Synthesis of 2′-β-fluoro-substituted nucleosides by a direct approach

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Abstract

Recent research activities directed toward the synthesis of 2′-β-fluoro-substituted nucleosides by nucleophilic displacement of an activated 2′-hydroxy group of preformed ribonucleosides are reviewed. In the pyrimidine-*C*-nucleoside area, direct fluorination of a 4,5′-anhydro-*C*-nucleoside triflate with TASF afforded the desired 2′-β-fluoro-1-methyl-ψ-uridine (*C*-FMAU). A similar strategy in regular pyrimidine series by using the corresponding 2,5′-*O*-, 2,3′-*O*- and 5′,6-anhydro nucleoside derivatives did not give the desired fluoro-containing products. An interesting triflyl migration was discovered when a triflate nucleoside was treated with LiCl in HMPA. The carbocyclic analog of the adenosine containing a fluorine in the 2′-β configuration was prepared from $O^{5'}$,$O^{3'}$,N^{6}-tribenzoylaristeromycin in reaction with DAST. A similar treatment of purine nucleosides led to decomposition. When, however, inosine, adenosine and guanosine were tritylated at the 3′,5′ positions of the sugar moiety and suitably protected at the base, the corresponding 2′-β-fluoro-substituted *arabino*-nucleosides were obtained by treatment with DAST in moderate to good yields. Deprotection afforded the desired F-*ara*-H, F-*ara*-A and F-*ara*-G. The role of the bulky trityl groups at the 3′,5′ positions of the sugar and the effect of C-3′-*endo* to C-2′-*endo* conformational shift on the reaction course of 2′-hydroxyl group with DAST is discussed.

Introduction

The syntheses of numerous pyrimidine [1] and purine [2] nucleosides containing fluorine in the C-2′-β (*arabino*) configuration have been reported in recent years from our laboratory. These 2′-β-fluoro analogs exhibit dramatically different biological activity from their parent 2′-deoxynucleosides. Several uracil and cytosine nucleosides bearing 2′-β-fluoro substituents have shown antitumor [3] and/or antiviral [4] activity. Most notable among them are 2′-fluoro-5-iodo-*ara*-C (FIAC), 2′-fluoro-5-methyl-*ara*-U (FMAU) and 2′-fluoro-5-ethyl-*ara*-U (FEAU, Fig. 1). These nucleosides are potent agents against many DNA viruses [5]. Some 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purines reported by us [2] and others [6] are also biologically active compounds. For example, 2′-fluoro-*ara*-A (F-*ara*-A) is cytotoxic [2],

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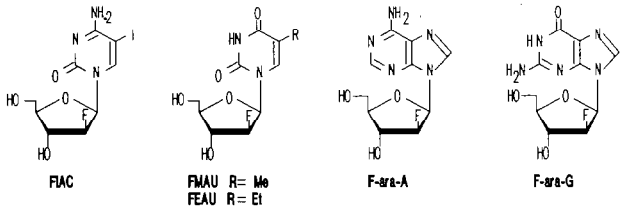


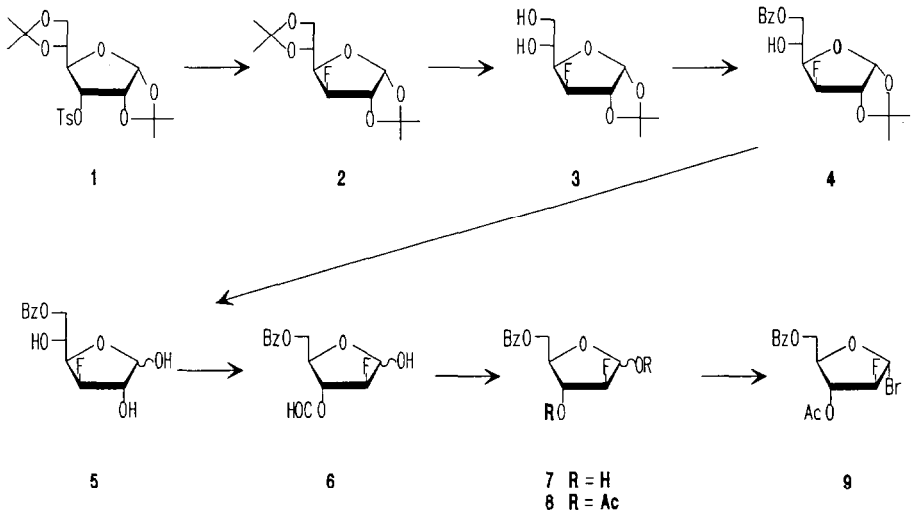
Fig. 1.

2′-fluoro-*ara*-G (F-*ara*-G, Fig. 1) was found to be selectively toxic to T-cells [7, 8], and hypoxantine nucleoside (F-*ara*-H) showed potent inhibitory activity against the growth of *Leischmania tropica* promastigotes [9]. Recently, a number of reports have been published on the synthesis and anti-HIV activity of 2′-β-fluoro-2′,3′-dideoxy-purine [10] and -pyrimidine [11] nucleosides. Such fluorine substitution has improved metabolic and chemical stability of these nucleosides over the parent antiretroviral 2′,3′-dideoxy nucleosides [12].

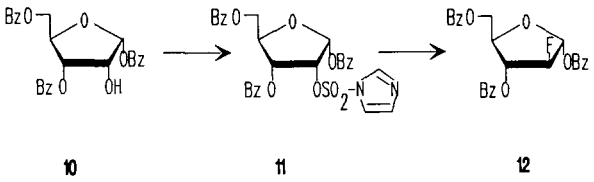
Although there is a growing interest in the preparation of 2′-β-fluoro-substituted nucleosides, the methods of their synthesis are neither simple nor straightforward. To date, all of these nucleosides have been synthesized by condensation of an appropriate 2-fluoro sugar derivative with a nucleobase. Preparation of the corresponding 2-fluoro sugar derivatives is a difficult task. The fluoride ion is a poor nucleophile but a strong base, which frequently catalyzes elimination reactions. It is also known that nucleophilic displacement of a leaving group at C-2 of pyranosides is generally difficult, but such a reaction is even less common in furanosides [13]. It has been suggested that nucleophilic displacement at C-2 creates an unfavorable alignment of dipoles in the transition state particularly when the substituent at C-1 is in the α-configuration [14].

In order to overcome such obstacles Reichman *et al.* [15] developed an indirect synthetic method via introduction of fluorine to the C-3 position of the furanoid ring (Scheme 1). Nucleophilic displacement of the 3-*O*-tosyl group of di-*O*-isopropylidene α-D-allofuranose (**1**) gave the 3-fluoro *gluco* derivative **2**. After selective mono-de-*O*-isoproylidenation and benzoylation on the primary hydroxyl group, compound **4** was obtained in a crystalline form. Removal of the 1,2-*O*-isopropylidene group of **4** under stringent conditions gave **5** in which there is one vicinal diol system. The crucial step in this approach was the conversion of **5** into the desired 2-deoxy-2-fluoro-3-*O*-formyl-D-arabinofuranose (**6**) via periodate oxidation. Removal of the formyl group and further conversion of the product **7** into the corresponding diacetate **8**, followed by hydrogen bromide treatment, afforded the desired 2-fluoro-2-deoxy-3-*O*-acetyl-5-*O*-benzoyl-D-arabinofuranosyl bromide (**9**).

This practical, seven-step procedure, was improved 10 years later by Tann *et al.* [16], who found that the 2-*O*-imidazoylsulfonate group of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**11**, Scheme 2) can be displaced with fluoride



Scheme 1.



Scheme 2.

ion under treatment with KHF_2 to give 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (**12**) in 50–60% yield.

Pyrimidine-*C*-nucleosides

The 2-fluoro-D-arabinose derivative is condensed with a nucleobase to obtain the desired 2′-fluoro-*arabino* nucleosides. Treatment of a pyrimidine nucleoside containing a 2′-imidazoylsulfonate group, or any other good leaving group such as a triflate group, with nucleophilic reagents, however, does not lead to the direct displacement. All attempts so far to introduce a substituent at the C-2′-β (*arabino*) position in pyrimidine nucleosides by nucleophilic reactions have failed, due to neighboring-group participation of the carbonyl function of the aglycon*. It is well recognized that the *intra*molecular attack of the 2-carbonyl group of the nucleobase on C-2′ of the sugar moiety supercedes the *inter*molecular nucleophilic substitution (Fig. 2). Thus, the rather efficient and usually stereoselective condensation of appropriate sugar halide with pyrimidine base remains the method of choice in the synthesis of 2′-β-fluoro-substituted nucleosides.

*For a review of our work covering this subject, see ref. 17.

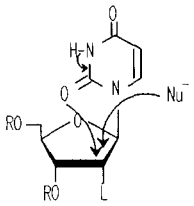
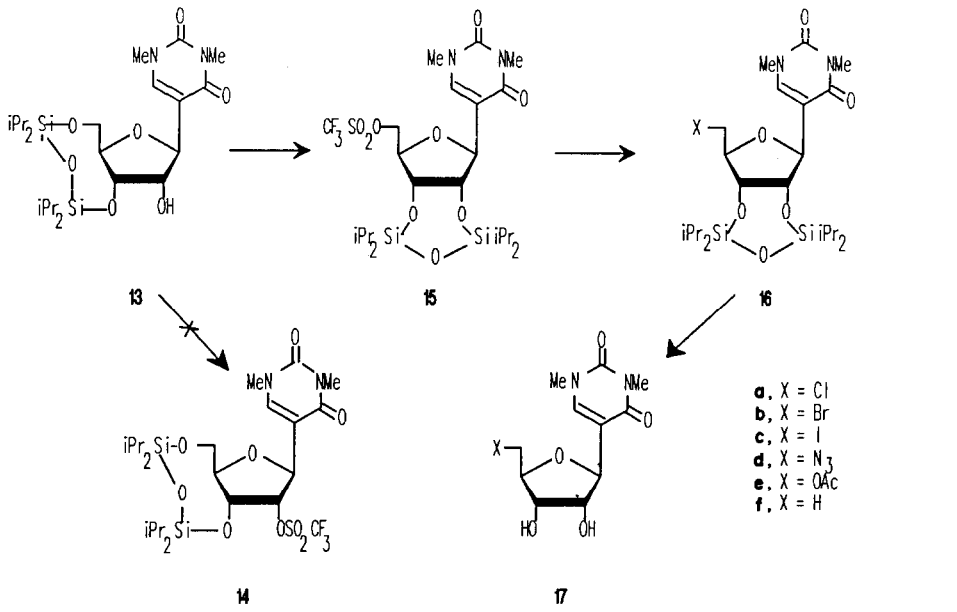


Fig. 2.

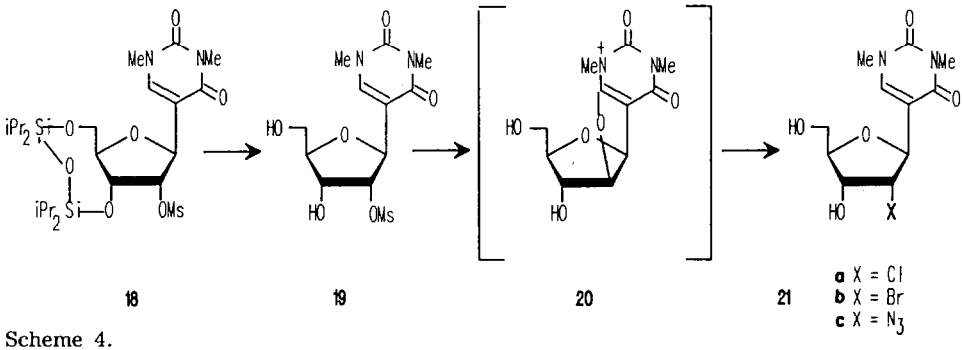
The interesting biological activity of many of these 2′-β-fluoro-substituted pyrimidine nucleosides prompted us to synthesize some of their *C*-nucleoside analogs. Such a synthesis seems to be rather challenging. The condensation procedure is not applicable in the *C*-nucleoside area. It requires an introduction of a three-carbon fragment at the anomeric position by C—C coupling [18], followed by chemical construction of the aglycon [19]. The coupling reaction or multi-step elongation and cyclization procedure would be inefficient due to the formation of isomers, a troublesome separation and the low yield of the desired products. A method of direct introduction of the 2′-β substituent into preformed pyrimidine-*C*-nucleosides is, therefore, of great interest. Although the direct introduction of the 2′-β-substituent is not possible in pyrimidine-*N*-nucleosides due to the close proximity of the 2-carbonyl oxygen of the aglycon to the C-2′ position of the sugar moiety, this may not be necessarily the case in the *C*-nucleoside series. First of all, the distance between the base and sugar in *C*-nucleosides is longer than the C—N glycosyl bond in regular nucleosides*. Second, the C—C glycosyl linkage should render a leaving group on C-2′ more susceptible to nucleophilic displacement than would the more electronegative C—N linkage in *N*-nucleosides or the C—O glycosyl bond in methyl 2-*O*-triflyl-D-ribofuranoside [21].

In order to examine if the direct introduction of a substituent into the C-2′ position of the ψ-uridine might be possible, we tried to synthesize 2′-*O*-triflyl-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-1,3-dimethyl-ψ-uridine (**14**, Scheme 3) for treatment with nucleophilic reagents. When the known 3′,5′-*O*-TiPDS-1,3-dimethyl-ψ-uridine [22] (**13**) was treated with triflic anhydride in CH_2Cl_2, a crystalline product was obtained in nearly *quantitative* yield, which to our surprise was not the desired 2′-triflate **14** but the isomeric 5′-triflate **15**. Nucleophilic displacement of the 5′-triflate group occurred smoothly when **15** was treated with LiCl, LiBr, KI, NaN_3 and NaOAc in HMPA, and the corresponding 5′-substituted *C*-nucleosides **17** were obtained in high yield after deprotection. Reduction of **17a** with Bu_3SnH afforded the 5′-deoxy derivative **17f**, giving a proof for 5′ substitution. It also established that rearrangement of the 3′,5′-cyclic disiloxanyl structure into the 2′,3′-cyclic isomer had occurred during triflation [23]. Similar rearrangement with

*The bond length of the glycosyl linkage in 1,3-dimethyl-2′-chloro-2′-deoxy-ψ-uridine is 1.53 Å [23] whereas that of 5-methyluridine is 1.481 Å [20].



Scheme 3.



Scheme 4.

3′,5′-*O*-TiPDS-protected *N*-nucleosides has been reported [24] to occur in low yield in DMF under acid catalysis.

Mesylation of **13** did not cause silyl rearrangement and the 2′-mesylate **18** was obtained in high yield (Scheme 4). After desilylation, the crystalline 2′-mesylate **19** was treated with LiCl, LiBr and NaN_3 to give the corresponding 2′-substituted 1,3-dimethyl-ψ-uridines **21**. X-Ray analysis of **21a** established that the 2′-Cl in **21a** is in the α- (*ribo*) configuration.

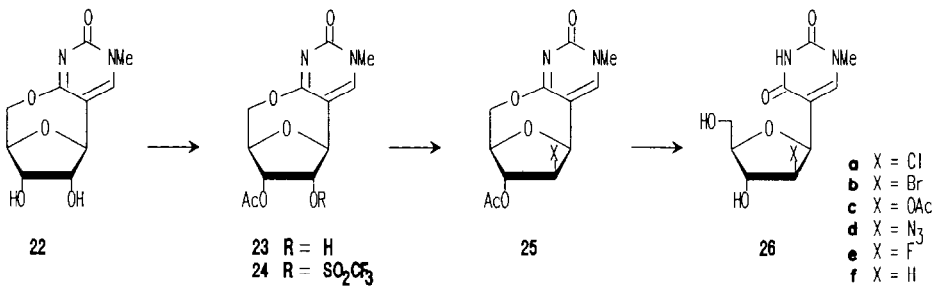
Thus, even in the *C*-nucleoside series, neighboring-group participation by the 4-carbonyl group prevented the intermolecular displacement of the 2′-*O*-mesyl function. The reaction proceeded via the 4,2′-anhydro intermediate **20** to give the 2′-α-substituted products.

It became clear from these studies that efficient prevention of the participation of the carbonyl function of the aglycon in the intramolecular reaction is necessary for successful displacement of the 2′-leaving group. If O-4 is tied up with C-5′ as in 4,5′-anhydro-1-methyl-ψ-uridine (**22**, Scheme 5), the carbonyl group cannot participate in the nucleophilic reaction which occurred at C-2′. Although anhydro linkages may be be susceptible to nucleophilic attack, it is interesting to investigate whether or not a good leaving group such as triflate would be more reactive than the anhydro bond towards nucleophilic displacement.

4,5′-Anhydro-1-methyl-ψ-uridine (**22**) was prepared from 1-methyl-ψ-uridine [25] by adaptation of the procedure developed by us for the synthesis of the ψ-citidine [26]. Monoacetylation of **22** via a dibutyltin derivative [27] afforded the 3′-*O*-acetyl nucleoside **23**, which was treated with triflyl chloride to give the desired 2′-triflate **24** in crystalline form in 66% yield. Displacement of the 2′-*O*-triflyl function occurred smoothly with LiCl, LiBr, NaOAc and NaN_3, and the corresponding 2′-β-substituted 1-methyl-ψ-uridines **26a–d** were obtained in 20–70% yield after hydrolysis of the anhydro linkage [28].

Similar treatment of the triflate nucleoside **24** with fluoride nucleophilic reagents such as Bu_4NF, Amberlyst A-26 (F^-), CsF or KF did not afford the fluoro-substituted product. For example, treatment of **24** with Amberlyst A-26 (F^-) in acetonitrile gave a major product, isolated in up to 30% yield, which was identical with 4,5′-anhydro-5-(2,3-di-*O*-acetyl-β-D-arabinofuranosyl)-1-methyl-uracil (**25c**) prepared by us via displacement of the triflate function of **24** with NaOAc. Apparently, the acetate ion was liberated from **24** during the reaction and then attacked the intact triflate at C-2′ giving rise to the 2′,3′-di-*O*-acetylarabino-*C*-nucleoside **25c**.

When tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) was used as the source of the fluoride ion, the desired 2′-β-fluoro-anhydro-*C*-nucleoside **25e** was obtained in 40% yield. Hydrolysis of the 4,5′-anhydro linkage with simultaneous removal of the 3′-*O*-acetyl group [Dowex 50 (H^+)] afforded *C*-FMAU (**26e**). The position of the substituents at C-2′ was firmly established by reduction of **26a** with Bu_3SnH to the known 2′-deoxy-1-methyl-ψ-uridine [28] (**26f**). The *arabino* configuration of these compounds was established



Scheme 5.

on the basis of their ^1H NMR spectra which are different from those of the known 2′-α- (*ribo*) -substituted *C*-nucleosides.

The inhibitory activity of *C*-FMAU against HSV-1 and HSV-2 was about 10-fold less than that of FMAU in tissue culture. *In vivo*, however, *C*-FMAU did not increase the survival of HSV-1 and HSV-2 infected mice.

Pyrimidine nucleosides

The successful synthesis of *C*-FMAU via direct introduction of the fluorine into the 2-β (*arabino*) position of 1-methyl-ψ-uridine prompted us to investigate the applicability of a similar approach in the *N*-nucleoside series. Two types of anhydro derivatives of uridine (A and B, Fig. 3) can be considered for the synthesis of the corresponding 2′-*O*-triflyl nucleosides for chemical manipulation at the 2′ position. Although 2,5′-anhydro-uridine (A) is known to be very susceptible to nucleophilic attack [29], the 2,3′-anhydro linkage of B is more stable [17]. The third possibility is offered by the structure of 6,5′-anhydro-1-β-D-ribofuranosyl barbituric acid [30] (C), which if successfully fluorinated at C-2′ may be converted into a uridine nucleoside by reduction of the 5,6-double bond followed by spontaneous opening of the 6,5′-anhydro linkage [31].

2,5′-Anhydro-2′-*O*-triflyl-3′-*O*-acetyluridine (**27**, Scheme 6) was prepared via selective 3′-acetylation of the 2′,3′-di-*O*-stannylene derivative of 2,5′-anhydro-uridine followed by triflylation. When **27** was treated with LiCl, LiBr,

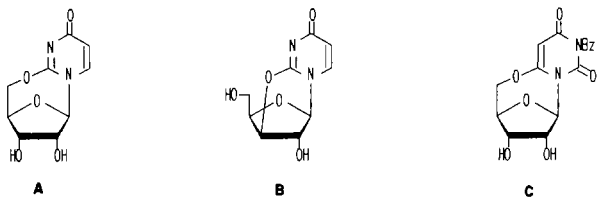
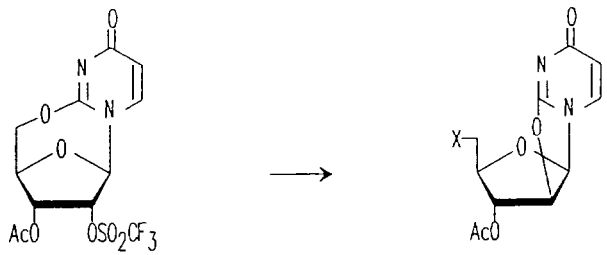


Fig. 3.



27

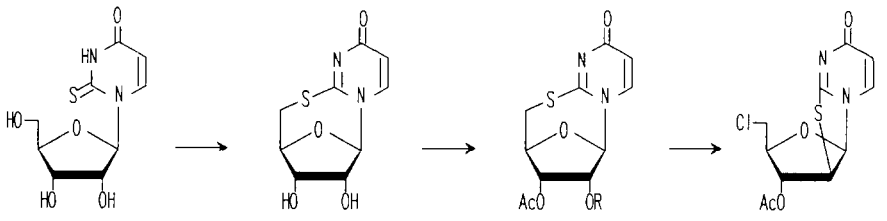
28a X = Cl
28b X = Br
28c X = N_3
28d X = OAc

Scheme 6.

NaN_3 or NaOAc, the only product obtained was the corresponding 5′-substituted 2,2′-anhydro-uridine **28a–d** [32]. Thus, intermolecular nucleophilic reaction occurred on the 5′ position, first liberating the 2-oxide which then attacked at C-2′ resulting in the formation of the 2,2′-anhydro nucleoside **28**.

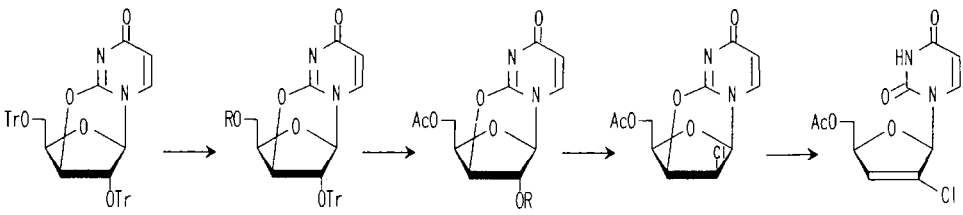
Since sulfur is larger in size but less electronegative than oxygen, the 2,5′-*S*-anhydro linkage might be more stable than the 2,5′-*O*-anhydro bond. It was found [33] that treatment of the 2,5′-anhydro-uridine with H_2S in pyridine afforded the 2-thiouridine **29** in 82% yield (Scheme 7). The 2-thiouridine was then converted to 2,5′-*S*-anhydro-2-thiouridine (**30**) by treatment with Ph_3P and diethyl azodicarboxylate. Dibutyltin oxide-catalyzed acetylation of **30** afforded 3′-*O*-acetyl-2,5′-*S*-anhydro-2-thiouridine (**31**). Upon treatment of **31** with triflyl chloride, a mixture of 2,2′-*S*-anhydro-3′-*O*-acetyl-5′-chloro-2-thiouridine (**32**, major product) and the 2′-*O*-triflyl nucleoside **31a** (minor component) was obtained. When the triflate **31a** was separated and treated with LiCl, nucleoside **32** was obtained in 50% yield. These results show that even C-5′ of the *S*-anhydro linkage of **31a** is more susceptible to nucleophilic attack than the triflate group on C-2′.

The use of the 2,3′-anhydro-uridine 2′-triflate **37** (Scheme 8) for nucleophilic displacement with LiCl appeared to be encouraging [34]. The starting material was prepared from the known 2′,5′-di-*O*-trityl-2,3′-anhydro-uridine [35] **33** from which the 5′-*O*-trityl group was selectively removed by treatment with 80% acetic acid. Acetylation of the free 5′-OH of **34**, followed by removal of 2′-*O*-trityl with 10% CF_3COOH in $CHCl_3$, afforded



29 **30** **31** R = H; **31a** R = SO_2CF_3 **32**

Scheme 7.



33 **34** R = H; **35** R = Ac **36** R = H; **37** R = SO_2CF_3 **38** **39**

Scheme 8.

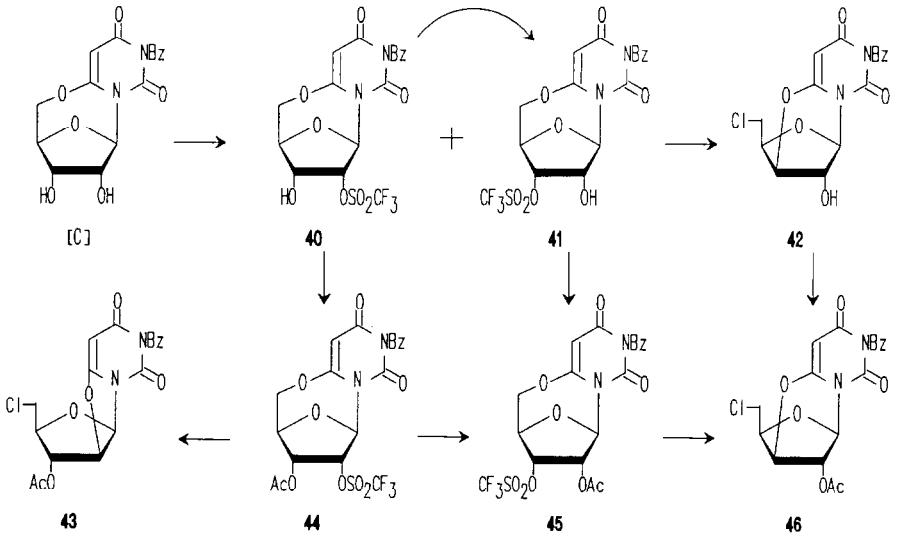
the anhydro-xylo nucleoside **36**. Triflylation of the free 2′-OH in **36** gave the nucleoside triflate **37** in high yield. Reaction of **37** with LiCl in HMPA at 100 °C gave the corresponding 2′-β-chloro derivative **38** in 63% yield. This compound was not identical to the known 2,2′-anhydro-(3-chloro-3-deoxy-5-*O*-acetyl-β-D-arabinofuranosyl)uracil [36], which would be formed as a result of attack of Cl^- on the 3′ position of **37** and subsequent displacement of the 2′-triflate function by the liberated 2-oxide. Thus, the 2-triflate was directly displaced by chloride ion. Unfortunately, all our attempts to open the 2,3′-anhydro linkage of **38** with formation of the desired 2′-β-chloro-substituted uridine by acid-catalyzed solvolysis [17] of **38** with sodium benzoate and benzoic acid failed. Instead of the desired 2′-chloro-2′-deoxy-β-D-arabinosyluracil, the olefin 5′-*O*-acetyl-2′-chloro-uridinene, **39** was the sole product. In contrast to the anhydro linkage of 5′-*O*-mesyl-2,3′-anhydro-xylosylthymine, which can be opened from the α-side with BzONa [17], similar treatment of **38** gave olefin **39**. This is due to activation of C-2′ proton by the geminal electronegative Cl substituent and the *trans* configuration of the H-2′ to the oxide at C-3′, which leads to elimination [34] with the formation of olefin **39**.

Although the synthesis of 2′-fluoro-*ara*-U was not achieved by this approach, it was found that the 2,3′-anhydro linkage as in B, in contrast to the 2,5′-anhydro bond of A, is stable enough for nucleophilic displacement of the triflate group at C-2′.

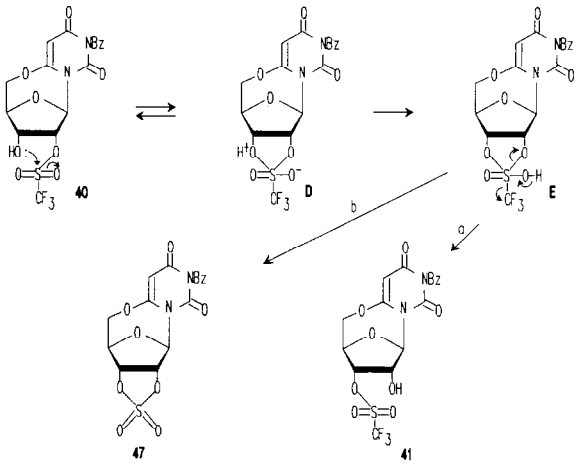
It was hoped then that the 6,5′-anhydro linkage as in C might also be more stable than the 2,5′-anhydro linkage in A. The carbonyl function at C-2 in C remains free, but the aglycon is restricted to the *anti* conformation of this nucleoside keeping O-2 far apart from the reaction center at C-2′. Treatment of the 2′,3′-di-*O*-butylstannylene derivative of 6,5′-anhydro-3-benzyl-1-β-D-ribofuranosylbarbituric acid with triflyl chloride in DMF afforded a 9:1 mixture of the isomeric 2′- and 3′-monotriflates [37] (**40** and **41**, respectively, Scheme 9). Compounds **40** and **41** were separated on a silica gel column, and isolated in crystalline form. When triflates **40** and **41** were treated separately with LiCl in HMPA, the identical 5′-chloro-6,3′-anhydro-xylo nucleoside **42** was obtained, which was then acetylated to the 2′-*O*-acetyl derivative **46**. The 6,2′-anhydro-arabino derivative **43** was not obtained from **40**. When triflates **40** and **41** were acetylated prior to LiCl treatment, the corresponding 5′-chloro-6,2′-anhydro-arabino- and 5′-chloro-6,3′-anhydro-xylo-nucleosides, **43** and **46**, were formed, respectively. Obviously, the 2′-*O*-triflyl group in **40** migrated to the 3′ position prior to reaction with LiCl and nucleoside **42** was formed. This is the first recorded observation of triflyl group migration [37].

A plausible mechanism for such migration would be an intramolecular alcoholysis as depicted in Scheme 10.

Attack of 3′-OH of **40** on the highly positive sulfur atom would lead to the formation of the zwitterion D which would be converted into the 1,3,2-dioxathiolane intermediate E by prototropy. Dissociation of the proton from E would result in the selective cleavage of the S—O-2′ bond (path a) since



Scheme 9.

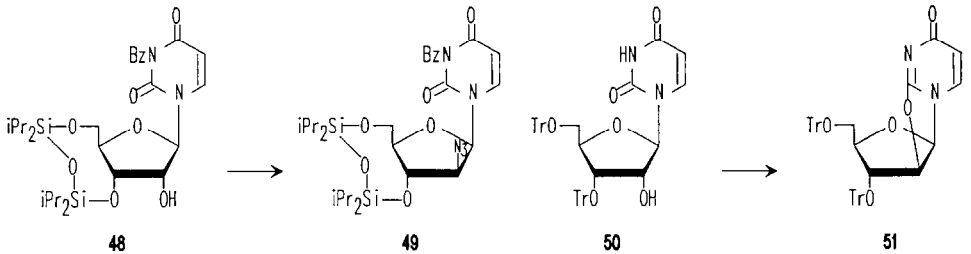


Scheme 10.

O-2′ is more electron-deficient than O-3′ due to the inductive effect of the aglycon. Thus, the migration occurs only from the 2′-triflate **40** to the 3′-triflate **41** and not *vice versa*.

When either triflate **40** or **41** was treated with Amberlyst A26 (F^-), the 2′,3′-*O*-cyclic sulfonyl nucleoside **47** was obtained in 26% yield. Apparently, fluoroform was eliminated from intermediate E by C—S bond fission via a mechanism similar to the cleavage of the C—C bond in haloform reaction (path b).

Thus, it was found that the idea of preventing participation of the carbonyl oxygen of the aglycon in the nucleophilic displacement of the 2′-leaving



Scheme 11.

group in the sugar moiety by using anhydro-nucleoside derivatives is useful in the synthesis of 2′-β-fluoro-substituted pyrimidine-*C*-nucleosides, but is not applicable to the synthesis of the corresponding *N*-nucleosides.

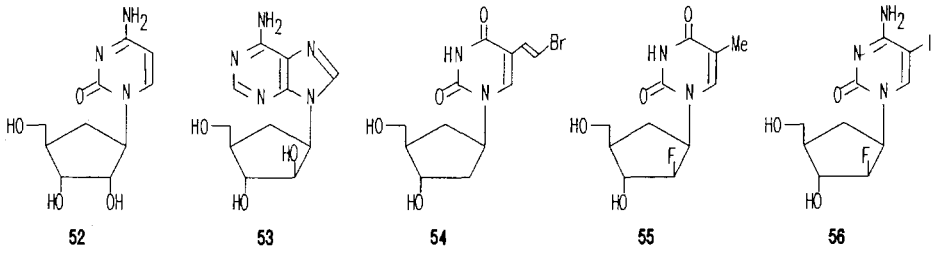
Another possible approach to the direct introduction of a substituent into the 2′-β position of pyrimidine nucleosides was demonstrated by Matsuda *et al.* [38]. The principle was based on an assumption that if the nucleophilicity of the 2-carbonyl oxygen could be reduced, the direct S_N2 reaction at 2′ position of uridine would be realized. These authors found [38] that 3′,5′-*O*-TiPDS-3-benzoyl-uridine (**48**, Scheme 11), under treatment with a mixture of hydrogen azide, Ph_3P and diethyl azodicarboxylate in THF, afforded the desired 2′-β-azido-substituted uridine **49** in 62% yield. In contrast, it is known that similar treatment of 3′,5′-di-*O*-trityluridine (**50**) resulted in exclusive formation of the 2,2′-anhydro-uridine **51** and the 2′-β-azido-substituted derivative was not obtained at all [39]. Thus, the electron-withdrawing effect of the benzoyl group at N-3 reduced the nucleophilicity of O-2, which allowed the nucleophilic substitution at C-2′ with azide ion.

Since no further examples of the synthesis of other 2′-β-substituted nucleosides have been published, it may be reasonable to assume that this approach is only applicable to very strong nucleophilic reagents such as azide.

Carbocyclic nucleosides

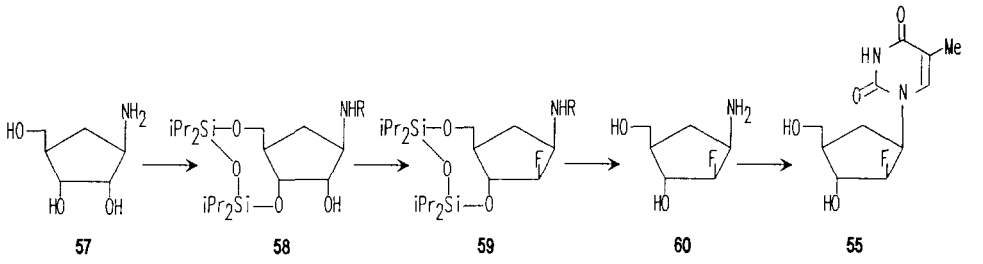
Replacement of the ring oxygen of the sugar moiety of nucleosides by a methylene group leads to carbocyclic nucleosides with greatly improved stability of the C—N glycosyl bond. It has been demonstrated that carbodine [40, 41] (**52**), cycladrine [40, 41] (**53**) and carbocyclic BVDU [42] **54** (Fig. 4) have interesting antiviral properties [42]. It has been suggested [43] that a fluoromethylene group is a better isostere of oxygen than a methylene group. Thus, Biggadike, Borthwick and other researchers from the Glaxo group have synthesized carbocyclic analogs of FMAU (**55**), FIAC (**56**) and other nucleosides containing fluorine substituent(s) in the 2′ and/or 6′ positions of the cyclopentane ring [44].

Most of these 2′-β-fluoro-carbocyclic pyrimidine nucleosides were biologically inactive or less active than the parent nucleosides. These compounds



52 53 54 55 56

Fig. 4.



57 58 59 60 55

Scheme 12.

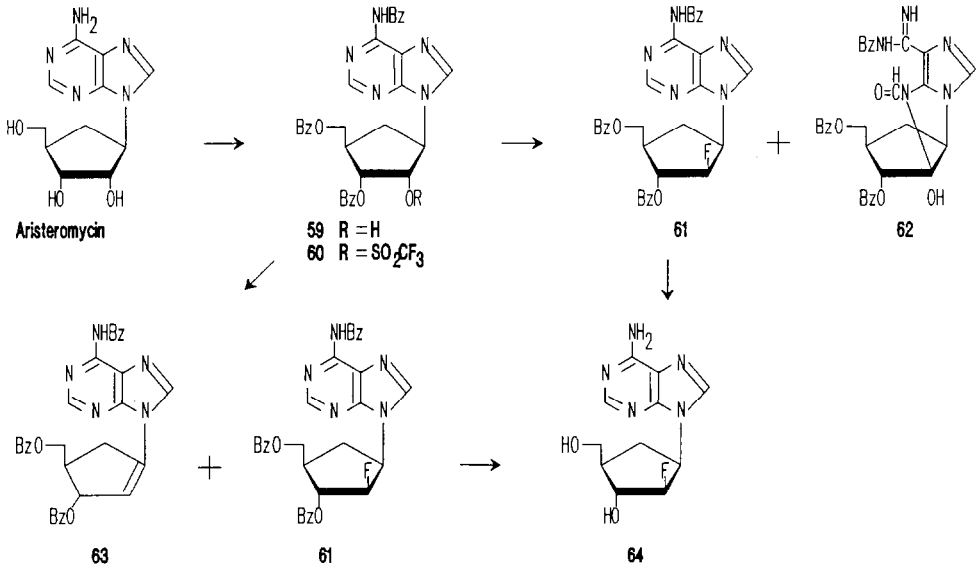
were prepared from the racemic aminotriol derivative **57** via fluorination (Scheme 12) with DAST, and subsequent chemical construction of the aglycon [45].

It was also established by the same group that the antiviral activity of these carbocyclic analogs resides largely, if not entirely, in the 'natural' enantiomer.

They also found that the carbocyclic analog of adenosine containing the fluorine in a 2-β (*arabino*) configuration is an active anti-herpes agent. This compound was prepared from aristeromycin as a pure enantiomer via direct introduction of the 2′-fluoro substituent into the carbocyclic nucleoside (Scheme 13). Thus, aristeromycin was fully benzoylated and then selectively 2′-debenzoylated [46] to give nucleoside **59**. Reaction of **59** with diethylaminosulfur trifluoride (DAST) afforded the required 2′-β-fluoro-substituted nucleoside **61** in 55% yield. The major by-product in this reaction was cyclonucleoside **62** (approx. 10% yield) arising via internal displacement of the 2′-leaving group [C—O—$SF_2(NEt_3)$] by adenine N-3, followed by hydrolysis during work-up. The same fluoro-nucleoside **61** was also obtained by the displacement of the 2′-*O*-triflyl group of nucleoside **60** with Bu_4NF in THF. The yield in this case was lower (25%) and the 1′,2′-olefin **63** was the predominant product.

Purine nucleosides

It is interesting to note (*vide infra*) that a similar approach to the synthesis of regular purine nucleosides, such as 9-(2-deoxy-2-fluoro-β-D-



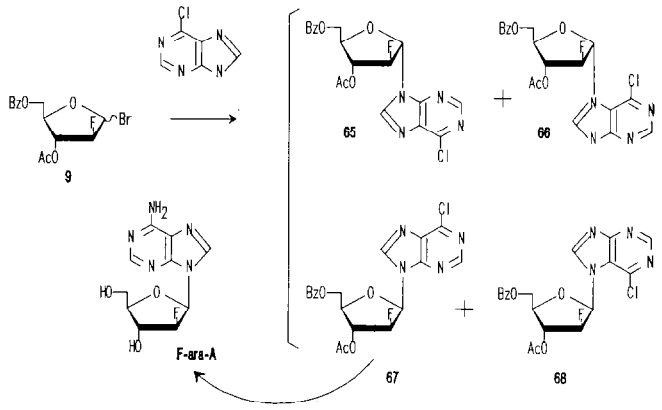
Scheme 13.

arabinofuranosyl)-adenine (F-*ara*-A) or -hypoxantine (F-*ara*-H), is not applicable at all. Apparently, this is due to differences in the glycosyl bond stability, conformational flexibility and reactivity of the leaving group at the C-2′ position in carbocyclic versus regular nucleosides.

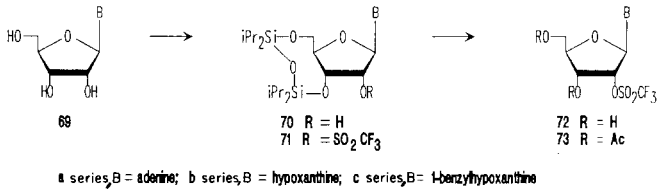
To date, all 2′-β-fluoro-purine nucleosides have been synthesized by condensation of the purine base and sugar. In contrast to the simple and efficient glycosylation of pyrimidines, the condensation of purines with 2-fluoro-2-deoxy-D-arabinofuranosyl halide is rather difficult. In fact, some purine bases do not react with the sugar halide. For example, F-*ara*-A was originally synthesized [47] by condensation of 5-*O*-benzyl-1,3-di-*O*-acetyl-2-deoxy-2-fluoro-D-arabinose with 2,6-dichloropurine by the fusion method. More recently, it has been prepared [2, 10] by condensation of 6-chloropurine (Scheme 14) with 2-fluoro-2-deoxy-D-arabinofuranosyl bromide (**9**) followed by conversion of purine **67** into adenine. The glycosylation reaction afforded a mixture of four isomers (**65–68**) from which the desired isomer **67** was separated in very low yield.

It has been reported that several 9-(2-deoxy-2-substituted β-D-arabinofuranosyl)-adenine derivatives (except F-*ara*-A) have been prepared [48] by direct displacement of the 2′-triflate group of the adenosine derivative with nucleophiles. Thus, we prepared 3′,5′-di-*O*-acetyl-2′-*O*-triflyl derivatives of adenosine, inosine and 1-benzylinosine (**73a, 73b** and **73c**, Scheme 15) for treatment with fluoride ion.

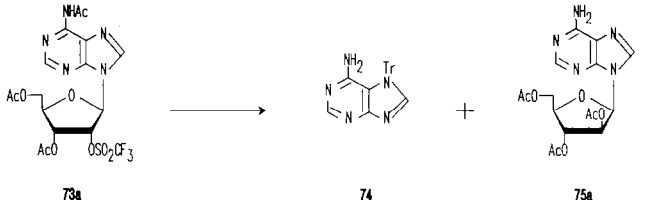
Treatment of the adenosine 2′-triflate **73a** with KF/dimethylformamide, Amberlyst A26 (F^-) in CH_3CN or tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) in CH_2Cl_2 always resulted in the formation of a mixture of adenine and 9-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)adenine (**75a**,



Scheme 14.



Scheme 15.

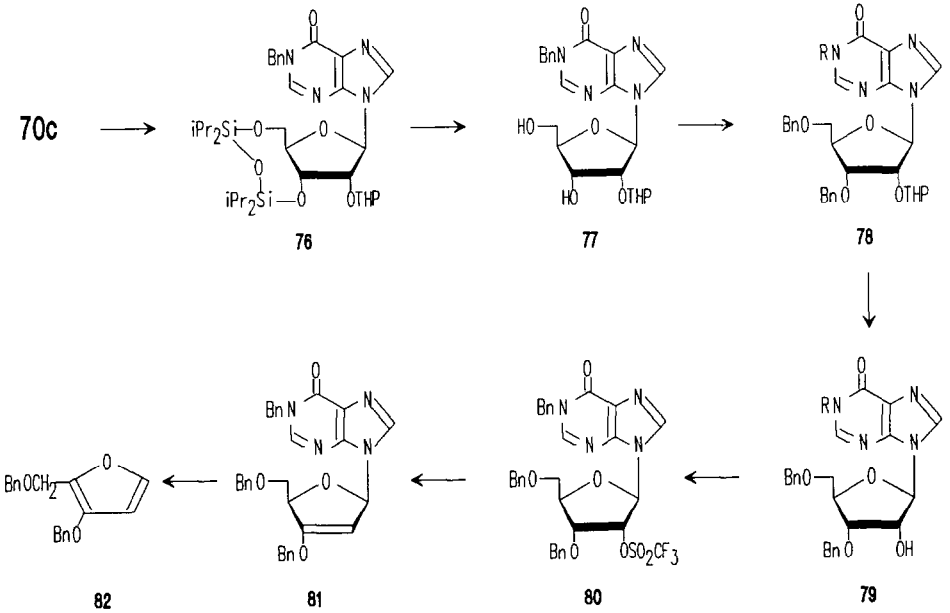


Scheme 16.

Scheme 16). The latter was isolated in 40% yield from the reaction mixture. No fluorinated nucleoside was detected.

In order to avoid the problems caused by acetate displacement of triflate, we used the more stable benzyl-protecting group and synthesized 3′,5′-di-*O*-benzyl-2′-*O*-triflyl-1-benzylinosine (**80**, Scheme 17). Thus, 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-1-benzylinosine (**70c**) was treated with dihydropyran (DHP)/TsOH and then desilylated with Et_3NHF/THF to obtain **77**. Benzylation of **77** followed by 2′-deprotection and triflylation afforded **78–80**. Contrary to our expectations, treatment of **80** with TASF afforded only the elimination products **81** and **82**. No trace of F-*ara*-H was detected in the reaction mixture.

Facile elimination of CF_3SO_3H from **80** with formation of the olefin **81** is probably due to the fact that the sugar has the C-3′-*endo* conformation (A, Fig. 5), in which the triflate group on C-2′ and the hydrogen on C-3′



Scheme 17.

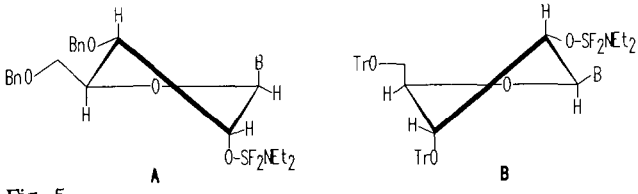


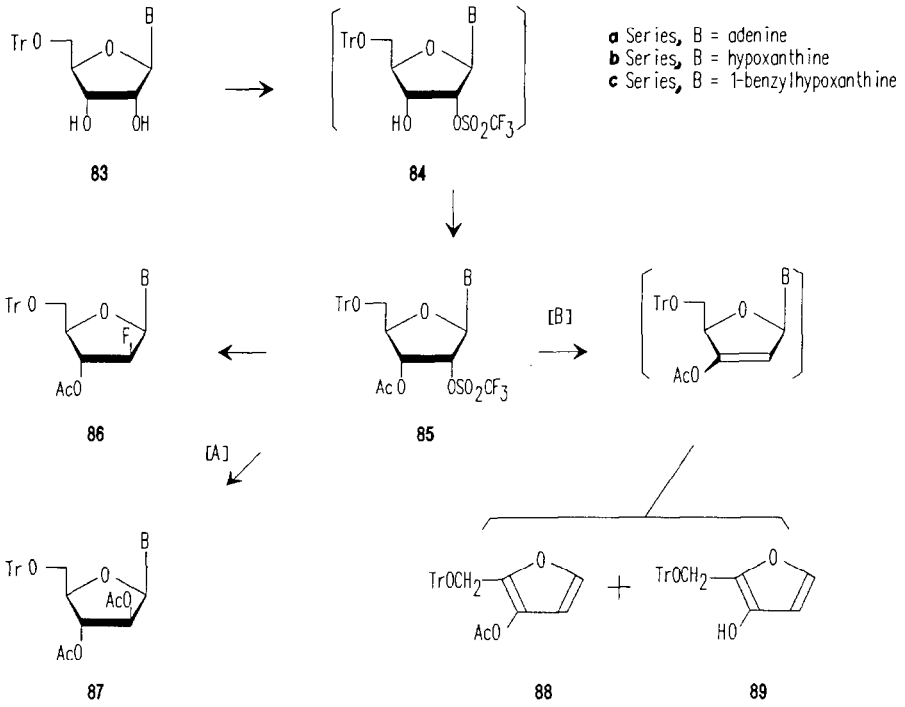
Fig. 5.

are almost in a *trans* di-axial configuration. Ikehara *et al.* [49] reported that the amount of C-3′-*endo* conformer in 2′-substituted adenosines increases linearly with the electronegativity of the 2′ substituent. Thus, the presence of the electronegative 2′-triflate group may force **80** to assume the C-3′-*endo* conformation, which favors elimination (A, Fig. 5).

The furanose ring conformation may be shifted toward C-2′-*endo* as in B by using bulky protecting groups at C-5′ and C-3′ of the purine nucleoside 2′-triflate. It has been suggested that a trityl group may force the furanose ring to assume an unfavorable conformation [50, 51] for *trans* elimination. We therefore synthesized 5′-*O*-trityl-3′-*O*-acetyl- and then 3′,5′-di-*O*-trityl-2′-*O*-triflyl nucleosides.

Treatment of compounds **83** (Scheme 18) with Bu_2SnO/MeOH followed by CF_3SO_2Cl yielded the corresponding 2′-*O*-triflyl nucleosides **84**, which, without isolation, were acetylated to **85**.

Treatment of **85a** and **85c** with TASF in CH_2Cl_2 afforded the desired protected F-*ara*-A and F-*ara*-H (**86a** and **86c**) in 4% and 10% yield,



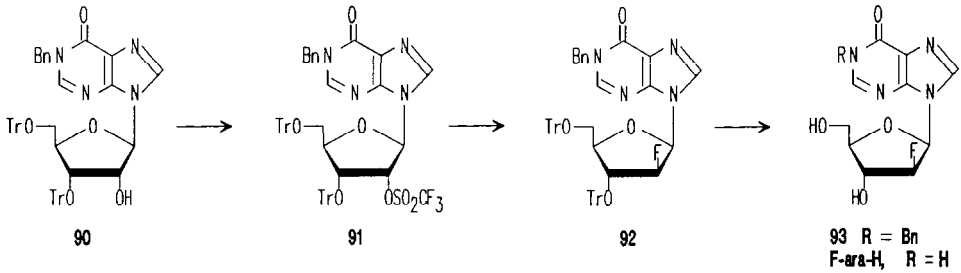
Scheme 18.

respectively. The reaction of **85b** with TASF, however, gave an inseparable mixture of the sugar fluorinated product **86b** and 2′,3′-di-*O*-acetyl derivative **87b** along with the furan derivatives **88** and **89**.

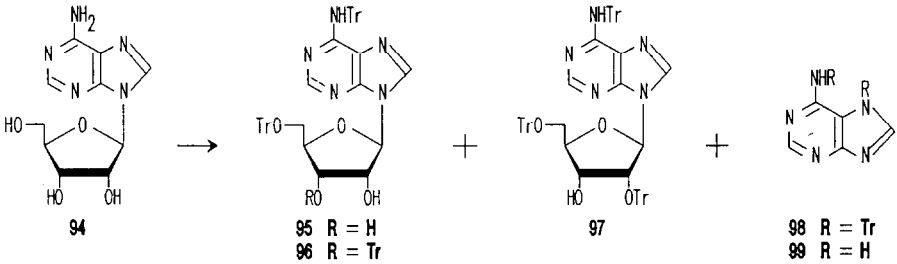
Detailed examination of the reaction of the triflates **85** with TASF revealed depurination to be the major course of the reaction. Displacement of the triflate group by acetate also occurs to give 9-(2,3-di-*O*-acetyl-5-*O*-trityl-β-D-arabinofuranosyl)purines (**87**, path A). Although nucleophilic displacement of the triflate group with fluoride ion takes place to some extent, a facile double elimination of triflate and the purine base (path B) affords the furan derivatives **88** and **89**. Compound **89** was converted into **88** by acetylation. Similar triflate elimination in carbohydrates in the presence of fluoride ion is known [52, 53].

In order to further promote conformational shift toward C-2′-*endo* and prevent the formation of acetate ion during the reaction, we prepared 3′,5′-di-*O*-trityl-2′-*O*-triflyl-1-benzylinosine (**91**, Scheme 19) via direct tritylation of 1-benzylinosine and separation of the 2′,5′- and 3′,5′-regioisomers on a silica gel column [54].

The relatively large $J_{1',2'}$ value of 7.1 Hz for the 3′,5′-di-*O*-trityl derivative **91** versus small 1′,2′ coupling (2.5–4.1 Hz) in **73**, **80** and **85** indicates that the trityl groups did cause the desired conformational change in **91** toward C-2′-*endo*. When **91** was treated with TASF, the yield of the desired 2′-β-



Scheme 19.



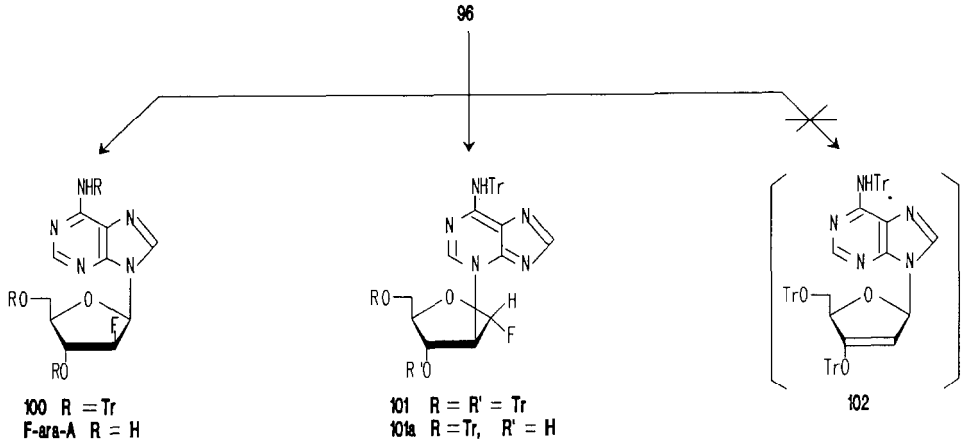
Scheme 20.

fluorinated arabinonucleoside **92** was increased to 30% [54]. Since DAST was reported as a useful reagent in the fluorination of nucleosides [55] and sugars, we also used DAST in reaction with our 3′,5′-di-*O*-trityl inosine **90** [56]. In this case, the desired 2′-β-fluoro derivative **92** was obtained in 79% yield. Detritylation of **92** with $CF_3COOH/CHCl_3$ [57] followed by hydrogenolysis with $Pd(OH)_2$ afforded a good yield of F-*ara*-H.

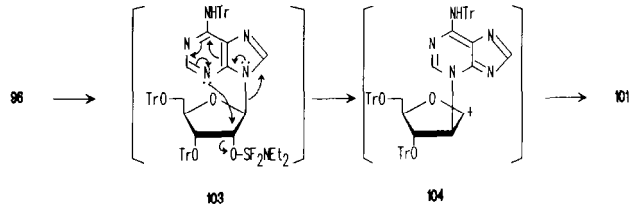
Our successful synthesis of F-*ara*-H [56] prompted us to check the applicability of the similar direct approach to the synthesis of F-*ara*-A and F-*ara*-G.

Thus, treatment of adenosine (**94**, Scheme 20) with trityl chloride in pyridine containing 4-dimethylaminopyridine [58] at 80 °C for 2–3 d afforded a mixture of $O^{5'},N^6$-ditrityladenosine (**95**), $O^{3'},O^{5'},N^6$-tritrityladenosine (**97**) and N^6,N^7-ditrityladenine (**98**). These compounds were separated on a silica gel column when the desired nucleoside **96** was obtained in crystalline form in 20% yield. Further tritylation of **95** afforded an additional amount of **96**, increasing the total yield of **96** up to 34%.

Treatment of the tritrityl derivative **96** with DAST gave a mixture of two components. A minor product **100** (Scheme 21) was isolated in 30% yield, which was detritylated with $CF_3COOH/CHCl_3$ to give the desired F-*ara*-A in good yield [56]. To our surprise, the major product was not the expected elimination product **102** but an isomer of **100** containing the fluorine atom. Its structure was established on the basis of spectral and elemental analyses as 2-deoxy-2-(6-trityladenin-3-yl)-3,5-di-*O*-trityl-β-D-arabinofuranosyl fluoride (**101**) [56].



Scheme 21.



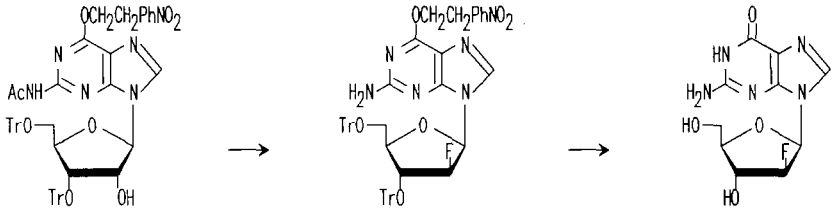
Scheme 22.

A possible mechanism of the conversion of **96** to **101** may be schematically illustrated as shown in Scheme 22. Attack of N-3 of the aglycone (see also Scheme 13) on the activated 2′-carbon of the alkoxy(dimethylamino)sulfur difluoride intermediate **103** may result in the formation of carbocation **104** via cleavage of the glycosyl bond of **103***. Subsequently, the fluoride ion attacks from the less-hindered α-side to give derivative **101**. Alternatively, the fluoride ion may cleave the glycosyl bond of intermediate **103** with inversion of configuration at the anomeric carbon atom.

It is well established that adenine N-3 participation in sugar transformations in adenosine series results in the undesired formation of intramolecular cyclization products between N-3 and the sugar moiety [60]. Recently, the attack of N-3 on C-3′ of the sugar of 5′-*O*-monomethoxytrityl-2′-deoxyadenosine under DAST treatment has been reported [61].

A similar tritylation of guanosine did not afford the desired product but gave only decomposition products. We, therefore, protected both the *exo* and *endo* cyclic nitrogen atoms of the nucleoside. Thus, we synthesized *N*-dimethylaminomethylene-1-benzylguanosine [62] (**105**) by treatment of guanosine with DMF–dimethyl acetal followed by DBU/benzyl bromide. Compound

*Detection of the alkoxy(dimethylamino)sulfur difluoride intermediate of 2′-deoxy-5′-*O*-dimethoxytritylcytidine has been reported recently [59].



Scheme 23.

105 was then treated with TrCl in a similar manner to adenosine. Again decomposition occurred. It was found, however, that when 2-*N*-acetyl-6-*O*-(4-nitrophenyl-ethyl)guanosine [63] was treated with TrCl under the same conditions as above, the desired mixture of 2′,5′- and 3′,5′-di-*O*-trityl derivatives was obtained in good yield. These compounds were separated on a silica gel column. The desired 3′,5′ tritylated regioisomer **106**, under treatment with DAST, was converted into 9-(2-deoxy-2-fluoro-3,5-di-*O*-trityl-β-D-arabinofuranosyl)-6-*O*-(4-nitrophenylethyl)guanine in 40% yield (**107**, Scheme 23). Deprotection of the fluoro derivative with DBU/pyridine followed by detritylation with $CF_3COOH/CHCl_3$, gave 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)guanine (F-*ara*-G, **108**) in good yield [64].

Conclusions

This review covers our research activities directed toward the synthesis of 2′-β-fluoro-substituted nucleosides via nucleophilic displacement of an activated 2′-hydroxyl group of preformed ribonucleosides. In the pyrimidine nucleoside area, the strategy to prevent participation of the carbonyl oxygen of the aglycone in nucleophilic reaction at C-2′ by using the corresponding 2,5′-*O*-, 2,5′-*S*-, 2,3′-*O*- and 5′,6-anhydro nucleoside derivatives did not work. Fortunately, the preparation of these 2′-β-fluoro pyrimidines by condensation of an appropriate fluorinated sugar bromide and pyrimidine base is relatively straightforward.

On the other hand, there is at present no method for the synthesis of pyrimidine-*C*-nucleosides containing fluorine at C-2′ in the β configuration. Also, all the known procedures for the condensation of purines with the fluoro sugar are quite laborious and inefficient. Thus, our method of direct fluorination of the 4,5′-anhydro-*C*-nucleoside (Scheme 5) with TASF afforded a convenient route to *C*-FMAU. Recently, using this compound as a starting material, an interesting but not active 1-methyl-5-(3-azido-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)uracil has been synthesized by us as a *C*-analog of AZT [65].

The discovery of the role of sugar protecting groups and the effect of C-3′-*endo* to C-2′-*endo* conformational shift on the reaction course of the 2′-hydroxyl group with DAST led to synthesis of 2′-β-fluoropurine nucleosides

such as F-*ara*-H, F-*ara*-A and F-*ara*-G. Thus, these direct approach procedures, although still not quite efficient, are far superior to the currently available multi-step synthesis of purine nucleosides containing 2′-β-fluoro substituent.

Acknowledgments

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