JOC Article

Syntheses of α-Fluoro-α,β-unsaturated Thioamides and Thiazolines from a Fluorophosphonodithioacetate

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A high-yielding synthesis of methyl fluoro(diethoxyphosphono)dithioacetate starting from its difluorinated analogue is reported. Fluorophosphonothioacetamides and -methylthiazolines, prepared from this new dithioester, have been successfully transformed into highly functionalized fluoroalkenes. Good stereoselectivity in favor of the *E* isomer was observed from the fluorophosphonomethylthiazolines. The potential of these new fluorinated olefinating reagents for the synthesis of modified peptides and glycosides is also disclosed.

Introduction

The incorporation of amide isosteres is a common approach to achieve the synthesis of non-hydrolyzable peptides as therapeutic agents. Such structural modifications are often used to prepare conformationally constrained peptidomimetics.[1] For example, the introduction of a carbon−carbon double bond or a heterocycle as a mimic of the peptidic bond can stabilize or probe the bioactive conformation of peptides.[2] In the field of vinylpeptides, the monofluorovinyl moiety has been described as the best isoelectronic and isosteric analogue of the peptidic bond.[3] Since the first syntheses of fluoroalkenes through a Horner−Wadworth−Emmons (HWE) reaction by using the easily available triethyl fluorophosphonoacetate,[4] an increasing number of alternative methods were reported.[5] Applied to the synthesis of dipeptides isosteres, most of these methods are based on divergent strategy and no one offers the flexibility to connect in one-step two amino acids by a fluorovinylic linkage. In contrast to the synthesis of alkenes, the preparation of nonterminal monofluoro olefins by HWE or Wittig reactions is limited to phosphonates or ylides bearing an electron-withdrawing group or an aromatic group.[6] In this paper, we report the synthesis of monofluoromethylphosphonates appended with a dithioester, a thioamide, or a thiazoline function and the use of the two latter derivatives in the olefination of carbonyl compounds. These new monofluorinated phosphonates open a convergent access to thiopeptides and glycopeptides analogues,[7,8] possessing a fluorovinylic linkage.

Results and Discussion

Dithioesters are excellent N-thioacylating reagents, and recently we applied this property to the one-step synthesis of *gem*-difluorophosphonothioacetamides such as **2** from the methyl difluoro(diethoxyphosphono)-dithioacetate **1** and α-aminoesters (Scheme 1).[9] However, competing formation of the monofluorinated dithioester **3** (5−15%) was noticed during the course of this reaction.

Our study is here extended to the preparation of parent monofluorophosphonates as fluoroalkene precursors to open a facile and flexible route to new classes of fluorovinyl peptides and glycosides. However, no preparation of the needed methyl fluorophosphonodithioacetate **3** is mentioned in the literature. Blackburn et al. attempted to prepare dithioester **3** (by a method similar to that used for the synthesis of **1**) from the diethoxyphosphinyldifluoromethyllithium, carbon disulfide, and iodomethane.[10] Due to the high acidity of the proton α to

(1) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720.
(2) Boeglin, D.; Heitz, A.; Martinez, J.; Fehrentz, J. A. *Eur. J. Org. Chem.* **2003**, 3139−3146.
(3) (a) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, 7297−7300. (b) Otaka, A.; Wanatabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, M.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285−287. (c) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845−5847.
(4) (a) Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *674*, 1−10. (b) Etemad-Moghadam, G.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1985**, 448−454.
(5) (a) Allmendinger, T. *Tetrahedron* **1991**, *47*, 4905−4914. (b) Satoh, T.; Itoh, N.; Onda, K.; Kitoh, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn* **1992**, *65*, 2800−2806. (c) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107−3111. (d) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291−304. (e) Kawasaki, T.; Ichige, T.; Kitazume, T. *J. Org. Chem.* **1998**, *63*, 7525−7528. (f) Xu, J.; Burton, D. J. *Org. Lett.* **2002**, *4*, 831−833. (g) Chevrie, D.; Lequeux, T.; Pommelet, J. C. *Tetrahedron* **2002**, *58*, 4759−4767.
(6) (a) Blackburn, G. M.; Rashid, A. *J. Chem. Soc., Chem. Commun.* **1989**, 40−41. (b) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7740. (c) Xu, Z.; DesMarteau, D. D. *J. Chem. Soc., Perkin Trans 1* **1992**, 313−315. (d) Burton, D. J.; Yang, Z.; Qui, W. *Chem. Rev.* **1996**, *96*, 1641−1715. (e) Veenstra, S. J.; Hauser, K.; Felber, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 351−354. (f) Boumendjel, A., Nuzillard, J. M.; Massiot, G. *Tetrahedron Lett.* **1999**, *40*, 9033−9036. (g) Van Steenis, J. H.; Boer, P. W. S.; Van der Hoeven, H. A.; Van der Gen, A. *Eur. J. Org. Chem.* **2001**, 911−918.
(7) Miwa, J. H.; Pallivathucal, L.; Gowda, S.; Lee, K. E. *Org. Lett.* **2002**, *4*, 4655−4657.
(8) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395−4422.
(9) Pfund, E.; Lequeux, T.; Masson, S.; Vazeux, M. *Org. Lett.* **2002**, *4*, 843−846.
(10) Blackburn, G. M.; Brown, D.; Martin, S. F. *J. Chem. Res., Synop.* **1985**, 92−93.

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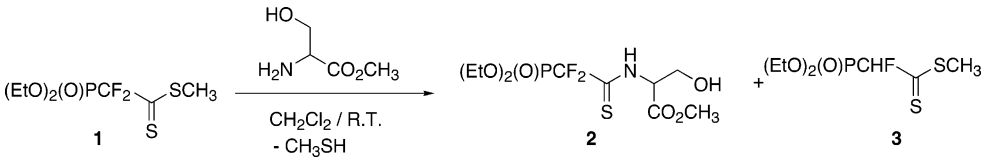
SCHEME 1



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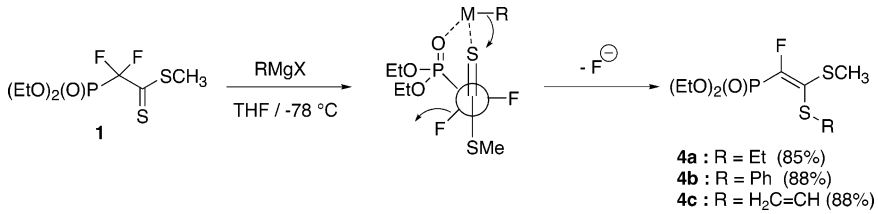

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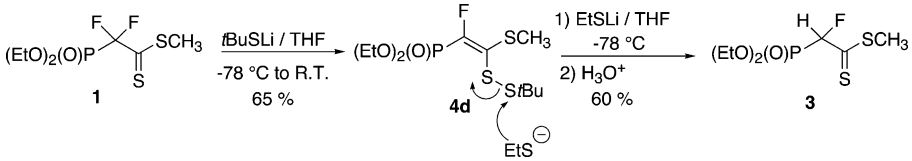
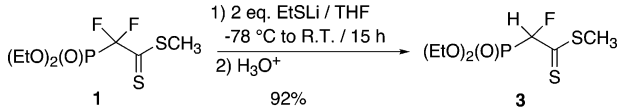


the fluorine and phosphorus atoms, a ketene dithioacetal was isolated instead of the expected dithioester **3**. Therefore, we studied the monodefluorination of **1** as a preparative method of **3**. The magnesium-promoted α-defluorination of trifluoromethyl ketones, esters, or imines is well documented to prepare *gem*-difluoromethylated parent compounds.[11] Besides, compared to esters, dithioesters are known, through their reactions with organometallics, as good examples of *umpolung* addition of nucleophiles.[12−14] The thiophilic addition is favored by the presence of an electronwithdrawing group α to the thiocarbonyl function which stabilizes the carbanion. Therefore, the reactivity of the difluorophosphonodithioacetate **1** toward organometallic reagents was investigated with the aim to create a carbanion α to the difluoromethylene group, which will be able to undergo defluorination (Scheme 2). As expected, the addition of Grignard reagents, in THF at −78 °C, proceeds via a thiophilic addition and induces the elimination a fluoride anion leading to ketene dithioacetals **4a**−**c**. These compounds were isolated by flash column chromatography in 85−88% yields. The elimination was selective and the *Z* isomer was obtained as the major product (*Z*/*E* > 9/1).[15] This selectivity presumes a chelation of the metallic center by the phosphoryl and the thiocarbonyl moieties which control through a concerted *anti*-elimination the formation of the (*Z*)-ketene dithioacetals.

Previous studies in our laboratory revealed that not only carbanions reacted through a thiophilic addition onto the dithioester function activated by an electron-withdrawing group but also thiolates.[16] Moreover, as shown in Scheme 1, the formation of small amount of monofluorodithioester **3** occurred due to the liberation of methanethiol in the medium.[9] These results incited us to investigate the synthesis of **3** from its difluorinated analogue **1** through successive sulfanylation−defluorination and desulfanylation reactions. At first, the reaction of dithioester **1** with 1 equiv of lithium *ter*butylthiolate at −78 °C was carried out and found to afford the monofluorinated ketenedithioacetal disulfide **4d** in 65% yield (Scheme 3). The desulfanylation was then accomplished by treating **4d** with 1 equiv of lithium ethanethiolate at −78 °C, which, by a thiaphilic attack, induced the selective cleavage of the sulfur−sulfur bond. The resulting enethiolate was finally protonated to provide the expected methyl fluoro(diethoxyphosphono)-dithioacetate **3** in 60% yield.

SCHEME 4



A more straightforward synthesis of **3** was attempted by treating directly the dithioester **1** with 2 equiv of lithium ethanethiolate. This one-pot procedure was found to give efficiently monofluorinated dithioacetate **3** in a very satisfactory yield (Scheme 4).

The synthesis of α-fluoro-α,β-unsaturated dithioesters was then investigated from **3** and aldehydes. Benzaldehyde or nonanal was added to a solution of the anion generated from **3** by deprotonation with LDA, *n*-BuLi,

(11) (a) Uneyama, K.; Mizutani, G. *Chem. Commun.* **1999**, 613−614. (b) Amii, H.; Kobayashi, T.; Matamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323−1324. (c) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893−7896. (d) Amii, H.; Koayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001−2003. (e) Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, *114*, 127−131. (f) Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099−6102.

(12) Léger, L.; Saquet, M. *Bull. Soc. Chim. Fr.* **1975**, 657−666.

(13) Meyers, A. I.; Tait, T. A.; Comins, D. L. *Tetrahedron Lett.* **1978**, 4657−4660.

(14) Portella, C.; Shermolovitch, Y. *Tetrahedron Lett.* **1997**, *38*, 4063−4064.

(15) Hartke, K.; Hoederath, W. *Sulfur Lett.* **1983**, *1*, 191−198 (The NMR spectra of ketenedithioacetals agree with the characteristic patterns of the *Z* isomers, and for **4a**, HOESY experiments showed a spatial proximity between the fluorine atom and the methylsulfanyl group).

(16) Bulpin, A.; Masson, S. *J. Org. Chem.* **1992**, *57*, 4507−4512.

SCHEME 5

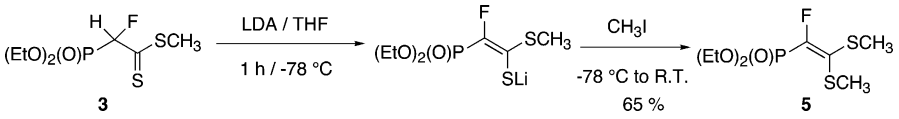
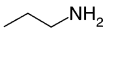
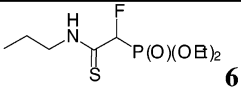
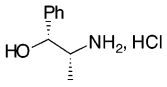
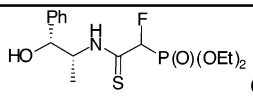
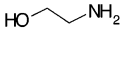
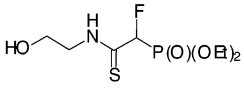
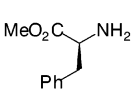
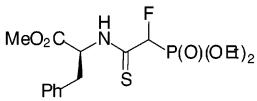
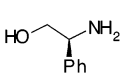
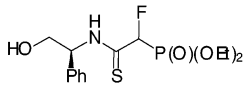
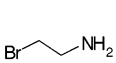
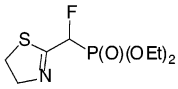
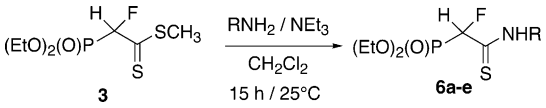


TABLE 1. Preparation of Fluorophosphonomethylthiazolines and -thioacetamides

Amine	Product	Yield (%)	Amine	Product	Yield (%)
	 **6a**	91		 **6d**	70[a]
	 **6b**	87		 **6e**	85[a]
	 **6c**	89[a]		 **7**	87

[a] A mixture of two isomers was obtained in a 1/1 ratio.

SCHEME 6

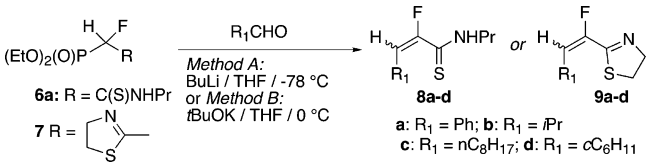


or *t*-BuOK at −78 or 0 °C. No reaction occurred, the starting materials being recovered unchanged after workup. On the other hand, when the lithiated anion was trapped at −78 °C with iodomethane, ketene dithioacetal **5** was produced (Scheme 5). The absence of reactivity of this anion as HWE reagent is probably due to the high stability of its enethiolate form.[10] It is interesting to note that alkyl phosphonodithioacetates themselves are not very efficient HWE reagents.[15]

By contrast, phosphonomethylthiazolines and -thioacetamides, prepared by thioacylation of amines, have been reported as good HWE reagents to give access to vinylthiazolines and α,*β*-unsaturated thioamides.[17] Consequently, we turned our attention to the synthesis of monofluorophosphonomethylthiazolines and -thioacetamides from **3**. This dithioester reacted smoothly at room temperature with primary amines, including protected amino acids and amino alcohols (Scheme 6). The α-fluorophosphonothioamides **6a**−**e** were isolated in 70−91% yields (Table 1).

From (*S*)-phenylglycinol, (*S*)-phenylalanine, and (1*R*,2*R*)-norephedrine resulted a 1/1 mixture of two diastereomeric thioamides **6c**−**e**. It has been previously observed that the reaction of the difluorophosphonodithioacetate **1** with enantiopure aminoesters and alcohols occurred without any racemization.[9] The formation of only two diastereomers for **6d** confirms also the absence of epimerization at the stereogenic centers of the norephedrine

SCHEME 7



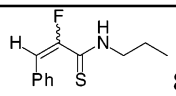
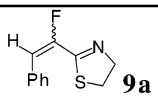
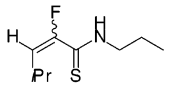
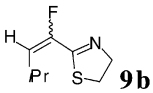
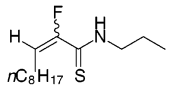
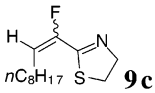
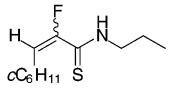
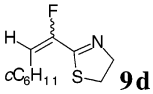
reagent during the thioacylation. From bromoethylamine, the intermediate *β*-bromothioamide was not isolated, and its spontaneous cyclization afforded the fluorophosphonomethylthiazoline **7** in 87% yield.

The use of α-fluoromethylenephosphonates **6a** or **7** as HWE reagents for the synthesis of the corresponding α-fluoro-α,*β*-unsaturated thioamides or α-fluorovinylthiazolines was then studied (Scheme 7, Table 2). At first, deprotonation of substrates **6a** and **7** were performed by addition of a solution of butyllithium at −78 °C, and the resulting carbanions were reacted with aldehydes (method A). In a second procedure, the reaction was carried out by addition of a THF solution of *t*-BuOK to a mixture of fluorophosphonates **6a** or **7** and aldehydes in THF at −78 or 0 °C (method B). The reactions were monitored by TLC analysis.

By using the method A, and for the four aldehydes tested, the conversion of **6a** or **7** was completed after 4 h at −78 °C. From benzaldehyde and the thioamide derivative **6a**, a mixture of fluoroolefin isomers **8a** was obtained in a 65/35 *E*/*Z* ratio and in 92% isolated yield. From aliphatic aldehydes and **6a**, the α-fluoro-α,*β*-unsaturated thioamides **8b**−**d** were isolated in 67−72% yields. The *E* alkene was also the major isomer but the selectivity was still moderate (*E*/*Z* up to 4/1). From the thiazoline derivative **7** and the four aldehydes examined here, fluorovinylthiazolines **9a**−**d** were isolated in good yields (90−93%). Compared to unsaturated thioamides **8b**−**d**, thiazolines **9b**−**d** were formed in a higher selectivity in favor of the *E* alkenes (*E*/*Z* up to 95/5). By using method B, no formation of fluoroalkenes occurred when the

(17) (a) Sundberg, R. J.; Biswas, S.; Murthi, K. K.; Rowe, D. *J. Med. Chem.* **1998**, *41*, 4317−4328. (b) Leflemme, N.; Marchand, P. Gulea, M.; Masson, S. *Synthesis* **2000**, 1143−1147. (c) LeRoy-Gourvennec, S.; Masson, S. *Synthesis* **1995**, 1393−1396. (d) Shaumann, E.; Fittkau, S. *Tetrahedron Lett.* **1984**, *25*, 2325−2328.

TABLE 2. Synthesis of α-Fluoro-α,β-unsaturated Thioamides and Thiazolines from 6a and 7

R_1CHO	reagent	product	Yield (%) (Method)[a,b]	E/Z[c]	reagent	product	Yield (%) (Method)	E/Z[c]
PhCHO	**6a**	 **8a**	92 (A) 93 (B)	65/35 60/40	**7**	 **9a**	92 (A) 90 (B)	65/35 77/23
*i*PrCHO	**6a**	 **8b**	72 (A) 60 (B)	70/30 60/40	**7**	 **9b**	90 (A) 88 (B)	92/8 75/25
$nC_8H_{17}CHO$	**6a**	 **8c**	67 (A) 55 (B)	80/20 60/40	**7**	 **9c**	91 (A) 91 (B)	90/10 80/20
$cC_6H_{11}CHO$	**6a**	 **8d**	72 (A) 72 (B)	78/22 60/40	**7**	 **9d**	95 (A) 93 (B)	95/5 75/25

[a] Method (A): 1.1 equiv of BuLi/THF/−78 °C/4 h. [b] Method (B): 1.1 equiv of *t*-BuOK/THF/0 °C/4 h. [c] Based on the $^3J_{HF}$ value.

reaction was carried out at −78 °C, and the starting phosphonates **6a** and **7** were recovered. Their complete consumption with aldehydes was observed when the reaction was performed at 0 °C over 4 h. The overall yields of α,β-unsaturated thioamides **8a**−**d** and vinylthiazolines **9a**−**d** were as high as those obtained by method A. Nevertheless, with the thiazoline derivative **7**, the *E*/*Z* selectivity decreased to a ratio of 75/25. As shown for the triethyl fluorophosphonoacetate,[4b] from **6a** and **7** a better *E* selectivity was observed when reactions were performed at −78 °C. It is noteworthy that the replacement of one hydrogen by one fluorine atom favors the relative cis relationship between the alkyl and thiazoline groups compared with the good trans selectivity of the alkenes obtained from aldehydes and nonfluorinated 2-phosphonomethylthiazolines.[17]

Numerous reports have described methods for the preparation of modified peptides as alternative peptide backbones, enzyme inhibitors (vinylogous peptides),[18] or stable glycopeptides isosteres (*C*-glycopeptides).[8] The incorporation of a fluorine atom appeared attractive to prepare fluorinated enzyme inhibitors or NMR probes for the study of metabolisms in biological systems. The rapid and simple methods described above for the syntheses of α-fluoro-α,β-unsaturated thioamides and fluorovinylthiazolines can be extended to the preparation of modified peptides and glycosides. A convergent one-step approach to design such structures was here explored from the reaction of PCHF-based phenylalanylthioamide **6e** and thiazoline **7** with functionalized aldehydes.

By using the method A or B, no reaction took place from **6e** or **7** and ethyl glyoxalate after 4 h at −78 °C. However, as shown in Table 3, the desired fluoroalkenes **10a** and **11a** were accessible provided the reaction of lithiated anion derived from **6e** and **7** is conducted between −78 and −10 °C. Thus, isomeric α-fluoro-α,β-unsaturated thioamides **10a** and fluorovinylthiazolines **11a** were isolated in satisfactory yields (60−79%) with a moderate but opposite selectivity. In an analogous way, with Garner's aldehyde the reaction takes place readily when subjected under basic conditions to fluorophosphonates **6e** and **7**; the yields of olefinic products **10b** and **11b** ranged from 78% to 83%, and the ratio of isomers was considerably shifted in favor of the *E* alkene. According to known procedures, a preliminary attempt for the deprotection of **10b** in the presence of Dowex-50 led to the formation of the vinylogous *N*-Boc-protected Ser-Phe thiopeptide in nonoptimized yield of 40%. Surprisingly, the *E*-fluorovinylic thiazolines **11a** and **11b** were found to slowly isomerize affording the *Z* olefin as the major product after 6 months at 4 °C. Fluoroalkenes **10b** and **11b**, prepared from Garner's aldehyde, showed two conformations as detected by ^{19}F NMR at 295 K. The average conformers were observed by heating a sample at 343 K, demonstrating a restricted rotation of the amide or thioamide functions. On the other hand, $^{19}F\{^1H\}$ NMR experiments revealed that **11a** exhibited an unexpected long-range coupling constant between the fluorine atom and the thiazolyl *N*-methylene protons ($^5J_{HF} = 3$ Hz) only for the *E*-isomer.

The synthesis of *C*-glycopeptide precursors, glycosylated at the *N*-terminus of the peptide chain through a vinylic linkage, has been previously described from phosphonates.[19] We carried out the reaction of the fluorophosphonothioacetamide **6e** with a protected galactosaldehyde. Despite a complete consumption of the starting materials, the fluoroolefin **10c** was isolated in modest yield (20%) without any selectivity. By contrast, the fluorophosphonomethylthiazoline **7** was more reactive, and the fluorovinylic pyranosylthiazoline **11c** was produced in good yield (79%) with high selectivity (*E*/*Z* = 98/2).

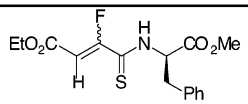
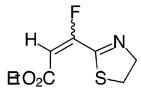
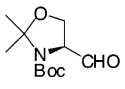
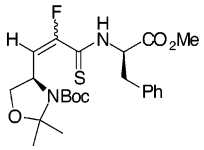
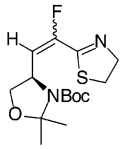
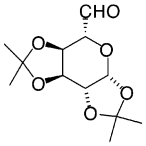
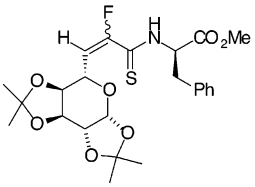
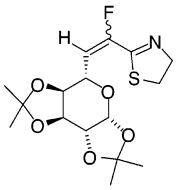
Conclusion

In conclusion, we have described the first preparation of a fluorophosphonomethyldithioacetate **3** through a one-

(18) Grison, C.; Genève, S.; Hablin, E.; Coutrot, P. *Tetrahedron* **2001**, *57*, 4903−4923.

(19) Coutrot, P.; Grison, C.; Lecouvey, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 27−45.

TABLE 3. Synthesis of Peptide Isosteres from Phosphonates 6e and 7

R_1CHO	reagent	product	Yield (%)	E/Z[a]	reagent	product	Yield (%)	E/Z[a]
EtO_2CCHO	**6e**	 **10a**	60	30/70	**7**	 **11a**	79	70/30
	**6e**	 **10b**	78 [b]	85/15	**7**	 **11b**	83 [b]	90/10
	**6e**	 **10c**	20	50/50	**7**	 **11c**	79	80/20

[a] Based on the $^3J_{HF}$ value. [b] Obtained as a mixture of confomers.

pot defluorination−desulfanylation procedure starting from its difluorinated precursor **1**. The thioacylation of amines, aminoesters, or amino alcohols with dithioester **3** allowed the preparation of a variety of fluorophosphonothioacetamides and -methylthiazolines as HWE reagents. These reagents were used to prepare new α-fluoro-α,β-unsaturated-thioamides and fluorovinylthiazolines from alkyl, aryl, and diversely functionalized aldehydes. The potential of this convergent method for the synthesis of modified peptides and glycosides was also illustrated through the preparation of the vinylogous dipeptide Ser-Phe precursor from Garner's aldehyde and modified glycosides from galactosaldehyde. We noticed a contrasted reactivity between fluorophosphonates **6a**, **6e**, and **7** substituted by a thioamide or a thiazoline function. Compound **7** gave almost selectively the *E*-fluorovinylthiazolines in good yields. Encouraged by these results, we are currently investigating the syntheses of conformationally constrained peptidomimetics and glycopeptides containing a fluorovinylthiazolyl linkage.

Experimental Section

Methyl (Diethoxyphosphoryl)difluoroethanedithioate (1). To a solution of LDA prepared from diisopropylamine (9 mL, 66.5 mmol) and BuLi 2.5 M (25.6 mL, 69.0 mmol) in 300 mL of anhydrous THF under N_2 was slowly added diethyl difluoromethylphosphonate (10 g, 53.0 mmol) at −78 °C. The mixture was stirred for 1 h at −78 °C, and carbon disulfide (16 mL, 265.0 mmol) was introduced dropwise. The solution was maintained at −78 °C for 30 min, and methyl iodide (16.5 mL, 265.0 mmol) was then added. The reaction mixture was stirred for 5 min, hydrolyzed with 1 M HCl, and extracted three times with Et_2O. The organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated. The resulting oil was purified by flash column chromatography (petroleum ether/ethyl acetate 6/4) affording the methyl (diethoxyphosphoryl)difluoroethanedithioate **1** (11.5 g, 78%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.70 (s, 3H), 4.30 (m, 4H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −98.7 (d, $^2J_{FP}$ = 104.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 3.6 (t, $^2J_{PF}$ = 104.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.3 (d, $^3J_{CP}$ = 5.7 Hz), 19.4 (t, $^4J_{CP}$ = 2.5 Hz), 65.6 (d, $^2J_{CP}$ = 6.8 Hz), 117.21 (dt, $^1J_{CP}$ = 209.7 Hz, $^1J_{CF}$ = 271.0 Hz), 219.8 (dt, $^2J_{CP}$ = 17.2 Hz, $^2J_{CF}$ = 21.7 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 278 ($M^{+\bullet}$ 17), 258 (20), 233 (16), 207 (15), 122 (12), 109 (14), 91 (100), 81 (12), 51 (30), 47 (66), 45 (86); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_7H_{13}F_2O_3PS_2$ 278.0012, found 278.0036.

Methyl (Diethoxyphosphoryl)fluoroethanedithioate (3). In a 250 mL flask containing 150 mL of anhydrous THF and ethanethiol (2.7 mL, 35.9 mmol) stirred under N_2 was slowly added BuLi 2.5 M (15 mL, 37.7 mmol) at −78 °C. After 30 min, methyl (diethoxyphosphoryl)difluoroethanedithioate **1** (5 g, 17.9 mmol) was introduced, and the mixture was stirred for 15 h from −78 °C to rt. The solution was then hydrolyzed with 1 M HCl and extracted with CH_2Cl_2. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. The methyl (diethoxyphosphoryl)fluoroethanedithioate **3** was isolated by flash chromatography (Et_2O/pentane 7/3) in 92% yield (4.3 g): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.69 (s, 3H), 4.35 (m, 4H), 5.74 (dd, $^2J_{HP}$ = 12.6 Hz, $^2J_{HF}$ = 47.2 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −183.2 (dd, $^2J_{FP}$ = 77.0 Hz, $^2J_{FH}$ = 47.2 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 10.2 (d, $^2J_{PF}$ = 77.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.7 (d, $^3J_{CP}$ = 6.1 Hz), 18.7 (d, $^4J_{CP}$ = 4.8 Hz), 64.7 and 65.0 (d, $^2J_{CP}$ = 6.7 Hz), 98.0 (dd, $^1J_{CP}$ = 160.3 Hz, $^1J_{CF}$ = 200.9 Hz), 224.8 (d, $^2J_{CP}$ = 16.3 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 260 ($M^{+\bullet}$ 97), 240 (28), 215 (23), 196 (62), 195 (43), 189 (21), 185 (24), 169 (46), 167 (24), 157 (27), 155 (20), 137 (25), 124 (33), 109 (100), 104 (32), 91 (68), 81 (49), 80 (23), 77 (26); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_7H_{14}FO_3PS_2$ 260.0106, found 260.0112.

General Procedure for the Synthesis of Ketene Fluorophosphonodithioacetals (4a−c). To a solution of difluorophosphonodithioacetate **1** (300 mg, 1.07 mmol) in 50 mL of anhydrous THF under N_2 was added dropwise ethyl-, phenyl-,

or vinylmagnesium bromide 1 M (5.4 mL, 10.7 mmol) at −78 °C. The reaction was monitored by TLC, and after complete conversion, the reaction mixture was hydrolyzed with 1 M HCl and extracted with CH_2Cl_2. The organic layer was dried with anhydrous $MgSO_4$ and filtered, and solvents were evaporated. The resulting oil was purified by flash chromatography affording the corresponding ketene phosphonodithioacetal derivative.

Diethyl (*Z*)-1-fluoro-2-(ethylsulfanyl)-2-(methylsulfanyl)vinylphosphonate (4a) (265 mg, 85%, eluent: Et_2O/pentane 55/45): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (m, 9H), 2.35 (s, 3H), 2.74 (q, $^3J_{HH}$ = 7.0 Hz, 2H), 4.12 (m, 4H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −95.3 (d, $^2J_{FP}$ = 105.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 4.3 (d, $^2J_{PF}$ = 105.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.4, 16.2 (d, $^4J_{CF}$ = 5.5 Hz), 16.5 (d, $^3J_{CP}$ = 6.5 Hz), 29.1, 63.5 (d, $^2J_{CP}$ = 6.0 Hz), 132.8 (dd, $^2J_{CP}$ = 16.7 Hz, $^2J_{CF}$ = 30.2 Hz), 151.4 (dd, $^1J_{CP}$ = 241.7 Hz, $^1J_{CF}$ = 286.1 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 288 ($M^{+\bullet}$, 71), 228 (29), 213 (62), 185 (60), 157 (100), 138 (24), 119 (65), 109 (26), 103 (26), 101 (25), 93 (22), 91 (52), 81 (48), 76 (23), 73 (26); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_9H_{18}FO_3PS_2$ 288.0419, found 288.0420.

Diethyl 1-Fluoro-2-(*tert*-butyldisulfanyl)-2-(methylsulfanyl)vinylphosphonate (4d). In a 50 mL flask containing 20 mL of anhydrous THF and *tert*-butyl thiol (135 μL, 1.18 mmol) at −78 °C stirred under N_2 was added dropwise BuLi 2.5 M (475 μL, 1.18 mmol). After 30 min, the difluorophosphonodithioacetate **1** (300 mg, 1.07 mmol) was introduced, and the solution was stirred for an additional 1 h at −78 °C. The mixture was hydrolyzed with HCl 1 M and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography column (Et_2O/pentane 1/1) affording the diethyl 1-fluoro-2-*tert*-butyldisulfanyl-2-methylsulfanylvinylphosphonate **4d** in 60% yield (225 mg): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 6H), 1.33 (s, 9H), 3.34 (s, 3H), 4.14 (m, 4H); ^{19}F NMR (235 MHz, $CDCl_3$) δ -96.0 (d, $^2J_{FP}$ = 105.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 1.7 (d, $^2J_{PF}$ = 105.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.6 (d, $^4J_{CF}$ = 6.3 Hz), 16.6 (d, $^3J_{CP}$ = 5.2 Hz), 30.2, 50.5, 63.7 (d, $^2J_{CP}$ = 5.9 Hz), 138.8 (dd, $^2J_{CP}$ = 13.0 Hz, $^2J_{CF}$ = 30.7 Hz), 148.3 (dd, $^1J_{CP}$ = 238.7 Hz, $^1J_{CF}$ = 283.8 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 348 (M^+, 12), 294 (40), 292 (100), 272 (47), 244 (32), 226 (63), 201 (86), 198 (33), 157 (58), 119 (42), 109 (53), 93 (25), 91 (60), 88 (23), 81 (67); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_{11}H_{22}FO_3PS_3$ 348.0452, found 348.0469.

Diethyl 1-Fluoro-2,2-bis(methylsulfanyl)vinylphosphonate (5). In a 25 mL flask containing 5 mL of anhydrous THF and difluorophosphonodithioacetate **1** (200 mg, 0.719 mmol) at −78 °C under N_2 was slowly added BuLi 2.5 M (335 μL, 0.790 mmol). The reaction mixture was stirred for 1 h, and methyl iodide (225 μL, 3.6 mmol) was then added. Stirring was maintained for 15 h from −78 to +20 °C, and the solution was hydrolyzed with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The diethyl 1-fluoro-2,2-bis(methylsulfanyl)vinylphosphonate **5** was obtained by flash chromatography (Et_2O/pentane 55/45) in 65% yield (130 mg): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.18 and 2.25 (two s, 6H), 4.13 (m, 4H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −95.1 (d, $^2J_{FP}$ = 109.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 4.2 (d, $^2J_{PF}$ = 109.0 Hz).

General Procedure for the Synthesis of Fluorinated Phosphonothioamides 6a−c,e. In a 50 mL flask containing 20 mL of anhydrous CH_2Cl_2 and the appropriate amine (4.25 mmol) under N_2 was introduced the fluorophosphonodithioacetate **3** (1 g, 3.84 mmol). The mixture was stirred for 15 h at room temperature, and the solvent was evaporated. The fluorinated phosphonothioamides **6a−c**,**e** were purified by flash column chromatography.

Diethyl 1-Fluoro-2-(propylamino)-2-thioxoethylphosphonate (6a). Isolated in 91% yield (950 mg; pentane/ethyl acetate 45/55) starting from **3** (1 g, 3.84 mmol) and propylamine (355 μL, 4.25 mmol): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.39 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 1.74 (m, 2H), 3.68 (m, 2H), 4.25 (m, 4H), 5.52 (dd, $^2J_{HP}$ = 11.9 Hz, $^2J_{HF}$ = 47.7 Hz, 1H), 8.23 (sbr, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −189.7 (ddd, $^4J_{FH}$ = 5.0 Hz, $^2J_{FH}$ = 47.0 Hz, $^2J_{FP}$ = 77.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 12.2 (d, $^2J_{PF}$ = 73.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.7, 16.7 (d, $^3J_{CP}$ = 5.9 Hz), 21.5, 47.1, 64.6 and 65.2 (d, $^2J_{CP}$ = 6.8 Hz), 92.4 (dd, $^1J_{CP}$ = 160.1 Hz, $^1J_{CF}$ = 203.4 Hz), 190.7 (d, $^2J_{CF}$ = 13.2 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 271 ($M^{+\bullet}$, 71), 251 (56), 236 (46), 218 (47), 195 (100), 140 (47), 134 (56), 115 (66), 114 (60), 87 (24), 81 (31), 77 (22); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_9H_{19}FNO_3PS$ 271.0807, found 271.0816.

Diethyl 1-Fluoro-2-[(2-hydroxy-1-methyl-2-phenylethyl)-amino]-2-thioxoethylphosphonate (6d). In a 25 mL flask containing 5 mL of CH_2Cl_2, NEt_3 (60 μL, 0.423 mmol), and (1*R*, 2*R*)-norephedrine (80 mg, 0.423 mmol) under N_2 was introduced the fluorophosphonodithioacetate **3** (100 mg, 0.384 mmol). The solution was stirred for 15 h at room temperature and then concentrated under vacuum. The thioamidophosphonate **6d** was isolated by flash chromatography (pentane/ethyl acetate 6/4) as two separate diastereomers in 70% overall yield (98 mg). Dia 1: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.07 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.36 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.37 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 4.25 (m, 4H), 4.35 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 4.85 (m, 1H), 5.31 (dd, $^3J_{HH}$ = 3.6 Hz, $^3J_{HH}$ = 3.0 Hz, 1H), 5.53 (dd, $^2J_{HP}$ = 10.0 Hz, $^2J_{HF}$ = 47.8 Hz, 1H), 7.29 (m, 5H), 8.35 (sbr, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −190.1 (ddd, $^4J_{FH}$ = 4.7 Hz, $^2J_{FH}$ = 47.0 Hz, $^2J_{FP}$ = 78.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 12.2 (d, $^2J_{PF}$ = 77.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.6, 16.7 (d, $^3J_{CP}$ = 5.9 Hz), 56.4, 72.0, 64.8 (d, $^2J_{CP}$ = 6.8 Hz), 66.1 (d, $^2J_{CP}$ = 6.9 Hz), 92.6 (dd, $^1J_{CP}$ = 159.3 Hz, $^1J_{CF}$ = 204.1 Hz), 126.0, 127.5, 128.6, 141.0, 189.8 (d, $^2J_{CF}$ = 13.7 Hz). *Dia 2*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.25 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 3.84 (d, $^3J_{HH}$ = 3.3 Hz, 1H), 4.15 (m, 4H), 4.87 (m, 1H), 5.02 (m, 1H), 5.48 (dd, $^2J_{HP}$ = 10.5 Hz, $^2J_{HF}$ = 47.1 Hz, 1H), 7.24 (m, 5H), 8.74 (sbr, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −190.2 (ddd, $^4J_{FH}$ = 5.0 Hz, $^2J_{FH}$ = 47.0 Hz, $^2J_{FP}$ = 75.0 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 12.0 (d, $^2J_{PF}$ = 74.7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.6, 16.7 (d, $^3J_{CP}$ = 5.9 Hz), 56.3, 73.9, 64.7 (d, $^2J_{CP}$ = 6.8 Hz), 65.4 (d, $^2J_{CP}$ = 6.9 Hz), 92.3 (dd, $^1J_{CP}$ = 159.3 Hz, $^1J_{CF}$ = 204.1 Hz), 126.1, 127.9, 128.7, 141.1, 189.7 (d, $^2J_{CP}$ = 13.7 Hz).

Diethyl (4,5-Dihydro-1,3-thiazol-2-yl)fluoromethylphosphonate (7). In a 100 mL flask were introduced bromoethylamine hydrobromide (1.75 g, 8.46 mmol), NEt_3 (1.2 mL, 8.46 mmol), and 40 mL of CH_2Cl_2 under N_2. The fluorophosphonodithioacetate **3** (2 g, 7.69 mmol) was then added, and the resulting salts were dissolved by further addition of NEt_3 (1.2 mL, 8.46 mmol). The solution was stirred for 15 h at room temperature and concentrated. The residue was purified by flash chromatography (ethyl acetate) to give the thiazolinophosphonate **7** in 87% yield (1.7 g): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, $^3J_{HH}$ = 6.9 Hz, 6H), 3.27 (m, 2H), 4.27 (m, 6H), 5.48 (dd, $^2J_{HP}$ = 10.0 Hz, $^2J_{HF}$ = 45.9 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −203.3 (dd, $^2J_{FH}$ = 47.0 Hz, $^2J_{FP}$ = 75.3 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 11.3 (d, $^2J_{PF}$ = 73.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.7, 16.7 (d, $^3J_{CP}$ = 5.5 Hz), 33.6, 64.3 and 64.6 (d, $^2J_{CP}$ = 6.7 Hz), 65.1 (d, $^4J_{CF}$ = 1.0 Hz), 87.9 (dd, $^1J_{CP}$ = 166.2 Hz, $^1J_{CF}$ = 186.9 Hz), 165.7 (d, $^2J_{CF}$ = 24.6 Hz); MS (EI, 70 eV) *m*/*z* (relative intensity) 255 ($M^{+\bullet}$, 34), 168 (22), 140 (86), 119 (100), 113 (37), 109 (30), 81 (26); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_8H_{15}FNO_3PS$ 255.0494, found 255.0453.

General Procedure for the Synthesis of Fluoroalkenes 8a−d and 9a−d. Method A. Phosphonate **6a** (200 mg, 0.738 mmol) or **7** (200 mg, 0.784 mmol) was dissolved in anhydrous THF (20 mL) under N_2. The solution was cooled to −78 °C, and BuLi 2.5 M (320 μL, 0.811 mmol or 350 μL, 0.862 mmol) was added dropwise. After 1 h at −78 °C, the corresponding aldehyde (0.811 or 0.862 mmol) was added. The mixture was

stirred for 4 h at −78 °C, hydrolyzed with 1 M HCl, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography or distilled to afford fluoroalkenes **8a**−**d** and **9a**−**d**. **Method B.** Phosphonate **6a** (200 mg, 0.738 mmol) or phosphonate **7** (200 mg, 0.784 mmol) and the corresponding aldehyde (0.811 or 0.862 mmol) were dissolved in THF (20 mL) under N_2 at 0 °C. A solution of *t*-BuOK (0.811 or 0.862 mmol) in anhydrous THF (1 mL) was slowly added. Stirring was maintained for 4 h, and then the solution was hydrolyzed with HCl 1 M and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography or distilled to afford fluoroalkenes **8a**−**d** and **9a**−**d**.

(*N*-Propyl-2-fluoro-3-phenyl)prop-2-enethioamide (8a). Isolated in 92% yield (152 mg; Et_2O/pentane 6/4), starting from **6a** (200 mg, 0.738 mmol) and benzaldehyde (80 μL, 0.811 mmol): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (t, $^3J_{HH}$ = 7.4 Hz, 3H, *E*) and 0.94 (t, $^3J_{HH}$ = 7.3 Hz, 3H, *Z*), 1.39 (sext, $^3J_{HH}$ = 7.4 Hz, 2H, *E*) and 1.68 (sext, $^3J_{HH}$ = 7.3 Hz, 2H, *Z*), 3.44 (dt, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.9 Hz, 2H, *E*) and 3.66 (dt, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.9 Hz, 2H, *Z*), 6.18 (d, $^3J_{HF}$ = 39.0 Hz, 1H, *Z*) and 6.38 (d, $^3J_{HF}$ = 18.7 Hz, 1H, *E*), 7.18−7.57 (m, 5H, *Z*) and 7.24 (m, 6H, *E*), 7.95 (sbr, 1H, *Z*); ^{19}F NMR (235 MHz, $CDCl_3$) δ -126.5 (dd, $^3J_{FH}$ = 39.0 Hz, $^4J_{FH}$ = 7.0 Hz, *Z*) and −98.9 (d, $^3J_{FH}$ = 18.7 Hz, *E*); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 11.7 (*E*) and 11.9 (*Z*), 20.9 (*E*) and 21.7 (*Z*), 47.4 (*E*) and 48.0 (*Z*), 110.6 (d, $^2J_{CF}$ = 28.5 Hz, *E*) and 117.9 (d, $^2J_{CF}$ = 9.2 Hz, *Z*), 129.1, 129.2 (*E*,*Z*), 129.8 (d, $^4J_{CF}$ = 2.3 Hz, *Z*) and 130.7 (d, $^4J_{CF}$ = 8.1 Hz, *E*), 131.8 (d, $^3J_{CF}$ = 9.9 Hz, *E*) and 132.3 (d, $^3J_{CF}$ = 3.9 Hz, *Z*), 153.9 (d, $^1J_{CF}$ = 249.9 Hz, *E*) and 154.4 (d, $^1J_{CF}$ = 272.1 Hz, *Z*), 186.3 (d, $^2J_{CF}$ = 17.6 Hz, *Z*) and 188.2 (d, $^2J_{CF}$ = 33.8 Hz, *E*); MS (EI, 70 eV) *m*/*z* (relative intensity) 223 ($M^{+\bullet}$, 100), 180 (35), 165 (41), 148 (26), 133 (54), 78 (11); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_{12}H_{14}FNS$ 223.0831, found 223.0847.

General Procedure for the Synthesis of Fluoroalkenes 10a−c and 11a−c. Phosphonate **6e** (200 mg, 0.511 mmol) or phosphonate **7** (200 mg, 0.784 mmol) and 20 mL of anhydrous THF were placed in a 50 mL flask under N_2. The solution was cooled at −78 °C, and BuLi 2.5 M (320 μL, 0.811 mmol or 350 μL, 0.862 mmol) was slowly added. After 1 h, the corresponding aldehyde (0.811 or 0.862 mmol) was added. The mixture was stirred for 2 h from −78 to −10 °C, hydrolyzed with 1 M HCl, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified with flash column chromatography to give fluoroalkenes **10a**−**c** and **11a**−**c**.

Methyl *N*-[4-Ethoxy-2-fluoro-4-oxobut-2-enethioyl]phenylalaninate (10a). Isolated in 60% yield (104 mg; Et_2O/pentane 45/55), starting from **6e** (200 mg, 0.511 mmol) and ethyl glyoxalate (111 μL, 0.562 mmol, 50% in toluene): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, *E*) and 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3H, *Z*), 3.24 (dd, $^3J_{HH}$ = 4.1 Hz, $^2J_{HH}$ = 13.9 Hz, 1H, *Z*) and 3.26 (dd, $^3J_{HH}$ = 6.0 Hz, $^2J_{HH}$ = 13.9 Hz, 1H, *E*), 3.39 (dd, $^2J_{HH}$ = 6.1 Hz, $^2J_{HH}$ = 13.9 Hz, 1H, *E*) and 3.40 (dd, $^3J_{HH}$ = 5.7 Hz, $^2J_{HH}$ = 13.9 Hz, 1H, *Z*), 3.72 (s, 3H, *E*) and 3.75 (s, 3H, *Z*), 4.21 (q, $^3J_{HH}$ = 7.1 Hz, 2H, *E*) and 4.23 (q, $^3J_{HH}$ = 7.0 Hz, 2H, *Z*), 5.36 (ddd, $^3J_{HH}$ = $^3J_{HH}$ = $^3J_{HH}$ = 6.3 Hz, 2H,), 5.96 (d, $^3J_{HF}$ = 19.2 Hz, 1H, *E*) and 6.78 (d, $^3J_{HF}$ = 32.0 Hz, 1H, *Z*), 7.18 (m, 10H), 8.45 (sbr, 1H, *Z*) and 10.75 (sbr, 1H, *E*); ^{19}F NMR (235 MHz, $CDCl_3$) δ −111.1 (dd, $^3J_{FH}$ = 32.0 Hz, $^4J_{FH}$ = 6.0 Hz, *Z*) and −78.6 (d, $^3J_{FH}$ = 19.2 Hz, *E*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.9 (*E*) and 14.1 (*Z*), 36.0 (*Z*) and 36.3 (*E*), 52.5 (*E*) and 52.7 (*Z*), 58.6 (*E*) and 59.4 (*Z*), 61.1 (*Z*) and 62.1 (*E*), 103.5 (d, $^2J_{CF}$ = 36.0 Hz, *E*) and 107.1 (d, $^2J_{CF}$ = 7.5 Hz, *Z*), 127.2, 128.5, 129.2 (*E*) and 127.5, 128.8, 129.1 (*Z*), 134.8 (*Z*) and 135.5 (*E*), 156.8 (d, $^1J_{CF}$ = 293.0 Hz, *E*) and 159.6 (d, $^1J_{CF}$ = 261.0 Hz, *Z*), 162.4 (d, $^3J_{CF}$ = 3.0 Hz, *Z*) and 165.7 (d, $^3J_{CF}$ = 22.0 Hz, *E*), 170.2 (s, *E*) and 170.4 (s, *Z*), 183.8 (d, $^2J_{CP}$ = 20.0 Hz, *Z*) and 184.1 (d, $^2J_{CF}$ = 38.0 Hz, *E*); MS (EI, 70 eV) *m*/*z* (relative intensity) 339 ($M^{+\bullet}$, 48), 310 (42), 293 (18), 162 (100), 161 (39), 133 (26), 131 (91), 116 (15), 91 (42); HRMS (EI, 70 eV) *m*/*z* [M^+] calcd for $C_{16}H_{18}FNO_4S$ 339.0940, found 339.0931.

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Supporting Information Available: Preparation of compounds **4b**,**c**, **6b**,**c**, **6e**, **8b**−**d**, **9a**−**d**, **10b**,**c**, and **11a**−**c** and selected ^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra of compounds **3**, **6a**,**d**,**e**, **7**, **8a**−**d**, **9a**−**d**, **10a**−**c**, and **11a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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