A Convenient Synthesis of α-Fluoro Carboxylic Acids

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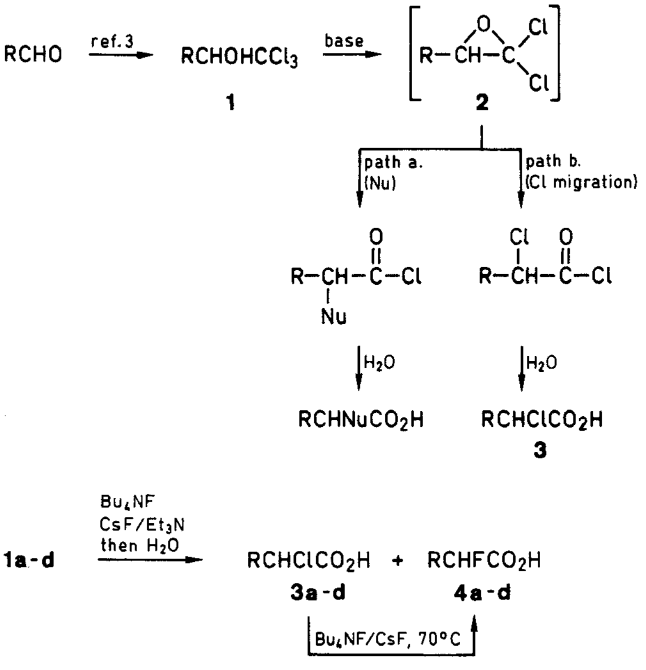
Conditions have been developed whereby treatment of 1,1,1-trichloro-2-carbinols with tetrabutylammonium fluoride and cesium fluoride provides 2-fluoro carboxylic acids. The methodology was used to prepare fluoro derivatives of two fatty acids and of the pheromone of the European corn borer.

Corey and Link recently described synthesis of α-amino acids[1] and α-hydroxy acids[2] from 1,1,1-trichloromethylcarbinols **1**. The Corey group[3] also described a convenient conversion of aldehydes to the latter (homologous) carbinols, making them readily available for synthetic applications.

Earlier work[4-6] had indicated that the formation of α-substituted acids from **1** occurred via labile 1,1-dichloroepoxides **2**. The latter can undergo ring opening by two pathways (Scheme 1): they can react with suitable nucleophiles at the 2-position to give substituted acid chlorides or transformation products therefrom (path a), or, alternatively, can undergo chloride migration to produce, after workup, α-chloro acids **3** (path b)[4,5]. Neither type of reaction seems to have been successful in nonaqueous media.



	R		R
a	C_9H_{19}	c	$C_8H_{17}C{\equiv}C(CH_2)_6$
b	$C_{16}H_{31}$	d	$C_2H_5C{\equiv}C(CH_2)_8$

$$\mathbf{4c}\xrightarrow{H_2/Pd/CaCO_3}\underset{(Z)}{C_8H_{17}CH{=}CH(CH_2)_6CHFCO_2H}\quad \mathbf{5}$$

$$\mathbf{4d}\xrightarrow[3.\ H_2/Pd/CaCO_3]{1.\ LiAlH_4\quad 2.\ Ac_2O}\underset{(Z)}{C_2H_5CH{=}CH(CH_2)_8CHFCH_2OAc}\quad \mathbf{6}$$

We hoped that a more direct conversion of **1** to **4** might be realized by generating dichloroepoxide **2** in the presence of fluoride ion. However, treatment of **1a** with potassium hydroxide and potassium fluoride in aqueous tetrahydrofuran led only to recovered starting material. Under conditions more closely approximating those employed by the Corey group[1,2] (aqueous dimethoxyethane with sodium hydroxide but in this case containing potasssium fluoride) a reaction occurred at room temperature and two acidic products resulted; these, however, proved to be the α-chloro acid **3a** and the corresponding α-hydroxy acid in the approximate ratio of 4:1. Variations involving heating of the mixtures or use of other cosolvents such as dimethylformamide were unpromising; methanol as a cosolvent led to the α-methoxy acid.[4,7]

More encouraging results were obtained with tetrabutylammonium fluoride in tetrahydrofuran. Treatment of 1 mmol of **1a** with 5 mL of 1 M tetrabutylammonium fluoride resulted in partial conversion to a mixture of **3a** and **4a**[8]; however, even after 30 h at room temperature, 55% of **1a** remained unchanged. Addition of a second 5 mmol of tetrabutylammonium fluoride furthered the conversion to approximately 13% **1a**, 33% **4a**, and 54% **3a** after another 1.5 days, but no change resulted thereafter. A variety of experimental conditions were then investigated, the results of which in some respects resemble those of Reeve, et al.,[5] i.e. a number of variables including solvent, temperature, stoichiometry, addition of inorganic fluoride, and addition of base all influenced the rate of reaction and/or product distribution, but none individually promoted a rapid and quantitative conversion of **1a** to **4a**.

Addition of potassium fluoride seemed to retard the reaction at room temperature, but the presence of excess cesium fluoride was advantageous as was the addition of a base (triethylamine was most often used; calcium hydride also promoted rapid reaction).[9] Introduction of **1a** as its trimethylsilyl ether slightly retarded the reaction, presumably by consuming an additional equivalent of fluoride. Higher initial temperatures increased the rate of disappearance of **1a**, but also led to the formation of as much as 20% of the α-hydroxy acid (possibly from the 5% water in commercial tetrabutylammonium fluoride/tetrahydrofuran). Dimethylformamide and dimethyl sulfoxide (usually made 1 M in tetrabutylammonium fluoride trihydrate to facilitate comparisons) were approximately equivalent to each other and somewhat superior to tetrahydrofuran as solvents; formamide, in which cesium fluoride is more soluble and which has been advantageous in certain fluoride displacement reactions[10] was totally ineffective. The use of 75% aqueous tetrabutylammonium fluoride in place of the trihydrate or the commercial tetrahydrofuran solution gave inferior results. A somewhat more active reagent could be prepared by dissolving 10 mmol of crystalline tetrabutylammonium fluoride trihydrate in 50–60 mL of dimethylformamide, then distilling at ≤ 20 mmHg until the final volume was ca. 10 mL (the residual water content was not measured), and a satisfactory concoction could similarly be prepared by partial distillation of water and dimethylformamide from the more economical 75 % aqueous tetrabutylammonium fluoride. "Anhydrous" tetrabutylammonium fluoride[11] appeared to offer no further advantages, and tetrabutylammonium difluorotriphenylstannate[12] failed to react with **1a**.

Most critical, from a practical standpoint, are the presence of excess cesium fluoride and a large excess of tetrabutylammonium fluoride. Under these conditions **1a** is rapidly converted to a mixture of **4a** and **3a** (usually ca. 3 : 1 to 4 : 1, respectively); application of heat at this point results in gradual further conversion of **3a** to **4a** (the actual intermediates prior to workup are not well defined and may consist of acids, acid chlorides, acid fluorides, etc., depending on water content and other variables). For small scale conversions, the convenience of the commercially available 1 M tetrahydrofuran solution seems to offset the modest advantages of dimethylformamide or dimethyl sulfoxide as solvents, and the majority of the preparative runs have been conducted with this reagent. The reactions are easily worked up via acid–base partitioning, and the α-fluoro acids tend to be solids recrystallizable from hexane or pentane. This ease of cleanup has in most cases made it attractive to prepare the precursor trichloromethylcarbinols **1**[3] as needed, and to use them directly with little or no purification.

To illustrate the utility of the method, we prepared analogs of two important dietary components, 2-fluorostearic acid (**4b**), and 2-fluorooleic acid (**5**). The former has been prepared previously,[8] but, somewhat suprisingly, the latter, which we obtained upon Lindlar[13] hydrogenation of **4c**, seems not to have been reported. Additionally, 1,1,1-trichloro-11-tetradecyn-2-ol (**1d**) (from 10-tridecyn-1-ol[14] via Swern[15] oxidation and the Corey, et al. homologization[3]) was converted to 2-fluoro-11-tetradecynoic acid (**4d**). The latter, via lithium aluminum hydride reduction, acetylation, and Lindlar hydrogenation, was cleanly converted into (*Z*)-2-fluoro-11-tetradecen-1-ol acetate (**6**). This compound is an analog of the sex pheromone of the European corn borer, *Ostrinia nubilalis*,[16] and studies of its properties will be reported at a later date.

To date, the procedure has been applied only to racemic substrates. We hope to address the stereochemical aspects in the near future.

Melting points were recorded on a Thomas Hoover apparatus and are uncorrected. Mass spectra were obtained from a Finnigan model 4510 GC/MS; electron ionization spectra were collected at 70 eV and a source block temperature of 150 °C. NMR spectra were obtained from a General Electric QE-300 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mention of a proprietary product does not imply endorsement by the U. S. Department of Agriculture.

2-Fluoro Carboxylic Acids 4a–d; General Procedure Exemplified by 2-Fluoroundecanoic Acid (4a):

CsF (2.1 g) was added to 1 M tetrabutylammonium fluoride in THF (Aldrich, 12 mL) in a flask equipped with stir bar, condenser, and drying tube. The mixture was stirred while heated briefly to reflux (an air gun can conveniently be used), then was cooled to *15–20 °C* and a solution of 1,1,1-trichloro-2-undecanol (**1a**) (275 mg, 1 mmol, prepared by the method of Corey, et al.[3]) in Et_3N (1 mL) was added. An amber color developed and after 15 min at r. t. the mixture was heated (oil bath 65–70 °C) for 2 h. After being cooled, it was transferred to a separatory funnel with 1 N NaOH (25 mL) plus ca. 25 mL water, and the aqueous phase was washed with 1 : 1 Et_2O–hexane (2 × 15 mL) (in some cases a third phase, usually an oil but in the preparation of **4b** a solid, separated that was kept with the aqueous phase). The aqueous phase was acidified with 2 N HCl and extracted with 1 : 1 Et_2O–hexane (3 × 20 mL). The combined organic extracts were rinsed again with 2 N HCl, then twice with water, dried ($MgSO_4$), filtered through ca. 1 g of silica gel, and concentrated in vacuo to provide 206 mg (100 %) of **2a** as a nearly white solid that consisted of essentially a single component by GC analysis (after treatment with CH_2N_2). Recrystallization from pentane (– 15 °C) provided 134 mg (65 %) of **2a** as a white solid, mp 64–64.5 °C (Lit.[8] mp 61–62 °C).

(Z)-2-Fluoro-9-octadecenoic Acid (2-Fluorooleic acid) (5):

A sample of unpurified **4c** (ca. 500 mg, ca. 1.67 mmol) in benzene (15 mL) was treated with Pb-poisoned 5 % Pd on $CaCO_3$ (41 mg) and the mixture was hydrogenated at 1 atm with agitation in a sonic cleaning bath for 75 min. After filtration and concentration, flash chromatography on silica gel with 25 % EtOAc in hexanes amended with 0.05 % trifluoroacetic acid gives 339 mg (ca. 68 %) of **5** as an oil that soon crystallized. Recrystallization from pentane provided a white solid, mp 40.5–41.5 °C.

(*Z*)-2-Fluoro-11-tetradecen-1-ol Acetate (6):

A solution of **4d** (726 mg, 3 mmol) in THF (2 mL) was added slowly to a cold suspension of $LiAlH_4$ (640 mg, 17 mmol) in THF. After stirring overnight at ca. 15 °C, Et_2O (15 mL) was added followed, with cooling, by the dropwise addition of H_2O (0.64 mL), 15 % NaOH (0.64 mL), and H_2O (1.9 mL). The mixture was stirred for several minutes, then filtered through Celite. The filtrate was transferred to a separatory funnel with Et_2O–hexane (1 : 1) and rinsed with 1 N HCl, H_2O, and sat. aq $NaHCO_3$, then dried and concentrated to provide a colorless oil that then crystallized (633 mg, 93 %). Recrystallization from hexanes gave 2-fluoro-11-tetradecyn-1-ol as a white solid; mp 41.5–42.5 °C.

MS: *m/z* (%) = 228 (M+, 0.05), 109 (15), 96 (6), 95 (23), 93 (6), 82 (32), 81 (32), 79 (15), 69 (16), 68 (100), 67 (76), 65 (6), 55 (29), 54 (6), 53 (10).

A sample of the above primary alcohol (104 mg, 0.46 mmol) in Ac_2O (0.2 mL) and pyridine (0.2 mL) was allowed to stand at r. t. for 75 min, and then diluted with $NaHCO_3$ and extracted with hexanes. The extract was rinsed with 1 N HCl, water, and sat. aq $NaHCO_3$, then dried, concentrated, and flash chromatographed (10 % EtOAc in hexanes) to give 98 mg of a colorless oil (80 %).

MS: *m/z* (%) = 270 (M +, 0.05), 109 (13), 95 (20), 93 (10), 82 (53), 81 (31), 80 (6), 79 (19), 69 (15), 68 (100), 67 (68), 65 (5), 55 (24), 54 (7), 53 (9).

^{1}H NMR ($CDCl_3$): δ = 1.11 (3 H, t, J = 7.5, CH_3), 1.25–1.75 (methylene), 2.10 (3 H, s, acetate methyl), 2.13 (4 H, m, propargylic), 4.17 (2 H, m, H-1a + H-1b), 4.66 (1 H, 2 × m at 4.57 and 4.74, J_{H-F} 51 Hz, H-2).

^{13}C NMR ($CDCl_3$): δ = 170.8 (acetate carbonyl), 65.9 (d, J_{C-F} = 22 Hz, C-1), 91.38 (d, J_{C-F} = 170.9 Hz, C-2), 81.65 and 79.52 (acetylenic).

To a solution of the acetylenic acetate (62 mg) in freshly distilled cyclohexene (4 mL) was added 5 % Pd on $CaCO_3$ (lead poisoned, Strem, 12 mg), and the mixture was hydrogenated at 1 atm for 30 min with agitation from a sonic cleaning bath. After filtration through Celite and evaporation, flash chromatography on a 5 g silica gel column gave pure (*Z*)-2-fluoro-11-tetradecen-1-ol acetate (**6**) (60 mg, eluted with ca. 7 % EtOAc in hexanes).

We are grateful to Ms. Dawn J. Harrison for mass spectral analyses.

Table. 2-Fluoro Compounds Prepared[a]

	Yield (%)	mp (Lit. mp) (°C)	^{1}H NMR (CDCl$_3$, 300 MHz) δ, J (Hz)	^{13}C NMR (CDCl$_3$, 75 MHz) δ, J (Hz)	MS (70 eV)[b] *m/z* (%)
4a	100	64–64.5 (61–62)[13]	0.88 (3 H, t, $J = 6$, CH$_3$), 1.27 (CH$_2$), 1.50 (2 H, m, H-4), 1.93 (2 H, m, H-3), 4.96 (1 H, t at 4.88, $J = 6$ and dd at 5.04, $J = 6$ and 6, $J_{H-F} = 48$, H-2)	175.28 (d, $J = 24$, C-1), 88.50 (d, $J = 183$, C-2)	218 (0.6), 171 (7), 161 (20), 157 (30), 147 (26), 115 (13), 109 (11), 105 (28), 101 (17), 95 (13), 92 (100), 87 (21), (81 (11), 71 (16), 59 (32), 57 (21), 55 (38)
4b	81	85–86 (88–90)[4]	0.88 (3 H, t, $J = 6$, CH$_3$, 1.26 (CH$_2$), 1.48 (ca. 2 H, m, H-4), 1.93 (2 H, m, H-3), 4.96 (1 H, t at 4.88, $J = 6$ and dd at 5.04, $J = 6$ and 6.9, $J_{H-F} = 48$, H-2).	175.20 (d, $J = 24.7$, C-1), 88.51 (d, $J = 182$, C-2)	316 (14), 255 (32), 213 (10), 199 (13), 161 (46), 147 (35), 141 (12), 127 (10), 109 (20), 105 (27), 101 (14), 95 (16), 92 (100), 87 (19), 85 (16), 81 (15), 71 (28), 69 (21), 67 (10), 59 (21), 57 (57), 56 (14), 55 (48)
4c	81	64–65	0.88 (3 H, t, $J = 6.9$, CH$_3$), 1.27 (CH$_2$), 1.25–1.55 (2 H, m, H-4), 1.88 (2 H, m, H-3), 2.14 (4 H, propargylic), 4.96 (1 H, t at 4.88, $J = 6$ and dd at 5.04, $J = 7.2$ and 7.2, $J_{HF} = 50$, H-2).	174.69 (d, $J = 24$, C-1), 88.48 (d, $J = 183.7$, C-2), 80.01 and 80.51 (acetylenic)	312 (0.2), 228 (25), 165 (13), 153 (23), 124 (17), 123 (11), 110 (19), 109 (29), 107 (31), 97 (11), 96 (34), 95 (71), 93 (23), 91 (10), 83 (15), 82 (67), 81 (100), 80 (14), 79 (37), 77 (10), 69 (29), 68 (74), 67 (91), 59 (22), 57 (12), 55 (65), 54 (58)
4d	76	69–70	1.11 (3 H, t, $J = 7.5$, CH$_3$), 1.32 (CH$_2$), 1.47 (ca. 2 H, m, H-4, 1.93 (2 H, m, H-3), 2.14 (4 H, m, propargylic), 4.96 (1 H, t at 4.88, $J = 6$ and dd at 5.04, $J = 6.9$ and 6.9, $J_{H-F} = 50$, H-2)	175.22 (d, $J = 24$, C-1), 88.47 (d, $J = 183.7$, C-2), 81.69 and 79.53 (acetylenic)	256 (0.1), 109 (22), 95 (33), 93 (9), 92 (6), 82 (62), 81 (44), 79 (19), 69 (20), 68 (100), 67 (80), 59 (17), 55 (31), 53 (13)
5		40.5–41.5	0.88 (3 H, t, $J = 6$), 1.27 and 1.34 (CH$_2$), 1.51 (2 H, m, H-4), 1.87 (2 H, m, H-3), 2.02 (4 H, m, allylic, 4.96 (1 H, t at 4.88, $J = 6$ and dd at 5.05, $J = 7$ and 6, $H_{H-F} = 50$, H-2), 5.35 (2 H, m, olefinic)	175.10 (d, $J = 24.7$, C-1), 88.49 (d, $J = 181.5$, C-2), 130.16 and 129.61 (olefinic).	314 (5), 220 (5), 214 (7), 161 (8), 147 (9), 141 (9), 127 (9), 123 (1), 113 (14), 112 (9), 111 (30), 109 (18), 98 (12), 97 (42), 96 (11), 95 (22), 93 (11), 92 (18), 87 (12), 85 (12), 84 (17), 83 (47), 82 (17), 81 (30), 71 (18), 70 (35), 69 (63), 67 (33), 59 (24), 57 (36), 56 (33), 55 (100), 54 (26)
6			0.95 (3 H, t, $J = 7.5$, CH$_3$), 2.02 (4 H, m, allylic), 2.10 (3 H, s, acetate CH$_3$), 4.17 (2 H, m, H-1a and H-1b), 4.66 (1 H, 2 m's at 4.57 and 4.74, $J_{H-F} = 51$), 5.34 (2 H, m, olefinic)	170.81 (acetate carbonyl), 65.92 (d, $J = 22.0$, C-1), 91.39 (d, $J = 171.8$, C-2), 131.58 and 129.29 (olefinic)	272 (0.2), 252 (6), 212 (6), 135 (18), 121 (22), 110 (11), 109 (19), 107 (12), 100 (14), 97 (13), 96 (23), 95 (38), 94 (18), 93 (18), 83 (18), 82 (42), 81 (60), 80 (24), 79 (20), 69 (54), 68 (47), 67 (74), 61 (16), 57 (10), 56 (21), 55 (100), 54 (30)

[a] Satisfactory C, H, and F combustion analyses were obtained for previously unreported compounds: C, H, N ± 0.4%.

[b] The mass spectra reported in this table are of *methyl esters* of the respective carboxylic acids, prepared by brief treatment with diazomethane prior to GC-MS analyses.

(1) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 906.

(2) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431.

(3) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435.

(4) Benner, J. P.; Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc., Perkin Trans. I* **1984**, 331.

(5) Reeve, W. J.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem.* **1980**, *58*, 485.

(6) Reeve, W.; Barron, E. *J. Org. Chem.* **1969**, *34*, 1005.

(7) Weizmann, Ch.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153.

(8) Gershon, H.; Parmegiani, R. *J. Medicin. Chem.* **1967**, *10*, 186.

(9) The base evidently acts as a HCl scavenger, and not as a reaction initiator, since **1a** failed to undergo any reaction with tetrabutylammonium chloride and triethylamine under similar conditions.

(10) Escoula, B.; Rico, I.; Lattes, A. *Bull. Soc. Chim. Fr.* **1989**, 256.

(11) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.

(12) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381.

(13) Lindlar, H.; Dubuis, R. *Org. Syn. Coll. Vol. 5*, **1973**, 880.

(14) Svirskaya, P. I.; Leznoff, C. C.; Weatherston, J.; Laing, J. E. *J. Chem. Eng. Data* **1979**, *24*, 152.

(15) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(16) Klun, J. A.; Miani, S. *Environ. Entomol.* **1979**, *8*, 423.