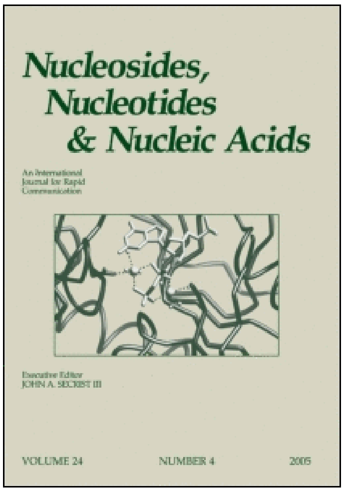

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Nucleotide Analogues Containing the P-F Bond. An Overview of the Synthetic Methods

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REVIEW

NUCLEOTIDE ANALOGUES CONTAINING THE P–F BOND. AN OVERVIEW OF THE SYNTHETIC METHODS[a]

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ABSTRACT: In this paper a short review is given of synthetic methods for the preparation of nucleoside phosphorofluoridates, nucleoside phosphorofluoridothioates and nucleoside phosphorofluoridodithioates.

INTRODUCTION

In the last decade, the emergence of antisense/antigene technology[1,2] held the promise of novel therapy for hard-to-treat diseases, including those associated with human genetic disorders. This technique, which is targeting the protein templates rather than their products, aims towards more effective drugs, with fewer side effects, that have the added virtue of being highly specific. To meet these expectations a profusion of oligonucleotide analogues, sometimes with ingeniously designed structural variations[2], have been synthesized[3]. Among these, those which carry a strong resemblance to natural nucleic acids, *e.g.* oligonucleoside phosphorothioate or C-phosphonates, are in the main focus of medical research[4-6].

Nucleic acid analogues bearing the phosphorofluoridate functionality, represent a class of compounds of potential therapeutic value that are recently gaining interest[7-

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[a] This paper is dedicated to the late Professor Tsujiaki Hata

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[17]. There are several features which make compounds containing the P–F bond an attractive surrogate of phosphate esters.

The high electronegativity of fluorine and its small size facilitate the π-bond formation with d-orbital of phosphorus (pπ-dπ bonding, "back-donation"), making the P–F bond unusually strong (~439 kJ mol^{-1})[18]. Since the fluorine atom also is smaller than the hydroxyl group (van der Waal's radii 1.35 and 2.20 Å, respectively), the substitution of the non-bridging oxygen in a phosphodiester moiety does not produce steric hindrance during interactions with enzymes. Although the introduction of the fluorine atom to phosphodiesters eliminates the formal negative charge, the produced analogue may still be involved in hydrophilic interactions with water important for biomolecules, owing to the ability of the fluorine to form hydrogen bonds[18].

The presence of the P–F functionality in a molecule can also be exploited, *e.g.* for the attachment of an oligonucleotide to proteins or it may serve *per se* as a reporter group in conformational studies of nucleic acids fragments. For the latter applications, ^{19}F NMR spectroscopy, which sensitivity is close to that of ^{1}H NMR, is particularly well suited[19]. Its most important advantages are that ^{19}F chemical shifts are larger and considerably more sensitive to environmental effects than ^{1}H NMR and the spectra are not cluttered by resonance from other parts of a molecule. Some additional structural information can also be obtained by the NMR relaxation technique, *e.g.* by determining the interatomic distance between fluorine and metal cations coordinated at distant places in a molecule.

Although the replacement of phosphorus-bound chlorine by fluoride is by far the most common way for the preparation of fluorophosphates, most of the older procedures are either inapplicable[20] or suffer from several disadvantages when it comes to the synthesis of natural product derivatives containing the P–F bond[21]. The major obstacles are usually poor availability of the corresponding phosphorochloridates and the elevated temperature often required to effect the replacement.

In this paper, a short review of recent synthetic methods for the introduction of the P–F bond to nucleic acids fragments or their components, is presented. The transformations, in most instances, occur under mild reaction conditions and seem to be of general applicability to the synthesis of phosphorus-containing natural products.

I. METHODS FOR THE PREPARATION OF NUCLEOSIDE PHOSPHOROFLUORIDATE ESTERS

I.1. Preparation of nucleoside phosphorofluoridate diesters.

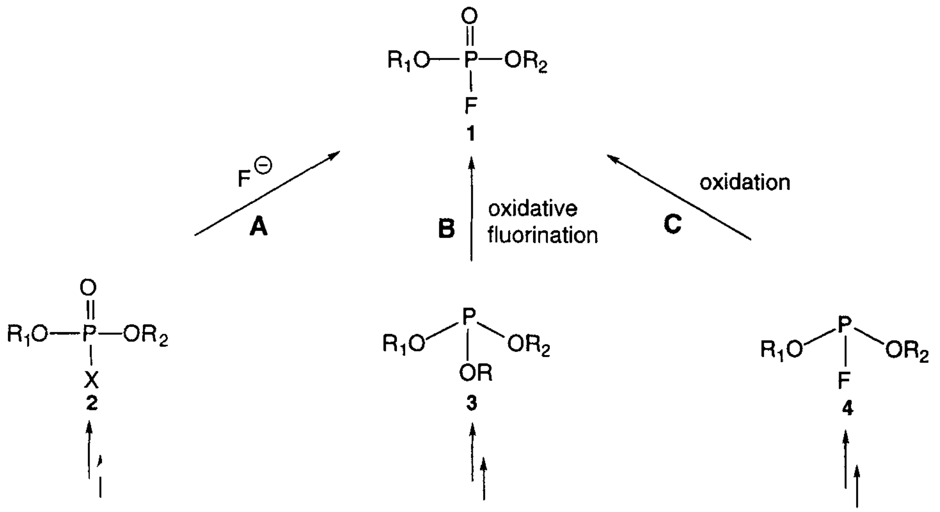
One can envisage at least three main pathways for the formation of phosphorofluoridate diesters **1** (SCHEME 1): (i) nucleophilic substitution effected by fluoride anion at the P(V) phosphorus centre (path A), (ii) oxidative fluorination of tervalent P(III) derivatives (path B), and (iii) oxidation of a suitable tervalent P(III) precursor already bearing the P–F linkage (path C).

Most synthetic approaches to phosphorofluoridate diesters **1** make use of pathway A, and only few of them utilize routes B or C. By choosing between these routes, accessibility of the intermediates **2**, **3** or **4** may be as important as the relative efficiency of the last steps A, B and C shown in SCHEME 1. This is particularly apparent from a comparison of methods utilizing the type **2** intermediate for the preparation of phosphorofluoridates **1**.

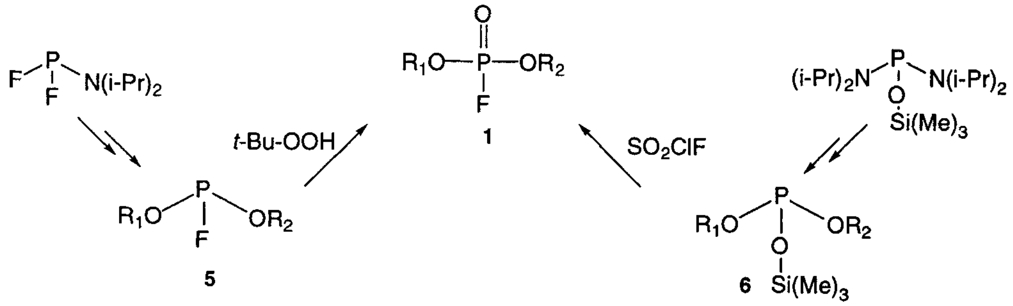
I.1.1 Preparation of nucleoside phosphorofluoridate diesters from tervalent P(III) precursors.

Two routes to phosphorofluoridates **1** *via* tervalent phosphorus derivatives have recently been investigated by Michalski *et al.* (SCHEME 2). They involve either oxidation of precursors **5** bearing the P–F bond with *tert*-butyl hydroperoxide[11,22] or oxidative fluorination of a silyl phosphite of type **6** using sulfuryl chloride fluoride[12,23,24].

Dinucleoside phosphorofluoridite **5** and dinucleoside trimethylsilyl phosphite **6** can be prepared from suitably protected nucleosides and the corresponding tervalent phosphorus reagents (diisopropylphosphoramidous difluoride[25] and trimethylsilyl bis-*N,N*-diisopropyl-phosphoramidite[26], respectively, SCHEME 2), in multiple step one-pot synthesis. The last steps of these transformations shown in SCHEME 2, usually proceed quantitatively. The intermediate **5**, in contradistinction to the silyl



SCHEME 1



R_1 and R_2 = nucleoside moieties

SCHEME 2

ester **6**, is stable enough to be purified by silica gel column chromatography and can be resolved into the diastereomers[9].

I.1.2 Preparation of nucleoside phosphorofluoridate diesters from P(V) derivatives.

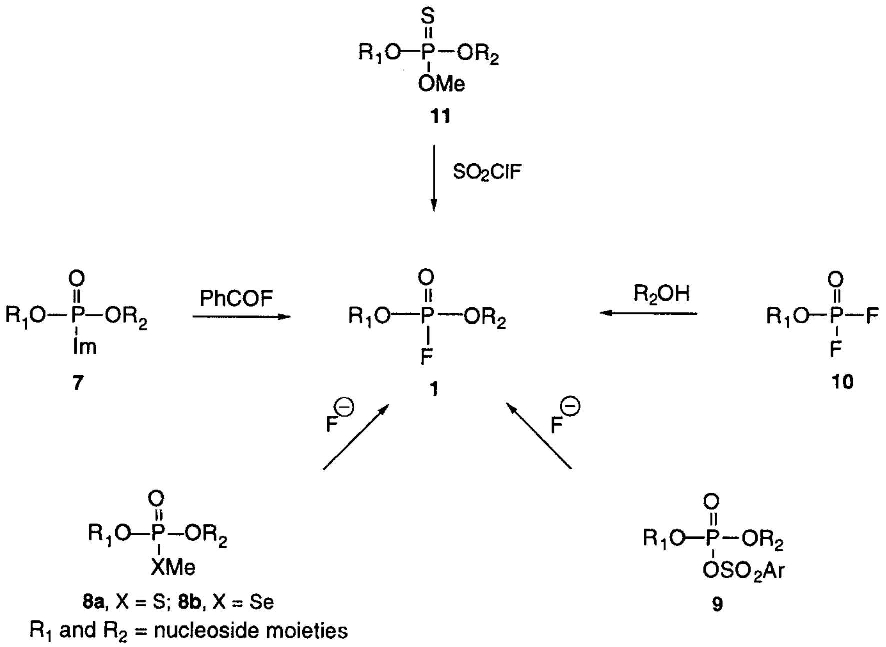
The reaction of phosphorochloridate diesters with alkali metal fluorides is the method of choice for the preparation of simple dialkyl phosphorofluoridates[21].

However, in the synthesis of natural product derivatives containing the P–F bond, this pathway was until recently of limited value, due to the scant availability of the corresponding phosphorochloridates and the often detrimental reaction conditions. To overcome these problems various synthetic routes based on P(V) compounds bearing other leaving groups, have been developed. Some of the approaches to nucleoside phosphorofluoridate diesters **1** which utilize azolides[27,28], thiomethyl[29,30], selenomethyl[14], arylsulfonyl[9], and fluoride[28] as leaving groups, are shown in SCHEME 3. The synthetic usefulness of a particular method for the formation of phosphorofluoridates **1** mainly depends on the availability of the corresponding precursors **7-11**.

Azolides **7** (*e.g.* imidazolides, triazolides) are usually readily accessible from the dinucleoside phosphodiesters and can be efficiently converted to the fully protected phosphorofluoridates **1** with equimolar amounts of benzoyl fluoride in methylene chloride[27,28]. Alternatively, **7** can be generated *in situ* from dinucleoside silyl phosphites **6** and oxalylazolides[26].

The pathway involving the phosphoric-sulfonic anhydride **9** was exploited for the preparation of thymidine cyclic 3',5'-phosphorofluoridate[31]. The total synthesis involved phosphorylation of a 3'-protected thymidine to produce the 5'-phosphorodiimidazolide, followed by its reaction with *p*-toluenesulfonic anhydride, N-methylimidazole-promoted cyclization to **9** (R_1 and R_2 are thymidin-3',5'-diyl moiety), and substitution of the sulfonyl group using CsF (total yield ~40%)[31].

Methylation of nucleoside phosphorothioate or phosphoroselenoate diesters with methyl iodide provides a convenient way to the precursor **8a**[30] or **8b**[14], respectively. The substitution of the S-methyl or Se-methyl group is effected by AgF or triethylammonium hydrofluoride in acetonitrile-water, acetonitrile-methanol, or acetonitrile-pyridine[30]. The reactions proceed to completion within 2-3 h, however, some instability of the phosphorofluoridates **1** under the reaction conditions was observed. Methylation of dinucleoside phosphoroselenoates followed by the replacement of the Se-methyl group by fluoride anion, was also carried out on unprotected dimers[14].

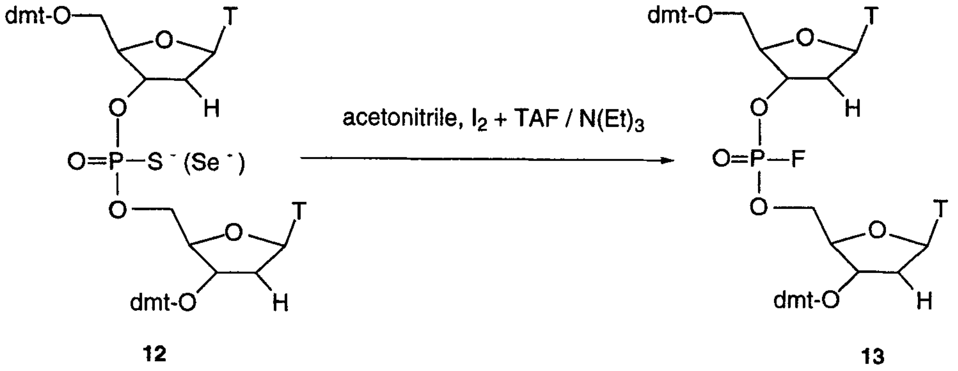


SCHEME 3

The reaction of sulfuryl chloride fluoride with the *R*P diastereomer of *O*-methyl phosphorothioate **11** leading to dinucleoside phosphorofluoridate **1** was found to be stereospecific, whereas that of the *S*P isomer, highly stereoselective[10,13]. The mechanism of this transformation is somewhat obscured.

Precursors of type **10**[28] (R_1 = nucleosid-5'-yl), can be obtained quantitatively from a suitably protected nucleoside by the phosphitylation with triimidazolylphosphine[32], followed by the reaction of the produced tervalent P(III) intermediate with two equivalents of benzoyl fluoride and the oxidation with iodine-water. The preparative utility of this method, which consists of a selective substitution of one fluorine in **10**, was demonstrated in the synthesis of dithymidine phosphorofluoridate **1** using equimolar amounts of phosphorodifluoridate **10**, CsF and the 5'-O-(9-phenylxanten-9-yl)thymidine[28].

In SCHEME 4, the most recent method[17] for the formation of the P–F bond is shown. It relies on a highly selective reaction of iodine with the sulfur or the selenium



SCHEME 4

centre in phosphorothioates[33] or phosphoroselenoates[34] which, when carried out in the presence of fluoride anion, quantitatively affords the corresponding nucleoside phosphorofluoridates **13**[17]. This method is of particular relevance to oligonucleotide analogue synthesis, since iodine-promoted desulfurization or deselenization can be performed on unprotected oligonucleotides[33-35] and it alleviates the problem of loosing the fluorine during the final deprotection of oligomers.

Due to the biochemical and medical importance of nucleoside phosphorothioates[36], **12** and related compounds with isosteric and isoelectronic modification at the phosphorus centre are at present easily accessible *via* efficient phosphoramidite[37] or H-phosphonate[38,39] methodology.

I.1.3 Preparation of nucleoside phosphorofluoridate diesters from H-phosphonate diesters.

In nucleophilic substitution at the phosphorus centre the choice of a source of nucleophilic fluoride is often a compromise between stability, solubility, and reactivity of the reagent. Among various investigated compounds, commercially available triethylamine trishydrofluoride (TAF) showed the most favourable properties being soluble in organic solvents and reactive enough to effect fast and clean nucleophilic substitution at phosphorus.

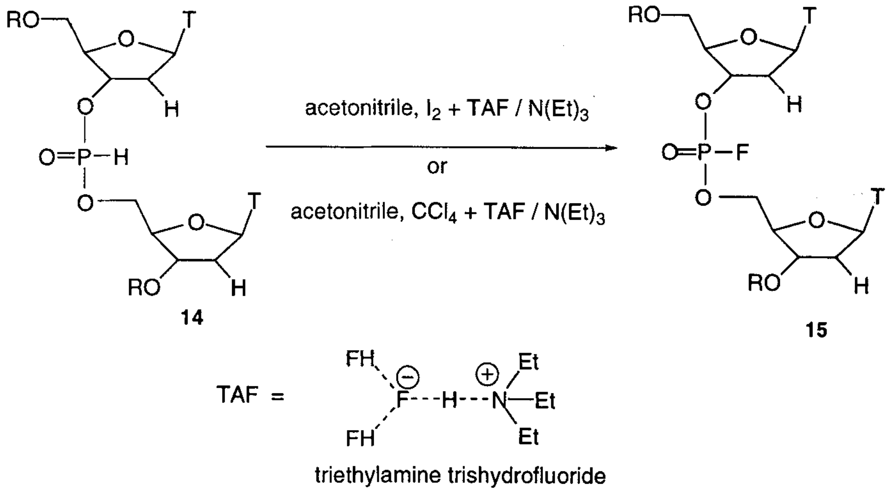
Recently, we have reported on an efficient method for the preparation of phosphorofluoridate diesters based on H-phosphonate chemistry utilizing TAF as a source of nucleophilic fluoride[15,40]. The rationale behind this method (SCHEME 5) is a known, easy oxidation of nucleoside H-phosphonate diesters **14** with iodine under anhydrous conditions[41] to generate the corresponding iodophosphate, that in turn, rapidly reacts with fluoride anion affording the phosphorofluoridate diesters **15**. Thus, the method makes use of an exceptionally favourable combination of a strong, phosphophilic attacking nucleophile (fluoride) and excellent leaving group (iodide) at the phosphorus centre. The transformation is clean, fast (< 5 min), and can be carried out as a one-pot operation under homogeneous reaction conditions. The Atherton-Todd oxidation[42] of H-phosphonate diesters **14** in the presence of TAF (SCHEME 5), also cleanly affords dinucleoside phosphorofluoridates **15** (ca 20 min). Since H-phosphonate diesters derived from natural products are readily available[38], this method provides a general approach to various phosphorofluoridate diesters.

I.2Methods for the preparation of nucleoside phosphorofluoridate monoesters.

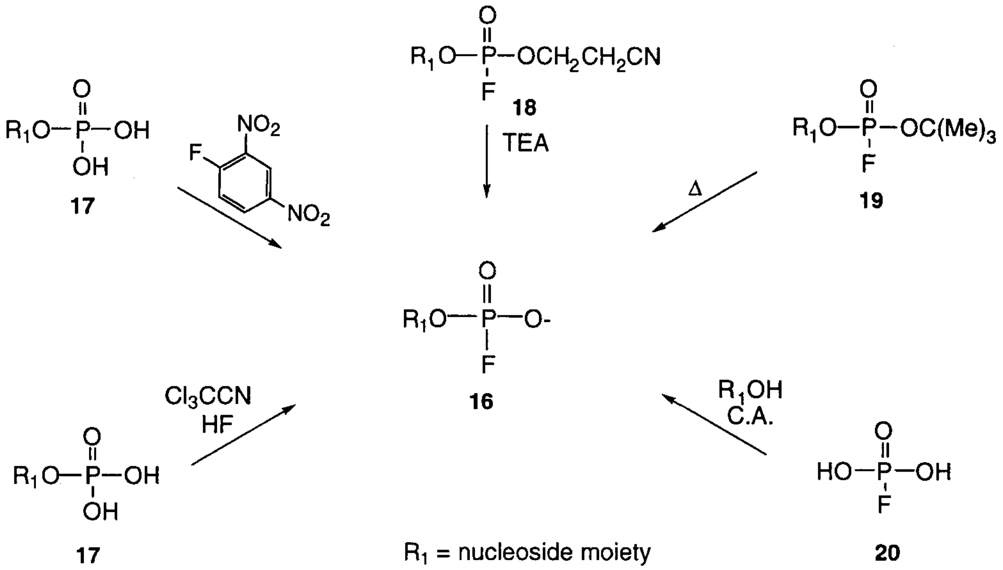
I.2.1 Preparation of nucleoside phosphorofluoridate monoesters from P(V) derivatives.

In contradistinction to phosphorofluoridates diesters, there are only a few synthetic methods available for the preparation of monoesters of fluorophosphoric acid. Those, which utilize P(V) derivatives as substrates are summarized in SCHEME 6. They include the formation of phosphorofluoridate monoesters **16** from (i) the corresponding phosphate monoesters (**17**), (ii) fluorophosphate diesters (*e.g.* **18**, **19**), and (iii) fluorophosphoric acid (**20**).

The reaction of phosphomonoesters with 2,4-dinitrofluorobenzene (DNFB), used for the first time by Wittmann for the preparation of nucleoside phosphorofluoridate[43], is probably the most common path to various phosphorofluoridates monoesters. The reaction is usually carried out in acetonitrile in the presence of triethylamine, and affords phosphorofluoridates **16** from unprotected nucleotides **17** in good yields (65-90%)[43]. Since DNFB occasionally may cause some



SCHEME 5



SCHEME 6

side reactions[44], the alternative two-step procedure, involving the generation of nucleoside 2,4-dinitrophenyl phosphate from **17** and 2,4-dinitrophenol in the presence of DCC, followed by the substitution of a 2,4-dinitrophenyl group by fluoride, was claimed to be superior[45] to Wittmann's original method. DNFB can also be substituted by 2-fluoro-N-methylpyridinium salts in the synthesis of phosphorofluoridates[46,47].

Two methods for the synthesis of phosphorofluoridates **16**, which are based on the use of condensing agents should be mentioned: (i) the trichloroacetonitrile-mediated condensation of nucleoside phosphomonoesters **17** with HF[48] and (ii) the phosphorylation of nucleosides with fluorophosphoric acid **20**[7,8]. The latter one, employing 2,4,6-triisopropylbenzenesulfonyl chloride as a condensing agent, has been successfully used in the synthesis of several phosphorofluoridates **16** carrying nucleoside moieties with established antiviral properties (*e.g.* AZT, ddT, FLT)[7,8].

Nucleoside phosphorofluoridate diesters (*cf* section I.1) with alkyl residues that can be selectively removed under mild conditions, can also serve as precursors to nucleoside phosphorofluoridate monoesters.

For example, nucleoside 2-cyanoethyl phosphorofluoridate **18**[11] can be converted to **16** by treatment with pyridine-triethylamine (10 min) and an analogous *tert*-butyl ester **19**[11], by thermal elimination of 2-methyl-1-propen (80 °C, 2h, CH_3CN). Both reactions afford nucleoside phosphorofluoridates **16** in >90% yields[11].

I.2.2 Preparation of nucleoside phosphorofluoridate monoesters from H-phosphonate derivatives.

Nucleoside H-phosphonate monoesters **21** are accessible *via* a variety of efficient methods[38,49] and thus can be useful precursors in the synthesis of the corresponding phosphorofluoridates **25**. Due to the presence of negative charge, however, they are more resistant to oxidation than H-phosphonate diesters. To overcome this problem, H-phosphonate monoesters are usually transformed to H-phosphonate diesters or to tervalent P(III) derivatives, prior to oxidation. A simple and efficient way to achieve these is to convert **21** into silyl derivatives[41,50].

A synthetic protocol, which includes the presilylation of nucleoside H-phosphonate **21**, is shown in SCHEME 7[16,40]. It involves oxidizing monosilyl (**22**) or disilyl (**23**) derivatives with iodine under anhydrous conditions in pyridine to produce the pyridine adduct of metaphosphate **24**[41]. The latter, rapidly reacts with fluoride anion (TAF) to the desired nucleoside phosphorofluoridates **25** (preparative yields >90%)[16].

Since fluoride is also a good nucleophile towards silicon, to avoid desilylation of the produced silyl intermediates **22** and **23**, oxidation with iodine and the treatment with TAF, should preferably be carried out separately as two consecutive reaction steps[16,40] (especially using **22**).

II. METHODS FOR THE PREPARATION OF NUCLEOSIDE PHOSPHOROFLUORIDOTHIOATE AND -DITHIOATE ESTERS

II.1 Preparation of nucleoside phosphorofluoridothioate diesters.

II.1.1 Preparation of nucleoside phosphorofluoridothioates from tervalent P(III) precursors.

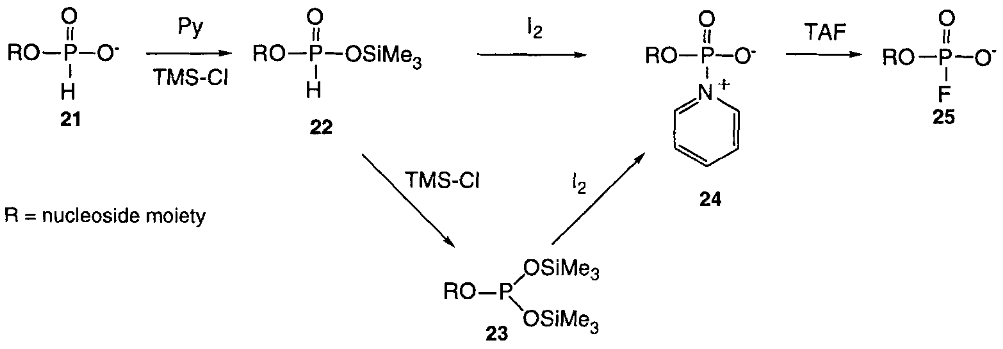
Dinucleoside phosphorofluoridite **5**[9] is a bifurcated intermediate, that provides access to dinucleoside phosphorofluoridates **1** (*cf* section I.1) or the phosphorofluoridothioate analogues **26**.

Since **5** can be resolved into P-diastereomers and the sulfurization with dibenzoyl disulfide[51,52] is a stereospecific process, by this means diastereomerically pure dinucleoside phosphorofluoridothioates **26** can be obtained[9].

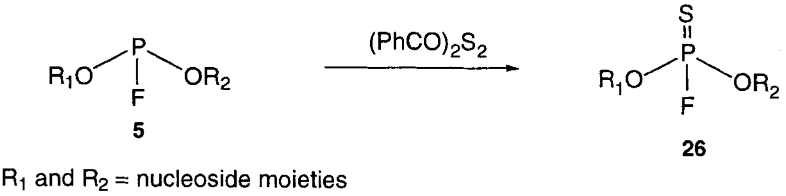
II.1.2 Preparation of nucleoside phosphorofluoridothioates from H-phosphonothioates.

Iodine-promoted oxidation of dinucleoside H-phosphonothioates **27** under anhydrous conditions in the presence of TAF provides an efficient entry to dinucleoside phosphorofluoridothioates **28** (SCHEME 9)[16,40]. The intermediate involved is most likely a dinucleoside phosphoroiodidothioate that (in the absence of fluoride anion) can be detected by ^{31}P NMR spectroscopy[53].

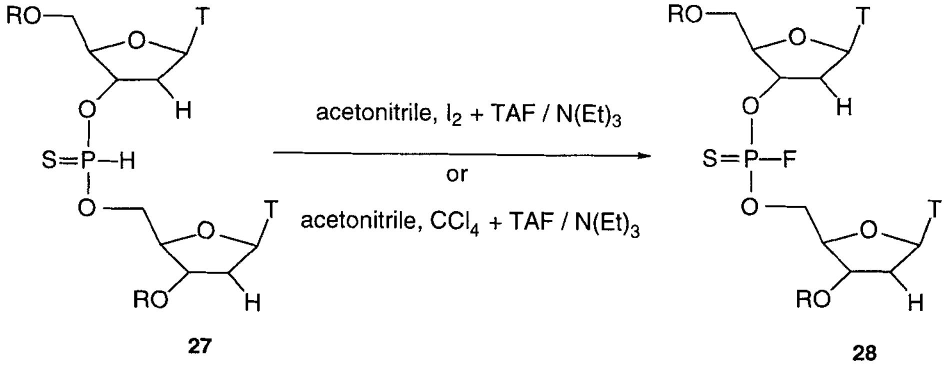
Similarly to H-phosphonate diesters (*cf* section I.1.3), dinucleoside phosphorochloridothioates, generated *in situ* form **27** in the Atherton-Todd reaction[42],



SCHEME 7



SCHEME 8



SCHEME 9

can also be efficiently converted to fluoridates **28**. In this instance, due to the ease of oxidation of H-phosphonothioate diesters of type **27**, acetonitrile and triethylamine can be replaced by pyridine, without affecting the efficiency of formation of **28**[16,40]. The starting material, dinucleoside H-phosphonothioate diesters **27**, can be obtained by chlorophosphate-promoted condensations of H-phosphonothioate monoesters with a nucleosidic component[54,55].

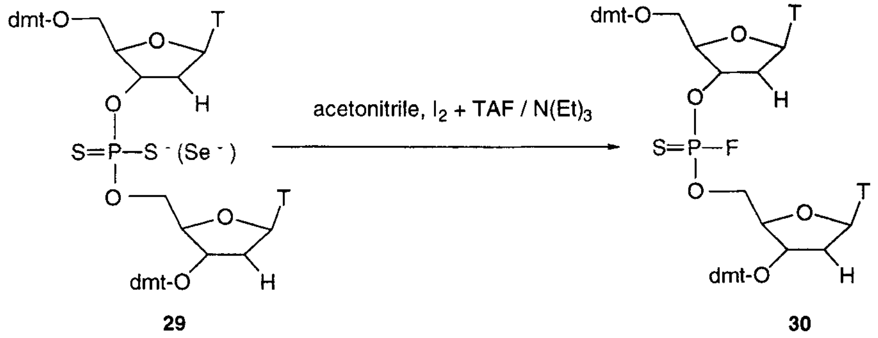
II.1.3 Preparation of nucleoside phosphorofluoridothioates from P(V) derivatives.

Dinucleoside phosphorofluoridothioates **30** are accessible *via* iodine promoted desulfurization or deselenization of suitable precursors **29** (*e.g.* dinucleoside phosphorodithioates[56,57] or dinucleoside phosphoroselenothioates[34,58]) in the presence of TAF (SCHEME 10)[17], analogously to the synthesis of dinucleoside phosphorofluoridates (*cf* section I.1). The reaction is fast and clean (yields of isolated products >90%). No desulfurization of phosphorofluoridothioates **30** was observed under the reaction conditions[17].

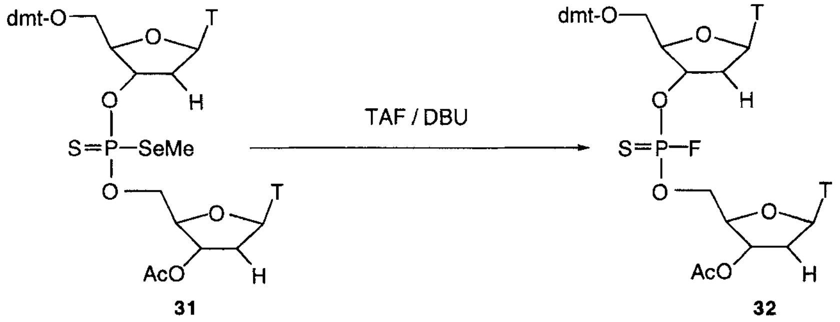
In phosphoroselenothioates **29**, having sulfur and selenium centers, the latter is exclusively attacked by iodine, apparently due to the difference in the standard reduction potential of selenium and sulfur[17].

Another method for the preparation of dinucleoside phosphorofluoridothioates is shown in SCHEME 11. The starting material in this approach is Se-methyl phosphoroselenothioate **31**, obtained from 5'-protected thymidine 3'-*O*-(2-seleno-1,3,2-dithiaphospholane) in the DBU-assisted reaction with 3'-*O*-acetylthymidine, followed by the alkylation with methyl iodide of the produced phosphoroselenothioate (SCHEME 11)[59].

The Se-methyl phosphoroselenothioates **31** are usually not particularly reactive and produce the corresponding phosphorofluoridothioates **32** only in low yields, when CsF or triethylammonium hydrofluoride is used as a source of fluoride anion. However, significant improvement in the efficiency of the substitution of the -SeMe group by fluoride was observed (yield ca 54%), when the reaction was carried out in the presence of TAF and DBU[59].



SCHEME 10



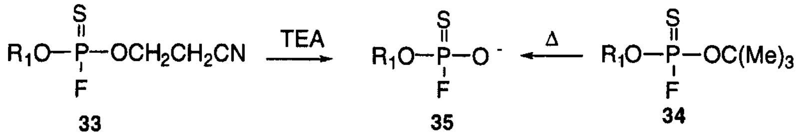
SCHEME 11

II.2 Preparation of nucleoside phosphorofluoridothioate and phosphorofluoridodithioate monoesters.

II.2.1 Preparation of nucleoside phosphorofluoridothioate monoesters from P(V) derivatives.

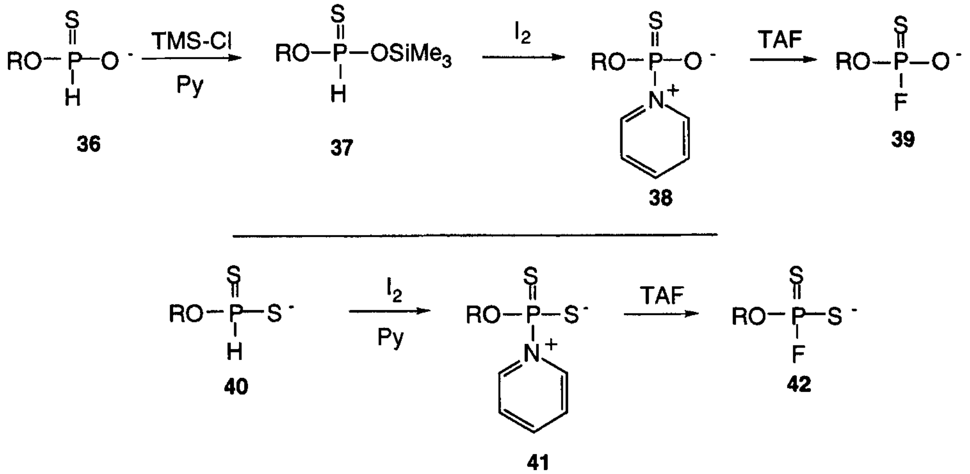
This is an analogous synthetic pathway to that of the formation of nucleoside phosphorofluoridates **16** from the appropriate asymmetric diesters **18** and **19**, discussed in section I.2.1. Selective removal of the 2-cyanoethyl group from **33** (β-elimination, effected by triethylamine-pyridine) or the *tert*-butyl from **34** (thermal elimination), furnishes nucleoside phosphorofluoridates **35** in high yields[11].

The starting materials for these syntheses are the corresponding nucleoside alkyl phosphorofluoridites, which add sulfur to produce phosphorofluoridothioate diesters **33** or **34**[11].



R1 = nucleoside moiety

SCHEME 12



TAF = triethylamine trishydrofluoride; R = nucleoside moiety

SCHEME 13

II.2.2Preparation of nucleoside phosphorofluoridothioate and phosphorofluoridodithioate monoesters from H-phosphonothioate and H-phosphonodithioate derivatives.

Oxidation of nucleoside H-phosphonothioates[54,60] **36** with iodine in pyridine in the presence of trimethylsilyl chloride, followed by addition of TAF provides the corresponding nucleoside phosphorofluoridothioates **39** in >90% yield (SCHEME 13)[16,40]. The reaction most likely involves the pyridine adduct of metathiophosphate **38** as an intermediate (^{31}P NMR)[16], formed from oxidation of the silyl derivative **37** with iodine.

Nucleoside H-phosphonodithioates **40**[61-63]in pyridine easily undergo oxidation with iodine to produce the pyridine adduct of metadithiophosphates **41**[16]. These, upon treatment with TAF afford phosphorofluoridodithioates **42** (yield ~85%) (SCHEME 13)[16]. This transformation can also be carried out in one step, as a four component reaction.

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