Studies Toward the Synthesis of α-Fluorinated Phosphonates via Tin-Mediated Cleavage of α-Fluoro-α-(pyrimidin-2-ylsulfonyl)alkylphosphonates. Intramolecular Cyclization of the α-Ph...

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MARCH 2002

Impact Factor: 4.72 · DOI: 10.1021/jo0111560

Stanislaw F Wnuk

Florida International University

Studies toward the Synthesis of α-Fluorinated Phosphonates via Tin-Mediated Cleavage of α-Fluoro-α-(pyrimidin-2-ylsulfonyl)alkylphosphonates. Intramolecular Cyclization of the α-Phosphonyl Radicals

Stanislaw F. Wnuk,* Luis A. Bergolla, and Pedro I. Garcia, Jr.

Department of Chemistry, Florida International University, Miami, Florida 33199

wnuk@fiu.edu

Received December 19, 2001

Treatment of the α carbanions generated from several α-(pyrimidin-2-ylsulfonyl)alkylphosphonates with Selectfluor gave high yields of the α-fluoro-α-(pyrimidin-2-ylsulfonyl)alkylphoshonates, which were desulfonylated [Bu_3SnH/2,2′-azobisisobutyronitrile (AIBN)/benzene or toluene/Δ] to give α-fluoroalkylphosphonates. "Catalytic" tin hydride, generated from tributyltin chloride and excess polymethylhydrosiloxane in the presence of potassium fluoride, also effected removal of the π-deficient α-(pyrimidin-2-ylsulfonyl) group from the phosphonate esters. Substitution of Bu_3SnD for Bu_3SnH gave access to α-deuterium-labeled phosphonates. Prolonged treatment of α-(pyridin-2-ylsulfonyl)alkylphosphonate with excess Bu_3SnH/AIBN or catalytic tin hydride also effected desulfonylation but in moderate yields. This represents a mild new methodology for removal of the synthetically useful π-deficient heterocyclic sulfone moiety and an alternative route for the preparation of α-fluorinated phosphonates. Desulfonylation is suggested to proceed via attack of tin radical at an oxygen (or sulfur) atom of the sulfonyl group to give a stabilized α-phosphonyl radical intermediate. The latter was found to undergo 5-*exo*-trig ring closure to give the corresponding 2-methylcyclopentylphosphonates. Treatment of diethyl 1-bromohex-6-enylphosphonate with Bu_3SnH/AIBN produced an analogous mixture of ring-closure products. Treatment of [(2-bromo-5- methoxyphenyl)(fluoro)(pyrimidin-2-ylsulfonyl)]methylphosphonate with Bu_3SnH resulted in an intramolecular radical [1,5]-*ipso* substitution reaction and migration of the pyrimidinyl ring to give fluoro[5-methoxy-2-(pyrimidin-2-yl)phenyl]methylphosphonate.

Introduction

Phosphonic acids structurally related to natural phosphates possess interesting biological properties.[1] Blackburn proposed that α-fluoro and α,α-difluoro substitution on methylenephosphonates should provide superior phosphate ester surrogates (closer isosteric and isopolar parallels).[2] The α-fluorinated phosphonates are often designed as nonhydrolyzable phosphate mimics, and are used as enzyme inhibitors and metabolite probes.[1b,3−5] α-Fluoro- and α,α-difluoromethylenephosphonates have been prepared by Arbuzov reactions with fluorohalomethanes,[6] fluorination of phosphonate-stabilized anions,[4,7] treatment of α-hydroxy phosphonates[2c] or α-oxo phosphonates[8] with diethylaminosulfur trifluoride, alkylation of (diethoxyphosphoryl)difluoromethyllithium[9a] or monofluorosilyllithium phosphonate species,[9b] and palladium-catalyzed addition of diethyl difluoroiodomethylphosphonate to alkenes.[10] Fluorinations of sulfonyl-stabilized phosphonate carbanions with perchloryl fluoride[11] and the Selectfluor reagent[12] have been described, and other methods were reviewed.[13] Chiral α-fluoro phosphonic acids were synthesized by fluorination of asymmetric phosphonamidates.[4c]

The sulfone group is a well-established activating moiety for construction of carbon−carbon skeletons and other transformations.[14] During work on the synthesis of a 6′-deoxy-6′-fluorohomonucleoside phosphonate from

To whom correspondence should be addressed. Phone: (305) 348-6195. Fax: (305) 348- 3772.

(1) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349−367. (b) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609−16644.
(2) (a) Blackburn, G. M. *Chem. Ind. (London)* **1981**, 134−138. (b) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119−1125. (c) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913−917.
(3) (a) Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, *113*, 315−317. (b) Chen, W.; Flavin, M. T.; Filler, R.; Xu, Z.-Q. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3979−3988. (c) Hamilton, C. J.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1051−1056.
(4) (a) Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Chen, M.-J. *Tetrahedron* **1998**, *54*, 1691−1714. (b) Wang, Q.; Huang, Z.; Ramachandran, C.; Dinaut, A. N.; Taylor, S. D. *Biol. Med. Chem. Lett.* **1998**, *8*, 345−350. (c) Kotoris, C. C.; Wen, W.; Lough, A.; Taylor, S. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1271−1281.
(5) (a) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498−4508. (b) Berkowitz, D. B.; Bose, M.; Asher, N. G. *Org. Lett.* **2001**, *3*, 2009−2012.
(6) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329−332.
(7) Differding, E.; Duthaler, R. O.; Krieger, A.; Rtiegg,-G. M.; Schmit, C. *Synlett* **1991**, 395−396.
(8) Burke, T. R., Jr.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336−1340.
(9) (a) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323−2326. (b) Waschbtisch, R.; Carran, J.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1135−1139.
(10) (a) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 4676−4683. (b) Hu, C.- M.; Chen, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 327−330.
(11) Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3959−3962.
(12) (a) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.
(13) (a) Waschbiisch, R.; Carran, J.; Marinetti, A.; Savignac, P. *Synthesis* **1996**, 127−743. (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431−12477.

10.1021/jo0111560 CCC: $22.00
Published on Web 03/27/2002

uridine, we noticed that standard procedures for desulfonylation[14b] were ineffective for removal of the pyridin-2-ylsulfonyl group from the α-carbon of phosphonic esters.[15] We found that tributyltin hydride effected such desulfonylation although Bu_3SnH[16] is generally recognized as ineffective for cleavage of saturated sulfones.[14b] We then investigated radical-mediated removal of π-deficient heterocyclic sulfones from the α-carbon of carboxylic esters.[17] Desulfonylation of β-ketosulfones[18] and *N*-sulfonylated amides[19] with Bu_3SnH and stannodesulfonylations of vinyl sulfones[20] have been noted.

We now report the synthesis of phosphonate α-(pyrimidin- or pyridin-2-yl sulfones), their α-fluorination with Selectfluor, and their desulfonylation with tributylstannane or a "catalytic" tin equivalent. This provides an alternative route for the preparation of α-fluoro phosphonates, and a mechanistic pathway via α-phosphonyl radical intermediates is suggested.

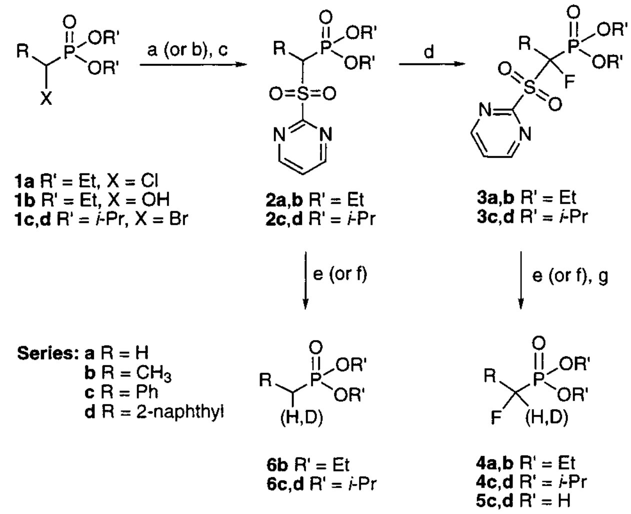
Results and Discussion

The α-(pyrimidin-2-ylsulfonyl)alkylphosphonate esters **2a,c,d** were prepared from the corresponding α-haloalkylphosphonates **1a,c,d** and sodium pyrimidine-2-thiolate, followed by oxidation [*m*-chloroperoxybenzoic acid (*m*-CPBA)] of the resulting α-(pyrimidin-2-ylthio)alkylphosphonates (~62−71% overall; Scheme 1). Treatment of diethyl 1-hydroxyethylphosphonate (**1b**) with pyrimidine-2-thiol in the presence of diethyl azodicarboxylate (DEAD)/Ph_3P[21] followed by oxidation produced sulfone **2b** (51% overall), whereas tosylation of **1b** and attempted displacement of the tosylate group with thiolate gave the thioether in lower yields (~10−15%). The α-(pyrimidin-2-ylsulfonyl)alkylphosphonates **2a**−**d** were treated with potassium hydride, and the enolates were quenched with Selectfluor[12] to give the α-fluoro-α-(pyrimidin-2-ylsulfonyl) phosphonates **3a**−**d** in good yields (61−80%).

Treatment of **2b** with Bu_3SnH (2.0 equiv)/2,2′-azobisisobutyronitrile (AIBN) (1.2 equiv)/benzene or toluene/Δ for 4 h caused cleavage of the sulfonyl linkage to give **6b** (56%) plus unchanged **2b** and minor decomposition products. Stoichiometric quantities of the initiator and its portionwise addition via syringe, or use of a syringe pump, were found to be necessary for efficient desulfonylation. Analogous treatment of **2c** gave clean conversion to **6c** (Table 1).

Tributylstannane-mediated desulfonylation of α-fluoro-α-(pyrimidin-2-ylsulfonyl) phosphonates **3a**−**d** gave α-fluoro phosphonate esters **4a**−**d**, which were deprotected to α-fluoro phosphonic acids (e.g., **5c,d**). In general,

Scheme 1[a]



[a] Reagents and conditions: (a) 2-pyrimidinethiol/NaH/DMF; (b) 2-pyrimidinethiol/DEAD/Ph_3P/benzene; (c) *m*-CPBA/CH_2Cl_2; (d) KH/Selectfluor/THF/DMF; (e) $Bu_3SnH(D)$/AIBN/benzene (or toluene)/Δ; (f) Bu_3SnCl/PMHS/KF/H_2O/toluene/Δ; (g) Me_3SiBr/CH_2Cl_2.

Table 1. Tributylstannane-Mediated Removal of π-Deficient Heterocyclic Sulfones from the α-Carbon of Phosphonate Esters

substrate	product	yield (%)[a]	substrate	product	yield (%)[a]
3a	**4a**	45,[b] 91[c]	**3d**	**4d**	78, 92[c]
3b	**4b**	61,[b] 82[c]	**2b**	**6b**	56,[b] 60[c]
9b	**4b**	48[b]	**7b**	**6b**	32[b]
3c	**4c**	80,[b] 94[c]	**2c**	**6c**	88[b]
9c	**4c**	40,[b] 73[c]	**7c**	**6c**	45,[b] 55[c]
10c	**4c**	not detected[d]	**2d**	**6d**	81[c]

[a] Isolated yields. [b] Desulfonylation with "equivalent" tin hydride: Bu_3SnH/AIBN/benzene (or toluene)/Δ (procedure D). [c] Desulfonylation with catalytic tin hydride: Bu_3SnCl/PMHS/KF/H_2O/toluene/Δ (procedure E). [d] Dephosphonylation product **11** was formed in 40%[b] and 60%[c] yields.

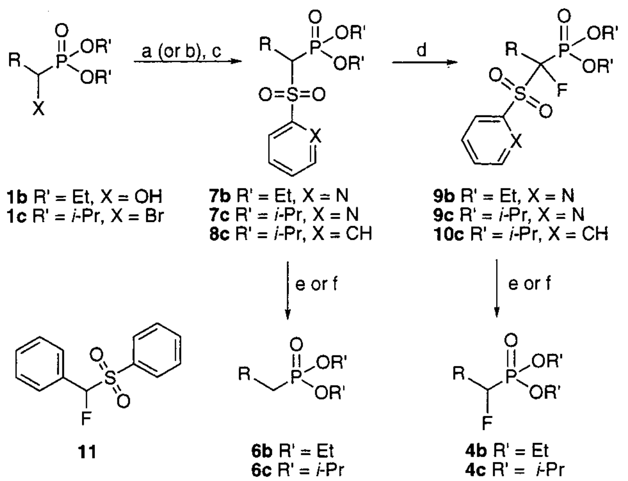
removal of the pyrimidin-2-ylsulfonyl group from the α-carbon of the benzylic-type phosphonates (series **c,d**; 78−80%) gave better results than that of the alkyl analogues (series **a,b**; 45−61%). In contrast to our mild radical methodology, attempted desulfonylation of diethyl fluoro(phenylsulfonyl)methylphosphonate with sodium amalgam resulted in cleavage of the phosphorus−carbon bond to give [(fluoromethyl)sulfonyl]benzene.[11] Attempted removal of the phenylsulfonyl group with Raney Ni also failed to produce α-fluoro phosphonates.[11] Conversely, Berkowitz and co-workers[5b] recently reported that treatment of sugar-derived α-fluoro-α-(phenylsulfonyl) phosphonates with fresh sodium amalgam effected desulfonylation, wheras treatment with Bu_3SnH/AIBN effected dephosphonylation (vide infra).

Our radical desulfonylation also gives access to deuterium-labeled phosphonates. Thus, treatment of **2b** and **3b** with Bu_3SnD gave 1- deuterioethylphosphonate **6b**-1-^{2}H and 1-deuterio-1-fluoroethylphosphonate **4b**-1-^{2}H, respectively, with ~90% incorporation of deuterium.

To reduce toxicity and purification problems associated with the use of Bu_3SnH, processes that are "catalyzed" by Bu_3SnH have been developed,[22,23] along with other approaches.[24] Treatment of **2b** with a catalytic tin hydride system [Bu_3SnCl (0.15 equiv)/AIBN (1.5 equiv)/PMHS (polymethylhydrosiloxane, excess)/KF/H_2O/toluene/Δ][23a] effected hydrogenolysis to give **6b** (60%), which was

(14) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658.
(15) Wnuk, S. F.; Robins M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2519−2520.
(16) (a) Neumann, W. P. *Synthesis* **1987**, 665−683. (b) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987.
(17) Wnuk, S. F.; Rios, J. M.; Khan, J.; Hsu, Y.;-L. *J. Org. Chem.* **2000**, *65*, 4169−4174.
(18) (a) Smith, A. B., III; Hale, K. J.; McCauley, J. P., Jr. *Tetrahedron Lett.* **1989**, *30*, 5579−5582. (b) Giovannini, R.; Petrini, M. *Synlett* **1995**, 973−974.
(19) (a) Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1996**, *37*, 1667−1670. (b) Knowles, H. S.; Parsons, A. F.; Pettifer, R. M.; Rickling, S. *Tetrahedron* **2000**, *56*, 979−988.
(20) (a) Watanabe, Y.; Ueno, Y.; Araki, T.; Endo, T.; Okawara, M. *Tetrahedron Lett.* **1986**, *27*, 215−218. (b) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1994**, *37*, 3579−3587.
(21) Gajda, T. *Synthesis* **1988**, 327−328.

Scheme 2[a]



b series, R =CH$_3$; **c** series, R = Ph

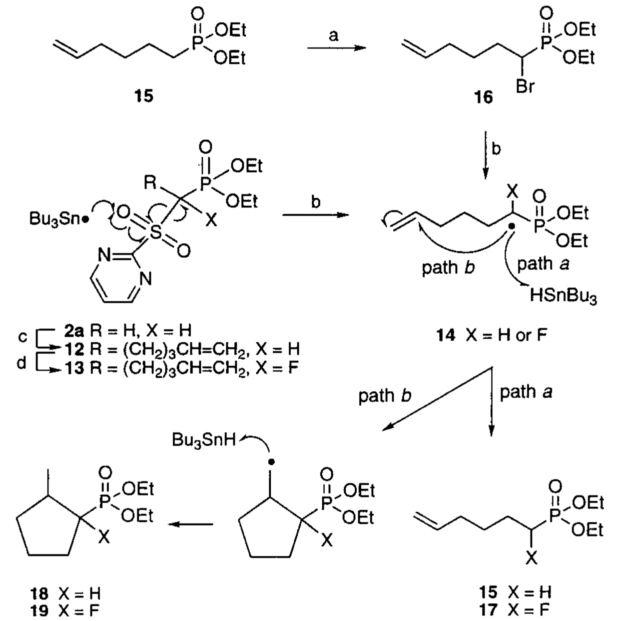
[a] Reagents and conditions: (a) 2-pyridinethiol or benzenethiol/NaH/DMF; (b) 2-pyridinethiol/DEAD/Ph$_3$P/benzene; (c) *m*-CPBA/CH$_2$Cl$_2$; (d) KH/Selectfluor/THF/DMF; (e) Bu$_3$SnH/AIBN/benzene (or toluene)/Δ; (f) Bu$_3$SnCl/PMHS/KF/H$_2$O/toluene/Δ.

readily purified. Analogous treatment of the α-(pyrimidin-2-ylsulfonyl) (**2d**) and α-fluoro-α-(pyrimidin-2-ylsulfonyl) (**3a**−**d**) phosphonates resulted in smooth desulfonylation to give phosphonate **6d** (81%) and α-fluoro phosphonates **4a**−**d** (82−94%), respectively.

We also studied radical-mediated removal of the α-(pyridin-2-ylsulfonyl) group because Barton's thiohydroxamic ester chemistry with vinylphosphonates[25] provides convenient access to α-(pyridin-2-ylsulfonyl) phosphonates. The α-(pyridin-2-ylsulfonyl)ethylphosphonate **7b** and its benzyl analogue **7c** were prepared as described above with pyridine-2-thiol in place of pyrimidine-2-thiol (Scheme 2). Fluorination of **7b,c** with Selectluor gave **9b,c**.

Treatment of **7b** with excess Bu$_3$SnH/AIBN for 48 h effected desulfonylation to give **6b** (32%) and recovered **7b** (50%). Parallel treatment (26 h) of **9b** produced α-fluoroethylphosphonate **4b** (48%). Reaction of **7c** and its fluoro analogue **9c** with excess Bu$_3$SnH/AIBN or catalytic tin hydride gave **6c** (45−55%) and **4c** (40−73%), respectively. As anticipated,[17] the α-fluoro substituent had little effect on the time required and yield of the radical desulfonylation reactions in contrast to the impact of the second nitrogen atom in the heterocyclic ring. Nevertheless, removal of the pyridin-2-ylsulfonyl group enhances the versatility of the radical-mediated desulfonylation, especially since the reactivity gap (toward desulfonylation) between pyridin-2-ylsulfonyl and its pyrimidine counterpart is narrowed in the phosphonate esters in comparison with carboxylate esters.[17]

Scheme 3[a]



[a] Reagents and conditions: (a) (i) *i*-Pr$_2$NH/BuLi/THF/Me$_3$SiCl, (ii) BrCCl$_2$CCl$_2$Br; (b) Bu$_3$SnH/AIBN/benzene (or toluene)/Δ; (c) 5-bromo-l-pentene/NaH/DMF; (d) KH/Selectfluor/THF/DMF.

We also prepared the α-fluoro-α-(phenylsulfonyl) phosphonate **10c** to corroborate literature reports[5b,11] (vide supra). Compound **10c** was chosen because the benzyl phosphonate **9c** produced the best desulfonylation results among the pyridin-2-yl sulfones. Treatment of **10c** with Bu$_3$SnH/AIBN or catalytic tin hydride effected dephosphonylation, as observed by Berkowitz and co-workers,[5b] to give the α-fluoro sulfone **11**. It is noteworthy that unfluorinated phosphonates substituted at the α-carbon with a phenyl- or methylsulfonyl or sulfinyl group were reported to be inert toward radical conditions (Bu$_3$SnH/AIBN).[26a]

Possible reaction mechanisms might involve attack by tin radical at an oxygen (or sulfur) atom of the sulfonyl group to give a stabilized α-phosphonyl radical[26,27] of type **14** which could abstract hydrogen from the stannane (path *a*), or might participate in cyclization reactions (path *b*; Scheme 3). This was investigated by desulfonylation of diethyl 1-(pyrimidin-2-sulfonyl)hex-6-enylphosphonate (**12**; prepared by alkylation of **2a** with 5-bromo-1-pentene) and its α-fluoro analogue **13**. Thus, treatment of **12** with Bu$_3$SnH/AIBN gave the unsaturated phosphonate **15** (21%; ^{31}P NMR) and the 5-*exo*-trig ring-closure products **18** (54%; *cis*/*trans*, ∼2:1) in addition to two minor products and unchanged **12** (13%). A tedious purification yielded **15** and the *cis* and *trans* isomers of the 2-methylcyclopentylphosphonates **18**. The stereochemistry in **18** was tentatively assigned by the parallel ^{13}C NMR shifts relative to those in the reported spectra[28]

(22) (a) Hays, D. V.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751−6752. (b) Tormo, J.; Hays, D. V.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 5296−5297.

(23) (a) Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342−343. (b) Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384−385.

(24) (a) Crich, D.; Sun, S. *J., Org. Chem.* **1996**, *61*, 7200−7201. (b) Curran, D. P.; Hadida, 20 S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607−6615.

(25) (a) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1000−1001. (b) Barton, D. H. R.; Gdro, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron* **1992**, *48*, 1627−1636.

(26) (a) Balczewski, P. *Phosphorus, Sulfur Silicon* **1995**, *104*, 113−121. (a) Balczewski, P.; Mikolajczyk, M. *Synthesis* **1995**, 392−396. (c) Balczewski, P.; Pietrzykowski, W. M.; Mikolajczyk, M. *Tetrahedron* **1995**, *51*, 7727−7740. (d) Balczewski, P.; Bialas, T.; Mikolajczyk, M. *New J. Chem.* **2001**, *25*, 659−663.

(27) Treatment of α-halo (or sulfur or seleno) substituted phosphonates with Bu$_3$SnH generates α-phosphonyl radicals which undergo intermolecular addition to alkenes.[26]

(28) Nifant'ev, E, E.; Magdeeva, R. K.; Dolidze, A. V.; Ingorokva, K. V.; Samkharadze, L. O.; Vasyanina, L. K.; Bekker, A. R. *Zh. Obshch. Khim.* **1991**, *61*, 96−106.

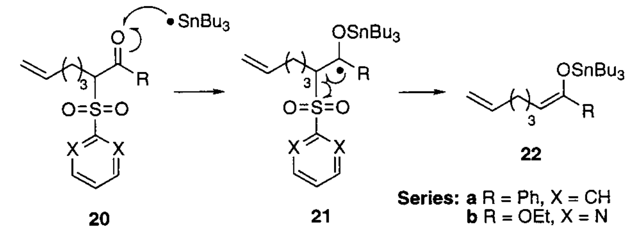


Figure 1.

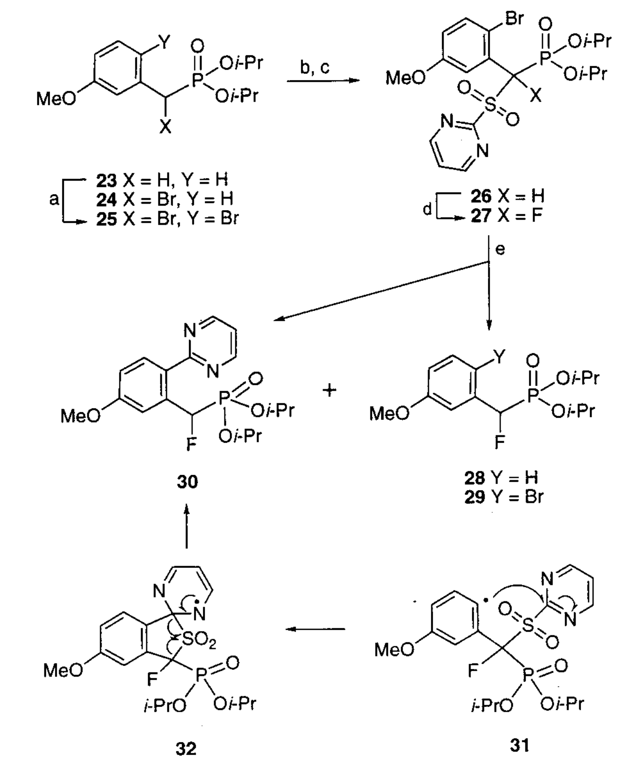
of the diisopropyl analogues of **18** (as well as ^{31}P NMR shifts of **18**[28]). Radical desulfonylation of the α-fluoro analogue **13** also gave ring-closure products **19** (53%; *cis/trans*, ~1.3:1; ^{31}P and ^{19}F NMR) in addition to five unidentified minor products and unchanged **13** (16%). The α-fluoro phosphonate **17**, if formed, was produced in low yield (<8%) and was not isolated. Single-electron transfer[18a,19] (SET) from the tin radical to the electronegative phosphonate systems (e.g., **13**) followed by heterolysis of sulfinate might also lead to the α-phosphonyl radicals. Such an SET process as well as cleavage of the sulfinate may be further enhanced by the presence of nitrogen(s) in the aromatic ring.

Generation of α-phosphonyl radicals upon treatment of α-halo phosphonates with Bu_3SnH/AIBN is well-known.[26,27] Therefore, we prepared 1-bromohex-6-enylphosphonate **16** by bromination[29] of independently synthesized **15**.[30] Treatment of **16** with Bu_3SnH gave **15** and **18** (*cis*/*trans*) in parallel with their formation during radical desulfonylation of **12**. This further supports formation of an α-phosphonyl radical intermediate.

An analogous attack by tin radicals on an oxygen or the sulfur of the phenylsulfonyl group has been considered[18] for radical desulfonylation of *β*-ketosulfones. However, the absence of 5-*exo* cyclization products with a terminal double-bonded compound, **20a**, was evidence against formation of α-keto radicals (Figure 1). Also there were no 5-*exo*-trig ring-closure products detected during radical-mediated removal of *π*-deficient heterocyclic sulfones from the α-carbon of unsaturated carboxylic ester **20b**.[17] Attack by tin radicals on the carbonyl oxygen and formation of ketyl-type radicals **21a,b** were proposed as alternative reaction pathways.[17−19] Radicals **21a,b** then afford tin enolates **22** via elimination of sulfonyl radicals. The α-phosphonyl radical generated from diethyl 1-(methylselenenyl)pent-4-enylphosphonate and Bu_3SnH did not undergo 4-*exo*-trig or 5-*endo*-trig cyclization.[26c] Single-electron-transfer-induced 6-*endo* radical cylization of allylic α-iodo-α-(dimethylphosphoryl)acetates has been reported.[31]

Bromination of diisopropyl 1-(3-methoxyphenyl)methylphosphonate (**23**) under radical conditions [NBS/$(BzO)_2$/CCl_4][32] did not yield the expected α-monobromo phosphonate **24** but resulted in formation of the dibromophosphonate **25** (65%; Scheme 4). Bromination of the phenyl ring was the initial reaction. Aromatic vs side-chain bromination of methyl-substituted anisoles by NBS has been reported.[33] The dibromo product **25** was converted to α-(pyrimidin-2-ylsulfonyl) derivative **26**, which was fluorinated to give **27** (50% overall).

Scheme 4[a]



[a] Reagents and conditions: (a) NBS/$(BzO)_2$/CCl_4; (b) 2-pyrimidinethiol/NaH/DMF; (c) *m*-CPBA/CH_2Cl_2; (d) KH/Selectfluor/THF/DMF; (e) Bu_3SnH/AIBN/benzene (or toluene)/Δ.

Treatment of **27** with Bu_3SnH or catalytic tin gave mixtures of products, which were laboriously separated/purified with reversed-phase (RP)-HPLC. Two products were the expected α-fluoro phosphonates **28** (20%) and **29** (34%; ^{19}F NMR). The third product was found to be **30** (20%; ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR). Formation of **30** involves bromine abstraction from **27** by a stannyl radical to give aryl radical[34] **31**. An intramolecular radical [1,5]-*ipso* substitution reaction[35] of the migrating pyrimidinyl ring gives **32**, which can rearomatize by loss of sulfur dioxide to produce **30**.

Conclusion

In summary, we have developed the syntheses of α-(pyrimidin- and pyridin-2-yl sulfones) of phosphonate esters, their α-fluorination with Selectfluor, and their desulfonylation with tributylstannane or catalytic tin reagents. The *π*-deficient heterocyclic sulfones were found to be advantageous (compared to the phenylsulfonyl group) in reactions that involve radical hydrogenolysis. Desulfonylation is suggested to proceed via the α-phosphonyl radical intermediates.

(29) Iorga, B.; Eymery, F.; Savignac, P. *Synthesis* **2000**, 576−580.

(30) Kelley, J. L.; McLean, E. W.; Crouch, R. C.; Averett, D.-V.; Tuttle, J. L. *J. Med. Chem.* **1995**, *38*, 1005−1014.

(31) Töke, L.; Jaszay, Z. S.; Petnehazy, I.; Clementis, G.; Vereczkey, G. D.; Kövesdi, I.; Rockenbauer, A.; Kovats, K. *Tetrahedron* **1995**, *51*, 9167−9178.

(32) Chakraborty, S. K.; Engel, R. *Synth. Commun.* **1991**, *21*, 1039−1046.

(33) (a) Goldberg, Y.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1992**, *57*, 6374−6376. (b) Gruter, G.-H. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473−4481.

(34) (a) Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169−7172. (b) Crich, D.; Hwang, J.-T.; Gastaldi, S.; Recupero, F.; Wink, D. J. *J. Org. Chem.* **1999**, 64, 2877−2882.

(35) (a) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137−140. (b) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 141−144. (c) Clive, D. L. J.; Kang, S. *J. Org. Chem.* **2001**, *66*, 6083−6091 and references therein.

Experimental Section

^{1}H (Me_4Si) NMR spectra were determined with solutions in $CDCl_3$ at 400 MHz, ^{13}C (Me_4Si) at 100.6 MHz, ^{19}F (CCl_3F) at 376.4 MHz, and ^{31}P (H_3PO_4) at 161.9 MHz. Mass spectra were obtained by atmospheric pressure chemical ionization (APCI) techniques. Reagent-grade chemicals were used, and solvents were dried by reflux over and distillation from CaH_2 under an argon atmosphere. Selectfluor fluorinating reagent (>95% active [F^+]) was purchased from Aldrich. TLC was performed on Merck Kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1:19) and EtOAc/hexane (1:2) as developing systems, and products were detected with 254 nm light or by development of color with I_2. Merck Kieselgel 60 (230−400 mesh) was used for column chromatography. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. The purity and identity of the products (crude and/or purified) were also established using a Hewlett-Packard (HP) GC/MS (EI) system with an HP 5973 mass-selective detector [capillary column HP-5MS (30 m × 0.25 mm)] or a RP-HPLC/MS (APCI) system (C18 column).

Diethyl (Pyrimidin-2-ylsulfonyl)methylphosphonate (2a). Procedure A. (a) Displacement. NaH (267 mg, 60%/mineral oil, 6.4 mmol) was washed (dried Et_2O) and suspended in dried DMF (35 mL) under N_2. 2-Pyrimidinethiol (720 mg, 6.4 mmol) was added slowly at ∼0 °C (ice bath). The resulting solution was stirred at ambient temperature for 1 h and cooled to ∼0 °C, and diethyl (chloromethyl)phosphonate (**1a**; 1.0 mL, 1.2 g, 6.4 mmol) was added. After 1 h, the mixture was allowed to warm to ambient temperature, stirred overnight, and evaporated, and the residue was partitioned (EtOAc/H_2O). The organic layer was washed ($NaHCO_3$/H_2O, brine), dried ($MgSO_4$), and evaporated to give the viscous thioether. That material was column chromatographed (50% → 90% EtOAc/hexanes) to give 1.4 g (83%) of pure diethyl (pyrimidin-2-ylthio)methylphosphonate: ^{1}H NMR δ 3.56 (d, $^2J_{CH_2-P}$ = 13.7 Hz, 2H); ^{31}P NMR [^{1}H] δ 24.39 (s).

(b) Oxidation. The above thioether was dissolved (CH_2Cl_2, 25 mL), cooled (ice bath), and treated dropwise with *m*-CPBA (3.68 g/75% reagent, 16 mmol) in $CHCl_3$/CH_2Cl_2 (1:1, 40 mL). After 2 h, the mixture was allowed to warm to ambient temperature and stirred for 18 h. Saturated $NaHCO_3$/H_2O (100 mL) was added, stirring was continued for 15 min, the organic layer was separated, and the aqueous layer was extracted (CH_2Cl_2, 25 mL). The combined organic phase was washed ($NaHCO_3$/H_2O, brine), dried ($MgSO_4$), evaporated, and chromatographed (30% hexanes/EtOAc → EtOAc → 5% MeOH/EtOAc) to give **2a** (1.39 g, 74% from **1a**) as a solidified oil: mp 65−67 °C; ^{1}H NMR δ 1.23 (t, J = 7.3 Hz, 6H), 4.05 ("quint", J = 7.4 Hz, 4H), 4.16 (d, J = 16.4, 2H), 7.56 (t, J = 4.9 Hz, 1H), 8.87 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 16.6 (d, J = 6.4 Hz), 48.5 (d, J = 138.2 Hz), 63.9 (d, J = 6.4 Hz), 124.6, 159.1, 165.6; ^{31}P NMR δ 12.19 ("nanoset", J = 8.0 Hz); ^{31}P NMR [^{1}H] δ 12.19 (s); MS *m/z* 295 (100, MH$^+$). Anal. Calcd for $C_9H_{15}N_2O_5PS$ (294.27): C, 36.73; H, 5.14; N, 9.52. Found: C, 36.46; H, 5.16; N, 9.41.

Diethyl 1-(Pyrimidin-2-ylsulfonyl)ethylphosphonate (2b). Procedure B. A solution of DEAD (2.1 g, 2.0 mL, 12 mmol) in benzene (5 mL) was added dropwise to a stirred solution of diethyl (1- hydroxyethyl)phosphonate (**1b**; 1.65 mL, 1.82 g, 10 mmol) and Ph_3P (3.14 g, 12 mmol) in benzene (20 mL) under N_2 at ambient temperature. After 5 min, 2-pyrimidinethiol (1.12 g, 10 mmol) in benzene (20 mL) was slowly added over a period of 20 min, and stirring was continued for 12 h. The precipitate formed was filtered off, the filtrate was evaporated, and the residue was partitioned (EtOAc//K_2CO_3/H_2O), washed (H_2O), dried ($MgSO_4$), and concentrated. The brown oily residue was column chromatographed (50% hexanes/EtOAc → EtOAc → 5% MeOH/EtOAc) to give 1.66 g (60%) of pure diethyl 1-(pyrimidin-2-ylthio)-ethylphosphonate: ^{1}H NMR δ 4.46 (dq, J = 16.8, 7.3 Hz, 1H); ^{31}P NMR δ 28.26 (m). Oxidation of this material with *m*-CPBA by procedure A (step b) gave **2b** (1.57 g, 85%) as an oil: ^{1}H NMR δ 1.31 ("q", J = 7.1 Hz, 6H), 1.68 (dd, J = 7.5, 15.5 Hz, 3H), 4.00−4.18 (m, 4H), 4.50 (dq, J = 17.5, 7.5, 1H), 7.57 (t, J = 4.9 Hz, 1H), 8.91 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 8.6 (d, J = 4.8 Hz), 16.58 and 16.62 (d, J = 5.7 Hz), 53.9 (d, J = 141.1 Hz), 63.4 and 64.6 (d, J = 6.5 Hz), 124.3, 158.9, 165.8; ^{31}P NMR δ 16.92 (m, J = 7.9 Hz); MS *m/z* 309 (100, MH$^+$). Anal. Calcd for $C_{10}H_{17}N_2O_5PS$ (308.29): C, 38.96; H, 5.56; N, 9.09. Found: C, 38.59; H, 5.89; N, 8.75.

Diethyl Fluoro(pyrimidin-2-ylsulfonyl)methylphosphonate (3a). Procedure C. KH (228 mg, 35%/mineral oil, 2 mmol, or 84 mg, 2.1 mmol; dried/pressed between filter paper) in a flame-dried flask under Ar was washed (Et_2O), and dried THF (10 mL) was added. The suspension was cooled (∼0 °C, ice bath), and compound **2a** (588 mg, 2 mmol) in THF (7 mL) was added (syringe). The solution was stirred (0 °C for 15 min, ambient temperature for 60 min, cooled to 0 °C), and Selectfluor (887 mg, 2.5 mmol) was added in one portion. After 15 min, dried DMF (5 mL) was added (syringe), the ice bath was removed after 5 min, and stirring was continued at ambient temperature for 2 h. The reaction mixture was cooled to ∼0 °C (ice bath), and CH_2Cl_2 (15 mL) and saturated NH_4Cl/H_2O (5 mL) were slowly added. After 5 min, the organic layer was separated, and the aqueous layer was extracted (CH_2Cl_2). The combined organic phase was washed (saturated $NaHCO_3$/H_2O, brine), dried ($MgSO_4$), evaporated, and chromatographed (30% hexanes/EtOAc → EtOAc → 5% MeOH/EtOAc) to give **3a** (393 mg, 63%): mp 64−67 °C; ^{1}H NMR δ 1.40 (t, J = 7.3 Hz, 6H), 4.05 ("sextet", J = 7.5 Hz, 4H), 6.40 (dd, J = 45.5, 6.5 Hz, 1H), 7.67 (t, J = 4.8 Hz, 1H), 9.00 (d, J = 4.8 Hz, 2H); ^{13}C NMR δ 16.71 and 16.74 (d, J = 5.8 Hz), 65.7 and 65.9 (d, J = 6.7 Hz), 94.0 (dd, $^1J_{C-P}$ = 159.0 Hz, $^1J_{C-F}$ = 230.5 Hz), 124.9, 159.4, 164.5 (d, J = 5.1 Hz); ^{19}F NMR δ −197.17 (dd, $^2J_{F-H}$ = 48.7 Hz, $^2J_{F-P}$ = 65.5 Hz); ^{19}F NMR [^{1}H] δ −197.17 (d, $^2J_{F-P}$ = 65.3 Hz); ^{31}P NMR δ 5.84 (d"sextet", $^2J_{P-F}$ = 65.0 Hz, J = 7.7 Hz); ^{31}P NMR [^{1}H] δ 5.84 (d, $^2J_{P-F}$ = 65.3 Hz); MS *m/z* 313 (100, MH$^+$). Anal. Calcd for $C_9H_{14}FN_2O_5PS$ (312.26): C, 34.62; H, 4.52; N, 8.97. Found: C, 35.01; H, 4.75; N, 8.84.

Diethyl 1-Fluoro-1-(pyrimidin-2-ylsulfonyl)ethylphosphonate (3b). Treatment of **2b** (308 mg, 1.0 mmol) with KH (1.3 mmol; 15 min at ∼0 °C and 30 min at ambient temperature) and Selectfluor (1.5 mmol; 1.5 h) by procedure C (chromatography: EtOAc → 4% MeOH/EtOAc) gave **3b** (260 mg, 80%; viscous oil): ^{1}H NMR δ 1.32 (dt, J = 2.5, 7.4 Hz, 6H), 2.08 (dd, J = 12.9, 23.8 Hz, 3H), 4.20−4.38 (m, 4H), 7.63 (t, J = 4.8 Hz, 1H), 9.01 (d, J = 4.8 Hz, 2H); ^{13}C NMR 6 16.7 (d, J = 5.6 Hz), 17.6 (d, J = 20.0 Hz), 65.4 and 65.8 (d, J = 6.7 Hz), 106.8 (dd, 11 $^1J_{C-F}$ = 230.0 Hz, $^1J_{C-P}$ = 167.8 Hz), 124.8, 159.1, 163.9; ^{19}F NMR δ −160.60 (dq, $^2J_{F-P}$= 77.2 Hz, $^3J_{F-H}$ = 23.8 Hz); ^{31}P NMR δ 9.58 (dm, $^2J_{P-F}$ = −77.8 Hz); MS *m/z* 327 (100, MH$^+$). Anal. Calcd for $C_{10}H_{16}FN_2O_5PS$ (326.28): C, 36.81; H, 4.94; N, 8.59. Found: C, 36.45; H, 5.24; N, 8.16.

Diethyl Fluoromethylphosphonate (4a). Procedure D. Argon was bubbled through a solution of **3a** (156 mg, 0.5 mmol) in benzene or toluene (3.0 mL) in a two-necked flask for 15 min, and Bu_3SnH (0.20 mL, 218 mg, 0.75 mmol) was added via syringe through a septum. Deoxygenation was continued for 15 min, AIBN (40 mg, 0.25 mmol) was added in one portion, and the solution was refluxed (benzene) or heated (toluene) at ∼85 °C for 45 min. A new portion of Bu_3SnH (0.067 mL, 73 mg, 0.25 mmol) and AIBN (24 mg, 0.15 mmol) in benzene or toluene (0.25 mL) were added via syringe, and the reflux (benzene) or heating (toluene) was continued for 75 min [additional AIBN (16 mg, 0.1 mmol) was added after 90 min]. The volatiles were evaporated, and the residue was column chromatographed (5 → 40% EtOAc/hexane) to give **4a** (38 mg, 45%) with data as reported.[3c,9b]

In a modification of procedure D, AIBN (0.125 mmol, 0.25 equiv) was added in one portion at the beginning of the reaction, and the remaining amount of AIBN (0.375 mmol, 0.75 equiv) dissolved in benzene or toluene (0.5 mL) was dispensed using a precision syringe pump over a period of 90 min (15 → 105 min of the reaction time).

To facilitate purification from tin species, the residue before chromatography was dissolved (EtOAc, 5 mL), and the resulting solution was stirred overnight with KF/H_2O (50 mg/0.5 mL). The organic layer was separated, washed (H_2O), dried ($MgSO_4$), and chromatographed.

Treatment of **3a** (78 mg, 0.25 nmmol) by procedure E gave **4a** (39 mg, 91%).

Diethyl 1-Fluoroethylphosphonate (4b). Procedure E. N_2 was bubbled through a solution of **3b** (117 mg, 0.36 mmol), Bu_3SnC1 (18 mg, 0,015 mL, 0.054 mmol), and AIBN (14 mg, 0.09 mmol) in toluene (3 mL) for 15 min. The solution was heated at reflux for 3 h, and PMHS (0.15 mL) and KF [42 mg (0.72 mmol) in H_2O (0.3 mL)] were added in three equal portions immediately after the boiling point was reached and after 1 and 2 h. Three extra portions of AIBN (14 mg, 0.09 mmol) in toluene (0.2 mL) were added via syringe after 45 min, 1.5 h, and 2 h. The volatiles were evaporated, and the residue was partitioned (EtOAc//$NaHCO_3/H_2O$). The organic layer was washed (brine), dried ($MgSO_4$), evaporated, and chromatographed (70 → 20% hexane/EtOAc) to give **4b** (54 mg, 82%) with data as reported:[9b,29] ^{19}F NMR δ −202.38 (ddq, $^2J_{F-P}$ = 76.0 Hz, $^2J_{F-H}$ = 46.8 Hz, $^3J_{F-H}$ = 24.4 Hz); ^{31}P NMR [^{1}H] δ 19.87 (d, $^2J_{P-F}$ = 75.4 Hz); ^{31}P NMR δ 19.87 (dm, $^2J_{P-F}$ = 75.2 Hz, J = 7.2 Hz); MS m/z 185 (100, MH$^+$).

Treatment of **3b** (0.25 mmol) with Bu_3SnH (0.625 mmol)/AIBN (0.5 mmol) by procedure D (3 h, toluene; 0.1 mmol of AIBN was added every 30 min) also gave **4b** (28 mg, 61%).

Analogous treatment of **9b** (81 mg, 0.25 mmol) by procedure D [26 h, benzene; Bu_3SnH (0.75 mmol), AIBN (0.5 mmol)] gave **4b** (22 mg, 48%). The crude reaction mixture in addition to the signals from **4b** (∼57%; ^{19}F and ^{31}P NMR) and **9b** (∼4%) showed peaks for an unidentified byproduct (∼39%): ^{1}H NMR δ 4.59 (dqd, J = 48.5, 7.7, 1.6 Hz); ^{19}F NMR δ −197.50 (ddq, J = 75.9, 48.2, 25.0 Hz); ^{31}P NMR [^{1}H] δ 8.33 (br d, J = 74.4 Hz). This byproduct was extracted to the aqueous layer upon partitioning of the reaction mixture between $NaHCO_3/D_2O$//$CDCl_3$.

Diethyl 1-Deuterio-l-fluoroethylphosphonate (4b-*1*-^{2}H). Treatment of **3b** (0.25 mmol) with Bu_3SnD (0.75 mmol)/AIBN (0.5 mmol) by procedure D gave **4b**-1-^{2}H (27 mg, 58%) and unchanged **3b** (21 mg, 26%). The ^{1}H NMR data for **4b**-1-^{2}H corresponded to those of **4b**[9b,29] except for traces of signals (∼5%) at δ 4.87 (dqd, J = 46.2, 7.0, 1.8 Hz, 1-CHF) and simplification of the signal at δ 1.60 (dd, J = 16.6, 24.0 Hz, 2-CH_3). Other data for **4b**-1-^{2}H: ^{19}F NMR δ −202.88 (dqt, $^2J_{F-P}$ = 76.2 Hz, $^3J_{F-H}$ = 24.1 Hz, $^2J_{F-D}$ = 7.1 Hz); ^{31}P NMR δ 19.84 (d, $^2J_{P-F}$ = 75.2 Hz); MS m/z 186 (100, MH$^+$).

Fluoro(phenyl)methylphosphophonic Acid (5c). (a) Desulfonylation. Treatment of **3c** (150 mg, 0.36 mmol) by procedure E (chromatography: $CHCl_3$) gave diisopropyl fluoro(phenyl)methylphosphonate (**4c**; 93 mg, 94%): ^{1}H NMR δ 1.18−1.36 (m, 12H), 4.75 (septet, J = 6.4 Hz, 2H), 5.65 (dd, J = 44.8, 7.9 Hz, 1H), 7.36−7.52 (m, 5H); ^{19}F NMR δ −201.09 (dd, $^2J_{F-P}$ = 86.0 Hz, $^2J_{F-H}$ = 44.5 Hz); ^{31}P NMR δ 14.67 (dq, $^2J_{P-F}$ = 85.2 Hz, J = 6.4 Hz); MS m/z 275 (100, MH$^+$).

(b) Deprotection. Trimethylsilyl bromide (0.1 mL, 120 mg, 0.8 13 mmol) was added to a stirred solution of **4c** (28 mg, 0.1 mmol) in dried CH_2Cl_2 (2 mL) under N_2 at ambient temperature. After 3 days, the reaction mixture was evaporated, coevaporated with MeOH (5×) and flash chromatographed (50% *i*-PrOH/25% CH_3CN/25% 50 mM NH_4HCO_3)[5a] to give pure **5c** (14 mg, 75%) with data as reported.[4c]

Treatment of **3c** (0.25 mmol) by procedure D [AIBN (0.1 mmol, total); column chromatography, $CHCl_3$] gave **4c** (55 mg, 80%).

Treatment of **9c** (41 mg, 0.1 mmol) by procedure D [30 h; Bu_3SnH (2.5 equiv) and AIBN (2.5 equiv added portionwise 8×)] gave a crude mixture (∼50:50; ^{19}F and ^{31}P NMR) of unchanged **9c** and **4c**. This material was stirred with KF/H_2O//EtOAc (24 h) and was column chromatographed (40% → 50% EtOAc/hexane) to give **4c** (11 mg, 40%).

Treatment of **9c** (41 mg, 0.1 mmol) by procedure E (12 h) also gave **4c** (20 mg, 73%).

Diethyl Ethylphosphonate (6b). Treatment of **2b** (46 mg, 0.15 mmol) with Bu_3SnH (0.3 mmol)/AIBN (0.225 mmol) by procedure D (4 h) gave **6b** (14 mg, 56%) with data as reported:[26a] ^{1}H NMR (selected signals) δ 1.15 (dt, J = 19.9, 7.7 Hz, 3H, 2-CH_3), 1.79 (dq, J = 18.5, 7.7 Hz, 2H, 1-CH_2); ^{31}P NMR [^{1}H] δ 34.57 (s); MS m/z 167 (100, MH$^+$). The ^{31}P NMR [^{1}H] spectrum of the crude reaction mixture showed singlets for **6b** (0.52P), unchanged **2b** (0.09P), and an unidentified byproduct at δ 24.9 (0.39P). This byproduct was extracted to the aqueous layer upon partitioning of the reaction mixture between $D_2O/CDCl_3$.

Treatment of **2b** (0.25 mmol) by procedure E gave **6b** (25 mg, 60%).

Analogous treatment of **7b** (46 mg, 0.15 mmol) by procedure D [48 h, benzene; Bu_3SnH (0.6 mmol), AIBN (0.30 mmol)] gave **6b** (8 mg, 32%). ^{31}P NMR (crude) showed peaks for **6b** (0.35P), unchanged **7b** (0.60P), and an unknown byproduct at δ 10.21 (0.05P).

Diethyl 1-Deuterioethylphosphonate (6b-*1*-^{2}H). Treatment of **2b** (31 mg, 0.1 mmol) with Bu_3SnD (0.3 mmol)/AIBN (0.25 mmol) by procedure D gave **6b**-1-^{2}H (28 mg, 67%). The ^{1}H NMR spectra corresponded to those of **6b** with a 50% reduction in the intensity of the signal at δ 1.79 (m, 1H, 1-CHD) and simplification of the signal at δ 1.15 (dd, J = 19.8, 7.5 Hz, 3H, 2-CH_3). Other data for **6b**-1-^{2}H: MS m/z 168 (100, MH$^+$).[14]

Diethyl 1-(Pyrimidin-2-ylsulfonyl)hex-5-enylphosphonate (12). NaH (51 mg, 50%/mineral oil, 1.06 mmol) was washed (dried Et_2O) and suspended in dried DMF (10 mL) under N_2. Compound **2a** (250 mg, 0.85 mmol) was added, and the resulting solution was stirred at ambient temperature for 30 min. 5-Bromo-1-pentene (0.2 mL, 253 mg, 1.7 mmol) was added (syringe), and after being stirred for 4 h, the mixture was heated for 48 h at ∼45 °C. The volatiles were evaporated, and the residue was partitioned (EtOAc//NH_4Cl/H_2O). The organic layer was washed ($NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed (10% hexanes/EtOAc → EtOAc → 5% MeOH/EtOAc) to give **12** (185 mg, 60%) as a syrup: ^{1}H NMR δ 1.28 ("q", J = 7.0 Hz, 6H), 1.71−1.90 (m, 2H), 2.10−2.22 (m, 3H), 2.32−2.47 (m, 1H), 4.06−4.25 (m, 4H), 4.51 (ddd, J = 17.2, 7.7, 5.1 Hz, 1H), 5.02 (dm, J = 10.2 Hz, 1H), 5.07 (dq, J = 16.5, 1.5 Hz, 1H), 5.77−5.87 (m, 1H), 7.56 (t, J = 4.9 Hz, 1H), 8.97 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 16.7 ("t", J = 5.9 Hz), 23.2 (d, J = 3.9 Hz), 27.7 (d, J = 3.9 Hz), 33.7, 57.8 (d, J = 139.5 Hz), 63.2 and 64.7 (d, J = 6.3 Hz), 115.9, 123.9, 137.9, 158.8, 166.5; ^{31}P NMR δ 17.07 (m); MS m/z 363 (100, MH$^+$). Anal. Calcd for $C_{14}H_{23}N_2O_5PS$ (362.38): C, 46.40; H, 6.40; N, 7.73. Found: C, 46.25; H, 6.54; N, 7.33.

Diethyl 1-Fluoro-l-(pyrimidin-2-ylsulfonyl)hex-5-enylphosphonate (13). Treatment of **12** (100 mg, 0.28 mmol) with KH (0.35 mmol; 10 min at ∼0 °C and 40 min at ambient temperature) and Selectfluor (147 mg, 0.41 mmol; 4 h) by procedure C (chromatography: 20% hexane/EtOAc → EtOAc → 4% MeOH/EtOAc) gave **13** (58 mg, 55%; viscous oil) and recovered **12** (20 mg, 20%). Data for **13**: ^{1}H NMR δ 1.32 ("q", J = 6.9 Hz, 6H), 1.76−1.94 (m, 2H), 2.09−2.17 (m, 2H), 2.32−2.52 (m, 2H), 4.19 ("quint", J = 7.1 Hz, 2H), 4.26 ("quint", J = 7.2 Hz, 2H), 4.98 (dm, J = 11.2 Hz, 1H), 5.03 (dm, J = 17.1, 1;5 Hz, 1H), 5.70−5.80 (m, 1H), 7.60 (t, J = 4.8 Hz, 1H), 8.98 (d, J = 4.8 Hz, 2H); ^{13}C NMR δ 16.7 (d, J = 5.6 Hz), 22.2 ("t", J = 3.9 Hz), 30.3 (d, J = 19.1 Hz), 34.0, 65.3, and 65.7 (d, J = 6.5 Hz), 108.9 (dd, $^1J_{C-P}$ = 166.3 Hz, $^1J_{C-F}$ = 234.0 Hz), 116.1, 124.6, 137.7, 159.0, 164.7; ^{19}F NMR δ −166.62 (ddd, $^2J_{F-P}$ = 81.0 Hz, $^1J_{F-H}$ = 27.0, 17.0 Hz); ^{31}P NMR δ 9.75 (dm, $^2J_{P-F}$ = 81.5 Hz, J = 9.0 Hz); MS m/z 381 (100 MH$^+$). Anal. Calcd for $C_{14}H_{22}FN_2O_5PS$ (380.37): C, 44.21; H, 5.83; N, 7.36. Found: C, 43.89; H, 5.96; N, 6.98.

Diethyl 1-Bromohex-5-enylphosphonate (16). A solution of *i*-Pr_2NH (3.05 mL, 2.2 g, 21.8 mmol) in dried THF (18 mL) was slowly added via syringe under N_2 to a solution of BuLi (1.6 M/hexane; 13.1 mL, 20.7 mmol) in THF (18 mL) at −78 °C. After 15 min, compound **15**[30] (2.0 g, 9.0 mmol; prepared in 85% yield by alkylation of the anion of diethyl methylphosphonate with 5-bromo-1-pentene[30]) in THF (18 mL) was added dropwise, and stirring was continued for 10 min. Me_3SiCl (1.27 mL, 1.09 g, 10 mmol) in dried THF (18 mL) was added, and the mixture was allowed to warm slowly to 0 °C, and then was cooled again to −78 °C. 1,2-Dibromotetrachoroethane (3.3 g, 10 mmol) in THF (18 mL) was added. The resulting solution was allowed to warm to 0 °C (∼15 min), and EtOLi/EtOH (1 M, 18 mL) was added. After 30 min, the mixture was poured with rapid stirring into a mixture of HCl (2 M, 14 mL)/CH_2Cl_2 (14 mL)/crushed ice, and then was extracted (CH_2Cl_2). The combined organic layer was washed ($NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and column chromatographed (10% → 40% EtOAc/hexane) to give **16** (2.1 g, 78%): ^{1}H NMR δ 1.32 (t, J = 7.0 Hz, 6H), 1.45−2.13 (m, 6H), 3.81 (dt, J = 3.2, 10.6 Hz, 1H), 4.21 ("sextet", J = 7.0 Hz, 4H), 4.98 (dm, J = 10.6 Hz, 1H), 5.03 (dm, J = 17.2 Hz, 1H), 5.79 (ddt, J = 17.0, 10.3, 6.7, 1H); ^{13}C NMR δ 16.82 and 16.84 (d, J = 5.9 Hz), 27.3 (d, J = 12.4 Hz), 32.1, 33.1, 42.5 (d, J = 157.9 Hz), 63.8 and 64.1 (d, J = 6.9 Hz), 115.7, 138.2; ^{31}P NMR [^{1}H] δ 21.40 (s); MS m/z 301 (98, $MH^+[^{81}Br]$), 299 (100, $MH^+[^{79}Br]$). Anal. Calcd for $C_{10}H_{20}BrO_3P$ (299.14): C, 40.15; H, 6.74. Found: C, 40.34; H, 7.10.

Diethyl Hex-5-enylphosphonate (15) and Diethyl 2-methylcyclpentylphosphonates (18). Reaction of 12 with Bu_3SnH. Treatment of **12** (72 mg, 0.2 mmol) by procedure D [7 h, benzene; Bu_3SnH (0.5 mmol)/AIBN (0.3 mmol) added portionwise] gave a mixture that was analyzed by ^{31}P NMR [^{1}H]: δ 36.45 (s, 0.36P; *cis*-**18**), 34.70 (s, 0.18P; *trans*-**18**), 34.25 (s, 0.06P), 33.74 (s, 0.21 P; **15**), 24.67 (s, 0.06P), 17.65 (s, 0.13P; **12**). This material was partitioned ($NaHCO_3/D_2O$//CDCI3), and the organic layer was evaporated and the residue chromatographed (hexane → 30% hexane/EtOAc) to give a colorless oil (31 mg): ^{31}P NMR [^{1}H] δ 36.45 (s, 0.51P), 34.70 (s, 0.21P), 34.25 (s, 0.07P), 33.74 (s, 16 0.21P). RP-HPLC/MS (MeOH/H_2O, 1:1; 1.0 mL/min) of this material showed three fractions at t_R = 6.68 (8%), 7.03 (85%), and 7.52 (7%) min, with all fractions having molecular ions at m/z 221 (100, MH^+) corresponding to the molecular mass of **15** and/or corresponding cyclic products. RP-HPLC (preparative column: MeOH/H_2O, 1:1; 2.5 mL/min) gave *trans*-**18**[28] (5 mg, 11%; t_R = 53 min), *cis*-**18**[28] (6 mg, 14%; t_R = 57 min), and **15**[30] (5 mg, 11%; t_R = 63 min). Compound **15** had data as reported:[30] ^{13}C NMR δ 16.79 (d, J = 5.9 Hz), 22.21 (d, J = 5.1 Hz), 25.83 (d, J = 140.6 Hz), 30.07 (d, J = 16.8 Hz), 33.52, 61.69 (d, J = 6.3 Hz), 115.13, 138.51; ^{31}P NMR [^{1}H] δ 33.65 (s); MS m/z 221 (100, MH^+).

Data for *cis*-**18**:[28,36] ^{1}H NMR δ 1.14 (d, J = 6.6 Hz, 3H), 1.34 ("dt", J = 1.1, 7.0 Hz, 6H), 1.62−1.98 (m, 7H), 2.15−2.28 (m. 1H), 4.08−4.16 (m, 4H); ^{13}C NMR δ 16.93 ("dd", J = 1.5, 5.9 Hz), 21.28 (d, J = 3.5 Hz), 25.65 (d, J = 11.0 Hz), 28.16 (d, J = 2.0 Hz), 36.29 (d, J = 2.4 Hz), 36.42, 42.94 (d, J = 143.9 Hz), 61.77 and 61.98 (d, J = 6.8 Hz); ^{31}P NMR [^{1}H] δ 36.45 (s); MS m/z 221 (100, MH^+).

Data for *trans*-**18**:[28,36] ^{1}H NMR δ 1.10 (d, J = 6.6 Hz, 3H), 1.33 ("dt", J = 1.5, 7.0 Hz, 6H), 1.58−1.97 (m, 7H), 2.30−2.41 (m. 1H), 4.03−4.14 (m, 4H); ^{13}C NMR δ 16.93 ("dd", J − 1.3, 6.1 Hz), 17.58 (d, J = 5.2 Hz), 24.03 (d, J = 14.6 Hz), 25.77, 35.21 (d, J = 14.4 Hz), 35.93, 40.38 (d, J = 143.1 Hz), 61.54 ("t", J = 6.9 Hz); ^{31}P NMR [^{1}H] δ 34.63 (s); MS m/z 221 (100, MH^+).

Reaction of 16 with Bu_3SnH. Treatment (30 min) of **16** (200 mg, 0.67 mmol) with Bu_3SnH (1.2 equiv)/AIBN (0.10 eqiuv) gave a mixture that was analyzed by ^{31}P NMR [^{1}H]: δ 36.08 (s, 0.35P; *cis*-**18**), 34.30 (s, 0.17P; *trans*-**18**), 33.37 (s, 31P; **15**), 21.57 (s, 0.12P; **16**) in addition to minor peaks at δ 36.84 (s, 0.02P) and 33.89 (s, 0.03P) (average values of the three experiments). Chromatography (hexane → 30% hexane/EtOAc) and RP-HPLC (preparative column: MeOH/H_2O, 1:1; 2.5 mL/min) gave *trans*-**18** (15 mg, 10%), *cis*-**18** (21 mg, 14%), and **15** (21 mg, 14%) with data as above and/or reported.[28,30,36]

Diethyl 1-Fluoro-2-methylcyclopentylphosphonates (19). Reaction of 13 with Bu_3SnH. Treatment of **13** (57 mg, 0.15 mmol) with Bu_3SnH (0.45 mmol)/AIBN (0.3 mmol) by procedure D (8 h, benzene) gave a mixture that was analyzed by ^{31}P NMR [^{1}H]: δ 21.43 (d, $^2J_{P-F}$ = 95.0 Hz, 0.30P; *cis*-**19**), 20.08 (d, J = 93.1 Hz, 0.23P; *trans*-**19**), 9.72 (d, J = 81.4 Hz, 0.16P, **13)** in addition to minor peaks at δ 21.11 (d, 0.04P), 19.10 (d, 0.07P), 16.42 (d, 0.08P), 1.12 (d, 0.06P), and −7.35 (s, 0.06P). The reaction mixture was partitioned ($NaHCO_3$/D_2O//$CDCl_3$), and the organic layer was evaporated and the residue chromatographed (hexane → 30% hexane/EtOAc) to give a colorless oil (~21 mg; *cis*/*trans*-**19**, ~90% pure on the basis of ^{19}F and ^{31}P NMR). RP-HPLC/MS (MeOH/H_2O, 1:1; 1 mL/min) of this material showed fractions at t_R = 6.58 and 7.08 min having molecular ions at m/z 239 (100, MH^+) corresponding to the molecular mass of **17** and/or corresponding cyclic products. RP-HPLC (preparative column: MeOH/H_2O, 1:1; 2.5 mL/min) gave *trans*-**19** (4 mg, 11%; t_R = 52−58 min) and *cis*-**19** (6 mg, 17%; t_R = 66−74 min).

Data for *cis*-**19** (1*S*,2*R*): ^{1}H NMR δ 1.16 (d, J = 6.9 Hz, 3H), 1.37 (t, J = 7.0 Hz, 6H), 1.50−2.39 (m, 7H), 4.30 ("quint", J = 7.11 Hz, 4H); ^{13}C NMR δ 13.34 (d, J = 8.5 Hz), 16.93 ("dd", J = 3.2, 5.5 Hz), 22.59 (d, J = 12.1 Hz), 33.18 (d, J = 14.3 Hz), 36.45 (dd, J = 7.7, 21.5 Hz), 41.37 (dd, J = 7.0, 20.4 Hz), 63.26 and 63.37 (d, J = 7.1 Hz), 103.08 (dd, J = 177.0, 188.5 Hz); ^{19}F NMR δ −183.42 (ddt, $^2J_{F-P}$ = 95.0 Hz, $^3J_{F-H}(trans)$ = 35.0 Hz, $^3J_{F-H}(cis)$ = 30.0 Hz); ^{31}P NMR [^{1}H] δ 21.78 (d, $^2J_{P-F}$ = 95.1 Hz); MS (APCI) m/z 239 (100, MH^+).

Data for *trans*-**19** (1*R*,2*R*): ^{1}H NMR δ 1.12 (d, J = 7.3 Hz, 3H), 1.38 (t, J = 7.1 Hz, 6H), 1.38−1.48 (m, 1H), 1.82 ("quint", J = 8.3 Hz, 2H), 2.02−2.12 (m, 2H), 2.25 (dm, J = 41.1 Hz, 1H), 2.47 (dm, J = 24.3 Hz, 1H), 4.30 ("sextet", J = 7.2 Hz, 4H); ^{13}C NMR δ 16.92 ("dd", J = 1.8, 6.2 Hz), 17.16 (d, J = 8.7 Hz), 21.74 (d, J = 12.9 Hz), 32.75 (d, J = 11.4 Hz), 33.62 (dd, J = 7.3, 21.2 Hz), 43.64 (dd, J = 7.7, 21.4 Hz), 63.03 and 63.32 (d, J = 7.0 Hz), 105.92 ("t", J = 178.7 Hz); ^{19}F NMR δ −157.34 (ddt, $^2J_{F-P}$ = 92.0 Hz, $^2J_{F-H}(cis)$ = 41.0 Hz, $^3J_{F-H(trans)}$ = 24.5 Hz); ^{31}P NMR [^{1}H] δ 20.56 (d, $^2J_{P-F}$ = 93.4 Hz); MS (APCI) m/z 239 (100, MH^+). Anal. Calcd for $C_{10}H_{20}FO_3P$ (238.24): C, 50.42; H, 8.46. Found: C, 50.79; H, 8.79.

Acknowledgment. This work was partially supported by an award from the American Heart Association, Florida/Puerto Rico Affillate. L.A.B. and P.I.G. were sponsored by the MBRS RISE program (NIH/NIGMS; Grant R25 GM61347). We thank Alberto J. Sabucedo (Advanced Mass Spectroscopy Facility at Florida International University) and Ya-Li Hsu for performing HPLC/MS and GC/MS analyses and Professor Morris J. Robins for a critical reading of the manuscript.

Supporting Information Available: Experimental procedures and characterization data for compounds **2c,d**, **3c,d**, **4d**, **5d**, **6c,d**, **7b,c**, **8c**, **9b,c**, **10c**, **11**, and **25**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0111560

(36) Kim, D. Y.; Suh, K. K. *Synth. Commun.* **1998**, *28*, 83−91.