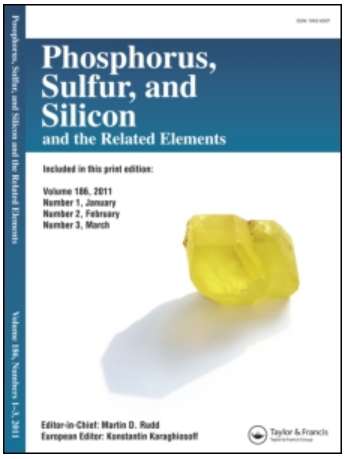

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A ONE-POT SYNTHESIS OF UNSYMMETRICAL AND SYMMETRICAL TETRASUBSTITUTED α-FLUORO-α,β-UNSATURATED ESTERS

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A ONE-POT SYNTHESIS OF UNSYMMETRICAL AND SYMMETRICAL TETRASUBSTITUTED· α-FLUORO-α,β-UNSATURATED ESTERS

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Acylation of $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **1** with acid chlorides RC(O)Cl or phosgene ClC(O)Cl and subsequent reaction of the acylated phosphonate with organometallic reagents (R′M) provide unsymmetrical and symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters, $RR'C{=}CFCO_2Et$ and $R'_2C{=}CFCO_2Et$, in moderate to good yields.

Key words: β-ketophosphonates, betaine, phosgene, perfluorinated Grignard reagents, Emmons reaction, olefins.

INTRODUCTION

α-Fluoro-α,β-unsaturated esters of defined stereochemistry constitute a useful class of compounds in organic synthesis and have been successfully employed as useful building blocks for the synthesis of biologically active monofluorinated retinoids,[1] fluorinated analogues of insect sex pheromones,[2] and pyrethroids.[3] The methods reported for the preparation of the title compounds include the reaction of fluorocarboalkoxy substituted dialkylphosphonate anions with ketones in 48–58% yields,[4] zinc(0)-copper(1) chloride promoted reaction of dichlorofluoroacetate with 3-pentanone in 20% ^{19}F NMR yield,[5] spray-dried potassium fluoride fluorination of chloromalonate in the presence of cyclohexanone in 52% ^{19}F NMR yield,[6] addition of chlorofluorocarbene to enoxysilane and subsequent rearrangement of the cyclopropane,[7] and addition of ketones to perfluorovinyl organometallic reagents.[8] Literature methods for the synthesis of the unsymmetrical and symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters generally lack generality, give low yields and are often limited to aldehydes and simple ketones. Recently, research from our laboratory has focused on the use of fluorocarboethoxy substituted phosphorus or phosphonate ylids as synthons for the preparation of α-fluorocarbonyl compounds such as α-fluoro-α-alkylesters,[9] α-fluoro-β-ketoesters,[10] α-fluoro-α,β-unsaturated esters[11] and α-fluoro-α,β-unsaturated diesters.[12] The reaction of acetylide anions and ylids with acylated phosphonium salts to produce enynes and triphen-

ylphosphine oxide has been reported.[13] Herein, we describe a general, one-pot synthesis of the unsymmetrical and symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters via an intramolecular Wadsworth-Emmons reaction.

RESULTS AND DISCUSSION

The anion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **1** generated from diethyl(carboethoxyfluoromethyl)phosphonate can be readily acylated with acid chlorides such as benzoyl chloride and propanoyl chloride to form the corresponding C-acylated β-ketophosphonates $[(EtO)_2P(O)CF(COR)CO_2Et]$ **2**. The acylated phosphonates exhibit a doublet (J = 76–78 Hz) in the ^{19}F NMR spectrum and the chemical shifts of the fluorine resonances for the acylated phosphonates lie in the range of −169 to −174 ppm. Treatment of the acylated phosphonates with Grignard reagents or lithium acetylides gives unsymmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters (E,Z)-RR'C=CFCO$_2$Et **3** in 52–63% isolated yields.

TABLE I

Preparation of RR'C=CFCO$_2$Et and R$'_2$C=CFCO$_2$Et

$(EtO)_2P(O)CFHCO_2Et \xrightarrow[2)\ RC(O)Cl \\ 3)\ R'M,\ -78°C\ to\ RT]{1)\ n\text{-}BuLi/-78°C} RR'C{=}CFCO_2Et$ (Method A)

$(EtO)_2P(O)CFHCO_2Et \xrightarrow[2)\ ClC(O)Cl \\ 3)\ 2R'M,\ -78°C\ to\ RT]{1)\ n\text{-}BuLi/-78°C} R'_2C{=}CFCO_2Et$ (Method B)

No.	R	R'	M	Method	Isolated[a] yields	E/Z[b]
3a	Ph	Me	MgI	A	63	98/2
3b	Et	C_6F_5	MgBr	A	52	90/10
3c	Et	PhC≡C	Li	A	60	56/44[c]
3d	Et	n-C_5H_{11}C≡C	Li	A	61	62/38
3e	Ph	Ph	MgBr	A	58	---
8a	--	C_2H_5	MgBr	B	51	---
8b	--	CH_3	MgI	B	49	---
8c	--	n-C_3H_7	MgCl	B	51	---
8d	--	Ph	MgBr	B	54	---
8e	--	C_5H_4N	MgBr	B	42[d]	---

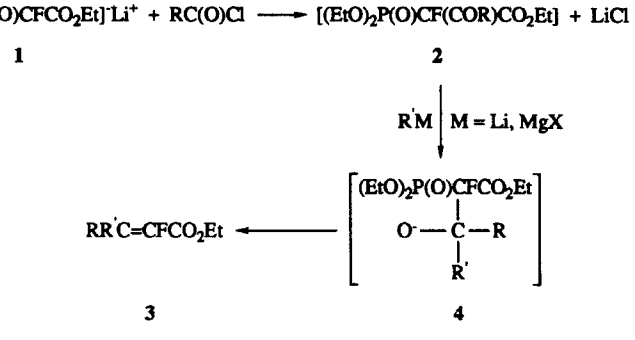
[a]Isolated yields are based on $(EtO)_2P(O)CFHCO_2Et$. [b]E/Z ratios were determined by integration of the vinyl fluoride signals in the ^{19}F NMR spectrum. [c]Ratio before isolation, after repeated column chromatography E/Z was 95/5. [d]^{19}F NMR yield.

The results for the preparation of unsymmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters (E,Z)-RR'C=CFCO$_2$Et **3(a–e)** are summarized in Table I.

The initial step in the synthesis of **3** is nucleophilic attack of the Grignard reagents or lithium acetylides at the ketone group of β-ketophosphonates **2** to form a betaine type intermediate **4**, which intramolecularly collapses to give unsymmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters (E,Z)-RR'C=CFCO$_2$Et **3(a–e)** in moderate to good yields (Scheme I).

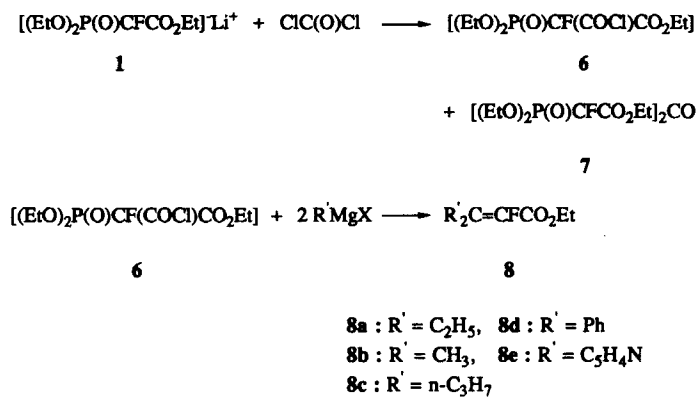
The E/Z ratios were determined by integration of the vinyl fluoride signals in the ^{19}F NMR spectrum. The E/Z assignments of stereochemistry are based on the reports that $^4J_{H,F(cis)}$ is larger than $^4J_{H,F(trans)}$ in typical compounds that contain the unit —HC=CFCO$_2$Et.[12,14] Further evidence for the proposed reaction pathway comes from the detection of the secondary alcohol [(EtO)$_2$P(O)CF(CHOHPh)CO$_2$Et] **5** via ^{19}F NMR analysis. Compound **5** exhibits two resonances at −190.2 ppm (d, d, $^2J_{PCF}$ = 77 Hz, $^3J_{FCCH}$ = 26 Hz) and at −193.5 ppm (d, d, $^2J_{PCF}$ = 83 Hz, $^3J_{FCCH}$ = 29 Hz). This alcohol, which results from the reaction of sodium borohydride with [(EtO)$_2$P(O)CF(COPh)CO$_2$Et], is converted to an E and Z mixture of PhCH=CFCO$_2$Et during work-up.

Similarly, reaction of equimolar quantities of [(EtO)$_2$P(O)CFCO$_2$Et]$^-$Li$^+$ **1** with phosgene ClC(O)Cl (toluene solution) gives the monoacylated phosphonate [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] **6** as the major product. A double acylated product [(EtO)$_2$P(O)CFCO$_2$Et]$_2$CO **7**, which was not isolated, was formed in minor quantities (<5%). The monoacylated phosphonate **6** exhibits a doublet at −161.6 ppm (d, J_{PCF} = 77 Hz) in the ^{19}F NMR spectrum and 3.9 ppm (d, J_{FCP} = 76 Hz) in ^{31}P NMR spectrum. The double acylated product **7** has a resonance at −174.9 ppm (d, d, J_{PCF} = 77, J_{FCCCF} = 10 Hz) in the ^{19}F NMR spectrum and 6.4 ppm (d, J_{FCP} = 79 Hz) in the ^{31}P NMR spectrum. Conversion of **6** to known compounds establishes its structure. Addition of ethanol, benzylamine or one equivalent of ethyl magnesium bromide to a THF solution of the monoacylated phosphonate [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] **6** converts **6** to [(EtO)$_2$P(O)CF(CO$_2$Et)$_2$],



3a : R = Ph, R' = Me
3b : R = Et, R' = C_6F_5
3c : R = Et, R' = PhC≡C
3d : R = Et, R' = n-C_5H_{11}C≡C
3e : R = Ph, R' = Ph

SCHEME I



SCHEME II

$[(EtO)_2P(O)CF(CONHCH_2Ph)CO_2Et]$ and $[(EtO)_2P(O)CF(COEt)CO_2Et]$, which exhibit signals at -175 ppm (d, $J_{FCP} = 78$ Hz), -175 ppm (d, $J_{FCP} = 76$ Hz) and -176 ppm (d, $J_{FCP} = 78$ Hz), respectively in the ^{19}F NMR spectrum.

Treatment of the THF solution of the monoacylated phosphonate **6** with two equivalents of Grignard reagents (R'MgX) transforms **6** to the symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters $R'_2C{=}CFCO_2Et$ **8(a–e)** (Scheme II).

Table I illustrates the results for the preparation of the unsymmetrical and symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters with respect to the acid chlorides, phosgene and organometallic reagents employed in the reaction. Nucleophiles such as Grignard reagents or lithium acetylides react with **2** to afford the unsymmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters (E,Z)-$RR'C{=}CFCO_2Et$ **3** in moderate yields. The use of terminal acetylide anions as nucleophiles provides a direct entry to α-fluoroenynes (**3c** and **3d**). The application of phosgene (toluene solution) as the acylating agent and Grignard reagents as nucleophiles affords the symmetrical tetrasubstituted α-fluoro-α,β-unsaturated esters $R'_2C{=}CFCO_2Et$ **8** with identical β-substituents. Reaction of the monoacylated phosphonate **6** with two equivalents of phenyl magnesium bromide gives **8d** which was identical to an authentic sample **3e** prepared by treatment of the acylated phosphonate $[(EtO)_2P(O)CF(COPh)CO_2Et]$ with one equivalent of phenyl magnesium bromide.

In summary, we have demonstrated that by choice of the appropriate acid halide and nucleophile, one can obtain either the symmetrical or the unsymmetrical tetrasubstituted unsaturated esters in moderate to good yields. Since the β-ketophosphonates, which were formed *in situ*, were allowed to react with organometallic reagents to afford the final products, our procedure provides the convenience of carrying out all the transformations in one pot.

EXPERIMENTAL

Diethyl(carboethoxyfluoromethyl)phosphonate was prepared by a modified literature procedure.[4] Ethyl bromofluoroacetate was prepared similar to the reported preparation of ethyl chlorofluoroacetate.[15] Normality of *n*-butyllithium and Grignard reagents was determined by the methods of Duhamel[16] and Bergbreiter,[17] respectively. Perfluorinated Grignard reagents C_6F_5MgX[18] and lithium acetylides ($PhC{\equiv}CLi$

or n-$C_5H_{11}C{\equiv}CLi$) were prepared by the halogen-metal or hydrogen-metal exchange reaction at low temperature. ^{19}F (against internal $CFCl_3$) and ^{31}P NMR (against external 85% H_3PO_4) spectra were recorded on a 90-MHz multinuclear spectrometer, ^1H and ^{13}C NMR spectra (against internal TMS) were recorded on a Bruker WM360X spectrometer. FTIR spectra were recorded on a Mattson Cygnus 100 FTIR spectrophotometer with a Hewlett-Packard plotter as CCl_4 solutions using a solution cell with 0.1 cm path length. All the GC-MS analyses were performed at 70 eV in the electron-impact mode on a TRIO-1 single quadrapole instrument interfaced to a HP 5895 gas chromatograph. The gas chromatograph was fitted with a 15-foot OV-101 column. High resolution mass spectral analyses were performed with a VG ZAB-HF spectrometer operating at 70 eV in the electron impact mode.

Preparation of Diethyl(carboethoxyfluoromethyl)phosphonate $(EtO)_2P(O)CFHCO_2Et$

A 300 mL three-necked flask equipped with a Teflon-coated magnetic stirbar, a thermometer, and an air condenser (15 cm) topped with a nitrogen tee tube leading to a source of nitrogen was charged with 0.96 mols (125 g, 129 mL) of freshly distilled triethyl phosphite and 0.54 mols (100 g, 63 mL) of ethyl bromofluoroacetate. The contents of the flask were heated to 145°C for 12 hours. Distillation of the reaction mixture at 111–114°C and 1.20 mmHg gave 92 g (71%) of the titled phosphonate; GLPC purity: 99%; ^{19}F NMR: −212.1 (d, d, J_{FCP} = 71.0; J_{FCH} = 46.0); ^{31}P NMR: 10.6 (J_{PCF} = 71.8, J_{PCH} = 9.5, J_{POCH} = 6.2); ^1H NMR: 5.24 (d, d, 1H, J = 46.0, J = 9.5), 4.37–4.21 (m, 6H), 1.31–1.25 (m, 9H); ^{13}C NMR: 164.8 (d, J_{CCF} = 21.8), 84.6 (d, d, J_{CF} = 196.1, J_{CP} = 158.4), 64.3, 64.2, 64.1, 16.4, 16.3, 14.1; GC-MS m/z (relative intensity): 243 (M^+ + 1, 0.31), 242 (M^+, 0.38), 214 (M^+—$CH_2{=}CH_2$, 11.84), 197 (M^+—OEt, 38.78), 187 (30.20), 186 (M^+—$2CH_2{=}CH_2$, 44.49), 169 (M^+—CO_2Et, 18.67), 159 (100.00), 155 (42.04), 137 (M^+—$CFHCO_2Et$, 26.94), 131 (40.82), 130 (31.43), 127 (38.37), 114 (64.08), 109 (93.06), 105 (M^+—$(EtO)_2P(O)$, 4.26), 99 (54.69), 93 (53.88), 81 (88.16), 78 (74.76), 65 (83.27). FTIR spectrum (CCl_4 solution, cm^{-1}): 2984 (m, C—H), 2939 (w), 2932 (w), 1764 (s, C=O), 1444 (m), 1370 (m), 1325 (s, C—F), 1275 (m, P=O), 1272 (s), 1232 (m, C—O—C), 1094 (m), 1053 (m), 1025 (m), 1029 (m, P—O—C), 979 (m).

General Procedure (Method A) for the Preparation of (E/Z)-RR'C=$CFCO_2Et$ **3** *as Described for the Preparation of (E) and (Z)-Ph(CH_3)C=$CFCO_2Et$* (**3a**)

A 250 mL two-necked flask equipped with a septum port, a magnetic stirbar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 40 mL of dry THF and 20.7 mmols (5.0 g) of $(EtO)_2P(O)CFCHCO_2Et$. The contents of the flask were cooled to −78°C via a Dry Ice/IPA slush bath. To the cooled solution, 21.0 mmols (8.4 mL) of a 2.5 M n-hexane solution of n-butyllithium was added dropwise. The resultant bright yellow solution was stirred at −78°C for 20 minutes and then 20.7 mmols (2.9 g) of freshly distilled benzoyl chloride was added dropwise via syringe. The resultant mixture was stirred at −78°C for one hour and then allowed to warm to room temperature over 4 hours. The reaction mixture was cooled again to −78°C then 20 mmols (6.7 mL) of a 3.0 M diethyl ether solution of methylmagnesium iodide was added. The resultant mixture was allowed to warm to room temperature over 6 hours and stirred at that temperature overnight. The reaction mixture was poured into water (50 mL), the organic layer was separated, and the water layer extracted with ether (3 × 40 mL). The ether extracts were combined with the organic layer and the combined fractions washed with dilute hydrochloric acid until the washings were neutral to litmus paper. The resulting solution was washed successively with saturated brine solution (25 mL) and water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to yield a yellow residue. The residue was loaded onto a flash chromatography column and eluted with a n-hexane/ethyl acetate (24/1) mixture to give 2.7 g (63%) of an E and Z mixture of Ph(CH_3)C=$CFCO_2Et$ **3a**; GLPC purity: 97%; bp 79–81°C/0.7 mm Hg. ^{19}F NMR: E/Z = 98/2, (Z)-**3a**: −126.3 (s), (E)-**3a**: −124.3 (q, $^4J_{F,H}$ = 4.4); ^1H NMR: 7.1–7.4 (m, 5H), 4.0 (q, 2H, $^3J_{H,H}$ = 7.0), 2.1 (d, 3H, $^4J_{H,F(cis)}$ = 4.4), 1.0 (t, 3H); ^{13}C NMR: 160.6 (d, $^2J_{C,F}$ = 36), 144.3 (d, $^1J_{C,F}$ = 252), 138.5 (d, $^2J_{C,F}$ = 6), 131.3 (d, $^2J_{C,F}$ = 17), 128.0 (s), 127.7 (s), 127.4 (s), 61.0 (s), 19.2 (d, $^3J_{C,F}$ = 6), 13.6 (s); GC-MS m/z (relative intensity): 209 (M^+ + 1, 1.9), 208 (M^+, 14.8), 162 (M^+—OEt—1, 32.7), 133 (46.6), 115 (M^+—Me—C_6H_5, 61.6), 77 ($C_6H_5^+$, 13.6), 29 ($C_2H_5^+$, 100.0). FTIR spectrum (CCl_4 solution, cm^{-1}): 3061 (w), 3026 (w, Ar-H), 2984 (w, C—H), 1738 (s, C=O), 1662 (w, C=C), 1377 (m), 1262 (s, C—F), 1154 (s, C—O—C).

Preparation of (E) and (Z)-Et(C_6F_5)C=$CFCO_2Et$ (**3b**). Yield: 52%; GLPC purity: 96%; bp 65–74°C/0.5 mmHg. ^{19}F NMR: E/Z = 90/10, (Z)-**3b**: −118.0 (s), (E)-**3b**: −113.5 (s), ortho: −141.5 (d, d, J = 22, J = 7.3), para: −156.4 (t, J = 22), meta: −164.0 (m, J = 7.3); ^1H NMR: 4.2 (q, 2H, $^3J_{H,H}$ = 7.0), 2.6 (q, d, 2H, $^4J_{H,F(cis)}$ = 3.5), 1.2 (t, 3H), 1.1 (t, 3H, $^3J_{H,H}$ = 7.5); ^{13}C NMR: 159.8 (d, $^2J_{C,F}$ = 35), 147.1 (d, $^1J_{C,F}$ = 264), 145.8 (m), 143.0 (m), 140.2 (m), 139.6 (m), 136.8 (m), 122.4 (d, $^2J_{C,F}$ = 24), 62.3 (s), 24.4 (d, $^3J_{C,F}$ = 4), 14.0 (s), 11.5 (s); GC-MS m/z (relative intensity): 313 (M^+ + 1,

9.4), 312 (M^+, 64.7), 284 (M^+ + 1-Et, 100.0), 267 (M^+—OEt, 24.1), 239 (M^+—CO_2Et, 36.0), 219 (63.8), 205 (37.4), 199 (35.3), 193 (45.0), 187 (31.9), 169 (65.9). FTIR spectrum (CCl_4 solution, cm^{-1}): 2983 (w), 2940 (w, C—H), 1735 (s, C=O), 1653 (m, C=C), 1521 (s), 1300 (s), 1210 (m, C—F), 1156 (m, C—O—C).
HRMS: Calcd: 312.0585; Found: 312.0575.

Preparation of (E) and (Z)-Et(PhC≡C)C=CFCO$_2$Et (**3c**). Yield: 60%, 100% pure by TLC. ^{19}F NMR: E/Z=56/44, (Z)-**3c**: −114.0 (s), (E)-**3c**: −121.0 (t, $^4J_{F,H}$ = 3.6); ^{1}H NMR: 7.51 (m, 2H), 7.36 (m, 3H), 4.35 (q, 2H, $^3J_{H,H}$ = 7.14), 2.47 (q, d, 2H, $^4J_{H,F(cis)}$ = 3.74), 1.37 (t, 3H), 1.23 (t, 3H, $^3J_{H,H}$ = 7.54); ^{13}C NMR: 159.8 (d, $^2J_{C,F}$ = 34), 150.5 (d, $^1J_{C,F}$ = 260), 131.7, 128.9, 128.4, 122.9, 119.3 (d, $^2J_{C,F}$ = 28), 100.3 (d, $^3J_{C,F}$ = 10), 84.7 (s) 61.6 (s), 24.0 (d, $^3J_{C,F}$ = 4), 14.2 (s), 12.2 (s); GC-MS m/z (relative intensity): (E)-**3c**: 248 (M^++2, 0.45), 247 (M^++1, 4.53), 246 (M^+, 30.46), 218 (M^+—CH_2=CH_2, 71.26), 217 (M^+—Et, 100), 201 (M^+—OEt, 17.10), 173 (M^+—CO_2Et, 52.30), 169 (M^+—C_2H_5, 17.24), 145 (M^+—PhC≡C, 8.80). (Z)-**3c**: 248 (M^+ + 2, 1.54), 247 (M^+ + 1, 0.02), 246 (M^+, 60.33), 218 (M^+—CH_2=CH_2, 92.56), 217 (M^+—Et, 100), 201 (M^+—OEt, 24.17), 173 (M^+—CO_2Et, 52.89), 169 (M^+—C_2H_5, 15.70), 145 (M^+—Ph—C≡C, 10.28). FTIR spectrum (CCl_4 solution, cm^{-1}): 3083 (w), 3063 (w), 3036 (w, Ar-H), 2907 (m), 2876 (w, C—H), 2206 (w, C≡C), 1729 (s, C=O), 1624 (m, C=C), 1370 (m), 1336 (s), 1277 (m, C—F), 1184 (m, C—O—C).
HRMS: Calcd: 246.1056; Found: 246.1050.

Preparation of (E) and (Z)-Et(n—C$_5$H$_{11}$C≡C)C=CFCO$_2$Et (**3d**). Yield: 61%; GLPC purity: 99.9%; bp 82–90°C/0.4 mmHg, ^{19}F NMR: E/Z = 62/38, (Z)-**3d**: −116.9 (s), (E)-**3d**: −123.3 (m); ^{1}H NMR: 4.30 (q, 2H, $^3J_{H,H}$ = 7.00), 2.40 (m, 2H), 1.34 (m, 11H), 1.30 (m, 3H), 1.10 (t, 3H); GC-MS m/z (relative intensity): 240 (M^+, 0.3), 156 (29.9), 155 (30.6), 109 (60.8), 91 (45.5), 83 (35.7), 81 (32.4), 51 (60.9). FTIR spectrum (CCl_4 solution, cm^{-1}): 2968 (s), 2873 (s, C—H), 2222 (w, C≡C), 1728 (s, C=O), 1626 (m, C=C), 1378 (m), 1305 (s), 1266 (s, C—F), 1156 (m, C—O—C).

General Procedure (Method B) for the Preparation of R$_2$C=CFCO$_2$Et **8** *as Described for the Preparation of (C$_2$H$_5$)$_2$C=CFCO$_2$Et* (**8a**)

A 200 mL two necked flask equipped with a septum port, a magnetic stirbar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 50 mL of dry THF and 16.0 mmols (3.9 g) of $(EtO)_2P(O)CFHCO_2Et$. The contents of the flask were cooled to −78°C via a Dry Ice/IPA slush bath. To the cooled solution, 16.0 mmols (6.4 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise. The resultant bright yellow solution was stirred at −78°C for 20 minutes and then 16.0 mmols (8.2 mL) of a 1.93 M toluene solution of phosgene was added dropwise via syringe. The resultant mixture was stirred at −78°C for one hour and then allowed to warm to room temperature over 4 hours. The reaction mixture was cooled again to −78°C then 30 mmols (10.0 mL) of a 3.0 M diethyl ether solution of ethylmagnesium bromide was added. The resultant mixture was allowed to warm to room temperature over 6 hours and stirred at that temperature overnight. The reaction mixture was poured into water (60 mL), the organic layer was separated, and the water layer extracted with ether (3 × 50 mL). The ether extracts were combined with the organic layer and the combined fractions washed with dilute hydrochloric acid until the washings were neutral to litmus paper. The resulting solution was washed successively with saturated brine solution (30 mL) and water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to yield a yellow residue. The residue was loaded onto a flash chromatography column and eluted with a *n*-hexane/ethyl acetate (24/1) mixture to give 1.4 g (51%) of **8a**; GLPC purity: 99%; bp 62–64°C/3.6 mmHg. ^{19}F NMR: −130.0 (s); ^{1}H NMR: 4.25 (q, 2H, $^3J_{H,H}$ = 7.08), 2.50 (q, d, 2H, $^4J_{H,F(trans)}$ = 1.46), 2.20 (q, d, 2H, $^4J_{H,F(cis)}$ = 3.51), 1.31 (t, 3H), 1.10 (t, d, 3H), 1.05 (t, 3H, $^3J_{H,H}$ = 7.56); ^{13}C NMR: 161.0 (d, $^2J_{C,F}$ = 35), 145.0 (d, $^1J_{C,F}$ = 248), 140.0 (d, $^2J_{C,F}$ = 11), 61.0 (s), 23.4 (d, $^3J_{C,F}$ = 8), 23.2 (s), 14.2 (s), 12.8 (s), 12.2 (s); GC-MS m/z (relative intensity): 174 (M^+, 32), 146 (M^+—CH_2=CH_2, 43), 129 (M^+—OEt, 33), 127 (24.8), 117 (M^+—Et—CH_2=CH_2, 100), 105 (51.0), 99 (53.9), 85 (45.0), 81 (33.5), 79 (51.0), 73 (45.7), 69 (30.5), 53 (66.5), 51 (48.3). FTIR spectrum (CCl_4 solution, cm^{-1}): 2982 (m, C—H), 2976 (vs), 2938 (m), 2877 (m), 1727 (vs, C=O), 1659 (m, C=C), 1464 (s), 1369 (m), 1299 (s), 1293 (s, C—F), 1290 (s), 1277 (m), 1213 (m, C—O—C), 1101 (s), 1029 (m).

Preparation of (CH$_3$)$_2$C=CFCO$_2$Et (**8b**). Yield: 1.10 g (49%); GLPC purity: 96%; ^{19}F NMR: −128.0 (s); ^{1}H NMR: 4.29 (q, 2H, $^3J_{H,H}$ = 7.11), 2.12 (d, 3H, $^4J_{H,F(trans)}$ = 3.16), 1.87 (d, 3H, $^4J_{H,F(cis)}$ = 4.15), 1.34 (t, 3H); ^{13}C NMR: 161.3 (d, $^2J_{C,F}$ = 35), 143.7 (d, $^1J_{C,F}$ = 245), 129.5 (d, $^2J_{C,F}$ = 14), 60.8 (s), 18.5 (s), 18.4 (s), 14.2 (s); GC-MS m/z (relative intensity): 146 (M^+, 32.9), 118 (M^+—CH_2=CH_2, 100.0), 103 (M^+—CH_2=CH_2—Me, 13.1), 101 (M^+—OEt, 79.9), 100 (72.7), 74 (23.5), 73 (44.7), 72 (58.0), 59 (75.3), 53 (51.1). FTIR spectrum (CCl_4 solution, cm^{-1}): 2981 (m), 2961 (m, C—H), 2934 (m), 1724 (s, C=O), 1700 (w), 1672 (s, C=C), 1476 (w), 1393 (m), 1383 (m), 1374 (s), 1368 (m), 1299 (s), 1236 (s, C—F), 1155 (m, C—O—C), 1023 (m).

Preparation of (n—C_3H_7)$_2$C=CFCO$_2$Et (**8c**). Yield: 1.60 g (51%); GLPC purity: 99%; bp 59–61°C/1.2 mmHg. ^{19}F NMR: −128.0 (s); ^{1}H NMR: 4.27 (q, 2H, $^3J_{H,H}$ = 7.08), 2.50 (t, d, 2H, $^4J_{H,F(trans)}$ = 1.32), 2.20 (t, d, 2H, $^4J_{H,F(cis)}$ = 3.59), 1.50 (sextet, d, 4H, $^3J_{H,H}$ = 7.56), 1.34 (t, 3H), 0.95 (t, 6H, $^3J_{H,H}$ = 7.30); ^{13}C NMR: 161.0 (d, $^2J_{C,F}$ = 35), 144.0 (d, $^1J_{C,F}$ = 247), 137.0 (d, $^2J_{C,F}$ = 11), 60.8 (s), 32.4 (d, $^3J_{C,F}$ = 7), 32.1 (s), 21.9 (s), 20.9 (s), 14.2 (s), 14.1 (s); GC-MS m/z (relative intensity): 202 (M^+, 27), 174 (M^+—CH_2=CH_2, 11), 159 (10.8), 157 (M^+—OEt, 31), 141 (25.0), 133 (16.5), 131 (M^+—C_3H_7—CH_2=CH_2, 40), 91 (30.9), 79 (33.2), 67 (38.7), 55 (53.9), 43 (69.2), 41 (100.0). FTIR spectrum (CCl_4 solution, cm^{-1}): 2964 (s), 2934 (m), 2874 (m, C—H), 1723 (s, C=O), 1655 (m, C=C), 1465 (m), 1446 (m), 1380 (w), 1368 (s), 1301 (s), 1280 (s), 1251 (m, C—F), 1101 (m), 1028 (m, C—O—C). HRMS: Calcd: 202.1369; Found: 202.1380.

Preparation of (Ph)$_2$C=CFCO$_2$Et (**8d**). Yield: 2.40 g (54%); GLPC purity: 93%; ^{19}F NMR: −123.0 (s); ^{1}H NMR: 7.18–7.82 (m, 10H), 4.09 (q, 2H, $^3J_{H,H}$ = 7.11), 1.34 (t, 3H); ^{13}C NMR: 161.0 (d, $^2J_{C,F}$ = 36), 144.0 (d, $^1J_{C,F}$ = 241), 137.6, 132.3, 130.0, 128.6, 128.2 (d, $^2J_{C,F}$ = 10.6), 61.3 (s), 13.6 (s); GC-MS m/z (relative intensity): 270 (M^+, 100), 241 (20.9), 225 (29.4), 198 (20.7), 197 (34.7), 196 (66.2), 74 (22.7), 59 (47.6). FTIR spectrum (CCl_4 solution, cm^{-1}): 3085 (m), 3026 (m, Ar-H), 2983 (m, C—H), 2960 (m), 1730 (vs, C=O), 1664 (s, C=C), 1600 (m), 1318 (s), 1276 (s), 1272 (s), 1268 (s, C—F), 1265 (s), 1134 (m, C—O—C), 1132 (s), 1119 (m).

Preparation of [(C_5H_4N)$_2$C=CFCO$_2$Et] (**8e**). Yield: 42%. ^{19}F NMR: −128.0 (s). ^{1}H NMR: 8.45 (2H), 7.56 (2H), 7.25 (4H), 4.28 (q, 2H, $^3J_{H,H}$ = 7.11), 1.33 (t, 3H).

Quenching of [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] with Ethanol

A 25 mL two-necked flask equipped with a septum port, a magnetic stirbar, and a reflux water condenser topped with a nitrogen tee tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 8 mL of dry THF and 4.0 mmols (0.96 g) of (EtO)$_2$P(O)CFHCO$_2$Et. The contents of the flask were cooled to −78°C via a Dry Ice/IPA slush bath. To the cooled solution, 4.0 mmols (1.60 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise via syringe. The resultant bright yellow solution was stirred at −78°C for 20 minutes and then 4.0 mmols (2.1 mL) of a 1.93 M toluene solution of phosgene was added dropwise via syringe. The resultant mixture was stirred at −78°C for one hour. ^{19}F NMR analysis at room temperature indicated the complete consumption of the ylide and the presence of the monoacylated phosphonate [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] at −161.6 ppm (d, J_{FCP} = 77). To an aliquot of the reaction mixture placed in a NMR tube, a few drops of ethanol were added and the resultant homogeneous solution was mixed thoroughly. ^{19}F NMR analysis of the resultant mixture indicated the absence of the original doublet at −161.6 ppm and the formation of a new doublet at −175.0 ppm (d, J_{FCP} = 78). The chemical shift and coupling constant of the doublet were identical to a sample of (EtO)$_2$P(O)CF(CO$_2$Et)$_2$ prepared via reaction of (EtO)$_2$P(O)CFCO$_2$Et with ClC(O)OEt.[19]

Quenching of [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] with Benzyl Amine

A solution of 2.1 mmols (0.51 g) of (EtO)$_2$P(O)CFHCO$_2$Et and 4 mL of dry THF were cooled to −78°C in a Dry Ice/IPA slush bath under N_2. To the cooled solution, 2.1 mmols (0.84 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise via syringe. The resultant bright yellow solution was stirred at −78°C for 20 minutes and then 2.1 mmols (1.1 mL) of a 1.93 M toluene solution of phosgene was added dropwise via syringe. The resultant mixture was stirred at −78°C for one hour and then allowed to warm to room temperature. The reaction mixture cooled to −50°C, 2.0 mmols (0.21 g, 0.22 mL) of freshly distilled benzyl amine was added via syringe. Addition of the amine changed the colorless monoacylated phosphonate solution to a white precipitate. The resultant heterogeneous mixture was allowed to warm to room temperature over 2 hours and stirred at that temperature overnight. ^{19}F NMR analysis of the reaction mixture indicated signals at −175.0 ppm (d, J_{FCP} = 76) and −194.0 ppm (d, J_{FCH} = 49). The doublets at −175.0 ppm and −194.0 ppm are consistent with related phosphonates[12] and substituted α-fluoromalonate derivatives[10] and were assigned to [(EtO)$_2$P(O)CF(CONHCH$_2$Ph)CO$_2$Et] and [PhCH$_2$NHCOCFHCO$_2$Et], respectively.

Quenching of [(EtO)$_2$P(O)CF(COCl)CO$_2$Et] with One Equivalent of Ethylmagnesium Bromide

A solution of 4.0 mmols (0.96 g) of (EtO)$_2$P(O)CFHCO$_2$Et and 8 mL of dry THF were cooled to −78°C in a Dry Ice/IPA slush bath under N_2. To the cooled solution, 4.0 mmols (1.60 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise via syringe. The resultant mixture was stirred at −78°C for 20 minutes and then 4.0 mmols (2.1 mL) of a 1.93 M toluene solution of phosgene was added dropwise via syringe. The resultant mixture was stirred at −78°C for one hour. ^{19}F NMR analysis at room temperature indicated the complete consumption of the ylide and the presence of the

$[(EtO)_2P(O)CF(COCl)CO_2Et]$. To the cooled solution, 4.0 mmols (1.4 mL) of a 3.0 M diethyl ether solution of ethylmagnesium bromide was added dropwise via syringe. The resultant mixture was stirred at −78°C for 20 minutes and then allowed to warm to 0°C over 4 hours. ^{19}F NMR analysis at room temperature indicated the absence of the original doublet at −161.6 ppm and the formation of a new doublet at −176.0 ppm (d, J_{FCP} = 78). The doublet at −176.0 ppm was similar to $[(EtO)_2P(O)CF(COPh)CO_2Et]$ prepared via reaction of $(EtO)_2P(O)\bar{C}FCO_2Et$ with $PhC(O)Cl$.[20]

Reaction of the $[(EtO)_2P(O)CF(COPh)CO_2Et]$ with Sodium Borohydride

A solution of 2.98 mmols (0.72 g) of $(EtO)_2P(O)CFHCO_2Et$ and 6 mL of dry THF were cooled to −78°C in a Dry Ice/IPA slush bath under N_2. To the cooled solution, 3.0 mmols (1.2 mL) of a 2.5 M *n*-hexane solution of *n*-butyllithium was added dropwise via syringe. The reaction mixture was stirred at −78°C for 20 minutes followed by dropwise addition of 2.98 mmols (0.42 g) freshly distilled benzoyl chloride. The resultant mixture was stirred at −78°C for one hour and then allowed to warm to room temperature. ^{19}F NMR analysis of the reaction mixture indicated the presence of the acylated phosphonate $[(EtO)_2P(O)CF(COPh)CO_2Et]$ at −168.0 ppm (d, J_{FCP} = 77). ^{31}P NMR: 7.21 ppm (d, J_{FCP} = 78). To the reaction mixture, 2.5 mmols (0.1 g) of sodium borohydride and 0.5 mL of water were added and the resultant mixture was stirred at room temperature for two hours. ^{19}F NMR analysis of the reaction mixture indicated 4 sets of signals at −116.3 ppm (d, J = 22); and −124.9 ppm (d, J = 37); −190.2 ppm (d, d, J = 77, J = 26) and −193.5 ppm (d, d, J = 83, J = 29). The two doublets at −116.3 ppm and −124.9 ppm were assigned to the two geometrical isomers of the unsaturated ester $PhCH{=}CFCO_2Et$, whereas, the two doublet of doublets at −190.2 ppm and −193.5 ppm were assigned to the two diastereoisomers of the reduced acylated phosphonate $[(EtO)_2P(O)CF(CHOHPh)CO_2Et]$.[10]

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