Preparation of Cyclonucleosides

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1. Introduction

The study of the biological activity of nucleosides has been a fundamental and fruitful field of research since the 1940s and 1950s. It was then that the role of nucleic acids in cells was established, ultimately resulting in the identification of the double-helix structure of DNA and the explanation of the genetic role. As their metabolic processes became understood, so the investigation of close analogues of the components of nucleic acids grew. Some of the compounds resulting from this work, indeed, modified pyrimidine and purine nucleoside derivatives, have been shown to possess antiviral, antimetabolic, and antibacterial properties.[1] The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. The main groups of bioactive, modified nucleosides which exhibited a wide range of activities and consequently received great attention from scientists include acyclic nucleosides,[2] possessing acyclic chains instead of a ribose ring, L-derivatives,[3] the counterparts of naturally occurring D-nucleosides, and carbocyclic nucleosides possessing a carbocyclic ring instead of a ribose ring.[4] Other useful modifications include introduction of fluorine atom(s) into the molecule,[5] exchange of the ribose ring for a heterocyclic ring containing sulfur or nitrogen,[6] or exchange of the glycoside C−N bond for a C−C bond (*C*-nucleosides).[7] One transformation has resulted in the preparation of cyclonucleosides, bearing additional linkages (C−O, C−N, C−S, C−C) between the heterocyclic ring and the sugar moiety. Although cyclonucleosides were the target of chemists for conformational studies as early as the 1960s with the pioneering work of Todd et al.[8] and by Ikehara's group,[9,10] the scientific literature is sparse on their application against biological targets, with little primary literature on the biological targets. Some of the obtained compounds possess a wide range of antiviral[11] or antitumor[12] activities. Among them, the 2,5′-*O*-anhydrouridine analogue of BVDU (5-bromovinyl-2′-deoxyuridine) exhibited an anti-HSV-1 activity,[13] while 2,5′-*O*-bridged analogues of AZT (3′-azido-3′-deoxythymidine) and AZU (3′-azido-3′-deoxyuridine) were tested against HIV and R-MuLV.[14] 8,5′-*O*-Anhydroadenosine inhibits *uridine phosphorylase*;[15] meanwhile, 6,5′-*O*-anhydrouridine and 8,3′-*O*-anhydroadenosine are inhibitors of *rhodopsin* kinase[16] (Figure 1). Cyclonucleosides **A1**−**A3** were used to study the influence of γ-radiation on DNA,[17,18] bridged acyclonucleoside analogues **B1**−**B2** exhibited biological activities,[19] and compound type **C1** exhibited anti-HCV activity.[20]

Recently, in 2005, N^3,5′-cycloxanthosine was isolated from an *Eryus* sp. of marine sponge.[21] This was the first natural occurrence of a cyclonucleoside. This discovery is of great importance as natural nucleosides from marine sponges

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Adam Mieczkowski, born in Warsaw, Poland (1977), received his B.S. (2000) and Ph.D. (2005) degrees in chemistry from the University of Warsaw (Poland) under the supervision of Professor J. Jurczak. While he was studying for his B.S., he was involved in research concerning diastereoselective synthesis, and then, while he was studying for his Ph.D., he joined a project concerning solid-supported synthesis of small heterocyclic molecules (β-turn mimetics, benzodiazepines). Dr. Mieczkowski held a two-year, postdoctoral appointment at the University of Orléans (France), working with Professor L. A. Agrofoglio on the synthesis of novel anti-HCV and anti-HIV nucleoside derivatives. Since 2008, after receiving a GCOE (Global Center of Excellence) fellowship followed by a JSPS (Japanese Society for the Promotion of Science) fellowship, he has held a second postdoctoral position at The University of Tokyo under the supervision of Professor Eiichi Nakamura, working on the modern aspects of catalysis and organometallic chemistry. His main interests include medicinal chemistry and the chemistry of heterocyclic compounds as well as the applications of organometallic chemistry and catalysis in the synthesis of bioactive molecules.

Vincent Roy was born in Perigueux, France, in 1978. He received his Ph.D. degree in organic chemistry in 2004 from the University of Limoges (France) under the direction of Professor Rachida Zerrouki and Professor Pierre Krausz, working on the synthesis of mono- and dinucleoside analogues. He conducted postdoctoral studies first at the Ecole Normale Superieure (2004) of Lyon (France) with CNRS Research Director Jean-Pierre Dutasta and in 2005 at the Institut of Organic and Analytical Chemistry (ICOA) of the University of Orléans (France) with Professor Luigi A. Agrofoglio. In 2006, he held his last postdoctoral position in the United States in the research group of Professor Raymond F. Schinazi at Emory University (Atlanta, GA). Since 2007, he has been Assistant Professor in the group of Pr. Luigi A. Agrofoglio at ICOA (France) in the group of Synthesis and Bioanalysis: Antiviral and Antitumoral Bioorganic Chemistry, where he works in the field of nucleoside and heterocyclic chemistry.

(spongothymidine and spongouridine isolated from a Caribbean sponge)[22] have inspired development of antileukemic and antiviral agents, Ara-C and Ara-A, respectively. In fact,

Luigi A. Agrofoglio, born in Antibes, France (1965), received his B.S. (1987) and Ph.D. (1993) degrees in chemistry from the University of Nice Sophia-Antipolis (France), working with Professor R. Condom on the synthesis of carbocyclic analogues of nucleosides. Dr. Agrofoglio held postdoctoral appointments at the University of Alabama at Birmingham, working with Professor J.-P. Sommadossi, as well as at the University of Georgia at Athens, working in the laboratory of Professor C. K. Chu. He joined the Institute of Organic and Analytical Chemistry, a CNRS research laboratory associated with the University of Orléans (France) as Assistant Professor in 1995. Nominated Full Professor in 2005, he is nowadays the group leader of the research team Synthesis and Bioanalysis: Antiviral and Antitumoral Bioorganic Chemistry. His main areas of expertise and interest deal with organic and medicinal chemistry of nucleosides and heterocycles, as well as bioanalysis and molecularly imprinted polymers. He has coauthored about eighty publications in these fields and two patents.

N^3,5′-cycloxanthosine was patented[23] in 2004 as a member of the family of "synthetic"' nucleosides with antiviral properties.

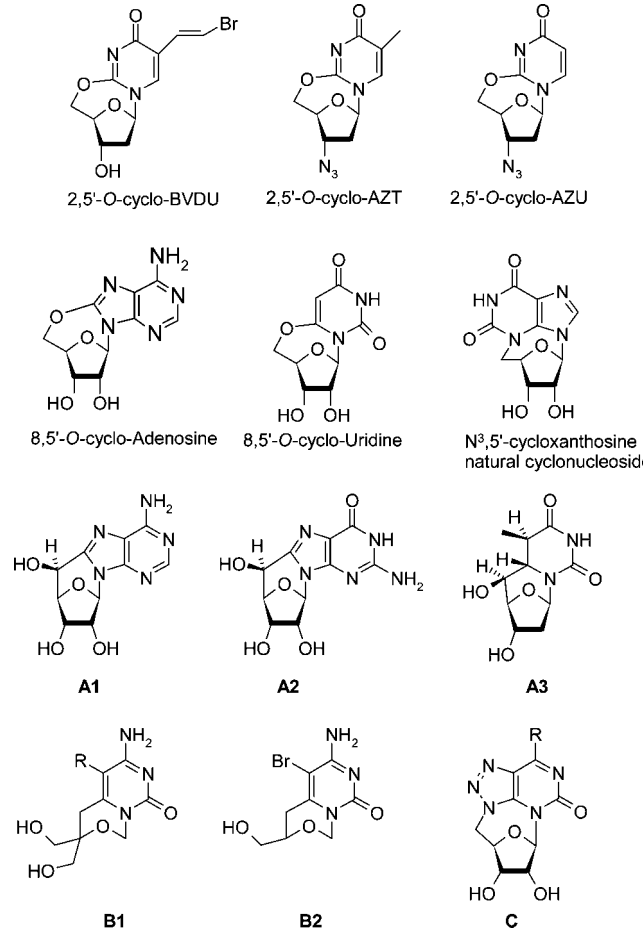


Figure 1. Structural diversity of bioactive cyclonucleosides.

While cyclonucleosides could be obtained in many different ways, the halogen-involved methods seem to be most common for compounds possessing oxy, thio, and amino bridges. These methods include formation of a new covalent bond between the sugar and base either during the introduction or basic elimination of a halogen on the nucleobase. In some approaches the covalent linkage between the sugar and pyrimidine base is formed initially, and then the classical, glycosidic bond is formed. Additionally, a lot of specific, nongeneral methods leading to pyrimidine cyclonucleosides, including rearrangements of cyclonucleosides, were developed giving cyclized products under various conditions.

Unfortunately, the present literature suffers from the lack of a comprehensive review. Therefore, our objective in this review is to draw together all of this material in a form which is easily consulted and at the same time guides the reader into the primary literature on the subject. The coverage is primarily from the point of view of organic and medicinal chemists. It is our intention to describe in detail those strategies that have been employed to make cyclonucleosides, including those with unusual substituents. The preparation of C-bridged cyclonucleosides has been recently reviewed by Len et al.[24] and thus will not be covered by this review. The pyrimidine cyclonucleosides possessing O^2-, S^2-, and N^2-linkages, the syntheses and reactivities of which are well-known,[9,10] are not fully covered by this review; only selected examples are shown. The literature has been surveyed through September 2009.

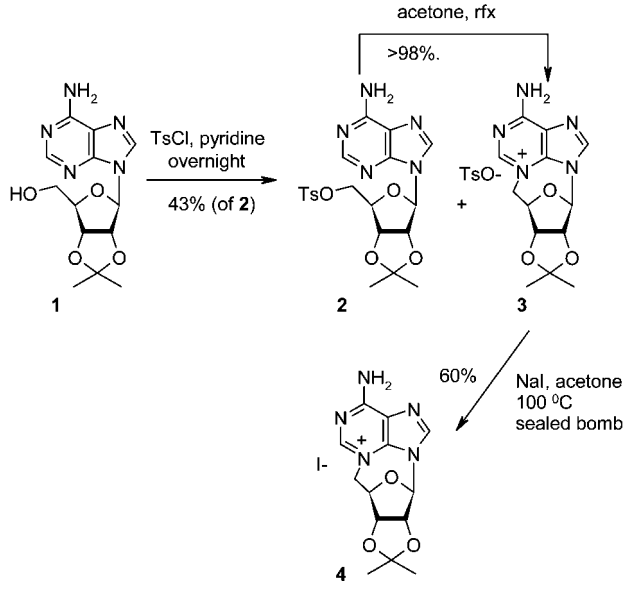
2. Synthesis of Purine Cyclonucleosides

2.1. From Sulfonates and Analogues

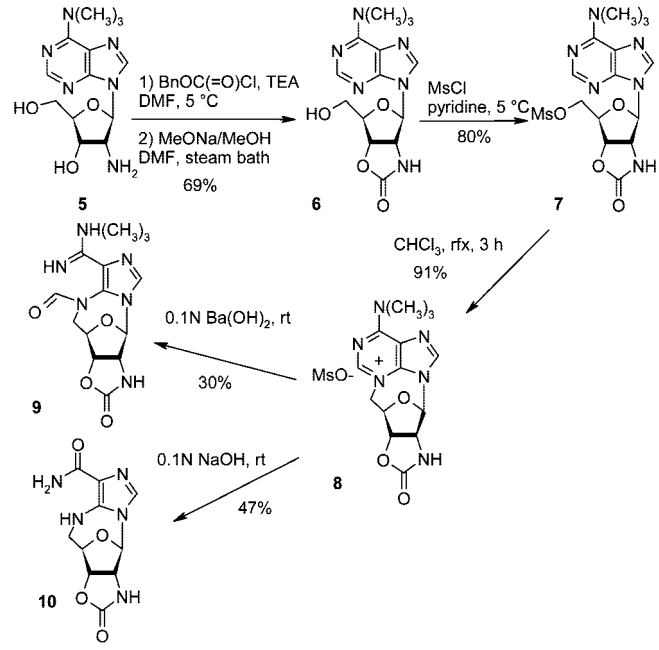
2.1.1. With a C5′−N Bridge by Cyclization−Quarternization

In 1951, Clark et al.[8] reported that during the toluene-*p*-sulfonylation of 2′,3′-*O*-isopropylideneadenosine (**1**), two isomeric products were isolated, corresponding to the expected 5′-tosyl ester derivative **2** and to the ionic N^3,5′-cyclo compound **3** containing the toluene-*p*-sulfonate anion (Scheme 1). On being heated in acetone, the ester **2** is rapidly converted into **3**, which leads to an ionic iodide, **4**, on

Scheme 1



Scheme 2



treatment with NaI. The observed intramolecular alkylation was bound up with the basic character of the adenine heterocycle; under the same conditions, no intramolecular cyclization was observed during the tosylation of inosine.

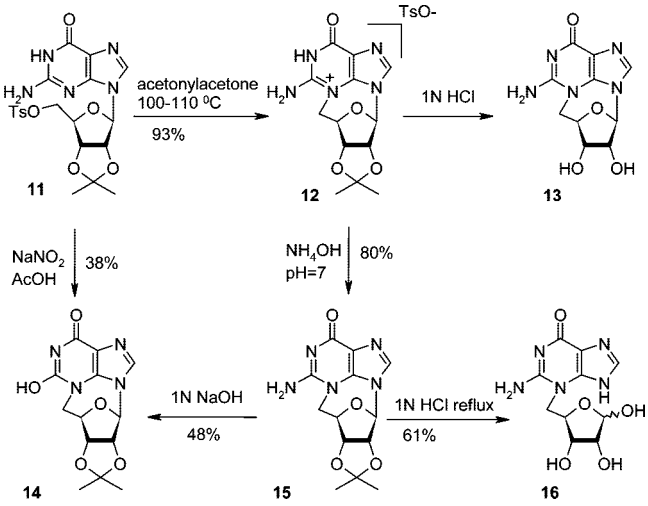
In 1955, Baker et al.,[25] working on puromycin analogues in view of anticancer and antiprotozoal activities, described the formation of a new cyclic salt, **8**, and its breakdown under basic conditions (Scheme 2).

Starting from the aminonucleoside **5**, the cyclic urethane **6**, obtained in a two-step reaction, was activated to the 5′-mesylate analogue **7**. Refluxing of the obtained mesylate **7** in chloroform led to the formation of the quaternary salt **8** in 91% yield. When **8** was allowed to react with 0.1 N barium hydroxide, the imidazole cyclonucleoside **9** was obtained; meanwhile, when treated with a solution of 0.1 N NaOH, the cyclonucleoside **10** was isolated in 47% yield. The great ease of cleavage of the quaternary **8** to an imidazole suggests that this sequence may have biological implications. Subsequently, formation of N^3,5′ cyclic salts of guanosine from the corresponding 5′-tosylguanosine derivative was also reported by Baker et al.[26] Later Holmes et al.[27] reported the preparation of some N^3,5′ purine cyclonucleosides by acid hydrolysis of the corresponding quaternary salt (Scheme 3).

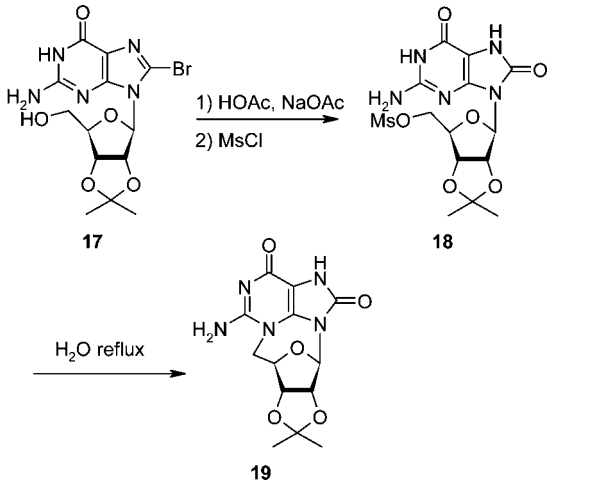
Heating 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-tolylsulfonyl)guanosine (**11**) in acetonylacetone (in the absence of NaI) causes cyclonucleoside **12** formation. Treatment with diluted hydrochloric acid gave N^3,5′-cycloguanosine (**13**). Treatment of the quaternary salt **12** with ammonium hydroxide gave the covalent derivative **15**. Further treatment of **15** with refluxed diluted hydrochloric acid led to **16** resulting from the cleavage of both the isopropylidene group and the glycosidic bond. 2′,3′-*O*-Isopropylidene-N^3,5′-cycloxanthosine (**14**) was obtained from **11** after treatment with sodium nitrite in glacial acetic acid. The replacement of the 2-amino group by hydroxyl proceeded by simultaneous cyclonucleoside formation at position 3. Direct treatment of **11** with sodium thiophenoxide led also to the formation of cyclonucleoside **15**.[28]

Ikehara et al.[29,30] reported the synthesis of 8-oxo-2′,3-*O*-isopropylidene-N^3,5′-cycloguanosine (**19**) starting from the

Scheme 3



Scheme 4

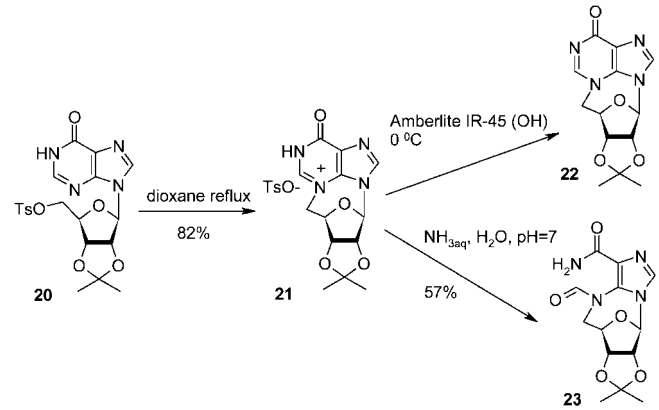


protected 8-bromoguanosine **17** (Scheme 4). Treatment of **17** with acetic acid−sodium acetate followed by mesylation gave **18**, which led to the cyclonucleoside **19** in refluxed water. As expected, a 5′-*O*-mesyl group seemed to accelerate the intramolecular cyclization.[31]

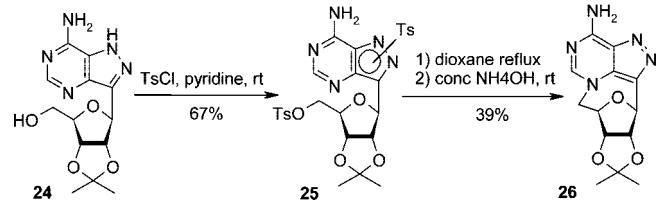
Robins et al.,[27] who first reported the synthesis of the quaternary salt **21** and its covalent inosine cyclonucleoside **22**,[32a−c] have proved by NMR[33] that a ring-opened derivative, N^5,5′-cyclo-1-(2′,3′-*O*-isopropylidene-β-D-*ribo*-furanosyl)-5-formamidoimidazole-4-carboxamide (**23**) can be obtained. Thus, the optimized preparation of **22** was accomplished by careful neutralization of the corresponding *p*-toluenesulfonate salt **21** on a column of Amberlite IR-45 (OH) at 0 °C; meanwhile the imidazolocyclonucleoside **23** was obtained from an aqueous solution after several days at room temperature (Scheme 5).

Thus, following the same approach, the syntheses of other purine cyclonucleosides were reported, as for the preparation of the cyclic salt of tubercidine,[34,35] an antibiotic nucleoside isolated from *Streptomyces tubercidicus* with antineoplastic, antifungal, and antiviral activities,[36] or the cyclic salt of 6-azatubercidine.[37] The synthesis of N^4,5′-cycloformycin, the cyclic form of formycin,[38] a representative pyrazolopyrimidine *C*-nucleoside exhibiting neoplastic and antiviral activity,[39] was simultaneously reported by Umezawa et al.[40] and Žemlička et al.[41] Following the Umezawa methodology, treatment of 2′,3′-*O*-isopropylideneformycin (**24**) with excess

Scheme 5



Scheme 6



tosyl chloride (3 equiv) in pyridine gave a mixture of 2′,3′-*O*-isopropylidene-N^1(or N^2),5′-*O*-*p*-(tolylsulfonyl)formycin (**25**), while treatment with 1 equiv of TsCl gave only the N^1- or N^2-tosyl derivative. Cyclization to **26** occurred by refluxing **25** in dry dioxane for 7 h followed by treatment of the resulting quaternary salt with concentrated NH_4OH (Scheme 6).

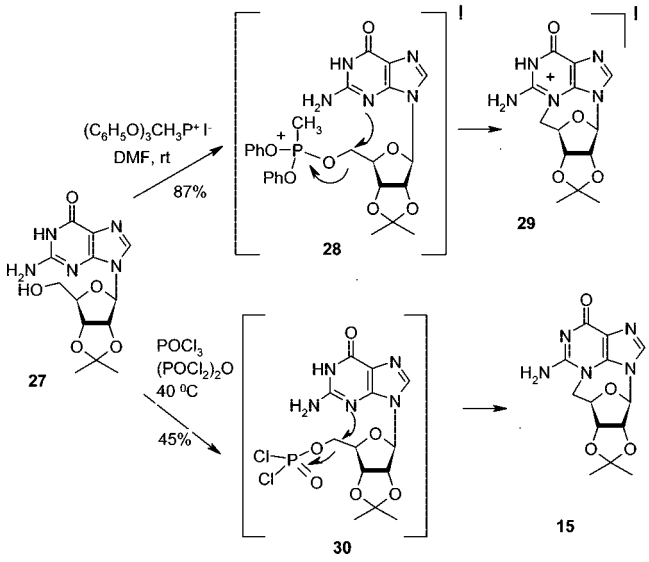
It is interesting to note that N^2,5′- and N^4,5′-cycloformycin exhibited a very strong fluorescence emission, ca. 4 and 2 times, respectively, more intense than that of formycin, accompanied by a bathochromic shift of the emission maximum.[42]

Leaving groups other than sulfonates or iodine at the C5′ position could also lead to cyclic ionic or covalent purine derivatives. For instance, the formation of cyclic purine salts was reported from 5′-di-*p*-nitrophenyl phosphates by heating in acetonitrile or by treatment with sodium benzoxide in benzyl alcohol.[43] In the latter case, the cyclization−quaternization was preferred to the transesterification. Reagents such as methyltriphenoxyphosphonium iodide, triphenylphosphite diiodide,[44] or phosphoryl chloride[32] can lead to the formation of a purine cyclonucleoside (Scheme 7). One exception was for inosine, which possesses a lower ability to form a cyclic salt and gave only the 5′-iodo derivative after treatment with methyltriphenylphosphonium iodide.

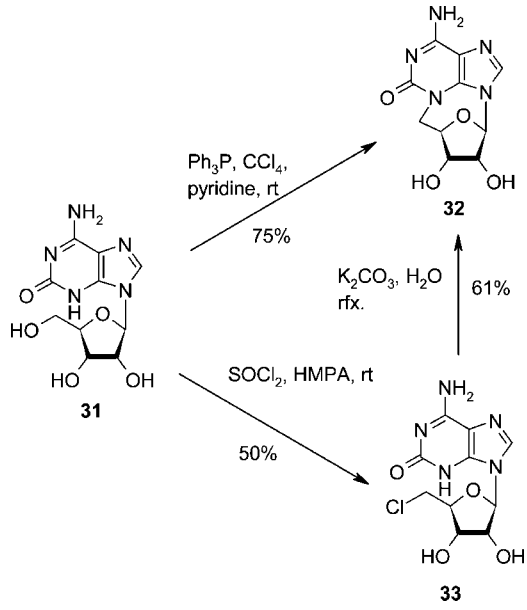
Chern et al. reported[45a,b] that treatment of isoguanosine (**31**) with triphenylphosphine in carbon tetrachloride led to the formation of N^3,5′-cycloisoguanosine (**32**). A similar compound was obtained by chlorination of the C5′ position of **31** with $SOCl_2$ in HMPA to 5′-chloro-5′-deoxy derivative **33**, followed by subsequent treatment with potassium carbonate (Scheme 8).[46]

It should be noted that three main factors have an influence on the formation of cyclic salts of purine nucleosides: (a) the basisity of the purine ring, (b) the protecting groups on the sugar moiety, and (c) the polarity of the solvent used for the reaction. The basisity of the purine ring could be reduced by acylation[47] or through N^1-oxidation[48] and the formation of a quaternary salt avoided. The 2′,3′-ketal group

Scheme 7



Scheme 8

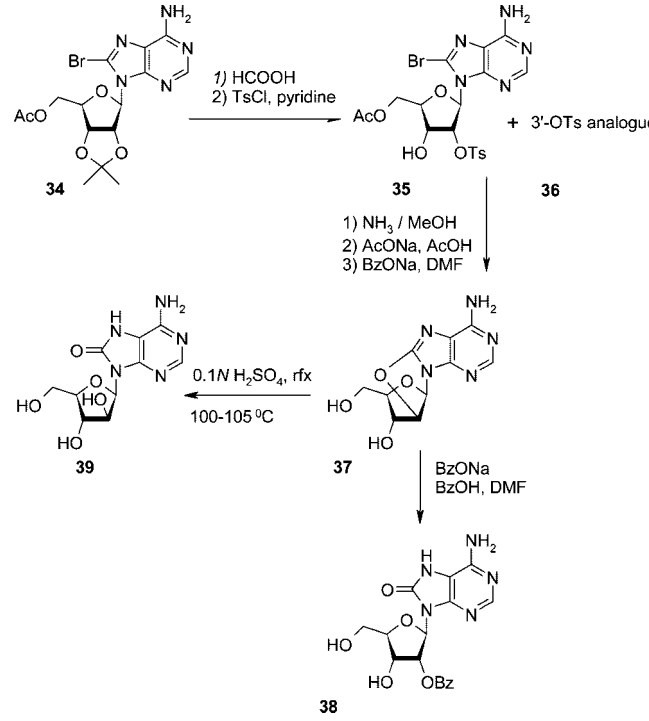


has been shown to cause a flattening of the sugar ring,[49] and this presumably enhances the rate of intramolecular cyclization, as for purine nucleosides lacking a 2′,3′-*O*-isopropylidene group, the ability for cyclization between N^3 and C5′ is significantly lower.[50a,b] Concerning the solvent, going from dimethyformamide to tetrahydrofuran or dichloromethane reduced significantly the intramolecular quaternarization.[51] Finally, Austin et al.[52] reported that during the azidation of the 5′-(diphenyl phosphate)-5′-deoxy-2′,3′-*O*-isopropylideneadenosine,[53] no intramolecular quaternarization of N^3 to C5′ occurred.

2.1.2. With an —O— Bridge

Those preliminary results concerning the cyclization of nucleosides prompted the scientists to investigate other approaches to synthesize cyclonucleosides. The first synthesis of a purine cyclonucleoside having an 8,2′-*O*-anhydro linkage, 8,2′-anhydro-8-hydroxy-9-(β-D-*arabino*-furanosyl)-adenine (**37**), was reported in 1966 by Ikehara et al.[54,55] (Scheme 9). Starting from the 8-bromo-protected adenosine

Scheme 9

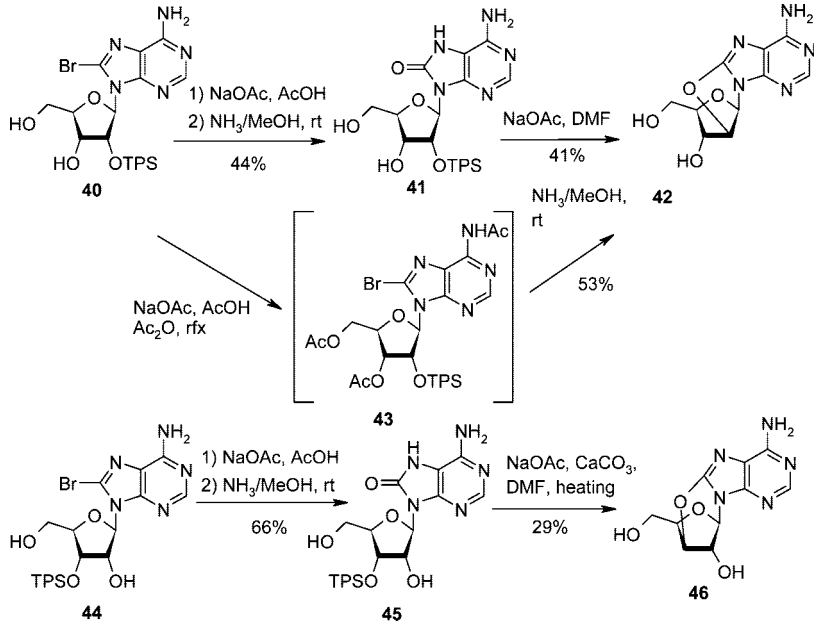


34, after removal of the 2′,3′-isopropylidene group, a tosylation with 1.1 equiv of *p*-toluenesulfonyl chloride in pyridine led to a mixture of 2′-*O*- and 3′-*O*-tosylates **35** and **36**, respectively. After deacylation, the mixture was refluxed with sodium acetate in acetic acid to yield a mixture of 8-hydroxy derivatives which by heating with sodium benzoate in DMF gave, after the separation of isomers, the expected cyclonucleoside **37**. Treatment of **37** with sodium benzoate gave the 2′-α-benzoyl derivative **38** (ribosyl configuration); meanwhile, the hydrolytic cleavage of **37** with 0.1 N sulfuric acid occurred at the C8 position and led to the *arabino* cyclonucleoside **39** (arabinosyl configuration).

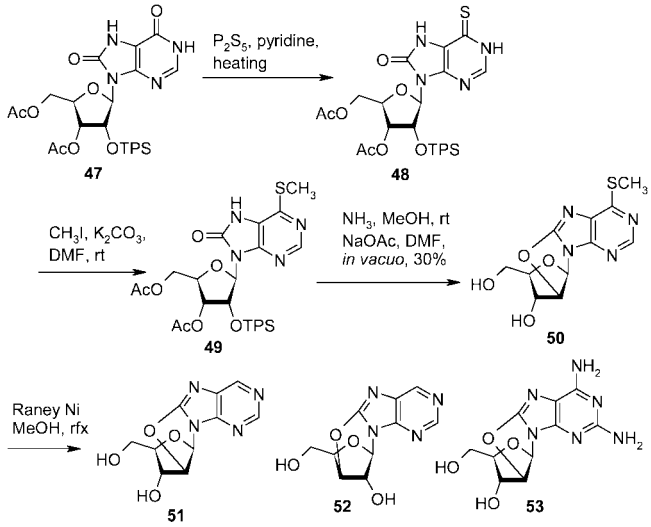
Following the same procedure, Ikehara et al.[56] reported in 1967 the first purine cyclonucleoside having an 8,3′-*O*-anhydro linkage. If intermediates **35** and **36** possessed similar R_f values and were thus used as a mixture of two isomers, their analogues possessing a (2,4,6-triisopropylphenyl)sulfonyl (TPS) group instead of a tosyl group, are easily separated by column chromatography and/or a crystallization process.[57] Detailed investigation of 8,2′- versus 8,3′-*O*-cyclization was undertaken by Ikehara et al.[58] TPS derivative **40** was refluxed with anhydrous sodium acetate in glacial acetic acid for 2 h. Substitution of the 8-bromo to an 8-oxy function was accompanied by partial acylation of NH_2 and sugar OH groups; further deacetylation with methanolic ammonia led to intermediate **41** obtained with 44% yield. Final cyclization with NaOAc in refluxed DMF led to cyclonucleoside **42**. The synthesis of **42** can be improved by peracetylation of **40** by refluxing with a mixture of sodium acetate, acetic acid, and acetic anhydride. The obtained intermediate **43** without purification was treated with a saturated solution of ammonia in methanol, which led to the cyclonucleoside **42** (Scheme 10).

When similar transformations were applied for 3′-*O*-TPS isomer **44**, the 8-oxy derivative **45** was obtained with 66% yield. Cyclization of **45** was attempted with methanolic ammonia, sodium benzoate in DMF, or potassium *tert*-butoxide in *tert*-butyl alcohol. In each case cyclization was

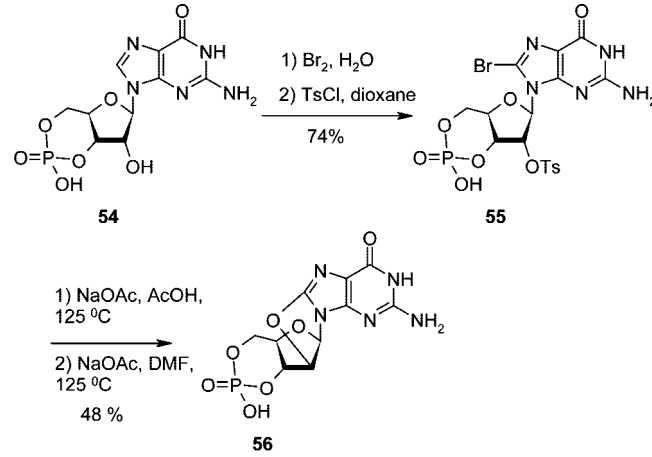
Scheme 10



Scheme 11



Scheme 12



incomplete and a complex mixture was isolated. When **45** was heated with sodium acetate in DMF for 7 min, **46** was isolated with 29% yield. Kinetic studies of the cyclization of **41** and **45** showed that compound **45** cyclized slower than **41**. When the 6-NH_2 of purine was activated as an N^6,N^6-dimethyl group, the cyclization occurred faster.

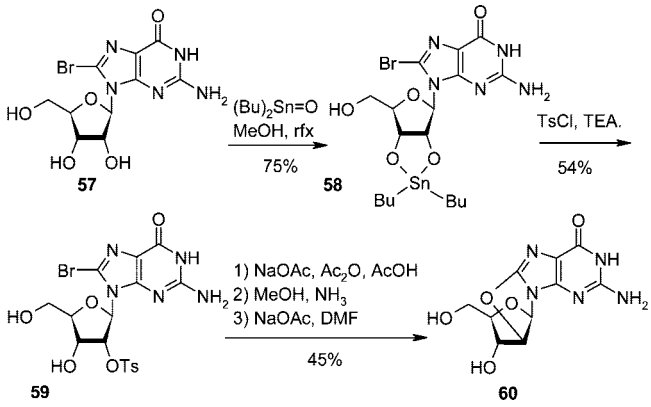
Following the same approach, the synthesis of 8,2′-*O*-cyclonebularine (**51**) was reported[59] from derivative **47** (Scheme 11). By being heated with phosphorus pentasulfide in pyridine, **47** was converted into its 6-thio derivative **48**. After methylation (**49**), the deacylation induced the intramolecular cyclization (**50**). A final desufurization with Raney nickel led to **51**. Using a similar synthetic pathway, 8,3′-*O*-cyclonebularine (**52**) and 2,6-diamino-8,2′-*O*-anhydro-8-hydroxy-9-(β-D-*arabino*-furanosyl)purine (**53**) were also obtained.[60]

In early syntheses of purine cyclonucleosides, a selective sulfonylation of the ribose moiety became a serious problem, as both 2′-OH and 3′-OH groups can easily undergo tosylation, leading to a mixture of inseparable tosylates. In 1974, Khwaja et al.[61] reported the synthesis of 3′,5′-cyclic phosphates of purine nucleosides (Scheme 12). The cyclic 3′,5′-*O*-phosphate ester of guanosine **54** was brominated with bromine in water, and as a result, the 8-bromo derivative was only tosylated at the 2′ position to **55**. After a two-step reaction, **55** was converted to the 8,3′-*O*-cyclonucleoside **56**.

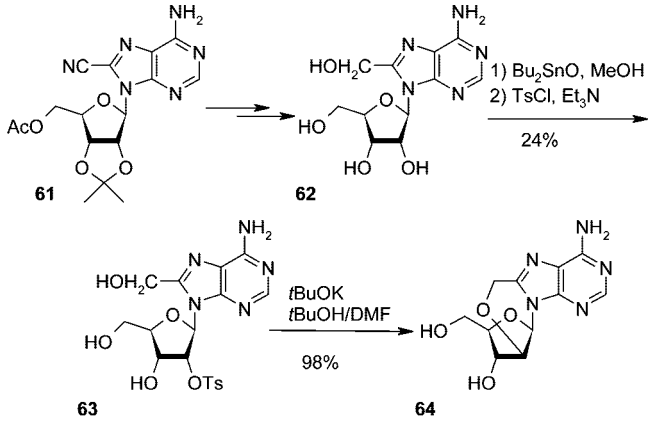
Ikehara et al.[62] also reported that the 5′-OH phosphorylation of adenosine prevents the tosylation of the 3′-OH group in alkaline solution; meanwhile it proceeds smoothly at 2′-OH. Three possible reasons for such selectivity were postulated by the authors: (1) the bulky phosphate group at 5′-OH sheltered the 3′-OH group from attacking species, (2) the 5′-phosphate group should exit with two negative charges, which makes dissociation of the neighboring 3′-OH group more difficult than that of 2′-OH, due to repulsion between nearer negative charges, (3) puckering of the furanose ring to the 2′-*endo* conformation may put the 2′-OH in a more favorable position than 3′-OH for the attack of tosylate.

Using di-*n*-butyltin oxide as an activation agent, Wagner et al.[63] reported a selective 2′-*O*-tosylation. This step was immediately applied for the synthesis of purine cyclonucleosides, which resulted in first synthesis of unprotected 8,2′-*O*-anhydro-8-hydroxy-9-(β-D-*arabino*-furanosyl)guanine nucleoside (**60**).[64] 8-Bromoguanosine (**57**) was transformed into 2′,3′-*O*-dibutylstannyl derivative **58**, which after treatment

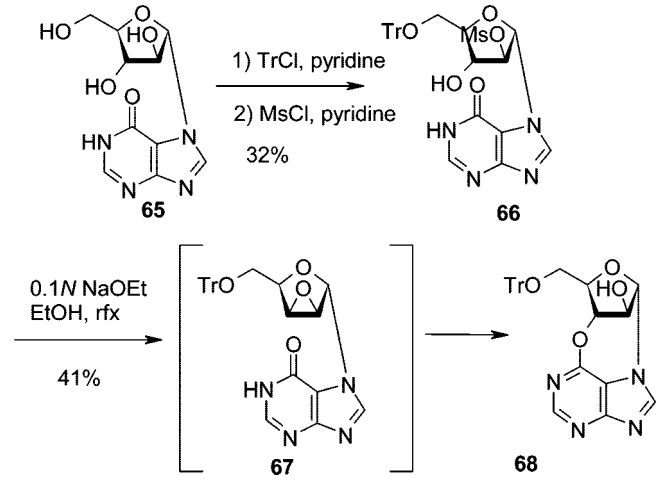
Scheme 13



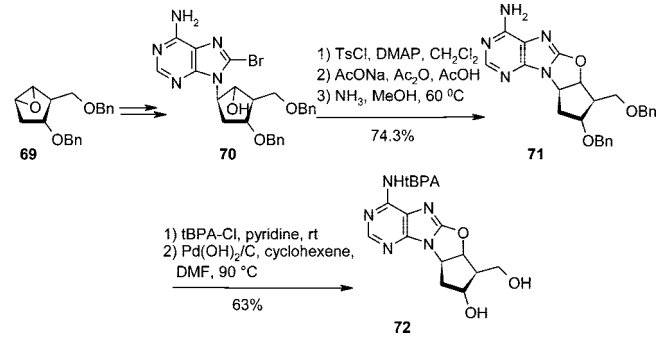
Scheme 14



Scheme 15



Scheme 16



with tosyl chloride in the presence of TEA gave exclusively 2′-*O*-tosyl derivative **59** (Scheme 13). Heating with sodium acetate, acetic acid, and acetic anhydride led to a mixture of tetra- and triacetylated products, which were deacetylated with methanolic ammonia. Classical heating with sodium acetate in DMF led to required cylonucleoside **60**. The same procedure was used for the synthesis of 8,2′-*O*-anhydronucleosides.[65,66] Direct tosylation of 8-bromo-5′-deoxyadenosine mediated with the dibutylstannyl derivative was not selective and led to a mixture of 2′- and 3′-*O*-tosylates in a ratio of 7:1.[67]

During their investigation of the structure−activity relationship of enzymes utilizing adenosine derivatives, Ueda et al.[68] described the synthesis of 8,2′-*O*-anhydro-8-(hydroxymethyl)-9-(β-D-*arabino*-furanosyl)adenine (**64**) (Scheme 14), starting from 5′-*O*-acetyl-8-cyano-2′,3′-*O*-isopropylideneadenosine (**61**),[69] which was converted in a three-step procedure to 8-(hydroxymethyl)adenosine (**62**). Treatment with di-*n*-butyltin oxide and tosyl chloride afforded 2′-*O*-tosylate **63**. Cyclization was performed by *t*-BuOK in a *t*-BuOH/DMF mixture, giving cyclonucleoside **64** in nearly quantitative yield.

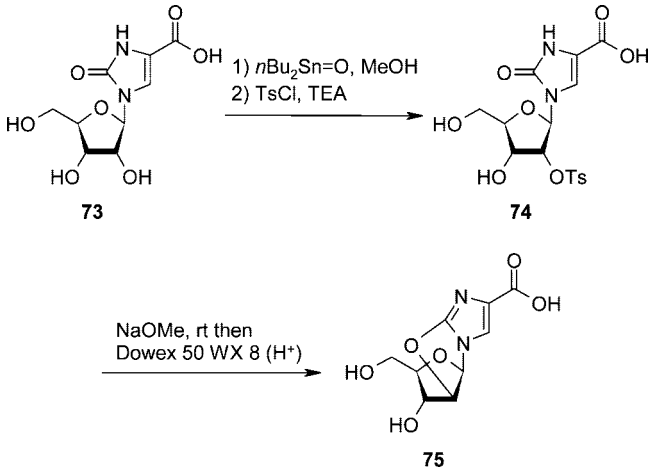
Generally, nucleosides are active with a β-configuration at the anomeric center. Thus, there are only a few reports concerning the synthesis of purine cyclonucleosides possessing an α-configuration. In 1974, Mizuno et al.[70] reported the synthesis of 5′-trityl-3′,6-*O*-anhydro-7-(α-D-*arabino*-furanosyl)hypoxanthine (**68**), the first purine cyclonucleoside having a 6,3′-*O*-anhydro linkage (Scheme 15). α-D-*arabino*-Furanosylhypoxanthine (**65**) after selective tritylation and mesylation afforded **66**, which by treatment with 0.1 N ethanolic sodium ethoxide led to the 3′,6-*O*-purine cyclonucleoside **68**, probably via an epoxide of the *lyxo* type, **67**. The authors observed unusual stability for the obtained product both under alkaline hydrolysis (full recovery of **68**) and under 1 N HCl at refluxing temperature, which gave only the detritylated product (not shown).

During research on heterochiral nucleotides containing the unnatural L-nucleoside in the natural sequence, Akagi et al.[71] reported the synthesis of racemic and optically active[72] carbocyclic purine nucleoside analogues with the restricted glycosyl conformation ($\chi = 180°$) (Scheme 16). The known (−)-epoxide **69**[73] was converted under a known procedure to **70**. The derivative **70** was tosylated at 6′-*O* and cyclized to afford the 8,6′-*O*-anhydro derivative **71** by refluxing with sodium acetate in an acetic acid/acetic anhydride mixture.

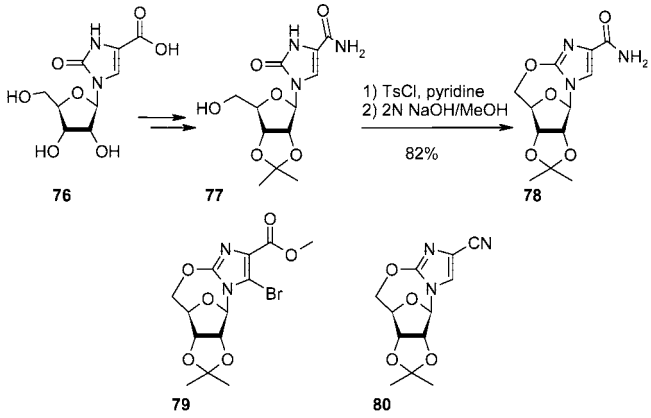
The anhydro link turned out to be labile under alkaline deprotecting conditions of oligonucleotides, substantial decomposition of **71** being observed during treatment with methanolic ammonia at 55 °C for 8 h. Thus, [(*tert*-butylphenyl)oxy]acetyl (tBPA) was employed for the protection of the 8-amino group of the adenine ring. Consequently, a further protection/deprotection sequence led to derivative **72**, which was incorporated into oligonucleotide chains.

Imidazole nucleosides are important components of the de novo synthesis of purine nucleosides, such as aminoimidazolecarboxamide (AICA) riboside or bredinin[74] from *Eupenicillium brefeldianum*, and can form cyclonucleoside analogues as their purine counterparts. The synthesis of imidazole 2,2′-anhydronucleoside was reported by König and Cech (Scheme 17).[75] Thus, 1-(β-D-*ribo*-furanosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**73**) was selectively tosylated at the C2′ position using treatment with di-*n*-butyltin oxide followed by tosyl chloride in pyridine. The obtained **74** was

Scheme 17



Scheme 18



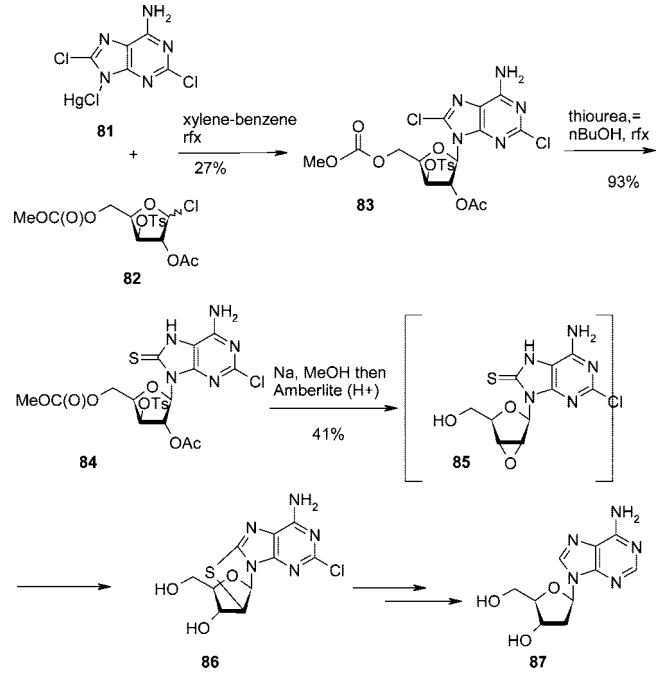
cyclized to 2,2′-*O*-anhydro-1-(β-D-*ribo*-furanosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**75**) by treatment with sodium methoxide.

Ueda et al.[76] reported the synthesis of 2,5′-*O*-cycloimidazole nucleosides **79**−**81** starting from 1-(β-D-*ribo*-furanosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**76**) (Scheme 18). Imidazoline nucleoside **76** was transformed in four steps into the amide **77**, which underwent tosylation and intramolecular cyclization, which led to the corresponding carboxyamide **78**. During the same synthesis, **79** and **80** were also obtained. The 2,5′-*O*-anhydro linkage was found to be unexpectedly stable to the sulfohydrolysis, ammonolysis, or treatment with sodium benzoate in hexamethylphosphoric triamide. These stabilities are comparable to those of the easy ring-opening of 8,5′-*O*-purine or 2,5′-*O*-uridine cyclonucleosides by the aforementioned methods.[77]

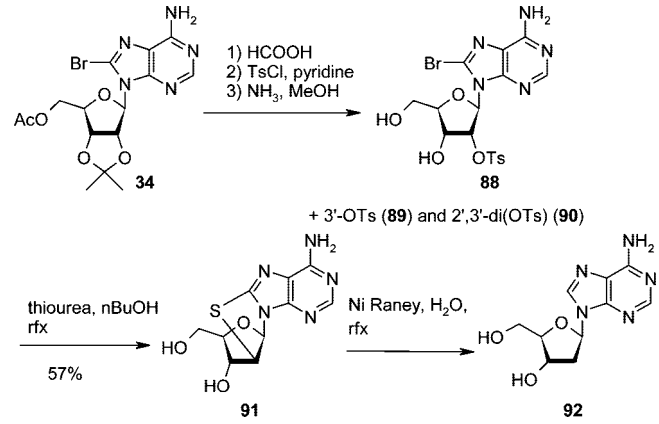
2.1.3. With a −S− Bridge

In 1965, Ikehara et al.[78] reported the synthesis of 2′-deoxyadenosine (**87**) through (1) the condensation of 2,8-dichloroadenine mercury salt **81** with 2′-*O*-acetyl-3′-*O*-tosyl-5′-*O*-(methoxycarbonyl)-D-*xylo*-furanosyl chloride (**82**)[79] to **83**, (2) its conversion via 8,3′-*S*-bridged **86** to the desired nucleoside. To selectively introduce the mercapto group at C8, **83** was refluxed with thiourea in 1-butanol. The intramolecular cyclization occurred with sodium methoxide in dry methanol at reflux through the 2′,3′-epoxide intermediate **86**. The position of the anhydro linkage was further confirmed by its transformation to **87** (Scheme 19).

Scheme 19



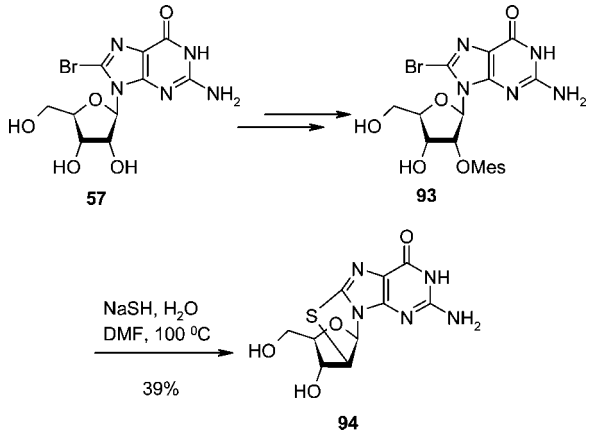
Scheme 20



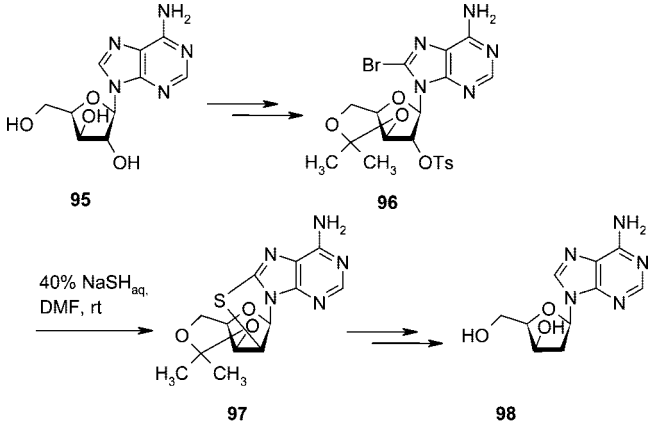
Other syntheses of deoxyadenosines were reported by Ikehara and Tada,[80] starting from 8-bromo-5′-*O*-acetyl-2′,3′-*O*-isopropylideneadenine (**34**). As selective methods for tosylation of the 2′-hydroxy versus 3′-hydroxy group were not yet described, those transformations led to a mixture of three different products (**88**−**90**), which can be separated by crystallization. Reflux of **88** with thiourea in 1-butanol led to 8,2′-anhydro-8-mercapto-β-D-*arabino*-furanosyladenine (**91**), which underwent desulfurization with Raney nickel to 2′-deoxyadenosine (**92**) (Scheme 20).

Different behavior for the cyclization reaction and formation of a sulfur bridge was observed in the case of 2′-tosyl- and 3′-tosylinosine derivatives.[81] When a mixture of 5′-*O*-acetyl-2′-*O*-tosyl-8-mercaptoinosine and its 3′-*O*-counterpart was treated with methanolic ammonia at 0 °C, the 2′-tosyl derivative was easily cyclized to the corresponding 8,2′-*S*-cyclonucleoside, while the 3′-tosyl derivative remained unchanged. Finally, following the same synthetic pathway, the synthesis of 8,5′-anhydro-8-mercapto-2′,3′-*O*-isopropylidene-β-D-*arabino*-furanosylguanine[82] and -adenine[83] was obtained by tosylation of its 8-bromo derivative at −20 °C followed by cyclization with H_2S in pyridine or thiourea in dioxane. Alternatively, sodium hydrogen sulfide in aqueous

Scheme 21



Scheme 22

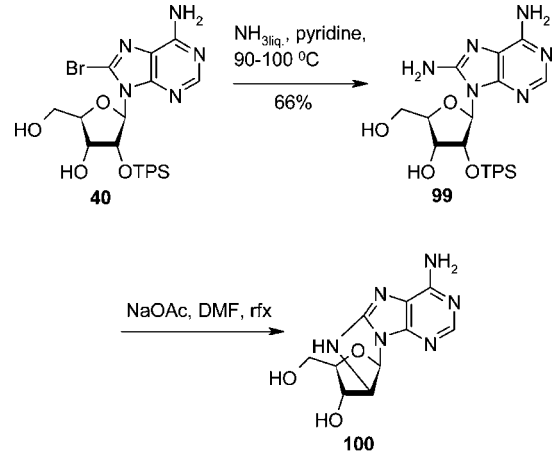


pyridine could be used in the cyclization step instead of hydrogen sulfide in pyridine.[84] An alternative synthesis was reported by Nagpal et al.[85] by treatment of the 8-bromonucleoside with NaSH in methanol. It should be emphasize that, during the in situ 8,5′-*S*-cyclization, the 8-mercapto group can compete with the attack from N^3. The synthesis of 2′,5′-dideoxyadenosine and 3′,5′-dideoxyadenosine was realized through the same approach.[86]

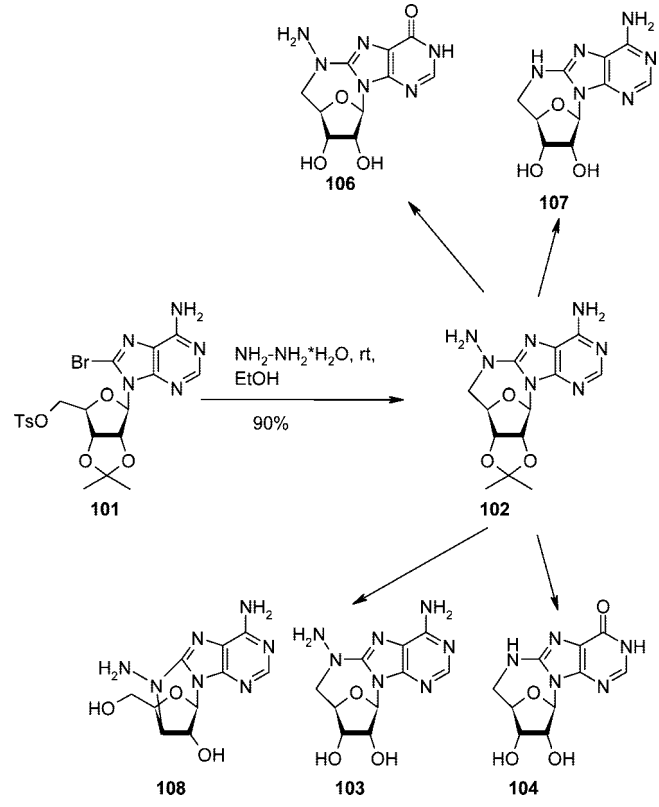
Compared to the synthesis of sulfur-bridged adenosine cyclonucleosides, the synthesis of their guanosine analogues was somehow less explored. Ogilvie et al.[87] reported the synthesis of 8,2-*S*-thioanhydroguanosine (**94**) from 8-bromoguanosine (**57**),[88] which was converted in several steps into 2′-(mesitylenesulfonyl)-8-bromoguanosine (**93**) (Scheme 21). The 8,2′-*S*-anhydro linkage **93** was treated with sodium hydrogen sulfite (11 equiv) in DMF and led to cyclonucleoside **94** with a 39% yield. An optimized synthesis of 8,2′-*S*-anhydroguanosine was reported by Ikehara et al.[89]

The developed methodology for synthesis of a sulfur bridge allowed the synthesis of *S*-cyclonucleosides derived from 9-(β-D-*xylo*-furanosyl)adenine (**95**) (Scheme 22).[90] The bromination of **95** at C8 using bromine in acetate buffer, its protection as a 3′,5′-*O*-isopropylidene by treatment with di-*p*-nitrophenyl phosphate in an acetone−dimethoxypropane mixture,[91] and subsequent tosylation gave 2′-*O*-tosyl-3′,5′-*O*-isopropylidene-8-bromo-9-(β-D-*xylo*-furanosyl)adenine (**96**). Treatment of **96** with sodium hydrogen sulfite in DMF at room temperature led to formation of 8,2′-anhydro-8-mercapto-3′,5′-*O*-isopropylidene-9-(β-D-*xylo*-furanosyl)adenine (**97**) with a high yield. **97** was converted in two steps to **98**.

Scheme 23



Scheme 24

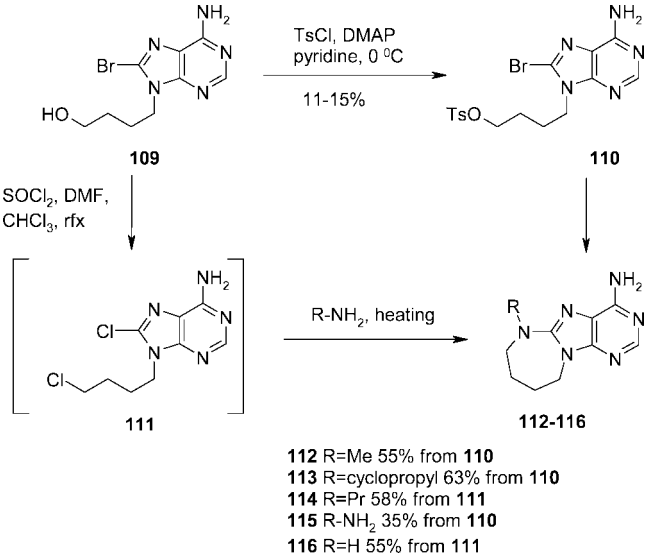


2.1.4. With a −N− Bridge

The first synthesis of purine cyclonucleosides possessing an amine linkage between the heterocycle and the sugar moiety was reported by Kaneko and Schimizu[92] (Scheme 23). 8-Bromo-2′-*O*-[(triisopropylphenyl)sulfonyl]adenosine (**40**) was treated with liquid ammonia in pyridine to afford 8-amino-2′-*O*-[(triisopropylphenyl)sulfonyl]adenosine (**99**), which by treatment with excess sodium acetate gave the desired 8,2′-*N*-cycloadenosine (**100**). Its *N*-methyl analogue was obtained from 8-(*N*-methylamino)-2′-*O*-[(triisopropylphenyl)sulfonyl]adenosine with 50% yield.

The synthesis of 8,5′-*N*-cycloadenosine analogues was reported by Sasaki et al.[93] (Scheme 24). Starting from the 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**101**) was treated with a large excess of hydrazine hydrate to lead to 8,5′-aminiminocyclonucleoside **102**, which was deprotected to **103**. Under various conditions **102** can be trans-

Scheme 25



formed to the 8,5′-iminonucleoside **107** or to hypoxanthine analogues **104** and **106**. Following the same approach, treatment of 8-bromo-3′-*O*-[(triisopropylphenyl)sulfonyl]-adenosine by excess hydrazine led to an unstable 8-hydrazino derivative, which was directly converted into 8,3′-aminimi-nocyclonucleoside **108**.[94]

Holey et al.[95] reported the synthesis of acyclic adenine 8,*N*-anhydronucleosides starting from 8-bromo-9-(4-hydroxy-butyl)adenine (**109**) (Scheme 25). Tosylation of the 4-hydroxybutyl derivative **109** gave the required tosylate **110**. Treatment of **110** with a primary amine (e.g., methylamine, propylamine, cyclopropylamine) at elevated temperatures gave the expected cylonucleosides **112**−**116** in high yields. In a second approach **109** was treated with thionyl chloride in DMF to convert the hydroxyl group into Cl. The reaction proceeded smoothly and was accompanied by halogen exchange at C8. The obtained 8-chloro-9-(4-chlorobutyl)-adenine (**111**) was directly engaged into the intramolecular cyclization with various amines.

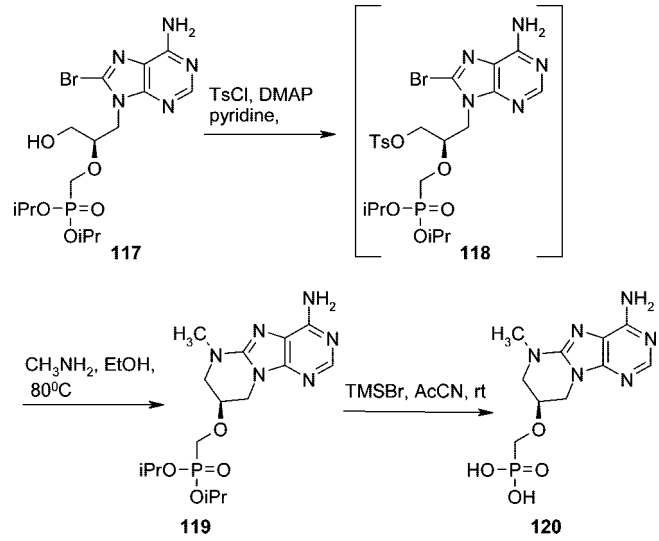
In a similar manner, Janeba et al.[96] reported the preparation of acyclic adenine 8,*N*-anhydronucleoside phosphonate **120**, starting from the phosphonic ester **117**. Tosylation of **117** afforded **118**, which was directly reacted with methylamine in ethanol to provide the acyclic adenine 8,*N*-anhydronucleo-side phosphonate **119**. Deprotection of **119** with trimethylsilyl bromide gave the free phosphonic acid **120** (Scheme 26). A similar cyclization was observed by Belmont et al.[97] during the deprotection of the Teoc group from the polyamino linker attached to the adenine ring, which resulted in formation of imidazo[1,2-*e*]purine derivatives.

Reese et al.[98] reported the preparation of the cyclonucleo-side **122** possessing a hydrazine bridge. When 8-bromo-2′-*O*-tosyladenosine (**88**) was treated with hydrazine hydrate in methanol, the corresponding 8-hydrazino-2′-*O*-(tolyl-*p*-sulfonyl)adenosine (**121**) was obtained. By refluxing in ethanol, the hydrazine-bridged cyclonucleoside **122** and its oxidized analogue **123** were obtained (Scheme 27).

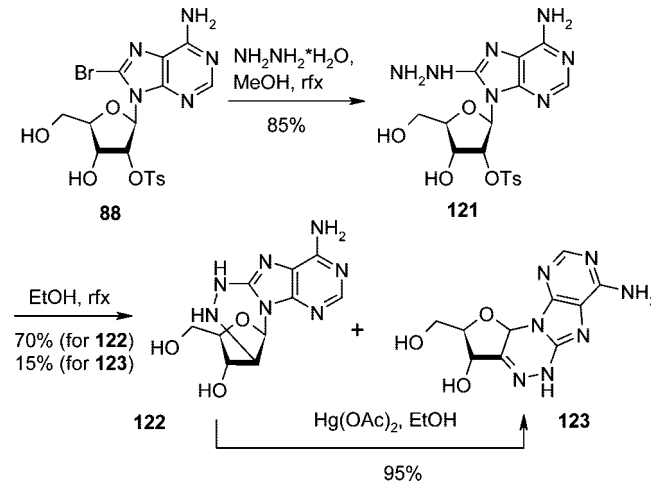
For expansion of the range of the model conformations of cyclonucleosides, synthesis of some long-bridged purine cyclonucleosides, **124**−**128**, has been achieved by Sasaki et al.[99] (Figure 2).

Surprisingly, the 9-[2′,3′-[(methylamino)epimino]-2′,3′-dideoxy-β-D-*lyxo*-furanosyl]adenine 8,*N*-cyclonucleoside

Scheme 26



Scheme 27



(**128**) possessing a 2′,3′-aziridine ring[100] linked to the adenine moiety was isolated. Similar transformations were also reported for inosine derivatives.

A purine cyclonucleoside possessing an 8,2′-oxamido linkage was reported by Sasaki (Scheme 28).[99] When **88** was heated with *N*-methylhydroxylamine, the expected cyclo-nucleoside **129** was isolated with 64% yield. When **88** was heated with a 15-fold excess of hydroxylamine, only the 8-hydroxylamino derivative **130** was obtained instead of the

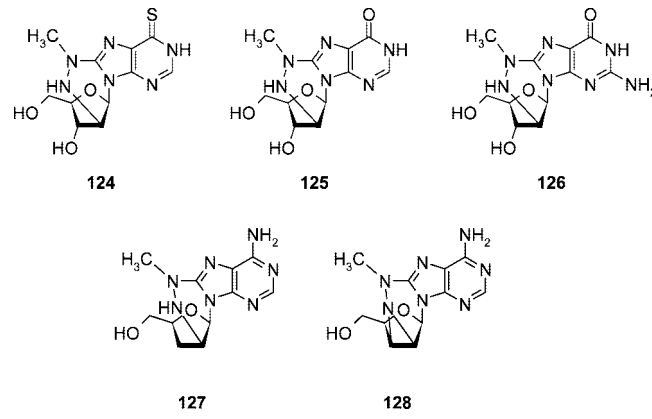
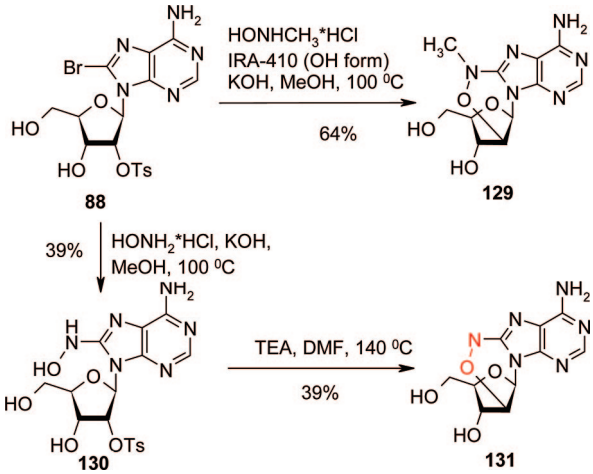
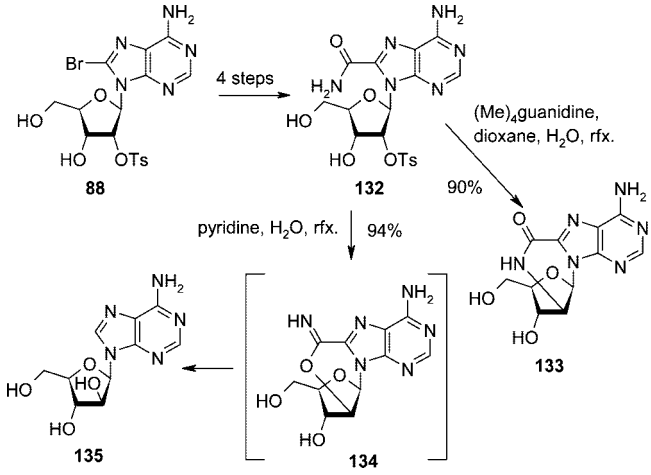


Figure 2. Purine cyclonucleosides possessing a hydrazine bridge.

Scheme 28



Scheme 29



expected **131**. This is due to the reduced nucleophilicity of the hydroxyamino group.

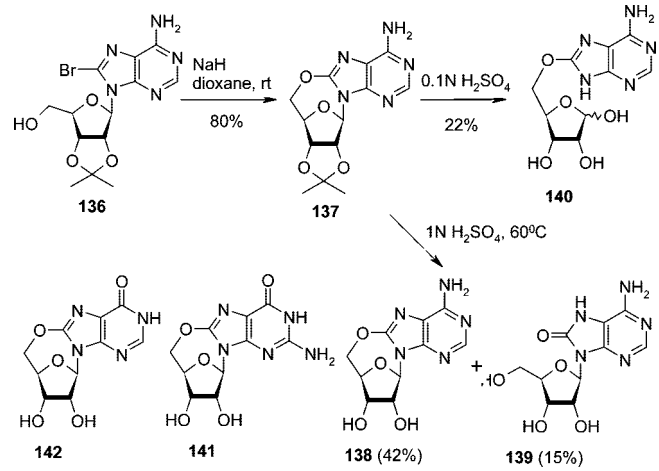
The only example concerning the synthesis of a purine cyclonucleoside possessing a carboxyamido 8,2′-bridge was reported by Reese et al.[101] (Scheme 29). **88**, transformed in four steps into 8-carbamoyl-2′-*O*-tosyladenosine (**132**), when treated with N^1,N^1,N^3,N^3-tetramethylguanidine in a dioxane−water mixture, gave the appropriate cyclonucleoside **133**, bearing the carboxyamido bridge, with a high yield. In contrast, when **132** was refluxed in a pyridine−water mixture, only 9-(β-D-*arabino*-furanosyl)adenine (**135**) was obtained as the sole product. Although the possible bridged intermediate **134** was not detected in the reaction mixture, the authors suggested its possible formation, further hydrolysis of which via the corresponding lactone gave Ara-A (**135**).

2.2. Various Syntheses of C8-Bridged Purine Cyclonucleosides

2.2.1. Synthesis from Classical Nucleosides

As the tosylate method is usually not suitable for the synthesis of purine cyclonucleosides bearing an 8,5′-*O*-linkage, leading in most cases to N^3,5′-cyclonucleosides, a new, complementary method was developed independently and published simultaneously by Ikehara[102] and Nagpal.[103] Using the sulfonate method, the cyclonucleosides are formed by the nucleophilic attack of a keto, thioketo, or N-containing group in the heterocyclic bases at the electron-deficient

Scheme 30



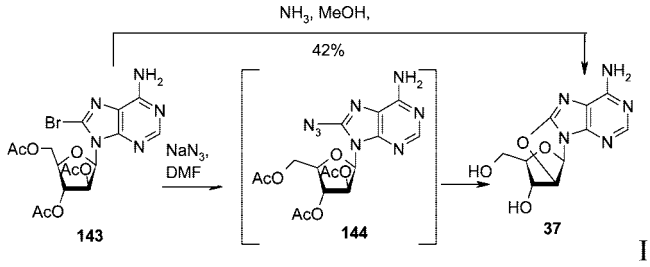
carbon atom bearing the leaving (arylsulfonyl)oxy group. In the following examples, an activated sugar OH would attack an electron-deficient carbon at position C8.

In the first report,[101] 8-bromo-2′,3′-*O*-isopropylideneadenosine (**136**) treated with excess sodium hydride gave 8,5′-*O*-anhydro-2′,3′-*O*-isopropylideneadenosine (**137**) (Scheme 30). Attempts to deprotect the isopropylidene group by heating with 1 N H_2SO_4 led to the requested 8,5′-*O*-anhydroadenosine (**138**) and 8-oxoadenosine (**139**), suggesting that the cleavage of the anhydro linkage occurred prior to the hydrolysis of the nucleosidic linkage. On the contrary, heating with 0.1 N H_2SO_4 led rather to cleavage of the glycosidic bond and formation of 5-(adenyl-8)-D-ribose (**140**). The fact that hydrolysis of the anhydro linkage occurred predominantly in the more concentrated acid may suggest that the protonation of N^7 was preceded by that of N^9.

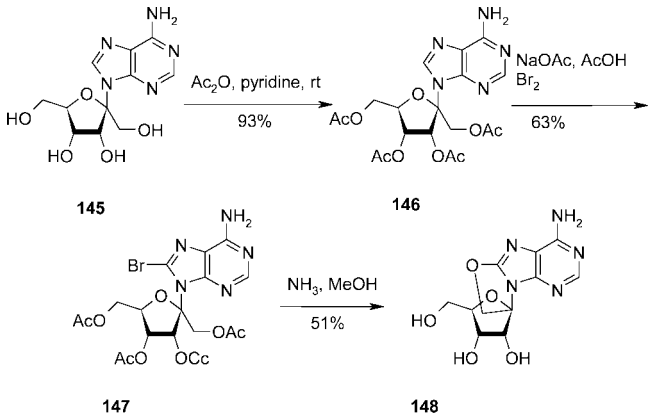
Attempts to directly cyclize unprotected 8-bromoadenosine led to a mixture of compounds, presumably oligomers having intermolecular ether linkages between the 8- and 2′-, 3′-, or 5′-carbons. The presence of a 2′,3′-isopropylidene group forced the appropriate position, suitable for formation of an internal linkage. In a similar way, guanosine (**141**)[104] and inosine (**142**)[105,59] analogues of **138** were described. It was found later that, instead of an 8-bromine atom, the presence of other leaving groups at the C8 position such as N_3, Cl, F, or SCH_3 could, after treatment by a base, induce the formation of purine cyclonucleosides. Honjo et al.[106] reported that heating **136** with potassium cyanide instead of sodium hydride led also to the formation of **137**. Butora et al.[107] observed that heating **136** with cesium fluoride led to halogen exchange and the obtained 8-fluoro derivative undergoes spontaneous ring closure, giving 8,5′-*O*-cyclonucleoside **137**.

During research on the synthesis of 8-substituted 9-(β-D-*arabino*-furanosyl)adenine derivatives, Goodman et al.[108] observed that when 8-bromo(2′,3′,5′-tri-*O*-acetyl-β-D-*arabino*-furanosyl)adenine (**143**) was treated with methanolic ammonia or methanolic sodium methoxide, deprotection of hydroxyl groups was accompanied by rapid cyclization, leading to 8,2′-*O*-anhydro-8-hydroxy-9-(β-D-*arabino*-furanosyl)adenine (**37**) (Scheme 31). Treatment of **143** with sodium azide in DMF gave 8-azido(2′,3′,5′-tri-*O*-acetyl-β-D-*arabino*-furanosyl)adenine (**144**), which was directly deacetylated to **37**. Similar cyclization to 8,2′-cyclonucleosides during cleavage of acetyl groups from the 8-bromo derivative of 9-(β-D-*arabino*-furanosyl)adenine, by treatment with methanolic ammonia, was observed by Maruyama et al.[109] and MacCoss et al.[110]

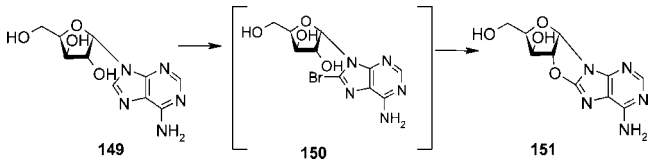
Scheme 31



Scheme 32



Scheme 33



2.2.2. From an Antibiotic Nucleoside

In 1981, Zavgorodny et al.[111] reported the synthesis of a novel cyclonucleoside having a psicofuranosyl moiety (Scheme 32). 9-(2-β-D-Psicofuranosyl)adenine (**145**) (psicofurnine, angustmycine),[112] a natural antibiotic nucleoside isolated from *Streptomyces hygroscopicus* var. *decoyicus*,[113] was acylated by treatment with acetic anhydride in pyridine to tetraacetate **146**. After bromination using a method developed by Holmes and Robins,[114] the 8-bromo derivative **147** was obtained. A final deprotection was accompanied by the simultaneous formation of the oxygen bridge and afforded **148**.

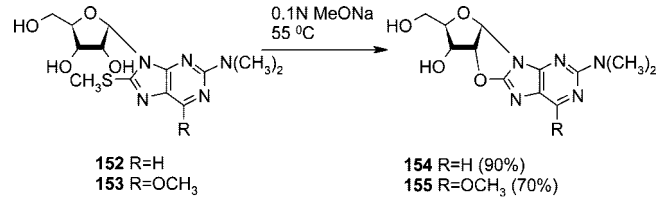
2.2.3. From Miscellaneous Nucleosides

The preparation of a purine α-cyclonucleoside was reported by Ikehara et al.,[99,115] who observed that when 9-(α-D-*xylo*-furanosyl)adenine (**149**) was brominated by bromide in water at pH 4, the 8-bromo derivative **150** formed rapidly, which cyclized in situ to 8,2′-*O*-anhydro-8-oxy-9-(α-D-*xylo*-furanosyl)adenine (**151**) (Scheme 33).

Rokos and Haspiel reported[116] that heating 8-(methylmercapto)-α-ribosides **152** and **153** in 0.1 N NaOMe or 0.1 N NaOH led to 8,2′-*O*-anhydro-α-nucleosides **154** and **155**, respectively (Scheme 34). Similar cyclization was observed by treating the parent nucleosides with a strongly basic ion exchanger (OH^- form) in aqueous methanol.

Finally, Townsend et al.[117] also reported the synthesis of α-cyclonucleosides **156**−**158** possessing halogenated benzimidazole instead of a purine (Figure 3).

Scheme 34



The first proof of possible formation of anhydro derivatives of acylic nucleosides as intermediates was reported by Holey et al.[118] during studies of the conversion of the bromide atom at the C8 position into an amine (Scheme 35). The reaction of 9(*R*/*S*)-(2,3-dihydroxypropyl)-8-bromoadenine (**159**), after treatment with 1,3-diaminopropane, gave the desired 8-amino derivative **162** and two side compounds, **163** and **164**, where one of the hydroxyl groups was replaced by a (3-aminopropyl)amino group (Scheme 35). The formation of products can result from the formation of a cyclic intermediate such as **160**, which in the presence of a strong nucleophile can either undergo a reaction at C8 to give compound **162** or afford the 2′,3′-epoxide **161**. Oxirane opening with the amine led to a mixture of **163** and **164**, respectively.

Formation of a seven-membered ring fused to the adenine system was observed by Reitz et al.[119] The treatment of 8-bromoacyclovir (**165**) with sodium hydride in DMSO led to the formation of 10*H*,12*H*,13*H*-1,5,3-dioxazepino[2,3-*e*]-9*H*-purin-6(1*H*)-one (**166**) (Scheme 36).

Jeneba et al.[120] have deeply investigated the formation of seven-membered ring acyclic purine nucleosides. After bromination of (2*S*,3*S*)-9-(2′,3′-*O*-isopropylidene-2,3,4-trihydroxybutyl)adenine (**167**), the obtained 8-bromo derivative

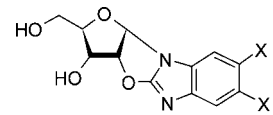
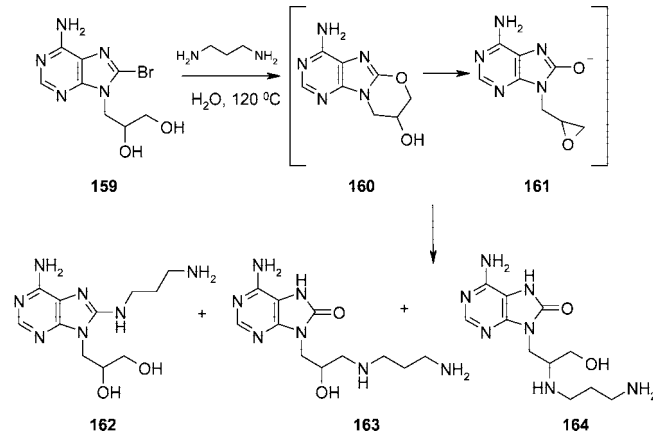
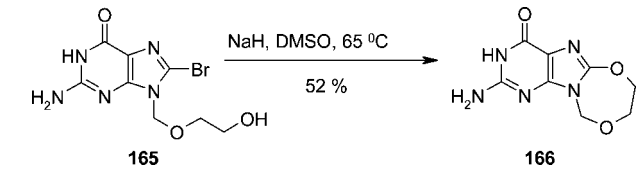


Figure 3. α-Cyclonucleosides.

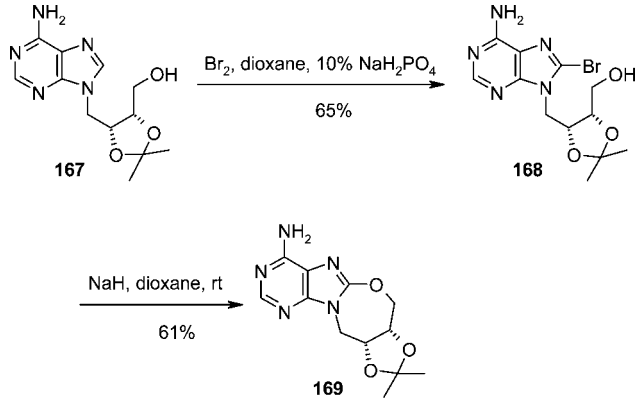
Scheme 35



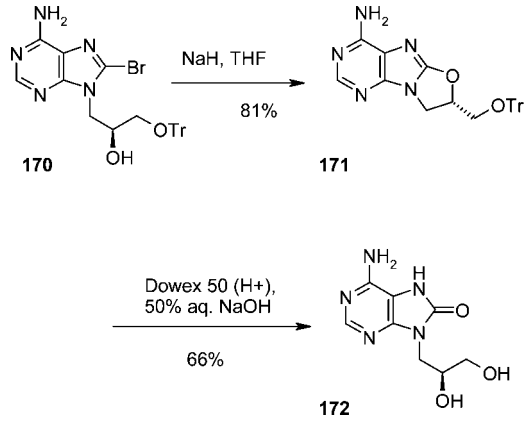
Scheme 36



Scheme 37



Scheme 38

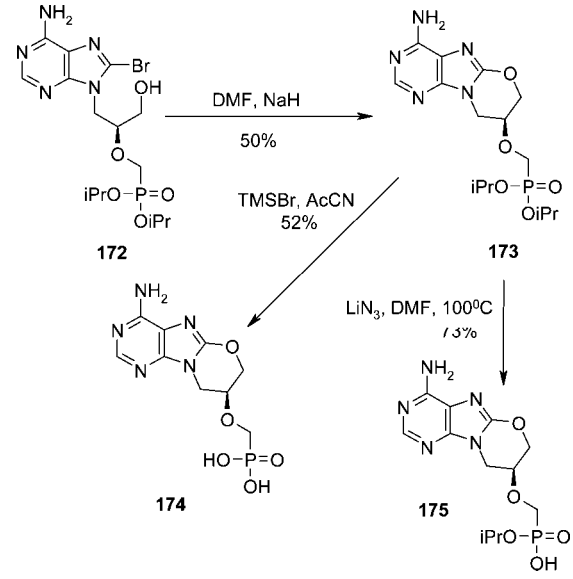


168 was treated with sodium hydride in dioxane to give (2*S*,3*S*)-8,4′-*O*-anhydro-9-(2′,3′-*O*-isopropylidene-2,3,4-trihydroxybutyl)adenine (**169**) (Scheme 37). Various *threo* and *erythro* isomers of **167** were subjected to internal cyclization. Those cyclonucleosides were stable to alkaline hydrolysis.

The formation of a five-membered ring was reported by Janeba et al.[121] After protection of the primary OH with a Tr group (**170**), subsequent cylization with sodium hydride gave **171**. Similar cyclization was observed with the 8-methylthio analogue of **170**,[122] proving that 8-SMe could serve as a leaving group in the intramolecular nucleophilic substitution. Compound **171** turned out to be unstable in acidic conditions, giving 8-oxopurine derivative **172** (Scheme 38).

Finally, the synthesis of novel acyclic purine nucleotide analogues possessing a six-membered ring fused to the purine system was reported[120] (Scheme 39). Treatment of acyclic 8-bromophosphononucleoside **172** with sodium hydride in DMF led to the formation of tricyclic phosphonic ester **173**. Standard deprotection with (TMS)Br led to free phosphonic acid **174**, while treatment with lithium azide in DMF led to monophosphonic ester **175**.

Scheme 39



3. Synthesis of Pyrimidine Cyclonucleosides

3.1. Halogen-Involved Methods

So far, halogen-involved approaches leading to pyrimidine cyclonucleosides seem to be the most common and popular methods for synthesis of this group of modified nucleoside analogues. The developed methods allow the synthesis of a wide range analogues from natural and unnatural pyrimidine nucleosides and carbocyclic and acyclic derivatives. Halogen-involved methods make possible synthesis of compounds possessing various O-, S-, and N-containing bridges differing from each other not only by heteroatom but also by the type of linkage (X^6,5′-, X^6,2′-, and X^6,3′-linkages, X = heteroatom).

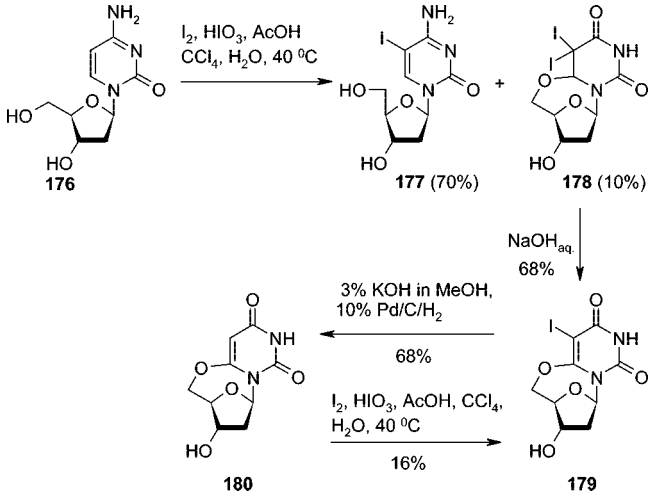
These methods could be divided into two groups. The first group includes methods where an anhydro linkage is formed during the halogenation reaction, and these methods are only applied to compounds possessing an ether linkage. The most common halogenation agents are *N*-halogenosuccinimides (*N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide), but halogenation−cyclization by treatment with I_2/HIO_3 and I_2/NH_4OH was also reported. The second group includes methods where the formation of the anhydro linkage is accompanied by elimination of a halogen from the C5 position initially present in the molecule. The dehalogenation−cyclization process is induced by treatment with the appropriate base; usually alkali-metal alkoxides (NaOMe, NaOEt, tBuOK) are applied, while organic bases (DBU, pyrimidine) are used not so often.

3.1.1. During Halogenation Reactions

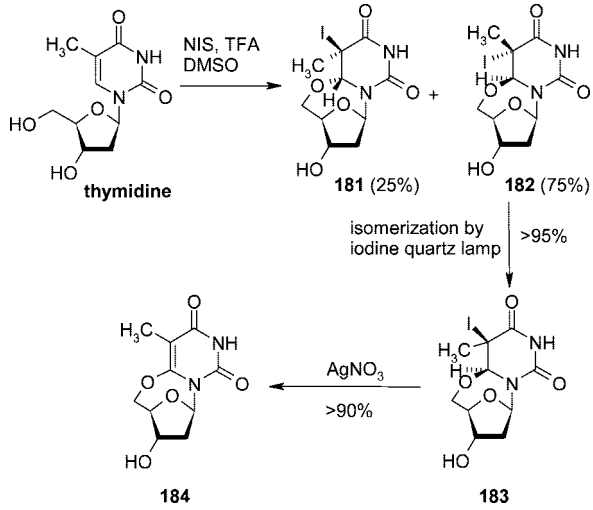
In 1963, Chang and Welch published a paper concerning the iodination of 2′-deoxycytidine (**176**).[123] An iodine/iodic acid mixture in glacial acetic acid afforded the expected 5-iodo-2′-deoxycitidine (**177**) together with 5,5-diiodo-5,6-dihydro-6,5′-*O*-anhydro-2′-deoxyuridine (**178**)[124] as the minor byproduct. Alkaline treatment of **178** gave 5-iodo-6,5′-*O*-anhydro-2′-deoxyuridine (**179**); further hydrogenation of **179** gave 6,5′-*O*-anhydro-2′-deoxyuridine (**180**), which could be iodinated back to **179** by a mixture of iodine/iodic acid (Scheme 40). Recently, Guo et al.[125] reported a novel method for the synthesis of **179** based on molecular iodine in ammonia−water under mild conditions without any other aprotic solvent.

Similar results were observed during the formation of 5,5-dibromo-6-hydroxyhydrouracil during bromination of uracil in an aqueous medium.[126] Lipkin and Rabi investigated the iodination of thymidine (Scheme 41).[127] By treatment of thymidine with NIS in anhydrous DMSO, (5*R*,6*R*)-5-bromo-5,6-dihydro-6,5′-*O*-anhydro-2′,3′-*O*-isopopylideneuridine (**181**) and (5*S*,6*S*)-5-bromo-5,6-dihydro-6,5′-*O*-

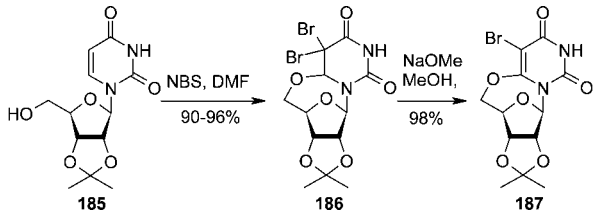
Scheme 40



Scheme 41



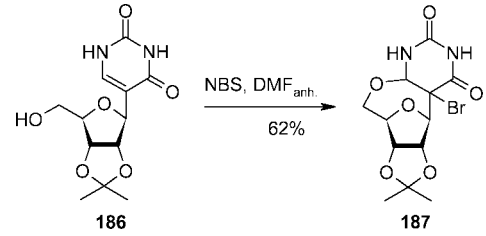
Scheme 42



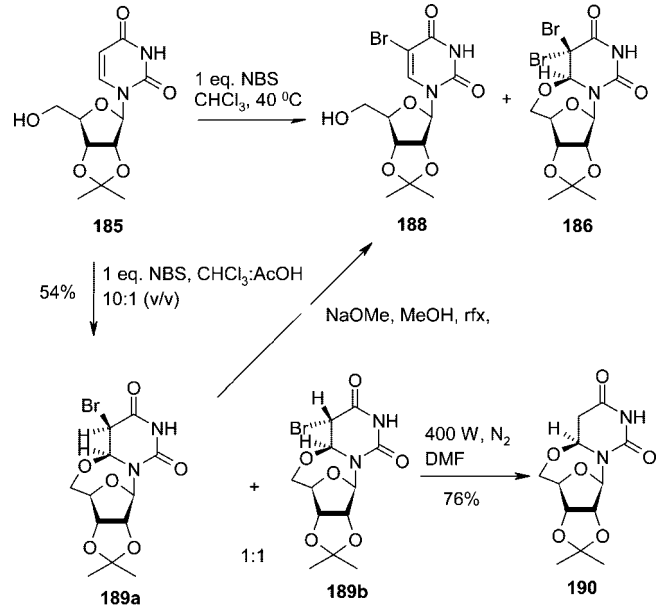
anhydro-2′,3′-*O*-isopopylideneuridine (**182**) were isolated. After illumination with an iodine quartz lamp, **182** isomerized to (5*S*,6*R*)-5-bromo-5,6-dihydro-6,5′-*O*-anhydro-2′,3′-*O*-isopropylideneuridine (**183**), which by treatment with silver nitrate led to 6,5′-*O*-anhydrothymidine (**184**).

More recently,[128] a similar procedure was applied to the synthesis of the cyclic 6,5′-*O*-anhydro-5-bromo analogue of antiviral 3′-azido-3′-deoxythymine. Bromination of uridine has been thoroughly investigated by Maki et al.[129] After treatment of 2′,3′-*O*-isopopropylideneuridine (**185**) with excess (3 equiv) *N*-bromosuccinimide, 5,5-dibromo-5,6-dihydro-6,5′-*O*-anhydro-2′,3′-*O*-isopropylideneuridine (**186**) was formed in a high yield (Scheme 42). When the bromination was carried out with 1 equiv of NBS, 5-bromo-2′,3′-*O*-isopropylideneuridine was obtained as the main product together with traces of **186**. However, 5-bromo-2′,3′-*O*-isopropylideneuridine, when treated with excess NBS,

Scheme 43



Scheme 44



forms exclusively the anhydronucleoside **186**. In the same manner dihalogeno derivatives of cytidine and *N*-benzoylcytidine were obtained. **186** by treatment with sodium methoxide led to 5-bromo-6,5′-*O*-anhydro-2′,3′-*O*-isopropylideneuridine (**187**).

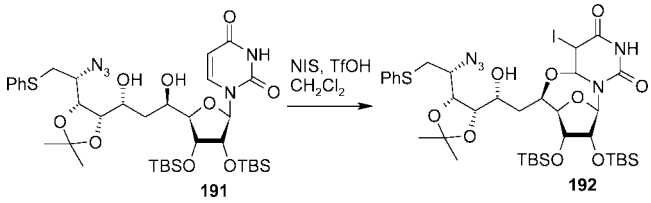
Recently, our group assessed the stereochemistry of the two diastereomers of **186** formed during the chlorination of **185**.[130] Following a similar procedure, the protected pseudouridine **188** was converted with a small excess of NBS to cyclonucleoside **189** (Scheme 43).

The same group investigated the bromination of **185** with NBS in chloroform (Scheme 44).[131] In neutral conditions, a mixture of two compounds was obtained: 5-bromo-2′,3′-*O*-isopropylideneuridine (**188**) and 5,5-dibromo-5,6-dihydro-6,5′-*O*-cyclo-2′,3′-*O*-isopropylideneuridine (**186**). However, in the presence of acetic acid, two diastereomeric cycloadducts, **189a** and **189b**, were obtained (ratio 1:1). Both isomers underwent photodebromination by irradiation in DMF to (6*S*)-5,6-dihydro-6,5′-*O*-cyclo-2′,3′-*O*-isopropylideneuridine (**190**).

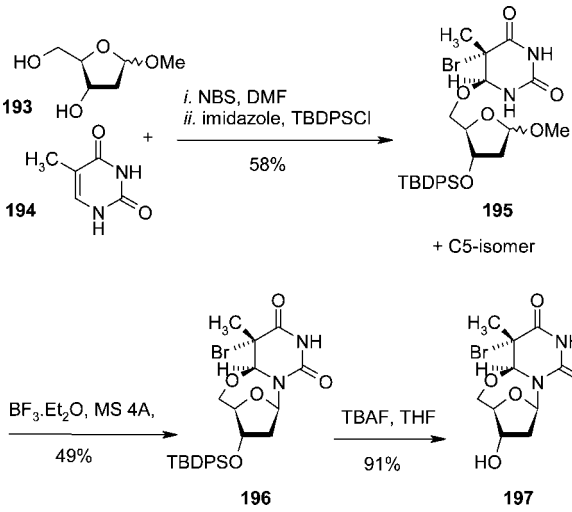
During the synthesis of tunicaminyluracil derivatives, Matsuda et al.[132] observed, instead of the expected intramolecular Pummerer reaction, a similar but undesired cyclization of intermediate **191** to cyclonucleoside **192** (Scheme 45).

It is well-known that, under Vorbrüggen or Hilbert−Jonhson cross-coupling between a 2′-deoxyribose and a nucleobase, a mixture of α,β-isomers is isolated. Thus, to circumvent this problem, Lipshutz et al.[133] envisaged a preliminary formation of a 6,5′-*O*-linkage, **195**, followed by intramolecular *N*-alkylation, affording only the β-isomer **196** (Scheme 46).

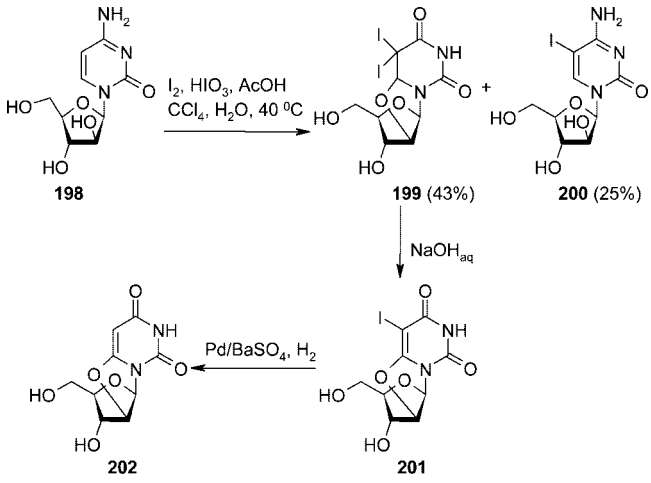
Scheme 45



Scheme 46



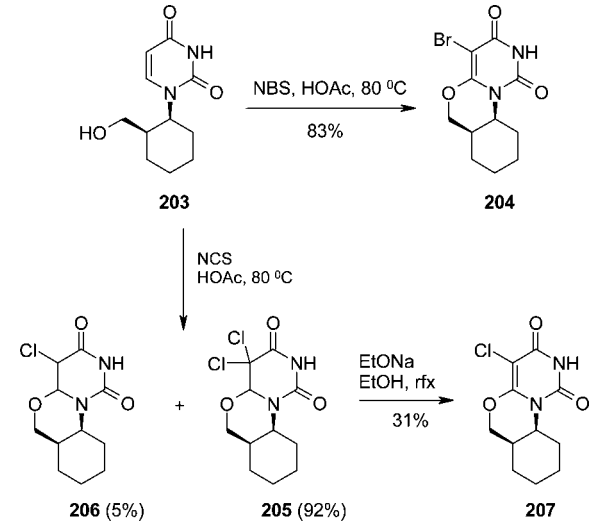
Scheme 47



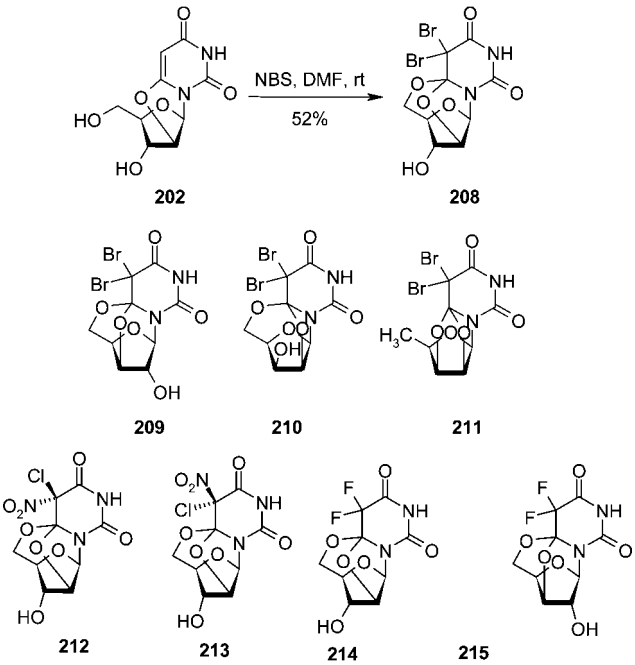
The formation of a 6,2′-*O*-anhydro bridge was realized for the arabinosylcytosine **198** (Scheme 47),[134] which under iodination conditions to give the desired product 5,5-diiodo-5,6-dihydro-O^6,2′-cyclo-1-(β-D-*arabino*-furanosyl)-uracil (**199**) and 5-iodo-1-(β-D-*arabino*-furanosyl)cytosine (**200**). Further treatment with alkali transformed **199** to 5-iodo-O^6,2′-cyclo-1-(β-D-*arabino*-furanosyl)uracil (**201**), which by hydrogenation led to **202**.

The carbocyclic nucleoside **203** analogue was halogenated (Scheme 48)[135] either to the (±)-*cis*-5-bromo analogue **204** or to a mixture of (±)-*cis*-5-chloro derivative **205** (major product) and **206** (minor byproduct). When **206** was subjected again to the same reaction conditions, it afforded **205** quantitatively after 5 h. A dehydrohalogenation of **205** with an ethanolic solution of sodium ethoxide gave (±)-*cis*-5-chloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6-*a*][3,1]benzoxazine-1,3(2*H*)-dione (**207**) with a low yield.

Scheme 48



Scheme 49



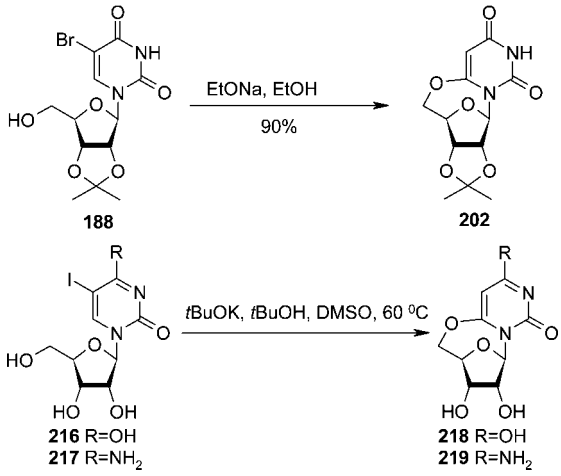
An additional halogenation of pyrimidine cyclonucleosides could lead to a derivative possessing two ether bridges. Such compounds were first reported by Honjo et al.[136] (Scheme 49). For instance, when 6,2′-*O*-cyclouridine (**202**) was treated with an excess of *N*-bromosuccinimide, the 6,2′:6,5′-bis-*O*-anhydronucleoside **208** was isolated as the main product. In a similar way, various nucleosides, **209**−**215**, were obtained.[137,138]

3.1.2. During Dehalogenation Reactions

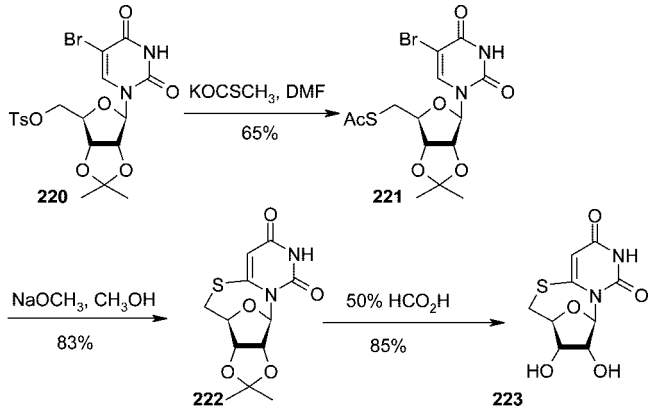
At the same time, Fox et al.[139,140] and Lipkin et al.[141] reported the formation of pyrimidine 6,5′-*O*-cyclonucleosides **202**, **218**, and **219** during the dehalogenation of **188** and **216** or **217**, respectively, with EtONa or *t*BuOK (Scheme 50). Similar results were obtained with 2′-deoxy analogues. Ueda et al.[142] reported that treatment of 5-bromo-2′,3′-*O*-isopropylideneuridine (**188**) with sodium cyanide in hot DMF led to a mixture of 5-cyanouridine, 6-cyanouridine, and cyclouridine (**202**) derivatives.

By analogy, Ueda et al. reported the synthesis of pyrimidine nucleosides possessing a 6,5′-*S*-thioanhydro bridge

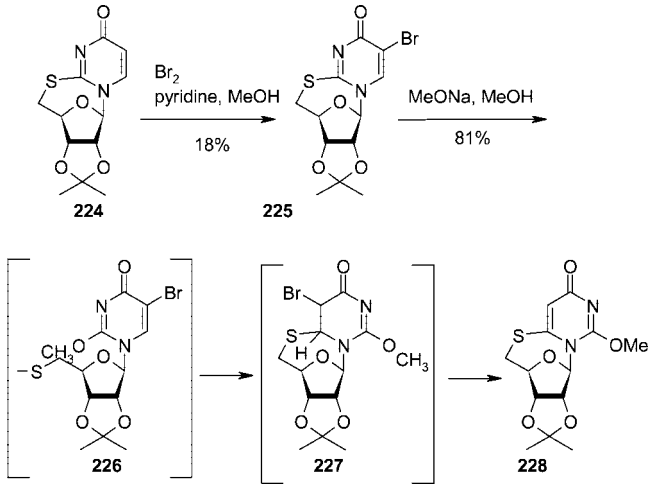
Scheme 50



Scheme 51



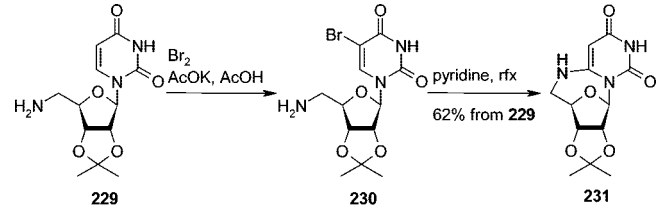
Scheme 52



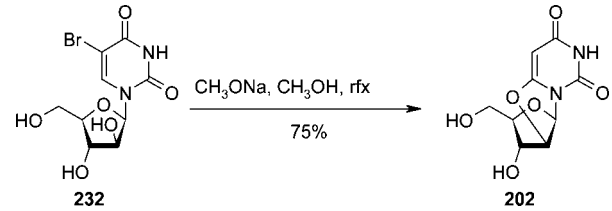
(Scheme 51).[143] 2′,3′-*O*-Isopropylidene-5′-*O*-tosyl-5-bromouridine (**220**) was treated with potassium thioacetate in DMF to afford a 5′-(acetylthio)-5′-deoxy derivative, **221**. Treatment of **221** with excess sodium methoxide in methanol at room temperature afforded 5′-deoxy-5′-thio-2′,3′-*O*-isopropylidene-6,5′-*S*-cyclouridine (**222**), which by acidic deprotection gave 5′-deoxy-5′-thio-6,5′-*S*-cyclouridine (**223**).

An interesting transformation including rearrangement and dehalogenation steps was reported by Ueda et al. (Scheme 52).[144] Treatment of 2′,3′-*O*-isopropylidene-6,2′-*S*-cyclo-2-thiouridine (**224**) with an excess of bromine afforded bromo derivative **225**, which with sodium methoxide led to the

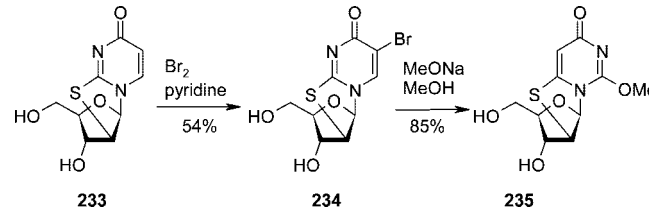
Scheme 53



Scheme 54



Scheme 55



cleavage of the sulfur bridge, giving intermediate **226**, which underwent rearrangement to **227** possessing a 6,5′-*S*-linkage. Final elimination of hydrogen bromide resulted in 2′,3′-*O*-isopropylidene-6,5′-*S*-thioanhydro-2-*O*-methyluridine (**228**).

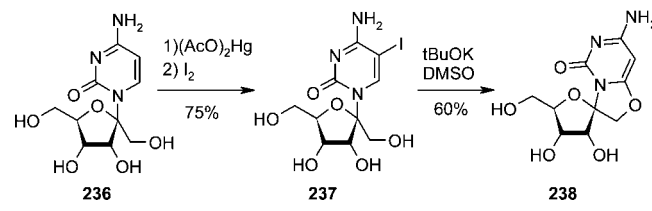
Ueda et al.[143] described some 6,5′-*N*-cyclopyrimidine nucleosides (Scheme 53) by initial bromination of 5′-amino-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**229**) to **230** and subsequent intramolecular cyclization to **231** by refluxing in pyridine for 15 min. Attempts to remove the isopropylidene group in acidic conditions resulted in degradation of this compound.

The synthesis of pyrimidine cyclonucloside[145] **202** possessing a 6,2′-*O*-anhydro bridge was realized by refluxing 1-(β-D-*arabino*-furanosyl)-5-bromouridine (**232**) with sodium methoxide (Scheme 54). This reaction highly depended on the base. Kanai also reported a similar reaction utilizing 1-(β-D-*arabino*-furanosyl)-5-iodocytosine.[146] Other examples were reported following the same procedure.[147]

The same rearrangement and dehalogenation steps as previously reported allowed the conversion of a 2,2′-*S*-thioanhydronucleoside into a 6,2′-*S*-bridge (Scheme 55). Thus, treatment of 2,2′-*S*-cyclo-2-thiouridine (**233**) with excess bromine in methanol−pyridine at room temperature afforded 5-bromo derivative **234**, which was treated with sodium methoxide in methanol to give 6,2′-*S*-cyclo-2-*O*-methyluridine (**235**).

Other cyclonucleoside analogues were also reported to be obtained by a dehalogenation step. For instance, Zavgorodny

Scheme 56



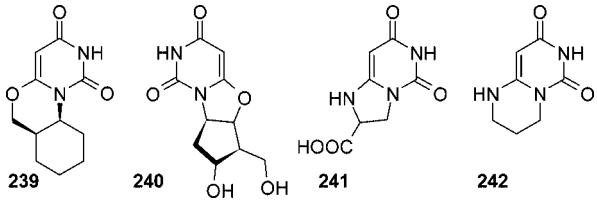
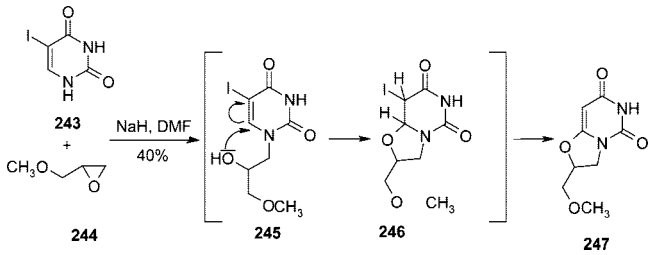


Figure 4. Cyclonucleosides by a cyclization−dehalogenation step.

Scheme 57



et al.[148] synthesized the cyclonucleoside analogue of 1-(2-β-D-psicofuranosyl)cytosine[149] (**236**) (Scheme 56). Heating **236** with a solution of mercury(II) acetate followed by iododemercuration afforded 5-iodo-1-(2-β-D-psicofuranosyl)-cytosine (**237**), which by treatment with potassium *tert*-butoxide afforded the cyclonucleoside **238**. The uracil analogue was also reported.[150]

Several other compounds were also reported to be obtained by a dehalogenation step (Figure 4).[151−154]

Similar cyclization−elimination reactions were also reported with acyclic N^1-substituted uracil derivatives.[155] Reaction of 5-iodoracil (**243**) and [(methyoxy)methyl]oxirane (**244**) gave the cyclic derivative **247** instead of the expected, linear, acyclic pyrimidine nucleoside (Scheme 57). As the cyclized product lost the iodine in the C5 position, this unexpected transformation was explained by a cyclization−elimination mechanism through intermediates **245** and **246**, respectively.

3.2. Under Radical Conditions

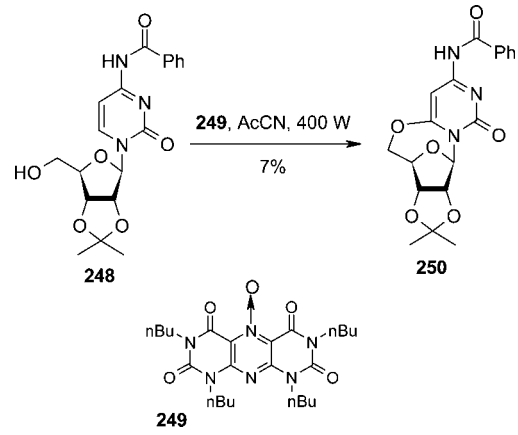
3.2.1. Formation of a 6,5′-O-Bridge

Besides halogenation−cyclization and dehalogenation−cyclization approaches, several authors reported the synthesis of pyrimidine cyclonucleosides using radical chemistry, such as Fourrey et al.[156] for the synthesis of (6*S*)-5,6-dihydro-6,5′-*O*-cyclo-2′,3′-*O*-isopopylideneuridine or Wang et al.[157] for the synthesis of (6*S*)- or (6*R*)-5,6-dihydro-2′-deoxy-5′,O^6-cyclouridines. The irradiation of N^4-benzoyl-2′,3′-*O*-isopropylidenecytidine[158] (**248**) with 2 equiv of pyrimido[5,4-*g*]pteridine *N*-oxide (**249**) in dry acetonitrile with a 400 W high-pressure mercury arc lamp through a Pyrex filter at ambient temperature under argon for 1.5 h led to the formation of N^4-benzoyl-5′,O^6-cyclo-2′,3′-*O*-isopopylidenecytidine (**250**). The ease of the reaction correlated well with the electron-donating capacity of the base moiety in the nucleosides employed (Scheme 58).

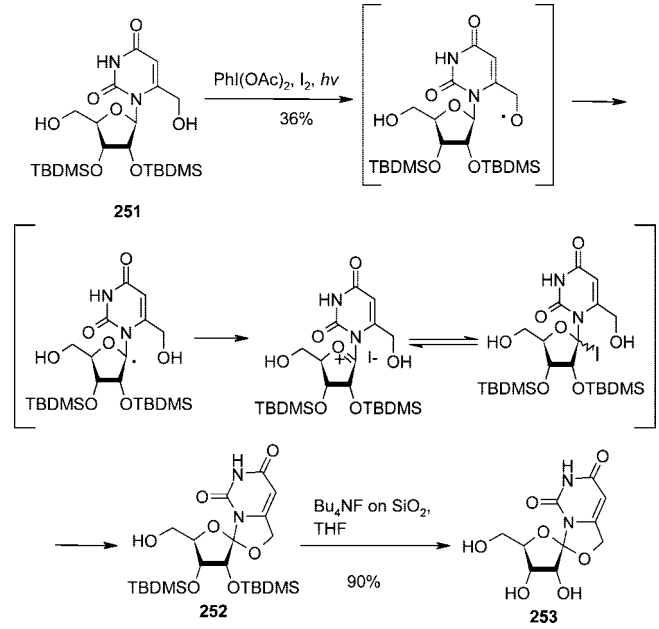
3.2.2. Formation of a 6,1′-Bridge (Spironucleoside)

The radical procedures were found to be a useful tool for the synthesis of pyrimidine spironucleosides. The first synthesis of this new class of anomeric spironucleosides possessing an unusual orthoamide structure was realized via

Scheme 58



Scheme 59



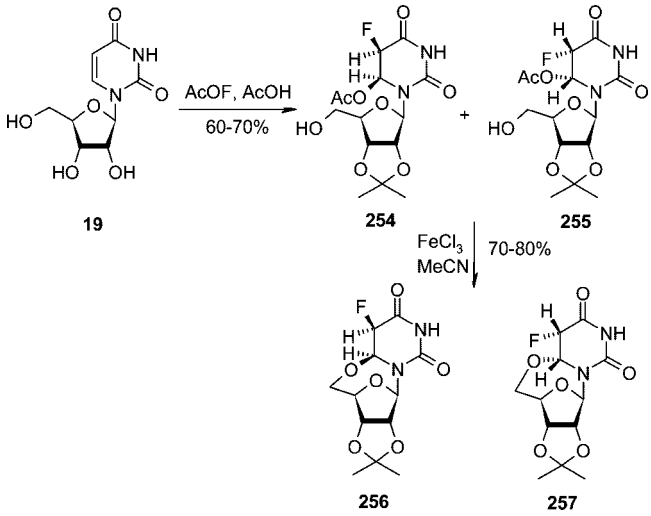
a [1,5]-radical translocation of alkoxy radicals to the anomeric position (Scheme 59).[159] Starting from 2′,3′-bis(*tert*-butyldimethylsilyl)-6-(hydroxymethyl)uridine (**251**), under Suárez conditions,[160] the main product **252** possessing a "spiro" structure was obtained in a moderate yield (36%). Deprotection of the silyl groups provided compound **253**. The mechanism for the formation of the spironucleoside involves the photolysis of the hypoiodite formed under the Suárez conditions, which generates an alkoxy radical intermediate undergoing a Barton-type hydrogen migration. A deep investigation of cyclization conditions leading to spironucleosides was published by Tanaka et al.[161]

3.3. Miscellaneous Approaches to Pyrimidine Cyclonucleosides

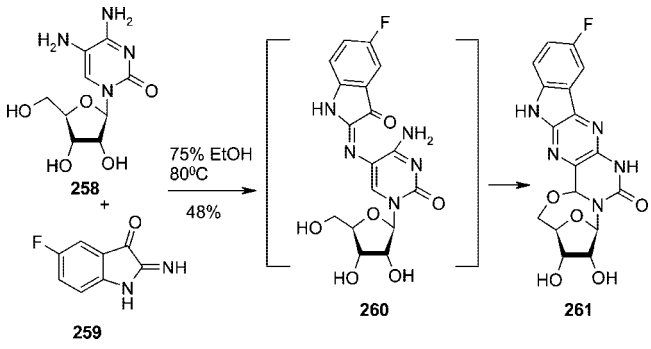
3.3.1. With an −O− Bridge

Visser et al.[162] reported an internal cyclization of unprotected pyrimidine nucleosides with acetyl hypofluorite. When uridine (**19**) was treated with AcOF, two isomeric adducts, **254** and **255**, were obtained; after a chromatography separation, they were cyclized in the presence of $FeCl_3$ in anhydrous MeCN to give **256** and **257**, respectively (Scheme 60). On the contrary, when compounds **254** and **255** were treated

Scheme 60



Scheme 61



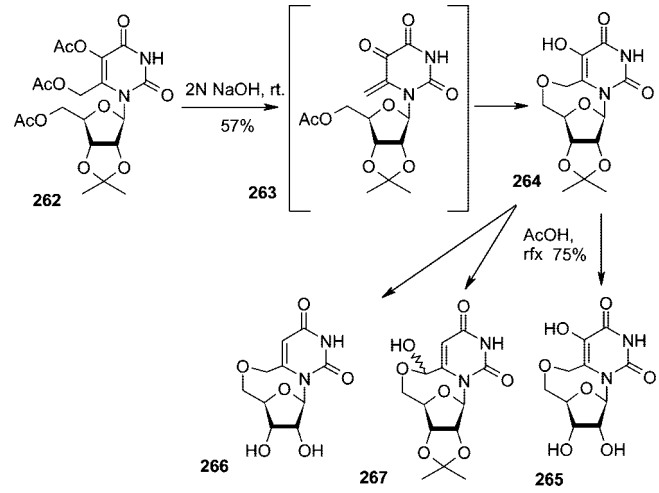
with Lewis acid $FeCl_3$ in wet MeCN, only the appropriate 6-hydroxy analogues were obtained.

During the reaction of 5-aminocytidine (**258**) with 1,2-dicarbonyl compound **259**, Kalman et al.[163] reported the formation of a fused pyrazine ring, **260,** which by a push−pull system can be intramolecularly cylized to **261** (Scheme 61).

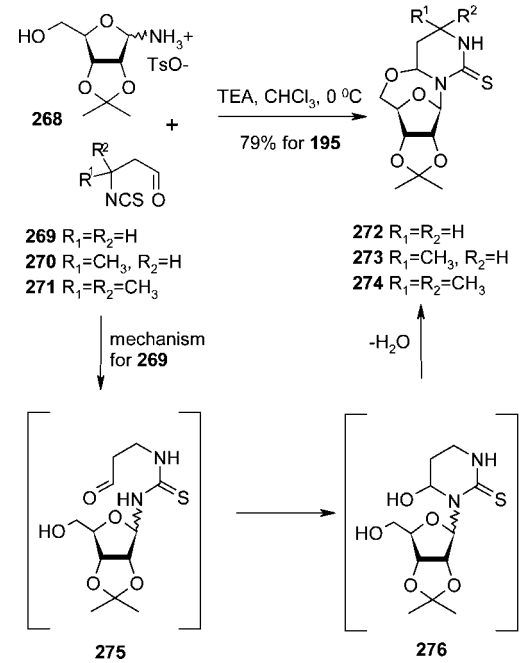
The synthesis of a novel type of pyrimidine cylonucleosides was reported by Otter et al.,[164] exploiting the basic property of 5-acetoxy-6-(acetoxymethyl)uridine **262**, which can easily be converted into the quinine methide-like intermediate **263** when treated with base in a protic solvent (Scheme 62). When the reaction was conducted in the presence of sodium hydroxide at pH 14, cyclization of intermediate **263** to cyclic pyrimidine derivative **264** occurred. **264** can then be transformed to **265**, **266**, or hemihydrate **267**.

Shutalev et al.[165] reported a series of papers concerning the synthesis of pyrimidine cyclonucleosides possessing hydrogenated pyrimidine-2-thione moieties (Scheme 63). Reaction of (2′,3′-*O*-isopropylidene-*ribo*-furanosyl)ammonium *p*-toluenesulfonate (**268**) with β-isothiocyanoaldehydes **269**−**271** in pyridine or in chloroform in the presence of TEA gave the expected cyclonucleosides **272**−**274**, respectively. The reaction proceeds with the formation of a thiourea derivative such as **275**, which cyclizes into the corresponding nucleoside derivative **276**. The intramolecular *O*-alkylation is facilitated by the steric proximity of the 5′-OH, and the hydroxyl group of the heterocycle led to the cyclonucleoside derivative **272**, for instance. During the cyclization step a new chiral center is formed at the C6 atom, resulting in two diastereosmers.

Scheme 62



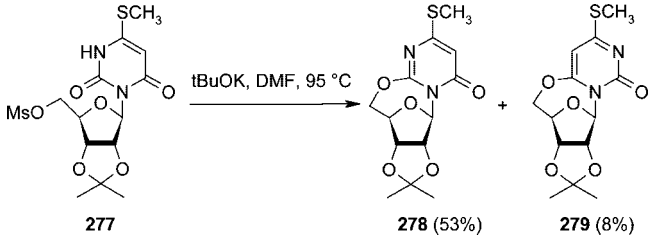
Scheme 63



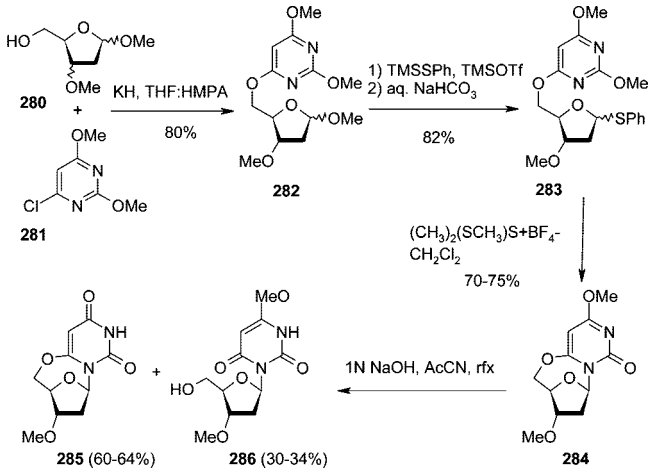
Some 6,5′-*O*-anhydronucleosides could also be obtained as a byproduct in the Heck reaction[166] or during the syntheses of 5-(phenylselenyl)uridine derivatives by treatment with diphenyl diselenide[167] or phenylselenyl chloride.[168] In 1970, Winkley et al.[169] reported the synthesis of two types of pyrimidine nucleosides, starting from 5′-*O*-(methylsulfonyl)-2′,3′-*O*-isopropylidene-3-(β-D-*ribo*-furanosyl)-6-(methylthio)-pyrimidine-2,4-dione (**277**). When **277** was treated with potassium *tert*-butoxide in hot DMF, two products, **278** and **279**, were isolated in 53% and 8% yield, respectively (Scheme 64).

In 1999, Castro et al.[170] reported an intramolecular *N*-glycosylation reaction using a 5′-oxygen tether to deliver the nucleobase to the anomeric center, which led exclusively to β-nucleoside analogues (Scheme 65). 6,5′-*O*-Bridged precursor **282** was prepared from commercially available 6-chloro-2,4-dimethoxypyrimidine (**281**) and methyl riboside (**280**) by treatment with potassium hydride in a THF/HMPA mixture. As treatment of **282** with Lewis acids led to the decomposition of starting material, and cleavage of the ether linkage, the authors transformed it into the corresponding

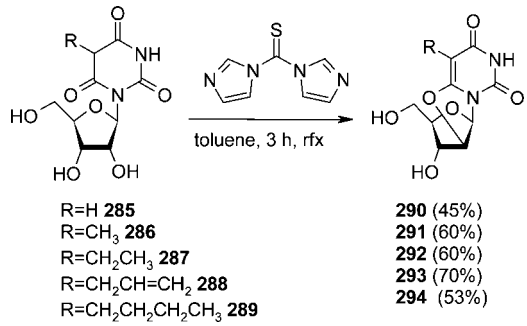
Scheme 64



Scheme 65



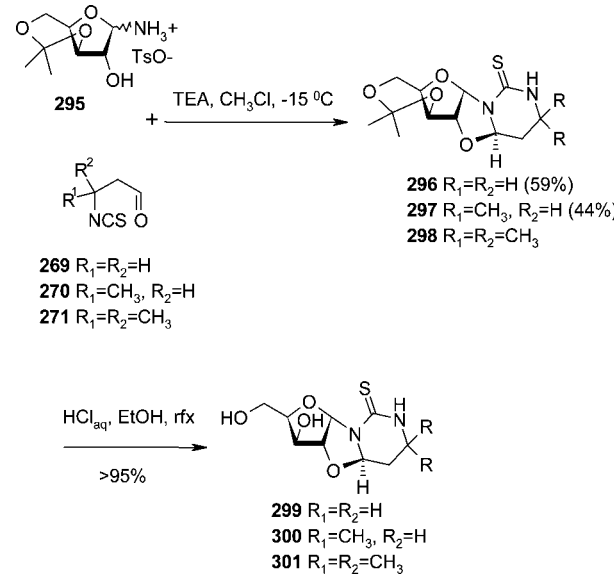
Scheme 66



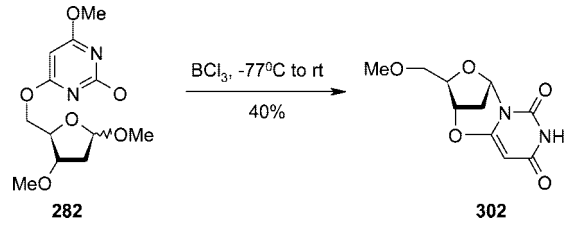
1′-thiophenyl derivative **283** by treatment with trimethylsilyl triflate ((TMS)OTf) and trimethyl(thiophenyl)silane ((TMS)-SPh). The critical cyclization step was accomplished using dimethyl(methylthio)sulfonium tetrafluoroborate as the activating agent and dichloromethane as a solvent. The cyclization reaction proved to be very sensitive to the solvent used. When acetonitrile was used as the reaction medium, only a trace of the desired product was identified by TLC. The removal of the pyrimidyl methoxy group from O^6,5′-cyclonucleoside **284** was accomplished by treatment with sodium hydroxide solution in refluxing acetonitrile. From the reaction mixture, products were separated: the desired O^6,5′-cyclonucleoside **285** in 60−64% yield with a minor byproduct, β-barbituric nucleoside **286**, derived from opening the ether bridge under basic conditions (30−35% yield).

Eger et al.[171] reported the synthesis of 6,2′-*O*-anhydropyrimidine nucleosides starting from 5-substituted barbituric acid nucleosides (Scheme 66). The starting materials—barbituric acid nucleosides **285**−**289**—were refluxed in toluene with (thiocarbonyl)diimidazole to afford the desired 6,2′-*O*-pyrimidine cyclonucleosides **290**−**294**, respectively, in good yield. This reaction is reversible.

Scheme 67



Scheme 68



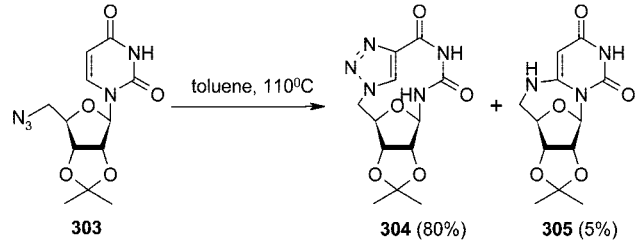
As mentioned above, Shutalev et al. also reported[172] the synthesis of derivatives with an α-configuration (Scheme 67). The condensation of (3′,5′-*O*-isopropylidene-D-*xylo*-furanosyl)ammonium *p*-toluenesulfonate (**295**) with β-isothiocyanoaldehydes **269**−**271** in the presence of triethylamine led to the formation of hydrogenated pyrimidine cyclonucleosides **296**−**298** as the major products, respectively. NMR spectroscopy revealed that new products **296** and **298** are formed entirely as single isomers and **297** is formed as a 1:1 mixture of two diastereoisomers. Acidic deprotection of xylosides **296**−**298** afforded the cyclonucleosides **299**−**301**.

During the studies of an intramolecular Vorbrüggen coupling, Jung et al.[173] reported a novel transformation, based on an internal cyclization and a rearrangement step, which led to pyrimidine 6,3′-*O*-α-anydronucleoside derivative **302** (Scheme 68). Compound **282** undergoes an unexpected Lewis acid-catalyzed rearrangement after treatment with boron trichloride, giving **302** with a fair yield.

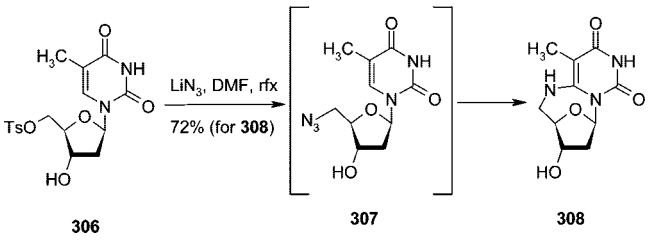
3.3.2. With a −N− Bridge

Azido derivatives of nucleosides possess valuable biological activities, which make them good candidates for drug design.[174] The azido group, attached either to the sugar or to the heterocycle, is an important source of nitrogen for the construction of pyrimidine cyclonucleosides possessing an amine bridge. Sasaki et al.[175] investigated the 1,3-dipolar cycloaddition of an azide group to the 5,6-double bond of the uracil ring (Scheme 69). Heating 5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**303**) in toluene led to two products. The main one was identified as the cyclic, allophanoyl-1,2,3-triazole derivative **304**, while the minor one, isolated with 5% yield, was identified as N^6,5′-cyclo-5′-amino-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**305**).

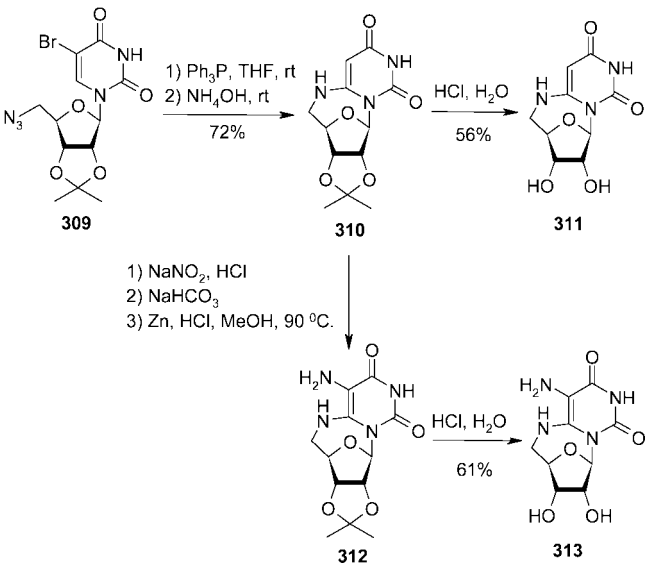
Scheme 69



Scheme 70



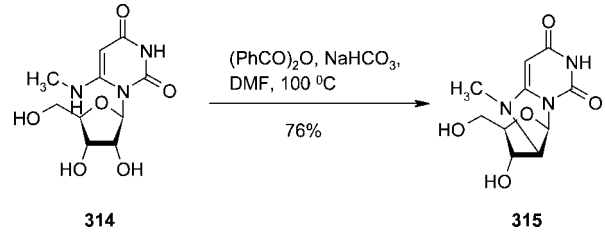
Scheme 71



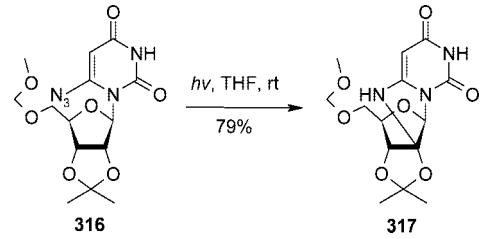
A similar reaction was also reported by Watanabe et al.,[176] who observed that treatment of 5′-tosylthymidine (**306**) with lithium azide in refluxed DMF gave the cyclonucleoside **308** with a high yield (Scheme 70). The authors suggested that the reaction proceeded via the formation of the intermediate 5′-azido-5′-deoxythymidine (**307**).

The improved synthesis of cyclonucleoside **310**, starting from 5′-azide, was reported by Chun et al. (Scheme 71).[177] 5-Bromo-5′-azido-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**309**) after treatment with triphenylphosphine in THF followed by addition of aqueous ammonia using a one-pot procedure gave **310** with a high, 72%, yield. Deprotection of **310** with hydrochloric acid gave N^6,5′-cyclo-5′-amino-5′-deoxyuridine (**311**). The treatment of **310** with sodium nitrite in acidic conditions led to the 5-nitroso intermediate, which without purification was directly reduced with Zn/HCl in methanol to give 5,5′-diamino-N^6,5′-cyclo-5′-deoxy-2′,3′-*O*-isopropylideneuridine (**312**). Deprotection of **312** with hydrochloric acid led to 5,5′-diamino-N^6,5′-cyclo-5′-deoxyuridine (**313**), which showed moderate activity against HCV virus ($EC_{90} = 85\ \mu M$). As the derivative **311** has no antiviral activity, the 5-amino group in the pyrimidine moiety was thought to be responsible for the observed activity of **313**.

Scheme 72



Scheme 73



Additionally, pyrimidine cyclonucleoside **312** was further used as an intermediate in the synthesis of purine cycloisonucleoside analogues possessing significant, anti-HCV activity.[178]

Finally, Ueda et al. mentioned[142−144,147] the application of the Mitsunobu reaction for the formation of a 6,5′-*N*-bridge. They described also that the treatment of 6-(methylamino)-uridine (**314**) with diphenyl carbonate in the presence of sodium bicarbonate led to the formation of pyrimidine cyclonucleoside **315**, which possesses a 6,2′-*N*-bridge (Scheme 72). It is interesting to note that the *N*-alkylation is preferred to the *O*-alkylation.

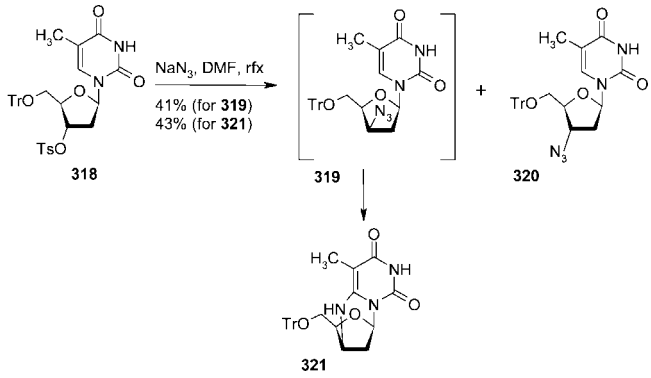
A different approach leading to a 6,2′-*N*-bridge was investigated by Miyasaka et al. (Scheme 73).[179] When 6-azido-2′,3′-*O*-isopropylidene-5′-*O*-(methoxymethyl)uridine (**316**) was irradiated with a 250 W high-pressure mercury lamp equipped with a Pyrex filter in dry THF, the photochemical intramolecular insertion of the 6-azido group led to the 6,2′-*N*-bridged cyclonucleoside **317**. Similar photochemical reactions were carried out for the N^3-methyl and 5-methyl derivatives of **316**, giving the respective cyclized products with 60% and 86% yield. The authors claimed that the efficiency of the intermolecular nitrene insertion may presumably be highly related to the suitable proximity of the base and sugar moieties.

When 5′-*O*-trityl-3′-*O*-mesylthymidine (**318**) was treated with sodium azide, the desired 3′-azido-3′-deoxy-5′-*O*-tritylthymidine (**319**) and the 6,3′-*N*-bridged thymidine derivative **321** were obtained. The authors found that in the first step of this transformation two isomeric azides, **319** and **320**, are formed, the first one in the direct intermolecular nucleophilic displacement process, and the second one in the intramolecular (neighboring group) reaction. When the reaction was carried out in a shorter time, derivative **320** was isolated from the reaction mixture, while prolonged heating led to the subsequent formation of **321** (Scheme 74).

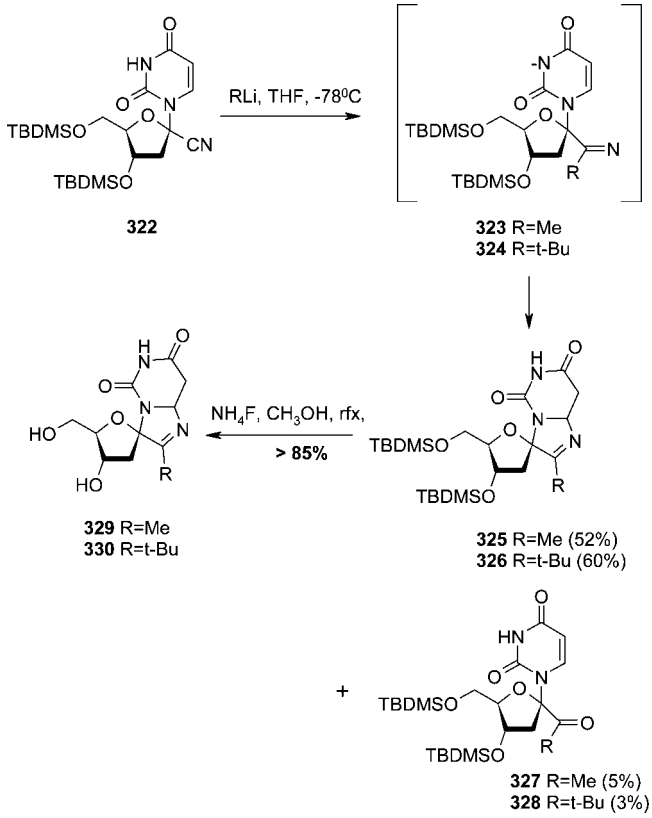
3.3.3. With Various Bridges

Besides pyrimidine cyclonucleosides possessing simple ether, thioether, and amine bridges, some other cyclic derivatives with other types of linkages were reported. For instance, Chatgilialoglu et al.[180] described reaction of 3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-1′-*C*-cyano-2′-deoxyuri-

Scheme 74



Scheme 75



dine (**322**) with organolithium reagents. The slow addition of organolithium reagent to the diluted THF solution of **322**, followed by quenching with a saturated aqueous solution of $NaHCO_3$, led to the predominant formation of a new type of cyclonucleosides, **325** and **326**, as single diastereomers, while 1′-acyl derivatives **327** and **328** were obtained as minor products (Scheme 75). Deprotection of spironucleosides **325** and **326** afforded the final cyclic derivatives **329** and **330**.

Other types of pyrimidine cyclonucleosides, **331**−**333** (with marginal activity against *Bacillus subtilis*), were reported by Tronchet et al.[181] (Figure 5).

Tronchet also reported novel pyrimidine cyclonucleoside analogues possessing a hydroxylamine linkage (Scheme 76).[182] When 2′,3′-*O*-cyclopentylideneuridine (**334**) was submitted to a Mitsunobu reaction using *N*-hydroxyphthalimide, the 5′-phthalimido derivative **335** was isolated. After hydrazinolysis of **335** to the 5′-*O*-aminouridine derivative **336**, treatment with 2-acetoxypropenenitrile in THF gave selectively the *N*-acetyl derivative (room temperature, 66% yield) or the product of the conjugate addition upon the uracil

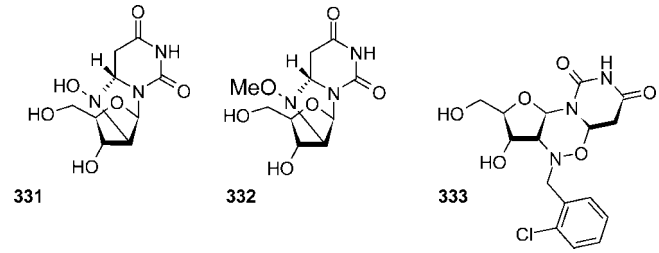
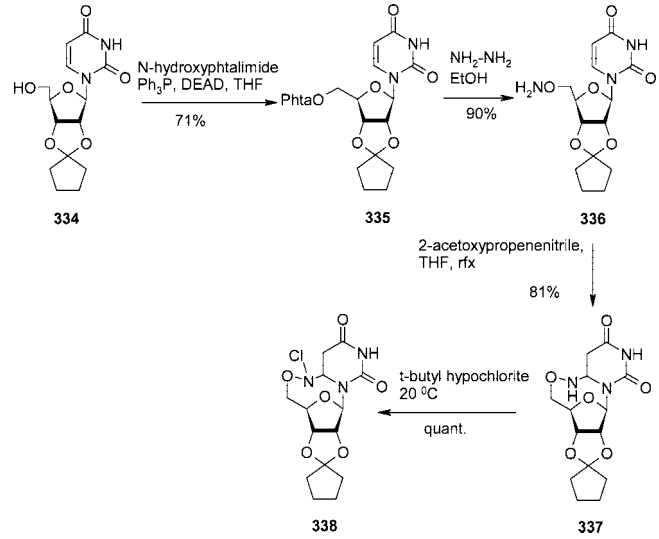
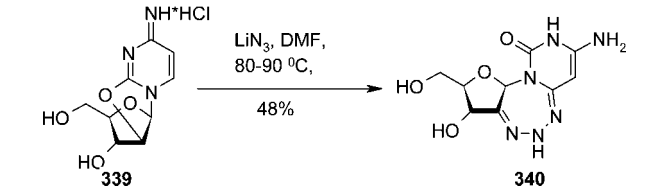


Figure 5. Pyrimidine cyclonucleosides with various bridges.

Scheme 76



Scheme 77



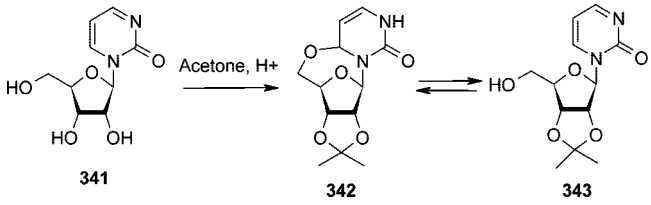
moiety **337** (refluxing THF, 81% yield). Treatment of cyclonucleoside **337** with *tert*-butyl hypochlorite gave quantitatively *N*-chloro derivative **338**.

Finally, a novel type of pyrimidine cyclonucleoside, 6,2′-triazacyclocytidine (**340**), starting from another type of 2,2′-*O*-cyclonucleoside, **339**, was described by Kikugawa et al.[183] (Scheme 77). Treatment of O^2,2′-cyclocytidine **339** with azide ion resulted in cleavage of the oxygen bridge and formation of a 2′-azido-substituted derivative. On the contrary, heating **339** with lithium azide in DMF led to the rearrangement and formation of previously unknown, unexpected cyclonucleoside **340**.

3.4. Equilibria between Nucleosides and Cyclonucleosides

Early investigations of 6,5′-*O*-pyrimidine cyclonucleosides showed that a 6,5′-*O*-anhydro bridge exists under basic conditions. It was observed[184] that, when 2′,3′-*O*-*iso*propylideneuridine is treated with MeONa and MeOD at 60 °C, the H5 atom is exchanged to deuterium by an apparent first-order process, while in the absence of the base, an exchange is not observed. Under identical conditions, the H5 atoms of 5′-deoxy-2′,3′-*O*-isopropylideneuridine and 1-methyluracil

Scheme 78



are not exchanged to deuterium. These results suggest that the introduction of a deuterium in place of H5 occurs through a 6,5′-*O*-anhydro intermediate and that the anchimeric assistance of the 5′-oxy anion plays a crucial role in this process. The 67-fold rate enhancement observed for the 6,5′-*O*-cyclouridine analogue compared to uridine and 2′-deoxyuridine was accounted for by the rigidity of the cyclonucleoside. Similar observations were reported by Fox et al.[185] for the reaction of 5-fluorouracil derivatives with sodium deuteroxide.

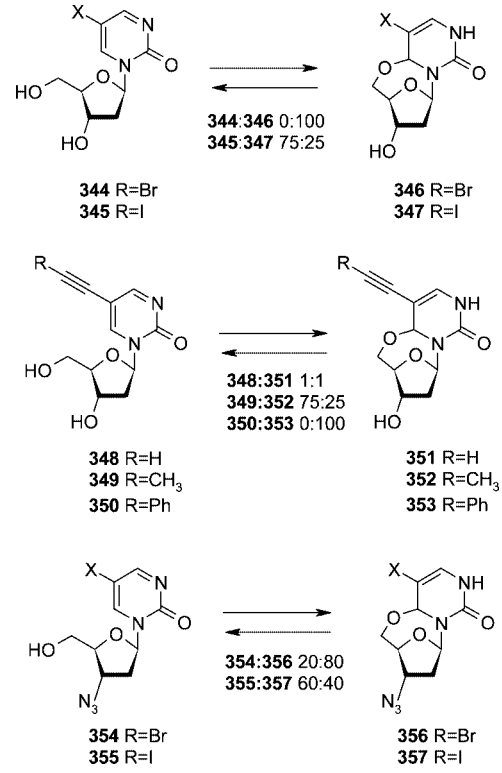
3.4.1. Equilibria of Nucleoside Analogues with Modified Nucleobases

The most popular and important group of pyrimidine nucleocleoside analogues which could exist in two forms is the 2-pyrimidone nucleosides. Such a possibility was initially reported by Marquez et al.,[186] who observed that 1-(β-D-*ribo*-furanosyl)-1,2-dihydropyrimidin-2-one (**341**), during protection with a 2′,3′-*O*-isopropylidene group, underwent a smooth transformation to the 6,5′-*O*-cyclonucleoside **342** (Scheme 78). Compound **342** exists in equilibrium with its open form **343** in aqueous solution as revealed by NMR spectroscopy in D_2O. After lyophilization, the material cyclized quantitatively to **342** and remained as such in an aprotic organic solvent. The authors explained the formation of the cyclic form **342** by the rigidity and skewing imposed by the acetonide group, since this intramolecular reaction was not observed with **341**.

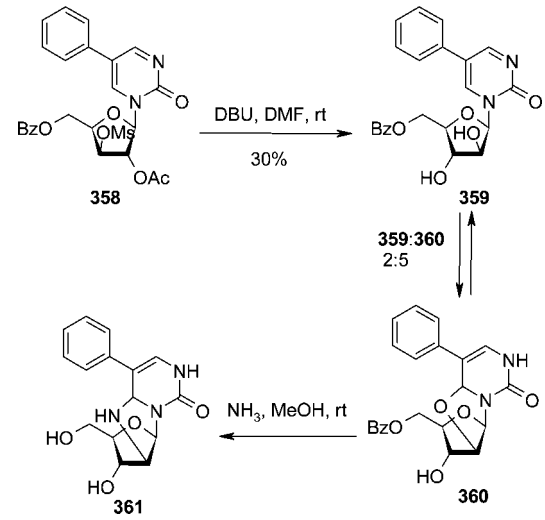
The susceptibility of 2-pyrimidone nucleosides for the formation of cyclic derivatives was also observed by Bardos et al.[187] starting from 5-bromo derivative **344** and 5-iodo derivative **345** (Scheme 79). The NMR spectrum of 1-(2′-deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (**344**) in DMSO-d_6 revealed that this molecule exists exclusively as the 6,5′-*O*-cyclonucleoside **346**. The 1-(2′-deoxy-β-D-*ribo*-furanosyl)-5-iodo-2-pyrimidinone (**345**), obtained initially in an open form, was partially transformed into the cyclic form **347** after repeated coevaporation with acetone (estimated at 25% of the mixture). The facile cyclic adduct formation of 2-pyrimidone nucleosides, attributed previously to the strain introduced by the presence of the isopropylidene functionality, in the case of 2′-deoxynucleosides reflected the level of electron deficiency at C4 and C6 of the pyrimidine ring and consequently depended on the nature of the substituent at C5. Other 5-alkynyl derivatives of 2-pyrimidone nucleoside,[188] **348**−**350**, or azido derivatives, **354** and **355**, are in equilibrium with their cyclized forms, **351**−**353** and **356** and **357**, respectively.

Treatment of 3′-*O*-mesyl derivative **358** with DBU led to an equilibrium mixture of 5′-*O*-benzoylated *arabino*-furanosyl nucleoside **359** and its 2′,O^6-cyclo derivative **360** in a ratio of 2:5. Attempts to obtain the free *arabino*-furanosyl derivative by reaction with methanolic ammonia led to a

Scheme 79



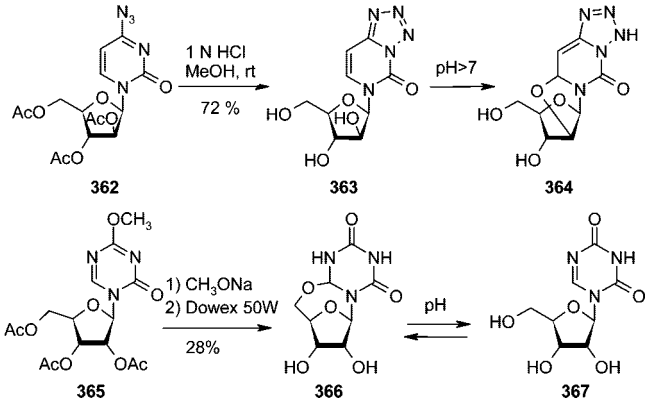
Scheme 80



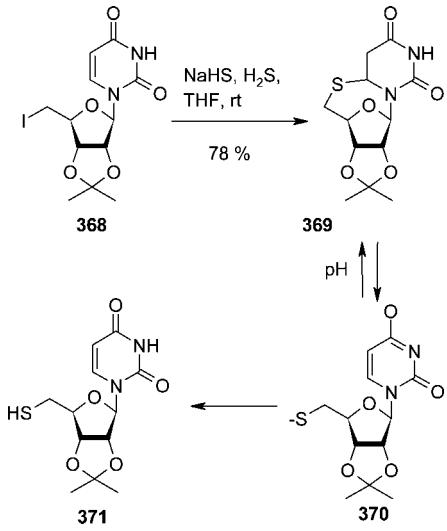
complex mixture from which compound **361**, possessing a 6,2′-*N*-anhydro bridge, was isolated with a low yield (Scheme 80).

Chu et al.[189] mentioned that nucleoside **362**, after acidic deprotection of the acetyl groups, afforded 1-(β-D-*arabino*-furanosyl)tetrazolo[4,5-*c*]pyrimidin-2-one (**363**) (Scheme 81). Further investigation of the stability revealed that **363** is stable in a methanol solution at pH 2, while in a neutral/basic solution it undergoes spontaneous rearrangement to the cyclonucleoside **364**. Piskala and Šorm reported[190] that deprotection of acetylated nucleoside **365** with sodium methoxide in methanol followed by Dowex 50 W (H^+) led to the cyclonucleoside derivative **366** through an intramolecular addition of the *C*5′-OH to the azomethine; the cyclonucleoside **366** could exist with its open form **367** depending on the pH of the solution.

Scheme 81



Scheme 82



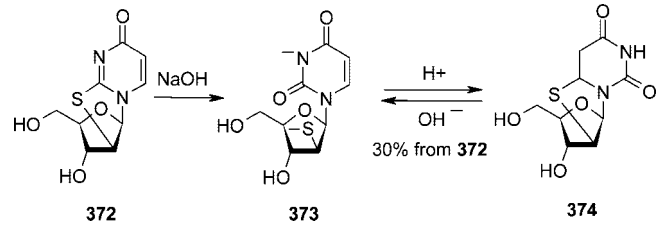
3.4.2. Equilibria of Nucleoside Analogues with a Modified Sugar Moiety

The modifications of the sugar moiety could facilitate the formation of equilibrium between the open and cyclic forms of nucleoside derivatives. In the early 1960s, Banister and Kagan reported[191] that treatment of 5′-deoxy-5′-iodo-2,3′-*O*-isopropylideneuridine (**368**) led to the formation cyclic 5′-deoxy-5′-thio-5,6-dihydro-6,5′-*O*-cyclo-2′,3′-*O*-isopropylideneuridine (**369**) rather then to the open form 5′-deoxy-5′-thio-2′,3′-*O*-isopropylideneuridine (**371**) (Scheme 82). Derivative **369** is in equilibrium with the dianion **370**, and the position of this equilibrium is pH dependent. At pH 9.8 equal amounts of **369** and **370** are present; below pH 9.8 **369** predominates, while above 9.8 the dianionic form **370** is the main component. Chambers and Kurkov also reported that **371** could be obtained by opening the episulfide ring in **369** by alkali followed by trapping by the rapid acidification of the solution.

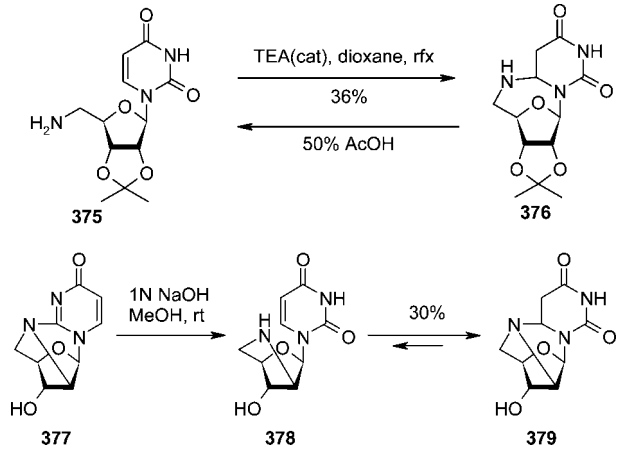
Finally, Ukita et al.[192] noted that treatment of 2′-deoxy-2′-thio-2,2′-*S*-cyclouridine (**372**) with sodium hydroxide led to the dianion **373**, which after subsequent neutralization with Dowex 50 W (H^+) gave a crystalline product identified as 5,6-dihydro-2′-deoxy-2′-thio-6,2′-*S*-thioanhydrouridine (**374**) (Scheme 83). A similar addition was also observed on acyclic uracil derivatives possessing a terminal thiol group.[193]

Isono and Azuma[194] observed that when 5′-deoxy-5′-amine-2,3′-*O*-isopropylideneuridine (**375**) was heated in anhydrous dioxane containing a catalytic amount of triethylamine, 5′-deoxy-5′-amino-5,6-dihydro-6,5′-*N*-cyclo-2′,3′-*O*-

Scheme 83



Scheme 84



isopropylideneuridine (**376**) was obtained in 36% yield (Scheme 84). A similar Michael-type addition was observed by Minamoto et al.[195] for the synthesis of multibridged nucleoside **377**, which when treated with a 1:1 mixture of 1 N NaOH and MeOH gave derivative **378**. During the reaction time, derivative **378** is subsequently transformed into the new multibridged cyclonucleoside **379** to attain finally equilibrium between both, in favor of the latter.

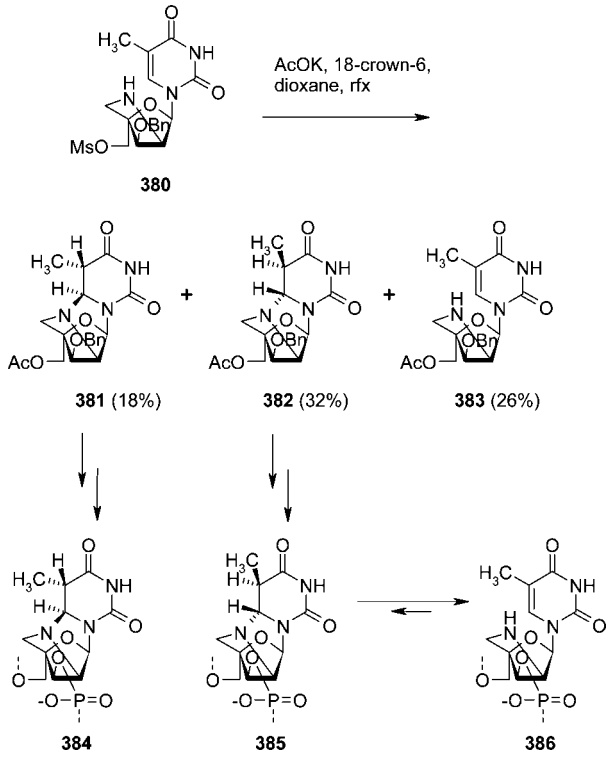
Finally, during synthesis and hybridization studies of locked LNA, Hrdlicka et al.[196] described the synthesis of novel, tetracyclic derivatives **381** and **382** (Scheme 85). Treatment of bicyclic nucleoside **380** with sodium acetate in the presence of 18-crown-6 led to tetracyclic derivatives **381** and **382**, together with the expected *C*5′-acetate **383**.

Tetracyclic nucleosides **381** and **382** are formed as a result of a diastereoselective conjugate 1,4-addition of the secondary *C*2′-amino group to the C6 position of the thymine moiety of nucleoside **380** in an intramolecular aza-Michael reaction, where the chiral sugar moiety is the main stereochemical controller. In the following steps, tetracyclic nucleosides **381** and **382** were transformed into the appropriate phosphoramidite derivatives and incorporated into the oligonucleotide chains (structures **384** and **385**, respectively). While tetracyclic nucleoside **384** exhibited significant stability during transformation into the phosphoramidite and incorporation into the oligonucleotides, its isomer **385** easily underwent a base-induced retro-aza-Michael reaction, leading to the formation of bicyclic structure **386**. Recently, a similar intermolecular Michael addition was also observed for the oxygen nucleophiles during synthesis on novel acyclic analogues of pyrimidine nucleosides.[197,198]

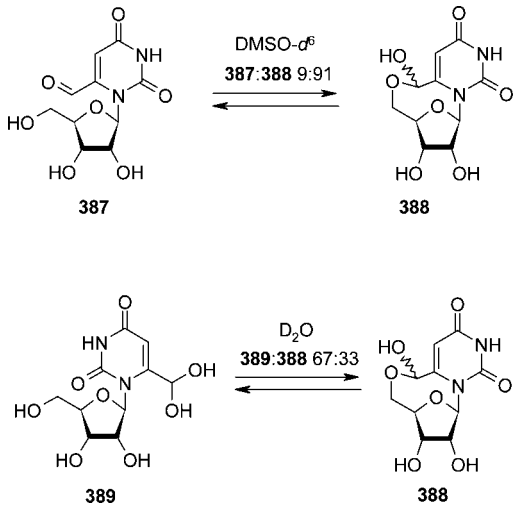
3.4.3. Miscellaneous Equilibria

During their investigations of 6-formyluridine derivatives, Groziak et al.[199] observed an unexpected formation of hemiketal cyclonucleosides. 3-Formyluridine (**387**) was found to exist in a DMSO solution in equilibrium with the

Scheme 85



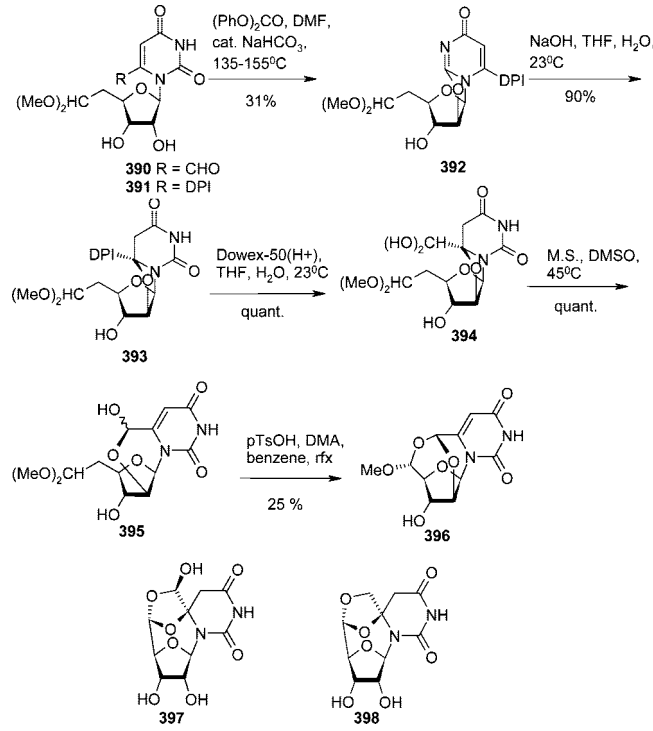
Scheme 86



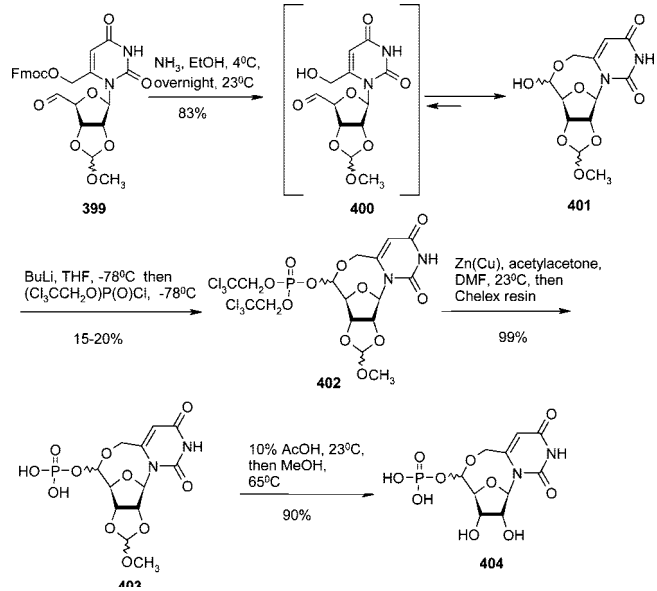
5′-cyclic hemiketal structure **388** in a ratio of 9:91 (Scheme 86). In D_2O solution, the 6-formyl derivative exists predominantly as *gem*-diol structure **389** in equilibrium with **388**, while in the solid state only the hemiketal form **388** was observed. Similar results were found with 6-formyl derivatives of 2′-deoxyuridine[200] or *arabino*-uridine.[201]

The synthesis of novel "caged" nucleoside **396** was developed by Groziak and Lin[202] (Scheme 87). The 6-DPI 5′-dimethyl acetal **391** (DPI = 1,3-diphenylimidazolidin-2-yl), obtained from its corresponding aldehyde **390**, when treated with diphenyl carbonate afforded the desired 2,2′-cyclonucleoside **392**. After saponification of **392**, the 6,5′-*O*-anhydronucleoside **393** was isolated and deprotected to the hydrate **394** in a quantitative yield. Upon desiccation by heating with 4 Å molecular sieves in DMSO, **395** was isolated and a final cyclization of **395** leading to the caged nucleoside **396** was achieved by heating with pTsOH in a mixture of benzene/DMA.

Scheme 87



Scheme 88



Following a similar approach, Groziak and Lin[203] reported the synthesis of the unusual spiro-fused dihydronucleosides **397** and **398**, the structures of which were confirmed by crystallographic methods.[204] More recently, the same group[205] synthesized the nucleotide cyclonucleoside **404** possessing a phosphate group at the C5′ position (Scheme 88).

The 5′-aldehyde **399** treated with ethanolic ammonia was converted to alcohol **400**, which exists exclusively as cyclic hemiacetal **401**. Phosphorylation of **401** was achieved by treatment with BuLi at −78 °C followed by addition of bis(2,2,2-trichloroethyl) phosphorochloridate, which resulted in formation of phosphate diester **402**. Following deprotection of the phosphate group with Zn(Cu), the free phosphonic acid **403** was converted to the target compound **404**, obtained as a 1:1 mixture of diastereomers.

3.5. Some Transformations of Pyrimidine Cyclonucleosides

3.5.1. At the C4 Position

The modifications at the C4 position of pyrimidine cyclonucleosides are usually achieved by using standard procedures applied for classical nucleosides. The C4 position in the uracil ring could undergo thiolation, chlorination, or substitution with a *C*4-triazolyl ring followed by further transformation into some other C4 analogues. Fox et al.[206] noted that 3′,5′-*O*-dibenzoyl-6,2′-*O*-cyclouridine (**405**) could be transformed into 4-thione **406** by refluxing with phosphorus pentasulfide in dioxane (Scheme 89). After deprotection, treatment of the obtained 4-thio derivative **407** with methyl iodide, in the presence of sodium hydroxide, led to the 4-methylthio compound **408**, while heating with an excess of hydroxylamine in methanolic solution resulted in formation of 4-hydroxyamino intermediate **409**. Reduction of **409** on palladium charcoal gave 6,2′-*O*-anhydrocytidine (**410**).

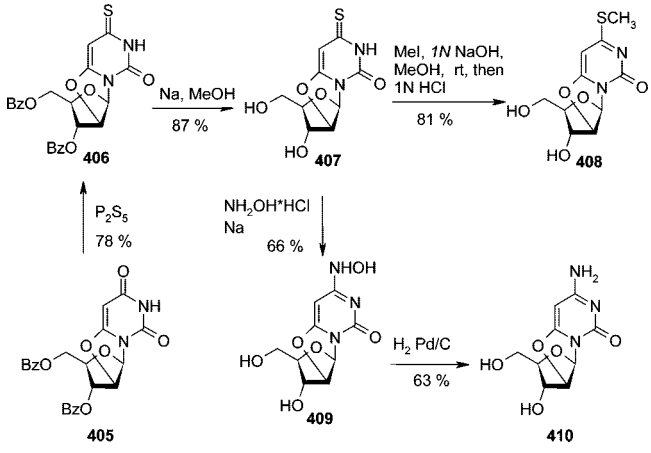
Following the known procedure, some cyclouridine was transformed into its cytosine analogue by treatment with triphenylphosphine/carbon tetrachloride[207] or through a *C*4-triazoyl derivative. The opposite transformation leading from cytidine to uracil nucleosides was also reported by Lipkin et al.,[141] who utilized an excess of $LiNO_2$ and glacial acetic acid in DMSO.

3.5.2. At the C5 Position

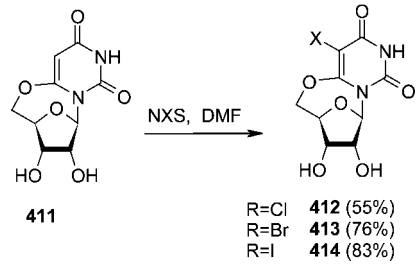
From their initial report, Chang et al.[123] described the *C*5-iodination of 2′-deoxy-6,5′-*O*-cyclouridine using a mixture of iodine and periodic acid. Generally, the halogenation of cyclonucleosides can be realized with NXS (X = Cl, Br, I) in DMF at room temperature (Scheme 90).

Kim et al.[168] found that electrophilic addition of phenylselenyl chloride to the C5−C6 double bond of the uracil ring

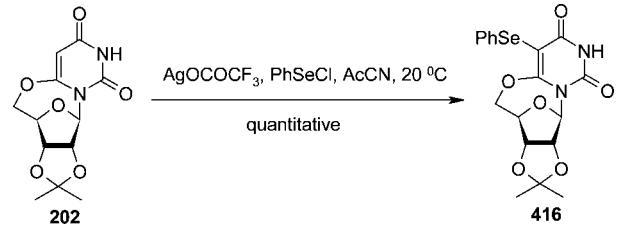
Scheme 89



Scheme 90



Scheme 91



in cyclonucleoside **202**, in the presence of silver trifluoroacetate, resulted in formation of the 5-phenylselenyl derivative **416** with quantitative yield (Scheme 91).

The synthesis of C5-substituted 6,5′-*O*-cyclonucleosides **417**−**424** (Figure 6) was thoroughly investigated by our group.[208] The key step involved a bromine−lithium exchange at the C5 position followed by exchange with an alkyl or alkenyl group. Palladium-mediated or palladium-catalyzed reactions, widely used in synthesis of new nucleoside analogues,[209] were also explored by our group[210] for the modification at the C5 of pyrimidine cyclonucleosides **425**−**430**.

3.5.3. Modifications at the C6 Position: Ring-Opening

The behavior of some pyrimidine cyclonucleosides in acidic conditions was investigated by Fox et al.[139,140] followed by Sano et al.,[141] who reported that treatment of 6,5′-*O*-cyclo-2′,3′-*O*-isopropylideneuridine (**202**) with dilute HCl led to the formation of 1-(β-D-*ribo*-furanosyl)barbituric acid (**431**). Treatment of **202** with BzONa induced a ring-opening and led to the formation of 5′-benzoyl derivative **432**. On the other hand, 5-substituted derivatives of **202** turn out to be stable for acidic conditions, and the isopropylidene group was safely removed in the acidic conditions, while the oxygen linkage was retained (Scheme 92).

The behavior of some pyrimidine cyclonucleosides in basic conditions was also investigated. Copik et al.[155] treated **202** and its 2′-deoxy analogue **433** with a 0.2 M solution of barium hydroxide in water or tetramethylammonium hydroxide in DMSO, which led to the opening of the oxygen bridge and formation of 6-hydroxycytidine (**434**) and 6-hydroxy-2′-deoxycytidine (**435**) (Scheme 93).

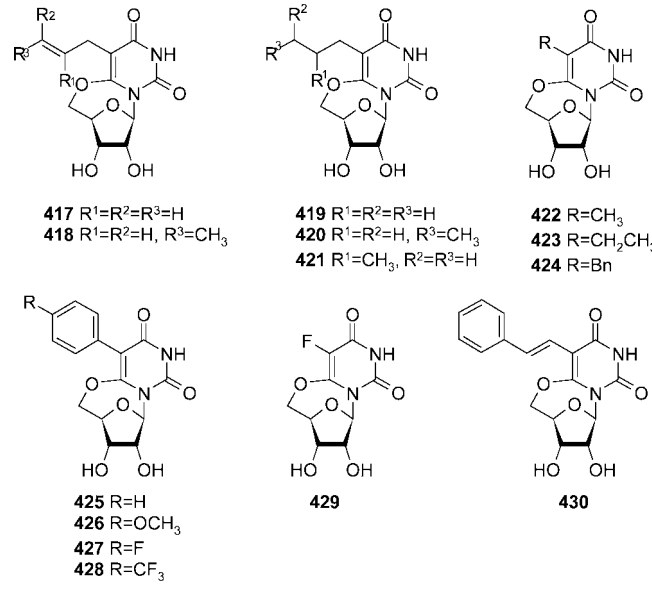
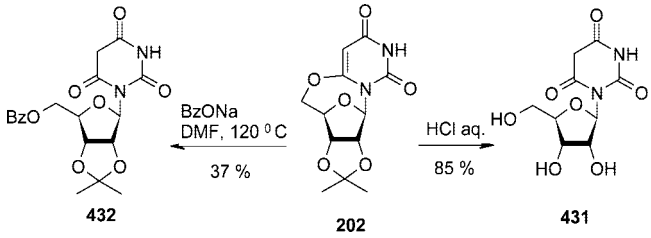


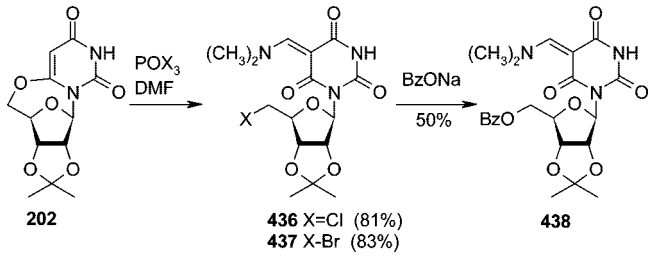
Figure 6. Palladium(0)-mediated syntheses of pyrimidine cyclonucleosides.

Scheme 92



Scheme 93

Scheme 94



The oxygen bridge in **202** could also be opened by treatment with amines, which led to the 6-amino-substituted uridine derivatives. 6-Amino-substituted uridine derivatives could also serve as useful intermediates in the synthesis of bicyclic derivatives, analogues of purine nucleosides.[211−213]

Hirota et al.[214] reported that treatment of **202** with Vilsmeier reagent led to the opening of the oxygen bridge, accompanied by chlorination of the C5′ position and substitution at the C5 position (Scheme 94). The obtained nucleoside **436** was then refluxed with sodium benzoate in methanol, which resulted in exchange of the *C5′*-chloride into *C5′-O*-benzoyl derivative **438**. Similar treatment of **202** with a phosphorus oxybromide in DMF led to the 5′-bromo derivative **437**.

4. Summary

The past several years have witnessed explosive new developments in nucleoside chemistry targeting many viruses and tumors, while the somewhat more elaborate cyclonucleosides have received relatively little attention. The recent discovery, in 2005, of the first natural N^3,5′-cycloxanthosine, isolated from an *Eryus* sp. of the marine sponge, is of great importance as natural nucleosides from marine sponges have already inspired development of antileukemic and antiviral agents. Thus, looking to the future, the widespread and wide field of application of nucleosides in chemotherapy, and the emergence of increasingly sophisticated stereo- or regioselective organic reactions, seems certain to ensure continued interest in the development of this class of "synthetic" nucleosides with antiviral properties. We thus hope that this review will provide a useful aid to medicinal and organic chemists dealing with nucleosides and heterocyclic systems on a daily basis.

5. References

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