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Synthesis of some fluorinated acids, ketones and alcohols derived from 3,3,3-trifluoropropionic acid

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Abstract

The stereoselective synthesis of 3-fluoro-2-alkenoic acids was achieved by the reaction of lithium 3,3,3-trifluoropropionate with Grignard reagents. 2,2,2-Trifluoroethyl alkyl ketones were prepared by the reaction of 3,3,3-trifluoropropionic acid chloride with either lithium dialkylcuprates or magnesium dialkylcuprates. Optically active 1,1,1-trifluoro-3-alkanols were obtained by the enzymatic hydrolysis of the corresponding acetates. © 1997 Elsevier Science S.A.

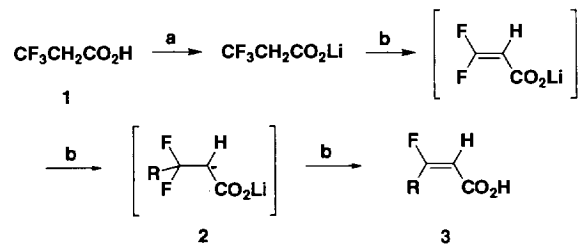
Keywords: Enzymatic hydrolysis; 3-Fluoro-2-alkenoic acids; 2,2,2-Trifluoroethyl alkyl ketones

1. Introduction

The chemical behaviour of the active methylene unit between trifluoromethyl and carbonyl groups (CF_3CH_2CO–) is of interest for the preparation of 2,2,2-trifluoroethyl alkyl ketones and optically active 1,1,1-trifluoro-3-alkanols and for the stereoselective construction of terminal fluoroalkenes [1]. In particular, terminal fluoroalkenes have been recognized as potential base-dependent enzyme inhibitors [2], and have found wide synthetic applications in radical addition reactions [3], electrophilic cyclizations [4] and Claisen rearrangements [5]. In this paper, we describe the stereoselective construction of (*E*)-3-fluoro-2-alkenoic acids and the synthesis of 2,2,2-trifluoroethyl alkyl ketones and optically active 1,1,1-trifluoro-3-alkanols.

2. Results and discussion

The preparation of (*E*)–(*Z*) mixtures of 3-fluoro-2-alkenoic acids ($RCF{=}CHCO_2H$, R ≡ Et, *n*-Bu, Ph) via the carboxylation of 2,2-difluorovinyllithium at −40 to −80 °C has been reported [6]. Our synthetic approach to these products, shown in Scheme 1, is mild and convenient. Firstly, lithium 3,3,3-trifluoropropionate was prepared from 3,3,3-trifluoropropionic acid and lithium hydroxide; the lithium salt was then reacted with a Grignard reagent in tetrahydrofuran (THF) at room temperature, producing a single stereoisomer. The stereochemistry of the product was confirmed by the ^1H nuclear magnetic resonance (NMR) coupling constant (J_{H-F}) and the chemical shift of the olefinic proton ($RCF{=}CHCO_2H$) (Table 1). It is well known that the coupling constant (J_{H-F}) of the (*Z*) isomer is 30–50 Hz, and that of the (*E*) isomer is 17–20 Hz. Furthermore, the signal from the olefinic proton in the (*Z*) isomer occurs in the region $\delta = 5.05$–5.20 ppm and that of the (*E*) isomer at $\delta = 5.50$–5.60 ppm [6]. On the basis of the chemical shift ($\delta = 5.50$–5.60 ppm) and coupling constant ($J_{H-F} \approx 20$ Hz), the product was identified as the (*E*) isomer.



Scheme 1. (a) LiOH, Et_2O, 0 °C; (b) RMgBr, THF, room temperature.

The preparation of 2,2,2-trifluoroethyl alkyl ketones **4** was achieved by the reaction of 3,3,3-trifluoropropionic acid chloride with lithium dialkylcuprates or magnesium dialkylcuprates at very low temperature (−100 to −110 °C) in diethyl ether (Scheme 2) (Table 2). In this reaction system, the (*Z*) isomer of ketone **7** was also produced to a minor extent via the 1,4-addition of cuprate to terminal difluoroolefin **5**, generated by the elimination of HF from the excess 2,2,2-trifluo-

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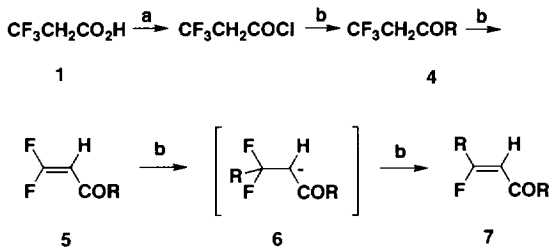
Table 1
Physical properties of (*E*)-3-fluoro-2-alkenoic acids (**3**)

Compound	R	Yield (%)	^{19}F NMR chemical shift[a]	^{1}H NMR chemical shift (δ, ppm) and coupling constant
3a	*n*-C_3H_7	65	91.1 (dt, J = 19.8, 25.9 Hz)	0.99 (3 H, t, J = 7.57 Hz), 1.65 (2 H, q, J = 7.57 Hz), 2.80 (2 H, dt, J = 7.57, 25.9 Hz), 5.60 (1 H, d, J = 19.3 Hz)
3b	*n*-C_4H_9	69	91.4 (dt, J = 19.8, 25.9 Hz)	0.93 (3 H, t, J = 7.32 Hz), 1.40 (2 H, q, J = 7.57 Hz), 1.56–1.62 (2 H, m), 2.82 (2 H, dt, J = 7.57, 26.0 Hz), 5.58 (1 H, d, J = 19.3 Hz)
3c	*n*-C_5H_{11}	68	91.3 (dt, J = 19.3, 25.9 Hz)	0.90 (3 H, t, J = 7.08 Hz), 1.32–1.37 (4 H, m), 1.61 (2 H, h, J = 7.57 Hz), 2.81 (2 H, dt, J = 7.57, 26.0 Hz), 5.58 (1 H, d, J = 19.3 Hz)
3d	*n*-C_6H_{13}	66	91.3 (dt, J = 19.8, 25.9 Hz)	0.90 (3 H, t, J = 7.08 Hz), 1.26–1.39 (6 H, m), 1.60 (2 H, q, J = 7.57 Hz), 2.81 (2 H, dt, J = 7.57, 26.0 Hz), 5.58 (1 H, d, J = 19.3 Hz)
3e	*n*-C_7H_{15}	70	91.3 (dt, J = 19.3, 25.9 Hz)	0.88 (3 H, t, J = 7.08 Hz), 1.23–1.39 (8 H, m), 1.60 (2 H, h, J = 7.57 Hz), 2.80 (2 H, dt, J = 7.57, 25.9 Hz), 5.58 (1 H, d, J = 19.3 Hz)

[a] δ (ppm) from internal C_6F_6.

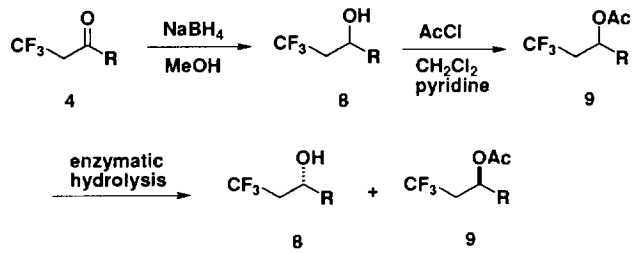


Scheme 2. (a) $C_6H_4(COCl)_2$; (b) R_2CuMet, Et_2O.

roethyl moiety. The reaction of 2,2,2-trifluoroethyl alkyl ketones **4** with lithium dialkylcuprate or magnesium dialkylcuprate at −78 °C in diethyl ether produced the (*Z*) isomer of ketone **7** as a main product.

We believe that the pathways of the stereoselective preparation of compounds **3** and **7** can be represented by Fig. 1. On the basis of the significant electrostatic component ($\sigma \rightarrow \sigma^*_{C-F}$) of the gauche effect [7] and the Li–F affinity, it can be assumed that conformer **A**, which leads to the (*E*) isomer, is more stable than conformer **B** of intermediate **2**. On the other hand, the Li–F affinity is not significant in the reaction intermediate **6**. From a consideration of the repulsion effects of bulky substituents (R and RCO groups) and the gauche effect ($\sigma \rightarrow \sigma^*_{C-F}$), conformer **C**, which leads to the (*Z*) isomer, is more stable than conformer **D** (Fig. 1).

The next synthetic goal was the preparation of optically active 1,1,1-trifluoro-3-alkanols **8**. To obtain these, we first examined the reduction of 2,2,2-trifluoroethyl alkyl ketones **4** with sodium borohydride in methanol to give racemic 1,1,1-trifluoro-3-alkanols **8** (Table 3). The racemic 1,1,1-trifluoro-3-alkanols **8** obtained were then converted to the corresponding acetate derivatives. Asymmetric hydrolysis [8] of **8** with lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd., 30 000 units g^{-1}) provided optically active 1,1,1-trifluoro-3-alkanols **8**. The results are shown in Table 4.



3. Experimental details

3.1. General

All commercially available reagents were used without further purification. Chemical shifts of ^{1}H (500 MHz) and ^{13}C NMR spectra were recorded in parts per million (δ) downfield from the internal standard Me_4Si (δ = 0.00). The ^{19}F (470 MHz) NMR spectra were recorded in parts per

Table 2
Physical properties of 2,2,2-trifluoroethyl alkyl ketones (**4**)

Compound	R	Yield (%)	^{19}F NMR chemical shift[a]	^{1}H NMR chemical shift (δ, ppm) and coupling constant
4a	*n*-C_4H_9	39	99.3 (t, J = 10.7 Hz)	0.92 (3 H, t, J = 7.57 Hz), 1.33 (2 H, m), 1.59 (2 H, m), 2.54 (2 H, t, J = 7.56 Hz), 3.22 (2 H, q, J = 10.5 Hz)
4b	*n*-C_5H_{11}	51	99.3 (t, J = 10.7 Hz)	0.90 (3 H, t, J = 7.08 Hz), 1.24–1.36 (4 H, m), 1.61 (2 H, m), 2.53 (2 H, t, J = 7.33 Hz), 3.21 (2 H, q, J = 10.5 Hz)
4c	*n*-C_6H_{13}	50	99.4 (t, J = 10.7 Hz)	0.89 (3 H, t, J = 7.08 Hz), 1.27–1.33 (6 H, m), 1.57–1.63 (2 H, m), 2.53 (2 H, t, J = 7.33 Hz), 3.21 (2 H, q, J = 10.5 Hz)
4d	*n*-C_7H_{15}	50	99.4 (t, J = 10.7 Hz)	0.88 (3 H, t, J = 7.08 Hz), 1.26–1.33 (8 H, m), 1.55–1.63 (2 H, m), 2.52 (2 H, t, J = 7.33 Hz), 3.21 (2 H, q, J = 10.5 Hz)

[a] δ (ppm) from internal C_6F_6.

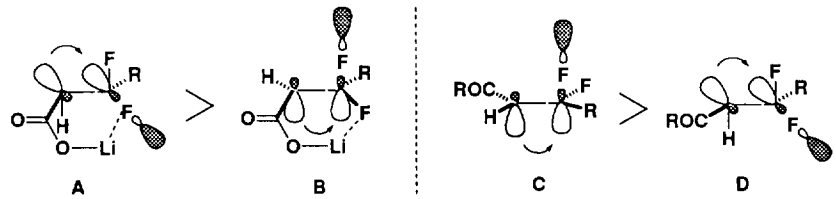


Fig. 1. Pathways of stereoselective preparation of compounds **3** and **7**.

Table 3
Physical properties of 1,1,1-trifluoro-3-alkanols (**8**)

Compound	R	Yield (%)	^{19}F NMR chemical shift[a]	^{1}H NMR chemical shift (δ, ppm) and coupling constant
8a	n-C_4H_9	57	98.2 (t, J = 10.7 Hz)	0.92 (3 H, t, J = 7.21 Hz), 1.30–1.38 (4 H, m), 1.40–1.60 (2 H, m), 1.79 (1 H, d, J = 4.40 Hz), 2.18–2.31 (2 H, m), 4.01 (1 H, m)
8b	n-C_5H_{11}	83	98.2 (t, J = 10.7 Hz)	0.90 (3 H, t, J = 7.08 Hz), 1.25–1.40 (6 H, m), 1.42–1.56 (2 H, m), 1.82 (1 H, d, J = 3.90 Hz), 2.20–2.30 (2 H, m), 4.02 (1 H, m)
8c	n-C_6H_{13}	77	98.2 (t, J = 10.7 Hz)	0.89 (3 H, t, J = 7.08 Hz), 1.25–1.38 (8 H, m), 1.40–1.60 (2 H, m), 1.78 (1 H, d, J = 4.39 Hz), 2.18–2.32 (2 H, m), 4.01 (1 H, m)
8d	n-C_7H_{15}	90	98.3 (t, J = 10.7 Hz)	0.89 (3 H, t, J = 7.08 Hz), 1.25–1.38 (10 H, m), 1.40–1.60 (2 H, m), 1.78 (1 H, d, J = 4.39 Hz), 2.18–2.32 (2 H, m), 4.01 (1 H, m)

[a] δ (ppm) from internal C_6F_6.

Table 4
Physical properties of optically active alkanols **8**

Compound	Conversion (%)	$[\alpha]_D^{21}$ ($CHCl_3$)	Optical purity (%)
8b	39	+1.50 (c = 0.38)	39
8c	35	+1.96 (c = 1.00)	50
8d	50	+1.41 (c = 0.67)	33

million downfield from the internal standard C_6F_6 in $CDCl_3$ using a VXR 500 instrument. Yields quoted are those of the products actually isolated.

3.2. (E)-3-Fluoro-2-hexenoic acid (3a)

To a diethyl ether solution (2 ml) of 3,3,3-trifluoropropionic acid **1** (2 mmol) was carefully added lithium hydroxide (2 mmol) at 0 °C, and the mixture was evaporated to dryness after neutralization was complete. The residue was thoroughly dried under reduced pressure at room temperature overnight and then dissolved in THF (6 ml). To this solution was added a solution of propylmagnesium bromide (4 mmol; 2 M in diethyl ether) at 0 °C, and the mixture was allowed to warm to room temperature with stirring for 20 h. The reaction was quenched by the addition of 2 M HCl, extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. On removal of the solvent, purification by silica gel flash chromatography (hexane–ethyl acetate, 5 : 1) gave (*E*)-3-fluoro-2-hexenoic acid **3a** in 65% yield. ^{1}H NMR ($CDCl_3$) δ: 0.99 (3 H, t, J = 7.57 Hz), 1.65 (2 H, q, J = 7.57 Hz), 2.80 (2 H, dt, J = 7.57, 25.9 Hz), 5.60 (1 H, d, J = 19.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.37, 19.38, 31.60 (d, J = 22.3 Hz), 100.79 (d, J = 30.4 Hz), 172.34 (d, J = 27.3 Hz), 179.26 (d, J = 275.9 Hz). ^{19}F NMR ($CDCl_3$) δ: 91.1 (dt, J = 19.8, 25.9 Hz). IR (neat): 1702 (C=O), 1655 (C=C) cm^{-1}.

3.3. (E)-3-Fluoro-2-heptenoic acid (3b)

This was obtained similarly in 69% yield using butylmagnesium bromide. ^{1}H NMR ($CDCl_3$) δ: 0.93 (3 H, t, J = 7.32 Hz), 1.40 (2 H, q, J = 7.57 Hz), 1.56–1.62 (2 H, m), 2.82 (2 H, dt, J = 7.57, 26.0 Hz), 5.58 (1 H, d, J = 19.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.66, 22.11, 27.99, 29.65 (d, J = 22.3 Hz), 100.56 (d, J = 30.5 Hz), 172.28 (d, J = 27.2 Hz), 179.54 (d, J = 276.1 Hz). ^{19}F NMR ($CDCl_3$) δ: 91.4 (dt, J = 19.8, 25.9 Hz). IR (neat): 1701 (C=O), 1654 (C=C) cm^{-1}. High-resolution mass for $C_7H_{11}O_2F$: calculated, 146.0742; found, 146.0737.

3.4. (E)-3-Fluoro-2-octenoic acid (3c)

This was obtained similarly in 68% yield using pentylmagnesium bromide. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3 H, t, J = 7.08 Hz), 1.32–1.37 (4 H, m), 1.61 (2 H, h, J = 7.57 Hz), 2.81 (2 H, dt, J = 7.57, 26.0 Hz), 5.58 (1 H, d, J = 19.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.81, 22.28, 23.62, 29.88 (d, J = 22.3 Hz), 31.11, 100.57 (d, J = 30.5 Hz), 172.41 (d, J = 27.3 Hz), 179.58 (d, J = 276.2 Hz). ^{19}F NMR ($CDCl_3$) δ: 91.3 (dt, J = 19.3, 25.9 Hz). IR (neat): 1700 (C=O), 1654 (C=C) cm^{-1}.

3.5. (E)-3-Fluoro-2-nanenoic acid (3d)

This was obtained similarly in 66% yield using hexylmagnesium bromide. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3 H, t, J = 7.08

Hz), 1.26–1.39 (6 H, m), 1.60 (2 H, q, $J=7.57$ Hz), 2.81 (2 H, dt, $J=7.57$, 26.0 Hz), 5.58 (1 H, d, $J=19.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.96, 22.44, 25.88, 28.63, 29.90 (d, $J=22.1$ Hz), 31.40, 100.56 (d, $J=30.5$ Hz), 172.37 (d, $J=27.3$ Hz), 179.56 (d, $J=276.1$ Hz). ^{19}F NMR ($CDCl_3$) δ: 91.3 (dt, $J=19.8$, 25.9 Hz). IR (neat): 1702 (C=O), 1654 (C=C) cm^{-1}.

3.6. (E)-3-Fluoro-2-decenoic acid (3e)

This was obtained similarly in 70% yield using heptylmagnesium bromide. ^1H NMR ($CDCl_3$) δ: 0.88 (3 H, t, $J=7.08$ Hz), 1.23–1.39 (8 H, m), 1.60 (2 H, h, $J=7.57$ Hz), 2.80 (2 H, dt, $J=7.57$, 25.9 Hz), 5.58 (1 H, d, $J=19.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 14.02, 22.60, 25.92, 28.92, 29.91 (d, $J=22.3$ Hz), 31.63, 100.57 (d, $J=30.6$ Hz), 172.34 (d, $J=27.2$ Hz), 179.57 (d, $J=276$ Hz). ^{19}F NMR ($CDCl_3$) δ: 91.3 (dt, $J=19.3$, 25.9 Hz). IR (neat): 1698 (C=O), 1654 (C=C) cm^{-1}. High-resolution mass for $C_{10}H_{17}O_2F$: calculated, 188.1212; found, 188.1218.

3.7. 3,3,3-Trifluoropropionic acid chloride

A mixture of 3,3,3-trifluoropropionic acid (10.2 g, 80 mmol) and phthaloyl chloride (24.4 g, 120 mmol) was refluxed for 3 h. Distillation gave 3,3,3-trifluoropropionic acid chloride (7.75 g) in 69% yield, boiling point (b.p.), 71–72 °C.

3.8. 2,2,2-Trifluoroethyl butyl ketone (4a)

To a solution of CuI (0.95 g, 5 mmol) in diethyl ether (10 ml), *n*-butyl lithium (1.6 M in hexane, 6.25 ml, 10 mmol) was added at −45 °C under an atmosphere of argon, and the mixture was stirred for 1 h at −25 °C. It was cooled to −110 °C (liquid nitrogen and ethanol bath), and then stirred for 30 min at that temperature. A solution of 3,3,3-trifluoropropionic acid chloride (1.02 g, 7 mmol) in diethyl ether (1 ml) was added at that temperature, and the mixture was stirred for 15 min. After the mixtures had been quenched with saturated aqueous NH_4Cl, oily materials were extracted with diethyl ether. The ethereal layer was washed with saturated aqueous NaCl, and dried over $MgSO_4$. After removal of the solvent, the residue was distilled to give 2,2,2-trifluoroethyl butyl ketone **4a** in 39% yield, b.p. 80–81 °C/50 mmHg. ^1H NMR ($CDCl_3$) δ: 0.92 (3 H, t, $J=7.57$ Hz), 1.33 (2 H, m), 1.54 (2 H, m), 2.54 (2 H, t, $J=7.56$ Hz), 3.22 (2 H, q, $J=10.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.64, 21.95, 25.13, 43.15, 46.01 (q, $J=28.0$ Hz), 123.63 (q, $J=275.2$ Hz), 200.29. ^{19}F NMR ($CDCl_3$) δ: 99.3 (t, $J=10.7$ Hz). IR (neat): 1729 (C=O) cm^{-1}.

3.9. 2,2,2-Trifluoroethyl pentyl ketone (4b)

To a solution of CuI (0.95 g, 5 mmol) in diethyl ether (10 ml), *n*-pentyl magnesium bromide (2.0 M in diethyl ether, 5 ml, 10 mmol) was added at −30 °C under an atmosphere of nitrogen, and the mixture was stirred for 1 h at −10 °C. The mixture was cooled to −100 to −110 °C (liquid nitrogen and ethanol bath), and stirred for 30 min at that temperature. A solution of 3,3,3-trifluoropropionic acid chloride (0.85 g, 5.8 mmol) in diethyl ether was added at that temperature, followed by stirring for 15 min. The mixture was quenched with saturated aqueous NH_4Cl; oily materials were extracted with diethyl ether. The ethereal layer was washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. After removal of the solvent, flash chromatography on silica gel (*n*-hexane–ethyl acetate, 15 : 1) gave 2,2,2-trifluoroethyl pentyl ketone **4b** in 51% yield. ^1H NMR ($CDCl_3$) δ: 0.90 (3 H, t, $J=7.08$ Hz), 1.24–1.36 (4 H, m), 1.61 (2 H, m), 2.53 (2 H, t, $J=7.33$ Hz), 3.21 (2 H, q, $J=10.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.78, 22.33, 22.79, 31.00, 43.41, 46.10 (q, $J=27.8$ Hz), 123.62 (q, $J=275.4$ Hz), 200.25. ^{19}F NMR ($CDCl_3$) δ: 91.3 (d, $J=10.7$ Hz). IR (neat): 1739 (C=O) cm^{-1}.

3.10. 2,2,2-Trifluoroethyl hexyl ketone (4c)

This was obtained similarly in 50% yield using magnesium dihexylcuprate. ^1H NMR ($CDCl_3$) δ: 0.89 (3 H, t, $J=7.08$ Hz), 1.27–1.33 (6 H, m), 1.55–1.63 (2 H, m), 2.53 (2 H, t, $J=7.33$ Hz), 3.21 (2 H, q, $J=10.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.94, 22.41, 23.09, 28.54, 31.47, 43.48, 46.13 (q, $J=27.9$ Hz), 123.65 (q, $J=275.6$ Hz), 200.29. ^{19}F NMR ($CDCl_3$) δ: 99.4 (t, $J=10.7$ Hz). IR (neat): 1732 (C=O) cm^{-1}.

3.11. 2,2,2-Trifluoroethyl heptyl ketone (4d)

This was obtained similarly in 50% yield using magnesium diheptylcuprate. ^1H NMR ($CDCl_3$) δ: 0.88 (3 H, t, $J=7.08$ Hz), 1.26–1.33 (8 H, m), 1.55–1.63 (2 H, m), 2.52 (2 H, t, $J=7.33$ Hz), 3.21 (2 H, q, $J=10.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.97, 22.53, 23.10, 28.81, 28.94, 31.56, 43.44, 46.07 (q, $J=28.0$ Hz), 123.63 (q, $J=275.5$ Hz), 200.27. ^{19}F NMR ($CDCl_3$) δ: 99.4 (t, $J=10.7$ Hz). IR (neat): 1719 (C=O) cm^{-1}.

3.12. (Z)-1-Butyloxyl-2-fluoro-1-hexene (7a)

To a solution of CuI (0.19 g, 1 mmol) in diethyl ether (2 ml), *n*-butyl lithium (1.6 M in hexane, 1.3 ml, 2 mmol) was added at −45 °C under an atmosphere of argon, and the mixture was stirred for 45 min at −25 °C, cooled to −78 °C and stirred for 30 min at that temperature. A solution of 2,2,2-trifluoroethyl butyl ketone (0.10 g, 0.6 mmol) in diethyl ether (1 ml) was added at that temperature, and the mixture was stirred for 30 min. The mixture was quenched with saturated aqueous NH_4Cl; oily materials were extracted with diethyl ether and the ethereal layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, flash chromatography on silica gel gave a mixture of (*Z*)- and (*E*)-1-butyloxyl-2-fluoro-1-hexene.

The ratio of (*Z*)- and (*E*)-1-butyloxyl-2-fluoro-1-hexene was 9 : 1. ^{1}H NMR ($CDCl_3$) δ: 0.89–0.95 (m), 1.30–1.44 (m), 1.52–1.61 (m); (*Z*) isomer: 2.29 (2 H, dt, J=7.57, 17.3 Hz), 2.64 (2 H, dt, J=2.20, 7.30 Hz), 5.32 (1 H, d, J=38.8 Hz); (*E*) isomer: 2.43 (2 H, t, J=7.56 Hz), 2.78 (2 H, dt, J=8.0, 26.0 Hz), 5.94 (1 H, d, J=20.5 Hz). ^{19}F NMR ($CDCl_3$) δ: (*Z*) isomer: 82.2 (dt, J=16.8, 39.6 Hz); (*E*) isomer: 85.9 (dt, J=21.4, 25.9 Hz).

3.13. 1,1,1-Trifluoro-3-heptanol (8a)

To a solution of sodium borohydride (0.102 g, 2.7 mmol) in methanol (0.5 ml), a solution of 2,2,2-trifluoroethyl butyl ketone **4a** (0.3 g, 1.70 mmol) in methanol (2 ml) was added via a syringe at 0 °C under an atmosphere of nitrogen, and the mixture was stirred for 30 min at 0 °C. After removal of the solvent, flash chromatography on silica gel (*n*-hexane–ethyl acetate (5 : 1) as eluent) gave 1,1,1-trifluoro-3-heptanol **8a** in 57% yield. ^{1}H NMR ($CDCl_3$) δ: 0.92 (3 H, t, J=7.21 Hz), 1.30–1.38 (4 H, m), 1.40–1.60 (2 H, m), 1.79 (1 H, d, J=4.40 Hz), 2.18–2.31 (2 H, m), 4.01 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.84, 22.41, 27.30, 36.84, 41.06 (q, J=26.3 Hz), 66.15 (q, J=2.83 Hz), 126.48 (q, J=275.4 Hz). ^{19}F NMR ($CDCl_3$) δ: 98.2 (t, J=10.7 Hz). IR (neat): 3377 (OH) cm^{-1}.

3.14. 1,1,1-Trifluoro-3-octanol (8b)

This was obtained similarly in 83% yield using 2,2,2-trifluoroethyl pentyl ketone **4b**. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3 H, t, J=7.08 Hz), 1.25–1.40 (6 H, m), 1.42–1.56 (2 H, m), 1.82 (1 H, d, J=3.90 Hz), 2.20–2.30 (2 H, m), 4.02 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.88, 22.50, 24.84, 31.53, 37.14, 41.09 (q, J=26.9 Hz), 66.11 (q, J=2.93 Hz), 126.49 (q, J=275.4 Hz). ^{19}F NMR ($CDCl_3$) δ: 98.2 (t, J=10.7 Hz). IR (neat): 3386 (OH) cm^{-1}.

3.15. 1,1,1-Trifluoro-3-nonanol (8c)

This was obtained similarly in 77% yield using 2,2,2-trifluoroethyl hexyl ketone (**4c**). ^{1}H NMR ($CDCl_3$) δ: 0.89 (3 H, t, J=7.08 Hz), 1.25–1.38 (8 H, m), 1.40–1.60 (2 H, m), 1.78 (1 H, d, J=4.39 Hz), 2.18–2.32 (2 H, m), 4.01 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.98, 22.54, 25.14, 29.02, 31.70, 37.17, 41.09 (q, J=26.2 Hz), 66.18 (q, J=2.83 Hz), 126.50 (q, J=275.3 Hz). ^{19}F NMR ($CDCl_3$) δ: 98.2 (t, J=10.7 Hz). IR (neat): 3385 (OH) cm^{-1}.

3.16. 1,1,1-Trifluoro-3-decanol (8d)

This was obtained similarly in 90% yield using 2,2,2-trifluoroethyl heptyl ketone **4d**. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3 H, t, J=7.08 Hz), 1.25–1.38 (10 H, m), 1.40–1.60 (2 H, m), 1.78 (1 H, d, J=4.15 Hz), 2.18–2.32 (2 H, m), 4.01 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.99, 22.60, 25.17, 29.16, 29.32, 31.74, 37.16, 41.10 (q, J=26.1 Hz), 66.20 (q, J=2.83 Hz), 126.50 (q, J=275.4 Hz). ^{19}F NMR ($CDCl_3$): δ 98.3 (t, J=10.7 Hz). IR (neat): 3386 (OH) cm^{-1}.

3.17. Acetate of 1,1,1-trifluoro-3-octanol (9b)

To a solution of 1,1,1-trifluoro-3-octanol **8b** (1 mmol) in dichloromethane (2.5 ml) were added acetyl chloride (1.5 mmol) and pyridine (1.5 mmol) at 0 °C under a nitrogen atmosphere; the mixture was stirred for 10 min at that temperature. After 30 min of stirring at room temperature, 2 N HCl (1 drop) was added to the mixture; oily materials were extracted with dichloromethane, and washed with saturated aqueous NaCl. Acetate **9b** was isolated by column chromatography on silica gel in 87% yield. ^{1}H NMR ($CDCl_3$) δ: 0.89 (3 H, t, J=6.83 Hz), 1.25–1.35 (6 H, m), 1.54–1.68 (2 H, m), 2.06 (3 H, s), 2.26–2.46 (2 H, m), 5.20 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.91, 20.93, 22.43, 24.52, 31.38, 34.13, 37.96 (q, J=27.9 Hz), 67.52 (q, J=2.63 Hz), 125.67 (q, J=275.3 Hz), 170.15. ^{19}F NMR ($CDCl_3$) δ: 97.8 (t, J=10.7 Hz). IR (neat): 1746 (C=O) cm^{-1}.

3.18. Acetate of 1,1,1-trifluoro-3-nonanol (9c)

This was obtained similarly in 88% yield using 1,1,1-trifluoro-3-nonanol **8c**. ^{1}H NMR ($CDCl_3$) δ: 0.88 (3 H, t, J=7.08 Hz), 1.24–1.34 (8 H, m), 1.54–1.68 (2 H, m), 2.06 (3 H, s), 2.26–2.46 (2 H, m), 5.20 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 13.95, 20.89, 22.48, 24.80, 28.87, 31.58, 34.16, 37.95 (q, J=27.9 Hz), 67.52 (q, J=2.83 Hz), 125.68 (q, J=275.4 Hz), 170.12. ^{19}F NMR ($CDCl_3$) δ: 97.8 (t, J=10.7 Hz). IR (neat): 1747 (C=O) cm^{-1}.

3.19. Acetate of 1,1,1-trifluoro-3-decanol (9d)

This was made in 90% yield using 1,1,1-trifluoro-3-decanol **8d**. ^{1}H NMR ($CDCl_3$) δ: 0.88 (3 H, t, J=7.08 Hz), 1.22–1.34 (10 H, m), 1.46–1.68 (2 H, m), 2.06 (3 H, s), 2.26–2.46 (2 H, m), 5.20 (1 H, m). ^{13}C NMR ($CDCl_3$) δ: 14.01, 20.90, 22.58, 24.85, 29.07, 29.18, 31.69, 34.16, 37.95 (q, J=27.9 Hz), 63.52 (q, J=2.83 Hz), 125.67 (q, J=275.4 Hz), 170.13. ^{19}F NMR ($CDCl_3$) δ: 97.9 (t, J=10.7 Hz). IR (neat): 1747 (C=O) cm^{-1}.

3.20. Asymmetric hydrolysis

A mixture of acetate of **9c** (1 mmol) and lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd., 30 000 units g^{-1}, 0.14 g) in a solution of 0.2 M phosphate buffer pH 7 (10 ml) was stirred at 38–40 °C. After 8 h of stirring, oily materials were extracted with ethyl acetate, the organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the hydrolysis ratio was determined from the ^{19}F NMR intensities, and the products were separated by column chromatography on silica gel (hexane–ethyl acetate, 5 : 1).

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