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Isolation and Characterization of Intermediate in the Synthesis of α-Fluorodiesters

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The anion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$, pregenerated from its precursor diethyl (carboethoxyfluoromethyl)phosphonate $(EtO)_2P(O)CFHCO_2Et$ and *n*-butyllithium, was added *via* syringe to a THF solution of ethyl oxalyl chloride to yield an acylated phosphonate $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$. *In situ* reaction with Grignard reagents RMgX produces the α-fluorodiesters (*E,Z*)-$R(CO_2Et)C{=}CFCO_2Et$ in good yields. In contrast, addition of ethyl oxalyl chloride to a THF solution of diethyl (carboethoxyfluoromethyl)phosphonate anion gives an isolated intermediate $(EtO)_2P(O)CFCO_2Et(CO_2Et)C{=}CFCO_2Et$. Subsequent reaction of this isolated intermediate with Grignard reagents also affords a one-pot synthesis of the α-fluorodiesters with high *E*-stereoselectivity. The *E*-stereoselectivity increases when HMPT or DMPU is used as a cosolvent in the preparation of diethyl 2-fluoro-3-phenylfumarate (*E,Z*)-$Ph(CO_2Et)C{=}CFCO_2Et$.

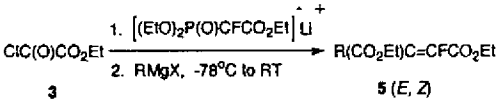
INTRODUCTION

Interest in new methods to generate vinyl fluorides has increased[1,2] because fluoroolefins are potential mechanism-based enzyme inhibitors[3,4] and can be used as isosteric replacements for an amide bond in peptides.[5] α-Fluoroesters are reagents of considerable interest in synthetic organofluorine chemistry, and a number of them have been successfully employed as intermediates in the synthesis of biologically active monofluorinated heterocycles[6,7] and fluorine-substituted isoprenyl derivatives.[8] Methods in the literature for the preparation of α-fluorodiesters generally lack stereospecificity and generality, and are often arduous to carry out on a practical scale. Thus, the condensation of carboethoxymethylenetriphenylphosphorane with diethyl oxalofluoroacetate in DMF gave a 1:1 mixture of ethylenic triethylesters $(EtO_2CCFH)(CO_2Et)C{=}CHCO_2Et$ and the isomerization product, $(EtO_2CCH_2)(CO_2Et)C{=}CFCO_2Et$.[9] Machleidt and Grell initially reported the reaction of diethyl (carboethoxyfluoromethyl)phosphonate anion with diethyl oxalate to give diethyl 2-fluoro-3-ethoxyfumarate in 30% yield.[10] Recently, we have demonstrated that addition of the pregenerated carbanion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ **2** to a THF solution of ethyl oxalyl chloride **3** at -78 °C forms the acylated phosphonate $(EtO)_2P(O)CF(COCO_2R)CO_2Et$ **4**. *In situ* reaction of **4** with Grignard reagents affords α-fluoro-α,β-unsaturated diesters $R(CO_2R)C{=}CFCO_2Et$ **5** in moderate to good yields with high *E*-stereoselectivity.[11,12] Herein, the different experimental methods for the synthesis of α-fluorodiesters are reported. Thus, addition of ethyl oxalyl chloride **3** to a THF solution of diethyl (carboethoxyfluoromethyl)phosphonate anion **2** gives an intermediate $(EtO)_2P(O)CFCO_2Et(CO_2Et)C{=}CFCO_2Et$ **6**. Subsequent reaction of this isolated intermediate with Grignard reagents also affords a one-pot synthesis of the α-fluorodiesters. A high degree *E*-isomer of product $Ph(CO_2Et)C{=}CFCO_2Et$ has been obtained in presence of HMPA or DMPU as a cosolvent. The possible reaction mechanism for the synthesis of α-fluorodiesters is also discussed.

RESULTS AND DISCUSSION

Addition of a THF solution of the anion **2** to a THF solution of ethyl oxalyl chloride **3** forms the corresponding C-acylated phosphonates $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$ **4** in 90% ^{19}F NMR yields.[12] Treatment of the acylated phosphonate **4** with one equivalent of Grignard reagents RMgX gave α-fluoro-α,β-unsaturated diesters $R(CO_2Et)C{=}CFCO_2Et$ **5** in good isolated yields (Scheme I, Method A).[11,12]

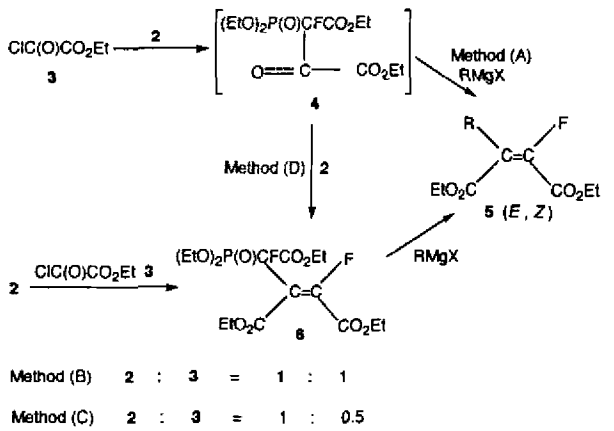
Scheme I



In contrast, the α-fluorodiesters (*E,Z*)-$R(CO_2Et)C{=}CFCO_2Et$ **5** were also obtained by the addition of ethyl oxalyl chloride to the anion **2** followed by the reaction with Grignard reagents. In this case, reaction of **2** with **4** leading the intermediate **6** (Scheme II) should be involved as a second step in the reaction pathway as described below.

Addition of 1.0 equivalent (Method B) or 0.5 equiva-

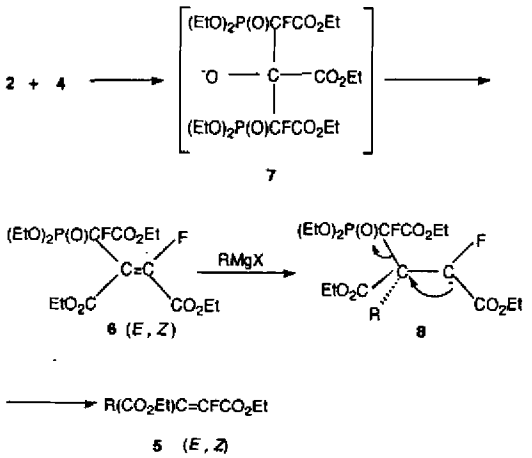
Scheme II



lent (Method C) of ethyl oxalyl chloride to a THF solution of the anion **2** at -78 °C gave the intermediate **6** in 50% isolated yield. This intermediate is identical to the product which is prepared by addition of **2** to an acylated phosphonate **4** (Method D). Compound **6** was isolated with flash column chromatography (hexane/ethyl acetate = 1/1).

The most likely mechanism for the reaction of **6** with Grignard reagents RMgX to give (*E,Z*)-R(CO_2Et)C=$CFCO_2$Et **5** is illustrated in Scheme III. Addition of 1.0 equivalent (Method B) or 0.5 equivalent (Method C) of ethyl oxalyl chloride to a THF solution of **2** gives α-fluoro-β-keto phosphonate **4**. Further attack of **2** on **4** affords the intermediate **6** through the adduct **7**. Addition-elimination of **6** with RMgX provides **5**. In Method B, the excess ethyl oxalyl chloride acidifies the reaction mixture once it is poured into water in the workup process.

Scheme III



The results for the preparation of several α-fluorodiesters **5** by different methods are summarized in Table 1.

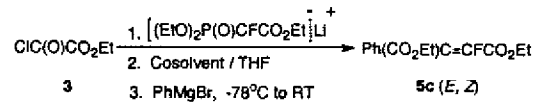
Table 1. Preparation of α-Fluorodiesters (*E,Z*)-R(CO_2Et)C=$CFCO_2$Et **5**

Products	R	X	*E/Z*[b]	Method	Isolated yields (%)[a]
5a	Me	I	100/0	A	52
5a	Me	I	100/0	B	51
5a	Me	I	100/0	C	51
5a	Me	I	100/0	D	24
5b	Et	Br	96/4	A	56
5b	Et	Br	96/4	B	52
5b	Et	Br	96/4	C	52
5b	Et	Br	96/4	D	25
5c	Ph	Br	60/40	A	55
5c	Ph	Br	60/40	B	60
5c	Ph	Br	60/40	C	60
5c	Ph	Br	60/40	D	26

[a] Isolated yields of Methods A and D are based on $(EtO)_2P(O)CFHCO_2Et$, methods B and C are based on $(EtO)_2P(O)CFCO_2Et(CO_2Et)C=CFCO_2Et$.
[b] *E/Z* ratio was obtained by ^{19}F NMR integration of the vinyl fluorine signals.

In Methods B, C or D, reaction of **6** with MeMgI, EtMgBr and PhMgBr gives (*E,Z*)-R(CO_2Et)C=$CFCO_2$Et **5a** (R = Me, *E/Z* = 100/0), **5b** (R = Et, *E/Z* = 96/4) and **5c** (R = Ph, *E/Z* = 60/40) which show the same *E/Z* ratios *via* the reaction of **4** with the corresponding Grignard reagents in Method A, respectively. A high degree of *E*-stereoselectivity was observed in most of the reactions reported in Table 1. The repulsive interactions between R and fluorine in the product **5** possibly resulted in the same *E/Z* ratios in methods A, B, C and D. The *E/Z* ratios of **5** were determined by integration of the vinyl fluorine signals in the ^{19}F NMR spectra. For compounds with the general formula R(CO_2Et)C=$CFCO_2$Et, the vinyl fluorine of the *Z*-isomer exhibits a downfield signal compared to the vinyl fluorine resonance of the *E*-isomer.[11,12,13] The assignment of Me(CO_2Et)C=$CFCO_2$Et **5a** was also confirmed by Nuclear Overhauser Effect (NOE) experiments.[11,12] The *E/Z* assignments of stereochemistry for **5a** and **5b** are also based on the reports that $^4J_{H,F(cis)}$ is larger than $^4J_{H,F(trans)}$ in typical compounds that contain the unit -HCC=$CFCO_2$Et,[11,12,13,14,15] and $^4J_{F,F(cis)}$ is larger than $^4J_{F,F(trans)}$ in typical compounds that contain the unit -FCC=$CFCO_2$Et.[16,17] The fluorine signals in (*E,Z*)-Et(CO_2Et)C=$CFCO_2$Et **5b** exhibit resonances at -128.4 ppm (t, *J* = 2.87 Hz) for *E*-isomer and -116.7 ppm (s) for *Z*-isomer. The stereoselectivity of **5c** prepared by Method A was studied in Table 2. The presence of hexamethylphosphoric triamide (HMPT) or *N,N'*-dimethylpropyleneurea (DMPU) as cosolvent increased the *E*-stereoselectivity from *E/Z* = 60/40 up to 74/26. However, the presence of lithium chloride (LiCl) in THF did not alter the *E/Z* ratio (59/41).

Table 2. Effect of Metal Ion and/or Cosolvent on the Stereochemistry of **5c**



No.	Metal ion or Cosolvent	*E/Z*[a]	Yields (%)[b]
1	THF	60/40	55[c]
2	THF/HMPT	70/30	69
3	THF/DMPU	74/26	68
4	THF/2LiCl	59/41	72

[a] *E/Z* ratio by ^{19}F NMR integration of the vinyl fluorine signals.
[b] ^{19}F NMR yields. $C_6H_5CF_3$ as internal standard.
[c] Isolated yield based on $(EtO)_2P(O)CFHCO_2Et$.

Although the exact cause for the same *E/Z* ratios in methods A, B, C and D was not clear, the nucleophilic addition of Ph group to the carbonyl group of α-fluoro-β-keto phosphonate **4** in method A to form the two diastereoisomeric intermediate alkoxide ions is well documented.[12,18] Different isomer ratios are possible for (*E,Z*)-$Ph(CO_2Et)C=CFCO_2Et$ **5c** when the alkoxide ions are associated with the lithium cation, or if the cation is coordinated by HMPT or DMPU and removed from the reaction site.

CONCLUSION

Addition of the pregenerated carbanion $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ to a THF solution of ethyl oxalyl chloride at -78 °C forms the acylated phosphonate $(EtO)_2P(O)CF(COCO_2R)CO_2Et$. *In situ* reaction of the acylated phosphonate with Grignard reagents affords α-fluorodiesters $R(CO_2R)C=CFCO_2Et$ in good yields with high *E*-stereoselectivity and clean reaction. However, addition of ethyl oxalyl chloride to a THF solution of diethyl (carboethoxyfluoromethyl)phosphonate anion gives an isolated intermediate $(EtO)_2P(O)CFCO_2Et(CO_2Et)C=CFCO_2Et$. Subsequent reaction of the intermediate with Grignard reagents also affords a one-pot synthesis of the α-fluorodiesters.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on a Bruker WM360X spectrometer and were referenced against internal $(CH_3)_4Si$. ^{31}P NMR spectra were recorded on a Bruker AM-300WB multinuclear spectrometer and were referenced against external 85% H_3PO_4. ^{19}F NMR spectra were recorded on a Bruker MSL-300 multinuclear spectrometer and were referenced against internal $CFCl_3$. FTIR spectra were recorded on a Mattson Cygnus 100 FTIR spectrophotometer in CCl_4 solutions using a solution cell with 0.1 cm path length. All the mass spectral 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. Diethyl (carboethoxyfluoromethyl)phosphonate was prepared by the reaction of ethyl bromofluoroacetate with triethyl phosphite.[12,19] Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Ethyl oxalyl chloride and hexamethylphosphoric triamide (HMPT) were distilled prior to use. *N,N'*-dimethylpropyleneurea (DMPU) and lithium chloride were used without further purification. Normality of 2.5 M *n*-butyllithium reagent was determined by the method of the Duhamel procedure.[20] Normality of Grignard reagents prepared from RX and turning magnesium were determined by the method of Bergbreiter and Pendergrass.[21]

General Procedure for Preparation of $R(CO_2Et)C=CFCO_2Et$ 5 as Described for Preparation of (*E*)- and (*Z*)-Diethyl 2-Fluoro-3-phenyl Fumarate 5c from 1 in Method A, B, C and D

Method A

Under nitrogen atmosphere, to a solution of $(EtO)_2P(O)CFHCO_2Et$ (3.90 g, 16.0 mmol) in THF (30 mL) cooled to -78 °C (dry ice/IPA bath), 2.5 M *n*-hexane solution of *n*-butyllithium (6.4 mL, 16.0 mmol) was added dropwise *via* syringe. The resultant bright yellow solution was stirred at -78 °C and maintained at that temperature. Into another 250 mL three-necked flask were placed ethyl oxalyl chloride (2.18 g, 16.0 mmol, 1.9 mL) and THF (20 mL). The contents of the flask were stirred and cooled to -78 °C, and then the cold anion solution in the first flask was added dropwise *via* syringe. The resulting mixture was stirred at -78 °C for one hour and then allowed to warm to -10 °C over 5 h. ^{19}F NMR analysis of the reaction mixture revealed the complete consumption of the anion and the presence of the product $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$ at -177.9 ppm (d, $^2J_{F,P}$ = 73.3 Hz). The reaction mixture was cooled again to -78 °C and to the solution, 16 mmol (5.4 mL) of a 3.0 M diethyl ether solution of phenylmagnesium bromide was added dropwise *via* syringe. The resultant mixture was allowed to warm to room temperature over 6 h and stirred at that temperature overnight. ^{19}F NMR analysis of the reaction mixture indicated the absenee of $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$ and the formation of the titled compound. The reaction mixture was poured into water (60 mL), the or-

ganic layer separated, and the water layer extracted with ether (3 × 50 mL). The ether extracts were combined with the organic layer, and the combined fractions were 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. The residue was loaded onto a flash chromatography column (120 g silica gel, 200-425 mesh) and eluted with a hexane/ethyl acetate (24/1) mixture to obtain 2.34 g (55%, based on $(EtO)_2P(O)CFHCO_2Et$) of the titled compound. *E/Z* ratio was determined by ^{19}F NMR analysis to be 60 to 40. (*E*-**5c**: ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -128.6 (s), GC-MS *m/z* (relative intensity): 266 (M^+, 56.76), 238 (M^+-CH_2=CH_2, 7.59), 221 (M^+-OEt, 20.97), 193 (M^+-CO_2Et, 84.95), 190 (M^+-Ph+H, 100), 165 (96.77). (*Z*)-**5c**: ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -113.3 (s); GC-MS *m/z* (relative intensity): 266 (M^+, 43.21), 238 (M^+-CH_2=CH_2, 6.70), 221 (M^+-OEt, 26.43), 193 (M^+-CO_2Et, 54.64), 190 (M^+-Ph+H, 95.57), 165 (M^+-CO_2Et-CH_2=CH_2, 100). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.27 (t, 3H), 1.37 (t, 3H), 4.28 (q, 2H, $^3J_{H,H}$ = 7.14 Hz), 4.35 (q, 2H, $^3J_{H,H}$ = 7.12 Hz), 7.26-7.55 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.0 (s), 14.0 (s), 62.0 (s), 62.1 (s), 128.0 (d), 128.3, 128.8 (d, $^2J_{C,F}$ = 15), 129, 130, 131, 134, 147.0 (d, $^1J_{C,F}$ = 275 Hz), 148.0 (d, $^1J_{C,F}$ = 273 Hz), 159.0 (d, $^2J_{C,F}$ = 34 Hz), 160.0 (d, $^2J_{C,F}$ = 36 Hz), 164.0 (s), 165.0 (d, $^3J_{C,F}$ = 12 Hz). FTIR spectrum (CCl_4 solution, cm^{-1}): 3087 (m), 3026 (m, Ar-H), 2984 (m), 2939 (m, C-H), 1748 (s), 1735 (s, C=O), 1652 (m, C=C), 1370 (s), 1296 (s, C-F), 1241 (s), 1146 (m, C-O-C).

Method B and C: *via* isolation of (*E,Z*)-$(EtO)_2P(O)$-$CFCO_2Et(CO_2Et)C$=$CFCO_2Et$ **6**

A solution of $(EtO)_2P(O)CFHCO_2Et$ (2.44 g, 10.0 mmol) and dry THF (24 mL) was cooled to -78 °C in a Dry Ice/IPA slush bath under N_2. To the cooled solution, 10.0 mmol (4.0 mL) of a 2.5 M hexane solution of *n*-butyllithium was added dropwise *via* syringe. The resultant bright yellow solution was stirred at -78 °C for 20 min and then 10.0 mmol (1.16 g, Method B) or 5.0 mmol (0.58 g, Method C) of ethyl oxalyl 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 5 h and stirred at that temperature overnight. The reaction mixture was poured into water (40 mL), the organic layer separated, and the water layer extracted with ether (3 × 40 mL). The combined ether extracts were washed with dilute hydrochloric acid until the washings were neutral. The organic layer was washed successively with saturated brine (20 mL) and water (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was loaded onto a flash chromatography column (80 g silica gel, 200-425 mesh) and eluted with hexane/ethyl acetate (1/1) mixture to give 2.16 g (50%, based on $(EtO)_2P(O)CFHCO_2Et$) of $(EtO)_2P(O)CFCO_2Et(CO_2Et)C$=$CFCO_2Et$ **6**. *E/Z* ratio was determined by ^{19}F NMR analysis to be 12 to 88. Both methods gave the same yields and *E/Z* ratios of **6**. (*E*)-**6**: ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -106.5 (s), -163.8 (d, $^2J_{F,F}$ = 80 Hz); ^{31}P NMR (282 MHz, $CDCl_3/H_3PO_4$): δ = 10.7 (d, $^2J_{P,F}$ = 80 Hz). (*Z*)-**6**: ^{19}F NMR (282 MHz, $CDCl_3$/$CFCl_3$): δ = -111.3 (d, $^4J_{F,F}$ = 17 Hz), -169.4 (dd, $^2J_{F,P}$ = 85 Hz, $^4J_{F,F}$ = 17 Hz); ^{31}P NMR: 9.3 (d, $^2J_{P,F}$ = 85 Hz). ^1H NMR ($CDCl_3$/TMS): δ = 1.30 (t, $^3J_{H,H}$ = 7.3 Hz), 4.30 (q, $^3J_{H,H}$ = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.7 (s), 13.8 (s), 13.9 (s), 16.2 (s), 16.3 (s), 62.7 (s), 63.0 (s), 63.5 (s), 65.2 (s), 65.4 (s), 92.2 (dd, $^1J_{C,F}$ = 204 Hz, $^1J_{C,F}$ = 166 Hz), 120.1 (dd, $^2J_{C,F}$ = 14 Hz, $^3J_{C,F}$ = 10 Hz), 149.3 (d, $^1J_{C,F}$ = 285 Hz), 158.8 (d, $^2J_{C,F}$ = 35 Hz), 161.1 (d, $^3J_{C,F}$ = 11 Hz), 164.2 (d, $^2J_{C,F}$ = 24 Hz). GC-MS *m/z* (relative intensity): 431 (M^++1, 0.08), 430 (M^+, 0.05), 401 (M^+-Et, 0.17), 385 (M^+-OEt, 6.44), 357 (M^+-CO_2Et, 8.12), 248 (M^+-OEt-$(EtO)_2P(O)$, 38.92), 220 (M^+-CO_2Et-$(EtO)_2P(O)$, 46.13), 192 (M^+-CO_2Et-$(EtO)_2P(O)$-CH_2=CH_2, 100), 174 (M^+-Me-$(EtO)_2P(O)CFCO_2Et$, 4.25). FTIR (CCl_4 solution, cm^{-1}): 2991 (m), 2985 (m), 2982 (m, C-H), 1754 (s), 1738 (s), 1731 (s, C=O), 1311 (s), 1305 (s, C-F), 1289 (m, P=O), 1255 (m, C-O-C), 1058 (m), 1063 (m, P-O-C).

The isolated **6** (2.16 g, 5 mmol) and 12 mL of dry THF was cooled again to -78 °C and to the cooled solution, 5 mmol (1.7 mL) of a 3.0 M diethyl ether solution of phenylmagnesium bromide was added dropwise *via* syringe. The resultant mixture was allowed to warm to room temperature over 6 h and stirred at that temperature overnight. After the extractive workup similar to that in Method A, the residue was loaded onto a flash chromatography column (60 g silica gel, 200-425 mesh) and eluted with a hexane/ethyl acetate (24/1) mixture to obtain 0.79 g (60%, based on **6**) of diethyl 2-fluoro-3-phenyl fumarate **5c**. *E/Z* ratio was determined by ^{19}F NMR analysis to be 60 to 40.

Method D

According to the procedure for the preparation of $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$ (Method A), the reaction of lithium salt of $(EtO)_2P(O)CFHCO_2Et$ with ethyl oxalyl chloride was performed in 5.0 mmol scale. To the cooled solution of $(EtO)_2P(O)CF(COCO_2Et)CO_2Et$, 5.0 mmol of a THF solution of $[(EtO)_2P(O)CFCO_2Et]^-Li^+$ was added dropwise *via* syringe. The resultant mixture was allowed to warm to room temperature over 6 h and stirred at that tem-

perature overnight. ^{19}F NMR analysis of the reaction mixture revealed the presence of the intermediate (*E,Z*)-$(EtO)_2P(O)CFCO_2Et(CO_2Et)C{=}CFCO_2Et$ **6**. The reaction mixture was cooled again to -78 °C and 5.0 mmol (1.7 mL) of a 3.0 M diethyl ether solution of phenylmagnesium bromide was added dropwise *via* syringe. The resultant mixture was allowed to warm to room temperature over 6 h and stirred at that temperature overnight. Extractive workup followed by purification gave 0.68 g (26%, based on $(EtO)_2P(O)CFHCO_2Et$) of diethyl 2-fluoro-3-phenyl fumarate **5c**. *E/Z* ratio was determined by ^{19}F NMR analysis to be 60 to 40.

Preparation of (*E*)-Diethyl 2-Fluoro-3-methyl Fumarate $Me(CO_2Et)C{=}CFCO_2Et$ (5a)

Yield: 1.56 g (52%). GLPC purity: 98%. ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -125.5 (q, $^4J_{F,H}$ = 3.84 Hz); ^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.32 (t, 3H), 1.33 (t, 3H), 2.05 (d, 3H, $^4J_{H,F(cis)}$ = 3.87 Hz), 4.27 (q, 2H, $^3J_{H,H}$ = 7.17 Hz), 4.29 (q, 2H, $^3J_{H,H}$ = 7.18 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 13.8 (s), 13.9 (d, $^3J_{C,F}$ = 5 Hz), 61.8 (s), 62.1 (s), 121.7 (d, $^2J_{C,F}$ = 18 Hz), 147.9 (d, $^1J_{C,F}$ = 266 Hz), 159.7 (d, $^2J_{C,F}$ = 35 Hz), 169.9 (d, $^3J_{C,F}$ = 13 Hz). GC-MS *m/z* (relative intensity): 204 (M^+, 0.4), 189 (4.9), 159 (11.0), 159 (11.0), 131 (100), 130 (12.8), 103 (7.5), 74 (28.2). FTIR (CCl_4 solution, cm^{-1}): 2984 (m), 1767 (m), 1739 (vs), 1675 (m), 1652 (m), 1456 (m), 1311 (s), 1287 (s), 1118 (m), 1111 (m). HRMS: Calcd 204.0798, Found 204.0813.

Preparation of (*E*)- and (*Z*)-Diethyl 2-Fluoro-3-ethyl Fumarate $Et(CO_2Et)C{=}CFCO_2Et$ (5b)

Yield: 1.95 g (56%). GLPC purity: 98%. (*E*)-**5b**: ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -128.4 (t, $^4J_{F,H}$ = 2.87 Hz); ^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.12 (t, 3H, $^3J_{H,H}$ = 7.58 Hz), 1.32 (t, 3H), 1.33 (t, 3H), 2.46 (d, q, 2H, $^4J_{H,F(cis)}$ = 2.97 Hz), 4.28 (q, 2H, $^3J_{H,H}$ = 7.15 Hz), 4.29 (q, 2H, $^3J_{H,H}$ = 7.14 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 11.7 (s), 13.9 (s), 14.0 (s), 20.9 (d, $^3J_{C,F}$ = 4 Hz), 62.1 (s), 62.7 (s), 127.9 (d, $^2J_{C,F}$ = 17 Hz), 146.7 (d, $^1J_{C,F}$ = 265 Hz), 159.8 (d, $^2J_{C,F}$ = 35 Hz), 166.5 (d, $^3J_{C,F}$ = 13 Hz); GC-MS *m/z* (relative intensity): 218 (M^+, 0.7), 189 (11.8), 173 (16.7), 172 (11.3), 145 (100), 144 (52.0), 117 (18.9), 116 (11.2), 99 (10.5); FTIR (CCl_4 solution, cm^{-1}): 2982 (m), 2940 (m), 1744 (s), 1741 (s), 1737 (s), 1735 (s), 1669 (m), 1370 (m), 1313 (s), 1288 (m), 1252 (m), 1184 (m), 1124 (m). (*Z*)-**5b**: ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): δ = -116.7 (s); GC-MS *m/z* (relative intensity): 173 (36.8), 172 (32.0), 145 (21.5), 144 (100), 117 (11.0), 116 (21.1), 115 (11.0).

General Procedure for Dependence of Metal Ion and/or Cosolvent on the Stereochemistry of (*E,Z*)-$(Ph)(CO_2Et)C{=}CFCO_2Et$ 5c as Described by Reaction of the Anion Derived from $(EtO)_2P(O)CFHCO_2Et$ Using *n*-BuLi in Tetrahydrofuran/Hexamethylphosphoric Triamide with Ethyl Oxalyl Chloride and Phenylmagnesium Bromide

To a solution of 4.1 mmol (0.55 g) of ethyl oxalyl chloride in a mixture of THF (8 mL) and HMPT (4 mmol, 0.6 mL) cooled to -78 °C, was added a solution of lithium salt of $(EtO)_2P(O)CFHCO_2Et$ (4.1 mmol) in THF (8 mL). The resulting mixture was stirred at -78 °C for 1 h and then allowed to warm to -10 °C over 5 h. The reaction mixture was cooled again to -78 °C then 4.0 mmol (1.1 mL) of a 3.0 M diethyl ether solution of phenylmagnesium bromide was added dropwise *via* syringe. The resultant mixture was allowed to warm to rt over 6 h and stirred at that temperature overnight to give 69% ^{19}F NMR yield of **5c**. The *E/Z* ratio of the unsaturated diester, determined by ^{19}F NMR spectrum, was 70 to 30.

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Key Words

Fluorophosphonates; Acylation; Cosolvent; Grignard reagents; *E*-stereoselectivity.

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