

Review

Fluorinated nucleosides

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Abstract

The synthesis and biological activity of deoxyfluoro nucleosides are reviewed. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

This review on fluorinated nucleosides is part of a series of mini-reviews on fluorinated sugars launched as a project by *Carbohydrate Research* (for a previous review on fluorinated nucleosides, see: [1]). Consequently, this article focuses on nucleosides that contain a fluorinated glycone moiety, and it does not cover a large group of nucleosides fluorinated at the nucleobase. Beilstein's CROSSFIRE search

revealed 362 structures containing a fluorine atom at the sugar moiety of nucleosides. These consist of 238 compounds fluorinated at C-2', 40 nucleosides doubly fluorinated at C-2', 29 derivatives substituted at C-3', 13 compounds with fluorine atoms at both the 2'- and 3'-position, two analogs containing fluorine at C-4', and finally a group of 42 nucleosides substituted at C-5'.

The objective of this chapter is not to present a list of known fluorinated nucleosides but rather to show the development of the field. Since some early-synthesized 2'-deoxy-2'-fluoro nucleosides showed promising thera-

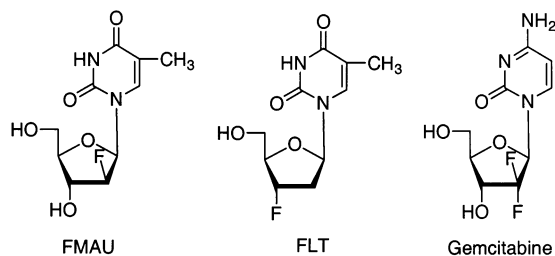
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peutic potential (mainly antiviral and anti-cancer), the synthesis of new generations of 2'-fluorinated nucleosides flourished in hope of new drug discovery. Thus, more than 77% of fluorinated nucleosides synthesized to date contain fluorine atom(s) at C-2' of the sugar. This also shows how frantic the competition was to produce new 2'-fluoro substituted analogs with improved biological activity. Several analogs reached clinical trials; however, up to date only one (gemcitabine) has been approved as a drug. As the field developed, great knowledge of structure–activity relationships has been accumulated that allows today for the design and synthesis of new compounds inaccessible ever before and for generating new ideas reaching well beyond the old limits.

To the best of this author's knowledge, none of formerly published reviews [1] have covered the topic of fluorinated nucleosides extensively, although many aspects of the chemistry of fluorinated nucleosides have been reviewed. For example, Bergstrom and Swartling [2] published a special issue on 'Fluorine Substituted Analogues of Nucleic Acid Components', Herdewjin et al. [3] described 'Synthesis of Nucleosides Fluorinated in the Sugar Moiety', and Pankiewicz and Watanabe [4] discussed 'Synthesis of 2'- β -Fluoro-substituted Nucleosides by Direct Approach'.

Introduction of fluorine atom(s) into components of nucleic acids in general and nucleosides in particular frequently leads to a dramatic change in their biological activity. For example, replacement of the 2'- β -hydrogen atom (arabino configuration) or the 3'-hydroxyl group of natural thymidine by fluorine afforded new nucleosides with potent antiviral properties, FMAU [5] and FLT [6], respectively. Substitution of both hydrogens of C-2' of deoxycytine with geminal fluorines (e.g., replacement of the $-\text{CH}_2-$ group by a $-\text{CF}_2-$

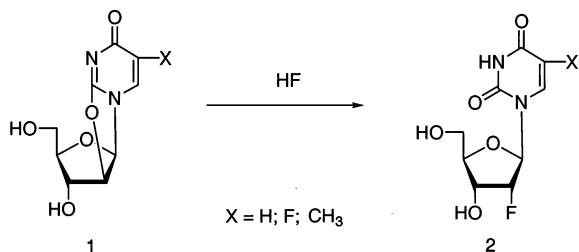


group at the 2'-position) resulted in the formation of gemcitabine [7], a nucleoside with potent anticancer activity.

A fluorine atom at a sugar carbon in nucleosides causes only a minor change of the shape of the modified structure. Fluorine is a good mimic of a proton (small size) or hydroxyl group (similar polarity) and is able to form hydrogen bonding (as an acceptor). However, fluorine seriously affects stereoelectronic properties of the molecule. These in turn restrict conformational equilibria [8]¹ of the sugar-fluorinated nucleoside [9]² 'locking' the sugar ring into a preferred conformation, stabilize the glycosylic bond (if placed in its proximity) towards hydrolysis, as well as affect the susceptibility of cytosine and adenosine analogs for enzymatic deamination. The $-\text{CF}_2-$ group has been suggested by Blackburn [10] as an isopolar and isosteric substituent for oxygen. Analogs of di- and triphosphates in which the $-\text{CF}_2-$ group has replaced the pyrophosphate oxygen have been used as substrates in enzymatic reactions. Since then the $-\text{CF}_2-$ group, as well as $-\text{CHF}-$, were used extensively to modify not only nucleotide but also nucleoside analogs.

2. Nucleosides containing a fluorine atom at C-2'

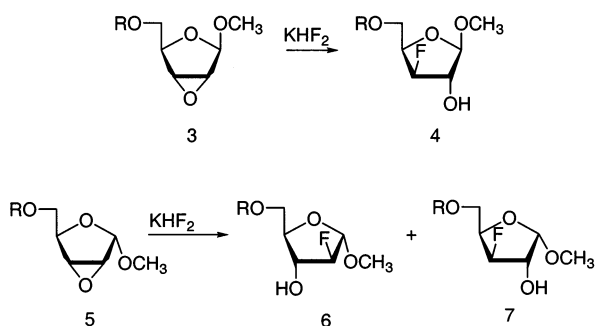
The first nucleoside with fluorine in the sugar moiety, 2'-deoxy-2'-fluorouridine (**2**, $\text{X} = \text{H}$), was synthesized in 1961 by Codington



Scheme 1.

¹ Extensive studies on the influence of intramolecular stereoelectronic gauche and anomeric effects on the conformation of the sugar moiety in modified nucleosides have been published recently by Chattopadhyaya and co-workers. See one of the last articles in the series.

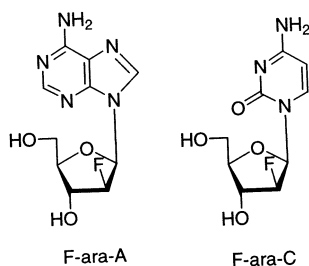
² Constructive conformational studies of mono- and difluorodeoxy nucleosides and discussion of the relationship between conformation of their fluorosugars and anti-HIV activity has been published.



Scheme 2.

et al. [11]. Since hydrogen or a hydroxyl group at C-2' distinguishes nucleosides as components of deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), it was interesting to investigate the biological properties of nucleosides containing fluorine that could mimic both H or OH to some extent. Compound 2 (X = H) was prepared by cleavage of the anhydro linkage of 2,2'-anhydrouridine (1) with anhydrous HF (Scheme 1). Later, Fox and co-workers [12] at the Sloan–Kettering Institute have synthesized 2'-fluoro-β-D-ribosylthymine and the 2'-fluoro analog of 5-fluorouridine (2, X = F).

Such a direct introduction of fluorine into the carbohydrate moiety of a nucleoside has obvious limitations restricting the substitution to the ribo configuration of pyrimidine nucleosides. In the 1960s 1-(β-D-arabinofuranosyl)adenine (*ara-A*) and -cytosine (*ara-C*), nucleosides containing an –OH group in the 2'-*arabino* configuration, were evaluated as potential anticancer drugs. It was found that the efficiency of both agents suffered due to enzymatic deamination to the corresponding inactive metabolites, *ara-I* and *ara-U*, respectively. It was therefore desirable to synthesize fluoro derivatives of these compounds, such as F-*ara-A* and F-*ara-C*, and compare their biological activity with the parent nucleosides. The direct displacement



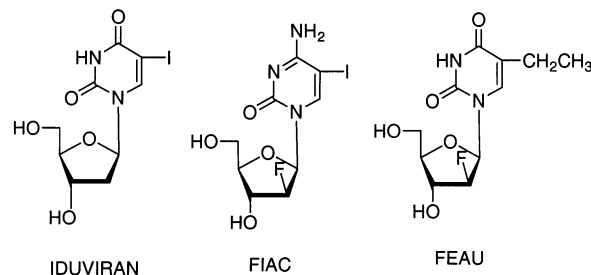
of a good leaving group at C-2' in ribo configuration with fluorine attacking from the β-face had not been considered to be successful due to the steric hindrance provided by the aglycone positioned above the sugar face. Also, the inductive effects from the aglycone and the lactol ring oxygen make the substitution at the C-2' position difficult. In addition, in the case of pyrimidine nucleosides, neighboring group participation of the carbonyl group at C-2 of the base resulted in formation of 2,2'-anhydro nucleosides, followed by introduction of fluorine in the ribo configuration (*vide supra*). Indeed, it was demonstrated that treatment of the methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribose (3, Scheme 2) with KHF₂ gave exclusively methyl 3-deoxy-3-fluoro-β-D-xylofuranoside (4) [13], whereas similar reaction of the corresponding α-D-ribose (5) afforded a mixture of the desired 2-deoxy-2-fluoro-α-D-arabinofuranoside (6, as the major product) and the xylo-substituted derivative 7 [14]. These compounds were separated on silica gel column, converted into their corresponding glycosyl bromides, and used for coupling with adenine and cytosine to give F-*ara-A*, F-*ara-C*, as well as the xylo-substituted derivatives [14,15]. It was also confirmed that a direct reaction of adenosine 2',3'-anhydride derivative with a fluoride resulted in a nucleophilic attack at the 3'-position, exclusively [16].

Since F-*ara-C* was reported [15] to show as potent inhibitory activity against L1210 leukemic cells as a clinically used anticancer agent, *ara-C*, large amounts of F-*ara-C* were required for further biological studies. However, such fluorinated nucleosides were barely accessible by the above-mentioned method due to low yield of preparation of the 2-fluoro sugar 6. Although, the introduction of a fluorine atom at C-2 of the carbohydrate by nucleophilic displacement reaction is rather difficult, the similar reaction at C-3 is not. This guided Watanabe and co-workers [17] to synthesize 3-deoxy-3-fluoro-D-glucose and then convert it into 2-deoxy-2-fluoro-D-arabinose. The key step of the synthesis (Scheme 3) is oxidation of the 3-deoxy-3-fluoro-D-glucose derivative 10 with sodium metaperiodate, which afforded the 2-deoxy-2-fluoro-D-ara-

binose that cyclized simultaneously (anomeric aldehyde and C-4-hydroxyl group) forming exclusively the desired 2'-deoxy-2-fluoro furanose **11**. The final glycosyl bromide **12** was then prepared and used extensively for the synthesis of numerous pyrimidine and purine nucleosides containing fluorine in the C-2'-*arabino* configuration. However, 2'-deoxy-2'-fluoro-*ara*-C showed little antitumor activity in mice.

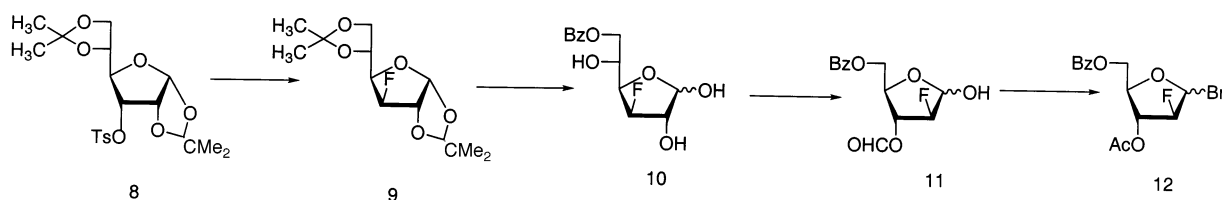
The first antiviral nucleoside, 2'-deoxy-5-iodo-uridine (Iduviran), was synthesized by Prusoff [18]. The glycosylic bond of this compound is not stable in acidic conditions. Therefore, it was interesting to prepare analogs of Iduviran containing a fluorine atom at C-2', which stabilizes the glycosylic linkage. Consequently, a number of 5-substituted uracil and cytosine nucleosides with fluorine in the *arabino* configuration were designed and prepared by Watanabe et al. [5]. Among them, FIAC, FEAU, and FMAU showed not only potent activity against HSV, but also an excellent activity against hepatitis B virus (HBV) and other viruses such as varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV). In addition FMAU was highly active against murine leukemias resistant to *ara*-C. Such a broad and promising biological activity of these new 2'-deoxy-2'-fluoroarabino nucleosides stimulated the progress of the field in the coming years. Indeed, a number of syn-

thetic procedures have been developed in order to make new analogs with even better chemotherapeutic potential.

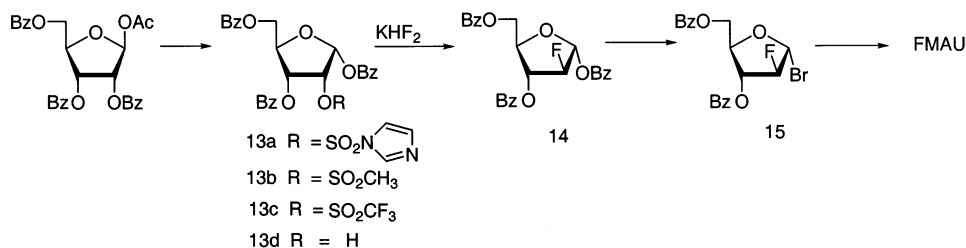


FIAC and FMAU were selected as candidates for clinical trials. This motivated Tann and researchers [19] at Bristol–Myers to develop an even more efficient method for the synthesis of FMAU. They found that direct displacement of 2-imidazoysulfonate (**13a**) with KHF_2 gave a 63% yield of the desired 2-deoxy-2-fluoro sugar **14** (Scheme 4). It is worthwhile to note that treatment of **13a** with TBAF gave only elimination products. The displacement of mesyl or triflate group at the 2-position (**13b** or **13c**) with KHF_2 or TBAF as well as reaction of **13d** with diethylaminosulfur trifluoride (DAST) did not afford the desired product either. Bromination of **14** produced quantitatively the glycosyl bromide **15**, which was coupled with silylated thymine to give FMAU in 95% (as a mixture of α,β anomers in the ratio of 1:7).

The easy access to the 2-deoxy-2-fluoroarabino sugar resulted in an avalanche of studies

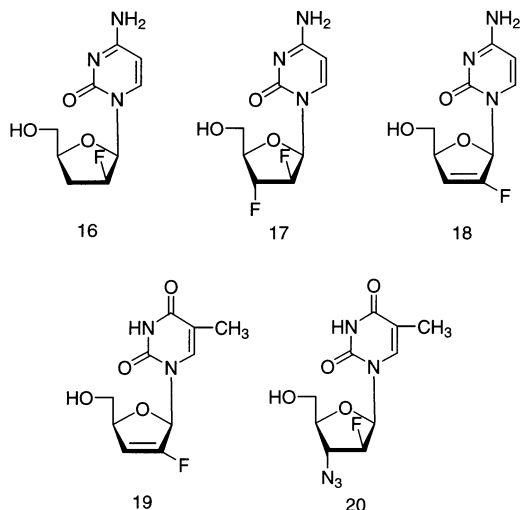


Scheme 3.



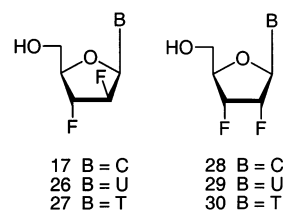
Scheme 4.

on the synthesis of 2'-deoxy-2'-fluorinated nucleosides. For example, Martin and researchers [20] at Roche prepared a number of 2'-deoxy-2'-fluoro-containing pyrimidine analogs of anti-HIV nucleosides. Among them analogs of ddC such as **16**, its 2',3'-difluoro derivative **17**, 2'-F-d4C **18**, and 2'-F-d4T **19** showed significant activity against HIV.

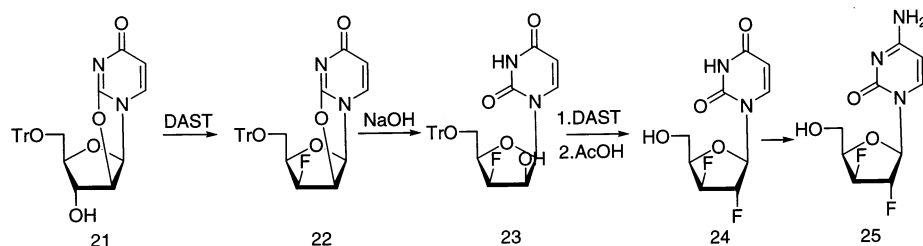


The analog of ddC containing fluorine in the 2'-*ribo* configuration was not active. Sterzycki et al. [21] (Bristol–Myers) synthesized an analog of AZT **20** as well as some of the above compounds and found they exhibit a potent antiviral activity, that was, however, not superior to that of AZT. Marquez et al.

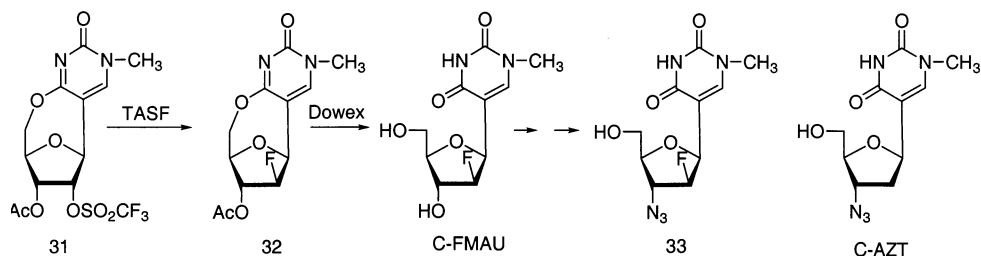
[9] examined the relationship between preferred ring-puckering of fluorine-substituted dideoxynucleosides in solution and their anti-HIV activity. He concluded that, for various aglycone moieties, a fluorine atom at positions 3'-'down' or 2'-'up' correlates with anti-HIV activity, whereas, nucleosides with fluorine atoms in the same positions but in inverted configuration are inactive. Interestingly, he prepared difluorodideoxy *xylo*-uridine (**24**) and *xylo*-cytidine (**25**) (Scheme 5) and found them inactive. With exception of *ara*-C analog **17**, earlier-synthesized difluoro derivatives of *ara*-U [20], *ara*-T [22] (**26**, **27**), as well as compounds containing two fluorine atoms in the ribo configuration (**28–30**) [22,23] did not show any activity.



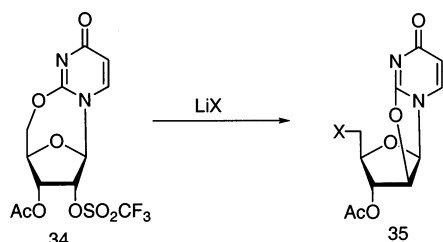
The C-nucleoside analog of FMAU (C-FMAU, Scheme 6) is an isosteric and isoelectronic isomer of FMAU, and therefore it was believed it might exhibit an antiviral activity similar to that of FMAU. Thus, the Watanabe group at Sloan–Kettering Institute synthesized C-FMAU [24] as well as its 3'-azido-3-



Scheme 5.



Scheme 6.



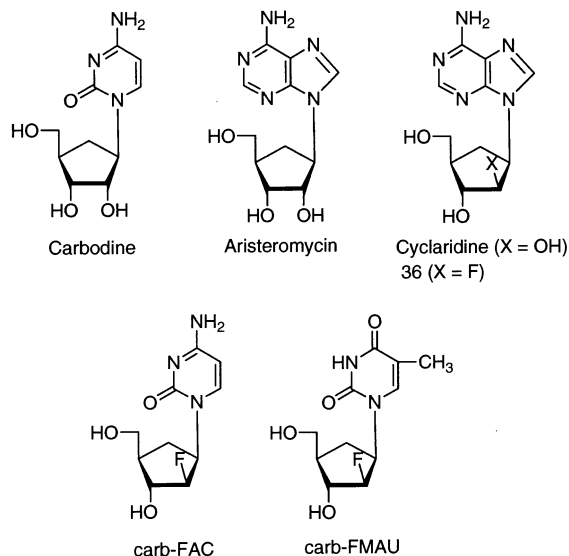
Scheme 7.

deoxy analog (**33**) [25], an analog of C-AZT. The key intermediate was 4,5'-anhydro-1-methyl-pseudouridine (**31**), in which oxygen at C-4 in the uracil ring is linked to C-5' and thereby precludes its participation in nucleophilic reaction that occurs on C-2'.

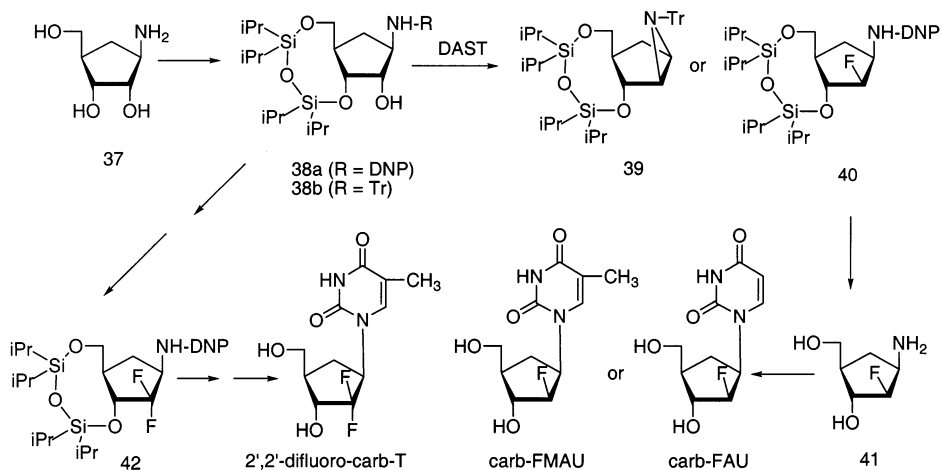
Fluorination went relatively smoothly when **31** was treated with tris(dimethylamino)sulfur (trimethylsilyl)-difluoride (TASF) to give **32** in 40% yield. Hydrolysis of the anhydro linkage afforded C-FMAU, which was further converted into **33**. These compounds did not exhibit any significant antiviral activity. It is interesting to note that treatment of natural nucleoside 3'-O-acetyl-2,5'-anhydro-2'-O-triflyl-uridine (**34**, Scheme 7) with a nucleophile such as LiCl or LiBr (LiX) resulted in the formation of the 5'-substituted-2,2'-anhydrouridine (**35**) due to preferential attack at C-5' that liberated the 2-oxide, which then displaced the C-2'-triflyl function forming the 2,2'-anhydro linkage [26].

At the same time, the synthesis of carbocyclic nucleosides became of considerable interest due to discovery of such nucleosides as aristeromycin and neplanocin in nature. These

natural products and analogs such as carbodine and cyclaridine have been synthesized and have been shown to have antiviral properties.



Since the presence of a 2'-*ara*-fluoro substituent has been found to confer potent antiviral activity, the Glaxo researchers [27] prepared a number of deoxy-fluoro carbocyclic nucleoside analogs, among them an analog of cyclaridine **36**, a carbocyclic analog of 2'-deoxy-2'-fluoro-*arabino*-C (carb-FAC), and carbocyclic FMAU. All carbocyclic pyrimidine nucleosides containing fluorine at the C-2'-*arabino* configuration were synthesized by construction of an appropriate pyrimidine base from the corresponding amino fluorocyclopentane-1,2-diol **41** (Scheme 8) [28]. In the case of the carbocyclic analog of ribose, the fluorine atom can be introduced into the 2'-

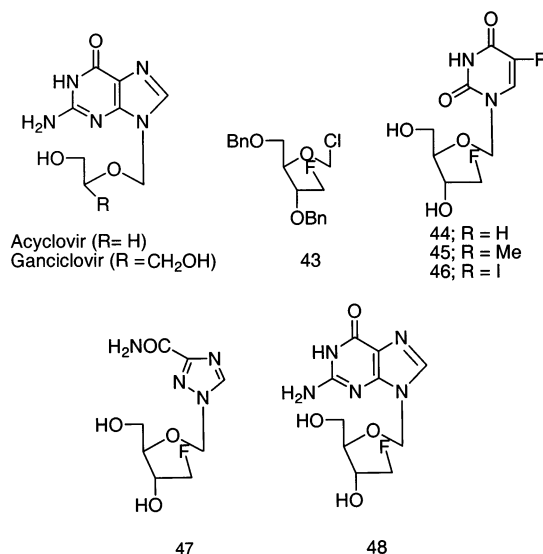


Scheme 8.

ara position by treatment of 3,5-tetraiso-propyldisiloxanyl-protected triol **38a** with DAST. The amino group of **38** must be protected with an electron-withdrawing group, such as a 2,4-dinitrophenyl moiety (DNP), to reduce the electron density on the nitrogen. Otherwise, as in the case of the trityl protected compound **38b**, the corresponding aziridine derivative **39** has been obtained exclusively. Interestingly, this work demonstrated the usefulness of the silyl protection in the reaction with DAST. In a similar manner the carbocyclic analog of 2',2'-difluoro thymidine has been synthesized from **38a**. This compound was oxidized to give the 2-keto derivative, which upon treatment with DAST afforded amino 2,2-difluorocyclopentane-1,3-diol derivative **42**, in low yield. Deprotection of **42**, followed by treatment with $\text{EtOCH}=\text{C}(\text{Me})\text{CONCO}$, afforded the desired 2',2'-difluoro-carb-T [29].

Since there is no aglycone involvement in neighboring group participation at C-2' in purine nucleosides, the Biggadike and Borthwick group at Glaxo [28] treated 3',5'-tetraiso-propyldisiloxanylaristeromycin with DAST and obtained the corresponding fluoro derivative, albeit in only 5% yield. However, the similar reaction of 3',5',*N*⁶-tribenzoylaristeromycin with DAST afforded, after debenzoylation, the desired 2'-fluoro-*arabino* analog **36** in 50% yield. Among pyrimidine fluoro carbocyclic nucleoside analogs, the most active against HSV-1 was carb-FMAU, although it was 88-fold less active than FMAU. No activity was found against HSV-2. Activity of other carbocyclic compounds was inferior to that of the parent nucleosides. In contrast, the 2'-fluoro analog of cyclaridine was shown to be 10 times more active than cyclaridine itself against HSV-1 and HSV-2 and more active than acyclovir against HSV-2 in the mouse systemic test.

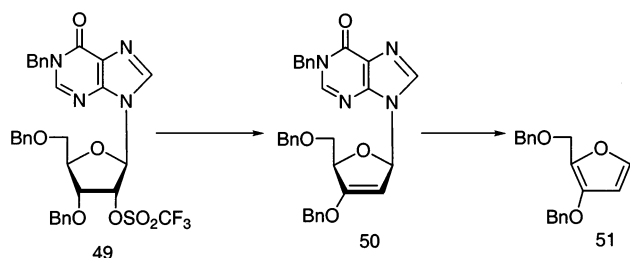
A similar rationale was behind the synthesis of fluorinated analogs of acyclic nucleosides, such as 2'-deoxy-2'-fluoro-1',2'-seconucleosides. Uridine (**44**), thymine (**45**), 5-iodouridine (**46**), ribavirin (**47**), and guanosine (**48**) analogs were obtained by coupling of (*R,R*)-2-(chloromethoxy)-1,3-bis(benzyloxy)-4-fluorobutane (**43**) with an appropriate base, followed by debenzoylation. The desired isomer of the sugar mimic **43** was prepared from D-



isoascorbic acid in five steps. These compounds were evaluated against RNA viruses and found to be inactive [30].

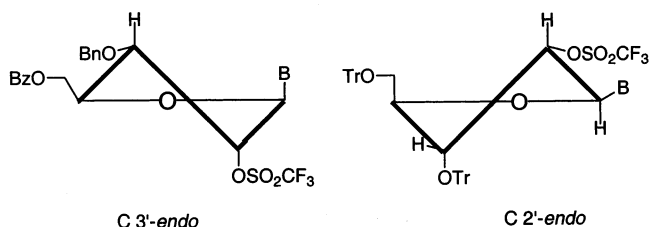
A majority of regular 2'- β -fluoro nucleosides have been synthesized by condensation of the nucleobase and sugar. In contrast to simple and efficient glycosylation of pyrimidines, however, the condensation of purines with 2-deoxy-2-fluoro-D-arabinofuranosyl halide is rather difficult. In fact, some purine bases do not react with the glycosyl halide. For example, F-*ara*-A was originally synthesized [14] by fusion of the fluoro sugar derivative with 2,6-dichloropurine, followed by conversion into the adenine derivative. Later, 6-chloropurine was condensed with the fluoro sugar to give a mixture of four isomers (7-, or 9-substituted, α,β anomers) from which the desired isomer was separated in low yield and converted into F-*ara*-A [31,32].

Direct nucleophilic displacement of a good leaving group in the 2'-*ribo* configuration with fluorine has been considered to be difficult, if not impossible, not only due to poor activity of C-2', but also due to the weak nucleophilicity of fluorine, which in addition is known as a rather strong base. Indeed, treatment of 2'-*O*-triflyl-3',5'-di-*O*-benzyl-*N*¹-benzylinosine (**49**) with TASF afforded elimination products **50** and **51** as expected (Scheme 9) [33]. Facile elimination of $\text{CF}_3\text{SO}_3\text{H}$ from **49** with the formation of olefins **50** and **51** is due to the fact that the sugar of **49** is in the C-3'-*endo* conformation. The presence of the electronegative substituent (triflyl group) forced **49** to



Scheme 9.

assume the C-3'-*endo* conformation [34].



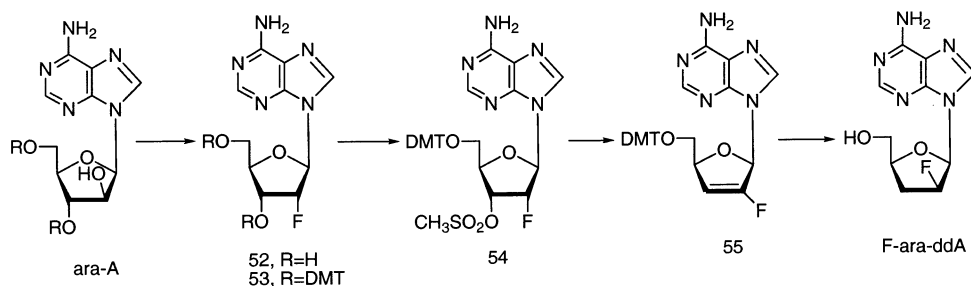
In such conformation the triflyl group and the hydrogen at C-3' are in a trans di-axial configuration, which favors elimination. Pankiewicz et al. [35,36] assumed that if the furanose ring conformation could be shifted toward C-2'-*endo* by using bulky protecting groups at C-5' and C-3' of the purine nucleoside 2'-triflate, then nucleophilic substitution might be possible. The C-2'-*endo* conformation of the furanose ring is unfavorable for trans elimination. Indeed, when *N*¹-benzyl-3',5'-di-*O*-trityl-inosine 2'-triflate was treated with TASF, the desired 2'-fluoro-*ara*-bino nucleoside was obtained in 30% yield [33]. The reaction is even more efficient when the 2'-hydroxyl group of the *N*¹-3',5'-di-*O*-trityl-benzylinosine is converted into the 2'-fluoro function by DAST [35]. F-*ara*-A and F-*ara*-G were also prepared by reaction of the corresponding 3',5'-ditrityl derivatives with DAST [36]. Recently it was reported [37] that a combination of a 5'-*O*-trityl group with 3'-*O*-benzoyl protection also worked efficiently in terms

of the introduction of fluorine at the 'up'-side of C-2'. Since the benzoyl group could be introduced regioselectively (via stannylation) at the 3'-position of nucleosides as well as the trityl group at C-5', there was no need for separation of the 3',5'- and 2',5'-ditrityl derivatives.

2',3'-Dideoxy purine nucleosides have potent anti-HIV activity, and the inosine analog (ddI) is in clinical use. The instability of these compounds in acidic conditions complicates oral administration. The 2'-fluorinated analogs were found, as expected, to be indefinitely stable to acidic conditions that completely decomposed ddI and ddA in minutes. While the erythro isomers were inactive, the threo isomers F-*ara*-ddI and F-*ara*-ddA were just as potent as parent drugs. A new convenient route to F-*ara*-ddA has been recently developed by Marquez and co-workers [38] at NIH (Scheme 10). It started with the facile introduction of fluorine at C-2' from the α -side of protected *ara*-A, followed by dimethoxytritylation and mesylation to give 54. Elimination of methanesulfonic acid from 54 afforded a stable vinyl intermediate 55.

Inversion of stereochemistry at C-2' was accomplished via stereoselective reduction of the double bond to give the desired F-*ara*-ddA.

The same group reported [39] an interesting chemistry of the DAST fluorination of 3'-deoxy-4'-thiopyrimidine nucleosides. Since 2',3'-dideoxy-4'-thiocytidine showed a moderated anti-HIV activity, they attempted to improve its activity by incorporation of fluorine into the sugar ring. Treatment of hydroxylated precursors 56 or 57 with DAST did not proceed with the usual inversion of configuration to give derivatives containing fluorine on the α -side of the sugar ring. Instead retention of configuration was observed, e.g., fluoro substi-



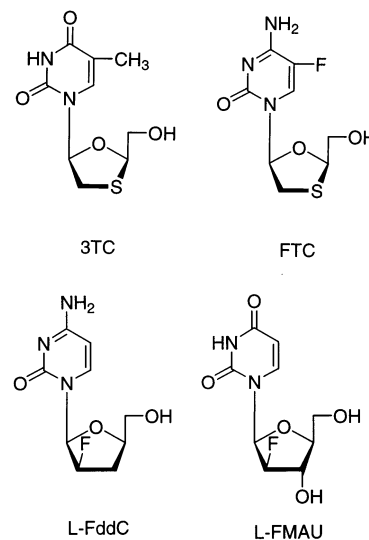
Scheme 10.

tution occurred from the β -face to give **58** or **59** (Scheme 11). The authors explain that participation of the 4'-thiofuranose sulfur was responsible for a double-inversion mechanism that resulted in retention of configuration.

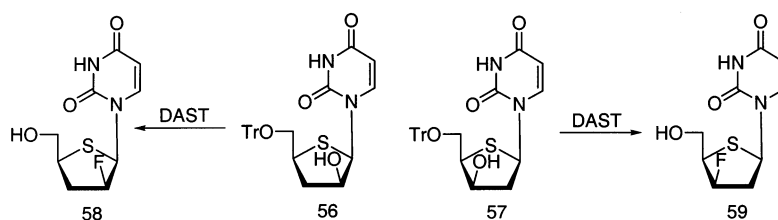
Interestingly, attempted fluorination of 3'-deoxy-4'-thiouridine protected with a MEM group at N-3 (**60**) gave the 3'-deoxy-2'-fluoro derivative **62** with retention of configuration (Scheme 12). Formation of the very reactive N-3-MEM-O², 2'-anhydronucleoside intermediate **61** that reacted with fluorine ion explains retention of the configuration [40].

Although, the synthesis and chemotherapeutic activity of 1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-pyrimidines such as FMAU, FIAU, FIAC stimulated the synthesis of a variety of nucleoside analogs containing a fluorine atom at the C-2'-*arabino* configuration, the clinical application of lead compounds ended up with disappointment and failure. Phase I trials of FMAU as an antileukemic agent were terminated by severe neurologic toxicity [41]. Fialuridine (FIAU) exhibited delayed toxicities due to the interference of mitochondrial function resulting in lactic acidosis and hepatic failure [42].

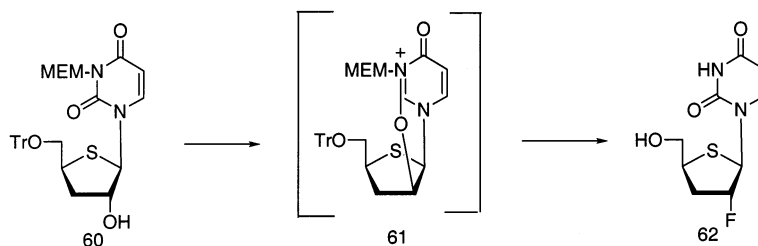
Recently, however, a number of nucleosides with the unnatural L-configuration have been reported as potent agents against HIV, HBV, and certain cancers. These include 3TC, FTC, L-FddC, and L-FMAU.



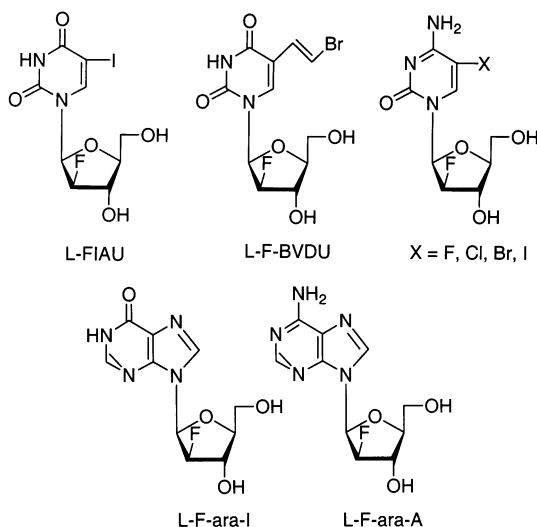
Interestingly, these L-nucleosides exhibit potent biological activity, while showing a much lower toxicity than their D-counterparts. Chu and co-workers [43] at the University of Georgia prepared the 2-fluoro L-arabinosyl bromide from L-ribose according to the method of Tann [19] that was used for the synthesis of D-FMAU. The starting L-ribose derivative was obtained first from L-xylose and then more efficiently from L-arabinose [44]. The L-glycosyl bromide was coupled with a number of nucleobases to give, among others, the L-nucleosides depicted below.



Scheme 11.

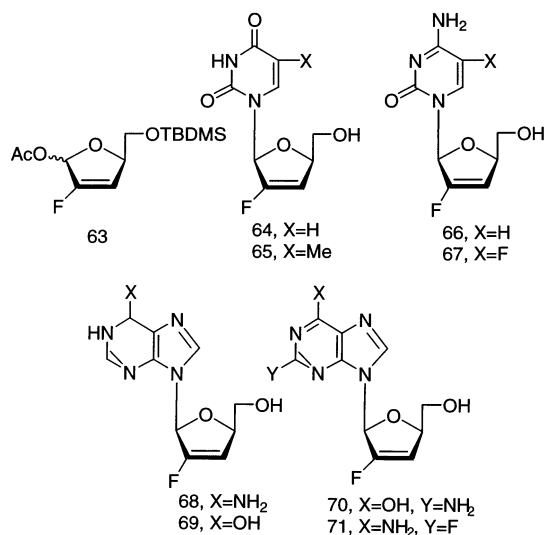


Scheme 12.



L-FMAU was found to be the most active as an anti-HBV agent among the synthesized compounds. It did not show any toxicity profiles that caused withdrawal of the D-counterpart from clinical studies. L-FMAU is currently considered as a clinical candidate for treatment of chronic HBV infection.

In addition to pyrimidine nucleosides, the group of Chu [45] has prepared a number of purine F-*ara*-L-nucleosides and found that L-F-*ara*-A and L-F-*ara*-I exhibit good anti-HBV activity without significant toxicity. Also, the synthesis of 2'-fluoro-2',3'-unsaturated L-nucleosides has been explored [46]. This was accomplished by condensation of the key 2'-vinyl fluoride acetate **63** with the appropriate heterocycles. The most potent compound in this series was an L-analog of 5-fluorocytidine derivative **67**.



During all these years application of 2'-fluorinated nucleosides has not been limited to their use as potential chemotherapeutics. Repeatedly, these compounds have been used for incorporation into oligonucleotides, and such modifications have been examined in terms of specific interactions with DNA, RNA and improved affinity to nucleic acid components. For example, it was demonstrated that modification of the Dickerson dodecamer with FMAU or FAC dramatically increases catalytic efficiency of EcoR1 endonuclease relative to the unmodified sequence [47] and that the presence of FMAU has a large stabilizing effect on the duplex [48,49].

Cook and co-workers [50] at Isis Pharmaceuticals incorporated 2'-deoxy-2'-fluoro-adenosine, -guanosine, -uridine, and -cytidine making 'uniformly' modified phosphodiester or phosphorothioate oligonucleotides. These compounds hybridized with RNA forming the duplex, which fully adopts the A-form conformation. It was also found that the modified phosphorothioate oligos were highly nuclease resistant and retained exceptional binding affinity to the RNA targets. An RNA hybrid duplex with uniformly 2'-fluoro-modified oligos did not support RNase H activity.

On the other hand it was found by Damha et al. [51] that 2'-deoxy-2'-fluoro-β-D-*arabino* nucleic acids (2'-F-ANA) showed an excellent binding affinity to RNA, and 2'-F-ANA/RNA duplexes are recognized and degraded by RNase H as well as DNA/RNA hybrids. Among over 60 types of modified oligos, none of them except phosphorothioates, boranophosphates, and now 2'-F-ANAs could trigger the activity of RNase H.

Recently, interesting studies that make use of 2'-deoxy-2'-fluorouridine and its 2'-fluoro-*arabino* isomer have been published by Stivers et al. [52,53] These authors took advantage of great stability of the glycosylic bond in 2'-fluorinated nucleosides to solve the mechanism of action of *Escherichia coli* uracil DNA glycosylase, which flips uracil from the DNA helix and then cleaves it in order to repair DNA. Since the 2'-fluorinated uridines incorporated into DNA could be flipped but not cleaved, the kinetic mechanism of damage site recognition has been conveniently observed.

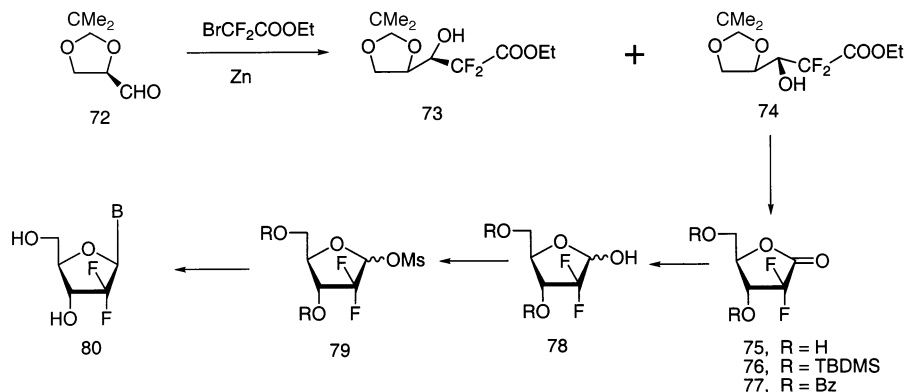
3. Nucleosides doubly fluorinated at C-2'

Gemcitabine (2'-deoxy-2',2'-difluorocytidine) has been recently approved by the FDA for treatment of pancreatic cancer, and its hydrochloride (Gemzar) is now marketed in many countries. Gemcitabine showed a complicated mechanism of action inhibiting the synthesis of DNA and RNA as well as inhibiting ribonucleotide reductase [54]. 2'-Deoxy-2',2'-difluoroguanosine was reported to exhibit a similar activity [55].

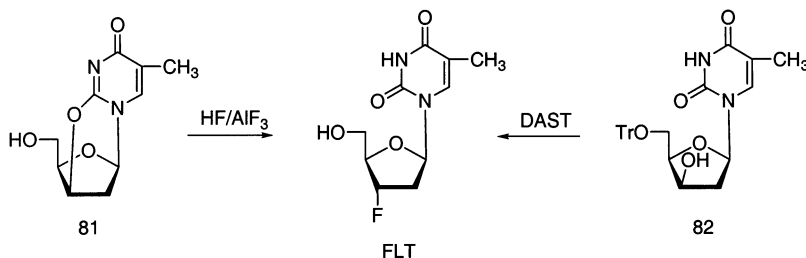
Gemcitabine was synthesized by Hertel and co-workers at Lilly Research Laboratories [7] by condensation of a silylated cytosine with 2-deoxy-2,2-difluoro-D-ribofuranose, prepared in a stereocontrolled manner (Scheme 13). Thus, (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**72**) was coupled with bromodifluoroacetate under Reformatskii conditions to give a 3:1 mixture of diastereoisomers **73** and **74**. These compounds were separated on a silica gel column, and the major isomer **74** was hydrolyzed with Dowex-50W (H⁺) to give cyclized lactone **75**. The lactone was protected with *tert*-butyldimethylsilyl (TBDMS) groups to give **76** and then reduced to **78**. Mesylation

of **78** (R = TBDMS) afforded **79**, a starting material for coupling with silylated cytosine and other nucleobases. Condensation of **79** with cytosine in the presence of trimethylsilyl triflate gave a 40% yield of the α anomer and only 10% of the desired β anomer **80**. Later this procedure was improved [56] by selecting the benzoyl instead of the TBDMS group as the protection for hydroxyl groups. With this modification selective crystallization of the lactone **77** from a distereomeric mixture containing the lactone obtained from **73** was possible. In addition, condensation of **79** (R = Bz) with the base afforded a 1:1 mixture of α,β anomers (instead of 4:1 as in case of TBDMS protection) from which the desired gemcitabine **80** could be separated by crystallization.

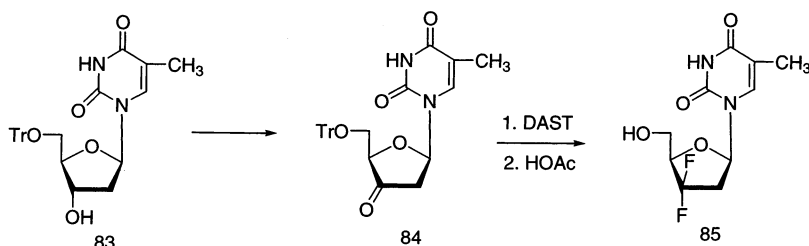
Recently, a number of pyrimidine and purine L-nucleosides containing –CF₂– at the 2'-position have been synthesized and studied [57,58]. These nucleosides were designed to take advantage of good activity and low toxicity of other L-nucleosides with potent antiviral properties such as (–)-FTC or L-FMAU. Unfortunately none of these new L-difluoro nucleosides showed expected biological activities.



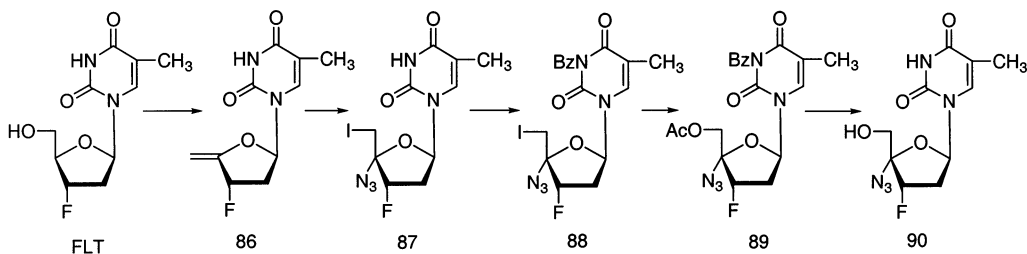
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

4. 3'-Deoxy-3'-fluoro nucleosides

FLT was originally synthesized in 1971 by Langen and co-workers [6] by opening the 2,3'-anhydro linkage of 2,3'-anhydrothymidine (**81**, Scheme 14) with HF/AlF_3 . Later, Herdewijn's group [59] synthesized FLT by treatment of 1-(2-deoxy-5-*O*-trityl- β -D-threo-pentofuranosyl)thymine (**82**) with DAST. In 1988 it was discovered that FLT was very active against HIV [60,61], and the compound was proved [62] to be even more potent as an inhibitor of HIV replication than AZT. The corresponding deoxyuridine, deoxycytidine, deoxyadenosine, and deoxyguanosine (FLG) derivatives have been prepared and found to be less active than FLT [59,62,63]. FLG has been shown to inhibit human and duck hepatitis B virus [64]. All these compounds are potential inhibitors of viral reverse transcriptase (RT) and chain terminators. Unfortunately they were found to be highly cytotoxic. A similar synthesis of 2',3'-dideoxy-3'-fluoro-5-fluorouridine by opening of the 2,3'-anhydro linkage of the 2'-deoxy-5-fluorouridine derivative has been reported [65]. Since 2'-deoxy-5-fluorouridine, a potent cytotoxic agent, is cleaved in the cell extensively by thymidine phosphorylase, to give 5-fluorouracil, itself a potent cytotoxic agent but with a different mode of action than that of 5-fluorouridine, the idea was to synthesize a 2'-deoxy-5-

fluorouridine derivative resistant to the action of thymidine phosphorylase. Indeed, replacement of the 3'-OH group of 2'-deoxy-5-fluorouridine with a fluorine atom afforded a desired compound with a much more stable glycosidic linkage; however, its activity was found to be inferior to that of the parent drug.

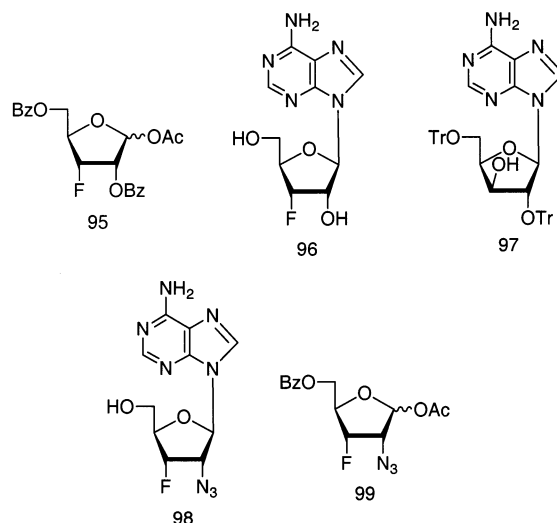
A simple synthesis of 3'-deoxy-3',3'-difluorothymidine (**85**) has been reported by Bergstrom et al. [66] (Scheme 15). Although nucleoside **85** resembles conformationally and sterically other thymidine analogs (which are active against HIV), compound **85** was found to be inactive.

The success of AZT inspired Prisbe and co-workers at Synthex to synthesize 4'-azidothymidine [67]. Although this compound retains 3'-hydroxyl group, it acts as a chain terminator and RT inhibitor. Since FLT is one of the most potent inhibitors of HIV known, it was interesting to learn if the presence of a fluorine at C-3' of 4'-azido-T would lead to better activity. 5'-Iodination of FLT, followed by methoxide-induced elimination, afforded 4',5'-unsaturated derivative **86** (Scheme 16), which upon IN_3 addition gave **87**. Oxidative displacement of 5'-iodide failed. However, protection of N-3 with a benzoyl group, followed by treatment of **88** with tetramethylammonium acetate in N^1,N^3 -dimethyltetrahydropyrimidone, gave the desired 5'-*O*-acetyl nucleoside **89**. Deprotec-

tion with ammonium hydroxide furnished the desired 4'-azido-3'-deoxy-3'-fluorothymidine (**90**). Contrary to expectation, **90** was much less active than AZT, 4'-azido-T, or FLT [68].

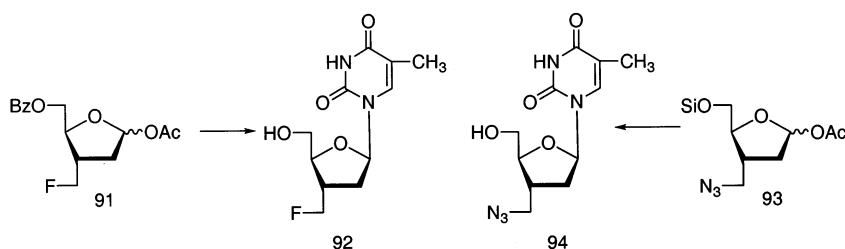
The activity of FLT and AZT inspired Lin et al. [69] to synthesize 3'-deoxy-3'-C-branched-chain substituted nucleosides. Condensation of the sugar precursors **91** and **93** (Scheme 17) with a silylated thymine afforded **92** and **94**, the corresponding analogs of FLT and AZT, respectively. None of these compounds demonstrated significant antiviral activity.

Synthesis of a number of nucleosides containing 3'-deoxy-3'-fluoro- and 2'-azido-2',3'-dideoxy-3'-fluoro-D-ribofuranoside has been reported by Mikhailopulo et al. [70]. These compounds were prepared by coupling an appropriate sugar **95** or **99** with heterocyclic bases (to give among others **96** and **98**) and were evaluated as antiviral or anticancer agents. 3'-Deoxy-3'-fluoroadenosine (**96**) was found to be the most active, both as a cytotoxic compound and as an antiviral. Morizawa et al. [71] reported the first synthesis of **96** by a glycosylation method, and later Van Aershot et al. [72,73] prepared **96** by DAST treatment of the 2',5'-di-O-tritylated adenine nucleoside containing the 3'-hydroxyl group in the xylo configuration (**97**), followed by detritylation.

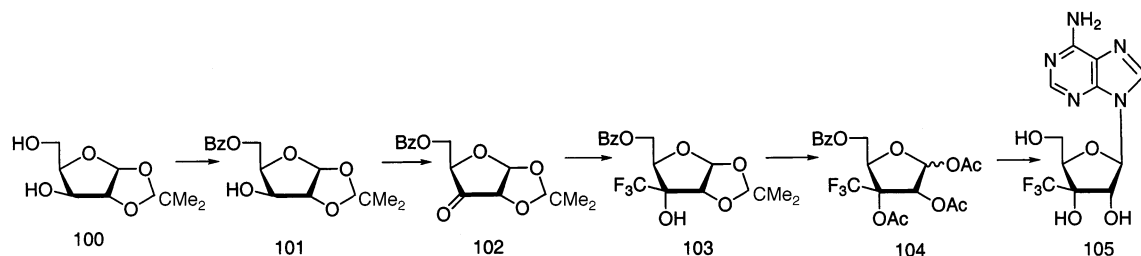


Since it was discovered that 2',5'-oligo-adenylates (2-5A) play a key role in the antiviral action of interferon [74], it was interesting to study the role of the 3'-hydroxyl group of 2-5A in binding to 2-5A-dependent endoribonuclease (RNase L). In this connection, 2-5A oligomers containing **96** and its xylo isomer were prepared, and it was found that their susceptibility to degradation is dependent upon the conformation of a modified 2-5A [75].

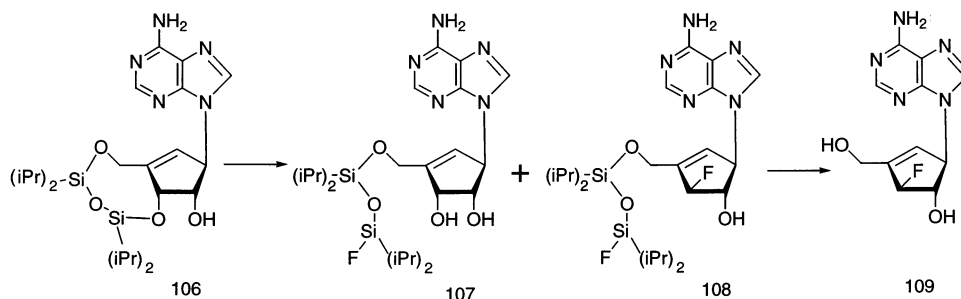
Since F and CF₃ showed comparatively close inductive effects, it was interesting to prepare nucleosides containing the 3-C-trifluoromethyl-β-D-ribofuranose moiety and evaluate their biological activity. Thus, 1,2-O-isopropylidene-α-D-xylofuranose (**100**, Scheme



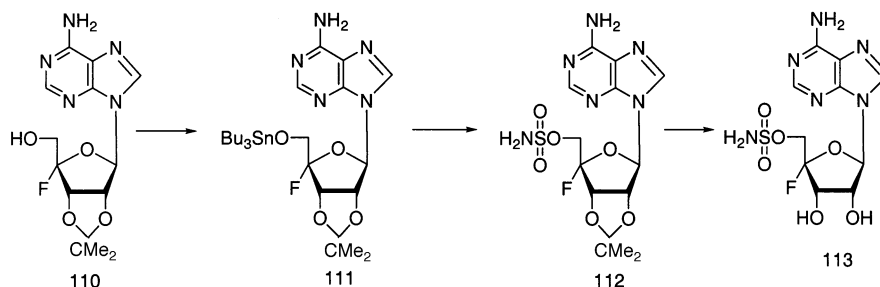
Scheme 17.



Scheme 18.



Scheme 19.



Scheme 20.

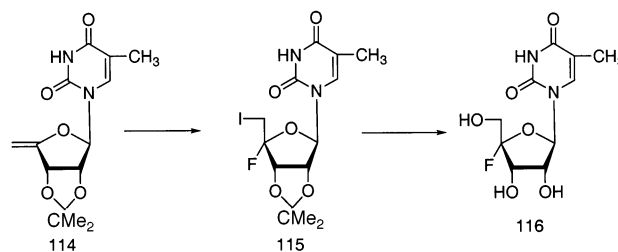
18) was selectively benzoylated to give compound **101**, which was then oxidized to the 3-keto derivative **102**. Reaction of **102** with CF_3SiMe_3 in the presence of tetrabutylammonium fluoride led to desired trifluoromethyl derivative **103** as the only isomer. This compound, upon hydrolysis with CF_3COOH , followed by acetylation, afforded starting material **104** for Vorbrüggen condensation with the appropriate silylated base. 9-(3-C-Trifluoromethyl- β -D-ribofuranosyl)-thymine, -uracil, and -adenine were prepared, and interestingly adenine nucleoside **105** was found to be active against HSV-1 [76].

Carbocyclic nucleosides containing fluorine at C-3' have attracted some attention. For example, neplanocin A has been efficiently converted in three steps into its 3'-deoxy-3'-fluoro-*xylo*-analog. Again the tetraisopropyl-disiloxanyl protecting group proved to be useful for treatment with DAST (see Scheme 8). Slow addition of 3',5'-tetraisopropylidisiloxanylnepanocin A (**106**, Scheme 19) to a mixture of DAST–pyridine in CH_2Cl_2 at 0°C gave the 3'-fluoro derivative **108** in 65% yield, with only a small amount (5%) of the diol **107**. Deprotection of **108** afforded the 3'-deoxy-3'-fluoro-*xylo*-neplanocin A (**109**) in good yield [77].

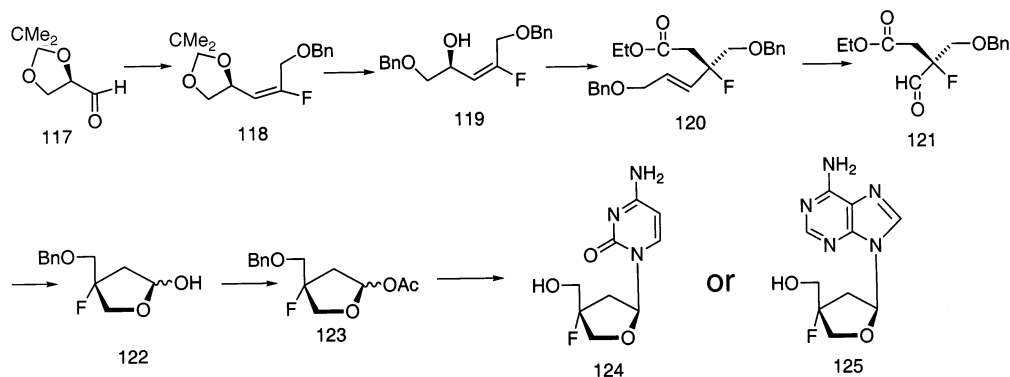
5. Nucleosides fluorinated at C-4'

Nucleocidin (**113**), an antitrypanosomal antibiotic, was first isolated [78] in 1957. The structure of nucleocidin (was established by Morton et al. [79], and the compound was synthesized by Moffat and co-workers [80] (Scheme 20). 4'-Fluoro-2',3'-O-isopropylideneadenosine (**110**) was converted into 5'-O-tributylstannylene derivative **111**, which was treated directly with sulfamoyl chloride to give **112**. Deprotection of **112** afforded nucleocidin in good yield.

The reaction of several 4',5'-dehydronucleosides with iodine and iodine fluoride were studied by Verheyden and Moffat [81]. They found, for example, that treatment of uridine derivative **114** with iodine fluoride afforded 5'-deoxy-4'-fluoro-5'-iodo-2',3'-O-isopropylidene-uridine (**115**), which was then converted to 4'-fluoro-5'-deoxy-2',3'-O-isopropylidene-uridine (**116**).



Scheme 21.



Scheme 22.

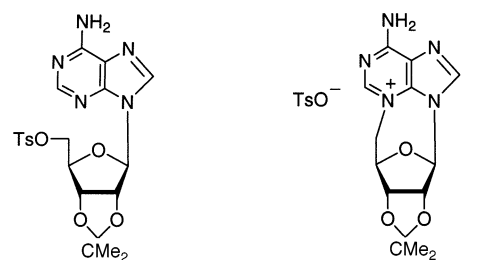
deneuridine (**115**). The iodo function of **115** was then converted into various 5'-substituted 4'-fluorouridines, including 4'-fluorouridine (Scheme 21, **116**).

Recently, Chu and co-workers published [82] an interesting work on an asymmetric fluorination of the tertiary carbon of nucleosides. They used the [3,3]-sigmatropic Claisen rearrangement reaction to introduce the required tert-fluorinated carbon. Thus, 2,3-*O*-isopropylidene-D-glyceraldehyde (Scheme 22, **117**) reacted with triethylphosphonoacetate to give (*E*)- α,β -unsaturated fluoro ethyl ester **118**. This compound was deisopropylidenated and selectively (via dibutyl tin oxide) benzylated to give **119**, which was subjected to the Claisen rearrangement conditions to give tertiary fluoro ethyl ester **120**. Ozonization afforded aldehyde **121**, which was reduced with DIBAL-H to give lactol **122**. Further conversion of **122** into a key derivative **123** and condensation with silylated *N*⁴-benzoylcytosine or 6-chloropurine under Vorbrüggen conditions afforded an anomeric mixture of the corresponding nucleosides. The desired β anomers were separated and converted into 3'-fluoro-apionucleosides of cytosine **124** and adenine **125**, respectively. In this iso-nucleoside numbering system, the fluorine atom is in the 3'-position; however, it can be considered as an equivalent to the 4'-position of regular nucleosides.

In a similar manner a number of 3'-fluoro-apionucleosides in the L series have been prepared [83], and their biological activity is now under evaluation.

6. Nucleosides containing fluorine(s) at C-5'

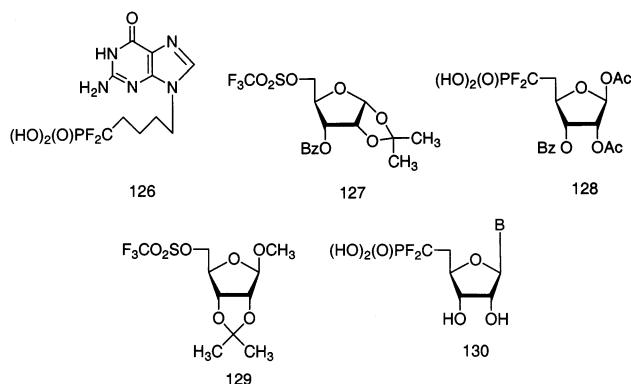
The last group of compounds to be discussed contain a fluorine atom at C-5'. Some of them were synthesized in order to eliminate the possibility of phosphorylation of these nucleosides to the corresponding mono-, di-, and triphosphates in cells. It was then investigated if these 5'-deoxy-5'-fluoro compounds would show any activity, which would not be dependent on their conversion into the corresponding nucleotides. These compounds were prepared either by condensation of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-fluoro- α,β -D-ribofuranose with an appropriate nucleobase [84] or by direct fluorination of nucleosides at C-5', which is not a difficult task. A variety of methods could be applied such as a nucleophilic displacement of mesylates (tosylates) with KF or tetrabutylammonium fluoride as well as direct displacement with DAST (see Herdewijn's review [3]). However, it is reasonable to expect that such 5'-fluorination of adenosine protected with the 2',3'-*O*-isopropylidene group should not proceed well. It is known that acetonide protection brings N-3 of the adenine base and C-5' of the sugar moiety to a close proximity. Thus, an intro-

5'-*O*-tosyl-2',3'-*O*-isopropylideneadenosine

3,5'-cyclo-derivative

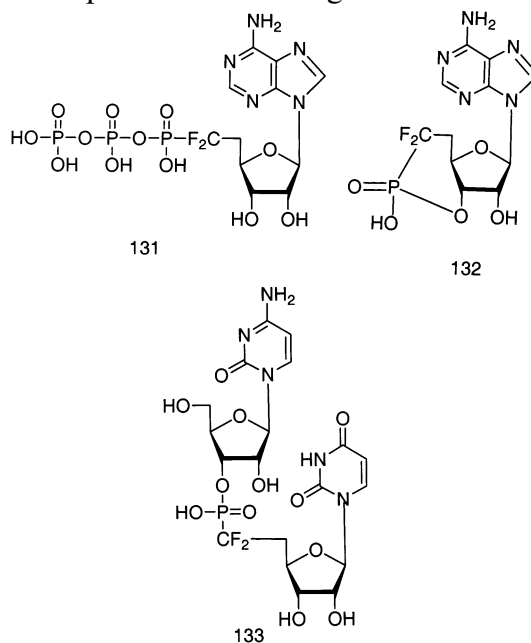
duction of a good leaving group at C-5' leads to the intramolecular displacement by N-3 resulting in the formation of the corresponding 3,5'-cyclonucleoside [85]. This can be avoided either by acylation of the N-6 of adenine or by protection of the 2'- and 3'-hydroxyls with groups that do not cause such conformational rigidity as acetonide protection.

More challenging was a replacement of the oxygen of the 5'-hydroxyl function with anisopolar and isosteric $-\text{CF}_2-$ group in order to synthesize difluoromethylene phosphonate nucleotides, e.g., to make the $-\text{CH}_2-\text{CF}_2-\text{P}-$ linkage a good mimic of the $-\text{CH}_2-\text{O}-\text{P}-$ moiety of natural nucleotides. Groups such as $-\text{CHF}-$ and $-\text{CF}_2-$ has been incorporated in place of 3'- or 5'-oxygens of nucleosides or as replacement for bridging oxygens in the corresponding di- and triphosphates. For example, the synthesis of 9-(5,5-difluoro-5-phosphonopentyl)guanine (**126**) was reported. This compound was designed as a potent multisubstrate inhibitor of purine nucleoside phosphorylase and indeed showed an excellent inhibitory activity [86].



A general method for synthesis of 5'-difluoromethylene phosphonates was described by Matulic-Adamic et al. [87]. They found that a direct displacement of 5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneuridine with $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$ or reaction of the 5'-aldehyde function of the uridine derivative with the same reagent did not work. However, an efficient synthesis of the sugar precursor **128**, followed by condensation with nucleobases, afforded the desired phosphonates. Thus, treatment of the triflate derivative **127** with $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$, followed by acetolysis under mild acidic conditions, gave the key sugar derivative **128**. It is

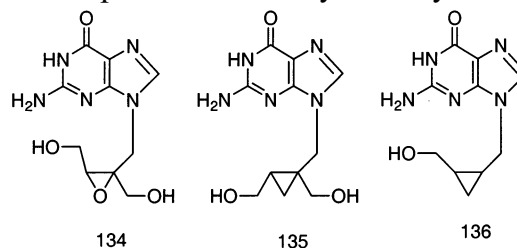
interesting to note that a similar displacement of the triflate group of the methyl furanoside **129** did not lead to a similar product due to intramolecular reaction of the 1-methoxy group with the 5-triflate function of **129**. Finally, condensation of **128** with silylated nucleobases afforded the corresponding phosphonates **130** ($\text{B} = \text{U}, \text{C}, \text{and A}$) in moderate yield. The rationale herein was to use these new compounds as starting



materials for synthesis of phosphonate analogs of biologically important molecules. Indeed, analogs of ATP and cAMP (**131** and **132**), as well as oligonucleotides containing non-hydrolyzable P–C bonds such as **133**, were successfully prepared [87], and their biological properties were evaluated.

7. Miscellaneous studies

It has been demonstrated in recent years that even such radically modified nucleoside analogs as the oxirane analog **134** and its more stable cyclopropane analogs **135** and **136** showed a potent inhibitory activity

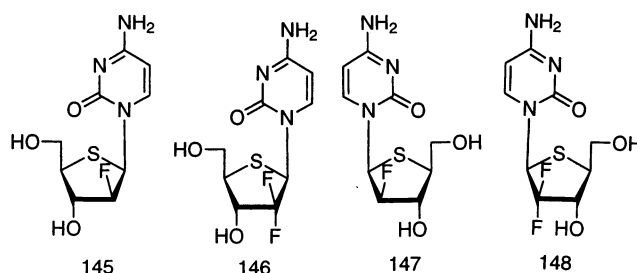


against herpesviruses [88,89], which inspired Qiu and Zemlicka [90] to synthesize new nucleoside analogs containing the difluorocyclopropane moiety as potential antiviral and/or antitumor agents. The difluorocyclopropane moiety is a close steric and electronic mimic of an oxirane ring, and in addition, gemcitabine and other nucleosides described in this review that contain the geminal difluoromethylene moiety showed an interesting antitumor or antiviral activity. *cis*-2-Butene-1,4-diol (**137**, Scheme 23) was monobenzylated and then converted into benzoate **139**. Addition of difluorocarbene afforded **140**, which after debenzoylation, followed by bromination, afforded a key derivative **142** for condensation with nucleobases. Thus, reaction of appropriate bases with **142** using K_2CO_3 in DMF gave, after deprotection, the desired nucleosides **143** in good yield (B = A, G, C, T).

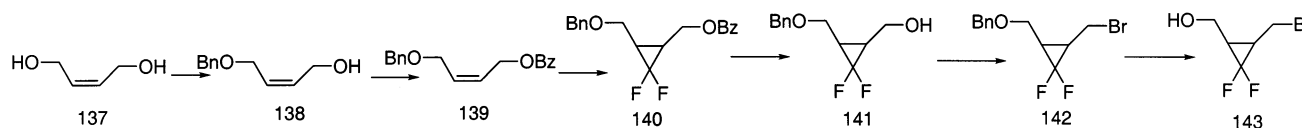
It is worthwhile to mention the recent publication by Townsend et al. [91] which shows that an idea of the introduction of a fluorine atom at C-2' in the arabino configuration in order to increase the stability and antiviral activity of nucleosides is still an attractive alternative. In the advanced stage of development at Glaxo Wellcome is now 2,5,6-trichloro-1- β -D-ribofuranosylbenzimidazole (TCRB) discovered in Townsend's laboratory as an anti-human-cytomegalovirus (HCMV) agent. This compound did not inhibit DNA, RNA, or protein synthesis, but acted by a unique mechanism, which involves inhibition

of viral DNA processing and virus assembly. However, the glycosidic bond of this nucleoside is not very stable, and accumulation of the aglycone in blood was observed. Therefore, the synthesis of F-*ara*-TCRB (Scheme 24) was accomplished by both a direct method of fluorination [33,35,36] of the corresponding 3',5'-ditrityl derivative of TCRB **144**, as well as by condensation of a sugar derivative **15** [14,17,19] with 2,5,6-trichlorobenzimidazole. Indeed, the compound was found to be stable, and the activity was retained.

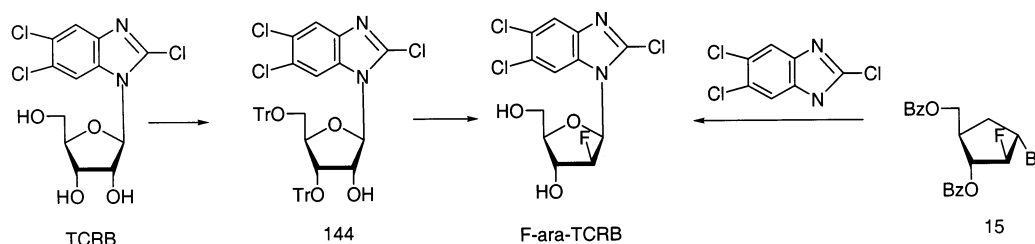
4'-Thionucleosides show antiviral and anticancer activities [92,93]. Several new 2'-modified 2'-deoxy-4'-thiocytidines, including 2'-fluoro **145** and 2',2'-difluoro derivatives **146**, have been prepared by Yoshimura et al. [94,95].



Among them the 2'-fluoro analog was found to have potent antineoplastic properties in vitro. Recently, Jeong et al. [96,97] synthesized the corresponding compounds in L-series, **147** and **148** expecting to combine the properties of 4'-thio- and L-nucleosides. None of these compounds, however, showed antitumor activity.



Scheme 23.



Scheme 24.

Acknowledgements

I wish to thank Prof. David C. Baker for his help in search of the literature and helpful comments.

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