Synthesis of Aryldifluoromethylphosphonothioic Acids from *O,O*-Diethyl Aryldifluoromethylphosphonothioates

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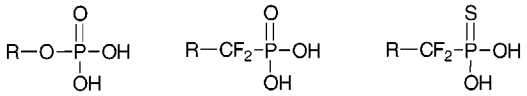
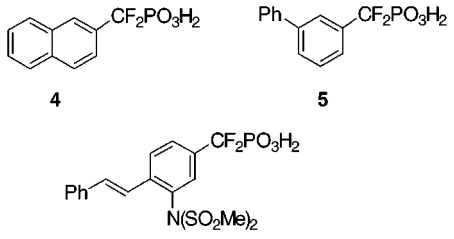
The ubiquitous presence of a phosphate group in a vast array of molecules of biological interest has stimulated intense research efforts in the search for structural analogues where different constitution and chemical reactivity allow them to be used as either mechanistic probes or potent inhibitors in enzymatic reactions.[1] Blackburn's postulate[2] that 1,1-difluoromethylenephosphonic acids (DFMPA) **2** are a hydrolytically stable mimic of the corresponding phosphate esters **1** has gained wide experimental support in recent years. As a result, many enzyme inhibitors with significant activity have been identified.[3] However, in some cases, the DFMPA functionality itself proved to be an insufficient anchor to bind the molecule to the active site of the target enzymes;[4a] additional functional groups should be installed to achieve significant binding affinities.[5] To seek more potent analogues for a phosphate ester, recent efforts in this research field are focused on developing new generation-mimetics of a phosphate ester.[6−8] Most recently, the first example of a new class of phosphate mimics, 1,1-difluoromethylenephosphonothioic acids **3**, has been reported by Piettre.[7]



1 **2** DFMPA **3**

Piettre reports that the second pK_a of **3** was determined to be ca. 3.0, thus reflecting a much stronger acidity than the corresponding DFMPA (pK_{a2} = ca. 5.4).[7a,9] While the 1,1-difluoromethylenephosphonothioic acids **3** are an interesting variant of phosphate mimics, the biological motifs related to the low pK_{a2} value have not been examined in detail yet.[7,8] In addition, for the synthesis of **3** from the corresponding diesters, deprotection of conventional simple dialkyl esters such as *O,O*-diethyl esters is problematic; preparation of the *O,O*-dibenzyl esters and the reductive debenzylation under the Birch conditions are required to obtain the phosphonothioic acids.[7a] To the best of our knowledge, no method is applicable for deprotection of the conventional *O,O*-diethyl esters of phosphonothioic acids to the free acids.

In the search for DFMPA-based inhibitors of protein tyrosine phosphatases (PTPs), key regulatory enzymes in many cellular processes such as cell proliferation and differentiation, we and others recently identified novel aromatic derivatives **4**−**6** of DFMPA, which acted as small molecular inhibitors for these enzymes.[10] As a part of our program to create small molecular inhibitors of PTPs that may be a better inhibition motif than that of **4**−**6**, we became interested in the synthesis and biological property of phosphonothioic acid analogues of **4**−**6**. Within this framework, we synthesized for the first time several *O,O*-diethyl difluoromethylenephosphonothioates conjugated to an aromatic functionality and examined their transformation to the free acids. In this paper, we disclose a new method for this transformation.



4 **5**

6

Our strategy for the transformation of *O,O*-diethyl aryldifluoromethylphosphonothioates **7** to the free acid **9** is outlined in Scheme 1. We anticipated that Pd-catalyzed deallylation[11] of *S*-allyl hydrogen aryldifluoromethylphosphonothioates **8** would afford the desired

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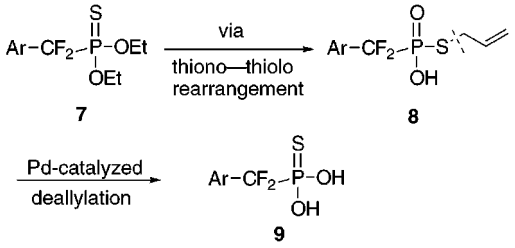
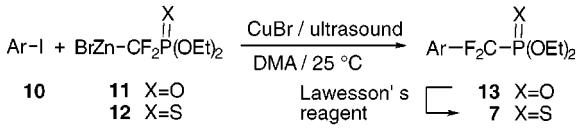
Scheme 1. Strategy for Transformation of *O,O*-Diethyl Phosphonothioates to the Free Acid



Scheme 2. Synthesis of Diethyl Aryldifluoromethylphosphonothioates



a: Ar=4-Me-C_6H_4; **b**: Ar=4-NC-C_6H_4; **c**: Ar=4-Br-C_6H_4; **d**: Ar=3-Ph-C_6H_4; **e**: Ar=1-naphthyl; **f**: Ar=2-naphthyl

Table 1. Preparation of *O,O*-Diethyl Aryldifluoromethylphosphonothioates 7a−f by Two Methods

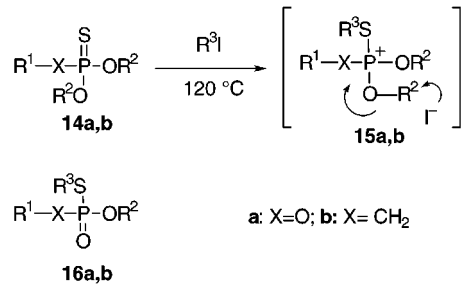
		yield, %	
entry	phosophonothioate	method A[a]	method B[b]
1	**7a**	65	10
2	**7b**	46	*c*
3	**7c**	60	7[d]
4	**7d**	78	17
5	**7e**	77	34
6	**7f**	71	5

[a] Overall yield from aryl iodides for the two steps. [b] Unoptimized isolated yield. [c] Not examined. [d] Determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis.

phosphonothioic acid **9** via tautomerization. (Scheme 1). The allyl derivatives **8** might be prepared by thiono-thiolo rearrangement of the diethyl esters **7** with 3-iodopropene under the modified conditions of Pishschimuka.[12]

First, two methods were examined for the synthesis of *O,O*-diethyl aryldifluoromethylphosphonothioates **7a**−**f** (Scheme 2 and Table 1). One method commenced with the cross-coupling reaction of the corresponding aryl iodides **10a**−**f** with the zinc reagent **11** using our protocol[13] to give the cross-coupling products **13a**−**f** in 81−95% yield. Subsequent thionylation of the resulting phosphonates **13a**−**f** with Lawesson's reagent [2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] in refluxing toluene (2 h) gave the desired phosphonothioates **7a**−**f** in good yield [**7a**, 65%; **7b**, 56%; **7c**, 75%; **7d**, 90%; **7e**, 91%; **7f**, 90%].[7] The two-step (method A) allowed us to synthesize a multigram quantity of **7a**−**f** possessing different aromatic groups in 46−78% overall yield (Table 1). The phosphonothioates **7a,c**−**f** were also obtained by means of the direct cross-coupling reactions (method B) between aryl iodides **10a,c**−**f** and the presumed zinc reagent **12** generated from *O,O*-diethyl bromodifluoromethylphosphonothioate[7] and zinc in dimethylacetamide (DMA) in an analogous manner.[14] However, the method B has less potentiality than the method A to give **7a,c**−**f** in low yield (Table 1).

Scheme 3



With a series of *O,O*-diethyl difluoromethylenephosphonothioate **7a**−**f** in hand, next, Pishschimuka reaction of **7a**−**f** with 3-iodopropene was examined. The Pishschimuka reaction involves the rearrangement of organophosphorus thiono esters **14a**,**b** to thiolo esters **16a,b** via the phosphonium ions **15a,b** by the action of iodoalkanes[12] (Scheme 3). The thiono-thiolo rearrangement by the procedure of Pishschimuka requires rather drastic conditions (neat, 120 °C).[12e] We anticipated that the thiono-thiolo rearrangement of **7a**−**f** with 3-iodopropene would proceed more readily under the influence of sodium iodide. Sodium iodide would act not only as an activator of the allylation of the sulfur atom but also for selective de-ethylation of the Pishschimuka products **17** to give the desired *S*-allyl hydrogen phosphonothioates **8a**−**e** in one pot (Scheme 4).

A solution of *O,O*-diethyl difluoromethylenephosphonothioate **7a** and 3-iodopropene (2.0 equiv) in 2-butanone in the presence of sodium iodide (2.0 equiv) was heated under reflux for 24 h. The resulting precipitate was collected to obtain the sodium salts **18a** in 95% yield. The acidification of the salts with concentrated HCl gave the acid **8a**. The structures of **8a** and **18a** were deduced by the ^{1}H NMR (400 MHz) analysis. The allylic methylene of **8a** and **18a** resonated at δ 3.31 (2H, dd, J = 2.2, 17.0 Hz) and 3.41 (2H, dd, J = 7.2, 16.9 Hz), respectively. The chemical shifts of the signals strongly suggested that the allyl group should be positioned on the sulfur atom. Other physical data including ^{31}P and ^{19}F NMR signals as well as the molecular weight were consistent with the assigned structure. The starting phosphonothioate remained unreactive when the reaction was carried out in

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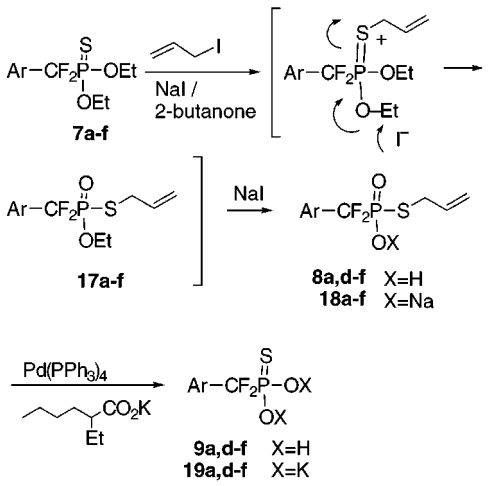
(14) *O,O*-Diethyl bromodifluoromethylphosphonothioate (**i**) reacted with zinc powder in DMA or DMF rather more slowly than the diethyl bromodifluoromethylphosphonate.[13a] The reaction of **i** with zinc powder in DMA was monitored by means of ^{31}P NMR (162 MHz, $CDCl_3$) spectroscopy. It takes over 6 h for the signals (δ 68.9, t, J_{PF} = 95.4 Hz) of **i** to disappear after addition of zinc powder at room temperature. Two new signals appeared at δ 85.7 (t, J_{PF} = 91.2 Hz) and 73.0 (t, J_{PF} = 94.9 Hz) in approximately the same intensity. The signals disappeared within 30 min upon treatment with CuBr and a clear new triplet (J_{PF} = 95.3 Hz) appeared at δ 72.4.

Scheme 4



a: Ar=4-MeC_6H_4; **b**: Ar=4-NCC_6H_4; **c**: Ar=4-BrC_6H_4; **d**: Ar=3-PhC_6H_4; **e**: Ar=1-naphthyl; **f**: Ar=2-naphthyl

Table 2. Sodium Iodide-Assisted Thiono-Thiolo Rearrangement of 7a−f with 3-Iodopropene[a]

	yield, %			
entry	**18**		**8**	
1	**18a**	95	**8a**	80
2	**18b**	96	**8b**	*b*
3	**18c**	98	**8c**	*b*
4	**18d**	96	**8d**	79
5	**18e**	97	**8e**	83
6	**18f**	97	**8f**	82

[a] All reactions were carried out in refluxing 2-butanone for 24 h in the presence of 2 equiv of NaI and 3-iodopropene. [b] Not examined.

the absence of sodium iodide in 2-butanone at varying temperatures (80−120 °C). Thus, sodium iodide was proved to be an effective reagent to induce the thiono-thiolo rearrangement with 3-iodopropene under mild conditions.[15] Using the sodium iodide-assisted thiono-thiolo rearrangement, the sodium *S*-allyl phosphonothioates **18b**−**f** were prepared from **7b**−**f** in good yield; the sodium salts **18d**−**f** were converted to the corresponding free acids **8d**−**f** (Table 2).

The Pd-catalyzed deallylation of **8a**,**d**−**f** was carried out under a variety of conditions varying the palladium catalysts and the allyl acceptors.[11] Among the conditions examined, the reagent combination of $Pd(PPh_3)_4$ and potassium 2-alkylhexanoate as reported by Berkowitz[11d] seems to be most suitable for the deallylation reaction (Scheme 4). Treatment of **8a** with $Pd(PPh_3)_4$ (20 mol %) in the presence of 2.0 equiv of potassium 2-ethylhexanoate in CH_2Cl_2 at 0 °C gave the desired phosphonothioic acid **9a**,[15] which was isolated as dipotassium salts **19a** in 30% yield[16] after reverse-phase column chromatography on ODS. In an analogous manner, the dipotassium salts **19d**−**f** of phosphonothioic acids **9d**−**f** were obtained in comparative yield (ca 20−35%).

In summary, several 1,1-difluoromethylenephosphonothioic acids conjugated to an aromatic group have been prepared for the first time from readily available *O*,*O*-diethyl aryldifluoromethylphosphonothioates via the sodium iodide-assisted thiono-thiolo rearrangement and subsequent Pd-catalyzed deallylation, albeit the yield of the deallylation reaction was modest. Biological evaluation of the phosphonothioic acids **9d**−**f** for PTP are now in progress and will be reported elsewhere.

Experimental Section

General. All melting points are uncorrected. All reactions were carried out under nitrogen atmosphere. The chemical shifts of ^{1}H NMR (400 MHz) are given in units of δ relative to $CHCl_3$ (δ 7.26) for $CDCl_3$ solution or 3-(trimethylsilyl)propionic-2,2,3,3,-d_4-acid sodium salt (TSP, δ 0) for D_2O solution. The chemical shifts of ^{13}C (100 MHz) are reported relative to $CDCl_3$ (δ 77.0) or TSP (δ 0). The chemical shifts of ^{31}P (162 MHz) are recorded relative to external 85% H_3PO_4 with broad-band ^{1}H decoupling. ^{19}F NMR spectra (376 MHz) were measured using benzotrifluoride (BTF) as an internal reference. IR spectra were recorded as a film or KBr disk. Fast atom bombardment mass spectra (FABMS) were obtained by either a positive or negative mode.

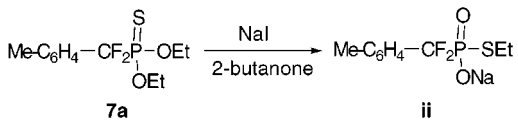
Thiono-Thiolo Rearrangement of Phosphonothioates 7a−f with 3-Iodopropene in the Presence of NaI. General Procedure. A solution of **7a**−**f** (1 mmol), 3-iodopropene (2 mmol), and NaI (300 mg, 2 mmol) in 2-butanone (5 mL) was heated under reflux for 24 h. After cooling to room temperature, a crystalline material was collected and washed with Et_2O/acetone 100:1 to give the sodium salts **18a**−**f**. The analytical samples were obtained by recrystallization from EtOAc. The sodium salts **18a,d**−**f** were dissolved in brine, and the solution was acidified with concentrated HCl. The mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on ODS eluted by H_2O to give the free acid **8a,d**−**f**. The physical data of **18a**−**f** and **8a,d**−**f** are shown below.

Sodium *S*-propenyl difluoro(4-methylphenyl)methylphosphonothioate 18a: mp = 224−226 °C; ^{1}H NMR (D_2O) δ 7.54 (2H, d, J = 7.8 Hz), 7.37 (2H, d, J = 7.8 Hz), 5.93−5.83 (1H, m), 5.22 (1H, dd, J = 1.2, 17.0 Hz), 5.11 (1H, d, J = 10.1 Hz), 3.31 (2H, dd, J = 7.3, 9.8 Hz), 2.xx (3H, s); ^{13} CNMR (100 MHz, D_2O) δ 143.9, 137.4 (d, J_{CP} = 5.2 Hz), 133.0 (dt, J_{CP} = 12.9 Hz, J_{CF} = 22.0 Hz), 131.8 (d, J_{CP} = 1.4 Hz), 129.1 (dt, J_{CP} = 1.5 Hz, J_{CF} = 6.4 Hz), 123.8 (dt, J_{CP} = 162.6 Hz, J_{CF} = 264.9 Hz), 120.4, 36.3 (d, J_{CP} = 2.8 Hz), 23.3; ^{19}F NMR (D_2O) δ −47.6 (d, J_{CF} = 123.3 Hz); IR (KBr) 3039, 1109, 1048, 597 cm^{-1}; FABMS *m*/*z* 277 (M^-). Anal. Calcd for $C_{11}H_{12}F_2O_2PSNa\cdot{}^3/_2H_2O$: C, 40.37; H, 4.62. Found: C, 40.17; H, 4.27.

Sodium *S*-propenyl (4-cyanophenyl)difluoromethylphosphonothioate 18b: mp = 259−261 °C; ^{1}H NMR (D_2O) δ 7.88 (2H, d, J = 8.2 Hz), 7.80 (2H, d, J = 8.0 Hz), 5.98−5.85 (1H, m), 5.27 (1H, d, J = 16.9 Hz), 5.17 (1H, d, J = 10.0 Hz), 3.38 (2H, dd, J = 7.2, 10.3 Hz); ^{13}C NMR (D_2O) δ 138.4 (dt, J_{CP} = 12.8 Hz, J_{CF} = 22.3 Hz), 134.6, 132.5, 127.3 (t, J_{CF} = 6.1 Hz), 120.0 (dt, J_{CP} = 156.9 Hz, J_{CF} = 242.4 Hz), 119.0, 117.9, 112.9, 33.8 (d, J_{CP} = 2.6 Hz); ^{31}P NMR (D_2O) δ 27.4 (t, J_{PF} = 104.1 Hz); ^{19}F NMR (D_2O) δ −44.9 (d, J_{FP} = 104.1 Hz); IR (KBr) 2332, 2237, 1634, 1259, 1108, 1053, 594 cm^{-1}; FABMS *m*/*z* 288 (M^-). Anal. Calcd for $C_{11}H_9F_2NO_2PSNa\cdot H_2O$: C, 40.13; H, 3.37; N, 4.25. Found: C, 40.50; H, 3.27; N, 4.12.

Sodium *S*-propenyl (4-bromophenyl)difluoromethylphosphonothioate 18c: mp = 255−257 °C; ^{1}H NMR (D_2O) δ 7.69 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.4 Hz), 5.92−5.82 (1H, m), 5.22 (1H, dd, J = 1.4, 17.0 Hz), 5.11 (1H, d, J = 10.3 Hz), 3.32 (2H, dd, J = 7.1, 10.3 Hz); ^{13} C NMR (D_2O) δ 137.3, 135.1 (dt, J_{CP} = 12.9 Hz, J_{CF} = 22.6 Hz), 134.3, 131.0 (t, J_{CF} = 6.1 Hz), 127.3 (d, J_{CP} = 1.6 Hz), 123.3 (dt, J_{CP} = 160.5 Hz, J_{CF} = 265.3),

(15) We found that the diethyl ester **7a** rapidly rearranged to the corresponding sodium *S*-ethyl phosphonothioate **ii** in good yield (80%) upon heating with sodium iodide (2 equiv) in 2-butanone in the absence of 3-iodopropene under reflux:



(16) In these reactions, potassium salts of the starting **8a**,**d**−**f** were recovered in 45−50% yield. No reactions occurred when the sodium salts **18a, d**−**f** were submitted to the Pd-catalyzed deallylation conditions.

120.5, 36.4 (J_{CP} = 2.4 Hz); ^{31}P NMR (D_2O) δ 27.7 (t, J_{PF} = 107.2 Hz); ^{19}F NMR (D_2O) δ −43.9 (d, J_{FP} = −107.2 Hz); IR (KBr) 3064, 1610, 1110, 1038, 606 cm^{-1}; FABMS *m*/*z* 339 (M^-). Anal. Calcd for $C_{10}H_9BrF_2O_2PSNa\cdot H_2O$: C, 31.35; H, 2.89. Found: C, 31.01; H, 2.65.

Sodium *S*-propenyl [1,1′-biphenyl]-3-yl(difluoro)methylphosphonothioate 18d: mp = 239−241 °C; ^{1}H NMR (D_2O) δ 7.77 (1H, s), 7.59−7.57 (1H, d, *J* = 7.6 Hz), 7.27−7.08 (4H, m), 7.03−6.95 (3H, m), 5.50−5.34 (1H, m), 4.74 (1H, d, *J* = 16.9 Hz), 4.63 (1H, d, *J* = 9.9 Hz), 3.39 (2H, dd, *J* = 7.0, 14.1 Hz); ^{13}C NMR (D_2O) δ 142.6, 142.3, 136.8 (dt, J_{CP} = 21.5 Hz, J_{CF} = 43.3 Hz), 136.5, 136.4, 131.3, 131.0, 130.8, 129.8, 129.2, 128.3, 127.5, 123.2 (dt, J_{CP} = 159.9 Hz, J_{CF} = 265.9 Hz), 119.9, 36.5 (d, J_{CP} = 2.4 Hz); ^{31}P NMR (D_2O) δ 27.7 (t, J_{PF} = 107.2 Hz); ^{19}F NMR (D_2O) δ −43.9 (d, J_{FP} = 107.2 Hz); IR (KBr) 3064, 1110, 1038, 606 cm^{-1}; FABMS *m*/*z* 339 (M^-). Anal. Calcd for $C_{16}H_{14}O_2F_2PSNa$: C, 53.04; H, 3.89. Found: C, 52.98; H, 4.12.

Sodium *S*-propenyl difluoro(1-naphthyl)methylphosphonothioate 18e: mp = 245−247 °C; ^{1}H NMR (400 MHz, D_2O) δ 8.49 (1H, d, *J* = 8.0 Hz), 8.07 (1H, d, *J* = 8.2 Hz), 7.99 (1H, *J* = 7.3 Hz), 7.87 (1H, d, *J* = 7.4 Hz), 7.63−7.60 (3H, m), 5.83−5.73 (1H, m), 5.14 (1H, dd, *J* = 1.3, 17.0 Hz), 5.05 (1H, d with small splits, *J* = 10.0 Hz), 3.24 (2H, dd, *J* = 7.2, 9.8 Hz); ^{13}C NMR (D_2O) δ 137.2, 136.6, 134.4, 133.7, 132.5, 131.9 (dt, J_{CP} = 12.6 Hz, J_{CF} = 20.1 Hz), 131.5, 129.8 (dt, J_{CP} = 1.9 Hz, J_{CF} = 9.8 Hz), 129.5, 129.0 (two carbons), 127.6, 125.6 (dt, J_{CP} = 158.8 Hz, J_{CF} = 266.2 Hz); ^{31}P NMR (D_2O) δ 28.6 (t, J_{PF} = 108.1 Hz); ^{19}F NMR (D_2O) δ −36.2 (d, J_{FP} = 108.1 Hz); IR (KBr) 3100, 1512, 1256, 1112, 613 cm^{-1}; FABMS *m*/*z* 313 (M^-). Anal. Calcd for $C_{14}H_{12}F_2O_2PSNa\ H_2O$: C, 47.46; H, 3.98. Found: C, 47.34; H, 3.61.

Sodium *S*-propenyl difluoro(2-naphthyl)methylphosphonothioate 18f: mp = 245−248 °C; ^{1}H NMR (D_2O) δ 8.07 (1H, s), 7.68 (2H, s), 7.64 (1H, d with small splits, *J* = 9.0 Hz), 7.51 (1H, d, with small splits, *J* = 9.0 Hz), 7.18 (2H, m), 5.54 (1H, m), 4.83 (1H, dd, *J* = 1.1, 17.0 Hz), 4.76 (1H, *J* = 10.0 Hz), 3.00 (2H, dd, *J* = 8.5, 8.5 Hz); ^{13}C NMR (D_2O) δ 136.9, (d, J_{CP} = 4.8 Hz), 136.2, 130.7, 130.2, 129.9, 129.3 (two carbons), 126.0 (t, J_{CF} = 5.1 Hz), 123.7 (dt, J_{CP} = 160.6 Hz, J_{CF} = 265.5 Hz), 120.2, 36.4 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (D_2O) δ 28.2 (d, J_{PF} = 108.9 Hz); ^{19}F NMR (D_2O) −43.0 (d, J_{FP} = 108.9 Hz); IR (KBr) 3150, 1604, 1250, 1112, 1040, 590 cm^{-1}; FABMS *m*/*z* 313 (M^-). Anal. Calcd for $C_{14}H_{12}F_2O_2PSNa\cdot{}^1/_3H_2O$: C, 49.03; H, 3.92. Found: C, 49.31; H, 3.91.

***S*-Propenyl hydrogen difluoro(4-methyphenyl)methylphosphonothioate 8a:** an oil; ^{1}H NMR ($CDCl_3$) δ 11.3 (1H, broad s), 7.47 (2H, *J* = 7.8 Hz), 7.23 (2H, d, *J* = 7.8 Hz), 5.84−5.71 (1H, m), 5.20 (1H, dd, *J* = 1.1, 16.9 Hz), 5.11 (1H, d, *J* = 10.0 Hz) 3.41 (2H, dd, *J* = 10.0 Hz), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 141.1, 132.9 (d, J_{CP} = 5.6 Hz), 128.4 (s), 128.4 (dt, J_{CP} = 14.0 Hz, J_{CF} = 22.2 Hz), 126.7, 126.2, 119.4 (dt, J_{CP} = 179.1 Hz, J_{CF} = 265.2 Hz), 118.9, 33.7 (d, J_{CP} = 2.5 Hz); ^{31}P NMR ($CDCl_3$) δ 39.4 (t, J_{PF} = 130.4 Hz), ^{19}F NMR ($CDCl_3$) δ −45.6 (d, J_{FP} = 130.4 Hz); IR (film) 2926, 1616, 1514, 1409, 1262, 598 cm^{-1}; EIMS *m*/*z* 278 (M^+); HREIMS *m*/*z* calcd for $C_{11}H_{13}O_2F_2PS$ 278.0342, found 278.0352.

***S*-Propenyl hydrogen [1,1′-biphenyl]-3-yl(difluoro)methylphosphonothioate 8d:** an oil; ^{1}H NMR ($CDCl_3$) δ 11.6 (1H, broad s), 7.80−7.61 (4H, m), 7.59−7.39 (4H, m), 5.90−5.75 (1H, m), 5.23 (1H, d, *J* = 16.9 Hz), 5.13 (1H, d, *J* = 10.0 Hz); ^{13}C NMR ($CDCl_3$) δ 141.3, 140.0, 132.7, 132.0 (dt, J_{CP} = 13.7 Hz, J_{CF} = 21.8 Hz), 129.5, 128.8, 128.6, 127.7, 127.1, 126.9, 125.6, 125.4, 119.1 (dt, J_{CP} = 176.7 Hz, J_{CF} = 265.7 Hz), 33.9 (d, J_{CP} = 2.2 Hz); ^{31}P NMR ($CDCl_3$) δ 38.8 (t, J_{PF} = 126.1 Hz); ^{19}F NMR ($CDCl_3$) δ −46.0 (d, J_{PF} = 126.1 Hz); IR (KBr) 3445, 3050, 1600, 1480, 1224, 756, 701 cm^{-1}; EIMS *m*/*z* 340 (M^+); HREIMS *m*/*z* calcd for $C_{16}H_{15}O_2F_2PS$ 340.0498, found 340.0495.

***S*-Propenyl hydrogen difluoro(1-naphthyl)methylphosphonothioate 8e:** an oil; ^{1}H NMR ($CDCl_3$) δ 12.0 (1H, broad s), 8.52 (1H, d, *J* = 9.2 Hz), 7.91 (1H, d, *J* = 8.1 Hz), 7.87−7.86 (1H, m), 5.08 (1H, d, *J* = 16.9 Hz), 5.01 (1H, d, *J* = 9.9 Hz), 3.26 (2H, dd, *J* = 7.2, 11.3 Hz); ^{13}C NMR ($CDCl_3$) δ 134.0, 132.7 (d, J_{CP} = 5.5 Hz), 132.2, 130.1, 128.5, 127−126.9 (two carbons, m), 126.8, 126.4−125.8 (two carbons, m), 124.3, 120.8 (dt, J_{CP} = 176.9 Hz, J_{CF} = 266.1 Hz), 118.9, 33.7 (d, J_{CP} = 2.4 Hz); ^{31}P NMR ($CDCl_3$) δ 40.0 (t, J_{PF} = 127.6 Hz); ^{19}F NMR ($CDCl_3$) δ −45.6 (d, J_{CF} = 127.6 Hz); IR (film) 3273, 3059, 1513, 1244, 772 cm^{-1}; EIMS *m*/*z* 314 (M^+); HREIMS *m*/*z* calcd for $C_{14}H_{13}O_2F_2PS$ 314.0342, found 314.0392.

***S*-Propenyl hydrogen difluoro(2-naphthyl)methylphosphonothioate 8f:** an oil; ^{1}H NMR ($CDCl_3$) δ 12.0 (1H, broad s), 8.08 (1H, s), 7.91−7.89 (3H, m), 7.65−7.58 (3H, m), 5.07 (1H, dd, *J* = 1.1, 16.8 Hz), 4.99 (1H, d, *J* = 10.2 Hz), 3.3 (2H, dd, *J* = 7.1, 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 134.2, 132.8 (d, J_{CP} = 5.5 Hz), 132.3, 128.8 (dt, J_{CP} = 12.9 Hz), 128.8, 128.1, 127.1, 127.6, 127.3 (dt, J_{CP} = 178.5 Hz, J_{CF} = 263.5 Hz), 126.7, 123.2 (t, J_{CF} = 5.4 Hz), 119.2 (dt, J_{CP} = 178.5 Hz, J_{CF} = 265.3 Hz), 118.8, 33.8 (d, J_{CP} = 2.7 Hz), ^{31}P NMR ($CDCl_3$) δ 38.4 (t, J_{PF} = 127.5 Hz); ^{19}F NMR ($CDCl_3$) δ −39.2 (d, J_{FP} = 127.5 Hz); IR (KBr) 3062, 1638, 1241, 1190, 1066, 967, 595 cm^{-1}; EIMS *m*/*z* 314 (M^+); HREIMS *m*/*z* calcd for $C_{14}H_{13}O_2F_2PS$ 314.0342, found 314.0356.

Typical Deprotection Procedure of the *S*-Allyl Phosphonothioate. Potassium difluoro(4-methylphenyl)methylphosphonothiate 19a. A solution of **8a** (556 mg, 2.0 mmol), potassium 2-ethylhexanoate (720 mg, 4.0 mmol), and $Pd(PPh_3)_4$ (231 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C in the dark for 4 h. The solvent was evaporated, and the residue was dissolved in 50% H_2O/MeOH (10 mL) and extracted with Et_2O. Evaporation of the aqueous layer gave crude **19a**. Column chromatography of the crude on ODS eluted with water gave **19a** in 30% yield: mp > 250 °C; ^{1}H NMR (D_2O) δ 7.52 (2H, d, *J* = 7.9 Hz), 7.27 (2H, d, *J* = 7.9 Hz), 2.34 (3H, s); ^{13}C NMR (D_2O) δ 147.8, 140.2 (dt, J_{CP} = 12.7 Hz, J_{CF} = 22.9 Hz), 136.2, 134.2 (t, J_{CF} = 6.3 Hz), 130.2 (dt, J_{CP} = 144.1 Hz, J_{CF} = 265.5 Hz), 28.2; ^{31}P NMR (D_2O) δ 45.9 (t, J_{PF} = 99.0 Hz); ^{19}F NMR (D_2O) δ −40.5 (d, J_{FP} = 99.9 Hz); IR (KBr) 1144, 1081, 1016, 653, 622 cm^{-1}; FABMS *m*/*z* 353 (MK^+), 315 (MH^+); HRMS (FAB) *m*/*z* calcd for $C_8H_7O_2F_2K_3PS$ (MK^+) 352.8784, found 352.8789. Anal. Calcd for $C_8H_7O_2F_2K_2PS\cdot 2H_2O$: C, 27.42; H, 3.17. Found: C, 27.51; H, 3.26.

Potassium [1,1′-biphenyl]-3-yl(difluoro)methylphosphonothioate 19d: yield 25%; mp > 250 °C; ^{1}H NMR (D_2O) δ 7.76 (1H, s), 7.60−7.53 (3H, m), 7.47 (1H, d, *J* = 7.7 Hz), 7.39−7.30 (3H, m), 7.24 (1H, t, *J* = 7.4 Hz); ^{13}C NMR (D_2O) δ 147.8, 147.6, 144.1 (dt, J_{CP} = 12.5 Hz, J_{CF} = 22.7 Hz), 136.8, 136.2, 135.5, 134.7, 133.3 (t, J_{CF} = 6.5 Hz), 132.8 (t, J_{CF} = 6.6 Hz), 129.8 (dt, J_{CP} = 143.4 Hz, J_{CF} = 266.2 Hz); ^{31}P NMR (D_2O) δ 45.9 (t, J_{PF} = 98.0 Hz); ^{19}F NMR (D_2O) δ −41.3 (d, J_{FP} = 98.0 Hz); IR (KBr) 1129, 1021, 628, cm^{-1}; FABMS *m*/*z* 415 (MK^+). Anal. Calcd for $C_{13}H_9O_2F_2K_2PS\cdot 2H_2O$: C, 37.85; H, 3.18. Found: C,37.42; H, 3.01.

Potassium difluoro(1-naphthyl)methylphosphonothioate 19e: yield 29%; mp > 250 °C; ^{1}H NMR (D_2O) d 8.60 (1H, d, *J* = 8.7 Hz), 7.92 (1H, d, *J* = 7.4 Hz), 7.68 (1H, d, *J* = 8.3 Hz), 7.59 (1H, d, *J* = 8.1 Hz), 7.52−7.40 (2H, m), 7.31 (1H, t, *J* = 7.4 Hz); ^{13}C NMR (D_2O) δ 131.8, 129.7 (dt, J_{CP} = 11.7 Hz, J_{CF} = 20.7 Hz), 128.8, 128.3, 126.6, 125.4, 125.3 (t, J_{CF} = 9.7 Hz), 124.3, 124.0, 122.8, 122.6 (dt, J_{CP} = 141.4 Hz, J_{CF} = 266.9 Hz); ^{31}P NMR (D_2O) δ 46.7 (t, J_{PF} = 97.1 Hz); ^{19}F NMR (D_2O) δ −33.1 (d, J_{FP} = 97.1 Hz); IR (KBr) 1596, 1499, 1254, 1141, 1105, 1008 cm^{-1}; FABMS *m*/*z* 389 (MK^+). Anal. Calcd for $C_{11}H_7O_2F_2K_2PS\cdot{}^5/_2H_2O$: C, 33.40; H, 3.06. Found: C, 33.33; H, 2.98.

Potassium difluoro(2-naphthyl)methylphosphonothioate 19f: yield 23%; mp > 250 °C; ^{1}H NMR (D_2O) δ 8.15 (1H, s), 8.01−7.89 (3H, m), 7.74 (1H, d, *J* = 8.5 Hz), 7.59−7.52 (2H, m); ^{13}C NMR (D_2O) δ 133.6, 133.6 (dt, J_{CP} = 11.8 Hz, J_{CF} = 22.3 Hz), 132.4, 128.9, 128.0, 127.8, 127.5, 127.1, 126.6 (t, J_{CF} = 6.8 Hz), 124.4 (t, J_{CF} = 5.7 Hz), 122.8 (dt, J_{CP} = 143.4 Hz, J_{CF} = 266.1 Hz); ^{31}P NMR (D_2O) δ 46.0 (t, J_{PF} = 98.2 Hz); ^{19}F NMR (D_2O) δ −40.7 (d, J_{FP} = 98.2 Hz); IR (KBr) 1125, 1016, 636 cm^{-1}; FABMS *m*/*z* 389 (MK^+), 351 (MH^+). Anal. Calcd for $C_{11}H_7O_2F_2K_2PS\cdot 3H_2O$: C, 32.67; H, 3.24. Found: C, 32.21; H, 2.74.

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Supporting Information Available: Experimental procedure and complete characterization data for new compounds **7a**−**f** and **13b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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