Angewandte Chemie

Radical Reactions

α,α-Difluoro-*H*-phosphinates: Useful Intermediates for a Variety of Phosphate Isosteres

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Dedicated to Professor Clayton Heathcock

Research efforts have long since established *H*-phosphinates **1** as important and valuable intermediates for the preparation of bioactive analogues of natural phosphates (Scheme 1).[1] Despite various methodologies for their easy preparation, the synthesis of phosphonate **2**, phosphonothioates **3**, and phosphinates **4** remains an area of intense activity.[2]

Moreover, major progress has been made in the chemistry of α,α-difluorophosphonates **7** since their introduction slightly more than two decades ago.[3] Indeed, physicochemical studies have provided some rationale for the isosteric behavior of the above functional group to the phosphate group, and numerous applications have flourished.[4] Among these, analogues targeting phospholipase C (PLC), purine nucleoside phosphorylase (PNP), and protein phosphotyrosine, phosphoserine, or phosphothreonine phosphatases have been reported.[5] This functional group has also been success-

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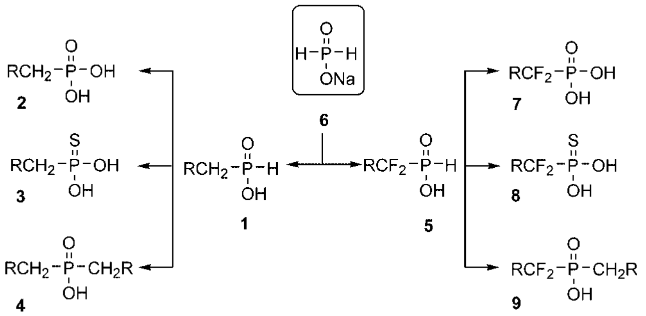


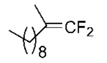
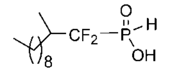
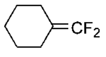
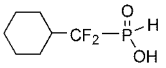
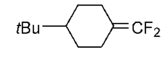
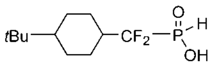
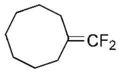
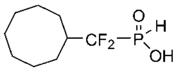
Scheme 1. General structure of *H*-phosphinates **1**, related structures **2**–**4** obtained therefrom, and target compounds **5**–**9**.

fully used to mimic the phosphate group in nucleotide monophosphates and triphosphates: analogues of adenosine monophosphate, cyclic adenosine monophosphate, adenosine triphosphate, and adenosyl adenosine triphosphate, as well as structurally related potent inhibitors of the reverse transcriptase of human immunodeficiency virus (HIV), have been described in the literature.[6]

Despite their potential both as a new class of isosteres of natural phosphates and as important intermediates in the synthesis of numerous α,α-difluorinated organophosphorus compounds, reports on fluorinated *H*-phosphinates **5** are scarce.[7] The main reasons behind this situation are the synthetic problems underlying their preparation. Indeed, processes such as nucleophilic substitution of halodifluorinated centers (including the Arbuzov reaction) have long been known to be disfavored,[8] and we and others have confirmed the sluggishness of phosphorus-centered radicals with respect to addition onto difluoroalkenes, when compared to their nonfluorinated analogues.[9] In this context, we found that the sodium salt **6** of hypophosphorous acid behaves in a unique way, and have developed an efficient and practical preparation of α,α-difluoro-*H*-phosphinates. As shown below, these compounds can be easily transformed into difluorophosphonates **7**, difluorophosphonothioates **8**, and difluorophosphinates **9** (Scheme 1).

When a solution of **6** (0.2 M, 1.3 equiv) in methanol was refluxed for four hours with difluoroalkene **10**–**13** in the presence of *tert*-butyl peroxypivalate (TBPP) or *tert*-butyl 2-ethylhexyl peroxycarbonate (TBEC)[10] as a radical initiator, complete consumption of the substrate occurred and led to the formation of a single product in each case. A simple workup led to the isolation of products **14**–**17** in 75, 85, 83, and 80 % yield, respectively, in the case of TBPP (Table 1). Later, we found that the Et_3B/O_2 system also allows a smooth conversion to take place.[11] The α,α-difluoro-*H*-phosphinates are stable for weeks under standard conditions (room temperature and air). As expected, the ^{31}P NMR spectra of compounds **14**–**17** displayed signals around 20 ppm with a P,H coupling constant of 590 Hz and P,F coupling constants of about 120 Hz. Similarly, the ^{19}F NMR spectra were characterized by signals with two-bond F,P and three-bond F,H couplings, in accordance with the depicted structures. Additionally, FTIR signals were detected at 1250(s) and around 2370(m) cm^{-1}, which correspond to the P=O and P–H bonds, respectively.[7]

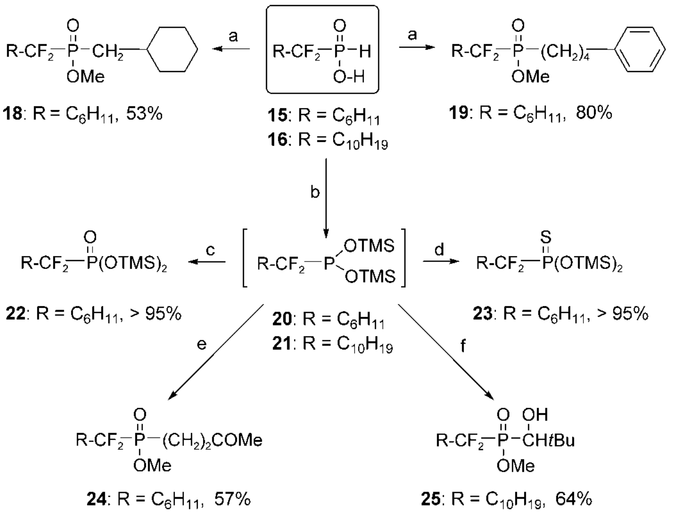
Table 1: Structures of *gem*-difluoroalkenes and α,α-difluoro-*H*-phosphinates, and yields of the latter.

Entry	Substrate	Product	Yield [%]
1	 **10**	 **14**	75[a]
2	 **11**	 **15**	85[a,b]
3	 **12**	 **16**	83[a,c]
4	 **13**	 **17**	80[a]

[a] Using TBPP. [b] A complete conversion also occurred with $B(Et)_3/O_2$. [c] Isolated as a 4:1 mixture of diastereoisomers.

The weak phosphorus–hydrogen bond present in adducts **14**–**17** renders it prone to homolytic cleavage and highlights the possibility of generating yet another phosphorus-centered radical by treating these compounds with a radical initiator, and of a second radical addition on an alkene. Thus, interaction of a 1.6 M methanolic solution of **15** with methylenecyclohexane in the presence of a catalytic amount of radical initiator (TBPP) led to the formation of the expected α,α-difluorophosphinic acid, which was isolated in the form of its methyl ester **18** (diazomethane) in 53 % yield (Scheme 2). A similar two-step process involving sequential addition of 4-phenylbut-1-ene and diazomethane gave methyl difluorophosphinate **19** in 80 % yield.

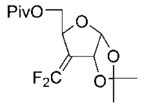
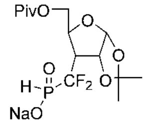
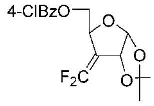
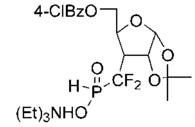
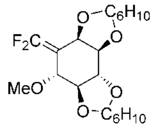
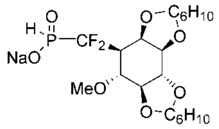
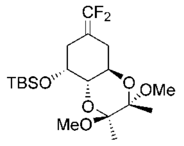
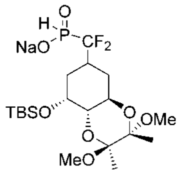
The documented tautomeric equilibrium between an *H*-phosphinate and the corresponding phosphite led us to envision the possible transformation of α,α-difluoro-*H*-phosphinates into the corresponding bis-*O*,*O*-silylated difluoroal-



Scheme 2. Transformation of α,α-difluoro-*H*-phosphinates into difluorophosphonates, difluorophosphonothioates, and difluorophosphinates. a) 1. Alkene, **6** (0.3 equiv), C_6H_6, 55 °C, 18 h; 2. CH_2N_2, Et_2O, 12 h; b) bis(trimethylsilyl)acetamide (BSA, 3 equiv), CH_2Cl_2, 25 °C, 1 h; c) O_2, CH_2Cl_2, 25 °C, 0.5 h; d) S_8, CH_2Cl_2, 25 °C, 0.5 h; e) 1. but-3-en-2-one, BSA (3 equiv), CH_2Cl_2, 25 °C, 18 h, 2. CH_2N_2, Et_2O, 12 h; f) 1. pivalaldehyde, BSA (5.5 equiv), CH_2Cl_2, 25 °C, 3 h, 2. CH_2N_2, Et_2O, 12 h.

kylphosphites, and the use of the nucleophilic P^{III} species.[12] Accordingly, treatment of **16** with a threefold excess of trimethylsilyl chloride (TMSCl) and pyridine led to quantitative formation of the corresponding air-sensitive phosphites **20** and **21**, as demonstrated by a shift of the ^{31}P NMR signals to about 130 ppm, and the lack of any one-bond P,H coupling. Exposure of the bis-*O,O*-trimethylsilyl phosphites to oxygen or elemental sulfur quickly transformed these products into difluorophosphonates **22** or difluorophosphonothioates **23**.

Table 2: Addition of hypophosphorous acid sodium salt, diethyl phosphite, and diethyl thiophosphite to difluoroalkenes **26**–**29**.

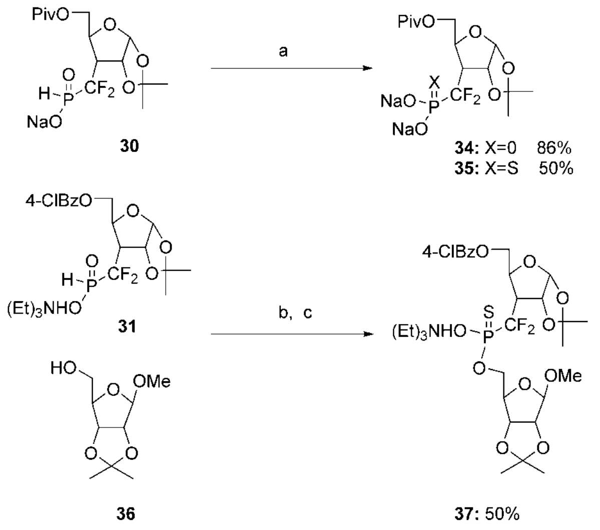
Entry	Substrate		Product		Phosphorus precursor	Conversion [%] (yield [%])
1		**26**		**30**	NaOP(O)H$_2$	100 (78[a,b])
2					(EtO)$_2$P(O)H	0
3					(EtO)$_2$P(S)H	0
4		**27**		**31**	NaOP(O)H$_2$	100 (63[b,c])
5					(EtO)$_2$P(O)H	0
6					(EtO)$_2$P(S)H	0
7		**28**		**32**	NaOP(O)H$_2$	100 (76[a])
8					(EtO)$_2$P(O)H	0
9					(EtO)$_2$P(S)H	0
10		**29**		**33**	NaOP(O)H$_2$	100 (70[a,d])
11					(EtO)$_2$P(O)H	0
12					(EtO)$_2$P(S)H	0

[a] Using TBPP. [b] The addition proceeded with a diastereoselectivity greater than 95%. [c] Using B(Et)$_3$/O$_2$. [d] Isolated as a 3:7 mixture of diastereoisomers.

Interactions between bissilylated difluoroalkylphosphites and electrophilic carbon atoms were exemplified through the 1,2- and 1,4-addition reactions (Abramov and Pudovic reactions, respectively).[13] Thus, a degassed solution of **15**, methyl vinyl ketone, BSA, and TMSCl in dichloromethane was stirred at room temperature, and the crude sample was sequentially subjected to a classical workup and treatment with diazomethane, which delivered difluorophosphinate **24** in 57% yield. Similarly, trimethylacetaldehyde (pivalaldehyde) reacted with **21** to furnish α,α-difluoro-α′-hydroxyphosphinate **25** (64% yield). Few examples of difluorophosphinates have so far been reported,[2b,9a,14] and the present methodology constitutes the first general preparation of these compounds. It was particularly gratifying to note that the presence of the fluorine atoms did not prevent the P^{III} species from interacting with electrophiles.

The scope of the methodology was investigated by developing an application in the field of ribofuranosyl and cyclitol phosphates. Thus, reaction between **6** and ribofuranose derivatives **26** or **27** resulted in complete conversions, and the desired adducts **30** and **31** could be isolated in yields of 78 and 63%, respectively (Table 2). Similarly, cyclitol derivatives **28** and **29** reacted smoothly with **6** to deliver compounds **32** and **33** in good yields. These results are significant in light of the complete lack of reactivity of both diethyl phosphite and diethyl thiophosphite under similar conditions.[15]

Table 2 clearly indicates the complete failure of any addition process in the case of phosphonyl and phosphonothioyl radicals, despite the demonstrated higher reactivity of the latter.[9a–b,16] The involvement of a tautomeric P^{III} species of the radical generated from **6** has been ruled out by Beckwith,[17] and the nature of this radical and those generated from phosphites and thiophosphites should therefore be similar. Additional physicochemical studies will be needed to explain the peculiar, but synthetically useful, behavior of **6** and shed light on the steric and electronic factors at play in this reaction.[18] α,α-Difluoro-*H*-phosphinates **30** and **31** are useful intermediates to various compounds with potential applications in the fields of modified nucleotides and oligonucleotides (hence the antisense and antigene strategies). For example, *H*-phosphinate **30** was easily transformed into difluorophosphonate **34** and difluorophosphonothioate **35** by treatment with TMSCl, pyridine, and the requisite O$_2$ or S$_8$ (Scheme 3).[2a,15,19] In addition, *H*-phosphinate **31** could easily be esterified by reaction with ribofuranose **36** in the presence of dicyclohexylcarbodiimide (DCC) and trifluoroacetic acid (TFA). The resultant *H*-phosphinate was treated with sulfur and TMSCl in pyridine to



Scheme 3. Transformation of α,α-difluoro-*H*-phosphinates **30** and **31** into difluorophosphonate **34** and difluorophosphonothioates **35** and **37**. a) Pyridine/TMSCl/O$_2$ or pyridine/TMSCl/S$_8$; b) DCC/TFA; c) pyridine/TMSCl/S$_8$. Bz = benzoyl, Piv = pivaloyl.

afford difluorophosphonothioic acid monoester **37** in 50% yield (a 1:1 mixture of two diastereoisomers at the phosphorus center).[2a] This last result demonstrated the efficacy of the methodology in providing precursors of modified dinucleotides with new phosphorus-centered linkers.

In summary, radical addition of **6** on *gem*-difluoroalkenes constitutes a powerful method of constructing the previously unreported α,α-difluoro-*H*-phosphinates. This new functional group is easily and efficiently transformed into difluorophosphonates, difluorophosphonothioates, and difluorophosphinates. The methodology can be expected to have a major impact on the preparation of difluorophosphonyl, difluorophosphonothioyl, and difluorophosphinyl analogues of natural phosphates.

Experimental Section

General procedure for the synthesis of α,α-difluoro-*H*-phosphinates using *tert*-butyl peroxypivalate or *tert*-butyl 2-ethylhexyl peroxycarbonate as initiator: The requisite 1,1-difluoroalkene[20–22] (1.0 equiv) and initiator (0.3 equiv) were added to a solution of hypophosphorous acid sodium salt monohydrate (0.2 M, 1.3 equiv) in degassed methanol. The solution was refluxed for 4 h under a nitrogen atmosphere and cooled to room temperature. The solution was poured into water and the aqueous phase was extracted with diethyl ether and lyophilized after separation of the layers. The solid was dissolved in aqueous $\mathrm{NaHSO_4}$ (2.0 M) and extracted with dichloromethane. The organic layer was dried and evaporated to give a viscous oil.

Gram-scale synthesis of **31**: Hypophosphorous acid sodium salt monohydrate (1.24 g, 1.7 mmol, 4.0 equiv) was added to a solution of **27** (1.0 g, 2.8 mmol, 1.0 equiv) in nondegassed methanol (25 mL) at room temperature in an open flask. Triethylborane (5 mL, 1 M solution in hexane, 5.0 mmol, 5.0 equiv) was added under vigorous stirring, and the solution was stirred for 10 min. This operation was repeated twice. The fast addition of $\mathrm{Et_3B}$ solution was crucial. After the third addition of $\mathrm{Et_3B}$, the solution was stirred for 1 h and then the solvent removed by evaporation. Water (50 mL) was added and the aqueous layer was extracted with ethyl acetate (20 mL). The aqueous layer was lyophilized and the crude solid was dissolved in aqueous triethylammonium carbonate (1.0 M, 30 mL). The solution was extracted twice with dichloromethane (30 mL); the organic layer was dried and evaporated to give a viscous oil (930 mg, 63%). $[\alpha]^{D}_{20} = +33.9$ ($c = 1.08$ in $\mathrm{CHCl_3}$); ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): $\delta = 7.10$ (dd, $J = 556$ Hz, $J = 6$ Hz, 1H), 7.92 (d, $J = 8.7$ Hz, 2H), 7.33 (d, $J = 8.7$ Hz, 2H), 5.80 (d, $J = 3.9$ Hz, 1H), 5.04 (t, $J = 3.9$ Hz, 1H), 4.8 (m, 1H), 4.73 (d, $J = 12$ Hz, 1H), 4.32 (dd, $J = 12$ Hz, $J = 5.5$ Hz, 1H), 3.00 (q, $J = 7.3$ Hz, 6H), 2.70 (m, 1H), 1.50 (s, 3H), 1.26 (s, 3H), 1.26 ppm (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (50 MHz, $\mathrm{CDCl_3}$): $\delta = 165.1$, 139.1, 130.9, 128.4, 128.1, 120.2 (td, $J = 257$ Hz, $J = 121$ Hz, $\mathrm{CF_2}$), 112.5, 104.7, 79.4 (d, $J = 7.6$ Hz), 74.4, 64.6, 49.0 (td, $J = 22.7$ Hz, $J = 13.6$ Hz), 45.3, 26.3 (d, $J = 6.1$ Hz), 8.26 ppm; ^{31}P NMR (81 MHz, $\mathrm{CDCl_3}$): $\delta = 9.7$ ppm (dd, $J = 92$ Hz, $J = 86$ Hz); ^{19}F NMR (188 MHz, $\mathrm{CDCl_3}$, $\mathrm{C_6F_6}$): $\delta = 51.5$ (ddt, $J = 301$ Hz, $J = 85$ Hz, $J = 10$ Hz), 47.4 ppm (ddd, $J = 301$ Hz, $J = 92$ Hz, $J = 23$ Hz); IR (NaCl): $\tilde{\nu} = 2986$, 1721, 1455, 1275, 1091 cm^{-1}. MS (MALDI, matrix: 2,4,6-trihydroxyacetophenone) $m/z = 425.1$ $[M-102.1]$.

37: Compound **24** (58 mg, 0.28 mmol, 1.5 equiv), DCC (118 mg, 0.76 mmol, 4.0 equiv), and trifluoroacetic acid (72 µL, 0.95 mmol, 5.0 equiv) were added to a solution of **31** (100 mg, 0.19 mmol, 1.0 equiv) in degassed dichloromethane (3 mL). A white precipitate immediately formed and the slurry was stirred for 10 min. Powdered $\mathrm{S_8}$ (200 mg, 6.2 mmol, 32.6 equiv), pyridine (1 mL, 12.2 mmol, 43.8 mmol), and TMSCl (1 mL, 7.9 mmol, 28.1 equiv) were then added sequentially. The reaction was stirred for an additional 15 min, then water (1 mL) was added, and the solution was filtered. The filtrate was extracted with ice-cold aqueous HCl (0.1 M, 10 mL), washed with aqueous triethylammonium carbonate (1.0 M), and evaporated. The residue was purified by flash chromatography over silica gel (AcOEt/MeOH/triethylamine 90:8:2) to give a viscous oil (70 mg, 50%) as a 1:1 mixture of two diastereoisomers (stereogenic phosphorus atom). A second chromatography procedure was performed which allowed partial separation of one of the diastereoisomers from the mixture. $[\alpha]^{D}_{25} = +17.2$ ($c = 0.5$ in $\mathrm{CHCl_3}$); ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): $\delta = 8.00$ (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 5.80 (d, $J = 3.7$ Hz, 1H), 5.10 (t, $J = 3.7$ Hz, 1H), 4.90 (s, 1H), 4.82 (d, $J = 5.8$ Hz, 1H), 4.70 (dd, $J = 10.2$ Hz, $J = 3.6$ Hz, 1H), 4.54 (d, $J = 5.8$ Hz, 1H), 4.40–3.90 (m, 4H), 3.30 (s, 3H), 3.10 (q, $J = 7.3$ Hz, 6H), 1.50 (s, 3H), 1.4 (s, 3H), 1.3–1.2 ppm (m, 16H); ^{13}C NMR (50 MHz, $\mathrm{CDCl_3}$): $\delta = 165.4$, 139.2, 131.0, 128.6, 128.4, 112.5, 111.9, 109.0, 104.5, 85.4, 84.9, 81.6, 80.4(m), 75.0, 66.7, 65.1, 54.6, 47.4(m), 45.4, 26.8, 26.3, 26.3, 24.8, 8.3 ppm ($\mathrm{CF_2}$ not observed); ^{31}P NMR (81 MHz, $\mathrm{CDCl_3}$): $\delta = 61.5$ ppm (dd, $J = 93$ Hz, $J = 90$ Hz); ^{19}F NMR (188 MHz, $\mathrm{CDCl_3}$, $\mathrm{C_6F_6}$): $\delta = 56.4$ (ddd, $J = 306$ Hz, $J = 97$ Hz, $J = 14$ Hz), 50.0 ppm (ddd, $J = 306$ Hz, $J = 97$ Hz, $J = 17$ Hz); IR (NaCl): $\tilde{\nu} = 2987$, 2935, 1722, 1274, 1108, 1093, 1013 cm^{-1}; MS (MALDI, matrix: 2,4,6-trihydroxyacetophenone) $m/z = 643.1$ $[M-103.1]$.

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