Methods for the Stereoselective Synthesis of 2-Fluoroalkenoates. Carbonyl Condensation Reactions of 3,3-Bis(methylthio)-2-fluoropropenal, a Highly-Functionalized Fluoroacrylate Cation Equivalent†

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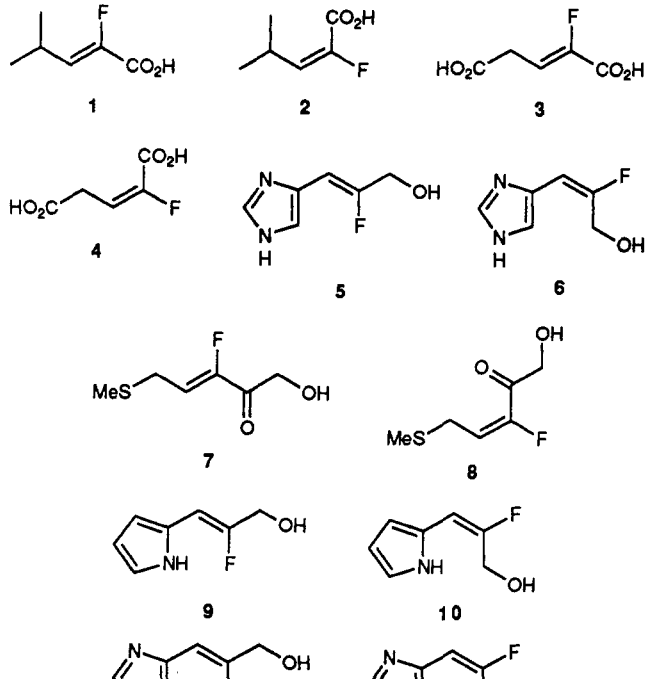
New methodology for the preparation of 2-fluoroacrylates has been developed on the basis of the reagent 3,3-bis(methylthio)-2-fluoropropenal. This highly-functionalized aldehyde is prepared by the condensation of carbon disulfide with fluoroacetonitrile followed by reduction of the nitrile. It is subjected to nucleophilic addition with organometallic reagents and enolates to yield allylic alcohol products that can be rearranged under acidic conditions to (*Z*)-2-fluoroacrylate thioesters. Other desired fluoroacrylates are also available via conventional fluorinated Horner–Wadsworth–Emmons or Reformatsky reagents.

Enols[1] are pervasive intermediates in biochemical transformation.[2] Biosynthetic pathways for seven of the genetically-coded amino acids[3] (Ile, Val, Leu, Glu, Gln, His, and Met) include transiently-generated enols that tautomerize to ketones that are then transaminated (Figure 1). Because of an interest in developing stereochemical probes and inhibitors for such enzymes, we have sought chemically-stable enol mimics and have previously reported the synthesis and properties of vinyl fluoride analogs of the enols in valine and isoleucine biosynthesis.[4] For the preparation of vinyl fluorides **1-8**, which are cognate to the other enols in Figure 1, and of **9-12**, heteroaromatic analogs of **5** and **6**, a conventional approach involving fluorinated Horner–Wadsworth–Emmons[5] or Reformatsky[6] reagents as fluoroacetate anion synthons (eq 1) was pursued. We were successful in preparing some of the desired targets; in other cases, decomposition occurred in attempted condensations with the aldehydes, stereoisomeric mixtures were produced, or particular stereoisomers were unavailable. Consequently, we have developed a new reagent that serves as a fluoroacrylate cation equivalent (eq 1) and has provided access to materials that could not be prepared via the aldehydes.

Results

Conventional Olefination—Successes and Failures. Literature precedents suggested that the fluorinated phosphonate and Reformatsky reagents would provide access to the (*E*) and (*Z*) stereoisomers, respectively, of fluoroacrylates which either are themselves desired as inhibitors (**1-4**) or serve as precursors to alcohol inhibitors (**5-12**). With isobutyraldehyde and pyrrolecarboxaldehyde, this proved to be the case. Compounds **1** and **2** werepreprared stereospecifically, while the fluoroacrylate precursors to **9** and **10** were produced as a readily-separated 3:1 mixture via the phosphonate reagent, as described in the supplementary material. The aldehydes required to prepare the other targets are not commercially available. However, *N*-tritylimidazole-4-carboxaldehyde (precursor



† Dedicated to Prof. William S. Johnson, Stanford University.

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(1) Chiang, Y.; Kresge, A. J. *Science* **1991**, *253*, 395-400. Hart, H. *Chem. Rev.* **1979**, *79*, 515-528.

(2) Richard, J. P. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley-Interscience: New York, 1990; Chapter 11.

(3) For Met: Myers, R. W.; Abeles, R. H. *J. Biol. Chem.* **1990**, *265*, 16913-16921. Furfine, E. S.; Abeles, R. H. *Ibid.* **1988**,*263*, 9598-9606. For Leu: Kohlhaw, G. B. *Methods Enzymol.* **1988**, *103*, 429. For Glu and Gln: Goldberg, D. M.; Ellis, G. *Methods Enz. Anal.* **1983**, *3*, 183. Plaut, G. *Enzymes* **1963**, 7, 112. For His: Miflin, B. J. In *The Biochemistry of Plants*; Academic Press: New York, 1980; Vol. V, Chapter 14. Martin, R. G.; Berberich, M. A.; Ames, B. N.; Davis, W. W.; Goldberger, R. F.; Yourno, J. D. *Methods Enzymol.* **1971**,*17B*, 3-44.

(4) Pirrung, M. C.; Ha, H.-J.; Holmes, C. P. *J. Org. Chem.* **1989**, *54*, 1543. Pirrung, M. C.; Holmes, C. P.; Horowitz, D. M.; Nunn, D. S. *J. Am. Chem. Soc.* **1991**, *113*, 1020.

(5) Etemad-Moghadam, G.; Seyden-Penne, *J. Bull. Soc. Chim. Fr.* **1985**, *3*, 448.

(6) Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145.

(7) Kelley, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721. Tomko, R.; Overberger, C. G.; *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 265.

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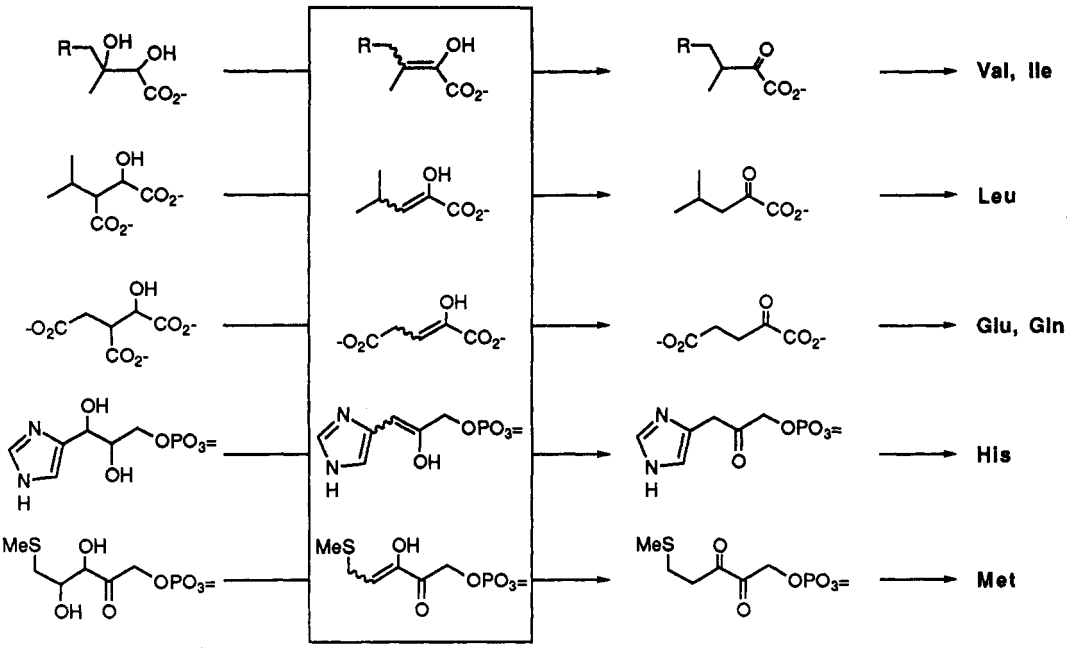
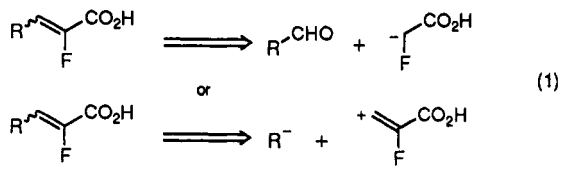


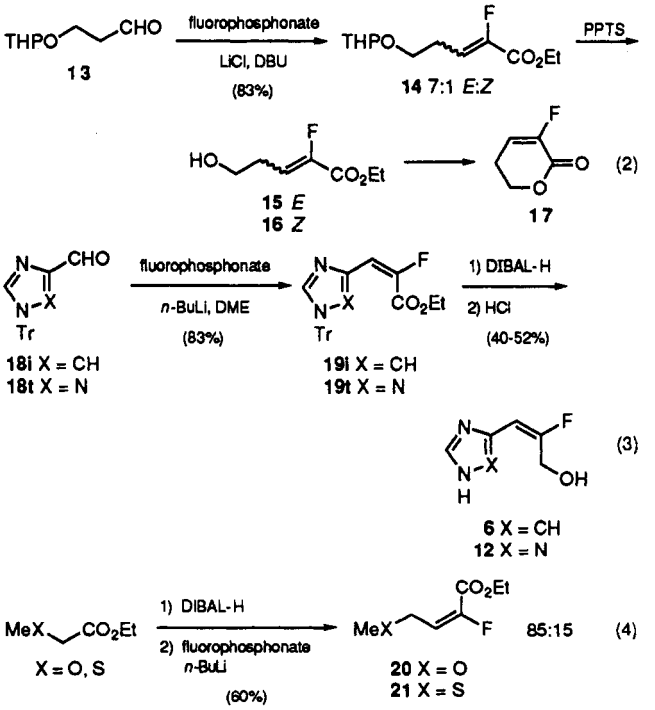
Figure 1.

to 5 and 6) and 1-*N*-trityltriazole-3-carboxaldehyde (precursor to 11 and 12) can be prepared by known routes.[7] Recognizing that formylacetate would be unsuitable in carbonyl addition reactions owing to its acidity, we chose a synthetic equivalent, 3-(tetrahydropyranyloxy)propanal (13),[8] based on the assumption that subsequent deprotection/oxidation would provide 3 and 4. As precursor to 7 and 8, methylthioacetaldehyde was deemed unattractive because of its expected volatility, stench, and tendency to hydrate and polymerize. However, using the procedure of Burton,[9] it was possible to generate the aldehyde *in situ* via reduction of ethyl (methylthio)acetate with DIBAL-H and condense it with the phosphonate. Likewise, this protocol was used with ethyl methoxyacetate to produce the oxygen analog.



(1)

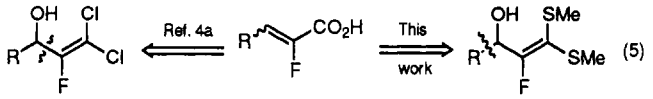
Carbonyl condensation processes of the aldehydes showed mixed results. For example, under the Roush–Masamune condensation conditions,[10] compound 13 produces a 7:1 mixture of adducts that can be readily rectified after acidic deprotection. Structures were assigned by lactonization (eq 2). Alcohols 15 and 16 are readily oxidized by Jones' reagent and esterified with diazomethane to provide the fluoroacrylates, but in the course of base-promoted hydrolysis, the stereochemistry is completely scrambled to the more stable (*Z*) isomer. This problem is undoubtedly related to the known stereochemical lability of glutaconate esters due to their vinylogous malonate character and the resulting opportunity for base-catalyzed alkene isomerization. While the phosphonate does condense with 18i to produce exclusively the (*E*) fluoroacrylate (eq 3), attempted application of the Reformatsky reagent to 18i leads to decomposition; thus, the (*Z*) isomer is unavailable. Likewise, the reaction of 18t with the phosphonate produces only the (*E*) isomer. With the heteroatom-substituted acetaldehydes, the phosphonate produces a mixture of isomers (eq 4).

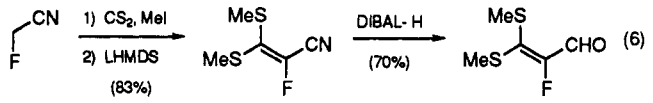


A Fluoroacrylate Cation Equivalent. Because of the foregoing difficulties, it was necessary to develop a new route to the target fluoroacrylate structures. A major consideration was the use of a readily-available fluorinated compound, since the introduction of fluorine into organic compounds under either electrophilic or nucleophilic conditions can be problematic. Fluoroacetate anion

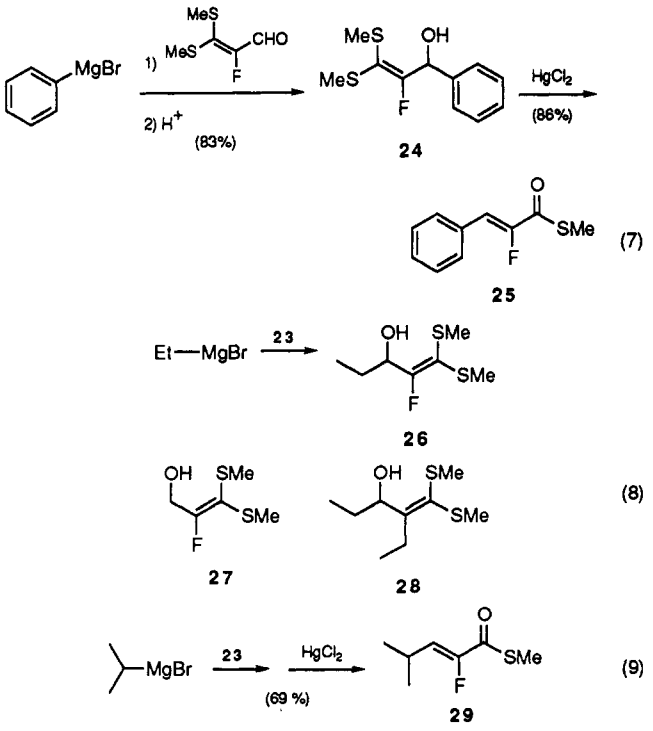
(8) Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *J. Chem. Soc., Perkin Trans. I* **1984**, 1237–1240.
(9) Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639.
(10) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

equivalents that were used above met this test, as did (fluorodichlorovinyl)lithium that had been used in our earlier work (eq 5).[4] We had also prepared benzyl fluoroacrylate[11] as a precursor to the vinyl fluoride enol pyruvate equivalent fluoroacrylic acid and considered using it as a fluoroacrylate cation synthon via Heck reactions but instead focused on a carbanionic process. Our target was a molecule with the same oxidation state at each carbon as the addition products generated from (fluorodichlorovinyl)lithium, but it was to be obtained by nucleophilic addition to a fluorinated aldehyde (eq 5). Solvolysis with allylic transposition would generate the acid oxidation state at C-1 and leave the fluorine at C-2 of the 3-carbon synthon.





The reports of Dieter[12] on the use of ketene dithioacetals (generated from active methylene compounds) to mask carboxylic acids during nucleophilic addition reactions to adjacent carbonyls suggested the unification of this methodology with the commercially-available fluoroacetonitrile. The condensation of this compound with carbon disulfide and methyl iodide is successful only if the carbanion is generated in the presence of the electrophile; otherwise, immediate generation of a dark color and polymeric compounds ensues. The desired product, the densely functionalized **22**, is reduced by DIBAL to provide the fluoroacrylate cation synthon 3,3-bis(methylthio)-2-fluoropropenal (**23**, eq 6).



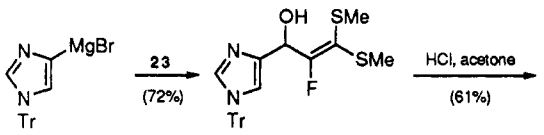
Condensations of **23** with organometallic reagents were first examined. Phenylmagnesium bromide provides the expected 1,2-adduct **24** in 83% yield (eq 7). Superior conditions for the allylic rearrangement were mercuric chloride in acetonitrile/water as described by Dieter, which produce **25** in 86% yield and 100% isomeric purity. An added advantage of the dithioacetal as a carboxyl equivalent is that it provides as product an activated thioester that can be converted to a variety of other carboxyl derivatives. In other experiments focused on Grignard additions, treatment of **23** with ethylmagnesium bromide provides the desired 1,2-adduct **26** only as a minor product (eq 8); two processes intervene to derail the intended reaction. With 2 equiv of Grignard, the allylic alcohols **26** and **28** were produced in the ratio 40:44. Compound **28** is formed as the ketene dithioacetal grouping that had been incorporated as a carboxyl surrogate works as a carbanion-stabilizing force and, in concert with the vinyl fluoride functionality, promotes nucleophilic vinyl substitution ("reverse Michael" addition) after the carbonyl addition process. We suggest that the reduction product **27** formed with 1 equiv of Grignard is the result of an electron-transfer and not a β-hydride transfer reaction, since it is even obtained with organometallic reagents that do not possess β-hydrogen atoms (*vide infra*). The amounts of these products can be influenced by the presence of various additives and the stoichiometries of organometallic reagents, as summarized in Table I. Superior conditions involve 1 equiv of Grignard in the presence of $CeCl_3$,[13] under which **26** can be obtained in 59% yield. Isopropyl Grignard also was added to the aldehyde, providing **29** in 69% overall yield when 1.8 equiv of Grignard is used without additives (eq 9). For the imidazole–fluoroacrylate target, the necessary organometallic reagent was prepared by the procedure of Lindell[14] and added to aldehyde **23**. The adduct was simultaneously detritylated and rearranged in acidic acetone to provide the stereochemically-pure (*Z*) isomer **31** in 61% yield as the hydrochloride salt (eq 10). While the lithiation of triazoles has been reported,[15] the protecting groups for the NH function used in previous work were not compatible with planned transformations of the adduct, so (meth-

Table I. Organometallic Additions to Aldehyde 23

reagent	molar equiv	solvent/ additive	% additn	% reductn	% SM	% double additn
i-PrMgCl	1.3	ether	35	8	15	0
i-PrMgCl	1.8	ether	69	15	0	0
i-PrMgCl	1.3	ether/HMPA	53	4	0	0
i-PrMgCl	1.3	ether/BF_3	trace	trace	trace	0
i-PrMgCl	1.8	ether/HMPA	51	8	trace	0
EtMgBr	1.0	THF	21	63	0	0
EtMgBr	2.0	THF	40	0	0	43
EtMgBr	1.3	THF/HMPA	52	6	0	0
EtMgBr	1.0	THF/$CeCl_3$	59	15	0	trace
MeMgI	1.0	ether	60	0	6	0
MeMgI	2.0	ether	90	0	0	0
PhMgBr	1.1	ether	83	0	6	0
BuLi	1.0	ether	0	0	100	0
BuLi	2.0	ether	50	0	0	50

(11) Nguyen, T.; Wakselman, C. *J. Org. Chem.* **1989**, *54*, 5640.
(12) Dieter, R. K.; Jenkitkasemwong-Lin, Y.; Dieter, J. W. *J. Org. Chem.* **1984**, *49*, 3183. Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029. Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031.
(13) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.
(14) Turner, R. M.; Lindell, S. D.; Ley, S. V. *J. Org. Chem.* **1991**, *56*, 5739.
(15) Anderson, D. K.; Sikorski, J. A.; Reitz, D. B.; Pilla, L. T. *J. Heterocycl. Chem.* **1986**, *23*, 1257.

oxymethyl)triazole was prepared.[16] On metalation with *n*-BuLi at −78 °C for 1.5 h, a 5-triazolyllithium reagent is generated as evidenced by isolation of a piperonal adduct in >70% yield. On treatment with **23**, the expected adduct is produced along with 9% of unreacted aldehyde and the allylic alcohol **27** (14%)derived from reduction of **23** (eq 11). It has not yet been possible to isolate a fluoroacrylate by treatment of **32** under the standard conditions for rearrangement. The convenience of this MOM-triazole makes it an advantageous reagent for the preparation of nucleophilic triazoles and subsequent reaction with electrophiles. Other organometallics studied in reactions with aldehyde **23** include methyl Grignard (Table I) and metalated ethyl propiolate (eq 12),[17] which gives the expected adduct **33** in 53% yield. In summary, reactions of aldehyde **23** with magnesium and lithium reagents to provide an allylic alcohol followed by allylic rearrangement constitute an effective route to fluoroacrylates, with high stereocontrol for the (*Z*) isomer.



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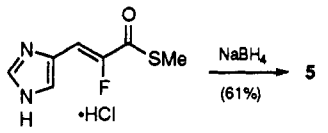

(10)

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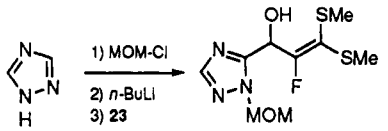

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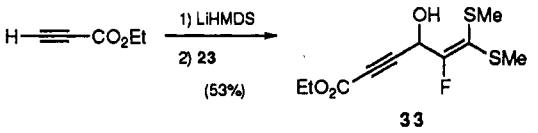
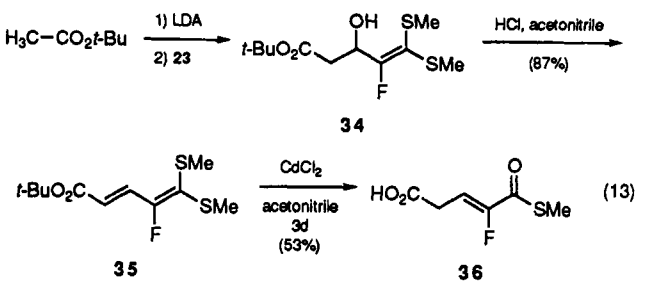


(12)

33

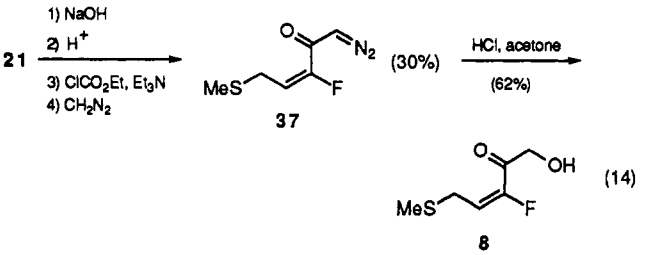
The reactivity of aldehyde **23** with an enolate was also examined as an alternative route to diacids **3** and **4**. Lithium *tert*-butylacetate (eq 13) provides an aldol adduct in excellent yield, but the product **34** is easily dehydrated instead of undergoing allylic rearrangement. Several reagents and conditions (BF_3· ether, trifluoroacetic anhydride, and HgX_2 in both aqueous and organic solvents; rt or reflux) that were studied primarily produce the dienoate. Acetonitrile/HCl proved to be the superior reagent for this elimination step. Compound **35** benefits from an extended conjugated system and thus is much more difficult to hydrolyze than the allylic alcohols. Treatment of **35** with $CdCl_2$/HCl/acetonitrile at reflux for 3 d converts it to the thioester/acid **36**. The exclusive formation of the (*Z*) stereoisomer undoubtedly represents thermodynamic control and, along with removal of the *tert*-butyl ester, is a reflection of the long and vigorous treatment required to hydrolyze the very stable diene **35**.

A final matter that required attention in the preparation of **1-12** is the conversions of fluoroacrylates to the target



(13)

skeletons. To obtain the alcohols, the esters are reduced with DIBAL-H and the thioesters are reduced with $NaBH_4$. The α-hydroxy ketone **8** was generated by conversion to the mixed anhydride and treatment with diazomethane to provide the diazo ketone **37** (eq 14). This material may serve as a direct precursor of the corresponding phosphate monoester, but for these purposes was simply converted to the hydroxy ketone via treatment with HCl/acetone.



(14)

Conclusion. The reagent and methods reported herein provide convenient access to a reactive, fluorinated 3-carbon synthon. They can provide vinyl fluorides that are used in mechanism-based enzyme inhibitors[18] and as peptide bond isosteres.[19] The compounds prepared will be used for enzymatic studies in our and other's laboratories. Of the targets desired, only **4** and **11** remain unavailable.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Dichloromethane, benzene, and triethylamine were distilled from calcium hydride. DMSO, DMF, and HMPA were vacuum distilled from calcium hydride. THF was distilled from sodium benzophenone ketyl. Reactions were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Brine refers to a saturated aqueous solution of sodium chloride. Rotary evaporation refers to the use of a Büchi-Brinkmann R100 Rotavapor at water aspirator pressures. Flash chromatography was performed using EM Reagents 0.042–0.063-mm grade silica gel (Kieselgel 60).

Infrared spectra were recorded on a Bomem MB-100 instrument. Only the largest or most diagnostic lines are reported. NMR spectra were recorded on a GE QE300 instrument. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Melting points were measured on a Haake-Buchler melting point apparatus and are uncorrected.

Ethyl 1′-Trityl-(*E*)-4′-imidazole-2-fluoro-3-acrylate (19i). To a solution of 0.49 g (2.0 mmol) of triethyl 2-fluoro-2-phosphonoacetate in 5 mL of DME at −78 °C was added 1.2 mL of *n*-BuLi (1.6 M in hexane, 1.9 mmol). After the solution was stirred for 30 min, a solution of 0.62 g (1.8 mmol) of 1-trityl-4-imidazolecarboxaldehyde in 10 mL of DME was added dropwise.

(16) Dallacker, F.; Minn, K. *Chem. Zeitung* **1986**, *110*, 101.
(17) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.
(18) McCarthy, J. R.; Jarvi, E. T.; Mathews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127.
(19) Shue, Y.-K.; Tufano, M. D.; Nadazan, A. M. *Tetrahedron Lett.* **1988**, *29*, 4041. Almendinger, T.; Furet, P.; Hungerbuhler, E. *Tetrahedron Lett.* **1990**, *31*, 7297.

The reaction was allowed to warm to room temperature overnight. Brine (1 mL) was added to the reaction mixture, and the volatiles were evaporated. The residue was dissolved in 10 mL of brine and extracted with three 10-mL portions of ether. The ether solutions were dried over $MgSO_4$, filtered, and evaporated to give a yellow solid which was purified by chromatography with 1:1 ether:petroleum ether, giving 0.50 g (65%) of a white solid: mp 128.6–129.9 °C; R_f 0.23 (1:1 ether:petroleum ether); ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.47 (s, 1H), 7.35 (m, 9H), 7.15 (m, 6H), 6.97 (d, J = 24.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.74 (d, J = 34.0 Hz), 44.92 (d, J = 242.6 Hz), 141.98, 138.84, 138.71 (m, J = 131.32, Hz), 129.69 (m, J = 128.12 Hz), 125.75, 117.12 (d, J = 31.5 Hz), 75.81, 61.18, 14.04; IR (KBr) 3198, 1713, 1650 cm^{-1}. Anal. Calcd for $C_{27}H_{23}FN_2O_2$: C, 76.04; H, 5.44; N, 6.57. Found: C, 75.98; H, 5.42; N, 6.59.

(*E*)-2-Fluoro-3-(4′-imidazolyl)-2-propenol (6). A solution of 4.3 g (10 mmol) of **19** in 100 mL of CH_2Cl_2 at 0 °C was treated with 22 mL (1.0 M in CH_2Cl_2, 22 mmol) of DIBAL-H. The reaction was allowed to warm to room temperature overnight and then treated with 100 mL of ammonium chloride solution. The layers were separated, and the aqueous layer was extracted with three 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Rotary evaporation gave 2.4 g (62%) of a white solid: mp 192.5–193.3 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 1H), 7.36 (m, 9H), 7.12 (m, 6H), 6.75 (s, 1H), 6.05 (d, J = 20.4 Hz, 1H), 4.44 (d, J = 15.0 Hz, 2H); IR (KBr) 3427, 1684, 1491, 1446, 1133 cm^{-1}.

A solution of 1.4 g (3.6 mmol) of this white solid in 65 mL of acetone was stirred with 1 mL of concentrated HCl overnight. The acetone was evaporated to give a white solid. Recrystallization from acetone/ether gave 0.41 g (64%) of a hydrochloride salt: ^{1}H NMR (DMSO) δ 9.11 (s, 1H), 7.71 (s, 1H), 6.23 (d, J = 18.0 Hz, 1H), 4.19 (d, J = 21.6 Hz, 2H); ^{13}C NMR (DMSO) δ 163.89 (d, J = 233.3 Hz), 134.25 (d, J = 18.5 Hz), 125.33 (d, J = 17.9 Hz), 116.81 (d, J = 13.5 Hz), 96.69 (d, J = 33.9 Hz), 56.44 (d, J = 27.8 Hz); IR (KBr) 3005, 1691, 1613, 1134, 1028 cm^{-1}. Anal. Calcd for $C_6H_8ClFN_2OCl$: C, 40.35; H, 4.52; N, 15.69. Found: C, 40.10; H, 4.49; N, 15.58.

Ethyl 4-(Methylthio)-2-fluorobut-2-enoate (21). A solution of 7.7 mL (60 mmol) of ethyl (methylthio)acetate in 40 mL of THF at −78 °C was treated with 60 mL (1.0 M in CH_2Cl_2, 60 mmol) of DIBAL. In another flask, a solution of 16.1 g (66.5 mmol) of triethyl fluorophosphonoacetate in 75 mL of THF at −78 °C was treated with 41.5 mL (1.6 M in hexanes, 66.5 mmol) of n-BuLi. After 30 min, the phosphonate anion solution was transferred to the DIBAL solution by cannula. The solution was allowed to warm to room temperature overnight and then carefully treated with 200 mL of 6 M HCl. The layers were separated, and the aqueous layer was extracted twice with 150-mL portions of ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the product was separated from unreacted thioacetate ester and phosphonoacetate by fractional distillation to give 6.4 g (60%) of a yellow oil, bp 64–65 °C/1.8 Torr. This material is an 85:15 mixture of (*E*) and (*Z*) isomers. The two isomers can be separated by chromatography with 10% ether in petroleum ether. (*E*) isomer: R_f 0.37 (90:10 petroleum ether:ether); ^{1}H NMR ($CDCl_3$) δ 5.97 (dt, J = 19.8, 9.0 Hz, 1H), 4.31 (q, J = 6.9 Hz, 2H), 3.62 (dd, J = 8.7, 1.2 Hz, 2H), 2.07 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 160.66 (d, J = 35.8 Hz), 147.76 (d, J = 256.0 Hz), 119.34 (d, J = 20.3 Hz), 61.51, 27.95 (d, J = 7.0 Hz), 14.29, 13.94; IR (neat) 1730, 1662 cm^{-1}; MS (EI) m/z calc for $C_7H_{11}FO_2S$ 178.0463, found 178.0463. (*Z*) isomer: R_f 0.24 (90:10 petroleum ether:ether); ^{1}H NMR ($CDCl_3$) δ 6.17 (dt, J = 30.9, 8.7 Hz, 1H), 4.31 (q, J = 6.9 Hz, 2H), 3.27 (dd, J = 8.4, 2.1 Hz, 2H), 2.07 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).

Ethyl 4-Methoxy-2-fluorobut-2-enoate (20). A solution of 9.5 mL (80 mmol) of ethyl methoxyacetate in 55 mL of THF at −78 °C was treated with 80 mL (1.0 M in CH_2Cl_2, 80 mmol) of DIBAL. In another flask, a solution of 21.4 g (88.4 mmol) of triethyl fluorophosphonoacetate in 100 mL of THF at −78 °C was treated with 44.0 mL (2.0 M in hexanes, 88.4 mmol) of n-BuLi. After 45 min, the phosphonate anion solution was transferred to the DIBAL solution by cannula. The solution was allowed to warm to room temperature overnight and then carefully treated with 200 mL of 6 M HCl. The layers were separated, and the aqueous layer was extracted twice with 150-mL portions of ethyl acetate. The combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the product was separated from unreacted methoxyacetate ester and phosphonoacetate by fractional distillation to give 7.9 g (61%) of a colorless oil, bp 50–68 °C/ 7.0 Torr. This material is an 85:15 mixture of (*E*) and (*Z*) isomers. (*E*) isomer: ^{1}H NMR ($CDCl_3$) δ 6.03 (dt, J = 19.8, 6.0 Hz, 1H), 4.42 (dd, J = 5.7, 3.0 Hz, 2H), 4.31 (q, J = 6.9 Hz, 2H), 3.37 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H); IR (neat) 1737, 1673 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 160.71 (d, J = 34.0 Hz), 142.41 (d, J = 267.5 Hz), 121.58 (d, J = 57.2 Hz), 66.86 (d, J = 6.9 Hz), 61.85, 58.42, 14.14; MS (EI) m/z calc for $C_7H_{11}FO_3$: 162.0692; found: 162.0693. (*Z*) isomer: ^{1}H NMR ($CDCl_3$) δ 6.23 (dt, J = 33.6, 6.6 Hz, 1H), 4.31 (q, J = 6.9 Hz, 2H), 4.19 (dd, J = 6.6, 3.0 Hz, 2H), 3.37 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H).

(*E*)-3-Fluoro-1-hydroxy-5-(methylthio)pent-3-en-2-one (8). A solution of 0.59 g (3.3 mmol) of (*E*)-ethyl 4-(methylthio)-2-fluorobut-2-enoate and 5 mL of 1 M NaOH was stirred at room temperature for 7 h. The solution was extracted with 30 mL of ether, acidified with concd HCl, and extracted with five 50-mL portions of ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered, and evaporated to give 0.40 g (82%) of a yellow oil.

To a solution of 0.40 g (2.7 mmol) of the above acid and 0.38 mL (2.9 mmol) of triethylamine at 0 °C was added 0.26 mL (2.7 mmol) of ethyl chloroformate. The mixture was stirred for 1 h at 0 °C and then stored in the freezer overnight. The white solids were filtered off and washed with ether. The filtrate was treated at 0 °C with a solution of 5.4 mmol of freshly-distilled diazomethane in ether. After 1 h, N_2 gas was bubbled through the solution until some of the yellow color faded and the ether was removed by rotary evaporation. Flash chromatography (30:70 ether:petroleum ether) gave 0.17 g (36%) of a yellow oil.

A solution of 51.2 mg (0.29 mmol) of **37** in 5 mL of acetone was treated at room temperature with 5 mL of 1 M HCl. After 30 min, the reaction mixture was extracted with three 5-mL portions of ethyl acetate. The organic extracts were dried over $MgSO_4$, filtered, and evaporated to give 28.3 mg (62%) of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.94 (dt, J = 21.0, 8.7 Hz, 1H), 4.41 (d, J = 3.0 Hz, 2H), 3.64 (d, J = 8.7 Hz, 2H), 2.05 (s, 3H); IR (neat) 3422, 1715, 1653, 1286 cm^{-1}.

The (*Z*) isomer **7** could be similarly prepared from (*Z*)-ethyl 4-(methylthio)-2-fluorobut-2-enoate in 15% overall yield: ^{1}H NMR ($CDCl_3$) δ 6.23 (dt, J = 32.7, 8.4 Hz, 1H), 4.47 (d, J = 3.0 Hz, 2H), 3.28 (d, J = 8.4 Hz, 2H), 2.08 (s, 3H).

3,3-Bis(methylthio)-2-fluoroacrylonitrile (22). To a solution of 2.2 mL (40 mmol) of fluoroacetonitrile, 2.6 mL (43 mmol) of carbon disulfide, 7.7 mL (44 mmol) of HMPA, and 7.0 mL (112 mmol) of methyl iodide in 220 mL of THF at −78 °C was slowly added 100 mL (1.0 M in THF, 100 mmol) of lithium hexamethyldisilazide over 2 h. The solution slowly warmed to room temperature and was stirred overnight. The reaction was quenched with 100 mL of ammonium chloride solution, and the solution was extracted with five 100-mL portions of ether. The extracts were washed with ammonium chloride solution and brine, and dried over $MgSO_4$. Kugelrohr distillation (60–70 °C/ 3.2 Torr) gave 4.2 g (66%) of yellow product. An analytical sample was prepared by flash chromatography (10% ether in petroleum ether): R_f 0.26 (90:10 petroleum ether:ether); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.10 (d, J = 19.7 Hz), 130.12 (d, J = 248.3z), 111.66 (d, J = 46.1z), 18.01, 16.17; IR (neat) 2218, 1577, 1426, 1318, 1203 cm^{-1}. Anal. Calcd for $C_5H_6FNS_2$: C, 36.79; H, 3.71; N, 8.58. Found: C, 36.92; H, 3.73; N, 8.33.

3,3-Bis(methylthio)-2-fluoropropenal (23). To a solution of 1.18 g (7.2 mmol) of 3,3-bis(methylthio)propenenitrile in 70 mL of dichloromethane at 0 °C was added 7.4 mL (1.0 M in CH_2Cl2, 7.2 mmol) of DIBAL. The reaction was stirred at 0 °C for 3 h and then poured into 100 mL of rapidly stirred 1 M HCl. The layers were separated, and the aqueous layer extracted twice with 75-mL portions of dichloromethane. The combined organic extracts were washed with brine and dried over $MgSO_4$. Flash chromatography (30% ether in petroleum ether) gave 0.83 g (70%) of a orange product: R_f 0.28 (70:30 petroleum ether:ether); ^{1}H NMR ($CDCl_3$) δ 9.99 (d, J=17.7 Hz, 1H), 2.54 (s, 3H), 2.44 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 178.38 (d, J = 22.7 Hz), 178.24 (23.0 Hz), 154.55 (d, J = 260.0 Hz), 18.63, 16.38; IR (neat) 2927, 2864, 1667, 1552 cm^{-1}; MS (CI (CH_4/NH_3)) m/z 184 ($M + NH_4^+$), 167 (MH^+), 136, 119, 91. Anal. Calcd for $C_5H_7FOS_2$: C, 36.13; H, 4.24. Found: C, 36.09; H, 4.20.

1,1-Bis(methylthio)-2-fluoro-3-phenylprop-1-en-3-ol (24). To a solution of 0.09 g (0.54 mmol) of aldehyde **23** in 5 mL of ether at room temperature was added 0.22 mL (3.0 M in ether, 0.66 mmol) of phenylmagnesium bromide. After 1 h at room temperature, the reaction was quenched with saturated ammonium chloride solution and the solution extracted with ether. Flash chromatography with 30% ether in petroleum ether gave 0.11 g (83%) of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.38 (m, 5H), 6.24 (d, J = 23.4 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.01 (d, J = 269.3 Hz), 139.28, 128.59, 128.14, 126.05, 115.60 (d, J = 21.0 Hz), 70.29 (d, J = 25.9 Hz), 17.08, 16.08; IR (neat) 3398, 1609 cm^{-1}. Anal. Calcd for $C_{11}H_{13}FOS_2$: C, 54.07; H, 5.36. Found: C, 53.95; H, 5.37.

Methyl (*Z*)-2-fluorocinnamothioate (25). A suspension of 70 mg (0.29 mmol) of alcohol **24** and 57 mg (0.31 mmol) of mercuric chloride in 3 mL acetonitrile and 0.5 mL of water was allowed to reflux for 3.5 h. The white solid was filtered off and washed with 10 mL of dichloromethane. The filtrate was washed with sodium bicarbonate solution and brine and dried over $MgSO_4$. Solvent evaporation gave 49 mg (86%) of the thioester: ^1H NMR ($CDCl_3$) δ 7.66 (m, 2H), 7.40 (m, 3H), 6.85 (d, J = 36.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 187.26, 152.22 (d, J = 259.6 Hz), 140.00, 130.79, 129.95, 128.93, 112.93 (d, J = 8.9 Hz), 11.24; IR (neat) 1676, 1640 cm^{-1}; MS (EI) m/z calcd for $C_{10}H_9FOS$ 197.0436, found 197.0435.

1,1-Bis(methylthio)-2-fluoropent-1-en-3-ol (26), 1,1-Bis(methylthio)-2-fluoroprop-1-en-3-ol (27), and 1,1-Bis(methylthio)-2-ethyl-pent-1-en-3-ol (28). To a solution of 40 mg (0.24 mmol) of aldehyde **23** in 1.5 mL of THF at room temperature was added 0.08 mL (3 M in THF, 0.24 mmol) of EtMgBr. The reaction was stirred overnight, poured into 5 mL of NH_4Cl solution, and extracted with ether. Drying over $MgSO_4$ and solvent evaporation gave 38 mg of the crude product. Flash chromatography with 40:60 ether:petroleum ether gave 10 mg (21%) of **26** and 23 mg (63%) of **27**. **26**: R_f 0.26 (70:30 petroleum ether:ether); ^1H NMR ($CDCl_3$) δ 4.95 (dt, J = 24.3, 6.9 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.68 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.44 (d, J = 269.3 Hz), 70.10 (d, J = 27.1 Hz), 27.44, 17.14, 16.10, 9.80; IR (neat) 3362, 1613, 1216 cm^{-1}. Anal. Calcd for $C_7H_{13}FOS_2$: C, 42.85; H, 6.68. Found: C, 42.97; H, 6.70. **27**: R_f 0.18 (70:30 petroleum ether:ether); ^1H NMR ($CDCl_3$) δ 4.57 (d, J = 19.2 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H); IR (neat) 3351, 1617, 1428, 1212 cm^{-1}; MS (EI) m/z calcd for $C_5H_9FOS_2$ 168.0079, found 168.0079.

To a solution of 39 mg (0.23 mmol) of aldehyde **23** in 1.5 mL of THF at room temperature was added 0.16 mL (3 M in THF, 0.48 mmol) of EtMgBr. The reaction mixture was stirred overnight, poured into 5 mL of NH_4Cl solution, and extracted with ether. Drying over $MgSO_4$ and solvent evaporation gave 38 mg of the crude product. Flash chromatography with 30:70 ether:petroleum ether gave 20 mg (44%) of **26**, 7 mg (15%) of **28**, and 12 mg (28%) of 1,1-bis(methylthio)-2-ethyl-1,3-pentadiene (dehydration of **28**). **28**: R_f 0.42 (70:30 petroleum ether:ether); ^1H NMR ($CDCl_3$) δ 4.98 (t, J = 7.2 Hz, 1H), 2.42 (q, J = 7.5 Hz, 2H), 2.28 (s, 3H), 2.24 (s, 3H), 1.60 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); IR (neat) 3396, 1441 cm^{-1}; MS (CI (CH_4/NH_3)) m/z 189 (100) ($MH^+ - H_2O$), 159 (3), 143 (2). **1,1-Bis(methylthio)-2-ethyl-1,3-pentadiene:** R_f 0.83 (70:30 petroleum ether:ether); ^1H NMR ($CDCl_3$) δ 6.95 (dq, J = 14.1, 1.5 Hz, 1H), 5.86 (dq, J = 14.1, 6.9 Hz, 1H), 2.65 (q, J = 7.5 Hz, 2H), 2.31 (s, 3H), 2.25 (s, 3H), 1.85 (dd, J = 6.9, 1.5 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); MS (CI (CH_4/NH_3)) m/z 189 (100%) (MH^+), 173 (6), 141 (14).

Methyl (*Z*)-2-Fluoro-4-methyl-2-pentenethioate (29). To a solution of 0.10 g (0.60 mmol) of aldehyde **23** in 10 mL of ether at room temperature was added 0.54 mL (2 M in ether, 0.108 mmol) of *i*-PrMgCl. The reaction mixture was stirred overnight, poured into 10 mL of NH_4Cl solution, and extracted with ether. Drying over $MgSO_4$ and solvent evaporation gave 0.12 g of the crude product. Flash chromatography with 30:70 ether:petroleum ether gave 20 mg (15%) of the reduction product **27** and 90 mg (69%) of the addition product: R_f 0.30 (70:30 petroleum ether:ether); ^1H NMR ($CDCl_3$) δ 4.68 (dd, J = 24.6, 8.7 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 1.93 (m, 1H), 1.57 (br s, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.37 (d, J = 269.0 Hz), 74.30 (d, J = 26.7 Hz), 32.40, 16.76, 17.05, 16.19; IR (neat) 3331, 1612, 1219 cm^{-1}. Anal. Calcd for $C_8H_{15}FOS_2$: C, 45.69; H, 7.19. Found: C, 45.75; H, 7.15.

A suspension of 66.0 mg (0.32 mmol) of the above alcohol and 88.0 mg (0.32 mmol) of mercuric chloride in 3 mL of acetonitrile and 1 mL of water was refluxed for 2 h. The white solid was filtered off and washed with 10 mL of dichloromethane. The filtrate was washed with sodium bicarbonate solution and brine and dried over $MgSO_4$. Solvent evaporation gave 51.1 mg (98%) of the crude thioester: ^1H NMR ($CDCl_3$) δ 5.75 (dd, J = 35.1, 9.6 Hz, 1H), 2.82 (m, 1H), 2.36 (s, 3H), 1.07 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 186.63 (d, J = 37.40 Hz) 151.78 (d, J = 257.6 Hz), 122.50 (d, J = 11.5 Hz), 24.49, 21.95, 10.94; IR (neat) 1677, 1670 cm^{-1}. This thioester was hydrolyzed with 1 N NaOH to give material whose NMR spectrum corresponded with that of compound **1**.

1,1-Bis(methylthio)-2-fluoro-3-((1′-trityl)-4′-imidazolyl)prop-1-en-3-ol (30). To a solution of 0.65 g (1.5 mmol) of 1-trityl-4-iodoimidazole in 10 mL of dichloromethane at room temperature was added 0.50 mL (3.0 M in ether, 1.5 mmol) of ethylmagnesium bromide. After 1 h, 0.25 g (1.5 mmol) of aldehyde **23** in 5 mL of dichloromethane was added and the reaction solution was allowed to stir overnight. The reaction mixture was poured into 40 mL of ammonium chloride solution and extracted with dichloromethane. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 0.60 g of material that was purified by flash chromatography with ether to give 0.51 g (72%) of a pale yellow solid: mp 136.7–137.8 °C; R_f 0.20 (ether); ^1H NMR ($CDCl_3$) δ 7.44 (s, 1H), 7.33 (m, 9H), 7.11 (m, 6H), 6.80 (s, 1H), 6.22 (d, J = 23.4 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.54, 160.48 (d, J = 272.3 Hz), 141.99, 139.07 (d, J = 48.1 Hz), 138.62, 129.71, 128.10, 128.04, 118.61, 75.67, 65.25 (d, J = 25.1 Hz), 17.21, 16.18; IR (KBr) 3152, 1609, 1490, 1444, 1215 cm^{-1}. Anal. Calcd for $C_{27}H_{25}FN_2OS_2$: C, 68.04; H, 5.29; N, 5.88. Found: C, 68.03; H, 5.29; N, 5.84.

Methyl (*Z*)-3-(4′-Imidazolyl)-2-fluorothioacrylate Hydrochloride (31). A solution of 86.2 mg (0.18 mmol) of **30** in 5 mL of acetone was stirred with 3 drops of concentrated HCl overnight. The acetone was evaporated to give a white solid. Recrystallization from acetone/ether gave 29.5 mg (61%) of a hydrochloride salt: ^1H NMR (DMSO) δ 9.23 (s, 1H), 8.08 (s, 1H), 7.17 (d, J = 36.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (DMSO) δ 184.79 (d, J = 33.9 Hz), 152.00 (d, J = 271.7 Hz), 135.74 (d, J = 19.1 Hz), 123.56, 122.20, 100.60, 10.94; IR (KBr) 2961, 2730, 1653 cm^{-1}. Anal. Calcd for $C_6H_8ClFN_2O$: C, 40.35; H, 4.52; N, 15.69. Found: C, 40.10; H, 4.49; N, 15.58.

(*Z*)-2-Fluoro-3-(4′-imidazolyl)-2-propenol (5). A suspension of 0.49 g (1.8 mmol) thioester **31** and 0.37 g (9.8 mmol) of $NaBH_4$ in 40 mL of ethanol was stirred at room temperature for 16 h. The reaction mixture was diluted with 100 mL of brine and extracted with four 50-mL portions of ethyl acetate. The organic extracts were dried over $MgSO_4$ and evaporated to give 0.31 g of a tan oil. The oil was dissolved in 2 mL of ethanol and stirred with 5 drops of cond HCl. The resulting white solid was filtered and recrystallized from acetone and ether to give 0.17 g (51%) of the tan solid hydrochloride salt: mp 153.6–155.3 °C; ^1H NMR (DMSO) δ 14.90 (br s, 1H), 9.11 (m, 1H), 7.68 (m, 1H), 6.09 (d, J = 38.7 Hz, 1H), 4.13 (d, J = 10.2 Hz, 2H), 3.60 (br s, 1H); ^{13}C NMR (DMSO) δ 162.94 (d, J = 269.3 Hz), 133.70, 125.31, 117.03, 92.71 (d, J = 6.2 Hz), 58.44 (d, J = 30.83 Hz); IR (KBr) 3339 (br), 3083 (br), 1591, 1159, 1079 cm^{-1}; MS (EI) m/z calcd for $C_6H_7FN_2O$ 142.0540, found 142.0540.

1,1-Bis(methylthio)-2-fluoro-3-(1′-(methoxymethyl)-1′,2′,4′-triazolyl-5′-prop-1-en-3-ol (32). To a solution of 0.05 g (0.44 mmol) of *N*-(methoxymethyl)triazole in 10 mL of THF at −78 °C was added 0.28 mL (1.6 M in hexanes, 0.45 mmol) of *n*-BuLi. After 1.5 h, 0.21 mL (1.2 mmol) of HMPA followed by 0.05 g (0.30 mmol) of aldehyde **23** in 1 mL of THF was added and the reaction solution was allowed to stir overnight. The reaction mixture was quenched with 1 mL of brine and extracted with ethyl acetate. The organic extracts were washed with brine and dried over

$MgSO_4$. Evaporation of the solvent and flash chromatography (2:1 ethyl acetate:petroleum ether) gave 62.5 mg (74%) of an orange oil: R_f 0.36 (2:1 ethyl acetate:petroleum ether); ^1H NMR ($CDCl_3$) δ 7.87 (s, 1H), 6.51 (dd, J = 24.0, 8.1 Hz, 1H), 5.59 (d, J = 11.1 Hz, 1H), 5.50 (d, J = 11.1 Hz, 1H), 4.37 (br d, J = 8.1 Hz, 1H), 3.37 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.30 (d, J = 268.9 Hz), 153.65, 150.14, 118.51 (d, J = 21.8 Hz), 79.22, 63.84 (d, J = 26.6 Hz), 57.15, 17.16, 15.91; IR (neat) 3252, 1616, 1093 cm^{-1}; MS (EI) m/z calc for $C_9H_{14}FN_3O_2S_2$ 280.0590, found 280.0593.

Ethyl 6,6-Bis(Methylthio)-4-hydroxy-5-fluorohex-5-en-2-ynoate (33). To a solution of 0.05 mL (0.49 mmol) of ethyl propiolate in 2 mL of THF at −78 °C was added 0.49 mL (1.0 M in THF, 0.49 mmol) of LiHMDS. The reaction solution was stirred for 20 min, and then 0.17 mL (0.98 mmol) of HMPA was added followed by a solution of 70.0 mg (0.42 mmol) of **23** in 2 mL of THF. The reaction was kept at −78 °C for 3 h. Acetic acid (0.1 mL) was added, and the reaction mixture was allowed to come to room temperature. The reaction mixture was poured into 25 mL of $NaHCO_3$ solution and extracted with three 25-mL portions of ether. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (1:1 ether:petroleum ether) gave 58.7 mg (53%) of an orange oil: R_f 0.37 (1:1 ether:petroleum ether); ^1H NMR ($CDCl_3$) δ 5.95 (d, J = 22.2 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 2.20 (br s, 1H), 1.32 (t, J = 7.2 Hz, 3H); IR (neat) 3453, 2240, 1713, 1669 cm^{-1}. Anal. Calcd for $C_{10}H_{13}FO_3S_2$: C, 45.44; H, 4.96. Found: C, 45.41; H, 4.95.

***tert*-Butyl 5,5-Bis(Methylthio)-3-hydroxy-4-fluoropent-4-enoate (34).** A solution of LDA was made from 0.57 mL (4.1 mmol) of diisopropylamine in 20 mL of THF and 2.6 mL (1.6 M in hexane, 4.2 mmol) of *n*-BuLi. The solution was cooled to −78 °C, and 0.55 mL (4.1 mmol) of *tert*-butyl acetate in 10 mL of THF was added dropwise via a dropping funnel. After 30 min at −78 °C, a solution of 0.56 g (3.4 mmol) of aldehyde **23** in 5 mL of THF was added. The reaction mixture was stirred for 5 min at −78 °C, and the reaction was quenched with 5 mL of ammonium chloride solution. The reaction solution was brought to room temperature, poured into 20 mL of ammonium chloride solution, and extracted with ether. The organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 0.90 g of material that was purified by flash chromatography with 1:1 ether:petroleum ether to give 0.72 g (73%) of an orange oil: R_f 0.44 (1:1 ether:petroleum ether); ^1H NMR ($CDCl_3$) δ 5.46 (ddd, J = 24.0, 8.7, 4.8 Hz, 1H), 2.69 (dd, J = 16.2, 8.7 Hz, 1H), 2.53 (dd, J = 16.2, 4.8 Hz, 1H), 2.78 (s, 3H), 2.32 (s, 3H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 181.47, 105.78 (d, J = 131.5 Hz), 96.01 (d, J = 13.9 Hz), 70.76, 65.27 (d, J = 25.4 Hz), 39.16, 28.06, 17.25, 16.07; IR (neat) 3435, 1722, 1613.9 cm^{-1}; MS (CI (CH_4/NH_3)) m/z 300 ($M + NH_4^+$), 283 (MH^+), 265 ($MH^+ - H_2O$), 209, 167; MS (EI) m/z calcd for $C_{11}H_{19}FO_3S_2$ 282.0759, found 282.0750.

***tert*-Butyl 5,5-Bis(methylthio)-4-fluoropenta-2,4-dienoate (35).** A solution of 50 mg (0.18 mmol) of **34** and 0.06 mL (0.78 mmol) of TFA in 2 mL THF was stirred at rt overnight. The reaction mixture was diluted with 5 mL of $NaHCO_3$ solution and extracted with ether to give 17 mg (36%) of **35**: ^1H NMR ($CDCl_3$) δ 7.80 (dd, J = 27.0, 15.6 Hz, 1H), 6.08 (d, J = 15.6 Hz, 1H), 2.42 (s, 3H), 2.31 (s, 3H), 1.51 (s, 9H). The aqueous layer was acidified with concd HCl and extracted with 10% *i*-PrOH in CH_2Cl_2 to give 19 mg (51%) of 5,5-bis(methylthio)-4-fluoropenta-2,4-dienoic acid: ^1H NMR ($CDCl_3$) δ 7.96 (dd, J = 26.7, 15.6 Hz, 1H), 6.12 (d, J = 15.6 Hz, 1H), 2.46 (s, 3H), 2.33 (s, 3H); MS (EI) m/z calcd for $C_{11}H_{17}FO_2S_2$ 264.0654, found 264.0666.

***S*-Methyl Hydrogen (*Z*)-2-Fluoro-2-pentene-1-thiodioate (36).** A suspension of 0.10 g (0.35 mmol) of **35** and 0.93 g (0.41 mmol) of $CdCl_2$ in 4 mL of acetonitrile and 2 mL of 1 M HCl was refluxed for 3 days. The reaction mixture was diluted with 15 mL of $NaHCO_3$ solution and extracted twice with 15 mL of CH_2Cl_2. The aqueous layer was acidified with concd HCl and extracted with four 15-mL portions of ethyl acetate. The organic extracts were dried over $MgSO_4$ and rotary evaporated to give 31.6 mg (53%) of the solid thioester: ^1H NMR ($CDCl_3$) δ 9.20 (br s), 6.23 (dt, J = 33.3, 7.5 Hz, 1H), 3.36 (dd, J = 7.5, 1.8 Hz, 2H), 2.40 (s, 3H). Hydrolysis of **36** with 1 M NaOH gave material whose NMR spectrum matched that of (*Z*)-2-fluoro-2-pentenedioic acid (**3**).

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Supplementary Material Available: Preparative procedures for **1-3, 9-10, 12, 14-17, 18t,** and **19t** and copies of ^1H NMR spectra of all compounds that were not subjected to combustion analysis (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.