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Difluoromethylenephosphonates: synthesis and transformations

K S Chunikhin, A A Kadyrov, P V Pasternak, N D Chkanikov

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Abstract. The data on the synthesis of organic compounds containing the difluoromethylenephosphonate group are analyzed and generalized. The attention is focused on the introduction of this group into various organic molecules and subsequent transformations of the compounds thus formed. Individual sections are devoted to the synthesis of heterocyclic compounds and analogues of natural substances containing difluoromethylenephosphonate groups. The bibliography includes 153 references.

I. Introduction

Phosphates play a unique role in biochemical processes that occur in living organisms, such as the metabolism, regulation and generation of genetic information. However, it is difficult to study *in vitro* the mechanisms of these processes because of low hydrolytic stability of the phosphodiester bond in the presence of phosphatases. This has stimulated extensive research on the design and synthesis of various phosphate analogues containing the phosphatase resistant P – C bond instead of the labile P – O bond. Among these compounds, phosphonates † and, particularly, difluoromethylenephosphonates, are most widely used. The latter compounds are postulated as stable biological models of natural phosphates. This is associated with the fact that the CF_2 group is an isoelectronic and isosteric analogue of the oxygen atom, wherein the fluorine atoms are considered as oxygen lone pairs. In the last 15 years, a wide range of biologically active compounds containing the difluoromethylene groups, which are derivatives of nucleosides, amino acids, sugars and heterocycles, were synthesized. These compounds are of interest as potent inhibitors of various enzymes and as probes for the elucidation of the mechanisms of biological processes with the participation of phosphates. Blackburn *et al.*[2, 3] developed a strategy for the use of difluoromethylenephosphonates in the design of enzyme inhibitors.

The first attempt to systematize the methods for the synthesis of α,α-difluoromethylenephosphonates was made by Burton *et al.*[4] in 1996. In one of the sections of their review devoted to the synthesis of phosphonates, methods for the synthesis of α,α-difluoromethylenephosphonates were considered; however, only 30 references were cited. One year later, O'Hagan and Rzepa [5] published a review, where the physicochemical and biological properties of various fluoroaliphatic compounds, including difluoromethylenephosphonates, were discussed in detail. In 2006, Romanenko and Kukhar [6] wrote a review on the synthesis and biological properties of various fluorinated phosphonates, including difluoromethylenephosphonates. The synthesis and biological properties of asymmetric phosphonates were considered in the review by Kolodyazhnyi,[7] where certain representatives of difluoromethylenephosphonates were mentioned.

Unlike the above reviews, the present review is focused exclusively on difluoromethylenephosphonates. Methods for the synthesis of derivatives used for the introduction of the difluoromethylenephosphonate moiety into organic compounds are briefly considered. Major attention is given to the introduction of this moiety into various organic compounds and transformations of the resulting difluoromethylenephosphonates. Individual sections are devoted to the synthesis of heterocyclic compounds containing the $(RO)_2P(O)CF_2$ group and CF_2 analogues of natural substances. In conclusion, methods for the synthesis of

K S Chunikhin, A A Kadyrov, P V Pasternak, N D Chkanikov
A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 119991 Moscow, Russian Federation. Fax (7-499) 135 61 66, tel. (7-499) 135 93 32,
e-mail: faftor353@ineos.ac.ru (K S Chunikhin),
tel. (7-499) 135 93 24, e-mail: aakad@ineos.ac.ru (A A Kadyrov),
tel. (7-499) 651 29 10, e-mail: nchkan@ineos.ac.ru (N D Chkanikov)

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difluoromethylenephosphonates by the fluorination of alkyl and acyl phosphonates at the α position are discussed.

II. Synthesis of reagents for the introduction of the difluoromethylenephosphonate group into organic molecules

This section briefly describes main methods for the synthesis of the compounds $(RO)_2P(O)CF_2EX_n$ containing the labile C–E bond (E is an element other than carbon; X = Hal, Alk, Ar or OAlk; $n = 0-3$), which are used for the introduction of the $(RO)_2P(O)CF_2$ group into organic compounds; H, I, Br, Li, Mg, Zn, Cd, S, Se, B, Si, *etc*. can serve as the E elements.

The most commonly used method for the preparation of derivatives $(RO)_2P(O)CF_2EX_n$ is based on the reaction of various halodifluoromethanes CF_2HalX (X = H, F, Cl, Br or I) with dialkyl phosphite salts $(RO)_2PONa$ (Michaelis–Becker reaction) or with tertiary phosphites $(RO)_3P$ (Arbuzov reaction). Examples of these reactions are given below. Thus, one of the first representatives of difluoromethylenephosphonates, *viz*., diethyl difluoromethylphosphonate (**1**), was synthesized in 1959 by the reaction of chlorodifluoromethane with sodium diethyl phosphite.[8]

$$HCF_2Cl + (EtO)_2PONa \xrightarrow[30-35\ ^\circ C]{\text{petroleum ether}} \underset{\mathbf{1}}{(EtO)_2P(O)CF_2H}$$

Isopropyl and n-butyl difluoromethylphosphonates were synthesized analogously.[8] Other examples of the synthesis of $(RO)_2P(O)CF_2E$ (E = H or Hal) were given in the review.[6]

In most cases, the phosphoryldifluoromethyl group is introduced into various organic compounds with the use of metal derivatives, which are prepared by the reactions of difluoromethylphosphonates or their halogen derivatives with the corresponding metals or their salts. Thus, [(diethoxyphosphoryl)difluoromethyl]lithium (**2**) stable at −78 °C is formed in the reaction of lithium diisopropylamide (LDA) or butyllithium with diethyl (difluoromethyl)-phosphonate (**1**).[9,10]

$$\left.\begin{array}{l}\underset{\mathbf{1}}{(EtO)_2P(O)CF_2H} + LiNPr^i_2 \xrightarrow[-78\ ^\circ C]{THF} \\ \underset{\mathbf{1}}{(EtO)_2P(O)CF_2H} + Bu^nLi \xrightarrow[-90\ ^\circ C]{THF}\end{array}\right\rightarrow \underset{\mathbf{2}}{(EtO)_2P(O)CF_2Li}$$

The zinc (**3**) and cadmium derivatives (**4**) were generated from bromide **5** and zinc metal[11] or cadmium metal.[12]

$$\underset{\mathbf{5}}{(EtO)_2P(O)CF_2Br} + M \xrightarrow{a \text{ or } b} \underset{\mathbf{3,4}}{(EtO)_2P(O)CF_2MBr}$$

M = Zn (**3**), Cd (**4**); (*a*) M = Zn, DMA, 60 °C, 3 h; (*b*) M = Cd, THF, 65 °C.

In turn, compound **4** can be transformed into trimethylsilyl derivative **6** and iodide **7**.[12]

$$\underset{\mathbf{4}}{(EtO)_2P(O)CF_2CdBr} \left\{\begin{array}{l}\xrightarrow{Me_3SiCl} \underset{\mathbf{6}}{(EtO)_2P(O)CF_2SiMe_3} \\ \xrightarrow{I_2} \underset{\mathbf{7}}{(EtO)_2P(O)CF_2I}\end{array}\right.$$

Borate **8** is another convenient reagent for the introduction of the $(RO)_2P(O)CF_2$ fragment into organic compounds. Compound **8** can be synthesized by the reaction of trimethyl borate with lithium derivative **2** or trimethylsilyl derivative **6**.[13] The latter reaction is performed in the presence of fluoride ions.

$$\left.\begin{array}{l}\underset{\mathbf{2}}{(EtO)_2P(O)CF_2Li} + B(OMe)_3 \\ \underset{\mathbf{6}}{(EtO)_2P(O)CF_2SiMe_3} + B(OMe)_3\end{array}\right\rightarrow \underset{\mathbf{8}}{(EtO)_2P(O)CF_2-\bar{B}(OMe)_3}$$

Sulfur- and selenium-containing derivatives $(EtO)_2P(O).CF_2ER$ (E = S or Se) are often used to introduce the $(EtO)_2P(O)CF_2$ moiety into organic molecules. One of the methods for the synthesis of these compounds is based on the reaction of [(dialkoxyphosphoryl)difluoromethyl]lithium with organic disulfides or diselenides. This method was applied to the synthesis, in particular, of diethyl (phenylsulfanyldifluoromethyl)phosphonate (**9**) and its selenium-containing analogue **10**.[14]

$$\underset{\mathbf{2}}{(EtO)_2P(O)CF_2Li} + PhXXPh \longrightarrow \underset{\mathbf{9,10}}{PhXCF_2P(O)(OEt)_2}$$

X = S (**9**), Se (**10**).

Compound **10** is formed also in the reaction of lithium derivative **2** with PhSeCl.[15]

Phosphonates $(RO)_2P(O)CF_2EX_n$ can also be synthesized by the fluorination of the corresponding derivatives $(RO)_2P(O)CH_2EX_n$ with the use of, for example, $Et_3N\cdot HF$, $FClO_3$, $(RSO_2)_2NF$ (R = Ph, CF_3), *etc*. as fluorinating agents. For instance, this method was used to synthesize various diisopropyl (alkylsulfanyldifluoromethyl)phosphonates **11a–d**.[16,17]

$$(Pr^iO)_2P(O)CH_2SR \xrightarrow[2)\ Et_3N\cdot(HF)_3,\ ZnBr_2,\ MeCN]{1)\ SO_2Cl_2,\ CH_2Cl_2} \underset{\mathbf{11a-d}}{(Pr^iO)_2P(O)CF_2SR}$$

R = Me (**a**), Et (**b**), Bu^n (**c**), Bn (**d**).

Compound **11a** is formed also by the replacement of the chlorine atoms in the dichloro derivative $MeSCCl_2P(O).(OPr^i)_2$ by fluorine atoms.[14]

$$MeSCCl_2P(O)(OPr^i)_2 \xrightarrow[ZnBr_2,\ MeCN]{Et_3N\cdot HF} \underset{\mathbf{11a}}{MeSCF_2P(O)(OPr^i)_2}$$

Phosphorylated aryl sulfides **12a** and aryl selenides **12b** were synthesized from methylsulfanyl derivative **11a** according to the following scheme:[17]

$$\underset{\mathbf{11a}}{(Pr^iO)_2P(O)CF_2SMe} \xrightarrow[2)\ PhXXPh]{1)\ BuLi,\ THF,\ -78\ ^\circ C} \underset{\mathbf{12a,b}}{(Pr^iO)_2P(O)CF_2XPh}$$

X = S (**12a**, 49%), Se (**12b**, 50%).

In the reactions with I_2 and Me_3SiCl, compound **11a** is transformed into $(Pr^iO)_2P(O)CF_2I$ and $(Pr^iO)_2P(O)CF_2SiMe_3$ in 70% and 69% yields, respectively.[17] As is evident from the above examples, compound **11a** is a convenient

building block for the synthesis of various derivatives $(Pr^iO)_2P(O)CF_2EX_n$.

The compounds $(RO)_2P(O)CF_2EX_n$ can be synthesized by the electrochemical fluorination of the derivatives $(RO)_2P(O)CH_2EX_n$. Thus, the electrochemical fluorination of sulfide $PhSCH_2P(O)(OEt)_2$ with $Et_4NF\cdot(HF)_4$ afforded fluorinated sulfide **9**.[18]

$$(EtO)_2P(O)CH_2SPh \xrightarrow{Et_4NF\cdot(HF)_4} (EtO)_2P(O)CF_2SPh$$
9

However, this procedure for the synthesis of sulfide **9** has not found practical application because of the technical problems and low yields of the target product.

III. Introduction of the $(RO)_2P(O)CF_2$ group into organic compounds accompanied by the formation of the C–C bond

1. Reactions of $(RO)_2P(O)CF_2EX_n$ with carbonyl compounds

The reactions of [(diethoxyphosphoryl)difluoromethyl]-lithium (**2**) with aldehydes and ketones occur smoothly to give alcohols **13**.[9, 19, 20]

$$(EtO)_2P(O)CF_2Li + R^1C(O)R^2 \xrightarrow[-78\ ^\circ C]{THF} \underset{\mathbf{13}\ (70\%-85\%)}{HO(R^1)(R^2)CF_2P(O)(OEt)_2}$$
2

R^1 = H, Alk, Ar; R^2 = Alk, Ar.

These reactions can be performed not only with compound **2** but also with trimethylsilyl derivative **6**,[21] which behaves analogously to Ruppert's reagent (CF_3SiMe_3).[22] In the latter case, the reactions are performed in the presence of catalytic amounts of caesium fluoride or tetrabutylammonium triphenyldifluorosilicate (TBAT). The reactions of the resulting silyl ethers **14** with aldehydes R^3CHO give phosphates **15** containing the CF_2 group at the β position with respect to the phosphate group.

$$(EtO)_2P(O)CF_2SiMe_3 + R^1C(O)R^2 \xrightarrow[DMF,\ r.\ t.,\ 4\ h]{TBAT\ (1\ mol.\%)}$$
6

$$\xrightarrow{1)\ initiator,\ R^3CHO,\ DMF,\ r.\ t.;\ 2)\ H_2O,\ r.\ t.,\ 2\ h} \underset{\mathbf{15}}{(EtO)_2(O)PO(OH)(R^2)(R^1)(R^3)(F)(F)}$$
14

R^1	R^2	R^3	Initiator	Time /h	Yield of **15** (%)
H	Ph	4-ClC_6H_4	TBAT	3	84
H	Ph	4-MeC_6H_4	CsF	1	73
H	4-ClC_6H_4	4-$MeOC_6H_4$	CsF	1.5	68
H	Ph	n-C_6H_{13}	TBAT	1	70
H	n-C_6H_{13}	Ph	CsF	3	64
H	n-C_6H_{13}	4-ClC_6H_4	CsF	3	62
Me	Me	4-ClC_6H_4	CsF	4	56

The nucleophilic difluoromethylenation of aldehydes and ketones by trimethylsilyl (difluoromethylene)phosphonate **6** can be performed at room temperature, unlike the difluoromethylenation by derivative **2**,[19, 20] which requires low temperatures.

The reactions of derivative **2** with various unsaturated aldehydes and ketones occur regioselectively to form allylic alcohols **16** as the addition products of phosphonate **2** at the carbonyl group.[10, 23]

$$(EtO)_2P(O)CF_2Li + \underset{R^3}{\overset{H}{}}\!\!\underset{R^1}{\overset{R^2}{}}\!\!=\!\!O \longrightarrow \underset{\mathbf{16}}{\underset{R^3}{\overset{H}{}}\!\!\underset{R^1}{\overset{R^2}{}}\!\!-\!\!OH,\ CF_2P(O)(OEt)_2}$$
2

R^1	R^2	R^3	Yield of **16** (%)
H	H	H	72
Me	H	H	72
H	Me	H	81
H	H	Ph	76
Ph	H	Ph	31
Ph	H	PhCH=CH	35
PhCH=CH	H	Ph	77
PhCH=CH–CH=CH	H	PhCH=CH	65

Sulfide **11a** is a convenient reagent for the introduction of the $(Pr^iO)_2P(O)CF_2$ group into aldehyde molecules. This compound was used in the synthesis of alcohols **17a–d**.[17]

$$(Pr^iO)_2P(O)CF_2SMe \xrightarrow[3)\ NH_4Cl]{1)\ Bu^tLi,\ THF,\ -78\ ^\circ C;\ 2)\ RCHO,\ -78\ ^\circ C,\ 1\ h} \underset{\mathbf{17a-d}}{R(OH)CF_2P(O)(OPr^i)_2}$$
11a

R = Ph (**17a**, 67%), Pr^i (**17b**, 72%), cyclo-C_6H_{11} (**17c**, 76%), n-C_8H_{17} (**17d**, 86%).

The reaction of sulfide **11a** with cyclohexanone gives the corresponding alcohol in 69% yield.[17]

The reactions of lithium derivative **2** with carbonyl compounds can occur also with the involvement of other functional groups of carbonyl compounds. For example, the addition of derivative **2** to 3-chlorobutan-2-one is accompanied by the elimination of the chlorine atom and the cyclization to give oxirane **18** in 51% yield.[9]

$$(EtO)_2P(O)CF_2Li + \underset{Me}{\overset{Cl}{}}\!\!\underset{O}{\overset{Me}{}}\!\!=\!\!O \xrightarrow[-78\ ^\circ C]{THF} \underset{\mathbf{18}}{\overset{Me}{\underset{O}{}}\!\!\overset{Me}{}\!\!-\!\!CF_2P(O)(OEt)_2}$$
2

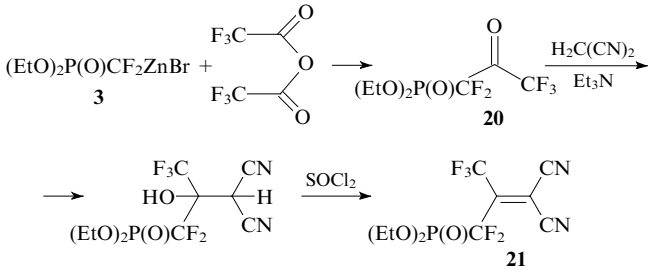
The reaction of compound **2** with esters in the presence of $CeCl_3$ gives α,α-difluoro-β-keto phosphonates **19**.[24, 25]

$$(EtO)_2P(O)CF_2Li \xrightarrow[HCl\ (aqueous)]{RCO_2Et,\ CeCl_3} \underset{\mathbf{19}}{R(O)CF_2P(O)(OEt)_2}$$
2

R = Et (88%), Ph (81%), CH_2=CH (40%), PhCH=CH (57%).

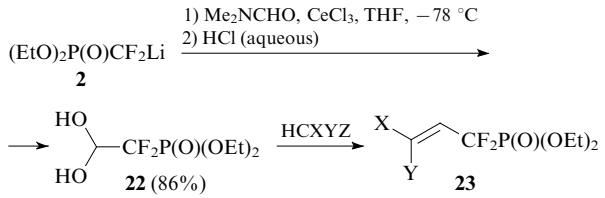
This type of compounds are of interest as analogues of acyl phosphates, which are intermediate electrophilic products of numerous enzymatic reactions involving phosphates.

In addition to derivative **2**, the acylation can be performed with the use of [(diethoxyphosphoryl)difluoromethyl]zinc bromide (**3**). In particular, this method was applied to the synthesis of diethoxyphosphorylpentafluoroacetone (**20**), which reacts with malononitrile to give unsaturated dinitrile **21**.[26]



Dinitrile **21** proved to be a convenient starting compound in the synthesis of various nitrogen-containing heterocyclic compounds.

The $CeCl_3$-initiated addition of [(diethoxyphosphoryl)-difluoromethyl]lithium (**2**) to dimethylformamide affords aldehyde **22** in the hydrated form (in 86% yield), which reacts with activated methylene derivatives of HCXYZ to give alkenes **23** containing the $(EtO)_2P(O)CF_2$ group (Refs 24, 27–29).

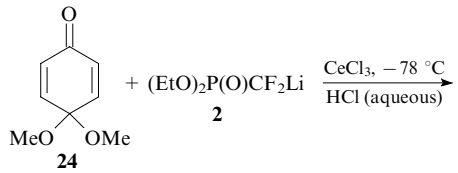


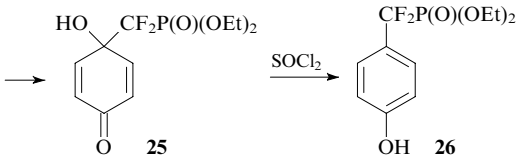
X	Y	Z	Conditions	Yield of **23** (%)
CO_2Et	H	$P(O)(OEt)_2$	LiBr, Et_3N, THF, r. t.	65
CO_2All	H	$P(O)(OEt)_2$	LiBr, Et_3N, THF, r. t.	78
CO_2Et	CO_2Et	H	KF, Pr^iOH, r. t.	60
SO_2Ph	H	$P(O)(OEt)_2$	LiBr, Et_3N, THF, r. t.	60
SOPh	H	$P(O)(OEt)_2$	K_2CO_3, Et_3N, THF, r. t.	43
NO_2	H	H	KF, Pr^iOH, r. t.	75

The structure of compound **22** was established by X-ray diffraction.[17]

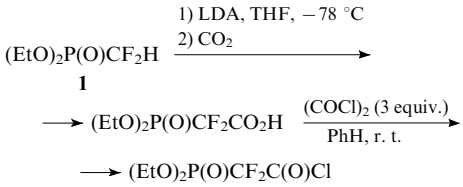
Alkenes **21** and **23** are characterized by high reactivity and serve as the starting compounds in various condensation reactions, in particular, they are widely used in the synthesis of biologically active heterocyclic compounds containing the phosphoryldifluoromethylene group (see Section V).

The reaction of lithium derivative **2** with benzoquinone dimethylacetal (**24**) in the presence of $CeCl_3$ occurs regioselectively at the carbonyl group. The resulting adduct **25** undergoes aromatization under mild conditions to give **26**, in which the $CF_2P(O)(OEt)_2$ group remains intact.[30]

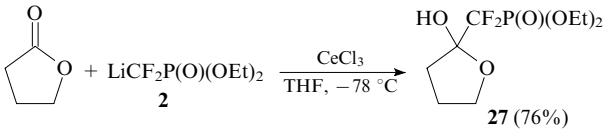




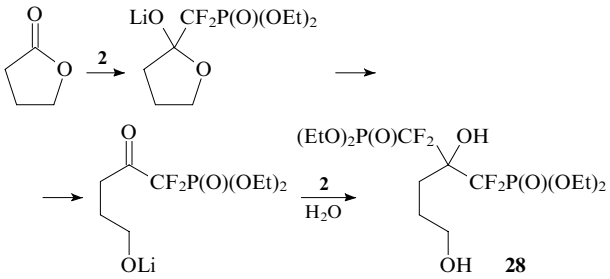
The reaction of [(diethoxyphosphoryl)difluoromethyl]-lithium with carbon dioxide gives difluoro(diethoxyphosphoryl)acetic acid, which reacts with an excess of oxalyl chloride in dry benzene to form difluoro(diethoxyphosphoryl)acetyl chloride, and the latter is used as the starting compound in numerous transformations involving difluoromethylenephosphonates.[31]



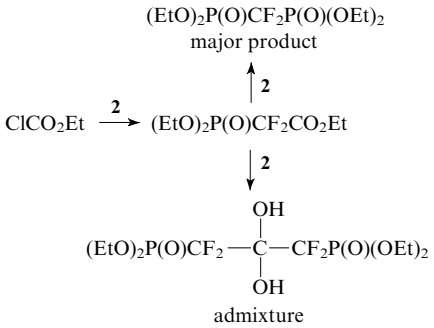
The addition of derivative **2** to γ-butyrolactone in the presence of $CeCl_3$ taken in a stoichiometric amount is accompanied by the formation of cyclic hemiacetal **27**.[25]



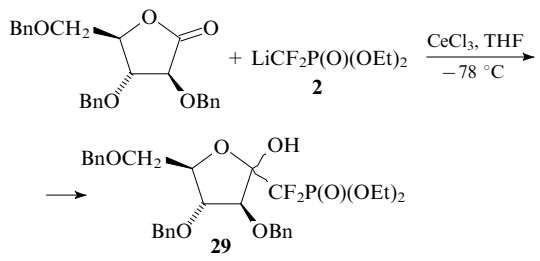
In the absence of $CeCl_3$, the reaction produces adduct **28**.



Previously, analogous bisphosphonates have been synthesized by Blackburn *et al.*[32] by the reaction of derivative **2** with ethyl chloroformate.

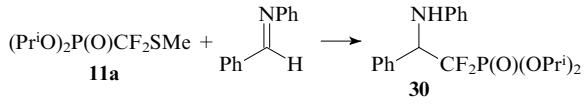


Since γ-butyrolactone is structurally similar to carbohydrates, it would be expected that the latter compounds will react with derivatives **2** analogously to butyrolactone. Actually, 2,3,5-tri-*O*-benzyl-D-arabinoic acid γ-lactone also reacts with compound **2** to give the difluoromethylenephosphonate derivative of furanose **29**.[33]

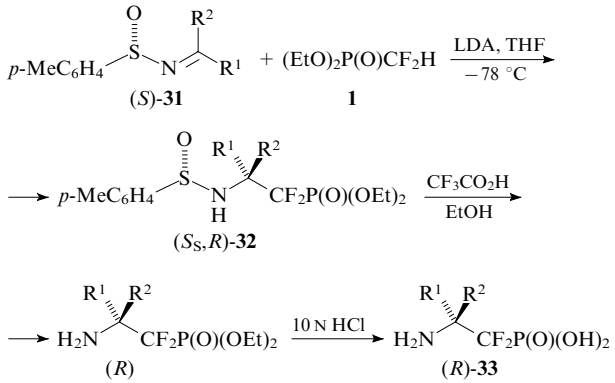


2. Addition of reagents $(RO)_2P(O)CF_2EX_n$ to imines

The addition of α,α-difluoromethylenephosphonates to imines occurs analogously to their addition to carbonyl compounds, *i.e.*, at the C=N double bond. Thus, the reaction of diisopropyl (methylsulfanyldifluoromethyl)-phosphonate (**11a**) with benzylideneanilines affords diisopropyl 2-anilino-1,1-difluoro-2-phenylethylphosphonate (**30**) in 70% yield.[17]



The reactions of *N*-sulfanylimines (*S*)-**31** with diethyl difluoromethyphosphonate (**1**) occur stereoselectively to form (S_S,*R*)-products **32**.[34–36]

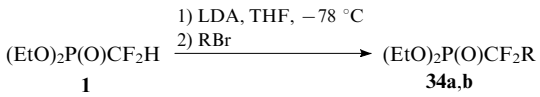


R^1	R^2	Yield of **32** (%)	*de* (%)
Ph	H	74	90
4-$MeOC_6H_4$	H	92	88
4-$CF_3C_6H_4$	H	70	88
2-Thienyl	H	67	84
n-C_5H_{11}	H	72	84
Pr^i	H	75	82
(*E*)-PhCH=CH	H	76	88
Ph	Me	40	92

β-Aminophosphonic acids **33** that are formed in these reactions are important structural analogues of the corresponding amino acids. These compounds exhibit antibacterial, antiviral and pesticidal activities.

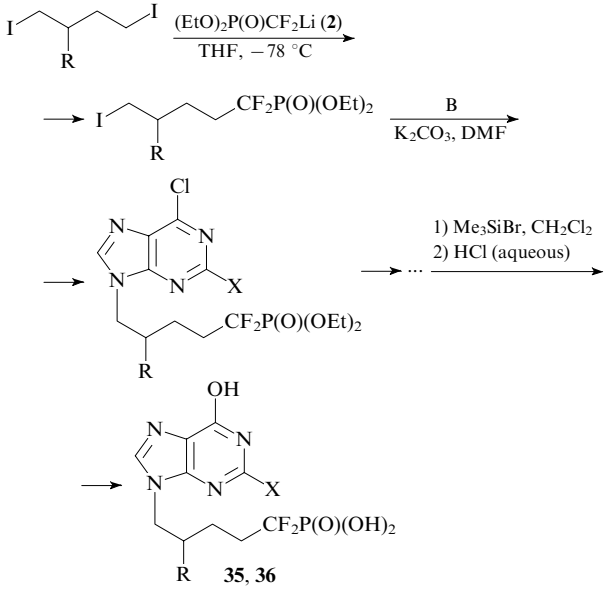
3. Nucleophilic addition of the difluoromethylenephosphonate anion

The nucleophilic substitution of halogen atoms in haloalkanes by the difluoromethylenephosphonate group was described for the first time in 1982 by Japanese researchers.[9] Products **34a**,**b** were obtained in good yields.



R = Et (**34a**, 82%), n-C_6H_{13} (**34b**, 66%).

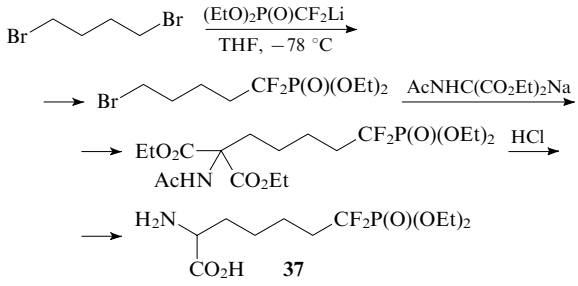
The complexity of these reactions is associated with thermal instability of the difluoromethylenephosphonate anion. Nevertheless, the substitution of halogen atoms (primary alkyl bromides or iodides are most often used in these reactions) was employed in the synthesis of a series of analogues of natural phosphates. This method was applied, for example, to the synthesis of purine nucleoside phosphorylase (PNP) inhibitors, *viz.*, compounds **35** and **36**. The synthesis of these compounds is based on the successive replacement of the iodine atoms in the corresponding 1,4-diiodoalkanes by the difluoromethylenephosphonate moiety and then by the purine base (B).[37, 38]



B is 2-amino-6-chloropurine, 6-chloropurine;
35: R = H, X = NH_2; **36**: R = Me; X = H, Me.

Other methods for the synthesis of PNP inhibitors containing the $(RO)_2P(O)CF_2$ group are considered below.

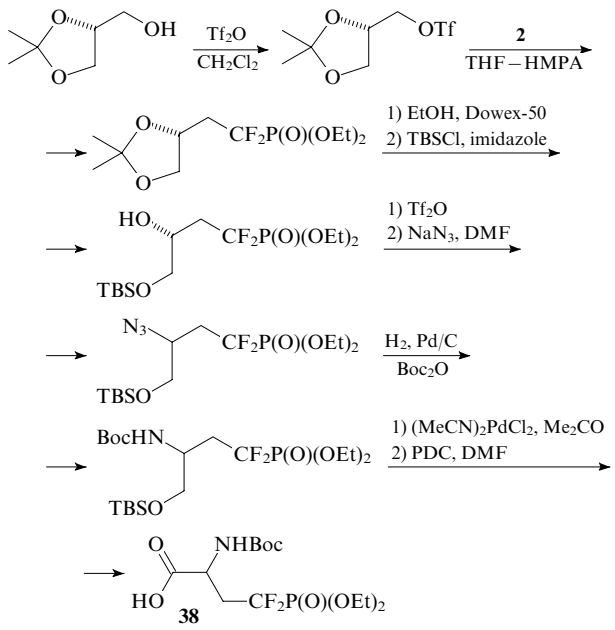
The synthesis of amino acid **37** containing the remote difluoromethylenephosphonate group was described in the study.[39] This method is based on the successive replacement of the bromide atoms in 1,4-dibromobutane by the difluoromethylenephosphonate group and then by the protected amino acid residue.



Amino acid **37** is the CF_2-containing analogue of L-2-amino-7,7-difluoro-7-phosphonoheptanoic acid, which is a

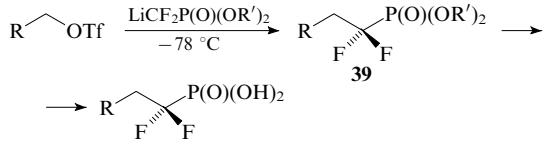
specific *N*-methyl-D-aspartate (NMDA) receptor antagonist.

In addition to the substitution of halogen atoms in haloalkanes, the replacement of triflate groups (OTf) in primary triflates is also used in the synthesis of CF_2-containing analogues of natural phosphates. These reactions generally occur more easily than the substitution of halogen atoms. Berkowitz and co-workers published a series of articles (see, for example, Refs 40–43), where the introduction of the $CF_2P(O)(OEt)_2$ group into various organic compounds by the replacement of the triflate group was described. In particular, the authors synthesized the α,α-difluoroalkylphosphonate analogue of L-phosphoserine **38** starting from available (*R*)-isopropylideneglycerol.[41]



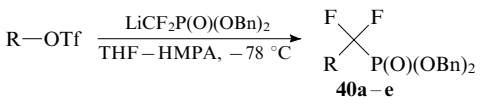
PDC is pyridinium dichromate.

Taking into account that the ease of deprotection plays an important role in the synthesis of unprotected phosphonic acids, Berkowitz *et al.*[42] investigated the hydrolysis of α,α-difluoroalkylphosphonates **39** containing various groups R′.

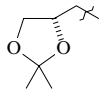
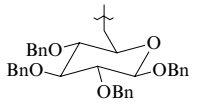
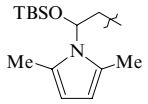
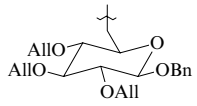
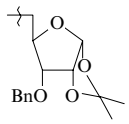


R′ = Et, All, Bn.

It appeared that compound **39** with R′ = Bn is most rapidly hydrolyzed. Taking into account this fact, Berkowitz suggested that [(dibenzyloxyphosphoryl)difluoromethyl]-lithium can be used in the triflate synthesis of phosphonate analogues of natural phosphates.[42,43] Difluoromethylenephosphonate analogues of phosphates of a series of natural compounds, such as amino acids and sugars, were synthesized in good yields according to this method.

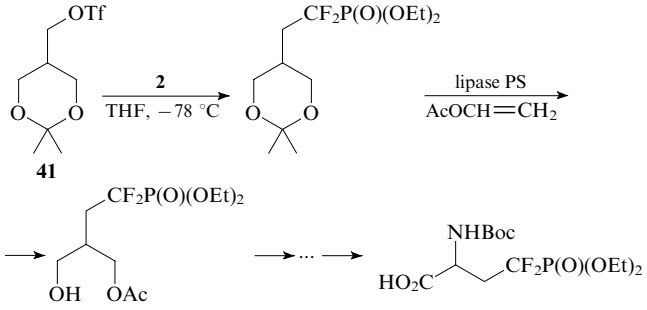


40a–e

Compound	R	Yield (%)	Compound	R	Yield (%)
40a		56	**40d**		52
40b		55	**40e**		50
40c		50			

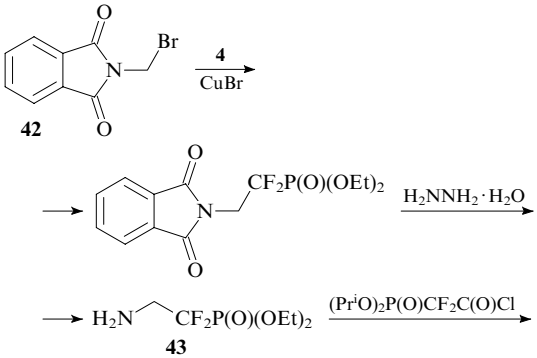
In particular, derivatives **40d** are of interest as the starting compounds in the synthesis of substrate analogues of glucose-6-phosphate dehydrogenase.

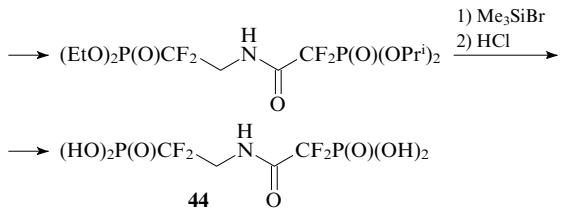
The CF_2-containing analogue of L-phosphoserine **38** was prepared by the replacement of the triflate group in protected isopropylidene-2-hydroxymethylpropane-1,3-diol **41** by the $CF_2P(O)(OEt)_2$ group in the reaction with lithium derivative **2**.[44] After the deprotection followed by the acylation by lipase PS, oxidation by the $CrO_3-H_2SO_4$ system and amination [$Ph_2P(O)N_3$, BnOH, Et_3N–MeO], ω-phosphono-α-amino acid **38** was obtained.



Amino acid **38** was then used in the peptide synthesis.

The replacement of the Br atom in derivative **42** by the $CF_2P(O)(OEt)_2$ group followed by the treatment of the resulting compound by hydrazine hydrate afforded amine **43**, whose reaction with phosphoryldifluoroacetyl chloride followed by the hydrolysis gave diphosphorylamide **44**. The substitution reaction was carried out in the presence of CuBr.[45]

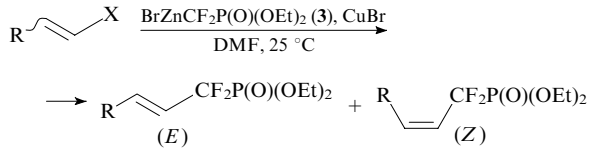




Compound **44** shows high activity as an inhibitor of phosphoglycerate kinase.[45]

The reaction of cadmium derivative **4** with allyl bromide is also accompanied by the replacement of the Br atom by the $(EtO)_2P(O)CF_2$ group to form $CH_2{=}CHCH_2CF_2P(O).(OEt)_2$ (62%),[46] which is a key compound in the synthesis of a substrate analogue of a particular glycolytic enzyme. The reaction of allyl bromide with zinc derivative **3** occurs slowly; however, the reaction in the presence of a catalytic amount of CuBr occurs more rapidly and gives 1,1-difluorobut-3-enylphosphonate in higher yield.[47]

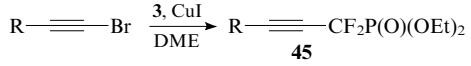
In the study,[48] difluoroallylphosphonates were synthesized starting from 1-haloalkenes and derivative **3** in the presence of stoichiometric amounts of CuBr (in the absence of copper bromide, the reactions do not occur).



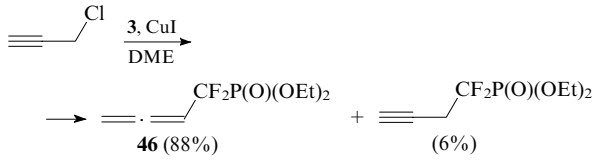
X = Br, I; R = Ph (67%, $E:Z = 98:2$), 4-$MeOC_6H_4$ (49%, $E:Z = 98:2$), Bu^n (81%, $E:Z = 99:1$).

The authors hypothesized that the reaction starts with the formation of the complex $Br_2Zn \cdot CuCF_2P(O)(OEt)_2$.

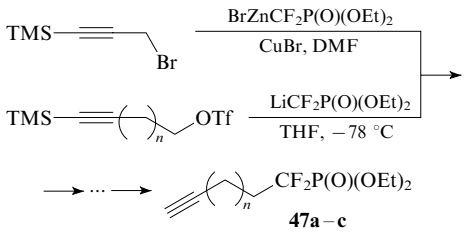
Acetylene derivatives **45** containing the difluoromethylenephosphonate group at the triple bond can be prepared by the reaction of zinc derivative **3** with the corresponding bromide.[49]



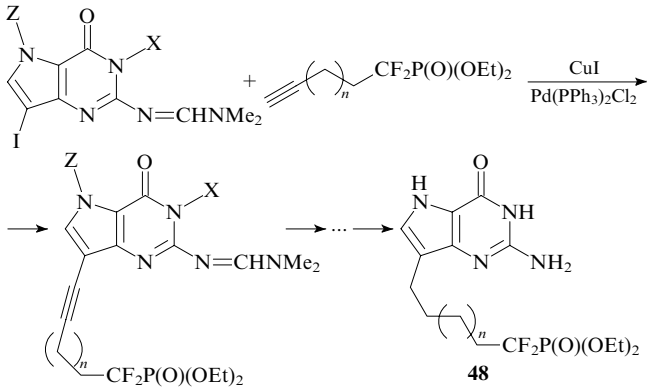
The reaction is carried out in the presence of Cu(I) salts. It is interesting that the reaction of zinc derivative **3** with propargyl chloride in dimethoxyethane (DME) gives allene product **46**, whereas the standard replacement product is formed only as an impurity.[50]



The synthesis of terminal α,α-difluoroalkynylphosphonates **47a–c**, which served as the starting compounds for the preparation of 9-deazaguanine derivatives **48** containing the difluoromethylenephosphonate group, was documented.[51] Compounds **48** are of interest as multisubstrate analogues of PNP inhibitors. Compounds **47** were synthesized [51] by the treatment of trimethylsilylpropargyl bromide with derivative **3** in the presence of CuBr or by the replacement of the triflate group (Berkowitz's method [40]).

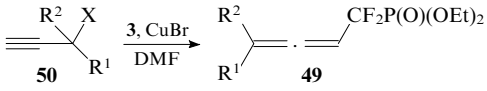


$n = 0$ (**a**), 1 (**b**), 2 (**c**).



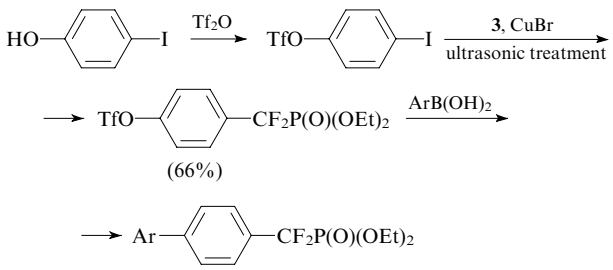
X and Z are protecting groups, $n = 0-2$.

Substituted allenes **49** are formed in the reactions of zinc derivative **3** with tosylates, acetates and carbonates of substituted propargyl alcohols **50** or propargyl bromide.[52] The reactions are performed in dimethylformamide in the presence of monovalent copper salts at room temperature.



X = OTs, OAc, OC(O)OMe, Br; R^1, R^2 = Me, Ph, Et.

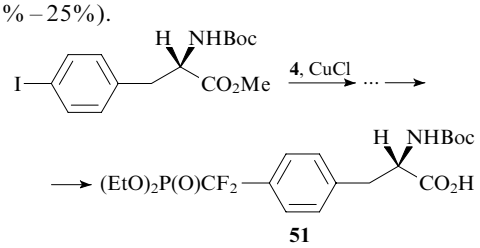
Aryl halides react with $(EtO)_2P(O)CF_2CdBr$ (**4**) to form substitution products. Thus, diethyl difluorobenzylphosphonate was synthesized for the first time by Burton and coworkers [53] by the reaction of iodobenzene with derivative **4**. Analogously, difluoromethylenephosphonate derivatives of biaryls were synthesized by the replacement of the iodine atom in 4-iodophenol by the $(EtO)_2P(O)CF_2$ group and the replacement of the hydroxy group by the aryl group [in the reaction with $ArB(OH)_2$].[54]



Ar = *p*-ClC_6H_4, *p*-BrC_6H_4, *o*-$OHCC_6H_4$, *m*-$NO_2C_6H_4$, 3,4-$Me_2C_6H_3$.

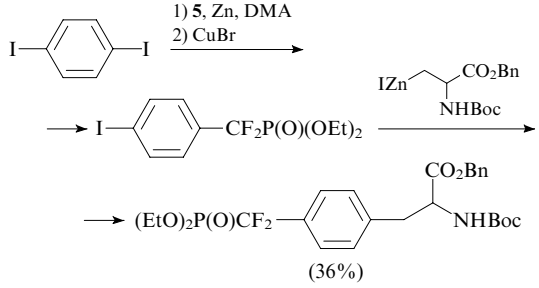
The synthesis of the tyrosine derivative by the reaction of compound **4** with 4-iodophenylalanine was documented.[55] In this reaction, CuCl was used as the catalyst. Product **51** was obtained in 87% yield (in the absence of the

Cu(I) salt, the yield of the amino acid was at most 15% – 25%).



51

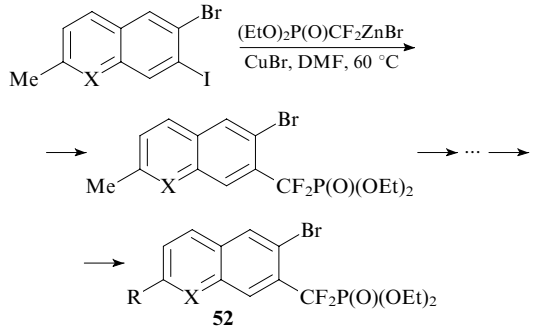
The $(EtO)_2P(O)CF_2$-containing tyrosine was synthesized from 4-iodo-α,α-difluorobenzylphosphonate and the zinc derivative of alanine,[54, 56] with the difference that in the study,[54] the starting 4-iodo-α,α-difluorobenzylphosphonate was prepared by replacing the iodine atom in 1,4-diiodobenzene by the $(EtO)_2P(O)CF_2$ group with the use of zinc derivative **3**. In these reactions, palladium complexes served as the catalysts. In the study,[56] the carbonyl group in 4-iodobenzoylphosphonate was fluorinated by (diethylamino)sulfur trifluoride (DAST).



(36%)

Tyrosine derivatives prepared according to the above-described procedures were used in the solid-phase peptide synthesis.

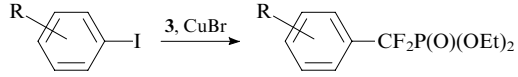
The replacement of iodine atoms in the naphthalene derivatives[57, 58] and quinoline derivatives[58] by the $(EtO)_2P(O)CF_2$ group afforded aromatic compounds **52**, which are potent inhibitors of protein tyrosine phosphatase 1B (PTP1B) acting as a negative regulator of insulin.



52

X = N, CH; R = CN, CH_2CN, CH_2OMe, CH_2SO_2Me, $C(O)NH_2$, C(O)NHBn, C(O)NHPh, *etc*.

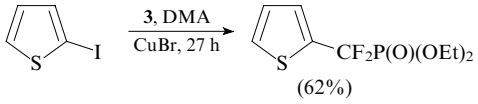
The synthesis of substituted α,α-difluorobenzylphosphonates was described in the studies.[57, 59]



R = *p*-Me, *p*-OMe, *p*-CO_2Me, *p*-Cl, *p*-I, *p*-OTf, *p*-$CF_2P(O)(OEt)_2$, *m*-OMe, *m*-CH_2OAc, *m*-CO_2Me, *o*-CH_2OAc, *o*-CO_2Me.

The derivative $PhCH{=}CHCF_2P(O)(OEt)_2$ was synthesized by the reaction of iodostyrene with compound **3**.[57] The reaction was carried out in dimethylformamide in the presence of a stoichiometric amount of CuBr.

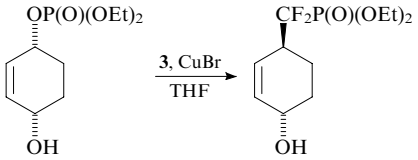
The difluoromethylenephosphonate group was introduced into halogen-substituted heterocyclic compounds, for example, into iodothiophene, with the use of zinc derivative **3**.[59]



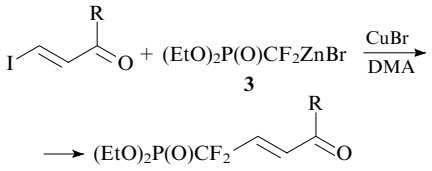
(62%)

Here, we give only one example of the introduction of the $CF_2P(O)(OEt)_2$ group into heterocycles. Methods for the synthesis of heterocyclic compounds containing the $CF_2P(O)(OR)_2$ group are considered below in Section V.

The nucleophilic displacement of the phosphate group by the difluoromethylenephosphonate group in the presence of CuBr was reported.[60]

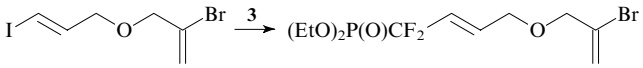


In the presence of monovalent copper salts, compound **3** is involved in the substitution reactions with unsaturated aldehydes and ketones containing the iodine atom at the C=C double bond[61] rather than in the addition reactions at the C=O bond, as was described above.



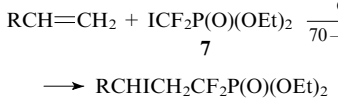
R = H (60%), Me (79%).

In alkene molecules containing simultaneously I and Br atoms, the iodine atom is replaced.[62]

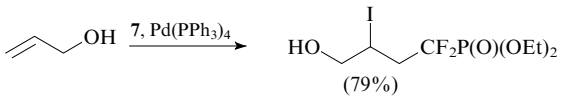


4. Addition of reagents $(RO)_2P(O)CF_2EX_n$ at carbon – carbon double and triple bonds

Yang and Burton[63] performed a detailed investigation of the addition of the reagent $(EtO)_2P(O)CF_2I$ (**7**) to aliphatic and cyclic alkenes, dienes and their derivatives. It was found that these reactions are catalyzed by transition metals. The copper-catalyzed addition of iodide **7** to alkenes occurs upon heating, whereas the addition in the presence of the complex $Pd(PPh_3)_4$ as the catalyst occurs at room temperature.

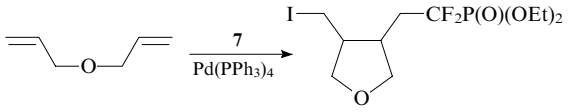


R = n-C_5H_{11} (75%), Me_3Si (75%), $AcCH_2CH_2$ (80%).

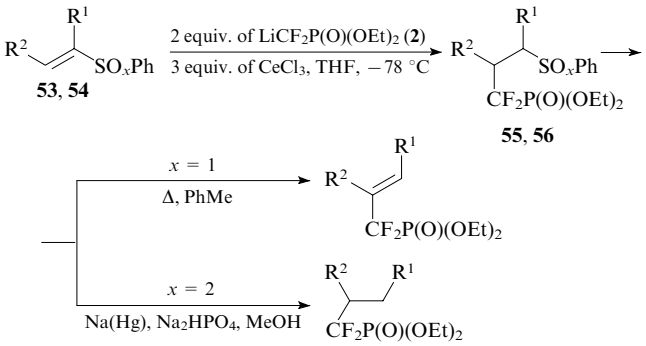


The reactions of 2 equiv. of iodide **7** with dienes give the corresponding bisphosphonates.

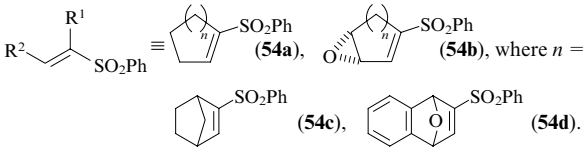
The reaction of iodide **7** with diallyl ether occurred unusually and afforded the tetrahydrofuran derivative instead of the expected bisphosphonate.[63]



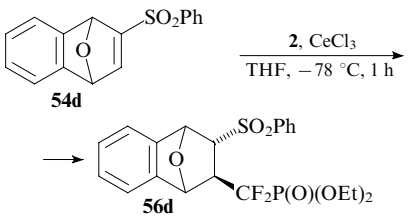
The functionalization of various acyclic and cyclic vinyl sulfoxides (**53**, $x = 1$) and vinyl sulfones (**54**, $x = 2$) at the double bond was performed with the use of $(EtO)_2P(O).CF_2Li$ (**2**).[64, 65]



53, **55** ($x = 1$): $R^1 = H$: R^2 = H, Et, Pr^i, Bu^n, Ph;
$R^1 - R^2 = -(CH_2)_3-$, $-(CH_2)_4-$;
54, **56** ($x = 2$): $R^1 = H$: R^2 = H, Et, Pr^i;

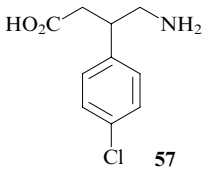


The reactions are carried out in the presence of cerium chloride as the catalyst. In the absence of the catalyst, the reactions do not occur. Compounds **55** are prepared in good yields (60%–70%) by the addition of the $(EtO)_2P(O)CF_2$ fragment to cyclic and acyclic sulfoxides **53**. In the reactions with vinyl sulfones **54**, good yields were achieved only in the case of the cyclic derivatives (compounds **54a–d**). In particular, compound **56d**, which was prepared by the addition of derivative **2** to sulfone **54d**, was isolated after chromatography in 63% yield.[65]

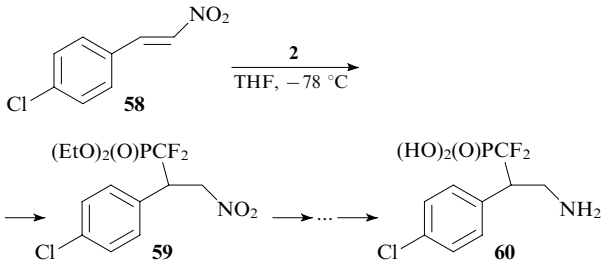


The addition of derivative **2** to acyclic vinyl sulfones **54** affords products in yields of at most 20%.

With the aim of preparing the difluoromethylenephosphonate analogue of the γ-aminobutyric acid β-receptor antagonist [phaclofen (**57**)]

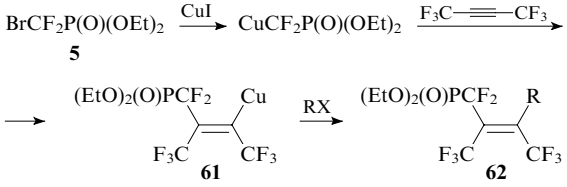


the $CF_2P(O)(OEt)_2$ group was added at the double bond of α,β-unsaturated nitro compound **58**.[66]



Addition product **59** was reduced and hydrolyzed to γ-amino-α,α-difluoropropylphosphonate **60**.

The reaction of bromo derivative **5** with monovalent copper salts gives the compound $CuCF_2P(O)(OEt)_2$, which is involved in the Michael addition to $F_3C-C\equiv C-CF_3$ to form adduct **61**. The treatment of compound **61** with various C-electrophiles affords alkenes **62** containing the difluoromethylenephosphonate group at the C=C bond.[67]

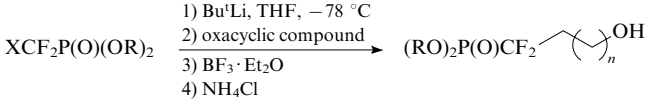


RX = MeI, ArI, $CH_2=CHCH_2Br$, $CF_3CF=CFI$.

5. Ring-opening reaction of oxacycles with reagents $(RO)_2P(O)CF_2EX_n$

Hydroxylated difluoromethylenephosphonates are important intermediates in the synthesis of analogues of natural phosphates. One of procedures for their synthesis is based on the ring opening of oxacycles by the reagents $(RO)_2P(O)CF_2EX_n$.

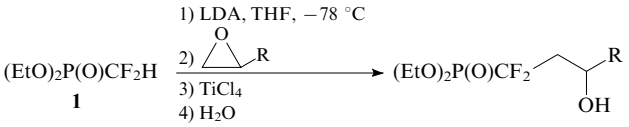
The ring-opening reactions of three-, four- and five-membered oxacycles with various sources of the anion of $CF_2P(O)(OR)_2$ giving primary and secondary ω-hydroxy-α,α-difluoroalkylphosphonates were documented.[68]



$n = 1$: R = Et; X = H, Br; $n = 1-3$: R = Pr^i, X = SMe.

The epoxide ring-opening generally requires the presence of Lewis acids (for example, $BF_3 \cdot Et_2O$) as the catalyst. The reactions with the use of the compounds $(EtO)_2P(O).CF_2X$ (X = H or Br) gave the corresponding alcohols **63** in low yields. However, the reactions with methylsulfanyldifluoromethyl phosphonate **11a** afforded the corresponding alcohols in satisfactory yields (from 60% to 70%).

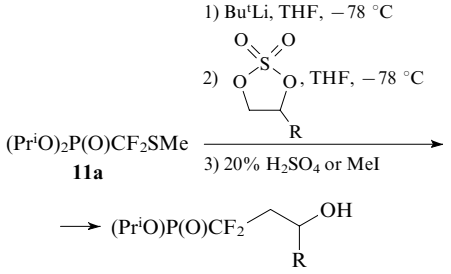
Recently, it has been shown[69] that the $TiCl_4$ complex and Grignard reagents (MeMgCl, AllMgCl, PhMgBr and BnMgCl) are good catalysts for the epoxide ring-opening.



R = Me (62%), Et (47%), Ph (34%).

It should be noted that, under these conditions (unlike the catalysis by $BF_3 \cdot Et_2O$), the ring opening of the oxolane moiety does not occur, due to which tetrahydrofuran can be used as the solvent.

The synthesis of primary and secondary alcohols by the ring opening of cyclic 1,2-glycol sulfates, sulfamidates and oxetanes with the use of compound **11a** was described in the study.[70] The ring opening of the 1,2,5-thiadioxolane moiety occurs in the absence of Lewis acids.



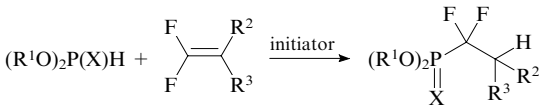
R = H (22%), $CH_2OC_6H_4OMe$-4 (69%), CH_2Cl (53%), C_6H_{13}-n (79%), Bn (83%), $(CH_2)_2Ph$ (71%), CH_2OBn (76%).

The ring opening of the oxetane moiety in 2-benzyloxymethyl- and 3-benzyloxymethyl-3-methyloxetanes was carried out in the presence of $BF_3 \cdot Et_2O$. The yields of the corresponding secondary alcohols were 57% and 65%, respectively.

6. Introduction of phosphoryl and phosphoryldifluoromethyl radicals into organic molecules under radical reaction conditions

In the above sections (see Sections III.1 – III.4), we give examples of the introduction of the difluoromethylenephosphonate group into organic molecules by the nucleophilic substitution and addition. In this section, we consider the synthesis of difluoromethylenephosphonates by radical reactions.

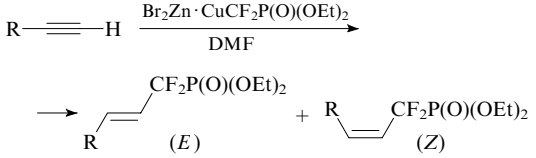
The synthesis of difluoromethylenephosphonates by the free radical reactions was reported for the first time in the studies,[71–73] where these compounds were prepared by the reactions of dialkyl phosphites with 1,1-difluoroalk-1-enes in the presence of radical initiators. However, the synthesis of difluoromethylenephosphonates by these reactions is complicated by the competitive oligomerization. The reactions gave mixtures of oligomers of the general formula $(R^1O)_2P(O)(CF_2CR^2R^3)_nH$ ($n = 2-10$). Only in the case of the addition products of the dialkylphosphinyl radical to terminal α,α-difluoroolefins $CF_2{=}CR^1R^2$, which cannot undergo the subsequent oligomerization, the desired difluoromethylenephosphonates were obtained in satisfactory yields.



Initiator	X	R^1	R^2	R^3	Yield (%)	Ref.
Bu^tOOBu^t	O	Me	F	F	see [a]	71
	O	Et	F	F	see [a]	71
	O	Bu^n	F	F	see [a]	71
γ-Irradiation	O	Me	F	CF_3	50	72
	O	Et	F	CF_3	20	72
	O	Pr^i	F	CF_3	38	72
	O	see [b]	F	CF_3	45	72
	O	Me	Cl	Cl	see [a]	73
	O	Et	Cl	Cl	see [a]	73
	O	Pr^i	Cl	Cl	see [a]	73
$Bu^tOOC(O)Bu^t$	O	Me	n-C_9H_{19}	Me	65	74
	O	Et	n-C_9H_{19}	Me	72	74
	S	Et	n-C_9H_{19}	Me	95	74
	S	Bn	n-C_9H_{19}	Me	65	74
	O	Ph	n-C_9H_{19}	Me	72	74
	O	Me	$-(CH_2)_5-$		66	74
	O	Et	$-(CH_2)_5-$		60	74
	O	see [b]	$-(CH_2)_5-$		71	74
	S	Et	Ph	Me	30	74
Bz_2O_2	O	Et	F	Cl	see [a]	75
	O	Me	F	Cl	see [a]	75

[a] A mixture of oligomers; [b] phosphonite HP(O)(OEt)Me was used as the starting compound.

Low yields of difluoromethylenephosphonates in the radical reactions with dialkyl phosphites have stimulated a search for new components of these reactions. In particular, it was suggested that the phosphoryldifluoromethyl group be used instead of the dialkylphosphinyl moiety. Thus, the difluoroallylphosphonates were synthesized by the reactions of the complex $Br_2Zn \cdot CuCF_2P(O)(OEt)_2$ with terminal alkynes.[48] The authors hypothesized that the reaction occurs by a radical mechanism through the formation of the radical $^{\bullet}CF_2P(O)(OEt)_2$.

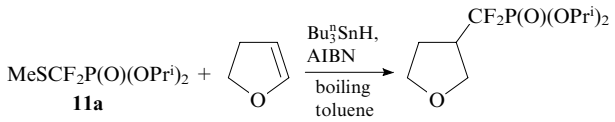


R = Ph (62%, $E:Z = 83:17$), 4-$MeOC_6H_4$ (23%, $E:Z = 95:5$), Bu^n (54%, $E:Z = 50:50$).

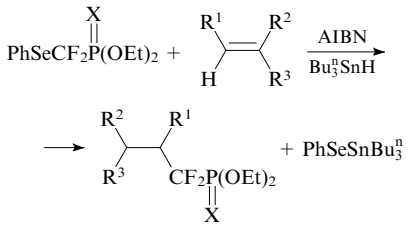
The compounds $R^2ECF_2P(X)(OR^1)_2$ (E = S or Se; X = O or S; R^1 = Et or Pr^i; R^2 = Me or Ph) are convenient precursors of the radicals $^{\bullet}CF_2P(X)(OR^1)_2$. The free radical reactions with these compounds are initiated by UV or γ radiation or with the use of chemical initiators, such as azobis(isobutyronitrile) (AIBN), tributyltin hydride, sodium dithionite, various peroxides, *etc*. Examples of the reactions of these precursors with various unsaturated compounds proceeding by a radical route are given below.

In the study,[14] tetrahydrofuranyl difluoromethylenephosphonate was synthesized by the reaction of compound

11a with 2,3-dihydrofuran with the use of azobis(isobutyronitrile) and tributyltin hydride as the radical initiators.



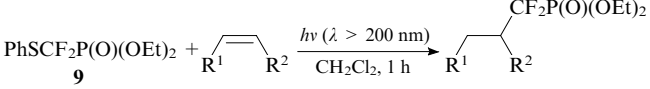
The addition of radicals generated from the compounds $PhSeCF_2P(X)(OEt)_2$ (X = O or S) to various cyclic and acyclic alkenes and their functional derivatives, as well as to terminal alkynes, was investigated in detail.[15] In these reactions, azobis(isobutyronitrile) and tributyltin hydride were used as the radical initiators.



R^1	R^2	R^3	Yield (%)	
			X = O	X = S
n-C_6H_{13}	H	H	45	54
H	$-(CH_2)_5-$		82	88
$-(CH_2)_3-$		H	10	22
Bu^n	H	H	46	81
$-CH_2CH_2O-$		H	68	78
$PhSO_2$	H	H	12	43

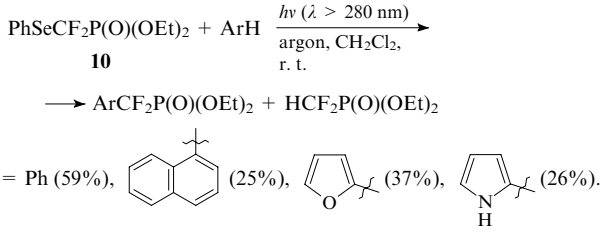
The authors speculated that the reaction of selenide $PhSeCF_2P(X)(OEt)_2$ with the radical $^{\bullet}SnBu^n_3$ gives the radical $^{\bullet}CF_2P(O)(OEt)_2$, which then adds to alkene. The reactions of the compounds $PhSeCF_2P(X)(OEt)_2$ with terminal alkynes occur analogously to give a mixture of *E* and *Z* isomers, with the *E* isomer predominating.

This reaction can be performed under conditions of the photochemical radical initiation. Thus, the radical initiation by UV radiation was used in the radical addition of phosphonate **9** to acyclic and cyclic alkenes and their derivatives.[76]



R^2 = H: R^1 = Bu^tO (49%), n-C_5H_{11} (44%);
R^1-R^2 = $-OCH_2CH_2-$ (56%), $-(CH_2)_4-$ (31%).

The reactions of compound **10** with arenes and hetarenes were performed in the study.[77] In this case, the irradiation of the reaction mixture at >280 nm leads to

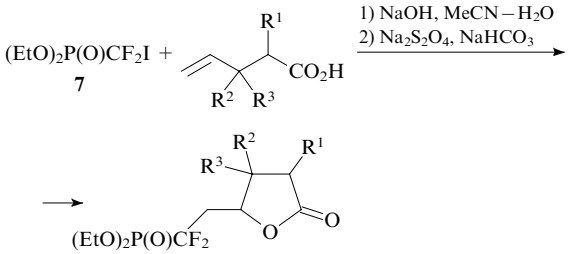


Ar = Ph (59%), (25%), (37%), (26%).

the replacement of the hydrogen atom by the radical $^{\bullet}CF_2P(O)(OEt)_2$.

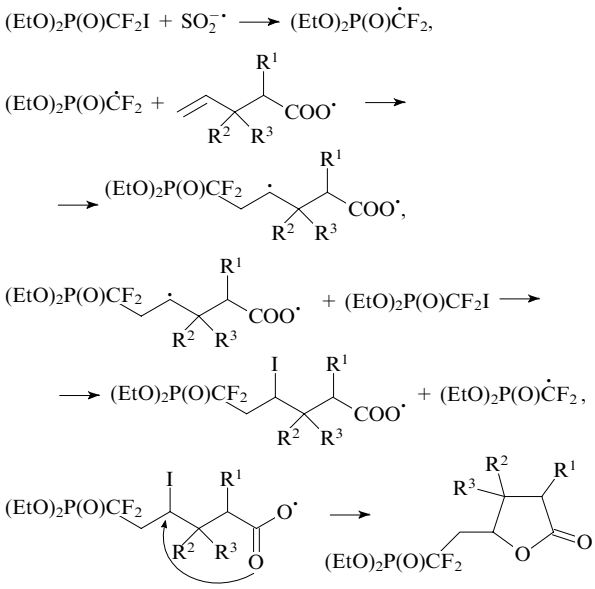
It should be noted that the radical aromatic substitution is one of the most popular methods for the C–C-bond formation.

Iodophosphonate is also often used in the synthesis of difluoromethylenephosphonates. These reactions are generally initiated by sodium dithionite. The reactions of iodide **7** with alkenes occur in a $MeCN-H_2O$ mixture (5 : 3) at room temperature during several hours.[78]

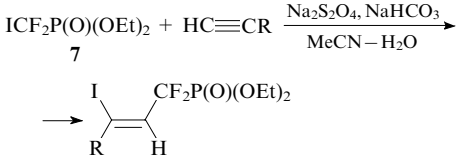


R^1 = H, R^2 = R^3 = Me; R^2 = R^3 = H: R^1 = Me, Et, Pr^n, Bu^n, Bn, Ph, NHC(O)Ph, $NHC(O)C_6H_4OMe$-4.

The following reaction mechanism was proposed:



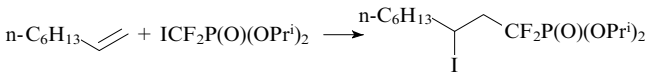
The alkylation of the C≡C bond in terminal alkynes by iodine derivative **7** is also performed in aqueous acetonitrile at 0 °C in the presence of sodium dithionite.[79]



R = Bu^n (79%), CH_2OH (74%), CO_2Me (65%), CO_2Et (67%), CH_2OMe (75%), Ph (62%), CH_2OEt (72%), $C(O)NMe_2$ (56%).

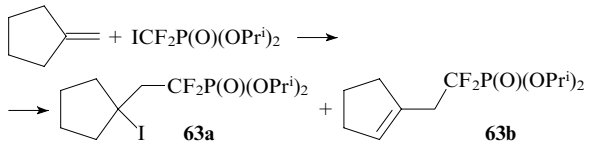
The radical addition to alkenes can be performed not only with the use of diethyl iododifluorophosphonate **7** but also with the use of its diisopropyl analogue. Thus, the addition of the radical $(Pr^iO)_2P(O)C^{\bullet}F_2$ to terminal normal alkenes, various methylidenecycloalkanes and unsaturated ketones was investigated[80] under different initiation con-

ditions: with the use of sodium dithionite (*a*), triethylboron (*b*) and dilauroyl peroxide (*c*). For example, the addition of $(Pr^iO)_2P(O)CF_2I$ to oct-1-ene under the conditions *a*, *b* and *c* affords the product in 75%, 76% and 45% yield, respectively.

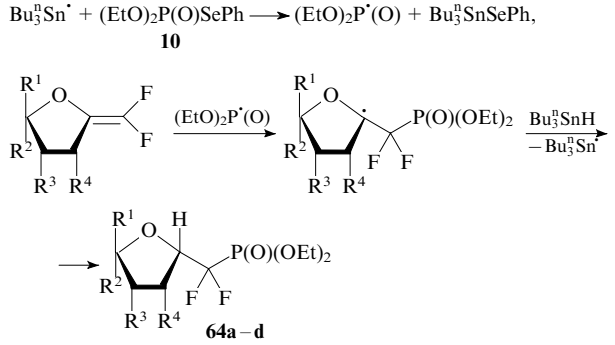


(*a*) $Na_2S_2O_4$, $NaHCO_3$, $MeCN-H_2O$ (5 : 3), r. t., 18 h;
(*b*) Et_3B (0.3 equiv.), CH_2Cl_2, r. t., 1 h;
(*c*) dilauroyl peroxide (0.3 equiv.), DCE, 80 °C, 3 h.

This reaction gives the dimer $[(Pr^iO)_2P(O)CF_2]_2$ as a by-product. The reaction with methylidenecyclobutane affords the addition product in 65% yield. However, the reaction with methylidenecyclopentane gives a mixture of addition product **63a** and elimination product **63b**.



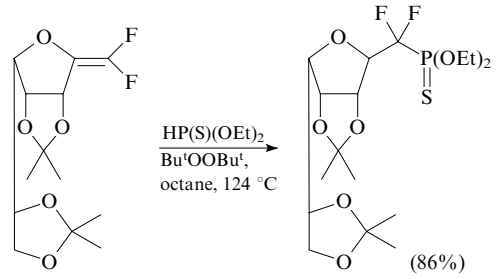
The free radical reactions with the phosphoryl radicals $(RO)_2P^{\bullet}(O)$ were used to synthesize furanosyl phosphonates. For instance, compounds **64a–d** were prepared by the addition of the radical $(EtO)_2P^{\bullet}(O)$ to 2,2-difluoromethylidenefuranoses.[81] The radical $(EtO)_2P^{\bullet}(O)$ was generated either from diethyl phosphite in the presence of *tert*-butyl peroxide as the initiator (method A)[82] or from diethyl phenylselenophosphate‡ in the presence of azobis(isobutyronitrile) or tributyltin hydride as the initiator (method B).



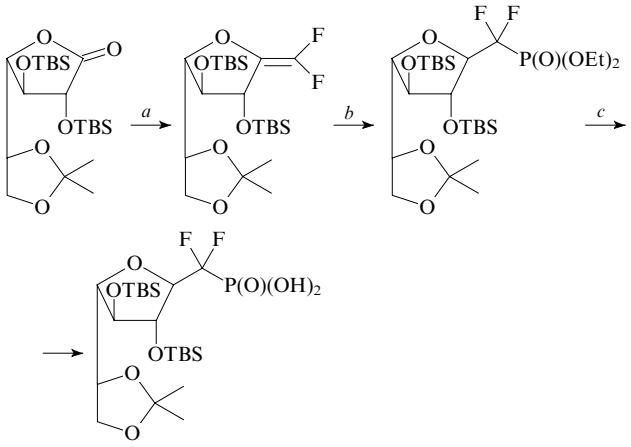
Compound	R^1/R^2	R^3	R^4	Yield (%)	
				method A	method B
64a	$Bu^n_3SiOCH_2$/H	H	H	5	52
64b	$Bu^n_3SiOCH_2$/H			47	73
64c	H/			23	29
64d	H/H			8	36

‡ The chemistry and biological activity of phosphonates were considered in the comprehensive review by Engel.[1]

The authors of the above studies applied this method to the synthesis of the corresponding thiophosphonates.[84] In all cases, the yields of thiophosphonates were higher than those of the corresponding phosphonates. For example, the thio analogue of furanosylphosphonate **64c** was prepared in 86% yield, whereas the yield of phosphonate was at most 29%. Apparently, this is associated with the higher lability of the H–P bond in dialkyl thiophosphites compared to that in dialkyl phosphites.



Since the D-galactofuranose fragment is present in polysaccharides and glycoconjugates of various pathogenic bacteria and fungi[85] but is absent in the human body, it was of interest to synthesize potent inhibitors of enzymes involved in the synthesis and transfer of the D-galactofuranose residue to the carbohydrate chain. The synthesis of the CF_2 analogue of D-galactofuranosyl phosphate was documented.[86, 87]

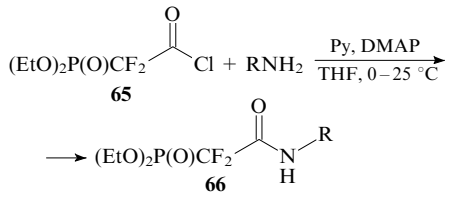


TBS = $SiBu^tMe_2$; (*a*) $P(NMe_2)_3$, CF_2Br_2, Zn, THF, 15 h, yield 62%;
(*b*) $HP(OEt)_2$, $Bu^tO_2C(O)Bu^t$, PhH, 48 h, yield 56%;
(*c*) Me_3SiI, CCl_4, yield 80%.

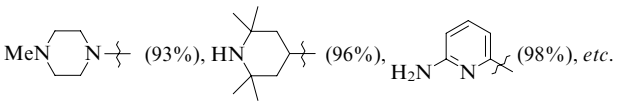
IV. Reactions with the participation of compounds $(RO)_2P(O)CF_2R'$

Compounds containing the difluoromethylenephosphonate groups are convenient reagents for the enlargement of molecular structures with the use of conventional procedures.

Recently, a convenient method has been developed for the synthesis of phosphonamides.[31] Difluoro(diethoxyphosphoryl)acetyl chloride (**65**) served as the starting compounds. The reactions of compound **65** with primary amines in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) give the corresponding phosphonamides **66** in high yields.

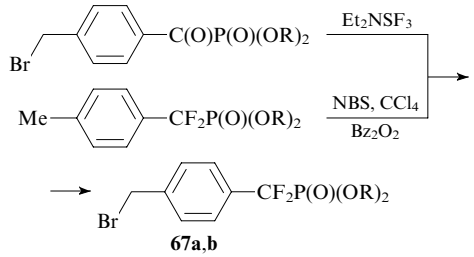


R = Bn (66%), XCH_2CH_2 (X = OH (68%), Br (92%), NH_2 (97%)), 2,4-$F_2C_6H_3$ (98%), $NH_2(CH_2)_6$ (93%), $NH_2(CH_2)_2S-S(CH_2)_2$ (93%),



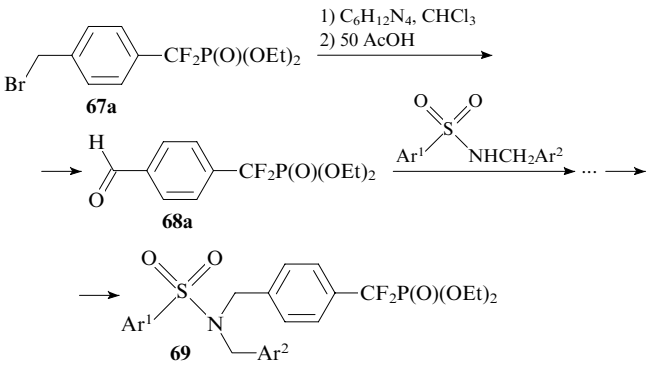
The synthesis of various derivatives based on α,α-difluorobut-3-enylphosphonate (Scheme 1) was described in the study.[88]

4-Bromomethyl-α,α-difluorobenzylphosphonates **67** are convenient reagents for the synthesis of various organic compounds containing the $CF_2P(O)(OR)_2$ fragment. Compounds **67** can be prepared by the bromination at the methyl group of 4-methyl-α,α-difluorobenzylphosphonate[89,90] or by the fluorination of α-keto phosphonate.[91,92]

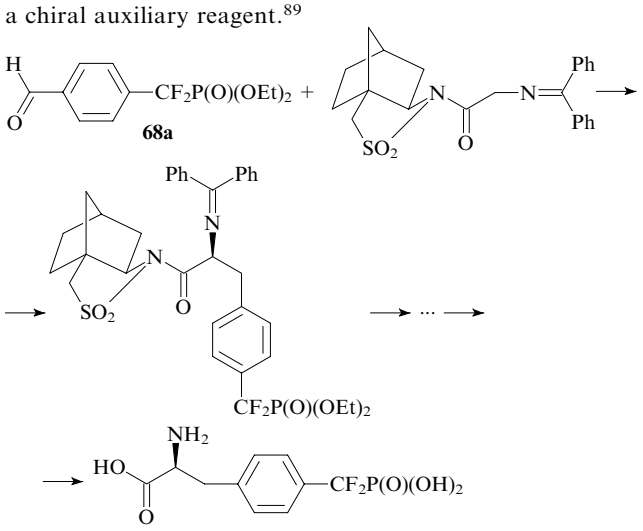


NBS is *N*-bromosuccinimide; R = Et (**a**), Bu^t (**b**).

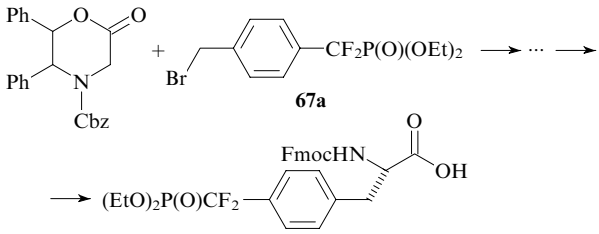
Derivatives **67** are involved in various reactions, in which the difluoromethylenephosphonate moiety remains intact. In particular, compound **67a** is transformed into aldehyde **68a** in the reactions with acetic acid in the presence of hexamethylenetetramine ($C_6H_{12}N_4$).[90] Compound **68a** was used in the synthesis of sulfonamides **69** containing the difluoromethylenephosphonate group, which are potent inhibitors of protein tyrosine phosphatase 1B.[90]



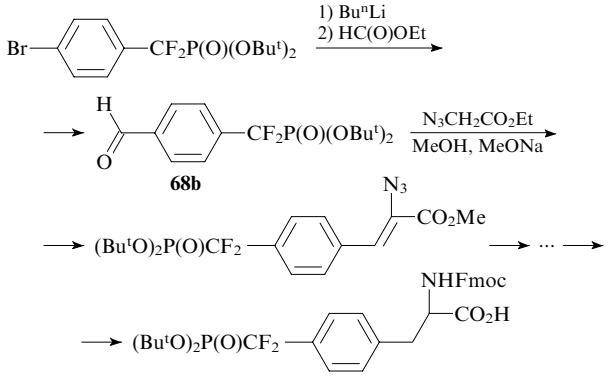
Compound **68a** was used in the synthesis of amino acids containing the remote $CF_2P(O)(OH)_2$ group, for example, in the enantioselective synthesis of L-4-(phosphonodifluoromethyl)phenylalanine in the presence of camphorsultam as a chiral auxiliary reagent.[89]



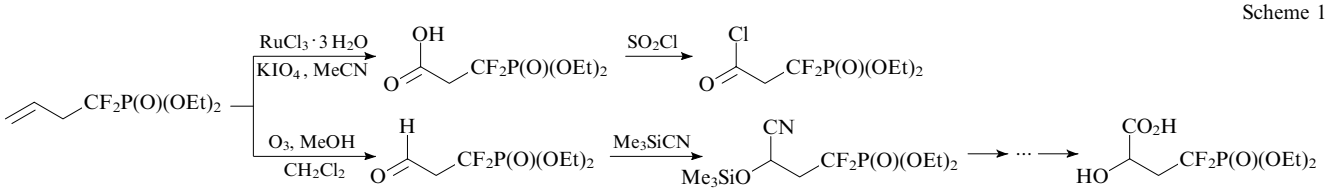
L-4-(Phosphonodifluoromethyl)phenylalanine was synthesized by the reaction of compound **67a** with protected 5,6-diphenylmorpholin-2-one.[91]



The di-*tert*-butyl analogue of aldehyde **68a**, *viz.*, compound **68b**, was generated from di(*tert*-butyl) 4-bromo-α,α-difluorobenzylphosphonate.[92] For this purpose, the bromide was initially transformed into the organolithium derivative, which was formylated by ethyl formate. The reaction of the resulting aldehyde with ethyl azidoacetate

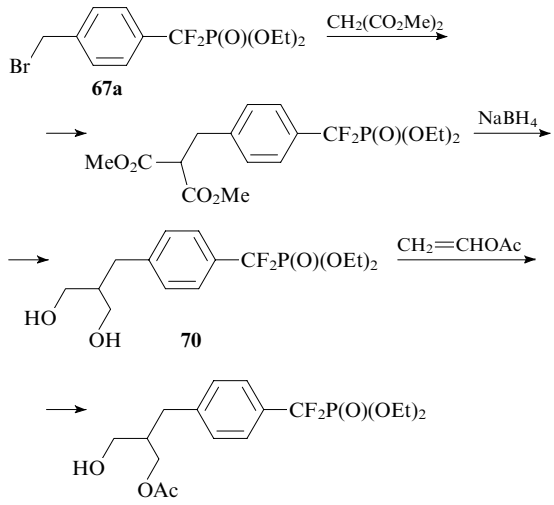


Scheme 1



gives phosphoryldifluoromethylphenylalanine, which can be used in the solid-phase peptide synthesis.

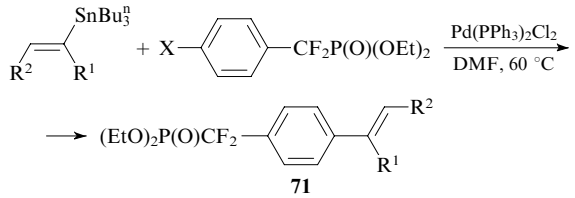
Compound **67a** easily reacts with CH-acids, for example, with dimethyl malonate. The reduction of the ester groups afforded a mixture of enantiomeric diols **70**, which was separated enzymatically.[93]



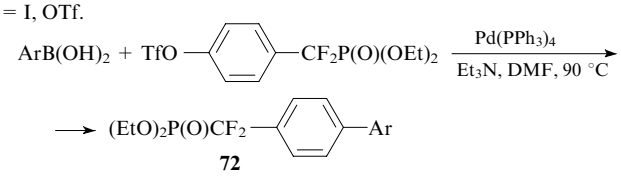
The subsequent transformations of compound **70** afforded diethoxyphosphoryldifluoromethylphenylalanine.

The analogue of compound **70**, *viz.*, propane-1,3-diol containing the diethoxyphosphoryl-1,1-difluoroethyl group at position 2, was used in the synthesis of acyclic nucleotide analogues of adenosine bisphosphates.[94]

The Stille reaction of 4-iodo-α,α-difluorobenzylphosphonate and its triflate analogue with vinyl- and hetaryltributylstannanes and the Suzuki reaction of these compounds with arylboronic acids give the corresponding coupling products **71** and **72** containing the $CF_2P(O)(OEt)_2$ group.[54] The yields of products **71** and **72** vary from 40% to 90%.

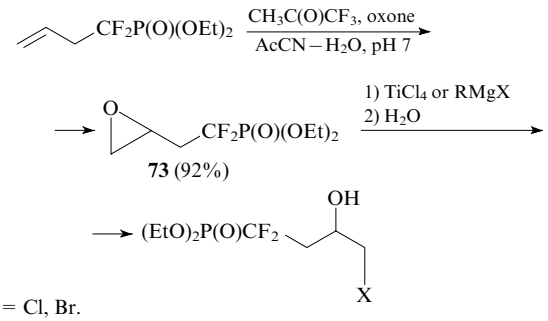


X = I, OTf.



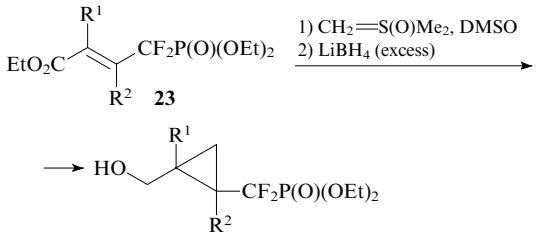
Ar = *p*-ClC_6H_4, *p*-BrC_6H_4, *o*-$OHCC_6H_4$, *m*-$NO_2C_6H_4$, 3,4-$Me_2C_6H_3$.

The methods for the synthesis of hydroxylated difluoromethylenephosphonates with the use of the reagents $(RO)_2P(O)CF_2EX_n$ are described above. Here, the synthesis of hydroxylated difluoromethylenephosphonates based on the compounds $(RO)_2P(O)CF_2R'$ is considered. The synthesis of $CF_2P(O)(OR)_2$-containing secondary alcohols starting from terminal alkenes was documented.[69] For this purpose, alkenes were transformed into epoxy derivatives **73**. The ring opening of the latter compounds by Lewis acids gave exclusively secondary alcohols.



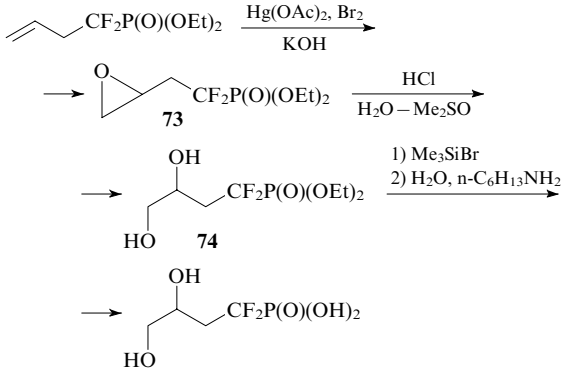
X = Cl, Br.

The synthesis of cyclopropylalkanols containing the $CF_2P(O)(OEt)_2$ group was reported.[95]

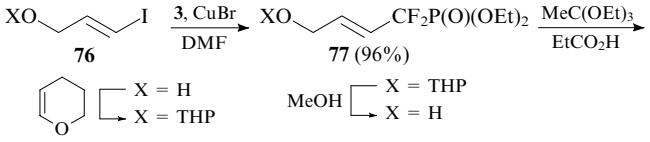


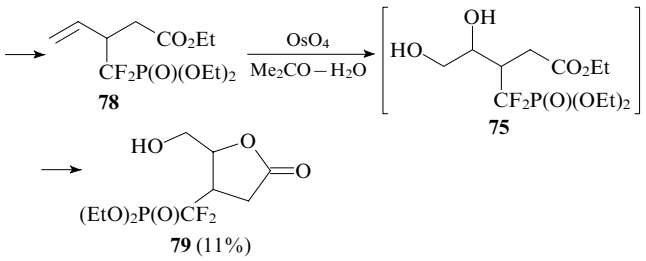
$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$; $R^2 = H$, $R^1 = Me$.

A series of studies were concerned with the synthesis of vicinal diols. Cyclohexylammonium 3,4-dihydroxy-1,1-difluorobutylphosphonate was synthesized for the first time by Chambers *et al.*[46] in 1988 with the use of 1,1-difluorobut-3-enylphosphonate, which was prepared by the reaction of cadmium derivative **4** with allyl bromide. This multistep synthesis involves the ring opening of the epoxide moiety in derivative **73** in the presence of hydrochloric acid as the catalyst in a H_2O-Me_2SO mixture (2 : 1). Under these conditions, *vic*-diol **74** was obtained in 95% yield.



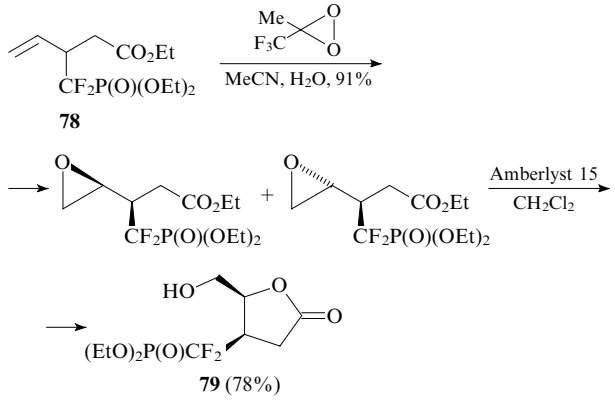
The scheme of the synthesis of *vic*-diols **75** from unsaturated haloalcohols **76** by the classical oxidative dihydroxylation was described in the study.[96] The reaction proceeds through unsaturated phosphonates **77** and **78**.



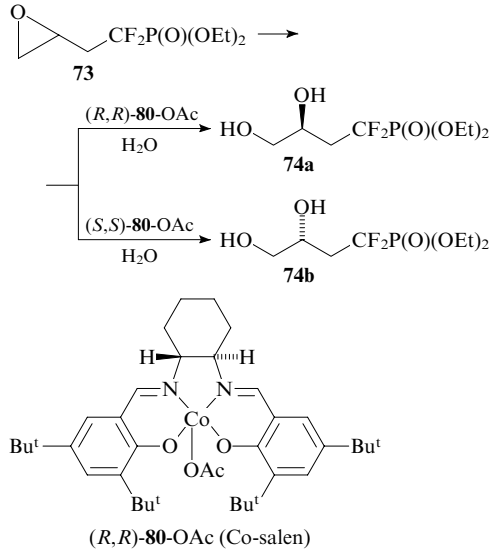


THP is tetrahydropyran-2-yl.

vic-Diols **75** are of interest as the starting compounds for the synthesis of lactones **79**, which are CF_2 analogues of nucleoside 3′-phosphates. However, the classical oxidative dihydroxylation of alkene **78** afforded lactone **79** in low yield (11%). Hence, it was suggested [96] that this lactone can be synthesized starting from epoxide derivatives, which were prepared by the oxidation of the corresponding alkenes by dioxirane. After the ring opening of the epoxide moiety in an acidic medium, lactone **79** was isolated in 78% yield.



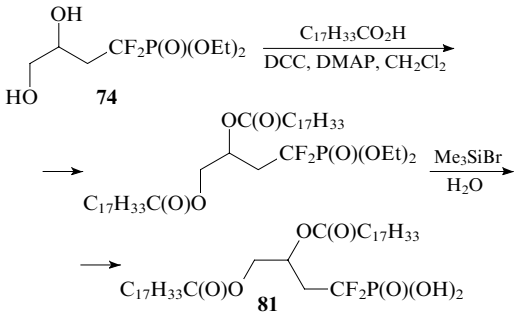
Chiral α,α-difluorobutylphosphonates **74a**,**b**, which are structural analogues of phosphatidic and lysophosphatidic acids (1- and 2-acyl-*sn*-glycerol 3-phosphates, respectively), were synthesized by the hydrolytic cleavage of 1,1-difluoro-3,4-epoxybutylphosphonate **73** by the chiral complex Co-salen (**80**).[97, 98]



(*R*,*R*)-**80**-OAc (Co-salen)

Hence, the epoxide derivatives proved to be very convenient starting compounds in the synthesis of *vic*-diols.

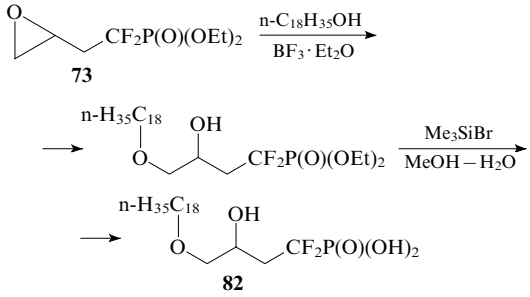
The acylation of compound **74** by oleinic acid afforded the hydrolytically stable analogue of phosphatidic acid, *viz*., derivative **81**.[97, 98]



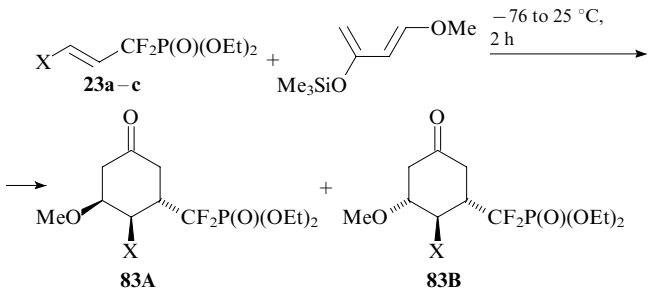
DCC is dicyclohexylcarbodiimide.

Phosphatidic acid, which is generated in the reactions of phospholipase D with phosphatidylcholine and other phospholipids, is an important intermediate in the biosynthesis of phosphatidylglycerols. This acid is a signaling molecule and plays a key role in the cell growth and protein transport.

The synthesis of the CF_2 analogue of alkylated lysophosphatidic acid (compound **82**) was documented.[99] The preparation of this derivative is based on the ring opening of the epoxide moiety in compound **73** by octadecenol in the presence of $BF_3 \cdot Et_2O$.



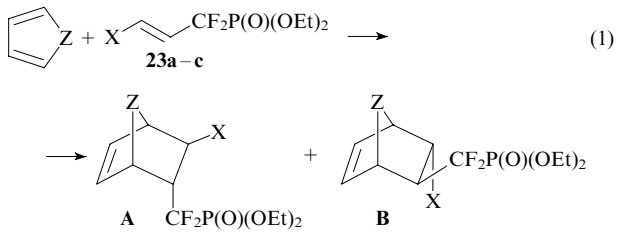
α,β-Unsaturated compounds **23a**–**c** containing the $CF_2P(O)(OEt)_2$ group at the double bond are easily involved in the diene synthesis. Thus, their reactions with 1-methoxy-3-(trimethylsiloxy)butadiene afford a mixture of *endo* and *exo* isomers of cyclohexanones **83A** and **83B** in good yields.[29]



X = NO_2 (yield of compound **83** is 57%, **A** : **B** = 7 : 3),
CO_2Et (41%, **A** : **B** = 1 : 1), SO_2Ph (50%).

In this reaction, both functional groups of alkene remain intact.

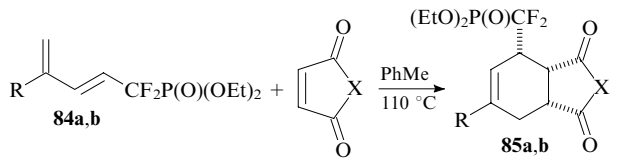
Compounds **23a**–**c** react with cyclic dienes (cyclopentadiene and furan) to give a mixture of *endo* and *exo* isomers as well:[29]



Z	X	Yield (%)	Ratio **A** : **B**
CH_2	NO_2	95	2 : 3
	CO_2Et	81	4 : 1
	SO_2Ph	93	2 : 3
O	NO_2	92	3 : 7
	CO_2Et	83	1 : 1
	SO_2Ph	60	2 : 3

As can be seen from the above data, the reaction (1) occurs with low *endo*–*exo* selectivity.

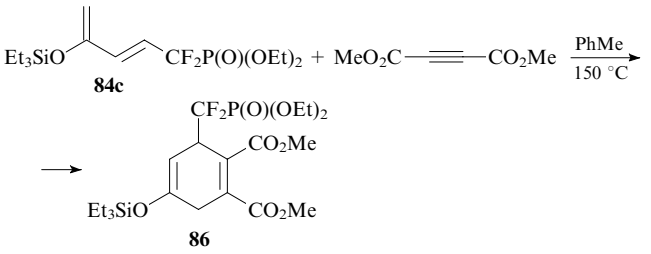
Unlike the reaction (1), the reactions of dienes **84a**,**b** with maleic anhydride and *N*-phenylmaleimide occur selectively to form *endo* isomers **85a**,**b**.[61]



R = H (**a**), Me (**b**).

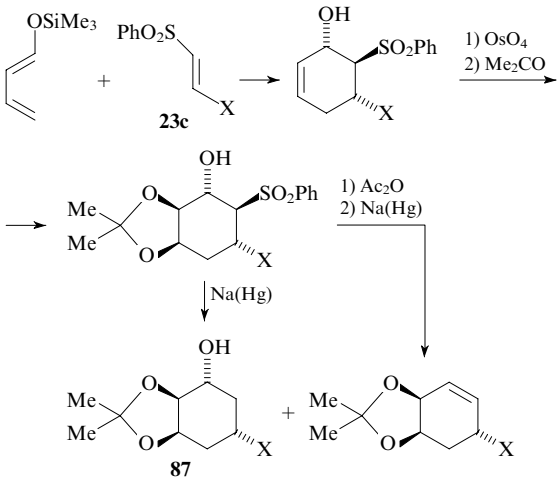
R	X	Yield (%)	*endo* : *exo*
H	O	61	> 99 : 1
	NPh	56	> 99 : 1
Me	O	81	> 99 : 1
	NPh	67	> 99 : 1

The Diels–Alder reaction of diene **84c** (R = Et_3SiO) with dimethyl acetylenedicarboxylate gives product **86** in 57% yield.[61]



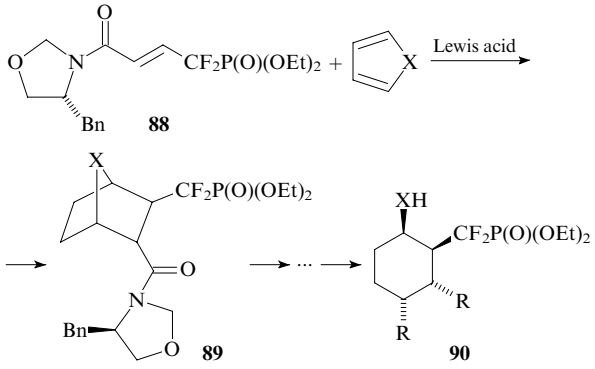
The yield of compound **86** can be increased to 74% by performing the reaction in refluxing benzene for 23 h.

The synthesis of polyhydroxy derivatives of cyclohexane containing the $CF_2P(O)(OEt)_2$ group was described in the study.[100] These compounds can be used as the building blocks in the synthesis of stable analogues of inositol phosphate. Commercially available 1-(trimethylsiloxy)buta-1,3-diene and alkene **23c** served as the starting compounds. Unlike the reaction (1), the latter reaction occurs stereoselectively and gives product **87** in 69% yield.



X = $CF_2P(O)(OEt)_2$.

The Diels–Alder reaction of five-membered heterocycles with alkene **88** affords norbornene derivatives **89**, which are transformed into substituted cyclohexanes **90** in several steps.



X = O, S, NH; R = H or OH.

Compounds **90** were covered by patents as inhibitors of inositol monophosphatase.[101, 102]

The hetero-Diels–Alder reaction of acyclic and cyclic dienes with methyl diethoxyphosphoryldifluorodithioacetate giving dihydrothiapyran derivatives (Scheme 2) was documented.[103]

The starting compound **91** was synthesized according to a procedure described in the study [104] by the reaction of CS_2 with reagent **2** followed by the treatment of acid $(EtO)_2P(O)CF_2C(S)SH$ with methyl chloride.

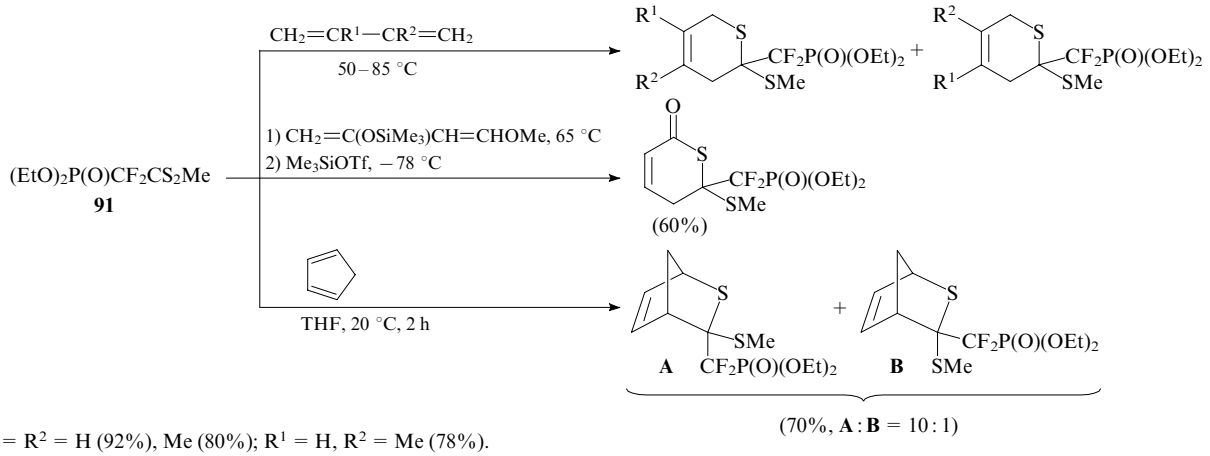
V. Synthesis of heterocyclic compounds containing the difluoromethylenephosphonate group

Heterocyclic compounds containing the $CF_2P(O)(OR)_2$ group have attracted attention because most of these compounds have biological activity.

1. Introduction of the difluoromethylenephosphonate group into heterocyclic compounds

The introduction of the $CF_2P(O)(OEt)_2$ group into heterocyclic molecules by the replacement of halogen atoms with the use of the compounds $(RO)_2P(O)CF_2EX_n$ was described above (see Section III.3). This section deals with the functionalization of heterocyclic compounds with the use

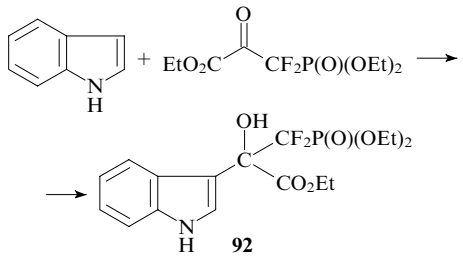
Scheme 2



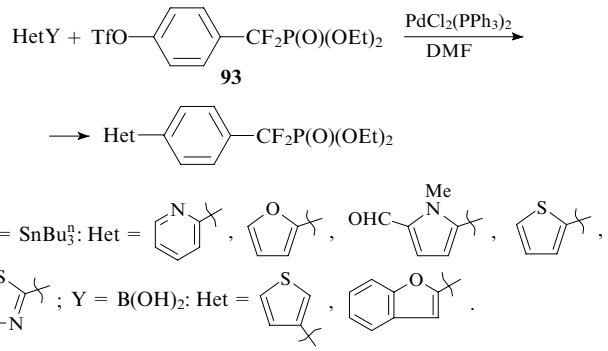
$R^1 = R^2 = H$ (92%), Me (80%); $R^1 = H$, $R^2 = Me$ (78%).

of the compounds $RCF_2P(O)(OEt)_2$ (R is a carbon-containing substituent).

The reaction of indole with α-keto carboxylic acid ethyl ester containing the $CF_2P(O)(OEt)_2$ group at the carbonyl carbon atom occurs at room temperature in chloroform to give tertiary alcohol **92**.[105]



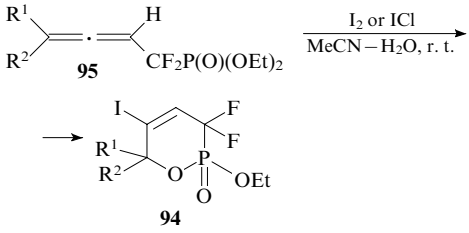
The functionalization of boryl- and tributylstannylhetarenes with compound **93** was described in the study.[54]



The reactions occur in the presence of palladium complexes in dimethylformamide.

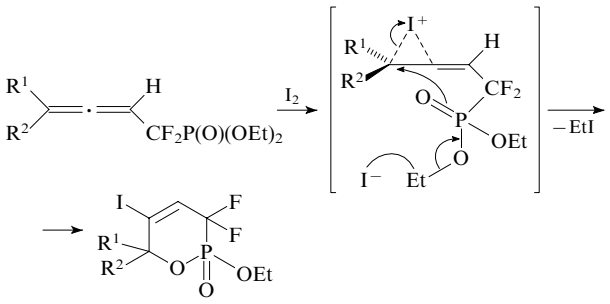
2. Synthesis of P,O-heterocyclic compounds by the cyclization of derivatives $RCF_2P(O)(OR)_2$

The cyclization of β-allenic phosphonates is the best studied reaction of this type. Thus, Chinese researchers [106] were the first to describe the synthesis of cyclic α-difluoromethylenephosphonates **94** by the cyclization of allenic derivatives **95** in the presence of molecular iodine or ICl.



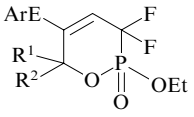
R^1	R^2	Electrophile	Yield of **94** (%)	R^1	R^2	Electrophile	Yield of **94** (%)
Me	Me	I_2	82	Me	Bu^t	I_2	53
Me	Me	ICl	83	Me	Ph	I_2	64
Et	Et	I_2	92	Et	H	I_2	25
$-(CH_2)_5-$		I_2	90	Et	H	ICl	80
$-(CH_2)_4-$		I_2	81	Pr^n	H	ICl	78
Me	Et	I_2	91	Pr^i	H	ICl	75

The following reaction mechanism was proposed:



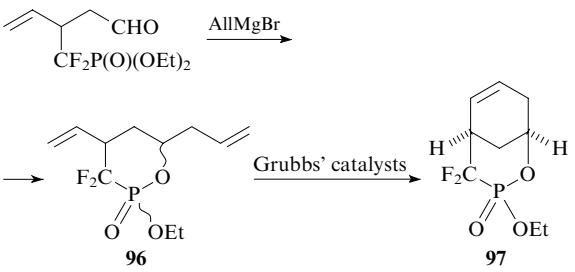
More recently, these authors have synthesized the related bromo derivative (87% yield). In this reaction, *N*-bromosuccinimide served as the electrophile, and the monoester $Me_2C{=}C{=}CHCF_2P(O)(OH)(OEt)$ was used as the allenic derivative.[107]

The compounds ArECl (E = S or Se) can also be used as the cyclizing agent. In this case, the electrophilic cyclization occurs under mild conditions (in MeCN) with high regioselectivity. Cyclic phosphonates are formed in high yields.[108]

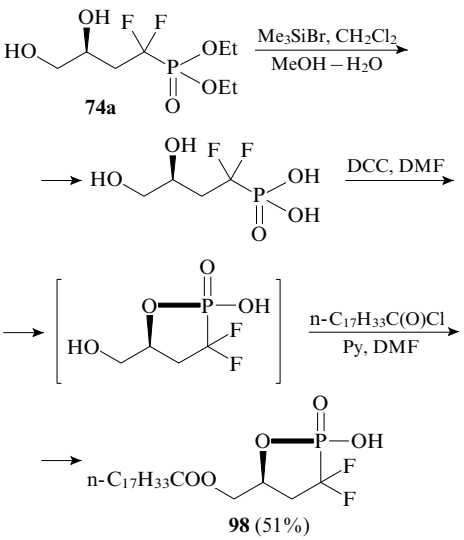


E = S, Ar = *p*-Tol: $R^1 = R^2$ = Me (84%), Et (78%),
R^1-R^2 = $-(CH_2)_5-$ (49%), $-(CH_2)_4-$ (62%);
R^2 = H: R^1 = Et (94%), Pr^n (89%), Pr^i (95%);
E = Se, Ar = Ph: $R^1 = R^2$ = Me (85%), Et (82%),
R^1-R^2 = $-(CH_2)_5-$ (47%), $-(CH_2)_4-$ (87%);
R^2 = H: R^1 = Et (95%), Pr^n (94%), Pr^i (93%).

The reaction of pent-4-enal containing the difluoromethylenephosphonate group at position 3 with allylmagnesium bromide gives a mixture of diastereomers **96**, which undergo cyclization to compounds **97** in the presence of transition metal carbene complexes as catalysts (Grubbs' catalysts).[96]



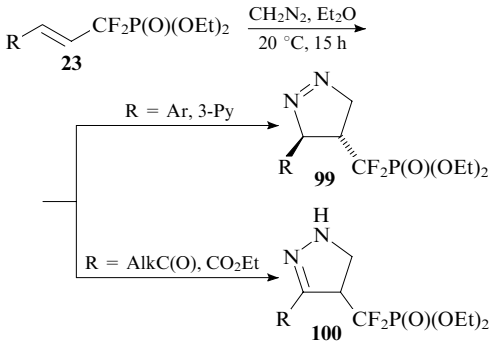
In addition to six-membered P,O-cyclic compounds, five-membered derivatives **98**, which are analogues of cyclic phosphatidic acid, were synthesized.[109] *vis*-Diols, in particular, *S* isomer **74a**, whose synthesis was described above, were used as the starting compounds.



Compound **98** is a lysophosphatidic acid receptor antagonist.

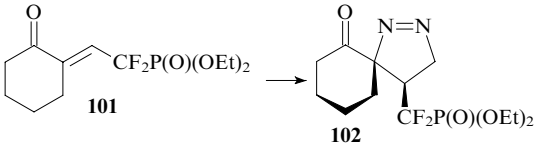
3. 1,3-Dipolar cycloaddition

Pyrazolines containing the $CF_2P(O)(OEt)_2$ substituent in heterocycles were synthesized by the reaction of diazomethane with allyl derivatives of phosphonates **23**.[110] Depending on the nature of the substituent R, this reaction gives two types of derivatives. The reactions with the use of aryl and hetaryl derivatives **23** (R = Ar or Het) afford compounds **99**, whereas the reactions with acyl and ester derivatives give compounds **100**.



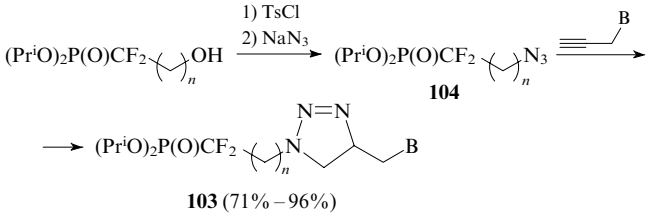
99: R = Ph (72%), 4-FC_6H_4 (83%), 4-$MeO_2CC_6H_4$ (64%), 3-Py (60%);
100: R = Ac (59%), EtC(O) (80%), $Pr^iC(O)$ (81%), CO_2Et (79%).

Under analogous conditions, the addition of diazomethane to cyclic derivative **101** affords spiro compound **102** in 65% yield.[110]



Compounds **99**, **100** and **102** are transformed under light into cyclopropane derivatives accompanied by the elimination of N_2.

The synthesis of acyclic nucleotide analogues, *viz*., compounds **103**, containing the difluoromethylenephosphonate group and the triazole ring, by the Cu(I) salt-catalyzed 1,3-dipolar cycloaddition of phosphorylated azides **104** to propargyl thymine and propargyl 2-amino-6-chloropurine (Huisgen reaction) was documented.[111]

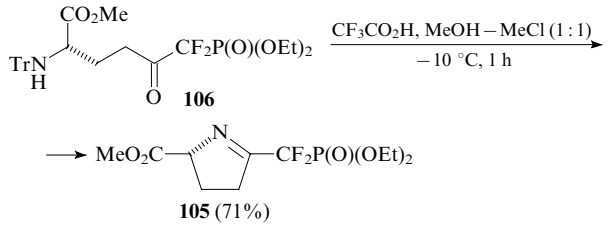


n = 2–4; B is thymin-1-yl, 2-amino-6-chloropurin-9-yl.

4. Intramolecular cyclization of compounds containing the difluoromethylenephosphonate group

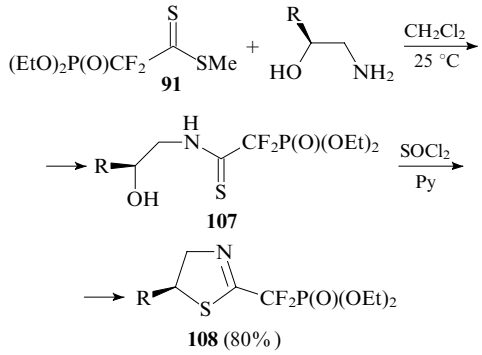
Heterocyclic compounds containing the difluoromethylenephosphonate group can be synthesized by the intramolecular cyclization of the corresponding unsaturated or (thio)carbonyl compounds.

For example, pyrroline **105** was prepared by the spontaneous cyclization of the difluoromethyl analogue of γ-glutamyl phosphate **106**, which is a potent inhibitor of glutamyl cysteine synthase and glutamine synthase, at the instant of the removal of the trityl (Tr) protecting group from the amino group. In the resulting thiazolines, the stereo configuration of the starting β-amino alcohols remains unchanged.[112]



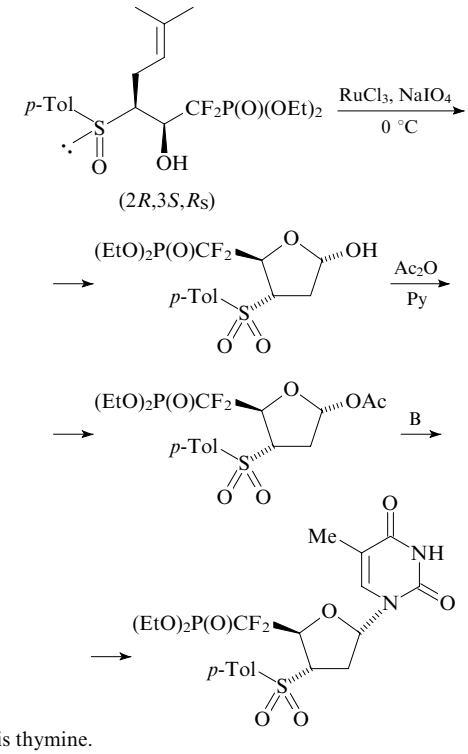
It should be noted that the salt of this phosphonate in an aqueous alkaline solution exists only in the cyclic form.

Thioamides **107**, which are formed by the amination of diethoxyphosphoryldifluorodithiomethyl acetate (**91**) by enantiomerically pure β-amino alcohols, undergo cyclization to thiazoline **108** when treated with thionyl chloride.[113]



In the resulting thiazolines, the stereo configuration of the starting β-amino alcohols remains unchanged.

The enantiomerically pure 3′-arylsulfonyl-4′-[(diethoxyphosphoryl)difluoromethyl] analogue of thymidine was synthesized in the study.[114, 115] Diethyl 1,1-difluoro-2-hydroxy-6-methylhept-5-enylphosphonate containing the *p*-toluoylsulfinyl substituent at position 3 was used as the starting compound.

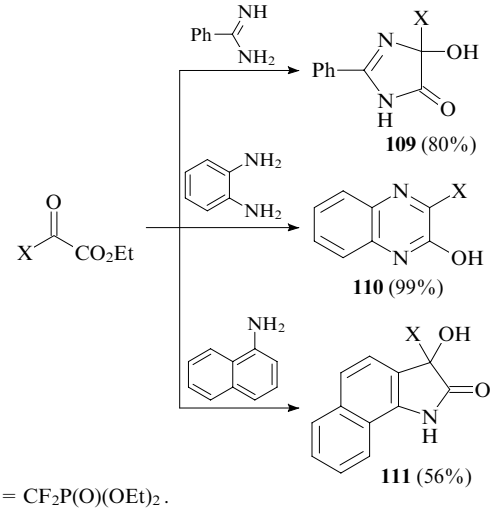


B is thymine.

5. Heterocyclization reactions

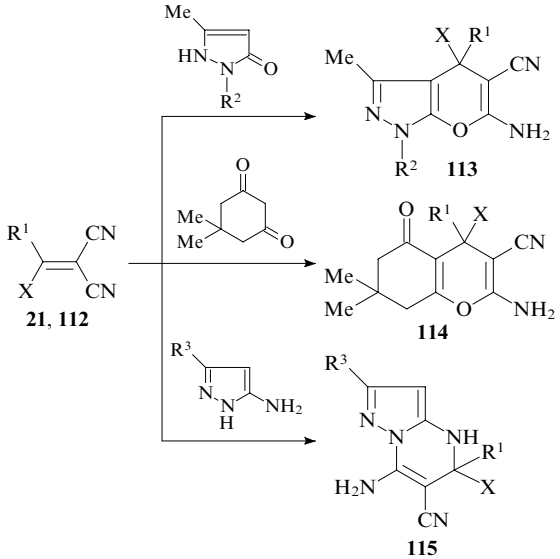
Heterocyclization reactions with organic compounds containing the difluoromethylenephosphonate group are widely used in the synthesis of heterocyclic compounds. In these reactions, the $CF_2P(O)(OR)_2$ group remains intact.

The reactions of keto ester with benzamidine, *o*-phenylenedimamine and α-naphthylamine afford pyrazolidone **109**, quinoxaline **110** and benzindolone **111**, respectively, in high yields.[105] All reactions were carried out in aprotic solvents at 20 °C.



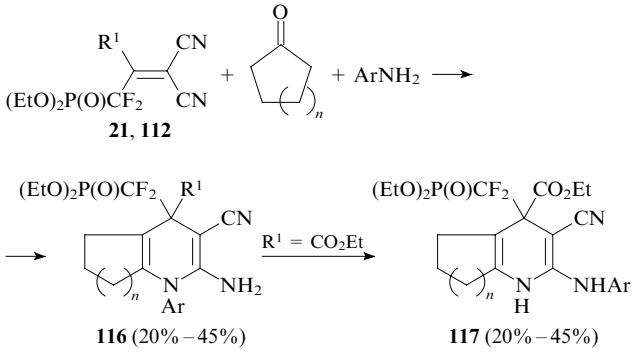
X = $CF_2P(O)(OEt)_2$.

3,3-Dicyano-1,1-difluoroallylphosphonates, *viz.*, compound **21** and its ethoxycarbonyl analogue **112**, are convenient reagents for the preparation of heterocycles. These compounds were used in the synthesis of a wide range of heterocyclic compounds.[26, 116] Thus, the reactions of compounds **21** and **112** with pyrazolinones, dimedone and aminopyrazoles afford heterocyclization products **113**–**115**.



X = $CF_2P(O)(OEt)_2$; R^1 = CF_3 (**21**), CO_2Et (**112**); R^2 = H, Alk, Ar; R^3 = Ar.

The reactions were carried out in aprotic solvents at 20 °C. Under the same conditions, the reactions of dinitriles **21** and **112** with enamines generated *in situ* from arylamines and ketones gave dihydropyridines **116**. In the reaction of compound **112**, product **116** was rearranged (Dimroth rearrangement) into derivative **117**.

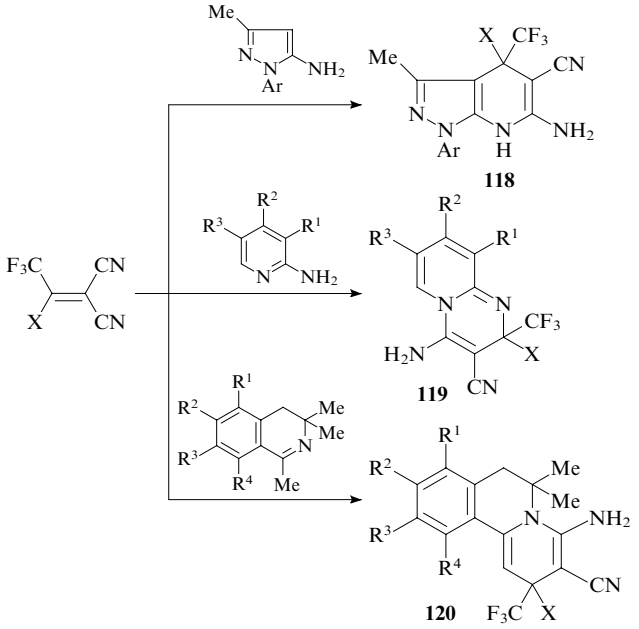


21, **112**

116 (20% – 45%) **117** (20% – 45%)

$R^1 = CF_3$, CO_2Et; $n = 1, 2$; Ar = 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 2-PhC_6H_4.

The heterocyclization reactions of compound **21** with 1-aryl-5-aminopyrazoles, 2-aminopyridines and 1,3,3-trimethylisoquinolines give pyrazolepyridines **118**, pyridopyrimidines **119** and pyridoisoquinolines **120**, respectively.[26]



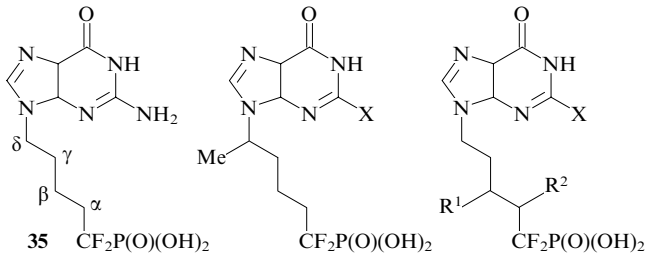
118 **119** **120**

X = $CF_2P(O)(OEt)_2$; $R^1 - R^4$ = H, Alk, Hal, *etc.*

VI. Synthesis of analogues of nucleosides, amino acids and sugars containing the difluoromethylenephosphonate group

The compounds $(RO)_2P(O)CF_2R$ with the F_2C-C bond (their synthesis was described in Section III) are important starting compounds in the synthesis of numerous analogues of natural substances and biologically active heterocyclic compounds.

Numerous examples of the functionalization of purine bases by haloalkanes, -alkenes or -alkynes containing the $CF_2P(O)(OEt)_2$ groups employed in the synthesis of analogues of natural phosphates were documented. Some of these reactions were considered above (see Section III.3). Iodine derivatives, such as 5-iodo-1,1-difluorohexyl-, 5-iodo-2(3)-methyl-1,1-difluoropentyl-, 5-iodo-1,1-difluoropentylphosphonates, *etc.* are often used as haloalkanes.[37] These compounds served as the starting compounds in the synthesis of acyclic nucleosides, such as compound **35** and its α-, β- and δ-methyl derivatives.

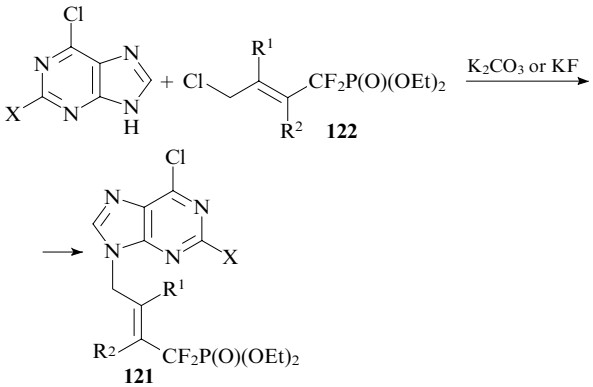


35

X = H, NH_2; R^1 = H, R^2 = Me; R^1 = Me, R^2 = H.

It was shown that the inhibiting activity of the methyl derivatives toward purine nucleoside phosphorylase substantially depends on the position of the methyl group. Thus, the δ-methyl derivative exhibits the highest inhibiting activity.[37]

The unsaturated analogue of compound **35**, *viz.*, derivative **121**, was synthesized by the alkylation of purine base by chloroalkene **122**.[23]

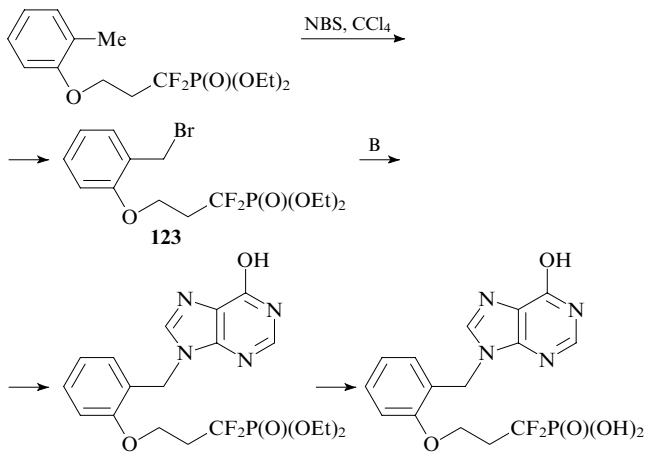


122 **121**

X = H: $R^1 = R^2$ = H (42%); X = NH_2: R^1 = Me, R^2 = H (30%); R^1 = H, R^2 = Me (55%).

The reaction of ω-alkynyl difluoromethylenephosphonates **47a** – **c** with protected 9-iodo-9-deazaguanine (Sonogashira reaction) gives 9-(ω,ω-difluoro-ω-phosphorylalkyl)-9-deazaguanines **48a** – **c** (see Section III.3).[51, 117]

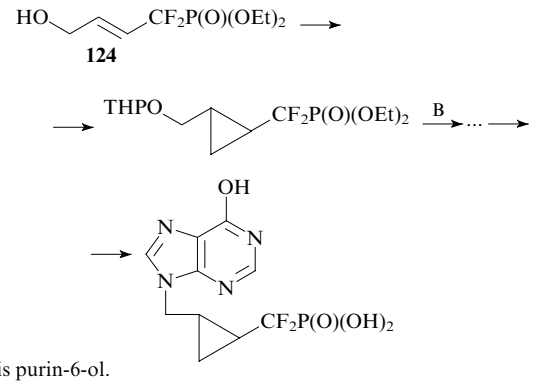
Purine bases can also be alkylated by bromobenzyl derivatives, for example, by compound **123**.[118]



123

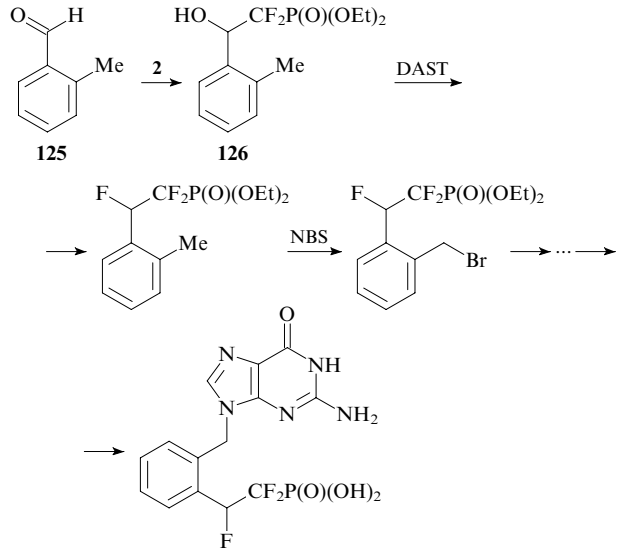
B is purin-6-ol.

The synthesis of cyclopropane [119, 120] and furan [121] analogues of compound **35** was documented. The former compound was prepared with the use of allyl alcohol **124**.[119]



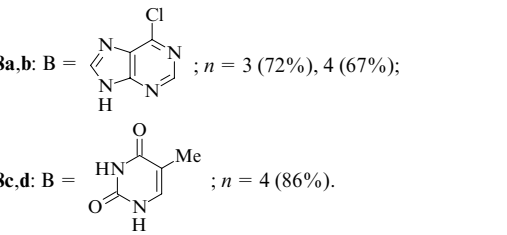
B is purin-6-ol.

Compound **126**, which is the addition product of lithium derivative **2** to aldehyde **125**, was also used for the modification of purine base.[118]



The synthesis of other N^9-benzylguanines containing the difluoromethylenephosphonate group in the benzene ring was described in the study.[122]

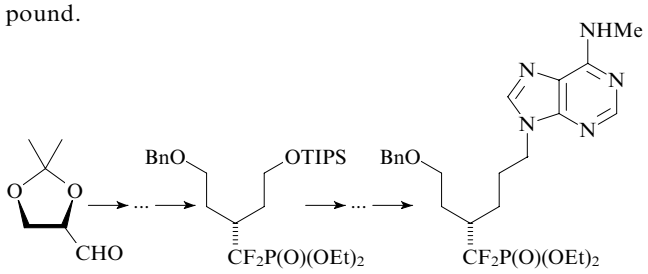
Alcohols **127a**,**b** [R = H; n = 3 (**a**), 4 (**b**)] were also used for the alkylation of nucleic bases, such as thymine and 6-chloropurine.[70] For this purpose, these compounds were first transformed into the corresponding tosylates **127a**,**b** (R = Ts). The alkylation of 6-chloropurine was carried out in dimethylformamide in the presence of K_2CO_3. The alkylation of thymine was performed in dimethyl sulfoxide in the presence of 1,1,3,3-tetramethylguanidine. The corresponding acyclic analogues of nucleotides **128a**–**d** were obtained in quantitative yields.



128a,**b**: B = ; n = 3 (72%), 4 (67%);

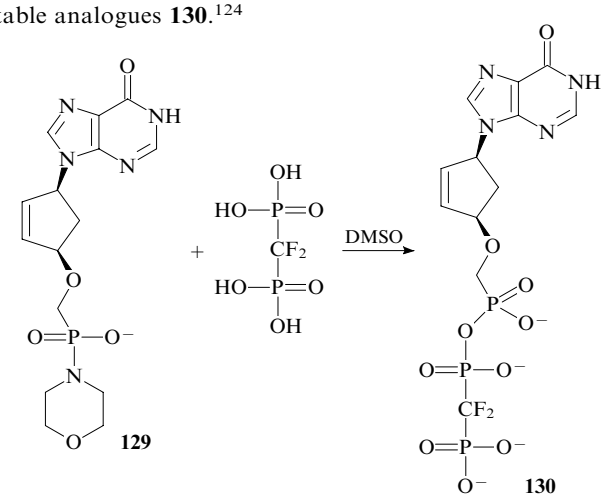
128c,**d**: B = ; n = 4 (86%).

Acyclic analogues of nucleotides containing the $CF_2P(O)(OEt)_2$ group in the side chain were synthesized in the study.[123] Pentane-1,5-diol containing the $CF_2P(O).(OEt)_2$ group at position 3 was used as the starting compound.



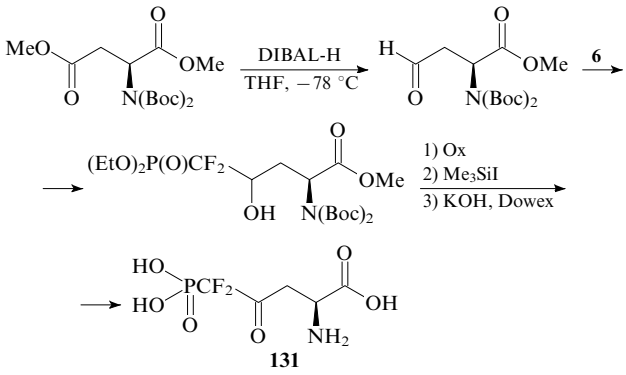
TIPS = $SiPr^i_3$.

(Difluoromethylene)bisphosphonates were employed for the modification of HIV inhibitors (compounds **129**) by the introduction of the CF_2 group to prepare hydrolytically stable analogues **130**.[124]



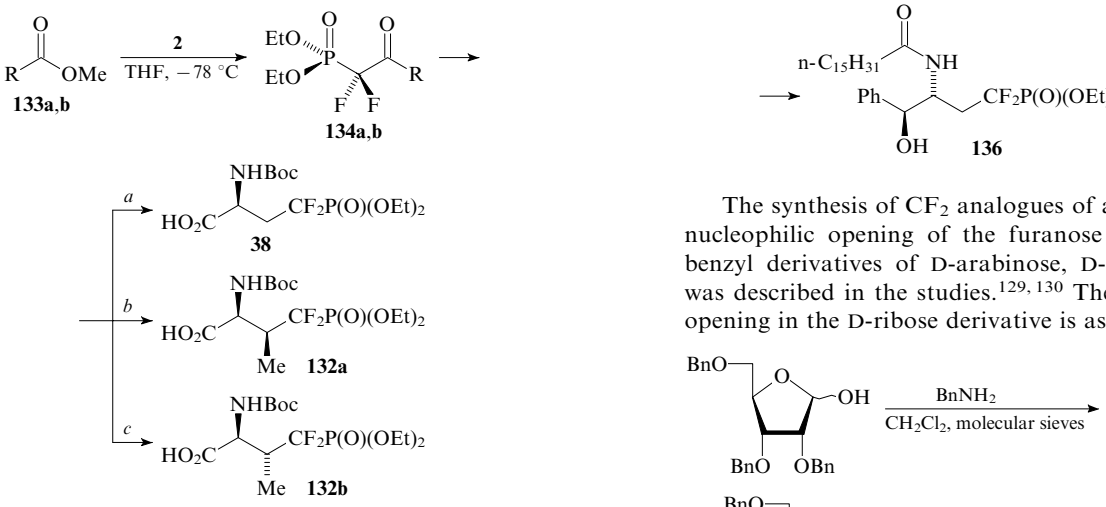
All the above-described purine derivatives exhibit the inhibiting activity toward purine nucleoside phosphorylase.

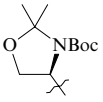
Some methods for the synthesis of amino acids containing the difluoromethylenephosphonate group, which are potent inhibitors of certain enzymes, were described above. In this section, some more examples of the synthesis of these inhibitors are considered. The difluoromethylene analogue of aspartate semialdehyde **131**, which is the first synthetic inhibitor of aspartate semialdehyde dehydrogenase, was synthesized in the study.[125] Dimethyl aspartate was used as the starting compound.

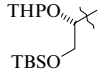


Ox is an oxidant.

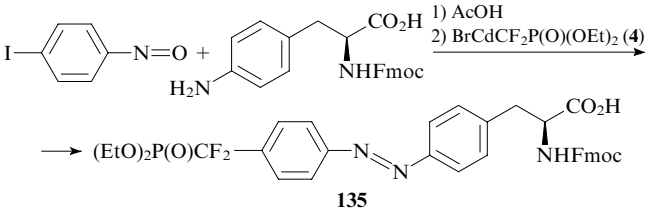
Berkowitz *et al.*[126] described the synthesis of difluoromethylenephosphonate analogues of L-phosphoserine (**38**), L-phosphoallothreonine (**132a**) and L-phosphothreonine (**132b**). Unlike the addition reactions of lithium derivative **2** to the corresponding aldehydes or primary triflates generally used for the preparation of these compounds, methoxycarbonyl derivatives **133** were used in the latter study. Compounds **38** and **132a**,**b** were synthesized according to the following scheme:



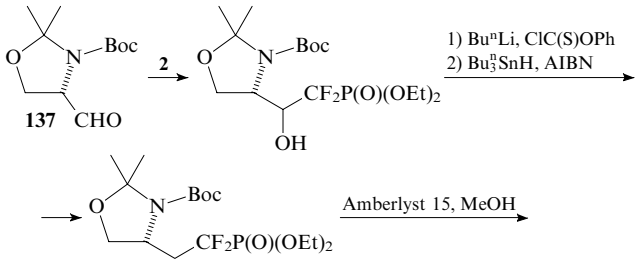
133a: R =  ; (*a*) 1) $LiBH_4$; 2) Bu^nLi, ClC(S)OPh, Bu^n_3SnH; 3) Dowex-50, MeOH, PDC, DMF; (*b*) 1) MeMgBr; 2) Bu^n_3Li, $ClC(O)CO_2Me$, Bu^n_3SnH; 3) Dowex-50, MeOH, PDC, DMF;

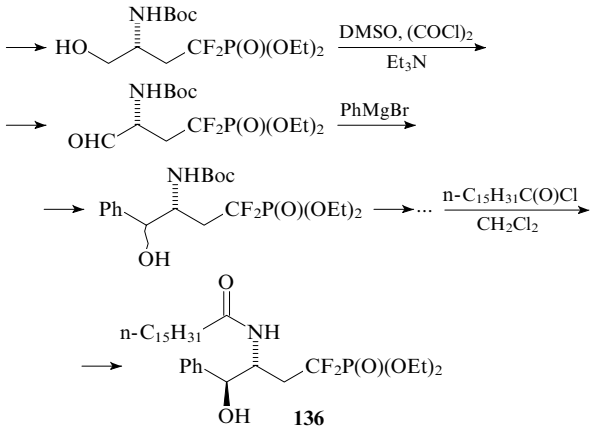
133b: R =  ; (*c*) 1) MeMgBr; 2) Bu^n_3Li, $ClC(O)CO_2Me$, Bu^n_3SnH; 3) $BF_3 \cdot Et_2O$, EtSH, Tf_2O, NaN_3; 4) H_2, Pd/C, Boc_2O; 5) ultrasonic treatment, MeOH, CCl_4; 6) PDC, DMF.

Photocontrolled CF_2 analogues of phosphoamino acids **135** were synthesized by the reaction of *p*-iodonitrobenzene with *p*-amino-L-phenylalanine followed by the replacement of the I atom by the $(EtO)_2P(O)CF_2$ group.[127]

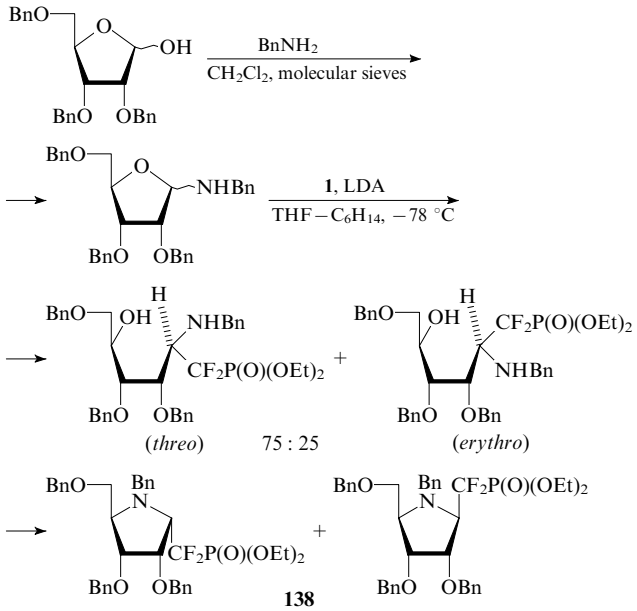


Compound **136**, which is a potent inhibitor of sphingomyelinase, was synthesized[128] starting from Garner's aldehyde **137**.

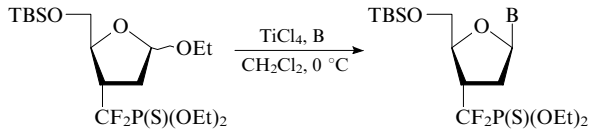




The synthesis of CF_2 analogues of azasugars **138** by the nucleophilic opening of the furanose ring in 2,3,5-tri-*O*-benzyl derivatives of D-arabinose, D-ribose and L-xylose was described in the studies.[129, 130] The scheme of the ring opening in the D-ribose derivative is as follows:



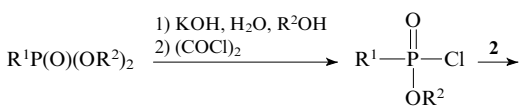
The N-glycosidation of 2,3-dideoxyfuranose derivatives containing the (diethoxythiophosphoryl)difluoromethyl group at position 3 was performed in the study.[131, 132]

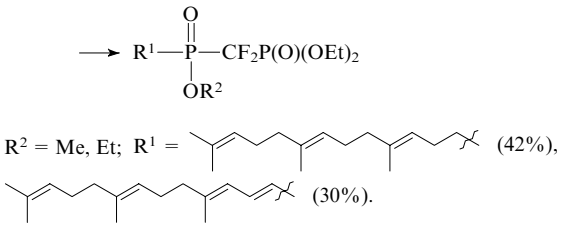


B are hydroxyl-protected thymine, uracil, 5-fluorouracil and adenine.

The starting 2,3-dideoxyfuranose derivatives were synthesized starting from isopropylidene glycerol aldehyde.

Isoprenoids containing the difluoromethylenephosphonate group were prepared in the study.[133]

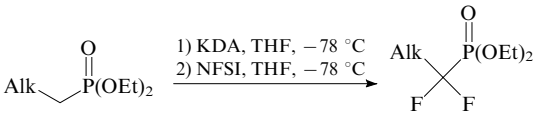




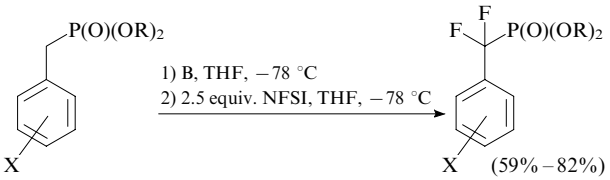
Other examples of the synthesis of natural substances containing the difluoromethylenephosphonate group were given in the recent review by Kukhar and Romanenko.[134]

VII. Synthesis of difluoromethylenephosphonates by fluorination

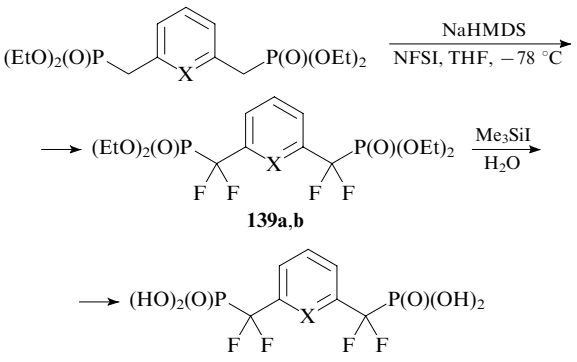
α,α-Difluoroalkylhosphonates were synthesized by the electrophilic fluorination of phosphonates $AlkCH_2P(O)(OR)_2$ by *N*-fluorobenzenesulfonimide (NFSI).[135] This synthesis started with the metallation by potassium or lithium diamide.



This reaction was applied also to the synthesis of α,α-difluorobenzyl derivatives,[136–139] 2,6-bis(diethoxyphosphoryldifluoromethyl) derivatives of pyridine (**139a**) and 1,3-derivatives of benzene (**139b**).[140]



R = Me, Et, Bn; X = H, Br, NO_2, OAlk, CO_2Alk, Ph;
B = KDA, LDA, M^IHMDS (M^I = Na, K, Li).

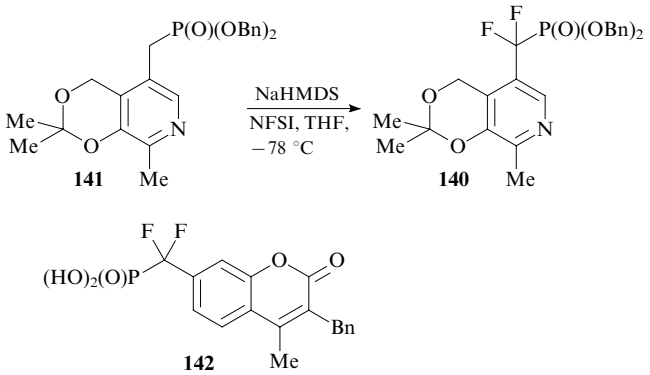


X = N (**139a**, 64%), CH (**139b**, 59%).

It was noted that the yield of the products depends on the nature of the base used in the reactions. The highest yield was obtained in the presence of sodium hexamethyldisilazide (NaHMDS). Sulfur diethylaminotrifluoride can also be used as the fluorinating agent, but the latter reactions afford products in lower yields. The fluorinating agent was taken in a 2.5–5-fold excess.

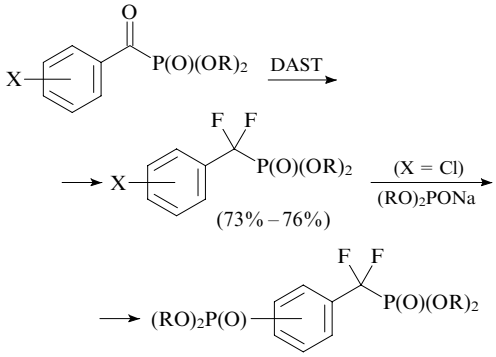
According to Blackburn and co-workers,[140] the activity of bis(difluoromethylenephosphonates) is higher than that of the corresponding monoderivatives. Compound **139a** is a competitive inhibitor of phosphoglycerate kinase (3-PGK).

Compound **140**, which is the difluoromethylenephosphonate analogue of pyridoxine phosphate, was also synthesized by the electrophilic fluorination of compound **141** by *N*-fluorobenzenesulfonimide. Derivative **140** was covered by a patent as a cardioprotector.[141–145] Coumarin **142** containing the difluoromethylenephosphonate group was proposed as an inhibitor of the tumour necrosis factor TNFα.[146]



Methylene and difluoromethylene analogues of uridine 4-phosphate and 3-deazauridine 4-phosphate were synthesized in the study.[147] Difluoromethylene analogues were prepared by the fluorination of the corresponding methylene derivatives by the KHMDS–NFSI system.

In addition to the electrophilic fluorination of the methylene group in alkylphosphonates, difluoromethylenephosphonates were synthesized also by the nucleophilic fluorination of the carbonyl group in α-keto phosphonates.[92, 140, 148] In the latter case, the best results were obtained with the use of sulfur diethylaminotrifluoride as the fluorinating agent.



A five-fold excess of *N*-fluorobenzenesulfonimide is required for this reaction to occur.

Other compounds, for example, $FClO_3$, AcOF and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4), can serve as the fluorinating agents; in addition to the above-described compounds, NaH, KH, Bu^nLi and $KOBu^t$ can be used as bases.[149, 150]

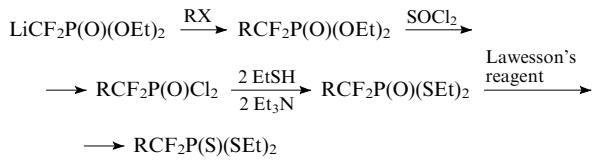
VIII. Conclusions

The review summarizes main methods for the synthesis and the most important transformations of compounds containing the $CF_2P(O)(OR)_2$ group. A detailed consideration of all published data on this subject is beyond the scope of the

present review. Emphasis was given to the most interesting, in our opinion, studies.

In conclusion, let us consider some aspects of the synthesis of thio analogues of difluoromethylenephosphonates. α,α-Difluoromethylenephosphonothioates can be prepared by the reaction of Lawesson's reagent with α,α-difluoromethylphosphonates.[151] The synthesis of various α,α-difluoromethylphosphonothionic acids was documented.[152] It should be noted that the reagent $LiCF_2P(O)(OEt)_2$, which is most widely used for the introduction of the $CF_2P(O)(OR)_2$ group into organic molecules, is stable at temperatures below −78 °C, whereas $LiCF_2P(S)(OEt)_2$ is stable at −40 °C. Hence, the thio analogues of reagent **2** can be employed when higher temperatures are requires.

S,*S*-Dialkyl difluoromethylenephosphonodithioates and -trithioates were synthesized for the first time by French researchers in 2003.[153] It appeared that the compounds $LiCF_2P(O)(SEt)_2$ and $LiCF_2P(S)(SEt)_2$ are unstable even at temperatures below −100 °C.



R = Bn, n-C_5H_{11}, $Cl(CH_2)_4$, Br; X = Hal.

It should be noted that the chemistry of difluoromethylenephosphonates is still actively developed because of high biological activity of fluorine- and phosphorus-containing compounds. The synthesis of new non-peptide inhibitors of various enzymes continue to attract considerable attention. Among these inhibitors, compounds containing the difluoromethylenephosphonate function occupy an important place.

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