Synthesis of γ-Fluoro-α,β-unsaturated Carboxylic Esters from Saturated α-Fluoro Aldehydes

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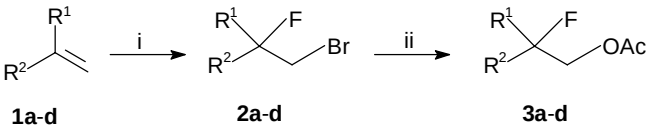
Abstract. γ-Fluoro-α,β-unsaturated carboxylic esters **7a**, **7b** and **7d** and 4-fluoro-4-phenylbut-3-enoic ester (**8**) are obtained by two alternative pathways from 2-fluoro aldehydes **5a**–**d**, either by Horner–Wadsworth–Emmons reaction or by Wittig reaction. The aldehydes **5a**–**d** are prepared by Swern oxidation of the corresponding fluorohydrins **4a**–**d**. These are available from α-olefins by bromofluorination, bromine-by-acetate replacement and subsequent hydrolysis.

Partially fluorinated organic materials – both analogues of naturally occurring compounds and synthetic substances – gain a continuously growing interest by organic chemists, medicinal chemists, material scientists and others due to the unique chemical properties and biological activity [1]. Hence, there is an enormous demand of synthetic methods for the introduction of a fluorine atom at a specific position in the molecule [2]. Among the carbonyl compounds α-fluorinated ketones and carboxylic acids are fully characterized [3]. Also α-fluoro-α,β-unsaturated aldehydes are well known and widely used, *e.g.* in synthesis of fluorinated analogues of vitamin A or derivatives [4]. Saturated 2-fluoro aldehydes have also been synthesized by different methods [5, 6]. However, these compounds are described to be rather unstable [6b, 6e, 6i]. 2-Fluoro aldehydes are expected to be useful building blocks joining the carbonyl group with the attribute of having a fluorine substituent. Thinking of the numerous well known reactions with non-fluorinated aldehydes, fluorinated molecules should be versatile building blocks.

We like to report on synthesis of different types of 2-fluoro aldehydes and their application as starting materials for the synthesis of γ-fluoro-α,β-unsaturated carboxylic esters by Horner–Wadsworth–Emmons (HWE) reaction or by Wittig reaction, respectively.

Results and Discussion

According to our well established procedure [7] the terminal olefins **1a**–**d** react in high yields to the bromo fluoro adducts **2a**–**d** by using *N*-bromosuccinimide (NBS) as a source of electrophilic bromine and triethylamine tris(hydrofluoride) [8] ($Et_3N \cdot 3HF$) or trimethylamine bis(hydrofluoride) ($Me_3N \cdot 2HF$) as a very mild nucleophilic fluorinating agent. Heating of **2a**–**d** with potassium acetate in dimethyl formamide led to β-fluoro acetates **3a**–**d** in moderate yields (62–69%), with the exception of **3c** (28%). This procedure is superior to that one we used in the past [9]. The main reason for low yield in the latter case is the favoured elimination of HBr to α-fluoro styrene. Hydrolysis of **3a**–**d** under basic conditions yielded the 2-fluoro alcohols **4a**–**d** (66–91%) (Scheme 1).



	a	b	c	d
R^1	CH_3	F	H	H
R^2	C_6H_5	C_6H_5	C_6H_5	C_8H_{17}

Scheme 1 Syntheses of 2-fluoroaldehydes; reagents and conditions: (i) NBS, $Et_3N \cdot 3HF$, CH_2Cl_2, 12 h, *r.t.*; (ii) KOAc, DMF, 26 h, 153 °C; (iii) KOH, methanol, 0.5–6 h, 0 °C or 20 °C; (iv) Oxalyl chloride/DMSO, Et_3N, CH_2Cl_2, 15 min, –60 °C.

Better yield of **4c** was obtained by ring opening of styrene oxide (**6**) with $Et_3N \cdot 3HF$ in the presence of 20 mol% of $BF_3 \cdot Et_2O$ at room temperature according to a procedure described for α-alkylstyrene oxides [9a] (Scheme 2).

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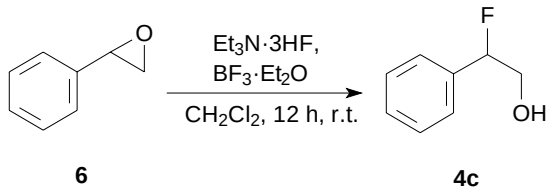
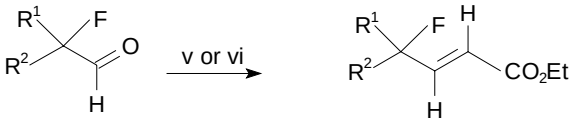


Scheme 2 Synthesis of 2-fluoro-2-phenylethanol

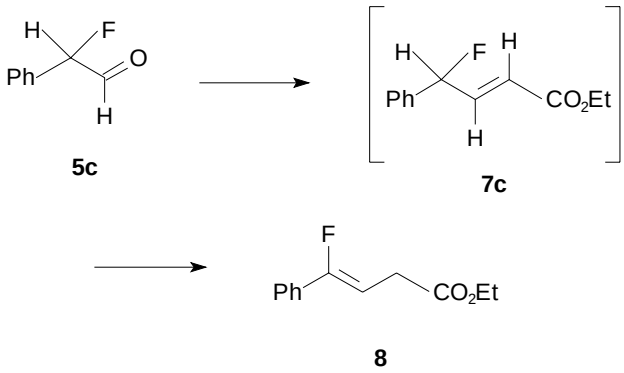
The selective oxidation of the fluorohydrins to 2-fluoro aldehydes **5a**–**d** is a key step of the shown sequence (Scheme 1). However, methods by Corey [10] according to a modified procedure [11] or Pfitzner and Moffatt [12] failed or gave low yield. Finally Swern oxidation [13] was found to be the most effective method. The handling is quite simple, there is no obstructing by-product and the yields are high (83–95%), except for **4c** (65%). All attempts to purify the 2-fluoro aldehydes **5a**–**d** failed (vacuum distillation at low temperature and liquid chromatography) as already reported by other authors [6b, 6e, 6i]. Thus, we used the freshly prepared crude products for further reactions. Treatment of triethyl phosphono acetate with sodium hydride formed the phosphonate anion [14] which on reaction with 2-fluoro aldehydes **5a**, **5b** and **5d** gave the γ-fluoro-α,β-unsaturated carboxylic esters **7a**, **7b** and **7d** in 52–76% yields over two steps (Scheme 3), similarly to a transformation Davis *et al*. reported for a 2-fluoropropionic aldehyde [6i]. As an alternative method the Wittig reaction yielded the same products (57–72% over two steps). In all cases the HWE reactions gave the (*E*)-isomers (^{1}H and ^{19}F NMR spectroscopy) and also in the Wittig reactions the (*E*)-isomers were formed almost exclusively (except for **7d**, *(E)*:(*Z)* = 85:15).



	a	b	d
R^1	CH_3	F	H
R^2	C_6H_5	C_6H_5	C_8H_{17}

Scheme 3 Wittig-olefinations of 2-fluoroaldehydes; reagents and conditions: (v) $(EtO)_2P(O)CH_2CO_2Et$, NaH, pentane, 2 h, 36 °C; (vi) $[Ph_3PCH_2CO_2Et]^+Br^-$, NaH, DMSO, 2 h, 80 °C.

However, the γ-fluoro-α,β-unsaturated carboxylic ester **7c** could not be isolated following the same procedures. This compound could not even be detected by NMR or other analytical methods in the crude product mixture. Under the conditions of the HWE or Wittig reactions, respectively it is obviously rearranged into the thermodynamically more stable styrene derivative, the γ-fluoro-β,γ-unsaturated carboxylic ester **8**, which was isolated in quite low yields (34% and 25% respectively, over two steps) (Scheme 4). No (*E*)-isomer was found by ^{1}H and ^{19}F NMR spectroscopy.



Scheme 4 Wittig olefination of 2-fluoro-2-phenylacetaldehyde

In conclusion, although the saturated 2-fluoro aldehydes **5a**–**d** could not be isolated as pure compounds they have been shown to be good building blocks for γ-fluoro-α,β-unsaturated carboxylic esters **7a**, **7b** and **7d** or the γ-fluoro-β,γ-unsaturated carboxylic ester **8**.

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Experimental

General: ^{1}H- (300 MHz), ^{13}C- (75.5 MHz) and ^{19}F- (282.3 MHz) NMR spectra were recorded using a Bruker WM 300 spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) or $CFCl_3$, respectively, as internal standards. – Mass spectra (electron impact ionization 70 eV, chemical ionization with NH_4^+) were determined using a GC/MS system: Varian GC 3400/MAT 8230 and data system of Finnigan/MAT. – Column chromatography was performed using silica gel (Merck, particle size 0.022–0.063 mm). – Thin layer chromatography was taken with TLC plates 60 F 254 by Merck. – Gas chromatographical analyses were performed with a Hewlett Packard 5890 II gas chromatograph (quartz capillary column 0.32 mm × 30 m, 0.25 µm SPB-1, Supelco). – Infrared spectra were recorded using a Nicolet 5DXC-FT-spectrophotometer. – Elemental analyses were taken at the Mikroanalytisches Laboratorium, OC, Universität Münster, with a Heraeus Elementaranalysator CHN–O-Rapid. – Triethylamine tris(hydrofluoride) and trimethylamine bis(hydrofluoride) were provided by Hoechst AG, Frankfurt/Main, and Bayer AG, Leverkusen. All other starting materials and reagents were obtained from Fluka, Merck, Aldrich,

Riedel deHaen and Janssen chemicals; dichloromethane and *N*,*N*-dimethyl formamide were purified by distillation and dried by storage over molecular sieves 0.4 nm.

Synthesis of Vicinal Bromo Fluoro Compounds 2a–d

According to the general procedure [7b] a mixture of 20 mmol of the α-olefin **1** and 5 ml (31 mmol) of $Et_3N \cdot 3HF$ or 4.7 ml (45 mmol) of $Me_3N \cdot 2HF$ in 50 ml of dry CH_2Cl_2 is cooled to 0 °C and treated in portions with 3.90 g (22 mmol) of NBS. After stirring for 15 min the solution is allowed to warm up at room temp. and stirred for another 4–6 hours. After the reaction has finished the mixture is poured into 500 ml of ice/water. It is neutralized with 25% aq. NH_3 and extracted with 50 ml of CH_2Cl_2 three times. The combined organic phases are washed two times with 50 ml of 0.1N HCl and subsequently with 5% aq. $NaHCO_3$ (3 × 50 ml), and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure the products are purified by distillation or liquid chromatography (silica gel, cyclohexane (**2b**), cyclohexane/ethyl acetate, 10:1 (**2a**, **2c**), cyclohexane/ethyl acetate, 20:1 (**2d**)).

1-Bromo-2-fluoro-2-phenylpropane (**2a**)

Prepared from 11.81 g (100 mmol) of 2-phenylprop-1-ene (**1a**) using 19.50 g (110 mmol) of NBS and 23.5 ml (225 mmol) of $Me_3N \cdot 2HF$; yield 20.40 g (94%, 95% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.45. Analytical and spectroscopic data agree with published values [7a].

2-Bromo-1,1-difluoro-1-phenylethane (**2b**)

Prepared from 6.30 g (31 mmol) of 1-fluoro-1-phenylethene [15] (**1b**) using 6.04 g (34 mmol) of NBS and 7.3 ml (69.8 mmol) $Me_3N \cdot 2HF$; yield 5.02 g (77%, 98% purity, GC). – TLC (cyclohexane): R_f = 0.28. Analytical and spectroscopic data agree with published values [16].

2-Bromo-1-fluoro-1-phenylethane (**2c**)

Prepared from 15.62 g (150 mmol) of styrene (**1c**) using 29.25 g (165 mmol) of NBS and 35.3 ml (338 mmol) of $Me_3N \cdot 2HF$; yield 26.14 g (85%, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.41. Analytical and spectroscopic data agree with published values [17].

1-Bromo-2-fluorodecane (**2d**)

Prepared from 14.02 g (100 mmol) of dec-1-ene (**1d**) as a 87:13 mixture of regioisomers with 2-bromo-1-fluorodecane using 19.50 g (110 mmol) of NBS and 25.0 ml (155 mmol) of $Et_3N \cdot 3HF$; yield 20.92 g (88%, 87% purity, GC). – TLC (cyclohexane/ethyl acetate, 20:1): R_f = 0.55. Analytical and spectroscopic data agree with published values [16b,17b].

Synthesis of 2-Fluoroalkyl Acetates 3a–d

A mixture of 10 mmol of the respective bromo fluoro compound **2** and 3.93 g (40 mmol) of KOAc in 50 ml of dry DMF is heated for 26 h at 153 °C under argon. After the reaction has been cooled down to room temp. 50 ml of a 1:1 mixture of cyclohexane and ethyl acetate is added and the solid is filtered off and washed carefully with the same solvent. The organic phase is washed with water (6 × 75 ml) and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure the products are isolated by column chromatography (silica gel, cyclohexane/ethyl acetate, 10:1).

1-Acetoxy-2-fluoro-2-phenylpropane (**3a**)

Prepared from 7.00 g (32 mmol) of 1-bromo-2-fluorophenylpropane (**2a**); yield 4.04 g (20.6 mmol, 64%, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.24. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1749 (C=O). – All other analytical and spectroscopic data agree with published values [9a].

2-Acetoxy-1,1-difluoro-1-phenylethane (**3b**)

Prepared from 1.97 g (8.9 mmol) of 2-bromo-1,1-difluoro-1-phenylethane (**2b**); yield 1.23 g (69%, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.22. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1756 (C=O). – ^{1}H NMR: δ/ppm = 2.07 (s, 3H, CH_3), 4.48 (t, $^3J_{H,F}$ = 13.1 Hz, 2H, CH_2), 7.40–7.54 (m, 5H, aromatic H). – ^{13}C NMR: δ/ppm = 20.5 (q, CH_3), 65.1 (tt, $^2J_{C,F}$ = 33.1 Hz, CH_2), 119.2 (ts, $^1J_{C,F}$ = 244.1 Hz, CF_2), 125.4 (td, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 128.5 (d, C-*p*), 130.5 (d, C-*m*), 134.0 (ts, $^2J_{C,F}$ = 17.8 Hz, C-*i*), 169.8 (s, C(O)CH_3). – ^{19}F NMR: δ/ppm = –104.9 (m). – GC/MS (70 eV), *m/z* (%): 201 (10) [MH^+], 200 (62) [M^+], 141 (6) [$MH^+ - CH_3CO_2H$], 140 (20) [$M^+ - CH_3CO_2H$], 128 (10) [$MH^+ - CH_2OAc$], 127 (100) [$M^+ - CH_2OAc$], 91 (12) [$C_7H_7^+$], 77 (16) [$C_6H_5^+$], 73 (26) [CH_2OAc^+], 51 (10) [$C_4H_3^+$], 43 (70) [$C_2H_3O^+$].

2-Acetoxy-1-fluoro-1-phenylethane (**3c**)

Prepared from 1.50 g (7.4 mmol) of 2-bromo-1-fluoro-1-phenylethane (**2c**); yield 0.38 g (28%, 96% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.26. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1748 (C=O). – ^{1}H NMR: δ/ppm = 2.11 (s, 3H, CH_3), 4.26–4.43 (m, 2H, CH_AH_B), 5.65 (ddd, $^3J_{X,A}$ = 4.3 Hz, $^3J_{X,B}$ = 6.7 Hz, $^2J_{X,F}$ = 48.4 Hz, 1H, CH_XF), 7.31–7.45 (m, 5H, aromatic H). – ^{13}C NMR: δ/ppm = 20.7 (q, CH_3), 66.8 (dt, $^2J_{C,F}$ = 22.9 Hz, CH_AH_B), 91.7 (dd, $^1J_{C,F}$ = 178.0 Hz, CH_XF), 125.8 (dd, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 128.7 (d, C-*p*), 129.0 (d, C-*m*), 135.9 (ds, $^2J_{C,F}$ = 20.3 Hz, C-*i*), 170.6 (s, C(O)CH_3). – ^{19}F NMR: δ/ppm = –184.9 (m). – GC/MS (70 eV), *m/z* (%): 181 (0.1) [M^+ – H], 162 (2) [M^+ – HF], 123 (46) [$M^+ - CH_3COO$], 122 (100) [$M^+ - CH_3CO_2H$], 109 (100) [$M^+ - CH_2CO_2CH_3$], 91 (16) [$C_7H_7^+$], 77 (22) [$C_6H_5^+$], 51 (28) [$C_4H_3^+$], 43 (100) [$COCH_3^+$], 39 (16) [$C_3H_3^+$].

1-Acetoxy-2-fluorodecane (**3d**)

Prepared as a 93:7 mixture of regioisomers with 2-acetoxy-1-fluorodecane from 21.80 g (91 mmol) of 1-bromo-2-fluorodecane (**2d**) (as a 87:13 mixture of regioisomers with 2-bromo-1-fluorodecane); yield 12.33 g (62%, 93% purity, GC). – TLC (cyclohexane/ethyl acetate, 20:1): R_f = 0.19. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1747 (C=O). – ^{13}C NMR: δ/ppm = 14.0 (q, C-10), 20.7 (q, C-12), 22.6, 24.7, 24.8, 29.1, 29.3, 31.8 (t, C-4–C-9), 31.4 (dt, $^2J_{C,F}$ = 20.3 Hz, C-3), 65.9 (dt, $^2J_{C,F}$ = 22.9 Hz, C-1), 91.4 (dd, $^1J_{C,F}$ = 172.9 Hz, C-2), 170.7 (s, C-11). – ^{19}F NMR: δ/ppm = –187.5 (m). – GC/MS (70 eV), *m/z* (%): 156 (5) [$M^+ - C_2H_3OF$], 96 (15) [$C_7H_{12}^+$], 82 (18) [$C_6H_{10}^+$], 55 (18) [$C_4H_7^+$], 43 (100) [$C_2H_3O^+$]. – ^{1}H NMR spectroscopic data agree with published values [18].

Synthesis of 2-Fluoroalkanols 4a–d

A mixture of 5 mmol of the 2-fluoro acetate **3** in 10 ml of methanol is added to a mixture of 0.84 g (15 mmol) of KOH in 20 ml of MeOH. After stirring (the reaction temp. and the time of stirring depend on the reactivity of the fluoro acetate) the solution is poured into 100 ml of ice/water and extracted

with CH_2Cl_2 (5 × 30 ml). The combined organic layers are washed three times with 50 ml of water and dried with $MgSO_4$. The solvent is evaporated *in vacuo*, and the product is isolated by column chromatography (silica gel, cyclohexane/ethyl acetate, 5:1).

2-Fluoro-2-phenylpropanol (**4a**)

Prepared from 0.58 g (3 mmol) of 1-acetoxy-2-fluoro-2-phenylpropane (**3a**); reaction temp.: 0 °C, reaction time: 15 min; yield 0.30 g (66%, 95% purity, GC). – TLC (cyclohexane/ethyl acetate, 5:1): R_f = 0.15. – Analytical and spectroscopic data agree with published values [9a].

2,2-Difluoro-2-phenylethanol (**4b**)

Prepared from 1.23 g (6 mmol) of 2-acetoxy-1,1-difluoro-1-phenylethane (**3b**); reaction temp.: 20 °C, reaction time: 4 h; yield 0.88 g (91%, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 5:1): R_f = 0.19. – GC/MS (70 eV), *m/z* (%): 159 (10) [MH^+], 158 (84) [M^+], 128 (70) [$MH^+ - CH_3O$], 127 (100) [$M^+ - CH_3O$], 107 (12) [$M^+ - CH_3OHF$], 91 (20) [$C_7H_7^+$], 77 (70) [$C_6H_5^+$], 51 (40) [$C_4H_3^+$], 39 (10) [$C_3H_3^+$]. – ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data agree with published values [6e].

2-Fluoro-2-phenylethanol (**4c**)

Prepared from 0.23 g (1.3 mmol) of 2-acetoxy-1-fluoro-1-phenylethane (**3c**); reaction temp.: 20 °C, reaction time: 2 h; yield 0.14 g (79%, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 5:1): R_f = 0.14. – Analytical and spectroscopic data agree with published values [19].

2-Fluoro-2-phenylethanol (**4c**) *by ring opening of styrene oxide* (**6**)

A mixture of 0.50 g (4.2 mmol) of styrene oxide (**6**), 2.0 g (12.4 mmol) of $Et_3N \cdot 3HF$, and 0.11 g (0.8 mmol) of $BF_3 \cdot Et_2O$ in 50 ml of dry CH_2Cl_2 is stirred at room temp. for 12 h. The working up procedure is the same as described for bromofluorination; yield 0.41 g (70%, 96% purity, GC).

2-Fluorodecanol (**4d**)

Prepared from 11.50 g (52.8 mmol) of 1-acetoxy-2-fluorodecane (**3d**) (as a 93:7 mixture of regioisomers with 2-acetoxy-1-fluorodecane); reaction temp.: 20 °C, reaction time: 4 h; yield 7.58 g (82%, 96% purity, GC). – TLC (cyclohexane/ethyl acetate, 5:1): R_f = 0.17. – ^{13}C NMR: δ/ppm = 14.0 (q, C-10), 22.6, 24.9, 24.9, 29.1, 29.4, 31.8 (t, C-4–C-9), 31.0 (dt, $^2J_{C,F}$ = 20.3 Hz, C-3), 65.1 (dt, $^2J_{C,F}$ = 22.9 Hz, C-1), 94.7 (dd, $^1J_{C,F}$ = 165.3 Hz, C-2). – GC/MS (70 eV), *m/z* (%): 97 (15) [$C_7H_{13}^+$], 96 (40) [$C_7H_{14}^+$], 83 (35) [$C_6H_{11}^+$], 81 (40) [$C_6H_9^+$], 71 (20) [$C_5H_{11}^+$], 69 (50) [$C_5H_9^+$], 57 (60) [$C_4H_9^+$], 55 (90) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$], 41 (85) [$C_3H_5^+$], EI; *m/z* (%): 194 (100) [$M^+ + NH_4$], 156 (8) [$M^+ - H_2O$], CI. – ^{1}H and ^{19}F NMR spectroscopic data agree with published values [6d, 20].

Synthesis of 2-Fluoro Aldehydes 5a – d

In a two necked round bottom flask a mixture of 0.28 g (2.2 mmol) of oxalyl chloride in 15 ml of dry CH_2Cl_2 is cooled to – 60 °C under argon. A solution of 0.37 g (4.7 mmol) of DMSO in 5 ml of dry CH_2Cl_2 is added dropwise. After 15 min stirring 2 mmol of the 2-fluoroalkanol **4** in 5 ml of dry CH_2Cl_2 is slowly dropped into the mixture. After 15 min 1.02 g (10 mmol) of Et_3N is added slowly. After stirring for 15 min the solution is allowed to warm up at room temp. within 1 h. After the reaction has finished the mixture is poured into 50 ml of ice/water and extracted three times with 30 ml of CH_2Cl_2. The combined organic phases are dried with $MgSO_4$ and the crude products are isolated by evaporation of the solvent. Attempts to purify the 2-fluoro aldehydes by chromatography or vacuum distillation at low temperature resulted in decomposition. Therefore, the aldehydes were used in crude form for further reactions.

2-Fluoro-2-phenylpropanal (**5a**)

Prepared from 0.15 g (1 mmol) of 2-fluoro-2-phenylpropanol (**4a**); yield 0.14 g crude product (94%, 95% purity, GC). – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1749 (C=O). – ^{1}H NMR: δ/ppm = 1.79 (d, $^3J_{H,F}$ = 22.7 Hz, 3H, CH_3), 7.28–7.43 (m, 5H, aromatic H), 9.70 (d, $^3J_{H,F}$ = 4.8 Hz, 1H, CHO). – ^{13}C NMR: δ/ppm = 22.1 (dq, $^2J_{C,F}$ = 22.9 Hz, CH_3), 98.7 (ds, $^1J_{C,F}$ = 178.0 Hz, $\underline{C}FCH_3$), 124.9 (dd, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 128.4 (d, C-*p*), 128.9 (C-*m*), 136.7 (ds, $^2J_{C,F}$ = 22.9 Hz, C-*i*), 197.4 (dd, $^2J_{C,F}$ = 40.7 Hz, CHO). – GC/MS (70 eV), *m/z* (%): 153 (0.5) [MH^+], 152 (5) [M^+], 123 (100) [$M^+ - HF$], 109 (10) [$C_7H_6F^+$], 103 (42) [$C_8H_7^+$], 77 (24) [$C_6H_5^+$], 51 (15) [$C_4H_3^+$]. – ^{19}F NMR spectroscopic data agree with published values [6b].

2,2-Difluoro-2-phenylethanal (**5b**)

Prepared from 0.27 g (1.7 mmol) of 2,2-difluoro-2-phenylethanol (**4b**); yield 0.24 g crude product (90%, 95% purity, GC). – GC/MS (70 eV), *m/z* (%): 156 (10) [M^+], 128 (10) [$C_7H_6F_2^+$], 127 (100) [$C_7H_5F_2^+$], 77 (18) [$C_6H_5^+$], 51 (10) [$C_4H_3^+$]. – ^{1}H NMR spectroscopic data agree with published values [6e].

2-Fluoro-2-phenylethanal (**5c**)

Prepared from 0.23 g (1.6 mmol) of 2-fluoro-2-phenylethanol (**4c**); yield 0.21 g crude product (65% purity, GC). – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1735 (C=O). – GC/MS (70 eV), *m/z* (%): 138 (18) [M^+], 110 (20) [$C_7H_7F^+$], 109 (100) [$C_7H_6F^+$], 51 (6) [$C_4H_3^+$]. – ^{1}H NMR spectroscopic data agree with published values [21].

2-Fluorodecanal (**5d**)

Prepared from 0.35 g (2 mmol) of 2-fluorodecanol (**4d**), yield 0.33 g crude product (94%, 83% purity, GC). – ^{13}C NMR: δ/ppm = 14.0 (q, C-10), 22.5, 24.1, 24.8, 29.4, 31.7 (t, 5-CH_2–9-CH_2), 29.1 (dt, $^3J_{C,F}$ = 7.6 Hz, C-4), 30.3 (dt, $^2J_{C,F}$ = 22.9 Hz, C-3), 95.0 (dd, $^1J_{C,F}$ = 178.0 Hz, C-2), 200.1 (dd, $^2J_{C,F}$ = 35.6 Hz, C-1). – GC/MS (70 eV), *m/z* (%): 174 (1) [M^+], 156 (0.2) [$M^+ - H_2O$], 131 (2) [$M^+ - C_2H_3O$], 83 (20) [$C_6H_{11}^+$], 71 (45) [$C_5H_{11}^+$], 69 (25) [$C_5H_9^+$], 57 (80) [$C_4H_9^+$], 55 (60) [$C_4H_7^+$], 43 (100) [$C_3H_7^+$, $C_2H_3O^+$], 41 (78) [$C_3H_5^+$]. – ^{1}H and ^{19}F NMR spectroscopic data agree with published values [6e].

Synthesis of the γ-Fluoro-α,β-unsaturated Carboxylic Acid Esters 7a, 7b and 7d by Horner–Wadsworth–Emmons Reaction

Under an argon atmosphere and with ice cooling a mixture of 2-fluoro aldehydes **5a**, **5b** or **5d** obtained by oxidation of 4 mmol of the corresponding 2-fluoroalkanols **4a**, **4b** or **4d** in

5 ml of dry Et_2O is added dropwise to a mixture of 0.12 g (4 mmol) of sodium hydride (80% in paraffine) and 0.90 g (4 mmol) of triethylphosphono acetate in 50 ml of dry Et_2O. After stirring and heating at 34 °C for three hours the mixture is poured into 50 ml of ice/water and extracted with Et_2O (3 × 30 ml). The combined organic phases are dried with $MgSO_4$, and after evaporation of the solvent under reduced pressure the products are isolated by column chromatography (cyclohexane/ethyl acetate, 10:1).

Synthesis of the γ-Fluoro-α,β-unsaturated Carboxylic Acid Esters 7a, 7b and 7d by Wittig reaction

A mixture of 0.79 g (3 mmol) of triphenylphosphine and 0.50 g (3 mmol) of ethyl bromo acetate in 40 ml of DMSO is heated for 3 hours at 80 °C. After cooling down to room temp. 0.09 g (3 mmol) of sodium hydride (80% in paraffine) is added, and the mixture is heated for another hour. A solution of the 2-fluoro aldehyde **5a**, **5b** or **5d** obtained by oxidation of 3 mmol of the corresponding 2-fluoroalkanol **4a**, **4b** or **4d** in 10 ml of DMSO is added to the cooled mixture containing the phosphonium salt and heated for another two hours. After the reaction has finished the mixture is poured into 100 ml of ice/water and worked up as mentioned above.

Ethyl (E)-4-fluoro-4-phenylpent-2-enoate (**7a**)

By HWE reaction: Prepared from 0.15 g (1 mmol) of 2-fluoro-2-phenylpropanol (**4a**) *via* 2-fluoro-2-phenylpropanal (**5a**); yield 0.17 g (76% over two steps, 99% purity, GC); by Wittig reaction: Prepared from 0.23 g (1.5 mmol) of 2-fluoro-2-phenylpropanol (**4a**) *via* 2-fluoro-2-phenylpropanal (**5a**); yield 0.24 g (72% over two steps, 99% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.28. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1717 (C=O). – ^{1}H NMR: δ/ppm = 1.28 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, 7-CH_3), 1.82 (d, $^3J_{H,F}$ = 22.2 Hz, 3H, 5-CH_3), 4.20 (q, $^3J_{H,H}$ = 7.2 Hz, 2H, 6-CH_2), 6.09 (dd, $^4J_{A,F}$ = 1.0 Hz, $^3J_{A,B}$ = 15.7 Hz, 1H, 2-CH_A), 7.10 (dd, $^3J_{B,A}$ = 15.7 Hz, $^3J_{B,F}$ = 18.6 Hz, 1H, 3-CH_B), 7.27–7.39 (m, 5H, aromatic H). – ^{13}C NMR: δ/ppm = 14.2 (q, C-7), 26.6 (dq, $^2J_{C,F}$ = 25.4 Hz, C-5), 60.6 (t, C-6), 95.1 (ds, $^1J_{C,F}$ = 175.5 Hz, C-4), 119.5 (dd, $^3J_{C,F}$ = 10.2 Hz, C-2), 124.6 (dd, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 128.2 (d, C-*p*), 128.6 (d, C-*m*), 141.6 (ds, $^2J_{C,F}$ = 22.9 Hz, C-*i*), 148.8 (dd, $^2J_{C,F}$ = 22.9 Hz, C-3), 166.2 (s, C-1). – ^{19}F NMR: δ/ppm = –145.8 (m). – GC/MS (70 eV), *m/z* (%): 223 (5) [MH^+], 222 (22) [M^+], 204 (8) [$M^+ - H_2O$], 177 (12) [$M^+ - C_2H_5O$], 149 (100) [$M^+ - C_3H_5O_2$], 129 (50) [$C_{10}H_9^+$], 123 (12) [$C_8H_8F^+$], 91 (20) [$C_7H_7^+$], 77 (12) [$C_6H_5^+$], 51 (8) [$C_4H_3^+$].

Ethyl (E)-4,4-difluoro-4-phenylbut-2-enoate (**7b**)

By HWE-reaction: Prepared from 0.24 g (1.5 mmol) of 2,2-difluoro-2-phenylethanol (**4b**) *via* 2,2-difluoro-2-phenylethanal (**5b**); yield 0.22 g (64% over two steps, 99% purity, GC); by Wittig reaction: Prepared from 0.24 g (1.5 mmol) of 2,2-difluoro-2-phenylethanol (**4b**) *via* 2,2-difluoro-2-phenylethanal (**5b**); yield 0.19 g (57% over two steps, 99% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.32. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1727 (C=O). – ^{1}H NMR: δ/ppm = 1.29 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, 6-CH_3), 4.23 (q, $^3J_{H,H}$ = 7.2 Hz, 2H, 5-CH_2), 6.26 (dt, $^4J_{A,F}$ = 2.4 Hz, $^3J_{A,B}$ = 15.7 Hz, 1H, 2-CH_A), 7.01 (dt, $^3J_{B,F}$ = 10.3 Hz, $^3J_{B,A}$ = 15.7 Hz, 1H, 3-CH_B), 7.39–7.52 (m, 5H, aromatic H). – ^{13}C NMR: δ/ppm = 14.1 (q, C-6), 61.2 (t, C-5), 118.4 (ts, $^1J_{C,F}$ = 241.6 Hz, C-4), 124.9 (td, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 125.3 (td, $^3J_{C,F}$ = 5.1 Hz, C-2), 128.7 (d, C-*p*), 130.4 (d, C-*m*), 135.2 (ts, $^2J_{C,F}$ = 25.4 Hz, C-*i*), 139.9 (td, $^2J_{C,F}$ = 30.5 Hz, C-3), 165.1 (s, C-1). – ^{19}F NMR: δ/ppm = –95.6 (m). – GC/MS (70 eV): *m/z* (%): 226 (40) [M^+], 198 (10) [$M^+ - C_2H_4$], 181 (30) [$M^+ - C_2H_5O$], 153 (80) [$M^+ - C_3H_5O_2$], 133 (100) [$M^+ - C_3H_5O_2 - HF$], 77 (30) [$C_6H_5^+$], 51 (15) [$C_4H_3^+$].

$C_{12}H_{12}F_2O_2$	Calcd.:	C 63.71 H 5.35
(226.2)	Found:	C 64.14 H 5.71.

Ethyl (E)-4-fluorododec-2-enoate (**7d**)

By HWE reaction: Prepared from 0.32 g (1.8 mmol) of 2-fluorodecanol (**4d**) *via* 2-fluorodecanal (**5d**); yield 0.23 g (52%, 98% purity, GC); by Wittig reaction: Prepared from 0.26 g (1.5 mmol) of 2-fluorodecanol (**4d**) *via* 2-fluorodecanal (**5d**); yield 0.25 g (70% over two steps, 98% purity, 85:15 mixture of diastereomers, GC). – TLC (cyclohexane/ethyl acetate, 20:1): R_f = 0.27. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1725 (C=O). – ^{1}H NMR: δ/ppm = 0.88 (t, $^3J_{H,H}$ = 6.7 Hz, 3H, 12-CH_3), 1.30 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, 14-CH_3), 1.27–1.78 (m, 14H, 5-CH_2–11-CH_2), 4.21 (q, $^3J_{H,H}$ = 7.2 Hz, 2H, 13-CH_2), 5.06 (dm, $^2J_{X,F}$ = 48.4 Hz, 1H, 4-CH_X), 6.04 (ddd, $^4J_{A,X}$ = 1.7 Hz, $^4J_{A,F}$ = 1.7 Hz, $^3J_{A,B}$ = 16.0 Hz, 1H, 2-CH_A), 6.89 (ddd, $^3J_{B,X}$ = 4.3 Hz, $^3J_{B,A}$ = 16.0 Hz, $^3J_{B,F}$ = 20.3 Hz, 1H, 3-CH_B). – ^{13}C NMR: δ/ppm = 14.0 (q, C-12), 14.2 (q, C-14), 22.6, 24.5, 29.1, 29.3, 29.4, 31.8 (t, C-6–C-11), 34.7 (dt, $^2J_{C,F}$ = 20.3 Hz, C-5), 60.5 (t, C-13), 91.3 (dd, $^1J_{C,F}$ = 172.9 Hz, C-4), 121.1 (dd, $^3J_{C,F}$ = 12.7 Hz, C-2), 145.1 (dd, $^2J_{C,F}$ = 17.8 Hz, C-3), 166.0 (s, C-1). – ^{19}F NMR: δ/ppm = –184.3 (m). – GC/MS (70 eV), *m/z* (%): 244 (1) [M^+], 224 (2) [M^+ – HF], 216 (3) [$M^+ - C_2H_4$], 199 (20) [$M^+ - C_2H_5O$], 71 (25) [$C_5H_{11}^+$], 69 (25) [$C_5H_9^+$], 57 (45) [$C_4H_9^+$], 55 (40) [$C_4H_7^+$], 43 (100) [$C_2H_3O^+$, $C_3H_7^+$], 41 (95) [$C_3H_5^+$].

Ethyl (Z)-4-fluoro-4-phenylbut-3-enoate (**8**)

Using the same procedures as for compounds **7**. By HWE reaction: Prepared from 0.28 g (2 mmol) of 2-fluoro-2-phenylethanol (**4c**) *via* 2-fluoro-2-phenylethanal (**5c**); yield 0.14 g (34% over two steps, 98% purity, GC); by Wittig reaction: Prepared from 0.21 g (1.5 mmol) of 2-fluoro-2-phenylethanol (**4c**) *via* 2-fluoro-2-phenylethanal (**5c**); yield 0.08 g (25% over two steps, 98% purity, GC). – TLC (cyclohexane/ethyl acetate, 10:1): R_f = 0.26. – IR (NaCl): $\tilde{\nu}$ /cm^{-1} = 1736 (C=O). – ^{1}H NMR: δ/ppm = 1.28 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, 6-CH_3), 3.34 (dd, $^4J_{H,F}$ = 1.7 Hz, $^3J_{H,H}$ = 7.2 Hz, 2H, 2-CH_2), 4.18 (q, $^3J_{H,H}$ = 7.2 Hz, 2H = 5-CH_2), 5.62 (dt, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,F}$ = 36.2 Hz, 1H, 3-CH), 7.31–7.42 (m, 3H, aromatic H), 7.50–7.54 (m, 2H, aromatic H). – ^{13}C NMR: δ/ppm = 14.2 (q, C-6), 30.0 (dt, $^3J_{C,F}$ = 5.1 Hz, C-2), 60.9 (t, C-5), 98.0 (dd, $^2J_{C,F}$ = 17.8 Hz, C-3), 124.2 (dd, $^3J_{C,F}$ = 7.6 Hz, C-*o*), 128.4 (d, C-*p*), 129.0 (d, C-*m*), 131.9 (ds, $^2J_{C,F}$ = 28.0 Hz, C-*i*), 158.1 (ds, $^1J_{C,F}$ = 249.2 Hz, C-4), 171.1 (s, C-1). – ^{19}F NMR: δ/ppm = –117.5 (m). – GC/MS (70 eV), *m/z* (%): 208 (25) [M^+], 190 (2) [$M^+ - H_2O$], 162 (2) [$M^+ - C_2H_6O$], 135 (100) [$M^+ - C_3H_5O_2$].

$C_{12}H_{13}FO_2$	Calcd.:	C 69.22 H 6.29
(208.2)	Found:	C 68.80 H 6.44.

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