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First and Efficient Synthesis of Phosphonodifluoromethylene Analogues of Nucleoside 3'-Phosphates: Crucial Role Played by Sulfur in Construction of the Target Molecules

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Abstract: Phosphoric esters of secondary alcohols are ubiquitous in biological systems. However, despite the obvious interest of the corresponding difluoromethylene phosphonates as isopolar mimics, a single example of such an analogue featuring this particular substitution pattern has so far been reported in the literature, due to synthetic problems associated with their preparation. The lithium salt of diethyl difluoromethylphosphonothioate **28d** provides a solution to this problem, as demonstrated by an 8-step synthesis of all five fully protected analogues of nucleoside 3'-phosphates in 9–18% overall yield, from readily available ketones. Sulfur is shown to play a crucial role in the introduction of the phosphorus-substituted difluoromethylene unit onto the furanose ring. Complete diastereoselectivity is observed in the three steps of the process requiring stereocontrol. The key conversion of the P=S bond into its oxygenated analogue is simply achieved by use of *m*-chloroperoxybenzoic acid. It is noteworthy that the synthesis can be carried out on large scale: a 31-g batch of compound **26b** has been prepared. The deprotected nucleoside 3'-phosphate analogues can be liberated from their precursors as exemplified by the conversion of **7b**, **8b**, and **9b** into the corresponding difluorophosphonic acids, isolated in the form of their disodium salts.

Introduction

Nucleotide analogues, as well as modified oligonucleotides (MONs) and oligodeoxynucleotides (MODNs), have been much used in recent years to regulate viral or cellular gene expression, with various results.¹ Resistance to enzymes, including phosphatases and nucleases, bioavailability, and cell membrane penetration, for example, are important parameters for which improvement may result in increased bioactivity.² Considerable research effort has been devoted to the replacement of the phosphate (polyphosphate) groups with other functionalities. In the past decade, phosphorothioate, methylphosphonate, phosphoramidate, amide, and boranophosphate links, for instance, have been developed and used to modify nucleotides or the backbone of oligonucleotides.³ This has recently resulted in the approval of Vitravene by the Food and Drug Administration (FDA) for the treatment of cytomegalovirus infection. Vitravene

is a MON in which some of the phosphate groups have been replaced by phosphorothioates, thereby increasing the stability toward enzymes and inducing a better antisense activity.⁴

Replacing the 3'-oxygen atom of a 3'-phosphorylated nucleoside with a carbon results in the formation of an essentially nonhydrolyzable C–P bond, a feature of obvious interest with regard to enzymatic stability. Thus, a variety of different routes has been reported in the literature for the preparation of 3'-phosphonomethylnucleosides.⁵ Until very recently, however, they had not been incorporated in oligonucleotides because of synthetic difficulties.^{5j} Furthermore, one of the known problems associated with the replacement of the 3'-oxygen atom with a CH₂ is the lack of an electronegative substituent at C3', which results in a conformational change of the furanose ring (C3'-endo to C2'-endo). Potential consequences of this are diminished

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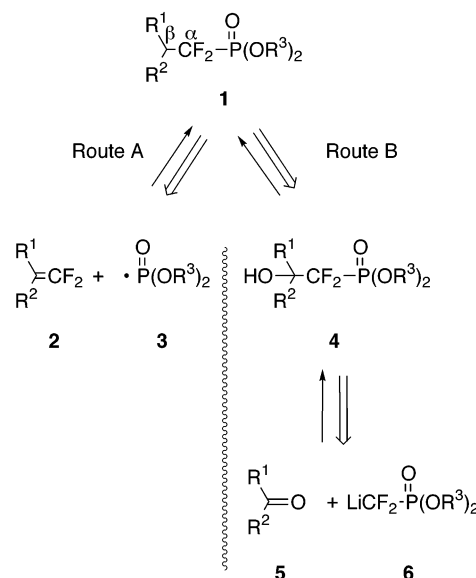
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binding interactions between the modified nucleotide and its target or, in the case of oligonucleotides, a lower stability of the RNA/MON duplex.⁶

A possible response to this undesirable behavior may be the replacement of the C3' oxygen atom by a difluoromethylene (CF₂) moiety. In addition to potentially bringing a solution to the above conformational problem, the presence of the fluorine atoms increases both the structural and electronic similarities between the phosphonate and the parent phosphate groups: Blackburn's seminal contributions in that field have been corroborated by many studies.^{7,8} Despite this, 3'- or 5'-phosphonodifluoromethylnucleosides have only received scant attention due to the problems and difficulties associated with their preparation. Thus, notwithstanding the many potential advantages of these compounds, only 5'-phosphonodifluoromethylnucleosides have been prepared by Usman and co-workers,⁹ and a dinucleotide analogue has been generated from the monomer.

Until recently, difluorophosphonates, featuring geminal disubstitution on the carbon atom β to the phosphorus atom, could not be synthesized, due to important limitations from the then-available methodologies.¹⁰ We and others have published solutions that allow the preparation of difluorophosphonates with this particular substitution pattern.¹¹ Thus, addition of phosphonyl (and phosphonothioyl) radicals **3** onto gem-disubstituted difluoroalkenes **2** followed by hydrogen quenching, or generation of tertiary alcohols from ketones **5** and lithiated species **6**

Scheme 1. Retrosynthetic Analysis of β,β -Disubstituted- α,α -difluorophosphonates **1**



followed by deoxygenation of the resultant adduct **4**, now provide the two established strategies allowing access to β,β -disubstituted difluorophosphonates **1** (routes A and B, Scheme 1).

To the best of our knowledge however, these methodologies have been applied only to the preparation of one L-phosphothreonine analogue.^{11c} We now report herein our own work, based on the dual approach depicted in Scheme 1, which has resulted in the preparation of all five fully protected C3'-phosphonodifluoromethyl analogues **7b**, **8b**, **9b**, **10b**, and **11b** of nucleoside 3'-phosphates, as well as the completely deprotected disodium difluorophosphonates **7c**, **8c**, and **9c** (Figure 1).

Retrosynthetic Analysis. Retrosynthetic analysis of both routes highlights the crucial issue of stereochemical control when constructing (route A, radical addition approach) or introducing (route B, anion addition approach) the phosphonodifluoromethyl unit.

(A) Radical Addition Approach. The sequence of events in this synthetic route was expected to lead to either the desired analogue, possessing the phosphonodifluoromethyl moiety on the α face of the furanose, or the undesired one (with the same unit on the other face) depending on the initial substrate (Scheme 2). Inasmuch as the base would exert an undesired directing effect in the quenching of radical **13**, thereby positioning the phosphate group mimic on the β -face and delivering adduct **14**, we decided to start from carefully chosen protected furanoses, construct the phosphonodifluoromethyl functional group first, and, finally, bring in the different bases.¹² Thus the well-known steric hindrance generated by an isopropylidene protecting group in the 1,2 positions of the furanose was expected to mainly furnish the desired stereoisomer **17** upon hydrogen atom capture by radical **16**. Data from the literature and from these laboratories support this assumption.¹³

(B) Anion Addition Approach. Here again, addition of the lithium salt **6** of difluoromethylphosphonate to nucleoside

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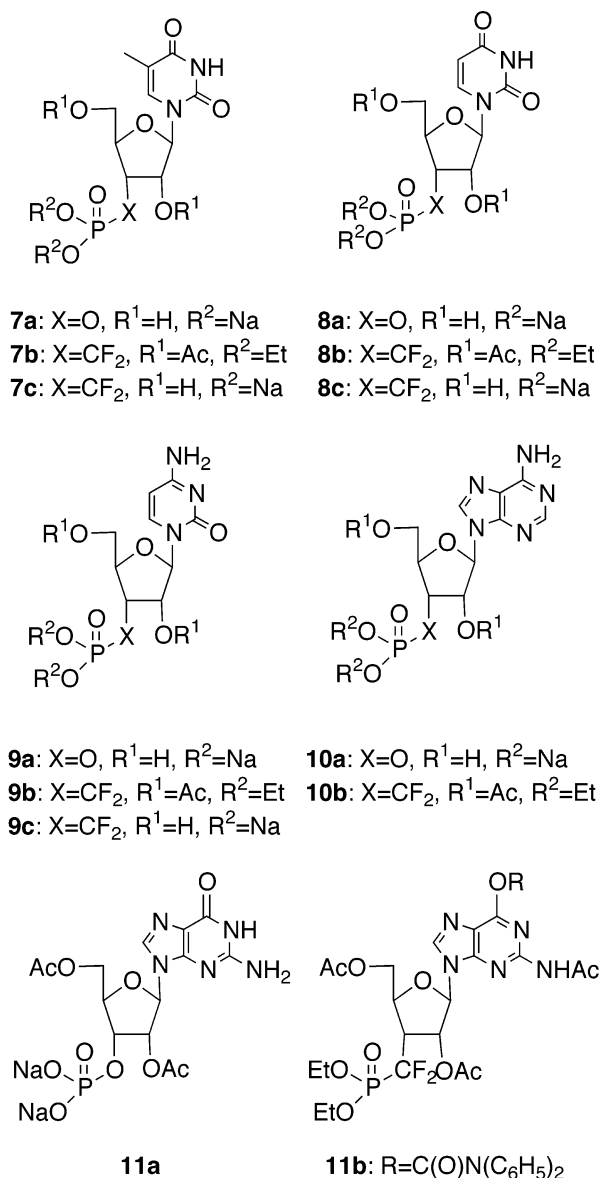
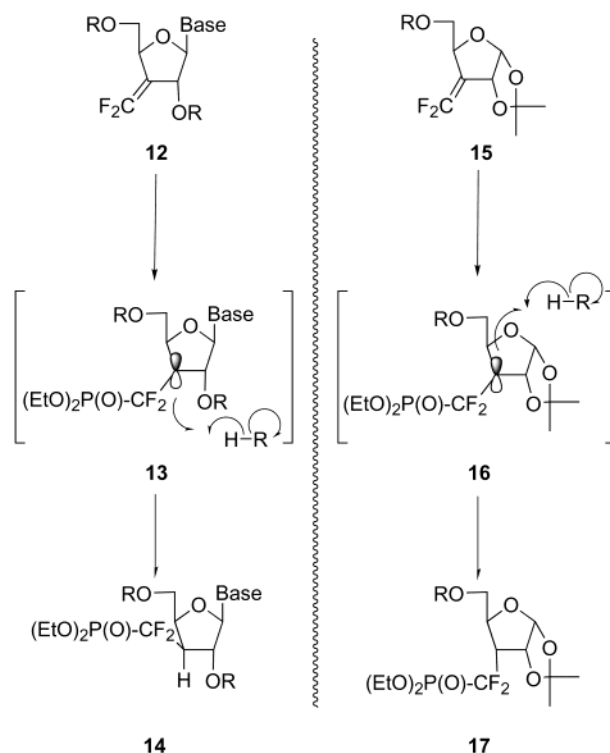


Figure 1. Target molecules **7b–11b** and **7c–9c** as phosphonodifluoromethylene analogues of nucleoside 3'-phosphates **7a–11a**.

derivative **18** would most probably lead to alcohol **19** [CF₂P(O)(OR)₂ unit on the α face], while addition onto ketone **20** would deliver alcohol **21**, with the CF₂P(O)(OR)₂ unit on the convex face (Scheme 3). Deoxygenation of products **19** and **21** and quenching of the intermediate radicals **13** and **16** should, as in the radical approach, result in the formation of products featuring the phosphate group mimic on the β face of the nucleotide analogue (undesired, **14**) or the concave face of the furanose (desired, **17**), respectively. Thus it was anticipated that,

Scheme 2. Expected Diastereoselection from Addition of Diethylphosphonyl Radical onto Difluoroalkene **12** or **15**



in both cases, quenching of the intermediate radicals should result in a *stereochemical inversion of the phosphonodifluoromethylene unit from one face of the furanose ring to the other*. Again, the undesirable stereodirecting effect of the base led us to consider furanoses of the type **20** as more suitable substrates for this approach.

Results

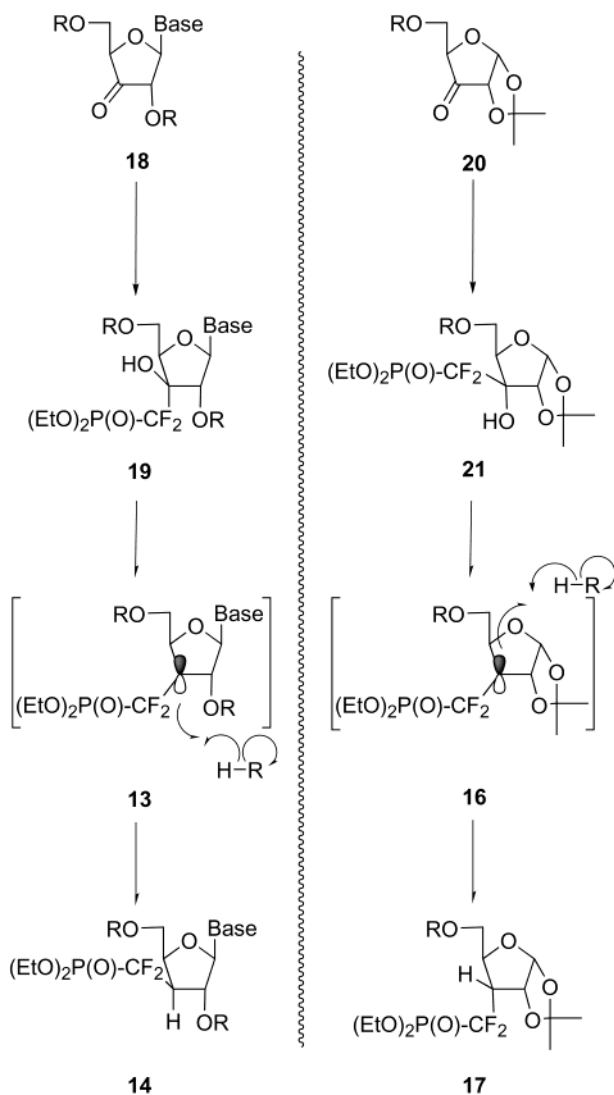
Route A. To test route A, the readily available glucofuranose derivative **22**¹⁴ was chosen as starting substrate and transformed into the corresponding difluoroalkene **23** (Scheme 4).¹⁵ However, all attempted reactions between **23** and diethyl phosphite **24a**, in the presence of various radical initiators and under a variety of conditions, failed to generate the desired adduct **26a** (or its epimer).¹⁶ *O,O*-Dialkylphosphonothioyl radicals, generated from the corresponding thiophosphites, have been reported to add more efficiently onto difluoroalkenes.^{11a,11c} However, in our case, the use of *O,O*-diethylthiophosphite **24b** also led to the recovery of unreacted difluoroalkene. Abstraction of a hydrogen atom from phosphite being an energetically difficult process, the use of selenenylated derivatives **24c** and **24d** in conjunction with a hydrogen atom donor was attempted;^{11a–c} this led only to the generation of phosphite **24a** and thiophosphite **24b**, the difluorinated substrate being once again recovered unchanged. Apparently, under the reaction conditions, hydrogen atom transfer to the phosphorus-centered radical is a faster process than its addition radical on the fluorinated alkene. The

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(14) Prepared by the action of the Dess–Martin reagent on the corresponding alcohol. See Supporting Information.

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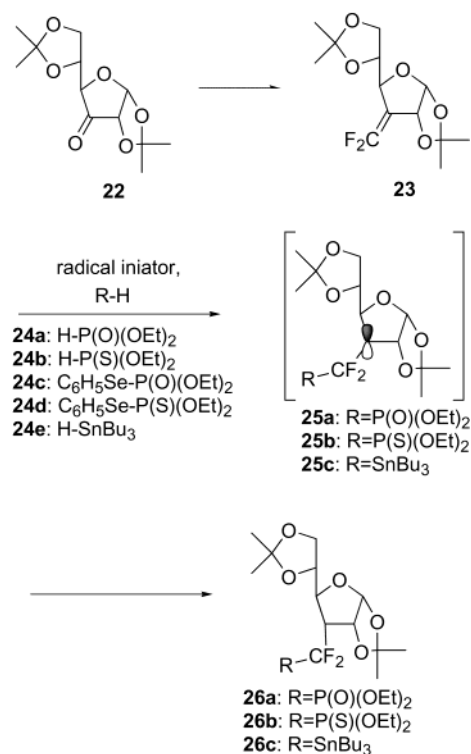
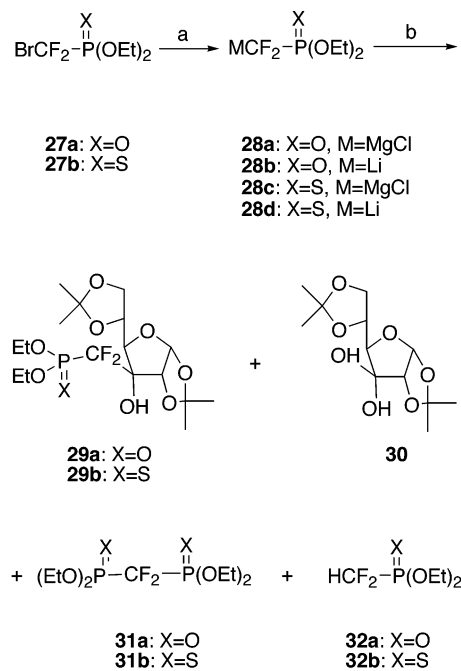
(16) These conditions included, in the case of phosphites and thiophosphites, the use of several radical initiators, such as *tert*-butyl peroxyphthalate or *tert*-butyl peroxide, for example, at various temperatures, and Et₃B/O₂. Tri-*n*-butyltin hydride and tris(trimethylsilyl)silane were used as hydrogen quenchers in the case of **24c** and **24d**.

Scheme 3. Expected Diastereoselection from Addition of the Lithium Salt of Diethyl Difluorophosphonate onto Ketone **18** or **20**

plausibility of this first approach was, however, verified by adding the tri-*n*-butyltin radical on difluoroalkene **23**. Thus, adding tri-*n*-butyltin hydride (**24e**) to **23** in the presence of azobis(isobutyronitrile) (AIBN) resulted in the formation of adduct **25c**, isolated in 73% yield. ^1H NMR spectrometric analysis (1D and 2D modes) of the pure product indicates a doublet of doublet for the hydrogen on carbon 2 ($^3J = 4.3, 4.4$ Hz), consistent with the depicted stereochemistry of adduct **26c**. The observed diastereomeric excess (>95%) demonstrated the validity of the approach, the 1,2-isopropylidene unit directing hydrogen quenching of the radical adduct exclusively from the convex face.

Route B. This approach involves the addition of metalated derivatives of difluoromethylphosphonate **32a** and its corresponding sulfur analogue, difluoromethylphosphonothioate **32b**.^{10,17} We elected to study the addition of organomagnesium and lithiated species **28a–28d** onto ketone **22** (Scheme 5).

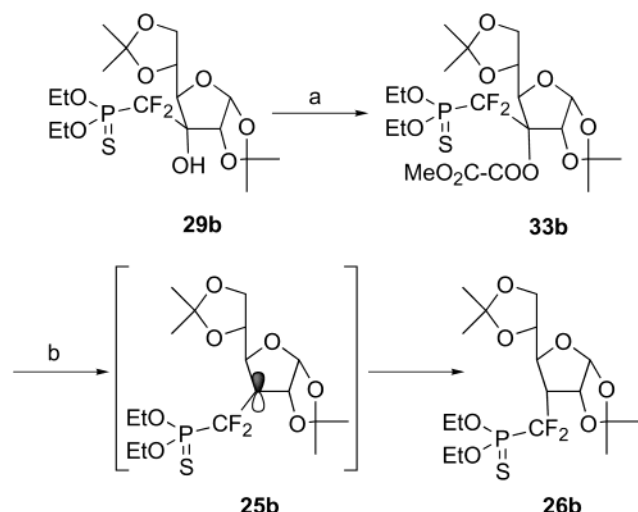
When bromide **27a** was sequentially subjected to a solution of isopropylmagnesium chloride, ketone **22** and workup, a

Scheme 4. Radical Addition Reactions onto Difluoroalkene **23****Scheme 5.** Addition of Reagents **28a–28d** onto Ketone **22**^a

^a Reagents and conditions: (a) *t*-BuLi or *i*-C₃H₇MgCl, -78°C . (b) **22**, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, then H₃O⁺.

mixture containing mainly a 1:1 adduct was formed. Byproducts included the hydrate **30** of unconsumed starting ketone, tetraethyl difluoromethyl bisphosphonate (**31a**), and diethyl difluoromethylphosphonate (**32a**). Purification of the adduct proved tedious and invariably led to an impure compound in low yield (<20%, contaminated by ketone hydrate **30**). The analogous sulfur reagent **28c** was similarly prepared and its reactivity toward ketone **22** was tested at -78°C . These experiments

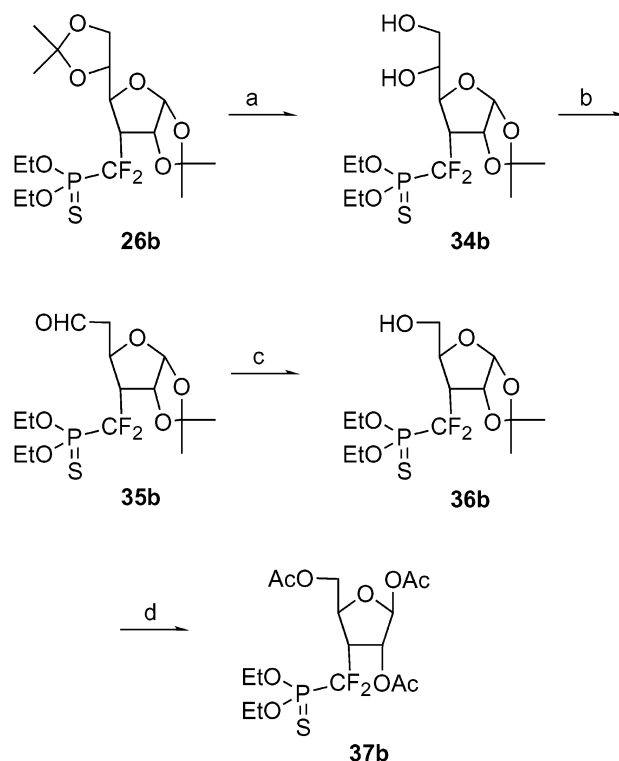
(17) (a) Piettre, S. R.; Raboisson, P. *Tetrahedron Lett.* **1996**, 37, 2229–2232.
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Scheme 6. Diastereoselective Deoxygenation of Adduct **29b**^a

^a Reagents and conditions: (a) (i) *n*-BuLi, -78°C ; (ii) ClCOCOOMe, -78°C , then 0°C . (b) *n*-Bu₃SnH, AIBN, toluene, 110°C (81%, 2 steps).

resulted in the formation of a single adduct, along with hydrate **30** and difluorophosphonothioate **32b**. Similarly however, purification afforded only 21% of adduct; while stereochemistry could not be ascertained at this time, it was presumed to be that of **29b**, on the basis of literature data.¹³ These disappointing yields led us to investigate the behavior of the two lithiated reagents **28b** and **28d**. Treatment of bromide **27a** with 2 equiv of *tert*-butyllithium at -78°C led to lithiated species **28b**; addition of ketone **22** and workup produced a mixture of one adduct (presumably **29a**), **31a**, and **32a**, the adduct and the bisphosphonate being formed in minor and major amounts, respectively. Purification led to the isolation of the adduct in only 7% yield. Remarkably, however, this picture changed dramatically when the corresponding sulfur reagent was used. Thus, reaction of the lithiated species **28d** with ketone **22** led in *perfectly reproducible fashion and with high isolated yields* (76–80%) to the same 1:1 adduct as above. The difference in behavior may be attributed to the reported lower stability of the lithium salt of difluoromethylphosphonates, when compared to its sulfur counterpart.^{17a} In addition, not a trace of bisphosphonothioate **31b** could ever be detected in the experiments involving **28b** or **28d**. It is noteworthy that the presence of sulfur also facilitates greatly the purification by chromatography.

Deoxygenation at carbon atom 3 was achieved by using the procedure of Berkowitz et al. (Scheme 6).^{11e} Thus sequential treatment of the above product **29b** with *n*-butyllithium and *O*-methyloxalyl chloride at -78°C furnished the crude phosphonothioate **33b** upon workup. This material was engaged without further purification in a reaction with tri-*n*-butyltin hydride and AIBN to give difluorophosphonothioate **26b** in 81% isolated yield (two steps). A single diastereoisomer was obtained as demonstrated by ¹H, ¹⁹F, and ³¹P NMR spectrometric analyses. Furthermore, the ¹H multiplicity of H-2 (doublet of doublet) and the H–H coupling constants (³*J* = 3.7, 3.8 Hz) were indicative of a *cis* relationship between H-1, H-2, and H-3. These results are in line with literature data and confirm at the strong stereodirecting effect of the 1,2-acetonide group in the hydrogen atom transfer step of the process.¹³ It is noteworthy that, under these conditions, not a trace of difluoroalkene **23** resulting from the homolytic scission of the P–CF₂ bond was detected. This

Scheme 7. Transformation of Hexofuranose **26b** into Pentofuranose **37b**^a

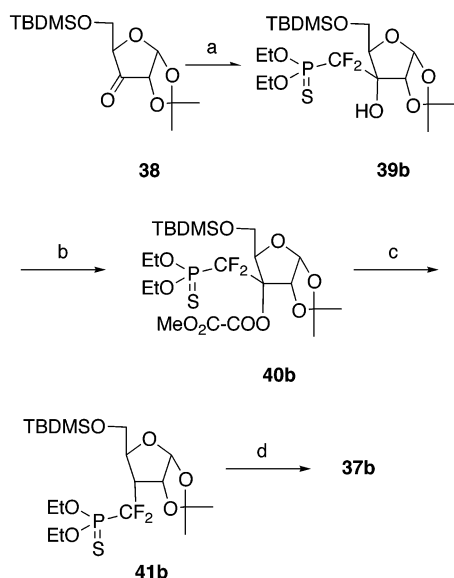
^a Reagents and conditions: (a) AcOH/H₂O (3:1), 95°C . (b) NaIO₄, EtOH/H₂O (1:1), room temperature. (c) NaBH₄, EtOH/H₂O (1:1), 0°C , then 25°C (42%, 3 steps). (d) Ac₂O, AcOH, H₂SO₄, room temperature (58%).

is indicative of a faster hydrogen atom transfer step than the homolytic β -scission, which would drive the equilibrium back toward the starting difluoroalkene and phosphonyl or phosphonothioyl radicals.

This three-step sequence of reactions successfully introduces the phosphonothiodifluoromethyl unit on position 3 of the furanose ring with a final, desired *R* configuration. Furthermore, it is amenable to larger scale preparations: a 31-g batch of **26b** has been prepared in this way.

The next task that we addressed was the transformation of the 6-carbon furanoside derivative into a 5-carbon one (Scheme 7).^{5d,9b,18} Deprotection of the 5,6-isopropylidene acetal was carried out with 75% aqueous acetic acid. Sodium periodate oxidation of the crude product followed by the reduction of the resultant aldehyde **35b** with sodium borohydride (NaBH₄) delivered alcohol **36b** in 42% overall yield (three steps). Treatment of compound **36b** with acetic anhydride in a mixture of acetic and sulfuric acids led to deprotection of the 1,2-acetonide and concomitant acetylation of all three hydroxyl groups, thus resulting in the production of triacetate **37b**, isolated in 58% yield. Stereoselection at carbon 1 was again observed to be complete: not a trace of the α -anomer could be detected by NMR spectrometry. This may result from the combined participation of the 2-acetoxy function and the phosphonothiodifluoromethylene group, whose sulfur could bridge posi-

(18) This was achieved by using standard, published procedures. See (a) Murray, H. D.; Prokop, J. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1968; p. 193. (b) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179.

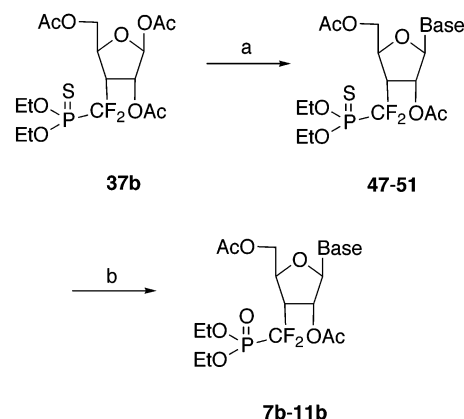
Scheme 8. Preparation of Furanose **37b** from Ketone **38**^a

^a Reagents and conditions: (a) **28d**, $-78 \rightarrow 0^\circ\text{C}$, then H_3O^+ . (b) (i) $n\text{-BuLi}$, -78°C ; (ii) ClCOCOOMe , -78°C , then 0°C . (c) $n\text{-Bu}_3\text{SnH}$, AIBN, toluene, 110°C (58%, 2 steps). (d) Ac_2O , AcOH , H_2SO_4 , room temperature (59%).

tions 1 and 3.¹⁹ This furanose is now well suited to undergo a Lewis acid-catalyzed introduction of the different heterocyclic bases.

An analogous procedure was also developed from D-xylose, a five-carbon furanose (Scheme 8). Thus, addition of the lithium salt of diethyl difluoromethylphosphonothioate **28d** onto ketone **38** (prepared in three steps²⁰) yielded adduct **39b** (70%) in a total stereoselective manner. Deoxygenation as above furnished ribofuranose derivative **41b** as a single adduct possessing the depicted stereochemistry (58% isolated yield). Once again, the procedure resulted in clean and complete stereochemical inversion of the phosphonothiodifluoromethylene unit from the convex face to the concave one. Treatment of product **41b** with acetic anhydride liberated triacetate **37b**, identical in every respect to the samples obtained from glucufuranose derivative **22**.

Introduction of thymine, uracil, and cytosine was achieved by use of Vorbrüggen's modification of the Hilbert–Johnson protocol, which calls for the use of the silylated bases **42**, **43**, and **44** and a Lewis acid (Scheme 9, Table 1).²¹ Unprotected adenine (**45**) and protected guanine **46** were introduced by adapting the procedures of Saneyoshi and Robins, respectively.²² All five phosphonothiodifluoromethyl analogues of the corre-

Scheme 9. Coupling Reaction between **37b** and Base Derivatives **42–46** and Conversion of Phosphonothioates **47–51** into Phosphonates **7b–11b**^a

^a Reagents and conditions: (a) See Table 1. (b) 80% *m*-CPBA, CH_2Cl_2 , room temperature (54–91%).

sponding nucleoside 3'-phosphates were thus obtained in good to excellent isolated yields. In each case, the reaction was found to be completely diastereoselective, due to the steric hindrance of the α -face of the intermediate anomeric cation resulting from the stabilizing participation by both the 2-acetoxy unit and the 3-phosphonothiodifluoromethyl group; despite the presence of the two fluorine atoms, it may be suggested that the longer $\text{P}=\text{S}$ bond (1.886 Å, compared to 1.580 Å for the $\text{P}=\text{O}$ bond) helps this group participation by bridging positions 1 and 3, in a way reminiscent of what Shibuya recently observed with the 2,3-dideoxy-3-phosphonothioyl analogue.^{5h}

The use of unprotected bases under Lewis acid catalysis led to low yields except in the case of adenine. Guanine is known to frequently furnish a mixture of regioisomers resulting from the competitive alkylation of the base on positions 7 and 9.²³ In our own case, the reported carbamoyl derivative **46** was sequentially treated with bis(trimethylsilyl)acetamide (BSA) and triacetate **37b** to afford exclusively the desired N9 isomer **51**.

The protected difluorophosphonothioates **47–51** were then converted into their oxygenated counterparts **7b–11b** (Scheme 9). Some time ago, we conducted an extensive study on the conversion of difluorophosphonothioates into the corresponding difluorophosphonates.²⁴ Our own experience indicates that many of the procedures available for the conversion of the nonfluorinated analogues are ineffective on the fluorinated phosphonothioates. We thus reported that dioxirane and perfluorooxaziridine are the reagents of choice for such a conversion and that purified *m*-chloroperoxybenzoic acid (*m*-CPBA) does not result in a clean transformation. We are pleased to report that commercially available *m*-CPBA (i.e., 80% pure, mixture with *m*-chlorobenzoic acid) (5 equiv) does oxidize cleanly all five phosphonothioates **47–51** to efficiently lead to the corresponding phosphonates **7b**, **8b**, **9b**, **10b**, and **11b** in good to excellent

(19) The literature reports a few cases in which complete selectivity was not observed during acetylation of an 1,2-acetonide moiety, despite the formation of a 2-acetoxy unit. The suggestion by Shibuya of the possible participation of a phosphonothioyl unit (the resultant of the longer $\text{P}=\text{S}$ bond, when compared to the $\text{P}=\text{O}$ bond) might be extended to the difluorinated analogue. See ref 5h.

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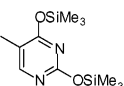
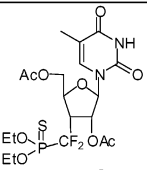
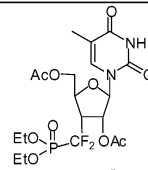
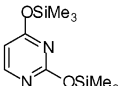
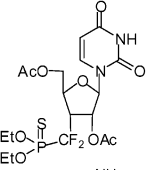
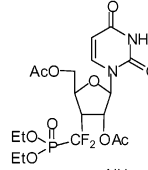
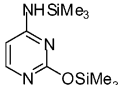
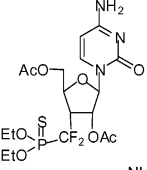
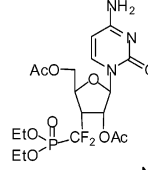
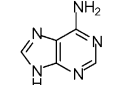
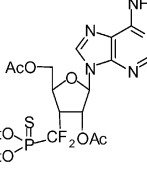
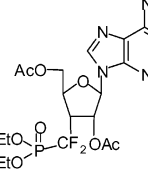
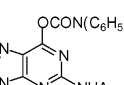
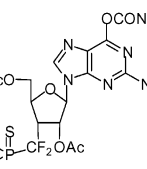
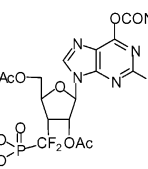
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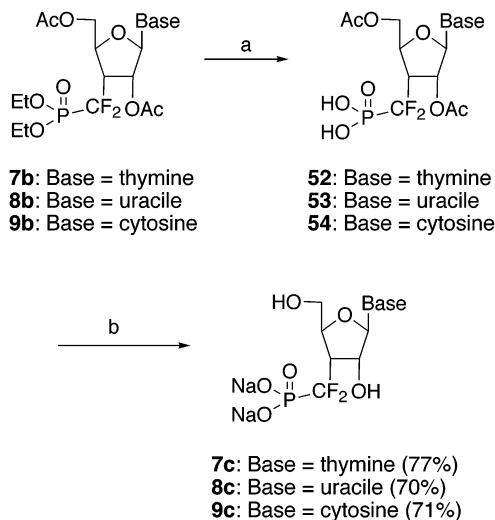
Table 1. Reaction Conditions, Products, and Yields for the Coupling between **37b** and Base Derivatives **42–46** and for the P=S/P=O Conversion

base	base derivative	conditions	products ^b	yields ^c	products ^b	yields ^c
thymine		42 (3 equiv), TMSOTf (5 equiv), ClCH ₂ CH ₂ Cl, 25°C, 1.5 h		47 92		7b 77
uracil		43 (3 equiv), TMSOTf (5 equiv), ClCH ₂ CH ₂ Cl, 25°C, 1.5 h		48 81		8b 54
cytosine		44 (2 equiv), TMSOTf (2 equiv), ClCH ₂ CH ₂ Cl, 80°C, 1 h		49 95		9b 91
adenine		45 (1.1 equiv), Base (1.1 equiv), SnCl ₄ (2 equiv), CH ₃ CN, 25°C, 18 h		50 87		10b 73
guanine		1) 46 (1 equiv), BSA ^a (2 equiv), ClCH ₂ CH ₂ Cl, 80°C, 0.25 h 2) 37b (0.5 equiv), TMSOTf (1 equiv), ClCH ₂ CH ₂ Cl, 80°C, 1 h		51 66		11b 66

a. BSA: bis(trimethylsilyl)acetamide. b. Obtained after treatment with NaHCO₃, work-up and purification (see experimental section). c. Isolated yields.

isolated yields (77%, 91%, 54%, 66%, and 73%, respectively) (Table 1).²⁵

The possibility of fully deprotecting the products was demonstrated by transforming difluorophosphonates **7b**, **8b**, and **9b** into their corresponding disodium phosphonates. Hydrolysis of the diesters was carried out in the conventional manner, via a transesterification process with trimethylsilyl bromide (TMS-Br).²⁶ Thus, for example, heating nucleotide analogue **7b** and 6 equiv of TMSBr in acetonitrile at 65 °C for 1 h, followed by evaporation of the volatiles and hydrolysis of the resultant bis-(silyl) ester, afforded phosphonic acid **52** (Scheme 10). Similar results were obtained with substrates **8b** and **9b**, and crude phosphonic acids were obtained as creamy solids. Stirring the acids in a mixture of ammonia and methanol²⁷ at room temperature for 24 h, evaporating the solvent and excess ammonia, and sequentially purifying the crude material, first on DEAE-Sephadex A-25 (HCO₃⁻) and then on Dowex 50

Scheme 10. Preparation of Deprotected Target Molecules **7c–9c**^a

^a Reagents and conditions: (a) TMSBr, CH₃CN, 80 °C. (b) (i) NH₃, MeOH, room temperature; (ii) DEAE-Sephadex A-25; (iii) Dowex 50 WX8 (Na⁺).

WX8 (Na⁺), yielded the disodium salts of the fully deprotected nucleotide analogues **7c–9c**, in the form of whitish powders.

Conclusion

Protected analogues of nucleosides 3'-phosphates, in which the esterified oxygen atom is replaced by a difluoromethylene

(25) Despite the possible oxidation of the base nuclei by *m*-CPBA (see Tanaka, T.; Letsinger, R. L. *Nucleic Acid Res.* **1982**, *10*, 3249–3260), the reactions were found to be very clean.

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unit, have been prepared for the first time in overall yields ranging from 9% to 18%. The key step of the synthesis, developed from readily available ketones, involves addition of the lithium salt of difluoromethylphosphonothioate. The beneficial presence of the sulfur atom in this reagent translates into greatly increased yields, reproducibilities, and ease of purification. It is noteworthy that total diastereoselectivity is observed in the three steps requiring stereocontrol (**22** → **29b**; **29b** → **26b**; and **37b** → **47–51**); the first two of these three steps feature a shift of the phosphonothiodifluoromethyl unit from the convex face to the concave face of the furanose ring. The successful, ionic approach (route B) results in the isolation of the fully protected difluorophosphonothioates as well as the corresponding difluorophosphonates. It is of interest to note that the presence of sulfur may result in higher resistance toward enzymatic hydrolysis, in a way reminiscent of phosphorothioates

and phosphates. Three of the final, deprotected nucleotide analogues are obtained in high yields by a sequence of two easily carried out procedures. Intermediates **47–51**, **7b–11b**, and **7c–9c** may find application in the production of either antiviral compounds or modified oligonucleotides. Work is in progress to develop these applications.

Acknowledgment. C.L. is grateful to MENRT (France) for providing a grant.

Supporting Information Available: Experimental procedures and analytical data for all new compounds as well as ^1H , ^{19}F , and ^{31}P NMR spectra for compounds **37b**, **47**, **48**, **49**, **50**, **51**, **7b**, **8b**, **9b**, **10b**, **11b**, **7c**, **8c**, and **9c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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