


oxathiolanyl nucleosides **282** and **283**. In all cases the trans isomers were obtained predominantly (Scheme 75).

Palumbo et al.[121] accomplished a ready asymmetric synthesis of oxathionucleosides in 3 steps from benzoyloxyethanal. The key step was the asymmetric synthesis of sulfoxide **284**, which was transformed into nucleosides **285** and **286** by condensation with the base in the presence of trimethylsilyl triflate and further deprotection with sodium methoxide (Scheme 76).

Condensation between 4-acetoxy-1,3-oxathiolane **287** and bis(silylated) pyrimidines afforded, after deprotection of the formed adduct mixtures, oxathiolanyl nucleosides **288** and **289**, which were separated by chromatographic methods.[122] Following the same protocol purine oxathiolanyl nucleosides **290** and **291** were also obtained (Scheme 77).

Scheme 76

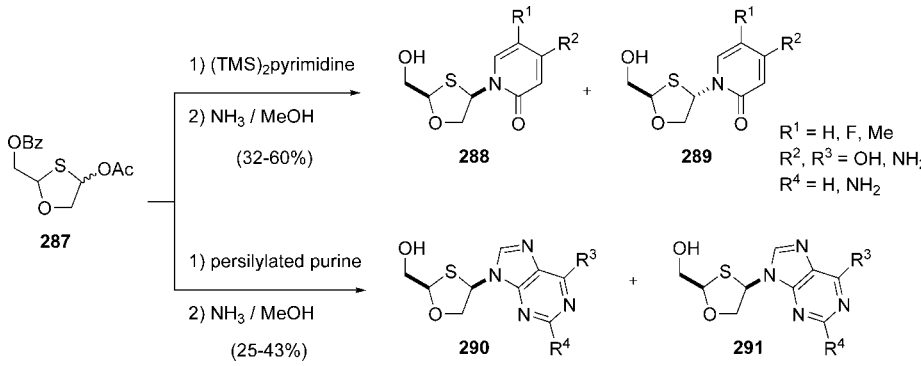


The same protocol applied to dioxolanyl nucleosides, as indicated above, was utilized for preparing oxathiolanyl nucleosides **293** and **294** starting from **277** (Scheme 78)[71] The enantiomeric series of nucleoside analogues was also synthesized using *ent*-**277** as a starting material.

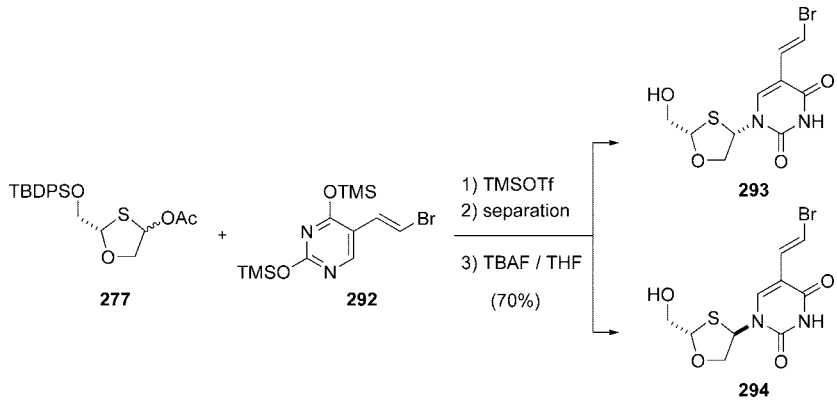
In a similar way to dioxolane analogues (see above), branched oxathiolane nucleosides **296** were prepared by reaction of orthoesters **295** with persilylated thymine or uracil (Scheme 79).[123] Unfortunately, the final nucleoside analogues were obtained in low yields due to dimerization side reactions.

The same methodology outlined in Scheme 57, developed by Chun et al.,[61] was applied for preparing branched oxathiolanyl nucleosides **298** and **299** (Scheme 80).

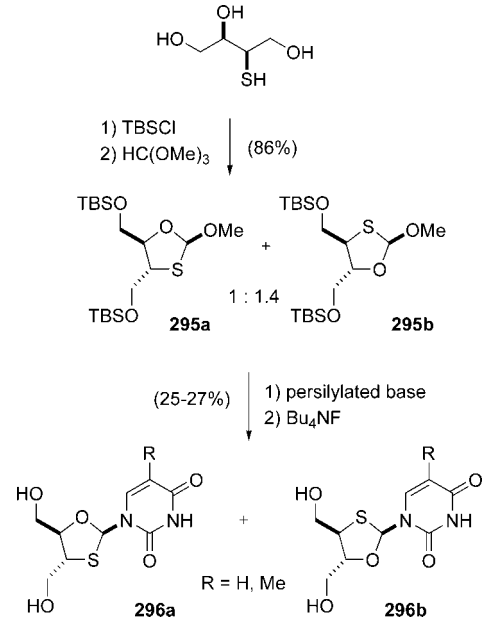
Scheme 77



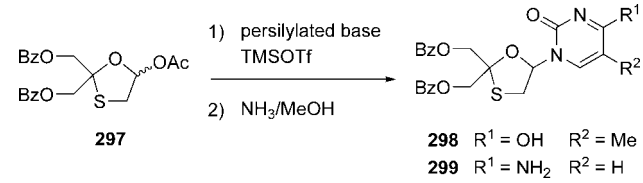
Scheme 78



Scheme 79



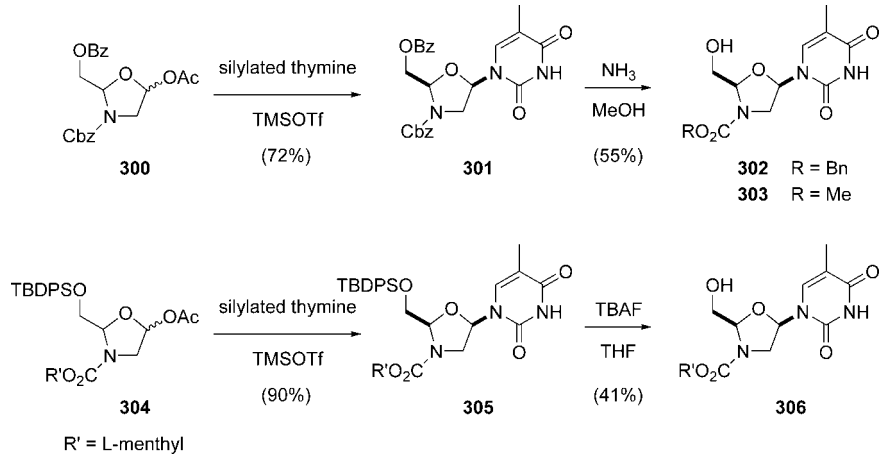
Scheme 80



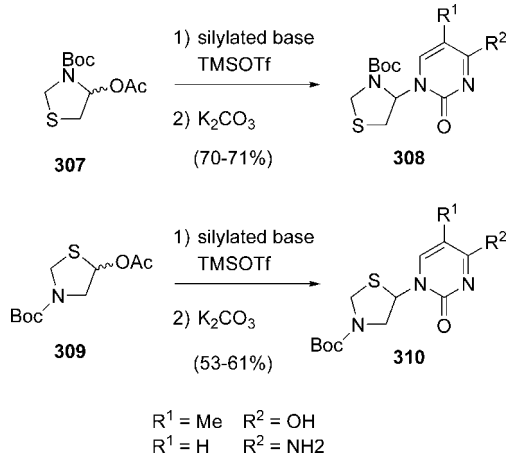
3.4. Oxazolidinyl Nucleosides

Chu et al.[124] prepared N-substituted oxazolidinyl nucleosides employing L-isoserine as a starting material for

Scheme 81



Scheme 82



constructing oxazolidine intermediates **300** and **304** in a stereoselective way. Classical Vörbruggen condensation with silylated thymine afforded protected nucleosides **301** and **305**. After deprotection compounds **302**, **303**, and **306** were obtained (Scheme 81).

3.5. Thiazolidinyl Nucleosides

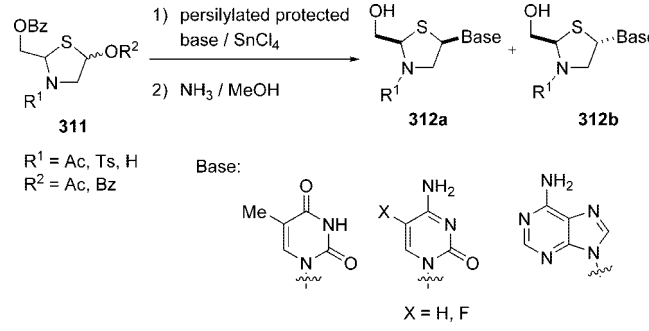
Rassu et al.[125] described two possible classes of thiazolidine nucleosides bearing the heterocyclic base vicinal to the sulfur atom or to the nitrogen atom. These authors reported that the same method is valid for their syntheses, the acetoxy precursors being synthesized from easily available starting compounds. After classical N-glycosylation and basic treatment compounds **307** and **309** were converted into thiazolidine nucleoside analogues **308** and **310**, respectively (Scheme 82).

The Pummerer rearrangement resulted in an adequate approach to prepare thiazolidine precursors **311** needed for the synthesis of nucleosides bearing a hydroxymethyl group like compounds **312** (Scheme 83).[126] Condensation of **311** with persilylated bases in the presence of $SnCl_4$ afforded mixtures of cis and trans nucleoside analogues.[127]

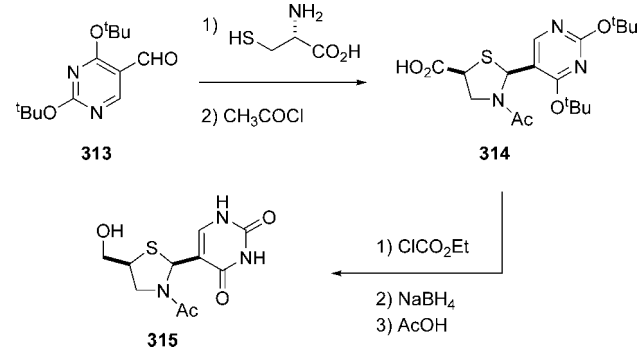
Starting from formyl pyrimidine **313**, 1,3-thiazolidinyl analogues of pseudouridine have been prepared by Bessho et al.[128] The formation of the thiazolidine ring was performed in a enantiodivergent way by using either D- or L-cysteine (only the L-series is showed in Scheme 84).

Kraus et al.[129] reported novel thiazolidine nucleoside analogues bearing an extended methylene bridge between

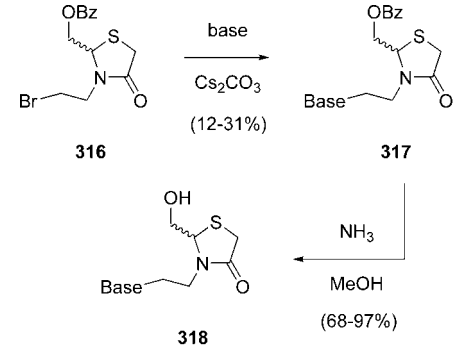
Scheme 83



Scheme 84



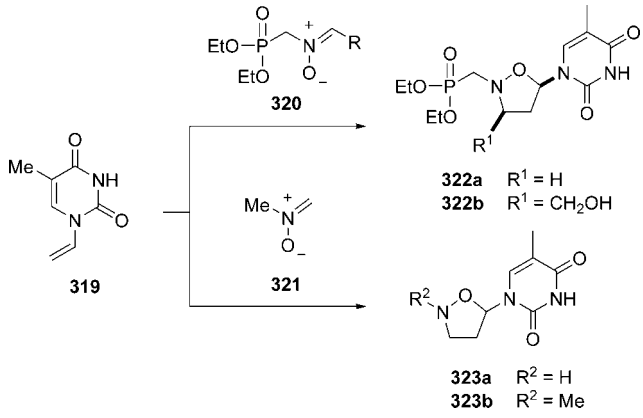
Scheme 85



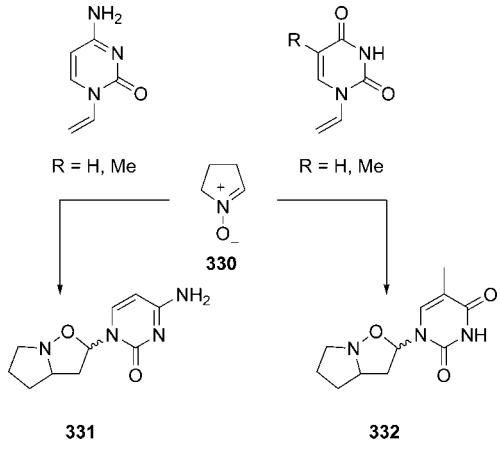
Base: cytosine, 5-fluorocytosine, thymine, adenine

the base moiety and the thiazolidine ring (Scheme 85). The introduction of the base was carried out by nucleophilic substitution mediated by cesium carbonate.

Scheme 86



Scheme 87



3.6. Isoxazolidinyl Nucleosides

The chemical synthesis of isoxazolidinyl nucleosides has been reviewed by Zhao et al.[130] The most evident route for constructing an isoxazolidine ring is the 1,3-dipolar cycloaddition between an alkene and a nitrone. This method gave rapid access to a variety of isoxazolidinyl nucleosides, such as **322** and **323**. Vinylthymine **319** was used as a dipolarophile and nitrones **320** and **321** as dipoles. By using nitrone **320**, phosphorylated compounds were obtained.[131] In the case of compounds **323**, a 1.7:1 mixture of cis and trans adducts was obtained (Scheme 86).[132]

By employment of the same methodology, the synthesis of nucleoside analogues **324**−**327** was also achieved by Sindona et al.[133] Isoxazolidinyl analogues **328** and **329** were prepared by the same research group, analogue **329** being

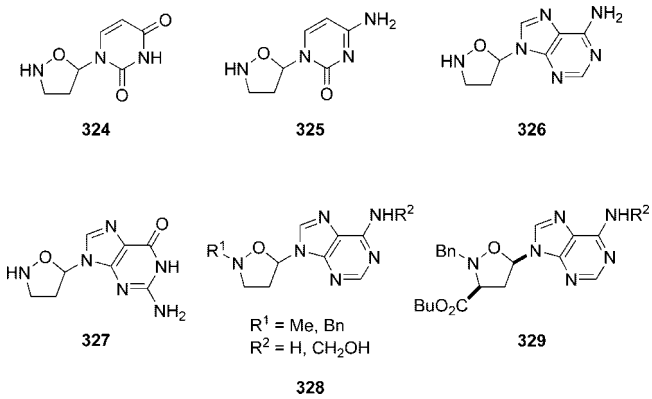
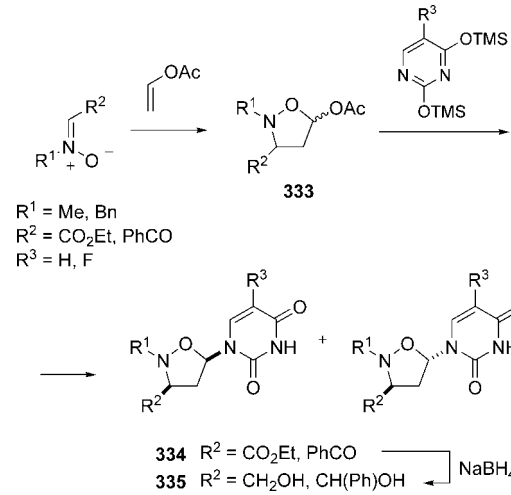
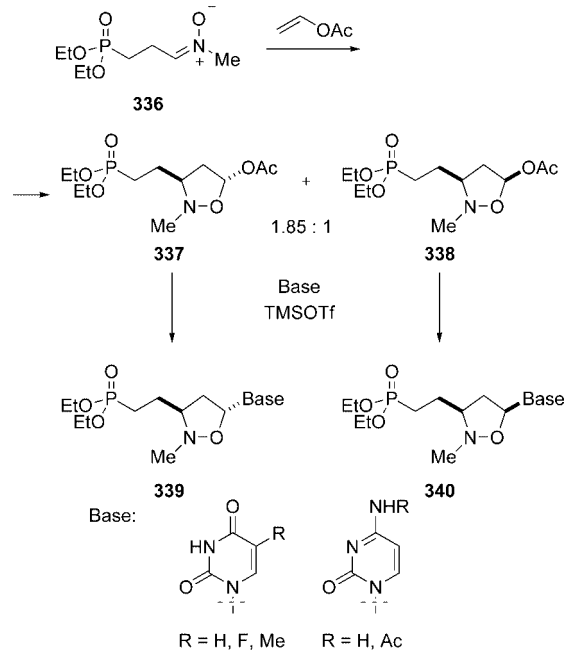


Figure 7.

Scheme 88



Scheme 89



resolved as the only enantiomer with pig liver esterase (Figure 7).[134] An improved method for obtaining **325** from **324** has been developed in a process that is amenable of large-scale preparation.[135]

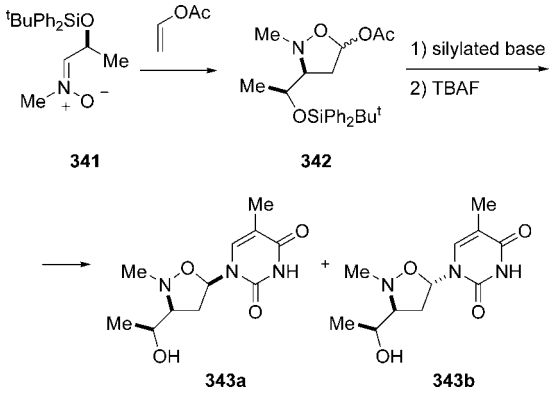
In order to obtain rigidity within the sugar moiety, the same authors reported the synthesis of locked bicyclic N,O-nucleoside analogues **331** and **332** from cyclic nitrones **330** (Scheme 87).[136]

Chiacchio and Romeo et al.[137] reported the N-glycosylation of acetoxy derivatives **333** obtained via 1,3-dipolar cycloaddition of a nitrone and vinyl acetate. Several *cis*- and *trans*-isoxazolidine nucleosides **334** and **335** were prepared by this synthetic route (Scheme 88).

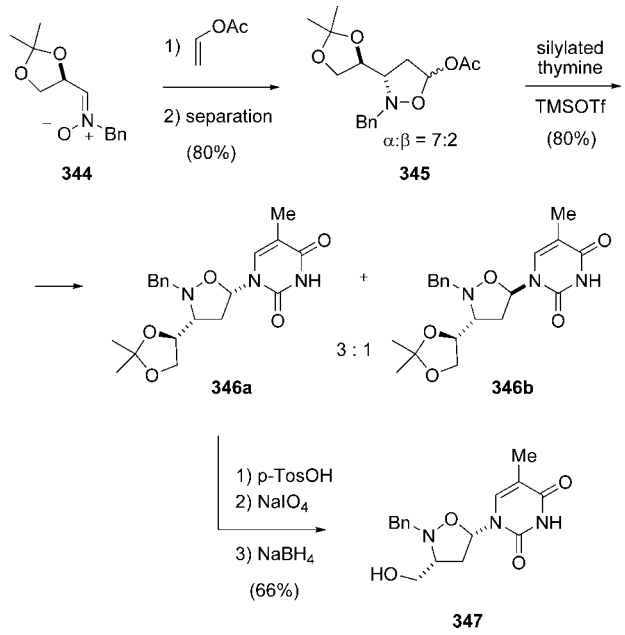
Application of the strategy depicted in Scheme 74 to C-phosphorylated nitrone **336** allowed the preparation of phosphonated derivatives **339** and **340** (Scheme 89).[138] The best results for glycosylation afforded mixtures of anomers with α/β ratios from 1:9 (*N*-acetylcytosine) to 3:7 (thymine and 5-fluorouracil).

By using chiral nonracemic nitrones **341** the same authors reported the synthesis of enantiomerically pure compounds.

Scheme 90



Scheme 91

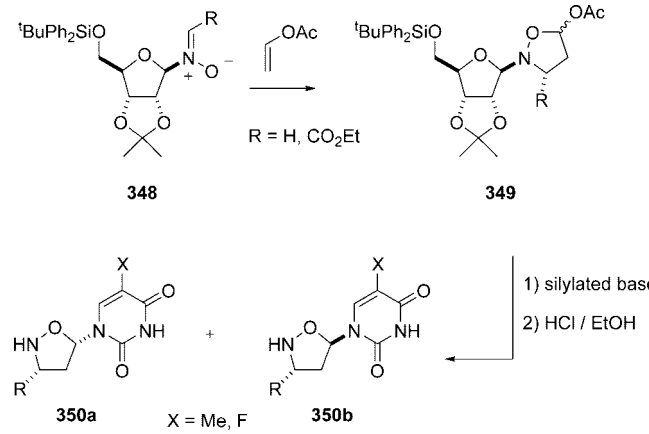


Branched nucleoside analogues **343** were prepared after N-glycosylation of intermediate **342** and further deprotection of the resulting adduct (Scheme 90).[139]

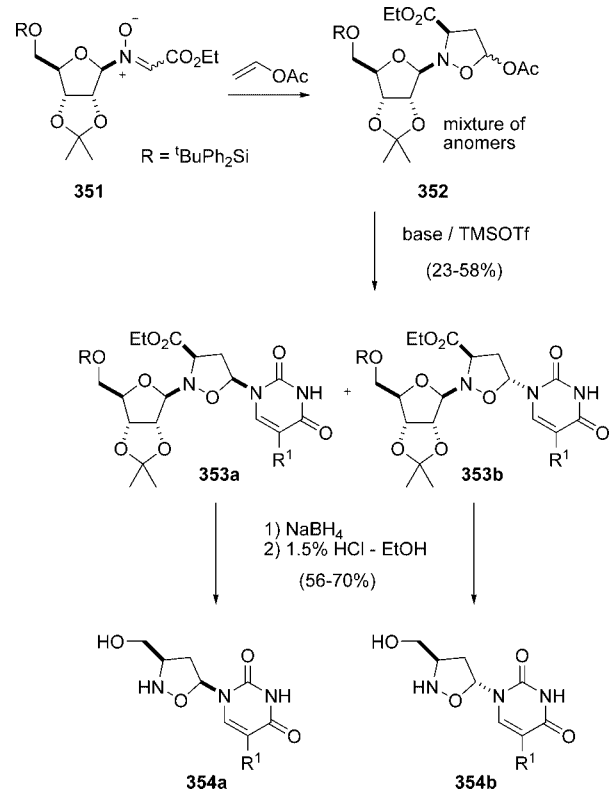
Starting from D-glyceraldehyde-derived nitrone **344**, Merino et al.[140] reported the synthesis of enantiomerically pure isoxazolidinyl nucleosides **347**. The cycloaddition step gave a mixture of three products from which the anomeric mixture **346** was separated in 80% yield. N-Glycosylation took place with good yield, producing two isomers which were separated and converted into the corresponding isoxazolidinyl nucleosides (only the cis isomer is shown in Scheme 91). The dioxolane group was used both to induce chirality and as a synthetic equivalent of the hydroxymethyl group, which was revealed after deprotection and oxidation. The authors also reported in the same work the synthesis of compound **347** by direct cycloaddition reaction between nitrone **344** and vinyl thymine. Three adducts were obtained in a ratio 8:2:1, the major one being the immediate precursor of **347**.

An improved method for obtaining unprotected enantiomerically pure isoxazolidinyl nucleosides was reported by the groups of Chiacchio and Romeo.[141] The use of chiral auxiliaries at the nitrogen atom of the nitrone functionality allowed elimination of the N-protecting group, thus furnishing free nucleoside analogues. Cycloaddition of vinyl acetate with nitrone **348** afforded adduct **349** predominantly, which

Scheme 92



Scheme 93



was converted into isoxazolidnyl nucleosides **350** after N-glycosylation and elimination of the chiral auxiliary by acidic hydrolysis (Scheme 92).

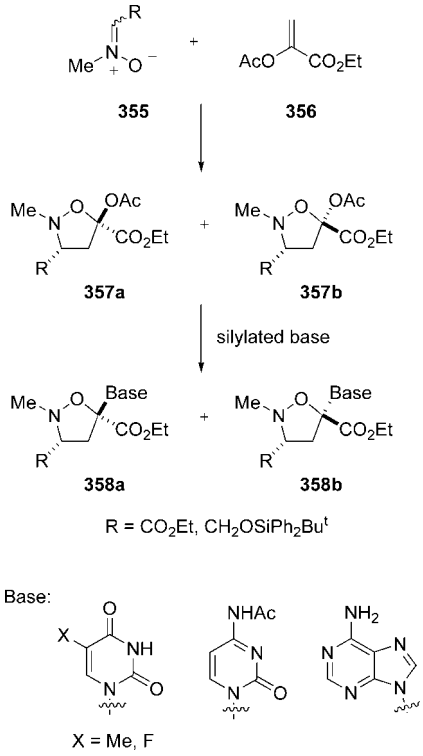
The same approach was used for synthesizing isoxazolidinyl nucleosides **354**. Using nitrone **351** as a suitable starting material, isoxazolidinyl nucleosides bearing a hydroxymethyl group could be prepared (Scheme 93).[142]

Psiconucleosides analogues **358** were also prepared by utilizing the cycloaddition approach for constructing the isoxazolidinyl ring.[143] Condensation between nitrones **355** and dipolarophile **356** afforded intermediates **357**, which were transformed in 2 steps into compounds **358** (Scheme 94).[144]

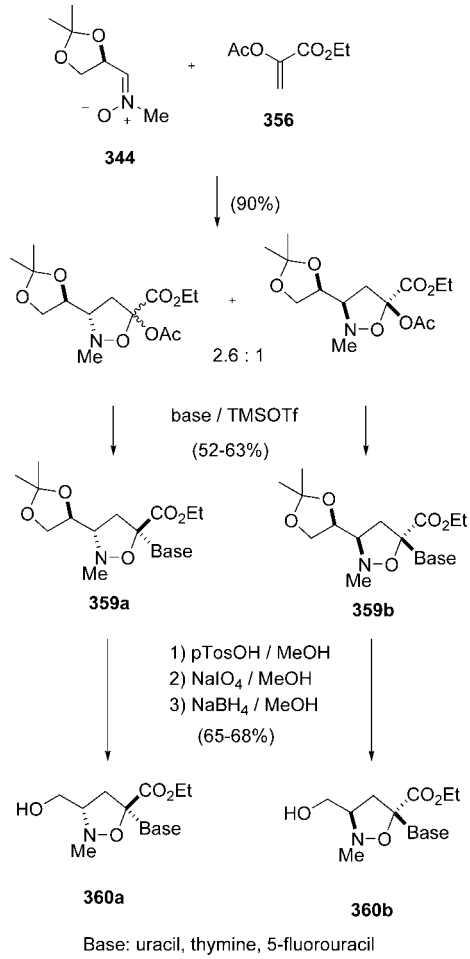
Enantiomerically pure isoxazolidinyl psiconucleosides were prepared by the same cycloaddition approach and using nitrone **344** as a chiral nonracemic starting material (Scheme 95).[145]

Isoxazolidinyl homonucleosides **363** have been synthesized through the 1,3-dipolar cycloaddition of nitrones **361** and allyl bases **362** (Scheme 96).[146] Several theoretical studies

Scheme 94

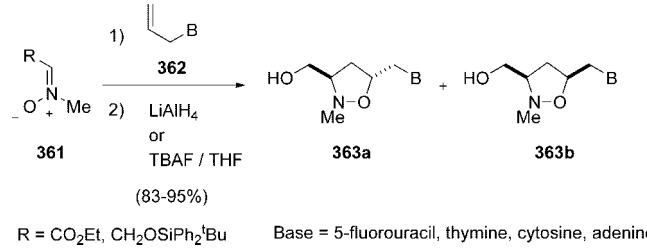


Scheme 95

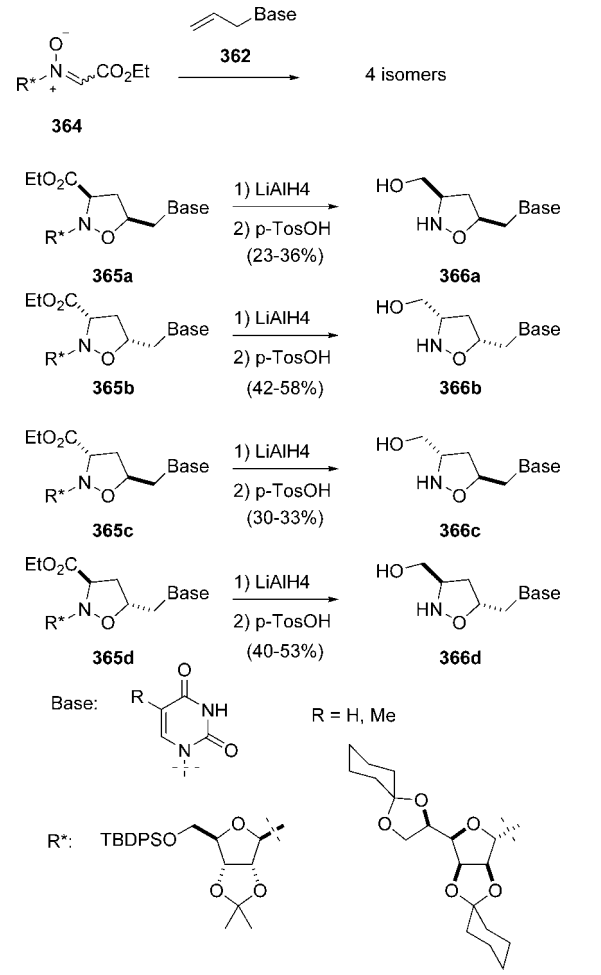


were conducted for these reactions, and they were found to be in agreement with the experimental results.

Scheme 96



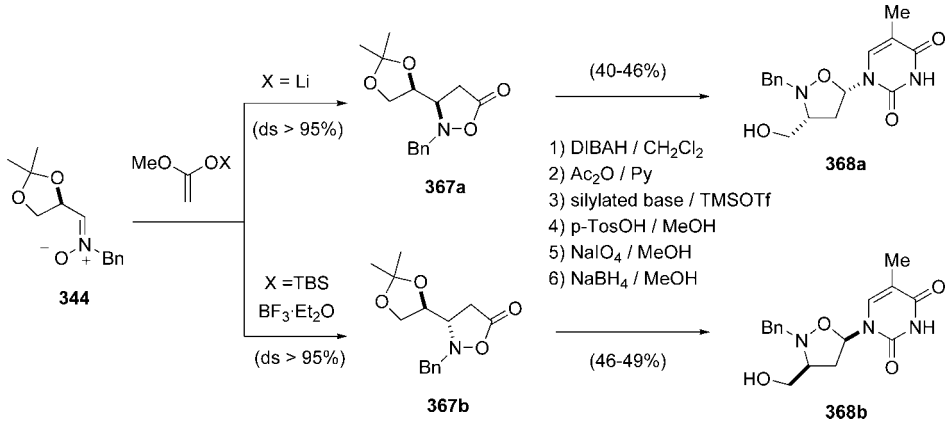
Scheme 97



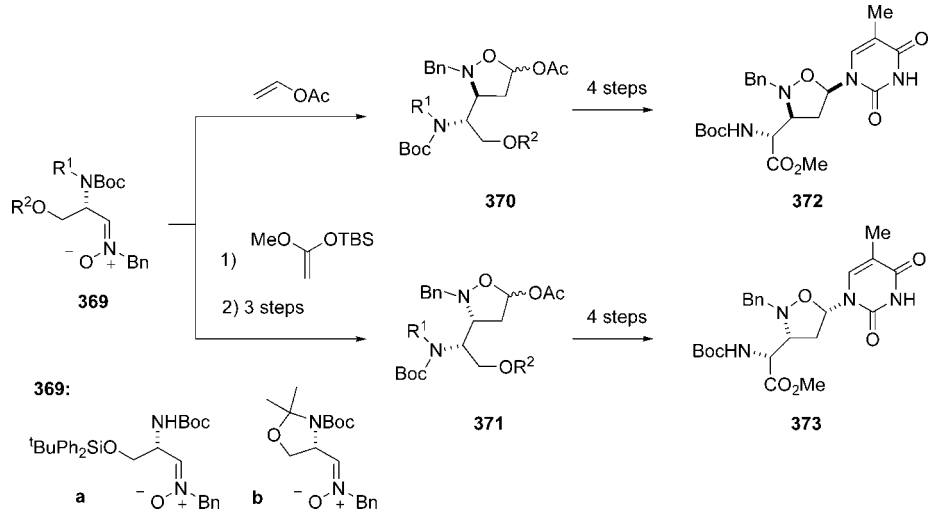
The enantioselective series of these compounds was prepared by following the same strategy as depicted in Scheme 97.[147] Nitrones derived from two different carbohydrate units, i.e., D-ribose and D-mannose, were used, both of them showing a good degree of enantioselectivity. By following this approach enantiomerically pure compunds **366** were obtained.

Merino et al.[148] reported an alternative method for constructing the isoxazolidine ring by means of the addition of ester-derived enolates to the nitrone **344**. The resulting isoxazolidinones **367** were transformed into the corresponding acetoxy derivatives isoxazolidinyl nucleosides **368** as described, which were converted into isoxazolidinyl nucleosides as described above (Scheme 98). The stereocontrolled addition of the enolates,[149] either as sodium enolates or as silyl ketene acetals in the presence of a Lewis acid, allowed the enantiodivergent synthesis of both series of isoxazolidinyl nucleosides **368**.

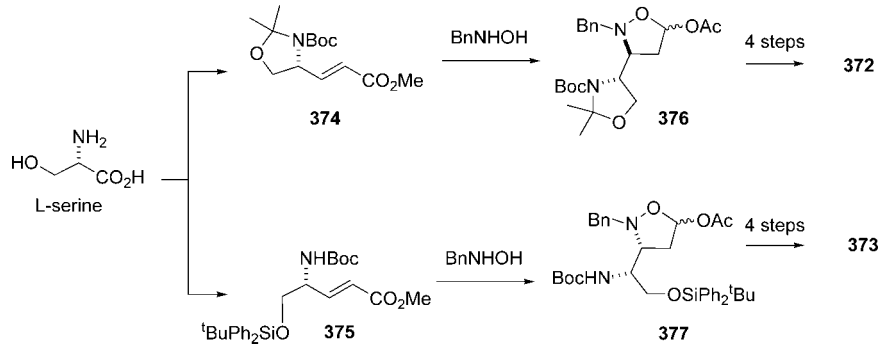
Scheme 98



Scheme 99



Scheme 100

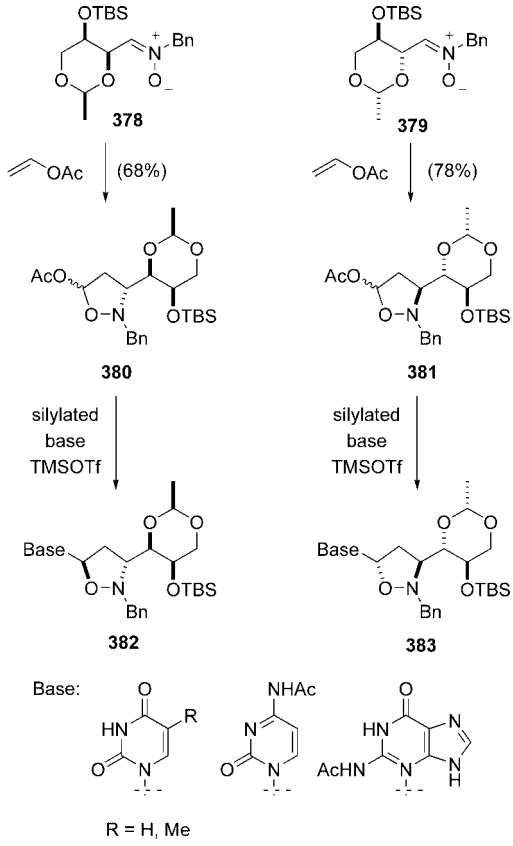


The same authors also reported[150] the synthesis of complex isoxazolidinyl nucleosides bearing an amino acid unit linked to the isoxazolidine ring. By using L-serine-derived nitrones **369** isoxazolidinyl analogues of thymine polyoxin C **372** and **373** were prepared. Three available routes for constructing the isoxazolidine ring, including Michael addition,[151] dipolar cycloaddition, and nucleophilic addition,[152] were explored. The cycloaddition route and nucleophilic addition were complementary since they led to syn and anti isoxazolidinones **370** and **371**, respectively (Scheme 99). Starting from these compounds, nucleoside analogues **372** and **373** with the opposite configuration at C-3 were prepared.

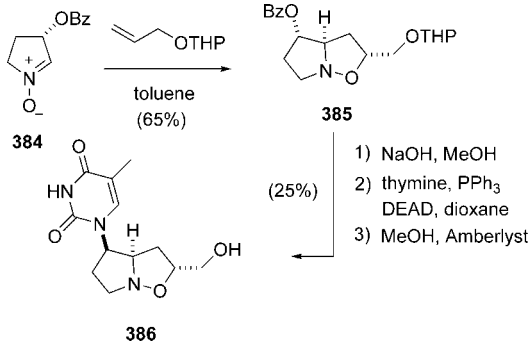
The Michael addition route[130] allowed a complete diastereodivergency since, depending on the protecting groups disposition at the starting material, opposite diastereofacial inductions were observed, thus allowing the stereocontrolled preparation of analogues **376** and **377** starting from L-serine as a common precursor (Scheme 100).

Isoxazolidinyl nucleosides bearing a polyhydroxylated chain in place of the characteristic hydroxymethyl group have been reported by Fisera et al.[153] Cycloaddition reaction between protected nitrone **378** and vinyl acetate afforded a 84:16 mixture of isomers from which **380** was separated. Introduction of the base moiety under typical Vörbruggen conditions afforded D-threo nucleoside ananlogues **382**. Similarly, by using D-erythro nitrone **379** the corresponding nucleoside analogues were obtained. The methodology was applied to both pyrimidine and purine nucleobases (Scheme 101). In all cases, the β-nucleosides were formed preferentially, although in some ones near 1:1 mixtures of anomers

Scheme 101



Scheme 102

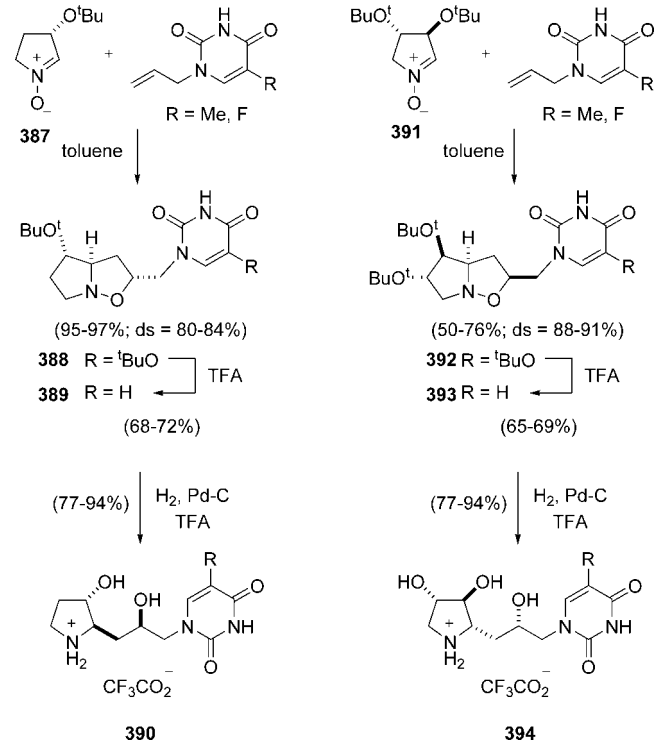


were found. The same authors applied this methodology for preparing the corresponding D-xylo-isoxazolidinyl nucleosides.[154]

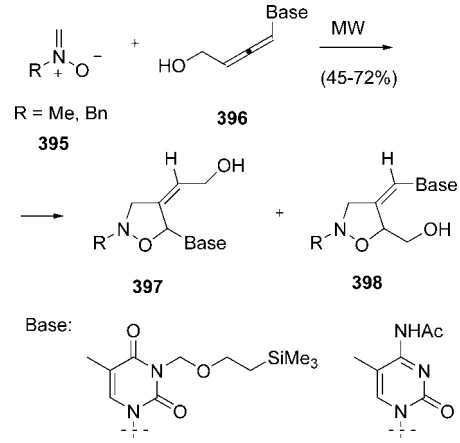
Bicyclic nucleoside analogue **386** containing an isoxazolidine nucleus was prepared through a 1,3-dipolar cycloaddition of enantiomerically pure cyclic nitrone **384** and protected allyl alcohol.[155] The reaction afforded a 5:1.7:1 mixture of three cycloadducts from which compound **385** was isolated in 65% yield. The introduction of thymine by a Mitsunobu reaction afforded the targeted iso-homonucleoside analogue (Scheme 102).

By carrying out the cycloaddition reaction with allyl bases a collection of new homonucleoside analogues **389** and **393** was described.[156] In these compounds the furanose ring of a typical nucleoside has been replaced by a pyrrolo[1,2-*b*]isoxazolidine system. Also, the reduction of the isoxazolidine ring, which can be considered as a synthetic equivalent of a 1,3-aminoalcohol unit, allowed the preparation of novel pyrrolidinyl analogues (azanucleosides) **390** and **394** (Scheme 103).

Scheme 103



Scheme 104

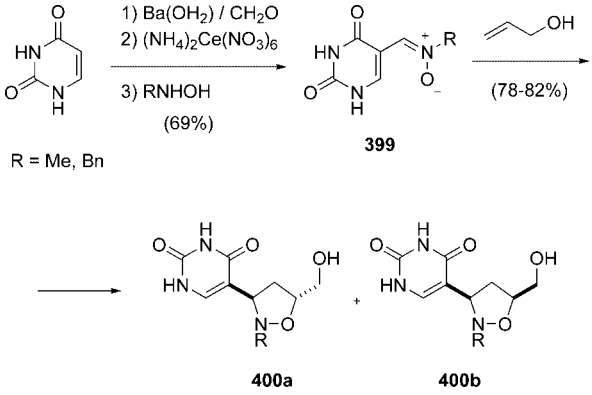


Conformationally locked isoxazolidinyl nucleosides were synthesized by using allenic nucleobases **396** as suitable dipolarophiles in cycloaddition reactions with nitrone **395**.[157] The reaction, carried out under microwave irradiation, gave rise to a mixture of two regiosiomeric analogues **397** and **398** (Scheme 104).

A new class of isoxazolidinyl C-nucleosides has been approached by using thymine-derived nitrones **399** (Scheme 105). Condensation of these compounds with allylic alcohol affords in only 1 step the new compounds **400**.[158] The reaction has been studied with model compounds, and use of Lewis acids showed promising results.[159] By employing the methodology outlined in Scheme 105, the isoxazolidinyl analogue of pseudouridine **400b** has been prepared.

The isoxazolidinyl analogue of the important C-nucleoside thiazofurin has also been reported.[160] The cycloaddition between nitrone **344** and acrylonitrile afforded compound **401** as the major adduct. Construction of the thiazole ring was made by conventional methods using L-cysteine. After unmasking of the hydroxymethyl group from the dioxolane

Scheme 105

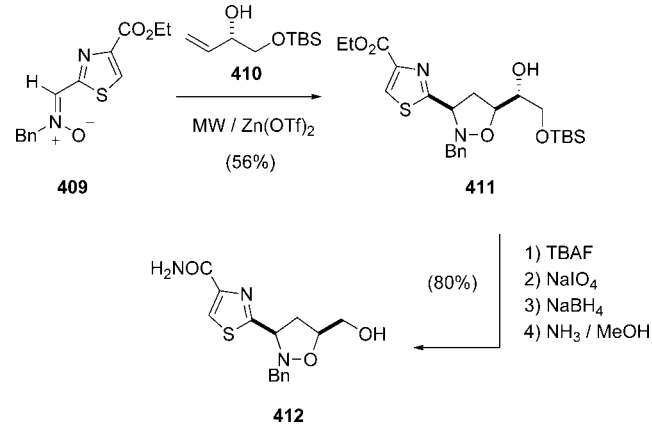


ring and treatment with liquid ammonia, the *N*-benzyl analogue **404** was obtained (Scheme 106).

In the same work, the authors also described an improved strategy which allowed the synthesis of debenzylated isoxazolidinyl thiazofurin **408**. Starting from nitrone **405**, the same methodology outlined in Scheme 106 furnished compound **407**, which was readily transformed into **408**. In addition, the two approaches illustrated in Schemes 107 and 108 were shown to be complementary since the two enantiomeric series were accessible depending on the starting nitrone employed in the initial step.

The reverse analogue of thiazofurin, i.e., that in which the thiazole ring is linked vicinal to the nitrogen atom of the isoxazolidine ring, has also been prepared.[161] In this case,

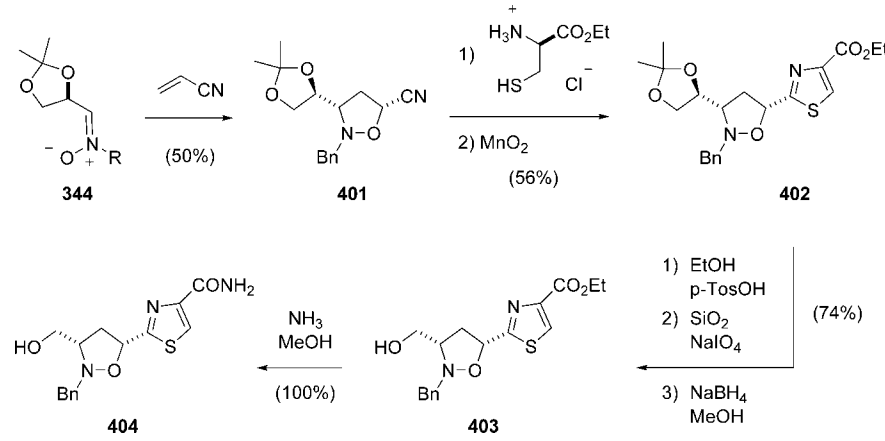
Scheme 108



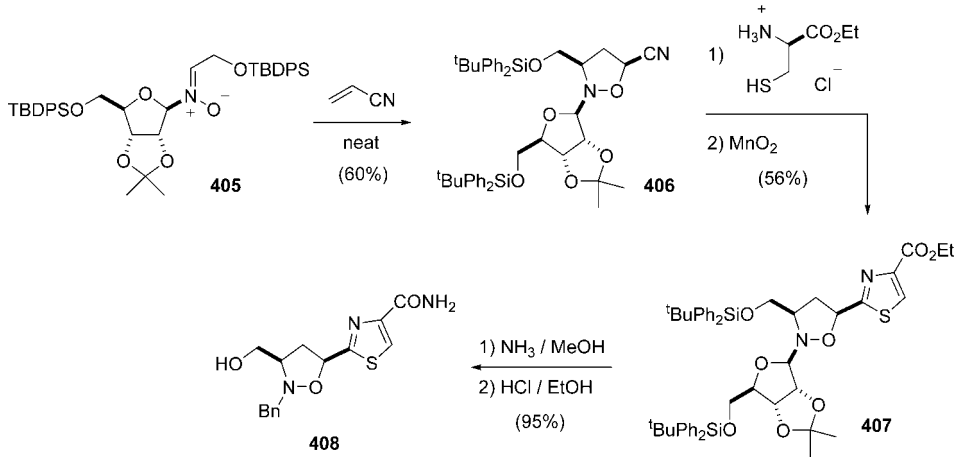
the new thiazolyl nitrone **409** was prepared and subjected to cycloaddition with the chiral nonracemic allylic alcohol **410**. Both the presence of Lewis acids and microwave irradiation were crucial for the success of the reaction. The major adduct **411** obtained was readily transformed into the thiazofurin analogue **412** (Scheme 108).

The 1,3-dipolar cycloaddition of the nitrone **414** generated in situ from N-Fmoc-protected glycynal **413** and a D-mannose-derived hydroxylamine furnished a mixture of adducts from which compound **415** was obtained in 92% and 72% d.r. N-Glycosylation of **415** and further elimination of the chiral auxiliary furnished a 1.6:1 mixture of isoxazolidinyl nucleosides **416**. The introduction of a *tert*-butoxy-

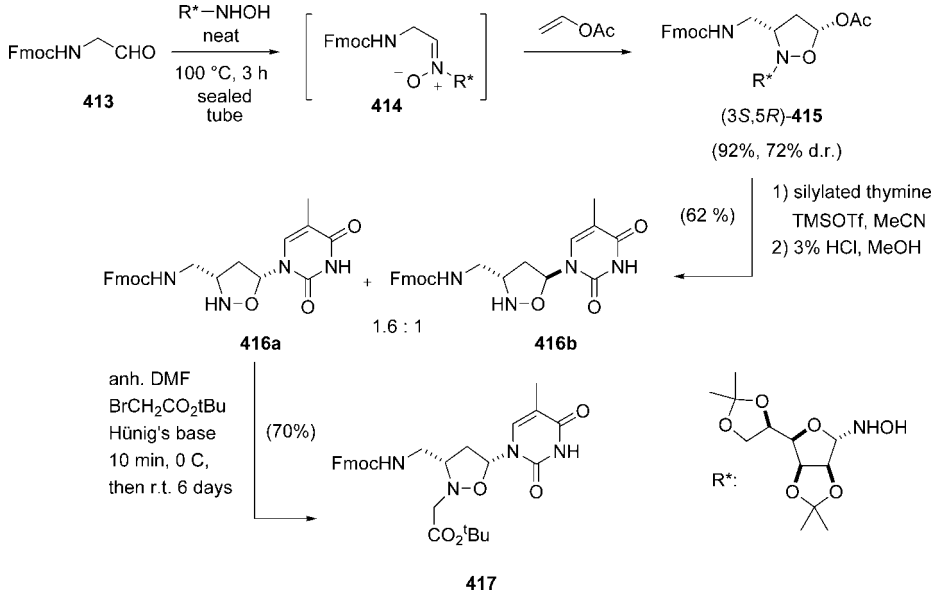
Scheme 106



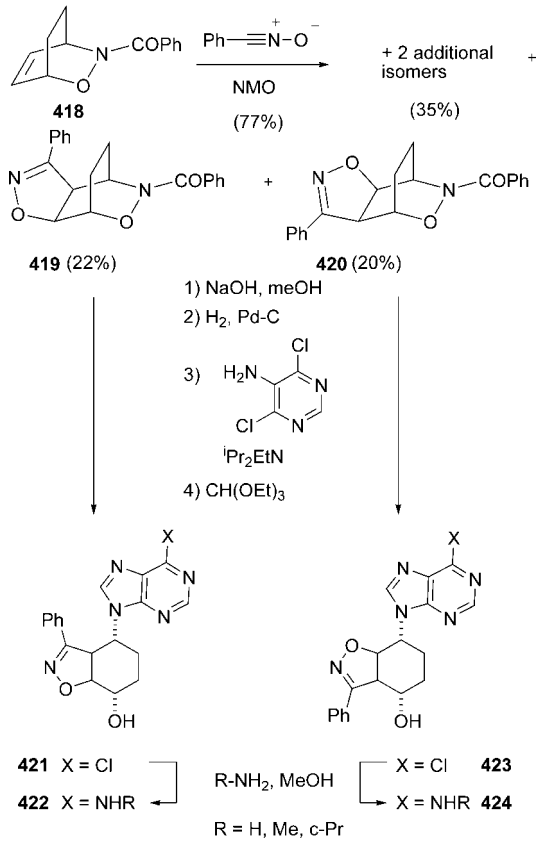
Scheme 107



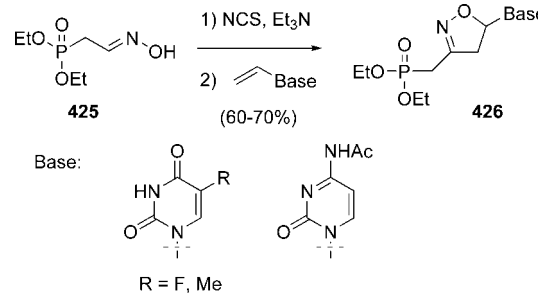
Scheme 109



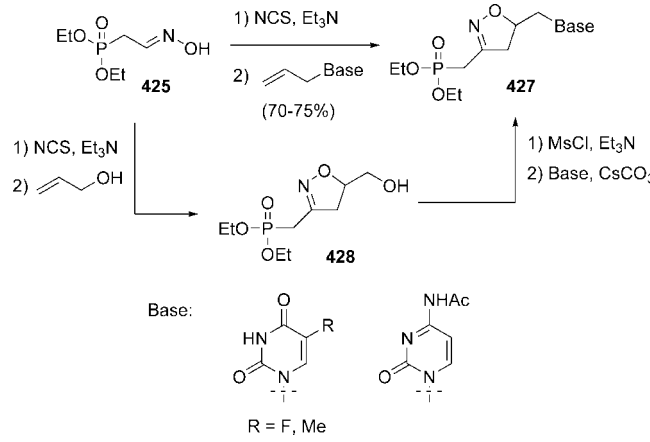
Scheme 110



Scheme 111



Scheme 112



carbonylmethyl moiety at the endocyclic nitrogen atom led to monomer **417** suitable for preparing PNA analogues bearing a isoxazolidine ring (Scheme 109).[162]

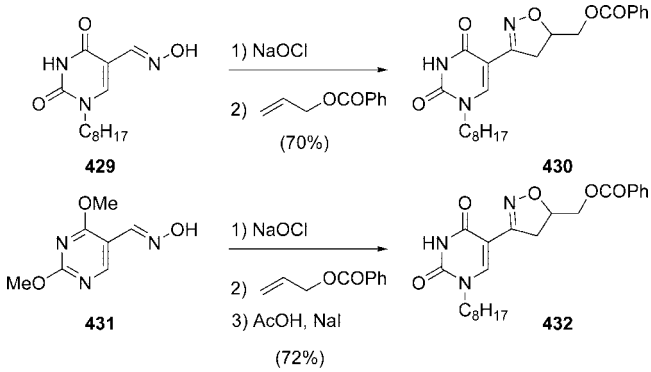
3.7. Isoxazoline Nucleosides

Quadrelli et al. reported the preparation of isoxazoline-based carbocyclic nucleosides **422** and **424**.[163] The bicyclic nucleus of these analogues was prepared through a cycloaddition reaction between 1,3-cyclohexadiene and acylnitroso compounds (Scheme 110).[164] After appropriate transformations the heterocyclic base moiety was constructed over the amino group emerged after reduction of the saturated N−O bond in compounds **419** and **420**. Substitution of the chlorine atom by the amino group was further studied by using several primary amines.[165]

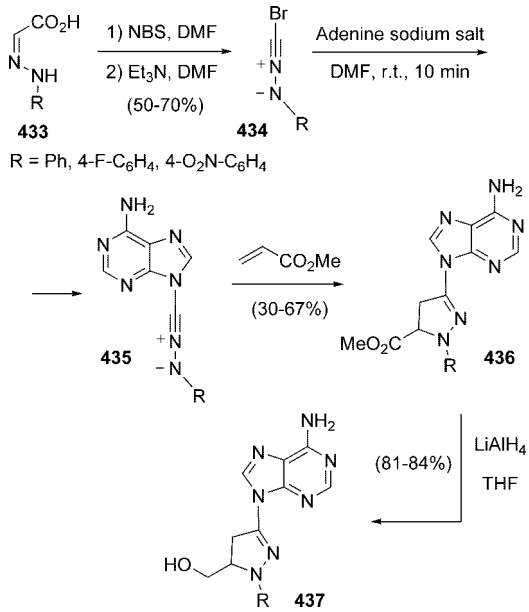
Romeo et al. reported the synthesis of phosphonated isoxazolinyl nucleosides **426** through the 1,3-dipolar cycloaddition of nitrile oxides and vinyl nucleobases (Scheme 111).[166]

The corresponding homonucleosides **427** have also been prepared by using as dipolarophiles allylnucleobases or, alternatively, allyl alcohol followed by introduction of the base moiety through a substitution reaction (Scheme 112).

Scheme 113



Scheme 114



Isoxazoline analogues of C-nucleosides related to pseudouridine have been reported.[167] Cycloaddition reactions of nitrile oxides derived from substituted uracils or dimethoxypyrimidines with suitable dipolarophiles afforded the target compounds **430** and **432** in good yields (Scheme 113). The authors used similar procedures for preparing the corresponding isoxazole and isoxazolidine analogues.

3.8. Pyrazolinyl Nucleosides

Cycloaddition of base-containing nitrilimines with methyl acrylate afforded immediate precursors of a novel class of nucleoside analogues bearing a pyrazole ring at the place of the furanose ring.[168] The bromonitrilimine **434** generated in situ from glyoxylic acid hydrazone **433** reacted directly with the sodium salt of adenine to form intermediate **435**, which underwent cycloaddition with methyl acrylate, affording adduct **436**. Reduction of **436** gave rise to the target pyazolinyl adenosine **437** in good overall yield (Scheme 114).

4. Concluding Remarks

The examples outlined in this review may illustrate that nucleoside analogues modified in the structural core of the ribose unit are now accessible with high efficiency and in preparative amounts. Whereas the typical structures modified in the ribose unit by changing or modifying substituents can be synthesized more or less routinely, the construction of specific heterocyclic rings as surrogates of the furanose ring demands more specific differentiation and intercompatibility of the different synthetic methods applied in the synthesis of the diverse structural motifs acting as spacers between the hydroxymethyl group and the nucleobase. Chemically synthesized heterocyclic nucleosides could now be added to the vast family of nucleoside analogues including carbocyclic nucleosides, which can be used as therapeutic drugs against a variety of important diseases and metabolic disorders. Several groups have taken steps in this direction with the conjugation of chemical and biological studies of the newly prepared compounds. In this fashion, a pleyade of new nucleoside analogues will be accessible in a short period of time. The extension of these approaches to include nucleoside analogues in which the furanose ring has been replaced by a different heterocyclic ring is a major frontier in nucleoside chemistry.

5. Acknowledgments

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