Reduction–Olefination of Esters: A New and Efficient Synthesis of α-Fluoro α,β-Unsaturated Esters[1]

Alagappan Thenappan and Donald J. Burton*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

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A reduction–olefination sequence has been used to convert esters to α-fluoro α,β-unsaturated esters. In the presence of diisobutylaluminum hydride, esters are reduced to aldehydes that react in situ with $[(EtO)_2P(O)CFC(O)OEt]^-Li^+$ to form the title compounds in good yields with high stereoselectivity. The reaction is applicable to aliphatic, aromatic, cyclic, unsaturated, perfluorinated, and partially fluorinated esters. The E/Z ratio of unsaturated esters formed in the reaction varies with the cations present in the reaction mixture. Solvents have very little influence on stereochemistry. The sequential transformation of $PhC(O)OBu^n$ to (*E*)-PhCH=CFC(O)OEt and then to (*E*,*E*)-PhCH=CFCH=CFC(O)OEt illustrates the scope of this methodology, which introduces a fluorine atom adjacent to an ester functionality with concomitant elongation of the chain by two carbon atoms.

Introduction

α-Fluoro α,β-unsaturated esters of defined stereochemistry constitute a useful class of compounds in organic synthesis, and a number of them have been successfully employed as precursors in the preparation of monofluorinated retinoids,[2] fluorinated analogues of insect sex pheromones,[3] and pyrethroids.[4] Substitution of fluorine adjacent to the ester functionality imparts significant biological activity to these compounds, as illustrated in vitamin A and pheromone chemistry.[5] Ethyl 12-fluororetinoate exhibits anticancer activity in mice.[5] Consequently, the synthesis of selectively fluorinated building blocks such as α-fluoro α,β-unsaturated esters has become an area of active investigation in recent years.

Literature methods for the preparation of the title compounds mainly lack stereospecificity and generality and are often arduous to carry out on a practical scale. Condensation of carbonyl compounds with toxic fluoroacetate or fluorooxaloacetate leads to a mixture of products in low yields.[6] The Horner–Wadsworth–Emmons reaction of fluorocarboalkoxy-substituted dialkyl phosphonate anions with aldehydes and ketones requires the availability of the appropriate carbonyl compounds.[7,8] The zinc(0)–copper(I) chloride promoted reaction of methyl dichlorofluoroacetate with carbonyl compounds is limited to aldehydes only.[9] Neither the addition of chlorofluorocarbene to enoxysilanes and subsequent rearrangement of the adducts[10] nor the reaction of carbonyl compounds with organometallic reagents[11] shows any stereoselectivity. Olefination of fluorinated aldehydes with $[(EtO)_2P(O)CFC(O)OEt]^-M^+$ has not been reported. The lack of a general synthetic method to prepare fluorinated aldehydes may be the main reason for this scarcity. The few fluorine-substituted aldehydes that are known are usually protected either as a hemiacetal or as an acetal and prior deprotection is required. Herein, we describe a general synthesis of α-fluoro α,β-unsaturated esters via the Horner–Wadsworth–Emmons reaction of $[(EtO)_2P(O)CFC(O)OEt]^-M^+$ and aldehydes produced in situ from esters.

Results and Discussion

Recently, Takacs[12] has reported that, in the presence of diisobutylaluminum hydride (DIBAL), esters and lactones **1** react with lithium trialkylphosphonoacetate to form the corresponding homologated unsaturated esters **2** in good yields with high stereoselectivity (eq 1). The

$$\underset{\mathbf{1}}{RC(O)OR'} \xrightarrow[[(EtO)_2P(O)CHC(O)OEt]^-Li^+,\ THF,\ -78\ ^\circ C]{DIBAL\ (1.0\ equiv)} \underset{\mathbf{2}\ (E\ and\ Z)\ (62\text{–}86\%)}{RCH{=}CHC(O)OEt} \quad (1)$$

R = $CH_3(CH_2)_4$, $(CH_3)_2CH$, $CH_3CH(OTBS)$, $-(CH_2)_3C(O)O-$, $-(CH_2)_4C(O)O-$, $CH_2CH(CH_2)_5$; R′ = CH_3, CH_2CH_3

two-carbon homologation of esters to unsaturated esters is performed by an initial half-reduction of the ester to an aldehyde and subsequent olefination of the aldehyde with the phosphonate anion. With a stoichiometric quantity of DIBAL, the overreduction of the starting and product esters is minimal (3%). However, with excess DIBAL (3.2 equiv), reduction of the unsaturated ester **2** to form the corresponding allylic alcohol **3** in 70% isolated yield has been reported[12] (eq 2).

$$CH_3(CH_2)_4C(O)OCH_3 \xrightarrow[[(EtO)_2P(O)CHC(O)OEt]^-Li^+]{DIBAL\ (3.2\ equiv)} \underset{\mathbf{3}\ (E\ and\ Z)}{CH_3(CH_2)_4CH{=}CHCH_2OH} \quad (2)$$

Takacs' report prompted us to investigate the related carbon homologation reaction of esters with $(EtO)_2P(O)CFHC(O)OEt$ (**4**), a fluorinated analogue of $(EtO)_2P(O)CH_2C(O)OEt$. Two-carbon chain elongation of esters by a reduction–olefination sequence thus permits the use of esters instead of aldehydes. This is invaluable in fluorocarbon chemistry, where the readily available fluorinated

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Table I. Preparation of α-Fluoro α,β-Unsaturated Esters (See Equations 3 and 4)

no.	R	R′	method	yield,[a] %	E/Z[b]
5a	CF_3	C_2H_5	B	63	83/17
5b	C_2F_5	C_2H_5	B	44	80/20
5c	$^nC_3F_7$	C_2H_5	A	66	77/23
5d	CF_2Cl	C_2H_5	B	64	89/11
5e	CF_2Br	C_2H_5	B	64	88/12
5f	CFHBr	C_2H_5	A	66	88/12
5g	$^nC_5H_{11}$	C_2H_5	A[c]	57	93/7
5h	$(CH_3)_2CH$	CH_3	B	54	95/5
5i	C_6H_5	$^nC_4H_9$	B	56	100/0
5j	(*E*)-CH_3CH=CH	CH_3	B	55	5/95[d]
5k	$-(CH_2)_3C(O)O-$		B	76	95/5
5l	(*E*)-C_6H_5CH=CF	C_2H_5	A[c]	45	100/0[d]
5m	H	C_2H_5	A[e]	62	

[a] Isolated yields based on RC(O)OR′. [b] E/Z ratios were determined by integration of the vinyl fluorine signals in the ^{19}F NMR spectrum. [c] DIBAL in toluene utilized. [d] EE/EZ ratio. [e] Et_2O solvent.

esters can be used as a viable source of fluorine-substituted aldehydes.

In the presence of DIBAL, esters **1** react with an anion derived from **4** to give the respective unsaturated esters **5** in good yields (eq 3). Observations in our laboratory

Method A

$$(EtO)_2P(O)CFHC(O)OEt \xrightarrow[\text{1. } n\text{-BuLi; 2. RCOOR′; 3. DIBAL; } -78\ ^\circ C \rightarrow +25\ ^\circ C]{\text{THF}} RCH{=}CFC(O)OEt \quad (3)$$

4 → **5** (*E* and *Z*)

indicate that the conversion of the esters to the final products is low via the Takacs procedure; i.e., when in situ reduction of esters to aldehydes was performed in the presence of $[(EtO)_2P(O)CFC(O)OEt]^-Li^+$ (method A), only 60–65% of the ester was converted to **5**. ^{19}F NMR analysis of the reaction mixture at periodic intervals allows us to calculate the percent conversion of ylide and ester **1** (when R = fluorine substituted). Excess DIBAL and prolonged stirring of the reaction mixture at room temperature did not improve the conversion. Although the exact cause for low conversion was not clear, the initial procedure was modified and better conversion (80–90%) was achieved by addition of a THF solution of the anion $[(EtO)_2P(O)CFC(O)OEt]^-Li^+$ to the in situ pregenerated aldehyde (method B) (eq 4). The requisite anion was generated

Method B

$$RC(O)OR' \xrightarrow[\text{1. DIBAL; 2. } [(EtO)_2P(O)CFC(O)OEt]^-Li^+; -78\ ^\circ C \rightarrow 25\ ^\circ C]{\text{THF}} RCH{=}CFC(O)OEt \quad (4)$$

1 → **5** (*E* and *Z*)

independently from $(EtO)_2P(O)CFHC(O)OEt$ and *n*-BuLi in THF at −78 °C and transferred to the aldehyde solution via syringe. The overreduction of esters to the corresponding alcohol is also minimal (<5%) by this procedure.

The homologation of esters to α-fluoro α,β-unsaturated esters is quite general with respect to the esters employed in the system (Table I). Aliphatic, aromatic, cyclic, α,β-unsaturated, perfluorinated, and partially fluorinated esters were all transformed to the respective title compounds in 45–76% isolated yields. The in situ reduction of methyl, ethyl, and *n*-butyl esters (entries **5h**, **5a**, and **5i**) to form the corresponding unsaturated compounds indicates the scope of this methodology. The highly stereoselective preparation of (*E*,*Z*)-CH_3CH=CHCH=CFC(O)OEt and (*E*,*E*)-PhCH=CFCH=CFC(O)OEt from (*E*)-CH_3CH=CHC(O)OEt and (*E*)-PhCH=CFC(O)OEt illustrates that the above methodology can be extended to form α-fluoro dienic esters in good yields. Furthermore, the sequential transformation of $PhC(O)OBu^n$ to (*E*)-PhCH=CFC(O)OEt and then to (*E*,*E*)-PhCH=CFCH=CFC(O)OEt exemplifies the synthetic utility of this method in two-carbon chain extension reactions.

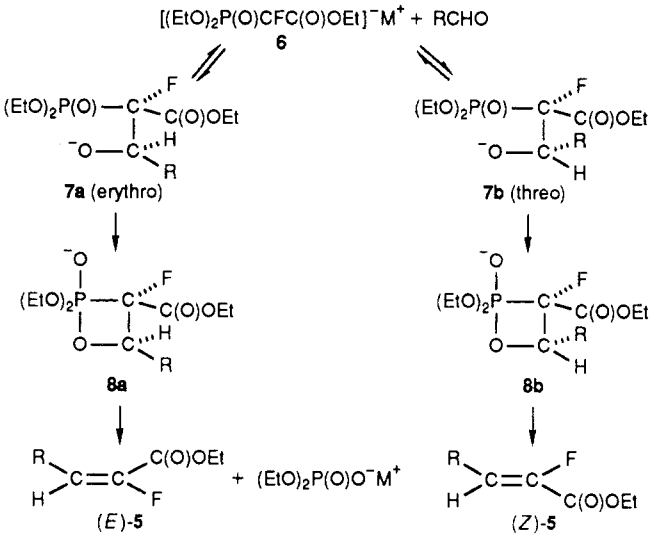
Table II. Effect of Solvent and Base on the Stereochemistry of Ethyl 2,4,4,4-Tetrafluoro-2-butenoate (5a)

$$(EtO)_2P(O)CFHC(O)OEt \xrightarrow[\text{1. base; 2. } CF_3C(O)OEt; \text{3. DIBAL}]{\text{solvent}} CF_3CH{=}CFC(O)OEt \quad (E \text{ and } Z)$$

no.	solvent	base	E/Z[a]
1	THF	^{n}BuLi	84/16
2	Et_2O	^{n}BuLi	74/26
3	*n*-hexane	^{n}BuLi	85/15
4	THF	$KOC(CH_3)_3$	55/45
5	THF	NaH	45/55
6	THF	LiH	74/26

[a] E/Z ratios were determined by integration of the vinyl CF_3 resonances in the ^{19}F NMR spectrum.

Scheme I



The stereochemistry of the unsaturated esters **5** formed in the homologation reaction depends on the cation present in the reaction mixture. The different isomer ratios obtained with various bases are illustrated in Table II. With lithium ion, the *E* isomer (E/Z = 84/16) predominates, while in the presence of sodium and potassium ions, the selectivity was insignificant. The pronounced effect of lithium salts toward isomer ratio can best be explained by invoking the mechanism of phosphonate–olefin production in hydrocarbon systems.

The formation of intermediate **7** from **6** (Scheme I) and carbonyl compounds is reversible,[13] and that intermediate can exist in two diastereoisomeric forms (**7a** and **7b**). Complexation of soluble lithium salts[14] with the interme-

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diate 7 will retard its reversibility between kinetic (**7a**) and thermodynamic (**7b**) isomers. Consequently, the irreversible decomposition of **7a** will lead to *E* isomer as the major olefin, whereas the thermodynamic product ((*Z*)-**5**) will form in minor quantities only. The decisive influence of dissolved lithium salts toward isomer ratio in Wittig and related reactions is well documented.[15]

Change of solvent (Table II) from THF to either diethyl ether or *n*-hexane has very little effect on the stereochemical outcome of the reaction sequence.

Unlike other literature procedures, our method utilizes readily available esters as substrates in the olefination reaction. This is very valuable in fluorocarbon chemistry, where stable, easily distillable fluorine-substituted esters can be employed as synthons for fluorinated aldehydes. Although the stereochemistry of products formed in our reaction sequence is comparable to other literature methods, the sequential elongation of the chain by two carbons to form dienic esters will prove useful in organic synthesis. Further extension of this methodology to P(O)-stabilized anions other than fluorocarboethoxy-substituted ions is in progress.

Experimental Section

General Procedures. All the reactions were performed in an oven-dried apparatus that consisted of a two- or three-necked round-bottomed flask equipped with a septum port, a Teflon-coated magnetic stirbar, and a reflux condenser connected to a nitrogen source and mineral oil bubbler. The extra necks of the flask were fitted with glass stoppers.

All boiling points are uncorrected. ^{19}F, ^{1}H, and $\{^{1}H\}^{31}P$ NMR spectra were recorded on a 90-MHz multinuclear spectrometer, and $\{^{1}H\}^{13}C$ NMR spectra were recorded on a 360-MHz spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$. FT-IR spectra were recorded as CCl_4 solutions. All the mass spectral analyses were performed at 70 eV in the electron impact mode. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector.

Materials. Ethyl bromofluoroacetate was prepared by a method similar to the *Organic Syntheses*[16] preparation of ethyl chlorofluoroacetate. Tetrahydrofuran (THF) was obtained from Fisher and was purified by distillation from sodium benzophenone ketyl. Anhydrous diethyl ether (Et_2O) was obtained from Mallinckrodt and was dried over 4-Å molecular sieves. Triethyl phosphite was obtained from Aldrich Chemical Co. and was distilled from sodium metal at reduced pressure. *n*-Butyllithium (2.5 M *n*-hexane solution) was obtained from Aldrich, and its concentration was determined by Duhamel's procedure (method B).[17] Diisobutylaluminum hydride solutions (1.0 M dichloromethane solution and 1.5 M toluene solution) were obtained from Aldrich. Perfluorinated and partially fluorinated esters were prepared by a literature method[18] from the corresponding fluorinated acids, absolute ethanol, and concentrated sulfuric acid. All the other esters were obtained from Aldrich and were distilled prior to use.

Preparation of Triethyl 2-Fluoro-2-phosphonoethanoate (4). Triethyl 2-fluoro-2-phosphonoethanoate was prepared by a modified literature procedure.[7] A 300-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, a glass stopper, a thermometer, and an air condenser connected to a nitrogen source was charged with a solution of 150 g of triethyl phosphite (0.91 mol) and 120 g of ethyl bromofluoroacetate (0.65 mol). The resulting mixture was stirred magnetically and heated under N_2 at 145 °C for 6 h, and then ^{19}F NMR analysis of the reaction mixture indicated that 80% of acetate had been converted to the corresponding phosphonate **4**. Distillation of the crude reaction mixture through a 6-in. Vigreux column at 104–106 °C (0.65 mm) gave 101 g (64%) of **4**: 93% pure by GLPC analysis; ^{19}F NMR −211.1 (dd) ($^{2}J_{FCP}$ = 70 Hz, $^{2}J_{FCH}$ = 44 Hz); ^{31}P NMR 10.0 (d) ($^{2}J_{PCF}$ = 72 Hz).

Representative Procedures for the Preparation of (*E*)- and (*Z*)-α-Fluoro-α,β-alkenoate Esters 5. Method A. Ethyl 2,4,4,5,5,6,6,6-Octafluoro-2-hexenoate (5c). A solution of 13.3 g (55 mmol) of **4** in 60 mL of THF was cooled at −78 °C, and 22.0 mL (55 mmol) of *n*-butyllithium was added dropwise via syringe. The resulting bright yellow solution was stirred at −78 °C for 20 min, and then 12.1 g (50 mmol) of $CF_3CF_2CF_2C(O)OEt$ was added in one portion via syringe. After the bath temperature was equilibrated to −78 °C, 50 mL (50 mmol) of a 1.0 M dichloromethane solution of DIBAL was added dropwise via syringe. The resultant mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature over 6 h, and then quenched with 80 mL of 6 M HCl. The organic layer was separated, washed successively with brine (2 × 25 mL) and water (25 mL), and subjected to steam distillation. The water layer of the steam distillate was extracted with diethyl ether (2 × 25 mL), and the combined organic materials were dried ($MgSO_4$). Removal of solvents via distillation at atmospheric pressure gave a yellow residue that was distilled again through a 6-in. Vigreux column to give 9.4 g (66%) of an *E* and *Z* mixture of **5c**: bp 61–65 °C (101 mm); 100% pure by GLPC analysis; *E*/*Z* = 77/23 by ^{19}F NMR analysis; (*E*)-**5c**: ^{19}F NMR (acetone-d_6) −127 (s, 2 F), −107 (dqd = m, 2 F, $^{3}J_{F,H}$ = 14 Hz, $^{4}J_{F,F_{trans}}$ = 5 Hz), −99 (dt, 1 F, $^{3}J_{F,H}$ = 18 Hz), −80.5 (t, 3 F, $^{4}J_{F,F}$ = 10 Hz); ^{1}H NMR (acetone-d_6) 6.3 (dt, 1 H, $^{3}J_{H,F}$ = 14 Hz, $^{3}J_{H,F_{cis}}$ = 18 Hz), 4.4 (q, 2 H, $^{3}J_{H,H}$ = 7 Hz), 1.4 (t, 3 H); ^{13}C NMR ($CDCl_3$) 158.8 (d, $^{2}J_{C,F}$ = 34 Hz), 156.2 (dt, $^{1}J_{C,F}$ = 277 Hz, $^{3}J_{C,F}$ = 6 Hz), 118.0 (qt, $^{1}J_{C,F}$ = 287 Hz, $^{3}J_{C,F}$ = 34 Hz), 108.8 (tq, $^{1}J_{C,F}$ = 265 Hz, $^{3}J_{C,F}$ = 38 Hz), 104.9 (dt, $^{2}J_{C,F}$ = 30 Hz, $^{2}J_{C,F}$ = 25 Hz), 63.4 (s), 13.7 (s); mass spectrum, *m*/*e* 287 (M^+ + 1, 0.1), 285 (M − 1^+, 0.2), 241 (98.7), 119 (56.6), 117 (100.0); IR, 1758 (s) (C=O), 1697 (m), 1201 (s), 1182 (s), (C–F), 1161 (s) (C–F), 1120 (s) cm^{-1}. (*Z*)-**5c**: ^{19}F NMR (acetone-d_6) −127.9 (d, $^{5}J_{F,F}$ = 7 Hz), −110 (ddq = m, 2 F, $^{4}J_{F,F_{cis}}$ = 24 Hz, $^{3}J_{F,H}$ = 14 Hz), −108.7 (m, 1 F), −81.3 (t, 3 F, $^{4}J_{F,F}$ = 10 Hz).

Method B. Ethyl 2,4,4,4-Tetrafluoro-2-butenoate (5a). A solution of 8.1 g (33.5 mmol) of **4** in 35 mL of THF was stirred and cooled at −78 °C, as 13.4 mL (33.5 mmol) of *n*-butyllithium was added via syringe. In another flask, a solution of 4.3 g (30 mmol) of $CF_3C(O)OEt$ in 20 mL of THF was stirred and cooled to −78 °C and 30 mL (30 mmol) of 1.0 M dichloromethane solution of DIBAL was added dropwise via syringe. The resultant mixture was stirred at −78 °C for 30 min, and then the cold anion solution generated in the first flask was added dropwise via syringe to the pregenerated aldehyde. The resultant mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature over 6 h, and then quenched with 60 mL of 6 M HCl. Isolation and purification as described in method A gave 3.5 g (63%) of an *E* and *Z* mixture of **5a**: bp 60–63 °C (144 mm); 100% pure by GLPC analysis; *E*/*Z* = 83/17 by ^{19}F NMR analysis. (*E*)-**5a**: ^{19}F NMR (acetone-d_6) −56.3 (dd, 3 F, $^{4}J_{F,F_{trans}}$ = 12 Hz, $^{3}J_{F,H}$ = 8 Hz), −106.5 (dq, 1 F, $^{3}J_{F,H_{cis}}$ = 17 Hz); ^{1}H NMR (acetone-d_6) 6.4 (dq, 1 H, $^{3}J_{H,F}$ = 8 Hz), 4.4 (q, 2 H, $^{3}J_{H,H}$ = 7 Hz), 1.3 (t, 3 H); ^{13}C NMR ($CDCl_3$) 158.4 (d, $^{2}J_{C,F}$ = 36 Hz), 154.7 (dq, $^{1}J_{C,F}$ = 274 Hz, $^{3}J_{C,F}$ = 6 Hz), 121.6 (qd, $^{1}J_{C,F_{geo}}$ = 269 Hz, $^{3}J_{C,F}$ = 22 Hz), 108.9 (qd, $^{2}J_{C,F}$ = 30 Hz, $^{2}J_{C,F}$ = 40 Hz), 63.2 (s), 13.7 (s); mass spectrum, *m*/*e* 185 (M^+ − 1, 0.4), 141 (100.0), 122 (35.6), 119 (29.2), 117 (59.6), 113 (74.6), 94 (18.0), 69 (24.3); IR, 1757 (s) (C=O), 1685 (m), 1188 (s), (C–F), 1161 (s) (C–F), 1105 (s), 1100 (s) cm^{-1}. (*Z*)-**5a**: ^{19}F NMR (acetone-d_6) −59.2 (dd, 3 F, $^{4}J_{F,F_{cis}}$ = 17 Hz, $^{3}J_{F,H}$ = 8 Hz), −110.9 (dq, 1 F, $^{3}J_{F,H_{trans}}$ = 29 Hz).

Ethyl 2,4,4,5,5,5-hexafluoro-2-pentenoate (5b): method B; yield 3.2 g (44%); bp 50–55 °C (140 mm); *E*/*Z* = 80/20; GLPC purity 100%. (*E*-**5b**): ^{19}F NMR (acetone-d_6) −85.3 (s, 3 F), −99.5 (dt, 1 F, $^{3}J_{F,H_{cis}}$ = 18 Hz), −109.5 (ddq, 2 F, $^{3}J_{F,H}$ = 15 Hz, $^{4}J_{F,F_{trans}}$ = 4 Hz, and $^{3}J_{F,F_{vic}}$ = 1 Hz); ^{1}H NMR (acetone-d_6) 6.5 (dt, 1 H, $^{3}J_{H,F}$ = 14 Hz, $^{3}J_{H,F_{cis}}$ = 18 Hz), 4.4 (q, 2 H, $^{3}J_{H,H}$ = 7 Hz), 1.3 (t, 3 H); ^{13}C NMR (acetone-d_6) 14.0 (s), 63.9 (s), 104.9 (dt, $^{2}J_{C,F}$ = 30 Hz, $^{2}J_{C,F}$ = 25 Hz), 118.1 (tq, $^{1}J_{C,F}$ = 283 Hz, $^{2}J_{C,F}$ = 37 Hz), 157.3 (dt, $^{1}J_{C,F}$ = 275 Hz, $^{3}J_{C,F}$ = 5 Hz), 158.7 (d, $^{2}J_{C,F}$ = 35 Hz);

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mass spectrum, m/e 237 (M + 1$^+$, 0.1), 235 (M - 1$^+$, 0.1), 191 (53.4), 189 (17.8), 163 (36.6), 119 (21.4), 117 (32.0), 113 (53.8), 94 (46.9), 93 (15.2), 91 (12.3), 75 (37.7), 69 (100.0); IR, 1758 (s) (C=O), 1695 (m), 1337 (s), 1211 (s), 1184 (s), (C-F), 1161 (m) cm^{-1}. (*Z*)-**5b**: ^{19}F NMR (acetone-d_6) -85.3 (s, 3 F), -108.3 (m, 1 F, $^3J_{F,H_{trans}}$ = 28 Hz), -112.5 (dd, 2 F, $^4J_{F,F_{cis}}$ = 23 Hz, $^3J_{F,H}$ = 15 Hz).

Ethyl 4-chloro-2,4,4-trifluoro-2-butenoate (5d): method B; yield 3.9 g (64%); bp 64-67 °C (98 mm); *E*/*Z* = 89/11; GLPC purity 98%. (*E*)-**5d**: ^{19}F NMR ($CDCl_3$) -44.1 (dd, 2 F, $^3J_{F,H}$ = 11 Hz, $^4J_{F,F_{trans}}$ = 9 Hz), -109.6 (dt, 1 F, $^3J_{F,H_{cis}}$ = 16 Hz); ^{1}H NMR ($CDCl_3$) 6.2 (dt, 1 H, $^3J_{H,F_{cis}}$ = 17 Hz, $^3J_{H,F}$ = 11 Hz), 4.4 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.4 (t, 3 H); ^{13}C NMR ($CDCl_3$) 13.8 (s), 63.1 (s), 114.6 (q, $^2J_{C,F}$ = 33 Hz), 122.2 (td, $^1J_{C,F}$ = 286 Hz, $^3J_{C,F}$ = 20 Hz), 152.5 (dt, $^1J_{C,F}$ = 273 Hz, $^3J_{C,F}$ = 6 Hz), 158 (d, $^2J_{C,F}$ = 36 Hz); high-resolution mass spectral data for $C_6H_5O_2F_3{}^{35}Cl$ (M - 1)$^+$, obsd 200.990 891 0, calcd 200.993 017 0; IR, 1753 (s) (C=O), 1687 (m), 1343 (s), 1185 (s) (C-F), 1160 (m), 1079 (s) cm^{-1}. (*Z*)-**5d**: -48 (dd, 2 F, $^4J_{F,F_{cis}}$ = 22 Hz, $^3J_{F,H}$ = 10 Hz), -112.7 (dt, 1 F, $^3J_{F,H_{trans}}$ = 27 Hz).

Ethyl 4-bromo-2,4,4-trifluoro-2-butenoate (5e): method B; yield 4.7 g (64%); bp 55-60 °C (67 mm); *E*/*Z* = 88/12; GLPC purity 93%. (*E*)-**5e**: ^{19}F NMR ($CDCl_3$) -39.8 (dd, 2 F, $^4J_{F,F_{trans}}$ = 9 Hz, $^3J_{F,H}$ = 11 Hz), -110.3 (dt, 1 F, $^3J_{F,H_{cis}}$ = 17 Hz); ^{1}H NMR ($CDCl_3$) 6.2 (dt, 1 H, $^3J_{H,F_{cis}}$ = 17 Hz, $^3J_{H,F}$ = 11 Hz), 4.4 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.4 (t, 3 H); ^{13}C NMR ($CDCl_3$) 13.8 (s), 63.1 (s), 112.5 (td, $^1J_{C,F}$ = 299 Hz, $^3J_{C,F}$ = 18 Hz), 116.4 (q, $^2J_{C,F}$ = 31 Hz), 151.7 (dt, $^1J_{C,F}$ = 273 Hz, $^3J_{C,F}$ = 7 Hz), 158.1 (d, $^2J_{C,F}$ = 35 Hz); high-resolution mass spectral data for $C_6H_7O_2F_3{}^{79}Br$ (M + 1)$^+$, obsd 246.955 627 0, calcd for M$^+$ 245.950 325 4 and 247.948 279 3; IR, 1753 (s) (C=O), 1680 (m), 1375 (s), 1343 (s), 1160 (s) (C-F), 1079 (s) cm^{-1}. (*Z*)-**5e**: ^{19}F NMR ($CDCl_3$) -43.6 (dd, 2 F, $^4J_{F,F_{cis}}$ = 22 Hz, $^3J_{F,H}$ = 11 Hz), -112.8 (dt, 1 F, $^3J_{F,H_{trans}}$ = 27 Hz).

Ethyl 4-bromo-2,4-difluoro-2-butenoate (5f): method A; yield 4.8 g (66%); bp 52-54 °C (12 mm); *E*/*Z* = 88/12; GLPC purity 100%. (*E*)-**5f**: ^{19}F NMR ($CDCl_3$) -117.6 (dd, 1 F, $^3J_{F,H_{cis}}$ = 17 Hz), -130.2 (ddd, 1 F, $^2J_{F,H_{gem}}$ = 51 Hz, $^3J_{F,H}$ = 15 Hz, $^4J_{F,F_{trans}}$ = 12 Hz); ^{1}H NMR ($CDCl_3$) 7.8 (dd, 1 H, $^2J_{H,F_{gem}}$ = 51 Hz, $^3J_{H,H}$ = 9 Hz), 6.4 (ddd, 1 H, $^3J_{H,F_{cis}}$ = 16 Hz, $^3J_{H,F}$ = 12 Hz), 4.4 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.4 (t, 3 H); ^{13}C NMR ($CDCl_3$) 14.0 (s), 62.8 (s), 85.6 (dd, $^1J_{C,F}$ = 243 Hz, $^3J_{C,F}$ = 12 Hz), 119.6 (dd, $^2J_{C,F}$ = 29 Hz, $^2J_{C,F}$ = 25 Hz), 147.3 (dd, $^1J_{C,F}$ = 273 Hz, $^3J_{C,F}$ = 12 Hz) 159.4 (d, $^2J_{C,F}$ = 34 Hz); mass spectrum, m/e 200 (0.2), 202 (0.2), 155 (4.3), 157 (4.5), 149 (21.8), 139 (11.5), 121 (100.0), 111 (16.4), 101 (71.5), 76 (20.2), 75 (17.3); IR, 1771 (m) (C=O), 1676 (m), 1320 (s), 1158 (m) (C-F), 1149 (m), 1034 (s) cm^1. (*Z*)-**5f**: -118.2 (dd, 1 F, $^3J_{F,H_{trans}}$ = 34 Hz), -137 (ddd, 1 F, $^2J_{F,H_{gem}}$ = 49 Hz, $^3J_{F,H}$ = 12 Hz, $^4J_{F,F_{cis}}$ = 5 Hz.

Ethyl 2-fluoro-2-octenoate (5g): method A; yield 3.0 g (57%); bp 67-70 °C (3 mm); *E*/*Z* = 93/7; GLPC purity 100%. (*E*)-**5g**: ^{19}F NMR ($CDCl_3$) -123.1 (d, 1 F, $^3J_{F,H_{cis}}$ = 22 Hz); ^{1}H NMR ($CDCl_3$) 0.9 (t, 3 H, $^3J_{H,H}$ = 6 Hz), 1.4 (m, 9 H), 2.4 (m, 2 H, $^3J_{H,H}$ = 8 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 5.9 (dt, 1 H, $^3J_{H,F_{cis}}$ = 22 Hz); ^{13}C NMR ($CDCl_3$) 14.0 (s), 14.2 (s), 22.5 (s), 25.5 (d, $^3J_{C,F}$ = 4 Hz), 29.0 (s), 31.4 (s), 61.3 (s), 123.7 (d, $^2J_{C,F}$ = 18 Hz), 147.0 (d, $^1J_{C,F}$ = 251 Hz), 161.1 (d, $^2J_{C,F}$ = 36 Hz); mass spectrum, m/e 188 (M$^+$, 27.2), 117 (100.0); IR, 2960 (s), 2933 (s), 2930 (s), 2927 (s), 1733 (s) (C=O), 1728 (s) cm^{-1}. (*Z*)-**5g**: ^{19}F NMR ($CDCl_3$) -131.4 (d, 1 F, $^3J_{F,H_{trans}}$ = 32 Hz).

Ethyl 2-fluoro-4-methyl-2-pentenoate (5h): method B; yield 3.0 g (54%); bp 52-58 °C (80 mm); *E*/*Z*, = 95/5; GLPC purity 100%. (*E*)-**5h**: ^{19}F NMR ($CDCl_3$) -125.3 (d, 1 F, $^3J_{F,H_{cis}}$ = 22 Hz); ^{1}H NMR ($CDCl_3$) 5.7 (dd, 1 H, $^3J_{H,F_{cis}}$ = 22 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 3.4 (m, 1 H, $^3J_{H,H}$ = 10 Hz), 1.3 (t, 3 H), 1.1 (d, 6 H, $^3J_{H,H}$ = 7 Hz); ^{13}C NMR ($CDCl_3$) 14.1 (s), 22.8 (s), 25.4 (s), 61.3 (s), 130.0 (d, $^2J_{C,F}$ = 16 Hz), 146.0 (d, $^1J_{C,F}$ = 231 Hz), 161.0 (d, $^2J_{C,F}$ = 36 Hz); mass spectrum, m/e 160 (M$^+$, 25.2), 132 (100.0); IR, 2967 (s), 1741 (s) (C=O), 1733 (s), 1351 (s), 1238 (s), 1166 (s) (C-F) cm^{-1}. (*Z*)-**5h**: ^{19}F NMR ($CDCl_3$) -131.9 (d, 1 F, $^3J_{F,H_{trans}}$ = 34 Hz).

Ethyl 2-fluoro-3-phenylpropenoate (5i): method B; yield 3.3 g (56%); bp 73-77 °C (0.7 mm) [lit.[19] bp 121-123 °C (8 mm)]; *E*/*Z* = 100/0; GLPC purity 100%. (*E*)-**5i**: ^{19}F NMR ($CDCl_3$) -117.6 (d, 1 F, $^3J_{F,H_{cis}}$ = 22 Hz); ^{1}H NMR ($CDCl_3$) 7.4 (m, 5 H), 6.9 (d, $^3J_{H,F_{cis}}$ = 22 Hz), 4.2 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.2 (t, 3 H); ^{13}C NMR ($CDCl_3$) 160.4 (d, $^2J_{C,F}$ = 36 Hz), 147.0 (d, $^1J_{C,F}$ = 256 Hz), 131.0 (d, $^3J_{C,F}$ = 10 Hz), 129.7 (s), 128.7 (s), 128.0 (s), 121.4 (d, $^2J_{C,F}$ = 26 Hz), 61.6 (s), 13.8 (s); mass spectrum, m/e 194 (M$^+$, 70.2), 195 (8.9), 166 (53.1), 165 (58.2), 149 (70.1), 146 (26.9), 135 (81.8), 130 (12.7), 129 (33.8), 122 (32.9), 121 (39.8), 120 (42.7), 118 (25.1), 109 (16.2), 102 (62.2), 101 (100.0), 95 (16.8), 94 (12.6), 92 (18.2), 91 (10.4), 77 (29.9), 76 (13.0), 74 (15.5), 75 (45.8), 64 (11.1), 63 (22.1), 51 (33.2), 50 (19.5); IR, 1744 (m) (C=O), 1380 (s), 1242 (s), 1144 (s) (C-F), 1134 (s), 1121 (s), 1112 (m) cm^{-1}.

Ethyl 2-fluoro-2,4-hexadienoate (5j): method B; yield 3.4 g (55%); bp 56-59 °C (52 mm); *EE*/*EZ* = 5/95; GLPC purity 100%. (*E*,*Z*)-**5j**: ^{19}F NMR ($CDCl_3$) -131.9 (d, 1 F, $^3J_{F,H_{trans}}$ = 29 Hz); ^{1}H NMR ($CDCl_3$) 6.2 (dq, 1 H, $^3J_{H,F_{trans}}$ = 33 Hz), 5.7 (m, 1 H, $^3J_{H,H_{trans}}$ = 14 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 4.1 (dq, 1 H), 1.8 (dd, 3 H, $^3J_{H,H}$ = 7 Hz, $^4J_{H,H}$ = 4 Hz), 1.3 (t, 3 H); ^{13}C NMR ($CDCl_3$) 160.8 (d, $^2J_{C,F}$ = 35 Hz), 149.1 (d, $^1J_{C,F}$ = 255 Hz), 130.6 (s), 127.6 (s), 118.4 (d, $^2J_{C,F}$ = 21 Hz), 61.5 (s), 14.2 (s), 9.6 (d); mass spectrum, m/e 132 (12.7), 117 (25.3), 104 (45.6), 87 (100.0), 59 (38.6), 57 (18.4), 45 (19.0); IR, 1742 (m) (C=O), 1685 (m), 1325 (s), 1283 (s), 1270 (s), 1140 (s) (C-F) cm^{-1}. (*E*,*E*)-**5j**: ^{19}F NMR ($CDCl_3$) -122.7 (d, 1 F, $^3J_{F,H_{cis}}$ = 17 Hz).

Ethyl 2-fluoro-6-hydroxy-2-hexenoate (5k): method B; yield 4.0 g (76%); bp 75-80 °C (0.7 mm); E/Z = 95/5; GLPC purity 100%. (*E*)-**5k**: ^{19}F NMR ($CDCl_3$) -122.3 (d, 1 F, $^3J_{F,H_{cis}}$ = 22 Hz); ^{1}H NMR ($CDCl_3$) 5.96 (dt, 1 H, $^3J_{H,F_{cis}}$ = 20 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 3.6 (t, 2 H, $^3J_{H,H}$ = 6 Hz), 3.3 (s, 1 H), 2.6 (dt, 2 H, $^3J_{H,H}$ = 8 Hz), 1.7 (pentet, 2 H, $^3J_{H,H}$ = 7 Hz), 1.3 (t, 3 H); ^{13}C NMR ($CDCl_3$) 161.3 (d, $^2J_{C,F}$ = 36 Hz), 147.4 (d, $^1J_{C,F}$ = 252 Hz), 123.1 (d, $^2J_{C,F}$ = 19 Hz), 61.5 (s), 61.3 (s), 31.9 (s), 22.0 (d, $^3J_{C,F}$ = 5 Hz), 14.1 (s); mass spectrum, m/e 176 (M$^+$, 1.0), 177 (0.5), 158 (16.7), 156 (59.1), 131 (16.5), 130 (89.5), 129 (13.3), 128 (38.6), 127 (43.2), 118 (19.4), 117 (56.0), 115 (100.0), 113 (23.4), 110 (45.5), 104 (19.8), 103 (16.6), 102 (41.4), 101 (17.3), 100 (10.0), 99 (35.1), 91 (11.2), 86 (12.5), 85 (29.6), 84 (20.3), 83 (39.5), 82 (47.0), 73 (12.8), 72 (12.2), 71 (18.6), 69 (15.2), 66 (24.9), 65 (12.6), 57 (36.2), 55 (16.5), 53 (11.9), 51 (14.9), 45 (27.4), 44 (11.3), 43 (44.5), 42 (12.6); IR, 3543 (m, br), 2984 (m), 1667 (w) (C=O), 1348 (s), 1135 (s) (C-F), 1133 (s) cm^{-1}. (*Z*)-**5k**: ^{19}F NMR ($CDCl_3$) -130.9 (d, 1 F, $^3J_{F,H_{trans}}$ = 34 Hz).

Ethyl 2,4-Difluoro-5-phenyl-2,4-pentadienoate (5l). Similarly, **5l** was prepared by the general procedure (method A). Ylide generation and addition of ester and DIBAL were accomplished at -50 °C. After the addition of DIBAL, the reaction mixture was stirred at -50 °C for 1 h, warmed to room temperature, and stirred overnight. The reaction mixture was quenched with 60 mL of 6 M HCl, and the organic layer was separated, washed with water (2 × 25 mL), and dried ($MgSO_4$). The dried material was filtered through a silica gel column (20 g of silica gel, 200-425 mesh, Fisher Scientific) to give a pale yellow liquid that was concentrated to afford a dark yellow residue that, on distillation, gave 2.5 g (58%) of **5l**: bp 68-82 °C (0.2 mm); *EE*/*EZ* = 100/0; GLPC purity 90%. ^{19}F NMR (acetone-d_6) (*E*,*E*)-**5l**: -112.3 (d, 1 F, $^3J_{FC=CH_{cis}}$ = 20 Hz), -100.2 (t, 1 F, $^3J_{FC=CH_{cis}}$ = 20 Hz, $^3J_{FCCH}$ = 20 Hz). ^{1}H NMR (acetone-d_6) 7.3 (s, 5 H), 6.6 (m, 2 H, $^3J_{H,F_{cis}}$ = 20 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.3 (t, 3 H); mass spectrum, m/e 239 (M + 1$^+$, 4.8), 238 (M$^+$, 38.2), 218 (11.9), 193 (14.1), 190 (24.6), 173 (40.4), 166 (10.5), 165 (100.0), 164 (90.0), 146 (29.6), 145 (57.1), 144 (12.1), 134 (11.3), 133 (40.4), 125 (13.4), 115 (18.4); IR, 3060 (w), 2984 (w), 1744 (s), 1216 (s), 1143 (m), 1022 (m) cm^{-1}.

Ethyl 2-fluoropropenoate (5m): method A; yield 7.3 g (62%); bp 102-104 °C (atmospheric pressure); GLPC purity 98%; ^{19}F NMR ($CDCl_3$): -117.6 (dd, $^3J_{H,F_{cis}}$ = 12 Hz, $^3J_{H,F_{trans}}$ = 44 Hz); ^{1}H NMR ($CDCl_3$) 5.67 (dd, 1 H (trans to fluorine), $^2J_{H,H_{gem}}$ = 3 Hz, $^3J_{H,F_{trans}}$ = 44 Hz), 5.31 (dd, 1 H, (cis to fluorine), $^3J_{H,F_{cis}}$ = 13 Hz), 4.3 (q, 2 H, $^3J_{H,H}$ = 7 Hz), 1.34 (t, 3 H), ^{13}C NMR ($CDCl_3$) 160.4 (d, $^2J_{C,F}$ = 36 Hz), 153.7 (d, $^1J_{C,F}$ = 262 Hz), 102.4 (d, $^2J_{C,F}$ = 15 Hz), 62.0 (s), 14.1 (s); IR, 1161 (s), 1176 (s), 1320 (s), 1737 (s), 1742 (s) cm^{-1}; high-resolution mass spectral data for $C_5H_7O_2F$, calcd 118.0430, obsd 118.0422.

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Supplementary Material Available: ^{19}F and ^{1}H NMR spectra (31 pages). Ordering information is given on any current masthead page.

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