

The Synthesis of Ribose and Nucleoside Derivatives

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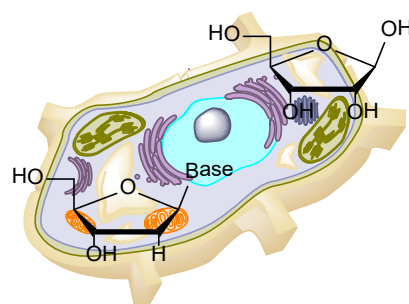
Abstract

Ribose and nucleoside derivatives are important molecules used as drugs. They are structural subunits of nucleic acids and usually obtained by chemical or enzymatic decomposition of nucleic acid. These derivatives are important organic molecules used in the transport of genetic information in living cells. For example, antiviral drugs like cyclovir are used to prevent viral replication in infected cells. The importance of synthesis of nucleoside, considering probiotics, is increasing because of medical usage for 50 years for patients with cancer or viral infections. The β -D-ribofuranose form of ribose is normal sugar and forms the backbone of RNA. Phosphorylated ribose derivatives such as ATP play important roles in metabolism. Although this study is concerned with the synthesis of ribose and nucleoside derivatives in literature, novel derivatives and methods for the synthesis of ribose and nucleoside analogues are still needed due to their biological importance in synthetic organic chemistry. This review covers the synthesized ribose and nucleoside analogues in literature reported from 1914 up to this day.

Keywords: Ribose; Nucleoside biological activity; Drug; Medicine

Introduction

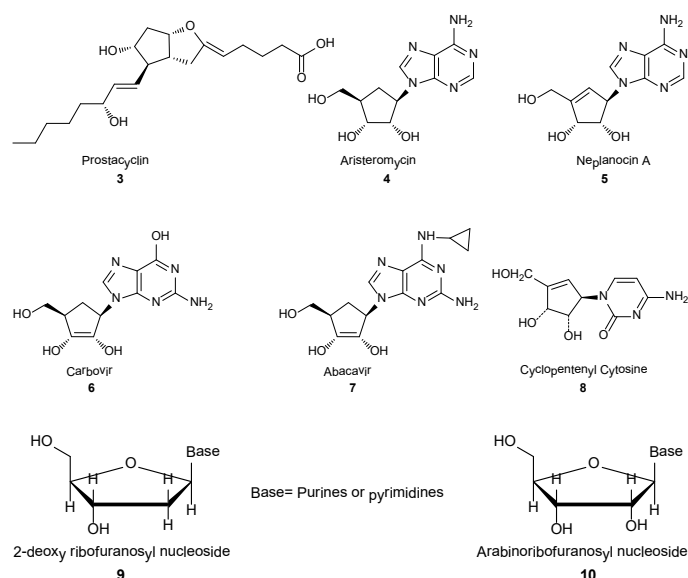
Ribose synthesized from the living body an organic compound classified as a monosaccharide is used as medicine and is also found in RNA as a kind of sugar (Scheme 1), for example, ribonucleotides, nucleic acids, riboflavin, etc. Nucleotides are important macromolecules that convey genetic information in cells. At the same time, they are the molecular building blocks of DNA and RNA. Many nucleosides represent important classes of antineoplastic and antiviral therapeutics.



Scheme 1. Ribose (1) and Nucleoside (2)

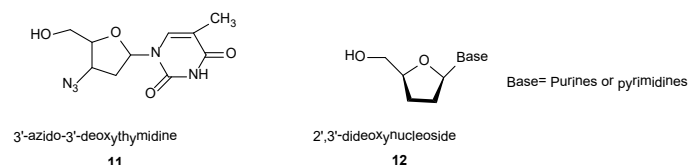
Prostacyclins (3) are molecules with potent aggregation-inhibitory, anti-inflammatory, and antiproliferative properties [1]. The poly (adenosine diphosphate [ADP]-ribose) polymerase plays a key role in the repair of DNA single-strand breaks and the repair of base excisions [2]. There are antitumor and antiviral effect of some natural carbocyclic nucleosides [1e] like aristeromycin [3] (4), neplanocin A [4] (5), carbovir [5] (6), abacavir

[6] (7), cyclopentenyl cytosine [7] (8), 2'-deoxy-ribofuranosyl nucleosides [8] (9) and arabinofuranosyl nucleosides [8] (10).



Scheme 2. Some of the effects of antitumor and antiviral molecules [1,2,3,4,5,6,7,8,9,10].

It is also known that 3'-azido-3'-deoxythymidine [9] (11) and 2', 3'-dideoxynucleosides [10] (12) are effective against the acquired immune deficiency syndrome (AIDS) and a therapeutic agent (Scheme 2).



Scheme 3. Biological active molecules 11 and 12 [9,10].

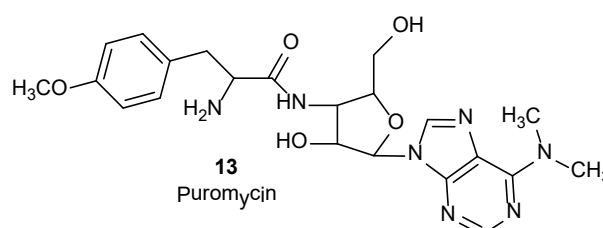
Synthesis of Ribose and Nucleoside Derivatives year by year

In 1914, Fischer and Helferich did studies on the synthesis of D-glukopyranosidoadenin with a method called "modification of Fischer and Helferich" [11]. In 1929 and 1930, Hilbert and Johnson disclosed a method for the synthesis of nucleosides which can be applied to other ring systems such as quinolones, pyridines and pyrazolones [12]. In 1937, Levene and Compton wrote an article on the synthesis of theophylline-D-allomethylsides [13].

In 1946 and 1947, Howard et al. developed a method for the synthesis of adenosine and purin nucleoside analogs in a series of studies [14]. The synthesis of methyl-D-ribofuranoside was obtained by oxidation in the presence of sodium metaperiodate and methylation by Barker in 1948 [15]. In another study, 2,3,5-trimethyl D-ribose anilide, 3,5-dimethyl D-ribose phenylzoazome, 2,3,5-trimethyl D-ribomolactone, and 2,3,5-trimethyl D-ribonophenylhydrazide were synthesized with high yields by Baker in 1948 [15].

Friedkin and Kalckar described the isolation and properties of the highly acidic phosphate ester obtained by the phosphorolytic cleavage of purine deoxyribose nucleosides

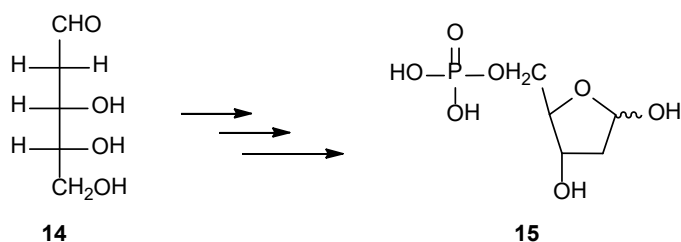
[16]. The phosphoric acid esters of 2-deoxy-D-ribose are important in biochemical transformain. Racker purified the deoxyribose-5-phosphate aldolase enzyme from E. coli extract and described a way for the biosynthesis of deoxyribose-5-phosphate in 1952 [17]. 2-Deoxy-D-ribose-5-phosphate aldolase (DERA) is widely found in animal tissues and microorganism. DERA is obtained from the aldol condensation of glyceraldehyde-3-phosphate and acetaldehyde. Kalckar explained that phosphoglycosyl compounds (ribose-1-phosphate, deoxyribose-1-phosphate and their corresponding 5-esters) can play a significant role in biosynthesis of nucleosides and nucleotides in the animal organism in 1953 [18]. Baker et al synthesized aminoglycoside purine derivatives starting from D-xylose, including the synthesis of puromycin (13), an aminonucleoside (1953; 1954) (Scheme 4) [19].



Scheme 4. Puromycin an aminodeoxyglycosido purine derivative [19].

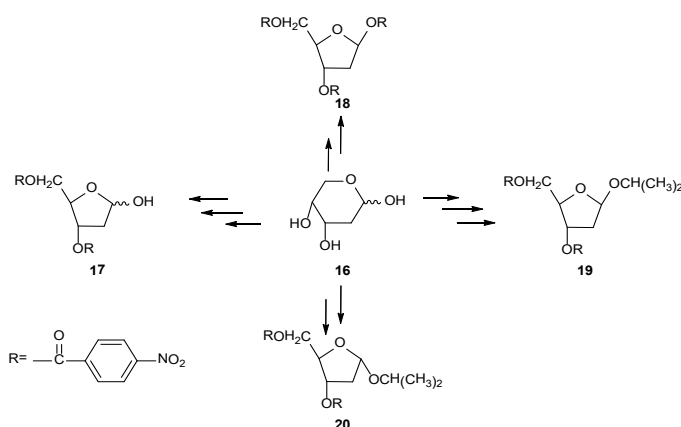
In the following years, in 1954, Ness et al. succeeded in preparing 2,3,5-tri-O-benzoyl-b-D-ribose from D-ribose as a stable precursor for the synthesis of D-ribofuranoside and benzyl-b-D-ribofuranoside tribenzoate derivatives at high yield [20]. Friedkin and Roberts succeeded in the enzymatic synthesis of thymidine, C¹⁴-thymidine and related pyrimidine nucleoside derivatives, reacting thymine with deoxyribose-1-phosphate, in 1954 [21a]. Friedkin described the isolation and synthesis of azaguanine riboside and azaguanine deoxyriboside, nucleoside obtained by the enzymatic reaction between 8-azaguanine and ribose-1-phosphate or deoxyribose-1-phosphate in the same year [21b]. Mowery reported the successful use of acidic ion exchange resins as catalysts in glycoside formation with the Fischer method in 1955 [22]. Cardwell and Kilner [23] than Barker et al [24] succeeded in synthesizing methyl ethers of ribose and its derivatives. Kissman et al. synthesized D-ribofuranosyl derivatives of 6-dimethylaminopurine in 1955 [25]. Baker studied puromycin and ribose chemistry with different groups [26].

In 1957, Kissman and Baker disclosed the synthesis of 1,2,3-tri-O-acetyl-5-Deoxy-D-ribofuranosylpurines, which is obtained in three steps by methyl 2,3-O-isopropylidene-5-O-mesyl-D-ribofuranoside [27]. In 1958, Shaw et al. synthesized derivatives of purine, pyrimidine and glyoxalines, which are used in the synthesis of ribofuranosides and b-D-ribofuranosylamines [28]. A deoxyribose phosphate aldolase is specially important since it is used as an enzyme. Mac Donald and Fletcher described the conversion of 2-deoxy-D-ribose (14) to 2-deoxy-D-ribose 5-phosphate (15) in 1959 (Scheme 5) [29].



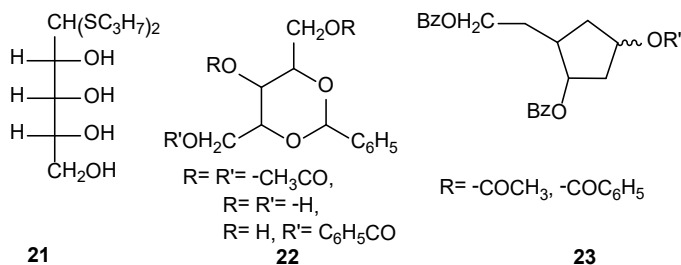
Scheme 5. The synthesis of 2-deoxy-D-ribose 5-phosphate (15) [29].

The synthesis of various glycofuranse derivatives was accomplished by acid-catalyzed condensation by reducing sugar with simple alcohol to form alkyl glycofuranosides for a long time. Ness et al. studied the synthesis of 2-deoxy-3, 5-di-*O*-*p*-nitrobenzoyl-D-ribose (17), 2-deoxy-D-ribofuranose tri-*p*-nitrobenzoate (18), isopropyl 2-deoxy-3, 5-di-*O*-*p*-nitrobenzoyl-D-ribosides (19,20) using crude methyl 2-deoxy-D-ribofuranoside (readily prepared from free sugar 16) in 1961 (Scheme 6) [30a].



Scheme 6. The synthesis of ribose derivatives (17-20) [30a].

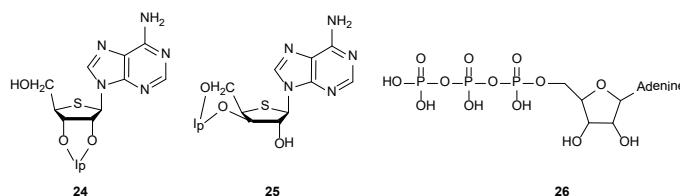
In the same year, Potgieger and Mac Donald made the condensation of benzaldehyde with D-ribose di-*n*-propyl ditioacetal and then converted to dimethyl acetals for the corresponding substituted D-riboses (21) and ribitols (22) (Scheme 7) [30b]. Fox et al succeeded in synthesizing 2'-deoxycytidine (V) (23) via condensation of 3, 5-di-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribosyl chloride with A'-acetylcytosine mercury in the same year (Scheme7) [30c].



Scheme 7. The synthesis of substituted ribose (21), ribitol (22) and 2'-deoxycytidine (23) [30b,c].

The following year, Mac Donald and Fletcher succeeded in synthesizing anomeric 2-deoxy-D-ribofuranose-1-phosphates by condensation with 2-deoxy-3, 5-di-*p*-toluoyl-D-ribosyl chloride in the presence of disilver phosphate [31a]. In the same year, Serfontein and Jordaan synthesized the D-ribose cyclic nitrogen mustard phosphamide ester, which has potent cancer growth inhibitory properties [31b].

The synthesis of 4-thio-D- and -L-ribofuranose and the corresponding adenine nucleosides (24, 25) from L-lyxose was successfully performed by Reist et al in 1964 (Scheme 8) [32a]. Moffatt succeeded in synthesizing nucleoside-5'triphosphates (26) using pyridine as a solvent (Scheme 8) [32b]. In four separate studies, the synthesis of di amino sugars was carried out by Baker and Neilson in the same year [32c]. Nucleosides containing the 1b-D-arabinofuranosyl moiety showed interesting biological properties. Underwood et al worked on cytosine arabinoside and other nucleosides in Herpes virus infections [32d].

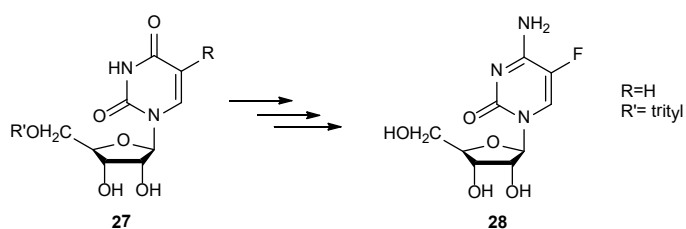


Scheme 8. The synthesis of thio-ribofuranose (24, 25) and nucleoside-5'triphosphates (26) [32a,b].

Leonard and Laursen synthesized 3-b-D-Ribofuranosyladenine and (3-b-D-ribofuranosyladenine)-5'-phosphate by alkylation of adenine with bromo tribenzoylribofuranose and debenzoylation with methanolic ammonia in 1965 [33a]. In the same year, they succeeded in synthesizing adenosine diphosphate, adenosine triphosphate, and nicotinamide-adenine dinucleotide analogs from 3-b-D-ribofuranosyladenine [33b]. Murray and Prokop synthesized of 9-(3-deoxyaldofuranosyl) adenies from 3-deoxy-D-glucose with some reactions such as benzoylation, acetolysis, halogenation, periodate oxidation, and borohydride reduction in 1965 [33c].

In 1965, Ferrier and Prasad succeeded in synthesizing of 3- and 2, 4-substituted ribose derivatives and wrote about the nature of phenylboronates of methyl b-L-arabino-, methyl a-D-lyxo-, and methyl b-D-ribo-pyranoside [34a]. In the same year, Baker and Hullah conducted two different studies on cis-2, 3-diamino sugar synthesis and the influence of neighboring groups [34b]. In the same year, Baker and Buss synthesized in a different study a-sulfonyloxy oxo sugar and 2(3)-acylamino-3(2)-oxopyranosyl [34c].

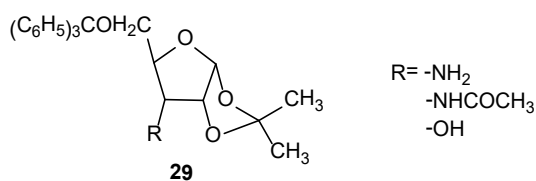
Fox and et al studied the reaction of the 5'-O-trityl derivative of uridine (27) with thiocarbonyldiimidazole. In the result of the reaction 2, 2'-anhydro-1-(b-D-arabinofuranosyl) urasile (28) occurred in high yields (Scheme 9) [35a]. Leonard and Carraway synthesized 5-amino-5-deoxyribose and its nucleoside derivative from 1-benzyl-5-cyano-4-ethoxymethylene amino imidazole cyclization. [35b] Reist et al. prepared D-ribose and L-lyxose derivatives using tosylation, hydrolysis and benzoylation reactions beginning with L-ribose in 1966 [36c]. In the same year, Baker and Buss succeeded in developing new branch-chain amino sugar types for methyl 2-benzamido-4, 6-O-benzylidene-2-deoxy-tetrahydrofuranoside, methyl 2-benzamido-4, 6-O-Deoxy-3-3C-methyl-[a]-D-allopyranoside [35d]. Lerner and Kohn also worked on the synthesis of 9-D-Mannofuranosyladenin from D-mannose [35e].



Scheme 9. The synthesis of 2, 2'-anhydro-1(β-D-arabinofuranosyl) urasile (28) [35a].

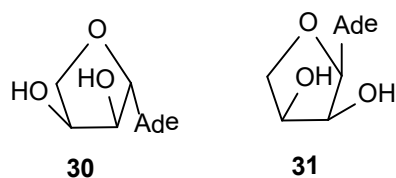
In 1967, Ali et al described the reaction of methyl β-d-ribose with sulfuryl chloride and pyridinium chloride in an article [36a]. The reaction of D-ribose with sulfuryl chloride yielded D-ribosepyranosyl chloride tri (chlorosulfate). In the same year, Onodera et al. achieved the synthesis of 9-a-D-ribofuranosyladenine [36b]. Eckstein and Gindl explained the synthesis of thymidine 5'-triphosphate and uridine 5'-di- and triphosphate using triimidazolyl-1-phosphinsulfide [36c].

In 1968, Fukami et al reported the synthesis of 5-deoxy-(±)-allose derivatives and 4-deoxy-(±)-ribose from myo-inositol [37a]. Lerner et al succeeded in synthesizing of 9-b-D-Gulofuranosyladenine and 9-a-L-Lyxofuranosyladenin by means of isopropylidene sugar derivatives [37b]. 3-Amino-3-deoxy-D-ribose and D-ribose (29) were synthesized from D-xylose 1, 2-O-Isopropylidene-5-O-triphenylmethyl-a-D-xylofuranos derivatives by Sowain the same year (Scheme 10) [37c].



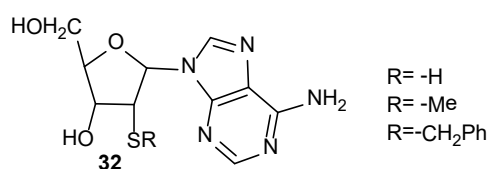
Scheme 10. The synthesis of amino-3-deoxy-D-ribose derivatives [37c].

O-isopropylidene derivative of D-ribose diethyl dithioacetal was synthesized by Lance et al. using copper sulfate as a catalyst in 1969 [38a]. Lerner also realized the synthesis of 9-a- and 9-b-L-erythrofuransyladenine (30, 31) via isopropylidene sugar derivatives (Scheme 11) [38b].



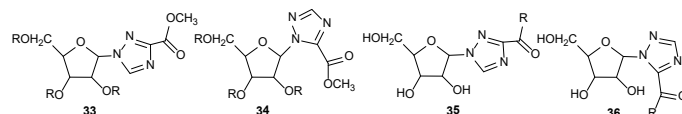
Scheme 11. The synthesis of 9-α- and 9-β-L-erythrofuransyladenine [38b].

Follman and Hogenkamp synthesized ¹⁸O-containing ribose and adenine nucleotides, and the isotope position in hydroxyl functions was confirmed by mass spectrometry in 1970 [39a]. Niedballa also provided the synthesis of pyrimidine nucleoside [39b]. In 1971, Ryan et al. succeeded in synthesizing furanose and pyranose 2-thio-D-ribose derivatives (32) from the corresponding S-alkyl-1-thio-a-arabinside 2-O-mesylate (Scheme 12) [40].



Scheme 12. The synthesis of 2-thio-D-ribose (32) [40].

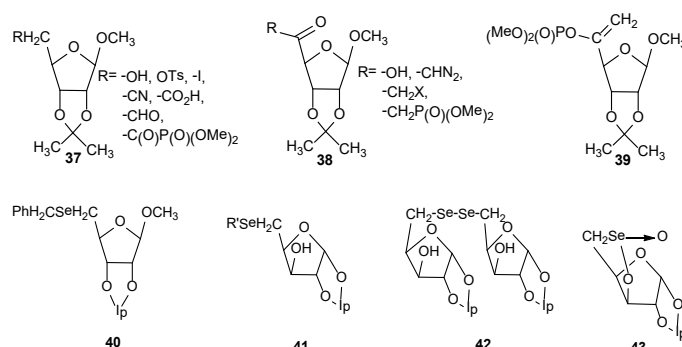
In 1972, Lerner synthesized 9-(6-Deoxy-b-L-glucopyranosyl) adenine, 9-(5, 6-dideoxyxylo-hex-5-enofuranosyl) adenine, 9-b-L-gulofuranosyladenine, 4', 5'-unsaturated hexofuranosyl nucleoside in three different studies [41a]. Witkowski et al obtained 1-b-D-Ribofuranosyl-1,2,4-triazole-3-carboxamid (33-36) and related nucleosides and then researched the antiviral activity of them (Scheme 13) [41b].



Scheme 13. The synthesis of 1-b-D-Ribofuranosyl-1,2,4-triazole-3-carboxamid (33-36) [41b].

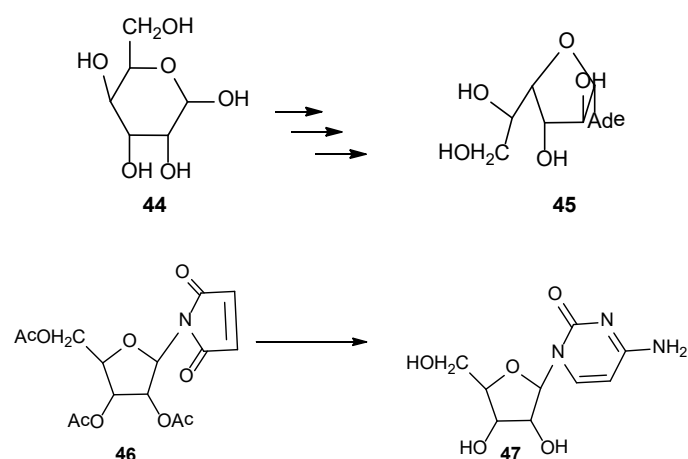
In 1973, 3-C-(dimethoxy) phosphinyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose was obtained from the reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose with dimethyl phosphite by Evely et al [42a]. In the same year, Rabelo et al obtained 5-seleno-D-ribose derivatives from methyl 2, 3-O-isopropylidene-D-ribofuranoside under various reaction conditions as reaction time, solvent and catalyst [42b]. Lerner worked on the synthesis and reexamination of the structure of 9-(6-deoxy-α-L-mannofuranosyl) adenine [42c].

Niedballa and Vorbrugg by noticed the pyrimidine nucleoside synthesis containing silylated hydroxy-, amino-, and mercapto pyrimidines using Friedel-Crafts catalysts in excellent yields in 1974 [43a]. The synthesis of D-ribose-5-phosphonate and -vinyl phosphate analogs (37-39) was carried out by Hampton et al in the same year (Scheme 14) [43b]. Rabelo and Es synthesized selenoxides of D-xylose and D-ribose derivatives (40-43) (Scheme 14) [43c].



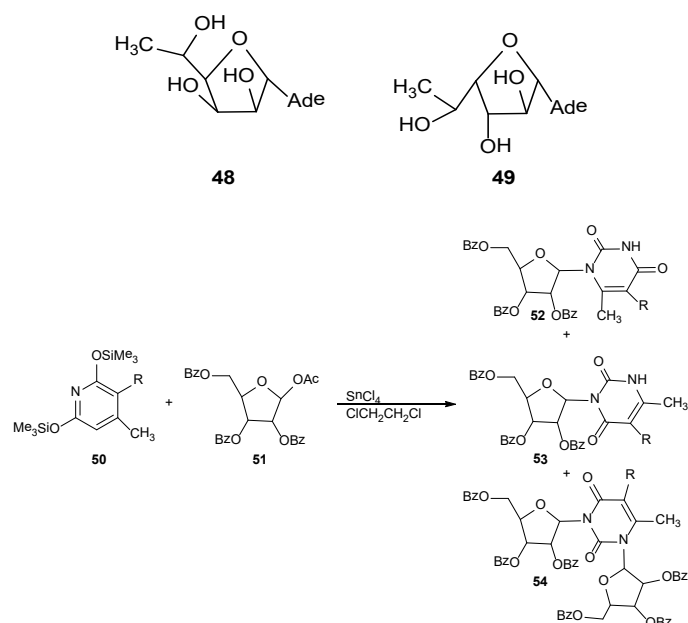
Scheme 14. Phosphonate, vinyl phosphate and selenoides analogs of ribose [43b,c].

The synthesis of 9-a-D-Idofuranosyladenine (45) starting from D-glucose and N-(2, 3, 5-Tri-O-acetyl-D-ribofuranosyl) maleimide (44) was performed by Lerner in 1975 (Scheme 15) [44a]. Schwartz and Lerner [44b] succeeded in synthesizing N-(2, 3, 5-tri-O-acetyl-D-ribofuranosyl) maleimide (47) with 25% yield using N⁴-acetylcytosine as base (Scheme 15).



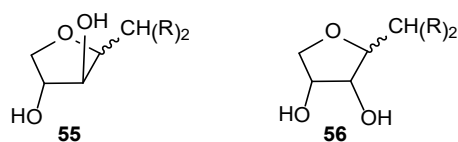
Scheme 15. The synthesis of nucleoside 45 and 47 [44a,b].

In 1976, Es succeeded in synthesizing of *O*-methyl derivatives of 4-thiopentofuranosides and an hydropentosesin 1976 [45a]. Lerner also developed a method for the synthesis of adenine nucleosides (48, 49) from 6-deoxyhexofuranoses (Scheme 16) [45b]. Niedballa and Vorbrüggen examined the effect of groups linked at positions 5 and 6 with silylated urasil in nucleoside synthesis (Scheme 16) [45c].



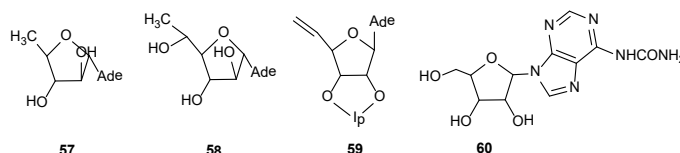
Scheme 16. Uracil nucleoside synthesis [45b,c].

In 1977, Blumberg et al studied selenium derivatives of L-arabinose, D-ribose, and D-xylose [46a]. Benzyl 2,3,4-tri-*O*-acetyl-1,5-diseleno-D-xylopyranoside, benzyl 2,3,4-tri-*O*-acetyl-1,5-diseleno-D-ribofuranoside, and benzyl 2,3,4-tri-*O*-acetyl-1,5-diseleno-D-arabinofuranoside which were synthesized at the end of the study [46a]. Es synthesized 2, 5- an hydropentose dibenzyl dithioacetates from pentose dibenzyl dithioacetates using D-ribose and D-xylose in acid solution (Scheme 17) [46b].



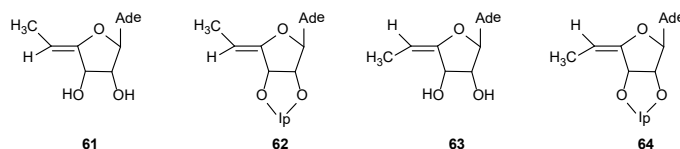
Scheme 17. The synthesis of ribose 55 and 56.

In 1978, Schaeffer et al synthesized a series of nucleoside analogs, suggesting that 9-(2-hydroxy-ethoxymethyl) guanine has significant antiviral activity in animal models of herpes virus infections [47a]. Lerner synthesized enantiomeric forms of 9-(5-deoxy- α -D-arabinofuranosyl) adenine (57) from D-ribose, 9-(6-Deoxyhexofuranosyl) adenine (58) from L-Rhamnose and 9-(5, 6-dideoxy- β -D-ribo-hex-5-enofuranosyl) adenine (59) from D-allose at various stages (Scheme 18) [47b]. Ueda et al succeeded in synthesizing 6-thioguanine and 2, 6-diaminopurine nucleosides (60) and nucleotides from adenine (Scheme 18) [47c].



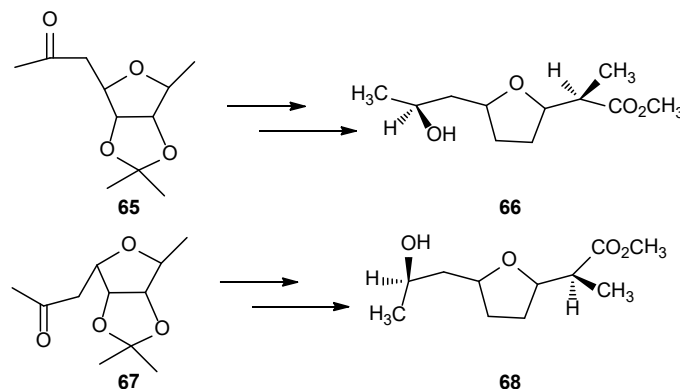
Scheme 18. Nucleoside derivatives (57-60).

Lerner performed the synthesis of 9-(5, 6-dideoxy- β -D-erythro-hex-4-enofuranosyl) adenine (61-64) E and Z isomers starting from 5, 6-dideoxy-5-iodo-2, 3-*O*-isopropylidene- β -D-allofuranoside and 5,6-dideoxy-5-iodo-2,3-*O*-isopropylidene- α -L-talofuranoside (Scheme 19) in 1979 [48a]. Quinazoline nucleosides were synthesized by Ferris et al. from ribose and antranilonitrile [48b]. Keyser et al disclosed a method for preparing alkylated acyclic nucleoside analogs using iodomethyl ether and thioether by reacting 1, 3-dioxolane and 1, 3-oxathiolane with trimethylsilyl iodide [48c].



Scheme 19. Nucleoside derivatives (61-64).

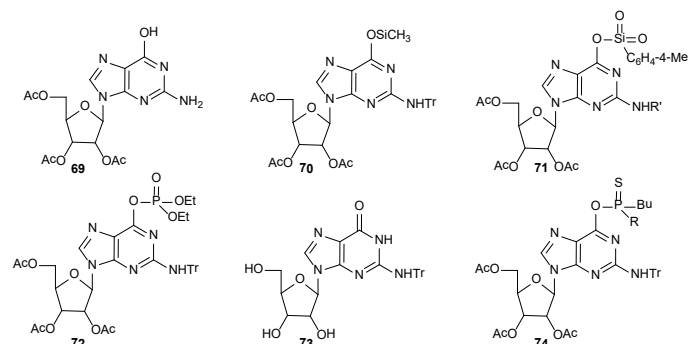
In 1980, Sun and Fraser-Reid developed a plan for the synthesis of analogs of the nactin family (66, 68) from the D-ribose derivative (Scheme 20) [49a]. Barrio et al prepared a direct method for the synthesis of 2-hydroxyethoxymethyl derivatives of guanine, adenine and cytosine [49b].



Scheme 20. Ribose derivatives (66, 68).

In 1981, Khadem and Nelson explained the synthesis of 6-deoxy-D-allo- and -L-talo-furanosyl bromide derivatives used for nucleoside synthesis [50a]. Daskalov et al synthesized *O*⁶-substituted Guanosine derivatives with phosphoryl,

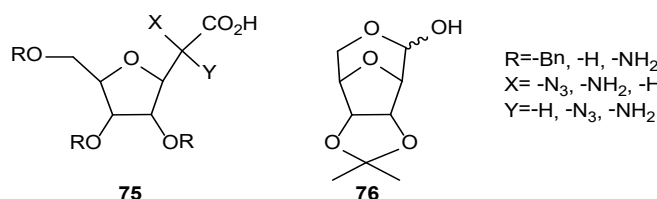
phosphinothioly, arylsulfonyl and silyl halides using 4-(dimethylamino) pyridine as catalyst in good yield [50b]. In Scheme 21 only a few examples (69-74) are shown. Vor bruggen obtained new Lewis acids $[(CH_3)_3SiOSO_2CF_3]$, $(CH_3)_5SiOSO_2C_4F_9$ and $(CH_3)_3SiClO_4$, which are highly selective and efficient Friedel-Crafts catalysts for the synthesis of nucleoside silylated heterocycles and peracylated sugars [50c].



Scheme 21. Nucleoside derivatives (69-74).

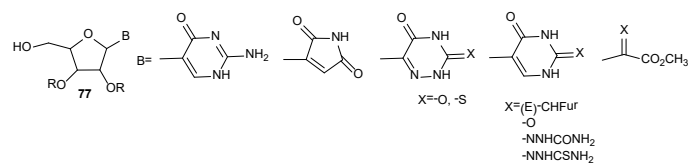
In 1982, Mukaiyama et al described an efficient method for stereo selective synthesis of 2-amino-2-deoxy-D-arabino and D-ribose [51a]. Pasque et al conducted a study titled "Ribose-enhanced myocardial recovery following ischemia in the isolated working rat heart" and explained ribose infusion as a biochemically plausible method to ameliorate postischemic myocardial ATP before and after ischemia [51b]. Sims et al synthesized poly (adenosinediphosphoribose) polymerase and explained how the poly (adenosinediphosphoribose) polymerase was inhibited by a six-membered aromatic ring compounds containing a carboxamide group and purine analogues [51c].

In 1983, Hiratsuka synthesized ribose modified, fluorescent adenine and guanine nucleoside and nucleotide derivatives in aqueous solution at mild pH and temperature [52a]. Robins and Parker explained the transformations of D-ribose to 3, 4-O-isopropylidene-2, 5-anhydro-D-allose, which was synthesized previously as a racemate and used to prepare C-nucleosides (Scheme 22) [52b].



Scheme 22. The transformations of D-ribose 3, 4-O-isopropylidene-2, 5-anhydro-D-allose.

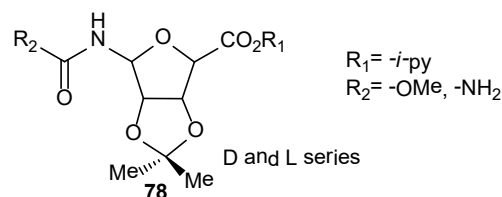
In 1984, Forrest and Schmist synthesized 4-amino-4-deoxy-D, L-ribose derivatives [53a]. Sato described the stereo controlled total synthesis and various biological properties of C-nucleosides (77) with different R groups (Scheme 23) [53b].



Scheme 23. The stereo controlled total synthesis of C-nucleoside (77).

In 1985, isopropylideneation of D-ribose diethyl dithioacetal and ribitol and the synthesis of α and β -D-ribofuranosylethyne were carried out by Aslani-Shotorbani et al [54a]. Yamamoto et al performed the stereo selective synthesis of 2-amino-2-deoxy-D-arabinose and 2-deoxy-D-ribose [54b]. Berger et al developed a new strategy for cancer chemotherapy using synthetic "C" nucleoside analogs [54c].

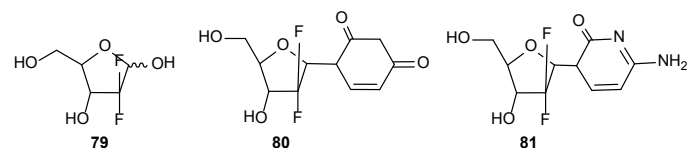
In 1986, Hughes and Wood disclosed the sulfur addition in displacement reactions of the sulfonate esters of 5-thio-D-ribose and 5-thio-D-xylose derivatives [55a]. Schmidt also did research on natural product synthesis, including ribose derivatives (78) (Scheme 24) [55b].



Scheme 24. The synthesis of ribose derivative 78.

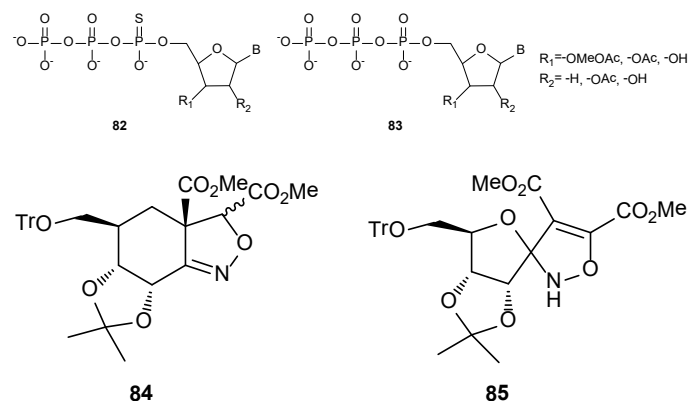
In 1987, Mc Elwain and Pollack found deoxyribonucleoside kinase activity in the first report of deoxyribonucleoside kinase activity dependent on PPI in Acholeplasma and Mycoplasma species [56a]. Beigelman et al prepared the synthesis of 2'-C-methylnucleosides (3-O-benzyl-1,2-O-isopropylidene-3-C-methyl- α -D-allofuranose and 1,2,3-tri-O-acetyl-2-C-methyl-5-O-p-methylbenzoyl-d-ribofuranose, 2-C-hydroxymethyl, 2, 3-O-isopropylidene-5-O-trityl-D-ribofuranose) starting from D-glucose and D-ribose [56b].

In 1988, Mc Elwain et al isolated the purine nucleoside phosphorylase (PNP) from a cytoplasmic fraction of Acholeplasma laidlawii B-PG9 and described its activity using a gel green affinity chromatography [57a]. Shapiro showed the prebiotic availability of D-ribose as a subunit in his article [57b]. Hennen et al explained the acylation and deacylation reaction of the furanose and pyranose derivatives with lipase enzyme [57c]. Wagner et al performed the synthesis of methyl 5-bromo-5-deoxy-2,3-O-isopropylidene- β -D-and- β -L-ribofuranoside from (-)-(1R,2S,4R)-2-exo-cyano-xabicyclo[2.2.1] hept-5-en-endo-yl(1'S)-camphanate and (+)-(1S,2R,4S)-2-exo-cyano-7-oxabicyclo [2.2.1] hept-5-en-2-endo-yl(1'R)-camphanate in 5 steps and with a total yield of 28% [57d]. A simple and stereo controlled 2-deoxy-2, 2-difluoro-D-ribose (79) and 2-deoxy-2, 2-difluoro-D-ribofuranosyl nucleosides synthesis (79-81) in the design and synthesis of potential nucleosides as anticancer and or antiviral agents was performed by Hertel et al (Scheme 25) [57e].



Scheme 25. The synthesis of 2-deoxy-2, 2-difluoro-D-ribose (79) and 2-deoxy-2, 2-difluoro-D-ribofuranosyl nucleosides (80, 81).

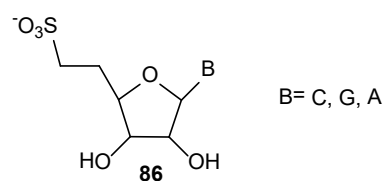
In 1989, Herdewijn et al described the use of diethylaminosulfur trifluoride (DAST) as a fluorinating agent in the nucleoside field [58a]. Hennen and Wong reported a method be applicable to the enzymatic ribosylation of purine analogs using 7-methylguanosine and 7-methylinosine [58b]. Ludwig and Eckstein performed a facile synthesis of the 5'-O-(L-thiotriphosphates) and showed that the 5'-triphosphates of eight common substances could be readily used for nucleoside synthesis (Scheme 26) [58c]. Yokoyama and Yamada succeeded in synthesizing spiro and bicyclic nucleosides from ribose nitrile oxide and dimethyl acetylenedicarboxylate (Scheme 26) [58d].



Scheme 26. The synthesis of monocyclic (82, 83) and bicyclic nucleotides (84, 85)

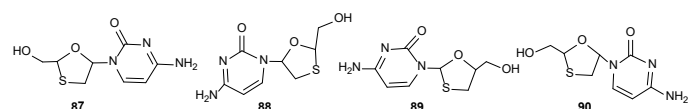
In 1990, Hutchinson prepared a review on the synthesis of antiviral nucleosides because new antiviral agents are needed worldwide [59].

In 1991, Musicki and Widlanski reported the synthesis of sulfonate analogues of adenine, cytidine and guanine monophosphates as well as the synthesis of ribose 3-sulfonate, sulfonyl disaccharides and dinucleotides (Scheme 27) [60].



Scheme 27. The synthesis of sulfonate analogues 86 of adenine, cytidine and guanine monophosphates.

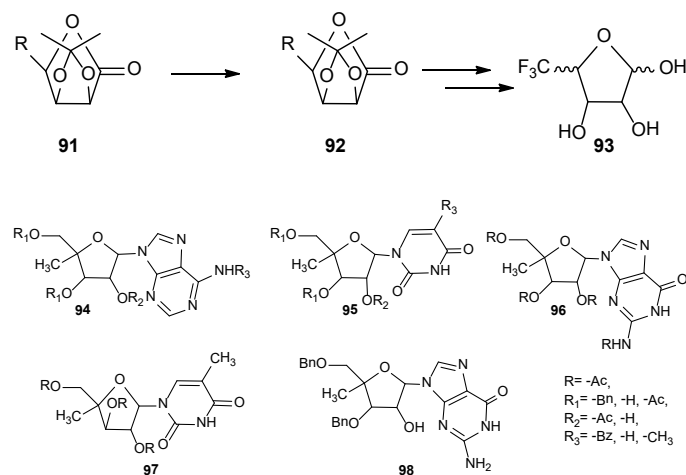
Beach et al studied the synthesis of enantiomerically pure (2'R, 5'S)-(-)-1-[2-(hydroxymethyl) oxathiolan-5-yl] cytosine and worked on antiviral activities against hepatitis B virus (HBV) and human immuno deficiency virus (HIV) in 1992 (Scheme 28) [61].



Scheme 28. The synthesis of enantiomerically pure nucleosides (87-90).

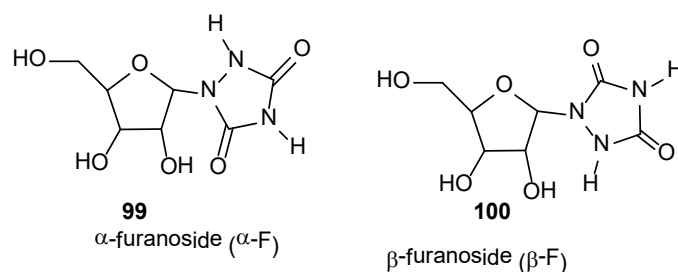
Matsuda et al synthesized 2'-deoxy-(2'-C-substituted) cytidines, examined the antitumor activities of synthesized products and showed the anticancer properties of the

molecules [62a]. Munier et al succeeded in synthesizing 5-deoxy-5, 5, 5-trifluoro-D and L-ribose and lyxose 93 derivatives from lactones 91 using CF₃SiMe₃ (Scheme 29) [62b]. Waga et al prepared appropriately conserved 4'-C-methyl-D-ribo- and xylo-pentofuranoses and their condensation reactions with nucleobases (Scheme 29) [62c].



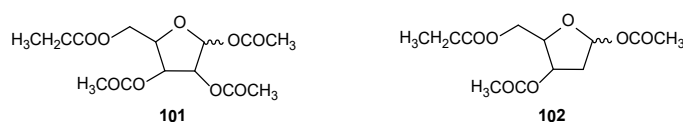
Scheme 29. The synthesis of ribose and nucleosides (94-98).

Ruff et al described a novel synthesis of chiral 2, 3-dideoxy nucleosides and their carbocyclic analogues starting from chiral cyclobutanone using a photo chemical ring-extension and a carbon ring extension in 1994 [63a]. Kolb et al determined thermodynamic and kinetic parameters for the urine reaction to be synthesized under prebiotic conditions using ribose from bureaucratic and hydrazine (Scheme 30) [63b].



Scheme 30. The synthesis of alpha- and beta-furanoside (99, 100).

In 1995, Prasad et al synthesized tri-O-acyl 2-deoxy-D-ribofuranose from 2-deoxy-D-ribose by a one-pot procedure in high yields and described the conversion to 2'-deoxynucleosides using monoacylations catalyzed by regioselective lipase (Scheme 31) [64].



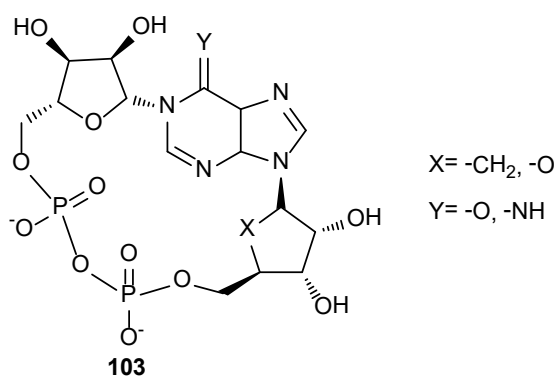
Scheme 31. The synthesis of tri-O-acyl 2-deoxy-D-ribofuranose 101 and 102.

In 1996, Sekine provided D-[5-¹³C] ribosylation from D-ribose to a [5'-¹³C] nucleoside, with an 8-step total yield of 70%, by coupling reaction [65].

In 1997, synthesis of 9-(2-O-β-D-ribofuranosyl)-β-D-ribofuranosyl adenine, guanine- and the pyrimidine

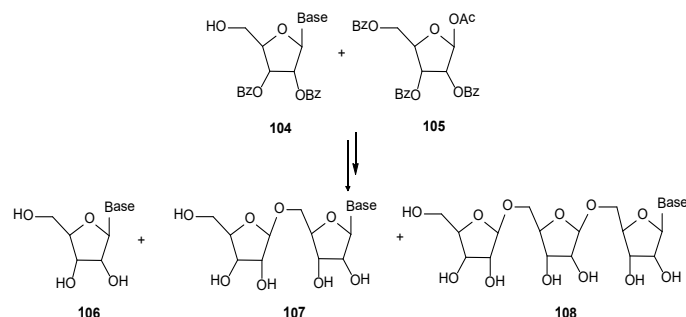
analogues (cytosine, thymine and uracil base) was performed by Mikhailov et al in a high yield [66a]. Choi et al worked on the synthesis of sulfated deoxy-ribofuranans with selective anti-AIDS virus activity by ring-opening copolymerization of 1, 4-anhydro ribose derivatives [66b].

In 1998, various adenosine analogues were tested by Zwart et al on adenosine A_{2B} receptor and found that the 5'-N-substituted carboxamidoadenosines were the strongest [67a]. Volpini et al synthesized deoxyribose nucleosides by coupling chloro purines with D-ribose derivatives and examined some of biological properties of the synthesized nucleosides [67b]. Shuto et al. performed the reaction with an 8-bromo-substitution of N-1-(carbocyclic-ribsyl) inosine 5', 6''-diphosphate 103 to obtain cyclic IDP-carbocyclic-ribose (Scheme 32) [67c]. Izawa and Shiragami developed enzymatic transglycosylation, chemical transpurination, and alkylauon for stavudine, acyclovir, ganciclovir, penciclovir and famciclovir [67d].



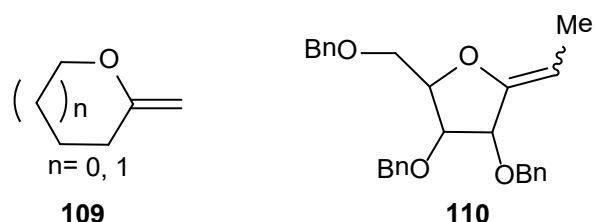
Scheme 32. The synthesis of N-1-(carbocyclic-ribsyl) inosine 5', 6''-diphosphate 103.

Also in 1998, trisaccharide nucleosides were obtained in good yield during synthesis of disaccharide nucleosides in the Mikhailov et al study [67e]. The use of 2', 3'-O-isopropylidene was observed in this study which inhibited the formation of trisaccharide nucleosides during disaccharide synthesis. Thus the yield of disaccharide nucleosides was increased (Scheme 33).



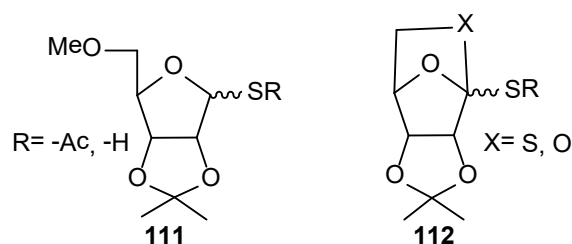
Scheme 33. The synthesis of mono-, di- and trisaccharide (106-108).

The same year, Efimtseva et al conducted a research on disaccharide nucleosides and their enzymatic properties and showed that oligonucleotides with reactive dialdehyde groups are effective against polymerases and restriction enzymes [67f]. Griffin et al realized the synthesis of exoglycosyls including ribose derivatives (Scheme 34) [67g].



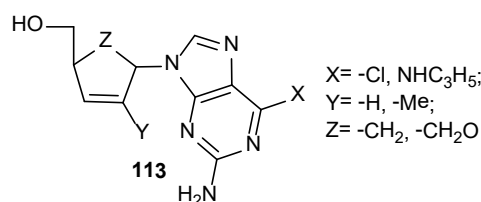
Scheme 34. The synthesis of ribose derivative 110.

In 1999, Vorbrüggen and Ruh-Pohlentz prepared a chapter with the synthesis of nucleosides (e.g. the formation of N-glycosides of heterocyclic nitrogen-based sugars such as D-ribose or 2-deoxy-D-ribose) [68a]. Mc Ewan studied the synthesis and biological activity of ribose-5'-carbamate derivatives of vitamin B₁₂ [68b]. As a result, it was found that Ribose carbamate derivatives have similar affinity for intrinsic factor with vitamin B₁₂ e-monocarboxylic acid. Fleetwood and Hughes succeeded in synthesizing 2, 3-O-isopropylidene-5-thio-D-ribose, 5-thio-D-ribose, 1, 4-anhydro-2, 3-O-isopropylidene-α-D-ribofuranose and 1, 4-anhydro-2, 3-O-isopropylidene-5-thio-α-D-ribofuranose (Scheme 35) [68c].



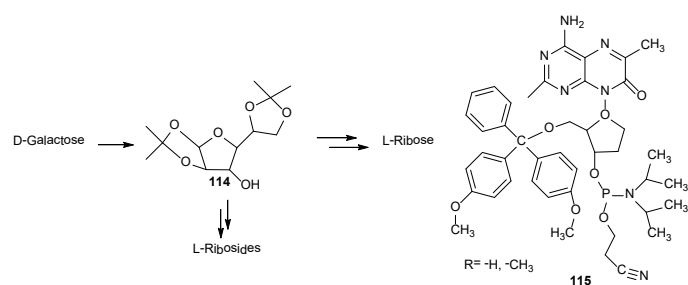
Scheme 35. The synthesis of thio-ribose derivatives 111 and 112.

In 2000, N-Cycloalkyl derivatives of adenosine and 1-dezaadenosine were synthesized by Vittori et al and identified their affinities and intrinsic activity in the A₁ adenosine receptor [69a]. It was seen that all compounds of the ribose-bearing series proved to be full agonists, the 1-deza derivatives showing affinities for the A₁ receptor were about 10-fold lower than adenosine analogues (Scheme 35) [69a]. Crimmins et al developed a method for the general and efficient synthesis of carbocyclic and hexenopyranosyl nucleosides (113) (Scheme 36) [69b].



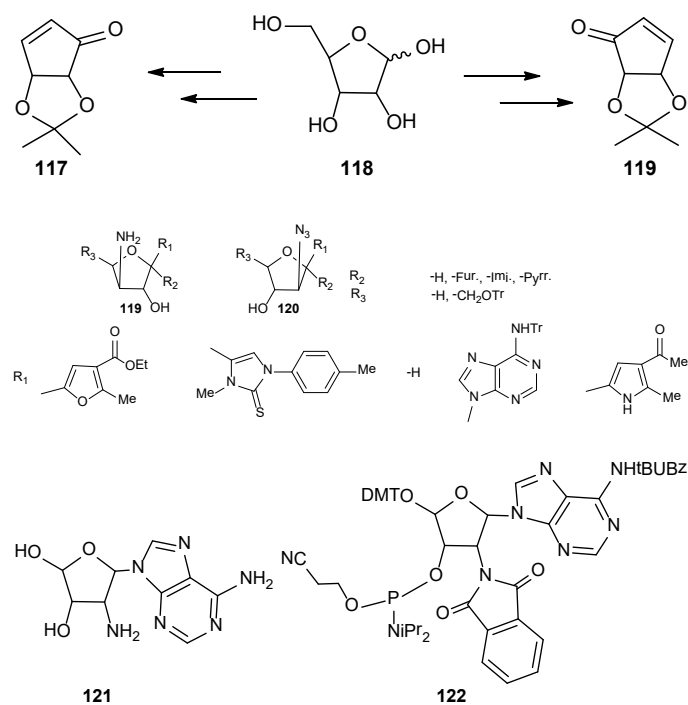
Scheme 36. The synthesis of hexeno pyranosyl (113) nucleoside analogues [69b].

In 2001, Shi et al performed stereospecific synthesis of L-ribose and L-ribosides from D-galactose with a total yield of 57% in ten steps (Scheme 36) [70a]. Hawkins et al studied the synthesis and fluorescence properties of pteridine adenosine nucleoside analogue 116 and then exhibited unique properties that make them extremely valuable for measuring the fine events in DNA (Scheme 37) [70b].



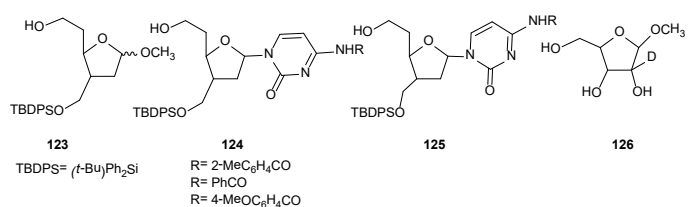
Scheme 37. L-ribose, L-ribosides and pteridine adenosine nucleoside 115

In 2002, Efimtseva and Mikhailov wrote a review on "Disaccharide nucleosides and oligonucleotides on their basis-New tools for the study of enzymes of nucleic acid metabolism" [71a]. Sivets et al synthesized peracylated derivatives of β -L-ribofuranose from D-ribose in 6 steps with a total yield of 50% [71b]. Moon et al obtained D- and L-cyclopent-2-enone (117 and 118), an intermediate for the synthesis of carbocyclic nucleosides, in six steps starting from D-ribose (Scheme 38) [71c]. Fuentes et al focused on the synthesis of azidonucleosides and fluoronucleosides (119, 120) because they are used in the treatment of diseases such as AIDS [71d]. He succeeded in synthesizing the fluoronucleosides, isothiocyanato C-nucleosides, and thioureylene di-C-nucleosides through cyclic sulfates. Karpeisky et al prepared 2'-Deoxy-2'-N-phthaloyl nucleosides (121, 122) from arabino nucleosides by triflate displacement with phthalimide in the presence of DBU (Scheme 38) [71e]. Khudyakov and Fields wrote a book called "Artificial DNA: Methods and Applications" in the same year [71f].



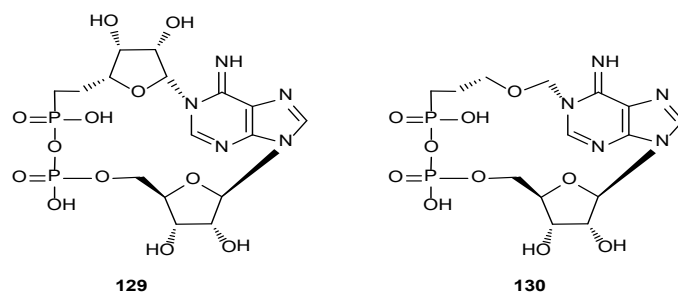
Scheme 38. The synthesis of ribose and nucleosides

In 2003, Schmidt et al presented a new route for the synthesis of 3'- and 5'-substituted nucleoside derivatives used in the synthesis of oligonucleotide analogues (Scheme 39) [72a]. Kundu et al worked on stereo selective synthesis of deuterated D-ribose derivatives (Scheme 39) [72b].



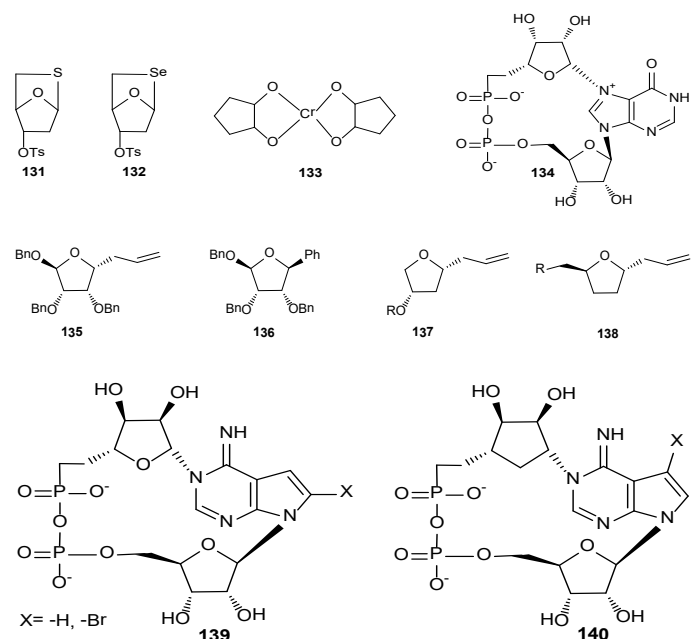
Scheme 39. The synthesis of nucleosides derivatives (123-126)

In 2004, Napoli et al made an important study for the synthesis of 2'-azido, 2'-deoxyuridine, ribose modified nucleosides and nucleic acid analogs, aminoacyl derivatives of 2'-deoxy and 2'-amino-uridine [73a]. Johnson and Widlanski described a methodology for the synthesis of nucleoside phosphates and polyphosphates [73b]. Gu et al performed the synthesis and biological evaluation of N1-[(5'-O-phosphorylethoxy) methyl]-5'-O-phosphorylinosine 5', 5''-cyclicpyrophosphate (cIDPRE) and 8-substituted derivatives (Scheme 40) [73c].



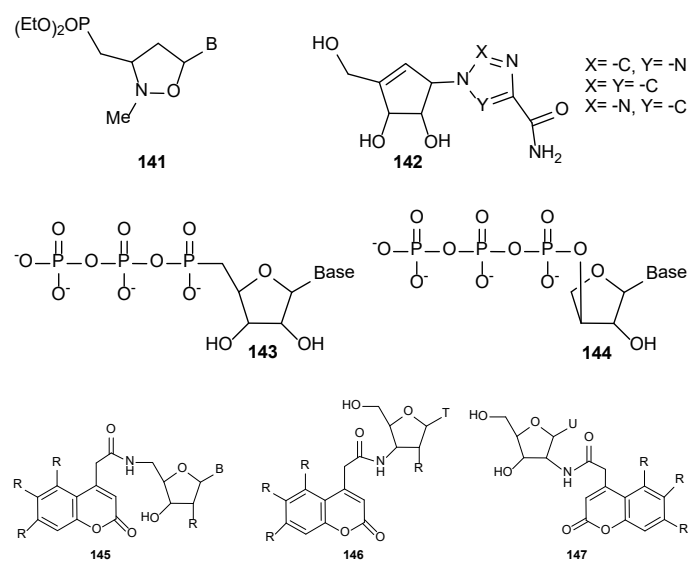
Scheme 40. The synthesis of nucleotide derivatives (129, 130).

In 2005, Srinhar et al developed a method for the synthesizing epithio and episeleno hexoses and pentoses with good yield (Scheme 41) [74a]. Wagner et al presented a concise synthesis of five new analogues of the second messenger cADPR (cyclic adenosine 5'-diphosphate ribose) using an unusual enzymatic cyclization reaction (Scheme 41) [74b]. Larsen et al examined the α -selective C-glycosylation reaction for the synthesis of 18 ribose derivatives, 4 of which are different in substitution at C-2, C-3, and C-4 given in Scheme 41 [74c].



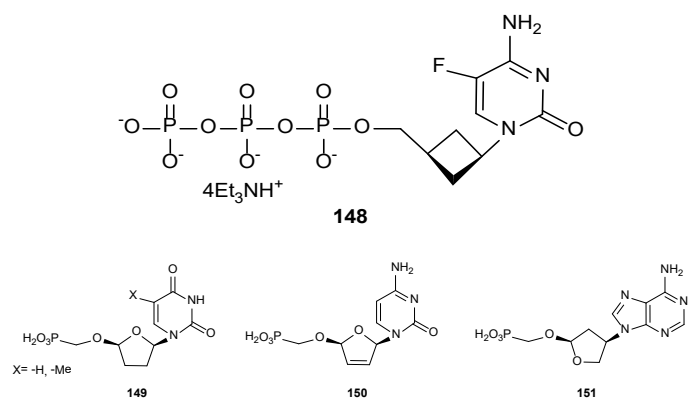
Scheme 41. The different ribose, nucleoside, nucleotide derivatives (131-140).

Romeo et al synthesized phosphonate disoxazoliny nucleosides from 1, 3-dipolar cyclo addition reaction of nitrile oxides with corresponding vinyl or allyl nucleo bases and examined the cytotoxicity, the anti-HSV activity and the RT-inhibitory activity of the resulting compounds (Scheme 42) [75a]. A synthesis of cyclopentenyl carbocyclic nucleosides from D-ribose was carried out by Cho et al at about 50% yield (Scheme 42) [75b]. Horhota et al explained the synthesis of glycerol nucleoside triphosphates and substrate activities for enzymatic polymerization (Scheme 42) [75c]. Kosiova et al developed a new approach for coumarin and ferrocene labeled nucleosides prepared with the intermolecular Staudinger ligation (Scheme 42) [75d].



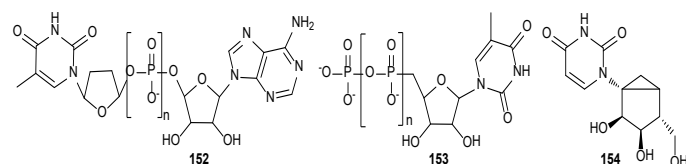
Scheme 42. Ribose derivatives (141-147)

In 2007, Oliviero et al announced the synthesis of nucleobase and ribose solid phase. in good yields. Li et al succeeded in the synthesizing 2'-substituted cyclobutyl nucleosides and worked on anti-HIV effect of the synthesized molecules (Scheme 43) [76a]. Li et al synthesized a series of ribosylated nucleoside phosphonate reverse transcriptase (RT) inhibitors, demonstrated anti-HIV activity and resistance profiles, and the strongest analyst showed [5-(6-amino-purin-9-yl)-2,5-dihydro-furan-2-ylloxymethyl]-phosphonic acid (d4AP), an HIV EC50= 2.1 μ M (Scheme 43) [76b]. Mackman synthesized a series of ribose modified nucleoside phosphonate reverse transcriptase (RT) inhibitors, explained their anti-HIV activity and resistance profiles and found that the most potent analog was phosphonic acid (d4AP) [76c].



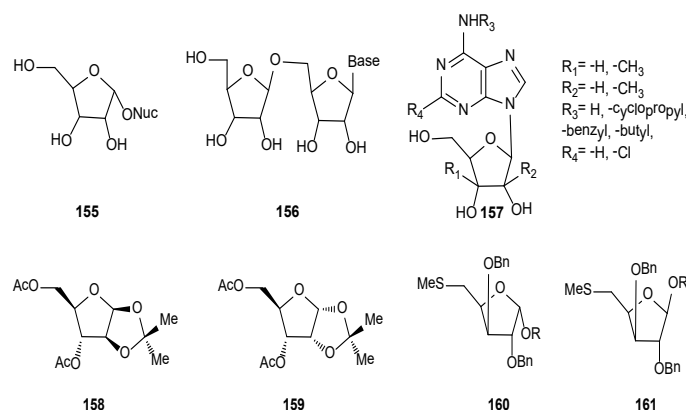
Scheme 43. Nucleoside analogues (148-151).

In 2008, Woodyer succeeded in synthesizing L-ribose as a model target because L-ribose is a potential starting material for many L-nucleoside-based biologically active compounds [77a]. Warnecke and Meier performed a method for the synthesis of nucleoside polyphosphates and nucleoside monophosphate sugars (Scheme 44) [77b]. Kulikova et al reported the first chemical synthesis of 2'-O- α -D-ribofuranosyl-nucleosides [77c]. Melman et al disclosed the synthesis of enantiomerically pure (S)-methanocarbaribo uracil nucleoside derivatives to use them as antiviral and P2Y receptor ligands (Scheme 44) [77d].



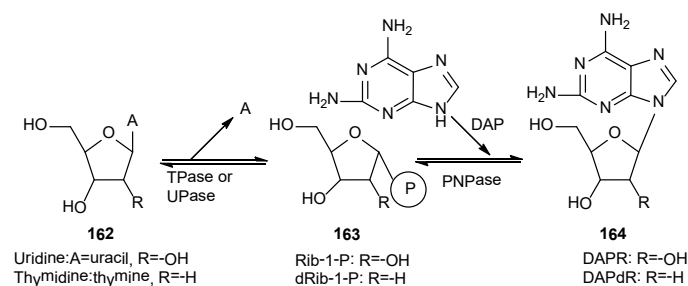
Scheme 44. Nucleoside derivatives (152-154)

A year later, Kulikova et al had developed an efficient and simple synthesis of 5'-O- β -D-ribofuranosyl-nucleosides, yielding 74-82% of this reaction and this reaction was carried out under mild condition (0 $^{\circ}$ C, 7-16 h) [78a]. Cosyn et al examined the synthesis of ribose-based nucleoside 5'-diphosphates, triphosphates, and related nucleotides and P2Y receptor activity [78b]. Powner et al the synthesized pyrimidine ribonucleosides in prebiotically plausible conditions [78c]. Okano summarized a review on L-ribose in the therapeutic area and technological progress in preparation [78d]. Helento et al developed a method for the production of L-nucleoside analogues used as antiviral drugs [78e]. The partially purified protein, which has both l-arabinose and L-ribose isomerase activity, was successfully used to convert l-arabinose to l-ribose. In addition, α -3, 5-O-acetyl-1, 2-O-isopropylidene-D-ribofuranoside was obtained by treating β -D-ribose tetraacetate with trimethyl aluminum in a high yield by More and Campbell (Scheme 46) [78f]. Stalford et al worked on the synthesis of mycobacterial oligo saccharides, investigating neighbouring group participation and addition to oxacarbenium ions in 2009 (Scheme 46) [78g].



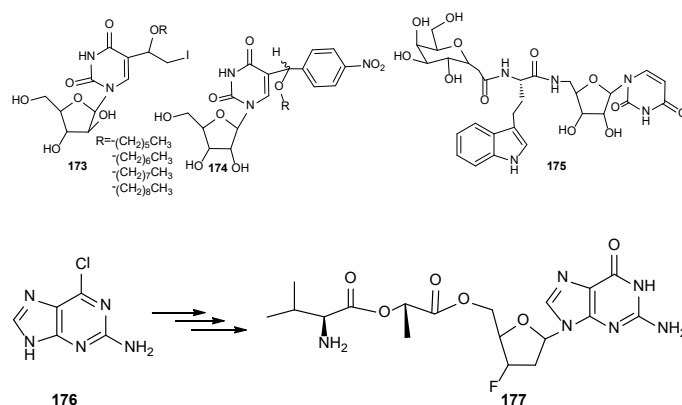
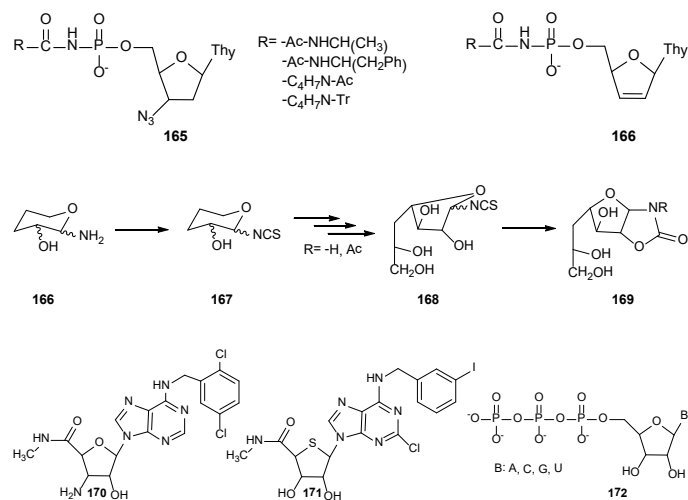
Scheme 45. Nucleoside (155-157) and ribose (158-161) derivatives

In 2010, in Ding's work, purine nucleoside phosphorylase and pyrimidine nucleoside phosphorylase were exogenously expressed in Escherichia coli and intact cells were used as a catalyst for biosynthesis of nucleosides (Scheme 47) [79].



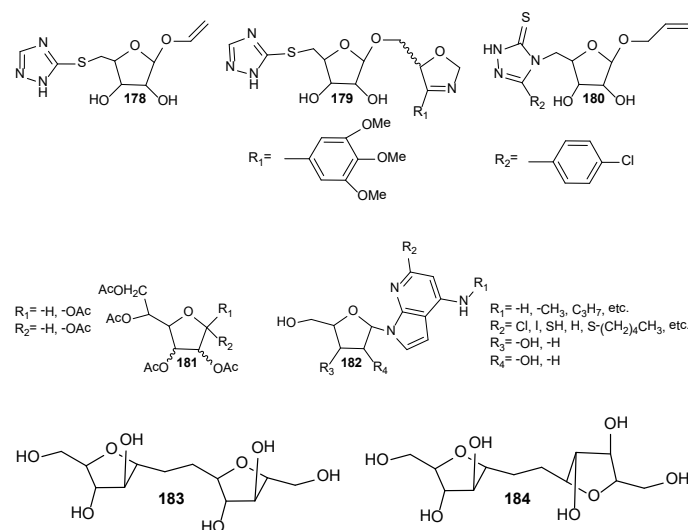
Scheme 47. The enzymatic synthesis nucleosides (164)

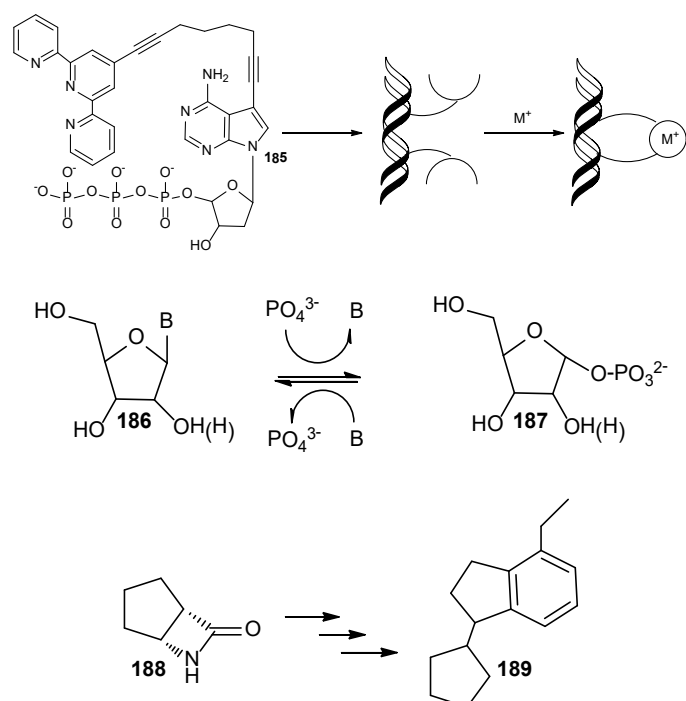
Baldoni et al. synthesized per-*O*-*tert*-butyldimethylsilyl β -D-galactofuranosyl isothiocyanate by KSCN with the reaction of per-*O*-TBS- β -D-galactofuranose in 2011 [80a]. That same year, Muller and Jacobson conducted a study on the potential of adenosine receptor ligands as new drugs for inflammatory diseases and cancer [80b]. Kulik et al prepared the nucleoside 5'-*O*-(*N*-acyl) phosphoramidates synthesis (Scheme 48) and examined its biological properties (antiviral activity) [80c]. Nucleoside 5'-triphosphates were synthesized by Caton-Williams using a selective phosphitylating reagent in situ in one pot [80d]. Ghoneim succeeded in synthesizing nucleoside derivatives from L-Rhamnose and 3,4,5-triacetoxy-2-methyl-7,9-diaza-1-oxa-spiro [4,5] decane-10-one-8-thione, which are biologically active and useful molecules such as β -L-rhamnosyl donors [80e]. Brulikova and Hlavac reported the synthesis, reactivity and biological activity (antiviral, cytotoxic and antibacterial) of 5-alkoxymethyluracil analogues (a few molecules are presented in Scheme 48) [80f]. Vembaiyan synthesized C- α -D-galactopyranosyl-amino acid-uridine and C-[α / β]-L-arabinofuranosyl-amino acid-uridine derivatives, a novel molecular structure type for glycosyltransferase inhibition, and then examined biological measurements (Scheme 48) [80g]. Brodzki et al achieved a five-step synthesis of the lagocyclovir valactate (2',3'-Dideoxy-3'-fluoro-5-*O*-[(*S*)-(+)-2-(1-valyloxy)-propionyl] guanosine) hepatitis B N-nucleoside analog from 2-amino-6-chloropurine (Scheme 48) [80h].



Scheme 48. Ribose and nucleoside derivatives (165, 166, 169-174, 175).

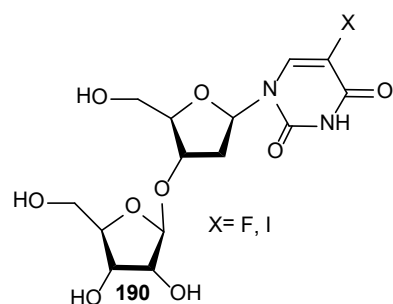
In 2012, Mohamady and Taylor performed the synthesis of nucleoside polyphosphates and their conjugates in excellent yields using sulfonyl imidazolium salts [81a]. Voorde studied the inhibition of pyrimidine and purine nucleoside phosphorylases with a 3, 5-dichlorobenzoyl-substituted 2-deoxy-D-ribose-1-phosphate derivative and demonstrated that Cf2891 inhibits the enzymatic degradation of therapeutic nucleoside derivatives [81b]. Lim et al explained the synthesis of L-ribose from L-ribulose with the tripesite mannose-6-phosphate isomerase variant from *Geobacillus thermodenitrificans* [81c]. Avanzo et al reported the design, synthesis and characterization of 1, 2, 4-triazole-D-ribose derivatives and studied their antitumor activity against T cell lymphoma cell line (Scheme 49) [81d]. Stevens explained the crystal preparation and characterization of the furanose pentacetate of eight aldohexosols in the D-series, except for L-idose (Scheme 48) [81e]. Vitali et al examined the in vitro antibacterial activity numerous adenosine derivatives (Scheme 48) [81f]. Patil et al developed a strategy on α - and β -C-arabinosides for the synthesis of the carba-disaccharide analog of Motif C of the cell wall AG complex of *Mtb* (Scheme 49) [81g]. Almendros explained synthetic nucleoside analogues such as 5-iodo uracil or 2, 6-diaminopurine and arabinoside [81h]. Boyle et al synthesized the carbocyclic nucleoside (-)-Abacavir starting from an easily obtainable β -lactam (Scheme 49) [81].





Scheme 49. Ribose, nucleoside, nucleotid derivatives (177- 188)

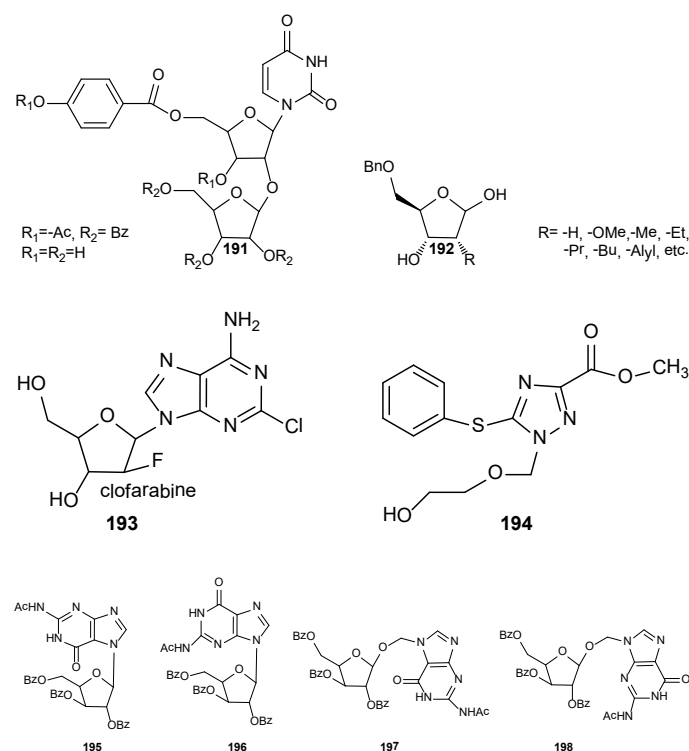
Efremova et al intended to develop approaches for the synthesis of disaccharide nucleoside analogs, which are heterocyclic compounds containing primary or secondary amide groups and used as potential inhibitors of human PARP-1, and to examine these analogs as potent inhibitors of human PARP-1 in 2013 (Scheme 50) [82a]. Kalachova et al synthesized modified nucleosides (dARs and dCRs) with 7-iodo-7-deaza-2'-deoxyadenosine and 5-iodo-2'-deoxycytidine with the corresponding bipyridine- or terpyridine-octadiynes and their complexation with Ni^{2+} and Fe^{2+} [82b].



Scheme 50. Disaccharide nucleoside analogues 189

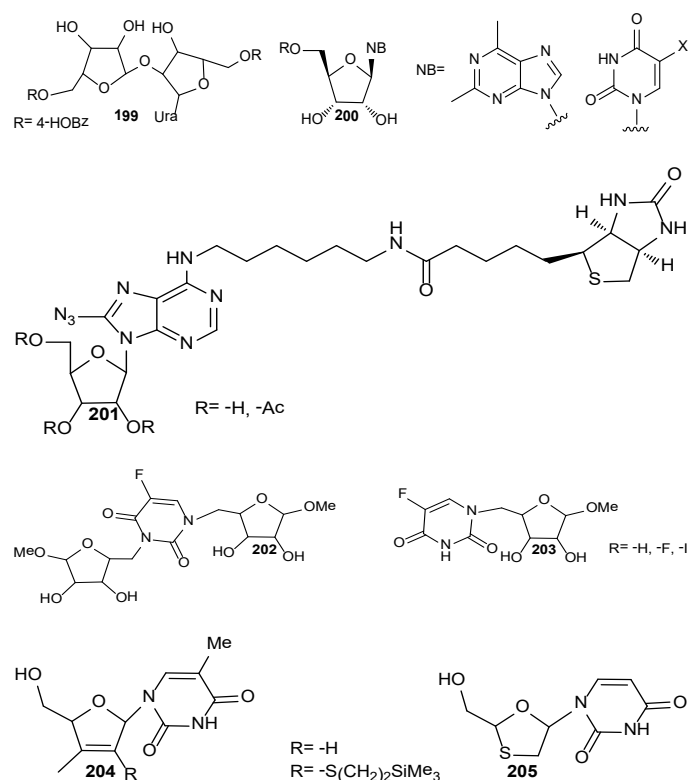
Sylla et al made a new disaccharide nucleoside isolation from *Helleborus caucasicus*, a plant native to Turkey and Greece, showing the stereo selective synthesis of hellecaucasidae and its β -anomer and its interesting biological properties, especially anti-cancer activities in 2014 [83a]. Liu et al explained a general method for the synthesis of nucleoside 5'-H-phosphonothioates containing the coupling of 2', 3'-O-isopropylidene-protected nucleosides with tiethylammonium phosphinate [83b]. Peifer presented a study on the synthesis of pharmaceutically active ribose derivatives, which are widely used clinically (Scheme 51) [83c]. Fateev et al studied the synthesis of 2-chloro-9-(2-deoxy-2-fluoro- β -D-arabinofuranosyl) adenine (clofarabine) and

related 2'-deoxyfluoroarabino nucleosides and 2'-deoxyfluoroarabino nucleosides (Scheme 51) [83d]. Lei et al (2014) synthesized 1-((2-hydroxyethoxy) methyl)-5-(phenylthio)-1H-1, 2, 4-triazole-3-carboxamide, which is used as anticancer nucleosides from 1, 2, 4-triazole nucleosides (Scheme 51). [83e] Kuchana et al synthesized the xylofuranosyloxymethyl nucleosides using $SnCl_4$ as the activator (Scheme 51) [83f].



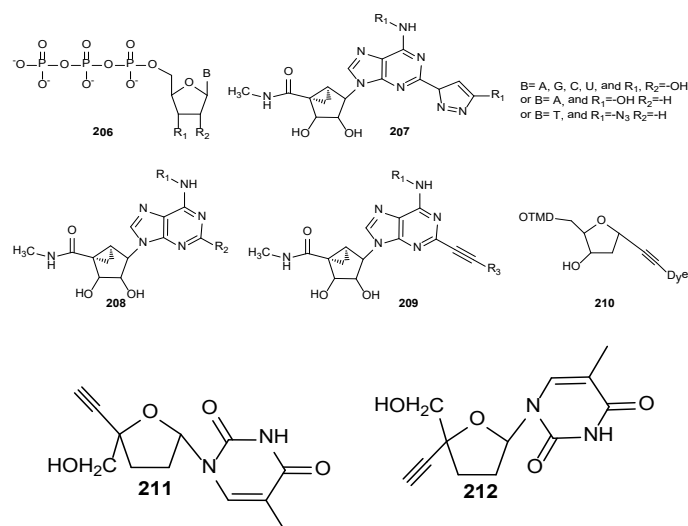
Scheme 51. Ribose, nucleoside analogues (190-198)

In 2015, Shaughnessy prepared a review on "Palladium-catalyzed modification of un protected nucleosides, nucleotides, and oligonucleotides" [84a]. Hellecaucaside A, obtained from the roots of *Helleborus caucasicus*, is a pyrimidine disaccharide nucleoside. Kulikova et al developed synthetic methods to obtain Hellecaucaside A in 2015 (Scheme 52) [84b]. Downey et al reported the one-pot synthesis of nucleosides from unprotected and 5-O-monoprotected D-ribose (Scheme 52) [84c]. Bergeron-Brek et al succeeded in a convergent synthesis of the imino-C-nucleoside and the iminosugars showing biological activity [84d]. Mahajan et al presented a new study on the development and application of a new AdoR photorefractive process [84e]. He designed a new modular strategy that would facilitate the future production of any 5'-substituted AdoR for Probin synthesis (Scheme 52). Zupancic et al presented the synthesis of nucleosides and condensation reactions with 5-halogen pyrimidines (Scheme 52) [84f]. Oliveira et al reported on a simple and efficient preparation of 2',3'-Didehydro-2', 3'-dideoxy-2'-(2''-(trimethylsilyl)ethylthio) thymidine, the key mediator for the synthesis of anticancer and / or antiviral 2'-substituted thionucleosides (Scheme 52) [84g]. Bessieres et al reviewed the synthesis of carbocyclic nucleosides [84h].



Scheme 52. Ribose, nucleoside derivatives (199-205)

In 2016, Elzagheid wrote a review of the synthesis of 1', 2', 3', 4'- and 5' sugar fluorinated nucleosides [85a]. Mohamady and Taylor synthesized nucleoside triphosphates from 2'-3'-protected nucleosides using trimetaphosphate as the key reagent with good yield (Scheme53) [85b]. Janowsky et al synthesized (N)-methanocarba adenosine derivatives characterized by DAT, NET, and SERT correlated these activities with the structure (Scheme 53) [85c]. Kölmel et al explained the procedure for the preparation of new alkynyl C-nucleosides used to prepare DNA-based polyfluorophores with various fluorophores (Scheme 53) [85d]. Singh et al synthesized 4'-C-ethynyl isomeric dioxolane nucleoside analogs (β -D, α -D, β -L, and α -L) and evaluated the anti-HIV-1 and anti-HIV-2 activities (Scheme 53). The selectivity indices and cytotoxic profiles of the synthesized nucleosides were found to be much better than standard drugs.



Scheme 53. Ribose, nucleoside, nucleotid analogues (206-212).

Conclusion

Nucleosides used in agriculture (eg herbicides), biotechnology (eg DNA sequencing) and medicine are useful molecules [1e,85]. Deoxyribonucleic acid is depicted as template for the development of organism. Deoxyribose is a monosaccharide of five carbon atoms with a hydroxyl group in each atom. Cyclopentitols as a ribose derivative is found as a component of an organism or as a product of microorganism. There are a number of studies for the synthesis of cyclopentitols, because they had an important role in synthetic organic chemistry in recent years [86]. The priorities of science around the world are new, more efficient and versatile researches showing anti-cancer, antibacterial, antitumor, antimicrobial and anti-hiv properties [1d]. In some natural and synthetic carbocyclic nucleosides, antiviral and antitumor effects such as aristeromycin (1), neplanocin A (2), carbovir (3), abacavir (4) were observed [1]. These important properties make cyclopentitols derivatives important for the synthesis of new drugs. In this paper, we aimed to explain the synthesis of several ribose and nucleoside derivatives that can act as key compounds for the preparation of biological active molecules.

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